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(71) Applicant: FUSION PHARMACEUTICALS INC.

[CA/CA]; 1280 Main St., W., Hamilton, ON L8S 4K1 (CA).

(72) Inventor; and

(71) Applicant (for US only): BURAK, Eric, Steven [US/CA];

40 James Street, Cambridge, ON N1S 1C5 (CA).

(72) Inventors: FORBES, John, Richard; 2210 Irving Street,

Burlington, ON L7L 6T3 (CA). HU, Meiduo; 10584

Bathurst Street, Maple, ON L9A 4Y4 (CA). VALLIANT,

John, Fitzmaurice; 15 Holkham Avenue, Ancaster, ON

L9K 1N8 (CA).

(74) Agent: GAUVREAU, Julie; Lavery, De Billy LLP, 1,

Place Ville-Marie, Suite 4000, Montreal, Québec H3B 4M4

(CA).

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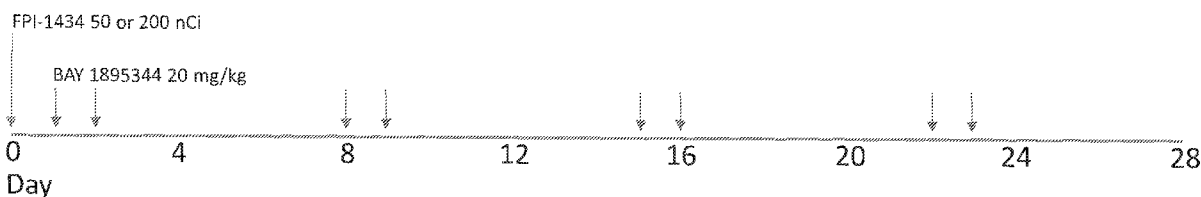


Figure 1

(57) Abstract: Combination therapies comprising administering radioimmunoconjugates and DNA damage response inhibitors.



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RADIOIMMUNOCONJUGATES AND DNA DAMAGE AND REPAIR INHIBITOR COMBINATION THERAPY

Related Application

The present application claims priority to U.S. Provisional Patent Application No. 62/774,847 filed December 3, 2018, the entire contents of which are hereby incorporated by reference for all purposes.

Background

DNA single stranded breaks and double stranded breaks occur for a variety of reasons, including the presence of mutations in the pathways that include the BRCA, PTEN and ATR proteins. Such DNA breaks are repaired through multiple pathways. PARP inhibition (PARPi) results in an accumulation of single and/or double stranded breaks. Existing PARP inhibitors act through both inhibitors of PARP enzyme inhibition activity and through the trapping of PARP proteins inside of chromatin (“DNA-trapping”). Tumor cells with BRCA and/or PTEN mutations are sensitive to PARPi’s, while ATR inhibition (ATRi) results in a failure to repair double stranded breaks—and therefore results in the accumulation of double stranded breaks. An increase in single or double stranded DNA breaks results in increased cell death.

DNA Damage Repair inhibitors (DDRIs) have been explored as cancer therapeutics. However, inhibiting the repair of DNA strand breaks has been observed to enhance normal tissue toxicity, and many DDRIs have exhibited only modest efficacy in vivo. There remains a need for improved treatments of cancer. In particular, there is a need for increases in efficacy, which do not enhance toxicity in the patient.

Summary

The present disclosure encompasses the insight that combining inhibition of DNA damage repair mechanisms with a therapy that targets DNA breaks to cancer cells may provide a less toxic therapy with improved efficacy. Radioactive decay can cause direct physical damage (such as single or double-stranded DNA breaks) or indirect damage (such as by-stander or crossfire effects) to the biomolecules that constitute a cell. The present disclosure combines radioimmunoconjugates targeted to cancer cells with DNA damage repair inhibition to treat or ameliorate cancer.

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

In some embodiments, the DDRi is administered in a lower effective dose. In some embodiments, the radioimmunoconjugate is administered in a lower effective dose. In some embodiments, both the DDRi and the radioimmunoconjugate are administered in lower effective doses.

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

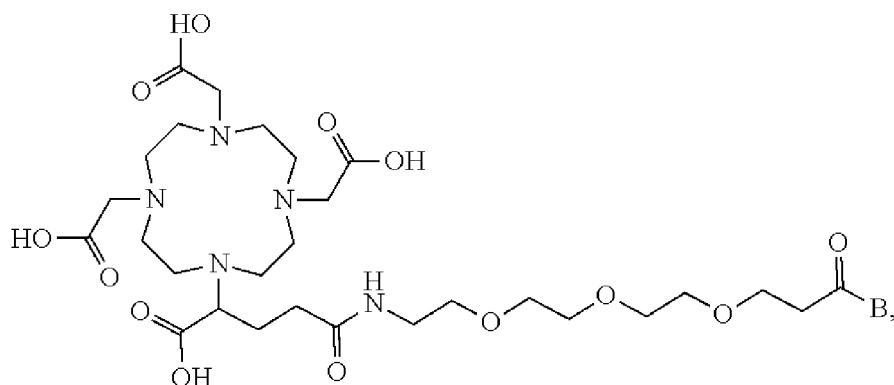
In some embodiments, the targeting moiety is an antibody or an antigen-binding fragment thereof.

In some embodiments, the antibody or antigen-binding fragment thereof is an IGF1-R antibody or an antigen-binding fragment thereof.

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

In some embodiments, the radioimmunoconjugate comprises a metal complex of a chelating moiety. In some embodiments, the metal complex comprises a radionuclide. In some embodiments, 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 embodiments, the radionuclide is ^{225}Ac .

In some embodiments, the radioimmunoconjugate comprises the following structure:



wherein B is the targeting moiety.

In some embodiments, the DDRi is a PARP inhibitor. In some embodiments, the PARP inhibitor is a small molecule PARP inhibitor, e.g., a PARP inhibitor selected from the group consisting of niraparib, niraparib, olaparib, talazoparib, pamiparib, rucaparib (camsylate), and veliparib, or an analog thereof. In
5 some embodiments, the small molecule PARP inhibitor is olaparib or an analog thereof.

In some embodiments, the DDRi is an ATR inhibitor. In some embodiments, 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 embodiments, the ATR inhibitor is
10 BAY-1895344 or an analog thereof.

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

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

In some embodiments, the mammal is a human.

In some embodiments, the mammal is diagnosed with cancer.

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

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

25 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
30 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
35 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

more, four substituents independently selected from the group consisting of: (1) C₁₋₆ alkoxy; (2) C₁₋₆ alkylsulfinyl; (3) amino, as defined herein (e.g., unsubstituted amino (i.e., -NH₂) or a substituted amino (i.e., -N(R^{N1})₂, where R^{N1} is as defined for amino); (4) C₆₋₁₀ aryl-C₁₋₆ alkoxy; (5) azido; (6) halo; (7) (C₂₋₉ heterocyclyl)oxy; (8) hydroxy, optionally substituted with an O-protecting group; (9) nitro; (10) oxo (e.g., carboxyaldehyde or acyl); (11) C₁₋₇ spirocyclyl; (12) thioalkoxy; (13) thiol; (14) -CO₂R^{A'}, optionally substituted with an O-protecting group and where R^{A'} is selected from the group consisting of (a) C₁₋₂₀ alkyl (e.g., C₁₋₆ alkyl), (b) C₂₋₂₀ alkenyl (e.g., C₂₋₆ alkenyl), (c) C₆₋₁₀ aryl, (d) hydrogen, (e) C₁₋₆ alk-C₆₋₁₀ aryl, (f) amino-C₁₋₂₀ alkyl, (g) polyethylene glycol of -(CH₂)_{s2}(OCH₂CH₂)_{s1}(CH₂)_{s3}OR', wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C₁₋₂₀ alkyl, and (h) amino-polyethylene glycol of -NR^{N1}(CH₂)_{s2}(CH₂CH₂O)_{s1}(CH₂)_{s3}NR^{N1}, wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C₁₋₆ alkyl; (15) -C(O)NR^{B'}R^{C'}, where each of R^{B'} and R^{C'} is, independently, selected from the group consisting of (a) hydrogen, (b) C₁₋₆ alkyl, (c) C₆₋₁₀ aryl, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (16) -SO₂R^{D'}, where R^{D'} is selected from the group consisting of (a) C₁₋₆ alkyl, (b) C₆₋₁₀ aryl, (c) C₁₋₆ alk-C₆₋₁₀ aryl, and (d) hydroxy; (17) -SO₂NR^{E'}R^{F'}, where each of R^{E'} and R^{F'} is, independently, selected from the group consisting of (a) hydrogen, (b) C₁₋₆ alkyl, (c) C₆₋₁₀ aryl and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (18) -C(O)R^{G'}, where R^{G'} is selected from the group consisting of (a) C₁₋₂₀ alkyl (e.g., C₁₋₆ alkyl), (b) C₂₋₂₀ alkenyl (e.g., C₂₋₆ alkenyl), (c) C₆₋₁₀ aryl, (d) hydrogen, (e) C₁₋₆ alk-C₆₋₁₀ aryl, (f) amino-C₁₋₂₀ alkyl, (g) polyethylene glycol of -(CH₂)_{s2}(OCH₂CH₂)_{s1}(CH₂)_{s3}OR', wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C₁₋₂₀ alkyl, and (h) amino-polyethylene glycol of -NR^{N1}(CH₂)_{s2}(CH₂CH₂O)_{s1}(CH₂)_{s3}NR^{N1}, wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C₁₋₆ alkyl; (19) -NR^{H'}C(O)R^{I'}, wherein R^{H'} is selected from the group consisting of (a1) hydrogen and (b1) C₁₋₆ alkyl, and R^{I'} is selected from the group consisting of (a2) C₁₋₂₀ alkyl (e.g., C₁₋₆ alkyl), (b2) C₂₋₂₀ alkenyl (e.g., C₂₋₆ alkenyl), (c2) C₆₋₁₀ aryl, (d2) hydrogen, (e2) C₁₋₆ alk-C₆₋₁₀ aryl, (f2) amino-C₁₋₂₀ alkyl, (g2) polyethylene glycol of -(CH₂)_{s2}(OCH₂CH₂)_{s1}(CH₂)_{s3}OR', wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C₁₋₂₀ alkyl, and (h2) amino-polyethylene glycol of -NR^{N1}(CH₂)_{s2}(CH₂CH₂O)_{s1}(CH₂)_{s3}NR^{N1}, wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C₁₋₆ alkyl; (20) -NR^{J'}C(O)OR^{K'}, wherein R^{J'} is selected from the group consisting of (a1) hydrogen and (b1) C₁₋₆ alkyl, and R^{K'} is selected from the group consisting of (a2) C₁₋₂₀ alkyl (e.g., C₁₋₆ alkyl), (b2) C₂₋₂₀ alkenyl (e.g., C₂₋

alkenyl), (c2) C₆₋₁₀ aryl, (d2) hydrogen, (e2) C₁₋₆ alk-C₆₋₁₀ aryl, (f2) amino-C₁₋₂₀ alkyl, (g2) polyethylene glycol of $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C₁₋₂₀ alkyl, and (h2) amino-polyethylene glycol of -

NR^{N1}(CH₂)_{s2}(CH₂CH₂O)_{s1}(CH₂)_{s3}NR^{N1}, wherein s₁ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s₂ and s₃, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C₁₋₆ alkyl; and (21) amidine. In some embodiments, each of these groups can be further substituted as described herein. For example, the alkylene group of a C₁-alkaryl can be further substituted with an oxo group to afford the respective aryloyl substituent.

The term "alkylene" and the prefix "alk-", as used herein, represent a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, and is exemplified by methylene, ethylene, isopropylene, and the like. The term "C_{x-y} alkylene" and the prefix "C_{x-y} alk-" represent alkylene groups having between x and y carbons.

Exemplary values for x are 1, 2, 3, 4, 5, and 6, and exemplary values for y are 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, or 20 (e.g., C₁₋₆, C₁₋₁₀, C₂₋₂₀, C₂₋₆, C₂₋₁₀, or C₂₋₂₀ alkylene). In some embodiments, the alkylene can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for an alkyl group.

The term "alkenyl," as used herein, represents monovalent straight or branched chain groups of, unless otherwise specified, from 2 to 20 carbons (e.g., from 2 to 6 or from 2 to 10 carbons) containing one or more carbon-carbon double bonds and is exemplified by ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like. Alkenyls include both cis and trans isomers. Alkenyl groups may be optionally substituted with 1, 2, 3, or 4 substituent groups that are selected, independently, from amino, aryl, cycloalkyl, or heterocyclyl (e.g., heteroaryl), as defined herein, or any of the exemplary alkyl substituent groups described herein.

