IV. Bispecific Molecules

[0010] The provision of bispecific molecules (*e.g.*, bispecific antibodies, bispecific diabodies, *etc.*) provides a significant advantage over monospecific natural antibodies: the capacity to co-ligate and co-localize cells that express different epitopes. Bispecific molecules thus have wide-ranging applications including therapy. Bispecificity allows for great flexibility in the design and engineering in various applications, providing enhanced avidity to multimeric antigens, the cross-linking of differing antigens, and directed targeting to specific cell types relying on the presence of both target antigens. PD-1 x LAG-3 bispecific molecules for use in the treatment of cancer and/or a disease associated with a pathogen are described in PCT Publication Nos. WO 2015/200119, WO 2017/025498, WO 2018/083087, WO 2018/185043, WO 2018/134279, and WO 2018/217940. In particular, PD-1 x LAG-3 bispecific diabodies having novel PD-1- and LAG-3-Binding Domains and exemplary activity are described in WO 2017/019846.

V. Tumor Antigens

[0011] Tumor Antigens ("TA") comprise cell membrane proteins that are present only on tumor cells and not on any other cell (*i.e.*, tumor-specific antigens) or are characteristically present on tumor cells, but are also present on certain normal cells (*i.e.*, **tumor-associated antigens**). Tumor antigens can be targeted by antibodies and used to stimulate the cells of the immune system to overcome tumor escape, and play a renewed role in tumor surveillance and clearance (Tan, S. *et al*. (2020) "*Cancer Immunotherapy: Pros, Cons And Beyond*," Biomed. Pharmacother. 124:109821:1-11; Finn, O.J. (2017) "*Human Tumor Antigens Yesterday, Today, and Tomorrow*," Cancer Immunol. Res. 5(5):347-354; Barros, L. *et al*. (2018) "*Immunological-Based Approaches For Cancer Therapy*," Clinics 73(suppl 1):e429s:1-11; Smith, C.C. *et al*. (2019) "*Alternative Tumour-Specific Antigens*," Nat. Rev. Cancer 19(8):465-478; Ehx, G. *et al*. (2019) "*Discovery And Characterization Of Actionable Tumor Antigens*," Genome Med. 11:29:1-3).

Summary ~~of the Invention~~

[0012] Provided herein are regimens capable of more vigorously directing the body's immune system to attack cancer cells. For although the adaptive immune system can be a potent defense mechanism against cancer and disease, it is often hampered by immune

suppressive/evasion mechanisms in the tumor microenvironment, mediated by PD-1/PD-L1 interactions or by the inhibitory activity of LAG-3. As provided herein, such immune suppressive/evasion mechanisms can be overcome by the administration of a PD-1 x LAG-3 bispecific molecule. As further provided herein, dual checkpoint inhibition of the PD/PD-L1 and LAG-3 checkpoint pathways can synergize with the anti-tumor activity of a TA-Binding Molecule (particularly one having enhanced ADCC activity).

[0013] The present ~~invention~~disclosure is directed to regimens for administering one or more Antibody-Based Molecules that bind PD-1 or PD-L1, and LAG-3 (*e.g.*, a PD-1 x LAG-3 bispecific molecule alone, or in combination with an Antibody-Based Molecule that binds a Tumor Antigen (TA) for the treatment of cancer. The ~~invention~~disclosure particularly concerns the use of such regimens in conjunction with PD-1 x LAG-3 bispecific molecules. The ~~invention~~disclosure is directed to the use of such molecules, and to the use of pharmaceutical compositions and pharmaceutical kits that that contain such molecules and that facilitate the use of such dosing regimens in the treatment of cancer.

[0013a] In one aspect, the present disclosure refers to use of:

(a) a bispecific molecule that immunospecifically binds both PD-1 and LAG-3 (PD-1 x LAG-3 bispecific molecule); or

(b) a molecule that immunospecifically binds PD-1 (PD-1-Binding Molecule) in combination with a molecule that immunospecifically binds LAG-3 (LAG-3-Binding Molecule); or

(c) a bispecific molecule that immunospecifically binds both PD-L1 and LAG-3 (PD-L1 x LAG-3 bispecific molecule); or

(d) a molecule that immunospecifically binds PD-L1 (PD-L1-Binding Molecule) in combination with a LAG-3-Binding Molecule;

for the manufacture of a medicament for the treatment of cancer.

[0014] The ~~invention~~disclosure particularly concerns methods of treating a cancer comprising administering a PD-1 x LAG-3 bispecific molecule to a subject in need thereof, wherein the method comprises administering the PD-1 x LAG-3 bispecific molecule to the subject at a flat dose of from about 120 mg to about 800 mg.

[0015] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of such a method, wherein the cancer is characterized by the expression of a Tumor Antigen (TA), and wherein the method further comprising administering to the subject a Tumor Antigen (TA) Binding Molecule (TA-Binding Molecule).

[0016] The ~~invention~~disclosure further concerns methods of treating a cancer in a subject, wherein the cancer is characterized by the expression of a TA, the method comprising administering a TA-Binding Molecule to the subject and:

(a) a bispecific PD-1 x LAG-3 bispecific molecule; or

(b) a molecule that immunospecifically binds PD-1 (PD-1-Binding Molecule) in combination with a molecule that immunospecifically binds LAG-3 (LAG-3-Binding Molecule); or

(c) a bispecific molecule that immunospecifically binds both PD-L1 and LAG-3 (PD-L1 x LAG-3 bispecific molecule); or

(d) a molecule that immunospecifically binds PD-L1 (PD-L1-Binding Molecule) in combination with a LAG-3-Binding Molecule.

[0017] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the TA-Binding Molecule comprises an ADCC-Enhanced Fc Domain.

