

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization

International Bureau

(43) International Publication Date
24 January 2019 (24.01.2019)



(10) International Publication Number
WO 2019/018730 A1

(51) International Patent Classification:

A61K 39/00 (2006.01) C07K 16/28 (2006.01)

(21) International Application Number:

PCT/US2018/043030

(22) International Filing Date:

20 July 2018 (20.07.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/534,798 20 July 2017 (20.07.2017) US
62/643,992 16 March 2018 (16.03.2018) US

(71) Applicant: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35,
4056 Basel (CH).

(72) Inventors; and

(71) Applicants (for US only): **STEIN, Andrew, Marc**
[US/US]; Novartis Institutes for Biomedical Research, Inc.,
250 Massachusetts Avenue, Cambridge, MA 02139 (US).
VOGL, Florian, Dominik [DE/CH]; Novartis Pharma AG,
Postfach, 4002 Basel (CH). **SELLAMI, Dalila** [US/US];
Novartis Pharmaceuticals Corporation, One Health Plaza,
East Hanover, NJ 07936-1080 (US).

(74) Agent: **LU, David** et al.; Lando & Anastasi, LLP, River-
front Office Park, One Main Street, Suite 1100, Cambridge,
MA 02142 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP,
KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,
SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

(54) Title: DOSAGE REGIMENS OF ANTI-LAG-3 ANTIBODIES AND USES THEREOF

(57) Abstract: Dosage regimens for antibody molecules that specifically bind to LAG-3 are disclosed. The antibody molecules can be used to treat or prevent cancerous or infectious conditions and disorders.

WO 2019/018730 A1

DOSAGE REGIMENS OF ANTI-LAG-3 ANTIBODIES AND USES THEREOF

Cross Reference to Related Applications

This application claims the benefit of U.S. Provisional Application No. 62/534,798, filed July 20, 2017, and U.S. Provisional Application No. 62/643,992, filed March 16, 2018. The contents of the aforementioned applications are hereby incorporated by reference in their entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on, July 17, 2018, is named C2160-7019WO_SL.txt and is 233,727 bytes in size.

BACKGROUND

Lymphocyte Activation Gene-3, or LAG-3 (also known as CD223), is a member of the immunoglobulin supergene family, and is expressed on activated T cells (Huard *et al.* (1994) *Immunogenetics* 39:213), NK cells (Triebel *et al.* (1990) *J. Exp. Med.* 171:1393-1405), regulatory T cells (Huang *et al.* (2004) *Immunity* 21:503-513; Camisaschi *et al.* (2010) *J Immunol.* 184:6545-6551; Gagliani *et al.* (2013) *Nat Med* 19:739-746), and plasmacytoid dendritic cells (DCs) (Workman *et al.* (2009) *J Immunol* 182:1885-1891). LAG-3 is a membrane protein encoded by a gene located on chromosome 12, and is structurally and genetically related to CD4.

Similar to CD4, LAG-3 can interact with MHC class II molecules on the cell surface (Baixeras *et al.* (1992) *J. Exp. Med.* 176:327-337; Huard *et al.* (1996) *Eur. J. Immunol.* 26:1180-1186). It has been suggested that the direct binding of LAG-3 to MHC class II plays a role in down-regulating antigen-dependent stimulation of CD4⁺ T lymphocytes (Huard *et al.* (1994) *Eur. J. Immunol.* 24:3216-3221) and LAG-3 blockade has also been shown to reinvigorate CD8⁺ lymphocytes in both tumor or self-antigen (Gross *et al.* (2007) *J Clin Invest.* 117:3383-3392) and viral models (Blackburn *et al.* (2009) *Nat. Immunol.* 10:29-37). Further, the intra-cytoplasmic region of LAG-3 can interact with LAP (LAG-3-associated protein), which is a signal transduction molecule involved in the downregulation of the CD3/TCR activation pathway (Iouzalen *et al.* (2001) *Eur. J. Immunol.* 31:2885-2891). Moreover, CD4⁺CD25⁺ regulatory T cells (T_{reg}) have been shown to express LAG-3 upon activation, which contributes to the suppressor activity of T_{reg} cells (Huang, C. *et al.* (2004) *Immunity* 21:503-513). LAG-3 can also negatively regulate T cell homeostasis by T_{reg} cells in both T cell-dependent and independent mechanisms (Workman, C. J. and Vignali, D. A. (2005) *J. Immunol.* 174:688-695).

Therefore, the need exists for novel therapeutic approaches that regulate LAG-3 functions and the functions of LAG-3 expressing cells, including dosage regimens and formulations for anti-LAG-3 antibody molecules to treat diseases, such as cancer.

SUMMARY

Disclosed herein, at least in part, are antibody molecules (*e.g.*, humanized antibody molecules) that bind to Lymphocyte Activation Gene-3 (LAG-3) with high affinity and specificity.

5 Pharmaceutical compositions and dose formulations comprising the anti-LAG-3 antibody molecules are also provided. The anti- LAG-3 antibody molecules disclosed herein can be used (alone or in combination with other therapeutic agents, procedures, or modalities) to treat or prevent disorders, such as cancerous disorders (*e.g.*, solid tumors and hematological cancers), as well as infectious diseases (*e.g.*, chronic infectious disorders or sepsis). Thus, methods, including dosage regimens, for
10 treating various disorders using the anti- LAG-3 antibody molecules are disclosed herein. In certain embodiments, the anti-LAG-3 antibody molecule is administered or used at a flat or fixed dose.

Accordingly, in one aspect, the disclosure features a method of treating (*e.g.*, inhibiting, reducing, ameliorating, or preventing) a disorder, *e.g.*, a hyperproliferative condition or disorder (*e.g.*,
15 a cancer) in a subject.

In certain embodiments, the method includes administering to the subject an anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule described herein, at a dose of about 300 mg to about 500 mg, about 500 mg to about 700 mg, or about 700 mg to about 900 mg, once every three weeks or once every four weeks.

20 In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to about 500 mg once every three weeks or once every four weeks. In other embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 500 mg to about 700 mg once every three weeks or once every four weeks. In other embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 700 mg to about 900 mg once every three weeks or once every four
25 weeks. In other embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to about 500 mg, about 500 mg to about 700 mg, or about 700 mg to about 900 mg, once every three weeks. In other embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to about 500 mg, about 500 mg to about 700 mg, or about 700 mg to about 900 mg, once every four weeks.

30 In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to about 500 mg, *e.g.*, about 350 mg to about 450 mg, about 300 mg to about 400 mg, or about 400 mg to about 500 mg, *e.g.*, about 300 mg, about 350 mg, about 400 mg, about 450 mg, or about 500 mg, once every three weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 350 mg to about 450 mg, *e.g.*, about 400 mg, once every three weeks.

35 In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 500 mg to about 700 mg, *e.g.*, about 550 mg to about 650 mg, about 500 mg to about 600 mg, or

about 600 mg to about 700 mg, *e.g.*, about 500 mg, about 533 mg, about 550 mg, about 600 mg, about 650 mg, or about 700 mg, once every four weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 500 mg to about 650 mg, *e.g.*, about 533 mg or about 600 mg, once every four weeks.

5 In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 700 mg to about 900 mg, *e.g.*, about 750 mg to about 850 mg, about 700 mg to about 800 mg, or about 800 mg to about 900 mg, *e.g.*, about 700 mg, about 750 mg, about 800 mg, about 850 mg, or about 900 mg, once every four weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 750 mg to about 850 mg, *e.g.*, about 800 mg, once every four weeks.

10

In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose or dosage schedule that results in one or both of the following:

(a) 50% or more (*e.g.*, 60% or more, 70% or more, 80% or more, 85% or more, 90% or more, 95% or more, 99% or more) of the soluble LAG-3 in the subject (*e.g.*, in the blood) is bound by the anti-LAG-3 antibody molecule; or

15

(b) 50% or more (*e.g.*, 60% or more, 70% or more, 80% or more, 85% or more, 90% or more, 95% or more, 99% or more) of the membrane-bound LAG-3 in the subject (*e.g.*, in the cancer) is bound by the anti-LAG-3 antibody molecule.

In some embodiments, the binding of the anti-LAG-3 antibody molecule to soluble LAG-3 is determined in a blood sample (*e.g.*, a serum sample or a plasma sample). In some embodiments, the binding of the anti-LAG-3 antibody molecule to membrane-bound LAG-3 is determined in the cancer (*e.g.*, a cancer sample).

20

In some embodiments, the binding of the anti-LAG-3 antibody molecule to soluble LAG-3, the binding of the anti-LAG-3 antibody molecule to membrane-bound LAG-3, or both, is determined when the subject has a steady state trough level of the anti-LAG-3 antibody molecule. In some embodiments, the trough level is the concentration of the anti-LAG-3 antibody molecule about 24 weeks after the administration, or the lowest concentration that the anti-LAG-3 antibody molecule reaches before the next dose is administered. In some embodiments, the binding of the anti-LAG-3 antibody molecule to soluble LAG-3, the binding of the anti-LAG-3 antibody molecule to membrane-bound LAG-3, or both, is determined, *e.g.*, measured *in vitro* (*e.g.*, by ELISA or a cell-based assay) or *in vivo* (*e.g.*, by imaging), or predicted from a PK/PD model, *e.g.*, a PK/PD model described herein.

25

In some embodiments, 60% or more of the soluble LAG-3 in a serum sample from the subject is bound by the anti-LAG-3 antibody molecule. In some embodiments, 80% or more of the soluble LAG-3 in a serum sample from the subject is bound by the anti-LAG-3 antibody molecule. In some embodiments, 90% or more of the soluble LAG-3 in a serum sample from the subject is bound by the anti-LAG-3 antibody molecule.

30

35

In some embodiments, 85% or more of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule. In some embodiments, 90% or more of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule. In some embodiments, 95% or more of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule.

In some embodiments, 70% or more, 80% or more, or 90% or more, of the soluble LAG-3 in a serum sample from the subject is bound by the anti-LAG-3 antibody molecule, and 85% or more, 90% or more, or 95% or more, of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule.

In some embodiments, 70% or more of the soluble LAG-3 in a serum sample from the subject is bound by the anti-LAG-3 antibody molecule, and 90% or more of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule. In some embodiments, 80% or more of the soluble LAG-3 in a serum sample from the subject is bound by the anti-LAG-3 antibody molecule, and 90% or more of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule. In some embodiments, 90% or more of the soluble LAG-3 in a serum sample from the subject is bound by the anti-LAG-3 antibody molecule, and 90% or more of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule.

In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to about 800 mg, *e.g.*, about 300 mg to about 500 mg (*e.g.*, about 400 mg) or about 600 mg to about 800 mg (*e.g.*, about 700 mg), once every three weeks. In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) once every three weeks.

In other embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 600 mg to about 1600 mg, *e.g.*, about 600 mg to about 1000 mg (*e.g.*, about 800 mg) or about 1200 mg to about 1600 mg (*e.g.*, about 1400 mg), once every four weeks. In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 600 mg to about 1000 mg (*e.g.*, about 800 mg) once every four weeks.

In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose or dosage schedule that reduces one or both of:

(a) the level of free soluble LAG-3 in the subject (*e.g.*, blood), *e.g.*, to 50% or less (*e.g.*, 40% or less, 30% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less) of a reference level of free soluble LAG-3; or

(b) the level of free membrane-bound LAG-3 in the subject (*e.g.*, cancer), *e.g.*, to 50% or less (*e.g.*, 40% or less, 30% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less) of a reference level of membrane-bound LAG-3.

5 In some embodiments, the level of free soluble LAG-3 is determined in a blood sample (*e.g.*, a serum sample or a plasma sample). In some embodiments, the reference level of free soluble LAG-3 is the baseline level of free soluble LAG-3 in the subject, *e.g.*, prior to administration of the anti-LAG-3 antibody molecule, *e.g.*, in accordance with the dosage schedule.

10 In some embodiments, the level of free membrane-bound LAG-3 is determined in the cancer (*e.g.*, a cancer sample). In some embodiments, the reference level of free membrane-bound LAG-3 is the baseline level of free membrane-bound LAG-3 in the subject, *e.g.*, prior to administration of the anti-LAG-3 antibody molecule, *e.g.*, in accordance with the dosage schedule.

15 In some embodiments, the level of free soluble LAG-3, the level of free membrane-bound LAG-3, or both, is determined when the subject has a steady state trough level of the anti-LAG-3 antibody molecule. In some embodiments, the trough level is the concentration of the anti-LAG-3 antibody molecule about 24 weeks after the administration, or the lowest concentration that the anti-LAG-3 antibody molecule reaches before the next dose is administered. In some embodiments, the level of free soluble LAG-3, the level of free membrane-bound LAG-3, or both, is determined, *e.g.*, measured *in vitro* (*e.g.*, by ELISA or a cell-based assay) or *in vivo* (*e.g.*, by imaging), or predicted from a PK/PD model, *e.g.*, a PK/PD model described herein.

20 In some embodiments, the level of free soluble LAG-3 is reduced to 30% or less of a reference level of free soluble LAG-3 in a serum sample from the subject. In some embodiments, the level of free soluble LAG-3 is reduced to 20% or less of a reference level of free soluble LAG-3 in a serum sample from the subject. In some embodiments, the level of free soluble LAG-3 is reduced to 10% or less of a reference level of free soluble LAG-3 in a serum sample from the subject.

25 In some embodiments, the level of free membrane-bound LAG-3 is reduced to 15% or less of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject. In some embodiments, the level of free membrane-bound LAG-3 is reduced to 10% or less of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject. In some embodiments, the level of free soluble LAG-3 is reduced to 5% or less of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject.

30 In some embodiments, the level of free soluble LAG-3 is reduced to 30% or less, 20% or less, or 10% or less, of a reference level of free soluble LAG-3 in a serum sample from the subject, and the level of free membrane-bound LAG-3 is reduced to 15% or less, 10% or less, or 5% or less, of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject.

35 In some embodiments, the level of free soluble LAG-3 is reduced to 30% or less of a reference level of free soluble LAG-3 in a serum sample from the subject, and the level of free membrane-bound LAG-3 is reduced to 10% or less of a reference level of free membrane-bound

LAG-3 in the cancer, or a cancer sample, from the subject. In some embodiments, the level of free soluble LAG-3 is reduced to 20% or less of a reference level of free soluble LAG-3 in a serum sample from the subject, and the level of free membrane-bound LAG-3 is reduced to 10% or less of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject.

5 In some embodiments, the level of free soluble LAG-3 is reduced to 10% or less of a reference level of free soluble LAG-3 in a serum sample from the subject, and the level of free membrane-bound LAG-3 is reduced to 10% or less of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject.

10 In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to about 800 mg, *e.g.*, about 300 mg to about 500 mg (*e.g.*, about 400 mg) or about 600 mg to about 800 mg (*e.g.*, about 700 mg) once every three weeks. In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) once every three weeks.

15 In other embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 600 mg to about 1600 mg, *e.g.*, about 600 mg to about 1000 mg (*e.g.*, about 800 mg) or about 1200 mg to about 1600 mg (*e.g.*, about 1400 mg), once every four weeks. In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 600 mg to about 1000 mg (*e.g.*, about 800 mg), once every four weeks.

20 In some embodiments, the disorder is a cancer, *e.g.*, a cancer described herein. In certain embodiments, the cancer is a solid tumor. In some embodiments, the cancer is brain tumor, *e.g.*, a glioblastoma, a gliosarcoma, or a recurrent brain tumor. In some embodiments, the cancer is a pancreatic cancer, *e.g.*, an advanced pancreatic cancer. In some embodiments, the cancer is a skin cancer, *e.g.*, a melanoma (*e.g.*, a stage II-IV melanoma, an HLA-A2 positive melanoma, an
25 unresectable melanoma, or a metastatic melanoma), or a Merkel cell carcinoma. In some embodiments, the cancer is a renal cancer, *e.g.*, a renal cell carcinoma (RCC) (*e.g.*, a metastatic renal cell carcinoma). In some embodiments, the cancer is a breast cancer, *e.g.*, a metastatic breast carcinoma or a stage IV breast carcinoma, *e.g.*, a triple negative breast cancer (TNBC). In some
30 embodiments, the cancer is a virus-associated cancer. In some embodiments, the cancer is an anal canal cancer (*e.g.*, a squamous cell carcinoma of the anal canal). In some embodiments, the cancer is a cervical cancer (*e.g.*, a squamous cell carcinoma of the cervix). In some embodiments, the cancer is a gastric cancer (*e.g.*, an Epstein Barr Virus (EBV) positive gastric cancer, or a gastric or gastro-
esophageal junction carcinoma). In some embodiments, the cancer is a head and neck cancer (*e.g.*, an HPV positive and negative squamous cell cancer of the head and neck (SCCHN)). In some
35 embodiments, the cancer is a nasopharyngeal cancer (NPC). In some embodiments, the cancer is a penile cancer (*e.g.*, a squamous cell carcinoma of the penile). In some embodiments, the cancer is a vaginal or vulvar cancer (*e.g.*, a squamous cell carcinoma of the vagina or vulva). In some

embodiments, the cancer is a colorectal cancer, *e.g.*, a relapsed colorectal cancer or a metastatic colorectal cancer, *e.g.*, a microsatellite unstable colorectal cancer, a microsatellite stable colorectal cancer, a mismatch repair proficient colorectal cancer, or a mismatch repair deficient colorectal cancer. In some embodiments, the cancer is a lung cancer, *e.g.*, a non-small cell lung cancer (NSCLC). In certain embodiments, the cancer is a hematological cancer. In some embodiments, the cancer is a leukemia. In some embodiments, the cancer is a lymphoma, *e.g.*, a Hodgkin lymphoma (HL) or a diffuse large B cell lymphoma (DLBCL) (*e.g.*, a relapsed or refractory HL or DLBCL). In some embodiments, the cancer is a myeloma.

10 In other embodiments, the cancer is an MSI-high cancer. In some embodiments, the cancer is a metastatic cancer. In other embodiments, the cancer is an advanced cancer. In other embodiments, the cancer is a relapsed or refractory cancer. In other embodiments, the cancer is a recurrent cancer.

In some embodiments, the anti-LAG-3 antibody molecule is administered by injection (*e.g.*, intravenously or subcutaneously) at a dose (*e.g.*, a flat dose) of about 300 mg to about 500 mg (*e.g.*, about 400 mg), about 500 mg to about 700 mg (*e.g.*, about 533 mg or about 600 mg), or about 700 mg to about 900 mg (*e.g.*, about 800 mg). The dosing schedule (*e.g.*, flat dosing schedule) can vary from *e.g.*, once every three weeks to once every four weeks. In one embodiment, the anti-LAG-3 antibody molecule is administered intravenously at a dose from about 300 mg to 500 mg (*e.g.*, about 400 mg) once every three weeks. In one embodiment, the anti-LAG-3 antibody molecule is administered intravenously at a dose from about 500 mg to 700 mg (*e.g.*, about 533 mg or about 600 mg) once every four weeks. In one embodiment, the anti-LAG-3 antibody molecule is administered intravenously at a dose from about 700 mg to 900 mg (*e.g.*, about 800 mg) once every four weeks.

20 In one embodiment, the anti-LAG-3 antibody molecule is administered intravenously at a dose about 400 mg once every three weeks to treat a cancer disclosed herein. In one embodiment, the anti-LAG-3 antibody molecule is administered intravenously at a dose about 533 mg or 600 mg once every four weeks to treat a cancer disclosed herein. In one embodiment, the anti-LAG-3 antibody molecule is administered intravenously at a dose about 800 mg once every four weeks to treat a cancer disclosed herein.

In one embodiment, the method further comprises administering to the subject a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule described herein) or a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule described herein). In one embodiment, the PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule described herein) is administered intravenously at a dose of about 200 mg to about 400 mg (*e.g.*, about 300 mg) once every three weeks. In certain embodiments, the subject is administered an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein) with an anti-PD-1 antibody molecule at a dose of about 200 mg to about 400 mg (*e.g.*, about 300 mg) once every three weeks. In certain embodiments, the anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein) is administered at a dose of about 300 mg to about

500 mg (*e.g.*, about 400 mg) once every three weeks and the PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule described herein) is administered at a dose of about 200 mg to about 400 mg (*e.g.*, about 300 mg) once every three weeks. In other embodiments, the subject is administered an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein) with an anti-PD-1 antibody molecule at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) once every four weeks. In certain embodiments, the anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein) is administered at a dose of about 600 mg to about 1000 mg (*e.g.*, about 800 mg) once every four weeks and the PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule described herein) is administered at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) once every four weeks. In one embodiment, the method comprises administering to the subject an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein) and a chemotherapeutic agent (*e.g.*, a platinum agent (*e.g.*, carboplatin, cisplatin, oxaliplatin, or tetraplatin) or a nucleotide analog or precursor analog (*e.g.*, capecitabine)). In one embodiment, the chemotherapeutic agent (*e.g.*, a platinum agent, *e.g.*, carboplatin) is administered intravenously at a dose to achieve an area under the curve (AUC) of about 4 to about 8 or about 5 to about 7 (*e.g.*, an AUC of about 6) once every three weeks. In certain embodiments, the anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein) is administered at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) once every three weeks and the chemotherapeutic agent (*e.g.*, a platinum agent, *e.g.*, carboplatin) is administered at a dose to achieve an area under the curve (AUC) of about 4 to about 8 or about 5 to about 7 (*e.g.*, an AUC of about 6) once every three weeks.

In one embodiment, the method comprises administering to the subject an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein), a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule described herein), and a chemotherapeutic agent (*e.g.*, a platinum agent (*e.g.*, carboplatin, cisplatin, oxaliplatin, or tetraplatin) or a nucleotide analog or precursor analog (*e.g.*, capecitabine)). In certain embodiments, the anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein) is administered at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) once every three weeks, the PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule described herein) is administered at a dose of about 200 mg to about 400 mg (*e.g.*, about 300 mg) once every three weeks, and the chemotherapeutic agent (*e.g.*, a platinum agent, *e.g.*, carboplatin) is administered at a dose to achieve an area under the curve (AUC) of about 4 to about 8 or about 5 to about 7 (*e.g.*, an AUC of about 6) once every three weeks.

In certain embodiments, the anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein), or the combination comprising the anti-LAG-3 antibody molecule (*e.g.*, the anti-LAG-3 antibody molecule in combination with one or both of a PD-1 inhibitor or a

chemotherapeutic agent), is used to treat a breast cancer, *e.g.*, a triple negative breast cancer (TNBC), *e.g.*, in accordance with a dosing schedule described herein.

In certain embodiments, the subject has not been treated with a PD-1 or PD-L1 therapy prior to receiving the anti-LAG-3 antibody molecule. In other embodiments, the subject has been treated
5 with a PD-1 or PD-L1 therapy prior to receiving the anti-LAG-3 antibody molecule.

In certain embodiments, the subject has not been treated with a chemotherapeutic agent (*e.g.*, a platinum agent (*e.g.*, carboplatin, cisplatin, oxaliplatin, or tetraplatin) or a nucleotide analog or precursor analog (*e.g.*, capecitabine)) prior to receiving the anti-LAG-3 antibody molecule. In other
10 embodiments, the subject has been treated with a chemotherapeutic agent (*e.g.*, a platinum agent (*e.g.*, carboplatin, cisplatin, oxaliplatin, or tetraplatin) or a nucleotide analog or precursor analog (*e.g.*, capecitabine)) prior to receiving the anti-LAG-3 antibody molecule.

In other embodiments, the subject has, or is identified as having, LAG-3 expression in tumor-infiltrating lymphocytes (TILs).

In another aspect, the disclosure features a method of reducing an activity (*e.g.*, growth, survival, or viability, or all), of a hyperproliferative (*e.g.*, a cancer) cell. The method includes contacting the cell with an anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule described herein. The method can be performed in a subject, *e.g.*, as part of a therapeutic protocol, *e.g.*, at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg), about 500 mg to about 700 mg
20 (*e.g.*, about 533 mg or about 600 mg), or about 700 mg to about 900 mg (*e.g.*, about 800 mg) of an anti-LAG-3 antibody molecule once every three weeks or once every four weeks. In certain embodiments, the dose is about 300 mg to about 500 mg (*e.g.*, about 400 mg) of an anti-LAG-3 antibody molecule once every three weeks. In other embodiments, the dose is about 500 mg to about 700 mg (*e.g.*, about 533 mg or about 600 mg) of an anti-LAG-3 antibody molecule once every four
25 weeks. In other embodiments, the dose is about 700 mg to about 900 mg (*e.g.*, about 800 mg) of an anti-LAG-3 antibody molecule once every four weeks.

The cancer cell can be, *e.g.*, a cell from a cancer described herein, such as a solid tumor or a hematological cancer, *e.g.*, a brain tumor (*e.g.*, a glioblastoma, a gliosarcoma, or a recurrent brain tumor), a pancreatic cancer (*e.g.*, an advanced pancreatic cancer), a skin cancer (*e.g.*, a melanoma
30 (*e.g.*, a stage II-IV melanoma, an HLA-A2 positive melanoma, an unresectable melanoma, or a metastatic melanoma), or a Merkel cell carcinoma), a renal cancer (*e.g.*, a renal cell carcinoma (RCC) (*e.g.*, a metastatic renal cell carcinoma)), a breast cancer (*e.g.*, a metastatic breast carcinoma or a stage IV breast carcinoma, *e.g.*, a triple negative breast cancer (TNBC)), a virus-associated cancer, an anal canal cancer (*e.g.*, a squamous cell carcinoma of the anal canal), a cervical cancer (*e.g.*, a squamous
35 cell carcinoma of the cervix), a gastric cancer (*e.g.*, an Epstein Barr Virus (EBV) positive gastric cancer, or a gastric or gastro-esophageal junction carcinoma), a head and neck cancer (*e.g.*, an HPV

positive and negative squamous cell cancer of the head and neck (SCCHN)), a nasopharyngeal cancer (NPC), a penile cancer (*e.g.*, a squamous cell carcinoma of the penile), a vaginal or vulvar cancer (*e.g.*, a squamous cell carcinoma of the vagina or vulva), a colorectal cancer (*e.g.*, a relapsed colorectal cancer or a metastatic colorectal cancer, *e.g.*, a microsatellite unstable colorectal cancer, a
5 microsatellite stable colorectal cancer, a mismatch repair proficient colorectal cancer, or a mismatch repair deficient colorectal cancer), a lung cancer (*e.g.*, a non-small cell lung cancer (NSCLC)), a leukemia, a lymphoma (*e.g.*, a Hodgkin lymphoma (HL) or a diffuse large B cell lymphoma (DLBCL), *e.g.*, a relapsed or refractory HL or DLBCL), or a myeloma.

In certain embodiments, the cancer is a solid tumor. In some embodiments, the cancer is
10 brain tumor, *e.g.*, a glioblastoma, a gliosarcoma, or a recurrent brain tumor. In some embodiments, the cancer is a pancreatic cancer, *e.g.*, an advanced pancreatic cancer. In some embodiments, the cancer is a skin cancer, *e.g.*, a melanoma (*e.g.*, a stage II-IV melanoma, an HLA-A2 positive melanoma, an unresectable melanoma, or a metastatic melanoma), or a Merkel cell carcinoma. In some embodiments, the cancer is a renal cancer, *e.g.*, a renal cell carcinoma (RCC) (*e.g.*, a metastatic
15 renal cell carcinoma). In some embodiments, the cancer is a breast cancer, *e.g.*, a metastatic breast carcinoma or a stage IV breast carcinoma, *e.g.*, a triple negative breast cancer (TNBC). In some embodiments, the cancer is a virus-associated cancer. In some embodiments, the cancer is an anal canal cancer (*e.g.*, a squamous cell carcinoma of the anal canal). In some embodiments, the cancer is a cervical cancer (*e.g.*, a squamous cell carcinoma of the cervix). In some embodiments, the cancer is
20 a gastric cancer (*e.g.*, an Epstein Barr Virus (EBV) positive gastric cancer, or a gastric or gastro-esophageal junction carcinoma). In some embodiments, the cancer is a head and neck cancer (*e.g.*, an HPV positive and negative squamous cell cancer of the head and neck (SCCHN)). In some embodiments, the cancer is a nasopharyngeal cancer (NPC). In some embodiments, the cancer is a penile cancer (*e.g.*, a squamous cell carcinoma of the penile). In some embodiments, the cancer is a
25 vaginal or vulvar cancer (*e.g.*, a squamous cell carcinoma of the vagina or vulva). In some embodiments, the cancer is a colorectal cancer, *e.g.*, a relapsed colorectal cancer or a metastatic colorectal cancer, *e.g.*, a microsatellite unstable colorectal cancer, a microsatellite stable colorectal cancer, a mismatch repair proficient colorectal cancer, or a mismatch repair deficient colorectal cancer. In some embodiments, the cancer is a lung cancer, *e.g.*, a non-small cell lung cancer (NSCLC). In
30 certain embodiments, the cancer is a hematological cancer. In some embodiments, the cancer is a leukemia. In some embodiments, the cancer is a lymphoma, *e.g.*, a Hodgkin lymphoma (HL) or a diffuse large B cell lymphoma (DLBCL) (*e.g.*, a relapsed or refractory HL or DLBCL). In some embodiments, the cancer is a myeloma.

In certain embodiments, the method further includes contacting the cell with one or both of a
35 PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule described herein) or a chemotherapeutic agent (*e.g.*, a platinum agent (*e.g.*, carboplatin, cisplatin, oxaliplatin, or tetraplatin) or a nucleotide analog or precursor analog (*e.g.*, capecitabine)). The method can be performed in a subject, *e.g.*, as part of a

therapeutic protocol, *e.g.*, at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) of an anti-LAG-3 antibody molecule once every three weeks and at a dose of about 200 mg to about 400 mg (*e.g.*, about 300 mg) of a PD-1 inhibitor once every three weeks. The method can be performed in a subject, *e.g.*, as part of a therapeutic protocol, *e.g.*, at a dose of about 600 mg to about 1000 mg (*e.g.*, about 800 mg) of an anti-LAG-3 antibody molecule once every four weeks and at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) of a PD-1 inhibitor once every four weeks. The method can be performed in a subject, *e.g.*, as part of a therapeutic protocol, *e.g.*, at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) of an anti-LAG-3 antibody molecule once every three weeks and at a dose to achieve an area under the curve (AUC) of about 4 to about 8 or about 5 to about 7 (*e.g.*, an AUC of about 6) of a chemotherapeutic agent once every three weeks. The method can be performed in a subject, *e.g.*, as part of a therapeutic protocol, *e.g.*, at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) of an anti-LAG-3 antibody molecule once every three weeks, at a dose of about 200 mg to about 400 mg (*e.g.*, about 300 mg) of a PD-1 inhibitor once every three weeks, and at a dose of a chemotherapeutic agent to achieve an area under the curve (AUC) of about 4 to about 8 or about 5 to about 7 (*e.g.*, an AUC of about 6) once every three weeks. In some embodiments, the cancer cell can be, *e.g.*, a breast cancer cell, *e.g.*, a TNBC cell. In certain embodiments of the methods disclosed herein, the method further includes determining the level of LAG-3 expression in tumor infiltrating lymphocytes (TILs) in the subject. In other embodiments, the level of LAG-3 expression is determined in a sample (*e.g.*, a tumor biopsy) acquired from the subject (*e.g.*, using immunohistochemistry). In certain embodiments, when there is a detectable level, or an elevated level, of LAG-3 in the subject, the anti-LAG-3 antibody molecule is administered (*e.g.*, the anti-LAG-3 antibody molecule is administered responsive to a detectable level, or an elevated level, of LAG-3 in the subject). The detection steps can also be used, *e.g.*, to monitor the effectiveness of a therapeutic agent described herein. For example, the detection step can be used to monitor the effectiveness of the anti-LAG-3 antibody molecule.

In another aspect, the disclosure features a composition (*e.g.*, one or more compositions or dosage forms), that includes an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule as described herein). Formulations, *e.g.*, dosage formulations, and kits, *e.g.*, therapeutic kits, that include an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule as described herein), are also described herein. In certain embodiments, the composition or formulation comprises about 300 mg to about 500 mg (*e.g.*, about 400 mg), about 500 mg to about 700 mg (*e.g.*, about 533 mg or about 600 mg), or about 700 mg to about 900 mg (*e.g.*, about 800 mg) of an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule as described herein). In some embodiments, the composition or formulation is administered or used once every three weeks or once every four weeks. In some embodiments, the composition or formulation comprises about 400 mg of an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule as described herein), and is

administered or used once every three weeks. In some embodiments, the composition or formulation comprises about 533 mg or 600 mg of an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule as described herein), and is administered or used once every four weeks. In some embodiments, the composition or formulation comprises about 800 mg of an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule as described herein), and is administered or used once every four weeks. In certain embodiments, the composition or formulation is used to treat a cancer, *e.g.*, a cancer disclosed herein.

Additional features or embodiments of the methods, compositions, dosage formulations, and kits described herein include one or more of the following.

Antibody Molecules to LAG-3

In one embodiment, the anti-LAG-3 antibody molecule comprises at least one, two, three, four, five or six complementarity determining regions (CDRs) (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 5 (*e.g.*, from the heavy and light chain variable region sequences of BAP050-Clone I or BAP050-Clone J disclosed in Table 5), or encoded by a nucleotide sequence shown in Table 5. In some embodiments, the CDRs are according to the Kabat definition (*e.g.*, as set out in Table 5). In some embodiments, the CDRs are according to the Chothia definition (*e.g.*, as set out in Table 5). In some embodiments, the CDRs are according to the combined CDR definitions of both Kabat and Chothia (*e.g.*, as set out in Table 5). In one embodiment, the combination of Kabat and Chothia CDR of VH CDR1 comprises the amino acid sequence GFTLTNYGMN (SEQ ID NO: 766). In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid substitutions (*e.g.*, conservative amino acid substitutions) or deletions, relative to an amino acid sequence shown in Table 5, or encoded by a nucleotide sequence shown in Table 5.

In one embodiment, the anti-LAG-3 antibody molecule comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 701, a VHCDR2 amino acid sequence of SEQ ID NO: 702, and a VHCDR3 amino acid sequence of SEQ ID NO: 703; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 710, a VLCDR2 amino acid sequence of SEQ ID NO: 711, and a VLCDR3 amino acid sequence of SEQ ID NO: 712, each disclosed in Table 5.

In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising a VHCDR1 encoded by the nucleotide sequence of SEQ ID NO: 736 or 737, a VHCDR2 encoded by the nucleotide sequence of SEQ ID NO: 738 or 739, and a VHCDR3 encoded by the nucleotide sequence of SEQ ID NO: 740 or 741; and a VL comprising a VLCDR1 encoded by the nucleotide sequence of SEQ ID NO: 746 or 747, a VLCDR2 encoded by the nucleotide sequence of SEQ ID NO: 748 or 749, and a VLCDR3 encoded by the nucleotide sequence of SEQ ID NO: 750 or 751, each

disclosed in Table 5. In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising a VHCDR1 encoded by the nucleotide sequence of SEQ ID NO: 758 or 737, a VHCDR2 encoded by the nucleotide sequence of SEQ ID NO: 759 or 739, and a VHCDR3 encoded by the nucleotide sequence of SEQ ID NO: 760 or 741; and a VL comprising a VLCDR1 encoded by the nucleotide sequence of SEQ ID NO: 746 or 747, a VLCDR2 encoded by the nucleotide sequence of SEQ ID NO: 748 or 749, and a VLCDR3 encoded by the nucleotide sequence of SEQ ID NO: 750 or 751, each disclosed in Table 5.

In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 706, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 706. In one embodiment, the anti-LAG-3 antibody molecule comprises a VL comprising the amino acid sequence of SEQ ID NO: 718, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 718. In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 724, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 724. In one embodiment, the anti-LAG-3 antibody molecule comprises a VL comprising the amino acid sequence of SEQ ID NO: 730, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 730. In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 706 and a VL comprising the amino acid sequence of SEQ ID NO: 718. In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 724 and a VL comprising the amino acid sequence of SEQ ID NO: 730.

In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 707 or 708, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 707 or 708. In one embodiment, the antibody molecule comprises a VL encoded by the nucleotide sequence of SEQ ID NO: 719 or 720, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 719 or 720. In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 725 or 726, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 725 or 726. In one embodiment, the antibody molecule comprises a VL encoded by the nucleotide sequence of SEQ ID NO: 731 or 732, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 731 or 732. In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 707 or 708 and a VL encoded by the nucleotide sequence of SEQ ID NO: 719 or 720. In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 725 or 726 and a VL encoded by the nucleotide sequence of SEQ ID NO: 731 or 732.

In one embodiment, the anti-LAG-3 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 709, or an amino acid sequence at least 85%, 90%, 95%, or

99% identical or higher to SEQ ID NO: 709. In one embodiment, the anti-LAG-3 antibody molecule comprises a light chain comprising the amino acid sequence of SEQ ID NO: 721, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 721. In one embodiment, the anti-LAG-3 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 727, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 727. In one embodiment, the anti-LAG-3 antibody molecule comprises a light chain comprising the amino acid sequence of SEQ ID NO: 733, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 733. In one embodiment, the anti-LAG-3 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 709 and a light chain comprising the amino acid sequence of SEQ ID NO: 721. In one embodiment, the anti-LAG-3 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 727 and a light chain comprising the amino acid sequence of SEQ ID NO: 733.

In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 716 or 717, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 716 or 717. In one embodiment, the antibody molecule comprises a light chain encoded by the nucleotide sequence of SEQ ID NO: 722 or 723, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 722 or 723. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 728 or 729, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 728 or 729. In one embodiment, the antibody molecule comprises a light chain encoded by the nucleotide sequence of SEQ ID NO: 734 or 735, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 734 or 735. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 716 or 717 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 722 or 723. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 728 or 729 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 734 or 735.

Other Exemplary LAG-3 Inhibitors

In one embodiment, the anti-LAG-3 antibody molecule is BMS-986016 (Bristol-Myers Squibb), also known as BMS986016. BMS-986016 and other anti-LAG-3 antibodies are disclosed in WO 2015/116539 and US 9,505,839, incorporated by reference in their entirety. In one embodiment, the anti-LAG-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of BMS-986016, *e.g.*, as disclosed in Table 6.

In one embodiment, the anti-LAG-3 antibody molecule is TSR-033 (Tesaro). In one embodiment, the anti-LAG-3 antibody molecule comprises one or more of the CDR sequences (or

collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of TSR-033.

In one embodiment, the anti-LAG-3 antibody molecule is IMP731 or GSK2831781 (GSK and Prima BioMed). IMP731 and other anti-LAG-3 antibodies are disclosed in WO 2008/132601 and US
5 9,244,059, incorporated by reference in their entirety. In one embodiment, the anti-LAG-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of IMP731, *e.g.*, as disclosed in Table 6. In one embodiment, the anti-LAG-3 antibody molecule
10 comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of GSK2831781.

In one embodiment, the anti-LAG-3 antibody molecule is IMP761 (Prima BioMed). In one embodiment, the anti-LAG-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the
15 heavy chain or light chain sequence of IMP761.

Further known anti-LAG-3 antibodies include those described, *e.g.*, in WO 2008/132601, WO 2010/019570, WO 2014/140180, WO 2015/116539, WO 2015/200119, WO 2016/028672, US 9,244,059, US 9,505,839, incorporated by reference in their entirety.

In one embodiment, the anti-LAG-3 antibody is an antibody that competes for binding with,
20 and/or binds to the same epitope on LAG-3 as, one of the anti-LAG-3 antibodies described herein.

In one embodiment, the anti-LAG-3 inhibitor is a soluble LAG-3 protein, *e.g.*, IMP321 (Prima BioMed), *e.g.*, as disclosed in WO 2009/044273, incorporated by reference in its entirety.

Formulations

25 The anti-LAG-3 antibody molecules described herein can be formulated into a formulation (*e.g.*, a dose formulation or dosage form) suitable for administration (*e.g.*, intravenous administration) to a subject as described herein. The formulation described herein can be a liquid formulation, a lyophilized formulation, or a reconstituted formulation.

In certain embodiments, the formulation is a liquid formulation. In some embodiments, the
30 formulation (*e.g.*, liquid formulation) comprises an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein) and a buffering agent.

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-LAG-3 antibody molecule present at a concentration of 25 mg/mL to 250 mg/mL, *e.g.*, 50 mg/mL to 200 mg/mL, 60 mg/mL to 180 mg/mL, 70 mg/mL to 150 mg/mL, 80 mg/mL to 120 mg/mL, 90 mg/mL to
35 110 mg/mL, 50 mg/mL to 150 mg/mL, 50 mg/mL to 100 mg/mL, 150 mg/mL to 200 mg/mL, or 100 mg/mL to 200 mg/mL, *e.g.*, 50 mg/mL, 60 mg/mL, 70 mg/mL, 80 mg/mL, 90 mg/mL, 100 mg/mL,

110 mg/mL, 120 mg/mL, 130 mg/mL, 140 mg/mL, or 150 mg/mL. In certain embodiments, the anti-LAG-3 antibody molecule is present at a concentration of 80 mg/mL to 120 mg/mL, *e.g.*, 100 mg/mL.

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises a buffering agent comprising histidine (*e.g.*, a histidine buffer). In certain embodiments, the buffering agent (*e.g.*, histidine buffer) is present at a concentration of 1 mM to 100 mM, *e.g.*, 2 mM to 50 mM, 5 mM to 40 mM, 10 mM to 30 mM, 15 to 25 mM, 5 mM to 40 mM, 5 mM to 30 mM, 5 mM to 20 mM, 5 mM to 10 mM, 40 mM to 50 mM, 30 mM to 50 mM, 20 mM to 50 mM, 10 mM to 50 mM, or 5 mM to 50 mM, *e.g.*, 2 mM, 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM, or 50 mM. In some embodiments, the buffering agent (*e.g.*, histidine buffer) is present at a concentration of 15 mM to 25 mM, *e.g.*, 20 mM. In other embodiments, the buffering agent (*e.g.*, a histidine buffer) or the formulation has a pH of 4 to 7, *e.g.*, 5 to 6, *e.g.*, 5, 5.5, or 6. In some embodiments, the buffering agent (*e.g.*, histidine buffer) or the formulation has a pH of 5 to 6, *e.g.*, 5.5. In certain embodiments, the buffering agent comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM) and has a pH of 5 to 6 (*e.g.*, 5.5). In certain embodiments, the buffering agent comprises histidine and histidine-HCl.

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-LAG-3 antibody molecule present at a concentration of 80 to 120 mg/mL, *e.g.*, 100 mg/mL; and a buffering agent that comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM), at a pH of 5 to 6 (*e.g.*, 5.5).

In some embodiments, the formulation (*e.g.*, liquid formulation) further comprises a carbohydrate. In certain embodiments, the carbohydrate is sucrose. In some embodiments, the carbohydrate (*e.g.*, sucrose) is present at a concentration of 50 mM to 500 mM, *e.g.*, 100 mM to 400 mM, 150 mM to 300 mM, 180 mM to 250 mM, 200 mM to 240 mM, 210 mM to 230 mM, 100 mM to 300 mM, 100 mM to 250 mM, 100 mM to 200 mM, 100 mM to 150 mM, 300 mM to 400 mM, 200 mM to 400 mM, or 100 mM to 400 mM, *e.g.*, 100 mM, 150 mM, 180 mM, 200 mM, 220 mM, 250 mM, 300 mM, 350 mM, or 400 mM. In some embodiments, the formulation comprises a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, *e.g.*, 220 mM.

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-LAG-3 antibody molecule present at a concentration of 80 to 120 mg/mL, *e.g.*, 100 mg/mL; a buffering agent that comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM); and a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, *e.g.*, 220 mM, at a pH of 5 to 6 (*e.g.*, 5.5).

In some embodiments, the formulation (*e.g.*, liquid formulation) further comprises a surfactant. In certain embodiments, the surfactant is polysorbate 20. In some embodiments, the surfactant or polysorbate 20) is present at a concentration of 0.005 % to 0.1% (w/w), *e.g.*, 0.01% to 0.08%, 0.02% to 0.06%, 0.03% to 0.05%, 0.01% to 0.06%, 0.01% to 0.05%, 0.01% to 0.03%, 0.06% to 0.08%, 0.04% to 0.08%, or 0.02% to 0.08% (w/w), *e.g.*, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%,

0.06%, 0.07%, 0.08%, 0.09%, or 0.1% (w/w). In some embodiments, the formulation comprises a surfactant or polysorbate 20 present at a concentration of 0.03% to 0.05%, *e.g.*, 0.04% (w/w).

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-LAG-3 antibody molecule present at a concentration of 80 to 120 mg/mL, *e.g.*, 100 mg/mL; a buffering agent that comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM); a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, *e.g.*, 220 mM; and a surfactant or polysorbate 20 present at a concentration of 0.03% to 0.05%, *e.g.*, 0.04% (w/w), at a pH of 5 to 6 (*e.g.*, 5.5).

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-LAG-3 antibody molecule present at a concentration of 100 mg/mL; a buffering agent that comprises a histidine buffer (*e.g.*, histidine/histidine-HCL) at a concentration of 20 mM); a carbohydrate or sucrose present at a concentration of 220 mM; and a surfactant or polysorbate 20 present at a concentration of 0.04% (w/w), at a pH of 5 to 6 (*e.g.*, 5.5).

A formulation described herein can be stored in a container. The container used for any of the formulations described herein can include, *e.g.*, a vial, and optionally, a stopper, a cap, or both. In certain embodiments, the vial is a glass vial, *e.g.*, a 6R white glass vial. In other embodiments, the stopper is a rubber stopper, *e.g.*, a grey rubber stopper. In other embodiments, the cap is a flip-off cap, *e.g.*, an aluminum flip-off cap. In some embodiments, the container comprises a 6R white glass vial, a grey rubber stopper, and an aluminum flip-off cap. In some embodiments, the container (*e.g.*, vial) is for a single-use container. In certain embodiments, 25 mg/mL to 250 mg/mL, *e.g.*, 50 mg/mL to 200 mg/mL, 60 mg/mL to 180 mg/mL, 70 mg/mL to 150 mg/mL, 80 mg/mL to 120 mg/mL, 90 mg/mL to 110 mg/mL, 50 mg/mL to 150 mg/mL, 50 mg/mL to 100 mg/mL, 150 mg/mL to 200 mg/mL, or 100 mg/mL to 200 mg/mL, *e.g.*, 50 mg/mL, 60 mg/mL, 70 mg/mL, 80 mg/mL, 90 mg/mL, 100 mg/mL, 110 mg/mL, 120 mg/mL, 130 mg/mL, 140 mg/mL, or 150 mg/mL, of the anti-LAG-3 antibody molecule, is present in the container (*e.g.*, vial).

In another aspect, the disclosure features therapeutic kits that include the anti-LAG-3 antibody molecules, compositions, or formulations described herein, and instructions for use, *e.g.*, in accordance with dosage regimens described herein.

30 **Therapeutic Use**

The anti-LAG-3 antibody molecules described herein can inhibit, reduce, or neutralize one or more activities of LAG-3, resulting in blockade or reduction of an immune checkpoint. Thus, the anti-LAG-3 antibody molecules described herein can be used to treat or prevent disorders (*e.g.*, cancer), where enhancing an immune response in a subject is desired.

35 Accordingly, in another aspect, a method of modulating an immune response in a subject is provided. The method comprises administering to the subject an anti-LAG-3 antibody molecule described herein in accordance with a dosage regimen described herein, alone or in combination with

one or more therapeutic agents, procedures, or modalities, such that the immune response in the subject is modulated. In one embodiment, the antibody molecule enhances, stimulates or increases the immune response in the subject. The subject can be a mammal, *e.g.*, a primate, preferably a higher primate, *e.g.*, a human (*e.g.*, a patient having, or at risk of having, a disorder described herein).

5 In one embodiment, the subject is in need of enhancing an immune response. In one embodiment, the subject has, or is at risk of, having a disorder described herein, *e.g.*, a cancer or an infectious disorder as described herein. In certain embodiments, the subject is, or is at risk of being, immunocompromised. For example, the subject is undergoing or has undergone a chemotherapeutic treatment and/or radiation therapy. Alternatively, or in combination, the subject is, or is at risk of
10 being, immunocompromised as a result of an infection.

In one aspect, a method of treating (*e.g.*, one or more of reducing, inhibiting, or delaying progression) a cancer or a tumor in a subject is provided. The method comprises administering to the subject an anti-LAG-3 antibody molecule described herein in accordance with a dosage regimen described herein, alone or in combination with one or more therapeutic agents, procedures, or
15 modalities.

In certain embodiments, the cancer treated with the anti-LAG-3 antibody molecule, includes but is not limited to, a solid tumor, a hematological cancer (*e.g.*, leukemia, lymphoma, myeloma, *e.g.*, multiple myeloma), and a metastatic lesion. In one embodiment, the cancer is a solid tumor. Examples of solid tumors include malignancies, *e.g.*, sarcomas and carcinomas, *e.g.*, adenocarcinomas
20 of the various organ systems, such as those affecting the lung, breast, ovarian, lymphoid, gastrointestinal (*e.g.*, colon), anal, genitals and genitourinary tract (*e.g.*, renal, urothelial, bladder cells, prostate), pharynx, CNS (*e.g.*, brain, neural or glial cells), head and neck, skin (*e.g.*, melanoma), and pancreas, as well as adenocarcinomas which include malignancies such as colon cancers, rectal cancer, renal cancer (*e.g.*, renal-cell carcinoma (clear cell or non-clear cell renal cell carcinoma)), liver cancer,
25 lung cancer (*e.g.*, non-small cell lung cancer (squamous or non-squamous non-small cell lung cancer)), cancer of the small intestine and cancer of the esophagus. The cancer may be at an early, intermediate, late stage or metastatic cancer.

In one embodiment, the cancer is chosen from a lung cancer (*e.g.*, a non-small cell lung cancer (NSCLC) (*e.g.*, a NSCLC with squamous and/or non-squamous histology, or a NSCLC
30 adenocarcinoma), or a small cell lung cancer (SCLC)), a skin cancer (*e.g.*, a Merkel cell carcinoma or a melanoma (*e.g.*, an advanced melanoma)), an ovarian cancer, a mesothelioma, a bladder cancer, a soft tissue sarcoma (*e.g.*, a hemangiopericytoma (HPC)), a bone cancer (a bone sarcoma), a kidney cancer (*e.g.*, a renal cancer (*e.g.*, a renal cell carcinoma)), a liver cancer (*e.g.*, a hepatocellular carcinoma), a cholangiocarcinoma, a sarcoma, a myelodysplastic syndrome (MDS), a prostate cancer,
35 a breast cancer (*e.g.*, a breast cancer that does not express one, two or all of estrogen receptor, progesterone receptor, or Her2/neu, *e.g.*, a triple negative breast cancer), a colorectal cancer, a nasopharyngeal cancer, a duodenal cancer, an endometrial cancer, a pancreatic cancer, a head and

neck cancer (*e.g.*, head and neck squamous cell carcinoma (HNSCC)), an anal cancer, a gastro-
esophageal cancer, a thyroid cancer (*e.g.*, anaplastic thyroid carcinoma), a cervical cancer, a
neuroendocrine tumor (NET) (*e.g.*, an atypical pulmonary carcinoid tumor), a lymphoproliferative
disease (*e.g.*, a post-transplant lymphoproliferative disease), a lymphoma (*e.g.*, T-cell lymphoma, B-
5 cell lymphoma, or a non-Hodgkin lymphoma), a myeloma (*e.g.*, a multiple myeloma), or a leukemia
(*e.g.*, a myeloid leukemia or a lymphoid leukemia).

In certain embodiments, the cancer is a solid tumor. In some embodiments, the cancer is
brain tumor, *e.g.*, a glioblastoma, a gliosarcoma, or a recurrent brain tumor. In some embodiments,
the cancer is a pancreatic cancer, *e.g.*, an advanced pancreatic cancer. In some embodiments, the
10 cancer is a skin cancer, *e.g.*, a melanoma (*e.g.*, a stage II-IV melanoma, an HLA-A2 positive
melanoma, an unresectable melanoma, or a metastatic melanoma), or a Merkel cell carcinoma. In
some embodiments, the cancer is a renal cancer, *e.g.*, a renal cell carcinoma (RCC) (*e.g.*, a metastatic
renal cell carcinoma). In some embodiments, the cancer is a breast cancer, *e.g.*, a metastatic breast
carcinoma or a stage IV breast carcinoma, *e.g.*, a triple negative breast cancer (TNBC). In some
15 embodiments, the cancer is a virus-associated cancer. In some embodiments, the cancer is an anal
canal cancer (*e.g.*, a squamous cell carcinoma of the anal canal). In some embodiments, the cancer is
a cervical cancer (*e.g.*, a squamous cell carcinoma of the cervix). In some embodiments, the cancer is
a gastric cancer (*e.g.*, an Epstein Barr Virus (EBV) positive gastric cancer, or a gastric or gastro-
esophageal junction carcinoma). In some embodiments, the cancer is a head and neck cancer (*e.g.*, an
20 HPV positive and negative squamous cell cancer of the head and neck (SCCHN)). In some
embodiments, the cancer is a nasopharyngeal cancer (NPC). In some embodiments, the cancer is a
penile cancer (*e.g.*, a squamous cell carcinoma of the penile). In some embodiments, the cancer is a
vaginal or vulvar cancer (*e.g.*, a squamous cell carcinoma of the vagina or vulva). In some
embodiments, the cancer is a colorectal cancer, *e.g.*, a relapsed colorectal cancer or a metastatic
25 colorectal cancer, *e.g.*, a microsatellite unstable colorectal cancer, a microsatellite stable colorectal
cancer, a mismatch repair proficient colorectal cancer, or a mismatch repair deficient colorectal cancer.
In some embodiments, the cancer is a lung cancer, *e.g.*, a non-small cell lung cancer (NSCLC).

