Combination of antibody-drug conjugate and anti-PD-1 antibody, and use thereof

Technical Field

[1] The present disclosure relates to the biopharmaceutical field, in particular, to a combination of antibody-drug conjugate and anti-PD-1 antibody, and use thereof.

Background

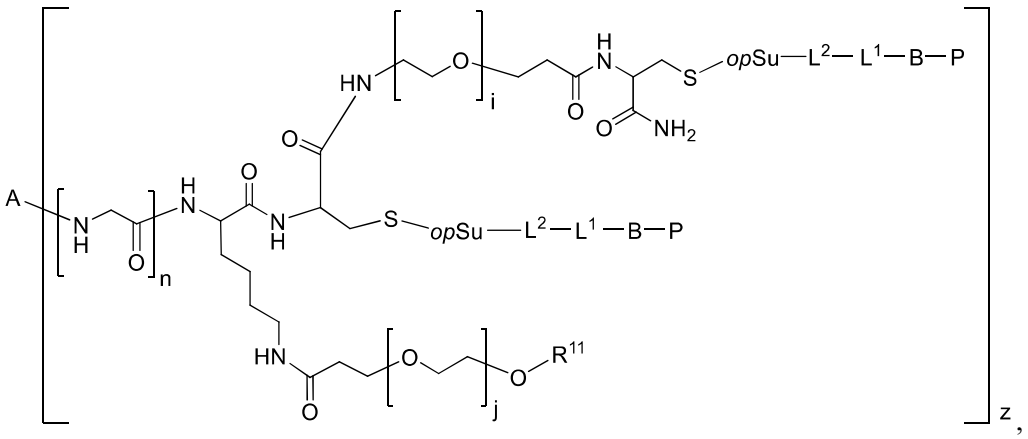
[2] TROP2 is a transmembrane protein and was found to be overexpressed in several cancer types, including endometrial cancer, prostate cancer, pancreatic cancer, colon cancer, stomach cancer, oral cancer, glioma, making it a natural candidate for the development of targeted therapies. TROP2 acts as a regulator in cellular self-renewal, proliferation and transformation. Experiments have shown that TROP2 can promote tumor growth, and tumor cell proliferation is disturbed when the TROP2 gene is knocked out. The limited tissue expression of TROP2 reduces the toxicity of the treatment, which is also the advantage of targeting TROP2 therapy. Multiple TROP2 targeting ADC have been proposed, such as DS-1062, TRODELVY, BAT8003. These therapeutic agents have significantly improved the survival of TROP2 positive cancer patients.

[3] DS-1062 is an antibody-conjugated drug developed by Daiichi Sankyo using its proprietary DXd ADC technology. It is composed of a monoclonal antibody targeting the Trop2 protein linked to DXd. The data, including more NSCLC patients, shows that DS-1062 exhibits good dose-dependent anticancer activity. As the dose was increased, more NSCLC patients' tumors shrank. TRODELVY is the first FDA-approved ADC specifically for relapsed or refractory metastatic TNBC and the first FDA-approved anti-TROP2 ADC. It consists of an antibody targeting TROP2 linked to SN-38, the active metabolite of the chemotherapeutic drug irinotecan.

[4] However, new ADC drugs targeting TROP2 are still in great demand, and high-safety ADCs are also one of the development directions of the new drugs.

Summary

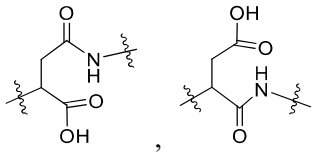
[4a] In an aspect, there is provided the use of an effective amount of an antibody drug conjugate for the manufacture of a medicament for the treatment of a subject with cancer to be used in combination with an effective amount of an anti PD-1 antibody, wherein the antibody drug conjugate is represented by the following structural formula:



wherein:

A is an anti TROP2 antibody or an antigen-binding fragment, wherein the antibody or antigen-binding fragment is modified to connect with the $(Gly)_n$ group;

R^{11} is C_{1-10} alkyl;

*op*Su is  or a mixture thereof;

i is an integer of 0 to 8;

j is an integer of 1 to 12;

z is an integer from 1 to 4;

n is 3;

L^2 is $-(CH_2)_p-(CH_2)_2(CO)-$ or is $-(C_2H_4-O)_p-(CH_2)_2(CO)-$;

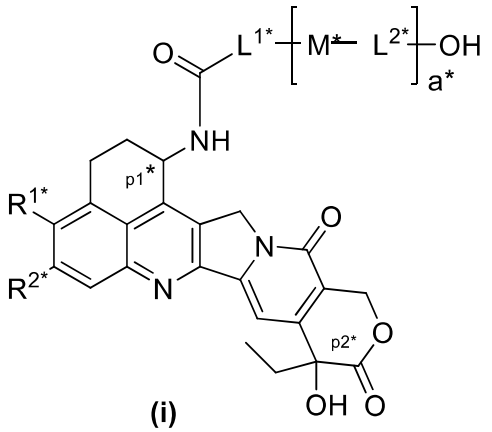
p is 2 to 4;

L^1 is Gly-Gly-Phe-Gly;

B is $-NH-CH_2-U-$ or absent or $-NH-CH_2-U-(CR^1R^2)_g-(CO)-$, U is absent, or U is O, g is 1;

R^1, R^2, are each independently selected from hydrogen, halogen, $-C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, C_{4-10} cycloalkylene; or R^1 and R^2 together with the carbon atom to which they are attached form a 3-6 membered cycloalkyl group; and

P is a payload having the structure of formula (i):



(i)

,

wherein:

a* is 0 or 1;

the carbon atoms marked with p1* and p2* each is asymmetric center, and the asymmetric center is *S* configured, *R* configured or racemic;

