Activation Gene-3 (CD223)," J. Immunol. 174:688-695) and have suggested that inhibiting LAG-3 function through antibody blockade can reverse LAG-3-mediated immune system inhibition and partially restore effector function (Grosso, J.F. *et al*. (2009) "*Functionally Distinct LAG-3 and PD-1 Subsets on Activated and Chronically Stimulated CD8 T-Cells*," J. Immunol. 182(11):6659-6669;). Antibodies capable of specifically binding to LAG-3 have been reported (see, *e.g.*, PCT Publication Nos. WO 2014/140180, WO 2015/138920, WO 2015/116539, WO 2016/028672, WO 2016/126858, WO 2016/200782 and WO 2017/015560).

[0013] Bispecific molecules binding to both PD-1 and LAG-3 ("PD-1 X LAG-3 bispecific molecules") 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 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.

SUMMARY

[0014] The present disclosure is in certain examples directed to dosing regimens for administering a B7-H3-ADC for the treatment of cancer, particularly a cancer associated with expression of B7-H3. The disclosure in certain examples concerns the use of such B7-H3-ADC optionally in combination with a PD-1 binding molecule for the treatment of cancer. Certain B7-H3-ADC and their uses in the treatment of cancer are described, for example, in PCT Publication No. WO 2017/180813. The disclosure in certain concerns the use of such B7-H3-ADC and an anti-PD-1 antibody, or a PD-1 X LAG-3 bispecific binding molecule. The dosing regimens for administering a B7-H3-ADC for the treatment of cancer, or a B7-H3-ADC in combination with a PD-1 binding molecule for the treatment of cancer, can include administration at regular dosing intervals or intermittent dosing intervals. In the dosing regimens where the B7-H3-ADC is administered in combination with a PD-1 binding molecule, their administration can be simultaneous or sequential in any order. The disclosure in certain examples is directed to the use of such molecules, and to the use of

pharmaceutical compositions and pharmaceutical kits that contain such molecules and that facilitate the use of such dosing regimens in the treatment of cancer.

[0015] In detail, the disclosure provides a method of treating a cancer comprising administering a B7-H3-ADC to a subject in need thereof, wherein said method comprises administering a B7-H3-ADC to a subject at a dose of about 0.5 mg/kg to about 5 mg/kg once about every 3 weeks.

[0015a] In one aspect, the present disclosure refers to use of an anti-B7-H3 antibody-drug conjugate (B7-H3-ADC) in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein said B7-H3-ADC conjugate is to be administered to a subject at a dose of from about 0.5 mg/kg to about 5 mg/kg once every 3 weeks.

[0016] The disclosure further provides a method of treating a cancer comprising administering a B7-H3-ADC to a subject in need thereof, wherein said method comprises administering a B7-H3-ADC to a subject at a dose of about 3 mg/kg to about 5 mg/kg once about every 3 weeks.

[0017] The disclosure further provides a method of treating a cancer comprising administering a B7-H3-ADC to a subject in need thereof, wherein said method comprises administering a B7-H3-ADC to a subject at a dose of 3 mg/kg to about 4 mg/kg once about every 3 weeks.

[0018] The disclosure further provides a method of treating a cancer comprising administering a B7-H3-ADC to a subject in need thereof, wherein said method comprises administering a B7-H3-ADC to a subject at a dose of about 4 mg/kg to about 5 mg/kg once about every 3 weeks.

[0019] The disclosure further provides the example of such method (i.e., "the example of such method" meaning an example of an applicable method described herein) comprising administering a B7-H3-ADC to a subject in need thereof, wherein said method comprises administering a B7-H3-ADC to a subject at a dose of about 0.5 mg/kg to about 5 mg/kg once about every 4 weeks.

[0020] The disclosure further provides a method of treating a cancer comprising administering a B7-H3-ADC to a subject in need thereof, wherein said method comprises administering a B7-H3-ADC to a subject at a dose of about 3 mg/kg to about 5 mg/kg once about every 4 weeks.

[0021] The disclosure further provides a method of treating a cancer comprising administering a B7-H3-ADC to a subject in need thereof, wherein said method comprises

administering a B7-H3-ADC to a subject at a dose of 3 mg/kg to about 4 mg/kg once about every 4 weeks.

