TREATING LOCALLY ADVANCED OR METASTATIC UROTHELIAL CANCER WITH ANTI-191P4D12 ANTIBODY DRUG CONJUGATES IN COMBINATION WITH PEMBROLIZUMAB

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Application No. 63/584,480, filed September 21, 2023, U.S. Application No. 63/620,610, filed January 12, 2024, U.S. Application No. 63/650,806, filed May 22, 2024, U.S. Application No. 63/672,135, filed July 16, 2024, and U.S. Application No. 63/694,044, filed on September 12, 2024 , the disclosure of each of which is incorporated by reference herein in its entirety.

SEQUENCE LISTING

[0002] This application contains an electronic Sequence Listing which has been submitted in XML file format with this application, the entire content of which is incorporated by reference herein in its entirety. The Sequence Listing XML file submitted with this application is entitled "14369-311-228_SEQ_LISTING.xml", was created on September 17, 2024, and is 62,860 bytes in size.

1. Field

[0003] Provided herein are methods for treating cancers with antibody drug conjugates (ADC) that bind to 191P4D12 protein (Nectin-4). In particular, provided herein are methods for treating cisplatin eligible and ineligible patients with unresectable locally advanced or metastatic urothelial cancer with antibody drug conjugates (ADC) that bind to 191P4D12 proteins in combination with pembrolizumab.

2. Background

[0004] Cancer is the leading cause of death in the US for people 35 to 65 years of age and it is the second leading cause of death worldwide. It was estimated in 2019 that there would be approximately 1.7 million new cancer cases and approximately 610000 deaths from cancer in the US (National Cancer Institute. 2019. Cancer Stat Facts: Cancer of Any Site. seer.cancer.gov/statfacts/html/all.html. Accessed 5 Jun 2019). Globally there were an estimated 18.1 million new cancer cases in 2018 and approximately 9.6 million deaths attributed to cancer in 2018 (World Health Organization. Press Release. Sept 2018. who.int/cancer/PRGlobocanFinal.pdf. Accessed 5 Jun 2019). Most deaths now occur in

patients with metastatic cancers. In fact, in the last 20 years, advances in treatment, including surgery, radiotherapy and adjuvant chemotherapy cured most patients with localized cancer. Patients whose cancer presented or recurred as metastatic disease obtained only modest benefit from conventional therapies in terms of overall survival (OS) and were rarely cured.

[0005] New therapeutic strategies for advanced and/or metastatic cancers include targeting molecular pathways important for cancer cell survival and novel cytotoxic compounds. The benefit of these novel drugs is reflected in prolonged survival; however, the outcome for most patients with distant metastases is still poor and novel therapies are needed.

[0006] 191P4D12 (which is also known as Nectin-4) is a 66 kDa type I transmembrane protein that belongs to the nectin family of adhesion molecules. It is composed of an extracellular domain (ECD) containing 3 immunoglobulin (Ig)-like subdomains, a transmembrane helix, and an intracellular region (Takai *et al.*, Annu Rev Cell Dev Biol (2008); 24: 309-42). Nectins are thought to mediate Ca^{2+}-independent cell-cell adhesion via both homophilic and heterophilic trans-interactions at adherens junctions where they can recruit cadherins and modulate cytoskeletal rearrangements (Rikitake *et al.*, Cell Mol Life Sci (2008); 65(2): 253-63.). Sequence identity of Nectin-4 to other Nectin family members is low and ranges between 25%–30% in the ECD (Reymond *et al.*, Biol Chem (2001); 276(46): 43205-15).

[0007] The 3 Ig-like subdomains in the ECD of Nectin-4 are designated V, C1 and C2. The C1 domain is responsible for cis-interaction (homodimerization), while V domains of most Nectin molecules contribute to trans-interaction and cell-cell adhesion (Mandai *et al.*, Curr Top Dev Biol (2015);112: 197-231; Takai *et al.*, Nat Rev Mol Cell Biol (2008); 9(8): 603-15.).

[0008] Nectin-4 was originally identified by bioinformatics and cloned from human trachea (Reymond *et al.*, J Biol Chem (2001) 276(46): 43205-15.). Nectin-4 was identified as markedly upregulated in urothelial cancer using suppression subtractive hybridization on a pool of urothelial cancer specimens. Characterization of expression in multiple tumor specimens, both at the ribonucleic acid (RNA) level and by immunohistochemistry (IHC), also demonstrated high levels of Nectin-4 in breast, pancreatic, lung, and other cancers (Challita-Eid *et al.*, Cancer Res (2016); 76(10): 3003-13.).

[0009] Nectin-4 has been found to be expressed in multiple cancers, particularly urothelial, breast, lung, pancreatic, and ovarian cancers. Higher levels of expression are associated with disease progression and/or poor prognosis (Fabre-Lafay *et al.*, BMC Cancer (2007); 7: 73).

[0010] PD-1

[0011] PD-1 is recognized as an important molecule in immune regulation and the maintenance of peripheral tolerance. PD-1 is moderately expressed on naive T, B and NKT cells and up-regulated by T/B cell receptor signaling on lymphocytes, monocytes and myeloid cells (Sharpe, Arlene H. *et al.*, The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. *Nature Immunology* (2007); 8:239-245).

[0012] Two known ligands for PD-1, PD-L1 (B7-H1) and PD-L2 (B7-DC), are expressed in human cancers arising in various tissues. In large sample sets of *e.g.* ovarian, renal, colorectal, pancreatic, liver cancers and melanoma, it was shown that PD-L1 expression correlated with poor prognosis and reduced overall survival irrespective of subsequent treatment (Dong, Haidong et al., Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med. 2002 Aug;8(8):793-800; Yang, Wanhua et al., PD-1 interaction contributes to the functional suppression of T-cell responses to human uveal melanoma cells *in vitro*. *Invest Ophthalmol Vis Sci*. 2008 Jun; 49(6 (2008): 49: 2518-2525; Ghebeh, Hazem et al., The B7-H1 (PD-L1) T lymphocyte-inhibitory molecule is expressed in breast cancer patients with infiltrating ductal carcinoma: correlation with important high-risk prognostic factors. *Neoplasia* (2006) 8: 190-198; Hamanishi, Junzo *et al.*, Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proc. Natl. Acad. Sci. USA* (2007): 104: 3360-3365; Thompson, R Houston, and Eugene D Kwon, Significance of B7-H1 overexpression in kidney cancer. Clinical genitourin *Cancer* (2006): 5: 206-211; Nomi, Takeo et al., Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clinical Cancer Research* (2007);13:2151-2157; Ohigashi, Yuichiro et al., Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand 2 expression in human esophageal cancer. *Clin. Cancer Research* (2005): 11: 2947-2953; Inman, Brant A et al., PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. *Cancer* (2007): 109: 1499-1505; Shimauchi, Takatoshi et al., Augmented expression of programmed death-1 in both neoplasmatic and nonneoplastic CD4+ T-cells in adult T-cell Leukemia/ Lymphoma. *Int. J. Cancer* (2007): 121:2585-2590; Gao, Qiang et al., Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. *Clinical Cancer Research* (2009) 15: 971-979; Nakanishi, Juro et al., Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. *Cancer*

Immunol Immunother. (2007) 56: 1173-1182; Hino et al., Tumor cell expression of programmed cell death-1 is a prognostic factor for malignant melanoma. *Cancer* (2010): 00: 1-9). Similarly, PD-1 expression on tumor infiltrating lymphocytes was found to mark dysfunctional T cells in breast cancer and melanoma (Ghebeh, Hazem et al., Foxp3+ tregs and B7-H1+/PD-1+ T lymphocytes co-infiltrate the tumor tissues of high-risk breast cancer patients: implication for immunotherapy. *BMC Cancer*. 2008 Feb 23;8:57; Ahmadzadeh, Mojgan et al., Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. *Blood* (2009) 114: 1537-1544) and to correlate with poor prognosis in renal cancer (Thompson, R Houston et al., PD-1 is expressed by tumor infiltrating cells and is associated with poor outcome for patients with renal carcinoma. *Clinical Cancer Research* (2007) 15: 1757-1761). Thus, it has been proposed that PD-L1-expressing tumor cells interact with PD-1-expressing T cells to attenuate T cell activation and evasion of immune surveillance, thereby contributing to an impaired immune response against the tumor.

[0013] Several monoclonal antibodies that inhibit the interaction between PD-1 and one or both of its ligands PD-L1 and PD-L2 have been approved for treating cancer. Pembrolizumab (KEYTRUDA®, Merck & Co., Inc., Rahway, NJ, USA) is a potent humanized immunoglobulin G4 (IgG4) mAb with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications and is indicated for the first-line treatment of patients with unresectable or metastatic CRC that is microsatellite instability-high or mismatch repair deficient (MSI-H/dMMR). Pembrolizumab is the current standard of care for first line MSI-H/dMMR mCRC.

[0014] **Urothelial Cancer**

[0015] According to the International Agency for Research on Cancer (IARC), urothelial cancer kills more than 165000 patients annually and is the ninth most common cancer overall worldwide. Approximately 151000 new cases of urothelial cancer are diagnosed annually in Europe, with 52000 deaths per year. Over 22000 new cases are diagnosed annually in Japan, with 7600 deaths per year (Cancer Fact Sheets: All cancers excluding Non-Melanoma Skin. International Agency for Research on Cancer 2017. Retrieved from gco.iarc.fr/today/fact-sheets- cancers?cancer=29&type=0&sex=0. Accessed 19 Dec 2017). In the U.S., the

National Cancer Institute estimates more than 79,000 new cases of bladder cancer were diagnosed in 2017, and more than 16,800 people died from the disease (National Cancer Institute 2018).

[0016] Metastatic urothelial cancer has a 5-year mortality rate of approximately 85% (American Cancer Society (ACS) 2016).

[0017] Urothelial cancer is the most common type of bladder cancer (90 percent of cases), and can also be found in the urothelial cells that line the renal pelvis (where urine collects inside the kidney), ureter (tube that connects the kidneys to the bladder) and urethra.

[0018] First-line therapy for metastatic urothelial cancer in patients with sufficient renal function consists of cis-diamminedichloroplatinum (II) (cisplatin)-based combinations, like methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) or gemcitabine plus cisplatin, which demonstrate an objective response rate (ORR) up to 55%, including approximately 12% complete responses (CRs) (von der Maase 2000). Despite initial chemosensitivity, patients are not cured and the outcome of metastatic urothelial cancer after these regimens is poor: median time to progression is 7 months and median overall survival (OS) is 14 months. Long-term survival is poor (approximately 15%) and the prognosis is particularly grim for patients with visceral metastases, for whom the five year survival rate is 7% (von der Maase 2005; Bellmunt 2011).

[0019] Almost half of urothelial cancer patients are unfit for cisplatin-containing chemotherapy due to impaired renal function, poor performance status, or comorbidity (Dash *et al.* Cancer (2006);107(3): 506-13). In these patients, no standard first-line treatment has been defined, but current options typically include cis-Diammine (cyclobutane 1,1 dicarboxylato) platinum (carboplatin)-based regimens or single-agent taxane or gemcitabine (Cathomas 2015). In this setting, long term survival is even lower (De Santis *et al.* J Clin Oncol (2009); 27(33): 5634-9). In April 2017, the Food and Drug Administration (FDA) approved the anti-programmed death-ligand 1 (PD-L1) immune checkpoint inhibitor (CPI) atezolizumab (TECENTRIQ®) as first line treatment for locally advanced or metastatic urothelial carcinoma (la/mUC) patients ineligible for cisplatin. The accelerated approval was based on an open-label single arm study that showed long durations of response, indicating activity in this difficult-to-treat population, with an objective response rate (ORR) of 23% that was similar across varying levels of target expression (Balar 2017). The median OS for these patients was 15.9 months, although this is a single arm study and any OS benefit will need to be confirmed in a randomized experience (Balar *et al.,* Lancet (2017); 389(10064): 67-76).

[0020] Pembrolizumab (Keytruda®) received accelerated approval from the FDA in May 2017 as first line treatment for patients with la/mUC ineligible for cisplatin. The study on which approval was based resulted in an ORR of 29% and median response duration not reached at the time of the analysis (median follow-up time of 7.8 months) (Pembrolizumab Prescribing Information, Merck Sharp and Dohme Corp., 2017). In May 2018, the FDA issued an alert regarding decreased survival of patients with low expression of PD-L1 being treated in the first line setting with pembrolizumab or atezolizumab, compared with platinum-based chemotherapy. Subsequently prescribing information for these two CPIs were revised to require high PD-L1 expression in first-line metastatic urothelial cancer patients who are eligible for platinum-containing chemotherapy. This development has further limited the options for metastatic urothelial cancer patients with low expression of PD-L1.

[0021] Other options for first line cisplatin-ineligible patients typically include carboplatin-based regimens or single-agent taxane or gemcitabine (Cathomas *et al.,* Hematol Oncol Clin North Am (2015); 29(2): 329-40.).

[0022] Few options are available for second-line treatment of metastatic disease. In the European Union, the small-molecule tubulin inhibitor vinflunine (Javlor®) was authorized in 2009 based on modest activity (overall response rate 9%), moderate survival benefit of 2 months (6.9 months for vinflunine + best supportive care (BSC) vs 4.6 months for BSC alone, hazard ratio 0.88), and a favorable safety profile (Bellmunt *et al.* Clin Oncol (2009); 27(27): 4454-61). In May 2016, the FDA provided accelerated approval of atezolizumab as the first salvage therapy following platinum agents for la/mUC in the US, followed by EU approval in September 2017. In February 2017, nivolumab (Opdivo®) became the second immunotherapy granted accelerated approval by the FDA, which was followed by EU approval in June 2017. In March and May 2017, the FDA granted accelerated approval for avelumab (Bavencio®) and durvalumab (Imfinzi™), respectively, both PD-L1 blocking antibodies indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Pembrolizumab received regular approval from the FDA in May 2017 as second-line treatment (Keytruda Prescribing Information, Merck, May 2017). The approval was based on the first randomized experience reported for a CPI in the locally advanced or metastatic post-platinum urothelial cancer setting, a phase 3 study in 542 patients showing an OS of 10.3 months as compared to 7.4 months with taxane chemotherapy or vinflunine. Additionally, ORR was 21% for pembrolizumab and 11% for

chemotherapy. No statistically significant difference in progression-free survival (PFS) between the two arms was observed (Bellmunt *et al.*, N Engl J Med (2017);376(11): 1015-26). EU approval for the same indication was granted in September 2017 and Japanese approval in January 2018. Other programmed cell death protein 1 (PD-1) and PD-L1 inhibitors are currently being evaluated in clinical trials for urothelial cancer, as first and second-line therapy (Mullane *et al.*, Curr Opin Urol (2016);26(6): 556-63).

[0023] While CPIs offer a new approach to treatment of metastatic urothelial cancer, tumor responses have occurred in a minority of patients and the improvement in long-term survival is only a few months. For example, in May 2017, Roche announced that a confirmatory phase 3 trial of second-line atezolizumab had failed to meet its primary endpoint of OS (Roche, press release "Roche provides update on phase III study of Tecentriq (atezolizumab) in people with previously treated advanced bladder cancer," 10-May-2017). Most patients with locally advanced or metastatic urothelial cancer do not respond to CPIs and many who do respond ultimately develop disease progression (Rosenberg *et al.*, Lancet (2016); 387(10031): 1909-20). Novel treatments are still needed, particularly for patients who have not responded to CPIs or who have progressed following CPI therapy.

[0024] **Bladder Cancer**

[0025] Of all new cases of cancer in the United States, bladder cancer represents approximately 5 percent in men (fifth most common neoplasm) and 3 percent in women (eighth most common neoplasm). The incidence is increasing slowly, concurrent with an increasing older population. American Cancer Society (cancer.org) estimates that there are 81,400 new cases annually, including 62,100 in men and 19,300 in women, which accounts for 4.5% of all cancer cases. The age-adjusted incidence in the United States is 20 per 100,000 for men and women. There are an estimated 17,980 deaths from bladder cancer in annually (13,050 in men and 4,930 in women), which accounts for 3% of cancer related deaths. Bladder cancer incidence and mortality strongly increase with age and will be an increasing problem as the population becomes more elderly. Globally, approximately 580,000 people will be diagnosed with bladder cancer in 2020, and bladder cancer will be attributed to approximately 210,000 deaths worldwide.

[0026] Most bladder cancers recur in the bladder. Bladder cancer is managed with a combination of transurethral resection of the bladder (TUR) and intravesical chemotherapy or immunotherapy. The multifocal and recurrent nature of bladder cancer points out the limitations of TUR. Most muscle-invasive cancers are not cured by TUR alone. Radical cystectomy and urinary diversion is the most effective means to eliminate the cancer but

carry an undeniable impact on urinary and sexual function. There continues to be a significant need for treatment modalities that are beneficial for bladder cancer patients.

[0027] There is a significant need for additional therapeutic methods for urothelial and bladder cancers. These include the use of antibodies and antibody drug conjugates, including in combination with other agents, as treatment modalities.

3. Summary

[0028] Provided herein are methods for the treatment of various cancers in subjects, such as human subjects, including methods for treating cisplatin eligible and ineligible patients with unresectable locally advanced or metastatic urothelial cancer with antibody drug conjugates (ADC) that bind to 191P4D12 proteins in combination with pembrolizumab.

[0029] In certain embodiments, the subject (e.g., a human subject) treated with the methods provided herein has not received previous treatment (e.g., treatment for unresectable, locally advanced or metastatic urothelial cancer (UC)). In certain embodiments, the subject (e.g., a human subject) treated with the methods provided herein has not received previous treatment with a PD-(L)-1 inhibitor (e.g., a PD-1 inhibitor or PD-L1 inhibitor (including, but not limited to, atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab)).

[0030] Embodiment 1. A method of treating cancer in a subject, comprising administering to the subject:

(a) an effective amount of an antibody drug conjugate (ADC) comprising an anti-191P4D12 antibody or antigen binding fragment thereof, and

(b) an effective amount of an anti-PD-1 antibody or antigen binding fragment thereof;

wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE);

wherein the anti-PD-1 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:32 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO: 27;

wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set

forth in SEQ ID NO:22 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23;

wherein the subject has urothelial or bladder cancer; and

wherein the subject is eligible to receive cisplatin treatment (cisplatin eligible).

[0031] Embodiment 2. The method of embodiment 1, wherein the subject has not previously received a PD-(L)-1 inhibitor.

[0032] Embodiment 3. The method of embodiment 1 or 2, wherein the subject has a GFR >60 mL/min.

[0033] Embodiment 4. The method of any one of embodiments 1 to 3, wherein the subject has NCI CTCAE Grade ≤1 audiometric hearing loss.

[0034] Embodiment 5. The method of any one of embodiments 1 to 4, wherein the subject does not have NYHA Class III heart failure.

[0035] Embodiment 6. The method of any one of embodiments 1 to 5, wherein:

(a) the subject has a progression free survival of at least or about 10, 11, 12, 13, 14, 14.6, 15, 16, 17, 18, or 19 months following the treatment, optionally wherein the subject has a progression free survival of at least or about 14.6 months following the treatment, further optionally wherein the subject has a progression free survival of 14 to 15 months following the treatment;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 10, 11, 12, 13, 14, 14.6, 15, 16, 17, 18, or 19 months, optionally wherein median progression free survival in the treated population is at least or about 14.6 months, further optionally wherein median progression free survival in the treated population is 14 to 15 months; or

(c) median progression free survival is at least or about 10, 11, 12, 13, 14, 14.6, 15, 16, 17, 18, or 19 months for a population of subjects treated with the method, optionally wherein median progression free survival is at least or about 14.6 months for a population of subjects treated with the method, further optionally wherein median progression free survival is 14 to 15 months for a population of subjects treated with the method.

[0036] Embodiment 7. The method of any one of embodiments 1 to 5, wherein:

(a) the subject has an overall survival of at least or about 27, 28, 29, 30, 31, 31.5, 32, 33, 34, 35, or 36 months following the treatment, optionally wherein the subject has an overall survival of at least or about 31.5 months following the treatment, further optionally wherein the subject has an overall survival of 31 to 32 months following the treatment;

(b) a population of the subjects is treated by the methods, and wherein median overall survival in the treated population is at least or about 27, 28, 29, 30, 31, 31.5, 32, 33, 34, 35, or 36 months, optionally wherein median overall survival in the treated population is at least or about 31.5 months, further optionally wherein median overall survival in the treated population is 31 to 32 months; or

(c) median overall survival is at least or about 27, 28, 29, 30, 31, 31.5, 32, 33, 34, 35, or 36 months for a population of subjects treated with the method, optionally whererin median overall survival is at least or about 31.5 months for a population of subjects treated with the method, further optionally wherein median overall survival is 31 to 32 months for a population of subjects treated with the method.

[0037] Embodiment 8. A method of treating cancer in a subject, comprising administering to the subject:

(a) an effective amount of an antibody drug conjugate (ADC) comprising an anti-191P4D12 antibody or antigen binding fragment thereof, and

(b) an effective amount of an anti-PD-1 antibody or antigen binding fragment thereof;

wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE);

wherein the anti-PD-1 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:32 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO: 27;

wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23;

wherein the subject has urothelial or bladder cancer; and

wherein:

(i) the subject has aspartate transferase (AST) and alanine transaminase (ALT) no more than 2.5 fold of upper limit of normal (ULN),

(ii) the subject has treated central nervous system (CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof, and/or

(iii) the subject has not received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof.

[0038] Embodiment 9. The method of embodiment 8, wherein:

(a) the subject has treated central nervous system (CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody; and

(b) the subject has not received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody.

[0039] Embodiment 10. The method of embodiment 8 or 9, wherein:

(a) the subject has a progression free survival of at least or about 12.5 months following the treatment, optionally wherein the subject has a progression free survival of 12 to 13 months following the treatment;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 12.5 months, optionally wherein median progression free survival in the treated population is 12 to 13 months; or

(c) median progression free survival is at least or about 12.5 months for a population of subjects treated with the method, optionally wherein median progression free survival is 12 to 13 months for a population of subjects treated with the method.

[0040] Embodiment 11. The method of embodiment 8 or 9, wherein:

(a) the subject has an overall survival of at least or about 31.5 months following the treatment, optionally wherein the subject has an overall survival of 31 to 32 months following the treatment;

(b) a population of the subjects is treated by the methods, and wherein median overall survival in the treated population is at least or about 31.5 months, optionally wherein median overall survival in the treated population is 31 to 32 months; or

(c) median overall survival is at least or about 31.5 months for a population of subjects treated with the method, optionally wherein median overall survival is 31 to 32 months for a population of subjects treated with the method.

[0041] Embodiment 12. The method of embodiment 8 or 9, wherein the subject is eligible to receive cisplatin treatment (cisplatin eligible), and wherein:

(a) the subject has a progression free survival of at least or about 14.6 months following the treatment, optionally wherein the subject has a progression free survival of 14 to 15 months following the treatment;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 14.6 months, optionally wherein median progression free survival in the treated population is 14 to 15 months; or

(c) median progression free survival is at least or about 14.6 months for a population of subjects treated with the method, optionally wherein median progression free survival is 14 to 15 months for a population of subjects treated with the method.

[0042] Embodiment 13. The method of embodiment 8 or 9, wherein the subject is ineligible to receive cisplatin treatment (cisplatin eligible), and wherein:

(a) the subject has a progression free survival of at least or about 10.6 months following the treatment, optionally wherein the subject has a progression free survival of 10 to 11 months;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 10.6 months, optionally wherein median progression free survival in the treated population is 10 to 11 months; or

(c) median progression free survival is at least or about 10.6 months for a population of subjects treated with the method, optionally wherein median progression free survival is 10 to 11 months for a population of subjects treated with the method.

[0043] Embodiment 14. The method of any one of embodiments 1 to 5, 8 or 9, wherein the subject has expression of PD-L1 no less than CPS of 10, and optionally wherein:

(a) the subject has a progression free survival of at least or about 18.5 months following the treatment, optionally wherein the subject has a progression free survival of 18 to 19 months following the treatment;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 18.5 months, optionally wherein median progression free survival in the treated population is 18 to 19 months; or

(c) median progression free survival is at least or about 18.5 months for a population of subjects treated with the method, optionally wherein median progression free survival is 18 to 19 months for a population of subjects treated with the method.

[0044] Embodiment 15. The method of any one of embodiments 1 to 5, 8 or 9, wherein the subject has expression of PD-L1 less than CPS of 10, and optionally wherein:

(a) the subject has a progression free survival of at least or about 10.5 months following the treatment, optionally wherein the subject has a progression free survival of 10 to 11 months;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 10.5 months, optionally wherein median progression free survival in the treated population is 10 to 11 months; or

(c) median progression free survival is at least or about 10.5 months for a population of subjects treated with the method, optionally wherein median progression free survival is 10 to 11 months for a population of subjects treated with the method.

[0045] Embodiment 16. The method of any one of embodiments 1 to 5, 8 or 9, wherein the subject does not have liver metastases, and optionally wherein:

(a) the subject has a progression free survival of at least or about 16.4 months following the treatment, optionally wherein the subject has a progression free survival of 16 to 17 months;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 16.4 months, optionally wherein median progression free survival in the treated population is 16 to 17 months; or

(c) median progression free survival is at least or about 16.4 months for a population of subjects treated with the method, optionally wherein median progression free survival is 16 to 17 months for a population of subjects treated with the method.

[0046] Embodiment 17. The method of any one of embodiments 1 to 5, 8 or 9, wherein the subject has liver metastases, and optionally wherein:

(a) the subject has a progression free survival of at least or about 8.2 months following the treatment, optionally wherein the subject has a progression free survival of 8 to 9 months;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 8.2 months, optionally wherein median progression free survival in the treated population is 8 to 9 months; or

(c) median progression free survival is at least or about 8.2 months for a population of subjects treated with the method, optionally wherein median progression free survival is 8 to 9 months for a population of subjects treated with the method.

[0047] Embodiment 18. The method of any one of embodiments 1 to 5, 8 or 9, wherein the race of the subject is white, and optionally wherein:

(a) the subject has a progression free survival of at least or about 10.4 months, optionally wherein the subject has a progression free survival of 10 to 11 months;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 10.4 months, optionally wherein median progression free survival in the treated population is 10 to 11 months; or

(c) median progression free survival is at least or about 10.4 months for a population of subjects treated with the method, optionally wherein median progression free survival is 10 to 11 months for a population of subjects treated with the method.

[0048] Embodiment 19. The method of any one of embodiments 1 to 5, 8 or 9, wherein the race of the subject is not white, and optionally wherein:

(a) the subject has a progression free survival of at least or about 22.3 months, optionally wherein the subject has a progression free survival of 22 to 23 months;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 22.3 months, optionally wherein median progression free survival in the treated population is 22 to 23 months; or

(c) median progression free survival is at least or about 22.3 months for a population of subjects treated with the method, optionally wherein median progression free survival is 22 to 23 months for a population of subjects treated with the method.

[0049] Embodiment 20. The method of any one of embodiments 1 to 19, wherein the subject has visceral metastases.

[0050] Embodiment 21. The method of any one of embodiments 1 to 19, wherein the subject has lymph nodes only disease.

[0051] Embodiment 22. The method of any one of embodiments 1 to 19, wherein the disease site of origin is in the upper tract.

[0052] Embodiment 23. The method of any one of embodiments 1 to 19, wherein the disease site of origin is in the lower tract.

[0053] Embodiment 24. The method of any one of embodiments 1 to 23, wherein the subject has a PD-L1 expression combined positive score (CPS) greater than or equal to 10.

[0054] Embodiment 25. The method of any one of embodiments 1 to 23, wherein the subject has a PD-L1 expression CPS less than 10.

[0055] Embodiment 26. The method of any one of embodiments 1 to 19, wherein the subject has a Nectin-4 H-score between 0 and 300.

[0056] Embodiment 27. The method of any one of embodiments 1 to 19, wherein the subject has a Nectin-4 H-score between 0 and 200.

[0057] Embodiment 28. The method of any one of embodiments 1 to 19, wherein the subject has a Nectin-4 H-score between 0 and 150.

[0058] Embodiment 29. The method of any one of embodiments 1 to 19, wherein the method does not comprise determining PD-L1 expression or Nectin-4 expression of the subject.

[0059] Embodiment 30. The method of any one of embodiments 1 to 29, wherein the subject has locally advanced or metastatic urothelial cancer.

[0060] Embodiment 31. The method of any one of embodiments 1 to 30, wherein the subject has locally advanced or metastatic bladder cancer.

[0061] Embodiment 32. The method of any one of embodiments 1 to 31, wherein the anti-PD-1 antibody or antigen binding fragment thereof comprises: (a) a light chain variable region comprising light chain CDR1 comprising the amino acid sequence of SEQ ID NO:24, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:25, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:26, respectively, and (b) a heavy chain variable region comprising heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:29, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:30, and heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:31, respectively.

[0062] Embodiment 33. The method of any one of embodiments 1 to 31, wherein the anti-PD-1 antibody or antigen binding fragment thereof comprises: (a) a light chain variable region comprising light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:24, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:25, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:26, respectively, and (b) a heavy chain variable region comprising heavy chain CDR1 consisting of the amino acid sequence of SEQ ID NO:29, a heavy chain CDR2 consisting of the amino acid sequence of SEQ ID NO:30, and heavy chain CDR3 consisting of the amino acid sequence of SEQ ID NO:31, respectively.

[0063] Embodiment 34. The method of any one of embodiments 1 to 33, wherein the anti-PD-1 antibody or antigen binding fragment thereof comprises (a) a heavy chain variable region comprising SEQ ID NO:32 or a variant thereof, and (b) a light chain variable region comprising SEQ ID NO:27 or a variant thereof.

[0064] Embodiment 35. The method of any one of embodiments 1 to 33, wherein the anti-PD-1 antibody comprises (a) a heavy chain comprising SEQ ID NO: 33 and (b) a light chain comprising SEQ ID NO:28.

[0065] Embodiment 36. The method of any one of embodiments 1 to 35, wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises CDR-H1 comprising the amino acid sequence of SEQ ID NO:9, CDR-H2 comprising the amino acid sequence of SEQ ID NO:10, CDR-H3 comprising the amino acid sequence of SEQ ID NO:11; CDR-L1 comprising the amino acid sequence of SEQ ID NO:12, CDR-L2 comprising the amino acid sequence of SEQ ID NO:13, and CDR-L3 comprising the amino acid sequence of SEQ ID NO:14, or

wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises CDR-H1 comprising the amino acid sequence of SEQ ID NO:16, CDR-H2 comprising the amino acid sequence of SEQ ID NO:17, CDR-H3 comprising the amino acid sequence of SEQ ID NO:18; CDR-L1 comprising the amino acid sequence of SEQ ID NO:19, CDR-L2 comprising the amino acid sequence of SEQ ID NO:20, and CDR-L3 comprising the amino acid sequence of SEQ ID NO:21.

[0066] Embodiment 37. The method of any one of embodiments 1 to 35, wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises CDR-H1 consisting of the amino acid sequence of SEQ ID NO:9, CDR-H2 consisting of the amino acid sequence of SEQ ID NO:10, CDR-H3 consisting of the amino acid sequence of SEQ ID NO:11; CDR-L1 consisting of the amino acid sequence of SEQ ID NO:12, CDR-L2 consisting of the amino acid sequence of SEQ ID NO:13, and CDR-L3 consisting of the amino acid sequence of SEQ ID NO:14, or

wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises CDR-H1 consisting of the amino acid sequence of SEQ ID NO:16, CDR-H2 consisting of the amino acid sequence of SEQ ID NO:17, CDR-H3 consisting of the amino acid sequence of SEQ ID NO:18; CDR-L1 consisting of the amino acid sequence of SEQ ID NO:19, CDR-L2 consisting of the amino acid sequence of SEQ ID NO:20, and CDR-L3 consisting of the amino acid sequence of SEQ ID NO:21.

[0067] Embodiment 38. The method of any one of embodiments 1 to 37, wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:22 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:23.

[0068] Embodiment 39. The method of any one of embodiments 1 to 38, wherein the anti-191P4D12 antibody comprises a heavy chain comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID

NO:7 and a light chain comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:8.

[0069] Embodiment 40. The method of any one of embodiments 1 to 34 and 36 to 37, wherein the anti-191P4D12 antigen binding fragment is an Fab, F(ab′)2, Fv, or scFv.

[0070] Embodiment 41. The method of any one of embodiments 1 to 35, wherein the anti-191P4D12 antibody is a fully human antibody.

[0071] Embodiment 42. The method of any one of embodiments 1 to 39 and 41, wherein the anti-191P4D12 antibody is an IgG1 and light chain is a kappa light chain.

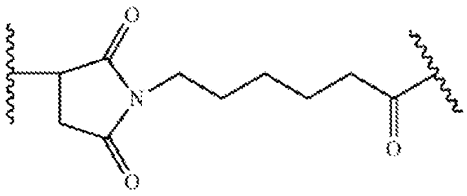
[0072] Embodiment 43. The method of any one of embodiments 1 to 42, wherein the anti-191P4D12 antibody or antigen binding fragment thereof is recombinantly produced.

[0073] Embodiment 44. The method of any one of embodiments 1 to 43, wherein the anti-191P4D12 antibody or antigen binding fragment is conjugated to each unit of MMAE via a linker.

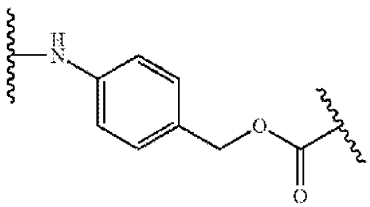
[0074] Embodiment 45. The method of embodiment 44, wherein the linker is an enzyme-cleavable linker, and wherein the linker forms a bond with a sulfur atom of the antibody or antigen binding fragment thereof.

[0075] Embodiment 46. The method of embodiment 44 or 45, wherein the linker has a formula of: –Aa–Ww–Yy–; wherein –A– is a stretcher unit, a is 0 or 1; –W– is an amino acid unit, w is an integer ranging from 0 to 12; and –Y– is a spacer unit, y is 0, 1, or 2.

[0076] Embodiment 47. The method of embodiment 46, wherein the stretcher unit has the structure of Formula (1) below; the amino acid unit is valine-citrulline; and the spacer unit is a PAB group comprising the structure of Formula (2) below:



Formula (1)



Formula (2).

[0077] Embodiment 48. The method of embodiment 46 or 47, wherein the stretcher unit forms a bond with a sulfur atom of the antibody or antigen binding fragment thereof; and wherein the spacer unit is linked to MMAE via a carbamate group.

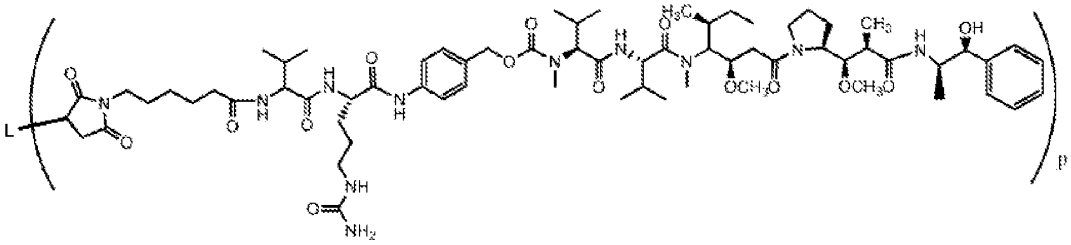
[0078] Embodiment 49. The method of any one of embodiments 1 to 48, wherein the ADC comprises from 1 to 20 units of MMAE per antibody or antigen binding fragment thereof.

[0079] Embodiment 50. The method of any one of embodiments 1 to 49, wherein the ADC comprises from 1 to 10 units of MMAE per antibody or antigen binding fragment thereof.

[0080] Embodiment 51. The method of any one of embodiments 1 to 50, wherein the ADC comprises from 2 to 8 units of MMAE per antibody or antigen binding fragment thereof.

[0081] Embodiment 52. The method of any one of embodiments 1 to 51, wherein the ADC comprises from 3 to 5 units of MMAE per antibody or antigen binding fragment thereof.

[0082] Embodiment 53. The method of any one of embodiments 1 to 52, wherein the ADC has the following structure:



wherein L- represents the anti-191P4D12 antibody or antigen binding fragment thereof and p is from 1 to 10.

[0083] Embodiment 54. The method of embodiment 53, wherein p is from 2 to 8.

[0084] Embodiment 55. The method of embodiment 53 or 54, wherein p is from 3 to 5.

[0085] Embodiment 56. The method of any one of embodiments 53 to 55, wherein p is from 3 to 4.

[0086] Embodiment 57. The method of any one of embodiments 53 to 56, wherein p is about 4.

[0087] Embodiment 58. The method of any one of embodiments 53 to 54, wherein the average p value of the effective amount of the antibody drug conjugates is about 3.8.

[0088] Embodiment 59. The method of any one of embodiments 1 to 58, wherein the ADC is administered to the subject at a dose of about 1 to about 10 mg/kg of the subject's body weight, about 1 to about 5 mg/kg of the subject's body weight, about 1 to about 2.5 mg/kg of the subject's body weight, or about 1 to about 1.25 mg/kg of the subject's body weight.

[0089] Embodiment 60. The method of any one of embodiments 1 to 59, wherein the ADC is administered to the subject at a dose of about 0.25 mg/kg, about 0.5 mg/kg, about 0.75 mg/kg, about 1.0 mg/kg, about 1.25 mg/kg, about 1.5 mg/kg, about 1.75 mg/kg, about 2.0 mg/kg, about 2.25 mg/kg, or about 2.5 mg/kg of the subject's body weight.

[0090] Embodiment 61. The method of any one of embodiments 1 to 60, wherein the ADC is administered to the subject at a dose of about 1 mg/kg of the subject's body weight.

[0091] Embodiment 62. The method of any one of embodiments 1 to 60, wherein the ADC is administered to the subject at a dose of about 1.25 mg/kg of the subject's body weight.

[0092] Embodiment 63. The method of any one of embodiments 1 to 62, wherein the ADC is administered to the subject by an intravenous (IV) injection or infusion.

[0093] Embodiment 64. The method of any one of embodiments 1 to 63, wherein the ADC is administered to the subject by an IV injection or infusion up to 2 days of a 21-day treatment cycle.

[0094] Embodiment 65. The method of any one of embodiments 1 to 64, wherein the ADC is administered to the subject by an IV injection or infusion on days 1 and 8 of a 21-day treatment cycle.

[0095] Embodiment 66. The method of any one of embodiments 1 to 65, wherein the ADC is administered to the subject by an IV injection or infusion over about 30 minutes up to 2 days of a 21-day treatment cycle.

[0096] Embodiment 67. The method of any one of embodiments 1 to 66, wherein the ADC is administered by an IV injection or infusion over about 30 minutes on days 1 and 8 of a 21-day treatment cycle.

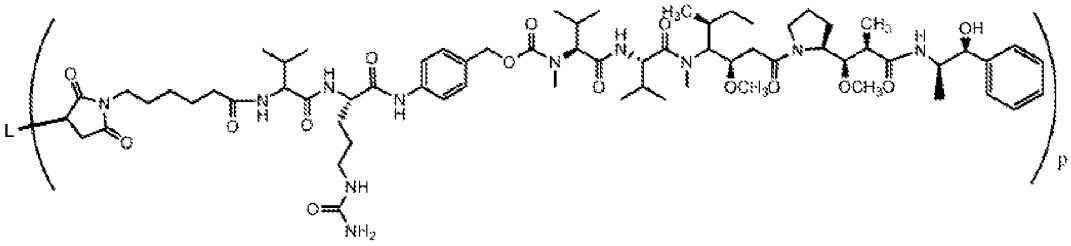
[0097] Embodiment 68. The method of any one of embodiments 1 to 67, wherein the ADC is formulated in a pharmaceutical composition comprising L-histidine, polysorbate-20 (TWEEN-20), and trehalose dehydrate.

[0098] Embodiment 69. The method of any one of embodiments 1 to 68, wherein the ADC is formulated in a pharmaceutical composition comprising about 20 mM L-histidine,

about 0.02% (w/v) TWEEN-20, about 5.5% (w/v) trehalose dihydrate, and hydrochloride, and wherein the pH of the pharmaceutical composition is about 6.0 at 25°C.

[0099] Embodiment 70. The method of any one of embodiments 1 to 68, wherein the ADC is formulated in a pharmaceutical composition comprising about 9 mM histidine, about 11 mM histidine hydrochloride monohydrate, about 0.02% (w/v) TWEEN-20, and about 5.5% (w/v) trehalose dihydrate, and wherein the pH of the pharmaceutical composition is about 6.0 at 25°C.

[00100] Embodiment 71. The method of any one of embodiments 1 to 70, wherein the ADC has the following structure:



wherein L- represents the antibody or antigen binding fragment thereof and p is from about 3 to about 4, the anti-191P4D12 antibody comprises a heavy chain comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID NO:7 and a light chain comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:8, wherein the ADC is administered at a dose of about 1.25 mg/kg of the subject's body weight, and wherein the dose is administered by an IV injection or infusion over about 30 minutes on days 1 and 8 of a 21-day treatment cycle.

[00101] Embodiment 72. The method of any one of embodiments 1 to 70, wherein the anti-PD-1 antibody is administered to the subject at a dose of about 100 mg to about 400 mg.

[00102] Embodiment 73. The method of any one of embodiments 1 to 70, wherein the anti-PD-1 antibody is administered to the subject at a dose of about 200 mg.

[00103] Embodiment 74. The method of embodiment 71, wherein:

(a) the anti-PD-1 antibody is administered to the subject at a dose of about 200 mg; and

(b) after step (a), the anti-PD-1 antibody is administered to the subject at a dose of about 400 mg every 42 days.

[00104] Embodiment 75. The method of any one of embodiments 1 to 74, wherein the anti-PD-1 antibody is administered to the subject by an IV infusion on 1 day of the 21-day treatment cycle.

[00105] Embodiment 76. The method of any one of embodiments 1 to 75, wherein the anti-PD-1 antibody is administered to the subject by an IV infusion on day 1 in each treatment cycle of 21 days.

[00106] Embodiment 77. The method of any one of embodiments 1 to 76, wherein the anti-PD-1 antibody is administered to the subject by an IV infusion over about 30 minutes on 1 day of the 21-day treatment cycle.

[00107] Embodiment 78. The method of any one of embodiments 1 to 75, wherein the anti-PD-1 antibody is administered to the subject by an IV infusion over about 30 minutes on day 1 in each treatment cycle of 21 days.

[00108] Embodiment 79. The method of any one of embodiments 1 to 76, whereby the subject has a complete response following the treatment.

[00109] Embodiment 80. The method of any one of embodiments 1 to 77, wherein the subject has a partial response following the treatment.

[00110] Embodiment 81. The method of any one of embodiments 1 to 78, wherein the subject has a stable disease following the treatment.

[00111] Embodiment 82. The method of any one of embodiments 1 to 81, wherein the subject has a Brief Pain Inventory Short Form (BPI-SF) worst pain score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has an improved BPI-SF worst pain score.

[00112] Embodiment 83. The method of any one of embodiments 1 to 81, wherein the subject has a BPI-SF worst pain baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from worst pain baseline score of about -0.3 to about -1.2.

[00113] Embodiment 84. The method of any one of embodiments 1 to 81, wherein the subject has a BPI-SF worst pain baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from worst pain baseline score of about -0.61.

[00114] The method of any one of embodiments 1 to 81, wherein the subject has a Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire (EORTC QLQ-C30) quality of life (QoL) baseline score of about zero (0) prior to administration of the ADC to

the subject, and wherein after administration of the ADC to the subject, the subject has an improved EORTC QLQ-C30 QoL score.

[00115] The method of any one of embodiments 1 to 81, wherein the subject has a EORTC QLQ-C30 QoL baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from EORTC QLQ-C30 QoL baseline score of about 10.0 to about 15.0.

[00116] Embodiment 85. The method of any one of embodiments 1 to 81, wherein the subject has a EORTC QLQ-C30 QoL baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from EORTC QLQ-C30 QoL baseline score of about 13.0.

[00117] Embodiment 86. The method of any one of embodiments 1 to 85, wherein the subject is human.

4. Brief Description of the Drawings

[00118] **FIGS. 1A-1E** depict the nucleotide and amino acid sequences of nectin-4 protein (**FIG. 1A**), the nucleotide and amino acid sequences of the heavy chain (**FIG. 1B**) and light chain (**FIG. 1C**) of Ha22-2(2.4)6.1, and the amino acid sequences of the heavy chain (**FIG. 1D**) and light chain of Ha22-2(2.4)6.1 (**FIG. 1E**).

[00119] **FIG. 2** depicts the study stages of the clinical study, which is a phase 3 study of enfortumab vedotin combined with pembrolizumab as first-line treatment in patients with unresectable locally advanced or metastatic urothelial cancer (la/mUC), as described in Section 6.1.

[00120] **FIGS. 3A-3C** depict RECIST Criteria, version 1.1. **FIG. 3A** shows Table 2, which provides time point response: patients with target (+/- non-target) disease. **FIG. 3B** shows Table 2, which provides time point response: patients with non-target disease only. **FIG. 3C** shows Table 3, which provides best overall response when confirmation of CR and PR are required.

[00121] **FIG. 4** depicts the European Organization for the Research and Treatment (EORTC) Core Quality of Life (QLQ-C-30) assessment (EORTC-QLQ-C-30, current version, Version 3), as described in Section 6.1.

[00122] **FIG. 5** depicts the EuroQol-5 Dimensions (EQ-5D-5L) described in Section 6.1.

[00123] **FIG. 6** depicts an initial graph of multiplicity adjustment (2 sided FWER=5%). ε is a positive number close to zero, indicating the potential to pass alpha to ORR only if both PFS and OS are statistically significant. FWER=family wise error rate.

[00124] **FIG. 7** depicts the overall study design of the clinical study described in Section 6.1.

[00125] **FIGS. 8A and 8B** show the statistical testing methods used in the clinical study described in Section 6.1. **FIG. 8A** shows the efficacy boundaries for PFS analysis. **FIG. 8B** shows the efficacy boundaries for OS analysis.

[00126] **FIG. 9** is a table showing a Summary of Disposition of subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00127] **FIG. 10** is a table showing Stratification Factors at Randomization for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00128] **FIG. 11** is a table showing a Summary of Demographics for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1. *Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple races, and others.

[00129] **FIG. 12** is a table showing a Summary of Baseline Characteristics for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00130] **FIG. 13** is a table showing a Summary of Disease Characteristics for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00131] **FIG. 14** is a table showing a Summary of Prior Anticancer Therapies for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00132] **FIG. 15** is a table showing the Duration of Treatment for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00133] **FIG. 16** is a table showing the Summary of Subsequent Anticancer Therapies for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00134] **FIGS. 17A and 17B** depict progression-free survival (PFS) per blinded independent central review for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1. **FIG. 17A** shows a graph of PFS (in %) versus time (in months). **FIG. 17B** is a table that provides PFS data in the EV + Pembro and Plat + Gem arms.

[00135] **FIGS. 18A, 18B, 18C, 18D, and 18E** depict progression-free survival (PFS) subgroup analysis by blinded independent central review (BICR). **FIG. 18A** is a table showing the progression-free survival (PFS) subgroup analysis of subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1. A "-" indicates that the PFS has not been reached. **FIG. 18B** shows a graph of PFS (in %) versus time (in

months) observed in subjects with liver metastases present. **FIG. 18C** shows a graph of PFS (in %) versus time (in months) observed in subjects with liver metastases absent. **FIG. 18D** shows a graph of PFS (in %) versus time (in months) observed in subjects with visceral metastases present. **FIG. 18E** shows a graph of PFS (in %) versus time (in months) observed in subjects with lymph node only metastases. The estimated HR and corresponding 95% confidence interval from the stratified Cox proportional hazards regression model is also presented. A hazard ratio <1 favors the EV+P arm.

[00136] **FIGS. 19A and 19B** depict progression-free survival (PFS) per blinded independent central review in the clinical study described in Section 6.1 for the cisplatin eligible (**FIG. 19A**) and ineligible (**FIG. 19B**) subgroups.

[00137] **FIGS. 20A and 20B** depict progression-free survival (PFS) per blinded independent central review in the clinical study described in Section 6.1 for the PD-L1 High Expression (CPS ≥ 10) (**FIG. 20A**) and the PD-L1 Low Expression (CPS < 10) (**FIG. 20B**) subgroups.

[00138] **FIGS. 21A and 21B** depict overall survival (OS) – ITT for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1. Median f/u = median follow-up time. **FIG. 21A** shows a graph of OS (in %) versus time (in months). **FIG. 21B** is a table that provides OS data in the EV + Pembro and Plat + Gem arms.

[00139] **FIGS. 22A, 22B, 22C, 22D, and 22E** depict subgroup analysis of overal survival (OS). **FIG. 22A** is a table showing the overall survival (OS) subgroup analysis of subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1. A "-" indicates that the OS has not been reached. **FIG. 22B** shows a graph of OS (in %) versus time (in months) observed in subjects with liver metastases present. **FIG. 22C** shows a graph of OS (in %) versus time (in months) observed in subjects with liver metastases absent. **FIG. 22D** shows a graph of OS (in %) versus time (in months) observed in subjects with visceral metastases present. **FIG. 22E** shows a graph of OS (in %) versus time (in months) observed in subjects with lymph node only metastases. The estimated HR and corresponding 95% confidence interval from the stratified Cox proportional hazards regression model is also presented. A hazard ratio <1 favors the EV+P arm.

[00140] **FIGS. 23A and 23B** depict overall survival (OS) per blinded independent central review in the clinical study described in Section 6.1 for the cisplatin eligible (**FIG. 23A**) and ineligible (**FIG. 23B**) subgroups.

[00141] **FIGS. 24A and 24B** depict overall survival (OS) per blinded independent central review in the clinical study described in Section 6.1 for the PD-L1 High Expression (CPS ≥ 10) (**FIG. 24A**) and the PD-L1 Low Expression (CPS < 10) (**FIG. 24B**) subgroups.

[00142] **FIG. 25** is a table showing the Objective Response Rate (ORR) per blinded independent central review for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00143] **FIG. 26** is a table showing the Objective Response Rate (ORR) subgroup analysis of subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1. A "-" indicates that the ORR has not been reached.

[00144] **FIGS. 27A and 27B** depict duration of response (DOR) per blinded independent central review for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1. **FIG. 27A** shows a graph of responders without PD or Death (in %) versus time (in months). **FIG. 27B** is a table that provides DOR data in the EV + Pembro and Plat + Gem arms.

[00145] **FIG. 28** is a table providing an overall summary of treatment-emergent adverse events (TEAEs) for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00146] **FIG. 29** is a table providing TEAEs occurring in ≥20% of subjects (by preferred term) for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00147] **FIG. 30** depicts TEAEs occurring in ≥15% of subjects (by preferred term) for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00148] **FIG. 31** is a table providing grade ≥3 TEAEs occurring in ≥5% of subjects (by preferred term) for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00149] **FIG. 32** depicts grade ≥3 TEAEs occurring in ≥5% of subjects (by preferred term) for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00150] **FIG. 33** is a table providing serious TEAEs Occurring in ≥2% of subjects (by preferred term) for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00151] **FIG. 34** is a table providing TEAEs leading to death (by preferred term) for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00152] **FIG. 35** is a table providing TEAEs leading to discontinuation of any study drugs occurring in ≥1% of subjects by preferred term for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1.

[00153] **FIG. 36** is a table providing adverse events of special interest (AESI) for Enfortumab Vedotin (EV) for subjects in the EV + Pembro and Plat + Gem arms of the clinical study described in Section 6.1 (and EV Monotherapy).

[00154] **FIG. 37** is a table providing pembrolizumab adverse events of special interest (AEOSI) occurring in >2 subjects in the EV+Pembro arm of the clinical study described in Section 6.1.

[00155] **FIG. 38** is a table providing key demographics and baseline characteristics for subjects in the EV + Pembro and chemotherapy arms of the clinical study described in Example 3 in connection with cisplatin-ineligible subjects. In **FIG. 38**, the superscript "a" indicates the following: [a]Includes renal pelvis, ureter, kidney. In **FIG. 38**, the superscript "b" indicates the following: [b]Includes bladder, urethra, other. In **FIG. 38**, the superscript "c" indicates the following: [c]A patient may have metastatic disease in more than one location. In **FIG. 38**, the superscript "d" indicates the following: [d]Patients had locally advanced disease without metastasis to lymph nodes or distant organs. In **FIG. 38**, the superscript "e" indicates the following: [e]CPS status was determined using the validated PD-(L)1 IHC 22C3 pharmDx assay at Neogenomics and Labcorp; 2 patients in the EV+P arm and 1 patient in the chemotherapy arm had samples that were of inadequate tissue quality for analysis.

[00156] **FIG. 39** is a table showing a summary of disposition of subjects in the EV + Pembro and chemotherapy arms of the clinical study described in Example 3 in connection with cisplatin-ineligible subjects. In **FIG. 39**, the superscript "a" indicates the following: [a]Patients in EV+P arm received EV until disease progression or toxicity (per protocol, there was no maximum number of EV cycles) or completion of maximum cycles. (35 cycles for P); chemotherapy could be given for a maximum of 6 cycles. In **FIG. 39**, the superscript "b" indicates the following: [b]Patients completed 35 cycles of P and had discontinued EV prior to P. In **FIG. 39**, the superscript "c" indicates the following:[c]6 patients on EV+P: Death (2), Grade 3 Asthenia outside of protocol reporting period (1), Lost to follow-up (1), Chronic Lymphatic Leukemia (1), General Deterioration (1); 1 patient on Chemotherapy: Patient insurance would not cover chemotherapy treatment on clinical trial (1).

[00157] **FIG. 40** is a table showing reasons for cisplatin ineligibility in connection with cisplatin-ineligible subjects in connection with the clinical study described in Example 3. In **FIG. 40**, the superscript "a" indicates the following: [a]Patients may be counted in more than one category for cisplatin-ineligibility.

[00158] **FIG. 41A** provides the best Overall Response Rate (ORR) per RECIST by blinded independent central review (BICR) for subjects in the EV + Pembro and chemotherapy arms of the clinical study described in Example 3 in connection with cisplatin-ineligible subjects. In **FIG. 41A**, the superscript "a" indicates the following: [a]Best overall response according to RECIST v1.1. CR or PR was confirmed with repeat scans ≥28 days after initial response. In **FIG. 41A**, the superscript "b" indicates the following: [b]Patients best overall response was determined to be not evaluable per RECIST v1.1 or patients had no response assessment post-baseline. **FIG. 41B** provides the time to objective response for the EV+P and chemotherapy arms in connection with cisplatin-ineligible subjects. In **FIG. 41B**, the superscript "a" indicates the following: [a]Any objective response defined as confirmed CR or PR. In **FIG. 41B**, the superscript "b" indicates the following: [b]Time from randomization to first documentation of CR or PR that is subsequently confirmed.

[00159] **FIG. 42** depicts duration of objective response (DOR) per blinded independent central review (BICR) for subjects in the EV + Pembro and chemotherapy arms of the clinical study described in Example 3 in connection with cisplatin-ineligible subjects. In particular, **FIG. 42** shows a graph of responders without PD or Death (in %) versus time (in months).

[00160] **FIG. 43** is a table showing the summary of subsequent therapies for subjects in the EV + Pembro and chemotherapy arms of the clinical study described in Example 3 in connection with cisplatin-ineligible subjects. In **FIG. 43**, the superscript "a" indicates the following: [a] 62 (31.3%) patients in the EV+P arm remained on treatment at DCO; all patients in chemotherapy arm were off study treatment. In **FIG. 43**, the superscript "b" indicates the following: [b]When platinum-based therapy and a PD-1/L1 agent were given in the same line of therapy, the therapy was categorized under Platinum-based therapy.

[00161] **FIG. 44** is a table showing the treatment-related adverse events for subjects in the EV + Pembro and chemotherapy arms of the clinical study described in Example 3 in connection with cisplatin-ineligible subjects. TRAEs shown are any grade by preferred term in ≥20% of patients for any grade in either arm.

[00162] **FIG. 45** is a table providing EV treatment-related adverse events of special interest (AESI) for subjects in the EV + Pembro and chemotherapy arms of the clinical study described in Example 3 in connection with cisplatin-ineligible subjects.

[00163] **FIG. 46** is a table providing pembrolizumab treatment-emergent adverse events of special interest (AEOSI) in connection with cisplatin-ineligible subjects. In **FIG. 46**, the asterisk "*" indicates the following: *There are differences in the rates of skin reactions reported for EV treatment-related AESIs and P TEAEs of special interest because these adverse events were reported via different methodologies developed for EV and P monotherapies, respectively.

[00164] **FIG. 47** is a table providing key demographics and baseline characteristics for subjects in the EV + Pembro and chemotherapy arms of the clinical study described in Example 4 in connection with cisplatin-eligible subjects. In **FIG. 47**, the superscript "a" indicates the following: [a]Includes renal pelvis, ureter, kidney. In **FIG. 47**, the superscript "b" indicates the following: [b]Includes bladder, urethra, other. In **FIG. 47**, the superscript "c" indicates the following: [c]A patient may have metastatic disease in more than one location. In **FIG. 47**, the superscript "d" indicates the following: [d]Patients had locally advanced disease without metastasis to lymph nodes or distant organs. In **FIG. 47**, the superscript "e" indicates the following: [e]CPS status was determined using the validated PD-(L)1 IHC 22C3 pharmDx assay at Neogenomics and Labcorp; 2 patients in the EV+P arm and 4 patients in the chemotherapy arm had samples that were of inadequate tissue quality for analysis.

[00165] **FIG. 48** is a table showing a summary of disposition of subjects in the EV + Pembro and chemotherapy arms of the clinical study described in Example 4 in connection with cisplatin-eligible subjects. In **FIG. 48**, the superscript "a" indicates the following: [a]Patients in EV+P arm received EV until disease progression or toxicity (per protocol, there was no maximum number of EV cycles) or completion of maximum cycles. (35 cycles for P); chemotherapy could be given for a maximum of 6 cycles. In **FIG. 48**, the superscript "b" indicates the following: [b]Patients completed 35 cycles of P and had discontinued EV prior to P. In **FIG. 48**, the superscript "c" indicates the following: [c]1 patient on EV+P: death; 1 patient on Chemotherapy: respiratory failure.

[00166] **FIG. 49A** provides the best Overall Response Rate (ORR) per RECIST by blinded independent central review (BICR) for subjects in the EV + Pembro and chemotherapy arms of the clinical study described in Example 4 in connection with cisplatin-eligible subjects. In **FIG. 49A**, the superscript "a" indicates the following: [a]Best overall response according to RECIST v1.1. CR or PR was confirmed with repeat scans ≥28 days

after initial response. In **FIG. 49A**, the superscript "b" indicates the following: [b]Patients best overall response was determined to be not evaluable per RECIST v1.1 or patients had no response assessment post-baseline. **FIG. 49B** provides the time to objective response for the EV+P and chemotherapy arms of the clinical study described in Example 4 in connection with cisplatin-eligible subjects. In **FIG. 49B**, the superscript "a" indicates the following: [a]Any objective response defined as confirmed CR or PR. In **FIG. 49B**, the superscript "b" indicates the following: [b]Time from randomization to first documentation of CR or PR that is subsequently confirmed.

[00167] **FIG. 50** depicts duration of objective response (DOR) per blinded independent central review (BICR) for subjects in the EV + Pembro and chemotherapy arms of the clinical study described in Example 4 in connection with cisplatin-eligible subjects. In particular, **FIG. 50** shows a graph of responders without PD or Death (in %) versus time (in months).

[00168] **FIG. 51** is a table showing the summary of subsequent therapies for subjects in the EV + Pembro and chemotherapy arms of the clinical study described in Example 4 in connection with cisplatin-eligible subjects. In **FIG. 51**, the superscript "a" indicates the following: [a]82 (33.6%) patients in the EV+P arm remained on treatment at DCO; all patients in chemotherapy arm were off study treatment. In **FIG. 51**, the superscript "b" indicates the following: [b]When platinum-based therapy and a PD-1/L1 agent were given in the same line of therapy, the therapy was categorized under Platinum-based therapy.

[00169] **FIG. 52** is a table showing the treatment-related adverse events for subjects in the EV + Pembro and chemotherapy arms of the clinical study described in Example 4 in connection with cisplatin-eligible subjects. In **FIG. 52**, the superscript "a" indicates the following: [a]TRAEs shown are any grade by preferred term in ≥20% of patients for any grade in either arm.

[00170] **FIG. 53** is a table providing EV treatment-related adverse events of special interest (AESI) for subjects in the EV + Pembro and chemotherapy arms of the clinical study described in Example 4 in connection with cisplatin-eligible subjects.

[00171] **FIG. 54** is a table providing pembrolizumab treatment-emergent adverse events of special interest (AEOSI) in connection with cisplatin-eligible subjects. In **FIG. 54**, the asterisk "*" indicates the following: *There are differences in the rates of skin reactions reported for EV treatment-related AESIs and P TEAEs of special interest because these adverse events were reported via different methodologies developed for EV and P monotherapies, respectively.

[00172] **FIG. 55** depicts progression-free survival (PFS) per blinded independent central review in the clinical study described in Section 6.5 for the pan-Asian subgroup. EV, enfortumab vedotin; Gem, gemcitabine; HR, hazard ratio; ITT, intention to treat; Pembro, pembrolizumab; PFS, progression-free survival; Plat, platinum.

[00173] **FIG. 56** depicts overall survival (OS) per blinded independent central review in the clinical study described in Section 6.5 for the pan-Asian subgroup. EV, enfortumab vedotin; Gem, gemcitabine; HR, hazard ratio; ITT, intention to treat; OS, overall survival; Pembro, pembrolizumab; Plat, platinum.

[00174] **FIG. 57A** depicts time to pain progression (TTPP) for subjects treated with enfortumab vedotin combined with pembrolizumab (EV+P) versus subjects treated with Plat + Gem. **FIG. 57B** provides data regarding TTPP for subjects treated with EV+P versus subjects treated with Plat + Gem.

[00175] **FIG. 58** depicts an EORTC-QLQ C30 Compliance. PRO FAS analysis. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire; EV+P, Enfortumab vedotin plus pembrolizumab; PRO FAS, Patient-reported outcome full analysis set.

[00176] **FIG. 59** depicts overall mean change from baseline at week 26 in Brief Pain Inventory – Short Form (BPI-SF) worst pain score. BPI-SF, Brief Pain Inventory Short Form; EV+P, Enfortumab vedotin plus pembrolizumab; PBC, platinum-based chemotherapy.

[00177] **FIG. 60** depicts LS mean change from baseline in BPI-SF scale scores through week 26. BPI-SF, Brief Pain Inventory Short Form; CI, confidence interval; EV+P, Enfortumab vedotin plus pembrolizumab; LS, least squares; SE, standard error.

[00178] **FIG. 61** depicts overall mean change from baseline through week 26 in BPI-SF score among those with moderate to severe pain at baseline. BPI-SF, Brief Pain Inventory Short Form; EV+P, Enfortumab vedotin plus pembrolizumab; PBC, platinum-based chemotherapy; PRO, patient reported outcome.

[00179] **FIG. 62** depicts LS mean change from baseline in BPI-SF scale scores through week 26 among those with moderate to severe pain at baseline. BPI-SF, Brief Pain Inventory Short Form; CI, confidence interval; EV+P, Enfortumab vedotin plus pembrolizumab; LS, least squares; SE, standard error.

[00180] **FIG. 63A** depicts overall mean change from baseline through week 26 in EORTC QLQ-C30 GHS/QoL. **FIG. 63B** depicts overall mean change from baseline through week 26 in functioning scale scores and GHS/QoL. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire; EV+P,

Enfortumab vedotin plus pembrolizumab; GHS, global health status; LS, least squares; QoL, quality of life; SE, standard error.

[00181] **FIG. 64A** depicts overall mean change from baseline through week 26 in EORTC QLQ-C30 GHS/QoL by cisplatin-eligibility: cisplatin-eligible. **FIG. 64B** depicts overall mean change from baseline through week 26 in EORTC QLQ-C30 GHS/QoL by cisplatin-eligibility: cisplatin-ineligible. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire; GHS, global health status; LS, least squares; QoL, quality of life.

[00182] **FIG. 65** depicts time to confirmed deterioration in EORTC QLQ-C30 QoL and functioning scales. CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire; EV+P, Enfortumab vedotin plus pembrolizumab; LS, least squares; mTTCD, median time to confirmed deterioration; PBC, platinum-based chemotherapy; QoL, quality of life; SD, standard deviation.

[00183] **FIG. 66A** depicts overall mean changes from baseline through week 26 in EORTC QLQ-C30 GHS/QoL. **FIG. 66B** depicts overall mean changes from baseline through week 26 in functioning scale scores in patients with moderate/severe pain at baseline.

[00184] **FIG. 67** depicts H-score of Nectin-4 expression by biopsy origin (i.e., either primary or metastatic tissues).

[00185] **FIG. 68A** depicts H-scores of Nectin-4 expression at across both arms (N=800). The y-axis shows Nectin-4 expression at baseline (H-score) and the x-axis shows individual patients. **FIG. 68B** provides data regarding H-scores of Nectin-4 expression in the EV+P and chemotherapy arms in each of the following subgroups: <150, ≥150 to <225, and ≥225.

[00186] **FIG. 69A** and **FIG. 69B** depict Kaplan–Meier plots of PFS for the <275 and ≥275 Nectin-4 H-score subgroups, respectively.

[00187] **FIG. 70A** and **FIG. 70B** depict Kaplan–Meier plots of OS for the <275 and ≥275 Nectin-4 H-score subgroups, respectively.

[00188] **FIG. 71A** and **FIG. 71B** depict PFS and OS subgroup analyses by Nectin-4 H-scores, respectively.

[00189] **FIG. 72** depicts ORR (%) for the <275 and ≥275 Nectin-4 H-score subgroups (wherein the median Nectin-4 H-score was 275 across patients in both arms), as well as for the <150, ≥150 to <225, and ≥225 Nectin-4 H-score subgroups.

[00190] **FIG. 73** depicts provides the expression distribution of Nectin-4 and PD-L1 in the EV+P (N=442) and chemotherapy (N=444) arms for the <275 and ≥275 Nectin-4 H-score

subgroups (wherein the median Nectin-4 H-score was 275 across patients in both arms), as well as for a subjects without nectin-4 results.

[00191] **FIG. 74A**, **FIG. 74B**, **FIG. 74C**, and **FIG. 74D** show Kaplan–Meier plots of PFS (%) for each of the following groups: (1) Subgroup having Nectin-4 H-score of <275 and a low level of PD-L1 expression (CPS <10) (*see* **FIG. 74A**); (2) Subgroup having Nectin-4 H-score of <275 and a high level of PD-L1 expression (CPS ≥10) (*see* **FIG. 74B**); (3) Subgroup having Nectin-4 H-score of ≥275 and a low level of PD-L1 expression (CPS <10) (*see* **FIG. 74C**); and (4) Subgroup having Nectin-4 H-score of ≥275 and a high level of PD-L1 expression (*see* **FIG. 74D**) (note for (1) to (4): the median Nectin-4 H-score was 275 across patients in both arms) (CPS ≥10).

[00192] **FIG. 75A**, **FIG. 75B**, **FIG. 75C**, and **FIG. 75D** show Kaplan–Meier plots of OS (%) for each of the following groups: (1) Subgroup having Nectin-4 H-score of <275 and a low level of PD-L1 expression (CPS <10) (*see* **FIG. 75A**); (2) Subgroup having Nectin-4 H-score of <275 and a high level of PD-L1 expression (CPS ≥10) (*see* **FIG. 75B**); (3) Subgroup having Nectin-4 H-score of ≥275 and a low level of PD-L1 expression (CPS <10) (*see* **FIG. 75C**); and (4) Subgroup having Nectin-4 H-score of ≥275 and a high level of PD-L1 expression (*see* **FIG. 75D**) (note for (1) to (4): the median Nectin-4 H-score was 275 across patients in both arms) (CPS ≥10).

5. Detailed Description

[00193] Before the present disclosure is further described, it is to be understood that the disclosure is not limited to the particular embodiments set forth herein, and it is also to be understood that the terminology used herein is for describing particular embodiments only, and is not intended to be limiting.

5.1 Definitions

[00194] Techniques and procedures described or referenced herein include those that are generally well understood and/or commonly employed using conventional methodology by those skilled in the art, such as, for example, the widely utilized methodologies described in Sambrook et al., Molecular Cloning: A Laboratory Manual (3d ed. 2001); Current Protocols in Molecular Biology (Ausubel et al. eds., 2003); Therapeutic Monoclonal Antibodies: From Bench to Clinic (An ed. 2009); Monoclonal Antibodies: Methods and Protocols (Albitar ed. 2010); and Antibody Engineering Vols 1 and 2 (Kontermann and Dübel eds., 2d ed. 2010).

[00195] Unless otherwise defined herein, technical and scientific terms used in the present description have the meanings that are commonly understood by those of ordinary skill in the

art. For purposes of interpreting this specification, the following description of terms will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa. In the event that any description of a term set forth conflicts with any document incorporated herein by reference, the description of the term set forth below shall control.

[00196] The term "antibody," "immunoglobulin," or "Ig" is used interchangeably herein, and is used in the broadest sense and specifically covers, for example, monoclonal antibodies (including agonist, antagonist, neutralizing antibodies, full length or intact monoclonal antibodies), antibody compositions with polyepitopic or monoepitopic specificity, polyclonal or monovalent antibodies, multivalent antibodies, multispecific antibodies (*e.g.*, bispecific antibodies so long as they exhibit the desired biological activity), formed from at least two intact antibodies, single chain antibodies, and fragments thereof, as described below. An antibody can be human, humanized, chimeric and/or affinity matured, as well as an antibody from other species, for example, mouse and rabbit, *etc.* The term "antibody" is intended to include a polypeptide product of B cells within the immunoglobulin class of polypeptides that is able to bind to a specific molecular antigen and is composed of two identical pairs of polypeptide chains, wherein each pair has one heavy chain (about 50-70 kDa) and one light chain (about 25 kDa), each amino-terminal portion of each chain includes a variable region of about 100 to about 130 or more amino acids, and each carboxy-terminal portion of each chain includes a constant region. *See, e.g.*, Antibody Engineering (Borrebaeck ed., 2d ed. 1995); and Kuby, Immunology (3d ed. 1997). In specific embodiments, the specific molecular antigen can be bound by an antibody provided herein, including a polypeptide or an epitope. Antibodies also include, but are not limited to, synthetic antibodies, recombinantly produced antibodies, camelized antibodies, intrabodies, anti-idiotypic (anti-Id) antibodies, and functional fragments (*e.g.*, antigen-binding fragments) of any of the above, which refers to a portion of an antibody heavy or light chain polypeptide that retains some or all of the binding activity of the antibody from which the fragment was derived. Non-limiting examples of functional fragments (*e.g.*, antigen-binding fragments) include single-chain Fvs (scFv) (*e.g.*, including monospecific, bispecific, *etc.*), Fab fragments, F(ab') fragments, $F(ab)_2$ fragments, $F(ab')_2$ fragments, disulfide-linked Fvs (dsFv), Fd fragments, Fv fragments, diabody, triabody, tetrabody, and minibody. In particular, antibodies provided herein include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, for example, antigen-binding domains or molecules that contain an antigen-binding site that binds to an antigen (*e.g.*, one or more CDRs of an antibody). Such antibody fragments can be found in, for example, Harlow and Lane, Antibodies: A Laboratory Manual

(1989); Mol. Biology and Biotechnology: A Comprehensive Desk Reference (Myers ed., 1995); Huston *et al.*, 1993, Cell Biophysics 22:189-224; Plückthun and Skerra, 1989, Meth. Enzymol. 178:497-515; and Day, Advanced Immunochemistry (2d ed. 1990). The antibodies provided herein can be of any class (*e.g.*, IgG, IgE, IgM, IgD, and IgA) or any subclass (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2) of immunoglobulin molecule. Antibodies may be agonistic antibodies or antagonistic antibodies.

[00197] The term "monoclonal antibody" refers to an antibody obtained from a population of substantially homogeneous antibodies, that is, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that can be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. In contrast to polyclonal antibody preparations, which can include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen.

[00198] An "antigen" is a structure to which an antibody can selectively bind. A target antigen may be a polypeptide, carbohydrate, nucleic acid, lipid, hapten, or other naturally occurring or synthetic compound. In some embodiments, the target antigen is a polypeptide. In certain embodiments, an antigen is associated with a cell, for example, is present on or in a cell, for example, a cancer cell.

[00199] An "intact" antibody is one comprising an antigen-binding site as well as a CL and at least heavy chain constant regions, CH1, CH2 and CH3. The constant regions may include human constant regions or amino acid sequence variants thereof. In certain embodiments, an intact antibody has one or more effector functions.

[00200] The terms "antigen binding fragment," "antigen binding domain," "antigen binding region," and similar terms refer to that portion of an antibody, which comprises the amino acid residues that interact with an antigen and confer on the binding agent its specificity and affinity for the antigen (*e.g.*, the CDRs). "Antigen-binding fragment" as used herein include "antibody fragment," which comprise a portion of an intact antibody, such as the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include, without limitation, Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies and di-diabodies (*see, e.g.*, Holliger *et al.*, 1993, Proc. Natl. Acad. Sci. 90:6444-48; Lu *et al.*, 2005, J. Biol. Chem. 280:19665-72; Hudson *et al.*, 2003, Nat. Med. 9:129-34; WO 93/11161; and U.S. Pat. Nos. 5,837,242 and 6,492,123); single-chain antibody molecules (*see, e.g.*, U.S. Pat. Nos. 4,946,778; 5,260,203; 5,482,858; and 5,476,786); dual variable domain antibodies (*see, e.g.*, U.S. Pat. No. 7,612,181); single variable domain antibodies (sdAbs) (*see, e.g.*, Woolven *et*

al., 1999, Immunogenetics 50: 98-101; and Streltsov *et al.*, 2004, Proc Natl Acad Sci USA. 101:12444-49); and multispecific antibodies formed from antibody fragments.

[00201] The terms "binds" or "binding" refer to an interaction between molecules including, for example, to form a complex. Interactions can be, for example, non-covalent interactions including hydrogen bonds, ionic bonds, hydrophobic interactions, and/or van der Waals interactions. A complex can also include the binding of two or more molecules held together by covalent or non-covalent bonds, interactions, or forces. The strength of the total non-covalent interactions between a single antigen-binding site on an antibody and a single epitope of a target molecule, such as an antigen, is the affinity of the antibody or functional fragment for that epitope. The ratio of dissociation rate (k_{off}) to association rate (k_{on}) of a binding molecule (*e.g.*, an antibody) to a monovalent antigen (k_{off}/k_{on}) is the dissociation constant K_D, which is inversely related to affinity. The lower the K_D value, the higher the affinity of the antibody. The value of K_D varies for different complexes of antibody and antigen and depends on both k_{on} and k_{off}. The dissociation constant K_D for an antibody provided herein can be determined using any method provided herein or any other method well-known to those skilled in the art. The affinity at one binding site does not always reflect the true strength of the interaction between an antibody and an antigen. When complex antigens containing multiple, repeating antigenic determinants, such as a polyvalent antigen, come in contact with antibodies containing multiple binding sites, the interaction of antibody with antigen at one site will increase the probability of a reaction at a second site. The strength of such multiple interactions between a multivalent antibody and antigen is called the avidity.

[00202] In connection with the antibody or antigen binding fragment thereof described herein terms such as "bind to," "that specifically bind to," and analogous terms are also used interchangeably herein and refer to binding molecules of antigen binding domains that specifically bind to an antigen, such as a polypeptide. An antibody or antigen binding fragment that binds to or specifically binds to an antigen may be cross-reactive with related antigens. In certain embodiments, an antibody or antigen binding fragment that binds to or specifically binds to an antigen does not cross-react with other antigens. An antibody or antigen binding fragment that binds to or specifically binds to an antigen can be identified, for example, by immunoassays, Octet®, Biacore®, or other techniques known to those of skill in the art. In some embodiments, an antibody or antigen binding fragment binds to or specifically binds to an antigen when it binds to an antigen with higher affinity than to any cross-reactive antigen as determined using experimental techniques, such as

radioimmunoassays (RIA) and enzyme linked immunosorbent assays (ELISAs). Typically, a specific or selective reaction will be at least twice background signal or noise and may be more than 10 times background. *See, e.g.*, Fundamental Immunology 332-36 (Paul ed., 2d ed. 1989) for a discussion regarding binding specificity. In certain embodiments, the extent of binding of an antibody or antigen binding fragment to a "non-target" protein is less than about 10% of the binding of the binding molecule or antigen binding domain to its particular target antigen, for example, as determined by fluorescence activated cell sorting (FACS) analysis or RIA. With regard terms such as "specific binding," "specifically binds to," or "is specific for" means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target, for example, an excess of non-labeled target. In this case, specific binding is indicated if the binding of the labeled target to a probe is competitively inhibited by excess unlabeled target. An antibody or antigen binding fragment that binds to an antigen includes one that is capable of binding the antigen with sufficient affinity such that the binding molecule is useful, for example, as a diagnostic agent in targeting the antigen. In certain embodiments, an antibody or antigen binding fragment that binds to an antigen has a dissociation constant (K_D) of less than or equal to 1000 nM, 800 nM, 500 nM, 250 nM, 100 nM, 50 nM, 10 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.9 nM, 0.8 nM, 0.7 nM, 0.6 nM, 0.5 nM, 0.4 nM, 0.3 nM, 0.2 nM, or 0.1 nM. In certain embodiments, an antibody or antigen binding fragment binds to an epitope of an antigen that is conserved among the antigen from different species (*e.g.*, between human and cyno species).

[00203] "Binding affinity" generally refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (*e.g.*, a binding protein such as an antibody) and its binding partner (*e.g.*, an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (*e.g.*, antibody and antigen). The affinity of a binding molecule X for its binding partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured by common methods known in the art, including those described herein. Low-affinity antibodies generally bind antigen slowly and tend to dissociate readily, whereas high-affinity antibodies generally bind antigen faster and tend to remain bound longer. A variety of methods of measuring binding affinity are known in the art, any of

which can be used for purposes of the present disclosure. Specific illustrative embodiments include the following. In one embodiment, the "K_D" or "K_D value" may be measured by assays known in the art, for example by a binding assay. The K_D may be measured in a RIA, for example, performed with the Fab version of an antibody of interest and its antigen (Chen et al., 1999, J. Mol Biol 293:865-81). The K_D or K_D value may also be measured by using biolayer interferometry (BLI) or surface plasmon resonance (SPR) assays by Octet®, using, for example, a Octet®QK384 system, or by Biacore®, using, for example, a Biacore®TM-2000 or a Biacore®TM-3000. An "on-rate" or "rate of association" or "association rate" or "kon" may also be determined with the same biolayer interferometry (BLI) or surface plasmon resonance (SPR) techniques described above using, for example, the Octet®QK384, the Biacore®TM-2000, or the Biacore®TM-3000 system.

[00204] In certain embodiments, the antibodies or antigen binding fragments can comprise "chimeric" sequences in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (*see* U.S. Pat. No. 4,816,567; and Morrison *et al.*, 1984, Proc. Natl. Acad. Sci. USA 81:6851-55).

[00205] In certain embodiments, the antibodies or antigen binding fragments can comprise portions of "humanized" forms of nonhuman (*e.g.*, murine) antibodies that are chimeric antibodies that include human immunoglobulins (*e.g.*, recipient antibody) in which the native CDR residues are replaced by residues from the corresponding CDR of a nonhuman species (*e.g.*, donor antibody) such as mouse, rat, rabbit, or nonhuman primate comprising the desired specificity, affinity, and capacity. In some instances, one or more FR region residues of the human immunoglobulin are replaced by corresponding nonhuman residues. Furthermore, humanized antibodies can comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. A humanized antibody heavy or light chain can comprise substantially all of at least one or more variable regions, in which all or substantially all of the CDRs correspond to those of a nonhuman immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. In certain embodiments, the humanized antibody will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see, Jones *et al.*, 1986, Nature 321:522-25; Riechmann

et al., 1988, Nature 332:323-29; Presta, 1992, Curr. Op. Struct. Biol. 2:593-96; Carter *et al.*, 1992, Proc. Natl. Acad. Sci. USA 89:4285-89; U.S. Pat. Nos: 6,800,738; 6,719,971; 6,639,055; 6,407,213; and 6,054,297.

[00206] In certain embodiments, the antibodies or antigen binding fragments can comprise portions of a "fully human antibody" or "human antibody," wherein the terms are used interchangeably herein and refer to an antibody that comprises a human variable region and, for example, a human constant region. In specific embodiments, the terms refer to an antibody that comprises a variable region and constant region of human origin. "Fully human" antibodies, in certain embodiments, can also encompass antibodies which bind polypeptides and are encoded by nucleic acid sequences which are naturally occurring somatic variants of human germline immunoglobulin nucleic acid sequence. The term "fully human antibody" includes antibodies comprising variable and constant regions corresponding to human germline immunoglobulin sequences as described by Kabat *et al.* (See Kabat *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). A "human antibody" is one that possesses an amino acid sequence which corresponds to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues. Human antibodies can be produced using various techniques known in the art, including phage-display libraries (Hoogenboom and Winter, 1991, J. Mol. Biol. 227:381; Marks *et al.*, 1991, J. Mol. Biol. 222:581) and yeast display libraries (Chao *et al.*, 2006, Nature Protocols 1: 755-68). Also available for the preparation of human monoclonal antibodies are methods described in Cole *et al.*, Monoclonal Antibodies and Cancer Therapy 77 (1985); Boerner *et al.*, 1991, J. Immunol. 147(1):86-95; and van Dijk and van de Winkel, 2001, Curr. Opin. Pharmacol. 5: 368-74. Human antibodies can be prepared by administering the antigen to a transgenic animal that has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled, *e.g.*, mice (*see, e.g.*, Jakobovits, 1995, Curr. Opin. Biotechnol. 6(5):561-66; Brüggemann and Taussing, 1997, Curr. Opin. Biotechnol. 8(4):455-58; and U.S. Pat. Nos. 6,075,181 and 6,150,584 regarding XENOMOUSE™ technology). See also, for example, Li *et al.*, 2006, Proc. Natl. Acad. Sci. USA 103:3557-62 regarding human antibodies generated via a human B-cell hybridoma technology.

[00207] In certain embodiments, the antibodies or antigen binding fragments can comprise portions of a "recombinant human antibody," wherein the phrase includes human antibodies

that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial human antibody library, antibodies isolated from an animal (*e.g.,* a mouse or cow) that is transgenic and/or transchromosomal for human immunoglobulin genes (*see e.g.,* Taylor, L. D. *et al.* (1992) *Nucl. Acids Res.* 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies can have variable and constant regions derived from human germline immunoglobulin sequences (See Kabat, E. A. *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[00208] In certain embodiments, the antibodies or antigen binding fragments can comprise a portion of a "monoclonal antibody," wherein the term as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *e.g.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts, and each monoclonal antibody will typically recognize a single epitope on the antigen. In specific embodiments, a "monoclonal antibody," as used herein, is an antibody produced by a single hybridoma or other cell. The term "monoclonal" is not limited to any particular method for making the antibody. For example, the monoclonal antibodies useful in the present disclosure may be prepared by the hybridoma methodology first described by Kohler *et al.*, 1975, Nature 256:495, or may be made using recombinant DNA methods in bacterial or eukaryotic animal or plant cells (*see, e.g.*, U.S. Pat. No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.*, 1991, Nature 352:624-28 and Marks *et al.*, 1991, J. Mol. Biol. 222:581-97, for example. Other methods for the preparation of clonal cell lines and of monoclonal antibodies expressed thereby are well-known in the art. *See, e.g.*, Short Protocols in Molecular Biology (Ausubel *et al.* eds., 5th ed. 2002).

[00209] A typical 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains. In the case of IgGs, the 4-

chain unit is generally about 150,000 daltons. Each L chain is linked to an H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain (VH) followed by three constant domains (CH) for each of the α and γ chains and four CH domains for μ and ε isotypes. Each L chain has at the N-terminus, a variable domain (VL) followed by a constant domain (CL) at its other end. The VL is aligned with the VH, and the CL is aligned with the first constant domain of the heavy chain (CH1). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a VH and VL together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, see, for example, Basic and Clinical Immunology 71 (Stites *et al.* eds., 8th ed. 1994); and Immunobiology (Janeway *et al.* eds., 5th ed. 2001).

[00210] The term "Fab" or "Fab region" refers to an antibody region that binds to antigens. A conventional IgG usually comprises two Fab regions, each residing on one of the two arms of the Y-shaped IgG structure. Each Fab region is typically composed of one variable region and one constant region of each of the heavy and the light chain. More specifically, the variable region and the constant region of the heavy chain in a Fab region are VH and CH1 regions, and the variable region and the constant region of the light chain in a Fab region are VL and CL regions. The VH, CH1, VL, and CL in a Fab region can be arranged in various ways to confer an antigen binding capability according to the present disclosure. For example, VH and CH1 regions can be on one polypeptide, and VL and CL regions can be on a separate polypeptide, similarly to a Fab region of a conventional IgG. Alternatively, VH, CH1, VL and CL regions can all be on the same polypeptide and oriented in different orders as described in more detail in the sections below.

[00211] The term "variable region," "variable domain," "V region," or "V domain" refers to a portion of the light or heavy chains of an antibody that is generally located at the amino-terminal of the light or heavy chain and has a length of about 120 to 130 amino acids in the heavy chain and about 100 to 110 amino acids in the light chain, and are used in the binding and specificity of each particular antibody for its particular antigen. The variable region of the heavy chain may be referred to as "VH." The variable region of the light chain may be referred to as "VL." The term "variable" refers to the fact that certain segments of the variable regions differ extensively in sequence among antibodies. The V region mediates antigen binding and defines specificity of a particular antibody for its particular antigen.

However, the variability is not evenly distributed across the 110-amino acid span of the variable regions. Instead, the V regions consist of less variable (*e.g.*, relatively invariant) stretches called framework regions (FRs) of about 15-30 amino acids separated by shorter regions of greater variability (*e.g.*, extreme variability) called "hypervariable regions" that are each about 9-12 amino acids long. The variable regions of heavy and light chains each comprise four FRs, largely adopting a β sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases form part of, the β sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (*see, e.g.*, Kabat *et al.*, Sequences of Proteins of Immunological Interest (5th ed. 1991)). The constant regions are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC). The variable regions differ extensively in sequence between different antibodies. In specific embodiments, the variable region is a human variable region.

[00212] The term "variable region residue numbering according to Kabat" or "amino acid position numbering as in Kabat", and variations thereof, refer to the numbering system used for heavy chain variable regions or light chain variable regions of the compilation of antibodies in Kabat *et al.*, *supra*. Using this numbering system, the actual linear amino acid sequence may contain fewer or additional amino acids corresponding to a shortening of, or insertion into, an FR or CDR of the variable domain. For example, a heavy chain variable domain may include a single amino acid insert (residue 52a according to Kabat) after residue 52 and three inserted residues (*e.g.*, residues 82a, 82b, and 82c, *etc.* according to Kabat) after residue 82. The Kabat numbering of residues may be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a "standard" Kabat numbered sequence. The Kabat numbering system is generally used when referring to a residue in the variable domain (approximately residues 1-107 of the light chain and residues 1-113 of the heavy chain) (*e.g.*, Kabat *et al.*, *supra*). The "EU numbering system" or "EU index" is generally used when referring to a residue in an immunoglobulin heavy chain constant region (*e.g.*, the EU index reported in Kabat *et al.*, supra). The "EU index as in Kabat" refers to the residue numbering of the human IgG 1 EU antibody. Other numbering systems have been described, for example, by AbM, Chothia, Contact, IMGT, and AHon.

[00213] The term "heavy chain" when used in reference to an antibody refers to a polypeptide chain of about 50-70 kDa, wherein the amino-terminal portion includes a variable region of about 120 to 130 or more amino acids, and a carboxy-terminal portion includes a constant region. The constant region can be one of five distinct types, (*e.g.*, isotypes) referred to as alpha (α), delta (δ), epsilon (ε), gamma (γ), and mu (μ), based on the amino acid sequence of the heavy chain constant region. The distinct heavy chains differ in size: α, δ, and γ contain approximately 450 amino acids, while μ and ε contain approximately 550 amino acids. When combined with a light chain, these distinct types of heavy chains give rise to five well-known classes (*e.g.*, isotypes) of antibodies, IgA, IgD, IgE, IgG, and IgM, respectively, including four subclasses of IgG, namely IgG1, IgG2, IgG3, and IgG4.

[00214] The term "light chain" when used in reference to an antibody refers to a polypeptide chain of about 25 kDa, wherein the amino-terminal portion includes a variable region of about 100 to about 110 or more amino acids, and a carboxy-terminal portion includes a constant region. The approximate length of a light chain is 211 to 217 amino acids. There are two distinct types, referred to as kappa (κ) or lambda (λ) based on the amino acid sequence of the constant domains.

[00215] As used herein, the terms "hypervariable region," "HVR," "Complementarity Determining Region," and "CDR" are used interchangeably. A "CDR" refers to one of three hypervariable regions (H1, H2 or H3) within the non-framework region of the immunoglobulin (Ig or antibody) VH β-sheet framework, or one of three hypervariable regions (L1, L2 or L3) within the non-framework region of the antibody VL β-sheet framework. Accordingly, CDRs are variable region sequences interspersed within the framework region sequences.

[00216] CDR regions are well-known to those skilled in the art and have been defined by well-known numbering systems. For example, the Kabat Complementarity Determining Regions (CDRs) are based on sequence variability and are the most commonly used (*see, e.g.*, Kabat *et al.*, *supra*). Chothia refers instead to the location of the structural loops (*see, e.g.*, Chothia and Lesk, 1987, J. Mol. Biol. 196:901-17). The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34). The AbM hypervariable regions represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling

software (*see, e.g.*, Antibody Engineering Vol. 2 (Kontermann and Dübel eds., 2d ed. 2010)). The "contact" hypervariable regions are based on an analysis of the available complex crystal structures. Another universal numbering system that has been developed and widely adopted is ImMunoGeneTics (IMGT) Information System® (Lafranc *et al.*, 2003, Dev. Comp. Immunol. 27(1):55-77). IMGT is an integrated information system specializing in immunoglobulins (IG), T-cell receptors (TCR), and major histocompatibility complex (MHC) of human and other vertebrates. Herein, the CDRs are referred to in terms of both the amino acid sequence and the location within the light or heavy chain. As the "location" of the CDRs within the structure of the immunoglobulin variable domain is conserved between species and present in structures called loops, by using numbering systems that align variable domain sequences according to structural features, CDR and framework residues are readily identified. This information can be used in grafting and replacement of CDR residues from immunoglobulins of one species into an acceptor framework from, typically, a human antibody. An additional numbering system (AHon) has been developed by Honegger and Plückthun, 2001, J. Mol. Biol. 309: 657-70. Correspondence between the numbering system, including, for example, the Kabat numbering and the IMGT unique numbering system, is well-known to one skilled in the art (*see, e.g.*, Kabat, *supra*; Chothia and Lesk, *supra*; Martin, *supra*; Lefranc *et al.*, *supra*). The residues from each of these hypervariable regions or CDRs are noted below in Table 1.

