COMBINATION THERAPY FOR COLORECTAL CARCINOMA

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This PCT application claims the priority benefit of U.S. Provisional Application No. 63/314,137, filed February 25, 2022, which is incorporated herein by reference in its entirety.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[0002] The content of the electronically submitted sequence listing (Name: 3338_293PC01_SeqListing_ST26; Size: 101,963 Bytes; and Date of Creation: February 7, 2023), filed with the application, is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0003] The present disclosure provides a method of treating human subjects afflicted with colorectal carcinoma (CRC) comprising an anti-lymphocyte activation gene-3 (LAG-3) antibody and an anti-programmed death-1 (PD-1) or anti-programmed death ligand-1 (PD-L1) antibody.

BACKGROUND OF THE INVENTION

[0004] Worldwide, CRC is the second most common form of cancer in women per year and the third most common form of cancer in men. This disease predominately occurs in developed regions with the highest rates being found in Australia/New Zealand and Western Europe and to a lesser extent in Africa and South-Central Asia. Each year, there are about 880,800 deaths from CRC, which is approximately 9% of all cancer deaths, making CRC the second most common cause of cancer death. At initial diagnosis, approximately 25% of patients present with metastatic disease and almost 50% of patients will develop metastasis, which contributes to the high mortality rate reported in CRC patients.

[0005] There is a need for improved methods for treating human subjects afflicted with CRC.

SUMMARY OF THE INVENTION

[0006] The present disclosure is directed to a method of treating a human subject afflicted with colorectal carcinoma (CRC), the method comprising administering to the subject: (a) about 480 mg of an anti-LAG-3 antibody, and (b) about 480 mg of an anti-PD-1 or anti-PD-L1 antibody.

[0007] In some aspects, the anti-LAG-3 antibody is a full-length antibody. In some aspects, the anti-LAG-3 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody. In some aspects, the multispecific antibody is a dual-affinity re-targeting antibody (DART), a DVD-Ig, or bispecific antibody.

[0008] In some aspects, the anti-LAG-3 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

[0009] In some aspects, the anti-LAG-3 antibody is BMS-986016 (relatlimab), IMP731 (H5L7BW), MK4280 (28G-10, favezelimab), REGN3767 (fianlimab), GSK2831781, humanized BAP050, IMP-701 (LAG525, ieramilimab), aLAG3(0414), aLAG3(0416), Sym022, TSR-033, TSR-075, XmAb841 (XmAb22841), MGD013 (tebotelimab), BI754111, FS118, P 13B02-30, AVA-017, 25F7, AGEN1746, RO7247669, INCAGN02385, IBI-110, EMB-02, IBI-323, LBL-007, ABL501, or comprises an antigen binding portion thereof.

[0010] In some aspects, the anti-LAG-3 antibody comprises CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:3, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:4.

[0011] In some aspects, the anti-LAG-3 antibody comprises: (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:5; (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:6; (c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:7; (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:8; (e) a light chain variable

region CDR2 comprising the sequence set forth in SEQ ID NO:9; and (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:10.

[0012] In some aspects, the anti-LAG-3 antibody comprises heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:3 and 4, respectively.

[0013] In some aspects, the anti-LAG-3 antibody comprises heavy and light chains comprising the sequences set forth in SEQ ID NOs:1 and 2, respectively.

[0014] In some aspects, the anti-LAG-3 antibody comprises heavy and light chains comprising the sequences set forth in SEQ ID NOs:21 and 2, respectively.

[0015] In some aspects, the anti-PD-1 antibody is a full-length antibody.

[0016] In some aspects, the anti-PD-1 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody. In some aspects, the multispecific antibody is a DART, a DVD-Ig, or bispecific antibody.

[0017] In some aspects, the anti-PD-1 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

[0018] In some aspects, the anti-PD-1 antibody is nivolumab, pembrolizumab, PDR001 (spartalizumab), MEDI-0680, TSR-042, cemiplimab, JS001, PF-06801591, BGB-A317, BI 754091, INCSHR1210, GLS-010, AM-001, STI-1110, AGEN2034, MGA012, BCD-100, IBI308, SSI-361, or comprises an antigen binding portion thereof.

[0019] In some aspects, the anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:13, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:14.

[0020] In some aspects, the anti-PD-1 antibody comprises: (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:15; (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:16; (c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:17; (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:18; (e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:19; and (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:20.

[0021] In some aspects, the anti-PD-1 antibody comprises heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:13 and 14, respectively.

[0022] In some aspects, the anti-PD-1 antibody comprises heavy and light chains comprising the sequences as set forth in SEQ ID NOs:11 and 12, respectively.

[0023] In some aspects, the anti-PD-L1 antibody is a full-length antibody.

[0024] In some aspects, the anti-PD-L1 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody. In some aspects, the multispecific antibody is a DART, a DVD-Ig, or bispecific antibody.

[0025] In some aspects, the anti-PD-L1 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

[0026] In some aspects, the anti-PD-L1 antibody is BMS-936559, atezolizumab, durvalumab, avelumab, STI-1014, CX-072, KN035, LY3300054, BGB-A333, ICO 36, FAZ053, CK-301, or comprises an antigen binding portion thereof.

[0027] In some aspects, the anti-LAG-3 antibody is formulated for intravenous administration and/or the anti-PD-1 antibody or anti-PD-L1 antibody is formulated for intravenous administration.

[0028] In some aspects, the anti-LAG-3 antibody and/or the anti-PD-1 antibody or anti-PD-L1 antibody is administered once about every one week, once about every two weeks, once about every three weeks, once about every four weeks, once about every five weeks, once about every six weeks, once about every seven weeks, once about every eight weeks, once about every nine weeks, once about every ten weeks, once about every eleven weeks, or once about every twelve weeks.

[0029] In some aspects, the anti-PD-1 antibody or anti-PD-L1 antibody is administered before the anti-LAG-3 antibody.

[0030] In some aspects, the anti-LAG-3 antibody is administered before the anti-PD-1 antibody or anti-PD-L1 antibody.

[0031] In some aspects, the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody are administered concurrently.

[0032] In some aspects, the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody are formulated separately.

[0033] In some aspects, the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody are formulated together.

[0034] The present disclosure is directed to a method of treating a human subject afflicted with colorectal carcinoma (CRC), the method comprising administering to the subject: (a) about 480 mg of an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:3, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:4, and (b) about 480 mg of an anti-PD-1 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:13, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:14.

[0035] In some aspects, the anti-LAG-3 antibody is a full-length antibody. In some aspects, the anti-LAG-3 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody. In some aspects, the multispecific antibody is a dual-affinity re-targeting antibody (DART), a DVD-Ig, or bispecific antibody.

[0036] In some aspects, the anti-LAG-3 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

[0037] In some aspects, the anti-LAG-3 antibody is BMS-986016 (relatlimab) or comprises an antigen binding portion thereof.

[0038] In some aspects, the anti-LAG-3 antibody comprises: (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:5; (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:6; (c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:7; (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:8; (e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:9; and (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:10.

[0039] In some aspects, the anti-LAG-3 antibody comprises heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:3 and 4, respectively.

[0040] In some aspects, the anti-LAG-3 antibody comprises heavy and light chains comprising the sequences set forth in SEQ ID NOs:1 and 2, respectively.

[0041] In some aspects, the anti-LAG-3 antibody comprises heavy and light chains comprising the sequences set forth in SEQ ID NOs:21 and 2, respectively.

[0042] In some aspects, the anti-PD-1 antibody is a full-length antibody.

[0043] In some aspects, the anti-PD-1 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody. In some aspects, the multispecific antibody is a DART, a DVD-Ig, or bispecific antibody.

[0044] In some aspects, the anti-PD-1 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

[0045] In some aspects, the anti-PD-1 antibody is nivolumab or comprises an antigen binding portion thereof.

[0046] In some aspects, the anti-PD-1 antibody comprises: (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:15; (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:16; (c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:17; (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:18; (e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:19; and (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:20.

[0047] In some aspects, the anti-PD-1 antibody comprises heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:13 and 14, respectively.

[0048] In some aspects, the anti-PD-1 antibody comprises heavy and light chains comprising the sequences as set forth in SEQ ID NOs:11 and 12, respectively.

[0049] In some aspects, the anti-LAG-3 antibody and/or the anti-PD-1 antibody is formulated for intravenous administration.

[0050] In some aspects, the anti-LAG-3 antibody and/or the anti-PD-1 antibody is administered once about every one week, once about every two weeks, once about every three weeks, once about every four weeks, once about every five weeks, once about every six weeks, once about every seven weeks, once about every eight weeks, once about every nine weeks, once about every ten weeks, once about every eleven weeks, or once about every twelve weeks.

[0051] In some aspects, the anti-PD-1 antibody is administered before the anti-LAG-3 antibody.

[0052] In some aspects, the anti-LAG-3 antibody is administered before the anti-PD-1 antibody.

[0053] In some aspects, the anti-LAG-3 antibody and the anti-PD-1 antibody or are administered concurrently.

[0054] In some aspects, the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody are formulated separately.

[0055] In some aspects, the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody are formulated together

[0056] In some aspects, the method is a first line therapy.

[0057] In some aspects, the method is a second line therapy.

[0058] In some aspects, the method is a third line therapy.

[0059] In some aspects, the subject has progressed on or is intolerant of a prior therapy. In some aspects, the prior therapy comprises a fluoropyrimidine, oxaliplatin, irinotecan, anti-vascular endothelial growth factor (VEGF) therapy, anti-epidermal growth factor receptor (EGFR) therapy for CRC comprising a Kristen Rat Sarcoma Viral Oncogene Homologue (KRAS) mutation, regorafenib, TAS-102, or any combination thereof.

[0060] In some aspects, the subject is naïve to prior systemic therapy for advanced and/or metastatic CRC.

[0061] In some aspects, the subject is naïve to prior immuno-oncology therapy, the subject is naïve to prior immuno-oncology therapy for CRC, or the CRC is naïve to prior immuno-oncology therapy.

[0062] In some aspects, the CRC comprises adenocarcinoma histology.

[0063] In some aspects, the CRC is unresectable, advanced, and/or metastatic.

[0064] In some aspects, the CRC is microsatellite stable (MSS) CRC.

[0065] In some aspects, the MSS CRC comprises high T cell activation and LAG-3 upregulation.

[0066] In some aspects, the CRC is high microsatellite instable (MSI-H) CRC.

[0067] In some aspects, the CRC comprises a KRAS mutation.

[0068] In some aspects, the CRC comprises wild-type KRAS.

[0069] In some aspects, one or more immune cells in tumor tissue from the subject express LAG-3. In some aspects, at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% of the immune cells express LAG-3. In some aspects, at least about 1% of the immune cells express LAG-3. In some aspects, the immune cells are tumor-infiltrating lymphocytes. In some aspects, the tumor-infiltrating lymphocytes are $CD8^+$ cells.

[0070] In some aspects, at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% of nucleated cells in tumor tissue from the subject express LAG-3. In some aspects, at least about 1% of the nucleated cells express LAG-3.

[0071] In some aspects, one or more cells in tumor tissue from the subject express PD-L1. In some aspects, the tumor tissue comprises a PD-L1 tumor proportion score (TPS) and/or combined positive score (CPS) of at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% of the tumor cells, wherein the TPS is the percentage of tumor cells in the tumor tissue that express PD-L1, and the CPS is the number of tumor and immune cells in the tumor tissue that express PD-L1 as a percentage of the total number of viable tumor cells. In some aspects, the tumor tissue comprises a PD-L1 TPS and/or CPS of at least about 1%.

[0072] In some aspects, at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% of nucleated cells in tumor tissue from the subject express PD-L1. In some aspects, at least about 1% of the nucleated cells express PD-L1.

[0073] In some aspects, the CRC is a colon cancer.

[0074] In some aspects, the CRC is a rectal cancer.

[0075] In some aspects, any of the above methods further comprise administering to the subject an additional therapeutic agent. In some aspects, the additional therapeutic agent comprises an anti-cancer agent. In some aspects, the anti-cancer agent comprises a tyrosine kinase inhibitor, a checkpoint inhibitor, a checkpoint stimulator, a chemotherapeutic agent, an immunotherapeutic agent, a platinum agent, an alkylating agent, a taxane, a nucleoside analog, an antimetabolite, a topoisomerase inhibitor, an anthracycline, a vinca alkaloid, or any combination thereof. In some aspects, the checkpoint inhibitor comprises a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, a T cell immunoglobulin and ITIM domain (TIGIT) inhibitor, a T cell immunoglobulin and mucin-domain containing-3 (TIM-3) inhibitor, a TIM-1 inhibitor, a TIM-4 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a B and T cell lymphocyte attenuator (BTLA) inhibitor, a V-domain Ig suppressor of T cell activation (VISTA) inhibitor, an indoleamine 2,3-dioxygenase (IDO) inhibitor, a nicotinamide adenine dinucleotide phosphate oxidase isoform 2 (NOX2) inhibitor, a killer-cell immunoglobulin-like receptor (KIR) inhibitor, an adenosine A2a receptor (A2aR) inhibitor, a transforming growth factor beta (TGF-β) inhibitor, a phosphoinositide 3-kinase (PI3K) inhibitor, a CD47 inhibitor, a CD48 inhibitor, a CD73 inhibitor, a CD113 inhibitor, a sialic acid-binding immunoglobulin-like lectin-7 (SIGLEC-7) inhibitor, a SIGLEC-9 inhibitor, a SIGLEC-15 inhibitor, a glucocorticoid-induced TNFR-related protein (GITR) inhibitor, a galectin-1 inhibitor, a galectin-9 inhibitor, a carcinoembryonic antigen-related cell adhesion molecule-1 (CEACAM-1) inhibitor, a G protein-coupled receptor 56 (GPR56) inhibitor, a glycoprotein A repetitions predominant (GARP) inhibitor, a 2B4 inhibitor, a programmed death-1 homolog (PD1H) inhibitor, a leukocyte-associated immunoglobulin-like receptor 1 (LAIR1) inhibitor, or any combination thereof. In some aspects, the checkpoint inhibitor comprises a CTLA-4 inhibitor. In some aspects, the CTLA-4 inhibitor is an anti-CTLA-4 antibody. In some aspects, the anti-CTLA-4 antibody is a full-length antibody. In some aspects, the anti-CTLA-4 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody. In some aspects, the multispecific antibody is a DART, a DVD-Ig, or bispecific antibody. In some aspects, the anti-CTLA-4 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide. In some aspects, the anti-CTLA-4 antibody is ipilimumab, tremelimumab, MK-1308, AGEN-1884, or comprises an antigen binding portion thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0076] The present disclosure provides a method of treating a human subject afflicted with colorectal carcinoma (CRC), the method comprising administering to the subject an anti-LAG-3 antibody and an anti-PD-1 or anti-PD-L1 antibody. Some aspects of the present disclosure are directed to a method of treating a human subject afflicted with CRC, wherein the method is a first, second, or third line therapy, and/or wherein the subject has progressed on or is intolerant to a prior therapy. Some aspects of the present disclosure are directed to a method of treating a human subject afflicted with unresectable, advanced, and/or metastatic CRC. Some aspects of the present disclosure are directed to a method of treating a human subject afflicted with microsatellite stable CRC. Some aspects of the present disclosure are directed to a method of treating a human subject afflicted with high microsatellite instable CRC. Some aspects of the present disclosure are directed to a method of treating a human subject afflicted with CRC, the method comprising administering to the subject an additional therapeutic agent (*e.g.*, an anti-cancer agent).

I. Terms

[0077] In order that the present disclosure can be more readily understood, certain terms are first defined. As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application.

[0078] It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, "a nucleotide sequence," is understood to represent one or more nucleotide sequences. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

[0079] The term "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0080] It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0081] The terms "about" or "comprising essentially of" refer to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, *i.e.*, the limitations of the measurement system. For example, "about" or "comprising essentially of" can mean within 1 or more than 1 standard deviation per the practice in the art. Alternatively, "about" or "comprising essentially of" can mean a range of up to 10% or 20% (*i.e.,* ±10% or ±20%). For example, about 3 mg can include any number between 2.7 mg and 3.3 mg (for 10%) or between 2.4 mg and 3.6 mg (for 20%). Furthermore, particularly with respect to biological systems or processes, the terms can mean up to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the application and claims, unless otherwise stated, the meaning of "about" or "comprising essentially of" should be assumed to be within an acceptable error range for that particular value or composition.

[0082] As described herein, any concentration range, percentage range, ratio range or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one-tenth and one-hundredth of an integer), unless otherwise indicated.

[0083] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 5th ed., 2013, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, 2006, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[0084] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range.

[0085] The headings provided herein are not limitations of the various aspects of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the

terms defined immediately below are more fully defined by reference to the specification in its entirety.

[0086] An "antagonist" shall include, without limitation, any molecule capable of blocking, reducing, or otherwise limiting an interaction or activity of a target molecule (*e.g.*, LAG-3). In some aspects, the antagonist is an antibody. In other aspects, the antagonist comprises a small molecule. The terms "antagonist" and "inhibitor" are used interchangeably herein.

[0087] An "antibody" (Ab) shall include, without limitation, a glycoprotein immunoglobulin which binds specifically to an antigen and comprises at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds. Each H chain comprises a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region (abbreviated herein as C_H). The heavy chain constant region comprises three constant domains, C_{H1}, C_{H2} and C_{H3}. Each light chain comprises a light chain variable region (abbreviated herein as V_L) and a light chain constant region (abbreviated herein as C_L). The light chain constant region comprises one constant domain, C_L. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L comprises three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies can mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system. A heavy chain can have the C-terminal lysine or not. Unless specified otherwise herein, the amino acids in the variable regions are numbered using the Kabat numbering system and those in the constant regions are numbered using the EU system.

[0088] An immunoglobulin can derive from any of the commonly known isotypes, including but not limited to IgA, secretory IgA, IgG and IgM. IgG subclasses are also well known to those in the art and include but are not limited to human IgG1, IgG2, IgG3 and IgG4. "Isotype" refers to the antibody class or subclass (*e.g.*, IgM or IgG1) that is encoded by the heavy chain constant region genes. The term "antibody" includes, by way of example, both naturally occurring and non-naturally occurring antibodies; monoclonal and polyclonal antibodies; chimeric and humanized antibodies; human or nonhuman

antibodies; wholly synthetic antibodies; single chain antibodies; monospecific antibodies; bispecific antibodies; and multi-specific antibodies. A nonhuman antibody can be humanized by recombinant methods to reduce its immunogenicity in humans. Where not expressly stated, and unless the context indicates otherwise, the term "antibody" also includes an antigen-binding fragment or an antigen-binding portion of any of the aforementioned immunoglobulins, and includes a monovalent and a divalent fragment or portion, that retains the ability to bind specifically to the antigen bound by the whole immunoglobulin. Examples of an "antigen-binding portion" or "antigen-binding fragment" include: (1) a Fab fragment (fragment from papain cleavage) or a similar monovalent fragment consisting of the V_L, V_H, L_C and C_{H1} domains; (2) a F(ab')2 fragment (fragment from pepsin cleavage) or a similar bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (3) a Fd fragment consisting of the VH and CH1 domains; (4) a Fv fragment consisting of the V_L and V_H domains of a single arm; (5) a single domain antibody (dAb) fragment (Ward *et al.*, (1989) *Nature* 341:544-46), which consists of a V_H domain; (6) a bi-single domain antibody which consists of two V_H domains linked by a hinge (dual-affinity re-targeting antibodies (DARTs)); or (7) a dual variable domain immunoglobulin. Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (scFv); *see, e.g.*, Bird *et al.* (1988) *Science* 242:423-426; and Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883).

[0089] An "isolated antibody" refers to an antibody that is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that binds specifically to LAG-3 is substantially free of antibodies that do not bind specifically to LAG-3). An isolated antibody that binds specifically to an antigen can, however, have cross-reactivity to other antigens (*e.g.*, an antibody that binds specifically to LAG-3 having cross-reactivity to LAG-3 molecules from different species). Moreover, an isolated antibody can be substantially free of other cellular material and/or chemicals.

[0090] The term "monoclonal antibody" ("mAb") refers to a non-naturally occurring preparation of antibody molecules of single molecular composition, *i.e.*, antibody molecules whose primary sequences are essentially identical, and which exhibits a single

binding specificity and affinity for a particular epitope. A mAb is an example of an isolated antibody. MAbs can be produced by hybridoma, recombinant, transgenic or other techniques known to those skilled in the art.

[0091] A "human" antibody (HuMAb) refers to an antibody having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region is also derived from human germline immunoglobulin sequences. The human antibodies of the invention can include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). However, the term "human antibody," as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. The terms "human" antibodies and "fully human" antibodies and are used synonymously.

[0092] A "humanized antibody" refers to an antibody in which some, most or all of the amino acids outside the CDR domains of a non-human antibody are replaced with corresponding amino acids derived from human immunoglobulins. In one aspect of a humanized form of an antibody, some, most or all of the amino acids outside the CDR domains have been replaced with amino acids from human immunoglobulins, whereas some, most or all amino acids within one or more CDR regions are unchanged. Small additions, deletions, insertions, substitutions or modifications of amino acids are permissible as long as they do not abrogate the ability of the antibody to bind to a particular antigen. A "humanized" antibody retains an antigenic specificity similar to that of the original antibody.

[0093] A "chimeric antibody" refers to an antibody in which the variable regions are derived from one species and the constant regions are derived from another species, such as an antibody in which the variable regions are derived from a mouse antibody and the constant regions are derived from a human antibody.

[0094] An "anti-antigen" antibody refers to an antibody that binds specifically to the antigen. For example, an anti-LAG-3 antibody binds specifically to LAG-3.

[0095] "LAG-3" refers to Lymphocyte Activation Gene-3. The term "LAG-3" includes variants, isoforms, homologs, orthologs and paralogs. For example, antibodies specific for

a human LAG-3 protein can, in certain cases, cross-react with a LAG-3 protein from a species other than human. In other aspects, the antibodies specific for a human LAG-3 protein can be completely specific for the human LAG-3 protein and not exhibit species or other types of cross-reactivity, or can cross-react with LAG-3 from certain other species, but not all other species (*e.g.*, cross-react with monkey LAG-3 but not mouse LAG-3). The term "human LAG-3" refers to human sequence LAG-3, such as the complete amino acid sequence of human LAG-3 having GenBank Accession No. NP_002277. The term "mouse LAG-3" refers to mouse sequence LAG-3, such as the complete amino acid sequence of mouse LAG-3 having GenBank Accession No. NP_032505. LAG-3 is also known in the art as, for example, CD223. The human LAG-3 sequence can differ from human LAG-3 of GenBank Accession No. NP_002277 by having, *e.g.*, conserved mutations or mutations in non-conserved regions, and the LAG-3 has substantially the same biological function as the human LAG-3 of GenBank Accession No. NP_002277. For example, a biological function of human LAG-3 is having an epitope in the extracellular domain of LAG-3 that is specifically bound by an antibody of the instant disclosure or a biological function of human LAG-3 is binding to MHC Class II molecules.

[0096] A particular human LAG-3 sequence will generally be at least about 90% identical in amino acid sequence to human LAG-3 of GenBank Accession No. NP_002277 and contains amino acid residues that identify the amino acid sequence as being human when compared to LAG-3 amino acid sequences of other species (*e.g.*, murine). In certain cases, a human LAG-3 can be at least about 95%, or even at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical in amino acid sequence to LAG-3 of GenBank Accession No. NP_002277. In certain aspects, a human LAG-3 sequence will display no more than 10 amino acid differences from the LAG-3 sequence of GenBank Accession No. NP_002277. In certain aspects, the human LAG-3 can display no more than 5, or even no more than 4, 3, 2, or 1 amino acid difference from the LAG-3 sequence of GenBank Accession No. NP_002277.

[0097] "Programmed Death-1 (PD-1)" refers to an immunoinhibitory receptor belonging to the CD28 family. PD-1 is expressed predominantly on previously activated T cells *in vivo*, and binds to two ligands, PD-L1 and PD-L2. The term "PD-1" as used herein includes human PD-1 (hPD-1), variants, isoforms, and species homologs of hPD-1, and analogs having at least one common epitope with hPD-1. The complete hPD-1 sequence can be

found under GenBank Accession No. U64863. "PD-1" and "PD-1 receptor" are used interchangeably herein.

[0098] "Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4)" refers to an immunoinhibitory receptor belonging to the CD28 family. CTLA-4 is expressed exclusively on T cells *in vivo*, and binds to two ligands, CD80 and CD86 (also called B7-1 and B7-2, respectively). The term "CTLA-4" as used herein includes human CTLA-4 (hCTLA-4), variants, isoforms, and species homologs of hCTLA-4, and analogs having at least one common epitope with hCTLA-4. The complete hCTLA-4 sequence can be found under GenBank Accession No. AAB59385.