[0022] The disclosure further provides a method of treating a cancer comprising administering a B7-H3-ADC to a subject in need thereof, wherein said method comprises administering a B7-H3-ADC to a subject at a dose of about 4 mg/kg to about 5 mg/kg once about every 4 weeks.

[0023] The disclosure further provides the example of such method comprising administering a B7-H3-ADC to a subject in need thereof, wherein said method comprises administering a B7-H3-ADC to a subject at a dose of about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.25 mg/kg, about 2.5 mg/kg, about 2.75 mg/kg, about 3 mg/kg, about 3.25 mg/kg, about 3.5 mg/kg, about 3.75 mg/kg, about 4 mg/kg, about 4.25 mg/kg, about 4.5 mg/kg, about 4.75 mg/kg or about 5 mg/kg.

[0024] The disclosure further provides the example of such method comprising administering to a subject in need thereof:

(A) a B7-H3-ADC; and

(B) a PD-1 binding molecule,

wherein the method comprises administering a B7-H3-ADC to the subject at a dose of about 0.5 mg/kg to about 5 mg/kg once every 3 weeks.

[0025] The disclosure further provides the example of such method comprising administering to a subject in need thereof:

(A) a B7-H3-ADC; and

(B) a PD-1 binding molecule,

wherein the method comprises administering a B7-H3-ADC to the subject at a dose of about 0.5 mg/kg to about 5 mg/kg once every 4 weeks.

[0026] The disclosure further provides the example of such method wherein a B7-H3-ADC is represented by the formula:

$$\mathbf{Ab\text{-}(LM)_m\text{-}(D)_n,}$$

wherein:

Ab is a humanized B7-H3 antibody or B7-H3 binding fragment thereof that binds to B7-H3 and comprises:

(i) the CDRL1 sequence RASESIYSYLA (**SEQ ID NO: 39**), the CDRL2 sequence NTKTLPE (**SEQ ID NO: 40**) and the CDRL3 sequence QHHYGTPPWT (**SEQ ID NO: 41**) in its Variable Light Chain (VL) domain, and

(ii) the CDRH1 sequence SYGMS (**SEQ ID NO: 42**), the CDRH2 sequence TINSGGSNTYY PDSLKG (**SEQ ID NO: 43**) and the CDRH3 sequence HDGGAMDY (**SEQ ID NO: 44**) in its Variable Heavy Chain (VH) domain;

D is a cytotoxic duocarmycin moiety;

LM comprises at least one bond or a Linker Molecule that covalently links Ab and D;

m is an integer between 0 and n and denotes the number of bonds or Linker Molecules of the B7-H3-ADC, except when **LM** is a bond, m is not 0;

and

n is an integer between 1 and 10 and denotes the number of cytotoxic duocarmycin moieties covalently linked to the B7-H3-ADC.

[0027] The disclosure further provides such **B7-H3-ADCs**, wherein the Linker Molecule is absent and **LM** is at least one bond (*i.e.*, **m** $\geq$ 1), and **B7-H3-ADCs** that possess more than one Linker Molecule **LM** (*i.e.*, **m** is an integer from 2 through **n**), each of which Linker Molecule **LM** covalently links a cytotoxic duocarmycin drug moiety **D** to the **Ab** of such **B7-H3-ADCs**. The disclosure further provides such **B7-H3-ADCs** whose **Ab** are covalently linked to more than one Linker Molecule **LM**, wherein all such Linker Molecules are identical. The cytotoxic duocarmycin drug moieties **D** that are covalently linked to the **Ab** of such **B7-H3-ADCs** may all be identical or may include 2, 3, 4, or more non-identical cytotoxic duocarmycin drug moieties **D**. The disclosure further provides such **B7-H3-ADCs** whose **Ab** are covalently linked to more than one Linker Molecule **LM**, wherein all such Linker Molecules are not identical. The cytotoxic duocarmycin drug moieties **D** that are covalently linked to the **Ab** of such **B7-H3-ADCs** may all be identical or may include 2, 3, 4, or more non-identical cytotoxic duocarmycin drug moieties **D**.