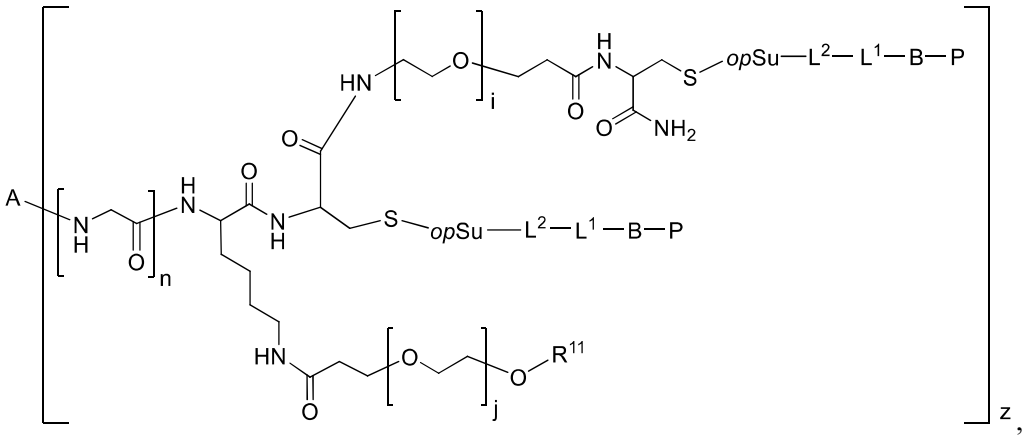
L^{1*} is selected from C_{1-6} alkylene, which is unsubstituted or substituted with one substituent selected from halogen, -OH and $-NH_2$;

M* is $-CH_2-$, -NH- or -O-;

L^{2*} is C_{1-3} alkylene; and

R^{1*} and R^{2*} are each independently selected from hydrogen, C_{1-6} alkyl, halogen and C_{1-6} alkoxy.

[4b] In another aspect, there is provided the use of an effective amount of an antibody drug conjugate and an effective amount of an anti-PD-1 antibody for the manufacture of a medicament for treating a subject suffering from a cancer or reducing the likelihood of cancer progression, wherein the antibody drug conjugate is represented by the following structural formula:

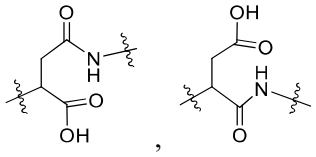


,

wherein:

A is an anti TROP2 antibody or an antigen-binding fragment, wherein the antibody or antigen-binding fragment is modified to connect with the $(Gly)_n$ group;

R^{11} is C_{1-10} alkyl;

*op*Su is  or a mixture thereof;

i is an integer of 0 to 8;

j is an integer of 1 to 12;

z is an integer from 1 to 4;

n is 3;

L^2 is $-(CH_2)_p-(CH_2)_2(CO)-$ or is $-(C_2H_4-O)_p-(CH_2)_2(CO)-$;

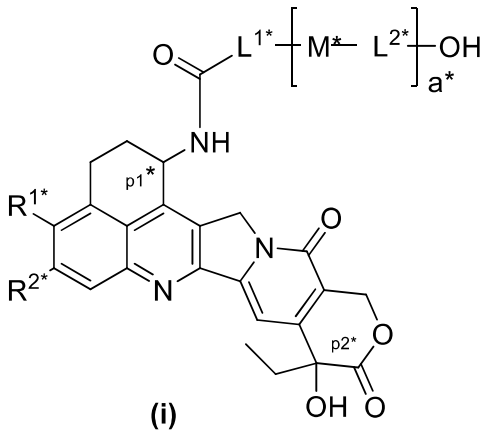
p is 2 to 4;

L^1 is Gly-Gly-Phe-Gly;

B is $-NH-CH_2-U-$ or absent or $-NH-CH_2-U-(CR^1R^2)_g-(CO)-$, U is absent, or U is O, g is 1;

R^1, R^2, are each independently selected from hydrogen, halogen, $-C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, C_{4-10} cycloalkylene; or R^1 and R^2 together with the carbon atom to which they are attached form a 3-6 membered cycloalkyl group; and

P is a payload having the structure of formula (i):



(i)

,

wherein:

a* is 0 or 1;

the carbon atoms marked with p1* and p2* each is asymmetric center, and the asymmetric center is *S* configured, *R* configured or racemic;

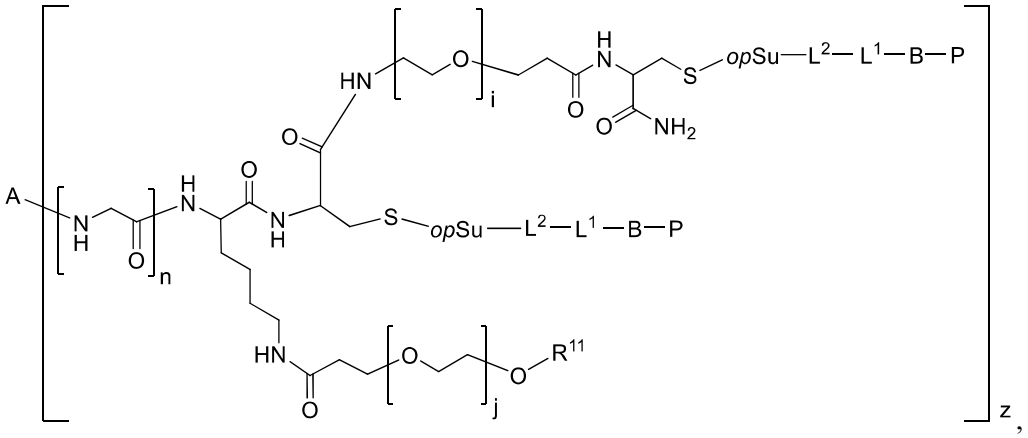
L^{1*} is selected from C_{1-6} alkylene, which is unsubstituted or substituted with one substituent selected from halogen, -OH and $-NH_2$;

M* is $-CH_2-$, -NH- or -O-;

L^{2*} is C_{1-3} alkylene; and

R^{1*} and R^{2*} are each independently selected from hydrogen, C_{1-6} alkyl, halogen and C_{1-6} alkoxy.