The term "alkynyl," as used herein, represents monovalent straight or branched chain groups from 2 to 20 carbon atoms (e.g., from 2 to 4, from 2 to 6, or from 2 to 10 carbons) containing a carbon-carbon triple bond and is exemplified by ethynyl, 1-propynyl, and the like. Alkynyl groups may be optionally substituted with 1, 2, 3, or 4 substituent groups that are selected, independently, from aryl, cycloalkyl, or heterocyclyl (e.g., heteroaryl), as defined herein, or any of the exemplary alkyl substituent groups described herein.

The term "amino," as used herein, represents $-N(R^{N1})_2$, wherein each R^{N1} is, independently, H, OH, NO₂, N(R^{N2})₂, SO₂OR^{N2}, SO₂R^{N2}, SOR^{N2}, an *N*-protecting group, alkyl, alkenyl, alkynyl, alkoxy, aryl, alkaryl, cycloalkyl, alkylcycloalkyl, carboxyalkyl (e.g., optionally substituted with an *O*-protecting group, such as optionally substituted arylalkoxycarbonyl groups or any described herein), sulfoalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), alkoxycarbonylalkyl (e.g., optionally substituted with an *O*-protecting group, such as optionally substituted arylalkoxycarbonyl groups or any described herein), heterocyclyl (e.g., heteroaryl), or alkheterocyclyl (e.g., alkheteroaryl), wherein each of these recited R^{N1}

groups can be optionally substituted, as defined herein for each group; or two R^{N1} combine to form a heterocyclyl or an *N*-protecting group, and wherein each R^{N2} is, independently, H, alkyl, or aryl. Amino groups can be unsubstituted amino (i.e., $-NH_2$) or substituted amino (i.e., $-N(R^{N1})_2$) groups. In a preferred embodiment, amino is $-NH_2$ or $-NHR^{N1}$, wherein R^{N1} is, independently, OH, NO_2 , NH_2 , NR^{N2} , SO_2OR^{N2} , SO_2R^{N2} , SOR^{N2} , alkyl, carboxyalkyl, sulfoalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), alkoxycarbonylalkyl (e.g., *t*-butoxycarbonylalkyl) or aryl, and each R^{N2} can be H, C_{1-20} alkyl (e.g., C_{1-6} alkyl), or C_{6-10} aryl.

The term "amino acid," as described herein, refers to a molecule having a side chain, an amino group, and an acid group (e.g., a carboxy group of $-CO_2H$ or a sulfo group of $-SO_3H$), wherein the amino acid is attached to the parent molecular group by the side chain, amino group, or acid group (e.g., the side chain). In some embodiments, the amino acid is attached to the parent molecular group by a carbonyl group, where the side chain or amino group is attached to the carbonyl group. Exemplary side chains include an optionally substituted alkyl, aryl, heterocyclyl, alkaryl, alkheterocyclyl, aminoalkyl, carbamoylalkyl, and carboxyalkyl. Exemplary amino acids include alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, hydroxynorvaline, isoleucine, leucine, lysine, methionine, norvaline, ornithine, phenylalanine, proline, pyrrollysine, selenocysteine, serine, taurine, threonine, tryptophan, tyrosine, and valine. Amino acid groups may be optionally substituted with one, two, three, or, in the case of amino acid groups of two carbons or more, four substituents independently selected from the group consisting of: (1) C_{1-6} alkoxy; (2) C_{1-6} alkylsulfinyl; (3) amino, as defined herein (e.g., unsubstituted amino (i.e., $-NH_2$) or a substituted amino (i.e., $-N(R^{N1})_2$, where R^{N1} is as defined for amino); (4) C_{6-10} aryl- C_{1-6} alkoxy; (5) azido; (6) halo; (7) (C_{2-9} heterocyclyl)oxy; (8) hydroxy; (9) nitro; (10) oxo (e.g., carboxyaldehyde or acyl); (11) C_{1-7} spirocyclyl; (12) thioalkoxy; (13) thiol; (14) $-CO_2R^A$, where R^A is selected from the group consisting of (a) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c) C_{6-10} aryl, (d) hydrogen, (e) C_{1-6} alk- C_{6-10} aryl, (f) amino- C_{1-20} alkyl, (g) polyethylene glycol of $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h) amino-polyethylene glycol of $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl; (15) $-C(O)NR^BR^C$, where each of R^B and R^C is, independently, selected from the group consisting of (a) hydrogen, (b) C_{1-6} alkyl, (c) C_{6-10} aryl, and (d) C_{1-6} alk- C_{6-10} aryl; (16) $-SO_2R^D$, where R^D is selected from the group consisting of (a) C_{1-6} alkyl, (b) C_{6-10} aryl, (c) C_{1-6} alk- C_{6-10} aryl, and (d) hydroxy; (17) $-SO_2NR^ER^F$, where each of R^E and R^F is, independently, selected from the group consisting of (a) hydrogen, (b) C_{1-6} alkyl, (c) C_{6-10} aryl and (d) C_{1-6} alk- C_{6-10} aryl; (18) $-C(O)R^G$, where R^G is selected from the group consisting of (a) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c) C_{6-10} aryl, (d) hydrogen, (e) C_{1-6} alk- C_{6-10} aryl, (f) amino- C_{1-20} alkyl, (g) polyethylene glycol of -

$(\text{CH}_2)_{s2}(\text{OCH}_2\text{CH}_2)_{s1}(\text{CH}_2)_{s3}\text{OR}'$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h) amino-polyethylene glycol of -

$\text{NR}^{\text{N1}}(\text{CH}_2)_{s2}(\text{CH}_2\text{CH}_2\text{O})_{s1}(\text{CH}_2)_{s3}\text{NR}^{\text{N1}}$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl;

(19) $-\text{NR}^{\text{H}}\text{C}(\text{O})\text{R}'$, wherein R^{H} is selected from the group consisting of (a1) hydrogen and (b1) C_{1-6} alkyl, and R' is selected from the group consisting of (a2) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b2) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c2) C_{6-10} aryl, (d2) hydrogen, (e2) C_{1-6} alk- C_{6-10} aryl, (f2) amino- C_{1-20} alkyl, (g2) polyethylene glycol of $-(\text{CH}_2)_{s2}(\text{OCH}_2\text{CH}_2)_{s1}(\text{CH}_2)_{s3}\text{OR}'$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h2) amino-polyethylene glycol of -

$\text{NR}^{\text{N1}}(\text{CH}_2)_{s2}(\text{CH}_2\text{CH}_2\text{O})_{s1}(\text{CH}_2)_{s3}\text{NR}^{\text{N1}}$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl;

(20) $-\text{NR}^{\text{J}}\text{C}(\text{O})\text{OR}^{\text{K}}$, wherein R^{J} is selected from the group consisting of (a1) hydrogen and (b1) C_{1-6} alkyl, and R^{K} is selected from the group consisting of (a2) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b2) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c2) C_{6-10} aryl, (d2) hydrogen, (e2) C_{1-6} alk- C_{6-10} aryl, (f2) amino- C_{1-20} alkyl, (g2) polyethylene glycol of $-(\text{CH}_2)_{s2}(\text{OCH}_2\text{CH}_2)_{s1}(\text{CH}_2)_{s3}\text{OR}'$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h2) amino-polyethylene glycol of -

$\text{NR}^{\text{N1}}(\text{CH}_2)_{s2}(\text{CH}_2\text{CH}_2\text{O})_{s1}(\text{CH}_2)_{s3}\text{NR}^{\text{N1}}$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl;

and (21) amidine. In some embodiments, each of these groups can be further substituted as described herein.

The term "aryl," as used herein, represents a mono-, bicyclic, or multicyclic carbocyclic ring system having one or two aromatic rings and is exemplified by phenyl, naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, anthracenyl, phenanthrenyl, fluorenyl, indanyl, indenyl, and the like, and may be optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of: (1) C_{1-7} acyl (e.g., carboxyaldehyde); (2) C_{1-20} alkyl (e.g., C_{1-6} alkyl, C_{1-6} alkoxy- C_{1-6} alkyl, C_{1-6} alkylsulfinyl- C_{1-6} alkyl, amino- C_{1-6} alkyl, azido- C_{1-6} alkyl, (carboxyaldehyde)- C_{1-6} alkyl, halo- C_{1-6} alkyl (e.g., perfluoroalkyl), hydroxy- C_{1-6} alkyl, nitro- C_{1-6} alkyl, or C_{1-6} thioalkoxy- C_{1-6} alkyl); (3) C_{1-20} alkoxy (e.g., C_{1-6} alkoxy, such as perfluoroalkoxy); (4) C_{1-6} alkylsulfinyl; (5) C_{6-10} aryl; (6) amino; (7) C_{1-6} alk- C_{6-10} aryl; (8) azido; (9) C_{3-8} cycloalkyl; (10) C_{1-6} alk- C_{3-8} cycloalkyl; (11) halo; (12) C_{1-12} heterocyclyl (e.g., C_{1-12} heteroaryl); (13) (C_{1-12} heterocyclyl)oxy; (14) hydroxy; (15) nitro; (16) C_{1-20} thioalkoxy (e.g., C_{1-6} thioalkoxy); (17) $-(\text{CH}_2)_q\text{CO}_2\text{R}^{\text{A}}$, where q is an integer from zero to four, and R^{A} is selected from the

group consisting of (a) C₁₋₆ alkyl, (b) C₆₋₁₀ aryl, (c) hydrogen, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (18) –(CH₂)_qCONR^BR^C, where q is an integer from zero to four and where R^B and R^C are independently selected from the group consisting of (a) hydrogen, (b) C₁₋₆ alkyl, (c) C₆₋₁₀ aryl, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (19) –(CH₂)_qSO₂R^D, where q is an integer from zero to four and where R^D is selected from the group consisting of (a) alkyl, (b) C₆₋₁₀ aryl, and (c) alk-C₆₋₁₀ aryl; (20) –(CH₂)_qSO₂NR^ER^F, where q is an integer from zero to four and where each of R^E and R^F is, independently, selected from the group consisting of (a) hydrogen, (b) C₁₋₆ alkyl, (c) C₆₋₁₀ aryl, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (21) thiol; (22) C₆₋₁₀ aryloxy; (23) C₃₋₈ cycloalkoxy; (24) C₆₋₁₀ aryl-C₁₋₆ alkoxy; (25) C₁₋₆ alk-C₁₋₁₂ heterocyclyl (e.g., C₁₋₆ alk-C₁₋₁₂ heteroaryl); (26) C₂₋₂₀ alkenyl; and (27) C₂₋₂₀ alkynyl. In some embodiments, each of these groups can be further substituted as described herein. For example, the alkylene group of a C₁-alkaryl or a C₁-alkheterocyclyl can be further substituted with an oxo group to afford the respective aryloyl and (heterocyclyl)oyl substituent group.

The term “arylalkyl,” as used herein, represents an aryl group, as defined herein, attached to the parent molecular group through an alkylene group, as defined herein. Exemplary unsubstituted arylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C₁₋₆ alk-C₆₋₁₀ aryl, C₁₋₁₀ alk-C₆₋₁₀ aryl, or C₁₋₂₀ alk-C₆₋₁₀ aryl). In some embodiments, the alkylene and the aryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups. Other groups preceded by the prefix “alk-” are defined in the same manner, where “alk” refers to a C₁₋₆ alkylene, unless otherwise noted, and the attached chemical structure is as defined herein.

The term “carbonyl,” as used herein, represents a C(O) group, which can also be represented as C=O.

The term “carboxy,” as used herein, means –CO₂H.

The term “cyano,” as used herein, represents an –CN group.

