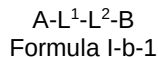


In one aspect, the present disclosure refers to use of a radioimmunoconjugate in the manufacture of a medicament for inducing an immune response to a tumor in a mammal, wherein the mammal is being co-administered one or more checkpoint inhibitors,

wherein the radioimmunoconjugate has the structure of Formula I-b-1, or a pharmaceutically acceptable salt thereof:



wherein

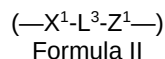
A is a metal complex of a chelating moiety,

wherein said chelating moiety is selected from the group consisting of DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTMA (1R,4R,7R,10R)- α , α' , α'' , α''' -tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DOTAM (1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane), DO3AM-acetic acid (2-(4,7,10-tris(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid), DOTP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid)), DOTA-4AMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis(acetamidomethylenephosphonic acid)), NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid), and HP-DO3A (hydroxypropyltetraazacyclododecanetriacetic acid),

wherein the metal of said metal complex is a radionuclide selected from the group consisting of ^{47}Sc , ^{55}Co , ^{60}Cu , ^{61}Cu , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{66}Ga , ^{67}Ga , ^{68}Ga , ^{82}Rb , ^{86}Y , ^{87}Y , ^{89}Zr , ^{90}Y , ^{97}Ru , ^{99}Tc , $^{99\text{m}}\text{Tc}$, ^{105}Rh , ^{109}Pd , ^{111}In , $^{117\text{m}}\text{Sn}$, ^{149}Pm , ^{149}Tb , ^{153}Sm , ^{166}Ho , ^{177}Lu , ^{186}Re , ^{188}Re , ^{198}Au , ^{199}Au , ^{201}Tl , ^{203}Pb , ^{211}At , ^{212}Pb , ^{212}Bi , ^{213}Bi , ^{223}Ra , ^{225}Ac , ^{227}Th , and ^{229}Th ;

L^1 is optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl;

L^2 has the structure of Formula II:



wherein

X^1 is $\text{C=O}(\text{NR}^1)$ or NR^1 , in which R^1 is H or optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl, optionally substituted aryl or heteroaryl;

L^3 is optionally substituted $\text{C}_1\text{-C}_{50}$ alkyl or optionally substituted $\text{C}_1\text{-C}_{50}$ heteroalkyl; and

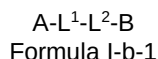
Z^1 is CH_2 , C=O , C=S , OC=O , $\text{NR}^1\text{C=O}$, or NR^1 , in which R^1 is hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, or pyrrolidine-2,5-dione,

B is a human or humanized IgG antibody or an antigen-binding fragment thereof, and

wherein the radioimmunoconjugate is to be administered in a lower effective dose relative to the therapeutically effective dose in a subject who is not receiving the one or more checkpoint inhibitors.

In one aspect, the present disclosure refers to use of a radioimmunoconjugate in the manufacture of a medicament for inducing an immune response to a tumor in a mammal, wherein the mammal is being co-administered one or more checkpoint inhibitors,

wherein the radioimmunoconjugate comprises the structure of Formula I-b-1, or a pharmaceutically acceptable salt thereof:



wherein

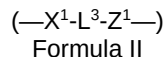
A is a metal complex of a chelating moiety,

wherein said chelating moiety is selected from the group consisting of DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTMA (1R,4R,7R,10R)- α , α' , α'' , α''' -tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DOTAM (1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane), DO3AM-acetic acid (2-(4,7,10-tris(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid), DOTP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid)), DOTA-4AMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis(acetamidomethylenephosphonic acid)), NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid), and HP-DO3A (hydroxypropyltetraazacyclododecanetriacetic acid),

