

ANTI-PD-L1 ANTIBODIES AND ANTIBODY-DRUG CONJUGATES AND THEIR USE IN THE TREATMENT OF CANCER

[0001] Incorporated by reference herein for all purposes are the contents of U.S. Provisional Patent Application No. 63/626,868 (filed January 30, 2024), U.S. Provisional Patent Application No. 63/557,770 (filed February 26, 2024), U.S. Provisional Patent Application No. 63/691,610 (filed September 6, 2024), and U.S. Provisional Patent Application No. 63/736,264 (filed December 19, 2024).

TECHNICAL FIELD

[0002] The present invention relates to methods and compositions for treating cancer, such as non-small cell lung cancer, head and neck cancer, esophageal cancer, ovarian cancer, melanoma, breast cancer, and gastric cancer, in a subject, such as by the administration of antibodies and antibody-drug conjugates that bind to Programmed Death-Ligand 1 (PD-L1).

BACKGROUND

[0003] PD-L1, which is also known as Programmed Death-Ligand 1, B7-H1, or CD274, is a protein that has been shown to be expressed in a variety of cancer cells. PD-L1 is a transmembrane protein that can interact with PD-1 and act as an “off” switch to inactivate T cells. PD-L1 is commonly overexpressed on tumor cells, and binding to PD-1 allows tumors to avoid a T cell immune response.

[0004] There are several cancers that express PD-L1, including melanoma. Melanoma is the most dangerous type of skin cancer. In 2015, there were 3.1 million people with active disease and melanoma resulted in 59,800 deaths. The five-year survival rate of stage IV disease is less than 10%, with median survival of only 6-12 months. Therefore, there is a need for improved treatments for melanoma, as well as other cancers that express PD-L1. One type of treatment for cancers that express PD-L1 includes administering anti-PD-L1 antibodies as an immunotherapy. Immuno-oncology is a promising field for cancer treatment, but there is room for improvement to current therapies.

[0005] The present invention meets the need for improved treatment of cancers such as non-small cell lung cancer, head and neck cancer, esophageal cancer, ovarian cancer,

melanoma, breast cancer, and gastric cancer, by providing highly specific and effective anti-PD-L1 antibody-drug conjugates.

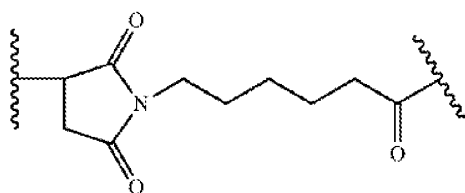
[0006] All references cited herein, including patent applications, patent publications, and scientific literature, are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

SUMMARY

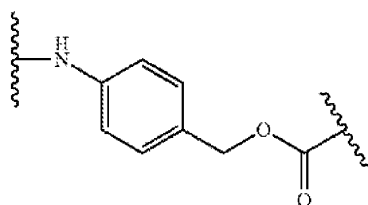
[0007] Provided herein are methods of treating cancer in a human subject. In some embodiments, the methods comprise administering to the subject an effective amount of an antibody drug conjugate (ADC) comprising an anti-PD-L1 antibody or antigen binding fragment thereof, and an effective amount of an anti-PD-1 antibody; wherein the anti-PD-L1 antibody or antigen binding fragment thereof binds to PD-L1 and is conjugated to one or more units of monomethyl auristatin E (MMAE); wherein the anti-PD-L1 antibody or antigen binding fragment thereof comprises: (i) a light chain variable region comprising light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 8, 9, and 10, respectively and (ii) a heavy chain variable region comprising heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 5, 6, and 7, respectively; and wherein the anti-PD-1 antibody comprises: (i) a light chain variable region comprising light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 20, 21, and 22 respectively and (ii) a heavy chain variable region comprising heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 17, 18, and 19, respectively.

[0008] In some embodiments, the anti-PD-L1 antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence at least 85% identical to the amino acid sequence of SEQ ID NO:3 and a light chain variable region comprising an amino acid sequence at least 85% identical to the amino acid sequence of SEQ ID NO:4. In some embodiments, the anti-PD-L1 antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:3 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:4. In some embodiments, the anti-PD-L1 antibody or antigen-binding fragment thereof comprises a heavy chain the amino acid sequence of SEQ ID NO:1 and a light chain comprising the amino acid sequence of SEQ ID NO:2.

[0009] In some embodiments, the anti-PD-L1 antibody or antigen-binding fragment thereof is conjugated to each unit of MMAE via a linker. In some embodiments, the linker is an enzyme-cleavable linker, wherein the linker forms a bond with a sulfur atom of the antibody or antigen binding fragment thereof. In some embodiments, 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. In some embodiments, 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:

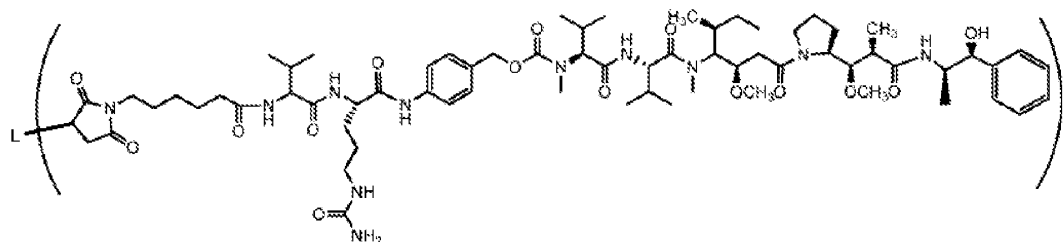


Formula (1)



Formula (2).

[0010] In some embodiments, the ADC comprises from 1 to 20 units of MMAE per antibody or antigen binding fragment thereof. In some embodiments, the ADC comprises from 1 to 10 units of MMAE per antibody or antigen binding fragment thereof. In some embodiments, the ADC comprises from 2 to 8 units of MMAE per antibody or antigen binding fragment thereof. In some embodiments, the ADC comprises from 3 to 5 units of MMAE per antibody or antigen binding fragment thereof. In some embodiments, the ADC has the following structure:



wherein L- represents the anti-PD-L1 antibody or antigen binding fragment thereof and p is from 1 to 10. In some embodiments, p is from 2 to 8. In some embodiments, p is from 3 to 5. In some embodiments, p is 4. In some embodiments, p is 8.

[0011] In some embodiments, the cancer is melanoma, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), head and neck squamous cell carcinoma (HNSCC), triple negative breast cancer (TNBC), esophageal squamous cell carcinoma (esophageal SCC), ovarian cancer, urothelial cancer, hepatocellular carcinoma (HCC), gastric cancer, or cervical cancer.

[0012] In some embodiments, the ADC is administered to the subject at a dose of about 0.25 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, or about 1 to about 2 mg/kg of the subject's body weight. In some embodiments, the subject's body weight is the subject's ideal body weight (IBW). In some embodiments, the subject's body weight is the subject's adjusted ideal body weight (AIBW). In some embodiments, the anti-PD-1 antibody is administered at a dose of 200 mg. In some embodiments, the ADC is administered once about every 1 week, once about every 2 weeks, once about every 3 weeks, or twice about every 3 weeks. In some embodiments, the ADC is administered on Days 1 and 8 of each 21-day cycle. In some embodiments, the anti-PD-1 antibody is administered once about every 1 week, once about every 2 weeks, once about every 3 weeks, or twice about every 3 weeks. In some embodiments, the anti-PD-1 antibody is administered on Day 1 of each 21-day cycle.

[0013] In some embodiments, the subject has metastatic or unresectable solid malignancy disease that is relapsed or refractory or intolerant to standard of care treatment. In some embodiments, the route of administration for the ADC is intravenous. In some embodiments, the route of administration for the anti-PD-1 antibody is intravenous. In some embodiments, one or more therapeutic effects in the subject is improved after administration of the antibody-drug conjugate relative to a baseline. In some embodiments, the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the

cancer, objective response rate, duration of response, time to response, progression free survival, and overall survival.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] FIG. 1 shows an overall study design of a phase one study to evaluate SGN-PDL1V. HNSCC=head and neck squamous cell carcinoma; NSCLC=non-small cell lung cancer; PD-L1=programmed death-ligand 1; SCC=squamous cell carcinoma; TNBC=triple negative breast cancer. (a) If necessary. May examine alternative doses and schedules; (b) Melanoma, ovarian cancer, TNBC, gastric cancer, or esophageal SCC; (c) NSCLC and HNSCC with negative PD-L1 expression, melanoma, ovarian cancer, TNBC, gastric cancer, or esophageal SCC.

[0015] FIG. 2 shows preliminary patient data for all subjects in dose escalation and dose optimization.

[0016] FIG. 3 shows preliminary patient data for all HNSCC subjects in dose escalation ≥ 1.25 mg/kg.

[0017] FIG.4 shows the incidence and grades of treatment-related AEs for SGN-PDL1V treatment.

[0018] FIG. 5 shows the pharmacokinetics of SGN-PDL1V as compared to unconjugated MMAE.

[0019] FIG. 6 shows the anti-tumor activity of SGN-PDL1V on PDL1+ tumors, as demonstrated by change in sum of tumor diameters.

[0020] FIG. 7 shows the durability of clinical responses by SGN-PDL1V on PDL1+ tumors, as demonstrated by change in tumor size over time.

[0021] FIG. 8 shows the anti-tumor activity of SGN-PDL1V on PDL1+ NSCLC, as demonstrated by change in sum of tumor diameters.

[0022] FIG. 9 shows the durability of clinical responses by SGN-PDL1V on PDL1+ NSCLC, as demonstrated by change in tumor size over time.

[0023] FIG. 10 shows the amount of live cells for PD-L1 negative cells (in monoculture), PD-L1 negative cells (in coculture) or PD-L1 positive cells (in coculture) when treated with the indicated concentration of PDL1V, isotype vedotin or MMAE. Raw fluorescence data

was analyzed using Flowjo software and plotted in Graphpad Prism 8 using the equation $[(\text{PDL1neg or PDL1pos live absolute count}) / (\text{average PDL1neg or PDL1pos live absolute count of untreated group}) * 100]$ to derive Live Cells as % Untreated values.

[0024] FIG. 11A shows the amount of extracellular ATP in each sample, where raw luminescence data was analyzed in Graphpad Prism 8 and plotted as fold-change over untreated using the equation $[\text{Value in experimental group} / \text{Mean of Untreated group}]$. Dotted line depicts average of untreated group values. FIG. 11B shows the amount of HMGB1 in supernatant for each sample, where raw luminescence values were extrapolated from a positive control HMGB1 standard curve and plotted in Graphpad Prism 8. Dotted line depicts average of untreated group values. FIG. 11C shows the amount of cell-surface Calreticulin for each sample, where raw fluorescence data was analyzed in Flowjo and % Calreticulin positive cells were plotted using Graphpad Prism 8. Dotted line depicts average of untreated group values.

[0025] FIGs. 12A and B show the amount of cell CD4+ cell death in Donor 1 and Donor 2, when treated with PDL1v, isotype vedotin, or positive control respectively. FIGs. 12C and D show the amount of cell CD8+ cell death in Donor 1 and Donor 2, when treated with PDL1v, isotype vedotin, or positive control respectively. Raw data were analyzed in Flowjo v10 and using Graphpad Prism 8, fit to a non-linear, 4-parameter curve with the equation $[Y = \text{Bottom} + ((\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogEC50} - X) * \text{HillSlope}))})]$. Data was calculated and displayed as % of untreated using the equation $[\text{Value in experimental group} / \text{Mean of Untreated group}] * 100$.

(2Q3W: day 1 and day 8 of a 21-day cycle; AiBW: adjusted ideal body weight; CI: confidence interval; cORR: confirmed objective response rate; CR: complete response; DCR: disease control rate; ESCC: esophageal squamous cell carcinoma; HNSCC: head and neck squamous cell carcinoma; mDOR: median duration of confirmed response; mPFS: median progression-free survival, NE/NA: not evaluable/not available; NSCLC: non-small cell lung cancer; ORR: objective response rate; PD: progressive disease; PD-L1: programmed cell death ligand 1; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease; TNBC: triple-negative breast cancer.)

DETAILED DESCRIPTION

I. Definitions

[0026] In order that the present disclosure can be more readily understood, certain terms are first defined. As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application.

[0027] The term "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "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 aspects: 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).

[0028] It is understood that aspects and embodiments of the invention described herein include "comprising," "consisting," and "consisting essentially of" aspects and embodiments.

[0029] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[0030] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. The headings provided herein are not limitations of the various aspects of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety.

[0031] The terms "PD-L1," "CD274," "B7-H1," and "programmed cell death ligand 1" are used interchangeably herein, and, unless specified otherwise, include any variants,

isoforms and species homologs of human PD-L1 which are generally expressed by cells or expressed on cells transfected with the PD-L1 gene.

[0032] The term "immunoglobulin" refers to a class of structurally related glycoproteins consisting of two pairs of polypeptide chains, one pair of light (L) low molecular weight chains and one pair of heavy (H) chains, all four inter-connected by disulfide bonds. The structure of immunoglobulins has been well characterized. See for instance Fundamental Immunology Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)). Briefly, each heavy chain typically is comprised of a heavy chain variable region (abbreviated herein as V_H or VH) and a heavy chain constant region (C_H or CH). The heavy chain constant region typically is comprised of three domains, C_{H1} , C_{H2} , and C_{H3} . The heavy chains are generally inter-connected via disulfide bonds in the so-called "hinge region." Each light chain typically is comprised of a light chain variable region (abbreviated herein as V_L or VL) and a light chain constant region (C_L or CL). The light chain constant region typically is comprised of one domain, C_L . The CL can be of κ (kappa) or λ (lambda) isotype. The terms "constant domain" and "constant region" are used interchangeably herein. An immunoglobulin can derive from any of the commonly known isotypes, including but not limited to IgA, secretory IgA, IgG, and IgM. IgG subclasses are also well known to those in the art and include but are not limited to human IgG1, IgG2, IgG3 and IgG4. "Isotype" refers to the antibody class or subclass (e.g., IgM or IgG1) that is encoded by the heavy chain constant region genes.

[0033] The term "variable region" or "variable domain" refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable regions of the heavy chain and light chain (V_H and V_L , respectively) of a native antibody may be further subdivided into regions of hypervariability (or hypervariable regions, which may be hypervariable in sequence and/or form of structurally defined loops), also termed complementarity-determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FRs). The terms "complementarity determining regions" and "CDRs," synonymous with "hypervariable regions" or "HVRs" are known in the art to refer to non-contiguous sequences of amino acids within antibody variable regions, which confer antigen specificity and/or binding affinity. In general, there are three CDRs in each heavy chain variable region (CDR-H1, CDR-H2, CDR-H3) and three CDRs in each light chain variable region (CDR-L1, CDR-L2, CDR-L3). "Framework regions" and "FR" are known in the art to refer to the non-CDR portions of the variable regions of the heavy and

light chains. In general, there are four FRs in each full-length heavy chain variable region (FR-H1, FR-H2, FR-H3, and FR-H4), and four FRs in each full-length light chain variable region (FR-L1, FR-L2, FR-L3, and FR-L4). Within each V_H and V_L , three CDRs and four FRs are typically arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4 (*See also Chothia and Lesk J. Mol. Biol.*, 195, 901-917 (1987)).

[0034] The term “antibody” (Ab) in the context of the present invention refers to an immunoglobulin molecule, a fragment of an immunoglobulin molecule, or a derivative of either thereof, which has the ability to specifically bind to an antigen under typical physiological conditions with a half-life of significant periods of time, such as at least about 30 min, at least about 45 min, at least about one hour (h), at least about two hours, at least about four hours, at least about eight hours, at least about 12 hours (h), about 24 hours or more, about 48 hours or more, about three, four, five, six, seven or more days, etc., or any other relevant functionally-defined period (such as a time sufficient to induce, promote, enhance, and/or modulate a physiological response associated with antibody binding to the antigen and/or time sufficient for the antibody to recruit an effector activity). The variable regions of the heavy and light chains of the immunoglobulin molecule contain a binding domain that interacts with an antigen. The constant regions of the antibodies (Abs) may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (such as effector cells) and components of the complement system such as C1q, the first component in the classical pathway of complement activation. An antibody may also be a bispecific antibody, diabody, multispecific antibody or similar molecule.

[0035] The term “monoclonal antibody” as used herein refers to a preparation of antibody molecules that are recombinantly produced with a single primary amino acid sequence. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. Accordingly, the term “human monoclonal antibody” refers to antibodies displaying a single binding specificity which have variable and constant regions derived from human germline immunoglobulin sequences. The human monoclonal antibodies may be generated by a hybridoma which includes a B cell obtained from a transgenic or transchromosomal non-human animal, such as a transgenic mouse, having a genome

comprising a human heavy chain transgene and a light chain transgene, fused to an immortalized cell.

[0036] An "isolated antibody" refers to an antibody that is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that binds specifically to PD-L1 is substantially free of antibodies that bind specifically to antigens other than PD-L1). An isolated antibody that binds specifically to PD-L1 can, however, have cross-reactivity to other antigens, such as PD-L1 molecules from different species. Moreover, an isolated antibody can be substantially free of other cellular material and/or chemicals. In one embodiment, an isolated antibody includes an antibody conjugate attached to another agent (*e.g.*, small molecule drug). In some embodiments, an isolated anti-PD-L1 antibody includes a conjugate of an anti-PD-L1 antibody with a small molecule drug (*e.g.*, MMAE or MMAF).

[0037] A "human antibody" (HuMAb) refers to an antibody having variable regions in which both the FRs and CDRs are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The human antibodies of the disclosure can include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). However, the term "human antibody," as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. The terms "human antibodies" and "fully human antibodies" are used synonymously.

[0038] The term "humanized antibody" as used herein, refers to a genetically engineered non-human antibody, which contains human antibody constant domains and non-human variable domains modified to contain a high level of sequence homology to human variable domains. This can be achieved by grafting of the six non-human antibody complementarity-determining regions (CDRs), which together form the antigen binding site, onto a homologous human acceptor framework region (FR) (see WO92/22653 and EP0629240). In order to fully reconstitute the binding affinity and specificity of the parental antibody, the substitution of framework residues from the parental antibody (*i.e.* the non-human antibody) into the human framework regions (back-mutations) may be required. Structural homology modeling may help to identify the amino acid residues in the framework regions that are

important for the binding properties of the antibody. Thus, a humanized antibody may comprise non-human CDR sequences, primarily human framework regions optionally comprising one or more amino acid back-mutations to the non-human amino acid sequence, and fully human constant regions. Optionally, additional amino acid modifications, which are not necessarily back-mutations, may be applied to obtain a humanized antibody with preferred characteristics, such as affinity and biochemical properties.

[0039] The term “chimeric antibody” as used herein, refers to an antibody wherein the variable region is derived from a non-human species (*e.g.* derived from rodents) and the constant region is derived from a different species, such as human. Chimeric antibodies may be generated by antibody engineering. “Antibody engineering” is a term used generic for different kinds of modifications of antibodies, and which is a well-known process for the skilled person. In particular, a chimeric antibody may be generated by using standard DNA techniques as described in Sambrook *et al.*, 1989, *Molecular Cloning: A laboratory Manual*, New York: Cold Spring Harbor Laboratory Press, Ch. 15. Thus, the chimeric antibody may be a genetically or an enzymatically engineered recombinant antibody. It is within the knowledge of the skilled person to generate a chimeric antibody, and thus, generation of the chimeric antibody according to the present invention may be performed by other methods than described herein. Chimeric monoclonal antibodies for therapeutic applications are developed to reduce antibody immunogenicity. They may typically contain non-human (*e.g.* murine) variable regions, which are specific for the antigen of interest, and human constant antibody heavy and light chain domains. The terms “variable region” or “variable domains” as used in the context of chimeric antibodies, refers to a region which comprises the CDRs and framework regions of both the heavy and light chains of the immunoglobulin.

[0040] An “anti-antigen antibody” refers to an antibody that binds to the antigen. For example, an anti-PD-L1 antibody is an antibody that binds to the antigen PD-L1.

[0041] An “antigen-binding portion” or “antigen-binding fragment” of an antibody refers to one or more fragments of an antibody that retain the ability to bind specifically to the antigen bound by the whole antibody. Examples of antibody fragments (*e.g.*, antigen-binding fragment) include but are not limited to Fv, Fab, Fab', Fab'-SH, F(ab')₂; diabodies; linear antibodies; single-chain antibody molecules (*e.g.* scFv); and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called “Fab” fragments, each with a single antigen-binding site, and a

residual “Fc” fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an F(ab')₂ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

[0042] “Percent (%) sequence identity” with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For example, the % sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % sequence identity of A to B will not equal the % sequence identity of B to A.

[0043] As used herein, the terms “binding”, “binds” or “specifically binds” in the context of the binding of an antibody to a pre-determined antigen typically is a binding with an affinity corresponding to a K_D of about 10⁻⁶ M or less, *e.g.* 10⁻⁷ M or less, such as about 10⁻⁸ M or less, such as about 10⁻⁹ M or less, about 10⁻¹⁰ M or less, or about 10⁻¹¹ M or even less when determined by for instance BioLayer Interferometry (BLI) technology in a Octet HTX instrument using the antibody as the ligand and the antigen as the analyte, and wherein the antibody binds to the predetermined antigen with an affinity corresponding to a K_D that is at least ten-fold lower, such as at least 100-fold lower, for instance at least 1,000-fold lower, such as at least 10,000-fold lower, for instance at least 100,000-fold lower than its K_D of

binding to a non-specific antigen (*e.g.*, BSA, casein) other than the predetermined antigen or a closely related antigen. The amount with which the K_D of binding is lower is dependent on the K_D of the antibody, so that when the K_D of the antibody is very low, then the amount with which the K_D of binding to the antigen is lower than the K_D of binding to a non-specific antigen may be at least 10,000-fold (that is, the antibody is highly specific).

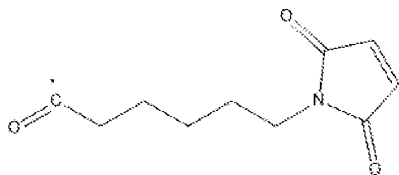
[0044] The term " K_D " (M), as used herein, refers to the dissociation equilibrium constant of a particular antibody-antigen interaction. Affinity, as used herein, and K_D are inversely related, that is that higher affinity is intended to refer to lower K_D , and lower affinity is intended to refer to higher K_D .

[0045] The term "ADC" refers to an antibody-drug conjugate, which in the context of the present invention refers to an anti-PD-L1 antibody, which is coupled to a drug moiety (*e.g.*, MMAE or MMAF) as described in the present application.

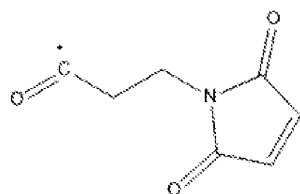
[0046] The abbreviations "vc" and "val-cit" refer to the dipeptide linker valine-citrulline.

[0047] The abbreviation VKG refers to the tripeptide linker valine-lysine-glycine.

[0048] The abbreviation "MC" refers to the stretcher maleimidocaproyl:



[0049] The abbreviation "MP" refers to the stretcher maleimidopropionyl:



[0050] "PEG Unit" as used herein is an organic moiety comprised of repeating ethylene-oxy subunits (PEGs or PEG subunits) and may be polydisperse, monodisperse or discrete (*i.e.*, having discrete number of ethylene-oxy subunits). Polydisperse PEGs are a heterogeneous mixture of sizes and molecular weights whereas monodisperse PEGs are

typically purified from heterogeneous mixtures and are therefore provide a single chain length and molecular weight. Preferred PEG Units comprises discrete PEGs, compounds that are synthesized in step-wise fashion and not via a polymerization process. Discrete PEGs provide a single molecule with defined and specified chain length.

[0051] The PEG Unit provided herein comprises one or multiple polyethylene glycol chains, each comprised of one or more ethyleneoxy subunits, covalently attached to each other. The polyethylene glycol chains can be linked together, for example, in a linear, branched or star shaped configuration. Typically, at least one of the polyethylene glycol chains prior to incorporation into a camptothecin conjugate is derivatized at one end with an alkyl moiety substituted with an electrophilic group for covalent attachment to the carbamate nitrogen of a methylene carbamate unit (i.e., represents an instance of R). Typically, the terminal ethyleneoxy subunit in each polyethylene glycol chains not involved in covalent attachment to the remainder of the Linker Unit is modified with a PEG Capping Unit, typically an optionally substituted alkyl such as $-\text{CH}_3$, CH_2CH_3 or $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$. A preferred PEG Unit has a single polyethylene glycol chain with 2 to 24 $-\text{CH}_2\text{CH}_2\text{O}-$ subunits covalently attached in series and terminated at one end with a PEG Capping Unit.

[0052] A "cancer" refers to a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. A "cancer" or "cancer tissue" can include a tumor. Unregulated cell division and growth results in the formation of malignant tumors that invade neighboring tissues and can also metastasize to distant parts of the body through the lymphatic system or bloodstream. Following metastasis, the distal tumors can be said to be "derived from" the pre-metastasis tumor.

[0053] The term "antibody-dependent cellular cytotoxicity", or ADCC, is a mechanism for inducing cell death that depends upon the interaction of antibody-coated target cells with immune cells possessing lytic activity (also referred to as effector cells). Such effector cells include natural killer cells, monocytes/macrophages and neutrophils. The effector cells attach to an Fc effector domain(s) of Ig bound to target cells via their antigen-combining sites. Death of the antibody-coated target cell occurs as a result of effector cell activity.

[0054] The term "antibody-dependent cellular phagocytosis", or ADCP, refers to the process by which antibody-coated cells are internalized, either in whole or in part, by phagocytic immune cells (e.g., macrophages, neutrophils and dendritic cells) that bind to an Fc effector domain(s) of Ig.

[0055] The term "complement-dependent cytotoxicity", or CDC, refers to a mechanism for inducing cell death in which an Fc effector domain(s) of a target-bound antibody activates a series of enzymatic reactions culminating in the formation of holes in the target cell membrane. Typically, antigen-antibody complexes such as those on antibody-coated target cells bind and activate complement component C1q which in turn activates the complement cascade leading to target cell death. Activation of complement may also result in deposition of complement components on the target cell surface that facilitate ADCC by binding complement receptors (e.g., CR3) on leukocytes.

[0056] A "cytostatic effect" refers to the inhibition of cell proliferation. A "cytostatic agent" refers to an agent that has a cytostatic effect on a cell, thereby inhibiting the growth and/or expansion of a specific subset of cells. Cytostatic agents can be conjugated to an antibody or administered in combination with an antibody.

[0057] "Treatment" or "therapy" of a subject refers to any type of intervention or process performed on, or the administration of an active agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, slowing down, or preventing the onset, progression, development, severity, or recurrence of a symptom, complication, condition, or biochemical indicia associated with a disease. In some embodiments, the disease is cancer.