[0018] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein:

(a) each molecule is in a separate composition; or

(b) each molecule is in the same composition; or

(c) the PD-1-Binding Molecule and the LAG-3-Binding Molecule are in the same composition, and the TA-binding molecule is in a separate composition; or

(d) the PD-L1-Binding Molecule and the LAG-3-Binding Molecule are in the same composition, and the TA-binding molecule is in a separate composition The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the TA-Binding Molecule is an antibody.

[0019] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the PD-1-Binding Molecule is an antibody, the PD-L1-Binding Molecule is an antibody, and the LAG-3-Binding Molecule is an antibody.

[0020] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the method comprises administering the TA-Binding Molecule and the PD-1 x LAG-3 bispecific molecule.

[0021] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the ADCC-Enhanced Fc Domain comprises:

(A) an engineered glycoform; and/or

(B) an amino acid substitution relative to a wild-type Fc Region.

[0022] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the ADCC-Enhanced Fc Domain comprises:

(A) an engineered glycoform that is a complex N-glycoside-linked sugar chain that does not contain fucose, and/or that comprises a bisecting O-GlcNAc; and/or

(B) comprises an amino acid substitution is selected from the group consisting of:

(a) one substitution selected from the group consisting of:

F243L, R292P, Y300L, V305I, I332E, and P396L;

(b) two substitutions selected from the group consisting of:

(1) F243L and P396L;

(2) F243L and R292P;

(3) R292P and V305I; and

(4) S239D and I332E;

(c) three substitutions selected from the group consisting of:

(1) F243L, R292P and Y300L;

(2) F243L, R292P and V305I;

(3) F243L, R292P and P396L; and

(4) R292P, V305I and P396L;

(d) four substitutions selected from the group consisting of:

(1) F243L, R292P, Y300L and P396L; and

(2) F243L, R292P, V305I and P396L; or

(e) five substitutions selected from the group consisting of:

(1) F243L, R292P, Y300L, V305I and P396L; and

(2) L235V, F243L, R292P, Y300L and P396L,

wherein the numbering is that of the EU index as in Kabat.

[0023] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the ADCC-Enhanced Fc Domain comprises the amino acid substitutions: L235V, F243L, R292P, Y300L and P396L, wherein the numbering is that of the EU index as in Kabat.

[0024] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein:

(A) the TA is selected from **Table 6A** or **Table 6B**; and/or

(B) the TA-Binding Molecule comprises the VL and VH Domains of an antibody selected from **Table 7**.

[0025] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein:

(A) the PD-1-Binding Molecule is an antibody that comprises:

(a) a PD-1 VL Domain that comprises the amino acid sequence of **SEQ ID NO:35**, and a PD-1 VH Domain that comprises the amino acid sequence of **SEQ ID NO:39**;

(b) a VH and VL Domain of an anti-PD-1 antibody selected from **Table 1**; or

(c) a light chain and a heavy chain of an anti-PD-1 antibody selected from **Table 1**;

(B) the PD-L1-Binding Molecule is an antibody that comprises:

(a) a PD-L1 VL Domain that comprises the amino acid sequence of **SEQ ID NO:43**, and a PD-L1 VH Domain that comprises the amino acid sequence of **SEQ ID NO:47**;

(b) a VH and VL Domain of an anti-PD-L1 antibody selected from **Table 2**; or

(c) a light chain and a heavy chain of an anti-PD-L1 antibody selected from **Table 2**; and

(C) the LAG-3-Binding Molecule is an antibody that comprises:

(a) a LAG-3 VL Domain that comprises the amino acid sequence of **SEQ ID NO:51**, and a LAG-3 VH Domain that comprises the amino acid sequence of **SEQ ID NO:55**;

(b) a VH and VL Domain of an anti-LAG-3 antibody selected from **Table 3**; or

(c) a light chain and heavy chain of an anti-LAG-3 antibody selected from **Table 3**.

[0026] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the PD-1 x LAG-3 bispecific molecule comprises:

(a) a PD-1 VL Domain that comprises the amino acid sequence of **SEQ ID NO:35**, and a PD-1 VH Domain that comprises the amino acid sequence of **SEQ ID NO:39**, or a VH and VL Domain of an anti-PD-1 antibody selected from **Table 1**; and/or

(b) a LAG-3 VL Domain that comprises the amino acid sequence of **SEQ ID NO:51**, and a LAG-3 VH Domain that comprises the amino acid sequence of **SEQ ID NO:55**, or a VH and VL Doman of an anti-LAG-3 antibody selected from **Table 3**; or

(c) a bispecific Antibody-Based Molecule selected from **Tables 4-5**.

[0027] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the PD-1 x LAG-3 bispecific molecule comprises:

(a) two of the PD-1-Binding Domains; and

(b) two of the LAG-3-Binding Domains.

[0028] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the PD-1 x LAG-3 bispecific molecule comprises the PD-1 VL Domain of **SEQ ID NO:35**, the PD-1 VH Domain of **SEQ ID NO:39**, the LAG-3 VL Domain of **SEQ ID NO:51**, and the LAG-3 VH Domain of **SEQ ID NO:55**.

[0029] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the PD-1 x LAG-3 bispecific molecule or the PD-L1 x LAG-3 bispecific molecule comprises an Fc Region and a Hinge Domain, and the ~~embodiment~~example, wherein the Fc Region and the Hinge Domain are both of the IgG4 isotype, and wherein the Hinge Domain comprises a stabilizing mutation.

[0030] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the Fc Region is a variant Fc Region that comprises:

(a) one or more amino acid modifications that reduces the affinity of the variant Fc Region for an FcγR; and/or

(b) one or more amino acid modifications that enhances the serum half-life of the variant Fc Region.

