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(71) Applicants: **MERCK SHARP & DOHME LLC**

[US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065 (US). **AGENSYS, INC.** [US/US]; 1 Astellas Way, Northbrook, Illinois 60062 (US). **SEAGEN INC.** [US/US]; 21717 30th Drive SE, Bothell, Washington 98021 (US).

(72) Inventors: **HOMET MORENO, Blanca**; 351 North Sum-

neytown Pike, North Wales, Pennsylvania 19454-2505 (US). **HEALY, Jane Anne**; 126 East Lincoln Avenue, Rah-

way, New Jersey 07065 (US). **RUBIN, Eric H.**; 351 North Sumneytown Pike, North Wales, Pennsylvania 19454-2505 (US).

(74) Agent: **HOOSON, Sarah L.**; 126 East Lincoln Avenue, Rahway, New Jersey 07065 (US).

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(54) Title: COMBINATION THERAPY OF A PD-1 ANTAGONIST, A LAG3 ANTAGONIST AND AN ANTIBODY DRUG CONJUGATE THAT BINDS 191P4D12 PROTEIN FOR TREATING PATIENTS WITH CANCER

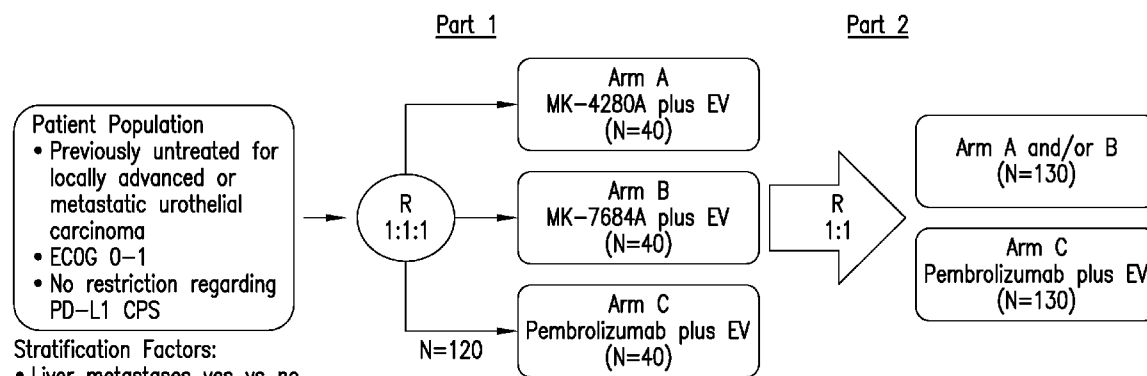


FIG.2

(57) Abstract: Provided herein are methods of treating cancer, which comprise administering to a human patient in need thereof: (a) a Lymphocyte-Activation Gene 3 (LAG3) antagonist; (b) a PD-1 antagonist; and (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE). Also provided are kits containing such agents and uses of therapeutic combinations of such agents for the treatment of cancer.

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- *as to the identity of the inventor (Rule 4.17(i))*
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COMBINATION THERAPY OF A PD-1 ANTAGONIST, A LAG3 ANTAGONIST AND AN ANTIBODY DRUG CONJUGATE THAT BINDS 191P4D12 PROTEIN FOR TREATING PATIENTS WITH CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims the benefit of U.S. Provisional Patent Application Serial No. 63,433,220 filed December 16, 2022, the entire content of which is incorporated by reference herein.

FIELD OF THE INVENTION

10 Provided herein are methods for treating cancer, using a combination of (a) an antagonist of Programmed Death 1 protein (PD-1), (b) an antagonist of Lymphocyte-Activation Gene 3 (LAG3), (c) an antibody drug conjugates (ADC) that binds to 191P4D12 proteins.

BACKGROUND OF THE INVENTION

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

20 Two known ligands for PD-1, PD-L1 (B7-H1) and PD-L2 (B7-DC), are expressed in human cancers arising in various tissues. In large sample sets of e.g., ovarian, renal, colorectal, pancreatic, liver cancers and melanoma, it was shown that PD-L1 expression correlated with poor prognosis and reduced overall survival irrespective of subsequent treatment (Dong *et al.*, *Nat Med.* 8(8):793-800 (2002); Yang *et al. Invest Ophthalmol Vis Sci.* 49: 2518-2525 (2008); Ghebeh *et al. Neoplasia* 8:190-198 (2006); Hamanishi *et al., Proc. Natl. Acad. Sci. USA* 104: 3360-3365 (2007); Thompson *et al., Cancer* 5: 206-211 (2006) ; Nomi *et al., Clin. Cancer Research* 13:2151-2157 (2007); Ohigashi *et al., Clin. Cancer Research* 11: 2947-2953 (2005); Inman *et al., Cancer* 109: 1499-1505 (2007); Shimauchi *et al. Int. J. Cancer* 121:2585-2590 (2007); Gao *et al. Clin. Cancer Research* 15: 971-979 (2009); Nakanishi J. *Cancer Immunol Immunother.* 56: 1173-1182 (2007); and Hino *et al., Cancer* 00: 1-9 (2010)).

30 Similarly, PD-1 expression on tumor infiltrating lymphocytes was found to mark dysfunctional T cells in breast cancer and melanoma (Ghebeh *et al., BMC Cancer.* 8:5714-15 (2008); Ahmadzadeh *et al., Blood* 114: 1537-1544 (2009)) and to correlate with poor prognosis in renal cancer (Thompson *et al., Clinical Cancer Research* 15: 1757-1761 (2007)). Thus, it has

been proposed that PD-L1 expressing tumor cells interact with PD-1 expressing T cells to attenuate T cell activation and evasion of immune surveillance, thereby contributing to an impaired immune response against the tumor.

Immune checkpoint therapies targeting the PD-1 axis have resulted in groundbreaking improvements in clinical response in multiple human cancers (Brahmer *et al.*, N Engl J Med 2012, 366: 2455-65; Garon *et al.* N Engl J Med 2015, 372: 2018-28; Hamid *et al.*, N Engl J Med 2013, 369: 134-44; Robert *et al.*, Lancet 2014, 384: 1109-17; Robert *et al.*, N Engl J Med 2015, 372: 2521-32; Robert *et al.*, N Engl J Med 2015, 372: 320-30; Topalian *et al.*, N Engl J Med 2012, 366: 2443-54; Topalian *et al.*, J Clin Oncol 2014, 32: 1020-30; Wolchok *et al.*, N Engl J Med 2013, 369: 122-33). Immune therapies targeting the PD-1 axis include monoclonal antibodies directed to the PD-1 receptor (KEYTRUDA™ (pembrolizumab), Merck Sharp & Dohme LLC, Rahway, NJ, USA; OPDIVO™ (nivolumab), Bristol-Myers Squibb Company, Princeton, NJ, USA, and LIBTAYO™ (cemiplimab), Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) and also those that bind to the PD-L1 ligand (MPDL3280A; TECENTRIQ™ (atezolizumab), Genentech, San Francisco, CA, USA; IMFINZI™ (durvalumab), AstraZeneca Pharmaceuticals LP, Wilmington, DE; BAVENCIO™ (avelumab), Merck KGaA, Darmstadt, Germany; JEMPERLI™ (dostarlimab), GlaxoSmithKline Biologics LLC, Philadelphia, PA, USA). Both therapeutic approaches have demonstrated anti-tumor effects in numerous cancer types.

Lymphocyte-Activation Gene 3 (LAG3) is an inhibitory immune modulatory receptor that regulates effector T cell homeostasis, proliferation, and activation, and has a role in the suppressor activity of regulatory T cells (Tregs). LAG3 is expressed on activated CD8+ and CD4+ T cells, Tregs and the Tr1 regulatory T-cell population, as well as on natural killer cells and a subset of tolerogenic plasmacytoid dendritic cells. Because of its proposed role on both effector T cells and Tregs, LAG3 is one of several immune checkpoint molecules where simultaneous blockade of both cell populations has the potential to enhance antitumor immunity.

LAG3 is structurally related to cluster of differentiation (CD) 4 and a member of the immunoglobulin (Ig) superfamily. Like CD4, its ligand is major histocompatibility complex (MHC) Class II molecules. Interaction with its ligand leads to dimerization and signal transduction resulting in altered T-cell activation. Following T-cell activation, LAG3 is transiently expressed on the cell surface. A large proportion of LAG3 molecules are found in intracellular stores and can be rapidly translocated to the cell membrane upon T-cell activation. LAG3 expression is regulated at the cell surface by extracellular cleavage to yield a soluble form of LAG3 (sLAG 3), which can be detected in serum. Expression of LAG3 is tightly regulated and represents a self-limiting mechanism to counter uncontrolled T-cell activity.

91P4D12 (which is also known as Nectin-4) is a 66 kDa type I transmembrane protein that belongs to the nectin family of adhesion molecules. It is composed of an extracellular domain (ECD) containing 3 immunoglobulin (Ig)-like subdomains, a transmembrane helix, and an intracellular region (Takai *et al.*, Annu Rev Cell Dev Biol (2008); 24: 309-42). Nectins are thought to mediate Ca²⁺-independent cell-cell adhesion via both homophilic and heterophilic trans-interactions at adherens junctions where they can recruit cadherins and modulate cytoskeletal rearrangements (Rikitake *et al.*, Cell Mol Life Sci (2008); 65(2): 253-63). Sequence identity of Nectin-4 to other Nectin family members is low and ranges between 25%-30% in the ECD (Reymond *et al.*, Biol Chem (2001); 276(46): 43205-15).

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

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

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

SUMMARY OF THE INVENTION

The present disclosure provides methods, pharmaceutical compositions, uses and kits related to treating cancer, using a combination of therapeutic agents, *e.g.*, a combination of antibodies or antigen binding fragments thereof.

The present disclosure provides methods of treating cancer, using a combination of a LAG3 antagonist (*e.g.*, antibody (*e.g.*, monoclonal antibody) or antigen binding fragment thereof), a PD-1 antagonist (*e.g.*, antibody (*e.g.*, monoclonal antibody) or antigen binding fragment thereof), and an antibody drug conjugate (ADC) that binds to 191P4D12.

Among other things, the present disclosure encompasses insights that certain combinations of immune checkpoint inhibitors (*e.g.*, a LAG3 antagonist and a PD-1 antagonist) in combination with an antibody drug conjugate that binds to 191P4D12, as provided herein may

enhance efficacy without significant added toxicity as compared with existing treatments. While it has been proposed that the efficacy of anti-LAG3 antagonistic antibodies and anti-PD-1 antagonistic antibodies might be enhanced if administered in combination with other approved or experimental cancer therapies, there are no clear guidelines as to which agent combined with the anti-LAG3 antagonistic antibodies and the anti-PD-1 antagonistic antibodies may be effective or in which patients the combination may enhance the efficacy of treatment.

The present disclosure further recognizes that a combination of a LAG3 antagonist, a PD-1 antagonist and an ADC comprising an anti-191P4D12 antibody provided herein may be beneficial because they have divergent metabolic pathways. For example, there may be no drug interactions from a combination of an LAG3 antagonist, a PD-1 antagonist and an ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

The present disclosure provides methods of treating cancer (*e.g.*, urothelial cancer, *etc.*) using a combination of a LAG3 antagonist, a PD-1 antagonist, and an ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

The present disclosure further provides kits including a LAG3 antagonist, a PD-1 antagonist, and an antibody drug conjugate (ADC) comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

Also provided herein are uses of a therapeutic combination for treating cancer (*e.g.*, urothelial cancer), wherein the therapeutic combination includes a LAG3 antagonist, a PD-1 antagonist, and an ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof, binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In one aspect, provided herein is a method of treating cancer, comprising administering to a human patient in need thereof:

- (a) a LAG3 antagonist;
- (b) a PD-1 antagonist; and
- (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In one aspect, provided herein are therapeutic combinations for use in treating cancer, comprising administering to a human patient in need thereof:

- (a) a LAG3 antagonist;
- (b) a PD-1 antagonist; and
- 5 (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In some embodiments of the methods of the invention, the cancer is selected from the
10 group consisting of: melanoma, non-small cell lung cancer, head and neck squamous cell cancer, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, bladder cancer, microsatellite instability-high or mismatch repair deficient cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, biliary tract cancer, a cancer characterized by a tumor having
15 a high mutational burden, cutaneous squamous cell carcinoma, and triple negative breast cancer.

In another aspect, provided herein is a kit comprising:

- (a) a LAG3 antagonist;
- (b) a PD-1 antagonist; and
- 20 (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In certain embodiments, the kit further comprises instructions for administering to a human patient the LAG3 antagonist, the PD-1 antagonist, and the antibody drug conjugate
25 comprising an anti-191P4D12 antibody.

In still another aspect, provided herein is use of a therapeutic combination for treating cancer in a human patient, wherein the therapeutic combination comprises:

- (a) a LAG3 antagonist;
- (b) a PD-1 antagonist; and
- 30 (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In certain embodiments of the methods, pharmaceutical compositions, kits, uses, or the
35 combinations for use provided herein, the subject is a human patient.

In certain embodiments of the methods, pharmaceutical compositions, kits, uses, or the combinations for use provided herein are useful for treating cancer.

In certain embodiments of the methods, pharmaceutical compositions, kits, or uses provided herein, the PD-1 antagonist is an anti-human PD-1 monoclonal antibody or antigen
5 binding fragment thereof.

In other embodiments of the methods, pharmaceutical compositions, kits, or uses provided herein, the PD-1 antagonist is an anti-human PD-L1 monoclonal antibody or antigen binding fragment thereof.

In some embodiments of the methods, pharmaceutical compositions, kits, or uses
10 provided herein, the anti-human PD-1 monoclonal antibody is a humanized antibody.

In other embodiments of the methods, pharmaceutical compositions, kits, or uses provided herein, the anti-human PD-1 monoclonal antibody is a human antibody.

In some embodiments of the methods, pharmaceutical compositions, kits, or uses provided herein, the anti-human PD-L1 monoclonal antibody is a humanized antibody.

In other embodiments of the methods, pharmaceutical compositions, kits, or uses
15 provided herein, the anti-human PD-L1 monoclonal antibody is a human antibody.

In certain embodiments of the methods, pharmaceutical compositions, kits, or uses provided herein, the LAG3 antagonist is an anti-human LAG3 monoclonal antibody or antigen binding fragment thereof.

In some embodiments of the methods, pharmaceutical compositions, kits, or uses
20 provided herein, the anti-human LAG3 monoclonal antibody is a humanized antibody.

In other embodiments of the methods, pharmaceutical compositions, kits, or uses provided herein, the anti-human LAG3 monoclonal antibody is a human antibody.

In still other embodiments of the methods, pharmaceutical compositions, kits, or uses
25 provided herein, the anti-PD-1 antibody is independently selected from pembrolizumab, nivolumab, cemiplimab, dostarlimab, sintilimab, tislelizumab, camrelizumab and toripalimab.

In one embodiment of the methods, pharmaceutical compositions, kits, or uses provided herein, the anti-human PD-1 monoclonal antibody is pembrolizumab.

In another embodiment of the methods, pharmaceutical compositions, kits, or uses
30 provided herein, the anti-human PD-1 monoclonal antibody is nivolumab.

In another embodiment of the methods, pharmaceutical compositions, kits, or uses provided herein, the anti-human PD-1 monoclonal antibody is cemiplimab.

In another embodiment of the methods, pharmaceutical compositions, kits, or uses provided herein, the anti-human PD-1 monoclonal antibody is dostarlimab.

In yet another embodiment of the methods, pharmaceutical compositions, kits, or uses provided herein, the anti-human PD-1 monoclonal antibody or antigen binding fragment thereof is pidilizumab (U.S. Pat. No. 7,332,582).

5 In yet another embodiment of the methods, pharmaceutical compositions, kits, or uses provided herein, the anti-human PD-1 monoclonal antibody or antigen binding fragment thereof is AMP-514 (MedImmune LLC, Gaithersburg, MD).

In yet another embodiment of the methods, pharmaceutical compositions, kits, or uses provided herein, the anti-human PD-1 monoclonal antibody or antigen binding fragment thereof is PDR001 (U.S. Pat. No. 9,683,048).

10 In yet another embodiment of the methods, pharmaceutical compositions, kits, or uses provided herein, the anti-human PD-1 monoclonal antibody or antigen binding fragment thereof is BGB-A317 (U.S. Pat. No. 8,735,553).

In yet another embodiment of the methods, pharmaceutical compositions, kits, or uses provided herein, the anti-human PD-1 monoclonal antibody or antigen binding fragment thereof
15 is MGA012 (MacroGenics, Rockville, MD).

In certain embodiments of the methods, kits, or uses provided herein, the anti-PD1 antibody comprises:

(a) light chain (LC) complementarity determining regions (CDRs) LC-CDR1, LC-CDR2 and LC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID NOs: 1, 2 and 3,
20 respectively, and heavy chain (HC) CDRs HC-CDR1, HC-CDR2 and HC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID NOs: 6, 7 and 8, respectively; or

(b) light chain CDRs LC-CDR1, LC-CDR2 and LC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID NOs: 11, 12 and 13, respectively and heavy chain CDRs HC-CDR1, HC-CDR2 and HC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID
25 NOs: 14, 15 and 16, respectively.

In certain embodiments of the methods, kits, or uses provided herein, the anti-PD1 antibody comprises a light chain (LC) complementarity determining regions (CDRs) LC-CDR1, LC-CDR2 and LC-CDR3 comprising a sequence of amino acids as set forth in SEQ ID NOs: 1, 2 and 3, respectively, and heavy chain (HC) CDRs HC-CDR1, HC-CDR2 and HC-CDR3
30 comprising a sequence of amino acids as set forth in SEQ ID NOs: 6, 7 and 8, respectively.

In some embodiments of the methods, kits, or uses provided herein, the anti-PD1 antibody comprises a heavy chain variable region comprising a sequence of amino acids as set forth in SEQ ID NO:9 and a light chain variable region comprising a sequence of amino acids as set forth in SEQ ID NO:4.

In some embodiments of the methods, kits, or uses provided herein, the anti-PD1 antibody comprises light (a) a heavy chain comprising or consisting of a sequence of amino acids as set forth in SEQ ID NO: 10 and (b) a light chain comprising or consisting of a sequence of amino acids as set forth in SEQ ID NO: 5.

5 In some embodiments of the methods, kits, or uses described herein, the human patient is administered about 200 mg, about 240 mg, or about 2 mg/kg pembrolizumab, and pembrolizumab is administered once every three weeks. In one embodiment, the human patient is administered about 200 mg pembrolizumab once every three weeks. In one embodiment, the human patient is administered about 240 mg pembrolizumab once every three weeks. In one
10 embodiment, the human patient is administered about 2 mg/kg pembrolizumab once every three weeks.

In certain embodiments of the methods, kits, or uses described herein, the human patient is administered about 400 mg pembrolizumab, and pembrolizumab is administered once every six weeks.

15 In other embodiments of the methods, kits, or uses described herein, the human patient is administered about 240 mg or about 3 mg/kg nivolumab once every two weeks, or about 480 mg nivolumab once every four weeks. In one specific embodiment, the human patient is administered about 240 mg nivolumab once every two weeks. In one specific embodiment, the human patient is administered about 3 mg/kg nivolumab once every two weeks. In one specific
20 embodiment, the human patient is administered about 480 mg nivolumab once every four weeks.

In yet other embodiments of the methods, kits, or uses described herein, the human patient is administered about 350 mg cemiplimab, and cemiplimab is administered once every three weeks.

In certain embodiments of the methods, kits, or uses provided herein, the anti-human
25 LAG3 monoclonal antibody comprises three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43,
30 and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44.

In some embodiments of the methods, kits, or uses provided herein the anti-human LAG3 monoclonal antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 25 and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 24.

In other embodiments of the methods, kits, or uses provided herein, the anti-human LAG3 monoclonal antibody or antigen binding fragment thereof comprises a light chain comprising or consisting of the amino acid sequence as set forth in SEQ ID NO: 22 and a heavy chain comprising or consisting of the amino acid sequence as set forth in SEQ ID NO: 23.

5 In one specific embodiment of the methods, kits, or uses provided herein, the PD-1 antagonist is pembrolizumab; and the LAG3 antagonist is a monoclonal antibody or antigen binding fragment thereof comprising three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID
10 NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 29, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44.

In some embodiments of the methods, kits, or uses described herein, the human patient is administered about 800 mg of the anti-human LAG3 monoclonal antibody or antigen binding
15 fragment thereof comprising (a) light chain CDRs SEQ ID NOs: 26, 27 and 28 and (b) heavy chain CDRs SEQ ID NOs: 29, 30 and 31, and the anti-human LAG3 monoclonal antibody or antigen binding fragment thereof is administered once every three weeks.

In one embodiment, the human patient is administered about 200 mg of the anti-human LAG3 monoclonal antibody or antigen binding fragment thereof once every three weeks. In one
20 embodiment, the human patient is administered about 240 mg of the anti-human LAG3 monoclonal antibody or antigen binding fragment thereof once every three weeks. In one embodiment, the human patient is administered about 2 mg/kg of the anti-human LAG3 monoclonal antibody or antigen binding fragment thereof once every three weeks.

In certain embodiments of the methods described herein, the human patient is
25 administered about 400 mg of the anti-human LAG3 monoclonal antibody or antigen binding fragment thereof comprising a light chain comprising or consisting of the amino acid sequence as set forth in SEQ ID NO: 35 and a heavy chain comprising or consisting of the amino acid sequence as set forth in SEQ ID NO: 36, and the anti-human LAG3 monoclonal antibody or antigen binding fragment thereof is administered once every six weeks.

30 In certain embodiments of the methods, kits, or uses provided herein, the antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof comprises CDR-H1 comprising the amino acid sequence of SEQ ID NO:53, CDR-H2 comprising the amino acid sequence of SEQ ID NO:54, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 55; CDR-L1 comprising the amino acid sequence of SEQ ID NO: 56, CDR-L2 comprising the

amino acid sequence of SEQ ID NO: 57, and CDR-L3 comprising the amino acid sequence of SEQ ID NO:58.

In certain embodiments of the methods, kits, or uses provided herein, the antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof comprises CDR-H1 comprising the amino acid sequence of SEQ ID NO:60, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 61, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 62; CDR-L1 comprising the amino acid sequence of SEQ ID NO: 63, CDR-L2 comprising the amino acid sequence of AAS, and CDR-L3 comprising the amino acid sequence of SEQ ID NO:65.

In certain embodiments of the methods, kits, or uses provided herein, the antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof comprises CDR-H1 consisting of the amino acid sequence of SEQ ID NO:53, CDR-H2 consisting of the amino acid sequence of SEQ ID NO: 54, CDR-H3 consisting of the amino acid sequence of SEQ ID NO:55; CDR-L1 consisting of the amino acid sequence of SEQ ID NO: 56, CDR-L2 consisting of the amino acid sequence of SEQ ID NO: 57, and CDR-L3 consisting of the amino acid sequence of SEQ ID NO: 58.

In certain embodiments of the methods, kits, or uses provided herein, the antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof comprises CDR-H1 consisting of the amino acid sequence of SEQ ID NO: 60, CDR-H2 consisting of the amino acid sequence of SEQ ID NO: 61, CDR-H3 consisting of the amino acid sequence of SEQ ID NO: 62; CDR-L1 consisting of the amino acid sequence of SEQ ID NO: 63, CDR-L2 consisting of the amino acid sequence of AAS, and CDR-L3 consisting of the amino acid sequence of SEQ ID NO: 65.

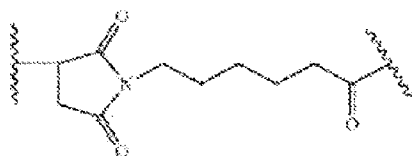
In certain embodiments of the methods, kits, or uses provided herein, the antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:66 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:67.

The method of any one of embodiments 1 to 29, wherein the anti-191P4D12 antibody comprises a heavy chain comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID NO:51 and a light chain comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:52.

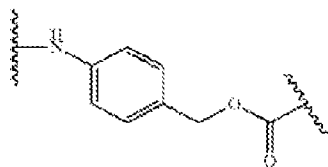
In certain embodiments of the methods, kits, or uses provided herein, the antibody drug conjugate comprising an anti-191P4D12 antigen binding fragment is an Fab, F(ab')₂, Fv or scFv.

In certain embodiments of the methods, kits, or uses provided herein, the antibody drug conjugate comprising an anti-191P4D12 antibody is a fully human antibody. In certain embodiments of the methods, kits, or uses provided herein, the antibody drug conjugate comprising an anti-191P4D12 antibody is an IgG1 and light chain is a kappa light chain. In certain embodiments of the methods, kits, or uses provided herein, the antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof is recombinantly produced. In certain embodiments of the methods, kits, or uses provided herein, the antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment is conjugated to each unit of MMAE via a linker. In certain embodiments of the methods, kits, or uses provided herein, 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.

In certain embodiments of the methods, kits, or uses provided herein, 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 a further embodiment, 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)



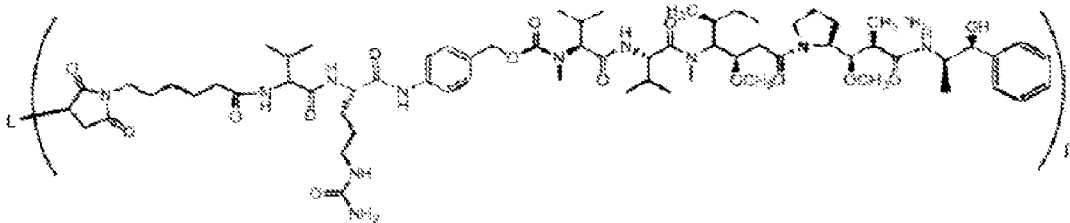
Formula (2).

In yet a further embodiment, 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.

In certain embodiments of the methods, kits, or uses provided herein, the ADC comprises from 1 to 20 units of MMAE per antibody or antigen binding fragment thereof. In certain embodiments of the methods, kits, or uses provided herein, the ADC comprises from 1 to 10 units of MMAE per antibody or antigen binding fragment thereof. In certain embodiments of the methods, kits, or uses provided herein, the ADC comprises from 2 to 8 units of MMAE per antibody or antigen binding fragment thereof. In certain embodiments of the methods, kits, or

uses provided herein, the ADC comprises from 3 to 5 units of MMAE per antibody or antigen binding fragment thereof.

In certain embodiments of the methods, kits, or uses provided herein, the ADC has the following structure:



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wherein L- represents the anti-191P4D12 antibody or antigen binding fragment thereof and p is from 1 to 10. In yet a further embodiment, the p is from 2 to 8. In yet a further embodiment, the p is from 3 to 5. In yet a further embodiment, the p is from 3 to 4. In yet a further embodiment, the p is 4. In yet a further embodiment, the average p value of the effective amount of the antibody drug conjugates is about 3.8.

In certain embodiments of the methods, kits, or uses provided herein, the ADC is administered to the subject at a dose of about 1 to about 10 mg/kg of the subject's body weight, about 1 to about 5 mg/kg of the subject's body weight, about 1 to about 2.5 mg/kg of the subject's body weight, or about 1 to about 1.25 mg/kg of the subject's body weight.

In certain embodiments of the methods, kits, or uses provided herein, the ADC is administered to the subject at a dose of about 0.25 mg/kg, about 0.5 mg/kg, about 0.75 mg/kg, about 1.0 mg/kg, about 1.25 mg/kg, about 1.5 mg/kg, about 1.75 mg/kg, about 2.0 mg/kg, about 2.25 mg/kg, or about 2.5 mg/kg of the subject's body weight.

In certain embodiments of the methods, kits, or uses provided herein, the ADC is administered to the subject at a dose of about 1 mg/kg of the subject's body weight.

In certain embodiments of the methods, kits, or uses provided herein, the ADC is administered to the subject at a dose of about 1.25 mg/kg of the subject's body weight.

In certain embodiments of the methods, kits, or uses provided herein, the ADC is administered to the subject by an intravenous (IV) injection or infusion.

In certain embodiments of the methods, kits, or uses provided herein, the ADC is administered to the subject by one or more IV injections or infusions on up to 2 days of a 21-day treatment cycle (e.g. day 1 and day 8).

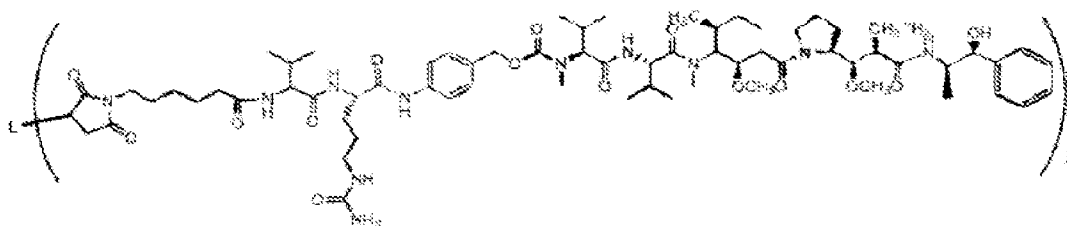
In certain embodiments of the methods, kits, or uses provided herein, the ADC is administered to the subject by an IV injection or infusion on days 1 and 8 of a 21-day treatment cycle.

In certain embodiments of the methods, kits, or uses provided herein, the ADC is administered to the subject by one or more IV injections or infusions, each over about 30 minutes on up to 2 days of a 21-day treatment cycle.

In certain embodiments of the methods, kits, or uses provided herein, the ADC is administered by an IV injection or infusion over about 30 minutes on days 1 and 8 of a 21-day treatment cycle.

In certain embodiments of the methods, kits, or uses provided herein, the ADC is formulated in a pharmaceutical composition comprising L-histidine, polysorbate-20 (TWEEN-20), and trehalose dehydrate. In yet a further embodiment, the ADC is formulated in a pharmaceutical composition comprising about 20 mM L-histidine, about 0.02% (w/v) TWEEN-20, about 5.5% (w/v) trehalose dihydrate, and hydrochloride, and wherein the pH of the pharmaceutical composition is about 6.0 at 25°C.

In certain embodiments of the methods, kits, or uses provided herein, the ADC is formulated in a pharmaceutical composition comprising about 9 mM histidine, about 11 mM histidine hydrochloride monohydrate, about 0.02% (w/v) TWEEN-20, and about 5.5% (w/v) trehalose dihydrate, and wherein the pH of the pharmaceutical composition is about 6.0 at 25°C.



wherein L- represents the antibody or antigen binding fragment thereof and p is from about 3 to about 4, the anti-191P4D12 antibody comprises a heavy chain comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID NO:51 and a light chain comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:52, wherein the ADC is administered at a dose of about 1.25 mg/kg of the subject's body weight, and wherein the dose is administered by an IV injection or infusion over about 30 minutes on days 1 and 8 of a 21-day treatment cycle.

In certain embodiments of the methods, kits, or uses provided herein, the antibody drug conjugate comprises an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:66 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:67.