[0058] A "subject" includes any human or non-human animal. The term "non-human animal" includes, but is not limited to, vertebrates such as non-human primates, sheep, dogs, and rodents such as mice, rats, and guinea pigs. In some embodiments, the subject is a human. The terms "subject" and "patient" and "individual" are used interchangeably herein.

[0059] An "effective amount" or "therapeutically effective amount" or "therapeutically effective dosage" of a drug or therapeutic agent is any amount of the drug that, when used alone or in combination with another therapeutic agent, protects a subject against the onset of a disease or promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. The ability of a therapeutic agent to promote disease regression can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.

[0060] By way of example for the treatment of tumors, a therapeutically effective amount of an anti-cancer agent inhibits cell growth or tumor growth by at least about 10%, by at least about 20%, by at least about 30%, by at least about 40%, by at least about 50%, by at least about 60%, by at least about 70%, or by at least about 80%, by at least about 90%, by at least about 95%, by at least about 96%, by at least about 97%, by at least about 98%, or by at least about 99% in a treated subject(s) (*e.g.*, one or more treated subjects) relative to an untreated subject(s) (*e.g.*, one or more untreated subjects). In some embodiments, a therapeutically effective amount of an anti-cancer agent inhibits cell growth or tumor growth by 100% in a treated subject(s) (*e.g.*, one or more treated subjects) relative to an untreated subject(s) (*e.g.*, one or more untreated subjects).

[0061] In other embodiments of the disclosure, tumor regression can be observed and continue for a period of at least about 20 days, at least about 30 days, at least about 40 days, at least about 50 days, or at least about 60 days.

[0062] A therapeutically effective amount of a drug (*e.g.*, anti-PD-L1 antibody-drug conjugate) includes a "prophylactically effective amount," which is any amount of the drug that, when administered alone or in combination with an anti-cancer agent to a subject at risk of developing a cancer (*e.g.*, a subject having a pre-malignant condition) or of suffering a recurrence of cancer, inhibits the development or recurrence of the cancer. In some embodiments, the prophylactically effective amount prevents the development or recurrence of the cancer entirely. "Inhibiting" the development or recurrence of a cancer means either lessening the likelihood of the cancer's development or recurrence, or preventing the development or recurrence of the cancer entirely.

[0063] As used herein, "subtherapeutic dose" means a dose of a therapeutic compound (*e.g.*, an anti-PD-L1 antibody-drug conjugate) that is lower than the usual or typical dose of the therapeutic compound when administered alone for the treatment of a hyperproliferative disease (*e.g.*, cancer).

[0064] An "immune-related response pattern" refers to a clinical response pattern often observed in cancer patients treated with immunotherapeutic agents that produce antitumor effects by inducing cancer-specific immune responses or by modifying native immune processes. This response pattern is characterized by a beneficial therapeutic effect that follows an initial increase in tumor burden or the appearance of new lesions, which in the evaluation of traditional chemotherapeutic agents would be classified as disease progression

and would be synonymous with drug failure. Accordingly, proper evaluation of immunotherapeutic agents can require long-term monitoring of the effects of these agents on the target disease.

[0065] By way of example, an "anti-cancer agent" promotes cancer regression in a subject. In some embodiments, a therapeutically effective amount of the drug promotes cancer regression to the point of eliminating the cancer. "Promoting cancer regression" means that administering an effective amount of the drug, alone or in combination with an anti-cancer agent, results in a reduction in tumor growth or size, necrosis of the tumor, a decrease in severity of at least one disease symptom, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. In addition, the terms "effective" and "effectiveness" with regard to a treatment includes both pharmacological effectiveness and physiological safety. Pharmacological effectiveness refers to the ability of the drug to promote cancer regression in the patient. Physiological safety refers to the level of toxicity or other adverse physiological effects at the cellular, organ and/or organism level (adverse effects) resulting from administration of the drug.

[0066] "Sustained response" refers to the sustained effect on reducing tumor growth after cessation of a treatment. For example, the tumor size may remain to be the same or smaller as compared to the size at the beginning of the administration phase. In some embodiments, the sustained response has a duration that is at least the same as the treatment duration, or at least 1.5, 2.0, 2.5, or 3 times longer than the treatment duration.

[0067] As used herein, "complete response" or "CR" refers to disappearance of all target lesions; "partial response" or "PR" refers to at least a 30% decrease in the sum of the longest diameters (SLD) of target lesions, taking as reference the baseline SLD; and "stable disease" or "SD" refers to neither sufficient shrinkage of target lesions to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest SLD since the treatment started.

[0068] As used herein, "progression free survival" or "PFS" refers to the length of time during and after treatment during which the disease being treated (*e.g.*, cancer) does not get worse. Progression-free survival may include the amount of time patients have experienced a complete response or a partial response, as well as the amount of time patients have experienced stable disease.

[0069] As used herein, "overall response rate" or "ORR" refers to the sum of complete response (CR) rate and partial response (PR) rate.

[0070] As used herein, "overall survival" or "OS" refers to the percentage of individuals in a group who are likely to be alive after a particular duration of time.

[0071] The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[0072] The phrase "pharmaceutically acceptable salt" as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound of the invention. Exemplary salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate "mesylate", ethanesulfonate, benzenesulfonate, p-toluenesulfonate, pamoate (*i.e.*, 4,4'-methylene-bis-(2-hydroxy-3-naphthoate)) salts, alkali metal (*e.g.*, sodium and potassium) salts, alkaline earth metal (*e.g.*, magnesium) salts, and ammonium salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counter ion. The counter ion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion.

[0073] "Administering" or "administration" refer to the physical introduction of a therapeutic agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Exemplary routes of administration for the anti-PD-L1 antibody-drug conjugate include intravenous, intramuscular, subcutaneous, intraperitoneal, spinal or other parenteral routes of administration, for example by injection or infusion (*e.g.*, intravenous infusion). The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal,

intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as *in vivo* electroporation. A therapeutic agent can be administered via a non-parenteral route, or orally. Other non-parenteral routes include a topical, epidermal or mucosal route of administration, for example, intranasally, vaginally, rectally, sublingually or topically. Administration can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

[0074] The terms "baseline" or "baseline value" used interchangeably herein can refer to a measurement or characterization of a symptom before the administration of the therapy (*e.g.*, an anti-PD-L1 antibody-drug conjugate as described herein) or at the beginning of administration of the therapy. The baseline value can be compared to a reference value in order to determine the reduction or improvement of a symptom of a PD-L1 -associated disease contemplated herein (*e.g.*, cancer). The terms "reference" or "reference value" used interchangeably herein can refer to a measurement or characterization of a symptom after administration of the therapy (*e.g.*, an anti-PD-L1 antibody-drug conjugate as described). The reference value can be measured one or more times during a dosage regimen or treatment cycle or at the completion of the dosage regimen or treatment cycle. A "reference value" can be an absolute value; a relative value; a value that has an upper and/or lower limit; a range of values; an average value; a median value; a mean value; or a value as compared to a baseline value.

[0075] Similarly, a "baseline value" can be an absolute value; a relative value; a value that has an upper and/or lower limit; a range of values; an average value; a median value; a mean value; or a value as compared to a reference value. The reference value and/or baseline value can be obtained from one individual, from two different individuals or from a group of individuals (*e.g.*, a group of two, three, four, five or more individuals).

[0076] The term "monotherapy" as used herein means that the anti-PD-L1 antibody-drug conjugate is the only anti-cancer agent administered to the subject during the treatment cycle. Other therapeutic agents, however, can be administered to the subject. For example, anti-inflammatory agents or other agents administered to a subject with cancer to treat symptoms associated with cancer, but not the underlying cancer itself, including, for example inflammation, pain, weight loss, and general malaise, can be administered during the period of monotherapy.

[0077] An "adverse event" (AE) as used herein is any unfavorable and generally unintended or undesirable sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a medical treatment. A medical treatment can have one or more associated AEs and each AE can have the same or different level of severity. Reference to methods capable of "altering adverse events" means a treatment regime that decreases the incidence and/or severity of one or more AEs associated with the use of a different treatment regime.

[0078] A "serious adverse event" or "SAE" as used herein is an adverse event that meets one of the following criteria:

- Is fatal or life-threatening (as used in the definition of a serious adverse event, "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, *i.e.*, defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Medical and scientific judgment must be exercised in deciding whether an AE is "medically significant"
- Requires inpatient hospitalization or prolongation of existing hospitalization, excluding the following: 1) routine treatment or monitoring of the underlying disease, not associated with any deterioration in condition; 2) elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent; and 3) social reasons and respite care in the absence of any deterioration in the patient's general condition.

[0079] The use of the alternative (*e.g.*, "or") should be understood to mean either one, both, or any combination thereof of the alternatives. As used herein, the indefinite articles "a" or "an" should be understood to refer to "one or more" of any recited or enumerated component.

[0080] The terms "about" or "comprising essentially of" refer to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, *i.e.*, the limitations of the measurement system. For example,

"about" or "comprising essentially of" can mean within 1 or more than 1 standard deviation per the practice in the art. Alternatively, "about" or "comprising essentially of" can mean a range of up to 20%. Furthermore, particularly with respect to biological systems or processes, the terms can mean up to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the application and claims, unless otherwise stated, the meaning of "about" or "comprising essentially of" should be assumed to be within an acceptable error range for that particular value or composition.

[0081] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" encompasses and describes "X."

[0082] The term "Combined Positive Score" or "CPS" as used herein, refers to an immunohistochemical method of measuring PD-L1 expression in a cancer, such as a tumor sample from a cancer. CPS is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. For some therapeutic treatments, a tumor sample is considered to have PD-L1 expression if $CPS \geq 1$. For example, a $CPS \geq 1$ is required for a subject to be eligible for certain PD-1 or PD-L1 inhibitor therapies, such as subjects with gastric cancer, cervical cancer, and head and neck squamous cell cancer. In some instances, a $CPS \geq 10$ is required for a subject to be eligible for certain PD-1 or PD-L1 inhibitor therapies, such as subjects with urothelial cancer (bladder cancer), esophageal squamous cell carcinoma (ESCC), or triple-negative breast cancer being treated with pembrolizumab.

[0083] The term "Tumor Proportion Score" or "TPS" as used herein, refers to an immunohistochemical method of measuring PD-L1 expression in a cancer, such as a tumor sample from a cancer. TPS is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. For some therapeutic treatments, a tumor sample is considered to have PD-L1 expression if $TPS \geq 1\%$ and high PD-L1 expression if $TPS \geq 50\%$. For example, a $TPS \geq 1\%$ is the required for a subject to be eligible for certain PD-1 or PD-L1 inhibitor therapies (e.g., pembrolizumab), such as subjects with non-small cell lung cancer. In some instances, a $TPS \geq 50\%$ is the required for a subject to be eligible for certain PD-1 or PD-L1 inhibitor therapies (e.g., cemiplimab).

[0084] The term "ideal body weight" or "IBW" as used herein, refers to a size descriptor that is unrelated to total body weight. IBW is an estimate of weight corrected for sex and

height, and optionally frame size. IBW can be calculated, for example, using the formulas $IBW = 0.9H - 88$ (for males) and $IBW = 0.9H - 92$ (for females), wherein H =height in cm. Alternatively, IBW can also be calculated, for example using the following formulas: IBW (men) $= 50\text{kg} + 2.3\text{kg} \times (\text{height, in} - 60)$; IBW (women) $= 45.5\text{kg} + 2.3\text{kg} \times (\text{height, in} - 60)$.

[0085] The term “adjusted ideal body weight” or “AIBW” as used herein refers to a size descriptor that accounts for sex, total body weight, and height. AIBW can be calculated, for example, using the formula $AIBW = IBW + 0.4(\text{weight in kg} - IBW)$.

[0086] As described herein, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated.

[0087] Various aspects of the disclosure are described in further detail in the following subsections.

II. General

[0087] Provided herein are methods for the treatment of various cancers in subjects using an antibody drug conjugate (ADC) that binds PD-L1. In one aspect, provided herein are methods for the treatment of cancer in a subject using an ADC that binds PD-L1 and an anti-PD-1 antibody (e.g., pembrolizumab). In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is head and neck cancer. In further embodiments, the cancer is head and neck squamous cell carcinoma (HNSCC). In further embodiments, the cancer is metastatic or unresectable HNSCC. In some embodiments, the cancer is breast cancer. In further embodiments, the cancer is triple negative breast cancer (TNBC). In some embodiments, the cancer is lung cancer. In further embodiments, the cancer is non-small cell lung cancer (NSCLC). In some embodiments, the cancer is esophageal cancer. In further embodiments, the cancer is esophageal squamous cell carcinoma (SCC). In some embodiments, the cancer is melanoma. In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is gastric cancer.

[0088] Pembrolizumab targets the immune checkpoint receptor PD-1 and blocks the PD-L1 interaction. In the tumor microenvironment, T cells can be inactivated through the binding of PD-1 (expressed on T cells) by PD-L1 (expressed on tumor cells). However, in the presence of anti-PD-L1 unconjugated antibodies, the interaction between PD-1 and PD-L1 is disrupted leading to antitumor T cell activity.

[0089] An ADC that binds to cell surface PD-L1 is uniquely positioned to combine with a PD-1 checkpoint inhibitor such as Pembrolizumab. In an embodiment, an ADC of the present invention comprises an anti-PD-L1 antibody conjugated to one or more units of monomethyl auristatin E (MMAE). In a further embodiment, this ADC elicits direct cytotoxicity to PD-L1 positive tumor cells which may reduce the overall immunosuppressive PD-1/PD-L1 signaling in the tumor microenvironment and therefore drive increased activation of cytotoxic T cells. In an embodiment, this ADC may also initiate the process of cancer immunity through MMAE-induced immunogenic cell death.

III. Target Molecules

[0090] Unless otherwise indicated, PD-L1 refers to human PD-L1. An exemplary human protein sequence is assigned UniProt ID NO. Q9NZQ7.

IV. Antibodies of the Invention

[0091] Previously, select antibodies already being used to treat cancer have been conjugated, without sequence modification, to cytotoxic agents to produce antibody-drug conjugates (ADCs). These ADCs have often proven as effective or more effective than the unconjugated antibody at killing tumor cells. Previously, if modifications to the antibody were contemplated during the process of preparing an ADC, some possible modifications were to increase binding affinity of the antibody or increase antibody action such as ADCC. However, it has been discovered that at least in some situations, modifying or tuning an ADC antibody by, for example, reducing its binding affinity or decreasing its ADCC activity, results in improving the effectiveness of the ADC compared to an ADC with the unmodified antibody. Some examples of this include ADCs with anti-PD-L1 antibodies (such as Ab1), which are surprisingly optimized by modifying the antibodies e.g., reducing their binding affinities. For example, in some cases an anti-PD-L1 ADC is more effective at killing tumor cells in vitro when the binding affinity of the antibody conjugated to a cytotoxic agent is reduced. In another example, in some cases an anti-PD-L1 ADC is more effective at killing tumor cells in vitro and in vivo when the binding affinity of the antibody conjugated to a cytotoxic agent is reduced.

[0092] The invention provides antibodies, such as humanized antibodies, that bind PD-L1. In some embodiments, an anti-PD-L1 antibody provided herein can have a heavy chain CDR1 of SEQ ID NO: 5, a heavy chain CDR2 of SEQ ID NO: 6, a heavy chain CDR3 of

SEQ ID NO: 7, a light chain CDR1 of SEQ ID NO: 8, a light chain CDR2 of SEQ ID NO: 9, and a light chain CDR3 of SEQ ID NO: 10.

[0093] Anti-PD-L1 antibodies of the present invention may also be described or specified in terms of their binding affinity to PD-L1 (*e.g.*, human PD-L1). In some embodiments, preferred binding affinities include those with a dissociation constant or K_D greater than 2.7 nM, 5 nM, 6 nM, 7 nM, 8 nM, 9 nM, 10 nM, 15 nM, 20 nM, 25 nM, 30 nM, 40 nM, 50 nM, 60 nM, 70 nM, 80 nM, 90 nM, 100 nM, 110 nM, 120 nM, 130 nM, 140 nM, 150 nM, 200 nM, 250 nM, 300 nM, 400 nM, or 500 nM. In some embodiments, preferred PD-L1 antibodies have a binding affinity between 3 nM and 300 nM, 3 nM and 200 nM, 3 nM and 100 nM, 3 nM and 50 nM, 3 nM and 40 nM, 3 nM and 20 nM, 3 nM and 15 nM, 5 nM and 300 nM, and 5 nM and 15 nM. In some embodiments, preferred PD-L1 antibodies have a binding affinity at least 2-fold, 3-fold, 3.7-fold, 4-fold, or 5-fold greater than the binding affinity of Ab1. In some of the above embodiments, the binding affinity is a monovalent binding affinity.

[0094] In some embodiments, the binding of an anti-PD-L1 antibody of the present invention is pH dependent, such that the antibody displays differential binding across a pH gradient. In some embodiments, the anti-PD-L1 antibody displays maximal binding between a pH of about 4 and a pH of about 10. In some embodiments, the maximal binding is between a pH of about 6 and a pH of about 9. In some embodiments, the maximal binding is between a pH of about 6.5 and a pH of about 8.

[0095] Preferred antibodies of the invention inhibit cancer (*e.g.*, growth of cells, metastasis and/or lethality to the organisms) as shown on cancerous cells propagating in culture, in an animal model or clinical trial. Animal models can be formed by implanting PD-L1-expressing human tumor cell lines into appropriate immunodeficient rodent strains, *e.g.*, athymic nude mice or SCID mice. These tumor cell lines can be established in immunodeficient rodent hosts either as solid tumor by subcutaneous injections or as disseminated tumors by intravenous injections.

[0096] Once established within a host, these tumor models can be applied to evaluate the therapeutic efficacies of the anti-PD-L1 antibodies or conjugated forms thereof as described in the Examples.

[0097] Anti-PD-L1 antibodies of the disclosure are preferably monoclonal, and may be multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab

fragments, F(ab') fragments, fragments produced by a Fab expression library, and PD-L1 binding fragments of any of the above. In some embodiments, the anti-PD-L1 antibodies of the disclosure specifically bind PD-L1. The immunoglobulin molecules of the disclosure can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In an embodiment, the anti-PD-L1 antibodies of the disclosure are of IgG1 type.

[0098] In certain embodiments of the disclosure, the anti-PD-L1 antibodies are antigen-binding fragments (*e.g.*, human antigen-binding fragments) as described herein and include, but are not limited to, Fab, Fab' and F(ab')₂, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a V_L or V_H domain. Antigen-binding fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, CH3 and CL domains. Also included in the present disclosure are antigen-binding fragments comprising any combination of variable region(s) with a hinge region, CH1, CH2, CH3 and CL domains. In some embodiments, the anti-PD-L1 antibodies or antigen-binding fragments thereof are human, murine (*e.g.*, mouse and rat), donkey, sheep, rabbit, goat, guinea pig, camelid, horse, or chicken.

[0099] The anti-PD-L1 antibodies of the present disclosure may be monospecific, bispecific, trispecific or of greater multi specificity. Multispecific antibodies may be specific for different epitopes of PD-L1 or may be specific for both PD-L1 as well as for a heterologous protein. *See, e.g.*, PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, *et al.*, 1991, J. Immunol. 147:60-69; U.S. Pat. Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny *et al.*, 1992, J. Immunol. 148:1547-1553.

[0100] Anti-PD-L1 antibodies of the present disclosure may be described or specified in terms of the particular CDRs they comprise. The precise amino acid sequence boundaries of a given CDR or FR can be readily determined using any of a number of well-known schemes, including those described by Kabat *et al.* (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD ("Kabat" numbering scheme); Al-Lazikani *et al.*, (1997) JMB 273,927-948 ("Chothia" numbering scheme); MacCallum *et al.*, J. Mol. Biol. 262:732-745 (1996), "Antibody-antigen interactions: Contact analysis and binding site topography," J. Mol. Biol. 262, 732-745."

(“Contact” numbering scheme); Lefranc MP *et al.*, “IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains,” *Dev Comp Immunol*, 2003 Jan;27(1):55-77 (“IMGT” numbering scheme); Honegger A and Plückthun A, “Yet another numbering scheme for immunoglobulin variable domains: an automatic modeling and analysis tool,” *J Mol Biol*, 2001 Jun 8;309(3):657-70, (“Aho” numbering scheme); and Martin *et al.*, “Modeling antibody hypervariable loops: a combined algorithm,” *PNAS*, 1989, 86(23):9268-9272, (“AbM” numbering scheme). The boundaries of a given CDR may vary depending on the scheme used for identification. In some embodiments, a “CDR” or “complementarity determining region,” or individual specified CDRs (*e.g.*, CDR-H1, CDR-H2, CDR-H3), of a given antibody or region thereof (*e.g.*, variable region thereof) should be understood to encompass a (or the specific) CDR as defined by any of the aforementioned schemes. For example, where it is stated that a particular CDR (*e.g.*, a CDR-H3) contains the amino acid sequence of a corresponding CDR in a given V_H or V_L region amino acid sequence, it is understood that such a CDR has a sequence of the corresponding CDR (*e.g.*, CDR-H3) within the variable region, as defined by any of the aforementioned schemes. The scheme for identification of a particular CDR or CDRs may be specified, such as the CDR as defined by the Kabat, Chothia, AbM or IMGT method.

[0101] CDR sequences of the anti-PD-L1 antibodies and of the anti-PD-L1 antibody-drug conjugates described herein are according to the Kabat numbering scheme as described in Kabat *et al.* (1991), “Sequences of Proteins of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD.

[0102] In one aspect, provided herein is an anti-PD-L1 antibody and/or anti-PD-L1 antibody-drug conjugate comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:5, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:6, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:7; and/or wherein the light chain variable region comprises (i) CDR-L1 comprising the amino acid sequence of SEQ ID NO:8, (ii) CDR-L2 comprising the amino acid sequence of SEQ ID NO:9, and (iii) CDR-L3 comprising the amino acid sequence of SEQ ID NO:10, wherein the CDRs of the anti-PD-L1 antibody are defined by the Kabat numbering scheme.

[0103] In one aspect, provided herein is an anti-PD-L1 antibody and/or anti-PD-L1 antibody-drug conjugate comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:3 and comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:4. In one aspect, provided herein is an anti-PD-L1 antibody and/or anti-PD-L1 antibody-drug conjugate comprising a heavy chain comprising the amino acid sequence of SEQ ID NO:1 and comprising a light chain comprising the amino acid sequence of SEQ ID NO:2.

[0104] In some embodiments, provided herein is an anti-PD-L1 antibody and/or anti-PD-L1 antibody-drug conjugate comprising a heavy chain variable domain comprising an amino acid sequence having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO:3. In certain embodiments, a heavy chain variable domain comprising an amino acid sequence having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO:3 contains substitutions (*e.g.*, conservative substitutions), insertions, or deletions relative to the reference sequence and retains the ability to bind to a PD-L1 (*e.g.*, human PD-L1). In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:3. In certain embodiments, substitutions, insertions, or deletions (*e.g.*, 1, 2, 3, 4, or 5 amino acids) occur in regions outside the CDRs (*i.e.*, in the FRs). In some embodiments, the anti-PD-L1 antibody comprises a heavy chain variable domain sequence of SEQ ID NO:3 including post-translational modifications of that sequence.

[0105] In some embodiments, provided herein is an anti-PD-L1 antibody and/or anti-PD-L1 antibody-drug conjugate comprising a light chain variable domain comprising an amino acid sequence having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO:4. In certain embodiments, a light chain variable domain comprising an amino acid sequence having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO:4 contains substitutions (*e.g.*, conservative substitutions), insertions, or deletions relative to the reference sequence and retains the ability to bind to a PD-L1 (*e.g.*, human PD-L1). In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:4. In certain embodiments, substitutions, insertions, or deletions (*e.g.*, 1, 2, 3, 4,

or 5 amino acids) occur in regions outside the CDRs (*i.e.*, in the FRs). In some embodiments, the anti-PD-L1 antibody comprises a light chain variable domain sequence of SEQ ID NO:4 including post-translational modifications of that sequence.

[0106] In some embodiments, the anti-PD-L1 antibody or the anti-PD-L1 antibody of the anti-PD-L1 antibody-drug conjugate is a monoclonal antibody.

[0107] There are five classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, having heavy chains designated α , δ , ϵ , γ and μ , respectively. The γ and α classes are further divided into subclasses *e.g.*, humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. IgG1 antibodies can exist in multiple polymorphic variants termed allotypes (reviewed in Jefferis and Lefranc 2009. *mAbs* Vol 1 Issue 4 1-7) any of which are suitable for use in some of the embodiments herein. Common allotypic variants in human populations are those designated by the letters a, f, n, z or combinations thereof. In any of the embodiments herein, the antibody may comprise a heavy chain Fc region comprising a human IgG Fc region. In further embodiments, the human IgG Fc region comprises a human IgG1.

[0108] The antibodies also include derivatives that are modified, *i.e.*, by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from binding to PD-L1 or from exerting a cytostatic or cytotoxic effect on cells. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, *e.g.*, 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 may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

Humanized Antibodies

[0109] A humanized antibody is a genetically engineered antibody in which the CDRs from a non-human "donor" antibody are grafted into human "acceptor" antibody sequences (see, *e.g.*, Queen, US 5,530,101 and 5,585,089; Winter, US 5,225,539; Carter, US 6,407,213; Adair, US 5,859,205; and Foote, US 6,881,557). The acceptor antibody sequences can be, for example, a mature human antibody sequence, a composite of such sequences, a consensus sequence of human antibody sequences, or a germline region sequence. A preferred acceptor sequence for the heavy chain is the germline V_H exon V_HL-2 (also referred to in the literature

as HV1-2) (Shin et al, 1991, EMBO J. 10:3641-3645) and for the hinge region (J_H), exon J_H -6 (Mattila et al, 1995, Eur. J. Immunol. 25:2578-2582). For the light chain, a preferred acceptor sequence is exon VK2-30 (also referred to in the literature as KV2-30) and for the hinge region exon JK-4 (Hieter et al, 1982, J. Biol. Chem. 257:1516-1522). Thus, a humanized antibody is an antibody having some or all CDRs entirely or substantially from a donor antibody and variable region framework sequences and constant regions, if present, entirely or substantially from human antibody sequences. Similarly, a humanized heavy chain has at least one, two and usually all three CDRs entirely or substantially from a donor antibody heavy chain, and a heavy chain variable region framework sequence and heavy chain constant region, if present, substantially from human heavy chain variable region framework and constant region sequences. Similarly a humanized light chain has at least one, two and usually all three CDRs entirely or substantially from a donor antibody light chain, and a light chain variable region framework sequence and light chain constant region, if present, substantially from human light chain variable region framework and constant region sequences. Other than nanobodies and dAbs, a humanized antibody comprises a humanized heavy chain and a humanized light chain. A CDR in a humanized antibody is substantially from a corresponding CDR in a non-human antibody when at least 60%, 85%, 90%, 95% or 100% of corresponding residues (as defined by Kabat) are identical between the respective CDRs. The variable region framework sequences of an antibody chain or the constant region of an antibody chain are substantially from a human variable region framework sequence or human constant region respectively when at least 85%, 90%, 95% or 100% of corresponding residues defined by Kabat are identical. In some embodiments, the PD-L1 antibodies of the invention are humanized antibodies.