[0028] The disclosure further provides the example of such method, wherein the B7-H3-ADC comprises:

(I) the humanized VL Domain comprising the amino acid sequence of **SEQ ID NO:17**, and

(II) the humanized VH Domain comprising the amino acid sequence of **SEQ ID NO:18**.

[0029] The disclosure further provides the example of such method, wherein the **Ab** is an antibody.

[0030] The disclosure further provides the example of such method, wherein the **Ab** further comprises an Fc Domain of a human IgG1.

[0031] The disclosure further provides the example of such method, wherein the B7-H3-ADC comprises a Light Chain comprising the amino acid sequence of **SEQ ID NO:19** and a Heavy Chain comprising the amino acid sequence of **SEQ ID NO:20**.

[0032] The disclosure further provides the example of such method, wherein at least one of the **LM** is a Linker Molecule, and particularly wherein the **LM** Linker Molecule is a peptidic linker and/or a cleavable linker.

[0033] The disclosure further provides the example of such method, wherein the peptidic linker is a valine-citrulline dipeptide linker.

[0034] The disclosure further provides the example of such method, wherein the **LM** Linker Molecule further comprises a self-eliminating spacer between the cleavable linker and **D**.

[0035] The disclosure further provides the example of such method, wherein the self-eliminating spacer comprises a para-aminobenzyloxycarbonyl moiety.

[0036] The disclosure further provides the example of such method, wherein the **LM** further comprises a maleimide linker moiety between the cleavable linker and **Ab.**

[0037] The disclosure further provides the example of such method, wherein **LM** is represented by the formula:

$$[V\text{-}(W)_k\text{-}(X)_1\text{-}A]$$

whereby the B7-H3-ADC is represented by the formula:

Ab – [V-(W)$_k$-(X)$_1$-A] – D

wherein:

V is a cleavable linker,

(W)$_k$-(X)$_1$-A is an elongated, self-eliminating spacer system, that self-eliminates via a l,(4+2n)-elimination,

W and **X** are each a l,(4+2n) electronic cascade spacer, being the same or different,

A is either a spacer group of formula (**Y**)$_m$, wherein **Y** is a l,(4+2n) electronic cascade spacer, or a group of formula **U**, being a cyclisation elimination spacer,

k, 1 and m are independently an integer of 0 (included) to 5 (included),

n is an integer of 0 (included) to 10 (included),

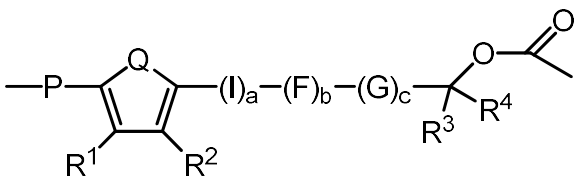
with the provisos that:

when **A** is (**Y**)$_m$: then k+l+m ≥ 1, and

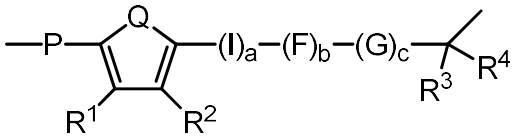
if k+l+m=l, then n>l;

when **A** is **U**: then k+1 ≥ 1.

W, **X**, and **Y** are independently selected from compounds having the formula:



or the formula:

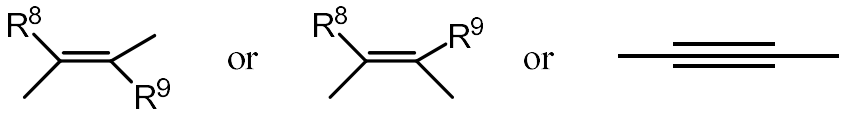


wherein: Q is -R^5C=CR^6-, S, O, NR^5, -R^5C=N-, or -N=CR^5-

P is NR^7, O or S

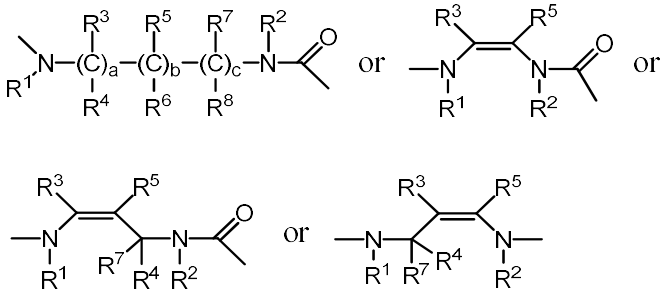
a, b, and c are independently an integer of 0 (included) to 5 (included);