In another aspect, provided herein is a method of enhancing T cell activity, comprising contacting the T cells with:

- (a) an anti-human LAG3 antibody (*e.g.*, monoclonal antibody) or antigen binding fragment thereof;
- (b) an anti-human PD-1 antibody (*e.g.*, monoclonal antibody) or antigen binding fragment thereof; and
- (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In some embodiments, the enhancement of T cell activity occurs *in vitro*. In other embodiments, the enhancement of T cell activity occurs *in vivo*. For example, the enhancement is in a subject including but not limited to a human subject or human patient.

In certain embodiments, the enhancement of T cell activity is measured by increased cytokine production. In other embodiments, the enhancement of T cell activity is measured by increased cell proliferation.

In some embodiments, provided herein is a method of increasing cytokine production of T cells, comprising contacting the T cells with:

- (a) an anti-human LAG3 antibody (*e.g.*, monoclonal antibody) or antigen binding fragment thereof;
- (b) an anti-human PD-1 antibody (*e.g.*, monoclonal antibody) or antigen binding fragment thereof; and
- (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In some embodiments, the increased cytokine production of T cells occurs *in vitro*. In other embodiments, the increased cytokine production of T cells occurs *in vivo*.

In some embodiments, the human patient is administered:

(a) about 200 mg, or about 2 mg/kg pembrolizumab once every three or six weeks;

(b) about 800 mg of an anti-human LAG3 antibody or antigen binding fragment thereof comprising three light chain CDRs: CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41, and three heavy chain CDRs: CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44 once every three weeks; and

(c) about 1.25 mg/kg of an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE) once every three weeks on days 1 and 8 of every cycle.

In certain embodiments, the human patient is administered:

(a) about 200 mg, or about 2 mg/kg pembrolizumab once every three weeks;

(b) about 800 mg of an anti-human LAG3 antibody or antigen binding fragment thereof comprising three light chain CDRs: CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41, and three heavy chain CDRs: CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44 once every three weeks; and

(c) about 1.25 mg/kg of an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE) once every three weeks on days 1 and 8 of every cycle.

In certain embodiments, the human patient is administered:

(a) about 200 mg pembrolizumab once every three weeks;

(b) about 800 mg of an anti-human LAG3 antibody or antigen binding fragment thereof comprising three light chain CDRs: CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO:

40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41, and three heavy chain CDRs: CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44 once every three weeks; and

(c) about 1.25 mg/kg of an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE) once every three weeks on days 1 and 8 of every cycle.

In certain embodiments, the human patient is administered:

(a) 200 mg pembrolizumab about once every three weeks;

(b) 800 mg of an anti-human LAG3 antibody or antigen binding fragment thereof comprising three light chain CDRs: CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41, and three heavy chain CDRs: CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44 about once every three weeks; and

(c) about 1.25 mg/kg of an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE) once every three weeks on days 1 and 8 of every cycle. In certain embodiments, the human patient is administered:

(a) about 240 mg pembrolizumab once every three weeks;

(b) about 800 mg of an anti-human LAG3 antibody or antigen binding fragment thereof comprising three light chain CDRs: CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41, and three heavy chain CDRs: CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44 once every three weeks; and

(c) about 1.25 mg/kg of an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or

antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE) once every three weeks on days 1 and 8 of every cycle.

In certain embodiments, the human patient is administered:

- 5 (a) about 2 mg/kg pembrolizumab once every three weeks;
- (b) about 800 mg of an anti-human LAG3 antibody or antigen binding fragment thereof comprising three light chain CDRs: CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41, and three
- 10 heavy chain CDRs: CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44 once every three weeks; and
- (c) about 1.25 mg/kg of an antibody drug conjugate comprising an anti-191P4D12
- 15 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE) once every three weeks on days 1 and 8 of every cycle.

In a specific embodiment, provided herein is a method of treating urothelial cancer, comprising

20 administering to a human patient in need thereof:

- (a) about 200 mg pembrolizumab once every three weeks;
- (b) about 800 mg of an anti-human LAG3 antibody or antigen binding fragment thereof comprising three light chain CDRs: CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41, and three
- 25 heavy chain CDRs: CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44 once every three weeks; and
- (c) about 1.25 mg/kg of an antibody drug conjugate comprising an anti-191P4D12
- 30 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE) once every three weeks on days 1 and 8 of every cycle.

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In certain embodiments of the methods, kits and uses provided herein, the anti-human LAG3 monoclonal antibody and the anti-human PD-1 monoclonal antibody are administered on the same day. In some embodiments, the anti-human LAG3 monoclonal antibody and the anti-human PD-1 monoclonal antibody are administered sequentially. In some embodiments, the anti-human LAG3 monoclonal antibody and the anti-human PD-1 monoclonal antibody are administered concurrently. In some embodiments, the anti-human LAG3 monoclonal antibody and the anti-human PD-1 monoclonal antibody are co-formulated.

BRIEF DESCRIPTION OF THE DRAWINGS

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

FIG. 2 shows the clinical trial study schema.

FIG. 3 shows amino acid sequences of the light chain and heavy chain for an exemplary anti-PD-1 monoclonal antibody useful in the invention (SEQ ID NOs: 5 and 10, respectively). Light chain and heavy chain variable regions are underlined (SEQ ID NOs: 4 and 9, respectively) and CDRs are bold.

DETAILED DESCRIPTION

Definitions

Certain technical and scientific terms are specifically defined below. Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this disclosure relates.

“About” when used to modify a numerically defined parameter (*e.g.*, the dose of an anti-LAG3 antibody or antigen binding fragment thereof, an anti-PD-1 antibody or antigen binding fragment thereof, or of an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE), or the length of treatment time with a combination therapy described herein) means that the parameter is within 20%, within 15%, within 10%, within 9%, within 8%, within 7%, within 6%, within 5%, within 4%, within 3%, within 2%, within 1%, or less of the stated numerical value or range for that parameter; where appropriate, the stated parameter may be rounded to the nearest whole number. For example, a dose of about 5 mg/kg may vary between 4.5 mg/kg and 5.5 mg/kg.

As used herein, including the appended claims, the singular forms of words such as “a,” “an,” and “the,” include their corresponding plural references unless the context clearly dictates otherwise.

As used herein, the terms “at least one” item or “one or more” item each include a single
5 item selected from the list as well as mixtures of two or more items selected from the list.

“Comprising” or variations such as “comprise”, “comprises” or “comprised of” are used throughout the specification and claims in an inclusive sense, i.e., to specify the presence of the stated features but not to preclude the presence or addition of further features that may materially enhance the operation or utility of any of the embodiments of the invention, unless the context
10 requires otherwise due to express language or necessary implication.

It is understood that wherever embodiments are described herein with the language “comprising,” otherwise analogous embodiments described in terms of “consisting of” and/or “consisting essentially of” are also provided.

“Consists essentially of,” and variations such as “consist essentially of” or “consisting
15 essentially of,” as used throughout the specification and claims, indicate the inclusion of any recited elements or group of elements, and the optional inclusion of other elements, of similar or different nature than the recited elements, that do not materially change the basic or novel properties of the specified dosage regimen, method, or composition.

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

Unless expressly stated to the contrary, all ranges cited herein are inclusive; i.e., the range
25 includes the values for the upper and lower limits of the range as well as all values in between. As an example, temperature ranges, percentages, ranges of equivalents, and the like described herein include the upper and lower limits of the range and any value in the continuum there between. Numerical values provided herein, and the use of the term “about”, may include variations of $\pm 1\%$, $\pm 2\%$, $\pm 3\%$, $\pm 4\%$, $\pm 5\%$, $\pm 10\%$, $\pm 15\%$, and $\pm 20\%$ and their numerical
30 equivalents. All ranges also are intended to include all included sub-ranges, although not necessarily explicitly set forth. For example, a range of 3 to 7 days is intended to include 3, 4, 5, 6, and 7 days. In addition, the term “or,” as used herein, denotes alternatives that may, where appropriate, be combined; that is, the term “or” includes each listed alternative separately as well as their combination.

Where aspects or embodiments of the disclosure are described in terms of a Markush group or other grouping of alternatives, the present disclosure encompasses not only the entire group listed as a whole, but each member of the group individually and all possible subgroups of the main group, but also the main group absent one or more of the group members. The present disclosure also envisages the explicit exclusion of one or more of any of the group members in the claims.

Unless otherwise defined, 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 relates. In case of conflict, the present specification, including definitions, will control.

Throughout this specification and claims, the word “comprise,” or variations such as “comprises” or “comprising” will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Any example(s) following the term “*e.g.*” or “for example” is not meant to be exhaustive or limiting.

Exemplary methods and materials are described herein, although methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure. The materials, methods, and examples are illustrative only and not intended to be limiting.

The terms “administration” or “administer” refers to the act of injecting or otherwise physically delivering a substance as it exists outside the body (*e.g.*, an anti-LAG3 antibody, an anti-PD-1 antibody, and of an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE) as described herein) into a patient or subject, such as by oral, mucosal, intradermal, intravenous, subcutaneous, intramuscular delivery, and/or any other methods of physical delivery described herein or known in the art.

The term “subject” (alternatively “patient”) as used herein refers to a mammal that has been the object of treatment, observation, or experiment. The mammal may be male or female. The mammal may be one or more selected from the group consisting of humans, bovine (*e.g.*, cows), porcine (*e.g.*, pigs), ovine (*e.g.*, sheep), capra (*e.g.*, goats), equine (*e.g.*, horses), canine (*e.g.*, domestic dogs), feline (*e.g.*, house cats), lagomorph (*e.g.*, rabbits), rodent (*e.g.*, rats or mice), *Procyon lotor* (*e.g.*, raccoons). In particular embodiments, the subject is human.

The term “subject in need thereof” as used herein refers to a subject diagnosed with or suspected of having cancer as defined herein.

As used herein, the term “antibody” refers to any form of immunoglobulin molecule that exhibits the desired biological or binding activity. Thus, it is used in the broadest sense and specifically covers, but is not limited to, monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies),
5 humanized, fully human antibodies, and chimeric antibodies. “Parental antibodies” are antibodies obtained by exposure of an immune system to an antigen prior to modification of the antibodies for an intended use, such as humanization of an antibody for use as a human therapeutic. As used herein, the term “antibody” encompasses not only intact polyclonal or monoclonal antibodies, but also, unless otherwise specified, fusion proteins comprising an antigen binding fragment thereof
10 that competes with the intact antibody for specific.

In general, the basic antibody structural unit comprises a tetramer. Each tetramer includes two identical pairs of polypeptide chains, each pair having one “light” (about 25 kDa) and one “heavy” chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition.
15 The variable regions of each light/heavy chain pair form the antibody binding site. Thus, in general, an intact antibody has two binding sites. The carboxy-terminal portion of the heavy chain may define a constant region primarily responsible for effector function. Typically, human light chains are classified as kappa and lambda light chains. Furthermore, human heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon, and define the antibody’s isotype
20 as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a “J” region of about 12 or more amino acids, with the heavy chain also including a “D” region of about 10 more amino acids. See generally, Fundamental Immunology Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989).

“Variable regions” or “V region” or “V chain” as used herein means the segment of IgG
25 chains which is variable in sequence between different antibodies. A “variable region” of an antibody refers to the variable region of the antibody light chain or the variable region of the antibody heavy chain, either alone or in combination. The variable region of the heavy chain may be referred to as “V_H.” The variable region of the light chain may be referred to as “V_L.”

Typically, the variable regions of both the heavy and light chains comprise three
30 hypervariable regions, also called complementarity determining regions (CDRs), which are located within relatively conserved framework regions (FR). The CDRs are usually aligned by the framework regions, enabling binding to a specific epitope. In general, from N-terminal to C-terminal, both light and heavy chains variable domains comprise FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. As referred to herein the light chain CDRs are CDRL1, CDRL2 and CDRL3,
35 respectively, and the heavy chain CDRs are CDRH1, CDRH2 and CDRH3, respectively. The

assignment of amino acids to each domain is, generally, in accordance with the definitions of Sequences of Proteins of Immunological Interest, Kabat, *et al.*; National Institutes of Health, Bethesda, Md.; 5th ed.; NIH Publ. No. 91-3242 (1991); Kabat (1978) Adv. Prot. Chem. 32:1-75; Kabat, *et al.*, (1977) J. Biol. Chem. 252:6609-6616; Chothia, *et al.*, (1987) J Mol. Biol. 196:901-917 or Chothia, *et al.*, (1989) Nature 342:878-883.

A “CDR” refers to one of three hypervariable regions (H1, H2, or H3) within the non-framework region of the antibody V_H β -sheet framework, or one of three hypervariable regions (L1, L2, or L3) within the non-framework region of the antibody V_L β -sheet framework.

Accordingly, CDRs are variable region sequences interspersed within the framework region

sequences. CDR regions are well known to those skilled in the art and have been defined by, for example, Kabat as the regions of most hypervariability within the antibody variable domains.

CDR region sequences also have been defined structurally by Chothia as those residues that are not part of the conserved β -sheet framework, and thus are able to adapt to different conformation.

Both terminologies are well recognized in the art. CDR region sequences have also been defined

by AbM, Contact, and IMGT. The positions of CDRs within a canonical antibody variable region have been determined by comparison of numerous structures (Al-Lazikani *et al.*, 1997, J. Mol.

Biol. 273:927-48; Morea *et al.*, 2000, Methods 20:267-79). Because the number of residues within a hypervariable region varies in different antibodies, additional residues relative to the canonical positions are conventionally numbered with a, b, c and so forth next to the residue

number in the canonical variable region numbering scheme (Al-Lazikani *et al.*, *supra*). Such nomenclature is similarly well known to those skilled in the art. Correspondence between the numbering system, including, for example, the Kabat numbering and the IMGT unique

numbering system, is well known to one skilled in the art and shown below in Table 1. In some embodiments, the CDRs are as defined by the Kabat numbering system. In other embodiments,

the CDRs are as defined by the IMGT numbering system. In yet other embodiments, the CDRs are as defined by the AbM numbering system. In still other embodiments, the CDRs are as defined by the Chothia numbering system. In yet other embodiments, the CDRs are as defined by the Contact numbering system.

Table 1. Correspondence between the CDR Numbering Systems

	Kabat + Chothia	IMGT	Kabat	AbM	Chothia	Contact
V _H CDR1	26-35	27-38	31-35	26-35	26-32	30-35
V _H CDR2	50-65	56-65	50-65	50-58	52-56	47-58
V _H CDR3	95-102	105-117	95-102	95-102	95-102	93-101
V _L CDR1	24-34	27-38	24-34	24-34	24-34	30-36
V _L CDR2	50-56	56-65	50-56	50-56	50-56	46-55

V _L CDR3	89-97	105-117	89-97	89-97	89-97	89-96
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“Chimeric antibody” refers to an antibody in which a portion of the heavy and/or light chain contains sequences derived from a particular species (*e.g.*, human) or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is derived from another species (*e.g.*, mouse) or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity.

“Co-formulated” or “co-formulation” or “coformulation” or “co-formulated” as used herein refers to at least two different proteins or agents which are formulated together and stored as a combined product in a single vial, container, device or vessel (for example an injection device) rather than being formulated and stored individually and then mixed before administration or separately administered.

“Human antibody” refers to an antibody that comprises human immunoglobulin protein sequences or derivatives thereof. A human antibody may contain murine carbohydrate chains if produced in a mouse, in a mouse cell, or in a hybridoma derived from a mouse cell. Similarly, “mouse antibody” or “rat antibody” refer to an antibody that comprises only mouse or rat immunoglobulin sequences or derivatives thereof, respectively.

“Humanized antibody” refers to forms of antibodies that contain sequences from non-human (*e.g.*, murine) antibodies as well as human antibodies. Such antibodies contain minimal sequence derived from non-human immunoglobulin. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. The prefix “hum”, “hu” or “h” may be added to antibody clone designations when necessary to distinguish humanized antibodies from parental rodent antibodies. The humanized forms of rodent antibodies will generally comprise the same CDR sequences of the parental rodent antibodies, although certain amino acid substitutions may be included to increase affinity, increase stability of the humanized antibody, or for other reasons.

“Monoclonal antibody” or “mAb” or “Mab”, as used herein, refers to a population of substantially homogeneous antibodies, *i.e.*, the antibody molecules comprising the population are identical in amino acid sequence except for possible naturally occurring mutations that may be present in minor amounts. In contrast, conventional (polyclonal) antibody preparations typically include a multitude of different antibodies having different amino acid sequences in their variable

domains, particularly their CDRs, which are often specific for different epitopes. The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by the hybridoma method first described by Kohler *et al.* (1975) *Nature* 256: 495, or may be made by recombinant DNA methods (*see, e.g.*, U.S. Pat. No. 4,816,567). The “monoclonal antibodies” may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.* (1991) *Nature* 352: 624-628 and Marks *et al.* (1991) *J. Mol. Biol.* 222: 581-597, for example. *See also* Presta (2005) *J. Allergy Clin. Immunol.* 116:731.

As used herein, unless otherwise indicated, “antibody fragment” or “antigen binding fragment” refers to a fragment of an antibody that retains the ability to bind specifically to the antigen, *e.g.*, fragments that retain one or more CDR regions and the ability to bind specifically to the antigen. An antibody that “specifically binds to” LAG3 or PD-1 is an antibody that exhibits preferential binding to LAG3 or PD-1 (as appropriate) as compared to other proteins, but this specificity does not require absolute binding specificity. An antibody is considered “specific” for its intended target if its binding is determinative of the presence of the target protein in a sample, *e.g.*, without producing undesired results such as false positives. Antibodies, or binding fragments thereof, will bind to the target protein with an affinity that is at least two-fold greater, preferably at least ten times greater, more preferably at least 20-times greater, and most preferably at least 100-times greater than the affinity with non-target proteins.

Antigen binding portions include, for example, Fab, Fab', F(ab')₂, Fd, Fv, fragments including CDRs, and single chain variable fragment antibodies (scFv), and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the antigen (*e.g.*, LAG3 or PD-1). An antibody includes an antibody of any class, such as IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the antibody amino acid sequence of the constant region of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), *e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The heavy-chain constant regions that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

An “antigen” is a structure to which an antibody can selectively bind. A target antigen may be a polypeptide, carbohydrate, nucleic acid, lipid, hapten, or other naturally occurring or

synthetic compound. In some embodiments, the target antigen is a polypeptide. In certain embodiments, an antigen is associated with a cell, for example, is present on or in a cell, for example, a cancer cell.

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

As used herein, the term "immune response" relates to any one or more of the following: specific immune response, non-specific immune response, both specific and non-specific response, innate response, primary immune response, adaptive immunity, secondary immune response, memory immune response, immune cell activation, immune cell-proliferation, immune cell differentiation, and cytokine expression.

The therapeutic agents and compositions provided by the present disclosure can be administered via any suitable enteral route or parenteral route of administration. The term "enteral route" of administration refers to the administration via any part of the gastrointestinal tract. Examples of enteral routes include oral, mucosal, buccal, and rectal route, or intragastric route. "Parenteral route" of administration refers to a route of administration other than enteral route. Examples of parenteral routes of administration include intravenous, intramuscular, intradermal, intraperitoneal, intratumor, intravesical, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, transtracheal, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal, subcutaneous, or topical administration. The therapeutic agents and compositions of the disclosure can be administered using any suitable method, such as by oral ingestion, nasogastric tube, gastrostomy tube, injection, infusion, implantable infusion pump, and osmotic pump. The suitable route and method of administration may vary depending on a number of factors such as the specific therapeutic agent being used, the rate of absorption desired, specific formulation or dosage form used, type or severity of the disorder being treated, the specific site of action, and conditions of the patient, and can be readily selected by a person skilled in the art.

"Chemotherapeutic agent" is a chemical compound useful in the treatment of cancer.

Classes of chemotherapeutic agents include, but are not limited to: alkylating agents, antimetabolites, kinase inhibitors, spindle poison plant alkaloids, cytotoxic/antitumor antibiotics, topoisomerase inhibitors, photosensitizers, anti-estrogens and selective estrogen receptor modulators (SERMs), anti-progesterones, estrogen receptor down-regulators (ERDs), estrogen receptor antagonists, leutinizing hormone-releasing hormone agonists, anti-androgens, aromatase inhibitors, EGFR inhibitors, VEGF inhibitors, and anti-sense oligonucleotides that inhibit

expression of genes implicated in abnormal cell proliferation or tumor growth. Chemotherapeutic agents useful in the treatment methods of the present invention include cytostatic and/or cytotoxic agents.

The term “variant” when used in relation to an antibody (*e.g.*, an anti-LAG3 antibody or an anti-PD-1 antibody) or an amino acid region within the antibody may refer to a peptide or polypeptide comprising one or more (such as, for example, about 1 to about 25, about 1 to about 20, about 1 to about 15, about 1 to about 10, or about 1 to about 5) amino acid sequence substitutions, deletions, and/or additions as compared to a native or unmodified sequence. For example, a variant of an anti-PD-1 antibody may result from one or more (such as, for example, about 1 to about 25, about 1 to about 20, about 1 to about 15, about 1 to about 10, or about 1 to about 5) changes to an amino acid sequence of a native or previously unmodified anti-PD-1 antibody. Variants may be naturally occurring or may be artificially constructed. Polypeptide variants may be prepared from the corresponding nucleic acid molecules encoding the variants. In specific embodiments, an antibody variant (*e.g.*, an anti-LAG3 antibody variant or an anti-PD-1 antibody variant) at least retains the antibody functional activity. In specific embodiments, an anti-LAG3 antibody variant binds to LAG3 and/or is antagonistic to LAG3 activity. In some embodiments, an anti-PD-1 antibody variant binds to PD-1 and/or is antagonistic to PD-1 activity.

“Conservatively modified variants” or “conservative substitution” refers to substitutions of amino acids in a protein with other amino acids having similar characteristics (*e.g.*, charge, side-chain size, hydrophobicity/hydrophilicity, backbone conformation and rigidity, *etc.*), such that the changes can frequently be made without altering the biological activity or other desired property of the protein, such as antigen affinity and/or specificity. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (*see, e.g.*, Watson *et al.* (1987) *Molecular Biology of the Gene*, The Benjamin/Cummings Pub. Co., p. 224 (4th Ed.)). In addition, substitutions of structurally or functionally similar amino acids are less likely to disrupt biological activity. Exemplary conservative substitutions are set forth in Table 2 below.

Table 2. Exemplary Conservative Amino Acid Substitutions

Original residue	Conservative substitution
Ala (A)	Gly; Ser
Arg (R)	Lys; His
Asn (N)	Gln; His
Asp (D)	Glu; Asn
Cys (C)	Ser; Ala
Gln (Q)	Asn

Original residue	Conservative substitution
Glu (E)	Asp; Gln
Gly (G)	Ala
His (H)	Asn; Gln
Ile (I)	Leu; Val
Leu (L)	Ile; Val
Lys (K)	Arg; His
Met (M)	Leu; Ile; Tyr
Phe (F)	Tyr; Met; Leu
Pro (P)	Ala
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr; Phe
Tyr (Y)	Trp; Phe
Val (V)	Ile; Leu

“Homology” refers to sequence similarity between two polypeptide sequences when they are optimally aligned. When a position in both of the two compared sequences is occupied by the same amino acid monomer subunit, *e.g.*, if a position in a light chain CDR of two different Abs is occupied by alanine, then the two Abs are homologous at that position. The percent of homology is the number of homologous positions shared by the two sequences divided by the total number of positions compared $\times 100$. For example, if 8 of 10 of the positions in two sequences are matched when the sequences are optimally aligned then the two sequences are 80% homologous. Generally, the comparison is made when two sequences are aligned to give maximum percent homology. For example, the comparison can be performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences.

The following references relate to BLAST algorithms often used for sequence analysis: BLAST ALGORITHMS: Altschul, S.F., *et al.*, (1990) *J. Mol. Biol.* 215:403-410; Gish, W., *et al.*, (1993) *Nature Genet.* 3:266-272; Madden, T.L., *et al.*, (1996) *Meth. Enzymol.* 266:131-141; Altschul, S.F., *et al.*, (1997) *Nucleic Acids Res.* 25:3389-3402; Zhang, J., *et al.*, (1997) *Genome Res.* 7:649-656; Wootton, J.C., *et al.*, (1993) *Comput. Chem.* 17:149-163; Hancock, J.M. *et al.*, (1994) *Comput. Appl. Biosci.* 10:67-70; ALIGNMENT SCORING SYSTEMS: Dayhoff, M.O., *et al.*, “A model of evolutionary change in proteins.” in *Atlas of Protein Sequence and Structure*, (1978) vol. 5, suppl. 3. M.O. Dayhoff (ed.), pp. 345-352, Natl. Biomed. Res. Found., Washington, DC; Schwartz, R.M., *et al.*, “Matrices for detecting distant relationships.” in *Atlas of Protein Sequence and Structure*, (1978) vol. 5, suppl. 3.” M.O. Dayhoff (ed.), pp. 353-358,

Natl. Biomed. Res. Found., Washington, DC; Altschul, S.F., (1991) *J. Mol. Biol.* 219:555-565; States, D.J., *et al.*, (1991) *Methods* 3:66-70; Henikoff, S., *et al.*, (1992) *Proc. Natl. Acad. Sci. USA* 89:10915-10919; Altschul, S.F., *et al.*, (1993) *J. Mol. Evol.* 36:290-300; ALIGNMENT STATISTICS: Karlin, S., *et al.*, (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268; Karlin, S., *et al.*, (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877; Dembo, A., *et al.*, (1994) *Ann. Prob.* 22:2022-2039; and Altschul, S.F. "Evaluating the statistical significance of multiple distinct local alignments." in *Theoretical and Computational Methods in Genome Research* (S. Suhai, ed.), (1997) pp. 1-14, Plenum, New York.

"RECIST 1.1 Response Criteria" as used herein means the definitions set forth in Eisenhauer, E.A. *et al.*, *Eur. J. Cancer* 45:228-247 (2009) for target lesions or nontarget lesions, as appropriate based on the context in which response is being measured.

"Sustained response" means a sustained therapeutic effect after cessation of treatment as described herein. 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.

"Non-responder patient", when referring to a specific anti-tumor response to treatment with a combination therapy described herein, means the patient did not exhibit the anti-tumor response.

"Responder patient" when referring to a specific anti-tumor response to treatment with a combination therapy described herein, means the patient exhibited the anti-tumor response.

"Treat" or "treating" cancer as used herein means to administer a therapeutic combination of an anti-human PD-1 monoclonal antibody or antigen binding fragment thereof, an anti-human LAG3 monoclonal antibody or antigen binding fragment thereof, and an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE), such as, *e.g.*, an anti-human PD-1 monoclonal antibody or antigen binding fragment thereof, an anti-human LAG3 monoclonal antibody or antigen binding fragment thereof, and an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE), to a subject having cancer or diagnosed with cancer to achieve at least one positive therapeutic effect, such as, for example, reduced number of cancer cells, reduced tumor size, reduced rate of cancer cell infiltration into peripheral organs, or reduced rate of tumor metastasis or tumor growth, comprising administration by oral, mucosal, intradermal, intravenous, subcutaneous, intramuscular delivery, and/or any other methods of

physical delivery described herein or known in the art. Typically, the agents of the therapeutic combination are administered in an amount effective to alleviate one or more disease symptoms in the treated subject or population, whether by inducing the regression of or inhibiting the progression of such symptom(s) by any clinically measurable degree. The amount of the agents of the therapeutic combination that is effective to alleviate any particular disease symptom may vary according to factors such as the disease state, age, and weight of the patient, and the ability of the therapeutic combination to elicit a desired response in the subject. Whether a disease symptom has been alleviated can be assessed by any clinical measurement typically used by physicians or other skilled healthcare providers to assess the severity or progression status of that symptom. "Treatment" may include one or more of the following: inducing/increasing an antitumor immune response, decreasing the number of one or more tumor markers, halting or delaying the growth of a tumor or blood cancer or progression of disease such as cancer, stabilization of disease, inhibiting the growth or survival of tumor cells, eliminating or reducing the size of one or more cancerous lesions or tumors, decreasing the level of one or more tumor markers, ameliorating or abrogating the clinical manifestations of disease, reducing the severity or duration of the clinical symptoms, prolonging the survival of patient relative to the expected survival in a similar untreated patient, and inducing complete or partial remission of a cancerous condition, wherein the disease is cancer, and in certain embodiments wherein the cancer is selected from the group consisting of melanoma, non-small cell lung cancer, head and neck squamous cell cancer, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high or mismatch repair deficient cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, a cancer characterized by a tumor having a high mutational burden, cutaneous squamous cell carcinoma, and triple negative breast cancer.

The amount of a therapeutic agent that is effective to alleviate any particular disease symptom may vary according to factors such as the disease state, age, and weight of the patient, and the ability of the drug to elicit a desired response in the subject. Whether a disease symptom has been alleviated can be assessed by any clinical measurement typically used by physicians or other skilled healthcare providers to assess the severity or progression status of that symptom.

Positive therapeutic effects in cancer can be measured in a number of ways (*See, W. A. Weber, J. Nucl. Med.* 50:1S-10S (2009)). For example, with respect to tumor growth inhibition, according to NCI standards, a $T/C \leq 42\%$ is the minimum level of anti-tumor activity. A $T/C < 10\%$ is considered a high anti-tumor activity level, with $T/C (\%) = \text{Median tumor volume of the treated} / \text{Median tumor volume of the control} \times 100$. In some embodiments, the treatment achieved by a combination therapy of the disclosure is any of PR, CR, OR, PFS, DFS, and OS. PFS, also

referred to as “Time to Tumor Progression” indicates the length of time during and after treatment that the cancer does not grow, and includes the amount of time patients have experienced a CR or PR, as well as the amount of time patients have experienced SD. DFS refers to the length of time during and after treatment that the patient remains free of disease. OS refers to a prolongation in life expectancy as compared to naive or untreated individuals or patients. In some embodiments, response to a combination therapy of the disclosure is any of PR, CR, PFS, DFS, or OR that is assessed using RECIST 1.1 response criteria. The treatment regimen for a combination therapy of the disclosure that is effective to treat a cancer patient may vary according to factors such as the disease state, age, and weight of the patient, and the ability of the therapy to elicit an anti-cancer response in the subject. While an embodiment of any of the aspects of the disclosure may not be effective in achieving a positive therapeutic effect in every subject, it should do so in a statistically significant number of subjects as determined by any statistical test known in the art such as the Student’s t-test, the chi²-test, the U-test according to Mann and Whitney, the Kruskal-Wallis test (H-test), Jonckheere-Terpstra-test and the Wilcoxon-test.

“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 NKT cell) and preferably also blocks binding of PD-L2 expressed on a cancer cell to the immune-cell expressed PD-1. Alternative names or synonyms for PD-1 and its ligands include: PDCD1, PD1, CD279 and SLEB2 for PD-1; PDCD1L1, PDL1, B7H1, B7-4, CD274 and B7-H for PD-L1; and PDCD1L2, PDL2, B7-DC, Btdc and CD273 for PD-L2. In any of the treatment method, medicaments and uses of the present invention in which a human individual is being treated, the PD-1 antagonist blocks binding of human PD-L1 to human PD-1, and preferably 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.