[0031] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the:

(a) modifications that reduce the affinity of the variant Fc Region for an FcγR comprise the substitution of L234A; L235A; or L234A and L235A; and

(b) modifications that enhances the serum half-life of the variant Fc Region comprise the substitution of M252Y; M252Y and S254T; M252Y and T256E; M252Y, S254T and T256E; or K288D and H435K,

wherein the numbering is that of the EU index as in Kabat.

[0032] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the PD-1 x LAG-3 bispecific molecule comprises two polypeptide chains of **SEQ ID NO:59** and two polypeptide chains of **SEQ ID NO:60**.

[0033] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the PD-1 x LAG-3 bispecific molecule or the PD-L1 x LAG-3 bispecific molecule is administered at a flat dose of about 300 mg, and the ~~embodiment~~example, wherein the PD-1 x LAG-3 bispecific molecule or the PD-L1 x LAG-3 bispecific molecule is administered at a flat dose of about 600 mg.

[0034] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the flat dose is administered once about every 2 weeks, and the ~~embodiment~~example, wherein the flat dose is administered once about every 3 weeks.

[0035] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the PD-1 x LAG-3 bispecific molecule or the PD-L1 x LAG-3 bispecific molecule is administered at a flat dose of about 600 mg once about every 2 weeks.

[0036] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the PD-1 x LAG-3 bispecific molecule or the PD-L1 x LAG-3 bispecific molecule is administered at a flat dose of about 600 mg once about every 3 weeks.

[0037] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the PD-1 x LAG-3 bispecific molecule or the PD-L1 x LAG-3 bispecific molecule is administered by intravenous (IV) infusion.

[0038] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the cancer is selected from the group consisting of: adrenal gland cancer, AIDS-associated cancer, alveolar soft part sarcoma, anal cancer (including squamous cell carcinoma of the anal canal (SCAC)), bladder cancer, bone cancer, brain and spinal cord cancer, breast cancer (including, $HER2^+$ breast cancer or Triple-Negative Breast Cancer

(TNBC)), carotid body tumor, cervical cancer (including, HPV-related cervical cancer), chondrosarcoma, chordoma, chromophobe renal cell carcinoma, clear cell carcinoma, colon cancer, colorectal cancer, desmoplastic small round cell tumor, ependymoma, endometrial cancer (including, unselected endometrial cancer, MSI-high endometrial cancer, dMMR endometrial cancer, and/or POLE exonuclease domain mutation positive endometrial cancer), Ewing's sarcoma, extraskeletal myxoid chondrosarcoma, gallbladder or bile duct cancer (including, cholangiocarcinoma bile duct cancer), gastric cancer, gastroesophageal junction (GEJ) cancer, gestational trophoblastic disease, germ cell tumor, glioblastoma, head and neck cancer (including, squamous cell carcinoma of head and neck (SCCHN)), a hematological malignancy, a hepatocellular carcinoma, islet cell tumor, Kaposi's Sarcoma, kidney cancer, leukemia (including, acute myeloid leukemia), liposarcoma/malignant lipomatous tumor, liver cancer (including, hepatocellular carcinoma liver cancer (HCC)), lymphoma (including, diffuse large B-cell lymphoma (DLBCL), non-Hodgkin's lymphoma (NHL)), lung cancer (including, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC)), medulloblastoma, melanoma (including, uveal melanoma), meningioma, Merkel cell carcinoma, mesothelioma (including, mesothelial pharyngeal cancer), multiple endocrine neoplasia, multiple myeloma, myelodysplastic syndrome, neuroblastoma, neuroendocrine tumors, ovarian cancer, pancreatic cancer, papillary thyroid carcinoma, parathyroid tumor, pediatric cancer, peripheral nerve sheath tumor, pharyngeal cancer, pheochromocytoma, pituitary tumor, prostate cancer (including, metastatic castration resistant prostate cancer (mCRPC)), posterious uveal melanoma, renal metastatic cancer, rhabdoid tumor, rhabdomyosarcoma, sarcoma, skin cancer, a small round blue cell tumor of childhood (including neuroblastoma and rhabdomyosarcoma), soft-tissue sarcoma, squamous cell cancer, stomach cancer, synovial sarcoma, testicular cancer, thymic carcinoma, thymoma, thyroid cancer, and uterine cancer.

[0039] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the cancer is selected from the group consisting of: anal cancer, breast cancer, bile duct cancer, cervical cancer, colorectal cancer, endometrial cancer, gastric cancer, GEJ cancer, head and neck cancer, liver cancer, lung cancer, lymphoma, melanoma, ovarian cancer and prostate cancer.

[0040] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the cancer is selected from the group consisting of: $HER2^+$ breast cancer, TNBC, cholangiocarcinoma bile duct cancer, HPV-related cervical cancer, SCCHN, HCC, SCLC or NSCLC, NHL, prostate cancer, gastric cancer and GEJ cancer.

[0041] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the TA-Binding Molecule is a HER2-Binding Molecule comprising a HER2-Binding Domain comprising a Light Chain Variable Domain (VL_{HER2}) and a Heavy Chain Variable Domain (VH_{HER2}), wherein:

(A) the Light Chain Variable Domain (VL_{HER2}) comprises the Light Chain Variable Domain of margetuximab that comprises the CDR_L1, CDR_L2 and CDR_L3 of **SEQ ID NO:61**, and the Heavy Chain Variable Domain (VH_{HER2}) comprises the Heavy Chain Variable Domain of margetuximab that comprises the CDR_H1, CDR_H2 and CDR_H3 of **SEQ ID NO:66**;

(B) the Light Chain Variable Domain (VL_{HER2}) comprises the CDR_L1, CDR_L2 and CDR_L3 of trastuzumab and the Heavy Chain Variable Domain (VH_{HER2}) comprises the CDR_H1, CDR_H2 and CDR_H3 of trastuzumab;

(C) the Light Chain Variable Domain (VL_{HER2}) comprises the CDR_L1, CDR_L2 and CDR_L3 of pertuzumab and the Heavy Chain Variable Domain (VH_{HER2}) comprises the CDR_H1, CDR_H2 and CDR_H3 of pertuzumab; or

(D) the Light Chain Variable Domain (VL_{HER2}) comprises the CDR_L1, CDR_L2 and CDR_L3 of hHER2 MAB-1 and the Heavy Chain Variable Domain (VH_{HER2}) comprises the CDR_H1, CDR_H2 and CDR_H3 of hHER2 MAB-1.