Table 1

	Kabat	**AbM**	**Chothia**	**Contact**	**IMGT**
CDR-L1	L24--L34	L24--L34	L24--L34	L30--L36	L27--L38
CDR-L2	L50--L56	L50--L56	L50--L56	L46--L55	L56--L65
CDR-L3	L89--L97	L89--L97	L89--L97	L89--L96	L105-L117
CDR-H1	H31--H35B (Kabat Numbering)	H26--H35B	H26--H32..34	H30--H35B	H27--H38
CDR-H1	H31--H35 (Chothia Numbering)	H26--H35	H26--H32	H30--H35	
CDR-H2	H50--H65	H50--H58	H52--H56	H47--H58	H56--H65
CDR-H3	H95--H102	H95--H102	H95--H102	H93--H101	H105-H117

[00217] The boundaries of a given CDR may vary depending on the scheme used for identification. Thus, unless otherwise specified, the terms "CDR" and "complementary

determining region" of a given antibody or region thereof, such as a variable region, as well as individual CDRs (*e.g.*, "CDR-H1, CDR-H2) of the antibody or region thereof, should be understood to encompass the complementary determining region as defined by any of the known schemes described herein above. In some instances, the scheme for identification of a particular CDR or CDRs is specified, such as the CDR as defined by the Kabat, Chothia, or Contact method. In other cases, the particular amino acid sequence of a CDR is given.

[00218] Hypervariable regions may comprise "extended hypervariable regions" as follows: 24-36 or 24-34 (L1), 46-56 or 50-56 (L2), and 89-97 or 89-96 (L3) in the VL, and 26-35 or 26-35A (H1), 50-65 or 49-65 (H2), and 93-102, 94-102, or 95-102 (H3) in the VH.

[00219] The term "constant region" or "constant domain" refers to a carboxy terminal portion of the light and heavy chain which is not directly involved in binding of the antibody to antigen but exhibits various effector function, such as interaction with the Fc receptor. The term refers to the portion of an immunoglobulin molecule comprising a more conserved amino acid sequence relative to the other portion of the immunoglobulin, the variable region, which contains the antigen binding site. The constant region may contain the CH1, CH2, and CH3 regions of the heavy chain and the CL region of the light chain.

[00220] The term "framework" or "FR" refers to those variable region residues flanking the CDRs. FR residues are present, for example, in chimeric, humanized, human, domain antibodies, diabodies, linear antibodies, and bispecific antibodies. FR residues are those variable domain residues other than the hypervariable region residues or CDR residues.

[00221] The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain, including, for example, native sequence Fc regions, recombinant Fc regions, and variant Fc regions. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is often defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region may be removed, for example, during production or purification of the antibody, or by recombinantly engineering the nucleic acid encoding a heavy chain of the antibody. Accordingly, a composition of intact antibodies may comprise antibody populations with all K447 residues removed, antibody populations with no K447 residues removed, and antibody populations comprising a mixture of antibodies with and without the K447 residue. A "functional Fc region" possesses an "effector function" of a native sequence Fc region. Exemplary "effector functions" include C1q binding; CDC; Fc receptor binding; ADCC; phagocytosis; downregulation of cell surface receptors (*e.g.*, B cell

receptor), *etc.* Such effector functions generally require the Fc region to be combined with a binding region or binding domain (*e.g.*, an antibody variable region or domain) and can be assessed using various assays known to those skilled in the art. A "variant Fc region" comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification (*e.g.*, substituting, addition, or deletion). In certain embodiments, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or to the Fc region of a parent polypeptide, for example, from about one to about ten amino acid substitutions, or from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of a parent polypeptide. The variant Fc region herein can possess at least about 80% homology with a native sequence Fc region and/or with an Fc region of a parent polypeptide, or at least about 90% homology therewith, for example, at least about 95% homology therewith.

[00222] As used herein, an "epitope" is a term in the art and refers to a localized region of an antigen to which a binding molecule (*e.g.*, an antibody) can specifically bind. An epitope can be a linear epitope or a conformational, non-linear, or discontinuous epitope. In the case of a polypeptide antigen, for example, an epitope can be contiguous amino acids of the polypeptide (a "linear" epitope) or an epitope can comprise amino acids from two or more non-contiguous regions of the polypeptide (a "conformational," "non-linear" or "discontinuous" epitope). It will be appreciated by one of skill in the art that, in general, a linear epitope may or may not be dependent on secondary, tertiary, or quaternary structure. For example, in some embodiments, a binding molecule binds to a group of amino acids regardless of whether they are folded in a natural three dimensional protein structure. In other embodiments, a binding molecule requires amino acid residues making up the epitope to exhibit a particular conformation (*e.g.*, bend, twist, turn or fold) in order to recognize and bind the epitope.

[00223] The terms "polypeptide" and "peptide" and "protein" are used interchangeably herein and refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid, including but not limited to, unnatural amino acids, as well as other modifications known in the art. It is understood that, because the polypeptides of this disclosure may be based upon

antibodies or other members of the immunoglobulin superfamily, in certain embodiments, a "polypeptide" can occur as a single chain or as two or more associated chains.

[00224] The term "pharmaceutically acceptable" as used herein means being approved by a regulatory agency of the Federal or a state government, or listed in United States Pharmacopeia, European Pharmacopeia, or other generally recognized Pharmacopeia for use in animals, and more particularly in humans.

[00225] "Excipient" means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. Excipients include, for example, encapsulating materials or additives such as absorption accelerators, antioxidants, binders, buffers, carriers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof. The term "excipient" can also refer to a diluent, adjuvant (*e.g.*, Freunds' adjuvant (complete or incomplete) or vehicle.

[00226] In one embodiment, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, e.g.*, Lippincott Williams & Wilkins: Philadelphia, PA, 2005; Handbook of Pharmaceutical Excipients, 6th ed.; Rowe et al., Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; Handbook of Pharmaceutical Additives, 3rd ed.; Ash and Ash Eds.; Gower Publishing Company: 2007; Pharmaceutical Preformulation and Formulation, 2nd ed.; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009. In some embodiments, pharmaceutically acceptable excipients are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. In some embodiments, a pharmaceutically acceptable excipient is an aqueous pH buffered solution.

[00227] The abbreviation "MMAE" refers to monomethyl auristatin E.

[00228] Unless otherwise indicated by context, a hyphen (-) designates the point of attachment to the pendant molecule.

[00229] The term "Chemotherapeutic Agent" refers to all chemical compounds that are effective in inhibiting tumor growth. Non-limiting examples of chemotherapeutic agents include alkylating agents; for example, nitrogen mustards, ethyleneimine compounds and alkyl sulphonates; antimetabolites, for example, folic acid, purine or pyrimidine antagonists;

mitotic inhibitors, for example, anti-tubulin agents such as vinca alkaloids, auristatins and derivatives of podophyllotoxin; cytotoxic antibiotics; compounds that damage or interfere with DNA expression or replication, for example, DNA minor groove binders; and growth factor receptor antagonists. In addition, chemotherapeutic agents include cytotoxic agents (as defined herein), antibodies, biological molecules and small molecules.

[00230] As used herein, the term "conservative substitution" refers to substitutions of amino acids are known to those of skill in this art and may be made generally without altering the biological activity of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (*see, e.g.*, Watson, *et al.*, MOLECULAR BIOLOGY OF THE GENE, The Benjamin/Cummings Pub. Co., p. 224 (4th Edition 1987)). Such exemplary substitutions are preferably made in accordance with those set forth in Table 2 and Table 3. For example, such changes include substituting any of isoleucine (I), valine (V), and leucine (L) for any other of these hydrophobic amino acids; aspartic acid (D) for glutamic acid (E) and vice versa; glutamine (Q) for asparagine (N) and vice versa; and serine (S) for threonine (T) and vice versa. Other substitutions can also be considered conservative, depending on the environment of the particular amino acid and its role in the three-dimensional structure of the protein. For example, glycine (G) and alanine (A) can frequently be interchangeable, as can alanine (A) and valine (V). Methionine (M), which is relatively hydrophobic, can frequently be interchanged with leucine and isoleucine, and sometimes with valine. Lysine (K) and arginine (R) are frequently interchangeable in locations in which the significant feature of the amino acid residue is its charge and the differing pK's of these two amino acid residues are not significant. Still other changes can be considered "conservative" in particular environments (*see, e.g.* Table 3 herein; pages 13-15 "Biochemistry" 2nd ED. Lubert Stryer ed (Stanford University); Henikoff *et al.*, PNAS 1992 Vol 89 10915-10919; Lei *et al.*, J Biol Chem 1995 May 19; 270(20):11882-11886). Other substitutions are also permissible and may be determined empirically or in accord with known conservative substitutions.

Table 2. Amino Acid Abbreviations

SINGLE LETTER	THREE LETTER	FULL NAME
F	Phe	phenylalanine
L	Leu	leucine
S	Ser	serine
Y	Tyr	tyrosine
C	Cys	cysteine
W	Trp	tryptophan

SINGLE LETTER	THREE LETTER	FULL NAME
P	Pro	proline
H	His	histidine
Q	Gln	glutamine
R	Arg	arginine
I	Ile	isoleucine
M	Met	methionine
T	Thr	threonine
N	Asn	asparagine
K	Lys	lysine
V	Val	valine
A	Ala	alanine
D	Asp	aspartic acid
E	Glu	glutamic acid
G	Gly	glycine

Table 3. Amino Acid Substitution or Similarity Matrix

Adapted from the GCG Software 9.0 BLOSUM62 amino acid substitution matrix (block substitution matrix). The higher the value, the more likely a substitution is found in related, natural proteins.

```
 A  C  D  E  F  G  H  I  K  L  M  N  P  Q  R  S  T  V  W  Y  .
 4  0 -2 -1 -2  0 -2 -1 -1 -1 -1 -2 -1 -1 -1  1  0  0 -3 -2 A
    9 -3 -4 -2 -3 -3 -1 -3 -1 -1 -3 -3 -3 -3 -1 -1 -1 -2 -2 C
       6  2 -3 -1 -1 -3 -1 -4 -3  1 -1  0 -2  0 -1 -3 -4 -3 D
          5 -3 -2  0 -3  1 -3 -2  0 -1  2  0  0 -1 -2 -3 -2 E
             6 -3 -1  0 -3  0  0 -3 -4 -3 -3 -2 -2 -1  1  3 F
                6 -2 -4 -2 -4 -3  0 -2 -2 -2  0 -2 -3 -2 -3 G
                   8 -3 -1 -3 -2  1 -2  0  0 -1 -2 -3 -2  2 H
                      4 -3  2  1 -3 -3 -3 -3 -2 -1  3 -3 -1 I
                         5 -2 -1  0 -1  1  2  0 -1 -2 -3 -2 K
                            4  2 -3 -3 -2 -2 -2 -1  1 -2 -1 L
                               5 -2 -2  0 -1 -1 -1  1 -1 -1 M
                                  6 -2  0  0  1  0 -3 -4 -2 N
                                     7 -1 -2 -1 -1 -2 -4 -3 P
                                        5  1  0 -1 -2 -2 -1 Q
                                           5 -1 -1 -3 -3 -2 R
                                              4  1 -2 -3 -2 S
                                                 5  0 -2 -2 T
                                                    4 -3 -1 V
                                                      11  2 W
```

7 Y

[00231] The term "homology" or "homologous" is intended to mean a sequence similarity between two polynucleotides or between two polypeptides. Similarity can be determined by comparing a position in each sequence, which can be aligned for purposes of comparison. If a given position of two polypeptide sequences is not identical, the similarity or conservativeness of that position can be determined by assessing the similarity of the amino acid of the position, for example, according to Table 3. A degree of similarity between sequences is a function of the number of matching or homologous positions shared by the sequences. The alignment of two sequences to determine their percent sequence similarity can be done using software programs known in the art, such as, for example, those described in Ausubel et al., Current Protocols in Molecular Biology, John Wiley and Sons, Baltimore, MD (1999). Preferably, default parameters are used for the alignment, examples of which are set forth below. One alignment program well known in the art that can be used is BLAST set to default parameters. In particular, programs are BLASTN and BLASTP, using the following default parameters: Genetic code = standard; filter = none; strand = both; cutoff = 60; expect = 10; Matrix = BLOSUM62; Descriptions = 50 sequences; sort by = HIGH SCORE; Databases = non-redundant, GenBank + EMBL + DDBJ + PDB + GenBank CDS translations + SwissProtein + SPupdate + PIR. Details of these programs can be found at the National Center for Biotechnology Information.

[00232] The term "homologs" of to a given amino acid sequence or a nucleic acid sequence is intended to indicate that the corresponding sequences of the "homologs" having substantial identity or homology to the given amino acid sequence or nucleic acid sequence.

[00233] The determination of percent identity between two sequences (*e.g.,* amino acid sequences or nucleic acid sequences) can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. U.S.A. 87:2264 2268, modified as in Karlin and Altschul, 1993, Proc. Natl. Acad. Sci. U.S.A. 90:5873 5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul *et al.*, 1990, J. Mol. Biol. 215:403. BLAST nucleotide searches can be performed with the NBLAST nucleotide program parameters set, *e.g.,* for score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecules described herein. BLAST protein searches can be performed with the XBLAST program parameters set, *e.g.,* to score 50, wordlength=3 to obtain amino acid sequences homologous to a protein molecule

described herein. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, 1997, Nucleic Acids Res. 25:3389 3402. Alternatively, PSI BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI Blast programs, the default parameters of the respective programs (*e.g.,* of XBLAST and NBLAST) can be used (*see, e.g.,* National Center for Biotechnology Information (NCBI) on the worldwide web, ncbi.nlm.nih.gov). Another non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11 17. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

[00234] The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, typically only exact matches are counted.

[00235] The term "cytotoxic agent" refers to a substance that inhibits or prevents the expression activity of cells, function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes, chemotherapeutic agents, and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof. Examples of cytotoxic agents include, but are not limited to auristatins (*e.g.*, auristatin E, auristatin F, MMAE and MMAF), auromycins, maytansinoids, ricin, ricin A-chain, combrestatin, duocarmycins, dolastatins, doxorubicin, daunorubicin, taxols, cisplatin, cc1065, ethidium bromide, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin, diphtheria toxin, Pseudomonas exotoxin (PE) A, PE40, abrin, abrin A chain, modeccin A chain, alpha-sarcin, gelonin, mitogellin, retstrictocin, phenomycin, enomycin, curicin, crotin, calicheamicin, Sapaonaria officinalis inhibitor, and glucocorticoid and other chemotherapeutic agents, as well as radioisotopes such as At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212} or ^{213}, P^{32} and radioactive isotopes of Lu including Lu^{177}. Antibodies may also be conjugated to an anti-cancer pro-drug activating enzyme capable of converting the pro-drug to its active form.

[00236] The term "effective amount" or "therapeutically effective amount" as used herein refers to the amount of binding molecule (*e.g.*, an antibody) or pharmaceutical composition provided herein which is sufficient to result in the desired outcome.

[00237] The terms "subject" and "patient" may be used interchangeably. As used herein, in certain embodiments, a subject is a mammal, such as a non-primate (*e.g.*, cow, pig, horse, cat, dog, rat, *etc.*) or a primate (*e.g.*, monkey and human). In specific embodiments, the subject is a human. In one embodiment, the subject is a mammal, *e.g.*, a human, diagnosed with a condition or disorder. In another embodiment, the subject is a mammal, *e.g.*, a human, at risk of developing a condition or disorder.

[00238] "Administer" or "administration" refers to the act of injecting or otherwise physically delivering a substance as it exists outside the body into a patient, such as by mucosal, intradermal, intravenous, intramuscular delivery, and/or any other method of physical delivery described herein or known in the art.

[00239] As used herein, the terms "treat," "treatment" and "treating" refer to the reduction or amelioration of the progression, severity, and/or duration of a disease or condition resulting from the administration of one or more therapies. Treating may be determined by assessing whether there has been a decrease, alleviation and/or mitigation of one or more symptoms associated with the underlying disorder such that an improvement is observed with the patient, despite that the patient may still be afflicted with the underlying disorder. The term "treating" includes both managing and ameliorating the disease. The terms "manage," "managing," and "management" refer to the beneficial effects that a subject derives from a therapy which does not necessarily result in a cure of the disease.

[00240] The terms "prevent," "preventing," and "prevention" refer to reducing the likelihood of the onset (or recurrence) of a disease, disorder, condition, or associated symptom(s) (*e.g.*, a cancer).

[00241] The term "cancer" or "cancer cell" is used herein to denote a tissue or cell found in a neoplasm which possesses characteristics which differentiate it from normal tissue or tissue cells. Among such characteristics include but are not limited to: degree of anaplasia, irregularity in shape, indistinctness of cell outline, nuclear size, changes in structure of nucleus or cytoplasm, other phenotypic changes, presence of cellular proteins indicative of a cancerous or pre-cancerous state, increased number of mitoses, and ability to metastasize. Words pertaining to "cancer" include carcinoma, sarcoma, tumor, epithelioma, leukemia, lymphoma, polyp, and scirrus, transformation, neoplasm, and the like.

[00242] As used herein, a "locally advanced" cancer refers to a cancer that has spread from where it started to nearby tissue or lymph nodes.

[00243] As used herein, a "metastatic" cancer refers to a cancer that has spread from where it started to different part of the body.

[00244] As used herein, the term "major surgery" may refer to a surgery that involves opening one of the major body cavities, such as, but not limited to, the abdomen (i.e., laparotomy), chest (i.e., thoracotomy), or skull (i.e., craniotomy).

[00245] The terms "about" and "approximately" mean within 20%, within 15%, within 10%, within 9%, within 8%, within 7%, within 6%, within 5%, within 4%, within 3%, within 2%, within 1%, or less of a given value or range.

[00246] As used in the present disclosure and claims, the singular forms "a", "an" and "the" include plural forms unless the context clearly dictates otherwise.

[00247] It is understood that wherever embodiments are described herein with the term "comprising" otherwise analogous embodiments described in terms of "consisting of" and/or "consisting essentially of" are also provided. It is also understood that wherever embodiments are described herein with the phrase "consisting essentially of" otherwise analogous embodiments described in terms of "consisting of" are also provided.

[00248] The term "and/or" as used in a phrase such as "A and/or B" herein is intended to include both A and B; A or B; A (alone); and B (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[00249] The term "variant" refers to a molecule that exhibits a variation from a described type or norm, such as a protein that has one or more different amino acid residues in the corresponding position(s) of a specifically described protein (*e.g.* the 191P4D12 protein shown in **FIG. 1A**.) An analog is an example of a variant protein. Splice isoforms and single nucleotides polymorphisms (SNPs) are further examples of variants.

[00250] The "191P4D12 proteins" and/or "191P4D12 related proteins" of the disclosure include those specifically identified herein (see, **FIG. 1A**), as well as allelic variants, conservative substitution variants, analogs and homologs that can be isolated/generated and characterized without undue experimentation following the methods outlined herein or readily available in the art. Fusion proteins that combine parts of different 191P4D12 proteins or fragments thereof, as well as fusion proteins of a 191P4D12 protein and a heterologous polypeptide are also included. Such 191P4D12 proteins are collectively referred to as the 191P4D12-related proteins, the proteins of the disclosure, or 191P4D12. The term "191P4D12-related protein" refers to a polypeptide fragment or a 191P4D12 protein sequence of 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more than 25 amino acids; or, at least 30, 35, 40, 45, 50, 55, 60, 65, 70, 80, 85, 90, 95, 100,

105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 225, 250, 275, 300, 325, 330, 335, 339 or more amino acids. The term "191P4D12" is used interchangeably with nectin-4

5.2 Methods of Treating Cancer

[00251] Urothelial carcinoma (UC), a carcinoma that encompasses both lower and upper urinary tract, is a malignancy with high unmet medical need. The worldwide incidence of UC is increasing, driven by overall population growth and aging. The prognosis for patients with locally advanced or metastatic urothelial carcinoma (la/mUC) is poor with relatively low (~5%) survival rates at 5 years.

[00252] For decades, platinum-based chemotherapy has been the first-line standard of care (SOC) for la/mUC. Despite survival benefits, treatment outcomes remain poor. Most patients initially respond to cisplatin- or carboplatin-based chemotherapy, however many patients will progress within 7 months, highlighting the need for new therapies in the first-line setting. Treatment guidelines recommend avelumab maintenance therapy as an option for a subset of patients with la/mUC who have not progressed with platinum-containing chemotherapy; however, most patients are unable to or do not receive maintenance therapy primarily because of disease progression or death (include proper references) on their initial therapy.

[00253] The disclosure thus provides demonstrated efficacious methods to treat patients (e.g., cisplatin eligible and ineligible patients) with urothelial cancer and/or bladder cancer (including locally advanced urothelial cancer, metastatic urothelial cancer, locally advanced metastatic urothelial cancer, locally advanced bladder cancer, and metastatic bladder cancer) (e.g., patients who have not received any previous treatment for the cancer).

[00254] In embodiments that refer to a method of treatment as described herein, such embodiments are also further embodiments to the antibody drug conjugate (ADC) and/or anti-PD-1 antibody, for use in the combination treatment, or to the use of the ADC and/or anti-PD-1 antibody in the manufacture of a medicament for use in the combination treatment.

5.2.1 Methods of Treating Cancer in General and for Selected Patients

[00255] Provided herein are methods for the first-line and second-line treatment of various cancers in subjects, including subjects with unresectable locally advanced or metastatic urothelial cancer (la/mUC) who are cisplatin eligible and ineligible, using an antibody drug conjugate (ADC) that binds 191P4D12 in combination with an anti-PD-1 antibody (e.g., pembrolizumab).

[00256] In one aspect, provided herein are methods for the treatment of cancer in a subject using an ADC that binds 191P4D12 and an anti-PD-1 antibody (e.g., pembrolizumab). In some embodiments, the human subject treated with the methods provided herein has not received previous cancer treatment other than the ADC that binds 191P4D12. In certain embodiments, the human subject treated with the methods provided herein has not received previous treatment that includes or consists of an immune checkpoint inhibitor (CPI). In some embodiments, the CPI is an anti-PD-1 antibody (e.g., pembrolizumab). In some embodiments, the CPI is a PD-1 inhibitor, PD-L1 inhibitor, or PD-L2 inhibitor (including, but not limited to, atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab). In particular embodiments, the CPI is atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab. In certain embodiments, the human subject treated with the methods provided herein has not received previous treatment that includes or consists of an PD-(L)-1 inhibitor. A PD-(L)-1 inhibitor is a PD-1 inhibitor or PD-L1 inhibitor. In some embodiments, the PD-(L)-1 inhibitor is an anti-PD-1 antibody (e.g., pembrolizumab). In some embodiments, the PD-(L)-1 inhibitor is a PD-1 inhibitor or PD-L1 inhibitor. In particular embodiments, the PD-(L)-1 inhibitor is atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab. In certain embodiments, the human subject treated with the methods provided herein has not received an agent directed to another stimulatory or co inhibitory T-cell receptor (including but not limited to CD137 agonists, CTLA 4 inhibitors, or OX-40 agonists). In particular embodiments, the agent directed to another stimulatory or co inhibitory T-cell receptor is a CD137 agonist, a CTLA 4 inhibitor, or an OX-40 agonist. In some embodiments, the human subject treated with the methods provided herein is ineligible to receive cisplatin treatment. In other embodiments, the human subject treated with the methods provided herein is ineligible to receive cisplatin treatment and has not received previous treatment including or consisting of a CPI. In certain embodiments, the human subject treated with the methods provided herein is ineligible to receive cisplatin treatment, has not received previous treatment including or consisting of a CPI, and has not received prior systemic therapy with the exceptions of neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. In some embodiments, the human subject treated with the methods provided herein is eligible to receive cisplatin treatment. In other embodiments, the human subject treated with the methods provided herein is eligible to receive cisplatin treatment and has not received previous treatment including or consisting of a CPI. In certain embodiments, the human subject treated with the methods provided herein is eligible to receive cisplatin treatment, has not received previous treatment including or

consisting of a CPI, and has not received prior systemic therapy with the exceptions of neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. In certain embodiments, the human subject treated with the methods provided herein is eligible to receive cisplatin treatment, has not received previous treatment including or consisting of a CPI, and has received neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. In some embodiments, the human subject treated with the methods provided herein is eligible to receive carboplatin treatment. In other embodiments, the human subject treated with the methods provided herein is eligible to receive carboplatin treatment and has not received previous treatment including or consisting of a CPI. In certain embodiments, the human subject treated with the methods provided herein is eligible to receive carboplatin treatment, has not received previous treatment including or consisting of a CPI, and has not received prior systemic therapy with the exceptions of neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. In certain embodiments, the human subject treated with the methods provided herein is eligible to receive carboplatin treatment, has not received previous treatment including or consisting of a CPI, and has received neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. In some embodiments, the human subject treated with the methods provided herein is ineligible or eligible to receive cisplatin treatment. In other embodiments, the human subject treated with the methods provided herein is ineligible or eligible to receive cisplatin treatment and has not received previous treatment including or consisting of a CPI. In certain embodiments, the human subject treated with the methods provided herein is ineligible or eligible to receive cisplatin treatment, has not received previous treatment including or consisting of a CPI, and has not received prior systemic therapy with the exceptions of neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. In certain embodiments, the human subject treated with the methods provided herein is ineligible or eligible to receive cisplatin treatment, has not received previous treatment including or consisting of a CPI, and has received neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. In some embodiments, the cancer is urothelial cancer. In certain embodiments, the cancer is bladder cancer. In certain embodiments, the cancer is cancer of the renal pelvis. In certain embodiments, the cancer is cancer of the ureter. In certain embodiments, the cancer is cancer of the urethra. In one embodiment, the cancer is locally advanced cancer. In another embodiment, the cancer is

metastatic cancer. In a further embodiment, the cancer is locally advanced urothelial cancer. In a further embodiment, the cancer is unresectable locally advanced urothelial cancer. In yet another embodiment, the cancer is metastatic urothelial cancer. In one embodiment, the cancer is locally advanced bladder cancer. In another embodiment, the cancer is metastatic bladder cancer.

5.2.1.1 *Cisplatin Ineligible Patients and Cisplatin Eligible Patients*

[00257] *Cisplatin Ineligible Patients*: Various conditions can be used to determine the cisplatin ineligibility for the human subjects for the methods provided herein, including but not limited to the methods of the preceding paragraphs. In one embodiment, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of impaired renal function (e.g., glomerular filtration rate (GFR) or creatinine clearance <60 mL/min but ≥30 mL/min (estimated by the Cockcroft-Gault formula, modification of diet in renal disease [MDRD] or 24 hour urine)). In certain embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of no less than Grade 2 hearing loss (e.g., CI CTCAE Version 4.03 Grade ≥ 2 hearing loss). In certain embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of NYHA Class III heart failure. In one embodiment, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2 and impaired renal function. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2 and no less than Grade 2 hearing loss. In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of impaired renal function and no less than Grade 2 hearing loss. In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of impaired renal function and NYHA Class III heart failure. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2, impaired renal function, and no less than Grade 2 hearing loss. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of impaired renal function, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any one of ECOG performance status score of 2, impaired renal function, and no less than Grade 2 hearing loss. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any one of impaired renal

function, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any two of ECOG performance status score of 2, impaired renal function, and no less than Grade 2 hearing loss, in any combination or permutation. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any two of impaired renal function, no less than Grade 2 hearing loss, and NYHA Class III heart failure, in any combination or permutation. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of all three of ECOG performance status score of 2, impaired renal function, and no less than Grade 2 hearing loss. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of all three of impaired renal function, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments of the methods provided herein, the subject did not receive prior systemic treatment for locally advanced or metastatic disease. In some embodiments, the subject has received neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. In some embodiments of the methods provided herein, wherein the subject has ECOG performance status score of 2, the subject (i) has Hemoglobin ≥10 g/dL; (ii) has GFR ≥ 50 mL/min; and (iii) does not have NYHA Class III heart failure.

[00258] Impaired renal function can be determined as various means known and available in the art. Various embodiments are provided herein to determine the impaired renal function for the human subjects for the methods provided herein, including but not limited to the methods of the preceding paragraph. In one embodiment, the impaired renal function is determined by glomerular filtration rate (GFR) less than 60 mL/min. In some embodiments, the impaired renal function is determined by GFR less than 60 but no less than 30 mL/min. In certain embodiments, the impaired renal function is determined by GFR less than 30 but no less than 15 mL/min. In some embodiments of the methods provided in this paragraph, the GFR is measured by 24 hour urine collection. In other embodiments of the methods provided in this paragraph, the GFR is estimated by the Cockcroft-Gault criteria. In other embodiments of the methods provided in this paragraph, the GFR is measured by modification of diet in renal disease [MDRD].

[00259] In a further embodiment, the impaired renal function is determined by creatinine clearance (CrCl) less than 60 mL/min. In some embodiments, the impaired renal function is determined by CrCl less than 60 but no less than 30 mL/min. In certain embodiments, the impaired renal function is determined by CrCl less than 30 but no less than 15 mL/min. In

some embodiments of the methods provided in this paragraph, the CrCl is measured by 24 hour urine collection. In other embodiments of the methods provided in this paragraph, the CrCl is estimated by the Cockcroft-Gault criteria.

[00260] As such, some specific conditions based on GFR or creatinine clearance can be used to determine the cisplatin ineligibility for the human subjects for the methods provided herein, including but not limited to the methods of the preceding paragraphs. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of GFR less than 60 mL/min. In one embodiment, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2 and CrCl less than 60 mL/min. In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of GFR less than 60 mL/min and no less than Grade 2 hearing loss. In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of GFR less than 60 mL/min, and NYHA Class III heart failure. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2, GFR less than 60 mL/min, and no less than Grade 2 hearing loss. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of GFR less than 60 mL/min, and no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any one of ECOG performance status score of 2, GFR less than 60 mL/min, and no less than Grade 2 hearing loss. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any one of GFR less than 60 mL/min, and no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any two of ECOG performance status score of 2, GFR less than 60 mL/min, and no less than Grade 2 hearing loss, in any combination or permutation. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any two of GFR l less than 60 mL/min, and no less than Grade 2 hearing loss, and NYHA Class III heart failure, in any combination or permutation. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of all three of ECOG performance status score of 2, GFR less than 60 mL/min, and no less than Grade 2 hearing loss. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of all three of GFR less than 60 mL/min, and no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments of the methods provided in this paragraph, the GFR is measured by 24 hour urine collection. In

other embodiments of the methods provided in this paragraph, the GFR is estimated by the Cockcroft-Gault criteria. In other embodiments of the methods provided in this paragraph, the GFR is measured by modification of diet in renal disease [MDRD]. In some embodiments of the methods provided herein, the subject did not receive prior systemic treatment for locally advanced or metastatic disease. In some embodiments, the subject has received neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. In some embodiments of the methods provided herein, wherein the subject has ECOG performance status score of 2, the subject (i) has Hemoglobin ≥10 g/dL; (ii) has GFR ≥ 50 mL/min; and (iii) does not have NYHA Class III heart failure.

[00261] In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of CrCl less than 60 mL/min. In one embodiment, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2 and CrCl less than 60 mL/min. In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of CrCl less than 60 mL/min and no less than Grade 2 hearing loss. In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of CrCl less than 60 mL/min, and NYHA Class III heart failure. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2, CrCl less than 60 mL/min, and no less than Grade 2 hearing loss. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of CrCl less than 60 mL/min, and no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any one of ECOG performance status score of 2, CrCl less than 60 mL/min, and no less than Grade 2 hearing loss. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any one of CrCl less than 60 mL/min, and no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any two of ECOG performance status score of 2, CrCl less than 60 mL/min, and no less than Grade 2 hearing loss, in any combination or permutation. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any two of CrCl less than 60 mL/min, and no less than Grade 2 hearing loss, and NYHA Class III heart failure, in any combination or permutation. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of all three of ECOG performance status score of 2, CrCl less than 60 mL/min, and no less than Grade 2 hearing loss. In some embodiments, the conditions for

determining the cisplatin ineligibility comprise or consist of all three of CrCl less than 60 mL/min, and no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments of the methods provided in this paragraph, the CrCl is measured by 24 hour urine collection. In other embodiments of the methods provided in this paragraph, the CrCl is estimated by the Cockcroft-Gault criteria. In some embodiments of the methods provided herein, the subject did not receive prior systemic treatment for locally advanced or metastatic disease. In some embodiments, the subject has received neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. In some embodiments of the methods provided herein, wherein the subject has ECOG performance status score of 2, the subject (i) has Hemoglobin ≥10 g/dL; (ii) has GFR ≥ 50 mL/min; and (iii) does not have NYHA Class III heart failure.

[00262] Alternatively, other specific conditions based on GFR or creatinine clearance can be used to determine the cisplatin ineligibility for the human subjects for the methods provided herein, including but not limited to the methods of the preceding paragraphs. In some embodiments, embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of GFR less than 60 but no less than 30 mL/min. In one embodiment, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2 and GFR less than 60 but no less than 30 mL/min. In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of GFR less than 60 but no less than 30 mL/min and no less than Grade 2 hearing loss. In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of GFR less than 60 but no less than 30 mL/min and NYHA Class III heart failure. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2, GFR less than 60 but no less than 30 mL/min, and no less than Grade 2 hearing loss. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of GFR less than 60 but no less than 30 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any one of ECOG performance status score of 2, GFR less than 60 but no less than 30 mL/min, and no less than Grade 2 hearing loss. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any one of GFR less than 60 but no less than 30 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any two of ECOG performance status score of 2, GFR less than 60 but no less than 30 mL/min, and no

less than Grade 2 hearing loss, in any combination or permutation. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any two of GFR less than 60 but no less than 30 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure, in any combination or permutation. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of all three of ECOG performance status score of 2, GFR less than 60 but no less than 30 mL/min, and no less than Grade 2 hearing loss. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of all three of GFR less than 60 but no less than 30 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments of the methods provided in this paragraph, the GFR is measured by 24 hour urine collection. In other embodiments of the methods provided in this paragraph, the GFR is estimated by the Cockcroft-Gault criteria. In other embodiments of the methods provided in this paragraph, the GFR is measured by modification of diet in renal disease [MDRD]. In some embodiments of the methods provided herein, the subject did not receive prior systemic treatment for locally advanced or metastatic disease. In some embodiments, the subject has received neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. In some embodiments of the methods provided herein, wherein the subject has ECOG performance status score of 2, the subject (i) has Hemoglobin ≥10 g/dL; (ii) has GFR ≥ 50 mL/min; and (iii) does not have NYHA Class III heart failure.

[00263] In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of CrCl less than 60 but no less than 30 mL/min. In one embodiment, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2 and CrCl less than 60 but no less than 30 mL/min. In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of CrCl less than 60 but no less than 30 mL/min and no less than Grade 2 hearing loss. In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of CrCl less than 60 but no less than 30 mL/min and NYHA Class III heart failure. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2, CrCl less than 60 but no less than 30 mL/min, and no less than Grade 2 hearing loss. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of CrCl less than 60 but no less than 30 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any one of ECOG performance status score of 2, CrCl less than 60 but no less than 30 mL/min, and no less than

Grade 2 hearing loss. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any one of CrCl less than 60 but no less than 30 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any two of ECOG performance status score of 2, CrCl less than 60 but no less than 30 mL/min, and no less than Grade 2 hearing loss, in any combination or permutation. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any two of CrCl less than 60 but no less than 30 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure, in any combination or permutation. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of all three of ECOG performance status score of 2, CrCl less than 60 but no less than 30 mL/min, and no less than Grade 2 hearing loss. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of all three of CrCl less than 60 but no less than 30 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments of the methods provided in this paragraph, the CrCl is measured by 24 hour urine collection. In other embodiments of the methods provided in this paragraph, the CrCl is estimated by the Cockcroft-Gault criteria. In some embodiments of the methods provided herein, the subject did not receive prior systemic treatment for locally advanced or metastatic disease. In some embodiments, the subject has received neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. In some embodiments of the methods provided herein, wherein the subject has ECOG performance status score of 2, the subject (i) has Hemoglobin ≥10 g/dL; (ii) has GFR ≥ 50 mL/min; and (iii) does not have NYHA Class III heart failure.

[00264] Similarly, further specific conditions based on GFR or creatinine clearance can be used to determine the cisplatin ineligibility for the human subjects for the methods provided herein, including but not limited to the methods of the preceding paragraphs. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of GFR less than 30 but no less than 15 mL/min. In one embodiment, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2 and GFR less than 30 but no less than 15 mL/min. In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of GFR less than 30 but no less than 15 mL/min and no less than Grade 2 hearing loss. In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of GFR less than 30 but no less than 15 mL/min, and NYHA Class III heart failure. In yet other embodiments,

the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2, GFR less than 30 but no less than 15 mL/min, and no less than Grade 2 hearing loss. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of GFR less than 30 but no less than 15 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any one of ECOG performance status score of 2, GFR less than 30 but no less than 15 mL/min, and no less than Grade 2 hearing loss. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any one of GFR less than 30 but no less than 15 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any two of ECOG performance status score of 2, GFR less than 30 but no less than 15 mL/min, and no less than Grade 2 hearing loss, in any combination or permutation. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any two of GFR less than 30 but no less than 15 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure, in any combination or permutation. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of all three of ECOG performance status score of 2, GFR less than 30 but no less than 15 mL/min, and no less than Grade 2 hearing loss. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of all three of GFR less than 30 but no less than 15 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments of the methods provided in this paragraph, the GFR is measured by 24 hour urine collection. In other embodiments of the methods provided in this paragraph, the GFR is estimated by the Cockcroft-Gault criteria. In other embodiments of the methods provided in this paragraph, the GFR is measured by modification of diet in renal disease [MDRD]. In some embodiments of the methods provided herein, the subject did not receive prior systemic treatment for locally advanced or metastatic disease. In some embodiments, the subject has received neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. In some embodiments of the methods provided herein, wherein the subject has ECOG performance status score of 2, the subject (i) has Hemoglobin ≥10 g/dL; (ii) has GFR ≥ 50 mL/min; and (iii) does not have NYHA Class III heart failure.

[00265] In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of CrCl less than 30 but no less than 15 mL/min. In one embodiment, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG

performance status score of 2 and CrCl less than 30 but no less than 15 mL/min. In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of CrCl less than 30 but no less than 15 mL/min and no less than Grade 2 hearing loss. In further embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of CrCl less than 30 but no less than 15 mL/min, and NYHA Class III heart failure. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of ECOG performance status score of 2, CrCl less than 30 but no less than 15 mL/min, and no less than Grade 2 hearing loss. In yet other embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of CrCl less than 30 but no less than 15 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any one of ECOG performance status score of 2, CrCl less than 30 but no less than 15 mL/min, and no less than Grade 2 hearing loss. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any one of CrCl less than 30 but no less than 15 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any two of ECOG performance status score of 2, CrCl less than 30 but no less than 15 mL/min, and no less than Grade 2 hearing loss, in any combination or permutation. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of any two of CrCl less than 30 but no less than 15 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure, in any combination or permutation. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of all three of ECOG performance status score of 2, CrCl less than 30 but no less than 15 mL/min, and no less than Grade 2 hearing loss. In some embodiments, the conditions for determining the cisplatin ineligibility comprise or consist of all three of CrCl less than 30 but no less than 15 mL/min, no less than Grade 2 hearing loss, and NYHA Class III heart failure. In some embodiments of the methods provided in this paragraph, the CrCl is measured by 24 hour urine collection. In other embodiments of the methods provided in this paragraph, the CrCl is estimated by the Cockcroft-Gault criteria. In some embodiments of the methods provided herein, the subject did not receive prior systemic treatment for locally advanced or metastatic disease. In some embodiments, the subject has received neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. In some embodiments of the methods provided herein, wherein the subject has ECOG performance status score of 2,

the subject (i) has Hemoglobin ≥10 g/dL; (ii) has GFR ≥ 50 mL/min; and (iii) does not have NYHA Class III heart failure.

[00266] *Cisplatin Eligible Patients*: Various conditions can be used to determine the cisplatin ineligibility (e.g., cisplatin eligible) for the human subjects for the methods provided herein, including but not limited to the methods of the preceding paragraphs. In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of glomerular filtration rate (GFR) or creatinine clearance >60 mL/min (estimated by the Cockcroft-Gault formula, modification of diet in renal disease [MDRD] or 24 hour urine). In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of NCI CTCAE Grade ≤1 audiometric hearing loss. In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of no NYHA Class III heart failure. In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of glomerular filtration rate (GFR) or creatinine clearance >60 mL/min and NCI CTCAE Grade ≤1 audiometric hearing loss. In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of glomerular filtration rate (GFR) or creatinine clearance >60 mL/min and no NYHA Class III heart failure. In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of NCI CTCAE Grade ≤1 audiometric hearing loss and no NYHA Class III heart failure. In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of glomerular filtration rate (GFR) or creatinine clearance >60 mL/min, NCI CTCAE Grade ≤1 audiometric hearing loss, and no NYHA Class III heart failure.

[00267] In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of glomerular filtration rate (GFR) >60 mL/min and NCI CTCAE Grade ≤1 audiometric hearing loss. In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of glomerular filtration rate (GFR) >60 mL/min and no NYHA Class III heart failure. In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of NCI CTCAE Grade ≤1 audiometric hearing loss and no NYHA Class III heart failure. In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of glomerular filtration rate (GFR) >60 mL/min, NCI CTCAE Grade ≤1 audiometric hearing loss, and no NYHA Class III heart failure.

[00268] In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of creatinine clearance >60 mL/min and NCI CTCAE Grade ≤1 audiometric hearing loss. In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of creatinine clearance >60 mL/min and no NYHA Class III

heart failure. In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of NCI CTCAE Grade ≤1 audiometric hearing loss and no NYHA Class III heart failure. In one embodiment, the conditions for determining the cisplatin eligibility comprise or consist of creatinine clearance >60 mL/min, NCI CTCAE Grade ≤1 audiometric hearing loss, and no NYHA Class III heart failure.

5.2.1.2 *Additional Patient Demographics*

[00269] Additionally, the human subjects for whom the methods provided herein can be used are human subjects having various other conditions. In some embodiments, the human subjects are cisplatin eligible or ineligible. In one embodiment, the human subjects for whom the methods provided herein may have histologically documented locally advanced or metastatic urothelial (previously known as transitional cell) cancer (e.g., cancer of the bladder, renal pelvis, ureter, or urethra). In some embodiments, the human subjects for whom the methods provided herein may be eligible for CPI therapy. In certain embodiments, the human subjects for whom the methods provided herein may have measurable disease according to RECIST Version 1.1. In certain embodiments, the human subjects for whom the methods provided herein may have measurable disease according to RECIST Version 1.1 that is outside the radiation field or has demonstrated unequivocal progression since completion of radiation therapy. In certain embodiments, the human subjects for whom the methods provided herein did not receive prior systemic therapy for locally advanced or metastatic cancer. In yet other embodiments, the human subjects for whom the methods provided herein can have ECOG performance status score of 0. In yet other embodiments, the human subjects for whom the methods provided herein can have ECOG performance status score of 1. In yet other embodiments, the human subjects for whom the methods provided herein can have ECOG performance status score of 2. In yet other embodiments, the human subjects for whom the methods provided herein can have ECOG performance status score of 1 to 2. In yet other embodiments, the human subjects for whom the methods provided herein can have ECOG performance status score of 1 or 2. In yet other embodiments, the human subjects for whom the methods provided herein can have ECOG performance status score of 0 to 1. In yet other embodiments, the human subjects for whom the methods provided herein can have ECOG performance status score of 0 or 1. In yet other embodiments, the human subjects for whom the methods provided herein can have ECOG performance status score of 0 to 2. In yet other embodiments, the human subjects for whom the methods provided herein can have ECOG performance status score of 0 or 2. In yet other embodiments, the human subjects for

whom the methods provided herein can have ECOG performance status score of 0, 1, or 2. In one embodiment, the human subjects for whom the methods provided herein may have an anticipated life expectancy of ≥12 weeks. Some embodiments of the methods provided in this paragraph may have any of the preceding embodiments in any combination or permutation.

[00270] In further embodiments of the methods provided herein, including the methods of the preceding paragraphs, the human subjects for whom the methods provided herein can be used are human subjects having various other conditions. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have treated central nervous system (CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof. In some embodiments, the human subjects for whom the methods provided herein can be used also have not received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof. In some embodiments, the human subjects for whom the methods provided herein can be used also (i) have the condition of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) no more than 2.5 fold of ULN, or (ii) have the condition of treated central nervous system (CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof. In some embodiments, the human subjects for whom the methods provided herein can be used also (i) have the condition of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) no more than 2.5 fold of ULN, or (ii) have not received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof. In some embodiments, the human subjects for whom the methods provided herein can be used also (i) have the condition of treated central nervous system (CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof, or (ii) have not received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof. In some embodiments, the human subjects for whom the methods provided herein can be used also (i) have the condition of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) no more than 2.5 fold of ULN, (ii) have the condition of treated central nervous system

(CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof, or (iii) have not received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof. In some embodiments, the human subjects for whom the methods provided herein can be used also (i) have the condition of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) no more than 2.5 fold of ULN, and (ii) have the condition of treated central nervous system (CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof. In some embodiments, the human subjects for whom the methods provided herein can be used also (i) have the condition of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) no more than 2.5 fold of ULN, and (ii) have not received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof. In some embodiments, the human subjects for whom the methods provided herein can be used also (i) have the condition of treated central nervous system (CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof, and (ii) have not received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof. In some embodiments, the human subjects for whom the methods provided herein can be used also (i) have the condition of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) no more than 2.5 fold of ULN, (ii) have the condition of treated central nervous system (CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof, and (iii) have not received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof. In some embodiments, the human subjects for whom the methods provided herein can be used also (i) have the condition of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) no more than 2.5 fold of ULN, (ii) have the condition of treated central nervous system (CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof, and/or (iii) have not received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof.

[00271] In further embodiments of the methods provided herein, including the methods of the preceding paragraphs, the human subjects for whom the methods provided herein can be used are human subjects having various other conditions. In one embodiment, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count (ANC) no less than 1500/μL. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 5.6 mmol/L. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 5.6 mmol/L. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of total bilirubin no more than either of 1.5 times of upper limit of normal (ULN), direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of CrCl no less than 30 mL/min. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of GFR no less than 30 mL/min. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of CrCl or GFR no less than 30 mL/min. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the condition of CrCl no less than 30 mL/min, wherein the subjects have total bilirubin levels >1.5× institutional ULN and/or ≤1.5 ULN. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the condition of GFR no less than 30 mL/min, wherein the subjects have total bilirubin levels >1.5× institutional ULN and/or ≤1.5 ULN. In another embodiment, the human subjects for whom the methods provided herein can be used also have the conditions of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) no more than 2.5 fold of ULN. In one embodiment, the human

subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL and platelet count no less than 100,000/μL. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL and hemoglobin no less than 9 g/dL or 5.6 mmol/L. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL and total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, and CrCl or GFR no less than 30 mL/min. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL and CrCl no less than 30 mL/min, wherein the subjects have total bilirubin levels >1.5× institutional ULN and/or ≤1.5 ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL and ALT and AST no more than 2.5 fold of ULN. In further embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL and hemoglobin no less than 9 g/dL or 5.6 mmol/L. In one embodiment, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL and total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL and CrCl or GFR no less than 30 mL/min. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL and ALT and AST no more than 2.5 fold of ULN. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L and total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease. In yet other embodiments,

the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L and CrCl or GFR no less than 30 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L and ALT and AST no more than 2.5 fold of ULN. In one embodiment, the human subjects for whom the methods provided herein can be used also have the conditions of total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease and CrCl no less than 30 mL/min. In another embodiment, the human subjects for whom the methods provided herein can be used also have the conditions of total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease and ALT and AST no more than 2.5 fold of ULN. In another embodiment, the human subjects for whom the methods provided herein can be used also have the conditions of CrCl or GFR no less than 30 mL/min and ALT and AST no more than 2.5 fold of ULN. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, and hemoglobin no less than 9 g/dL or 5.6 mmol/L. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL and total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease. In further embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, and CrCl or GFR no less than 30 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L and total bilirubin no more than either of 1.5 times of ULN or 3 times ULN for patients with Gilbert's disease. In certain

embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and CrCl or GFR no less than 30 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and ALT and AST no more than 2.5 fold of ULN. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and CrCl or GFR no less than 30 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and CrCl or GFR no less than 30 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and ALT and AST no more than 2.5 fold of ULN. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients

with Gilbert's disease, and CrCl or GFR no less than 30 mL/min. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and CrCl or GFR no less than 30 mL/min. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and ALT and AST no more than 2.5 fold of ULN. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease. In further embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute

neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and CrCl or GFR no less than 30 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and CrCl or GFR no less than 30 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and CrCl or GFR no less than 30 mL/min. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and ALT and AST no more than 2.5 fold of ULN. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, CrCl or GFR no less than 30

mL/min, and ALT and AST no more than 2.5 fold of ULN. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In further embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and CrCl or GFR no less than 30 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and ALT and AST no more than 2.5 fold of ULN. In further embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less

than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and CrCl or GFR no less than 30 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than

1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of any one of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of any two of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN, in any combination or permutation. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of any three of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN, in any combination or permutation. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of any four of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN, in any combination or permutation. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of any five of absolute neutrophil count no less than 1500/μL, platelet count no less than

100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN, in any combination or permutation. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of all six of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR no less than 30 mL/min, and ALT and AST no more than 2.5 fold of ULN.

[00272] In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the condition of CrCl >60 mL/min, wherein the subjects have total bilirubin levels >1.5× institutional ULN and/or ⩽1.5 ULN. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the condition of GFR >60 mL/min, wherein the subjects have total bilirubin levels >1.5× institutional ULN and/or ⩽1.5 ULN. In another embodiment, the human subjects for whom the methods provided herein can be used also have the conditions of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) no more than 2.5 fold of ULN. In one embodiment, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL and platelet count no less than 100,000/μL. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL and hemoglobin no less than 9 g/dL or 5.6 mmol/L. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL and total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ⩽ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, and CrCl or GFR >60 mL/min. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute

neutrophil count no less than 1500/μL and CrCl >60 mL/min, wherein the subjects have total bilirubin levels >1.5× institutional ULN and/or ⩽1.5 ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL and ALT and AST no more than 2.5 fold of ULN. In further embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL and hemoglobin no less than 9 g/dL or 5.6 mmol/L. In one embodiment, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL and total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ⩽ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL and CrCl or GFR >60 mL/min. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL and ALT and AST no more than 2.5 fold of ULN. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L and total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ⩽ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L and CrCl or GFR >60 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L and ALT and AST no more than 2.5 fold of ULN. In one embodiment, the human subjects for whom the methods provided herein can be used also have the conditions of total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ⩽ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease and CrCl >60 mL/min. In another embodiment, the human subjects for whom the methods provided herein can be used also have the conditions of total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ⩽ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3

times ULN for patients with Gilbert's disease and ALT and AST no more than 2.5 fold of ULN. In another embodiment, the human subjects for whom the methods provided herein can be used also have the conditions of CrCl or GFR >60 mL/min and ALT and AST no more than 2.5 fold of ULN. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, and hemoglobin no less than 9 g/dL or 5.6 mmol/L. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL and total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease. In further embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, and CrCl or GFR >60 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L and total bilirubin no more than either of 1.5 times of ULN or 3 times ULN for patients with Gilbert's disease. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and CrCl or GFR >60 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and ALT and AST no more than 2.5 fold of ULN. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and CrCl or GFR >60 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, total bilirubin no more

than either of 1.5 times of ULN, direct bilirubin ⩽ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ⩽ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and CrCl or GFR >60 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and ALT and AST no more than 2.5 fold of ULN. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ⩽ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and CrCl or GFR >60 mL/min. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ⩽ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ⩽ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and CrCl or GFR >60

mL/min. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and ALT and AST no more than 2.5 fold of ULN. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease. In further embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and CrCl or GFR >60 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and CrCl or GFR >60 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤

ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and CrCl or GFR >60 mL/min. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and ALT and AST no more than 2.5 fold of ULN. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In yet other embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert' s disease, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In further embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and CrCl or GFR >60 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN,

direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and ALT and AST no more than 2.5 fold of ULN. In further embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and CrCl or GFR >60 mL/min. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In certain embodiments, the human

subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In certain embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of any one of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of any two of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL,

hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN, in any combination or permutation. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of any three of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN, in any combination or permutation. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of any four of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN, in any combination or permutation. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of any five of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN, in any combination or permutation. In some embodiments, the human subjects for whom the methods provided herein can be used also have the conditions of all six of absolute neutrophil count no less than 1500/μL, platelet count no less than 100,000/μL, hemoglobin no less than 9 g/dL or 5.6 mmol/L, total bilirubin no more than either of 1.5 times of ULN, direct bilirubin ≤ ULN, wherein the human subjects have the conditions of total bilirubin levels >1.5 × ULN, or total bilirubin 3 times ULN for patients with Gilbert's disease, CrCl or GFR >60 mL/min, and ALT and AST no more than 2.5 fold of ULN.

[00273] In certain embodiments, including any of the embodiments disclosed herein, such as any of the above embodiments, the human subjects for whom the methods provided herein may have treated central nervous system (CNS) metastases that have been clinically stable

for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof. In certain embodiments, the human subjects (1) may have treated central nervous system (CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof, and (2) have the condition of ALT and AST no more than 2.5 fold of ULN. In certain embodiments, the human subjects (1) may have treated central nervous system (CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof, (2) have the condition of ALT and AST no more than 2.5 fold of ULN, and (3) may not have received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof.

[00274] In certain embodiments, including any of the embodiments disclosed herein, such as any of the above embodiments, the human subjects for whom the methods provided herein may not have received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof. In certain embodiments, the human subjects (1) may have treated central nervous system (CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof, and (2) may not have received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof.

[00275] In certain embodiments, the human subjects for whom the methods provided herein may have previously had prostate cancer treated surgically or with radiation therapy at least 1 year prior to treatment with any of the methods provided herein, wherein the subject is prostate cancer-free and wherein (i) if the subject has undergone or received radical prostatectomy, the subject must have undetectable PSA for >1 year prior to treatment with any of the methods provided herein, (ii) if the subject has received radiation, the subject has a PSA doubling time >1 year (based on at least 3 values determined >1 month apart) and a total PSA value that does not meet Phoenix criteria for biochemical recurrence (e.g., <2.0 ng/mL above nadir). In certain embodiments, the human subjects for whom the methods provided herein may have untreated low-risk prostate cancer, wherein the subject has a Gleason score ≤6, on active surveillance with PSA doubling time >1 year (based on at least 3 values determined >1 month apart).

[00276] In other embodiments of the methods provided herein, including the methods of the preceding paragraphs, the human subjects for whom the methods provided herein can be

used are human subjects free from certain conditions. In one embodiment, the human subjects for whom the methods provided herein have not received any prior treatment with a CPI. A CPI is defined as a PD-1 inhibitor, PD-L1 inhibitor, or PD-L2 inhibitor (including, but not limited to, atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab). In some embodiments, the human subjects for whom the methods provided herein have not received a PD-1 inhibitor, PD-L1 inhibitor, or PD-L2 inhibitor. In certain embodiments, the human subjects for whom the methods provided herein have not received atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab. In certain embodiments, the human subject treated with the methods provided herein has not received previous treatment that includes or consists of an PD-(L)-1 inhibitor. A PD-(L)-1 inhibitor is a PD-1 inhibitor or PD-L1 inhibitor. In some embodiments, the PD-(L)-1 inhibitor is an anti-PD-1 antibody (e.g., pembrolizumab). In some embodiments, the PD-(L)-1 inhibitor is a PD-1 inhibitor or PD-L1 inhibitor. In particular embodiments, the PD-(L)-1 inhibitor is atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab. In certain embodiments, the human subjects for whom the methods provided herein have not received any prior treatment with an agent directed to another stimulatory or co inhibitory T-cell receptor (including, but not limited to, CD137 agonists, CTLA 4 inhibitors, or OX-40 agonists). In certain embodiments, the human subjects for whom the methods provided herein have not received any prior treatment with CD137 agonists, CTLA 4 inhibitors, or OX-40 agonists. In certain embodiments, the human subjects have received anti-cancer treatment with chemotherapy, biologics, or inventigational agents, wherein the human subjects have completed the anti-cancer treatment 4 or more weeks prior to receiving a first dose of an antibody drug conjugate (ADC) that binds 191P4D12 in combination with an anti-PD-1 antibody (e.g., pembrolizumab). In one embodiment, the human subjects for whom the methods provided herein can have no more than Grade 2 sensory or motor neuropathy. In one embodiment, the human subjects for whom the methods provided herein can have no active central nervous system metastases. In one embodiment, the human subjects for whom the methods provided herein can have no uncontrolled diabetes. In one embodiment, the human subjects for whom the methods provided herein can have no more than Grade 2 sensory or motor neuropathy and no active central nervous system metastases. In some embodiments, the human subjects for whom the methods provided herein can have no more than Grade 2 sensory or motor neuropathy and no uncontrolled diabetes. In yet other embodiments, the human subjects for whom the methods provided herein can have no more than Grade 2 sensory or motor neuropathy no active central nervous system metastases, and no uncontrolled diabetes. In

some embodiments, the human subjects for whom the methods provided herein can have any one of no more than Grade 2 sensory or motor neuropathy, no active central nervous system metastases, and no uncontrolled diabetes. In some embodiments, the human subjects for whom the methods provided herein can have any two of no more than Grade 2 sensory or motor neuropathy, no active central nervous system metastases, and no uncontrolled diabetes, in any combination or permutation. In some embodiments, the human subjects for whom the methods provided herein can have all three of no more than Grade 2 sensory or motor neuropathy, no active central nervous system metastases, and no uncontrolled diabetes. In one embodiment of the methods provided in this paragraph, the uncontrolled diabetes is determined by hemoglobin A1c (HbA1c) no less than 8%. In some embodiments of the methods provided in this paragraph, the uncontrolled diabetes is determined by HbA1c between 7 and 8% with associated diabetes symptoms that are not otherwise explained. In further embodiments of the methods provided in this paragraph, the associated diabetes symptoms comprise or consist of polyuria. In some other embodiments of the methods provided in this paragraph, the associated diabetes symptoms comprise or consist of polydipsia. In yet other embodiments of the methods provided in this paragraph, the associated diabetes symptoms comprise or consist of both polyuria and polydipsia.

[00277] In certain embodiments, the human subjects for whom the methods provided herein may have no ongoing clinically significant toxicity associated with prior treatment that has not resolved to ≤ Grade 1 or returned to baseline. In certain embodiments, the human subjects for whom the methods provided herein may have no ongoing clinically significant toxicity associated with prior treatment that has not resolved to ≤ Grade 1 or returned to baseline, wherein the prior treatment is radiotherapy or surgery. In certain embodiments, the prior treatment is radiotherapy. In certain embodiments, the prior treatment is surgery. In one embodiment, the human subjects for whom the methods provided herein may have no conditions requiring high doses of steroids (e.g., >10 mg/day of prednisone or equivalent) or other immunosuppressive medications. In one embodiment, the human subjects for whom the methods provided herein may have no conditions requiring high doses of steroids or other immunosuppressive medications, wherein the steroids or other immunosuppressive medications are not inhaled or topical steroids. In certain embodiments, the human subjects for whom the methods provided herein may have no history of another invasive malignancy within 3 years before treatment with the methods provided herein. In certain embodiments, the human subjects for whom the methods provided herein may have no evidence of residual disease from a previously diagnosed malignancy. In certain embodiments, the human

subjects for whom the methods provided herein may not receive systemic antimicrobial treatment for active infection, wherein the infection is a viral, bacterial, or fungal infection. In certain embodiments, the human subjects for whom the methods provided herein does not have active hepatitis B, wherein the hepatitis B is HBsAg reactive. In certain embodiments, the human subjects for whom the methods provided herein may have no active hepatitis C infection or known human immunodeficiency virus (HIV) infection. In certain embodiments, the human subjects for whom the methods provided herein may have no active tuberculosis. In certain embodiments, the human subjects for whom the methods provided herein may have no documented history of a cerebral vascular event (e.g., a stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with NYHA Class IV. In certain embodiments, the human subjects for whom the methods provided herein may have no radiotherapy within 2 weeks prior to treatment or major surgery within 4 weeks prior to treatment with the methods provided herein. In certain embodiments, the human subjects for whom the methods provided herein may have no treatment with chemotherapy, biologics, or investigational agents not completed 4 weeks prior to treatment with the methods provided herein. In certain embodiments, the human subjects for whom the methods provided herein may have no known severe (≥ Grade 3) hypersensitivity to enfortumab vedotin or to any excipient contained in the drug formulation of enfortumab vedotin (including histidine, trehalose dihydrate, and polysorbate 20). In certain embodiments, the human subjects for whom the methods provided herein may have no known severe (≥ Grade 3) hypersensitivity to pembrolizumab or to any excipient contained in the drug formulations of pembrolizumab. In certain embodiments, the human subjects for whom the methods provided herein may have no known severe (≥ Grade 3) hypersensitivity to gemcitabine. In certain embodiments, the human subjects for whom the methods provided herein may have no active keratitis or corneal ulcerations. In certain embodiments, the human subjects for whom the methods provided herein may have no active autoimmune disease that has required systemic treatment in past 2 years (e.g., use of disease modifying agents, corticosteroids, or immunosuppressive drugs). In certain embodiments, the human subjects for whom the methods provided herein may have no active autoimmune disease that has required systemic treatment in past 2 years, wherein the systemic treatment comprises disease modifying agents, corticosteroids, or immunosuppressive drugs. In some embodiments, the systemic treatment is not replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency). In some embodiments, the systemic treatment is not thyroxine, insulin, or physiologic

corticosteroid replacement therapy for adrenal or pituitary insufficiency. In some embodiments, the systemic treatment is not corticosteroids, wherein the corticosteroids are administered for less than 7 days. In some embodiments, the human subjects have vitiligo, psoriasis, type 1 diabetes mellitus, hypothyroidism, or resolved childhood asthma/atopy. In some embodiments, the systemic treatment is not bronchodilators, inhaled steroids, or local steroids administered by injection. In some embodiments, the human subjects have hypothyroidism, wherein the hypothyroidism is stable with hormone replacement therapy. In some embodiments, the human subjects have Sjogren's syndrome. In certain embodiments, the human subjects for whom the methods provided herein may have no history of idiopathic pulmonary fibrosis; organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. In certain embodiments, the human subjects for whom the methods provided herein may have no prior allogeneic stem cell or solid organ transplant. In certain embodiments, the human subjects for whom the methods provided herein may not have received a live, attenuated vaccine within 30 days prior to treatment with the methods provided herein. In particular, embodiments, the live vaccine is a measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette Guerin (BCG), or typhoid vaccine. In particular, embodiments, the live, attenuated vaccine is an intranasal influenza vaccine. In certain embodiments, the human subjects for whom the methods provided herein may have no underlying medical condition that impairs the ability of the subject to receive or tolerate the methods provided herein.

[00278] In some embodiments of the methods provided herein, the CrCl is measured by 24 hour urine collection. In other embodiments of the methods provided herein, the CrCl is estimated by the Cockcroft-Gault criteria.

[00279] In some embodiments of the methods provided herein, the GFR is measured by 24 hour urine collection. In other embodiments of the methods provided herein, the GFR is estimated by the Cockcroft-Gault criteria. In other embodiments of the methods provided in this paragraph, the GFR is measured by modification of diet in renal disease [MDRD].

[00280] In some embodiments of the methods provided herein, the subject has been treated with one or more other cancer treatments. In certain embodiments of the methods provided herein, the urothelial cancer, including locally advanced or metastatic urothelial cancer, has been treated with one or more other cancer treatments.

[00281] In some embodiments, the CPI described herein can comprise or consist of any CPI as described in this Section (Section 5.2.1).

[00282] In all the methods provided herein and specifically those described in the preceding paragraphs: the ADCs that can be used are described in Sections 3, 5.2, 5.3, 5.4, 5.5, and 6, selection of patients for treatment is described herein and exemplified in this Section (Section 5.2) and Sections 3 and 6, dosing regimens and pharmaceutical composition for administering the therapeutic agent are described in this Section (Section 5.2), Sections5.4, 5.6, 5.7 and 6 below, the biomarkers that can be used for identifying the therapeutic agents, selecting the patients, determining the outcome of these methods, and/or serving as criteria in any way for these methods are described herein and exemplified in this Section (Section 5.2, including 5.2.1 and 5.2.2) and Section 6, the biomarkers can be determined as described in Section 5.9 or as known in the art, therapeutic outcomes for the methods provided herein are described in this Section (Section 5.2 including Section 5.2.1.4) and Sections 3 and 6, additional therapeutic outcomes for the methods provided herein can be improvement of the biomarkers described herein, for example, those described and exemplified in this Section (Section 5.2 including 5.2.2) and Sections 3 and 6, and combination therapies including the ADCs and other therapeutic agents are described in this Section (Section 5.2) and in Section 5.5. Therefore, a person skilled in the art would understand that the methods provided herein include all permutations and combinations of the patients, therapeutic agents, dosing regiments, biomarkers, and therapeutic outcomes as described above and below.

[00283] In certain embodiments, the methods provided herein are used for treating subjects having urothelial cancers that express 191P4D12 RNA, express 191P4D12 protein, or express both 191P4D12 RNA and 191P4D12 protein. In one embodiment, the methods provided herein are used for treating subjects who have urothelial cancers that express 191P4D12 RNA, express 191P4D12 protein, or express both 191P4D12 RNA and 191P4D12 protein.

[00284] In certain embodiments, the methods provided herein are used for treating subjects having locally advanced urothelial cancers that express 191P4D12 RNA, express 191P4D12 protein, or express both 191P4D12 RNA and 191P4D12 protein. In one embodiment, the methods provided herein are used for treating subjects who have locally advanced urothelial cancers that express 191P4D12 RNA, express 191P4D12 protein, or express both 191P4D12 RNA and 191P4D12 protein and who have been previously treated with a CPI or a PD-(L)-1 inhibitor.

[00285] In certain embodiments, the methods provided herein are used for treating subjects having metastatic cancers that express 191P4D12 RNA, express 191P4D12 protein, or

express both 191P4D12 RNA and 191P4D12 protein. In one embodiment, the methods provided herein are used for treating subjects who have metastatic urothelial cancers that express 191P4D12 RNA, express 191P4D12 protein, or express both 191P4D12 RNA and 191P4D12 protein.

[00286] In some embodiments, the 191P4D12 RNA expression in the cancers is determined by polynucleotide hybridization, sequencing (assessing the relative abundance of the sequences), and/or PCR (including RT-PCR). In some embodiments, the 191P4D12 protein expression in the cancers is determined by IHC, analysis in fluorescence-activated cell sorting (FACS), and/or western blotting. In some embodiments, the 191P4D12 protein expression in the cancers is determined by more than one method. In some embodiments, the 191P4D12 protein expression in the cancers is determined by two methods of IHC.

[00287] In some embodiments, the locally advanced or metastatic urothelial cancers are confirmed histologically, cytologically, or both histologically and cytologically. In some embodiments, the locally advanced or metastatic bladder cancers are confirmed histologically, cytologically, or both histologically and cytologically.

[00288] In some embodiments, the subject has visceral metastases. In some embodiments, the subject has lymph nodes only disease. In some embodiments, the disease site of origin is in the upper tract. In some embodiments, the disease site of origin is in the lower tract.

[00289] In some embodiments, the subject has a PD-L1 expression combined positive score (CPS) greater than or equal to 10. PD-L1 protein expression is determined by using the Combined Positive Score (CPS), which is the number of PD-L1 positive cells (i.e., tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, and then multiplied by 100. In some embodiments, the subject has a PD-L1 expression CPS less than 10. Nectin H-scores range from 0-300, based upon the following calculation: H-score = [(0 x % negative cells) + (1 x %weakly positive cells) + (2 x %moderately positive cells) + (3 x %strongly positive cells)]. Urothelial cancer generally has a median H-score from 260-270. In some embodiments, the subject has a Nectin-4 H-score between 0 and 300. In some embodiments, the subject has a Nectin-4 H-score between 0 and 250, between 0 and 200, between 0 and 150, between 0 and 100, or between 0 and 50. In some embodiments, the subject has a Nectin-4 H-score between 0 and 200. In some embodiments, the subject has a Nectin-4 H-score between 0 and 150. In some embodiments, the method does not comprise determining PD-L1 expression or Nectin-4 expression of the subject. In some embodiments, the method does not comprise determining PD-L1 expression or Nectin-4 expression of the subject prior to treatment of the subject with the ADC. In some embodiments, the method

does not comprise determining PD-L1 expression of the subject. In some embodiments, the method does not comprise determining PD-L1 expression of the subject prior to treatment of the subject with the ADC. In some embodiments, the method does not comprise determining Nectin-4 expression of the subject. In some embodiments, the method does not comprise determining Nectin-4 expression of the subject prior to treatment of the subject with the ADC.

5.2.1.3 *Checkpoint Inhibitors and Combination Therapy with Pembrolizumab*

[00290] Checkpoint Inhibitors

[00291] In some embodiments, the subjects that can be treated in the methods provided herein have certain phenotypic or genotypic characteristics. In some embodiments, the subjects have any permutation and combination of the phenotypic or genotypic characteristics described herein.

[00292] In some embodiments, the phenotypic or genotypic characteristics are determined histologically, cytologically, or both histologically and cytologically. In some embodiments of methods provided herein, the histological and/or the cytological determination of the phenotypic and/or genotypic characteristics are performed as described in American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines based on the most recently analyzed tissue, which is incorporated herein in their entirety by reference. In some embodiments, the phenotypic or genotypic characteristics are determined by sequencing including the next generation sequencing (*e.g.* NGS from Illumina, Inc), DNA hybridization, and/or RNA hybridization.

[00293] In various aspects or embodiments of the methods provided herein, including the methods provided in this Section (Section 5.2) such as the methods provided in this and the preceding paragraphs, the human subjects for whom the methods are provided herein have not received any prior treatment with a CPI. A CPI is defined as a PD-1 inhibitor, PD-L1 inhibitor, or PD-L2 inhibitor (including, but not limited to, atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab). In some embodiments, the human subjects for whom the methods provided herein have not received prior treatment with a PD-1 inhibitor, PD-L1 inhibitor, or PD-L2 inhibitor. In certain embodiments, the human subjects for whom the methods provided herein have not received prior treatment with atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab.

[00294] In various aspects or embodiments of the methods provided herein, including the methods provided in this Section (Section 5.2) such as the methods provided in this and the

preceding paragraphs, the human subjects for whom the methods are provided herein have not received any prior treatment with a PD-(L)-1 inhibitor. A PD-(L)-1 inhibitor is defined as a PD-1 inhibitor or PD-L1 inhibitor (including, but not limited to, atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab). Thus, PD-(L)-1 inhibitors include CPI inhibitors that are PD-1 inhibitors or PD-L1 inhibitors. In some embodiments, the human subjects for whom the methods provided herein have not received prior treatment with a PD-1 inhibitor or a PD-L1 inhibitor. In certain embodiments, the human subjects for whom the methods provided herein have not received prior treatment with atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab.

[00295] As used herein, the term "immune checkpoint inhibitor" or "checkpoint inhibitor" (CPI) refers to molecules that totally or partially reduce, inhibit, interfere with or modulate one or more checkpoint proteins. Numerous checkpoint proteins are known, such as CTLA-4 and its ligands CD80 and CD86; and PD-1 with its ligands PD-Ll and PD-L2 (Pardoll, *Nature Reviews Cancer*, **2012**, *12*, 252-264). Other exemplary checkpoint proteins include LAG-3, B7, TIM3 (HAVCR2), OX40 (CD134), GITR, CD137, CD40, VTCN1, IDO1, CD276, PVRIG, TIGIT, CD25 (IL2RA), IFNAR2, IFNAR1, CSF1R, VSIR (VISTA), or HLA. These proteins appear responsible for co-stimulatory or inhibitory interactions of T-cell responses. Immune checkpoint proteins appear to regulate and maintain self-tolerance and the duration and amplitude of physiological immune responses. Immune checkpoint inhibitors include antibodies or are derived from antibodies.

[00296] In certain embodiments, the checkpoint inhibitor for the methods provided herein can be an inhibitors or activators against a checkpoint protein that upregulated in cancer. In some specific embodiments, the checkpoint inhibitor for the methods provided herein can be an inhibitors or activators against a checkpoint protein including LAG-3, B7, TIM3 (HAVCR2), OX40 (CD134), GITR, CD137, CD40, VTCN1, IDO1, CD276, PVRIG, TIGIT, CD25 (IL2RA), IFNAR2, IFNAR1, CSF1R, VSIR (VISTA), or HLA. In some embodiments, the checkpoint inhibitor for the methods provided herein can be an inhibitors or activators selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, a CTLA-4 inhibitor, a LAG-3 inhibitor, a B7 inhibitor, a TIM3 (HAVCR2) inhibitor, an OX40 (CD134) inhibitor, a GITR agonist, a CD137 agonist, or a CD40 agonist, a VTCN1 inhibitor, an IDO1 inhibitor, a CD276 inhibitor, a PVRIG inhibitor, a TIGIT inhibitor, a CD25 (IL2RA) inhibitor, an IFNAR2 inhibitor, an IFNAR1 inhibitor, a CSF1R inhibitor, a VSIR (VISTA) inhibitor, or a therapeutic agent targeting HLA. Such inhibitors, activators, or therapeutic agents are further provided below.

[00297] In some embodiments, the checkpoint inhibitor is a CTLA-4 inhibitor. In one embodiment, the CTLA-4 inhibitor is an anti-CTLA-4 antibody. Examples of anti-CTLA-4 antibodies include, but are not limited to, those described in US Patent Nos: 5,811,097; 5,811,097; 5,855,887; 6,051,227; 6,207,157; 6,682,736; 6,984,720; and 7,605,238, all of which are incorporated herein in their entireties. In one embodiment, the anti-CTLA-4 antibody is tremelimumab (also known as ticilimumab or CP-675,206). In another embodiment, the anti-CTLA-4 antibody is ipilimumab (also known as MDX-010 or MDX-101). Ipilimumab is a fully human monoclonal IgG antibody that binds to CTLA-4. Ipilimumab is marketed under the trade name Yervoy™.

[00298] In certain embodiments, the checkpoint inhibitor is a PD-1/PD-L1 inhibitor. Examples of PD-l/PD-L1 inhibitors include, but are not limited to, those described in US Patent Nos. 7,488,802; 7,943,743; 8,008,449; 8,168,757; 8,217,149, and PCT Patent Application Publication Nos. WO2003042402, WO2008156712, WO2010089411, WO2010036959, WO2011066342, WO2011159877, WO2011082400, and WO2011161699, all of which are incorporated herein in their entireties.

[00299] "PD-1 antagonist" means any chemical compound or biological molecule that blocks binding of PD-L1 expressed on a cancer cell to PD-1 expressed on an immune cell (T cell, B cell or Natural Killer T cell) and in specific embodiments also blocks binding of PD-L2 expressed on a cancer cell to the immune-cell expressed PD-1. Alternative names or synonyms for PD-1 and its ligands include: PDCD1, PD1, CD279 and SLEB2 for PD-1; PDCD1L1, PDL1, B7H1, B7-4, CD274 and B7-H for PD-L1; and PDCD1L2, PDL2, B7-DC, Btdc and CD273 for PD-L2. In any of the treatment method, medicaments and uses of the present invention in which a human individual is being treated, the PD-1 antagonist blocks binding of human PD-L1 to human PD-1, and in specific embodiments blocks binding of both human PD-L1 and PD-L2 to human PD-1. Human PD-1 amino acid sequences can be found in NCBI Locus No.: NP_005009. Human PD-L1 and PD-L2 amino acid sequences can be found in NCBI Locus No.: NP_054862 and NP_079515, respectively.

[00300] In some embodiments, the checkpoint inhibitor is a PD-1 inhibitor or antagonist. In one embodiment, the PD-1 inhibitor or antagonist is an anti-PD-1 antibody. In one embodiment, the anti-PD-1 antibody is BGB-A317, nivolumab (also known as ONO-4538, BMS-936558, or MDX1106) or pembrolizumab (also known as MK-3475, SCH 900475, or lambrolizumab). In one embodiment, the anti-PD-1 antibody is nivolumab. Nivolumab is a human IgG4 anti-PD-1 monoclonal antibody, and is marketed under the trade name Opdivo™. In another embodiment, the anti-PD-1 antibody is pembrolizumab.

Pembrolizumab is a humanized monoclonal IgG4 antibody and is marketed under the trade name Keytruda™. In yet another embodiment, the anti-PD-1 antibody is CT-011, a humanized antibody. CT-011 administered alone has failed to show response in treating acute myeloid leukemia (AML) at relapse. In yet another embodiment, the anti-PD-1 antibody is AMP-224, a fusion protein. In another embodiment, the PD-1 antibody is BGB-A317. BGB-A317 is a monoclonal antibody in which the ability to bind Fc gamma receptor I is specifically engineered out, and which has a unique binding signature to PD-1 with high affinity and superior target specificity. In one embodiment, the PD-1 antibody is cemiplimab. In another embodiment, the PD-1 antibody is camrelizumab. In a further embodiment, the PD-1 antibody is sintilimab. In some embodiments, the PD-1 antibody is tislelizumab. In certain embodiments, the PD-1 antibody is TSR-042. In yet another embodiment, the PD-1 antibody is PDR001. In yet another embodiment, the PD-1 antibody is toripalimab.

[00301] In certain embodiments, the checkpoint inhibitor is a PD-L1 inhibitor. In one embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody. In one embodiment, the anti-PD-L1 antibody is MEDI4736 (durvalumab). In another embodiment, the anti-PD-L1 antibody is BMS-936559 (also known as MDX-1105-01). In yet another embodiment, the PD-L1 inhibitor is atezolizumab (also known as MPDL3280A, and Tecentriq®). In a further embodiment, the PD-L1 inhibitor is avelumab.

[00302] In one embodiment, the checkpoint inhibitor is a PD-L2 inhibitor. In one embodiment, the PD-L2 inhibitor is an anti-PD-L2 antibody. In one embodiment, the anti-PD-L2 antibody is rHIgM12B7A.

[00303] In one embodiment, the checkpoint inhibitor is a lymphocyte activation gene-3 (LAG-3) inhibitor. In one embodiment, the LAG-3 inhibitor is IMP321, a soluble Ig fusion protein (Brignone *et al.*, *J. Immunol.*, **2007**, *179*, 4202-4211). In another embodiment, the LAG-3 inhibitor is BMS-986016.

[00304] In one embodiment, the checkpoint inhibitors is a B7 inhibitor. In one embodiment, the B7 inhibitor is a B7-H3 inhibitor or a B7-H4 inhibitor. In one embodiment, the B7-H3 inhibitor is MGA271, an anti-B7-H3 antibody (Loo *et al.*, *Clin. Cancer Res.*, **2012**, 3834).

[00305] In one embodiment, the checkpoint inhibitors is a TIM3 (T-cell immunoglobulin domain and mucin domain 3) inhibitor (Fourcade *et al.*, *J. Exp. Med.*, **2010**, *207*, 2175-86; Sakuishi *et al.*, *J. Exp. Med.*, **2010**, *207*, 2187-94).

[00306] In one embodiment, the checkpoint inhibitor is an OX40 (CD134) agonist. In one embodiment, the checkpoint inhibitor is an anti-OX40 antibody. In one embodiment, the anti-

OX40 antibody is anti-OX-40. In another embodiment, the anti-OX40 antibody is MEDI6469.

[00307] In one embodiment, the checkpoint inhibitor is a GITR agonist. In one embodiment, the checkpoint inhibitor is an anti-GITR antibody. In one embodiment, the anti-GITR antibody is TRX518.

[00308] In one embodiment, the checkpoint inhibitor is a CD137 agonist. In one embodiment, the checkpoint inhibitor is an anti-CD137 antibody. In one embodiment, the anti-CD137 antibody is urelumab. In another embodiment, the anti-CD137 antibody is PF-05082566.

[00309] In one embodiment, the checkpoint inhibitor is a CD40 agonist. In one embodiment, the checkpoint inhibitor is an anti-CD40 antibody. In one embodiment, the anti-CD40 antibody is CF-870,893.

[00310] In one embodiment, the checkpoint inhibitor is recombinant human interleukin-15 (rhIL-15).

[00311] In one embodiment, the checkpoint inhibitor is a VTCN inhibitor. In one embodiment, the VTCN inhibitor is FPA150.

[00312] In one embodiment, the checkpoint inhibitor is an IDO inhibitor. In one embodiment, the IDO inhibitor is INCB024360. In another embodiment, the IDO inhibitor is indoximod. In one embodiment, the IDO inhibitor is epacadostat. In another embodiment, the IDO inhibitor is BMS986205. In yet another embodiment, the IDO inhibitor is Navoximod. In one embodiment, the IDO inhibitor is PF-06840003. In another embodiment, the IDO inhibitor is KHK2455. In yet another embodiment, the IDO inhibitor is RG70099. In one embodiment, the IDO inhibitor is IOM-E. In another embodiment, the IDO inhibitor is or IOM-D.

[00313] In some embodiments, the checkpoint inhibitor is a TIGIT inhibitor. In certain embodiments, the TIGIT inhibitor is an anti-TIGIT antibody. In one embodiment, the TIGIT inhibitor is MTIG7192A. In another embodiment, the TIGIT inhibitor is BMS-986207. In yet another embodiment, the TIGIT inhibitor is OMP-313M32. In one embodiment, the TIGIT inhibitor is MK-7684. In another embodiment, the TIGIT inhibitor is AB154. In yet another embodiment, the TIGIT inhibitor is CGEN-15137. In one embodiment, the TIGIT inhibitor is SEA-TIGIT. In another embodiment, the TIGIT inhibitor is ASP8374. In yet another embodiment, the TIGIT inhibitor is AJUD008.

[00314] In some embodiments, the checkpoint inhibitor is a VSIR inhibitor. In certain embodiments, the VSIR inhibitor is an anti-VSIR antibody. In one embodiment, the VSIR

inhibitor is MTIG7192A. In another embodiment, the VSIR inhibitor is CA-170. In yet another embodiment, the VSIR inhibitor is JNJ 61610588. In one embodiment, the VSIR inhibitor is HMBD-002.

[00315] In some embodiments, the checkpoint inhibitor is a TIM3 inhibitor. In certain embodiments, the TIM3 inhibitor is an anti-TIM3 antibody. In one embodiment, the TIM3 inhibitor is AJUD009.

[00316] In some embodiments, the checkpoint inhibitor is a CD25 (IL2RA) inhibitor. In certain embodiments, the CD25 (IL2RA) inhibitor is an anti-CD25 (IL2RA) antibody. In one embodiment, the CD25 (IL2RA) inhibitor is daclizumab. In another embodiment, the CD25 (IL2RA) inhibitor is basiliximab.

[00317] In some embodiments, the checkpoint inhibitor is an IFNAR1 inhibitor. In certain embodiments, the IFNAR1 inhibitor is an anti-IFNAR1 antibody. In one embodiment, the IFNAR1 inhibitor is anifrolumab. In another embodiment, the IFNAR1 inhibitor is sifalimumab.

[00318] In some embodiments, the checkpoint inhibitor is a CSF1R inhibitor. In certain embodiments, the CSF1R inhibitor is an anti-CSF1R antibody. In one embodiment, the CSF1R inhibitor is pexidartinib. In another embodiment, the CSF1R inhibitor is emactuzumab. In yet another embodiment, the CSF1R inhibitor is cabiralizumab. In one embodiment, the CSF1R inhibitor is ARRY-382. In another embodiment, the CSF1R inhibitor is BLZ945. In yet another embodiment, the CSF1R inhibitor is AJUD010. In one embodiment, the CSF1R inhibitor is AMG820. In another embodiment, the CSF1R inhibitor is IMC-CS4. In yet another embodiment, the CSF1R inhibitor is JNJ-40346527. In one embodiment, the CSF1R inhibitor is PLX5622. In another embodiment, the CSF1R inhibitor is FPA008.

[00319] In some embodiments, the checkpoint inhibitor is a therapeutic agent targeting HLA. In certain embodiments, the therapeutic agent targeting HLA is an anti-HLA antibody. In one embodiment, the therapeutic agent targeting HLA is GSK01. In another embodiment, the therapeutic agent targeting HLA is IMC-C103C. In yet another embodiment, the therapeutic agent targeting HLA is IMC-F106C. In one embodiment, the therapeutic agent targeting HLA is IMC-G107C. In another embodiment, the therapeutic agent targeting HLA is ABBV-184.

[00320] The methods described herein can be used in combination with one or more second active agents as described herein where appropriate for treating diseases described herein and understood in the art.

[00321] PD-1 Antagonists and Pembrolizumab

[00322] Provided herein are methods for the treatment of various cancers in subjects, including subjects with unresectable locally advanced or metastatic urothelial cancer (la/mUC) who are unable to receive cisplatin-based chemotherapy, using an antibody drug conjugate (ADC) that binds 191P4D12 in combination with pembrolizumab. In certain embodiments, the treatment is a first-line treatment. In other embodiments, the treatment is a second-line treatment.

[00323] "Pembrolizumab" (formerly known as MK-3475, SCH 900475 and lambrolizumab) alternatively referred to herein as "pembro," is a humanized IgG4 mAb with the structure described in WHO Drug Information, Vol. 27, No. 2, pages 161-162 (2013) and which comprises the heavy and light chain amino acid sequences and CDRs described in Table 4. Pembrolizumab has been approved by the U.S. FDA as described in the Prescribing Information for KEYTRUDA™ (Merck & Co., Inc., Rahway, NJ, USA; initial U.S. approval 2014, updated March 2021).

[00324] As used herein, a "pembrolizumab variant" or "a variant thereof" pertaining to a pembrolizumab sequence means a monoclonal antibody that comprises heavy chain and light chain sequences that are substantially identical to those in pembrolizumab, except for having three, two or one conservative amino acid substitutions at positions that are located outside of the light chain CDRs and six, five, four, three, two or one conservative amino acid substitutions that are located outside of the heavy chain CDRs, e.g., the variant positions are located in the FR regions or the constant region, and optionally has a deletion of the C-terminal lysine residue of the heavy chain. In other words, pembrolizumab and a pembrolizumab variant comprise identical CDR sequences, but differ from each other due to having a conservative amino acid substitution at no more than three or six other positions in their full length light and heavy chain sequences, respectively. A pembrolizumab variant is substantially the same as pembrolizumab with respect to the following properties: binding affinity to PD-1 and ability to block the binding of each of PD-L1 and PD-L2 to PD-1.

[00325] In one embodiment, the PD-1 antagonist useful in the treatment, medicaments and uses of the present invention include a monoclonal antibody (mAb), or antigen binding fragment thereof, that specifically binds to PD-1 or PD-L1, and preferably specifically binds to human PD-1 or human PD-L1. The mAb may be a human antibody, a humanized antibody or a chimeric antibody, and may include a human constant region. In some embodiments the human constant region is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4 constant regions, and in some embodiments, the human constant region is an IgG1 or IgG4

constant region. In some embodiments, the antigen binding fragment is selected from the group consisting of Fab, Fab'-SH, F(ab')2, scFv and Fv fragments.

[00326] Examples of mAbs that bind to human PD-1, and useful in the treatment method, medicaments and uses of the present invention, are described in U.S. patent nos. US7488802, US7521051, US8008449, US8354509, and US8168757, and International application publn. nos. WO2004/004771, WO2004/072286, WO2004/056875, US2011/0271358, and WO 2008/156712. Specific anti-human PD-1 mAbs useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present invention include: pembrolizumab (also known as MK-3475), a humanized IgG4 mAb with the structure described in WHO Drug Information, Vol. 27, No. 2, pages 161-162 (2013) and that comprises the heavy and light chain amino acid sequences shown in Table 2; nivolumab (BMS-936558), a human IgG4 mAb with the structure described in WHO Drug Information, Vol. 27, No. 1, pages 68-69 (2013) and that comprises the heavy and light chain amino acid sequences shown in Table 2; the humanized antibodies h409A11, h409A16 and h409A17, which are described in WO2008/156712, and AMP-514, which is being developed by MedImmune; cemiplimab; camrelizumab; sintilimab; tislelizumab; and toripalimab. Additional anti-PD-1 antibodies contemplated for use herein include MEDI0680 (U.S. Patent no. 8609089), BGB-A317 (U.S. Patent publ. no. 2015/0079109), INCSHR1210 (SHR-1210) (PCT International application publ. no. WO2015/085847), REGN-2810 (PCT International application publ. no. WO2015/112800), PDR001 (PCT International application publ. no. WO2015/112900), TSR-042 (ANB011) (PCT International application publ. no. WO2014/179664) and STI-1110 (PCT International application publ. no. WO2014/194302).

[00327] Examples of mAbs that bind to human PD-L1, and useful in the treatment method, medicaments and uses of the present invention, are described in US8383796. Specific anti-human PD-L1 mAbs useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present invention include BMS-936559, MEDI4736, and MSB0010718C.

[00328] In some embodiments, the PD-1 antagonist is pembrolizumab (KEYTRUDA™, Merck & Co., Inc., Rahway, NJ, USA), nivolumab (OPDIVO™, Bristol-Myers Squibb Company, Princeton, NJ, USA), atezolizumab (TECENTRIQ™, Genentech, San Francisco, CA, USA), durvalumab (IMFINZI™, AstraZeneca Pharmaceuticals LP, Wilmington, DE), cemiplimab (LIBTAYO™, Regeneron Pharmaceuticals, Tarrytown, NY, USA) avelumab (BAVENCIO™, Merck KGaA, Darmstadt, Germany) or dostarlimab (JEMPERLI™, GlaxoSmithKline LLC, Philadelphia, PA). In other embodiments, the PD-1 antagonist is pidilizumab (U.S. Pat. No. 7,332,582), AMP-514 (MedImmune LLC, Gaithersburg, MD,

USA), PDR001 (U.S. Pat. No. 9,683,048), BGB-A317 (U.S. Pat. No. 8,735,553), or MGA012 (MacroGenics, Rockville, MD).

[00329] In one embodiment, the PD-1 antagonist useful in the methods of the invention is an anti-PD-1 antibody that blocks the binding of PD-1 to PD-L1 and PD-L2.

[00330] In some embodiments of the treatment methods, the anti-PD-1 antibody comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:32 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO: 27;

[00331] In some embodiments of the treatment methods, medicaments and uses of the present invention, the PD-1 antagonist is a monoclonal antibody, or antigen binding fragment thereof, that comprises: (a) a light chain variable region comprising light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 24, 25 and 26, respectively and (b) a heavy chain variable region comprising heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 29, 30 and 31, respectively.

