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.

[0028a] In one aspect, provided herein is use of an antibody drug conjugate (ADC) in the preparation of a first medicament and use of an anti-PD-1 antibody in the preparation of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating cancer in a subject;

wherein the ADC comprises an anti-191P4D12 antibody or antigen binding fragment thereof that 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).

[0028b] In another aspect, provided herein is use of an antibody drug conjugate (ADC) and an anti-PD-1 antibody in the preparation of a medicament for combination therapy for treating cancer in a subject;

wherein the ADC comprises an anti-191P4D12 antibody or antigen binding fragment thereof that 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).

[0028c] In another aspect, provided herein is use of an antibody drug conjugate (ADC) in the preparation of a medicament for use in combinatorial therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with an anti-PD-1 antibody;

wherein the ADC comprises an anti-191P4D12 antibody or antigen binding fragment thereof that 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).

[0029] In certain examples, 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 examples, 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] Example 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] Example 2. The method of example 1, wherein the subject has not previously received a PD-(L)-1 inhibitor.

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

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

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

[0035] Example 6. The method of any one of examples 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] Example 7. The method of any one of examples 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] Example 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] Example 9. The method of example 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] Example 10. The method of example 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] Example 11. The method of example 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] Example 12. The method of example 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] Example 13. The method of example 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] Example 14. The method of any one of examples 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] Example 15. The method of any one of examples 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] Example 16. The method of any one of examples 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] Example 17. The method of any one of examples 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] Example 18. The method of any one of examples 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] Example 19. The method of any one of examples 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] Example 20. The method of any one of examples 1 to 19, wherein the subject has visceral metastases.

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

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

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

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

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

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

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

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

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

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

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

[0061] Example 32. The method of any one of examples 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] Example 33. The method of any one of examples 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] Example 34. The method of any one of examples 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] Example 35. The method of any one of examples 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] Example 36. The method of any one of examples 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] Example 37. The method of any one of examples 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] Example 38. The method of any one of examples 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] Example 39. The method of any one of examples 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] Example 40. The method of any one of examples 1 to 34 and 36 to 37, wherein the anti-191P4D12 antigen binding fragment is an Fab, F(ab′)2, Fv, or scFv.

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

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

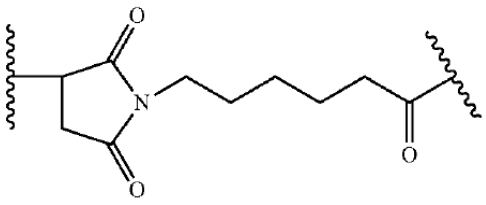
[0072] Example 43. The method of any one of examples 1 to 42, wherein the anti-191P4D12 antibody or antigen binding fragment thereof is recombinantly produced.

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

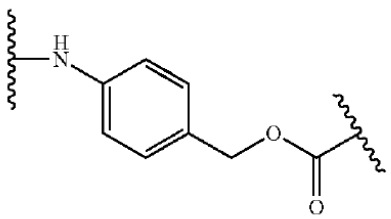
[0074] Example 45. The method of example 44, wherein the linker is an enzyme-cleavable linker, and wherein the linker forms a bond with a sulfur atom of the antibody or antigen binding fragment thereof.

[0075] Example 46. The method of example 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] Example 47. The method of example 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] Example 48. The method of example 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.

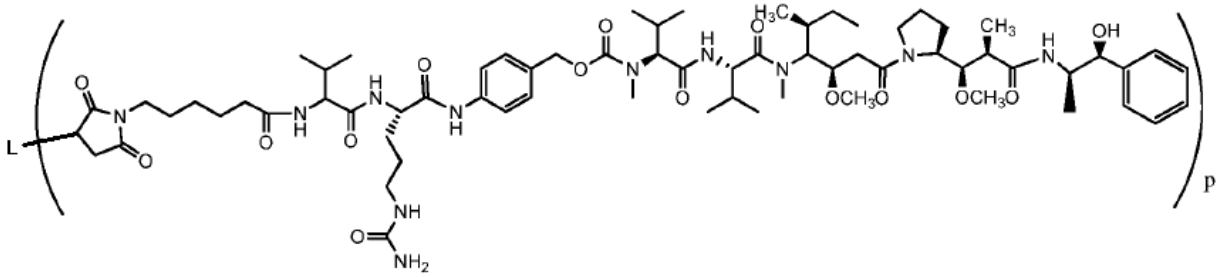
[0078] Example 49. The method of any one of examples 1 to 48, wherein the ADC comprises from 1 to 20 units of MMAE per antibody or antigen binding fragment thereof.