[0099] "Programmed Death Ligand-1 (PD-L1)" is one of two cell surface glycoprotein ligands for PD-1 (the other being PD-L2) that downregulate T cell activation and cytokine secretion upon binding to PD-1. The term "PD-L1" as used herein includes human PD-L1 (hPD-L1), variants, isoforms, and species homologs of hPD-L1, and analogs having at least one common epitope with hPD-L1. The complete hPD-L1 sequence can be found under GenBank Accession No. Q9NZQ7.

[0100] "Programmed Death Ligand-2 (PD-L2)" as used herein includes human PD-L2 (hPD-L2), variants, isoforms, and species homologs of hPD-L2, and analogs having at least one common epitope with hPD-L2. The complete hPD-L2 sequence can be found under GenBank Accession No. Q9BQ51.

[0101] A "patient" as used herein includes any patient who is afflicted with a CRC (*e.g.*, metastatic CRC). The terms "subject" and "patient" are used interchangeably herein.

[0102] "Administering" refers to the physical introduction of a therapeutic agent to a subject (*e.g.*, a composition or formulation comprising the therapeutic agent), using any of the various methods and delivery systems known to those skilled in the art. Exemplary routes of administration include intravenous, intramuscular, subcutaneous, intraperitoneal, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as *in vivo*

electroporation. In some aspects, the formulation is administered via a non-parenteral route, in some aspects, orally. Other non-parenteral routes include a topical, epidermal or mucosal route of administration, for example, intranasally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

[0103] As used herein, "Eastern Cooperative Oncology Group Performance Status (ECOG PS)" is a numbering scale used to define the population of patients to be studied in a trial, so that it can be uniformly reproduced among physicians who enroll patients. The ECOG PS utilizes standard criteria for measuring how the disease impacts a patient's daily living abilities. Example definitions for ECOG PS include: "0" for a patient who is fully active and able to carry on all pre-disease performance without restriction; "1" for a patient who is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; "2" for a patient who is ambulatory and capable of all self-care, up and about more than 50% of waking hours, but unable to carry out any work activities; "3" for a patient who is capable of only limited self-care and is confined to a bed or chair more than 50% of waking hours; and "4" for a patient who is completely disabled, cannot carry on any self-care, and is totally confined to bed or chair.

[0104] "Treatment" or "therapy" of a subject refers to any type of intervention or process performed on, or the administration of an active agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, slowing down progression, development, severity or recurrence of a symptom, complication or condition, or biochemical indicia associated with a disease. Response Evaluation Criteria In Solid Tumors (RECIST) is a measure for treatment efficacy and are established rules that define when tumors respond, stabilize, or progress during treatment. RECIST v1.1 is the current guideline to solid tumor measurement and definitions for objective assessment of change in tumor size for use in adult and pediatric cancer clinical trials.

[0105] As used herein, "effective treatment" refers to treatment producing a beneficial effect, *e.g.*, amelioration of at least one symptom of a disease or disorder. A beneficial effect can take the form of an improvement over baseline, *i.e.*, an improvement over a measurement or observation made prior to initiation of therapy according to the method. A beneficial effect can also take the form of arresting, slowing, retarding, or stabilizing of a deleterious progression of a marker of solid tumor. Effective treatment can refer to

alleviation of at least one symptom of a solid tumor. Such effective treatment can, *e.g.*, reduce patient pain, reduce the size and/or number of lesions, can reduce or prevent metastasis of a tumor, and/or can slow tumor growth.

[0106] The term "effective amount" refers to an amount of an agent that provides the desired biological, therapeutic, and/or prophylactic result. That result can be reduction, amelioration, palliation, lessening, delaying, and/or alleviation of one or more of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. In reference to solid tumors, an effective amount comprises an amount sufficient to cause a tumor to shrink and/or to decrease the growth rate of the tumor (such as to suppress tumor growth) or to delay other unwanted cell proliferation. In some aspects, an effective amount is an amount sufficient to prevent or delay tumor recurrence. An effective amount can be administered in one or more administrations. The effective amount of the drug or composition can: (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent and can stop cancer cell infiltration into peripheral organs; (iv) inhibit (*i.e.*, slow to some extent and can stop tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer. In one example, an "effective amount" is the amount of anti-LAG-3 antibody alone or the amount of anti-LAG-3 antibody and the amount an additional therapeutic agent (*e.g.*, anti-PD-1 antibody), in combination, clinically proven to affect a significant decrease in cancer or slowing of progression of cancer, such as an advanced solid tumor.

[0107] As used herein, the terms "fixed dose", "flat dose" and "flat-fixed dose" are used interchangeably and refer to a dose that is administered to a patient without regard for the weight or body surface area (BSA) of the patient. The fixed or flat dose is therefore not provided as a mg/kg dose, but rather as an absolute amount of the agent (*e.g.*, an amount in μg or mg).

[0108] The use of the term "fixed dose combination" with regard to a composition of the invention means that two or more different inhibitors as described herein (*e.g.*, an anti-LAG-3 antibody and an anti-PD-1 antibody) in a single composition are present in the composition in particular (fixed) ratios with each other. In some aspects, the fixed dose is based on the weight (*e.g.*, mg) of the inhibitors. In certain aspects, the fixed dose is based on the concentration (*e.g.*, mg/ml) of the inhibitors. In some aspects, the ratio is at least

about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:6, about 1:7, about 1:8, about 1:9, about 1:10, about 1:15, about 1:20, about 1:30, about 1:40, about 1:50, about 1:60, about 1:70, about 1:80, about 1:90, about 1:100, about 1:120, about 1:140, about 1:160, about 1:180, about 1:200, about 200:1, about 180:1, about 160:1, about 140:1, about 120:1, about 100:1, about 90:1, about 80:1, about 70:1, about 60:1, about 50:1, about 40:1, about 30:1, about 20:1, about 15:1, about 10:1, about 9:1, about 8:1, about 7:1, about 6:1, about 5:1, about 4:1, about 3:1, or about 2:1 mg first inhibitor to mg second inhibitor. For example, the 1:1 ratio of a first inhibitor and a second inhibitor can mean that a vial can contain about 480 mg of the first inhibitor and 480 mg of the second inhibitor.

[0109] The term "weight based dose" as referred to herein means that a dose that is administered to a patient is calculated based on the weight of the patient.

[0110] "Dosing interval," as used herein, means the amount of time that elapses between multiple doses of a formulation disclosed herein being administered to a subject. Dosing interval can thus be indicated as ranges.

[0111] The term "dosing frequency" as used herein refers to the frequency of administering doses of a formulation disclosed herein in a given time. Dosing frequency can be indicated as the number of doses per a given time, *e.g.*, once a week or once in two weeks, etc.

[0112] The terms "about once a week," "once about every week," "once about every two weeks," or any other similar dosing interval terms as used herein means approximate number, and "about once a week" or "once about every week" can include every seven days ± two days, *i.e.,* every five days to every nine days. The dosing frequency of "once a week" thus can be every five days, every six days, every seven days, every eight days, or every nine days. "Once about every three weeks" can include every 21 days ± 3 days, *i.e.*, every 25 days to every 31 days. Similar approximations apply, for example, to once about every two weeks, once about every four weeks, once about every five weeks, once about every six weeks, once about every seven weeks, once about every eight weeks, once about every nine weeks, once about every ten weeks, once about every eleven weeks, and once about every twelve weeks. In some aspects, a dosing interval of once about every six weeks or once about every twelve weeks means that the first dose can be administered any day in the first week, and then the next dose can be administered any day in the sixth or twelfth week, respectively. In other aspects, a dosing interval of once about every six weeks or once about every twelve weeks means that the first dose is administered on a particular day of the first

week (*e.g.*, Monday) and then the next dose is administered on the same day of the sixth or twelfth weeks (*i.e.*, Monday), respectively.

[0113] An "adverse event" (AE) as used herein is any unfavorable and generally unintended or undesirable sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a medical treatment. For example, an adverse event can be associated with activation of the immune system or expansion of immune system cells (*e.g.*, T cells) in response to a treatment. A medical treatment can have one or more associated AEs and each AE can have the same or different level of severity.

[0114] The term "tumor" as used herein refers to any mass of tissue that results from excessive cell growth or proliferation, either benign (non-cancerous) or malignant (cancerous), including pre-cancerous lesions.

[0115] The term "biological sample" as used herein refers to biological material isolated from a subject. The biological sample can contain any biological material suitable for analysis, for example, by sequencing nucleic acids in the tumor (or circulating tumor cells) and identifying a genomic alteration in the sequenced nucleic acids. The biological sample can be any suitable biological tissue or fluid such as, for example, tumor tissue, blood, blood plasma, and serum. The biological sample can be a test tissue sample (*e.g.*, a tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells). In one aspect, the sample is a tumor tissue biopsy, *e.g.*, a formalin-fixed, paraffin-embedded (FFPE) tumor tissue or a fresh-frozen tumor tissue or the like. In another aspect, the biological sample is a liquid biopsy that, in some aspects, comprises one or more of blood, serum, plasma, circulating tumor cells, exoRNA, ctDNA, and cfDNA.

[0116] By way of example, an "anti-cancer agent" promotes cancer regression in a subject. In preferred aspects, a therapeutically effective amount of the agent promotes cancer regression to the point of eliminating the cancer. "Promoting cancer regression" means that administering an effective amount of the anti-cancer agent, alone or in combination with another agent, results in a reduction in tumor growth or size, necrosis of the tumor, a decrease in severity of at least one disease symptom, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. In addition, the terms "effective" and "effectiveness" with regard to a treatment includes both pharmacological effectiveness and physiological safety. Pharmacological effectiveness refers to the ability of the agent to promote cancer regression

in the patient. Physiological safety refers to the level of toxicity, or other adverse physiological effects at the cellular, organ and/or organism level (adverse effects) resulting from administration of the agent.

[0117] By way of example for the treatment of tumors, a therapeutically effective amount of an anti-cancer agent can inhibit cell growth or tumor growth by at least about 20%, at least about 40%, at least about 60%, or at least about 80% relative to untreated subjects. In other aspects of the disclosure, tumor regression can be observed and continue for a period of at least about 20 days, more preferably at least about 40 days, or at least about 60 days. Notwithstanding these measurements of therapeutic effectiveness, evaluation of immunotherapeutic drugs must also make allowance for immune-related response patterns.

[0118] As used herein, an "immuno-oncology" therapy or an "I-O" or "IO" therapy refers to a therapy that comprises utilizing an immune response to target and treat a tumor in a subject. As such, as used herein, an I-O therapy is a type of anti-cancer therapy. In some aspects, an I-O therapy comprises administering an antibody to a subject. In some aspects, an I-O therapy comprises administering to a subject an immune cell, *e.g.*, a T cell, *e.g.*, a modified T cell, *e.g.*, a T cell modified to express a chimeric antigen receptor or a particular T cell receptor. In some aspects, the I-O therapy comprises administering a therapeutic vaccine to a subject. In some aspects, the I-O therapy comprises administering a cytokine or a chemokine to a subject. In some aspects, the I-O therapy comprises administering an interleukin to a subject. In some aspects, the I-O therapy comprises administering an interferon to a subject. In some aspects, the I-O therapy comprises administering a colony stimulating factor to a subject.

[0119] An "immune response" refers to the action of a cell of the immune system (for example, T lymphocytes, B lymphocytes, natural killer (NK) cells, macrophages, eosinophils, mast cells, dendritic cells and neutrophils) and soluble macromolecules produced by any of these cells or the liver (including antibodies, cytokines, and complement) that results in selective targeting, binding to, damage to, destruction of, and/or elimination from a vertebrate's body of invading pathogens, cells or tissues infected with pathogens, cancerous or other abnormal cells, or, in cases of autoimmunity or pathological inflammation, normal human cells or tissues.

[0120] A "tumor-infiltrating inflammatory cell" or "tumor-associated inflammatory cell" is any type of cell that typically participates in an inflammatory response in a subject and

which infiltrates tumor tissue. Such cells include tumor-infiltrating lymphocytes (TILs), macrophages, monocytes, eosinophils, histiocytes and dendritic cells.

[0121] The term "LAG-3 positive" or "LAG-3 expression positive," relating to LAG-3 expression, refers to tumor tissue (*e.g.*, a test tissue sample) that is scored as expressing LAG-3 based on the proportion (*i.e.*, percentage) of immune cells (*e.g.*, tumor-infiltrating lymphocytes such as CD8+ T cells) expressing LAG-3 (*e.g.*, greater than or equal to 1% expression) or based on the proportion (*i.e.*, percentage) of nucleated cells expressing LAG-3 (*i.e.*, the immune cells that express LAG-3 as a proportion of total nucleated cells, *e.g.*, greater than or equal to 1% expression).

[0122] "LAG-3 negative" or "LAG-3 expression negative," refers to tumor tissue (*e.g.*, a test tissue sample) that is not scored as expressing LAG-3 (*e.g.*, less than 1% LAG-3 expression).

[0123] The term "PD-L1 positive" or "PD-L1 expression positive," relating to cell surface PD-L1 expression, refers to tumor tissue (*e.g.*, a test tissue sample) that is scored as expressing PD-L1 based on the tumor proportion score (TPS), which is the proportion (*i.e.*, percentage) of tumor cells expressing PD-L1 (*e.g.*, greater than or equal to 1% expression), or based on the combined positive score (CPS), which is the number of tumor and immune cells (*e.g.*, tumor cells, lymphocytes, and macrophages) in the tumor tissue that express PD-L1 as a percentage of the total number of viable tumor cells (*i.e.*, the number of tumor and immune cells expressing PD-L1 divided by the total number of viable tumor cells and multiplied by 100 (*i.e.*, *e.g.*, greater than or equal to 1%)), or based on the proportion (*i.e.*, percentage) of nucleated cells expressing PD-L1 (*i.e.*, the tumor cells that express PD-L1 as a proportion of total nucleated cells, *e.g.*, greater than or equal to 1% expression).

[0124] The term "PD-L1 negative" or "PD-L1 expression negative" refers to tumor tissue (*e.g.*, a test tissue sample) that is not scored as expressing PD-L1 (*e.g.*, less than 1% expression).

[0125] Various aspects of the invention are described in further detail in the following subsections.

II. Methods of the Disclosure

[0126] Provided herein are methods of treating a human subject afflicted with colorectal carcinoma (CRC), the methods comprising administering to the subject an anti-LAG-3 antibody and an anti-PD-1 or anti-PD-L1 antibody.

[0127] In some aspects, the CRC is a colon cancer, a rectal cancer, or a combination thereof.

[0128] Colon cancer presents in five stages: Stage 0 (Carcinoma in Situ), Stage I, Stage II, Stage III and Stage IV. Standard of care treatments for colon cancer include: 1) surgery, including a local excision, resection of the colon with anastomosis, or resection of the colon with colostomy; 2) radiofrequency ablation; 3) cryosurgery; 4) chemotherapy; 5) radiation therapy; and 6) targeted therapies, including monoclonal antibodies and angiogenesis inhibitors. In some aspects, a method of the disclosure further comprises administering a standard of care therapy for the treatment of colon cancer.

[0129] Rectal cancer presents in five stages: Stage 0 (Carcinoma in Situ), Stage I, Stage II, Stage III and Stage IV. Standard of care treatments for rectal cancer include: 1) Surgery, including polypectomy, local excision, resection, radiofrequency ablation, cryosurgery, and pelvic exenteration; 2) radiation therapy; 3) chemotherapy; and 4) targeted therapy, including monoclonal antibody therapy. In some aspects, a method of the disclosure further comprises administering a standard of care therapy for the treatment of rectal cancer.

[0130] In some aspects, the method is a first line (1L) therapy.

[0131] In some aspects, the method is a second line (2L) therapy.

[0132] In some aspects, the method is a third line (3L) therapy.

[0133] In some aspects, the subject has progressed on or is intolerant to a prior therapy (*e.g.*, a standard of care therapy, including a standard of care 1L or 2L therapy).

[0134] The predominant first-line treatment options for patients with metastatic CRC (mCRC), for example, are 5-fluorouracil (5-FU) containing regimens in combination with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) with a biologic agent such as bevacizumab. Combination with the epidermal growth factor receptor (EGFR) inhibitors, cetuximab and panitumumab, are also options if Kirsten Rat Sarcoma Viral Oncogene Homologue (KRAS) status is non-mutated.

[0135] FOLFIRI has been used in second-line therapy for those patients who have had first-line therapy with FOLFOX or another 5-FU-containing therapy. Bevacizumab, ramucirumab, and ziv-afilbercept have also been used for second-line treatment in combination with chemotherapy.

[0136] Regorafenib (also known as STIVARGA®), an oral multi-kinase inhibitor, and TAS-102 (also known as LONSURF®), an oral combination therapy of trifluridine and

tipiracil hydrochloride, each have been used as a later-line therapy in patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-vascular endothelial growth factor (VEGF) therapy, and, if KRAS WT, anti-epidermal growth factor receptor (EGFR) therapy.

[0137] In some aspects, the prior therapy comprises a fluoropyrimidine, oxaliplatin, irinotecan, anti-vascular endothelial growth factor (VEGF) therapy, anti-epidermal growth factor receptor (EGFR) therapy (*e.g.*, cetuximab or panitumumab) for CRC comprising a Kristen Rat Sarcoma Viral Oncogene Homologue (KRAS) mutation, regorafenib, TAS-102, or any combination thereof.

[0138] In some aspects, the subject has received one, two, three, four, or more prior therapies.

[0139] In some aspects, the subject is naïve to prior systemic therapy for advanced and/or metastatic CRC.

[0140] In some aspects, the subject is naïve to prior immuno-oncology (I-O) therapy. In some aspects, the subject has never received I-O therapy, has received I-O therapy for a cancer other than CRC, or has received I-O therapy for a previous CRC but not a current CRC. In some aspects, the subject is naïve to prior I-O therapy, the subject is naïve to prior I-O therapy for CRC, or the CRC is naïve to prior I-O therapy. In some aspects, the prior I-O therapy is an antibody. In some aspects, the antibody binds to a checkpoint inhibitor. In some aspects, the prior I-O therapy is an anti-PD-1 antibody and/or the combination of an anti-PD-1 antibody and an anti-CTLA-4 antibody.

[0141] In some aspects, a method of the disclosure increases duration of progression-free survival (PFS), objective response rate (ORR), overall survival (OS), or any combination thereof as compared to a standard of care therapy and/or a prior therapy such as disclosed herein.

[0142] In some aspects, a method of the disclosure reduces the size of a tumor, inhibits growth of a tumor, eliminates a tumor from the subject, prevents relapse of CRC, induces remission of CRC, provides a complete response or partial response, or any combination thereof.

[0143] In some aspects, the CRC comprises adenocarcinoma histology.

[0144] In some aspects, the CRC is unresectable, advanced, and/or metastatic.

[0145] Approximately 4% of CRCs are associated with high microsatellite instability (MSI-H), which is a condition of genetic hypermutability that results from deficient DNA mismatch repair (dMMR). The presence of MSI-H represents phenotypic evidence of dMMR. In most cases, the genetic basis for MSI-H CRC is an inherited germline alteration in any one or more of the five human MMR genes: MLH1, MSH2, MSH6, PMS1, or PMS2.

[0146] In contrast to MSI-H, microsatellite stability (MSS) is the molecular fingerprint of a proficient mismatch repair (pMMR) system. The term MSS is widely accepted as a surrogate terminology for pMMR tumors. Approximately 85% CRCs display MSS without novel microsatellite alleles.

[0147] In colorectal cancer, MSI-H is associated with increases in immune infiltration and expression of immune checkpoint regulators, while MSS is typically associated with an immunosuppressive tumor microenvironment that blunts activation of anti-tumor immune responses. But, a subset of MSS CRC patients displays a MSI-like tumor immune contexture, characterized by high T cell activation and LAG-3 upregulation.

[0148] Patients with MSI-H mCRC are less likely to benefit from conventional chemotherapy than patients with MSS mCRC. But, studies have confirmed that MSS identification can be prognostic in that MSS CRC has a worse prognosis than MSI-H CRC.

[0149] There are several well-established methods to differentiate MSS from MSI-H. One is immunohistochemistry (IHC) for MMR. IHC MMR testing consists of staining of tumor tissue for loss of expression of four mismatch repair proteins known to be mutated in Lynch syndrome: MLH1, MSH2, MSH6, and PMS2. If at least one of these is not normally expressed, then the testing indicates the dMMR (MSI-H) phenotype. Polymerase chain reaction (PCR) amplification of a set of mono- and/or di-nucleotide repeats on tumor and normal DNA, followed by comparison of the peak patterns by capillary electrophoresis, can also assess for MSI with three categories: MSI-H, MSI-Low, and MSS. The clinicopathologic and most molecular characteristics in MSI-Low tumors do not seem to differ from MSS tumors. Therefore, unless otherwise noted, MSS CRC in a method of the disclosure includes MSI-Low CRC.

[0150] In some aspects, the CRC is MSS CRC.

[0151] In some aspects the MSS CRC comprises high T cell activation and LAG-3 upregulation.

[0152] In some aspects, the MSS CRC does not include MSI-Low CRC (*i.e.*, the MSS CRC excludes MSI-Low CRC).

[0153] In some aspects, the CRC comprises normal expression of MMR proteins (*e.g.*, as compared to a reference expressing the corresponding wildtype MMR proteins). In some aspects, the MMR proteins are MLH1, MSH2, MSH6, and PMS2. In some aspects, the MMR proteins are MLH1, MSH2, MSH6, PMS1, and PMS2.

[0154] In some aspects, the CRC is MSI-H CRC.

[0155] In some aspects, the CRC comprises reduced expression of a MMR protein (*e.g.*, as compared to a reference expressing the corresponding wildtype MMR protein). In some aspects, the MMR protein is MLH1, MSH2, MSH6, PMS2, or a combination thereof. In some aspects, the MMR protein is MLH1, MSH2, MSH6, PMS1, PMS2, or a combination thereof.

[0156] In some aspects, the CRC comprises a KRAS mutation, a NRAS mutation, a B-rapidly accelerated fibrosarcoma proto-oncogene (BRAF) mutation, or a combination thereof.

[0157] In some aspects, the CRC comprises wild-type KRAS, wild-type NRAS, wild-type BRAF, or a combination thereof.

[0158] In some aspects, the methods of the disclosure comprise administering to the subject an anti-LAG-3 antibody and an anti-PD-1 or anti-PD-L1 antibody based on the subject's performance status. Performance status can be indicated by any one or more systems in the art. In some aspects, the system is Eastern Cooperative Oncology Group Performance Status (ECOG PS). In some aspects, the subject has an ECOG PS of 0 or 1. In some aspects, the subject has an ECOG PS of 0, 1, or 2. In some aspects, the subject has an ECOG PS of 0, 1, 2, or 3. In some aspects, the subject has an ECOG PS of 0, 1, 2, 3, or 4.

[0159] In some aspects, one or more immune cells in tumor tissue from the subject express LAG-3 (*i.e.*, tumor tissue from the subject is LAG-3 positive) and/or one or more cells in tumor tissue from the subject express PD-L1 (*i.e.*, tumor tissue from the subject is PD-L1 positive). In some aspects, one or more immune cells in tumor tissue from the subject express LAG-3. In some aspects, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 7%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least

about 80%, at least about 90%, or about 100% of the immune cells express LAG-3. In some aspects, at least about 1% of the immune cells express LAG-3. In some aspects, greater than about 1% of the immune cells express LAG-3. In some aspects, at least about 5% of the immune cells express LAG-3. In some aspects, the immune cells are tumor-infiltrating lymphocytes. In some aspects, the tumor-infiltrating lymphocytes are $CD8^+$ cells. In some aspects, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 7%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% of nucleated cells in tumor tissue from the subject express LAG-3 (*i.e.*, the immune cells that express LAG-3 as a proportion of total nucleated cells). In some aspects, at least about 1% of the nucleated cells express LAG-3. In some aspects, greater than about 1% of the nucleated cells express LAG-3. In some aspects, at least about 5% of the nucleated cells express LAG-3. In some aspects, one or more cells in tumor tissue from the subject express PD-L1. In some aspects, the tumor tissue from the subject has a PD-L1 tumor proportion score (TPS) as defined herein and/or a combined positive score (CPS) as defined herein of at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 7%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100%. In some aspects, the tumor tissue from the subject has a PD-L1 TPS and/or CPS of at least about 1%. In some aspects, the tumor tissue from the subject has a PD-L1 TPS and/or CPS of greater than about 1%. In some aspects, the tumor tissue from the subject has a PD-L1 TPS and/or CPS of at least about 5%. In some aspects, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 7%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% of nucleated cells in tumor tissue from the subject express PD-L1 (*i.e.*, the tumor cells that express PD-L1 as a proportion of total nucleated cells). In some aspects, at least about 1% of the nucleated cells in tumor tissue from the subject express PD-L1. In some aspects, at least about 1% of the nucleated cells in tumor

tissue from the subject express PD-L1. In some aspects, greater than about 1% of the nucleated cells in tumor tissue from the subject express PD-L1. In some aspects, at least about 5% of the nucleated cells in tumor tissue from the subject express PD-L1. In some aspects, any of the values of "at least about X%" is "≥X%").