[0042] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the HER2-Binding Molecule is an anti-HER2 antibody.

[0043] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the anti-HER2 antibody is margetuximab, and the method comprises administering margetuximab at a dosage of about 6 mg/kg to about 18 mg/kg once about every 3 weeks.

[0044] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the method further comprises administered a chemotherapeutic agent.

[0045] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the cancer is a HER2 expressing cancer, and particularly, wherein, wherein the HER2 expressing cancer is selected from the group consisting of: breast cancer, metastatic breast cancer, bladder, gastric cancer, GEJ cancer, ovarian cancer, pancreatic cancer, and stomach cancer.

[0046] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the TA-Binding Molecule is a B7-H3-Binding Molecule comprising a B7-H3-Binding Domain comprising a Light Chain Variable Domain (VL) and a Heavy Chain Variable Domain (VH), wherein:

the VL comprises the CDR_L1, CDR_L2 and CDR_L3 of **SEQ ID NO:71**, and the VH the CDR_H1, CDR_H2 and CDR_H3 of **SEQ ID NO:76**.

[0047] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the TA-Binding Molecule is enoblituzumab and the method comprises administering enoblituzumab at a dosage of about 6 mg/kg to about 18 mg/kg once about every 3 weeks.

[0048] The method of any one of claims 2-33 or 40-41, wherein the cancer is a B7-H3 expressing cancer, and particularly wherein the B7-H3 expressing cancer is selected from the group consisting of: anal cancer, SCAC, a breast cancer, TNBC, a head and neck cancer, SCCHN, lung cancer, NSCLC, melanoma, uveal melanoma, prostate cancer, and mCRPC.

[0049] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein the TA-binding molecule is administered by intravenous (IV) infusion.

[0050] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein cells expressing LAG-3 are present in a biopsy of the cancer prior to the treatment, and the ~~embodiment~~example, wherein cells expressing PD-1 are present in a biopsy of the cancer prior to the treatment.

[0051] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein co-expression of LAG-3 and PD-1 in a biopsy of the cancer prior to the treatment is indicative that such patient that is a candidate for such methods, and the ~~embodiment~~example, wherein expression is gene expression.

[0052] The ~~invention~~disclosure additionally concerns the ~~embodiment~~example of the above described methods, wherein PD-L1 expression on the surface of cells of the cancer, prior to the treatment, is less than 1% as determined using a Combined Positive Score (CPS) or a Tumor Proportion Score (TPS).

Brief Description of the Drawings

[0053] **Figure 1** provide schematics showing representative covalently bonded tetravalent diabodies having four epitope-binding sites composed of two pairs of polypeptide chains (*i.e.*, four polypeptide chains in all). One polypeptide of each pair has an E-coil Heterodimer-Promoting Domain and the other polypeptide of each pair has a K-coil Heterodimer-Promoting Domain. As shown, a cysteine residue may be present in a linker and/or in the Heterodimer-Promoting Domain. One polypeptide of each pair possesses a linker comprising a cysteine (which linker may comprise all or a portion of a hinge region) and CH2 and/or CH3 Domain, such that the associated chains form all or part of an Fc Region. VL and VH Domains that recognize the same epitope are shown using the same shading or fill pattern. In such embodiments wherein the two pairs of polypeptide chains are the same and the VL and VH Domains recognize different epitopes (as shown), the resulting molecule possesses four epitope-binding sites and is bispecific and bivalent with respect to each bound epitope. Alternatively, in such embodiments wherein the two pairs of polypeptides may be different and the VL and VH Domains of each pair of polypeptides recognize different epitopes, the resulting molecule possesses four epitope-binding sites and is tetraspecific and monovalent with respect to each bound epitope.

[0054] **Figure 2** shows observed and model-fitted PK profiles of the PD-1 x LAG-3 bispecific molecule, DART-I, over a dose range of 1 mg to 1200 mg. Symbols represent observed data in individual patients and the solid lines represent model-fitted median curves for the dose group. The horizontal dashed line represents target threshold concentration based on clinical experience with other PD-1 targeting agents.

[0055] **Figures 3A-3D** plot the mean (SD) percent receptor occupancy (RO) of CD4+ cells (**Figures 3A** and **3C**) and CD8+ cells (**Figures 3B** and **3D**) by the PD-1 x LAG-3 bispecific molecule, DART-I, on Day 1 of Cycle 1 (**Figures 3A** and **3B**) or Cycle 2 (**Figures 3C** and **3D**) at the end of administration of DART-I and prior to the administration of the next dose of that cycle. EOI = end of infusion after the administration of the first dose of Cycle 1 or Cycle 2.

acid sequence of the Fab domain of pertuzumab is found in Protein Data Bank Accession No. 1l7i). Antibody "**8H11**" is a murine anti-HER2 monoclonal antibody that binds an epitope of HER2 that is distinct from the epitope recognized by margetuximab, trastuzumab and pertuzumab (PCT Publication No. WO 2001/036005). Humanized variants of Antibody **8H11** (designated "**hHER2 MAB-1**") been described (see for example, WO 2018/156740) and representative humanized VH and VL Domains are provided below. In addition to the above-identified HER2-Binding Molecules, the invention contemplates the use of any of the following HER2-Binding Molecules: **1.44.1; 1.140; 1.43; 1.14.1; 1.100.1; 1.96; 1.18.1; 1.20; 1.39; 1.24;** and **1.71.3** (disclosed in US Patent No. 8,350,011; 8,858,942; and PCT Publication No. WO 2008/019290); **F5** and **C1** (disclosed in US Patent Nos. 7,892,554; 8,173,424; 8,974,792; and PCT Publication No. WO 99/55367); and also the HER2-Binding Molecules of US Patent Publication 2011/0097323, 2013/017114, 2014/0328836, 2016/0130360 and 2016/0257761, and PCT Patent Publication WO2011/147986.

