

WHAT IS CLAIMED IS:

Claim 1. ~~A method of treating a cancer comprising administering~~Use of an anti-B7-H3 antibody-drug conjugate (B7-H3-ADC) in the manufacture of a medicament for treating cancer~~to~~ in a subject in need thereof, wherein said ~~method comprises administering 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.

Claim 2. The ~~method~~use of claim 1, wherein said B7-H3-ADC is represented by the formula:



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 TINSGGSENTYY 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 said 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 said B7-H3-ADC molecule.

- Claim 3. The ~~method-use~~ of claim 2, wherein said Ab comprises:
- (i) a humanized Variable Light Chain (VL) domain comprising the amino acid sequence of **SEQ ID NO:17**; and
 - (ii) a humanized Variable Heavy Chain (VH) domain comprising the amino acid sequence of **SEQ ID NO:18**.
- Claim 4. The ~~method-use~~ of any one of claims 2 or 3, wherein said Ab further comprises an Fc Domain of a human IgG.
- ~~Claim 5. The method of claim 4, wherein said human IgG is a human IgG1, IgG2, IgG3, or IgG4.~~
- Claim 56. The ~~method-use~~ of ~~any one of~~ claims ~~4 or 5~~, wherein said Fc Domain is a variant Fc Domain that comprises:
- (a) one or more amino acid modifications that reduces the affinity of the variant Fc Domain for an FcγR, wherein said modifications comprise the substitution of L234A; L235A; or L234A and L235A, wherein said numbering is that of the EU index as in Kabat; and/or
 - (b) one or more amino acid modifications that enhances the serum half-life of the variant Fc Domain, wherein said modifications 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 7. The method of claim 6, wherein said modifications that reduces the affinity of the variant Fc Domain for an FcγR comprise the substitution of L234A; L235A; or L234A and L235A, wherein said numbering is that of the EU index as in Kabat.~~
- ~~Claim 8. The method of any one of claims 5 or 6, wherein said modifications that enhances the serum half life of the variant Fc Domain 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 9. — The method of any one of claims 2-8, wherein at least one of said LM is a Linker Molecule.~~

Claim 610. The ~~method-use~~ of any one of claims 2-59, wherein said LM is a Linker Molecule that is a peptidic linker.

Claim 711. The ~~method-use~~ of claim 610, wherein said peptidic linker is a valine-citrulline dipeptide linker.

Claim 812. The ~~method-use~~ of any one of claims 2-711, wherein said LM Linker Molecule further comprises:

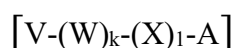
(a) — a self-eliminating spacer between the cleavable linker and D; and optionally,

(b) — a maleimide linker moiety between the cleavable linker and Ab.

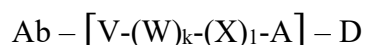
Claim 913. The ~~method-use~~ of claim 812, wherein said self-eliminating spacer comprises a para-aminobenzyloxycarbonyl moiety.

~~Claim 14. — The method of any one of claims 2-13, wherein said Linker Molecule further comprises a maleimide linker moiety between the cleavable linker and Ab.~~

Claim 1015. The ~~method-use~~ of any one of claims 1-914, wherein LM is represented by the formula:



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



wherein:

V is a cleavable linker,

(W)_k-(X)_l-A is an elongated, self-eliminating spacer system, that self-eliminates via a 1,(4+2n)-elimination,

W and X are each a 1,(4+2n) electronic cascade spacer, being the same or different,

A is either a spacer group of formula (Y)_m, wherein Y is a 1,(4+2n) electronic cascade spacer, or a group of formula U, being a cyclisation elimination spacer,

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

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

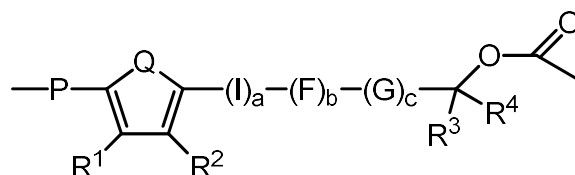
with the provisos that:

when A is (Y)_m: then k+l+m ≥ 1, and

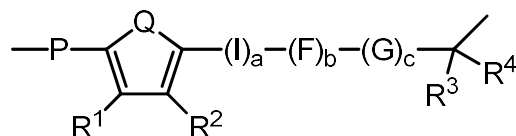
if k+l+m=1, then n>1;

when A is U: then k+1 ≥ 1.