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

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

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

[0082] Example 53. The method of any one of examples 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] Example 54. The method of example 53, wherein p is from 2 to 8.

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

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

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

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

[0088] Example 59. The method of any one of examples 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] Example 60. The method of any one of examples 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] Example 61. The method of any one of examples 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] Example 62. The method of any one of examples 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] Example 63. The method of any one of examples 1 to 62, wherein the ADC is administered to the subject by an intravenous (IV) injection or infusion.

[0093] Example 64. The method of any one of examples 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] Example 65. The method of any one of examples 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] Example 66. The method of any one of examples 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] Example 67. The method of any one of examples 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.

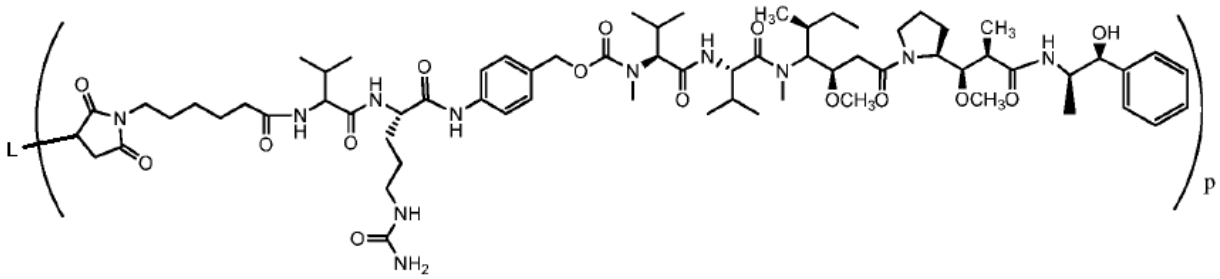
[0097] Example 68. The method of any one of examples 1 to 67, wherein the ADC is formulated in a pharmaceutical composition comprising L-histidine, polysorbate-20 (TWEEN-20), and trehalose dehydrate.

[0098] Example 69. The method of any one of examples 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] Example 70. The method of any one of examples 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] Example 71. The method of any one of examples 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] Example 72. The method of any one of examples 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] Example 73. The method of any one of examples 1 to 70, wherein the anti-PD-1 antibody is administered to the subject at a dose of about 200 mg.

[00103] Example 74. The method of example 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] Example 75. The method of any one of examples 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] Example 76. The method of any one of examples 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] Example 77. The method of any one of examples 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] Example 78. The method of any one of examples 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] Example 79. The method of any one of examples 1 to 76, whereby the subject has a complete response following the treatment.

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

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

[00111] Example 82. The method of any one of examples 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] Example 83. The method of any one of examples 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] Example 84. The method of any one of examples 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 examples 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 examples 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] Example 85. The method of any one of examples 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] Example 86. The method of any one of examples 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.

What is claimed is:

1. Use of an antibody drug conjugate (ADC) in the preparation of a first medicament and use of an anti-PD-1 antibody in the preparation of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating cancer in a subject;

wherein the ADC comprises an anti-191P4D12 antibody or antigen binding fragment thereof that 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. Use of an antibody drug conjugate (ADC) and an anti-PD-1 antibody in the preparation of a medicament for combination therapy for treating cancer in a subject;

wherein the ADC comprises an anti-191P4D12 antibody or antigen binding fragment thereof that 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).