[0110] Although humanized antibodies often incorporate all six CDRs (preferably as defined by Kabat) from a mouse antibody, they can also be made with less than all CDRs (e.g., at least 3, 4, or 5) CDRs from a mouse antibody (e.g., Pascalis et al., J. Immunol. 169:3076, 2002; Vajdos et al., Journal of Molecular Biology, 320: 415-428, 2002; Iwahashi et al., Mol. Immunol. 36:1079-1091, 1999; Tamura et al, Journal of Immunology, 164:1432-1441, 2000).

Selection of Constant Region

[0111] The heavy and light chain variable regions of humanized antibodies can be linked to at least a portion of a human constant region. The choice of constant region depends, in

part, whether antibody-dependent cell-mediated cytotoxicity, antibody dependent cellular phagocytosis and/or complement dependent cytotoxicity are desired. For example, human isotopes IgG1 and IgG3 have strong complement-dependent cytotoxicity, human isotype IgG2 weak complement-dependent cytotoxicity and human. IgG4 lacks complement-dependent cytotoxicity. Human IgG1 and IgG3 also induce stronger cell mediated effector functions than human IgG2 and IgG4. Light chain constant regions can be lambda or kappa. Antibodies can be expressed as tetramers containing two light and two heavy chains, as separate heavy chains, light chains, as Fab, Fab', F(ab')₂, and Fv, or as single chain antibodies in which heavy and light chain variable domains are linked through a spacer.

[0112] Human constant regions show allotypic variation and isoallotypic variation between different individuals, that is, the constant regions can differ in different individuals at one or more polymorphic positions. Isoallotypes differ from allotypes in that sera recognizing an isoallotype binds to a non-polymorphic region of a one or more other isotypes.

[0113] One or several amino acids at the amino or carboxy terminus of the light and/or heavy chain, such as the C-terminal lysine of the heavy chain, may be missing or derivatized in a proportion or all of the molecules. Substitutions can be made in the constant regions to reduce or increase effector function such as complement-mediated cytotoxicity or ADCC (see, e.g., Winter et al., US Patent No. 5,624,821; Tso et al., US Patent No. 5,834,597; and Lazar et al., Proc. Natl. Acad. Sci. USA 103:4005, 2006), or to prolong half-life in humans (see, e.g., Hinton et al., J. Biol. Chem. 279:6213, 2004).

[0114] Exemplary substitution include the amino acid substitution of the native amino acid to a cysteine residue is introduced at amino acid position 234, 235, 237, 239, 267, 298, 299, 326, 330, or 332, preferably an S239C mutation in a human IgG1 isotype (US 20100158909). The presence of an additional cysteine residue allows interchain disulfide bond formation. Such interchain disulfide bond formation can cause steric hindrance, thereby reducing the affinity of the Fc region-FcγR binding interaction. The cysteine residue(s) introduced in or in proximity to the Fc region of an IgG constant region can also serve as sites for conjugation to therapeutic agents (i.e., coupling cytotoxic drugs using thiol specific reagents such as maleimide derivatives of drugs. The presence of a therapeutic agent causes steric hindrance, thereby further reducing the affinity of the Fc region-FcγR binding

interaction. Other substitutions at any of positions 234, 235, 236 and/or 237 reduce affinity for Fcγ receptors, particularly FcγRI receptor {see, e.g., US 6,624,821, US 5,624,821}.

[0115] The *in vivo* half-life of an antibody can also impact on its effector functions. The half-life of an antibody can be increased or decreased to modify its therapeutic activities. FcRn is a receptor that is structurally similar to MHC Class I antigen that non-covalently associates with β2-microglobulin. FcRn regulates the catabolism of IgGs and their transcytosis across tissues (Ghetie and Ward, 2000, *Annu. Rev. Immunol.* 18:739-766; Ghetie and Ward, 2002, *Immunol. Res.* 25:97-113). The IgG-FcRn interaction takes place at pH 6.0 (pH of intracellular vesicles) but not at pH 7.4 (pH of blood); this interaction enables IgGs to be recycled back to the circulation (Ghetie and Ward, 2000, *Ann. Rev. Immunol.* 18:739-766; Ghetie and Ward, 2002, *Immunol. Res.* 25:97-113). The region on human IgG1 involved in FcRn binding has been mapped (Shields et al, 2001, *J. Biol. Chem.* 276:6591-604). Alanine substitutions at positions Pro238, Thr256, Thr307, Gln311, Asp312, Glu380, Glu382, or Asn434 of human IgG1 enhance FcRn binding (Shields et al, 2001, *J. Biol. Chem.* 276:6591-604). IgG1 molecules harboring these substitutions have longer serum half-lives. Consequently, these modified IgG1 molecules may be able to carry out their effector functions, and hence exert their therapeutic efficacies, over a longer period of time compared to unmodified IgG1. Other exemplary substitutions for increasing binding to FcRn include a Gln at position 250 and/or a Leu at position 428. EU numbering is used for all position in the constant region.

[0116] Oligosaccharides covalently attached to the conserved Asn297 are involved in the ability of the Fc region of an IgG to bind FcγR (Lund et al, 1996, *J. Immunol.* 157:4963-69; Wright and Morrison, 1997, *Trends Biotechnol.* 15:26-31). Engineering of this glycoform on IgG can significantly improve IgG-mediated ADCC. Addition of bisecting N-acetylglucosamine modifications (Umana et al, 1999, *Nat. Biotechnol.* 17:176-180; Davies et al, 2001, *Biotech. Bioeng.* 74:288-94) to this glycoform or removal of fucose (Shields et al, 2002, *J. Biol. Chem.* 277:26733-40; Shinkawa et al, 2003, *J. Biol. Chem.* 278:6591-604; Niwa et al., 2004, *Cancer Res.* 64:2127-33) from this glycoform are two examples of IgG Fc engineering that improves the binding between IgG Fc and FcγR, thereby enhancing Ig-mediated ADCC activity.

[0117] A systemic substitution of solvent-exposed amino acids of human IgG1 Fc region has generated IgG variants with altered FcγR binding affinities (Shields et al, 2001, *J. Biol.*

Chem. 276:6591-604). When compared to parental IgG1, a subset of these variants involving substitutions at Thr256/Ser298, Ser298/Glu333, Ser298/Lys334, or Ser298/Glu333 Lys334 to Ala demonstrate increased in both binding affinity toward FcγR and ADCC activity (Shields et al, 2001, J. Biol. Chem. 276:6591-604; Okazaki et al, 2004, J. Mol. Biol. 336:1239-49).

[0118] Complement fixation activity of antibodies (both C1q binding and CDC activity) can be improved by substitutions at Lys326 and Glu333 (Idusogie et al., 2001, J. Immunol. 166:2571-2575). The same substitutions on a human IgG2 backbone can convert an antibody isotype that binds poorly to C1q and is severely deficient in complement activation activity to one that can both bind C1q and mediate CDC (Idusogie et al, 2001, J. Immunol. 166:2571-75). Several other methods have also been applied to improve complement fixation activity of antibodies. For example, the grafting of an 18- amino acid carboxyl-terminal tail piece of IgM to the carboxyl -termini of IgG greatly enhances their CDC activity. This is observed even with IgG4, which normally has no detectable CDC activity (Smith et al, 1995, J. Immunol. 154:2226-36). Also, substituting Ser444 located close to the carboxy-terminal of IgG 1 heavy chain with Cys induced tail-to-tail dimerization of IgG 1 with a 200-fold increase of CDC activity over monomeric IgG1 (Shopes et al, 1992, J. Immunol. 148:2918-22). In addition, a bispecific diabody construct with specificity for C1q also confers CDC activity (Kontermann et al., 1997, Nat. Biotech. 15:629-31).

[0119] Complement activity can be reduced by mutating at least one of the amino acid residues 318, 320, and 322 of the heavy chain to a residue having a different side chain, such as Ala. Other alkyl-substituted non-ionic residues, such as Gly, Leu, or Val, or such aromatic non-polar residues as Phe, Tyr, Trp and Pro in place of any one of the three residues also reduce or abolish C1q binding. Ser, Thr, Cys, and Met can be used at residues 320 and 322, but not 318, to reduce or abolish C1q binding activity.

[0120] Replacement of the 318 (Glu) residue by a polar residue may modify but not abolish C1q binding activity. Replacing residue 297 (Asn) with Ala results in removal of lytic activity but only slightly reduces (about three fold weaker) affinity for C1q. This alteration destroys the glycosylation site and the presence of carbohydrate that is required for complement activation. Any other substitution at this site also destroys the glycosylation site. The following mutations and any combination thereof also reduce C1q binding: D270A, K322A, P329A, and P31 IS (see WO 06/036291). The L234A/L235A mutation (or LALA

mutation) also reduces C1q binding, as well as FcγR binding. In an embodiment, an anti-PD-L1 antibody of the invention includes the L234A/L235A mutation.

[0121] Reference to a human constant region includes a constant region with any natural allotype or any permutation of residues occupying polymorphic positions in natural allotypes. Also, up to 1, 2, 5, or 10 mutations may be present relative to a natural human constant region, such as those indicated above to reduce Fcγ receptor binding or increase binding to FcRN.

V. Expression of Recombinant Antibodies

[0122] Humanized antibodies are typically produced by recombinant expression. Recombinant polynucleotide constructs typically include an expression control sequence operably linked to the coding sequences of antibody chains, including naturally- associated or heterologous promoter regions. Preferably, the expression control sequences are eukaryotic promoter systems in vectors capable of transforming or transfecting eukaryotic host cells. Once the vector has been incorporated into the appropriate host, the host is maintained under conditions suitable for high level expression of the nucleotide sequences, and the collection and purification of the crossreacting antibodies.

[0123] Mammalian cells are a preferred host for expressing nucleotide segments encoding immunoglobulins or fragments thereof. See Winnacker, *From Genes to Clones*, (VCH Publishers, NY, 1987). A number of suitable host cell lines capable of secreting intact heterologous proteins have been developed in the art, and include CHO cell lines (e.g., DG44), various COS cell lines, HeLa cells, HEK293 cells, L cells, and non- antibody-producing myelomas including Sp2/0 and NS0. Preferably, the cells are nonhuman. Expression vectors for these cells can include expression control sequences, such as an origin of replication, a promoter, an enhancer (Queen et al., *Immunol. Rev.* 89:49 (1986)), and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences. Preferred expression control sequences are promoters derived from endogenous genes, cytomegalovirus, SV40, adenovirus, bovine papillomavirus, and the like. See Co et al., *J. Immunol.* 148:1149 (1992).

[0124] Once expressed, antibodies can be purified according to standard procedures of the art, including HPLC purification, column chromatography, gel electrophoresis and the like (see generally, Scopes, *Protein Purification* (Springer- Verlag, NY, 1982)).

VI. Nucleic Acids

[0125] The invention further provides nucleic acids encoding any of the humanized heavy and light chains described above. Typically, the nucleic acids also encode a signal peptide fused to the mature heavy and light chains. Coding sequences on nucleic acids can be in operable linkage with regulatory sequences to ensure expression of the coding sequences, such as a promoter, enhancer, ribosome binding site, transcription termination signal and the like. The nucleic acids encoding heavy and light chains can occur in isolated form or can be cloned into one or more vectors. The nucleic acids can be synthesized by for example, solid state synthesis or PCR of overlapping oligonucleotides. Nucleic acids encoding heavy and light chains can be joined as one contiguous nucleic acid, e.g., within an expression vector, or can be separate, e.g., each cloned into its own expression vector.

[0126] In some aspects, also provided herein are nucleic acids encoding an anti-PD-L1 antibody or antigen-binding fragment thereof as described herein. Further provided herein are vectors comprising the nucleic acids encoding an anti-PD-L1 antibody or antigen-binding fragment thereof as described herein. Further provided herein are host cells expressing the nucleic acids encoding an anti-PD-L1 antibody or antigen-binding fragment thereof as described herein. Further provided herein are host cells comprising the vectors comprising the nucleic acids encoding an anti-PD-L1 antibody or antigen-binding fragment thereof as described herein.

[0127] The anti-PD-L1 antibodies described herein may be prepared by well-known recombinant techniques using well known expression vector systems and host cells. In one embodiment, the antibodies are prepared in a CHO cell using the GS expression vector system as disclosed in De la Cruz Edmunds *et al.*, 2006, *Molecular Biotechnology* 34; 179-190, EP216846, U.S. Pat. No. 5,981,216, WO 87/04462, EP323997, U.S. Pat. No. 5,591,639, U.S. Pat. No. 5,658,759, EP338841, U.S. Pat. No. 5,879,936, and U.S. Pat. No. 5,891,693.

[0128] Monoclonal anti-PD-L1 antibodies described herein may *e.g.* be produced by the hybridoma method first described by Kohler *et al.*, *Nature*, 256, 495 (1975), or may be produced by recombinant DNA methods. Monoclonal antibodies may also be isolated from phage antibody libraries using the techniques described in, for example, Clackson *et al.*, *Nature*, 352, 624-628 (1991) and Marks *et al.*, *JMol. Biol.*, 222(3):581-597 (1991). Monoclonal antibodies may be obtained from any suitable source. Thus, for example, monoclonal antibodies may be obtained from hybridomas prepared from murine splenic B

cells obtained from mice immunized with an antigen of interest, for instance in form of cells expressing the antigen on the surface, or a nucleic acid encoding an antigen of interest. Monoclonal antibodies may also be obtained from hybridomas derived from antibody-expressing cells of immunized humans or non-human mammals such as rats, dogs, primates, etc.

Antibody-Drug Conjugates

[0129] Anti-PD-L1 antibodies can be conjugated to cytotoxic or cytostatic moieties (including pharmaceutically compatible salts thereof) to form an antibody drug conjugate (ADC). Particularly suitable moieties for conjugation to antibodies are cytotoxic agents (e.g., chemotherapeutic agents), prodrug converting enzymes, radioactive isotopes or compounds, or toxins (these moieties being collectively referred to as a therapeutic agent). For example, an anti-PD-L1 antibody can be conjugated to a cytotoxic agent such as a chemotherapeutic agent, or a toxin (e.g., a cytostatic or cytotoxic agent such as, e.g., abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin).

[0130] An anti-PD-L1 antibody can be conjugated to a pro-drug converting enzyme. The pro-drug converting enzyme can be recombinantly fused to the antibody or chemically conjugated thereto using known methods. Exemplary pro-drug converting enzymes are carboxypeptidase G2, beta-glucuronidase, penicillin- V-amidase, penicillin- G-amidase, β -lactamase, β -glucosidase, nitroreductase and carboxypeptidase A.

[0131] Techniques for conjugating therapeutic agents to proteins, and in particular to antibodies, are well-known. (See, e.g., Arnon et al, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy," in *Monoclonal Antibodies And Cancer Therapy* (Reisfeld et al. eds., Alan R. Liss, Inc., 1985); Hellstrom et al, "Antibodies For Drug Delivery," in *Controlled Drug Delivery* (Robinson et al. eds., Marcel Dekker, Inc., 2nd ed. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review," in *Monoclonal Antibodies '84: Biological And Clinical Applications* (Pinchera et al. eds., 1985); "Analysis, Results, and Future Prospective of the Therapeutic Use of Radiolabeled Antibody In Cancer Therapy," in *Monoclonal Antibodies For Cancer Detection And Therapy* (Baldwin et al. eds., Academic Press, 1985); and Thorpe et al, 1982, *Immunol. Rev.* 62:119-58. See also, e.g., PCT publication WO 89/12624.)

[0132] The therapeutic agent can be conjugated in a manner that reduces its activity unless it is cleaved off the antibody (e.g., by hydrolysis, by antibody degradation or by a

cleaving agent). Such a therapeutic agent is attached to the antibody with a cleavable linker that is sensitive to cleavage in the intracellular environment of the PD-L1-expressing cancer cell but is not substantially sensitive to the extracellular environment, such that the conjugate is cleaved from the antibody when it is internalized by the PD-L1-expressing cancer cell (e.g., in the endosomal or, for example by virtue of pH sensitivity or protease sensitivity, in the lysosomal environment or in the caveolar environment).

[0133] Typically the ADC comprises a linker region between the therapeutic agent and the anti-PD-L1 antibody. As noted supra, typically, the linker is cleavable under intracellular conditions, such that cleavage of the linker releases the therapeutic agent from the antibody 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 a lysosomal or endosomal protease. Typically, the peptidyl linker is at least two amino acids long or at least three amino acids long. Cleaving agents can include cathepsins B and D and plasmin (see, e.g., Dubowchik and Walker, 1999, *Pharm. Therapeutics* 83:67-123). Most typical are peptidyl linkers that are cleavable by enzymes that are present in PD-L1-expressing cells. 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 linker comprising a Phe-Leu or a Gly-Phe-Leu-Gly peptide). Other such linkers are described, e.g., in U.S. Patent No. 6,214,345. In specific embodiments, the peptidyl linker cleavable by an intracellular protease comprises a Val-Cit linker or a Phe-Lys dipeptide (see, e.g., U.S. patent 6,214,345, which describes the synthesis of doxorubicin with the Val-Cit linker). One advantage of using intracellular proteolytic release of the therapeutic agent is that the agent is typically attenuated when conjugated and the serum stabilities of the conjugates are typically high.

[0134] The cleavable linker can be pH-sensitive, i.e., sensitive to hydrolysis at certain pH values. Typically, the pH-sensitive linker is 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. (See, e.g., U.S. Patent Nos. 5,122,368; 5,824,805; 5,622,929; Dubowchik and Walker, 1999, *Pharm. Therapeutics* 83:67-123; Neville et al, 1989, *Biol. Chem.* 264: 14653-14661.) Such linkers are relatively stable under neutral pH conditions, such as those in the blood, but are unstable at below pH 5.5 or 5.0, the approximate pH of the lysosome. In

certain embodiments, the hydrolyzable linker is a thioether linker (such as, e.g., a thioether attached to the therapeutic agent via an acylhydrazone bond (see, e.g., U.S. Patent No. 5,622,929)).

[0135] Other linkers are cleavable under reducing conditions (e.g., a disulfide linker). Disulfide linkers include 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- α -methyl- α -(2-pyridyl-dithio)toluene), SPDB and SMPT. {See, e.g., Thorpe et al, 1987, Cancer Res. 47:5924-5931; Wawrzynczak et al, In Immunoconjugates: Antibody Conjugates in Radioimagery and Therapy of Cancer (C. W. Vogel ed., Oxford U. Press, 1987. See also U.S. Patent No. 4,880,935.)

[0136] The linker can also be a malonate linker (Johnson et al, 1995, Anticancer Res. 15:1387-93), a maleimidobenzoyl linker (Lau et al, 1995, Bioorg-Med-Chem. 3(10):1299-1304), or a 3'-N-amide analog (Lau et al, 1995, Bioorg-Med-Chem. 3(10):1305-12). The linker can also be a malonate linker (Johnson et al, 1995, Anticancer Res. 15:1387-93), a maleimidobenzoyl linker (Lau et al, 1995, Bioorg-Med-Chem. 3(10):1299-1304), or a 3'-N-amide analog (Lau et al, 1995, Bioorg-Med-Chem. 3(10):1305-12).

[0137] The linker also can be a non-cleavable linker, such as an maleimido-alkylene- or maleimide-aryl linker that is directly attached to the therapeutic agent (e.g., a drug). An active drug-linker is released by degradation of the antibody.

[0138] Typically, the linker is not substantially sensitive to the extracellular environment meaning that no more than about 20%, typically no more than about 15%, more typically no more than about 10%, and even more typically no more than about 5%, no more than about 3%, or no more than about 1% of the linkers in a sample of the ADC is cleaved when the ADC present in an extracellular environment (e.g., in plasma).

[0139] Whether a linker is not substantially sensitive to the extracellular environment can be determined, for example, by incubating independently with plasma both (a) the ADC (the "ADC sample") and (b) an equal molar amount of unconjugated antibody or therapeutic agent (the "control sample") for a predetermined time period (e.g., 2, 4, 8, 16, or 24 hours) and then comparing the amount of unconjugated antibody or therapeutic agent present in the ADC sample with that present in control sample, as measured, for example, by high performance liquid chromatography.

[0140] The linker can also promote cellular internalization. The linker can promote cellular internalization when conjugated to the therapeutic agent (i.e., in the milieu of the linker-therapeutic agent moiety of the ADC or ADC derivative as described herein). Alternatively, the linker can promote cellular internalization when conjugated to both the therapeutic agent and the anti-PD-L1 antibody (i.e., in the milieu of the ADC as described herein).

[0141] The anti-PD-L1 antibody can be conjugated to the linker via a heteroatom of the antibody. These heteroatoms can be present on the antibody in its natural state or can be introduced into the antibody. In some aspects, the anti-PD-L1 antibody will be conjugated to the linker via a nitrogen atom of a lysine residue. In other aspects, the anti-PD-L1 antibody will be conjugated to the linker via a sulfur atom of a cysteine residue. The cysteine residue can be naturally-occurring or one that is engineered into the antibody. Methods of conjugating linkers and drug-linkers to antibodies via lysine and cysteine residues are known in the art.

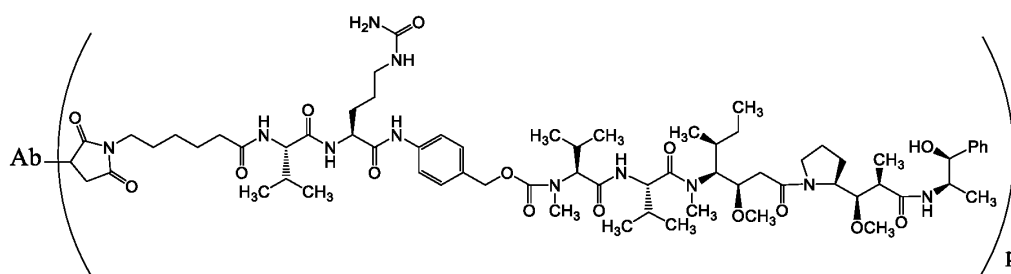
[0142] Exemplary antibody-drug conjugates include auristatin based antibody-drug conjugates (i.e., the drug component is an auristatin drug). Auristatins bind tubulin, have been shown to interfere with microtubule dynamics and nuclear and cellular division, and have anticancer activity. Typically the auristatin based antibody-drug conjugate comprises a linker between the auristatin drug and the anti-PD-L1 antibody. The linker can be, for example, a cleavable linker (e.g., a peptidyl linker, a carbohydrate linker) or a non-cleavable linker (e.g., linker released by degradation of the antibody). Auristatins include auristatin T, MMAF, and MMAE. The synthesis and structure of exemplary auristatins are described in U.S. Publication Nos. 7,659,241, 7,498,298, 2009-0111756, 2009-0018086, and 7,968, 687 each of which is incorporated herein by reference in its entirety and for all purposes.

[0143] Exemplary antibody-drug conjugates also include camptothecin based antibody-drug conjugates (i.e., the drug component is a camptothecin drug). Camptothecins are topoisomerase inhibitors that have been shown to have anticancer activity. Typically the camptothecin based antibody-drug conjugate comprises a linker between the camptothecin drug and the anti-PD-L1 antibody. The linker can be, for example, a cleavable linker (e.g., a peptidyl linker, a carbohydrate linker) or a non-cleavable linker (e.g., linker released by degradation of the antibody). The synthesis and structure of exemplary camptothecin drug-

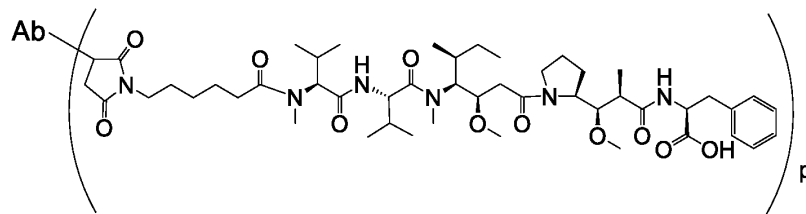
linkers is described in PCT/US19/025968 (filed April 5, 2019), which is incorporated herein by reference in its entirety and for all purposes.

[0144] Other exemplary antibody-drug conjugates include maytansinoid antibody-drug conjugates (i.e., the drug component is a maytansinoid drug), and benzodiazepine antibody drug conjugates (i.e., the drug component is a benzodiazepine (e.g., pyrrolo[1,4]benzodiazepine dimers (PBD dimer), indolinobenzodiazepine dimers, and oxazolidinobenzodiazepine dimers)).

[0145] Exemplary antibody drug conjugates include vcMMAE and mcMMAF antibody drug conjugates as follows wherein p represents the drug load and Ab represents the anti-PD-L1 antibody:



vcMMAE

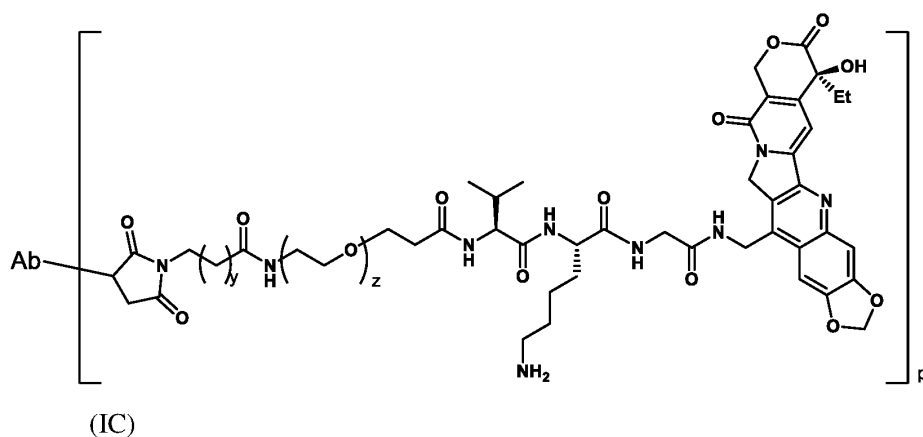


mcMMAF

or a pharmaceutically acceptable salt thereof.