[0160] In some aspects, one or more immune cells in tumor tissue from the patient does not express LAG-3 (*i.e.*, tumor tissue from the patient is LAG-3 negative). In some aspects, the tumor tissue is LAG-3 negative when less than about 1% of the immune cells express LAG-3. In some aspects, the tumor tissue is LAG-3 negative when less than about 1% of nucleated cells express LAG-3.

[0161] In some aspects, one or more cells in tumor tissue from the patient does not express PD-L1 (*i.e.*, tumor tissue from the patient is PD-L1 negative). In some aspects, the tumor tissue is PD-L1 negative when it has a TPS and/or CPS of less than about 1%. In some aspects, the tumor tissue is PD-L1 negative when less than about 1% of nucleated cells express PD-L1.

[0162] In some aspects, LAG-3 and/or PD-L1 expression in the subject's tumor tissue is determined from a test tissue sample. In some aspects, a test tissue sample includes, but is not limited to, any clinically relevant tissue sample, such as a tumor biopsy, a core biopsy, an incisional biopsy, an excisional biopsy, a surgical specimen, a fine needle aspirate, or a sample of bodily fluid, such as blood, plasma, serum, lymph, ascites fluid, cystic fluid, or urine. In some aspects, the test tissue sample is from a primary tumor. In some aspects, the test tissue sample is from a metastasis. In some aspects, test tissue samples are from multiple time points, for example, before treatment, during treatment, and/or after treatment. In some aspects, test tissue samples are from different locations in the subject, for example, from a primary tumor and from a metastasis.

[0163] In some aspects, the test tissue sample is a paraffin-embedded fixed tissue sample. In some aspects, the test tissue sample is a formalin-fixed paraffin embedded (FFPE) tissue sample. In some aspects, the test tissue sample is a fresh tissue (*e.g.*, tumor) sample. In some aspects, the test tissue sample is a frozen tissue sample. In some aspects, the test tissue sample is a fresh frozen (FF) tissue (*e.g.*, tumor) sample. In some aspects, the test tissue sample is a cell isolated from a fluid. In some aspects, the test tissue sample comprises circulating tumor cells (CTCs). In some aspects, the test tissue sample comprises tumor-infiltrating lymphocytes (TILs). In some aspects, the test tissue sample comprises tumor

cells and tumor-infiltrating lymphocytes (TILs). In some aspects, the test tissue sample comprises circulating lymphocytes. In some aspects, the test tissue sample is an archival tissue sample. In some aspects, the test tissue sample is an archival tissue sample with known diagnosis, treatment, and/or outcome history. In some aspects, the sample is a block of tissue. In some aspects, the test tissue sample is dispersed cells. In some aspects, the sample size is from about 1 cell to about 1 x 10^6 cells or more. In some aspects, the sample size is about 1 cell to about 1 x 10^5 cells. In some aspects, the sample size is about 1 cell to about 10,000 cells. In some aspects, the sample size is about 1 cell to about 1,000 cells. In some aspects, the sample size is about 1 cells to about 100 cells. In some aspects, the sample size is about 1 cell to about 10 cells. In some aspects, the sample size is a single cell.

[0164] In some aspects, LAG-3 and/or PD-L1 expression is assessed by performing an assay to detect the presence of LAG-3 and/or PD-L1 RNA, respectively. In some aspects, the presence of LAG-3 and/or PD-L1 RNA is detected by RT-PCR, *in situ* hybridization or RNase protection.

[0165] In some aspects, LAG-3 and/or PD-L1 expression is assessed by performing an assay to detect the presence of LAG-3 and/or PD-L1 polypeptide, respectively. In some aspects, the presence of LAG-3 and/or PD-L1 polypeptide is detected by immunohistochemistry (IHC), enzyme-linked immunosorbent assay (ELISA), *in vivo* imaging, or flow cytometry.

[0166] In some aspects, the subject has progressed on or is intolerant to a prior therapy, and the CRC is MSS mCRC comprising adenocarcinoma histology and wild-type KRAS, and tumor tissue from the subject comprises a PD-L1 TPS and/or CPS of at least about 1%.

[0167] In some aspects, the subject has progressed on or is intolerant to a prior therapy, and the CRC is MSS mCRC comprising adenocarcinoma histology and a KRAS mutation, and tumor tissue from the subject comprises a PD-L1 TPS and/or CPS of at least about 1%.

[0168] In some aspects, the subject has progressed on or is intolerant to a prior therapy, and the CRC is MSS mCRC comprising adenocarcinoma histology and wild-type KRAS, and tumor tissue from the subject comprises a PD-L1 TPS and/or CPS of less than about 1%.

[0169] In some aspects, the subject has progressed on or is intolerant to a prior therapy, and the CRC is MSS mCRC comprising adenocarcinoma histology and a KRAS mutation,

and tumor tissue from the subject comprises a PD-L1 TPS and/or CPS of less than about 1%.

II.A. Anti-LAG-3 Antibodies

[0170] Antibodies that bind to LAG-3 have been disclosed, for example, in Int'l Publ. No. WO/2015/042246 and U.S. Publ. Nos. 2014/0093511 and 2011/0150892, each of which is incorporated by reference herein in its entirety.

[0171] An exemplary LAG-3 antibody useful in the present disclosure is 25F7 (described in U.S. Publ. No. 2011/0150892). An additional exemplary LAG-3 antibody useful in the present disclosure is BMS-986016 (relatlimab). In some aspects, an anti-LAG-3 antibody useful in the present disclosure cross-competes with 25F7 or BMS-986016. In some aspects, an anti-LAG-3 antibody useful in the present disclosure binds to the same epitope as 25F7 or BMS-986016. In some aspects, an anti-LAG-3 antibody comprises six CDRs of 25F7 or BMS-986016.

[0172] Other art-recognized anti-LAG-3 antibodies that can be used in the methods of the disclosure include IMP731 (H5L7BW) described in US 2011/007023, MK-4280 (28G-10, favezelimab) described in WO2016028672 and U.S. Publication No. 2020/0055938, REGN3767 (fianlimab) described in Burova E, *et al*., *J. Immunother. Cancer* (2016); 4(Supp. 1):P195 and U.S. Patent No. 10,358,495, humanized BAP050 described in WO2017/019894, GSK2831781, IMP-701 (LAG-525; ieramilimab) described in U.S. Patent No. 10,711,060 and U.S. Publ. No. 2020/0172617, aLAG3(0414), aLAG3(0416), Sym022, TSR-033, TSR-075, XmAb841 (previously XmAb22841), MGD013 (tebotelimab), BI754111, FS118, P 13B02-30, AVA-017, AGEN1746, RO7247669, INCAGN02385, IBI-110, EMB-02, IBI-323, LBL-007, and ABL501. These and other anti-LAG-3 antibodies useful in the claimed invention can be found in, for example: US 10,188,730, WO 2016/028672, WO 2017/106129, WO2017/062888, WO2009/044273, WO2018/069500, WO2016/126858, WO2014/179664, WO2016/200782, WO2015/200119, WO2017/019846, WO2017/198741, WO2017/220555, WO2017/220569, WO2018/071500, WO2017/015560, WO2017/025498, WO2017/087589, WO2017/087901, WO2018/083087, WO2017/149143, WO2017/219995, US2017/0260271, WO2017/086367, WO2017/086419, WO2018/034227, WO2018/185046, WO2018/185043, WO2018/217940, WO19/011306, WO2018/208868, WO2014/140180, WO2018/201096, WO2018/204374, and

WO2019/018730. The contents of each of these references are incorporated by reference in their entirety.

[0173] Anti-LAG-3 antibodies that can be used in the methods of the disclosure also include isolated antibodies that bind specifically to human LAG-3 and cross-compete for binding to human LAG-3 with any anti-LAG-3 antibody disclosed herein, *e.g.,* relatlimab. In some aspects, the anti-LAG-3 antibody binds the same epitope as any of the anti-LAG-3 antibodies described herein, *e.g.,* relatlimab.

[0174] In some aspects, the antibodies that cross-compete for binding to human LAG-3 with, or bind to the same epitope region as, any anti-LAG-3 antibody disclosed herein, *e.g.*, relatlimab, are monoclonal antibodies. For administration to human subjects, these cross-competing antibodies are chimeric antibodies, engineered antibodies, or humanized or human antibodies. Such chimeric, engineered, humanized or human monoclonal antibodies can be prepared and isolated by methods well known in the art.

[0175] The ability of antibodies to cross-compete for binding to an antigen indicates that the antibodies bind to the same epitope region of the antigen and sterically hinder the binding of other cross-competing antibodies to that particular epitope region. These cross-competing antibodies are expected to have functional properties very similar those of the reference antibody, *e.g.*, relatlimab, by virtue of their binding to the same epitope region. Cross-competing antibodies can be readily identified based on their ability to cross-compete in standard binding assays such as Biacore analysis, ELISA assays or flow cytometry (*see*, *e.g.*, WO 2013/173223).

[0176] Anti-LAG-3 antibodies that can be used in the methods of the disclosure also include antigen-binding portions of any of the above full-length antibodies. It has been amply demonstrated that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody.

[0177] In some aspects, the anti-LAG-3 antibody is a full-length antibody.

[0178] In some aspects, the anti-LAG-3 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody. In some aspects, the multispecific antibody is a dual-affinity re-targeting antibody (DART), a DVD-Ig, or bispecific antibody.

[0179] In some aspects, the anti-LAG-3 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

[0180] In some aspects, the anti-LAG-3 antibody is BMS-986016 (relatlimab), IMP731 (H5L7BW), MK4280 (28G-10, favezelimab), REGN3767 (fianlimab), GSK2831781, humanized BAP050, IMP-701 (LAG525, ieramilimab), aLAG3(0414), aLAG3(0416), Sym022, TSR-033, TSR-075, XmAb841 (XmAb22841), MGD013 (tebotelimab), BI754111, FS118, P 13B02-30, AVA-017, 25F7, AGEN1746, RO7247669, INCAGN02385, IBI-110, EMB-02, IBI-323, LBL-007, ABL501, or comprises an antigen binding portion thereof.

[0181] In some aspects, the anti-LAG-3 antibody is relatlimab. In some aspects, relatlimab is administered intravenously at about 80 mg, about 120 mg, about 240 mg, about 360 mg, about 480 mg, or about 960 mg once about every 2, 3, or 4 weeks.

[0182] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:3, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:4.

[0183] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising: (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:5; (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:6; (c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:7; (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:8; (e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:9; and (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:10.

[0184] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:3 and 4, respectively.

[0185] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:1 and 2, respectively.

[0186] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:21 and 2, respectively.

[0187] In some aspects, the anti-LAG-3 antibody is MGD013 (tebotelimab), which is a bispecific PD-1 × LAG-3 DART. In some aspects, tebotelimab is administered intravenously at about 300 mg or about 600 mg once about every 2, 3, or 4 weeks. In some aspects, tebotelimab is administered intravenously at about 300 mg once about every 2 weeks. In some aspects, tebotelimab is administered intravenously at about 600 mg once about every 3 weeks.

[0188] In some aspects, the anti-LAG-3 antibody is REGN3767 (fianlimab). In some aspects, fianlimab is administered intravenously at about 1 mg/kg, about 3 mg/kg, about 10 mg/kg, or about 20 mg/kg once about every 3 weeks. In some aspects, fianlimab is administered intravenously at about 1600 mg once about every 3 weeks.

[0189] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:25, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:26.

[0190] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising: (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:27; (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:28; (c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:29; (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:30; (e) a light chain variable region CDR2 comprising the sequence DAS; and (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:32.

[0191] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:25 and 26, respectively.

[0192] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:23 and 24, respectively.

[0193] In some aspects, the anti-LAG-3 antibody is LAG525 (ieramilimab). In some aspects, ieramilimab is administered intravenously at about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, or about 1300 mg once about every 2, 3, or 4 weeks.

[0194] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:47, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:49.

[0195] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:48, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:50.

[0196] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising: (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:51; (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:52; (c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:53; (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:54; (e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:55; and (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:56.

[0197] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:47 and 49, respectively.

[0198] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:48 and 50, respectively.

[0199] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:43 and 45, respectively.

[0200] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:44 and 46, respectively.

[0201] In some aspects, the anti-LAG-3 antibody is MK4280 (favezelimab). In some aspects, favezelimab is administered intravenously at about 7 mg, about 21 mg, about 70 mg, about 210 mg, about 700 mg, or about 800 mg once about every 3 weeks or once about every 6 weeks. In some aspects, favezelimab is administered intravenously at about 200

mg once about every 3 weeks. In some aspects, favezelimab is administered intravenously at about 800 mg once about every 6 weeks. In some aspects, favezelimab is administered intravenously at about 800 mg on Day 1, then once about every 3 weeks. In some aspects, favezelimab is administered for up to 35 cycles. In some aspects, favezelimab is administered intravenously at about 800 mg for about 30 minutes on Day 1 of a three-week cycle for up to 35 cycles.

[0202] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:69, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:70.

[0203] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising: (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:71; (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:72; (c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:73; (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:74; (e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:75; and (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:76.

[0204] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:69 and 70, respectively.

[0205] In some aspects, the methods of the disclosure comprise an anti-LAG-3 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:67 and 68, respectively.

[0206] In some aspects, an anti-LAG-3 antibody is used to determine LAG-3 expression. In some aspects, an anti-LAG-3 antibody is selected for its ability to bind to LAG-3 in formalin-fixed, paraffin-embedded (FFPE) tissue specimens. In some aspects, an anti-LAG-3 antibody is capable of binding to LAG-3 in frozen tissues. In some aspects, an anti-LAG-3 antibody is capable of distinguishing membrane bound, cytoplasmic, and/or soluble forms of LAG-3.

[0207] In some aspects, an anti-LAG-3 antibody useful for assaying, detecting, and/or quantifying LAG-3 expression in accordance with the methods disclosed herein is the 17B4

mouse IgG1 anti-human LAG-3 monoclonal antibody. *See*, *e.g.*, Matsuzaki, J *et al*., *PNAS* (2010); 107:7875.

[0208] In some aspects, an anti-LAG-3 antibody as disclosed herein is formulated for intravenous administration.

[0209] In some aspects, an anti-LAG-3 antibody as disclosed herein is administered at a flat dose.

[0210] In some aspects, an anti-LAG-3 antibody as disclosed herein is administered at from at least about 0.25 mg to about 2000 mg, about 0.25 mg to about 1600 mg, about 0.25 mg to about 1200 mg, about 0.25 mg to about 800 mg, about 0.25 mg to about 400 mg, about 0.25 mg to about 100 mg, about 0.25 mg to about 50 mg, about 0.25 mg to about 40 mg, about 0.25 mg to about 30 mg, about 0.25 mg to about 20 mg, about 20 mg to about 2000 mg, about 20 mg to about 1600 mg, about 20 mg to about 1200 mg, about 20 mg to about 800 mg, about 20 mg to about 400 mg, about 20 mg to about 100 mg, about 100 mg to about 2000 mg, about 100 mg to about 1800 mg, about 100 mg to about 1600 mg, about 100 mg to about 1400 mg, about 100 mg to about 1200 mg, about 100 mg to about 1000 mg, about 100 mg to about 800 mg, about 100 mg to about 600 mg, about 100 mg to about 400 mg, about 400 mg to about 2000 mg, about 400 mg to about 1800 mg, about 400 mg to about 1600 mg, about 400 mg to about 1400 mg, about 400 mg to about 1200 mg, or about 400 mg to about 1000 mg.

[0211] In some aspects, an anti-LAG-3 antibody as disclosed herein is administered at about 0.25 mg, about 0.5 mg, about 0.75 mg, about 1 mg, about 1.25 mg, about 1.5 mg, about 1.75 mg, about 2 mg, 2.25 mg, about 2.5 mg, about 2.75 mg, about 3 mg, about 3.25 mg, about 3.5 mg, about 3.75 mg, about 4 mg, about 4.25 mg, about 4.5 mg, about 4.75 mg, about 5 mg, about 5.25 mg, about 5.5 mg, about 5.75 mg, about 6 mg, about 6.25 mg, about 6.5 mg, about 6.75 mg, about 7 mg, about 7.25 mg, about 7.5 mg, about 7.75 mg, about 8 mg, about 8.25 mg, about 8.5 mg, about 8.75 mg, about 9 mg, about 9.25 mg, about 9.5 mg, about 9.75 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg,

about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, about 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 980 mg, about 990 mg, about 1000 mg, about 1040 mg, about 1080 mg, about 1100 mg, about 1140 mg, about 1180 mg, about 1200 mg, about 1240 mg, about 1280 mg, about 1300 mg, about 1340 mg, about 1380 mg, about 1400 mg, about 1440 mg, about 1480 mg, about 1500 mg, about 1540 mg, about 1580 mg, about 1600 mg, about 1640 mg, about 1680 mg, about 1700 mg, about 1740 mg, about 1780 mg, about 1800 mg, about 1840 mg, about 1880 mg, about 1900 mg, about 1940 mg, about 1980 mg, or about 2000 mg.

[0212] In some aspects, an anti-LAG-3 antibody as disclosed herein is administered at a weight-based dose.

[0213] In some aspects, an anti-LAG-3 antibody as disclosed herein is administered at from at least about 0.003 mg/kg to about 25 mg/kg, about 0.003 mg/kg to about 20 mg/kg, about 0.003 mg/kg to about 15 mg/kg, about 0.003 mg/kg to about 10 mg/kg, about 0.003 mg/kg to about 5 mg/kg, about 0.003 mg/kg to about 1 mg/kg, about 0.003 mg/kg to about 0.9 mg/kg, about 0.003 mg/kg to about 0.8 mg/kg, about 0.003 mg/kg to about 0.7 mg/kg, about 0.003 mg/kg to about 0.6 mg/kg, about 0.003 mg/kg to about 0.5 mg/kg, about 0.003 mg/kg to about 0.4 mg/kg, about 0.003 mg/kg to about 0.3 mg/kg, about 0.003 mg/kg to about 0.2 mg/kg, about 0.003 mg/kg to about 0.1 mg/kg, about 0.1 mg/kg to about 25 mg/kg, about 0.1 mg/kg to about 20 mg/kg, about 0.1 mg/kg to about 15 mg/kg, about 0.1 mg/kg to about 10 mg/kg, about 0.1 mg/kg to about 5 mg/kg, about 0.1 mg/kg to about 1 mg/kg, about 1 mg/kg to about 25 mg/kg, about 1 mg/kg to about 20 mg/kg, about 1 mg/kg to about 15 mg/kg, about 1 mg/kg to about 10 mg/kg, about 1 mg/kg to about 5 mg/kg, about 5 mg/kg to about 25 mg/kg, about 5 mg/kg to about 20 mg/kg, about 5 mg/kg to about 15 mg/kg,

about 5 mg/kg to about 10 mg/kg, about 10 mg/kg to about 25 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 15 mg/kg, about 15 mg/kg to about 25 mg/kg, about 15 mg/kg to about 20 mg/kg, or about 20 mg/kg to about 25 mg/kg.

[0214] In some aspects, an anti-LAG-3 antibody as disclosed herein is administered at about 0.003 mg/kg, about 0.004 mg/kg, about 0.005 mg/kg, about 0.006 mg/kg, about 0.007 mg/kg, about 0.008 mg/kg, about 0.009 mg/kg, about 0.01 mg/kg, about 0.02 mg/kg, about 0.03 mg/kg, about 0.04 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1.0 mg/kg, about 2.0 mg/kg, about 3.0 mg/kg, about 4.0 mg/kg, about 5.0 mg/kg, about 6.0 mg/kg, about 7.0 mg/kg, about 8.0 mg/kg, about 9.0 mg/kg, about 10.0 mg/kg, about 11.0 mg/kg, about 12.0 mg/kg, about 13.0 mg/kg, about 14.0 mg/kg, about 15.0 mg/kg, about 16.0 mg/kg, about 17.0 mg/kg, about 18.0 mg/kg, about 19.0 mg/kg, about 20.0 mg/kg, about 21.0 mg/kg, about 22.0 mg/kg, about 23.0 mg/kg, about 24.0 mg/kg, or about 25.0 mg/kg.

[0215] In some aspects, the dose of an anti-LAG-3 antibody as disclosed herein is administered in a constant amount.

[0216] In some aspects, the dose of an anti-LAG-3 antibody as disclosed herein is administered in a varying amount. For example, in some aspects, the maintenance (or follow-on) dose of an anti-LAG-3 antibody as disclosed herein can be higher or the same as the loading dose which is first administered. In some aspects, the maintenance dose of an anti-LAG-3 antibody as disclosed herein can be lower or the same as the loading dose.

[0217] In some aspects, an anti-LAG-3 antibody as disclosed herein is administered once about every one week, once about every two weeks, once about every three weeks, once about every four weeks, once about every five weeks, once about every six weeks, once about every seven weeks, once about every eight weeks, once about every nine weeks, once about every ten weeks, once about every eleven weeks, or once about every twelve weeks.

II.B. Anti-PD-1 and Anti-PD-L1 Antibodies

II.B.1. Anti-PD-1 Antibodies

[0218] Anti-PD-1 antibodies that are known in the art can be used in the methods of the disclosure. Various human monoclonal antibodies that bind specifically to PD-1 with high

affinity have been disclosed in U.S. Patent No. 8,008,449. Anti-PD-1 human antibodies disclosed in U.S. Patent No. 8,008,449 have been demonstrated to exhibit one or more of the following characteristics: (a) bind to human PD-1 with a K_D of 1 x 10^{-7} M or less, as determined by surface plasmon resonance using a Biacore biosensor system; (b) do not substantially bind to human CD28, CTLA-4 or ICOS; (c) increase T-cell proliferation in a Mixed Lymphocyte Reaction (MLR) assay; (d) increase interferon-γ production in an MLR assay; (e) increase IL-2 secretion in an MLR assay; (f) bind to human PD-1 and cynomolgus monkey PD-1; (g) inhibit the binding of PD-L1 and/or PD-L2 to PD-1; (h) stimulate antigen-specific memory responses; (i) stimulate antibody responses; and (j) inhibit tumor cell growth *in vivo*. Anti-PD-1 antibodies usable in the present disclosure include monoclonal antibodies that bind specifically to human PD-1 and exhibit at least one, in some aspects, at least five, of the preceding characteristics.

[0219] Other anti-PD-1 monoclonal antibodies that can be used in the methods of the disclosure have been described in, for example, U.S. Patent Nos. 6,808,710, 7,488,802, 8,168,757 and 8,354,509, US Publication No. 2016/0272708, and PCT Publication Nos. WO 2012/145493, WO 2008/156712, WO 2015/112900, WO 2012/145493, WO 2015/112800, WO 2014/206107, WO 2015/35606, WO 2015/085847, WO 2014/179664, WO 2017/020291, WO 2017/020858, WO 2016/197367, WO 2017/024515, WO 2017/025051, WO 2017/123557, WO 2016/106159, WO 2014/194302, WO 2017/040790, WO 2017/133540, WO 2017/132827, WO 2017/024465, WO 2017/025016, WO 2017/106061, WO 2017/19846, WO 2017/024465, WO 2017/025016, WO 2017/132825, and WO 2017/133540 each of which is incorporated by reference in its entirety.

[0220] Anti-PD-1 antibodies that can be used in the methods of the disclosure include nivolumab (also known as OPDIVO®, 5C4, BMS-936558, MDX-1106, and ONO-4538), pembrolizumab (Merck; also known as KEYTRUDA®, lambrolizumab, and MK3475; *see* WO 2008/156712), PDR001 (Novartis; also known as spartalizumab; *see* WO 2015/112900 and U.S. Patent No. 9,683,048), MEDI-0680 (AstraZeneca; also known as AMP-514; *see* WO 2012/145493), TSR-042 (Tesaro Biopharmaceutical; also known as ANB011 or dostarlimab; *see* WO 2014/179664), cemiplimab (Regeneron; also known as LIBTAYO® or REGN2810; *see* WO 2015/112800 and U.S. Patent No. 9,987,500), JS001 (TAIZHOU JUNSHI PHARMA; also known as toripalimab; *see* Si-Yang Liu et al., *J. Hematol. Oncol. 10*:136 (2017)), PF-06801591 (Pfizer; also known as sasanlimab; US

2016/0159905), BGB-A317 (Beigene; also known as tislelizumab; *see* WO 2015/35606 and US 2015/0079109), BI 754091 (Boehringer Ingelheim; *see* Zettl M *et al*., *Cancer. Res*. (2018);78(13 Suppl):Abstract 4558), INCSHR1210 (Jiangsu Hengrui Medicine; also known as SHR-1210 or camrelizumab; *see* WO 2015/085847; Si-Yang Liu et al., *J. Hematol. Oncol. 10*:136 (2017)), GLS-010 (Wuxi/Harbin Gloria Pharmaceuticals; also known as WBP3055; *see* Si-Yang Liu et al., *J. Hematol. Oncol. 10*:136 (2017)), AM-0001 (Armo), STI-1110 (Sorrento Therapeutics; *see* WO 2014/194302), AGEN2034 (Agenus; *see* WO 2017/040790), MGA012 (Macrogenics, *see* WO 2017/19846), BCD-100 (Biocad; Kaplon et al., *mAbs 10(2)*:183-203 (2018), IBI308 (Innovent; also known as sintilimab; *see* WO 2017/024465, WO 2017/025016, WO 2017/132825, and WO 2017/133540), and SSI-361 (Lyvgen Biopharma Holdings Limited, US 2018/0346569).