“Pembrolizumab” (formerly known as MK-3475, SCH 900475 and lambrolizumab) alternatively referred to herein as “pembro,” is a humanized IgG4 mAb with the structure described in *WHO Drug Information*, Vol. 27, No. 2, pages 161-162 (2013) and which comprises the heavy and light chain amino acid sequences and CDRs described in Table 4. Pembrolizumab has been approved by the U.S. FDA as described in the Prescribing Information for KEYTRUDA™ (Merck & Co., Inc., Rahway, NJ USA; initial U.S. approval 2014, updated November 2023).

“Pembrolizumab variant” as used herein means a monoclonal antibody that comprises heavy chain and light chain sequences that are identical to those in pembrolizumab, except for

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

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

The "191P4D12 proteins" and/or "191P4D12 related proteins" of the disclosure include those specifically identified herein (see, FIG. 1A), as well as allelic variants, conservative substitution variants, analogs and homologs that can be isolated/generated and characterized without undue experimentation following the methods outlined herein or readily available in the art. Fusion proteins that combine parts of different 191P4D12 proteins or fragments thereof, as well as fusion proteins of a 191P4D12 protein and a heterologous polypeptide are also included. Such 191P4D12 proteins are collectively referred to as the 191P4D12-related proteins, the proteins of the disclosure, or 191P4D12. The term

"191P4D12-related protein" refers to a polypeptide fragment or a 191P4D12 protein sequence of 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more than 25 amino acids; or, at least 30, 35, 40, 45, 50, 55, 60, 65, 70, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 225, 250, 275, 300, 325, 330, 335, 339 or more amino acids. The term "191P4D12" is used interchangeably with nectin-4.

"Pharmaceutical formulation" refers to preparations that contain an active ingredient and one or more pharmaceutically acceptable excipients and that are in such form as to permit the active ingredients to be effective, and which contains no additional components which are toxic to the subjects to which the formulation would be administered.

The term "co-formulation" refers to a formulation comprising two or more of therapeutic agents (i.e., two or more active ingredients). In some embodiments, co-formulation comprises a LAG3 antagonist and a PD-1 antagonist.

"Pharmaceutically acceptable" refers to excipients (vehicles, additives) and compositions that can reasonably be administered to a subject to provide an effective dose of the active

ingredient employed and that are “generally regarded as safe” e.g., that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset and the like, when administered to a human. In another embodiment, this term refers to molecular entities and compositions approved by a regulatory agency of the federal or a state government or listed in the U.S. Pharmacopeia or another generally recognized pharmacopeia for use in animals, and more particularly in humans.

The term “pharmaceutically acceptable carrier” refers to any inactive substance that is suitable for use in a formulation for the delivery of a therapeutic agent. A carrier may be an anti-adherent, binder, coating, disintegrant, filler or diluent, preservative (such as antioxidant, antibacterial, or antifungal agent), sweetener, absorption delaying agent, wetting agent, emulsifying agent, buffer, and the like. Examples of suitable pharmaceutically acceptable carriers include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), dextrose, vegetable oils (such as olive oil), saline, buffer, buffered saline, and isotonic agents such as sugars, polyalcohols, sorbitol, and sodium chloride.

As used herein, the terms “combination,” “combination therapy,” and “therapeutic combination” refer to treatments in which at least one anti-human LAG3 monoclonal antibody or antigen-binding fragment thereof, at least one anti-human PD-1 monoclonal antibody or antigen-binding fragment thereof, and ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE), such as, e.g., an anti-human PD-1 monoclonal antibody or antigen binding fragment thereof, an anti-human LAG3 monoclonal antibody or antigen binding fragment thereof, and ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE), and optionally additional therapeutic agents, each are administered to a patient in a coordinated manner, over an overlapping period of time as part of a treatment regimen. The period of treatment with the at least one anti-human LAG3 monoclonal antibody (or antigen-binding fragment thereof) (the “anti-LAG3 treatment”) is the period of time that a patient undergoes treatment with the anti-human LAG3 monoclonal antibody (or antigen-binding fragment thereof); that is, the period of time from the initial dosing with the anti-human LAG3 monoclonal antibody (or antigen-binding fragment thereof) through the final day of a treatment cycle. Similarly, the period of treatment with the at least one anti-human PD-1 monoclonal antibody (or antigen-binding fragment thereof) (the “anti-PD-1 treatment”) is the period of time that a patient undergoes treatment with the anti-human PD-1 monoclonal antibody (or antigen-binding fragment thereof); that is, the period of time from the initial dosing with the anti-human PD-1 monoclonal antibody (or antigen-binding fragment thereof) through the final day of a treatment cycle. The period of treatment with the ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE);

(the “ADC treatment”) is the period of time that a patient undergoes treatment with the ADC; that is, the period of time from the initial dosing with the ADC through the final day of a treatment cycle. In the methods, uses, and therapeutic combinations described herein, the anti-LAG3 treatment overlaps by at least one day with the anti-PD-1 treatment and overlaps by at least one day with the ADC treatment. In certain embodiments, the anti-LAG3 treatment, the anti-PD-1 treatment, and the ADC treatment are the same period of time. In some embodiments, the anti-LAG3 treatment begins prior to the anti-PD-1 and/or the ADC treatment. In other embodiments, the anti-LAG3 treatment begins after the anti-PD-1 and/or the ADC treatment. In yet other embodiments, the anti-PD-1 treatment begins prior to the anti-LAG3 and/or the ADC treatment. In still other embodiments, the anti-PD-1 treatment begins after the anti-LAG3 and/or the ADC treatment. In some embodiments, the ADC treatment begins prior to the anti-PD-1 and/or the anti-LAG3 treatment. In other embodiments, the ADC treatment begins after the anti-PD-1 and/or the anti-LAG3 treatment. In certain embodiments, the anti-LAG3 treatment is terminated prior to termination of the anti-PD-1 and/or the ADC treatment. In other embodiments, the anti-LAG3 treatment is terminated after termination of the anti-PD-1 and/or the ADC treatment. In yet other embodiments, the anti-PD-1 treatment is terminated prior to termination of the anti-LAG3 and/or the ADC treatment. In still other embodiments, the anti-PD-1 treatment is terminated after termination of the anti-LAG3 and/or the ADC treatment. In certain embodiments, the ADC treatment is terminated prior to termination of the anti-PD-1 and/or the anti-LAG3 treatment. In other embodiments, the ADC treatment is terminated after termination of the anti-PD-1 and/or the anti-LAG3 treatment.

The terms “treatment regimen,” “dosing protocol,” and “dosing regimen” are used interchangeably to refer to the dose and timing of administration of each therapeutic agent in a combination therapy of the disclosure.

The terms “cancer”, “cancerous”, or “malignant” refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, leukemia, blastoma, and sarcoma. More particular examples of such cancers include, but are not limited to, squamous cell carcinoma, myeloma, small-cell lung cancer, non-small cell lung cancer, glioma, Hodgkin lymphoma, non-Hodgkin lymphoma, acute myeloid leukemia (AML), multiple myeloma, gastrointestinal (tract) cancer, renal cancer, ovarian cancer, liver cancer, lymphoblastic leukemia, lymphocytic leukemia, colorectal cancer, endometrial cancer, kidney cancer, prostate cancer, thyroid cancer, melanoma, chondrosarcoma, neuroblastoma, pancreatic cancer, glioblastoma multiforme, cervical cancer, brain cancer, stomach cancer, bladder cancer, hepatoma,

hepatocellular carcinoma, biliary cancer, esophageal cancer, breast cancer, triple negative breast cancer, colon carcinoma, and head and neck cancer.

“Tumor” as it applies to a subject diagnosed with, or suspected of having, a cancer refers to a malignant or potentially malignant neoplasm or tissue mass of any size, and includes primary tumors and secondary neoplasms. Non-limiting examples of tumors include solid tumor (*e.g.*, sarcoma (such as chondrosarcoma), carcinoma (such as colon carcinoma), blastoma (such as hepatoblastoma), *etc.*) and blood tumor (*e.g.*, leukemia (such as acute myeloid leukemia (AML)), lymphoma (such as DLBCL), multiple myeloma (MM), *etc.*).

“Tumor burden” also referred to as “tumor load”, refers to the total amount of tumor material distributed throughout the body. Tumor burden refers to the total number of cancer cells or the total size of tumor(s), throughout the body, including lymph nodes and bone marrow. Tumor burden can be determined by a variety of methods known in the art, such as, *e.g.*, by measuring the dimensions of tumor(s) upon removal from the subject, *e.g.*, using calipers, or while in the body using imaging techniques, *e.g.*, ultrasound, bone scan, computed tomography (CT) or magnetic resonance imaging (MRI) scans.

The term “tumor volume” or “tumor size” refers to the total size of the tumor which can be measured as the length and width of a tumor. Tumor size may be determined by a variety of methods known in the art, such as, *e.g.*, by measuring the dimensions of tumor(s) upon removal from the subject, *e.g.*, using calipers, or while in the body using imaging techniques, *e.g.*, bone scan, ultrasound, CT or MRI scans.

As used herein, the term “effective amount” refer to an amount of an anti-LAG3 antibody or antigen binding fragment, an anti-PD-1 antibody or antigen binding fragment of the invention, and an ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE), such as, *e.g.*, an anti-human PD-1 monoclonal antibody or antigen binding fragment thereof, an anti-human LAG3 monoclonal antibody or antigen binding fragment thereof, and an ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE), that, when administered alone or in combination with an additional therapeutic agent to a cell, tissue, or subject, is effective to cause a measurable improvement in one or more symptoms of an infection or a disease, for example cancer or the progression of cancer. An effective amount further refers to that amount of the antibody or fragment sufficient to result in at least partial amelioration of symptoms, *e.g.*, tumor shrinkage or elimination, lack of tumor growth, increased survival time. When applied to an individual active ingredient administered alone, an effective dose refers to that ingredient alone. When applied to a combination, an effective dose refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. An

effective amount of a therapeutic may result in an improvement of a diagnostic measure or parameter by at least 10%; usually by at least 20%; preferably at least about 30%; more preferably at least 40%, and most preferably by at least 50%. An effective amount can also result in an improvement in a subjective measure in cases where subjective measures are used to assess disease severity. Toxicity and therapeutic efficacy of the antibodies or antigen binding fragments of the invention, administered alone or in combination with another therapeutic agent, can be determined by any number of systems or means. For example, the toxicity and therapeutic efficacy of the antibodies or antigen binding fragments or compounds of the invention can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index (LD50/ ED50). The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration.

“ORR” or “objective response rate” refers in some embodiments to CR + PR, and ORR_(week 24) refers to CR and PR measured using irRECIST in each patient in a cohort after 24 weeks of anti-cancer treatment.

As used herein, an “Ab6 antibody” means a monoclonal antibody that consists of two heavy chain and two light chain sequences of SEQ ID NO: 36 and SEQ ID NO: 35, respectively.

As used herein, an “Ab6 variant” means a monoclonal antibody that comprises heavy chain and light chain sequences that are substantially identical to those in Ab6 described herein (as described below and in International patent publn. no. WO2016028672, incorporated by reference in its entirety), except for having three, two or one conservative amino acid substitutions at positions that are located outside of the light chain CDRs and six, five, four, three, two or one conservative amino acid substitutions that are located outside of the heavy chain CDRs, *e.g.*, the variant positions are located in the FR regions or the constant region, and optionally has a deletion of the C-terminal lysine residue of the heavy chain. In other words, Ab6 and a Ab6 variant comprise identical CDR sequences, but differ from each other due to having a conservative amino acid substitution at no more than three or six other positions in their full length light and heavy chain sequences, respectively. An Ab6 variant is substantially the same as Ab6 with respect to the following properties: binding affinity to human LAG3 and ability to block the binding of human LAG3 to human MHC Class II.

“LAG3 antagonist” means any chemical compound or biological molecule that blocks binding of LAG3 expressed on an immune cell (T cell, Tregs, or NK cell etc.) to MHC Class II molecules. Human LAG3 comprises the amino acid sequence:

MWEAQFLGLL FLQPLWVAPV KPLQPGAIEV VVWAQEGAPA QLPCSPTIPL

5 QDLSLLRRAG
 VTWQHQPDSG PPAAAPGHPL APGPHPAAPS SWGPRPRRYT VLSVGPGLR
 SGRLPLQPRV
 QLDERGRQRG DFSLWLRPAR RADAGEYRAA VHLRDRALSC RLRLRLGQAS
 MTASPPGSLR
 10 ASDWVILNCS FSRPDRPASV HWFRNRGQGR VPVRESPHHH LAESFLFLPQ
 VSPMDSGPWG
 CILTYRDGFN VSIMYNLTVL GLEPPTPLTV YAGAGSRVGL PCRLPAGVGT
 RSFLTAKWTP
 PGGGPDLLVT GDNGDFTLRL EDVSQAQAGT YTCHIHLEEQ QLNATVTLAI
 15 ITVTPKSFGS
 PGSLGKLLCE VTPVSGQERF VWSSLDTPSQ RSFSGPWLEA QEAQLLSQPW
 QCQLYQGERL
 LGAAVYFTEL SSPGAQRSGR APGALPAGHL LLFLILGVLS LLLLVGTGAFG
 FHLWRRQWRP
 20 RRFSALEQGI HPPQAQSKIE ELEQEPEPEP EPEPEPEPEP EPEQL
 (SEQ ID NO: 68); see also Uniprot accession no. P18627.

Table 3: Abbreviations

Abbreviation	Expanded Term
1L	First line
ADA	antidrug antibody
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
APaT	All-Participants-as-Treated
aPTT	Activated partial thromboplastin time
BCG	Bacillus Calmette–Guérin
BICR	blinded independent central review
BID	One dose twice daily
BOR	Best overall response
BP	blood pressure
BRAF	v-raf murine sarcoma viral oncogene homolog B1

C1	Cycle 1
C2	Cycle 2
C3	Cycle 3
C4	Cycle 4
C5	Cycle 5
C6	Cycle 6
C10	Cycle 10
C14	Cycle 14
C1D1	Cycle 1 Day 1
CBR	Clinical Benefit Rate = CR + PR + durable SD
CD	cluster of differentiation
CDR	Complementary determining region
CD28	cluster of differentiation 28
CHO	Chinese hamster ovary
CIV	central imaging vendor
CNS	central nervous system
CR	complete response
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, version 5.0
D1	Day 1
D8	Day 8
D15	Day 15
D/C	discontinue/discontinuing
DCR	Disease Control Rate = CR + PR + SD
DLT	dose-limiting toxicity
DFS	Disease free survival
DNA	deoxyribonucleic acid
DOR	Duration of Response
DSDR	Durable Stable Disease Rate
ECG	Electrocardiogram
ECHO	Echocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EORTC	European Organization for the Research and Treatment of Cancer
EOT	End of treatment
EU	European Union
EV	Enfortumab Vedotin
FR	framework region
HBsAg	Hepatitis B surface antigen

HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
IA	interim analysis
IB	Investigator's Brochure
IC50	mean inhibitory concentration
ICF	Informed Consent Form
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
IgG	Immunoglobulin G
IgG1	Immunoglobulin G, subclass 1
IMP	Investigational medicinal product
IND	Investigational New Drug
IO	immuno-oncology
IP	Intraperitoneal
iPR	iRECIST partial response
irAE	immune-related adverse event
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
iSD	iRECIST stable disease
IT	Intratumoral
ITT	immunoglobulin tail tyrosine
ITIM	immunoreceptor tyrosine-based inhibitory motif
iUPD	iRECIST unconfirmed progressive disease
IV	Intravenous
IVD	in vitro diagnostic
LAG3	Lymphocyte Activating 3
kg	Kilogram
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mL	Milliliter
Mm	Millimeter
mm ³	cubic millimeter, 0.001 mL
MMAE	Monomethyl auristatin E
MPK	milligram per kilogram
MRI	magnetic resonance imaging
MSD	Merck Sharp and Dohme LLC., a subsidiary of Merck & Co., Inc.
MSI	microsatellite instability
mTPI	modified Toxicity Probability Interval
MUGA	multiple-gated acquisition

N	number of subjects in a treatment group
NCBI	National Center for Biotechnology Information
NCI	National Cancer Institute
NE	not estimable
NK	Natural killer (cells)
NK T	Natural killer T (cells)
NSCLC	non-small cell lung cancer
OR	overall response
ORR	objective response rate
OS	overall survival
PBPK	physiologically-based PK
PD	Progressive disease
PD-1	programmed cell-death 1
PDGFR	platelet-derived growth factor receptor
PD-L1	programmed cell-death ligand 1
PD-L2	programmed cell-death ligand 2
PE	Physical examination
PET	positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PO	by mouth (orally)
PP	Per Protocol
pPR	pathological partial response
PR	partial response
PRO	patient-reported outcome
pRR	pathological response rate
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
Q9W	every 9 weeks
Q12W	every 12 weeks
Q24W	every 24 weeks
QD	once daily / one dose per day
Q5D	dose every 5 days
Q7D	dose every 7 days
Q10D	dose every 10 days
QLC	Quality of Life questionnaire
QoL	quality of life
QTc	The QTc interval is the length of time it take the electrical system in the heart to repolarize, adjusted for heart rate.

RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RECIST 1.1	Response Evaluation Criteria in Solid Tumors 1.1
RENCA	Renal cell carcinoma
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR	Respiratory rate
SAE	serious adverse event
SD	stable disease
SEM	standard error of the mean
SoA	Schedule of Activities
T3	Triiodothyronine
T/C	median tumor volume of the treated animal/Median tumor volume of the control animal
TSH	thyroid-stimulating hormone
μg, ug, UG	Microgram
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptors
V _H	immunoglobulin heavy chain variable region
V _K	immunoglobulin kappa light chain variable region
V _L	immunoglobulin light chain variable region
WOCBP	woman/women of childbearing potential

PD-1 ANTAGONISTS

Examples of mAbs that bind to human PD-1, useful in the treatment methods, compositions, and uses of the invention, are described in US 7,521,051, US 8,008,449, and US 8,354,509. Specific anti-human PD-1 mAbs useful as the PD-1 antagonist in the treatment methods, compositions, and uses of the present invention include: pembrolizumab (formerly known as MK-3475, SCH 900475 and lambrolizumab), a humanized IgG4 mAb with the structure described in *WHO Drug Information*, Vol. 27, No. 2, pages 161-162 (2013) and which comprises the heavy and light chain amino acid sequences shown in FIGURE 3, and the humanized antibodies h409A11, h409A16 and h409A17, which are described in WO 2008/156712.

Provided herein are PD-1 antagonists or anti-human PD-1 monoclonal antibodies that can be used in any of the methods, compositions, kits, and uses disclosed herein, including any chemical compound or biological molecule that blocks binding of PD-L1 to PD-1 and preferably also blocks binding of PD-L2 to PD-1.

Any monoclonal antibodies that bind to a PD-1 polypeptide, a PD-1 polypeptide fragment, a PD-1 peptide, or a PD-1 epitope and block the interaction between PD-1 and its ligand PD-L1 or PD-L2 can be used. In some embodiments, the anti-human PD-1 monoclonal antibody binds to a PD-1 polypeptide, a PD-1 polypeptide fragment, a PD-1 peptide, or a PD-1 epitope and blocks the interaction between PD-1 and PD-L1. In other embodiments, the anti-human PD-1 monoclonal antibody binds to a PD-1 polypeptide, a PD-1 polypeptide fragment, a PD-1 peptide, or a PD-1 epitope and blocks the interaction between PD-1 and PD-L2. In yet other embodiments, the anti-human PD-1 monoclonal antibody binds to a PD-1 polypeptide, a PD-1 polypeptide fragment, a PD-1 peptide, or a PD-1 epitope and blocks the interaction between PD-1 and PD-L1 and the interaction between PD-1 and PD-L2.

Any monoclonal antibodies that bind to a PD-L1 polypeptide, a PD-L1 polypeptide fragment, a PD-L1 peptide, or a PD-L1 epitope and block the interaction between PD-L1 and PD-1 can also be used.

In certain embodiments, the anti-human PD-1 monoclonal antibody is selected from the group consisting of pembrolizumab, nivolumab, cemiplimab, dostarlimab, pidilizumab (U.S. Pat. No. 7,332,582), AMP-514 (MedImmune LLC, Gaithersburg, MD), PDR001 (U.S. Pat. No. 9,683,048), BGB-A317 (U.S. Pat. No. 8,735,553), and MGA012 (MacroGenics, Rockville, MD). In one embodiment, the anti-human PD-1 monoclonal antibody is pembrolizumab. In one embodiment, the anti-human PD-1 monoclonal antibody is nivolumab. In another embodiment, the anti-human PD-1 monoclonal antibody is cemiplimab. In yet another embodiment, the anti-human PD-1 monoclonal antibody is pidilizumab. In one embodiment, the anti-human PD-1 monoclonal antibody is AMP-514. In another embodiment, the anti-human PD-1 monoclonal antibody is PDR001. In yet another embodiment, the anti-human PD-1 monoclonal antibody is BGB-A317. In still another embodiment, the anti-human PD-1 monoclonal antibody is MGA012.

In some embodiments, an anti-human PD-1 antibody or antigen binding fragment thereof for use in the methods, kits, uses and co-formulations of the invention comprises three light chain CDRs of CDRL1, CDRL2 and CDRL3 and/or three heavy chain CDRs of CDRH1, CDRH2 and CDRH3.

In one embodiment of the invention, CDRL1 has the amino acid sequence as set forth in SEQ ID NO:1 or a variant of the amino acid sequence as set forth in SEQ ID NO:1, CDRL2 has the amino acid sequence as set forth in SEQ ID NO:2 or a variant of the amino acid sequence as set forth in SEQ ID NO:2, and CDRL3 has the amino acid sequence as set forth in SEQ ID NO:3 or a variant of the amino acid sequence as set forth in SEQ ID NO:3.

In one embodiment, CDRH1 has the amino acid sequence as set forth in SEQ ID NO:6 or a variant of the amino acid sequence as set forth in SEQ ID NO:6, CDRH2 has the amino acid sequence as set forth in SEQ ID NO:7 or a variant of the amino acid sequence as set forth in SEQ ID NO:7, and CDRH3 has the amino acid sequence as set forth in SEQ ID NO:8 or a variant of the amino acid sequence as set forth in SEQ ID NO:8.

In one embodiment, the three light chain CDRs have the amino acid sequences as set forth in SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and the three heavy chain CDRs have the amino acid sequences as set forth in SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8.

In an alternative embodiment of the invention, CDRL1 has the amino acid sequence as set forth in SEQ ID NO:11 or a variant of the amino acid sequence as set forth in SEQ ID NO:11, CDRL2 has the amino acid sequence as set forth in SEQ ID NO:12 or a variant of the amino acid sequence as set forth in SEQ ID NO:12, and CDRL3 has the amino acid sequence as set forth in SEQ ID NO:13 or a variant of the amino acid sequence as set forth in SEQ ID NO:13.

In one embodiment, CDRH1 has the amino acid sequence as set forth in SEQ ID NO:16 or a variant of the amino acid sequence as set forth in SEQ ID NO:16, CDRH2 has the amino acid sequence as set forth in SEQ ID NO:17 or a variant of the amino acid sequence as set forth in SEQ ID NO:17, and CDRH3 has the amino acid sequence as set forth in SEQ ID NO:18 or a variant of the amino acid sequence as set forth in SEQ ID NO:18.

In one embodiment, the three light chain CDRs have the amino acid sequences as set forth in SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and the three heavy chain CDRs have the amino acid sequences as set forth in SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8.

In an alternative embodiment, the three light chain CDRs have the amino acid sequences as set forth in SEQ ID NO:11, SEQ ID NO:12, and SEQ ID NO:13 and the three heavy chain CDRs have the amino acid sequences as set forth in SEQ ID NO:16, SEQ ID NO:17 and SEQ ID NO:18.

In a further embodiment of the invention, CDRL1 has the amino acid sequence as set forth in SEQ ID NO:21 or a variant of the amino acid sequence as set forth in SEQ ID NO:21, CDRL2 has the amino acid sequence as set forth in SEQ ID NO:22 or a variant of the amino acid sequence as set forth in SEQ ID NO:22, and CDRL3 has the amino acid sequence as set forth in SEQ ID NO:23 or a variant of the amino acid sequence as set forth in SEQ ID NO:23.

In yet another embodiment, CDRH1 has the amino acid sequence as set forth in SEQ ID NO:24 or a variant of the amino acid sequence as set forth in SEQ ID NO:24, CDRH2 has the amino acid sequence as set forth in SEQ ID NO: 25 or a variant of the amino acid sequence as set forth in SEQ ID NO:25, and CDRH3 has the amino acid sequence as set forth in SEQ ID NO:26 or a variant of the amino acid sequence as set forth in SEQ ID NO:26.

In another embodiment, the three light chain CDRs have the amino acid sequences as set forth in SEQ ID NO:21, SEQ ID NO:22, and SEQ ID NO:23 and the three heavy chain CDRs have the amino acid sequences as set forth in SEQ ID NO:24, SEQ ID NO:25 and SEQ ID NO:26.

5 Some anti-human PD-1 antibody and antigen binding fragments of the invention comprise a light chain variable region and a heavy chain variable region. In some embodiments, the light chain variable region comprises the amino acid sequence as set forth in SEQ ID NO:4 or a variant of the amino acid sequence as set forth in SEQ ID NO:4, and the heavy chain variable region comprises the amino acid sequence as set forth in SEQ ID NO:9 or a variant of the amino acid sequence as set forth in SEQ ID NO:9. In further embodiments, the light chain variable region comprises the amino acid sequence as set forth in SEQ ID NO:14 or a variant of the amino acid sequence as set forth in SEQ ID NO:14, and the heavy chain variable region comprises the amino acid sequence as set forth in SEQ ID NO:19 or a variant of the amino acid sequence as set forth in SEQ ID NO:19. In further embodiments, the heavy chain variable region comprises the amino acid sequence as set forth in SEQ ID NO:27 or a variant of the amino acid sequence as set forth in SEQ ID NO:27 and the light chain variable region comprises the amino acid sequence as set forth in SEQ ID NO:28 or a variant of the amino acid sequence as set forth in SEQ ID NO:28, the amino acid sequence as set forth in SEQ ID NO:29 or a variant of the amino acid sequence as set forth in SEQ ID NO:29, or the amino acid sequence as set forth in SEQ ID NO:30 or a variant of the amino acid sequence as set forth in SEQ ID NO:30. In such embodiments, a light chain variable region or heavy chain variable region sequence is identical to the reference sequence except having one, two, three, four or five amino acid substitutions. In some embodiments, the substitutions are in the framework region (*i.e.*, outside of the CDRs). In some embodiments, one, two, three, four or five of the amino acid substitutions are conservative substitutions.

25 In one embodiment of the co-formulations, methods, kits or uses of the invention, the anti-human PD-1 antibody or antigen binding fragment comprises a light chain variable region comprising or consisting of the amino acid sequence as set forth in SEQ ID NO:4 and a heavy chain variable region comprising or consisting of the amino acid sequence as set forth in SEQ ID NO:9. In a further embodiment, the anti-human PD-1 antibody or antigen binding fragment comprises a light chain variable region comprising or consisting of the amino acid sequence as set forth in SEQ ID NO:14 and a heavy chain variable region comprising or consisting of the amino acid sequence as set forth in SEQ ID NO:19. In one embodiment of the formulations of the invention, the anti-human PD-1 antibody or antigen binding fragment comprises a light chain variable region comprising or consisting of the amino acid sequence as set forth in SEQ ID NO:28 and a heavy chain variable region comprising or consisting of the amino acid sequence as

set forth in SEQ ID NO:27. In a further embodiment, the anti-human PD-1 antibody or antigen binding fragment comprises a light chain variable region comprising or consisting of the amino acid sequence as set forth in SEQ ID NO:29 and a heavy chain variable region comprising or consisting of the amino acid sequence as set forth in SEQ ID NO:27. In another embodiment, the antibody or antigen binding fragment comprises a light chain variable region comprising or consisting of the amino acid sequence as set forth in SEQ ID NO:30 and a heavy chain variable region comprising or consisting of the amino acid sequence as set forth in SEQ ID NO:27.

In another embodiment, the co-formulations, methods, kits or uses of the invention comprise an anti-human PD-1 antibody or antigen binding protein that has a V_L domain and/or a V_H domain with at least 95%, 90%, 85%, 80%, 75% or 50% sequence homology to one of the V_L domains or V_H domains described above, and exhibits specific binding to PD-1. In another embodiment, the anti-human PD-1 antibody or antigen binding protein of the co-formulations of the invention comprises V_L and V_H domains having up to 1, 2, 3, 4, or 5 or more amino acid substitutions, and exhibits specific binding to PD-1.

In any of the embodiments above, the PD-1 antagonist may be a full-length anti-PD-1 antibody or an antigen binding fragment thereof that specifically binds human PD-1. In certain embodiments, the PD-1 antagonist is a full-length anti-PD-1 antibody selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA, and IgE. Preferably, the antibody is an IgG antibody. Any isotype of IgG can be used, including IgG₁, IgG₂, IgG₃, and IgG₄. Different constant domains may be appended to the V_L and V_H regions provided herein. For example, if a particular intended use of an antibody (or fragment) of the present invention were to call for altered effector functions, a heavy chain constant domain other than IgG1 may be used. Although IgG1 antibodies provide for long half-life and for effector functions, such as complement activation and antibody-dependent cellular cytotoxicity, such activities may not be desirable for all uses of the antibody. In such instances an IgG4 constant domain, for example, may be used.

In embodiments of the invention, the PD-1 antagonist is an anti-PD-1 antibody comprising a light chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:5 and a heavy chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:10. In alternative embodiments, the PD-1 antagonist is an anti-PD-1 antibody comprising a light chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:15 and a heavy chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:20. In further embodiments, the PD-1 antagonist is an anti-PD-1 antibody comprising a light chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:32 and a heavy chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:31. In additional

embodiments, the PD-1 antagonist is an anti-PD-1 antibody comprising a light chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:33 and a heavy chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:31. In yet additional embodiments, the PD-1 antagonist is an anti-PD-1 antibody comprising a light chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:34 and a heavy chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:31. In some co-formulations of the invention, the PD-1 antagonist is pembrolizumab or a pembrolizumab biosimilar. In some co-formulations of the invention, the PD-1 antagonist is nivolumab or a nivolumab biosimilar.

Ordinarily, amino acid sequence variants of the anti-PD-1 antibodies and antigen binding fragments of the invention and the anti-LAG3 antibodies and antigen binding fragments will have an amino acid sequence having at least 75% amino acid sequence identity with the amino acid sequence of a reference antibody or antigen binding fragment (*e.g.* heavy chain, light chain, V_H, V_L, or humanized sequence), more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, and most preferably at least 95, 98, or 99%. Identity or homology with respect to a sequence is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the anti-PD-1 residues, 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. None of N-terminal, C-terminal, or internal extensions, deletions, or insertions into the antibody sequence shall be construed as affecting sequence identity or homology.