[0146] Exemplary anti-PD-L1 antibody drug conjugates include camptothecin antibody drug conjugates as follows wherein p represents the drug load and Ab represents the anti-PD-L1 antibody:

[0147] In some embodiments, the camptothecin ADC has the formula (IC):



or a pharmaceutically acceptable salt thereof;

wherein

Ab is an anti-PD-L1 antibody;

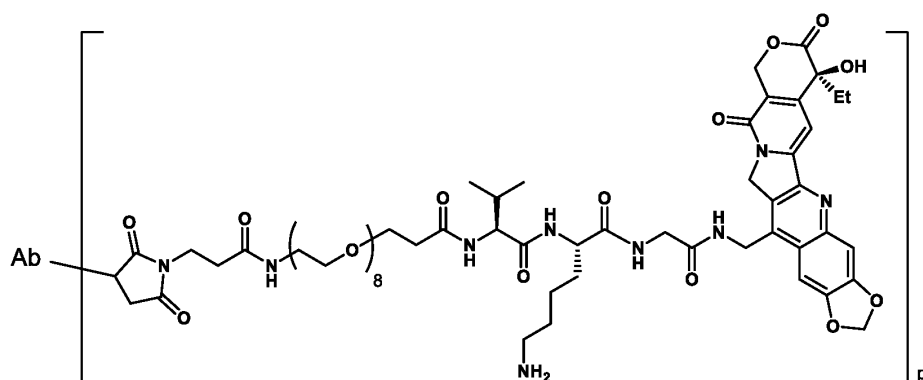
y is 1, 2, 3, or 4, or is 1 or 4; and

z is an integer from 2 to 12, or is 2, 4, 8, or 12;

and p is 1-16.

[0148] In some aspect of these embodiments, p is 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some aspect, p is 2, 4 or 8.

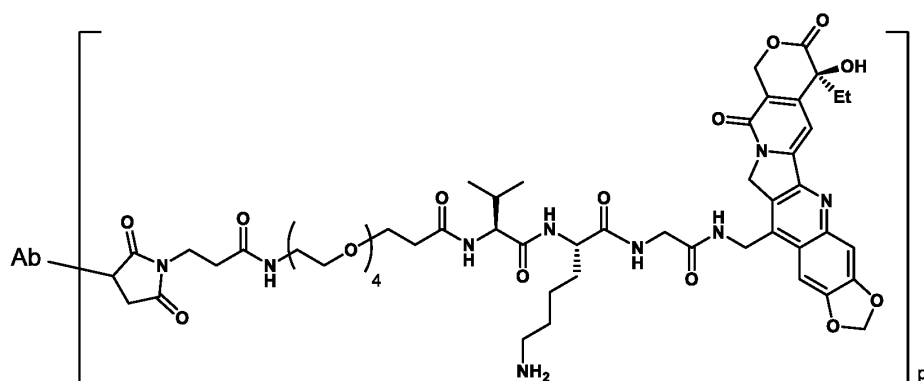
[0149] In some embodiments, the camptothecin ADC has the formula:



or a pharmaceutically acceptable salt thereof;

wherein p is 2, 4, or 8, preferably p is 8.

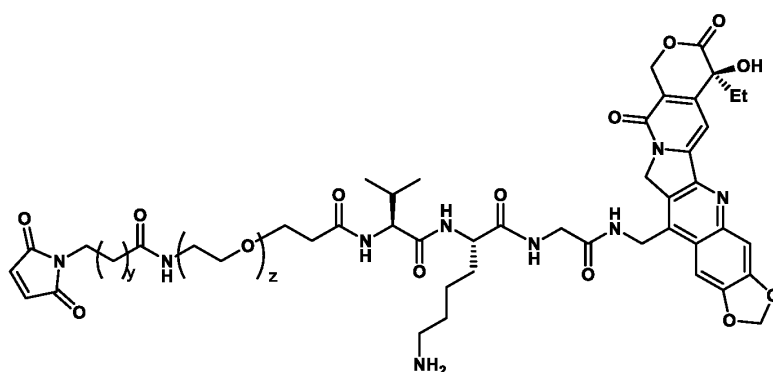
[0150] In some embodiments, the camptothecin ADC has the formula:



or a pharmaceutically acceptable salt thereof;

wherein p is 2, 4, or 8, preferably p is 8.

[0151] In some embodiments, the camptothecin drug-linker has the formula:



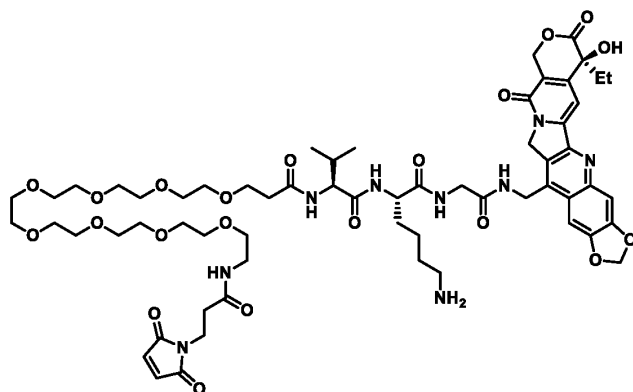
or a pharmaceutically acceptable salt thereof;

wherein

y is 1, 2, 3, or 4, or is 1 or 4; and

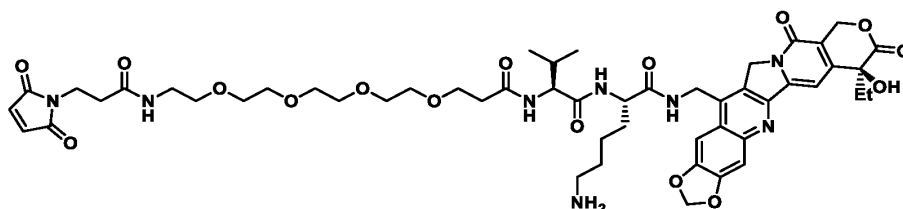
z is an integer from 2 to 12, or is 2, 4, 8, or 12.

[0152] In some embodiments, the camptothecin drug-linker has the formula:



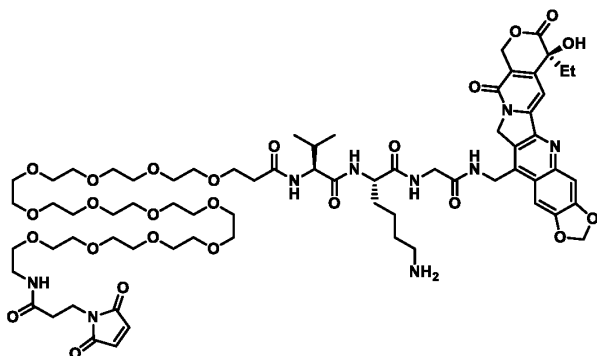
MP-PEG8-VKG-CAMPTOTHECIN

[0153] In some embodiments, the camptothecin drug-linker has the formula:



MP-PEG4-VKG-CAMPTOTHECIN

[0154] In some embodiments, the camptothecin drug-linker has the formula:



MP-PEG12-VKG-CAMPTOTHECIN

[0155] Referring to the PD-L1 targeted antibody-drug conjugates, the subscript p represents the drug load and, depending on the context, can represent the number of molecules of drug-linker molecules attached to an individual antibody molecule and as such,

is an integer value, or can represent an average drug load and, as such, can be an integer or non-integer value but is typically a non-integer value. An average drug load represents the average number of drug- linker molecules per antibody in a population. Often, but not always, when we refer to an antibody, e.g., a monoclonal antibody, we are referring to a population of antibody molecules. In a composition comprising a population of antibody-drug conjugate molecules, the average drug load is an important quality attribute as it determines the amount of drug that can be delivered to a target cell. The percentage of unconjugated antibody molecules in the composition is included in the average drug load value.

[0156] In preferred aspects of the present invention, the average drug load when referring to a composition comprising a population of antibody-drug conjugate compounds is from 1 to about 16, preferably about 2 to about 14, more preferably about 2 to about 10.

[0157] For the MMAE and camptothecin ADCs, such as those exemplified herein, preferred average drug load is about 2, 4, or 8, and a particularly preferred average drug load is about 8. In an embodiment, the preferred average drug load for MMAE ADCs is 2 or 4. In an embodiment, the preferred average drug load for camptothecin ADCs is 4 or 8. In exemplary embodiments, the drug-linkers are conjugated to the cysteine residues of the reduced inter-chain disulfides. In some aspects, the actual drug load for individual antibody molecules in the population of antibody-drug conjugate compounds is from 1 to 10 (or from 6 to 10 or from 6 to 8) with a predominant drug loading of 8. A higher drug load can be achieved, for example, if, in addition to the interchain disulfides, drug- linker is conjugated to introduced cysteine residues (such as a cysteine residue introduced at position 239, according to the EU index).

[0158] The PEG (polyethylene glycol) portion of the drug linker can range from 2 to 36. The subscript *z* in all of the embodiments above is preferably 2 to 12, 4 to 12, 8 to 14, 8 to 12, 10 to 12 or 10 to 14, is more preferably 2, 4, 8, or 12, and is most preferably 8.

[0159] Polydisperse PEGs, monodisperse PEGs and discrete PEGs can be used to make the PEGylated antibody drug conjugates of the present invention. Polydisperse PEGs are a heterogeneous mixture of sizes and molecular weights whereas monodisperse PEGs are typically purified from heterogeneous mixtures and are therefore provide a single chain length and molecular weight. Preferred PEG Units are discrete PEGs, compounds that are synthesized in step-wise fashion and not via a polymerization process. Discrete PEGs provide a single molecule with defined and specified chain length. As with the subscript "*p*", when

referring to populations of antibody-drug conjugates, the value for the subscript "n" can be an average number and can be an integer or non-integer number.

[0160] Useful classes of cytotoxic agents to conjugate to anti-PD-L1 antibodies include, for example, antitubulin agents, DNA minor groove binding agents, DNA replication inhibitors, chemotherapy sensitizers, or the like. Other exemplary classes of cytotoxic agents include anthracyclines, auristatins, camptothecins, duocarmycins, etoposides, maytansinoids and vinca alkaloids. Some exemplary cytotoxic agents include auristatins (e.g., auristatin T, auristatin E, AFP, monomethyl auristatin F (MMAF), lipophilic monomethyl auristatin F, monomethyl auristatin E (MMAE)), DNA minor groove binders (e.g., enediyne and lexitropsins), duocarmycins, taxanes (e.g., paclitaxel and docetaxel), vinca alkaloids, nicotinamide phosphoribosyltransferase inhibitor (NAMPTi), tubulysin M, doxorubicin, morpholino-doxorubicin, and cyanomorpholino-doxorubicin.

[0161] The cytotoxic agent can be a chemotherapeutic such as, for example, doxorubicin, paclitaxel, melphalan, vinca alkaloids, methotrexate, mitomycin C or etoposide. The agent can also be a CC-1065 analogue, calicheamicin, maytansine, an analog of dolastatin 10, rhizoxin, or palytoxin.

[0162] The cytotoxic agent can also be an auristatin. The auristatin can be an auristatin E derivative is, e.g., an ester formed between auristatin E and a keto acid. For example, auristatin E can be reacted with paraacetyl benzoic acid or benzoylvaleric acid to produce AEB and AEVB, respectively. Other typical auristatins include auristatin T, AFP, MMAF, and MMAE. The synthesis and structure of various auristatins are described in, for example, US 2005-0238649 and US2006-0074008.

[0163] The cytotoxic agent can be a DNA minor groove binding agent. (See, e.g., U.S. Patent No. 6,130,237.) For example, the minor groove binding agent can be a CBI compound or an enediyne (e.g., calicheamicin).

[0164] The cytotoxic or cytostatic agent can be an anti-tubulin agent. Examples of anti-tubulin agents include taxanes (e.g., Taxol® (paclitaxel), Taxotere® (docetaxel)), T67 (Tularik), vinca alkyls (e.g., vincristine, vinblastine, vindesine, and vinorelbine), and auristatins (e.g., auristatin E, AFP, MMAF, MMAE, AEB, AEVB). Exemplary auristatins are shown below in formulae III-XIII. Other suitable antitubulin agents include, for example, baccatin derivatives, taxane analogs (e.g., epothilone A and B), nocodazole, colchicine and

colcemid, estramustine, cryptophysins, cemadotin, maytansinoids, combretastatins, discodermoide and eleuthrobin.

[0165] The cytotoxic agent can be a maytansinoid, another group of anti-tubulin agents (e.g., DM1, DM2, DM3, DM4). For example, the maytansinoid can be maytansine or a maytansine containing drug linker such as DM-1 or DM-4 (ImmunoGen, Inc.; see also Chari et al., 1992, Cancer Res.).

VIII. Therapeutic Applications

[00166] Provided herein are methods for the treatment of various cancers in subjects using an antibody drug conjugate (ADC) that binds PD-L1 in combination with an anti-PD-1 antibody (e.g., pembrolizumab).

[00167] In one aspect, provided herein are methods for the treatment of cancer in a subject using an ADC that binds PD-L1 and an anti-PD-1 antibody (e.g., pembrolizumab). In some embodiments, the human subject treated with the methods provided herein has received previous cancer treatment. In certain embodiments, the human subject treated with the methods provided herein has 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 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 adjuvant/neoadjuvant platinum-based therapy within 12 months

prior to randomization. In still further 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, has not received adjuvant/neoadjuvant platinum-based therapy within 12 months prior to randomization, and has not received prior systemic treatment for locally advanced or metastatic disease.

[0168] Examples of cancers associated with PD-L1 expression and amenable to treatment include melanoma, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), head and neck cancer, triple negative breast cancer (TNBC), ovarian cancer, urothelial cancer, hepatocellular carcinoma (HCC), gastric cancer, and cervical cancer. In some embodiments, the antibodies or antibody-drug conjugates of the invention are used in methods of treating melanoma. In some embodiments, the antibodies or antibody-drug conjugates of the invention are used in methods of treating NSCLC. In some embodiments, the antibodies or antibody-drug conjugates of the invention are used in methods of treating SCLC. In some embodiments, the antibodies or antibody-drug conjugates of the invention are used in methods of treating head and neck cancer. In some embodiments, the antibodies or antibody-drug conjugates of the invention are used in methods of treating TNBC. A triple negative breast cancer is a term of art for a cancer lacking detectable estrogen and progesterone receptors and lacking overexpression of HER2/neu. In some embodiments, the antibodies or antibody-drug conjugates of the invention are used in methods of treating ovarian cancer. In some embodiments, the antibodies or antibody-drug conjugates of the invention are used in methods of treating urothelial cancer. In some embodiments, the antibodies or antibody-drug conjugates of the invention are used in methods of treating HCC. In some embodiments, the antibodies or antibody-drug conjugates of the invention are used in methods of treating gastric cancer. In some embodiments, the antibodies or antibody-drug conjugates of the invention are used in methods of treating cervical cancer. The treatment can be applied to patients having primary or metastatic tumors of these kinds. The treatment can also be applied to patients who are refractory to conventional treatments, or who have relapsed following a response to such treatments.

[0169] Antibodies of the present invention, such as humanized antibodies, alone or as conjugates thereof, are administered in an effective regime meaning a dosage, route of administration and frequency of administration that delays the onset, reduces the severity, inhibits further deterioration, and/or ameliorates at least one sign or symptom of cancer. If a

patient is already suffering from cancer, the regime can be referred to as a therapeutically effective regime. If the patient is at elevated risk of the cancer relative to the general population but is not yet experiencing symptoms, the regime can be referred to as a prophylactically effective regime. In some instances, therapeutic or prophylactic efficacy can be observed in an individual patient relative to historical controls or past experience in the same patient. In other instances, therapeutic or prophylactic efficacy can be demonstrated in a preclinical or clinical trial in a population of treated patients relative to a control population of untreated patients.

[0170] Exemplary dosages for a monoclonal antibody are 0.1 mg/kg to 50 mg/kg of the patient's body weight, more typically 0.5 mg/kg to 30 mg/kg, 1 mg/kg to 30 mg/kg, 1 mg/kg to 20 mg/kg, 1 mg/kg to 15 mg/kg, 1 mg/kg to 12 mg/kg, or 1 mg/kg to 10 mg/kg, 1, or 2 mg/kg to 30 mg/kg, 2 mg/kg to 20 mg/kg, 2 mg/kg to 15 mg/kg, 2 mg/kg to 12 mg/kg, or 2 mg/kg to 10 mg/kg, or 3 mg/kg to 30 mg/kg, 3 mg/kg to 20 mg/kg, 3 mg/kg to 15 mg/kg, 3 mg/kg to 12 mg/kg, or 3 mg/kg to 10 mg/kg. Exemplary dosages for a monoclonal antibody or antibody drug conjugates thereof are 0.5 mg/kg to 7.5 mg/kg, 1 mg/kg to 7.5 mg/kg, or 2 mg/kg to 7.5 mg/kg or 3 mg/kg to 7.5 mg/kg of the subject's body weight, or 0.1-20, or 0.5-5 mg/kg body weight (e.g., 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 mg/kg) or 10-1500 or 200-1500 mg as a fixed dosage. In some methods, the patient is administered a dose of at least 0.5 mg/kg, 1.0 mg/kg, 1.5 mg/kg, at least 2 mg/kg or at least 3 mg/kg, administered once every three weeks or greater. In some methods, the patient is administered a dose of at least 0.5 mg/kg, 1.0 mg/kg, 1.5 mg/kg, 2 mg/kg or 3 mg/kg, administered once every three weeks or more frequently. In some methods, the patient is administered a dose of about any one of 0.5 mg/kg, 0.75 mg/kg, 1.0 mg/kg, 1.25 mg/kg, 1.5 mg/kg, 1.75 mg/kg, 2 mg/kg or 3 mg/kg, administered once every three weeks or more frequently. The dosage depends on the frequency of administration, condition of the patient and response to prior treatment, if any, whether the treatment is prophylactic or therapeutic and whether the disorder is acute or chronic, among other factors.

[0171] Administration can be parenteral, intravenous, oral, subcutaneous, intra-arterial, intracranial, intrathecal, intraperitoneal, topical, intranasal or intramuscular. Administration can also be localized directly into a tumor. Administration into the systemic circulation by intravenous or subcutaneous administration is preferred. Intravenous administration can be, for example, by infusion over a period such as 30-90 min or by a single bolus injection.

[0172] The frequency of administration depends on the half-life of the antibody or conjugate in the circulation, the condition of the patient and the route of administration among other factors. The frequency of administration of an anti-PD-L1 antibody or antibody-drug conjugate described herein can be daily, weekly, once every two weeks, twice every three weeks, once every three weeks, monthly, quarterly, or at irregular intervals in response to changes in the patient's condition or progression of the cancer being treated. In some embodiments, the frequency of administration is about weekly. In some embodiments, the weekly administration is on about Days 1, 8, and 15 of a 21-day cycle. In some embodiments, the frequency of administration is once about every two weeks. In some embodiments, the frequency of administration is twice about every three weeks. In some embodiments, the frequency of administration is on about Days 1 and 8 of a 21-day cycle. In some embodiments, the frequency of administration is once about every three weeks. In some embodiments, the frequency of administration is weekly. In some embodiments, the weekly administration is on Days 1, 8, and 15 of a 21-day cycle. In some embodiments, the frequency of administration is once every two weeks. In some embodiments, the frequency of administration is on Days 1 and 8 of a 21-day cycle. In some embodiments, the frequency of administration is twice every three weeks. In some embodiments, the frequency of administration is once every three weeks. For subcutaneous administration, an exemplary dosing frequency is daily to monthly, although more or less frequent dosing is also possible. An exemplary frequency for intravenous administration is between twice a week and quarterly over a continuous course of treatment, although more or less frequent dosing is also possible. Other exemplary frequencies for intravenous administration are between weekly or three out of every four weeks over a continuous course of treatment, although more or less frequent dosing is also possible. Other exemplary frequencies for intravenous administration are once every two weeks or once every three weeks over a continuous course of treatment, although more or less frequent dosing is also possible. In some embodiments, the dose is administered is based on the subject's body weight. In some embodiments, the subject's body weight is the subject's ideal body weight (IBW). In some embodiments, the subject's body weight is the subjects adjusted ideal body weight (AIBW). In some embodiments, the dose is 0.5 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 0.5 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 0.5 mg/kg and is administered twice about every 3 weeks. In some embodiments, the dose is 0.5 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is

[illegible]

[illegible]

2.2 mg/kg and is administered twice about every 3 weeks. In some embodiments, the dose is 2.2 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 2.3 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 2.3 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 2.3 mg/kg and is administered twice about every 3 weeks. In some embodiments, the dose is 2.3 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 2.4 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 2.4 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 2.4 mg/kg and is administered twice about every 3 weeks. In some embodiments, the dose is 2.4 mg/kg and is administered once about every 3 weeks. In some embodiments, the dose is 2.5 mg/kg and is administered once about every 1 week. In some embodiments, the dose is 2.5 mg/kg and is administered once about every 2 weeks. In some embodiments, the dose is 2.5 mg/kg and is administered twice about every 3 weeks. In some embodiments, the dose is 2.5 mg/kg and is administered once about every 3 weeks. In some methods, the patient is administered a dose of about any one of 0.5 mg/kg, 0.75 mg/kg, 1.0 mg/kg, 1.25 mg/kg, 1.5 mg/kg, 1.75 mg/kg, 2 mg/kg or 3 mg/kg, administered on Days 1, 8, and 15 of a 21-day cycle. In some methods, the patient is administered a dose of 1.25 mg/kg, administered on Days 1, 8, and 15 of a 21-day cycle. In some methods, the patient is administered a dose of 1.5 mg/kg, administered on Days 1, 8, and 15 of a 21-day cycle. In some methods, the patient is administered a dose of about any one of 0.5 mg/kg, 0.75 mg/kg, 1.0 mg/kg, 1.25 mg/kg, 1.5 mg/kg, 1.75 mg/kg, 2 mg/kg or 3 mg/kg, administered on Days 1 and 8 of a 21-day cycle. In some methods, the patient is administered a dose of 1.25 mg/kg, administered on Days 1 and 8 of a 21-day cycle. In some methods, the patient is administered a dose of 1.5 mg/kg, administered on Days 1 and 8 of a 21-day cycle.

[0173] The number of dosages administered depends on the nature of the cancer (e.g., whether presenting acute or chronic symptoms) and the response of the disorder to the treatment. For acute disorders or acute exacerbations of a chronic disorder between 1 and 10 doses are often sufficient. Sometimes a single bolus dose, optionally in divided form, is sufficient for an acute disorder or acute exacerbation of a chronic disorder. Treatment can be repeated for recurrence of an acute disorder or acute exacerbation. For chronic disorders, an antibody can be administered at regular intervals, e.g., weekly, fortnightly, monthly, quarterly, every six months for at least 1, 5 or 10 years, or the life of the patient.

[0174] Pharmaceutical compositions for parenteral administration are preferably sterile and substantially isotonic and manufactured under GMP conditions. Pharmaceutical compositions can be provided in unit dosage form (i.e., the dosage for a single administration). Pharmaceutical compositions can be formulated using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries. The formulation depends on the route of administration chosen. For injection, antibodies can be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline or acetate buffer (to reduce discomfort at the site of injection). The solution can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively antibodies can be in lyophilized form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. The concentration of antibody in a liquid formulation can be e.g., 1-100 mg/ml, such as 10 mg/ml.

[0175] Treatment with antibodies of the invention can be combined with chemotherapy, radiation, stem cell treatment, surgery other treatments effective against the disorder being treated. Useful classes of other agents that can be administered with antibodies and antibody-drug conjugates to PD-L1 as described herein include, for example, antibodies to other receptors expressed on cancerous cells, antitubulin agents (e.g., auristatins), DNA minor groove binders, DNA replication inhibitors, alkylating agents (e.g., platinum complexes such as cisplatin, mono(platinum), bis(platinum) and tri-nuclear platinum complexes and carboplatin), anthracyclines, antibiotics, antifolates, antimetabolites, chemotherapy sensitizers, duocarmycins, etoposides, fluorinated pyrimidines, ionophores, lexitropsins, nitrosoureas, platinols, pre-forming compounds, purine antimetabolites, puromycins, radiation sensitizers, steroids, taxanes, topoisomerase inhibitors, vinca alkaloids, and the like.

[0176] Treatment with the PD-L1 antibody or antibody-drug conjugate, optionally in combination with any of the other agents or regimes described above alone or as an antibody drug conjugate, can increase the median progression-free survival or overall survival time of patients with tumors (e.g., melanoma, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), head and neck cancer, triple negative breast cancer (TNBC), ovarian cancer, urothelial cancer, hepatocellular carcinoma (HCC), gastric cancer, and cervical cancer), especially when relapsed or refractory, by at least 30% or 40% but preferably 50%, 60% to 70% or even 100% or longer, compared to the same treatment (e.g., chemotherapy) but without an anti-PD-L1 antibody alone or as a conjugate. In addition or alternatively,

treatment (e.g., standard chemotherapy) including the anti-PD-L1 antibody alone or as a conjugate can increase the complete response rate, partial response rate, or objective response rate (complete + partial) of patients with tumors by at least 30% or 40% but preferably 50%, 60% to 70% or even 100% compared to the same treatment (e.g., chemotherapy) but without the anti-PD-L1 antibody alone or as a conjugate.

[0177] Typically, in a clinical trial (e.g., a phase II, phase II/III or phase III trial), the aforementioned increases in median progression-free survival and/or response rate of the patients treated with standard therapy plus the anti-PD-L1 antibody alone or as conjugate, relative to the control group of patients receiving standard therapy alone (or plus placebo), are statistically significant, for example at the $p = 0.05$ or 0.01 or even 0.001 level. The complete and partial response rates are determined by objective criteria commonly used in clinical trials for cancer, e.g., as listed or accepted by the National Cancer Institute and/or Food and Drug Administration.

[0178] In some embodiments, the anti-PD-L1 antibodies or antibody-drug conjugates described herein are administered in combination with an anti-PD-1 antibody. In a further embodiment, the anti-PD-1 antibody is pembrolizumab. In some embodiments, the anti-PD-1 antibody is administered simultaneously with the anti-PD-L1 antibodies or antibody-drug conjugates described herein. In some embodiments, the anti-PD-1 antibody and the anti-PD-L1 antibodies or antibody-drug conjugates described herein are administered sequentially. In some embodiments, simultaneous means that the anti-PD-L1 antibodies or antibody-drug conjugates described herein and the anti-PD-1 antibody are administered to the subject less than one hour apart, such as less than about 30 minutes apart, less than about 15 minutes apart, less than about 10 minutes apart or less than about 5 minutes apart. In some embodiments, sequential administration means that the anti-PD-L1 antibodies or antibody-drug conjugates described herein and the anti-PD-1 antibody are administered a least 1 hour apart, at least 2 hours apart, at least 3 hours apart, at least 4 hours apart, at least 5 hours apart, at least 6 hours apart, at least 7 hours apart, at least 8 hours apart, at least 9 hours apart, at least 10 hours apart, at least 11 hours apart, at least 12 hours apart, at least 13 hours apart, at least 14 hours apart, at least 15 hours apart, at least 16 hours apart, at least 17 hours apart, at least 18 hours apart, at least 19 hours apart, at least 20 hours apart, at least 21 hours apart, at least 22 hours apart, at least 23 hours apart, at least 24 hours apart, at least 2 days apart, at least 3 days apart, at least 4 days apart, at least 5 days apart, at least 5 days apart, at least 7

days apart, at least 2 weeks apart, at least 3 weeks apart, at least 4 weeks apart, at least 6 weeks apart, at least 2 months apart, at least 3 months apart, at least 4 months apart, at least 5 months apart, or at least 6 months apart.