[00178] In certain embodiments the TA-Binding molecule binds the B7-H3 TA ("B7-H3-Binding Molecule"). In one embodiment, a B7-H3-Binding Molecule of the present invention is an anti-B7-H3 antibody. Antibodies that bind human B7-H3 include "**enoblituzumab,**" and "**omburtamab**," and "**mirzotamab**." Enoblituzumab (also known as MGA271~~MGAH22~~; CAS Reg No. 1353485-38-7~~1350624-75-7~~, KEGG D11752, see for example, US Patent No. 8,802,093) is an Fc-optimized monoclonal antibody that binds to B7-H3~~HER2~~ and mediates enhanced ADCC activity. The sequence of enoblituzumab~~margetuximab~~ is provided below. Omburtamab (also known as 8H9; CAS Reg No. 1895083-75-6, see for example, US Patent No. 7,737,258) is a murine monoclonal antibody. The amino acid sequence of omburtamab is found in WHO Drug Information 2018, Proposed INN: List 119, 32(2):339-340). Humanized versions of 8H9 are disclosed in WO 2016/033225. Mirzotamab clezutoclax (also known as ABBV-155; CAS Reg No. 2229859-12-3, see for example WO 2017/214322) is a humanized antibody having IgG1/kappa constant regions. The amino acid sequence of mirzotamab is found in WHO Drug Information 2019, Proposed INN: List 121, 33(2): 294-6). In addition to the above-identified B7-H3-Binding Molecules, the invention contemplates the use of any of the following B7-H3-Binding Molecules: BRCA84D, BRCA69D and PRCA157 (disclosed in WO2011109400); L7, L8, L11, M30, and M31 (disclosed in US2013/0078234), hmAb-C, and B7-H3 Antibody hmAb-D (disclosed in WO 2017/180813).

WHAT IS CLAIMED IS:

~~Claim 1. A method of treating a cancer comprising administering a PD-1 x LAG-3 bispecific molecule to a subject in need thereof, wherein said method comprises administering said PD-1 x LAG-3 bispecific molecule to said subject at a flat dose of from about 120 mg to about 800 mg.~~

~~Claim 2. The method of claim 1, wherein said cancer is characterized by the expression of a Tumor Antigen (TA), and wherein said method further comprising administering to said subject a Tumor Antigen (TA) Binding Molecule (TA-Binding Molecule).~~

Claim ~~3~~1. Use of~~A method of treating a cancer in a subject, wherein said cancer is characterized by the expression of a TA, said method comprising administering a TA-Binding Molecule to said subject and~~:

(a) a bispecific molecule that immunospecifically binds both PD-1 and LAG-3 (PD-1 x LAG-3 bispecific molecule); or

(b) a molecule that immunospecifically binds PD-1 (PD-1-Binding Molecule) in combination with a molecule that immunospecifically binds LAG-3 (LAG-3-Binding Molecule); or

(c) a bispecific molecule that immunospecifically binds both PD-L1 and LAG-3 (PD-L1 x LAG-3 bispecific molecule); or

(d) a molecule that immunospecifically binds PD-L1 (PD-L1-Binding Molecule) in combination with a LAG-3-Binding Molecule;

for the manufacture of a medicament for the treatment of cancer.

Claim 2. The use of claim 1, wherein said cancer is characterized by the expression of a Tumor Antigen (TA), and wherein said use further comprises a Tumor Antigen (TA) Binding Molecule (TA-Binding Molecule) to be administered to said subject.

Claim ~~4~~3. The use~~method~~ of ~~any one of claims 2-3~~claim 2, wherein said TA-Binding Molecule comprises an ADCC-Enhanced Fc Domain.

~~Claim 5. The method of any one of claims 2-4, wherein:~~

~~(a) each molecule is in a separate composition; or~~

~~(b) each molecule is in the same composition; or~~

~~(c) said PD-1-Binding Molecule and said LAG-3-Binding Molecule are in the same composition, and said TA-binding molecule is in a separate composition; or~~

~~(d) said PD-L1-Binding Molecule and said LAG-3-Binding Molecule are in the same composition, and said TA-binding molecule is in a separate composition.~~

Claim ~~6~~4. The use~~method~~ of any one of claims 2-~~5~~3, ~~-~~wherein said TA-Binding Molecule is an antibody.

Claim ~~7~~5. The use~~method~~ of any one of claims ~~2-6~~1-4, wherein said PD-1-Binding Molecule is an antibody, said PD-L1-Binding Molecule is an antibody, and said LAG-3-Binding Molecule is an antibody.

Claim ~~8~~6. The use~~method~~ of any one of claims ~~3~~2-~~6~~5, wherein said use~~method~~ comprises ~~administering~~ administration of said TA-Binding Molecule and said PD-1 x LAG-3 bispecific molecule.