[00332] In some embodiments of the treatment methods, medicaments and uses of the present invention, the PD-1 antagonist is a monoclonal antibody, or antigen binding fragment thereof, that comprises: (a) a light chain variable region comprising light chain CDR1 comprising the amino acid sequence of SEQ ID NO:24, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:25, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:26, respectively, and (b) a heavy chain variable region comprising heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:29, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:30, and heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:31, respectively.

[00333] In some embodiments of the treatment methods, medicaments and uses of the present invention, the PD-1 antagonist is a monoclonal antibody, or antigen binding fragment thereof, that comprises: (a) a light chain variable region comprising light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:24, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:25, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:26, respectively, and (b) a heavy chain variable region comprising heavy chain CDR1 consisting of the amino acid sequence of SEQ ID NO:29, a heavy chain CDR2 consisting of the amino acid sequence of SEQ ID NO:30, and heavy chain CDR3 consisting of the amino acid sequence of SEQ ID NO:31, respectively.

[00334] In other embodiments of the treatment methods, medicaments and uses of the present invention, the PD-1 antagonist is a monoclonal antibody, or antigen binding fragment thereof, that specifically binds to human PD-1 and comprises (a) a heavy chain variable region comprising SEQ ID NO:32 or a variant thereof, and (b) a light chain variable region comprising SEQ ID NO:27 or a variant thereof. A variant of a heavy chain variable region sequence is identical to the reference sequence except having up to six conservative amino acid substitutions in the framework region (i.e., outside of the CDRs). A variant of a light chain variable region sequence is identical to the reference sequence except having up to three conservative amino acid substitutions in the framework region (i.e., outside of the CDRs).

[00335] In another embodiment of the treatment methods, medicaments and uses of the present invention, the PD-1 antagonist is a monoclonal antibody that specifically binds to human PD-1 and comprises (a) a heavy chain comprising SEQ ID NO: 33 and (b) a light chain comprising SEQ ID NO:28. In one embodiment, the PD-1 antagonist is an anti-PD-1 antibody that comprises two heavy chains and two light chains, and wherein the heavy and light chains comprise the amino acid sequences in SEQ ID NO:33 and SEQ ID NO:28, respectively.

[00336] In all of the above treatment methods, medicaments and uses, the PD-1 antagonist inhibits the binding of PD-L1 to PD-1, and in specific embodiments also inhibits the binding of PD-L2 to PD-1. In some embodiments of the above treatment methods, medicaments and uses, the PD-1 antagonist is a monoclonal antibody, or an antigen binding fragment thereof, that specifically binds to PD-1 or to PD-L1 and blocks the binding of PD-L1 to PD-1.

[00337] Table 4 below provides a list of the amino acid sequences of exemplary anti-PD-1 mAbs for use in the treatment method, medicaments and uses of the present invention.

Table 4. Exemplary PD-1 Antibody Sequences

Antibody Feature	Amino Acid Sequence	SEQ ID NO.
Pembrolizumab Light Chain		
CDR1	RASKGVSTSGYSYLH	24
CDR2	LASYLES	25
CDR3	QHSRDLPLT	26
Variable Region	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWY QQKPGQAPRLLIYLASYLESGVPARFSGSGSGTDFTLTISSL EPEDFAVYYCQHSRDLPLTFGGGTKVEIK	27
Light Chain	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWY QQKPGQAPRLLIYLASYLESGVPARFSGSGSGTDFTLTISSL	28

Antibody Feature	Amino Acid Sequence	SEQ ID NO.
	EPEDFAVYYCQHSRDLPLTFGGGTKVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC	
Pembrolizumab Heavy Chain		
CDR1	NYYMY	29
CDR2	GINPSNGGTNFNEKFKN	30
CDR3	RDYRFDMGFDY	31
Variable Region	QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVR QAPGQGLEWMGGINPSNGGTNFNEKFKNRVTLTTDSSTT TAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTT VTVSS	32
Heavy Chain	QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVR QAPGQGLEWMGGINPSNGGTNFNEKFKNRVTLTTDSSTT TAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTT VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLG GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGK	33

Table 5. Additional PD-1 Antibodies and Antigen Binding Fragments Useful in the Formulations, Methods and Uses Provided Herein

A. Antibodies and antigen binding fragments comprising light and heavy chain CDRs of hPD-1.08A in WO 2008/156712		
CDRL1	RASKSVSTSGFSYLH	SEQ ID NO:34
CDRL2	LASNLES	SEQ ID NO:35
CDRL3	QHSWELPLT	SEQ ID NO:36
CDRH1	SYYLY	SEQ ID NO:37
CDRH2	GVNPSNGGTNFSEKFK	SEQ ID NO:38
CDRH3	RDSNYDGGFDY	SEQ ID NO:39
C. Antibodies and antigen binding fragments comprising the mature h109A heavy chain variable region and one of the mature K09A light chain variable regions in WO 2008/156712		
Heavy chain VR	MDWTWSILFLVAAPTGAHSQVQ LVQSGVEVKKPGASVKVSCKAS	SEQ ID NO:40

	GYTFTNYYMYWVRQAPGQGLEW MGGINPSNGGTNFNEKFKNRVT LTTDSSTTTAYMELKSLQFDDT AVYYCARRDYRFDMGFDYWGQG TTVTVSS	
Light chain VR	MAPVQLLGLLVLFLPAMRCEIV LTQSPATLSLSPGERATLSCRA SKGVSTSGYSYLHWYQQKPGQA PRLLIYLASYLESGVPARFSGS GSGTDFTLTISSLEPEDFAVYY CQHSRDLPLTFGGGTKVEIK	SEQ ID NO:41 or
	MAPVQLLGLLVLFLPAMRCEIV LTQSPLSLPVTPGEPASISCRA SKGVSTSGYSYLHWYLQKPGQS PQLLIYLASYLESGVPDRFSGS GSGTDFTLKISRVEAEDVGVYY CQHSRDLPLTFGQGTKLEIK	SEQ ID NO:42 or
	MAPVQLLGLLVLFLPAMRCDIV MTQTPLSLPVTPGEPASISCRA SKGVSTSGYSYLHWYLQKPGQS PQLLIYLASYLESGVPDRFSGS GSGTAFTLKISRVEAEDVGLYY CQHSRDLPLTFGQGTKLEIK	SEQ ID NO:43
D. Antibodies and antigen binding fragments comprising the mature 409 heavy chain and one of the mature K09A light chains in WO 2008/156712		
Heavy chain	MAVLGLLFCLVTFPSCVLSQVQ LVQSGVEVKKPGASVKVSCKAS GYTFTNYYMYWVRQAPGQGLEW MGGINPSNGGTNFNEKFKNRVT LTTDSSTTTAYMELKSLQFDDT AVYYCARRDYRFDMGFDYWGQG TTVTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTKTY TCNVDHKPSNTKVDKRVESKYG PPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVS QEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLD SDGSFFLYSRLTVDKSRWQEGN	SEQ ID NO:44

	VFSCSVMHEALHNHYTQKSLSL SLGK	
Light chain	MAPVQLLGLLVLFLPAMRCEIV LTQSPATLSLSPGERATLSCRA SKGVSTSGYSYLHWYQQKPGQA PRLLIYLASYLESGVPARFSGS GSGTDFTLTISSLEPEDFAVYY CQHSRDLPLTFGGGTKVEIKRT VAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC	SEQ ID NO:45 or
	MAPVQLLGLLVLFLPAMRCEIV LTQSPLSLPVTPGEPASISCRA SKGVSTSGYSYLHWYLQKPGQS PQLLIYLASYLESGVPDRFSGS GSGTDFTLKISRVEAEDVGVYY CQHSRDLPLTFGQGTKLEIKRT VAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC	SEQ ID NO:46 or
	MAPVQLLGLLVLFLPAMRCDIV MTQTPLSLPVTPGEPASISCRA SKGVSTSGYSYLHWYLQKPGQS PQLLIYLASYLESGVPDRFSGS GSGTAFTLKISRVEAEDVGLYY CQHSRDLPLTFGQGTKLEIKRT VAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC	SEQ ID NO:47

[00338] In one embodiment, the anti-PD-1 antibody or antigen-binding fragment thereof comprises a heavy chain constant region, e.g. a human constant region, such as g1, g2, g3, or g4 human heavy chain constant region or a variant thereof. In another embodiment, the anti-PD-1 antibody or antigen-binding fragment thereof comprises a light chain constant region, e.g. a human light chain constant region, such as lambda or kappa human light chain region or a variant thereof. By way of example, and not limitation, the human heavy chain constant region can be g4 and the human light chain constant region can be kappa. In an alternative embodiment, the Fc region of the antibody is g4 with a Ser228Pro mutation (Schuurman, J *et.al.*, *Mol. Immunol.* 38: 1-8, 2001). In some embodiments, different constant domains may

be appended to humanized VL and VH regions derived from the CDRs provided herein. For example, if a particular intended use of an antibody (or fragment) of the present invention were to call for altered effector functions, a heavy chain constant domain other than human IgG1 may be used, or hybrid IgG1/IgG4 may be utilized. Although human IgG1 antibodies provide for long half-life and for effector functions, such as complement activation and antibody-dependent cellular cytotoxicity, such activities may not be desirable for all uses of the antibody. In such instances a human IgG4 constant domain, for example, may be used. The present invention includes the use of anti-PD-1 antibodies or antigen-binding fragments thereof which comprise an IgG4 constant domain. In one embodiment, the IgG4 constant domain can differ from the native human IgG4 constant domain (Swiss-Prot Accession No. P01861.1) at a position corresponding to position 228 in the EU system and position 241 in the KABAT system, where the native Ser108 is replaced with Pro, in order to prevent a potential inter-chain disulfide bond between Cys106 and Cys109 (corresponding to positions Cys 226 and Cys 229 in the EU system and positions Cys 239 and Cys 242 in the KABAT system) that could interfere with proper intra-chain disulfide bond formation. See Angal *et al.* (1993) *Mol. Imunol.* 30:105. In other instances, a modified IgG1 constant domain which has been modified to increase half-life or reduce effector function can be used.

[00339] In another embodiment, the PD-1 antagonist is an antibody or antigen binding protein that has a variable light domain and/or a variable heavy domain with at least 95%, 90%, 85%, 80%, 75% or 50% sequence identity to one of the variable light domains or variable heavy domains described above, and exhibits specific binding to PD-1. In another embodiment of the methods of treatment of the invention, the PD-1 antagonist is an antibody or antigen binding protein comprising variable light and variable heavy domains having up to 1, 2, 3, 4, or 5 or more amino acid substitutions, and exhibits specific binding to PD-1.

[00340] In some embodiments, the checkpoint inhibitor is administered after the administration of the ADCs provided herein. In other embodiments, the checkpoint inhibitor is administered simultaneously (*e.g.*, in the same dosing period) with the ADCs provided herein. In yet other embodiments, the checkpoint inhibitor is administered after the administration of the ADCs provided herein.

[00341] In some embodiments, the amount of the checkpoint inhibitor for the various methods provided herein can be determined by standard clinical techniques. In certain embodiments, the amount of the PD-1 antagonist, e.g., pembrolizumab, for the various methods are provided in Section 5.6.

[00342] In some embodiments, the subjects that can be treated in the methods provided herein is a mammal. In some embodiments, the subjects that can be treated in the methods provided herein is a human.

5.2.1.4 *Therapeutic Outcome of the Methods Provided Herein*

[00343] The methods provided herein, including in methods described in this Section (Section 5.2) and Sections 3 and 6, can provide beneficial therapeutic outcomes for cisplatin eligible and ineligible human subjects. In one embodiment, the human subject has a complete response following the treatment by a method provided herein. In another embodiment, the human subject has a partial response following the treatment by a method provided herein. In another embodiment, the human subject has complete response or a partial response following the treatment by a method provided herein.

[00344] In some embodiments, the response (complete or partial response) is determined by evaluating the tumor or cancer site (lesions). The criteria for determining complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD) are described in **FIG. 3A**, **FIG. 3B**, and **FIG. 3C**.

[00345] In some embodiments, the human subjects and patients are used interchangeably. Therefore, a person skilled in the art would understand that the human subjects can be interchangeable with patients in any of the methods provided herein.

[00346] The therapeutic outcome of the methods provided herein thus can be evaluated based on any one or more of the response criteria described above.

[00347] In one embodiment, the human subject has a partial response following the treatment by a method provided herein. In another embodiment, the human subject has a partial response following the treatment by a method provided herein, wherein the partial response is defined by an at least or about 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. In another embodiment, the human subject has a partial response following the treatment by a method provided herein, wherein the partial response is defined by an at least or about 35% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. In a further embodiment, the human subject has a partial response following the treatment by a method provided herein, wherein the partial response is defined by an at least or about 40% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. In yet another embodiment, the human subject has a partial response following the treatment by a method provided herein, wherein the partial response is defined by an at least or about

45% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. In one embodiment, the human subject has a partial response following the treatment by a method provided herein, wherein the partial response is defined by an at least or about 50% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. In another embodiment, the human subject has a partial response following the treatment by a method provided herein, wherein the partial response is defined by an at least or about 55% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. In a further embodiment, the human subject has a partial response following the treatment by a method provided herein, wherein the partial response is defined by an at least or about 60% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. In yet another embodiment, the human subject has a partial response following the treatment by a method provided herein, wherein the partial response is defined by an at least or about 65% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. In one embodiment, the human subject has a partial response following the treatment by a method provided herein, wherein the partial response is defined by an at least or about 70% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. In another embodiment, the human subject has a partial response following the treatment by a method provided herein, wherein the partial response is defined by an at least or about 75% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. In a further embodiment, the human subject has a partial response following the treatment by a method provided herein, wherein the partial response is defined by an at least or about 80% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. In yet another embodiment, the human subject has a partial response following the treatment by a method provided herein, wherein the partial response is defined by an at least or about 85% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. In one embodiment, the human subject has a partial response following the treatment by a method provided herein, wherein the partial response is defined by an at least or about 90% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. In another embodiment, the human subject has a partial response following the treatment by a method provided herein, wherein the partial response is defined by an at least or about 95% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. In some embodiments, the diameter is determined according to the longest diameter of a lesion. In certain embodiments,

the diameter is determined according to the longest diameter of a lesion in the plane of measurement. In some embodiments, the diameter is determined according to the longest diameter of a lesion in the plane of measurement with a minimal size of 10mm by CT scan. In certain embodiments, the diameter is determined according to the longest diameter of a lesion in the plane of measurement with a minimal size of 10mm by CT scan and CT slice thickness no greater than 5 mm.

[00348] The therapeutic outcomes of the methods provided herein can also be evaluated based on whether the disease is stable following the treatment. In one embodiment, the human subject has a stable disease following the treatment by a method provided herein. In another embodiment, the human subject does not have a progressive disease following the treatment by a method provided herein.

[00349] Alternatively, therapeutic outcomes based on the complete response, partial response, or stable disease can be evaluated with respect to a population of human subjects treated by a method provided herein by evaluating the percentage of the subjects having complete response, partial response, or stable disease in the treated population. As such, in some embodiments, the therapeutic outcome or efficacy measure applies to outcomes achieved by actually treating a population of subjects. In other embodiments, the therapeutic outcome or efficacy measure refers to the outcome or efficacy that is capable of being achieved if a population of human subjects was treated with a method as disclosed herein. While the following sections discuss the treatment of an actual population of human subjects, is should be understood that corresponding methods in which the outcome or efficacy measure is capable of being achieved in a patient population are also encompassed herein. In short, both scenarios described above apply to the following sections; only one scenario is described below in the interest of simplicity and to avoid redundancy.

[00350] In some embodiments of the methods provided herein, including, but not limited to, in Sections 3, 5.3, 5.8, and 6 and this Section (Section 5.2), the ADC is enfortumab vedotin. In certain embodiments of the methods provided herein, including, but not limited to, in Sections 3, 5.3, 5.8, and 6 and this Section (Section 5.2), the ADC is a biosimilar of enfortumab vedotin. In some embodiments of the methods provided herein, including, but not limited to, in Sections 3, 5.2.1.3, 5.8, and 6 and this Section (Section 5.2), the PD-1 antagonist or anti-PD-1 antibody is pembrolizumab.

[00351] In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having complete response in the treated population is at least or about 15%. In another embodiment, a population of the

human subjects is treated by a method provided herein, wherein the percentage of the subjects having complete response in the treated population is at least or about 20%. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having complete response in the treated population is at least or about 25%. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having complete response in the treated population is at least or about 29.1%. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having complete response in the treated population is at least or about 30%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having complete response in the treated population is at least or about 31%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having complete response in the treated population is at least or about 32%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having complete response in the treated population is at least or about 33%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having complete response in the treated population is at least or about 34%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having complete response in the treated population is at least or about 35%.

[00352] In one embodiment, the complete response rate is at least or about 10% for a population of subjects treated with the method. In another embodiment, the complete response rate is at least or about 15% for a population of subjects treated with the method. In another embodiment, the complete response rate is at least or about 20% for a population of subjects treated with the method. In another embodiment, the complete response rate is at least or about 25% for a population of subjects treated with the method. In another embodiment, the complete response rate is at least or about 29.1% for a population of subjects treated with the method. In another embodiment, the complete response rate is at least or about 30% for a population of subjects treated with the method. In another embodiment, the complete response rate is at least or about 31% for a population of subjects treated with the method. In another embodiment, the complete response rate is at least or about 32% for a population of subjects treated with the method. In another embodiment, the complete response rate is at least or about 33% for a population of subjects treated with the

method. In another embodiment, the complete response rate is at least or about 34% for a population of subjects treated with the method. In another embodiment, the complete response rate is at least or about 35% for a population of subjects treated with the method.

[00353] Similarly, using percentage of partial response as the criteria, in one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having partial response in the treated population is at least or about 15%. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having partial response in the treated population is at least or about 20%. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having partial response in the treated population is at least or about 25%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having partial response in the treated population is at least or about 30%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having partial response in the treated population is at least or about 35%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having partial response in the treated population is at least or about 38.7%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having partial response in the treated population is at least or about 40%. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having partial response in the treated population is at least or about 45%. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having partial response in the treated population is at least or about 50%. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having partial response in the treated population is at least or about 55%. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having partial response in the treated population is at least or about 60%. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having partial response in the treated population is at least or about 65%.

[00354] In one embodiment, the partial response rate is at least or about 15% for a population of subjects treated with the method. In another embodiment, the partial response

rate is at least or about 25% for a population of subjects treated with the method. In another embodiment, the partial response rate is at least or about 20% for a population of subjects treated with the method. In another embodiment, the partial response rate is at least or about 25% for a population of subjects treated with the method. In another embodiment, the partial response rate is at least or about 30% for a population of subjects treated with the method. In another embodiment, the partial response rate is at least or about 35% for a population of subjects treated with the method. In another embodiment, the partial response rate is at least or about 38.7% for a population of subjects treated with the method. In another embodiment, the partial response rate is at least or about 40% for a population of subjects treated with the method. In another embodiment, the partial response rate is at least or about 45% for a population of subjects treated with the method. In another embodiment, the partial response rate is at least or about 50% for a population of subjects treated with the method. In another embodiment, the partial response rate is at least or about 55% for a population of subjects treated with the method. In another embodiment, the partial response rate is at least or about 60% for a population of subjects treated with the method. In another embodiment, the partial response rate is at least or about 65% for a population of subjects treated with the method.

[00355] Moreover, percentage of the subjects having stable disease can be used as the evaluation criteria for the therapeutic outcome in the human subjects treated by a method provided herein. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having stable disease in the treated population is at least or about 10%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having stable disease in the treated population is at least or about 12%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having stable disease in the treated population is at least or about 15%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having stable disease in the treated population is at least or about 18%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having stable disease in the treated population is at least or about 18.8%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having stable disease in the treated population is at least or about 20%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having stable disease in the treated population is at

least or about 25%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having stable disease in the treated population is at least or about 30%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having stable disease in the treated population is at least or about 35%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having stable disease in the treated population is at least or about 40%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the percentage of the subjects having stable disease in the treated population is at least or about 45%.

[00356] In one embodiment, the stable disease rate is at least or about 10% for a population of subjects treated with the method. In one embodiment, the stable disease rate is at least or about 12% for a population of subjects treated with the method. In one embodiment, the stable disease rate is at least or about 15% for a population of subjects treated with the method. In one embodiment, the stable disease rate is at least or about 18% for a population of subjects treated with the method. In one embodiment, the stable disease rate is at least or about 18.8% for a population of subjects treated with the method. In one embodiment, the stable disease rate is at least or about 20% for a population of subjects treated with the method. In one embodiment, the stable disease rate is at least or about 25% for a population of subjects treated with the method. In one embodiment, the stable disease rate is at least or about 30% for a population of subjects treated with the method. In one embodiment, the stable disease rate is at least or about 35% for a population of subjects treated with the method. In one embodiment, the stable disease rate is at least or about 40% for a population of subjects treated with the method. In one embodiment, the stable disease rate is at least or about 45% for a population of subjects treated with the method.

[00357] Likewise, objective response rate, which is the sum of percentage of subjects having completed response and those having partial response, can be used as the evaluation criteria for the therapeutic outcome in the human subjects treated by a method provided herein. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population is at least or about 45%. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population is at least or about 50%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population is at least or about

55%. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population is at least or about 60%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population is at least or about 65%. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population is at least or about 67%. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population is at least or about 67.7%. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population is at least or about 68%. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population is at least or about 70%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population is at least or about 75%. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population is at least or about 80%. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population is at least or about 85%. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population is at least or about 90%.

[00358] In one embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 40% to 80%. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 40% to 75%. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 40% to 70%. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 45% to 80%. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 45% to 75%. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 45% to 70%. In a further embodiment, a population of the human subjects is treated by a method

provided herein, wherein objective response rate in the treated population ranges from 50% to 80%. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 50% to 75%. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 50% to 70%. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 55% to 80%. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 55% to 75%. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 55% to 70%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 60% to 80%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 60% to 75%. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 60% to 70%. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 60% to 67.7%. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 65% to 80%. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 65% to 75%. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein objective response rate in the treated population ranges from 65% to 70%.

[00359] In one embodiment, the objective response rate is at least or about 35% for a population of subjects treated with the method. In another embodiment, the objective response rate is at least or about 40% for a population of subjects treated with the method. In another embodiment, the objective response rate is at least or about 45% for a population of subjects treated with the method. In another embodiment, the objective response rate is at least or about 50% for a population of subjects treated with the method. In another embodiment, the objective response rate is at least or about 55% for a population of subjects treated with the method. In another embodiment, the objective response rate is at least or about 60% for a population of subjects treated with the method. In another embodiment, the

objective response rate is at least or about 65% for a population of subjects treated with the method. In another embodiment, the objective response rate is at least or about 67% for a population of subjects treated with the method. In another embodiment, the objective response rate is at least or about 67.7% for a population of subjects treated with the method. In another embodiment, the objective response rate is at least or about 68% for a population of subjects treated with the method. In another embodiment, the objective response rate is at least or about 70% for a population of subjects treated with the method. In another embodiment, the objective response rate is at least or about 75% for a population of subjects treated with the method. In another embodiment, the objective response rate is at least or about 80% for a population of subjects treated with the method. In another embodiment, the objective response rate is at least or about 85% for a population of subjects treated with the method. In another embodiment, the objective response rate is at least or about 90% for a population of subjects treated with the method.

[00360] In one embodiment, the objective response rate is from 40% to 80% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 40% to 75% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 40% to 70% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 45% to 80% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 45% to 75% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 45% to 70% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 50% to 80% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 50% to 75% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 50% to 70%. for a population of subjects treated with the method. In another embodiment, the objective response rate is from 55% to 80% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 55% to 75% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 55% to 70% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 55% to 65% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 60% to 80% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 60% to 75% for a population of subjects treated with the

method. In another embodiment, the objective response rate is from 60% to 70% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 60% to 65% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 60% to 67.7% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 65% to 80% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 65% to 75% for a population of subjects treated with the method. In another embodiment, the objective response rate is from 65% to 70% for a population of subjects treated with the method.

[00361] Additionally, the therapeutic outcome of the methods provided herein can be evaluated based on the duration of response as set forth in Section 6.1.8.3. In one embodiment, the human subject has a duration of response of at least or about 5 months following the treatment. In another embodiment, the human subject has a duration of response of at least or about 6 months following the treatment. In a further embodiment, the human subject has a duration of response of at least or about 7 months following the treatment. In yet another embodiment, the human subject has a duration of response of at least or about 8 months following the treatment. In one embodiment, the human subject has a duration of response of at least or about 9 months following the treatment. In another embodiment, the human subject has a duration of response of at least or about 10 months following the treatment. In yet another embodiment, the human subject has a duration of response of at least or about 11 months following the treatment. In one embodiment, the human subject has a duration of response of at least or about 12 months following the treatment. In another embodiment, the human subject has a duration of response of at least or about 13 months following the treatment. In a further embodiment, the human subject has a duration of response of at least or about 14 months following the treatment. In yet another embodiment, the human subject has a duration of response of at least or about 15 months following the treatment. In one embodiment, the human subject has a duration of response of at least or about 16 months following the treatment. In another embodiment, the human subject has a duration of response of at least or about 17 months following the treatment. In a further embodiment, the human subject has a duration of response of at least or about 18 months following the treatment. In yet another embodiment, the human subject has a duration of response of at least or about 19 months following the treatment. In a further embodiment, the human subject has a duration of response of at least or about 20 months following the treatment. In a further embodiment, the human subject has a duration of

response of at least or about 21 months following the treatment. In a further embodiment, the human subject has a duration of response of at least or about 22 months following the treatment. In a further embodiment, the human subject has a duration of response of at least or about 23 months following the treatment. In a further embodiment, the human subject has a duration of response of at least or about 24 months following the treatment. In a further embodiment, the human subject has a duration of response of at least or about 25 months following the treatment. In a further embodiment, the human subject has a duration of response of at least or about 26 months following the treatment. In a further embodiment, the human subject has a duration of response of at least or about 27 months following the treatment. In a further embodiment, the human subject has a duration of response of at least or about 28 months following the treatment. In a further embodiment, the human subject has a duration of response of at least or about 29 months following the treatment. In a further embodiment, the human subject has a duration of response of at least or about 30 months following the treatment.

[00362] In another embodiment, the human subject has a duration of response ranging from 5 to 30 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 5 to 29 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 5 to 28 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 5 to 27 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 5 to 26 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 5 to 25 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 5 to 24 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 5 to 23 months following the treatment. In some embodiments, the human subject has a duration of response ranging from 5 to 22 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 5 to 21 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 5 to 20 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 5 to 19 months following the treatment. In one embodiment, the human subject has a duration of response ranging from 5 to 18 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 5 to 17 months following the treatment. In a further embodiment, the human subject

has a duration of response ranging from 5 to 16 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 5 to 15 months following the treatment. In one embodiment, the human subject has a duration of response ranging from 5 to 14 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 5 to 13 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 5 to 12 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 6 to 30 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 6 to 29 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 6 to 28 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 6 to 27 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 6 to 26 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 6 to 25 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 6 to 24 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 6 to 23 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 6 to 22 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 6 to 21 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 6 to 20 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 6 to 19 months following the treatment. In one embodiment, the human subject has a duration of response ranging from 6 to 18 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 6 to 17 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 6 to 16 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 6 to 15 months following the treatment. In one embodiment, the human subject has a duration of response ranging from 6 to 14 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 6 to 13 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 6 to 12 months following the treatment. In one embodiment, the human subject has a duration of response ranging from 7

to 22 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 7 to 21 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 7 to 20 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 7 to 19 months following the treatment. In one embodiment, the human subject has a duration of response ranging from 7 to 18 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 7 to 17 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 7 to 16 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 7 to 15 months following the treatment. In one embodiment, the human subject has a duration of response ranging from 7 to 14 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 7 to 13 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 7 to 12 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 8 to 30 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 9 to 30 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 10 to 30 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 11 to 30 months following the treatment. In one embodiment, the human subject has a duration of response ranging from 12 to 30 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 13 to 30 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 14 to 30 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 15 to 30 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 16 to 30 months following the treatment. In one embodiment, the human subject has a duration of response ranging from 17 to 30 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 18 to 30 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 8 to 27 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 9 to 27 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 10 to 27 months following the

treatment. In a further embodiment, the human subject has a duration of response ranging from 11 to 27 months following the treatment. In one embodiment, the human subject has a duration of response ranging from 12 to 27 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 13 to 27 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 14 to 27 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 15 to 27 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 16 to 27 months following the treatment. In one embodiment, the human subject has a duration of response ranging from 17 to 27 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 18 to 27 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 8 to 22 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 9 to 22 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 10 to 22 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 11 to 22 months following the treatment. In one embodiment, the human subject has a duration of response ranging from 12 to 22 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 13 to 22 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 14 to 22 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 15 to 22 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 16 to 22 months following the treatment. In one embodiment, the human subject has a duration of response ranging from 17 to 22 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 18 to 22 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 6 to 21 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 7 to 20 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 8 to 19 months following the treatment. In one embodiment, the human subject has a duration of response ranging from 9 to 18 months following the treatment. In another embodiment, the human subject has a duration of response ranging from 10 to 17 months following the treatment. In a further embodiment, the

human subject has a duration of response ranging from 11 to 16 months following the treatment. In yet another embodiment, the human subject has a duration of response ranging from 12 to 15 months following the treatment. In a further embodiment, the human subject has a duration of response ranging from 13 to 14 months following the treatment.

[00363] In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 5 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 6 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 7 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 8 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 9 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 10 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 11 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 12 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 13 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 14 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 15 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 16 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein,

wherein the duration of response in the treated population is at least or about 17 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 18 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 19 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 20 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 21 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 22 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 23 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 24 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 25 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 26 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 27 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 28 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 29 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response in the treated population is at least or about 30 months following the treatment.

[00364] In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 30 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 29 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 28 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 27 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 26 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 25 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 24 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 23 months. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 22 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 21 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 20 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 19 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 18 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 17 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 16 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 15 months. In yet another embodiment, a population of the human subjects

is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 14 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 13 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 5 to 12 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 30 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 29 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 28 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 27 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 26 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 25 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 24 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 23 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 22 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 21 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 20 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 19 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 18 months. In one embodiment, a population of the human subjects is treated by a method provided herein,

wherein the duration of response of in the treated population ranges from 6 to 17 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 16 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 15 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 14 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 13 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 12 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 30 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 29 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 28 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 27 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 26 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 25 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 24 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 23 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 22 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 21 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 20 months. In

a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 19 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 18 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 17 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 16 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 15 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 14 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 13 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 12 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 22 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 8 to 22 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 9 to 22 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 10 to 22 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 11 to 22 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 12 to 12 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 13 to 22 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 14 to 22 months. In one embodiment, a population of the human

subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 15 to 22 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 16 to 22 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 17 to 22 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 18 to 22 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 27 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 8 to 27 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 9 to 27 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 10 to 27 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 11 to 27 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 12 to 27 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 13 to 27 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 14 to 27 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 15 to 27 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 16 to 27 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 17 to 27 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 18 to 27 months. In yet another embodiment, a population of the human subjects is treated by a method provided

herein, wherein the duration of response of in the treated population ranges from 19 to 27 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 20 to 27 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 21 to 27 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 22 to 27 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 23 to 27 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 24 to 27 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 30 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 8 to 30 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 9 to 30 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 10 to 30 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 11 to 30 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 12 to 30 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 13 to 30 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 14 to 30 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 15 to 30 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 16 to 30 months. In a further embodiment, a population of the human subjects is treated by a method

provided herein, wherein the duration of response of in the treated population ranges from 17 to 30 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 18 to 30 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 19 to 30 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 20 to 30 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 21 to 30 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 22 to 30 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 23 to 30 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 24 to 30 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 25 to 30 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 26 to 30 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 27 to 30 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 6 to 21 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 7 to 20 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 8 to 19 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 9 to 18 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 10 to 17 months. In another embodiment, a population of the human subjects is treated

by a method provided herein, wherein the duration of response of in the treated population ranges from 11 to 16 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 12 to 15 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the duration of response of in the treated population ranges from 13 to 24 months.

[00365] In certain embodiments, the duration of response is at least or about 5 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 6 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 7 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 8 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 9 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 10 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 11 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 12 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 13 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 14 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 15 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 16 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 17 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 18 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 19 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 20 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 21 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 22 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 23 months for a population of

subjects treated with the method. In certain embodiments, the duration of response is at least or about 24 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 25 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 26 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 27 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 28 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 29 months for a population of subjects treated with the method. In certain embodiments, the duration of response is at least or about 30 months for a population of subjects treated with the method.

[00366] Alternatively, the therapeutic outcome of the methods provided herein can be evaluated based on the progression free survival as set forth in Section 6.1.8.3(v). In one embodiment, the human subject has a progression free survival of at least or about 5 months following the treatment. In another embodiment, the human subject has a progression free survival of at least or about 6 months following the treatment. In a further embodiment, the human subject has a progression free survival of at least or about 7 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 8 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 8.2 months following the treatment. In one embodiment, the human subject has a progression free survival of at least or about 9 months following the treatment. In another embodiment, the human subject has a progression free survival of at least or about 10 months following the treatment. In another embodiment, the human subject has a progression free survival of at least or about 10.4 months following the treatment. In another embodiment, the human subject has a progression free survival of at least or about 10.5 months following the treatment. In another embodiment, the human subject has a progression free survival of at least or about 10.6 months following the treatment. In a further embodiment, the human subject has a progression free survival of at least or about 11 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 12 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 12.5 months following the treatment. In one embodiment, the human subject has a progression free survival of at least or about 13 months following the treatment. In another embodiment, the human subject has a progression free survival of at least or about 14 months

following the treatment. In another embodiment, the human subject has a progression free survival of at least or about 14.6 months following the treatment. In a further embodiment, the human subject has a progression free survival of at least or about 15 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 16 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 16.4 months following the treatment. In one embodiment, the human subject has a progression free survival of at least or about 17 months following the treatment. In another embodiment, the human subject has a progression free survival of at least or about 18 months following the treatment. In certain embodiments, the human subject has a progression free survival of at least or about 18.5 months following the treatment. In a further embodiment, the human subject has a progression free survival of at least or about 19 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 20 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 21 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 22 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 22.3 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 23 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 24 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 25 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 26 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 27 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 28 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 29 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 30 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 31 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 32 months following the treatment. In yet another embodiment, the human subject has a progression free survival of at least or about 33

months following the treatment. In certain embodiments, the human subject is eligible to receive cisplatin treatment (cisplatin eligible). In certain embodiments, the human subject is eligible to receive cisplatin treatment (cisplatin eligible) and the human subject has a progression free survival of at least or about 14.6 months following the treatment. In certain embodiments, the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible). In certain embodiments, the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible) and the human subject has a progression free survival of at least or about 10.6 months following the treatment. In certain embodiments, the human subject does not have liver metastases. In certain embodiments, the human subject does not have liver metastases and the human subject has a progression free survival of at least or about 16.4 months following the treatment. In certain embodiments, the human subject has liver metastases. In certain embodiments, the human subject has a progression free survival of at least or about 8.2 months following the treatment and the human subject has liver metastases. In certain embodiments, the human subject has expression of PD-L1 no less than CPS of 10. In certain embodiments, the human subject has expression of PD-L1 no less than CPS of 10 and the human subject has a progression free survival of at least or about 18.5 months following the treatment. In certain embodiments, the human subject has expression of PD-L1 less than CPS of 10. In certain embodiments, the human subject has expression of PD-L1 less than CPS of 10 and the human subject has a progression free survival of at least or about 10.5 months following the treatment. In certain embodiments, the race of the human subject is white. In certain embodiments, the race of the human subject is white and the human subject has a progression free survival of at least or about 10.4 months following the treatment. In certain embodiments, the race of the human subject is not white. In certain embodiments, the race of the human subject is not white and the human subject has a progression free survival of at least or about 22.3 months following the treatment.

[00367] In another embodiment, the human subject has a progression free survival ranging from 5 to 33 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 5 to 32 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 5 to 31 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 5 to 30 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 5 to 29 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 5 to 28 months following the treatment. In another embodiment, the human subject has

a progression free survival ranging from 5 to 27 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 5 to 26 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 5 to 25 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 5 to 24 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 5 to 23 months following the treatment. In some embodiments, the human subject has a progression free survival ranging from 5 to 22 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 5 to 21 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 5 to 20 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 5 to 19 months following the treatment. In one embodiment, the human subject has a progression free survival ranging from 5 to 18 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 5 to 17 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 5 to 16 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 5 to 15 months following the treatment. In one embodiment, the human subject has a progression free survival ranging from 5 to 14 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 5 to 13 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 5 to 12 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 6 to 33 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 6 to 32 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 6 to 31 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 6 to 30 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 6 to 29 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 6 to 28 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 6 to 27 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 6 to 26 months following the treatment. In yet another

embodiment, the human subject has a progression free survival ranging from 6 to 25 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 6 to 22 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 6 to 24 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 6 to 23 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 6 to 22 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 6 to 21 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 6 to 20 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 6 to 19 months following the treatment. In one embodiment, the human subject has a progression free survival ranging from 6 to 18 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 6 to 17 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 6 to 16 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 6 to 15 months following the treatment. In one embodiment, the human subject has a progression free survival ranging from 6 to 14 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 6 to 13 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 6 to 12 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 7 to 33 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 7 to 32 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 7 to 31 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 7 to 30 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 7 to 29 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 7 to 28 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 7 to 27 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 7 to 26 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 7 to 25 months following the

treatment. In another embodiment, the human subject has a progression free survival ranging from 7 to 24 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 7 to 23 months following the treatment. In one embodiment, the human subject has a progression free survival ranging from 7 to 22 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 7 to 21 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 7 to 20 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 7 to 19 months following the treatment. In one embodiment, the human subject has a progression free survival ranging from 7 to 18 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 7 to 17 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 7 to 16 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 7 to 15 months following the treatment. In one embodiment, the human subject has a progression free survival ranging from 7 to 14 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 7 to 13 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 7 to 12 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 8 to 22 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 9 to 22 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 10 to 22 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 11 to 22 months following the treatment. In one embodiment, the human subject has a progression free survival ranging from 12 to 22 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 13 to 22 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 14 to 22 months following the treatment. In yet another embodiment, the human subject has a progression free survival progression free survival ranging from 15 to 22 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 16 to 22 months following the treatment. In one embodiment, the human subject has a progression free survival ranging from 17 to 22 months following the treatment. In another embodiment, the human subject has a progression free

survival ranging from 18 to 22 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 8 to 33 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 9 to 33 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 10 to 33 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 11 to 33 months following the treatment. In one embodiment, the human subject has a progression free survival ranging from 12 to 33 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 13 to 33 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 14 to 33 months following the treatment. In yet another embodiment, the human subject has a progression free survival progression free survival ranging from 15 to 33 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 16 to 33 months following the treatment. In one embodiment, the human subject has a progression free survival ranging from 17 to 33 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 18 to 33 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 19 to 33 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 20 to 33 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 21 to 33 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 22 to 33 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 23 to 33 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 24 to 33 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 25 to 33 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 8 to 29 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 9 to 29 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 10 to 29 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 11 to 29 months following the treatment. In one embodiment, the human subject has a progression free survival ranging from 12 to 29 months following the treatment. In another

embodiment, the human subject has a progression free survival ranging from 13 to 29 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 14 to 29 months following the treatment. In yet another embodiment, the human subject has a progression free survival progression free survival ranging from 15 to 29 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 16 to 29 months following the treatment. In one embodiment, the human subject has a progression free survival ranging from 17 to 29 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 18 to 29 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 19 to 29 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 20 to 29 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 21 to 29 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 22 to 29 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 23 to 29 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 24 to 29 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 25 to 29 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 6 to 21 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 7 to 20 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 8 to 19 months following the treatment. In one embodiment, the human subject has a progression free survival ranging from 9 to 18 months following the treatment. In another embodiment, the human subject has a progression free survival ranging from 10 to 17 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 11 to 16 months following the treatment. In yet another embodiment, the human subject has a progression free survival ranging from 12 to 15 months following the treatment. In a further embodiment, the human subject has a progression free survival ranging from 13 to 14 months following the treatment. In certain embodiments, the human subject is eligible to receive cisplatin treatment (cisplatin eligible). In certain embodiments, the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible). In certain embodiments, the human subject does not have liver metastases. In certain embodiments, the human subject

has liver metastases. In certain embodiments, the human subject has expression of PD-L1 no less than CPS of 10. In certain embodiments, the human subject has expression of PD-L1 less than CPS of 10. In certain embodiments, the race of the human subject is white. In certain embodiments, the race of the human subject is not white.

[00368] In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 5 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 6 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 7 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 8 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 8.2 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 9 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 10 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 10.4 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 10.5 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 10.6 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 11 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 12 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided

herein, wherein the progression free survival in the treated population is at least or about 12.5 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 13 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 14 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 14.6 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 15 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 16 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 16.4 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 17 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 18 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 18.5 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 19 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 20 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 21 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 22 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the

treated population is at least or about 22.3 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 23 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 24 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 25 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 26 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 27 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 28 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 29 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 30 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 31 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 32 months following the treatment. In certain embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 33 months following the treatment. In certain embodiments, the human subject is eligible to receive cisplatin treatment (cisplatin eligible). In certain embodiments, the human subject is eligible to receive cisplatin treatment (cisplatin eligible) and a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 14.6 months following the treatment. In certain embodiments, the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible). In certain embodiments, the human subject is ineligible to receive cisplatin treatment (cisplatin

ineligible) and a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 10.6 months following the treatment. In certain embodiments, the human subject does not have liver metastases. In certain embodiments, the human subject does not have liver metastases and a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 16.4 months following the treatment. In certain embodiments, the human subject has liver metastases. In certain embodiments, the human subject has liver metastases and a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 8.2 months following the treatment. In certain embodiments, the human subject has expression of PD-L1 no less than CPS of 10. In certain embodiments, the human subject has expression of PD-L1 no less than CPS of 10 and a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 18.5 months following the treatment. In certain embodiments, the human subject has expression of PD-L1 less than CPS of 10. In certain embodiments, the human subject has expression of PD-L1 less than CPS of 10 and a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 10.5 months following the treatment. certain embodiments, the race of the human subject is white. In certain embodiments, the race of the human subject is not white. In certain embodiments, the race of the human subject is not white and a population of the human subjects is treated by a method provided herein, wherein the progression free survival in the treated population is at least or about 22.3 months following the treatment.

[00369] In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 33 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 32 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 31 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 30 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 29 months. In some embodiments, a population

of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 28 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 27 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 26 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 25 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 24 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 23 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 22 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 21 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 20 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 19 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 18 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 17 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 16 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 15 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 14 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 13 months. In another

embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 5 to 12 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 33 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 32 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 31 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 30 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 29 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 28 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 27 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 26 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 25 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 24 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 23 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 22 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 21 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 20 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 19 months. In yet

another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 18 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 17 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 16 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 15 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 14 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 13 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 12 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 33 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 32 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 31 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 30 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 29 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 28 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 27 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 26 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 25 months.

In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 24 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 23 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 22 months. In some embodiments, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 21 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 20 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 19 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 18 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 17 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 16 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 15 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 14 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 13 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 12 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6.41 to 22 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 8 to 33 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated

population ranges from 9 to 33 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 10 to 33 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 11 to 33 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 12 to 33 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 13 to 33 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 14 to 33 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 15 to 33 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 16 to 33 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 17 to 33 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 18 to 33 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 19 to 33 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 20 to 33 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 21 to 33 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 22 to 33 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 23 to 33 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 24 to 33 months. In yet another embodiment, a population of the human subjects

is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 25 to 33 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 26 to 33 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 27 to 33 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 28 to 33 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 29 to 33 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 8 to 29 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 9 to 29 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 10 to 29 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 11 to 29 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 12 to 29 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 13 to 29 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 14 to 29 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 15 to 29 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 16 to 29 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 17 to 29 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 18 to 29

months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 19 to 29 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 20 to 29 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 21 to 29 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 22 to 29 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 23 to 29 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 24 to 29 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 25 to 29 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 26 to 29 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 27 to 29 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 28 to 29 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 8 to 22 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 9 to 22 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 10 to 22 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 11 to 22 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 12 to 12 months. In a further embodiment, a population of the human subjects is treated by a method provided

herein, wherein the progression free survival of in the treated population ranges from 13 to 22 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 14 to 22 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 15 to 22 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 16 to 22 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 17 to 22 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 18 to 22 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 6 to 21 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 7 to 20 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 8 to 19 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 9 to 18 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 10 to 17 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 11 to 16 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 12 to 15 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the progression free survival of in the treated population ranges from 13 to 24 months. In certain embodiments, the human subject is eligible to receive cisplatin treatment (cisplatin eligible). In certain embodiments, the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible). In certain embodiments, the human subject does not have liver metastases. In certain embodiments, the human subject has liver metastases. In certain embodiments, the human subject has

expression of PD-L1 no less than CPS of 10. In certain embodiments, the human subject has expression of PD-L1 less than CPS of 10. In certain embodiments, the race of the human subject is white. In certain embodiments, the race of the human subject is not white.

[00370] In some embodiments, the progression free survival is at least or about 6 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 5 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 6 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 7 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 8 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 8.2 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 9 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 10 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 10.4 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 10.5 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 10.6 months for a population of subjects treated with the method.In some embodiments, some embodiments, the progression free survival is at least or about 11 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 12 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 12.5 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 13 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 14 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 14.6 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 15 months for a population of

subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 16 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 16.4 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 17 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 18 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 18.5 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 19 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 20 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 21 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 22 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 22.3 for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 23 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 24 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 25 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 26 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 27 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 28 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 29 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 30 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 31 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression

free survival is at least or about 32 months for a population of subjects treated with the method. In some embodiments, some embodiments, the progression free survival is at least or about 33 months for a population of subjects treated with the method. In certain embodiments, the human subject is eligible to receive cisplatin treatment (cisplatin eligible). In certain embodiments, the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible). In certain embodiments, the human subject does not have liver metastases. In certain embodiments, the human subject has liver metastases. In certain embodiments, the human subject has expression of PD-L1 no less than CPS of 10. In certain embodiments, the human subject has expression of PD-L1 less than CPS of 10. In certain embodiments, the race of the human subject is white. In certain embodiments, the race of the human subject is not white.

[00371] Alternatively, the therapeutic outcome of the methods provided herein can be evaluated based on the overall survival as set forth in Section 6.1.8.3(vi). In one embodiment, the human subject has an overall survival of at least or about 5 months following the treatment. In another embodiment, the human subject has an overall survival of at least or about 6 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 7 months following the treatment. In yet another embodiment, the human subject has an overall survival of at least or about 8 months following the treatment. In one embodiment, the human subject has an overall survival of at least or about 9 months following the treatment. In another embodiment, the human subject has an overall survival of at least or about 10 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 11 months following the treatment. In yet another embodiment, the human subject has an overall survival of at least or about 12 months following the treatment. In one embodiment, the human subject has an overall survival of at least or about 13 months following the treatment. In another embodiment, the human subject has an overall survival of at least or about 14 months following the treatment. In yet another embodiment, the human subject has an overall survival of at least or about 15 months following the treatment. In one embodiment, the human subject has an overall survival of at least or about 16 months following the treatment. In another embodiment, the human subject has an overall survival of at least or about 17 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 18 months following the treatment. In yet another embodiment, the human subject has an overall survival of at least or about 19 months following the treatment. In one embodiment, the human subject has an overall survival of at least or about

20 months following the treatment. In another embodiment, the human subject has an overall survival of at least or about 21 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 22 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 23 months following the treatment. In yet another embodiment, the human subject has an overall survival of at least or about 24 months following the treatment. In one embodiment, the human subject has an overall survival of at least or about 25 months following the treatment. In another embodiment, the human subject has an overall survival of at least or about 26 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 27 months following the treatment. In one embodiment, the human subject has an overall survival of at least or about 28 months following the treatment. In another embodiment, the human subject has an overall survival of at least or about 29 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 30 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 31 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 31.5 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 32 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 33 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 34 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 35 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 36 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 37 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 38 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 39 months following the treatment. In a further embodiment, the human subject has an overall survival of at least or about 40 months following the treatment. In certain embodiments, the human subject is eligible to receive cisplatin treatment (cisplatin eligible) and the human subject has an overall survival of at least or about 31.5 months following the treatment. In certain embodiments, the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible).In one embodiment, the human subject has an overall survival ranging from 10 to 35 months following the treatment. In another embodiment, the human subject has an overall survival ranging from

10 to 34 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 10 to 33 months following the treatment. In yet another embodiment, the human subject has an overall survival ranging from 10 to 32 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 10 to 31 months following the treatment. In another embodiment, the human subject has an overall survival ranging from 10 to 30 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 10 to 29 months following the treatment. In yet another embodiment, the human subject has an overall survival ranging from 10 to 28 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 10 to 27 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 10 to 26 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 10 to 25 months following the treatment. In another embodiment, the human subject has an overall survival ranging from 11 to 35 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 12 to 35 months following the treatment. In yet another embodiment, the human subject has an overall survival ranging from 13 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 14 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 14 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 15 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 16 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 17 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 18 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 19 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 20 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 21 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 22 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 23 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 24 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 25 to 35 months following the treatment. In one

embodiment, the human subject has an overall survival ranging from 26 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 27 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 28 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 29 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 30 to 35 months following the treatment. In one embodiment, the human subject has an overall survival ranging from 31 to 35 months following the treatment. In another embodiment, the human subject has an overall survival ranging from 15 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 16 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 17 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 18 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 19 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 20 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 21 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 22 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 23 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 24 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 25 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 26 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 27 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 28 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 29 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 30 to 32 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 31 to 32 months following the treatment. In another embodiment, the human subject has an overall survival ranging from 15 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 16 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival

ranging from 17 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 18 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 19 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 20 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 21 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 22 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 23 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 24 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 25 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 26 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 27 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 28 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 29 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 30 to 40 months following the treatment. In a further embodiment, the human subject has an overall survival ranging from 31 to 40 months following the treatment. In certain embodiments, the human subject is eligible to receive cisplatin treatment (cisplatin eligible). In certain embodiments, the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible).

[00372] Additionally, in some embodiments, the overall survival is evaluated for a population of human subjects treated by a method provided herein by evaluating the median or mean overall survival in the treated population. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 5 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 6 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 7 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 8 months. In one embodiment, a population of the human

subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 9 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 10 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 11 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 12 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 13 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 14 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 15 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 16 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 17 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 18 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 19 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 20 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 21 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 22 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 23 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the median

or mean overall survival in the treated population is at least or about 24 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 25 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 26 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 27 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 28 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 29 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 30 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 31 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 31.5 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 32 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 33 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 34 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 35 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 36 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 37 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at

least or about 38 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 39 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 40 months. In certain embodiments, the human subject is eligible to receive cisplatin treatment (cisplatin eligible). In certain embodiments, the human subject is eligible to receive cisplatin treatment (cisplatin eligible) and a population of the human subjects is treated by a method provided herein, wherein the median or mean overall survival in the treated population is at least or about 31.5 months. In certain embodiments, the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible).In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 10 to 35 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 10 to 34 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 10 to 33 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 10 to 32 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 11 to 32 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 12 to 32 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 13 to 32 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 14 to 32 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 15 to 32 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 16 to 32 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 17 to 32 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 18

to 32 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 19 to 32 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 20 to 32 months.In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 10 to 35 months. In another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 11 to 35 months. In a further embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 12 to 35 months. In yet another embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 13 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 14 to 35 months. In one embodiment, 14 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 15 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 16 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 17 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 18 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 19 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 20 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 21 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 22 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 23 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated

population ranges from 24 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 25 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 26 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 27 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 28 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 29 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 30 to 35 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 20 to 40 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 21 to 40 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 22 to 40 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 23 to 40 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 24 to 40 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 25 to 40 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 26 to 40 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 27 to 40 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 28 to 40 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated population ranges from 29 to 40 months. In one embodiment, a population of the human subjects is treated by a method provided herein, wherein the overall survival in the treated

population ranges from 30 to 40 months. In certain embodiments, the human subject is eligible to receive cisplatin treatment (cisplatin eligible). In certain embodiments, the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible).

[00373] In one embodiment, the median overall survival is at least or about 5 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 6 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 7 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 8 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 9 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 10 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 11 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 12 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 13 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 14 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 15 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 16 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 17 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 18 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 19 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 20 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 21 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 22 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 22.3 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 23 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 24 months for a population of subjects treated with the method.

In one embodiment, the median overall survival is at least or about 25 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 26 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 27 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 28 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 29 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 30 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 31 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 31.5 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 32 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 33 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 34 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 35 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 36 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 37 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 38 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 39 months for a population of subjects treated with the method. In one embodiment, the median overall survival is at least or about 40 months for a population of subjects treated with the method. In certain embodiments, the human subject is eligible to receive cisplatin treatment (cisplatin eligible). In certain embodiments, the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible).

[00374] In one embodiment, the overall survival is from 10 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 10 to 34 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 10 to 33 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 10 to 32 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 10 to 35 months for a

population of subjects treated with the method. In one embodiment, the overall survival is from 11 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 12 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 13 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 14 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 15 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 16 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 17 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 18 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 19 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 20 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 21 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 22 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 23 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 24 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 25 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 26 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 27 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 28 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 29 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 30 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 31 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 10 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 11 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 12 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 13 to 35 months for a population of subjects treated with the method. In one

embodiment, the overall survival is from 14 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 15 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 16 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 17 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 18 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 19 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 20 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 21 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 22 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 23 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 24 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 25 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 26 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 27 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 28 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 29 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 30 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 31 to 35 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 10 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 11 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 12 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 13 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 14 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 15 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 16 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 17 to 40 months for a

population of subjects treated with the method. In one embodiment, the overall survival is from 18 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 19 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 20 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 21 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 22 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 23 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 24 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 25 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 26 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 27 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 28 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 29 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 30 to 40 months for a population of subjects treated with the method. In one embodiment, the overall survival is from 31 to 40 months for a population of subjects treated with the method. In certain embodiments, the human subject is eligible to receive cisplatin treatment (cisplatin eligible). In certain embodiments, the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible).

[00375] In some embodiments, the subject has a Brief Pain Inventory Short Form (BPI-SF) worst pain score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has an improved BPI-SF worst pain score. In some embodiments, the subject has a BPI-SF worst pain baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from worst pain baseline score of about -0.3 to about -1.2. In some embodiments, the subject has a BPI-SF worst pain baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from worst pain baseline score of about -0.3 to about -1.2, about -0.4 to about -1.2, about -0.5 to about -1.2, about -0.6 to about -1.2, about -0.7 to about -1.2, about -0.8 to about -1.2, about -0.9 to about -1.2, about -1.0 to about -1.2, about -1.1 to about -1.2, about -0.3 to about -1.1, about -

0.3 to about -1.0, about -0.3 to about -0.9, about -0.3 to about -0.8, about -0.3 to about -0.7, about -0.3 to about -0.6, about -0.3 to about -0.5, about -0.3 to about -0.4, about -0.3 to about -0.5, about -0.4 to about -0.6, about -0.5 to about -0.7, about -0.6 to about -0.8, about -0.7 to about -0.9, about -0.8 to about -1.0, about -0.9 to about -1.1, or about -1.0 to about -0.2. In some embodiments, the subject has a BPI-SF worst pain baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from worst pain baseline score of about -0.3, -0.4, -0.5, -0.6, -0.61, -0.7, -0.8, -0.9, -1.0, -1.1, or -1.2. In some embodiments, the subject has a BPI-SF worst pain baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from worst pain baseline score of about -0.61. In some embodiments, the subject has a BPI-SF worst pain baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from worst pain baseline score of about -0.61 at about week 26 after administration of the ADC

[00376] In some embodiments, the subject has a Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire (EORTC QLQ-C30) quality of life (QoL) baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has an improved EORTC QLQ-C30 QoL score. In some embodiments, the subject has a EORTC QLQ-C30 QoL baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from EORTC QLQ-C30 QoL baseline score of about 10.0 to about 15.0. In some embodiments, the subject has a EORTC QLQ-C30 QoL baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from EORTC QLQ-C30 QoL baseline score of about 10.0 to about 15.0, 11.0 to about 15.0, about 12.0 to about 15.0, about 13.0 to about 15.0, about 14.0 to about 15.0, about about 10.0 to about 14.0, about 10.0 to about 13.0, about 10.0 to about 12.0, about 10.0 to about 11.0, about 11.0 to about 13.0, about 12.0 to about 14.0, or about 13.0 to about 15.0. In some embodiments, the subject has a EORTC QLQ-C30 QoL baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from EORTC QLQ-C30 QoL baseline score of about 10.0, about 11.0, about 12.0, about 13.0, about 14.0, or about 15.0. In some embodiments, the subject has a EORTC QLQ-C30 QoL baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to

the subject, the subject has a change from EORTC QLQ-C30 QoL baseline score of about 13.0.

5.2.2 Methods of Treating Cancer in Patient Populations Based on Additional Selection Criteria

[00377] Provided herein are methods for the treatment of various cancers in subjects, wherein the cancers have any of the suitable markers and/or characteristics as provided in Section 6. Also provided herein are methods for the treatment of various cancers in subjects, wherein the subjects have any of the suitable characteristics as provided in Section 6.

[00378] In one aspect, provided herein is a method of preventing or treating cancer in a subject, comprising administering to the subject an effective amount of an antibody drug conjugate, wherein the antibody drug conjugate comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 conjugated to one or more units of monomethyl auristatin E (MMAE), wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23; and wherein the subject has any of the suitable characteristics as provided in Section 6.

[00379] In some aspect, provided herein is a method of preventing or treating cancer in a subject, comprising administering to the subject an effective amount of an antibody drug conjugate, wherein the antibody drug conjugate comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 conjugated to one or more units of monomethyl auristatin E (MMAE), wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23; and wherein the cancer has any of the suitable markers and/or characteristics as provided in Section 6.

[00380] In another aspect, provided herein is a method of preventing or treating cancer in a subject, comprising administering to the subject an effective amount of an antibody drug conjugate, wherein the antibody drug conjugate comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 conjugated to one or more units of monomethyl

auristatin E (MMAE), and wherein the subject has any of the suitable characteristics as provided in Section 6. In a further aspect, provided herein is a method of preventing or treating cancer in a subject, comprising administering to the subject an effective amount of an antibody drug conjugate, wherein the antibody drug conjugate comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 conjugated to one or more units of monomethyl auristatin E (MMAE), and wherein the cancer has any of the suitable markers and/or characteristics as provided in Section 6.

[00381] In some embodiments of the methods provided herein including in Section 5.2 including Sections 5.2.1 and 5.2.2 and Sections 3 and 6, the subject is a human subject.

[00382] In all the methods provided herein and specifically those described in the Sections 5.2.1 and 5.2.2: the therapeutic agents including ADCs that can be used are described in Sections 3, 5.2, 5.3, 5.4, 5.5, and 6, selection of patients for treatment is described herein and exemplified in Section 5.2 including Sections 5.2.1 and 5.2.2 and Sections 3 and 6, dosing regimens and pharmaceutical composition for administering the therapeutic agent are described in Section 5.4, 5.6, 5.7, and Section 6 below, the biomarkers that can be used for identifying the therapeutic agents, selecting the patients, determining the outcome of these methods, and/or serving as criteria in any way for these methods are described herein and exemplified in Section 5.2 including Sections 5.2.1 and 5.2.2 and Sections 3 and 6, the biomarkers can be determined as described in Section 5.9 or as known in the art, therapeutic outcomes for the methods provided herein are described in this Section (Section 5.2 including Section 5.2.1.4) and Sections 3 and 6, additional therapeutic outcomes for the methods provided herein can be improvement of the biomarkers described herein, for example, those described and exemplified in in Section 5.2 including Sections 5.2.1 and 5.2.2 and Sections 3 and 6, and combination therapies including the ADCs and other therapeutic agents are described in this Section (Section 5.2) and in Section 5.5. Therefore, a person skilled in the art would understand that the methods provided herein include all permutations and combinations of the patients, therapeutic agents, dosing regiments, biomarkers, and therapeutic outcomes as described above and below.

5.3 Antibody Drug Conjugates for the Methods

[00383] In various embodiments of the methods provided herein, including the methods provided in Section 5.2, the ADC used in the methods comprises or is an anti-191P4D12 ADC described herein and/or in US Patent No. 8,637,642, which is herein incorporated in its entirety by reference. In some embodiments, the anti-191P4D12 antibody drug conjugate

provided for the methods herein comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 as provided herein, including in Sections 3, 5.3.1, and 6, conjugated to one or more units of cytotoxic agents (drug units, or D) as provided herein, including in Sections 3 and 6 and this Section (Section 5.3) with further disclosures in Sections 5.3.2 and 5.3.4. In certain embodiments, the cytotoxic agents (drug units, or D) can be covalently linked directly or via a linker unit (LU) as provided herein, including in Sections 3 and 6 and this Section (Section 5.3) with further disclosures in Section 5.3.3.

[00384] In some embodiments, the antibody drug conjugate compound has the following formula:

$$L - (LU\text{-}D)_p \qquad \textbf{(I)}$$

or a pharmaceutically acceptable salt or solvate thereof; wherein:

L is the antibody unit, *e.g.*, the anti-nectin-4 antibody or an antigen binding fragment thereof for example as provided in Sections 3, 5.3.1, and 6, and

(LU-D) is a linker unit-drug unit moiety, wherein:

LU- is a linker unit for example as provided in Sections 3 and 6 and this Section (Section 5.3) with further disclosures in Section 5.3.3, and

D is a drug unit having cytostatic or cytotoxic activity against a target cell for example as provided Sections 3 and 6 and this Section (Section 5.3) with further disclosures in Sections 5.3.2 and 5.3.4; and

p is an integer from 1 to 20 with further examples provided in Sections 3 and 6 and this Section (Section 5.3).

[00385] In some embodiments, p ranges from 1 to 20, 1 to 19, 1 to 18, 1 to 17, 1 to 16, 1 to 15, 1 to 14, 1 to 13, 1 to 12, 1 to 11, 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 to 2. In some embodiments, p ranges from 2 to 20, 2 to 19, 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, 2 to 13, 2 to 12, 2 to 11, 2 to 10, 2 to 9, 2 to 8, 2 to 7, 2 to 6, 2 to 5, 2 to 4 or 2 to 3. In some embodiments, p ranges from 3 to 20, 3 to 19, 3 to 18, 3 to 17, 3 to 16, 3 to 15, 3 to 14, 3 to 13, 3 to 12, 3 to 11, 3 to 10, 3 to 9, 3 to 8, 3 to 7, 3 to 6, 3 to 5, or 3 to 4. In some embodiments, p is about 1. In some embodiments, p is about 2. In some embodiments, p is about 3. In some embodiments, p is about 4. In some embodiments, p is about 3.8. In some embodiments, p is about 5. In some embodiments, p is about 6. In some embodiments, p is about 7. In some embodiments, p is about 8. In some embodiments, p is about 9. In some embodiments, p is about 10. In some embodiments, p is about 11. In some embodiments, p is about 12. In some embodiments, p is about 13. In some embodiments, p is about 14. In some

embodiments, p is about 15. In some embodiments, p is about 16. In some embodiments, p is about 17. In some embodiments, p is about 18. In some embodiments, p is about 19. In some embodiments, p is about 20.

[00386] In some embodiments, the antibody drug conjugate compound has the following formula:

$$L - (A_a\text{-}W_w\text{-}Y_y\text{-}D)_p \qquad \textbf{(II)}$$

or a pharmaceutically acceptable salt or solvate thereof, wherein:

L is the Antibody unit, *e.g.*, the anti-nectin-4 antibody or an antigen binding fragment thereof for example as provided in Sections 3, 5.3.1, and 6; and

$-A_a-W_w-Y_y-$ is a linker unit (LU), wherein:

-A- is a stretcher unit,

a is 0 or 1,

each -W- is independently an amino acid unit,

w is an integer ranging from 0 to 12,

-Y- is a self-immolative spacer unit,

y is 0, 1 or 2,

each for example as provided in Sections 3 and 6 and this Section (Section 5.3) with further disclosures in Section 5.3.3;

D is a drug units having cytostatic or cytotoxic activity against the target cell for example as provided Sections 3 and 6 and this Section (Section 5.3) with further disclosures in Sections 5.3.2 and 5.3.4; and

p is an integer from 1 to 20 with further examples provided in Sections 3 and 6 and this Section (Section 5.3).

[00387] In some embodiments, a is 0 or 1, w is 0 or 1, and y is 0, 1 or 2. In some embodiments, a is 0 or 1, w is 0 or 1, and y is 0 or 1. In some embodiments, p ranges from 1 to 20, 1 to 19, 1 to 18, 1 to 17, 1 to 16, 1 to 15, 1 to 14, 1 to 13, 1 to 12, 1 to 11, 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 to 2. In some embodiments, p ranges from 2 to 20, 2 to 19, 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, 2 to 13, 2 to 12, 2 to 11, 2 to 10, 2 to 9, 2 to 8, 2 to 7, 2 to 6, 2 to 5, 2 to 4 or 2 to 3. In some embodiments, p ranges from 3 to 20, 3 to 19, 3 to 18, 3 to 17, 3 to 16, 3 to 15, 3 to 14, 3 to 13, 3 to 12, 3 to 11, 3 to 10, 3 to 9, 3 to 8, 3 to 7, 3 to 6, 3 to 5, or 3 to 4. In some embodiments, p is about 1. In some embodiments, p is about 2. In some embodiments, p is about 3. In some embodiments, p is about 4. In some embodiments, p is about 3.8. In some embodiments, p is about 5. In some embodiments, p is

about 6. In some embodiments, p is about 7. In some embodiments, p is about 8. In some embodiments, p is about 9. In some embodiments, p is about 10. In some embodiments, p is about 11. In some embodiments, p is about 12. In some embodiments, p is about 13. In some embodiments, p is about 14. In some embodiments, p is about 15. In some embodiments, p is about 16. In some embodiments, p is about 17. In some embodiments, p is about 18. In some embodiments, p is about 19. In some embodiments, p is about 20. In some embodiments, when w is not zero, y is 1 or 2. In some embodiments, when w is 1 to 12, y is 1 or 2. In some embodiments, w is 2 to 12 and y is 1 or 2. In some embodiments, a is 1 and w and y are 0.

[00388] In some specific embodiments of the methods provided herein, including the methods provided in Section 5.2, the cytotoxic agent as part of any of the ADCs provided herein for the methods comprises, consists of, or is MMAE.

[00389] For compositions comprising a plurality antibodies or antigen binding fragments thereof, the drug loading is represented by p, the average number of drug molecules per antibody unit. Drug loading can range from 1 to 20 drugs (D) per antibody. The average number of drugs per antibody in preparation of conjugation reactions can be characterized by conventional means such as mass spectroscopy, ELISA assay, and HPLC. The quantitative distribution of antibody drug conjugates in terms of p can also be determined. In some instances, separation, purification, and characterization of homogeneous antibody drug conjugates where p is a certain value from antibody drug conjugates with other drug loadings can be achieved by means such as reverse phase HPLC or electrophoresis. In certain exemplary embodiments, p is from 2 to 8.

[00390] Additional embodiments of the ADC for the methods provided herein have been described in US Patent No. 8,637,642 and International Application No. PCT/US2019/056214 (Publication No. WO2020/117373), both of which are hereby incorporated in their entireties by reference.

[00391] In some embodiments of the methods provided herein, including in Sections 3, 5.2, and 6 and this Section (Section 5.3), the ADC is enfortumab vedotin. In certain embodiments of the methods provided herein, including in Sections 3, 5.2, and 6 and this Section (Section 5.3), the ADC is a biosimilar of enfortumab vedotin.

5.3.1 Anti-191P4D12 Antibodies or Antigen Binding Fragments

[00392] In one embodiment, the antibody or antigen binding fragment thereof that binds to nectin-4-related proteins is an antibody or antigen binding fragment that specifically binds to nectin-4 protein comprising amino acid sequence of SEQ ID NO:2 (see **FIG. 1A**). The

corresponding cDNA encoding the 191P4D12 protein has a sequence of SEQ ID NO:1 (see **FIG. 1A**).

[00393] The antibody that specifically binds to nectin-4 protein comprising amino acid sequence of SEQ ID NO:2 includes antibodies that can bind to other nectin-4-related proteins. For example, antibodies that bind nectin-4 protein comprising amino acid sequence of SEQ ID NO:2 can bind nectin-4-related proteins such as nectin-4 variants and the homologs or analogs thereof.

[00394] In some embodiments, the anti-nectin-4 antibody provided herein is a monoclonal antibody.

[00395] In some embodiments, the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO:4 (cDNA sequence of SEQ ID NO:3), and/or a light chain comprising an amino acid sequence of SEQ ID NO:6 (cDNA sequence of SEQ ID NO:5), as shown in **FIGS. 1B** and **1C**.

[00396] In some embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 (which is the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 136th amino acid (serine) of SEQ ID NO:7) and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23 (which is the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 130th amino acid (arginine) of SEQ ID NO:8). In certain embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining region 1 (CDR-H1), CDR-H2, and CDR-H3 comprising the amino acid sequences of the corresponding CDR-H1, CDR-H2, and CDR-H3 in the heavy chain variable region sequence set forth in SEQ ID NO:22 (which is the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 136th amino acid (serine) of SEQ ID NO:7) and a light chain variable region comprising CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of the corresponding CDR-L1, CDR-L2, and CDR-L3 in the light chain variable region sequence set forth in SEQ ID NO:23 (which is the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 130th amino acid (arginine) of SEQ ID NO:8). In some embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) consisting of the amino acid sequences of the CDRs of the heavy chain

variable region set forth in SEQ ID NO:22 (which is the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 136th amino acid (serine) of SEQ ID NO:7) and a light chain variable region comprising CDRs consisting of the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23 (which is the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 130th amino acid (arginine) of SEQ ID NO:8). In certain embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining region 1 (CDR-H1), CDR-H2, and CDR-H3 consisting of the amino acid sequences of the corresponding CDR-H1, CDR-H2, and CDR-H3 in the heavy chain variable region sequence set forth in SEQ ID NO:22 (which is the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 136th amino acid (serine) of SEQ ID NO:7) and a light chain variable region comprising CDR-L1, CDR-L2, and CDR-L3 consisting of the amino acid sequences of the corresponding CDR-L1, CDR-L2, and CDR-L3 in the light chain variable region sequence set forth in SEQ ID NO:23 (which is the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 130th amino acid (arginine) of SEQ ID NO:8). SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:7 and SEQ ID NO:8 are as shown in **FIGS. 1D** and **1E** and listed below:

SEQ ID NO:22

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYNMNWVRQAPGKGLEWVSYISSSSST
IYYADSVKGRFTISRDNAKNSLSLQMNSLRDEDTAVYYCARAYYYGMDVWGQGTT
VTVSS

SEQ ID NO:23

DIQMTQSPSSVSASVGDRVTITCRASQGISGWLAWYQQKPGKAPKFLIYAASTLQSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPPTFGGGTKVEIKR

SEQ ID NO:7

MELGLCWVFLVAILEGVQCEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYNMNWV
RQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISRDNAKNSLSLQMNSLRDEDTAVY
YCARAYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK
CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA

VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGK

SEQ ID NO:8

MDMRVPAQLLGLLLLWFPGSRCDIQMTQSPSSVSASVGDRVTITCRASQGISGWLA
WYQQKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAN
SFPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK
SFNRGEC

[00397] CDR sequences can be determined according to well-known numbering systems. As described above, CDR regions are well-known to those skilled in the art and have been defined by well-known numbering systems. For example, the Kabat Complementarity Determining Regions (CDRs) are based on sequence variability and are the most commonly used (*see, e.g.*, Kabat *et al.*, *supra*). Chothia refers instead to the location of the structural loops (*see, e.g.*, Chothia and Lesk, 1987, J. Mol. Biol. 196:901-17). The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34). The AbM hypervariable regions represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software (*see, e.g.*, Antibody Engineering Vol. 2 (Kontermann and Dübel eds., 2d ed. 2010)). The "contact" hypervariable regions are based on an analysis of the available complex crystal structures. Another universal numbering system that has been developed and widely adopted is ImMunoGeneTics (IMGT) Information System® (Lafranc *et al.*, 2003, Dev. Comp. Immunol. 27(1):55-77). IMGT is an integrated information system specializing in immunoglobulins (IG), T-cell receptors (TCR), and major histocompatibility complex (MHC) of human and other vertebrates. Herein, the CDRs are referred to in terms of both the amino acid sequence and the location within the light or heavy chain. As the "location" of the CDRs within the structure of the immunoglobulin variable domain is conserved between species and present in structures called loops, by using numbering systems that align variable domain sequences according to structural features, CDR and framework residues are readily identified. This information can be used in grafting and replacement of CDR residues from immunoglobulins of one species into an acceptor framework from, typically, a human

antibody. An additional numbering system (AHon) has been developed by Honegger and Plückthun, 2001, J. Mol. Biol. 309: 657-70. Correspondence between the numbering system, including, for example, the Kabat numbering and the IMGT unique numbering system, is well-known to one skilled in the art (*see, e.g.*, Kabat, *supra*; Chothia and Lesk, *supra*; Martin, *supra*; Lefranc *et al.*, *supra*). The residues from each of these hypervariable regions or CDRs are noted in Table 1 above.

[00398] In some embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 according to Kabat numbering and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23 according to Kabat numbering.

[00399] In some embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 according to AbM numbering and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23 according to AbM numbering.

[00400] In other embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 according to Chothia numbering and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23 according to Chothia numbering.

[00401] In other embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 according to Contact numbering and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23 according to Contact numbering.

[00402] In yet other embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 according to IMGT numbering and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23 according to IMGT numbering.

[00403] In some embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) consisting of the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 according to Kabat numbering and a light chain variable region comprising CDRs consisting of the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23 according to Kabat numbering.

[00404] In some embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) consisting of the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 according to AbM numbering and a light chain variable region comprising CDRs consisting of the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23 according to AbM numbering.

[00405] In other embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) consisting of the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 according to Chothia numbering and a light chain variable region comprising CDRs consisting of the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23 according to Chothia numbering.

[00406] In other embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) consisting of the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 according to Contact numbering and a light chain variable region comprising CDRs consisting of the amino acid

sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23 according to Contact numbering.

[00407] In yet other embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) consisting of the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 according to IMGT numbering and a light chain variable region comprising CDRs consisting of the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23 according to IMGT numbering.

[00408] As described above, the CDR sequences according to different numbering systems can be readily determined, *e.g.*, using online tools such as the one provided by Antigen receptor Numbering And Receptor ClassificatIon (ANARCI). For example, the heavy chain CDR sequences within SEQ ID NO:22, and the light chain CDR sequences within SEQ ID NO:23 according to Kabat numbering as determined by ANARCI are listed in Table 6 below.

Table 6.

	VH of SEQ ID NO:22	**VL of SEQ ID NO:23**
CDR1	SYNMN (SEQ ID NO:9)	RASQGISGWLA (SEQ ID NO:12)
CDR2	YISSSSSTIYYADSVKG (SEQ ID NO:10)	AASTLQS (SEQ ID NO:13)
CDR3	AYYYGMDV (SEQ ID NO:11)	QQANSFPPT (SEQ ID NO:14)

[00409] For another example, the heavy chain CDR sequences within SEQ ID NO:22, and the light chain CDR sequences within SEQ ID NO:23 according to IMGT numbering as determined by ANARCI are listed in Table 7 below.

Table 7.

	VH of SEQ ID NO:22	**VL of SEQ ID NO:23**
CDR1	GFTFSSYN (SEQ ID NO:16)	QGISGW (SEQ ID NO:19)
CDR2	ISSSSSTI (SEQ ID NO:17)	AAS (SEQ ID NO:20)
CDR3	ARAYYYGMDV (SEQ ID NO:18)	QQANSFPPT (SEQ ID NO:21)

[00410] In some embodiments, the antibody or antigen binding fragment thereof comprises CDR-H1 comprising an amino acid sequence of SEQ ID NO:9, CDR-H2 comprising an amino acid sequence of SEQ ID NO:10, CDR-H3 comprising an amino acid sequence of SEQ ID NO:11, CDR-L1 comprising an amino acid sequence of SEQ ID NO:12,

CDR-L2 comprising an amino acid sequence of SEQ ID NO:13, and CDR-L3 comprising an amino acid sequence of SEQ ID NO:14.

[00411] In some embodiments, the antibody or antigen binding fragment thereof comprises CDR-H1 comprising an amino acid sequence of SEQ ID NO:16, CDR-H2 comprising an amino acid sequence of SEQ ID NO:17, CDR-H3 comprising an amino acid sequence of SEQ ID NO:18, CDR-L1 comprising an amino acid sequence of SEQ ID NO:19, CDR-L2 comprising an amino acid sequence of SEQ ID NO:20, and CDR-L3 comprising an amino acid sequence of SEQ ID NO:21.

[00412] In some embodiments, the antibody or antigen binding fragment thereof comprises CDR-H1 consisting of an amino acid sequence of SEQ ID NO:9, CDR-H2 consisting of an amino acid sequence of SEQ ID NO:10, CDR-H3 consisting of an amino acid sequence of SEQ ID NO:11, CDR-L1 consisting of an amino acid sequence of SEQ ID NO:12, CDR-L2 consisting of an amino acid sequence of SEQ ID NO:13, and CDR-L3 consisting of an amino acid sequence of SEQ ID NO:14.

[00413] In some embodiments, the antibody or antigen binding fragment thereof comprises CDR-H1 consisting of an amino acid sequence of SEQ ID NO:16, CDR-H2 consisting of an amino acid sequence of SEQ ID NO:17, CDR-H3 consisting of an amino acid sequence of SEQ ID NO:18, CDR-L1 consisting of an amino acid sequence of SEQ ID NO:19, CDR-L2 consisting of an amino acid sequence of SEQ ID NO:20, and CDR-L3 consisting of an amino acid sequence of SEQ ID NO:21.

[00414] In some embodiments, the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:22 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:23.

[00415] In some embodiments, the antibody or antigen binding fragment thereof comprises a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO:22 and a light chain variable region consisting of the amino acid sequence of SEQ ID NO:23.

[00416] In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID NO:7 and a light chain comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:8.

[00417] In some embodiments, the antibody comprises a heavy chain consisting of the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino

acid (lysine) of SEQ ID NO:7 and a light chain consisting of the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:8.

[00418] In some embodiments, amino acid sequence modification(s) of antibodies described herein are contemplated. For example, it may be desirable to optimize the binding affinity and/or other biological properties of the antibody, including but not limited to specificity, thermostability, expression level, effector functions, glycosylation, reduced immunogenicity, or solubility. Thus, in addition to the antibodies described herein, it is contemplated that antibody variants can be prepared. For example, antibody variants can be prepared by introducing appropriate nucleotide changes into the encoding DNA, and/or by synthesis of the desired antibody or polypeptide. Those skilled in the art who appreciate that amino acid changes can alter post-translational processes of the antibody, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

[00419] In some embodiments, the antibodies provided herein are chemically modified, for example, by the covalent attachment of any type of molecule to the antibody. The antibody derivatives can include antibodies that have been chemically modified, for example, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, *etc.* Any of numerous chemical modifications can be carried out by known techniques, including, but not limited to, specific chemical cleavage, acetylation, formulation, metabolic synthesis of tunicamycin, *etc.* Additionally, the antibody can contain one or more non-classical amino acids.

[00420] Variations can be a substitution, deletion, or insertion of one or more codons encoding the single domain antibody or polypeptide that results in a change in the amino acid sequence as compared with the original antibody or polypeptide. Amino acid substitutions can be the result of replacing one amino acid with another amino acid comprising similar structural and/or chemical properties, such as the replacement of a leucine with a serine, *e.g.*, conservative amino acid replacements. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule provided herein, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which results in amino acid substitutions. Insertions or deletions can optionally be in the range of about 1 to 5 amino acids. In certain embodiments, the substitution, deletion, or insertion includes fewer than 25 amino acid substitutions, fewer than 20 amino acid substitutions, fewer than 15 amino acid substitutions, fewer than 10 amino acid substitutions,

fewer than 5 amino acid substitutions, fewer than 4 amino acid substitutions, fewer than 3 amino acid substitutions, or fewer than 2 amino acid substitutions relative to the original molecule. In a specific embodiment, the substitution is a conservative amino acid substitution made at one or more predicted non-essential amino acid residues. The variation allowed can be determined by systematically making insertions, deletions, or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the parental antibodies.

[00421] Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing multiple residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue.

[00422] Antibodies generated by conservative amino acid substitutions are included in the present disclosure. In a conservative amino acid substitution, an amino acid residue is replaced with an amino acid residue comprising a side chain with a similar charge. As described above, families of amino acid residues comprising side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (*e.g.,* lysine, arginine, histidine), acidic side chains (*e.g.,* aspartic acid, glutamic acid), uncharged polar side chains (*e.g.,* glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.,* alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.,* threonine, valine, isoleucine) and aromatic side chains (*e.g.,* tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed and the activity of the protein can be determined conservative (*e.g.*, within an amino acid group with similar properties and/or side chains) substitutions can be made, so as to maintain or not significantly change the properties.

[00423] Amino acids can be grouped according to similarities in the properties of their side chains (*see, e.g.*, Lehninger, Biochemistry 73-75 (2d ed. 1975)): (1) non-polar: Ala (A), Val (V), Leu (L), Ile (I), Pro (P), Phe (F), Trp (W), Met (M); (2) uncharged polar: Gly (G), Ser (S), Thr (T), Cys (C), Tyr (Y), Asn (N), Gln (Q); (3) acidic: Asp (D), Glu (E); and (4) basic: Lys (K), Arg (R), His(H). Alternatively, naturally occurring residues can be divided into groups based on common side-chain properties: (1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln; (3) acidic: Asp, Glu; (4) basic:

His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; and (6) aromatic: Trp, Tyr, Phe.

[00424] For example, any cysteine residue not involved in maintaining the proper conformation of the antibody also can be substituted, for example, with another amino acid, such as alanine or serine, to improve the oxidative stability of the molecule and to prevent aberrant crosslinking.

[00425] The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis (*see, e.g.*, Carter, 1986, Biochem J. 237:1-7; and Zoller *et al.*, 1982, Nucl. Acids Res. 10:6487-500), cassette mutagenesis (*see, e.g.*, Wells *et al.*, 1985, Gene 34:315-23), or other known techniques can be performed on the cloned DNA to produce the anti-anti-MSLN antibody variant DNA.

[00426] Covalent modifications of antibodies are included within the scope of the present disclosure. Covalent modifications include reacting targeted amino acid residues of an antibody with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the antibody. Other modifications include deamidation of glutaminyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α-amino groups of lysine, arginine, and histidine side chains (*see, e.g.*, Creighton, Proteins: Structure and Molecular Properties 79-86 (1983)), acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

[00427] Other types of covalent modification of the antibody included within the scope of this present disclosure include altering the native glycosylation pattern of the antibody or polypeptide (*see, e.g.*, Beck *et al.*, 2008, Curr. Pharm. Biotechnol. 9:482-501; and Walsh, 2010, Drug Discov. Today 15:773-80), and linking the antibody to one of a variety of nonproteinaceous polymers, *e.g.*, polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth, for example, in U.S. Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192; or 4,179,337.

[00428] In certain embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having certain homology or identity to the heavy chain as set forth in SEQ ID NO:7 and a light chain having certain homology or identity to the light chain as set forth in SEQ ID NO:8. Such embodiments of heavy/light chains with homology or identity are further provided as follows. In some embodiments, the antibody or antigen

binding fragment provided herein comprises a heavy chain having more than 70% homology or identity to the heavy chain as set forth in SEQ ID NO:7. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having more than 75% homology or identity to the heavy chain as set forth in SEQ ID NO:7. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having more than 80% homology or identity to the heavy chain as set forth in SEQ ID NO:7. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having more than 85% homology or identity to the heavy chain as set forth in SEQ ID NO:7. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having more than 90% homology or identity to the heavy chain as set forth in SEQ ID NO:7. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having more than 95% homology or identity to the heavy chain as set forth in SEQ ID NO:7. In certain embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having any of the provided homology or identity to the heavy chain as set forth in SEQ ID NO:7, wherein the CDRs (CDR-H1, CDR-H2, and CDR-H3) are identical to the CDRs in the heavy chain as set forth in SEQ ID NO:7. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain having more than 70% homology or identity to the light chain as set forth in SEQ ID NO:8. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain having more than 75% homology or identity to the light chain as set forth in SEQ ID NO:8. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain having more than 80% homology or identity to the light chain as set forth in SEQ ID NO:8. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain having more than 85% homology or identity to the light chain as set forth in SEQ ID NO:8. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain having more than 90% homology or identity to the light chain as set forth in SEQ ID NO:8. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain having more than 95% homology or identity to the light chain as set forth in SEQ ID NO:8. In certain embodiments, the antibody or antigen binding fragment provided herein comprises a light chain having any of the provided homology or identity to the light chain as set forth in SEQ ID NO:8, wherein the CDRs (CDR-L1, CDR-L2, and CDR-L3) are identical to the CDRs in the light chain as set forth in SEQ ID NO:8. In certain embodiments, the antibody or antigen binding fragment provided herein comprises any

homologous light chain and any homologous heavy chain as provided in this paragraph in any combination or permutation.

[00429] In certain embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain variable region having certain homology or identity to the heavy chain variable region as set forth in SEQ ID NO:22 and a light chain variable region having certain homology or identity to the light chain variable region as set forth in SEQ ID NO:23. Such embodiments of heavy chain variable regions and light chain variable regions with homology or identity are further provided as follows. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain variable region having more than 70% homology or identity to the heavy chain variable region as set forth in SEQ ID NO:22. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain variable region having more than 75% homology or identity to the heavy chain variable region as set forth in SEQ ID NO:22. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain variable region having more than 80% homology or identity to the heavy chain variable region as set forth in SEQ ID NO:22. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain variable region having more than 85% homology or identity to the heavy chain variable region as set forth in SEQ ID NO:22. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain variable region having more than 90% homology or identity to the heavy chain variable region as set forth in SEQ ID NO:22. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain variable region having more than 95% homology or identity to the heavy chain variable region as set forth in SEQ ID NO:22. In certain embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain variable region having any of the provided homology or identity to the heavy chain variable region as set forth in SEQ ID NO:22, wherein the CDRs (CDR-H1, CDR-H2, and CDR-H3) are identical to the CDRs in the heavy chain variable region as set forth in SEQ ID NO:22. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain variable region having more than 70% homology or identity to the light chain variable region as set forth in SEQ ID NO:23. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain variable region having more than 75% homology or identity to the light chain variable region as set forth in SEQ ID NO:23. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain variable region having more than 80% homology or identity to

the light chain variable region as set forth in SEQ ID NO:23. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain variable region having more than 85% homology or identity to the light chain variable region as set forth in SEQ ID NO:23. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain variable region having more than 90% homology or identity to the light chain variable region as set forth in SEQ ID NO:23. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain variable region having more than 95% homology or identity to the light chain variable region as set forth in SEQ ID NO:23. In certain embodiments, the antibody or antigen binding fragment provided herein comprises a light chain variable region having any of the provided homology or identity to the light chain variable region as set forth in SEQ ID NO:23, wherein the CDRs (CDR-L1, CDR-L2, and CDR-L3) are identical to the CDRs in the light chain variable region as set forth in SEQ ID NO:23. In certain embodiments, the antibody or antigen binding fragment provided herein comprises any homologous light chain variable region and any homologous heavy chain variable region as provided in this paragraph in any combination or permutation.

[00430] In some embodiments, the anti-nectin-4 antibody provided herein comprises heavy and light chain CDR regions of an antibody designated Ha22-2(2,4)6.1 produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267, or heavy and light chain CDR regions comprising amino acid sequences that are homologous to the amino acid sequences of the heavy and light chain CDR regions of Ha22-2(2,4)6.1, and wherein the antibodies retain the desired functional properties of the anti-nectin-4 antibody designated Ha22-2(2,4)6.1 produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267.

[00431] In some embodiments, the anti-nectin-4 antibody provided herein comprises heavy and light chain CDR regions (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) of an antibody designated Ha22-2(2,4)6.1 produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267, or heavy and light chain CDR regions consisting of amino acid sequences that are homologous to the amino acid sequences of the heavy and light chain CDR regions of Ha22-2(2,4)6.1, and wherein the antibodies retain the desired functional properties of the anti-nectin-4 antibody designated Ha22-2(2,4)6.1 produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267.

[00432] In some embodiments, the antibody or antigen binding fragment thereof provided herein comprises a humanized heavy chain variable region and a humanized light chain variable region, wherein:

(a) the heavy chain variable region comprises CDRs (CDR-H1, CDR-H2, and CDR-H3) comprising the amino acid sequences of the heavy chain variable region CDRs set forth in the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267;

(b) the light chain variable region comprises CDRs (CDR-L1, CDR-L2, and CDR-L3) comprising the amino acid sequences of the light chain variable region CDRs set forth in the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267.

[00433] In some embodiments, the antibody or antigen binding fragment thereof provided herein comprises a humanized heavy chain variable region and a humanized light chain variable region, wherein:

(a) the heavy chain variable region comprises CDRs (CDR-H1, CDR-H2, and CDR-H3) consisting of the amino acid sequences of the heavy chain variable region CDRs set forth in the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267;

(b) the light chain variable region comprises CDRs (CDR-L1, CDR-L2, and CDR-L3) consisting of the amino acid sequences of the light chain variable region CDRs set forth in the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267.

[00434] In some embodiments, the anti-nectin-4 antibody provided herein comprises heavy and light chain variable regions of an antibody designated Ha22-2(2,4)6.1 produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267, or heavy and light variable regions comprising amino acid sequences that are homologous to the amino acid sequences of the heavy and light chain variable regions of Ha22-2(2,4)6.1, and wherein the antibodies retain the desired functional properties of the anti-nectin-4 antibody provided herein. In some embodiments, the anti-nectin-4 antibody provided herein comprises heavy and light chain variable regions of an antibody designated Ha22-2(2,4)6.1 produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267, or heavy and light variable regions consisting of amino acid sequences that are homologous to the amino acid sequences of the heavy and light chain variable regions of Ha22-2(2,4)6.1, and wherein the antibodies retain

the desired functional properties of the anti-nectin-4 antibody provided herein. As the constant region of the antibody of the disclosure, any subclass of constant region can be chosen. In one embodiment, human IgG1 constant region as the heavy chain constant region and human Ig kappa constant region as the light chain constant region can be used.

[00435] In some embodiments, the anti-nectin-4 antibody provided herein comprises heavy and light chains of an antibody designated Ha22-2(2,4)6.1 produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267, or heavy and light chains comprising amino acid sequences that are homologous to the amino acid sequences of the heavy and light chains of Ha22-2(2,4)6.1, and wherein the antibodies retain the desired functional properties of the anti-nectin-4 antibody provided herein. In some embodiments, the anti-nectin-4 antibody provided herein comprises heavy and light chains of an antibody designated Ha22-2(2,4)6.1 produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267, or heavy and light chains consisting of amino acid sequences that are homologous to the amino acid sequences of the heavy and light chains of Ha22-2(2,4)6.1, and wherein the antibodies retain the desired functional properties of the anti-nectin-4 antibody provided herein.