The term “cycloalkyl,” as used herein represents a monovalent saturated or unsaturated non-aromatic cyclic hydrocarbon group from three to eight carbons, unless otherwise specified, and is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicycle heptyl, and the like. When the cycloalkyl group includes one carbon-carbon double bond or one carbon-carbon triple bond, the cycloalkyl group can be referred to as a “cycloalkenyl” or “cycloalkynyl” group respectively. Exemplary cycloalkenyl and cycloalkynyl groups include cyclopentenyl, cyclohexenyl, cyclohexynyl, and the like. Cycloalkyl groups can be optionally substituted with: (1) C₁₋₇ acyl (e.g., carboxyaldehyde); (2) C₁₋₂₀ alkyl (e.g., C₁₋₆ alkyl, C₁₋₆ alkoxy-C₁₋₆ alkyl, C₁₋₆ alkylsulfanyl-C₁₋₆ alkyl, amino-C₁₋₆ alkyl, azido-C₁₋₆ alkyl, (carboxyaldehyde)-C₁₋₆ alkyl, halo-C₁₋₆ alkyl (e.g., perfluoroalkyl), hydroxy-C₁₋₆ alkyl, nitro-C₁₋₆ alkyl, or C₁₋₆ thioalkoxy-C₁₋₆ alkyl); (3) C₁₋₂₀ alkoxy (e.g., C₁₋₆ alkoxy, such as perfluoroalkoxy); (4) C₁₋₆ alkylsulfanyl; (5) C₆₋₁₀ aryl; (6) amino; (7) C₁₋₆ alk-C₆₋₁₀ aryl; (8) azido; (9) C₃₋₈ cycloalkyl; (10) C₁₋₆ alk-C₃₋₈ cycloalkyl; (11) halo; (12) C₁₋₁₂ heterocyclyl (e.g., C₁₋₁₂ heteroaryl); (13) (C₁₋₁₂ heterocyclyl)oxy; (14) hydroxy; (15) nitro; (16) C₁₋₂₀ thioalkoxy (e.g., C₁₋₆ thioalkoxy); (17) –(CH₂)_qCO₂R^A, where q is an integer from zero to four, and R^A is selected from the group consisting of (a) C₁₋₆ alkyl, (b) C₆₋₁₀ aryl, (c)

hydrogen, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (18) $-(CH_2)_qCONR^B R^C$, where q is an integer from zero to four and where R^B and R^C are independently selected from the group consisting of (a) hydrogen, (b) C₆₋₁₀ alkyl, (c) C₆₋₁₀ aryl, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (19) $-(CH_2)_qSO_2R^D$, where q is an integer from zero to four and where R^D is selected from the group consisting of (a) C₆₋₁₀ alkyl, (b) C₆₋₁₀ aryl, and (c) C₁₋₆ alk-C₆₋₁₀ aryl; (20) $-(CH_2)_qSO_2NR^E R^F$, where q is an integer from zero to four and where each of R^E and R^F is, independently, selected from the group consisting of (a) hydrogen, (b) C₆₋₁₀ alkyl, (c) C₆₋₁₀ aryl, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (21) thiol; (22) C₆₋₁₀ aryloxy; (23) C₃₋₈ cycloalkoxy; (24) C₆₋₁₀ aryl-C₁₋₆ alkoxy; (25) C₁₋₆ alk-C₁₋₁₂ heterocyclyl (e.g., C₁₋₆ alk-C₁₋₁₂ heteroaryl); (26) oxo; (27) C₂₋₂₀ alkenyl; and (28) C₂₋₂₀ alkynyl. In some embodiments, each of these groups can be further substituted as described herein. For example, the alkylene group of a C₁-alkaryl or a C₁-alkheterocyclyl can be further substituted with an oxo group to afford the respective aryloyl and (heterocyclyl)oyl substituent group.

The term "diastereomer," as used herein means stereoisomers that are not mirror images of one another and are non-superimposable on one another.

The term "enantiomer," as used herein, means each individual optically active form of a compound, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e., at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

The term "halogen," as used herein, represents a halogen selected from bromine, chlorine, iodine, or fluorine.

The term "heteroalkyl," as used herein, refers to an alkyl group, as defined herein, in which one or two of the constituent carbon atoms have each been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups. The terms "heteroalkenyl" and "heteroalkynyl," as used herein refer to alkenyl and alkynyl groups, as defined herein, respectively, in which one or two of the constituent carbon atoms have each been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkenyl and heteroalkynyl groups can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups.

The term "heteroaryl," as used herein, represents that subset of heterocyclyls, as defined herein, which are aromatic: i.e., they contain 4n+2 pi electrons within the mono- or multicyclic ring system. Exemplary unsubstituted heteroaryl groups are of 1 to 12 (e.g., 1 to 11, 1 to 10, 1 to 9, 2 to 12, 2 to 11, 2 to 10, or 2 to 9) carbons. In some embodiment, the heteroaryl is substituted with 1, 2, 3, or 4 substituents groups as defined for a heterocyclyl group.

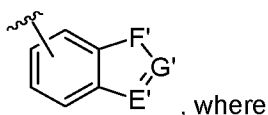
The term "heteroarylalkyl" refers to a heteroaryl group, as defined herein, attached to the parent molecular group through an alkylene group, as defined herein. Exemplary unsubstituted heteroarylalkyl groups are from 2 to 32 carbons (e.g., from 2 to 22, from 2 to 18, from 2 to 17, from 2 to 16, from 3 to 15, from 2 to 14, from 2 to 13, or from 2 to 12 carbons, such as C₁₋₆ alk-C₁₋₁₂ heteroaryl, C₁₋₁₀ alk-C₁₋₁₂ heteroaryl, or C₁₋₂₀ alk-C₁₋₁₂ heteroaryl). In some embodiments, the alkylene and the heteroaryl each can

be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective group. Heteroarylalkyl groups are a subset of heterocyclylalkyl groups.

The term "heterocyclyl," as used herein represents a 5-, 6- or 7-membered ring, unless otherwise specified, containing one, two, three, or four heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The 5-membered ring has zero to two double bonds, and the 6- and 7-membered rings have zero to three double bonds. Exemplary unsubstituted heterocyclyl groups are of 1 to 12 (e.g., 1 to 11, 1 to 10, 1 to 9, 2 to 12, 2 to 11, 2 to 10, or 2 to 9) carbons. The term "heterocyclyl" also represents a heterocyclic compound having a bridged multicyclic structure in which one or more carbons and/or heteroatoms bridges two non-adjacent members of a monocyclic ring, e.g., a quinuclidinyl group. The term "heterocyclyl" includes bicyclic, tricyclic, and tetracyclic groups in which any of the above heterocyclic rings is fused to one, two, or three carbocyclic rings, e.g., an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring, or another monocyclic heterocyclic ring, such as indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl, benzothienyl and the like. Examples of fused heterocyclyls include tropanes and 1,2,3,5,8,8a-hexahydroindolizine.

Heterocyclics include pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, indazolyl, quinolyl, isoquinolyl, quinoxalyl, dihydroquinoxalyl, quinazolyl, cinnolyl, phthalazinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzothiadiazolyl, furyl, thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl (e.g., 1,2,3-oxadiazolyl), purinyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl), tetrahydrofuranlyl, dihydrofuranlyl, tetrahydrothienyl, dihydrothienyl, dihydroindolyl, dihydroquinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, dihydroisoquinolyl, pyranlyl, dihydropyranlyl, dithiazolyl, benzofuranlyl, isobenzofuranlyl, benzothienyl, and the like, including dihydro and tetrahydro forms thereof, where one or more double bonds are reduced and replaced with hydrogens. Still other exemplary heterocyclyls include: 2,3,4,5-tetrahydro-2-oxo-oxazolyl; 2,3-dihydro-2-oxo-1H-imidazolyl; 2,3,4,5-tetrahydro-5-oxo-1H-pyrazolyl (e.g., 2,3,4,5-tetrahydro-2-phenyl-5-oxo-1H-pyrazolyl); 2,3,4,5-tetrahydro-2,4-dioxo-1H-imidazolyl (e.g., 2,3,4,5-tetrahydro-2,4-dioxo-5-methyl-5-phenyl-1H-imidazolyl); 2,3-dihydro-2-thioxo-1,3,4-oxadiazolyl (e.g., 2,3-dihydro-2-thioxo-5-phenyl-1,3,4-oxadiazolyl); 4,5-dihydro-5-oxo-1H-triazolyl (e.g., 4,5-dihydro-3-methyl-4-amino 5-oxo-1H-triazolyl); 1,2,3,4-tetrahydro-2,4-dioxypyridinyl (e.g., 1,2,3,4-tetrahydro-2,4-dioxo-3,3-diethylpyridinyl); 2,6-dioxo-piperidinyl (e.g., 2,6-dioxo-3-ethyl-3-phenylpiperidinyl); 1,6-dihydro-6-oxopyrimidinyl; 1,6-dihydro-4-oxopyrimidinyl (e.g., 2-(methylthio)-1,6-dihydro-4-oxo-5-methylpyrimidin-1-yl); 1,2,3,4-tetrahydro-2,4-dioxypyrimidinyl (e.g., 1,2,3,4-tetrahydro-2,4-dioxo-3-ethylpyrimidinyl); 1,6-dihydro-6-oxo-pyridazinyl (e.g., 1,6-dihydro-6-oxo-3-ethylpyridazinyl); 1,6-dihydro-6-oxo-1,2,4-triazinyl (e.g., 1,6-dihydro-5-isopropyl-6-oxo-1,2,4-triazinyl); 2,3-dihydro-2-oxo-1H-indolyl (e.g., 3,3-dimethyl-2,3-dihydro-2-oxo-1H-indolyl and 2,3-dihydro-2-oxo-3,3'-spiropropane-1H-indol-1-yl); 1,3-dihydro-1-oxo-2H-iso-indolyl; 1,3-dihydro-1,3-dioxo-2H-iso-indolyl; 1H-benzopyrazolyl (e.g., 1-(ethoxycarbonyl)- 1H-benzopyrazolyl); 2,3-dihydro-2-oxo-1H-

benzimidazolyl (e.g., 3-ethyl-2,3-dihydro-2-oxo-1*H*-benzimidazolyl); 2,3-dihydro-2-oxo-benzoxazolyl (e.g., 5-chloro-2,3-dihydro-2-oxo-benzoxazolyl); 2,3-dihydro-2-oxo-benzoxazolyl; 2-oxo-2*H*-benzopyranlyl; 1,4-benzodioxanyl; 1,3-benzodioxanyl; 2,3-dihydro-3-oxo-4*H*-1,3-benzothiazinyl; 3,4-dihydro-4-oxo-3*H*-quinazolinyl (e.g., 2-methyl-3,4-dihydro-4-oxo-3*H*-quinazolinyl); 1,2,3,4-tetrahydro-2,4-dioxo-3*H*-quinazolyl (e.g., 1-ethyl-1,2,3,4-tetrahydro-2,4-dioxo-3*H*-quinazolyl); 1,2,3,6-tetrahydro-2,6-dioxo-7*H*-purinyl (e.g., 1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7*H*-purinyl); 1,2,3,6-tetrahydro-2,6-dioxo-1*H*-purinyl (e.g., 1,2,3,6-tetrahydro-3,7-dimethyl-2,6-dioxo-1*H*-purinyl); 2-oxobenz[*c,d*]indolyl; 1,1-dioxo-2*H*-naphth[1,8-*c,d*]isothiazolyl; and 1,8-naphthylenedicarboxamido. Additional heterocyclics include 3,3a,4,5,6,6a-hexahydro-pyrrolo[3,4-*b*]pyrrol-(2*H*)-yl, and 2,5-diazabicyclo[2.2.1]heptan-2-yl, homopiperazinyl (or diazepanyl), tetrahydropyranyl, dithiazolyl, benzofuranyl, benzothienyl, oxepanyl, thiepanyl, azocanyl, oxecanyl, and thiocanyl. Heterocyclic groups also include groups of the formula



E' is selected from the group consisting of -N- and -CH-; F' is selected from the group consisting of -N=CH-, -NH-CH₂-, -NH-C(O)-, -NH-, -CH=N-, -CH₂-NH-, -C(O)-NH-, -CH=CH-, -CH₂-, -CH₂CH₂-, -CH₂O-, -OCH₂-, -O-, and -S-; and G' is selected from the group consisting of -CH- and -N-. Any of the heterocyclyl groups mentioned herein may be optionally substituted with one, two, three, four or five substituents independently selected from the group consisting of: (1) C₁₋₇ acyl (e.g., carboxyaldehyde); (2) C₁₋₂₀ alkyl (e.g., C₁₋₆ alkyl, C₁₋₆ alkoxy-C₁₋₆ alkyl, C₁₋₆ alkylsulfinyl-C₁₋₆ alkyl, amino-C₁₋₆ alkyl, azido-C₁₋₆ alkyl, (carboxyaldehyde)-C₁₋₆ alkyl, halo-C₁₋₆ alkyl (e.g., perfluoroalkyl), hydroxy-C₁₋₆ alkyl, nitro-C₁₋₆ alkyl, or C₁₋₆ thioalkoxy-C₁₋₆ alkyl); (3) C₁₋₂₀ alkoxy (e.g., C₁₋₆ alkoxy, such as perfluoroalkoxy); (4) C₁₋₆ alkylsulfinyl; (5) C₆₋₁₀ aryl; (6) amino; (7) C₁₋₆ alk-C₆₋₁₀ aryl; (8) azido; (9) C₃₋₈ cycloalkyl; (10) C₁₋₆ alk-C₃₋₈ cycloalkyl; (11) halo; (12) C₁₋₁₂ heterocyclyl (e.g., C₂₋₁₂ heteroaryl); (13) (C₁₋₁₂ heterocyclyl)oxy; (14) hydroxy; (15) nitro; (16) C₁₋₂₀ thioalkoxy (e.g., C₁₋₆ thioalkoxy); (17) -(CH₂)_qCO₂R^{A'}, where q is an integer from zero to four, and R^{A'} is selected from the group consisting of (a) C₁₋₆ alkyl, (b) C₆₋₁₀ aryl, (c) hydrogen, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (18) -(CH₂)_qCONR^{B'}R^{C'}, where q is an integer from zero to four and where R^{B'} and R^{C'} are independently selected from the group consisting of (a) hydrogen, (b) C₁₋₆ alkyl, (c) C₆₋₁₀ aryl, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (19) -(CH₂)_qSO₂R^{D'}, where q is an integer from zero to four and where R^{D'} is selected from the group consisting of (a) C₁₋₆ alkyl, (b) C₆₋₁₀ aryl, and (c) C₁₋₆ alk-C₆₋₁₀ aryl; (20) -(CH₂)_qSO₂NR^{E'}R^{F'}, where q is an integer from zero to four and where each of R^{E'} and R^{F'} is, independently, selected from the group consisting of (a) hydrogen, (b) C₁₋₆ alkyl, (c) C₆₋₁₀ aryl, and (d) C₁₋₆ alk-C₆₋₁₀ aryl; (21) thiol; (22) C₆₋₁₀ aryloxy; (23) C₃₋₈ cycloalkoxy; (24) arylalkoxy; (25) C₁₋₆ alk-C₁₋₁₂ heterocyclyl (e.g., C₁₋₆ alk-C₁₋₁₂ heteroaryl); (26) oxo; (27) (C₁₋₁₂ heterocyclyl)imino; (28) C₂₋₂₀ alkenyl; and (29) C₂₋₂₀ alkynyl. In some embodiments, each of these groups can be further substituted as described herein. For example, the alkylene group of a C₁-alkaryl or a C₁-alkheterocyclyl can be further substituted with an oxo group to afford the respective aryloyl and (heterocyclyl)oyl substituent group.