wherein the metal of said metal complex is a radionuclide selected from the group consisting of ^{47}Sc , ^{55}Co , ^{60}Cu , ^{61}Cu , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{66}Ga , ^{67}Ga , ^{68}Ga , ^{82}Rb , ^{86}Y , ^{87}Y , ^{89}Zr , ^{90}Y , ^{97}Ru , ^{99}Tc , $^{99\text{m}}\text{Tc}$, ^{105}Rh , ^{109}Pd , ^{111}In , $^{117\text{m}}\text{Sn}$, ^{149}Pm , ^{149}Tb , ^{153}Sm , ^{166}Ho , ^{177}Lu , ^{186}Re , ^{188}Re , ^{198}Au , ^{199}Au , ^{201}Tl , ^{203}Pb , ^{211}At , ^{212}Pb , ^{212}Bi , ^{213}Bi , ^{223}Ra , ^{225}Ac , ^{227}Th , and ^{229}Th ;

L^1 is optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl;

L^2 has the structure of Formula II:



wherein

X^1 is $C=O(NR^1)$ or NR^1 , in which R^1 is H or optionally substituted C_1 - C_6 alkyl or optionally substituted C_1 - C_6 heteroalkyl, optionally substituted aryl or heteroaryl;

L^3 is optionally substituted C_1 - C_{50} alkyl or optionally substituted C_1 - C_{50} heteroalkyl; and

Z^1 is CH_2 , $C=O$, $C=S$, $OC=O$, $NR^1C=O$, or NR^1 , in which R^1 is hydrogen, optionally substituted C_1 - C_6 alkyl, or pyrrolidine-2,5-dione,

B is a human or humanized IgG antibody or an antigen-binding fragment thereof,

wherein administration results in an increase of at least 15% of the total T cell population in a sample from the mammal being specific for a tumor-associated antigen or tumor specific antigen expressed on the cancer.

In some examples, said method comprises administering to a mammal one or more checkpoint inhibitors, wherein the mammal has received or is receiving a radioimmunoconjugate. In some examples, the one or more checkpoint inhibitors is administered in a lower effective dose. In some examples, the radioimmunoconjugate is administered in a lower effective dose. In some examples, both the one or more checkpoint inhibitors and the radioimmunoconjugate are administered in lower effective doses.

In some examples, the radioimmunoconjugate comprises (i) a targeting moiety, (ii) a linker, and (iii) a chelating moiety or a metal complex of a chelating moiety.

In some examples, the targeting moiety is capable of binding to a tumor-associated antigen. In some examples, the tumor-associated antigen is a tumor-specific antigen.

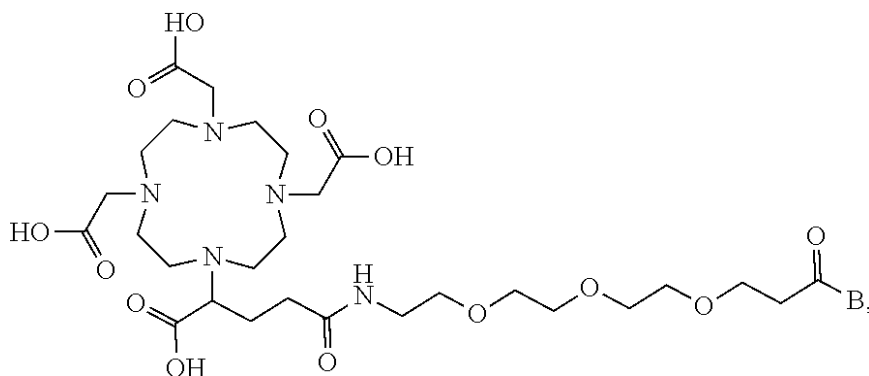
In some examples, the targeting moiety is an antibody or an antigen-binding fragment thereof.

In some examples, the antibody or antigen-binding fragment thereof is an IGF-1R antibody or an antigen-binding fragment thereof.

In some examples, the antibody or antigen-binding fragment thereof is an endosialin (TEM-1) antibody or an antigen-binding fragment thereof.