[00436] In some embodiments, the antibody or antigen binding fragment thereof provided herein comprises a heavy chain variable region and a light chain variable region, wherein:

(a) the heavy chain variable region comprises an amino acid sequence that is at least 80% homologous or identical to the heavy chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267; and

(b) the light chain variable region comprises an amino acid sequence that is at least 80% homologous or identical to the light chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267.

[00437] In certain embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain variable region having certain homology or identity to the heavy chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267 and a light chain variable region having certain homology or identity to the light chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. Such embodiments of heavy chain variable regions and light chain variable regions with homology

or identity are further provided as follows. In some embodiments, the heavy chain variable region comprises an amino acid sequence that is at least 85% homologous or identical to the heavy chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In other embodiments, the heavy chain variable region comprises an amino acid sequence that is at least 90% homologous or identical to the heavy chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In yet other embodiments, the heavy chain variable region comprises an amino acid sequence that is at least 95% homologous or identical to the heavy chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In other embodiments, the heavy chain variable region can be 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homologous or identical to the heavy chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In some embodiments, the light chain variable region comprises an amino acid sequence that is at least 85% homologous or identical to the light chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In other embodiments, the light chain variable region comprises an amino acid sequence that is at least 90% homologous or identical to the light chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In yet other embodiments, the light chain variable region comprises an amino acid sequence that is at least 95% homologous or identical to the light chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In other embodiments, the light chain variable region can be 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homologous or identical to the light chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In certain embodiments, the antibody or antigen binding fragment provided herein comprises any homologous light chain variable region and any homologous heavy chain variable region as provided in this paragraph in any combination or permutation.

[00438] In other embodiments, the antibody or antigen binding fragment thereof provided herein comprises a heavy chain and a light chain, wherein:

(a) the heavy chain comprises an amino acid sequence that is at least 80% homologous or identical to the heavy chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267; and

(b) the light chain comprises an amino acid sequence that is at least 80% homologous or identical to the light chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267.

[00439] In certain embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having certain homology or identity to the heavy chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267 and a light chain having certain homology or identity to the light chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. Such embodiments of heavy chains and light chains with homology or identity are further provided as follows. In some embodiments, the heavy chain comprises an amino acid sequence that is at least 85% homologous or identical to the heavy chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In other embodiments, the heavy chain comprises an amino acid sequence that is at least 90% homologous or identical to the heavy chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In yet other embodiments, the heavy chain comprises an amino acid sequence that is at least 95% homologous or identical to the heavy chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In other embodiments, the heavy chain can be 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homologous or identical to the heavy chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In some embodiments, the light chain comprises an amino acid sequence that is at least 85% homologous or identical to the light chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In other embodiments, the light chain comprises an amino acid sequence that is

at least 90% homologous or identical to the light chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In yet other embodiments, the light chain comprises an amino acid sequence that is at least 95% homologous or identical to the light chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In other embodiments, the light chain can be 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homologous or identical to the light chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In certain embodiments, the antibody or antigen binding fragment provided herein comprises any homologous light chain and any homologous heavy chain as provided in this paragraph in any combination or permutation.

[00440] In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to a specific epitope in 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to VC1 domain of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to VC1 domain but not to C1C2 domain of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 1st to 147th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to an epitope located in the 1st to 147th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 1st to 10th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 11th to 20th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 21st to 30th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 31st to 40th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 41st to 50th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 51st to 60th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 61st to 70th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 71st to 80th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the

81st to 90th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 91st to 100th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 101st to 110th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 111th to 120th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 121st to 130th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 131st to 140th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 141st to 147th amino acid residues of 191P4D12. The binding epitopes of certain embodiments the antibodies or antigen binding fragments thereof provided herein have been determined and described in WO 2012/047724, which is incorporated herein in its entirety by reference.

[00441] In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to epitopes in 191P4D12 that are common between the 191P4D12 variants observed in human. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to epitopes in 191P4D12 that are common between the 191P4D12 polymorphism observed in human. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to epitopes in 191P4D12 that are common between the 191P4D12 polymorphism observed in human cancers. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to epitopes in 191P4D12 that would bind, internalize, disrupt or modulate the biological function of 191P4Dl2 or 191P4D12 variants. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to epitopes in 191P4D12 that would disrupt the interaction between 191P4D12 with ligands, substrates, and binding partners.

[00442] Engineered antibodies provided herein include those in which modifications have been made to framework residues within VH and/or VL (*e.g.* to improve the properties of the antibody). Typically, such framework modifications are made to decrease the immunogenicity of the antibody. For example, one approach is to "backmutate" one or more framework residues to the corresponding germline sequence. More specifically, an antibody that has undergone somatic mutation can contain framework residues that differ from the germline sequence from which the antibody is derived. Such residues can be identified by comparing the antibody framework sequences to the germline sequences from which the antibody is derived. To return the framework region sequences to their germline

configuration, the somatic mutations can be "backmutated" to the germline sequence by, for example, site-directed mutagenesis or PCR-mediated mutagenesis (*e.g.*, "backmutated" from leucine to methionine). Such "backmutated" antibodies are also intended to be encompassed by the disclosure.

[00443] Another type of framework modification involves mutating one or more residues within the framework region, or even within one or more CDR regions, to remove T-cell epitopes to thereby reduce the potential immunogenicity of the antibody. This approach is also referred to as "deimmunization" and is described in further detail in U.S. Patent Publication No. 2003/0153043 by Carr et al.

[00444] In addition or alternative to modifications made within the framework or CDR regions, antibodies of the disclosure can be engineered to include modifications within the Fc region, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity. Furthermore, an anti-191P4D12 antibody provided herein can be chemically modified (*e.g.*, one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody. Each of these embodiments is described in further detail below.

[00445] In one embodiment, the hinge region of CH1 is modified such that the number of cysteine residues in the hinge region is altered, *e.g.*, increased or decreased. This approach is described further in U.S. Pat. No. 5,677,425 by Bodmer et al. The number of cysteine residues in the hinge region of CH1 is altered to, for example, facilitate assembly of the light and heavy chains or to increase or decrease the stability of the anti-191P4D12 antibody.

[00446] In another embodiment, the Fc hinge region of an antibody is mutated to decrease the biological half-life of the anti-191P4D12 antibody. More specifically, one or more amino acid mutations are introduced into the CH2-CH3 domain interface region of the Fc-hinge fragment such that the antibody has impaired Staphylococcyl protein A (SpA) binding relative to native Fc-hinge domain SpA binding. This approach is described in further detail in U.S. Pat. No. 6,165,745 by Ward et al.

[00447] In another embodiment, the anti-191P4D12 antibody is modified to increase its biological half-life. Various approaches are possible. For example, mutations can be introduced as described in U.S. Pat. No. 6,277,375 to Ward. Alternatively, to increase the biological half-life, the antibody can be altered within the CH1 or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Pat. Nos. 5,869,046 and 6,121,022 by Presta et al.

[00448] In yet other embodiments, the Fc region is altered by replacing at least one amino acid residue with a different amino acid residue to alter the effector function(s) of the antibody. For example, one or more amino acids selected from amino acid specific residues can be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Pat. Nos. 5,624,821 and 5,648,260, both by Winter et al.

[00449] Reactivity of the anti-191P4D12 antibodies with a 191P4D12-related protein can be established by a number of well-known means, including Western blot, immunoprecipitation, ELISA, and FACS analyses using, as appropriate, 191P4D12-related proteins, 191P4D12-expressing cells or extracts thereof. A 191P4D12 antibody or fragment thereof can be labeled with a detectable marker or conjugated to a second molecule. Suitable detectable markers include, but are not limited to, a radioisotope, a fluorescent compound, a bioluminescent compound, chemiluminescent compound, a metal chelator or an enzyme. Further, bi-specific antibodies specific for two or more 191P4D12 epitopes are generated using methods generally known in the art. Homodimeric antibodies can also be generated by cross-linking techniques known in the art (*e.g.*, Wolff *et al.*, Cancer Res. 53: 2560-2565).

[00450] In yet another specific embodiment, the anti-191P4D12 antibody provided herein is an antibody comprising heavy and light chain of an antibody designated Ha22-2(2,4)6.1. The heavy chain of Ha22-2(2,4)6.1 consists of the amino acid sequence ranging from 20th E residue to the 466th K residue of SEQ ID NO:7 and the light chain of Ha22-2(2,4)6.1 consists of amino acid sequence ranging from 23rd D residue to the 236th C residue of SEQ ID NO:8 sequence.

[00451] The hybridoma producing the antibody designated Ha22-2(2,4)6.1 was sent (via Federal Express) to the American Type Culture Collection (ATCC), P.O. Box 1549, Manassas, VA 20108 on 18-August-2010 and assigned Accession number PTA-11267.

[00452] Additional embodiments of anti-nectin-4 antibody have been described in US Patent No. 8,637,642 and International Application No. PCT/US2019/056214 (Publication No. WO2020/117373), both of which are hereby incorporated in their entireties by reference.

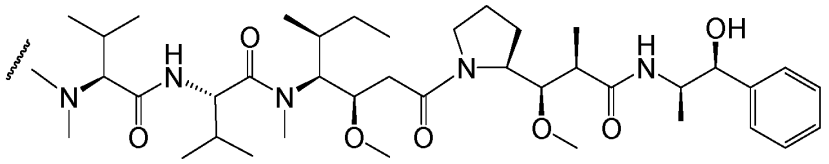
5.3.2 Cytotoxic Agents (Drug Units)

[00453] As the ADC used in the methods provided herein comprises an antibody or antigen binding fragment thereof conjugated to a cytotoxic agent, the disclosure further

provides various embodiments for the cytotoxic agent as part of the ADC for use in the methods. In various embodiments of the methods provided herein, including the methods provided in Section 5.2, the cytotoxic agent as part of any of the ADCs provided herein for the methods comprises, consists of, or is a tubulin disrupting agent. In one embodiment, the cytotoxic agent is a tubulindisrupting agent. In some embodiments, the tubulin disrupting agent is selected from the group consisting of a dolastatin, an auristatin, a hemiasterlin, a vinca alkaloid, a maytansinoid, an eribulin, a colchicine, a plocabulin, a phomopsin, an epothilone, a cryptophycin, and a taxane. In one specific embodiment, the tubulin disrupting agent is an auristatin. In a further specific embodiment, the auristatin is monomethyl auristatin E (MMAE), monomethyl auristatin F (MMAF), AFP, or auristain T. In yet another specific embodiment, the auristatin is monomethyl auristatin E (MMAE).

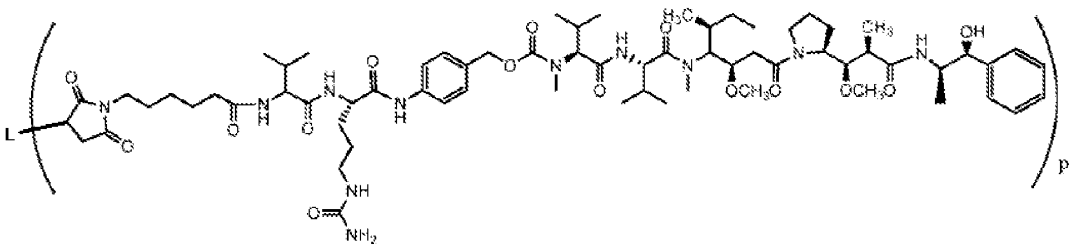
[00454] In various embodiments of the methods provided herein, including the methods provided in Section 5.2, the cytotoxic agent as part of any of the ADCs provided herein for the methods comprises, consists of, or is any agent selected from the cytotoxic agents described in US Patent No. 8,637,642 and International Application No. PCT/US2019/056214 (Publication No. WO2020/117373), both of which are hereby incorporated in their entireties by reference

[00455] In some embodiments, the auristatin is MMAE (wherein the wavy line indicates the covalent attachment to a linker of an antibody drug conjugate).



MMAE

[00456] In some embodiments, an exemplary embodiment comprising MMAE and a linker component (described further herein) has the following structure (wherein L presents the antibody (*e.g.* anti-nectin-4 antibody or antigen binding fragment thereof) and p ranges from 1 to 12):



[00457] In some embodiments of the formula described in the preceding paragraph, p ranges from 1 to 20, 1 to 19, 1 to 18, 1 to 17, 1 to 16, 1 to 15, 1 to 14, 1 to 13, 1 to 12, 1 to 11, 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 to 2. In some embodiments of the formula described in the preceding paragraph, p ranges from 2 to 20, 2 to 19, 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, 2 to 13, 2 to 12, 2 to 11, 2 to 10, 2 to 9, 2 to 8, 2 to 7, 2 to 6, 2 to 5, 2 to 4 or 2 to 3. In some embodiments of the formula described in the preceding paragraph, p ranges from 3 to 20, 3 to 19, 3 to 18, 3 to 17, 3 to 16, 3 to 15, 3 to 14, 3 to 13, 3 to 12, 3 to 11, 3 to 10, 3 to 9, 3 to 8, 3 to 7, 3 to 6, 3 to 5, or 3 to 4. In some embodiments of the formula described in the preceding paragraph, p is about 1. In some embodiments of the formula described in the preceding paragraph, p is about 2. In some embodiments of the formula described in the preceding paragraph, p is about 3. In some embodiments of the formula described in the preceding paragraph, p is about 4. In some embodiments of the formula described in the preceding paragraph, p is about 3.8. In some embodiments of the formula described in the preceding paragraph, p is about 5. In some embodiments of the formula described in the preceding paragraph, p is about 6. In some embodiments of the formula described in the preceding paragraph, p is about 7. In some embodiments of the formula described in the preceding paragraph, p is about 8. In some embodiments of the formula described in the preceding paragraph, p is about 9. In some embodiments of the formula described in the preceding paragraph, p is about 10. In some embodiments of the formula described in the preceding paragraph, p is about 11. In some embodiments of the formula described in the preceding paragraph, p is about 12. In some embodiments of the formula described in the preceding paragraph, p is about 13. In some embodiments of the formula described in the preceding paragraph, p is about 14. In some embodiments of the formula described in the preceding paragraph, p is about 15. In some embodiments of the formula described in the preceding paragraph, p is about 16. In some embodiments of the formula described in the preceding paragraph, p is about 17. In some embodiments of the formula described in the preceding paragraph, p is about 18. In some embodiments of the formula described in the preceding paragraph, p is about 19. In some embodiments of the formula described in the preceding paragraph, p is about 20.

[00458] Typically, peptide-based drug units can be prepared by forming a peptide bond between two or more amino acids and/or peptide fragments. Such peptide bonds can be prepared, for example, according to the liquid phase synthesis method (see E. Schröder and K. Lübke, "The Peptides", volume 1, pp 76-136, 1965, Academic Press) that is well-known in the field of peptide chemistry. The auristatin/dolastatin drug units can be prepared

according to the methods of: US 5635483; US 5780588; Pettit et al (1989) J. Am. Chem. Soc. 111:5463-5465; Pettit et al (1998) Anti-Cancer Drug Design 13:243-277; Pettit, G.R., et al. Synthesis, 1996, 719-725; Pettit et al (1996) J. Chem. Soc. Perkin Trans. 1 5:859-863; and Doronina (2003) Nat Biotechnol 21(7):778-784.

[00459] Additional embodiments of cytotoxic agent have been described in US Patent No. 8,637,642 and International Application No. PCT/US2019/056214 (Publication No. WO2020/117373), both of which are hereby incorporated in their entireties by reference.

5.3.3 Linkers

[00460] Typically, the antibody drug conjugates comprise a linker unit between the drug unit (*e.g.*, MMAE) and the antibody unit (*e.g.*, the anti-191P4D12 antibody or antigen binding fragment thereof). In some embodiments, the linker is cleavable under intracellular conditions, such that cleavage of the linker releases the drug unit from the antibody in the intracellular environment. In yet other embodiments, the linker unit is not cleavable and the drug is released, for example, by antibody degradation. In some embodiments, the linker is cleavable by a cleaving agent that is present in the intracellular environment (*e.g.*, within a lysosome or endosome or caveolea). The linker can be, *e.g.*, a peptidyl linker that is cleaved by an intracellular peptidase or protease enzyme, including, but not limited to, a lysosomal or endosomal protease. For example, a peptidyl linker that is cleavable by the thiol-dependent protease cathepsin-B, which is highly expressed in cancerous tissue, can be used (e.g., a Phe-Leu or a Gly-Phe-Leu-Gly linker (SEQ ID NO:15)). In some embodiments, the peptidyl linker is at least two amino acids long or at least three amino acids long. In other embodiments, the cleavable linker is pH-sensitive, *i.e.*, sensitive to hydrolysis at certain pH values. Typically, the pH-sensitive linker hydrolyzable under acidic conditions. For example, an acid-labile linker that is hydrolyzable in the lysosome (*e.g.*, a hydrazone, semicarbazone, thiosemicarbazone, cis-aconitic amide, orthoester, acetal, ketal, or the like) can be used. In yet other embodiments, the linker is cleavable under reducing conditions (*e.g.*, a disulfide linker). A variety of disulfide linkers are known in the art, including, for example, those that can be formed using SATA (N-succinimidyl-S-acetylthioacetate), SPDP (N-succinimidyl-3-(2-pyridyldithio)propionate), SPDB (N-succinimidyl-3-(2-pyridyldithio)butyrate) and SMPT (N-succinimidyl-oxycarbonyl-alpha-methyl-alpha-(2-pyridyl-dithio)toluene), SPDB and SMPT.

[00461] A "linker unit" (LU) is a bifunctional compound that can be used to link a drug unit and an antibody unit to form an antibody drug conjugate. In some embodiments, the linker unit has the formula:

$$-A_a-W_w-Y_y-$$

wherein:-A- is a stretcher unit,

a is 0 or 1,

each -W- is independently an amino acid unit,

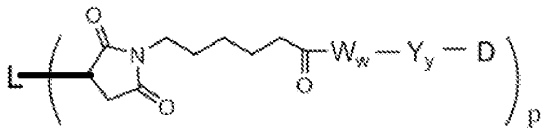
w is an integer ranging from 0 to 12,

-Y- is a self-immolative spacer unit, and

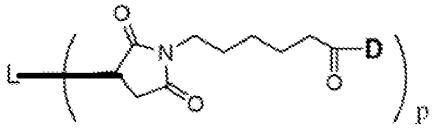
y is 0, 1 or 2.

[00462] In some embodiments, a is 0 or 1, w is 0 or 1, and y is 0, 1 or 2. In some embodiments, a is 0 or 1, w is 0 or 1, and y is 0 or 1. In some embodiments, when w is 1 to 12, y is 1 or 2. In some embodiments, w is 2 to 12 and y is 1 or 2. In some embodiments, a is 1 and w and y are 0. The linker and each of the stretcher unit, the amino acid unit, and the spacer unit have been described in US Patent No. 8,637,642 and International Application No. PCT/US2019/056214 (Publication No. WO2020/117373), both of which are hereby incorporated in their entireties by reference.

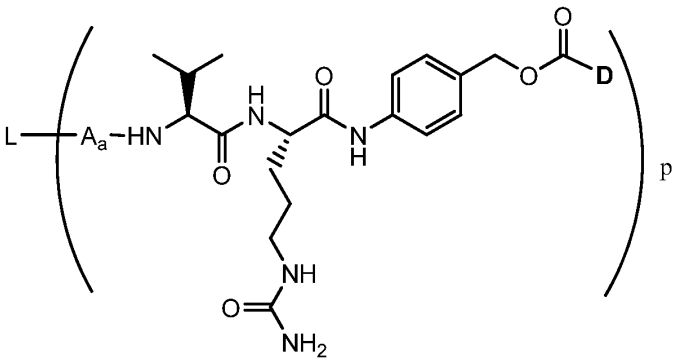
[00463] Embodiments of the antibody-drug conjugates can include:

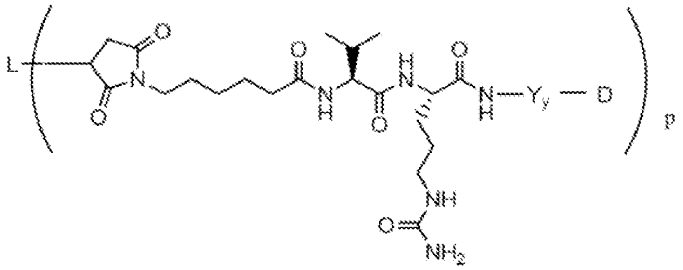


wherein w and y are each 0, 1 or 2, and,

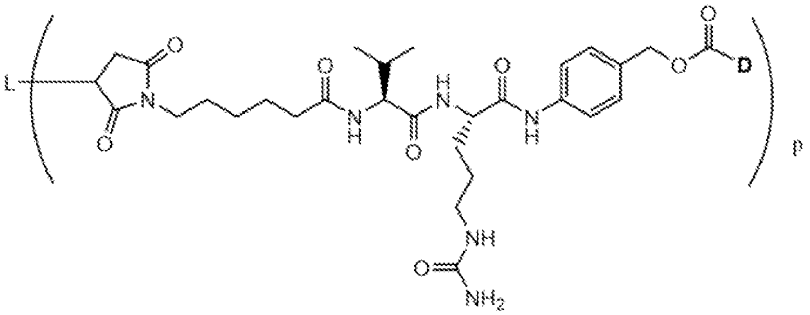


wherein w and y are each 0,





, and



5.3.4 Drug Loading

[00464] Drug loading is represented by p and is the average number of drug units per antibody in a molecule. Drug loading can range from 1 to 20 drug units (D) per antibody. The ADCs provided herein include collections of antibodies or antigen binding fragments conjugated with a range of drug units, *e.g.*, from 1 to 20. The average number of drug units per antibody in preparations of ADC from conjugation reactions can be characterized by conventional means such as mass spectroscopy and, ELISA assay. The quantitative distribution of ADC in terms of p can also be determined. In some instances, separation, purification, and characterization of homogeneous ADC where p is a certain value from ADC with other drug loadings can be achieved by means such as electrophoresis.

[00465] In certain embodiments, the drug loading for an ADC provided herein ranges from 1 to 20. In certain embodiments, the drug loading for an ADC provided herein ranges from 1 to 18. In certain embodiments, the drug loading for an ADC provided herein ranges from 1 to 15. In certain embodiments, the drug loading for an ADC provided herein ranges from 1 to 12. In certain embodiments, the drug loading for an ADC provided herein ranges from 1 to 10. In certain embodiments, the drug loading for an ADC provided herein ranges from 1 to 9. In certain embodiments, the drug loading for an ADC provided herein ranges from 1 to 8. In certain embodiments, the drug loading for an ADC provided herein ranges from 1 to 7. In certain embodiments, the drug loading for an ADC provided herein ranges from 1 to 6. In certain embodiments, the drug loading for an ADC provided herein ranges from 1 to 5. In certain embodiments, the drug loading for an ADC provided herein ranges from 1 to 4. In certain embodiments, the drug loading for an ADC provided herein ranges from 1 to 3. In certain embodiments, the drug loading for an ADC provided herein ranges from 2 to 12. In certain embodiments, the drug loading for an ADC provided herein ranges from 2 to 10. In certain embodiments, the drug loading for an ADC provided herein ranges from 2 to 9. In certain embodiments, the drug loading for an ADC provided herein ranges from 2 to 8. In certain embodiments, the drug loading for an ADC provided herein ranges from 2 to 7. In certain embodiments, the drug loading for an ADC provided herein ranges from 2 to 6. In certain embodiments, the drug loading for an ADC provided herein ranges from 2 to 5. In certain embodiments, the drug loading for an ADC provided herein ranges from 2 to 4. In certain embodiments, the drug loading for an ADC provided herein ranges from 3 to 12. In certain embodiments, the drug loading for an ADC provided herein ranges from 3 to 10. In certain embodiments, the drug loading for an ADC provided herein ranges from 3 to 9. In certain embodiments, the drug loading for an ADC provided herein ranges from 3 to 8. In certain embodiments, the drug loading for an ADC provided herein ranges from 3 to 7. In certain embodiments, the drug loading for an ADC provided herein ranges from 3 to 6. In certain embodiments, the drug loading for an ADC provided herein ranges from 3 to 5. In certain embodiments, the drug loading for an ADC provided herein ranges from 3 to 4.

[00466] In certain embodiments, the drug loading for an ADC provided herein ranges from 1 to about 8; from about 2 to about 6; from about 3 to about 5; from about 3 to about 4; from about 3.1 to about 3.9; from about 3.2 to about 3.8; from about 3.2 to about 3.7; from about 3.2 to about 3.6; from about 3.3 to about 3.8; or from about 3.3 to about 3.7.

[00467] In certain embodiments, the drug loading for an ADC provided herein is about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11,

about 12, or more. In some embodiments, the drug loading for an ADC provided herein is about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, or about 3.9.

[00468] In some embodiments, the drug loading for an ADC provided herein ranges from 2 to 20, 2 to 19, 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, or 2 to 13. In some embodiments, the drug loading for an ADC provided herein ranges from 3 to 20, 3 to 19, 3 to 18, 3 to 17, 3 to 16, 3 to 15, 3 to 14, or 3 to 13. In some embodiments, the drug loading for an ADC provided herein is about 1. In some embodiments, the drug loading for an ADC provided herein is about 2. In some embodiments, the drug loading for an ADC provided herein is about 3. In some embodiments, the drug loading for an ADC provided herein is about 4. In some embodiments, the drug loading for an ADC provided herein is about 3.8. In some embodiments, the drug loading for an ADC provided herein is about 5. In some embodiments, the drug loading for an ADC provided herein is about 6. In some embodiments, the drug loading for an ADC provided herein is about 7. In some embodiments, the drug loading for an ADC provided herein is about 8. In some embodiments, the drug loading for an ADC provided herein is about 9. In some embodiments, the drug loading for an ADC provided herein is about 10. In some embodiments, the drug loading for an ADC provided herein is about 11. In some embodiments, the drug loading for an ADC provided herein is about 12. In some embodiments, the drug loading for an ADC provided herein is about 13. In some embodiments, the drug loading for an ADC provided herein is about 14. In some embodiments, the drug loading for an ADC provided herein is about 15. In some embodiments, the drug loading for an ADC provided herein is about 16. In some embodiments, the drug loading for an ADC provided herein is about 17. In some embodiments, the drug loading for an ADC provided herein is about 18. In some embodiments, the drug loading for an ADC provided herein is about 19. In some embodiments, the drug loading for an ADC provided herein is about 20.

[00469] In certain embodiments, fewer than the theoretical maximum of drug units are conjugated to an antibody during a conjugation reaction. An antibody can contain, for example, lysine residues that do not react with the drug-linker intermediate or linker reagent. Generally, antibodies do not contain many free and reactive cysteine thiol groups which can be linked to a drug unit; indeed most cysteine thiol residues in antibodies exist as disulfide bridges. In certain embodiments, an antibody can be reduced with a reducing agent such as dithiothreitol (DTT) or tricarbonylethylphosphine (TCEP), under partial or total reducing

conditions, to generate reactive cysteine thiol groups. In certain embodiments, an antibody is subjected to denaturing conditions to reveal reactive nucleophilic groups such as lysine or cysteine. In some embodiments, the linker unit or a drug unit is conjugated via a lysine residue on the antibody unit. In some embodiments, the linker unit or a drug unit is conjugated via a cysteine residue on the antibody unit.

[00470] In some embodiments, the amino acid that attaches to a linker unit or a drug unit is in the heavy chain of an antibody or antigen binding fragment thereof. In some embodiments, the amino acid that attaches to a linker unit or a drug unit is in the light chain of an antibody or antigen binding fragment thereof. In some embodiments, the amino acid that attaches to a linker unit or a drug unit is in the hinge region of an antibody or antigen binding fragment thereof. In some embodiments, the amino acid that attaches to a linker unit or a drug unit is in the Fc region of an antibody or antigen binding fragment thereof. In other embodiments, the amino acid that attaches to a linker unit or a drug unit is in the constant region (*e.g.*, CH1, CH2, or CH3 of a heavy chain, or CH1 of a light chain) of an antibody or antigen binding fragment thereof. In yet other embodiments, the amino acid that attaches to a linker unit or a drug unit is in the VH framework regions of an antibody or antigen binding fragment thereof. In yet other embodiments, the amino acid that attaches to a linker unit or a drug unit is in the VL framework regions of an antibody or antigen binding fragment thereof.

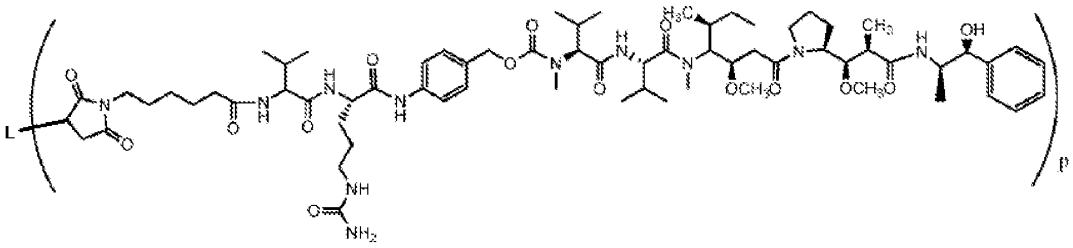
[00471] The loading (drug/antibody ratio) of an ADC can be controlled in different ways, *e.g.*, by: (i) limiting the molar excess of drug-linker intermediate or linker reagent relative to antibody, (ii) limiting the conjugation reaction time or temperature, (iii) partial or limiting reductive conditions for cysteine thiol modification, (iv) engineering by recombinant techniques the amino acid sequence of the antibody such that the number and position of cysteine residues is modified for control of the number and/or position of linker-drug attachments (such as thioMab or thioFab prepared as disclosed herein and in WO2006/034488 (herein incorporated by reference in its entirety)).

[00472] It is to be understood that where more than one nucleophilic group reacts with a drug-linker intermediate or linker reagent followed by drug unit reagent, then the resulting product is a mixture of ADC compounds with a distribution of one or more drug unit attached to an antibody unit. The average number of drugs per antibody can be calculated from the mixture by a dual ELISA antibody assay, which is specific for antibody and specific for the drug. Individual ADC molecules can be identified in the mixture by mass spectroscopy and separated by HPLC, *e.g.* hydrophobic interaction chromatography (*see, e.g.*, Hamblett, K.J., et al. “Effect of drug loading on the pharmacology, pharmacokinetics, and toxicity of an anti-

CD30 antibody-drug conjugate," Abstract No. 624, American Association for Cancer Research, 2004 Annual Meeting, March 27-31, 2004, Proceedings of the AACR, Volume 45, March 2004; Alley, S.C., et al. "Controlling the location of drug attachment in antibody-drug conjugates," Abstract No. 627, American Association for Cancer Research, 2004 Annual Meeting, March 27-31, 2004, Proceedings of the AACR, Volume 45, March 2004). In certain embodiments, a homogeneous ADC with a single loading value can be isolated from the conjugation mixture by electrophoresis or chromatography.

[00473] Methods for preparing, screening, and characterizing the antibody drug conjugates are known to a person of ordinary skill in the art, for example, as described in US Patent No. 8,637,642, which is herein incorporated in its entirety by reference.

[00474] In some embodiments, the antibody drug conjugate for the methods provided herein is AGS-22M6E, which is prepared according to the methods described in US Patent No. 8,637,642 and has the following formula:



wherein L is Ha22-2(2,4)6.1 and p is from 1 to 20.

[00475] In some embodiments, p ranges from 1to 20, 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 to 2. In some embodiments, p ranges from 2 to 10, 2 to 9, 2 to 8, 2 to 7, 2 to 6, 2 to 5, 2 to 4 or 2 to 3. In other embodiments, p is about 1. In other embodiments, p is about 2. In other embodiments, p is about 3. In other embodiments, p is about 4. In other embodiments, p is about 5. In other embodiments, p is about 6. In other embodiments, p is about 7. In other embodiments, p is about 8. In other embodiments, p is about 9. In other embodiments, p is about 10. In some embodiments, p is about 3.1. In some embodiments, p is about 3.2. In some embodiments, p is about 3.3. In some embodiments, p is about 3.4. In some embodiments, p is about 3.5. In other embodiments, p is about 3.6. In some embodiments, p is about 3.7. In some embodiments, p is about 3.8. In some embodiments, p is about 3.9. In some embodiments, p is about 4.0. In some embodiments, p is about 4.1. In some embodiments, p is about 4.2. In some embodiments, p is about 4.3. In some embodiments, p is about 4.4. In some embodiments, p is about 4.5. In other embodiments, p

is about 4.6. In some embodiments, p is about 4.7. In some embodiments, p is about 4.8. In some embodiments, p is about 4.9. In some embodiments, p is about 5.0.

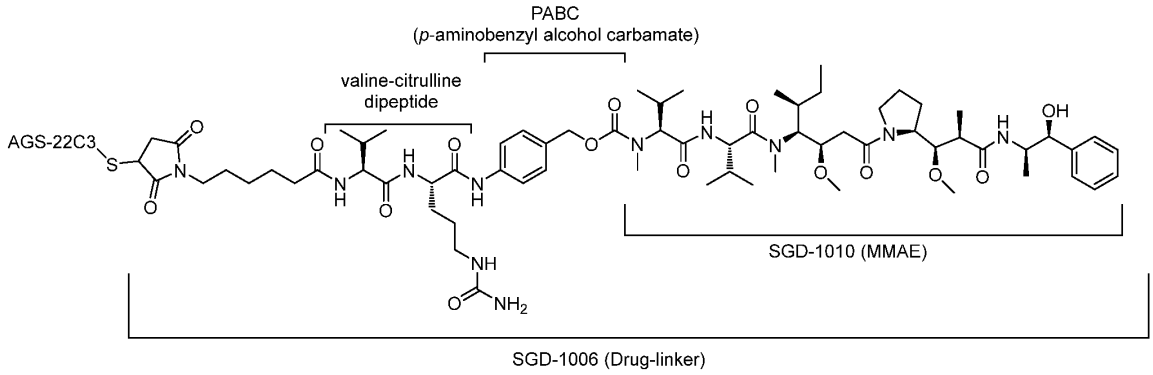
[00476] In some embodiments, the ADC used in the methods provided herein is enfortumab vedotin. Enfortumab vedotin is an ADC comprised of a fully human immunoglobulin G1 kappa ($IgG1_K$) antibody conjugated to the microtubule-disrupting agent (MMAE) via a protease-cleavable linker (Challita-Eid PM et al, Cancer Res. 2016;76(10):3003-13]. Enfortumab vedotin induces antitumor activity by binding to 191P4D12 protein on the cell surface leading to internalization of the ADC-191P4D12 complex, which then traffics to the lysosomal compartment where MMAE is released via proteolytic cleavage of the linker. Intracellular release of MMAE subsequently disrupts tubulin polymerization resulting in G2/M phase cell cycle arrest and apoptotic cell death (Francisco JA et al, Blood. 2003 Aug 15;102(4):1458-65).

[00477] As described above and in in US Patent No. 8,637,642, AGS-22M6E is an ADC derived from a murine hybridoma cell line. Enfortumab vedotin is a Chinese hamster ovary (CHO) cell line-derived equivalent of AGS-22M6E ADC and is an exemplary product used for human treatment. Enfortumab vedotin has the same amino acid sequence, linker and cytotoxic drug as AGS-22M6E. The comparability between enfortumab vedotin and AGS-22M6E was confirmed through extensive analytical and biological characterization studies, such as binding affinity to 191P4D12, in vitro cytotoxicity, and in vivo antitumor activity.

[00478] In one embodiment, the ADC provided herein is enfortumab vedotin, also known as EV, PADCEV, AGS-22M6E, AGS-22C3E, ASG-22C3E. The enfortumab vedotin includes an anti-191P4D12 antibody, wherein the antibody or antigen binding fragment thereof comprises a heavy chain comprising amino acid residue 20 to amino acid residue 466 of SEQ ID NO:7 and a light chain comprising amino acid residue 23 to amino acid residue 236 of SEQ ID NO:8.

[00479] Enfortumab vedotin is a Nectin-4 directed antibody -drug conjugate (ADC) comprised of a fully human anti-nectin-4 IgG1 kappa monoclonal antibody (AGS-22C3) conjugated to the small molecule microtubule disrupting agent, monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline (vc) linker (SGD-1006). Conjugation takes place on cysteine residues that comprise the interchain disulfide bonds of the antibody to yield a product with a drug-to-antibody ratio of approximately 3.8:1. The molecular weight is approximately 152 kDa.

[00480] Enfortumab vedotin has the following structural formula:



[00481] Approximately 4 molecules of MMAE are attached to each antibody molecule. Enfortumab vedotin is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells and the small molecule components are produced by chemical synthesis.

[00482] Enfortumab vedotin injection is provided as a sterile, preservative-free, white to off-white lyophilized powder in single-dose vials for intravenous use. Enfortumab vedotin is supplied as a 20 mg per vial and a 30 mg per vial and requires reconstitution with Sterile Water for Injection, USP, (2.3 mL and 3.3 mL, respectively) resulting in a clear to slightly opalescent, colorless to slightly yellow solution with a final concentration of 10 mg/mL. After reconstitution, each vial allows the withdrawal of 2 mL (20 mg) and 3 mL (30 mg). Each mL of reconstituted solution contains 10 mg of enfortumab vedotin, histidine (1.4 mg), histidine hydrochloride monohydrate (2.31 mg), polysorbate 20 (0.2 mg) and trehalose dihydrate (55 mg) with a pH of 6.0.

5.4 Pharmaceutical Compositions

[00483] In certain embodiments of the methods provided herein, the active ingredient such as the ADC and pembrolizumab used in the methods is provided in "pharmaceutical compositions." Such pharmaceutical compositions include an antibody drug conjugate provided herein, and one or more pharmaceutically acceptable or physiologically acceptable excipients. In some embodiments, the antibody drug conjugate are provided in combination with, or separate from, a checkpoint inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., pembrolizumab) or a PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., pembrolizumab). In some embodiments, the antibody drug conjugate are provided in combination with, or separate from pembrolizumab. Also provided is a composition comprising the antibody drug conjugate and pembrolizumab and one or more pharmaceutically acceptable or physiologically acceptable excipients. In particular

embodiments, the antibody drug conjugate and pembrolizumab are present in a therapeutically acceptable amount. In certain embodiments, the antibody drug conjugate and pembrolizumab are provided in combination with, or separate from, one or more additional agents. Also provided is a composition comprising such one or more additional agents and one or more pharmaceutically acceptable or physiologically acceptable excipients. In particular embodiments, the antibody drug conjugate and an additional agent(s) are present in a therapeutically acceptable amount. The pharmaceutical compositions can be used in accordance with the methods and uses provided herein. Thus, for example, the pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice treatment methods and uses provided herein. Pharmaceutical compositions provided herein can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein.

[00484] In some embodiments, provided are pharmaceutical compositions of antibody drug conjugates and pembrolizumab that modulate a cancer or tumor.

[00485] In certain embodiments of the methods provided herein, the pharmaceutical compositions comprising the ADCs and pembrolizumab can further comprise other therapeutically active agents or compounds disclosed herein or known to the skilled artisan which can be used in the treatment or prevention of various diseases and disorders as set forth herein (*e.g.*, a cancer). As set forth above, the additional therapeutically active agents or compounds can be present in a separate pharmaceutical composition(s).

[00486] Pharmaceutical compositions typically comprise a therapeutically effective amount of at least one of the antibody drug conjugates provided herein and pembrolizumab and one or more pharmaceutically acceptable formulation agents. In certain embodiments, the pharmaceutical composition further comprises one or more additional agents described herein.

[00487] In one embodiment, a pharmaceutical composition comprises an antibody drug conjugate provided herein and pembrolizumab. In some embodiments, a pharmaceutical composition comprises a therapeutically effective amount of an antibody drug conjugate provided herein and pembrolizumab. In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable excipient.

[00488] In some embodiments, the antibody drug conjugate in the pharmaceutical composition provided herein is selected from the antibody drug conjugates described in Section 5.3 above.

[00489] In certain embodiments, the pharmaceutical composition comprises the antibody drug conjugate provided herein in an amount such that the dosage of antibody drug conjugate administered to a subject is about 0.1 mg/kg, about 0.5 mg/kg, about 0.75 mg/kg, about 1 mg/kg, about 1.25 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg.

[00490] In certain embodiments, the pharmaceutical composition comprises the antibody drug conjugate provided herein in an amount such that the dosage of antibody drug conjugate administered to a subject is 0.1 mg/kg, 0.5 mg/kg, 0.75 mg/kg, 1 mg/kg, 1.25 mg/kg, 1.5 mg/kg, 2 mg/kg, 2.5 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, 100 mg/kg.

[00491] In certain embodiments, the pharmaceutical composition comprises the antibody drug conjugate provided herein in an amount such that the dosage of the antibody drug conjugate administered to a subject is about 0.1 mg/kg to about 100 mg/kg of the subject's body weight. In some embodiments, the dosage administered to the patient is about 1 mg/kg to about 75 mg/kg of the subject's body weight. In some embodiments, the dosage administered to a patient is between about 1 mg/kg and about 20 mg/kg of the subject's body weight, such as about 1 mg/kg to about 5 mg/kg of the subject's body weight.

[00492] In certain embodiments, the pharmaceutical composition comprises the antibody drug conjugate provided herein in an amount such that the dosage of the antibody drug conjugate administered to a subject is 0.1 mg/kg to 100 mg/kg of the subject's body weight. In some embodiments, the dosage administered to the patient is 1 mg/kg to 75 mg/kg of the subject's body weight. In some embodiments, the dosage administered to a patient is between 1 mg/kg and 20 mg/kg of the subject's body weight, such as 1 mg/kg to 5 mg/kg of the subject's body weight.

[00493] In certain embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of from 0.1 -100 mg/mL. In some embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of from 1 to 20 mg/mL. In other embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of from 5 to 15 mg/mL. In other embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of

from 8 to 12 mg/mL. In other embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of from 9 to 11 mg/mL. In some embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of about 9.5 mg/mL. In some embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of about 9.6 mg/mL. In some embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of about 9.7 mg/mL. In some embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of about 9.8 mg/mL. In some embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of about 9.9 mg/mL. In yet other embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of about 10 mg/mL. In yet other embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of about 10.1 mg/mL. In some embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of about 10.2 mg/mL. In some embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of about 10.3 mg/mL. In some embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of about 10.3 mg/mL. In some embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of about 10.4 mg/mL. In some embodiments, the pharmaceutical composition comprises the antibody drug conjugate at a concentration of about 10.5 mg/mL.

In some embodiments, the pharmaceutical composition provided herein comprises L-histidine, TWEEN-20, and at least one of trehalose dihydrate or sucrose. In some embodiments, the pharmaceutical composition provided herein further comprises hydrochloric acid (HCl) or succinic acid.

[00494] In certain embodiments, the pharmaceutical composition comprises pembrolizumab in an amount of about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg or about 500 mg. In particular embodiments, the pharmaceutical composition comprises pembrolizumab in an amount of about 200 mg.

[00495] In certain embodiments, the pharmaceutical composition comprises pembrolizumab in an amount of 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, about 400 mg, 450 mg or 500 mg. In particular embodiments, the pharmaceutical composition comprises pembrolizumab in an amount of 200 mg.

[00496] In certain embodiments, the pharmaceutical composition comprises pembrolizumab in an amount of about 100 mg to about 500 mg, about 150 mg to about 500 mg, about 200 mg to about 500 mg, about 250 mg to about 500 mg, about 300 mg to about 500 mg, about 350 mg to about 500 mg, about 400 mg to about 500 mg, or about 450 mg to about 500 mg. In certain embodiments, the pharmaceutical composition comprises pembrolizumab in an amount of about 100 mg to about 450 mg, about 100 mg to about 400 mg, about 100 mg to about 350 mg, about 100 mg to about 300 mg, about 100 mg to about 250 mg, about 100 mg to about 200 mg, or about 100 mg to about 150 mg. In certain embodiments, the pharmaceutical composition comprises pembrolizumab in an amount of about 150 mg to about 450 mg, about 150 to about 400 mg, about 150 to about 350 mg, about 200 mg to about 450 mg, about 200 mg to about 400 mg, about 200 mg to about 300 mg, or about 200 mg to about 250 mg.

[00497] In certain embodiments, the pharmaceutical composition comprises pembrolizumab in an amount of 100 mg to 500 mg, 150 mg to 500 mg, 200 mg to 500 mg, 250 mg to 500 mg, 300 mg to 500 mg, 350 mg to 500 mg, 400 mg to 500 mg, or 450 mg to 500 mg. In certain embodiments, the pharmaceutical composition comprises pembrolizumab in an amount of 100 mg to 450 mg, 100 mg to 400 mg, 100 mg to 350 mg, 100 mg to 300 mg, 100 mg to 250 mg, 100 mg to 200 mg, or 100 mg to 150 mg. In certain embodiments, the pharmaceutical composition comprises pembrolizumab in an amount of 150 mg to 450 mg, 150 to 400 mg, 150 to 350 mg, 200 mg to 450 mg, 200 mg to 400 mg, 200 mg to 300 mg, or 200 mg to 250 mg.

[00498] In some embodiments, the concentration of L-histidine useful in the pharmaceutical compositions provided herein is in the range of between 5 and 50 mM. In some embodiments, the concentration of L-histidine in the pharmaceutical compositions provided herein is in the range of between 10 and 40 mM. In some embodiments, the concentration of L-histidine in the pharmaceutical compositions provided herein is in the range of between 15 and 35 mM.

[00499] In some embodiments, the concentration of L-histidine in the pharmaceutical compositions provided herein is in the range of between 15 and 30 mM. In some embodiments, the concentration of L-histidine in the pharmaceutical compositions provided herein is in the range of between 15 and 25 mM. In some embodiments, the concentration of L-histidine in the pharmaceutical compositions provided herein is in the range of between 15 and 35 mM. In some embodiments, the concentration of L-histidine in the pharmaceutical compositions provided herein is about 16 mM. In some embodiments, the concentration of L-

histidine in the pharmaceutical compositions provided herein is about 17 mM. In some embodiments, the concentration of L-histidine in the pharmaceutical compositions provided herein is about 18 mM. In some embodiments, the concentration of L-histidine in the pharmaceutical compositions provided herein is about 19 mM. In some embodiments, the concentration of L-histidine in the pharmaceutical compositions provided herein is about 20 mM. In some embodiments, the concentration of L-histidine in the pharmaceutical compositions provided herein is about 21 mM. In some embodiments, the concentration of L-histidine in the pharmaceutical compositions provided herein is about 22 mM. In some embodiments, the concentration of L-histidine in the pharmaceutical compositions provided herein is about 23 mM. In some embodiments, the concentration of L-histidine in the pharmaceutical compositions provided herein is about 24 mM. In some embodiments, the concentration of L-histidine in the pharmaceutical compositions provided herein is about 25 mM.

[00500] In some embodiments, the concentration of TWEEN-20 useful in the pharmaceutical compositions provided herein is in the range of from 0.001 to 0.1% (v/v). In another embodiment, the concentration of TWEEN-20 is in the range of from 0.0025 to 0.075% (v/v). In one embodiment, the concentration of TWEEN-20 is in the range of from 0.005 to 0.05% (v/v). In another embodiment, the concentration of TWEEN-20 is in the range of from 0.0075 to 0.025% (v/v). In another embodiment, the concentration of TWEEN-20 is in the range of from 0.0075 to 0.05% (v/v). In another embodiment, the concentration of TWEEN-20 is in the range of from 0.01 to 0.03% (v/v). In one particular embodiment, the concentration of TWEEN-20 is about 0.01% (v/v). In one particular embodiment, the concentration of TWEEN-20 is about 0.015% (v/v). In one particular embodiment, the concentration of TWEEN-20 is about 0.016% (v/v). In one particular embodiment, the concentration of TWEEN-20 is about 0.017% (v/v). In one particular embodiment, the concentration of TWEEN-20 is about 0.018% (v/v). In one particular embodiment, the concentration of TWEEN-20 is about 0.019% (v/v). In one particular embodiment, the concentration of TWEEN-20 is about 0.02% (v/v). In one particular embodiment, the concentration of TWEEN-20 is about 0.021% (v/v). In one particular embodiment, the concentration of TWEEN-20 is about 0.022% (v/v). In one particular embodiment, the concentration of TWEEN-20 is about 0.023% (v/v). In one particular embodiment, the concentration of TWEEN-20 is about 0.024% (v/v). In one particular embodiment, the concentration of TWEEN-20 is about 0.025% (v/v).

[00501] In one embodiment, the concentration of trehalose dihydrate useful in the pharmaceutical compositions provided herein is in the range of between 1% and 20% (w/v). In another embodiment, the concentration of trehalose dihydrate is in the range of 2% and 15% (w/v). In one embodiment, the concentration of trehalose dihydrate is in the range of 3% and 10% (w/v). In another embodiment, the concentration of trehalose dihydrate is in the range of 4% and 9% (w/v). In another embodiment, the concentration of trehalose dihydrate is in the range of 4% and 8% (w/v). In another embodiment, the concentration of trehalose dihydrate is in the range of 4% and 7% (w/v). In another embodiment, the concentration of trehalose dihydrate is in the range of 4% and 6% (w/v). In another embodiment, the concentration of trehalose dihydrate is in the range of 4.5% and 6% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 4.6% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 4.7% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 4.8% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 4.9% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 5.0% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 5.1% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 5.2% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 5.3% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 5.4% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 5.5% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 5.6% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 5.7% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 5.8% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 5.9% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 6.0% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 6.1% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 6.2% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 6.3% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 6.4% (w/v). In another embodiment, the concentration of trehalose dihydrate is about 6.5% (w/v).

[00502] In certain embodiments, the molarity of the trehalose dihydrate is from 50 to 300 mM. In other embodiments, the molarity of the trehalose dihydrate is from 75 to 250 mM. In some embodiments, the molarity of the trehalose dihydrate is from 100 to 200 mM. In other embodiments, the molarity of the trehalose dihydrate is from 130 to 150 mM. In some

embodiments, the molarity of the trehalose dihydrate is from 135 to 150 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 135 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 136 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 137 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 138 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 139 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 140 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 141 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 142 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 143 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 144 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 145 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 146 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 150 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 151 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 151 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 152 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 153 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 154 mM. In certain embodiments, the molarity of the trehalose dihydrate is about 155 mM.

[00503] In one embodiment, the concentration of sucrose useful in the pharmaceutical compositions provided herein is in the range of between 1% and 20% (w/v). In another embodiment, the concentration of sucrose is in the range of 2% and 15% (w/v). In one embodiment, the concentration of sucrose is in the range of 3% and 10% (w/v). In another embodiment, the concentration of sucrose is in the range of 4% and 9% (w/v). In another embodiment, the concentration of sucrose is in the range of 4% and 8% (w/v). In another embodiment, the concentration of sucrose is in the range of 4% and 7% (w/v). In another embodiment, the concentration of sucrose is in the range of 4% and 6% (w/v). In another embodiment, the concentration of sucrose is in the range of 4.5% and 6% (w/v). In another embodiment, the concentration of sucrose is about 4.6% (w/v). In another embodiment, the concentration of sucrose is about 4.7% (w/v). In another embodiment, the concentration of sucrose is about 4.8% (w/v). In another embodiment, the concentration of sucrose is about 4.9% (w/v). In another embodiment, the concentration of sucrose is about 5.0% (w/v). In another embodiment, the concentration of sucrose is about 5.1% (w/v). In another

embodiment, the concentration of sucrose is about 5.2% (w/v). In another embodiment, the concentration of sucrose is about 5.3% (w/v). In another embodiment, the concentration of sucrose is about 5.4% (w/v). In another embodiment, the concentration of sucrose is about 5.5% (w/v). In another embodiment, the concentration of sucrose is about 5.6% (w/v). In another embodiment, the concentration of sucrose is about 5.7% (w/v). In another embodiment, the concentration of sucrose is about 5.8% (w/v). In another embodiment, the concentration of sucrose is about 5.9% (w/v). In another embodiment, the concentration of sucrose is about 6.0% (w/v). In another embodiment, the concentration of sucrose is about 6.1% (w/v). In another embodiment, the concentration of sucrose is about 6.2% (w/v). In another embodiment, the concentration of sucrose is about 6.3% (w/v). In another embodiment, the concentration of sucrose is about 6.4% (w/v). In another embodiment, the concentration of sucrose is about 6.5% (w/v).

[00504] In certain embodiments, the molarity of the sucrose is from 50 to 300 mM. In other embodiments, the molarity of the sucrose is from 75 to 250 mM. In some embodiments, the molarity of the sucrose is from 100 to 200 mM. In other embodiments, the molarity of the sucrose is from 130 to 150 mM. In some embodiments, the molarity of the sucrose is from 135 to 150 mM. In certain embodiments, the molarity of the sucrose is about 135 mM. In certain embodiments, the molarity of the sucrose is about 136 mM. In certain embodiments, the molarity of the sucrose is about 137 mM. In certain embodiments, the molarity of the sucrose is about 138 mM. In certain embodiments, the molarity of the sucrose is about 139 mM. In certain embodiments, the molarity of the sucrose is about 140 mM. In certain embodiments, the molarity of the sucrose is about 141 mM. In certain embodiments, the molarity of the sucrose is about 142 mM. In certain embodiments, the molarity of the sucrose is about 143 mM. In certain embodiments, the molarity of the sucrose is about 144 mM. In certain embodiments, the molarity of the sucrose is about 145 mM. In certain embodiments, the molarity of the sucrose is about 146 mM. In certain embodiments, the molarity of the sucrose is about 150 mM. In certain embodiments, the molarity of the sucrose is about 151 mM. In certain embodiments, the molarity of the sucrose is about 151 mM. In certain embodiments, the molarity of the sucrose is about 152 mM. In certain embodiments, the molarity of the sucrose is about 153 mM. In certain embodiments, the molarity of the sucrose is about 154 mM. In certain embodiments, the molarity of the sucrose is about 155 mM.

[00505] In some embodiments, the pharmaceutical composition provided herein comprises HCl. In other embodiments, the pharmaceutical composition provided herein comprises succinic acid.

[00506] In some embodiments, the pharmaceutical composition provided herein has a pH in a range of 5.5 to 6.5. In other embodiments, the pharmaceutical composition provided herein has a pH in a range of 5.7 to 6.3. In some embodiments, the pharmaceutical composition provided herein has a pH of about 5.7. In some embodiments, the pharmaceutical composition provided herein has a pH of about 5.8. In some embodiments, the pharmaceutical composition provided herein has a pH of about 5.9. In some embodiments, the pharmaceutical composition provided herein has a pH of about 6.0. In some embodiments, the pharmaceutical composition provided herein has a pH of about 6.1. In some embodiments, the pharmaceutical composition provided herein has a pH of about 6.2. In some embodiments, the pharmaceutical composition provided herein has a pH of about 6.3.

[00507] In some embodiments, the pH is taken at room temperature. In other embodiments, the pH is taken at 15°C to 27°C. In yet other embodiments, the pH is taken at 4°C. In yet other embodiments, the pH is taken at 25°C.

[00508] In some embodiments, the pH is adjusted by HCl. In some embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH in a range of 5.5 to 6.5 at room temperature. In some embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH in a range of 5.7 to 6.3 at room temperature. In some more specific embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH of about of 5.7 at room temperature. In some more specific embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH of about of 5.8 at room temperature. In some more specific embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH of about of 5.9 at room temperature. In some more specific embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH of about of 6.0 at room temperature. In some more specific embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH of about of 6.1 at room temperature. In some more specific embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH of about of 6.2 at room temperature. In some more specific embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH of about of 6.3 at room temperature.

[00509] In some embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH in a range of 5.5 to 6.5 at 15°C to 27°C. In some

embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH in a range of 5.7 to 6.3 at 15°C to 27°C. In some more specific embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH of about of 5.7 at 15°C to 27°C. In some more specific embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH of about of 5.8 at 15°C to 27°C. In some more specific embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH of about of 5.9 at 15°C to 27°C. In some more specific embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH of about of 6.0 at 15°C to 27°C. In some more specific embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH of about of 6.1 at 15°C to 27°C. In some more specific embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH of about of 6.2 at 15°C to 27°C. In some more specific embodiments, the pharmaceutical composition comprises HCl, and the pharmaceutical composition has a pH of about of 6.3 at 15°C to 27°C.

[00510] In some embodiments, the pH is adjusted by succinic acid. In some embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH in a range of 5.5 to 6.5 at room temperature. In some embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH in a range of 5.7 to 6.3 at room temperature. In some more specific embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH of about of 5.7 at room temperature. In some more specific embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH of about of 5.8 at room temperature. In some more specific embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH of about of 5.9 at room temperature. In some more specific embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH of about of 6.0 at room temperature. In some more specific embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH of about of 6.1 at room temperature. In some more specific embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH of about of 6.2 at room temperature. In some more specific embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH of about of 6.3 at room temperature.

[00511] In some embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH in a range of 5.5 to 6.5 at 15°C to 27°C. In some embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH in a range of 5.7 to 6.3 at 15°C to 27°C. In some more specific embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH of about of 5.7 at 15°C to 27°C. In some more specific embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH of about of 5.8 at 15°C to 27°C. In some more specific embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH of about of 5.9 at 15°C to 27°C. In some more specific embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH of about of 6.0 at 15°C to 27°C. In some more specific embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH of about of 6.1 at 15°C to 27°C. In some more specific embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH of about of 6.2 at 15°C to 27°C. In some more specific embodiments, the pharmaceutical composition comprises succinic acid, and the pharmaceutical composition has a pH of about of 6.3 at 15°C to 27°C.

[00512] In some specific embodiments, the pharmaceutical composition provided herein comprises about 20 mM L-histidine, about 0.02% (w/v) TWEEN-20, and at least one of about 5.5% (w/v) trehalose dihydrate or about 5% (w/v) sucrose. In some embodiments, the pharmaceutical composition provided herein further comprises HCl or succinic acid. In some embodiments, the pH is about 6.0 at room temperature. In some embodiments, the pH is about 6.0 at 25°C.

[00513] In some specific embodiments, the pharmaceutical composition provided herein comprises about 20 mM L-histidine, about 0.02% (w/v) TWEEN-20, about 5.5% (w/v) trehalose dihydrate and HCl. In some embodiments, the pH is about 6.0 at room temperature. In some embodiments, the pH is about 6.0 at 25°C.

[00514] In some specific embodiments, the pharmaceutical composition provided herein comprises about 20 mM L-histidine, about 0.02% (w/v) TWEEN-20, about 5% (w/v) sucrose and HCl. In some embodiments, the pH is about 6.0 at room temperature. In some embodiments, the pH is about 6.0 at 25°C.

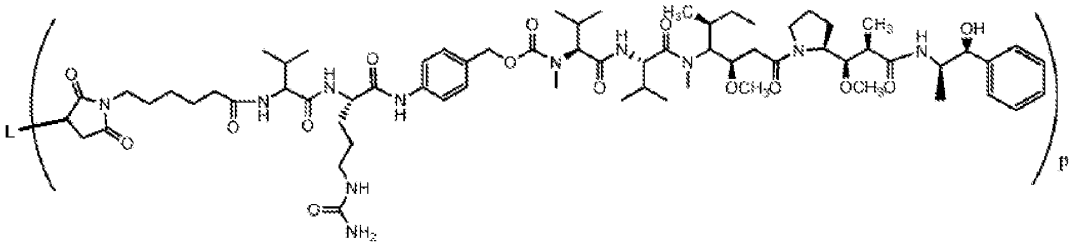
[00515] In other specific embodiments, the pharmaceutical composition provided herein comprises about 20 mM L-histidine, about 0.02% (w/v) TWEEN-20, about 5.5% (w/v)

trehalose dihydrate and succinic acid. In some embodiments, the pH is about 6.0 at room temperature. In some embodiments, the pH is about 6.0 at 25°C.

[00516] In some specific embodiments, the pharmaceutical composition provided herein comprises about 20 mM L-histidine, about 0.02% (w/v) TWEEN-20, about 5% (w/v) sucrose and succinic acid. In some embodiments, the pH is about 6.0 at room temperature. In some embodiments, the pH is about 6.0 at 25°C.

[00517] In a specific embodiment, provided herein comprises

(a) an antibody drug conjugate comprising the following structure:

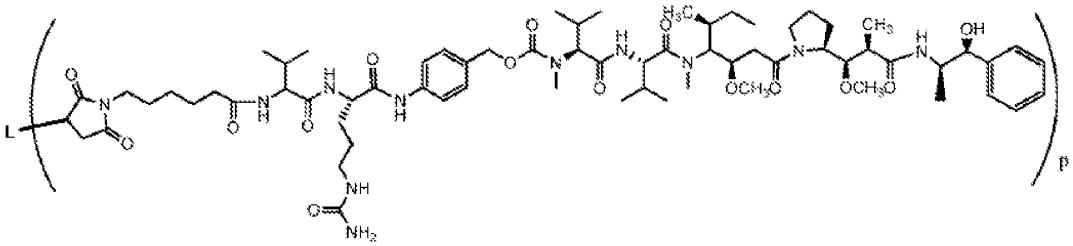


wherein L- represents the antibody or antigen binding fragment (*e.g.* anti-nectin-4 antibody or antigen binding fragment thereof) thereof and p is from 1 to10; and

(b) a pharmaceutically acceptable excipient comprising about 20 mM L-histidine, about 0.02% (w/v) TWEEN-20, about 5.5% (w/v) trehalose dihydrate, and HCl, wherein the antibody drug conjugate is at the concentration of about 10 mg/mL, and wherein the pH is about 6.0 at 25°C.

[00518] In another specific embodiment, the pharmaceutical composition provided herein comprises:

(a) an antibody drug conjugate comprising the following structure:



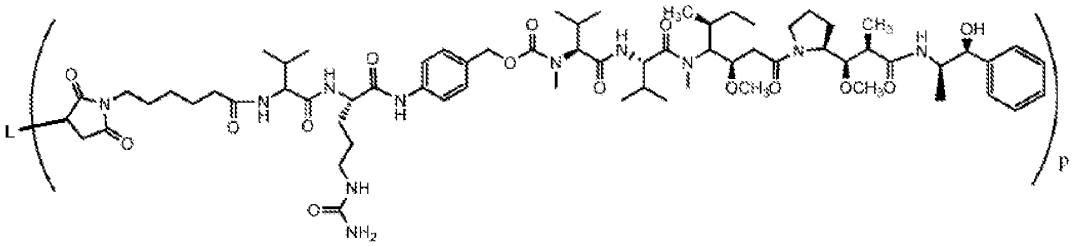
wherein L- represents the antibody or antigen binding fragment thereof (*e.g.* anti-nectin-4 antibody or antigen binding fragment thereof) and p is from 1 to10; and

(b) a pharmaceutically acceptable excipient comprising about 20 mM L-histidine, about 0.02% (w/v) TWEEN-20, about 5.5% (w/v) trehalose dihydrate, and succinic acid,

wherein the antibody drug conjugate is at the concentration of about 10 mg/mL, and wherein the pH is about 6.0 at 25°C.

[00519] In yet another specific embodiment, the pharmaceutical composition provided herein comprises:

(a) an antibody drug conjugate comprising the following structure:



wherein L- represents the antibody or antigen binding fragment thereof (*e.g.* anti-nectin-4 antibody or antigen binding fragment thereof) and p is from 1 to10; and

(b) a pharmaceutically acceptable excipient comprising about 20 mM L-histidine, about 0.02% (w/v) TWEEN-20, about 5.0% (w/v) sucrose, and HCl,

wherein the antibody drug conjugate is at the concentration of about 10 mg/mL, and wherein the pH is about 6.0 at 25°C.

[00520] Although certain numbers (and numerical ranges thereof) are provided, it is understood that, in certain embodiments, numerical values within, *e.g.,* 2%, 5%, 10%, 15% or 20% of said numbers (or numerical ranges) are also contemplated.

[00521] A primary solvent in a vehicle can be either aqueous or non-aqueous in nature. In addition, the vehicle can contain other pharmaceutically acceptable excipients for modifying or maintaining the pH, osmolarity, viscosity, sterility or stability of the pharmaceutical composition. In certain embodiments, the pharmaceutically acceptable vehicle is an aqueous buffer. In other embodiments, a vehicle comprises, for example, sodium chloride and/or sodium citrate.

[00522] Pharmaceutical compositions provided herein can contain still other pharmaceutically acceptable formulation agents for modifying or maintaining the rate of release of an antibody drug conjugate and/or an additional agent, as described herein. Such formulation agents include those substances known to artisans skilled in preparing sustained-release formulations. For further reference pertaining to pharmaceutically and physiologically acceptable formulation agents, see, for example, Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, Pa. 18042) pages 1435-1712, The Merck Index, 12th Ed. (1996, Merck Publishing Group, Whitehouse, NJ); and Pharmaceutical Principles of

Solid Dosage Forms (1993, Technonic Publishing Co., Inc., Lancaster, Pa.). Additional pharmaceutical compositions appropriate for administration are known in the art and are applicable in the methods and compositions provided herein.

[00523] In some embodiments, the pharmaceutical composition provided herein is in a liquid form. In other embodiments, the pharmaceutical composition provided herein is lyophilized.

[00524] A pharmaceutical composition can be formulated to be compatible with its intended route of administration. Thus, pharmaceutical compositions include excipients suitable for administration by routes including parenteral (*e.g.*, subcutaneous (s.c.), intravenous, intramuscular, or intraperitoneal), intradermal, oral (*e.g.*, ingestion), inhalation, intracavity, intracranial, and transdermal (topical). Other exemplary routes of administration are set forth herein.

[00525] Pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension can be formulated using suitable dispersing or wetting agents and suspending agents disclosed herein or known to the skilled artisan. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that can be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed, including synthetic mono- or diglycerides. Moreover, fatty acids such as oleic acid find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (*e.g.*, aluminum monostearate or gelatin).

[00526] In one embodiment, the pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, and subcutaneous administration.

[00527] In one embodiment, the pharmaceutical compositions provided herein can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid

forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, e.g.,* Remington, *The Science and Practice of Pharmacy*, *supra*).

[00528] In one embodiment, the pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[00529] In one embodiment, suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (*e.g.*, polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

[00530] In one embodiment, suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (*e.g.*, benzethonium chloride), methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents include those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium

hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

[00531] In one embodiment, the pharmaceutical compositions provided herein can be formulated for single or multiple dosage administration. The single dosage formulations are packaged in an ampoule, a vial, or a syringe. The multiple dosage parenteral formulations can contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[00532] In one embodiment, the pharmaceutical compositions are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[00533] In one embodiment, the pharmaceutical compositions provided herein can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00534] Dispersible powders and granules suitable for preparation of an aqueous suspension by addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

[00535] Pharmaceutical compositions can also include excipients to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including implants, liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, can be employed. Prolonged absorption of injectable pharmaceutical compositions can be achieved by including an agent that delays absorption, for example, aluminum monostearate or gelatin. Prevention of the action of microorganisms can be achieved by various antibacterial and

antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like.

[00536] The pharmaceutical composition provided herein can be stored at -80°C, 4°C, 25°C or 37°C.

[00537] A lyophilized composition can be made by freeze-drying the liquid pharmaceutical composition provided herein. In a specific embodiment, the pharmaceutical composition provided here is a lyophilized pharmaceutical composition. In some embodiments, the pharmaceutical formulations are lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They can also be reconstituted and formulated as solids or gels.

[00538] In some embodiments, preparation of the lyophilized formulation provided herein involves batching of the formulated bulk solution for lyophilization, aseptic filtration, filling in vials, freezing vials in a freeze-dryer chamber, followed by lyophilization, stoppering and capping.

[00539] A lyophilizer can be used in preparing the lyophilized formulation. For example, a VirTis Genesis Model EL pilot unit can be employed. The unit incorporates a chamber with three working shelves (to a total usable shelf area of ca 0.4 square meters), an external condenser, and a mechanical vacuum pumping system. Cascaded mechanical refrigeration allows the shelves to be cooled to -70°C or lower, and the external condenser to -90°C or lower. Shelf temperature and chamber pressure were controlled automatically to +/- 0.5°C and +/- 2 microns (milliTorr), respectively. The unit was equipped with a capacitance manometer vacuum gauge, a Pirani vacuum gauge, a pressure transducer (to measure from 0 to 1 atmosphere), and a relative humidity sensor.

[00540] The lyophilized powder can be prepared by dissolving an antibody drug conjugate provided herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. In some embodiments, the lyophilized powder is sterile. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. In one embodiment, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage or multiple dosages of the antibody drug conjugate. The lyophilized powder can be stored under appropriate conditions, such as at about 4 °C to room temperature.

[00541] Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, the lyophilized powder is

added to sterile water or other suitable excipient. Such amount can be empirically determined and adjusted according to specific needs.

[00542] An exemplary reconstitution procedure is illustrated as follows: (1) fit the 5 mL or 3 mL syringe with a with a 18 or 20 Gauge needle and filled the syringe with water of the grade Water for Injection (WFI); (2) measure appropriate amount of WFI using the syringe graduations, ensuring that the syringe was free of air bubbles; (3) inserted the needle through the rubber stopper; (4) dispense the entire contents of the syringe into the container down the vial wall, removed the syringe and needle and put into the sharp container; (4) swirl the vial continuously to carefully solubilize the entire vial contents until fully reconstituted (*e.g.*, about 20-40 seconds) and minimize excessive agitation of the protein solution that could result in foaming.

[00543] In some embodiments, the pharmaceutical composition provided herein is supplied as a dry sterilized lyophilized powder or water free concentrate in a hermetically sealed container and can be reconstituted, *e.g.,* with water or saline to the appropriate concentration for administration to a subject. In certain embodiments, the antibody drug conjugate is supplied as a dry sterile lyophilized powder in a hermetically sealed container at a unit dosage of at least 0.1 mg, at least 0.5 mg, at least 1 mg, at least 2 mg, at least 3 mg, at least 5 mg, at least 10 mg, at least 15 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 45 mg, at least 50 mg, at least 60 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, or at least 100 mg. The lyophilized antibody drug conjugate can be stored at between 2 and 8° C in its original container and the antibody drug conjugate can be administered within 12 hours, such as within 6 hours, within 5 hours, within 3 hours, or within 1 hour after being reconstituted. In an alternative embodiment, the pharmaceutical composition comprising the antibody drug conjugate provided herein is supplied in liquid form in a hermetically sealed container indicating the quantity and concentration of the antibody drug conjugate. In certain embodiments, the liquid form of the antibody drug conjugate is supplied in a hermetically sealed container at least 0.1 mg/ml, at least 0.5 mg/ml, at least 1 mg/ml, at least 5 mg/ml, at least 10 mg/ml, at least 15 mg/ml, at least 25 mg/ml, at least 30 mg/ml, at least 40 mg/ml, at least 50 mg/ml, at least 60 mg/ml, at least 70 mg/ml, at least 80 mg/ml, at least 90 mg/ml, or at least 100 mg/ml.

[00544] Additional embodiments for the pharmaceutical compositions have been described in US Patent No. 8,637,642 and International Application No. PCT/US2019/056214 (Publication No. WO2020/117373), both of which are hereby incorporated in their entireties by reference.

5.5 Methods for a Combination Therapy

[00545] The method for inhibiting growth of tumor cells using the pharmaceutical composition provided herein in combination with chemotherapy or radiation or both comprises administering the present pharmaceutical composition before, during, or after commencing chemotherapy or radiation therapy, as well as any combination thereof (*i.e.* before and during, before and after, during and after, or before, during, and after commencing the chemotherapy and/or radiation therapy). Depending on the treatment protocol and the specific patient needs, the method is performed in a manner that will provide the most efficacious treatment and ultimately prolong the life of the patient. Additional embodiments for such combination therapy have been described in US Patent No. 8,637,642 and International Application No. PCT/US2019/056214 (Publication No. WO2020/117373), both of which are hereby incorporated in their entireties by reference.

5.6 Doses of the Immune Checkpoint Inhibitors (e.g. Pembrolizumab)

[00546] In some embodiments, the amount of the checkpoint inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor e.g., an anti-PD-1 antibody, e.g., pembrolizumab), for the various methods provided herein be determined by standard clinical techniques.

[00547] A dosage of the checkpoint inhibitor or PD-(L)-1 inhibitor results in a serum titer of from about 0.1 μg/ml to about 450 μg/ml, and in some embodiments at least 0.1 μg/ml, at least 0.2 μg/ml, at least 0.4 μg/ml, at least 0.5 μg/ml, at least 0.6 μg/ml, at least 0.8 μg/ml, at least 1 μg/ml, at least 1.5 μg/ml, such as at least 2 μg/ml, at least 5 μg/ml, at least 10 μg/ml, at least 15 μg/ml, at least 20 μg/ml, at least 25 μg/ml, at least 30 μg/ml, at least 35 μg/ml, at least 40 μg/ml, at least 50 μg/ml, at least 75 μg/ml, at least 100 μg/ml, at least 125 μg/ml, at least 150 μg/ml, at least 200 μg/ml, at least 250 μg/ml, at least 300 μg/ml, at least 350 μg/ml, at least 400 μg/ml, or at least 450 μg/ml can be administered to a human for the prevention and/or treatment of a cancer. It is to be understood that the precise dose of the checkpoint inhibitor or PD-(L)-1 inhibitor to be employed will also depend on the route of administration, and the seriousness of a cancer in a subject, and should be decided according to the judgment of the practitioner and each patient's circumstances.

[00548] In some embodiments, the dosage of the checkpoint inhibitor PD-(L)-1 inhibitor (*e.g.*, a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the subject's body weight. In

some embodiments, the dosage administered to the patient is about 1 mg/kg to about 75 mg/kg of the subject's body weight. In some embodiments, the dosage administered to a patient is between 1 mg/kg and 20 mg/kg of the subject's body weight, such as 1 mg/kg to 5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 1 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 1.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 2 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 2.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 3 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 3.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 4 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 4.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 5.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 6 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 6.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 7 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 7.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 8 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 8.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 9.0 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 10.0 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 15.0 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 20.0 mg/kg of the subject's body weight.

[00549] In certain embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg or about 500 mg. In particular embodiments, the checkpoint inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of about 200 mg.

[00550] In certain embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of about 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg or 500 mg. In particular embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of about 200 mg. In particular embodiments, the pembrolizumab is administered at a dose of about 200 mg.

[00551] In certain embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of about 100 mg to about 500 mg, about 150 mg to about 500 mg, about 200 mg to about 500 mg, about 250 mg to about 500 mg, about 300 mg to about 500 mg, about 350 mg to about 500 mg, about 400 mg to about 500 mg, or about 450 mg to about 500 mg. In certain embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of about 100 mg to about 450 mg, about 100 mg to about 400 mg, about 100 mg to about 350 mg, about 100 mg to about 300 mg, about 100 mg to about 250 mg, about 100 mg to about 200 mg, or about 100 mg to about 150 mg. In certain embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of about 150 mg to about 450 mg, about 150 to about 400 mg, about 150 to about 350 mg, about 200 mg to about 450 mg, about 200 mg to about 400 mg, about 200 mg to about 300 mg, or about 200 mg to about 250 mg.

[00552] In certain embodiments, the checkpoint inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of 100 mg to 500 mg, 150 mg to 500 mg, 200 mg to 500 mg, 250 mg to 500 mg, 300 mg to 500 mg, 350 mg to 500 mg, 400 mg to 500 mg, or 450 mg to 500 mg. In certain embodiments, the checkpoint inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of 100 mg to 450 mg, 100 mg to 400 mg, 100 mg to 350 mg, 100 mg to 300 mg, 100 mg to 250 mg, 100 mg to 200 mg, or 100 mg to 150 mg. In certain embodiments, the checkpoint inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of 150 mg to 450 mg, 150 to 400 mg, 150 to 350 mg, 200 mg to 450 mg, 200 mg to 400 mg, 200 mg to 300 mg, or 200 mg to 250 mg.

[00553] In some embodiments, (a) the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of about 100 mg to about 400 mg; and (b) after step (a), the anti-PD-1 antibody is administered to the subject at a dose of about 300 mg to about 500 mg mg every 40 to 45 days. In some embodiments, (a) the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of about 100 mg to about 300 mg; and (b) after step (a), the anti-PD-1 antibody is administered to the subject at a dose of about 350 mg to about 450 mg mg every 40 to 45 days. In some embodiments, (a) the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of about 150 mg to about 250 mg; and (b) after step (a), the anti-PD-1 antibody is administered to the subject at a dose of about 350 mg to about 450 mg mg every 40 to 45 days. In certain embodiments, (a) the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of about 200 mg; and (b) after step (a), the anti-PD-1 antibody is administered to the subject at a dose of about 400 mg every 42 days.

[00554] In some embodiments, (a) the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of 100 mg to 400 mg; and (b) after step (a), the anti-PD-1 antibody is administered to the subject at a dose of 300 mg to 500 mg mg every 40 to 45 days. In some embodiments, (a) the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of 100 mg to 300 mg; and (b) after step (a), the anti-PD-1 antibody is administered to the subject at a dose of 350 mg to 450 mg mg every 40 to 45 days. In some embodiments, (a) the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of 150 mg to 250 mg; and (b) after step (a), the anti-PD-1 antibody is administered to the subject at a dose of 350 mg to 450 mg mg every 40 to 45 days. In certain embodiments, (a) the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., an anti-PD-1 antibody, e.g., pembrolizumab) is administered at a dose of 200 mg; and (b) after step (a), the anti-PD-1 antibody is administered to the subject at a dose of 400 mg every 42 days.

[00555] In some embodiments, pembrolizumab is administered at a dose of about 200 mg. In some embodiments, pembrolizumab is administered at a dose of about 200 mg every 3

weeks. In some embodiments, pembrolizumab is administered at a dose of about 200 mg on day 1 of each 3 week cycle.

[00556] In some embodiments, pembrolizumab is administered at a dose of about 400 mg. In some embodiments, pembrolizumab is administered at a dose of about 400 mg every 6 weeks. In some embodiments, pembrolizumab is administered at a dose of about 400 mg on day 1 of each 6 week cycle.

[00557] In some embodiment, pembrolizumab is administered at a dose of about 2 mg/kg. In some embodiment, pembrolizumab is administered at a dose of about 2 mg/kg every three weeks. In some embodiment, pembrolizumab is administered at a dose of about 2 mg/kg on day 1 of each 3 week cycle. In particular embodiments, the patient is a pediatric patient.

[00558] In some embodiment, pembrolizumab is administered as a 30 minute (-5 minutes /+10 minutes) intravenous infusion. In one embodiment, the selected dose of pembrolizumab is administered by IV infusion over a time period of between 25 and 40 minutes, or about 30 minutes.

[00559] In one aspect, pembrolizumab in included in a pharmaceutical composition with a pharmaceutically acceptable carrier or diluent and may include additional pharmaceutically acceptable excipients.

[00560] In particular embodiments, the patient is an adult patient. In particular embodiments, the patient is an adult patient, wherein the adult patient is 18 years or older.

5.7 Dosage of the ADCs for the Methods

[00561] In some embodiments, the amount of a prophylactic or therapeutic agent (*e.g.,* an antibody drug conjugate provided herein), or a pharmaceutical composition provided herein that will be effective in the prevention and/or treatment of a cancer can be determined by standard clinical techniques.

[00562] In some embodiments, the ADC of the methods for which the various dosages are described in this Section (Section 5.7) is enfortumab vedotin (EV).

[00563] Accordingly, a dosage of an antibody drug conjugate in the pharmaceutical composition that results in a serum titer of from about 0.1 μg/ml to about 450 μg/ml, and in some embodiments at least 0.1 μg/ml, at least 0.2 μg/ml, at least 0.4 μg/ml, at least 0.5 μg/ml, at least 0.6 μg/ml, at least 0.8 μg/ml, at least 1 μg/ml, at least 1.5 μg/ml, such as at least 2 μg/ml, at least 5 μg/ml, at least 10 μg/ml, at least 15 μg/ml, at least 20 μg/ml, at least 25 μg/ml, at least 30 μg/ml, at least 35 μg/ml, at least 40 μg/ml, at least 50 μg/ml, at least 75 μg/ml, at least 100 μg/ml, at least 125 μg/ml, at least 150 μg/ml, at least 200 μg/ml, at least

250 μg/ml, at least 300 μg/ml, at least 350 μg/ml, at least 400 μg/ml, or at least 450 μg/ml can be administered to a human for the prevention and/or treatment of a cancer. It is to be understood that the precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of a cancer in a subject, and should be decided according to the judgment of the practitioner and each patient's circumstances.

[00564] Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[00565] For the pharmaceutical composition comprising the antibody drug conjugate provided herein, the dosage of the antibody drug conjugate administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the subject's body weight. In some embodiments, the dosage administered to the patient is about 1 mg/kg to about 75 mg/kg of the subject's body weight. In some embodiments, the dosage administered to a patient is between 1 mg/kg and 20 mg/kg of the subject's body weight, such as 1 mg/kg to 5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 0.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 0.75 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 1 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 1.25 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 1.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 2 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 2.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 3 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 3.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 4 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 4.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 5.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 6 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 6.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 7 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 7.5 mg/kg of the subject's body weight. In some embodiments, dosage administered to a patient is about 8 mg/kg of the

subject's body weight. In some embodiments, dosage administered to a patient is about 8.5 mg/kg of the subject's body weight.

[00566] In some embodiments, the antibody drug conjugate formulated in the pharmaceutical composition provided herein is administered based on the patient's actual body weight at baseline and doses will not change unless the patient's weight changes by ≥10% from baseline of the previous cycle, or the dose adjustment criteria is met. In some embodiments, actual weight will be used except for patients weighing greater than 100 kg, in such cases, the dose will be calculated based on a weight of 100 kg. In some embodiments, the maximum doses are 100 mg for patients receiving the 1.00 mg/kg dose level and 125 mg for patients receiving the 1.25 mg/kg dose level.

[00567] In one embodiment, approximately 100 mg/kg or less, approximately 75 mg/kg or less, approximately 50 mg/kg or less, approximately 25 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 1.5 mg/kg or less, approximately 1.25 mg/kg or less, approximately 1 mg/kg or less, approximately 0.75 mg/kg or less, approximately 0.5 mg/kg or less, or approximately 0.1 mg/kg or less of an antibody drug conjugate formulated in the present pharmaceutical composition is administered 5 times, 4 times, 3 times, 2 times or 1 time to treat a cancer. In some embodiments, the pharmaceutical composition comprising the antibody drug conjugate provided herein is administered about 1-12 times, wherein the doses can be administered as necessary, *e.g.*, weekly, biweekly, monthly, bimonthly, trimonthly, *etc.*, as determined by a physician. In some embodiments, a lower dose (*e.g.*, 0.1-15 mg/kg) can be administered more frequently (*e.g.*, 3-6 times). In other embodiments, a higher dose (*e.g.*, 25-100 mg/kg) can be administered less frequently (*e.g.*, 1-3 times).

[00568] In some embodiments, a single dose of an antibody drug conjugate formulated in the pharmaceutical composition provided herein is administered to a patient to prevent and/or treat a cancer 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26 times for every two-week cycle (*e.g.*, about 14 day) over a time period (*e.g.*, a year), wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 0.75 mg/kg, about 1 mg/kg, about 1.25 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about

100 mg/kg, or a combination thereof (*i.e.,* each dose monthly dose may or may not be identical).

[00569] In some embodiments, a single dose of an antibody drug conjugate formulated in the pharmaceutical composition provided herein is administered to a patient to prevent and/or treat a cancer 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26 times for every three-week cycle (*e.g.,* about 21 day) over a time period (*e.g.*, a year), wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 0.75 mg/kg, about 1 mg/kg, about 1.25 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (*i.e.,* each dose monthly dose may or may not be identical).

[00570] In some embodiments, a single dose of an antibody drug conjugate formulated in the pharmaceutical composition provided herein is administered to a patient to prevent and/or treat a cancer 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26 times for every four-week cycle (*e.g.,* about 28 day) over a time period (*e.g.*, a year), wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 0.75 mg/kg, about 1 mg/kg, about 1.25 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (*i.e.,* each dose monthly dose may or may not be identical).

[00571] In another embodiment, a single dose of an antibody drug conjugate formulated in the pharmaceutical composition provided herein is administered to patient to prevent and/or treat a cancer 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times at about monthly (*e.g.,* about 30 day) intervals over a time period (*e.g.*, a year), wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 0.75 mg/kg, about 1 mg/kg, about 1.25 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg,

about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (*i.e.,* each dose monthly dose may or may not be identical).

[00572] In another embodiment, a single dose of an antibody drug conjugate formulated in the pharmaceutical composition provided herein is administered to patient to prevent and/or treat a cancer 1, 2, 3, 4, 5, or 6 times at about bi-monthly (*e.g.,* about 60 day) intervals over a time period (*e.g.*, a year), wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 0.75 mg/kg, about 1 mg/kg, about 1.25 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (*i.e.,* each dose monthly dose may or may not be identical).

[00573] In yet another embodiment, a single dose of an antibody drug conjugate formulated in the pharmaceutical composition provided herein is administered to patient to prevent and/or treat a cancer 1, 2, 3 or 4 times at about tri-monthly (*e.g.,* about 120 day) intervals over a time period (*e.g.*, a year), wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 0.75 mg/kg, about 1 mg/kg, about 1.25 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (*i.e.,* each dose monthly dose may or may not be identical).

[00574] In certain embodiments, the route of administration for a dose of an antibody drug conjugate formulated in the pharmaceutical composition provided herein to a patient is intranasal, intramuscular, intravenous, or a combination thereof, but other routes described herein are also acceptable. Each dose may or may not be administered by an identical route of administration. In some embodiments, an antibody drug conjugate formulated in the pharmaceutical composition provided herein can be administered via multiple routes of administration simultaneously or subsequently to other doses of one or more additional therapeutic agents.

[00575] In some more specific embodiments, the antibody drug conjugate formulated in the pharmaceutical composition provided herein is administered at a dose of about 0.5 mg/kg, about 0.75 mg/kg, about 1 mg/kg, about 1.25 mg/kg, or about 1.5 mg/kg of the subject's body weight by an intravenous (IV) injection or infusion.

[00576] In some more specific embodiments, the antibody drug conjugate formulated in the pharmaceutical composition provided herein is administered at a dose of about 0.5 mg/kg, about 0.75 mg/kg, about 1 mg/kg, about 1.25 mg/kg, or about 1.5 mg/kg of the subject's body weight by an intravenous (IV) injection or infusion over about 30 minutes twice every three-week cycle. In some embodiments, the antibody drug conjugate formulated in the pharmaceutical composition is administered by an intravenous (IV) injection or infusion over about 30 minutes on Days 1 and 8 of every three-week cycle. In some embodiments, the method further comprises administering an immune checkpoint inhibitor or PD-(L)-1 inhibitor by an intravenous (IV) injection or infusion one or more times in each three-week cycle. In some embodiments, the method further comprises administering an immune checkpoint inhibitor or PD-(L)-1 inhibitor by an intravenous (IV) injection or infusion on Day 1 of every three-week cycle. In some embodiments, the method further comprises administering an immune checkpoint inhibitor or PD-(L)-1 inhibitor by an intravenous (IV) injection or infusion one or more times in each three-week cycle. In some embodiments, the method further comprises administering an immune checkpoint inhibitor or PD-(L)-1 inhibitor by an intravenous (IV) injection or infusion on Day 1 of every three-week cycle after completion of the antibody drug conjugate infusion. In some embodiments, the immune checkpoint inhibitor is pembrolizumab, and wherein pembrolizumab is administered at amount of about 200 mg over about 30 minutes. In some embodiments, the antibody drug conjugate is administered to patients with locally advanced urothelial or bladder cancer who have shown disease progression or relapse during or after treatment with another cancer treatment. In some embodiments, the ADC of the methods for which the various dosages are described in this paragraph is enfortumab vedotin (EV).

[00577] In other more specific embodiments, the antibody drug conjugate formulated in the pharmaceutical composition provided herein is administered at a dose of about 0.5 mg/kg, about 0.75 mg/kg, 1 mg/kg, about 1.25 mg/kg, or about 1.5 mg/kg of the subject's body weight by an intravenous (IV) injection or infusion over about 30 minutes three times every four-week cycle. In some embodiments, the antibody drug conjugate formulated in the pharmaceutical composition is administered on Days 1, 8 and 15 of every 28-day (four-week) cycle. In some embodiments, the antibody drug conjugate formulated in the pharmaceutical

composition is administered by an intravenous (IV) injection or infusion over about 30 minutes on Days 1, 8 and 15 of every 28-day (four-week) cycle. In some embodiments, the method further comprises administering an immune checkpoint inhibitor or PD-(L)-1 inhibitor by an intravenous (IV) injection or infusion one or more times in each four-week cycle. In some embodiments, the immune checkpoint inhibitor or PD-(L)-1 inhibitor is pembrolizumab. In other embodiments, the immune checkpoint inhibitor or PD-(L)-1 inhibitor is atezolizumab. In some embodiments, the antibody drug conjugate is administered to patients with urothelial or bladder cancer who have shown disease progression or relapse during or after treatment with another cancer treatment. In some embodiments, the antibody drug conjugate is administered to patients with metastatic urothelial or bladder cancer who have shown disease progression or relapse during or after treatment with another cancer treatment. In some embodiments, the antibody drug conjugate is administered to patients with locally advanced urothelial or bladder cancer who have shown disease progression or relapse during or after treatment with another cancer treatment. In some embodiments, the ADC of the methods for which the various dosages are described in this paragraph is enfortumab vedotin (EV).

[00578] In some embodiments of the various methods provided herein, the ADC is administered at a dose of about 0.25 to about 10 mg/kg of the subject's body weight, about 0.25 to about 5 mg/kg of the subject's body weight, about 0.25 to about 2.5 mg/kg of the subject's body weight, about 0.25 to about 1.25 mg/kg of the subject's body weight, about 0.5 to about 10 mg/kg of the subject's body weight, about 0.5 to about 5 mg/kg of the subject's body weight, about 0.5 to about 2.5 mg/kg of the subject's body weight, about 0.5 to about 1.25 mg/kg of the subject's body weight, about 0.75 to about 10 mg/kg of the subject's body weight, about 0.75 to about 5 mg/kg of the subject's body weight, about 0.75 to about 2.5 mg/kg of the subject's body weight, or about 0.75 to about 1.25 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of about 1 to about 10 mg/kg of the subject's body weight. In certain embodiments, the ADC is administered at a dose of about 1 to about 5 mg/kg of the subject's body weight. In other embodiments, the ADC is administered at a dose of about 1 to about 2.5 mg/kg of the subject's body weight. In further embodiments, the ADC is administered at a dose of about 1 to about 1.25 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of about 0.25 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of about 0.5 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of about 0.75 mg/kg of the subject's body weight. In some

embodiments, the ADC is administered at a dose of about 1.0 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of about 1.25 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of about 1.5 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of about 1.75 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of about 2.0 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of about 2.25 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of about 2.5 mg/kg of the subject's body weight.