3. Use of an antibody drug conjugate (ADC) in the preparation of a medicament for use in combinatorial therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with an anti-PD-1 antibody;

wherein the ADC comprises an anti-191P4D12 antibody or antigen binding fragment thereof that 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).

4. The use of any one of claims 1 to 3, wherein the subject has not previously received a PD-(L)-1 inhibitor.

5. The use of any one of claims 1 to 4, wherein the subject has a GFR >60 mL/min or creatinine clearance >60 mL/min.

6. The use of any one of claims 1 to 5, wherein the subject has NCI CTCAE Grade ≤1 audiometric hearing loss.

7. The use of any one of claims 1 to 6, wherein the subject does not have NYHA Class III heart failure.

8. The use of any one of claims 1 to 7, 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 to be treated, 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, optionally wherein median progression free survival is at least or about 14.6 months for a population of subjects treated, further optionally wherein median progression free survival is 14 to 15 months for a population of subjects treated.

9. The use of any one of claims 1 to 7, 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 to be treated, 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, optionally wherein median overall survival is at least or about 31.5 months for a population of subjects treated, further optionally wherein median overall survival is 31 to 32 months for a population of subjects treated.

10. The use of claim 1, 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.

11. The use of any one of claims 1 to 7, or 10, 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 to be treated, 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, optionally wherein median progression free survival is 12 to 13 months for a population of subjects treated.

12. The use of any one of claims 1 to 7, or 10, 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 to be treated, 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, optionally wherein median overall survival is 31 to 32 months for a population of subjects treated.

13. The use of any one of claims 1 to 7, or 10, 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 to be treated, 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, optionally wherein median progression free survival is 14 to 15 months for a population of subjects treated.

14. The use of any one of claims 1 to 7, or 10, 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 to be treated, 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, optionally wherein median progression free survival is 18 to 19 months for a population of subjects treated.

15. The use of any one of claims 1 to 7, or 10, 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 to be treated, 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, optionally wherein median progression free survival is 10 to 11 months for a population of subjects treated.

16. The use of any one of claims 1 to 7, or 10, 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 to be treated, 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, optionally wherein median progression free survival is 16 to 17 months for a population of subjects treated.

17. The use of any one of claims 1 to 7, or 10, 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 to be treated, 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, optionally wherein median progression free survival is 8 to 9 months for a population of subjects treated.

18. The use of any one of claims 1 to 7, or 10, 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 to be treated, 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, optionally wherein median progression free survival is 10 to 11 months for a population of subjects treated.

19. The use of any one of claims 1 to 7, or 10, 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 to be treated, 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, optionally wherein median progression free survival is 22 to 23 months for a population of subjects treated.

20. The use of any one of claims 1 to 19, wherein the subject has visceral metastases.

21. The use of any one of claims 1 to 19, wherein the subject has lymph nodes only disease.

22. The use of any one of claims 1 to 21, wherein the disease site of origin is in the upper tract.

23. The use of any one of claims 1 to 21, wherein the disease site of origin is in the lower tract.

24. The use of any one of claims 1 to 23, wherein the subject has a PD-L1 expression combined positive score (CPS):

(i) greater than or equal to 10; or

(ii) less than 10.

25. The use of any one of claims 1 to 19, wherein the subject has a Nectin-4 H-score:

(i) between 0 and 300;

(ii) between 0 and 200; or

(iii) between 0 and 150.

26. The use of any one of claims 1 to 19, wherein the use does not comprise determining PD-L1 expression or Nectin-4 expression of the subject.

27. The use of any one of claims 1 to 26, wherein the subject has locally advanced or metastatic urothelial cancer.

28. The use of any one of claims 1 to 27, wherein the subject has locally advanced or metastatic bladder cancer.

29. The use of any one of claims 1 to 28, wherein:

(i) 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; or

(ii) 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.

30. The use of any one of claims 1 to 29, 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.

31. The use of any one of claims 1 to 29, 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.

32. The use of any one of claims 1 to 31, 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.

33. The use of any one of claims 1 to 31, 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.

34. The use of any one of claims 1 to 33, 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.

35. The use of any one of claims 1 to 34, 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.

36. The use of any one of claims 1 to 30 and 32 to 34, wherein the anti-191P4D12 antigen binding fragment is an Fab, F(ab′)2, Fv, or scFv.