Sequence identity refers to the degree to which the amino acids of two polypeptides are the same at equivalent positions when the two sequences are optimally aligned. Sequence identity can be determined using a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences. The following references relate to BLAST algorithms often used for sequence analysis: BLAST ALGORITHMS: Altschul, S.F., *et al.*, (1990) J. Mol. Biol. 215:403-410; Gish, W., *et al.*, (1993) Nature Genet. 3:266-272; Madden, T.L., *et al.*, (1996) Meth. Enzymol. 266:131-141; Altschul, S.F., *et al.*, (1997) Nucleic Acids Res. 25:3389-3402; Zhang, J., *et al.*, (1997) Genome Res. 7:649-656; Wootton, J.C., *et al.*, (1993) Comput. Chem. 17:149-163; Hancock, J.M. *et al.*, (1994) Comput. Appl. Biosci. 10:67-70; ALIGNMENT SCORING SYSTEMS: Dayhoff, M.O., *et al.*, "A model of evolutionary change in proteins." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3. M.O. Dayhoff (ed.), pp. 345-352, Natl. Biomed. Res. Found., Washington, DC; Schwartz, R.M., *et al.*, "Matrices for detecting distant relationships." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3." M.O.

Dayhoff (ed.), pp. 353-358, Natl. Biomed. Res. Found., Washington, DC; Altschul, S.F., (1991) J. Mol. Biol. 219:555-565; States, D.J., *et al.*, (1991) Methods 3:66-70; Henikoff, S., *et al.*, (1992) Proc. Natl. Acad. Sci. USA 89:10915-10919; Altschul, S.F., *et al.*, (1993) J. Mol. Evol. 36:290-300; ALIGNMENT STATISTICS: Karlin, S., *et al.*, (1990) Proc. Natl. Acad. Sci. USA 87:2264-2268; Karlin, S., *et al.*, (1993) Proc. Natl. Acad. Sci. USA 90:5873-5877; Dembo, A., *et al.*, (1994) Ann. Prob. 22:2022-2039; and Altschul, S.F. "Evaluating the statistical significance of multiple distinct local alignments." in Theoretical and Computational Methods in Genome Research (S. Suhai, ed.), (1997) pp. 1-14, Plenum, New York.

Likewise, either class of light chain can be used in the compositions and methods herein. Specifically, kappa, lambda, or variants thereof are useful in the present compositions and methods.

Table 4. Exemplary PD-1 Antibody Sequences

Antibody Feature	Amino Acid Sequence	SEQ ID NO.
Pembrolizumab Light Chain		
CDR1	RASKGVSTSGYSYLH	1
CDR2	LASYLES	2
CDR3	QHSRDLPLT	3
Variable Region	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWY QQKPGQAPRLLIYLA SYLESGV PARFSGSGSGTDFTLT ISSLEPEDFAVYYCQHSRDLPLTFGGG TKVEIK	4
Light Chain	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWY QQKPGQAPRLLIYLA SYLESGV PARFSGSGSGTDFTLT ISSLEPEDFAVYYCQHSRDLPLTFGGG TKVEIKRTVAAPS VFI FPPSDEQLKSGTASV VCLLN NFYPRE AKVQW KVDNALQ SGNSQESVTEQD SKDSTY LSSTLT LSKADY EKHKVY ACEVTHQGLSSPV TKSFNR GEC	5
Pembrolizumab Heavy Chain		
CDR1	NYMY	6
CDR2	GINPSNGGTNFNEKFKN	7
CDR3	RDYRFDMGFDY	8
Variable Region	QVQLVQSGVEVKKPGASVKV SCKASGYTFTNYYMYWV RQAPGQGLEWMGGINPSNGGT NFNEKFKNRVTLT TDSSTTAYMELKSLQFDDTAVYYC ARRDYRFDMGFDYWGQG TTVTVSS	9
Heavy Chain	QVQLVQSGVEVKKPGASVKV SCKASGYTFTNYYMYWV RQAPGQGLEWMGGINPSNGGT NFNEKFKNRVTLT TDSSTTAYMELKSLQFDDTAVYYC ARRDYRFDMGFDYWGQG TTVTVSSASTKGPSV FPLAPCSRSTSESTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVP SSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCAP EFLGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSDQEDPE VQFNWYVDGVEVHNAKTKPREEQ FNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVY	10

Antibody Feature	Amino Acid Sequence	SEQ ID NO.
	TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLGK	
Nivolumab Light Chain		
CDR1	RASQSVSSYLA	11
CDR2	DASNRAT	12
CDR3	QQSSNWPRT	13
Variable Region	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLT ISSLEPEDEFAVYYCQQSSNWPRTFGQGGTKVEIK	14
Light Chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLT ISSLEPEDEFAVYYCQQSSNWPRTFGQGGTKVEIK KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSPV TKSFNRGEC	15
Nivolumab Heavy Chain		
CDR1	NSGMH	16
CDR2	VIWYDGSKRYYADSVK	17
CDR3	NDDY	18
Variable Region	QVQLVESGGGVVQPGRSLRLDCKASGITFSN SGMHWVRQAPGKGLEWVAVIWIYDGSKRYYADSVKGR FTISRDNSTNTLFLQMNSLRAEDTAVYYCATNDDYWGQ GTLVTVSS	19
Heavy Chain	QVQLVESGGGVVQPGRSLRLDCKASGITFSN SGMHWVRQAPGKGLEWVAVIWIYDGSKRYYADSVKGR FTISRDNSTNTLFLQMNSLRAEDTAVYYCATNDDYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYTCNVDPKPSNTKVDKRVE SKYGPPCPCPEFLGGPSVFLFPPKPKDTLMISRTPEV TCVVDVVSQEDPEVQFNWYVDGVEVHNAKTKPREEQ FNSTYRVVSVLTVLHQDWLNGKEYCKKVS NKGFLPSSIEKTIKAKGQPREPQVYTLPPSQEEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLGK	20

Table 5. Additional PD-1 Antibodies and Antigen Binding Fragments Useful in the Co-Formulations, Compositions, Methods, Kits and Uses of the Invention.

A. Antibodies and antigen binding fragments comprising light and heavy chain CDRs of hPD-1.08A in WO2008/156712		
CDRL 1	RASKSVSTSGFSYLH	SEQ ID NO:21
CDRL 2	LASNLES	SEQ ID NO:22

CDRL 3	QHSWELPLT	SEQ ID NO:23
CDR H1	SYLY	SEQ ID NO:24
CDR H2	GVNPSNGGTNFSEKFKS	SEQ ID NO:25
CDR H3	RDSNYDGGFDY	SEQ ID NO:26
B. Antibodies and antigen binding fragments comprising the mature h109A heavy chain variable region and one of the mature K09A light chain variable regions in WO 2008/156712		
Heavy chain VR	QVQLVQSGVEVKKPGASVKVSCASGYTFTNY YMYWVRQAPGQGLEWMGGINPSNGGTNFNEKF KNRVTLTTDSSTTTAYM ELKSLQFDDTAVYYCARRDYRFDM GFDYWGQGTTVTVSS	SEQ ID NO:27
Light chain VR	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYS YLHWYQQKPGQAPRLLIYLA SYLESGVPARFSGS GSGTDFLT TISSLEPEDFAVYYCQHSRDLPLTFGG GTKVEIK	SEQ ID NO:28 or
	EIVLTQSPLSLPVTGPGEPA SISCASKGVSTSGYSYL HWYLQKPGQSPQLLIYLA SYLESGVPDRFSGSGS GTDFTLKISRVEAEDVGVYYCHSRDLPLTFGQGT KLEIK	SEQ ID NO:29 or
	DIVMTQTPLSLPVTGPGEPA SISCASKGVSTSGYSY LHWYLQKPGQSPQLLIYLA SYLESGVPDRFSGSG SGTAFTLKISRVEAEDVGLYYC QHSRDLPLTFGQGTKLEIK	SEQ ID NO:30
C. Antibodies and antigen binding fragments comprising the mature 409 heavy chain and one of the mature K09A light chains in WO 2008/156712		
Heavy chain	QVQLVQSGVEVKKPGASVKVSCASGYTFTNYY MWVRQAPGQGLEWMGGINPSNGGTNFNEKFKN RVTLTTDSSTTTAYM ELKSLQFDDTAVYYCARRDYRFDMFDYWGQGT TVTVSSASTKGPSVFPLAPC SRSTSESTAALGC LVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS	SEQ ID NO:31

	SLGTKTYTC NVDHKPSNTKVDKRVESKYGPPC PPC PAPEFLGGPSV FLFPPKPKDTLMSRTPEVTCVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYK C KVSNGKLPSSIEKTISKAKGQPREPQVYTLPPSQE EM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPVLDS DGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGK	
Light chain	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYS YLHWYQQKPGQAPRLLIYLAstyleSGVPARFSGS GSGTDFTLTISSLEPEDFAVYYCQHSR DLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDYSLSTLTLSKADYEKHK VYAC EVTHQGLSSP VTKSFNRGEC	SEQ ID NO:32 or
	EIVLTQSPLSLPVTGPGEPAISCRASKGVSTSGYSY LHWYLQKPGQSPQLLIYLAstyleSGVPDRFSGSG SGTDFTLKISRVEAEDVGYYCHSRDLPLTFGQG TKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSK DYSLSTLTLSKADYEKHKVYACETHQGLSSP VTKSFNRGEC	SEQ ID NO:33 or
	DIVMTQTPLSLPVTGPGEPAISCRASKGVSTSGYS YLHWYLQKPGQSPQLLIYLAstyleSGVPDRFSGS GSGTAFTLKISRVEAEDVGLYYC QHSRDLPLTFGQGTKLEIKRTVAAPSVFIFPPSDE Q LKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDYSLSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO:34

In another preferred embodiment of the invention, the PD-1 antagonist in the combination therapy is pembrolizumab, or a pembrolizumab variant, that is administered in a liquid medicament at a dose selected from the group consisting of 1 mg/kg Q2W, 2 mg/kg Q2W, 3 mg/kg Q2W, 5 mg/kg Q2W, 10 mg/kg Q2W, 1 mg/kg Q3W, 2 mg/kg Q3W, 3 mg/kg Q3W, 5 mg/kg Q3W, 10 mg/kg Q3W and flat-dose equivalents of any of these doses, i.e., such as 200 mg Q3W or 400 mg Q6W. In some embodiments, pembrolizumab is provided as a liquid medicament that comprises 25 mg/ml pembrolizumab, 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80 in 10 mM histidine buffer pH 5.5. In other embodiments, pembrolizumab is provided as a liquid medicament that comprises about 125 to about 200 mg/mL of pembrolizumab, or an antigen binding fragment thereof; about 10 mM histidine buffer; about 10 mM L-methionine, or a pharmaceutically acceptable salt thereof; about 7% (w/v) sucrose; and about 0.02 % (w/v) polysorbate 80.

In some embodiments, the selected dose of pembrolizumab is administered by IV infusion. In one embodiment, the selected dose of pembrolizumab is administered by IV infusion over a time period of between 25 and 40 minutes, or about 30 minutes. In other embodiments, the selected dose of pembrolizumab is administered by subcutaneous injection.

LAG3 ANTAGONISTS

LAG3 antagonists useful in the treatment methods, medicaments and uses of the present invention include a monoclonal antibody (mAb), or antigen binding fragment thereof, that specifically binds to LAG3. The mAb may be a human antibody, a humanized antibody or a chimeric antibody, and may include a human constant region. In some embodiments the human constant region is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4 constant regions, and in preferred embodiments, the human constant region is an IgG1 or IgG4 constant region. In some embodiments, the antigen binding fragment is selected from the group consisting of Fab, Fab'-SH, F(ab')₂, scFv and Fv fragments.

In one embodiment, the anti-LAG3 antibody is Ab6: an antibody consisting of two light chains and two heavy chains, each light chain and heavy chain consisting of the following amino acid sequence:

light chain

DIVMTQTPLSLSVTPGQPASISCKASQSLDYEGDSMDNWWYLQKPGQPPQLLIYGA
SNLESGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSTEDPRTFGGGTKVEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD
STYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

(SEQ ID NO: 35); and

heavy chain

QMQLVQSGPEVKKPGTSVKVSCASGYTFTDYNVDWVRQARGQRLEWIGDINPNDGG
 TIYAQKFQERVITITVDKSTSTAYMELSSLRSEDTAVYYCARNYRWFGAMDHWGQGTTV
 TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
 5 LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLG
 GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQ
 FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ
 EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDK
 SRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

10 (SEQ ID NO: 36).

In certain embodiments, the C-terminal lysine ("k") is not present in the heavy chain of anti-LAG3 antibody Ab6.

Ab6 light chain variable domain amino acid sequence:

DIVMTQTPLSLSVTPGQPASISCKASQSLDYEGDSMDNWLQKPGQPPQLLIYGASNLES
 15 GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSTEDPRTFGGGTKVEIK

(SEQ ID NO: 37); and

Ab6 heavy chain variable domain amino acid sequence:

QMQLVQSGPEVKKPGTSVKVSCASGYTFTDYNVDWVRQARGQRLEWIGDINPNDGG
 TIYAQKFQERVITITVDKSTSTAYMELSSLRSEDTAVYYCARNYRWFGAMDHWGQGTTV
 20 TVSS

(SEQ ID NO: 38).

Ab6 CDRs:

CDR-L1: KASQSLDYEGDSMDN (SEQ ID NO: 39);

CDR-L2: GASNLES (SEQ ID NO: 40);

25 CDR-L3: QQSTEDPRT (SEQ ID NO: 41);

CDR-H1: DYNVD (SEQ ID NO: 42);

CDR-H2: DINPNDGGTIYAQKFQE (SEQ ID NO: 43); and

CDR-H3: NYRWFGAMDH (SEQ ID NO: 44).

30 In some preferred embodiments of the treatment methods, medicaments and uses of the present invention, the LAG3 antagonist is a monoclonal antibody, or antigen binding fragment thereof, that comprises: (a) light chain CDRs SEQ ID NOs: 39, 40 and 41 and (b) heavy chain CDRs SEQ ID NOs: 42, 43 and 44.

35 In one embodiment, the anti-LAG3 antibody is favezelimab, which comprises three light chain CDRs: CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino

acid sequence as set forth in SEQ ID NO: 41, and three heavy chain CDRs: CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44. Favezelimab is also referred to as MK-4280.

5 In other embodiments of the treatment methods, medicaments and uses of the present invention, the LAG3 antagonist is a monoclonal antibody, or antigen binding fragment thereof, that specifically binds to human LAG3 and comprises (a) a heavy chain variable region comprising SEQ ID NO:38 or a variant thereof, and (b) a light chain variable region comprising SEQ ID NO:37 or a variant thereof. A variant of a heavy chain variable region sequence is
10 identical to the reference sequence except having up to 5 conservative amino acid substitutions in the framework region (i.e., outside of the CDRs). A variant of a light chain variable region sequence is identical to the reference sequence except having up to three conservative amino acid substitutions in the framework region (i.e., outside of the CDRs).

In another embodiment of the treatment methods, medicaments and uses of the present
15 invention, the LAG3 antagonist is a monoclonal antibody that specifically binds to human LAG3 and comprises (a) a heavy chain comprising SEQ ID NO: 36, or optionally wherein the C-terminal lysine is removed and (b) a light chain comprising SEQ ID NO:35. In another preferred embodiment of the treatment methods, medicaments and uses of the present invention, the LAG3 antagonist is a monoclonal antibody that specifically binds to human LAG3 and comprises (a) a
20 heavy chain variable region comprising SEQ ID NO: 38 and (b) a light chain variable region comprising SEQ ID NO:37. In some embodiments, the C-terminal lysine is absent from the heavy chain amino acid sequence.

Other examples of mAbs that bind to human LAG3, and are useful in the treatment methods, medicaments and uses of the present invention, are relatlimab disclosed in International
25 patent application publication no. WO2014/008218 as LAG3.5 (*WHO Drug Information*, Vol. 32, No. 2, 2018), IMP731, IMP701, and the anti-LAG3 antibodies disclosed in U.S. patent application publication no. US2017101472. Other LAG3 antagonists useful in the treatment method, medicaments and uses of the present invention include an immunoadhesin that specifically binds to human LAG3, e.g., a fusion protein containing the extracellular LAG3 fused
30 to a constant region such as an Fc region of an immunoglobulin molecule.

In one embodiment, each of the anti-PD-1 or anti-LAG3 antibodies or antigen-binding fragments thereof comprises a heavy chain constant region, e.g., a human constant region, such as $\gamma 1$, $\gamma 2$, $\gamma 3$, or $\gamma 4$ human heavy chain constant region or a variant thereof. In another
embodiment, each of the anti-PD-1 or anti-LAG3 antibodies or antigen-binding fragments
35 thereof comprises a light chain constant region, e.g., a human light chain constant region, such as

lambda or kappa human light chain region or a variant thereof. By way of example, and not limitation, the human heavy chain constant region can be $\gamma 4$ and the human light chain constant region can be kappa. In an alternative embodiment, the Fc region of the antibody is $\gamma 4$ with a Ser228Pro mutation (Schuurman, J *et. al.*, *Mol. Immunol.* 38: 1-8, 2001).

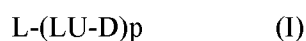
5 In some embodiments, different constant domains may be appended to humanized V_L and V_H regions derived from the CDRs provided herein. For example, if a particular intended use of an antibody (or fragment) of the present invention were to call for altered effector functions, a heavy chain constant domain other than human IgG1 may be used, or hybrid IgG1/IgG4 may be utilized.

10 Although human IgG1 antibodies provide for long half-life and for effector functions, such as complement activation and antibody-dependent cellular cytotoxicity, such activities may not be desirable for all uses of the antibody. In such instances a human IgG4 constant domain, for example, may be used. The present invention includes the use of anti-PD-1 antibodies or anti-LAG3 antibodies and antigen-binding fragments thereof which comprise an IgG4 constant
15 domain. In one embodiment, the IgG4 constant domain can differ from the native human IgG4 constant domain (Swiss-Prot Accession No. P01861.1) at a position corresponding to position 228 in the EU system and position 241 in the KABAT system, where the native Ser108 is replaced with Pro, in order to prevent a potential inter-chain disulfide bond between Cys106 and Cys109 (corresponding to positions Cys 226 and Cys 229 in the EU system and positions Cys
20 239 and Cys 242 in the KABAT system) that could interfere with proper intra-chain disulfide bond formation. *See Angal et al.* (1993) *Mol. Immunol.* 30:105. In other instances, a modified IgG1 constant domain which has been modified to increase half-life or reduce effector function can be used.

25 Antibody Drug Conjugates

In various embodiments of the methods provided herein, the ADC used in the methods comprises or is an anti-191P4D12 ADC described herein and/or in US Patent No. 8,637,642, which is herein incorporated in its entirety by reference. In some embodiments, the anti-191P4D12 antibody drug conjugate provided for the methods herein comprises an antibody or
30 antigen binding fragment thereof that binds to 191P4D12 as provided herein, conjugated to one or more units of cytotoxic agents (drug units, or D) as provided herein. In certain embodiments, the cytotoxic agents (drug units, or D) can be covalently linked directly or via a linker unit (LU) as provided herein.

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



or a pharmaceutically acceptable salt or solvate thereof; wherein:

L is the antibody unit, e.g., the anti-nectin-4 antibody or an antigen binding fragment thereof, and

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

5 LU- is a linker unit, and

D is a drug unit having cytostatic or cytotoxic activity against a target cell; and

p is an integer from 1 to 20.

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



10 or a pharmaceutically acceptable salt or solvate thereof, wherein:

L is the antibody unit, e.g., the anti-nectin-4 antibody or an antigen binding fragment thereof; and

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

-A- is a stretcher unit,

15 a is 0 or 1,

each -W- is independently an amino acid unit,

w is an integer ranging from 0 to 12,

-Y- is a self-immolative spacer unit,

y is 0, 1 or 2,

20 D is a drug units having cytostatic or cytotoxic activity against the target cell; and

p is an integer from 1 to 20.

In some embodiments, a is 0 or 1, w is 0 or 1, and y is 0, 1 or 2. In some embodiments, a is 0 or 1, w is 0 or 1, and y is 0 or 1.

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

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

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

30 about 1. In some embodiments, p is about 2. In some embodiments, p is about 3. In some

embodiments, p is about 4. In some embodiments, p is about 3.8. In some embodiments, p is

about 5. In some embodiments, p is about 6. In some embodiments, p is about 7. In some

embodiments, p is about 8. In some embodiments, p is about 9. In some embodiments, p is about

10. In some embodiments, p is about 11. In some embodiments, p is about 12. In some

35 embodiments, p is about 13. In some embodiments, p is about 14. In some embodiments, p is

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

5 In some embodiments, when w is not zero, y is 1 or 2. In some embodiments, when w is 1 to 12, y is 1 or 2. In some embodiments, w is 2 to 12 and y is 1 or 2. In some embodiments, a is 1 and w and y are 0.

In some specific embodiments of the methods provided herein, the cytotoxic agent as part of any of the ADCs provided herein for the methods comprises, consists of, or is MMAE.

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

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

In some embodiments of the methods provided herein, the ADC is enfortumab vedotin. In certain embodiments of the methods provided herein, the ADC is a biosimilar of enfortumab vedotin.

25 Anti-191P4D12 Antibodies or Antigen Binding Fragments

In one embodiment, the antibody or antigen binding fragment thereof that binds to nectin-4-related proteins is an antibody or antigen binding fragment that specifically binds to nectin-4 protein comprising amino acid sequence of SEQ ID NO:46 (see FIG. 1A). The corresponding
30 cDNA encoding the 191P4D12 protein has a sequence of SEQ ID NO: 45 (see FIG. 1A).

The antibody that specifically binds to nectin-4 protein comprising amino acid sequence of SEQ ID NO:46 includes antibodies that can bind to other nectin-4-related proteins. For example, antibodies that bind nectin-4 protein comprising amino acid sequence of SEQ ID NO:46 can bind nectin-4-related proteins such as nectin-4 variants and the homologs or analogs
35 thereof.

In some embodiments, the anti-nectin-4 antibody provided herein is a monoclonal antibody. In some embodiments, the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO:48 (cDNA sequence of SEQ ID NO:47), and/or a light chain comprising an amino acid sequence of SEQ ID NO:50 (cDNA sequence of SEQ ID NO:49), as shown in
5 FIGS. 1B and 1C.

In some embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:66 (which is the amino acid sequence ranging from the 20th amino acid
10 (glutamic acid) to the 136th amino acid (serine) of SEQ ID NO:51) and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:67 (which is the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 130th amino acid (arginine) of SEQ ID NO:52). In certain embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy
15 chain variable region comprising complementarity determining region 1 (CDR-H1), CDR-H2, and CDR-H3 comprising the amino acid sequences of the corresponding CDR-H1, CDR-H2, and CDR-H3 in the heavy chain variable region sequence set forth in SEQ ID NO:66 (which is the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 136th amino acid (serine) of SEQ ID NO:51) and a light chain variable region comprising CDR-L1, CDR-L2, and
20 CDR-L3 comprising the amino acid sequences of the corresponding CDR-L1, CDR-L2, and CDR-L3 in the light chain variable region sequence set forth in SEQ ID NO:67 (which is the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 130th amino acid (arginine) of SEQ ID NO:52). In some embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity
25 determining regions (CDRs) consisting of the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:66 (which is the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 136th amino acid (serine) of SEQ ID NO:51) and a light chain variable region comprising CDRs consisting of the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:67 (which is the amino acid sequence
30 ranging from the 23rd amino acid (aspartic acid) to the 130th amino acid (arginine) of SEQ ID NO:52). In certain embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining region 1 (CDR-H1), CDR-H2, and CDR-H3 consisting of the amino acid sequences of the corresponding CDR-H1, CDR-H2, and CDR-H3 in the heavy chain variable region sequence set forth in SEQ
35 ID NO:66 (which is the amino acid sequence ranging from the 20th amino acid (glutamic acid) to

- the 136th amino acid (serine) of SEQ ID NO:51) and a light chain variable region comprising CDR-L1, CDR-L2, and CDR-L3 consisting of the amino acid sequences of the corresponding CDR-L1, CDR-L2, and CDR-L3 in the light chain variable region sequence set forth in SEQ ID NO:67 (which is the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 130th amino acid (arginine) of SEQ ID NO:52). SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:51 and SEQ ID NO:52 are as shown in FIGS. 1D and 1E and listed below:

SEQ ID NO:66	EVQLVESGGGLVQPGGSLRLSCAASGFTSSYNMNWVRQAPGKGLEWVS YISSSST IYY ADSVKGRFTISRDN AKNSLSLQMNSLRDEDTA VYYCARAYYYGMDVWGQGT VTVSS
SEQ ID NO:67	DIQMTQSPSSVSASVGDRVTITCRASQGISGWLAWYQQKPGKAPKFLIYAAS TLQSG VPSRFSGSGSGTDFTLTISSLQPEDF A TYQCQQANSFPPTFGGGTKVEIKR
SEQ ID NO:51	MELGLCWVFLV AILEGVQCEVQLVESGGGLVQPGGSLRLSCAASGFTSSYNMNWV RQAPGKGLEWVS YISSSSTIYY ADSVKGRFTISRDN AKNSLSLQMNSLRDEDTAVYYCARA YYYGMDVWGQGT VTVSSASTKGPSVFPLAPSSKSTSGGT AALGCL VKDYF PEPVTVSWNSGAL TSGVHTFPA VLQSSGL YSLSSVTVPSSSLGTQTYICNVN HKPSN TKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL TCL VKGFPYPSDIA VEWESNGQPENNYKTPPVLDSDGSFFL YSKL TVDKSR WQQGNVFSCSVMHEALHN HYTQKSLSLSPGK
SEQ ID NO:51	MDMR VP AQLLGLLLLWFGSRCDIQMTQSPSSVSASVGDRVTITCRASQGISGWL A WYQQKPGKAPKFLIY AASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQAN SFPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC

CDR sequences can be determined according to well-known numbering systems. As described above, CDR regions are well-known to those skilled in the art and have been defined by well-known numbering systems. For example, the Kabat Complementarity Determining Regions (CDRs) are based on sequence variability and are the most commonly used (see, e.g., Kabat *et al.*, supra). Chothia refers instead to the location of the structural loops (see, e.g., Chothia and Lesk, 1987, J. Mol. Biol. 196:901-17). The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34). The AbM hypervariable regions represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software (see, e.g., Antibody Engineering Vol. 2 (Kontermann and Dubel eds., 2d ed. 2010)). The "contact" hypervariable regions are based on an analysis of the available complex crystal structures. Another universal numbering system that has been developed and widely adopted is ImMunoGeneTics (IMGT) Information System® (Lafranc *et al.*, 2003, Dev. Comp. Immunol. 27(1):55-77). IMGT is an integrated information system specializing in immunoglobulins (IG), T-cell receptors (TCR), and major histocompatibility complex (MHC) of human and other vertebrates. Herein, the CDRs are referred to in terms of both the amino acid sequence and the location within the light or heavy chain. As the "location" of the CDRs within the structure of the immunoglobulin variable domain is conserved between species and present in structures called loops, by using numbering systems that align variable domain sequences according to structural features, CDR and framework residues are readily identified. This information can be used in grafting and replacement of CDR residues from immunoglobulins of one species into an acceptor framework from, typically, a human antibody. An additional numbering system (AHon) has been developed by Honegger and Plickthun, 2001, J. Mol. Biol. 309: 657-70. Correspondence between the numbering system, including, for example, the Kabat numbering and the IMGT unique numbering system, is well-known to one skilled in the art (see, e.g., Kabat, supra; Chothia and Lesk, supra; Martin, supra; Lefranc *et al.*, supra). The residues from each of these hypervariable regions or CDRs are noted in Table above.

In some embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:66 according to Kabat numbering and a light chain

variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:67 according to Kabat numbering.

In some embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:66 according to AbM numbering and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:67 according to AbM numbering.

In other embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:66 according to Chothia numbering and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:67 according to Chothia numbering.

In other embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:66 according to Contact numbering and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:67 according to Contact numbering.

In yet other embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:66 according to IMGT numbering and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:67 according to IMGT numbering.

In some embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) consisting of the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:66 according to Kabat numbering and a light chain variable region comprising CDRs consisting of the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:67 according to Kabat numbering.

In some embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) consisting of the amino acid sequences of the CDRs of the heavy

chain variable region set forth in SEQ ID NO:66 according to AbM numbering and a light chain variable region comprising CDRs consisting of the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:67 according to AbM numbering.

In other embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) consisting of the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:66 according to Chothia numbering and a light chain variable region comprising CDRs consisting of the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:67 according to Chothia numbering.

In other embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) consisting of the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:66 according to Contact numbering and a light chain variable region comprising CDRs consisting of the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:67 according to Contact numbering.

In yet other embodiments, the anti-nectin-4 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising CDRs (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) consisting of the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:66 according to IMGT numbering and a light chain variable region comprising CDRs consisting of the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:67 according to IMGT numbering.

As described above, the CDR sequences according to different numbering systems can be readily determined, e.g., using online tools such as the one provided by Antigen receptor Numbering And Receptor Classification (ANARCI). For example, the heavy chain CDR sequences within SEQ ID NO:66, and the light chain CDR sequences within SEQ ID NO:67 according to Kabat numbering as determined by ANARCI are listed in Table 6 below.

Table 6: Heavy and Light chain CDR sequences according to Kabat numbering

	VH of SEQ ID NO:66	VL of SEQ ID NO:67
CDR1	SYNMN (SEQ ID NO:53)	RASQGISGWL A (SEQ ID NO: 56)
CDR2	YISSSSTIYYADSVKG (SEQ ID NO: 54)	AATLQS (SEQ ID NO: 57)
CDR3	AYYYGMDV (SEQ ID NO: 55)	QQANSFPPT (SEQ ID NO:58)

For another example, the heavy chain CDR sequences within SEQ ID NO:66, and the light chain CDR sequences within SEQ ID NO:67 according to IMGT numbering as determined by ANARCI are listed in Table 7 below.

5 Table 7: Heavy and Light chain CDR sequences according to IMGT numbering

	VH of SEQ ID NO:66	VL of SEQ ID NO:67
CDR1	GFTFSSYN (SEQ ID NO: 60)	QGISGW (SEQ ID NO: 63)
CDR2	ISSSSSTI (SEQ ID NO: 61)	AAS
CDR3	ARAYYYGMDV (SEQ ID NO: 62)	QQANSFPPT (SEQ ID NO:65)

In some embodiments, the antibody or antigen binding fragment thereof comprises CDR-H1 comprising an amino acid sequence of SEQ ID NO:53, CDR-H2 comprising an amino acid sequence of SEQ ID NO:54, CDR-H3 comprising an amino acid sequence of SEQ ID NO: 55,
 10 CDR-L1 comprising an amino acid sequence of SEQ ID NO: 56, CDR-L2 comprising an amino acid sequence of SEQ ID NO:57, and CDRL3 comprising an amino acid sequence of SEQ ID NO: 58.

In some embodiments, the antibody or antigen binding fragment thereof comprises CDR-H1 comprising an amino acid sequence of SEQ ID NO:60, CDR-H2 comprising an amino acid sequence of SEQ ID NO: 61, CDR-H3 comprising an amino acid sequence of SEQ ID NO: 62,
 15 CDR-L1 comprising an amino acid sequence of SEQ ID NO: 63, CDR-L2 comprising an amino acid sequence of AAS, and CDRL3 comprising an amino acid sequence of SEQ ID NO:65.