[00579] In certain embodiments of the various methods provided herein, the ADC is administered at a dose of 0.25 to 10 mg/kg of the subject's body weight, 0.25 to 5 mg/kg of the subject's body weight, 0.25 to 2.5 mg/kg of the subject's body weight, 0.25 to 1.25 mg/kg of the subject's body weight, 0.5 to 10 mg/kg of the subject's body weight, 0.5 to 5 mg/kg of the subject's body weight, 0.5 to 2.5 mg/kg of the subject's body weight, 0.5 to 1.25 mg/kg of the subject's body weight, 0.75 to 10 mg/kg of the subject's body weight, 0.75 to 5 mg/kg of the subject's body weight, 0.75 to 2.5 mg/kg of the subject's body weight, or 0.75 to 1.25 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of 1 to 10 mg/kg of the subject's body weight. In certain embodiments, the ADC is administered at a dose of 1 to 5 mg/kg of the subject's body weight. In other embodiments, the ADC is administered at a dose of 1 to 2.5 mg/kg of the subject's body weight. In further embodiments, the ADC is administered at a dose of 1 to 1.25 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of 0.25 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of 0.5 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of 0.75 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of 1.0 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of 1.25 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of 1.5 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of 1.75 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of 2.0 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of 2.25 mg/kg of the subject's body weight. In some embodiments, the ADC is administered at a dose of 2.5 mg/kg of the subject's body weight.

[00580] In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the first dose of the ADC is a dose of about 0.25 to about 10 mg/kg of the subject's body weight, about 0.25 to about 5 mg/kg of the subject's body weight, about 0.25 to about 2.5 mg/kg of the subject's body weight, about 0.25 to about 1.25 mg/kg of the subject's body weight, about 0.5 to about 10 mg/kg of the subject's body weight, about 0.5 to about 5 mg/kg of the subject's body weight, about 0.5 to about 2.5 mg/kg of the subject's body weight, about 0.5 to about 1.25 mg/kg of the subject's body weight, about 0.75 to about 10 mg/kg of the subject's body weight, about 0.75 to about 5 mg/kg of the subject's body weight, about 0.75 to about 2.5 mg/kg of the subject's body weight, or about 0.75 to about 1.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the first dose of the ADC is a dose of about 1 to about 10 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the first dose of the ADC is a dose of about 1 to about 5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the first dose of the ADC is a dose of about 1 to about 2.5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the first dose of the ADC is a dose of about 1 to about 1.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the first dose of the ADC is a dose of about 0.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the first dose of the ADC is a dose of about 0.5 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of about 0.75 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of about 1.0 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of about 1.25 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of about 1.5 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of about 1.75 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of about 2.0 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of about 2.25 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of or about 2.5 mg/kg of the subject's body weight.

[00581] In certain embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the first dose of the ADC is a dose of 0.25 to 10 mg/kg of the subject's body weight, 0.25 to 5 mg/kg of the subject's body weight, 0.25 to 2.5 mg/kg of the subject's body weight, 0.25 to 1.25 mg/kg of the subject's body weight, 0.5 to 10 mg/kg of the subject's body weight, 0.5 to 5 mg/kg of the subject's body weight, 0.5 to 2.5 mg/kg of the subject's body weight, 0.5 to 1.25 mg/kg of the subject's body weight, 0.75 to 10 mg/kg of the subject's body weight, 0.75 to 5 mg/kg of the subject's body weight, 0.75 to 2.5 mg/kg of the subject's body weight, or 0.75 to 1.25 mg/kg of the subject's body weight. In certain embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the first dose of the ADC is a dose of 1 to 10 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the first dose of the ADC is a dose of 1 to 5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the first dose of the ADC is a dose of 1 to 2.5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the first dose of the ADC is a dose of 1 to 1.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the first dose of the ADC is a dose of 0.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the first dose of the ADC is a dose of 0.5 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of 0.75 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of 1.0 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of 1.25 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of 1.5 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of 1.75 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of 2.0 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of 2.25 mg/kg of the subject's body weight. In some embodiments, the first dose of the ADC is a dose of 2.5 mg/kg of the subject's body weight.

[00582] In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 0.1 mg/kg to about 2 mg/kg of the subject's body weight. In some

embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 0.1 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 0.2 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 0.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 0.3 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 0.4 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 0.5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 0.6 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 0.7 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 0.75 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 0.8 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 0.9 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 1 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 1.1 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the

ADC is lower than the first dose by about 1.2 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 1.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 1.3 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 1.4 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 1.5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 1.6 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 1.7 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 1.75 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 1.8 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 1.9 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by about 2 mg/kg of the subject's body weight.

[00583] In certain embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 0.1 mg/kg to 2 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 0.1 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 0.2 mg/kg of the subject's body weight. In some embodiments of the various

methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 0.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 0.3 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 0.4 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 0.5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 0.6 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 0.7 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 0.75 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 0.8 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 0.9 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 1 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 1.1 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 1.2 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 1.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the

first dose by 1.3 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 1.4 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 1.5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 1.6 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 1.7 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 1.75 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 1.8 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 1.9 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is lower than the first dose by 2 mg/kg of the subject's body weight.

[00584] In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 0.25 to about 10 mg/kg of the subject's body weight, about 0.25 to about 5 mg/kg of the subject's body weight, about 0.25 to about 2.5 mg/kg of the subject's body weight, about 0.25 to about 1.25 mg/kg of the subject's body weight, about 0.5 to about 10 mg/kg of the subject's body weight, about 0.5 to about 5 mg/kg of the subject's body weight, about 0.5 to about 2.5 mg/kg of the subject's body weight, about 0.5 to about 1.25 mg/kg of the subject's body weight, about 0.75 to about 10 mg/kg of the subject's body weight, about 0.75 to about 5 mg/kg of the subject's body weight, about 0.75 to about 2.5 mg/kg of the subject's body weight, or about 0.75 to about 1.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 1 to about 10 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein,

including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 1 to about 5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 1 to about 2.5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 1 to about 1.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 0.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 0.5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 0.75 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 1.0 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 1.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 1.5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 1.75 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 2.0 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 2.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of about 2.5 mg/kg of the subject's body weight.

[00585] In certain embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 0.25 to 10 mg/kg of the subject's body weight, 0.25 to 5 mg/kg of the subject's body weight, 0.25 to 2.5 mg/kg of the subject's body weight, 0.25 to 1.25 mg/kg of the subject's body weight, 0.5

to 10 mg/kg of the subject's body weight, 0.5 to 5 mg/kg of the subject's body weight, 0.5 to 2.5 mg/kg of the subject's body weight, 0.5 to 1.25 mg/kg of the subject's body weight, 0.75 to 10 mg/kg of the subject's body weight, 0.75 to 5 mg/kg of the subject's body weight, 0.75 to 2.5 mg/kg of the subject's body weight, or 0.75 to 1.25 mg/kg of the subject's body weight. In certain embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 1 to 10 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 1 to 5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 1 to 2.5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 1 to 1.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 0.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 0.5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 0.75 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 1.0 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 1.25 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 1.5 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 1.75 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 2.0 mg/kg of the subject's body weight. In some embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 2.25 mg/kg of the subject's body weight. In some embodiments of

the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is a dose of 2.5 mg/kg of the subject's body weight.

[00586] In certain embodiments of the various methods provided herein, including those methods requiring a first and a second dose, the second dose of the ADC is identical to the first dose of the ADC.

[00587] In some embodiments of the methods provided herein, the ADC is administered by an intravenous (IV) injection or infusion. In one embodiment, the first dose of the ADC is administered by an IV injection. In another embodiment, the first dose of the ADC is administered by an IV infusion. In yet another embodiment, the second dose of the ADC is administered by an IV injection. In yet another embodiment, the second dose of the ADC is administered by an IV injection infusion. In one embodiment, the first dose of the ADC is administered by an IV injection and the second dose of the ADC is administered by an IV injection. In another embodiment, the first dose of the ADC is administered by an IV infusion and the second dose of the ADC is administered by an IV injection. In yet another embodiment, the second dose of the ADC is administered by an IV injection and the second dose of the ADC is administered by an IV injection infusion. In yet another embodiment, the second dose of the ADC is administered by an IV injection infusion and the second dose of the ADC is administered by an IV injection infusion. In some embodiments, the ADC of the methods for which the various dosages are described in this paragraph is enfortumab vedotin (EV).

[00588] In certain embodiments of the methods provided herein, the ADC is administered by an IV injection or infusion three times every four-week cycle. In some embodiments of the methods provided herein, the first dose of the ADC is administered by an IV injection or infusion three times every four-week cycle. In some embodiments of the methods provided herein, the second dose of the ADC is administered by an IV injection or infusion three times every four-week cycle. In some embodiments of the methods provided herein, the first dose of the ADC is administered by an IV injection or infusion three times every four-week cycle and the second dose of the ADC is administered by an IV injection or infusion three times every four-week cycle. In some embodiments, the ADC of the methods for which the various dosages are described in this paragraph is enfortumab vedotin (EV).

[00589] In some embodiments of the methods provided herein, the ADC is administered by an IV injection or infusion on Days 1, 8 and 15 of every four-week cycle. In some embodiments, the first dose of ADC is administered by an IV injection or infusion on Days 1, 8 and 15 of every four-week cycle. In some embodiments, the second dose of ADC is

administered by an IV injection or infusion on Days 1, 8 and 15 of every four-week cycle. In some embodiments, the first dose of ADC is administered by an IV injection or infusion on Days 1, 8 and 15 of every four-week cycle and the second dose of ADC is administered by an IV injection or infusion on Days 1, 8 and 15 of every four-week cycle. In some embodiments, the ADC of the methods for which the various dosages are described in this paragraph is enfortumab vedotin (EV).

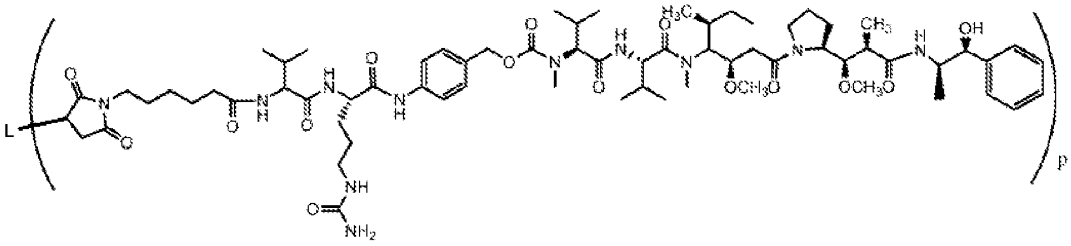
[00590] In certain embodiments of the methods provided herein, the ADC is administered by an IV injection or infusion over about 30 minutes three times every four-week cycle. In some embodiments, the first dose of the ADC is administered by an IV injection or infusion over about 30 minutes three times every four-week cycle. In some embodiments, the second dose of the ADC is administered by an IV injection or infusion over about 30 minutes three times every four-week cycle. In some embodiments, the first dose of the ADC is administered by an IV injection or infusion over about 30 minutes three times every four-week cycle and the second dose of the ADC is administered by an IV injection or infusion over about 30 minutes three times every four-week cycle. In some embodiments, the ADC of the methods for which the various dosages are described in this paragraph is enfortumab vedotin (EV).

[00591] In some embodiments of the methods provided herein, the ADC is administered by an IV injection or infusion over about 30 minutes on Days 1, 8 and 15 of every four-week cycle. In some embodiments of the methods provided herein, the first dose of the ADC is administered by an IV injection or infusion over about 30 minutes on Days 1, 8 and 15 of every four-week cycle. In some embodiments of the methods provided herein, the second dose of the ADC is administered by an IV injection or infusion over about 30 minutes on Days 1, 8 and 15 of every four-week cycle. In some embodiments of the methods provided herein, the first dose of the ADC is administered by an IV injection or infusion over about 30 minutes on Days 1, 8 and 15 of every four-week cycle and the second dose of the ADC is administered by an IV injection or infusion over about 30 minutes on Days 1, 8 and 15 of every four-week cycle. In some embodiments, the ADC of the methods for which the various dosages are described in this paragraph is enfortumab vedotin (EV).

[00592] In other more specific embodiments, the antibody drug conjugate formulated in the pharmaceutical composition provided herein is administered at a dose of about 1 mg/kg, 1.25 mg/kg, or about 1.5 mg/kg of the subject's body weight by an intravenous (IV) injection or infusion over about 30 minutes three times every 28-day cycle. In some embodiments, the antibody drug conjugate formulated in the pharmaceutical composition is administered by an intravenous (IV) injection or infusion over about 30 minutes on Days 1, 8 and 15 of every 28-

day cycle. In some embodiments, the method further comprises administering an immune checkpoint inhibitor by an intravenous (IV) injection or infusion one or more times in each four-week cycle. In some embodiments of the methods provided herein, the ADC is administered three times within a 28 day cycle. In some embodiments of the methods provided herein, the ADC is administered on Days 1, 8 and 15 of a 28 day cycle. In some embodiments, the ADC of the methods for which the various dosages are described in this paragraph is enfortumab vedotin (EV).

[00593] In one specific embodiment of the methods provided herein, the ADC has the following structure:



wherein L- represents the antibody or antigen binding fragment thereof and p is from about 3 to about 4, the antibody comprises a heavy chain comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID NO:7 and a light chain comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:8, wherein the ADC is administered at a dose of about 1.25 mg/kg of the subject's body weight, and wherein the dose is administered by an IV injection or infusion over about 30 minutes on Days 1, 8 and 15 of every four-week cycle.

5.8 Combination Therapies

[00594] Provided herein are combination therapies using an antibody drug conjugate, wherein the antibody drug conjugate comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 conjugated to one or more units of monomethyl auristatin E (MMAE) in combination with a checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., pembrolizumab) for treating cancer in a subject. In any of the embodiments disclosed herein, the checkpoint inhibitor or PD-(L)-1 inhibitor may be pembrolizumab.

[00595] In some embodiments, a pharmaceutically effective amount of the antibody drug conjugate is administered. In some embodiments, a pharmaceutically effective amount of the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor,

e.g., pembrolizumab) is administered. In some embodiments, a pharmaceutically effective amount of the antibody drug conjugate is administered and a pharmaceutically effective amount of the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., pembrolizumab) is administered. In some embodiments, a pharmaceutically effective amount of the antibody drug conjugate is administered and a pharmaceutically effective amount of pembrolizumab is administered. In some embodiments, an effective amount of the antibody drug conjugate is administered and an effective amount of the checkpoint inhibitor or PD-(L)-1 inhibitor (such as a PD-1 inhibitor or a PD-L1 inhibitor, e.g., pembrolizumab) is administered. In some embodiments, an effective amount of the antibody drug conjugate is administered and an effective amount of pembrolizumab is administered.

[00596] In some embodiments, the subject is a human. In some embodiments, the subject is a subject diagnosed with cancer, e.g., urothelial cancer, bladder cancer, cancer of the renal pelvis, cancer of the ureter, cancer of the urethra, locally advanced cancer, metastatic cancer, locally advanced urothelial cancer, unresectable locally advanced urothelial cancer, metastatic urothelial cancer, locally advanced bladder cancer, or metastatic bladder cancer.

[00597] The amount of the antibody drug conjugate provided herein or pembrolizumab, or a pharmaceutical composition that will be effective in the prevention and/or treatment of cancer can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the cancer , and in some embodiments, should be decided according to the judgment of the practitioner and each patient's circumstances.

[00598] In some embodiments, the antibody drug conjugate provided herein is administered to the subject as part a composition. In some embodiments, the composition is a pharmaceutical composition described in Section 5.4

[00599] In some embodiments, the antibody drug conjugate and checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) may be formulated in different pharmaceutical compositions and administered separately to the subject in need thereof. In other embodiments, the antibody drug conjugate and checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) are administered together in the same pharmaceutical composition.

[00600] In other embodiments, the antibody drug conjugate and checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) are administered simultaneously. The term

"simultaneously" means at the same time or within a short period of time, for example, less than 1 hour, less than 2 hours, less than 3 hours, less than 4 hours, or less than 12 hours.

[00601] In some embodiments, the antibody drug conjugate and checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) are not administered simultaneously, and instead the two compounds are administered at different times.

[00602] In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered before the administration of the antibody drug conjugate.

[00603] In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered after the administration of the antibody drug conjugate.

[00604] In certain embodiments, the subject has been previously treated with the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) prior to the administration of the antibody drug conjugate.

[00605] In certain embodiments, the subject has been previously treated with the antibody drug conjugate prior to the administration of the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab).

[00606] In certain embodiments, the subject has not been previously treated with the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) prior to the co-administration of the antibody drug conjugate and the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab).

[00607] In certain embodiments, the co-administration of the antibody drug conjugate and the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is concomitant administration.

[00608] In certain embodiments, the co-administration of the antibody drug conjugate and the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is pharmaceutically effective to treat a cancer.

[00609] Any amount or dose of the antibody drug conjugate disclosed herein may be administered in combination with any amount or dose of the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) disclosed herein. In some embodiments, the antibody drug conjugate and the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) are administered at least once during a dosing period. A dosing period as used herein is meant a period of time, during which each therapeutic agent has been administered at least once. A dosing cycle can be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days. In some embodiments, a dosing cycle is

1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks. In certain embodiments, a dosing period is a dosing cycle.

[00610] The therapeutic agent (the antibody drug conjugate provided herein and/or the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab)) can be delivered as a single dose (e.g., a single bolus injection), or over time (e.g., continuous infusion over time or divided bolus doses over time). The agent can be administered repeatedly if necessary, for example, until the patient experiences stable disease or regression, or until the patient experiences disease progression or unacceptable toxicity. Stable disease or lack is determined by methods known in the art such as evaluation of patient symptoms, physical examination, and visualization of the tumor that has been imaged using X-ray, CAT, PET, MRI scan, or other commonly accepted evaluation modalities.

[00611] The therapeutic agent (the antibody drug conjugate provided herein and/or the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) can be administered once daily (QD) or divided into multiple daily doses such as twice daily (BID), three times daily (TID), and four times daily (QID). In addition, the administration can be continuous (i.e., daily for consecutive days or every day) or intermittent, e.g., in cycles (i.e., including days, weeks, or months of rest without drug). As used herein, the term "daily" is intended to mean that a therapeutic compound is administered once or more than once each day, for example, for a period of time. The term "continuous" is intended to mean that a therapeutic compound is administered daily for an uninterrupted period of, e.g., at least 10 days. The term "intermittent" or "intermittently" as used herein is intended to mean stopping and starting at either regular or irregular intervals. For example, intermittent administration of the compound is administration for one to six days per week, administration in cycles (e.g., daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week), or administration on alternate days.

[00612] In some embodiments, the frequency of administration is in the range of about a daily dose to about a monthly dose. In certain embodiments, administration is once a day, twice a day, three times a day, four times a day, once every other day, twice every other day, three times every other day, four times every other day, twice a week, three times a week, four times a week, five times a week, once a week, once every two weeks, once every three weeks, or once every four weeks.

[00613] In certain embodiments, the compound is administered once per day, twice a day, three times a day, or four times a day from one day to six months, from one week to three

months, from one week to four weeks, from one week to three weeks, or from one week to two weeks.

[00614] In some embodiments, the antibody drug conjugate provided herein is administered in a therapeutically effective amount and the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered in a therapeutically effective amount. A therapeutically effective amount of the antibody drug conjugate may be any amount or dose of the antibody drug conjugate disclosed herein. A therapeutically effective amount of the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) may be any amount or dose of the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) disclosed herein. In certain embodiments, any amount or dose of the antibody drug conjugate disclosed herein may be administered in combination with any amount or dose of the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) disclosed herein (see, e.g., Sections 5.2.1.3, 5.4, and 5.7).

[00615] The antibody drug conjugate and/or the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) may be administered or dosed according to body weight (mg/kg) or body surface area (BSA) (mg/m^2). As an example, which is intended to be illustrative, and not limiting, the average body mass globally has been calculated to be 62 kg. (*See* Walpole *et al.*, 2012, *BMC Public Health*, 12:439 (doi: 10.1186/1471-2458-12-439).

[00616] In certain embodiments, the antibody drug conjugate provided herein is administered at a dose of about 0.1 mg/kg, about 0.5 mg/kg, about 0.75 mg/kg, about 1 mg/kg, about 1.25 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg.

[00617] In certain embodiments, the antibody drug conjugate provided herein is administered at a dose of about 0.1 mg/kg to about 100 mg/kg of the subject's body weight. In some embodiments, the antibody drug conjugate provided herein is administered at a dose of about 1 mg/kg to about 75 mg/kg of the subject's body weight. In some embodiments, the antibody drug conjugate provided herein is administered at a dose of between about 1 mg/kg and about 20 mg/kg of the subject's body weight, such as about 1 mg/kg to about 5 mg/kg of the subject's body weight, about 1 mg/kg to about 4 mg/kg of the subject's body weight, about 1 mg/kg to about 3 mg/kg of the subject's body weight, or about 1 mg/kg to about 2 mg/kg of the subject's body weight.

[00618] In certain embodiments , the pembrolizumab is administered at a dose of about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg or about 500 mg. In particular embodiments, the pembrolizumab is administered at a dose of about 200 mg.

[00619] In certain embodiments, the pembrolizumab is administered at a dose of about 100 mg to about about 500 mg, about 150 mg to about about 500 mg, about 200 mg to about 500 mg, about 250 mg to about 500 mg, about 300 mg to about 500 mg, about 350 mg to about 500 mg, about 400 mg to about 500 mg, or about 450 mg to about 500 mg. In certain embodiments, the pembrolizumab is administered at a dose of about 100 mg to about about 450 mg, about 100 mg to about about 400 mg, about 100 mg to about about 350 mg, about 100 mg to about 300 mg, about 100 mg to about 250 mg, about 100 mg to about 200 mg, or about 100 mg to about 150 mg. In certain embodiments, the pembrolizumab is administered at a dose of about 150 mg to about 450 mg, about 150 to about 400 mg, about 150 to about 350 mg, about 200 mg to about 450 mg, about 200 mg to about 400 mg, about 200 mg to about 300 mg, or about 200 mg to about 250 mg.

[00620] In some embodiments, the antibody drug conjugate provided herein is administered daily during each treatment cycle of 14 days, 21 days, 28 days, 35 days, or 42 days. In some embodiments, the antibody drug conjugate is administered for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days of a treatment cycle of 14 days. In some embodiments, the antibody drug conjugate is administered for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days of a treatment cycle of 21 days (i.e., 3 weeks). In some embodiments, the antibody drug conjugate is administered for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 days of a treatment cycle of 28 days. In some embodiments, the antibody drug conjugate is administered for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 days of a treatment cycle of 35 days. In some embodiments, the antibody drug conjugate is administered for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, or 42 days of a treatment cycle of 42 days. In some embodiments, the antibody drug conjugate is administered on 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days of a treatment cycle of 21 days. In certain embodiments, the antibody drug conjugate is administered on days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, and/or 21 of a treatment cycle of 21 days. In particular embodiments, the antibody drug conjugate is administered on days 1 and 8 of a treatment cycle of 21 days. In some embodiments, the

antibody drug conjugate is administered for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 treatment cycles.

[00621] In some embodiments, the antibody drug conjugate is administered once, two times, three times, or four times daily during each treatment cycle of 14 days, 21 days, 28 days, 35 days, or 42 days. In some embodiments, the antibody drug conjugate is administered once, two times, three times, or four times daily for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days of each treatment cycle of 14 days. In some embodiments, the antibody drug conjugate is administered once, two times, three times, or four times daily for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days of each treatment cycle of 21 days. In some embodiments, the antibody drug conjugate is administered once, two times, three times, or four times daily for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 days of each treatment cycle of 28 days. In some embodiments, the antibody drug conjugate is administered once, two times, three times, or four times daily for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 days of each treatment cycle of 35 days. In some embodiments, the antibody drug conjugate is administered once, two times, three times, or four times daily for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, or 42 days of each treatment cycle of 42 days. In certain embodiments, the antibody drug conjugate is administered once, two times, three times, or four times daily for 2 days of each treatment cycle of 21 days.

[00622] In certain embodiments, the antibody drug conjugate is administered at a daily dose of about 1.25 mg/kg for 2 days in each treatment cycle of 21 days. In certain embodiments, the antibody drug conjugate is administered at a daily dose of about 1.25 mg/kg on days 1 and 8 in each treatment cycle of 21 days. In certain embodiments, the antibody drug conjugate is administered at a daily dose of about 1.25 mg/kg on days 1 and 8 in each treatment cycle of 21 days by an intravenous injection or infusion. In certain embodiments, the antibody drug conjugate is administered at a daily dose of about 1.25 mg/kg on days 1 and 8 in each treatment cycle of 21 days by intravenous infusion.

[00623] In some embodiments, the antibody drug conjugate is administered intravenously. In some embodiments, the antibody drug conjugate is administered by an intravenous injection or infusion. In some embodiments, the antibody drug conjugate is administered by intravenous infusion. In some embodiments, the antibody drug conjugate is administered as a

30 minute (-5 minutes /+10 minutes) intravenous infusion. In one embodiment, the selected dose of the antibody drug conjugate is administered by intravenous infusion over a time period of between 25 and 40 minutes, or about 30 minutes (-5 minutes /+10 minutes).

[00624] In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered daily during each treatment cycle of 14 days, 21 days, 28 days, 35 days, or 42 days. In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days of a treatment cycle of 14 days. In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days of a treatment cycle of 21 days (i.e., 3 weeks). In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 days of a treatment cycle of 28 days. In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 days of a treatment cycle of 35 days. In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, or 42 days of a treatment cycle of 42 days. In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered on 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days of a treatment cycle of 21 days. In certain embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered on days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, and/or 21 of a treatment cycle of 21 days. In particular embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered on day 1 of a treatment cycle of 21 days. In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 treatment cycles.

[00625] In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered once, two times, three times, or four times daily during each treatment cycle of 14 days, 21 days, 28 days, 35 days, or 42 days. In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered once, two times, three times, or four times daily for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days

of each treatment cycle of 14 days. In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered once, two times, three times, or four times daily for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days of each treatment cycle of 21 days. In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered once, two times, three times, or four times daily for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 days of each treatment cycle of 28 days. In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered once, two times, three times, or four times daily for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 days of each treatment cycle of 35 days. In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered once, two times, three times, or four times daily for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, or 42 days of each treatment cycle of 42 days. In certain embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered once, two times, three times, or four times daily for 1 day of each treatment cycle of 21 days.

[00626] In certain embodiments, pembrolizumab is administered at a daily dose of about 200 mg for 1 day in each treatment cycle of 21 days. In certain embodiments, pembrolizumab is administered at a daily dose of about 200 mg on day 1 in each treatment cycle of 21 days. In certain embodiments, pembrolizumab is administered at a daily dose of about 200 mg on day 1 in each treatment cycle of 21 days as an intravenous infusion. In certain embodiments, pembrolizumab is administered at a daily dose of about 200 mg on day 1 in each treatment cycle of 21 days by intravenous infusion.

[00627] In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered intravenously. In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered as an intravenous infusion. In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered by intravenous infusion. In some embodiments, the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered as a 30 minute (-5 minutes /+10 minutes) intravenous infusion.

[00628] In some embodiments, the antibody drug conjugate is administered to the subject up to 2 days of a 21-day treatment cycle, and the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered to the subject on 1 day of the 21-day treatment

cycle. In some embodiments, the antibody drug conjugate is administered to the subject on days 1 and 8 of a 21-day treatment cycle, and the checkpoint inhibitor or PD-(L)-1 inhibitor (such as pembrolizumab) is administered to the subject on day 1 of the 21-day treatment cycle.

[00629] In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg to about 5 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 100 mg to about 300 mg on 1 day of the 21-day treatment cycle as an intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg to about 5 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 100 mg to about 300 mg on 1 day of the 21-day treatment cycle as an intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg to about 5 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 100 mg to about 300 mg on 1 day of the 21-day treatment cycle as an intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg to about 5 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 100 mg to about 300 mg on day 1 of the 21-day treatment cycle by intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg to about 5 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 100 mg to about 300 mg on day 1 of the 21-day treatment cycle by intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg to about 5 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered at a dose of about 100 mg to about 300 mg to the subject on day 1 of the 21-day treatment cycle by intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg to about 5 mg/kg up to 2 days of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 100 mg to about 300 mg on 1

day of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg to about 5 mg/kg up to 2 days of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 100 mg to about 300 mg on 1 day of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg to about 5 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 100 mg to about 300 mg on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg to about 5 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 100 mg to about 300 mg on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg to about 5 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered at a dose of about 100 mg to about 300 mg to the subject on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate.

[00630] In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg to 5 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of 100 mg to 300 mg on 1 day of the 21-day treatment cycle as an intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg to 5 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of 100 mg to 300 mg on 1 day of the 21-day treatment cycle as an intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg to 5 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of 100 mg to 300 mg on 1 day of the 21-day treatment cycle as an intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug

conjugate is administered to the subject at a dose of 1.0 mg/kg to 5 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered to the subject at a dose of 100 mg to 300 mg on day 1 of the 21-day treatment cycle by intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg to 5 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered to the subject at a dose of 100 mg to 300 mg on day 1 of the 21-day treatment cycle by intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg to 5 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered at a dose of 100 mg to 300 mg to the subject on day 1 of the 21-day treatment cycle by intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg to 5 mg/kg up to 2 days of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of 100 mg to 300 mg on 1 day of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg to 5 mg/kg up to 2 days of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of 100 mg to 300 mg on 1 day of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg to 5 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of 100 mg to 300 mg on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg to 5 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of 100 mg to 300 mg on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg to 5 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered at a dose of 100 mg to 300 mg to the subject on

day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate.

[00631] In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.25 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on 1 day of the 21-day treatment cycle as an intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.25 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on 1 day of the 21-day treatment cycle as an intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.25 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on 1 day of the 21-day treatment cycle as an intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.25 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on day 1 of the 21-day treatment cycle by intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.25 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on day 1 of the 21-day treatment cycle by intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.25 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered at a dose of about 200 mg to the subject on day 1 of the 21-day treatment cycle by intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.25 mg/kg up to 2 days of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on 1 day of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.25 mg/kg up to 2 days of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of about

200 mg on 1 day of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.25 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.25 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.25 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered at a dose of about 200 mg to the subject on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate.

[00632] In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.25 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on 1 day of the 21-day treatment cycle as an intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.25 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on 1 day of the 21-day treatment cycle as an intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.25 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on 1 day of the 21-day treatment cycle as an intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.25 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on day 1 of the 21-day treatment cycle by intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.25 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on day 1 of the 21-day treatment cycle by intravenous infusion 30 minutes after

administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.25 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered at a dose of 200 mg to the subject on day 1 of the 21-day treatment cycle by intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.25 mg/kg up to 2 days of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on 1 day of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.25 mg/kg up to 2 days of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on 1 day of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.25 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.25 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.25 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered at a dose of 200 mg to the subject on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate.

[00633] In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on 1 day of the 21-day treatment cycle as an intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on 1 day of the 21-day treatment cycle

as an intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on 1 day of the 21-day treatment cycle as an intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on day 1 of the 21-day treatment cycle by intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on day 1 of the 21-day treatment cycle by intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered at a dose of about 200 mg to the subject on day 1 of the 21-day treatment cycle by intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg up to 2 days of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on 1 day of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg up to 2 days of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on 1 day of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of about 200 mg on day 1 of the 21-day treatment cycle

as a 30 minute intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of about 1.0 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered at a dose of about 200 mg to the subject on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate.

[00634] In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on 1 day of the 21-day treatment cycle as an intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on 1 day of the 21-day treatment cycle as an intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg up to 2 days of a 21-day treatment cycle as an intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on 1 day of the 21-day treatment cycle as an intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on day 1 of the 21-day treatment cycle by intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on day 1 of the 21-day treatment cycle by intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg on days 1 and 8 of a 21-day treatment cycle by intravenous infusion, and pembrolizumab is administered at a dose of 200 mg to the subject on day 1 of the 21-day treatment cycle by intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg up to 2 days of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on 1 day of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after administration of the antibody drug conjugate.

In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg up to 2 days of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on 1 day of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered to the subject at a dose of 200 mg on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after administration of the antibody drug conjugate. In some embodiments, the antibody drug conjugate is administered to the subject at a dose of 1.0 mg/kg on days 1 and 8 of a 21-day treatment cycle as a 30 minute intravenous infusion, and pembrolizumab is administered at a dose of 200 mg to the subject on day 1 of the 21-day treatment cycle as a 30 minute intravenous infusion 30 minutes after completion of the administration of the antibody drug conjugate.

[00635] In some embodiments, an ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof as dislosed herein (e.g., enfortumab vedotin) is administered to the subject at a dose of about 1.25 mg/kg of the subject's body weight by an IV injection or infusion on days 1 and 8 of a 21-day treatment cycle and an anti-PD-1 antibody or antigen binding fragment thereof as dislosed herein (e.g., pembrolizumab) is administered to the subject at a dose of about 200 mg by an IV infusion on day 1 of the 21-day treatment cycle, optionally wherein the anti-PD-1 antibody is administered after the ADC.

[00636] In any embodiment disclosed herein, the terms "treatment cycle" and "cycle" are interchangeable.

5.9 Methods for Determining the Biomarkers

[00637] The disclosure provides that the expression of any of the markers provided herein can be determined by various methods known in the field. In some embodiments, the expression of the markers can be determined by the amount or relative amount of mRNA transcribed from the marker genes. In one embodiment, the expression of the marker genes can be determined by the amount or relative amount of the protein products encoded by the

marker genes. In another embodiment, the expression of the marker genes can be determined by the level of biological or chemical response induced by the protein products encoded by the marker genes. Additionally, in certain embodiments, the expression of the marker genes can be determined by the expression of one or more genes that correlates with the expression of the marker genes.

[00638] As described above, levels or amounts of gene transcripts (*e.g.* mRNA) of the marker genes can be used as a proxy for the expression levels of markers genes. Numerous different PCR or qPCR protocols are known in the art including those exemplified herein. In some embodiments, the various PCR or qPCR methods are applied or adapted for determining the mRNA level of the various marker genes. Quantitative PCR (qPCR) (also referred as real-time PCR) is applied and adapted in some embodiments as it provides not only a quantitative measurement, but also reduced time and contamination. As used herein, "quantitative PCR (or "qPCR") refers to the direct monitoring of the progress of PCR amplification as it is occurring without the need for repeated sampling of the reaction products. In quantitative PCR, the reaction products can be monitored via a signaling mechanism (*e.g.*, fluorescence) as they are generated and are tracked after the signal rises above a background level but before the reaction reaches a plateau. The number of cycles required to achieve a detectable or "threshold" level of fluorescence varies directly with the concentration of amplifiable targets at the beginning of the PCR process, enabling a measure of signal intensity to provide a measure of the amount of target nucleic acid in a sample in real time. When qPCR is applied to determine mRNA expression level, an extra step of reverse-transcription of mRNA to DNA is performed before the qPCR analysis. Examples of PCR methods can be found in the literature (Wong et al., BioTechniques 39:75-85 (2005); D'haene et al., Methods 50:262–270 (2010)), which is incorporated by reference herein in its entirety. Examples of PCR assays can also be found in U.S. Patent No. 6,927,024, which is incorporated by reference herein in its entirety. Examples of RT-PCR methods can be found in U.S. Patent No. 7,122,799, which is incorporated by reference herein in its entirety. A method of fluorescent in situ PCR is described in U.S. Patent No. 7,186,507, which is incorporated by reference herein in its entirety.

[00639] In one specific embodiment, qPCR can be performed to determine or measure the mRNA levels of the marker genes as follows. Briefly, mean Ct (cycle threshold) values (or referred to herein interchangeably as Cq (quantification cycle)) of replicate qPCR reactions for the marker genes and one or more housekeeping genes are determined. Mean Ct values for the marker genes can be then normalized to the Ct values of the housekeeping

genes using the following exemplary formula: marker-gene-ΔCt = (mean Ct of marker gene – mean Ct of housekeeping gene A). The relative marker-gene-ΔCt can then be used to determine relative level of marker gene mRNA, for example by using the formula of mRNA expression = $2^{-\Delta Ct}$. For a summary of Ct and Cq values, see MIQE guideline (Bustin et al., The MIQE Guidelines: Minimum Information for Publication of Quantitative Real-Time PCR Experiments, Clinical Chemistry 55:4 (2009)).

[00640] Other commonly used methods known in the art can also be used for the quantification of RNA transcripts of the marker genes in a sample as the proxy for the expression of the marker genes, including northern blotting and in situ hybridization (Parker & Barnes, Methods in Molecular Biology 106:247-283 (1999)); RNAse protection assays (Hod, Biotechniques 13:852- 854 (1992)); microarrays (Hoheisel *et al.*, Nature Reviews Genetics 7:200-210 (2006); Jaluria *et al.*, Microbial Cell Factories 6:4 (2007)); and polymerase chain reaction (PCR) (Weis *et al*, Trends in Genetics 8:263-264 (1992)). RNA *in situ* hybridization (ISH) is a molecular biology technique widely used to measure and localize specific RNA sequences, for example, messenger RNAs (mRNAs), long non-coding RNAs (lncRNAs), and microRNAs (miRNAs) within cells, such as circulating tumor cells (CTCs) or tissue sections, while preserving the cellular and tissue context. ISH is a type of hybridization that uses a directly or indirectly labeled complementary DNA or RNA strand, such as a probe, to bind to and localize a specific nucleic acid, such as DNA or RNA, in a sample, in particular a portion or section of tissue or cells (*in situ*). The probe types can be double stranded DNA (dsDNA), single stranded DNA (ssDNA), single stranded complimentary RNA (sscRNA), messenger RNA (mRNA), micro RNA (miRNA), ribosomal RNA, mitochondrial RNA, and/or synthetic oligonucleotides. The term "fluorescent *in situ* hybridization" or "FISH" refers to a type of ISH utilizing a fluorescent label. The term "chromogenic *in situ* hybridization" or "CISH" refers to a type of ISH with a chromogenic label. ISH, FISH and CISH methods are well known to those skilled in the art (see, for example, Stoler, *Clinics in Laboratory Medicine* 10(1):215-236 (1990); *In situ hybridization. A practical approach*, Wilkinson, ed., IRL Press, Oxford (1992); Schwarzacher and Heslop-Harrison, *Practical in situ hybridization*, BIOS Scientific Publishers Ltd, Oxford (2000)). RNA ISH therefore provides for spatial-temporal visualization as well as quantification of gene expression within cells and tissues. It has wide applications in research and in diagnostics (Hu et al., *Biomark. Res.* 2(1):1-13, doi: 10.1186/2050-7771-2-3 (2014); Ratan et al., *Cureus* 9(6):e1325. doi: 10.7759/cureus.1325 (2017); Weier et al., *Expert Rev. Mol. Diagn.* 2(2):109-119 (2002)). Fluorescent RNA ISH utilizes fluorescent dyes and fluorescent

microscopes for RNA labeling and detection, respectively. Fluorescent RNA ISH can provides for multiplexing of four to five target sequences.

[00641] Alternatively, RNA transcripts of the marker genes in a sample as the proxy for the expression of the marker genes can be determined by sequencing techniques. Representative methods for sequencing-based gene expression analysis include Serial Analysis of Gene Expression (SAGE), and gene expression analysis by massively parallel signature sequencing (MPSS).

[00642] In some embodiments, expression of the marker genes can be determined by the relative abundance of the RNA transcripts (including for example mRNA) of the marker genes in a pool of total transcribed RNA. Such relative abundance of the RNA transcripts of the marker genes can be determined by next generation sequencing, which is known as RNA-seq. In one example of the RNA-seq procedure, RNAs from different sources (blood, tissue, cells) are purified, optionally enriched (*e.g.* with oligo (dT) primers), converted to cDNA, and fragmented. Millions or even billions of short sequence reads are generated from the randomly fragmented cDNA library. *See* Zhao *et al. BMC genomics* 16: 97 (2015); Zhao *et al. Scientific Reports* 8: 4781 (2018); Shanrong Zhao *et al.*, *RNA*, published in advance April 13, 2020, doi: 10.1261/rna.074922.120, all of which are incorporated herein in their entirety by reference. The expression level of each mRNA transcript of the marker genes is determined by the total number of mapped fragments upon normalization, which is directly proportional to its abundance level. A few normalization schemes are known and used to facilitate the use of the abundance of the RNA transcripts as the parameter for determining gene expression, including RPKM (Reads Per Kilobase Million), FPKM (Fragments Per Kilobase Million), and/or TPM (Transcripts Per Kilobase Million). Briefly, RPKM can be calculated as follows: count up the total reads in a sample and divide that number by 1,000,000 – which is the "per million" scaling factor; divide the read counts by the "per million" scaling factor, which normalizes for sequencing depth, giving the reads per million (RPM); and divide the RPM values by the length of the gene, in kilobases, which gives RPKM. FPKM is closely related to RPKM except with fragment replacing read. RPKM was made for single-end RNA-seq, where every read corresponded to a single fragment that was sequenced. FPKM was made for paired-end RNA-seq, in which two reads can correspond to a single fragment, or, if one read in the pair did not map, one read can correspond to a single fragment. TPM is very similar to RPKM and FPKM and is calculated as follows: divide the read counts by the length of each gene in kilobases, which gives the reads per kilobase (RPK); count up all the RPK values in a sample and divide this number by 1,000,000, which

gives the "per million" scaling factor; divide the RPK values by the "per million" scaling factor, which gives TPM. *See* Zhao *et al. BMC genomics* 16: 97 (2015); Zhao *et al. Scientific Reports* 8: 4781 (2018); Shanrong Zhao *et al.*, *RNA*, published in advance April 13, 2020, doi: 10.1261/rna.074922.120, all of which are incorporated herein in their entirety by reference.

[00643] In one embodiment, the expression of the marker genes is determined by RNA-seq, for example by TPM, RPKM, and/or FPKM. In some embodiments, the expression of the marker genes is determined by TPM. In some embodiments, the expression of the marker genes is determined by RPKM. In some embodiments, the expression of the marker genes is determined by FPKM.

[00644] As described earlier, the expression of the marker genes can be determined in a sample from a subject. In some embodiments, the sample is a blood sample, a serum sample, a plasma sample, bodily fluid (*e.g.* tissue fluid including cancer tissue fluid), or a tissue (*e.g.* cancer tissue or the tissue surrounding the cancer). In some embodiments, the sample is a tissue sample. In some embodiments, the tissue sample is tissue fractions isolated or extracted from a mammal, in particular a human. In some embodiments, the tissue sample is a population of cells isolated or extracted from a mammal, in particular a human. In some embodiments, the tissue sample is a sample obtained from a biopsy. In certain embodiments, the samples can be obtained from a variety of organs of a subject, including a human subject. In some embodiments, the samples are obtained from organs of a subject having a cancer. In some embodiments, the samples are obtained from organs having a cancer in a subject having a cancer. In other embodiments, the samples, for example reference samples, are obtained from normal organs from the patient or from a second human subject.

[00645] In certain embodiments of the methods provided herein, the tissue includes a tissue from bladder, ureter, breast, lung, colon, rectum, ovary, Fallopian tube, esophagus, cervix, uterine endometrium, skin, larynx, bone marrow, salivary gland, kidney, prostate, brain, spinal cord, placenta, adrenal, pancreas, parathyroid, hypophysis, testis, thyroid, spleen, tonsil, thymus, heart, stomach, small intestine, liver, skeletal muscle, peripheral nerve, mesothelium, or eye.

[00646] In further embodiments of the methods provided herein, the expression of the various marker genes can be detected by a variety of immunoassays known in the art, including an immunohistochemistry (IHC) assay, an immunoblotting assay, a FACS assay, and an ELISA.

[00647] The expression of the various marker genes can be detected by antibodies against the protein products encoded by the marker genes in a variety of IHC assays. IHC staining of tissue sections has been shown to be a reliable method of assessing or detecting the presence of proteins in a sample. IHC techniques utilize an antibody to probe and visualize cellular antigens in situ, generally by chromogenic or fluorescent methods. Primary antibodies or antisera, such as polyclonal antisera and monoclonal antibodies that specifically target the protein products encoded by the marker genes, can be used to detect expression of the marker genes in an IHC assay. In some embodiments, the tissue sample is contacted with a primary antibody for a specific target for a period of time sufficient for the antibody-target binding to occur. As discussed in detail earlier, the antibodies can be detected by direct labels on the antibodies themselves, for example, radioactive labels, fluorescent labels, hapten labels such as biotin, or an enzyme such as horse radish peroxidase or alkaline phosphatase. Alternatively, unlabeled primary antibody is used in conjunction with a labeled secondary antibody, comprising antisera, polyclonal antisera or a monoclonal antibody specific for the primary antibody. IHC protocols and kits are well known in the art and are commercially available. Automated systems for slide preparation and IHC processing are available commercially. The Leica BOND Autostainer and Leica Bond Refine Detection system is an example of such an automated system.

[00648] In some embodiments, an IHC assay is performed with an unlabeled primary antibody in conjunction with a labeled secondary antibody in an indirect assay. The indirect assay utilizes two antibodies for the detection of the protein products encoded by the marker genes in a tissue sample. First, an unconjugated primary antibody was applied to the tissue (first layer), which reacts with the target antigen in the tissue sample. Next, an enzyme-labeled secondary antibody is applied, which specifically recognize the antibody isotype of the primary antibody (second layer). The secondary antibody reacts with the primary antibody, followed by substrate-chromogen application. The second-layer antibody can be labeled with an enzyme such as a peroxidase, which reacts with the chromogen 3, 3'-diaminobenzidine (DAB) to produce brown precipitate at the reaction site. This method is sensitive and versatile due to the potential signal amplification through a signal amplification system.

[00649] In certain embodiments to increase the sensitivity of the detection, a signal amplification system can be used. "A signal amplification system", as used herein, means a system of reagents and methods that can be used to increase the signal from detecting the bound primary or the secondary antibody. A signal amplification system increases the

sensitivity of the target protein detection, increases the detected signal, and decreases the lower boundary of the detection limits. There are several types of signal amplification systems including an enzyme labeling system and macrolabeling system. These systems/approaches are not mutually exclusive and can be used in combination for additive effect.

[00650] Macrolabels or macrolabeling system are collections of labels numbering in the tens (*e.g.* phycobiliproteins) to millions (*e.g.* fluorescent microspheres) attached to or incorporated in a common scaffold. The scaffold can be coupled to a target-specific affinity reagent such as an antibody, and the incorporated labels are thereby collectively associated with the target upon binding. The labels in the macrolabels can be any of the labels described herein such as fluorophores, haptens, enzymes, and/or radioisotopes. In one embodiment of the signal amplification system, a labeled chain polymer-conjugated secondary antibody was used. The polymer technology utilized an HRP enzyme-labeled inert "spine" molecule of dextran to which 1, 2, 3, 4, 5, 6, 7, 8, 9 10, 15, 20, 25, 30, 50 or more molecules of secondary antibodies can be attached, making the system even more sensitive.

[00651] Signal amplification system based on an enzyme labeling system utilizes the catalytic activity of enzymes, such as horseradish peroxidase (HRP) or alkaline phosphatase to generate high-density labeling of a target protein or nucleic acid sequence in situ. In one embodiment, tyramide can be used to increase the signal of HRP. In such a system, HRP enzymatically converts the labeled tyramide derivative into highly reactive, short-lived tyramide radicals. The labeled active tyramide radicals then covalently couple to residues (principally the phenol moiety of protein tyrosine residues) in the vicinity of the HRP-antibody–target interaction site, resulting amplification of the number of labels at the site with minimal diffusion-related loss of signal localization. Consequently, the signal can be amplified 1, 2, 3, 4, 5, 6, 7, 8, 9 10, 15, 20, 25, 30, 50, 75, or 100 folds. As known to a person skilled in the art, the labels on the tyramide can be any labels described herein, including fluorophores, enzymes, haptens, radioisotopes, and/or photophores. Other enzyme-based reactions can be utilized to create signal amplification as well. For example, Enzyme-Labeled Fluorescence (ELF) signal amplification is available for alkaline phosphatase, wherein the alkaline phosphatase enzymatically cleaves a weakly blue-fluorescent substrate (ELF 97 phosphate) and converts it into a bright yellow-green-fluorescent precipitate that exhibits an unusually large Stokes shift and excellent photostability. Both tyramide-based signal amplification system and ELF signal amplification are available commercially, for example from ThermoFisher Scientific (Waltham, MA USA 02451).

[00652] Thus in some embodiments of the methods provided herein, the expression level of the marker genes is detected with IHC using a signal amplification system. In some embodiments, the specimen is then counterstained to identify cellular and subcellular elements.

[00653] In some embodiments, the expression level of the protein products encoded by the marker genes can also be detected with antibodies against the protein products encoded by the marker genes using an immunoblotting assay. In some embodiments of an immunoblotting assay, proteins are often (but do not have to be) separated by electrophoresis and transferred onto membranes (usually nitrocellulose or PVDF membrane). Similar to the IHC assays, primary antibodies or antisera, such as polyclonal antisera and monoclonal antibodies that specifically target the protein products encoded by the marker genes, can be used to detect expression of the marker genes. In some embodiments, the membrane is contacted with a primary antibody for a specific target for a period of time sufficient for the antibody-antigen binding to occur and the bound antibodies can be detected by direct labels on the primary antibodies themselves, *e.g.* with radioactive labels, fluorescent labels, hapten labels such as biotin, or enzymes such as horseradish peroxidase or alkaline phosphatase. In other embodiments, unlabeled primary antibody is used in an indirect assay as described above in conjunction with a labeled secondary antibody specific for the primary antibody. As described herein, the secondary antibodies can be labeled, for example, with enzymes or other detectable labels such as fluorescent labels, luminescent labels, colorimetric labels, or radioisotopes. Immunoblotting protocols and kits are well known in the art and are commercially available. Automated systems for immunoblotting, *e.g.* iBind Western Systems for Western blotting (ThermoFisher, Waltham, MA USA 02451), are available commercially. Immunoblotting includes, but is not limited to, Western blot, in-cell Western blot, and dot blot. Dot blot is a simplified procedure in which protein samples are not separated by electrophoresis but are spotted directly onto a membrane. In cell Western blot involves seeding cells in microtiter plates, fixing/permeabilizing the cells, and subsequent detection with a primary labeled primary antibody or unlabelled primary antibody followed by labeled secondary antibody as described herein.

[00654] In other embodiments, the expression levels of the protein products encoded by the marker genes can also be detected with the antibodies described herein in a flow cytometry assay, including a fluorescence-activated cell sorting (FACS) assay. Similar to the IHC or immunoblotting assays, primary antibodies or antisera, such as polyclonal antisera and monoclonal antibodies that specifically target the protein products encoded by the marker

genes, can be used to detect protein expression in a FACS assay. In some embodiments, cells are stained with primary antibodies against specific target protein for a period of time sufficient for the antibody-antigen binding to occur and the bound antibodies can be detected by direct labels on the primary antibodies, for example, fluorescent labels or hapten labels such as biotin on the primary antibodies. In other embodiments, unlabeled primary antibody is used in an indirect assay as described above in conjunction with a fluorescently labeled secondary antibody specific for the primary antibody. FACS provides a method for sorting or analyzing a mixture of fluorescently labeled biological cells, one cell at a time, based upon the specific light scattering and fluorescent characteristics of each cell. The flow cytometer thus detects and reports the intensity of the fluorichrome-tagged antibody, which indicates the expression level of the target protein. Therefore, the expression level of the protein products encoded by the marker genes can be detected using antibodies against such protein products. Non-fluorescent cytoplasmic proteins can also be observed by staining permeablized cells. Methods for performing FACS staining and analyses are well known to a person skilled in the art and are described by Teresa S. Hawley and Robert G. Hawley in Flow Cytometry Protocols, Humana Press, 2011 (ISBN 1617379506, 9781617379505).

[00655] In other embodiments, the expression levels of the protein products encoded by the marker genes can also be detected using immunoassays such as an Enzyme Immune Assay (EIA) or an ELISA. Both EIA and ELISA assays are known in the art, *e.g.* for assaying a wide variety of tissues and samples, including blood, plasma, serum or bone marrow. A wide range of ELISA assay formats are available, see, *e.g.*, U.S. Pat. Nos. 4,016,043, 4,424,279, and 4,018,653, which are hereby incorporated by reference in their entireties. These include both single-site and two-site or “sandwich” assays of the non-competitive types, as well as in the traditional competitive binding assays. These assays also include direct binding of a labeled antibody to a target protein. Sandwich assays are commonly used assay format. A number of variations of the sandwich assay technique exist. For example, in a typical forward assay, an unlabelled antibody is immobilized on a solid substrate, and the sample to be tested brought into contact with the bound molecule. After a suitable period of incubation, for a period of time sufficient to allow formation of an antibody-antigen complex, a second antibody specific to the antigen, labeled with a reporter molecule capable of producing a detectable signal is then added and incubated, allowing time sufficient for the formation of another complex of antibody-antigen-labeled antibody. Any unreacted material is washed away, and the presence of the antigen is determined by

observation of a signal produced by the reporter molecule. The results can either be qualitative, by simple observation of the visible signal, or can be quantitated by comparing with a control sample containing known amounts of target protein.

[00656] In some embodiments of the EIA or ELISA assays, an enzyme is conjugated to the second antibody. In other embodiments, fluorescently labeled secondary antibodies can be used in lieu of the enzyme-labeled secondary antibody to produce a detectable signal an ELISA assay format. When activated by illumination with light of a particular wavelength, the fluorochrome-labeled antibody adsorbs the light energy, inducing a state to excitability in the molecule, followed by emission of the light at a characteristic color visually detectable with a light microscope. As in the EIA and ELISA, the fluorescent labeled antibody is allowed to bind to the first antibody-target protein complex. After washing off the unbound reagent, the remaining tertiary complex is then exposed to the light of the appropriate wavelength; the fluorescence observed indicates the presence of the target protein of interest. Immunofluorescence and EIA techniques are both very well established in the art and are disclosed herein.

[00657] For the immunoassays described herein, any of a number of enzymes or non-enzyme labels can be utilized so long as the enzymatic activity or non-enzyme label, respectively, can be detected. The enzyme thereby produces a detectable signal, which can be utilized to detect a target protein. Particularly useful detectable signals are chromogenic or fluorogenic signals. Accordingly, particularly useful enzymes for use as a label include those for which a chromogenic or fluorogenic substrate is available. Such chromogenic or fluorogenic substrates can be converted by enzymatic reaction to a readily detectable chromogenic or fluorescent product, which can be readily detected and/or quantified using microscopy or spectroscopy. Such enzymes are well known to those skilled in the art, including but not limited to, horseradish peroxidase, alkaline phosphatase, β-galactosidase, glucose oxidase, and the like (see Hermanson, *Bioconjugate Techniques*, Academic Press, San Diego (1996)). Other enzymes that have well known chromogenic or fluorogenic substrates include various peptidases, where chromogenic or fluorogenic peptide substrates can be utilized to detect proteolytic cleavage reactions. The use of chromogenic and fluorogenic substrates is also well known in bacterial diagnostics, including but not limited to the use of α- and β-galactosidase, β-glucuronidase,6-phospho-β-D-galatoside 6-phosphogalactohydrolase, β-gluosidase, α-glucosidase, amylase, neuraminidase, esterases, lipases, and the like (Manafi et al., *Microbiol. Rev.* 55:335-348 (1991)), and such enzymes

with known chromogenic or fluorogenic substrates can readily be adapted for use in methods of the present disclosure.

[00658] Various chromogenic or fluorogenic substrates to produce detectable signals are well known to those skilled in the art and are commercially available. Exemplary substrates that can be utilized to produce a detectable signal include, but are not limited to, 3,3'-diaminobenzidine (DAB), 3,3',5,5'-tetramethylbenzidine (TMB), Chloronaphthol (4-CN)(4-chloro-1-naphthol), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS), o-phenylenediamine dihydrochloride (OPD), and 3-amino-9-ethylcarbazole (AEC) for horseradish peroxidase; 5-bromo-4-chloro-3-indolyl-1-phosphate (BCIP), nitroblue tetrazolium (NBT), Fast Red (Fast Red TR/AS-MX), and p-Nitrophenyl Phosphate (PNPP) for alkaline phosphatase; 1-Methyl-3-indolyl-β-D-galactopyranoside and 2-Methoxy-4-(2-nitrovinyl)phenyl β-D-galactopyranoside for β-galactosidase; 2-Methoxy-4-(2-nitrovinyl)phenyl β-D-glucopyranoside for β-glucosidase; and the like. Exemplary fluorogenic substrates include, but are not limited to, 4-(Trifluoromethyl)umbelliferyl phosphate for alkaline phosphatase; 4-Methylumbelliferyl phosphate bis (2-amino- 2-methyl-1,3-propanediol), 4-Methylumbelliferyl phosphate bis (cyclohexylammonium) and 4-Methylumbelliferyl phosphate for phosphatases; QuantaBlu™ and QuantaRed™ for horseradish peroxidase; 4-Methylumbelliferyl β-D-galactopyranoside, Fluorescein di(β-D-galactopyranoside) and Naphthofluorescein di-(β-D-galactopyranoside) for β-galactosidase; 3-Acetylumbelliferyl β-D-glucopyranoside and 4-Methylumbelliferyl-β- D-glucopyranoside for β-glucosidase; and 4-Methylumbelliferyl-α- D-galactopyranoside for α-galactosidase. Exemplary enzymes and substrates for producing a detectable signal are also described, for example, in US publication 2012/0100540. Various detectable enzyme substrates, including chromogenic or fluorogenic substrates, are well known and commercially available (Pierce, Rockford IL; Santa Cruz Biotechnology, Dallas TX; Invitrogen, Carlsbad CA; 42 Life Science; Biocare). Generally, the substrates are converted to products that form precipitates that are deposited at the site of the target nucleic acid. Other exemplary substrates include, but are not limited to, HRP-Green (42 Life Science), Betazoid DAB, Cardassian DAB, Romulin AEC, Bajoran Purple, Vina Green, Deep Space Black™, Warp Red™, Vulcan Fast Red and Ferangi Blue from Biocare (Concord CA; biocare.net/products/detection/chromogens).

[00659] In some embodiments of the immunoassays, a detectable label can be directly coupled to either the primary antibody or the secondary antibody that detects the unlabeled

primary antibody can have. Exemplary detectable labels are well known to those skilled in the art, including but not limited to chromogenic or fluorescent labels (see Hermanson, *Bioconjugate Techniques*, Academic Press, San Diego (1996)). Exemplary fluorophores useful as labels include, but are not limited to, rhodamine derivatives, for example, tetramethylrhodamine, rhodamine B, rhodamine 6G, sulforhodamine B, Texas Red (sulforhodamine 101), rhodamine 110, and derivatives thereof such as tetramethylrhodamine-5-(or 6), lissamine rhodamine B, and the like; 7-nitrobenz-2-oxa-1,3-diazole (NBD); fluorescein and derivatives thereof; napthalenes such as dansyl (5-dimethylaminonapthalene-1-sulfonyl); coumarin derivatives such as 7-amino-4-methylcoumarin-3-acetic acid (AMCA), 7-diethylamino-3-[(4'-(iodoacetyl)amino)phenyl]-4-methylcoumarin (DCIA), Alexa fluor dyes (Molecular Probes), and the like; 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY™) and derivatives thereof (Molecular Probes; Eugene Oreg.); pyrenes and sulfonated pyrenes such as Cascade Blue™ and derivatives thereof, including 8-methoxypyrene-1,3,6-trisulfonic acid, and the like; pyridyloxazole derivatives and dapoxyl derivatives (Molecular Probes); Lucifer Yellow (3,6-disulfonate-4-amino-naphthalimide) and derivatives thereof; CyDye™ fluorescent dyes (Amersham/GE Healthcare Life Sciences; Piscataway NJ), and the like. Exemplary chromophores include, but are not limited to, phenolphthalein, malachite green, nitroaromatics such as nitrophenyl, diazo dyes, dabsyl (4-dimethylaminoazobenzene-4'-sulfonyl), and the like.

[00660] Methods well known to a person skilled in the art such as microscopy or spectroscopy can be utilized to visualize chromogenic or fluorescent detectable signals associated with the bound primary or secondary antibodies.

[00661] The methods provided in this Section (Section 5.8) can be used with various cancer models known in the art. In one embodiment, mouse xenograft cancer models are used. Briefly, T-24 and UM-UC-3 cells are purchased from ATCC and cultured using the recommended media conditions. The T-24 hNectin-4 (human nectin-4) and the UM-UC-3 Nectin-4 cells are generated by transducing parental cells with lentivirus containing the human Nectin-4 using the pRCDCMEP-CMV-hNectin-4 EF1-Puro construct and selected using puromycin. The T-24 Nectin-4 (clone 1A9) cells are implanted into nude mice and passaged via trocar, allowed to reach approximately 200mm^3 tumor volume, and subsequently treated with a single intraperitoneal (IP) dose of enfortumab vedotin (3mg/kg) or non-binding ADC (3 mg/kg) with 7 animals per treatment group. Follow-up ICD studies with this model involve collecting tumors 5 days post treatment for downstream analysis by RNA-seq, flow, immunohistochemistry (IHC), and Luminex. Tumors are fixed in formalin

and prepared as FFPE tissue blocks. Blocks are cut at 4 μm and immunohistochemistry is performed using F4/80, CD11c. The immunohistochemically stained slides sections are scanned with a Leica AT2 digital whole slide scanner, and the images are analyzed with Visiopharm software by use of custom-made algorithms for Nectin 4, CD11c and F4/80 staining. The algorithms are optimized on the basis of staining intensity and background staining. Percent positive staining is calculated for Nectin 4 and positive cells per mm^2 is calculated for F480 and CD11c.

[00662] Sections of tumor are lysed in Cell Lysis Buffer 2 (R&D Systems®, Catalog # 895347). The cytokines and chemokines from the tumor samples are measured using the MILLIPLEX MAP mouse cytokine/chemokine magnetic bead panel (Millipore) and read on the LUMINEX MAGPIX system.

[00663] For the RNA-seq analysis RNA from flash frozen tumors is isolated using the TRIZOL Plus RNA Purification Kit (Life Technologies) according to the manufacturer's protocol yielding high quality RNA (average RNA integrity number > 8). RNA selection method is using Poly(A) selection and the mRNA Library Prep Kit from Illumina and read on the Hi-Seq 2 x 150bp, single index (Illumina). The sequence reads are mapped to the human and mouse transcriptome and total reads per million were determined.

[00664] The disclosure is generally provided using affirmative language to describe the numerous embodiments. The disclosure also specifically includes embodiments in which particular subject matter is excluded, in full or in part, such as substances or materials, method steps and conditions, protocols, procedures, assays or analysis. Thus, even though the disclosure is generally not expressed herein in terms of what the disclosure does not include, aspects that are not expressly included in the disclosure are nevertheless disclosed herein.

[00665] Particular embodiments of this disclosure are described herein, including the best mode known to the inventors for carrying out the disclosure. Upon reading the foregoing description, variations of the disclosed embodiments can become apparent to individuals working in the art, and it is expected that those skilled artisans can employ such variations as appropriate. Accordingly, it is intended that the disclosure be practiced otherwise than as specifically described herein, and that the disclosure includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the disclosure unless otherwise indicated herein or otherwise clearly contradicted by context.

[00666] All publications, patent applications, accession numbers, and other references cited in this specification are herein incorporated by reference in their entireties as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

[00667] A number of embodiments of the disclosure have been described. Nevertheless, it will be understood that various modifications can be made without departing from the spirit and scope of the disclosure.

5.10 Pharmaceutical Products

[00668] In one aspect, described herein are finished packaged and labeled pharmaceutical products or kits. In one embodiment, a pharmaceutical product or a kit comprises a unit dosage form of an antibody drug conjugate (ADC) comprising (i) an anti-191P4D12 antibody or antigen binding fragment thereof as disclosed herein in an appropriate vessel or container (e.g., a glass vial or other container that is hermetically sealed) and (ii) an anti-PD-1 antibody or antigen binding fragment thereof as disclosed herein in an appropriate vessel or container (e.g., a glass vial or other container that is hermetically sealed). In some embodiments, the unit dosage form of an ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof as disclosed herein is a lyophilized form of the antibody drug conjugate (ADC) comprising an anti-191P4D12 antibody or antigen binding fragment thereof as disclosed herein, and under those circumstances, the pharmaceutical product may contain a second container with sterile saline or sterile water for reconstituting the lyophilized form of the ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof. In some embodiments, the unit dosage form of an anti-PD-1 antibody or antigen binding fragment thereof as disclosed herein is a lyophilized form of the anti-PD-1 antibody or antigen binding fragment thereof as disclosed herein, and under those circumstances, the pharmaceutical product may contain a second container with sterile saline or sterile water for reconstituting the lyophilized form of the anti-PD-1 antibody or antigen binding fragment thereof. In other embodiments, the unit dosage form of an ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof as disclosed herein is an aqueous form of the antibody drug conjugate (ADC) comprising an anti-191P4D12 antibody or antigen binding fragment thereof that does not require reconstitution before administration to a subject. In other embodiments, the unit dosage form of an anti-PD-1 antibody or antigen binding fragment thereof as disclosed herein is an aqueous form of the anti-PD-1 antibody or antigen binding fragment thereof that does not require reconstitution before administration to

a subject. In specific embodiments, the unit dosage form of an ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof as disclosed herein contains the ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof in an amount sufficient for the administration of an effective amount to a subject (e.g., a dose of the ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof as disclosed herein). In specific embodiments, the unit dosage form of an anti-PD-1 antibody or antigen binding fragment thereof as disclosed herein contains the anti-PD-1 antibody or antigen binding fragment thereof in an amount sufficient for the administration of an effective amount to a subject (e.g., a dose of the anti-PD-1 antibody or antigen binding fragment thereof as disclosed herein). In certain embodiments, the unit dosage form of an ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof as disclosed herein is suitable for the selected route of administration of the ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof to a subject. In certain embodiments, the unit dosage form of an anti-PD-1 antibody or antigen binding fragment thereof as disclosed herein is suitable for the selected route of administration of the anti-PD-1 antibody or antigen binding fragment thereof to a subject. In a specific embodiment, the unit dosage form of an ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof as disclosed herein is suitable for intravenous delivery to a subject. In a specific embodiment, the unit dosage form of an anti-PD-1 antibody or antigen binding fragment thereof as disclosed herein is suitable for intravenous delivery to a subject.

[00669] In one embodiment, a pharmaceutical product or a kit comprises (i) a unit dosage form of an ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof as disclosed herein in an appropriate vessel or container (e.g., glass vial or other container that is hermetically sealed) and an infusion pump or syringe pump for the administration of the ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof to a subject and (ii) an anti-PD-1 antibody or antigen binding fragment thereof as disclosed herein in an appropriate vessel or container (e.g., glass vial or other container that is hermetically sealed) and an infusion pump or syringe pump for the administration of the anti-PD-1 antibody or antigen binding fragment thereof to a subject.

[00670] As with any pharmaceutical product or kit, the packaging material and container are designed to protect the stability of the product during storage and shipment. Further, the pharmaceutical product includes instructions for use or other informational material that advise the physician, technician or patient on how to appropriately treat cancer (e.g., urothelial or bladder cancer) as disclosed herein. In other words, the pharmaceutical product

includes instruction means indicating or suggesting a dosing regimen including, but not limited to, actual doses (e.g., a dose of an ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof as disclosed herein and a dose of an anti-PD-1 antibody or antigen binding fragment thereof as disclosed herein), monitoring procedures, and other monitoring information.

6. Examples

[00671] The following is a description of various methods and materials used in the studies, and are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below were performed and are all of the experiments that may be performed. It is to be understood that exemplary descriptions written in the present tense were not necessarily performed, but rather that the descriptions can be performed to generate the data and the like associated with the teachings of the present invention. Efforts have been made to ensure accuracy with respect to numbers used (*e.g.*, amounts, temperature, *etc.*), but some experimental errors and deviations should be accounted for.

6.1 Example 1 – A Phase 3 Study of Enfortumab Vedotin Combined with Pembrolizumab Versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer.

6.1.1 Drug Used in the Clinical Study

[00672] Enfortumab vedotin (EV) is an antibody drug conjugate (ADC) comprised of a fully human anti Nectin 4 IgG1 kappa monoclonal antibody (mAb) conjugated to the small molecule microtubule disrupting agent, monomethyl auristatin E (MMAE), via a protease cleavable maleimidocaproyl valine citrulline linker. Conjugation takes place on cysteine residues that comprise the interchain disulfide bonds of the antibody to yield a product with a drug to antibody ratio of approximately 3.8. Nectin 4 is a 66 kDa type I transmembrane protein that belongs to the Nectin family of adhesion molecules. Nectins are thought to mediate Ca2+ independent cell-cell adhesion via both homophilic and heterophilic transinteractions at adherens junctions and support a wide range of biological functions, including cell movement, proliferation, polarization, survival and differentiation. Nectin 4 is expressed in multiple cancers, particularly urothelial, breast, lung, pancreatic, and ovarian cancers (Challita Eid 2016). Higher levels of expression are associated with disease progression and/or poor prognosis in some cancers (Fabre Lafay 2007).

[00673] EV binds to the V domain of Nectin 4 protein (Challita Eid 2016). In the presumed mechanism of action, the drug binds to the Nectin 4 protein on the cell surface and is internalized, causing proteolytic cleavage of the valine citrulline linker and intracellular release of MMAE. Free MMAE subsequently disrupts tubulin polymerization and leads to mitotic arrest.

6.1.2 Summary of the Study

6.1.2.1 *Synopsis*

(i) **Name of Study Drug**

[00674] Enfortumab Vedotin (ASG-22CE)

(ii) **Phase of Development**

[00675] Phase 3

(iii) **Title of Study**

[00676] An open label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer.

(iv) **Study Objective(s)**

[00677] Primary Objectives

- To compare progression free survival (PFS) between the experimental arm (enfortumab vedotin + pembrolizumab [Arm A]) and the control arm (gemcitabine + cisplatin or carboplatin [Arm B]) by blinded independent central review (BICR)
- To compare overall survival (OS) between the experimental arm (Arm A) and the control arm (Arm B)

[00678] Secondary Objectives

- To compare the objective response rate (ORR) between the experimental arm (Arm A) and the control arm (Arm B) by BICR
- To compare time to pain progression (TTPP) from the subject perspective between the experimental arm (Arm A) and the control arm (Arm B)
- To compare average change in pain from the subject perspective between the experimental arm (Arm A) and the control arm (Arm B)
- To evaluate PFS between the experimental arm (Arm A) and the control arm (Arm B) by investigator assessment

- To evaluate ORR between the experimental arm (Arm A) and the control arm (Arm B) by investigator assessment
- To evaluate the duration of response (DOR) between the experimental arm (Arm A) and the control arm (Arm B)
- To evaluate the disease control rate (DCR) between the experimental arm (Arm A) and the control arm (Arm B)
- To evaluate the impact of study treatment on quality of life (QOL), functioning, and symptoms from the subject perspective
- To evaluate the safety profile of each treatment regimen

[00679] Additional Objectives

- To assess PFS, ORR, and DOR per the modified RECIST v1.1 for immune based therapeutics (iRECIST) in Arm A
- To assess subject reported health resource utilization (HRU)
- To assess the pharmacokinetics (PKs) of enfortumab vedotin and monomethyl auristatin E (MMAE)
- To assess the development of anti therapeutic antibody (ATA) to enfortumab vedotin
- To assess biomarkers of biological activity, resistance, and predictive biomarkers of response

(v) **Study Population**

[00680] The population studied includes subjects with histologically documented, unresectable, previously untreated locally advanced or metastatic urothelial cancer (UC) and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

[00681] Eligible subjects must be ≥18 years of age, and must have an anticipated life expectancy of ≥12 weeks as assessed by the investigator. Subjects must not have received prior systemic therapy with the exceptions of neoadjuvant or adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status Score of 0, 1, or 2, with adequate baseline hematologic, hepatic, and renal function. In addition, subjects must be considered eligible to receive cisplatin- or carboplatin-based chemotherapy and pembrolizumab, in the investigator's judgment.

[00682] Subjects with locally advanced urothelial cancer (UC) that is resectable with curative intent are not eligible. Subjects must not have received previous treatment with

enfortumab vedotin or other monomethyl auristatin E (MMAE)-based antibody-drug conjugates (ADCs), or a checkpoint inhibitor, defined as a programmed cell death protein-1 (PD-1) inhibitor or programmed cell death ligand-1 (PD-L1) inhibitor (including, but not limited to, atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab). Subjects must not have ongoing sensory or motor neuropathy (Grade 2 or higher) or active central nervous system (CNS) metastases. Subjects must not have a history of another malignancy within 3 years or any evidence of residual disease from a previously diagnosed malignancy. Subjects are also excluded if they are currently receiving systemic antimicrobial treatment for active infection or high dose steroids. Subjects with uncontrolled diabetes are excluded. Uncontrolled diabetes is defined as hemoglobin A1c (HbA1c) ≥8% or HbA1c 7%–<8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.

(vi) **Number of Planned Patients**

[00683] Approximately 860 subjects (approximately 430 subjects per arm) are randomized in the global portion of this study. After enrollment of the global portion of the study is completed, the study may remain open to enrollment in China alone until approximately 130 subjects in China (including those randomized in the global portion and China portion) have been randomized.

(vii) **Study Design**

[00684] This is a phase 3 open label, 2 arm randomized, controlled multicenter study to evaluate the combination of enfortumab vedotin + pembrolizumab versus standard of care gemcitabine + platinum containing chemotherapy in subjects with previously untreated locally advanced or metastatic UC. The study is designed to assess the dual primary endpoints of progression free survival (PFS) and overall survival (OS) of experimental Arm A (enfortumab vedotin + pembrolizumab) compared to control Arm B (gemcitabine + cisplatin or carboplatin). Subjects are randomized in a 1:1 manner to one of the study arms with the following stratification factors: cisplatin eligibility (eligible or ineligible), PD L1 expression (high or low), and liver metastases (present or absent).

[00685] Subjects in Arm A receive enfortumab vedotin at 1.25 mg/kg, administered as an intravenous (IV) infusion on Days 1 and 8 of every 3 week cycle, and pembrolizumab 200 mg as an IV infusion on Day 1 of every 3 week cycle, after completion of the enfortumab vedotin infusion.

[00686] Subjects in Arm B receive gemcitabine at 1000 mg/m^2 as an IV infusion on Days 1 and 8 of every 3 week cycle. Cisplatin (70 mg/m^2) or carboplatin (area under the curve

[AUC] 4.5, or AUC of 5 according to local guidelines) are administered on Day 1 of every 3 week cycle, with adequate pre- and post-hydration, by IV infusion per institutional standards.

[00687] Response is assessed by computed tomography (CT) scans with contrast (unless contraindicated) every 9 weeks (±1 week) timed from the randomization date. For subjects who cannot receive CT scans with contrast, other protocol specified imaging methods may be used Section 6.1.12). Brain scans should be repeated at this time point in subjects with a history of CNS metastasis or signs/symptoms of CNS metastasis. Bone imaging should also be repeated at this time point in subjects with a history of skeletal metastasis or suspicion of skeletal metastases based on imaging or symptoms. Objective responses are confirmed per RECIST v1.1 with repeat scans done at the next scheduled response assessment per protocol after first documentation of response. Subsequent response assessments should be performed every 9 weeks (±1 week) until 18 months after randomization, then every 12 weeks (±1 week). Tumor imaging should also be performed, and blinded independent central review (BICR) evaluation triggered, whenever disease progression is suspected.

[00688] Subjects may continue on study treatment until progressive disease (BICR confirmed or clinical progression (see Section 6.1.7.4), an adverse event (AE), pregnancy, investigator decision, start of a subsequent anticancer therapy, subject decision (non AE), study termination by the sponsor, completion of the maximum number of drug cycles allowed, or other reason unrelated to an AE (see Section 6.1.5.3). Treatment beyond disease progression per RECIST v1.1 may be considered in subjects in study Arm A (enfortumab vedotin [EV] + pembrolizumab) who are deriving clinical benefit as defined in Section 6.1.6.7. Subjects treated beyond disease progression per RECIST v1.1 may continue until confirmed disease progression per modified RECIST 1.1 for immune based therapeutics (iRECIST) as assessed by the investigator (Seymour 2017) (Section 6.1.14). Confirmatory scans must be performed 4 to 9 weeks after disease progression per RECIST v1.1 by BICR. Treatment with gemcitabine and treatment with platinum containing chemotherapy may be given up to 6 cycles. Treatment with pembrolizumab is discontinued once the subject has received a maximum of 35 administrations (approximately 2 years). There is no upper limit to the number of cycles of enfortumab vedotin permitted. Palliative radiotherapy on a nontarget bone lesion that is not progressing is permitted and is not considered a subsequent anticancer therapy; however, radiotherapy on any new or progressing lesion, per RECIST v1.1 as assessed by the investigator or after BICR confirmed progression, is considered a subsequent anticancer therapy and subjects are not permitted to resume study treatment.

Surgical resection for curative intent during study treatment may be permitted in subjects with favorable tumor response after discussion with the medical monitor.

[00689] Subjects who discontinue treatment for reasons other than disease progression or consent withdrawal continue to receive response assessments every 9 weeks (±1 week) for the first 18 months timed from the randomization date, and every 12 weeks (±1 week) thereafter, until the subject has radiologically confirmed disease progression per RECIST v1.1 guidelines as determined by BICR, dies, withdraws consent, or the study closes, whichever occurs first. Subjects who initiate a subsequent anticancer therapy but do not have disease progression per BICR continue to receive response assessments until radiologically confirmed progression per BICR, death, consent withdrawal, or the study closes, whichever occurs first. After discontinuation of study treatment, all randomized subjects are followed every 12 weeks (±1 week) to obtain information on subsequent anticancer therapy, and to assess survival status until death, study closure, lost to follow up, or subject withdraws consent, whichever occurs first.

[00690] Safety is monitored over the course of the study by an Independent Data Monitoring Committee (IDMC).

(viii) **Test Product, Dose, and Mode of Administration**

[00691] Enfortumab vedotin (Arm A)

[00692] Enfortumab vedotin 1.25 mg/kg is administered as an IV infusion over approximately 30 minutes on Days 1 and 8 of every 3-week cycle.

[00693] Pembrolizumab (Arm A)

[00694] Pembrolizumab 200 mg is administered as an IV infusion after completion of the enfortumab vedotin Arm A. Infusion on Day 1 of every 3-week cycle.

[00695] Cisplatin (Arm B)

[00696] On Day 1 (or Day 2 if required per institutional guidelines) of each 3-week cycle, cisplatin 70 mg/m^2 is administered (with adequate pre- and post-hydration) as an IV infusion per institutional standards. The body surface area used to calculate cisplatin dose may be capped per institutional standards.

[00697] Carboplatin (Arm B)

[00698] On Day 1 of each 3-week cycle, carboplatin at AUC 4.5, or AUC of 5 according to local guidelines, is administered (with adequate pre- and post-hydration) as an IV infusion per institutional standards. Body weight used to calculate carboplatin may be capped as per institutional standards.

[00699] Gemcitabine (Arm B)

[00700] On Days 1 and 8 of each 3-week cycle, gemcitabine at 1000 mg/m^2 is administered as an IV infusion.

(ix) **Duration of Treatment**

[00701] Subjects should continue on study treatment until one of the following protocol defined reasons for treatment discontinuation occur: progressive disease (BICR confirmed or clinical progression [see Section 6.1.7.4]), an AE, pregnancy, investigator decision, start of a subsequent anticancer therapy, subject decision(non AE), study termination by the sponsor, completion of the maximum number of drug cycles allowed, or other reason unrelated to an AE.

[00702] Pembrolizumab may be administered for up to a maximum of 35 cycles.

[00703] Cisplatin, carboplatin, and/or gemcitabine may be administered for up to a maximum of 6 cycles.

[00704] Maintenance therapy (e.g., avelumab) may be used following completion and/or discontinuation of platinum containing therapy, if locally available, and provided the subject is deemed appropriate by the investigator (see Section 6.1.5.3(i)).

[00705] Enfortumab vedotin may be administered for an unlimited number of cycles until a protocol defined reason for treatment discontinuation occurs. In Arm A, subjects who experience an unacceptable AE that is attributable only to pembrolizumab may continue on enfortumab vedotin monotherapy until a protocol defined reason for treatment discontinuation. Subjects who experience an unacceptable AE that is attributable only to enfortumab vedotin may continue on pembrolizumab monotherapy up to a maximum of 35 cycles.

[00706] In Arm B, subjects who experience an unacceptable AE that is attributable only to platinum containing chemotherapy may continue on gemcitabine monotherapy for up to 6 cycles. Subjects who experience an unacceptable AE that is attributable only to gemcitabine may continue on platinum containing chemotherapy for up to 6 cycles.

(x) **Efficacy Assessments**

[00707] Computed tomography (CT) scans with contrast (unless contraindicated), including chest, abdomen, and pelvis at the minimum, is used to assess antitumor activity at protocol specified time points. Subjects must receive the same imaging method throughout the study for response assessments. For subjects who cannot receive CT scans with contrast, other protocol specified imaging methods may be used (see Section 6.1.12). Bone imaging

and/or brain scans should be repeated at disease assessment time points, and as clinically indicated throughout the study, in subjects with a history of skeletal metastasis or suspicion of skeletal metastasis based on imaging or symptoms, or a history of CNS metastasis or signs/symptoms of CNS metastasis. Objective responses are confirmed per RECIST v1.1 by BICR with repeat scans done at the next scheduled scan per protocol, after first documentation of response.

(xi) **Pharmacokinetic and Immunogenicity Assessments**

[00708] Blood samples for pharmacokinetic (PK) and anti therapeutic antibody (ATA) analyses are collected for Arm A only, at specific time points. Validated or qualified assays are used to measure the concentrations of enfortumab vedotin and MMAE in serum or plasma. A validated assay is used to determine ATA for enfortumab vedotin in serum. Pharmacokinetic and ATA samples for pembrolizumab are collected.

(xii) **Biomarker Assessments**

[00709] Biomarker assessments are performed from archival or fresh tumor tissue, peripheral blood and urine. Subjects are stratified by PD-L1 status, as determined by the Dako/Agilent PD-L1 immunohistochemistry (IHC) 22C3 PharmDx on tumor biospecimens. Other biomarker assessments may include central assessment of Nectin 4 expression by IHC, and Next Generation Sequencing for assessment of tumor subtyping and mutations associated with response to enfortumab vedotin in metastatic UC.

(xiii) **Other Assessments**

[00710] Patient reported outcome (PRO) assessments include quality of life (QOL) measures, both general and oncology specific (EuroQOL 5 dimensions [EQ 5D 5L] and European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Core 30 [QLQ C30] Questionnaire, respectively), as well as outcome specific PROs around pain (Brief Pain Inventory Short Form [BPI SF]). Impact on pain may also be correlated to pain medication use collected in the case report form (CRF). A health resource utilization (HRU) questionnaire also aims to measure clinical burden outside of the clinical trial setting.

(xiv) **Safety Assessments**

[00711] Safety assessments include surveillance and recording of AEs, including serious adverse events (SAEs), concomitant medications, physical examination findings, vital signs, protocol specified laboratory tests, ECOG status, electrocardiograms (ECGs), ophthalmologic

examination findings and pregnancy testing. Safety is monitored over the course of the study by the IDMC.

(xv) **Statistical Methods**

(a) Stratification

[00712] Subject are stratified based on the following variables:

1. Cisplatin eligibility (eligible or ineligible)
2. PD-L1 expression by IHC (High [combined positive score (CPS) ≥10] or Low [CPS <10])
3. Liver metastases (present or absent)

(b) Multiplicity

[00713] The 2 arm study has dual primary endpoints of PFS and OS. The study can be considered positive if enfortumab vedotin plus pembrolizumab (Arm A) is superior to the control arm (Arm B) in either PFS or OS. A graphical approach with group sequential testing outlined in Maurer and Bretz (Maurer 2013) is used to strongly control the family wise type I error rate at a two sided 5% level.

[00714] The initial alpha allocation for the dual primary endpoints of PFS and OS are 0.5% and 4.5%, respectively. If only 1 of the primary endpoints is statistically significant at the specified level, alpha recycling is applied to evaluate the other primary endpoint at the 5% significance level.

[00715] When the null hypotheses for PFS and OS are both rejected, selected secondary endpoints are tested in the following order using a gatekeeping testing strategy:

1. ORR by BICR
2. Time to pain progression (TTPP)
3. Mean change from baseline in worst pain at Week 26

[00716] Each test is at the 5% significance level (2-sided) as long as all preceding null hypotheses are rejected. These secondary endpoints are only tested once at either the OS interim or final analysis after the null hypotheses for PFS and OS are both rejected, and the test statistics for inferential testing are computed from the data at the time of OS interim analysis (IA). In the event that only the null hypothesis for PFS is rejected and the superiority boundary for OS has not been crossed at the time of OS IA, these secondary endpoints are not tested and are only analyzed descriptively.

(c) Sample Size Considerations

[00717] Approximately 860 subjects are randomized in a 1:1 ratio to one of the study arms.

[00718] With 430 subjects per arm, the estimated number of OS events between Arm A and Arm B is 489, providing 93% power to demonstrate superiority at a two sided alpha of 4.5% with 1 IA around 72.8% information fraction under the following assumptions:

4. OS curves follow piecewise exponential distribution with a reduced hazard rate (50% of the initial rate) starting from 24 months
5. hazard ratio (HR) of OS is 0.73 between the experimental and control arms
6. median OS for the control arm is 15.3 months
7. an enrollment period of 30 months
8. a yearly dropout rate of 5%

[00719] The number of PFS events between the 2 arms is estimated to be 526 events, providing 90% power to demonstrate superiority at a two sided alpha of 0.5% with 430 subjects per arm based on the following assumptions:

1. PFS curves follow piecewise exponential distribution with a reduced hazard rate (20% of the initial rate) starting from 15 months
2. HR of PFS is 0.70 between the experimental and the control arms
3. median PFS for the control arm is 7 months
4. an enrollment period of 30 months
5. a yearly dropout rate of 5%

[00720] To evaluate the consistency of efficacy and safety in a China subpopulation compared with the global population, after completion of enrollment in the global portion, subjects in China may continue to be randomized in a 1:1 ratio to either the experimental arm or the control arm until the planned sample size of approximately 130 subjects in China is reached, including those randomized in the global portion and China portion. Subjects in China randomized after completion of enrollment in the global portion are not included in the analysis of the global portion.

(d) Timing of Analyses

[00721] A single planned analysis (final analysis) for PFS takes place when approximately 526 PFS events or 356 OS events (72.8% information fraction) in the intent to treat (ITT) analysis set have occurred, whichever is later.

[00722] Two analyses are planned for OS. OS IA is planned at the time of the final PFS analysis. At IA, the OS events in total are approximately 356 (about 72.8% of information).

O'Brien Fleming boundaries are used to calculate the rejection boundaries based on the actual information fraction observed. The final OS analysis is planned when approximately 489 OS events have occurred in total.

(e) Analysis Methods

[00723] Efficacy. The ITT analysis set is used for the primary analysis of OS and PFS. All subjects who are randomized are included in the ITT analysis set. For primary endpoints of OS and PFS, a log rank test stratified by randomization stratification factors is used to compare the experimental arm to the control arm. The estimated HR and corresponding 95% confidence interval from the stratified Cox proportional hazards regression model is also presented. The median survival time is estimated using the Kaplan Meier method and is reported along with the corresponding 95% confidence interval by treatment arm. Similar estimation methods are used for the other time to event endpoints. Duration of response (DOR) is summarized descriptively by Kaplan Meier methods for subjects with a confirmed response (complete response or partial response per RECIST v1.1). ORR, DCR, and DOR are analyzed using the response evaluable set.

[00724] Objective response rate and disease control rate is estimated for each arm based on the response evaluable set. P value comparing between experimental arm and the control arm using the Cochran Mantel Haenszel test stratified by randomization stratification factors is reported.

[00725] Safety. The frequency of AEs and SAEs is summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. In addition, summary statistics or listings are provided for the following safety parameters: laboratory values, vital sign measurements, ECGs, and ECOG performance status.

[00726] Pharmacokinetics. Descriptive statistics are provided for antibody drug conjugate and unconjugated drug (MMAE) concentrations in Arm A at each PK sampling time point.

[00727] Pembrolizumab PK and immunogenicity analyses are performed only if required.

[00728] The incidence of ATA is summarized.

[00729] Patient Reported Outcomes. Completion and compliance rates along with change from baseline for each domain of the PROs, including EQRTC QLQ C30, EQ 5D 5L, and BPI SF are summarized. Cumulative incidence of HRU, including length of stay, hospitalizations, and emergency room (ER) visits are summarized by treatment arm and by cycle. Additionally, TTPP and mean changes from baseline in worst pain at Week 26 are evaluated.

6.1.3 Objectives

[00730] This study evaluates the efficacy, safety, and PK of enfortumab vedotin in combination with pembrolizumab versus standard of care gemcitabine plus platinum containing chemotherapy in subjects with previously untreated locally advanced or metastatic UC. Specific objectives and corresponding endpoints for the study are summarized in Table 8.

Table 8. Study Objectives

Primary Objectives	Corresponding Dual Primary Endpoints
To compare PFS between the experimental arm (enfortumab vedotin + pembrolizumab [Arm A]) and the control arm (gemcitabine + cisplatin or carboplatin [Arm B]) by blinded independent central review (BICR)	PFS per RECIST v1.1 by BICR
To compare overall survival (OS) between the experimental arm (Arm A) and the control arm (Arm B)	OS
Secondary Objectives	Corresponding Secondary Endpoints
To compare ORR between the experimental arm (Arm A) and the control arm (Arm B) by BICR	ORR per RECIST v1.1 by BICR
To compare time to pain progression (TTPP) from the subject perspective between the experimental arm (Arm A) and the control arm (Arm B)	TTPP
To compare average change in pain from the subject perspective between the experimental arm (Arm A) and the control arm (Arm B)	Mean change from baseline in worst pain at Week 26
To evaluate PFS between the experimental arm (Arm A) and the control arm (Arm B) by investigator assessment	PFS per RECIST v1.1 by investigator assessment
To evaluate ORR between the experimental arm (Arm A) and the control arm (Arm B) by investigator assessment	ORR per RECIST v1.1 by investigator assessment
To evaluate DOR) the experimental arm (Arm A) and the control arm (Arm B)	DOR per RECIST v1.1 by BICR DOR per RECIST v1.1 by investigator assessment
To evaluate DCR between the experimental arm (Arm A) and the control arm (Arm B)	DCR per RECIST v1.1 by BICR DCR per RECIST v1.1 by investigator assessment
To evaluate the impact of study treatment on quality of life (QOL), functioning, and symptoms from the subject perspective	Mean scores and change from baseline of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core 30 (QLQ-C30), and EuroQOL 5-dimensions (EQ-5D-5L), visual analogue scale (VAS), and utility scores

To evaluate the safety profile of each treatment regimen	Type, incidence, relatedness, severity and seriousness of AEs Type, incidence and severity of laboratory abnormalities Treatment discontinuation rate due to AEs
Exploratory Objectives	Corresponding Exploratory Endpoints
To assess PFS, ORR, and DOR per the modified RECIST v1.1 for immune-based therapeutics (iRECIST) in Arm A	PFS, ORR, and DOR per iRECIST by investigator assessment in Arm A
To assess subject reported health resource utilization (HRU)	Cumulative incidence of HRU as reported by subject
To assess the pharmacokinetics of enfortumab vedotin and MMAE To assess the development of anti-therapeutic antibody (ATA) to enfortumab vedotin	Plasma or serum concentrations of enfortumab vedotin and MMAE Incidence of ATA to enfortumab vedotin
To assess biomarkers of biological activity, resistance, and predictive biomarkers of response	Exploratory biomarkers of clinical activity

6.1.4 Study Plan

6.1.4.1 *Summary of Study Design*

[00731] This is a global phase 3 open label, 2 arm randomized multicenter study to evaluate the combination of enfortumab vedotin + pembrolizumab versus standard of care gemcitabine + platinum containing chemotherapy, in subjects with previously untreated locally advanced or metastatic UC. *See* **FIG. 2**.

