In one example, provided are methods for treating or ameliorating cancer, said methods comprising: (i) administering to a mammal a radioimmunoconjugate, wherein the mammal has received or is receiving a DNA damage response inhibitor (DDRi); (ii) administering to a mammal a DDRi, wherein the mammal has received or is receiving a radioimmunoconjugate; or (iii) administering to the mammal a DDRi at the same time as administering the mammal a radioimmunoconjugate.

In one aspect, the present disclosure refers to use of a radioimmunoconjugate in the manufacture of a medicament for treating or ameliorating cancer in a mammal, wherein the mammal has received or is receiving a DNA damage response inhibitor (DDRi).

In one aspect, the present disclosure refers to use of a DDRi in the manufacture of a medicament for treating or ameliorating cancer in a mammal, wherein the mammal has received or is receiving a radioimmunoconjugate.

In one aspect, the present disclosure refers to use of a DDRi in the manufacture of a medicament for treating or ameliorating cancer in a mammal, wherein the medicament is to be administered at the same time as administration of a radioimmunoconjugate.

In some examples, said method comprises administering to a mammal a DDRi, wherein the mammal has received or is receiving a radioimmunoconjugate.

In some examples, the DDRi is administered in a lower effective dose. In some examples, the radioimmunoconjugate is administered in a lower effective dose. In some examples, both the DDRi 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.

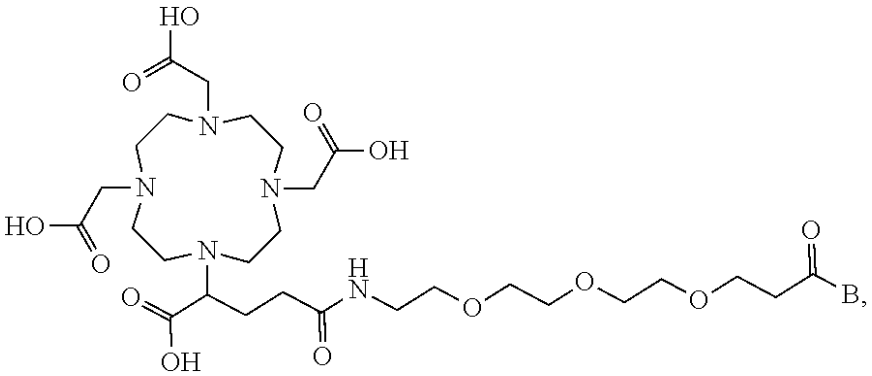
In some examples, the targeting moiety is an antibody or an antigen-binding fragment thereof.

In some examples, the antibody or antigen-binding fragment thereof is an IGF1-R 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 DDRi is a PARP inhibitor. In some examples, the PARP inhibitor is a small molecule PARP inhibitor, e.g., a PARP inhibitor selected from the group consisting of niparib, niraparib, olaparib, talazoparib, pamiparib, rucaparib (camsylate), and veliparib, or an analog thereof. In some examples, the small molecule PARP inhibitor is olaparib or an analog thereof.

In some examples, the DDRi is an ATR inhibitor. In some examples, the ATR inhibitor is a small molecule ATR inhibitor, e.g., an ATR inhibitor is selected from the group consisting of AZ20, AZD0156, AZD1390, AZD6738, BAY-1895344, EPT-46464, M3541, M4344, M6620 (formerly known as VE-922 or VX-970), NU6027, VE-821, or an analog thereof. In some examples, the ATR inhibitor is BAY-1895344 or an analog thereof.

In some examples, the DDRi is a WEE1 inhibitor, a Chk1 inhibitor, or a Chk2 inhibitor.

In some examples, the DDRi is a DNA-protein kinase (DNA-PK) inhibitor.

In some examples, the mammal is a human.

In some examples, the mammal is diagnosed with cancer.

In some examples, the cancer is selected from the group comprising: 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, or acute myeloid leukemia.

In some examples, the mammal has at least one solid tumor.

In some examples, said administering results in a therapeutic effect. In some examples, said therapeutic effect comprises a decrease in tumor volume, a stable tumor volume, or a reduced rate of increase in tumor volume. In some examples, said therapeutic effect comprises a decreased incidence of recurrence or metastasis.

Definitions

Chemical Terms:

The term "acyl," as used herein, represents a hydrogen or an alkyl group (e.g., a haloalkyl group), as defined herein, that is attached to the parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl (i.e., a carboxyaldehyde group), acetyl, trifluoroacetyl, propionyl, butanoyl and the like. Exemplary unsubstituted acyl groups include from 1 to 7, from 1 to 11, or from 1 to 21 carbons. In some embodiments, the alkyl group is further substituted with 1, 2, 3, or 4 substituents as described herein.