In certain embodiments, the cancer is a hematological cancer. In some embodiments, the
cancer is a leukemia. In some embodiments, the cancer is a lymphoma, *e.g.*, a Hodgkin lymphoma
30 (HL) or a diffuse large B cell lymphoma (DLBCL) (*e.g.*, a relapsed or refractory HL or DLBCL). In
some embodiments, the cancer is a myeloma

In another embodiment, the cancer is chosen from a carcinoma (*e.g.*, advanced or metastatic
carcinoma), melanoma or a lung carcinoma, *e.g.*, a non-small cell lung carcinoma. In one
embodiment, the cancer is a lung cancer, *e.g.*, a non-small cell lung cancer or small cell lung cancer.
35 In some embodiments, the non-small cell lung cancer is a stage I (*e.g.*, stage Ia or Ib), stage II (*e.g.*,
stage IIa or IIb), stage III (*e.g.*, stage IIIa or IIIb), or stage IV, non-small cell lung cancer. In one
embodiment, the cancer is a melanoma, *e.g.*, an advanced melanoma. In one embodiment, the cancer

is an advanced or unresectable melanoma that does not respond to other therapies. In other embodiments, the cancer is a melanoma with a BRAF mutation (*e.g.*, a BRAF V600 mutation). In another embodiment, the cancer is a hepatocarcinoma, *e.g.*, an advanced hepatocarcinoma, with or without a viral infection, *e.g.*, a chronic viral hepatitis. In another embodiment, the cancer is a prostate cancer, *e.g.*, an advanced prostate cancer. In yet another embodiment, the cancer is a myeloma, *e.g.*, multiple myeloma. In yet another embodiment, the cancer is a renal cancer, *e.g.*, a renal cell carcinoma (RCC) (*e.g.*, a metastatic RCC, a non-clear cell renal cell carcinoma (nccRCC), or clear cell renal cell carcinoma (CCRCC)).

In one embodiment, the cancer microenvironment has an elevated level of LAG-3 expression.

In one embodiment, the cancer microenvironment has an elevated level of PD-L1 expression.

Alternatively, or in combination, the cancer microenvironment can have increased IFN γ and/or CD8 expression.

In some embodiments, the subject has, or is identified as having, a tumor that has one or more of high PD-L1 level or expression, or as being Tumor Infiltrating Lymphocyte (TIL)+ (*e.g.*, as having an increased number of TILs), or both. In certain embodiments, the subject has, or is identified as having, a tumor that has high PD-L1 level or expression and that is TIL+. In some embodiments, the methods described herein further include identifying a subject based on having a tumor that has one or more of high PD-L1 level or expression, or as being TIL+, or both. In certain embodiments, the methods described herein further include identifying a subject based on having a tumor that has high PD-L1 level or expression and as being TIL+. In some embodiments, tumors that are TIL+ are positive for CD8 and IFN γ . In some embodiments, the subject has, or is identified as having, a high percentage of cells that are positive for one, two or more of PD-L1, CD8, and/or IFN γ . In certain embodiments, the subject has or is identified as having a high percentage of cells that are positive for all of PD-L1, CD8, and IFN γ .

In some embodiments, the methods described herein further include identifying a subject based on having a high percentage of cells that are positive for one, two or more of PD-L1, CD8, and/or IFN γ . In certain embodiments, the methods described herein further include identifying a subject based on having a high percentage of cells that are positive for all of PD-L1, CD8, and IFN γ . In some embodiments, the subject has, or is identified as having, one, two or more of PD-L1, CD8, and/or IFN γ , and one or more of a lung cancer, *e.g.*, squamous cell lung cancer or lung adenocarcinoma (*e.g.*, an NSCLC); a head and neck cancer; a squamous cell cervical cancer; a stomach cancer; an esophageal cancer; a thyroid cancer (*e.g.*, anaplastic thyroid carcinoma); a skin cancer (*e.g.*, a Merkel cell carcinoma or a melanoma), a breast cancer (*e.g.*, a TNBC), and/or a nasopharyngeal cancer (NPC). In certain embodiments, the methods described herein further describe identifying a subject based on having one, two or more of PD-L1, CD8, and/or IFN γ , and one or more of a lung cancer, *e.g.*, squamous cell lung cancer or lung adenocarcinoma (*e.g.*, an NSCLC); a head and neck cancer; a squamous cell cervical cancer; a stomach cancer; a thyroid cancer (*e.g.*, anaplastic

thyroid carcinoma); a skin cancer (*e.g.*, a Merkel cell carcinoma or a melanoma), an neuroendocrine tumor, a breast cancer (*e.g.*, a TNBC), and/or a nasopharyngeal cancer.

Methods, compositions, and formulations disclosed herein are useful for treating metastatic lesions associated with the aforementioned cancers.

5 In a further aspect, the disclosure provides a method of treating an infectious disease (*e.g.*, an infectious disease described herein) in a subject, comprising administering to the subject an anti-LAG-3 antibody molecule described herein in accordance with a dosage regimen described herein.

10 Still further, the invention provides a method of enhancing an immune response to an antigen in a subject, comprising administering to the subject: (i) the antigen; and (ii) an anti-LAG-3 antibody molecule described herein, in accordance with a dosage regimen described herein, such that an immune response to the antigen in the subject is enhanced. The antigen can be, for example, a tumor antigen, a viral antigen, a bacterial antigen or an antigen from a pathogen.

15 The anti-LAG-3 antibody molecule described herein can be administered to the subject systemically (*e.g.*, orally, parenterally, subcutaneously, intravenously, rectally, intramuscularly, intraperitoneally, intranasally, transdermally, or by inhalation or intracavitary installation), topically, or by application to mucous membranes, such as the nose, throat and bronchial tubes. In certain embodiments, the anti-LAG-3 antibody molecule is administered intravenously at a flat dose described herein.

20 **Combination Therapies**

The anti-LAG-3 antibody molecules described herein can be used in combination with other therapeutic agents, procedures or modalities.

25 In one embodiment, the methods described herein include administering to the subject a combination comprising an anti-LAG-3 antibody molecule described herein, in combination with a therapeutic agent, procedure, or modality, in an amount effective to treat or prevent a disorder. In certain embodiments, the anti-LAG-3 antibody molecule is administered or used in accordance with a dosage regimen described herein. In other embodiments, the antibody molecule is administered or used as a composition or formulation described herein.

30 The anti-LAG-3 antibody molecule and the therapeutic agent, procedure, or modality can be administered or used simultaneously or sequentially in any order. Any combination and sequence of the anti-LAG-3 antibody molecule and the therapeutic agent, procedure, or modality (*e.g.*, as described herein) can be used. The antibody molecule and/or the therapeutic agent, procedure or modality can be administered or used during periods of active disorder, or during a period of remission or less active disease. The antibody molecule can be administered before, concurrently
35 with, or after the treatment with the therapeutic agent, procedure or modality.

In certain embodiments, the anti-LAG-3 antibody molecule described herein is administered in combination with one or more of other antibody molecules, chemotherapy, other anti-cancer

therapy (*e.g.*, targeted anti-cancer therapies, gene therapy, viral therapy, RNA therapy bone marrow transplantation, nanotherapy, or oncolytic drugs), cytotoxic agents, immune-based therapies (*e.g.*, cytokines or cell-based immune therapies), surgical procedures (*e.g.*, lumpectomy or mastectomy) or radiation procedures, or a combination of any of the foregoing. The additional therapy may be in the form of adjuvant or neoadjuvant therapy. In some embodiments, the additional therapy is an enzymatic inhibitor (*e.g.*, a small molecule enzymatic inhibitor) or a metastatic inhibitor. Exemplary cytotoxic agents that can be administered in combination include antimicrotubule agents, topoisomerase inhibitors, anti-metabolites, mitotic inhibitors, alkylating agents, anthracyclines, vinca alkaloids, intercalating agents, agents capable of interfering with a signal transduction pathway, agents that promote apoptosis, proteasome inhibitors, and radiation (*e.g.*, local or whole body irradiation (*e.g.*, gamma irradiation)). In other embodiments, the additional therapy is surgery or radiation, or a combination thereof. In other embodiments, the additional therapy is a therapy targeting one or more of PI3K/AKT/mTOR pathway, an HSP90 inhibitor, or a tubulin inhibitor.

Alternatively, or in combination with the aforesaid combinations, the anti-LAG-3 antibody described herein can be administered or used in combination with, one or more of: an immunomodulator (*e.g.*, an activator of a costimulatory molecule or an inhibitor of an inhibitory molecule, *e.g.*, an immune checkpoint molecule); a vaccine, *e.g.*, a therapeutic cancer vaccine; or other forms of cellular immunotherapy.

In certain embodiments, the anti-LAG-3 molecule described herein is administered or used in combination with a modulator of a costimulatory molecule or an inhibitory molecule, *e.g.*, a co-inhibitory ligand or receptor.

In one embodiment, the anti-LAG-3 antibody molecule described herein is administered or used in combination with a modulator, *e.g.*, agonist, of a costimulatory molecule. In one embodiment, the agonist of the costimulatory molecule is chosen from an agonist (*e.g.*, an agonistic antibody or antigen-binding fragment thereof, or a soluble fusion) of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3 or CD83 ligand.

In another embodiment, the anti-LAG-3 antibody molecule described herein is administered or used in combination with a GITR agonist, *e.g.*, an anti-GITR antibody molecule.

In one embodiment, the anti-LAG-3 antibody molecule described herein is administered or used in combination with an inhibitor of an inhibitory (or immune checkpoint) molecule chosen from PD-1, PD-L1, PD-L2, CTLA-4, TIM-3, LAG-3, CEACAM (*e.g.*, CEACAM-1, CEACAM-3, and/or CEACAM-5), VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGF beta. In one embodiment, the inhibitor is a soluble ligand (*e.g.*, a CTLA-4-Ig), or an antibody or antibody fragment that binds to PD-1, LAG-3, PD-L1, PD-L2, or CTLA-4.

In another embodiment, the anti-LAG-3 antibody molecule described herein is administered or used in combination with a PD-1 inhibitor, *e.g.*, an anti-PD-1 antibody molecule. In another

embodiment, the anti-LAG-3 antibody molecule described herein is administered or used in combination with a TIM-3 inhibitor, *e.g.*, an anti-TIM-3 antibody molecule. In another embodiment, the anti-LAG-3 antibody molecule described herein is administered or used in combination with a PD-L1 inhibitor, *e.g.*, an anti-PD-L1 antibody molecule.

5 In another embodiment, the anti-LAG-3 antibody molecule described herein is administered or used in combination with a chemotherapeutic agent. In certain embodiments, the chemotherapeutic agent comprises a platinum agent (*e.g.*, carboplatin, cisplatin, oxaliplatin, or tetraplatin). In certain embodiments, the chemotherapeutic agent comprises cisplatin, perimetrexed, or both. Cisplatin is also known as cisplatinum, platamin, neoplatin, cismaplat, or cis-diamminedichloridoplatinum(II) (CDDP).
10 Perimetrexed is also known as (S)-2-(4-(2-(2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzamido)pentanedioic acid. In certain embodiments, the chemotherapeutic agent comprises a nucleotide analog or precursor analog (*e.g.*, capecitabine, azacitidine, azathioprine, cytarabine, doxifluridine, fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, or tioguanine (thioguanine)). In certain embodiments, the chemotherapeutic agent comprises a
15 hypomethylating agent (*e.g.*, decitabine). In one embodiment, the chemotherapeutic agent comprises nab-paclitaxel.

Other exemplary chemotherapeutic agents that can be used in combination with the anti-LAG-3 antibody molecule include, but are not limited to, an alkylating agent (*e.g.*, a bifunctional alkylator (*e.g.*, cyclophosphamide, a mechlorethamine, chlorambucil, or melphalan)), a
20 monofunctional alkylator (*e.g.*, dacarbazine (DTIC), nitrosoureas, or temozolomide (oral dacarbazine)), an anthracycline (*e.g.*, daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, or valrubicin), a cytoskeletal disruptor or taxane (*e.g.*, paclitaxel, docetaxel, abraxane, or taxotere), an epothilone, a histone deacetylase inhibitor (*e.g.*, vorinostat or romidepsin), an inhibitor of topoisomerase I (*e.g.*, irinotecan or topotecan), an inhibitor of topoisomerase II (*e.g.*, etoposide,
25 teniposide, or tafluposide), a kinase inhibitor (*e.g.*, bortezomib, erlotinib, gefitinib, imatinib, vemurafenib, or vismodegib), a peptide antibiotic (*e.g.*, bleomycin or actinomycin), a retinoid (*e.g.*, tretinoin, alitretinoin, or bexarotene), or a vinca alkaloid or derivative thereof (*e.g.*, vinblastine, vincristine, vindesine, or vinorelbine).

In another embodiment, the anti-LAG-3 antibody molecule described herein is administered
30 or used in combination with a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule) and a TIM-3 inhibitor (*e.g.*, an anti-TIM-3 antibody molecule). In another embodiment, the anti-LAG-3 antibody molecule described herein is administered or used in combination with a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule) and a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule). In another embodiment, the anti-LAG-3 antibody molecule described herein is administered or used in
35 combination with a TIM-3 inhibitor (*e.g.*, an anti-TIM-3 antibody molecule) and a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule). In another embodiment, the anti-LAG-3 antibody molecule described herein is administered or used in combination with a PD-1 inhibitor (*e.g.*, an anti-PD-1

antibody molecule) and a chemotherapeutic agent (*e.g.*, a platinum agent (*e.g.*, carboplatin, cisplatin, oxaliplatin, or tetraplatin) or a nucleotide analog or precursor analog (*e.g.*, capecitabine)). In another embodiment, the anti-LAG-3 antibody molecule described herein is administered or used in combination with a CEACAM inhibitor (*e.g.*, CEACAM-1, CEACAM-3, and/or CEACAM-5 inhibitor), *e.g.*, an anti-CEACAM antibody molecule. In another embodiment, the anti-LAG-3 antibody molecule is administered or used in combination with a CEACAM-1 inhibitor, *e.g.*, an anti-CEACAM-1 antibody molecule. In another embodiment, the anti-LAG-3 antibody molecule is administered or used in combination with a CEACAM-3 inhibitor, *e.g.*, an anti-CEACAM-3 antibody molecule. In another embodiment, the anti-LAG-3 antibody molecule is administered or used in combination with a CEACAM-5 inhibitor, *e.g.*, an anti-CEACAM-5 antibody molecule.

The combination of antibody molecules disclosed herein can be administered separately, *e.g.*, as separate antibody molecules, or linked, *e.g.*, as a bispecific or trispecific antibody molecule. In one embodiment, a bispecific antibody that includes an anti-LAG-3 antibody molecule and an anti-PD-1, anti-CEACAM (*e.g.*, anti-CEACAM-1, CEACAM-3, and/or anti-CEACAM-5), anti-PD-L1, or anti-TIM-3 antibody molecule, is administered. In certain embodiments, the combination of antibodies disclosed herein is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor or a hematologic malignancy).

In another embodiment, the anti-LAG-3 antibody molecule is administered or used in combination with an anti-PD-1 antibody molecule, *e.g.*, to treat a brain cancer (*e.g.*, a glioblastoma), a melanoma, a renal cancer (*e.g.*, a renal cell carcinoma), a virus-associated cancer (*e.g.*, an anal canal cancer, a cervical cancer, a gastric cancer, a head and neck cancer, a nasopharyngeal cancer (NPC), a penile cancer, or a vaginal or vulvar cancer), a colorectal cancer, or a lung cancer (*e.g.*, a non-small cell lung cancer (NSCLC)). In certain embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with an anti-PD-1 antibody molecule, *e.g.*, to treat a breast cancer, *e.g.*, a triple negative breast cancer (TNBC).

In another embodiment, the anti-LAG-3 antibody molecule is administered or used in combination with a chemotherapeutic agent (*e.g.*, gemcitabine, paclitaxel), *e.g.*, to treat a pancreatic cancer or a breast cancer.

In another embodiment, the anti-LAG-3 antibody molecule is administered or used in combination with a chemotherapeutic agent (*e.g.*, a platinum agent (*e.g.*, carboplatin, cisplatin, oxaliplatin, or tetraplatin) or a nucleotide analog or precursor analog (*e.g.*, capecitabine)), *e.g.*, to treat a breast cancer, *e.g.*, a TNBC. In certain embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with an anti-PD-1 antibody molecule and a chemotherapeutic agent (*e.g.*, a platinum agent (*e.g.*, carboplatin, cisplatin, oxaliplatin, or tetraplatin) or a nucleotide analog or precursor analog (*e.g.*, capecitabine)), *e.g.*, to treat a breast cancer, *e.g.*, a TNBC. In other embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with a cytokine. The cytokine can be administered as a fusion molecule to the anti-LAG-3 antibody

molecule, or as separate compositions. In other embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with one, two, three or more cytokines, *e.g.*, as a fusion molecule or as separate compositions. In one embodiment, the cytokine is an interleukin (IL) chosen from one, two, three or more of IL-1, IL-2, IL-12, IL-15 or IL-21. In one embodiment, a bispecific antibody molecule has a first binding specificity to a first target (*e.g.*, to LAG-3), a second binding specificity to a second target (*e.g.*, PD-1, TIM-3, or PD-L1), and is optionally linked to an interleukin (*e.g.*, IL-12) domain *e.g.*, full length IL-12 or a portion thereof. In certain embodiments, the combination of anti-LAG-3 antibody molecule and the cytokine described herein is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor).

10 In other embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with an antibody specific against an HLA C, *e.g.*, an antibody specific to Killer-cell Immunoglobulin-like Receptors (also referred to herein as an “anti-KIR antibody”). In certain embodiments, the combination of anti-LAG-3 antibody molecule and anti-KIR antibody is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor, *e.g.*, an advanced solid tumor).

15 In other embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with a cellular immunotherapy (*e.g.*, PROVENGE® (*e.g.*, Sipuleucel-T)), and optionally in combination with cyclophosphamide. In certain embodiments, the combination of anti-LAG-3 antibody molecule, PROVENGE® and/or cyclophosphamide is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a prostate cancer, *e.g.*, an advanced prostate cancer).

20 In other embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with a vaccine, *e.g.*, a cancer vaccine, (*e.g.*, a dendritic cell renal carcinoma (DC-RCC) vaccine). In one embodiment, the vaccine is peptide-based, DNA-based, RNA-based, or antigen-based, or a combination thereof. In embodiments, the vaccine comprises one or more peptides, nucleic acids (*e.g.*, DNA or RNA), antigens, or a combination thereof. In certain embodiments, the combination of anti-TIM-3 antibody molecule and the DC-RCC vaccine is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a renal carcinoma, *e.g.*, metastatic renal cell carcinoma (RCC) or clear cell renal cell carcinoma (CCRCC)).

In other embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with an adjuvant.

30 In other embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with chemotherapy, and/or immunotherapy. For example, the anti-LAG-3 antibody molecule can be used to treat a myeloma, alone or in combination with one or more of: chemotherapy or other anti-cancer agents (*e.g.*, thalidomide analogs, *e.g.*, lenalidomide), an anti-PD-1 antibody molecule, tumor antigen-pulsed dendritic cells, fusions (*e.g.*, electrofusions) of tumor cells and dendritic cells, or vaccination with immunoglobulin idiotype produced by malignant plasma cells. In other embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with an anti-PD-1 antibody molecule to treat a myeloma, *e.g.*, a multiple myeloma.

In other embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with chemotherapy to treat a lung cancer, *e.g.*, non-small cell lung cancer. In other embodiments, the anti-LAG-3 antibody molecule is administered or used with standard lung, *e.g.*, NSCLC, chemotherapy, *e.g.*, platinum doublet therapy, to treat lung cancer. In other embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with an indoleamine-pyrrole 2,3-dioxygenase (IDO) inhibitor (*e.g.*, (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine (also known as INCB24360), indoximod (1-methyl-D-tryptophan), α -cyclohexyl-5H-Imidazo[5,1-a]isoindole-5-ethanol (also known as NLG919), etc.) in a subject with advanced or metastatic cancer (*e.g.*, a patient with metastatic and recurrent NSCL cancer).

In yet other embodiments, In other embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with one or more of: an immune-based strategy (*e.g.*, interleukin-2 or interferon- α), a targeting agent (*e.g.*, a VEGF inhibitor such as a monoclonal antibody to VEGF); a VEGF tyrosine kinase inhibitor such as sunitinib, sorafenib, axitinib and pazopanib; an RNAi inhibitor; or an inhibitor of a downstream mediator of VEGF signaling, *e.g.*, an inhibitor of the mammalian target of rapamycin (mTOR), *e.g.*, everolimus and temsirolimus. Any of such combinations can be used to treat a renal cancer, *e.g.*, renal cell carcinoma (RCC) (*e.g.*, clear cell renal cell carcinoma (CCRCC) or a non-clear cell renal cell carcinoma (nccRCC) or metastatic RCC), or a liver cancer (*e.g.*, a hepatocellular carcinoma).

In other embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with a MEK inhibitor (*e.g.*, a MEK inhibitor as described herein). In some embodiments, the combination of the anti-LAG-3 antibody molecule and the MEK inhibitor is used to treat a cancer (*e.g.*, a cancer described herein). In some embodiments, the cancer treated with the combination is chosen from a melanoma, a colorectal cancer, a non-small cell lung cancer, an ovarian cancer, a breast cancer, a prostate cancer, a pancreatic cancer, a hematological malignancy or a renal cell carcinoma. In certain embodiments, the cancer includes a BRAF mutation (*e.g.*, a BRAF V600E mutation), a BRAF wildtype, a KRAS wildtype or an activating KRAS mutation. The cancer may be at an early, intermediate or late stage.

In other embodiments, the anti-LAG-3 antibody molecule is administered or used in combination with one, two or all of a chemotherapeutic agent (*e.g.*, a platinum agent (*e.g.*, carboplatin, oxaliplatin, cisplatin, or tetraplatin) or a nucleotide analog or precursor analog (*e.g.*, capecitabine)), leucovorin or 5-FU (*e.g.*, a FOLFOX co-treatment). Alternatively or in combination, combination further includes a VEGF inhibitor (*e.g.*, a VEGF inhibitor as disclosed herein). In some embodiments, the combination of the anti-LAG-3 antibody molecule, the FOLFOX co-treatment, and the VEGF inhibitor is used to treat a cancer (*e.g.*, a cancer described herein). In some embodiments, the cancer treated with the combination is chosen from a melanoma, a colorectal cancer, a non-small cell lung cancer, an ovarian cancer, a breast cancer, a prostate cancer, a pancreatic cancer, a

hematological malignancy or a renal cell carcinoma. The cancer may be at an early, intermediate or late stage.

In other embodiments, the anti-LAG-3 antibody molecule is administered or used with a tyrosine kinase inhibitor (*e.g.*, axitinib) to treat renal cell carcinoma and other solid tumors.

5 In other embodiments, the anti-LAG-3 antibody molecule is administered or used with a 4-1BB receptor targeting agent (*e.g.*, an antibody that stimulates signaling through 4-1BB (CD-137), *e.g.*, PF-2566). In other embodiments, the anti-TIM-3 antibody molecule is administered or used in combination with a tyrosine kinase inhibitor (*e.g.*, axitinib) and a 4-1BB receptor targeting agent.

10 The anti-LAG-3 antibody molecule can be bound to a substance, *e.g.*, a cytotoxic agent or moiety (*e.g.*, a therapeutic drug; a compound emitting radiation; molecules of plant, fungal, or bacterial origin; or a biological protein (*e.g.*, a protein toxin) or particle (*e.g.*, a recombinant viral particle, *e.g.*, via a viral coat protein). For example, the antibody can be coupled to a radioactive isotope such as an α -, β -, or γ -emitter, or a β -and γ -emitter.

15 Immunomodulators

The anti-LAG-3 antibody molecules described herein can be used in combination with one or more immunomodulators.

In certain embodiments, the immunomodulator is an inhibitor of an immune checkpoint molecule. In one embodiment, the immunomodulator is an inhibitor of PD-1, PD-L1, PD-L2, CTLA-4, TIM-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4
20 and/or TGF beta. In one embodiment, the inhibitor of an immune checkpoint molecule inhibits PD-1, PD-L1, TIM-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), CTLA-4, or any combination thereof.

Inhibition of an inhibitory molecule can be performed at the DNA, RNA or protein level. In embodiments, an inhibitory nucleic acid (*e.g.*, a dsRNA, siRNA or shRNA), can be used to inhibit
25 expression of an inhibitory molecule. In other embodiments, the inhibitor of an inhibitory signal is, a polypeptide *e.g.*, a soluble ligand (*e.g.*, PD-1-Ig or CTLA-4 Ig), or an antibody molecule that binds to the inhibitory molecule; *e.g.*, an antibody molecule that binds to PD-1, PD-L1, PD-L2, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), CTLA-4, TIM-3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGF beta, or a combination thereof.

30 In certain embodiments, the anti-LAG-3 antibody molecule is in the form of a bispecific or multispecific antibody molecule. In one embodiment, the bispecific antibody molecule has a first binding specificity to LAG-3 and a second binding specificity, *e.g.*, a second binding specificity to, PD-1, PD-L1, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), TIM-3, or PD-L2. In one embodiment, the bispecific antibody molecule binds to (i) PD-1 or PD-L1 (ii) and LAG-3. In another embodiment, the
35 bispecific antibody molecule binds to LAG-3 and TIM-3. In another embodiment, the bispecific antibody molecule binds to LAG-3 and CEACAM (*e.g.*, CEACAM-1, -3 and/or -5). In another embodiment, the bispecific antibody molecule binds to LAG-3 and CEACAM-1. In still another

embodiment, the bispecific antibody molecule binds to LAG-3 and CEACAM-3. In yet another embodiment, the bispecific antibody molecule binds to LAG-3 and CEACAM-5.

In other embodiments, the anti-LAG-3 antibody molecule is used in combination with a bispecific or multispecific antibody molecule. In another embodiment, the bispecific antibody
5 molecule binds to PD-1 or PD-L1. In yet another embodiment, the bispecific antibody molecule binds to PD-1 and PD-L2. In another embodiment, the bispecific antibody molecule binds to CEACAM
(*e.g.*, CEACAM-1, -3 and/or -5) and TIM-3.

Any combination of the aforesaid molecules can be made in a multispecific antibody molecule, *e.g.*, a trispecific antibody that includes a first binding specificity to LAG-3, and a second
10 and third binding specificities to two or more of: PD-1, PD-L1, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), TIM-3, or PD-L2.

In certain embodiments, the immunomodulator is an inhibitor of PD-1, *e.g.*, human PD-1. In another embodiment, the immunomodulator is an inhibitor of PD-L1, *e.g.*, human PD-L1. In one embodiment, the inhibitor of PD-1 or PD-L1 is an antibody molecule to PD-1 or PD-L1 (*e.g.*, an anti-
15 PD-1 or anti-PD-L1 antibody molecule as described herein).

The combination of the PD-1 or PD-L1 inhibitor with the anti-LAG-3 antibody molecule can further include one or more additional immunomodulators, *e.g.*, in combination with an inhibitor of TIM-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5) or CTLA-4. In one embodiment, the inhibitor of PD-1 or PD-L1 (*e.g.*, the anti-PD-1 or PD-L1 antibody molecule) is administered in combination with
20 the anti-LAG-3 antibody molecule and a TIM-3 inhibitor (*e.g.*, an anti-TIM-3 antibody molecule). In another embodiment, the inhibitor of PD-1 or PD-L1 (*e.g.*, the anti-PD-1 or PD-L1 antibody molecule) is administered in combination with the anti-LAG-3 antibody molecule and a CEACAM inhibitor (*e.g.*, CEACAM-1, -3 and/or -5 inhibitor), *e.g.*, an anti-CEACAM antibody molecule. In another embodiment, the inhibitor of PD-1 or PD-L1 (*e.g.*, the anti-PD-1 or PD-L1 antibody
25 molecule) is administered in combination with the anti-LAG-3 antibody molecule and a CEACAM-1 inhibitor (*e.g.*, an anti-CEACAM-1 antibody molecule). In another embodiment, the inhibitor of PD-1 or PD-L1 (*e.g.*, the anti-PD-1 or PD-L1 antibody molecule) is administered in combination with the anti-LAG-3 antibody molecule and a CEACAM-5 inhibitor (*e.g.*, an anti-CEACAM-5 antibody molecule). In yet other embodiments, the inhibitor of PD-1 or PD-L1 (*e.g.*, the anti-PD-1 or PD-L1
30 antibody molecule) is administered in combination with the anti-LAG-3 antibody molecule and a TIM-3 inhibitor (*e.g.*, an anti-TIM-3 antibody molecule). Other combinations of immunomodulators with the anti-LAG-3 antibody molecule and a PD-1 inhibitor including, *e.g.*, one or more of PD-L2, CTLA-4, LAG-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGF beta) are also within the present invention. Any of the antibody molecules
35 known in the art or disclosed herein can be used in the aforesaid combinations of inhibitors of checkpoint molecule.

In other embodiments, the immunomodulator is an inhibitor of CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), *e.g.*, human CEACAM (*e.g.*, CEACAM-1, -3 and/or -5). In one embodiment, the immunomodulator is an inhibitor of CEACAM-1, *e.g.*, human CEACAM-1. In another embodiment, the immunomodulator is an inhibitor of CEACAM-3, *e.g.*, human CEACAM-3. In another
5 embodiment, the immunomodulator is an inhibitor of CEACAM-5, *e.g.*, human CEACAM-5. In one embodiment, the inhibitor of CEACAM (*e.g.*, CEACAM-1, -3 and/or -5) is an antibody molecule to CEACAM (*e.g.*, CEACAM-1, -3 and/or -5). The combination of the CEACAM (*e.g.*, CEACAM-1, -3 and/or -5) inhibitor and the anti-LAG-3 antibody molecule can further include one or more additional immunomodulators, *e.g.*, in combination with an inhibitor of TIM-3, PD-1, PD-L1 or
10 CTLA-4.

In other embodiments, the immunomodulator is an inhibitor of TIM-3, *e.g.*, human TIM-3. In one embodiment, the inhibitor of TIM-3 is an antibody molecule to TIM-3. The combination of the TIM-3 inhibitor and the anti-LAG-3 antibody molecule can further include one or more additional immunomodulators, *e.g.*, in combination with an inhibitor of CEACAM (*e.g.*, CEACAM-1, -3 and/or
15 -5), PD-1, PD-L1 or CTLA-4.

In certain embodiments, the immunomodulator used in the combinations disclosed herein (*e.g.*, in combination with a therapeutic agent chosen from an antigen-presentation combination) is an activator or agonist of a costimulatory molecule. In one embodiment, the agonist of the costimulatory molecule is chosen from an agonist (*e.g.*, an agonistic antibody or antigen-binding fragment thereof,
20 or a soluble fusion) of OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFRR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, or CD83 ligand.

In other embodiments, the immunomodulator is a GITR agonist. In one embodiment, the GITR agonist is an antibody molecule to GITR. The anti-GITR antibody molecule and the anti-LAG-3 antibody molecule may be in the form of separate antibody composition, or as a bispecific antibody molecule. The combination of the GITR agonist with the anti-LAG-3 antibody molecule can further include one or more additional immunomodulators, *e.g.*, in combination with an inhibitor of PD-1, PD-L1, CTLA-4, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), or TIM-3. In some embodiments, the anti-GITR antibody molecule is a bispecific antibody that binds to GITR and PD-1, PD-L1, CTLA-4,
25 CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), or TIM-3. In other embodiments, a GITR agonist can be administered in combination with one or more additional activators of costimulatory molecules, *e.g.*, an agonist of OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), CD30, CD40, BAFRR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, or CD83 ligand.

In other embodiments, the immunomodulator is an OX40 agonist. In one embodiment, the OX40 agonist is an antibody molecule to OX40. The OX40 antibody molecule and the anti-LAG-3 antibody molecule may be in the form of separate antibody composition, or as a bispecific antibody
35

molecule. The combination of the OX40 agonist with the anti-LAG-3 antibody molecule can further include one or more additional immunomodulators, *e.g.*, in combination with an inhibitor of PD-1, PD-L1, CTLA-4, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), or TIM-3. In some embodiments, the anti-OX40 antibody molecule is a bispecific antibody that binds to OX40 and PD-1, PD-L1, CTLA-4, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), or TIM-3. In other embodiments, the OX40 agonist can be administered in combination with other costimulatory molecule, *e.g.*, an agonist of GITR, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, Nkp80, CD160, B7-H3, or CD83 ligand.

It is noted that only exemplary combinations of inhibitors of checkpoint inhibitors or agonists of costimulatory molecules are provided herein. Additional combinations of these agents are within the scope of the present invention.

Biomarkers

In certain embodiments, any of the methods disclosed herein further includes evaluating or monitoring the effectiveness of a therapy (*e.g.*, a monotherapy or a combination therapy) described herein, in a subject (*e.g.*, a subject having a cancer, *e.g.*, a cancer described herein). The method includes acquiring a value of effectiveness to the therapy, wherein said value is indicative of the effectiveness of the therapy.

In embodiments, the value of effectiveness to the therapy comprises a measure of one, two, three, four, five, six, seven, eight, nine or more (*e.g.*, all) of the following:

- (i) a parameter of a tumor infiltrating lymphocyte (TIL) phenotype;
- (ii) a parameter of a myeloid cell population;
- (iii) a parameter of a surface expression marker;
- (iv) a parameter of a biomarker of an immunologic response;
- (v) a parameter of a systemic cytokine modulation;
- (vi) a parameter of circulating free DNA (cfDNA);
- (vii) a parameter of systemic immune-modulation;
- (viii) a parameter of microbiome;
- (ix) a parameter of a marker of activation in a circulating immune cell; or
- (x) a parameter of a circulating cytokine.

In some embodiments, the parameter of a TIL phenotype comprises the level or activity of one, two, three, four or more (*e.g.*, all) of Hematoxylin and eosin (H&E) staining for TIL counts, CD8, FOXP3, CD4, or CD3, in the subject, *e.g.*, in a sample from the subject (*e.g.*, a tumor sample).

In some embodiments, the parameter of a myeloid cell population comprises the level or activity of one or both of CD68 or CD163, in the subject, *e.g.*, in a sample from the subject (*e.g.*, a tumor sample).

In some embodiments, the parameter of a surface expression marker comprises the level or activity of one, two, three or more (*e.g.*, all) of TIM-3, PD-1, PD-L1, or LAG-3, in the subject, *e.g.*, in a sample from the subject (*e.g.*, a tumor sample). In certain embodiments, the level of TIM-3, PD-1, PD-L1, or LAG-3 is determined by immunohistochemistry (IHC). In certain embodiments, the level
5 of TIM-3 is determined.

In some embodiments, the parameter of a biomarker of an immunologic response comprises the level or sequence of one or more nucleic acid-based markers, in the subject, *e.g.*, in a sample from the subject (*e.g.*, a tumor sample).

In some embodiments, the parameter of systemic cytokine modulation comprises the level or
10 activity of one, two, three, four, five, six, seven, eight, or more (*e.g.*, all) of IL-18, IFN- γ , ITAC (CXCL11), IL-6, IL-10, IL-4, IL-17, IL-15, or TGF-beta, in the subject, *e.g.*, in a sample from the subject (*e.g.*, a blood sample, *e.g.*, a plasma sample).

In some embodiments, the parameter of cfDNA comprises the sequence or level of one or more circulating tumor DNA (cfDNA) molecules, in the subject, *e.g.*, in a sample from the subject
15 (*e.g.*, a blood sample, *e.g.*, a plasma sample).

In some embodiments, the parameter of systemic immune-modulation comprises phenotypic characterization of an activated immune cell, *e.g.*, a CD3-expressing cell, a CD8-expressing cell, or both, in the subject, *e.g.*, in a sample from the subject (*e.g.*, a blood sample, *e.g.*, a PBMC sample).

In some embodiments, the parameter of microbiome comprises the sequence or expression
20 level of one or more genes in the microbiome, in the subject, *e.g.*, in a sample from the subject (*e.g.*, a stool sample).

In some embodiments, the parameter of a marker of activation in a circulating immune cell comprises the level or activity of one, two, three, four, five or more (*e.g.*, all) of circulating CD8+, HLA-DR+Ki67+, T cells, IFN- γ , IL-18, or CXCL11 (IFN- γ induced CCK) expressing cells, in a
25 sample (*e.g.*, a blood sample, *e.g.*, a plasma sample).

In some embodiments, the parameter of a circulating cytokine comprises the level or activity of IL-6, in the subject, *e.g.*, in a sample from the subject (*e.g.*, a blood sample, *e.g.*, a plasma sample).

In some embodiments of any of the methods disclosed herein, the therapy comprises a combination of an anti-TIM-3 antibody molecule described herein and a second inhibitor of an
30 immune checkpoint molecule, *e.g.*, an inhibitor of PD-1 (*e.g.*, an anti-PD-1 antibody molecule) or an inhibitor of PD-L1 (*e.g.*, an anti-PD-L1 antibody molecule).

In some embodiments of any of the methods disclosed herein, the measure of one or more of (i)-(x) is obtained from a sample acquired from the subject. In some embodiments, the sample is chosen from a tumor sample, a blood sample (*e.g.*, a plasma sample or a PBMC sample), or a stool
35 sample.

In some embodiments of any of the methods disclosed herein, the subject is evaluated prior to receiving, during, or after receiving, the therapy.

In some embodiments of any of the methods disclosed herein, the measure of one or more of (i)-(x) evaluates a profile for one or more of gene expression, flow cytometry or protein expression.

In some embodiments of any of the methods disclosed herein, the presence of an increased level or activity of one, two, three, four, five, or more (*e.g.*, all) of circulating CD8+, HLA-DR+Ki67+,
5 T cells, IFN- γ , IL-18, or CXCL11 (IFN- γ induced CCK) expressing cells, and/or the presence of an decreased level or activity of IL-6, in the subject or sample, is a positive predictor of the effectiveness of the therapy.

Alternatively, or in combination with the methods disclosed herein, responsive to said value, performing one, two, three, four or more (*e.g.*, all) of:

- 10 (i) administering to the subject the therapy;
(ii) administered an altered dosing of the therapy;
(iii) altering the schedule or time course of the therapy;
(iv) administering to the subject an additional agent (*e.g.*, a therapeutic agent described herein)
in combination with the therapy; or
15 (v) administering to the subject an alternative therapy.

Additional Embodiments

In certain embodiments, any of the methods disclosed herein further includes identifying in a subject or a sample (*e.g.*, a subject's sample comprising cancer cells and/or immune cells such as
20 TILs) the presence of LAG-3, thereby providing a value for LAG-3. The method can further include comparing the LAG-3 value to a reference value, *e.g.*, a control value. If the LAG-3 value is greater than the reference value, *e.g.*, the control value, administering a therapeutically effective amount of an anti-LAG-3 antibody molecule described herein to the subject, and optionally, in combination with a second therapeutic agent, procedure, or modality described herein, thereby treating a cancer.

25 In other embodiments, any of the methods disclosed herein further includes identifying in a subject or a sample (*e.g.*, a subject's sample comprising cancer cells and/or immune cells such as TILs) the presence of PD-L1, thereby providing a value for PD-L1. The method can further include comparing the PD-L1 value to a reference value, *e.g.*, a control value. If the PD-L1 value is greater than the reference value, *e.g.*, the control value, administering a therapeutically effective amount of an
30 anti-LAG-3 antibody molecule described herein to the subject, and optionally, in combination with a second therapeutic agent, procedure, or modality described herein, thereby treating a cancer.

In other embodiments, any of the methods disclosed herein further includes identifying in a subject or a sample (*e.g.*, a subject's sample comprising cancer cells and optionally immune cells such as TILs) the presence of one, two or all of PD-L1, CD8, or IFN- γ , thereby providing a value for one,
35 two or all of PD-L1, CD8, and IFN- γ . The method can further include comparing the PD-L1, CD8, and/or IFN- γ values to a reference value, *e.g.*, a control value. If the PD-L1, CD8, and/or IFN- γ values are greater than the reference value, *e.g.*, the control values, administering a therapeutically

effective amount of an anti-LAG-3 antibody molecule described herein to the subject, and optionally, in combination with a second therapeutic agent, procedure, or modality described herein, thereby treating a cancer.

The subject may have a cancer described herein, such as a solid tumor or a hematological cancer, *e.g.*, a brain tumor (*e.g.*, a glioblastoma, a gliosarcoma, or a recurrent brain tumor), a pancreatic cancer (*e.g.*, an advanced pancreatic cancer), a skin cancer (*e.g.*, a melanoma (*e.g.*, a stage II-IV melanoma, an HLA-A2 positive melanoma, an unresectable melanoma, or a metastatic melanoma), or a Merkel cell carcinoma), a renal cancer (*e.g.*, a renal cell carcinoma (RCC) (*e.g.*, a metastatic renal cell carcinoma)), a breast cancer (*e.g.*, a metastatic breast carcinoma or a stage IV breast carcinoma, *e.g.*, a triple negative breast cancer (TNBC)), a virus-associated cancer, an anal canal cancer (*e.g.*, a squamous cell carcinoma of the anal canal), a cervical cancer (*e.g.*, a squamous cell carcinoma of the cervix), a gastric cancer (*e.g.*, an Epstein Barr Virus (EBV) positive gastric cancer, or a gastric or gastro-esophageal junction carcinoma), a head and neck cancer (*e.g.*, an HPV positive and negative squamous cell cancer of the head and neck (SCCHN)), a nasopharyngeal cancer (NPC), a penile cancer (*e.g.*, a squamous cell carcinoma of the penile), a vaginal or vulvar cancer (*e.g.*, a squamous cell carcinoma of the vagina or vulva), a colorectal cancer (*e.g.*, a relapsed colorectal cancer or a metastatic colorectal cancer, *e.g.*, a microsatellite unstable colorectal cancer, a microsatellite stable colorectal cancer, a mismatch repair proficient colorectal cancer, or a mismatch repair deficient colorectal cancer), a lung cancer (*e.g.*, a non-small cell lung cancer (NSCLC)), a leukemia, a lymphoma (*e.g.*, a Hodgkin lymphoma (HL) or a diffuse large B cell lymphoma (DLBCL), *e.g.*, a relapsed or refractory HL or DLBCL), a myeloma, or a metastatic lesion of the cancer.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

DETAILED DESCRIPTION

LAG-3 (CD223) is an immune checkpoint inhibitor that binds MHC II, LSECtin, and Galectin-3. LAG-3 is expressed on the surface of immune cells including CD4+ and CD8+ T effector cells, regulatory T cells (Tregs), natural killer (NK) cells, and plasmacytoid dendritic cells. LAG-3 engagement has been shown to negatively regulate T cell signaling and to increase the suppressive function of Tregs, which is expected to then reduce T-cell activity against tumor cells. Blockade of LAG-3 has been shown to activate T cells by increasing T cell proliferation and cytokine secretion (IFN- γ).

Accordingly, disclosed herein are, at least in part, are antibody molecules (*e.g.*, humanized antibody molecules) that bind LAG-3 with high affinity and specificity. Pharmaceutical compositions and dose formulations comprising the anti-LAG-3 antibody molecules are also provided. The anti-LAG-3 antibody molecules disclosed herein can be used (alone or in combination with other
5 therapeutic agents, procedures, or modalities) to treat or prevent disorders, such as cancerous disorders (*e.g.*, solid tumors and hematological cancers), as well as infectious diseases (*e.g.*, chronic infectious disorders or sepsis). For example, the anti-LAG-3 antibody molecules described herein can be used in combination with other therapeutic agents (*e.g.*, one or both of a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule described herein) or a chemotherapeutic agent (*e.g.*, a platinum agent
10 (*e.g.*, carboplatin, cisplatin, oxaliplatin, or tetraplatin) or a nucleotide analog or precursor analog (*e.g.*, capecitabine))), *e.g.*, to treat or prevent a cancer (*e.g.*, a cancer described herein), *e.g.*, a breast cancer, *e.g.* a triple negative breast cancer (TNBC). Thus, methods, including dosage regimens, for treating various disorders using the anti-LAG-3 antibody molecules are disclosed herein. In certain embodiments, the anti-LAG-3 antibody molecule is administered or used at a flat or fixed dose.

15

Definitions

Additional terms are defined below and throughout the application.

As used herein, the articles “a” and “an” refer to one or to more than one (*e.g.*, to at least one) of the grammatical object of the article.

20

The term “or” is used herein to mean, and is used interchangeably with, the term “and/or,” unless context clearly indicates otherwise.

25

“About” and “approximately” shall generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary degrees of error are within 20 percent (%), typically, within 10%, and more typically, within 5% of a given value or range of values.

30

By “a combination” or “in combination with,” it is not intended to imply that the therapy or the therapeutic agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope described herein. The therapeutic agents in the combination can be administered concurrently with, prior to, or subsequent to, one or more other
35 additional therapies or therapeutic agents. The therapeutic agents or therapeutic protocol can be administered in any order. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. It will further be appreciated that the additional therapeutic agent utilized in this combination may be administered together in a single composition or administered separately in different compositions. In general, it is expected that additional therapeutic agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

In embodiments, the additional therapeutic agent is administered at a therapeutic or lower-than therapeutic dose. In certain embodiments, the concentration of the second therapeutic agent that is required to achieve inhibition, *e.g.*, growth inhibition, is lower when the second therapeutic agent is administered in combination with the first therapeutic agent, *e.g.*, the anti-LAG-3 antibody molecule, than when the second therapeutic agent is administered individually. In certain embodiments, the concentration of the first therapeutic agent that is required to achieve inhibition, *e.g.*, growth inhibition, is lower when the first therapeutic agent is administered in combination with the second therapeutic agent than when the first therapeutic agent is administered individually. In certain embodiments, in a combination therapy, the concentration of the second therapeutic agent that is required to achieve inhibition, *e.g.*, growth inhibition, is lower than the therapeutic dose of the second therapeutic agent as a monotherapy, *e.g.*, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, or 80-90% lower. In certain embodiments, in a combination therapy, the concentration of the first therapeutic agent that is required to achieve inhibition, *e.g.*, growth inhibition, is lower than the therapeutic dose of the first therapeutic agent as a monotherapy, *e.g.*, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, or 80-90% lower.

The term “inhibition,” “inhibitor,” or “antagonist” includes a reduction in a certain parameter, *e.g.*, an activity, of a given molecule, *e.g.*, an immune checkpoint inhibitor. For example, inhibition of an activity, *e.g.*, a PD-1 or PD-L1 activity, of at least 5%, 10%, 20%, 30%, 40% or more is included by this term. Thus, inhibition need not be 100%.

The term “activation,” “activator,” or “agonist” includes an increase in a certain parameter, *e.g.*, an activity, of a given molecule, *e.g.*, a costimulatory molecule. For example, increase of an activity, *e.g.*, a costimulatory activity, of at least 5%, 10%, 25%, 50%, 75% or more is included by this term.

The term “anti-cancer effect” refers to a biological effect which can be manifested by various means, including but not limited to, *e.g.*, a decrease in tumor volume, a decrease in the number of cancer cells, a decrease in the number of metastases, an increase in life expectancy, decrease in cancer cell proliferation, decrease in cancer cell survival, or amelioration of various physiological symptoms associated with the cancerous condition. An “anti-cancer effect” can also be manifested by the ability of the peptides, polynucleotides, cells and antibodies in prevention of the occurrence of cancer in the first place.

The term “anti-tumor effect” refers to a biological effect which can be manifested by various means, including but not limited to, *e.g.*, a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in tumor cell proliferation, or a decrease in tumor cell survival.

The term “cancer” refers to a disease characterized by the rapid and uncontrolled growth of aberrant cells. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body. Examples of various cancers are described herein and include but are not limited to, solid tumors, *e.g.*, lung cancer, breast cancer, prostate cancer, ovarian cancer, cervical

cancer, skin cancer, pancreatic cancer, colorectal cancer, renal cancer, liver cancer, and brain cancer, and hematologic malignancies, *e.g.*, lymphoma and leukemia, and the like. The terms “tumor” and “cancer” are used interchangeably herein, *e.g.*, both terms encompass solid and liquid, *e.g.*, diffuse or circulating, tumors. As used herein, the term “cancer” or “tumor”

5 includes premalignant, as well as malignant cancers and tumors.

The term “antigen presenting cell” or “APC” refers to an immune system cell such as an accessory cell (*e.g.*, a B-cell, a dendritic cell, and the like) that displays a foreign antigen complexed with major histocompatibility complexes (MHC’s) on its surface. T-cells may recognize these complexes using their T-cell receptors (TCRs). APCs process antigens and

10 present them to T-cells.

The term “costimulatory molecule” refers to the cognate binding partner on a T cell that specifically binds with a costimulatory ligand, thereby mediating a costimulatory response by the T cell, such as, but not limited to, proliferation. Costimulatory molecules are cell surface molecules other than antigen receptors or their ligands that are required for an

15 efficient immune response. Costimulatory molecules include, but are not limited to, an MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signalling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS

20 (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL,

25 DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83.

“Immune effector cell,” or “effector cell” as that term is used herein, refers to a cell

30 that is involved in an immune response, *e.g.*, in the promotion of an immune effector response. Examples of immune effector cells include T cells, *e.g.*, alpha/beta T cells and gamma/delta T cells, B cells, natural killer (NK) cells, natural killer T (NKT) cells, mast cells, and myeloid-derived phagocytes.

“Immune effector” or “effector” “function” or “response,” as that term is used herein,

35 refers to function or response, *e.g.*, of an immune effector cell, that enhances or promotes an immune attack of a target cell. *E.g.*, an immune effector function or response refers a property of a T or NK cell that promotes killing or the inhibition of growth or proliferation, of

a target cell. In the case of a T cell, primary stimulation and co-stimulation are examples of immune effector function or response.

The term “effector function” refers to a specialized function of a cell. Effector function of a T cell, for example, may be cytolytic activity or helper activity including the secretion of cytokines.

5 As used herein, the terms “treat,” “treatment” and “treating” refer to the reduction or amelioration of the progression, severity and/or duration of a disorder, *e.g.*, a proliferative disorder, or the amelioration of one or more symptoms (preferably, one or more discernible symptoms) of the disorder resulting from the administration of one or more therapies. In specific embodiments, the terms “treat,” “treatment” and “treating” refer to the amelioration of at least one measurable physical
10 parameter of a proliferative disorder, such as growth of a tumor, not necessarily discernible by the patient. In other embodiments the terms “treat,” “treatment” and “treating” refer to the inhibition of the progression of a proliferative disorder, either physically by, *e.g.*, stabilization of a discernible symptom, physiologically by, *e.g.*, stabilization of a physical parameter, or both. In other embodiments the terms “treat,” “treatment” and “treating” refer to the reduction or stabilization of
15 tumor size or cancerous cell count.

The compositions, formulations, and methods of the present invention encompass polypeptides and nucleic acids having the sequences specified, or sequences substantially identical or similar thereto, *e.g.*, sequences at least 85%, 90%, 95% identical or higher to the sequence specified. In the context of an amino acid sequence, the term “substantially identical” is used herein to refer to a
20 first amino acid that contains a sufficient or minimum number of amino acid residues that are i) identical to, or ii) conservative substitutions of aligned amino acid residues in a second amino acid sequence such that the first and second amino acid sequences can have a common structural domain and/or common functional activity. For example, amino acid sequences that contain a common structural domain having at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%
25 identity to a reference sequence, *e.g.*, a sequence provided herein.

In the context of nucleotide sequence, the term “substantially identical” is used herein to refer to a first nucleic acid sequence that contains a sufficient or minimum number of nucleotides that are identical to aligned nucleotides in a second nucleic acid sequence such that the first and second
nucleotide sequences encode a polypeptide having common functional activity, or encode a common
30 structural polypeptide domain or a common functional polypeptide activity. For example, nucleotide sequences having at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to a reference sequence, *e.g.*, a sequence provided herein.

The term “functional variant” refers to polypeptides that have a substantially identical amino acid sequence to the naturally-occurring sequence, or are encoded by a substantially identical
35 nucleotide sequence, and are capable of having one or more activities of the naturally-occurring sequence.

Calculations of homology or sequence identity between sequences (the terms are used interchangeably herein) are performed as follows.

To determine the percent identity of two amino acid sequences, or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, 60%, and even more preferably at least 70%, 80%, 90%, 100% of the length of the reference sequence. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid “identity” is equivalent to amino acid or nucleic acid “homology”).

The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch ((1970) *J. Mol. Biol.* 48:444-453) algorithm which has been incorporated into the GAP program in the GCG software package (available at www.gcg.com), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (available at www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. A particularly preferred set of parameters (and the one that should be used unless otherwise specified) are a Blossum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5.

The percent identity between two amino acid or nucleotide sequences can be determined using the algorithm of E. Meyers and W. Miller ((1989) *CABIOS*, 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences described herein can be used as a “query sequence” to perform a search against public databases, for example, to identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous

to a nucleic acid (SEQ ID NO: 1) molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. *See* www.ncbi.nlm.nih.gov.

As used herein, the term “hybridizes under low stringency, medium stringency, high stringency, or very high stringency conditions” describes conditions for hybridization and washing. Guidance for performing hybridization reactions can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6, which is incorporated by reference. Aqueous and nonaqueous methods are described in that reference and either can be used. Specific hybridization conditions referred to herein are as follows: 1) low stringency hybridization conditions in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by two washes in 0.2X SSC, 0.1% SDS at least at 50°C (the temperature of the washes can be increased to 55°C for low stringency conditions); 2) medium stringency hybridization conditions in 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 60°C; 3) high stringency hybridization conditions in 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C; and preferably 4) very high stringency hybridization conditions are 0.5M sodium phosphate, 7% SDS at 65°C, followed by one or more washes at 0.2X SSC, 1% SDS at 65°C. Very high stringency conditions (4) are the preferred conditions and the ones that should be used unless otherwise specified.

It is understood that the molecules of the present invention may have additional conservative or non-essential amino acid substitutions, which do not have a substantial effect on their functions.