In some examples, the radioimmunoconjugate comprises a metal complex of a chelating moiety. In some examples, the metal complex comprises a radionuclide. In some examples, the radionuclide is an alpha emitter, e.g., an alpha emitter selected from the group consisting of Astatine-211 (^{211}At), Bismuth-212 (^{212}Bi), Bismuth-213 (^{213}Bi), Actinium-225 (^{225}Ac), Radium-223 (^{223}Ra), Lead-212 (^{212}Pb), Thorium-227 (^{227}Th), and Terbium-149 (^{149}Tb). In some examples, the radionuclide is ^{225}Ac .

In some examples, the radioimmunoconjugate comprises the following structure:



wherein B is the targeting moiety.

In some examples, the one or more checkpoint inhibitors comprise a PD-1 inhibitor. In some examples, the PD-1 inhibitor is an antibody.

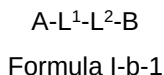
In some examples, the one or more checkpoint inhibitors comprise a CTLA-4 inhibitor. In some examples, the CTLA-4 inhibitor is an antibody.

In some examples, the one or more checkpoint inhibitors comprises both a PD-1 inhibitor and a CTLA-4 inhibitor.

CLAIMS

1. Use of a radioimmunoconjugate in the manufacture of a medicament for inducing an immune response to a tumor in a mammal, wherein the mammal is being co-administered one or more checkpoint inhibitors,

wherein the radioimmunoconjugate has the structure of Formula I-b-1, or a pharmaceutically acceptable salt thereof:



wherein

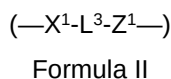
A is a metal complex of a chelating moiety,

wherein said chelating moiety is selected from the group consisting of DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTMA (1R,4R,7R,10R)- α , α' , α'' , α''' -tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DOTAM (1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane), DO3AM-acetic acid (2-(4,7,10-tris(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid), DOTP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid)), DOTA-4AMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis(acetamido-methylenephosphonic acid), NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid), and HP-DO3A (hydroxypropyltetraazacyclododecanetriacetic acid),

wherein the metal of said metal complex is a radionuclide selected from the group consisting of ^{47}Sc , ^{55}Co , ^{60}Cu , ^{61}Cu , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{66}Ga , ^{67}Ga , ^{68}Ga , ^{82}Rb , ^{86}Y , ^{87}Y , ^{89}Zr , ^{90}Y , ^{97}Ru , ^{99}Tc , $^{99\text{m}}\text{Tc}$, ^{105}Rh , ^{109}Pd , ^{111}In , $^{117\text{m}}\text{Sn}$, ^{149}Pm , ^{149}Tb , ^{153}Sm , ^{166}Ho , ^{177}Lu , ^{186}Re , ^{188}Re , ^{198}Au , ^{199}Au , ^{201}Tl , ^{203}Pb , ^{211}At , ^{212}Pb , ^{212}Bi , ^{213}Bi , ^{223}Ra , ^{225}Ac , ^{227}Th , and ^{229}Th ;

L^1 is optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl;

L^2 has the structure of Formula II:



wherein

X^1 is $\text{C=O}(\text{NR}^1)$ or NR^1 , in which R^1 is H or optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl, optionally substituted aryl or heteroaryl;

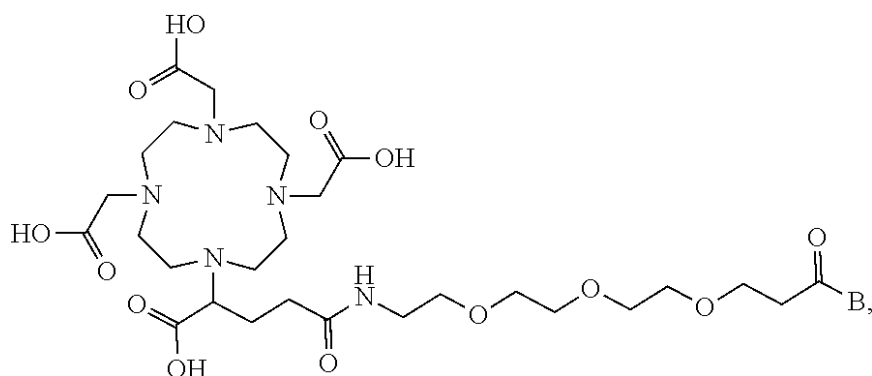
L^3 is optionally substituted $\text{C}_1\text{-C}_{50}$ alkyl or optionally substituted $\text{C}_1\text{-C}_{50}$ heteroalkyl; and