In some embodiments, the antibody or antigen binding fragment thereof comprises CDR-H1 consisting of an amino acid sequence of SEQ ID NO:53, CDR-H2 consisting of an amino acid sequence of SEQ ID NO: 54, CDR-H3 consisting of an amino acid sequence of SEQ ID NO: 55, CDR-L1 consisting of an amino acid sequence of SEQ ID NO: 56, CDR-L2 consisting of an amino acid sequence of SEQ ID NO: 57, and CDRL3 consisting of an amino acid sequence of SEQ ID NO: 58.

In some embodiments, the antibody or antigen binding fragment thereof comprises CDR-H1 consisting of an amino acid sequence of SEQ ID NO: 60, CDR-H2 consisting of an amino acid sequence of SEQ ID NO: 61, CDR-H3 consisting of an amino acid sequence of SEQ ID NO: 62, CDR-L1 consisting of an amino acid sequence of SEQ ID NO:63, CDR-L2 consisting of an amino acid sequence of AAS, and CDRL3 consisting of an amino acid sequence of SEQ ID NO:65.

In some embodiments, the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:66 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:67.

5 In some embodiments, the antibody or antigen binding fragment thereof comprises a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO:66 and a light chain variable region consisting of the amino acid sequence of SEQ ID NO:67.

10 In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID NO:51 and a light chain comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:52.

In some embodiments, the antibody comprises a heavy chain consisting of the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID NO:51 and a light chain consisting of the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:52.

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

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

Variations can be a substitution, deletion, or insertion of one or more codons encoding the single domain antibody or polypeptide that results in a change in the amino acid sequence as
35 compared with the original antibody or polypeptide. Amino acid substitutions can be the result of

replacing one amino acid with another amino acid comprising similar structural and/or chemical properties, such as the replacement of a leucine with a serine, e.g., conservative amino acid replacements. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule provided herein, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which results in amino acid substitutions. Insertions or deletions can optionally be in the range of about 1 to 5 amino acids. In certain embodiments, the substitution, deletion, or insertion includes fewer than 25 amino acid substitutions, fewer than 20 amino acid substitutions, fewer than 15 amino acid substitutions, fewer than 10 amino acid substitutions, fewer than 5 amino acid substitutions, fewer than 4 amino acid substitutions, fewer than 3 amino acid substitutions, or fewer than 2 amino acid substitutions relative to the original molecule. In a specific embodiment, the substitution is a conservative amino acid substitution made at one or more predicted non-essential amino acid residues. The variation allowed can be determined by systematically making insertions, deletions, or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the parental antibodies.

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

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

Amino acids can be grouped according to similarities in the properties of their side chains (see, e.g., Lehninger, Biochemistry 73-75 (2d ed. 1975)): (1) non-polar: Ala (A), Val (V), Leu (L), Ile (I), Pro (P), Phe (F), Trp (W), Met (M); (2) uncharged polar: Gly (G), Ser (S), Thr (T), Cys (C), Tyr (Y), Asn (N), Gln (Q); (3) acidic: Asp (D), Glu (E); and (4) basic: Lys (K), Arg (R), His(H). Alternatively, naturally occurring residues can be divided into groups based on common side-chain properties: (1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln; (3) acidic: Asp, Glu; (4) basic: His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; and (6) aromatic: Trp, Tyr, Phe.

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

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

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

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

In certain embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having certain homology or identity to the heavy chain as set forth in

SEQ ID NO:51 and a light chain having certain homology or identity to the light chain as set forth in SEQ ID NO:52. Such embodiments of heavy/light chains with homology or identity are further provided as follows. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having more than 70% homology or identity to the heavy chain as set forth in SEQ ID NO:51. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having more than 75% homology or identity to the heavy chain as set forth in SEQ ID NO:51. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having more than 80% homology or identity to the heavy chain as set forth in SEQ ID NO:51. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having more than 85% homology or identity to the heavy chain as set forth in SEQ ID NO:51. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having more than 90% homology or identity to the heavy chain as set forth in SEQ ID NO:51. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having more than 95% homology or identity to the heavy chain as set forth in SEQ ID NO:51. In certain embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain having any of the provided homology or identity to the heavy chain as set forth in SEQ ID NO:51, wherein the CDRs (CDR-H1, CDR-H2, and CDR-H3) are identical to the CDRs in the heavy chain as set forth in SEQ ID NO:51. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain having more than 70% homology or identity to the light chain as set forth in SEQ ID NO:52. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain having more than 75% homology or identity to the light chain as set forth in SEQ ID NO:52. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain having more than 80% homology or identity to the light chain as set forth in SEQ ID NO:52. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain having more than 85% homology or identity to the light chain as set forth in SEQ ID NO:52. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain having more than 90% homology or identity to the light chain as set forth in SEQ ID NO:52. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain having more than 95% homology or identity to the light chain as set forth in SEQ ID NO:52. In certain embodiments, the antibody or antigen binding fragment provided herein comprises a light chain having any of the provided homology or identity to the light chain as set forth in SEQ ID NO:52, wherein the CDRs (CDR-L1, CDR-L2, and CDR-L3) are identical to the CDRs in the light chain as set forth in SEQ ID NO:52. In

certain embodiments, the antibody or antigen binding fragment provided herein comprises any homologous light chain and any homologous heavy chain as provided in this paragraph in any combination or permutation.

In certain embodiments, the antibody or antigen binding fragment provided herein
5 comprises a heavy chain variable region having certain homology or identity to the heavy chain variable region as set forth in SEQ ID NO:66 and a light chain variable region having certain homology or identity to the light chain variable region as set forth in SEQ ID NO:67. Such embodiments of heavy chain variable regions and light chain variable regions with homology or identity are further provided as follows. In some embodiments, the antibody or antigen binding
10 fragment provided herein comprises a heavy chain variable region having more than 70% homology or identity to the heavy chain variable region as set forth in SEQ ID NO:66. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain variable region having more than 75% homology or identity to the heavy chain variable region as set forth in SEQ ID NO:66. In some embodiments, the antibody or antigen binding fragment
15 provided herein comprises a heavy chain variable region having more than 80% homology or identity to the heavy chain variable region as set forth in SEQ ID NO:66. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain variable region having more than 85% homology or identity to the heavy chain variable region as set forth in SEQ ID NO:66. In some embodiments, the antibody or antigen binding fragment provided
20 herein comprises a heavy chain variable region having more than 90% homology or identity to the heavy chain variable region as set forth in SEQ ID NO:66. In some embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain variable region having more than 95% homology or identity to the heavy chain variable region as set forth in SEQ ID NO:66. In certain embodiments, the antibody or antigen binding fragment provided
25 herein comprises a heavy chain variable region having any of the provided homology or identity to the heavy chain variable region as set forth in SEQ ID NO:66, wherein the CDRs (CDR-H1, CDR-H2, and CDR-H3) are identical to the CDRs in the heavy chain variable region as set forth in SEQ ID NO:66. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain variable region having more than 70% homology or identity to the
30 light chain variable region as set forth in SEQ ID NO:67. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain variable region having more than 75% homology or identity to the light chain variable region as set forth in SEQ ID NO:67. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain variable region having more than 80% homology or identity to the light chain variable
35 region as set forth in SEQ ID NO:67. In some embodiments, the antibody or antigen binding

fragment provided herein comprises a light chain variable region having more than 85% homology or identity to the light chain variable region as set forth in SEQ ID NO:67. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain variable region having more than 90% homology or identity to the light chain variable region as set forth in SEQ ID NO:67. In some embodiments, the antibody or antigen binding fragment provided herein comprises a light chain variable region having more than 95% homology or identity to the light chain variable region as set forth in SEQ ID NO:67. In certain embodiments, the antibody or antigen binding fragment provided herein comprises a light chain variable region having any of the provided homology or identity to the light chain variable region as set forth in SEQ ID NO:67, wherein the CDRs (CDR-L1, CDR-L2, and CDR-L3) are identical to the CDRs in the light chain variable region as set forth in SEQ ID NO:67. In certain embodiments, the antibody or antigen binding fragment provided herein comprises any homologous light chain variable region and any homologous heavy chain variable region as provided in this paragraph in any combination or permutation.

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

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

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

(a) the heavy chain variable region comprises CDRs (CDR-H1, CDR-H2, and CDRH3) comprising the amino acid sequences of the heavy chain variable region CDRs set forth in the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267;

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

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

(a) the heavy chain variable region comprises CDRs (CDR-H1, CDR-H2, and CDRH3) consisting of the amino acid sequences of the heavy chain variable region CDRs set forth in the antibody produced by a hybridoma deposited under the American Type Culture Collection
15 (ATCC) Accession NO: PTA-11267;

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

20 In some embodiments, the anti-nectin-4 antibody provided herein comprises heavy and light chain variable regions of an antibody designated Ha22-2(2,4)6.1 produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267, or heavy and light variable regions comprising amino acid sequences that are homologous to the amino acid sequences of the heavy and light chain variable regions of Ha22-2(2,4)6.1, and
25 wherein the antibodies retain the desired functional properties of the anti-nectin-4 antibody provided herein. In some embodiments, the anti-nectin-4 antibody provided herein comprises heavy and light chain variable regions of an antibody designated Ha22-2(2,4)6.1 produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267, or heavy and light variable regions consisting of amino acid sequences that are
30 homologous to the amino acid sequences of the heavy and light chain variable regions of Ha22-2(2,4)6.1, and wherein the antibodies retain the desired functional properties of the anti-nectin-4 antibody provided herein. As the constant region of the antibody of the disclosure, any subclass of constant region can be chosen. In one embodiment, human IgG1 constant region as the heavy chain constant region and human Ig kappa constant region as the light chain constant region can
35 be used.

In some embodiments, the anti-nectin-4 antibody provided herein comprises heavy and light chains of an antibody designated Ha22-2(2,4)6. 1 produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267, or heavy and light chains comprising amino acid sequences that are homologous to the amino acid sequences of the heavy and light chains of Ha22-2(2,4)6. 1, and wherein the antibodies retain the desired functional properties of the anti-nectin-4 antibody provided herein. In some embodiments, the anti-nectin-4 antibody provided herein comprises heavy and light chains of an antibody designated Ha22-2(2,4)6. 1 produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267, or heavy and light chains consisting of amino acid sequences that are homologous to the amino acid sequences of the heavy and light chains of Ha22-2(2,4)6. 1, and wherein the antibodies retain the desired functional properties of the anti-nectin-4 antibody provided herein.

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

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

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

In certain embodiments, the antibody or antigen binding fragment provided herein comprises a heavy chain variable region having certain homology or identity to the heavy chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267 and a light chain variable region having certain homology or identity to the light chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. Such embodiments of heavy chain variable regions and light chain variable regions with homology or identity are further provided as follows. In some embodiments, the heavy chain variable region comprises an amino acid sequence that is at least 85% homologous or identical to the heavy chain variable region amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In other embodiments, the heavy chain variable region comprises an amino acid sequence that is at least 90% homologous or identical to

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

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

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

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

5 homology or identity to the light chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. Such embodiments of heavy chains and light chains with homology or identity are further provided as follows. In some embodiments, the heavy chain comprises an amino acid sequence that is at least 85% homologous or identical to the heavy chain amino acid sequence of the

10 antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In other embodiments, the heavy chain comprises an amino acid sequence that is at least 90% homologous or identical to the heavy chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In yet other embodiments, the heavy chain

15 comprises an amino acid sequence that is at least 95% homologous or identical to the heavy chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In other embodiments, the heavy chain can be 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homologous or identical to the heavy chain amino acid sequence of the

20 antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In some embodiments, the light chain comprises an amino acid sequence that is at least 85% homologous or identical to the light chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In other embodiments, the light chain comprises an amino

25 acid sequence that is at least 90% homologous or identical to the light chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In yet other embodiments, the light chain comprises an amino acid sequence that is at least 95% homologous or identical to the light chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture

30 Collection (ATCC) Accession NO: PTA-11267. In other embodiments, the light chain can be 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homologous or identical to the light chain amino acid sequence of the antibody produced by a hybridoma deposited under the American Type Culture Collection (ATCC) Accession NO: PTA-11267. In certain embodiments, the antibody or antigen binding fragment provided herein

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

In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to a specific epitope in 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to VC1 domain of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to VC1 domain but not to C1C2 domain of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 1st to 147th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to an epitope located in the 1st to 147th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 1st to 10th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 11th to 20th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 21st to 30th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 31st to 40th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 41st to 50th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 51st to 60th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 61st to 70th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 71st to 80th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 81st to 90th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 91st to 100th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 101st to 110th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 111th to 120th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 121st to 130th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 131st to 140th amino acid residues of 191P4D12. In some embodiments, the antibody or antigen binding fragment thereof provided herein binds to the 141st to 147th amino acid residues of 191P4D12. The binding epitopes of certain embodiments

the antibodies or antigen binding fragments thereof provided herein have been determined and described in WO 2012/047724, which is incorporated herein in its entirety by reference.

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

Engineered antibodies provided herein include those in which modifications have been made to framework residues within VH and/or VL (e.g. to improve the properties of the antibody). Typically, such framework modifications are made to decrease the immunogenicity of the antibody. For example, one approach is to "backmutate" one or more framework residues to the corresponding germline sequence. More specifically, an antibody that has undergone somatic mutation can contain framework residues that differ from the germline sequence from which the antibody is derived. Such residues can be identified by comparing the antibody framework sequences to the germline sequences from which the antibody is derived. To return the framework region sequences to their germline configuration, the somatic mutations can be "backmutated" to the germline sequence by, for example, site-directed mutagenesis or PCR-mediated mutagenesis (e.g., "backmutated" from leucine to methionine). Such "backmutated" antibodies are also intended to be encompassed by the disclosure.

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

In addition or alternative to modifications made within the framework or CDR regions, antibodies of the disclosure can be engineered to include modifications within the Fe region, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fe receptor binding, and/or antigen-dependent cellular cytotoxicity. Furthermore, an anti-191P4D12 antibody provided herein can be chemically modified (e.g., one

or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody. Each of these embodiments is described in further detail below.

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

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

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

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

25 Reactivity of the anti-191P4D12 antibodies with a 191P4D12-related protein can be established by a number of well-known means, including Western blot, immunoprecipitation, ELISA, and FACS analyses using, as appropriate, 191P4D12-related proteins, 191P4D12-expressing cells or extracts thereof. A 191P4D12 antibody or fragment thereof can be labeled with a detectable marker or conjugated to a second molecule. Suitable detectable markers include, but are not limited to, a radioisotope, a fluorescent compound, a bioluminescent compound, chemiluminescent compound, a metal chelator or an enzyme. Further,

bi-specific antibodies specific for two or more 191P4D12 epitopes are generated using methods generally known in the art. Homodimeric antibodies can also be generated by cross-linking techniques known in the art (e.g., Wolff *et al.*, Cancer Res. 53: 2560-2565).

In yet another specific embodiment, the anti-191P4D12 antibody provided herein is an antibody comprising heavy and light chain of an antibody designated Ha22-2(2,4)6. 1. The heavy chain of Ha22-2(2,4)6. 1 consists of the amino acid sequence ranging from 20th E residue to the 466th K residue of SEQ ID NO:51 and the light chain of Ha22-2(2,4)6. 1 consists of amino acid sequence ranging from 23rd D residue to the 236th C residue of SEQ ID NO:52 sequence.

The hybridoma producing the antibody designated Ha22-2(2,4)6. 1 was sent (via Federal Express) to the American Type Culture Collection (ATCC), P.O. Box 1549, Manassas, VA 20108 on 18-August-2010 and assigned Accession number PTA-11267.

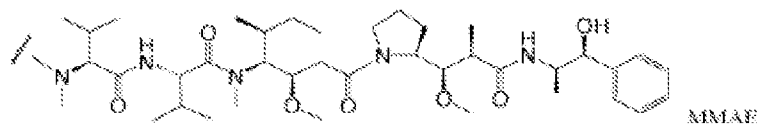
Additional embodiments of anti-nectin-4 antibody have been described in US Patent No. 8,637,642 and International Application No. PCT/US2019/056214 (Publication No. WO2020/117373), both of which are hereby incorporated in their entireties by reference.

Cytotoxic Agents (Drug Units)

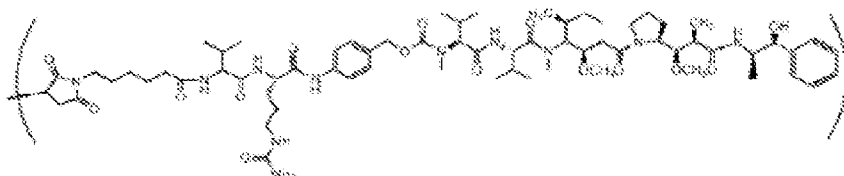
As the ADC used in the methods provided herein comprises an antibody or antigen binding fragment thereof conjugated to a cytotoxic agent, the disclosure further provides various embodiments for the cytotoxic agent as part of the ADC for use in the methods. In various embodiments of the methods provided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

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

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



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



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

paragraph, p is about 16. In some embodiments of the formula described in the preceding paragraph, p is about 17. In some embodiments of the formula described in the preceding paragraph, p is about 18. In some embodiments of the formula described in the preceding paragraph, p is about 19. In some embodiments of the formula described in the preceding paragraph, p is about 20.

Typically, peptide-based drug units can be prepared by forming a peptide bond between two or more amino acids and/or peptide fragments. Such peptide bonds can be prepared, for example, according to the liquid phase synthesis method (see E. Schroder and K. Lubke, "The Peptides", volume 1, pp 76-136, 1965, Academic Press) that is well-known in the field of peptide chemistry. The auristatin/dolastatin drug units can be prepared according to the methods of: US 5635483; US 5780588; Pettit et al. (1989) J. Am. Chem. Soc. 111:5463-5465; Pettit et al. (1998) Anti-Cancer Drug Design 13:243-277; Pettit, G.R., *et al.* Synthesis, 1996, 719-725; Pettit et al. (1996) J. Chem. Soc. Perkin Trans. 1 5:859-863; and Doronina (2003) Nat Biotechnol 21(7):778-784.

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

Linkers

Typically, the antibody drug conjugates comprise a linker unit between the drug unit (e.g., MMAE) and the antibody unit (e.g., the anti-191P4D12 antibody or antigen binding fragment thereof). In some embodiments, the linker is cleavable under intracellular conditions, such that cleavage of the linker releases the drug unit from the antibody in the intracellular environment. In yet other embodiments, the linker unit is not cleavable and the drug is released, for example, by antibody degradation. In some embodiments, the linker is cleavable by a cleaving agent that is present in the intracellular environment (e.g., within a lysosome or endosome or caveolea). The linker can be, e.g., a peptidyl linker that is cleaved by an intracellular peptidase or protease enzyme, including, but not limited to, a lysosomal or endosomal protease. For example, a peptidyl linker that is cleavable by the thiol-dependent protease cathepsin-B, which is highly expressed in cancerous tissue, can be used (e.g., a PheLeu or a Gly-Phe-Leu-Gly linker (SEQ ID NO:59)). In some embodiments, the peptidyl linker is at least two amino acids long or at least three amino acids long. In other embodiments, the cleavable linker is pH-sensitive, i.e., sensitive to hydrolysis at certain pH values. Typically, the pH-sensitive linker hydrolyzable under acidic conditions. For example, an acid-labile linker that is hydrolyzable in the lysosome (e.g., a hydrazone, semicarbazone, thiosemicarbazone, cis-

aconitic amide, orthoester, acetal, ketal, or the like) can be used. In yet other embodiments, the linker is cleavable under reducing conditions (e.g., a disulfide linker). A variety of disulfide linkers are known in the art, including, for example, those that can be formed using SATA (N-succinimidyl-S-acetylthioacetate), SPDP (N-succinimidyl-3-(2-pyridyldithio)propionate), SPDB (N-succinimidyl-3-(2-pyridyldithio)butyrate) and SMPT (N-succinimidyl-oxy carbonyl-alpha-methyl-alpha-(2-pyridyl-dithio)toluene), SPDB and SMPT.

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



10

wherein: -A- is a stretcher unit,

a is 0 or 1,

each -W- is independently an amino acid unit, w is an integer ranging from 0 to 12,

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

15

y is 0, 1 or 2.

In some embodiments, a is 0 or 1, w is 0 or 1, and y is 0, 1 or 2. In some embodiments, a is 0 or 1, w is 0 or 1, and y is 0 or 1. In some embodiments, when w is 1 to 12, y is 1 or 2. In some embodiments, w is 2 to 12 and y is 1 or 2. In some embodiments, a is

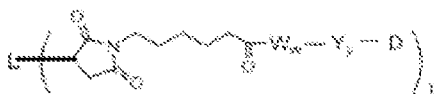
1 and w and y are 0. The linker and each of the stretcher unit, the amino acid unit, and the spacer

20

unit have been described in US Patent No. 8,637,642 and International Application No.

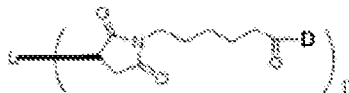
PCT/US2019/056214 (Publication No. WO2020/117373), both of which are hereby incorporated in their entireties by reference.

Embodiments of the antibody-drug conjugates can include:

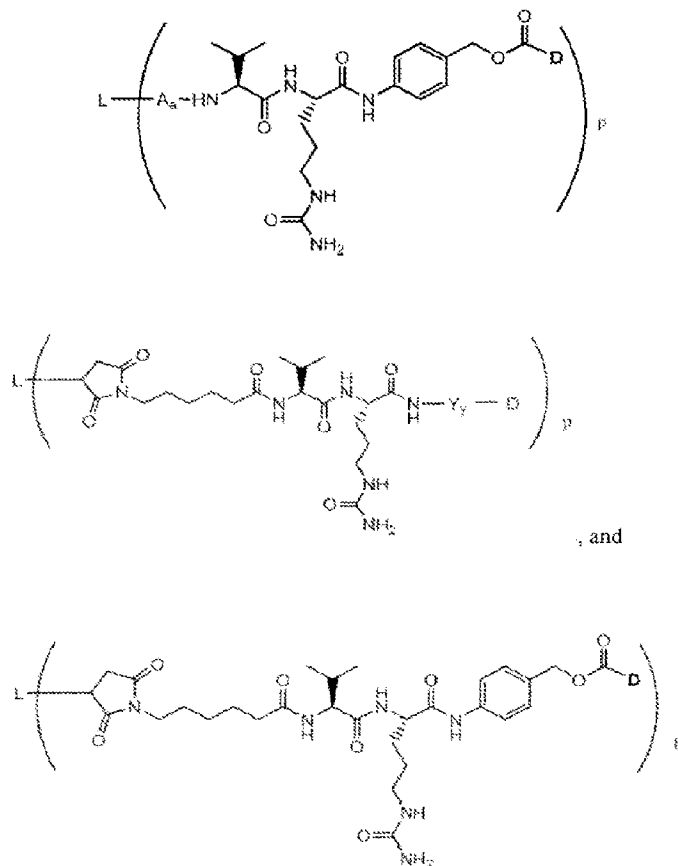


25

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



wherein w and y are each 0,



Methods of Treating Cancer Using a Combination of a PD-1 Antagonist, a LAG3 Antagonist, and an Antibody Drug Conjugate that binds 191P4D12

In another aspect, provided herein are methods of treating cancer (*e.g.*, urothelial) using a combination of a LAG3 antagonist, a PD-1 antagonist, and an antibody drug conjugate that binds 191P4D12.

In certain embodiments, the LAG3 antagonist is an anti-LAG3 antibody or antigen binding fragment thereof. In some embodiments, the PD-1 antagonist is an anti-PD-1 antibody or antigen binding fragment thereof.

In certain embodiments, the method of treating cancer comprises administering to a human patient in need thereof:

(a) a LAG3 antagonist;

(b) a PD-1 antagonist; and

(c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In some embodiments, the cancer is selected from the group consisting of: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma) colorectal; Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome); hematopoietic tumors of the lymphoid lineage, include leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, acute lymphoblastic leukemia, B-

cell lymphoma, T-cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, hairy cell lymphoma, mantle cell lymphoma, myeloma, and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and
5 rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas; and other tumors, including melanoma, skin (non-melanoma) cancer, mesothelioma (cells), seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratoanthoma, thyroid follicular cancer and Kaposi's sarcoma. In one embodiment, the foregoing cancers are advanced, unresectable or metastatic.

10 In some embodiments, the cancer is selected from the group consisting of melanoma, non-small cell lung cancer, head and neck squamous cell cancer, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high or mismatch repair deficient cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, a
15 cancer characterized by a tumor having a high mutational burden, cutaneous squamous cell carcinoma, and triple negative breast cancer.

In some embodiments, the cancer is selected from the group consisting of urothelial cancer and bladder cancer (including locally advanced urothelial cancer, metastatic urothelial cancer, and locally advanced bladder cancer and metastatic bladder cancer).

20 A combination of a LAG3 antagonist, a PD-1 antagonist, and an antibody drug conjugate that binds 191P4D12 may provide enhanced efficacy as compared with existing treatments.

In certain embodiments, provided herein is a method of treating urothelial cancer, comprising administering to a human patient in need thereof:

- (a) a LAG3 antagonist;
- 25 (b) a PD-1 antagonist; and
- (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

30 In certain embodiments, the PD-1 antagonist is an anti-human PD-1 monoclonal antibody or antigen binding fragment thereof. In some embodiments, the anti-human PD-1 monoclonal antibody is a human antibody. In other embodiments, the anti-human PD-1 monoclonal antibody is a humanized antibody.

In certain embodiments, the PD-1 antagonist is an anti-human PD-L1 monoclonal antibody or antigen binding fragment thereof. In some embodiments, the anti-human PD-L1

monoclonal antibody is a human antibody. In other embodiments, the anti-human PD-L1 monoclonal antibody is a humanized antibody.

In certain embodiments, the LAG3 antagonist is an anti-human LAG3 monoclonal antibody or antigen binding fragment thereof. In some embodiments, the anti-human LAG3 monoclonal antibody is a human antibody. In other embodiments, the anti-human LAG3 monoclonal antibody is a humanized antibody.

Thus, in certain embodiments, provided herein is a method for treating cancer, comprising administering to a human patient in need thereof:

- (a) a human or humanized anti-human LAG3 monoclonal antibody or antigen binding fragment thereof;
- (b) a human or humanized anti-human PD-1 monoclonal antibody or antigen binding fragment thereof; and
- (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In some embodiments, provided herein is a method for treating cancer, comprising administering to a human patient in need thereof:

- (a) a human anti-human LAG3 monoclonal antibody or antigen binding fragment thereof;
- (b) a human anti-human PD-1 monoclonal antibody or antigen binding fragment thereof; and
- (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In other embodiments, provided herein is a method for treating cancer, comprising administering to a human patient in need thereof:

- (a) a humanized anti-human LAG3 monoclonal antibody or antigen binding fragment thereof;
- (b) a humanized anti-human PD-1 monoclonal antibody or antigen binding fragment thereof; and
- (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In one embodiment of the methods provided herein, the anti-human PD-1 monoclonal antibody or antigen binding fragment thereof is pembrolizumab.

In one embodiment of the methods provided herein, ADC is enfortumab vedotin.

In one specific embodiment of the methods, kits and uses provided herein, the method for treating cancer comprises administering to a human patient in need thereof:

- 5 (a) an anti-LAG3 antibody or antigen binding fragment thereof comprises three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44;
- 10 (b) pembrolizumab; and
- (c) enfortumab vedotin.

In one specific embodiment of the methods, kits and uses provided herein, the method for treating urothelial cancer comprises administering to a human patient in need thereof:

- 15 (a) an anti-LAG3 antibody or antigen binding fragment thereof comprises three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and
- 20 CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44;
- (b) pembrolizumab; and
- (c) enfortumab vedotin.

In one aspect of the foregoing embodiments, the patient with cancer progressed after anti-PD-1 or anti-PD-L1 treatment. In one embodiment, the patient with cancer progressed after combination therapy of anti-PD-1 or anti-PD-L1 and anti-LAG3 treatment. In one embodiment, the patient with cancer has not received prior anti-PD-1 or anti-PD-L1 treatment.

25

The methods, medicaments and uses of the invention may also comprise one or more additional therapeutic agents. The additional therapeutic agent may be, e.g., a chemotherapeutic, a biotherapeutic agent, an immunogenic agent (for example, attenuated cancerous cells, tumor antigens, antigen presenting cells such as dendritic cells pulsed with tumor derived antigen or nucleic acids, immune stimulating cytokines (for example, IL-2, IFN α 2, GM-CSF), and cells transfected with genes encoding immune stimulating cytokines such as but not limited to GM-CSF). The specific dosage and dosage schedule of the additional therapeutic agent can further vary, and the optimal dose, dosing schedule and route of administration will be determined based upon the specific therapeutic agent that is being used.

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Each therapeutic agent in the methods, medicaments and uses of the invention may be administered either alone or in a medicament (also referred to herein as a pharmaceutical composition) that comprises the therapeutic agent and one or more pharmaceutically acceptable carriers, excipients and diluents, according to standard pharmaceutical practice.

5 Each therapeutic agent in the methods, medicaments and uses of the invention may be administered simultaneously (i.e., in the same medicament), concurrently (i.e., in separate medicaments administered one right after the other in any order) or sequentially in any order. Sequential administration is particularly useful when the therapeutic agents in the combination therapy are in different dosage forms (one agent is a tablet or capsule and another agent is a
10 sterile liquid) and/or are administered on different dosing schedules, e.g., a chemotherapeutic that is administered at least daily and a biotherapeutic that is administered less frequently, such as once weekly, once every two weeks, or once every three weeks.

In some embodiments, the LAG3 antagonist is administered before administration of the PD-1 antagonist, while in other embodiments, the LAG3 antagonist is administered after
15 administration of the PD-1 antagonist. In another embodiment, the LAG3 antagonist is administered concurrently with the PD-1 antagonist.