[00732] Subjects are enrolled regardless of PD-L1 expression status, however, PD-L1 status (high or low) is a stratification factor for randomization. The study is designed to assess the dual primary endpoints of PFS and OS of experimental Arm A (enfortumab vedotin + pembrolizumab) compared to control Arm B (gemcitabine + cisplatin or carboplatin).

[00733] A total of 860 subjects are randomized in a 1:1 manner to one of the study arms with the following stratification factors: cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent).

[00734] Subjects in Arm A receive enfortumab vedotin at 1.25 mg/kg, administered as an IV infusion on Days 1 and 8 of every 3 week cycle, and pembrolizumab 200 mg as an IV infusion on Day 1 of every 3 week cycle, after completion of the enfortumab vedotin infusion.

[00735] Subjects in Arm B receive gemcitabine at 1000 mg/m^2 as an IV infusion on Days 1 and 8 of every 3 week cycle, and either cisplatin (70 mg/m^2) or carboplatin (area under the curve [AUC] 4.5, or AUC 5 according to local guidelines) on Day 1 of every 3 week cycle, with adequate pre- and post-hydration, by IV infusion per institutional standards.

[00736] Response is assessed by computed tomography (CT) scans with contrast (unless contraindicated) every 9 weeks (±1 week) timed from the randomization date. For subjects who cannot receive CT scans with contrast, other protocol specified imaging methods may be used (Section 6.1.12). Brain scans should be repeated at this time point in subjects with a history of central nervous system (CNS) metastasis or signs/symptoms of CNS metastasis. Bone imaging should also be repeated at this time point in subjects with a history of skeletal metastasis or suspicion of skeletal metastasis based on imaging or symptoms. Objective responses are confirmed per RECIST v1.1 (Eisenhauer 2009) (**FIG. 3A, FIG. 3B, and FIG. 3C**) with repeat scans at the next scheduled response assessment per protocol after first documentation of response. Subsequent response assessments should be performed every 9 weeks (±1 week) until 18 months after randomization, then every 12 weeks (±1 week). Response assessment should also be performed, and BICR evaluation triggered, whenever disease progression is suspected.

[00737] Subjects may continue on study treatment until progressive disease (BICR confirmed or clinical progression [see Section 6.1.7.4]), an AE, pregnancy, investigator decision, start of a subsequent anticancer therapy, subject decision (non AE), study termination by the sponsor, completion of the maximum number of drug cycles allowed, or other reason unrelated to an AE. Treatment beyond disease progression per RECIST v1.1 may be considered for subjects in study Arm A (EV + pembrolizumab) who are deriving clinical benefit as defined in Section 6.1.6.7. Subjects treated beyond disease progression per RECIST v1.1 may continue until confirmed disease progression per modified RECIST 1.1 for immune based therapeutics (iRECIST) as assessed by the investigator (Seymour 2017) (Section 6.1.14). Confirmatory scans must be performed 4 to 9 weeks after disease progression per RECIST v1.1 by BICR. Treatment with gemcitabine and treatment with platinum containing chemotherapy may be given up to 6 cycles. Treatment with pembrolizumab is discontinued once the subject has received a maximum of 35 administrations of pembrolizumab (approximately 2 years). There is no upper limit to the number of cycles of enfortumab vedotin permitted. To date in metastatic UC, enfortumab vedotin has been administered until disease progression or an unacceptable AE.

[00738] Palliative radiotherapy on a nontarget bone lesion that is not progressing is permitted and is not considered a subsequent anticancer therapy; however, radiotherapy on any new or progressing lesion, per RECIST v1.1 as assessed by the investigator or after BICR confirmed progression, is considered a subsequent anticancer therapy and subjects are not permitted to resume study treatment. Surgical resection for curative intent during study treatment may be permitted in subjects with favorable tumor response after discussion with the medical monitor.

[00739] Subjects who discontinue treatment for reasons other than disease progression or consent withdrawal continue to receive response assessments every 9 weeks (±1 week) for the first 18 months timed from the randomization date, and every 12 weeks (±1 week) thereafter, until the subject has radiologically confirmed disease progression per RECIST v1.1 guidelines as determined by BICR, dies, withdraws consent, or the study closes, whichever occurs first. After discontinuation of study treatment, all randomized subjects are followed every 12 weeks (±1 week) to obtain information on subsequent anticancer therapy, and to assess survival status until death, study closure, lost to follow up, or subject withdraws consent, whichever occurs first.

[00740] Crossover to the experimental arm of the trial (Arm A) is not permitted for subjects in the control arm (Arm B).

[00741] *China Portion of the Study*. After completion of enrollment in the global portion, subjects in China may continue to be randomized in a 1:1 ratio to either the experimental arm or the control arm until the planned sample size of approximately 130 subjects in China is reached.

6.1.4.2 *Discussion and Rationale for Study Design*

[00742] As outlined in Section 5, despite the availability of cisplatin containing chemotherapy which offers a survival benefit in the first line metastatic UC setting, the majority of patients receiving cisplatin chemotherapy do not achieve long term disease free survival, and for patients ineligible for cisplatin, outcomes are even worse (De Santis 2012; Rosenberg 2019a). This global phase 3, randomized study evaluates enfortumab vedotin administered in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic UC. The study enrolls an all comer first line locally advanced or metastatic UC population without pre selection based on a tissue biomarker.

(i) Rationale for Endpoints

[00743] OS is a well established endpoint for oncology drug approvals in metastatic UC. However, the OS endpoint may be impacted by subsequent therapies or non cancer related causes of death (e.g., accidents, comorbidities, and natural deaths in the elderly). The effect of later lines of treatments on the OS results are of concern for studies conducted in the earlier lines of treatment. Multiple PD 1/PD L1 inhibitors are approved in the post platinum containing setting. OS also generally requires larger sample sizes and longer follow up time, potentially delaying the time to availability of an active treatment to subjects. The study tests for superiority in the PFS endpoint, in addition to the OS endpoint. PFS may better isolate effects of the study treatment without as much influence by external factors such as subsequent treatments and "cross over" in the control arm. PFS can also be viewed as a measure of clinical benefit to patients, whereby prolonging the time to progression of cancer would have a direct impact on an individual patient's sense of well being, as well as delaying the need for subsequent treatments with the associated side effects. Of note, quality of life (QOL) data and patient reported outcomes (PROs) are also collected in this study to better understand the impact of improved PFS on subjects' daily lives.

[00744] With these considerations in mind, the sponsors designate both PFS and OS as dual primary endpoints in the EV 302 study design, providing the opportunity to robustly evaluate the clinical benefit of enfortumab vedotin and pembrolizumab over the standard of care.

(ii) Rationale for Study Population

(a) Rationale for Enrollment of a Biomarker-Unselected Population

[00745] The current trial enrolls an all-comer population with no preselection for tumor-specific biomarkers, including Nectin 4 and PD-L1 expression. The rationale for this approach is supported by data from the phase 1 and phase 2 trials of enfortumab vedotin, which showed no evidence to support an expression response relationship between either Nectin 4 or PD-L1 and enfortumab vedotin therapy.

[00746] Subjects in the ongoing EV 201 and EV 301 studies investigating EV monotherapy in second line and third line metastatic UC, as well as study EV 103 investigating EV combinations in first line metastatic UC, are all enrolled in an unselected manner with regard to the biomarkers Nectin 4 and PD L1.

[00747] In the EV 101 (ASG 22CE 13 2) phase 1 study, more than 97% of archival tumor samples from screened subjects expressed Nectin 4 using a immunohistochemistry (IHC) assay with a median H score of 280 out of a maximum of 300 (Petrylak 2017). Based upon the observed prevalence of high Nectin 4 expression, the protocol for phase 1 study EV 101

is amended to eliminate the enrollment requirement for H score ≥150 in metastatic UC subjects.

[00748] In the EV 201 trial, there was no pre selection by Nectin 4 expression and Nectin 4 expression was detectable by IHC in tumor biopsies from all treated subjects who had adequate tumor tissue for testing. The vast majority of subjects had high Nectin 4 expression levels, with a median H score of 290 out of 300 (Rosenberg 2019b).

[00749] In the EV 201 study, PD-L1 levels at baseline were assessed by a validated 22C3 PD-L1 IHC assay. Of the 120 subjects, previously treated with both platinum containing chemotherapy and a PD-1/PD-L1 inhibitor (Cohort 1), who had evaluable PD-L1 expression data, 65% had a CPS <10 and 35% had a CPS ≥10. Responses to enfortumab vedotin were observed in subjects with both high and low PD-L1 expression, with an ORR of 36% and 47%, respectively (Petrylak 2019). In the EV 201 trial, responses were observed regardless of PD-L1 expression level.

[00750] In the ongoing study EV 103 in 1L metastatic UC, subjects are enrolled regardless of PD-L1 expression. As of the data cut-off date of 08 October 2019, an ORR of 73.3% has been observed, which further supports enrollment of a PD-L1 unselected first line metastatic UC population. Forty two percent (42%) of subjects had low PD-L1 expression (CPS <10), 31% had high PD L1 expression (CPS ≥10), and 27% were not evaluable. Responses were observed regardless of expression level.

[00751] Given the current understanding that PD-L1 expression is important for the use of pembrolizumab monotherapy in 1L metastatic UC, and of uncertain relevance when pembrolizumab is used in combination with cytotoxic agents, PD-L1 expression (high [CPS ≥10] versus low [CPS <10] as determined by the Dako/Agilent PD L1 IHC 22C3 PharmDx assay) are included as a stratification factor in the EV 302 study. Baseline tumor PD-L1 expression is assessed in all subjects prior to randomization to evaluate any predictive or prognostic role for PD-L1 expression in this study.

(b) Rationale for Control Arm Selection and Stratification Factors

[00752] Gemcitabine plus cisplatin is a preferred first line regimen for patients with locally advanced or metastatic UC who are cisplatin eligible (von der Maase 2000). For patients who are cisplatin ineligible, gemcitabine plus carboplatin is a preferred regimen (De Santis 2012). Contemporary phase 3 trials conducted by the EORTC cooperative group with gemcitabine plus platinum containing chemotherapy control arms include EORTC 30987 using gemcitabine plus cisplatin (Bellmunt 2012) and EORTC 30986 using gemcitabine plus carboplatin (De Santis 2012). More recently, the CALGB cooperative group presented data

from the 90601 trial, including gemcitabine plus cisplatin control arm (Rosenberg 2019a). Several additional recent and ongoing phase 3 studies use gemcitabine plus platinum containing chemotherapy in control arms, including the DANUBE study (NCT02516241), NILE (NCT03682068), KEYNOTE 361 (NCT02853305), IMvigor130 (NCT02807636), and CheckMate901 (NCT03036098).

[00753] Together, these data support the use of gemcitabine plus cisplatin or carboplatin, the current standard of care for 1L treatment of subjects with locally advanced or metastatic UC, as the control arm for the current study.

(iii) Stratification Factors

[00754] Given the different outcomes observed between the cisplatin eligible and the cisplatin ineligible 1L metastatic UC populations, cisplatin eligibility is included as a stratification factor to ensure balance across treatment arms. Investigators determine a subject's cisplatin eligibility at the time of enrollment, per protocol. A subject may be considered cisplatin ineligible provided they meet at least one of the following criteria: glomerular filtration rate (GFR) <60 mL/min, Eastern Cooperative Oncology Group (ECOG) or World Health Organization (WHO) performance status of 2, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≥2 audiometric hearing loss, or New York Heart Association (NYHA) Class III heart failure. Subjects are stratified by cisplatin eligibility for randomization, with the intent to support approval for both cisplatin eligible and cisplatin ineligible (carboplatin eligible) subject populations. Subjects are stratified by PD L1 expression into either PD L1 high (CPS ≥10) or PD-L1 low (CPS <10) categories according to the Dako/Agilent PD L1 IHC 22C3 PharmDx. Additional stratification factors include presence or absence of liver metastases at randomization, which is an established prognostic factor in patients with metastatic UC (Bajorin 1999) (Sonpavde 2016).

(iv) Method of Assigning Subjects to Treatment Groups

[00755] Subjects are randomized in a 1:1 manner to 1 of the 2 treatment arms based on the following stratification factors: cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and liver metastases (present or absent). Interactive Response Technology (IRT) is used for randomization.

(v) Rationale for Selection of Doses

[00756] Enfortumab vedotin administered at 1.25 mg/kg on Days 1, 8, and 15 of every 28 day cycle is the approved dose and schedule for locally advanced or metastatic UC in second

line patients who have previously received a PD-1/PD-L1 inhibitor and platinum containing chemotherapy (PADCEV® Prescribing Information, Seagen, December 2019). Based on PK data from previous studies, the half-life of enfortumab vedotin is approximately 3 to 4 days. No notable intra-cycle accumulation (<30%) of ADC was observed with this monotherapy dosing regimen at any dose level. Minimal intra-cycle accumulation (<50%) of MMAE was observed.

[00757] In this combination study, additional drugs in the regimen (pembrolizumab, gemcitabine and platinum containing chemotherapy) are administered in a 21 day cycle. Enfortumab vedotin is administered on Days 1 and 8 of a 21 day cycle. When comparing the same dose level, the average weekly total exposure of enfortumab vedotin following administration on Days 1 and 8 of each 21 day cycle is predicted to be similar to that observed for dosing on Days 1, 8, and 15 of a 28 day cycle. Thus, the dosing schedule in the current combination study achieves ADC exposures over each 3 week cycle that may lead to a favorable balance of antitumor activity and safety. Similar to the monotherapy dosing regimen, no to minimal accumulation of ADC and MMAE, respectively, is expected on the 21 day cycle.

[00758] Enfortumab vedotin is administered at a dose of 1.25 mg/kg as an IV infusion over approximately 30 minutes on Days 1 and 8 of each 3 week cycle.

[00759] The dose of pembrolizumab for this study is 200 mg administered on Day 1 of each 21 day cycle in combination with enfortumab vedotin. This is the approved dose and schedule for pembrolizumab for urothelial cancer in both first line cisplatin ineligible patients and second line patients (Keytruda Prescribing Information, June 2019).

[00760] Gemcitabine 1000 mg/m^2 is administered on Days 1 and 8 of each 21 day cycle. Either cisplatin 70 mg/m2 or carboplatin AUC=4.5 (or AUC=5 according to local guidelines) is administered on Day 1 of each 21 day cycle. Cisplatin and gemcitabine at these doses have been tested in both 21 day and 28 day cycles with similar efficacy outcomes (von der Maase 2000; Rosenberg 2019a). The 21 day cycle has been a preferred schedule when tested in combination with other agents administered on a 21 day schedule (Rosenberg 2019a); (KEYNOTE 361 NCT02853305). The carboplatin and gemcitabine regimen at this dose and schedule was established as a standard of care for the cisplatin ineligible population (De Santis 2012).

(vi) Blinding and Unblinding

[00761] This trial evaluates the experimental arm (enfortumab vedotin plus pembrolizumab) compared to the standard of care control arm (platinum containing

chemotherapy plus gemcitabine). As the control arm contains agents not contained in the experimental arm, blinding with placebo control would be difficult and could complicate the ability to assess attribution of overlapping toxicities. Given this, the study is conducted in an open label fashion. Although this is an open label study, to maintain trial integrity, until database lock and study unblinding for the pre-planned analyses, analyses or summaries by treatment assignment are only for the purpose of the IDMC monitoring and are conducted by an external vendor. The primary endpoint of PFS along with response based secondary endpoints are assessed by BICR.

(vii) Overall End of Study

[00762] The study ends 5 years after enrollment of the last subject, or when no subjects remain in survival follow up.

6.1.5 Study Population

[00763] Subjects with previously untreated locally advanced or metastatic UC. Subjects must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived and are subject to review in the event of a good clinical practice audit and/or health regulatory authority inspection.

6.1.5.1 *Inclusion Criteria*

[00764] Inclusion Criterion 1. Subjects must have histologically documented, unresectable locally advanced or metastatic urothelial carcinoma (i.e., cancer of the bladder, renal pelvis, ureter, or urethra). Subjects with squamous or sarcomatoid differentiation or mixed cell types are eligible.

[00765] Inclusion Criterion 2. Subjects must have measurable disease by investigator assessment according to RECIST v1.1 (**FIG. 3A, FIG. 3B, and FIG. 3C**). Subjects with prior definitive radiation therapy must have measurable disease per RECIST v1.1 that is outside the radiation field or has demonstrated unequivocal progression since completion of radiation therapy.

[00766] Inclusion Criterion 3. Subjects must not have received prior systemic therapy for locally advanced or metastatic urothelial carcinoma with the following exceptions:

- Subjects that received neoadjuvant chemotherapy with recurrence >12 months from completion of therapy are permitted.
- Subjects that received adjuvant chemotherapy following cystectomy with recurrence >12 months from completion of therapy are permitted.

[00767] Inclusion Criterion 4. Subjects must be considered eligible to receive cisplatin- or carboplatin-containing chemotherapy, in the investigator's judgment. Subjects are considered cisplatin-ineligible, and receive carboplatin, if they meet at least one of the following criteria:

- GFR <60 mL/min but ≥30 mL/min (measured by the Cockcroft Gault formula, Modification of Diet in Renal Disease [MDRD] or 24 hour urine).
    - •Subjects with a GFR ≥50 mL/min and no other cisplatin ineligibility criteria may be considered cisplatin eligible based on the investigator's clinical judgment.
- ECOG or WHO performance status of 2 (refer to Inclusion 7 for additional criteria for ECOG 2 subjects).
- NCI CTCAE Grade ≥2 audiometric hearing loss
- NYHA Class III heart failure

[00768] Inclusion Criterion 5. Subjects must be age 18 years or older

[00769] Inclusion Criterion 6. Archival tumor tissue comprising muscle invasive urothelial carcinoma, or a biopsy of metastatic urothelial carcinoma must be provided for PD L1 testing prior to randomization. If adequate archival tumor sample is not available, or evaluable, a new biopsy sample may be performed (see Section 6.1.7.6).

[00770] Inclusion Criterion 7. Subjects must have an ECOG Performance Status score of 0, 1, or 2 (see Table 23 for conversion of performance status using Karnofsky, if applicable). Subjects with ECOG performance status of 2 must additionally meet the following criteria:

- Hemoglobin ≥10 g/dL
- GFR ≥50 mL/min
- May not have NYHA Class III heart failure

[00771] Inclusion Criterion 8. Subjects must have adequate hematologic and organ function as defined by the baseline laboratory values in Table 9.

Table 9. Baseline laboratory values

System	Laboratory Value
Hematological	
ANC	≥1500/μL
Platelets	≥100,000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L
Renal	
Measured or calculated[a] creatinine clearance (CrCl) (GFR can also be used in place of creatinine or CrCl)	≥30 mL/min
Hepatic	
Total bilirubin	≤1.5× ULN OR direct bilirubin ≤ ULN for subjects with total bilirubin levels >1.5× ULN ≤3× ULN for subjects with Gilbert's disease
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for subjects with liver metastases
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin (aPTT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulation

Note: This table includes eligibility defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies. ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); ANC=absolute neutrophil count; AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl=creatinine clearance; GFR=glomerular filtration rate

[a] Creatinine clearance should be calculated via either Cockcroft Gault, Modification of Diet in Renal Disease (MDRD) equations or 24h urine, per institutional standard. The same method should be used consistently for a subject over the course of the study with the exception of carboplatin dose calculation where Cockcroft Gault method should be used in all subjects.

[00772] Inclusion Criterion 9. A female subject of childbearing potential is anyone born female who has experienced menarche and who has not undergone surgical sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed

menopause. Menopause is defined clinically as 12 months of amenorrhea in a person over age 45 in the absence of other biological, physiological, or pharmacological causes. Female subjects of childbearing potential must meet the following conditions:

- Agree not to try to become pregnant during the study and for at least 6 months after the final dose of study drug.
- Must have a negative urine or serum pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β hCG]) within 1 day prior to administration of study drug. Female subjects with false positive results and documented verification of negative pregnancy status are eligible for participation.
- If heterosexually active, must consistently use highly effective methods of birth control, with a failure rate of less than 1% (as described in Section 6.1.13) starting at screening, throughout the study period, and for at least 6 months after the final dose of study drug.
- Female subjects must agree not to breastfeed or donate ova starting at screening and throughout the study period, and for at least 6 months after the final dose of study drug.

[00773] Inclusion Criterion 10. A male subject who can father children is anyone born male who has testes and who has not undergone surgical sterilization (e.g., vasectomy followed by a clinical test proving that the procedure was effective). Male subjects who can father children, must meet the following conditions:

- Must not donate sperm starting at screening and throughout the study period, and for at least 6 months after the final dose of study drug. Male subjects are informed about the negative risk to reproductive function and fertility from the study treatment. Prior to treatment male subjects should be advised to seek information on fertility preservation and sperm cryoconservation.
- Must consistently use highly effective methods of birth control, with a failure rate of less than 1% (as described in Section 6.1.13) starting at screening and continue throughout study period and for at least 6 months after the final dose of study drug.
- Male subjects with a pregnant or breastfeeding partner(s) must consistently use one of 2 contraception options for preventing secondary exposure to seminal fluid (as described in Section 6.1.13) for the duration of the pregnancy or time partner is

breastfeeding throughout the study period and for at least 6 months after the final dose of study drug.

[00774] Inclusion Criterion 11. Subjects must provide written informed consent.

6.1.5.2 *Exclusion Criteria*

[00775] Exclusion Criterion 1. Subjects who have previously received enfortumab vedotin or other MMAE based ADCs.

[00776] Exclusion Criterion 2. Subjects who have received prior treatment with a PD-(L)-1 inhibitor for any malignancy, including earlier stage UC, defined as a PD-1 inhibitor or PD-L1 inhibitor (including, but not limited to, atezolizumab, pembrolizumab, nivolumab, durvalumab, or avelumab).

[00777] Exclusion Criterion 3. Subjects who have previously received any prior treatment with an agent directed to another stimulatory or co inhibitory T-cell receptor (including but not limited to CD137 agonists, CTLA-4 inhibitors, or OX-40 agonists).

[00778] Exclusion Criterion 4. Subjects who have received anti-cancer treatment with chemotherapy, biologics, or investigational agents not otherwise prohibited by exclusion criteria 1–3 that is not completed 4 weeks prior to first dose of study treatment (ongoing hormonal/anti hormonal treatment, e.g., for breast cancer, is allowed, provided that the subject is eligible per exclusion criterion 14).

[00779] Exclusion Criterion 5. Subjects with uncontrolled diabetes. Uncontrolled diabetes is defined as hemoglobin A1c (HbA1c) $\geq$8% or HbA1c 7% to <8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.

[00780] Exclusion Criterion 6. Subjects with an estimated life expectancy <12 weeks.

[00781] Exclusion Criterion 7. Subjects with ongoing sensory or motor neuropathy Grade 2 or higher.

[00782] Exclusion Criterion 8. Subjects with active CNS metastases. Subjects with treated CNS metastases are permitted on study if all of the following are true: a) CNS metastases have been clinically stable for at least 4 weeks prior to screening and baseline scans show no evidence of new or enlarged metastasis; b) the subject is on a stable dose of $\leq$10 mg/day of prednisone or equivalent for at least 2 weeks (if requiring steroid treatment); c) subject does not have leptomeningeal disease.

[00783] Exclusion Criterion 9. Subjects with ongoing clinically significant toxicity associated with prior treatment (including radiotherapy or surgery) that has not resolved to $\leq$ Grade 1 or returned to baseline.

[00784] Exclusion Criterion 10. Currently receiving systemic antimicrobial treatment for active infection (viral, bacterial, or fungal) at the time of randomization. Routine antimicrobial prophylaxis is permitted.

[00785] Exclusion Criterion 11. Subjects who have known active hepatitis B (defined as HBsAg reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] detected) infection, testing for hepatitis B and hepatitis C is required if mandated by country health authority. Subjects who have been curatively treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks.

[00786] Exclusion Criterion 12. Has a known history of human immunodeficiency virus (HIV) infection. Testing is not required unless mandated by the local health authority.

[00787] Exclusion Criterion 13. Subjects with conditions requiring high doses of steroids (>10 mg/day of prednisone or equivalent) or other immunosuppressive medications are excluded. Inhaled or topical steroids are permitted in the absence of active autoimmune disease. Physiologic replacement doses of corticosteroids are permitted for subjects with adrenal insufficiency.

[00788] Exclusion Criterion 14. Subjects with a history of another invasive malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Subjects with nonmelanoma skin cancer or carcinoma in situ of any type (if complete resection was performed) are allowed.

a. A history of prostate cancer (T2NXMX or lower with Gleason score ≤7) treated with definitive intent (surgically or with radiation therapy) at least 1 year prior to study entry is acceptable, provided that the subject is considered prostate cancer-free and the following criteria are met:

i. Participants who have undergone radical prostatectomy must have undetectable PSA for >1 year and at screening.

ii. Participants who have had radiation must have a PSA doubling time >1 year (based on at least 3 values determined >1 month apart) and a total PSA value that does not meet Phoenix criteria for biochemical recurrence (i.e., <2.0 ng/mL above nadir).

b. Participants with untreated low risk prostate cancer (Gleason score ≤6) on active surveillance with PSA doubling time >1 year (based on at least 3 values determined >1 month apart) are also eligible.

[00789] Exclusion Criterion 15. Subjects with a documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac

symptoms consistent with NYHA Class IV within 6 months prior to randomization (Section 6.1.10).

[00790] Exclusion Criterion 16. Subjects who have received radiotherapy within 2 weeks prior to randomization. Subject must have recovered adequately from the toxicity from the intervention prior to starting study treatment.

[00791] Exclusion Criterion 17. Subjects who have received major surgery within 4 weeks prior to randomization. Subject must have recovered adequately from complications from the intervention prior to starting study treatment.

[00792] Exclusion Criterion 18. Subjects with known severe (≥ Grade 3) hypersensitivity to any enfortumab vedotin excipient contained in the drug formulation of enfortumab vedotin (including histidine, trehalose dihydrate, and polysorbate 20). Subjects with known severe (≥ Grade 3) hypersensitivity to any pembrolizumab excipient contained in the drug formulations of pembrolizumab. Subjects with known severe (≥ Grade 3) hypersensitivity to the platinum agent selected by the investigator for study treatment. Subjects with known severe (≥ Grade 3) hypersensitivity to the gemcitabine.

[00793] Exclusion Criterion 19. Subjects with active keratitis or corneal ulcerations. Subjects with superficial punctate keratitis are allowed if the disorder is being adequately treated in the opinion of the investigator.

[00794] Exclusion Criterion 20. History of autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).

a. Replacement therapy (e.g., thyroxine, insulin, physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

b. Brief (<7 days) use of systemic corticosteroids is allowed when use is considered standard of care.

c. Subjects with vitiligo, psoriasis, type 1 diabetes mellitus, hypothyroidism, or resolved childhood asthma/atopy are not excluded.

d. Subjects requiring intermittent use of bronchodilators, inhaled steroids, or local steroid injections are not excluded.

e. Subjects with hypothyroidism that is stable with hormone replacement or Sjögren's syndrome are not excluded.

[00795] Exclusion Criterion 21. Subjects with a history of idiopathic pulmonary fibrosis, organizing pneumonia, drug induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.

[00796] Exclusion Criterion 22. Subjects who have received a prior allogeneic stem cell or solid organ transplant.

[00797] Exclusion Criterion 23. Subjects who have received a live attenuated vaccine within 30 days prior to randomization. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

[00798] Exclusion Criterion 24. Subjects with active tuberculosis

[00799] Exclusion Criterion 25. Subjects with another underlying medical condition that, in the opinion of the investigator, would impair the ability of the subject to receive or tolerate the planned treatment and follow up; any known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.

6.1.5.3 *Removal of Subjects From Therapy or Assessment*

(i) Discontinuation of Study Treatment

[00800] A subject's study treatment is discontinued for any of the following reasons:

- Progressive disease (BICR-confirmed or clinical progression [see Section 6.1.7.4)
    - Confirmed progressive disease per iRECIST (Section 6.1.14) as assessed by investigator in subjects in study Arm A treated beyond BICR-confirmed disease progression (see criteria in Section 6.1.6.7)
- AE
- Pregnancy
- Investigator decision
- Start of a subsequent anticancer therapy
- Subject decision, non-AE
- Study termination by sponsor
- Completion of study treatment
- Other, non-AE

[00801] Subjects who discontinue from study treatment remain on study for follow-up unless they withdraw consent.

[00802] Pembrolizumab may be administered for up to a total of 35 cycles (approximately 2 years).

[00803] Cisplatin, carboplatin, and gemcitabine may be administered for up to a total of 6 cycles.

[00804] Maintenance therapy (e.g., avelumab) may be used following completion and/or discontinuation of platinum-containing therapy, if locally available, and provided the subject is deemed appropriate by the investigator. Avelumab must be used in accordance with the latest version of the Summary of Product Characteristics (SmPC) currently available. The following conditions should also be met:

- Completion of end of treatment (EOT) visit
- All study-related procedures occurring post-EOT, including all disease assessments until BICR-confirmed disease progression occurs, should be continued per the Schedule of Assessments (see Table 20).

(ii) Subject Discontinuation From Study

[00805] Any subject may be discontinued from the study for any of the following reasons:

- Subject withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Death

6.1.6 Treatments

6.1.6.1 *Treatments Administered*

6.1.6.2 *Investigational Study Drugs*

(i) **Description - Enfortumab vedotin**

[00806] Enfortumab vedotin is generated by conjugation of a chemical intermediate that contains both the MMAE and linker subunits to cysteine residues of the antibody. The resulting ADC contains an average of 3.8 drug molecules per antibody. The enfortumab vedotin drug product is a sterile, preservative free, white to off-white lyophilized powder reconstituted for IV administration. Enfortumab vedotin is supplied in 30 mg single-dose vials.

[00807] Enfortumab vedotin (Arm A)

[00808] Enfortumab vedotin 1.25 mg/kg is administered as an IV infusion over approximately 30 minutes on Days 1 and 8 of every 3 week cycle. Interventions and treatment arms are presented in Table 10.

[00809] Pembrolizumab (Arm A)

[00810] Pembrolizumab 200 mg is administered as an IV infusion approximately 30 minutes after completion of enfortumab vedotin (Arm A) on Cycle 1 Day 1. A delay of 15 minutes may be used for subsequent infusions if the previous infusion was well tolerated.

[00811] Gemcitabine (Arm B)

[00812] Gemcitabine 1000 mg/m^2 is administered as an IV infusion on Days 1 and 8 of each 3 week cycle.

[00813] Cisplatin (Arm B)

[00814] On Day 1 (or Day 2 if required per institutional guidelines) of each 3 week cycle, cisplatin 70 mg/m^2 is administered (with adequate pre- and post-hydration) as an IV infusion per institutional standards (Arm B). The body surface area used to calculate cisplatin dose may be capped per institutional standards.

[00815] Carboplatin (Arm B)

[00816] On Day 1 of each 3 week cycle, carboplatin at AUC 4.5, or AUC of 5 according to local guidelines, is administered (with adequate pre and post hydration) as an IV infusion per institutional standards (Arm B). Body weight used to calculate carboplatin may be capped as per institutional standards.

Table 10. Interventions and treatment arms

Agent (IV)	Arm A (EV+Pembro)	Arm B[a] (Gemcitabine + Cisplatin/Carboplatin)
Enfortumab vedotin	1.25 mg/kg over 30 min on Days 1 and 8	
Pembrolizumab	200 mg over 30 min on Day 1	
Gemcitabine		1000 mg/m^2 on Days 1 and 8
Cisplatin[b]		70 mg/m^2 on Day 1 over 1 hour, or per local label or institutional standards
Carboplatin[c]		AUC 4.5 on Day 1 over 1 hour, or per local label or institutional standards

a Subjects receive either cisplatin or carboplatin.
b Can be given on Day 2 if required per institutional standards.
c A starting dose of AUC 5 can be given according to local guidelines.

(a) Dose and Administration

[00817] Enfortumab vedotin is administered on Days 1 and 8 of every 3 week cycle by IV infusion given over approximately 30 minutes. In the absence of IRRs, the infusion rate for all subjects should be calculated in order to achieve a 30 minute infusion period. Enfortumab vedotin must not be administered as an IV push or bolus. Enfortumab vedotin should not be mixed with other medications.

[00818] Enfortumab vedotin may be administered for an unlimited number of cycles until a protocol defined reason for treatment discontinuation occurs (see Section 6.1.6.7).

[00819] Weight based dosing is based on the subject's actual body weight. Doses must be adjusted for subjects who experience a ≥10% change in weight from baseline or previous cycle. Subject weight must be measured during all relevant assessment windows, e.g., per institutional standards, if applicable. Other dose adjustments for changes in body weight <10% are permitted per institutional standard. An exception to weight based dosing of enfortumab vedotin is made for subjects weighing greater than 100 kg; doses are based on 100 kg for these individuals. The maximum dose permitted on study is 125 mg.

[00820] The subject is observed during enfortumab vedotin administration and for at least 60 minutes following the infusion during the first 3 cycles. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards.

[00821] The infusion site should be monitored closely for redness, swelling, pain, and infection during and at any time after administration. Subjects should be advised to report redness or discomfort promptly at the time of administration or after infusion. For subjects with difficult peripheral venous access or who are at risk for extravasation (i.e., limited vein selection, small or fragile veins, local neuropathies, or lymphedema), placement of a central venous port or catheter should be considered. Institutional guidelines are followed for the administration of chemotherapy agents and precautions taken to prevent extravasation per institutional standards and as described in (Polovich 2014) and (Perez Fidalgo 2012). In case of enfortumab vedotin extravasation, the combination drug(s) should be held until consultation and further discussion with the medical monitor/sponsor.

(b) Dose Modifications for Enfortumab Vedotin

[00822] Dose modification recommendations for enfortumab vedotin associated toxicity (hematologic and non hematologic, by CTCAE v4.03 grade) are presented in Table 11 and Table 12.

[00823] Dose reduction or delay for other enfortumab vedotin associated toxicity is permitted at the discretion of the site investigator. Dose reduction from 1.25 mg/kg to 1 mg/kg or to 0.75 mg/kg is allowed depending on the type and severity of toxicity. Subjects requiring a dose reduction may be re-escalated by 1 dose level (i.e., subjects reduced to 0.75 mg/kg may only be re escalated to 1 mg/kg) provided the toxicity does not require study drug discontinuation and has returned to baseline or ≤ Grade 1. If the toxicity recurs, re-escalation is be permitted. Subjects with ≥ Grade 2 corneal AEs are not permitted to dose re-escalate.

[00824] The Day 8 dose of enfortumab vedotin must be given within 4 days of the planned dose (Day 8 + 4 days). If the Day 8 dose cannot be administered within this timeframe, the dose should be held until Day 1 of the next treatment cycle. Dose delay for other EV associated toxicity is permitted at the discretion of the site investigator. A dose delay may last up to 6 weeks (2 cycles). Dose delays for subjects who are deriving clinical benefit from treatment may be extended beyond 6 weeks, if the subject's toxicity does not otherwise require permanent discontinuation. If there is a dose delay, the schedule for response assessments is not adjusted.

[00825] Enfortumab vedotin may be delayed for situations other than treatment related AEs such as medical/surgical events or logistical reasons not related to study therapy. Subjects should resume study therapy as soon as clinically safe as assessed by the investigator. For delays longer than 6 weeks, the medical monitor should be consulted before resuming study therapy. The reason for delay should be documented in the subject's case report form (CRF).

[00826] For subjects in the enfortumab vedotin plus pembrolizumab treatment arm who develop a rash or a skin reaction that is determined by the investigator to be related to study treatment, initial management actions (i.e., to withhold or discontinue study treatment) should apply to both study treatments, and the investigator should follow the most conservative dose modification recommendations described below in Table 12 for enfortumab vedotin or in Section 6.1.6.2(ii)(c) (Table 13) for pembrolizumab. However, for Grade 2 skin reactions that are stable (not worsening and in the absence of fever) with supportive measures and not limiting the subject's activities of daily living, continued dosing of enfortumab vedotin may be considered following consultation with the sponsor. Neither enfortumab vedotin nor pembrolizumab should be administered in the setting of a Grade ≥3 skin reaction.

Table 11. Recommended dose modifications for enfortumab vedotin-associated hematologic toxicity

Grade 1	Grade 2	Grade 3	Grade 4
Continue at same dose level.	Continue at same dose level. For Grade 2 thrombocytopenia, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level. Transfusions or growth factors may be used as indicated per institutional guidelines.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then reduce dose by 1 dose level and resume treatment or discontinue at the discretion of the investigator. Transfusions or growth factors may be used as indicated per institutional guidelines. For anemia, treatment discontinuation should be strongly considered.

Note: Hematologic toxicity refers to anemia, thrombocytopenia, neutropenia, and febrile neutropenia.

Table 12. Recommended dose modifications for enfortumab vedotin-associated nonhematologic toxicity

Toxicity	Grade			
Skin reactions	Any Grade			
	For suspected Stevens-Johnson syndrome (SJS), suspected toxic epidermal necrolysis (TEN), or bullous lesions, immediately withhold enfortumab vedotin and refer the subject to a dermatologist/specialist for diagnosis and specialized care. For confirmed SJS or TEN, permanently discontinue treatment. If SJS or TEN is ruled out, see recommendations provided below for skin reactions.			
	Grade 1	Grade 2	Grade 3	Grade 4
	For Grade 1 rash or skin reactions, may continue at same dose level. See also Section 6.1.6.4(vii) for recommended management of rash.	Continue at same dose level. For worsening rash or skin reactions or skin reactions with concomitant fever, withhold enfortumab vedotin until toxicity is ≤ Grade 1 or	For Grade 3 rash or skin reactions withhold enfortumab vedotin until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 level. Consider referral	For confirmed SJS or TEN, or Grade 4 rash, permanently discontinue treatment.

		has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 level. Consider referral of the subject to a dermatologist/ specialist for diagnosis and specialized care.	of the subject to a dermatologist/ specialist for diagnosis and specialized care. Subjects who have confirmed SJS or recurrent Grade 3 rash events should have therapy permanently discontinued.	

Ocular	Grade 1	Grade 2	Grade 3	Grade 4
	Continue at same dose level. If ocular symptoms and/or changes in vision are identified, the subject should be evaluated by an optometrist or ophthalmologist.	For Grade 2 corneal AEs, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level. For the second occurrence of Grade 2 corneal AEs, withhold dose until toxicity is ≤ Grade 1, then reduce the dose by 1 dose level and resume treatment. If ocular symptoms and/or changes in vision are identified, the subject should be evaluated by an optometrist or ophthalmologist.	For Grade 3 corneal AEs, discontinue treatment at the discretion of the investigator. If ocular symptoms and/or changes in vision are identified, the subject should be evaluated by an optometrist or ophthalmologist.	For Grade 4 AEs, discontinue treatment.
Neuropathy	Grade 1	Grade 2	Grade 3	Grade 4
	Continue at same dose level.	For Grade 2 neuropathy AEs, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level. For the	For Grade 3 neuropathy AEs, discontinue treatment at the discretion of the investigator.	For Grade 4 AEs, discontinue treatment.

		second occurrence of Grade 2 neuropathy withhold dose until toxicity is ≤ Grade 1, then reduce the dose by 1 dose level and resume treatment.		
Gastrointestinal	Grade 1	Grade 2	Grade 3	Grade 4
	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level.	For Grade 4 AEs, discontinue treatment. Grade 4 vomiting and/or diarrhea that improves to ≤ Grade 2 within 72 hours with supportive management does not require discontinuation.
Hyperglycemia	Grade 1	Grade 2	Grade 3	Grade 4

	Continue at same dose level.	Continue at same dose level.	For Grade 3 hyperglycemia/elevated blood glucose, withhold enfortumab vedotin treatment. Resume treatment once hyperglycemia/elevated blood glucose has improved to ≤ Grade 2 and subject is clinically and metabolically stable. See also pembrolizumab dose modification recommendations for hyperglycemia in Table 13	For Grade 4 hyperglycemia/elevated blood glucose withhold enfortumab vedotin treatment and undertake a full evaluation of the hyperglycemia to determine the underlying diagnosis. Once blood glucose returns to ≤ Grade 2, drug dosing may resume with close monitoring after consultation with the medical monitor. See also pembrolizumab dose modification recommendations for hyperglycemia in Table 13
Pneumonitis/ILD	Grade 1	Grade 2	Grade 3	Grade 4
	Continue at same dose level.	Withhold dose until ≤ Grade 1, then resume at the same dose level or consider dose reduction by 1 dose level.	Permanently discontinue treatment.	Permanently discontinue treatment.
All Other (not previously mentioned)	Grade 1	Grade 2	Grade 3	Grade 4
	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider	For Grade 4 AEs, discontinue treatment.*

			dose reduction by 1 dose level.*	

* Grade 3/4 electrolyte imbalances/laboratory abnormalities, except hyperglycemia, that are not associated with clinical sequelae or are corrected with supplementation/appropriate management within 72 h of their onset do not require discontinuation (e.g., Grade 4 hypouricemia). Grade 3 or 4 elevations of amylase or lipase, if asymptomatic do not require treatment delay.

(c) Storage and Handling

[00827] Refrigeration is set at 2–8°C for storage of vials and solutions containing enfortumab vedotin. The controlled location must be accessible only to the pharmacist, the investigator, or a duly designated person. Study drug must be reconstituted before administration.

[00828] Vials of enfortumab vedotin lyophilized powder, reconstituted drug product and/or dosing solutions should be protected from direct sunlight.

[00829] Do not shake reconstituted vials of the study drug.

[00830] Any partially used vials or prepared dosing solutions should be destroyed by the site according to institutional drug disposal procedures. Unused vials should be destroyed by the site.

(d) Preparation

[00831] Recommended safety measures for handling and preparation include masks, protective clothing, gloves (double glove with nitrile gloves), and vertical laminar airflow safety cabinets.

(ii) **Description - Pembrolizumab**

[00832] Pembrolizumab is a humanized mAb that blocks the interaction between PD 1 and its ligands, PD L1 and PD L2. Pembrolizumab is an IgG4 kappa Ig with an approximate molecular weight of 149 kDa.

[00833] Pembrolizumab injection is a sterile, preservative free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, United States Pharmacopeia (USP).

(a) Method of Procurement

[00834] Pembrolizumab is provided to all study sites by the sponsor. In countries outside the U.S., pembrolizumab is also relabeled by the sponsor, to meet country specific regulatory requirements.

(b) Dose and Administration

[00835] Pembrolizumab is administered at a dose of 200 mg on Day 1 of every 3-week cycle by IV infusion given over approximately 30 minutes.

[00836] Pembrolizumab may be administered for a maximum of 35 cycles.

(c) Dose Modifications

(1) Dose Delays and Toxicity Management for Immune-related Adverse Events Associated with Pembrolizumab

[00837] AEs associated with pembrolizumab exposure may represent an immunologic etiology. These imAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. The dose of pembrolizumab should not be reduced. Based on existing clinical study data, most imAEs were reversible and could be managed with a delay of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected imAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and/or skin biopsy may be included as part of the evaluation. Based on the severity of imAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose delay and toxicity management guidelines for imAEs associated with pembrolizumab are provided in Table 13 and are also detailed in the pembrolizumab package insert.

Table 13. Guidelines for management of pembrolizumab immune related adverse events

General instructions:
1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening imAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if imAEs cannot be controlled by corticosteroids.

Immune-mediated AEs	Toxicity Grade or Conditions (CTCAE v4.03)	Action Taken to Pembrolizumab	imAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent) followed by taper	Monitor subjects for signs and symptoms of pneumonitis Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent) followed by taper	Monitor subjects for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus) Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Grade 4 or recurrent Grade 3	Permanently discontinue		
AST/ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5–1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent) followed by taper	

Immune-mediated AEs	Toxicity Grade or Conditions (CTCAE v4.03)	Action Taken to Pembrolizumab	imAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[a]	Initiate insulin replacement therapy for subjects with T1DM Administer anti-hyperglycemic in subjects with hyperglycemia	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes See also enfortumab vedotin dose modification recommendations and management for hyperglycemia in Table 12
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thioamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hypothyroidism	Grade 2–4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1–2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All other immune-mediated AEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue[b].		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Note: Non-immune related (ir)AE are managed as appropriate, following clinical practice recommendations.

a The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

b Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Drug Rash with Eosinophilia and Systemic Symptom (DRESS), Stevens-Johnson Syndrome, toxic epidermal necrolysis, myelitis, and other clinically important irAEs (e.g., vasculitis and sclerosing cholangitis).

(2) Dose Delays and Toxicity Management of Infusion-reactions Related to Pembrolizumab

[00838] Pembrolizumab may cause severe or life threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 h of completion of infusion. Dose delay and treatment guidelines on pembrolizumab associated infusion reaction are provided in Table 14.

Table 14. Pembrolizumab infusion reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing is held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention.	Subject may be premedicated 1.5 h (±30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500–1000 mg PO (or equivalent dose of analgesic).
Grade 3 or 4 **Grade 3** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief	**Stop Infusion** Additional appropriate medical therapy may include but is not limited to: Epinephrine**, IV	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4** Life-threatening; pressor or ventilator support indicated	fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, pressors, and corticosteroids. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Subject is permanently discontinued from further pembrolizumab treatment.	

[00839] Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 at the website accessible at ctep.cancer.gov.

(d) Other Allowed Dose Delays for Enfortumab Vedotin and Pembrolizumab

[00840] Enfortumab vedotin and/or pembrolizumab may be delayed for situations other than treatment related AEs such as medical/surgical events or logistical reasons not related to study therapy. Subjects should resume study therapy as soon as clinically safe as assessed by the investigator. For delays longer than 6 weeks, the medical monitor should be consulted before resuming study therapy. The reason for delay should be documented in the subject's CRF.

(iii) Cisplatin

(a) Description

[00841] Alone or in combination with other anticancer agents, cis diamminedichloroplatinum (II) (cisplatin) is used in the management of many solid malignancies, including for advanced UC that is no longer amenable to local treatments, such as surgery and/or radiotherapy. Cisplatin is a platinum containing anticancer agent classified as a direct DNA interacting agent.

[00842] Cisplatin is a yellow to orange crystalline powder with the molecular formula $PtCl_2H_6N_2$, and a molecular weight of 300.1. Cisplatin is a heavy metal complex containing a

central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. It is soluble in water or saline at 1 mg/mL.

[00843] Cisplatin injection infusion concentrate is a clear, colorless, sterile aqueous solution available in amber vials. Each 50, 100, or 200 mL amber vial of infusion concentrate contains 1 mg/mL cisplatin, 9 mg/mL sodium chloride, hydrochloric acid and sodium hydroxide to approximate pH of 4.0, and water for injection to a final volume of 50, 100, or 200 mL, respectively. Cisplatin Injection infusion concentrate must be further diluted prior to administration.

(b) Method of Procurement

[00844] Cisplatin is commercially available and details regarding sourcing of cisplatin may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements (CTA).

(c) Dose and Administration

[00845] Subjects that are determined to be cisplatin-eligible per protocol should receive cisplatin.

[00846] Cisplatin is administered with adequate pre- and post-hydration at a dose of 70 mg/m2 on Day 1 (or Day 2 if required by institutional guidelines) of each 3 week cycle as an IV infusion per institutional standards (Arm B). Cisplatin may be administered for a maximum of 6 cycles.

[00847] Weight based dosing of cisplatin is based on the subject's actual body weight. Doses must be adjusted for subjects who experience a ≥10% change in weight from baseline or previous cycle. Subject weight must be measured during all relevant assessment windows as described in the schedule of events as well as per institutional standards, if applicable. Other dose adjustments for changes in body weight <10% are permitted per institutional standard.

[00848] The body surface area used to calculate cisplatin dose may be capped per institutional standards. Split dosing of cisplatin is not allowed. See the cisplatin package insert for detailed instructions.

[00849] Cisplatin dose modifications are shown below in Table 15. Additional details can be found in the package insert.

Table 15. Dose modifications for cisplatin toxicity

Worst Toxicity in Previous Cycle	Cisplatin Dose for Next Cycle[a]
Grade 4 platelets ≥5 days, Grade 4 ANC ≥5 days[b], thrombocytopenic bleeding, or febrile neutropenia	Decrease dose by 25%
Grade 2 neurotoxicity or ototoxicity	Decrease dose by 25% or discontinue depending on risk-benefit
Grade 3 or 4 neurotoxicity or ototoxicity	Discontinue
Other Grade 3 non-hematologic/organ toxicity	Decrease dose by 25%
Other Grade 4 non-hematologic/organ toxicity	Discontinue

a Do not retreat until platelets ≥100,000/μL, ANC ≥1500/μL, and toxicity has recovered to ≤ Grade 2 (Grade 1 for neurotoxicity).

b Growth factor support is allowed per institutional standards.

(d) Dosage with Renal Impairment

[00850] Renal function should return to baseline before subjects are retreated. Cisplatin dosing should be discontinued if creatinine clearance (CrCl) is <30 mL/min. The same method to determine CrCl should be used consistently for a subject over the course of the study with the exception of carboplatin dose calculation where Cockcroft Gault method should be used in all subjects.

[00851] If a subject develops acute kidney injury that fails to resolve during treatment with cisplatin containing therapy, a one time switch from cisplatin to carboplatin for the remaining cycles is permitted if deemed appropriate by the investigator. In the event that kidney function improves, switching back to cisplatin is not permitted. Switching due to lack of response or disease progression is not permitted.

(iv) Carboplatin

(a) Description

[00852] Alone or in combination with other anticancer agents, cis Diammine (cyclobutane 1,1 dicarboxylato)platinum (carboplatin) is used in the management of many solid malignancies, including for advanced UC which is no longer amenable to local treatments, such as surgery and/or radiotherapy, and which is not eligible for treatment with cisplatin as defined by a consensus working group (Galsky 2011). Carboplatin is a platinum containing anticancer agent classified as a cisplatin analog, with similar actions and uses.

[00853] Carboplatin is a crystalline powder with the molecular formula C6H12N2O4Pt and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5 to 7.

[00854] Carboplatin injection is supplied as a sterile, pyrogen free, aqueous solution of carboplatin, USP. Each 50, 150, 450, or 600 mL multidose vial of solution contains 10 mg/mL carboplatin.

(b) Method of Procurement

[00855] Carboplatin is commercially available and details regarding sourcing of carboplatin may vary by site and/or region as outlined in other documents such as CTAs.

(c) Dose and Administration

[00856] Subjects that are determined to be cisplatin-ineligible per protocol should receive carboplatin.

[00857] Carboplatin is administered with adequate pre- and post-hydration at a dose of AUC 4.5, or AUC of 5 according to local guidelines, on Day 1 of each 3 week cycle as an IV infusion per institutional standards (Arm B).

[00858] Carboplatin may be administered for a maximum of 6 cycles.

[00859] The recommended dose of carboplatin is for a targeted AUC of 4.5 mg/mL per minute calculated based on the Calvert formula; carboplatin dose in mg=AUC × (CrCl + 25) administered (with adequate pre- and post-administration hydration) as an IV infusion. The IDMC and/or the sponsor may recommend using a targeted AUC of 5 mg/mL per minute based on the totality of the data available at that time (adjusted carboplatin dose in mg=AUC × [CrCl + 25]). Hydration may be administered during gemcitabine infusions (Arm B). CrCl (mL/min) is estimated by the Cockcroft Gault formula (CrCl [mL/min] = [((140 age) × weight in kgs)/(72 × serum creatinine in mg/dL)] x 0.85 [if female]). The estimated CrCl for calculating carboplatin dose should not exceed 125 mL/min. Body weight may be capped per institutional standards. See the carboplatin package insert for detailed instructions.

[00860] Dosing of carboplatin is based on the subject's actual body weight and estimated CrCl on Day 1 of each treatment cycle.

[00861] If the performance status or renal function of a subject improves during treatment with carboplatin containing therapy such that the subject is deemed eligible for cisplatin therapy, a one time switch from carboplatin to cisplatin for the remaining cycles is permitted if deemed appropriate by the investigator. If the subject experiences a subsequent AE to cisplatin that prevents further treatment, switching back to carboplatin is not permitted and

platinum containing chemotherapy must be discontinued. Switching due to lack of response or disease progression is not permitted.

[00862] Carboplatin dose modifications are shown below in Table 16. Additional details can be found in the package insert.

Table 16. Dose modification for carboplatin toxicity

Worst Toxicity in Previous Cycle	Carboplatin Dose for Next Cycle*
Grade ≥3 platelets and/or thrombocytopenic bleeding, Grade 4 ANC ≥5 days and/or febrile neutropenia	Decrease dose by 25%
Grade 2 neurotoxicity	Hold dose until event resolves to Grade 0 or 1 or discontinue depending on risk-benefit
Grade 3 or 4 neurotoxicity	Discontinue
Other Grade 3 non-hematologic/organ toxicity	Decrease dose by 25%
Other Grade 4 non-hematologic/organ toxicity	Discontinue

* Do not retreat until platelets ≥100,000/μL, ANC ≥1500/μL, and toxicity has recovered to ≤Grade 2 (Grade 1 for neurotoxicity).

(d) Dosage for Renal Impairment

[00863] Renal function should return to baseline before subjects are retreated. Carboplatin dosing should be discontinued if CrCl is <30 mL/min per the Cockcroft Gault formula.

(v) Gemcitabine

(a) Description

[00864] Alone or in combination with other anticancer agents, 4-Amino-1-(2-deoxy-2,2-difluoro-β-D-ribofuranosyl)pyrimidin-2(1H)-one hydrochloride; 2'-Deoxy-2',2'-difluorocytidine hydrochloride (gemcitabine) is a pyrimidine antimetabolite that is structurally similar to cytarabine and has demonstrated antitumor activity in several malignancies. In advanced UC, it is commonly used as a combination product, or in patients that are not eligible for treatment with platinum containing therapy.

[00865] Gemcitabine is a white or almost white powder with a molecular formula $C_9H_{11}F_2N_3O_4 \cdot HCl$ and a molecular weight of 299.66. A 1% solution in water has a pH of 2.0 to 3.0.

[00866] Gemcitabine injection is a clear and colorless to light straw colored solution available in sterile single use vials containing gemcitabine: 200 mg, 1 g, and 2 g. Each mL contains equivalent of 38 mg of gemcitabine in water for injection, USP.

(b) Method of Procurement

[00867] Gemcitabine is commercially available and details regarding sourcing of gemcitabine may vary by site and/or region as outlined in other documents such as CTAs.

(c) Dose and Administration

[00868] Gemcitabine is administered at a dose of 1000 mg/m^2 on Days 1 and 8 of every 3 week cycle as an IV infusion. BSA may be capped per institutional standards.

[00869] Weight based dosing of gemcitabine is based on the subject's actual body weight. Doses must be adjusted for subjects who experience a ≥10% change in weight from baseline or previous cycle. Subject weight must be measured during all relevant assessment windows as described in the schedule of events as well as per institutional standards, if applicable. Other dose adjustments for changes in body weight <10% are permitted per institutional standard.

[00870] Gemcitabine may be administered for a maximum of 6 cycles.

(d) Dose Modifications

[00871] Dose modifications of gemcitabine are allowed per the local label or institutional standards. See the local label for further information.

[00872] The Day 8 dose of gemcitabine must be given within 4 days of the planned dose (Day 8 [–1 to + 4 days]). If the Day 8 dose cannot be administered within this timeframe, the dose should be held until Day 1 of the next treatment cycle.

6.1.6.3 *Concomitant Therapy*

[00873] All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care except for those medications identified as prohibited (see Section 6.1.6.3(iii)).

[00874] All concomitant medications and blood products administered are recorded from Day 1 (predose) through 30 days after the last study treatment, or 90 days after the last study treatment for SAEs related to pembrolizumab (see Section 6.1.7.10(i)(c) and Section 6.1.7.10(i)(f)). Any concomitant medication given for a study protocol related AE should be recorded from the time of informed consent.

(i) Required Concomitant Therapy

[00875] There are no required concomitant therapies.

(ii) Allowed Concomitant Therapy

[00876] During study treatment, palliative radiotherapy on a stable (not growing), symptomatic nontarget bone lesion is allowed and is not considered a subsequent anticancer

therapy. Study treatment should be held for at least 7 days prior to and 14 days following administration of radiation.

[00877] Surgical resection for curative intent, including TUR for papillary lesions, during study treatment may be permitted in subjects with favorable tumor response after discussion with the medical monitor.

[00878] The use of anti emetics is permitted. For subjects randomized to the platinum containing treatment arm, substance P/neurokinin 1 inhibitors (e.g/, Aprepitant), 5 HT3 antagonists (eg, Ondansetron), and short courses (≤1 week) of corticosteroids (eg, Dexamethasone) may be administered per local label and/or institutional guidelines for platinum related nausea prevention.

[00879] Granulocyte stimulating growth factors (e.g., Filgrastim) may be administered on or after Day 9 of each treatment cycle for neutropenia prevention/treatment according to local guidelines.

[00880] The use of insulin is permitted as part of standard of care. Pre-medications for IRRs per Section 6.1.6.4(ii) are permitted; however, prophylactic premedication prior to combination treatment on Cycle 1 Day 1 for prevention of IRRs may not be administered.

[00881] Therapy to manage enfortumab vedotin-associated toxicity as recommended in Section 6.1.6.2(i)(b) is permitted, including hematopoietic growth factors and transfusions.

[00882] Subjects who are receiving strong CYP3A4 inhibitors or P-glycoprotein inhibitors concomitantly with enfortumab vedotin should be monitored for adverse reactions.

[00883] Routine prophylaxis with vaccines is permitted; however, subjects may not be treated with a live, attenuated vaccine during the study and for 90 days after the last dose of study treatment.

[00884] Antimicrobial prophylaxis or ongoing treatment of resolving and/or controlled infection is permitted during the study.

[00885] The following applies to subjects receiving pembrolizumab (Arm A):

[00886] With approval from the medical monitor, concomitant chronic prednisone (or equivalent) may be used at a dose of ≤10 mg/day to manage pre existing conditions. Higher doses of prednisone (or equivalent) are permitted for limited duration to treat acute conditions that arise during the study as medically indicated. The medical monitor should be notified of subjects requiring systemic steroids (≥10 mg prednisone or equivalent) for longer than 24 hours for management of a treatment related AE. Chronic use of inhaled or topical steroids are permitted in the absence of active autoimmune disease.

[00887] All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

(iii) Prohibited Concomitant Therapy

[00888] Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the course of study treatment. If there is a clinical indication for any medication or vaccination specifically prohibited during study treatment, discontinuation of study treatment may be required. The investigator should discuss any questions regarding this with the medical monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study treatment requires the mutual agreement of the investigator, the sponsor, and the subject.

[00889] Listed below are specific restrictions for concomitant therapy or vaccination during the course of study treatment:

- Systemic antineoplastic therapy with the exception of adjuvant hormonal therapy for localized breast or prostate cancer that has undergone definitive treatment
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or enfortumab vedotin
- Radiation therapy (Note: Radiation therapy to a stable (not growing) symptomatic nontarget bone lesion is permitted at the investigator's discretion (see Section 6.1.6.3(ii)).
- Live vaccines within 30 days prior to the first dose of study treatment, while participating in the study, and for 90 days after the last dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist) are live attenuated vaccines and are not allowed.

[00890] Subjects who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from study treatment.

6.1.6.4 *Management of Adverse Reactions*

(i) Overlapping Adverse Reactions

[00891] Some AEs, including rash or skin reactions or pneumonitis/interstitial lung disease (ILD), may represent overlapping toxicities for enfortumab vedotin and pembrolizumab, and attribution to an individual study treatment may be difficult. For overlapping AEs of skin reaction or pneumonitis/ILD, the management actions (i.e., to withhold or discontinue study treatment) should apply to both enfortumab vedotin and pembrolizumab, and the investigator should follow the most conservative dose modification guidelines as described in Section 6.1.6.2(i)(b) (Table 12) and Section 6.1.6.2(ii)(c) (Table 13). However, for Grade 2 skin reactions that are stable (not worsening and in the absence of fever) with supportive measures and not limiting the subject's activities of daily living, continued dosing of enfortumab vedotin may be considered.

(ii) Management of Infusion Reactions – Enfortumab Vedotin

[00892] An IRR may occur during the infusion of study treatment. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards. Supportive measures may include administering medications for IRRs.

[00893] Pre-medications for IRRs are permitted as described below; however, prophylactic premedication prior to combination treatment on Cycle 1 Day 1 for prevention of IRRs may not be administered. Subjects who have experienced an IRR may be premedicated for subsequent infusions. Premedication may include pain medication (e.g., acetaminophen or equivalent), an antihistamine (e.g., diphenhydramine hydrochloride), and a corticosteroid administered approximately 30–60 minutes prior to each enfortumab vedotin infusion or according to institutional standards. Should a subject experience IRRs in the setting of premedication, continued treatment must be discussed with the medical monitor prior to the next planned dose.

[00894] If anaphylaxis occurs, study treatment administration should be immediately and permanently discontinued.

(iii) Management of Infusion Reactions – Pembrolizumab

[00895] For management of infusion reactions, see Table 14, *supra*.

(iv) Infusion-related Reaction of Uncertain Cause

[00896] Anaphylactic like reactions to carboplatin have been reported and may occur within minutes of administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

[00897] Anaphylactic like reactions to cisplatin have been reported. Facial edema, bronchoconstriction, tachycardia, and hypotension may occur within minutes of cisplatin administration. Epinephrine, corticosteroids, and antihistamines have been effectively employed to alleviate symptoms.

[00898] If anaphylaxis occurs, administration of the implicated drug should be immediately and permanently discontinued.

[00899] If a subject experiences an IRR after receiving study treatments and a single cause of the IRR cannot be determined, appropriate sets of guidelines for IRRs must be followed. For chemotherapy combinations, institutional guidelines should be followed.

(v) Supportive Care Guidelines for Pembrolizumab

[00900] Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.1.6.2(ii)(c), and Table 13. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

[00901] Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 13 in Section 6.1.6.2(ii)(c)for guidelines regarding dose modification and supportive care.

[00902] It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

(vi) Management of Hyperglycemia

[00903] Investigators should monitor blood glucose levels and are advised to perform additional assessments if any symptoms of hyperglycemia are observed, including a thorough

evaluation for infection. In addition, if steroids are used to treat any other condition, blood glucose levels may require additional monitoring. If elevated blood glucose levels are observed, subjects should be treated according to local standard of care and referral to endocrinology may be considered.

[00904] Subjects, especially those with a history of or ongoing diabetes mellitus or hyperglycemia, should be advised to immediately notify their physician if their glucose level becomes difficult to control or if they experience symptoms suggestive of hyperglycemia such as frequent urination, increased thirst, blurred vision, fatigue, and headache.

[00905] Subjects who enter the study with an elevated HbA1c (≥6.5%) at baseline should be referred to an appropriate provider during Cycle 1 for glucose management. Blood glucose should be checked prior to each dosing and dose should be withheld for blood glucose >250 mg/dL (Grade 3 or higher). Dosing may continue once the subject's blood glucose has improved to ≤ Grade 2 and subject is clinically and metabolically stable. The use of insulin is permitted as part of standard of care. Blood glucose >500 mg/dL (Grade 4) considered related to enfortumab vedotin requires drug interruption and a full evaluation of the hyperglycemia to determine the underlying diagnosis. Once hyperglycemia/elevated blood glucose has improved to ≤ Grade 2, drug dosing may resume with close monitoring after consultation with medical monitor.

(vii) Management of Rash Related to Enfortumab Vedotin

[00906] Enfortumab vedotin is a Nectin 4 directed antibody drug conjugate. Nectin 4 is a cell adhesion molecule that is highly expressed in urothelial carcinoma. Low to moderate levels of Nectin 4 are also expressed on normal tissues, including skin keratinocytes, sweat glands and hair follicles; thus, skin reactions are anticipated events. As such, skin reactions are adverse events of interest in all clinical studies with enfortumab vedotin.

[00907] A cumulative review of post marketing safety data from 18 Dec 2019 (the approval date of enfortumab vedotin in the US) through 22 Oct 2020 identified reports of severe cutaneous adverse reactions in 15 patients receiving enfortumab vedotin, some of whom had fatal outcomes. These reactions occurred predominantly during the first cycle of treatment. Adverse events reported in these cases included SJS (5 cases), blister (3 cases), dermatitis bullous (3 cases), symmetrical drug related intertriginous and flexural exanthema (SDRIFE; 2 cases), and 1 case each of dermatitis exfoliative, exfoliative rash, epidermal necrosis, oropharyngeal blistering, stomatitis, and TEN.

[00908] In enfortumab vedotin monotherapy studies of urothelial carcinoma, SAEs of severe cutaneous adverse reactions were reported in 11 of 749 subjects (1.5%) and included dermatitis bullous (0.4%), drug eruption (0.4%), blister (0.1%), conjunctivitis (0.1%), SJS (0.1%), stomatitis (0.1%), and toxic skin eruption (0.1%).

[00909] Subjects should be informed that rash and severe skin reactions have occurred after administration of enfortumab vedotin and to contact the Investigator immediately if they have signs and symptoms of skin reactions, oral mucosal and ocular abnormalities including mucositis or conjunctivitis. Starting in the first cycle and throughout treatment, closely monitor subjects for skin reactions. For mild to moderate skin reactions, consider appropriate treatment, such as topical corticosteroids and antihistamines as clinically indicated. For recommendations regarding dose modifications for skin reactions due to enfortumab vedotin, refer to Section 6.1.6.2(i)(b).

(viii) Management of Pneumonitis/ILD Related to Enfortumab Vedotin

[00910] Severe, life-threatening or fatal pneumonitis/ILD have occurred in patients receiving enfortumab vedotin. Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. For recommendations regarding dose modifications for pneumonitis/ILD due to enfortumab vedotin, refer to Section 6.1.6.2(i)(b).

6.1.6.5 *Management of Overdose*

(i) Enfortumab Vedotin

[00911] Weight based dosing for enfortumab vedotin is based on the subject's actual body weight, with the exception of subjects weighing greater than 100 kg; doses is based on 100 kg for these individuals. The maximum dose calculated per cycle in this study is 125 mg.

[00912] In the event of an overdose of enfortumab vedotin >10%, study personnel should:

- Care for and medically stabilize the subject until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of enfortumab vedotin.
- Notify the Medical Monitor as soon as they become aware of the overdose, to discuss details of the overdose (eg, exact amount of enfortumab vedotin administered, subject weight) and AEs, if any.

(ii) Pembrolizumab

[00913] For this study, an overdose of pembrolizumab is defined as ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of

pembrolizumab. In the event of an overdose, the site should notify the sponsor as soon as they are aware of the overdose. The subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

(iii) Cisplatin

[00914] For cisplatin, the maximum dose calculated per cycle in this study is 70 mg/m^2. In the event of an overdose (≥10% of the calculated dose) of cisplatin, the event should be managed according to the product label and/or institutional standard of care, and promptly reported to the sponsor.

(iv) Carboplatin

[00915] For carboplatin, the maximum dose calculated per cycle in this study is calculated using an AUC=5. In the event of an overdose (≥10% of the calculated dose) of carboplatin, the event should be managed according to the product label and/or institutional standard of care, and promptly reported to the sponsor.

(v) Gemcitabine

[00916] For gemcitabine, the maximum dose calculated per cycle in this study is 1000 mg/m^2. In the event of an overdose (≥10% of the calculated dose) of gemcitabine, the event should be managed according to the product label and/or institutional standard of care, and promptly reported to the sponsor.

6.1.6.6 *Treatment Compliance*

[00917] Study drug administration is performed by study site staff and documented in source documents and the CRF.

6.1.6.7 *Treatment Duration*

[00918] Enfortumab vedotin may be administered for an unlimited number of cycles until a protocol defined reason for treatment discontinuation occurs. Pembrolizumab may be administered for a maximum of 35 cycles or a protocol defined reason for treatment discontinuation occurs, whichever is first. Cisplatin, carboplatin, and/or gemcitabine may be administered for a maximum of 6 cycles or a protocol defined reason for treatment discontinuation occurs, whichever is first.

[00919] Subjects may continue on study treatment until one of the following protocol defined reasons for treatment discontinuation occurs:

- Progressive disease (BICR confirmed or clinical progression [see Section 6.1.7.4])

- Confirmed progressive disease per iRECIST (Section 6.1.14) as assessed by investigator in subjects in study Arm A treated beyond BICR confirmed disease progression (see criteria below)

- AE
- Pregnancy
- Investigator decision
- Start of a subsequent anticancer therapy
- Subject decision, non AE
- Study termination by the sponsor.
- Completion of study treatment
- Other, non AE

[00920] In Arm A, subjects who experience an unacceptable AE that is attributable only to pembrolizumab may continue on enfortumab vedotin monotherapy until a protocol defined reason for treatment discontinuation. Subjects who experience toxicity that is attributable only to enfortumab vedotin may continue on pembrolizumab monotherapy up to a maximum of 35 cycles.

[00921] In Arm B, subjects who experience an unacceptable AE that is attributable only to platinum containing chemotherapy may continue on gemcitabine for up to 6 cycles. Subjects who experience an unacceptable AE that is attributable only to gemcitabine may continue on platinum containing chemotherapy for up to 6 cycles.

[00922] Subjects in Arm A may be treated beyond disease progression per RECIST v1.1 provided they are deriving clinical benefit, as defined by all of the following:

- Improvement in clinical symptoms or functional status as assessed by the investigator
- No decline in WHO or ECOG performance status attributable to disease progression
- Absence of symptoms or signs (including worsening laboratory values) of unequivocal disease progression
- Absence of disease progression at critical anatomic sites (eg, CNS, spinal cord compression)

[00923] The subject should additionally be informed of other available treatment options. If all of the above criteria have been met, the subject may be treated beyond disease progression per RECIST v1.1. Protocol treatment must be discontinued upon confirmed disease progression by iRECIST per investigator (see Section 6.1.14).

[00924] Study drug that is discontinued cannot be subsequently restarted.

6.1.7 Study Assessments

6.1.7.1 *Screening/Baseline Assessments*

[00925] Only subjects who meet all inclusion and exclusion criteria specified in Section 6.1.5 are enrolled in this study.

[00926] Subject medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant medications.

6.1.7.2 *Locally Advanced or Metastatic Urothelial Cancer*

[00927] Acquisition of a new tumor biopsy tissue or collection of an archived tumor specimen, an ophthalmologic examination (see Table 20), brain scan (MRI with gadolinium contrast preferred; see Section 6.1.12 for preferred imaging methods), bone scan, CT scan with contrast (preferred; see Section 6.1.12 for preferred imaging methods) for baseline tumor imaging, INR/PT/PTT, urinalysis (with reflexive microscopy, if abnormal), HbA1c, amylase, lipase, and thyroid function tests are required for all subjects at screening. A pregnancy test (either urine or serum, for females of childbearing potential), physical examination (including weight), collection of height, vital signs, CBC with differential, serum chemistry panel, CrCl (see Section 6.1.7.10(ii)), ECOG performance status assessment, and ECG are required at baseline.

6.1.7.3 *Randomization*

[00928] Randomization occurs at Day –3 to 1, prior to the first dose of study drug.

6.1.7.4 *Response/Efficacy Assessments*

[00929] CT scans with contrast (unless contraindicated), including chest, abdomen, and pelvis at the minimum, are used to assess antitumor activity at protocol specified time points. Subjects must receive the same imaging method throughout the study for response assessments. For subjects who cannot receive CT scans with contrast, MRI may be used as long as it continues to be used for all disease assessments. Bone imaging and/or brain scans should be repeated at disease assessment time points, and as clinically indicated throughout the study, in subjects with a history of skeletal metastasis or suspicion of skeletal metastasis based on imaging or symptoms, or a history of CNS metastasis or signs/symptoms of CNS metastasis. Other regions should be scanned if the subject has known disease or new symptoms suggestive of disease in that region.

[00930] Objective responses are assessed according to RECIST v1.1 (Eisenhauer 2009) (**FIG. 3A, FIG. 3B, and FIG. 3C**) by BICR. Response assessments should be performed every 9 weeks (±1 week) timed from the randomization date until 18 months after randomization, then every 12 weeks (±1 week) thereafter. Tumor imaging should also be performed, and BICR evaluation triggered, whenever disease progression is suspected. Objective responses are also assessed according to iRECIST per investigator assessment for all subjects in Arm A.

[00931] Treatment beyond disease progression per RECIST v1.1 may be considered for subjects in study Arm A who are deriving clinical benefit as defined in Section 6.1.6.7. Subjects treated beyond disease progression per RECIST v1.1 may continue until confirmed disease progression per iRECIST (Seymour 2017) (Section 6.1.14) as assessed by the investigator. Confirmatory scans must be performed 4 to 9 weeks after disease progression per RECIST v1.1 by BICR (see Table 17).

Table 17. Imaging and treatment after first radiologic evidence of progressive disease

	Clinically Stable	
	Imaging	Treatment
First radiologic evidence of PD by RECIST v1.1 per BICR	Repeat imaging at 4 to 9 weeks to confirm PD.	May continue study intervention after the subject's consent and at the investigator's discretion while awaiting confirmed PD by iRECIST per investigator assessment.
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment.	No additional imaging required.	Discontinue treatment
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment.	Repeat imaging at next regularly scheduled imaging visit. If this scan is within 4 weeks of the next scheduled timepoint, it can be used to satisfy both imaging timepoints.	Continue study intervention at the investigator's discretion.
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study intervention at the investigator's discretion.

iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iPR=iRECIST partial response; iRECIST=modified Response Evaluation Criteria in Solid

Tumors 1.1 for immune based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease

Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the CRO, but no expedited review occurs.

[00932] In the event disease progression is suspected by the investigator, the images must be transferred to the Imaging Contract Research Organization (CRO) for expedited BICR. The investigator seeking an expedited review should indicate this request to the Imaging CRO on a designated form. In all instances, the process at the Imaging CRO ensures that the BICR remains blinded to the results of the local assessment and to the nature of the review. The result of the BICR is communicated directly to the trial site.

[00933] Every effort should be made to continue the subject on study treatment during the BICR period, as long as it is clinically acceptable. If the BICR verifies disease progression, the subject must permanently discontinue study treatment unless they are eligible per the criteria in Section 6.1.6.7 for treatment beyond disease progression per iRECIST.

[00934] If the BICR does not verify disease progression, every effort must be made to continue study treatment, as long as it is clinically acceptable. Subjects should continue on trial radiological evaluation.

[00935] Subjects who discontinue study treatment for reasons other than radiographically confirmed disease progression per BICR or consent withdrawal continue to receive CT scans with contrast (unless contraindicated) every 9 weeks (±1 week) for the first 18 months timed from the randomization date, then every 12 weeks (±1 week) until the subject has BICR confirmed disease progression per RECIST v1.1, dies, the study closes, or the subject withdraws consent, whichever occurs first. For subjects that initiate subsequent anticancer therapy prior to disease progression per BICR, response assessment should be continued and submitted until BICR confirmed disease progression. Sites should contact the medical monitor prior to discontinuing study disease assessments and/or initiating subsequent anti cancer therapy.

[00936] Survival status and information on subsequent anticancer therapy is updated every 12 weeks (±1 week) until death, withdrawal of consent, lost to follow up, or study closure, whichever occurs first.

[00937] Subjects' clinical data must be available for CRF source verification. Copies of tumor images must be made available.

6.1.7.5 *Pharmacokinetic and Immunogenicity Assessments*

[00938] Blood samples for PK and ATA are collected for Arm A only, per the sample collection schedule provided in Table 18. Validated or qualified assays are used to measure the concentrations of enfortumab vedotin and MMAE in serum or plasma. A validated assay is used to determine the levels of ATA for enfortumab vedotin in serum. PK and ATA samples for pembrolizumab are collected. Determination of serum levels for pembrolizumab concentrations and pembrolizumab ATA is performed only if required.

[00939] If at some point prospective PK blood sample collection is no longer required, sites are notified.

6.1.7.6 *Biomarker Studies*

[00940] To identify markers of sensitivity, resistance, and possible AEs, samples for biomarker analyses are collected at protocol specified time points (see Table 18). All subjects must provide pre treatment tumor non decalcified tissue collected by core needle biopsy or excision for biomarker analysis (fine needle aspirate is not acceptable). Archived tumor tissue, not previously irradiated, should be collected after completion of the most recent prior systemic therapy, ideally within 12 months prior to enrollment, if possible. If adequate archival tumor samples are not available, a fresh biopsy may be performed. A formalin fixed, paraffin embedded (FFPE) tumor block is preferred.

[00941] To understand the relationship between the biological characteristics of tumors before treatment and subject outcomes, tumor tissue from pre treatment biopsies are examined. Tumor tissue from any standard of care biopsies may also be collected to assess the on treatment effects of enfortumab vedotin. Subjects are stratified prior to randomization according to PD L1 status (PD L1 high: CPS $\geq$10 and PD L1 low: CPS <10 based on Dako/Agilent PD L1 IHC 22C3 PharmDx). Exploratory biomarker assessments on pre treatment tumor tissue may include, but are not limited to, Nectin 4 expression, assessment of tumor subtyping, tumor microenvironment, and mutations associated with response to enfortumab vedotin in metastatic UC. Biomarkers from serially collected peripheral blood and urine may include, but are not limited to, cell free tumor DNA, cytokines, and T cell clonality analyses as markers of tumor response or resistance. Methods of analysis may include, but are not limited to, IHC, next generation sequencing of DNA and RNA, and immunoassays. These assessments are compared to similar assessments conducted in enfortumab vedotin monotherapy trials and may provide insight into treatment related changes.

Table 18. Pharmacokinetic, immunogenicity, and biomarker sample collection time points

	Study Day	Time	Window	Relative Time	Pharmacokinetics and Immunogenicity **(Arm A only)**				Blood Biomarkers (All arms)		Urine Biomarkers (All arms)	Tissue Biomarkers (All arms)
					EV PK	Pembro PK	ATA EV	ATA Pembro	Serum	Plasma	Urine	Tumor Tissue
Screening	Days –42 to RND	N/A	N/A	N/A								X
Cycles 1 and 2	Day 1	Predose	Within 4 h	Start of EV, gemcitabine or platinum infusion	X	X[A]	X	X	X	X	X[A]	
		End of EV IV infusion	Within 15 min	End of EV infusion	X							
		End of Pembro IV infusion	Within 15 min	End of Pembro infusion		X[A]						
	Day 8	Predose	Within 4 h	Start of EV infusion	X							
		End of EV IV infusion	Within 15 min	End of EV infusion	X							
Cycle 3 and every odd-numbered cycle thereafter	Day 1	Predose	Within 24 h	Start of EV, gemcitabine or platinum infusion	X[C]	X[C]	X[C]	X[C]	X[B]	X[B]	X[B]	

	Study Day	Time	Window	Relative Time	Pharmacokinetics and Immunogenicity **(Arm A only)**				Blood Biomarkers (All arms)		Urine Biomarkers (All arms)	Tissue Biomarkers (All arms)
					EV PK	Pembro PK	ATA EV	ATA Pembro	Serum	Plasma	Urine	Tumor Tissue
End of Treatment (within 30–37 days of last dose)				N/A	X	X	X	X	X	X	X	

RND=randomization.

A Cycle 1 only.

B Cycle 3 and 5.

C Up to Cycle 9 only.

WO 2025/064741 PCT/US2024/047585

6.1.7.7 *Biospecimen Repository*

[00942] In the US only, for subjects who provide additional consent, remaining de-identified unused blood and/or tissue and/or urine are retained by Seagen and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of ADC sensitivity and resistance mechanisms, and the identification of biomarkers of ADCs. Blood, urine, and tissue samples donated for future research are retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples are destroyed after the study has been completed and all applicable regulatory obligations have been met.

6.1.7.8 *Electronic Patient Reported Outcomes (ePRO)*

[00943] Electronic PRO assessments include the EuroQOL 5 dimensions (EQ 5D 5L), EORTC Quality of Life Core 30 (QLQ C30), Brief Pain Inventory – Short Form (BPI SF), and HRU questionnaires. Electronic PROs are administered per the schedule outlined in Table 19.

Table 19. Electronic Patient Reported Outcomes Schedule of Events

	ePRO Assessment Timepoints				
Questionnaires[a]	Week 0	Week 1	Weeks 2[b] to 12	Week 14	Week 17+
Time Interval	Day 1	+3 to 4 days from Week 0	Weekly	Once	Every 3 weeks[c]
EuroQOL 5-dimensions	X	X	X	X	X
Brief Pain Inventory – Short Form	X	X	X	X	X
EORTC Quality of Life Core 30	X	X	X	X	X
Healthcare Resource Utilization	X	X	X	X	X

EORTC=European Organisation for Research and Treatment of Cancer; ePRO=electronic patient reported outcome; QOL=quality of life.

a If study procedures/assessments are performed on ePRO completion day, questionnaires should be done first.

b Week 2 questionnaires are completed on Days 11 to 12.

c Through disease progression and survival follow up.

Table 20. Schedule of events

		Screening/ Baseline			Every 3-week Cycle			EOT	Follow-up	Survival Follow-up
	Day	D –42 to RND	D –28 to RND	D –7 to RND	D1[A]	D8[A]	D15	Within 30 to 37 d of last dose[B]	Every 9 weeks[G]	Every 12 weeks
	Visit window[W]				±2 d[U]	–1 to +4 d	±1 d		±7 d	±7 d
Screening/Baseline Assessments	Inclusion/Exclusion, medical history		X							
	Informed consent	X								
	Acquire and submit archival or fresh tumor biopsy tissue[C]	X								
	Ophthalmologic examination[D]		X							
	Brain scan (if indicated)		X[E]		X[R]			X[R]	X[R]	
	Bone scan		X[E]		X[R]			X[R]	X[R]	
	INR/PT/PTT		X							
	HbA1c[N]		X							
	Urinalysis (with reflexive microscopy, if abnormal)		X							
	Pregnancy test (urine or serum; only for females of childbearing potential)			X[Q]	X			X		
	Randomization[Y]			X						
Safety Assessments	Physical exam (including weight)			X	X[F,T]			X	X[G]	
	Height			X						
	Vital signs			X	X[T]	X[T]		X		
	CBC with differential[O]			X	X[F,T]	X[T]	X[Z]	X		
	Serum chemistry panel[O]			X	X[F,S,T]	X[S,T]	X[Z]	X		
	Amylase		X							
	Lipase		X							

		Screening/ Baseline			Every 3-week Cycle			EOT	Follow-up	Survival Follow-up
	Day	D –42 to RND	D –28 to RND	D –7 to RND	D1[A]	D8[A]	D15	Within 30 to 37 d of last dose[B]	Every 9 weeks[G]	Every 12 weeks
	Visit window[W]				±2 d[U]	–1 to +4 d	±1 d		±7 d	±7 d
	CrCl[BB]			X						
	Thyroid function tests[X]		X		X[F]					
	ECOG performance status			X	X[F,T]			X	X[G]	
	ECG			X						
	Transthoracic ECHO or MUGA[AA]	X								
	Concomitant medications	Related to study procedures[H]			Collect from Day 1 (predose) through 30 days (AEs/SAEs) post last dose, or 90 days (SAEs related to pembrolizumab) post last dose (30 days post last dose if new anticancer therapy is started). For AESIs, AEs and concomitant medications may be followed until AE resolution, return to baseline, subject withdrawal, study closure, or the event becomes chronic.				
	Adverse event collection									
Patient-Reported Outcome Assessments	Quality of Life (QOL) and Pain Assessment				See Electronic Patient-Reported Outcomes Schedule of Events table for assessment details[V]					
	Healthcare Resource Utilization (HRU)									
Treatment	Enfortumab vedotin administration[P]				X	X				
	Pembrolizumab administration[I]				X					
	Gemcitabine administration[I]				X	X				
	Cisplatin administration[I]				X					
	Carboplatin administration[I]				X					
PK/Immunogenicity/ Biomarker	Blood, urine and tissue sample collection	See PK, Immunogenicity, and Biomarker table for sample collection details[A]								
Response Assessment	CT/MRI scan with contrast[J]		X		X[K]			X[L]	X[K]	
	Survival status									X[M]

RND=Randomization

A See Table 18 for PK, immunogenicity, and biomarker sampling.

B EOT evaluations should be obtained before the initiation of non protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.

C Archival tumor tissue must be available for participation in the study. Archived tumor tissue, not previously irradiated, should be collected after completion of the most recent prior systemic therapy, ideally within 12 months prior to enrollment, if possible. If adequate archival tumor sample is not available, a new biopsy may be performed. Tumor FFPE block is preferred. Core needle biopsy or excision of non decalcified tissue is required (fine needle aspirate is not acceptable).

D A complete ophthalmologic examination includes, but is not limited to, visual acuity, slit lamp, tonometry examination and dilated fundus examination. Subsequent ophthalmology assessments should be performed as clinically indicated. End of treatment slit lamp examinations are required for subjects who experience corneal AEs during the study and must be performed ≥4 weeks from last dose.

E Brain scans are conducted at screening/baseline in subjects with a history of CNS metastasis or signs/symptoms of CNS metastasis. Bone scans are conducted at screening/baseline in subjects with a history of skeletal metastasis or suspicion of skeletal metastasis based on imaging or symptoms. See Section 6.1.12 for preferred imaging methods.

F Clinical laboratory assessments, physical exam, weight, and ECOG performance status are not required if performed within 1 day prior to administration of study drug.

G Subjects who discontinue study treatment for reasons other than BICR confirmed radiographically confirmed disease progression by RECIST v1.1 guidelines or consent withdrawal have physical exams, ECOG, and disease assessments every 9 weeks (±1 week) for the first 18 months timed from the randomization date, then every 12 weeks (±1 week) until the subject has BICR confirmed radiologically confirmed disease progression (per RECIST v1.1), subject death, study closure, or withdrawal of consent, whichever occurs first. ECOG status and physical

exams may be discontinued at start of subsequent anticancer therapy. Palliative radiotherapy on a nontarget lesion that is not progressing is not considered a subsequent anticancer therapy; however, radiotherapy on any new or progressing target lesion is a subsequent anticancer therapy.

H From time of informed consent.

I On Day 1 of each cycle, pembrolizumab should be administered approximately 30 minutes after completion of enfortumab vedotin administration (Arm A). On Day 1, or Day 2 if required per institutional standards for cisplatin, of each cycle, cisplatin or carboplatin and gemcitabine should be administered per institutional standard (Arm B).

J Computed tomography (CT) scan with contrast, including chest, abdomen, and pelvis. Other regions should be scanned if the subject has known disease or new symptoms suggestive of disease in that region. Response assessment is evaluated using RECIST v1.1.

K Response assessment is performed every 9 weeks (±1 week) from the randomization date. Objective responses are confirmed per RECIST v1.1 with repeat scans done at the next scheduled scan per protocol. Subsequent scans are to be performed every 9 weeks ((±1 week) until 18 months after randomization, then every 12 weeks (±1 week). Tumor imaging should also be performed whenever disease progression is suspected.

L Not required if conducted <4 weeks prior to EOT.

M Contact subject for survival status and collection of subsequent anticancer treatment information every 12 weeks (±1 week) after BICR-confirmed radiologically-confirmed progressive disease per RECIST v1.1 guidelines until death, study closure, lost to follow up, or subject withdraws consent, whichever occurs first. Additional follow up contacts may be required per sponsor request for analysis purposes.

N If HbA1c is elevated (≥6.5%), refer subject to appropriate provider during Cycle 1 for glucose management.

O Safety labs may be collected 1 day prior to dosing.

P At least 6 days must elapse between doses of enfortumab vedotin

Q Either serum or urine pregnancy test. May be performed within 1 day prior to administration of study drug.

R Brain scans should be repeated every 9 weeks (± 1 week) for the first 18 months timed from the randomization date, then every 12 weeks (±1 week) thereafter, and as clinically indicated in subjects with a history of CNS metastasis or signs/symptoms of CNS metastasis. Bone

imaging should be repeated every 9 weeks (± 1 week) for the first 18 months timed from the randomization date, then every 12 weeks (±1 week) thereafter, and as clinically indicated in subjects with a history of skeletal metastasis or suspicion of skeletal metastasis based on imaging or symptoms. See Section 6.1.12 for preferred imaging methods.

S Verify blood glucose is <250 mg/dL prior to dosing. Subjects with diabetes must be tested in the clinic and blood glucose must be <250 mg/dL prior to dosing. Use of insulin is permitted as part of the standard of care.

T Procedures should be conducted pre dose.

U Window applies to Cycle 2+

V The EQ 5D 5L, BPI SF, EORTC QLQ C30, and HRU questionnaires are completed in clinic at Cycle 1 Day 1 before any study procedures/assessments. Questionnaires are completed by the subject at home in between clinic visits on the ePRO device beginning with Cycle 1 Day 4 or 5, once weekly for the first 12 weeks, on Week 14 and once every 3 weeks for the remainder of the study through disease progression and survival follow up. See Section 6.1.7.8; Table 19.

W Visit windows do not apply to QOL, Pain, or HRU assessments.

X Thyroid function tests (see Section 6.1.7.10(ii)) should be conducted for all subjects at screening/baseline. Subjects in Arm A should be tested at Cycle 2, and every even cycle thereafter. Subjects in Arm B should be tested as clinically indicated.

Y All screening/baseline procedures should occur prior to randomization. Randomization is allowed at Day –3 to 1 and must occur prior to the first dose of study drug.

Z Cycles 1 and 2 only, unless clinically indicated.

AA A transthoracic echocardiogram or multiple gated acquisition (MUGA) scan with left ventricular ejection fraction (LVEF) is required for subjects with NYHA Class III Heart Failure or a history of coronary heart disease, arrhythmia, or other significant heart disease.

BB The same method to determine CrCl should be used consistently for a subject over the course of the study with the exception of carboplatin dose calculation, where the Cockcroft Gault method should be used in all subjects.