[0179] In some embodiments, the PD-1 antibody is pembrolizumab, or a biosimilar thereof. In some embodiments, the pembrolizumab or biosimilar thereof is administered at a dose of about 200 mg. In some embodiments, the pembrolizumab or biosimilar thereof is administered at a dose of 200 mg. In some embodiments, the pembrolizumab or biosimilar thereof is administered at a dose of about 400 mg. In some embodiments, the pembrolizumab or biosimilar thereof is administered at a dose of 400 mg. In some embodiments, the pembrolizumab or biosimilar thereof is administered once about every 3 weeks. In some embodiments, the pembrolizumab or biosimilar thereof is administered once every 3 weeks. In some embodiments, the pembrolizumab or biosimilar thereof is administered once about every 6 weeks. In some embodiments, the pembrolizumab or biosimilar thereof is administered once every 6 weeks. In some embodiments, pembrolizumab or biosimilar thereof is administered at a dose of about 200 mg once about every 3 weeks. In some embodiments, pembrolizumab or biosimilar thereof is administered at a dose of 200 mg once every 3 weeks. In some embodiments, pembrolizumab or biosimilar thereof is administered at a dose of about 400 mg once about every 6 weeks. In some embodiments, pembrolizumab or biosimilar thereof is administered at a dose of 400 mg once every 6 weeks. In some embodiments, the route of administration of the pembrolizumab or biosimilar thereof is intravenous. In some embodiments, the first dose of the anti-PD-L1 antibody or antibody drug conjugate is administered to the subject prior to the administration of the first dose of pembrolizumab or biosimilar thereof. In some embodiments, the first dose of the anti-PD-L1 antibody or antibody drug conjugate is administered to the subject at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months prior to the administration of the first dose of pembrolizumab or biosimilar thereof.

[0180] Treatment with the anti-PD-L1 antibody or antibody-drug conjugate, optionally in combination with an anti-PD-1 antibody as described above, can increase the median progression-free survival or overall survival time of patients with cancer, including solid tumors. In some embodiments, the cancer is melanoma, non-small cell lung cancer (NSCLC),

small cell lung cancer (SCLC), head and neck squamous cell carcinoma (HNSCC), triple negative breast cancer (TNBC), esophageal squamous cell carcinoma (esophageal SCC), ovarian cancer, urothelial cancer, hepatocellular carcinoma (HCC), gastric cancer, or cervical cancer.

[0181] In some embodiments, treatment with the anti-PD-L1 antibody or antibody-drug conjugate, optionally in combination with an anti-PD-1 antibody as described above, can drive bystander effect-based cytotoxicity of PD-L1-negative tumor cells. In some embodiments, treatment with the anti-PD-L1 antibody or antibody-drug conjugate, optionally in combination with an anti-PD-1 antibody as described above, can drive bystander effect-based cytotoxicity of PD-L1-negative tumor cells when the PD-L1 negative tumor cells are within a tumor microenvironment that also comprises PD-L1 positive tumor cells. In some further embodiments, treatment with the anti-PD-L1 antibody or antibody-drug conjugate causes bystander effect-based cytotoxicity of PD-L1-negative tumor cells at a level that is at least about any one of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 2-fold, 5-fold, 10-fold, 100-fold, 1000-fold or higher than that caused by an antibody or antibody-drug conjugate not specific for PD-L1, optionally wherein the PD-L1 negative tumor cells are within a tumor microenvironment that also comprises PD-L1 positive tumor cells.

[0182] Immunogenic cell death is a regulated activation of immune cell recruitment to the tumor microenvironment, is caused by tumor cell release of damage-associated molecular patterns (DAMPs) such as cell surface chaperone calreticulin (CRT), extracellular adenosine triphosphate (eATP), and High Mobility Group Box 1 protein (HMGB1). In some embodiments, treatment with the anti-PD-L1 antibody or antibody-drug conjugate, optionally in combination with an anti-PD-1 antibody as described above, can drive increased immunogenic cell death. In some embodiments, treatment with the anti-PD-L1 antibody or antibody-drug conjugate, optionally in combination with an anti-PD-1 antibody as described above, can cause activation of immune cell recruitment to the tumor microenvironment. In some embodiments, treatment with the anti-PD-L1 antibody or antibody-drug conjugate, optionally in combination with an anti-PD-1 antibody as described above, can cause activation of immune cell recruitment to the tumor microenvironment at a level that is at least about any one of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 2-fold, 5-fold, 10-fold, 100-fold, 1000-fold or higher than that caused by an antibody or antibody-drug

conjugate not specific for PD-L1. In some embodiments, treatment with the anti-PD-L1 antibody or antibody-drug conjugate, optionally in combination with an anti-PD-1 antibody as described above, can cause release of one or more of CRT, eATP, and/or HMGB1 at a level that is at least about any one of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 2-fold, 5-fold, 10-fold, 100-fold, 1000-fold or higher than that caused by an antibody or antibody-drug conjugate not specific for PD-L1.

[0183] In some embodiments, treatment with the anti-PD-L1 antibody or antibody-drug conjugate, optionally in combination with an anti-PD-1 antibody as described above, does not result in significant depletion of immune cells. In some embodiments, treatment with the anti-PD-L1 antibody or antibody-drug conjugate, optionally in combination with an anti-PD-1 antibody as described above, causes death of less than about any one of 2%, 5%, 10%, 15%, 20%, or 30% the immune cells as compared to at start of treatment. In some embodiments, treatment with the anti-PD-L1 antibody or antibody-drug conjugate, optionally in combination with an anti-PD-1 antibody as described above, causes immune cell death at a level that is at least any one of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 2-fold, 5-fold, 10-fold, 100-fold, or 1000-fold less than that caused by an antibody or antibody-drug conjugate not specific for PD-L1. In some embodiments, the immune cells comprise one or more of CD4+ T cell, CD8+ T cell, macrophages and/or dendritic cells.

[0184] In some embodiments, treatment with the anti-PD-L1 antibody or antibody-drug conjugate, optionally in combination with an anti-PD-1 antibody as described above, results in targeted depletion of immunosuppressive cells, such as immune cells which suppress natural antitumor immunity. In some embodiments, treatment with the anti-PD-L1 antibody or antibody-drug conjugate, optionally in combination with an anti-PD-1 antibody as described above, causes death of at least about any one of 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, or more of the immunosuppressive cells as compared to at start of treatment. In some embodiments, treatment with the anti-PD-L1 antibody or antibody-drug conjugate, optionally in combination with an anti-PD-1 antibody as described above, causes death of immunosuppressive cells at a level that is at least any one of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 2-fold, 5-fold, 10-fold, 100-fold, or 1000-fold higher than that caused by an antibody or antibody-drug conjugate not specific for PD-L1. In some embodiments, the immunosuppressive cells comprise one or more of regulatory T cells (Tregs), myeloid-derived suppressive cells (MDSCs), tumor-associated macrophages

(TAMs), tumor-associated neutrophils (TANs), and/or tumor-associated dendritic cells (tDCs).

Checkpoint Inhibitors and Combination Therapy with Pembrolizumab

[00185] 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.

[00186] 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.

[00187] In various aspects or embodiments of the methods provided herein, the human subjects for whom the methods are provided herein have not received any prior treatment with a checkpoint inhibitor (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. 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-L1 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.

[00188] 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.

[00189] 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™.

[00190] In certain embodiments, the checkpoint inhibitor is a PD-1/PD-L1 inhibitor. Examples of PD-1/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.

[00191] “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, PD-1, CD279 and SLEB2 for PD-1; PDCD1L1, PDL1, B7H1, B7-4, CD274 and B7-H for PD-L1; and PDCD1L2, PDL2, B7-DC, Btde 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.

[00192] 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.

[00193] 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.

[00194] 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.

[00195] 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.

[00196] 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).

[00197] 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).

[00198] 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.

[00199] 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.

[00200] 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.

[00201] 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.

[00202] In one embodiment, the checkpoint inhibitor is recombinant human interleukin-15 (rhIL-15).

[00203] In one embodiment, the checkpoint inhibitor is a VTCN inhibitor. In one embodiment, the VTCN inhibitor is FPA150.

[00204] 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.

[00205] 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.

[00206] 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.

[00207] 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.

[00208] 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.

[00209] 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.

[00210] 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.

[00211] 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.

[00212] 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.

PD-1 Antagonists and Pembrolizumab

[00213] Provided herein are methods for the treatment of various cancers in subjects, using an antibody drug conjugate (ADC) that binds PD-L1 in combination with a PD-1 antagonist. In some embodiments, the PD-1 antagonist is an anti-PD-1 antibody. In further embodiments, the anti-PD-1 antibody is pembrolizumab. In some embodiments, the PD-1 antagonist is selected from a group comprising: pembrolizumab, nivolumab, cemiplimab, durvalumab, atezolizumab, dostarlimab, avelumab, or pidilizumab. In certain embodiments, the treatment is a first-line treatment. In other embodiments, the treatment is a second-line treatment.

[00214] “Pembrolizumab” or “pembro” is a humanized IgG4 mAb with the structure described in WHO Drug Information, Vol. 27, No. 2, pages 161-162 (2013). Pembrolizumab has a heavy chain CDR1 of SEQ ID NO: 17, a heavy chain CDR2 of SEQ ID NO: 18, a

heavy chain CDR3 of SEQ ID NO: 19, a light chain CDR1 of SEQ ID NO: 20, a light chain CDR2 of SEQ ID NO: 21, and a light chain CDR3 of SEQ ID NO: 22. Pembrolizumab has a heavy chain sequence of SEQ ID NO: 23 and a light chain sequence of SEQ ID NO: 24. Pembrolizumab has a heavy chain variable region sequence of SEQ ID NO: 25 and a light chain variable region sequence of SEQ ID NO: 26.

[00215] In another embodiment, the PD-1 antagonist is an antibody or antigen binding protein comprising a heavy chain variable region or light chain variable region with at least 95%, 90%, 85%, 80%, 75% or 50% sequence identity to SEQ ID NO:25 or SEQ ID NO:26, respectively, and exhibits specific binding to PD-1. In another embodiment, the PD-1 antagonist is an antibody or antigen binding protein comprising a heavy chain variable region or light chain variable region having up to 1, 2, 3, 4, or 5 or more amino acid substitutions to SEQ ID NO:25 or SEQ ID NO:26, respectively, and exhibits specific binding to PD-1.

[00216] In some embodiments, the PD-1 antagonist is administered after the administration of the ADCs provided herein. In other embodiments, the PD-1 antagonist is administered simultaneously (*e.g.*, in the same dosing period) with the ADCs provided herein. In yet other embodiments, the PD-1 antagonist is administered after the administration of the ADCs provided herein.

[00217] In some embodiments, the amount of the PD-1 antagonist 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 the Examples.

[00218] 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.

IX. Articles of Manufacture and Kits

[00219] 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. In another aspect, an article of manufacture or kit is provided which comprises an anti-PD-L1 antibody or anti-PD-L1 antibody-drug conjugate described herein. The article of manufacture or kit may further comprise instructions for use of the anti-PD-L1 antibody or anti-PD-L1 antibody-drug conjugate described herein in the methods of the invention. Thus, in certain embodiments, the article of manufacture or kit comprises

instructions for the use of an anti-PD-L1 antibody or anti-PD-L1 antibody-drug conjugate described herein in methods for treating cancer (*e.g.*, melanoma, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), head and neck cancer, triple negative breast cancer (TNBC), ovarian cancer, urothelial cancer, hepatocellular carcinoma (HCC), gastric cancer, and cervical cancer) in a subject comprising administering to the subject an effective amount of an anti-PD-L1 antibody or anti-PD-L1 antibody-drug conjugate described herein. In some embodiments, the subject is a human.

[00220] The article of manufacture or kit may further comprise a container. Suitable containers include, for example, bottles, vials (*e.g.*, dual chamber vials), syringes (such as single or dual chamber syringes) and test tubes. In some embodiments, the container is a vial. The container may be formed from a variety of materials such as glass or plastic. The container holds the formulation.

[00221] The article of manufacture or kit may further comprise a label or a package insert, which is on or associated with the container, may indicate directions for reconstitution and/or use of the formulation. The label or package insert may further indicate that the formulation is useful or intended for subcutaneous, intravenous (*e.g.*, intravenous infusion), or other modes of administration for treating cancer in a subject (*e.g.*, melanoma, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), head and neck cancer, triple negative breast cancer (TNBC), ovarian cancer, urothelial cancer, hepatocellular carcinoma (HCC), gastric cancer, and cervical cancer). The container holding the formulation may be a single-use vial or a multi-use vial, which allows for repeat administrations of the reconstituted formulation. The article of manufacture or kit may further comprise a second container comprising a suitable diluent. The article of manufacture or kit may further include other materials desirable from a commercial, therapeutic, and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

[00222] The article of manufacture or kit herein optionally further comprises a container comprising a second medicament, wherein the anti-PD-L1 antibody or anti-PD-L1 antibody-drug conjugate is a first medicament, and which article or kit further comprises instructions on the label or package insert for treating the subject with the second medicament, in an effective amount. In some embodiments, the second medicament is for eliminating or reducing the severity of one or more adverse events.

[0223] In some embodiments, the anti-PD-L1 antibody or anti-PD-L1 antibody-drug conjugate is present in the container as a lyophilized powder. In some embodiments, the lyophilized powder is in a hermetically sealed container, such as a vial, an ampoule or sachette, indicating the quantity of the active agent. Where the pharmaceutical is administered by injection, an ampoule of sterile water for injection or saline can be, for example, provided, optionally as part of the kit, so that the ingredients can be mixed prior to administration. Such kits can further include, if desired, one or more of various conventional pharmaceutical components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Printed instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components can also be included in the kit.

[0224] In some embodiments, the anti-PD-L1 antibody-drug conjugate is a sterile, preservative-free, white to off-white cake or powder supplied in a single-dose glass vial for reconstitution for IV administration. The formulation may contain compendial excipients. The drug product will be provided with appropriate packaging and storage conditions. In some embodiments, the anti-PD-L1 antibody drug conjugate may be reconstituted with 4.4 mL sterile water for injection, USP, Ph. Eur., or equivalent. In some embodiments, for administration, the reconstituted solution is diluted with 5% dextrose injection, USP, or equivalent, prior to IV infusion.

X. Other Applications

[0225] The anti-PD-L1 antibodies described herein, such as humanized anti-PD-L1, antibodies can be used for detecting PD-L1 in the context of clinical diagnosis or treatment or in research. Expression of PD-L1 on a cancer provides an indication that the cancer is amenable to treatment with the antibodies of the present invention. The antibodies can also be sold as research reagents for laboratory research in detecting cells bearing PD-L1 and their response to various stimuli. In such uses, monoclonal antibodies can be labeled with fluorescent molecules, spin-labeled molecules, enzymes or radioisotopes, and can be provided in the form of kit with all the necessary reagents to perform the assay for PD-L1. The antibodies described herein, can be used to detect PD-L1 protein expression and determine whether a cancer is amenable to treatment with PD-L1 ADCs.

[0226] All patent filings, website, other publications, accession numbers and the like cited above or below are incorporated by reference in their entirety for all purposes to the same extent as if each individual item were specifically and individually indicated to be so incorporated by reference. If different versions of a sequence are associated with an accession number at different times, the version associated with the accession number at the effective filing date of this application is meant. The effective filing date means the earlier of the actual filing date or filing date of a priority application referring to the accession number if applicable. Likewise if different versions of a publication, website or the like are published at different times, the version most recently published at the effective filing date of the application is meant unless otherwise indicated. Any feature, step, element, embodiment, or aspect of the invention can be used in combination with any other unless specifically indicated otherwise. Although the present invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims.

EXAMPLES

Example 1: A Phase 1 Study of SGN-PDL1V in Advanced Solid Tumors

[0227] A phase 1, open-label, multicenter study was designed to evaluate the safety, tolerability, PK, and antitumor activity of SGN-PDL1V, as monotherapy or in combination with pembrolizumab, in adults with select advanced solid tumors. SGN-PDL1V is an ADC comprising an anti-PD-L1 antibody conjugated to MMAE. The anti-PD-L1 antibody comprises a heavy chain variable region comprising heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 5, 6, and 7, respectively, and a light chain variable region comprising light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 8, 9, and 10, respectively. The anti-PD-L1 antibody also comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4. The anti-PD-L1 antibody also comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:1 and a light chain comprising the amino acid sequence of SEQ ID NO:2.

[0228] SGN-PDL1V, which binds to cell surface PD-L1, is uniquely positioned to combine with a PD-1 checkpoint inhibitor such as pembrolizumab. SGN-PDL1V elicits direct cytotoxicity to PD-L1 positive tumor cells which may reduce the overall

immunosuppressive PD-1/PD-L1 signaling in the tumor microenvironment and therefore drive increased activation of cytotoxic T cells. SGN-PDL1V may also initiate the process of cancer immunity through MMAE-induced immunogenic cell death. Finally, SGN-PDL1V has demonstrated promising clinical activity in solid tumor patients relapsed/refractory to checkpoint inhibitors such as pembrolizumab, suggesting a combination of PD-L1+ tumor debulking from SGN-PDL1V with PD-(L)1 blockade from pembrolizumab may provide an additive therapeutic benefit to patients beyond pembrolizumab alone.

[0229] The study includes multiple tumor types for the dose escalation (Part A), followed by cohorts for dose and schedule optimization (Part B, as relevant), disease-specific cohorts in dose expansion monotherapy (Part C), and a combination safety run-in cohort (Part D) with pembrolizumab.

[0230] The study includes dose escalation (Part A) enrolling subjects with HNSCC, non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC), or esophageal squamous cell carcinoma (SCC) who have programmed death-ligand 1 (PD-L1) expression ≥ 1 by combined positive score (CPS), tumor proportion score (TPS), or immune cell score (% IC), based on historical testing. The initial dosing schedule to be tested is Day 1 and Day 8 of a 21-day cycle (2Q3W). The initial dose level to be evaluated in the 2Q3W schedule is 0.5 mg/kg. Dose escalation proceeds by increments of 0.25 mg/kg, up to the dose level of 2.5 mg/kg, if tolerated. At any time, an alternative dosing schedule (eg, Day 1, Day 8, and Day 15 of a 28-day cycle [3Q4W], or Day 1 and Day 15 of a 28-day cycle [2Q4W], or Day 1 of a 21-day cycle [Q3W]) may be activated with additional subjects. The initial dose for the alternative dosing schedule is the same as the dose cleared in the initial dosing schedule (ie, 2Q3W) as long as the dose intensity is the same or lower. The modified toxicity probability interval (mTPI) dose escalation rules is applied separately to each dosing schedule.

[0231] Dose and schedule optimization (Part B) may be activated to additionally evaluate the SGN-PDL1V dosing schedules recommended from Part A in different tumor types. This part will allow optimization of the dose and schedule that will be recommended for expansion. The choice of which schedule(s) to open for enrollment will be made by the sponsor in consultation with the Safety Monitoring Committee (SMC), on the basis of available data on safety, dose-limiting toxicity (DLT), PK, and initial antitumor activity. Subjects of select tumor types who meet the eligibility criteria as described in Part A may be enrolled in Part B. Different doses/schedules in different tumor types may be evaluated in

parallel cohorts. Subjects participating in Part B will be randomized to allocate to different dose and schedules with equal probability for a specific tumor type. If following Part A, there is sufficient evidence to support bringing a dosing schedule forward for SGN-PDL1V, Part B may be omitted, provided at least 6 subjects have been dosed at the recommended dose and schedule.

[0232] Once a recommended expansion dose and schedule are selected by the SMC, dose expansion (Part C) with disease-specific expansion cohorts, and a combination safety run-in (Part D) with SGN-PDL1V in combination with pembrolizumab may be activated to further evaluate the safety, tolerability, and antitumor activity of SGN-PDL1V.

During dose expansion (Part C) the following cohorts may be evaluated:

- HNSCC; independent of PD-L1 expression.
- NSCLC; independent of PD-L1 expression.
- An additional signal-seeking cohort in subjects with melanoma, ovarian cancer, TNBC, gastric cancer, or esophageal SCC.
- A biology cohort including NSCLC and HNSCC with negative PD-L1 expression, TNBC, esophageal SCC, melanoma, gastric cancer, or ovarian cancer may also be activated.

[0233] During Part D, the combination of SGN-PDL1V with pembrolizumab will be evaluated in first line (1L) HNSCC with PD-L1 expression ≥ 1 by TPS or CPS.

Approximately 12 subjects will be enrolled in the cohort. To evaluate the safety of the combination therapy, an initial 6 subjects will be administered SGN-PDL1V plus pembrolizumab. Dose decisions for subsequent subjects in the cohort will be based on the incidence of DLTs. If the combination of SGN-PDL1V with pembrolizumab is deemed safe by the SMC, a future protocol amendment may expand this cohort to approximately 40 subjects. A future protocol amendment may also explore additional combinations.

[0234] The planned dose of pembrolizumab in Part D of this study is 200 mg IV once every 3 weeks (Q3W). Based on the totality of data generated in the pembrolizumab development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications.

As outlined below, the 200 mg Q3W dose is justified by:

- Clinical data from 8 randomized studies in melanoma and non-small cell lung cancer (NSCLC) tumor types demonstrating that flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5- to 7.5-fold exposure range (refer to the pembrolizumab IB).

- Population pharmacokinetic (PK) analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W.
- Clinical data showing improvement in benefit-risk including overall survival at 200 mg Q3W across multiple tumor types, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically based PK [PBPK] analysis) at 200 mg Q3W.

[0235] Among the 8 randomized dose-comparison studies, a total of 2262 patients were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck squamous cell carcinoma (HNSCC), bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the MOA of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

[0236] Additionally, pharmacology data show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

[0237] Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other patient covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and

2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

Benefit/Risk Assessment

[0238] ADCs such as SGN-PDL1V have the potential for antitumor activity in relapsed and refractory solid tumors and could provide benefit to this patient population with a poor prognosis who have otherwise exhausted all available treatment options. The toxicities observed in nonclinical studies of SGN-PDL1V were generally consistent with MMAE toxicities previously reported with other vedotin ADCs and no toxicities considered target-related were observed. The nonclinical studies are representative of potential toxicities of SGN-PDL1V and support evaluation in human clinical studies. This patient population needs new treatment options with the potential for benefit and risks that are monitorable and manageable.

TRIAL OBJECTIVES AND PURPOSE

[0239] This study will evaluate the safety, tolerability, PK, and antitumor activity of SGN-PDL1V (monotherapy) in subjects with advanced solid malignancies and in combination with pembrolizumab in subjects with metastatic or unresectable HNSCC. Specific objectives and corresponding endpoints for the study are summarized in Table 1.

Table 1: Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary	
<u>Parts A, B and C (monotherapy)</u> - To evaluate the safety and tolerability of SGN-PDL1V monotherapy in subjects with advanced solid tumors. - To identify the MTD of SGN-PDL1V monotherapy in subjects with advanced solid tumors. - To identify a recommended dose and schedule for SGN-PDL1V monotherapy.	<u>Parts A, B, C, and D</u> - Type, incidence, severity, seriousness, and relatedness of AEs - Type, incidence, and severity of laboratory abnormalities - Incidence of DLTs - Incidence of DLTs and cumulative safety by dose level
<u>Part D (combination therapy)</u> - To evaluate safety and tolerability of SGN-PDL1V in combination with pembrolizumab. - To identify a recommended dose and schedule for SGN-PDL1V in combination with pembrolizumab.	
Secondary	
<u>Parts A, B and C</u> - To assess the antitumor activity of SGN-PDL1V monotherapy. - To assess the PK and immunogenicity of SGN-PDL1V monotherapy.	<u>Parts A, B, C and D</u> - Confirmed ORR per RECIST v1.1 as assessed by the investigator. - DOR per RECIST v1.1 as assessed by the investigator. - PFS per RECIST v1.1 as assessed by the investigator. - OS - Plasma or serum concentrations and PK parameters of SGN-PDL1V Tab, ac-MMAE, and unconjugated MMAE. - Incidence of ADAs.
<u>Part D</u> - To assess antitumor activity of SGN-PDL1V in combination with pembrolizumab. - To assess the PK and immunogenicity of SGN-PDL1V in combination with pembrolizumab.	

Objectives	Corresponding Endpoints
Exploratory	
• To characterize the pharmacodynamics of SGN-PDL1V in monotherapy and combination. • To assess the PK/PD relationships of SGN-PDL1V in monotherapy and combination. • To assess exploratory markers of clinical outcomes, PK, and pharmacodynamics. • To assess PRO for quality of life per validated tools (Part C in HNSCC subjects only).	• ORR (regardless of confirmation) per RECIST v1.1 as assessed by the investigator. • Confirmed ORR per iRECIST (Part D only) as assessed by the investigator. • DOR per iRECIST (Part D only) as assessed by the investigator. • PFS per iRECIST (Part D only) as assessed by the investigator. • Exploratory biomarkers of SGN-PDL1V mediated pharmacodynamic effects • Correlative analyses of PK and pharmacodynamics exposure measurements • Correlative analyses of predictive and pharmacodynamics measurements with response, toxicity, and resistance assessments • PRO analyses based on EORTC QLQ-C30, EORTC QLQ-HN35, and EORTC Item List 46 for HNSCC (Part C cohorts only)

ac-MMAE=antibody-conjugated monomethyl auristatin E, ADA=antidrug antibody; AE=adverse event; DLT=dose-limiting toxicity; DOR=duration of response; EORTC=European Organisation for Research and Treatment of Cancer; HNSCC=head and neck squamous cell carcinoma; iRECIST: Modified RECIST 1.1 for Immune-based Therapeutics MMAE=monomethyl auristatin E; MTD=maximum tolerated dose; ORR=objective response rate; OS=overall survival; PFS=progression free survival; PK/PD=pharmacokinetic/pharmacodynamics; PRO=patient-reported outcome; QLQ=quality of life questionnaires (core and head and neck); RECIST v1.1=Response Evaluation Criteria in Solid Tumors Version 1.1

INVESTIGATIONAL PLAN

Overall Study Design

[0240] This is a phase 1, open-label, dose-escalation and dose-expansion multicenter study to evaluate the safety and tolerability of SGN-PDL1V monotherapy and combination therapy in adults with histologically or cytologically confirmed metastatic or unresectable solid malignancy with disease that is relapsed or refractory or intolerant to SoC. Once the safety and tolerability of SGN-PDL1V has been established (dose-escalation and dose/schedule optimization, Parts A and B, respectively), and a dose and schedule for expansion has been recommended by the SMC, SGN-PDL1V will be evaluated as a monotherapy in Part C and in combination with pembrolizumab (Part D). FIG. 1 presents the overall study design.

[0241] In Part A, approximately 80 subjects are expected to be evaluated in dose-escalation of this study. The dose-escalation portion of this study will be conducted using the modified toxicity probability interval (mTPI) design to evaluate safety and tolerability, and to identify the MTD of SGN-PDL1V. Initially, the dosing schedule tested will be Day 1 and Day 8 of a 21-day cycle (2Q3W). At any time, an alternative dosing schedule (eg, Day 1, Day 8, and Day 15 of a 28-day cycle [3Q4W], Day 1 and Day 15 of a 28-day cycle [2Q4W], or Day 1 of a 21-day cycle [Q3W]) may be activated with additional subjects. The mTPI dose escalation rules will be applied separately to each dosing schedule. Not all alternative dosing schedules will necessarily be evaluated.