37. The use of any one of claims 1 to 31, wherein the anti-191P4D12 antibody is a fully human antibody.

38. The use of any one of claims 1 to 35 and 37, wherein the anti-191P4D12 antibody is an IgG1 and the light chain is a kappa light chain.

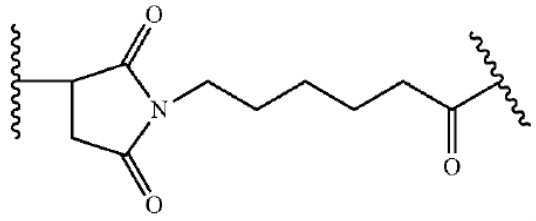
39. The use of any one of claims 1 to 38, wherein the anti-191P4D12 antibody or antigen binding fragment thereof is recombinantly produced.

40. The use of any one of claims 1 to 39, wherein the anti-191P4D12 antibody or antigen binding fragment is conjugated to each unit of MMAE via a linker.

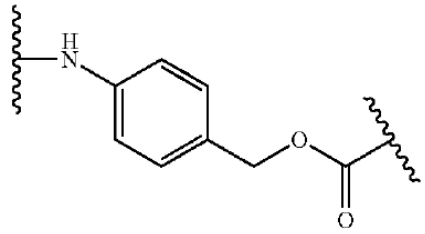
41. The use of claim 40, wherein the linker is an enzyme-cleavable linker, and wherein the linker forms a bond with a sulfur atom of the antibody or antigen binding fragment thereof.

42. The use of claim 40 or 41, 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.

43. The use of claim 42, 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).

44. The use of claim 42 or 43, 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.

45. The use of any one of claims 1 to 44, wherein the ADC comprises:

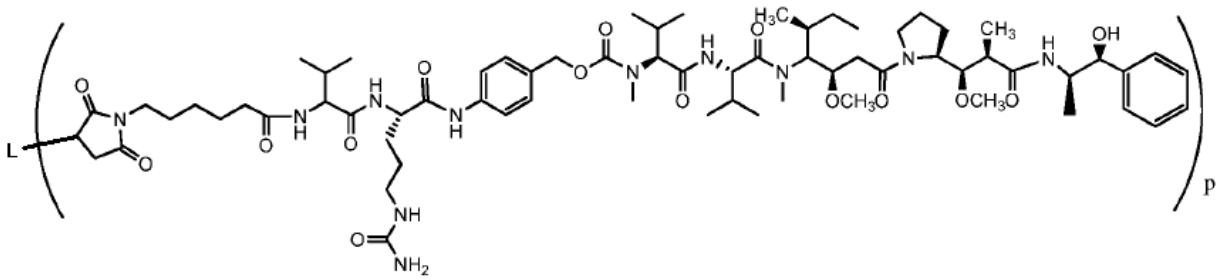
(i) from 1 to 20 units of MMAE per antibody or antigen binding fragment thereof;

(ii) from 1 to 10 units of MMAE per antibody or antigen binding fragment thereof;

(iii) from 2 to 8 units of MMAE per antibody or antigen binding fragment thereof; or

(iv) from 3 to 5 units of MMAE per antibody or antigen binding fragment thereof.

46. The use of any one of claims 1 to 45, wherein the ADC has the following structure:



wherein L- represents the anti-191P4D12 antibody or antigen binding fragment thereof and wherein:

(i) p is from 1 to 10;

(ii) p is from 3 to 5;

(iii) p is from 3 to 4;

(iv) p is about 4;

(v) the average p value of the effective amount of the antibody drug conjugates is about 3.8.

47. The use of any one of claims 1 to 46, wherein the ADC is to be administered to the subject at a dose of:

(i) 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;

(ii) 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;

(iii) about 1 mg/kg of the subject's body weight; or

(iv) about 1.25 mg/kg of the subject's body weight.