The term "hydrocarbon," as used herein, represents a group consisting only of carbon and hydrogen atoms.

The term "hydroxyl," as used herein, represents an –OH group. In some embodiments, the hydroxyl group can be substituted with 1, 2, 3, or 4 substituent groups (e.g., O-protecting groups) as defined herein for an alkyl.

The term "isomer," as used herein, means any tautomer, stereoisomer, enantiomer, or diastereomer of any compound. It is recognized that the compounds can have one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric E/Z isomers) or diastereomers (e.g., enantiomers (i.e., (+) or (-)) or cis/trans isomers). Unless otherwise noted, chemical structures depicted herein encompass all of the corresponding stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, e.g., racemates. Enantiomeric and stereoisomeric mixtures of compounds can typically be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and stereoisomers can also be obtained from stereomerically or enantiomerically pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

The term "*N*-protected amino," as used herein, refers to an amino group, as defined herein, to which is attached one or two *N*-protecting groups, as defined herein.

The term "*N*-protecting group," as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used *N*-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis," 3rd Edition (John Wiley & Sons, New York, 1999), which is incorporated herein by reference. *N*-protecting groups include acyl, aryloyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries such as protected or unprotected D, L or D, L-amino acids such as alanine, leucine, phenylalanine, and the like; sulfonyl-containing groups such as benzenesulfonyl, p-toluenesulfonyl, and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl,

phenylthiocarbonyl, and the like, alkaryl groups such as benzyl, triphenylmethyl, benzyloxymethyl, and the like and silyl groups, such as trimethylsilyl, and the like. Preferred *N*-protecting groups are formyl, acetyl, benzoyl, pivaloyl, *t*-butylacetyl, alanyl, phenylsulfonyl, benzyl, *t*-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

5 The term "O-protecting group," as used herein, represents those groups intended to protect an oxygen containing (e.g., phenol, hydroxyl, or carbonyl) group against undesirable reactions during synthetic procedures. Commonly used O-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis," 3rd Edition (John Wiley & Sons, New York, 1999), which is incorporated herein by reference. Exemplary O-protecting groups include acyl, aryloyl, or carbamyl groups, such as formyl,
 10 acetyl, propionyl, pivaloyl, *t*-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, *o*-nitrophenoxyacetyl, α -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, *t*-butyldimethylsilyl, tri-*iso*-propylsilyloxymethyl, 4,4'-dimethoxytrityl, isobutyryl, phenoxyacetyl, 4-isopropylphenoxyacetyl, dimethylformamido, and 4-nitrobenzoyl; alkylcarbonyl groups, such as acyl, acetyl, propionyl, pivaloyl, and the like; optionally substituted arylcarbonyl groups, such as benzoyl; silyl
 15 groups, such as trimethylsilyl (TMS), tert-butyldimethylsilyl (TBDMS), tri-*iso*-propylsilyloxymethyl (TOM), triisopropylsilyl (TIPS), and the like; ether-forming groups with the hydroxyl, such as methyl, methoxymethyl, tetrahydropyranyl, benzyl, *p*-methoxybenzyl, trityl, and the like; alkoxycarbonyls, such as methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *n*-isopropoxycarbonyl, *n*-butyloxycarbonyl, isobutyloxycarbonyl, sec-butyloxycarbonyl, *t*-butyloxycarbonyl, 2-ethylhexyloxycarbonyl,
 20 cyclohexyloxycarbonyl, methyloxycarbonyl, and the like; alkoxyalkoxycarbonyl groups, such as methoxymethoxycarbonyl, ethoxymethoxycarbonyl, 2-methoxyethoxycarbonyl, 2-ethoxyethoxycarbonyl, 2-butoxyethoxycarbonyl, 2-methoxyethoxymethoxycarbonyl, allyloxycarbonyl, propargyloxycarbonyl, 2-butenoxycarbonyl, 3-methyl-2-butenoxycarbonyl, and the like; haloalkoxycarbonyls, such as 2-chloroethoxycarbonyl, 2-chloroethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, and the like; optionally
 25 substituted arylalkoxycarbonyl groups, such as benzyloxycarbonyl, *p*-methylbenzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, 2,4-dinitrobenzyloxycarbonyl, 3,5-dimethylbenzyloxycarbonyl, *p*-chlorobenzyloxycarbonyl, *p*-bromobenzyloxy-carbonyl, fluorenylmethyloxycarbonyl, and the like; and optionally substituted aryloxycarbonyl groups, such as phenoxy-carbonyl, *p*-nitrophenoxycarbonyl, *o*-nitrophenoxycarbonyl, 2,4-dinitrophenoxycarbonyl, *p*-methyl-
 30 phenoxy-carbonyl, *m*-methylphenoxycarbonyl, *o*-bromophenoxy-carbonyl, 3,5-dimethylphenoxycarbonyl, *p*-chlorophenoxy-carbonyl, 2-chloro-4-nitrophenoxy-carbonyl, and the like); substituted alkyl, aryl, and alkaryl ethers (e.g., trityl; methylthiomethyl; methoxymethyl; benzyloxymethyl; siloxymethyl; 2,2,2-trichloroethoxymethyl; tetrahydropyranyl; tetrahydrofuranyl; ethoxyethyl; 1-[2-(trimethylsilyl)ethoxy]ethyl; 2-trimethylsilylethyl; *t*-butyl ether; *p*-chlorophenyl, *p*-methoxyphenyl, *p*-nitrophenyl, benzyl, *p*-
 35 methoxybenzyl, and nitrobenzyl); silyl ethers (e.g., trimethylsilyl; triethylsilyl; triisopropylsilyl; dimethylisopropylsilyl; *t*-butyldimethylsilyl; *t*-butyldiphenylsilyl; tribenzylsilyl; triphenylsilyl; and diphenylmethylsilyl); carbonates (e.g., methyl, methoxymethyl, 9-fluorenylmethyl; ethyl; 2,2,2-

trichloroethyl; 2-(trimethylsilyl)ethyl; vinyl, allyl, nitrophenyl; benzyl; methoxybenzyl; 3,4-dimethoxybenzyl; and nitrobenzyl); carbonyl-protecting groups (e.g., acetal and ketal groups, such as dimethyl acetal, 1,3-dioxolane, and the like; acylal groups; and dithiane groups, such as 1,3-dithianes, 1,3-dithiolane, and the like); carboxylic acid-protecting groups (e.g., ester groups, such as methyl ester, benzyl ester, t-butyl ester, orthoesters, and the like; and oxazoline groups.

The term "oxo" as used herein, represents =O.

The term "polyethylene glycol," as used herein, represents an alkoxy chain comprised of one or more monomer units, each monomer unit consisting of $-\text{OCH}_2\text{CH}_2-$. Polyethylene glycol (PEG) is also sometimes referred to as polyethylene oxide (PEO) or polyoxyethylene (POE), and these terms may be considered interchangeable for the purpose of this disclosure. For example, a polyethylene glycol may have the structure, $-(\text{CH}_2)_{s2}(\text{OCH}_2\text{CH}_2)_{s1}(\text{CH}_2)_{s3}\text{O}-$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), and each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10). Polyethylene glycol may also be considered to include an amino-polyethylene glycol of $-\text{NR}^{\text{N}1}(\text{CH}_2)_{s2}(\text{CH}_2\text{CH}_2\text{O})_{s1}(\text{CH}_2)_{s3}\text{NR}^{\text{N}1}-$, wherein $s1$ is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of $s2$ and $s3$, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each $\text{R}^{\text{N}1}$ is, independently, hydrogen or optionally substituted C_{1-6} alkyl.

The term "stereoisomer," as used herein, refers to all possible different isomeric as well as conformational forms which a compound may possess (e.g., a compound of any formula described herein), in particular all possible stereochemically and conformationally isomeric forms, all diastereomers, enantiomers and/or conformers of the basic molecular structure. Some compounds may exist in different tautomeric forms, all of the latter being included within the scope of the present disclosure.

The term "sulfonyl," as used herein, represents an $-\text{S}(\text{O})_2-$ group.

The term "thiol," as used herein represents an $-\text{SH}$ group.

Other terms

As used herein, the term "administered in combination," "combined administration," or "co-administered" means that two or more agents are administered to a subject at the same time or within an interval such that there may be an overlap of an effect of each agent on the patient. Thus, two or more agents that are administered in combination need not be administered together. In some embodiments, they are administered within 90 days (e.g., within 80, 70, 60, 50, 40, 30, 20, 10, 5, 4, 3, 2, or 1 day(s)), within 28 days (e.g., with 14, 7, 6, 5, 4, 3, 2, or 1 day(s)), within 24 hours (e.g., 12, 6, 5, 4, 3, 2, or 1 hour(s)), or within about 60, 30, 15, 10, 5, or 1 minute of one another. In some embodiments, the administrations of the agents are spaced sufficiently closely together such that a combinatorial effect is achieved.

As used herein, "administering" an agent to a subject includes contacting cells of said subject with the agent.

As used herein, "antibody" refers to a polypeptide whose amino acid sequence including immunoglobulins and fragments thereof which specifically bind to a designated antigen, or fragments thereof. Antibodies may be of any type (e.g., IgA, IgD, IgE, IgG, or IgM) or subtype (e.g., IgA1, IgA2, IgG1, IgG2, IgG3, or IgG4). Those of ordinary skill in the art will appreciate that a characteristic sequence
5 or portion of an antibody may include amino acid sequences found in one or more regions of an antibody (e.g., variable region, hypervariable region, constant region, heavy chain, light chain, and combinations thereof). Moreover, those of ordinary skill in the art will appreciate that a characteristic sequence or portion of an antibody may include one or more polypeptide chains and may include sequence elements found in the same polypeptide chain or in different polypeptide chains.

10 As used herein, "antigen-binding fragment" refers to a portion of an antibody that retains the binding characteristics of the parent antibody.

The terms "bifunctional chelate" or "bifunctional conjugate" as used interchangeably herein, refer to a compound that contains a chelating group or metal complex thereof, a linker group, and a therapeutic moiety, targeting moiety, or cross-linking group.

15 The term "cancer" refers to any cancer caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, and lymphomas. A "solid tumor cancer" is a cancer comprising an abnormal mass of tissue, e.g., sarcomas, carcinomas, and lymphomas. A "hematological cancer" or "liquid cancer," as used interchangeably herein, is a cancer present in a body fluid, e.g., lymphomas and leukemias.

20 The term "chelate" as used herein, refers to an organic compound or portion thereof that can be bonded to a central metal or radiometal atom at two or more points.

The term "conjugate," as used herein, refers to a molecule that contains a chelating group or metal complex thereof, a linker group, and which optionally contains a therapeutic moiety, targeting moiety, or cross-linking group.

25 As used herein, the term "compound," is meant to include all stereoisomers, geometric isomers, and tautomers of the structures depicted.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be
30 isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are
35 described and may be isolated as a mixture of isomers or as separated isomeric forms.

Compounds of the present disclosure also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond and the concomitant migration of a

proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Examples prototropic tautomers include ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, amide – imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, such as, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual subcombination of the members of such groups and ranges. For example, the term “C₁₋₆ alkyl” is specifically intended to individually disclose methyl, ethyl, C₃ alkyl, C₄ alkyl, C₅ alkyl, and C₆ alkyl. Herein a phrase of the form “optionally substituted X” (e.g., optionally substituted alkyl) is intended to be equivalent to “X, wherein X is optionally substituted” (e.g., “alkyl, wherein said alkyl is optionally substituted”). It is not intended to mean that the feature “X” (e.g., alkyl) *per se* is optional.