[00944] Questionnaires are completed by the subject on an electronic device. On Cycle 1 Day 1, subjects complete the questionnaires in the clinic up to 24 hours prior to the first dose of study treatment and before any study procedures/assessments are conducted. After Cycle 1 Day 1, questionnaires are completed at home several days prior to a clinic visit. Subjects are provided with digital support (e.g., instruction) to fill in the questionnaires at home in between clinic visits, with the exception of Cycle 1 Day 1. The ePRO device notifies subjects to complete the questionnaires at the appropriate time points. This ensures that data are collected in between study treatments.

[00945] The information completed by the subject on the electronic device is automatically uploaded into a central website. The investigator or site designee closely monitors the questionnaire data on the website for each subject during study treatment and the follow up period and address any compliance issues that may arise. If a subject does not complete the questionnaires per protocol, the investigator or site designee should document the event as a protocol deviation.

[00946] The investigator or site designee, and site personnel are trained on how to provide support to each subject on the use of the ePRO device. Refer to the ePRO site user guide for additional information on the questionnaire schedule and ePRO device operation.

(i) **EORTC Core Quality of Life (QLQ-C-30) Questionnaire**

[00947] The QLQ C30 was developed to measure aspects of QOL pertinent to patients with a broad range of cancers who are participating in clinical trials (Aaronson 1993; Sneeuw 1998). The current version of the core instrument (QLQ C30, Version 3) is a 30 item questionnaire consisting of the following:

- 5 functional domains (physical, role, cognitive, emotional, social)
- 3 symptoms scales (fatigue, pain, nausea and vomiting)
- Single items for symptoms (shortness of breath, loss of appetite, sleep disturbance, constipation, diarrhea) and financial impact of the disease, and
- 2 global items (health, overall QOL)

[00948] Each domain is scored from 0 to 100. For the global health status/QOL and functional domain scores, higher scores represent better QOL and functioning, respectively. For symptom scales, higher scores represent greater symptomatology (see **FIG. 4**).

(ii) **EuroQol-5 Dimensions**

[00949] The EQ-5D is a standardized instrument developed by the EuroQOL Group for use as a generic, preference based measure of health outcomes. It is applicable to a wide range of

health conditions and treatments and provides a simple descriptive profile and a single index value for health status. The EQ 5D is a 5 item self reported measure of functioning and well being, which assesses 5 dimensions of health, including mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises 3 levels (no problems, some/moderate problems, extreme problems). A unique EQ 5D health state is defined by combining 1 level from each of the 5 dimensions. Responses to the 5 items are then converted to a weighted health state index (utility score) based on values derived from general population samples (Herdman 2011). The health utility score is between 0 and 1, where 0 is death and 1 is perfect health. In addition to the utility score, this questionnaire also records the respondent's self rated health status on a vertical graduated (0 to 100) visual analogue scale (VAS) (See **FIG. 5**).

6.1.7.9 *Brief Pain Inventory – Short Form (BPI-SF)*

[00950] The BPI SF is a validated PRO designed to assess the severity of pain and its impact on functioning specifically in the clinical trial setting (Cleeland 1994; Atkinson 2011). The BPI SF measures worst, least, and average pain experienced in the last 24 hours, the location of the pain and the medications used for treatment of the pain. Additionally, it also asks questions about the interference due to pain in general activity, mood, walking, normal work, relationships, sleep and enjoyment of life. The pain severity and interference questions are answered on a 10 point Likert scale and scoring is calculated using arithmetic mean of the four severity items to provide measurement of the pain severity and the arithmetic mean of the seven interference items to measure of pain interference. Individual scores for each severity item as well as each interference item can also be done. Higher scores are associated with higher pain levels.

6.1.7.10 *Safety Assessments*

[00951] The assessment of safety during the course of this study consists of the surveillance and recording of AEs, including SAEs, recording of concomitant medication, and measurements of protocol specified physical examination findings, vital signs, protocol specified laboratory tests, ECOG status, ECGs, ophthalmologic examination findings and pregnancy testing.

[00952] Safety is monitored over the course of the study by an IDMC.

(i) **Adverse Events**

(a) Definitions

[00953] **Adverse Event**

[00954] According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations 312.32, Investigational New Drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a subject or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

[00955] The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events and Pre existing Conditions CRF:

- From the time of informed consent through the day prior to study Day 1 only study protocol related AEs should be recorded. A protocol related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (during and post dose) through the end of the safety reporting period (see Section 6.1.7.10(i)(c)). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record “anemia” rather than “low hemoglobin”).

[00956] **Serious Adverse Events**

[00957] An AE should have been classified as an SAE if it met one of the criteria in Table 21 below.

Table 21. SAE Criteria

Fatal:	AE resulted in death
Life threatening:	The AEs placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical

Fatal:	AE resulted in death
	procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 6.1.7.10(i)(b) for the definition of potential DILI.)

[00958] Adverse Event Severity

[00959] AE severity should be graded using the NCI CTCAE, version 4.03.

[00960] AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for SAEs, above).

[00961] Relationship of the Adverse Event to Study Treatment

[00962] The relationship of each AE to enfortumab vedotin, pembrolizumab, and/or cisplatin or carboplatin, and gemcitabine and cisplatin or carboplatin should be evaluated by the investigator using the criteria in Table 22 below.

Table 22. Evaluation Criteria

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

Unrelated:	Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

(b) Procedures for Eliciting and Recording Adverse Events

[00963] Investigator and study personnel report all AEs and SAEs whether elicited during subject questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

[00964] **Eliciting Adverse Events**

[00965] An open ended or non directed method of questioning should be used at each study visit to elicit the reporting of AEs.

[00966] **Recording Adverse Events**

[00967] The following information should be recorded on the Adverse Events and Pre existing Conditions CRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

[00968] **Diagnosis vs. Signs or Symptoms**

[00969] In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

[00970] Important exceptions for this study are adverse reactions associated with the infusion of study drug. For this study, adverse reactions associated with the infusion of study drugs must be recorded as a NCI CTCAE term, which includes IRR, or a more specific diagnosis if appropriate (ie, 'cytokine release syndrome,' 'acute infusion reaction,' or 'allergic or hypersensitivity reaction'). Each sign or symptom that occurs within a given infusion related event (ie, chills, fever, rash) must also be recorded. Level of severity for both the overall IRR term and the individual signs and symptoms should be recorded.

[00971] Recording Serious Adverse Events

[00972] For SAEs, record the event(s) on both the CRF and an SAE form.

[00973] The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

[00974] Progression of the Underlying Cancer

[00975] Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms "Disease Progression", "Progression of Disease", or "Malignant disease progression" and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs.

[00976] Pregnancy

[00977] Notification to Drug Safety: Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 6 months after the last dose of study drug(s) including any pregnancies that occur in the partner of a study subject who is able to father a child. Only report pregnancies that occur in a subject's partner if the estimated date of conception is after the subject's first study drug dose. Email or fax to the sponsor's Drug Safety Department within 48 hours of becoming aware of a pregnancy. As part of the study all pregnancies are monitored for the full duration and all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

[00978] Collection of data on the CRF: All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s) are also recorded on the Adverse Events CRF.

[00979] Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 6.1.7.10(i)(a)) should be reported as SAEs.

[00980] Corneal Adverse Events

[00981] Corneal ulcer or keratitis AEs ≥ Grade 2 should be graded within their respective NCI CTCAE categories. Grade 1 corneal ulcer or keratitis AEs should be graded per "Eye disorders – Other, specify" criteria. Other corneal AEs should be recorded and graded per "Eye disorders – Other, specify" criteria.

[00982] **Diabetes and Hyperglycemia**

[00983] Grading for diabetes should be based on the NCI CTCAE v4.03 event term of glucose intolerance. Grading for hyperglycemia should be based on the NCI CTCAE v4.03 event term of hyperglycemia.

[00984] **Potential Drug Induced Liver Injury**

[00985] The observation of the critical importance of altered liver function has been referred to informally as Hy's Law (Reuben 2004). Hy's Law can be used to estimate severity and the likelihood that a study drug may cause an increased incidence of severe hepatotoxicity.

[00986] The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential hepatotoxicity in the clinical setting(s) being studied. However, finding 1 Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe DILI.

(i) Definition

[00987] Briefly, potential Hy's Law cases include the following 3 components:

1. Aminotransferase (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) elevation >3x upper limit of normal (ULN)

AND

2. Total bilirubin >2x ULN, without initial findings of cholestasis (i.e., elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

(ii) Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

[00988] In general, an increase of serum ALT or AST to >3x ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

[00989] Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, consider withholding study drug.

(c) Reporting Periods for Adverse Events and Serious Adverse Events

[00990] The safety reporting period for all AEs and SAEs (except SAEs related to pembrolizumab) is from study Day 1 (predose) through 30 days after the last study treatment. However, all study protocol related AEs are to be recorded from the time of informed consent. The reporting period for SAEs related to pembrolizumab is from study Day 1 (predose) through 90 days after the last study treatment, or 30 days following cessation of study treatment if the subject initiates a new anticancer therapy. All SAEs that occur after the safety reporting period and are considered study treatment related should also be reported.

[00991] SAEs are followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the subject dies or withdraws consent. All non serious AEs are followed through the safety reporting period. Certain non serious AEs of interest may be followed until resolution, return to baseline, or study closure (see Section 6.1.7.10(i)(f)).

(d) Serious Adverse Events Require Immediate Reporting

[00992] Within 24 hours of observing or learning of an SAE, investigators are to report the event, regardless of the relationship of the event to the study treatment regimen.

[00993] For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Subject number
- Date of event onset
- Description of the event
- Investigator's causality assessment
- Study treatment, if known

(e) Adverse Events of Special Interest

[00994] Certain non serious AESIs may be followed (including collection of relevant concomitant medications) until resolution, return to baseline, subject withdrawal, study closure, or the events become chronic to the extent that they are adequately characterized.

[00995] **Enfortumab vedotin**

[00996] AESIs related to enfortumab vedotin or enfortumab vedotin in combination with pembrolizumab for this purpose include those events in the list below (*denotes that event must be Grade ≥2 or any grade resulting in a dose modification to be considered an AESI):

- Skin reactions
- Neuropathy (PN, Guillain Barre)
- Corneal event or uveitis
- Hyperglycemia or Type 1 diabetes
- IRR
- Pneumonitis*
- Diarrhea* or colitis*
- Hepatitis* or AST/ALT increased* or bilirubin increased*
- Endocrinopathy* (defined as hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism)
- Nephritis or acute renal failure
- Myocarditis
- Pancreatitis
- Myasthenia gravis or syndrome
- Vasculitis
- Sclerosing cholangitis

[00997] AESIs should be promptly reported by electronic data capture (EDC). If an event is medically significant or meets serious criteria it should be reported as a serious event within 24 hours (see Section 6.1.7.10(i)).

(f) Adverse Events of Special Interest Requiring Immediate Reporting

[00998] For the time period beginning at Cycle 1, Day 1 through 30 days following the last study drug dose, any AESI listed below, or follow up to an AESI, whether or not related to the sponsor's product, must be reported within 24 hours to the sponsor, either by electronic media or by paper. AESIs for this purpose include:

- An overdose of sponsor's product, as defined in Section 6.1.6.5(i) (enfortumab vedotin) and Section 6.1.6.5(ii) (pembrolizumab) that is not associated with clinical symptoms or abnormal laboratory results.
- Increased LFTs not otherwise explained by an underlying liver condition as defined in Section 6.1.11. Additional recommendations for liver safety monitoring and assessment are also included in Section 6.1.11.

(h) Vital Signs

[00999] Vital sign measurements are performed to include heart rate (bpm), diastolic and systolic blood pressure (mmHg), and temperature. Vital sign values are recorded, and any diagnosis associated with clinically significant abnormal vital signs are recorded as an AE or pre existing condition.

(ii) **Clinical Laboratory Tests**

[001000] Samples are drawn for local laboratory testing. Local lab results are sent to a local laboratory data repository.

[001001] Local laboratory testing includes institutional standard tests for evaluating study eligibility, safety and making clinical decisions. If local laboratory testing for bicarbonate is not available, a central laboratory performs the test. The following laboratory assessments are performed by the local lab to evaluate safety at scheduled timepoints (see Table 20) during the course of the study:

- The chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen, calcium, creatinine, chloride, lactate dehydrogenase, phosphorus, potassium, sodium, non fasting glucose, and total bilirubin.
- Amylase and lipase
- The CBC with differential is to include the following tests: white blood cell count with five part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, hemoglobin, and hematocrit.
- CrCl at baseline should be calculated via either Cockcroft Gault, MDRD or 24 hour urine, per institutional standard. The same method to determine CrCl should be used consistently for a subject over the course of the study with the exception of carboplatin dose calculation where Cockcroft Gault method should be used in all subjects.
- Thyroid function tests, including:
    - Triiodothyronine or free triiodothyronine
    - Free thyroxine
    - Thyroid stimulating hormone
- Standard urinalysis (with reflexive microscopy, if abnormal)
- INR/PT/PTT (at baseline and as clinically indicated thereafter)
- A serum or urine β hCG pregnancy test for females of childbearing potential

- HbA1c. If HbA1c is elevated (≥6.5%), refer subject to appropriate provider during Cycle 1 for glucose management.

(iii) **Physical Examination Including Weight**

[001002] Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Height isonly collected at the Baseline visit. Weight is collected at specified time points (see Table 20) and additionally per institutional standards, if applicable, but does not need to be collected at visits following EOT.

(iv) **ECOG Performance Status**

[001003] ECOG performance status (Table 23) is evaluated at protocol specified time points (see Table 20).

Table 23. Performance Status Scales Conversion

Karnofsky		ECOG	
Percent	Description	Score	Description
100	Normal, no complaints, no evidence of disease.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.		
80	Normal activity with effort; some signs or symptoms of disease.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.		
60	Requires occasional assistance but is able to care for most of his/her needs.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.		
40	Disabled, requires special care and assistance.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.		
20	Very sick, hospitalization indicated. Death not imminent.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

10	Moribund, fatal processes progressing rapidly.		
0	Dead.	5	Dead.

[001004] Cardiac Monitoring

[001005] ECGs are conducted at baseline. Routine 12 lead ECGs are performed after the subject has been in a supine position for at least 5 minutes. For subjects with NYHA Class III Heart Failure (see Section 6.1.10) or a history of coronary heart disease, arrhythmia or other significant heart disease, a transthoracic ECHO or MUGA scan with left ventricular ejection fraction is required.

(v) **Ophthalmologic Examination**

[001006] Subjects have a complete ophthalmologic examination at screening including, but not limited to, visual acuity, slit lamp, tonometry examination and dilated fundus examination. Subsequent ophthalmology assessments should be performed as clinically indicated throughout the study. EOT slit lamp examinations are required for subjects who experience corneal AEs during the study and must be performed ≥4 weeks from the last dose.

(vi) **Pregnancy Testing**

[001007] For subjects of childbearing potential, a serum or urine β hCG pregnancy test with sensitivity of at least 25 mIU/mL are performed at baseline, on Day 1 of every cycle, and at the EOT visit. A negative pregnancy result is required before the subject may receive study drug on Day 1 of each cycle. The pregnancy test may be performed within 1 day prior to administration of study drug. Pregnancy tests may also be repeated as requested per Institutional Review Board/Independent Ethics Committee (IRB/IEC) or if required by local regulations.

6.1.7.11 *Post-treatment Assessments*

(i) **Follow-up Assessments**

[001008] Subjects who discontinue study treatment receive physical exams and ECOG assessment. Physical exams and ECOG assessments may be discontinued for subjects that start a new anticancer therapy. Response assessments every 9 weeks (±1 week) for the first 18 months timed from the randomization date, and every 12 weeks (±1 week) thereafter. ePRO questionnaires (QLQ C30, EQ 5D 5L, BPI SF, HRU) continue to be completed per the schedule outlined in Table 19. Scans are to be done until BICR confirmed progressive disease

per RECIST v1.1 (**FIG. 3A, FIG. 3B, and FIG. 3C**), subject death, study closure, or withdrawal of consent, whichever occurs first.

[001009] During study treatment, palliative radiotherapy on a nontarget bone lesion that is not progressing is not considered a subsequent anticancer therapy; however, radiotherapy on any new or progressing lesion, per RECIST v1.1 as assessed by the investigator or after BICR confirmed progression, is considered a subsequent anticancer therapy and subjects are not permitted to resume study treatment. Surgical resection for curative intent during study treatment may be permitted in subjects with favorable tumor response after discussion with the medical monitor.

(ii) **Survival follow-up Assessments**

[001010] After discontinuation of study treatment, all randomized subjects are contacted every 12 weeks (±1 week) to obtain information on subsequent anticancer therapy and survival status. ePRO questionnaires (QLQ C30, EQ–5D 5L, BPI SF, HRU) continue to be completed per the schedule outlined in Table 19. Survival follow up continues until subject death, study closure, lost to follow up, or withdrawal of consent, whichever occurs first.

6.1.7.12 *Appropriateness of Measurements*

[001011] The safety measures that are used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications.

[001012] The determination of antitumor is based on BICR confirmed radiographically confirmed objective response assessments as defined by RECIST v1.1 (Eisenhauer 2009) (**FIG. 3A, FIG. 3B, and FIG. 3C**). Treatment decisions by the investigator are based on investigator assessed disease progression per RECIST v1.1 with BICR confirmation. RECIST criteria are considered standard in oncological practice for this type of neoplasm, and the intervals of evaluation in this protocol are appropriate for disease management. iRECIST guidelines are newly published criteria that are applied as exploratory criteria for this study in cohorts that utilize pembrolizumab. These guidelines allow consideration that immunotherapeutics, such as pembrolizumab, may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The guidelines are identical to those of RECIST v1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression (Seymour 2017) (Section 6.1.14).

[001013] Immunogenicity is commonly assessed for biologics; therefore, standard tests are performed to detect the possible presence of specific antibodies to enfortumab vedotin.

[001014] PK assessments are also common in clinical studies to help characterize dose exposure response relationships.

[001015] Exploratory biomarker measurements in peripheral blood samples enable correlation with PK assessments and are common in clinical studies. Assessments conducted on pre treatment tumor tissue are similarly common. Peripheral blood, urine and tissue biomarker samples are assessed using commonly employed, standard tests.

6.1.8 Data Analysis Methods

6.1.8.1 *Determination of Sample Size*

[001016] Approximately 860 subjects are randomized in a 1:1 ratio to one of the study arms. Control arm assumptions are based on recent trials: EORTC 30987, which tested gemcitabine + cisplatin (Bellmunt 2012), EORTC 30986, which tested gemcitabine + carboplatin (De Santis 2012), CALGB 90601 which included gemcitabine + cisplatin + placebo (Rosenberg 2019a) and IMvigor130 which included gemcitabine + cisplatin or carboplatin + placebo (Galsky 2020). Median PFS for the EORTC trials gemcitabine + platinum containing control arms was 7.6 and 5.8 months, respectively, and corresponding median OS was 12.7 months and 9.3 months. In the CALGB 90601 trial, the gemcitabine + cisplatin reference arm achieved a median PFS of 6.6 months and median OS of 14.3 months. In IMvigor130, median PFS for the control arm was 6.3 months and median OS was 13.4 months. Notably, the proportion of carboplatin treated subjects approached 70% due to an initial study design which only enrolled cisplatin ineligible subjects. In the JAVELIN Bladder 100 trial, median OS was 21.4 months for the avelumab arm and 14.3 months for the control arm (best supportive care alone) (BAVENCIO® US Prescribing Information, EMD Serono, Nov 2020).

[001017] PFS and OS assumptions for the control arm for the currently proposed trial were calculated utilizing a weighted average (anticipating 60% cisplatin eligible/40% carboplatin eligible enrollment). Thus, median OS and PFS assumptions for the control arm of the current trial were adjusted for expected improvement in survival outcomes in the contemporary era; the current trial assumes a control arm median PFS of 7 months and median OS of 15.3 months accounting for subjects receiving maintenance therapy.

[001018] This sample size of 430 subjects per arm is determined by providing a sufficient power in OS superiority test between Arms A and B. More specifically, with 430 subjects per arm, approximately 489 OS events are required to provide 93% power to demonstrate superiority at a two sided alpha of 4.5% without alpha roll over with 1 IA around 72.8% information fraction under the following assumptions:

1. OS curves follow piecewise exponential distribution with a reduced hazard rate (50% of the initial rate) starting from 24 months;
2. hazard ratio (HR) of OS is 0.73 between the experimental and control arms;
3. median OS for the control arm is 15.3 months;
4. an enrollment period of 30 months;
5. a yearly dropout rate of 5%.

[001019] The estimated time to achieve 489 OS events is around 17 months after enrollment completion.

[001020] With 430 subjects per arm, the number of PFS events in total is estimated to be 526 events, providing 90% power to demonstrate superiority at a two sided alpha of 0.5% without alpha roll over based on the following assumptions:

1. PFS curves follow piecewise exponential distribution with a reduced hazard rate (20% of the initial rate) starting from 15 months;
2. HR of PFS is 0.70 between the experimental and control arms;
3. median PFS for the control arm is 7 months;
4. an enrollment period of 30 months;
5. a yearly dropout rate of 5%.

6.1.8.2 *China Portion of the Study*

[001021] To evaluate the consistency of efficacy and safety in a China subpopulation compared with the global population, after completion of enrollment in the global portion, subjects in China may continue to be randomized in a 1:1 ratio to either the experimental arm or the control arm until the planned sample size of approximately 130 subjects in China is reached, including those randomized in the global portion and China portion. Subjects in China randomized after completion of enrollment in the global portion are not included in the analysis of the global portion. Subjects enrolled in China are analyzed separately for efficacy and safety (Section 6.1.8.4(i)). Details of analysis of the China portion of the study are provided in the statistical analysis plan (SAP).

6.1.8.3 *Study Endpoint Definitions*

[001022] PFS per BICR and OS are the dual primary endpoints for the study. See Section 6.1.3 for a complete list of endpoints.

(i) **Progression-Free Survival Per BICR**

[001023] DOR data PFS per BICR is defined as the time from randomization to first documentation of disease progression per RECIST v1.1 by BICR, or to death due to any cause, whichever comes first.

[001024] If a subject has neither progressed nor died, the subject is censored at the date of last radiological assessment. Subjects who receive new anticancer therapy (excluding maintenance therapy [eg, avelumab] following first line platinum containing chemotherapy) for locally advanced or metastatic UC before disease progression is censored at the date of the last radiological assessment before the anticancer therapy started. Subjects lacking radiological assessment data beyond the day of randomization are censored at the day of randomization.

[001025] Details of the censoring scheme for the primary analysis of PFS are described in the SAP.

(ii) **Objective Response Rate (ORR)**

[001026] ORR is defined as the proportion of subjects with confirmed CR or PR according to RECIST v1.1 (Eisenhauer 2009) (**FIG. 3A, FIG. 3B, and FIG. 3C**). Subjects who do not have at least 2 (initial response and confirmation scan) post baseline response assessments are counted as non responders for the primary analysis of ORR. The definitions of confirmed CR and PR are specified in the SAP. ORR per investigator and per BICR is analyzed.

(iii) **Duration of Response (DOR)**

[001027] DOR is defined as the time from first documented response of CR or PR (that is subsequently confirmed) to the first documented disease progression per RECIST v1.1 (Eisenhauer 2009) (**FIG. 3A, FIG. 3B, and FIG. 3C**), or to death due to any cause, whichever comes first. DOR is only calculated for the subjects achieving a confirmed CR or PR. DOR per investigator and per BICR is analyzed.

(iv) **Disease Control Rate (DCR)**

[001028] DCR is defined as the proportion of subjects with confirmed CR, PR, or SD according to RECIST v1.1 (Eisenhauer 2009) (**FIG. 3A, FIG. 3B, and FIG. 3C**). The definition of confirmed CR and PR is specified in the SAP. DCR per investigator and per BICR is analyzed.

(v) **Progression-free Survival Per Investigator Assessment (PFS)**

[001029] PFS, per investigator assessment, is defined as the time from randomization to first documentation of disease progression per RECIST v1.1 (Eisenhauer 2009) (**FIG. 3A, FIG. 3B, and FIG. 3C**), or to death due to any cause, whichever comes first.

[001030] The same censoring rules outlined in Section 6.1.8.3(i) for PFS per BICR is applied to PFS per investigator.

(vi) **Overall Survival**

[001031] OS is defined as the time from date of randomization to date of death due to any cause. In the absence of confirmation of death, survival time is censored at the last date the subject is known to be alive.

6.1.8.4 *Statistical and Analytical Plans*

[001032] The statistical and analytical plans are presented below. Additional analysis details of the global portion and China population are provided in the SAP. A change to the data analysis methods described in the protocol requires a protocol amendment only if it alters site conduct (e.g., adding baseline assessments to define a subgroup). Changes in the SAP related to primary or secondary endpoints after the study has begun, but prior to database lock for primary analysis are documented in a SAP amendment and are described and justified in the clinical study report.

(i) **General Considerations**

[001033] Overall, descriptive statistics are used to summarize continuous data (e.g., number of subjects, mean, standard deviation, median, minimum and maximum). Categorical data are summarized using frequency and percentage.

[001034] Tabular summaries are presented by treatment arm unless otherwise specified.

[001035] **Randomization and Blinding**

[001036] Subjects are randomized in a 1:1 ratio to one of the treatment arms based on the following stratification factors: cisplatin eligibility (eligible or ineligible), PD L1 expression (high or low), and liver metastases (present or absent).

[001037] Although this is an open label study, to maintain trial integrity, until database lock and study unblinding for the pre planned analyses, analyses or summaries by treatment assignment are only planned for the purpose of the IDMC monitoring and are conducted by an external vendor. In addition, the primary endpoint of PFS by BICR is based on assessment of radiological scans by BICR without knowledge of treatment assignment.

[001038] **Adjustments for Covariates**

[001039] The randomization scheme includes the following stratification factors: Cisplatin eligibility (eligible or ineligible), PD-L1 expression (high or low), and Liver metastases (present or absent). These stratification factors used for randomization are included in both the

stratified log rank test and the stratified Cox proportional hazards model for the analyses of the primary endpoints of PFS and OS.

[001040] Multiple Comparisons and Multiplicity

[001041] The proposed 2 arm study has dual primary endpoints of PFS and OS. The study can be considered positive if enfortumab vedotin plus pembrolizumab (Arm A) is superior to the control arm (Arm B) in either PFS or OS. A graphical approach with group sequential testing outlined in Maurer and Bretz (Maurer 2013) is used to strongly control the family wise type I error rate at a two sided 5% level.

[001042] The initial alpha allocation for each test with lines connecting between hypotheses: 4.5% and 0.5% two sided alpha for comparisons between Arm A and Arm B in OS and PFS, respectively, as shown in **FIG. 6**. These are also the alpha values used for sample size and power planning. The updated graph and rejection boundaries are derived using the algorithm outlined in Maurer and Bretz (Maurer 2013). O'Brien Fleming boundaries are used to calculate the rejection boundaries based on the actual information fraction observed for OS data. As an example, if the null hypothesis for PFS is rejected, the 0.5% alpha of PFS ia passed to OS. Thus, OS can be re tested using a 2 sided alpha of 5%. The rejection boundaries of OS IA and final analysis (FA) are re calculated based on 5% alpha and actual information fraction using the O'Brien Fleming function.

[001043] When the null hypotheses for PFS and OS are both rejected, selected secondary endpoints are tested in the following order using a gatekeeping testing strategy:

1. ORR by BICR
2. Time to pain progression (TTPP)
3. Mean change from baseline in worst pain at Week 26

[001044] Each test is at the 5% significance level (2 sided) as long as all preceding null hypotheses are rejected. These secondary endpoints are only tested once at either the OS interim or final analysis after the null hypotheses for PFS and OS are both rejected, and the test statistics for inferential testing are computed from the data at the time of OS IA. In the event that only the null hypothesis for PFS is rejected and the superiority boundary for OS has not been crossed at the time of OS IA, these secondary endpoints are not tested and are only analyzed descriptively.

[001045] Data Transformations and Derivations

[001046] Time variables based on 2 dates (e.g., start date and end date) are calculated as (end date – start date +1 [in days]) unless otherwise specified.

[001047] Baseline values used in all statistical analyses are the most recent non missing measurement prior to the first dose of study drug unless otherwise specified.

[001048] Analysis Sets

[001049] All subjects who are randomized are included in the intent to treat (ITT) analysis set. Subjects are included in the treatment group assigned at randomization regardless of the actual treatment received. The primary analysis of the efficacy endpoints of OS and PFS is based on the ITT analysis set. Demographic and baseline characteristics are summarized for the ITT analysis set.

[001050] The response evaluable set includes all randomized subjects who have measurable disease per RECIST v1.1 at baseline. Subjects are analyzed according to the treatment arm assigned at randomization regardless of the actual treatment received. The response evaluable set is used for primary analysis of response related endpoints, eg, ORR, DCR, and DOR.

[001051] The safety analysis set includes all randomized subjects who received at least 1 dose of investigational product (or any component of combination therapy). Subjects are evaluated by the treatment actually received. Treatment exposure and AE is summarized in the safety analysis set.

[001052] The PRO FAS includes all randomized subjects who have received at least 1 dose of investigational product (or any component of combination therapy) and have completed at least 1 PRO assessment at baseline. Subjects are analyzed according to the treatment arm assigned at randomization. The PRO FAS are used for PRO analyses, unless otherwise specified.

[001053] Subjects in China who are randomized in the China portion are not included in the analysis population for the global portion. The China ITT population, including all subjects in China randomized in both the global portion and the China portion, are analyzed in the China specific efficacy analyses. The China safety analysis set, including all randomized subjects in China (from both the global portion and the China portion) who receive at least 1 dose of investigational product (or any component of combination therapy) are analyzed in the China specific safety analyses.

[001054] Additional analysis sets of subjects may be defined in the SAP.

[001055] Examination of Subgroups

[001056] As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Subgroup analyses include an analysis of OS, PFS, and ORR by PD L1 status at baseline (low or high). Detailed methodology for all subgroups analyses is provided in the SAP.

[001057] Interim Analysis

[001058] A single planned analysis (FA) for PFS takes place when approximately 526 PFS events or 356 OS events (72.8% information fraction) in the ITT analysis set have occurred, whichever is later.

[001059] Two analyses are planned for OS. OS IA is planned at the time of the final PFS analysis. At IA, the OS events in total are approximately 356 (about 72.8% of information). O'Brien Fleming boundaries are used to calculate the rejection boundaries based on the actual information fraction observed. The final OS analysis is planned when approximately 489 OS events have occurred in total.

[001060] Estimated analyses timing and the rejection boundaries at the planned PFS and OS analyses are presented in Table 24. The results are based on the initial alpha allocated to each hypothesis before any alpha recycling. O'Brien Fleming boundaries are used to calculate the rejection boundaries for the interim and final OS analyses based on the actual number of deaths observed in the study.

Table 24. Summary of timing of analyses and estimated rejection boundaries

Analysis		2-sided α^{d}	Est. Time after Enrollment Completion	Planned # of Events	p-value (2-sided) at Boundary	Approx. Obs. HR at Boundary	Planned Power
Analysis Time 1[a]	FA: PFS	0.5%	7 months	526	0.005	0.783	90%
	IA: OS	1.5%	7 months	356 (72.8% info.)	0.015	0.773	70%[b]
Analysis Time 2	FA: OS	4.5%	17 months	489	0.040	0.831	93%[c]

a. Analysis Time 1 is triggered by the planned number of PFS events in total (526 events) or 356 OS events (72.8% information fraction), whichever is later.

b. Probability to cross the efficacy boundary at the interim analysis

c. Overall power at the final OS analysis

d. Cumulative alpha assigned for each test without alpha roll over. For OS IA, 1.5% is the estimated alpha spent at IA.

(ii) **Subject Disposition**

[001061] Subject enrollment and disposition are summarized by each treatment arm and also by total. The number and percentage of subjects who discontinue study treatment and subjects

who withdraw from the study are summarized with reason for discontinuation or withdrawal. The number of subjects who signed informed consent and the number of subjects in each analysis set are summarized by treatment group and total.

(iii) **Patient Characteristics**

[001062] Demographics and other baseline characteristics are summarized by treatment arm and by total with counts and percentages for categorical variables and with summary statistics for continuous variable. Details are provided in the SAP.

(iv) **Efficacy Analyses**

[001063] The primary analysis of efficacy endpoints of OS and PFS are analyzed using the ITT analysis set. ORR, DCR, and DOR are analyzed using the response evaluable set.

[001064] For the primary endpoints of OS and PFS, a log rank test stratified by randomization stratification factors are used to compare the experimental arm to the control arm. The estimated HR and corresponding 95% CI from the stratified Cox proportional hazards regression model is also presented. The median survival is estimated using the Kaplan Meier (KM) method and is reported along with estimated KM curves and the corresponding 95% CI by treatment arm. Similar estimation methods are used for the other time to event endpoints. DOR is summarized descriptively by Kaplan Meier methods for subjects with a confirmed response (complete response or partial response per RECIST v1.1 [**FIG. 3A, FIG. 3B, and FIG. 3C**]).

[001065] ORR and disease control rate are estimated for each treatment arm based on the response evaluable set based on the response evaluable set. Additionally, p value between treatment arms using the Cochran Mantel Haenszel test, controlling for randomization stratification factors is provided.

[001066] Due to the limited sample size of subjects receiving enfortumab vedotin + platinum + pembrolizumab, only a listing of efficacy data is provided for subjects randomized to this treatment arm. Additional sensitivity analyses for the efficacy endpoints and the exploratory analysis per iRECIST (Section 6.1.14) are specified in the SAP.

(v) **Pharmacokinetic and Immunogenicity Analyses**

[001067] Descriptive statistics are provided for antibody drug conjugate and unconjugated drug (MMAE) concentrations in the experimental arm at each PK sampling time point. Any additional PK and PK/pharmacodynamic analyses may be described in a separate analysis plan and presented in a separate report. The incidence of ATA is summarized.

[001068] Pembrolizumab PK and immunogenicity analysis are performed only if required.

(vi) **Patient Reported Outcomes Analyses**

[001069] Descriptive analyses for EORTC QLQ C30, EQ 5D 5L, and BPI SF are performed on the PRO FAS. Compliance and completion rate is summarized for each scheduled assessment by treatment arm using the ITT analysis set for Arm A and Arm B.

[001070] PRO based secondary endpoints TTPP and mean change from baseline in worst pain at Week 26 are hierarchically tested when OS, PFS, and ORR are all statistically significant. Additional PRO analyses of remaining BPI SF, EORTC QLQ C30, and EQ 5D-5L questionnaires are described in the supplemental PRO SAP.

(vii) **Biomarker Analyses**

[001071] Relationships of biomarker parameters (e.g., baseline values, absolute and relative changes from baseline) to efficacy, safety, and PK may be explored. Relationships and associated data that are determined to be of interest are summarized. Details are described separately.

(a) Time to Pain Progression

[001072] TTPP is defined as the time from randomization to the first date a subject experiences a pain progression. Pain progression is defined as either an increase of 2 or more points from baseline on question 3 of the BPI SF or initiation of new opioid pain medication.

[001073] TTPP is compared between the experimental and control arms using a stratified log-rank test. Kaplan Meier curves and the median TTPP with 95% CI are presented. Further details on the TTPP analysis, are provided in the SAP.

(b) Mean Change from Baseline in Worst Pain at Week 26

[001074] Using the BPI SF question 3, mean change from baseline in worst pain is calculated for each postbaseline assessment timepoint for Arm A and Arm B. A mixed model for repeated measures (MMRM) is used to estimate marginal mean change scores and differences between Arm A and Arm B. The difference in mean change from baseline between treatment arms at Week 26 is evaluated for statistical significance.

(viii) **Safety Analyses**

[001075] The safety analysis set is used to summarize all safety endpoints.

(a) Extent of Exposure

[001076] Duration of treatment is summarized and listed.

[001077] Duration of treatment, number of cycles, total dose and dose intensity are summarized by treatment arm. Details are provided in the SAP.

(b) Adverse Events

[001078] An overview of TEAEs provides a tabulation of the number and incidence of TEAEs, treatment related TEAEs, Grade 3 and higher TEAEs, serious TEAEs, treatment related serious TEAEs, TEAE leading to deaths, and TEAEs leading to study treatment discontinuation. AEs are defined as treatment emergent if they are newly occurring or worsen after the first dose of study treatment through 30 days after the last dose of the study drug or through 90 days after the last dose of study treatment for SAE in Arms A and C.

[001079] AEs are listed and summarized by MedDRA, system organ class (SOC), preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in one subject, the AE is counted once as the occurrence. The incidence of TEAEs is tabulated by preferred term and treatment group. TEAEs leading to premature discontinuation of study drug is summarized and listed in the same manner.

(c) Deaths and Serious Adverse Events

[001080] SAEs are listed and summarized in the same manner as all AEs. Events with a fatal outcome are listed.

(d) Clinical Laboratory Results

[001081] For laboratory values (e.g., chemistry and hematology), summary statistics of actual values and change from baseline may be presented as appropriate by scheduled visit. Laboratory shift tables are also provided by treatment group. Laboratory values are listed with grade per NCI CTCAE v4.03 and flagged when values are outside the normal reference range. Details are provided in the SAP.

(e) **Other Safety Analyses**

[001082] **Vital Signs**

[001083] Vital signs are listed by subject and scheduled visit.

[001084] **ECOG Status**

[001085] Shifts from baseline to the best and worst post baseline score may be tabulated.

[001086] **ECG**

[001087] A by-subject listing is generated.

6.1.9 List of Abbreviations and Descriptions of Terms

[001088]	1L	first line
[001089]	2L	second line
[001090]	ADC	antibody-drug conjugate
[001091]	AE	adverse event
[001092]	AESI	adverse event of special interest

[001093]	AKI	acute kidney injury
[001094]	ALT	alanine aminotransferase
[001095]	ANC	absolute neutrophil count
[001096]	aPTT	activated partial thromboplastin
[001097]	AST	aspartate aminotransferase
[001098]	ATAs	Anti-therapeutic antibodies
[001099]	AUC	area under the curve
[001100]	β-hCG	beta human chorionic gonadotropin
[001101]	BICR	blinded independent central review
[001102]	BPI SF	Brief Pain Inventory – Short Form
[001103]	CBC	complete blood count
[001104]	CD3ζ	CD3 zeta
[001105]	CI	confidence interval
[001106]	CNS	central nervous system
[001107]	CPS	combined positive score
[001108]	CR	complete response
[001109]	CrCl	creatinine clearance
[001110]	CRF	case report form
[001111]	CRO	Contract Research Organization
[001112]	CT	computed tomography
[001113]	CTA	Clinical Trial Agreement
[001114]	CTLA04	cytotoxic T lymphocyte-associated protein 4
[001115]	DCR	disease control rate
[001116]	DILI	drug-induced liver injury
[001117]	DKA	diabetic ketoacidosis
[001118]	DLT	dose-limiting toxicity
[001119]	DOR	duration of response
[001120]	ECD	extracellular domain
[001121]	ECG	electrocardiogram
[001122]	ECHO	echocardiogram
[001123]	ECOG	Eastern Cooperative Oncology Group
[001124]	eCRF	electronic case report form
[001125]	EDC	electronic data capture
[001126]	EORTC	European Organisation for Research and Treatment of Cancer

[001127]	EOT	end of treatment
[001128]	ePROs	electronic patient reported outcomes
[001129]	EQ-5D-5L	EuroQOL 5-dimensions
[001130]	EU	European Union
[001131]	EV	enfortumab vedotin
[001132]	FA	final analysis
[001133]	FAS	full analysis set
[001134]	FDA	Food and Drug Administration
[001135]	FFPE	formalin-fixed paraffin embedded
[001136]	GFR	glomerular filtration rate
[001137]	HbA1c	hemoglobin A1c
[001138]	HBsAg	hepatitis B surface antigen
[001139]	HCV	hepatitis C virus
[001140]	HR	hazard ratio
[001141]	HRU	health resource utilization
[001142]	IA	interim analysis
[001143]	ICD	immunogenic cell death
[001144]	ICH	International Council for Harmonisation
[001145]	iCPD	confirmed immune progressive disease
[001146]	IDMC	Independent Data Monitor Committee
[001147]	IEC	independent ethics committee
[001148]	Ig	immunoglobulin
[001149]	IHC	immunohistochemistry
[001150]	ILD	interstitial lung disease
[001151]	imAE	immune mediated adverse events
[001152]	IND	investigational new drug
[001153]	INR	international normalized ratio
[001154]	iRECIST	modified RECIST 1.1 for immune based therapeutics
[001155]	IRB	institutional review board
[001156]	IRR	infusion related reaction
[001157]	IRT	Interactive Response Technology
[001158]	ITT	intent to treat
[001159]	iUPD	unconfirmed immune progressive disease
[001160]	IV	intravenous

[001161] LVEF left ventricular ejection fraction

[001162] mAb monoclonal antibody

[001163] MDRD Modification of Diet in Renal Disease

[001164] MedDRA Medical Dictionary for Regulatory Activities

[001165] MMAE monomethyl auristatin E

[001166] MMRM mixed model for repeated measures

[001167] mOS median overall survival

[001168] mPFS median progression-free survival

[001169] MRI magnetic resonance imaging

[001170] mUC metastatic urothelial cancer

[001171] MUGA multiple gated acquisition

[001172] MVAC methotrexate, vinblastine, doxorubicin, cisplatin

[001173] NCI CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events

[001174] NLT new lesions-target

[001175] NLNT new lesion non target

[001176] NSAID nonsteroidal anti-inflammatory drug

[001177] NYHA New York Heart Association

[001178] ORR objective response rate

[001179] OS overall survival

[001180] PD progressive disease

[001181] PD-1 programmed cell death protein-1

[001182] PD-L1 programmed cell death ligand-1

[001183] PD-L2 programmed cell death ligand-2

[001184] Pembro pembrolizumab

[001185] PFS progression free survival

[001186] PK pharmacokinetic

[001187] PKCθ protein kinase C theta

[001188] PN peripheral neuropathy

[001189] PO by mouth

[001190] PR partial response

[001191] PRO patient reported outcome

[001192] PT prothrombin time

[001193] PTT partial thromboplastin time

[001194]	QLQ-C30	Quality of Life Core 30
[001195]	QOL	quality of life
[001196]	RECIST	Response Evaluation Criteria in Solid Tumors
[001197]	RNA	ribonucleic acid
[001198]	SAE	serious adverse event
[001199]	SAP	statistical analysis plan
[001200]	SD	stable disease
[001201]	SJS	Stevens Johnson Syndrome
[001202]	SmPC	Summary of Product Characteristics
[001203]	SMQ	standardized MedDRA query
[001204]	SOC	system organ class
[001205]	SSQ	sponsor specified query
[001206]	SUSARs	suspected unexpected serious adverse reactions
[001207]	T1DM	type 1 diabetes mellitus
[001208]	TEAE	treatment emergent adverse events
[001209]	TEN	toxic epidermal necrolysis
[001210]	TTPP	time to pain progression
[001211]	UC	urothelial cancer
[001212]	ULN	upper limit of normal
[001213]	US	United States
[001214]	USP	United States Pharmacopeia
[001215]	VAS	Visual Analogue Scale
[001216]	VHP	Voluntary Harmonization Procedure
[001217]	WHO	World Health Organization
[001218]	ZAP70	zeta-chain associated protein kinase

6.1.10 New York Heart Association Classification

[001219] A Functional and Therapeutic Classification for Prescription of Physical Activity for Cardiac Patients:

[001220] Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.

[001221] Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

[001222] Class III: patients with marked limitation of activity; they are comfortable only at rest.

[001223] Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

[001224] On line source: www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes of Heart Failure_UCM_306328_Article.jsp

6.1.11 Liver Safety Monitoring and Assessment

[001225] In the absence of an explanation for increased LFTs, such as viral hepatitis, pre existing or acute liver disease, or exposure to other agents associated with liver injury, the subject may be discontinued from the study treatment. The investigator may determine that it is not in the subject's best interest to continue study treatment. Discontinuation of treatment should be considered if any of the severe liver abnormalities listed below should occur.

[001226] Any subject with an increase of serum aminotransferases to >3× ULN or bilirubin >2× ULN should undergo detailed testing for liver enzymes (including at least alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin). To confirm the abnormality, testing should be repeated within 72 hours of notification of the test results.

[001227] **Description of Liver Abnormalities:**

[001228] Confirmed liver abnormalities are characterized as Moderate and Severe:

[001229] **Moderate**

- ALT or AST >3× ULN **OR** Total Bilirubin >2× ULN

[001230] **Severe**

- ALT or AST >3× ULN **AND** Total Bilirubin >2× ULN (** See Hy's Law Definition)
- ALT or AST >8× ULN
- ALT or AST >5× ULN for more than 2 weeks
- ALT or AST >3× ULN and international normalized ratio (INR) >1.5 (if INR testing is applicable/evaluated)
- ALT or AST >3× ULN with the appearance of symptoms suggestive of liver injury (eg, right upper quadrant pain or tenderness) and/or eosinophilia (>5%)

[001231] The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow up.

[001232] * The following recommendations are from the Food and Drug Administration (FDA) Guidance for Industry titled "Drug Induced Liver Injury: Premarketing Clinical Evaluation" issued July 2009.

[001233] ** Hy's Law Definition: Drug induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10% to 50% mortality (or transplant). The 2 "requirements" for Hy's Law are: 1) Evidence that a drug can cause hepatocellular type injury, generally shown by an increase in transaminase elevations higher 3× ULN ("2× ULN elevations are too common in treated and untreated patients to be discriminating"). 2) Cases of increased bilirubin (at least 2× ULN) with concurrent transaminase elevations at least 3× ULN and no evidence of intra or extra hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome (Temple 2006).**Follow-up Procedures**

[001234] Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. Subjects with confirmed abnormal liver function testing should be followed as described below.

[001235] Confirmed moderately abnormal liver function tests (LFTs) should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

[001236] Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

[001237] To further assess abnormal hepatic laboratory finding, it is recommended that the investigator:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Illnesses and conditions such as hypotensive events and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic subjects and may be associated with fluctuating aminotransferase levels.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets.

- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
    - Acute viral hepatitis (A, B, C, D, E or other infectious agents),
    - Ultrasound or other imaging to assess biliary tract disease,
    - Other laboratory tests including INR, direct bilirubin.
- Consider gastroenterology or hepatology consultations.

[001238] Conduct additional testing as determined by the investigator to further evaluate possible etiology.

6.1.12 Scanning and Contrast Options

[001239] In decreasing order of preference

[001240] **Brain Scan**

1. Brain magnetic resonance imaging (MRI) with gadolinium

[001241] **If gadolinium is medically contraindicated:**

2. Brain MRI without gadolinium
3. Brain computed tomography (CT) with intravenous (IV) contrast
4. Brain CT without IV contrast

[001242] **Chest-Abdomen-Pelvis Scans:**

1. Chest Abdomen Pelvis CT with IV contrast

[001243] **If iodine media is medically contraindicated:**

2. Chest CT without IV contrast and Abdomen Pelvis MRI with gadolinium
3. Chest Abdomen Pelvis CT without IV contrast (oral contrast is recommended)
4. Chest Abdomen Pelvis MRI with gadolinium

[001244] **CT Oral Contrast**

5. Radio opaque agents (e.g., iodine and barium based agents)
6. Radio lucent agents (whole milk, VoLumen®, water)

[001245] Important: Imaging modality, anatomical coverage and acquisition parameters should remain consistent across all imaging visits for each patient.

6.1.13 Guidance on Contraception

[001246] For the purposes of this guidance, complete abstinence, if consistent with the subject's preferred lifestyle, is an acceptable form of contraception. Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of systemic exposure (at least 6 months after the final dose of study drug; see Section 6.1.5.1).

[001247] Acceptable methods for highly effective birth control (preventing conception) Subjects who are of childbearing potential[a] or whose partners are of childbearing potential[a] and who are sexually active in a way that could lead to pregnancy may choose any TWO of the following methods (please see acceptable combinations below):

- Hormonal methods of contraception (excluding progestin only pills; method must be associated with inhibition of ovulation), unless contraindicated
- Intrauterine device with failure rate <1%
- Tubal ligation
- Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)
- Barrier method (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)[b]
- a. A person of childbearing potential is defined as anyone born female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person born female over age 45 in the absence of other biological, physiological, or pharmacological causes.
- b. A barrier method should only be used with a highly effective birth control method that is not a barrier method. Barrier methods alone, including a double barrier method, are not considered highly effective contraceptive measures (see unacceptable methods of contraception).

[001248] Acceptable combinations of contraceptive methods include hormonal method and vasectomy, hormonal method and barrier method, intrauterine device and vasectomy, intrauterine device and barrier method, tubal ligation and vasectomy, and tubal ligation and barrier method.

[001249] Acceptable methods for preventing secondary exposure to seminal fluid are as follows: Subjects born male and who are sexually active with a pregnant or breastfeeding person must use the contraceptives in Options 1 or 2: option 1 - male condom (with or without spermicide) and cervical cap and option 2 – male condom (with or without spermicide) and diaphragm. Unacceptable methods of contraception include periodic abstinence, spermicide only, no method, progestin-only pills, withdrawal, concomitant use of

female and male condoms, rhythm, and barrier methods alone (including double-barrier methods).

6.1.14 iRECIST: Guidelines for Response Criteria For Use in Trials Testing Immunotherapeutics

[001250] Response is also assessed using modified RECIST v1.1 for immune based therapeutics (iRECIST) guidelines (Seymour 2017). Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST v1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

[001251] Key differences are described below. All responses defined using iRECIST guidelines are designated with a prefix. iRECIST time point and best responses are recorded separately.

[001252] **Confirming Disease Progression**

[001253] Unlike RECIST v1.1, the iRECIST guidelines require the confirmation of progression and uses the terms unconfirmed immune progressive disease (iUPD) and confirmed immune progressive disease (iCPD). Confirmatory scans should be performed at least 4 weeks, but no longer than 9 weeks after iUPD.

[001254] iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by 1 or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST v1.1 definitions of progression had been met (from nadir) in target, nontarget disease or new lesions
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
    - Continued unequivocal progression in nontarget disease with an increase in tumor burden
    - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST v1.1 criteria are met in lesions types (target or nontarget or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

[001255] If iUPD is not confirmed at the next assessment, then the appropriate response is assigned (iUPD if the criteria are still met, but no worsening, or immune stable disease [iSD], immune partial response [iPR] or immune complete response [iCR] if those criteria are met compared to baseline).

[001256] New Lesions

[001257] New lesions should be assessed and measured as they appear using RECIST v1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions Target (NLT) and New Lesion Non Target (NLNT) to allow clear differentiation from baseline target and nontarget lesions.

[001258] New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements are collected separately in the case report form.

6.2 Example 2 – Results from the Phase 3 Study of Enfortumab Vedotin Combined with Pembrolizumab Versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer.

6.2.1 Background

[001259] As discussed *supra*, urothelial carcinoma (UC), a carcinoma that encompasses both lower and upper urinary tract, is a malignancy with high unmet medical need. Urothelial cancer, or bladder cancer, begins in the urothelial cells, which line the urethra, bladder, ureters, renal pelvis, and some other organs. If bladder cancer has spread to surrounding organs or muscles, it is called locally advanced disease. If the cancer has spread to other parts of the body, it is called metastatic disease. Globally, approximately 573,000 new cases of bladder cancer and 212,000 deaths are reported annually. It is estimated that approximately 82,290 people in the U.S. will be diagnosed with bladder cancer in 2023. It is estimated that approximately 200,000 people in Europe and 24,000 people in Japan are diagnosed with bladder cancer annually. Urothelial cancer accounts for 90% of all bladder cancers and can also be found in the renal pelvis, ureter and urethra. Approximately 12% of cases are locally advanced or metastatic urothelial cancer at diagnosis. Thus, a significant unmet need remains for cisplatin-eligible and cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer (la/mUC).

6.2.2 Methods

[001260] The following Example presents results from the protocol described in Example 1, *supra*, which enrolled patients with previously untreated la/mUC who were eligible for cisplatin- or carboplatin-containing chemotherapy regardness of PD-L1 status. The protocol described in Example 1 is an open-label, randomized, controlled Phase 3 study, evaluating enfortumab vedotin in combination with pembrolizumab versus chemotherapy in patients with previously untreated la/mUC. In this study, patients were randomized to receive either enfortumab vedotin in combination with pembrolizumab or chemotherapy. The dual primary endpoints of the protocol described in Example 1 are OS and PFS per RECIST v1.1 by blinded independent central review (BICR). **FIG. 7** shows the design of the study. The study was designed to assess the dual primary endpoints of PFS and OS. Secondary endpoints include ORR, TTPP, change from baseline in worst pain at wk 26, DOR, DCR, PFS per investigator, PRO, and safety. **FIG. 6** and **FIGS. 8A and 8B** show the statistical testing methods used in the protocol. To maintain strong control of the family-wise type I error rate at 0.05 (2-sided), the initial alpha allocation is 0.005 to PFS and 0.045 to OS. If one of the primary endpoints is statistically significant, the alpha initially assigned to that endpoint can be rolled over to the other endpoint. **FIG. 8A** shows the efficacy boundaries for PFS analysis. **FIG. 8B** shows the efficacy boundaries for OS analysis.

6.2.3 Results

[001261] The Phase 3 Study of Enfortumab Vedotin Combined with Pembrolizumab Versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer completed enrollment with 886 subjects enrolled.

[001262] As shown in **FIG. 9**, the number of subjects who received any amount of study drug in the EV + Pembrolizumab ("EV + pembro") arm of the study was 440. The number of subjects who received any amount of study drug in the standard of care gemcitabine plus platinum containing chemotherapy arm (i.e., gemcitabine + cisplatin or carboplatin; i.e., "Plat + Gem") was 433. In the EV+pembro arm, N = 442 and in the Plat + Gem arm, N = 444.

[001263] Regarding disposition, as shown in **FIG. 9**, progressive disease was the most common reason for treatment discontinuation in the EV + pembro arm. Completed treatment was the most comment reason for treatment discontinuation in the Plat + Gem arm. 144 subjects remained on treatment in the EV + Pembro arm of the study and 0 subjects remained on treatment in the Plat + Gem arm of the study.

[001264] Subjects were stratified and randomized as described in the protocol described in Example 1, *supra*. Stratification factors at randomization are shown in **FIG. 10**. Overall, 52 subjects (5.9%) were mis-stratified.

[001265] Regarding demographics, as shown in **FIG. 11**, the demographics and baseline disease characteristics are representative of the 1L LA or mUC population.

[001266] The baseline characteristics of the study population, as shown in **FIG.12**, are consistent with the 1L LA/mUC population.

[001267] The baseline disease characteristics, as shown in **FIG. 13**, are reflective of high unmet medical need in a population with known poor prognostic factors including renal impairment, upper tract disease, and visceral disease (including liver metastases).

[001268] **FIG. 14** provides a summary of prior anticancer therapies in the EV + pembro arm and Plat + Gem arm (as well as totals). For example, **FIG. 14** indicates subjects who received prior systemic therapy in a neoadjuvant/adjuvant setting (e.g., platinum-based therapy and non-platinum-based therapy), prior surgery (e.g., cystectomy, nephrectomy/ureterectomy, and metastasectomy), and prior radiation therapy. The majority of subjects received prior surgery (165 subjects (37.3%) in the EV + Pembro arm and 163 subjects (36.7%) in the Plat + Gem arm, with 328 total subjects (37.0%) having received prior surgery).

[001269] Using duration of treatment as a parameter for summary of exposure, as shown in **FIG. 15**, median treatment duration was 9.43 months with a median number of cycles of 12 in the EV + Pembro arm.

[001270] **FIG. 16** provides a summary of subsequent anticancer therapies in the EV + Pembro arm and Plat + Gem arm. 32.2% of subjects in Plat + Gem arm received maintenance therapy (i.e., maintenance PD-1/L1 inhibitor-containing therapy). For the EV + Pembro arm, the number of subjects who received subsequent anticancer therapies was 140 (31.7%). For the Plat + Gem arm, the number of subjects who received subsequent anticancer therapies was 313 (70.5%). For the EV + Pembro arm, 94 subjects (21.3%) received 1 line of subsequent systemic therapies, 22 subjects (5.0%) received 2 lines of subsequent systemic therapies, and 12 subjects (2.7%) received ≥ 3 lines of subsequent systemic therapies. For the Plat + Gem arm, 196 subjects (44.1%) received 1 line of subsequent systemic therapies, 75 subjects (16.9%) received 2 lines of subsequent systemic therapies, and 23 subjects (5.2%) received ≥ 3 lines of subsequent systemic therapies. For the EV + Pembro arm, 110 subjects (24.9%) received a platinum-based therapy as the first subsequent systemic therapy received, 1 subject (0.2%) received maintenance PD-1/L1 inhibitor-containing therapy (i.e., Avelumab (1 subject (0.2%)) as the first subsequent systemic therapy received, 8 subjects (1.8%) received other

PD-1/L1 inhibitor-containing therapy, and 11 subjects (2.5%) received "other" therapy as the first subsequent systemic therapy received. For the Plat + Gem arm, 17 subjects (3.8%) received a platinum-based therapy as the first subsequent systemic therapy received, 143 subjects (32.2%) received maintenance PD-1/L1 inhibitor-containing therapy (of which 135 subjects (30.4%) received Avelumab), 118 received (26.6%) other PD-1/L1 inhibitor-containing therapy, and 18 subjects (4.1%) received "other" therapy as the first subsequent systemic therapy received.

[001271] Regarding efficacy of treatment, PFS, OS, ORR, and DOR were assessed.

[001272] According to the blinded independent central review, as shown in **FIG. 17A** and **FIG. 17B**, median PFS for the EV + Pembro arm was 12.5 months (95% CI: 10.4, 16.6) and median PFS for the Plat + Gem arm was 6.3 months (95% CI: 6.2, 6.5). Thus, the median PFS for the EV + Pembro arm was approximately two (2) times the median PFS for the Plat + Gem arm (*see* **FIG. 17A** and **FIG. 17B)**. The risk of progression or death was reduced by 55% in subjects who received EV + Pembro (*see* **FIG. 17A** and **FIG. 17B)**. At 6 months, the PFS for the EV + Pembro arm was 72.8 % and the PFS for the Plat + Gem arm was 60.7% (*see* **FIG. 17B)**. At 12 months, the PFS for the EV + Pembro arm was 50.7% and the PFS for the Plat + Gem arm was 21.6% (*see* **FIG. 17B)**. At 18 months, the PFS for the EV + Pembro arm was 43.9% and the PFS for the Plat + Gem arm was 11.7% (*see* **FIG. 17B)**.

[001273] According to the blinded independent central review, in the PFS subgroup analysis of subjects in the EV + Pembro and Plat + Gem arms, as shown in **FIG. 18A**, a PFS benefit was consistently observed across pre-specified subgroups. In particular, a PFS benefit was consistently observed in the EV + Pembro arm relative to the Plat + Gem arm. As indicated *supra*, the overall median PFS for the EV + Pembro arm was 12.5 months (10.4, 16.6) and the overall median PFS for the Plat + Gem arm was 6.3 (6.2, 6.5). Meaningful improvement was observed in the EV + Pembro arm relative to the Plat + Gem arm in both cisplatin-eligible (HR = 0.483) and cisplatin-ineligible (HR = 0.429) subgroups (*see* **FIG. 18A** and **FIGS. 19A and 19B**). For example, a median PFS of 14.6 months was observed in cisplatin eligible subjects in the EV + Pembro arm, whereas a median PFS of 6.5 months was observed in cisplatin eligible subjects in the Plat + Gem arm (*see* **FIG. 18A** and **FIG. 19A)**. In addition, a median PFS of 10.6 months was observed in cisplatin ineligible subjects in the EV + Pembro arm, whereas a median PFS of 6.1 months was observed in cisplatin ineligible subjects in the Plat + Gem arm (*see* **FIG. 18A** and **FIG. 19B)**. Meaningful improvement was also observed in the EV + Pembro arm relative to the Plat + Gem arm in subjects having high (CPS $\geq$10) PD-L1 expression (HR = 0.415) and in subjects having low (CPS <10) PD-L1 expression (HR

= 0.501) subgroups (*see* **FIG. 18A** and **FIGS. 20A and 20B**). A median PFS of 18.5 months was observed in subjects having high (CPS ≥ 10) PD-L1 expression in the EV + Pembro arm, whereas a median PFS of 6.2 months was observed in subjects having high (CPS ≥ 10) PD-L1 expression in the Plat + Gem arm (*see* **FIG. 18A** and **FIG. 20A)**. A median PFS of 10.5 months was observed in subjects having low (CPS < 10) PD-L1 expression in the EV + Pembro arm, whereas a median PFS of 6.3 months was observed in subjects having low (CPS < 10) PD-L1 expression in the Plat + Gem arm (*see* **FIG. 18A** and **FIG. 20B)**. Additional examples of other subgroups in the analysis in **FIG. 18A** include the following. Notably, a median PFS of 16.4 months was observed in subjects with liver metastases absent in the EV + Pembro arm (*see* **FIG. 18A** and **FIG. 18C**, dark upper line in graph), whereas a median PFS of 6.4 months was observed in subjects with liver metastases absent in the Plat + Gem arm (*see* **FIG. 18A** and **FIG. 18C**, light lower line in graph) (HR; 95% CI: 0.43; 0.35-0.52). A median PFS of 8.2 months was observed in subjects with liver metastases present in the EV + Pembro arm (*see* **FIG. 18A** and **FIG. 18B**, dark upper line in graph), whereas a median PFS of 6.0 months was observed in subjects with liver metastases present in the Plat + Gem arm (*see* **FIG. 18A** and **FIG. 18B**, light lower line in graph) (HR; 95% CI: 0.53; 0.38-0.76). A median PFS of 10.4 months was observed in subjects with visceral metastases present in the EV + Pembro arm (*see* **FIG. 18A** and **FIG. 18D**, dark upper line in graph), whereas a median PFS of 6.2 months was observed in subjects with visceral metastases present in the Plat + Gem arm (*see* **FIG. 18A** and **FIG. 18D**, light lower line in graph) (HR; 95% CI: 0.45; 0.37-0.55). A median PFS was not reached in subjects with lymph node only metastases in the EV + Pembro arm (*see* **FIG. 18A** and **FIG. 18E**, dark upper line in graph), whereas a median PFS of 8.3 months was observed in subjects with lymph node only metastases in the Plat + Gem arm (*see* **FIG. 18A** and **FIG. 18E**, light lower line in graph) (HR; 95% CI: 0.40; 0.26-0.62). A median PFS of 10.4 months was observed in subjects of white race in the EV + Pembro arm, whereas a median PFS of 6.2 months was observed in subjects of white race in the Plat + Gem arm (*see* **FIG. 18A**). A median PFS of 22.3 months was observed in subjects of "other" race in the EV + Pembro arm, whereas a median PFS of 6.5 months was observed in subjects of "other" race in the Plat + Gem arm (*see* **FIG. 18A**). A median PFS of 22.3 months was observed in subjects having ECOG PS of 0 in the EV + Pembro arm, whereas a median PFS of 6.7 months was observed in subjects having ECOG PS of 0 in the Plat + Gem arm (*see* **FIG. 18A**). A median PFS of 9.3 months was observed in subjects having ECOG PS of 1-2 in the EV + Pembro arm, whereas a median PFS of 6.1 months was observed in subjects having ECOG PS of 1-2 in the Plat + Gem arm (*see* **FIG. 18A**). A median PFS of 18.7 months was

observed in subjects having normal renal function in the EV + Pembro arm, whereas a median PFS of 6.7 months was observed in subjects having normal renal function in the Plat + Gem arm (*see* **FIG. 18A**). A median PFS of 12.7 months was observed in subjects having mild renal function in the EV + Pembro arm, whereas a median PFS of 6.3 months was observed in subjects having mild renal function in the Plat + Gem arm (*see* **FIG. 18A)**. A median PFS of 10.5 months was observed in subjects having moderate/severe renal function in the EV + Pembro arm, whereas a median PFS of of 6.2 months was observed in subjects having moderate/severe renal function in the Plat + Gem arm (*see* **FIG. 18A**).

[001274] According to the blinded independent central review, as shown in **FIG. 21A** and **FIG. 21B**, median OS for for the EV + Pembro arm was 31.5 months (95% CI: 25.4, -) and median OS for the Plat + Gem arm was 16.1 months (95% CI: 13.9, 18.3). Thus, the median OS for the EV + Pembro arm was approximately two (2) times the median OS for the Plat + Gem arm (*see* **FIG. 21A** and **FIG. 21B**). Risk of death was reduced by 53.2% in subjects who received EV + Pembro. At 6 months, the OS for the EV + Pembro arm was 90.2% and the OS for the Plat + Gem arm was 81.9% (*see* **FIG. 21B)**. At 12 months, the OS for the EV + Pembro arm was 78.2% and the OS for the Plat + Gem arm was 61.4% (*see* **FIG. 21B)**. At 18 months, the OS for the EV + Pembro arm was 69.5% and the OS for the Plat + Gem arm was 44.7% (*see* **FIG. 21B)**. The median follow-up time was 17.2 (0.07, 37.16).

[001275] According to the blinded independent central review, in the OS subgroup analysis of subjects in the EV + Pembro and Plat + Gem arms, as shown in **FIG. 22A**, an OS benefit was consistently observed across pre-specified subgroups. In particular, an OS benefit was consistently observed in the EV + Pembro arm relative to the Plat + Gem arm. As indicated *supra*, the overall median OS for the EV + Pembro arm was 31.5 months (25.4, -) and overall median PFS for the Plat + Gem arm was 16.1 months (13.9, 18.3). Meaningful improvement was observed in the EV + Pembro arm relative to the Plat + Gem arm in both cisplatin-eligible (HR = 0.528) and cisplatin-ineligible (HR = 0.428) subgroups (*see* **FIG. 22A** and **FIGS. 23A and 23B**). For example, a median OS of 31.5 months was observed in cisplatin eligible subjects in the EV + Pembro arm, whereas a median OS of 18.4 months was observed in cisplatin eligible subjects in the Plat + Gem arm (*see* **FIG. 22A** and **FIG. 23A)**. In addition, a median OS was not reached in cisplatin ineligible subjects in the EV + Pembro arm, whereas a median OS of 12.7 months was observed in cisplatin ineligible subjects in the Plat + Gem arm (*see* **FIG. 22A** and **FIG. 23B)**. Meaningful improvement was also observed in the EV + Pembro arm relative to the Plat + Gem arm in subjects having high (CPS ≥10) PD-L1 expression (HR = 0.492) and in subjects having low (CPS <10) PD-L1 expression (HR =

0.435) subgroups (*see* **FIG. 22A** and **FIGS. 24A and 24B**). A median OS of 31.5 months was observed in subjects having high (CPS ≥ 10) PD-L1 expression in the EV + Pembro arm, whereas a median OS of 16.6 months was observed in subjects having high (CPS ≥ 10) PD-L1 expression in the Plat + Gem arm (*see* **FIG. 22A** and **FIG. 24A)**. A median OS was not reached in subjects having low (CPS < 10) PD-L1 expression in the EV + Pembro arm, whereas a median OS of 15.5 months was observed in subjects having low (CPS < 10) PD-L1 expression in the Plat + Gem arm (*see* **FIG. 22A** and **FIG. 24B)**. Additional examples of other subgroups in the analysis in **FIG. 22A** include the following. A median OS was not reached in subjects with liver metastases absent in the EV + Pembro arm (*see* **FIG. 22A** and **FIG. 22C**, dark upper line in graph), whereas a median OS of 17.9 months was observed in subjects with liver metastases absent in the Plat + Gem arm (*see* **FIG. 22A** and **FIG. 22C**, light lower line in graph) (HR; 95% CI: 0.47; 0.36-0.61). A median OS of 19.1 months was observed in subjects with liver metastases present in the EV + Pembro arm (*see* **FIG. 22A** and **FIG. 22B**, dark upper line in graph), whereas a median OS of 10.1 months was observed in subjects with liver metastases present in the Plat + Gem arm (*see* **FIG. 22A** and **FIG. 22B**, light lower line in graph) (HR; 95% CI: 0.47; 0.32-0.71). A median OS of 25.6 months was observed in subjects with visceral metastasis in the EV + Pembro arm (*see* **FIG. 22A** and **FIG. 22D**, dark upper line in graph), whereas a median OS of 13.6 months was observed in subjects with visceral metastasis in the Plat + Gem arm (*see* **FIG. 22A** and **FIG. 22D**, light lower line in graph) (HR; 95% CI: 0.47; 0.37-0.60). A median OS was not reached in subjects with lymph node only in the EV + Pembro arm (*see* **FIG. 22A** and **FIG. 22E**, dark upper line in graph), whereas a median OS of 27.5 months was observed in subjects with lymph node only in the Plat + Gem arm (*see* **FIG. 22A** and **FIG. 22E**, light lower line in graph) (HR; 95% CI: 0.46; 0.27-0.78). A median OS of 26.1 months was observed in subjects of white race in the EV + Pembro arm, whereas a median OS of 15.3 months was observed in subjects of white race in the Plat + Gem arm (*see* **FIG. 22A)**. A median OS was not reached in subjects of "other" race in the EV + Pembro arm, whereas a median OS of 19.3 months was observed in subjects of "other" race in the Plat + Gem arm (*see* **FIG. 22A)**. A median OS was not reached in subjects having ECOG PS of 0 in the EV + Pembro arm, whereas a median OS of 18.4 months was observed in subjects having ECOG PS of 0 in the Plat + Gem arm (*see* **FIG. 22A)**. A median OS of 25.4 months was observed in subjects having ECOG PS of 1-2 in the EV + Pembro arm, whereas a median OS of 13.1 months was observed in subjects having ECOG PS of 1-2 in the Plat + Gem arm (*see* **FIG. 22A)**. A median OS of 26.1 months was observed in subjects having normal renal function in the EV + Pembro arm, whereas a median

OS of 18.4 months was observed in subjects having normal renal function in the Plat + Gem arm (*see* **FIG. 22A)**. A median OS was not reached in subjects having mild renal function in the EV + Pembro arm, whereas a median OS of 16.4 months was observed in subjects having mild renal function in the Plat + Gem arm (*see* **FIG. 22A)**. A median OS of 31.5 months was observed in subjects having moderate/severe renal function in the EV + Pembro arm, whereas a median OS of of 13.3 months was observed in subjects having moderate/severe renal function in the Plat + Gem arm (*see* **FIG. 22A)**.

[001276] According to the blinded independent central review (BICR) (per RECIST), the overall response rate (ORR) for the EV + Pembro arm was 67.7% (95% CI: 63.1, 72.1) with a complete response (CR) of 29.1%, and the overall response rate (ORR) for the Plat + Gem arm was 44.4% (95% CI: 39.7, 49.2) (2-sided p-value <0.00001), as shown in **FIG. 25**. The EV + Pembro arm demonstrates statistically significant and clinically meaningful improvement in ORR compared to the Plat + Gem arm. The ORR per investigator assessment was consistent with BICR assessment. The concordance between investigator and BICR was 88.8%. The complete response (CR) in the EV + Pembro arm was 29.1%, whereas the CR in the Plat + Gem arm was 12.5% (*see* **FIG. 25)**. The partial response (PR) in the EV + Pembro arm was 38.7%, whereas the PR in the Plat + Gem arm was 32.0% (*see* **FIG. 25)**. The stable disease (SD) in the EV + Pembro arm was 18.8%, whereas the SD in the Plat + Gem arm was 33.8% (*see* **FIG. 25)**. Progressive disease (PD) in the EV + Pembro arm was 8.7%, whereas PD in the Plat + Gem arm was 13.6% (*see* **FIG. 25)**. 0% and 0.9% of subjects were not evaluable in the EV + Pembro and Plat + Gem arms, respectively (*see* **FIG. 25)**. 4.8% and 7.3% of subjects were not assessed in the EV + Pembro and Plat + Gem arms, respectively (*see* **FIG. 25)**. Median time to response in the EV + Pembro arm was 2.10 months (1.3, 12.3) and median time to response in the Plat + Gem arm was 2.10 months (1.6, 8.3) (*see* **FIG. 25)**.

[001277] According to the blinded independent central review, in the ORR subgroup analysis of subjects in the EV+Pembro arm and Plat + Gem arm as shown in **FIG. 26**, an ORR benefit was observed across pre-specified subgroups. A confirmed ORR with EV + Pembro was >60% for all subgroups (*see* **FIG. 26**). As indicated *supra*, the ORR for the EV + Pembro arm was 67.7% and the ORR for the Plat + Gem arm was 44.4% (*see* **FIG. 26**). Exemplary comparisons of ORR data for the EV + Pembro arm and Plat + Gem arm in subgroups are as follows. For example, an ORR of 70.8% was observed in cisplatin eligible subjects in the EV + Pembro arm, whereas an ORR of 53.0% was observed in cisplatin eligible subjects in the Plat + Gem arm (*see* **FIG. 26)**. In addition, an ORR of 63.9% was observed in cisplatin ineligible subjects in the EV + Pembro arm, whereas an ORR of 34.9%

was observed in cisplatin ineligible subjects in the Plat + Gem arm (*see* **FIG. 26)**. An ORR of 71.1% was observed in subjects having high (CPS ≥ 10) PD-L1 expression in the EV + Pembro arm, whereas an ORR of 46.6% was observed in subjects having high (CPS ≥ 10) PD-L1 expression in the Plat + Gem arm (*see* **FIG. 26)**. An ORR of 63.3% was observed in subjects having low (CPS < 10) PD-L1 expression in the EV + Pembro arm, whereas an ORR of 41.0% was observed in subjects having low (CPS < 10) PD-L1 expression in the Plat + Gem arm (*see* **FIG. 26)**. An ORR of 70.0% was observed in subjects with liver metastases absent in the EV + Pembro arm, whereas an ORR of 45.3% was observed in subjects with liver metastases absent in the Plat + Gem arm (*see* **FIG. 26**). An ORR of 60% was observed in subjects with liver metastases present in the EV + pembro arm, whereas an ORR of 41.4% was observed in subjects with liver metastases present in the Plat + Gem arm (*see* **FIG. 26**). An ORR of 66.4% was observed in subjects of white race in the EV + Pembro arm, whereas an ORR of 45.0% was observed in subjects of white race in the Plat + Gem arm (*see* **FIG. 26)**. An ORR of 70.8% was observed in subjects of "other" race in the EV + Pembro arm, whereas an ORR of 43.4% was observed in subjects of "other" race in the Plat + Gem arm (*see* **FIG. 26)**. An ORR of 72.5% was observed in subjects having ECOG PS of 0 in the EV + Pembro arm, whereas an ORR of 49.8% was observed in subjects having ECOG PS of 0 in the Plat + Gem arm (*see* **FIG. 26)**. An ORR of 62.8% was observed in subjects having ECOG PS of 1-2 in the EV + Pembro arm, whereas an ORR of 39.4% was observed in subjects having ECOG PS of 1-2 in the Plat + Gem arm (*see* **FIG. 26)**. An ORR of 69.0% was observed in subjects having normal renal function in the EV + Pembro arm, whereas an ORR of 55.8% was observed in subjects having normal renal function in the Plat + Gem arm (*see* **FIG. 26)**. An ORR of 68.1% was observed in subjects having mild renal function in the EV + Pembro arm, whereas an ORR of 45.0% was observed in subjects having mild renal function in the Plat + Gem arm (*see* **FIG. 26)**. An ORR of 66.8% was observed in subjects having moderate/severe renal function in the EV + Pembro arm, whereas an ORR of of 38.2% was observed in subjects having moderate/severe renal function in the Plat + Gem arm (*see* **FIG. 26)**.

[001278] According to the blinded independent central review, median duration of response (mDOR) was not reached in EV + Pembro arm (95% CI: 20.2, -) (*see* **FIGS. 27A and FIG. 27B)**. mDOR in the Plat + Gem arm was 7.0 months (95% CI: 6.2, 10.2) (*see* **FIG. 27A** and **FIG. 27B)**. In the EV + Pembro arm, the DOR's at 12 and 18 months were 67.3% and 59.6%, respectively (*see* **FIG. 27B)**. In contrast, in the Plat + Gem arm, the DOR's at 12 and 18 months were 35.2% and 19.3%, respectively (*see* **FIG. 27B)**. In the EV + Pembro arm, the

DOR at 6 months was 85.9% (*see* **FIG. 27B)**. In the Plat + Gem arm, the DOR at 6 months was 60.6% (*see* **FIG. 27B)**.

[001279] Regarding the overall summary of treatment-emergent adverse events (TEAEs), the safety profile of the EV + Pembro combination was manageable and tolerable in the 1L la/mUC population, as shown in **FIG. 28**. Differences between the EV + Pembro combination and the Plat + Gem arm may be due to different mechanisms of action of the agents and differing durations of treatment.

[001280] Most common TEAEs (all grades) occurring in ≥ 20% subjects (by preferred term) are shown in **FIG. 29**. TEAEs observed were consistent with the underlying disease, pre-existing comorbidities, advanced age of the study population, and the known safety profile of the respective agents.

[001281] **FIG. 30** shows the TEAEs occurring in greater than or equal to 15% of subjects (by preferred term).

[001282] **FIG. 31** and **FIG. 32** show the TEAEs with greater than or equal to Grade 3 occurring in greater than or equal to 5% of subjects (by preferred term). Grade 3 to 5 TEAEs observed with administration of the EV + Pembro combination were consistent with the known safety profile of EV, Pembro, or both.

[001283] Serious adverse events (SAEs) occurring in greater than or equal to 2% of subjects are shown in **FIG. 33** (by preferred term). SAEs observed were consistent with historical data and the known safety profile of the respective agents.

[001284] **FIG. 34** shows TEAEs leading to death. TEAEs leading to death on EV + Pembro were heavily confounded by disease progression, pre-existing comorbidities, and/or advanced age of the study population.

[001285] **FIG. 35** shows TEAEs leading to discontinuation of any study drugs occurring in ≥1% of subjects (by preferred term). Peripheral sensory neuropathy was the most common TEAE leading to treatment discontinuation in the EV + Pembro arm. Anemia and Acute kidney injury (AKI) are two common TEAEs leading to treatment discontinuation in the Plat + Gem arm.

[001286] **FIG. 36** shows adverse events of special interest (AESI) for enfortumab vedotin. EV AESI occurred at a higher frequency for the EV + Pembro arm (compared to the Plat + Gem arm) but were generally consistent with historical EV monotherapy data. Skin reactions and peripheral neuropathy (PN) occurred at a higher frequency in the EV + Pembro arm compared to EV monotherapy.

[001287] **FIG. 37** shows pembrolizumab adverse events of special interest (AEOSI) occurring in >2 subjects in the EV + Pembro arm. Pembrolizumab AEOSI occurred at a higher frequency in the EV + Pembro arm but were generally consistent with historical pembrolizumab data. Severe skin reactions and pneumonitis occurred at a higher frequency in the EV + Pembro combination as compared to pembrolizumab monotherapy.

6.2.4 Conclusion

[001288] All in all, the study described *supra* met its dual primary endpoints of overall survival (OS) and progression-free survival (PFS), compared to chemotherapy. OS crossed the pre-specified efficacy boundary at interim analysis. The safety results of the combination are consistent with those of enfortumab vedotin in combination with pembrolizumab previously reported in cisplatin-ineligible patients with la/mUC.

[001289] Results from the EV + Pembro arm demonstrated a statistically significant and clinically meaningful improvement in PFS, OS, and ORR as compared to standard platinum containing chemotherapy (i.e., the Plat + Gem arm) in the 1L LA/mUC setting. In particular, the median PFS was 12.5 months in the EV + Pembro arm, whereas the median PFS was 6.3 months in the Plat + Gem arm; thus, the risk of disease progression or death was reduced by 55% in subjects who received EV + Pembro relative to subjects who received Plat + Gem (HR = 0.45; 2-sided p-value < 0.00001). In addition, the median OS was 31.5 months in the EV + Pembro arm, whereas the median OS was 16.1 months in the Plat + Gem arm; thus, the risk of death was reduced by 53.2% in subjects who received EV + Pembro relative to subjects who received Plat + Gem (HR = 0.468; 2-sided p-value < 0.00001). Thus, median PFS and median OS were nearly doubled in the EV + Pembro arm compared to median PFS and median OS in the chemotherapy arm. The confirmed ORR by BICR was 67.7% (95% CI: 63.1%, 72.1%) in the EV + Pembro arm, whereas the confirmed ORR by BICR was 44.4% (95% CI: 39.7%, 49.2%) in the Plat + Gem arm (p-value < 0.00001). The magnitude of benefit observed with the EV + Pembro arm was similar between cisplatin-eligible and cisplatin-ineligible subgroups. Consistent results were observed across all pre-defined subgroups. That is, the benefit from treatment with EV + Pembro observed in all pre-specified subgroups was consistent with the overall patient population. The safety profile for EV + Pembro were generally tolerable and manageable. Accordingly, no new safety concerns emerged. Skin reactions and pneumonitis are known risks associated with EV and Pembro monotherapies. Higher rates observed in the EV + Pembro arm are likely indicative of a contribution from both components of therapy. The data herein supports a positive benefit/risk for EV +

Pembro as a first line (1L) treatment option for patients with LA/mUC. All in all, the positive results herein provide a potential new standard of care – i.e., the combination of EV and pembrolizumab – for first line metastatic bladder cancer, including advanced-stage urothelial cancer, which is aggressive and associated with devastating outcomes.

6.3 Example 3 – Additional Results from the Phase 3 Study of Enfortumab Vedotin Combined with Pembrolizumab Versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer: Analysis of the Cisplatin-Ineligible Population.

6.3.1 Methods

[001290] The following Example presents additional results from the protocol described in Example 1, *supra*, which enrolled patients with previously untreated la/mUC who were eligible for cisplatin- or carboplatin-containing chemotherapy regardless of PD-L1 status. The protocol described in Example 1 is an open-label, randomized, controlled Phase 3 study, evaluating enfortumab vedotin in combination with pembrolizumab versus chemotherapy in patients with previously untreated la/mUC. Since cisplatin eligibility status has long defined the first line of treatment, the following analysis provides results for patients who were ineligible for cisplatin at randomization.

[001291] Patients with previously untreated la/mUC were randomized 1:1 to receive 3-week cycles of EV (1.25 mg/kg IV; Days 1 and 8) and P (200 mg IV; Day 1) or platinum-based chemotherapy (PBC)/chemotherapy (gemcitabine with cisplatin (cis) or carboplatin (carbo)). Select secondary endpoints included confirmed objective response rate (ORR), duration of response (DOR), and safety. Subjects were deemed eligible or ineligible for cisplatin based upon protocol-defined criteria and stratified accordingly.

[001292] Key demographics and baseline characteristics are shown in **FIG. 38**. Compared with the intent-to-treat (ITT) population, cisplatin-ineligible subjects were older, had higher ECOG PS scores, and a higher rate of upper tract disease. ITT age: 69.0 (EV+P); 69.0 (chemo). ITT ECOG PS: 0: 50.5%, 1: 46.2%, 2: 3.4% (EV+P); 0: 48.4%, 1: 48.6%, 2: 2.5% (chemo). ITT upper tract disease: 30.5% (EV+P); 23.4% (chemo).

[001293] As shown in **FIG. 39**, which provides a summary of disposition of subjects, the number of cisplatin-ineligible subjects randomized who received any amount of study drug in the EV + Pembrolizumab ("EV + pembro") arm of the study was 198. The number of subjects randomized who received any amount of study drug in the chemotherapy arm (i.e., gemcitabine + cisplatin or carboplatin (i.e., "Plat + Gem") was 210. Thus, 408 subjects total

(EV+P: 198, PBC: 210) were cisplatin-ineligible at randomization. The number of cisplatin-ineligible subjects who received any amount of study drug in the EV + Pembrolizumab ("EV + pembro") arm of the study was 197. 205 cisplatin-ineligible subjects (97.6%) in the PBC arm received carboplatin at Cycle 1 (5 patients were not treated).

[001294] **FIG. 40** provides reasons for cisplatin ineligibility for the cisplatin ineligible subjects in this analysis.

[001295] As provided in Example 2, *supra*, a median PFS of 6.1 months was observed in cisplatin ineligible subjects in the chemotherapy / Plat + Gem arm (HR: 0.43, 95% CI, 0.33, 0.55) (*see* **FIG. 19B)**. Further, the 12-month PFS rate for EV+P was 46.7% and the 12-month PFS rate for the chemotherapy arm was 16.8%. In addition, the 18-month PFS rate for EV+P was 41.1% and the 18-month PFS rate for the chemotherapy arm was 7.6%.

[001296] Also provided in Example 2, *supra*, mOS was not reached for EV+P and a median OS of 12.7 months was observed in cisplatin ineligible subjects in the chemotherapy / Plat + Gem arm (HR: 0.43, 95% CI, 0.31, 0.59) (*see* **FIG. 23B**). Further, the 12-month OS rate for EV+P was 74.1% and the 12-month OS rate for the chemotherapy arm was 54.3%. In addition, the 18-month OS rate for EV+P was 68.4% and the 18-month PFS rate for the chemotherapy arm was 38.2%.

[001297] According to the blinded independent central review (BICR) (per RECIST), the overall response rate (ORR) for the EV + Pembro arm was 63.9% (95% CI: 56.7, 70.7) with a complete response (CR) of 24.7% and a partial response (PR) of 39.2%, and the ORR for the chemotherapy arm was 34.9% (95% CI: 28.5, 41.8) with a CR of 9.1% and a PR of 25.8%, as shown in **FIG. 41A**. **FIG. 41B** provides the time to objective response for EV+P, which was 2.1 months (2.0, 2.2), and for the chemotherapy arm, which was 2.1 months (2.0, 2.3).

[001298] Median duration of response (mDOR) (95% CI) for EV+P was not reached (16.3 months, NR) (*see* **FIG. 42**). For the chemotherapy arm, mDOR (95% CI) was 6.6 months (5.6, 10.2) (*see* **FIG. 42**).

[001299] **FIG. 43** provides a summary of subsequent anticancer therapies in the EV + Pembro arm and chemotherapy arm. In EV+P arm, 62 subjects (31.3%) remained on treatment at data cutoff (DCO). For the EV + Pembro arm, the number of subjects who received subsequent anticancer therapies was 55 (27.8%). For the chemotherapy arm, the number of subjects who received subsequent anticancer therapies was 140 (66.7%). For the EV + Pembro arm, 38 (19.2%) received a platinum-based therapy as the first subsequent systemic therapy received, 10 (5.1%) received a cisplatin-based therapy, and 27 (13.6%) received a carboplatin-based therapy. 4 subjects (2%) received PD-1/L1 inhibitor-containing

therapy (0 subjects received maintenance therapy and 0 subjects received Avelumab maintenance therapy), 4 subjects (2%) received PD-1/L1 inhibitor-containing therapy following progression, and 4 subjects (2%) received "other" therapy as the first subsequent systemic therapy received. In chemotherapy arm, all subjects were off study treatment at DCO. For the chemotherapy arm, 7 subjects (3.3%) received a platinum-based therapy as the first subsequent systemic therapy received, 2 subjects (1.0%) received a cisplatin-based therapy, and 4 subjects (1.9%) received a carboplatin-based therapy. 114 subjects (54.3%) received PD-1/L1 inhibitor-containing therapy (56 subjects (26.7%) received maintenance therapy and 52 subjects (24.8%) received Avelumab maintenance therapy), 58 subjects (27.6%) received PD-1/L1 inhibitor-containing therapy following progression as second line treatment, and 11 subjects (5.2%) received "other" therapy as the first subsequent systemic therapy received. Notably, 26.7% of patients in the chemotherapy arm received maintenance therapy; the majority of these patients received avelumab.

[001300] **FIG. 44** provides treatment-related adverse events. Serious TRAEs were observed in 60 subjects (30.5%) treated with EV+P and in 45 subjects (22.0%) treated with chemotherapy. TRAEs leading to death (per investigator) included diarrhea and multiple organ dysfunction syndrome in patients treated with EV+P (i.e., 2 subjects (1.0%)). In subjects treated with chemotherapy, TRAEs leading to death (per investigator) included febrile neutropenia, neutropenic sepsis, and sepsis (i.e., 3 subjects (1.5%)). Grade ≥3 TRAEs occurred in 58.4% of subjects with EV+P and 77.1% of subjects with chemotherapy. As shown in **FIG. 45**, the most common grade ≥3 TRAEs of special interest for EV were skin reactions (16.2%), peripheral neuropathy (8.1%), and hyperglycemia (4.1%). As shown in **FIG. 46**, the most common grade ≥3 treatment-emergent AEs of special interest for pembrolizumab were severe skin reaction (14.7%), hepatitis (2.0%), and pneumonitis (2.0%). There were no new safety signals in the cisplatin-ineligible subgroup.

[001301] Conclusion: In this patient population with historically poor prognosis, EV administered in combination with pembrolizumab (EV+P) improved clinical outcomes in subjects who were ineligible for cisplatin with previously untreated 1L la/mUC. The risk of death was reduced by more than 50%. The efficacy results for the cisplatin-ineligible population were consistent with those of the overall population. The adverse event (AE) profile of EV+P was generally manageable with no new safety signals in this patient population. The results of this analysis support EV+P as a new standard of care (SOC) for la/mUC, including for subjects who are ineligible for cisplatin.

6.4 Example 4 – Additional Results from the Phase 3 Study of Enfortumab Vedotin Combined with Pembrolizumab Versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer: Analysis of the Cisplatin-eligible Population.

6.4.1 Methods

[001302] The following Example presents additional results from the protocol described in Example 1, *supra*, which enrolled patients with previously untreated la/mUC who were eligible for cisplatin- or carboplatin-containing chemotherapy regardness of PD-L1 status. The protocol described in Example 1 is an open-label, randomized, controlled Phase 3 study, evaluating enfortumab vedotin in combination with pembrolizumab versus chemotherapy in patients with previously untreated la/mUC. Since cisplatin eligibility status has long defined the first line of treatment, the following analysis provides results for patients who were eligible for cisplatin at randomization.

[001303] Patients with previously untreated la/mUC were randomized 1:1 to receive 3-week cycles of EV (1.25 mg/kg IV; Days 1 and 8) and P (200 mg IV; Day 1) or PBC/chemotherapy (gemcitabine with cisplatin (cis) or carboplatin (carbo)). Select secondary endpoints included confirmed objective response rate (ORR), duration of response (DOR), and safety. Subjects were deemed eligible or ineligible for cisplatin based upon protocol-defined criteria and stratified accordingly.

[001304] Key demographics and baseline characteristics are shown in **FIG. 47**. Compared with the ITT population, cisplatin-eligible patients were younger, had lower ECOG PS scores, and a lower rate of upper tract disease. ITT age is 69.0 (EV+P) and 69.0 (chemo). ITT ECOG PS is 0: 50.5%, 1: 46.2%, 2: 3.4% (EV+P); 0: 48.4%, 1: 48.6%, 2: 2.5% (chemo). ITT upper tract disease is 30.5% (EV+P); 23.4% (chemo).