The term "amino acid" is intended to embrace all molecules, whether natural or synthetic, which include both an amino functionality and an acid functionality and capable of being included in a polymer of naturally-occurring amino acids. Exemplary amino acids include naturally-occurring amino acids; analogs, derivatives and congeners thereof; amino acid analogs having variant side chains; and all stereoisomers of any of any of the foregoing. As used herein the term "amino acid" includes both the D- or L- optical isomers and peptidomimetics.

A “conservative amino acid substitution” is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine).

The terms “polypeptide,” “peptide” and “protein” (if single chain) are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation, such as conjugation with a labeling component. The polypeptide can be isolated from natural sources, can be produced by recombinant techniques from a eukaryotic or prokaryotic host, or can be a product of synthetic procedures.

The terms “nucleic acid,” “nucleic acid sequence,” “nucleotide sequence,” or “polynucleotide sequence,” and “polynucleotide” are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. The polynucleotide may be either single-stranded or double-stranded, and if single-stranded may be the coding strand or non-coding (antisense) strand. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. The nucleic acid may be a recombinant polynucleotide, or a polynucleotide of genomic, cDNA, semisynthetic, or synthetic origin which either does not occur in nature or is linked to another polynucleotide in a nonnatural arrangement.

The term “isolated,” as used herein, refers to material that is removed from its original or native environment (*e.g.*, the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or polypeptide, separated by human intervention from some or all of the co-existing materials in the natural system, is isolated. Such polynucleotides could be part of a vector and/or such polynucleotides or polypeptides could be part of a composition, and still be isolated in that such vector or composition is not part of the environment in which it is found in nature.

Various aspects of the invention are described in further detail below. Additional definitions are set out throughout the specification.

30 Dosage Regimens

The anti-LAG-3 antibody molecules described herein can be administered according to a dosage regimen described herein to treat (*e.g.*, inhibit, reduce, ameliorate, or prevent) a disorder, *e.g.*, a hyperproliferative condition or disorder (*e.g.*, a cancer) in a subject. In certain embodiments, the anti-LAG-3 antibody molecule is administered to the subject at a dose of about 200 mg to about 2000 mg, *e.g.*, once every two, three, or four weeks.

In some aspect, the disclosure features a method of treating a cancer in a subject, the method comprising administering to the subject an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein) at a dose or dosage schedule described herein.

In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose or dosage
5 schedule that results in binding, *e.g.*, saturates, soluble LAG-3 in the subject. In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose or dosage schedule that results in at least 50%, 60%, 70%, 80%, 85%, 90%, 95%, 98%, or 99% binding, *e.g.*, saturation, of soluble LAG-3 in the subject, *e.g.*, within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, 24, 36, or 48 weeks of administration.

In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose or dosage
10 schedule that results in at least 50%, 60%, 70%, 80%, 90%, 95%, 98%, or 99% binding, *e.g.*, occupancy, of LAG-3 in a tumor in the subject, *e.g.*, within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 36, or 48 weeks of administration.

In other embodiments, the anti-LAG-3 antibody molecule is administered at a dose or dosage
15 schedule that results in at least 50%, 60%, 70%, 80%, 85%, 90%, 95%, 98%, or 99% binding, *e.g.*, saturation, of soluble LAG-3 in the subject; and that results in at least 50%, 60%, 70%, 80%, 85%, 90%, 95%, 98%, or 99% binding, *e.g.*, occupancy, of LAG-3 in a tumor in the subject. In embodiments, the saturation and/or occupancy occurs, *e.g.*, within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 36, or 48 weeks of administration.

In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose or dosage
20 schedule that results one or both of the following:

(a) 40% or more (*e.g.*, 50% or more, 60% or more, 70% or more, 80% or more, 85% or more, 90% or more, 95% or more, 99% or more) of the soluble LAG-3 in the subject (*e.g.*, blood) is bound by the anti-LAG-3 antibody molecule; or

(b) 50% or more (*e.g.*, 60% or more, 70% or more, 80% or more, 85% or more, 90% or more,
25 95% or more, 99% or more) of the membrane-bound LAG-3 in the subject (*e.g.*, cancer) is bound by the anti-LAG-3 antibody molecule.

In some embodiments, the binding of the anti-LAG-3 antibody molecule to soluble LAG-3 is determined in a blood sample (*e.g.*, a serum sample or a plasma sample). In some embodiments, the binding of the anti-LAG-3 antibody molecule to membrane-bound LAG-3 is determined in the cancer
30 (*e.g.*, a cancer sample).

In some embodiments, the binding of the anti-LAG-3 antibody molecule to soluble LAG-3, the binding of the anti-LAG-3 antibody molecule to membrane-bound LAG-3, or both, is determined when the subject has a steady state trough level of the anti-LAG-3 antibody molecule. In some
35 embodiments, the trough level is the concentration of the anti-LAG-3 antibody molecule about 24 weeks after the administration, or the lowest concentration that the anti-LAG-3 antibody molecule reaches before the next dose is administered. In some embodiments, the binding of the anti-LAG-3 antibody molecule to soluble LAG-3, the binding of the anti-LAG-3 antibody molecule to membrane-

bound LAG-3, or both, is determined, *e.g.*, measured *in vitro* (*e.g.*, by ELISA or a cell-based assay) or *in vivo* (*e.g.*, by imaging), or predicted from a PK/PD model, *e.g.*, a PK/PD model described herein.

In some embodiments, 50% or more of the soluble LAG-3 in a serum sample from the subject is bound by the anti-LAG-3 antibody molecule. In some embodiments, 60% or more of the soluble
5 LAG-3 in a serum sample from the subject is bound by the anti-LAG-3 antibody molecule. In some embodiments, 70% or more of the soluble LAG-3 in a serum sample from the subject is bound by the anti-LAG-3 antibody molecule. In some embodiments, 80% or more of the soluble LAG-3 in a serum sample from the subject is bound by the anti-LAG-3 antibody molecule. In some embodiments, 90% or more of the soluble LAG-3 in a serum sample from the subject is bound by the anti-LAG-3
10 antibody molecule.

In some embodiments, 85% or more of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule. In some
embodiments, 90% or more of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule. In some embodiments, 95% or more of
15 the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule.

In some embodiments, 50% or more, 60% or more, 70% or more, 80% or more, or 90% or more, of the soluble LAG-3 in a serum sample from the subject is bound by the anti-LAG-3 antibody molecule, and 85% or more, 90% or more, or 95% or more, of the membrane-bound LAG-3 in the
20 cancer, or a cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule.

In some embodiments, 50% or more of the soluble LAG-3 in a serum sample from the subject is bound by the anti-LAG-3 antibody molecule, and 90% or more of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule. In
some embodiments, 60% or more of the soluble LAG-3 in a serum sample from the subject is bound
25 by the anti-LAG-3 antibody molecule, and 90% or more of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule. In some
embodiments, 70% or more of the soluble LAG-3 in a serum sample from the subject is bound by the
anti-LAG-3 antibody molecule, and 90% or more of the membrane-bound LAG-3 in the cancer, or a
cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule. In some
30 embodiments, 80% or more of the soluble LAG-3 in a serum sample from the subject is bound by the
anti-LAG-3 antibody molecule, and 90% or more of the membrane-bound LAG-3 in the cancer, or a
cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule. In some
embodiments, 90% or more of the soluble LAG-3 in a serum sample from the subject is bound by the
anti-LAG-3 antibody molecule, and 90% or more of the membrane-bound LAG-3 in the cancer, or a
35 cancer sample, from the subject, is bound by the anti-LAG-3 antibody molecule.

In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose or dosage schedule that reduces one or both of:

(a) the level of free soluble LAG-3 in the subject, *e.g.*, to 40% or less (*e.g.*, 50% or less, 40% or less, 30% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less) of a reference level of free soluble LAG-3; or

(b) the level of free membrane-bound LAG-3 in the subject, *e.g.*, to 50% or less (*e.g.*, 40% or less, 30% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less) of a reference level of membrane-bound LAG-3.

In some embodiments, the level of free soluble LAG-3 is determined in a blood sample (*e.g.*, a serum sample or a plasma sample). In some embodiments, the reference level of free soluble LAG-3 is the baseline level of free soluble LAG-3 in the subject, *e.g.*, prior to administration of the anti-LAG-3 antibody molecule, *e.g.*, in accordance with the dosage schedule.

In some embodiments, the level of free membrane-bound LAG-3 is determined in the cancer (*e.g.*, a cancer sample). In some embodiments, the reference level of free membrane-bound LAG-3 is the baseline level of free membrane-bound LAG-3 in the subject, *e.g.*, prior to administration of the anti-LAG-3 antibody molecule, *e.g.*, in accordance with the dosage schedule.

In some embodiments, the level of free soluble LAG-3, the level of free membrane-bound LAG-3, or both, is determined when the subject has a steady state trough level of the anti-LAG-3 antibody molecule. In some embodiments, the trough level is the concentration of the anti-LAG-3 antibody molecule about 24 weeks after the administration, or the lowest concentration that the anti-LAG-3 antibody molecule reaches before the next dose is administered. In some embodiments, the level of free soluble LAG-3, the level of free membrane-bound LAG-3, or both, is determined, *e.g.*, measured *in vitro* (*e.g.*, by ELISA or a cell-based assay) or *in vivo* (*e.g.*, by imaging), or predicted from a PK/PD model, *e.g.*, a PK/PD model described herein.

In some embodiments, the level of free soluble LAG-3 is reduced to 50% or less of a reference level of free soluble LAG-3 in a serum sample from the subject. In some embodiments, the level of free soluble LAG-3 is reduced to 40% or less of a reference level of free soluble LAG-3 in a serum sample from the subject. In some embodiments, the level of free soluble LAG-3 is reduced to 30% or less of a reference level of free soluble LAG-3 in a serum sample from the subject. In some embodiments, the level of free soluble LAG-3 is reduced to 20% or less of a reference level of free soluble LAG-3 in a serum sample from the subject. In some embodiments, the level of free soluble LAG-3 is reduced to 10% or less of a reference level of free soluble LAG-3 in a serum sample from the subject.

In some embodiments, the level of free membrane-bound LAG-3 is reduced to 15% or less of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject. In some embodiments, the level of free membrane-bound LAG-3 is reduced to 10% or less of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject. In some embodiments, the level of free soluble LAG-3 is reduced to 5% or less of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject.

In some embodiments, the level of free soluble LAG-3 is reduced to 50% or less, 40% or less, 30% or less, 20% or less, or 10% or less, of a reference level of free soluble LAG-3 in a serum sample from the subject, and the level of free membrane-bound LAG-3 is reduced to 15% or less, 10% or less, or 5% or less, of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject.

In some embodiments, the level of free soluble LAG-3 is reduced to 50% or less of a reference level of free soluble LAG-3 in a serum sample from the subject, and the level of free membrane-bound LAG-3 is reduced to 10% or less of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject. In some embodiments, the level of free soluble LAG-3 is reduced to 40% or less of a reference level of free soluble LAG-3 in a serum sample from the subject, and the level of free membrane-bound LAG-3 is reduced to 10% or less of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject. In some embodiments, the level of free soluble LAG-3 is reduced to 30% or less of a reference level of free soluble LAG-3 in a serum sample from the subject, and the level of free membrane-bound LAG-3 is reduced to 10% or less of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject. In some embodiments, the level of free soluble LAG-3 is reduced to 20% or less of a reference level of free soluble LAG-3 in a serum sample from the subject, and the level of free membrane-bound LAG-3 is reduced to 10% or less of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject. In some embodiments, the level of free soluble LAG-3 is reduced to 10% or less of a reference level of free soluble LAG-3 in a serum sample from the subject, and the level of free membrane-bound LAG-3 is reduced to 10% or less of a reference level of free membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject.

In certain embodiments, the dose or dosage schedule results in a trough level (*e.g.*, a steady state trough level) of the anti-LAG-3 antibody molecule that is above a C_{crit} (*e.g.*, as described in Example 1). In some embodiments, the C_{crit} is a concentration below which non-linear PK is observed. In some embodiments, the C_{crit} is about 60 nM.

In some embodiments, the anti-LAG-3 antibody molecule is administered at a dosage regimen disclosed herein.

In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 200 mg to about 1600 mg, about 300 mg to about 1500 mg, about 400 mg to about 1400 mg, about 500 mg to about 1300 mg, about 600 mg to about 1200 mg, about 700 mg to about 1100 mg, about 800 mg to about 1000 mg, about 200 mg to about 1400 mg, about 200 mg to about 1200 mg, about 200 mg to about 1000 mg, about 200 mg to about 800 mg, about 200 mg to about 600 mg, about 200 mg to about 400 mg, about 1400 mg to about 1600 mg, about 1200 mg to about 1600 mg, about 1000 mg to about 1600 mg, about 800 mg to about 1600 mg, about 600 mg to about 1600 mg, about 400 mg to about 1600 mg, about 200 mg to about 600 mg, about 300 mg to about 700 mg, about 400 mg

to about 800 mg, about 500 mg to about 900 mg, about 600 mg to about 1000 mg, about 700 mg to about 1100 mg, about 800 mg to about 1200 mg, about 900 mg to about 1300 mg, about 1000 mg to about 1400 mg, about 1100 mg to about 1500 mg, or about 1200 mg to about 1600 mg, *e.g.*, once every two weeks, once every three weeks, or once every four weeks.

5 In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 200 mg to about 600 mg, about 250 mg to about 550 mg, about 300 mg to about 500 mg, about 350 mg to about 450 mg, about 200 mg to about 400 mg, about 400 mg to about 600 mg, *e.g.*, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, *e.g.*, once every three weeks or once every four weeks. In certain
10 embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to about 500 mg, *e.g.*, about 300 mg, about 320 mg, about 340 mg, about 360 mg, about 380 mg, about 400 mg, about 420 mg, about 440 mg, about 460 mg, about 480 mg, or about 500 mg, once every three weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 350 mg to about 450 mg, *e.g.*, about 400 mg, once every three weeks.

15 In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 600 mg to about 1000 mg, about 650 mg to about 950 mg, about 700 mg to about 900 mg, about 750 mg to about 950 mg, about 600 mg to about 800 mg, about 800 mg to about 1000 mg, *e.g.*, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, *e.g.*, once every three weeks or once every four weeks. In certain
20 embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 900 mg to about 1100 mg, *e.g.*, about 900 mg, about 920 mg, about 940 mg, about 960 mg, about 980 mg, about 900 mg, about 920 mg, about 940 mg, about 960 mg, about 980 mg, or about 1000 mg, once every four weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 950 mg to about 1050 mg, *e.g.*, about 1000 mg, once every four weeks.

25 In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 500 mg to about 900 mg, about 550 mg to about 850 mg, about 600 mg to about 800 mg, about 650 mg to about 750 mg, *e.g.*, about 500 mg, about 550mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, *e.g.*, once every three weeks or once every
30 four weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 600 mg to about 800 mg, *e.g.*, about 600 mg, about 620 mg, about 640 mg, about 660 mg, about 680 mg, about 700 mg, about 720 mg, about 740 mg, about 760 mg, about 780 mg, or about 800 mg, once every three weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 650 mg to about 750 mg, *e.g.*, about 700 mg, once every three weeks.

35 In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 1200 mg to about 1600 mg, about 1250 mg to about 1550 mg, about 1300 mg to about 1500 mg, about 1350 mg to about 1450 mg, *e.g.*, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, *e.g.*, once every

three weeks or once every four weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 1300 mg to about 1500 mg, *e.g.*, about 1300 mg, about 1320 mg, about 1340 mg, about 1360 mg, about 1380 mg, about 1400 mg, about 1420 mg, about 1440 mg, about 1460 mg, about 1480 mg, or about 1500 mg, once every four weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 1350 mg to about 1450 mg, *e.g.*, about 1400 mg, once every four weeks.

In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 400 mg to about 700 mg, about 450 mg to about 650 mg, about 500 mg to about 600 mg, about 450 mg to about 550 mg, about 500 mg to about 600 mg, about 550 mg to about 650 mg, about 600 mg to about 700 mg, about 500 mg to about 550 mg, about 550 mg to about 600 mg, about 600 mg to about 650 mg, *e.g.*, about 400 mg, about 450 mg, about 500 mg, about 533 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, *e.g.*, once four weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 450 mg to about 650 mg, *e.g.*, about 450 mg, about 500 mg, about 533 mg, about 550 mg, about 600 mg, or about 650 mg, once every four weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 500 mg to about 650 mg, *e.g.*, about 533 mg or about 600 mg, once every four weeks.

In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 2000 mg or less, about 1900 mg or less, about 1800 mg or less, about 1700 mg or less, about 1600 mg or less, about 1500 mg or less, about 1400 mg or less, about 1300 mg or less, about 1200 mg or less, about 1100 mg or less, about 1000 mg or less, about 900 mg or less, about 800 mg or less, about 700 mg or less, about 600 mg or less, about 533 mg or less, about 500 mg or less, about 400 mg or less, about 300 mg or less, about 250 mg or less, or about 200 mg or less, once every two weeks, once every three weeks, or once every four weeks.

In some embodiments, the disorder is a cancer, *e.g.*, a cancer described herein. In certain embodiments, the cancer is a solid tumor. In some embodiments, the cancer is brain tumor, *e.g.*, a glioblastoma, a gliosarcoma, or a recurrent brain tumor. In some embodiments, the cancer is a pancreatic cancer, *e.g.*, an advanced pancreatic cancer. In some embodiments, the cancer is a skin cancer, *e.g.*, a melanoma (*e.g.*, a stage II-IV melanoma, an HLA-A2 positive melanoma, an unresectable melanoma, or a metastatic melanoma), or a Merkel cell carcinoma. In some embodiments, the cancer is a renal cancer, *e.g.*, a renal cell carcinoma (RCC) (*e.g.*, a metastatic renal cell carcinoma). In some embodiments, the cancer is a breast cancer, *e.g.*, a metastatic breast carcinoma or a stage IV breast carcinoma, *e.g.*, a triple negative breast cancer (TNBC). In some embodiments, the cancer is a virus-associated cancer. In some embodiments, the cancer is an anal canal cancer (*e.g.*, a squamous cell carcinoma of the anal canal). In some embodiments, the cancer is a cervical cancer (*e.g.*, a squamous cell carcinoma of the cervix). In some embodiments, the cancer is a gastric cancer (*e.g.*, an Epstein Barr Virus (EBV) positive gastric cancer, or a gastric or gastro-esophageal junction carcinoma). In some embodiments, the cancer is a head and neck cancer (*e.g.*, an

HPV positive and negative squamous cell cancer of the head and neck (SCCHN)). In some embodiments, the cancer is a nasopharyngeal cancer (NPC). In some embodiments, the cancer is a penile cancer (*e.g.*, a squamous cell carcinoma of the penile). In some embodiments, the cancer is a vaginal or vulvar cancer (*e.g.*, a squamous cell carcinoma of the vagina or vulva). In some
5
embodiments, the cancer is a colorectal cancer, *e.g.*, a relapsed colorectal cancer or a metastatic colorectal cancer, *e.g.*, a microsatellite unstable colorectal cancer, a microsatellite stable colorectal cancer, a mismatch repair proficient colorectal cancer, or a mismatch repair deficient colorectal cancer. In some embodiments, the cancer is a lung cancer, *e.g.*, a non-small cell lung cancer (NSCLC). In certain embodiments, the cancer is a hematological cancer. In some embodiments, the cancer is a
10
leukemia. In some embodiments, the cancer is a lymphoma, *e.g.*, a Hodgkin lymphoma (HL) or a diffuse large B cell lymphoma (DLBCL) (*e.g.*, a relapsed or refractory HL or DLBCL). In some embodiments, the cancer is a myeloma.

In other embodiments, the cancer is an MSI-high cancer. In some embodiments, the cancer is a metastatic cancer. In other embodiments, the cancer is an advanced cancer. In other embodiments,
15
the cancer is a relapsed or refractory cancer. In other embodiments, the cancer is an unresectable cancer.

In one embodiment, the cancer is a Merkel cell carcinoma. In other embodiments, the cancer is a melanoma. In other embodiments, the cancer is a breast cancer, *e.g.*, a triple negative breast cancer (TNBC) or a HER2-negative breast cancer. In other embodiments, the cancer is a renal cell
20
carcinoma (*e.g.*, a clear cell renal cell carcinoma (CCRCC) or a non-clear cell renal cell carcinoma (nccRCC)). In other embodiments, the cancer is a thyroid cancer, *e.g.*, an anaplastic thyroid carcinoma (ATC). In other embodiments, the cancer is a neuroendocrine tumor (NET), *e.g.*, an atypical pulmonary carcinoid tumor or an NET in pancreas, gastrointestinal (GI) tract, or lung. In certain embodiments, the cancer is a non-small cell lung cancer (NSCLC) (*e.g.*, a squamous NSCLC
25
or a non-squamous NSCLC). In certain embodiments, the cancer is a fallopian tube cancer. In certain embodiments, the cancer is a microsatellite instability-high colorectal cancer (MSI-high CRC) or a microsatellite stable colorectal cancer (MSS CRC).

In some embodiments, the anti-LAG-3 antibody molecule is administered in combination with an anti-PD-1 antibody molecule (*e.g.*, an anti-PD-1 antibody molecule described herein).
30
Without wishing to be bound by theory, it is believed that in some embodiments, anti-LAG-3 therapy is expected to have an additive effect in combination with anti-PD-1 therapy, as has been observed in mice (Woo *et al. Cancer Research* 72: 917-927 (2012)). The anti-PD-1 antibody molecule can be administered with or without a chemotherapeutic agent (*e.g.*, a platinum agent (*e.g.*, carboplatin, cisplatin, oxaliplatin, or tetraplatin) or a nucleotide analog or precursor analog (*e.g.*, capecitabine)).
35
Without wishing to be bound by theory, it is believed that in some embodiments, addition of a chemotherapeutic agent will further enhance the efficacy of anti-LAG-3 immunotherapy, singly or in

combination with anti-PD-1 immunotherapy, by making the tumor more immuno-reactive and/or by altering the tumor microenvironment to achieve an optimal anti-tumor immune response.

In certain embodiments, the anti-PD-1 antibody molecule is administered at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) once every four weeks or about 200 mg to about 400 mg (*e.g.*, about 300 mg) once every three weeks. In some embodiments, the anti-PD-1 antibody molecule is administered at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) once every four weeks. In some embodiments, the anti-PD-1 antibody molecule is administered at a dose of about 200 mg to about 400 mg (*e.g.*, about 300 mg) once every three weeks.

In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to 500 mg (*e.g.*, about 400 mg) once every three weeks and the anti-PD-1 antibody molecule is administered at a dose of about 200 mg to about 400 mg (*e.g.*, about 300 mg) once every three weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to 500 mg (*e.g.*, about 400 mg) once every three weeks and the anti-PD-1 antibody molecule is administered at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) once every four weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 700 mg to 900 mg (*e.g.*, about 800 mg) once every four weeks and the anti-PD-1 antibody molecule is administered at a dose of about 200 mg to about 400 mg (*e.g.*, about 300 mg) once every three weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 700 mg to 900 mg (*e.g.*, about 800 mg) once every four weeks and the anti-PD-1 antibody molecule is administered at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) once every four weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 500 mg to 650 mg (*e.g.*, about 533 mg or about 600 mg) once every four weeks and the anti-PD-1 antibody molecule is administered at a dose of about 200 mg to about 400 mg (*e.g.*, about 300 mg) once every three weeks. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 500 mg to 650 mg (*e.g.*, about 533 mg or about 600 mg) once every four weeks and the anti-PD-1 antibody molecule is administered at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) once every four weeks.

In some embodiments, the anti-TIM-3 antibody molecule is administered in combination with a chemotherapeutic agent (*e.g.*, a platinum agent (*e.g.*, carboplatin, cisplatin, oxaliplatin, or tetraplatin) or a nucleotide analog or precursor analog (*e.g.*, capecitabine)). In some embodiments, the chemotherapeutic agent is a platinum agent. In certain embodiments, the platinum agent is carboplatin. In certain embodiments, the platinum agent is cisplatin. In certain embodiments, the platinum agent is oxaliplatin. In certain embodiments, the platinum agent is tetraplatin.

In some embodiments, the chemotherapeutic agent is a nucleotide analog or precursor analog. In certain embodiments, the nucleotide analog or precursor analog is capecitabine.

In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to 500 mg (*e.g.*, about 400 mg) once every three weeks and the chemotherapeutic agent (*e.g.*,

a platinum agent, *e.g.*, carboplatin) is administered at a dose to achieve an area under the curve (AUC) of about 4 to about 8 or about 5 to about 7 (*e.g.*, an AUC of about 6) once every three weeks.

In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to 500 mg (*e.g.*, about 400 mg) once every three weeks, the anti-PD-1 antibody molecule is administered at a dose of about 200 mg to about 400 mg (*e.g.*, about 300 mg) once every three weeks, and the chemotherapeutic agent (*e.g.*, a platinum agent, *e.g.*, carboplatin) is administered at a dose to achieve an area under the curve (AUC) of about 4 to about 8 or about 5 to about 7 (*e.g.*, an AUC of about 6) once every three weeks.

In certain embodiments, the anti-LAG-3 antibody molecule is LAG525 and the anti-PD-1 antibody molecule is PDR001 (spartalizumab).

In some embodiments, the anti-LAG-3 antibody molecule is LAG525 and the chemotherapeutic agent is a platinum agent. In certain embodiments, the anti-LAG-3 antibody molecule is LAG525 and the platinum agent is carboplatin. In certain embodiments, the anti-LAG-3 antibody molecule is LAG525 and the platinum agent is cisplatin. In certain embodiments, the anti-LAG-3 antibody molecule is LAG525 and the platinum agent is oxaliplatin. In certain embodiments, the anti-LAG-3 antibody molecule is LAG525 and the platinum agent is tetraplatin.

In some embodiments, the anti-LAG-3 antibody molecule is LAG525, the chemotherapeutic agent is a platinum agent, and the anti-PD-1 antibody molecule is PDR001 (spartalizumab). In certain embodiments, the anti-LAG-3 antibody molecule is LAG525, the platinum agent is carboplatin, and the anti-PD-1 antibody molecule is PDR001 (spartalizumab). In certain embodiments, the anti-LAG-3 antibody molecule is LAG525, the platinum agent is cisplatin, and the anti-PD-1 antibody molecule is PDR001 (spartalizumab). In certain embodiments, the anti-LAG-3 antibody molecule is LAG525, the platinum agent is oxaliplatin, and the anti-PD-1 antibody molecule is PDR001 (spartalizumab). In certain embodiments, the anti-LAG-3 antibody molecule is LAG525, the platinum agent is tetraplatin, and the anti-PD-1 antibody molecule is PDR001 (spartalizumab).

In some embodiments, the anti-LAG-3 antibody molecule is LAG525 and the chemotherapeutic agent is a nucleotide analog or precursor analog. In certain embodiments, the anti-LAG-3 antibody molecule is LAG525 and the nucleotide analog or precursor analog is capecitabine.

In some embodiments, the anti-LAG-3 antibody molecule is LAG525, the chemotherapeutic agent is a nucleotide analog or precursor analog, and the anti-PD-1 antibody molecule is PDR001 (spartalizumab). In certain embodiments, the anti-LAG-3 antibody molecule is LAG525, the nucleotide analog or precursor analog is capecitabine, and the anti-PD-1 antibody molecule is PDR001 (spartalizumab).

Any of the doses disclosed herein can be repeat once, twice, three times, four times, five time, six time, seven time, eight times, nine times, ten times, or more.

Antibody Molecules

Disclosed herein methods, compositions, and formulations that include an antibody molecule that binds to a mammalian, *e.g.*, human, LAG-3. For example, the antibody molecule binds specifically to an epitope, *e.g.*, linear or conformational epitope, (*e.g.*, an epitope as described herein) on LAG-3.

As used herein, the term “antibody molecule” refers to a protein, *e.g.*, an immunoglobulin chain or fragment thereof, comprising at least one immunoglobulin variable domain sequence. The term “antibody molecule” includes, for example, a monoclonal antibody (including a full length antibody which has an immunoglobulin Fc region). In an embodiment, an antibody molecule comprises a full length antibody, or a full length immunoglobulin chain. In an embodiment, an antibody molecule comprises an antigen binding or functional fragment of a full length antibody, or a full length immunoglobulin chain. In an embodiment, an antibody molecule is a multispecific antibody molecule, *e.g.*, it comprises a plurality of immunoglobulin variable domain sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In an embodiment, a multispecific antibody molecule is a bispecific antibody molecule.

In an embodiment, an antibody molecule is a monospecific antibody molecule and binds a single epitope. For example, a monospecific antibody molecule can have a plurality of immunoglobulin variable domain sequences, each of which binds the same epitope.

In an embodiment, an antibody molecule is a multispecific antibody molecule, *e.g.*, it comprises a plurality of immunoglobulin variable domains sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In an embodiment, the first and second epitopes are on the same antigen, *e.g.*, the same protein (or subunit of a multimeric protein). In an embodiment, the first and second epitopes overlap. In an embodiment, the first and second epitopes do not overlap. In an embodiment, the first and second epitopes are on different antigens, *e.g.*, the different proteins (or different subunits of a multimeric protein). In an embodiment, a multispecific antibody molecule comprises a third, fourth or fifth immunoglobulin variable domain. In an embodiment, a multispecific antibody molecule is a bispecific antibody molecule, a trispecific antibody molecule, or tetraspecific antibody molecule,

In an embodiment, a multispecific antibody molecule is a bispecific antibody molecule. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody molecule is characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. In an embodiment, the first and second epitopes are on the same antigen, *e.g.*, the same protein (or subunit of a multimeric protein). In an embodiment, the first and second epitopes

overlap. In an embodiment the first and second epitopes do not overlap. In an embodiment, the first and second epitopes are on different antigens, *e.g.*, the different proteins (or different subunits of a multimeric protein). In an embodiment, a bispecific antibody molecule comprises a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a first epitope and a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a second epitope. In an embodiment, a bispecific antibody molecule comprises a half antibody having binding specificity for a first epitope and a half antibody having binding specificity for a second epitope. In an embodiment, a bispecific antibody molecule comprises a half antibody, or fragment thereof, having binding specificity for a first epitope and a half antibody, or fragment thereof, having binding specificity for a second epitope. In an embodiment, a bispecific antibody molecule comprises a scFv, or fragment thereof, have binding specificity for a first epitope and a scFv, or fragment thereof, have binding specificity for a second epitope. In an embodiment, the first epitope is located on LAG-3 and the second epitope is located on a PD-1, TIM-3, CEACAM (*e.g.*, CEACAM-1 and/or CEACAM-5), PD-L1, or PD-L2.

Protocols for generating multi-specific (*e.g.*, bispecific or trispecific) or heterodimeric antibody molecules are known in the art; including but not limited to, for example, the “knob in a hole” approach described in, *e.g.*, US5731168; the electrostatic steering Fc pairing as described in, *e.g.*, WO 09/089004, WO 06/106905 and WO 2010/129304; Strand Exchange Engineered Domains (SEED) heterodimer formation as described in, *e.g.*, WO 07/110205; Fab arm exchange as described in, *e.g.*, WO 08/119353, WO 2011/131746, and WO 2013/060867; double antibody conjugate, *e.g.*, by antibody cross-linking to generate a bi-specific structure using a heterobifunctional reagent having an amine-reactive group and a sulfhydryl reactive group as described in, *e.g.*, US4433059; bispecific antibody determinants generated by recombining half antibodies (heavy-light chain pairs or Fabs) from different antibodies through cycle of reduction and oxidation of disulfide bonds between the two heavy chains, as described in, *e.g.*, US 4444878; trifunctional antibodies, *e.g.*, three Fab' fragments cross-linked through sulfhydryl reactive groups, as described in, *e.g.*, US5273743; biosynthetic binding proteins, *e.g.*, pair of scFvs cross-linked through C-terminal tails preferably through disulfide or amine-reactive chemical cross-linking, as described in, *e.g.*, US5534254; bifunctional antibodies, *e.g.*, Fab fragments with different binding specificities dimerized through leucine zippers (*e.g.*, c-fos and c-jun) that have replaced the constant domain, as described in, *e.g.*, US5582996; bispecific and oligospecific mono-and oligovalent receptors, *e.g.*, VH-CH1 regions of two antibodies (two Fab fragments) linked through a polypeptide spacer between the CH1 region of one antibody and the VH region of the other antibody typically with associated light chains, as described in, *e.g.*, US5591828; bispecific DNA-antibody conjugates, *e.g.*, crosslinking of antibodies or Fab fragments through a double stranded piece of DNA, as described in, *e.g.*, US5635602; bispecific fusion proteins, *e.g.*, an expression construct containing two scFvs with a hydrophilic helical peptide linker between them and a full constant region, as described in, *e.g.*, US5637481; multivalent and multispecific binding

proteins, *e.g.*, dimer of polypeptides having first domain with binding region of Ig heavy chain variable region, and second domain with binding region of Ig light chain variable region, generally termed diabodies (higher order structures are also disclosed creating bispecific, trispecific, or tetraspecific molecules, as described in, *e.g.*, US5837242; minibody constructs with linked VL and VH chains further connected with peptide spacers to an antibody hinge region and CH3 region, which can be dimerized to form bispecific/multivalent molecules, as described in, *e.g.*, US5837821; VH and VL domains linked with a short peptide linker (*e.g.*, 5 or 10 amino acids) or no linker at all in either orientation, which can form dimers to form bispecific diabodies; trimers and tetramers, as described in, *e.g.*, US5844094; String of VH domains (or VL domains in family members) connected by peptide linkages with crosslinkable groups at the C-terminus further associated with VL domains to form a series of FVs (or scFvs), as described in, *e.g.*, US5864019; and single chain binding polypeptides with both a VH and a VL domain linked through a peptide linker are combined into multivalent structures through non-covalent or chemical crosslinking to form, *e.g.*, homobivalent, heterobivalent, trivalent, and tetravalent structures using both scFV or diabody type format, as described in, *e.g.*, US5869620.

Additional exemplary multispecific and bispecific molecules and methods of making the same are found, for example, in US5910573, US5932448, US5959083, US5989830, US6005079, US6239259, US6294353, US6333396, US6476198, US6511663, US6670453, US6743896, US6809185, US6833441, US7129330, US7183076, US7521056, US7527787, US7534866, US7612181, US2002/004587A1, US2002/076406A1, US2002/103345A1, US2003/207346A1, US2003/211078A1, US2004/219643A1, US2004/220388A1, US2004/242847A1, US2005/003403A1, US2005/004352A1, US2005/069552A1, US2005/079170A1, US2005/100543A1, US2005/136049A1, US2005/136051A1, US2005/163782A1, US2005/266425A1, US2006/083747A1, US2006/120960A1, US2006/204493A1, US2006/263367A1, US2007/004909A1, US2007/087381A1, US2007/128150A1, US2007/141049A1, US2007/154901A1, US2007/274985A1, US2008/050370A1, US2008/069820A1, US2008/152645A1, US2008/171855A1, US2008/241884A1, US2008/254512A1, US2008/260738A1, US2009/130106A1, US2009/148905A1, US2009/155275A1, US2009/162359A1, US2009/162360A1, US2009/175851A1, US2009/175867A1, US2009/232811A1, US2009/234105A1, US2009/263392A1, US2009/274649A1, EP346087A2, WO00/06605A2, WO02/072635A2, WO04/081051A1, WO06/020258A2, WO2007/044887A2, WO2007/095338A2, WO2007/137760A2, WO2008/119353A1, WO2009/021754A2, WO2009/068630A1, WO91/03493A1, WO93/23537A1, WO94/09131A1, WO94/12625A2, WO95/09917A1, WO96/37621A2, WO99/64460A1. The contents of the above-referenced applications are incorporated herein by reference in their entireties.

In other embodiments, the anti-LAG-3 antibody molecule (*e.g.*, a monospecific, bispecific, or multispecific antibody molecule) is covalently linked, *e.g.*, fused, to another partner *e.g.*, a protein *e.g.*, one, two or more cytokines, *e.g.*, as a fusion molecule for example a fusion protein. In other embodiments, the fusion molecule comprises one or more proteins, *e.g.*, one, two or more cytokines. In one embodiment, the cytokine is an interleukin (IL) chosen from one, two, three or more of IL-1,

IL-2, IL-12, IL-15 or IL-21. In one embodiment, a bispecific antibody molecule has a first binding specificity to a first target (*e.g.*, to LAG-3), a second binding specificity to a second target (*e.g.*, PD-1 or TIM-3), and is optionally linked to an interleukin (*e.g.*, IL-12) domain *e.g.*, full length IL-12 or a portion thereof.

5 A “fusion protein” and a “fusion polypeptide” refer to a polypeptide having at least two portions covalently linked together, where each of the portions is a polypeptide having a different property. The property may be a biological property, such as activity *in vitro* or *in vivo*. The property can also be simple chemical or physical property, such as binding to a target molecule, catalysis of a reaction, etc. The two portions can be linked directly by a single peptide bond or through a peptide
10 linker, but are in reading frame with each other.

In an embodiment, an antibody molecule comprises a diabody, and a single-chain molecule, as well as an antigen-binding fragment of an antibody (*e.g.*, Fab, F(ab')₂, and Fv). For example, an antibody molecule can include a heavy (H) chain variable domain sequence (abbreviated herein as VH), and a light (L) chain variable domain sequence (abbreviated herein as VL). In an embodiment
15 an antibody molecule comprises or consists of a heavy chain and a light chain (referred to herein as a half antibody). In another example, an antibody molecule includes two heavy (H) chain variable domain sequences and two light (L) chain variable domain sequence, thereby forming two antigen binding sites, such as Fab, Fab', F(ab')₂, Fc, Fd, Fd', Fv, single chain antibodies (scFv for example), single variable domain antibodies, diabodies (Dab) (bivalent and bispecific), and chimeric (*e.g.*,
20 humanized) antibodies, which may be produced by the modification of whole antibodies or those synthesized de novo using recombinant DNA technologies. These functional antibody fragments retain the ability to selectively bind with their respective antigen or receptor. Antibodies and antibody fragments can be from any class of antibodies including, but not limited to, IgG, IgA, IgM, IgD, and IgE, and from any subclass (*e.g.*, IgG1, IgG2, IgG3, and IgG4) of antibodies. The preparation of
25 antibody molecules can be monoclonal or polyclonal. An antibody molecule can also be a human, humanized, CDR-grafted, or *in vitro* generated antibody. The antibody can have a heavy chain constant region chosen from, *e.g.*, IgG1, IgG2, IgG3, or IgG4. The antibody can also have a light chain chosen from, *e.g.*, kappa or lambda. The term “immunoglobulin” (Ig) is used interchangeably with the term “antibody” herein.

30 Examples of antigen-binding fragments of an antibody molecule include: (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a diabody (dAb) fragment, which consists of a VH
35 domain; (vi) a camelid or camelized variable domain; (vii) a 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); (viii) a single domain antibody. These antibody fragments are obtained using conventional techniques

known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

The term “antibody” includes intact molecules as well as functional fragments thereof. Constant regions of the antibodies can be altered, *e.g.*, mutated, to modify the properties of the antibody (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function).

Antibody molecules can also be single domain antibodies. Single domain antibodies can include antibodies whose complementary determining regions are part of a single domain polypeptide. Examples include, but are not limited to, heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional 4-chain antibodies, engineered antibodies and single domain scaffolds other than those derived from antibodies. Single domain antibodies may be any of the art, or any future single domain antibodies. Single domain antibodies may be derived from any species including, but not limited to mouse, human, camel, llama, fish, shark, goat, rabbit, and bovine. According to another aspect of the invention, a single domain antibody is a naturally occurring single domain antibody known as heavy chain antibody devoid of light chains. Such single domain antibodies are disclosed in WO 94/04678, for example. For clarity reasons, this variable domain derived from a heavy chain antibody naturally devoid of light chain is known herein as a VHH or nanobody to distinguish it from the conventional VH of four chain immunoglobulins. Such a VHH molecule can be derived from antibodies raised in *Camelidae* species, for example in camel, llama, dromedary, alpaca and guanaco. Other species besides *Camelidae* may produce heavy chain antibodies naturally devoid of light chain; such VHHs are within the scope of the invention.

The VH and VL regions can be subdivided into regions of hypervariability, termed “complementarity determining regions” (CDR), interspersed with regions that are more conserved, termed “framework regions” (FR or FW).

The extent of the framework region and CDRs has been precisely defined by a number of methods (*see*, Kabat, E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Chothia, C. *et al.* (1987) *J. Mol. Biol.* 196:901-917; and the AbM definition used by Oxford Molecular’s AbM antibody modeling software. *See*, generally, *e.g.*, *Protein Sequence and Structure Analysis of Antibody Variable Domains*. In: *Antibody Engineering Lab Manual* (Ed.: Duebel, S. and Kontermann, R., Springer-Verlag, Heidelberg).

The terms “complementarity determining region,” and “CDR,” as used herein refer to the sequences of amino acids within antibody variable regions which confer antigen specificity and binding affinity. In general, there are three CDRs in each heavy chain variable region (HCDR1, HCDR2, and HCDR3) and three CDRs in each light chain variable region (LCDR1, LCDR2, and LCDR3).

The precise amino acid sequence boundaries of a given CDR can be determined using any of a number of well-known schemes, including those described by Kabat *et al.* (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD ("Kabat" numbering scheme), Al-Lazikani *et al.*, (1997) *JMB* 273,927-948 ("Chothia" numbering scheme). As used herein, the CDRs defined according to the "Chothia" number scheme are also sometimes referred to as "hypervariable loops."

For example, under Kabat, the CDR amino acid residues in the heavy chain variable domain (VH) are numbered 31-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3); and the CDR amino acid residues in the light chain variable domain (VL) are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3). Under Chothia the CDR amino acids in the VH are numbered 26-32 (HCDR1), 52-56 (HCDR2), and 95-102 (HCDR3); and the amino acid residues in VL are numbered 26-32 (LCDR1), 50-52 (LCDR2), and 91-96 (LCDR3). By combining the CDR definitions of both Kabat and Chothia, the CDRs consist of amino acid residues 26-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3) in human VH and amino acid residues 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3) in human VL.

Generally, unless specifically indicated, the anti-LAG-3 antibody molecules can include any combination of one or more Kabat CDRs and/or Chothia hypervariable loops. In one embodiment, the following definitions are used for the anti-LAG-3 antibody molecules: HCDR1 according to the combined CDR definitions of both Kabat and Chothia, and HCCDRs 2-3 and LCCDRs 1-3 according to the CDR definition of Kabat. Under all definitions, each VH and VL typically includes three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

As used herein, an "immunoglobulin variable domain sequence" refers to an amino acid sequence which can form the structure of an immunoglobulin variable domain. For example, the sequence may include all or part of the amino acid sequence of a naturally-occurring variable domain. For example, the sequence may or may not include one, two, or more N- or C-terminal amino acids, or may include other alterations that are compatible with formation of the protein structure.

The term "antigen-binding site" refers to the part of an antibody molecule that comprises determinants that form an interface that binds to the LAG-3 polypeptide, or an epitope thereof. With respect to proteins (or protein mimetics), the antigen-binding site typically includes one or more loops (of at least four amino acids or amino acid mimics) that form an interface that binds to the LAG-3 polypeptide. Typically, the antigen-binding site of an antibody molecule includes at least one or two CDRs and/or hypervariable loops, or more typically at least three, four, five or six CDRs and/or hypervariable loops.

The terms "compete" or "cross-compete" are used interchangeably herein to refer to the ability of an antibody molecule to interfere with binding of an anti-LAG-3 antibody molecule, *e.g.*, an anti-LAG-3 antibody molecule provided herein, to a target, *e.g.*, human LAG-3. The interference

with binding can be direct or indirect (*e.g.*, through an allosteric modulation of the antibody molecule or the target). The extent to which an antibody molecule is able to interfere with the binding of another antibody molecule to the target, and therefore whether it can be said to compete, can be determined using a competition binding assay, for example, a FACS assay, an ELISA or BIACORE
5 assay. In some embodiments, a competition binding assay is a quantitative competition assay. In some embodiments, a first anti-LAG-3 antibody molecule is said to compete for binding to the target with a second anti-LAG-3 antibody molecule when the binding of the first antibody molecule to the target is reduced by 10% or more, *e.g.*, 20% or more, 30% or more, 40% or more, 50% or more, 55%
10 or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, 99% or more in a competition binding assay (*e.g.*, a competition assay described herein).

The terms “monoclonal antibody” or “monoclonal antibody composition” as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. A monoclonal
15 antibody can be made by hybridoma technology or by methods that do not use hybridoma technology (*e.g.*, recombinant methods).

An “effectively human” protein is a protein that does not evoke a neutralizing antibody response, *e.g.*, the human anti-murine antibody (HAMA) response. HAMA can be problematic in a number of circumstances, *e.g.*, if the antibody molecule is administered repeatedly, *e.g.*, in treatment
20 of a chronic or recurrent disease condition. A HAMA response can make repeated antibody administration potentially ineffective because of an increased antibody clearance from the serum (*see, e.g.*, Saleh *et al.*, *Cancer Immunol. Immunother.* 32:180-190 (1990)) and also because of potential allergic reactions (*see, e.g.*, LoBuglio *et al.*, *Hybridoma*, 5:5117-5123 (1986)).

The antibody molecule can be a polyclonal or a monoclonal antibody. In other embodiments,
25 the antibody can be recombinantly produced, *e.g.*, produced by phage display or by combinatorial methods.

Phage display and combinatorial methods for generating antibodies are known in the art (as described in, *e.g.*, Ladner *et al.* U.S. Patent No. 5,223,409; Kang *et al.* International Publication No. WO 92/18619; Dower *et al.* International Publication No. WO 91/17271; Winter *et al.* International
30 Publication WO 92/20791; Markland *et al.* International Publication No. WO 92/15679; Breitling *et al.* International Publication WO 93/01288; McCafferty *et al.* International Publication No. WO 92/01047; Garrard *et al.* International Publication No. WO 92/09690; Ladner *et al.* International Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum Antibody Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993)
35 *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J Mol Biol* 226:889-896; Clackson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *PNAS* 89:3576-3580; Garrard *et al.* (1991) *Bio/Technology* 9:1373-

1377; Hoogenboom *et al.* (1991) *Nuc Acid Res* 19:4133-4137; and Barbas *et al.* (1991) *PNAS* 88:7978-7982, the contents of all of which are incorporated by reference herein).

In one embodiment, the antibody is a fully human antibody (*e.g.*, an antibody made in a mouse which has been genetically engineered to produce an antibody from a human immunoglobulin sequence), or a non-human antibody, *e.g.*, a rodent (mouse or rat), goat, primate (*e.g.*, monkey), camel antibody. Preferably, the non-human antibody is a rodent (mouse or rat antibody). Methods of producing rodent antibodies are known in the art.

Human monoclonal antibodies can be generated using transgenic mice carrying the human immunoglobulin genes rather than the mouse system. Splenocytes from these transgenic mice immunized with the antigen of interest are used to produce hybridomas that secrete human mAbs with specific affinities for epitopes from a human protein (*see, e.g.*, Wood *et al.* International Application WO 91/00906, Kucherlapati *et al.* PCT publication WO 91/10741; Lonberg *et al.* International Application WO 92/03918; Kay *et al.* International Application 92/03917; Lonberg, N. *et al.* 1994 *Nature* 368:856-859; Green, L.L. *et al.* 1994 *Nature Genet.* 7:13-21; Morrison, S.L. *et al.* 1994 *Proc. Natl. Acad. Sci. USA* 81:6851-6855; Bruggeman *et al.* 1993 *Year Immunol* 7:33-40; Tuailleon *et al.* 1993 *PNAS* 90:3720-3724; Bruggeman *et al.* 1991 *Eur J Immunol* 21:1323-1326).

An antibody can be one in which the variable region, or a portion thereof, *e.g.*, the CDRs, are generated in a non-human organism, *e.g.*, a rat or mouse. Chimeric, CDR-grafted, and humanized antibodies are within the invention. Antibodies generated in a non-human organism, *e.g.*, a rat or mouse, and then modified, *e.g.*, in the variable framework or constant region, to decrease antigenicity in a human are within the invention.

Chimeric antibodies can be produced by recombinant DNA techniques known in the art (*see* Robinson *et al.*, International Patent Publication PCT/US86/02269; Akira, *et al.*, European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison *et al.*, European Patent Application 173,494; Neuberger *et al.*, International Application WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567; Cabilly *et al.*, European Patent Application 125,023; Better *et al.* (1988 *Science* 240:1041-1043); Liu *et al.* (1987) *PNAS* 84:3439-3443; Liu *et al.*, 1987, *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *PNAS* 84:214-218; Nishimura *et al.*, 1987, *Canc. Res.* 47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; and Shaw *et al.*, 1988, *J. Natl Cancer Inst.* 80:1553-1559).

A humanized or CDR-grafted antibody will have at least one or two but generally all three recipient CDRs (of heavy and or light immunoglobulin chains) replaced with a donor CDR. The antibody may be replaced with at least a portion of a non-human CDR or only some of the CDRs may be replaced with non-human CDRs. It is only necessary to replace the number of CDRs required for binding of the humanized antibody to PD-1. Preferably, the donor will be a rodent antibody, *e.g.*, a rat or mouse antibody, and the recipient will be a human framework or a human consensus framework. Typically, the immunoglobulin providing the CDRs is called the "donor" and the immunoglobulin providing the framework is called the "acceptor." In one embodiment, the donor immunoglobulin is a

non-human (*e.g.*, rodent). The acceptor framework is a naturally-occurring (*e.g.*, a human) framework or a consensus framework, or a sequence about 85% or higher, preferably 90%, 95%, 99% or higher identical thereto.

As used herein, the term “consensus sequence” refers to the sequence formed from the most frequently occurring amino acids (or nucleotides) in a family of related sequences (*see, e.g.*, Winnaker, From Genes to Clones (Verlagsgesellschaft, Weinheim, Germany 1987). In a family of proteins, each position in the consensus sequence is occupied by the amino acid occurring most frequently at that position in the family. If two amino acids occur equally frequently, either can be included in the consensus sequence. A “consensus framework” refers to the framework region in the consensus immunoglobulin sequence.

An antibody can be humanized by methods known in the art (*see, e.g.*, Morrison, S. L., 1985, *Science* 229:1202-1207, by Oi *et al.*, 1986, *BioTechniques* 4:214, and by Queen *et al.* US 5,585,089, US 5,693,761 and US 5,693,762, the contents of all of which are hereby incorporated by reference).

Humanized or CDR-grafted antibodies can be produced by CDR-grafting or CDR substitution, wherein one, two, or all CDRs of an immunoglobulin chain can be replaced. *See, e.g.*, U.S. Patent 5,225,539; Jones *et al.* 1986 *Nature* 321:552-525; Verhoeyan *et al.* 1988 *Science* 239:1534; Beidler *et al.* 1988 *J. Immunol.* 141:4053-4060; Winter US 5,225,539, the contents of all of which are hereby expressly incorporated by reference. Winter describes a CDR-grafting method which may be used to prepare the humanized antibodies of the present invention (UK Patent Application GB 2188638A, filed on March 26, 1987; Winter US 5,225,539), the contents of which is expressly incorporated by reference.

Also within the scope of the invention are humanized antibodies in which specific amino acids have been substituted, deleted or added. Criteria for selecting amino acids from the donor are described in US 5,585,089, *e.g.*, columns 12-16 of US 5,585,089, *e.g.*, columns 12-16 of US 5,585,089, the contents of which are hereby incorporated by reference. Other techniques for humanizing antibodies are described in Padlan *et al.* EP 519596 A1, published on December 23, 1992.

The antibody molecule can be a single chain antibody. A single-chain antibody (scFV) may be engineered (*see, for example*, Colcher, D. *et al.* (1999) *Ann N Y Acad Sci* 880:263-80; and Reiter, Y. (1996) *Clin Cancer Res* 2:245-52). The single chain antibody can be dimerized or multimerized to generate multivalent antibodies having specificities for different epitopes of the same target protein.

In yet other embodiments, the antibody molecule has a heavy chain constant region chosen from, *e.g.*, the heavy chain constant regions of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE; particularly, chosen from, *e.g.*, the (*e.g.*, human) heavy chain constant regions of IgG1, IgG2, IgG3, and IgG4. In another embodiment, the antibody molecule has a light chain constant region chosen from, *e.g.*, the (*e.g.*, human) light chain constant regions of kappa or lambda. The constant region can be altered, *e.g.*, mutated, to modify the properties of the antibody (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues,

effector cell function, and/or complement function). In one embodiment the antibody has: effector function; and can fix complement. In other embodiments the antibody does not; recruit effector cells; or fix complement. In another embodiment, the antibody has reduced or no ability to bind an Fc receptor. For example, it is an isotype or subtype, fragment or other mutant, which does not support
5 binding to an Fc receptor, *e.g.*, it has a mutagenized or deleted Fc receptor binding region.

Methods for altering an antibody constant region are known in the art. Antibodies with altered function, *e.g.* altered affinity for an effector ligand, such as FcR on a cell, or the C1 component of complement can be produced by replacing at least one amino acid residue in the constant portion of the antibody with a different residue (*see, e.g.*, EP 388,151 A1, U.S. Pat. No. 5,624,821 and U.S. Pat.
10 No. 5,648,260, the contents of all of which are hereby incorporated by reference). Similar type of alterations could be described which if applied to the murine, or other species immunoglobulin would reduce or eliminate these functions.

An antibody molecule can be derivatized or linked to another functional molecule (*e.g.*, another peptide or protein). As used herein, a "derivatized" antibody molecule is one that has been
15 modified. Methods of derivatization include but are not limited to the addition of a fluorescent moiety, a radionucleotide, a toxin, an enzyme or an affinity ligand such as biotin. Accordingly, the antibody molecules of the invention are intended to include derivatized and otherwise modified forms of the antibodies described herein, including immunoadhesion molecules. For example, an antibody molecule can be functionally linked (by chemical coupling, genetic fusion, noncovalent association or
20 otherwise) to one or more other molecular entities, such as another antibody (*e.g.*, a bispecific antibody or a diabody), a detectable agent, a cytotoxic agent, a pharmaceutical agent, and/or a protein or peptide that can mediate association of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag).