Z^1 is CH_2 , C=O , C=S , OC=O , $\text{NR}^1\text{C=O}$, or NR^1 , in which R^1 is hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, or pyrrolidine-2,5-dione,

B is a human or humanized IgG antibody or an antigen-binding fragment thereof, and

wherein the radioimmunoconjugate is to be administered in a lower effective dose relative to the therapeutically effective dose in a subject who is not receiving the one or more checkpoint inhibitors.

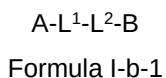
2. The use according to claim 1, wherein the human or humanized IgG antibody or an antigen-binding fragment thereof is capable of binding to a tumor-associated antigen.
3. The use according to claim 2, wherein the antibody or antigen-binding fragment thereof is an IGF-1R antibody or an antigen-binding fragment thereof or an endosialin (TEM-1) antibody or an antigen-binding fragment thereof.
4. The use according to claim 1 or 2, wherein the radioimmunoconjugate comprises a metal complex of a chelating moiety, wherein the metal complex comprises a radionuclide selected from the group consisting of Astatine-211 (^{211}At), Bismuth-212 (^{212}Bi), Bismuth-213 (^{213}Bi), Actinium-225 (^{225}Ac), Radium-223 (^{223}Ra), Lead-212 (^{212}Pb), Thorium-227 (^{227}Th), and Terbium-149 (^{149}Tb).
5. The use according to claim 4, wherein the radionuclide is ^{225}Ac .
6. The use according to any one of claims 1-5, wherein the radioimmunoconjugate comprises the following structure:



wherein B is the human or humanized IgG antibody or an antigen-binding fragment thereof.

7. The use according to any one of claims 1-6, wherein the one or more checkpoint inhibitors comprise a PD-1 inhibitor, a CTLA-4 inhibitor, or both a PD-1 inhibitor and a CTLA-4 inhibitor.
8. The use according to claim 7, wherein the PD-1 inhibitor is an antibody, and wherein the CTLA-4 inhibitor is antibody.

9. The use according to any one of claims 1-8, wherein the mammal is a human.
10. The use according to claim 9, wherein the mammal is diagnosed with a cancer selected from the group consisting of: breast cancer, non-small cell lung cancer, small cell lung cancer, pancreatic cancer, head and neck cancer, prostate cancer, colorectal cancer, sarcoma, adrenocortical carcinoma, neuroendocrine cancer, Ewing's Sarcoma, multiple myeloma, and acute myeloid leukemia.
11. The use according to any one of claims 1-10, wherein said administration results in an increase in T cells specific for the tumor-associated antigen.
12. The use according to claim 11, wherein said increase in T cells occurs in the tumor relative to in the spleen.
13. The use according to claim 11 or 12, wherein said administration results in at least 15% of the total T cell population in a sample from the mammal being specific for the tumor-associated antigen.
14. The use according to any one of claims 1-13, wherein said administration results in a therapeutic effect comprising a decrease in tumor volume, a stable tumor volume, a reduced rate of increase in tumor volume, or a decreased incidence of recurrence or metastasis.
15. Use of a radioimmunoconjugate in the manufacture of a medicament for inducing an immune response to a tumor in a mammal, wherein the mammal is being co-administered one or more checkpoint inhibitors,
 wherein the radioimmunoconjugate comprises the structure of Formula I-b-1, or a pharmaceutically acceptable salt thereof:



wherein

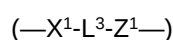
A is a metal complex of a chelating moiety,