The term “cross-linking group” as used herein refers to any reactive group that is able to join two or more molecules by a covalent bond. In some embodiments, the cross-linking group is an amino-reactive or thiol-reactive cross-linking group. In some embodiments, the amino-reactive or thiol-reactive cross-linking group comprises an activated ester such as a hydroxysuccinimide ester, 2,3,5,6-tetrafluorophenol ester, 4-nitrophenol ester or an imidate, anhydride, thiol, disulfide, maleimide, azide, alkyne, strained alkyne, strained alkene, halogen, sulfonate, haloacetyl, amine, hydrazide, diazine, phosphine, tetrazine, isothiocyanate. In some embodiments, the cross-linking group may be glycine-glycine and/or leucine-proline-(any amino acid)-threonine-glycine, which are the recognition sequences for coupling targeting agents with the linker using a sortase-mediated coupling reaction. The person having ordinary skill in the art will understand that the use of cross-linking groups are not limited to the specific constructs disclosed herein, but rather may include other known cross-linking groups.

As used herein, the terms “decrease,” “decreased,” “increase,” “increased,” or “reduction,” “reduced,” (e.g., in reference to therapeutic outcomes or effects) have meanings relative to a reference level. In some embodiments, the reference level is a level as determined by the use of said method with a control in an experimental animal model or clinical trial. In some embodiments, the reference level is a level in the same subject before or at the beginning of treatment. In some embodiments, the reference level is the average level in a population not being treated by said method of treatment.

As used herein “detection agent” refers to a molecule or atom which is useful in diagnosing a disease by locating the cells containing the antigen. Various methods of labeling polypeptides with detection agents are known in the art. Examples of detection agents include, but are not limited to, radioisotopes and radionuclides, dyes (such as with the biotin-streptavidin complex), contrast agents, luminescent agents (e.g., FITC, rhodamine, lanthanide phosphors, cyanine, and near IR dyes), and magnetic agents, such as gadolinium chelates.

The term “DNA damage and repair inhibitor” (DDRi) refers to an agent which prevents the repair of cellular DNA damage caused by endogenous or exogenous chromosomal insults, and which acts through the inhibition of normally occurring DNA repair mechanisms and associated processes necessary for the maintenance of cellular viability.

5 The term an “effective amount” of an agent (e.g., any of the foregoing conjugates), as used herein, is that amount sufficient to effect beneficial or desired results, such as clinical results, and, as such, an “effective amount” depends upon the context in which it is being applied.

10 The term “immunoconjugate,” as used herein, refers to a conjugate that includes a targeting moiety, such as an antibody, nanobody, affibody, or a consensus sequence from Fibronectin type III domain. In some embodiments, the immunoconjugate comprises an average of at least 0.10 conjugates per targeting moiety (e.g., an average of at least 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 4, 5, or 8 conjugates per targeting moiety).

15 The term “lower effective dose,” when used as a term in conjunction with an agent (e.g., a therapeutic agent) refers to a dosage of the agent which is effective therapeutically in the combination therapies of the invention and which is lower than the dose which has been determined to be effective therapeutically when the agent is used as a monotherapy in reference experiments or by virtue of other therapeutic guidance.

20 The term “pharmaceutical composition,” as used herein, represents a composition containing a compound described herein formulated with a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other formulation described herein.

25 A “pharmaceutically acceptable excipient,” as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluent), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, radioprotectants, sorbents, suspending or dispersing agents, sweeteners, or waters of hydration. Exemplary excipients include, but are not limited to: ascorbic acid, histidine, phosphate buffer, butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone,

povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

The term "pharmaceutically acceptable salt," as use herein, represents those salts of the
5 compounds described here that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, or allergic response. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts
10 can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting the free base group with a suitable organic acid.

Compounds may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of compounds, be prepared from inorganic or organic bases. Frequently,
15 the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases are well-known in the art, such as hydrochloric, sulphuric, hydrobromic, acetic, lactic, citric, or tartaric acids for forming acid addition salts, and potassium hydroxide, sodium hydroxide, ammonium hydroxide, caffeine, various amines for forming basic salts. Methods for preparation of the appropriate salts are well-
20 established in the art.

Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-
25 hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, among others.

Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, and
30 magnesium, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, and ethylamine.

The term "polypeptide" as used herein refers to a string of at least two amino acids attached to one another by a peptide bond. In some embodiments, a polypeptide may include at least 3-5 amino
35 acids, each of which is attached to others by way of at least one peptide bond. Those of ordinary skill in the art will appreciate that polypeptides can include one or more "non-natural" amino acids or other entities that nonetheless are capable of integrating into a polypeptide chain. In some embodiments, a

polypeptide may be glycosylated, e.g., a polypeptide may contain one or more covalently linked sugar moieties. In some embodiments, a single "polypeptide" (e.g., an antibody polypeptide) may comprise two or more individual polypeptide chains, which may in some cases be linked to one another, for example by one or more disulfide bonds or other means.

5 The term "radioconjugate," as used herein, refers to any conjugate that includes a radioisotope or radionuclide, such as any of the radioisotopes or radionuclides described herein.

 The term "radioimmunoconjugate," as used herein, refers to any immunoconjugate that includes a radioisotope or radionuclide, such as any of the radioisotopes or radionuclides described herein.

 The term "radioimmunotherapy," as used herein, refers a method of using a
10 radioimmunoconjugate to produce a therapeutic effect. In some embodiments, radioimmunotherapy may include administration of a radioimmunoconjugate to a subject in need thereof, wherein administration of the radioimmunoconjugate produces a therapeutic effect in the subject. In some embodiments, radioimmunotherapy may include administration of a radioimmunoconjugate to a cell, wherein administration of the radioimmunoconjugate kills the cell. Wherein radioimmunotherapy involves the
15 selective killing of a cell, in some embodiments the cell is a cancer cell in a subject having cancer.

 As used herein, the term "radionuclide," refers to an atom capable of undergoing radioactive decay (e.g., ^3H , ^{14}C , ^{15}N , ^{18}F , ^{35}S , ^{47}Sc , ^{55}Co , ^{60}Cu , ^{61}Cu , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{75}Br , ^{76}Br , ^{77}Br , ^{89}Zr , ^{86}Y , ^{87}Y , ^{90}Y , ^{97}Ru , ^{99}Tc , $^{99\text{m}}\text{Tc}$, ^{105}Rh , ^{109}Pd , ^{111}In , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{149}Pm , ^{149}Tb , ^{153}Sm , ^{166}Ho , ^{177}Lu , ^{186}Re , ^{188}Re , ^{198}Au , ^{199}Au , ^{203}Pb , ^{211}At , ^{212}Pb , ^{212}Bi , ^{213}Bi , ^{223}Ra , ^{225}Ac , ^{227}Th , ^{229}Th , ^{68}Ga , ^{67}Ga , ^{68}Ga , ^{82}Rb , $^{117\text{m}}\text{Sn}$, ^{201}Tl). The terms radioactive nuclide, radioisotope, or radioactive isotope may also be used to describe a
20 radionuclide. Radionuclides may be used as detection agents, as described above. In some embodiments, the radionuclide is an alpha-emitting radionuclide.

 By "subject" is meant a human or non-human animal (e.g., a mammal).

 By "substantial identity" or "substantially identical" is meant a polypeptide sequence that has the
25 same polypeptide sequence, respectively, as a reference sequence, or has a specified percentage of amino acid residues, respectively, that are the same at the corresponding location within a reference sequence when the two sequences are optimally aligned. For example, an amino acid sequence that is "substantially identical" to a reference sequence has at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the reference amino acid sequence. For polypeptides,
30 the length of comparison sequences will generally be at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 50, 75, 90, 100, 150, 200, 250, 300, or 350 contiguous amino acids (e.g., a full-length sequence). Sequence identity may be measured using sequence analysis software, e.g., on the default setting (e.g., Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705). Such software may
35 match similar sequences by assigning degrees of homology to various substitutions, deletions, and other modifications.

The term “targeting moiety” as used herein refers to any molecule or any part of a molecule that binds to a given target. In some embodiments, the targeting moiety is a protein or polypeptide such as an antibody or antigen binding fragment thereof, a nanobody, an affibody, or a consensus sequence from a Fibronectin type III domain.

5 The term “therapeutic moiety” as used herein refers to any molecule or any part of a molecule that confers a therapeutic benefit. In some embodiments, the therapeutic moiety is a protein or polypeptide, e.g., an antibody, an antigen-binding fragment thereof. In some embodiments, the therapeutic moiety is a small molecule.

10 As used herein, and as well understood in the art, “to treat” a condition or “treatment” of the condition (e.g., the conditions described herein such as cancer) is an approach for obtaining beneficial or desired results, such as clinical results. Beneficial or desired results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions; diminishment of extent of disease, disorder, or condition; stabilized (i.e., not worsening) state of disease, disorder, or condition; preventing spread of disease, disorder, or condition; delay or slowing the progress of the disease, disorder, or condition; amelioration or palliation of the disease, disorder, or condition; and remission (whether partial or total), whether detectable or undetectable. In the context of cancer treatment, “ameliorating” may include, for example, reducing incidence of metastases, reducing tumor volume, reducing tumor vascularization and/or reducing the rate of tumor growth. “Palliating” a disease, disorder, or condition means that the extent and/or undesirable clinical manifestations of the disease, disorder, or condition are lessened and/or time course of the progression is slowed or lengthened, as compared to the extent or time course in the absence of treatment.

15 As used herein, the term “tumor-associated antigen” means an antigen that is present on tumor cells at a significantly greater amount than on normal cells.

20 As used herein, the term “tumor-specific antigen” refers to an antigen that is endogenously present only on tumor cells.

Brief Description of the Drawings

Figure 1 is a schematic demonstrating the dosing schedule for [²²⁵Ac]-FPI-1434 and BAY-1895344 (an ATR inhibitor) in two xenograft models: Colo-205 and A549. See Example 1.

30 Figures 2A-2B illustrate the relative tumor volume in Colo-205 (Figure 2A) and A549 (Figure 2B) after treatment with BAY-1895344 and [²²⁵Ac]-FPI-1434 alone or in combination. See Example 1.

Figure 3 is a schematic demonstrating the dosing schedule for [²²⁵Ac]-FPI-1434 and BAY-1895344 in the Colo-205 (colorectal cancer) xenograft model. See Example 2.

35 Figure 4 illustrates the relative tumor volume in Colo-205 after treatment with BAY-1895344 and [²²⁵Ac]-

FPI-1434 alone or in combination. See Example 2.

Figure 5 is a schematic demonstrating the dosing schedule for olaparib for treatment in two xenograft models: Colo-205 and A549. See Example 3.

5

Figures 6A-6B illustrate relative tumor volume in Colo-205 (Figure 6A) and A549 (Figure 6B) after treatment with olaparib. See Example 3.

10

Figure 7 is a schematic demonstrating the dosing schedule for [²²⁵Ac]-FPI-1434 and olaparib for treatment in two xenograft models: Colo-205 and A549. See Example 4.

Figures 8A-8B illustrate relative tumor volume in Colo-205 (Figure 8A) and A549 (Figure 8B) after treatment with olaparib and [²²⁵Ac]-FPI-1434 alone or in combination. See Example 4.

15

Figure 9 is a schematic demonstrating the dosing schedule for [²²⁵Ac]-FPI-1434 and olaparib for treatment in the Colo-205 xenograft model. See Example 5.

20

Figure 10 illustrates relative tumor volume in Colo-205 after treatment with olaparib and [²²⁵Ac]-FPI-1434 alone or in combination. See Example 5.

Figure 11 is a schematic demonstrating the dosing schedule for [²²⁵Ac]-FPI-1434 and olaparib used in the multiple-dose in vivo experiments described in Example 6.

Figure 12 shows relative tumor volumes in animals administered lower effective doses of [²²⁵Ac]-FPI-1434 (20 nCi) and olaparib (25 mg/kg) in the experiment described in Example 6.

25

Figures 13A-13C show relative tumor volumes in animals administered 20 nCi (Figure 13A), 50 nCi (Figure 13B), or 100 nCi (Figure 13C) [²²⁵Ac]-FPI-1434 with olaparib (25 mg/kg or 50 mg/kg).

30

It is to be understood that the figures are not necessarily drawn to scale, nor are the objects in the figures necessarily drawn to scale in relationship to one another. The figures are depictions that are intended to bring clarity and understanding to various embodiments of apparatuses, systems, and methods disclosed herein. Wherever possible, the same reference numbers will be used throughout the drawings to refer to the same or like parts. Moreover, it should be appreciated that the drawings are not intended to limit the scope of the present teachings in any way.

Detailed Description

35

The present disclosure relates to combination therapies for treating or ameliorating cancer, using radioimmunoconjugates and DNA damage and repair inhibitors (DDRIs). In some embodiments, a lower

effective dose of the radioimmunoconjugate and/or of the DDRi is used.