[0221] Anti-PD-1 antibodies that can be used in the methods of the disclosure also include isolated antibodies that bind specifically to human PD-1 and cross-compete for binding to human PD-1 with any anti-PD-1 antibody disclosed herein, *e.g.,* nivolumab (*see*, *e.g.*, U.S. Patent No. 8,008,449 and 8,779,105; WO 2013/173223). In some aspects, the anti-PD-1 antibody binds the same epitope as any of the anti-PD-1 antibodies described herein, *e.g.,* nivolumab.

[0222] In some aspects, the antibodies that cross-compete for binding to human PD-1 with, or bind to the same epitope region as, any anti-PD-1 antibody disclosed herein, *e.g.*, nivolumab, are monoclonal antibodies. For administration to human subjects, these cross-competing antibodies are chimeric antibodies, engineered antibodies, or humanized or human antibodies. Such chimeric, engineered, humanized or human monoclonal antibodies can be prepared and isolated by methods well known in the art.

[0223] Anti-PD-1 antibodies that can be used in the methods of the disclosure also include antigen-binding portions of any of the above full-length antibodies.

[0224] Anti-PD-1 antibodies that can be used in the methods of the disclosure are antibodies that bind to PD-1 with high specificity and affinity, block the binding of PD-L1 and or PD-L2, and inhibit the immunosuppressive effect of the PD-1 signaling pathway. In any of the compositions or methods disclosed herein, an anti-PD-1 "antibody" includes an antigen-binding portion or fragment that binds to the PD-1 receptor and exhibits the functional properties similar to those of whole antibodies in inhibiting ligand binding and

up-regulating the immune system. In certain aspects, the anti-PD-1 antibody or antigen-binding portion thereof cross-competes with nivolumab for binding to human PD-1.

[0225] In some aspects, the anti-PD-1 antibody is a full-length antibody. In some aspects, the anti-PD-1 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody. In some aspects, the multispecific antibody is a DART, a DVD-Ig, or bispecific antibody.

[0226] In some aspects, the anti-PD-1 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

[0227] In some aspects, the anti-PD-1 antibody is nivolumab, pembrolizumab, PDR001 (spartalizumab), MEDI-0680, TSR-042, cemiplimab, JS001, PF-06801591, BGB-A317, BI 754091, INCSHR1210, GLS-010, AM-001, STI-1110, AGEN2034, MGA012, BCD-100, IBI308, SSI-361, or comprises an antigen binding portion thereof.

[0228] In some aspects, the anti-PD-1 antibody is nivolumab. Nivolumab is a fully human IgG4 (S228P) PD-1 immune checkpoint inhibitor antibody that selectively prevents interaction with PD-1 ligands (PD-L1 and PD-L2), thereby blocking the down-regulation of antitumor T-cell functions (U.S. Patent No. 8,008,449; Wang et al., 2014 *Cancer Immunol Res. 2(9)*:846-56).

[0229] In some aspects, nivolumab is administered at about 240 mg, about 360 mg, or about 480 mg once about every 2, 3, or 4 weeks.

[0230] In some aspects, nivolumab is administered intravenously at about 240 mg for about 30 minutes on Day 1 of a two-week cycle.

[0231] In some aspects, nivolumab is administered intravenously at about 480 mg for about 30 minutes on Day 1 of a four-week cycle.

[0232] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:13, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:14.

[0233] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising: (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:15; (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:16; (c) a heavy chain variable region CDR3 comprising the sequence set

forth in SEQ ID NO:17; (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:18; (e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:19; and (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:20.

[0234] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:13 and 14, respectively.

[0235] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:11 and 12, respectively.

[0236] In some aspects, the methods of the disclosure comprise a combination of relatlimab and nivolumab.

[0237] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:3, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:4; and (b) an anti-PD-1 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:13, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:14.

[0238] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising a heavy chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, respectively, and a light chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10, respectively, and (b) an anti-PD-1 antibody comprising a heavy chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17, respectively, and a light chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20, respectively.

[0239] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:3 and 4, respectively, and (b) an anti-PD-1 antibody comprising heavy

and light chain variable regions comprising the sequences set forth in SEQ ID NOs:13 and 14, respectively.

[0240] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:1 and 2, respectively, and (b) an anti-PD-1 antibody comprises heavy and light chains comprising the sequences as set forth in SEQ ID NOs:11 and 12, respectively.

[0241] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:21 and 2, respectively, and (b) an anti-PD-1 antibody comprises heavy and light chains comprising the sequences as set forth in SEQ ID NOs:11 and 12, respectively.

[0242] In some aspects, the anti-PD-1 antibody is pembrolizumab. Pembrolizumab is a humanized monoclonal IgG4 (S228P) antibody directed against human cell surface receptor PD-1. Pembrolizumab is described, for example, in U.S. Patent Nos. 8,354,509 and 8,900,587.

[0243] In some aspects, pembrolizumab is administered at about 200 mg once about every 2 weeks. In some aspects, pembrolizumab is administered at about 200 mg once about every 3 weeks. In some aspects, pembrolizumab is administered at about 400 mg once about every 4 weeks. In some aspects, pembrolizumab is administered at about 400 mg once about every 6 weeks. In some aspects, pembrolizumab is administered at about 300 mg once about every 4-5 weeks.

[0244] In some aspects, pembrolizumab is administered intravenously at about 200 mg on Day 1, then once about every 3 weeks. In some aspects, pembrolizumab is administered for up to 35 cycles. In some aspects, pembrolizumab is administered intravenously at about 200 mg for about 30 minutes on Day 1 of a three-week cycle for up to 35 cycles.

[0245] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:79, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:80.

[0246] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising: (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:81; (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:82; (c) a heavy chain variable region CDR3 comprising the sequence set

forth in SEQ ID NO:83; (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:84; (e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:85; and (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:86.

[0247] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:79 and 80, respectively.

[0248] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:77 and 78, respectively.

[0249] In some aspects, the methods of the disclosure comprise a combination of favezelimab and pembrolizumab. In some aspects, 200 mg or 700 mg of favezelimab and 200 mg of pembrolizumab are administered intravenously on Day 1, then once about every 3 weeks. In some aspects, the combination of favezelimab and pembrolizumab is administered for up to 35 cycles. In some aspects, 200 mg or 700 mg of favezelimab and 200 mg of pembrolizumab are administered intravenously for about 30 minutes on Day 1 of a three-week cycle for up to 35 cycles.

[0250] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:69, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:70; and (b) an anti-PD-1 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:79, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:80.

[0251] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising a heavy chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:71, SEQ ID NO:72, and SEQ ID NO:73, respectively, and a light chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76, respectively, and (b) an anti-PD-1 antibody comprising a heavy chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:81, SEQ ID NO:82, and SEQ ID NO:83,

respectively, and a light chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:84, SEQ ID NO:85, and SEQ ID NO:86, respectively.

[0252] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:69 and 70, respectively, and (b) an anti-PD-1 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:79 and 80, respectively.

[0253] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:67 and 68, respectively, and (b) an anti-PD-1 antibody comprises heavy and light chains comprising the sequences as set forth in SEQ ID NOs:77 and 78, respectively.

[0254] In some aspects, the anti-PD-1 antibody is cemiplimab (REGN2810). Cemiplimab is described, for example, in WO 2015/112800 and U.S. Patent No. 9,987,500.

[0255] In some aspects, cemiplimab is administered intravenously at about 3 mg/kg or about 350 mg once about every 3 weeks.

[0256] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:35, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:36.

[0257] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising: (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:37; (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:38; (c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:39; (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:40; (e) a light chain variable region CDR2 comprising the sequence AAS; and (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:42.

[0258] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:35 and 36, respectively.

[0259] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:33 and 34, respectively.

[0260] In some aspects, the methods of the disclosure comprise a combination of fianlimab and cemiplimab.

[0261] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:25, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:26; and (b) an anti-PD-1 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:35, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:36.

[0262] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising a heavy chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:27, SEQ ID NO:28, and SEQ ID NO:29, respectively, and a light chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:30, the sequence DAS, and the sequence set forth in SEQ ID NO:32, respectively, and (b) an anti-PD-1 antibody comprising a heavy chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:37, SEQ ID NO:38, and SEQ ID NO:39, respectively, and a light chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:40, the sequence AAS, and the sequence set forth in SEQ ID NO:42, respectively.

[0263] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:25 and 26, respectively, and (b) an anti-PD-1 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:35 and 36, respectively.

[0264] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:23 and 24, respectively, and (b) an anti-PD-1 antibody comprises heavy and light chains comprising the sequences as set forth in SEQ ID NOs:33 and 34, respectively.

[0265] In some aspects, the anti-PD-1 antibody is spartalizumab (PDR001). Spartalizumab is described, for example, in WO 2015/112900 and U.S. Patent No. 9,683,048.

[0266] In some aspects, spartalizumab is administered intravenously at about 300 mg once about every 3 weeks or about 400 mg once about every 4 weeks.

[0267] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:59, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:60.

[0268] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising: (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:61; (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:62; (c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:63; (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:64; (e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:65; and (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:66.

[0269] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:59 and 60, respectively.

[0270] In some aspects, the methods of the disclosure comprise an anti-PD-1 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:57 and 58, respectively.

[0271] In some aspects, the methods of the disclosure comprise a combination of ieramilimab and spartalizumab. In some aspects, ieramilimab is administered intravenously at about 400 mg once about every three weeks and spartalizumab is administered intravenously at about 300 mg once about every 3 weeks. In some aspects, ieramilimab is administered intravenously at about 600 mg once about every four weeks and spartalizumab is administered intravenously at about 400 mg once about every 4 weeks.

[0272] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:47, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:49; and (b) an

anti-PD-1 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:59, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:60.

[0273] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:48, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:50; and (b) an anti-PD-1 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:59, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:60.

[0274] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising a heavy chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:51, SEQ ID NO:52, and SEQ ID NO:53, respectively, and a light chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:54, SEQ ID NO:55, and SEQ ID NO:56, respectively, and (b) an anti-PD-1 antibody comprising a heavy chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:61, SEQ ID NO:62, and SEQ ID NO:63, respectively, and a light chain variable region CDR1, CDR2, and CDR3 comprising the sequence set forth in SEQ ID NO:64, SEQ ID NO:65, and SEQ ID NO:66, respectively.

[0275] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:47 and 49, respectively, and (b) an anti-PD-1 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:59 and 60, respectively.

[0276] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:48 and 50, respectively, and (b) an anti-PD-1 antibody comprising heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:59 and 60, respectively.

[0277] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:43 and 45, respectively, and (b) an anti-PD-1 antibody comprises heavy and light chains comprising the sequences as set forth in SEQ ID NOs:57 and 58, respectively.

[0278] In some aspects, the methods of the disclosure comprise: (a) an anti-LAG-3 antibody comprising heavy and light chains comprising the sequences set forth in SEQ ID NOs:44 and 46, respectively, and (b) an anti-PD-1 antibody comprises heavy and light chains comprising the sequences as set forth in SEQ ID NOs:57 and 58, respectively.

II.B.2. Anti-PD-L1 Antibodies

[0279] Anti-PD-L1 antibodies that are known in the art can be used in the methods of the disclosure. Examples of anti-PD-L1 antibodies useful in the compositions and methods of the present disclosure include the antibodies disclosed in US Patent No. 9,580,507. Anti-PD-L1 human monoclonal antibodies disclosed in U.S. Patent No. 9,580,507 have been demonstrated to exhibit one or more of the following characteristics: (a) bind to human PD-L1 with a K_D of 1 x 10^{-7} M or less, as determined by surface plasmon resonance using a Biacore biosensor system; (b) increase T-cell proliferation in a Mixed Lymphocyte Reaction (MLR) assay; (c) increase interferon-γ production in an MLR assay; (d) increase IL-2 secretion in an MLR assay; (e) stimulate antibody responses; and (f) reverse the effect of T regulatory cells on T cell effector cells and/or dendritic cells. Anti-PD-L1 antibodies usable in the present disclosure include monoclonal antibodies that bind specifically to human PD-L1 and exhibit at least one, in some aspects, at least five, of the preceding characteristics.

[0280] Anti-PD-L1 antibodies that can be used in the methods of the disclosure include BMS-936559 (also known as 12A4, MDX-1105; *see*, *e.g.,* U.S. Patent No. 7,943,743 and WO 2013/173223), atezolizumab (Roche; also known as TECENTRIQ®; MPDL3280A, RG7446; *see* US 8,217,149; *see*, *also*, Herbst et al. (2013) J Clin Oncol 31(suppl):3000), durvalumab (AstraZeneca; also known as IMFINZI™, MEDI-4736; *see* WO 2011/066389), avelumab (Pfizer; also known as BAVENCIO®, MSB-0010718C; *see* WO 2013/079174), STI-1014 (Sorrento; *see* WO2013/181634), CX-072 (Cytomx; *see* WO2016/149201), KN035 (3D Med/Alphamab; *see* Zhang et al., *Cell Discov. 7*:3 (March 2017), LY3300054 (Eli Lilly Co.; *see*, *e.g.*, WO 2017/034916), BGB-A333 (BeiGene; *see*

Desai et al., *JCO 36 (15suppl)*:TPS3113 (2018)), ICO 36, FAZ053 (Novartis), and CK-301 (Checkpoint Therapeutics; *see* Gorelik et al., AACR:Abstract 4606 (Apr 2016)).

[0281] Anti-PD-L1 antibodies that can be used in the methods of the disclosure also include isolated antibodies that bind specifically to human PD-L1 and cross-compete for binding to human PD-L1 with any anti-PD-L1 antibody disclosed herein, *e.g.*, atezolizumab, durvalumab, and/or avelumab. In some aspects, the anti-PD-L1 antibody binds the same epitope as any of the anti-PD-L1 antibodies described herein, *e.g.*, atezolizumab, durvalumab, and/or avelumab. In certain aspects, the antibodies that cross-compete for binding to human PD-L1 with, or bind to the same epitope region as, any anti-PD-L1 antibody disclosed herein, *e.g.*, atezolizumab, durvalumab, and/or avelumab, are monoclonal antibodies. For administration to human subjects, these cross-competing antibodies are chimeric antibodies, engineered antibodies, or humanized or human antibodies. Such chimeric, engineered, humanized or human monoclonal antibodies can be prepared and isolated by methods well known in the art.

[0282] Anti-PD-L1 antibodies that can be used in the methods of the disclosure also include antigen-binding portions of any of the above full-length antibodies.

[0283] Anti-PD-L1 antibodies that can be used in the methods of the disclosure are antibodies that bind to PD-L1 with high specificity and affinity, block the binding of PD-1, and inhibit the immunosuppressive effect of the PD-1 signaling pathway. In any of the compositions or methods disclosed herein, an anti-PD-L1 "antibody" includes an antigen-binding portion or fragment that binds to PD-L1 and exhibits the functional properties similar to those of whole antibodies in inhibiting receptor binding and up-regulating the immune system. In certain aspects, the anti-PD-L1 antibody or antigen-binding portion thereof cross-competes with atezolizumab, durvalumab, and/or avelumab for binding to human PD-L1.

[0284] In some aspects, an anti-PD-L1 antibody is substituted for the anti-PD-1 antibody in any of the methods disclosed herein.

[0285] In some aspects, the anti-PD-L1 antibody is a full-length antibody.

[0286] In some aspects, the anti-PD-L1 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody. In some aspects, the multispecific antibody is a DART, a DVD-Ig, or bispecific antibody.

[0287] In some aspects, the anti-PD-L1 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

[0288] In some aspects, the anti-PD-L1 antibody is BMS-936559, atezolizumab, durvalumab, avelumab, STI-1014, CX-072, KN035, LY3300054, BGB-A333, ICO 36, FAZ053, CK-301, or comprises an antigen binding portion thereof.

[0289] In some aspects, the PD-L1 antibody is atezolizumab. Atezolizumab is a fully humanized IgG1 monoclonal anti-PD-L1 antibody. In some aspects, atezolizumab is administered at about 800 mg once about every 2 weeks. In some aspects, atezolizumab is administered at about 840 mg once about every 2 weeks.

[0290] In some aspects, atezolizumab is administered intravenously at about 1,200 mg on Day 1 of a three-week cycle.

[0291] In some aspects, atezolizumab is administered intravenously at about 1,200 mg on Day 1 of a three-week cycle, and bevacizumab is administered at about 15 mg/kg on Day 1 of each cycle.

[0292] In some aspects, the PD-L1 antibody is durvalumab. Durvalumab is a human IgG1 kappa monoclonal anti-PD-L1 antibody. In some aspects, durvalumab is administered at about 10 mg/kg once about every 2 weeks. In some aspects, durvalumab is administered at about 10 mg/kg once about every 2 weeks for up to 12 months. In some aspects, durvalumab is administered at about 800 mg/kg once about every 2 weeks. In some aspects, durvalumab is administered at about 1200 mg/kg once about every 3 weeks.

[0293] In some aspects, the PD-L1 antibody is avelumab. Avelumab is a human IgG1 lambda monoclonal anti-PD-L1 antibody. In some aspects, avelumab is administered at about 800 mg once about every 2 weeks.

II.B.3. Administration of Antibodies

[0294] In some aspects, an anti-PD-1 or anti-PD-L1 antibody as disclosed herein is formulated for intravenous administration.

[0295] In some aspects, an anti-PD-1 or anti-PD-L1 antibody as disclosed herein is administered at a flat dose.

[0296] In some aspects, an anti-PD-1 or anti-PD-L1 antibody as disclosed herein is administered at from at least about 0.25 mg to about 2000 mg, about 0.25 mg to about 1600 mg, about 0.25 mg to about 1200 mg, about 0.25 mg to about 800 mg, about 0.25 mg to

about 400 mg, about 0.25 mg to about 100 mg, about 0.25 mg to about 50 mg, about 0.25 mg to about 40 mg, about 0.25 mg to about 30 mg, about 0.25 mg to about 20 mg, about 20 mg to about 2000 mg, about 20 mg to about 1600 mg, about 20 mg to about 1200 mg, about 20 mg to about 800 mg, about 20 mg to about 400 mg, about 20 mg to about 100 mg, about 100 mg to about 2000 mg, about 100 mg to about 1800 mg, about 100 mg to about 1600 mg, about 100 mg to about 1400 mg, about 100 mg to about 1200 mg, about 100 mg to about 1000 mg, about 100 mg to about 800 mg, about 100 mg to about 600 mg, about 100 mg to about 400 mg, about 400 mg to about 2000 mg, about 400 mg to about 1800 mg, about 400 mg to about 1600 mg, about 400 mg to about 1400 mg, about 400 mg to about 1200 mg, or about 400 mg to about 1000 mg.

[0297] In some aspects, an anti-PD-1 or anti-PD-L1 antibody as disclosed herein is administered at about 0.25 mg, about 0.5 mg, about 0.75 mg, about 1 mg, about 1.25 mg, about 1.5 mg, about 1.75 mg, about 2 mg, 2.25 mg, about 2.5 mg, about 2.75 mg, about 3 mg, about 3.25 mg, about 3.5 mg, about 3.75 mg, about 4 mg, about 4.25 mg, about 4.5 mg, about 4.75 mg, about 5 mg, about 5.25 mg, about 5.5 mg, about 5.75 mg, about 6 mg, about 6.25 mg, about 6.5 mg, about 6.75 mg, about 7 mg, about 7.25 mg, about 7.5 mg, about 7.75 mg, about 8 mg, about 8.25 mg, about 8.5 mg, about 8.75 mg, about 9 mg, about 9.25 mg, about 9.5 mg, about 9.75 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, about 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg,

about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 980 mg, about 990 mg, about 1000 mg, about 1040 mg, about 1080 mg, about 1100 mg, about 1140 mg, about 1180 mg, about 1200 mg, about 1240 mg, about 1280 mg, about 1300 mg, about 1340 mg, about 1380 mg, about 1400 mg, about 1440 mg, about 1480 mg, about 1500 mg, about 1540 mg, about 1580 mg, about 1600 mg, about 1640 mg, about 1680 mg, about 1700 mg, about 1740 mg, about 1780 mg, about 1800 mg, about 1840 mg, about 1880 mg, about 1900 mg, about 1940 mg, about 1980 mg, or about 2000 mg.

[0298] In some aspects, an anti-PD-1 or anti-PD-L1 antibody as disclosed herein is administered at a weight-based dose.

[0299] In some aspects, an anti-PD-1 or anti-PD-L1 antibody as disclosed herein is administered at from at least about 0.003 mg/kg to about 25 mg/kg, about 0.003 mg/kg to about 20 mg/kg, about 0.003 mg/kg to about 15 mg/kg, about 0.003 mg/kg to about 10 mg/kg, about 0.003 mg/kg to about 5 mg/kg, about 0.003 mg/kg to about 1 mg/kg, about 0.003 mg/kg to about 0.9 mg/kg, about 0.003 mg/kg to about 0.8 mg/kg, about 0.003 mg/kg to about 0.7 mg/kg, about 0.003 mg/kg to about 0.6 mg/kg, about 0.003 mg/kg to about 0.5 mg/kg, about 0.003 mg/kg to about 0.4 mg/kg, about 0.003 mg/kg to about 0.3 mg/kg, about 0.003 mg/kg to about 0.2 mg/kg, about 0.003 mg/kg to about 0.1 mg/kg, about 0.1 mg/kg to about 25 mg/kg, about 0.1 mg/kg to about 20 mg/kg, about 0.1 mg/kg to about 15 mg/kg, about 0.1 mg/kg to about 10 mg/kg, about 0.1 mg/kg to about 5 mg/kg, about 0.1 mg/kg to about 1 mg/kg, about 1 mg/kg to about 25 mg/kg, about 1 mg/kg to about 20 mg/kg, about 1 mg/kg to about 15 mg/kg, about 1 mg/kg to about 10 mg/kg, about 1 mg/kg to about 5 mg/kg, about 5 mg/kg to about 25 mg/kg, about 5 mg/kg to about 20 mg/kg, about 5 mg/kg to about 15 mg/kg, about 5 mg/kg to about 10 mg/kg, about 10 mg/kg to about 25 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 15 mg/kg, about 15 mg/kg to about 25 mg/kg, about 15 mg/kg to about 20 mg/kg, or about 20 mg/kg to about 25 mg/kg.

[0300] In some aspects, an anti-PD-1 or anti-PD-L1 antibody as disclosed herein is administered at about 0.003 mg/kg, about 0.004 mg/kg, about 0.005 mg/kg, about 0.006 mg/kg, about 0.007 mg/kg, about 0.008 mg/kg, about 0.009 mg/kg, about 0.01 mg/kg, about 0.02 mg/kg, about 0.03 mg/kg, about 0.04 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg,

about 0.8 mg/kg, about 0.9 mg/kg, about 1.0 mg/kg, about 2.0 mg/kg, about 3.0 mg/kg, about 4.0 mg/kg, about 5.0 mg/kg, about 6.0 mg/kg, about 7.0 mg/kg, about 8.0 mg/kg, about 9.0 mg/kg, about 10.0 mg/kg, about 11.0 mg/kg, about 12.0 mg/kg, about 13.0 mg/kg, about 14.0 mg/kg, about 15.0 mg/kg, about 16.0 mg/kg, about 17.0 mg/kg, about 18.0 mg/kg, about 19.0 mg/kg, about 20.0 mg/kg, about 21.0 mg/kg, about 22.0 mg/kg, about 23.0 mg/kg, about 24.0 mg/kg, or about 25.0 mg/kg.

[0301] In some aspects, the dose of an anti-PD-1 or anti-PD-L1 antibody as disclosed herein is administered in a constant amount.

[0302] In some aspects, the dose of an anti-PD-1 or anti-PD-L1 antibody as disclosed herein is administered in a varying amount. For example, in some aspects, the maintenance (or follow-on) dose of an anti-PD-1 or anti-PD-L1 antibody as disclosed herein can be higher or the same as the loading dose which is first administered. In some aspects, the maintenance dose of an anti-PD-1 or anti-PD-L1 antibody as disclosed herein can be lower or the same as the loading dose.