One type of derivatized antibody molecule is produced by crosslinking two or more
25 antibodies (of the same type or of different types, *e.g.*, to create bispecific antibodies). Suitable crosslinkers include those that are heterobifunctional, having two distinctly reactive groups separated by an appropriate spacer (*e.g.*, m-maleimidobenzoyl-N-hydroxysuccinimide ester) or homobifunctional (*e.g.*, disuccinimidyl suberate). Such linkers are available from Pierce Chemical Company, Rockford, Ill.

Useful detectable agents with which an antibody molecule of the invention may be
30 derivatized (or labeled) to include fluorescent compounds, various enzymes, prosthetic groups, luminescent materials, bioluminescent materials, fluorescent emitting metal atoms, *e.g.*, europium (Eu), and other anthanides, and radioactive materials (described below). Exemplary fluorescent detectable agents include fluorescein, fluorescein isothiocyanate, rhodamine, 5dimethylamine-1-
35 naphthalenesulfonyl chloride, phycoerythrin and the like. An antibody may also be derivatized with detectable enzymes, such as alkaline phosphatase, horseradish peroxidase, β -galactosidase, acetylcholinesterase, glucose oxidase and the like. When an antibody is derivatized with a detectable

enzyme, it is detected by adding additional reagents that the enzyme uses to produce a detectable reaction product. For example, when the detectable agent horseradish peroxidase is present, the addition of hydrogen peroxide and diaminobenzidine leads to a colored reaction product, which is detectable. An antibody molecule may also be derivatized with a prosthetic group (*e.g.*,
5 streptavidin/biotin and avidin/biotin). For example, an antibody may be derivatized with biotin, and detected through indirect measurement of avidin or streptavidin binding. Examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; and examples of bioluminescent materials include luciferase, luciferin, and
10 aequorin.

Labeled antibody molecule can be used, for example, diagnostically and/or experimentally in a number of contexts, including (i) to isolate a predetermined antigen by standard techniques, such as affinity chromatography or immunoprecipitation; (ii) to detect a predetermined antigen (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the
15 protein; (iii) to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to determine the efficacy of a given treatment regimen.

An antibody molecules may be conjugated to another molecular entity, typically a label or a therapeutic (*e.g.*, a cytotoxic or cytostatic) agent or moiety. Radioactive isotopes can be used in diagnostic or therapeutic applications.

20 The invention provides radiolabeled antibody molecules and methods of labeling the same. In one embodiment, a method of labeling an antibody molecule is disclosed. The method includes contacting an antibody molecule, with a chelating agent, to thereby produce a conjugated antibody.

As is discussed above, the antibody molecule can be conjugated to a therapeutic agent. Therapeutically active radioisotopes have already been mentioned. Examples of other therapeutic
25 agents include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, maytansinoids, *e.g.*, maytansinol (*see, e.g.*, U.S. Pat. No. 5,208,020), CC-1065 (*see, e.g.*, U.S. Pat. Nos. 5,475,092, 5,585,499, 5,846, 545) and analogs or
30 homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, CC-1065, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and
35 cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine, vinblastine, taxol and maytansinoids).

In one aspect, the disclosure provides a method of providing a target binding molecule that specifically binds to a target disclosed herein, *e.g.*, LAG-3. For example, the target binding molecule is an antibody molecule. The method includes: providing a target protein that comprises at least a portion of non-human protein, the portion being homologous to (at least 70, 75, 80, 85, 87, 90, 92, 94, 5 95, 96, 97, 98% identical to) a corresponding portion of a human target protein, but differing by at least one amino acid (*e.g.*, at least one, two, three, four, five, six, seven, eight, or nine amino acids); obtaining an antibody molecule that specifically binds to the antigen; and evaluating efficacy of the binding agent in modulating activity of the target protein. The method can further include administering the binding agent (*e.g.*, antibody molecule) or a derivative (*e.g.*, a humanized antibody 10 molecule) to a human subject.

This disclosure provides an isolated nucleic acid molecule encoding the above antibody molecule, vectors and host cells thereof. The nucleic acid molecule includes but is not limited to RNA, genomic DNA and cDNA.

15 *Exemplary Anti-LAG-3 Antibody Molecules*

In one embodiment, the LAG-3 inhibitor is an anti-LAG-3 antibody molecule as disclosed in US 2015/0259420, published on September 17, 2015, entitled "Antibody Molecules to LAG-3 and Uses Thereof," incorporated by reference in its entirety.

In one embodiment, the anti-LAG-3 antibody molecule comprises at least one, two, three, 20 four, five or six complementarity determining regions (CDRs) (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 5 (*e.g.*, from the heavy and light chain variable region sequences of BAP050-Clone I or BAP050-Clone J disclosed in Table 5), or encoded by a nucleotide sequence shown in Table 5. In some embodiments, the CDRs are according to the Kabat definition (*e.g.*, as set out in Table 5). In some embodiments, the CDRs 25 are according to the Chothia definition (*e.g.*, as set out in Table 5). In some embodiments, the CDRs are according to the combined CDR definitions of both Kabat and Chothia (*e.g.*, as set out in Table 5). In one embodiment, the combination of Kabat and Chothia CDR of VH CDR1 comprises the amino acid sequence GF~~T~~L~~T~~N~~T~~YGMN (SEQ ID NO: 766). In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid 30 substitutions (*e.g.*, conservative amino acid substitutions) or deletions, relative to an amino acid sequence shown in Table 5, or encoded by a nucleotide sequence shown in Table 5.

In one embodiment, the anti-LAG-3 antibody molecule comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 701, a VHCDR2 amino acid sequence of SEQ ID NO: 702, and a VHCDR3 amino acid sequence of SEQ ID NO: 703; and a 35 light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 710, a VLCDR2 amino acid sequence of SEQ ID NO: 711, and a VLCDR3 amino acid sequence of SEQ ID NO: 712, each disclosed in Table 5.

In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising a VHCDR1 encoded by the nucleotide sequence of SEQ ID NO: 736 or 737, a VHCDR2 encoded by the nucleotide sequence of SEQ ID NO: 738 or 739, and a VHCDR3 encoded by the nucleotide sequence of SEQ ID NO: 740 or 741; and a VL comprising a VLCDR1 encoded by the nucleotide sequence of SEQ ID NO: 746 or 747, a VLCDR2 encoded by the nucleotide sequence of SEQ ID NO: 748 or 749, and a VLCDR3 encoded by the nucleotide sequence of SEQ ID NO: 750 or 751, each disclosed in Table 5. In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising a VHCDR1 encoded by the nucleotide sequence of SEQ ID NO: 758 or 737, a VHCDR2 encoded by the nucleotide sequence of SEQ ID NO: 759 or 739, and a VHCDR3 encoded by the nucleotide sequence of SEQ ID NO: 760 or 741; and a VL comprising a VLCDR1 encoded by the nucleotide sequence of SEQ ID NO: 746 or 747, a VLCDR2 encoded by the nucleotide sequence of SEQ ID NO: 748 or 749, and a VLCDR3 encoded by the nucleotide sequence of SEQ ID NO: 750 or 751, each disclosed in Table 5.

In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 706, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 706. In one embodiment, the anti-LAG-3 antibody molecule comprises a VL comprising the amino acid sequence of SEQ ID NO: 718, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 718. In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 724, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 724. In one embodiment, the anti-LAG-3 antibody molecule comprises a VL comprising the amino acid sequence of SEQ ID NO: 730, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 730. In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 706 and a VL comprising the amino acid sequence of SEQ ID NO: 718. In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 724 and a VL comprising the amino acid sequence of SEQ ID NO: 730.

In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 707 or 708, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 707 or 708. In one embodiment, the antibody molecule comprises a VL encoded by the nucleotide sequence of SEQ ID NO: 719 or 720, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 719 or 720. In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 725 or 726, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 725 or 726. In one embodiment, the antibody molecule comprises a VL encoded by the nucleotide sequence of SEQ ID NO: 731 or 732, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 731 or 732. In one embodiment, the antibody molecule comprises a VH

encoded by the nucleotide sequence of SEQ ID NO: 707 or 708 and a VL encoded by the nucleotide sequence of SEQ ID NO: 719 or 720. In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 725 or 726 and a VL encoded by the nucleotide sequence of SEQ ID NO: 731 or 732.

5 In one embodiment, the anti-LAG-3 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 709, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 709. In one embodiment, the anti-LAG-3 antibody molecule comprises a light chain comprising the amino acid sequence of SEQ ID NO: 721, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 721. In one
10 embodiment, the anti-LAG-3 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 727, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 727. In one embodiment, the anti-LAG-3 antibody molecule comprises a light chain comprising the amino acid sequence of SEQ ID NO: 733, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 733. In one embodiment, the anti-LAG-3
15 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 709 and a light chain comprising the amino acid sequence of SEQ ID NO: 721. In one embodiment, the anti-LAG-3 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 727 and a light chain comprising the amino acid sequence of SEQ ID NO: 733.

 In one embodiment, the antibody molecule comprises a heavy chain encoded by the
20 nucleotide sequence of SEQ ID NO: 716 or 717, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 716 or 717. In one embodiment, the antibody molecule comprises a light chain encoded by the nucleotide sequence of SEQ ID NO: 722 or 723, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 722 or 723. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide
25 sequence of SEQ ID NO: 728 or 729, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 728 or 729. In one embodiment, the antibody molecule comprises a light chain encoded by the nucleotide sequence of SEQ ID NO: 734 or 735, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 734 or 735. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO:
30 716 or 717 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 722 or 723. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 728 or 729 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 734 or 735.

 The antibody molecules described herein can be made by vectors, host cells, and methods
35 described in US 2015/0259420, incorporated by reference in its entirety.

Table 5. Amino acid and nucleotide sequences of exemplary anti-LAG-3 antibody molecules

BAP050-Clone I HC		
SEQ ID NO: 701 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 702 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 703 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 704 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 705 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 703 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 706	VH	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQARGQ RLEWIGWINTDTGEPTYADDFKGRFVFLDTSVSTAYLQISSLKAE DTAVYYCARNPPYYYGTNNAEAMDYWGQGTITVTVSS
SEQ ID NO: 707	DNA VH	CAAGTGCAGCTGGTGCAGTCGGGAGCCGAAGTGAAGAAGCCTG GAGCCTCGGTGAAGGTGTCGTGCAAGGCATCCGGATTACCCT CACCAATTACGGGATGAACTGGGTCAGACAGGCCCGGGGTCAA CGGCTGGAGTGGATCGGATGGATTAACACCGACACCGGGGAGC CTACCTACCGGACGATTTCAAGGACGGTTCGTGTTCTCCCTC GACACCTCCGTGTCCACCGCCTACCTCCAAATCTCCTCACTGAA AGCGGAGGACACCGCCGTGTACTATTGCGCGAGGAACCCGCC TACTACTACGGAACCAACAACGCCGAAGCCATGGACTACTGGG GCCAGGGCACCCTGTGACTGTGTCCAGC
SEQ ID NO: 708	DNA VH	CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCTG GCGCCTCCGTGAAGGTGTCCTGCAAGGCCTCTGGCTTACCCTG ACCAACTACGGCATGAACTGGGTGCGACAGGCCAGGGGCCAGC GGCTGGAATGGATCGGCTGGATCAACACCGACACCGGCGAGCC TACCTACGCCGACGACTTCAAGGGCAGATTCGTGTTCTCCCTGG ACACCTCCGTGTCCACCGCCTACCTGCAGATCTCCAGCCTGAAG GCCGAGGATACCGCCGTGTACTACTGCGCCCGGAACCCCTT ACTACTACGGCACCAACAACGCCGAGGCCATGGACTATTGGGG CCAGGGCACCACCGTGACCGTGTCTCT
SEQ ID NO: 709	Heavy chain	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQARGQ RLEWIGWINTDTGEPTYADDFKGRFVFLDTSVSTAYLQISSLKAE DTAVYYCARNPPYYYGTNNAEAMDYWGQGTITVTVSSASTKGPS VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPKNTKVDKRV ESKYGPPCPPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPS QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLD SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLS LG
SEQ ID NO: 716	DNA heavy chain	CAAGTGCAGCTGGTGCAGTCGGGAGCCGAAGTGAAGAAGCCTG GAGCCTCGGTGAAGGTGTCGTGCAAGGCATCCGGATTACCCT CACCAATTACGGGATGAACTGGGTCAGACAGGCCCGGGGTCAA CGGCTGGAGTGGATCGGATGGATTAACACCGACACCGGGGAGC CTACCTACCGGACGATTTCAAGGACGGTTCGTGTTCTCCCTC GACACCTCCGTGTCCACCGCCTACCTCCAAATCTCCTCACTGAA

	<p>AGCGGAGGACACCGCCGTGACTATTGCGCGAGGAACCCGCC TACTACTACGGAACCAACAACGCCGAAGCCATGGACTACTGGG GCCAGGGCACCACACTGTGACTGTGTCCAGCGCGTCCACTAAGGG CCCGTCCGTGTTCCCCCTGGCACCTTGTAGCCGGAGCACTAGCG AATCCACCGCTGCCCTCGGCTGCCTGGTCAAGGATTACTTCCCG GAGCCCCTGACCGTGTCTTGAACAGCGGAGCCCTGACCTCCG GAGTGCACACCTTCCCCGCTGTGCTGCAGAGCTCCGGGCTGTAC TCGCTGTCGTCCGGTGGTCACGGTGCCTTCATCTAGCCTGGGTAC CAAGACCTACACTTGCAACGTGGACCACAAGCCTTCCAACACT AAGGTGGACAAGCGCGTCAATCGAAGTACGGCCCACCGTGCC CGCCTTGTCCCGCGCCGGAGTTCCTCGGCGTCCCTCGGTCTTT CTGTTCCACCGAAGCCCAAGGACACTTTGATGATTTCCCGCAC CCCTGAAGTGACATGCGTGGTTCGTGGACGTGTACAGGAAGAT CCGGAGGTGCAGTTCAATTGGTACGTGGATGGCGTCGAGGTGC ACAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAACTCCAC TTACCGCGTTCGTGTCCTGCTGACGGTGTGCATCAGGACTGGC TGAACGGGAAGGAGTACAAGTGCAAGTGTCCAACAAGGGAC TTCCTAGCTCAATCGAAAAGACCATCTCGAAAGCCAAGGGACA GCCCCGGGAACCCCAAGTGTATACCCTGCCACCGAGCCAGGAA GAAATGACTAAGAACCAAGTCTCATTGACTTGCTTGTGAAGG GCTTCTACCCATCGGATATCGCCGTGGAATGGGAGTCCAACGG CCAGCCGAAAACAACACTACAAGACCACCCCTCCGGTGTGGAC TCAGACGGATCCTTCTTCTTACTCGCGGCTGACCGTGGATAA GAGCAGATGGCAGGAGGAAATGTGTTTCAGCTGTTCTGTGATG CATGAAGCCCTGCACAACCACTACACTCAGAAGTCCCTGTCCCT CTCCCTGGGA</p>
SEQ ID NO: 717	<p>DNA heavy chain</p> <p>CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCTG GCGCCTCCGTGAAGGTGTCTTGAAGGCCTCTGGCTTACCCCTG ACCAACTACGGCATGAACTGGGTGCGACAGGCCAGGGGCCAGC GGCTGGAATGGATCGGCTGGATCAACACCGACACCGGCGAGCC TACCTACGCCGACGACTTCAAGGGCAGATTTCGTGTTCTCCCTGG ACACCTCCGTGTCCACCGCCTACCTGCAGATCTCCAGCCTGAAG GCCGAGGATACCGCCGTGTACTACTGCGCCCGGAACCCCTT ACTACTACGGCACCAACAACGCCGAGGCCATGGACTATTGGGG CCAGGGCACCACCGTGACCGTGTCTTCTGCTTCTACCAAGGGG CCAGCGTGTTCCTTGGCCCCCTGCTCCAGAAGCACCAGCGA GAGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCC GAGCCCCTGACCGTGTCTTGAACAGCGGAGCCCTGACCAGCG GCGTGCACACCTTCCCCGCGTGTGCTGCAGAGCAGCGCCTGTA CAGCCTGAGCAGCGTGGTGACCGTGCCAGCAGCAGCCTGGGC ACCAAGACCTACACCTGTAACGTGGACCACAAGCCAGCAACA CCAAGGTGGACAAGAGGGTGGAGAGCAAGTACGGCCCACCCT GCCCCCTGCCAGCCCCGAGTTCCTGGGCGGACCCAGCGT GTTCTGTTCCCCCAAGCCCAAGGACACCCTGATGATCAGCA GAACCCCCGAGGTGACCTGTGTGGTGGTGGACGTGTCCCAGGA GGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAG GTGCACAACGCCAAGACCAAGCCCAGAGAGGAGCAGTTTAAACA GCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGCTGACCAGGA CTGGCTGAACGGCAAAGAGTACAAGTGAAGGTCTCCAACAAG GGCCTGCCAAGCAGCATCGAAAAGACCATCAGCAAGGCCAAG GGCCAGCCTAGAGAGCCCCAGGTCTACACCCTGCCACCCAGCC AAGAGGAGATGACCAAGAACCAGGTGTCCTGACCTGTCTGGT</p>

		GAAGGGCTTCTACCCAAGCGACATCGCCGTGGAGTGGGAGAGC AACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCAGTGC TGGACAGCGACGGCAGCTTCTTCTGTACAGCAGGCTGACCGT GGACAAGTCCAGATGGCAGGAGGGCAACGTCTTTAGCTGCTCC GTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGCC TGAGCCTGTCCCTGGGC
BAP050-Clone I LC		
SEQ ID NO: 710 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 711 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 712 (Kabat)	LCDR3	QYYNLPWT
SEQ ID NO: 713 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 714 (Chothia)	LCDR2	YTS
SEQ ID NO: 715 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 718	VL	DIQMTQSPSSLSASVGDRTITCASSQDISNYLNWYLQKPGQSPQL LIYYTSTLHLGVPSRFSGSGSGTEFTLTISLQPDFFATYYCQYYN LPWTFGQGTKVEIK
SEQ ID NO: 719	DNA VL	GATATTCAGATGACTCAGTCACCTAGTAGCCTGAGCGCTAGTGT GGGCGATAGAGTGACTATCACCTGTAGCTCTAGTCAGGATATCT CTAACTACCTGAACTGGTATCTGCAGAAGCCCGGTCAATCACCT CAGCTGCTGATCTACTACACTAGCACCTGCACCTGGGCGTGCC CTCTAGGTTTAGCGGTAGCGGTAGTGGCACCGAGTTCACCTGA CTATCTTAGCCTGCAGCCCGACGACTTCGCTACCTACTACTGT CAGCAGTACTATAACCTGCCCTGGACCTTCGGTCAAGGCACTA AGGTCGAGATTAAG
SEQ ID NO: 720	DNA VL	GACATCCAGATGACCCAGTCCCCCTCCAGCCTGTCTGCTTCCGT GGGCGACAGAGTGACCATCACCTGTTCCCTCCAGCCAGGACATC TCCAACCTGAACTGGTATCTGCAGAAGCCCGGCCAGTCCCC TCAGCTGCTGATCTACTACACTCCACCTGCACCTGGGCGTGC CCTCCAGATTTTCCGGCTCTGGCTCTGGCACCGAGTTTACCCTG ACCATCAGCTCCCTGCAGCCCGACGACTTCGCCACCTACTACTG CCAGCAGTACTACAACCTGCCCTGGACCTTCGGCCAGGGCACC AAGGTGGAATCAAG
SEQ ID NO: 721	Light chain	DIQMTQSPSSLSASVGDRTITCASSQDISNYLNWYLQKPGQSPQL LIYYTSTLHLGVPSRFSGSGSGTEFTLTISLQPDFFATYYCQYYN LPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLTKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 722	DNA light chain	GATATTCAGATGACTCAGTCACCTAGTAGCCTGAGCGCTAGTGT GGGCGATAGAGTGACTATCACCTGTAGCTCTAGTCAGGATATCT CTAACTACCTGAACTGGTATCTGCAGAAGCCCGGTCAATCACCT CAGCTGCTGATCTACTACACTAGCACCTGCACCTGGGCGTGCC CTCTAGGTTTAGCGGTAGCGGTAGTGGCACCGAGTTCACCTGA CTATCTTAGCCTGCAGCCCGACGACTTCGCTACCTACTACTGT CAGCAGTACTATAACCTGCCCTGGACCTTCGGTCAAGGCACTA AGGTCGAGATTAAGCGTACGGTGGCCGCTCCCAGCGTGTTTCAT CTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGC GTGGTGTGCTGCTGAACAACCTTACCCCCGGGAGGCCAAGG TGCAGTGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCA

		GGAGAGCGTCACCGAGCAGGACAGCAAGGACTCCACCTACAGC CTGAGCAGCACCCCTGACCCTGAGCAAGGCCGACTACGAGAAGC ATAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAG CCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
SEQ ID NO: 723	DNA light chain	GACATCCAGATGACCCAGTCCCCCTCCAGCCTGTCTGCTTCCGT GGGCGACAGAGTGACCATCACCTGTTCTCCAGCCAGGACATC TCCAACCTACCTGAACTGGTATCTGCAGAAGCCCGGCCAGTCCCC TCAGCTGCTGATCTACTACACCTCCACCCTGCACCTGGGCGTGC CCTCCAGATTTTCCGGCTCTGGCTCTGGCACCGAGTTTACCCTG ACCATCAGCTCCCTGCAGCCCCGACGACTTCGCCACCTACTACTG CCAGCAGTACTACAACCTGCCCTGGACCTTCGGCCAGGGCACC AAGGTGAAATCAAGCGTACGGTGGCCGCTCCAGCGTGTTC TCTCCCCCAAGCGACGAGCAGCTGAAGAGCGGCACCGCCAG CGTGGTGTGTCTGCTGAACAATTCTACCCCAGGGAGGCCAAG GTGCAGTGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCC AGGAGAGCGTCACCGAGCAGGACAGCAAGGACTCCACCTACA GCCTGAGCAGCACCCCTGACCCTGAGCAAGGCCGACTACGAGAA GCACAAGGTGTACGCCTGTGAGGTGACCCACCAGGGCCTGTCC AGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
BAP050-Clone J HC		
SEQ ID NO: 701 (Kabat)	HCDR1	NYGMN
SEQ ID NO: 702 (Kabat)	HCDR2	WINTDTGEPTYADDFKG
SEQ ID NO: 703 (Kabat)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 704 (Chothia)	HCDR1	GFTLTNY
SEQ ID NO: 705 (Chothia)	HCDR2	NTDTGE
SEQ ID NO: 703 (Chothia)	HCDR3	NPPYYYGTNNAEAMDY
SEQ ID NO: 724	VH	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQAPGQ GLEWMGWINTDTGEPTYADDFKGRFVFLDTSVSTAYLQISSLKA EDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
SEQ ID NO: 725	DNA VH	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCG GCGCTAGTGTGAAAGTCAGCTGTAAAGCTAGTGGCTTCACCCT GACTAACTACGGGATGAACTGGGTCCGCCAGGCCCCAGGTCAA GGCCTCGAGTGGATGGGCTGGATTAACACCGACACCGGCGAGC CTACCTACGCCGACGACTTTAAGGGCAGATTTCGTGTTTAGCCTG GACACTAGTGTGTCTACCGCCTACCTGCAGATCTCTAGCCTGAA GGCCGAGGACACCGCCGTCTACTACTGCGCTAGAAACCCCCC TACTACTACGGCACTAACAACGCCGAGGCTATGGACTACTGGG GTCAAGGCACTACCGTGACCGTGTCTAGC
SEQ ID NO: 726	DNA VH	CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCTG GCGCCTCCGTGAAGGTGTCCTGCAAGGCCTCTGGCTTCACCCTG ACCAACTACGGCATGAACTGGGTGCGACAGGCCCCCTGGACAGG GCCTGGAATGGATGGGCTGGATCAACACCGACACCGGCGAGCC TACCTACGCCGACGACTTCAAGGGCAGATTTCGTGTTCTCCCTGG ACACCTCCGTGTCCACCGCCTACCTGCAGATCTCCAGCCTGAAG GCCGAGGATACCGCCGTGTACTACTGCGCCCGGAACCCCCCTT ACTACTACGGCACCAACAACGCCGAGGCCATGGACTATTGGGG CCAGGGCACCACCGTGACCGTGTCTCT
SEQ ID NO: 727	Heavy	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQAPGQ

	chain	<p>GLEWMGWINTDTGEPTYADDFKGRFVFLDTSVSTAYLQISSLKA EDTAVYYCARNPPYYYGTNNAEAMDYWGQTTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVTVPSSSLGTKYTCNVDHKPSNTKVDKRV ESKYGPPCPPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPS QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLS LG</p>
SEQ ID NO: 728	DNA heavy chain	<p>CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCG GCGCTAGTGTGAAAGTCAGCTGTAAAGCTAGTGGCTCACCCCT GACTAACTACGGGATGAACTGGGTCCGCCAGGCCCCAGGTCAA GGCCTCGAGTGGATGGGCTGGATTAACACCGACACCGGCGAGC CTACCTACGCCGACGACTTTAAGGGCAGATTCTGTGTTTAGCCTG GACACTAGTGTGTCTACCGCTACCTGCAGATCTCTAGCCTGAA GGCCGAGGACACCGCCGTCTACTACTGCGCTAGAAACCCCCCT TACTACTACGGCACTAACAACGCCGAGGCTATGGACTACTGGG GTCAAGGCACTACCGTGACCGTGTCTAGCGCTAGCACTAAGGG CCCGTCCGTGTTCCCCCTGGCACCTTGTAGCCGGAGCACTAGCG AATCCACCGCTGCCCTCGGCTGCCTGGTCAAGGATTACTTCCCG GAGCCCGTGACCGTGTCTGGAACAGCGGAGCCCTGACCTCCG GAGTGCACACCTTCCCCGCTGTGCTGCAGAGCTCCGGGCTGTAC TCGCTGTGCTCGGTGGTCACGGTGCCTTCATCTAGCCTGGGTAC CAAGACCTACACTTGCAACGTGGACCACAAGCCTTCCAACACT AAGGTGGACAAGCGCGTCAATCGAAGTACGGCCCACCGTGCC CGCCTTGTCCCGCGCCGGAGTTCCTCGGCGGTCCCTCGGTCTTT CTGTTCCCACCGAAGCCCAAGGACACTTTGATGATTTCCCGCAC CCCTGAAGTGACATGCGTGGTCTGTGGACGTGCACAGGAAGAT CCGGAGGTGCAGTTCAATTGGTACGTGGATGGCGTCGAGGTGC ACAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAACTCCAC TTACCGCGTCTGTCCGTGCTGACGGTGTGTCATCAGGACTGGC TGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGGAC TTCCTAGCTCAATCGAAAAGACCATCTCGAAAGCCAAGGGACA GCCCCGGGAACCCCAAGTGATACCCTGCCACCGAGCCAGGAA GAAATGACTAAGAACCAAGTCTCATTGACTTGCCTTGTGAAGG GCTTCTACCCATCGGATATCGCCGTGGAATGGGAGTCCAACGG CCAGCCGAAAACAACACTACAAGACCACCCCTCCGGTGTGAGC TCAGACGGATCCTTCTCCTCTACTCGCGGCTGACCGTGGATAA GAGCAGATGGCAGGAGGGAAATGTGTTTCAGCTGTTCTGTGATG CATGAAGCCCTGCACAACCACTACACTCAGAAGTCCCTGTCCCT CTCCCTGGGA</p>
SEQ ID NO: 729	DNA heavy chain	<p>CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCTG GCGCCTCCGTGAAGGTGTCTGCAAGGCCTCTGGCTCACCCCTG ACCAACTACGGCATGAACTGGGTGCGACAGGCCCCCTGGACAGG GCCTGGAATGGATGGGCTGGATCAACACCGACACCGGCGAGCC TACCTACGCCGACGACTTCAAGGGCAGATTCTGTGTTCTCCCTGG ACACCTCCGTGTCCACCGCCTACCTGCAGATCTCCAGCCTGAAG GCCGAGGATACCGCCGTGTAATACTGCGCCCGGAACCCCTT ACTACTACGGCACCAACAACGCCGAGGCCATGGACTATTGGGG CCAGGGCACCACCGTGACCGTGTCTCTGCTTCTACCAAGGGGC CCAGCGTGTCCCCCTGGCCCCCTGCTCCAGAAGCACCAGCGA</p>

		GAGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCC GAGCCCCGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTA CAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGC ACCAAGACCTACACCTGTAACGTGGACCACAAGCCCAGCAACA CCAAGGTGGACAAGAGGGTGGAGAGCAAGTACGGCCCACCCT GCCCCCCTGCCAGCCCCGAGTTCCTGGGCGGACCCAGCGT GTTCTGTTCCCCCCAAGCCAAGGACACCCTGATGATCAGCA GAACCCCCGAGGTGACCTGTGTGGTGGTGGACGTGTCCCAGGA GGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAG GTGCACAACGCCAAGACCAAGCCCAGAGAGGAGCAGTTTAAACA GCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGCACCAGGA CTGGCTGAACGGCAAAGAGTACAAGTGTAAGGTCTCCAACAAG GGCCTGCCAAGCAGCATCGAAAAGACCATCAGCAAGGCCAAG GGCCAGCCTAGAGAGCCCCAGGTCTACACCCTGCCACCCAGCC AAGAGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCTGGT GAAGGGCTTCTACCCAAGCGACATCGCCGTGGAGTGGGAGAGC AACGGCCAGCCGAGAACAATAAGACCACCCCCCAGTGC TGGACAGCGACGGCAGCTTCTTCTGTACAGCAGGCTGACCGT GGACAAGTCCAGATGGCAGGAGGGCAACGTCTTTAGCTGCTCC GTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGCC TGAGCCTGTCCCTGGGC
BAP050-Clone J LC		
SEQ ID NO: 710 (Kabat)	LCDR1	SSSQDISNYLN
SEQ ID NO: 711 (Kabat)	LCDR2	YTSTLHL
SEQ ID NO: 712 (Kabat)	LCDR3	QYYNLPWT
SEQ ID NO: 713 (Chothia)	LCDR1	SQDISNY
SEQ ID NO: 714 (Chothia)	LCDR2	YTS
SEQ ID NO: 715 (Chothia)	LCDR3	YYNLPW
SEQ ID NO: 730	VL	DIQMTQSPSSLSASVGDRTITCSSSQDISNYLNWYQQKPKAPKL LIYYTSTLHLGIPPRFSGSYGTDFTLTINNIESEDAAYYFCQYYN LPWTFGQGTKVEIK
SEQ ID NO: 731	DNA VL	GATATTCAGATGACTCAGTCACCTAGTAGCCTGAGCGTAGTGT GGGCGATAGAGTGACTATCACCTGTAGCTCTAGTCAGGATATCT CTAACTACCTGAACTGGTATCAGCAGAAGCCCGGTAAGCCCC TAAGCTGCTGATCTACTACACTAGCACCTGCACCTGGGAATCC CCCCTAGGTTTAGCGGTAGCGGCTACGGCACCGACTTCACCCTG ACTATTAACAATATCGAGTCAGAGGACGCCCTACTACTTCTG TCAGCAGTACTATAACCTGCCCTGGACCTTCGGTCAAGGCACTA AGGTCGAGATTAAG
SEQ ID NO: 732	DNA VL	GACATCCAGATGACCCAGTCCCCCTCCAGCCTGTCTGCTTCCGT GGGCGACAGAGTGACCATCACCTGTTCCCTCCAGCCAGGACATC TCCAACCTACCTGAACTGGTATCAGCAGAAGCCCGGCAAGGCC CCAAGCTGCTGATCTACTACACCTCCACCCTGCACCTGGGCATC CCCCCTAGATTCTCCGGCTCTGGCTACGGCACCGACTTCACCCT GACCATCAACAACATCGAGTCCGAGGACGCCCTACTACTTC TGCCAGCAGTACTACAACCTGCCCTGGACCTTCGGCCAGGGCA CCAAGGTGGAAATCAAG

SEQ ID NO: 733	Light chain	DIQMTQSPSSLSASVGDRTITCSSSQDISNYLNWYQQKPGKAPKL LIYYTSTLHLGIPPRFSGSYGTDFTLTINNIESEDAAYYFCQQYYN LPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLTKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 734	DNA light chain	GATATTCAGATGACTCAGTCACCTAGTAGCCTGAGCGCTAGTGT GGGCGATAGAGTGACTATCACCTGTAGCTCTAGTCAGGATATCT CTAACTACCTGAACTGGTATCAGCAGAAGCCCGGTAAGCCCC TAAGCTGCTGATCTACTACACTAGCACCTGCACCTGGGAATCC CCCCTAGGTTTAGCGGTAGCGGCTACGGCACCGACTTCACCCCTG ACTATTAACAATATCGAGTCAGAGGACGCCCTACTACTTCTG TCAGCAGTACTATAACCTGCCCTGGACCTTCGGTCAAGGCACTA AGGTCGAGATTAAGCGTACGGTGGCCGCTCCAGCGTGTTCAT CTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGC GTGGTGTGCCTGCTGAACAACCTTACCCCCGGGAGGCCAAGG TGCAGTGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCA GGAGAGCGTCACCGAGCAGGACAGCAAGGACTCCACCTACAGC CTGAGCAGCACCCCTGACCCTGAGCAAGGCCGACTACGAGAAGC ATAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAG CCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
SEQ ID NO: 735	DNA light chain	GACATCCAGATGACCCAGTCCCCCTCCAGCCTGTCTGCTTCCGT GGGCGACAGAGTGACCATCACCTGTTCTCCAGCCAGGACATC TCCAACTACCTGAACTGGTATCAGCAGAAGCCCGGCAAGGCC CCAAGCTGCTGATCTACTACACCTCCACCCTGCACCTGGGCATC CCCCCTAGATTCTCCGGCTCTGGCTACGGCACCGACTTCACCT GACCATCAACAACATCGAGTCCGAGGACGCCCTACTACTTC TGCCAGCAGTACTACAACCTGCCCTGGACCTTCGGCCAGGGCA CCAAGGTGGAATCAAGCGTACGGTGGCCGCTCCAGCGTGTT CATTTCCCCCAAGCGACGAGCAGCTGAAGAGCGGCACCGCC AGCGTGGTGTGTCTGCTGAACAACCTTACCCAGGGAGGCCA AGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAACA GCCAGGAGAGCGTCACCGAGCAGGACAGCAAGGACTCCACCTA CAGCCTGAGCAGCACCCCTGACCCTGAGCAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGTGAGGTGACCCACCAGGGCCTGT CCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
BAP050-Clone 1 HC		
SEQ ID NO: 736 (Kabat)	HCDR1	AATTACGGGATGAAC
SEQ ID NO: 737 (Kabat)	HCDR1	AACTACGGCATGAAC
SEQ ID NO: 738 (Kabat)	HCDR2	TGGATTAACACCGACACCGGGGAGCCTACCTACGCGGACGATT TCAAGGGA
SEQ ID NO: 739 (Kabat)	HCDR2	TGGATCAACACCGACACCGGCGAGCCTACCTACGCCGACGACT TCAAGGGC
SEQ ID NO: 740 (Kabat)	HCDR3	AACCCGCCCTACTACTACGGAACCAACAACGCCGAAGCCATGG ACTAC
SEQ ID NO: 741 (Kabat)	HCDR3	AACCCCCCTTACTACTACGGCACCAACAACGCCGAGGCCATGG ACTAT
SEQ ID NO: 742 (Chothia)	HCDR1	GGATTCACCCTACCAATTAC
SEQ ID NO: 743 (Chothia)	HCDR1	GGCTTCACCCTGACCAACTAC
SEQ ID NO: 744	HCDR2	AACACCGACACCGGGGAG

(Chothia)		
SEQ ID NO: 745 (Chothia)	HCDR2	AACACCGACACCGGCGAG
SEQ ID NO: 740 (Chothia)	HCDR3	AACCCGCCCTACTACTACGGAAACCAACAACGCCGAAGCCATGG ACTAC
SEQ ID NO: 741 (Chothia)	HCDR3	AACCCCCCTTACTACTACGGCACCAACAACGCCGAGGCCATGG ACTAT
BAP050-Clone I LC		
SEQ ID NO: 746 (Kabat)	LCDR1	AGCTCTAGTCAGGATATCTCTAACTACCTGAAC
SEQ ID NO: 747 (Kabat)	LCDR1	TCCTCCAGCCAGGACATCTCCAACCTACCTGAAC
SEQ ID NO: 748 (Kabat)	LCDR2	TACACTAGCACCTGCACCTG
SEQ ID NO: 749 (Kabat)	LCDR2	TACACCTCCACCCTGCACCTG
SEQ ID NO: 750 (Kabat)	LCDR3	CAGCAGTACTATAACCTGCCCTGGACC
SEQ ID NO: 751 (Kabat)	LCDR3	CAGCAGTACTACAACCTGCCCTGGACC
SEQ ID NO: 752 (Chothia)	LCDR1	AGTCAGGATATCTCTAACTAC
SEQ ID NO: 753 (Chothia)	LCDR1	AGCCAGGACATCTCCAACCTAC
SEQ ID NO: 754 (Chothia)	LCDR2	TACACTAGC
SEQ ID NO: 755 (Chothia)	LCDR2	TACACCTCC
SEQ ID NO: 756 (Chothia)	LCDR3	TACTATAACCTGCCCTGG
SEQ ID NO: 757 (Chothia)	LCDR3	TACTACAACCTGCCCTGG
BAP050-Clone J HC		
SEQ ID NO: 758 (Kabat)	HCDR1	AACTACGGGATGAAC
SEQ ID NO: 737 (Kabat)	HCDR1	AACTACGGCATGAAC
SEQ ID NO: 759 (Kabat)	HCDR2	TGGATTAACACCGACACCGGCGAGCCTACCTACGCCGACGACT TTAAGGGC
SEQ ID NO: 739 (Kabat)	HCDR2	TGGATCAACACCGACACCGGCGAGCCTACCTACGCCGACGACT TCAAGGGC
SEQ ID NO: 760 (Kabat)	HCDR3	AACCCCCCTTACTACTACGGCACTAACAACGCCGAGGCTATGG ACTAC
SEQ ID NO: 741 (Kabat)	HCDR3	AACCCCCCTTACTACTACGGCACCAACAACGCCGAGGCCATGG ACTAT
SEQ ID NO: 761 (Chothia)	HCDR1	GGCTTCACCCTGACTAACTAC
SEQ ID NO: 743 (Chothia)	HCDR1	GGCTTCACCCTGACCAACTAC
SEQ ID NO: 744 (Chothia)	HCDR2	AACACCGACACCGGGGAG
SEQ ID NO: 745 (Chothia)	HCDR2	AACACCGACACCGGCGAG
SEQ ID NO: 760 (Chothia)	HCDR3	AACCCCCCTTACTACTACGGCACTAACAACGCCGAGGCTATGG ACTAC
SEQ ID NO: 741 (Chothia)	HCDR3	AACCCCCCTTACTACTACGGCACCAACAACGCCGAGGCCATGG ACTAT

BAP050-Clone J LC		
SEQ ID NO: 746 (Kabat)	LCDR1	AGCTCTAGTCAGGATATCTCTAACTACCTGAAC
SEQ ID NO: 747 (Kabat)	LCDR1	TCCTCCAGCCAGGACATCTCCAACCTACCTGAAC
SEQ ID NO: 748 (Kabat)	LCDR2	TACTACTAGCACCTGCACCTG
SEQ ID NO: 749 (Kabat)	LCDR2	TACACCTCCACCCTGCACCTG
SEQ ID NO: 750 (Kabat)	LCDR3	CAGCAGTACTATAACCTGCCCTGGACC
SEQ ID NO: 751 (Kabat)	LCDR3	CAGCAGTACTACAACCTGCCCTGGACC
SEQ ID NO: 752 (Chothia)	LCDR1	AGTCAGGATATCTCTAACTAC
SEQ ID NO: 753 (Chothia)	LCDR1	AGCCAGGACATCTCCAACCTAC
SEQ ID NO: 754 (Chothia)	LCDR2	TACTACTAGC
SEQ ID NO: 755 (Chothia)	LCDR2	TACACCTCC
SEQ ID NO: 756 (Chothia)	LCDR3	TACTATAACCTGCCCTGG
SEQ ID NO: 757 (Chothia)	LCDR3	TACTACAACCTGCCCTGG

In one embodiment, the anti-LAG-3 antibody molecule includes at least one or two heavy chain variable domain (optionally including a constant region), at least one or two light chain variable domain (optionally including a constant region), or both, comprising the amino acid sequence of any of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (e.g., BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; or as described in Table 1 of US 2015/0259420, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In yet another embodiment, the anti- LAG-3 antibody molecule includes at least one, two, or three complementarity determining regions (CDRs) from a heavy chain variable region and/or a light chain variable region of an antibody described herein, e.g., an antibody chosen from any of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17,

BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.*, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J; or as described in Table 1 of US 2015/0259420, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In yet another embodiment, the anti- LAG-3 antibody molecule includes at least one, two, or three CDRs (or collectively all of the CDRs) from a heavy chain variable region comprising an amino acid sequence shown in Table 1 of US 2015/0259420, or encoded by a nucleotide sequence shown in Table 1. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid substitutions or deletions, relative to the amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1.

In yet another embodiment, the anti-LAG-3 antibody molecule includes at least one, two, or three CDRs (or collectively all of the CDRs) from a light chain variable region comprising an amino acid sequence shown in Table 1 of US 2015/0259420, or encoded by a nucleotide sequence shown in Table 1. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid substitutions or deletions, relative to the amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1. In certain embodiments, the anti-PD-L1 antibody molecule includes a substitution in a light chain CDR, *e.g.*, one or more substitutions in a CDR1, CDR2 and/or CDR3 of the light chain.

In another embodiment, the anti- LAG-3 antibody molecule includes at least one, two, three, four, five or six CDRs (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1 of US 2015/0259420. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid substitutions or deletions, relative to the amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1.

Other Exemplary Anti-LAG-3 Antibody Molecules

In one embodiment, the anti-LAG-3 antibody molecule is BMS-986016 (Bristol-Myers Squibb), also known as BMS986016. BMS-986016 and other anti-LAG-3 antibodies are disclosed in WO 2015/116539 and US 9,505,839, incorporated by reference in their entirety. In one embodiment, the anti-LAG-3 antibody molecule comprises one or more of the CDR sequences (or collectively all

of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of BMS-986016, *e.g.*, as disclosed in Table 6.

In one embodiment, the anti-LAG-3 antibody molecule is TSR-033 (Tesaro). In one embodiment, the anti-LAG-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of TSR-033.

In one embodiment, the anti-LAG-3 antibody molecule is IMP731 or GSK2831781 (GSK and Prima BioMed). IMP731 and other anti-LAG-3 antibodies are disclosed in WO 2008/132601 and US 9,244,059, incorporated by reference in their entirety. In one embodiment, the anti-LAG-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of IMP731, *e.g.*, as disclosed in Table 6. In one embodiment, the anti-LAG-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of GSK2831781.

In one embodiment, the anti-LAG-3 antibody molecule is IMP761 (Prima BioMed). In one embodiment, the anti-LAG-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of IMP761.

Further known anti-LAG-3 antibodies include those described, *e.g.*, in WO 2008/132601, WO 2010/019570, WO 2014/140180, WO 2015/116539, WO 2015/200119, WO 2016/028672, US 9,244,059, US 9,505,839, incorporated by reference in their entirety.

In one embodiment, the anti-LAG-3 antibody is an antibody that competes for binding with, and/or binds to the same epitope on LAG-3 as, one of the anti-LAG-3 antibodies described herein.

In one embodiment, the anti-LAG-3 inhibitor is a soluble LAG-3 protein, *e.g.*, IMP321 (Prima BioMed), *e.g.*, as disclosed in WO 2009/044273, incorporated by reference in its entirety.

Table 6. Amino acid sequences of other exemplary anti-LAG-3 antibody molecules

BMS-986016		
SEQ ID NO: 762	Heavy chain	QVQLQQWGAGLLKPSETLSLTCAVYGGFSFDYYWNWIRQPPGKGLE WIGEINHRGSTNSNPSLKSRTLSDTSKNQFSLKLRVTAADTAVYYC AFGYSDYEYNWFDPWGQGLTVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKT ISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHE ALHNHYTQKSLSLGK
SEQ ID NO: 763	Light chain	EIVLTQSPATLSLSPGERATLSCRASQSISSYLAWYQQKPGQAPRLLIYD

		ASN RATGIPARFSGSGSGTDFLTISSELPEDFAVYYCQQRSNWPLTFG QGTNLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
IMP731		
SEQ ID NO: 764	Heavy chain	QVQLKESGPGLVAPSQLSITCTVSGFSLTAYGVNWVRQPPGKGLEWL GMIWDDGSTDYNSALKSRLSISKDNSKQVFLKMNSLQTTDDTARYYC AREGDVAFDYWGQTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKEPKSCDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEA LHNHYTQKLSLSLSPGK
SEQ ID NO: 765	Light chain	DIVMTQSPSSLAIVSFGQKVTMSCKSSQSLNNGSNQKNYLAWYQQKPG QSPKLLVYFASTRDSGVPDRFIGSGSGTDFLTISVVAEDLADYFCLQ HFGTPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC

PD-1 Inhibitors

In certain embodiments, the anti-LAG-3 antibody molecule described herein is administered in combination with a PD-1 inhibitor. In some embodiments, the PD-1 inhibitor is chosen from PDR001 or Spartalizumab (Novartis), Nivolumab (Bristol-Myers Squibb), Pembrolizumab (Merck & Co), Pidilizumab (CureTech), MEDI0680 (Medimmune), REGN2810 (Regeneron), TSR-042 (Tesaro), PF-06801591 (Pfizer), BGB-A317 (Beigene), BGB-108 (Beigene), INCSHR1210 (Incyte), or AMP-224 (Amplimmune).

10 *Exemplary PD-1 Inhibitors*

In one embodiment, the PD-1 inhibitor is an anti-PD-1 antibody molecule. In one embodiment, the PD-1 inhibitor is an anti-PD-1 antibody molecule as described in US 2015/0210769, published on July 30, 2015, entitled “Antibody Molecules to PD-1 and Uses Thereof,” incorporated by reference in its entirety.

15 In one embodiment, the anti-PD-1 antibody molecule comprises at least one, two, three, four, five or six complementarity determining regions (CDRs) (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 1 (e.g., from the heavy and light chain variable region sequences of BAP049-Clone-E or BAP049-Clone-B disclosed in Table 1), or encoded by a nucleotide sequence shown in Table 1. In some embodiments, 20 the CDRs are according to the Kabat definition (e.g., as set out in Table 1). In some embodiments, the CDRs are according to the Chothia definition (e.g., as set out in Table 1). In some embodiments, the CDRs are according to the combined CDR definitions of both Kabat and Chothia (e.g., as set out

in Table 1). In one embodiment, the combination of Kabat and Chothia CDR of VH CDR1 comprises the amino acid sequence GYTFTTYWMH (SEQ ID NO: 541). In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid substitutions (*e.g.*, conservative amino acid substitutions) or deletions, relative to an amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1.

In one embodiment, the anti-PD-1 antibody molecule comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 501, a VHCDR2 amino acid sequence of SEQ ID NO: 502, and a VHCDR3 amino acid sequence of SEQ ID NO: 503; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 510, a VLCDR2 amino acid sequence of SEQ ID NO: 511, and a VLCDR3 amino acid sequence of SEQ ID NO: 512, each disclosed in Table 1.

In one embodiment, the antibody molecule comprises a VH comprising a VHCDR1 encoded by the nucleotide sequence of SEQ ID NO: 524, a VHCDR2 encoded by the nucleotide sequence of SEQ ID NO: 525, and a VHCDR3 encoded by the nucleotide sequence of SEQ ID NO: 526; and a VL comprising a VLCDR1 encoded by the nucleotide sequence of SEQ ID NO: 529, a VLCDR2 encoded by the nucleotide sequence of SEQ ID NO: 530, and a VLCDR3 encoded by the nucleotide sequence of SEQ ID NO: 531, each disclosed in Table 1.

In one embodiment, the anti-PD-1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 506, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 506. In one embodiment, the anti-PD-1 antibody molecule comprises a VL comprising the amino acid sequence of SEQ ID NO: 520, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 520. In one embodiment, the anti-PD-1 antibody molecule comprises a VL comprising the amino acid sequence of SEQ ID NO: 516, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 516. In one embodiment, the anti-PD-1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 506 and a VL comprising the amino acid sequence of SEQ ID NO: 520. In one embodiment, the anti-PD-1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 506 and a VL comprising the amino acid sequence of SEQ ID NO: 516.

In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 507, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 507. In one embodiment, the antibody molecule comprises a VL encoded by the nucleotide sequence of SEQ ID NO: 521 or 517, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 521 or 517. In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 507 and a VL encoded by the nucleotide sequence of SEQ ID NO: 521 or 517.

In one embodiment, the anti-PD-1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 508, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 508. In one embodiment, the anti-PD-1 antibody molecule comprises a light chain comprising the amino acid sequence of SEQ ID NO: 522, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 522. In one embodiment, the anti-PD-1 antibody molecule comprises a light chain comprising the amino acid sequence of SEQ ID NO: 518, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 518. In one embodiment, the anti-PD-1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 508 and a light chain comprising the amino acid sequence of SEQ ID NO: 522. In one embodiment, the anti-PD-1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 508 and a light chain comprising the amino acid sequence of SEQ ID NO: 518.

In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 509, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 509. In one embodiment, the antibody molecule comprises a light chain encoded by the nucleotide sequence of SEQ ID NO: 523 or 519, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 523 or 519. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 509 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 523 or 519.

The antibody molecules described herein can be made by vectors, host cells, and methods described in US 2015/0210769, incorporated by reference in its entirety.