Radiolabelled targeting moieties (also known as radioimmunoconjugates) are designed to target a protein or receptor that is upregulated in a disease state and/or specific to diseased cells (e.g., tumor cells) to deliver a radioactive payload to damage and kill cells of interest. "Radioimmunotherapy" refers to this therapy when the targeting moiety comprises an antibody, typically a monoclonal antibody. Radioactive decay of the payload produces an alpha, beta, or gamma particle or Auger electron that can cause direct effects to DNA (such as single or double stranded DNA breaks) or indirect effects such as by-stander or crossfire effects.

Radioimmunoconjugates typically contain a biological targeting moiety (e.g., an antibody or antigen binding fragment thereof that specifically binds to a molecule expressed on or by a tumor, e.g., IGF-1R or TEM-1/endosialin), a chelating moiety or a metal complex of a chelating moiety (e.g., comprising a radioisotope), and a linker. Conjugates may be formed by appending a bifunctional chelate to the biological targeting molecule so that structural alterations are minimal while maintaining target affinity. A radioimmunoconjugate may be formed by radiolabelling such a conjugate.

Bifunctional chelates structurally contain a chelate, a linker, and a cross-linking group. When developing new bifunctional chelates, most efforts focus around the chelating portion of the molecule. Several examples of bifunctional chelates have been described with various cyclic and acyclic structures conjugated to a targeted moiety. [Bioconjugate Chem. 2000, 11, 510-519, Bioconjugate Chem. 2012, 23, 1029-1039, Mol Imaging Biol (2011) 13:215-221, Bioconjugate Chem. 2002, 13, 110-115].

Radioimmunoconjugates

Radioimmunoconjugates suitable for use in accordance with the present disclosure generally have the structure of Formula I-a:

A-L-B

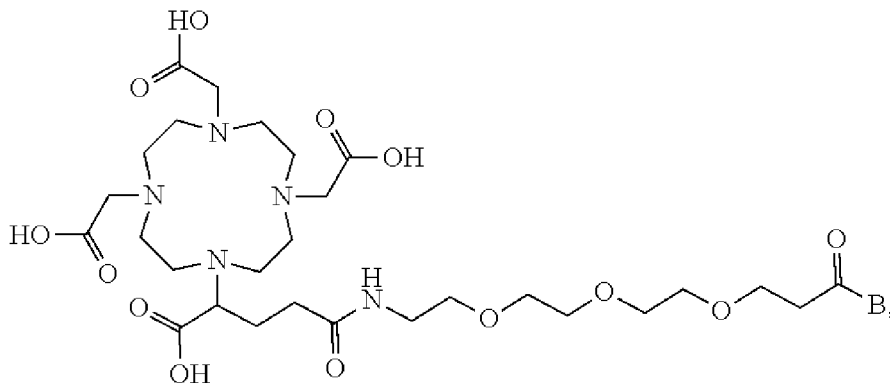
Formula I-a

wherein A is a chelating moiety or metal complex thereof),

wherein B is a targeting moiety, and

wherein L is a linker.

In some embodiments, the radioimmunoconjugate comprises the following structure:



wherein B is the targeting moiety.

5

Targeting moieties

Targeting moieties include any molecule or any part of a molecule that is capable of binding to a given target. In some embodiments, the targeting moiety comprises a protein or polypeptide. In some embodiments, the targeting moiety is selected from the group consisting of antibodies or antigen binding fragments thereof, nanobodies, affibodies, and consensus sequences from Fibronectin type III domains (e.g., Centyrins or Adnectins). In some embodiments, a moiety is both a targeting and a therapeutic moiety, i.e., the moiety is capable of binding to a given target and also confers a therapeutic benefit.

15

Antibodies

Antibodies typically comprise two identical light polypeptide chains and two identical heavy polypeptide chains linked together by disulfide bonds. The first domain located at the amino terminus of each chain is variable in amino acid sequence, providing the antibody-binding specificities of each individual antibody. These are known as variable heavy (VH) and variable light (VL) regions. The other domains of each chain are relatively invariant in amino acid sequence and are known as constant heavy (CH) and constant light (CL) regions. Light chains typically comprise one variable region (VL) and one constant region (CL). An IgG heavy chain includes a variable region (VH), a first constant region (CH1), a hinge region, a second constant region (CH2), and a third constant region (CH3). In IgE and IgM antibodies, the heavy chain includes an additional constant region (CH4).

25 Antibodies described herein can include, for example, monoclonal antibodies, polyclonal antibodies, multispecific antibodies, human antibodies, humanized antibodies, camelid antibodies, chimeric antibodies, single-chain Fvs (scFv), disulfide-linked Fvs (sdFv), and anti-idiotypic (anti-Id) antibodies, and antigen-binding fragments of any of the above. In some embodiments, the antibody or antigen-binding fragment thereof is humanized. In some embodiments, the antibody or antigen-binding

fragment thereof is chimeric. Antibodies can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass.

The term "antigen binding fragment" of an antibody, as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen. Examples of binding fragments encompassed within the term "antigen binding fragment" of an antibody include a Fab fragment, a F(ab')₂ fragment, a Fd fragment, a Fv fragment, a scFv fragment, a dAb fragment (Ward et al., (1989) Nature 341:544-546), and an isolated complementarity determining region (CDR). In some embodiments, an "antigen binding fragment" comprises a heavy chain variable region and a light chain variable region. These antibody fragments can be obtained using conventional techniques known to those with skill in the art, and the fragments can be screened for utility in the same manner as are intact antibodies.

Antibodies or fragments described herein can be produced by any method known in the art for the synthesis of antibodies (see, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Brinkman et al., 1995, J. Immunol. Methods 182:41-50; WO 92/22324; WO 98/46645). Chimeric antibodies can be produced using the methods described in, e.g., Morrison, 1985, Science 229:1202, and humanized antibodies by methods described in, e.g., U.S. Pat. No. 6,180,370.

Additional antibodies described herein are bispecific antibodies and multivalent antibodies, as described in, e.g., Segal et al., J. Immunol. Methods 248:1-6 (2001); and Tutt et al., J. Immunol. 147: 60 (1991).

Insulin-like growth factor 1 (IGF-1R) Antibodies

Insulin-like growth factor 1 receptor is a transmembrane protein found on the surface of human cells activated by insulin-like growth factor 1 (IGF-1) and 2 (IGF-2). In some embodiments, radioimmunoconjugates comprise antibodies against insulin-like growth factor-1 receptor (IGF-1R). Although not a typical oncogene, IGF-1R promotes initiation and progression of cancer, playing a critical role in mitogenic transformation and maintenance of the transformed phenotype. IGF-1R has been associated with development of multiple common cancers including breast, lung (e.g., non-small lung), liver, prostate, pancreas, ovarian, colon, melanoma, adrenocortical carcinoma, and various types of sarcomas. IGF-1R signaling stimulates tumour cell proliferation and metabolism, supports angiogenesis, and confers protection from apoptosis. It affects metastatic factors (e.g., HIF-1 dependent hypoxia signaling), anchorage independent growth, as well as growth and survival of tumour metastases after extravasation. IGF-1R has also been implicated in the development, maintenance and enrichment of therapeutic resistant cancer stem cell populations.

Despite the abundance of data implicating IGF-1R's role in cancer, therapeutics targeting IGF-1R have yet to demonstrate a significant impact on disease. There has been much speculation for this lack of efficacy including the inability to identify appropriate biomarkers for patient identification, complexity and

interdependency of the IGF-1/IR signaling pathway and the development of other growth hormone compensatory mechanisms [Beckwith and Yee, *Mol Endocrinol*, November 2015, 29(11):1549–1557]. Radioimmunotherapy, however, may provide a viable mechanism for treating cancers overexpressing the IGF-1 receptor by utilizing the ability of IGF-1R to undergo antibody triggered internalization and lysosomal degradation to deliver targeted radioisotopes inside cancer cells. Internalization and lysosomal degradation of an IGF-1R targeted radioimmunoconjugate prolongs the residence time of the delivered radioisotope inside cancer cells, thereby maximizing the potential for a cell killing emission to occur. In the case of actinium-225, which yields 4 alpha particles per decay chain, cell death can be accomplished by as little as 1 atom of radionuclide delivered per cell [Sgouros, et al. *J Nucl Med*. 2010, 51:311-2]. Cell killing due to direct DNA impact and breakage by an alpha particle may occur in the targeted cell or in a radius of 2 or 3 non-targeted cells for a given alpha particle decay. In addition to having very high potential anti-tumour potency, IGF-1R targeted radioimmunoconjugates may not generate mechanistic resistance as they do not rely on blocking ligand binding to the receptor to inhibit the oncologic process, as needed with a therapeutic antibody.

Several IGF-1R antibodies have been developed and investigated for the treatment of various types of cancers, including figitumumab, cixutumumab, ganitumab, AVE1642 (also known as humanized EM164 and huEM164), BII002, robatumumab, and teprotumumab. After binding to IGF-1R, these antibodies are internalized into the cell and degraded by lysosomal enzymes. The combination of overexpression on tumor cells and internalization offers the possibility of delivering detection agents directly to the tumor site while limiting the exposure of normal tissues to toxic agents.

The CDRs of the light chain variable region of AVE1642 have the sequences:

SEQ ID NO: 1 (CDR-L1) RSSQSIVHSNVNTYLE

SEQ ID NO: 2 (CDR-L2) KVSNRFS

SEQ ID NO: 3 (CDR-L3) FQGSHVPPT

The light chain variable region of AVE1642 has the sequence:

SEQ ID NO: 4

DVVMQTPLSLPVSLGDPASISCRSSQSIVHSNVNTYLEWYLQKPGQSPRLLIYKVSNR

SGVPDRFSGSGAGTDFTLRISRVEAEDLGIYYCFQGSHVPPTFGGGTKLEIKRTVAAPSV

FIFPPSDEQLKSGTASVVCLLNNFYPREAK

The CDRs of the heavy chain variable region of AVE1642 have the sequences:

SEQ ID NO: 5 (CDR-H1) SYWMH

SEQ ID NO: 6 (CDR-H2) GEINPSNGRTNY NQKFQG

SEQ ID NO: 7 (CDR-H3) GRPDYYGSSKQY FDV

The heavy chain variable region of AVE1642 has the sequence:

SEQ ID NO: 8

QVQLVQSGAEVVKPGASVKLSCKASGYTFTSYWMHWWKQRPQGQLEWIGEINPSNGRTNY
 NQKFQGKATLTVDKSSSTAYMQLSSLTSEDSAVYYFARGRPDYYGSSKWYFDVWGQGTTV
 5 TVSSASTKGPSVFPLAPSSKSTSGGTAALG

Endosialin (TEM-1) antibodies

Endosialin, also known as TEM-1 or CD-248, is an antigen expressed by tumor-associated endothelial cells, stromal cells, and pericytes.

10 Examples of endosialin antibodies include hMP-E-8.3 (disclosed in WO 2017/134234, the entire contents of which are incorporated by reference herein) and ontuxizumab (MORAb-004).

In some embodiments, the endosialin antibody or antigen-binding fragment thereof recognizes an epitope having an amino acid sequence of SRDHQIPVIAAN (SEQ ID NO: 9).