48. The use of any one of claims 1 to 47, wherein the ADC is to be administered to the subject by:

(i) an intravenous (IV) injection or infusion;

(ii) an IV injection or infusion up to 2 days of a 21-day treatment cycle;

(iii) an IV injection or infusion on days 1 and 8 of a 21-day treatment cycle;

(iv) an IV injection or infusion over about 30 minutes up to 2 days of a 21-day treatment cycle; and/or

(v) an IV injection or infusion over about 30 minutes on days 1 and 8 of a 21-day treatment cycle.

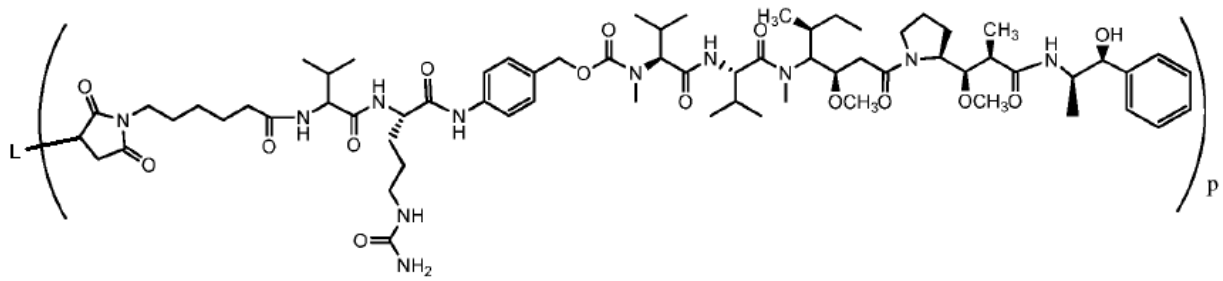
49. The use of any one of claims 1 to 48, wherein the ADC is formulated in a pharmaceutical composition comprising:

(i) L-histidine, polysorbate-20, and trehalose dihydrate;

(ii) about 20 mM L-histidine, about 0.02% (w/v) polysorbate-20, about 5.5% (w/v) trehalose dihydrate, and hydrochloride, and wherein the pH of the pharmaceutical composition is about 6.0 at 25℃; or

(iii) about 9 mM histidine, about 11 mM histidine hydrochloride monohydrate, about 0.02% (w/v) polysorbate-20, and about 5.5% (w/v) trehalose dihydrate, and wherein the pH of the pharmaceutical composition is about 6.0 at 25℃.

50. The use of any one of claims 1 to 49, 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 to be administered at a dose of about 1.25 mg/kg of the subject's body weight, and wherein the dose is to be administered by an IV injection or infusion over about 30 minutes on days 1 and 8 of a 21-day treatment cycle.

51. The use of any one of claims 1 to 49, wherein the anti-PD-1 antibody is to be administered to the subject at a dose of:

(i) about 100 mg to about 400 mg; or

(ii) about 200 mg.

52. The use of claim 50, wherein:

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

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

53. The use of any one of claims 1 to 52, wherein:

(i) the anti-PD-1 antibody is to be administered to the subject by an IV infusion on day 1 of the 21-day treatment cycle;

(ii) the anti-PD-1 antibody is to be administered to the subject by an IV infusion on day 1 in each treatment cycle of 21 days;

(iii) the anti-PD-1 antibody is to be administered to the subject by an IV infusion over about 30 minutes on day 1 of the 21-day treatment cycle; or

(iv) the anti-PD-1 antibody is to be administered to the subject by an IV infusion over about 30 minutes on day 1 in each treatment cycle of 21 days.

54. The use of any one of claims 1 to 53, whereby the subject has:

(i) a complete response following the treatment;

(ii) a partial response following the treatment; or

(iii) a stable disease following the treatment.

55. The use of any one of claims 1 to 54, wherein the subject has:

(i) 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;

(ii) 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;

(iii) 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;

(iv) 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;

(v) 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; or

(vi) 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.

56. The use of any one of claims 1 to 55, wherein the subject is human.