[0303] In some aspects, an anti-PD-1 or anti-PD-L1 antibody as disclosed herein is administered once about every one week, once about every two weeks, once about every three weeks, once about every four weeks, once about every five weeks, once about every six weeks, once about every seven weeks, once about every eight weeks, once about every nine weeks, once about every ten weeks, once about every eleven weeks, or once about every twelve weeks.

[0304] Any amount of an anti-PD-1 or anti-PD-L1 antibody as described herein can be administered in combination with any amount of an anti-LAG-3 antibody as described herein.

[0305] In some aspects, the amount of the anti-LAG-3 antibody is about 80 mg.

[0306] In some aspects, the amount of the anti-LAG-3 antibody is about 160 mg.

[0307] In some aspects, the amount of the anti-LAG-3 antibody is about 360 mg.

[0308] In some aspects, the amount of the anti-LAG-3 antibody is about 480 mg.

[0309] In some aspects, the amount of the anti-LAG-3 antibody is about 720 mg.

[0310] In some aspects, the amount of the anti-LAG-3 antibody is about 800 mg.

[0311] In some aspects, the amount of the anti-LAG-3 antibody is about 960 mg.

[0312] In some aspects, the amount of the anti-PD-1 antibody or anti-PD-L1 antibody is about 200 mg.

[0313] In some aspects, the amount of the anti-PD-1 antibody or anti-PD-L1 antibody is about 240 mg.

[0314] In some aspects, the amount of the anti-PD-1 antibody or anti-PD-L1 antibody is about 360 mg.

[0315] In some aspects, the amount of the anti-PD-1 antibody or anti-PD-L1 antibody is about 480 mg.

[0316] In some aspects, the amount of the anti-LAG-3 antibody is about 80 mg and the amount of the anti-PD-1 antibody or anti-PD-L1 antibody is about 240 mg.

[0317] In some aspects, the amount of the anti-LAG-3 antibody is about 80 mg and the amount of the anti-PD-1 antibody or anti-PD-L1 antibody is about 480 mg.

[0318] In some aspects, the amount of the anti-LAG-3 antibody is about 160 mg and the amount of the anti-PD-1 antibody or anti-PD-L1 antibody is about 480 mg.

[0319] In some aspects, the amount of the anti-LAG-3 antibody is about 360 mg and the amount of the anti-PD-1 antibody or anti-PD-L1 antibody is about 360 mg.

[0320] In some aspects, the amount of the anti-LAG-3 antibody is about 480 mg and the amount of the anti-PD-1 antibody or anti-PD-L1 antibody is about 480 mg.

[0321] In some aspects, the amount of the anti-LAG-3 antibody is about 720 mg and the amount of the anti-PD-1 antibody or anti-PD-L1 antibody is about 360 mg.

[0322] In some aspects, the amount of the anti-LAG-3 antibody is about 800 mg and the amount of the anti-PD-1 antibody or anti-PD-L1 antibody is about 200 mg.

[0323] In some aspects, the amount of the anti-LAG-3 antibody is about 960 mg and the amount of the anti-PD-1 antibody or anti-PD-L1 antibody is about 480 mg.

[0324] In some aspects, the amount of the anti-LAG-3 antibody is about 2 mg/kg and the amount of the anti-PD-1 antibody or anti-PD-L1 antibody is about 6 mg/kg.

[0325] In some aspects, the amount of the anti-LAG-3 antibody is about 1 mg/kg and the amount of the anti-PD-1 antibody or anti-PD-L1 antibody is about 6 mg/kg.

[0326] Provided herein is a method of treating a human subject afflicted with CRC, the method comprising administering to the subject: (a) about 480 mg of an anti-LAG-3 antibody, and (b) about 480 mg of an anti-PD-1 antibody or an anti-PD-L1 antibody.

[0327] Provided herein is a method of treating a human subject afflicted with CRC, the method comprising administering to the subject: (a) about 480 mg of an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region

having the sequence set forth in SEQ ID NO:3, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:4, and (b) about 480 mg of an anti-PD-1 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:13, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:14.

[0328] In some aspects, the anti-LAG-3 antibody and/or the anti-PD-1 antibody or anti-PD-L1 antibody is formulated for intravenous administration.

[0329] In some aspects, the anti-LAG-3 antibody and/or the anti-PD-1 antibody or anti-PD-L1 antibody is administered once about every one week, once about every two weeks, once about every three weeks, once about every four weeks, once about every five weeks, once about every six weeks, once about every seven weeks, once about every eight weeks, once about every nine weeks, once about every ten weeks, once about every eleven weeks, or once about every twelve weeks.

[0330] In some aspects, the anti-PD-1 antibody or anti-PD-L1 antibody is administered before the anti-LAG-3 antibody.

[0331] In some aspects, the anti-LAG-3 antibody is administered before the anti-PD-1 antibody or anti-PD-L1 antibody.

[0332] In some aspects, the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody are administered concurrently.

[0333] In some aspects, the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody are formulated separately.

[0334] In some aspects, the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody are formulated together.

II.C. Additional Therapeutic Agents and Therapies

[0335] In some aspects, the methods of the disclosure further comprise administering to the subject an additional therapeutic agent and/or anti-cancer therapy.

[0336] The additional anti-cancer therapy can comprise any therapy known in the art for the treatment of a tumor in a subject and/or any standard-of-care therapy, as disclosed herein. In some aspects, the additional anti-cancer therapy comprises a surgery, a radiation therapy, a chemotherapy, an immunotherapy, or any combination thereof. In some aspects, the additional anti-cancer therapy comprises a chemotherapy, including any

chemotherapeutic agent disclosed herein. In some aspects, the chemotherapy comprises platinum-doublet chemotherapy.

[0337] In some aspects, the additional therapeutic agent comprises an anti-cancer agent. In some aspects, the anti-cancer agent comprises a tyrosine kinase inhibitor, an anti-angiogenesis agent, a checkpoint inhibitor, a checkpoint stimulator, a chemotherapeutic agent, an immunotherapeutic agent, a platinum agent, an alkylating agent, a taxane, a nucleoside analog, an antimetabolite, a topoisomerase inhibitor, an anthracycline, a vinca alkaloid, or any combination thereof.

[0338] In some aspects, the tyrosine kinase inhibitor comprises sorafenib (*e.g.*, sorafenib tosylate, also known as NEXAVAR®), lenvatinib (*e.g.*, lenvatinib mesylate, also known as LENVIMA®), regorafenib (*e.g.*, STIVARGA®), cabozantinib (*e.g.*, cabozantinib S-malate, also known as CABOMETYX®), sunitinib (*e.g.*, sunitinib malate, also known as SUTENT®), brivanib, linifanib, pemigatinib (also known as PEMAZYRE™), everolimus (also known as AFINITOR® or ZORTRESS®), gefitinib (IRESSA®, a small-molecule TKI of EGFR), imatinib (*e.g.*, imatinib mesylate), lapatinib (*e.g.*, lapatinib ditosylate, also known as TYKERB®), nilotinib (*e.g.*, nilotinib hydrochloride, also known as TASIGNA®), pazopanib (*e.g.*, pazopanib hydrochloride, also known as VOTRIENT®), temsirolimus (also known as TORISEL®), erlotinib (*e.g.*, erlotinib hydrochloride, also known as TARCEVA®, a small-molecule TKI of EGFR), afatinib (GILOTRIF®, a small-molecule TKI of EGFR), dacomitinib (VIZIMPRO®, a small-molecule TKI of EGFR), osimeritinb (TAGRISSO®, a small-molecule TKI of EGFR), alectinib (ALECENSA®, a small-molecule TKI of ALK), ceritinib (ZYKADIA®, a small-molecule TKI of ALK and ROS-1), brigatinib (ALUNBRIG®, a small-molecule TKI of ALK), crizotinib (XALKORI®, a small-molecule TKI of ALK and ROS-1), lorlatinib (LORBRENA®, a small-molecule TKI of ALK and ROS-1), entrectinib (ROZLYTREK®, a small-molecule TKI of ROS-1 and NTRK), dabrafenib (TAFINLAR®, a small-molecule TKI of BRAF) trametinib (MEKINIST®, a small-molecule TKI of BRAF), vemurafenib (ZELBORAF®, a small-molecule TKI of BRAF), larotrectinib (ROZLYTREK®, a small-molecule TKI of NTRK), or any combination thereof.

[0339] In some aspects, the anti-angiogenesis agent comprises an inhibitor of a vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR), platelet-derived growth factor (PDGF), PDGF receptor (PDGFR), angiopoietin (Ang), tyrosine kinase with Ig-like

and EGF-like domains (Tie) receptor, hepatocyte growth factor (HGF), tyrosine-protein kinase Met (c-MET), C-type lectin family 14 member A (CLEC14A), multimerin 2 (MMRN2), shock protein 70-1A (HSP70-1A), epidermal growth factor (EGF), EGFR, or any combination thereof. In some aspects, the anti-angiogenesis agent comprises bevacizumab (also known as AVASTIN®), ranibizumab (also known as LUCENTIS®), ramucirumab (also known as CYRAMZA®), aflibercept (also known as EYLEA® or ZALTRAP®), tanibirumab, olaratumab (also known as LARTRUVO™), nesvacumab, AMG780, MEDI3617, vanucizumab, rilotumumab, ficlatuzumab, TAK-701, onartuzumab, emibetuzumab, or any combination thereof.

[0340] In some aspects, the checkpoint stimulator comprises an agonist of B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, GITR, inducible T cell co-stimulator (ICOS), ICOS-L, OX40, OX40L, CD70, CD27, CD40, death receptor 3 (DR3), CD28H, or any combination thereof.

[0341] In some aspects, the chemotherapeutic agent comprises an alkylating agent, an antimetabolite, an antineoplastic antibiotic, a mitotic inhibitor, a hormone or hormone modulator, a protein tyrosine kinase inhibitor, an epidermal growth factor inhibitor, a proteasome inhibitor, other neoplastic agent, or any combination thereof.

[0342] In some aspects, the immunotherapeutic agent comprises an antibody that specifically binds to EGFR (*e.g.*, cetuximab (ERBITUX®)), ALK, ROS-1, NTRK, BRAF, ICOS, CD137 (4-1BB), CD134 (OX40), NKG2A, CD27, CD96, GITR, Herpes Virus Entry Mediator (HVEM), PD-1, PD-L1, CTLA-4, BTLA, TIM-3, A2aR, Killer cell Lectin-like Receptor G1 (KLRG-1), Natural Killer Cell Receptor 2B4 (CD244), CD160, TIGIT, VISTA, KIR, TGFβ, IL-10, IL-8, B7-H4, Fas ligand, CSF1R, CXCR4, mesothelin, CEACAM-1, CD52, HER2, MICA, MICB, or any combination thereof.

[0343] In some aspects, the platinum agent comprises cisplatin, carboplatin, oxaliplatin, satraplatin, picoplatin, nedaplatin, triplatin (*e.g.*, triplatin tetranitrate), lipoplatin, phenanthriplatin, or any combination thereof.

[0344] In some aspects, the alkylating agent comprises altretamine, bendamustine, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, lomustine, mechlorethamine, melphalan, oxaliplatin, procarbazine, streptozocin, temozolomide, thiotepa, or any combination thereof.

[0345] In some aspects, the taxane comprises paclitaxel, albumin-bound paclitaxel, docetaxel, cabazitaxel, or any combination thereof.

[0346] In some aspects, the nucleoside analog comprises cytarabine, gemcitabine, lamivudine, entecavir, telbivudine, or any combination thereof.

[0347] In some aspects, the antimetabolite comprises capecitabine, cladribine, clofarabine, cytarabine, floxuridine, fludarabine, fluorouracil, gemcitabine, mercaptopurine, methotrexate, pemetrexed, pentostatin, pralatrexate, thioguanine, or any combination thereof.

[0348] In some embodiments, the topoisomerase inhibitor comprises etoposide, mitoxantrone, doxorubicin, irinotecan, topotecan, camptothecin, or any combination thereof.

[0349] In some aspects, the anthracycline is doxorubicin, daunorubicin, epirubicin, idarubicin, or any combination thereof.

[0350] In some aspects, the vinca alkaloid is vinblastine, vincristine, vinorelbine, vindesine, vincaminol, vineridine, vinburnine, or any combination thereof.

II.C.1. Checkpoint inhibitors

[0351] In some aspects, the anti-cancer agent that is administered as an additional therapeutic agent in the methods of the disclosure is a checkpoint inhibitor.

[0352] In some aspects, the checkpoint inhibitor comprises a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, a T cell immunoglobulin and ITIM domain (TIGIT) inhibitor, a T cell immunoglobulin and mucin-domain containing-3 (TIM-3) inhibitor, a TIM-1 inhibitor, a TIM-4 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a B and T cell lymphocyte attenuator (BTLA) inhibitor, a V-domain Ig suppressor of T cell activation (VISTA) inhibitor, an indoleamine 2,3-dioxygenase (IDO) inhibitor, a nicotinamide adenine dinucleotide phosphate oxidase isoform 2 (NOX2) inhibitor, a killer-cell immunoglobulin-like receptor (KIR) inhibitor, an adenosine A2a receptor (A2aR) inhibitor, a transforming growth factor beta (TGF-β) inhibitor, a phosphoinositide 3-kinase (PI3K) inhibitor, a CD47 inhibitor, a CD48 inhibitor, a CD73 inhibitor, a CD113 inhibitor, a sialic acid-binding immunoglobulin-like lectin-7 (SIGLEC-7) inhibitor, a SIGLEC-9 inhibitor, a SIGLEC-15 inhibitor, a glucocorticoid-induced TNFR-related protein (GITR) inhibitor, a galectin-1 inhibitor, a galectin-9 inhibitor, a carcinoembryonic antigen-related

cell adhesion molecule-1 (CEACAM-1) inhibitor, a G protein-coupled receptor 56 (GPR56) inhibitor, a glycoprotein A repetitions predominant (GARP) inhibitor, a 2B4 inhibitor, a programmed death-1 homolog (PD1H) inhibitor, a leukocyte-associated immunoglobulin-like receptor 1 (LAIR1) inhibitor, or any combination thereof.

[0353] In some aspects, the checkpoint inhibitor is formulated for intravenous administration.

[0354] In some aspects, the checkpoint inhibitor is administered at a flat dose.

[0355] In some aspects, the checkpoint inhibitor is administered at from at least about 0.25 mg to about 2000 mg, about 0.25 mg to about 1600 mg, about 0.25 mg to about 1200 mg, about 0.25 mg to about 800 mg, about 0.25 mg to about 400 mg, about 0.25 mg to about 100 mg, about 0.25 mg to about 50 mg, about 0.25 mg to about 40 mg, about 0.25 mg to about 30 mg, about 0.25 mg to about 20 mg, about 20 mg to about 2000 mg, about 20 mg to about 1600 mg, about 20 mg to about 1200 mg, about 20 mg to about 800 mg, about 20 mg to about 400 mg, about 20 mg to about 100 mg, about 100 mg to about 2000 mg, about 100 mg to about 1800 mg, about 100 mg to about 1600 mg, about 100 mg to about 1400 mg, about 100 mg to about 1200 mg, about 100 mg to about 1000 mg, about 100 mg to about 800 mg, about 100 mg to about 600 mg, about 100 mg to about 400 mg, about 400 mg to about 2000 mg, about 400 mg to about 1800 mg, about 400 mg to about 1600 mg, about 400 mg to about 1400 mg, about 400 mg to about 1200 mg, or about 400 mg to about 1000 mg.

[0356] In some aspects, the checkpoint inhibitor is administered at about 0.25 mg, about 0.5 mg, about 0.75 mg, about 1 mg, about 1.25 mg, about 1.5 mg, about 1.75 mg, about 2 mg, about 2.25 mg, about 2.5 mg, about 2.75 mg, about 3 mg, about 3.25 mg, about 3.5 mg, about 3.75 mg, about 4 mg, about 4.25 mg, about 4.5 mg, about 4.75 mg, about 5 mg, about 5.25 mg, about 5.5 mg, about 5.75 mg, about 6 mg, about 6.25 mg, about 6.5 mg, about 6.75 mg, about 7 mg, about 7.25 mg, about 7.5 mg, about 7.75 mg, about 8 mg, about 8.25 mg, about 8.5 mg, about 8.75 mg, about 9 mg, about 9.25 mg, about 9.5 mg, about 9.75 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about

310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, about 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 980 mg, about 990 mg, about 1000 mg, about 1040 mg, about 1080 mg, about 1100 mg, about 1140 mg, about 1180 mg, about 1200 mg, about 1240 mg, about 1280 mg, about 1300 mg, about 1340 mg, about 1380 mg, about 1400 mg, about 1440 mg, about 1480 mg, about 1500 mg, about 1540 mg, about 1580 mg, about 1600 mg, about 1640 mg, about 1680 mg, about 1700 mg, about 1740 mg, about 1780 mg, about 1800 mg, about 1840 mg, about 1880 mg, about 1900 mg, about 1940 mg, about 1980 mg, or about 2000 mg.

[0357] In some aspects, the checkpoint inhibitor is administered as a weight-based dose.

[0358] In some aspects, the checkpoint inhibitor is administered at from at least about 0.003 mg/kg to about 25 mg/kg, about 0.003 mg/kg to about 20 mg/kg, about 0.003 mg/kg to about 15 mg/kg, about 0.003 mg/kg to about 10 mg/kg, about 0.003 mg/kg to about 5 mg/kg, about 0.003 mg/kg to about 1 mg/kg, about 0.003 mg/kg to about 0.9 mg/kg, about 0.003 mg/kg to about 0.8 mg/kg, about 0.003 mg/kg to about 0.7 mg/kg, about 0.003 mg/kg to about 0.6 mg/kg, about 0.003 mg/kg to about 0.5 mg/kg, about 0.003 mg/kg to about 0.4 mg/kg, about 0.003 mg/kg to about 0.3 mg/kg, about 0.003 mg/kg to about 0.2 mg/kg, about 0.003 mg/kg to about 0.1 mg/kg, about 0.1 mg/kg to about 25 mg/kg, about 0.1 mg/kg to about 20 mg/kg, about 0.1 mg/kg to about 15 mg/kg, about 0.1 mg/kg to about 10 mg/kg, about 0.1 mg/kg to about 5 mg/kg, about 0.1 mg/kg to about 1 mg/kg, about 1 mg/kg to about 25 mg/kg, about 1 mg/kg to about 20 mg/kg, about 1 mg/kg to about 15 mg/kg, about 1 mg/kg to about 10 mg/kg, about 1 mg/kg to about 5 mg/kg, about 5 mg/kg to about 25 mg/kg, about 5 mg/kg to about 20 mg/kg, about 5 mg/kg to about 15 mg/kg, about 5 mg/kg

to about 10 mg/kg, about 10 mg/kg to about 25 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 15 mg/kg, about 15 mg/kg to about 25 mg/kg, about 15 mg/kg to about 20 mg/kg, or about 20 mg/kg to about 25 mg/kg.

[0359] In some aspects, the checkpoint inhibitor is administered at about 0.003 mg/kg, about 0.004 mg/kg, about 0.005 mg/kg, about 0.006 mg/kg, about 0.007 mg/kg, about 0.008 mg/kg, about 0.009 mg/kg, about 0.01 mg/kg, about 0.02 mg/kg, about 0.03 mg/kg, about 0.04 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1.0 mg/kg, about 2.0 mg/kg, about 3.0 mg/kg, about 4.0 mg/kg, about 5.0 mg/kg, about 6.0 mg/kg, about 7.0 mg/kg, about 8.0 mg/kg, about 9.0 mg/kg, about 10.0 mg/kg, about 11.0 mg/kg, about 12.0 mg/kg, about 13.0 mg/kg, about 14.0 mg/kg, about 15.0 mg/kg, about 16.0 mg/kg, about 17.0 mg/kg, about 18.0 mg/kg, about 19.0 mg/kg, about 20.0 mg/kg, about 21.0 mg/kg, about 22.0 mg/kg, about 23.0 mg/kg, about 24.0 mg/kg, or about 25.0 mg/kg.

[0360] In some aspects, the dose of the checkpoint inhibitor is administered in a constant amount.

[0361] In some aspects, the dose of the checkpoint inhibitor is administered in a varying amount. For example, in some aspects, the maintenance (or follow-on) dose of the checkpoint inhibitor can be higher or the same as the loading dose which is first administered. In some aspects, the maintenance dose of the checkpoint inhibitor can be lower or the same as the loading dose.

[0362] In some aspects, the checkpoint inhibitor is administered every one week, every two weeks, every three weeks, every four weeks, every five weeks, every six weeks, every seven weeks, every eight weeks, every nine weeks, every ten weeks, every eleven weeks, or every twelve weeks.

II.C.1.a. CTLA-4 inhibitors

[0363] In some aspects, the checkpoint inhibitor as disclosed herein comprises a CTLA-4 inhibitor. In some aspects, the CTLA-4 inhibitor is an anti-CTLA-4 antibody.

[0364] Anti-CTLA-4 antibodies that can be used in the methods of the disclosure bind to human CTLA-4 and disrupt the interaction of CTLA-4 with a human B7 receptor. Because the interaction of CTLA-4 with B7 transduces a signal leading to inactivation of T-cells

bearing the CTLA-4 receptor, disruption of the interaction effectively induces, enhances, or prolongs the activation of such T cells, thereby inducing, enhancing or prolonging an immune response.

[0365] Human monoclonal antibodies that bind specifically to CTLA-4 with high affinity have been disclosed in U.S. Patent Nos. 6,984,720. Other anti-CTLA-4 monoclonal antibodies have been described in, for example, U.S. Patent Nos. 5,977,318, 6,051,227, 6,682,736, and 7,034,121 and International Publication Nos. WO 2012/122444, WO 2007/113648, WO 2016/196237, and WO 2000/037504, each of which is incorporated by reference herein in its entirety. The anti-CTLA-4 human monoclonal antibodies disclosed in U.S. Patent No. Nos. 6,984,720 have been demonstrated to exhibit one or more of the following characteristics: (a) binds specifically to human CTLA-4 with a binding affinity reflected by an equilibrium association constant (K_a) of at least about 10^7 M^{-1}, or about 10^9 M^{-1}, or about 10^{10} M^{-1} to 10^{11} M^{-1} or higher, as determined by Biacore analysis; (b) a kinetic association constant (k_a) of at least about 10^3, about 10^4, or about 10^5 m^{-1} s^{-1}; (c) a kinetic disassociation constant (k_d) of at least about 10^3, about 10^4, or about 10^5 m^{-1} s^{-1}; and (d) inhibits the binding of CTLA-4 to B7-1 (CD80) and B7-2 (CD86). Anti-CTLA-4 antibodies useful for the present disclosure include monoclonal antibodies that bind specifically to human CTLA-4 and exhibit at least one, at least two, or at least three of the preceding characteristics.

[0366] Anti-CTLA-4 antibodies that can be used in the methods of the disclosure include ipilimumab (also known as YERVOY®, MDX-010, 10D1; *see* U.S. Patent No. 6,984,720), MK-1308 (Merck), AGEN-1884 (Agenus Inc.; *see* WO 2016/196237), and tremelimumab (AstraZeneca; also known as ticilimumab, CP-675,206; *see* WO 2000/037504 and Ribas, *Update Cancer Ther. 2(3)*: 133-39 (2007)).

[0367] In some aspects, the anti-CTLA-4 antibody binds specifically to human CTLA-4 and cross-competes for binding to human CTLA-4 with any anti-CTLA-4 antibody disclosed herein, *e.g.*, ipilimumab and/or tremelimumab. In some aspects, the anti-CTLA-4 antibody binds the same epitope as any of the anti-CTLA-4 antibodies described herein, *e.g.*, ipilimumab and/or tremelimumab.

[0368] In some aspects, the antibodies that cross-compete for binding to human CTLA-4 with, or bind to the same epitope region as, any anti-CTLA-4 antibody disclosed herein, *e.g.*, ipilimumab and/or tremelimumab, are monoclonal antibodies. For administration to

human subjects, these cross-competing antibodies are chimeric antibodies, engineered antibodies, or humanized or human antibodies.

[0369] Anti-CTLA-4 antibodies that can be used in the methods of the disclosure also include antigen-binding portions of any of the above full-length antibodies.

[0370] In some aspects, the anti-CTLA-4 antibody is a full-length antibody. In some aspects, the anti-CTLA-4 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody. In some aspects, the multispecific antibody is a DART, a DVD-Ig, or bispecific antibody.

[0371] In some aspects, the anti-CTLA-4 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

[0372] In some aspects, the anti-CTLA-4 antibody is ipilimumab, tremelimumab, MK-1308, AGEN-1884, or comprises an antigen binding portion thereof.