15 In some embodiments, the heavy chain variable region of the endosialin antibody or antibody-binding fragment thereof comprises the complementarity determining regions (CDRs) having the following sequences:

CDR-H1: GYGVN (SEQ ID NO: 10) or GFSLTGYGVN (SEQ ID NO: 11)

CDR-H2: MIWWDGSTDYNSALKS (SEQ ID NO: 12)

CDR-H3: GYGAMDY (SEQ ID NO: 13)

20

In some embodiments, the light chain variable region of the endosialin antibody or antibody-binding fragment thereof comprises the complementarity determining regions (CDRs) having the following sequences:

25 CDR-L1: HASQNINVWLT (SEQ ID NO: 14)

CDR-L2: KASNLHT (SEQ ID NO: 15)

CDR-L3: QQGQSYJWT (SEQ ID NO: 16)

30 In some embodiments, the endosialin antibody or antigen-binding fragment thereof is a humanized antibody.

In some embodiments, the heavy chain variable region of the endosialin antibody or antigen-binding fragment thereof comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 17, 18, 19, or 20:

35 Humanized VH1:

QVQLQESGPGLVKPSSETLSLTCTVSGFSLTGYGVNWIRQPPGKGLEWIGMIWWDGSTDYN
 SALKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARGGYGAMDYWGQGTLTVSS

(SEQ ID NO: 17)

Humanized VH2:

QVQLQESGPGLVKPSSETLSLTCTVSGFSLTGYGVNWIRQPPEKGLEWIGMIWWDGSTDYN

5 SALKSRVNISVDTSKNQFSLKLSSVTAADTAVYYCARGGYGAMDYWGQGTLVTVSS

(SEQ ID NO: 18)

Humanized VH3:

QLQLQESGPGLVKPSSETLSLTCTVSGFSLTGYGVNWIRQPPGKGLEWIGMIWWDGSTDYN

10 SALKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCARGGYGAMDYWGQGTLVTVSS

(SEQ ID NO: 19)

Humanized VH4:

QLQLQESGPGLVKPSSETLSLTCTVSGFSLTGYGVNWIRQPPEKGLEWIGMIWWDGSTDYN

15 SALKSRVNISVDKSKNQFSLKLSSVTAADTAVYYCARGGYGAMDYWGQGTLVTVSS

(SEQ ID NO: 20)

In some embodiments, the light chain variable region of the endosialin antibody or antigen-binding fragment thereof comprises an amino acid sequence selected from the group consisting of SEQ
20 ID NO: 21, 22, 23, or 24:

Humanized VL1:

DIQMTQSPSSVSASVGDRVTITCHASQNINVWLTWYQQKPGKAPKLLIYKASNLHTGVPS

RFSGSGSGTDFTLTISLQPEDFATYYCQQGQSYPWTFGGGTKLEIK

25 (SEQ ID NO: 21)

Humanized VL2:

DIQMTQSPSTLSASVGDRVTITCHASQNINVWLTWYQQKPGKAPKLLIYKASNLHTGVPS

RFSGSGSGTEFTLTISLQPDDEFATYYCQQGQSYPWTFGGGTKLEIK

30 (SEQ ID NO: 22)

Humanized VL3:

DIQMTQSPSSLSASVGDRVTITCHASQNINVWLTWYQQKPGKAPKLLIYKASNLHTGVPS

RFSGSGSGTDFTFTISLQPEDFATYYCQQGQSYPWTFGGGTKLEIK

35 (SEQ ID NO: 23)

Humanized VL4:

DIQMTQSPSSLSASVGDRVTITCHASQNINVLWTWYQQKPEKAPKSLIYKASNLHTGVPS
 RFSGSGSGTDFTLTISSLQPEDFATYYCQQGQSYPTWTFGGGTKLEIK
 (SEQ ID NO: 24)

5 Nanobodies

Nanobodies are antibody fragments consisting of a single monomeric variable antibody domain. Nanobodies may also be referred to as single-domain antibodies. Like antibodies, nanobodies bind selectively to a specific antigen. Nanobodies may be heavy-chain variable domains or light chain domains. Nanobodies may occur naturally or be the product of biological engineering. Nanobodies may
 10 be biologically engineered by site-directed mutagenesis or mutagenic screening (e.g., phage display, yeast display, bacterial display, mRNA display, ribosome display).

Affibodies

Affibodies are polypeptides or proteins engineered to bind to a specific antigen. As such,
 15 affibodies may be considered to mimic certain functions of antibodies. Affibodies may be engineered variants of the B-domain in the immunoglobulin-binding region of staphylococcal protein A. Affibodies may be engineered variants of the Z-domain, a B-domain that has lower affinity for the Fab region. Affibodies may be biologically engineered by site-directed mutagenesis or mutagenic screening (e.g., phage display, yeast display, bacterial display, mRNA display, ribosome display).

20 Affibody molecules showing specific binding to a variety of different proteins (e.g. insulin, fibrinogen, transferrin, tumor necrosis factor- α , IL-8, gp120, CD28, human serum albumin, IgA, IgE, IgM, HER2 and EGFR) have been generated, demonstrating affinities (K_d) in the μ M to pM range.

Fibronectin type III domains

25 The Fibronectin type III domain is an evolutionarily conserved protein domain found in a wide-variety of extracellular proteins. The Fibronectin type III domain has been used as a molecular scaffold to produce molecules capable of selectively binding a specific antigen. Variants of the Fibronectin type III domains (FN3) that have been engineered for selective-binding may also be referred to as monobodies. FN3 domains may be biologically engineered by site-directed mutagenesis or mutagenic screening (e.g.,
 30 CIS-display, phage display, yeast display, bacterial display, mRNA display, ribosome display).

Modified polypeptides

Polypeptides used in accordance with the disclosure may have a modified amino acid sequence. Modified polypeptides may be substantially identical to the corresponding reference polypeptide (e.g., the
 35 amino acid sequence of the modified polypeptide may have at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence of the reference polypeptide). In certain embodiments, the modification does not destroy significantly a desired biological

activity (e.g., binding to IGF-1R or to endosialin). The modification may reduce (e.g., by at least 5%, 10%, 20%, 25%, 35%, 50%, 60%, 70%, 75%, 80%, 90%, or 95%), may have no effect, or may increase (e.g., by at least 5%, 10%, 25%, 50%, 100%, 200%, 500%, or 1000%) the biological activity of the original polypeptide. The modified polypeptide may have or may optimize a characteristic of a polypeptide, such as in vivo stability, bioavailability, toxicity, immunological activity, immunological identity, and conjugation properties.

Modifications include those by natural processes, such as post-translational processing, or by chemical modification techniques known in the art. Modifications may occur anywhere in a polypeptide including the polypeptide backbone, the amino acid side chains and the amino- or carboxy-terminus. The same type of modification may be present in the same or varying degrees at several sites in a given polypeptide, and a polypeptide may contain more than one type of modification. Polypeptides may be branched as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from post-translational natural processes or may be made synthetically. Other modifications include pegylation, acetylation, acylation, addition of acetamidomethyl (Acm) group, ADP-ribosylation, alkylation, amidation, biotinylation, carbamoylation, carboxyethylation, esterification, covalent attachment to flavin, covalent attachment to a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of drug, covalent attachment of a marker (e.g., fluorescent or radioactive), covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation and ubiquitination.

A modified polypeptide can also include an amino acid insertion, deletion, or substitution, either conservative or non-conservative (e.g., D-amino acids, desamino acids) in the polypeptide sequence (e.g., where such changes do not substantially alter the biological activity of the polypeptide). In particular, the addition of one or more cysteine residues to the amino or carboxy-terminus of a polypeptide can facilitate conjugation of these polypeptides by, e.g., disulfide bonding. For example, a polypeptide can be modified to include a single cysteine residue at the amino-terminus or a single cysteine residue at the carboxy-terminus. Amino acid substitutions can be conservative (i.e., wherein a residue is replaced by another of the same general type or group) or non-conservative (i.e., wherein a residue is replaced by an amino acid of another type). In addition, a naturally occurring amino acid can be substituted for a non-naturally occurring amino acid (i.e., non-naturally occurring conservative amino acid substitution or a non-naturally occurring non-conservative amino acid substitution).

Polypeptides made synthetically can include substitutions of amino acids not naturally encoded by DNA (e.g., non-naturally occurring or unnatural amino acid). Examples of non-naturally occurring

amino acids include D-amino acids, N-protected amino acids, an amino acid having an acetylaminoethyl group attached to a sulfur atom of a cysteine, a pegylated amino acid, the omega amino acids of the formula $\text{NH}_2(\text{CH}_2)_n\text{COOH}$ wherein n is 2-6, neutral nonpolar amino acids, such as sarcosine, t-butyl alanine, t-butyl glycine, N-methyl isoleucine, and norleucine. Phenylglycine may substitute for Trp, Tyr, or Phe; citrulline and methionine sulfoxide are neutral nonpolar, cysteic acid is acidic, and ornithine is basic. Proline may be substituted with hydroxyproline and retain the conformation conferring properties.

Analogs may be generated by substitutional mutagenesis and retain the biological activity of the original polypeptide. Examples of substitutions identified as "conservative substitutions" are shown in Table 1. If such substitutions result in a change not desired, then other type of substitutions, denominated "exemplary substitutions" in Table 1, or as further described herein in reference to amino acid classes, are introduced and the products screened.

Table 1: Amino acid substitutions

Original residue	Exemplary substitution	Conservative substitution
Ala (A)	Val, Leu, Ile	Val
Arg (R)	Lys, Gln, Asn	Lys
Asn (N)	Gln, His, Lys, Arg	Gln
Asp (D)	Glu	Glu
Cys (C)	Ser	Ser
Gln (Q)	Asn	Asn
Glu (E)	Asp	Asp
Gly (G)	Pro	Pro
His (H)	Asn, Gln, Lys, Arg	Arg
Ile (I)	Leu, Val, Met, Ala, Phe, norleucine	Leu
Leu (L)	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys (K)	Arg, Gln, Asn	Arg
Met (M)	Leu, Phe, Ile	Leu
Phe (F)	Leu, Val, Ile, Ala	Leu
Pro (P)	Gly	Gly
Ser (S)	Thr	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr	Tyr
Tyr (Y)	Trp, Phe, Thr, Ser	Phe
Val (V)	Ile, Leu, Met, Phe, Ala, norleucine	Leu

Substantial modifications in function or immunological identity are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain.

5

Chelating moieties and metal complexes thereof

Chelating moieties

Examples of suitable chelating moieties include, but are not limited to, 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), DOTPA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra propionic acid), DO3AM-acetic acid (2-(4,7,10-tris(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid), DOTA-GA anhydride (2,2',2''-(10-(2,6-dioxotetrahydro-2H-pyran-3-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid, DOTP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid)), DOTMP (1,4,6,10-tetraazacyclodecane-1,4,7,10-tetramethylene phosphonic acid, DOTA-4AMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis(acetamido-methylenephosphonic acid), CB-TE2A (1,4,8,11-tetraazabicyclo[6.6.2]hexadecane-4,11-diacetic acid), NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid), NOTP (1,4,7-triazacyclononane-1,4,7-tri(methylene phosphonic acid), TETPA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetrapropionic acid), TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetra acetic acid), HEHA (1,4,7,10,13,16-hexaazacyclohexadecane-1,4,7,10,13,16-hexaacetic acid), PEPA (1,4,7,10,13-pentaazacyclopentadecane-N,N',N'',N''', N''''-pentaacetic acid), H₄octapa (N,N'-bis(6-carboxy-2-pyridylmethyl)-ethylenediamine-N,N'-diacetic acid), H₂dedpa (1,2-[[6-(carboxy)-pyridin-2-yl]-methylamino]ethane), H₆phospa (N,N'-(methylenephosphonate)-N,N'-[6-(methoxycarbonyl)pyridin-2-yl]-methyl-1,2-diaminoethane), TTHA (triethylenetetramine-N,N,N',N'',N''', N''''-hexaacetic acid), DO2P (tetraazacyclododecane dimethanephosphonic acid), HP-DO3A (hydroxypropyltetraazacyclododecanetriacetic acid), EDTA (ethylenediaminetetraacetic acid), Deferoxamine, DTPA (diethylenetriaminepentaacetic acid), DTPA-BMA (diethylenetriaminepentaacetic acid-bismethylamide), HOPO (octadentate hydroxypyridinones), or porphyrins.

In some embodiments, radioimmunoconjugates comprise a metal complex of a chelating moiety. For example, chelating groups may be used in metal chelate combinations with metals, such as manganese, iron, and gadolinium and isotopes (e.g., isotopes in the general energy range of 60 to 4,000 keV), such as any of the radioisotopes and radionuclides discussed herein.^{2, 2 2,}

35

In some embodiments, chelating moieties are useful as detection agents, and radioimmunoconjugates comprising such detectable chelating moieties can therefore be used as diagnostic or theranostic agents.

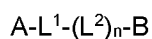
Radioisotopes and Radionuclides

In some embodiments, the metal complex comprises a radionuclide. Examples of suitable radioisotopes and radionuclides include, but are not limited to, ^3H , ^{14}C , ^{15}N , ^{18}F , ^{35}S , ^{47}Sc , ^{55}Co , ^{60}Cu , ^{61}Cu , ^{62}Cu , ^{64}Cu , ^{66}Ga , ^{67}Ga , ^{67}Cu , ^{68}Ga , ^{75}Br , ^{76}Br , ^{77}Br , ^{82}Rb , ^{89}Zr , ^{86}Y , ^{87}Y , ^{90}Y , ^{97}Ru , ^{99}Tc , $^{99\text{m}}\text{Tc}$, ^{105}Rh , ^{109}Pd , ^{111}In , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{149}Pm , ^{149}Tb , ^{153}Sm , ^{166}Ho , ^{177}Lu , $^{117\text{m}}\text{Sn}$, ^{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 .

In some embodiments, the radionuclide is an alpha emitter, e.g., 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), or Terbium-149 (^{149}Tb).

Linkers

In some embodiments, the linker is as shown within the structure of Formula I-b, as that part of Formula I-b absent A and B:

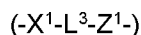
**Formula I-b**

(A and B are as defined in Formula I-a.)