Claim ~~9~~7. The use~~method~~ of any one of claims ~~4~~3-~~8~~6, wherein said ADCC-Enhanced Fc Domain comprises:

(A) an engineered glycoform; and/or

(B) an amino acid substitution relative to a wild-type Fc Region.

Claim ~~10~~8. The use~~method~~ of claim ~~9~~7, wherein said ADCC-Enhanced Fc Domain comprises:

(A) an engineered glycoform that is a complex N-glycoside-linked sugar chain that does not contain fucose, and/or that comprises a bisecting O-GlcNAc; and/or

(B) ~~comprises~~ an amino acid substitution is selected from the group consisting of:

(a) one substitution selected from the group consisting of:
F243L, R292P, Y300L, V305I, I332E, and P396L;

(b) two substitutions selected from the group consisting of:

(1) F243L and P396L;

(2) F243L and R292P;

(3) R292P and V305I; and

(4) S239D and I332E;

(c) three substitutions selected from the group consisting of:

(1) F243L, R292P and Y300L;

(2) F243L, R292P and V305I;

(3) F243L, R292P and P396L; and

(4) R292P, V305I and P396L;

(d) four substitutions selected from the group consisting of:

(1) F243L, R292P, Y300L and P396L; and

(2) F243L, R292P, V305I and P396L; or

(e) five substitutions selected from the group consisting of:

(1) F243L, R292P, Y300L, V305I and P396L; and

(2) L235V, F243L, R292P, Y300L and P396L,

wherein the numbering is that of the EU index as in Kabat.

Claim ~~11~~9. The use~~method~~ of any one of claims ~~9-10~~7-8, wherein said ADCC-Enhanced Fc Domain comprises the amino acid substitutions: L235V, F243L, R292P, Y300L and P396L, wherein the numbering is that of the EU index as in Kabat.

Claim ~~12~~10. The use~~method~~ of any one of claims 2-~~11~~9, wherein:

(A) said TA is selected from **Table 6A** or **Table 6B**; and/or

(B) said TA-Binding Molecule comprises the VL and VH Domains of an antibody selected from **Table 7**.

Claim ~~13~~11. The use~~method~~ of any one of claims ~~3-7~~2-5, or ~~9-12~~7-10, wherein:

(A) said PD-1-Binding Molecule is an antibody that comprises:

(a) a PD-1 VL Domain that comprises the amino acid sequence of **SEQ ID NO:35**, and a PD-1 VH Domain that comprises the amino acid sequence of **SEQ ID NO:39**;

(b) a VH and VL Domain of an anti-PD-1 antibody selected from **Table 1**; or

(c) a light chain and a heavy chain of an anti-PD-1 antibody selected from **Table 1**;

(B) said PD-L1-Binding Molecule is an antibody that comprises:

(a) a PD-L1 VL Domain that comprises the amino acid sequence of **SEQ ID NO:43**, and a PD-L1 VH Domain that comprises the amino acid sequence of **SEQ ID NO:47**;

(b) a VH and VL Domain of an anti-PD-L1 antibody selected from **Table 2**; or

(c) a light chain and a heavy chain of an anti-PD-L1 antibody selected from **Table 2**; and

(C) said LAG-3-Binding Molecule is an antibody that comprises:

(a) a LAG-3 VL Domain that comprises the amino acid sequence of **SEQ ID NO:51**, and a LAG-3 VH Domain that comprises the amino acid sequence of **SEQ ID NO:55**;

(b) a VH and VL Domain of an anti-LAG-3 antibody selected from **Table 3**; or

(c) a light chain and heavy chain of an anti-LAG-3 antibody selected from **Table 3**.

Claim ~~14~~12. The use~~method~~ of any one of claims 1-~~6~~4, ~~8,~~ or ~~9-12~~6-10, wherein said PD-1 x LAG-3 bispecific molecule comprises:

(a) a PD-1 VL Domain that comprises the amino acid sequence of **SEQ ID NO:35**, and a PD-1 VH Domain that comprises the amino acid sequence of **SEQ ID NO:39**, or a VH and VL Domain of an anti-PD-1 antibody selected from **Table 1**; and/or

(b) a LAG-3 VL Domain that comprises the amino acid sequence of **SEQ ID NO:51**, and a LAG-3 VH Domain that comprises the amino acid sequence of **SEQ ID NO:55**, or a VH and VL Doman of an anti-LAG-3 antibody selected from **Table 3**; or

(c) a bispecific Antibody-Based Molecule selected from **Tables 4-5**.

Claim ~~15~~13. The use~~method~~ of any one of claims 1-~~6~~4, ~~8, 9-12~~6-10 or ~~14~~12, wherein said PD-1 x LAG-3 bispecific molecule comprises:

(a) two of said PD-1-Binding Domains; and

(b) two of said LAG-3-Binding Domains.

Claim ~~16~~14. The use~~method~~ of any one of claims 1-~~6~~4, ~~8, 9-12~~6-10~~,~~ or ~~14-15~~12-13, wherein said PD-1 x LAG-3 bispecific molecule comprises the PD-1 VL Domain of **SEQ ID NO:35**, the PD-1 VH Domain of **SEQ ID NO:39**, the LAG-3 VL Domain of **SEQ ID NO:51**, and the LAG-3 VH Domain of **SEQ ID NO:55**.

Claim ~~17~~15. The use~~method~~ of any one of claims 1-~~6~~4, ~~8, 9-12~~6-10~~,~~ or ~~14-16~~12-14, wherein said PD-1 x LAG-3 bispecific molecule or said PD-L1 x LAG-3 bispecific molecule comprises an Fc Region and a Hinge Domain.

Claim ~~18~~16. The use~~method~~ of claim ~~17~~15, wherein said Fc Region and said Hinge Domain are both of the IgG4 isotype, and wherein said Hinge Domain comprises a stabilizing mutation.