[0373] In some aspects, the anti-CTLA-4 antibody is ipilimumab. Ipilimumab is a fully human, IgG1 monoclonal antibody that blocks the binding of CTLA-4 to its B7 ligands, thereby stimulating T cell activation. In some aspects, ipilimumab is administered at about 3 mg/kg once about every 3 weeks. In some aspects, ipilimumab is administered at about 10 mg/kg once about every 3 weeks. In some aspects, ipilimumab is administered at about 10 mg/kg once about every 12 weeks. In some aspects, the ipilimumab is administered for four doses. In some aspects, ipilimumab is administered on Day 1 of each cycle.

III. Pharmaceutical Compositions

[0374] Therapeutic agents of the present disclosure can be constituted in a composition, *e.g.*, a pharmaceutical composition containing an inhibitor, antibody, and/or agent as disclosed herein and a pharmaceutically acceptable carrier. As used herein, a "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible.

[0375] In some aspects, the carrier for a composition containing an inhibitor, antibody, and/or agent as disclosed herein is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (*e.g.*, by injection or infusion). In some aspects, the carrier is suitable for non-parenteral, *e.g.*, oral, administration. In some aspects, a subcutaneous injection is based on Halozyme Therapeutics' ENHANZE® drug-delivery

technology (*see* U.S. Patent No. 7,767,429, which is incorporated by reference herein in its entirety). ENHANZE® uses a co-formulation of an antibody with recombinant human hyaluronidase enzyme (rHuPH20), which removes traditional limitations on the volume of biologics and drugs that can be delivered subcutaneously due to the extracellular matrix (*see* U.S. Patent No. 7,767,429). A pharmaceutical composition of the disclosure can include one or more pharmaceutically acceptable salts, anti-oxidant, aqueous and non-aqueous carriers, and/or adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. In some aspects, the pharmaceutical composition for the present disclosure can further comprise recombinant human hyaluronidase enzyme, e.g., rHuPH20.

[0376] Treatment is continued as long as clinical benefit is observed or until unacceptable toxicity or disease progression occurs. Dosage and frequency vary depending on the half-life of the inhibitor, antibody, and/or agent in the subject. In general, human antibodies show the longest half-life, followed by humanized antibodies, chimeric antibodies, and nonhuman antibodies. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is typically administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and preferably until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

[0377] Actual dosage levels of the active ingredients (*i.e.*, inhibitors, antibodies, and/or agents) in the pharmaceutical compositions of the present disclosure can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being unduly toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present disclosure employed, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts. A

composition of the present disclosure can be administered via one or more routes of administration using one or more of a variety of methods well known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results.

[0378] Provided herein is a pharmaceutical composition comprising any amount of an anti-LAG-3 antibody and any amount of an anti-PD-1 antibody or anti-PD-L1 antibody as described herein.

[0379] In some aspects, the pharmaceutical composition is for treating a human subject with CRC as described herein, including unresectable or metastatic CRC.

[0380] In some aspects, a method for treating a human subject with CRC as described herein comprises administering a pharmaceutical composition as described herein.

[0381] In some aspects, the pharmaceutical composition comprises relatlimab and an anti-PD-1 antibody or anti-PD-L1 antibody as described herein. In some aspects, the anti-PD-1 antibody is nivolumab, pembrolizumab, cemiplimab, or spartalizumab. In some aspects, the anti-PD-1 antibody is nivolumab. In some aspects, the anti-PD-L1 antibody is BMS-936559, atezolizumab, durvalumab, avelumab, STI-1014, CX-072, KN035, LY3300054, BGB-A333, ICO 36, FAZ053, or CK-301.

[0382] In some aspects, the pharmaceutical composition comprises favezelimab and an anti-PD-1 antibody or anti-PD-L1 antibody as described herein. In some aspects, the anti-PD-1 antibody is nivolumab, pembrolizumab, cemiplimab, or spartalizumab. In some aspects, the anti-PD-1 antibody is pembrolizumab. In some aspects, the anti-PD-L1 antibody is BMS-936559, atezolizumab, durvalumab, avelumab, STI-1014, CX-072, KN035, LY3300054, BGB-A333, ICO 36, FAZ053, or CK-301.

[0383] In some aspects, the pharmaceutical composition comprises fianlimab and an anti-PD-1 antibody or anti-PD-L1 antibody as described herein. In some aspects, the anti-PD-1 antibody is nivolumab, pembrolizumab, cemiplimab, or spartalizumab. In some aspects, the anti-PD-1 antibody is cemiplimab. In some aspects, the anti-PD-L1 antibody is BMS-936559, atezolizumab, durvalumab, avelumab, STI-1014, CX-072, KN035, LY3300054, BGB-A333, ICO 36, FAZ053, or CK-301.

[0384] In some aspects, the pharmaceutical composition comprises ieramilimab and an anti-PD-1 antibody or anti-PD-L1 antibody as described herein. In some aspects, the anti-PD-1 antibody is nivolumab, pembrolizumab, cemiplimab, or spartalizumab. In some

aspects, the anti-PD-1 antibody is spartalizumab. In some aspects, the anti-PD-L1 antibody is BMS-936559, atezolizumab, durvalumab, avelumab, STI-1014, CX-072, KN035, LY3300054, BGB-A333, ICO 36, FAZ053, or CK-301.

[0385] In some aspects, the pharmaceutical composition comprises a ratio of anti-LAG-3 antibody to anti-PD-1 antibody or anti-PD-L1 antibody of about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:6, about 1:7, about 1:8, about 1:9, about 1:10, about 1:15, about 1:20, about 1:30, about 1:40, about 1:50, about 1:60, about 1:70, about 1:80, about 1:90, about 1:100, about 1:120, about 1:140, about 1:160, about 1:180, about 1:200, about 200:1, about 180:1, about 160:1, about 140:1, about 120:1, about 100:1, about 90:1, about 80:1, about 70:1, about 60:1, about 50:1, about 40:1, about 30:1, about 20:1, about 15:1, about 10:1, about 9:1, about 8:1, about 7:1, about 6:1, about 5:1, about 4:1, about 3:1, or about 2:1.

[0386] In some aspects, the pharmaceutical composition comprises a ratio of anti-LAG-3 antibody to anti-PD-1 antibody or anti-PD-L1 antibody of about 1:6.

[0387] In some aspects, the pharmaceutical composition comprises a ratio of anti-LAG-3 antibody to anti-PD-1 antibody or anti-PD-L1 antibody of about 1:3.

[0388] In some aspects, the pharmaceutical composition comprises a ratio of anti-LAG-3 antibody to anti-PD-1 antibody or anti-PD-L1 antibody of about 1:1

[0389] In some aspects, the pharmaceutical composition comprises a ratio of anti-LAG-3 antibody to anti-PD-1 antibody or anti-PD-L1 antibody of about 2:1.

[0390] In some aspects, the pharmaceutical composition comprises a ratio of anti-LAG-3 antibody to anti-PD-1 antibody or anti-PD-L1 antibody of about 4:1.

[0391] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the pharmaceutical composition is about 20 mg/mL, about 25 mg/mL, about 30 mg/mL, about 35 mg/mL, about 40 mg/mL, about 45 mg/mL, about 50 mg/mL, about 55 mg/mL, about 60 mg/mL, about 65 mg/mL, about 70 mg/mL, about 75 mg/mL, about 80 mg/mL, about 85 mg/mL, about 90 mg/mL, about 95 mg/mL, about 100 mg/mL, about 105 mg/mL, about 110 mg/mL, about 115 mg/mL, about 120 mg/mL, about 125 mg/mL, about 130 mg/mL, about 135 mg/mL, about 140 mg/mL, about 145 mg/mL, about 150 mg/mL, about 155 mg/mL, about 160 mg/mL, about 165 mg/mL, about 170 mg/mL, about 175 mg/mL, about 180 mg/mL, about 185 mg/mL, about 190 mg/mL, about 195 mg/mL, about 200 mg/mL, about 205 mg/mL, about 210 mg/mL, about 215 mg/mL, about

220 mg/mL, about 225 mg/mL, about 230 mg/mL, about 235 mg/mL, about 240 mg/mL, about 245 mg/mL, about 250 mg/mL, about 255 mg/mL, about 260 mg/mL, about 265 mg/mL, about 270 mg/mL, about 275 mg/mL, about 280 mg/mL, about 285 mg/mL, about 290 mg/mL, about 295 mg/mL, about 300 mg/mL, about 305 mg/mL, about 310 mg/mL, about 315 mg/mL, about 320 mg/mL, about 325 mg/mL, about 330 mg/mL, about 335 mg/mL, about 340 mg/mL, about 345 mg/mL, about 350 mg/mL, about 355 mg/mL, about 360 mg/mL, about 365 mg/mL, about 370 mg/mL, about 375 mg/mL, about 380 mg/mL, about 385 mg/mL, about 390 mg/mL, about 395 mg/mL, about 400 mg/mL, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, about 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 980 mg, about 990 mg, about 1000 mg, about 1010 mg, about 1020 mg, about 1030 mg, about 1040 mg, about 1050 mg, about 1060 mg, about 1070 mg, about 1080 mg, about 1090 mg, about 1100 mg, about 1110 mg, about 1120 mg, about 1130 mg, about 1140 mg, about 1150 mg, about 1160 mg, about 1170 mg, about 1180 mg, about 1190 mg, about 1200 mg, about 1210 mg, about 1220 mg, about 1230 mg, about 1240 mg, about 1250 mg, about 1260 mg, about 1270 mg, about 1280 mg, about 1290 mg, about 1300 mg, about 1310 mg, about 1320 mg, about 1330 mg, about 1340 mg, about 1350 mg, about 1360 mg, about 1370 mg, about 1380 mg, about 1390 mg, about 1400 mg, about 1410 mg, about 1420 mg, about 1430 mg, about 1440 mg, about 1450 mg, about

1460 mg, about 1470 mg, about 1480 mg, about 1490 mg, about 1500 mg, about 1510 mg, about 1520 mg, about 1530 mg, about 1540 mg, about 1550 mg, about 1560 mg, about 1570 mg, about 1580 mg, about 1590 mg, about 1600 mg, about 1610 mg, about 1620 mg, about 1630 mg, about 1640 mg, about 1650 mg, about 1660 mg, about 1670 mg, about 1680 mg, about 1690 mg, about 1700 mg, about 1710 mg, about 1720 mg, about 1730 mg, about 1740 mg, about 1750 mg, about 1760 mg, about 1770 mg, or about 1780 mg.

[0392] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the pharmaceutical composition is about 25 mg/mL.

[0393] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the pharmaceutical composition is about 50 mg/mL.

[0394] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the pharmaceutical composition is about 150 mg/mL.

[0395] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the pharmaceutical composition is about 50 mg.

[0396] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the pharmaceutical composition is about 320 mg.

[0397] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the pharmaceutical composition is about 480 mg.

[0398] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the pharmaceutical composition is about 560 mg.

[0399] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the pharmaceutical composition is about 640 mg.

[0400] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the pharmaceutical composition is about 720 mg.

[0401] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the pharmaceutical composition is about 960 mg.

[0402] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the pharmaceutical composition is about 1000 mg.

[0403] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the pharmaceutical composition is about 1080 mg.

[0404] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the pharmaceutical composition is about 1440 mg.

[0405] In some aspects, the pharmaceutical composition comprises about 10 mg/mL, about 12.5 mg/mL, about 15 mg/mL, about 17.5 mg/mL, about 20 mg/mL, about 22.5 mg/mL, about 25 mg/mL, about 27.5 mg/mL, about 30 mg/mL, about 32.5 mg/mL, about 35 mg/mL, about 37.5 mg/mL, about 40 mg/mL, about 42.5 mg/mL, about 45 mg/mL, about 47.5 mg/mL, about 50 mg/mL, about 55 mg/mL, about 60 mg/mL, about 65 mg/mL, about 70 mg/mL, about 75 mg/mL, about 80 mg/mL, about 85 mg/mL, about 90 mg/mL, about 95 mg/mL, about 100 mg/mL, about 105 mg/mL, about 110 mg/mL, about 115 mg/mL, about 120 mg/mL, about 125 mg/mL, 130 mg/mL, about 135 mg/mL, about 140 mg/mL, about 145 mg/mL, about 150 mg/mL, about 155 mg/mL, about 160 mg/mL, about 165 mg/mL, about 170 mg/mL, about 175 mg/mL, about 180 mg/mL, about 185 mg/mL, about 190 mg/mL, about 195 mg/mL, about 200 mg/mL, about 7 mg, about 21 mg, about 70 mg, about 80 mg, about 120 mg, about 160 mg, about 200 mg, about 210 mg, about 300 mg, about 360 mg, about 400 mg, about 480 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 960 mg, about 1000 mg, about 1100 mg, about 1200 mg, or about 1300 mg of an anti-LAG-3 antibody.

[0406] In some aspects, the pharmaceutical composition comprises about 10 mg/mL, about 12.5 mg/mL, about 15 mg/mL, about 17.5 mg/mL, about 20 mg/mL, about 22.5 mg/mL, about 25 mg/mL, about 27.5 mg/ml, about 30 mg/mL, about 32.5 mg/mL, about 35 mg/mL, about 37.5 mg/mL, about 40 mg/mL, about 42.5 mg/mL, about 45 mg/mL, about 47.5 mg/mL, about 50 mg/mL, about 55 mg/mL, about 60 mg/mL, about 65 mg/mL, about 70 mg/mL, about 75 mg/mL, about 80 mg/mL, about 85 mg/mL, about 90 mg/mL, about 95 mg/mL, about 100 mg/mL, about 105 mg/mL, about 110 mg/mL, about 115 mg/mL, about 120 mg/mL, about 125 mg/mL, 130 mg/mL, about 135 mg/mL, about 140 mg/mL, about 145 mg/mL, about 150 mg/mL, about 155 mg/mL, about 160 mg/mL, about 165 mg/mL, about 170 mg/mL, about 175 mg/mL, about 180 mg/mL, about 185 mg/mL, about 190 mg/mL, about 195 mg/mL, about 200 mg/mL, about 40 mg, about 100 mg, about 200 mg, about 240 mg, about 300 mg, about 350 mg, about 360 mg, about 400 mg, or about 480 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0407] In some aspects, the pharmaceutical composition comprises about 12.5 mg/mL of an anti-LAG-3 antibody and about 37.5 mg/mL of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0408] In some aspects, the pharmaceutical composition comprises about 20 mg/mL of an anti-LAG-3 antibody and about 5 mg/mL of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0409] In some aspects, the pharmaceutical composition comprises about 75 mg/mL of an anti-LAG-3 antibody and about 75 mg/mL of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0410] In some aspects, the pharmaceutical composition comprises about 100 mg/mL of an anti-LAG-3 antibody and about 50 mg/mL of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0411] In some aspects, the pharmaceutical composition comprises about 80 mg of an anti-LAG-3 antibody and about 240 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0412] In some aspects, the pharmaceutical composition comprises about 80 mg of an anti-LAG-3 antibody and about 480 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0413] In some aspects, the pharmaceutical composition comprises about 120 mg of an anti-LAG-3 antibody and about 360 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0414] In some aspects, the pharmaceutical composition comprises about 160 mg of an anti-LAG-3 antibody and about 480 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0415] In some aspects, the pharmaceutical composition comprises about 360 mg of an anti-LAG-3 antibody and about 360 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0416] In some aspects, the pharmaceutical composition comprises about 480 mg of an anti-LAG-3 antibody and about 480 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0417] In some aspects, the pharmaceutical composition comprises about 720 mg of an anti-LAG-3 antibody and about 360 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0418] In some aspects, the pharmaceutical composition comprises about 800 mg of an anti-LAG-3 antibody and about 200 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0419] In some aspects, the pharmaceutical composition comprises about 960 mg of an anti-LAG-3 antibody and about 480 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0420] In some aspects, the pharmaceutical composition comprises from about 5 mM to about 50 mM of histidine, from about 50 mM to about 300 mM of sucrose, from about 5 μM to about 1 mM of diethylenetriaminepentaacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA), and from about 0.001% to about 1% (w/v) of polysorbate or poloxamer (*e.g.*, polysorbate 80 (PS80), polysorbate 20 (PS20), poloxamer 188 (PX188), or any combination thereof).

[0421] In some aspects, the pharmaceutical composition comprises about 20 mM histidine, about 250 mM sucrose, about 50 μM DTPA, and 0.05% PS80.

[0422] In some aspects, the pH of the pharmaceutical composition is from about 5 to about 6.5. In some aspects, the pH is about 5.3 to about 6.3. In some aspects, the pH is 5.8. In some aspects, the pH is 5.7.

[0423] Provided herein is a vial, syringe, or intravenous bag comprising a pharmaceutical composition as described herein. In some aspects, the disclosure includes an autoinjector comprising a pharmaceutical composition described herein.

[0424] In some aspects, a vial comprises a pharmaceutical composition as described herein, and the vial further comprises a stopper and a seal. In some aspects, the total volume in the vial is about 5 mL, about 6 mL, about 7 mL, about 8 mL, about 9 mL, about 10 mL, about 11 mL, about 12 mL, about 13 mL, about 14 mL, about 15 mL, about 16 mL, about 17 mL, about 18 mL, about 19 mL, or about 20 mL.

IV. Kits

[0425] Also within the scope of the present invention are kits for treating a human subject with CRC as described herein, including unresectable or metastatic CRC, comprising any of the antibodies, therapeutic agents, and/or anti-cancer therapies described herein.

[0426] Kits typically include a label indicating the intended use of the contents of the kit and instructions for use. The term "label" includes any writing, or recorded material supplied on or with the kit, or which otherwise accompanies the kit.

[0427] Provided herein is a kit for treating a human subject afflicted with CRC, comprising: (a) an anti-LAG-3 antibody; and (b) an anti-PD-1 antibody or anti-PD-L1 antibody; and (c) instructions for using the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody in a method for treating a human subject afflicted with CRC.

[0428] The anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody can be provided at any of the amounts or combinations of amounts described herein.

[0429] In some aspects, the kit comprises relatlimab and an anti-PD-1 antibody or anti-PD-L1 antibody as described herein. In some aspects, the anti-PD-1 antibody is nivolumab, pembrolizumab, cemiplimab, or spartalizumab. In some aspects, the anti-PD-1 antibody is nivolumab. In some aspects, the anti-PD-L1 antibody is BMS-936559, atezolizumab, durvalumab, avelumab, STI-1014, CX-072, KN035, LY3300054, BGB-A333, ICO 36, FAZ053, or CK-301.

[0430] In some aspects, the kit comprises favezelimab and an anti-PD-1 antibody or anti-PD-L1 antibody as described herein. In some aspects, the anti-PD-1 antibody is nivolumab, pembrolizumab, cemiplimab, or spartalizumab. In some aspects, the anti-PD-1 antibody is pembrolizumab. In some aspects, the anti-PD-L1 antibody is BMS-936559, atezolizumab, durvalumab, avelumab, STI-1014, CX-072, KN035, LY3300054, BGB-A333, ICO 36, FAZ053, or CK-301.

[0431] In some aspects, the kit comprises fianlimab and an anti-PD-1 antibody or anti-PD-L1 antibody as described herein. In some aspects, the anti-PD-1 antibody is nivolumab, pembrolizumab, cemiplimab, or spartalizumab. In some aspects, the anti-PD-1 antibody is cemiplimab. In some aspects, the anti-PD-L1 antibody is BMS-936559, atezolizumab, durvalumab, avelumab, STI-1014, CX-072, KN035, LY3300054, BGB-A333, ICO 36, FAZ053, or CK-301.

[0432] In some aspects, the kit comprises ieramilimab and an anti-PD-1 antibody or anti-PD-L1 antibody as described herein. In some aspects, the anti-PD-1 antibody is nivolumab, pembrolizumab, cemiplimab, or spartalizumab. In some aspects, the anti-PD-1 antibody is spartalizumab. In some aspects, the anti-PD-L1 antibody is BMS-936559, atezolizumab, durvalumab, avelumab, STI-1014, CX-072, KN035, LY3300054, BGB-A333, ICO 36, FAZ053, or CK-301.

[0433] In some aspects, the kit comprises a ratio of the anti-LAG-3 antibody to the anti-PD-1 antibody or anti-PD-L1 antibody of about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:6, about 1:7, about 1:8, about 1:9, about 1:10, about 1:15, about 1:20, about 1:30, about 1:40, about 1:50, about 1:60, about 1:70, about 1:80, about 1:90, about 1:100, about 1:120, about 1:140, about 1:160, about 1:180, about 1:200, about 200:1, about 180:1, about 160:1, about 140:1, about 120:1, about 100:1, about 90:1, about 80:1, about 70:1, about 60:1, about 50:1, about 40:1, about 30:1, about 20:1, about 15:1, about 10:1, about 9:1, about 8:1, about 7:1, about 6:1, about 5:1, about 4:1, about 3:1, or about 2:1.

[0434] In some aspects, the kit comprises a ratio of anti-LAG-3 antibody to anti-PD-1 antibody or anti-PD-L1 antibody of about 1:6.

[0435] In some aspects, the kit comprises a ratio of the anti-LAG-3 antibody to the anti-PD-1 antibody or anti-PD-L1 antibody of about 1:3.

[0436] In some aspects, the kit comprises a ratio of the anti-LAG-3 antibody to the anti-PD-1 antibody or anti-PD-L1 antibody of about 1:1

[0437] In some aspects, the kit comprises a ratio of the anti-LAG-3 antibody to the anti-PD-1 antibody or anti-PD-L1 antibody of about 2:1.

[0438] In some aspects, the kit comprises a ratio of anti-LAG-3 antibody to anti-PD-1 antibody or anti-PD-L1 antibody of about 4:1.

[0439] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the kit is about 20 mg/mL, about 25 mg/mL, about 30 mg/mL, about 35 mg/mL, about 40 mg/mL, about 45 mg/mL, about 50 mg/mL, about 55 mg/mL, about 60 mg/mL, about 65 mg/mL, about 70 mg/mL, about 75 mg/mL, about 80 mg/mL, about 85 mg/mL, about 90 mg/mL, about 95 mg/mL, about 100 mg/mL, about 105 mg/mL, about 110 mg/mL, about 115 mg/mL, about 120 mg/mL, about 125 mg/mL, about 130 mg/mL, about 135 mg/mL, about 140 mg/mL, about 145 mg/mL, about 150 mg/mL, about 155 mg/mL, about 160 mg/mL, about 165 mg/mL, about 170 mg/mL, about 175 mg/mL, about 180 mg/mL, about 185 mg/mL, about 190 mg/mL, about 195 mg/mL, about 200 mg/mL, about 205 mg/mL, about 210 mg/mL, about 215 mg/mL, about 220 mg/mL, about 225 mg/mL, about 230 mg/mL, about 235 mg/mL, about 240 mg/mL, about 245 mg/mL, about 250 mg/mL, about 255 mg/mL, about 260 mg/mL, about 265 mg/mL, about 270 mg/mL, about 275 mg/mL, about 280 mg/mL, about 285 mg/mL, about 290 mg/mL, about 295 mg/mL, about 300 mg/mL, about 305 mg/mL, about 310 mg/mL, about 315 mg/mL, about 320 mg/mL, about 325 mg/mL, about 330 mg/mL, about 335 mg/mL, about 340 mg/mL, about 345 mg/mL, about 350 mg/mL, about 355 mg/mL, about 360 mg/mL, about 365 mg/mL, about 370 mg/mL, about 375 mg/mL, about 380 mg/mL, about 385 mg/mL, about 390 mg/mL, about 395 mg/mL, about 400 mg/mL, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg,

about 680 mg, about 690 mg, about 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 980 mg, about 990 mg, about 1000 mg, about 1010 mg, about 1020 mg, about 1030 mg, about 1040 mg, about 1050 mg, about 1060 mg, about 1070 mg, about 1080 mg, about 1090 mg, about 1100 mg, about 1110 mg, about 1120 mg, about 1130 mg, about 1140 mg, about 1150 mg, about 1160 mg, about 1170 mg, about 1180 mg, about 1190 mg, about 1200 mg, about 1210 mg, about 1220 mg, about 1230 mg, about 1240 mg, about 1250 mg, about 1260 mg, about 1270 mg, about 1280 mg, about 1290 mg, about 1300 mg, about 1310 mg, about 1320 mg, about 1330 mg, about 1340 mg, about 1350 mg, about 1360 mg, about 1370 mg, about 1380 mg, about 1390 mg, about 1400 mg, about 1410 mg, about 1420 mg, about 1430 mg, about 1440 mg, about 1450 mg, about 1460 mg, about 1470 mg, about 1480 mg, about 1490 mg, about 1500 mg, about 1510 mg, about 1520 mg, about 1530 mg, about 1540 mg, about 1550 mg, about 1560 mg, about 1570 mg, about 1580 mg, about 1590 mg, about 1600 mg, about 1610 mg, about 1620 mg, about 1630 mg, about 1640 mg, about 1650 mg, about 1660 mg, about 1670 mg, about 1680 mg, about 1690 mg, about 1700 mg, about 1710 mg, about 1720 mg, about 1730 mg, about 1740 mg, about 1750 mg, about 1760 mg, about 1770 mg, or about 1780 mg.