The term "alkyl," as used herein, is inclusive of both straight chain and branched chain saturated groups from 1 to 20 carbons (e.g., from 1 to 10 or from 1 to 6), unless otherwise specified. Alkyl groups are exemplified by methyl, ethyl, n- and iso-propyl, n-, sec-, iso- and tert-butyl, neopentyl, and the like, and may be optionally substituted with one, two, three, or, in the case of alkyl groups of two carbons or

CLAIMS

1. Use of a radioimmunoconjugate in the manufacture of a medicament for treating or ameliorating cancer in a mammal, wherein the mammal has received or is receiving a DNA damage response inhibitor (DDRi).

2. Use of a DDRi in the manufacture of a medicament for treating or ameliorating cancer in a mammal, wherein the mammal has received or is receiving a radioimmunoconjugate.

3. Use of a DDRi in the manufacture of a medicament for treating or ameliorating cancer in a mammal, wherein the medicament is to be administered at the same time as administration of a radioimmunoconjugate.

4. The use according to claim 2 or 3, wherein the mammal has received or is receiving a radioimmunoconjugate.

5. The use according to any one of claims 1-4, wherein the DDRi is to be administered in a lower effective dose.

6. The use according to any one of claims 1-5, wherein the radioimmunoconjugate is to be administered in a lower effective dose.

7. The use according to any one of claims 1-3, wherein the radioimmunoconjugate comprises (i) a targeting moiety, (ii) a linker, and (iii) a chelating moiety or a metal complex of a chelating moiety.

8. The use according to claim 7, wherein the targeting moiety is capable of binding to a tumor-associated antigen.

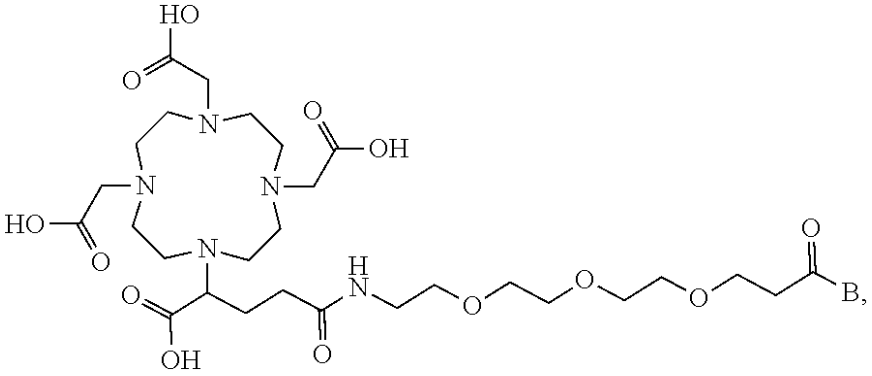
9. The use according to claim 8, wherein the targeting moiety is an antibody or an antigen-binding fragment thereof.

10. The use according to claim 9, wherein the antibody or antigen-binding fragment thereof is an IGF1-R antibody or an antigen-binding fragment thereof or an endosialin (TEM-1) antibody or an antigen-binding fragment thereof.

11. The use according to any one of claims 7-10, 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).

12. The use according to claim 11, wherein the radionuclide is ^{225}Ac.

13. The use according to any one of claims 7-12, wherein the radioimmunoconjugate comprises the following structure:



wherein B is the targeting moiety.

14. The use according to any one of claims 1-13, wherein the DDRi is a PARP inhibitor, an ATR inhibitor, a WEE1 inhibitor, a Chk1 inhibitor, a Chk2 inhibitor, or a DNA-protein kinase (DNA-PK) inhibitor.

15. The use according to claim 14, wherein:

the PARP inhibitor is a small molecule PARP inhibitor selected from the group consisting of niparib, niraparib, olaparib, talazoparib, pamiparib, rucaparib (camsylate), and veliparib, or an analog thereof; or

the ATR inhibitor is a small molecule ATR inhibitor selected from the group consisting of AZ20, AZD0156, AZD1390, AZD6738, BAY-1895344, EPT-46464, M3541, M4344, M6620 (formerly known as VE-922 or VX-970), NU6027, VE-821, or an analog thereof.

16. The use according to claim 15, wherein the small molecule PARP inhibitor is olaparib or an analog thereof.

17. The use according to claim 15, wherein the ATR inhibitor is BAY-1895344 or an analog thereof.

18. The use according to any one of claims 1-17, wherein the mammal is a human.

19. The use according to any one of claims 1-18, wherein the mammal is diagnosed with a cancer selected from the group comprising: 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, or acute myeloid leukemia.

20. The use according to any one of claims 1-19, 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.