I, F and G are independently selected from compounds having the formula:



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 independently represent H, C_{1-6} alkyl, C_{3-20} heterocyclyl, C_{5-20} aryl, C_{1-6} alkoxy, hydroxy (OH), amino (NH_2), mono-substituted amino (NR_xH), di-substituted amino ($NR_x^1R_x^2$), nitro (NO_2), halogen, CF_3, CN, $CONH_2$, SO_2Me, CONHMe, cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_x), tetrazole, carboxy (COOH), carboxylate ($COOR_x$), sulphoxy ($S(=O)_2OH$), sulphonate ($S(=O)_2OR_x$), sulphonyl ($S(=O)_2R_x$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR_x$), sulphinyl ($S(=O)R_x$), phosphonooxy ($OP(=O)(OH)_2$), and phosphate ($OP(=O)(OR_x)_2$), where R_x, R_x^1 and R_x^2 are independently selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group, two or more of the substituents R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, or R^9 optionally being connected to one another to form one or more aliphatic or aromatic cyclic structures;

U is selected from compounds having the formula:



wherein:

a, b and c are independently selected to be an integer of 0 or 1; provided that a + b + c = 2 or 3;

R^1 and/or R^2 independently represent H, C1-6 alkyl, the alkyl being optionally substituted with one or more of the following groups: hydroxy (OH), ether (OR_x), amino (NH_2), mono-substituted amino (NR_xH), disubstituted amino ($NR_x^1R_x^2$), nitro (NO_2), halogen, CF_3, CN, $CONH_2$, SO_2Me, CONHMe, cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_X),

tetrazole, carboxy (COOH), carboxylate ($COOR_x$), sulphoxy ($S(=O)_2OH$), sulphonate ($S(=O)_2OR_X$), sulphonyl ($S(=O)_2R_x$), sulphixy (S(=O)OH), sulphinate (S(=O)ORx), sulphinyl (S(=O)Rx), phosphonooxy ($OP(=O)(OH)_2$), and phosphate ($OP(=O)(OR_x)_2$), where R_x, R_x^1 and R_x^2 are selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group; and

R^3, R^4, R^5, R^6, R^7 and R^8 independently represent H, C_{1-6} alkyl, C_{3-20} heterocyclyl, C_{5-20} aryl, C_{1-6} alkoxy, hydroxy (OH), amino (NH_2), mono-substituted amino (NR_xH), disubstituted amino ($NR_x^1R_x^2$), nitro (NO_2), halogen, CF_3, CN, $CONH_2$, SO_2Me, CONHMe, cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_x), tetrazole, carboxy (COOH), carboxylate ($COOR_x$), sulphoxy ($S(=O)_2OH$), sulphonate ($S(=O)_2OR_x$), sulphonyl ($S(=O)_2R_x$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR_x$), sulphinyl ($S(=O)R_x$), phosphonooxy ($OP(=O)(OH)_2$), and phosphate ($OP(=O)(OR_x)_2$), where R_x, R_x^1 and R_x^2 are selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group, and two or more of the substituents R^1, R^2, R^3, R^4, R^5, R^6, R^7, or R^8 are optionally connected to one another to form one or more aliphatic or aromatic cyclic structures.

[0038] The disclosure further provides the example of such method, wherein the **LM** Linker Molecule comprises:

(1) p-aminobenzyloxycarbonyl-p-aminobenzyloxycarbonyl;

(2) p-aminobenzyloxycarbonyl-p-aminobenzyloxycarbonyl-p-aminobenzyloxycarbonyl;

(3) p-ammocinnamyloxycarbonyl;

(4) p-aminocinnamyloxycarbonyl-p-aminobenzyloxycarbonyl;

(5) p-amino-benzyloxycarbonyl-p-aminocinnamyloxycarbonyl;

(6) p-aminocinnamyloxycarbonyl-p-aminocinnamyloxycarbonyl;