[0242] At the completion of dose escalation, dose and schedule optimization (Part B) may be activated to further evaluate different SGN-PDL1V doses and/or schedules recommended from Part A after consultation with the SMC. This part will allow optimization of the dose and schedule that will be recommended for expansion. Subjects of select tumor types who meet the eligibility criteria as described in Part A may be enrolled in Part B. Different doses and schedules in different tumor types may be evaluated in parallel cohorts. Subjects participating in Part B will be randomized to allocate to different dose and schedules with equal probability for a specific tumor type. If, following Part A, there is sufficient evidence to support bringing a dosing schedule forward for SGN-PDL1V, Part B may be omitted, provided at least 6 subjects have been dosed at the recommended dose and schedule.

[0243] FIG. 2 shows preliminary patient data for all subjects in dose escalation (Part A) and dose optimization (Part B). The uORR was 23%. FIG. 3 shows preliminary patient data for HNSCC subjects in dose escalation (≥ 1.25 mg/kg, Part A), where the cORR was 21% and the uORR was 50%.

[0244] Dose expansion (Part C) will be conducted with selected disease-specific cohorts. At the completion of dose escalation (Part A) and dose and schedule optimization (Part B, if necessary), disease-specific cohorts HNSCC independent of PD-L1 expression may be activated by the sponsor in consultation with the SMC. Additional disease-specific cohort for NSCLC independent of the PD-L1 expression may also be activated. An additional signal-seeking cohort of subjects with melanoma, ovarian cancer, triple negative breast cancer (TNBC), gastric cancer, or esophageal squamous cell carcinoma (SCC) may be activated, as well as a biology cohort may also be activated. The dose(s) to be examined in Part C will be at or below the MTD and/or the recommended dose and schedule determined in Parts A and B.

[0245] Combination safety run-in (Part D) will enroll approximately 12 subjects to assess the combination of SGN-PDL1V and pembrolizumab. To evaluate the safety of the combination therapy, an initial 6 subjects will be administered SGN-PDL1V plus pembrolizumab. Dose decisions for subsequent subjects in the cohort will be based on the incidence of DLTs.

[0246] In Part D, the SGN-PDL1V starting dose will be 1 dose level lower than the recommended monotherapy dose identified in Part A and/or B in combination with the standard, approved dose of pembrolizumab in Q3W cycles. Part D will be initiated once a recommended expansion monotherapy dose and schedule is determined to be safe and tolerable by the SMC. If the combination of SGN-PDL1V with pembrolizumab is deemed safe by the SMC, a future protocol amendment may expand this cohort to approximately 40 subjects (Part E). A future protocol amendment may also explore additional combinations.

Tumor Types Included in Dose Escalation (Part A) and Dose and Schedule Optimization (Part B)

[0247] For dose escalation (Part A) and dose and schedule optimization (Part B), subjects must have NSCLC, HNSCC, TNBC, or esophageal SCC. Additionally, all subjects must have

PD-L1 expression ≥ 1 by tumor proportion score (TPS), CPS, or immune cell score (%IC) based on historical testing.

Part A: Dose-Escalation Cohorts

[0248] Approximately 80 subjects are expected to be evaluated in the dose-escalation portion of this trial. Dose escalation will be conducted using the mTPI design to evaluate the safety and tolerability and to identify the MTD and recommended dose of SGN-PDL1V. Safety, PK, pharmacodynamics, biomarker analyses, and preliminary antitumor activity may be used to determine a recommended dose and schedule.

[0249] The mTPI design uses a Bayesian model to compute the posterior probabilities of 3 intervals that reflect the relative distance between the toxicity rate of each dose level to the target dose-limiting toxicity (DLT) rate. Dosing-decision rules are determined for a target DLT rate of 25% with a 5% margin. The 3 intervals will be (0%, 20%), [20%, 30%], and (30%, 100%), and the corresponding dosing decision rules will be:

1. Escalate if the current dose DLT rate is likely <20%,
2. Continue if the current dose DLT rate is likely between 20% and 30%,
3. De-escalate if the current dose DLT rate is likely >30%.

[0250] Dose-finding decisions are shown in Table 2. “E” represents escalating the dose, “S” represents staying at the same dose, and “D” represents de-escalating the dose. Decision “DU” means that the current dose level may be unacceptable because of high toxicity. A dose will be defined as having unacceptable toxicity if the posterior probability that the DLT rate is higher than 25% is more than 95%.

[0251] Enrollment in Part A will occur on a cohort-by-cohort basis. Decisions on dose escalation, dose level modification, and subsequent cohort size will be made by the sponsor in consultation with the SMC. Dose levels will not be skipped. When a dose level is initially being evaluated, subjects in this cohort must be observed for the full duration of the DLT period before enrollment may proceed at a higher dose. Note: For each new dose-escalation cohort recommended for initiation by the SMC, no more than 1 subject should receive treatment within a 24-hour period.

[0252] At least 2 DLT-evaluable (DE) subjects will be treated per dose level until the first DLT is observed. After the first DLT is observed, a minimum of 3 DE subjects per dose level will be required before escalation to all higher doses. Subjects who are considered not evaluable for DLT during Cycle 1 may be replaced. A minimum of 6 DE subjects will be observed at the estimated MTD or recommended dose before it is determined. The MTD will be estimated based on data from all subjects across all evaluated doses. If the MTD is not reached, safety, PK, pharmacodynamics, and biomarker analyses, as well as preliminary antitumor activity, will be used to determine a recommended dose. De-escalation to a lower or intermediate dose level may be performed at any time by the sponsor in consultation with the SMC.

[0253] During dose escalation, additional subjects may be enrolled at tested dose levels deemed tolerable (hereafter referred to as “backfilling”). DLTs observed at lower dose levels will be taken into account with the totality of the data; the SMC will base recommendations for future escalation on the mTPI model for the current and lower dose levels at which DLTs were observed in backfilling subjects.

[0254] Subjects with solid tumors may continue on treatment until progressive disease (PD) per the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), clinical progression, unacceptable toxicity, withdrawal of consent, or study termination, whichever occurs first.

Table 2: Dose Finding Spreadsheet for mTPI Design

	Number of DLT-Evaluable Subjects at Current Dose														
		2	3	4	5	6	7	8	9	10	11	12	13	14	15
Number of DLTs	0	E	E	E	E	E	E	E	E	E	E	E	E	E	E
	1	S	S	S	S	E	E	E	E	E	E	E	E	E	E
	2	DU	D	D	S	S	S	S	S	S	S	S	S	E	E
	3		DU	DU	DU	D	S	S	S	S	S	S	S	S	S
	4			DU	DU	DU	DU	DU	D	S	S	S	S	S	S
	5				DU	DU	DU	DU	DU	DU	D	S	S	S	S
	6					DU	DU	DU	DU	DU	DU	DU	DU	D	S
	7						DU	DU	DU	DU	DU	DU	DU	DU	DU
	8							DU	DU	DU	DU	DU	DU	DU	DU
	9								DU	DU	DU	DU	DU	DU	DU
	10									DU	DU	DU	DU	DU	DU
	11										DU	DU	DU	DU	DU
	12											DU	DU	DU	DU
	13												DU	DU	DU
	14													DU	DU
	15														DU

D=de-escalate to the next lower dose; DLT=dose-limiting toxicity; DU=current dose is unacceptably toxic; E=escalate to the next higher dose; mTPI=modified toxicity probability interval; S=stay at the current dose.

[0255] Initially, SGN-PDL1V will be administered 2Q3W at the dose levels shown in Table 3. At any time, another dosing schedule may be activated (Table 4). The initial dose for the alternative dosing schedule will be the same as the dose cleared in the initial schema as long as the dose intensity is the same or lower. The mTPI dose escalation rules will be applied separately to each dosing schedule. Not all alternative dosing schedules will necessarily be evaluated.

Part B: Dose and Schedule Optimization

[0256] Dose and schedule optimization may be activated to evaluate SGN-PDL1V dosing schedules recommended from Part A after consultation with the SMC. This part will allow optimization of the dose and schedule that will be recommended for expansion. Subjects of select tumor types who meet the eligibility criteria as described in Part A may be enrolled in Part B. Approximately 80 subjects will be evaluated in Part B. Subjects participating in Part

B will be randomized to allocate to different dose and schedules with equal probability for a specific tumor type.

[0257] If, following the completion of Part A, there is sufficient evidence to support bringing a dose and schedule forward, Part B may be omitted, provided at least 6 subjects have been dosed at the recommended dose and dosing schedule. The SMC will make a recommendation, based on data from Parts A and B to the sponsor to bring forward a dose and schedule to be evaluated in Part C and Part D (as well as Part E). The sponsor will make the final decision regarding dose and schedule.

Table 3: Planned Dose Levels

Dose Levels (mg/kg)	Dose intensity at Planned Dose Levels for Each Schedule (mg/kg/week)			
	Initial Schedule	Alternative Schedules		
	2Q3W	3Q4W	2Q4W	Q3W
0.5	0.33	0.38	0.25	0.17
0.75	0.5	0.56	0.38	0.25
1.0	0.67	0.75	0.5	0.33
1.25	0.83	0.94	0.63	0.42
1.5	1.00	1.13	0.75	0.5
1.75	1.17	1.31	0.88	0.58
2.0	1.33	1.5	1.00	0.67
2.25	1.5	1.69	1.13	0.75
2.5	1.67	1.88	1.25	0.83

2Q3W=Days 1, 8 q21 days; 3Q4W=Days 1, 8, 15 q28 days; 2Q4W=Days 1, 15 q28 days; Q3W=Day 1 q21 days.

Table 4: Initial and Alternative Treatment Schedules

	Schedule name	Schedule description	Cycle length (days)	Treatment days		
				Day 1	Day 8	Day 15
Initial schedule	2Q3W	Day 1, 8 q21 days	21	X	X	-
Alternative Schedules	3Q4W	Day 1, 8, 15 q28 days	28	X	X	X
	2Q4W	Day 1, 15 q28 days	28	X	-	X
	Q3W	Day 1 q21 days	21	X	-	-

[0258] Preliminary Results were collected and analyzed for Part A and Part B.

[0259] Table 5 shows that the preliminary baseline characteristics of patients enrolled in the dose escalation and optimization cohorts were consistent with a study population with heavily pre-treated PD-L1+ tumors. Patients received a median of 3 prior lines of treatment.

Table 5. Baseline characteristics of patients

	All Patients Enrolled in Dose Escalation/Optimization Dose Levels*						
Characteristics	0.5 mg/kg (N=2)	0.75 [†] mg/kg (N=4)	1.0 mg/kg (N=6)	1.25 mg/kg (N=33)	1.5 mg/kg (N=37)	1.75 mg/kg (N=12)	Total (N=94)
Age (years), median (min, max)	67.0 (66, 68)	50.0 (36, 57)	57.5 (39, 61)	63.0 (34, 72)	60.0 (24, 78)	56.5 (31, 70)	59.5 (24, 78)
Sex, n (%)							
Male	1 (50.0)	1 (25.0)	3 (50.0)	16 (48.5)	27 (73.0)	9 (75.0)	57 (60.6)
Female	1 (50.0)	3 (75.0)	3 (50.0)	17 (51.5)	10 (27.0)	3 (25.0)	37 (39.4)
ECOG performance status, n (%)							
0	0	1 (25.0)	2 (33.3)	7 (21.2)	10 (27.0)	4 (33.3)	24 (25.5)
1	2 (100)	3 (75.0)	4 (66.7)	26 (78.8)	27 (73.0)	8 (66.7)	70 (74.5)
Disease diagnosis, n (%)							
Head and Neck Squamous Cell Cancer	1 (50.0)	1 (25.0)	4 (66.7)	18 (54.5)	19 (51.4)	7 (58.3)	50 (53.2)
Non-Small Cell Lung Cancer	1 (50.0)	1 (25.0)	1 (16.7)	14 (42.4)	15 (40.5)	3 (25.0)	35 (37.2)
Triple Negative Breast Cancer	0	2 (50.0)	1 (16.7)	1 (3.0)	2 (5.4)	2 (16.7)	8 (8.5)
Esophageal Cancer	0	0	0	0	1 (2.7)	0	1 (1.1)
# prior lines of systemic treatment in recurrent or metastatic settings, median (min, max)	2.5 (2, 3)	1.0 (1, 4)	2.0 (1, 3)	3.0 (1, 6)	3.0 (1, 7)	3.0 (1, 6)	3.0 (1, 7)
Prior treatment in any setting							
CPIs, n (%)	2 (100)	2 (50.0)	4 (66.7)	32 (97.0)	33 (89.2)	11 (91.7)	84 (89.4)
Taxanes, n (%)	1 (50.0)	4 (100)	5 (83.3)	22 (66.7)	28 (75.7)	7 (58.3)	67 (71.3)

(CPI: Check Point Inhibitor; ECOG: Eastern Cooperative Oncology Group)

[0260] Table 6 displays a preliminary summary for adverse events, showing that overall PDL1V had a manageable safety profile, with low amounts of high grade treatment-related AEs. No dose-limiting toxicities or treatment related deaths were seen across all dose levels ranging from 0.5 to 1.75 milligrams per kilogram. As also shown in FIG.4, the majority of treatment-related adverse events (TRAEs) were low-grade (Grade 1/2), with few Grade 3 or 4 events.

Table 6 Occurrence of Adverse Events at the indicated dose levels

	Dose Levels *						
Adverse Events	0.5 mg/kg N=2	0.75 [†] mg/kg N=4	1.0 mg/kg N=6	1.25 mg/kg N=33	1.5 mg/kg N=37	1.75 mg/kg N=12	Total N=94
TEAEs, n (%)	2 (100)	4 (100)	6 (100)	33 (100)	37 (100)	12 (100)	94 (100)

Treatment-related TEAEs, n (%)	2 (100)	2 (50.0)	4 (66.7)	20 (60.6)	29 (78.4)	10 (83.3)	67 (71.3)
≥Grade 3 treatment-related TEAEs, n (%)	1 (50.0)	1 (25.0)	0	2 (6.1)	12 (32.4)	6 (50.0)	22 (23.4)
Serious treatment-related TEAEs, n (%)	1 (50.0)	0	1 (16.7)	3 (9.1)	4 (10.8)	4 (33.3)	13 (13.8)
Treatment discontinue due to treatment-related TEAEs, n (%)	0	0	0	1 (3.0)	3 (8.1)	2 (16.7)	6 (6.4)
TEAEs resulting in dose modification, n (%)	2 (100)	2 (50.0)	1 (16.7)	17 (51.5)	23 (62.2)	7 (58.3)	52 (55.3)
Dose reduction	0	2 (50.0)	0	2 (6.1)	9 (24.3)	6 (50.0)	19 (20.2)
Dose delay	1 (50.0)	2 (50.0)	0	8 (24.2)	14 (37.8)	7 (58.3)	32 (34.0)
Dose elimination	1 (50.0)	1 (25.0)	0	7 (21.2)	11 (29.7)	1 (8.3)	21 (22.3)

* Day 1, 8 of 21-day Cycles using adjusted ideal body weight. AE: adverse event; DLT: dose-limiting toxicity; TEAE: treatment-emergent adverse event

[0261] FIG.5 shows that across clinically active dose levels (1.25 mg/kg-1.75 mg/kg) with dosing on day-1 and day-8 of a 21-day cycle, there is negligible accumulation of PDL1V; terminal elimination half-life is about 3.8 day. As shown FIG.5, antibody-conjugated MMAE (left panel) and unconjugated MMAE (right panel) showed pharmacokinetics that were dose-proportional at active dose levels.

[0262] FIG.6 shows preliminary patient data for all subjects in dose escalation (Part A) and dose optimization (Part B). Tumor reductions were seen across tumor types with the largest reduction seen in patients with NSCLC and HNSCC indicated by the green circles and purple triangles. Evidence of activity was observed at active dose levels of 1.25 mg/kg or higher. Table 7 shows that across tumor types, there appeared to be a dose-response relationship with higher confirmed objective response rates (cORR) observed at higher dose levels.

Table 7 Response Rates at the indicated dose levels

	Dose Levels*		
	1.25 mg/kg N=33	1.5 mg/kg N=37	1.75 mg/kg N=12
Confirmed Response per RECIST v.1.1 Assessed by Investigator (%)			
ORR	12.1	18.9	25.0
DCR	63.6	62.2	66.7
Best Overall Response per RECIST v.1.1 Assessed by Investigator (%)			
CR	6.1	0	0
PR	6.1	18.9	25.0
SD	51.5	43.2	41.7
PD	21.2	27.0	33.3
NE/NA	15.2	10.8	0

[0263] Table 8 also shows that cORR was observed across varying levels of PD-L1 expression of NSCLC and HNSCC. FIG.7 shows the clinical response across active doses was durable with the median duration of response of 7.9 months. The median follow up of the patients was 9.4 months.

Table 8 Response Rates in Patients with NSCLC or HNSCC with the indicated PDL-1 Expression

Number of Patients with Confirmed Response by PD-L1 Expression Per Local Testing			
NSCLC (Tumor proportion score)	1 to 49 (N=14)	>50 (N=17)	Unknown (N=1)
PRs	3	3	1
HNSCC (Combined positive score)	1 to 19 (N=18)	>20 (N=21)	Unknown (N=5)
CRs/PRs	3	2	2

[0264] As shown in Table 9, with NSCLC on the left panel and HNSCC on the right panel, the cORR was generally observed at the higher dose levels in both tumor types. The

best overall response (ORR) was observed at 1.5 mg/kg for NSCLC. In HNSCC, the highest response was observed at 1.75 mg/kg D1, D8 every 21-day schedule. However, because frequent dose modifications were needed at this dose level, exploration of 1.75 mg/kg every other week is ongoing. Expansion cohorts were also initiated at 1.5 mg/kg D1, D8 every 21 days in both NSCLC and HNSCC.

Table 9 PDL1V Antitumor Activity in NSCLC and HNSCC

	Dose Levels*					
	NSCLC			HNSCC		
	1.25 mg/kg N=14	1.5 mg/kg N=15	1.75 mg/kg N=3	1.25 mg/kg N=18	1.5 mg/kg N=19	1.75 mg/kg N=7
Confirmed Response per RECIST v.1.1 Assessed by Investigator (%)						
ORR	14.3	33.3	0	11.1	10.5	42.9
DCR	78.6	66.7	100	55.6	63.2	71.4
Best Overall Response per RECIST v.1.1 Assessed by Investigator (%)						
CR	0	0	0	11.1	0	0
PR	14.3	33.3	0	0	10.5	42.9
SD	64.3	33.3	100	44.4	52.6	28.6
PD	7.1	20.0	0	27.8	26.3	28.6
NE/NA	14.3	13.3	0	16.7	10.5	0

[0265] For the 32 patients with PD-L1+ NSCLC, FIG.8 shows that antitumor activity was observed across different histologic subtypes, specifically, in adenocarcinoma (~69% of the samples), adenosquamous (marked with a dark green diamond) and squamous histologies (marked with an orange diamond). Furthermore, FIG.9 shows that these clinical responses were durable with a median duration of response of 5.6 months. Of the 32 Patients, the best cORR (33.3%) was seen in the patients who received 1.5 mg/kg (2Q3W), which was determined to be a recommended dose moving forward into the dose expansion phase of this study

[0266] Overall, the investigator-assessed objective response rate (ORR) across all doses and tumor types was 27.3% (12.7% confirmed), and the median duration of confirmed responses was 7.9 months. Objective responses were observed starting at 1.25 mg/kg and

independent of PDL1 expression. In particular, clinically meaningful and durable responses were observed in patients with heavily pretreated NSCLC and HNSCC.

Part C: Dose Expansion

[0267] There are 2 dose expansion cohorts (Part C) along with a signal-seeking cohort and a biology cohort that may be activated after determination of the MTD, or recommended dose is identified. Approximately 150 subjects will be treated in disease-specific expansion cohorts at or below the MTD or recommended dose to further characterize the safety, tolerability, PK, and antitumor activity of SGN-PDL1V.

[0268] Part C cohorts may include:

- Subjects with HNSCC independent of PD-L1 expression (approximately 40 subjects),
- Subjects with NSCLC independent of PD-L1 expression (approximately 40 subjects),
- A signal-seeking cohort with ovarian cancer, TNBC, gastric cancer, or esophageal SCC or melanoma (approximately 40 subjects).
- A biology cohort: Subjects (approximately 30 subjects) in the biology cohort with NSCLC and HNSCC with negative PD-L1 expression, melanoma, ovarian cancer, TNBC, gastric cancer, or esophageal SCC will be gated based on data generated from other cohorts and will require additional biopsies be asked to provide additional tissue to enable biomarker studies of SGN-PDL1V, comparing pre- and post-treatment tumor samples to characterize the clinical MOA and correlates of sensitivity/resistance at the MTD or recommended dose. Subjects enrolled in the biology cohort must have tumor present at appropriate, accessible, and feasible biopsy sites.

[0269] For each expansion cohort with a planned sample size of approximately 40 subjects, an interim analysis (IA) will be conducted after approximately 15 subjects are evaluable for response, while the enrollment is uninterrupted. A futility assessment will be performed using the predictive probability of success (PPoS) method with success being defined as having more than 0.80 posterior probability that the response rate is greater than the background response rate. If the estimated PPoS given the interim data is <10%, the sponsor in consultation with the SMC may decide to stop further enrollment of the cohort after careful assessment of the totality of data.

Part D: Combination Safety Run-in

[0270] Part D is designed to evaluate the safety and tolerability of SGN-PDL1V in combination with pembrolizumab. Approximately 12 subjects will be enrolled in the safety run-in cohort.

[0271] SGN-PDL1V will be administered starting at 1 dose level lower than the recommended monotherapy expansion dose and schedule determined by the sponsor and in consultation with the SMC based on the results from Parts A and B.

[0272] In order to evaluate safety of this combination, an initial 6 subjects will be administered SGN-PDL1V plus pembrolizumab. Safety will be evaluated by the incidence of DLTs. Dose decisions will be made using the following rules:

1. The starting dose for the initial 6 subjects will be 1 dose level lower than the recommended expansion dose identified in Part A and/or B plus 200 mg pembrolizumab Q3W.
 - i. If 0 or 1 of the initial 6 subjects experience a DLT, 6 additional subjects will receive SGN-PDL1V at the recommend expansion dose plus 200 mg pembrolizumab Q3W.
 - ii. If 2 or more of the initial 6 subjects (described in 1) experience a DLT, the SMC will conduct further data review and recommend whether approximately 6 additional subjects will receive SGN-PDL1V at 2 dose levels lower than the recommended monotherapy expansion dose plus 200 mg pembrolizumab Q3W or if the combination may be considered for closure.

Duration of Treatment

[0273] Subjects may continue on treatment with SGN-PDL1V until PD per RECIST v1.1 (Parts A, B and C) or confirmed PD per iRECIST (Part D only), unacceptable toxicity, clinical progression, start of subsequent therapy, withdrawal of consent, death or study termination, whichever occurs first. In Part D, 200 mg pembrolizumab will only be administered in combination with SGN-PDL1V at Q3W dosing schedule for up to 35 administrations (approximately 2 years). If subjects in Part D discontinue any study drug for any reason, the subjects will be considered as discontinued from both study treatments.

Dose-Limiting Toxicity

[0274] DLTs will be evaluated during dose escalation in Part A for monotherapy, and for combination therapy in Part D. The DLT evaluation period will be the first cycle (21 days or 28 days). A DLT is defined as any of the below criteria related to SGN-PDL1V monotherapy or in combination with pembrolizumab, that cannot be attributed to pembrolizumab alone, during the DLT evaluation period, excluding toxicities clearly related to disease progression or intercurrent illness. Grading will be according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0:

- Grade 5 toxicity
- $\geq$ Grade 3 or 4 non-hematologic toxicity (not laboratory), with the following exceptions:
 - Grade 3 fatigue or constipation that resolves within 72 hours, with or without intervention
 - Grade 3 nausea/vomiting or diarrhea for ≤ 72 hours with adequate antiemetic and other supportive care
 - Grade 3 IRRs regardless of duration
Note: In the event of a Grade 3 IRR in $\geq 20\%$ of subjects (ie, 2 or more in the first 10 subjects), all subsequent subjects will require premedication and/or modification of infusion approach per the recommendation of the SMC and the protocol will be amended. For subsequent subjects, any $\geq$ Grade 3 IRR will be considered a DLT.
- Grade 3 or higher electrolyte/non-hematologic laboratory abnormality, with the following exception: lasts ≤ 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions.
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia lasting > 7 days
- Grade 4 anemia
- Grade 4 hematologic toxicity (other than anemia) lasting > 7 days
- $\geq$ Grade 3 febrile neutropenia
- Dose delay ≥ 14 days due to toxicity

Rationale for Study Design

[0275] This is first in human (FIH), phase 1 study, includes dose-escalation (Part A), dose and schedule optimization (Part B), dose-expansion with signal-seeking and biology cohorts (Part C), and combination therapy with pembrolizumab (Part D) to evaluate the safety and tolerability of SGN-PDL1V initially administered on 2Q3W, and to estimate the MTD and/or

determine a recommended dose and schedule in subjects with selected advanced solid tumors. Initial clinical development of SGN-PDL1V will involve its evaluation in subjects who have no appropriate standard therapeutic options and are candidates for SGN-PDL1V administration in the opinion of the treating physician. Dose escalation will be used to estimate the MTD and/or determine a recommended dose or schedule for SGN-PDL1V. Safety evaluation may include type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities, incidence of DLTs, and detection of antidrug antibodies (ADAs). Part B to optimize the dose and schedule may be opened and may enroll approximately 80 subjects.

[0276] Once expansion dose and schedule are selected by the SMC, dose expansion (Part C) with up to 4 disease-specific expansion cohorts and a combination safety run-in (Part D) with SGN-PDL1V in combination with pembrolizumab (FIG.1), may be enrolled.

Rationale for Selection of Doses

[0277] The starting dose of 0.5 mg/kg for SGN-PDL1V was based on data from a GLP nonclinical toxicology study in cynomolgus monkeys and was considered to be a reasonable starting dose likely to result in minimal toxicities associated with MMAE delivery by SGN-PDL1V while having the potential for pharmacologic activity, consistent with ICH S6 and S9 guidance documents. Subsequent dose levels used in Parts C and D will be based on clinical data from Parts A and/or B and based on SMC recommendation.

[0278] The planned dose of pembrolizumab in Part D of this study is 200 mg Q3W, which is an approved dose of pembrolizumab for adults across all indications (see pembrolizumab IB/Product Information).

SELECTION AND WITHDRAWAL OF SUBJECTS

[0279] Subjects must meet all of the eligibility criteria to be enrolled in this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of a good clinical practice audit and/or health regulatory authority inspection.