Table 1. Amino acid and nucleotide sequences of exemplary anti-PD-1 antibody molecules

BAP049-Clone-B HC		
SEQ ID NO: 501 (Kabat)	HCDR1	TYWMH
SEQ ID NO: 502 (Kabat)	HCDR2	NIYPGTGGSNFDEKFKN
SEQ ID NO: 503 (Kabat)	HCDR3	WTTGTGAY
SEQ ID NO: 504 (Chothia)	HCDR1	GYTFTTY
SEQ ID NO: 505 (Chothia)	HCDR2	YPGTGG
SEQ ID NO: 503 (Chothia)	HCDR3	WTTGTGAY
SEQ ID NO: 506	VH	EVQLVQSGAEVKKPGESLRISCKGSGYTFTTYWMHWVRQATGQG LEWMGNIPGTGGSNFDEKFKNRVTITADKSTSTAYMELSSLRSE DTAVYYCTRWTTGTGAYWGQGTITVTVSS
SEQ ID NO: 507	DNA VH	GAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAGCCCG GCGAGTCACTGAGAATTAGCTGTAAAGGTTCAAGCTACACCTT CACTACCTACTGGATGCACTGGGTCCGCCAGGCTACCGGTCAA GGCCTCGAGTGGATGGGTAATATCTACCCGGCACC GGCGGCT CTAACTTCGACGAGAAGTTTAAGAATAGAGTGACTATCACCGC

		CGATAAGTCTACTAGCACCCGCTATATGGAACTGTCTAGCCTGA GATCAGAGGACACCCGCGTCTACTACTGCACTAGGTGGACTAC CGGCACAGGCGCCTACTGGGGTCAAGGCACTACCGTGACCGTG TCTAGC
SEQ ID NO: 508	Heavy chain	EVQLVQSGAEVKKPGESLRISCKGSGYFTFTYWMHWVRQATGQG LEWMGNIYPGTGGSNFDEKFKNRVTITADKSTSTAYMELSSLRSE DTAVYYCTRWTTGTGAYWGQTTVTVSSASTKGPSVFLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YLSVVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPCCPP CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRL TVDKSRWQEGNVFSCYSVMHEALHNHYTQKSLSLSLG
SEQ ID NO: 509	DNA heavy chain	GAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAGCCCC GCGAGTCACTGAGAATTAGCTGTAAAGGTTCAAGCTACACCTT CACTACCTACTGGATGCACTGGGTCCGCCAGGCTACCGGTCAA GGCCTCGAGTGGATGGGTAATATCTACCCCGGCACCGGCGGCT CTAACTTCGACGAGAAGTTTAAGAATAGAGTGACTATCACCGC CGATAAGTCTACTAGCACCCGCTATATGGAACTGTCTAGCCTGA GATCAGAGGACACCCGCGTCTACTACTGCACTAGGTGGACTAC CGGCACAGGCGCCTACTGGGGTCAAGGCACTACCGTGACCGTG TCTAGCGCTAGCACTAAGGGCCCCGTCCGTGTTCCCCCTGGCACC TTGTAGCCGGAGCACTAGCGAATCCACCGCTGCCCTCGGCTGCC TGGTCAAGGATTACTTCCCGGAGCCCGTGACCGTGTCTGGAAC AGCGGAGCCCTGACCTCCGGAGTGCACACCTTCCCCGCTGTGCT GCAGAGCTCCGGGCTGTACTCGCTGTCGTCCGTGGTACGGTGC CTTCATCTAGCCTGGGTACCAAGACCTACACTTGCAACGTGGAC CACAAGCCTTCCAACACTAAGGTGGACAAGCGCGTCAATCGA AGTACGGCCCACCGTGCCCGCCTTGTCCCGCGCCGGAGTTCCTC GGCGGTCCCTCGGTCTTTCTGTTCACCGAAGCCCAAGGACAC TTTGATGATTTCCCGCACCCCTGAAGTGACATGCGTGGTTCGTGG ACGTGTCACAGGAAGATCCGGAGGTGCAGTTCAATTGGTACGT GGATGGCGTCGAGGTGCACAACGCCAAAACCAAGCCGAGGGA GGAGCAGTTCAACTCCACTTACCGCGTCGTGTCCGTGCTGACGG TGCTGCATCAGGACTGGCTGAACGGGAAGGAGTACAAGTGCAA AGTGTCCAACAAGGGACTTCTAGCTCAATCGAAAAGACCATC TCGAAAGCCAAGGGACAGCCCCGGGAACCCCAAGTGTATACCC TGCCACCGAGCCAGGAAGAAATGACTAAGAACCAAGTCTCATT GACTTGCCCTTGTGAAGGGCTTCTACCCATCGGATATCGCCGTGG AATGGGAGTCCAACGGCCAGCCGGAACCAACTACAAGACCA CCCCCTCCGGTGTGGACTCAGACGGATCCTTCTTCCCTACTCG CGGCTGACCGTGGATAAGAGCAGATGGCAGGAGGGAAATGTGT TCAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACTACACT CAGAAGTCCCTGTCCCTCTCCCTGGGA
BAP049-Clone-B LC		
SEQ ID NO: 510 (Kabat)	LCDR1	KSSQSLDLSGNQKNFLT
SEQ ID NO: 511 (Kabat)	LCDR2	WASTRES
SEQ ID NO: 512 (Kabat)	LCDR3	QNDYSYPYT
SEQ ID NO: 513 (Chothia)	LCDR1	SQSLDLSGNQKNF

SEQ ID NO: 514 (Chothia)	LCDR2	WAS
SEQ ID NO: 515 (Chothia)	LCDR3	DYSYPY
SEQ ID NO: 516	VL	EIVLTQSPATLSLSPGERATLSCKSSQSLDSDGNQKNFLTWYQQKPK GKAPKLLIYWASTRESGVPSRFSGSGSGTDFTFTISSLPEDIATYY CQNDYSYPYTFGQGTKVEIK
SEQ ID NO: 517	DNA VL	GAGATCGTCTGACTCAGTCACCCGCTACCCTGAGCCTGAGCCC TGGCGAGCGGGCTACACTGAGCTGTAAATCTAGTCAGTCACTG CTGGATAGCGGTAATCAGAAGAACTTCCTGACCTGGTATCAGC AGAAGCCCGGTAAAGCCCTAAGCTGCTGATCTACTGGGCCTC TACTAGAGAATCAGGCGTGCCCTCTAGGTTTAGCGGTAGCGGT AGTGGCACCGACTTCACCTTACTATCTCTAGCCTGCAGCCCGA GGATATCGCTACCTACTACTGTCAGAACGACTATAGCTACCCCT ACACCTTCGGTCAAGGCACTAAGGTCGAGATTAAG
SEQ ID NO: 518	Light chain	EIVLTQSPATLSLSPGERATLSCKSSQSLDSDGNQKNFLTWYQQKPK GKAPKLLIYWASTRESGVPSRFSGSGSGTDFTFTISSLPEDIATYY CQNDYSYPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 519	DNA light chain	GAGATCGTCTGACTCAGTCACCCGCTACCCTGAGCCTGAGCCC TGGCGAGCGGGCTACACTGAGCTGTAAATCTAGTCAGTCACTG CTGGATAGCGGTAATCAGAAGAACTTCCTGACCTGGTATCAGC AGAAGCCCGGTAAAGCCCTAAGCTGCTGATCTACTGGGCCTC TACTAGAGAATCAGGCGTGCCCTCTAGGTTTAGCGGTAGCGGT AGTGGCACCGACTTCACCTTACTATCTCTAGCCTGCAGCCCGA GGATATCGCTACCTACTACTGTCAGAACGACTATAGCTACCCCT ACACCTTCGGTCAAGGCACTAAGGTCGAGATTAAGCGTACGGT GGCCGCTCCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCAGC TGAAGAGCGGCACCGCCAGCGTGGTGTGCTGCTGAACAATT CTACCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCC CTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGAC AGCAAGGACTCCACCTACAGCCTGAGCAGCACCCCTGACCCTGA GCAAGGCCGACTACGAGAAGCATAAGGTGTACGCCTGCGAGGT GACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAAC AGGGGCGAGTGC
BAP049-Clone-E HC		
SEQ ID NO: 501 (Kabat)	HCDR1	TYWMH
SEQ ID NO: 502 (Kabat)	HCDR2	NIYPGTGGSNFDEKFKN
SEQ ID NO: 503 (Kabat)	HCDR3	WTTGTGAY
SEQ ID NO: 504 (Chothia)	HCDR1	GYTFTTY
SEQ ID NO: 505 (Chothia)	HCDR2	YPGTGG
SEQ ID NO: 503 (Chothia)	HCDR3	WTTGTGAY
SEQ ID NO: 506	VH	EVQLVQSGAEVKKPAGESLRISCKGSGYFTFTTYWMHWVRQATGQG LEWMGNIPYPTGGSNFDEKFKNRVTITADKSTSTAYMELSSLRSE DTAVYYCTRWTTGTGAYWGQGTITVTVSS
SEQ ID NO: 507	DNA VH	GAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAGCCCG GCGAGTCACTGAGAATTAGCTGTAAAGGTTTAGGCTACACCTT

		CACTACCTACTGGATGCACTGGGTCCGCCAGGCTACCGGTCAA GGCCTCGAGTGGATGGGTAATATCTACCCCGGCACCGGCGGCT CTAACTTCGACGAGAAGTTTAAGAATAGAGTGACTATCACCGC CGATAAGTCTACTAGCACCGCCTATATGGAAGTGTCTAGCCTGA GATCAGAGGACACCGCCGTCTACTACTGCACTAGGTGGACTAC CGGCACAGGCGCCTACTGGGGTCAAGGCACTACCGTGACCGTG TCTAGC
SEQ ID NO: 508	Heavy chain	EVQLVQSGAEVKKPGESLRISCKGSGYFTFTYWMHWVRQATGQG LEWMGNIYPGTGGSNFDEKFKNRVTITADKSTSTAYMELSSLRSE DTAVYYCTRWTTGTGAYWGQTTTVTVSSASTKGPSVFLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YLSVVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPPCPP CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKISKAKGQPREPQVYTLPPSQEEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRL TVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLG
SEQ ID NO: 509	DNA heavy chain	GAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAGCCCG GCGAGTCACTGAGAATTAGCTGTAAAGGTTCCAGGCTACACCTT CACTACCTACTGGATGCACTGGGTCCGCCAGGCTACCGGTCAA GGCCTCGAGTGGATGGGTAATATCTACCCCGGCACCGGCGGCT CTAACTTCGACGAGAAGTTTAAGAATAGAGTGACTATCACCGC CGATAAGTCTACTAGCACCGCCTATATGGAAGTGTCTAGCCTGA GATCAGAGGACACCGCCGTCTACTACTGCACTAGGTGGACTAC CGGCACAGGCGCCTACTGGGGTCAAGGCACTACCGTGACCGTG TCTAGCGCTAGCACTAAGGGCCCCGTCCGTGTTCCCCCTGGCACC TTGTAGCCGGAGCACTAGCGAATCCACCGCTGCCCTCGGCTGCC TGGTCAAGGATTACTTCCCGGAGCCCGTGACCGGTGCTCTGGAAC AGCGGAGCCCTGACCTCCGGAGTGCACACCTTCCCCGCTGTGCT GCAGAGCTCCGGGCTGTACTCGCTGTCGTCGGTGGTACGGTGC CTTCATCTAGCCTGGGTACCAAGACCTACACTTGCAACGTGGAC CACAAGCCTTCCAACACTAAGGTGGACAAGCGCGTCAATCGA AGTACGGCCCACCGTGCCCGCCTTGTCCCGCGCCGGAGTTCCTC GGCGGTCCCTCGGTCTTTCTGTTCACCGAAGCCCAAGGACAC TTTGATGATTTCCCGCACCCCTGAAGTGACATGCGTGGTTCGTGG ACGTGTACAGGAAGATCCGGAGGTGCAGTTCAATTGGTACGT GGATGGCGTCGAGGTGCACAACGCCAAAACCAAGCCGAGGGA GGAGCAGTTCAACTCCACTTACCGCGTCGTGTCCGTGCTGACGG TGCTGCATCAGGACTGGCTGAACGGGAAGGAGTACAAGTGCAA AGTGTCCAACAAGGGACTTCTAGCTCAATCGAAAAGACCATC TCGAAAGCCAAGGGACAGCCCCGGGAACCCCAAGTGTATACCC TGCCACCGAGCCAGGAAGAAATGACTAAGAACCAAGTCTCATT GACTTGCCCTGTGAAGGGCTTCTACCCATCGGATATCGCCGTGG AATGGGAGTCCAACGGCCAGCCGAAAACAATAAAGACCA CCCCCTCCGGTGTGGACTCAGACGGATCCTTCTTCTACTCG CGGCTGACCGTGGATAAGAGCAGATGGCAGGAGGGAAATGTGT TCAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACTACACT CAGAAGTCCCTGTCCCTCTCCCTGGGA
BAP049-Clone-E LC		
SEQ ID NO: 510 (Kabat)	LCDR1	KSSQSLDSDGNQKNFLT
SEQ ID NO: 511 (Kabat)	LCDR2	WASTRES

SEQ ID NO: 512 (Kabat)	LCDR3	QNDYSYPYT
SEQ ID NO: 513 (Chothia)	LCDR1	SQSLLDSGNQKNF
SEQ ID NO: 514 (Chothia)	LCDR2	WAS
SEQ ID NO: 515 (Chothia)	LCDR3	DYSYPY
SEQ ID NO: 520	VL	EIVLTQSPATLSLSPGERATLSCKSSQSLLD SGNQKNFLT WYQKP GQAPRLLIYWASTRESGVPSRFSGSGSGTDFTF TISSLEAEDAATYY CQNDYSYPYTFGQGTKVEIK
SEQ ID NO: 521	DNA VL	GAGATCGTCTGACTCAGTCACCCGCTACCCTGAGCCTGAGCCC TGGCGAGCGGGCTACACTGAGCTGTAAATCTAGTCAGTCACTG CTGGATAGCGGTAATCAGAAGA ACTTCCTGACCTGGTATCAGC AGAAGCCCGGTCAAGCCCTAGACTGCTGATCTACTGGGCCTCT ACTAGAGAATCAGGCGTGCCCTCTAGGTTTAGCGGTAGCGGTA GTGGCACCGACTTCACCTTCACTATCTCTAGCCTGGAAGCCGAG GACGCCGCTACCTACTACTGTG CAGAACGACTATAGCTACCCCTA CACCTTCGGTCAAGGCACTAAGGTCGAGATTAAG
SEQ ID NO: 522	Light chain	EIVLTQSPATLSLSPGERATLSCKSSQSLLD SGNQKNFLT WYQKP GQAPRLLIYWASTRESGVPSRFSGSGSGTDFTF TISSLEAEDAATYY CQNDYSYPYTFGQGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 523	DNA light chain	GAGATCGTCTGACTCAGTCACCCGCTACCCTGAGCCTGAGCCC TGGCGAGCGGGCTACACTGAGCTGTAAATCTAGTCAGTCACTG CTGGATAGCGGTAATCAGAAGA ACTTCCTGACCTGGTATCAGC AGAAGCCCGGTCAAGCCCTAGACTGCTGATCTACTGGGCCTCT ACTAGAGAATCAGGCGTGCCCTCTAGGTTTAGCGGTAGCGGTA GTGGCACCGACTTCACCTTCACTATCTCTAGCCTGGAAGCCGAG GACGCCGCTACCTACTACTGTG CAGAACGACTATAGCTACCCCTA CACCTTCGGTCAAGGCACTAAGGTCGAGATTAAGCGTACGGTG GCCGCTCCAGCGTGTCATCTTCCCCCAGCGACGAGCAGCT GAAGAGCGGCACCGCCAGCGTGGTGTGCTGCTGAACA ACTTC TACCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCC TGCAGAGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACA GCAAGGACTCCACCTACAGCCTGAGCAGCACCTGACCCTGAG CAAGGCCGACTACGAGAAGCATAAGGTGTACGCCTGCGAGGTG ACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACA GGGGCGAGTGC
BAP049-Clone-B HC		
SEQ ID NO: 524 (Kabat)	HCDR1	ACCTACTGGATGCAC
SEQ ID NO: 525 (Kabat)	HCDR2	AATATCTACCCCGGCACCGGCGGCTCTAACTTCGACGAGAAGT TTAAGAAT
SEQ ID NO: 526 (Kabat)	HCDR3	TGGACTACCGGCACAGGCGCCTAC
SEQ ID NO: 527 (Chothia)	HCDR1	GGCTACACCTTCACTACCTAC
SEQ ID NO: 528 (Chothia)	HCDR2	TACCCCGGCACCGGCGGC
SEQ ID NO: 526 (Chothia)	HCDR3	TGGACTACCGGCACAGGCGCCTAC
BAP049-Clone-B LC		

SEQ ID NO: 529 (Kabat)	LCDR1	AAATCTAGTCAGTCACTGCTGGATAGCGGTAATCAGAAGAAGT TCCTGACC
SEQ ID NO: 530 (Kabat)	LCDR2	TGGGCCTCTACTAGAGAATCA
SEQ ID NO: 531 (Kabat)	LCDR3	CAGAACGACTATAGCTACCCCTACACC
SEQ ID NO: 532 (Chothia)	LCDR1	AGTCAGTCACTGCTGGATAGCGGTAATCAGAAGAAGTTC
SEQ ID NO: 533 (Chothia)	LCDR2	TGGGCCTCT
SEQ ID NO: 534 (Chothia)	LCDR3	GACTATAGCTACCCCTAC
BAP049-Clone-E HC		
SEQ ID NO: 524 (Kabat)	HCDR1	ACCTACTGGATGCAC
SEQ ID NO: 525 (Kabat)	HCDR2	AATATCTACCCCGGCACCGGCGGCTCTAACTTCGACGAGAAGT TTAAGAAT
SEQ ID NO: 526 (Kabat)	HCDR3	TGGACTACCGGCACAGGCGCCTAC
SEQ ID NO: 527 (Chothia)	HCDR1	GGCTACACCTTCACTACCTAC
SEQ ID NO: 528 (Chothia)	HCDR2	TACCCCGGCACCGGCGGC
SEQ ID NO: 526 (Chothia)	HCDR3	TGGACTACCGGCACAGGCGCCTAC
BAP049-Clone-E LC		
SEQ ID NO: 529 (Kabat)	LCDR1	AAATCTAGTCAGTCACTGCTGGATAGCGGTAATCAGAAGAAGT TCCTGACC
SEQ ID NO: 530 (Kabat)	LCDR2	TGGGCCTCTACTAGAGAATCA
SEQ ID NO: 531 (Kabat)	LCDR3	CAGAACGACTATAGCTACCCCTACACC
SEQ ID NO: 532 (Chothia)	LCDR1	AGTCAGTCACTGCTGGATAGCGGTAATCAGAAGAAGTTC
SEQ ID NO: 533 (Chothia)	LCDR2	TGGGCCTCT
SEQ ID NO: 534 (Chothia)	LCDR3	GACTATAGCTACCCCTAC

Other Exemplary PD-1 Inhibitors

In one embodiment, the anti-PD-1 antibody molecule is Nivolumab (Bristol-Myers Squibb), also known as MDX-1106, MDX-1106-04, ONO-4538, BMS-936558, or OPDIVO®. Nivolumab (clone 5C4) and other anti-PD-1 antibodies are disclosed in US 8,008,449 and WO 2006/121168, incorporated by reference in their entirety. In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of Nivolumab, *e.g.*, as disclosed in Table 2.

In one embodiment, the anti-PD-1 antibody molecule is Pembrolizumab (Merck & Co), also known as Lambrolizumab, MK-3475, MK03475, SCH-900475, or KEYTRUDA®. Pembrolizumab and other anti-PD-1 antibodies are disclosed in Hamid, O. *et al.* (2013) *New England Journal of Medicine* 369 (2): 134–44, US 8,354,509, and WO 2009/114335, incorporated by reference in their

entirety. In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of Pembrolizumab, *e.g.*, as disclosed in Table 2.

In one embodiment, the anti-PD-1 antibody molecule is Pidilizumab (CureTech), also known
5 as CT-011. Pidilizumab and other anti-PD-1 antibodies are disclosed in Rosenblatt, J. *et al.* (2011) *J Immunotherapy* 34(5): 409-18, US 7,695,715, US 7,332,582, and US 8,686,119, incorporated by reference in their entirety. In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of Pidilizumab, *e.g.*, as disclosed
10 in Table 2.

In one embodiment, the anti-PD-1 antibody molecule is MEDI0680 (Medimmune), also known as AMP-514. MEDI0680 and other anti-PD-1 antibodies are disclosed in US 9,205,148 and WO 2012/145493, incorporated by reference in their entirety. In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR
15 sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of MEDI0680.

In one embodiment, the anti-PD-1 antibody molecule is REGN2810 (Regeneron). In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the
20 heavy chain or light chain sequence of REGN2810.

In one embodiment, the anti-PD-1 antibody molecule is PF-06801591 (Pfizer). In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of PF-06801591.

In one embodiment, the anti-PD-1 antibody molecule is BGB-A317 or BGB-108 (Beigene).
25 In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of BGB-A317 or BGB-108.

In one embodiment, the anti-PD-1 antibody molecule is INCSHR1210 (Incyte), also known
30 as INCSHR01210 or SHR-1210. In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of INCSHR1210.

In one embodiment, the anti-PD-1 antibody molecule is TSR-042 (Tesarro), also known as ANB011. In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR
35 sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of TSR-042.

Further known anti-PD-1 antibodies include those described, *e.g.*, in WO 2015/112800, WO 2016/092419, WO 2015/085847, WO 2014/179664, WO 2014/194302, WO 2014/209804, WO 2015/200119, US 8,735,553, US 7,488,802, US 8,927,697, US 8,993,731, and US 9,102,727, incorporated by reference in their entirety.

5 In one embodiment, the anti-PD-1 antibody is an antibody that competes for binding with, and/or binds to the same epitope on PD-1 as, one of the anti-PD-1 antibodies described herein.

In one embodiment, the PD-1 inhibitor is a peptide that inhibits the PD-1 signaling pathway, *e.g.*, as described in US 8,907,053, incorporated by reference in its entirety. In one embodiment, the PD-1 inhibitor is an immunoadhesin (*e.g.*, an immunoadhesin comprising an extracellular or PD-1

10 binding portion of PD-L1 or PD-L2 fused to a constant region (*e.g.*, an Fc region of an immunoglobulin sequence). In one embodiment, the PD-1 inhibitor is AMP-224 (B7-DCI_g (Amplimmune), *e.g.*, disclosed in WO 2010/027827 and WO 2011/066342, incorporated by reference in their entirety).

15 **Table 2.** Amino acid sequences of other exemplary anti-PD-1 antibody molecules

Nivolumab		
SEQ ID NO: 535	Heavy chain	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAV IWYDGSKRYYADSVKGRFTISRDNKNTLFLQMNSLRAEDTAVYYCATND DYWGQGTLLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDHKPSN TKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSR WQEGNVFSCSVMEALHNHYTQKSLSLGLK
SEQ ID NO: 536	Light chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLIYDASN RATGIPARFSGSGTDFTLTISSLEPEDFAVYYCQQSNWPRTFGGQTKVEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC
Pembrolizumab		
SEQ ID NO: 537	Heavy chain	QVQLVQSGVEVKKPGASVKVCSKASGYTFTNYYMYWVRQAPGQGLEWM GGINPSNGGTNFKNEKFNKRVTLTDSSTTTAYMELKSLQFDDTAVYYCARR DYRFDMGFDYWGQGTITVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYT CNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYS RLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLK
SEQ ID NO: 538	Light chain	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLI YLASYLESGVPARFSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPLTFGGG TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC

Pidilizumab		
SEQ ID NO: 539	Heavy chain	QVQLVQSGSELKKPGASVKISCKASGYTFTNYGMNWRQAPGQGLQWMG WINTDSGESTYAEFKGRFVFLDTSVNTAYLQITSLTAEDTGMVFCVVRVGY DALDYWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHHK PSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 540	Light chain	EIVLTQSPSSLSASVGRVTITCSARSSVSYMHWFQKPKGKAPKLWIYRTSN LASGVPSRFSGSGSGTSYCLTINSIQPEDFATYYCQQRSSPFTFGGGTKLEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNFPYPREAKVQWKVDNALQSGN SQESVTEQDSKDYSLSSITLTSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC

PD-L1 Inhibitors

In certain embodiments, the anti-LAG-3 antibody molecule described herein is administered in combination with a PD-L1 inhibitor. In some embodiments, the PD-L1 inhibitor is chosen from
 5 FAZ053 (Novartis), Atezolizumab (Genentech/Roche), Avelumab (Merck Serono and Pfizer), Durvalumab (MedImmune/AstraZeneca), or BMS-936559 (Bristol-Myers Squibb).

Exemplary PD-L1 Inhibitors

In one embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule. In one
 10 embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule as disclosed in US 2016/0108123, published on April 21, 2016, entitled “Antibody Molecules to PD-L1 and Uses Thereof,” incorporated by reference in its entirety.

In one embodiment, the anti-PD-L1 antibody molecule comprises at least one, two, three, four, five or six complementarity determining regions (CDRs) (or collectively all of the CDRs) from a
 15 heavy and light chain variable region comprising an amino acid sequence shown in Table 3 (e.g., from the heavy and light chain variable region sequences of BAP058-Clone O or BAP058-Clone N disclosed in Table 3), or encoded by a nucleotide sequence shown in Table 3. In some embodiments, the CDRs are according to the Kabat definition (e.g., as set out in Table 3). In some embodiments, the CDRs are according to the Chothia definition (e.g., as set out in Table 3). In some embodiments,
 20 the CDRs are according to the combined CDR definitions of both Kabat and Chothia (e.g., as set out in Table 3). In one embodiment, the combination of Kabat and Chothia CDR of VH CDR1 comprises the amino acid sequence GYTFTSYWY (SEQ ID NO: 647). In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, e.g., amino acid substitutions (e.g., conservative amino acid substitutions) or deletions, relative to an amino
 25 acid sequence shown in Table 3, or encoded by a nucleotide sequence shown in Table 3.

In one embodiment, the anti-PD-L1 antibody molecule comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 601, a VHCDR2 amino acid sequence of SEQ ID NO: 602, and a VHCDR3 amino acid sequence of SEQ ID NO: 603; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 609, a
5 VLCDR2 amino acid sequence of SEQ ID NO: 610, and a VLCDR3 amino acid sequence of SEQ ID NO: 611, each disclosed in Table 3.

In one embodiment, the anti-PD-L1 antibody molecule comprises a VH comprising a VHCDR1 encoded by the nucleotide sequence of SEQ ID NO: 628, a VHCDR2 encoded by the nucleotide sequence of SEQ ID NO: 629, and a VHCDR3 encoded by the nucleotide sequence of
10 SEQ ID NO: 630; and a VL comprising a VLCDR1 encoded by the nucleotide sequence of SEQ ID NO: 633, a VLCDR2 encoded by the nucleotide sequence of SEQ ID NO: 634, and a VLCDR3 encoded by the nucleotide sequence of SEQ ID NO: 635, each disclosed in Table 3.

In one embodiment, the anti-PD-L1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 606, or an amino acid sequence at least 85%, 90%, 95%, or 99%
15 identical or higher to SEQ ID NO: 606. In one embodiment, the anti-PD-L1 antibody molecule comprises a VL comprising the amino acid sequence of SEQ ID NO: 616, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 616. In one embodiment, the anti-PD-L1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 620, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO:
20 620. In one embodiment, the anti-PD-L1 antibody molecule comprises a VL comprising the amino acid sequence of SEQ ID NO: 624, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 624. In one embodiment, the anti-PD-L1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 606 and a VL comprising the amino acid sequence of SEQ ID NO: 616. In one embodiment, the anti-PD-L1 antibody molecule
25 comprises a VH comprising the amino acid sequence of SEQ ID NO: 620 and a VL comprising the amino acid sequence of SEQ ID NO: 624.

In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 607, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or
higher to SEQ ID NO: 607. In one embodiment, the antibody molecule comprises a VL encoded by
30 the nucleotide sequence of SEQ ID NO: 617, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 617. In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 621, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 621. In one embodiment, the antibody molecule comprises a VL encoded by the nucleotide sequence of SEQ ID NO: 625, or a nucleotide
35 sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 625. In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 607 and a VL encoded by the nucleotide sequence of SEQ ID NO: 617. In one embodiment, the

antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 621 and a VL encoded by the nucleotide sequence of SEQ ID NO: 625.

In one embodiment, the anti-PD-L1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 608, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 608. In one embodiment, the anti-PD-L1 antibody molecule comprises a light chain comprising the amino acid sequence of SEQ ID NO: 618, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 618. In one embodiment, the anti-PD-L1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 622, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 622. In one embodiment, the anti-PD-L1 antibody molecule comprises a light chain comprising the amino acid sequence of SEQ ID NO: 626, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 626. In one embodiment, the anti-PD-L1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 608 and a light chain comprising the amino acid sequence of SEQ ID NO: 618. In one embodiment, the anti-PD-L1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 622 and a light chain comprising the amino acid sequence of SEQ ID NO: 626.

In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 615, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 615. In one embodiment, the antibody molecule comprises a light chain encoded by the nucleotide sequence of SEQ ID NO: 619, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 619. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 623, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 623. In one embodiment, the antibody molecule comprises a light chain encoded by the nucleotide sequence of SEQ ID NO: 627, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 627. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 615 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 619. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 623 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 627.

The antibody molecules described herein can be made by vectors, host cells, and methods described in US 2016/0108123, incorporated by reference in its entirety.

Table 3. Amino acid and nucleotide sequences of exemplary anti-PD-L1 antibody molecules

BAP058-Clone O HC		
SEQ ID NO: 601 (Kabat)	HCDR1	SYWMY
SEQ ID NO: 602 (Kabat)	HCDR2	RIDPNSGSTKYNEKFKN

SEQ ID NO: 603 (Kabat)	HCDR3	DYRKGLYAMDY
SEQ ID NO: 604 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 605 (Chothia)	HCDR2	DPNSGS
SEQ ID NO: 603 (Chothia)	HCDR3	DYRKGLYAMDY
SEQ ID NO: 606	VH	EVQLVQSGAEVKKPGATVKISCKVSGYTFTSYWMYWVRQARGQ RLEWIGRIDPNSGSTKYNEKFKNRFTISRDN SKNTLYLQMN SLRA EDTAVYYCARDYRKGLYAMDYWGQGT TVTVSS
SEQ ID NO: 607	DNA VH	GAAGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCC GGCGCTACCGTGAAGATTAGCTGTAAAGTCTCAGGCTACACCT TACTAGCTACTGGATGTACTGGGTCCGACAGGCTAGAGGGCA AAGACTGGAGTGGATCGGTAGAATCGACCCTAATAGCGGCTC TACTAAGTATAACGAGAAGTTTAAGAATAGGTTCACTATTAGT AGGGATAACTCTAAGAACACCCTGTACCTGCAGATGAATAGC CTGAGAGCCGAGGACACCGCCGCTACTACTGCGCTAGAGACT ATAGAAAGGGCCTGTACGCTATGGACTACTGGGGTCAAGGCA CTACCGTGACCGTGTCTTCA
SEQ ID NO: 608	Heavy chain	EVQLVQSGAEVKKPGATVKISCKVSGYTFTSYWMYWVRQARGQ RLEWIGRIDPNSGSTKYNEKFKNRFTISRDN SKNTLYLQMN SLRA EDTAVYYCARDYRKGLYAMDYWGQGT TVTVSSASTKGPSVFPL APCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSVHTFPAV LQSSGLYSLSSVTVPSSSLGKTYTCNV D HKPSNTKVDKRVESK YGPCCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVS QEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLD SDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKLSL SLG
SEQ ID NO: 615	DNA heavy chain	GAAGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCC GGCGCTACCGTGAAGATTAGCTGTAAAGTCTCAGGCTACACCT TACTAGCTACTGGATGTACTGGGTCCGACAGGCTAGAGGGCA AAGACTGGAGTGGATCGGTAGAATCGACCCTAATAGCGGCTC TACTAAGTATAACGAGAAGTTTAAGAATAGGTTCACTATTAGT AGGGATAACTCTAAGAACACCCTGTACCTGCAGATGAATAGC CTGAGAGCCGAGGACACCGCCGCTACTACTGCGCTAGAGACT ATAGAAAGGGCCTGTACGCTATGGACTACTGGGGTCAAGGCA CTACCGTGACCGTGTCTTCACTAGCTAGCTAAGGGCCCGTCCGT GTTCCCCCTGGCACCTTGTAGCCGAGCACTAGCGAATCCACC GCTGCCCTCGGCTGCCTGGTCAAGGATTACTCCCGAGCCCG TGACCGTGTCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCA CACCTTCCCCGCTGTGCTGCAGAGCTCCGGGCTGTACTCGCTG TCGTCGGTGGTACGGTGCCTTCATCTAGCCTGGGTACCAAGA CCTACACTTGCAACGTGGACCACAAGCCTTCCAACACTAAGGT GGACAAGCGCGTCAATCGAAGTACGGCCACCGTGCCCGCC TTGTCCCGCGCCGGAGTTCCTCGGCGGTCCCTCGGTCTTTCTGT TCCCACCGAAGCCCAAGGACACTTTGATGATTTCCCGCACCCC TGAAGTGACATGCGTGGTTCGTGGACGTGTCACAGGAAGATCC GGAGGTGCAGTCAATTGGTACGTGGATGGCGTCCGAGGTGCA CAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAACTCCAC TTACCGGTCGTGTCCGTGCTGACGGTGTGTCATCAGGACTGG CTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGGA CTTCTAGCTCAATCGAAAAGACCATCTCGAAAGCCAAGGGA CAGCCCCGGGAACCCCAAGTGTATAACCTGCCACCGAGCCAG GAAGAAATGACTAAGAACCAAGTCTCATTGACTTGCTTGTGA AGGGCTTCTACCCATCGGATATCGCCGTGGAATGGGAGTCCAA CGGCCAGCCGGAAAACA ACTACAAGACCACCCCTCCGGTGTG GACTCAGACGGATCCTTCTTCTCTACTCGCGGCTGACCGTG

		GATAAGAGCAGATGGCAGGAGGGAAATGTGTTCAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACTACACTCAGAAGTCCC TGTCCCTCTCCCTGGGA
BAP058-Clone O LC		
SEQ ID NO: 609 (Kabat)	LCDR1	KASQDVGTAVA
SEQ ID NO: 610 (Kabat)	LCDR2	WASTRHT
SEQ ID NO: 611(Kabat)	LCDR3	QQYNSYPLT
SEQ ID NO: 612 (Chothia)	LCDR1	SQDVGTA
SEQ ID NO: 613 (Chothia)	LCDR2	WAS
SEQ ID NO: 614 (Chothia)	LCDR3	YNSYPL
SEQ ID NO: 616	VL	AIQLTQSPSSLSASVGDVRTITCKASQDVGTA VAWYLQKPGQSPQ LLIYWASTRHTGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQY NSYPLTFGQGTKVEIK
SEQ ID NO: 617	DNA VL	GCTATTCAGCTGACTCAGTCACCTAGTAGCCTGAGCGCTAGTG TGGGCGATAGAGTGACTATCACCTGTAAAGCCTCTCAGGACGT GGGCACCGCCGTGGCCTGGTATCTGCAGAAGCCTGGTCAATCA CCTCAGCTGCTGATCTACTGGGCCTCTACTAGACACACCGGCG TGCCCTCTAGGTTTAGCGGTAGCGGTAGTGGCACCAGCTTAC CTTCACTATCTCTTCACTGGAAGCCGAGGACGCCGCTACCTAC TACTGTCAGCAGTATAATAGCTACCCCTGACCTTCGGTCAAG GCACTAAGGTTCGAGATTAAG
SEQ ID NO: 618	Light chain	AIQLTQSPSSLSASVGDVRTITCKASQDVGTA VAWYLQKPGQSPQ LLIYWASTRHTGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQY NSYPLTFGQGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 619	DNA light chain	GCTATTCAGCTGACTCAGTCACCTAGTAGCCTGAGCGCTAGTG TGGGCGATAGAGTGACTATCACCTGTAAAGCCTCTCAGGACGT GGGCACCGCCGTGGCCTGGTATCTGCAGAAGCCTGGTCAATCA CCTCAGCTGCTGATCTACTGGGCCTCTACTAGACACACCGGCG TGCCCTCTAGGTTTAGCGGTAGCGGTAGTGGCACCAGCTTAC CTTCACTATCTCTTCACTGGAAGCCGAGGACGCCGCTACCTAC TACTGTCAGCAGTATAATAGCTACCCCTGACCTTCGGTCAAG GCACTAAGGTTCGAGATTAAGCGTACGGTGGCCGCTCCCAGCGT GTTTCATCTCCCCCAGCGACGAGCAGCTGAAGAGCGGCACC GCCAGCGTGGTGTGCCTGCTGAACAACCTTACCCCGGGAGG CCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCA ACAGCCAGGAGAGCGTCACCGAGCAGGACAGCAAGGACTCCA CCTACAGCCTGAGCAGCACCTGACCCTGAGCAAGGCCGACT ACGAGAAGCATAAGGTGTACGCTGCGAGGTGACCCACCAGG GCCTGTCCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGT GC
BAP058-Clone N HC		
SEQ ID NO: 601 (Kabat)	HCDR1	SYWMY
SEQ ID NO: 602 (Kabat)	HCDR2	RIDPNSGSTKYNEKFKN
SEQ ID NO: 603 (Kabat)	HCDR3	DYRKGLYAMDY
SEQ ID NO: 604 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 605 (Chothia)	HCDR2	DPNSGS
SEQ ID NO: 603 (Chothia)	HCDR3	DYRKGLYAMDY
SEQ ID NO: 620	VH	EVQLVQSGAEVKKPGATVKISCKVSGYFTFTSYWMYWVRQATGQ

		GLEWMGRIDPNSGSKYNEKFKNRVTITADKSTSTAYMELSSLRS EDTAVYYCARDYRKGLYAMDYWGQGTTVTVSS
SEQ ID NO: 621	DNA VH	GAAGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCC GGCGTACCCTGAAGATTAGCTGTAAAGTCTCAGGCTACACCT TCACTAGCTACTGGATGTACTGGGTCCGACAGGCTACCGGTCA AGGCCTGGAGTGGATGGGTAGAATCGACCCTAATAGCGGCTC TACTAAGTATAACGAGAAGTTTAAGAATAGAGTACTATCACC GCCGATAAGTCTACTAGCACCCTATATGGAAGTGTCTAGCC TGAGATCAGAGGACACCGCCGTCTACTACTGCGCTAGAGACTA TAGAAAGGGCCTGTACGCTATGGACTACTGGGGTCAAGGCAC TACCGTGACCGTGTCTTCA
SEQ ID NO: 622	Heavy chain	EVQLVQSGAEVKKPGATVKISCKVSGYTFTSYWMYWVRQATGQ GLEWMGRIDPNSGSKYNEKFKNRVTITADKSTSTAYMELSSLRS EDTAVYYCARDYRKGLYAMDYWGQGTTVTVSSASTKGPSVFPL APCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKVDKRVESK YGPCCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVS QEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNKEYKCKVSNKGLPSSIEKTKSKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLD SDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKLSLSL SLG
SEQ ID NO: 623	DNA heavy chain	GAAGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCC GGCGTACCCTGAAGATTAGCTGTAAAGTCTCAGGCTACACCT TCACTAGCTACTGGATGTACTGGGTCCGACAGGCTACCGGTCA AGGCCTGGAGTGGATGGGTAGAATCGACCCTAATAGCGGCTC TACTAAGTATAACGAGAAGTTTAAGAATAGAGTACTATCACC GCCGATAAGTCTACTAGCACCCTATATGGAAGTGTCTAGCC TGAGATCAGAGGACACCGCCGTCTACTACTGCGCTAGAGACTA TAGAAAGGGCCTGTACGCTATGGACTACTGGGGTCAAGGCAC TACCGTGACCGTGTCTTACGCTAGCACTAAGGGCCCGTCCGTG TTCCCCCTGGCACCTTGTAGCCGGAGCACTAGCGAATCCACCG CTGCCCTCGGCTGCCTGGTCAAGGATTACTTCCCGGAGCCCGT GACCGTGTCTTGGAACAGCGGAGCCCTGACCTCCGGAGTGCA CACCTTCCCGCTGTGCTGCAGAGCTCCGGGTGTACTCGTGT TCGTGGTGGTACCGGTGCCTTTCATCTAGCTGGGTACCAAGA CCTACACTTGCAACGTGGACCACAAGCCTTCCAACACTAAGGT GGACAAGCGCGTCGAATCGAAGTACGGCCACCGTGCCCGCC TTGTCCCGCGCCGGAGTTCCTCGGCGGTCCCTCGGTCTTTCTGT TCCCACCGAAGCCCAAGGACACTTTGATGATTTCCCGCACCCC TGAAAGTACATGCGTGGTCTGACGCTGTCACAGGAAGATCC GGAGGTGCAGTTCAATTGGTACGTGGATGGCGTTCGAGGTGCA CAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAACTCCAC TTACCGGTCTGTGCTCCGTGCTGACGGTGTGTCATCAGGACTGG CTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGGA CTTCTAGCTCAATCGAAAAGACCATCTCGAAAGCCAAGGGA CAGCCCCGGGAACCCCAAGTGTATAACCTGCCACCGAGCCAG GAAGAAATGACTAAGAACCAAGTCTCATTGACTTGCTTGTGA AGGGCTTCTACCCATCGGATATCGCCGTGGAATGGGAGTCCAA CGGCCAGCCGAAAACAACACTACAAGACCACCCCTCCGGTGTCT GGACTCAGACGGATCCTTCTTCTCTACTCGCGGCTGACCGTG GATAAGAGCAGATGGCAGGAGGAAATGTGTTCAGCTGTTCT GTGATGCATGAAGCCCTGCACAACCACTACACTCAGAAGTCCC TGTCCTCTCCCTGGGA
BAP058-Clone N LC		
SEQ ID NO: 609 (Kabat)	LCDR1	KASQDVGTAVA
SEQ ID NO: 610 (Kabat)	LCDR2	WASTRHT
SEQ ID NO: 611(Kabat)	LCDR3	QQYNSYPLT

SEQ ID NO: 612 (Chothia)	LCDR1	SQDVGTA
SEQ ID NO: 613 (Chothia)	LCDR2	WAS
SEQ ID NO: 614 (Chothia)	LCDR3	YNSYPL
SEQ ID NO: 624	VL	DVVMTQSPLSLPVTLGQPASISCKASQDVGTA VAWYQQKPGQAP RLLIYWASTRHTGVPSRFSGSGSGTEFTLTISLQPDFFATYYCQQ YNSYPLTFGQGTKVEIK
SEQ ID NO: 625	DNA VL	GACGTCGTGATGACTCAGTCACCCCTGAGCCTGCCCGTGACCC TGGGGCAGCCCCGCTCTATTAGCTGTAAAGCCTCTCAGGACGT GGGCACCGCCGTGGCCTGGTATCAGCAGAAGCCAGGGCAAGC CCCTAGACTGCTGATCTACTGGGCCTCTACTAGACACACCCGGC GTGCCCTCTAGGTTTAGCGGTAGCGGTAGTGGCACCGAGTTCA CCCTGACTATCTCTTCACTGCAGCCCGACGACTTCGCTACCTAC TACTGTCAGCAGTATAATAGCTACCCCTGACCTTCGGTCAAG GCACTAAGGTTCGAGATTAAG
SEQ ID NO: 626	Light chain	DVVMTQSPLSLPVTLGQPASISCKASQDVGTA VAWYQQKPGQAP RLLIYWASTRHTGVPSRFSGSGSGTEFTLTISLQPDFFATYYCQQ YNSYPLTFGQGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 627	DNA light chain	GACGTCGTGATGACTCAGTCACCCCTGAGCCTGCCCGTGACCC TGGGGCAGCCCCGCTCTATTAGCTGTAAAGCCTCTCAGGACGT GGGCACCGCCGTGGCCTGGTATCAGCAGAAGCCAGGGCAAGC CCCTAGACTGCTGATCTACTGGGCCTCTACTAGACACACCCGGC GTGCCCTCTAGGTTTAGCGGTAGCGGTAGTGGCACCGAGTTCA CCCTGACTATCTCTTCACTGCAGCCCGACGACTTCGCTACCTAC TACTGTCAGCAGTATAATAGCTACCCCTGACCTTCGGTCAAG GCACTAAGGTTCGAGATTAAGCGTACGGTGGCCGCTCCAGCGT GTTTCATCTTCCCCCAGCGACGAGCAGCTGAAGAGCGGCACC GCCAGCGTGGTGTGCCTGCTGAACA ACTTCTACCCCGGGAGG CCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCA ACAGCCAGGAGAGCGTCACCGAGCAGGACAGCAAGGACTCCA CCTACAGCCTGAGCAGCACCCCTGACCCTGAGCAAGGCCGACT ACGAGAAGCATAAGGTGTACGCCTGCGAGGTGACCCACCAGG GCCTGTCCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGT GC
BAP058-Clone O HC		
SEQ ID NO: 628 (Kabat)	HCDR1	AGCTACTGGATGTAC
SEQ ID NO: 629 (Kabat)	HCDR2	AGAATCGACCCTAATAGCGGCTCTACTAAGTATAACGAGAAG TTTAAGAAT
SEQ ID NO: 630 (Kabat)	HCDR3	GACTATAGAAAGGGCCTGTACGCTATGGACTAC
SEQ ID NO: 631 (Chothia)	HCDR1	GGCTACACCTTCACTAGCTAC
SEQ ID NO: 632 (Chothia)	HCDR2	GACCCTAATAGCGGCTCT
SEQ ID NO: 630 (Chothia)	HCDR3	GACTATAGAAAGGGCCTGTACGCTATGGACTAC
BAP058-Clone O LC		
SEQ ID NO: 633 (Kabat)	LCDR1	AAAGCCTCTCAGGACGTGGGCACCGCCGTGGCC
SEQ ID NO: 634 (Kabat)	LCDR2	TGGGCCTCTACTAGACACACC
SEQ ID NO: 635 (Kabat)	LCDR3	CAGCAGTATAATAGCTACCCCTGACC
SEQ ID NO: 636 (Chothia)	LCDR1	TCTCAGGACGTGGGCACCGCC
SEQ ID NO: 637 (Chothia)	LCDR2	TGGGCCTCT

SEQ ID NO: 638 (Chothia)	LCDR3	TATAATAGCTACCCCCTG
BAP058-Clone N HC		
SEQ ID NO: 628 (Kabat)	HCDR1	AGCTACTGGATGTAC
SEQ ID NO: 629 (Kabat)	HCDR2	AGAATCGACCCTAATAGCGGCTCTACTAAGTATAACGAGAAG TTTAAGAAT
SEQ ID NO: 630 (Kabat)	HCDR3	GACTATAGAAAGGGCCTGTACGCTATGGACTAC
SEQ ID NO: 631 (Chothia)	HCDR1	GGCTACACCTTCACTAGCTAC
SEQ ID NO: 632 (Chothia)	HCDR2	GACCCTAATAGCGGCTCT
SEQ ID NO: 630 (Chothia)	HCDR3	GACTATAGAAAGGGCCTGTACGCTATGGACTAC
BAP058-Clone N LC		
SEQ ID NO: 633 (Kabat)	LCDR1	AAAGCCTCTCAGGACGTGGGCACCGCCGTGGCC
SEQ ID NO: 634 (Kabat)	LCDR2	TGGGCCTCTACTAGACACACC
SEQ ID NO: 635 (Kabat)	LCDR3	CAGCAGTATAATAGCTACCCCCTGACC
SEQ ID NO: 636 (Chothia)	LCDR1	TCTCAGGACGTGGGCACCGCC
SEQ ID NO: 637 (Chothia)	LCDR2	TGGGCCTCT
SEQ ID NO: 638 (Chothia)	LCDR3	TATAATAGCTACCCCCTG

Other Exemplary PD-L1 Inhibitors

In one embodiment, the anti-PD-L1 antibody molecule is Atezolizumab (Genentech/Roche), also known as MPDL3280A, RG7446, RO5541267, YW243.55.S70, or TECENTRIQ™.

5 Atezolizumab and other anti-PD-L1 antibodies are disclosed in US 8,217,149, incorporated by reference in its entirety. In one embodiment, the anti-PD-L1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of Atezolizumab, *e.g.*, as disclosed in Table 4.

10 In one embodiment, the anti-PD-L1 antibody molecule is Avelumab (Merck Serono and Pfizer), also known as MSB0010718C. Avelumab and other anti-PD-L1 antibodies are disclosed in WO 2013/079174, incorporated by reference in its entirety. In one embodiment, the anti-PD-L1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain
15 sequence of Avelumab, *e.g.*, as disclosed in Table 4.

In one embodiment, the anti-PD-L1 antibody molecule is Durvalumab (MedImmune/AstraZeneca), also known as MEDI4736. Durvalumab and other anti-PD-L1 antibodies are disclosed in US 8,779,108, incorporated by reference in its entirety. In one
20 embodiment, the anti-PD-L1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of Durvalumab, *e.g.*, as disclosed in Table 4.

In one embodiment, the anti-PD-L1 antibody molecule is BMS-936559 (Bristol-Myers Squibb), also known as MDX-1105 or 12A4. BMS-936559 and other anti-PD-L1 antibodies are disclosed in US 7,943,743 and WO 2015/081158, incorporated by reference in their entirety. In one embodiment, the anti-PD-L1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of BMS-936559, *e.g.*, as disclosed in Table 4.

Further known anti-PD-L1 antibodies include those described, *e.g.*, in WO 2015/181342, WO 2014/100079, WO 2016/000619, WO 2014/022758, WO 2014/055897, WO 2015/061668, WO 2013/079174, WO 2012/145493, WO 2015/112805, WO 2015/109124, WO 2015/195163, US 8,168,179, US 8,552,154, US 8,460,927, and US 9,175,082, incorporated by reference in their entirety.

In one embodiment, the anti-PD-L1 antibody is an antibody that competes for binding with, and/or binds to the same epitope on PD-L1 as, one of the anti-PD-L1 antibodies described herein.

Table 4. Amino acid sequences of other exemplary anti-PD-L1 antibody molecules

Atezolizumab		
SEQ ID NO: 639	Heavy chain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWRQAPGKGLEWVAWI SPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWP GGFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTIKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFPYSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 640	Light chain	DIQMTQSPSSLSASVGRVTITCRASQDVSTAVAWYQQKPKAPKLLIYSASF LYSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQYLYHPATFGQGKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKSTYLSLSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNR GEC
Avelumab		
SEQ ID NO: 641	Heavy chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYIMMWVRQAPGKGLEWVSSII PSGGITFYADTVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARIKLGTV TTVDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTIKAKGQPREPQVYTLPPSRDELTKNQ VSLTCLVKGFPYSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 642	Light chain	QSALTQPASVSGSPGQSITISCTGTSSDVGGINYSWYQQHPGKAPKLMIID VSNRPSGVSNRFSKSGNTASLTISGLQAEDEADYYCSSYTSSTRVFGTGT KVTVLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGS PVKAGVETTKPSKQSNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKT VAPTECS

Durvalumab		
SEQ ID NO: 643	Heavy chain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVANI KQDGSEKYYVDSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCAREGG WFGELAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV NPKPSNTKVDKRVKPKSCDKTHTCPPCPAPEFEGGPSVFLPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 644	Light chain	EIVLTQSPGTLTLSPGERATLSCRASQRVSSSYLAWYQQKPGQAPRLLIYDAS SRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGLPWTFGQGTKVEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKSTYLSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC
BMS-936559		
SEQ ID NO: 645	VH	QVQLVQSGAEVKKPGSSVKVCKTSGDFTSTY AISWVRQAPGQGLEWMGGII PIFGKAHYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYFCARKFHFVSG SPFGMDVWGQGTITVTVSS
SEQ ID NO: 646	VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASN RATGIPARFSGSGSGTDFTLTISLEPEDFAVYYCQQRSNWPTFGQGTKVEIK

TIM-3 Inhibitors

In certain embodiments, the anti-LAG-3 antibody molecule described herein is administered in combination with a TIM-3 inhibitor. In some embodiments, the TIM-3 inhibitor is MGB453 (Novartis) or TSR-022 (Tesaro).

Exemplary TIM-3 Inhibitors

In one embodiment, the TIM-3 inhibitor is an anti-TIM-3 antibody molecule. In one embodiment, the TIM-3 inhibitor is an anti-TIM-3 antibody molecule as disclosed in US 2015/0218274, published on August 6, 2015, entitled “Antibody Molecules to TIM-3 and Uses Thereof,” incorporated by reference in its entirety.

In one embodiment, the anti-TIM-3 antibody molecule comprises at least one, two, three, four, five or six complementarity determining regions (CDRs) (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 7 (e.g., from the heavy and light chain variable region sequences of ABTIM3-hum11 or ABTIM3-hum03 disclosed in Table 7), or encoded by a nucleotide sequence shown in Table 7. In some embodiments, the CDRs are according to the Kabat definition (e.g., as set out in Table 7). In some embodiments, the CDRs are according to the Chothia definition (e.g., as set out in Table 7). In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, e.g., amino acid substitutions (e.g., conservative amino acid substitutions) or deletions, relative to an amino acid sequence shown in Table 7, or encoded by a nucleotide sequence shown in Table 7.

In one embodiment, the anti-TIM-3 antibody molecule comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 801, a VHCDR2 amino acid sequence of SEQ ID NO: 802, and a VHCDR3 amino acid sequence of SEQ ID NO: 803; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 810, a
5 VLCDR2 amino acid sequence of SEQ ID NO: 811, and a VLCDR3 amino acid sequence of SEQ ID NO: 812, each disclosed in Table 7. In one embodiment, the anti-TIM-3 antibody molecule comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 801, a VHCDR2 amino acid sequence of SEQ ID NO: 820, and a VHCDR3 amino acid sequence of SEQ ID NO: 803; and a light chain variable region (VL) comprising a VLCDR1 amino
10 acid sequence of SEQ ID NO: 810, a VLCDR2 amino acid sequence of SEQ ID NO: 811, and a VLCDR3 amino acid sequence of SEQ ID NO: 812, each disclosed in Table 7.

In one embodiment, the anti-TIM-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 806, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 806. In one embodiment, the anti-TIM-3 antibody molecule
15 comprises a VL comprising the amino acid sequence of SEQ ID NO: 816, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 816. In one embodiment, the anti-TIM-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 822, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 822. In one embodiment, the anti-TIM-3 antibody molecule comprises a VL comprising the amino
20 acid sequence of SEQ ID NO: 826, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 826. In one embodiment, the anti-TIM-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 806 and a VL comprising the amino acid sequence of SEQ ID NO: 816. In one embodiment, the anti-TIM-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 822 and a VL comprising the
25 amino acid sequence of SEQ ID NO: 826.

In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 807, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 807. In one embodiment, the antibody molecule comprises a VL encoded by the nucleotide sequence of SEQ ID NO: 817, or a nucleotide sequence at least 85%, 90%, 95%, or
30 99% identical or higher to SEQ ID NO: 817. In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 823, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 823. In one embodiment, the antibody molecule comprises a VL encoded by the nucleotide sequence of SEQ ID NO: 827, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 827. In one
35 embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 807 and a VL encoded by the nucleotide sequence of SEQ ID NO: 817. In one embodiment, the

antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 823 and a VL encoded by the nucleotide sequence of SEQ ID NO: 827.

In one embodiment, the anti-TIM-3 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 808, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 808. In one embodiment, the anti-TIM-3 antibody molecule comprises a light chain comprising the amino acid sequence of SEQ ID NO: 818, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 818. In one embodiment, the anti-TIM-3 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 824, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 824. In one embodiment, the anti-TIM-3 antibody molecule comprises a light chain comprising the amino acid sequence of SEQ ID NO: 828, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 828. In one embodiment, the anti-TIM-3 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 808 and a light chain comprising the amino acid sequence of SEQ ID NO: 818. In one embodiment, the anti-TIM-3 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 824 and a light chain comprising the amino acid sequence of SEQ ID NO: 828.

In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 809, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 809. In one embodiment, the antibody molecule comprises a light chain encoded by the nucleotide sequence of SEQ ID NO: 819, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 819. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 825, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 825. In one embodiment, the antibody molecule comprises a light chain encoded by the nucleotide sequence of SEQ ID NO: 829, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 829. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 809 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 819. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 825 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 829.

The antibody molecules described herein can be made by vectors, host cells, and methods described in US 2015/0218274, incorporated by reference in its entirety.