(7) p-aminophenylpentadienyloxycarbonyl;

(8) p-aminophenylpentadienyloxycarbonyl-p-arninocinnamyloxycarbonyl;

(9) p-aminophenylpentadienyloxycarbonyl-paminobenzyloxycarbonyl;

(10) p-aminophenylpentadienyloxycarbonyl-p-aminophenylpentadienyloxycarbonyl;

(11) p-aminobenzyloxycarbonyl(methylamino)ethyl(methylamino) carbonyl;

(12) p-aminocinnamyloxycarbonyl(methylamino)ethyl(methylamino) carbonyl;

(13) p-aminobenzyloxycarbonyl-p-aminobenzyloxycarbonyl(methylamino) ethyl(methylamino)carbonyl;

(14) p-aminocinnamyloxycarbonyl-p-aminobenzyloxycarbonyl (methylamino)ethyl(methylamino)carbonyl;

(15) p-aminobenzyloxycarbonyl-p-arninocinnamyloxycarbonyl (methylamino)ethyl(methylamino)-carbonyl;

(16) p-aminocinnamyloxycarbonyl-p-aminocinnamyloxycarbonyl (methylamino)ethyl(methylamino)carbonyl;

(17) p-aminobenzyloxycarbonyl-p-aminobenzyl;

(18) p-aminobenzyloxycarbonyl-p-aminobenzyloxycarbonyl -p-aminobenzyl;

(19) p-aminocinnamyl;

(20) p-aminocinnamyloxycarbonyl-p-aminobenzyl;

(21) p-aminobenzyloxycarbonyl-p-aminocinnamyl;

(22) p-amino-cinnamyloxycarbonyl-p-aminocinnamyl;

(23) p-aminophenylpentadienyl;

(24) p-aminophenylpentadienyloxycarbonyl-p-aminocinnamyl;

(25) p-aminophenylpentadienyloxycarbonyl-p-aminobenzyl;

or

(26) p-aminophenylpentadienyloxycarbonyl-p-aminophenylpentadienyl.

[0039] The disclosure further provides the example of such method wherein the **LM** Linker Molecule is conjugated to the side chain of an amino acid of a polypeptide chain of **Ab** and binds the **Ab** to a molecule of the cytotoxic duocarmycin moiety **D.**

[0040] The disclosure further provides the example of such method wherein the cytotoxic duocarmycin moiety **D** comprises a duocarmycin cytotoxin selected from the

group consisting of duocarmycin A, duocarmycin B1, doucarmycin B2, duocarmycin C1, duocarmycin C2, duocarmycin D, duocarmycin SA, CC-1065, adozelesin, bizelesin, carzelesin (U-80244) and spiro-duocarmycin (DUBA)).

[0041] The disclosure further provides the example of such method, wherein the cytotoxic duocarmycin moiety **D** comprises *seco*-duocarmycin.

[0042] The disclosure further provides the example of such method, wherein the **LM** Linker Molecule is covalently linked to the **Ab** via reduced inter-chain disulfides.

[0043] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 2 mg/kg.

[0044] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 2.25 mg/kg.

[0045] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 2.5 mg/kg.

[0046] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 2.75 mg/kg.

[0047] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 3 mg/kg.

[0048] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 3.25 mg/kg.

[0049] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 3.5 mg/kg.

[0050] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 3.75 mg/kg.

[0051] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 4 mg/kg.

[0052] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 4.25 mg/kg.

[0053] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 4.5 mg/kg.

[0054] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 4.75 mg/kg.

[0055] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 5 mg/kg.

[0056] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered by intravenous (IV) infusion over a period of about 60 minutes.

[0057] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered in combination with a therapeutically effective dose of a PD-1 binding molecule.

[0058] The disclosure further provides the example of such method, wherein the PD-1 binding molecule is selected from the group consisting of an antibody, a single chain antibody, an Fab fragment, an F(ab')2 fragment, an Fab' fragment, an Fsc fragment, an Fv fragment, an scFv, an sc(Fv)2, and a diabody.

[0059] The disclosure further provides the example of such method, wherein the PD-1 binding molecule is selected from the group consisting of hPD-1 mAb-A, pembrolizumab, nivolumab and PD-1 X LAG-3 BD.