[001305] As shown in **FIG. 48**, which provides a summary of disposition of subjects, the number of cisplatin-eligible subjects randomized who received any amount of study drug in the EV + Pembrolizumab ("EV + pembro") arm of the study was 244. The number of subjects randomized who received any amount of study drug in the chemotherapy arm (i.e., gemcitabine + cisplatin or carboplatin (i.e., "Plat + Gem") was 234. Thus, 478 subjects total (EV+P: 244, PBC: 234) were cisplatin-eligible at randomization. The number of cisplatin-eligible subjects who received any amount of study drug in the EV + Pembrolizumab ("EV + pembro") arm of the study was 243 (99.6%). 228 cisplatin-eligible subjects (97.4%) in the PBC arm received chemotherapy (220/234 (94.0%) of cisplatin-eligible patients received

cisplatin at Cycle 1, 8 patients received carboplatin at Cycle 1, and 6 patients were not treated).

[001306] As provided in Example 2, *supra*, a median PFS of 6.5 months was observed in cisplatin eligible subjects in the chemotherapy / Plat + Gem arm (HR: 0.48, 95% CI, 0.38, 0.62) (*see* **FIG. 19A**). Further, the 12-month PFS rate for EV+P was 53.9% and the 12-month PFS rate for the chemotherapy arm was 25.8%. In addition, the 18-month PFS rate for EV+P was 46.1% and the 18-month PFS rate for the chemotherapy arm was 15.5%.

[001307] Also provided in Example 2, *supra*, mOS of 31.5 months was observed for EV+P and a median OS of 18.4 months was observed in cisplatin eligible subjects in the chemotherapy / Plat + Gem arm (HR: 0.53, 95% CI, 0.39-0.72) (*see* **FIG. 23A**). Further, the 12-month OS rate for EV+P was 81.4% and the 12-month OS rate for the chemotherapy arm was 68.0%. In addition, the 18-month OS rate for EV+P was 70.4% and the 18-month PFS rate for the chemotherapy arm was 50.7%.

[001308] According to the blinded independent central review (BICR) (per RECIST), the overall response rate (ORR) for the EV + Pembro arm was 70.8% (95% CI: 64.6, 76.4) with a complete response (CR) of 32.5% and a partial response (PR) of 38.3%, and the ORR for the chemotherapy arm was 53.0% (95% CI: 46.4, 59.6) with a CR of 15.5% and a PR of 37.5%, as shown in **FIG. 49A**. **FIG. 49B** provides the time to objective response for EV+P, which was 2.1 months (2.0, 2.2), and for the chemotherapy arm, which was 2.1 months (2.0, 2.2).

[001309] Median duration of response (mDOR) (95% CI) for EV+P was not reached (18.2 months, NR) (*see* **FIG. 50**). For the chemotherapy arm, mDOR (95% CI) was 8.3 months (5.9-10.9) (*see* **FIG. 50**).

[001310] **FIG. 51** provides a summary of subsequent anticancer therapies in the EV + Pembro arm and chemotherapy arm. In EV+P arm, 82 subjects (33.6%) remained on treatment at data cutoff (DCO). For the EV + Pembro arm, the number of subjects who received subsequent anticancer therapies was 85 (34.8%). For the chemotherapy arm, the number of subjects who received subsequent anticancer therapies was 173 (73.9%). For the EV + Pembro arm, 72 (29.%) received a platinum-based therapy as the first subsequent systemic therapy received, 43 (17.6%) received a cisplatin-based therapy, and 229 (11.9%) received a carboplatin-based therapy. 3 subjects (1.2%) received PD-1/L1 inhibitor-containing therapy (0 subjects received maintenance therapy and 0 subjects received Avelumab maintenance therapy), 3 subjects (1.2%) received PD-1/L1 inhibitor-containing therapy following progression, and 7 subjects (2.9%) received "other" therapy as the first subsequent systemic therapy received. In chemotherapy arm, all subjects were off study

treatment at DCO. For the chemotherapy arm, 10 subjects (4.3%) received a platinum-based therapy as the first subsequent systemic therapy received, 6 subjects (2.6%) received a cisplatin-based therapy, and 4 subjects (1.7%) received a carboplatin-based therapy. 146 subjects (62.4%) received PD-1/L1 inhibitor-containing therapy (87 subjects (37.2%) received maintenance therapy and 83 subjects (35.5%) received Avelumab maintenance therapy), 59 subjects (25.2%) received PD-1/L1 inhibitor-containing therapy following progression as second line treatment, and 6 subjects (2.6%) received "other" therapy as the first subsequent systemic therapy received.

[001311] **FIG. 52** provides treatment-related adverse events. Serious TRAEs were observed in 62 subjects (25.5%) treated with EV+P and in 40 subjects (17.5%) treated with chemotherapy. TRAEs leading to death (per investigator) included immune-mediated lung disease and asthenia in patients treated with EV+P (i.e., 2 subjects (0.8%)). In subjects treated with chemotherapy, TRAEs leading to death (per investigator) included myocardial infarction (i.e., 1 subject (0.4%)). Grade ≥3 TRAEs occurred in 53.9% of subjects with EV+P and 62.7% of subjects with chemotherapy. As shown in **FIG. 53**, the most common grade ≥3 TRAEs of special interest for EV were skin reactions (14.8%), hyperglycemia (7.8%), and peripheral neuropathy (5.8%). As shown in **FIG. 54**, the most common grade ≥3 treatment-emergent AEs of special interest for pembrolizumab were severe skin reaction (9.5%), pneumonitis (4.9%), and colitis (2.9%). There were no new safety signals in the cisplatin-eligible subgroup.

[001312] Conclusion: EV administered in combination with pembrolizumab (EV+P) improved clinical outcomes in subject who were eligible for cisplatin with previously untreated la/mUC, thereby reducing the risk of death by 47% compared with chemotherapy. The efficacy results for the cisplatin-eligible population were consistent with those of the overall population. The AE profile of EV+P was generally manageable with no new safety signals in this patient population. The results of this analysis support EV+P as a new standard of care (SOC) for la/mUC, including for subjects who are eligible for cisplatin.

6.5 Example 5 – Additional Results from the Phase 3 Study of Enfortumab Vedotin Combined with Pembrolizumab Versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer: Analysis of the post-hoc pan-Asian subgroup.

6.5.1 Methods

[001313] The following Example presents additional results from the protocol described in Example 1, *supra*, which enrolled patients with previously untreated la/mUC who were eligible for cisplatin- or carboplatin-containing chemotherapy regardless of PD-L1 status. The protocol described in Example 1 is an open-label, randomized, controlled Phase 3 study, evaluating enfortumab vedotin in combination with pembrolizumab versus chemotherapy in patients with previously untreated la/mUC. In the Phase 3 study, EV+P demonstrated statistically significantly prolonged overall survival (OS) and progression-free survival (PFS) vs chemo in patients with previously untreated la/mUC. The additional results presented in this Example relate to an analysis of the post hoc pan-Asian subgroup of the Phase 3 study.

[001314] Patients with previously untreated la/mUC were randomly assigned 1:1 to receive 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and Pembrolizumab (200 mg; IV) on Day 1 or gemcitabine with cisplatin or carboplatin (chemo). Dual primary endpoints were PFS per RECIST v1.1 by BICR and OS. Select secondary endpoints included objective response rate (ORR) and safety. Patients from China, Japan, Korea, Singapore, Thailand, and Taiwan were included in this analysis.

6.5.2 Results

[001315] In the Phase 3 Study of Enfortumab Vedotin Combined with Pembrolizumab Versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer, 886 patients/subjects were randomly assigned; 176 patients/subjects (EV+P arm: 94 patients/subjects; chemotherapy arm: 82 patients/subjects) were from Asian countries, and patient characteristics were balanced between arms. At the data cutoff, the median follow-up time was 15.6 months. As shown in **FIG. 55**, for the pan-Asian subgroup, median PFS was prolonged in subjects treated with EV+P vs subjects treated with chemotherapy, thereby reducing the risk of progression or death by 70% (hazard ratio (HR) 0.30; [95% CI: 0.19–0.48]). In particular, a median PFS was not reached (14.5, -) in subjects in the EV + Pembro arm, whereas a median PFS of 6.3 months (4.1, 8.1) was observed in subjects in the Plat + Gem arm (*see* **FIG. 55**) (HR of 0.300 (95% CI: 0.187, 0.482) for EV+P vs chemotherapy). As shown in **FIG. 56**, for median OS, EV+P reduced the risk of death by 66% (HR 0.34; [95% CI: 0.18–0.65]) vs chemo. In particular, a median OS was not reached (-, -) in the EV + Pembro arm and a median OS was not reached (12.7, -) in the Plat + Gem arm (*see* **FIG. 56**) (HR of 0.344 (95% CI: 0.183, 0.646) for EV+P vs chemotherapy). Confirmed ORR was 72.2% and 35.0% in EV+P and chemotherapy arms, respectively.

[001316] Regarding safety, grade ≥ 3 treatment-related adverse events (TRAEs) occurred in 64.9% of subjects treated with EV+P and 68.4% of subjects treated with chemotherapy. The most common grade ≥ 3 TRAEs observed were maculopapular rash (11.7%), hyperglycemia (10.6%), and peripheral sensory neuropathy (7.4%) for subjects treated with EV+P and neutropenia (25.0%), anemia (19.7%), and neutrophil count decreased (18.4%) for subjects treated with chemotherapy. The most common grade ≥ 3 TRAEs of special interest for EV were skin reactions (27.7%), hyperglycemia (10.6%), and peripheral neuropathy (8.5%). The most common grade ≥ 3 treatment-emergent AEs of special interest for P were severe skin reactions (18.1%) and pneumonitis (6.4%).

6.5.3 Conclusions

[001317] Consistent with results of the overall analysis *supra*, this pan-Asian subgroup analysis showed that EV+P improved outcomes in subjects with previously untreated la/mUC, and the safety profile was generally manageable. These results further support EV+P as a new first-line treatment for patients with la/mUC.

6.6 Example 6 – Additional Results from the Phase 3 Study of Enfortumab Vedotin Combined with Pembrolizumab Versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer: Patient-Reported Outcomes

6.6.1 Background

[001318] Locally advanced or metastatic urothelial cancer (la/mUC) is an aggressive disease, with a 5-year survival rate of less than 8% (SEER*Explorer: An interactive website for SEER cancer statistics. Surveillance Research Program. 2023 April 19, 2023. [Accessed May 12 2023.]; Available from: https://seer.cancer.gov/statistics-network/explorer/; Ripoll, J., *et al.*, *BMC Cancer*, 2021. 21(1): p. 676; von der Maase, H., et al., *J. Clin. Oncol.*, 2005. 23(21): p. 4602-8). La/mUC is often associated with a high symptom burden including pain and emotional impacts which reduce patient quality of life (QoL) and functioning (Martin, S., *et al.*, *Bladder Cancer*, 2022. 8(1): p. 45-53; Rosenberg, J.E., *et al.*, *Eur. Urol.*, 2024. 85(6): p. 574-585; Milowsky, M.I., *et al.*, *J. Clin. Oncol.*, 2024: p. Jco2301547). Until recently, the preferred first-line (1L) treatment option for patients with la/mUC was platinum-based chemotherapy (PBC) with gemcitabine plus either cisplatin or carboplatin, followed by maintenance avelumab in eligible patients (Flaig, T.W., *et al.*, *J. Natl. Compr. Canc. Netw.*, 2020. 18(3): p. 329-354; Powles, T., *et al.*, *Ann. Oncol.*, 2022. 33(3): p. 244-258; Sridhar, S.S., *et al.*, *J. Clin. Oncology*, 2023. 41(6_suppl): p. 508-508).

[001319] Examples 2, 3, 4, and 5, *supra*, provide efficacy and safety results from the phase 3 study of enfortumab vedotin combined with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer – i.e., the protocol described in Example 1.

[001320] In the the phase 3 study of enfortumab vedotin combined with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer described *supra*, median time to pain progression (TTPP) in EV-302 was 14.2 months (6.6, -) in patients treated with EV+P versus 10.0 months (5.9, -) in those treated with PBC, as shown in **FIG. 57A** and **FIG. 57B**. The between-group difference in the time to pain progression was not significant (hazard ratio, 0.92; 95% CI, 0.72 to 1.17; P = 0.48), as shown in **FIG. 57A** and **FIG. 57B**. **FIG. 57B** further provides that 55.7% of EV + Pembro treated subjects and 55.2% of Plat + Gem subjects were without pain progression at 6 months and 51.0% of EV + Pembro treated subjects and 46.9% of Plat + Gem subjects were without pain progression at 12 months.

[001321] The following Example presents additional results from the protocol described in Example 1, *supra*, which enrolled patients with previously untreated la/mUC who were eligible for cisplatin- or carboplatin-containing chemotherapy regardless of PD-L1 status.

6.6.2 Methods

[001322] The protocol described in Example 1 is an open-label, randomized, controlled Phase 3 study, evaluating enfortumab vedotin in combination with pembrolizumab versus chemotherapy in patients with previously untreated la/mUC. In this study, patients were randomized to receive either enfortumab vedotin in combination with pembrolizumab or chemotherapy. In the following Example, additional pre-specified, descriptive patient-reported outcomes (PRO) from the Phase 3 study described in Example 1, including the impact on patient QoL, functioning and disease symptoms.

[001323] Study Treatments: Patients were randomized 1:1 to receive EV (1.25 mg/kg, intravenously) on Days 1 and 8 of 3-week cycles plus pembrolizumab ("P"; 200 mg, intravenously) on Day 1 of each cycle; or platinum-based chemotherapy (PBC) consisting of gemcitabine (1000 mg/m^2, intravenously) on Days 1 and 8 of each cycle plus either cisplatin (70 mg/m^2) or carboplatin (area under the curve [AUC] 4.5 or 5 according to local guidelines) on day 1 per 3-week cycle for up to 6 cycles. Maintenance avelumab could be used, per investigators' decision, following completion and/or discontinuation of PBC and absence of

disease progression. Randomization was stratified by cisplatin-eligibility, PD-L1 expression status and presence/absence of liver metastases.

[001324] Study Assessments: This Example provides descriptive secondary endpoints assessing patient QoL, functioning and symptoms assessed using two PRO questionnaires: the Brief Pain Inventory-Short Form (BPI-SF), and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire (EORTC QLQ-C30). The BPI-SF is a pain assessment tool validated in patients with metastatic cancer to assess the severity of pain and its impact on functioning (Martin, S., *et al.*, *Bladder Cancer*, 2022. 8(1): p. 45-53; Poquet, N. and C. Lin, *J. Physiotherapy*, 2016. 62(1): p. 52). In this Example, an increase of ≥2 points from baseline in the BPI-SF Question 3 (worst pain in the last 24 hours [worst pain]) constituted a meaningful within-patient change (Dworkin, R.H., *et al.*, *J. Pain*, 2008. 9(2): p. 105-121; Farrar, J.T., *et al.*, *Pain*, 2000. 88(3): p. 287-294).

[001325] The EORTC QLQ-C30 questionnaire assesses QoL in patients with cancer across functioning and symptom domains, and a separate global health status (GHS)/QoL domain comprised of two questions (European Organisation for Research and Treatment of Cancer. EORTC QLQ-C30 Scoring Manual. 2001 [Accessed 25 July 2023]; Available from: https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf). The EORTC QLQ-C30 has been validated in a population of patients with la/mUC and has been used in previous la/mUC therapy trials (Milowsky, M.I., et al., J. Clin. Oncol., 2024: p. Jco2301547; Luckett, T., *et al.*, *Ann. Oncol.*, 2011. 22(10): p. 2179-90). In this study a 10-point mean change in EORTC QLQ-30 symptoms, functioning or GHS score from baseline was considered clinically meaningful change (Cocks, K., *et al.*, *European J. Cancer*, 2012. 48(11): p. 1713-1721; Osoba, D., *et al.*, *J. Clin. Oncology*, 1998. 16(1): p. 139-144).

[001326] Patients completed PRO questionnaires electronically before receiving their assigned study treatment at baseline (Cycle 1 Day 1), once weekly for the first 12 weeks, then at week 14 and once every 3 weeks for the remainder of the study through progression and survival follow-up.

[001327] Study Outcomes: Mean change from baseline in BPI-SF worst pain score at week 26 was a prespecified secondary endpoint, however, this was not formally tested as per the statistical hierarchy gatekeeping strategy. Mean change from baseline in worst pain was calculated using the BPI-SF worst pain score for each post-baseline assessment timepoint for each treatment.

[001328] Additional prespecified secondary endpoints included median time to confirmed deterioration (TTCD) and least squares (LS) mean change from baseline through week 26 in

BPI-SF and EORTC QLQ-C30 domains. These analyses were descriptive only, with no adjustment for multiplicity. TTCD was defined as a clinically meaningful decrease (a 10-point worsening in EORTC QLQ-C30; a 2-point decrease in BPI-SF) from baseline for two consecutive assessments.

[001329] Descriptive responder analyses were conducted to assess categorical changes from baseline through week 26 in all BPI-SF and EORTC QLQ-C30 domains. In particular, descriptive responder analyses were conducted to assess time to clinically meaningful improvement and time to clinically meaningful deterioration in all BPI-SF and EORTC QLQ-C30 domains. Patients were classified into responder groups using pre-specified MWPC thresholds for BPI-SF and EORTC QLQ-C30, based on the following responder definitions: (1) "Improved, ≥2 categores" if their change from baseline score suggested improvement that was greater than or equal to twice the MWPC threshold; (2) "Improved, 1 category" if their change from baseline score suggested improvement that was greater than or equal to the MWPC threshold but not more than twice the MWPC threshold; (3) "Deteriorated, 1 category" if their change from baseline score suggested deterioration that exceeded or was equal to the MWPC threshold but not more than twice the MWPC threshold; (4) "Deteriorated, ≥2 categories" if their change from baseline score suggested deterioration that exceeded or was equal to twice the MWPC threshold; and (5) "Stable" if their change from baseline score was not included in any of the above categories. Proportions of patients in each responder group were presented by treatment group for all post-baseline assessments.

[001330] Time to clinically meaningful deterioration analyses were conducted for all BPI-SF and EORTC QLQ-C30 and domains. The time to deterioration was initially defined as the number of months between the date of randomization and the time of the first clinically meaningful deterioration as defined by the MWPC thresholds. "Meaningful deterioration" was defined as a deterioration in score from baseline by ≥1 MWPC threshold in magnitude. If a patient did not experience a deterioration event over the course of the study, their time to deterioration was censored at their last PRO assessment. For each PRO domain score, time to deterioration were calculated and summarized as quartiles, median, and their 95% CI for each treatment group. Kaplan-Meier curves by treatment group were presented. Where stricter criteria were required depending on the degree of fluctuation in scores over time, time to confirmed or definitive deterioration was examined. A confirmed deterioration event definition required ≥2 consecutive assessments that met the MWPC threshold for deterioration. Definitive deterioration required no improvement (within 1 MWPC threshold relative to baseline) at any subsequent assessment.

[001331] Time to clinically meaningful improvement analyses were also conducted for BPI-SF and EORTC QLQ-C30 domains. Time to confirmed improvement was analyzed using the same methods as for time to deterioration. The time to confirmed improvement was defined as the number of months between the date of randomization and the time of the first meaningful improvement, as per pre-specified MWPC thresholds for the BPI-SF and the EORTC QLQ-C30, where that meaningful improvement was sustained for ≥2 consecutive assessments. Alternative event definitions (e.g., definitive improvement, improvement that requires no deterioration at subsequent assessments, or sensitivity analyses) were explored in additional *post hoc* analyses.

[001332] Statistical Analysis: The PRO Full Analysis Set (FAS) consisted of all randomized patients who had received any amount of study treatment and had completed at least one PRO questionnaire at baseline and, unless specified otherwise, all analyses were performed on the PRO FAS.

[001333] Patients with moderate to severe pain at baseline (defined as pain score of ≥5 in BPI-SF worst pain) were a prespecified subgroup of interest.

[001334] Compliance rate analysis: Completion and compliance rates were summarized for each treatment group and by scheduled assessments for the BPI-SF and EORTC QLQ-C30 assessments. The completion rate was defined as the proportion of patients who completed the instrument among the PRO FAS. The compliance rate was defined as the proportion of patients who completed the instrument among those who were expected to complete it at a given visit.

[001335] Missing data for PROs were handled according to the user manuals for each PRO instrument (European Organisation for Research and Treatment of Cancer. EORTC QLQ-C30 Scoring Manual. 2001 [Accessed 25 July 2023]; Available from: https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf; Cleeland, C. and K. Ryan, *Annals of the Academy of Medicine*, Singapore, 1994. 23(2): p. 129-138; EuroQoL. EQ-5D-5L User Guide (version 3.0, September 2019). 2019 [Accessed 25 July 2023]; Available from: https://euroqol.org/publications/user-guides/). Following the main compliance rate analysis, post-hoc sensitivity analyses were conducted to investigate patient PRO compliance against treatment compliance until end of study treatment, and PRO compliance until disease progression.

[001336] PRO analyses: TTPP was compared between treatment arms for statistical significance and was assessed using stratified log-rank tests and hazard ratios (HR, with 95% confidence intervals [CI]), and estimated using Cox proportional hazards regression models

adjusted for age (<65 or ≥65 years old), sex, region, and stratification factors. Patients were censored at their last assessment date if pain progression had not occurred before initiation of subsequent therapy (not including maintenance therapy), death, or end of follow up. *See* Table 25 for further details.

Table 25. Censoring rules for TTCD and TTPP analyses

Situation	**Censored**	**Date of censor or end date**
Recorded clinically meaningful response during the study	No (event)	Date of first clinically meaningful response (equal to or beyond MWPC threshold)
Patient is within 1 MWPC of worst or best possible score, for time to deterioration or improvement analyses, respectively, at baseline.	Yes	Date of randomization
Patient has no recorded clinically meaningful response at data cut-off	Yes	Date of last PRO assessment the patient was known not to have recorded a clinically meaningful response
Subsequent anticancer treatment started before clinically meaningful response	Yes	Date of last PRO assessment on or prior to the start of subsequent therapy
Death before recorded clinically meaningful response	Yes	Date of last PRO assessment

MWPC, meaningful within-person change; PRO, patient reported outcome; TTCD, time to confirmed deterioration; TTPP, time to pain progression.

[001337] A mixed effect model for repeated measures (MMRM) was used to estimate the change from baseline in BPI-SF worst pain score at week 26, and the overall changes from baseline across the treatment period through week 26 in EORTC QLQ-C30 domains and single items by treatment received. The MMRM controlled for timepoint (categorical week), age (<65 or ≥65 years old), sex, region, baseline domain score, stratification factors and a treatment-by-timepoint interaction. MMRM results were reported as LS means, treatment differences in LS means and 95% CIs across the treatment period up to week 26.

[001338] TTCD was compared between treatment arms descriptively. For each PRO domain score, TTCD was calculated and summarized as quartiles, medians, and their 95% CI for each treatment arm. Kaplan-Meier (KM) curves were generated for each treatment arm. KM estimates of the median TTCD and the 2-sided 95% CI were calculated. KM estimates of the

25th and 75th percentiles and nominal p-values were reported, though they were non-inferential and not adjusted for multiplicity. The HR between both arms and its 95% CI were estimated using a Cox proportional hazards regression model controlling for age (<65 or ≥65 years old), sex, region, and stratification factors.

6.6.3 Results

6.6.3.1 *Baseline demographic and clinical characteristics*

[001339] At the data cutoff timepoint, a total of 886 patients were enrolled in the study. In total 731 patients (82.5%) completed at least one PRO questionnaire at baseline and were defined as the PRO FAS, with 376 treated with EV+P and 355 with PBC. Patient characteristics were generally balanced between each treatment arm, as shown in Table 26.

Table 26. Baseline demographic and clinical characteristics

Characteristic		**EV+P (n=376)**	**PBC (n=355)**
Median age, years (range)		68.0 (37, 87)	69.0 (32, 91)
Male sex, n (%)		297 (79.0)	273 (76.9)
Ethnicity, n (%)	**Asian**	96 (25.5)	79 (22.3)
	Black/African American	1 (0.3)	5 (1.4)
	White	250 (66.5)	229 (64.5)
	Multiple	0 (0)	4 (1.1)
	Other ethnic group[a]/Unknown	9 (2.4)	8 (2.3)
	Not reportable	20 (5.3)	30 (8.5)
Mean body weight, kg (SD)		75.3 (17.2)	76.3 (18.5)
Mean BMI, kg/m^2 (SD)		26.1 (4.7)	26.6 (5.2)
ECOG performance status, n (%)	**0**	191 (50.8)	169 (47.6)
	1	171 (45.5)	177 (49.9)
	2	14 (3.7)	8 (2.3)
	Missing / unknown	0 (0)	1 (0.3)
Renal function based on creatinine clearance, n (%)	**Normal, ≥90 mL/min**	74 (19.7)	70 (19.7)
	Mild decrease: ≥60 and <90 mL/min	140 (37.2)	130 (36.6)

Characteristic		EV+P (n=376)	PBC (n=355)
	Moderate decrease: ≥30 and <60 mL/min	157 (41.8)	150 (42.3)
	Severe decrease: ≥15 and <30 mL/min	5 (1.3)	5 (1.4)
Metastatic disease site(s), n (%)	**Bone**	68 (18.1)	86 (24.2)
	Kidney	44 (11.7)	27 (7.6)
	Liver	79 (21.0)	75 (21.1)
	Lung	144 (38.3)	133 (37.5)
	Lymph nodes	271 (72.1)	242 (68.2)
Using an opioid medication at baseline, n (%)[b]		73 (19.4)	69 (19.4)

[a]American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander ancestry, and any other ethnic background; [b]Reported by patients.

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PBC, platinum-based chemotherapy; SD, standard deviation.

[001340] PRO questionnaire compliance and treatment duration: Questionnaire compliance was >70% from baseline through to week 17 in both treatment arms. However, rates diverged thereafter with compliance remaining >70% through to week 29 for the EV+P arm, as shown in **FIG. 58**. As compliance was not balanced between study arms, two post-hoc sensitivity analyses were performed to investigate patient compliance with EORTC QLQ-C30.

[001341] Median treatment duration was longer in the EV+P arm (EV+P, 9.4 months versus PBC, 4.1 months). Therefore, the first sensitivity analysis investigated patient compliance with EORTC QLQ-C30 assessments until the end of study treatment (maximum of 6 cycles of PBC in the PBC arm). The second sensitivity analysis investigated compliance until disease progression. These analyses demonstrated that questionnaire compliance was balanced between treatment arms and was >70% in each arm until the end of study treatment. Questionnaire compliance prior to disease progression was similar to that in the PRO FAS in the base compliance analysis with questionnaire compliance in the PBC arm falling to less than 70% after week 20. This indicates that questionnaire compliance fell after the end of study treatment prior to disease progression.

6.6.3.2 *Brief Pain Inventory Short Form (BPI-SF)*

[001342] BPI-SF scores at baseline: BPI-SF scores at baseline were similar between EV+P and PBC arms. Over one-third of enrolled patients reported moderate to severe pain at baseline, as shown in Table 27.

Table 27. BPI-SF and EORTC QLQ-C30 scores at baseline

Parameter	**EV+P (n=376)**	**PBC (n=355)**
BPI-SF[a]		
Mean worst pain, SD	3.1 (2.8)	3.3 (3.0)
Patients with moderate to severe pain at baseline, n (%)[b]	128 (34.0)	128 (36.1)
Patients reporting taking opioid medication at baseline, n (%)	73 (19.4)	69 (19.4)
EORTC QLQ-C30[c]**, mean (SD)**		
GHS/QoL	62.4 (22.5)	60.3 (25.4)
Functioning scales, mean (SD)		
Cognitive functioning	84.3 (19.6)	83.9 (19.9)
Social functioning	77.3 (27.4)	76.3 (26.3)
Emotional functioning	75.5 (20.7)	74.6 (22.0)
Physical functioning	76.5 (22.7)	72.8 (24.3)
Role functioning	75.8 (28.3)	73.2 (29.4)
Cancer-related symptom scales and items, mean (SD)		
Fatigue	33.1 (25.0)	35.5 (26.1)
Sleep disturbances	33.3 (30.3)	32.9 (32.3)
Pain	31.0 (28.7)	32.9 (29.4)
Appetite loss	24.6 (30.2)	27.4 (31.7)
Constipation	20.2 (27.7)	27.5 (31.8)
Dyspnea	14.1 (22.4)	16.1 (23.9)
Nausea/vomiting	6.3 (15.1)	6.4 (13.7)
Diarrhea	6.1 (14.9)	5.5 (14.8)

[a]Scores range from 0-10 with higher scores representing more pain. [b]Moderate to severe pain was defined as a baseline BPI-SF worst pain score of ≥5. [c]Scores range from 0-100 with higher score represents greater symptom burden, higher functioning, and better QoL

BPI-SF, Brief Pain Inventory Short Form; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire; EV+P, Enfortumab vedotin plus pembrolizumab; GHS, global health status; PBC, platinum-based chemotherapy; QoL, quality of life; SD, standard deviation.

[001343] Changes in BPI-SF scores in the overall patient population: There was a numerically greater improvement in the change from baseline in the BPI-SF worst pain score at week 26 in the EV+P arm than in the PBC arm (LS mean, -0.61 vs -0.03; LS mean difference: -0.58 (-1.05 to -0.11); nominal 2-sided p-value: 0.01467), as shown in **FIG. 59** (*see* Powles, T., *et al.*, *N. Engl. J. Med.*, 2024. 390(10): p. 875-888). All additional analyses of changes in BPI-SF and EORTC QLQ-C30 domains are descriptive only with no adjustment for multiplicity. Overall, patients in the EV+P arm, compared with the PBC arm, had a greater improvement in pain across all BPI-SF domains, including worst pain, from baseline through week 26, as shown in **FIG. 60**. A similar number of confirmed new opioid medication initiation events were seen in the EV+P arm compared with the PBC arm (39 [10.4%] vs 37 [10.4%]).

[001344] Changes in BPI-SF scores in patients with moderate to severe pain at baseline: Overall, 256 patients (35.0%) had moderate to severe pain at baseline. Clinically meaningful improvements in mean BPI-SF worst pain score were observed from baseline through week 26 in both EV+P and PBC arms, and improvements in pain were larger in the EV+P arm than those observed in the PBC arm (LS mean change: -2.96 vs -2.4; LS mean difference: -0.53 [95% CI: -1.03, -0.02], nominal p-value: 0.04), as shown in **FIG. 61** and **FIG. 62**. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire (EORTC QLQ-C30).

[001345] EORTC QLQ-C30 scores at baseline were similar between EV+P and PBC arms, as shown in Table 28.

Table 28. BPI-SF and EORTC QLQ-C30 scores at baseline

Parameter	**EV+P (n=376)**	**PBC (n=355)**
BPI-SF[a]		
Mean worst pain, SD	3.1 (2.8)	3.3 (3.0)
Patients with moderate to severe pain at baseline, n (%)[b]	128 (34.0)	128 (36.1)

Parameter	EV+P (n=376)	PBC (n=355)
Patients reporting taking opioid medication at baseline, n (%)	73 (19.4)	69 (19.4)
EORTC QLQ-C30[c], mean (SD)		
GHS/QoL	62.4 (22.5)	60.3 (25.4)
Functioning scales, mean (SD)		
Cognitive functioning	84.3 (19.6)	83.9 (19.9)
Social functioning	77.3 (27.4)	76.3 (26.3)
Emotional functioning	75.5 (20.7)	74.6 (22.0)
Physical functioning	76.5 (22.7)	72.8 (24.3)
Role functioning	75.8 (28.3)	73.2 (29.4)
Cancer-related symptom scales and items, mean (SD)		
Fatigue	33.1 (25.0)	35.5 (26.1)
Sleep disturbances	33.3 (30.3)	32.9 (32.3)
Pain	31.0 (28.7)	32.9 (29.4)
Appetite loss	24.6 (30.2)	27.4 (31.7)
Constipation	20.2 (27.7)	27.5 (31.8)
Dyspnea	14.1 (22.4)	16.1 (23.9)
Nausea/vomiting	6.3 (15.1)	6.4 (13.7)
Diarrhea	6.1 (14.9)	5.5 (14.8)

[a]Scores range from 0-10 with higher scores representing more pain. [b]Moderate to severe pain was defined as a baseline BPI-SF worst pain score of ≥5. [c]Scores range from 0-100 with higher score represents greater symptom burden, higher functioning, and better QoL
BPI-SF, Brief Pain Inventory Short Form; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire; EV+P, Enfortumab vedotin plus pembrolizumab; GHS, global health status; PBC, platinum-based chemotherapy; QoL, quality of life; SD, standard deviation.

[001346] Changes in EORTC QLQ-C30 scores. Overall patient population: The observed change from baseline in EORTC QLQ-C30 QoL scores through week 26 favored EV+P with a difference of 2.54 (95% CI: 0.41, 4.67, nominal p-value: 0.02), as shown in **FIG. 63A**. Patients in the EV+P arm demonstrated improved scores across all functioning domains (role, physical, emotional, social, cognitive) from baseline through week 26 compared to patients in

the PBC arm. Fatigue, nausea/vomiting, pain, dyspnea and constipation symptom scale scores were lower (less symptomatic) for EV+P (nominal p-value<0.05). Similar scores were observed for insomnia and appetite loss, and a more favorable score for PBC, compared with EV+P, was observed for diarrhea. No clinically significant differences in EORTC QLQ-C30 QoL, functioning, and cancer-related symptom scale scores were observed from baseline through week 26 (*see* **FIG. 62A** and **FIG. 62B**).

[001347] Changes in EORTC QLQ-C30 scores by cisplatin-eligibility: Changes in EORTC QLQ-C30 QoL scores from baseline through week 26 were similar in both cisplatin-eligible and cisplatin-ineligible patients, as shown in **FIG. 64A** and **FIG. 64B**, respectively. Both cisplatin-eligible and cisplatin-ineligible patients in the EV+P arm demonstrated a transient worsening in GHS/QoL through week 3 that returned to baseline by week 4.

[001348] Time to confirmed deterioration in EORTC QLQ-C30 QoL and functioning scales in the overall patient population: The HR for TTCD favored EV+P for cognitive and role functioning domains, all other functioning domains were similar between treatment arms (*see* **FIG. 65)**. Median TTCD was numerically longer in the EV+P arm than in the PBC arm for EORTC QLQ-C30 QoL (5.9 vs 3.2 months respectively), and across all functioning scales.

[001349] Changes in EORTC QLQ-C30 scores in patients with moderate to severe pain at baseline: Clinically meaningful improvements in mean EORTC QLQ-C30 QoL were observed from baseline through week 26 in the EV+P arm. Improvements tended to be greater in the EV+P arm than in the PBC arm (LS mean change: 8.9 versus 4.1; LS mean difference: -4.8 [95% CI: 1.2, 8.3], nominal p-value: 0.008) (**FIG. 66A**). Improvements in all EORTC QLQ-C30 functioning domain scores from baseline through week 26 were larger in the EV+P arm than in the PBC arm, with the largest differences seen in the role, emotional and social functioning domains. Decreases in domain scores were observed in the PBC arm from baseline through week 26 for the role functioning and physical functioning domains (**FIG. 66B**).

[001350] Responder analysis: In the descriptive responder analyses assessing category changes in BPI-SF and EORTC scores, proportions of patients in each response category (deteriorated, stable, or improved) were similar between the EV+P and PBC arms, as shown in Table 29 and Table 30.

Table 29. Responder analysis. Categorical change from baseline to week 26 for BPI-SF score domains

Domain	Response status, n (%)	EV+P (n=376)	PBC (n=355)
Worst pain	Deteriorated, ≥2 categories	24 (9.9%)	18 (10.5%)
	Deteriorated, 1 category	26 (10.7%)	20 (11.6%)
	Stable	113 (46.7%)	77 (44.8%)
	Improved, 1 category	43 (17.8%)	33 (19.2%)
	Improved, ≥2 categories	36 (14.9%)	24 (14.0%)
Average pain	Deteriorated, ≥2 categories	16 (6.6%)	12 (7.0%)
	Deteriorated, 1 category	31 (12.8%)	20 (11.6%)
	Stable	124 (51.2%)	89 (51.7%)
	Improved, 1 category	41 (16.9%)	34 (19.8%)
	Improved, ≥2 categories	30 (12.4%)	17 (9.9%)
Pain interference	Deteriorated, ≥2 categories	19 (7.9%)	12 (7.0%)
	Deteriorated, 1 category	27 (11.2%)	20 (11.6%)
	Stable	142 (58.7%)	111 (64.5%)
	Improved, 1 category	28 (11.6%)	13 (7.6%)
	Improved, ≥2 categories	26 (10.7%)	16 (9.3%)
Pain severity	Deteriorated, ≥2 categories	13 (5.4%)	11 (6.4%)
	Deteriorated, 1 category	26 (10.7%)	17 (9.9%)
	Stable	148 (61.2%)	101 (58.7%)
	Improved, 1 category	34 (14.0%)	29 (16.9%)
	Improved, ≥2 categories	21 (8.7%)	14 (8.1%)

BPI-SF, Brief Pain Inventory Short Form; PBC, platinum-based chemotherapy.

Table 30. Responder analysis. Categorical change from baseline to week 26 for EORTC QLQ-C30 domains

Functioning domain/symptom scale	Response status, n (%)	EV+P (n=376)	PBC (n=355)
QoL	Deteriorated, ≥2 categories	30 (12.6%)	25 (14.7%)
	Deteriorated, 1 category	31 (13.0%)	22 (12.9%)
	Stable	105 (44.1%)	76 (44.7%)
	Improved, 1 category	32 (13.4%)	18 (10.6%)
	Improved, ≥2 categories	40 (16.8%)	29 (17.1%)
	Deteriorated, ≥2 categories	51 (21.4%)	40 (23.5%)

Functioning domain/symptom scale	Response status, n (%)	EV+P (n=376)	PBC (n=355)
Physical functioning	Deteriorated, 1 category	27 (11.3%)	15 (8.8%)
	Stable	113 (47.5%)	84 (49.4%)
	Improved, 1 category	14 (5.9%)	9 (5.3%)
	Improved, ≥2 categories	33 (13.9%)	22 (12.9%)
Role functioning	Deteriorated, ≥2 categories	64 (26.9%)	43 (25.3%)
	Deteriorated, 1 category	23 (9.7%)	26 (15.3%)
	Stable	91 (38.2%)	71 (41.8%)
	Improved, 1 category	24 (10.1%)	14 (8.2%)
	Improved, ≥2 categories	36 (15.1%)	16 (9.4%)
Emotional functioning	Deteriorated, ≥2 categories	27 (11.3%)	22 (12.9%)
	Deteriorated, 1 category	20 (8.4%)	8 (4.7%)
	Stable	131 (55.0%)	92 (54.1%)
	Improved, 1 category	18 (7.6%)	29 (17.1%)
	Improved, ≥2 categories	42 (17.6%)	19 (11.2%)
Cognitive functioning	Deteriorated, ≥2 categories	28 (11.8%)	20 (11.8%)
	Deteriorated, 1 category	44 (18.5%)	30 (17.6%)
	Stable	114 (47.9%)	92 (54.1%)
	Improved, 1 category	31 (13.0%)	18 (10.6%)
	Improved, ≥2 categories	21 (8.8%)	10 (5.9%)
Social functioning	Deteriorated, ≥2 categories	55 (23.1%)	25 (14.7%)
	Deteriorated, 1 category	27 (11.3%)	24 (14.1%)
	Stable	88 (37.0%)	83 (48.8%)
	Improved, 1 category	24 (10.1%)	18 (10.6%)
	Improved, ≥2 categories	44 (18.5%)	20 (11.8%)
Fatigue	Deteriorated, ≥2 categories	65 (27.3%)	47 (27.6%)
	Deteriorated, 1 category	34 (14.3%)	21 (12.4%)
	Stable	68 (28.6%)	45 (26.5%)
	Improved, 1 category	29 (12.2%)	25 (14.7%)
	Improved, ≥2 categories	42 (17.6%)	32 (18.8%)
Nausea and vomiting	Deteriorated, ≥2 categories	11 (4.6%)	12 (7.1%)
	Deteriorated, 1 category	12 (5.0%)	20 (11.8%)
	Stable	180 (75.6%)	114 (67.1%)

Functioning domain/symptom scale	Response status, n (%)	EV+P (n=376)	PBC (n=355)
	Improved, 1 category	20 (8.4%)	16 (9.4%)
	Improved, ≥2 categories	15 (6.3%)	8 (4.7%)
Pain	Deteriorated, ≥2 categories	31 (13.0%)	32 (18.8%)
	Deteriorated, 1 category	36 (15.1%)	19 (11.2%)
	Stable	82 (34.5%)	62 (36.5%)
	Improved, 1 category	36 (15.1%)	28 (16.5%)
	Improved, ≥2 categories	53 (22.3%)	29 (17.1%)
Dyspnea	Deteriorated, ≥2 categories	50 (21.0%)	49 (28.8%)
	Deteriorated, 1 category	0 (0%)	0 (0%)
	Stable	158 (66.4%)	102 (60.0%)
	Improved, 1 category	0 (0%)	0 (0%)
	Improved, ≥2 categories	30 (12.6%)	19 (11.2%)
Insomnia	Deteriorated, ≥2 categories	46 (19.3%)	32 (18.8%)
	Deteriorated, 1 category	0 (0%)	0 (0%)
	Stable	107 (45.0%)	92 (54.1%)
	Improved, 1 category	0 (0%)	0 (0%)
	Improved, ≥2 categories	85 (35.7%)	46 (27.1%)
Appetite Loss	Deteriorated, ≥2 categories	59 (24.8%)	33 (19.4%)
	Deteriorated, 1 category	0 (0%)	0 (0%)
	Stable	121 (50.8%)	87 (51.2%)
	Improved, 1 category	0 (0%)	0 (0%)
	Improved, ≥2 categories	58 (24.4%)	50 (29.4%)
Constipation	Deteriorated, ≥2 categories	48 (20.2%)	28 (16.5%)
	Deteriorated, 1 category	0 (0%)	0 (0%)
	Stable	129 (54.2%)	86 (50.6%)
	Improved, 1 category	0 (0%)	0 (0%)
	Improved, ≥2 categories	61 (25.6%)	56 (32.9%)
Diarrhea	Deteriorated, ≥2 categories	32 (13.4%)	15 (8.8%)
	Deteriorated, 1 category	0 (0%)	0 (0%)
	Stable	181 (76.1%)	135 (79.4%)
	Improved, 1 category	0 (0%)	0 (0%)
	Improved, ≥2 categories	25 (10.5%)	20 (11.8%)

QoL, quality of life; PBC, platinum-based chemotherapy.

6.6.4 Conclusions

[001351] The results presented in this Example demonstrated that treatment of subjects having previously untreated la/mUC with EV+P was associated with no detriment to overall GHS/QoL functioning or symptoms compared with PBC, while observing a longer duration of treatment and the unique adverse event profile of EV+P (*See* Powles, T., *et al.*, 2024, *N. Engl. J. Med.*, 390(10):875-888).

[001352] The key secondary endpoint data, although not formally tested, suggest that EV+P use resulted in greater improvements in BPI-SF worst pain compared with PBC at week 26. Pain endpoints were selected for this study as previous studies demonstrated that pain is relevant to patients with la/mUC, with some patients shown to experience significant cancer-related pain which negatively impacts their QoL (Martin, S., *et al.*, *Bladder Cancer*, 2022, 8(1): p. 45-53; Galsky, M.D., *et al.*, *Urol. Oncol.*, 2022. 40(9): p. 411.e9-411.e18). Pain was assessed in this study along with patient QoL/GHS and functioning. These PROs were assessed both during study treatment, and beyond disease progression in order to capture the patient experience over the entire treatment journey.

[001353] Patients in this study had a substantial symptom burden at baseline, with over half of patients having an ECOG performance status ≥1, over one-third reporting moderate to severe pain, and approximately 20% of patients reporting using an opioid medication. Among patients with moderate to severe pain at baseline, EV+P was shown to result in clinically meaningful improvements in mean BPI-SF worst pain score from baseline through week 26, with larger improvements than seen in the PBC arm. EORTC QLQ-C30 results also favored EV+P, with a greater observed change in EORTC QLQ-C30 QoL score from baseline through week 26 seen in the EV+P arm than in the PBC arm. Changes in all EORTC QLQ-C30 functioning domain scores and most symptom scale scores also showed larger improvements in the EV+P arm than in the PBC arm.

[001354] In the data presented in this Example, there was a ≥10-point mean change from baseline through week 26 in EORTC QLQ-30 emotional functioning among patients with moderate to severe pain at baseline in the EV+P arm. A 10-point change is thought to be the threshold for clinically meaningful change based on previous publications (Cocks, K., *et al.*, *Eur. J. Cancer*, 2012. 48(11): p. 1713-1721; Osoba, D., *et al.*, *J. Clin. Oncol.*, 1998. 16(1): p. 139-144). Changes in QoL, role functioning and social functioning scores for patients with moderate to severe pain at baseline in the EV+P arm were between 5 and 10 over this time

period, and therefore did not meet the prespecified criteria for a clinically meaningful change although other studies have suggested that lower cut-offs may be clinically meaningful in some cases (Musoro, J.Z., *et al.*, *Eur. J. Cancer*, 2023. 188: p. 171-182; Clarke, N.A., *et al.*, A Review of Meaningful Change Thresholds for EORTC QLQ-C30 and FACT-G Within Oncology. Value Health, 2024). Overall the improvements in QoL, functioning, and pain reported here, coupled with the improvements in OS and PFS with EV+P compared with PBC described herein in the Examples provided herein, provide further evidence that EV+P may help to address the unmet need for first line (1L) treatment options in la/mUC without detrimental impact on patient QoL (Morgans, A.K., *et al.*, *Urol. Oncol.*, 2021. 39(10): p. 733.e1-733.e10; Cheng, L.-J., *et al.*, *J. Clin. Oncol.*, 2023. 41(6_suppl): p. 462-462; Alimohamed, N., *et al.*, *Curr. Oncol.*, 2022. 29(10): p. 7587-7597).

[001355] As described in the Examples herein, Patients treated with EV+P have improved PFS and OS compared with those treated with PBC, without detrimental impact on their QoL, pain, or functioning. In descriptive analyses patients with moderate/severe pain at baseline treated with EV+P had clinically meaningful improvements in worst pain and QoL from baseline through week 26. The PRO data presented in this Example complement the clinical efficacy and safety data described *supra* add the patient perspective, and provide further evidence to support the use of EV+P as a preferred treatment option for patients with previously untreated la/mUC.

6.7 Example 7: Analysis of Nectin-4 Expression and Response to 1L Enfortumab Vedotin (EV) + Pembrolizumab (P) in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer (la/mUC)

6.7.1 Background

[001356] Nectin-4 is a cell-adhesion molecule involved in multiple cellular processes associated with oncogenesis, and is highly expressed on the surface of most urothelial cancer (UC) cells. Examples 2, 3, 4, 5, and 6, *supra*, provide efficacy and safety results, including patient-reported outcomes (*see* Example 6), from the phase 3 study of enfortumab vedotin combined with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer – i.e., the protocol described in Example 1.

[001357] The following Example presents results from a retrospective analysis of Nectin-4 expression and its association with outcomes using data from the phase 3 study of enfortumab vedotin combined with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer described in Examples 2, 3, 4, 5, and 6, *supra*.

6.7.2 Methods

[001358] Nectin-4 expression in primary or metastatic tumor tissue samples (fresh or archived tumor tissue was collected from either the primary or metastatic biopsies after completion of most recent prior systemic therapy) was measured retrospectively using a CAP/CLIA validated Nectin-4 IHC assay. Nectin-4 expression in tumor samples was measured retrospectively by IHC using a validated assay with a Nectin-4 antibody (clone M22-321b41.1) as previously described (Rosenberg J. et al., 2020, *J. Clin. Oncol.*, 38(10):1041-1049; O'Donnell P. *et al.*, 2023, *J. Clin. Oncol.*, 41(25):4107-4117; Klümper N. *et al.*, 2023, *Clin. Cancer Res.* 29(8):1496-1505). Nectin-4 expression and Nectin-4/PD-L1 expression were available for 800 of 886 randomized patients (EV+P: n=394; chemotherapy: n=406). PD-L1 expression status was determined as high (CPS ≥10) or low (CPS <10) using a validated PD-L1 IHC assay. In particular, PD-L1 expression was assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). Clinical efficacy (PFS, OS, and ORR) was assessed in Nectin-4 expression subgroups.

6.7.3 Results

[001359] Data from a total of 800 patients was available for analysis. High nectin-4 H-scores were observed in patients regardless of the biopsy origin (*see* **FIG. 67**). The majority (69%) of biopsy samples submitted were of primary origin. In particular, the median H-score for primary tumor tissue samples was 267 (interquartile range (IQR): 215-295) (n=554) and the median H-score for metastatic tumor tissue samples was 287 (IQR: 235-300), as shown in **FIG. 67**.

[001360] The distribution of nectin-4 H-scores was skewed toward high expression, as shown in **FIG. 68A** and **FIG. 68B**. Nectin-4 expression data were summarized by subgroups of H-score values <150 (selected as the midpoint of the H-score range), 150–225 (with 225 selected as the midpoint between 150 and 300), and >225. Acccordingly, subgroups were defined by Nectin-4 H-score (<150, 150–225, >225) from both the enfortumab vedotin plus pembrolizumab (EV+P) and chemotherapy treatment arms, as shown in **FIG. 68A** and **FIG. 68B**. **FIG. 68A** showns the H-score of Nectin-4 expression at across both arms (n=800). For subjects in the EV+P arm (n=394), the median H-score was 280 (IQR: 230-298) and for subjects in the chemotherapy arm (n=406), the median H-score was 270 (IQR: 215-297) (*see* **FIG. 68B**). **FIG. 68B** further provides H-scores for each subgroup. 38 patients (9.6%) in the EV+P arm had an H-score value of <150 (i.e., were in the <150 subgroup), and 50 patients (12.3%) in the chemotherapy arm had an H-score value of <150 (i.e., were in the <150

subgroup) (*see* **FIG. 68B)**. 50 patients (12.7%) in the EV+P arm had an H-score value of ≥150 to <225 (i.e., were in the ≥150 to <225 subgroup), and 56 patients (13.8%) in the chemotherapy arm had an H-score value of ≥150 to <225 (i.e., were in the ≥150 to <225 subgroup) (*see* **FIG. 68B)**. Notably, 306 patients (77.7%) in the EV+P arm had an H-score value of ≥225 (i.e., were in the ≥225 group), and 300 patients (73.9%) in the chemotherapy arm had an H-score value of ≥225 (i.e., were in the ≥225 group) (*see* **FIG. 68B)**. On the other hand, only 3 patients (0.8%) in the EV+P arm had an H-score value of 0, and only 6 patients (1.5%) in the chemotherapy arm had an H-score value of 0 (*see* **FIG. 68B)**.

[001361] A consistent progression-free survival (PFS) benefit was observed in the EV+P arm in both the <275 and ≥275 Nectin-4 H-score subgroups compared to the chemotherapy arm, as shown in **FIG. 69A** and **FIG. 69B**. Kaplan–Meier plots of PFS for the <275 and ≥275 Nectin-4 H-score subgroups are shown in **FIG. 69A** and **FIG. 69B**, respectively. For the <275 Nectin-4 H-score subgroup, in the EV+P arm (N=177), the median PFS was 10.4 months (95% CI: 8.2, 14.5; Stratified HR (95% CI): 0.503; Events: 95), and in the chemotherapy arm (N=212), the median PFS was 6.2 months (95% CI: 5.9, 6.4; Stratified HR (95% CI): (0.385, 0.657); Events: 150) (*see* **FIG. 69A**). For the ≥275 Nectin-4 H-score subgroup, in the EV+P arm (N=217), the median PFS was 15.3 months (95% CI: 10.5, -; Stratified HR (95% CI): 0.410; Events: 106), and in the chemotherapy arm (N=194), the median PFS was 6.4 months (95% CI: 6.2, 8.1; Stratified HR (95% CI): 0.313, 0.537); Events: 130) (*see* **FIG. 69B**).

[001362] In addition, a consistent overall survival (OS) benefit was observed in the EV+P arm in both <275 and ≥275 Nectin-4 H-score subgroups compared to the chemotherapy arm, as shown in **FIG. 70A** and **FIG. 70B**. Kaplan–Meier plots of OS for the <275 and ≥275 Nectin-4 H-score subgroups are shown in **FIG. 70A** and **FIG. 70B**, respectively. For the <275 Nectin-4 H-score subgroup, in the EV+P arm (N=177), the median OS was 26.1 months (95% CI: 22.3, -; Stratified HR (95% CI): 0.518; Events: 57), and in the chemotherapy arm (N=212), the median OS was 13.9 months (95% CI: 11.6, 19.7; Stratified HR (95% CI): (0.372, 0.721); Events: 108) (*see* **FIG. 70A**). For the ≥275 Nectin-4 H-score subgroup, in the EV+P arm (N=217), the median OS was not reached (95% CI: 25.6, -; Stratified HR (95% CI): 0.426; Events: 62), and in the chemotherapy arm (N=194), the median OS was 17.1 months (95% CI: 14.7, 19.3; Stratified HR (95% CI): (0.305, 0.595); Events: 95) (*see* **FIG. 70B**).

[001363] Consistent PFS and OS benefits were observed in the EV+P arm across <150, ≥150 to <225, and ≥225 H-score subgroups Nectin-4 H-score subgroups, as shown in **FIG.**

71A and **FIG. 71B**. PFS and OS subgroup analyses by Nectin-4 H-scores are shown in **FIG. 71A** and **FIG. 71B**, respectively. Overall, the median PFS in the EV+P arm was 12.5 months (223 events; N=442) and the median PFS in the chemotherapy arm was 6.3 months (307 events; N=444) (HR: 0.450, CI: 0.377 to 0.538) (*see* **FIG. 71A**). PFS was assessed for the <150, ≥150 to <225, and ≥225 Nectin-4 H-score subgroups. For the <150 Nectin-4 H-score subgroup, the median PFS in the EV+P arm was 10.4 months (19 events; N=38) and the median PFS in the chemotherapy arm was 6.2 months (34 events; N=50) (HR: 0.538, 95% CI: 0.290 to 0.998) (*see* **FIG. 71A**). For the ≥150 to <225 Nectin-4 H-score subgroup, the median PFS in the EV+P arm was 6.3 months (34 events; N=50) and the median PFS in the chemotherapy arm was 6.2 months (41 events; N=56) (HR: 0.680; CI: 0.408 to 1.133) (*see* **FIG. 71A**). For the ≥225 Nectin-4 H-score subgroup, the median PFS in the EV+P arm was 14.6 months (148 events; N=306) and the median PFS in the chemotherapy arm was 6.4 months (205 events; N=300) (HR: 0.399, CI: 0.320 to 0.497) (*see* **FIG. 71A**). Overall, the median OS in the EV+P arm was 31.5 months (133 events; N=442) and the median OS in the chemotherapy arm was 16.1 months (226 events; N=444) (HR: 0.468, CI: 0.376 to 0.582) (*see* **FIG. 71B**). OS was assessed for the <150, ≥150 to <225, and ≥225 Nectin-4 H-score subgroups. For the <150 Nectin-4 H-score subgroup, the median OS in the EV+P arm was 18.4 months (15 events; N=38) and the median OS in the chemotherapy arm was 10.4 months (28 events; N=50) (HR: 0.531, CI: 0.268 to 1.052) (*see* **FIG. 71B**). For the ≥150 to <225 Nectin-4 H-score subgroup, the median OS in the EV+P arm was 25.4 months (16 events; N=50) and the median OS in the chemotherapy arm was 11.8 months (32 events; N=56) (HR: 0.435, CI: 0.220 to 0.857) (*see* **FIG. 71B**). For the ≥225 Nectin-4 H-score subgroup, the median OS in the EV+P arm was 31.5 months (88 events; N=306) and the median OS in the chemotherapy arm was 17.1 months (143 events; N=300) (HR: 0.466, CI: 0.355 to 0.613) (*see* **FIG. 71B**).

[001364] A consistent overall response rate (ORR) benefit was observed in the EV+P across all Nectin-4 subgroups, as shown in **FIG. 72**. In the overall population, the ORR in the EV+P arm was 67.7% (n=437) and the ORR in the chemotherapy arm was 44.4% (n=441) (*see* **FIG. 72**). ORR was assessed for the <275 and ≥275 Nectin-4 H-score subgroups (wherein the median Nectin-4 H-score was 275 across patients in both arms), as well as for the <150, ≥150 to <225, and ≥225 Nectin-4 H-score subgroups. For the <275 Nectin-4 H-score subgroup, the ORR in the EV+P arm was 63.6% (n=173) and the ORR in the chemotherapy arm was 40.5% (n=210) (*see* **FIG. 72**). For the ≥275 Nectin-4 H-score subgroup, the ORR in the EV+P arm was 71.8% (n=216) and the ORR in the chemotherapy arm was 47.2% (n=193) (*see* **FIG. 72**).

For the <150 Nectin-4 H-score subgroup, the ORR in the EV+P arm was 52.6% (n=38) and the ORR in the chemotherapy arm was 38% (n=50) (*see* **FIG. 72**). For the ≥150 to <225 Nectin-4 H-score subgroup, the ORR in the EV+P arm was 58% (n=50) and the ORR in the chemotherapy arm was 42.9% (n=56) (*see* **FIG. 72**). For the ≥225 Nectin-4 H-score subgroup, the ORR in the EV+P arm was 71.8% (n=301) and the ORR in the chemotherapy arm was 44.8% (n=297) (*see* **FIG. 72**). For responders with Nectin-4 expression data available, the median Nectin-4 H-score in the EV+P arm (n=437) was 284.5 (IQR: 240-300) and the median Nectin-4 H-score in the chemotherapy arm (n=441) was 280 (IQR: 225-300) (*see* **FIG. 72**). For non-responders with Nectin-4 expression data available, the median Nectin-4 H-score in the EV+P arm (n=437) was 270 (IQR: 210-295) and the median Nectin-4 H-score in the chemotherapy arm (n=441) was 265 (IQR: 210-295) (*see* **FIG. 72**).

[001365] **FIG. 73** provides the expression distribution of Nectin-4 and PD-L1 in the EV+P (N=442) and chemotherapy (N=444) arms for the <275 and ≥275 Nectin-4 H-score subgroups (wherein the median Nectin-4 H-score was 275 across patients in both arms), as well as for subjects without nectin-4 results (i.e., labeled as a "missing" subgroup). In this analysis, a low level of PD-L1 expression was defined as CPS <10, and a high level of PD-L1 expression was defined as CPS ≥10. For the EV+P arm, 70 subjects (15.8%) (n=184) had a Nectin-4 H-score of <275, in which PD-L1 expression was low (CPS <10), and 107 subjects (24.2%) (n=254) had a Nectin-4 H-score of <275, in which PD-L1 expression was high (CPS ≥10) (*see* **FIG. 73**). For the chemotherapy arm, 86 subjects (19.4%) (n=185) had a Nectin-4 H-score of <275, in which PD-L1 expression was low (CPS <10), and 126 subjects (28.4%) (n=254) had a Nectin-4 H-score of <275, in which PD-L1 expression was high (CPS ≥10) (*see* **FIG. 73**). For the EV+P arm, 97 subjects (21.9%) (n=184) had a Nectin-4 H-score of ≥275, in which PD-L1 expression was low (CPS <10), and 120 subjects (27.1%) (n=254) had a Nectin-4 H-score of ≥275, in which PD-L1 expression was high (CPS ≥10) (*see* **FIG. 73**). For the chemotherapy arm, 84 subjects (18.9%) (n=185) had a Nectin-4 H-score of ≥275, in which PD-L1 expression was low (CPS <10), and 109 subjects (24.5%) (n=254) had a Nectin-4 H-score of ≥275, in which PD-L1 expression was high (CPS ≥10) (*see* **FIG. 73**). For the EV+P arm, 17 subjects (3.8%) (n=184) did not have nectin-4 results, in which PD-L1 expression was low (CPS <10), and 27 subjects (6.1%) (n=254) did not have nectin-4 results, in which PD-L1 expression was high (CPS ≥10) (*see* **FIG. 73**). For the chemotherapy arm, 15 subjects (3.4%) (n=185) did not have nectin-4 results, in which PD-L1 expression was low (CPS <10), and 19 subjects (4.3%) did not have nectin-4 results, in which PD-L1 expression was high (CPS ≥10) (*see* **FIG. 73**).

[001366] A consistent PFS benefit was observed in the EV+P arm across Nectin-4 and PD-L1 subgroups, as shown in **FIG. 74A**, **FIG. 74B**, **FIG. 74C**, and **FIG. 74D**. **FIG. 74A**, **FIG. 74B**, **FIG. 74C**, and **FIG. 74D** show Kaplan–Meier plots of PFS for each of the following groups: (1) Subgroup having Nectin-4 H-score of <275 and a low level of PD-L1 expression (CPS <10) (*see* **FIG. 74A**); (2) Subgroup having Nectin-4 H-score of <275 and a high level of PD-L1 expression (CPS ≥10) (*see* **FIG. 74B**); (3) Subgroup having Nectin-4 H-score of ≥275 and a low level of PD-L1 expression (CPS <10) (*see* **FIG. 74C**); and (4) Subgroup having Nectin-4 H-score of ≥275 and a high level of PD-L1 expression (*see* **FIG. 74D**) (note for (1) to (4): the median Nectin-4 H-score was 275 across patients in both arms) (CPS ≥10). In the subgroup having Nectin-4 H-score of <275 and a low level of PD-L1 expression (CPS <10), in the EV+P arm (N=70), the median PFS was 9.2 months (95% CI: 6.2, 12.0; stratified HR (95% CI): 0.543; Events: 42), and in the chempotherapy arm (N=86), the median PFS was 6.2 months (95% CI: 4.9, 6.8; stratified HR (95% CI): (0.359, 0.820); Events: 60) (*see* **FIG. 74A**). In the subgroup having Nectin-4 H-score of <275 and a high level of PD-L1 expression (CPS ≥10), in the EV+P arm (N=107), the median PFS was 10.6 months (95% CI: 8.1, - ; stratified HR (95% CI): 0.476; Events: 53), and in the chempotherapy arm (N=126), the median PFS was 6.2 months (95% CI: 5.7, 6.4; stratified HR (95% CI): (0.334, 0.677); Events: 90) (*see* **FIG. 74B**). In the subgroup having Nectin-4 H-score of ≥275 and a low level of PD-L1 expression (CPS <10), in the EV+P arm (N=97), the median PFS was 11.6 months (95% CI: 8.2, 22.3; stratified HR (95% CI): 0.463; Events: 54), and in the chempotherapy arm (N=84), the median PFS was 6.5 months (95% CI: 6.0, 8.1; stratified HR (95% CI): (0.311, 0.688); Events: 57) (*see* **FIG. 74C**). In the subgroup having Nectin-4 H-score of ≥275 and a high level of PD-L1 expression, in the EV+P arm (N=120), the median PFS was 20.4 months (95% CI: 12.0, - ; stratified HR (95% CI): 0.373; Events: 52), and in the chempotherapy arm (N=109), the median PFS was 6.4 months (95% CI: 6.2, 8.3; stratified HR (95% CI): (0.258, 0.539); Events: 72) (*see* **FIG. 74D**).

[001367] A consistent OS benefit was observed in the EV+P arm across Nectin-4 and PD-L1 subgroups, as shown in **FIG. 75A**, **FIG. 75B**, **FIG. 75C**, and **FIG. 75D**. **FIG. 75A**, **FIG. 75B**, **FIG. 75C**, and **FIG. 75D** show Kaplan–Meier plots of OS for each of the following groups: (1) Subgroup having Nectin-4 H-score of <275 and a low level of PD-L1 expression (CPS <10) (*see* **FIG. 75A**); (2) Subgroup having Nectin-4 H-score of <275 and a high level of PD-L1 expression (CPS ≥10) (*see* **FIG. 75B**); (3) Subgroup having Nectin-4 H-score of ≥275 and a low level of PD-L1 expression (CPS <10) (*see* **FIG. 75C**); and (4) Subgroup having Nectin-4 H-score of ≥275 and a high level of PD-L1 expression (*see* **FIG. 75D**) (note for (1)

to (4): the median Nectin-4 H-score was 275 across patients in both arms) (CPS ≥10). In the subgroup having Nectin-4 H-score of <275 and a low level of PD-L1 expression (CPS <10), in the EV+P arm (N=70), the median OS was 22.3 months (95% CI: 17.0, - ; stratified HR (95% CI): 0.522; Events: 22), and in the chempotherapy arm (N=86), the median OS was 15.5 months (95% CI: 10.1, 27.5; stratified HR (95% CI): (0.310, 0.880), Events: 44) (*see* **FIG. 75A**). In the subgroup having Nectin-4 H-score of <275 and a high level of PD-L1 expression (CPS ≥10), in the EV+P arm (N=107), the median OS was 31.5 months (95% CI: 25.4, - ; stratified HR (95% CI): 0.516; Events: 35), and in the chempotherapy arm (N=126), the median OS was 13.9 months (95% CI: 11.0, 20.6; stratified HR (95% CI): (0.337, 0.790); Events: 64) (*see* **FIG. 75B**). In the subgroup having Nectin-4 H-score of ≥275 and a low level of PD-L1 expression (CPS <10), in the EV+P arm (N=97), the median OS was not reached (95% CI: -, - ; stratified HR (95% CI): 0.410; Events: 26), and in the chempotherapy arm (N=84), the median OS was 16.4 months (95% CI: 14.5, 19.3; stratified HR (95% CI): (0.250, 0.675); Events: 44) (*see* **FIG. 75C**). In the subgroup having Nectin-4 H-score of ≥275 and a high level of PD-L1 expression, in the EV+P arm (N=120), the median OS was 25.6 months (95% CI: 21.2, - ; stratified HR (95% CI): 0.438; Events: 36), and in the chempotherapy arm (N=109), the median OS was 18.3 months (95% CI: 13.1, - ; stratified HR (95% CI): (0.279, 0.688); Events: 51) (*see* **FIG. 75D**).

6.7.4 Conclusions

[001368] Nectin-4 is highly expressed in nearly all available EV-302 patient tumor samples and shows consistency between primary and metastatic sites of origin. This is the first comprehensive assessment to demonstrate a consistent benefit of EV+P vs chemotherapy across all Nectin-4 subgroups and evaluated endpoints (PFS, OS, and ORR). The observed benefit of EV+P remains regardless of Nectin-4 expression and PD-L1 status. These data further establish EV+P as the standard of care (SOC) in first line (1L) treatment across the overall la/mUC population and evaluated subgroups, and confirm that testing for Nectin-4 expression or PD-L1 status is not required.

What is claimed is:

1. A method of treating cancer in a subject, comprising administering to the subject:

(a) an effective amount of an antibody drug conjugate (ADC) comprising an anti-191P4D12 antibody or antigen binding fragment thereof, and

(b) an effective amount of an anti-PD-1 antibody or antigen binding fragment thereof;

wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE);

wherein the anti-PD-1 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:32 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO: 27;

wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23;

wherein the subject has urothelial or bladder cancer; and

wherein the subject is eligible to receive cisplatin treatment (cisplatin eligible).

2. The method of claim 1, wherein the subject has not previously received a PD-(L)-1 inhibitor.

3. The method of claim 1 or 2, wherein the subject has a GFR >60 mL/min or creatinine clearance >60 mL/min.

4. The method of any one of claims 1 to 3, wherein the subject has NCI CTCAE Grade ≤1 audiometric hearing loss.

5. The method of any one of claims 1 to 4, wherein the subject does not have NYHA Class III heart failure.

6. The method of any one of claims 1 to 5, wherein:

(a) the subject has a progression free survival of at least or about 10, 11, 12, 13, 14, 14.6, 15, 16, 17, 18, or 19 months following the treatment, optionally wherein the subject has a progression free survival of at least or about 14.6 months following the treatment, further optionally wherein the subject has a progression free survival of 14 to 15 months following the treatment;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 10, 11, 12, 13, 14, 14.6, 15, 16, 17, 18, or 19 months, optionally wherein median progression free survival in the treated population is at least or about 14.6 months, further optionally wherein median progression free survival in the treated population is 14 to 15 months; or

(c) median progression free survival is at least or about 10, 11, 12, 13, 14, 14.6, 15, 16, 17, 18, or 19 months for a population of subjects treated with the method, optionally wherein median progression free survival is at least or about 14.6 months for a population of subjects treated with the method, further optionally wherein median progression free survival is 14 to 15 months for a population of subjects treated with the method.

7. The method of any one of claims 1 to 5, wherein:

(a) the subject has an overall survival of at least or about 27, 28, 29, 30, 31, 31.5, 32, 33, 34, 35, or 36 months following the treatment, optionally wherein the subject has an overall survival of at least or about 31.5 months following the treatment, further optionally wherein the subject has an overall survival of 31 to 32 months following the treatment;

(b) a population of the subjects is treated by the methods, and wherein median overall survival in the treated population is at least or about 27, 28, 29, 30, 31, 31.5, 32, 33, 34, 35, or 36 months, optionally wherein median overall survival in the treated population is at least or about 31.5 months, further optionally wherein median overall survival in the treated population is 31 to 32 months; or

(c) median overall survival is at least or about 27, 28, 29, 30, 31, 31.5, 32, 33, 34, 35, or 36 months for a population of subjects treated with the method, optionally whererin median overall survival is at least or about 31.5 months for a population of subjects treated with the method, further optionally wherein median overall survival is 31 to 32 months for a population of subjects treated with the method.

8. A method of treating cancer in a subject, comprising administering to the subject:

(a) an effective amount of an antibody drug conjugate (ADC) comprising an anti-191P4D12 antibody or antigen binding fragment thereof, and

(b) an effective amount of an anti-PD-1 antibody or antigen binding fragment thereof;

wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE);

wherein the anti-PD-1 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:32 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO: 27;

wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23;

wherein the subject has urothelial or bladder cancer; and

wherein:

(i) the subject has aspartate transferase (AST) and alanine transaminase (ALT) no more than 2.5 fold of upper limit of normal (ULN),

(ii) the subject has treated central nervous system (CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof, and/or

(iii) the subject has not received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof.

9. The method of claim 8, wherein the subject has treated central nervous system (CNS) metastases that have been clinically stable for at least 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof; and

wherein the subject has not received major surgery within 4 weeks prior to the administration of the ADC and the anti-PD-1 antibody or antigen binding fragment thereof.

10. The method of claim 8 or 9, wherein:

(a) the subject has a progression free survival of at least or about 12.5 months following the treatment, optionally wherein the subject has a progression free survival of 12 to 13 months following the treatment;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 12.5 months, optionally wherein median progression free survival in the treated population is 12 to 13 months; or

(c) median progression free survival is at least or about 12.5 months for a population of subjects treated with the method, optionally wherein median progression free survival is 12 to 13 months for a population of subjects treated with the method.

11. The method of claim 8 or 9, wherein:

(a) the subject has an overall survival of at least or about 31.5 months following the treatment, optionally wherein the subject has an overall survival of 31 to 32 months following the treatment;

(b) a population of the subjects is treated by the methods, and wherein median overall survival in the treated population is at least or about 31.5 months, optionally wherein median overall survival in the treated population is 31 to 32 months; or

(c) median overall survival is at least or about 31.5 months for a population of subjects treated with the method, optionally wherein median overall survival is 31 to 32 months for a population of subjects treated with the method.

12. The method of claim 8 or 9, wherein the subject is eligible to receive cisplatin treatment (cisplatin eligible), and wherein:

(a) the subject has a progression free survival of at least or about 14.6 months following the treatment, optionally wherein the subject has a progression free survival of 14 to 15 months following the treatment;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 14.6 months, optionally wherein median progression free survival in the treated population is 14 to 15 months; or

(c) median progression free survival is at least or about 14.6 months for a population of subjects treated with the method, optionally wherein median progression free survival is 14 to 15 months for a population of subjects treated with the method.

13. The method of claim 8 or 9, wherein the subject is ineligible to receive cisplatin treatment (cisplatin eligible), and wherein:

(a) the subject has a progression free survival of at least or about 10.6 months following the treatment, optionally wherein the subject has a progression free survival of 10 to 11 months;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 10.6 months, optionally wherein median progression free survival in the treated population is 10 to 11 months; or

(c) median progression free survival is at least or about 10.6 months for a population of subjects treated with the method, optionally wherein median progression free survival is 10 to 11 months for a population of subjects treated with the method.

14. The method of any one of claims 1 to 5, 8 or 9, wherein the subject has expression of PD-L1 no less than CPS of 10, and optionally wherein:

(a) the subject has a progression free survival of at least or about 18.5 months following the treatment, optionally wherein the subject has a progression free survival of 18 to 19 months following the treatment;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 18.5 months, optionally wherein median progression free survival in the treated population is 18 to 19 months; or

(c) median progression free survival is at least or about 18.5 months for a population of subjects treated with the method, optionally wherein median progression free survival is 18 to 19 months for a population of subjects treated with the method.

15. The method of any one of claims 1 to 5, 8 or 9, wherein the subject has expression of PD-L1 less than CPS of 10, and optionally wherein:

(a) the subject has a progression free survival of at least or about 10.5 months following the treatment, optionally wherein the subject has a progression free survival of 10 to 11 months;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 10.5 months, optionally wherein median progression free survival in the treated population is 10 to 11 months; or

(c) median progression free survival is at least or about 10.5 months for a population of subjects treated with the method, optionally wherein median progression free survival is 10 to 11 months for a population of subjects treated with the method.

16. The method of any one of claims 1 to 5, 8 or 9, wherein the subject does not have liver metastases, and optionally wherein:

(a) the subject has a progression free survival of at least or about 16.4 months following the treatment, optionally wherein the subject has a progression free survival of 16 to 17 months;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 16.4 months, optionally wherein median progression free survival in the treated population is 16 to 17 months; or

(c) median progression free survival is at least or about 16.4 months for a population of subjects treated with the method, optionally wherein median progression free survival is 16 to 17 months for a population of subjects treated with the method.

17. The method of any one of claims 1 to 5, 8 or 9, wherein the subject has liver metastases, and optionally wherein:

(a) the subject has a progression free survival of at least or about 8.2 months following the treatment, optionally wherein the subject has a progression free survival of 8 to 9 months;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 8.2 months, optionally wherein median progression free survival in the treated population is 8 to 9 months; or

(c) median progression free survival is at least or about 8.2 months for a population of subjects treated with the method, optionally wherein median progression free survival is 8 to 9 months for a population of subjects treated with the method.

18. The method of any one of claims 1 to 5, 8 or 9, wherein the race of the subject is white, and optionally wherein:

(a) the subject has a progression free survival of at least or about 10.4 months, optionally wherein the subject has a progression free survival of 10 to 11 months;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 10.4 months, optionally wherein median progression free survival in the treated population is 10 to 11 months; or

(c) median progression free survival is at least or about 10.4 months for a population of subjects treated with the method, optionally wherein median progression free survival is 10 to 11 months for a population of subjects treated with the method.

19. The method of any one of claims 1 to 5, 8 or 9, wherein the race of the subject is not white, and optionally wherein:

(a) the subject has a progression free survival of at least or about 22.3 months, optionally wherein the subject has a progression free survival of 22 to 23 months;

(b) a population of the subjects is treated by the methods, and wherein median progression free survival in the treated population is at least or about 22.3 months, optionally wherein median progression free survival in the treated population is 22 to 23 months; or

(c) median progression free survival is at least or about 22.3 months for a population of subjects treated with the method, optionally wherein median progression free survival is 22 to 23 months for a population of subjects treated with the method.

20. The method of any one of claims 1 to 19, wherein the subject has visceral metastases.

21. The method of any one of claims 1 to 19, wherein the subject has lymph nodes only disease.

22. The method of any one of claims 1 to 21, wherein the disease site of origin is in the upper tract.

23. The method of any one of claims 1 to 21, wherein the disease site of origin is in the lower tract.

24. The method of any one of claims 1 to 23, wherein the subject has a PD-L1 expression combined positive score (CPS) greater than or equal to 10.

25. The method of any one of claims 1 to 23, wherein the subject has a PD-L1 expression CPS less than 10.

26. The method of any one of claims 1 to 19, wherein the subject has a Nectin-4 H-score between 0 and 300.

27. The method of any one of claims 1 to 19, wherein the subject has a Nectin-4 H-score between 0 and 200.

28. The method of any one of claims 1 to 19, wherein the subject has a Nectin-4 H-score between 0 and 150.

29. The method of any one of claims 1 to 19, wherein the method does not comprise determining PD-L1 expression or Nectin-4 expression of the subject.

30. The method of any one of claims 1 to 29, wherein the subject has locally advanced or metastatic urothelial cancer.

31. The method of any one of claims 1 to 30, wherein the subject has locally advanced or metastatic bladder cancer.

32. The method of any one of claims 1 to 31, wherein the anti-PD-1 antibody or antigen binding fragment thereof comprises: (a) a light chain variable region comprising light chain CDR1 comprising the amino acid sequence of SEQ ID NO:24, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:25, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:26, respectively, and (b) a heavy chain variable region comprising heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:29, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:30, and heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:31, respectively.

33. The method of any one of claims 1 to 31, wherein the anti-PD-1 antibody or antigen binding fragment thereof comprises: (a) a light chain variable region comprising light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:24, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:25, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:26, respectively, and (b) a heavy chain variable region comprising heavy chain CDR1 consisting of the amino acid sequence of SEQ ID NO:29, a heavy chain CDR2 consisting of the amino acid sequence of SEQ ID NO:30, and heavy chain CDR3 consisting of the amino acid sequence of SEQ ID NO:31, respectively.

34. The method of any one of claims 1 to 33, wherein the anti-PD-1 antibody or antigen binding fragment thereof comprises (a) a heavy chain variable region comprising SEQ ID NO:32 or a variant thereof, and (b) a light chain variable region comprising SEQ ID NO:27 or a variant thereof.

35. The method of any one of claims 1 to 33, wherein the anti-PD-1 antibody comprises (a) a heavy chain comprising SEQ ID NO: 33 and (b) a light chain comprising SEQ ID NO:28.

36. The method of any one of claims 1 to 35, wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises CDR-H1 comprising the amino acid sequence of SEQ ID NO:9, CDR-H2 comprising the amino acid sequence of SEQ ID NO:10, CDR-H3 comprising the amino acid sequence of SEQ ID NO:11; CDR-L1 comprising the amino acid sequence of SEQ ID NO:12, CDR-L2 comprising the amino acid sequence of SEQ ID NO:13, and CDR-L3 comprising the amino acid sequence of SEQ ID NO:14, or

wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises CDR-H1 comprising the amino acid sequence of SEQ ID NO:16, CDR-H2 comprising the amino acid sequence of SEQ ID NO:17, CDR-H3 comprising the amino acid sequence of SEQ ID NO:18; CDR-L1 comprising the amino acid sequence of SEQ ID NO:19, CDR-L2 comprising the amino acid sequence of SEQ ID NO:20, and CDR-L3 comprising the amino acid sequence of SEQ ID NO:21.

37. The method of any one of claims 1 to 35, wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises CDR-H1 consisting of the amino acid sequence of SEQ ID NO:9, CDR-H2 consisting of the amino acid sequence of SEQ ID NO:10, CDR-H3 consisting of the amino acid sequence of SEQ ID NO:11; CDR-L1

consisting of the amino acid sequence of SEQ ID NO:12, CDR-L2 consisting of the amino acid sequence of SEQ ID NO:13, and CDR-L3 consisting of the amino acid sequence of SEQ ID NO:14, or

wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises CDR-H1 consisting of the amino acid sequence of SEQ ID NO:16, CDR-H2 consisting of the amino acid sequence of SEQ ID NO:17, CDR-H3 consisting of the amino acid sequence of SEQ ID NO:18; CDR-L1 consisting of the amino acid sequence of SEQ ID NO:19, CDR-L2 consisting of the amino acid sequence of SEQ ID NO:20, and CDR-L3 consisting of the amino acid sequence of SEQ ID NO:21.

38. The method of any one of claims 1 to 37, wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:22 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:23.

39. The method of any one of claims 1 to 38, wherein the anti-191P4D12 antibody comprises a heavy chain comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID NO:7 and a light chain comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:8.

40. The method of any one of claims 1 to 34 and 36 to 38, wherein the anti-191P4D12 antigen binding fragment is an Fab, F(ab′)2, Fv, or scFv.

41. The method of any one of claims 1 to 35, wherein the anti-191P4D12 antibody is a fully human antibody.

42. The method of any one of claims 1 to 39 and 41, wherein the anti-191P4D12 antibody is an IgG1 and light chain is a kappa light chain.

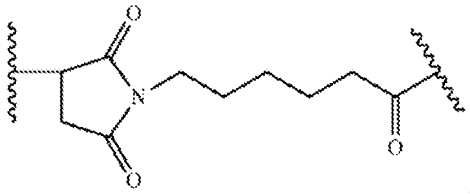
43. The method of any one of claims 1 to 42, wherein the anti-191P4D12 antibody or antigen binding fragment thereof is recombinantly produced.

44. The method of any one of claims 1 to 43, wherein the anti-191P4D12 antibody or antigen binding fragment is conjugated to each unit of MMAE via a linker.

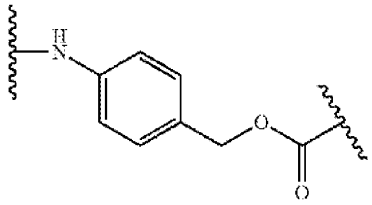
45. The method of claim 44, wherein the linker is an enzyme-cleavable linker, and wherein the linker forms a bond with a sulfur atom of the antibody or antigen binding fragment thereof.

46. The method of claim 44 or 45, wherein the linker has a formula of: –Aa–Ww–Yy–; wherein –A– is a stretcher unit, a is 0 or 1; –W– is an amino acid unit, w is an integer ranging from 0 to 12; and –Y– is a spacer unit, y is 0, 1, or 2.

47. The method of claim 46, wherein the stretcher unit has the structure of Formula (1) below; the amino acid unit is valine-citrulline; and the spacer unit is a PAB group comprising the structure of Formula (2) below:



Formula (1)



Formula (2).

48. The method of claim 46 or 47, wherein the stretcher unit forms a bond with a sulfur atom of the antibody or antigen binding fragment thereof; and wherein the spacer unit is linked to MMAE via a carbamate group.

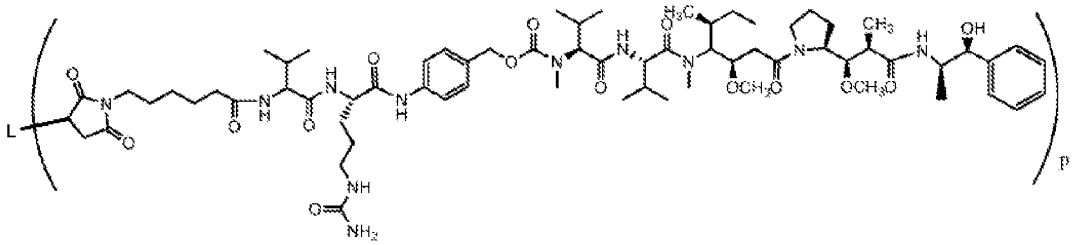
49. The method of any one of claims 1 to 48, wherein the ADC comprises from 1 to 20 units of MMAE per antibody or antigen binding fragment thereof.

50. The method of any one of claims 1 to 49, wherein the ADC comprises from 1 to 10 units of MMAE per antibody or antigen binding fragment thereof.

51. The method of any one of claims 1 to 50, wherein the ADC comprises from 2 to 8 units of MMAE per antibody or antigen binding fragment thereof.

52. The method of any one of claims 1 to 51, wherein the ADC comprises from 3 to 5 units of MMAE per antibody or antigen binding fragment thereof.

53. The method of any one of claims 1 to 52, wherein the ADC has the following structure:



wherein L- represents the anti-191P4D12 antibody or antigen binding fragment thereof and p is from 1 to 10.

54. The method of claim 53, wherein p is from 2 to 8.

55. The method of claim 53 or 54, wherein p is from 3 to 5.

56. The method of any one of claims 53 to 55, wherein p is from 3 to 4.

57. The method of any one of claims 53 to 56, wherein p is about 4.

58. The method of any one of claims 53 to 56, wherein the average p value of the effective amount of the antibody drug conjugates is about 3.8.

59. The method of any one of claims 1 to 58, wherein the ADC is administered to the subject at a dose of about 1 to about 10 mg/kg of the subject's body weight, about 1 to about 5 mg/kg of the subject's body weight, about 1 to about 2.5 mg/kg of the subject's body weight, or about 1 to about 1.25 mg/kg of the subject's body weight.

60. The method of any one of claims 1 to 59, wherein the ADC is administered to the subject at a dose of about 0.25 mg/kg, about 0.5 mg/kg, about 0.75 mg/kg, about 1.0 mg/kg, about 1.25 mg/kg, about 1.5 mg/kg, about 1.75 mg/kg, about 2.0 mg/kg, about 2.25 mg/kg, or about 2.5 mg/kg of the subject's body weight.

61. The method of any one of claims 1 to 60, wherein the ADC is administered to the subject at a dose of about 1 mg/kg of the subject's body weight.

62. The method of any one of claims 1 to 60, wherein the ADC is administered to the subject at a dose of about 1.25 mg/kg of the subject's body weight.

63. The method of any one of claims 1 to 62, wherein the ADC is administered to the subject by an intravenous (IV) injection or infusion.

64. The method of any one of claims 1 to 63, wherein the ADC is administered to the subject by an IV injection or infusion up to 2 days of a 21-day treatment cycle.

65. The method of any one of claims 1 to 64, wherein the ADC is administered to the subject by an IV injection or infusion on days 1 and 8 of a 21-day treatment cycle.

66. The method of any one of claims 1 to 65, wherein the ADC is administered to the subject by an IV injection or infusion over about 30 minutes up to 2 days of a 21-day treatment cycle.

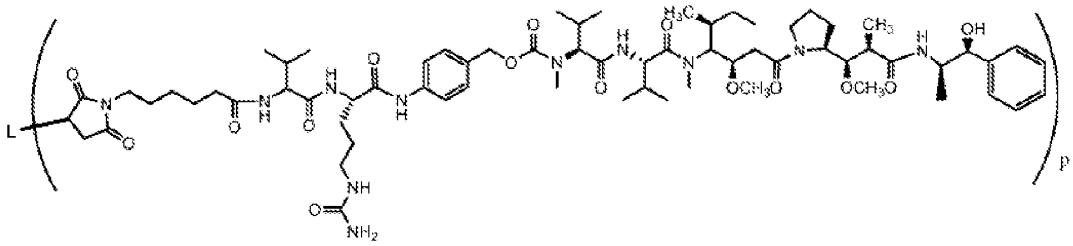
67. The method of any one of claims 1 to 66, wherein the ADC is administered by an IV injection or infusion over about 30 minutes on days 1 and 8 of a 21-day treatment cycle.

68. The method of any one of claims 1 to 67, wherein the ADC is formulated in a pharmaceutical composition comprising L-histidine, polysorbate-20 (TWEEN-20), and trehalose dehydrate.

69. The method of any one of claims 1 to 68, wherein the ADC is formulated in a pharmaceutical composition comprising about 20 mM L-histidine, about 0.02% (w/v) TWEEN-20, about 5.5% (w/v) trehalose dihydrate, and hydrochloride, and wherein the pH of the pharmaceutical composition is about 6.0 at 25°C.

70. The method of any one of claims 1 to 68, wherein the ADC is formulated in a pharmaceutical composition comprising about 9 mM histidine, about 11 mM histidine hydrochloride monohydrate, about 0.02% (w/v) TWEEN-20, and about 5.5% (w/v) trehalose dihydrate, and wherein the pH of the pharmaceutical composition is about 6.0 at 25°C.

71. The method of any one of claims 1 to 70, wherein the ADC has the following structure:



wherein L- represents the antibody or antigen binding fragment thereof and p is from about 3 to about 4, the anti-191P4D12 antibody comprises a heavy chain comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID NO:7 and a light chain comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:8, wherein the ADC is administered at a dose of about 1.25 mg/kg of the subject's body weight, and wherein the dose is administered by an IV injection or infusion over about 30 minutes on days 1 and 8 of a 21-day treatment cycle.

72. The method of any one of claims 1 to 70, wherein the anti-PD-1 antibody is administered to the subject at a dose of about 100 mg to about 400 mg.

73. The method of any one of claims 1 to 70, wherein the anti-PD-1 antibody is administered to the subject at a dose of about 200 mg.

74. The method of claim 71, wherein:

(a) the anti-PD-1 antibody is administered to the subject at a dose of about 200 mg; and

(b) after step (a), the anti-PD-1 antibody is administered to the subject at a dose of about 400 mg every 42 days.

75. The method of any one of claims 1 to 74, wherein the anti-PD-1 antibody is administered to the subject by an IV infusion on 1 day of the 21-day treatment cycle.

76. The method of any one of claims 1 to 75, wherein the anti-PD-1 antibody is administered to the subject by an IV infusion on day 1 in each treatment cycle of 21 days.

77. The method of any one of claims 1 to 76, wherein the anti-PD-1 antibody is administered to the subject by an IV infusion over about 30 minutes on 1 day of the 21-day treatment cycle.

78. The method of any one of claims 1 to 75, wherein the anti-PD-1 antibody is administered to the subject by an IV infusion over about 30 minutes on day 1 in each treatment cycle of 21 days.

79. The method of any one of claims 1 to 78, whereby the subject has a complete response following the treatment.

80. The method of any one of claims 1 to 78, wherein the subject has a partial response following the treatment.

81. The method of any one of claims 1 to 78, wherein the subject has a stable disease following the treatment.

82. The method of any one of claims 1 to 81, wherein the subject has a Brief Pain Inventory Short Form (BPI-SF) worst pain score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has an improved BPI-SF worst pain score.

83. The method of any one of claims 1 to 81, wherein the subject has a BPI-SF worst pain baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from worst pain baseline score of about -0.3 to about -1.2.

84. The method of any one of claims 1 to 81, wherein the subject has a BPI-SF worst pain baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from worst pain baseline score of about -0.61.

85. The method of any one of claims 1 to 81, wherein the subject has a Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire (EORTC QLQ-C30) quality of life (QoL) baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has an improved EORTC QLQ-C30 QoL score.

86. The method of any one of claims 1 to 81, wherein the subject has a EORTC QLQ-C30 QoL baseline score of about zero (0) prior to administration of the ADC to the

subject, and wherein after administration of the ADC to the subject, the subject has a change from EORTC QLQ-C30 QoL baseline score of about 10.0 to about 15.0.

87. The method of any one of claims 1 to 81, wherein the subject has a EORTC QLQ-C30 QoL baseline score of about zero (0) prior to administration of the ADC to the subject, and wherein after administration of the ADC to the subject, the subject has a change from EORTC QLQ-C30 QoL baseline score of about 13.0.

88. The method of any one of claims 1 to 85, wherein the subject is human.