wherein said chelating moiety is selected from the group consisting of DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTMA (1R,4R,7R,10R)- α , α' , α'' , α''' -tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DOTAM (1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane), DO3AM-acetic acid (2-(4,7,10-tris(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid), DOTP (1,4,7,10-

tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid)), DOTA-4AMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis(acetamido-methylenephosphonic acid), NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid), and HP-DO3A (hydroxypropyltetraazacyclododecanetriacetic acid), wherein the metal of said metal complex is a radionuclide selected from the group consisting of ⁴⁷Sc, ⁵⁵Co, ⁶⁰Cu, ⁶¹Cu, ⁶²Cu, ⁶⁴Cu, ⁶⁷Cu, ⁶⁶Ga, ⁶⁷Ga, ⁶⁸Ga, ⁸²Rb, ⁸⁶Y, ⁸⁷Y, ⁸⁹Zr, ⁹⁰Y, ⁹⁷Ru, ⁹⁹Tc, ^{99m}Tc, ¹⁰⁵Rh, ¹⁰⁹Pd, ¹¹¹In, ^{117m}Sn, ¹⁴⁹Pm, ¹⁴⁹Tb, ¹⁵³Sm, ¹⁶⁶Ho, ¹⁷⁷Lu, ¹⁸⁶Re, ¹⁸⁸Re, ¹⁹⁸Au, ¹⁹⁹Au, ²⁰¹Tl, ²⁰³Pb, ²¹¹At, ²¹²Pb, ²¹²Bi, ²¹³Bi, ²²³Ra, ²²⁵Ac, ²²⁷Th, and ²²⁹Th;

L₁ is optionally substituted C₁-C₆ alkyl or optionally substituted C₁-C₆ heteroalkyl;

L^2 has the structure of Formula II:



Formula II

wherein

X¹ is C=O(NR¹) or NR¹, in which R¹ is H or optionally substituted C₁-C₆ alkyl or optionally substituted C₁-C₆ heteroalkyl, optionally substituted aryl or heteroaryl;

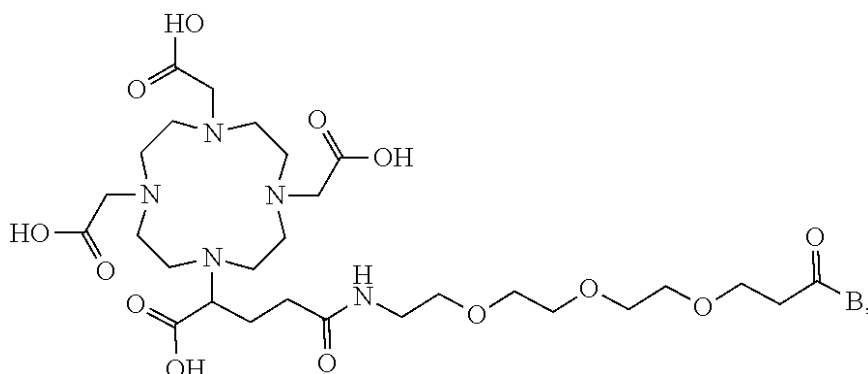
L³ is optionally substituted C₁-C₅₀ alkyl or optionally substituted C₁-C₅₀ heteroalkyl; and

Z¹ is CH₂, C=O, C=S, OC=O, NR¹C=O, or NR¹, in which R¹ is hydrogen, optionally substituted C₁-C₆ alkyl, or pyrrolidine-2,5-dione,

B is a human or humanized IgG antibody or an antigen-binding fragment thereof,

wherein administration results in an increase of at least 15% of the total T cell population in a sample from the mammal being specific for a tumor-associated antigen or tumor specific antigen expressed on the cancer.

16. The use according to claim 15, wherein the radionuclide is ^{225}Ac .
17. The use according to claim 16, wherein the radioimmunoconjugate comprises the following structure:



wherein B is the human or humanized IgG antibody or an antigen-binding fragment thereof.