[0060] The disclosure further provides the example of such method, wherein the PD-1 binding molecule is hPD-1 mAb-A or PD-1 x LAG-3 BD.

[0061] The disclosure further provides the example of such method, wherein the PD-1 binding molecule comprises a variable heavy (VH) domain comprising VH complementarity determining region (CDR)1, VH CDR2 and VH CDR3, wherein

the VH CDR1 comprises the amino acid sequence SYWMN (**SEQ ID NO:23**);

the VH CDR2 comprises the amino acid sequence VIHPSDSETWLDQKFKD (**SEQ ID NO:24**);

the VH CDR3 comprises the amino acid sequence EHYGTSPFAY (**SEQ ID NO:25**); and

wherein the antibody comprises a variable light (VL) domain comprising VL CDR1, VL CDR2, and VL CDR3, wherein:

the VL CDR1 comprises the amino acid sequence RASESVDNYGMSFMNW (**SEQ ID NO:26**);

the VL CDR2 comprises the amino acid sequence AASNQGS (**SEQ ID NO:27**); and

the VL CDR3 comprises the amino acid sequence QQSKEVPYT (**SEQ ID NO:28**).

[0062] The disclosure further provides the example of such method, wherein the VH domain of the PD-1 binding molecule comprises the amino acid sequence set forth in **SEQ ID NO:32** and said VL domain comprises the amino acid sequence set forth in **SEQ ID NO:31**.

[0063] The disclosure further provides the example of such method, wherein the PD-1 binding molecule is hPD-1 mAb-A.

[0064] The disclosure further provides the example of such method, wherein the method comprises administering hPD-1 mAb-A once about every 3 weeks at a flat dose selected from the group consisting of about 375 mg, about 500 mg, and about 750 mg.

[0065] The disclosure further provides the example of such method, wherein the method comprises administering hPD-1 mAb-A once about every 4 weeks at a flat dose selected from the group consisting of about 375 mg, about 500 mg, and about 750 mg.

[0066] The disclosure further provides the example of such method, wherein hPD-1 mAb-A is administered once about every 3 weeks at a flat dose of about 375 mg.

[0067] The disclosure further provides the example of such method, wherein hPD-1 mAb-A is administered once about every 3 weeks at a flat dose of about 500 mg.

[0068] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 3 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 3 weeks.

[0069] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 3.25 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 3 weeks.

[0070] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 3.5 mg/kg and hPD-1 mAb A is administered at a flat dose of about 375 mg once every 3 weeks.

[0071] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 3.75 mg/kg and hPD-1 mAb A is administered at a flat dose of about 375 mg once every 3 weeks.

[0072] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 4 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 3 weeks.

[0073] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 4.25 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 3 weeks.

[0074] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 4.5 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 3 weeks.

[0075] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 4.75 mg/kg and hPD-1 mAb A is administered at a flat dose of about 375 mg once every 3 weeks.

[0076] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 5 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 3 weeks.

[0077] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 3 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 4 weeks.

[0078] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 3.25 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 4 weeks.

[0079] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 3.5 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 4 weeks.

[0080] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 3.75 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 4 weeks.

[0081] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 4 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 4 weeks.

[0082] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 4.25 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 4 weeks.

[0083] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 4.5 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 4 weeks.

[0084] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 4.75 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 4 weeks.

[0085] The disclosure further provides the example of such method, wherein a B7-H3-ADC is administered at a dose of about 5 mg/kg and hPD-1 mAb-A is administered at a flat dose of about 375 mg once every 4 weeks.

[0086] The disclosure further provides the example of such method, wherein hPD-1 mAb-A is administered by IV infusion over a period of about 60 minutes.

[0087] The disclosure further provides the example of such method, wherein the antibody that binds to human PD-1 is pembrolizumab.

[0088] The disclosure further provides the example of such method, wherein pembrolizumab is administered once about every 3 weeks at a flat dose of about 200 mg.

[0089] The disclosure further provides the example of such method, wherein pembrolizumab is administered by IV infusion over a period of about 30 minutes.

[0090] The disclosure further provides the example of such method, wherein the PD-1 binding molecule is nivolumab.