[0440] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the kit is about 25 mg/mL.

[0441] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the kit is about 50 mg/mL.

[0442] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the kit is about 150 mg/mL.

[0443] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the kit is about 50 mg.

[0444] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the kit is about 320 mg.

[0445] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the kit is about 480 mg.

[0446] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the kit is about 560 mg.

[0447] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the kit is about 640 mg.

[0448] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the kit is about 720 mg.

[0449] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the kit is about 960 mg.

[0450] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the kit is about 1000 mg.

[0451] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the kit is about 1080 mg.

[0452] In some aspects, the total amount of anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies in the kit is about 1440 mg.

[0453] In some aspects, the kit comprises about 10 mg/mL, about 12.5 mg/mL, about 15 mg/mL, about 17.5 mg/mL, about 20 mg/mL, about 22.5 mg/mL, about 25 mg/mL, about 27.5 mg/mL, about 30 mg/mL, about 32.5 mg/mL, about 35 mg/mL, about 37.5 mg/mL, about 40 mg/mL, about 42.5 mg/mL, about 45 mg/mL, about 47.5 mg/mL, about 50 mg/mL, about 55 mg/mL, about 60 mg/mL, about 65 mg/mL, about 70 mg/mL, about 75 mg/mL, about 80 mg/mL, about 85 mg/mL, about 90 mg/mL, about 95 mg/mL, about 100 mg/mL, about 105 mg/mL, about 110 mg/mL, about 115 mg/mL, about 120 mg/mL, about 125 mg/mL, about 130 mg/mL, about 135 mg/mL, about 140 mg/mL, about 145 mg/mL, about 150 mg/mL, about 155 mg/mL, about 160 mg/mL, about 165 mg/mL, about 170 mg/mL, about 175 mg/mL, about 180 mg/mL, about 185 mg/mL, about 190 mg/mL, about 195 mg/mL, about 200 mg/mL, about 7 mg, about 21 mg, about 70 mg, about 80 mg, about 120 mg, about 160 mg, about 200 mg, about 210 mg, about 300 mg, about 360 mg, about 400 mg, about 480 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 960 mg, about 1000 mg, about 1100 mg, about 1200 mg, or about 1300 mg of an anti-LAG-3 antibody.

[0454] In some aspects, the kit comprises about 10 mg/mL, about 12.5 mg/mL, about 15 mg/mL, about 17.5 mg/mL, about 20 mg/mL, about 22.5 mg/mL, about 25 mg/mL, about 27.5 mg/ml, about 30 mg/mL, about 32.5 mg/mL, about 35 mg/mL, about 37.5 mg/mL,

about 40 mg/mL, about 42.5 mg/mL, about 45 mg/mL, about 47.5 mg/mL, about 50 mg/mL, about 55 mg/mL, about 60 mg/mL, about 65 mg/mL, about 70 mg/mL, about 75 mg/mL, about 80 mg/mL, about 85 mg/mL, about 90 mg/mL, about 95 mg/mL, about 100 mg/mL, about 105 mg/mL, about 110 mg/mL, about 115 mg/mL, about 120 mg/mL, about 125 mg/mL, 130 mg/mL, about 135 mg/mL, about 140 mg/mL, about 145 mg/mL, about 150 mg/mL, about 155 mg/mL, about 160 mg/mL, about 165 mg/mL, about 170 mg/mL, about 175 mg/mL, about 180 mg/mL, about 185 mg/mL, about 190 mg/mL, about 195 mg/mL, about 200 mg/mL, about 40 mg, about 100 mg, about 200 mg, about 240 mg, about 300 mg, about 350 mg, about 360 mg, about 400 mg, or about 480 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0455] In some aspects, the kit comprises about 12.5 mg/mL of an anti-LAG-3 antibody and about 37.5 mg/mL of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0456] In some aspects, the kit comprises about 20 mg/mL of an anti-LAG-3 antibody and about 5 mg/mL of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0457] In some aspects, the kit comprises about 75 mg/mL of an anti-LAG-3 antibody and about 75 mg/mL of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0458] In some aspects, the kit comprises about 100 mg/mL of an anti-LAG-3 antibody and about 50 mg/mL of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0459] In some aspects, the kit comprises about 80 mg of an anti-LAG-3 antibody and about 240 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0460] In some aspects, the kit comprises about 80 mg of an anti-LAG-3 antibody and about 480 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0461] In some aspects, the kit comprises about 120 mg of an anti-LAG-3 antibody and about 360 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0462] In some aspects, the kit comprises about 160 mg of an anti-LAG-3 antibody and about 480 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0463] In some aspects, the kit comprises about 360 mg of an anti-LAG-3 antibody and about 360 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0464] In some aspects, the kit comprises about 480 mg of an anti-LAG-3 antibody and about 480 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0465] In some aspects, the kit comprises about 720 mg of an anti-LAG-3 antibody and about 360 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0466] In some aspects, the kit comprises about 800 mg of an anti-LAG-3 antibody and about 200 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0467] In some aspects, the kit comprises about 960 mg of an anti-LAG-3 antibody and about 480 mg of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0468] Provided herein is a kit for treating a human subject afflicted with CRC, comprising: (a) about 480 mg of an anti-LAG-3 antibody; (b) about 480 mg of an anti-PD-1 antibody or anti-PD-L1 antibody; and (c) instructions for using the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody in a method for treating a human subject afflicted with CRC.

[0469] In some aspects, the anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies are co-packaged in a single unit dosage form.

[0470] In some aspects, the anti-LAG-3 and anti-PD-1 antibodies or anti-PD-L1 antibodies are packaged as separate unit dosage forms.

[0471] In some aspects, about 80 mg of the anti-LAG-3 antibody is provided in a unit dosage form.

[0472] In some aspects, about 120 mg of the anti-LAG-3 antibody is provided in a unit dosage form.

[0473] In some aspects, about 160 mg of the anti-LAG-3 antibody is provided in a unit dosage form.

[0474] In some aspects, about 360 mg of the anti-LAG-3 antibody is provided in a unit dosage form.

[0475] In some aspects, about 480 mg of the anti-LAG-3 antibody is provided in a unit dosage form.

[0476] In some aspects, about 960 mg of the anti-LAG-3 antibody is provided in a unit dosage form.

[0477] In some aspects, about 50 mg/mL of the anti-LAG-3 antibody is provided in a unit dosage form.

[0478] In some aspects, about 100 mg/mL of the anti-LAG-3 antibody is provided in a unit dosage form.

[0479] In some aspects, about 130 mg/mL of the anti-LAG-3 antibody is provided in a unit dosage form.

[0480] In some aspects, about 150 mg/mL of the anti-LAG-3 antibody is provided in a unit dosage form.

[0481] In some aspects, about 175 mg/mL of the anti-LAG-3 antibody is provided in a unit dosage form.

[0482] In some aspects, about 200 mg/mL of the anti-LAG-3 antibody is provided in a unit dosage form.

[0483] In some aspects, about 40 mg of the anti-PD-1 antibody or anti-PD-L1 antibody is provided in a unit dosage form.

[0484] In some aspects, about 100 mg of the anti-PD-1 antibody or anti-PD-L1 antibody is provided in a unit dosage form.

[0485] In some aspects, about 240 mg of the anti-PD-1 antibody or anti-PD-L1 antibody is provided in a unit dosage form.

[0486] In some aspects, about 360 mg of the anti-PD-1 antibody or anti-PD-L1 antibody is provided in a unit dosage form.

[0487] In some aspects, about 480 mg of the anti-PD-1 antibody or anti-PD-L1 antibody is provided in a unit dosage form.

[0488] In some aspects, about 10 mg/mL of the anti-PD-1 antibody or anti-PD-L1 antibody is provided in a unit dosage form.

[0489] In some aspects, about 50 mg/mL of the anti-PD-1 antibody or anti-PD-L1 antibody is provided in a unit dosage form.

[0490] In some aspects, about 100 mg/mL of the anti-PD-1 antibody or anti-PD-L1 antibody is provided in a unit dosage form.

[0491] In some aspects, about 150 mg/mL of the anti-PD-1 antibody or anti-PD-L1 antibody is provided in a unit dosage form.

[0492] In some aspects, about 175 mg/mL of the anti-PD-1 antibody or anti-PD-L1 antibody is provided in a unit dosage form.

[0493] In some aspects, about 200 mg/mL of the anti-PD-1 antibody or anti-PD-L1 antibody is provided in a unit dosage form.

[0494] In some aspects, the unit dosage form comprises from about 5 mM to about 50 mM of histidine, from about 50 mM to about 300 mM of sucrose, from about 5 μM to about 1 mM of diethylenetriaminepentaacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA), and from about 0.001% to about 1% (w/v) of polysorbate or poloxamer (*e.g.*,

polysorbate 80 (PS80), polysorbate 20 (PS20), poloxamer 188 (PX188), or any combination thereof).

[0495] In some aspects, the unit dosage form comprises about 20 mM histidine, about 250 mM sucrose, about 50 μM DTPA, and 0.05% PS80.

[0496] In some aspects, the unit dosage form comprises a pH of from about 5 to about 6.5. In some aspects, the pH is about 5.3 to about 6.3. In some aspects, the pH is 5.8. In some aspects, the pH is 5.7.

[0497] In some aspects, the unit dosage form is a vial, syringe, or intravenous bag. In some aspects, the unit dosage form is an autoinjector. In some aspects, the unit dosage form is a vial comprising a stopper and a seal. In some aspects, the total volume in the vial is about 5 mL, about 6 mL, about 7 mL, about 8 mL, about 9 mL, about 10 mL, about 11 mL, about 12 mL, about 13 mL, about 14 mL, about 15 mL, about 16 mL, about 17 mL, about 18 mL, about 19 mL, or about 20 mL.

[0498] In some aspects, the kit provides instructions for administering the anti-LAG-3 antibody and/or the anti-PD-1 antibody or anti-PD-L1 antibody intravenously for about 30 minutes.

[0499] All of the references cited above, as well as all references cited herein, are incorporated herein by reference in their entireties.

[0500] The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

EXAMPLE 1

Safety and Efficacy of Anti-LAG-3 Antibody in Combination with Anti-PD-1 Antibody in Treatment of Colorectal Cancer

[0501] An open-label, sponsor blinded, multi-center Phase 3 trial will evaluate the safety and efficacy of a fixed-dose combination of relatlimab and nivolumab as compared to a regorafenib or trifluridine/tipiracil (TAS-102) standard of care therapy in the treatment of proficient mismatch repair (pMMR)/microsatellite stable (MSS) metastatic colorectal cancer (mCRC).

[0502] Patients will be ≥ 18 years, or local age of majority, and will be selected based on eligibility criteria that includes the following: (1) histologically-confirmed, previously-

treated CRC with adenocarcinoma histology and metastatic or recurrent unresectable disease at study entry; (2) confirmed tumor MSS/pMMR status as per local standard testing, with MSS/pMMR results from initial diagnosis being acceptable; (3) progression during or within approximately three months following the last administration of approved standard therapies (at least one but not more than four prior lines of therapies), which must include a fluoropyrimidine, oxaliplatin, irinotecan, an anti-VEGF therapy, and anti-EGFR therapy (if KRAS wild-type), if approved in the respective country; i) participants treated in adjuvant/neoadjuvant setting should have progressed during or within six months of completion of adjuvant therapy to be considered refractory to that therapy; ii) adjuvant/neoadjuvant therapy or maintenance therapy will NOT be considered as one line of prior therapy for study entry unless disease progressed during or within six months of completion of that adjuvant therapy; iii) participants who have KRAS mutant tumors and have received FOLFOXIRI with an anti-VEGF therapy for first-line treatment will be eligible to enroll in the study; iv) participants who were intolerant to prior systemic chemotherapy regimens will be eligible if there is documented evidence of clinically significant intolerance despite adequate supportive measures; (4) KRAS mutation status must be documented based on available historical or local testing results as part of medical history prior to study enrollment; (5) NRAS (extended RAS) and BRAF mutation status are strongly encouraged as part of medical history if testing is available from historical or local results prior to study treatment; (6) evaluable PD-L1 expression results during the screening period prior to randomization; (7) measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided the lesion(s) have demonstrated clear progression and can be measured accurately; and (8) Eastern Cooperative Oncology Group PS 0 or 1.

[0503] Patients will not be eligible for the study if they have had prior treatment with immunotherapy (anti-LAG-3, anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) with regorafenib or with TAS-102.

[0504] Approximately 700 patients will be randomized 1:1 in Arms A and B, respectively.

[0505] Patients in Arm A will be administered a fixed dose combination of 480 mg of relatlimab and 480 mg of nivolumab on Day 1 of every 4-week cycle (Q4W).

[0506] Patients in Arm B will be administered either 160 mg daily of regorafenib for 21 days of a 28-day cycle or 35 mg/m^2 twice daily of TAS-102 for Days 1 to 5 and Days 8 to 12 of each 28-day cycle. The study is designed to allow the investigator the choice of administering either regorafenib or TAS-102 given the difference in toxicity profiles of these two agents, taking into consideration the patient's medical status and the availability of the drugs.

[0507] Stratification factors for randomization will be PD-L1 combined positive score (CPS) expression level (≥ 1 vs < 1 [including indeterminate expression]), region (Asia vs US/Canada/Western Europe/Australia vs Rest of World), and KRAS status (wild-type vs mutant/amplified).

[0508] PD-L1 expression on tumor and immune cells will be measured using analytically validated immunohistochemical (IHC) assay. PD-L1 expression will be assessed primarily based on a CPS, defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. PD-L1 positivity will be defined by CPS ≥1. PD-L1 may be also assessed by tumor proportion score (TPS), which reflects the percentage of tumor cells that are positive for PD-L1 expression. IHC analysis will also be used to evaluate an association between tumor LAG-3 status (defined as the percentage of LAG-3+ cells in a tumor specimen) and treatment efficacy and/or safety. The effect of LAG-3 positivity using 1% threshold and, potentially, other cutoff levels will be interrogated retrospectively.

[0509] Relatlimab-nivolumab FDC administration will continue until progression, toxicity, withdrawal of consent, or a maximum of 2 years, whichever occurs first. Continuous safety evaluations and tumor assessments will guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit.

[0510] Regorafenib or TAS-102 administration will continue until progression, toxicity, or withdrawal of consent, whichever occurs first.

SEQUENCES

SEQ ID NO:1 Heavy Chain Amino Acid Sequence; Anti-LAG-3 mAb (BMS-986016)

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSDYYWNWIRQPPGKGLEWIGEINHRGSTNSNPSLKS
RVTLSLDTSKNQFSLKLRSVTAADTAVYYCAFGYSDYEYNWFDPWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO:2 Light Chain Amino Acid Sequence; Anti-LAG-3 mAb (BMS-986016)

EIVLTQSPATLSLSPGERATLSCRASQSISSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGS
GSGTDFTLTISSLEPEDFAVYYCQQRSNWPLTFGQGTNLEIKRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE
VTHQGLSSPVTKSFNRGEC

SEQ ID NO:3 Heavy Chain Variable Region (VH) Amino Acid Sequence; Anti-LAG-3 mAb (BMS-986016)

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSDYYWNWIRQPPGKGLEWIGEINHRGSTNSNPSLKS
RVTLSLDTSKNQFSLKLRSVTAADTAVYYCAFGYSDYEYNWFDPWGQGTLVTVSS

SEQ ID NO:4 Light Chain Variable Region (VL) Amino Acid Sequence; Anti-LAG-3 mAb (BMS-986016)

EIVLTQSPATLSLSPGERATLSCRASQSISSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGS
GSGTDFTLTISSLEPEDFAVYYCQQRSNWPLTFGQGTNLEIK

SEQ ID NO:5 Heavy Chain CDR1 Amino Acid Sequence; Anti-LAG-3 mAb (BMS-986016)

DYYWN

SEQ ID NO:6 Heavy Chain CDR2 Amino Acid Sequence; Anti-LAG-3 mAb (BMS-986016)

EINHRGSTNSNPSLKS

SEQ ID NO:7 Heavy Chain CDR3 Amino Acid Sequence; Anti-LAG-3 mAb (BMS-986016)

GYSDYEYNWFDP

SEQ ID NO:8 Light Chain CDR1 Amino Acid Sequence; Anti-LAG-3 mAb (BMS-986016)

RASQSISSYLA

SEQ ID NO:9 Light Chain CDR2 Amino Acid Sequence; Anti-LAG-3 mAb (BMS-986016)

DASNRAT

SEQ ID NO:10 Light Chain CDR3 Amino Acid Sequence; Anti-LAG-3 mAb (BMS-986016)

QQRSNWPLT

SEQ ID NO:11 Heavy Chain Amino Acid Sequence; Anti-PD-1 mAb (BMS-936558)

QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYADSVK
GRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSASTKGPSVFPLAPCSRS
TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYT
CNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
QEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI
EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO:12 Light Chain Amino Acid Sequence; Anti-PD-1 mAb (BMS-936558)

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGS
GSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

SEQ ID NO:13 Heavy Chain Variable Region (VH) Amino Acid Sequence; Anti-PD-1 mAb (BMS-936558)

QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYADSVK
GRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSS

SEQ ID NO:14 Light Chain Variable Region (VL) Amino Acid Sequence; Anti-PD-1 mAb (BMS-936558)

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGS
GSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIK

SEQ ID NO:15 Heavy Chain CDR1 Amino Acid Sequence; Anti-PD-1 mAb (BMS-936558)

NSGMH

SEQ ID NO:16 Heavy Chain CDR2 Amino Acid Sequence; Anti-PD-1 mAb (BMS-936558)

VIWYDGSKRYYADSVKG

SEQ ID NO:17 Heavy Chain CDR3 Amino Acid Sequence; Anti-PD-1 mAb (BMS-936558)

NDDY

SEQ ID NO:18 Light Chain CDR1 Amino Acid Sequence; Anti-PD-1 mAb (BMS-936558)

RASQSVSSYLA

SEQ ID NO:19 Light Chain CDR2 Amino Acid Sequence; Anti-PD-1 mAb (BMS-936558)

DASNRAT

SEQ ID NO:20 Light Chain CDR3 Amino Acid Sequence; Anti-PD-1 mAb (BMS-936558)

QQSSNWPRT

SEQ ID NO:21 Heavy Chain Amino Acid Sequence; Anti-LAG-3 mAb (BMS-986016) without terminal lysine

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSDYYWNWIRQPPGKGLEWIGEINHRGSTNSNPSLKS
RVTLSLDTSKNQFSLKLRSVTAADTAVYYCAFGYSDYEYNWFDPWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG

SEQ ID NO:22 Lymphocyte Activation Gene 3 Protein Amino Acid Sequence (Homo Sapiens, NP_002277)

MWEAQFLGLLFLQPLWVAPVKPLQPGAEVPVVWAQEGAPAQLPCSPTIPLQDLSLLRRAGVTWQH
QPDSGPPAAAPGHPLAPGPHPAAPSSWGPRPRRYTVLSVGPGGLRSGRLPLQPRVQLDERGRQRG
DFSLWLRPARRADAGEYRAAVHLRDRALSCRLRLRLGQASMTASPPGSLRASDWVILNCSFSRPD
RPASVHWFRNRGQGRVPVRESPHHHLAESFLFLPQVSPMDSGPWGCILTYRDGFNVSIMYNLTVL
GLEPPTPLTVYAGAGSRVGLPCRLPAGVGTRSFLTAKWTPPGGGPDLLVTGDNGDFTLRLEDVSQ
AQAGTYTCHIHLQEQQLNATVTLAIITVTPKSFGSPGSLGKLLCEVTPVSGQERFVWSSLDTPSQ
RSFSGPWLEAQEAQLLSQPWQCQLYQGERLLGAAVYFTELSSPGAQRSGRAPGALPAGHLLLFLI
LGVLSLLLLVTGAFGFHLWRRQWRPRRFSALEQGIHPPQAQSKIEELEQEPEPEPEPEPEPEPEP
EPEQL

SEQ ID NO:23 Heavy Chain Amino Acid Sequence; Anti-LAG-3 mAb (REGN3767)

QVQLVESGGGVVQPGRSLRLSCVASGFTFSSYGMHWVRQAPGKGLEWVAIIWYDGSNKYY
ADSVKGRFTISRDNSKNTQYLQMNSLRAEDTAVYYCASVATSGDFDYYGMDVWGQGTTVT
VSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPPVAGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ
EGNVFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO:24 Light Chain Amino Acid Sequence; Anti-LAG-3 mAb (REGN3767)

EIVLTQSPATLSLSPGERTTLSCRASQRISTYLAWYQQKPGQAPRLLIYDASKRATGIPA
RFSGSGSGTGFTLTISSLEPEDFAVYYCQQRSNWPLTFGGGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:25 Heavy Chain Variable Region (VH) Amino Acid Sequence; Anti-LAG-3 mAb (REGN3767)

QVQLVESGGGVVQPGRSLRLSCVASGFTFSSYGMHWVRQAPGKGLEWVAIIWYDGSNKYY
ADSVKGRFTISRDNSKNTQYLQMNSLRAEDTAVYYCASVATSGDFDYYGMDVWGQGTTVT
VSS

SEQ ID NO:26 Light Chain Variable Region (VL) Amino Acid Sequence; Anti-LAG-3 mAb (REGN3767)

EIVLTQSPATLSLSPGERTTLSCRASQRISTYLAWYQQKPGQAPRLLIYDASKRATGIPA
RFSGSGSGTGFTLTISSLEPEDFAVYYCQQRSNWPLTFGGGTKVEIK

SEQ ID NO:27 Heavy Chain CDR1 Amino Acid Sequence; Anti-LAG-3 mAb (REGN3767)

GFTFSSYG

SEQ ID NO:28 Heavy Chain CDR2 Amino Acid Sequence; Anti-LAG-3 mAb (REGN3767)

IWYDGSNK

SEQ ID NO:29 Heavy Chain CDR3 Amino Acid Sequence; Anti-LAG-3 mAb (REGN3767)

ASVATSGDFDYYGMDV

SEQ ID NO:30 Light Chain CDR1 Amino Acid Sequence; Anti-LAG-3 mAb (REGN3767)

QRISTY

Light Chain CDR2 Amino Acid Sequence; Anti-LAG-3 mAb (REGN3767)

DAS

SEQ ID NO:32 Light Chain CDR3 Amino Acid Sequence; Anti-LAG-3 mAb (REGN3767)

QQRSNWPLT

SEQ ID NO:33 Heavy Chain Amino Acid Sequence; Anti-PD-1 mAb (REGN2810)

EVQLLESGGVLVQPGGSLRLSCAASGFTFSNFGMTWVRQAPGKGLEWVSGISGGGRDTYF
ADSVKGRFTISRDNSKNTLYLQMNSLKGEDTAVYYCVKWGNIYFDYWGQGTLVTVSSAST
KGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVF
SCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO:34 Light Chain Amino Acid Sequence; Anti-PD-1 mAb (REGN2810)

DIQMTQSPSSLSASVGDSITITCRASLSINTFLNWYQQKPGKAPNLLIYAASSLHGGVPS
RFSGSGSGTDFTLTIRTLQPEDFATYYCQQSSNTPFTFGPGTVVDFRRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:35 Heavy Chain Variable Region (VH) Amino Acid Sequence; Anti-PD-1 mAb (REGN2810)

EVQLLESGGVLVQPGGSLRLSCAASGFTFSNFGMTWVRQAPGKGLEWVSGISGGGRDTYF
ADSVKGRFTISRDNSKNTLYLQMNSLKGEDTAVYYCVKWGNIYFDYWGQGTLVTVSS

SEQ ID NO:36 Light Chain Variable Region (VL) Amino Acid Sequence; Anti-PD-1 mAb (REGN2810)

DIQMTQSPSSLSASVGDSITITCRASLSINTFLNWYQQKPGKAPNLLIYAASSLHGGVPS
RFSGSGSGTDFTLTIRTLQPEDFATYYCQQSSNTPFTFGPGTVVDFR

SEQ ID NO:37 Heavy Chain CDR1 Amino Acid Sequence; Anti-PD-1 mAb (REGN2810)

GFTFSNFG

SEQ ID NO:38 Heavy Chain CDR2 Amino Acid Sequence; Anti-PD-1 mAb (REGN2810)

ISGGGRDT

SEQ ID NO:39 Heavy Chain CDR3 Amino Acid Sequence; Anti-PD-1 mAb (REGN2810)

VKWGNIYFDY

SEQ ID NO:40 Light Chain CDR1 Amino Acid Sequence; Anti-PD-1 mAb (REGN2810)

