CLAIMS

1. A radioimmunoconjugate or a pharmaceutical composition thereof for use in inducing infiltration of a CD8+ T cell population into the core of a tumor in a subject in need thereof, wherein the radioimmunoconjugate comprises the following structure:

A-L-B

Formula I-a

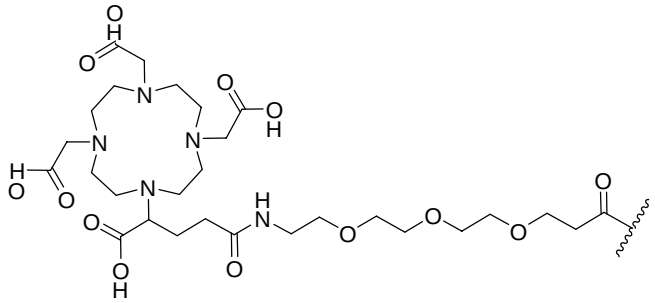
wherein

A is a metal complex of a chelating moiety, wherein the metal complex comprises Actinium-225 (^{225}Ac) or a progeny thereof,

L is a linker, and

B is a targeting moiety capable of binding a first tumor-associated antigen expressed by at least some cells in the tumor;

with the proviso that if A-L- is a metal complex of Compound 1 as shown below, then B is not AVE1642



(Compound 1);

wherein said $CD8^+$ T cell population comprises CD8+ T cells expressing a T-cell receptor (TCR) specific for a second tumor-associated antigen expressed by at least some cells in the tumor; and

wherein the CD8+ T cell is capable of preferentially killing a cell expressing the second tumor-associated antigen.

2. Use of a radioimmunoconjugate or a pharmaceutical composition thereof in the manufacture of a medicament for inducing infiltration of a CD8+ T cell population into the core of a tumor in a subject in need thereof, wherein the radioimmunoconjugate comprises the following structure:

A-L-B

Formula I-a

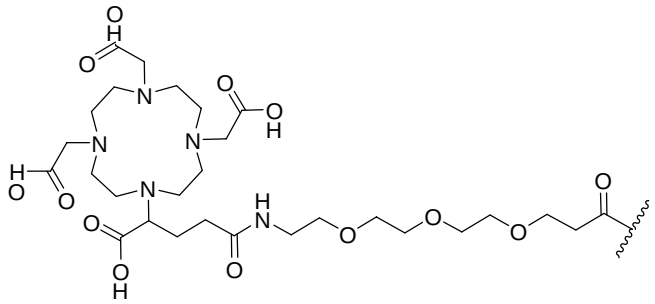
wherein

A is a metal complex of a chelating moiety, wherein the metal complex comprises Actinium-225 (^{225}Ac) or a progeny thereof,

L is a linker, and

B is a targeting moiety capable of binding a first tumor-associated antigen expressed by at least some cells in the tumor;

with the proviso that if A-L- is a metal complex of Compound 1 as shown below, then B is not AVE1642



(Compound 1);

wherein said $CD8^+$ T cell population comprises CD8+ T cells expressing a T-cell receptor (TCR) specific for a second tumor-associated antigen expressed by at least some cells in the tumor; and

wherein the CD8+ T cell is capable of preferentially killing a cell expressing the second tumor-associated antigen.

3. The radioimmunoconjugate or pharmaceutical composition thereof for use of claim 1 or the use of claim 2, wherein said CD8+ T cell population is detectable in the core of the tumor at a level greater than a reference level.

4. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-3, wherein the first tumor-associated antigen is different than the second tumor-associated antigen.

5. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-4, wherein the tumor is not highly immunogenic.

6. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of claim 5, wherein the tumor is immunologically cold.

7. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-6, wherein the tumor is a solid tumor.

8. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-7, wherein the tumor is a liquid tumor.

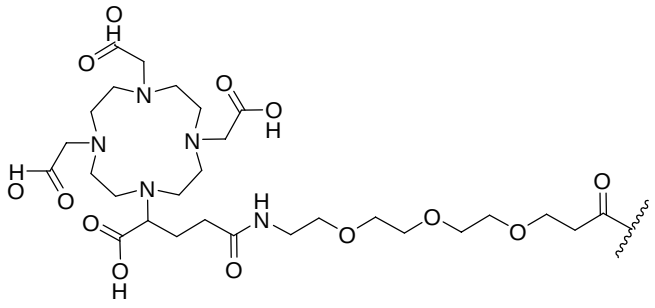
9. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-8, wherein said use results in inhibition of cell proliferation in the core of the tumor.

10. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-9, wherein said use results in slowing or inhibiting progression of the tumor.

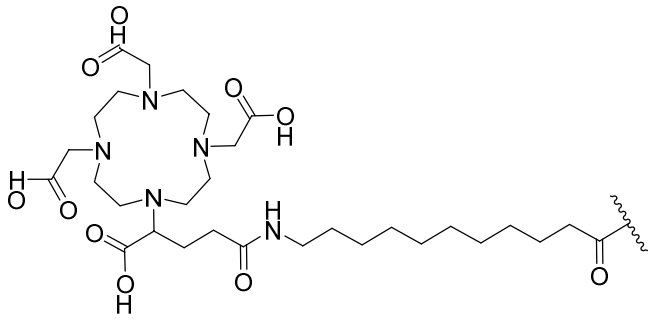
11. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of claim 10, wherein said use results in regression of the tumor.

12. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-11, wherein A-L- is a metal complex of a compound selected from the group consisting of

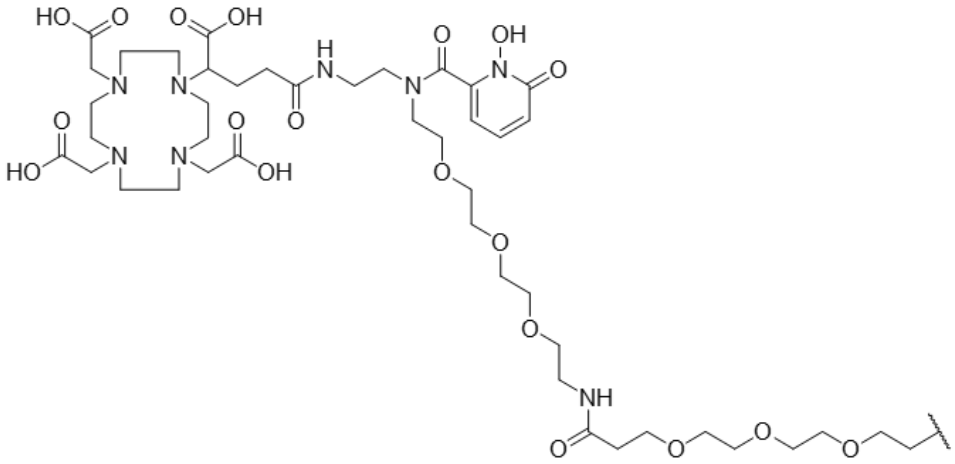
(i)



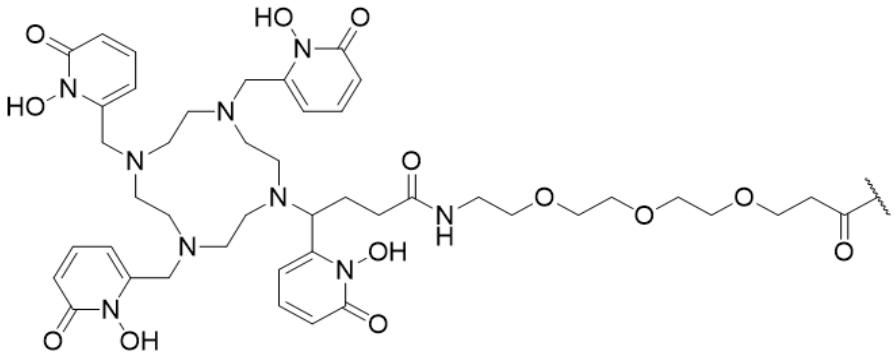
(Compound 1),

(ii) 

(Compound 2),

(iii) 

(Compound 3), and

(iv) 

(Compound 4).

13. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-12, wherein L has the structure $-L^1-(L^2)_n-$, as shown within Formula I-b:

$$A\text{-}L^1\text{-}(L^2)_n\text{-}B$$

Formula I-b

wherein

A is a metal complex of chelating moiety, wherein the metal complex comprises a Actinium-225 (^{225}Ac) or a progeny thereof;

B is a targeting moiety;

L^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted aryl or heteroaryl;

n is 1-5; and

each L^2, independently, has the structure:

$$(-X^1\text{-}L^3\text{-}Z^1\text{-})$$

Formula III

wherein

X^1 is $C{=}O(NR^1)$, $C{=}S(NR^1)$, $OC{=}O(NR^1)$, $NR^1C{=}O(O)$, $NR^1C{=}O(NR^1)$, $\text{-}CH_2PhC{=}O(NR^1)$, $\text{-}CH_2Ph(NH)C{=}S(NR^1)$, O, or NR^1; and each R^1 independently is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted aryl or heteroaryl, in which C_1-C_6 alkyl can be substituted by oxo (=O), heteroaryl, or a combination thereof;

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 , wherein R^1 is a hydrogen or optionally substituted C_1-C_6 alkyl or pyrrolidine-2,5-dione.

14. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-13, wherein the targeting moiety comprises a polypeptide.

15. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of claim 14, wherein the targeting moiety comprises an antibody or an antigen-binding fragment thereof.

16. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-15, wherein the targeting moiety has a molecular weight of at least 100 kDa.

17. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-16, wherein the targeting moiety is a small molecule.

18. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-17, wherein the subject is a mammal.

19. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-18, wherein the subject is in need of treatment or prevention of cancer.

20. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-19, wherein the use comprises systemic administration of the radioimmunoconjugate.

21. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-20, wherein the use comprises local administration of the radioimmunoconjugate.

22. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of any one of claims 1-21, wherein an additional therapeutic agent is to be administered to the subject after the administration of the radioimmunoconjugate.

23. The radioimmunoconjugate or pharmaceutical composition thereof for use or the use of claim 22, wherein the radioimmunoconjugate or the additional therapeutic agent is to be administered in a lower effective dose.