A combination therapy of the invention can be administered to a human patient who has a cancer that tests positive for one or both of PD-L1 and PD-L2, and preferably tests positive for PD-L1 expression. In some preferred embodiments, PD-L1 expression is detected using a
20 diagnostic anti-human PD-L1 antibody, or antigen binding fragment thereof, in an IHC assay on an FFPE or frozen tissue section of a tumor sample removed from the patient. Typically, the patient's physician would order a diagnostic test to determine PD-L1 expression in a tumor tissue sample removed from the patient prior to initiation of treatment with the PD-1 antagonist, the LAG3 antagonist and/or ADC, but it is envisioned that the physician could order the first or
25 subsequent diagnostic tests at any time after initiation of treatment, such as for example after completion of a treatment cycle. In one embodiment, the PD-L1 expression is measured by the PD-L1 IHC 22C3 pharmDx assay. In another embodiment, the patient has a Mononuclear Inflammatory Density Score for PD-L1 expression ≥ 2 . In another embodiment, the patient has a Mononuclear Inflammatory Density Score for PD-L1 expression ≥ 3 . In another embodiment, the
30 patient has a Mononuclear Inflammatory Density Score for PD-L1 expression ≥ 4 . In another embodiment, Tumor Proportion Score for PD-L1 expression is used for selection of non-small cell lung cancer patients. In another embodiment, the patient has a Tumor Proportion Score for PD-L1 expression $\geq 1\%$. In another embodiment, the patient has a Tumor Proportion Score for PD-L1 expression $\geq 10\%$. In another embodiment, the patient has a Tumor Proportion Score for
35 PD-L1 expression $\geq 20\%$. In another embodiment, the patient has a Tumor Proportion Score for

PD-L1 expression $\geq 30\%$. In another embodiment, the patient has a Tumor Proportion Score for PD-L1 expression $\geq 50\%$. In a further embodiment, the patient has a Combined Positive Score for PD-L1 expression $\geq 1\%$. In a further embodiment, the patient has a Combined Positive Score for PD-L1 expression between 1 and 20 %. In a further embodiment, the patient has a Combined Positive Score for PD-L1 expression $\geq 2\%$. In a further embodiment, the patient has a Combined Positive Score for PD-L1 expression $\geq 5\%$. In yet a further embodiment, the patient has a Combined Positive Score for PD-L1 expression $\geq 10\%$. In a further embodiment, the patient has a Combined Positive Score for PD-L1 expression $\geq 15\%$. In yet a further embodiment, the patient has a Combined Positive Score for PD-L1 expression $\geq 20\%$.

In one embodiment, the combination therapy is for first line treatment. In another embodiment, the combination therapy is for second or third line treatment.

Dosing and Administration

Further provided herein are dosing regimens and routes of administration for treating cancer (e.g., urothelial) using a combination of a LAG3 antagonist (e.g., an anti-LAG3 monoclonal antibody or antigen binding fragment thereof), a PD-1 antagonist (e.g., an anti-PD-1 monoclonal antibody or antigen binding fragment thereof), and an ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

The anti-LAG3 antibody (e.g., anti-LAG3 monoclonal antibody) or antigen binding fragment thereof, the anti-PD-1 antibody (e.g., anti-PD-1 monoclonal antibody) or antigen binding fragment thereof, or an ADC comprising an anti-191P4D12 antibody or antigen binding fragment thereof, disclosed herein may be administered by doses administered, e.g., daily, 1-7 times per week, weekly, bi-weekly, tri-weekly, every four weeks, every five weeks, every 6 weeks, monthly, bimonthly, quarterly, semiannually, annually, *etc.* Doses may be administered, e.g., intravenously, subcutaneously, topically, orally, nasally, rectally, intramuscular, intracerebrally, intraspinally, or by inhalation. In certain embodiments, the doses are administered intravenously. In certain embodiments, the doses are administered subcutaneously. In certain embodiments, the doses are administered orally.

Anti-LAG3 antibody dosing

In some embodiments, the anti-LAG3 antibody (e.g., anti-LAG3 monoclonal antibody) thereof is administered subcutaneously or intravenously, on a weekly, biweekly, triweekly, every 4 weeks, every 5 weeks, every 6 weeks, or every 8 weeks.

In some specific methods, 7-1200 mg of the anti-LAG3 antibody is administered. In another embodiment, 100-800 mg of the anti-LAG3 antibody is administered. In another embodiment, 200 mg of the anti-LAG3 antibody is administered. In another embodiment, 700 mg of the anti-LAG3 antibody is administered. In another embodiment, 800 mg of the anti-LAG3 antibody is administered. In another embodiment, 200-800 mg of the anti-LAG3 antibody is administered. In another embodiment, 200-700 mg of the anti-LAG3 antibody is administered. In another embodiment, 200-700 mg of the anti-LAG3 antibody is administered. In a further embodiment, 200-900 mg of the anti-LAG3 antibody is administered. In a further embodiment, 200-1000 mg of the anti-LAG3 antibody is administered. In a further embodiment, 800-1200 mg of the anti-LAG3 antibody is administered. In one aspect of the foregoing embodiments, the anti-LAG3 antibody is administered every three weeks.

In some embodiments of the methods, compositions, kits and uses described herein, the anti-LAG3 antibody (*e.g.*, anti-LAG3 monoclonal antibody) comprises three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44, the human patient is administered about 100 mg, about 150 mg, about 200 mg, about 240 mg, about 400 mg, about 480 mg, about 800 mg, about 900 mg, or about 1000 mg anti-LAG3 antibody (*e.g.*, anti-LAG3 monoclonal antibody), and the anti-LAG3 antibody is administered once every three. In one embodiment, the human patient is administered about 800 mg anti-LAG3 antibody (*e.g.*, anti-LAG3 monoclonal antibody) once every three weeks.

In certain embodiments of the methods described herein, the anti-LAG3 antibody (*e.g.*, anti-LAG3 monoclonal antibody) comprises three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44, the human patient is administered 800 mg anti-LAG3 antibody (*e.g.*, anti-LAG3 monoclonal antibody), and the anti-LAG3 antibody (*e.g.*, anti-LAG3 monoclonal antibody) is administered once every three weeks.

Anti-PD-1 antibody dosing

In some embodiments, the anti-PD-1 antibody (*e.g.*, anti-PD-1 monoclonal antibody) or antigen binding fragment thereof is administered subcutaneously or intravenously, on a weekly, biweekly, triweekly, every 4 weeks, every 5 weeks, every 6 weeks, monthly, bimonthly, or quarterly basis at about 10, about 20, about 50, about 80, about 100, about 200, about 300, about 400, about 500, about 1000 or about 2500 mg/subject.

In some specific methods, the dose of the anti-PD-1 antibody (*e.g.*, anti-PD-1 monoclonal antibody) or antigen binding fragment thereof is from about 0.01 mg/kg to about 50 mg/kg, from about 0.05 mg/kg to about 25 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, from about 0.2 mg/kg to about 9 mg/kg, from about 0.3 mg/kg to about 8 mg/kg, from about 0.4 mg/kg to about 7 mg/kg, from about 0.5 mg/kg to about 6 mg/kg, from about 0.6 mg/kg to about 5 mg/kg, from about 0.7 mg/kg to about 4 mg/kg, from about 0.8 mg/kg to about 3 mg/kg, from about 0.9 mg/kg to about 2 mg/kg, from about 1.0 mg/kg to about 1.5 mg/kg, from about 1.0 mg/kg to about 2.0 mg/kg, from about 1.0 mg/kg to about 3.0 mg/kg, or from about 2.0 mg/kg to about 4.0 mg/kg.

In some specific methods, the dose of the anti-PD-1 antibody (*e.g.*, anti-PD-1 monoclonal antibody) or antigen binding fragment thereof is from about 10 mg to about 500 mg, from about 25 mg to about 500 mg, from about 50 mg to about 500 mg, from about 100 mg to about 500 mg, from about 200 mg to about 500 mg, from about 150 mg to about 250 mg, from about 175 mg to about 250 mg, from about 200 mg to about 250 mg, from about 150 mg to about 240 mg, from about 175 mg to about 240 mg, or from about 200 mg to about 240 mg. In some embodiments, the dose of the anti-PD-1 antibody (*e.g.*, anti-PD-1 monoclonal antibody) or antigen binding fragment thereof is about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 240 mg, about 250 mg, about 300 mg, about 400 mg, or about 500 mg.

In some embodiments of the methods, compositions, kits and uses described herein, the anti-human PD-1 antibody (*e.g.*, anti-PD-1 monoclonal antibody) or antigen binding fragment thereof is pembrolizumab, the human patient is administered about 200 mg, about 240 mg, about 400 mg, about 480 mg, or about 2 mg/kg pembrolizumab, and pembrolizumab is administered once every three or six weeks. In one embodiment, the human patient is administered about 200 mg pembrolizumab once every three weeks. In one embodiment, the human patient is administered about 240 mg pembrolizumab once every three weeks. In one embodiment, the human patient is administered 2 mg/kg pembrolizumab once every three weeks. In one embodiment, the human patient is administered 400 mg pembrolizumab once every three weeks.

In certain embodiments of the methods, compositions, kits and uses described herein, the anti-human PD-1 monoclonal antibody or antigen binding fragment thereof is pembrolizumab,

the human patient is administered 400 mg pembrolizumab, and pembrolizumab is administered once every six weeks.

In some embodiments of the methods, compositions, kits and uses described herein, the anti-human PD-1 monoclonal antibody or antigen binding fragment thereof is pembrolizumab, the human patient is administered about 200 mg, about 240 mg, about 400 mg, about 480 mg, or about 2 mg/kg pembrolizumab, and pembrolizumab is administered once every six weeks. In one embodiment, the human patient is administered about 200 mg pembrolizumab once every six weeks. In one embodiment, the human patient is administered about 240 mg pembrolizumab once every six weeks. In one embodiment, the human patient is administered about 400 mg pembrolizumab once every six weeks. In one embodiment, the human patient is administered 480 mg pembrolizumab once every six weeks. In one embodiment, the human patient is administered 2 mg/kg pembrolizumab once every six weeks.

In some embodiments, pembrolizumab is provided as a liquid medicament that comprises 25 mg/ml pembrolizumab, 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80 in 10 mM histidine buffer pH 5.5. In other embodiments, pembrolizumab is provided as a liquid medicament that comprises about 125 to about 200 mg/mL of pembrolizumab, or an antigen binding fragment thereof; about 10 mM histidine buffer; about 10 mM L-methionine, or a pharmaceutically acceptable salt thereof; about 7% (w/v) sucrose; and about 0.02 % (w/v) polysorbate 80.

In some embodiments, the selected dose of pembrolizumab is administered by IV infusion. In one embodiment, the selected dose of pembrolizumab is administered by IV infusion over a time period of between 25 and 40 minutes, or about 30 minutes. In other embodiments, the selected dose of pembrolizumab is administered by subcutaneous injection.

In some embodiments of the invention, the anti-LAG3 antibody, or antigen binding fragment thereof, and the anti-PD-1 antibody, or antigen binding fragment thereof, are administered to the patient once every approximately six weeks for 12 weeks or more. In other embodiments, the anti-LAG3 antibody, or antigen binding fragment and the anti-PD-1 antibody, or antigen binding fragment thereof, are administered to the patient once every six weeks for 18 weeks or more, 24 weeks or more, 30 weeks or more, 36 weeks or more, 42 weeks or more, 48 weeks or more, 54 weeks or more, 60 weeks or more, 66 weeks or more, 72 weeks or more, 78 weeks or more, 84 weeks or more, or 90 weeks or more. In one embodiment, the administration occurs on the same day.

In a sub-embodiment, the anti-LAG3 antibody, or antigen binding fragment thereof, and the anti-PD-1 antibody, or antigen binding fragment thereof, are administered on the same day simultaneously (*e.g.*, in a single formulation, a co-formulation or concurrently as separate formulations). In an alternative embodiment, the anti-LAG3 antibody or antigen binding

fragment thereof and the anti-PD-1 antibody or antigen binding fragment thereof are administered sequentially on the same day (*e.g.*, as separate formulations), in either order. In one embodiment of same day sequential administration, the anti-LAG3 antibody or antigen binding fragment thereof is administered first. In another embodiment of same day sequential administration, the anti-PD-1 antibody or antigen binding fragment thereof is administered first.

In certain embodiments of the methods, compositions, kits and uses described herein, the anti-human PD-1 monoclonal antibody or antigen binding fragment thereof is pembrolizumab, the human patient is administered about 200 mg pembrolizumab, and pembrolizumab is administered once every three weeks. In certain embodiments of the methods, compositions, kits and uses described herein, the anti-human PD-1 monoclonal antibody or antigen binding fragment thereof is pembrolizumab, the human patient is administered about 400 mg pembrolizumab, and pembrolizumab is administered once every six weeks.

In other embodiments of the methods, compositions, kits and uses described herein, the anti-human PD-1 monoclonal antibody or antigen binding fragment thereof is nivolumab, the human patient is administered about 240 mg or about 3 mg/kg nivolumab, and nivolumab is administered once every two weeks. In one specific embodiment, the human patient is administered about 240 mg nivolumab once every two weeks. In one specific embodiment, the human patient is administered about 3 mg/kg nivolumab once every two weeks. In other embodiments of the methods, compositions, kits and uses described herein, the anti-human PD-1 monoclonal antibody or antigen binding fragment thereof is nivolumab, the human patient is administered about 480 mg nivolumab, and nivolumab is administered once every four weeks.

In yet other embodiments of the methods, compositions, kits and uses described herein, the anti-human PD-1 monoclonal antibody or antigen binding fragment thereof is cemiplimab, the human patient is administered about 350 mg cemiplimab, and cemiplimab is administered once every three weeks.

In some embodiments, an anti-LAG3 antibody and anti-PD-1 antibody are co-formulated. In one embodiment, a co-formulated product with about 200 mg pembrolizumab or a pembrolizumab variant and 800 mg of an anti-LAG3 antibody comprising three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 30, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44 is used for intravenous infusion.

Anti-191P4D12 Antibody or Antigen Binding Fragments Dosing

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

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

embodiments, the drug loading for an ADC provided herein ranges from 3 to 6. In certain embodiments, the drug loading for an ADC provided herein ranges from 3 to 5. In certain embodiments, the drug loading for an ADC provided herein ranges from 3 to 4.

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

10 In certain embodiments, the drug loading for an ADC provided herein is about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, or more. In some embodiments, the drug loading for an ADC provided herein is about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, or about 3.9.

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

35 In certain embodiments, fewer than the theoretical maximum of drug units are conjugated to an antibody during a conjugation reaction. An antibody can contain, for example, lysine

residues that do not react with the drug-linker intermediate or linker reagent. Generally, antibodies do not contain many free and reactive cysteine thiol groups which can be linked to a drug unit; indeed most cysteine thiol residues in antibodies exist as disulfide bridges. In certain embodiments, an antibody can be reduced with a reducing agent such as dithiothreitol (DTT) or tricarbo-
5 tricarbonyl ethylphosphine (TCEP), under partial or total reducing conditions, to generate reactive cysteine thiol groups. In certain embodiments, an antibody is subjected to denaturing conditions to reveal reactive nucleophilic groups such as lysine or cysteine. In some embodiments, the linker unit or a drug unit is conjugated via a lysine residue on the antibody unit. In some embodiments, the linker unit or a drug unit is conjugated via a cysteine residue on the antibody unit.

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

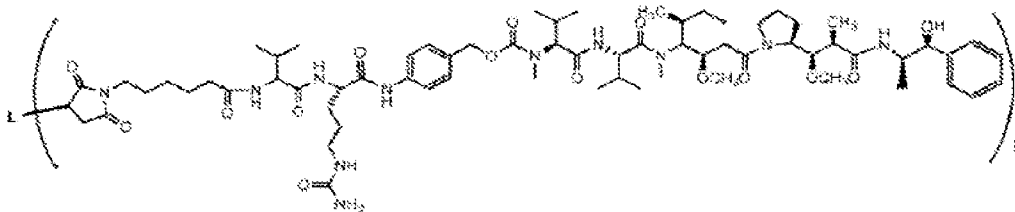
The loading (drug/antibody ratio) of an ADC can be controlled in different ways, e.g., by: (i) limiting the molar excess of drug-linker intermediate or linker reagent relative to antibody, (ii)
25 limiting the conjugation reaction time or temperature, (iii) partial or limiting reductive conditions for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

It is to be understood that where more than one nucleophilic group reacts with a drug-linker intermediate or linker reagent followed by drug unit reagent, then the resulting product is a mixture of ADC compounds with a distribution of one or more drug unit attached to an antibody unit. The average number of drugs per antibody can be calculated from the mixture by a dual
35 ELISA antibody assay, which is specific for antibody and specific for the drug. Individual ADC

molecules can be identified in the mixture by mass spectroscopy and separated by HPLC, e.g., hydrophobic interaction chromatography (see, e.g., Hamblett, K.J., *et al.* "Effect of drug loading on the pharmacology, pharmacokinetics, and toxicity of an antiCD30 antibody-drug conjugate," Abstract No. 624, American Association for Cancer Research, 2004 Annual Meeting, March 27-31, 2004, Proceedings of the AACR, Volume 45, March 2004; Alley, S.C., *et al.* "Controlling the location of drug attachment in antibody-drug conjugates," Abstract No. 627, American Association for Cancer Research, 2004 Annual Meeting, March 27-31, 2004, Proceedings of the AACR, Volume 45, March 2004). In certain embodiments, a homogeneous ADC with a single loading value can be isolated from the conjugation mixture by electrophoresis or chromatography.

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

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



wherein Lis Ha22-2(2,4)6. l and p is from 1 to 20.

In some embodiments, p ranges from 1 to 20, 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 to 2. In some embodiments, p ranges from 2 to 10, 2 to 9, 2 to 8, 2 to 7, 2 to 6, 2 to 5, 2 to 4 or 2 to 3. In other embodiments, p is about 1. In other embodiments, p is about 2. In other embodiments, p is about 3. In other embodiments, p is about 4. In other embodiments, p is about 5. In other embodiments, p is about 6. In other embodiments, p is about 7. In other embodiments, p is about 8. In other embodiments, p is about 9. In other embodiments, p is about 10. In some embodiments, p is about 3.1. In some embodiments, p is about 3.2. In some embodiments, p is about 3.3. In some embodiments, p is about 3.4. In some embodiments, p is about 3.5. In other embodiments, p is about 3.6. In some embodiments, p is about 3.7. In some embodiments, p is about 3.8. In some embodiments, p is about 3.9. In some embodiments, p is about 4.0. In some embodiments, p is about 4.1. In some embodiments, p is about 4.2. In some embodiments, p is about 4.3. In some embodiments, p is about 4.4. In some embodiments, p is about 4.5. In other embodiments, p is about 4.6. In some embodiments, p is about 4.7. In some

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

In some embodiments, the ADC used in the methods provided herein is enfortumab vedotin. Enfortumab vedotin is an ADC comprised of a fully human immunoglobulin G 1 kappa (IgG 1K) antibody conjugated to the microtubule-disrupting agent (MMAE) via a protease-cleavable linker (Challita-Eid PM et al., Cancer Res.

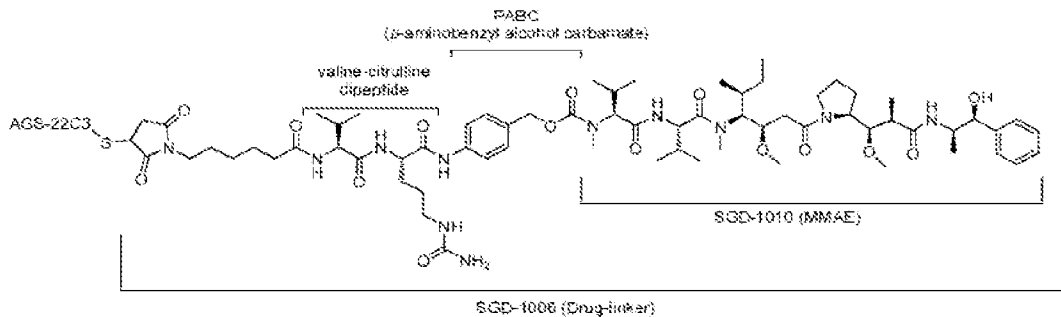
2016;76(10):3003-13]. Enfortumab vedotin induces antitumor activity by binding to 191P4D12 protein on the cell surface leading to internalization of the ADC-191P4D12 complex, which then traffics to the lysosomal compartment where MMAE is released via proteolytic cleavage of the linker. Intracellular release of MMAE subsequently disrupts tubulin polymerization resulting in G2/M phase cell cycle arrest and apoptotic cell death (Francisco JA et al., Blood. 2003 Aug 15;102(4):1458-65).

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

In one embodiment, the ADC provided herein is enfortumab vedotin, also known as EV, PADCEV, AGS-22M6E, AGS-22C3E, ASG-22C3E. The enfortumab vedotin includes an anti-191P4D12 antibody, wherein the antibody or antigen binding fragment thereof comprises a heavy chain comprising amino acid residue 20 to amino acid residue 466 of SEQ ID NO:51 and a light chain comprising amino acid residue 23 to amino acid residue 236 of SEQ ID NO:52.

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

“Enfortumab vedotin” has the following structural formula:



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

Thus, in some embodiments of the methods, compositions, kits and uses provided herein, the human patient is administered:

- (a) about 800 to about 1200 mg of an anti-LAG3 antibody or antigen binding fragment thereof comprising three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44;
 - (b) about 100 mg, about 150 mg, about 200 mg, about 250 mg, or about 400 mg, or about 2 mg/kg pembrolizumab; and
 - (c) about 1.25 mg/kg enfortumab vedotin;
- wherein each (a) and (b) are administered once every three or six weeks, and wherein (c) is administered once every three weeks on days 1 and 8 every cycle.

In certain embodiments of the methods, compositions, kits and uses provided herein, the human patient is administered:

- (a) about 800 mg of an anti-LAG3 antibody or antigen binding fragment thereof comprising three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as

set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44;

(b) about 200 mg pembrolizumab; and

(c) about 1.25 mg/kg enfortumab vedotin;

5 wherein each (a) and (b) are administered once every three weeks, and wherein (c) is administered once every three weeks on days 1 and 8 every cycle.

In certain embodiments of the methods, compositions, kits and uses provided herein, the human patient is administered:

(a) about 800 mg of an anti-LAG3 antibody or antigen binding fragment thereof

10 comprising a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 38 and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 37;

(b) about 200 mg pembrolizumab; and

(c) about 1.25 mg/kg enfortumab vedotin;

15 wherein each (a) and (b) are administered once every three weeks, and wherein (c) is administered once every three weeks on days 1 and 8 every cycle.

In certain embodiments of the methods, compositions, kits and uses provided herein, the human patient is administered:

(a) about 2 mg/kg of an anti-LAG3 antibody or antigen binding fragment thereof

20 comprising three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44;

(b) about 2 mg/kg pembrolizumab; and

(c) about 1.25 mg/kg enfortumab vedotin;

25 wherein each (a) and (b) are administered once every three weeks, and wherein (c) is administered once every three weeks on days 1 and 8 every cycle.

30 In certain embodiments of the methods, compositions, kits and uses provided herein, the human patient is administered:

(a) about 800 mg of an anti-LAG3 antibody or antigen binding fragment thereof

comprising three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in

35 SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO:

41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44;

(b) about 400 mg pembrolizumab; and

5 (c) about 1.25 mg/kg enfortumab vedotin;

wherein each (a) and (b) are administered once every six weeks, and wherein (c) is administered once every three weeks on days 1 and 8 every cycle.

In certain embodiments of the methods, compositions, kits and uses provided herein, the human patient is administered:

10 (a) about 800 mg of an anti-LAG3 antibody or antigen binding fragment thereof comprising three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44 once every three weeks;

(b) about 400 mg pembrolizumab once every six weeks; and

(c) about 1.25 mg/kg enfortumab vedotin;

20 wherein each (a) and (b) are administered once every three weeks, and wherein (c) is administered once every three weeks on days 1 and 8 every cycle. In some embodiments, (a) and (b) are co-formulated or co-administered.

In certain embodiments of the methods, compositions, kits and uses described herein, a co-formulation of pembrolizumab and of an anti-LAG3 antibody or antigen binding fragment thereof comprising three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44 are administered by IV infusion. In some embodiments, the co-formulation is administered for about 30 minutes every three weeks. In some embodiments, the co-formulation is administered for from about 25 to about 40 minutes every three weeks.

In some embodiments, at least one of the therapeutic agents (*e.g.*, the anti-LAG3 monoclonal antibody or binding fragment thereof, the anti-PD-1 monoclonal antibody or binding

fragment thereof, or the ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE)), in the combination therapy is administered using the same dosage regimen (dose, frequency, and duration of treatment) that is typically employed when the agent is used as monotherapy for treating the same condition. In other embodiments, the patient receives a lower total amount of at least one of the therapeutic agents (*e.g.*, the anti-LAG3 monoclonal antibody or binding fragment thereof, the anti-PD-1 monoclonal antibody or binding fragment thereof, or the ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE)) in the combination therapy than when the agent is used as monotherapy, *e.g.*, smaller doses, less frequent doses, and/or shorter treatment duration.

A combination therapy disclosed herein may be used prior to or following surgery to remove a tumor and may be used prior to, during, or after radiation treatment.

In some embodiments, a combination therapy disclosed herein is administered to a patient who has not previously been treated with a biotherapeutic or chemotherapeutic agent, *i.e.*, is treatment-naïve. In other embodiments, the combination therapy is administered to a patient who failed to achieve a sustained response after prior therapy with the biotherapeutic or chemotherapeutic agent, *i.e.*, is treatment-experienced.

The therapeutic combination disclosed herein may be used in combination with one or more other active agents, including but not limited to, other anti-cancer agents that are used in the prevention, treatment, control, amelioration, or reduction of risk of a particular disease or condition (*e.g.*, cancer). Such other active agents may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with one or more of the therapeutic agents in the combinations disclosed herein.

The one or more additional active agents may be co-administered with the anti-LAG3 monoclonal antibody or antigen binding fragment thereof, the anti-PD-1 monoclonal antibody or antigen binding fragment thereof, or the ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE). The additional active agent(s) can be administered in a single dosage form with one or more co-administered agent selected from the anti-LAG3 monoclonal antibody or antigen binding fragment thereof, the anti-PD-1 monoclonal antibody or antigen binding fragment thereof, and the ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE). The additional active agent(s) can also be administered in separate dosage form(s) from the dosage forms containing the anti-LAG3 monoclonal antibody or antigen binding fragment thereof, the anti-PD-1 monoclonal antibody or antigen binding fragment thereof, or the ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

Pharmaceutical Compositions

In yet another aspect, provided herein are pharmaceutical compositions comprising the therapeutic agents disclosed herein (e.g., a LAG3 antagonist, a PD-1 antagonist, and an ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE)).

5 In certain embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

The pharmaceutical compositions comprising an anti-human LAG3 antibody (e.g., anti-LAG3 monoclonal antibody) or antigen binding fragment thereof, an anti-human PD-1 antibody (e.g., anti-PD-1 monoclonal antibody) or antigen binding fragment thereof, and an ADC that
10 binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE), can be prepared for storage by mixing the antibodies or compounds having the desired degree of purity with optionally physiologically acceptable carriers, excipients, or stabilizers (*see, e.g.,* Remington, *Remington's Pharmaceutical Sciences* (18th ed. 1980)) in the form of aqueous solutions or lyophilized or other dried forms.

15 Pharmaceutically acceptable excipients of the present disclosure include for instance, solvents, bulking agents, buffering agents, tonicity adjusting agents, and preservatives (*see, e.g.,* Pramanick *et al.*, *Pharma Times*, 45:65-77, 2013). In some embodiments the pharmaceutical compositions may comprise an excipient that functions as one or more of a solvent, a bulking agent, a buffering agent, and a tonicity adjusting agent (e.g., sodium chloride in saline may serve
20 as both an aqueous vehicle and a tonicity adjusting agent).

In some embodiments, the pharmaceutical compositions comprise an aqueous vehicle as a solvent. Suitable vehicles include for instance sterile water, saline solution, phosphate buffered saline, and Ringer's solution. In some embodiments, the composition is isotonic.

The pharmaceutical compositions may comprise a bulking agent. Bulking agents are
25 particularly useful when the pharmaceutical composition is to be lyophilized before administration. In some embodiments, the bulking agent is a protectant that aids in the stabilization and prevention of degradation of the active agents during freeze or spray drying and/or during storage. Suitable bulking agents are sugars (mono-, di- and polysaccharides) such as sucrose, lactose, trehalose, mannitol, sorbitol, glucose and raffinose.

30 The pharmaceutical compositions may comprise a buffering agent. Buffering agents control pH to inhibit degradation of the active agent during processing, storage and optionally reconstitution. Suitable buffers include for instance salts comprising acetate, citrate, phosphate or sulfate. Other suitable buffers include for instance amino acids such as arginine, glycine, histidine, and lysine. The buffering agent may further comprise hydrochloric acid or sodium
35 hydroxide. In some embodiments, the buffering agent maintains the pH of the composition

within a range of 4 to 9. In some embodiments, the pH is greater than (lower limit) 4, 5, 6, 7 or 8. In some embodiments, the pH is less than (upper limit) 9, 8, 7, 6 or 5. That is, the pH is in the range of from about 4 to 9 in which the lower limit is less than the upper limit.

The pharmaceutical compositions may comprise a tonicity adjusting agent. Suitable
5 tonicity adjusting agents include for instance dextrose, glycerol, sodium chloride, glycerin and mannitol.

The pharmaceutical compositions may comprise a preservative. Suitable preservatives include for instance antioxidants and antimicrobial agents. However, in preferred embodiments, the pharmaceutical composition is prepared under sterile conditions and is in a single use
10 container, and thus does not necessitate inclusion of a preservative.

The pharmaceutically acceptable carriers, excipients, or stabilizers are non-toxic to the cell or mammalian being exposed thereto at the dosage and concentrations employed. Often the pharmaceutically acceptable carrier is an aqueous pH buffered solution. Examples of pharmaceutically acceptable carriers include buffers, such as phosphate, citrate, acetate, and
15 other organic acids; antioxidants, such as ascorbic acid; low molecular weight (*e.g.*, fewer than about 10 amino acid residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulin; hydrophilic polymers, such as polyvinylpyrrolidone; amino acids, such as glycine, glutamine, asparagine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates, including glucose, mannose, or dextrans; chelating agents, such as EDTA; sugar
20 alcohols, such as mannitol or sorbitol; salt-forming counterions, such as sodium; and/or nonionic surfactants, such as TWEENTM, polyethylene glycol (PEG), and PLURONICSTM. The pharmaceutically acceptable carriers can also refer to a diluent, adjuvate (*e.g.*, Freund's adjuvate (complete or incomplete)), excipient, or vehicle. Such carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as
25 peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water is an exemplary carrier when a composition (*e.g.*, a pharmaceutical composition) is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable excipients (*e.g.*, pharmaceutical excipients) include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate,
30 glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol, and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. Compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations, and the like.

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

In some embodiments, a medicament comprising an anti-PD-1 antibody as the PD-1 antagonist may be provided as a liquid formulation or prepared by reconstituting a lyophilized powder with sterile water for injection prior to use. PCT International application publ. no. WO 2012/135408 describes the preparation of liquid and lyophilized medicaments comprising pembrolizumab that are suitable for use in the present invention. In some embodiments, a medicament comprising pembrolizumab is provided in a glass vial that contains about 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP. The solution requires dilution for IV infusion.

In some embodiments, a medicament comprising an anti-LAG3 antibody as the LAG3 antagonist may be provided as a liquid formulation or prepared by reconstituting a lyophilized powder with sterile water for injection prior to use. In one embodiment, the liquid formulation comprises about 25 mg/mL anti-LAG3 antibody; about 50 mg/mL sucrose; about 0.2 mg/mL polysorbate 80; about 10 mM L-histidine buffer at about pH 5.8-6.0; about 70 mM L-Arginine-HCl thereof; and optionally about 10 mM L-methionine.