Claim ~~19~~17. The use~~method~~ of any one of claims ~~17-18~~15-16, wherein said Fc Region is a variant Fc Region that comprises:

(a) one or more amino acid modifications that reduces the affinity of the variant Fc Region for an FcγR; and/or

(b) one or more amino acid modifications that enhances the serum half-life of the variant Fc Region.

Claim ~~20~~18. The use~~method~~ of claim ~~19~~17, wherein said:

(a) modifications that reduce the affinity of the variant Fc Region for an FcγR comprise the substitution of L234A; L235A; or L234A and L235A; and

(b) modifications that enhances the serum half-life of the variant Fc Region comprise the substitution of M252Y; M252Y and S254T; M252Y and T256E; M252Y, S254T and T256E; or K288D and H435K,

wherein said numbering is that of the EU index as in Kabat.

Claim ~~21~~19. The use~~method~~ of any one of claims 1-~~6~~4, ~~9-12~~7-10~~,~~ or ~~14-20~~12-18, wherein said PD-1 x LAG-3 bispecific molecule is to be administered and comprises two polypeptide chains of **SEQ ID NO:59** and two polypeptide chains of **SEQ ID NO:~~:~~60**.

Claim ~~22~~20. The use~~method~~ of any one of claims 1-4, 7-10 or 12-19~~1-6, 9-12, or 14-21~~, wherein said PD-1 x LAG-3 bispecific molecule or said PD-L1 x LAG-3 bispecific molecule is to be administered at a flat dose of about 300 mg.

Claim ~~23~~21. The use~~method~~ of any one of claims 1-4, 7-10 or 12-19~~1-6, 9-12, or 14-21~~, wherein said PD-1 x LAG-3 bispecific molecule or said PD-L1 x LAG-3 bispecific molecule is to be administered at a flat dose of about 600 mg.

Claim ~~24~~22. The use~~method~~ of any one of claims 1-4, 7-10 or 12-21~~1-6, 9-12, or 14-23~~, wherein said flat dose is to be administered once about every 2 weeks.

Claim ~~25~~23. The use~~method~~ of any one of claims 1-4, 7-10 or 12-21~~1-6, 9-12, or 14-23~~, wherein said flat dose is to be administered once about every 3 weeks.

~~Claim 26. The method of any one of claims 1-6, 9-12, 14-21, 23, or 24, wherein said PD-1 x LAG-3 bispecific molecule or said PD-L1 x LAG-3 bispecific molecule is administered at a flat dose of about 600 mg once about every 2 weeks.~~

~~Claim 27. The method of any one of claims 1-6, 9-12, 14-21, 23, or 25, wherein said PD-1 x LAG-3 bispecific molecule or said PD-L1 x LAG-3 bispecific molecule is administered at a flat dose of about 600 mg once about every 3 weeks.~~

Claim ~~28~~24. The use~~method~~ of any one of claims 1-4, 7-10 or 12-23~~1-6, 9-12, or 14-27~~, wherein said PD-1 x LAG-3 bispecific molecule or said PD-L1 x LAG-3 bispecific molecule is to be administered by intravenous (IV) infusion.

Claim ~~29~~25. The use~~method~~ of any one of claims 1-~~28~~24, wherein said cancer is selected from the group consisting of: adrenal gland cancer, AIDS-associated cancer, alveolar soft part sarcoma, anal cancer (including squamous cell carcinoma of the anal canal (SCAC)), bladder cancer, bone cancer, brain and spinal cord cancer, breast cancer (including, $HER2^+$ breast cancer or Triple-Negative Breast Cancer (TNBC)), carotid body tumor, cervical cancer (including, HPV-related cervical cancer), chondrosarcoma, chordoma, chromophobe renal cell carcinoma, clear cell carcinoma, colon cancer, colorectal cancer, desmoplastic small round cell tumor, ependymoma, endometrial cancer (including, unselected endometrial cancer, MSI-high endometrial cancer, dMMR

endometrial cancer, and/or POLE exonuclease domain mutation positive endometrial cancer), Ewing's sarcoma, extraskeletal myxoid chondrosarcoma, gallbladder or bile duct cancer (including, cholangiocarcinoma bile duct cancer), gastric cancer, gastroesophageal junction (GEJ) cancer, gestational trophoblastic disease, germ cell tumor, glioblastoma, head and neck cancer (including, squamous cell carcinoma of head and neck (SCCHN)), a hematological malignancy, a hepatocellular carcinoma, islet cell tumor, Kaposi's Sarcoma, kidney cancer, leukemia (including, acute myeloid leukemia), liposarcoma/malignant lipomatous tumor, liver cancer (including, hepatocellular carcinoma liver cancer (HCC)), lymphoma (including, diffuse large B-cell lymphoma (DLBCL), non-Hodgkin's lymphoma (NHL)), lung cancer (including, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC)), medulloblastoma, melanoma (including, uveal melanoma), meningioma, Merkel cell carcinoma, mesothelioma (including, mesothelial pharyngeal cancer), multiple endocrine neoplasia, multiple myeloma, myelodysplastic syndrome, neuroblastoma, neuroendocrine tumors, ovarian cancer, pancreatic cancer, papillary thyroid carcinoma, parathyroid tumor, pediatric cancer, peripheral nerve sheath tumor, pharyngeal cancer, pheochromocytoma, pituitary tumor, prostate cancer (including, metastatic castration resistant prostate cancer (mCRPC)), posterious uveal melanoma, renal metastatic cancer, rhabdoid tumor, rhabdomyosarcoma, sarcoma, skin cancer, a small round blue cell tumor of childhood (including neuroblastoma and rhabdomyosarcoma), soft-tissue sarcoma, squamous cell cancer, stomach cancer, synovial sarcoma, testicular cancer, thymic carcinoma, thymoma, thyroid cancer, and uterine cancer.