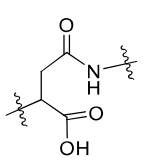
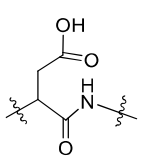
[4c] In another aspect, there is provided a pharmaceutical composition, comprising an effective amount of an antibody drug conjugate and an effective amount of an anti-PD-1 antibody, wherein the antibody drug conjugate is represented by the following structural formula:



wherein:

A is an anti TROP2 antibody or an antigen-binding fragment, wherein the antibody or antigen-binding fragment is modified to connect with the $(Gly)_n$ group;

R^{11} is C_{1-10} alkyl;

*op*Su is  ,  or a mixture thereof;

i is an integer of 0 to 8;

j is an integer of 1 to 12;

z is an integer from 1 to 4;

n is 3;

L^2 is $-(CH_2)_p-(CH_2)_2(CO)-$ or is $-(C_2H_4-O)_p-(CH_2)_2(CO)-$;

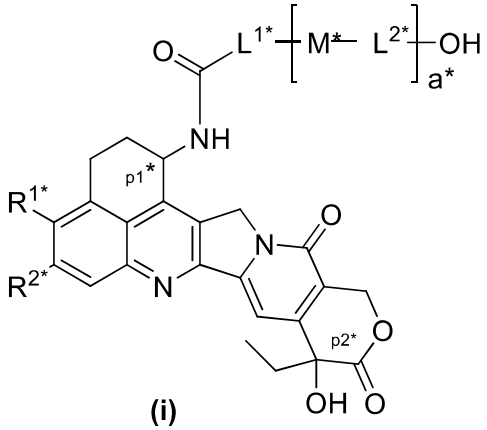
p is 2 to 4;

L^1 is Gly-Gly-Phe-Gly;

B is $-NH-CH_2-U-$ or absent or $-NH-CH_2-U-(CR^1R^2)_g-(CO)-$, U is absent, or U is O, g is 1;

R^1, R^2, are each independently selected from hydrogen, halogen, $-C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, C_{4-10} cycloalkylene; or R^1 and R^2 together with the carbon atom to which they are attached form a 3-6 membered cycloalkyl group; and

P is a payload having the structure of formula (i):



(i)

,

wherein:

a* is 0 or 1;

the carbon atoms marked with p1* and p2* each is asymmetric center, and the asymmetric center is *S* configured, *R* configured or racemic;

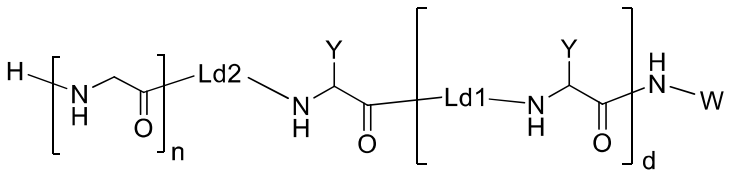
L^{1*} is selected from C_{1-6} alkylene, which is unsubstituted or substituted with one substituent selected from halogen, -OH and $-NH_2$;

M* is $-CH_2-$, -NH- or -O-;

L^{2*} is C_{1-3} alkylene; and

R^{1*} and R^{2*} are each independently selected from hydrogen, C_{1-6} alkyl, halogen and C_{1-6} alkoxy.

[5] In a first example, provided is a compound of formula (I):



formula (I)

wherein,

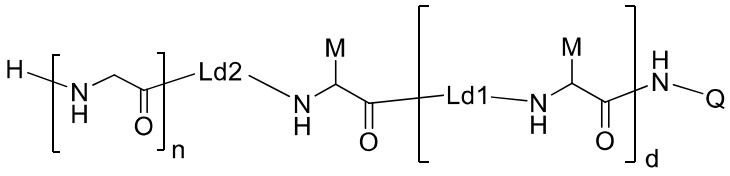
W is hydrogen, LKb or $-C_2H_4-(PEG)_t-(CO)NH_2$;

Y is hydrogen or is LKa-LKb;

provided that W and Y are not simultaneously hydrogen;

each t is independently an integer of 1-100, preferably 1 to 20; preferably each t is independently an integer of 1 to 12; more preferably 8 to 12; particularly 8 or 12.

[6] In a second example, provided is a compound having the structure of formula (II)



formula (II)

wherein

Q is hydrogen, $-C_2H_4-(PEG)_t-(CO)NH_2$ or LKb—P;

M is hydrogen or LKa-LKb—P;

provided that Q and M are not simultaneously hydrogen;

P is a payload which is linked to the B moiety or L^1 moiety of the compound of formula (I);

n, d, Ld1, Ld2, t, LKa and LKb are as defined in formula (I);

preferably, M is hydrogen or LKa-L^2—L^1—B—P; wherein each B is independently absent, or is a combination of the following 1) and 2): 1) a self-immolative spacer Sp1; and 2) a bond, or one of or a combination of two or more of the bivalent groups selected from: $-CR^1R^2-$, C_{1-10} alkylene, C_{4-10} cycloalkylene, C_{4-10} heterocyclylene and -(CO)-;

preferably, Sp1 is selected from PABC, acetal, heteroacetal and the combination thereof; more preferably, Sp1 is acetal, heteroacetal or PABC; further preferably, the heteroacetal is selected from N,O- heteroacetal; more preferably, Sp1 is $-O-CH_2-U-$ or $-NH-CH_2-U-$; wherein the -O- or the -NH- is connected to Cleavable sequence 1, and U is absent, or is O, S or NH, preferably O or S.

[7] In a third example, provided is an anti-TROP2 antibody or antigen-binding fragment thereof, comprising a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein

the V_H comprises:

(i) HCDR1 comprising the amino acid sequence of X_1AGMN (SEQ ID NO: 45), wherein X_1 is N or A;

(ii) HCDR2 comprising the amino acid sequence of WINTDSGEPTYTDDFKG (SEQ ID NO: 10) or WINTYTGEPTYTDDFKG (SEQ ID NO: 8); and

(iii) HCDR3 comprising the amino acid sequence of GGFGSSYWYFDV (SEQ ID NO: 11); and/or

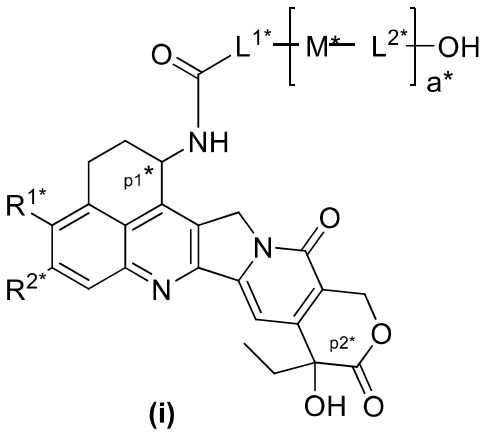
the V_L comprises:

(i) LCDR1 comprising the amino acid sequence of KASQDVSIAVA (SEQ ID NO:13) or KASQDVSTAVA (SEQ ID NO:14);

(ii) LCDR2 comprising the amino acid sequence of SASYRYT (SEQ ID NO:15); and

(iii) LCDR3 comprising the amino acid sequence of QQHYITPLT (SEQ ID NO: 16).