LSINTF

Light Chain CDR2 Amino Acid Sequence; Anti-PD-1 mAb (REGN2810)

AAS

SEQ ID NO:42 Light Chain CDR3 Amino Acid Sequence; Anti-PD-1 mAb (REGN2810)

QQSSNTPFT

SEQ ID NO:43 Heavy Chain Amino Acid Sequence; Anti-LAG-3 mAb (LAG525)

QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQARGQRLEWIGWINTDTGEPTY
ADDFKGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTT
VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFL
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQ
FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ

EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS
RWQEGNVFSCSVMHEALHNHYTQKSLSLSLG

SEQ ID NO:44 Heavy Chain Amino Acid Sequence; Anti-LAG-3 mAb (LAG525)

QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQAPGQGLEWMGWINTDTGEPTY
ADDFKGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTT
VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFL
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQ
FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS
RWQEGNVFSCSVMHEALHNHYTQKSLSLSLG

SEQ ID NO:45 Light Chain Amino Acid Sequence; Anti-LAG-3 mAb (LAG525)

DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYLQKPGQSPQLLIYYTSTLHLGVPS
RFSGSGSGTEFTLTISSLQPDDFATYYCQQYYNLPWTFGQGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:46 Light Chain Amino Acid Sequence; Anti-LAG-3 mAb (LAG525)

DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYQQKPGKAPKLLIYYTSTLHLGIPP
RFSGSGYGTDFTLTINNIESEDAAYYFCQQYYNLPWTFGQGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:47 Heavy Chain Variable Region (VH) Amino Acid Sequence; Anti-LAG-3 mAb (LAG525)

QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQARGQRLEWIGWINTDTGEPTY
ADDFKGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTT
VTVSS

SEQ ID NO:48 Heavy Chain Variable Region (VH) Amino Acid Sequence; Anti-LAG-3 mAb (LAG525)

QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQAPGQGLEWMGWINTDTGEPTY
ADDFKGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTT
VTVSS

SEQ ID NO:49 Light Chain Variable Region (VL) Amino Acid Sequence; Anti-LAG-3 mAb (LAG525)

DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYLQKPGQSPQLLIYYTSTLHLGVPS
RFSGSGSGTEFTLTISSLQPDDFATYYCQQYYNLPWTFGQGTKVEIK

SEQ ID NO:50 Light Chain Variable Region (VL) Amino Acid Sequence; Anti-LAG-3 mAb (LAG525)

DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYQQKPGKAPKLLIYYTSTLHLGIPP
RFSGSGYGTDFTLTINNIESEDAAYYFCQQYYNLPWTFGQGTKVEIK

SEQ ID NO:51 Heavy Chain CDR1 Amino Acid Sequence; Anti-LAG-3 mAb (LAG525)

NYGMN

SEQ ID NO:52 Heavy Chain CDR2 Amino Acid Sequence; Anti-LAG-3 mAb (LAG525)

WINTDTGEPTYADDFKG

SEQ ID NO:53 Heavy Chain CDR3 Amino Acid Sequence; Anti-LAG-3 mAb (LAG525)

NPPYYYGTNNAEAMDY

SEQ ID NO:54 Light Chain CDR1 Amino Acid Sequence; Anti-LAG-3 mAb (LAG525)

SSSQDISNYLN

SEQ ID NO:55 Light Chain CDR2 Amino Acid Sequence; Anti-LAG-3 mAb (LAG525)

YTSTLHL

SEQ ID NO:56 Light Chain CDR3 Amino Acid Sequence; Anti-LAG-3 mAb (LAG525)

QQYYNLPWT

SEQ ID NO:57 Heavy Chain Amino Acid Sequence; Anti-PD-1 mAb (PDR001)

EVQLVQSGAEVKKPGESLRISCKGSGYTFTTYWMHWVRQATGQGLEWMGNIYPGTGGSNF
DEKFKNRVTITADKSTSTAYMELSSLRSEDTAVYYCTRWTTGTGAYWGQGTTVTVSSAST
KGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVF
SCSVMHEALHNHYTQKSLSLSLG

SEQ ID NO:58 Light Chain Amino Acid Sequence; Anti-PD-1 mAb (PDR001)

EIVLTQSPATLSLSPGERATLSCKSSQSLLDSGNQKNFLTWYQQKPGQAPRLLIYWASTR
ESGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQNDYSYPYTFGQGTKVEIKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:59 Heavy Chain Variable Region (VH) Amino Acid Sequence; Anti-PD-1 mAb (PDR001)

EVQLVQSGAEVKKPGESLRISCKGSGYTFTTYWMHWVRQATGQGLEWMGNIYPGTGGSNF
DEKFKNRVTITADKSTSTAYMELSSLRSEDTAVYYCTRWTTGTGAYWGQGTTVTVSS

SEQ ID NO:60 Light Chain Variable Region (VL) Amino Acid Sequence; Anti-PD-1 mAb (PDR001)

EIVLTQSPATLSLSPGERATLSCKSSQSLLDSGNQKNFLTWYQQKPGQAPRLLIYWASTR
ESGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQNDYSYPYTFGQGTKVEIK

SEQ ID NO:61 Heavy Chain CDR1 Amino Acid Sequence; Anti-PD-1 mAb (PDR001)

TYWMH

SEQ ID NO:62 Heavy Chain CDR2 Amino Acid Sequence; Anti-PD-1 mAb (PDR001)

NIYPGTGGSNFDEKFKN

SEQ ID NO:63 Heavy Chain CDR3 Amino Acid Sequence; Anti-PD-1 mAb (PDR001)

WTTGTGAY

SEQ ID NO:64 Light Chain CDR1 Amino Acid Sequence; Anti-PD-1 mAb (PDR001)

KSSQSLLDSGNQKNFLT

SEQ ID NO:65 Light Chain CDR2 Amino Acid Sequence; Anti-PD-1 mAb (PDR001)

WASTRES

SEQ ID NO:66 Light Chain CDR3 Amino Acid Sequence; Anti-PD-1 mAb (PDR001)

QNDYSYPYT

SEQ ID NO:67 Heavy Chain Amino Acid Sequence; Anti-LAG-3 mAb (MK4280)

QMQLVQSGPEVKKPGTSVKVSCKASGYTFTDYNVDWVRQARGQRLEWIGDINPNDGGTIY
AQKFQERVTITVDKSTSTAYMELSSLRSEDTAVYYCARNYRWFGAMDHWGQGTTVTVSSA
STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGN
VFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO:68 Light Chain Amino Acid Sequence; Anti-LAG-3 mAb (MK4280)

DIVMTQTPLSLSVTPGQPASISCKASQSLDYEGDSDMNWYLQKPGQPPQLLIYGASNLES
GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSTEDPRTFGGGTKVEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS

STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:69 Heavy Chain Variable Region (VH) Amino Acid Sequence; Anti-LAG-3 mAb (MK4280)

QMQLVQSGPEVKKPGTSVKVSCKASGYTFTDYNVDWVRQARGQRLEWIGDINPNDGGTIY
AQKFQERVTITVDKSTSTAYMELSSLRSEDTAVYYCARNYRWFGAMDHWGQGTTVTVSS

SEQ ID NO:70 Light Chain Variable Region (VL) Amino Acid Sequence; Anti-LAG-3 Anti-LAG-3 mAb (MK4280)

DIVMTQTPLSLSVTPGQPASISCKASQSLDYEGDSDMNWYLQKPGQPPQLLIYGASNLES
GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSTEDPRTFGGGTKVEIK

SEQ ID NO:71 Heavy Chain CDR1 Amino Acid Sequence; Anti-LAG-3 mAb (MK4280)

DYNVD

SEQ ID NO:72 Heavy Chain CDR2 Amino Acid Sequence; Anti-LAG-3 mAb (MK4280)

DINPNDGGTIYAQKFQE

SEQ ID NO:73 Heavy Chain CDR3 Amino Acid Sequence; Anti-LAG-3 mAb (MK4280)

NYRWFGAMDH

SEQ ID NO:74 Light Chain CDR1 Amino Acid Sequence; Anti-LAG-3 mAb (MK4280)

KASQSLDYEGDSDMN

SEQ ID NO:75 Light Chain CDR2 Amino Acid Sequence; Anti-LAG-3 mAb (MK4280)

GASNLES

SEQ ID NO:76 Light Chain CDR3 Amino Acid Sequence; Anti-LAG-3 mAb (MK4280)

QQSTEDPRT

SEQ ID NO:77 Heavy Chain Amino Acid Sequence; Anti-PD-1 mAb (MK3475)

QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSS
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEG
NVFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO:78 Light Chain Amino Acid Sequence; Anti-PD-1 mAb (MK3475)

EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLES
GVPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS
STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:79 Heavy Chain Variable Region (VH) Amino Acid Sequence; Anti-PD-1 mAb (MK3475)

QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSS

SEQ ID NO:80 Light Chain Variable Region (VL) Amino Acid Sequence; Anti-PD-1 mAb (MK3475)

EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLES
GVPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIK

SEQ ID NO:81 Heavy Chain CDR1 Amino Acid Sequence; Anti-PD-1 mAb (MK3475)

NYYMY

SEQ ID NO:82 Heavy Chain CDR2 Amino Acid Sequence; Anti-PD-1 mAb (MK3475)

GINPSNGGTNFNEKFKN

SEQ ID NO:83 Heavy Chain CDR3 Amino Acid Sequence; Anti-PD-1 mAb (MK3475)

RDYRFDMGFDY

SEQ ID NO:84 Light Chain CDR1 Amino Acid Sequence; Anti-PD-1 mAb (MK3475)

RASKGVSTSGYSYLH

SEQ ID NO:85 Light Chain CDR2 Amino Acid Sequence; Anti-PD-1 mAb (MK3475)

LASYLES

SEQ ID NO:86 Light Chain CDR3 Amino Acid Sequence; Anti-PD-1 mAb (MK3475)

QHSRDLPLT

WHAT IS CLAIMED IS:

1. A method of treating a human subject afflicted with colorectal carcinoma (CRC), the method comprising administering to the subject:
   (a) about 480 mg of an anti-LAG-3 antibody, and
   (b) about 480 mg of an anti-PD-1 or anti-PD-L1 antibody.

2. The method of claim 1, wherein the anti-LAG-3 antibody is a full-length antibody.

3. The method of claim 1 or 2, wherein the anti-LAG-3 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody.

4. The method of claim 3, wherein the multispecific antibody is a dual-affinity re-targeting antibody (DART), a DVD-Ig, or bispecific antibody.

5. The method of claim 1, wherein the anti-LAG-3 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

6. The method of any one of claims 1-5, wherein the anti-LAG-3 antibody is BMS-986016 (relatlimab), IMP731 (H5L7BW), MK4280 (28G-10, favezelimab), REGN3767 (fianlimab), GSK2831781, humanized BAP050, IMP-701 (LAG525, ieramilimab), aLAG3(0414), aLAG3(0416), Sym022, TSR-033, TSR-075, XmAb841 (XmAb22841), MGD013 (tebotelimab), BI754111, FS118, P 13B02-30, AVA-017, 25F7, AGEN1746, RO7247669, INCAGN02385, IBI-110, EMB-02, IBI-323, LBL-007, ABL501, or comprises an antigen binding portion thereof.

7. The method of any one of claims 1-6, wherein the anti-LAG-3 antibody comprises CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:3, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:4.

8. The method of any one of claims 1-7, wherein the anti-LAG-3 antibody comprises:
   (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:5;

(b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:6;

(c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:7;

(d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:8;

(e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:9; and

(f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:10.

9. The method of any one of claims 1-8, wherein the anti-LAG-3 antibody comprises heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:3 and 4, respectively.

10. The method of any one of claims 1-4 and 6-9, wherein the anti-LAG-3 antibody comprises heavy and light chains comprising the sequences set forth in SEQ ID NOs:1 and 2, respectively.

11. The method of any one of claims 1-4 and 6-9, wherein the anti-LAG-3 antibody comprises heavy and light chains comprising the sequences set forth in SEQ ID NOs:21 and 2, respectively.

12. The method of any one of claims 1-11, wherein the anti-PD-1 antibody is a full-length antibody.

13. The method of claim 12, wherein the anti-PD-1 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody.

14. The method of claim 13, wherein the multispecific antibody is a DART, a DVD-Ig, or bispecific antibody.

15. The method of any one of claims 1-11, wherein the anti-PD-1 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

16. The method of any one of claims 1-15, wherein the anti-PD-1 antibody is nivolumab, pembrolizumab, PDR001 (spartalizumab), MEDI-0680, TSR-042, cemiplimab, JS001, PF-06801591, BGB-A317, BI 754091, INCSHR1210, GLS-010, AM-001, STI-1110, AGEN2034, MGA012, BCD-100, IBI308, SSI-361, or comprises an antigen binding portion thereof

17. The method of any one of claims 1-16, wherein anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:13, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:14.

18. The method of any one of claims 1-17, wherein the anti-PD-1 antibody comprises:
    (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:15;
    (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:16;
    (c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:17;
    (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:18;
    (e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:19; and
    (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:20.

19. The method of any one of claims 1-18, wherein the anti-PD-1 antibody comprises heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:13 and 14, respectively.

20. The method of any one of claims 1-14 or 16-19, wherein the anti-PD-1 antibody comprises heavy and light chains comprising the sequences set forth in SEQ ID NOs:11 and 12, respectively.

21. The method of any one of claims 1-11, wherein the anti-PD-L1 antibody is a full-length antibody.

22. The method of any one of claims 1-11 or 21, wherein the anti-PD-L1 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody.

23. The method of claim 22, wherein the multispecific antibody is a DART, a DVD-Ig, or bispecific antibody.

24. The method of any one of claims 1-11, wherein the anti-PD-L1 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

25. The method of any one of claims 1-11 or 21-24, wherein the anti-PD-L1 antibody is BMS-936559, atezolizumab, durvalumab, avelumab, STI-1014, CX-072, KN035, LY3300054, BGB-A333, ICO 36, FAZ053, CK-301, or comprises an antigen binding portion thereof.

26. The method of any one of claims 1-25, wherein the anti-LAG-3 antibody is formulated for intravenous administration and/or the anti-PD-1 antibody or anti-PD-L1 antibody is formulated for intravenous administration.

27. The method of any one of claims 1-26, wherein the anti-LAG-3 antibody and/or the anti-PD-1 antibody or anti-PD-L1 antibody is administered once about every one week, once about every two weeks, once about every three weeks, once about every four weeks, once about every five weeks, once about every six weeks, once about every seven weeks, once about every eight weeks, once about every nine weeks, once about every ten weeks, once about every eleven weeks, or once about every twelve weeks.

28. The method of any one of claims 1-27, wherein the anti-PD-1 antibody or anti-PD-L1 antibody is administered before the anti-LAG-3 antibody.

29. The method of claim 1-27, wherein the anti-LAG-3 antibody is administered before the anti-PD-1 antibody or anti-PD-L1 antibody.

30. The method of any one of claims 1-27, wherein the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody are administered concurrently.

31. The method of any one of claims 1-30, wherein the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody are formulated separately.

32. The method of any one of claims 1-27 or 30, wherein the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody are formulated together.

33. A method of treating a human subject afflicted with colorectal carcinoma (CRC), the method comprising administering to the subject:

(a) about 480 mg of an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:3, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:4, and

(b) about 480 mg of an anti-PD-1 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:13, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:14.

34. The method of claim 33, wherein the anti-LAG-3 antibody is a full-length antibody.

35. The method of claim 34, wherein the anti-LAG-3 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody.

36. The method of claim 35, wherein the multispecific antibody is a dual-affinity re-targeting antibody (DART), a DVD-Ig, or bispecific antibody.

37. The method of claim 33, wherein the anti-LAG-3 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

38. The method of any one of claims 33-37, wherein the anti-LAG-3 antibody is BMS-986016 (relatlimab) or comprises an antigen binding portion thereof.

39. The method of any one of claims 33-38, wherein the anti-LAG-3 antibody comprises:

(a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:5;

(b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:6;

(c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:7;

(d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:8;

(e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:9; and

(f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:10.

40. The method of any one of claims 33-39, wherein the anti-LAG-3 antibody comprises heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:3 and 4, respectively.

41. The method of any one of claims 33-36 or 38-40, wherein the anti-LAG-3 antibody comprises heavy and light chains comprising the sequences set forth in SEQ ID NOs:1 and 2, respectively.

42. The method of any one of claims 33-36 or 38-40, wherein the anti-LAG-3 antibody comprises heavy and light chains comprising the sequences set forth in SEQ ID NOs:21 and 2, respectively.

43. The method of any one of claims 33-42, wherein the anti-PD-1 antibody is a full-length antibody.

44. The method of claim 43, wherein the anti-PD-1 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody.

45. The method of claim 44, wherein the multispecific antibody is a DART, a DVD-Ig, or bispecific antibody.

46. The method of any one of claims 33-42, wherein the anti-PD-1 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

47. The method of any one of claims 33-46, wherein the anti-PD-1 antibody is nivolumab or comprises an antigen binding portion thereof.

48. The method of any one of claims 33-47, wherein the anti-PD-1 antibody comprises:
    (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:15;
    (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:16;
    (c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:17;
    (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:18;
    (e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:19; and
    (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:20.

49. The method of any one of claims 33-48, wherein the anti-PD-1 antibody comprises heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:13 and 14, respectively.

50. The method of any one of claims 33-45 or 47-49, wherein the anti-PD-1 antibody comprises heavy and light chains comprising the sequences set forth in SEQ ID NOs:11 and 12, respectively.

51. The method of any one of claims 33-50, wherein the anti-LAG-3 antibody and/or the anti-PD-1 antibody is formulated for intravenous administration.

52. The method of any one of claims 33-51, wherein the anti-LAG-3 antibody and/or the anti-PD-1 antibody is administered once about every one week, once about every two weeks, once about every three weeks, once about every four weeks, once about every five weeks, once about every six weeks, once about every seven weeks, once about every eight weeks, once about every nine weeks, once about every ten weeks, once about every eleven weeks, or once about every twelve weeks.

53. The method of any one of claims 33-52, wherein the anti-PD-1 antibody is administered before the anti-LAG-3 antibody.

54. The method of claim 33-52, wherein the anti-LAG-3 antibody is administered before the anti-PD-1 antibody.

55. The method of any one of claims 33-52, wherein the anti-LAG-3 antibody and the anti-PD-1 antibody or are administered concurrently.

56. The method of any one of claims 33-54, wherein the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody are formulated separately.

57. The method of any one of claims 33-52 or 55, wherein the anti-LAG-3 antibody and the anti-PD-1 antibody or anti-PD-L1 antibody are formulated together

58. The method of any one of claims 1-57, wherein the method is a first line therapy.

59. The method of any one of claims 1-57, wherein the method is a second line therapy.

60. The method of any one of claims 1-57, wherein the method is a third line therapy.

61. The method of claim 59 or 60, wherein the subject has progressed on or is intolerant of a prior therapy.

62. The method of claim 61, wherein the prior therapy comprises a fluoropyrimidine, oxaliplatin, irinotecan, anti-vascular endothelial growth factor (VEGF) therapy, anti-epidermal growth factor receptor (EGFR) therapy for CRC comprising a Kristen Rat Sarcoma Viral Oncogene Homologue (KRAS) mutation, regorafenib, TAS-102, or any combination thereof.

63. The method of any one of claims 1-58, wherein the subject is naïve to prior systemic therapy for advanced and/or metastatic CRC.

64. The method of any one of claims 1-63, wherein the subject is naïve to prior immuno-oncology therapy, the subject is naïve to prior immuno-oncology therapy for CRC, or the CRC is naïve to prior immuno-oncology therapy.

65. The method of any one of claims 1-64, wherein the CRC comprises adenocarcinoma histology.

66. The method of any one of claims 1-65, wherein the CRC is unresectable, advanced, and/or metastatic.

67. The method of any one of claims 1-66, wherein the CRC is microsatellite stable (MSS) CRC.

68. The method of claim 67, wherein the MSS CRC comprises high T cell activation and LAG-3 upregulation.

69. The method of any one of claims 1-66, wherein the CRC is high microsatellite instable (MSI-H) CRC.

70. The method of any one of claims 1-69, wherein the CRC comprises a KRAS mutation.

71. The method of any one of claims 1-69, wherein the CRC comprises wild-type KRAS.

72. The method of any one of claims 1-71, wherein one or more immune cells in tumor tissue from the subject express LAG-3.

73. The method of claim 72, wherein at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% of the immune cells express LAG-3.

74. The method of claim 72 or 73, wherein at least about 1% of the immune cells express LAG-3.

75. The method of any one of claims 72-74, wherein the immune cells are tumor-infiltrating lymphocytes.

76. The method of claim 75, wherein the tumor-infiltrating lymphocytes are $CD8^+$ cells.

77. The method of any one of claims 1-76, wherein one or more cells in tumor tissue from the subject express PD-L1.

78. The method of claim 77, wherein the tumor tissue comprises a PD-L1 tumor proportion score (TPS) and/or combined positive score (CPS) of at least about 1%, at least about 3%,

at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% of the tumor cells, wherein the TPS is the percentage of tumor cells in the tumor tissue that express PD-L1, and the CPS is the number of tumor and immune cells in the tumor tissue that express PD-L1 as a percentage of the total number of viable tumor cells.

79. The method of claim 77 or 78, wherein the tumor tissue comprises a PD-L1 TPS and/or CPS of at least about 1%.

80. The method of any one of claims 1-79, wherein the CRC is a colon cancer.

81. The method of any one of claims 1-79, wherein the CRC is a rectal cancer

82. The method of any one of claims 1-81, further comprising administering to the subject an additional therapeutic agent.

83. The method of claim 82, wherein the additional therapeutic agent comprises an anti-cancer agent.

84. The method of claim 83, wherein the anti-cancer agent comprises a tyrosine kinase inhibitor, an anti-angiogenesis agent, a checkpoint inhibitor, a checkpoint stimulator, a chemotherapeutic agent, an immunotherapeutic agent, a platinum agent, an alkylating agent, a taxane, a nucleoside analog, an antimetabolite, a topoisomerase inhibitor, an anthracycline, a vinca alkaloid, or any combination thereof.

85. The method of claim 84, wherein the checkpoint inhibitor comprises a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, a T cell immunoglobulin and ITIM domain (TIGIT) inhibitor, a T cell immunoglobulin and mucin-domain containing-3 (TIM-3) inhibitor, a TIM-1 inhibitor, a TIM-4 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a B and T cell lymphocyte attenuator (BTLA) inhibitor, a V-domain Ig suppressor of T cell activation (VISTA) inhibitor, an indoleamine 2,3-dioxygenase (IDO) inhibitor, a nicotinamide adenine dinucleotide phosphate oxidase isoform 2 (NOX2) inhibitor, a killer-cell immunoglobulin-like receptor (KIR) inhibitor, an adenosine A2a receptor (A2aR)

inhibitor, a transforming growth factor beta (TGF-β) inhibitor, a phosphoinositide 3-kinase (PI3K) inhibitor, a CD47 inhibitor, a CD48 inhibitor, a CD73 inhibitor, a CD113 inhibitor, a sialic acid-binding immunoglobulin-like lectin-7 (SIGLEC-7) inhibitor, a SIGLEC-9 inhibitor, a SIGLEC-15 inhibitor, a glucocorticoid-induced TNFR-related protein (GITR) inhibitor, a galectin-1 inhibitor, a galectin-9 inhibitor, a carcinoembryonic antigen-related cell adhesion molecule-1 (CEACAM-1) inhibitor, a G protein-coupled receptor 56 (GPR56) inhibitor, a glycoprotein A repetitions predominant (GARP) inhibitor, a 2B4 inhibitor, a programmed death-1 homolog (PD1H) inhibitor, a leukocyte-associated immunoglobulin-like receptor 1 (LAIR1) inhibitor, or any combination thereof.

86. The method of claim 84 or 85, wherein the checkpoint inhibitor comprises a CTLA-4 inhibitor.

87. The method of claim 86, wherein the CTLA-4 inhibitor is an anti-CTLA-4 antibody.

88. The method of claim 87, wherein the anti-CTLA-4 antibody is a full-length antibody.

89. The method of claim 87 or 88, wherein the anti-CTLA-4 antibody is a monoclonal, human, humanized, chimeric, or multispecific antibody.

90. The method of claim 89, wherein the multispecific antibody is a DART, a DVD-Ig, or bispecific antibody.

91. The method of claim 87, wherein the anti-CTLA-4 antibody is a $F(ab')_2$ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, a dAb fragment, or a single chain binding polypeptide.

92. The method of any one of claims 87-91, wherein the anti-CTLA-4 antibody is ipilimumab, tremelimumab, MK-1308, AGEN-1884, or comprises an antigen binding portion thereof.