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



or the formula:

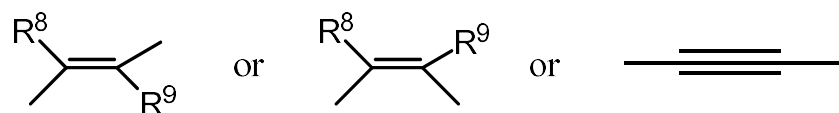


wherein: Q is -R⁵C=CR⁶-, S, O, NR⁵, -R⁵C=N-, or -N=CR⁵-

P is NR⁷, O or S

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

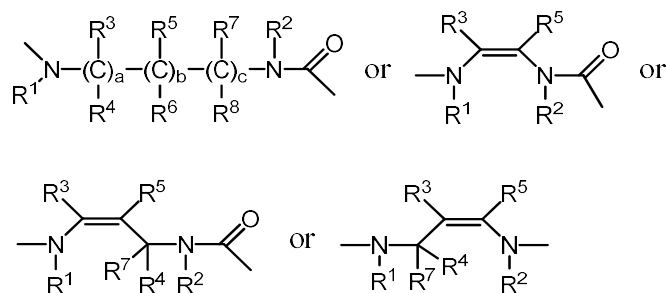
I, F and G are independently selected from compounds having the formula:



wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ independently represent H, C₁₋₆ alkyl, C₃₋₂₀ heterocyclyl, C₅₋₂₀ aryl, C₁₋₆ alkoxy, hydroxy (OH), amino (NH₂), mono-substituted amino (NR_xH), di-substituted amino (NR_x¹R_x²), nitro (NO₂), halogen, CF₃, CN,

CONH₂, SO₂Me, CONHMe, cyclic C₁₋₅ alkylamino, imidazolyl, C₁₋₆ alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_x), tetrazole, carboxy (COOH), carboxylate (COOR_x), sulphonyl (S(=O)₂R_x), sulphoxy (S(=O)₂OH), sulphonate (S(=O)₂OR_x), sulphoxyl (S(=O)OR_x), sulphoxy (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_x¹ and R_x² are independently selected from a C₁₋₆ alkyl group, a C₃₋₂₀ heterocyclyl group or a C₅₋₂₀ aryl group, two or more of the substituents R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, or R⁹ 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;

R¹ and/or R² 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 (NH₂), mono-substituted amino (NR_xH), disubstituted amino (NR_x¹R_x²), nitro (NO₂), halogen, CF₃, CN, CONH₂, SO₂Me, CONHMe, cyclic C₁₋₅ alkylamino, imidazolyl, C₁₋₆ alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_x), tetrazole, carboxy (COOH), carboxylate (COOR_x), sulphonyl (S(=O)₂R_x), sulphoxy (S(=O)₂OH), sulphonate (S(=O)₂OR_x), sulphoxyl (S(=O)OR_x), sulphoxy (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_x¹ and R_x² are selected from a C₁₋₆ alkyl group, a C₃₋₂₀ heterocyclyl group or a C₅₋₂₀ aryl group; and

R³, R⁴, R⁵, R⁶, R⁷ and R⁸ independently represent H, C₁₋₆ alkyl, C₃₋₂₀ heterocyclyl, C₅₋₂₀ aryl, C₁₋₆ alkoxy, hydroxy (OH), amino (NH₂), mono-substituted amino (NR_xH), disubstituted amino (NR_x¹R_x²), nitro (NO₂), halogen, CF₃, CN, CONH₂, SO₂Me, CONHMe, cyclic C₁₋₅ alkylamino, imidazolyl, C₁₋₆ alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_x), tetrazole, carboxy (COOH), carboxylate (COOR_x), sulphony (S(=O)₂OH), sulphonate (S(=O)₂OR_x), sulphonyl (S(=O)₂R_x), sulphoxy (S(=O)OH), sulphinate (S(=O)OR_x), sulphinyl (S(=O)R_x), phosphonoxy (OP(=O)(OH)₂), and phosphate (OP(=O)(OR_x)₂), where R_x, R_x¹ and R_x² are selected from a C₁₋₆ alkyl group, a C₃₋₂₀ heterocyclyl group or a C₅₋₂₀ aryl group, and two or more of the substituents R¹, R², R³, R⁴, R⁵, R⁶, R⁷, or R⁸ are optionally connected to one another to form one or more aliphatic or aromatic cyclic structures.

Claim ~~114~~6. The ~~method-use~~ of claim ~~104~~5, wherein said 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-aminocinnamyloxycarbonyl;
- (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-aminocinnamyloxycarbonyl(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.

Claim 1217. The ~~method-use~~ of any one of claims 2-1116, wherein said LM Linker Molecule is:

- (a) -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; and/or
- (b) covalently linked to the Ab via reduced inter-chain disulfides.

Claim 1318. The ~~method-use~~ of any one of claims 2-1217, wherein said cytotoxic duocarmycin moiety D comprises a duocarmycin cytotoxin selected from the group consisting of: duocarmycin A, duocarmycin B1, duocarmycin B2, duocarmycin C1, duocarmycin C2, duocarmycin D, duocarmycin SA, CC-1065, adozelesin, bizelesin, carzelesin (U-80244), *seco*-duocarmycin and spiro-duocarmycin (DUBA).