[8] In a fourth example, provided is a cytotoxin having the structure of formula (i):



(i)

wherein,

a* is 0 or 1;

the carbon atoms marked with p1* and p2* each is asymmetric center, and the asymmetric center is *S* configured, *R* configured or racemic;

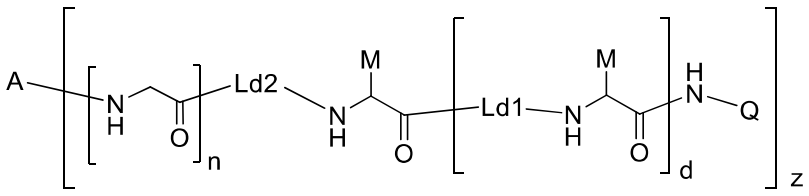
L^{1*} is selected from C_{1-6} alkylene, which is unsubstituted or substituted with one substituent selected from halogen, -OH and $-NH_2$;

M* is $-CH_2-$, -NH- or -O-;

L^{2*} is C_{1-3} alkylene;

R^{1*} and R^{2*} are each independently selected from hydrogen, C_{1-6} alkyl, halogen and C_{1-6} alkoxy.

[9] In a fifth example, provided is a pharmaceutical combination, comprising a conjugate and anti-PD-1 antibody, wherein the conjugate having the structure of formula (III):

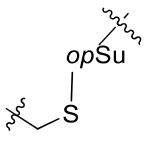
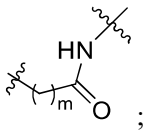


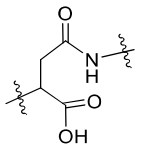
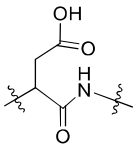
formula (III)

wherein,

Q is hydrogen, $-C_2H_4-(PEG)_t-(CO)NH_2$ or LKb—P;

M is hydrogen or LKa-LKb—P;

each LKa is independently selected from  and ;

*op*Su is ,  or a mixture thereof;

each LKb is independently L^2—L^1—B;

m, n, d, Ld1, Ld2, t, LKa and LKb are as defined in formula (I);

each B is independently absent, or is a combination of the following 1) and 2): 1) a self-immolative spacer Sp1; and 2) a bond, or one of or a combination of two or more of the bivalent groups selected

from: -CR^1R^2-, C_{1-10} alkylene, C_{4-10} cycloalkylene, C_{4-10} heterocyclylene and -(CO)-; preferably, B is -NH-CH_2-U-, absent, -NH-CH_2-U-$(CR^1R^2)_g$-(CO)- or NH-CH_2-U-$(CH_2)_g$-(CO)-;

provided that Q and M are not simultaneously hydrogen;

P is a payload which is linked to the B moiety or L^1 moiety of the compound of formula (I);

each L^1 is independently Cleavable sequence 1 comprising an amino acid sequence which can be cleaved by enzyme, and Cleavable sequence 1 comprises 1-10 amino acids;

each L^2 is independently a bond; or a C_{2-20} alkylene wherein one or more -CH_2- structures in the alkylene is optionally replaced by -CR^3R^4-, -O-, -(CO)-, -$S(=O)_2$-, -NR^5-, -$N^{\oplus}R^6R^7$-, C_{4-10} cycloalkylene, C_{4-10} heterocyclylene, phenylene; wherein the cycloalkylene, heterocyclylene and phenylene are each independently unsubstituted or substituted with at least one substituent selected from halogen, -C_{1-10} alkyl, -C_{1-10} haloalkyl, -C_{1-10} alkylene-NH-R^8 and -C_{1-10} alkylene-O-R^9;

-$(PEG)_t$-, -$(PEG)_i$- and -$(PEG)_j$- are each a PEG fragment, which comprises the denoted number of consecutive -$(O\text{-}C_2H_4)$- structure units or consecutive -$(C_2H_4\text{-}O)$- structure units, with an optional additional C_{1-10} alkylene at one terminal;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 are each independently selected from hydrogen, halogen, -C_{1-10} alkyl, -C_{1-10} haloalkyl, C_{4-10} cycloalkylene; or

R^1 and R^2 together with the carbon atom to which they are attached form a 3-6 membered cycloalkyl group; or

R^3 and R^4 together with the carbon atom to which they are attached form a 3-6 membered cycloalkyl group;

each i is independently an integer of 0-100, preferably 0 to 20; preferably each i is independently an integer of 0 to 12; more preferably 0 to 8; particularly 4;

each j is independently an integer of 1-100, preferably 1 to 20; preferably each j is independently an integer of 1 to 12; more preferably 8 to 12; particularly 8 or 12;

each t is independently an integer of 1-100, preferably 1 to 20; preferably each t is independently an integer of 1 to 12; more preferably 8 to 12; particularly 8 or 12;

each g is independently an integer of 1-10, for example, 1, 2, 3, 4, 5, 6, 7;

A is anti-TROP2 antibody or antigen-binding fragment thereof which is linked to the G_n moiety of the compound of formula (I); G is Glycine;

z is an integer of 1 to 20.

[10] In some examples, the pharmaceutical combination further comprises at least one pharmaceutically acceptable carrier.

[11] In another example, provided is a kit comprising the pharmaceutical combination.

[12] In another example, provided is use of the pharmaceutical combination or the kit in the manufacture of a medicament for preventing or treating a disease; wherein the disease is a tumor.

[13] In another example, provided is a method for treating a subject suffering a disease or preventing disease progression, comprises administering the pharmaceutical combination or the kit; and the disease is a tumor.

[14] In one example, the tumor is TROP2-associated tumor.

[15] In some examples, the disease is a tumor. In some examples, the disease includes TROP2-positive tumor. In some examples, the disease includes tumor overexpressing TROP2 or tumor with TROP2 gene mutation. In some examples, the disease is selected from the group consisting of: fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendothelial sarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon cancer, pancreatic cancer, breast cancer, thyroid cancer, endometrial cancer, melanoma, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, bronchial carcinoma, renal cell carcinoma, liver cancer, bile duct cancer, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung cancer, small cell lung cancer, bladder cancer, epithelial cancer, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, neuroblastoma and retinoblastoma. In one example, the TROP2-associated tumor is selected from breast cancer, gastric cancer, lung cancer, ovarian cancer, and urothelial cancer.