Inclusion Criteria

1. The subject must provide written informed consent.
1. Tumor types:
 - i. Dose-escalation (Part A) and dose and schedule optimization (Part B):
 - Subjects must have histologically- or cytologically-confirmed metastatic or unresectable HNSCC, NSCLC, TNBC, or esophageal SCC.
 - Subjects must have disease that is relapsed or refractory, that has progressed on approved therapies, be intolerant to or refused such therapies, or such therapies are contraindicated and in the judgment of the investigator, should have no appropriate SoC therapeutic option. If a SoC therapy is available that has not been administered, the reason that the therapy is not appropriate (eg, intolerance or refusal) must be documented.
 - Subjects in France may only be eligible after experiencing PD following treatment with local SoC or if they had an intolerance to available therapies.
 - All subjects in dose escalation must have PD-L1 expression ≥ 1 by TPS, CPS, or % IC based on historical testing.
 - For subjects with locally advanced/metastatic NSCLC, determination of tumor genomic alterations for which there are approved and available targeted agents, including but not limited to sensitizing epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangements and ROS1 arrangements must be determined prior to enrollment.
 - Subjects with such tumor genomic aberrations must have received approved mutation-specific targeted therapies and experienced PD, unless contraindicated or the subject experienced intolerance due to toxicity.
 - Subjects who do not have tumor genomic alterations for which there are approved targeted agents must have received anti-PD-1 or anti-PD-L1 therapy, if available, and a platinum-based chemotherapy doublet regimen, either concurrently or sequentially, and progressed on those regimens unless the treatment is contraindicated or the subject experienced intolerance due to toxicity.
 - Subjects with HNSCC must have received anti-PD-1 therapy, if available, and a platinum-based chemotherapy regimen, either concurrently or sequentially, and progressed on those regimens unless the treatment is contraindicated or the subject experienced intolerance due to toxicity.

- Tumor tissue is required for enrollment. Archival tumor tissue collected at <24 months of enrollment is requested. If archival tissue is not available, a newly obtained biopsy must be submitted.

ii. Dose expansion (Part C):

Subjects must have disease that is relapsed or refractory or be intolerant to SoC therapies as specified below, unless contraindicated:

- **HNSCC; independent of PD-L1 expression.**

- Subjects must have histologically or cytologically-confirmed HNSCC.
 - Primary tumor site must arise from the oral cavity, oropharynx, hypopharynx, nasopharynx, or larynx.
 - Subjects must have received prior anti-PD-1 therapy, if eligible, and have received a platinum-based chemotherapy regimen, either concurrently or sequentially, and progressed on them unless the treatment is contraindicated or the subject experienced intolerance due to toxicity. Subjects have not received >1 prior line of cytotoxic therapy in the locally advanced or metastatic setting. Platinum regimens administered as part of multimodal therapy in the curative setting would count as a regimen if relapse occurred ≤6 months after completion.
- Subjects must have been previously tested for PD-L1 expression and should have PD-L1 expression ≥1 or <1 by TPS or CPS based on historical testing.
- Tumor tissue is required for enrollment. The most recent archival tumor tissue collected at <24 months of enrollment is requested. If archival tissue is not available, a newly obtained biopsy must be submitted.

- **NSCLC; independent of PD-L1 expression:**

- Subjects must have histologically or cytologically confirmed NSCLC (Stage IIIB, IIIC, IV). Subjects with both SCC and non-SCC histology are eligible. Note: Subjects with a neuroendocrine component or histology are not eligible.
- For subjects with NSCLC, determination of tumor genomic alterations for which there are approved and available targeted agents, including but not limited to sensitizing EGFR mutations, ALK rearrangements and ROS1 arrangements must be determined prior to enrollment.
 - Subjects with such tumor genomic aberrations must have received no more than 2 approved mutation-specific targeted therapies and experienced PD, unless contraindicated or the subject experienced intolerance due to toxicity. Subjects may also have received up to 1 PD-L1 or anti-PD-1 therapy (concurrently or sequentially with platinum-based chemotherapy).
 - For subjects who do not have tumor genomic alterations for which there are approved targeted agents must have received anti PD-1 or anti PD-L1 therapy, if available, and a platinum-based

chemotherapy regimen, either concurrently or sequentially and progressed/relapsed on them unless the treatment is contraindicated or the subject experienced intolerance due to toxicity. Subjects must not have received >2 prior lines of cytotoxic therapy. Subject who progressed or relapsed ≤ 6 months of the last dose of platinum-based therapy in the adjuvant, neoadjuvant, or concomitant chemoradiation regimen for early-stage or locally advanced stage disease, may be eligible.

- Subjects must have been previously tested for PD-L1 expression and should have PD-L1 expression ≥ 1 or < 1 by CPS or TPS based on historical testing.
 - Tumor tissue is required for enrollment. The most recent archival tumor tissue collected at <24 months of enrollment is requested. If archival tissue is not available, a newly obtained biopsy must be submitted.
 - **Signal-seeking cohort:**
 - Subjects with TNBC, ovarian cancer, esophageal SCC, gastric cancer, or melanoma.
 - Subjects must have disease that is relapsed or refractory, that has progressed on approved therapies, be intolerant to or refused such therapies, or such therapies are contraindicated and in the judgment of the investigator, should have no appropriate SoC therapeutic option. If an SoC therapy is available that has not been administered, the reason that the therapy is not appropriate (eg, intolerance or refusal) must be documented.
 - Subjects in France may only be eligible after experiencing PD following treatment with local SoC or if they had an intolerance to available therapies.
 - Tumor tissue is required for enrollment. The most recent archival tumor tissue collected at <24 months of enrollment is requested. If archival tissue is not available, a newly obtained biopsy must be submitted.
 - **Biology cohort:**
 - Subjects with NSCLC and HNSCC with negative PD-L1 expression, TNBC, esophageal SCC, melanoma, gastric cancer or ovarian cancer who meet the criteria noted above for dose expansion.
 - No specific number of subjects per tumor type.
 - Subjects must have accessible tumors for multiple (up to 3) fresh biopsies.
 - Fresh baseline biopsy is required, if feasible; an on-treatment biopsy from same lesion as the predose biopsy is required, if feasible (Cycle 1 only); a fresh biopsy of any lesion demonstrating progression is required, if feasible.
- iii. Combination (Part D):
- **Safety run-in:**
 - Subjects must have histologically or cytologically-confirmed disease of the HNSCC.

- Primary tumor site must arise from the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx.
 - Subjects must not have received anti-PD-1 or PD-L1 therapies or other immunotherapy agents.
 - Subjects must have not received prior lines of cytotoxic therapy in the metastatic setting. Cytotoxic therapy can be used only in the adjuvant/neoadjuvant setting if subject's disease progressed or relapsed 6 or more months after the last dose.
 - Subjects must have PD-L1 expression by TPS or CPS ≥ 1 based on historical local testing.
 - Tumor tissue is required for enrollment. The most recent archival tumor tissue collected at < 24 months of enrollment is requested. If archival tissue is not available, a newly obtained biopsy must be submitted.
- 2. Be at least 18 years of age, and legally an adult at time of consent and $\geq$ the age of majority per regional requirements.
- 3. An Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1.
- 4. Measurable disease per RECIST v1.1 at baseline.
- 5. The following baseline laboratory data:
 - absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$
 - hemoglobin (Hgb) ≥ 9 g/dL
 - platelet count $\geq 100,000/\mu\text{L}$
 - serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) or $\leq 3 \times$ ULN for subjects with Gilbert's disease
 - estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73 m² using the Modification of Diet in Renal Disease (MDRD) study equation and multiplying by body surface area (BSA) as applicable.
 - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 3 \times$ ULN ($\leq 5 \times$ ULN if there is evidence of hepatic involvement by malignant disease)
- 6. Subjects of childbearing potential, under the following conditions:
 - i. Must have a negative serum or urine pregnancy test (minimum sensitivity 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β -hCG]) result within 7 days prior to the first dose of SGN-PDL1V. Subjects with false positive results and documented verification that the subject is not pregnant are eligible for participation.
 - ii. Must agree not to try to become pregnant during the study and for at least 2 months after the final dose of SGN-PDL1V and 4 months after the final dose of pembrolizumab (Part D only).
 - iii. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 2 months after the final dose of SGN-PDL1V and 4 months after the final dose of pembrolizumab (Part D only).

- iv. If sexually active in a way that could lead to pregnancy, must consistently use at least 2 acceptable methods of birth control (contraception), at least 1 of which must be highly effective starting at time of informed consent and continuing throughout the study and for at least 2 months after the final dose of SGN-PDL1V and 4 months after the final dose of pembrolizumab (Part D only).
- 7. Subjects who can get someone pregnant, under the following conditions:
 - i. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 4 months after the final dose of study drug.
 - ii. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use at least 2 acceptable methods of birth control (contraception), at least 1 of which must be highly effective starting at time of informed consent and continuing throughout the study and for at least 4 months after the final dose of study drug.
 - iii. If sexually active with a person who is pregnant or breastfeeding, must consistently use a condom starting at time of informed consent and continuing throughout the study and for at least 4 months after the final dose of study drug.

Exclusion Criteria

1. History of another malignancy within 3 years before the first dose of SGN-PDL1V, or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (eg, 5-year overall survival [OS] $\geq 90\%$), such as adequately-treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.
2. Known active central nervous system metastases. Subjects with previously-treated brain metastases may participate provided they are clinically stable for at least 4 weeks prior to study entry after brain metastasis treatment, they have no new or enlarging brain metastases, and are off of corticosteroids prescribed for symptoms associated with brain metastases for at least 7 days prior to the first dose of SGN-PDL1V.
3. Leptomeningeal disease.
4. Prior treatment with an anti-PD-L1 agent (where indicated per protocol) within less than 5 half-lives (refer to Table 10).

Table 10: Washout Periods for Prior Anti-PDL1 Treatment

Anti-PDL1 Agent	Prior Treatment Washout Period (Months)
Atezolizumab	4.5
Durvalumab	3
Avelumab	1

Note: If subject has been exposed to an anti-PDL1 agent not listed above, contact the medical monitor to obtain the washout period.

5. Previous receipt of an MMAE-containing agent.
6. Pre-existing neuropathy $\geq$ Grade 2 per NCI CTCAE v5.0.

7. Active viral, bacterial, or fungal infection of any grade (per the NCI CTCAE, Version 5.0) within 2 weeks prior to the first dose of SGN-PDL1V, unless deemed not clinically significant by the investigator (eg, onychomycosis). Routine antimicrobial prophylaxis is permitted.
8. Known or suspected autoimmune disease or significant autoimmune-related toxicity from prior immune-oncology-based therapy that is currently active, has not fully resolved, or is at risk of recurrence.
9. Uncontrolled diabetes mellitus, defined as Hgb A1c $\geq 8\%$ or Hgb A1c between 7% and $<8\%$ with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.
10. Known to be positive for hepatitis B by surface antigen expression. Known to have active hepatitis C infection (positive by polymerase chain reaction [PCR] or on antiviral therapy for hepatitis C within the last 6 months). Subjects who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks.
11. Known to be positive for human immunodeficiency virus (HIV).
12. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, congestive heart failure, or cardiac symptoms consistent with New York Heart Association Class III-IV within 6 months prior to their first dose of SGN-PDL1V.
13. History of noninfectious ILD or pneumonitis that required steroids, current ILD or pneumonitis, $\geq$ Grade 3 pulmonary disease unrelated to underlying malignancy, prior radiation therapy to the lung that is >30 Gy within 6 months of the first dose of study treatment and known diffusing capacity of the lung for carbon monoxide [DLCO]; adjusted for hemoglobin $<50\%$ predicted. Subjects with chronic obstructive pulmonary disease (COPD) are eligible if not requiring supplemental oxygen or systemic corticosteroids >10 mg daily prednisone or equivalent.
14. Treatment with strong inducers or inhibitors of cytochrome P450 3A (CYP3A) within 14 days prior to first dose of SGN-PDL1V.
15. Chemotherapy, immunotherapy, biologics, and/or other approved or investigational antitumor treatment (where indicated per protocol) that is not completed 4 weeks prior to first dose of SGN-PDL1V, or within 2 weeks prior to the first dose of SGN-PDL1V if the underlying disease has progressed on treatment.
16. Focal radiotherapy or major surgery that is not completed 2 weeks prior to the first dose of SGN-PDL1V.
17. Subjects who are breastfeeding, pregnant, or planning to become pregnant from time of informed consent until 2 months after final dose of SGN-PDL1V and 4 months after the final dose of pembrolizumab (Part D only).
18. Known hypersensitivity to any excipient contained in the drug formulation of SGN-PDL1V or pembrolizumab.
19. Estimated life expectancy <12 weeks in the opinion of the investigator.
20. Subjects who received live vaccines within 30 days of first dose of SGN-PDL1V.

21. Other serious underlying medical condition that, in the opinion of the investigator, would impair the subject's ability to receive or tolerate the planned treatment and follow-up.
22. Any toxicity associated with prior therapy that has not returned to baseline or that is >Grade 1, with the exception of alopecia.

Parts C and D only:

23. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
24. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

TREATMENT OF SUBJECTS

Treatments Administered

[0280] All subjects will receive SGN-PDL1V, the investigational agent under study in this protocol. Subjects in Part D will also receive pembrolizumab. Administration of the combination agents must begin with IV dosing of pembrolizumab first followed by SGN-PDL1V. At least 30 minutes should have elapsed after completion of administration of pembrolizumab before the administration of the SGN-PL1V can be initiated. All doses will be administered as an IV infusion.

Dose and Administration

[0281] SGN-PDL1V will initially be administered on 2Q3W cycles by IV infusion. An alternative frequency of dosing, that may be evaluated in Part B, such as dosing on Q3W, 2Q4W, or 3Q4W may be implemented if recommended by the SMC. SGN-PDL1V should not be mixed with other medications.

[0282] Dosing will be based on adjusted ideal body weight (AIBW). AIBW may reduce SGN-PDL1V pharmacokinetic variability across body weight groups by increasing exposure in low body weight subjects and reducing exposure in high body weight subjects, thereby mitigating the risks of potential under-dosing and over-dosing across all body weights. AIBW provides adjustment to ideal body weight (IBW) when the subject's actual total body weight (TBW) differs from their IBW. Since AIBW is calculated using subjects' gender, height, and TBW, the percent adjustment to total dose will depend on the body mass index (BMI) groups.

[0283] During dose escalation in Part A, on Cycles 1, 2, and 3 on Day 1, subjects will be observed in the clinic for at least 4 hours after completion of SGN-PDL1V administration. Additional monitoring for subsequent cycles will be considered upon review of safety data with the SMC. During dose and schedule optimization in Part B the observation period will only be required on Cycle 1, Day 1 and may be reduced to 2 hours if the SMC determines that safety is adequate after review of data from the dose escalation cohorts.

[0284] Infusion duration will vary depending on the method of infusion administration and the dose. Please refer to the Pharmacy Binder for further details. The initial approach to SGN-PDL1V administration will be stepwise infusion. In a stepwise infusion, the infusion

rate is increased at set time intervals until a defined maximum rate of infusion is reached. The first infusion of SGN-PDL1V will be initiated at a rate of 50 mg/hour. If the first 30 minutes is well tolerated, the rate will be incrementally increased (no greater than 2-fold increase in rate) every 30 minutes as tolerated until a maximum rate (800 mg/hour) is reached. With subsequent infusions, the infusion rate may be increased more rapidly in shorter time intervals: eg, after the first 15 minutes, the rate can be incrementally increased (no greater than 2-fold increase in rate) every 15 minutes as tolerated until the maximum rate is reached.

[0285] As clinical experience with stepwise infusions evolves, the maximum rate may be increased or decreased based on accumulating safety data and/or recommendations of the SMC; the SMC may also recommend a longer or shorter total duration of infusion.

Alternative approaches to SGN-PDL1V administration may be also evaluated. This may include systematic implementation of strategies such as changing the planned infusion duration, administration at a fixed infusion rate, divided-dose administration, weight-capped dose administration, flat dose administration, or change in pre-medications. See the Pharmacy Binder for details. Any substantial changes to SGN-PDL1V dosing or administration will only be implemented after approval by the regulatory authority as appropriate per local regulatory requirements.

[0286] If an individual subject does not tolerate the infusion, the infusion duration for that subject may be increased; the infusion duration in subsequent infusions may also be increased per investigator discretion upon consultation with the medical monitor. Conversely, if a subject tolerates consecutive infusions without IRR Grade >1, the infusion duration may be shortened (ie, administered at a faster rate) at the discretion of the investigator upon consultation with the medical monitor, the implementation of which may be dose-cohort specific.

[0287] 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.

Weight-Capped Dose Administration

[0288] As PK, pharmacodynamics, and clinical activity data evolve, weight-capped IV dose administration may be implemented upon SMC recommendation. In contrast to weight-based dosing, in which the total dose is calculated with no upper limit on subject

weight, weight-capped dosing limits the weight to be used for the total dose calculation. The upper limit to be used in dose calculation is to be defined based on emerging data.

[0289] For example, if the weight cap is 100 kg, a subject with body weight ≥ 100 kg will use a weight of 100 kg to calculate the total dose to be administered. In a subject with body weight < 100 kg, the total dose to be administered is calculated using the subject's actual weight.

Weight-Based Dose Administration

[0290] Weight-based dosing is based on the subject's actual body weight, or per institutional standards. Doses must be adjusted for subjects who experience a $\geq 10\%$ change in weight from baseline. Subject weight must be measured during all relevant assessment windows as described in the schedule of events. Other dose adjustments for changes in body weight are permitted per institutional standard. Rounding to the nearest whole number of milligrams is permissible within 5% of the nominal dose.

Dose Modifications

[0291] For SGN-PDL1V, dose reductions or dosing interval lengthening for toxicity, including DLT, may be considered on a per-subject basis in consultation with the medical monitor. On a per-subject basis, dose modifications for toxicity, including DLT, may be allowed upon consultation with the medical monitor (Table 11). For subjects treated at the lowest dose level, the dose may be lowered to 25% of the most recently administered dose, the dosing frequency may be decreased (eg, if initial dosing is 2Q3W, dosing may be altered to Q3W), or the subject may be discontinued from treatment. Subjects who experience DLT in Cycle 1 should not receive further treatment with SGN-PDL1V unless toxicity is adequately managed and after consultation with the medical monitor. The type and severity of the AE observed will inform the decision. For subjects treated at the lowest dose level, the dose may be lowered to 25% of the most recently administered dose, the dosing frequency may be decreased, or the subject may be discontinued from treatment.

[0292] If a subject has a clinically significant, unresolved treatment-emergent adverse event (TEAE) on the next schedule dosing day of Cycle 1 or beyond, the next dose may be delayed for up to 7 days. Delays due to other reasons or lasting > 7 days must be discussed

with the medical monitor. Subjects requiring a dose delay >7 days due to an unresolved TEAE may be dosed in subsequent cycles at a reduced dose or the dosing frequency may be decreased upon discussion with the medical monitor.

[0293] During the DLT period (Cycle 1), growth factor and transfusion support is discouraged unless medically indicated; subjects who receive growth factor (eg, G-CSF or GM-CSF) or transfusion support during this period for reasons other than DLT may not be evaluable for DLT in Parts A and D. Consideration should be given for growth factor support for prophylaxis or treatment of cytopenias in subsequent cycles. Discontinuation, decreasing the dosing frequency, or dose reduction to 1 dose level below the current dose may be considered for subjects with recurrent Grade 4 neutropenia despite the use of growth factors. Table 11 describes the recommended dose modifications for study treatment-associated toxicity. Medical monitor consultation is required for continued study treatment after occurrence of a $\geq$ Grade 3 AE potentially associated with SGN-PDL1V treatment.

Table 11: Recommended dose modifications for SGN-PDL1V-associated toxicity

Toxicity	Grade 1	Grade 2	Grade 3 ^a	Grade 4 ^d
Non-hematologic (except peripheral neuropathy and elevated blood glucose) ^c	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity resolves to $\leq$ Grade 1 or baseline, then resume treatment at the next lower dose level ^b	Discontinue treatment. In consultation with the medical monitor, treatment may continue. If treatment is continued, withhold dose until toxicity resolves to $\leq$ Grade 1 or baseline, then resume treatment at the next lower dose level. If the AE recurs $>$ Grade 3, discontinue treatment.
Peripheral neuropathy	Continue at same dose level	Withhold until toxicity resolves to $\leq$ Grade 1; then resume treatment at the next lower dose level	If, after evaluating the subject, the investigator, in consultation with the medical monitor, agree that the benefit-risk assessment remains favorable, withhold dose until toxicity resolves to $\leq$ Grade 1 and then resume treatment at the next lower dose level ^b , otherwise discontinue treatment.	Discontinue treatment
Hyperglycemia	Recommend withholding dose for blood glucose >250 mg/dL or >13.9 mmol/L. Subjects with diabetes or other confounding factors who have a higher blood glucose level may be allowed to receive the dose per investigator clinical judgement in consultation with the medical monitor. Resume treatment once elevated blood glucose has improved to a lesser			

Toxicity	Grade 1	Grade 2	Grade 3 ^a	Grade 4 ^d
	value required for dose interruption ≤ 250 mg/dL or ≤ 13.9 mmol/L and subject is clinically and metabolically stable			
Hematologic ^d	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity resolves to $\leq$ Grade 1 or baseline (without transfusion), then resume treatment at same dose level or consider reduction by one dose level^b. For asymptomatic anemia withhold dose until toxicity resolves to $\leq$ Grade 2 or baseline (without transfusion), then resume treatment at same dose level or consider reduction by one dose level^b. For neutropenia, strongly consider growth factor support, then resume treatment at the same dose level or consider reduction by one dose level^b. Prophylactic growth factor support should be strongly considered for subsequent cycles.	Withhold until toxicity resolves to $\leq$ Grade 1 or baseline (for febrile neutropenia withhold until complete resolution), then resume treatment with reduction by one dose level or permanently discontinue. For neutropenia, strongly consider growth factor support (for febrile neutropenia of any grade, growth factor support is required), then resume treatment with reduction by one dose level^b or permanently discontinue. Prophylactic growth factor support is required for all subsequent cycles.
Pneumonitis/ILD	For Radiographic changes only: Consider withholding study treatment Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults, and microbiologic evaluation For follow-up management: Re-assess at least 3 weeks. If worsens: Treat as Grade 2 or Grade 3 to Grade 4	For mild to moderate new symptoms: Withhold study treatment Pulmonary and Infectious Disease consults, and microbiologic evaluation Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	Severe new symptoms; New/worsening hypoxia; Initial Management: Permanently discontinue study treatment. Hospitalize Pulmonary and Infectious Disease consults, and microbiologic evaluation 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	Life-Threatening: Initial Management: Permanently discontinue study treatment. Hospitalize Pulmonary and Infectious Disease consults, and microbiologic evaluation 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy For follow-up management: If improves to $\leq$ Grade 1: Taper steroids over at least 1 month. If not improving after 48 hours or worsening: Add additional

Toxicity	Grade 1	Grade 2	Grade 3 ^a	Grade 4 ^d
		Consider bronchoscopy, lung biopsy For follow-up management: Re-assess every 1 to 3 days if improves: When symptoms return to $\leq$ Grade 1, taper steroids over at least 1 month, and then resume study treatment following steroids taper. If not improving after 2 weeks or worsening: Treat as Grade 3 to Grade 4.	Consider bronchoscopy, lung biopsy For follow-up management: If improves to $\leq$ Grade 1: Taper steroids over at least 1 month. If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).	immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).

For subjects at or below dose level 2, resume treatment at 50% of the most recently administered dose. If the subject has their dose reduced twice for the same AE (other than neutropenia) and this AE recurs, treatment must be permanently discontinued.

AE=adverse event; ILD=interstitial lung disease; IV=intravenous; IRR=infusion related reactions

a Continued study treatment after occurrence of a $\geq$ Grade 3 AE potentially associated with SGN-PDL1V treatment may continue after consultation with the medical monitor.

b If toxicity recurs at Grade 3 (or Grade 4 for neutropenia) despite dose reduction, the dosing frequency may be decreased after consultation with the medical monitor.

c If a subject experiences a Grade 4 IRR, allergic reaction, or anaphylaxis, SGN-PDL1V must be permanently discontinued.

d For all grades of febrile neutropenia, follow dose modification guidance for Grade 4 hematologic toxicity.

[0294] Intrасubject dose escalation may be permitted only if the subject meets protocol criteria for receiving the next cycle of SGN-PDL1V, $\leq$ Grade 2 toxicity was observed during the previous treatment cycle, and in the opinion of the investigator, the subject may have a clinical benefit from the dose escalation. The maximal intrасubject dose escalation level should be 1 level below or at the current actively enrolling level. Additional treatment cycles may be administered at the discretion of the investigator and upon discussion with the medical monitor at a dose and schedule previously considered to be safe by the SMC.

Pembrolizumab

Description of Pembrolizumab

[0295] In order to evaluate safety of this combination, an initial 6 subjects will be administered SGN-PDL1V plus pembrolizumab. Safety will be evaluated by the incidence of DLTs. 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.

[0296] Pembrolizumab will be supplied as a 100 mg/4 mL (25 mg/mL) solution in a single-use vial. Pembrolizumab for 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, polysorbate, sucrose, and WFI USP.

Dose and Administration

[0297] In Part D, study treatment of pembrolizumab will be administered at a dose of 200 mg Q3W using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between –5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min + 10 min). Administration of the combination agents must begin with IV dosing of pembrolizumab first followed by SGN-PDL1V. At least 30 minutes should have elapsed after completion of administration of pembrolizumab before the administration of SGN-PDL1V can be initiated. Unless otherwise specified, administration of study treatment drug should be performed as per Product Information or institutional guidelines.

Dose Modifications

[0298] Please refer to the pembrolizumab Product Information for dose modification and toxicity management guidelines for pembrolizumab. For combination cohorts, AEs may be attributable to 1 study treatment alone or the combination of study treatments. The final decision regarding causality is at the discretion of the investigator. If the event is clearly related to one of the agents, follow the instructions specific for that agent. If the event is related to more than 1 agent, follow the instructions for all agents to which it is related. There may be circumstances when a subject may not tolerate combination therapy but may benefit from treatment with 1 agent alone. These cases must be discussed and approved by the sponsor before the subject may continue treatment. In a situation where attribution to an

individual study treatment may be difficult, the management actions to withhold or discontinue study treatment should apply to all study treatment administered.

Management of Treatment-Emergent Adverse Events

[0299] The IB for SGN-PDL1V and Product Information for pembrolizumab, individually describe AEs commonly observed relative to individual study treatments, as well as less common serious findings. Subjects receiving pembrolizumab should be monitored for AEs per guidance in the Product Information.