Claim ~~30~~26. The use~~method~~ of claim ~~29~~25, wherein said cancer is selected from the group consisting of: anal cancer, breast cancer, bile duct cancer, cervical cancer, colorectal cancer, endometrial cancer, gastric cancer, GEJ cancer, head and neck cancer, liver cancer, lung cancer, lymphoma, melanoma, ovarian cancer and prostate cancer.

Claim ~~31~~27. The use~~method~~ of any one of claims ~~28~~ 24 or ~~29~~25, wherein said cancer is selected from the group consisting of: $HER2^+$ breast cancer, TNBC,

cholangiocarcinoma bile duct cancer, HPV-related cervical cancer, SCCHN, HCC, SCLC or NSCLC, NHL, prostate cancer, gastric cancer and GEJ cancer.

Claim ~~32~~28. The use~~method~~ of any one of claims 2-~~31~~27, wherein said TA-Binding Molecule is a HER2-Binding Molecule comprising a HER2-Binding Domain comprising a Light Chain Variable Domain (VL_{HER2}) and a Heavy Chain Variable Domain (VH_{HER2}), wherein:

(A) said Light Chain Variable Domain (VL_{HER2}) comprises the Light Chain Variable Domain of margetuximab that comprises the CDR_L1, CDR_L2 and CDR_L3 of **SEQ ID NO:61**, and said Heavy Chain Variable Domain (VH_{HER2}) comprises the Heavy Chain Variable Domain of margetuximab that comprises the CDR_H1, CDR_H2 and CDR_H3 of **SEQ ID NO:66**;

(B) said Light Chain Variable Domain (VL_{HER2}) comprises the CDR_L1, CDR_L2 and CDR_L3 of trastuzumab and said Heavy Chain Variable Domain (VH_{HER2}) comprises the CDR_H1, CDR_H2 and CDR_H3 of trastuzumab;

(C) said Light Chain Variable Domain (VL_{HER2}) comprises the CDR_L1, CDR_L2 and CDR_L3 of pertuzumab and said Heavy Chain Variable Domain (VH_{HER2}) comprises the CDR_H1, CDR_H2 and CDR_H3 of pertuzumab; or

(D) said Light Chain Variable Domain (VL_{HER2}) comprises the CDR_L1, CDR_L2 and CDR_L3 of hHER2 MAB-1 and said Heavy Chain Variable Domain (VH_{HER2}) comprises the CDR_H1, CDR_H2 and CDR_H3 of hHER2 MAB-1.

Claim ~~33~~29. The use~~method~~ of any one of claims 2-~~32~~28, wherein said HER2-Binding Molecule is an anti-HER2 antibody.

Claim ~~34~~30. The use~~method~~ of claim ~~33~~29, wherein said anti-HER2 antibody is margetuximab, and said ~~method~~ use comprises ~~administering~~ administration of margetuximab at a dosage of about 6 mg/kg to about 18 mg/kg once about every 3 weeks.

~~Claim 35. The method of any one of claims 32-34, wherein said method further comprises administered a chemotherapeutic agent.~~

Claim ~~36~~31. The use~~method~~ of any one of claims 2-~~35~~30, wherein said cancer is a HER2 expressing cancer.

Claim ~~37~~32. The use~~method~~ of claim ~~36~~31, wherein said HER2 expressing cancer is selected from the group consisting of: breast cancer, metastatic breast cancer, bladder, gastric cancer, GEJ cancer, ovarian cancer, pancreatic cancer, and stomach cancer.

Claim ~~38~~33. The use~~method~~ of any one of claims 2-~~31~~27, wherein said TA-Binding Molecule is a B7-H3-Binding Molecule comprising a B7-H3-Binding Domain comprising a Light Chain Variable Domain (VL) and a Heavy Chain Variable Domain (VH), wherein:
said VL comprises the CDR_L1, CDR_L2 and CDR_L3 of **SEQ ID NO:71**, and said VH the CDR_H1, CDR_H2 and CDR_H3 of **SEQ ID NO:76**.

Claim ~~39~~34. The use~~method~~ of any one of claims 2-~~31~~ 27 or ~~38~~33, wherein said TA-Binding Molecule is enoblituzumab and said ~~method~~ use comprises ~~administering~~ administration of enoblituzumab at a dosage of about 6 mg/kg to about 18 mg/kg once about every 3 weeks.

Claim ~~40~~35. The use~~method~~ of any one of claims 2-~~31~~ 27 or ~~38~~33-~~39~~34, wherein said cancer is a B7-H3 expressing cancer.

Claim ~~41~~36. The use~~method~~ of claim ~~40~~35, wherein said B7-H3 expressing cancer is selected from the group consisting of: anal cancer, SCAC, a breast cancer, TNBC, a head and neck cancer, SCCHN, lung cancer, NSCLC, melanoma, uveal melanoma, prostate cancer, and mCRPC.

Claim ~~42~~37. The use~~method~~ of any one of claims 2-~~41~~36, wherein said TA-binding molecule is to be administered by intravenous (IV) infusion.

Claim ~~43~~38. The use~~method~~ of any one of claims 1-~~42~~37, wherein cells expressing LAG-3 are present in a biopsy of said cancer prior to said treatment.

Claim ~~44~~39. The use~~method~~ of any one of claims 1-~~43~~38, wherein cells expressing PD-1 are present in a biopsy of said cancer prior to said treatment.

Claim ~~45~~40. The use~~method~~ of any one of claims 2-~~44~~39, wherein PD-L1 expression on the surface of cells of said cancer, prior to said treatment, is less than 1% as determined using a Combined Positive Score (CPS) or a Tumor Proportion Score (TPS).