[16] In another example, provided is a method for treating a subject suffering from a cancer or reducing the likelihood of cancer progression, comprising administering to the subject an effective amount of the conjugate and administering to the subject an effective amount of an anti-PD-1 antibody.

[17] In another example, provided is use of an effective amount of the conjugate for the manufacture of a medicament for the treatment of a subject with cancer to be used in combination with an effective amount of an anti PD-1 antibody.

Brief Description of the Drawings

[18] Figure 1.1 shows the antibody internalization on MBA-MD-468, Figure 1.2 shows the binding activity on Trop2 ECD, Figure 1.3 shows the internalization on NCI-N87.

[19] Figure 2 shows the effect of ADC-7 and DS1062a on the viability of FaDu cells.

[24] Figure 3 shows the effect of ADC-1 and DS1062a on the viability of human pancreatic cancer cell BxPC-3.

[25] Figure 4 shows the effect of ADC-1 and DS1062a on the viability of human breast cancer cell MDA-MB-468.

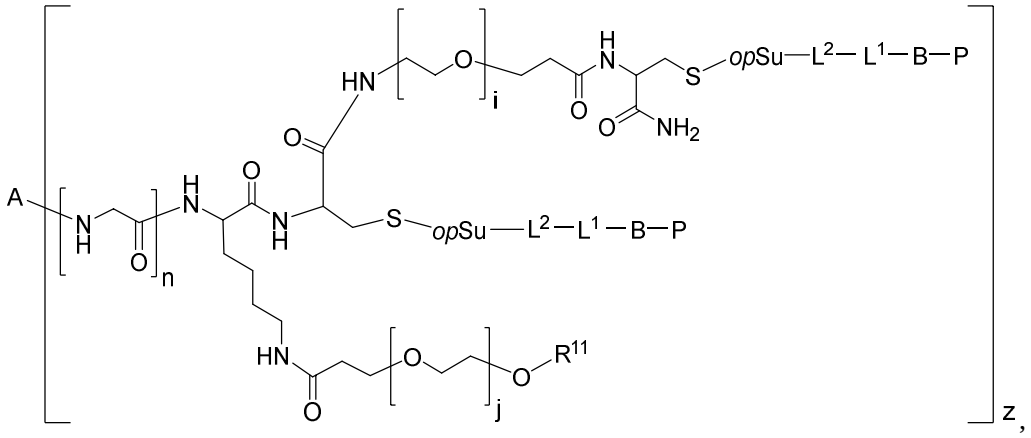
[26] Figure 5 shows the effect of ADC-7 and DS1062a on the viability of gastric cancer cell NCI-N87.

[27] Figure 6 shows the effect of ADC-2, ADC-3 and ADC-1 on the viability of pharyngeal squamous cells carcinoma FaDu.

[28] Figure 7.1 shows the effect of ADC-2, ADC-3 and ADC-1 on the proliferation of human pancreatic cancer cell BxPC-3, Figure 7.2 shows the effect of ADC-2 on the proliferation of BxPC-3, Figure 7.3 shows the effect of ADC-2 on the proliferation of FaDu, Figure 7.4 shows the effect of ADC-2 on the proliferation of NCI-N87.

Claim

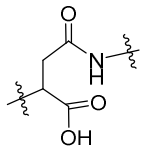
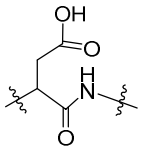
1. Use of an effective amount of an antibody drug conjugate for the manufacture of a medicament for the treatment of a subject with cancer to be used in combination with an effective amount of an anti PD-1 antibody, wherein the antibody drug conjugate is represented by the following structural formula:



wherein:

A is an anti TROP2 antibody or an antigen-binding fragment, wherein the antibody or antigen-binding fragment is modified to connect with the $(Gly)_n$ group;

R^{11} is C_{1-10} alkyl;

*op*Su is  ,  or a mixture thereof;

i is an integer of 0 to 8;

j is an integer of 1 to 12;

z is an integer from 1 to 4;

n is 3;

L^2 is $-(CH_2)_p-(CH_2)_2(CO)-$ or is $-(C_2H_4-O)_p-(CH_2)_2(CO)-$;

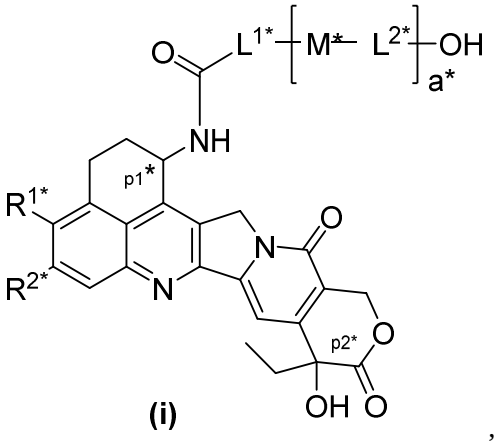
p is 2 to 4;

L^1 is Gly-Gly-Phe-Gly;

B is $-NH-CH_2-U-$ or absent or $-NH-CH_2-U-(CR^1R^2)_g-(CO)-$, U is absent, or U is O, g is 1;

R^1, R^2, are each independently selected from hydrogen, halogen, -C_{1-10} alkyl, -C_{1-10} haloalkyl, C_{4-10} cycloalkylene; or R^1 and R^2 together with the carbon atom to which they are attached form a 3-6 membered cycloalkyl group; and

P is a payload having the structure of formula (i):



(i) ,

wherein:

a* is 0 or 1;

the carbon atoms marked with p1* and p2* each is asymmetric center, and the asymmetric center is *S* configured, *R* configured or racemic;

L^{1*} is selected from C_{1-6} alkylene, which is unsubstituted or substituted with one substituent selected from halogen, -OH and -NH_2;

M* is -CH_2-, -NH- or -O-;

L^{2*} is C_{1-3} alkylene; and

R^{1*} and R^{2*} are each independently selected from hydrogen, C_{1-6} alkyl, halogen and C_{1-6} alkoxy.

2. The use of claim 1, wherein:

i is 4;

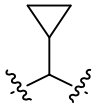
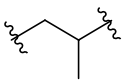
j is an integer from 8 to 12;

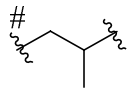
z is 2; and

a* is 0.