Table 7. Amino acid and nucleotide sequences of exemplary anti-TIM-3 antibody molecules

ABTIM3-hum11		
SEQ ID NO: 801 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 802 (Kabat)	HCDR2	DIYPGNGDTSYNQKFKG
SEQ ID NO: 803 (Kabat)	HCDR3	VGGAFPMDY

SEQ ID NO: 804 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 805 (Chothia)	HCDR2	YPGNGD
SEQ ID NO: 803 (Chothia)	HCDR3	VGGAFPM DY
SEQ ID NO: 806	VH	QVQLVQSGAEVKKPGSSVKV SCKASGYTFTSYNMHWVRQAPG QGLEWMGDIYPGNGDTSYNQKFKGRVTITADKSTSTVYMELSS LRSEDTAVYYCARVGGAFPM DYWGOGTTVTVSS
SEQ ID NO: 807	DNA VH	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACC CGGCTCTAGCGTGAAAGTTTCTTGTAAGCTAGTGGCTACAC CTTCACTAGCTATAATATGCACTGGGTTCCGCCAGGCCCCAGG GCAAGGCCTCGAGTGGATGGGCGATATCTACCCCGGGAACGG CGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGTCACTAT CACCGCCGATAAGTCTACTAGCACCGTCTATATGGAAGTGAAG TTCCCTGAGGTCTGAGGACACCGCCGTCTACTACTGCGCTAG AGTGGGCGGAGCCTTCCCTATGGACTACTGGGGTCAAGGCAC TACCGTGACCGTGTCTAGC
SEQ ID NO: 808	Heavy chain	QVQLVQSGAEVKKPGSSVKV SCKASGYTFTSYNMHWVRQAPG QGLEWMGDIYPGNGDTSYNQKFKGRVTITADKSTSTVYMELSS LRSEDTAVYYCARVGGAFPM DYWGOGTTVTVSSASTKGPSVFP LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVTVPSSSLGKTYTCNV DHPKPSNTKVDKRV ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTL PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTP PVLDSGDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQ KSLSLSLG
SEQ ID NO: 809	DNA heavy chain	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACC CGGCTCTAGCGTGAAAGTTTCTTGTAAGCTAGTGGCTACAC CTTCACTAGCTATAATATGCACTGGGTTCCGCCAGGCCCCAGG GCAAGGCCTCGAGTGGATGGGCGATATCTACCCCGGGAACGG CGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGTCACTAT CACCGCCGATAAGTCTACTAGCACCGTCTATATGGAAGTGAAG TTCCCTGAGGTCTGAGGACACCGCCGTCTACTACTGCGCTAG AGTGGGCGGAGCCTTCCCTATGGACTACTGGGGTCAAGGCAC TACCGTGACCGTGTCTAGCGCTAGCACTAAGGGCCCCTCCGT GTTCCCCCTGGCACCTTGTAGCCGGAGCACTAGCGAATCCAC CGTGACCGTGTCTGGAACAGCGGAGCCCTGACCTCCGGAGT GCACACCTTCCCCGCTGTGCTGCAGAGCTCCGGCTGTACTC GCTGTCTGTCGGTGGTACGGTGCCTTCATCTAGCCTGGGTACC AAGACCTACACTTGCAACGTGGACCACAAGCCTTCCAACACT AAGGTGGACAAGCGCGTCAATCGAAGTACGGCCACCGTG CCCGCCTTGTCCCGCGCCGGAGTTCCTCGGCGGTCCCTCGGTC TTTCTGTTCCCACCGAAGCCCAAGGACACTTTGATGATTTCCC GCACCCCTGAAGTGACATGCGTGGTCTGTTGACGTGTACAGG AAGATCCGGAGGTGCAGTTCAATTGGTACGTGGATGGCGTGC AGGTGCACAACGCCAAAACCAAGCCGAGGAGGAGCAGTTC AACTCCACTTACCGCGTCTGTGCTCCGTGCTGACGGTGTGCATC AGGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCC AACAAGGGACTTCTAGCTCAATCGAAAAGACCATCTCGAAA GCCAAGGGACAGCCCCGGGAACCCCAAGTGTATACCCTGCCA CCGAGCCAGGAAGAAATGACTAAGAACCAAGTCTCATTGACT TGCCTTGTGAAGGGCTTCTACCCA TCGGATATCGCCGTGGAA TGGGAGTCCAACGGCCAGCCGAAAACA ACTACAAGACCAC CCCTCCGGTGTGGACTCAGACGGATCCTTCTTCTCTACTCG CGGCTGACCGTGGATAAGAGCAGATGGCAGGAGGAAATGT GTTCAAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACTA CACTCAGAAGTCCCTGTCCCTCTCCCTGGGA
SEQ ID NO: 810 (Kabat)	LCDR1	RASESVEYYGTS LMQ
SEQ ID NO: 811 (Kabat)	LCDR2	AASNVES

SEQ ID NO: 812 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 813 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 814 (Chothia)	LCDR2	AAS
SEQ ID NO: 815 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 816	VL	AIQLTQSPSSLSASVGDVVTITCRASESVEYYGTSLMQWYQQKP GKAPKLLIYAASNVEGVPVSRFSGSGSGTDFLTITISLQPEDFATY FCQQSRKDPSTFGGGTKVEIK
SEQ ID NO: 817	DNA VL	GCTATTCAGCTGACTCAGTCACCTAGTAGCCTGAGCGCTAGT GTGGGCGATAGAGTACTATCACCTGTAGAGCTAGTGAATCA GTCGAGTACTACGGCACTAGCCTGATGCAGTGGTATCAGCAG AAGCCCGGGAAAGCCCTAAGCTGCTGATCTACGCCGCCTCT AACGTGGAATCAGGCGTGCCCTCTAGGTTTAGCGGTAGCGGT AGTGGCACCGACTTCACCTGACTATCTCTAGCCTGCAGCCC GAGGACTTCGCTACCTACTTCTGTCAGCAGTCTAGGAAGGAC CCTAGCACCTTCGGCGGAGGCACTAAGGTCGAGATTAAG
SEQ ID NO: 818	Light chain	AIQLTQSPSSLSASVGDVVTITCRASESVEYYGTSLMQWYQQKP GKAPKLLIYAASNVEGVPVSRFSGSGSGTDFLTITISLQPEDFATY FCQQSRKDPSTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYS LSSTLTLISKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 819	DNA light chain	GCTATTCAGCTGACTCAGTCACCTAGTAGCCTGAGCGCTAGT GTGGGCGATAGAGTACTATCACCTGTAGAGCTAGTGAATCA GTCGAGTACTACGGCACTAGCCTGATGCAGTGGTATCAGCAG AAGCCCGGGAAAGCCCTAAGCTGCTGATCTACGCCGCCTCT AACGTGGAATCAGGCGTGCCCTCTAGGTTTAGCGGTAGCGGT AGTGGCACCGACTTCACCTGACTATCTCTAGCCTGCAGCCC GAGGACTTCGCTACCTACTTCTGTCAGCAGTCTAGGAAGGAC CCTAGCACCTTCGGCGGAGGCACTAAGGTCGAGATTAAGCGT ACGGTGGCCGCTCCAGCGTGTTTCATCTTCCCCCAGCGAC GAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTG AACAACTTCTACCCCGGGAGGCCAAGGTGCAGTGAAGGTG GACAACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCAC CGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCA CCCTGACCTGAGCAAGGCCGACTACGAGAAGCATAAGGTGT ACGCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACAGGGGCGAGTGC
ABTIM3-hum03		
SEQ ID NO: 801 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 820 (Kabat)	HCDR2	DIYPGQGDTSYNQKFKG
SEQ ID NO: 803 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 804 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 821 (Chothia)	HCDR2	YPGQGD
SEQ ID NO: 803 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 822	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPG QGLEWIGDIYPGQGDTSYNQKFKGRATMTADKSTSTVYMELSS LRSEDTAVYYCARVGGAFPMDYWGQGLVTVSS
SEQ ID NO: 823	DNA VH	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACC CGGCGCTAGTGTGAAAGTTAGCTGTAAAGCTAGTGGCTATAC TTTCACTTCTTATAATATGCACTGGGTCCGCCAGGCCCCAGGT CAAGGCCTCGAGTGGATCGGCGATATCTACCCCGGTCAAGGC GACACTTCTATAATCAGAAGTTTAAGGGTAGAGCTACTATG ACCGCCGATAAGTCTACTTCTACCGTCTATAATGGAAGTGAAGT CCCTGAGGTCTGAGGACACCGCGTCTACTACTGCGCTAGAG TGGGCGGAGCCTTCCCAATGGACTACTGGGTCAAGGCACCC TGGTCAACCGTGTCTAGC
SEQ ID NO: 824	Heavy chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPG QGLEWIGDIYPGQGDTSYNQKFKGRATMTADKSTSTVYMELSS LRSEDTAVYYCARVGGAFPMDYWGQGLVTVSSASTKGPSVFP LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP

		AVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDHKPSNTKVDKRV ESKYGPPCPPCAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTP PVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMHLEALHNHYTQ KSLSLSLG
SEQ ID NO: 825	DNA heavy chain	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACC CGGCGCTAGTGTGAAAGTTAGCTGTAAAGCTAGTGGCTATAC TTTCACTTCTTATAATATGCACTGGGTCCGCCAGGCCCCAGGT CAAGGCCTCGAGTGGATCGGCGATATCTACCCCGGTCAAGGC GACACTTCTATAATCAGAAGTTTAAGGGTAGAGCTACTATG ACCGCCGATAAGTCTACTTCTACCGTCTATATGGAAGTGAAGT CCCTGAGGTCTGAGGACACCGCCGTCTACTACTGCGCTAGAG TGGGCGGAGCCTTCCCAATGGACTACTGGGTCAAGGCCACC TGGTCAACCGTGTCTAGCGCTAGCACTAAGGGCCCGTCCGTGT TCCCCCTGGCACCTTGTAGCCGGAGCACTAGCGAATCCACCG CTGCCCTCGGCTGCCTGGTCAAGGATTACTTCCCGGAGCCCGT GACCGTGTCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCA CACCTTCCCGCTGTGCTGCAGAGCTCCGGGCTGTACTCGCTG TCGTCCGTGGTACCGGTGCCTTCATCTAGCCTGGGTACCAAG ACCTACACTTGCAACGTGGACCACAAGCCTTCCAACACTAAG GTGGACAAGCGCGTCAATCGAAGTACGGCCACCGTGCCCG CCTTGTCCCGCGCCGAGTTCCTCGGCGGTCCCTCGGTCTTTT TGTTCCACCGAAGCCCAAGGACACTTTGATGATTTCCCGCA CCCCTGAAGTGACATGCGTGGTCTGACGTGGACGTACAGGAAG ATCCGGAGGTGCAGTTCAATTGGTACGTGGATGGCGTCCGAGG TGCACAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAAC TCCACTTACCGCGTCTGTCCGTGCTGACGGTGTGCATCAGG ACTGGCTGAACGGGAAGGAGTACAAGTGC AAAGTGTCCAAC AAGGGACTTCCCTAGCTCAATCGAAAAGACCATCTCGAAAGCC AAGGGACAGCCCCGGGAACCCCAAGTGTATACCCTGCCACCG AGCCAGGAAGAAATGACTAAGAACCAAGTCTCATTGACTTGC CTTGTGAAGGGCTTCTACCCATCGGATATCGCCGTGGAATCC GAGTCCAACGGCCAGCCGAAAACA ACTACAAGCCACCC TCCGGTGTGGACTCAGACGGATCCTTCTTCTACTCGCGG CTGACCGTGGATAAGAGCAGATGGCAGGAGGAAATGTGTT CAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACTACAC TCAGAAGTCCCTGTCCCTCTCCCTGGGA
SEQ ID NO: 810 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 811 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 812 (Kabat)	LCDR3	QQRKDPST
SEQ ID NO: 813 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 814 (Chothia)	LCDR2	AAS
SEQ ID NO: 815 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 826	VL	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQK PQPPKLLIYAASNVESGVPDRFSGSGSGTDFTLTISLQAEDVAV YYCQQRKDPSTFGGGTKVEIK
SEQ ID NO: 827	DNA VL	GATATCGTCTGACTCAGTCACCCGATAGCCTGGCCGTCAGC CTGGGCGAGCGGGCTACTATTAAGTGTAGAGCTAGTGAATCA GTTCGAGTACTACGGCACTAGCCTGATGCAGTGGTATCAGCAG AAGCCCGGTCAACCCCTAAGCTGCTGATCTACGCCGCTCT AACGTGGAATCAGGCGTGCCCGATAGGTTTAGCGGTAGCGGT AGTGGCACCGACTTACCCTGACTATTAGTAGCCTGCAGGCC GAGGACGTGGCCGTCTACTACTGTCAGCAGTCTAGGAAGGAC CCTAGCACCTTCGGCGGAGGCACTAAGGTCGAGATTAAG
SEQ ID NO: 828	Light chain	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQK PQPPKLLIYAASNVESGVPDRFSGSGSGTDFTLTISLQAEDVAV YYCQQRKDPSTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTA

		SVVCLLNFPYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO: 829	DNA light chain	GATATCGTCCTGACTCAGTCACCCGATAGCCTGGCCGTCAGC CTGGGCGAGCGGGCTACTATTAAGTGTAGAGCTAGTGAATCA GTCGAGTACTACGGCACTAGCCTGATGCAGTGGTATCAGCAG AAGCCCGGTCAACCCCTAAGCTGCTGATCTACGCCGCTCT AACGTGGAATCAGGCGTGCCCGATAGGTTTAGCGGTAGCGGT AGTGGCACCGACTTACCCTGACTATTAGTAGCCTGCAGGCC GAGGACGTGGCCGTCTACTACTGTCAGCAGTCTAGGAAGGAC CCTAGCACCTTCGGCGGAGGCACTAAGGTCGAGATTAAGCGT ACGGTGGCCGCTCCAGCGTGTTTCATCTTCCCCCAGCGAC GAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTG ACAACCTTACCCCGGGAGGCCAAGGTGCAGTGAAGGTG GACAACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCAC CGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCA CCCTGACCTGAGCAAGGCCGACTACGAGAAGCATAAGGTGT ACGCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACAGGGGCGAGTGC

Other Exemplary TIM-3 Inhibitors

In one embodiment, the anti-TIM-3 antibody molecule is TSR-022 (AnaptysBio/Tesaro). In one embodiment, the anti-TIM-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of TSR-022. In one embodiment, the anti-TIM-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of APE5137 or APE5121, *e.g.*, as disclosed in Table 8. APE5137, APE5121, and other anti-TIM-3 antibodies are disclosed in WO 2016/161270, incorporated by reference in its entirety.

In one embodiment, the anti-TIM-3 antibody molecule is the antibody clone F38-2E2. In one embodiment, the anti-TIM-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of F38-2E2.

Further known anti-TIM-3 antibodies include those described, *e.g.*, in WO 2016/111947, WO 2016/071448, WO 2016/144803, US 8,552,156, US 8,841,418, and US 9,163,087, incorporated by reference in their entirety.

In one embodiment, the anti-TIM-3 antibody is an antibody that competes for binding with, and/or binds to the same epitope on TIM-3 as, one of the anti-TIM-3 antibodies described herein.

Table 8. Amino acid sequences of other exemplary anti-TIM-3 antibody molecules

APE5137		
SEQ ID NO: 830	VH	EVQLLESGGGLVQPGGSLRLSCAAASGFTFSSYDMSWVRQAPGKGLDWVS TISGGGTYYTYQDSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCASMD YWGQGTITVTVSSA
SEQ ID NO: 831	VL	DIQMTQSPSSLSASVGDRTITCRASQSIRRYLNWYHQKPGKAPKLLIYGAS TLQSGVPSRFSGSGSGTDFLTITISLQPEDFAVYYCQQSHSAPLTFGGGKVE

		IKR
APE5121		
SEQ ID NO: 832	VH	EVQVLES GGGLVQPGGSLRLYCVASGFTFSGSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKKY YVGPADYWGGQGLTVTSSG
SEQ ID NO: 833	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQHKPGQPPK LLIYWASTRESGVPDRFSGSGSGTDFLTITISLQAEDVAVYYCQYYSSPLTF GGGTKIEVK

GITR Agonists

In certain embodiments, the anti-LAG-3 antibody molecule described herein is administered in combination with a GITR agonist. In some embodiments, the GITR agonist is GWN323 (NVS),
 5 BMS-986156, MK-4166 or MK-1248 (Merck), TRX518 (Leap Therapeutics), INCAGN1876 (Incyte/Agenus), AMG 228 (Amgen) or INBRX-110 (Inhibrx).

Exemplary GITR Agonists

In one embodiment, the GITR agonist is an anti-GITR antibody molecule. In one
 10 embodiment, the GITR agonist is an anti-GITR antibody molecule as described in WO 2016/057846, published on April 14, 2016, entitled “Compositions and Methods of Use for Augmented Immune Response and Cancer Therapy,” incorporated by reference in its entirety.

In one embodiment, the anti-GITR antibody molecule comprises at least one, two, three, four,
 15 five or six complementarity determining regions (CDRs) (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 9 (e.g., from the heavy and light chain variable region sequences of MAB7 disclosed in Table 9), or encoded by a nucleotide sequence shown in Table 9. In some embodiments, the CDRs are according to the Kabat definition (e.g., as set out in Table 9). In some embodiments, the CDRs are according to the Chothia definition (e.g., as set out in Table 9). In one embodiment, one or more of the CDRs (or collectively
 20 all of the CDRs) have one, two, three, four, five, six or more changes, e.g., amino acid substitutions (e.g., conservative amino acid substitutions) or deletions, relative to an amino acid sequence shown in Table 9, or encoded by a nucleotide sequence shown in Table 9.

In one embodiment, the anti-GITR antibody molecule comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 909, a VHCDR2 amino
 25 acid sequence of SEQ ID NO: 911, and a VHCDR3 amino acid sequence of SEQ ID NO: 913; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 914, a VLCDR2 amino acid sequence of SEQ ID NO: 916, and a VLCDR3 amino acid sequence of SEQ ID NO: 918, each disclosed in Table 9.

In one embodiment, the anti-GITR antibody molecule comprises a VH comprising the amino
 30 acid sequence of SEQ ID NO: 901, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 901. In one embodiment, the anti-GITR antibody molecule

comprises a VL comprising the amino acid sequence of SEQ ID NO: 902, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 902. In one embodiment, the anti-GITR antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 901 and a VL comprising the amino acid sequence of SEQ ID NO: 902.

5 In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 905, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 905. In one embodiment, the antibody molecule comprises a VL encoded by the nucleotide sequence of SEQ ID NO: 906, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 906. In one embodiment, the antibody molecule comprises a
 10 VH encoded by the nucleotide sequence of SEQ ID NO: 905 and a VL encoded by the nucleotide sequence of SEQ ID NO: 906.

In one embodiment, the anti-GITR antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 903, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 903. In one embodiment, the anti-GITR antibody molecule
 15 comprises a light chain comprising the amino acid sequence of SEQ ID NO: 904, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 904. In one embodiment, the anti-GITR antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 903 and a light chain comprising the amino acid sequence of SEQ ID NO: 904.

20 In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 907, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 907. In one embodiment, the antibody molecule comprises a light chain encoded by the nucleotide sequence of SEQ ID NO: 908, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 908. In one embodiment, the antibody
 25 molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 907 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 908.

The antibody molecules described herein can be made by vectors, host cells, and methods described in WO 2016/057846, incorporated by reference in its entirety.

30 **Table 9:** Amino acid and nucleotide sequences of exemplary anti-GITR antibody molecule

MAB7		
SEQ ID NO: 901	VH	EVQLVESGGGLVQSGGSLRLSCAASGFSLSSYGVDWVRQAP GKGLEWVGVWGGGGTY YASSLMGRFTISRDN SKNTLYLQ MNSLRAEDTAVYYCARHAYGHDGGFAMDYWGQGLTVTS S
SEQ ID NO: 902	VL	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQQRPGQ APRLLIYGASN RATGIPARFSGSGSGTDFLTISRLEPEDFAVY YCGQSYSPFTFGQGTKLEIK

SEQ ID NO: 903	Heavy Chain	EVQLVESGGGLVQSGGSLRLSCAASGFLSSYGVDWVRQAP GKGLEWVGVWGGGGTYASSLMGRFTISRDNKNTLYLQ MNSLRAEDTAVYYCARHAYGHDGGFAMDYWGQGLVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICN VNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKLSLSLSPGK
SEQ ID NO: 904	Light Chain	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQQRPGQ APRLLIYGASNRAIGIPARFSGSGSDFTLTISRLEPEDFAVY YCGQSYSPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC
SEQ ID NO: 905	DNA VH	GAGGTGCAGCTGGTGAATCTGGCGGCGGACTGGTGCAG TCCGGCGGCTCTCTGAGACTGTCTTGCGCTGCCTCCGGCTT CTCCTGTCTCTTACGGCGTGGACTGGGTGCGACAGGCC CCTGGCAAGGCGCTGGAATGGGTGGGAGTGATCTGGGGC GGAGGCGGCACCTACTACGCCTCTTCCCTGATGGGCCGGT TCACCATCTCCCGGACAACCTCAAGAACACCCTGTACCT GCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTAC TACTGCGCCAGACACGCCTACGGCCACGACGGCGGCTTCG CCATGGATTATTGGGGCCAGGGCACCTGGTGACAGTGTC CTCC
SEQ ID NO: 906	DNA VL	GAGATCGTGATGACCCAGTCCCCCGCCACCCTGTCTGTGT CTCCCGGCGAGAGAGCCACCCTGAGCTGCAGAGCCTCCGA GTCCGTGTCCTCCAACGTGGCCTGGTATCAGCAGAGACCT GGTCAGGCCCTCGGCTGCTGATCTACGGCGCCTCTAACC GGGCCACCGGCATCCCTGCCAGATTCTCCGGCTCCGGCAG CGGCACCGACTTCACCCTGACCATCTCCCGGCTGGAACCC GAGGACTTCGCCGTGTACTACTGCGGCCAGTCTACTCAT ACCCCTTACCTTCGGCCAGGGCACCAAGCTGGAAATCAA G

<p>SEQ ID NO: 907</p>	<p>DNA Heavy Chain</p>	<p>GAGGTGCAGCTGGTGAATCTGGCGGCGGACTGGTGCAG TCCGGCGGCTCTCTGAGACTGTCTTGGCGTGCCTCCGGCTT CTCCCTGTCTCTTACGGCGTGGACTGGGTGCGACAGGCC CCTGGCAAGGGCCTGGAATGGGTGGGAGTGATCTGGGGC GGAGGCGGCACCTACTACGCCTCTCCCTGATGGGCCGGT TCACCATCTCCCGGACAACCTCCAAGAACACCCTGTACCT GCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTAC TACTGCGCCAGACACGCCTACGGCCACGACGGCGGCTTCG CCATGGATTATTGGGGCCAGGGCACCCCTGGTGACAGTGTC CTCCGCTAGCACCAAGGGCCCAAGTGTGTTTCCCCTGGCC CCCAGCAGCAAGTCTACTTCCGGCGGAACTGCTGCCCTGG GTTGCCTGGTGAAGGACTACTTCCCCGAGCCCCTGACAGT GTCCTGGAACCTCTGGGGCTCTGACTTCCGCGTGCACACC TCCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGA GCAGCGTGGTGACAGTGCCCTCCAGCTCTCTGGAACCCA GACCTATATCTGCAACGTGAACCACAAGCCAGCAACACC AAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCGACAAG ACCCACACCTGCCCCCCTGCCAGCTCCAGAAGTGTGG GAGGGCCTTCCGTGTTCCCTGTTCCCCCAAGCCCAAGGA CACCTGATGATCAGCAGGACCCCGAGGTGACCTGCGTG GTGGTGGACGTGTCCACGAGGACCCAGAGGTGAAGTTC AACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAG ACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGG GTGGTGTCCGTGCTGACCGTGTGCACCAGGACTGGCTGA ACGGCAAAGAATACAAGTGCAAAGTCTCCAACAAGGCC TGCCAGCCCCAATCGAAAAGACAATCAGCAAGGCCAAGG GCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCAG CCGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACCTG TCTGGTGAAGGGCTTCTACCCAGCGATATCGCCGTGGAG TGGGAGAGCAACGGCCAGCCGAGAACAATAAAGACC ACCCCCCAAGTGTGACAGCGACGGCAGCTTCTTCCCTGT ACAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGG GCAACGTGTTACGTGCAGCGTGATGCACGAGGCCCTGCA CAACCACTACCCCAGAAGTCCCTGAGCCTGAGCCCCGGC AAG</p>
<p>SEQ ID NO: 908</p>	<p>DNA Light Chain</p>	<p>GAGATCGTGATGACCCAGTCCCCCGCCACCCTGTCTGTGT CTCCCGGCGAGAGAGCCACCCTGAGCTGCAGAGCCTCCGA GTCCGTGTCTCCAACGTGGCCTGGTATCAGCAGAGACCT GGTCAGGCCCCTCGGCTGCTGATCTACGGCGCCTCTAACC GGGCCACCGCATCCCTGCCAGATTCTCCGGCTCCGGCAG CGGCACCGACTTCACCCTGACCATCTCCCGGTGGAACCC GAGGACTTCGCCGTGTAATACTGCGGCCAGTCTACTCAT ACCCCTTACCTTCGGCCAGGGCACCAAGCTGGAAATCAA GCGTACGGTGGCCGCTCCCAGCGTGTTCATCTTCCCCC AGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTG TGCCTGCTGAACAATCTACCCCCGGGAGGCCAAGGTGC AGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCC AGGAGAGCGTCACCGAGCAGGACAGCAAGGACTCCACCT ACAGCCTGAGCAGCACCCCTGACCCTGAGCAAGGCCGACT ACGAGAAGCATAAAGGTGTACGCCTGCGAGGTGACCCACC AGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACAGGG GCGAGTGC</p>
<p>SEQ ID NO: 909 (KABAT)</p>	<p>HCDR1</p>	<p>SYGVD</p>
<p>SEQ ID NO: 910 (CHOTHIA)</p>	<p>HCDR1</p>	<p>GFSLSSY</p>
<p>SEQ ID NO: 911 (KABAT)</p>	<p>HCDR2</p>	<p>VIWGGGGTYIYASSLMG</p>
<p>SEQ ID NO: 912 (CHOTHIA)</p>	<p>HCDR2</p>	<p>WGGGG</p>
<p>SEQ ID NO: 913 (KABAT)</p>	<p>HCDR3</p>	<p>HAYGHDGGFAMDY</p>
<p>SEQ ID NO: 913 (CHOTHIA)</p>	<p>HCDR3</p>	<p>HAYGHDGGFAMDY</p>
<p>SEQ ID NO: 914 (KABAT)</p>	<p>LCDR1</p>	<p>RASESVSSNVA</p>
<p>SEQ ID NO: 915 (CHOTHIA)</p>	<p>LCDR1</p>	<p>SESVSSN</p>

SEQ ID NO: 916 (KABAT)	LCDR2	GASNRAT
SEQ ID NO: 917 (CHOTHIA)	LCDR2	GAS
SEQ ID NO: 918 (KABAT)	LCDR3	GQSYSYPFT
SEQ ID NO: 919 (CHOTHIA)	LCDR3	SYSYPF

Other Exemplary GITR Agonists

In one embodiment, the anti-GITR antibody molecule is BMS-986156 (Bristol-Myers Squibb), also known as BMS 986156 or BMS986156. BMS-986156 and other anti-GITR antibodies are disclosed, *e.g.*, in US 9,228,016 and WO 2016/196792, incorporated by reference in their entirety. In one embodiment, the anti-GITR antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of BMS-986156, *e.g.*, as disclosed in Table 10.

In one embodiment, the anti-GITR antibody molecule is MK-4166 or MK-1248 (Merck). MK-4166, MK-1248, and other anti-GITR antibodies are disclosed, *e.g.*, in US 8,709,424, WO 2011/028683, WO 2015/026684, and Mahne *et al. Cancer Res.* 2017; 77(5):1108-1118, incorporated by reference in their entirety. In one embodiment, the anti-GITR antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of MK-4166 or MK-1248.

In one embodiment, the anti-GITR antibody molecule is TRX518 (Leap Therapeutics). TRX518 and other anti-GITR antibodies are disclosed, *e.g.*, in US 7,812,135, US 8,388,967, US 9,028,823, WO 2006/105021, and Ponte J *et al. (2010) Clinical Immunology*; 135:S96, incorporated by reference in their entirety. In one embodiment, the anti-GITR antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of TRX518.

In one embodiment, the anti-GITR antibody molecule is INCAGN1876 (Incyte/Agenus). INCAGN1876 and other anti-GITR antibodies are disclosed, *e.g.*, in US 2015/0368349 and WO 2015/184099, incorporated by reference in their entirety. In one embodiment, the anti-GITR antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of INCAGN1876.

In one embodiment, the anti-GITR antibody molecule is AMG 228 (Amgen). AMG 228 and other anti-GITR antibodies are disclosed, *e.g.*, in US 9,464,139 and WO 2015/031667, incorporated by reference in their entirety. In one embodiment, the anti-GITR antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of AMG 228.

In one embodiment, the anti-GITR antibody molecule is INBRX-110 (Inhibrx). INBRX-110 and other anti-GITR antibodies are disclosed, *e.g.*, in US 2017/0022284 and WO 2017/015623, incorporated by reference in their entirety. In one embodiment, the GITR agonist comprises one or

more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of INBRX-110.

In one embodiment, the GITR agonist (*e.g.*, a fusion protein) is MEDI 1873 (MedImmune), also known as MEDI1873. MEDI 1873 and other GITR agonists are disclosed, *e.g.*, in US 2017/0073386, WO 2017/025610, and Ross *et al. Cancer Res* 2016; 76(14 Suppl): Abstract nr 561, incorporated by reference in their entirety. In one embodiment, the GITR agonist comprises one or more of an IgG Fc domain, a functional multimerization domain, and a receptor binding domain of a glucocorticoid-induced TNF receptor ligand (GITRL) of MEDI 1873.

Further known GITR agonists (*e.g.*, anti-GITR antibodies) include those described, *e.g.*, in WO 2016/054638, incorporated by reference in its entirety.

In one embodiment, the anti-GITR antibody is an antibody that competes for binding with, and/or binds to the same epitope on GITR as, one of the anti-GITR antibodies described herein.

In one embodiment, the GITR agonist is a peptide that activates the GITR signaling pathway. In one embodiment, the GITR agonist is an immunoadhesin binding fragment (*e.g.*, an immunoadhesin binding fragment comprising an extracellular or GITR binding portion of GITRL) fused to a constant region (*e.g.*, an Fc region of an immunoglobulin sequence).

Table 10: Amino acid sequence of other exemplary anti-GITR antibody molecules

BMS-986156		
SEQ ID NO: 920	VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGL EWVAVIWYEGSNKYADSVKGRFTISRDNKNTLYLQMNSLRAED TAVYYCARGGSMVRGDYYYGMDVWGQGTTVTVSS
SEQ ID NO: 921	VL	AIQLTQSPSSLSASVGDRTITCRASQGISSALAWYQKPKAPKLLI YDASSLESQVPSRFSGSGSDFTLTISLQPEDFATYYCQQFNSYPY TFGQGTKLEIK

IL15/IL-15Ra complexes

In certain embodiments, the anti-LAG-3 antibody molecule described herein is administered in combination with an IL-15/IL-15Ra complex. In some embodiments, the IL-15/IL-15Ra complex is chosen from NIZ985 (Novartis), ATL-803 (Altor) or CYP0150 (Cytune).

Exemplary IL-15/IL-15Ra complexes

In one embodiment, the IL-15/IL-15Ra complex comprises human IL-15 complexed with a soluble form of human IL-15Ra. The complex may comprise IL-15 covalently or noncovalently bound to a soluble form of IL-15Ra. In a particular embodiment, the human IL-15 is noncovalently bonded to a soluble form of IL-15Ra. In a particular embodiment, the human IL-15 of the composition comprises an amino acid sequence of SEQ ID NO: 1001 in Table 11 and the soluble form of human IL-15Ra comprises an amino acid sequence of SEQ ID NO:1002 in Table 11, as described in WO 2014/066527, incorporated by reference in its entirety. The molecules described

herein can be made by vectors, host cells, and methods described in WO 2007/084342, incorporated by reference in its entirety.

Table 11. Amino acid and nucleotide sequences of exemplary IL-15/IL-15Ra complexes

NIZ985		
SEQ ID NO: 1001	Human IL-15	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLEL QVISLESGDASIHTVENLILANNSLSSNGNVTESGCKECELEEKNI KEFLQSFVHIVQMFINTS
SEQ ID NO: 1002	Human Soluble IL-15Ra	ITCPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLN KATNV AHWTTPSLKCIRD PALVHQR PAPPSTVTTAGVTPQPESLSPSG KEPAASSPSSNNTAATTAIVPGSQLMPSKSPSTGTTEISSHESHGTPS QTTAKNWELTASASHOPPGVYPQG

5

Other Exemplary IL-15/IL-15Ra Complexes

In one embodiment, the IL-15/IL-15Ra complex is ALT-803, an IL-15/IL-15Ra Fc fusion protein (IL-15N72D:IL-15RaSu/Fc soluble complex). ALT-803 is disclosed in WO 2008/143794, incorporated by reference in its entirety. In one embodiment, the IL-15/IL-15Ra Fc fusion protein

10

comprises the sequences as disclosed in Table 12.

In one embodiment, the IL-15/IL-15Ra complex comprises IL-15 fused to the sushi domain of IL-15Ra (CYP0150, Cytune). The sushi domain of IL-15Ra refers to a domain beginning at the first cysteine residue after the signal peptide of IL-15Ra, and ending at the fourth cysteine residue after said signal peptide. The complex of IL-15 fused to the sushi domain of IL-15Ra is disclosed in

15

Table 12. Amino acid sequences of other exemplary IL-15/IL-15Ra complexes

ALT-803 (Altor)		
SEQ ID NO: 1003	IL-15N72D	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLEL QVISLESGDASIHTVENLILANDSLSSNGNVTESGCKECELEEKNI KEFLQSFVHIVQMFINTS
SEQ ID NO: 1004	IL-15RaSu/ Fc	ITCPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLN KATNV AHWTTPSLKCIREPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK
IL-15/ IL-15Ra sushi domain fusion (Cytune)		
SEQ ID NO:1005	Human IL-15	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLEL QVISLESGDASIHTVENLILANNSLSSNGNVTESGCKECELEEKNI KEFLQSFVHIVQMFINTS Where X is E or K
SEQ ID NO:1006	Human IL- 15Ra sushi and hinge domains	ITCPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLN KATNV AHWTTPSLKCIRD PALVHQR PAPP

Pharmaceutical Compositions, Formulations, and Kits

In another aspect, the disclosure provides compositions, *e.g.*, pharmaceutically acceptable compositions, which include an anti-LAG-3 antibody molecule described herein, formulated together
5 with a pharmaceutically acceptable carrier. As used herein, “pharmaceutically acceptable carrier” includes any and all solvents, dispersion media, isotonic and absorption delaying agents, and the like that are physiologically compatible. The carrier can be suitable for intravenous, intramuscular, subcutaneous, parenteral, rectal, spinal or epidermal administration (*e.g.* by injection or infusion).

The compositions described herein may be in a variety of forms. These include, for example,
10 liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.*, injectable and infusible solutions), dispersions or suspensions, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions. The preferred mode of administration is parenteral (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular). In a preferred embodiment, the
15 antibody is administered by intravenous infusion or injection. In another preferred embodiment, the antibody is administered by intramuscular or subcutaneous injection.

The phrases “parenteral administration” and “administered parenterally” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular,
20 intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion.

Therapeutic compositions typically should be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high antibody concentration. Sterile injectable
25 solutions can be prepared by incorporating the active compound (*e.g.*, antibody or antibody portion) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the
30 preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions
35 can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

An anti-LAG-3 antibody molecule or a composition described herein can be formulated into a formulation (*e.g.*, a dose formulation or dosage form) suitable for administration (*e.g.*, intravenous administration) to a subject as described herein. The formulation described herein can be a liquid formulation, a lyophilized formulation, or a reconstituted formulation.

5 In certain embodiments, the formulation is a liquid formulation. In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein) and a buffering agent.

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-LAG-3 antibody molecule present at a concentration of 25 mg/mL to 250 mg/mL, *e.g.*, 50 mg/mL to 200
10 mg/mL, 60 mg/mL to 180 mg/mL, 70 mg/mL to 150 mg/mL, 80 mg/mL to 120 mg/mL, 90 mg/mL to 110 mg/mL, 50 mg/mL to 150 mg/mL, 50 mg/mL to 100 mg/mL, 150 mg/mL to 200 mg/mL, or 100 mg/mL to 200 mg/mL, *e.g.*, 50 mg/mL, 60 mg/mL, 70 mg/mL, 80 mg/mL, 90 mg/mL, 100 mg/mL, 110 mg/mL, 120 mg/mL, 130 mg/mL, 140 mg/mL, or 150 mg/mL. In certain embodiments, the anti-LAG-3 antibody molecule is present at a concentration of 80 mg/mL to 120 mg/mL, *e.g.*, 100 mg/mL.

15 In some embodiments, the formulation (*e.g.*, liquid formulation) comprises a buffering agent comprising histidine (*e.g.*, a histidine buffer). In certain embodiments, the buffering agent (*e.g.*, histidine buffer) is present at a concentration of 1 mM to 100 mM, *e.g.*, 2 mM to 50 mM, 5 mM to 40 mM, 10 mM to 30 mM, 15 to 25 mM, 5 mM to 40 mM, 5 mM to 30 mM, 5 mM to 20 mM, 5 mM to 10 mM, 40 mM to 50 mM, 30 mM to 50 mM, 20 mM to 50 mM, 10 mM to 50 mM, or 5 mM to 50
20 mM, *e.g.*, 2 mM, 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM, or 50 mM. In some embodiments, the buffering agent (*e.g.*, histidine buffer) is present at a concentration of 15 mM to 25 mM, *e.g.*, 20 mM. In other embodiments, the buffering agent (*e.g.*, a histidine buffer) has a pH of 4 to 7, *e.g.*, 5 to 6, *e.g.*, 5, 5.5, or 6. In some embodiments, the buffering agent (*e.g.*, histidine buffer) has a pH of 5 to 6, *e.g.*, 5.5. In certain embodiments, the buffering agent comprises a
25 histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM) and has a pH of 5 to 6 (*e.g.*, 5.5). In certain embodiments, the buffering agent comprises histidine and histidine-HCl.

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-LAG-3 antibody molecule present at a concentration of 80 to 120 mg/mL, *e.g.*, 100 mg/mL; and a buffering agent that comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM) and has a
30 pH of 5 to 6 (*e.g.*, 5.5).

In some embodiments, the formulation (*e.g.*, liquid formulation) further comprises a carbohydrate. In certain embodiments, the carbohydrate is sucrose. In some embodiments, the carbohydrate (*e.g.*, sucrose) is present at a concentration of 50 mM to 500 mM, *e.g.*, 100 mM to 400
35 mM, 150 mM to 300 mM, 180 mM to 250 mM, 200 mM to 240 mM, 210 mM to 230 mM, 100 mM to 300 mM, 100 mM to 250 mM, 100 mM to 200 mM, 100 mM to 150 mM, 300 mM to 400 mM, 200 mM to 400 mM, or 100 mM to 400 mM, *e.g.*, 100 mM, 150 mM, 180 mM, 200 mM, 220 mM, 250

mM, 300 mM, 350 mM, or 400 mM. In some embodiments, the formulation comprises a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, *e.g.*, 220 mM.

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-LAG-3 antibody molecule present at a concentration of 80 to 120 mg/mL, *e.g.*, 100 mg/mL; a buffering agent that comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM) and has a pH of 5 to 6 (*e.g.*, 5.5); and a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, *e.g.*, 220 mM.

In some embodiments, the formulation (*e.g.*, liquid formulation) further comprises a surfactant. In certain embodiments, the surfactant is polysorbate 20. In some embodiments, the surfactant or polysorbate 20 is present at a concentration of 0.005 % to 0.1% (w/w), *e.g.*, 0.01% to 0.08%, 0.02% to 0.06%, 0.03% to 0.05%, 0.01% to 0.06%, 0.01% to 0.05%, 0.01% to 0.03%, 0.06% to 0.08%, 0.04% to 0.08%, or 0.02% to 0.08% (w/w), *e.g.*, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, or 0.1% (w/w). In some embodiments, the formulation comprises a surfactant or polysorbate 20 present at a concentration of 0.03% to 0.05%, *e.g.*, 0.04% (w/w).

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-LAG-3 antibody molecule present at a concentration of 80 to 120 mg/mL, *e.g.*, 100 mg/mL; a buffering agent that comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM) and has a pH of 5 to 6 (*e.g.*, 5.5); a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, *e.g.*, 220 mM; and a surfactant or polysorbate 20 present at a concentration of 0.03% to 0.05%, *e.g.*, 0.04% (w/w).

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-LAG-3 antibody molecule present at a concentration of 100 mg/mL; a buffering agent that comprises a histidine buffer (*e.g.*, histidine/histidine-HCL) at a concentration of 20 mM) and has a pH of 5.5; a carbohydrate or sucrose present at a concentration of 220 mM; and a surfactant or polysorbate 20 present at a concentration of 0.04% (w/w).

In some embodiments, the liquid formulation is prepared by diluting a formulation comprising an anti-LAG-3 antibody molecule described herein. For example, a drug substance formulation can be diluted with a solution comprising one or more excipients (*e.g.*, concentrated excipients). In some embodiments, the solution comprises one, two, or all of histidine, sucrose, or polysorbate 20. In certain embodiments, the solution comprises the same excipient(s) as the drug substance formulation. Exemplary excipients include, but are not limited to, an amino acid (*e.g.*, histidine), a carbohydrate (*e.g.*, sucrose), or a surfactant (*e.g.*, polysorbate 20). In certain embodiments, the liquid formulation is not a reconstituted lyophilized formulation. In other embodiments, the liquid formulation is a reconstituted lyophilized formulation. In some embodiments, the formulation is stored as a liquid. In other embodiments, the formulation is prepared as a liquid and then is dried, *e.g.*, by lyophilization or spray-drying, prior to storage.

In certain embodiments, 0.5 mL to 10 mL (*e.g.*, 0.5 mL to 8 mL, 1 mL to 6 mL, or 2 mL to 5 mL, *e.g.*, 1 mL, 1.2 mL, 1.5 mL, 2 mL, 3 mL, 4 mL, 4.5 mL, or 5 mL) of the liquid formulation is filled per container (*e.g.*, vial). In other embodiments, the liquid formulation is filled into a container (*e.g.*, vial) such that an extractable volume of at least 1 mL (*e.g.*, at least 1.2 mL, at least 1.5 mL, at least 2 mL, at least 3 mL, at least 4 mL, or at least 5 mL) of the liquid formulation can be withdrawn per container (*e.g.*, vial). In certain embodiments, the liquid formulation is extracted from the container (*e.g.*, vial) without diluting at a clinical site. In certain embodiments, the liquid formulation is diluted from a drug substance formulation and extracted from the container (*e.g.*, vial) at a clinical site. In certain embodiments, the formulation (*e.g.*, liquid formulation) is injected to an infusion bag, *e.g.*, within 1 hour (*e.g.*, within 45 minutes, 30 minutes, or 15 minutes) before the infusion starts to the patient.

A formulation described herein can be stored in a container. The container used for any of the formulations described herein can include, *e.g.*, a vial, and optionally, a stopper, a cap, or both. In certain embodiments, the vial is a glass vial, *e.g.*, a 6R white glass vial. In other embodiments, the stopper is a rubber stopper, *e.g.*, a grey rubber stopper. In other embodiments, the cap is a flip-off cap, *e.g.*, an aluminum flip-off cap. In some embodiments, the container comprises a 6R white glass vial, a grey rubber stopper, and an aluminum flip-off cap. In some embodiments, the container (*e.g.*, vial) is for a single-use container. In certain embodiments, 25 mg/mL to 250 mg/mL, *e.g.*, 50 mg/mL to 200 mg/mL, 60 mg/mL to 180 mg/mL, 70 mg/mL to 150 mg/mL, 80 mg/mL to 120 mg/mL, 90 mg/mL to 110 mg/mL, 50 mg/mL to 150 mg/mL, 50 mg/mL to 100 mg/mL, 150 mg/mL to 200 mg/mL, or 100 mg/mL to 200 mg/mL, *e.g.*, 50 mg/mL, 60 mg/mL, 70 mg/mL, 80 mg/mL, 90 mg/mL, 100 mg/mL, 110 mg/mL, 120 mg/mL, 130 mg/mL, 140 mg/mL, or 150 mg/mL, of the anti-LAG-3 antibody molecule, is present in the container (*e.g.*, vial).

In some embodiments, the formulation is a lyophilized formulation. In certain embodiments, the lyophilized formulation is lyophilized or dried from a liquid formulation comprising an anti-LAG-3 antibody molecule described herein. For example, 1 to 5 mL, *e.g.*, 1 to 2 mL, of a liquid formulation can be filled per container (*e.g.*, vial) and lyophilized.

In some embodiments, the formulation is a reconstituted formulation. In certain embodiments, the reconstituted formulation is reconstituted from a lyophilized formulation comprising an anti-LAG-3 antibody molecule described herein. For example, a reconstituted formulation can be prepared by dissolving a lyophilized formulation in a diluent such that the protein is dispersed in the reconstituted formulation. In some embodiments, the lyophilized formulation is reconstituted with 1 mL to 5 mL, *e.g.*, 1 mL to 2 mL, *e.g.*, 1.2 mL, of water or buffer for injection. In certain embodiments, the lyophilized formulation is reconstituted with 1 mL to 2 mL of water for injection, *e.g.*, at a clinical site.

In some embodiments, the reconstituted formulation comprises an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein) and a buffering agent.

In some embodiments, the reconstituted formulation comprises an anti-LAG-3 antibody molecule present at a concentration of 25 mg/mL to 250 mg/mL, *e.g.*, 50 mg/mL to 200 mg/mL, 60 mg/mL to 180 mg/mL, 70 mg/mL to 150 mg/mL, 80 mg/mL to 120 mg/mL, 90 mg/mL to 110 mg/mL, 50 mg/mL to 150 mg/mL, 50 mg/mL to 100 mg/mL, 150 mg/mL to 200 mg/mL, or 100 mg/mL to 200 mg/mL, *e.g.*, 50 mg/mL, 60 mg/mL, 70 mg/mL, 80 mg/mL, 90 mg/mL, 100 mg/mL, 110 mg/mL, 120 mg/mL, 130 mg/mL, 140 mg/mL, or 150 mg/mL. In certain embodiments, the anti-LAG-3 antibody molecule is present at a concentration of 80 mg/mL to 120 mg/mL, *e.g.*, 100 mg/mL.

In some embodiments, the reconstituted formulation comprises a buffering agent comprising histidine (*e.g.*, a histidine buffer). In certain embodiments, the buffering agent (*e.g.*, histidine buffer) is present at a concentration of 1 mM to 100 mM, *e.g.*, 2 mM to 50 mM, 5 mM to 40 mM, 10 mM to 30 mM, 15 to 25 mM, 5 mM to 40 mM, 5 mM to 30 mM, 5 mM to 20 mM, 5 mM to 10 mM, 40 mM to 50 mM, 30 mM to 50 mM, 20 mM to 50 mM, 10 mM to 50 mM, or 5 mM to 50 mM, *e.g.*, 2 mM, 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM, or 50 mM. In some embodiments, the buffering agent (*e.g.*, histidine buffer) is present at a concentration of 15 mM to 25 mM, *e.g.*, 20 mM. In other embodiments, the buffering agent (*e.g.*, a histidine buffer) has a pH of 4 to 7, *e.g.*, 5 to 6, *e.g.*, 5, 5.5, or 6. In some embodiments, the buffering agent (*e.g.*, histidine buffer) has a pH of 5 to 6, *e.g.*, 5.5. In certain embodiments, the buffering agent comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM) and has a pH of 5 to 6 (*e.g.*, 5.5). In certain embodiments, the buffering agent comprises histidine and histidine-HCl.

In some embodiments, the reconstituted formulation comprises an anti-LAG-3 antibody molecule present at a concentration of 80 to 120 mg/mL, *e.g.*, 100 mg/mL; and a buffering agent that comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM) and has a pH of 5 to 6 (*e.g.*, 5.5).

In some embodiments, the reconstituted formulation further comprises a carbohydrate. In certain embodiments, the carbohydrate is sucrose. In some embodiments, the carbohydrate (*e.g.*, sucrose) is present at a concentration of 50 mM to 500 mM, *e.g.*, 100 mM to 400 mM, 150 mM to 300 mM, 180 mM to 250 mM, 200 mM to 240 mM, 210 mM to 230 mM, 100 mM to 300 mM, 100 mM to 250 mM, 100 mM to 200 mM, 100 mM to 150 mM, 300 mM to 400 mM, 200 mM to 400 mM, or 100 mM to 400 mM, *e.g.*, 100 mM, 150 mM, 180 mM, 200 mM, 220 mM, 250 mM, 300 mM, 350 mM, or 400 mM. In some embodiments, the formulation comprises a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, *e.g.*, 220 mM.

In some embodiments, the reconstituted formulation comprises an anti-LAG-3 antibody molecule present at a concentration of 80 to 120 mg/mL, *e.g.*, 100 mg/mL; a buffering agent that comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM) and has a pH of 5 to 6 (*e.g.*, 5.5); and a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, *e.g.*, 220 mM.

In some embodiments, the reconstituted formulation further comprises a surfactant. In certain embodiments, the surfactant is polysorbate 20. In some embodiments, the surfactant or polysorbate 20 is present at a concentration of 0.005 % to 0.1% (w/w), *e.g.*, 0.01% to 0.08%, 0.02% to 0.06%, 0.03% to 0.05%, 0.01% to 0.06%, 0.01% to 0.05%, 0.01% to 0.03%, 0.06% to 0.08%, 0.04% to 5 0.08%, or 0.02% to 0.08% (w/w), *e.g.*, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, or 0.1% (w/w). In some embodiments, the formulation comprises a surfactant or polysorbate 20 present at a concentration of 0.03% to 0.05%, *e.g.*, 0.04% (w/w).

In some embodiments, the reconstituted formulation comprises an anti-LAG-3 antibody molecule present at a concentration of 80 to 120 mg/mL, *e.g.*, 100 mg/mL; a buffering agent that 10 comprises a histidine buffer at a concentration of 15 mM to 25 mM (*e.g.*, 20 mM) and has a pH of 5 to 6 (*e.g.*, 5.5); a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, *e.g.*, 220 mM; and a surfactant or polysorbate 20 present at a concentration of 0.03% to 0.05%, *e.g.*, 0.04% (w/w).

In some embodiments, the reconstituted formulation comprises an anti-LAG-3 antibody 15 molecule present at a concentration of 100 mg/mL; a buffering agent that comprises a histidine buffer (*e.g.*, histidine/histidine-HCL) at a concentration of 20 mM and has a pH of 5.5; a carbohydrate or sucrose present at a concentration of 220 mM; and a surfactant or polysorbate 20 present at a concentration of 0.04% (w/w).

In some embodiments, the formulation is reconstituted such that an extractable volume of at 20 least 1 mL (*e.g.*, at least 1.2 mL, 1.5 mL, 2 mL, 2.5 mL, or 3 mL) of the reconstituted formulation can be withdrawn from the container (*e.g.*, vial) containing the reconstituted formulation. In certain embodiments, the formulation is reconstituted and/or extracted from the container (*e.g.*, vial) at a clinical site. In certain embodiments, the formulation (*e.g.*, reconstituted formulation) is injected to an infusion bag, *e.g.*, within 1 hour (*e.g.*, within 45 minutes, 30 minutes, or 15 minutes) before the 25 infusion starts to the patient.

Other exemplary buffering agents that can be used in the formulation described herein include, but are not limited to, an arginine buffer, a citrate buffer, or a phosphate buffer. Other exemplary carbohydrates that can be used in the formulation described herein include, but are not limited to, 30 trehalose, mannitol, sorbitol, or a combination thereof. The formulation described herein may also contain a tonicity agent, *e.g.*, sodium chloride, and/or a stabilizing agent, *e.g.*, an amino acid (*e.g.*, glycine, arginine, methionine, or a combination thereof).

The antibody molecules can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred route/mode of administration is intravenous injection or infusion. For example, the antibody molecules can be administered by intravenous 35 infusion at a rate of more than 20 mg/min, *e.g.*, 20-40 mg/min, and typically greater than or equal to 40 mg/min to reach a dose of about 35 to 440 mg/m², typically about 70 to 310 mg/m², and more typically, about 110 to 130 mg/m². In embodiments, the antibody molecules can be administered by

intravenous infusion at a rate of less than 10mg/min; preferably less than or equal to 5 mg/min to reach a dose of about 1 to 100 mg/m², preferably about 5 to 50 mg/m², about 7 to 25 mg/m² and more preferably, about 10 mg/m². As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. In certain embodiments, the active
5 compound may be prepared with a carrier that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. *See,*
10 *e.g., Sustained and Controlled Release Drug Delivery Systems*, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

In certain embodiments, an antibody molecule can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The compound (and other ingredients, if desired) may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated
15 directly into the subject's diet. For oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. To administer a compound of the invention by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. Therapeutic compositions can
20 also be administered with medical devices known in the art.

Dosage regimens are adjusted to provide the optimum desired response (*e.g.*, a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral
25 compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique
30 characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an antibody molecule is 50 mg to 1500 mg, typically 80 mg to 1200 mg. In certain embodiments,
35 the anti-LAG-3 antibody molecule is administered by injection (*e.g.*, subcutaneously or intravenously) at a dose (*e.g.*, a flat dose) of about 60 mg to about 100 mg (*e.g.*, about 80 mg), about 200 mg to about 300 mg (*e.g.*, about 240 mg), or about 1000 mg to about 1500 mg (*e.g.*, about 1200 mg). The dosing

schedule (*e.g.*, flat dosing schedule) can vary from *e.g.*, once a week to once every 2, 3, 4, 5, or 6 weeks. In one embodiment, the anti-LAG-3 antibody molecule is administered at a dose from about 60 mg to 100 mg (*e.g.*, about 80 mg) once every two weeks or once every four weeks. In one embodiment, the anti-LAG-3 antibody molecule is administered at a dose from about 200 mg to about 300 mg (*e.g.*, about 240 mg) once every two weeks or once every four weeks. In one embodiment, the anti-LAG-3 antibody molecule is administered at a dose from about 1000 mg to about 1500 mg (*e.g.*, about 1200 mg) once every two weeks or once every four weeks. In one embodiment, the anti-LAG-3 antibody molecule is administered at a dose about 80 mg once every four weeks. In one embodiment, the anti-LAG-3 antibody molecule is administered at a dose about 240 mg once every four weeks. In one embodiment, the anti-LAG-3 antibody molecule is administered at a dose about 1200 mg once every four weeks. While not wishing to be bound by theory, in some embodiments, flat or fixed dosing can be beneficial to patients, for example, to save drug supply and to reduce pharmacy errors.