SGN-PDL1V

Management of Infusion-Related Reactions

[0300] An IRR is characterized by an adverse reaction to the infusion of pharmacological or biological substances. IRRs occur within 24 hours of infusion and may manifest as a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rash, urticaria, dyspnea, nausea, vomiting, back or abdominal pain, and/or hypotension.

[0301] IRRs 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 recommended subject care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for IRRs. If Grade 3 IRRs occur in >20% of subjects, subsequent subjects will require premedication or modification. It is recommended that subjects remain in close proximity to a medical facility for 24 hours after administration of SGN-PDL1V to enable prompt evaluation in case of a delayed IRR.

[0302] During dose escalation, additional mitigation strategies may be explored to manage IRRs, as recommended or required by the SMC. These mitigation strategies may include, but are not limited to, any or all of the following:

- Slowing, interruption, or other adjustments in the administration of SGN-PDL1V
- Potential premedication or postmedication for infusions, for example:
 - Antihistamines, such as diphenhydramine 50 mg IV or equivalent and famotidine 40 mg IV or equivalent
 - Antipyretics, such as acetaminophen or paracetamol 500 to 1,000 mg by mouth (PO) or equivalent

- Antiemetics, such as ondansetron
- IV fluid support, such as normal saline
- Anti-rigor medication, such as meperidine
- Vasopressors
- Corticosteroids, such as hydrocortisone 100 mg IV or equivalent, or methylprednisolone 40 mg IV or equivalent

[0303] Recommendations for the management of IRRs are detailed in Table 12.

Table 12: Management of SGN-PDL1V Related Infusion-Related Reactions

IRR Grade (Per NCI CTCAE version 5.0)			
Grade 1	Grade 2	Grade 3	Grade 4
Mild transient reaction; SGN-PDL1V treatment interruption not indicated; intervention not indicated	SGN-PDL1V treatment interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated
Treatment Recommendations			
Monitor vital signs more frequently until symptoms have resolved and subject is medically stable. Administer symptomatic treatment as medically indicated.	Hold SGN-PDL1V treatment. Monitor vital signs more frequently until symptoms have resolved and subject is medically stable. Administer symptomatic treatment as medically indicated. If subject responds promptly and is medically stable in the opinion of the investigator, SGN-PDL1V treatment may be continued at a slower rate.	Stop SGN-PDL1V treatment. Institute additional medical management as indicated. Consider hospitalization.	Stop SGN-PDL1V treatment immediately. Hospitalization.
Dose Modifications			
Consider premedication with subsequent SGN-PDL1V treatment.	Consider premedication with subsequent SGN-PDL1V treatment. Consider slower infusion rate. If recurrent after the above measures, discuss with medical monitor whether to consider dose	Subjects with an IRR that resolves to baseline or Grade 1 or lower within approximately 2 hours after intervention may continue SGN-PDL1V with altered premedication, infusion rate, and/or reduced dose for subsequent infusions, upon	Permanently discontinue from study treatment.

IRR Grade (Per NCI CTCAE version 5.0)			
Grade 1	Grade 2	Grade 3	Grade 4
	reduction to 1 dose level below current dose.	consultation with the medical monitor; dose reduction to 1 dose level below current dose may be considered. OR Permanently discontinue from study treatment.	

IRR=infusion-related reaction; IV=intravenous; NSAIDs=non-steroid anti-inflammatory drugs

[0304] All Grade 3 or higher events of IRR (with onset during infusion or within ≤ 24 hours after infusion) or hypersensitivity reaction (with onset occurring > 24 hours after infusion) should be reported to the medical monitor immediately, regardless of relationship to SGN-PDL1V. Grade 4 events of IRR should result in immediate and permanent discontinuation of SGN-PDL1V for that subject. Serious adverse events (SAEs) are to be reported within the SAE reporting timeframe of 24 hours via the standard SAE forms.

Adverse Events

Definitions

Adverse Event

[0305] According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 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.

[0306] 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 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 that increase in NCI CTCAE grade should be recorded.

- Medical conditions present or ongoing predose on study Day 1 that worsen in severity, increase in frequency, become related to SGN-PDL1V, or worsen in any other way but do not meet the threshold for increase in NCI CTCAE grade should be recorded.
- All AEs (regardless of relationship to SGN-PDL1V) should be recorded from study Day 1 (predose) through the end of the safety reporting period. Complications that occur in association with any procedure (eg, biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- 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 (eg, record “anemia” rather than “low hemoglobin”).
-

Serious Adverse Events

[0307] An AE should be classified as an SAE if it meets one of the following criteria:

Term	Definition
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 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.

Adverse Event Severity

[0308] AE severity should be graded using the NCI CTCAE, Version 5.0. 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.

Relationship of the Adverse Event to Study Treatment

[0309] The relationship of each AE to one or more agents in the study treatment, SGN-PDL1V and /or pembrolizumab, should be evaluated by the investigator using the following criteria:

Term	Definition
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 (eg, tendon rupture)
Unrelated:	Another cause of the AE is more plausible (eg, 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

DATA ANALYSIS METHODS

Determination of Sample Size

[0310] Approximately 160 subjects may be enrolled in Parts A and B of this study. This number is based on the assumption that approximately 80 subjects are expected to be evaluated in dose-escalation cohorts in Part A and approximately 80 subjects may be evaluated for dose and schedule optimization (Part B) to, if needed. To evaluate SGN-PDL1V in combination with pembrolizumab, approximately 12 subjects will be enrolled in a safety run-in cohort (Part D).

[0311] Dose escalation and identification of MTD will be guided by the mTPI design using the DE analysis set. The exact sample size of the mTPI design in Part A cannot be prespecified in advance due to a dynamic feature of the design. Approximately 80 subjects are expected to be evaluated in Part A..

[0312] The sample size of 40 for a disease-specific expansion cohort in Part C is determined to ensure reasonable precision in the estimate of objective response rate (ORR). The exact 2-sided confidence intervals (CIs) given observed ORRs are presented below.

Cohort Size (N)	Scenario	Observed ORR	80% Exact CIs	90% Exact CIs	95% Exact CIs
40	1	25%	(16.2%, 35.9%)	(14.2%, 38.7%)	(12.7%, 41.2%)
	2	30%	(20.5%, 41.2%)	(18.3%, 44.0%)	(16.6%, 46.5%)
	3	35%	(24.9%, 46.3%)	(22.6%, 49.2%)	(20.6%, 51.7%)
	4	40%	(29.4%, 51.4%)	(26.9%, 54.2%)	(24.9%, 56.7%)

Study Endpoint Definitions

Objective Response Rate

[0313] The ORR (regardless of confirmation) is defined as the proportion of subjects with a PR or CR per RECIST v1.1 as assessed by the investigator. Confirmed ORR is defined as the proportion of subjects with CR or PR which is subsequently confirmed as assessed according to RECIST v1.1. Subjects whose disease response cannot be evaluated per the response criteria will be scored as “not evaluable” for calculating the ORR. Subjects who do not have a post-baseline response assessment or have a response that is “not evaluable” will be counted as non-responders in the calculation of ORR.

Progression Free Survival

[0314] Progression free survival (PFS) is defined as the time from the start of study treatment to the first documentation of PD (per RECIST v1.1 as assessed by the investigator) or death due to any cause, whichever comes first. PFS data will be censored on the date of the last valid disease assessment for subjects who do not have PD, or the date of the last valid disease assessment documenting absence of PD prior to the initiation of non-protocol antitumor treatment. Subjects lacking an evaluation of tumor response after their first dose of study treatment will have their event time censored at Day 1. Details of the censoring rules will be provided in the SAP.

Overall Survival

[0315] IOS is defined as the time from the start of study treatment to death due to any cause. OS will be censored on the last known alive date for subjects who are not known to have died.

Duration of Objective Response

[0316] Duration of response (DOR) is defined as the time from the start of the first documentation of objective tumor response (CR or PR that is subsequently confirmed) to the first documentation of PD (per RECIST v1.1 as assessed by the investigator) or to death due to any cause, whichever comes first. DOR data will be censored on the date of the last adequate disease assessment documenting absence of PD for subjects who do not have PD at the time of an analysis, or the date of the last valid disease assessment documenting absence of PD prior to the initiation of subsequent anticancer treatment. Details of the censoring rules will be provided in the SAP. DOR will only be calculated for the subgroup of subjects achieving a CR or PR.

Examination of Subgroups

[0317] All analyses will be presented by dose level/cohort and total for selected endpoints, as appropriate.

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Subgroups may include but are not limited to the following:

- Prior therapies
- Disease subtype
- PD-L1 expression level

Example 2: Modeling on mechanisms of tumor cell killing

Bystander Activity

[0318] PDL1V is potently cytotoxic to a variety of PD-L1-positive cancer cell lines *in vitro*. A flow cytometry-based viability assay was performed to assess if PDL1V also drives dose-dependent bystander effect-based cytotoxicity of PD-L1-negative tumor cells when co-cultured with PD-L1-positive tumor cells.

[0319] Methods: SUDHL4 cells were engineered to express PD-L1 and wildtype PD-L1 negative cells were thawed from cryovials stored at -210°C into complete growth media (RPMI 1640 cell culture medium + 10% FBS). Cells were counted and 40K (PD-L1 positive) and/or 10K (PD-L1 negative) cells per well were seeded into 12-well flat-bottom plates in duplicates. PDL1V, Isotype vedotin ADC, and positive control free MMAE were prepared in complete media and added to appropriate wells (complete media with no treatment was added to wells corresponding to untreated condition) at concentrations of PDL1V: 50 ng/ml, 5 ng/ml, or 0.5 ng/ml; isotype vedotin: 50 ng/ml, or MMAE: 1.5 nM. Assay plates were allowed to incubate for 96 hours at 37C and 5% CO₂. Cells were harvested and an anti-PD-L1 antibody and a fluorescent viability stain were added to all wells of a 96-well assay plate and incubated for 30 minutes on ice. Unbound antibody was removed and the cells were incubated with counting beads for 15 minutes at room temperature. Fluorescence was determined using an Attune flow cytometer.

[0320] As shown in FIG. 10, PDL1V caused dose-dependent bystander effect-based cytotoxicity of PD-L1-negative tumor cells when co-cultured with PD-L1-positive tumor cells. For example, at 5 ng/ml PDL1V, ~ 100% of the PD-L1-negative cells in monoculture were live, whereas only ~ 50% of the PD-L1-negative cells and ~ 10% of the PD-L1-positive cells in coculture were live at the endpoint of the assay (as compared to untreated). At 50 ng/ml PDL1V, ~ 100% of the PD-L1-negative cells in monoculture were live, whereas only ~ 10% of the PD-L1-negative cells and 0% of the PD-L1-positive cells in coculture were live and the endpoint of the assay (as compared to untreated).

Immunogenic Cell death

[0321] Immunogenic Cell death (ICD), a regulated activation of immune cell recruitment to the tumor microenvironment, is caused by tumor cell release of damage-associated molecular patterns (DAMPs) such as cell surface chaperone calreticulin (CRT), extracellular adenosine triphosphate (eATP), and High Mobility Group Box 1 protein (HMGB1). As demonstrated in this example, PD-L1-positive cancer cells treated with PDL1V *in vitro* released all three DAMPs, suggesting that targeted delivery of the MMAE payload drives induction of ICD.

[0322] Methods (eATP release): Karpas 299 cells were thawed from cryovials stored at -21°C into complete growth media (RPMI 1640 cell culture medium + 10% FBS). Cells were counted and 20K cells per well were seeded into 96-well flat-bottom plates in triplicates. PDL1V, Isotype vedotin ADC, unconjugated PD-L1 antibody, and positive control free MMAE were prepared in complete media and added to appropriate wells (complete media with no treatment was added to wells corresponding to untreated condition). RealTime Glo eATP reagent substrate was added to each well of the assay plate according to manufacturer's instructions. Assay plates were mixed on an orbital shaker at 500 rpm for 30 seconds to create a homogenous mixture, and the luminescence from each well was determined using a Cytation (Agilent/Bio Tek).

[0323] As shown in FIG. 11A, PD-L1-positive cancer cells treated with PDL1V *in vitro* released much higher levels of eATP as compared to untreated and negative controls (isotype vedotin, PD-L1 mAb) and at a level similar to positive control (MMAE).

[0324] Methods (HMGB1 release): Karpas 299 cells were thawed from cryovials stored at -21°C into complete growth media (RPMI 1640 cell culture medium + 10% FBS). Cells were counted and 200K cells per well were seeded into 12-well flat-bottom plates in duplicates. PDL1V, isotype vedotin ADC, unconjugated PD-L1 antibody, and positive control free MMAE were prepared in complete media and added to appropriate wells (complete media with no treatment was added to wells corresponding to untreated condition). Assay plates were allowed to incubate for 42 hours at 37°C and 5% CO₂. The supernatant from each well was transferred to appropriate wells of a new plate, and cell supernatants were incubated with anti-human HMGB1 antibody mixture for 90 minutes at room temperature. Luminescent detection buffer was added to each well and after a 4 minute incubation at room

temperature, the luminescence from each well was determined using an EnVision plate reader (PerkinElmer).

[0325] As shown in FIG. 11B, PD-L1-positive cancer cells treated with PDL1V *in vitro* released much higher levels of HMGB1 as compared to untreated and negative controls (isotype vedotin, PD-L1 mAb) and at a level similar to positive control (MMAE).

[0326] Methods (Calreticulin release): Karpas 299 cells were thawed from cryovials stored at -21°C into complete growth media (RPMI 1640 cell culture medium + 10% FBS). Cells were counted and $1.5\text{E}6$ cells per well were seeded into 6-well flat-bottom plates. PDL1V, Isotype vedotin ADC, unconjugated PD-L1 antibody, and positive control free MMAE were prepared in complete media and added to appropriate wells (complete media with no treatment was added to wells corresponding to untreated condition). Assay plates were allowed to incubate for 42 hours at 37°C and 5% CO_2 . Cells were harvested, counted, and seeded at 250K cells per well in a 96-well U-bottom plate. Anti-human Calreticulin or anti-human isotype antibodies were added to appropriate wells of assay plate and incubated for 30 minutes on ice. Unbound antibody was removed and the cells were incubated with a fluorescent viability stain for 15 minutes at room temperature. Fluorescence was determined using an Attune flow cytometer.

[0327] As shown in FIG. 11C, PD-L1-positive cancer cells treated with PDL1V *in vitro* displayed much higher levels of cell-surface calreticulin as compared to untreated and negative controls (isotype vedotin, PD-L1 mAb) and at a level similar to positive control (MMAE).

Effect of PDL1V on immune cell viability

[0328] As an immune checkpoint protein, PD-L1 is expressed on antigen presenting cells and T cells. Depletion of these cells could affect the tolerability of PDL1V as a monotherapy, or limit its efficacy when in combination with anti-PD-1 therapies. To investigate the potential for immune cell depletion, $\text{CD}4^{+}$ and $\text{CD}8^{+}$ T cells were evaluated in an *in vitro* fluorescence-based cytotoxicity assay. As shown in this example, PDL1V had minimal cytotoxic activity across all three cell types, despite their expression of PD-L1. These data support PDL1V as selectively cytotoxic to PD-L1-positive and negative cancer cells of the tumor microenvironment, and not cytotoxic to PD-L1-positive immune cells involved in natural antitumor immunity.

[0329] Methods: CD3+ Pan T cells were thawed from cryovials stored at -21°C into complete growth media (RPMI 1640 cell culture medium + 10% FBS). Pan T cells were counted, labeled with amine-reactive CFSE dye, and plated into 96-well U-bottom microplates in duplicates (Donor 2) or triplicates (donor 1). CD3/CD28 crosslinking beads and 10-point, 3-fold serial dilutions of PDL1V, Isotype vedotin ADC, as well as positive control drug were prepared in complete media and added to appropriate wells. Assay plates were allowed to incubate for 96 hours at 37°C and 5% CO_2 .

[0330] A fluorescent viability stain and antibodies binding CD3, CD4, CD8, and PD-L1 were prepared according to the manufacturer's instructions and added to each well of the assay plates. After a 30 minute incubation on ice, the cells were washed with 1X PBS and fluorescence was measured on an Attune flow cytometer

[0331] As shown in FIG. 12A and FIG. 12B, PDL1V had minimal cytotoxic activity in CD4+ T cells for both Donor 1 and Donor 2, despite the expression of PD-L1 in the T cells.

[0332] As shown in FIG. 12C and FIG. 12D, PDL1V had minimal cytotoxic activity in CD8+ T cells for both Donor 1 and Donor 2, despite the expression of PD-L1 in the T cells.

INFORMAL SEQUENCE LISTING

SEQ ID NO:1 - SG-559-01 LALA hIgG1 heavy chain - protein

QVQLVQSGAEVKKPGSSVKVSKCTSGDTFSTA AISWVRQAPGQGLEWMGGIIPIFGKAHYAQKFQGRVTITADES
TSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMDVWGQGT TTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS
CDKTHCTCPPEAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLS
PGK

SEQ ID NO:2 - SG-559-01 kappa light chain - protein

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRTGIPARFSGSGSGTDFTLTI
SSLEPEDFAVYYCQQRSNWPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD
NALQSGNSQESVTEQDSKSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:3 - SG-559-01 heavy chain variable region - protein

QVQLVQSGAEVKKPGSSVKVSKCTSGDTFSTA AISWVRQAPGQGLEWMGGIIPIFGKAHYAQKFQGRVTITADES
TSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMDVWGQGT TTVTVSS

SEQ ID NO:4 - SG-559-01 light chain variable region - protein

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRTGIPARFSGSGSGTDFTLTI
SSLEPEDFAVYYCQQRSNWPTFGQGTKVEIK

SEQ ID NO:5 - SG-559-01 heavy chain CDR1 - protein

TAAIS

SEQ ID NO:6 - SG-559-01 heavy chain CDR2 - protein

GIIPFGKAHYAQKFQG

SEQ ID NO:7 - SG-559-01 heavy chain CDR3 - protein

KFHFVSGSPFGMDV

SEQ ID NO:8 - SG-559-01 light chain CDR1 - protein

RASQSVSSYLA

SEQ ID NO:9 - SG-559-01 light chain CDR2 - protein

DASNRAT

SEQ ID NO:10 - SG-559-01 light chain CDR3 - protein

QQRSNWPT

SEQ ID NO:11 - SG-559-01 hIgG1 heavy chain - protein

QVQLVQSGAEVKKPGSSSVKVSCKTSGDTFSTA AISWVRQAPGQGLEWMGGIIPIFGKAHYAQKFQGRVTITADES
TSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMDVWGQGT TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS
CDKTHCTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLS
PGK

SEQ ID NO:12 - SG-559-01 variable heavy region - nucleic acid

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SEQ ID NO:13 - SG-559-01 variable light region - nucleic acid

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agcagcctagagcctgaagattttgagtttattactgtcagcagcgtagcaactggccgacgttcggccaaggg
accaaggtggaatcaaa

SEQ ID NO:14 - SG-559-01 LALA hIgG1 heavy chain - nucleic acid

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SEQ ID NO:15 - SG-559-01 kappa light chain - nucleic acid

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SEQ ID NO:16 - SG-559-01 hIgG1 heavy chain - nucleic acid

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SEQ ID NO:17 - Pembrolizumab heavy chain CDR1 - protein

NYMY

SEQ ID NO:18 - Pembrolizumab heavy chain CDR2 - protein

GINPSNGGTNFNEKFKN

SEQ ID NO:19 - Pembrolizumab heavy chain CDR3 - protein

RDYRFDMGFDY

SEQ ID NO:20 - Pembrolizumab light chain CDR1 - protein

RASKGVSTSGYSYLH

SEQ ID NO:21 - Pembrolizumab light chain CDR2 - protein

LASYLES

SEQ ID NO:22 - Pembrolizumab light chain CDR3 - protein

QHSRDLPLT

SEQ ID NO:23 - Pembrolizumab heavy chain - protein

QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNFNEKFKNRVTLTDDSS
TTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVK
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CPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO:24 - Pembrolizumab light chain - protein

EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLAASYLESQVPAFSGSGSGTDF
TLTISSLEPEDEFAVYYCQHSRDLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:25 - Pembrolizumab heavy chain variable region - protein

QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNFNEKFKNRVTLTDDSS
TTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSS

SEQ ID NO:26 - Pembrolizumab light chain variable region - protein

EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLAASYLESQVPAFSGSGSGTDF
TLTISSLEPEDEFAVYYCQHSRDLPLTFGGGTKVEIK

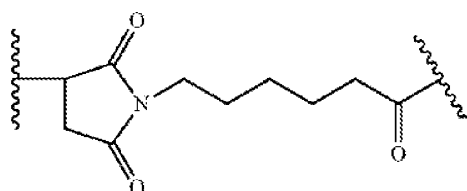
CLAIMS

1. A method of treating cancer in a human subject, comprising administering to the subject:
 - (a) an effective amount of an antibody drug conjugate (ADC) comprising an anti-PD-L1 antibody or antigen binding fragment thereof and
 - (b) an effective amount of an anti-PD-1 antibody;wherein the anti-PD-L1 antibody or antigen binding fragment thereof binds to PD-L1 and is conjugated to one or more units of monomethyl auristatin E (MMAE);
wherein the anti-PD-L1 antibody or antigen binding fragment thereof comprises: (i) a light chain variable region comprising light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 8, 9, and 10, respectively and (ii) a heavy chain variable region comprising heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 5, 6, and 7, respectively; and
wherein the anti-PD-1 antibody comprises: (i) a light chain variable region comprising light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 20, 21, and 22 respectively and (ii) a heavy chain variable region comprising heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 17, 18, and 19, respectively.
2. The method of claim 1, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence at least 85% identical to the amino acid sequence of SEQ ID NO:3 and a light chain variable region comprising an amino acid sequence at least 85% identical to the amino acid sequence of SEQ ID NO:4.
3. The method of claim 1 or claim 2, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:3 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:4.
4. The method of any one of claims 1-3, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:1 and a light chain comprising the amino acid sequence of SEQ ID NO:2.
5. The method of any one of claims 1-4, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is conjugated to each unit of MMAE via a linker.

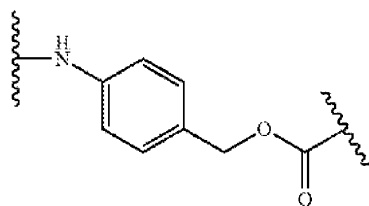
6. The method of claim 5, wherein the linker is an enzyme-cleavable linker, and wherein the linker forms a bond with a sulfur atom of the antibody or antigen binding fragment thereof.

7. The method of claim 5 or 6, 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.

8. The method of claim 7, 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).

9. The method of claim 7 or 8, 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.

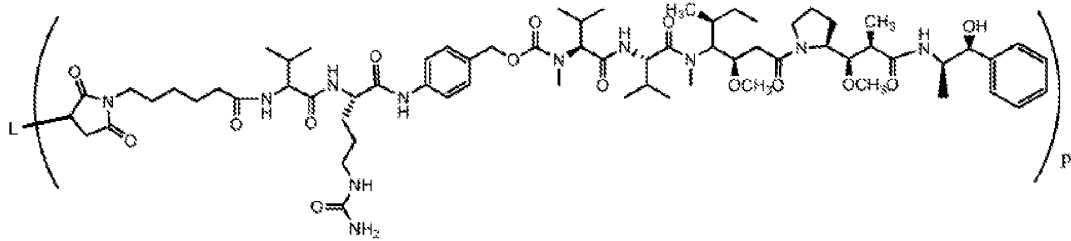
10. The method of any one of claims 1-9, wherein the ADC comprises from 1 to 20 units of MMAE per antibody or antigen binding fragment thereof.

11. The method of any one of claims 1-10, wherein the ADC comprises from 1 to 10 units of MMAE per antibody or antigen binding fragment thereof.

12. The method of any one of claims 1-11, wherein the ADC comprises from 2 to 8 units of MMAE per antibody or antigen binding fragment thereof.

13. The method of any one of claims 1-12, wherein the ADC comprises from 3 to 5 units of MMAE per antibody or antigen binding fragment thereof.

14. The method of any one of claims 1-13, wherein the ADC has the following structure:



wherein L- represents the anti-PD-L1 antibody or antigen binding fragment thereof and p is from 1 to 10.

15. The method of claim 14, wherein p is from 2 to 8.

16. The method of claim 14, wherein p is from 3 to 5.

17. The antibody of claim 14, wherein p is 4.

18. The antibody of claim 14, wherein p is 8.

19. The method of any of claims 1-18, wherein the cancer is melanoma, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), head and neck squamous cell carcinoma (HNSCC), triple negative breast cancer (TNBC), esophageal squamous cell carcinoma (esophageal SCC), ovarian cancer, urothelial cancer, hepatocellular carcinoma (HCC), gastric cancer, or cervical cancer.

20. The method of claim 19, wherein the cancer is NSCLC, HNSCC, TNBC, or esophageal SCC.

21. The method of claim 19, wherein the cancer is NSCLC.

22. The method of claim 19, wherein the cancer is HNSCC.

23. The method of claim 19, wherein the cancer is TNBC.

24. The method of claim 19, wherein the cancer is esophageal SCC.

25. The method of any one of claims 1-24, wherein the ADC is administered to the subject at a dose of about 0.25 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, or about 1 to about 2 mg/kg of the subject's

body weight, optionally wherein the ADC is administered to the subject at a dose of 1.25 mg/kg or 1.5 mg/kg of the subject's body weight.

26. The method of any one of claims 1-25, wherein the subject's body weight is the subject's ideal body weight (IBW).

27. The method of any one of claims 1-25, wherein the subject's body weight is the subject's adjusted ideal body weight (AIBW).

28. The method of any one of claims 1-27, wherein the anti-PD-1 antibody is administered at a dose of 200 mg.

29. The method of any one of claims 1-28, wherein the ADC is administered once about every 1 week, once about every 2 weeks, once about every 3 weeks, or twice about every 3 weeks.

30. The method of any of claims 1-29, wherein the ADC is administered twice about every 3 weeks.

31. The method of any of claims 1-30, wherein the ADC is administered on Days 1 and 8 of each 21-day cycle.

32. The method of any of claims 1-31, wherein the anti-PD-1 antibody is administered once about every 1 week, once about every 2 weeks, once about every 3 weeks, or twice about every 3 weeks.

33. The method of any of claims 1-32, wherein the anti-PD-1 antibody is administered once about every 1 week.

34. The method of any of claims 1-32, wherein the anti-PD-1 antibody is administered on Day 1 of each 21-day cycle.

35. The method of any of claims 1-34, wherein the subject has metastatic or unresectable solid malignancy disease that is relapsed or refractory or intolerant to standard of care treatment.

36. The method of any of claims 1-35, wherein the route of administration for the ADC is intravenous.

37. The method of any of claims 1-36, wherein the route of administration for the anti-PD-1 antibody is intravenous.

38. The method of any one of claims 1-37, wherein one or more therapeutic effects in the subject is improved after administration of the antibody-drug conjugate relative to a baseline.

39. The method of claim 38, wherein the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the cancer, objective response rate, duration of response, time to response, progression free survival, and overall survival.