3. The use of claim 1 or 2, wherein

R^{1*} and R^{2*} are independently selected from C_{1-6} alkyl and halogen; and

L^{1*} is selected from C_{1-6} linear alkylene, C_{1-6} branched alkylene, C_{3-6} cyclic alkylene and C_{3-4} cyclic alkyl–C_{1-2} linear alkylene group, wherein the alkylene and cyclic alkylene are each independently unsubstituted or substituted with one substituent selected from halogen, -OH and $-NH_2$; preferably, L^{1*} is selected from C_{1-4} alkylene, wherein the alkylene is unsubstituted or substituted with one substituent selected from halogen, -OH and $-NH_2$; more preferably, L^{1*} is selected from $-CH_2-$, $-C_2H_4-$, , , , , , which are each independently unsubstituted or substituted with at least one substituent selected from halogen, -OH and $-NH_2$; most preferably, L^{1*} is selected from $-CH_2-$, 

and , wherein "#" marks the position attached to carbonyl.

4. The use of any one of claims 1-3, wherein the anti-TROP2 antibody or antigen-binding fragment thereof comprises a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein

the V_H comprises:

(i) HCDR1 comprising the amino acid sequence of NYGMN (SEQ ID NO: 4);

(ii) HCDR2 comprising the amino acid sequence of WINTYTGEPTYTDDFKG (SEQ ID NO: 8); and

(iii) HCDR3 comprising the amino acid sequence of GGFGSSYWYFDV (SEQ ID NO: 11); and

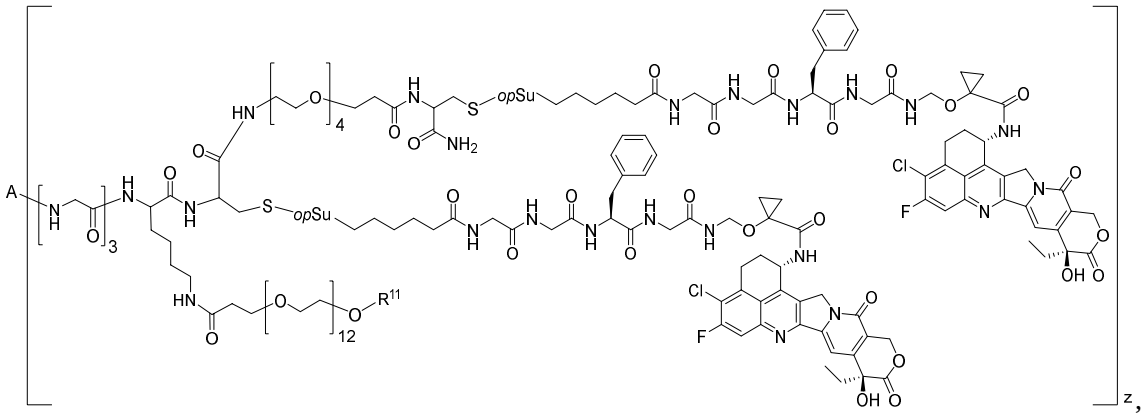
the V_L comprises:

(i) LCDR1 comprising the amino acid sequence of KASQDVSIAVA (SEQ ID NO:13);

(ii) LCDR2 comprising the amino acid sequence of SASYRYT (SEQ ID NO:15); and

(iii) LCDR3 comprising the amino acid sequence of QQHYITPLT (SEQ ID NO: 16).

5. The use of any one of claims 1-4, wherein the conjugate is represented by the following structural formula:

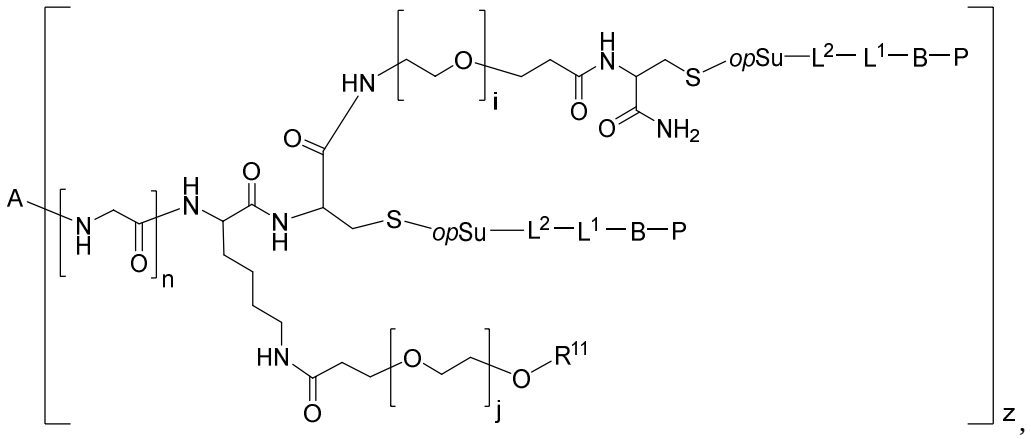


wherein

A is the antibody GQhRS7 in which the heavy chain is SEQ ID NO: 30 and the light chain is SEQ ID NO: 40, wherein the light chain is modified by cleaving the upstream peptide bond of the GG in the LPETGG sequence to link to the free N-terminal of G_3 via a new peptide bond to result in the amino acid sequence $LPETG_3$; and

R^{11} is methyl.

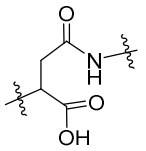
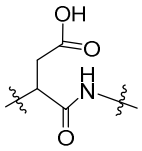
6. Use of an effective amount of an antibody drug conjugate and an effective amount of an anti-PD-1 antibody for the manufacture of a medicament for treating a subject suffering from a cancer or reducing the likelihood of cancer progression, wherein the antibody drug conjugate is represented by the following structural formula:



wherein:

A is an anti TROP2 antibody or an antigen-binding fragment, wherein the antibody or antigen-binding fragment is modified to connect with the $(Gly)_n$ group;

R^{11} is C_{1-10} alkyl;

*op*Su is  ,  or a mixture thereof;

i is an integer of 0 to 8;

j is an integer of 1 to 12;

z is an integer from 1 to 4;

n is 3;

L^2 is $-(CH_2)_p-(CH_2)_2(CO)-$ or is $-(C_2H_4-O)_p-(CH_2)_2(CO)-$;

