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 decreasing tumor volume, stabilizing tumor volume, or reducing rate of increase in tumor volume in a mammal, wherein the mammal is being co-administered a DNA damage response inhibitor (DDRi), wherein the radioimmunoconjugate comprises (i) a targeting moiety, (ii) a linker, and (iii) a metal complex of a chelating moiety, which metal complex comprises ^{225}Ac, and wherein (a) the DDRi is a PARP inhibitor, or (b) the mammal is to be administered at least a first dose of the DDRi after the first dose of the radioimmunoconjugate is administered.

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.

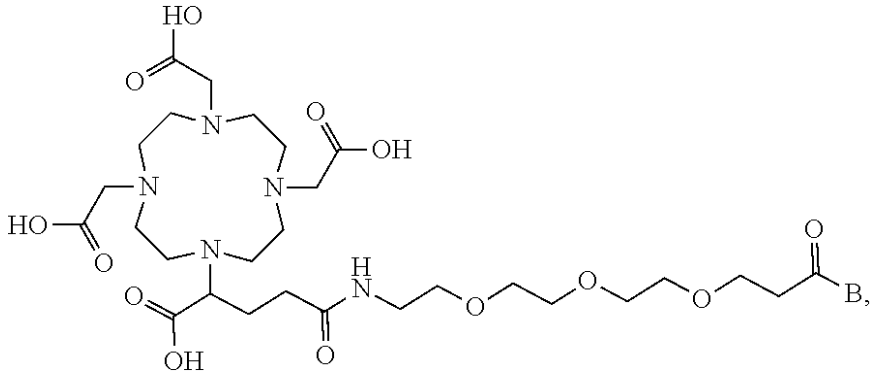
In some examples, the targeting moiety is an antibody or an antigen-binding fragment thereof.

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.

CLAIMS

1. Use of a radioimmunoconjugate in the manufacture of a medicament for decreasing tumor volume, stabilizing tumor volume, or reducing rate of increase in tumor volume in a mammal, wherein the mammal is being co-administered a DNA damage response inhibitor (DDRi),
wherein the radioimmunoconjugate comprises (i) a targeting moiety, (ii) a linker, and (iii) a metal complex of a chelating moiety, which metal complex comprises ^{225}Ac, and
wherein
(a) the DDRi is a PARP inhibitor, or
(b) the mammal is to be administered at least a first dose of the DDRi after the first dose of the radioimmunoconjugate is administered.

2. The use according to claim 1, wherein the DDRi is to be administered in a lower effective dose as compared to an effective dose when the DDRi is used as a monotherapy.

3. The use according to claim 1 or 2, wherein the radioimmunoconjugate is to be administered in a lower effective dose as compared to an effective dose when the radioimmunoconjugate is used as a monotherapy.

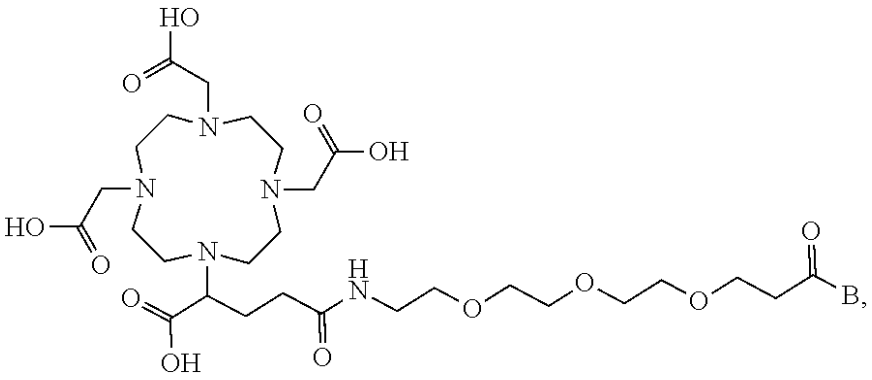
4. The use according to any one of claims 1-3, wherein the targeting moiety is capable of binding to a tumor-associated antigen.

5. The use according to claim 4, wherein the tumor-associated antigen is a tumor-specific antigen.

6. The use according to claim 4 or 5, wherein the targeting moiety is an antibody or an antigen-binding fragment thereof.

7. The use according to claim 6, 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.

8. The use according to any one of claims 4-7, wherein the radioimmunoconjugate comprises the following structure:



wherein B is the targeting moiety.

9. The use according to any one of claims 1-10, 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.

10. The use according to claim 9, 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.

11. The use according to claim 10, wherein the small molecule PARP inhibitor is olaparib or an analog thereof.

12. The use according to claim 10, wherein the ATR inhibitor is BAY-1895344 or an analog thereof.

13. The use according to any one of claims 1-12, wherein the mammal is a human.

14. The use according to any one of claims 1-13, 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.