In other aspects, the medicament is a co-formulation of an anti-LAG3 antibody or antigen binding fragment and an anti-PD-1 antibody or antigen binding fragment with 20 mg/mL of Ab6 or Ab6 variant, 5 mg/mL or pembrolizumab or pembrolizumab variant, 56 mM L-Arginine HCl, 5.4% sucrose, 8.0 mM methionine, 0.02% PS-80, and 10 mM Histidine buffer.

Kits

In still another aspect, provided herein are kits comprising the therapeutic agents disclosed herein (*e.g.*, a LAG3 antagonist, a PD-1 antagonist, and an ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE)) or pharmaceutical compositions thereof, packaged into suitable packaging material. A kit optionally includes a label or packaging insert that include a description of the components or instructions for use *in vitro*, *in vivo*, or *ex vivo*, of the components therein.

In some embodiments, the kit comprises

- (a) a LAG3 antagonist;
- (b) a PD-1 antagonist; and
- (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In certain embodiments, the kit further comprises instructions for administering to a human patient the LAG3 antagonist, the PD-1 antagonist, and the ADC that binds to 191P4D12.

In some embodiments, the LAG3 antagonist is an anti-LAG3 monoclonal antibody or antigen-binding fragment thereof. In some embodiments, the PD-1 antagonist is an anti-PD-1 monoclonal antibody or antigen-binding fragment thereof. In some embodiments, the PD-1 antagonist is an anti-PD-L1 monoclonal antibody or antigen-binding fragment thereof.

In one embodiment, the kit comprises: (a) one or more dosages of an anti-LAG3 antibody (*e.g.*, anti-LAG3 monoclonal antibody) or antigen binding fragment thereof; (b) one or more dosages of an anti-PD-1 antibody (*e.g.*, anti-PD-1 monoclonal antibody or antigen binding fragment thereof); (c) one or more dosages of an ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE); and (d) instructions for administering to a human patient the anti-human LAG3 antibody (*e.g.*, anti-LAG3 monoclonal antibody) or antigen binding fragment thereof, the anti-human PD-1 antibody (*e.g.*, anti-PD-1 monoclonal antibody) or antigen binding fragment thereof, and the ADC that binds to 191P4D12.

In some embodiments, the anti-PD-1 monoclonal antibody or antigen binding fragment thereof is pembrolizumab. In some embodiments, the anti-PD-1 monoclonal antibody or antigen binding fragment thereof is nivolumab. In some embodiments, the anti-PD-1 monoclonal antibody or antigen binding fragment thereof is cemiplimab.

The dosages for the anti-LAG3 antibody (*e.g.*, anti-LAG3 monoclonal antibody), the anti-PD-1 antibody (*e.g.*, anti-PD-1 monoclonal antibody), or the ADC that binds to 191P4D12; described herein can be used in the kits herein. In some embodiments, a kit comprises dosages of each component sufficient for a certain period of treatment (*e.g.*, 3, 6, 12, or 24 weeks, *etc.*). For example, a kit can comprise a dosage of about 200 mg pembrolizumab, a dosage of about 800 mg anti-LAG3 antibody, and 2 dosages of about 1.25 mg/kg (or equivalent amount of an ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE)), which are sufficient for a 3-week treatment. Or, a kit can also comprise a dosage of about 400 mg pembrolizumab, 1 dosage of about 800 mg anti-LAG3 antibody, and 4 dosages of about 1.25 mg/kg (or equivalent amount of an ADC that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE)), which are sufficient for a 6-week treatment.

In some embodiments, the kit comprises means for separately retaining the components, such as a container, divided bottle, or divided foil packet. A kit of this disclosure can be used for administration of different dosage forms, for example, oral and parenteral, for administration of the separate compositions at different dosage intervals, or for titration of the separate compositions against one another.

Uses of a Therapeutic Combination for Treating Cancer

In still another aspect, provided herein are uses of a therapeutic combination for treating cancer (*e.g.*, urothelial) in a human patient, wherein the therapeutic combination comprises:

- (a) a LAG3 antagonist;
- (b) a PD-1 antagonist; and
- (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In still another aspect, provided herein are a therapeutic combination for use in treating cancer (*e.g.*, urothelial) in a human patient, wherein the therapeutic combination comprises:

- a LAG3 antagonist;
- a PD-1 antagonist; and
- an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In some embodiments, the cancer is selected from the group consisting of melanoma, non-small cell lung cancer, head and neck squamous cell cancer, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high or mismatch repair deficient cancer, gastric cancer, esophageal cancer, cervical cancer, biliary tract cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, a cancer characterized by a tumor having a high mutational burden, cutaneous squamous cell carcinoma, and triple negative breast cancer.

In some embodiments, the cancer is selected from the group consisting of urothelial cancer and bladder cancer (including locally advanced urothelial cancer, metastatic urothelial cancer, and locally advanced bladder cancer and metastatic bladder cancer).

In certain embodiments, the cancer is metastatic. In some embodiments, the cancer is relapsed. In other embodiments, the cancer is refractory. In yet other embodiments, the cancer is relapsed and refractory.

In one embodiment, the cancer is urothelial cancer.

In one embodiment, provided herein is use of a therapeutic combination for treating endometrial cancer in a human patient, wherein the therapeutic combination comprises:

- (a) a LAG3 antagonist;
- 5 (b) a PD-1 antagonist; and
- (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

10 In other embodiments, provided herein is use of a therapeutic combination for treating HCC in a human patient, wherein the therapeutic combination comprises:

- (a) a LAG3 antagonist;
- (b) a PD-1 antagonist; and
- (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

15 In still other embodiments, provided herein is use of a therapeutic combination for treating cancer, wherein the therapeutic combination comprises:

- (a) a LAG3 antagonist as disclosed in the present disclosure;
- (b) a PD-1 antagonist as disclosed in the present disclosure; and
- 20 (c) an antibody drug conjugate as disclosed in the present disclosure.

In certain embodiments, the LAG3 antagonist is an anti-human LAG3 monoclonal antibody or antigen binding fragment thereof. In some embodiments, the anti-human LAG3 monoclonal antibody is a human antibody. In other embodiments, the anti-human LAG3 monoclonal antibody is a humanized antibody.

25 In certain embodiments, the PD-1 antagonist is an anti-human PD-1 monoclonal antibody or antigen binding fragment thereof. In some embodiments, the anti-human PD-1 monoclonal antibody is a human antibody. In other embodiments, the anti-human PD-1 monoclonal antibody is a humanized antibody.

30 Thus, in certain embodiments, provided herein is use of a therapeutic combination for treating cancer, wherein the therapeutic combination comprises:

- (a) a human or humanized anti-human LAG3 monoclonal antibody or antigen binding fragment thereof;
- (b) a human or humanized anti-human PD-1 monoclonal antibody or antigen binding fragment thereof; and

(c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

5 In some embodiments, provided herein is use of a therapeutic combination for treating cancer, wherein the therapeutic combination comprises:

(a) a human anti-human LAG3 monoclonal antibody or antigen binding fragment thereof;

(b) a human anti-human PD-1 monoclonal antibody or antigen binding fragment thereof;

and

10 (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In other embodiments, provided herein is use of a therapeutic combination for treating cancer, wherein the therapeutic combination comprises:

15 (a) a humanized anti-human LAG3 monoclonal antibody or antigen binding fragment thereof;

(b) a humanized anti-human PD-1 monoclonal antibody or antigen binding fragment thereof; and

20 (c) an antibody drug conjugate comprising an anti-191P4D12 antibody or antigen binding fragment thereof, wherein the anti-191P4D12 antibody or antigen binding fragment thereof binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE).

In some embodiments of the uses provided herein, the anti-PD-1 monoclonal antibody or antigen binding fragment thereof is pembrolizumab. In some embodiments of the uses provided herein, the anti-PD-1 monoclonal antibody or antigen binding fragment thereof is nivolumab. In some embodiments of the uses provided herein, the anti-PD-1 monoclonal antibody or antigen binding fragment thereof is cemiplimab.

25 In certain embodiments of various uses provided herein, the anti-LAG3 antibody or antigen binding fragment thereof comprises three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 30, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44.

In some embodiments of various uses provided herein, the anti-LAG3 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising the amino acid

sequence as set forth in SEQ ID NO: 38 and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 37.

In other embodiments of various uses provided herein, the anti-human LAG3 monoclonal antibody or antigen binding fragment thereof comprises a light chain comprising or consisting of the amino acid sequence as set forth in SEQ ID NO:35 and a heavy chain comprising or consisting of the amino acid sequence as set forth in SEQ ID NO:36.

Thus, in one specific embodiment, provided herein is use of a therapeutic combination for treating cancer, wherein the therapeutic combination comprises:

- (a) anti-LAG3 antibody or antigen binding fragment thereof comprises three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44;
- (b) pembrolizumab; and
- (c) enfortumab vedotin.

In one specific embodiment, provided herein is use of a therapeutic combination for treating cancer, wherein the therapeutic combination comprises:

- (a) anti-LAG3 antibody or antigen binding fragment thereof comprises three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44;
- (b) nivolumab; and
- (c) enfortumab vedotin.

In one specific embodiment, provided herein is use of a therapeutic combination for treating cancer, wherein the therapeutic combination comprises:

- (a) anti-LAG3 antibody or antigen binding fragment thereof comprises three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO:

42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44;

(b) cemiplimab; and

(c) enfortumab vedotin.

5 In one specific embodiment, provided herein is use of a therapeutic combination for treating endometrial cancer, wherein the therapeutic combination comprises:

(a) anti-LAG3 antibody or antigen binding fragment thereof comprises three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO:

39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3

10 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain

CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO:

42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3

having the amino acid sequence as set forth in SEQ ID NO: 44;

(b) pembrolizumab; and

15 (c) enfortumab vedotin.

In one specific embodiment, provided herein is use of a therapeutic combination for treating endometrial cancer, wherein the therapeutic combination comprises:

(a) anti-LAG3 antibody or antigen binding fragment thereof comprises three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO:

20 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3

having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain

CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO:

42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3

having the amino acid sequence as set forth in SEQ ID NO: 44;

25 (b) nivolumab; and

(c) enfortumab vedotin.

In one specific embodiment, provided herein is use of a therapeutic combination for treating endometrial cancer, wherein the therapeutic combination comprises:

(a) anti-LAG3 antibody or antigen binding fragment thereof comprises three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO:

30 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3

having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain

CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO:

42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3

35 having the amino acid sequence as set forth in SEQ ID NO: 44;

- (b) cemiplimab; and
- (c) enfortumab vedotin.

In one specific embodiment, provided herein is use of a therapeutic combination in the manufacture of a medicament for treating cancer, wherein the therapeutic combination
5 comprises:

- (a) anti-LAG3 antibody or antigen binding fragment thereof comprises three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising
10 CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44;

- (b) pembrolizumab; and
- (c) enfortumab vedotin.

- 15 In one specific embodiment, provided herein is a method for treating cancer in an individual comprising co-administering a therapeutic combination, wherein the therapeutic combination comprises:

- (a) anti-LAG3 antibody or antigen binding fragment thereof comprises three light chain CDRs comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising
20 CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44;

- 25 (b) pembrolizumab; and
- (c) enfortumab vedotin.

- A number of embodiments of the invention have been described. It will be understood that various modifications may be made without departing from the spirit and scope of the invention. It will be further understood that each embodiment may be combined with one or more
30 other embodiments, to the extent that such a combination is consistent with the description of the embodiments.

General Methods

- Standard methods in molecular biology are described Sambrook, Fritsch and Maniatis (1982 & 1989 2nd Edition, 2001 3rd Edition) *Molecular Cloning, A Laboratory Manual*, Cold
35 Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Sambrook and Russell (2001)

Molecular Cloning, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Wu (1993) *Recombinant DNA*, Vol. 217, Academic Press, San Diego, CA). Standard methods also appear in Ausbel, *et al.* (2001) *Current Protocols in Molecular Biology*, Vols. 1-4, John Wiley and Sons, Inc. New York, NY, which describes cloning in bacterial cells and DNA mutagenesis (Vol. 1), cloning in mammalian cells and yeast (Vol. 2), glycoconjugates and protein expression (Vol. 3), and bioinformatics (Vol. 4).

Methods for protein purification including immunoprecipitation, chromatography, electrophoresis, centrifugation, and crystallization are described (Coligan, *et al.* (2000) *Current Protocols in Protein Science*, Vol. 1, John Wiley and Sons, Inc., New York). Chemical analysis, chemical modification, post-translational modification, production of fusion proteins, glycosylation of proteins are described (see, *e.g.*, Coligan, *et al.* (2000) *Current Protocols in Protein Science*, Vol. 2, John Wiley and Sons, Inc., New York; Ausubel, *et al.* (2001) *Current Protocols in Molecular Biology*, Vol. 3, John Wiley and Sons, Inc., NY, NY, pp. 16.0.5-16.22.17; Sigma-Aldrich, Co. (2001) *Products for Life Science Research*, St. Louis, MO; pp. 45-89; Amersham Pharmacia Biotech (2001) *BioDirectory*, Piscataway, N.J., pp. 384-391). Production, purification, and fragmentation of polyclonal and monoclonal antibodies are described (Coligan, *et al.* (2001) *Current Protocols in Immunology*, Vol. 1, John Wiley and Sons, Inc., New York; Harlow and Lane (1999) *Using Antibodies*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Harlow and Lane, *supra*). Standard techniques for characterizing ligand/receptor interactions are available (see, *e.g.*, Coligan, *et al.* (2001) *Current Protocols in Immunology*, Vol. 4, John Wiley, Inc., New York).

Monoclonal, polyclonal, and humanized antibodies can be prepared (see, *e.g.*, Sheperd and Dean (eds.) (2000) *Monoclonal Antibodies*, Oxford Univ. Press, New York, NY; Kontermann and Dubel (eds.) (2001) *Antibody Engineering*, Springer-Verlag, New York; Harlow and Lane (1988) *Antibodies A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pp. 139-243; Carpenter, *et al.* (2000) *J. Immunol.* 165:6205; He, *et al.* (1998) *J. Immunol.* 160:1029; Tang *et al.* (1999) *J. Biol. Chem.* 274:27371-27378; Baca *et al.* (1997) *J. Biol. Chem.* 272:10678-10684; Chothia *et al.* (1989) *Nature* 342:877-883; Foote and Winter (1992) *J. Mol. Biol.* 224:487-499; U.S. Pat. No. 6,329,511).

An alternative to humanization is to use human antibody libraries displayed on phage or human antibody libraries in transgenic mice (Vaughan *et al.* (1996) *Nature Biotechnol.* 14:309-314; Barbas (1995) *Nature Medicine* 1:837-839; Mendez *et al.* (1997) *Nature Genetics* 15:146-156; Hoogenboom and Chames (2000) *Immunol. Today* 21:371-377; Barbas *et al.* (2001) *Phage Display: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New

York; Kay *et al.* (1996) *Phage Display of Peptides and Proteins: A Laboratory Manual*, Academic Press, San Diego, CA; de Bruin *et al.* (1999) *Nature Biotechnol.* 17:397-399).

Purification of antigen is not necessary for the generation of antibodies. Animals can be immunized with cells bearing the antigen of interest. Splenocytes can then be isolated from the immunized animals, and the splenocytes can fused with a myeloma cell line to produce a hybridoma (see, *e.g.*, Meyaard *et al.* (1997) *Immunity* 7:283-290; Wright *et al.* (2000) *Immunity* 13:233-242; Preston *et al.*, *supra*; Kaithamana *et al.* (1999) *J. Immunol.* 163:5157-5164).

Antibodies can be conjugated, *e.g.*, to small drug molecules, enzymes, liposomes, polyethylene glycol (PEG). Antibodies are useful for therapeutic, diagnostic, kit or other purposes, and include antibodies coupled, *e.g.*, to dyes, radioisotopes, enzymes, or metals, *e.g.*, colloidal gold (see, *e.g.*, Le Doussal *et al.* (1991) *J. Immunol.* 146:169-175; Gibellini *et al.* (1998) *J. Immunol.* 160:3891-3898; Hsing and Bishop (1999) *J. Immunol.* 162:2804-2811; Everts *et al.* (2002) *J. Immunol.* 168:883-889).

Methods for flow cytometry, including fluorescence activated cell sorting (FACS), are available (see, *e.g.*, Owens, *et al.* (1994) *Flow Cytometry Principles for Clinical Laboratory Practice*, John Wiley and Sons, Hoboken, NJ; Givan (2001) *Flow Cytometry*, 2nd ed.; Wiley-Liss, Hoboken, NJ; Shapiro (2003) *Practical Flow Cytometry*, John Wiley and Sons, Hoboken, NJ). Fluorescent reagents suitable for modifying nucleic acids, including nucleic acid primers and probes, polypeptides, and antibodies, for use, *e.g.*, as diagnostic reagents, are available (Molecular Probes (2003) *Catalogue*, Molecular Probes, Inc., Eugene, OR; Sigma-Aldrich (2003) *Catalogue*, St. Louis, MO).

Standard methods of histology of the immune system are described (see, *e.g.*, Muller-Harmelink (ed.) (1986) *Human Thymus: Histopathology and Pathology*, Springer Verlag, New York, NY; Hiatt, *et al.* (2000) *Color Atlas of Histology*, Lippincott, Williams, and Wilkins, Philadelphia, PA; Louis, *et al.* (2002) *Basic Histology: Text and Atlas*, McGraw-Hill, New York, NY).

Software packages and databases for determining, *e.g.*, antigenic fragments, leader sequences, protein folding, functional domains, glycosylation sites, and sequence alignments, are available (see, *e.g.*, GenBank, Vector NTI® Suite (Informax, Inc, Bethesda, MD); GCG Wisconsin Package (Accelrys, Inc., San Diego, CA); DeCypher® (TimeLogic Corp., Crystal Bay, Nevada); Menne, *et al.* (2000) *Bioinformatics* 16: 741-742; Menne, *et al.* (2000) *Bioinformatics Applications Note* 16:741-742; Wren, *et al.* (2002) *Comput. Methods Programs Biomed.* 68:177-181; von Heijne (1983) *Eur. J. Biochem.* 133:17-21; von Heijne (1986) *Nucleic Acids Res.* 14:4683-4690).

Analytical Methods

Analytical methods suitable for evaluating the product stability include size exclusion chromatography (SEC), dynamic light scattering test (DLS), differential scanning calorimetry (DSC), iso-asp quantification, potency, UV at 340 nm, UV spectroscopy, and Fourier-transform infrared spectroscopy (FTIR). SEC (J. Pharm. Scien., 83:1645-1650, (1994); Pharm. Res., 11:485 (1994); J. Pharm. Bio. Anal., 15:1928 (1997); J. Pharm. Bio. Anal., 14:1133-1140 (1986)) measures percent monomer in the product and gives information of the amount of soluble aggregates. DSC (Pharm. Res., 15:200 (1998); Pharm. Res., 9:109 (1982)) gives information of protein denaturation temperature and glass transition temperature. DLS (American Lab., November (1991)) measures mean diffusion coefficient, and gives information of the amount of soluble and insoluble aggregates. UV at 340 nm measures scattered light intensity at 340 nm and gives information about the amounts of soluble and insoluble aggregates. UV spectroscopy measures absorbance at 278 nm and gives information of protein concentration. FTIR (Eur. J. Pharm. Biopharm., 45:231 (1998); Pharm. Res., 12:1250 (1995); J. Pharm. Scien., 85:1290 (1996); J. Pharm. Scien., 87:1069 (1998)) measures IR spectrum in the amide one region, and gives information of protein secondary structure.

The iso-asp content in the samples is measured using the Isoquant Isoaspartate Detection System (Promega). The kit uses the enzyme Protein Isoaspartyl Methyltransferase (PIMT) to specifically detect the presence of isoaspartic acid residues in a target protein. PIMT catalyzes the transfer of a methyl group from S-adenosyl-L-methionine to isoaspartic acid at the.alpha.-carboxyl position, generating S-adenosyl-L-homocysteine (SAH) in the process. This is a relatively small molecule, and can usually be isolated and quantitated by reverse phase HPLC using the SAH HPLC standards provided in the kit.

The potency or bioidentity of an antibody can be measured by its ability to bind to its antigen. The specific binding of an antibody to its antigen can be quantitated by any method known to those skilled in the art, for example, an immunoassay, such as ELISA (enzyme-linked immunosorbant assay).

All publications mentioned herein are incorporated by reference for the purpose of describing and disclosing methodologies and materials that might be used in connection with the present invention.

Having described different embodiments of the invention herein with reference to the accompanying drawings, it is to be understood that the invention is not limited to those precise embodiments, and that various changes and modifications may be effected therein by one skilled in the art without departing from the scope or spirit of the invention as defined in the appended claims.

EXAMPLES

The example in this section is offered by way of illustration, and not by way of limitation.

Example 1: Clinical Trial of Administering a Combination of Pembrolizumab and Enfortumab

5 Vedotin (EV) in combination with Favezelimab (MK-4280) in patients with advanced urothelial carcinoma.

The Phase 1/2 Study evaluates the safety and efficacy of Pembrolizumab Plus Enfortumab Vedotin (EV) in Combination With Investigational Agents Versus Pembrolizumab Plus EV, as First-Line Treatment for Participants With Advanced Urothelial Carcinoma.

10 The study has 2 parts. Part 1 (base) is intended to evaluate Arm A (MK-4280A plus EV) and Arm B (MK-7684A plus EV) versus Arm C (pembrolizumab plus EV). Patients are identified as having locally advanced (Stage IIIB) or metastatic (Stage IV) urothelial carcinoma. The indication is locally advanced/unresectable or metastatic urothelial carcinoma previously untreated for their advanced disease.

15 Participants in Arm A will receive EV at 1.25 mg/kg, administered as an IV infusion over approximately 30 minutes on Days 1 and 8 of every 3-week cycle, and MK-4280A (800 mg MK-4280/200 mg pembrolizumab) as an IV infusion on Day 1 of every 3-week cycle (Q3W), after completion of the EV infusion.

20 Participants in Arm B will receive EV at 1.25 mg/kg, administered as an IV infusion on Days 1 and 8 of every 3-week cycle, and MK-7684A (200 mg MK-7684/200 mg pembrolizumab) as an IV infusion on Day 1 of every 3-week cycle (Q3W), after completion of the EV infusion.

25 Participants in Arm C will receive EV at 1.25 mg/kg, administered as an IV infusion on Days 1 and 8 of every 3-week cycle, and pembrolizumab 200 mg as an IV infusion on Day 1 of every 3-week cycle (Q3W), after completion of the EV infusion.

In Cycle 1, on Day 1, MK-4280A (Arm A) and MK-7684A (Arm B) will be administered approximately 30 minutes after completion of EV infusion. In subsequent cycles, a delay of 15 minutes between the MK-4280A or MK-7684A and the EV infusion may be considered if the Cycle 1 Day 1 infusion was well tolerated.

30 Route of Administration is IV.

Table 8: Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Regimen/ Treatment Period	Use
Arm A	EV	1.25 mg/kg	Q3W on Days 1 and 8 every cycle	Until disease progression verified by BICR, intolerable toxicity, or investigator decision.	Test Product
	MK-4280A (Coformulation MK-4280/ Pembrolizumab)	800 mg/ 200 mg	Q3W on Day 1 of every cycle	Up to ~2 years (35 cycles)	Test Product
Arm B	EV	1.25 mg/kg	Q3W on Days 1 and 8 every cycle	Until disease progression verified by BICR, intolerable toxicity, or investigator decision.	Test Product
	MK-7684A (Coformulation MK-7684/ Pembrolizumab)	200 mg/ 200 mg	Q3W on Day 1 of every cycle	Up to ~2 years (35 cycles)	Test Product
Arm C	EV	1.25 mg/kg	Q3W on Days 1 and 8 every cycle	Until disease progression verified by BICR, intolerable toxicity, or investigator decision	Test Product
	Pembrolizumab	200 mg	Q3W on Day 1 of every cycle	Up to ~2 years (35 cycles)	Test Product

MK-4280A = MK-4280 (favezelimab) plus pembrolizumab coformulated,

MK-7684A = MK-7684 (vibostolimab) plus pembrolizumab coformulated, MK-3475 =

5 pembrolizumab

Note: EV will be administered up to a maximum dose of 125 mg.

Duration:

The Sponsor estimates that the study will require approximately 4 years from the time the first participant (or their legally acceptable representative) provides documented informed

consent until the last participant's last study related contact. After a screening phase of up to 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. After the end of treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy.

- 5 Participants who discontinue for reasons other than radiographic disease progression per RECIST 1.1 by BICR will have posttreatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met. All participants will be followed for OS until death, withdrawal of consent, or the end of the substudy.

Table 9: Objectives and Endpoints

Objectives	Endpoints
Primary	
Objective (Part 1): To evaluate ORR in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C) per RECIST 1.1 by BICR.	OR: CR or PR.
Objective (Part 1): To evaluate the safety and tolerability in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C).	AEs. Discontinuations of study interventions due to an AE. Dose-limiting toxicity (DLT).
Objective (Part 2): To compare EV plus MK-4280A (Arm A) and/or EV plus MK-7684A (Arm B) to EV plus pembrolizumab (Arm C) with respect to PFS per RECIST 1.1 by BICR. Hypothesis (H1; Part 2): EV plus MK-4280A (Arm A) and/or EV plus MK-7684A (Arm B) are superior to EV plus pembrolizumab (Arm C) with respect to PFS per RECIST 1.1 by BICR.	PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
Secondary	Endpoints
Objective (Part 1): To evaluate PFS in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C) per RECIST 1.1 by BICR.	PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
Objective (Part 2): To compare EV plus MK-4280A (Arm A) and/or EV plus MK-7684A (Arm B) versus EV plus pembrolizumab (Arm	OS: The time from randomization to death due to any cause.

C) with respect to OS. • Hypothesis (H2; Part 2): EV plus MK-4280A (Arm A) and/or EV plus MK-7684A (Arm B) are superior to EV plus pembrolizumab (Arm C) with respect to OS.	
Objective (Part 2): To evaluate ORR in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C) per RECIST 1.1 by BICR.	OR: CR or PR.
Objective (Part 2): To evaluate the safety and tolerability in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C).	AEs. Discontinuations of study interventions due to an AE. Dose-limiting toxicity (DLT).
Objective (Part 1 and Part 2): To evaluate DOR in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C) per RECIST 1.1 by BICR.	DOR: For participants who show CR or PR, DOR is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
Objective (Part 1 and Part 2): To evaluate changes in patient-reported outcomes from baseline and TTD using the EORTC QLQ-C30 instrument and EQ-5D-5L in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B) and pembrolizumab plus EV (Arm C).	Change from baseline in: - The global health status/quality of life of the EORTC QLQ-C30 - The physical functioning scale of the EORTC QLQ-C30. - EQ-5D-5L visual analog score (VAS). The time-to-deterioration, defined as the time from baseline to first onset of patient reported outcome deterioration based on established minimal important differences threshold, in: - The global health status/quality of life of the EORTC QLQ-C30 - The physical functioning scale of the EORTC QLQ-C30. - EQ-5D-5L VAS.

Tertiary/Exploratory	
Objective (Part 1 and Part 2): To assess the PK of MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C).	Selected plasma or serum PK parameters of MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C).
Objective (Part 1 and Part 2): To assess the development of ADA to MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C).	Incidence of ADA to MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C).
Objective (Part 1 and Part 2): To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, and/or the mechanism of action of MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C).	Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.
Objective (Part 1 and Part 2): To evaluate depth of response in participants treated with EV plus MK-4280A (Arm A) and EV plus MK-7684A (Arm B), versus EV plus pembrolizumab (Arm C) per RECIST 1.1 by BICR.	Depth of Response: Percent change from baseline in sum of diameters of target lesions. Deep Response: Substantial tumor reduction (e.g., 75%) in the sum of diameters of target lesion from baseline in the absence of a new lesion(s) or unequivocal progression of nontarget lesions.
Objective (Part 1 and Part 2): To evaluate changes in patient-reported outcomes from baseline using the EORTC QLQ-C30 instrument and EQ-5D-5L in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B) and pembrolizumab plus EV (Arm C).	Change of patient-reported outcomes from baseline in: - EORTC QLQ-C30 functioning scales (other than physical functioning) and symptoms scales - EQ-5D-5L utility score
Objective (Part 2): To compare EV plus MK-4280A (Arm A) and/or EV plus MK-7684A (Arm B) to EV plus pembrolizumab (Arm C)	PFS: The time from randomization to the first documented disease progression or death due to any cause.

with respect to PFS per RECIST 1.1 by investigator assessment.	whichever occurs first.
Objective (Part 1 and Part 2): To evaluate ORR in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C) per RECIST 1.1 by investigator assessment.	OR: CR of PR.

Dose Level for Study Intervention

MK-4280A plus EV (Arm A): Dose Level 0: MK-4280 800 mg plus MK-3475 200 mg plus EV
1.25 mg/kg Q3W

- 5 MK-7684A plus EV(Arm B): Does Level 0: MK-7684 200 mg plus MK-3475 200 mg plus EV
1.25 mg/kg Q3W

Dose-Limiting Toxicity

Study participants will be followed for DLTs for the first cycle after the first dose of
10 study intervention.

All toxicities will be graded using NCI CTCAE 5.0 based on the investigator assessment.
The occurrence of any of the following toxicities will be considered a DLT, as assessed by the
investigator and considered related to the novel combination (excluding toxicities clearly not
related to the drug such as disease progression, environmental factors, unrelated trauma, etc.):

- 15 • Recurrent Grade 3 infusion-related reaction despite premedication

NOTE: For pembrolizumab, MK-4280A and MK-7684A, Grade 3 or 4 severity will lead to
permanent discontinuation on the first occurrence.

- Infusion-related reaction with anaphylaxis or Grade 4 severity on the first occurrence for
any study medication
- 20 • Any TRAE that causes a delay in initiating the next cycle, for >14 days, with the
exception of skin adverse reactions for which a delay in initiating the next cycle for >21 days will
be considered a DLT
- Hy's law
- AST or ALT >3 times the upper limit of normal AND
- 25 - A total bilirubin >2 times the upper limit of normal AND
- Alkaline phosphatase <2 times the upper limit of normal AND
- No other reason for liver injury

- For participants with hepatic metastases, AST or ALT >8x ULN or AST or ALT >5x ULN for ≥14 days
- Grade 4 nonhematologic toxicity (not laboratory)
- Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia
- 5 - Grade 4 thrombocytopenia of any duration
- Grade 3 thrombocytopenia associated with bleeding that requires a platelet transfusion
- Any nonhematologic Grade 3 AE lasting ≥7 days despite optimal supportive care, with the following exceptions: Grade 3 diarrhea, nausea, or vomiting without use of antiemetics or antidiarrheals per SOC lasting ≥7 days; Grade 3 skin adverse reactions that do not improve to
- 10 ≤Grade 2 in <21 days, despite optimal supportive care
- Grade 3 or 4 nonhematologic laboratory abnormalities for which clinically significant intervention is required, leads to hospitalization, or persists without improvement for >1 week
- The DLT definition may exclude:
 - Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically
 - 15 complicated, and resolves spontaneously or responds to conventional medical interventions
 - Grade 3 or higher amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis
 - Grade 5 toxicity

20 **Safety IA1 and Safety IA2**

In Part 1, there will be 2 Safety IAs. The first Safety IA will be conducted after approximately 60 participants are enrolled on Arms A, B, and C (approximately 20 participants on each arm) or approximately 6 months have elapsed since the first participant was enrolled, whichever is first, and the second Safety IA will be conducted at the time of the

25 Efficacy IA. The main purpose of these safety interim analyses is to evaluate the safety and tolerability of EV plus MK-4280A and EV plus MK-7684A by the iDMC. The safety of the experimental Arm A and Arm B will be evaluated during the safety lead-in within the context of the safety profile of Arm C as well as within the known safety profile for the combination of pembrolizumab and EV (see Section 2.2.2.5). The Sponsor will monitor for any AE not

30 consistent with the frequency and characteristics of the adverse events described with the combination of pembrolizumab and EV. In addition, throughout this open-label study, rigorous medical monitoring will be conducted by the Sponsor to ensure participants' safety. Participants will be evaluated by the investigator in the clinic per the SoA, and regularly scheduled teleconferences will be held with the Sponsor and investigators during the Safety Lead-in Phase.