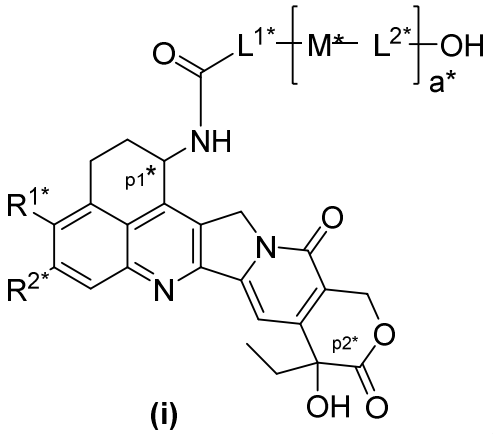
p is 2 to 4;

L^1 is Gly-Gly-Phe-Gly;

B is $-NH-CH_2-U-$ or absent or $-NH-CH_2-U-(CR^1R^2)_g-(CO)-$, U is absent, or U is O, g is 1;

R^1, R^2, are each independently selected from hydrogen, halogen, $-C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, C_{4-10} cycloalkylene; or R^1 and R^2 together with the carbon atom to which they are attached form a 3-6 membered cycloalkyl group; and

P is a payload having the structure of formula (i):



(i) ,

wherein:

a* is 0 or 1;

the carbon atoms marked with p1* and p2* each is asymmetric center, and the asymmetric center is *S* configured, *R* configured or racemic;

L^{1*} is selected from C_{1-6} alkylene, which is unsubstituted or substituted with one substituent selected from halogen, -OH and $-NH_2$;

M* is $-CH_2-$, -NH- or -O-;

L^{2*} is C_{1-3} alkylene; and

R^{1*} and R^{2*} are each independently selected from hydrogen, C_{1-6} alkyl, halogen and C_{1-6} alkoxy.

7. The use of claim 6, wherein:

i is 4;

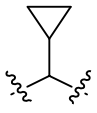
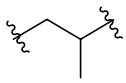
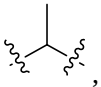
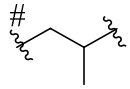
j is an integer from 8 to 12;

z is 2; and

a* is 0.

8. The use of claims 6 or 7, wherein

R^{1*} and R^{2*} are independently selected from C_{1-6} alkyl and halogen; and

L^{1*} is selected from C_{1-6} linear alkylene, C_{1-6} branched alkylene, C_{3-6} cyclic alkylene and C_{3-4} cyclic alkyl–C_{1-2} linear alkylene group, wherein the alkylene and cyclic alkylene are each independently unsubstituted or substituted with one substituent selected from halogen, -OH and $-NH_2$; preferably, L^{1*} is selected from C_{1-4} alkylene, wherein the alkylene is unsubstituted or substituted with one substituent selected from halogen, -OH and $-NH_2$; more preferably, L^{1*} is selected from $-CH_2-$, $-C_2H_4-$, , , , , , which are each independently unsubstituted or substituted with at least one substituent selected from halogen, -OH and $-NH_2$; most preferably, L^{1*} is selected from $-CH_2-$,  and , wherein "#" marks the position attached to carbonyl.

9. The use of any one of claims 6-8, wherein the anti-TROP2 antibody or antigen-binding fragment thereof comprises a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein

the V_H comprises:

(i) HCDR1 comprising the amino acid sequence of NYGMN (SEQ ID NO: 4);

(ii) HCDR2 comprising the amino acid sequence of WINTYTGEPTYTDDFKG (SEQ ID NO: 8); and

(iii) HCDR3 comprising the amino acid sequence of GGFGSSYWYFDV (SEQ ID NO: 11); and

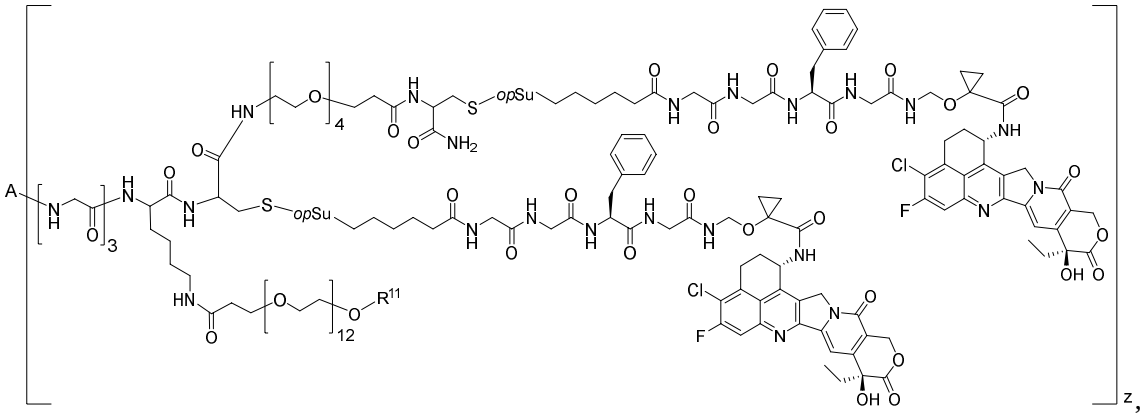
the V_L comprises:

(i) LCDR1 comprising the amino acid sequence of KASQDVSIAVA (SEQ ID NO:13);

(ii) LCDR2 comprising the amino acid sequence of SASYRYT (SEQ ID NO:15); and

(iii) LCDR3 comprising the amino acid sequence of QQHYITPLT (SEQ ID NO: 16).

10. The use of any one of claims 6-9, wherein the conjugate is represented by the following structural formula:



wherein

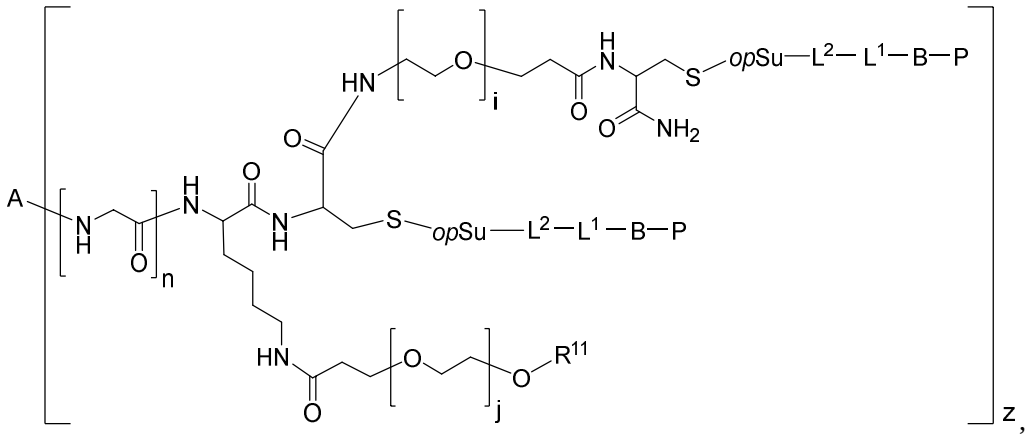
A is the antibody GQhRS7 in which the heavy chain is SEQ ID NO: 30 and the light chain is SEQ ID NO: 40, wherein the light chain is modified by cleaving the upstream peptide bond of the GG in the LPETGG sequence to link to the free N-terminal of G_3 via a new peptide bond to result in the amino acid sequence $LPETG_3$; and

R^{11} is methyl.