The antibody molecule can be administered by intravenous infusion at a rate of more than 20 mg/min, *e.g.*, 20-40 mg/min, and typically greater than or equal to 40 mg/min to reach a dose of about 35 to 440 mg/m², typically about 70 to 310 mg/m², and more typically, about 110 to 130 mg/m². In embodiments, the infusion rate of about 110 to 130 mg/m² achieves a level of about 3 mg/kg. In other embodiments, the antibody molecule can be administered by intravenous infusion at a rate of less than 10 mg/min, *e.g.*, less than or equal to 5 mg/min to reach a dose of about 1 to 100 mg/m², *e.g.*, about 5 to 50 mg/m², about 7 to 25 mg/m², or, about 10 mg/m². In some embodiments, the antibody is infused over a period of about 30 min. It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition.

The pharmaceutical compositions of the invention may include a "therapeutically effective amount" or a "prophylactically effective amount" of an antibody or antibody portion of the invention. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the modified antibody or antibody fragment may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibody portion to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the modified antibody or antibody fragment is outweighed by the therapeutically beneficial effects. A "therapeutically effective dosage" preferably inhibits a measurable parameter, *e.g.*, tumor growth rate by at least about 20%, more preferably by at least about 40%, even more preferably by at least about 60%, and still more preferably by at least about 80%

relative to untreated subjects. The ability of a compound to inhibit a measurable parameter, *e.g.*, cancer, can be evaluated in an animal model system predictive of efficacy in human tumors. Alternatively, this property of a composition can be evaluated by examining the ability of the compound to inhibit, such inhibition *in vitro* by assays known to the skilled practitioner.

5 A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

Also within the scope of the disclosure is a kit comprising an anti-LAG-3 antibody molecule,
10 composition, or formulation described herein. The kit can include one or more other elements including: instructions for use (*e.g.*, in accordance a dosage regimen described herein); other reagents, *e.g.*, a label, a therapeutic agent, or an agent useful for chelating, or otherwise coupling, an antibody to a label or therapeutic agent, or a radioprotective composition; devices or other materials for preparing the antibody for administration; pharmaceutically acceptable carriers; and devices or other
15 materials for administration to a subject.

Use of Anti-LAG-3 Antibody Molecules

The anti-LAG-3 antibody molecules described herein can be used to modify an immune response in a subject. In some embodiments, the immune response is enhanced, stimulated or up-
20 regulated. In certain embodiments, the immune response is inhibited, reduced, or down-regulated. For example, these antibody molecules can be administered to cells in culture, *e.g. in vitro* or *ex vivo*, or in a subject, *e.g., in vivo*, to treat, prevent, and/or diagnose a variety of disorders, such as cancers, immune disorders, and infectious diseases.

As used herein, the term "subject" is intended to include human and non-human animals. In
25 some embodiments, the subject is a human subject, *e.g.*, a human patient having a disorder or condition characterized by abnormal LAG-3 functioning. Generally, the subject has at least some LAG-3 protein, including the LAG-3 epitope that is bound by the antibody molecule, *e.g.*, a high enough level of the protein and epitope to support antibody binding to LAG-3. The term "non-human animals" includes mammals and non-mammals, such as non-human primates. In some embodiments,
30 the subject is a human. In some embodiments, the subject is a human patient in need of enhancement of an immune response. The methods and compositions described herein are suitable for treating human patients having a disorder that can be treated by modulating (*e.g.*, augmenting or inhibiting) an immune response. In certain embodiments, the patient has or is at risk of having a disorder described herein, *e.g.*, a breast cancer, *e.g.*, a triple negative breast cancer (TNBC). In certain embodiments, a
35 patient with TNBC is more immunogenic than other breast cancer subtypes, has higher expression of PD-L1, and/or has increased infiltration by tumor-infiltrating lymphocytes (TILs) (Loi *et al.* (2014)

Ann Oncol; 25: 1544-50; Mittendorf *et al.* (2014) Cancer Immunol Res; 2:361-70). In one embodiment, the patient does not exhibit liver metastasis.

Combination immunotherapy approaches suggest that synergistic blockade of co-inhibitory receptors demonstrates greater antitumor activity than the single agent (Wolchok *et al.* (2013) New Engl J Med; 369: 122-33). LAG-3 is a co-inhibitory receptor that may cooperate with PD-1 to inhibit immune responses (Anderson *et al.* (2016) Immunity; 44: 989-1004). The combined inhibition of PD-1 and LAG-3 checkpoints synergistically enhances antitumor responses over inhibition of either checkpoint alone (Woo *et al.* (2012) Cancer Res; 72: 917-27).

Also, there is increasing evidence that cytotoxic agents influence the tumor-host environment to be more favorable to the immune response, and consequently, the combination of immunotherapy with cytotoxic agents may synergize to increase therapeutic efficacy (Zitvogel *et al.* (2013) Immunity; 39: 74-88). Importantly, chemotherapy can induce immunogenic cell death, which facilitates efficient antigen presentation, and has been shown to trigger potent T cell responses in preclinical models (Kroemer *et al.* (2013) Immunol; 31:51-72; Pfirschke *et al.* (2016) Immunity; 44:343-54; Lu *et al.* (2017) Biomedical Res; 28:828-34). Without wishing to be bound by theory, it is believed that in some embodiments, chemotherapy (*e.g.*, a platinum agent), will create an environment early during T cell activation (*e.g.*, increased antigen concentration and/or antigen availability) that will favor the arising of LAG-3+CD8+ T cells, which will require only LAG3 inhibition to differentiate into tumor antigen specific effector cells. While the main mechanism of action of platinum agents is believed to be the induction of cancer cell apoptosis as a response of their covalent binding to DNA, recent studies have indicated that cellular molecules other than DNA may potentially act as targets, and that part of the antitumor effects of platinum drugs occurs through modulation of the immune system (Hato *et al.* (2014) Clin Cancer Res; 20: 2831-7). These immunogenic effects include modulation of STAT signaling (Lesterhuis *et al.* (2011) J Clin Invest; 121:3100-08); induction of an immunogenic type of cancer cell death through exposure of calreticulin and release of ATP and high-mobility group protein box-1 (HMGB-1) (Kroemer *et al.* (2013) Immunol; 31:51-72; Tesniere *et al.* (2010) Oncogene; 29: 482-91); and enhancement of the effector immune response through modulation of programmed death receptor 1-ligand and mannose-6-phosphate receptor expression (Liu *et al.* (2010) Br J Cancer; 102:115-23). Without wishing to be bound by theory, it is believed that in some embodiments, combining platinum with immune checkpoint blockade will enhance the immunotherapy, in that platinum can provide immunogenic cell death, tumor cell sensitization to CTL lysis, and downregulation of PD-Ls.

In some embodiments, the subject has not been treated with a therapeutic agent, procedure, or modality prior to receiving the anti-LAG-3 antibody molecule. In other embodiments, the subject has been treated with a therapeutic agent, procedure, or modality prior to receiving the anti-LAG-3 antibody molecule.

In certain embodiments, the subject has not been treated with an anti-LAG-3 therapy prior to receiving the anti-LAG-3 antibody molecule. In other embodiments, the subject has been treated with an anti-LAG-3 therapy prior to receiving the anti-LAG-3 antibody molecule.

In certain embodiments, the subject has not been treated with a PD-1/PD-L1 therapy prior to receiving the anti-LAG-3 antibody molecule. In other embodiments, the subject has been treated with a PD-1/PD-L1 therapy prior to receiving the anti-LAG-3 antibody molecule.

In certain embodiments, the subject has not been treated with a chemotherapeutic agent (*e.g.*, a platinum agent (*e.g.*, carboplatin, cisplatin, oxaliplatin, or tetraplatin) or a nucleotide analog or precursor analog (*e.g.*, capecitabine)) prior to receiving the anti-LAG-3 antibody molecule. In other embodiments, the subject has been treated with a chemotherapeutic agent (*e.g.*, a platinum agent (*e.g.*, carboplatin, cisplatin, oxaliplatin, or tetraplatin) or a nucleotide analog or precursor analog (*e.g.*, capecitabine)) prior to receiving the anti-LAG-3 antibody molecule.

In certain embodiments, the subject has been identified as having LAG-3 expression in tumor infiltrating lymphocytes. In other embodiments, the subject does not have detectable level of LAG-3 expression in tumor infiltrating lymphocytes.

Methods of Treating Cancer

In one aspect, the disclosure relates to treatment of a subject *in vivo* using an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein), or a composition or formulation comprising an anti-LAG-3 antibody molecule (*e.g.*, a composition or formulation described herein) such that growth of cancerous tumors is inhibited or reduced.

In certain embodiments, the anti-LAG-3 antibody molecule is administered in an amount effective to treat a cancer or a metastatic lesion thereof. In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose from about 100 mg to about 2000 mg once every two week, once every three weeks, or once every four weeks. For example, the anti-LAG-3 antibody molecule can be administered at a dose from about 200 mg to about 1000 mg, about 300 mg to about 900 mg, about 200 mg to about 600 mg, about 300 mg to about 500 mg, about 600 to about 1000 mg, about 700 mg to about 900 mg, or about 400 mg to about 800 mg, once every three weeks or once every four weeks. In one embodiment, the anti-LAG-3 antibody molecule is administered at a dose from about 300 mg to 500 mg (*e.g.*, about 400 mg) once every three weeks. In one embodiment, the anti-LAG-3 antibody molecule is administered at a dose from about 700 mg to about 900 mg (*e.g.*, about 800 mg) once every four weeks. In one embodiment, the anti-LAG-3 antibody molecule is administered at a dose from about 500 mg to about 700 mg (*e.g.*, about 533 mg or about 600 mg) once every four weeks.

An anti-LAG-3 antibody, or a composition or formulation comprising an anti-LAG-3 antibody molecule, may be used alone to inhibit the growth of cancerous tumors. Alternatively, an

anti-LAG-3 antibody, or a composition or formulation comprising an anti-LAG-3 antibody molecule, may be used in combination with one or more of: a standard of care treatment (*e.g.*, for cancers or infectious disorders), another antibody or antigen-binding fragment thereof, an immunomodulator (*e.g.*, an activator of a costimulatory molecule or an inhibitor of an inhibitory molecule); a vaccine, *e.g.*, a therapeutic cancer vaccine; or other forms of cellular immunotherapy, as described herein.

Accordingly, in one embodiment, the disclosure provides a method of inhibiting growth of tumor cells in a subject, comprising administering to the subject a therapeutically effective amount of an anti-LAG-3 antibody molecule described herein, *e.g.*, in accordance with a dosage regimen described herein. In an embodiment, the anti-LAG-3 antibody molecule is administered in the form of a composition or formulation described herein.

In one embodiment, the method is suitable for the treatment of cancer *in vivo*. To achieve antigen-specific enhancement of immunity, the anti-LAG-3 antibody molecule can be administered together with an antigen of interest. When an anti-LAG-3 antibody is administered in combination with one or more agents, the combination can be administered in either order or simultaneously.

In another aspect, a method of treating a subject, *e.g.*, reducing or ameliorating, a hyperproliferative condition or disorder (*e.g.*, a cancer), *e.g.*, solid tumor, a hematological cancer, soft tissue tumor, or a metastatic lesion, in a subject is provided. The method includes administering to the subject an anti-LAG-3 antibody molecule, or a composition or formulation comprising an anti-LAG-3 antibody molecule, as disclosed herein, in accordance with a dosage regimen disclosed herein.

As used herein, the term “cancer” is meant to include all types of cancerous growths or oncogenic processes, metastatic tissues or malignantly transformed cells, tissues, or organs, irrespective of histopathological type or stage of invasiveness. Examples of cancerous disorders include, but are not limited to, solid tumors, hematological cancers, soft tissue tumors, and metastatic lesions. Examples of solid tumors include malignancies, *e.g.*, sarcomas, and carcinomas (including adenocarcinomas and squamous cell carcinomas), of the various organ systems, such as those affecting liver, lung, breast, lymphoid, gastrointestinal (*e.g.*, colon), genitourinary tract (*e.g.*, renal, urothelial, bladder cells), prostate, CNS (*e.g.*, brain, neural or glial cells), skin, pancreas, and pharynx. Adenocarcinomas include malignancies such as most colon cancers, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine and cancer of the esophagus. Squamous cell carcinomas include malignancies, *e.g.*, in the lung, esophagus, skin, head and neck region, oral cavity, anus, and cervix. In one embodiment, the cancer is a melanoma, *e.g.*, an advanced stage melanoma. Metastatic lesions of the aforementioned cancers can also be treated or prevented using the methods and compositions of the invention.

Exemplary cancers whose growth can be inhibited using the antibodies molecules, compositions, or formulations, as disclosed herein, include cancers typically responsive to immunotherapy. Non-limiting examples of typical cancers for treatment include melanoma (*e.g.*, metastatic malignant melanoma), renal cancer (*e.g.*, clear cell carcinoma), prostate cancer (*e.g.*,

hormone refractory prostate adenocarcinoma), breast cancer, colon cancer and lung cancer (*e.g.*, non-small cell lung cancer). Additionally, refractory or recurrent malignancies can be treated using the antibody molecules described herein.

Examples of other cancers that can be treated include, but are not limited to, basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and CNS cancer; primary CNS lymphoma; neoplasm of the central nervous system (CNS); breast cancer; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer; intra-epithelial neoplasm; kidney cancer; larynx cancer; leukemia (including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic or acute leukemia); liver cancer; lung cancer (*e.g.*, small cell and non-small cell); lymphoma including Hodgkin's and non-Hodgkin's lymphoma; lymphocytic lymphoma; melanoma, *e.g.*, cutaneous or intraocular malignant melanoma; myeloma; neuroblastoma; oral cavity cancer (*e.g.*, lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; sarcoma; skin cancer; stomach cancer; testicular cancer; thyroid cancer; uterine cancer; cancer of the urinary system, hepatocarcinoma, cancer of the anal region, carcinoma of the fallopian tubes, carcinoma of the vagina, carcinoma of the vulva, cancer of the small intestine, cancer of the endocrine system, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, as well as other carcinomas and sarcomas, and combinations of said cancers.

In some embodiments, the disorder is a cancer, *e.g.*, a cancer described herein. In certain embodiments, the cancer is a solid tumor. In some embodiments, the cancer is brain tumor, *e.g.*, a glioblastoma, a gliosarcoma, or a recurrent brain tumor. In some embodiments, the cancer is a pancreatic cancer, *e.g.*, an advanced pancreatic cancer. In some embodiments, the cancer is a skin cancer, *e.g.*, a melanoma (*e.g.*, a stage II-IV melanoma, an HLA-A2 positive melanoma, an unresectable melanoma, or a metastatic melanoma), or a Merkel cell carcinoma. In some embodiments, the cancer is a renal cancer, *e.g.*, a renal cell carcinoma (RCC) (*e.g.*, a metastatic renal cell carcinoma) or a treatment-naïve metastatic kidney cancer. In some embodiments, the cancer is a breast cancer, *e.g.*, a metastatic breast carcinoma or a stage IV breast carcinoma, *e.g.*, a triple negative breast cancer (TNBC). In some embodiments, the cancer is a virus-associated cancer. In some embodiments, the cancer is an anal canal cancer (*e.g.*, a squamous cell carcinoma of the anal canal). In some embodiments, the cancer is a cervical cancer (*e.g.*, a squamous cell carcinoma of the cervix). In some embodiments, the cancer is a gastric cancer (*e.g.*, an Epstein Barr Virus (EBV) positive gastric cancer, or a gastric or gastro-esophageal junction carcinoma). In some embodiments, the

cancer is a head and neck cancer (*e.g.*, an HPV positive and negative squamous cell cancer of the head and neck (SCCHN)). In some embodiments, the cancer is a nasopharyngeal cancer (NPC). In some embodiments, the cancer is a penile cancer (*e.g.*, a squamous cell carcinoma of the penile). In some embodiments, the cancer is a vaginal or vulvar cancer (*e.g.*, a squamous cell carcinoma of the vagina or vulva). In some embodiments, the cancer is a colorectal cancer, *e.g.*, a relapsed colorectal cancer or a metastatic colorectal cancer, *e.g.*, a microsatellite unstable colorectal cancer, a microsatellite stable colorectal cancer, a mismatch repair proficient colorectal cancer, or a mismatch repair deficient colorectal cancer. In some embodiments, the cancer is a lung cancer, *e.g.*, a non-small cell lung cancer (NSCLC). In certain embodiments, the cancer is a hematological cancer. In some
10 embodiments, the cancer is a leukemia. In some embodiments, the cancer is a lymphoma, *e.g.*, a Hodgkin lymphoma (HL) or a diffuse large B cell lymphoma (DLBCL) (*e.g.*, a relapsed or refractory HL or DLBCL). In some embodiments, the cancer is a myeloma. In some embodiments, the cancer is an MSI-high cancer. In some embodiments, the cancer is a metastatic cancer. In other
15 embodiments, the cancer is an advanced cancer. In other embodiments, the cancer is a relapsed or refractory cancer.

In one embodiment, the cancer is a Merkel cell carcinoma. In other embodiments, the cancer is a melanoma. In other embodiments, the cancer is a breast cancer, *e.g.*, a triple negative breast cancer (TNBC) or a HER2-negative breast cancer. In other embodiments, the cancer is a renal cell carcinoma (*e.g.*, a clear cell renal cell carcinoma (CCRCC) or a non-clear cell renal cell carcinoma
20 (nccRCC)). In other embodiments, the cancer is a thyroid cancer, *e.g.*, an anaplastic thyroid carcinoma (ATC). In other embodiments, the cancer is a neuroendocrine tumor (NET), *e.g.*, an atypical pulmonary carcinoid tumor or an NET in pancreas, gastrointestinal (GI) tract, or lung. In certain embodiments, the cancer is a non-small cell lung cancer (NSCLC) (*e.g.*, a squamous NSCLC or a non-squamous NSCLC). In certain embodiments, the cancer is a fallopian tube cancer. In certain
25 embodiments, the cancer is a microsatellite instability-high colorectal cancer (MSI-high CRC) or a microsatellite stable colorectal cancer (MSS CRC).

In other embodiments, the cancer is a hematological malignancy or cancer including but is not limited to a leukemia or a lymphoma. For example, an anti-LAG-3 antibody molecule can be used to treat cancers and malignancies including, but not limited to, *e.g.*, an acute leukemia, *e.g.*, B-cell acute
30 lymphoid leukemia (“BALL”), T-cell acute lymphoid leukemia (“TALL”), acute lymphoid leukemia (ALL); a chronic leukemia, *e.g.*, chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); an additional hematologic cancer or hematologic condition, *e.g.*, B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt’s lymphoma, diffuse large B cell lymphoma, Follicular lymphoma, Hairy cell leukemia, small cell- or a large cell-follicular
35 lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin’s lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenström

macroglobulinemia, and “preleukemia” which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells, and the like.

As used herein, the term “subject” is intended to include human and non-human animals. In some embodiments, the subject is a human subject, *e.g.*, a human patient having a disorder or
5 condition characterized by abnormal LAG-3 functioning. Generally, the subject has at least some LAG-3 protein, including the LAG-3 epitope that is bound by the antibody molecule, *e.g.*, a high enough level of the protein and epitope to support antibody binding to LAG-3. The term “non-human animals” includes mammals and non-mammals, such as non-human primates. In some embodiments, the subject is a human. In some embodiments, the subject is a human patient in need of enhancement
10 of an immune response. The methods and compositions described herein are suitable for treating human patients having a disorder that can be treated by modulating (*e.g.*, augmenting or inhibiting) an immune response.

In some embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered as a single agent. In other
15 embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered in combination with a second therapeutic agent or modality, *e.g.*, a PD-1 inhibitor, a PD-L1 inhibitor, or a chemotherapeutic agent. In some embodiments, the PD-1 inhibitor is an anti-PD-1 antibody molecule, *e.g.*, an anti-PD-1 antibody described herein. In some embodiments, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule,
20 *e.g.*, an anti-PD-L1 antibody molecule described herein. In some embodiments, the chemotherapeutic agent is a platinum agent. In certain embodiments, the platinum agent is carboplatin. In certain embodiments, the platinum agent is cisplatin. In certain embodiments, the platinum agent is oxaliplatin. In certain embodiments, the platinum agent is tetraplatin.

In some embodiments, the chemotherapeutic agent is a nucleotide analog or precursor analog.
25 In certain embodiments, the nucleotide analog or precursor analog is capecitabine.

In certain embodiments, the cancer is a solid tumor. In some embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered as a single agent to treat the solid tumor. In other embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule,
30 is administered in combination with a second therapeutic agent or modality, *e.g.*, a PD-1 inhibitor or a PD-L1 inhibitor, to treat the solid tumor. In some embodiments, the PD-1 inhibitor is an anti-PD-1 antibody molecule, *e.g.*, an anti-PD-1 antibody described herein. In certain embodiments, the anti-PD-1 antibody molecule is PDR001 (spartalizumab). In certain embodiments, the anti-PD-1 antibody molecule is REGN2810. In other embodiments, the anti-PD-1 antibody molecule is nivolumab. In
35 some embodiments, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule, *e.g.*, an anti-PD-L1 antibody molecule described herein.

In certain embodiments, the cancer is a breast cancer, *e.g.*, a triple negative breast cancer (TNBC). In some embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered as a single agent to treat the breast cancer (*e.g.*, the TNBC). In other embodiments, the anti-LAG-3 antibody molecule, or the
5 composition or formulation comprising the anti-LAG-3 antibody molecule, is administered in combination with a second therapeutic agent, *e.g.*, a PD-1 inhibitor, to treat the breast cancer (*e.g.*, the TNBC). In some embodiments, the PD-1 inhibitor is an anti-PD-1 antibody molecule, *e.g.*, an anti-PD-1 antibody described herein. In certain embodiments, the anti-PD-1 antibody molecule is PDR001 (spartalizumab). In certain embodiments, the anti-PD-1 antibody molecule is REGN2810.
10 In other embodiments, the anti-PD-1 antibody molecule is nivolumab. In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) once every three weeks and the PD-1 inhibitor is administered at a dose of about 200 mg to about 400 mg (*e.g.*, about 300 mg) once every three weeks to treat the breast cancer (*e.g.*, TNBC). In certain embodiments, the anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule
15 described herein) is administered at a dose of about 600 mg to about 1000 mg (*e.g.*, about 800 mg) once every four weeks and the PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule described herein) is administered at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) once every four weeks to treat the breast cancer (*e.g.*, TNBC).

In certain embodiments, the cancer is a breast cancer, *e.g.*, a triple negative breast cancer
20 (TNBC). In some embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered in combination with a second therapeutic agent, *e.g.*, a chemotherapeutic agent, to treat the breast cancer (*e.g.*, the TNBC). In some embodiments, the chemotherapeutic agent is a platinum agent. In certain embodiments, the platinum agent is carboplatin. In certain
25 embodiments, the platinum agent is cisplatin. In certain embodiments, the platinum agent is oxaliplatin. In certain embodiments, the platinum agent is tetraplatin. In some embodiments, the chemotherapeutic agent is a nucleotide analog or precursor analog. In certain embodiments, the nucleotide analog or precursor analog is capecitabine. In certain
30 embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to about 500 mg (*e.g.*, about 400 mg) once every three weeks and the chemotherapeutic agent is administered at a dose to achieve an area under the curve (AUC) of about 4 to about 8 or about 5 to about 7 (*e.g.*, an AUC of about 6) once every three weeks to treat the breast cancer (*e.g.*, TNBC).

In certain embodiments, the cancer is a breast cancer, *e.g.*, a triple negative breast cancer (TNBC). In some embodiments, the anti-LAG-3 antibody molecule, or the composition or
35 formulation comprising the anti-LAG-3 antibody molecule is administered in combination with a PD-1 inhibitor and a chemotherapeutic agent to treat the breast cancer (*e.g.*, the TNBC). In some embodiments, the PD-1 inhibitor is an anti-PD-1 antibody molecule, *e.g.*, an anti-PD-1 antibody described herein. In certain embodiments, the anti-PD-1 antibody molecule is PDR001

(spartalizumab). In certain embodiments, the anti-PD-1 antibody molecule is REGN2810. In other
embodiments, the anti-PD-1 antibody molecule is nivolumab. In some embodiments, the
chemotherapeutic agent is a platinum agent. In certain embodiments, the platinum agent is
carboplatin. In certain embodiments, the platinum agent is cisplatin. In certain embodiments, the
5 platinum agent is oxaliplatin. In certain embodiments, the platinum agent is tetraplatin. In some
embodiments, the chemotherapeutic agent is a nucleotide analog or precursor analog. In certain
embodiments, the nucleotide analog or precursor analog is capecitabine. In certain embodiments, the
anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to about 500 mg (*e.g.*, about
400 mg) once every three weeks, the PD-1 inhibitor is administered at a dose of about 200 mg to
10 about 400 mg (*e.g.*, about 300 mg) once every three weeks, and the chemotherapeutic agent is
administered at a dose to achieve an AUC of about 4 to about 8 or about 5 to about 7 (*e.g.*, an AUC of
about 6) once every three weeks to treat the breast cancer (*e.g.*, TNBC).

In certain embodiments, the cancer is a brain tumor. In some embodiments, the brain tumor is
a glioblastoma (*e.g.*, a recurrent glioblastoma). In some embodiments, the anti-LAG-3 antibody
15 molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is
administered as a single agent to treat the brain tumor. In other embodiments, the anti-LAG-3
antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule,
is administered in combination with a second therapeutic agent or modality, *e.g.*, a PD-1 inhibitor or a
PD-L1 inhibitor, to treat the brain tumor. In some embodiments, the PD-1 inhibitor is an anti-PD-1
20 antibody molecule, *e.g.*, an anti-PD-1 antibody described herein. In certain embodiments, the anti-
PD-1 antibody molecule is PDR001 (spartalizumab). In other embodiments, the anti-PD-1 antibody
molecule is nivolumab. In some embodiments, the PD-L1 inhibitor is an anti-PD-L1 antibody
molecule, *e.g.*, an anti-PD-L1 antibody molecule described herein.

In certain embodiments, the cancer is a pancreatic cancer. In some embodiments, the
25 pancreatic cancer is an advanced pancreatic cancer. In some embodiments, the anti-LAG-3 antibody
molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is
administered as a single agent to treat the pancreatic cancer. In other embodiments, the anti-LAG-3
antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule,
is administered in combination with a second therapeutic agent or modality, to treat the pancreatic
30 cancer. In some embodiments, the second therapeutic agent or modality comprises a
chemotherapeutic agent (*e.g.*, gemcitabine).

In certain embodiments, the cancer is a melanoma. In some embodiments, the melanoma is
an HLA-A2 positive, a stage II, III, or IV melanoma, an unresectable melanoma, or a metastatic
melanoma. In some embodiments, the anti-LAG-3 antibody molecule, or the composition or
35 formulation comprising the anti-LAG-3 antibody molecule, is administered as a single agent to treat
the melanoma. In other embodiments, the anti-LAG-3 antibody molecule, or the composition or
formulation comprising the anti-LAG-3 antibody molecule, is administered in combination with a

second therapeutic agent or modality, to treat the melanoma. In some embodiments, the second therapeutic agent or modality is an HLA-A2 peptide. In certain embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, and optionally, the HLA-A2 peptide, is administered to a disease-free melanoma patient. In some
5 embodiments, the second therapeutic agent or modality comprises a PD-1 inhibitor or a PD-L1 inhibitor. In some embodiments, the PD-1 inhibitor is an anti-PD-1 antibody molecule, *e.g.*, an anti-PD-1 antibody described herein. In certain embodiments, the anti-PD-1 antibody molecule is PDR001. In some embodiments, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule, *e.g.*, an anti-PD-L1 antibody molecule described herein.

10 In certain embodiments, the cancer is a renal cancer. In some embodiments, the renal cancer is a renal cell carcinoma (RCC), *e.g.*, a metastatic renal cell carcinoma. In some embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered as a single agent to treat the renal cancer. In other embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3
15 antibody molecule, is administered in combination with a second therapeutic agent or modality, *e.g.*, a PD-1 inhibitor or a PD-L1 inhibitor, to treat the renal cancer. In some embodiments, the PD-1 inhibitor is an anti-PD-1 antibody molecule, *e.g.*, an anti-PD-1 antibody described herein. In certain embodiments, the anti-PD-1 antibody molecule is PDR001. In some embodiments, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule, *e.g.*, an anti-PD-L1 antibody molecule described herein.

20 In certain embodiments, the cancer is a breast cancer. In some embodiments, the breast cancer is a metastatic breast carcinoma. In some embodiments, the breast cancer is a triple negative breast cancer (TNBC). In some embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered as a single agent to treat the breast cancer. In other embodiments, the anti-LAG-3 antibody molecule, or the composition
25 or formulation comprising the anti-LAG-3 antibody molecule, is administered in combination with a second therapeutic agent or modality, to treat the breast cancer. In certain embodiments, the second therapeutic agent or modality is a chemotherapeutic agent (*e.g.*, paclitaxel). In certain embodiments, the anti-LAG-3 antibody molecule is administered at a dose of about 700 mg to about 900 mg once every four weeks to treat the breast cancer (*e.g.*, TNBC).

30 In certain embodiments, the cancer is a virus-associated tumor. In some embodiments, the virus-associated tumor is chosen from an anal canal cancer (*e.g.*, a squamous cell carcinoma of the anal canal), a cervical cancer (*e.g.*, a squamous cell carcinoma of the cervix), a gastric cancer (*e.g.*, an Epstein Barr Virus (EBV) positive gastric cancer, or a gastric or gastro-esophageal junction carcinoma), a head and neck cancer (*e.g.*, an HPV positive and negative squamous cell cancer of the
35 head and neck (SCCHN)), a nasopharyngeal cancer (NPC), a penile cancer (*e.g.*, a squamous cell carcinoma of the penile), a vaginal or vulvar cancer (*e.g.*, a squamous cell carcinoma of the vagina or vulva). In some embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation

comprising the anti-LAG-3 antibody molecule, is administered as a single agent to treat the virus-associated tumor. In other embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered in combination with a second therapeutic agent or modality, *e.g.*, a PD-1 inhibitor or a PD-L1 inhibitor, to treat the virus-associated tumor. In some embodiments, the PD-1 inhibitor is an anti-PD-1 antibody molecule, *e.g.*, an anti-PD-1 antibody described herein. In certain embodiments, the anti-PD-1 antibody molecule is PDR001. In other embodiments, the anti-PD-1 antibody molecule is nivolumab. In some embodiments, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule, *e.g.*, an anti-PD-L1 antibody molecule described herein.

In certain embodiments, the cancer is chosen from an anal canal cancer (*e.g.*, a squamous cell carcinoma of the anal canal), a cervical cancer (*e.g.*, a squamous cell carcinoma of the cervix), a gastric cancer (*e.g.*, an Epstein Barr Virus (EBV) positive gastric cancer, or a gastric or gastro-esophageal junction carcinoma), a head and neck cancer (*e.g.*, an HPV positive and negative squamous cell cancer of the head and neck (SCCHN)), a nasopharyngeal cancer (NPC), a penile cancer (*e.g.*, a squamous cell carcinoma of the penile), or a vaginal or vulvar cancer (*e.g.*, a squamous cell carcinoma of the vagina or vulva). In some embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered as a single agent to treat the cancer. In other embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered in combination with a second therapeutic agent or modality, *e.g.*, a PD-1 inhibitor or a PD-L1 inhibitor, to treat the cancer. In some embodiments, the PD-1 inhibitor is an anti-PD-1 antibody molecule, *e.g.*, an anti-PD-1 antibody described herein. In certain embodiments, the anti-PD-1 antibody molecule is PDR001. In other embodiments, the anti-PD-1 antibody molecule is nivolumab. In some embodiments, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule, *e.g.*, an anti-PD-L1 antibody molecule described herein.

In certain embodiments, the cancer is a colorectal cancer. In some embodiments, the colorectal cancer is a relapsed colorectal cancer, a metastatic colorectal cancer, a microsatellite unstable colorectal cancer, a microsatellite stable colorectal cancer, a mismatch repair proficient colorectal cancer, or a mismatch repair deficient colorectal cancer. In some embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered as a single agent to treat the colorectal cancer. In other embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered in combination with a second therapeutic agent or modality, *e.g.*, a PD-1 inhibitor or a PD-L1 inhibitor, to treat the colorectal cancer. In some embodiments, the PD-1 inhibitor is an anti-PD-1 antibody molecule, *e.g.*, an anti-PD-1 antibody described herein. In certain embodiments, the anti-PD-1 antibody molecule is PDR001. In other embodiments, the anti-PD-1

antibody molecule is nivolumab. In some embodiments, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule, *e.g.*, an anti-PD-L1 antibody molecule described herein.

In certain embodiments, the cancer is a lung cancer. In some embodiments, the lung cancer is a non-small cell lung cancer (NSCLC). In some embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered as a single agent to treat the lung cancer. In other embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered in combination with a second therapeutic agent or modality, *e.g.*, a PD-1 inhibitor or a PD-L1 inhibitor, to treat the lung cancer. In some embodiments, the PD-1 inhibitor is an anti-PD-1 antibody molecule, *e.g.*, an anti-PD-1 antibody described herein. In certain embodiments, the anti-PD-1 antibody molecule is PDR001. In other embodiments, the anti-PD-1 antibody molecule is nivolumab. In some embodiments, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule, *e.g.*, an anti-PD-L1 antibody molecule described herein.

In certain embodiments, the cancer is a hematological cancer. In some embodiments, the hematological cancer is a lymphoma, *e.g.*, a Hodgkin lymphoma (HL) or a diffuse large B cell lymphoma (DLBCL) (*e.g.*, a relapsed or refractory HL or DLBCL). In some embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered as a single agent to treat the hematological cancer. In other embodiments, the anti-LAG-3 antibody molecule, or the composition or formulation comprising the anti-LAG-3 antibody molecule, is administered in combination with a second therapeutic agent or modality, to treat the hematological cancer.

Methods and compositions disclosed herein are useful for treating metastatic lesions associated with the aforementioned cancers.

In some embodiments, the method further comprises determining whether a tumor sample is positive for one or more of PD-L1, CD8, and IFN- γ , and if the tumor sample is positive for one or more, *e.g.*, two, or all three, of the markers, then administering to the patient a therapeutically effective amount of an anti-LAG-3 antibody molecule, optionally in combination with one or more other immunomodulators or anti-cancer agents, as described herein.

In some embodiments, the anti-LAG-3 antibody molecule is used to treat a cancer that expresses LAG-3. LAG-3-expressing cancers include, *e.g.*, colorectal cancer (Xiao and Freeman *Cancer Discov.* 2015; 5(1):16-8), breast cancer (Bottai *et al. Breast Cancer Res.* 2016; 18(1): 121), prostate cancer (Sfanos *et al. Clin Cancer Res.* 2008; 14(11):3254-61), lung cancer (He *et al. J Thorac Oncol.* 2017; 12(5): 814-823), and liver cancer (Pedroza-Gonzalez *et al. Oncoimmunology.* 2015; 4(6):e1008355). The LAG-3-expressing cancer may be a metastatic cancer.

In other embodiments, the anti-LAG-3 antibody molecule is used to treat a cancer that is characterized by microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). The identification of MSI-H or dMMR tumor status for patients can be determined using, *e.g.*, polymerase

chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR. Methods for identification of MSI-H or dMMR tumor status are described, *e.g.*, in Ryan *et al. Crit Rev Oncol Hematol.* 2017; 116:38-57; Dietmaier and Hofstadter. *Lab Invest* 2001, 81:1453-1456; Kawakami *et al. Curr Treat Options Oncol.* 2015; 16(7): 30).

5 The combination therapies described herein can include a composition of the present invention co-formulated with, and/or co-administered with, one or more additional therapeutic agents, *e.g.*, one or more anti-cancer agents, cytotoxic or cytostatic agents, hormone treatment, vaccines, and/or other immunotherapies. In other embodiments, the antibody molecules are administered in combination with other therapeutic treatment modalities, including surgery, radiation, cryosurgery,
10 and/or thermotherapy. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the various monotherapies.

 The methods, compositions and combinations described herein (*e.g.*, anti-LAG-3 antibodies and methods of using them) can be used in combination with other agents or therapeutic modalities,
15 *e.g.*, a second therapeutic agent chosen from one or more of the agents listed in Table 6 of WO 2017/019897, the content of which is incorporated by reference in its entirety. In one embodiment, the methods described herein include administering to the subject an anti-LAG-3 antibody molecule as described in WO2017/019894 (optionally in combination with one or more inhibitors of PD-1, PD-L1, TIM-3, CEACAM (*e.g.*, CEACAM-1 and/or CEACAM-5), or CTLA-4)), further include
20 administration of a second therapeutic agent chosen from one or more of the agents listed in Table 6 of WO 2017/019897, in an amount effective to treat or prevent a disorder, *e.g.*, a disorder as described herein, *e.g.*, a cancer. When administered in combination, the anti-LAG-3 antibody molecule, the additional agent (*e.g.*, second or third agent), or all, can be administered in an amount or dose that is higher, lower or the same than the amount or dosage of each agent used individually, *e.g.*, as a
25 monotherapy. In certain embodiments, the administered amount or dosage of the anti-LAG-3 antibody molecule, the additional agent (*e.g.*, second or third agent), or all, is lower (*e.g.*, at least 20%, at least 30%, at least 40%, or at least 50%) than the amount or dosage of each agent used individually, *e.g.*, as a monotherapy. In other embodiments, the amount or dosage of the anti-LAG-3 antibody molecule, the additional agent (*e.g.*, second or third agent), or all, that results in a desired effect (*e.g.*,
30 treatment of cancer) is lower (*e.g.*, at least 20%, at least 30%, at least 40%, or at least 50% lower).

 In other embodiments, the additional therapeutic agent is chosen from one or more of the agents listed in Table 6 of WO 2017/019894. In some embodiments, the additional therapeutic agent is chosen from one or more of: 1) a protein kinase C (PKC) inhibitor; 2) a heat shock protein 90 (HSP90) inhibitor; 3) an inhibitor of a phosphoinositide 3-kinase (PI3K) and/or target of rapamycin
35 (mTOR); 4) an inhibitor of cytochrome P450 (*e.g.*, a CYP17 inhibitor or a 17alpha-Hydroxylase/C17-20 Lyase inhibitor); 5) an iron chelating agent; 6) an aromatase inhibitor; 7) an inhibitor of p53, *e.g.*, an inhibitor of a p53/Mdm2 interaction; 8) an apoptosis inducer; 9) an angiogenesis inhibitor; 10) an

aldosterone synthase inhibitor; 11) a smoothened (SMO) receptor inhibitor; 12) a prolactin receptor (PRLR) inhibitor; 13) a Wnt signaling inhibitor; 14) a CDK4/6 inhibitor; 15) a fibroblast growth factor receptor 2 (FGFR2)/fibroblast growth factor receptor 4 (FGFR4) inhibitor; 16) an inhibitor of macrophage colony-stimulating factor (M-CSF); 17) an inhibitor of one or more of c-KIT, histamine release, Flt3 (*e.g.*, FLK2/STK1) or PKC; 18) an inhibitor of one or more of VEGFR-2 (*e.g.*, FLK-1/KDR), PDGFRbeta, c-KIT or Raf kinase C; 19) a somatostatin agonist and/or a growth hormone release inhibitor; 20) an anaplastic lymphoma kinase (ALK) inhibitor; 21) an insulin-like growth factor 1 receptor (IGF-1R) inhibitor; 22) a P-Glycoprotein 1 inhibitor; 23) a vascular endothelial growth factor receptor (VEGFR) inhibitor; 24) a BCR-ABL kinase inhibitor; 25) an FGFR inhibitor; 10 26) an inhibitor of CYP11B2; 27) a HDM2 inhibitor, *e.g.*, an inhibitor of the HDM2-p53 interaction; 28) an inhibitor of a tyrosine kinase; 29) an inhibitor of c-MET; 30) an inhibitor of JAK; 31) an inhibitor of DAC; 32) an inhibitor of 11 β -hydroxylase; 33) an inhibitor of IAP; 34) an inhibitor of PIM kinase; 35) an inhibitor of Porcupine; 36) an inhibitor of BRAF, *e.g.*, BRAF V600E or wild-type BRAF; 37) an inhibitor of HER3; 38) an inhibitor of MEK; or 39) an inhibitor of a lipid kinase, *e.g.*, 15 as described in Table 6 of WO 2017/019894.

Additional embodiments of combination therapies comprising an anti-LAG-3 antibody molecule described herein are described in WO 2017/019894, which is incorporated by reference in its entirety.

20 **Methods of Treating Infectious Diseases**

Disclosed herein are methods of treating infectious diseases using an anti-LAG-3 antibody molecule (*e.g.*, an anti-LAG-3 antibody molecule described herein), or a composition or formulation comprising an anti-LAG-3 antibody molecule (*e.g.*, a composition or formulation described herein). In certain embodiments, the antibody molecule, composition, or formulation is administered to a 25 subject in accordance with a dosage regimen described herein.

In certain embodiments, the anti-LAG-3 antibody molecule is administered in an amount effective to treat an infectious disease or a symptom thereof. In some embodiments, the anti-LAG-3 antibody molecule is administered at a dose from about 100 mg to about 2000 mg once every two weeks, once every three weeks, or once every four weeks. For example, the anti-LAG-3 antibody 30 molecule can be administered at a dose from about 200 mg to about 1000 mg, about 300 mg to about 900 mg, about 200 mg to about 600 mg, about 300 mg to about 500 mg, about 600 to about 1000 mg, about 700 mg to about 900 mg, or about 400 mg to about 800 mg, once every three weeks or once every four weeks. In one embodiment, the anti-LAG-3 antibody molecule is administered at a dose from about 300 mg to 500 mg (*e.g.*, about 400 mg) once every three weeks. In one embodiment, the 35 anti-LAG-3 antibody molecule is administered at a dose from about 700 mg to about 900 mg (*e.g.*, about 800 mg) once every four weeks. In one embodiment, the anti-LAG-3 antibody molecule is

administered at a dose from about 500 mg to about 700 mg (*e.g.*, about 533 mg or about 600 mg) once every four weeks.

Certain methods described herein are used to treat subjects that have been exposed to particular toxins or pathogens. Without wishing to be bound by theory, it is believed that in some
5 embodiments, anti-LAG-3 antibodies can stimulate NK cell mediated killing of target cells and can enhance IFN-gamma secretion and proliferation of CD4+ T cells. Accordingly, in certain
embodiments, the anti-LAG-3 antibody molecules, compositions, and formulations described herein are suitable for use in stimulating an immune response against an infectious agent. Accordingly,
another aspect of the invention provides a method of treating an infectious disease in a subject
10 comprising administering to the subject an anti-LAG-3 antibody molecule, or a composition or formulation comprising an anti-LAG-3 antibody molecule, *e.g.*, in accordance with a dosage regimen
described herein, such that the subject is treated for the infectious disease. In the treatment of infection (*e.g.*, acute and/or chronic), administration of the anti-LAG-3 antibody molecules can be
combined with conventional treatments in addition to or in lieu of stimulating natural host immune
15 defenses to infection. Natural host immune defenses to infection include, but are not limited to inflammation, fever, antibody-mediated host defense, T-lymphocyte-mediated host defenses,
including lymphokine secretion and cytotoxic T-cells (especially during viral infection), complement mediated lysis and opsonization (facilitated phagocytosis), and phagocytosis. The ability of the anti-
LAG-3 antibody molecules to reactivate dysfunctional T-cells would be useful to treat chronic
20 infections, in particular those in which cell-mediated immunity is important for complete recovery.

Similar to its application to tumors as discussed in the previous section, the anti-LAG-3 antibody molecules, compositions, and formulations described herein can be used alone, or in
combination with a second therapeutic agent or modality, or as an adjuvant, in combination with a
vaccine, to stimulate an immune response to a pathogen or toxin. Examples of pathogens for which
25 this therapeutic approach may be particularly useful, include pathogens for which there is currently no effective vaccine, or pathogens for which conventional vaccines are less than completely effective.
These include, but are not limited to HIV, Hepatitis (A, B, & C), Influenza, Herpes, Giardia, Malaria, Leishmania, *Staphylococcus aureus*, *Pseudomonas aeruginosa*. Anti-LAG-3 antibody molecule
therapy is also useful against established infections by agents such as HIV that present altered
30 antigens over the course of the infections.

Accordingly, in some embodiments, an anti-LAG-3 antibody molecule, composition, or
formulation described herein is used to treat a subject that has an infection or is at risk of having an
infection. An infection refers to, *e.g.*, a disease or condition attributable to the presence in a host of a
foreign organism or agent that reproduces within the host. Infections typically involve breach of a
35 normal mucosal or other tissue barrier by an infectious organism or agent. A subject that has an
infection is a subject having objectively measurable infectious organisms or agents present in the
subject's body. A subject at risk of having an infection is a subject that is predisposed to develop an

infection. Such a subject can include, for example, a subject with a known or suspected exposure to an infectious organism or agent. A subject at risk of having an infection also can include a subject with a condition associated with impaired ability to mount an immune response to an infectious organism or agent, *e.g.*, a subject with a congenital or acquired immunodeficiency, a subject
 5 undergoing radiation therapy or chemotherapy, a subject with a burn injury, a subject with a traumatic injury, a subject undergoing surgery or other invasive medical or dental procedure.

Infections are broadly classified as bacterial, viral, fungal, or parasitic based on the category of infectious organism or agent involved. Other less common types of infection include, *e.g.*, infections involving rickettsiae, mycoplasmas, and agents causing scrapie, bovine spongiform
 10 encephalopathy (BSE), and prion diseases (*e.g.*, kuru and Creutzfeldt-Jacob disease). Examples of bacteria, viruses, fungi, and parasites which cause infection are well known in the art. An infection can be acute, sub-acute, chronic, or latent, and it can be localized or systemic. Furthermore, an infection can be predominantly intracellular or extracellular during at least one phase of the infectious organism's or agent's life cycle in the host.

15 *Viruses*

In certain embodiments, the anti-LAG-3 antibody molecule, composition, or formulation described herein is used to treat a viral infection or a disease associated with a virus.

Examples of viruses that have been found to cause infections in humans include but are not
 20 limited to: Retroviridae (*e.g.*, human immunodeficiency viruses, such as HIV-1 (also referred to as HTLV-III), HIV-2, LAV or HTLV-III/LAV, or HIV-III, and other isolates, such as HIV-LP; Picornaviridae (*e.g.*, polio viruses, hepatitis A virus; enteroviruses, human Coxsackie viruses, rhinoviruses, echoviruses); Calciviridae (*e.g.*, strains that cause gastroenteritis); Togaviridae (*e.g.*, equine encephalitis viruses, rubella viruses); Flaviviridae (*e.g.*, dengue viruses, encephalitis viruses,
 25 yellow fever viruses); Coronaviridae (*e.g.*, coronaviruses); Rhabdoviridae (*e.g.*, vesicular stomatitis viruses, rabies viruses); Filoviridae (*e.g.*, ebola viruses); Paramyxoviridae (*e.g.*, parainfluenza viruses, mumps virus, measles virus, respiratory syncytial virus); Orthomyxoviridae (*e.g.*, influenza viruses); Bungaviridae (*e.g.*, Hantaan viruses, bunga viruses, phleboviruses and Nairo viruses); Arena viridae (hemorrhagic fever viruses); Reoviridae (*e.g.*, reoviruses, orbiviruses and rotaviruses); Birnaviridae;
 30 Hepadnaviridae (Hepatitis B virus); Parvoviridae (parvoviruses); Papovaviridae (papilloma viruses, polyoma viruses); Adenoviridae (most adenoviruses); Herpesviridae (herpes simplex virus (HSV) 1 and 2, varicella zoster virus, cytomegalovirus (CMV), herpes virus; Poxviridae (variola viruses, vaccinia viruses, pox viruses); and Iridoviridae (*e.g.*, African swine fever virus); and unclassified viruses (*e.g.*, the etiological agents of Spongiform encephalopathies, the agent of delta hepatitis
 35 (thought to be a defective satellite of hepatitis B virus), the agents of non-A, non-B hepatitis (class 1=enterally transmitted; class 2=parenterally transmitted (i.e., Hepatitis C); Norwalk and related viruses, and astroviruses). Some examples of pathogenic viruses causing infections treatable by

methods herein include HIV, hepatitis (A, B, or C), herpes virus (*e.g.*, VZV, HSV-1, HAV-6, HSV-II, and CMV, Epstein Barr virus), adenovirus, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, cornovirus, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus and arboviral encephalitis virus.

For infections resulting from viral causes, the anti-LAG-3 antibody molecules can be combined by application simultaneous with, prior to or subsequent to application of standard therapies for treating viral infections. Such standard therapies vary depending upon type of virus, although in almost all cases, administration of human serum containing antibodies (*e.g.*, IgA, IgG) specific to the virus can be effective.

Some examples of pathogenic viruses causing infections treatable by methods include HIV, hepatitis (A, B, or C), herpes virus (*e.g.*, VZV, HSV-1, HAV-6, HSV-II, and CMV, Epstein Barr virus), adenovirus, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, cornovirus, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus, arboviral encephalitis virus, and ebolaviruses (*e.g.*, BDBV, EBOV, RESTV, SUDV and TAFV).

In one embodiment, the infection is an influenza infection. Influenza infection can result in fever, cough, myalgia, headache and malaise, which often occur in seasonal epidemics. Influenza is also associated with a number of postinfectious disorders, such as encephalitis, myopericarditis, Goodpasture's syndrome, and Reye's syndrome. Influenza infection also suppresses normal pulmonary antibacterial defenses, such that patients recovering from influenza have an increased risk of developing bacterial pneumonia. Influenza viral surface proteins show marked antigenic variation, resulting from mutation and recombination. Thus, cytolytic T lymphocytes are the host's primary vehicle for the elimination of virus after infection. Influenza is classified into three primary types: A, B and C. Influenza A is unique in that it infects both humans and many other animals (*e.g.*, pigs, horses, birds and seals) and is the principal cause of pandemic influenza. Also, when a cell is infected by two different influenza A strains, the segmented RNA genomes of two parental virus types mix during replication to create a hybrid replicant, resulting in new epidemic strains. Influenza B does not replicate in animals and thus has less genetic variation and influenza C has only a single serotype.

Most conventional therapies are palliatives of the symptoms resulting from infection, while the host's immune response actually clears the disease. However, certain strains (*e.g.*, influenza A) can cause more serious illness and death. Influenza A may be treated both clinically and prophylactically by the administration of the cyclic amines inhibitors amantadine and rimantadine, which inhibit viral replication. However, the clinical utility of these drugs is limited due to the relatively high incidence of adverse reactions, their narrow anti-viral spectrum (influenza A only), and the propensity of the virus to become resistant. The administration of serum IgG antibody to the major influenza surface proteins, hemagglutinin and neuraminidase can prevent pulmonary infection,

whereas mucosal IgA is required to prevent infection of the upper respiratory tract and trachea. The most effective current treatment for influenza is vaccination with the administration of virus inactivated with formalin or β -propiolactone.

In another embodiment, the infection is a hepatitis infection, *e.g.*, a Hepatitis B or C infection.

5 Hepatitis B virus (HB-V) is the most infectious known bloodborne pathogen. It is a major cause of acute and chronic hepatitis and hepatic carcinoma, as well as life-long, chronic infection. Following infection, the virus replicates in hepatocytes, which also then shed the surface antigen HBsAg. The detection of excessive levels of HBsAg in serum is used a standard method for diagnosing a hepatitis B infection. An acute infection may resolve or it can develop into a chronic
10 persistent infection. Current treatments for chronic HBV include α -interferon, which increases the expression of class I human leukocyte antigen (HLA) on the surface of hepatocytes, thereby facilitating their recognition by cytotoxic T lymphocytes. Additionally, the nucleoside analogs ganciclovir, famciclovir and lamivudine have also shown some efficacy in the treatment of HBV infection in clinical trials. Additional treatments for HBV include pegylated α -interferon, adenfovir,
15 entecavir and telbivudine. While passive immunity can be conferred through parental administration of anti-HBsAg serum antibodies, vaccination with inactivated or recombinant HBsAg also confers resistance to infection. The anti-LAG-3 antibody molecules may be combined with conventional treatments for hepatitis B infections for therapeutic advantage.

Hepatitis C virus (HC-V) infection may lead to a chronic form of hepatitis, resulting in
20 cirrosis. While symptoms are similar to infections resulting from Hepatitis B, in distinct contrast to HB-V, infected hosts can be asymptomatic for 10-20 years. The anti-LAG-3 antibody molecule can be administered as a monotherapy, or combined with the standard of care for hepatitis C infection. For example, the anti-LAG-3 antibody molecule can be administered with one or more of Sovaldi (sofosbuvir) Olysio (simeprevir), plus ribavirin or pegylated interferon. Although regimens that
25 include Incivek (telaprevir) or Victrelis (boceprevir) plus ribavirin and pegylated interferon are also approved, they are associated with increased side effects and longer duration of treatment and are therefore not considered preferred regimens.

Conventional treatment for HC-V infection includes the administration of a combination of α -interferon and ribavirin. A promising potential therapy for HC-V infection is the protease inhibitor
30 telaprevir (VX-960). Additional treatments include: anti-PD-1 antibody (MDX-1106, Medarex), bavituximab (an antibody that binds anionic phospholipid phosphatidylserine in a B2-glycoprotein I dependent manner, Peregrine Pharmaceuticals), anti-HPV viral coat protein E2 antibody(ies) (*e.g.*, ATL 6865–Ab68+Ab65, XTL Pharmaceuticals) and Civacir® (polyclonal anti-HCV human immune globulin). The anti-LAG-3 antibodies of the invention may be combined with one or more of these
35 treatments for hepatitis C infections for therapeutic advantage. Protease, polymerase and NS5A inhibitors which may be used in combination with the anti-LAG-3 antibody molecules to specifically

molecules may be combined with conventional treatments for HIV infections for therapeutic advantage.