35 During the Safety IAs, the iDMC will review the safety data to make recommendations on the

safety and tolerability of Arms A and B. Arm C safety data will be provided to the iDMC to help review the safety data of Arms A and B. The iDMC may consider:

- Arms A and/or B are deemed tolerable.
- Arms A and/or B are not deemed tolerable.

5 Additional iDMC safety reviews will occur at regular intervals during the substudy (e.g., every 6 months), scheduled incorporating advice from the iDMC regarding timing.

At Safety IA1, a decision might be made to stop enrollment early for one or more investigational arms based on a risk/benefit ratio assessment.

10 **Efficacy IA**

In Part 1, an Efficacy IA will be conducted after approximately 120 participants (including participants enrolled during the Safety Lead-in Phase) are enrolled (approximately 40 participants enrolled per Arm) and have a minimum of 18 weeks efficacy follow-up (at least 2 post-baseline scans). BICR per RECIST 1.1 will be used to assess the primary endpoint ORR, secondary endpoint DOR, and exploratory endpoint DRR in Arms A, B, and C. ORR will be evaluated per investigator assessment as an exploratory endpoint. Refer to Section 3 for details. PFS will not be evaluated at this IA and hypothesis testing on PFS will not be performed.

As a result of this IA, further development of Arms A and/or B may be considered, either as part of a separate study or within Part 2.

20

Efficacy FA

If the decision is made to conduct Part 2, additional participants will be enrolled in Arms A and/or B and C, as described in Section 4.1.1.2. Only in that case, a Part 2 FA, including participants from both Part 1 and Part 2, will be conducted. The Part 2 FA will be event-driven and will occur once approximately 187 PFS events from both Part 1 and Part 2 have occurred on Arm A and/or Arm B and Arm C. It is projected that the number of PFS events mentioned above would be reached approximately 18 months after all Part 2 participants have been randomized to the substudy. The primary objective of Part 2 is to compare PFS (per RECIST 1.1 by BICR) between Arm A and/or B and Arm C. OS will also be tested at 2.5% type I error (one-sided) after PFS is positive at 2.5% type I error (one-sided).

30

Evaluation in All Treatment Arms:

Participants will be evaluated with radiographic imaging to assess response to study intervention every 9 weeks (63 ± 7 days) from randomization through 36 weeks, every 12 weeks through Week 96 ($672 \text{ days} \pm 7 \text{ days}$) and every 24 weeks thereafter until RECIST 1.1 PD is assessed by the site and verified by BICR or initiation of a new anticancer regimen. Participants who discontinue study treatments in the absence of BICR-verified PD must continue

35

to have radiographic imaging in follow-up until PD is verified by BICR. Participants should continue study treatment until BICR-verified PD by RECIST 1.1 or until any discontinuation criterion is met. Progressive disease documented by investigator by RECIST 1.1, must be verified by BICR prior to discontinuation of study treatment. If PD is not verified by BICR, refer to Section 8.2.1 for next steps. All imaging obtained during the study will be assessed using RECIST 1.1 (Section 4.2.1.1) for determination of PFS, ORR, DOR, and DRR.

Survival follow-up will continue after BICR-verified PD or the start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the study.

AE monitoring will be ongoing throughout the study. AEs will be graded in severity according to the guidelines outlined in the NCI CTCAE 5.0.

If the investigator attributes toxicity to study medication, dose modifications will be allowed when appropriate.

Treatment with MK-4280A, MK-7684A or pembrolizumab will continue for a maximum of 35 doses (~2 years), or until a discontinuation criterion is met. Discontinuation of treatment with MK-4280A in Arm A, MK-7684A in Arm B, or pembrolizumab in Arm C may be considered for participants who have attained a confirmed RECIST 1.1 CR per local assessment and have been treated for at least 4 doses (4 cycles) of MK-4280A or MK-7684A or pembrolizumab, with at least 2 additional doses beyond the date when the initial CR was declared.

There is no upper limit to the number of cycles of EV permitted. To date in metastatic urothelial carcinoma, EV has been administered until disease progression or unacceptable toxicity.

All participants will be permitted to continue study treatment beyond PD per RECIST 1.1 as assessed by investigator, as long as the treating investigator considers that the participant may experience clinical benefit with continued treatment, and the participant is clinically stable and tolerating study intervention, until PD is verified by BICR. Continuation of study treatment beyond BICR-verified PD may occur after consultation with the Sponsor. Communication with the Sponsor is required before stopping study intervention, imaging, or starting new anticancer therapy in a participant that does not have BICR-verified PD.

CLAIMS

1. A method of treating cancer, comprising administering to a human patient in need thereof an effective amount of a therapeutic combination comprising:

(a) a LAG3 antagonist, wherein the LAG3 antagonist is an antibody or antigen binding fragment thereof comprising three light chain CDRs: CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44;

(b) pembrolizumab; and

(c) enfortumab vedotin.

2. The method of claim 1, wherein the cancer is selected from the group consisting of melanoma, non-small cell lung cancer, head and neck squamous cell cancer, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high or mismatch repair deficient cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, biliary tract cancer, endometrial carcinoma, a cancer characterized by a tumor having a high mutational burden, cutaneous squamous cell carcinoma, and triple negative breast cancer.

3. The method of claim 2, wherein the cancer is urothelial carcinoma.

4. The method of claim 3, wherein the urothelial carcinoma is locally advanced urothelial carcinoma.

5. The method of claim 3, wherein the urothelial carcinoma is metastatic urothelial carcinoma.

6. A kit comprising:

(a) a LAG3 antagonist, wherein the LAG3 antagonist is an antibody or antigen binding fragment thereof comprising three light chain CDRs: CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42,

CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44;

- (b) pembrolizumab; and
- (c) enfortumab vedotin.

7. The kit of claim 6, further comprising instructions for administering to a human patient the LAG3 antagonist antibody or antigen binding fragment thereof, pembrolizumab, and enfortumab vedotin.

8. The kit of claim 6, wherein the cancer is selected from the group consisting of melanoma, non-small cell lung cancer, head and neck squamous cell cancer, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high or mismatch repair deficient cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, biliary tract cancer, Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, a cancer characterized by a tumor having a high mutational burden, cutaneous squamous cell carcinoma, and triple negative breast cancer.

9. The kit of claim 8, wherein the cancer is urothelial carcinoma.

10. The kit of claim 9, wherein the urothelial carcinoma is locally advanced urothelial carcinoma.

11. The kit of claim 9, wherein the urothelial carcinoma is metastatic urothelial carcinoma.

12. Use of an effective amount of a therapeutic combination for treating cancer in a human patient, wherein the therapeutic combination comprises:

- (a) a LAG3 antagonist;
- (b) pembrolizumab; and
- (c) enfortumab vedotin.

13. The use of claim 12, wherein the cancer is selected from the group consisting of melanoma, non-small cell lung cancer, head and neck squamous cell cancer, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high or mismatch repair deficient cancer, gastric cancer, esophageal cancer, cervical

cancer, hepatocellular carcinoma, biliary tract cancer, Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, a cancer characterized by a tumor having a high mutational burden, cutaneous squamous cell carcinoma, and triple negative breast cancer.

14. The use of claim 13, wherein the cancer is urothelial carcinoma.
15. The use of claim 14, wherein the urothelial carcinoma is locally advanced urothelial carcinoma.
16. The use of claim 14, wherein the urothelial carcinoma is metastatic urothelial carcinoma.
17. The method, kit, or use of any one of claims 1-16, wherein pembrolizumab and the LAG3 antagonist are co-formulated.
18. The method, kit, or use of any one of claims 1-16, wherein pembrolizumab and the LAG3 antagonist are in a fixed dose combination.
19. The method, kit, or use of any one of claims 1-16, wherein pembrolizumab and the LAG3 antagonist are formulated separately.
20. The method, kit, or use of any one of claims 1-19, wherein the LAG3 antagonist is an anti-human LAG3 monoclonal antibody.
21. The method, kit, or use of claim 20 wherein the anti-human LAG3 monoclonal antibody is a humanized antibody.
22. The method, kit, or use of claim 20 wherein the anti-human LAG3 monoclonal antibody is favezelimab.
23. The method, kit, or use of any one of claims 1-22, wherein the LAG3 antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 38 and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 37.

24. The method, kit, or use of claim 23, wherein the LAG3 antibody or antigen binding fragment thereof comprises a light chain comprising or consisting of the amino acid sequence as set forth in SEQ ID NO: 35 and a heavy chain comprising or consisting of the amino acid sequence as set forth in SEQ ID NO: 36.

25. The method of any one of claims 1-24, wherein the human patient is administered about 200 mg, or about 2 mg/kg pembrolizumab once every three weeks.

26. The method of claim 25, wherein the human patient is administered about 200 mg pembrolizumab once every three weeks.

27. The method of any one of claims 1-26, wherein the human patient is administered from about 50 mg to about 1200 mg of the LAG3 antagonist, and wherein the LAG3 antagonist is administered once every three weeks.

28. The method of claim 27, wherein the human patient is administered about 200 mg to about 1000 mg of the LAG3 antagonist once every three weeks.

29. The method of any one of claims 1-28, wherein the human patient is administered about 800 mg of the LAG3 antagonist once every three weeks.

30. The method of any one of claims 1-30 wherein the human patient is administered about 1.25 mg/kg enfortumab vedotin, and wherein enfortumab vedotin is administered every three weeks on day 1 and day 8 of every cycle.

31. A method of treating urothelial cancer, comprising administering to a human patient in need thereof an effective amount of a therapeutic combination comprising:

(a) about 200 mg pembrolizumab;

(b) about 800 mg of an anti- LAG3 antibody or antigen binding fragment thereof comprising three light chain CDRs: CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44; and

(c) about 1.25 mg/kg enfortumab vedotin.

32. The method of claim 32, wherein (a) and (b) are administered once every three weeks.

33. The method of any one of claims 32-33, wherein (c) is administered on day 1 and day 8 of every cycle.

34. The method of claim 32, wherein (a) and (b) are administered on the same day, and wherein (a) and (b) are administered sequentially or concurrently.

35. The method of claim 32, wherein (a) and (b) are co-formulated.

36. The method of claim 32, wherein (a) and (b) are in a fixed dose combination.

37. A method of treating urothelial cancer, comprising administering to a human patient in need thereof an effective amount of a therapeutic combination comprising:

(a) about 200 mg pembrolizumab;

(b) about 800 mg of an anti- LAG3 antibody or antigen binding fragment thereof comprising three light chain CDRs: comprising CDRL1 having the amino acid sequence as set forth in SEQ ID NO: 39, CDRL2 having the amino acid sequence as set forth in SEQ ID NO: 40, and CDRL3 having the amino acid sequence as set forth in SEQ ID NO: 41 and three heavy chain CDRs comprising CDRH1 having the amino acid sequence as set forth in SEQ ID NO: 42, CDRH2 having the amino acid sequence as set forth in SEQ ID NO: 43, and CDRH3 having the amino acid sequence as set forth in SEQ ID NO: 44; and

(c) about 1.25 mg/kg of enfortumab vedotin.

38. The method of claim 38, wherein (a) and (b) are administered once every three weeks.

39. The method of any one of claims 38-39, wherein (c) is administered every three weeks on day 1 and day 8.

40. The method of claim 38, wherein (a) and (b) are administered on the same day, and wherein (a) and (b) are administered sequentially or concurrently.

41. The method of claim 38, wherein (a) and (b) are co-formulated.
42. The method of claim 38, wherein the anti-human LAG3 monoclonal antibody is favezelimab.

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The cDNA (SEQ ID NO:45) and amino acid sequence (SEQ ID NO:46) of 191P4D12. The start methionine is underlined. The open reading frame extends from nucleic acid 264–1796 including the stop codon.

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1  ggccgtcgttggtggccacagcgtgggaagcagctctgggggagctcggagctcccgatc
61  acggcttcttggggtagctacggctgggtgtgtagaacggggccggggctggggctggg
121  tcccctagtggagacccaagtgcgagaggcaagaactctgcagcttctgccttctgggt
181  cagttccttattcaagtctgcagccggctcccagggagatctcgggtggaacttcagaac
1      M P L S L G A E M W G P E
241  gctgggcagctctgcctttcaaccATGCCCTGTCCCTGGGAGCCGAGATGTGGGGCCTG
14   A W L L L L L L L A S F T G R C P A G E
301  AGGCCTGGCTGCTGCTGCTGCTACTGCTGGCATCATTTACAGGCCGGTGCCCCGCGGTG
34   L E T S D V V T V V L G Q D A K L P C F
361  AGCTGGAGACCTCAGACGTGGTAACTGTGGTGTGGGCCAGGACGCAAACTGCCCTGCT
54   Y R G D S G E Q V G Q V A W A R V D A G
421  TCTACCGAGGGGACTCCGGCGAGCAAGTGGGGCAAGTGGCATGGGCTCGGCTGGACGCGG
74   E G A Q E L A L L H S K Y G L H V S P A
481  GCGAAGGCGCCCAGGAAGTACGCTACTGCACTCCAAATACGGGCTTCATGTAGCCCGG
94   Y E G R V E Q P P P P R N P L D G S V L
541  CTTACGAGGGCCGCTGGAGCAGCCGCCGCCACGCAACCCCTGGACGGCTCAGTGC
114  L R N A V Q A D E G E Y E C R V S T F P
601  TCCTGCGCAACGCAGTGCAGGCGGATGAGGGCGAGTACGAGTGCCGGGTCAGCACCTTCC
134  A G S F Q A R L R L R V L V P P L P S L
661  CCGCCGCGAGCTTCCAGGCGCGCTGCGGCTCCGAGTGTGGTGCCTCCCCTGCCCTCAC
154  N P G P A L E E G Q G L T L A A S C T A
721  TGAATCCTGGTCCAGCACTAGAAGAGGGCCAGGGCCTGACCCTGGCAGCCTCCTGCACAG
174  E G S P A P S V T W D T E V K G T T S S
781  CTGAGGGCAGCCAGCCCCAGCGTGACCTGGGACACGGAGGTCAAAGGCACAACGTCCA
194  R S F K H S R S A A V T S E F H L V P S
841  GCCGTTCTTCAAGCACTCCCGCTCTGCTGCCGTCACCTCAGAGTTCCACTTGGTGCCTA
214  R S M N G Q P L T C V V S H P G L L Q D
901  GCCGCAGCATGAATGGGCAGCCACTGACTTGTGTGGTGTCCATCCTGGCCTGCTCCAGG
234  Q R I T H I L H V S F L A E A S V R G L
961  ACCAAAGGATCACCCACATCCTCCACGTGTCCTTCTTGCTGAGGCCTCTGTGAGGGGCC
254  E D Q N L W H I G R E G A M L K C L S E
1021  TTGAAGACCAAAATCTGTGGCACATTGGCAGAGAAGGAGCTATGCTCAAGTGCCTGAGTG
274  G Q P P P S Y N W T R L D G P L P S G V
1081  AAGGGCAGCCCCCTCCCTCATACAACTGGACACGGCTGGATGGGCCTCTGCCCAGTGGGG
294  R V D G D T L G F P P L T T E H S G I Y
1141  TACGAGTGGATGGGGACACTTTGGGCTTTCCCCACTGACCACTGAGCACAGCGGCATCT
324  V C H V S N E F S S R D S Q V T V D V L
1201  ACGTCTGCCATGTCAGCAATGAGTTCTCCTCAAGGGATTCTCAGGTCACTGTGGATGTTG
334  D P Q E D S G K Q V D L V S A S V V V V

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FIG. 1A

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1261 TTGACCCCAAGGAAGACTCTGGGAAGCAGGTGGACCTAGTGTACGCTCGGTGGTGGTGG
354 G V I A A L L F C L L V V V V V L M S R
1321 TGGGTGTGATCGCCGCACTCTTGTCTGCCTTCTGGTGGTGGTGGTGGTGCATGTCCC
374 Y H R R K A Q Q M T Q K Y E E E L T L T
1381 GATACCATCGGCGCAAGGCCAGCAGATGACCCAGAAATATGAGGAGGAGCTGACCCTGA
394 R E N S I R R L H S H H T D P R S Q P E
1441 CCAGGGAGAACTCCATCCGGAGGCTGCATTCCCATCACACGGACCCAGGAGCCAGCCGG
414 E S V G L R A E G H P D S L K D N S S C
1501 AGGAGAGTGTAGGGCTGAGAGCCGAGGCCACCCTGATAGTCTCAAGGACAACAGTAGCT
434 S V M S E E P E G R S Y S T L T T V R E
1561 GCTCTGTGATGAGTGAAGAGCCCGAGGCCGAGTACTCCACGCTGACCACGGTGAGGG
454 I E T Q T E L L S P G S G R A E E E E D
1621 AGATAGAAACACAGACTGAACTGCTGTCTCCAGGCTCTGGGCGGGCCGAGGAGGAGGAAG
474 Q D E G I K Q A M N H F V Q E N G T L R
1681 ATCAGGATGAAGGCATCAACAGGCCATGAACATTTTGTTCAGGAGAATGGGACCCCTAC
494 A K P T G N G I Y I N G R G H L V *
1741 GGGCCAAGCCCAAGGGCAATGGCATCTACATCAATGGGCGGGGACACCTGGTCTGAccca
1801 ggectgcctcccttccctagggctggctccttctgttgacatgggagattttagctcctc
1861 ttgggggctccttaaacacccccatttcttgcggaagatgctccccatcccactgactg
1921 cttgacctttacctccaaccttctgttcategggagggctccaccaattgagctctctcc
1981 caccatgcatgcaggctcactgtgtgtgtgcatgtgtgctgtgtgagtgttgactgactg
2041 tgtgtgtgtggaggggtgactgtccgtggaggggtgactgtgtccgtggtgtgtattatg
2101 ctgtcatatcagagtcaagtgaactgtggtgtatgtgccacgggatttgagtgggtgcgt
2161 gggcaacactgtcaggggttgccgtgtgtgtcatgtggtgtgtgtgacctctgcctgaa
2221 aaagcaggtattttctcagaccccagagcagttatgatgcagaggttgaggaggagaga
2281 ggtggagactgtggctcagacccaggtgtgcgggcatagctggagctggaatctgcctcc
2341 ggtgtgaggggaacctgtctcctaccacttcggagccatgggggaagtgtgaagcagcca
2401 gtccctgggtcagccagaggttgaaactgttacagaagccctctgcctctggtggcctc
2461 tgggctgctgcatgtacatatcttctgtaaatatcatgcgccgggagcttcttgacagg
2521 aatactgctccgaatcacttttaattttttcttttttttcttgccctttccattagt
2581 tgtattttttatttttttttttttttttttttttagagatggagtctcactatgttgc
2641 tcaggctggccttgaactcctgggctcaagcaatcctcctgcctcagcctccctagtagc
2701 tgggactttaagtgtacaccactgtgcctgcttgaatcctttacgaagagaaaaaaaa
2761 attaaagaagccttttagatttatccaatgtttactactgggattgcttaagtgaggcc
2821 cctccaacaccagggggttaattcctgtgattgtgaaaggggctacttccaaggcatctt
2881 catgcaggcagcccttgggagggcacctgagagctggtagagtctgaaattagggatgt
2941 gagcctcgtggttactgagtaaggtaaaaattgcatccaccattgtttgtgataccttagg
3001 gaattgcttggacctggtgacaagggtcctgttcaatagtgggtgttggggagagagaga
3061 gcagtgtattatagaccgagagagtaggaggttaggtgaggtgaaggaggtgctgggggtg

FIG. 1A
(Continued)

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3121 agaatgtcgcccttccccctgggttttggatcactaattcaaggctcttctggatgtttc
3181 tctgggttggggtggagttcaatgaggtttatctttagctggcccaccagatacactc
3241 agccagaatacctagatttagtaccctaaactcttcttagtctgaaatctgctggatttct
3301 ggcctaaggagagaggctcccatccttcgttccccagccagcctaggacttcgaatgtgga
3361 gcctgaagatctaagatcctaacaatgtacattttatgtaaatgtgcataattgtacat
3421 aaaatgatattctgtttttaataaacagacaaaacttgaaaaa

FIG. 1A

(Continued)

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The cDNA (SEQ ID NO:47) and amino acid sequence (SEQ ID NO:48) of Ha22-2(2,4)6.1 heavy chain. Double-underlined is the leader sequence, underlined is the heavy chain variable region, and underlined with a dashed line is the human IgG1 constant region.

M E L G L C W V F L V A I L E

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1  GGTGATCAGCACTGAACACAGAGGACTCACCATGGAGTTGGGGCTGTGCTGGGTTTTCTTGTTGCTATTTTAGA
   • G V Q C E V Q L V E S G G G L V Q P G G S L R L S
76 AGGTGTCCAGTGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGCCTTGGTACAGCCTGGGGGCTCCCTGAGACTCTC
   • C A A D G F T F S S Y N M N W V R Q A P G K G L E
151 CTGTGCAGCCTCTGGATTACCTTCAGTAGCTATAACATGAACTGGGTCCGCCAGGCTCCAGGAAGGGGCTGGA
   • W V S Y I S S S S S T I Y Y A D S V K G R F T I S
226 GTGGGTTTCATACATTAGTAGTAGTAGTAGTACCATATACTACGCAGACTCTGTGAAGGGCCGATTACCATCTC
   • R D N A K N S L S L Q M N S L R D E D T A V Y Y C
301 CAGAGACAATGCCAAGAACTCACTGTCTCTGCAAATGAACAGCCTGAGAGACGAGGACACGGCTGTGTATTACTG
   • A R A Y Y Y G M D V W G Q G T T V T V S S A S T K
376 TGCGAGAGCATACTACTACGGTATGGAGCTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCCACCAA
   • G P S V F P L A P S S K S T S G G T A A L G C L V
451 GGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGT
   • K D Y F P E P V T V S W N S G A L T S G V H T F P
526 CAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGAACTCAGGCGCCCTGACCAGCGCGGTGCACACCTTCCC
   • A V L Q S S G L Y S L S S V V T V P S S S L G T Q
601 GGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCA
   • T Y I C N V N H K P S N T K V D K R V E P K S C D
676 GACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTA
   • K T H T C P P C P A P E L L G G P S V F L F P P K
751 CAAACTCACACATGCCCACCGTGCCAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCTTCCCCCCTT
   • P K D T L M I S R T P E V T C V V V D V S H E D P
826 ACCCAAGGACACCCTCATGATCTCCCGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCC
   • E V K F N W Y V D G V E V H N A K T K P R E E Q Y
901 TGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGAGGAGCAGTA
   • N S T Y R V V S V L T V L H Q D W L N G K E Y K C
976 CAACAGCACGTACCGTGTGGTCAGCGTCTCACCGTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTG
   • K V S N K A L P A P I E K T I S K A K G Q P R E P
1051 CAAGGTCTCCAACAAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCAAAGCCAAAGGCAGCCCCGAGAACC
   • Q V Y T L P P S R E E M T K N Q V S L T C L V K G
1126 ACAGGTGTACACCCTGCCCCATCCCGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGG
   • F Y P S D I A V E W E S N G Q P E N N Y K T T P P
1201 CTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGCCAGCCGGAACAACACTACAAGACCACGCCTCC
   • V L D S D G S F F L Y S K L T V D K S R W Q Q G N
1276 CGTGCTGGACTCCGACGGCTCCTTCTTCTCTATAGCAAGCTACCGTGCACAAGAGCAGGTGGCAGCAGGGGAA
   • V F S C S V M H E A L H N H Y T Q K S L S L S P G
1351 CGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGACCTCTCCTGTCCCCGGG
   • K *
1426 TAAATGA

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FIG. 1B

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The cDNA (SEQ ID NO:49) and amino acid sequence (SEQ ID NO:50) of Ha22-2(2,4)6.1 light chain. Double-underlined is the leader sequence, underlined is the light chain variable region, and underlined with a dashed line is the human kappa constant region.

M D M R V P A Q L L G L L L L W F

1 AGTCAGACCCAGTCAGGACACAGCATGGACATGAGGGTCCCCGCTCAGCTCCTGGGGCTCCTGCTGCTCTGGTTC
P G S R C D I Q M T Q S P S S V S A S V G D R V T

76 CCAGGTTCCAGATGCGACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTTGGAGACAGAGTCACC
I T C R A S Q G I S G W L A W Y Q Q K P G K A P K

151 ATCACTTGTGGGCGAGTCAGGGTATTAGCGGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAG
F L I Y A A S T L Q S G V P S R F S G S G S G T D

226 TTCCTGATCTATGCTGCATCCACTTTGCAAAGTGGGGTCCCATCAAGTTACGCGGAGTGGATCTGGGACAGAT
F T L T I S S L Q P E D F A T Y Y C Q Q A N S F P

301 TTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCACTTACTATTGTCAACAGGCTAACAGTTTCCCT
P T F G G G T K V E I K R T V A A P S V F I F P P

376 CCCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCA
S D E Q L K S G T A S V V C L L N N F Y P R E A K

451 TCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA
V Q W K V D N A L Q S G N S Q E S V T E Q D S K D

526 GTACAGTGAAGGTGGATAACGCCCTCCAATCGGGTAAGTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGAC
S T Y S L S S T L T L S K A D Y E K H K V Y A C E

601 AGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA
V T H Q G L S S P V T K S F N R G E C *

676 GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

FIG. 1C

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The amino acid sequence (SEQ ID NO:51 of Ha22-2(2,4)6.1 heavy chain. Double-underlined is the leader sequence, underlined is the heavy chain variable region, (SEQ ID NO:66, which is the sequence ranging from the 20th to the 136th amino acid of SEQ ID NO:51) and underlined with a dashed line is the human IgG1 constant region.

```

1  MELGLCWFLVAILEGVQCEVQLVESGGGLVQPGGSLRLSCAASGFTFSS
51 YNNMWVRQAPGKGLEWWSYISSSSSTIYYADSVKGRFTISRDNAKNSLSL
101 QMNSLRDEDTAVYYCARAYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPS
151 SKSTSGGTAALGCLVKDYFPEPVTSVWNSGALTSGVHTFPAVLQSSGLYS
201 LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPA
251 PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
301 VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNKEYKCKVSNKALPAP
351 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
401 ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEA
451 LHNHYTQKSLSLSPGK

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FIG. 1 D

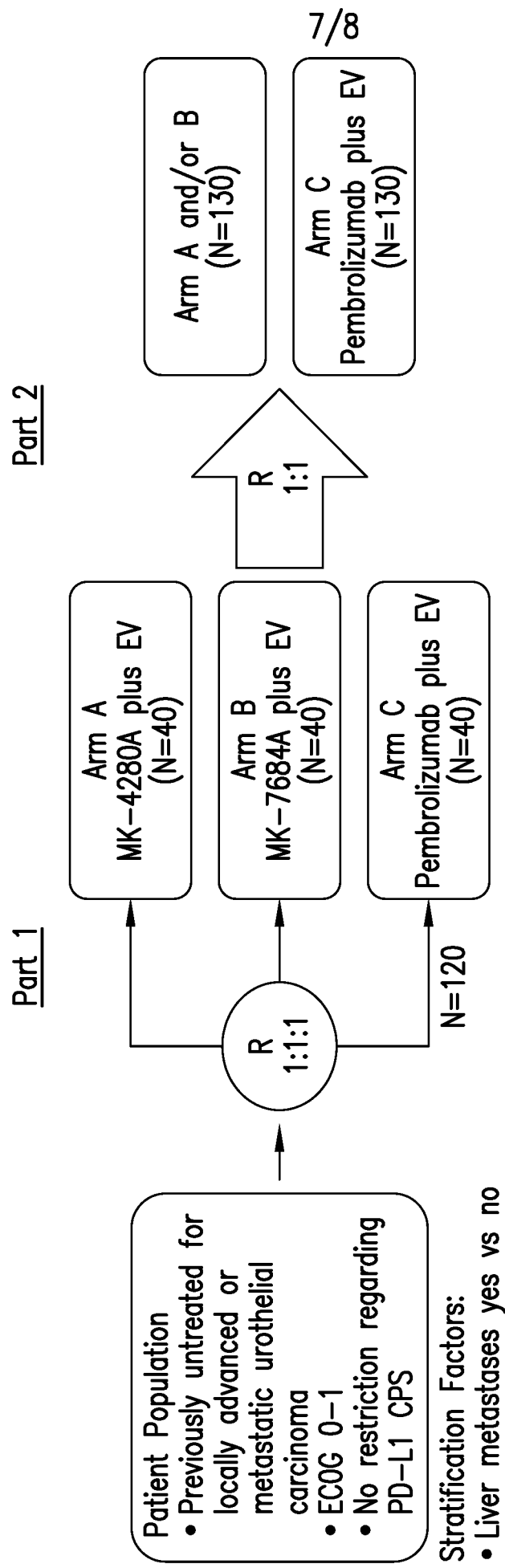
The amino acid sequence (SEQ ID NO:52) of Ha22-2(2,4)6.1 light chain. Double-underlined is the leader sequence, underlined is the light chain variable region (SEQ ID NO:67, which is the sequence ranging from the 23rd to the 130th amino acid of SEQ ID NO:52) and underlined with a dashed line is the human kappa constant region.

```

1  MDMRVPAQLLGLLLLWFPGSRCDIQMTQSPSSVSASVGDRVTITCRASQG
51 ISGWLAWYQQKPGKAPKFLIYAASTLQSGVPSRFSSGSGSGTDFTLTISSL
101 QPEDFATYYCQANSFPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG
151 TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSS
201 LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

```

FIG. 1 E



Abbreviations: CPS=combined positive score; ECOG=Eastern Cooperative Oncology Group: EV=enfortumab vedotin: PD-L1=programmed cell death ligand 1.
Note: Study MK-3475-04B is open-label with signal-finding Intent.

FIG.2

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Pembrolizumab Light Chain

EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLESGVPARFSGSGSGTDFTLTISSL
EPEDFAVYYCQHSRDLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG
NSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:5).

Pembrolizumab Heavy Chain

QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYMYWVRQAPGQGLEWMGGINPSNGGTNFNEKFKNRVTLTTDSS
TTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYF
PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPE
FLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSMHEALHNHYTQKSLSLSLGK (SEQ ID NO:10).

FIG.3