11. The use of any one of claims 6-10, wherein the cancer is breast cancer, gastric cancer, lung cancer, ovarian cancer, prostatic cancer, colon carcinoma, pharyngeal squamous cells carcinoma, and urothelial cancer.

12. The use of any one of claims 6-11, wherein the anti-PD-1 antibody is selected from: Pembrolizumab, Nivolumab, Toripalimab, Tislelizumab, Sintilimab and Camrelizumab.

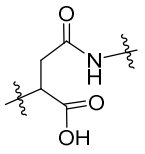
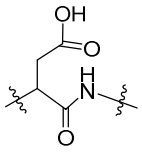
13. A pharmaceutical composition, comprising an effective amount of an antibody drug conjugate and an effective amount of an anti-PD-1 antibody, wherein the antibody drug conjugate is represented by the following structural formula:



wherein:

A is an anti TROP2 antibody or an antigen-binding fragment, wherein the antibody or antigen-binding fragment is modified to connect with the $(Gly)_n$ group;

R^{11} is C_{1-10} alkyl;

*op*Su is  ,  or a mixture thereof;

i is an integer of 0 to 8;

j is an integer of 1 to 12;

z is an integer from 1 to 4;

n is 3;

L^2 is $-(CH_2)_p-(CH_2)_2(CO)-$ or is $-(C_2H_4-O)_p-(CH_2)_2(CO)-$;

p is 2 to 4;

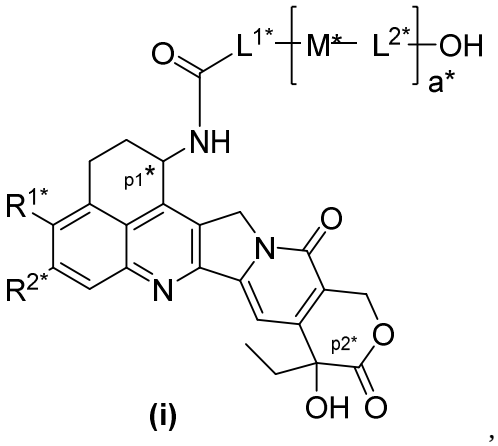
L^1 is Gly-Gly-Phe-Gly;

B is $-NH-CH_2-U-$ or absent or $-NH-CH_2-U-(CR^1R^2)_g-(CO)-$, U is absent, or U is O, g is 1;

R^1, R^2, are each independently selected from hydrogen, halogen, $-C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, C_{4-10}

cycloalkylene; or R^1 and R^2 together with the carbon atom to which they are attached form a 3-6 membered cycloalkyl group; and

P is a payload having the structure of formula (i):



(i)

,

wherein:

a* is 0 or 1;

the carbon atoms marked with p1* and p2* each is asymmetric center, and the asymmetric center is *S* configured, *R* configured or racemic;

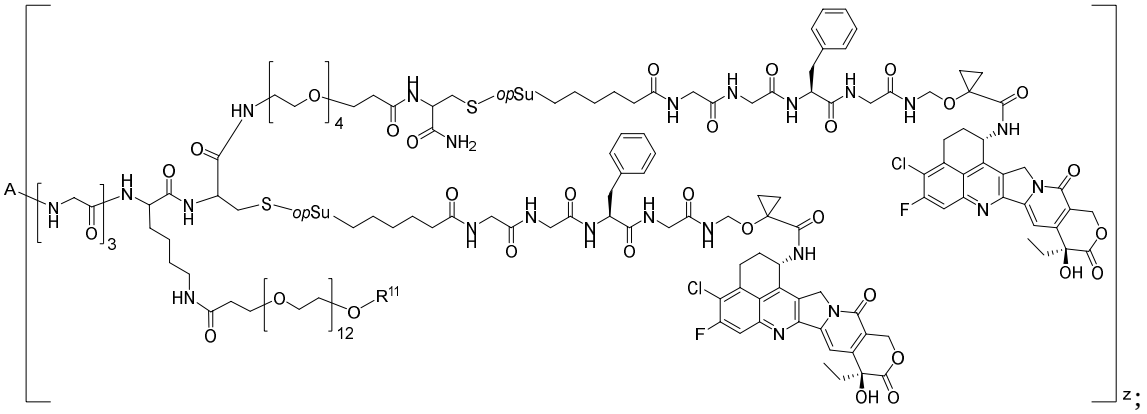
L^{1*} is selected from C_{1-6} alkylene, which is unsubstituted or substituted with one substituent selected from halogen, -OH and $-NH_2$;

M* is $-CH_2-$, -NH- or -O-;

L^{2*} is C_{1-3} alkylene; and

R^{1*} and R^{2*} are each independently selected from hydrogen, C_{1-6} alkyl, halogen and C_{1-6} alkoxy.

14. The pharmaceutical composition of claim 13, wherein the conjugate is represented by the following structural formula:



wherein

A is the antibody GQhRS7 in which the heavy chain is SEQ ID NO: 30 and the light chain is SEQ ID NO: 40, wherein the light chain is modified by cleaving the upstream peptide bond of the GG in the LPETGG sequence to link to the free N-terminal of G_3 via a new peptide bond to result in the amino acid sequence $LPETG_3$; and

R^{11} is methyl.

15. The pharmaceutical composition of claim 13 or 14, wherein the anti-PD-1 antibody is selected from: Pembrolizumab, Nivolumab, Toripalimab, Tislelizumab, Sintilimab and Camrelizumab.