Claim 1419. The ~~method-use~~ of claim 1318, wherein the cytotoxic duocarmycin moiety D comprises *seco*-duocarmycin.

~~Claim 20. The method of any of claims 2-19, wherein said LM Linker Molecule is covalently linked to the Ab via reduced inter-chain disulfides.~~

Claim 1521. The ~~method-use~~ of any one of claims 1-1320, wherein said B7-H3-ADC is to be administered at a dose of about 3 mg/kg.

Claim 1622. The ~~method-use~~ of any one of claims 1-1320, wherein said B7-H3-ADC is to be administered at a dose of about 3.5 mg/kg.

Claim 1723. The ~~method-use~~ of any one of claims 1-1320, wherein said B7-H3-ADC is to be administered at a dose of about 4 mg/kg.

Claim 1824. The ~~method-use~~ of any one of claims 1-1723, wherein said B7-H3-ADC is to be administered by intravenous (IV) infusion.

~~Claim 25. The method of claim 24, wherein said IV infusion is over a period of about 60 minutes.~~

Claim 1926. The ~~method-use~~ of any one of claims 1-1825, wherein said B7-H3-ADC is to be administered in combination with a therapeutically effective dose of a PD-1 binding molecule.

Claim 2027. The ~~method-use~~ of any one of claims 1-1926, wherein said 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, 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, a HER2+ breast cancer, 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, an acute myeloid leukemia, a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, 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, 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, a neuroblastoma, a soft-tissue sarcoma, a squamous cell cancer, 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, a thyroid metastatic cancer, and a uterine cancer.

~~Claim 28. — The method of claim 27, wherein said cancer is selected from the group consisting of: adrenal cancer, anal cancer, SCAC, bladder cancer, breast cancer, colorectal cancer, gastric cancer, glioblastoma, kidney cancer, lung cancer, NSCLC, acute lymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, hairy cell leukemia, Burkett's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, mesothelioma pharyngeal cancer, non-Hodgkin's lymphoma, small lymphocytic lymphoma, multiple myeloma, melanoma, ovarian cancer, pancreatic cancer, a posterior uveal melanoma, prostate cancer, mCRPC, skin cancer, renal cell carcinoma, small round blue cell tumors of childhood, neuroblastoma, rhabdomyosarcoma, squamous cell cancer,~~

~~SCCHN, testicular cancer, thyroid cancer, thyroid metastatic cancer, and
uterine cancer.~~

Claim ~~2129~~. The ~~method-use~~ of ~~any one of claims 27 or 28~~20, wherein said cancer is a
prostate cancer, an anal cancer, a squamous cell cancer, a breast cancer, a
melanoma, or a lung cancer.

Claim ~~2230~~. The ~~method-use~~ of any one of claims ~~20 or 21~~27-29, wherein:

- (a) -said prostate cancer is mCRPC;
- (b) said anal cancer is SCAC;
- (c) said squamous cell cancer is SCCHN;
- (d) said breast cancer is TNBC;
- (e) said melanoma is a uveal melanoma; or
- (f) said lung cancer is NSCLC.

~~Claim 31. The method of any one of claims 27 or 28, wherein said cancer is anal
cancer.~~

~~Claim 32. The method of any one of claims 27, 28, or 31, wherein said anal cancer is
SCAC.~~

~~Claim 33. The method of any one of claims 28 or 28, wherein said cancer is a
squamous cell cancer.~~

~~Claim 34. The method of any one of claims 27, 28, or 33, wherein said squamous cell
cancer is SCCHN.~~

~~Claim 35. The method of any one of claims 27 or 28, wherein said cancer is breast
cancer.~~

~~Claim 36. The method of any one of claims 27, 28, or 35, wherein said breast cancer
is TNBC.~~

~~Claim 37. The method of any one of claims 27 or 28, wherein said cancer is
melanoma.~~

~~Claim 38. The method of any one of claims 27, 28, or 37, wherein said melanoma is a uveal melanoma.~~

~~Claim 39. The method of any one of claims 27 or 28, wherein said cancer is lung cancer.~~

~~Claim 40. The method of any one of claims 27, 28, or 39, wherein said lung cancer is NSCLC.~~

Claim 2341. The ~~method-use~~ of any one of claims 1-2240, ~~further comprising administering wherein~~ a therapeutically or prophylactically effective amount of one or more additional therapeutic agents or chemotherapeutic agents is to be further administered.

Claim 2442. The ~~method-use~~ of claim 2341, wherein said chemotherapeutic agent is:
(a) -a platinum-based chemotherapeutic agent; or
(b) a taxane.

~~Claim 43. The method of claim 41, wherein said chemotherapeutic agent is a taxane.~~

Claim 2544. The ~~method-use~~ of any one of claims 1-2443, wherein said subject in need thereof is a human.