[0091] The disclosure further provides the example of such method, wherein nivolumab is administered once about every 2 weeks at a flat dose of about 240 mg.

[0092] The disclosure further provides the example of such method, wherein nivolumab is administered once about every 4 weeks at a flat dose of about 480 mg.

[0093] The disclosure further provides the example of such method, wherein nivolumab is administered by IV infusion over a period of about 30 minutes.

[0094] The disclosure further provides the example of such method, wherein the PD-1 binding molecule is PD-1 X LAG-3 BD.

[0095] The disclosure further provides the example of such method, wherein PD-1 X LAG-3 BD comprises two polypeptide chains that comprise the amino acid sequence of **SEQ ID NO:37** and two polypeptide chains that comprises the amino acid sequence of **SEQ ID NO:38**.

[0096] The disclosure further provides the example of such method, wherein PD-1 X LAG-3 BD is administered at a flat dose of about 300 mg once every 2 weeks.

[0097] The disclosure further provides the example of such method, wherein PD-1 X LAG-3 BD is administered at a flat dose of about 300 mg once every 3 weeks.

[0098] The disclosure further provides the example of such method, wherein PD-1 X LAG-3 BD is administered at a flat dose of about 600 mg once every 2 weeks.

[0099] The disclosure further provides the example of such method, wherein PD-1 X LAG-3 BD is administered at a flat dose of about 600 mg once every 3 weeks.

[00100] The disclosure further provides the example of such method, wherein PD-1 X LAG-3 BD is administered by IV infusion over a period of 30-240 minutes.

[00101] The disclosure further provides the example of such method, wherein PD-1 X LAG-3 BD is administered by IV infusion over a period of about 30-90 minutes.

[00102] The disclosure further provides the example of such method, wherein a B7-H3-ADC and hPD-1 mAb-A are administered sequentially to a subject in separate pharmaceutical compositions.

[00103] The disclosure further provides the example of such method, wherein the pharmaceutical composition comprising hPD-1 mAb-A is administered before the administration of the pharmaceutical composition comprising a B7-H3-ADC.

[00104] The disclosure further provides the example of such method, wherein a B7-H3-ADC and pembrolizumab are administered sequentially to a subject in separate pharmaceutical compositions.

[00105] The disclosure further provides the example of such method, wherein a B7-H3-ADC and nivolumab are administered sequentially to a subject in separate pharmaceutical compositions.

[00106] The disclosure further provides the example of such method, wherein a B7-H3-ADC and PD-1 X LAG-3 BD are administered sequentially to a subject in separate pharmaceutical compositions.

[00107] The disclosure further provides the example of such method, wherein a B7-H3-ADC is provided in a pharmaceutical kit that comprises:

(A) a pharmaceutical composition comprising from about 0.5 mg/ml to about 5 mg/ml of a B7-H3-ADC; and

(B) an instructional material,

wherein the instructional material instructs that the pharmaceutical composition comprising a B7-H3-ADC is to be administered optionally in combination with a pharmaceutical composition comprising a PD-1 binding molecule.

The disclosure further provides the example of such method, wherein the PD-1 binding molecule is hPD-1 mAb-A, pembrolizumab, nivolumab or PD-1 X LAG-3 BD.

[00108] The disclosure further provides the example of such method, wherein a B7-H3-ADC is provided in a pharmaceutical kit wherein the B7-H3-ADC comprises:

(I) the humanized VL Domain comprising the amino acid sequence of **SEQ ID NO:17**, and

(II) the humanized VH Domain comprising the amino acid sequence of **SEQ ID NO:18.**

[00109] The disclosure further provides the example of such method, wherein the instructional manual of such pharmaceutical kit instructs that a B7-H3-ADC is administered at a dose of about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.25 mg/kg, about 2.5 mg/kg, about 2.75 mg/kg, about 3 mg/kg, about 3.25 mg/kg, about 3.5 mg/kg, about 3.75 mg/kg, about 4 mg/kg, about 4.25 mg/kg, about 4.5 mg/kg, about 4.75 mg/kg or about 5 mg/kg.

[00110] The disclosure further provides the example of such method, wherein the instructional manual of such pharmaceutical kit instructs that hPD-1 mAb-A is administered at a flat dose of about 375 mg or about 500 mg once every 3 weeks.

