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 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 disclosure particularly concerns the use of such regimens in conjunction with PD-1 x LAG-3 bispecific molecules. The 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, wherein said cancer is characterized by the expression of a Tumor Antigen (TA), wherein said use further comprises administering to said subject a Tumor Antigen (TA) Binding Molecule (TA-Binding Molecule), wherein the TA-Binding Molecule comprises an ADCC-Enhanced Fc Domain, and wherein the cancer is a B7-H3 expressing cancer.

[0014] The 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 disclosure additionally concerns the 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 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

WHAT IS CLAIMED IS:

Claim 1. 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, wherein said cancer is characterized by the expression of a Tumor Antigen (TA), wherein said use further comprises administering to said subject a Tumor Antigen (TA) Binding Molecule (TA-Binding Molecule), wherein the TA-Binding Molecule comprises an ADCC-Enhanced Fc Domain, and wherein the cancer is a B7-H3 expressing cancer.

Claim 2. The use of claim 1, wherein said TA-Binding Molecule is an antibody.

Claim 3. The use of any one of claims 1-2, 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 4. The use of any one of claims 1-3, wherein said use comprises to be administered said TA-Binding Molecule and said PD-1 x LAG-3 bispecific molecule.

Claim 5. The use of any one of claims 1-4, 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 6. The use of claim 5, 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) 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 7. The use of any one of claims 5-6, 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 8. The use of any one of claims 1-7, 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 9. The use of any one of claims 1-8, 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 10. The use of any one of claims 1-9, 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 11. The use of any one of claims 1-10, 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 12. The use of any one of claims 1-11, 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 13. The use of claim 12, wherein said Fc Region and said Hinge Domain are both of the IgG4 isotype, and wherein said Hinge Domain comprises a stabilizing mutation, wherein said stabilizing mutation is the substitution of S228P.

Claim 14. The use of any one of claims 12-13, 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, wherein the modifications that reduce the affinity of the variant Fc Region for an FcγR comprise the substitution of L234A; L235A; or L234A and L235A; and/or

(b) one or more amino acid modifications that enhances the serum half-life of the variant Fc Region, wherein the 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 15. The use of any one of claims 1-14, 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 16. The use of any one of claims 1-15, 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 from 120 mg to 800 mg.

Claim 17. The use of any one of claims 1-15, 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 18. The use of any one of claims 1-15, 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 19. The use of any one of claims 1-18, wherein said flat dose is to be administered once about every 2 weeks.

Claim 20. The use of any one of claims 1-18, wherein said flat dose is to be administered once about every 3 weeks.

Claim 21. The use of any one of claims 1-20, 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 22. The use of any one of claims 1-21, 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 23. The use of any one of claims 1-22, 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 24. The use of any one of claims 1-23, wherein said TA-Binding Molecule is enoblituzumab and said use comprises administration of enoblituzumab at a dosage of 6 mg/kg to 18 mg/kg once about every 3 weeks.

Claim 25. The use of claim 24, 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 26. The use of any one of claims 1-25, wherein said TA-binding molecule is to be administered by intravenous (IV) infusion.

Claim 27. The use of any one of claims 1-26, wherein cells expressing LAG-3 are present in a biopsy of said cancer prior to said treatment.

Claim 28. The use of any one of claims 1-27, wherein cells expressing PD-1 are present in a biopsy of said cancer prior to said treatment.

Claim 29. The use of any one of claims 1-29, 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).