In another embodiment, the infection is a Cytomegalovirus (CMV). CMV infection is often associated with persistent, latent and recurrent infection. CMV infects and remains latent in monocytes and granulocyte-monocyte progenitor cells. The clinical symptoms of CMV include mononucleosis-like symptoms (*i.e.*, fever, swollen glands, malaise), and a tendency to develop allergic skin rashes to antibiotics. The virus is spread by direct contact. The virus is shed in the urine, saliva, semen and to a lesser extent in other body fluids. Transmission can also occur from an infected mother to her fetus or newborn and by blood transfusion and organ transplants. CMV infection results in general impairment of cellular immunity, characterized by impaired blastogenic responses to nonspecific mitogens and specific CMV antigens, diminished cytotoxic ability and elevation of CD8 lymphocyte number of CD4⁺ lymphocytes.

Treatments of CMV infection include the anti-virals ganciclovir, foscarnet and cidofovir, but these drugs are typically only prescribed in immunocompromised patients. The anti-LAG-3 antibody molecules may be combined with conventional treatments for cytomegalovirus infections for therapeutic advantage.

In another embodiment, the infection is Epstein-Barr virus (EBV). EBV can establish persistent and latent infections and primarily attacks B cells. Infection with EBV results in the clinical condition of infectious mononucleosis, which includes fever, sore throat, often with exudate, generalized lymphadenopathy and splenomegaly. Hepatitis is also present, which can develop into jaundice.

While typical treatments for EBV infections are palliative of symptoms, EBV is associated with the development of certain cancers such as Burkitt's lymphoma and nasopharyngeal cancer. Thus, clearance of viral infection before these complications result would be of great benefit. The anti-LAG-3 antibody molecules may be combined with conventional treatments for Epstein-Barr virus infections for therapeutic advantage.

In another embodiment, the infection is Herpes simplex virus (HSV). HSV is transmitted by direct contact with an infected host. A direct infection may be asymptomatic, but typically result in blisters containing infectious particles. The disease manifests as cycles of active periods of disease, in which lesions appear and disappear as the virus latently infects the nerve ganglion for subsequent outbreaks. Lesions may be on the face, genitals, eyes and/or hands. In some cases, an infection can also cause encephalitis.

Treatments for herpes infections are directed primarily to resolving the symptomatic outbreaks, and include systemic antiviral medicines such as: acyclovir (*e.g.*, Zovirax®), valaciclovir, famciclovir, penciclovir, and topical medications such as docosanol (Abreva®), tromantadine and zilactin. The clearance of latent infections of herpes would be of great clinical benefit. The anti-LAG-

3 antibody molecules may be combined with conventional treatments for herpes virus infections for therapeutic advantage.

In another embodiment, the infection is Human T-lymphotropic virus (HTLV-1, HTLV-2). HTLV is transmitted via sexual contact, breast feeding or exposure to contaminated blood. The virus
5 activates a subset of T_H cells called Th1 cells, resulting in their overproliferation and overproduction of Th1 related cytokines (*e.g.*, IFN- γ and TNF- α). This in turn results in a suppression of Th2 lymphocytes and reduction of Th2 cytokine production (*e.g.*, IL-4, IL-5, IL-10 and IL-13), causing a reduction in the ability of an infected host to mount an adequate immune response to invading organisms requiring a Th2-dependent response for clearance (*e.g.*, parasitic infections, production of
10 mucosal and humoral antibodies).

HTLV infections cause lead to opportunistic infections resulting in bronchiectasis, dermatitis and superinfections with *Staphylococcus* spp. and *Strongyloides* spp. resulting in death from polymicrobial sepsis. HTLV infection can also lead directly to adult T-cell leukemia/lymphoma and progressive demyelinating upper motor neuron disease known as HAM/TSP. The clearance of HTLV
15 latent infections would be of great clinical benefit. The anti-LAG-3 antibody molecules may be combined with conventional treatments for HTLV infections for therapeutic advantage.

In another embodiment, the infection is Human papilloma virus (HPV). HPV primarily affects keratinocytes and occurs in two forms: cutaneous and genital. Transmission is believed to occur through direct contact and/or sexual activity. Both cutaneous and genital HPV infection, can
20 result in warts and latent infections and sometimes recurring infections, which are controlled by host immunity which controls the symptoms and blocks the appearance of warts, but leaves the host capable of transmitting the infection to others.

Infection with HPV can also lead to certain cancers, such as cervical, anal, vulvar, penile and oropharyngeal cancer. There are no known cures for HPV infection, but current treatment is topical
25 application of Imiquimod, which stimulates the immune system to attack the affected area. The clearance of HPV latent infections would be of great clinical benefit. The anti-LAG-3 antibodies of the invention may be combined with conventional treatments for HPV infections for therapeutic advantage.

In another embodiment, the infection is Ebola virus (EBOV). EBOV is one of five known
30 viruses within the Ebolavirus genus. EBOV causes severe and often fatal hemorrhagic fever in humans and mammals, known as Ebola virus disease (EVD). Transmission occurs through contact with blood, secretions, organs, or other bodily fluids of infected patients. Currently, there is no proven treatment or vaccine.

35 *Bacteria*

In certain embodiments, the anti-LAG-3 antibody molecule, composition, or formulation described herein is used to treat a bacterial infection or a disease associated with a bacterium.

Bacteria include both Gram negative and Gram positive bacteria. Examples of Gram positive bacteria include, but are not limited to *Pasteurella* species, *Staphylococci* species, and *Streptococcus* species. Examples of Gram negative bacteria include, but are not limited to, *Escherichia coli*, *Pseudomonas* species, and *Salmonella* species. Specific examples of infectious bacteria include but are not limited to: *Helicobacter pylori*, *Borrelia burgdorferi*, *Legionella pneumophila*, *Mycobacteria* spp. (e.g., *M. tuberculosis*, *M. avium*, *M. intracellulare*, *M. kansasii*, *M. goodii*), *Staphylococcus aureus*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Listeria monocytogenes*, *Streptococcus pyogenes* (Group A *Streptococcus*), *Streptococcus agalactiae* (Group B *Streptococcus*), *Streptococcus* (viridans group), *Streptococcus faecalis*, *Streptococcus bovis*, *Streptococcus* (anaerobic spp.),

10 *Streptococcus pneumoniae*, pathogenic *Campylobacter* spp., *Enterococcus* spp., *Haemophilus influenzae*, *Bacillus anthracis*, *Corynebacterium diphtheriae*, *Corynebacterium* spp., *Erysipelothrix rhusiopathiae*, *Clostridium perfringens*, *Clostridium tetani*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Pasteurella multocida*, *Bacteroides* spp., *Fusobacterium nucleatum*, *Streptobacillus moniliformis*, *Treponema pallidum*, *Treponema pertenue*, *Leptospira*, *Mycobacterium leprae*,

15 *Rickettsia*, and *Actinomyces israelii*. Some examples of pathogenic bacteria causing infections treatable by methods herein include chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumococci, meningococci and conococci, klebsiella, proteus, serratia, pseudomonas, legionella, diphtheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, and Lyme disease bacteria.

20 Some examples of pathogenic bacteria causing infections treatable by methods of the invention include syphilis, *chlamydia*, *rickettsial bacteria*, *mycobacteria*, *staphylococci*, *streptococci*, *pneumonococci*, *meningococci* and *conococci*, *klebsiella*, *proteus*, *serratia*, *pseudomonas*, *legionella*, *diphtheria*, *salmonella*, *bacilli*, *cholera*, *tetanus*, *botulism*, *anthrax*, *plague*, *leptospirosis*, and *Lyme disease bacteria*. The anti-LAG-3 antibody molecules can be used in combination with existing

25 treatment modalities for the aforesaid infections. For example, Treatments for syphilis include penicillin (e.g., penicillin G.), tetracycline, doxycycline, ceftriaxone and azithromycin.

Lyme disease, caused by *Borrelia burgdorferi* is transmitted into humans through tick bites. The disease manifests initially as a localized rash, followed by flu-like symptoms including malaise, fever, headache, stiff neck and arthralgias. Later manifestations can include migratory and

30 polyarticular arthritis, neurologic and cardiac involvement with cranial nerve palsies and radiculopathy, myocarditis and arrhythmias. Some cases of Lyme disease become persistent, resulting in irreversible damage analogous to tertiary syphilis. Current therapy for Lyme disease includes primarily the administration of antibiotics. Antibiotic-resistant strains may be treated with hydroxychloroquine or methotrexate. Antibiotic refractory patients with neuropathic pain can be

35 treated with gabapentin. Minocycline may be helpful in late/chronic Lyme disease with neurological or other inflammatory manifestations.

Other forms of borreliosis, such as those resulting from *B. recurrentis*, *B. hermsii*, *B. turicatae*, *B. parikeri*, *B. hispanica*, *B. duttonii* and *B. persica*, as well leptospirosis (E.g., *L. interrogans*), typically resolve spontaneously unless blood titers reach concentrations to cause intrahepatic obstruction.

5

Fungi and Parasites

In certain embodiments, the anti-LAG-3 antibody molecule, composition, or formulation described herein is used to treat a fungal or parasitic infection or a disease associated with a fungus or a parasite.

10

Examples of fungi include: *Aspergillus spp.*, *Blastomyces dermatitidis*, *Candida albicans*, other *Candida spp.*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Chlamydia trachomatis*, *Nocardia spp.*, *Pneumocystis carinii*. Some examples of pathogenic fungi causing infections treatable by methods herein include *Candida* (*albicans*, *krusei*, *glabrata*, *tropicalis*, etc.), *Cryptococcus neoformans*, *Aspergillus* (*fumigatus*, *niger*, etc.), Genus *Mucorales* (*mucor*, *absidia*, *rhizophus*), *Sporothrix schenckii*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Coccidioides immitis* and *Histoplasma capsulatum*.

15

Parasites include but are not limited to blood-borne and/or tissues parasites such as *Babesia microti*, *Babesia divergens*, *Entamoeba histolytica*, *Giardia lamblia*, *Leishmania tropica*, *Leishmania spp.*, *Leishmania braziliensis*, *Leishmania donovani*, *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale*, *Plasmodium vivax*, and *Toxoplasma gondii*, *Trypanosoma gambiense* and *Trypanosoma rhodesiense* (African sleeping sickness), *Trypanosoma cruzi* (Chagas' disease), and *Toxoplasma gondii*, flat worms, round worms. Some examples of pathogenic parasites causing infections treatable by methods herein include *Entamoeba histolytica*, *Balantidium coli*, *Naegleria fowleri*, *Acanthamoeba sp.*, *Giardia lamblia*, *Cryptosporidium sp.*, *Pneumocystis carinii*, *Plasmodium vivax*, *Babesia microti*, *Trypanosoma brucei*, *Trypanosoma cruzi*, *Leishmania donovani*, *Toxoplasma gondii*, and *Nippostrongylus brasiliensis*.

20

25

Some examples of pathogenic fungi causing infections treatable by methods of the invention include *Candida* (*albicans*, *krusei*, *glabrata*, *tropicalis*, etc.), *Cryptococcus neoformans*, *Aspergillus* (*fumigatus*, *niger*, etc.), Genus *Mucorales* (*mucor*, *absidia*, *rhizophus*), *Sporothrix schenckii*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Coccidioides immitis* and *Histoplasma capsulatum*.

30

Some examples of pathogenic parasites causing infections treatable by methods described herein include *Entamoeba histolytica*, *Balantidium coli*, *Naegleria fowleri*, *Acanthamoeba sp.*, *Giardia lamblia*, *Cryptosporidium sp.*, *Pneumocystis carinii*, *Plasmodium vivax*, *Babesia microti*, *Trypanosoma brucei*, *Trypanosoma cruzi*, *Leishmania donovani*, *Toxoplasma gondii*, and *Nippostrongylus brasiliensis*.

35

Nucleic Acids

The anti-LAG-3 antibody molecules described herein can be encoded by nucleic acids described herein. The nucleic acids can be used to produce the anti-LAG-3 antibody molecules described herein.

5 In certain embodiments, the nucleic acid comprises nucleotide sequences that encode heavy and light chain variable regions and CDRs of the anti-LAG-3 antibody molecules, as described herein. For example, the present disclosure features a first and second nucleic acid encoding heavy and light chain variable regions, respectively, of an anti-LAG-3 antibody molecule chosen from one or more of the antibody molecules disclosed herein, *e.g.*, an antibody of Table 1 of US 2015/0259420. The
10 nucleic acid can comprise a nucleotide sequence encoding any one of the amino acid sequences in the tables herein, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from the sequences provided in Table 1. For example, disclosed herein is a first and second nucleic acid encoding heavy and light chain variable regions, respectively, of an anti-LAG-3 antibody
15 molecule chosen from one or more of, *e.g.*, any of BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (*e.g.*, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser,
20 BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser, or BAP050-hum20-Ser), BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone-I, or BAP050-Clone-J, as summarized in Table 1, or a sequence substantially identical
25 thereto.

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs from a heavy chain variable region having an amino acid sequence as set forth in Table 1, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one or more substitutions, *e.g.*,
30 conserved substitutions). In some embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs from a light chain variable region having an amino acid sequence as set forth in Table 1, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one or more substitutions, *e.g.*, conserved substitutions). In some embodiments, the nucleic acid can comprise a nucleotide
35 sequence encoding at least one, two, three, four, five, or six CDRs from heavy and light chain variable regions having an amino acid sequence as set forth in Table 1, or a sequence substantially

homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one or more substitutions, *e.g.*, conserved substitutions).

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs from a heavy chain variable region having the nucleotide sequence as set forth in Table 1, a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein). In some embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs from a light chain variable region having the nucleotide sequence as set forth in Table 1, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein). In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, three, four, five, or six CDRs from heavy and light chain variable regions having the nucleotide sequence as set forth in Table 1, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein). The nucleic acids disclosed herein include deoxyribonucleotides or ribonucleotides, or analogs thereof. The polynucleotide may be either single-stranded or double-stranded, and if single-stranded may be the coding strand or non-coding (antisense) strand. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. The nucleic acid may be a recombinant polynucleotide, or a polynucleotide of genomic, cDNA, semisynthetic, or synthetic origin which either does not occur in nature or is linked to another polynucleotide in a nonnatural arrangement.

In certain embodiments, the nucleotide sequence that encodes the anti-LAG-3 antibody molecule is codon optimized.

In some embodiments, nucleic acids comprising nucleotide sequences that encode heavy and light chain variable regions and CDRs of the anti-LAG-3 antibody molecules, as described herein, are disclosed. For example, the disclosure provides a first and second nucleic acid encoding heavy and light chain variable regions, respectively, of an anti-LAG-3 antibody molecule according to Table 1 or a sequence substantially identical thereto. For example, the nucleic acid can comprise a nucleotide sequence encoding an anti-LAG-3 antibody molecule according to Table 1, or a sequence substantially identical to that nucleotide sequence (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from the aforementioned nucleotide sequence. .

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs, or hypervariable loops, from a heavy chain variable region having an

amino acid sequence as set forth in Table 1, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs, or hypervariable loops, from a light chain variable region having an amino acid sequence as set forth in Table 1, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, three, four, five, or six CDRs, or hypervariable loops, from heavy and light chain variable regions having an amino acid sequence as set forth in Table 1, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the nucleic acid is isolated or recombinant.

The nucleic acids described herein may be present in a single vector or separate vectors present in the same host cell or separate host cell, as described in more detail herein.

Vectors and Host Cells

The anti-LAG-3 antibody molecules described herein can be produced using host cells and vectors containing the nucleic acids described herein. The nucleic acids may be present in a single vector or separate vectors present in the same host cell or separate host cell.

In one embodiment, the vectors comprise nucleotides encoding an antibody molecule described herein. In one embodiment, the vectors comprise the nucleotide sequences described herein. The vectors include, but are not limited to, a virus, plasmid, cosmid, lambda phage or a yeast artificial chromosome (YAC).

Numerous vector systems can be employed. For example, one class of vectors utilizes DNA elements which are derived from animal viruses such as, for example, bovine papilloma virus, polyoma virus, adenovirus, vaccinia virus, baculovirus, retroviruses (Rous Sarcoma Virus, MMTV or MOMLV) or SV40 virus. Another class of vectors utilizes RNA elements derived from RNA viruses such as Semliki Forest virus, Eastern Equine Encephalitis virus and Flaviviruses.

Additionally, cells which have stably integrated the DNA into their chromosomes may be selected by introducing one or more markers which allow for the selection of transfected host cells. The marker may provide, for example, prototrophy to an auxotrophic host, biocide resistance (*e.g.*, antibiotics), or resistance to heavy metals such as copper, or the like. The selectable marker gene can be either directly linked to the DNA sequences to be expressed, or introduced into the same cell by cotransformation. Additional elements may also be needed for optimal synthesis of mRNA. These

elements may include splice signals, as well as transcriptional promoters, enhancers, and termination signals.

Once the expression vector or DNA sequence containing the constructs has been prepared for expression, the expression vectors may be transfected or introduced into an appropriate host cell.

5 Various techniques may be employed to achieve this, such as, for example, protoplast fusion, calcium phosphate precipitation, electroporation, retroviral transduction, viral transfection, gene gun, lipid based transfection or other conventional techniques. In the case of protoplast fusion, the cells are grown in media and screened for the appropriate activity. Methods and conditions for culturing the resulting transfected cells and for recovering the antibody molecule produced are known to those
10 skilled in the art, and may be varied or optimized depending upon the specific expression vector and mammalian host cell employed, based upon the present description.

In certain embodiments, the host cell comprises a nucleic acid encoding an anti-LAG-3 antibody molecule described herein. In other embodiments, the host cell is genetically engineered to comprise a nucleic acid encoding the anti-LAG-3 antibody molecule.

15 In one embodiment, the host cell is genetically engineered by using an expression cassette. The phrase "expression cassette," refers to nucleotide sequences, which are capable of affecting expression of a gene in hosts compatible with such sequences. Such cassettes may include a promoter, an open reading frame with or without introns, and a termination signal. Additional factors necessary or helpful in effecting expression may also be used, such as, for example, an inducible
20 promoter. In certain embodiments, the host cell comprises a vector described herein.

The cell can be, but is not limited to, a eukaryotic cell, a bacterial cell, an insect cell, or a human cell. Suitable eukaryotic cells include, but are not limited to, Vero cells, HeLa cells, COS cells, CHO cells, HEK293 cells, BHK cells and MDCKII cells. Suitable insect cells include, but are not limited to, Sf9 cells.

25 In some embodiments, the host cell is a eukaryotic cell, *e.g.*, a mammalian cell, an insect cell, a yeast cell, or a prokaryotic cell, *e.g.*, *E. coli*. For example, the mammalian cell can be a cultured cell or a cell line. Exemplary mammalian cells include lymphocytic cell lines (*e.g.*, NSO), Chinese hamster ovary cells (CHO), COS cells, oocyte cells, and cells from a transgenic animal, *e.g.*, mammary epithelial cell.

30

EXAMPLES

The Examples below are set forth to aid in the understanding of the inventions but are not intended, and should not be construed, to limit its scope in any way.

Example 1: Population Pharmacokinetics and Pharmacodynamics of an Exemplary Anti-LAG-3 Antibody and Soluble LAG-3

Summary

The objectives of this study are to predict the relationship between serum anti-LAG-3 antibody concentration and LAG-3 occupancy in serum (soluble LAG-3) and in tumor (membrane-bound LAG-3); to assess the relationship between anti-LAG-3 antibody dose and pharmacokinetics (PK), and whether PK variability depends upon the dose; to assess expected variability in anti-LAG-3 steady state trough levels from fixed and weight-based dosing; and to assess whether co-administration of anti-PD-1 antibody affects anti-LAG-3 antibody exposure.

The following methods were used in this study. A two compartment, linear population PK model was used to describe the anti-LAG-3 antibody concentration. A standard binding model to describe target mediated drug disposition was used to describe the soluble LAG-3 data; the quasi-equilibrium approximation was used. A covariate analysis was used to estimate the impact of weight on clearance and both central and peripheral volume. A graphical analysis was used to assess the impact on co-administration of anti-PD-1 antibody on anti-LAG-3 antibody clearance. Model simulation was then performed to identify the relationship between anti-LAG-3 antibody dose and free LAG-3 for both the soluble LAG-3 in serum and the membrane-bound LAG-3 in the tumor.

The following results were obtained from this study. The relationship between dose and free LAG-3 in serum and in the tumor was characterized. Anti-LAG-3 antibody PK appears nonlinear at doses below 80 mg every 2-4 weeks and linear at doses above 240 mg every 3-4 weeks. Fixed and weight-based dosing regimens were predicted to give comparable variability of trough concentrations at steady state. No obvious impact of co-administration with anti-PD-1 antibody on anti-LAG-3 antibody PK was observed.

The relationship between anti-LAG-3 antibody dose and receptor occupancy of both serum soluble LAG-3 and intratumoral membrane-bound LAG-3 receptor occupancy at doses of 240 mg and above was well characterized by the model. At lower doses (*e.g.* 80 mg every 2-4 weeks), a nonlinearity in the anti-LAG-3 antibody PK was observed in some patients. Above 240 mg every 3-4 weeks, anti-LAG-3 antibody PK appeared linear. The nonlinearity is thought to be due to target mediated drug disposition, as observed for many other monoclonal antibodies. Fixed and body-weight based dosing were predicted to give comparable variability in the steady state trough levels of anti-LAG-3 antibody. Co-administration of anti-PD-1 antibody did not show any obvious impact on the anti-LAG-3 antibody PK.

The observations illustrated in this Example can be used to guide dose selection for anti-LAG-3 antibody molecules described herein.

35

Data

This study used data from the dose escalation study in patients with advanced solid tumors, where an exemplary anti-LAG-3 antibody, LAG525, was given both as monotherapy and in combination with an exemplary anti-PD-1 antibody, PDR001. The anti-LAG-3 antibody concentration and the soluble LAG-3 concentration were measured at various times (pre-infusion, hour 1, day 1, 7, 10, 14).

The anti-LAG-3 antibody was quantified by liquid chromatography mass spectroscopy (LC/MS) with lower limit of quantification of 250 ng/ml (1.7 nM). Total soluble LAG-3 was quantified by an enzyme linked immunosorbent assay (ELISA) in human serum with lower limit of quantification of 0.146 ng/ml (1 pM).

A single dataset was generated and validated at the most critical level. All anti-LAG-3 antibody and soluble LAG-3 measurements were included in this analysis. No data was excluded or classified as outliers.

Methods

This study was performed using a nonlinear mixed effects modeling approach, where the model has two components: a structural model which accounts for the systematic trends in the data and the random effects model, which accounts for both inter-subject variability and residual variability about those trends. The covariate model describes how covariates are incorporated. A PopPKPD model was simultaneously fit to both the PK and soluble LAG-3 data. Model simulations with additional assumptions were then performed to make predictions about the membrane-bound LAG-3 inhibition in the tumor.

The analysis was performed using the Monolix software system, version 2016R1 utilizing the MODESIM high performance computing environment. The technical computing package R was used to explore the data, assist in model building, and report the final results.

While many models were explored when first analyzing this data, only a single structural model was used because it was found that this model was adequate for meeting the objectives.

Structural model. The structural PKPD model for anti-LAG-3, soluble LAG-3, and complex concentration is a standard binding model used for describing target mediated drug disposition (TMDD) with the quasi-equilibrium approximation (Mager & Krzyzanski. *Pharmaceutical Research* 22, 1589–1596 (2005)), such that the differential equations describe the total drug, total target, and peripheral drug concentration and the algebraic expressions further below are used to calculate the free drug, free target, and complex concentrations.

A Michaelis-Menten version of this model was also fit. In the exploratory analysis, this model did not improve the fits, and so it was not explored further.

Random effects model. The PK model is parameterized by the following four parameters: clearance, central volume, peripheral volume, and inter-compartmental clearance and the PD (soluble LAG-3) model adds the following four parameters: initial sLAG-3, steady state sLAG-3 for a large dose of anti-LAG-3 antibody, antibody-sLAG-3 complex elimination rate, and dissociation constant.

5 Lognormal random effects are added to all eight parameters.

Covariate model. A covariate analysis was used to assess the impact of weight on clearance and central volume. Graphical analysis was used to assess the impact of anti-PD-1 antibody on anti-LAG-3 antibody PK, by comparing the anti-LAG-3 antibody concentrations in patients who received

10 identical anti-LAG-3 antibody dosing regimens and either did or did not receive anti-PD-1 antibody. A formal covariate analysis was not performed because patients at the lowest anti-LAG-3 antibody dose (0.3 mg/kg q2w) had the fastest rate of elimination and also always received anti-PD-1 antibody. It is thought that faster elimination at the lowest dose is due to target mediated drug disposition, but this effect was observed to confound a formal assessment of anti-PD-1 antibody as a covariate on

15 clearance.

Comparing fixed and body-weight scaled dosing regimens. The anti-LAG-3 antibody trough levels at week 24 (approximately 6 months) were simulated for 1000 patients using the model for 10 mg/kg or 700 mg given every 2, 3, or 4 weeks. Preliminary model fits showed the terminal half-life

20 of anti-LAG-3 antibody was around 2 weeks, so all patients were expected to be at steady state by week 24; also, week 24 was a trough for all dosing regimens tested (q2w, q3w, q4w). The median and 95% prediction interval values were plotted. It was assumed that the typical patient weighed 80 kg so that the equivalent fixed dose regimen could be calculated (*e.g.* 1 mg/kg corresponds to 80 mg). However, the median weight in the population in this study was closer to 70 kg. For that reason, for

25 this particular simulation, 10 mg/kg was compared to 700 mg.

Predicting LAG-3 inhibition in serum and in tumor. Simulation from the above PKPD model was used to estimate LAG-3 occupancy at the 6 month trough levels, when the PK is at steady state. Two different LAG-3 occupancy estimates are provided: (1) the ratio of free soluble LAG-3 in

30 serum compared to baseline soluble LAG-3, which is computed directly from the PKPD model; and (2) the occupancy of membrane-bound LAG-3 in tumor (RO).

The prediction for the intra-tumoral LAG-3 inhibition is thought to be more relevant for guiding dose selection because this is the site at which the tumor infiltrating lymphocytes interact with the tumor.

35 Using this approach to predict target occupancy in the tumor involves a number of assumptions: (1) the estimated dissociation constant for the anti-LAG-3 antibody to sLAG-3 in the serum is the same as the dissociation for anti-LAG-3 antibody to membrane-bound LAG-3 in the

tumor; (2) that $ABC_{ISF} = 30\%$ in human tumors, based on mouse data (Deng *et al. MAbs*, vol. 8, 593–603 (2016)); (3) the tumor can be treated like a homogenous tissues; (4) membrane-bound LAG-3 in the tumor does not accumulate in the presence of drug; (5) the anti-LAG-3 antibody is in vast excess to the membrane-bound LAG-3 concentration in the tumor; and (6) the binding between LAG-3 and its endogenous binding partners (*e.g.* MHCII) is not modeled and it is assumed that this does not significantly impact the prediction for suppression.

In addition to these assumptions, a desired level of inhibition for a desired fraction of the patient population must be selected. Typically, 60-90% suppression is required for antagonists and so an occupancy of 90-95% is targeted for this analysis (Grimwood & Hartig. *Pharmacology & Therapeutics* 122, 281–301 (2009); Tiwari *et al. The AAPS Journal* 1-10 (2016); Agoram. *British Journal of Clinical Pharmacology* 67, 153-160 (2009)).

For these trial simulations, the following doses were tested at q2w, q3w, and q4w regimens for 1000 patients: 10, 20, 30, 50, 70, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000 mg. Then, the 5, 25, 50, 75, 95 percentile is computed for the PK, and for soluble LAG-3 occupancy in the serum and membrane-bound LAG-3 occupancy in the tumor.

Results

A total of 196 patients were included in this analysis with median follow up times of 30 and 29.5 days for the anti-LAG-3 antibody and soluble-LAG-3 assessments respectively. A summary of the number of patients on each dosing regimen, sorted by total monthly dose (average total dose over four weeks) is shown in **Table 13**.

Table 13. Summary of dosing regimens and number of patients

Average total anti-LAG-3 dose every 4 weeks (mg)	Category	Anti-LAG-3 regimen	Anti-PD-1 regimen	Number of pts.	Number of pts. with PK	Number of pts. with sLAG-3
2400	high	15 mg/kg q2w	none	6	6	6
1600	high	10 mg/kg q2w	none	6	6	6
1000	high	1000 mg q4w	400 mg q4w	6	6	1
800	high	10 mg/kg q4w	none	11	11	11
800	high	600 mg q3w	300 mg q3w	12	7	6
800	high	800 mg q4w	400 mg q4w	12	7	6
800	high	400 mg q2w	none	23	16	16
800	high	5 mg/kg q2w	none	6	6	6
600	medium	300 mg q2w	400 mg q4w	6	5	5
533	medium	400 mg q3w	300 mg q3w	6	5	4
480	medium	240 mg q2w	400 mg q4w	6	4	3
480	medium	240 mg q2w	none	23	15	15
480	medium	240 mg q2w	240 mg q2w	6	6	6
480	medium	3 mg/kg q2w	none	12	11	11
400	medium	5 mg/kg q4w	none	6	6	6
400	medium	400 mg q4w	400 mg q4w	6	3	3

400	medium	400 mg q4w	none	5	5	5
320	medium	240 mg q3w	300 mg q3w	20	12	9
240	medium	3 mg/kg q4w	none	5	5	5
160	low	1 mg/kg q2w	1 mg/kg q2w	6	6	6
160	low	80 mg q2w	80 mg q2w	6	6	6
160	low	80 mg q2w	240 mg q2w	5	5	5
160	low	80 mg q2w	400 mg q4w	11	11	8
160	low	1 mg/kg q2w	none	13	13	13
80	low	80 mg q4w	240 mg q4w	7	7	7
48	very low	0.3 mg/kg q2w	1 mg/kg q2w	6	6	6

The anti-LAG-3 antibody and soluble LAG-3 data were obtained. The anti-LAG-3 antibody concentration data during the first 4 weeks were normalized by the first dose by mg. The anti-LAG-3 antibody dose was stratified into four groups (very low, low, medium, and high) based on the estimated total monthly dosing (over 28 days, in mg). For body-weight scaled doses, the total mg dose is calculated for the 80 kg patient. A larger decline in anti-LAG-3 antibody concentration was observed in some patients for the very low and low dose data than for the medium and high dose data, indicating nonlinear PK at the lower doses. The stratification groups were chosen to illustrate this nonlinearity.

The normalized anti-LAG-3 antibody concentrations two weeks (all regimens) after the first dose were obtained. At the lower doses (80 mg and below), there was a decline in the normalized drug concentration in some patients, indicating a nonlinearity in the PK. A model-based analysis of the data can also help to better characterize this nonlinearity using all available data.

PKPD Model fits

The PK parameters used were typical for a monoclonal antibody. Simulating the parameters, the terminal half-life and its 5-95% prediction interval was estimated to be 17.0 (7.0, 59.9) days. The estimated dissociation constant of 1.5 nM (Kd) was higher than measured in the Biacore assay (0.1 nM), but comparable to what was measured in the *in vitro* cell-based assays (1.9 - 2.3 nM). Visual predictive check of anti-LAG-3 antibody concentration normalized by total monthly dose showed good description of the PK data except in the low and very low dose groups where the PK nonlinearity was observed. A simulation of the largest anti-LAG-3 antibody dose within each panel was performed. The simulation describes the sLAG-3 curves well for all doses above 3 mg/kg (or 240 mg) q4w. For the low dose data, the PK was overestimated and thus the sLAG-3 was also overestimated.

Given the more rapid elimination at lower doses, a Michaelis-Menten PK model with nonlinear elimination was previously explored. However, the fits were not considerably better. Moreover, the additive error was generally estimated to be around 20 nM, much larger than the trough concentrations observed at 0.3 mg/kg q2w or 80 mg q4w, even for the models with nonlinear

elimination. Thus in this Example, only a linear model was used, with the caveat that the model over-estimates the trough concentrations at lower doses (e.g. 80 mg q2w).

To establish a threshold for when the nonlinearity in the PK becomes relevant, the anti-LAG-3 antibody population prediction vs measurement was examined. Note that below a critical concentration $C_{crit} = 60$ nM, the population prediction over predicts the measurement; it is below C_{crit} that the nonlinear PK begins to be observed. Using the trial simulation, the fraction of patients expected to stay above C_{crit} at trough was estimated in **Table 14**.

Fixed vs weight-based dosing predictions

Simulations of the anti-LAG-3 antibody trough level at 6 months for 700 mg and 10 mg/kg dosing were performed for both fixed and body-scaled dosing. Because the exponent relating weight to clearance was close to 0.5, the predicted variability in the anti-LAG-3 antibody trough is comparable for patients receiving fixed or body-weight based dosing, as also observed for other drugs (Bai et al. Clinical pharmacokinetics 51, 119–135 (2012); Wang et al., The Journal of Clinical Pharmacology 49, 1012–1024 (2009)). As the anti-LAG-3 antibody PK model is linear above 240 mg, similar results would be observed for any dose above 240 mg.

LAG-3 occupancy predictions

The simulated free LAG-3 concentration was compared to baseline from the PKPD model. Recall that this model did not capture the nonlinearity in the PK observed in lower doses and so below doses of 240 mg, there is likely less LAG-3 inhibition than predicted. Reducing the free soluble LAG-3 to 10% requires doses that are over 10x higher than for reducing the intra-tumoral membrane-bound LAG-3 to 10%. This is because the soluble LAG-3 accumulates about 75x in the serum, whereas it is not expected that membrane-bound LAG-3 would accumulate.

The results from the simulation above are summarized in **Table 14**, where the dose needed for 75, 90, and 95% of patients to meet the following three criteria at steady state are summarized:

1. LAG525 trough above C_{crit}
2. Tumor, membrane-bound LAG-3 free receptor below 10% of baseline
3. Serum soluble LAG-3 free receptor below 10% of baseline

Table 14. Predicted dose (mg) needed for 75%, 90%, and 95% of patients at steady state to meet the PK or PD criteria specified under q2w, q3w, and q4w regimens.

Dose for 75% patients to meet criteria:			
Criteria	q2w	q3w	q4w
LAG525 trough above C_{crit}	100	210	350

Free tumor mLAG-3 < 10% Baseline	100	200	400
Free serum sLAG-3 < 10% Baseline	>2000	>2000	>2000
Dose for 90% patients to meet criteria:			
Criteria	q2w	q3w	q4w
LAG525 trough above Ccrit	170	410	740
Free tumor mLAG-3 < 10% Baseline	200	400	800
Free serum sLAG-3 < 10% Baseline	>2000	>2000	>2000
Dose for 95% patients to meet criteria:			
Criteria	q2w	q3w	q4w
LAG525 trough above Ccrit	270	670	1190
Free tumor mLAG-3 < 10% Baseline	400	700	1400
Free serum sLAG-3 < 10% Baseline	>2000	>2000	>2000

Note that the doses needed for linear PK (anti-LAG-3 antibody trough > C_{crit}) and the dose needed to reduce the free tumor mLAG-3 concentration to < 10% from baseline are similar. This result is consistent with the hypothesis that target mediated drug disposition by the tumor infiltrating lymphocytes is what drives the rapid elimination at lower doses.

For antagonists, it is typical to target 90-95% receptor occupancy (or 5-10% free target compared to baseline) throughout the dosing interval, but this rule of thumb has not been validated for LAG-3 or for immune checkpoint inhibitors in general. If it is desired to achieve such receptor occupancy in most patients, it would be important to give a large enough dose such that rapid elimination at lower concentrations is not observed. Visual predictive check of anti-LAG-3 antibody concentration normalized by total monthly dose suggests that doses above 240 mg q4w may be sufficient to avoid this nonlinearity. **Table 14** predicts that 400 mg q3w or 800 mg q4w would give 90% receptor occupancy (10% free LAG-3 vs baseline) in 90% of patients.

Thus, this study shows that the relationship between the dose of an exemplary anti-LAG-3 antibody, LAG525, and receptor occupancy of both serum soluble LAG-3 and intratumoral membrane-bound LAG-3 receptor occupancy at doses of 240 mg and above was well characterized by the model. At lower doses (e.g. 80 mg every 2-4 weeks), a nonlinearity in the anti-LAG-3 antibody PK was observed in some patients. Above 240 mg every 3-4 weeks, anti-LAG-3 antibody PK appeared linear. The nonlinearity is thought to be due to target mediated drug disposition, as observed for many other monoclonal antibodies. Fixed and body-weight based dosing were predicted to give comparable variability in the steady state trough levels of anti-LAG-3 antibody. Co-administration of an anti-PD-1 antibody, PDR001, did not show any obvious impact on the anti-LAG-3 antibody PK.

INCORPORATION BY REFERENCE

All publications, patents, and Accession numbers mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference.

5

EQUIVALENTS

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

10

What is claimed is:

1. An anti-LAG-3 antibody molecule for use at a dose of about 300 mg to about 500 mg once every three weeks, or about 700 mg to about 900 mg once every four weeks, in treating a cancer in a subject,

wherein the anti-LAG-3 antibody molecule comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 701, a VHCDR2 amino acid sequence of SEQ ID NO: 702, and a VHCDR3 amino acid sequence of SEQ ID NO: 703; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 710, a VLCDR2 amino acid sequence of SEQ ID NO: 711, and a VLCDR3 amino acid sequence of SEQ ID NO: 712.

2. A method of treating a cancer in a subject, the method comprising administering to the subject an anti-LAG-3 antibody molecule at a dose of about 300 mg to about 500 mg once every three weeks, or about 700 mg to about 900 mg once every four weeks,

wherein the anti-LAG-3 antibody molecule comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 701, a VHCDR2 amino acid sequence of SEQ ID NO: 702, and a VHCDR3 amino acid sequence of SEQ ID NO: 703; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 710, a VLCDR2 amino acid sequence of SEQ ID NO: 711, and a VLCDR3 amino acid sequence of SEQ ID NO: 712.

3. The antibody molecule for use of claim 1, or the method of claim 2, wherein the anti-LAG-3 antibody molecule is used at a dose of about 300 mg to about 500 mg once every three weeks.

4. The antibody molecule for use of claim 3, or the method of claim 3, wherein the anti-LAG-3 antibody molecule is used at a dose of about 400 mg once every three weeks.

5. The antibody molecule for use of claim 1, or the method of claim 2, wherein the anti-LAG-3 antibody molecule is used at a dose of about 700 mg to about 900 mg once every four weeks.

6. The antibody molecule for use of claim 5, or the method of claim 5, wherein the anti-LAG-3 antibody molecule is used at a dose of about 800 mg once every four weeks.

7. The antibody molecule for use of any of claims 1 or 3-6, or the method of any of claims 2-6, wherein the antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 706 and a VL comprising the amino acid sequence of SEQ ID NO: 718.

8. The antibody molecule for use of any of claims 1 or 3-7, or the method of any of claims 2-7, wherein the antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 709 and a light chain comprising the amino acid sequence of SEQ ID NO: 721.

9. The antibody molecule for use of any of claims 1 or 3-6, or the method of any of claims 2-6, wherein the antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 724 and a VL comprising the amino acid sequence of SEQ ID NO: 730.

10. The antibody molecule for use of any of claims 1, 3-6, or 9, or the method of any of claims 2-6 or 9, wherein the antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 727 and a light chain comprising the amino acid sequence of SEQ ID NO: 733.

11. The antibody molecule for use of any of claims 1 or 3-10, or the method of any of claims 2-10, wherein the cancer is a solid tumor or a hematological cancer.

12. The antibody molecule for use of any of claims 1 or 3-11, or the method of any of claims 2-11, wherein the cancer is chosen from a brain cancer, a pancreatic cancer, a skin cancer, a renal cancer, a breast cancer, a virus-associated cancer, an anal canal cancer, a cervical cancer, a gastric cancer, a head and neck cancer, a nasopharyngeal cancer (NPC), a penile cancer, a vaginal or vulvar cancer, a colorectal cancer, a lung cancer, a leukemia, a lymphoma, a myeloma, or a metastatic lesion of the cancer.

13. The antibody molecule for use of claim 12, or the method of claim 12, wherein the brain cancer is a glioblastoma or a gliosarcoma.

14. The antibody molecule for use of claim 12, or the method of claim 12, wherein the skin cancer is a melanoma or a Merkel cell carcinoma.

15. The antibody molecule for use of claim 12, or the method of claim 12, wherein the renal cancer is a renal cell carcinoma (RCC).

16. The antibody molecule for use of claim 12, or the method of claim 12, wherein the breast cancer is a breast carcinoma or a triple negative breast cancer (TNBC).

17. The antibody molecule for use of claim 12, or the method of claim 12, wherein the virus-associated cancer is chosen from an anal canal cancer, a cervical cancer, a gastric cancer, a head and neck cancer, a nasopharyngeal cancer (NPC), a penile cancer, or a vaginal or vulvar cancer.

18. The antibody molecule for use of claim 12, or the method of claim 12, wherein the colorectal cancer is chosen from a microsatellite unstable colorectal cancer, a microsatellite stable colorectal cancer, a mismatch repair proficient colorectal cancer, or a mismatch repair deficient colorectal cancer.

19. The antibody molecule for use of claim 12, or the method of claim 12, wherein the lung cancer is a non-small cell lung cancer (NSCLC).

20. The antibody molecule for use of claim 12, or the method of claim 12, wherein the lymphoma is a Hodgkin lymphoma (HL) or a diffuse large B cell lymphoma (DLBCL).

21. The antibody molecule for use of any of claims 1 or 3-20, or the method of any of claims 2-20, wherein the cancer is an advanced cancer, a metastatic cancer, a recurrent cancer, a relapsed cancer, or an unresectable cancer.

22. The antibody molecule for use of any of claims 1 or 3-21, or the method of any of claims 2-21, wherein the anti-LAG-3 antibody molecule is used in combination with a second therapeutic agent or modality.

23. The antibody molecule for use of any of claims 1 or 3-22, or the method of any of claims 2-22, wherein the anti-LAG-3 antibody molecule is used in combination with a PD-1 inhibitor.

24. The antibody molecule for use of claim 23, or the method of claim 23, wherein the PD-1 inhibitor is chosen from PDR001, nivolumab, pembrolizumab, pidilizumab, MEDI0680, REGN2810, PF-06801591, BGB-A317, INCHR1210, TSR-042, or AMP-224.

25. The antibody molecule for use of claim 23 or 24, or the method of claim 23 or 24, wherein the PD-1 inhibitor is used at a dose of about 300 mg once every three weeks or about 400 mg once every four weeks.

26. The antibody molecule for use of any of claims 1 or 3-25, or the method of any of claims 2-25, wherein the anti-LAG-3 antibody molecule is used in combination with a PD-L1 inhibitor.

27. The antibody molecule for use of claim 26, or the method of claim 26, wherein the PD-L1 inhibitor is chosen from FAZ053, atezolizumab, avelumab, durvalumab, or BMS-936559.

28. The antibody molecule for use of any of claims 1 or 3-27, or the method of any of claims 2-27, wherein the anti-LAG-3 antibody molecule is used in combination with a chemotherapeutic agent.

29. The antibody molecule for use of claim 28, or the method of claim 28, wherein the chemotherapeutic agent is chosen from a platinum agent and a nucleotide analog or precursor analog.

30. The antibody molecule for use of claim 29, or the method of claim 29, wherein the platinum agent is chosen from carboplatin, cisplatin, oxaliplatin, or tetraplatin.

31. The antibody molecule for use of claim 29, or the method of claim 29, wherein the nucleotide analog or precursor analog comprises capecitabine.

32. The antibody molecule for use of any of claims 1 or 3-31, or the method of any of claims 2-31, wherein the anti-LAG-3 antibody molecule is used to treat a cancer chosen from an NSCLC, a melanoma, a renal cancer, a glioblastoma, a virus-associated cancer, or a colorectal cancer.

33. The antibody molecule for use of claim 32, or the method of claim 32, wherein the anti-LAG-3 antibody molecule is used in combination with an anti-PD-1 antibody molecule.

34. The antibody molecule for use of any of claims 1 or 3-31, or the method of any of claims 2-31, wherein the anti-LAG-3 antibody molecule is used to treat a pancreatic cancer or a breast cancer.

35. The antibody molecule for use of claim 34, or the method of claim 34, wherein the breast cancer is TNBC.

36. The antibody molecule for use of claim 34 or 35, or the method of claim 34 or 35, wherein the anti-LAG-3 antibody molecule is used in combination with an anti-PD-1 antibody molecule.

37. The antibody molecule for use of any of claims 34-36, or the method of any of claims 34-36, wherein the anti-LAG-3 antibody molecule is used in combination with a chemotherapeutic agent.

38. The antibody molecule for use of claim 37, or the method of claim 37, wherein the chemotherapeutic agent is chosen from a platinum agent and a nucleotide analog or precursor analog.

39. The antibody molecule for use of claim 38, or the method of claim 38, wherein the platinum agent is chosen from carboplatin, cisplatin, oxaliplatin, or tetraplatin.

40. The antibody molecule for use of claim 38, or the method of claim 38, wherein the nucleotide analog or precursor analog comprises capecitabine.

41. The antibody molecule for use of any of claims 1 or 3-40, or the method of any of claims 2-40, wherein the subject has, or is identified as having, LAG-3 expression in tumor-infiltrating lymphocytes (TILs).

42. The antibody molecule for use of any of claims 1 or 3-41, or the method of any of claims 2-41, wherein the subject has, or is identified as having, a cancer that expresses PD-L1.

43. A pharmaceutical composition or dose formulation comprising an anti-LAG-3 antibody molecule for use at a dose of about 300 mg to about 500 mg once every three weeks, or about 700 mg to about 900 mg once every four weeks, in treating a cancer in a subject, wherein the anti-LAG-3 antibody molecule comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 701, a VHCDR2 amino acid sequence of SEQ ID NO: 702, and a VHCDR3 amino acid sequence of SEQ ID NO: 703; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 710, a VLCDR2 amino acid sequence of SEQ ID NO: 711, and a VLCDR3 amino acid sequence of SEQ ID NO: 712.

44. The pharmaceutical composition or dose formulation of claim 43, wherein the dose is about 300 mg to about 500 mg once every three weeks.

45. The pharmaceutical composition or dose formulation of claim 43, wherein the dose is about 700 mg and about 900 mg once every four weeks.

46. The pharmaceutical composition or dose formulation of any of claims 43-45, wherein the antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 706 and a VL comprising the amino acid sequence of SEQ ID NO: 718.

47. The pharmaceutical composition or dose formulation of any of claims 43-46, wherein the antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 709 and a light chain comprising the amino acid sequence of SEQ ID NO: 721.

48. The pharmaceutical composition or dose formulation of any of claims 43-45, wherein the antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 724 and a VL comprising the amino acid sequence of SEQ ID NO: 730.

49. The pharmaceutical composition or dose formulation of any of claims 43-45 or 48, wherein the antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 727 and a light chain comprising the amino acid sequence of SEQ ID NO: 733.

50. The pharmaceutical composition or dose formulation of any of claims 43-49 for use to treat a cancer.

51. The pharmaceutical composition or dose formulation of claim 50, wherein the cancer is a solid tumor or a hematological cancer.

52. The pharmaceutical composition or dose formulation of claim 50 or 51, wherein the cancer is chosen from a brain cancer, a pancreatic cancer, a skin cancer, a renal cancer, a breast cancer, a virus-associated cancer, an anal canal cancer, a cervical cancer, a gastric cancer, a head and neck cancer, a nasopharyngeal cancer (NPC), a penile cancer, a vaginal or vulvar cancer, a colorectal cancer, a lung cancer, a leukemia, a lymphoma, a myeloma, or a metastatic lesion of the cancer.

53. An anti-LAG-3 antibody molecule for use in treating a cancer in a subject at a dose or dosage schedule that results in one or both of: (a) 50% or more of the soluble LAG-3 in the serum, or a serum sample, from the subject is bound by the anti-LAG-3 antibody molecule; or (b) 90% or more of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject is bound by the anti-LAG-3 antibody molecule.

54. A method of treating a cancer in a subject, the method comprising administering to the subject an anti-LAG-3 antibody molecule at a dose or dosage schedule that results in one or both of: (a) 50% or more of the soluble LAG-3 in the serum, or a serum sample, from the subject is bound

by the anti-LAG-3 antibody molecule; or (b) 90% or more of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject is bound by the anti-LAG-3 antibody molecule.

55. The antibody molecule for use of claim 53, or the method of claim 54, wherein the dosage schedule results in one or both of: (a) 60% or more of the soluble LAG-3 in the serum, or a serum sample, from the subject is bound by the anti-LAG-3 antibody molecule; or (b) 90% or more of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject is bound by the anti-LAG-3 antibody molecule.

56. The antibody molecule for use of claim 53 or 55, or the method of claim 54 or 55, wherein the dosage schedule results in one or both of: (a) 70% or more of the soluble LAG-3 in the serum, or a serum sample, from the subject is bound by the anti-LAG-3 antibody molecule; or (b) 90% or more of the membrane-bound LAG-3 in the cancer, or a cancer sample, from the subject is bound by the anti-LAG-3 antibody molecule.

57. The antibody molecule for use of any of claims 53 or 55-56, or the method of any of claims 54-56, wherein the anti-LAG-3 antibody molecule comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 701, a VHCDR2 amino acid sequence of SEQ ID NO: 702, and a VHCDR3 amino acid sequence of SEQ ID NO: 703; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 710, a VLCDR2 amino acid sequence of SEQ ID NO: 711, and a VLCDR3 amino acid sequence of SEQ ID NO: 712.

58. The antibody molecule for use of any of claims 53 or 55-57, or the method of any of claims 54-57, wherein the antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 706 and a VL comprising the amino acid sequence of SEQ ID NO: 718.

59. The antibody molecule for use of any of claims 53 or 55-58, or the method of any of claims 54-58, wherein the antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 709 and a light chain comprising the amino acid sequence of SEQ ID NO: 721.

60. The antibody molecule for use of any of claims 53 or 55-57, or the method of any of claims 54-57, wherein the antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 724 and a VL comprising the amino acid sequence of SEQ ID NO: 730.

61. The antibody molecule for use of any of claims 53, 55-57, or 60, or the method of any of claims 54-57 or 60, wherein the antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 727 and a light chain comprising the amino acid sequence of SEQ ID NO: 733.

62. The antibody molecule for use of any of claims 54-61, or the method of any of claims 54-61, wherein the anti-LAG-3 antibody molecule is administered at a dose of about 300 mg to about 500 mg once every three weeks or about 700 mg to about 900 mg once every four weeks.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/043030

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 53-62
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/043030

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/00 C07K16/28
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/138920 A1 (NOVARTIS AG) 17 September 2015 (2015-09-17) page 49 - page 51 page 104 page 109 - page 111 page 225	1-52
X	WO 2017/019894 A1 (NOVARTIS AG [CH]; IMMUTEP S A S [FR]; DRANOFF GLENN [US]; TRIEBEL FRÉD) 2 February 2017 (2017-02-02) page 221 - page 231	1-52
A	WO 2015/116539 A1 (SQUIBB BRISTOL MYERS CO [US]) 6 August 2015 (2015-08-06) claim 1	1-6, 43-45
	----- -/--	

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 12 September 2018	Date of mailing of the international search report 28/09/2018
--	--

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Galli, Ivo
--	--------------------------------------

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/043030

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2017/106656 A1 (NOVARTIS AG [CH]; BILIC SANELA [US]; HOWARD DANNY RONALD JR [US]; CAME) 22 June 2017 (2017-06-22) * LAG525 and PDR001 3 -----	22-27
L	Hong D.S. et al.: "Phase I/II study of LAG525 spartalizumab (PDR001) in patients (pts) with advanced malignancies.", 2018 ASCO Annual Meeting J. Clin. Onc., vol. 36, no. Suppl., 3012, 4 May 2018 (2018-05-04), XP002784659, Retrieved from the Internet: URL: http://abstracts.asco.org/214/AbstView_214_222927.html [retrieved on 2018-09-11] the whole document -----	1-52

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2018/043030

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015138920 A1	17-09-2015	AU 2015229103 A1	04-08-2016
		BR 112016018408 A2	26-12-2017
		CA 2936962 A1	17-09-2015
		CL 2016002112 A1	09-06-2017
		CN 106103484 A	09-11-2016
		CR 20160425 A	26-05-2017
		EA 201691765 A1	30-12-2016
		EP 3116909 A1	18-01-2017
		JP 2017516489 A	22-06-2017
		KR 20160134668 A	23-11-2016
		PE 00712017 A1	17-03-2017
		PH 12016501545 A1	14-09-2016
		SG 11201605951Y A	28-10-2016
		TW 201540727 A	01-11-2015
		US 2015259420 A1	17-09-2015
		US 2017210804 A1	27-07-2017
		US 2018086830 A1	29-03-2018
UY 36032 A	30-10-2015		
WO 2015138920 A1	17-09-2015		
WO 2017019894 A1	02-02-2017	EP 3317301 A1	09-05-2018
		WO 2017019894 A1	02-02-2017
WO 2015116539 A1	06-08-2015	CA 2937503 A1	06-08-2015
		CN 105992595 A	05-10-2016
		EA 201691361 A1	30-12-2016
		EP 3099716 A1	07-12-2016
		JP 2017505773 A	23-02-2017
		KR 20160106762 A	12-09-2016
		US 2016326248 A1	10-11-2016
		US 2018244773 A1	30-08-2018
WO 2015116539 A1	06-08-2015		
WO 2017106656 A1	22-06-2017	AU 2016369537 A1	28-06-2018
		CN 108495651 A	04-09-2018
		KR 20180088907 A	07-08-2018
		WO 2017106656 A1	22-06-2017

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 53-62

Claims 53-56 concern generic anti-LAG3 antibodies for use in treating cancer, defined by physiological outcomes. Neither the identity of the antibody nor the dose/frequency of administration is given.

Claims 57-61 concern the same, specifying only which antibody is to be used. The dose/frequency is not specified.

Claim 62 concerns the same, specifying the dose/frequency, but not the antibody to be used.

Such claims so lack clarity, support and disclosure in the sense of Art. 5-6 PCT that they cannot be searched.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.