[00111] The disclosure further provides the example of such method, wherein the instructional manual of such pharmaceutical kit instructs that pembrolizumab is administered with a flat dose of about 200 mg of once every 3 weeks.

[00112] The disclosure further provides the example of such method, wherein the instructional manual of such pharmaceutical kit instructs that PD-1 X LAG-3 BD is administered at a flat dose of about 300 mg or about 600 mg once every 2 weeks or once every 3 weeks.

[00113] The disclosure further provides the example of such method, wherein the instructional manual of such pharmaceutical kit instructs that a B7-H3-ADC and hPD-1 mAb-A are administered by IV infusion over a period of about 60 minutes.

[00114] The disclosure further provides the example of such method, wherein the instructional manual of such pharmaceutical kit instructs that a B7-H3-ADC is administered by IV infusion over a period of about 60 minutes and PD-1 X LAG-3 BD is administered by IV infusion over a period of about 30-90 minutes.

[00115] The disclosure further provides the example of such method, wherein the instructional manual of such pharmaceutical kit instructs that a B7-H3-ADC is administered by IV infusion over a period of about 60 minutes and PD-1 X LAG-3 BD is administered by IV infusion over a period of about 30-240 minutes.

[00116] The disclosure further provides the example of such method, wherein a B7-H3-ADC is to be administered in combination with the PD-1 binding molecule for the treatment of a cancer in which B7-H3 is expressed.

[00117] The disclosure further provides the example of such method, wherein the cancer is selected from the group consisting of: an adrenal gland cancer, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, an anal cancer (e.g., squamous cell carcinoma of the anal canal (SCAC)), a bladder cancer, a bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a B-cell cancer, a breast cancer (e.g., a HER2+ breast cancer or triple negative breast cancer (TNBC)), a carotid body tumors, a cervical cancer, a chondrosarcoma, a chordoma, a chromophobe renal cell carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a cutaneous benign fibrous histiocytoma, a desmoplastic small round cell tumor, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a fibrogenesis imperfecta ossium, a fibrous dysplasia of the bone, a gallbladder or bile duct cancer, a gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, a glioblastoma, a hematological malignancy, a hepatocellular carcinoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia (e.g., an acute myeloid leukemia), a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer (e.g., a non-small-cell lung cancer (NSCLC)), a medulloblastoma, a melanoma, a meningioma, a mesothelioma pharyngeal cancer, a multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a

neuroblastoma, a neuroendocrine tumors, an ovarian cancer, a pancreatic cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a pheochromocytoma, a pituitary tumor, a prostate cancer (e.g., a metastatic castration resistant prostate cancer (mCRPC)), a posterior uveal melanoma, a renal metastatic cancer, a rhabdoid tumor, a rhabdomyosarcoma, a sarcoma, a skin cancer, a small round blue cell tumor of childhood (e.g, neuroblastoma or rhabdomyosarcoma), a soft-tissue sarcoma, a squamous cell cancer (e.g., a squamous cell cancer of the head and neck (SCCHN), a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid cancer (e.g., a thyroid metastatic cancer), and a uterine cancer.

[00118] The disclosure further provides the example of such method, wherein the cancer is a prostate cancer, an anal cancer, a squamous cell cancer, a breast cancer, a melanoma, or a lung cancer.

[00119] The disclosure further provides the example of such method, wherein the cancer is mCRPC, SCAC, SCCHN, TNBC, uveal melanoma, or NSCLC.

[00120] The disclosure further provides the example of such method, further comprising administering a therapeutically or prophylactically effective amount of one or more additional therapeutic agents or chemotherapeutic agents.

[00121] The disclosure further provides the example of such method, wherein the chemotherapeutic agent is a platinum-based chemotherapeutic agent.

[00122] The disclosure further provides the example of such method, wherein the chemotherapeutic agent is a taxane.

[00123] The disclosure further provides the example of such method, wherein the subject in need thereof is a human.

BRIEF DESCRIPTION OF THE DRAWINGS

[00124] **Figure 1** provides a schematic showing representative covalently bonded tetravalent diabodies, such as a PD-1 X LAG-3 BD, 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