Thus, in some embodiments, the linker is $\text{-L}^1\text{-(L}^2\text{)}_n\text{-}$, wherein L^1 is optionally substituted $\text{C}_1\text{-C}_6$ alkyl, substituted $\text{C}_1\text{-C}_6$ heteroalkyl, substituted aryl or heteroaryl;

n is 1-5; and

each L^2 , independently, has the structure:

**Formula II**

wherein X^1 is $\text{C=O(NR}^1\text{)}$, $\text{C=S(NR}^1\text{)}$, $\text{OC=O(NR}^1\text{)}$, $\text{NR}^1\text{C=O(O)}$, $\text{NR}^1\text{C=O(NR}^1\text{)}$, $\text{-CH}_2\text{PhC=O(NR}^1\text{)}$, $\text{-CH}_2\text{Ph(NH)C=S(NR}^1\text{)}$, O , or NR^1 ; and each R^1 independently is H or optionally substituted $\text{C}_1\text{-C}_6$ alkyl or optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl, substituted aryl or heteroaryl, in which $\text{C}_1\text{-C}_6$ alkyl can be substituted by oxo ($=\text{O}$), heteroaryl, or a combination thereof;

L^3 is optionally substituted $\text{C}_1\text{-C}_{50}$ alkyl or optionally substituted $\text{C}_1\text{-C}_{50}$ heteroalkyl or $\text{C}_5\text{-C}_{20}$ polyethylene glycol; Z^1 is CH_2 , C=O , C=S , OC=O , $\text{NR}^1\text{C=O}$, NR^1 and R^1 is a hydrogen or optionally substituted $\text{C}_1\text{-C}_6$ alkyl, pyrrolidine-2,5-dione.

Cross-linking groups

In some embodiments, radioimmunoconjugates comprise a cross-linking group instead of or in addition to the targeting moiety or therapeutic moiety (e.g., B in Formula I comprises a cross-linking group).

A cross-linking group is a reactive group that is able to join two or more molecules by a covalent bond. Cross-linking groups may be used to attach the linker and chelating moiety to a therapeutic or targeting moiety. Cross-linking groups may also be used to attach the linker and chelating moiety to a target *in vivo*. In some embodiments, the cross-linking group is an amino-reactive, methionine reactive or thiol-reactive cross-linking group, or a sortase-mediated coupling. In some embodiments, the amino-reactive or thiol-reactive cross-linking group comprises an activated ester such as a hydroxysuccinimide ester, 2,3,5,6-tetrafluorophenol ester, 4-nitrophenol ester or an imidate, anhydride, thiol, disulfide, maleimide, azide, alkyne, strained alkyne, strained alkene, halogen, sulfonate, haloacetyl, amine, hydrazide, diazirine, phosphine, tetrazine, isothiocyanate, or oxaziridine. In some embodiments, the sortase recognition sequence may comprise of a terminal glycine-glycine-glycine (GGG) and/or LPTXG amino acid sequence, where X is any amino acid. A person having ordinary skill in the art will understand that the use of cross-linking groups is not limited to the specific constructs disclosed herein, but rather may include other known cross-linking groups.

DNA Damage and Repair Inhibitors (DDRi)

In various embodiments, a DNA Damage and Repair inhibitor (DDRi) is co-administered with a radioimmunoconjugate. DNA repair involves multiple molecular pathways that repair DNA single strand breaks (e.g., the PARP pathway) and double stranded breaks (e.g., BRCA and other genes such as ATR/ATM). PARP inhibition (PARPi) results in a failure of single stranded break repair, which further leads to double stranded breaks. Available PARP inhibitors act through both PARP enzyme inhibition and DNA-trapping. Tumor cells with BRCA and/or PTEN mutations are sensitive to PARPi. ATR inhibition (ATRi) results in a failure to repair double stranded breaks—the accumulation of double stranded breaks results in cell death. These inhibitors act by preventing homologous recombination and non-homologous end joining mechanisms.

The present disclosure relates to combination therapy with radioimmunoconjugates and DNA Damage and Repair inhibitors. It has been found that this type of combination therapy results in unexpected improvement in the treatment of cancer, especially in cancers that would not be expected to be responsive to the DDRi. In some embodiments, the DDRi is a PARP inhibitor (PARPi). In some embodiments, the PARPi is selected from the group comprising: nipaib, niraparib, olaparib, pamiparib, rucaparib (camsylate), talazoparib, veliparib, or an analog thereof. In some embodiments, the DDRi is an

ATM/ATR inhibitor. In some embodiments the ATM/ATR inhibitor is selected from the group comprising 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 embodiments, the PARPi is adavosertib, AZD2811, or an analog thereof. In some embodiments, the DDRi is a WEE1 inhibitor, a

5 Chk1 inhibitor, or a Chk2 inhibitor. In some embodiments, the DDRi is a DNA-dependent protein kinase (DNA-PK) inhibitor. Non-limiting examples of DNA-PK inhibitors include AZD7648, KU-0060648, NU7026, NU7441 (KU-57788), PI-103, PIK-75 HCl, PP121, SF2523, and analogs thereof.

Subjects

10 In some disclosed methods, a therapy (e.g., comprising a therapeutic agent) is administered to a subject. In some embodiments, the subject is a mammal, e.g., a human.

In some embodiments, the subject has received or is receiving another therapy. For example, in some embodiments, the subject has received or is receiving a radioimmunoconjugate. In some

embodiments, the subject has received or is receiving a DNA damage and repair inhibitor (DDRi).

15 In some embodiments, the subject has cancer or is at risk of developing cancer. For example, the subject may have been diagnosed with cancer. The cancer may be a primary cancer or a metastatic cancer. Subjects may have any stage of cancer, e.g., stage I, stage II, stage III, or stage IV with or without lymph node involvement and with or without metastases. Provided compositions may prevent or reduce further growth of the cancer and/or otherwise ameliorate the cancer (e.g., prevent or

20 reduce metastases). In some embodiments, the subject does not have cancer but has been determined to be at risk of developing cancer, e.g., because of the presence of one or more risk factors such as environmental exposure, presence of one or more genetic mutations or variants, family history, etc. In some embodiments, the subject has not been diagnosed with cancer.

In some embodiments, the cancer is a solid tumor.

25 In some embodiments, the solid tumor cancer is 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 embodiments, the cancer is a non-solid (e.g., liquid (e.g., hematologic)) cancer.

Administration and dosage

Effective and lower effective doses

The present disclosure provides combination therapies in which the amounts of each therapeutic may or may not be, on their own, therapeutically effective. For example, provided are methods comprising administering a first therapy and a second therapy in amounts that together are effective to treat or

35 ameliorate a disorder, e.g., cancer. In some embodiments, at least one of the first and second therapy is

administered to the subject in a lower effective dose. In some embodiments, both the first and the second therapies are administered in lower effective doses.

In some embodiments, the first therapy comprises a radioimmunoconjugate and the second therapy comprises a DNA damage response inhibitor (DDRi).

5 In some embodiments, the first therapy comprises a DDRi and the second therapy comprises a radioimmunoconjugate.

10 In some embodiments, therapeutic combinations as disclosed herein are administered to a subject in a manner (e.g., dosing amount and timing) sufficient to cure or at least partially arrest the symptoms of the disorder and its complications. In the context of a single therapy (a "monotherapy"), an amount adequate to accomplish this purpose is defined as a "therapeutically effective amount," an amount of a compound sufficient to substantially improve at least one symptom associated with the disease or a medical condition. The "therapeutically effective amount" typically varies depending on the therapeutic. For known therapeutic agents, the relevant therapeutically effective amounts may be known
15 to or readily determined by those of skill in the art.

For example, in the treatment of cancer, an agent or compound that decreases, prevents, delays, suppresses, or arrests any symptom of the disease or condition would be therapeutically effective. A therapeutically effective amount of an agent or compound is not required to cure a disease or condition but will provide a treatment for a disease or condition such that the onset of the disease or condition is
20 delayed, hindered, or prevented, or the disease or condition symptoms are ameliorated, or the term of the disease or condition is changed or, for example, is less severe or recovery is accelerated in an individual. For example, a treatment may be therapeutically effective if it causes a cancer to regress or to slow the cancer's growth.

The dosage regimen (e.g., amounts of each therapeutic, relative timing of therapies, etc.) that is
25 effective for these uses may depend on the severity of the disease or condition and the weight and general state of the subject. For example, the therapeutically effective amount of a particular composition comprising a therapeutic agent applied to mammals (e.g., humans) can be determined by the ordinarily-skilled artisan with consideration of individual differences in age, weight, and the condition of the mammal. Because certain conjugates of the present disclosure exhibit an enhanced ability to target
30 cancer cells and residualize, the dosage of these compounds can be lower than (e.g., less than or equal to about 90%, 75%, 50%, 40%, 30%, 20%, 15%, 12%, 10%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.1% of) the equivalent dose of required for a therapeutic effect of the unconjugated agent.

Therapeutically effective and/or optimal amounts can also be determined empirically by those of skill in the art. Thus, lower effective doses can also be determined by those of skill in the art.

35 Single or multiple administrations of a composition (e.g., a pharmaceutical composition comprising a therapeutic agent) can be carried out with dose levels and pattern being selected by the treating physician. The dose and administration schedule can be determined and adjusted based on the

severity of the disease or condition in the subject, which may be monitored throughout the course of treatment according to the methods commonly practiced by clinicians or those described herein.

In the disclosed combination therapy methods, the first and second therapies may be administered sequentially or concurrently to a subject. For example, a first composition comprising a first therapeutic agent and a second composition comprising a second therapeutic agent may be administered sequentially or concurrently to a subject. Alternatively or additionally, a composition comprising a combination of a first therapeutic agent and a second therapeutic agent may be administered to the subject.

In some embodiments, the radioimmunoconjugate is administered in a single dose. In some embodiments, the radioimmunoconjugate is administered more than once. When the radioimmunoconjugate is administered more than once, the dose of each administration may be the same or different.

In some embodiments, the DDRi is administered in a single dose. In some embodiments, the DDRi is administered more than once, e.g., at least twice, at least three times, etc. In some embodiments, the DDRi is administered multiple times according to a regular or semi-regular schedule, e.g., once every approximately two weeks, once a week, twice a week, three times a week, or more than three times a week. When the DDRi is administered more than once, the dose of each administration may be the same or different. For example, the DDRi may be administered in an initial dose amount, and then subsequent dosages of the DDRi may be higher or lower than the initial dose amount.

In some embodiments, the first dose of the DDRi is administered at the same time as the first dose of the radioimmunoconjugate. In some embodiments, the first dose of the DDRi is administered before the first dose of radioimmunoconjugate. In some embodiments, the first dose of the DDRi is administered after the first dose of radioimmunoconjugate. In some embodiments, subsequent doses of the DDRi are administered.

In some embodiments, radioimmunoconjugates (or a composition thereof) and DDRis (or a composition thereof) are administered within 28 days (e.g., within 14, 7, 6, 5, 4, 3, 2, or 1 day(s)) of each other.

In some embodiments, radioimmunoconjugates (or a composition thereof) and DDRis (or a composition thereof) are administered within 90 days (e.g., within 80, 70, 60, 50, 40, 30, 20, 10, 5, 4, 3, 2, or 1 day(s)) of each other. In various embodiments the DDRi is administered at the same time as radioimmunoconjugate. In various embodiments, the DDRi is administered multiple times after the first administration of radioimmunoconjugate.

In some embodiments, compositions (such as compositions comprising radioimmunoconjugates) are administered for radiation treatment planning or diagnostic purposes. When administered for

radiation treatment planning or diagnostic purposes, compositions may be administered to a subject in a diagnostically effective dose and/or an amount effective to determine the therapeutically effective dose. In some embodiments, a first dose of disclosed conjugate or a composition (e.g., pharmaceutical composition) thereof is administered in an amount effective for radiation treatment planning, followed
5 administration of a combination therapy including a conjugate as disclosed herein and another therapeutic.

Pharmaceutical compositions comprising one or more agents (e.g., radioimmunoconjugates and/or DDRis) can be formulated for use in accordance with disclosed methods and systems in a variety of
10 drug delivery systems. One or more physiologically acceptable excipients or carriers can also be included in the composition for proper formulation. Examples of suitable formulations are found in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Philadelphia, PA, 17th ed., 1985. For a brief review of methods for drug delivery, see, e.g., Langer (*Science* 249:1527-1533, 1990).

15 *Formulations*

Pharmaceutical compositions may be formulated for parenteral, intranasal, topical, oral, or local administration, such as by a transdermal means, for prophylactic and/or therapeutic treatment. Pharmaceutical compositions can be administered parenterally (e.g., by intravenous, intramuscular, or
20 subcutaneous injection), or by oral ingestion, or by topical application or intraarticular injection at areas affected by the vascular or cancer condition. Examples of additional routes of administration include intravascular, intra-arterial, intratumor, intraperitoneal, intraventricular, intraepidural, as well as nasal, ophthalmic, intrascleral, intraorbital, rectal, topical, or aerosol inhalation administration. Also specifically contemplated are sustained release administration, by such means as depot injections or erodible
25 implants or components. Suitable compositions include compositions comprising include agents (e.g., compounds as disclosed herein) dissolved or suspended in an acceptable carrier, preferably an aqueous carrier, e.g., water, buffered water, saline, or PBS, among others, e.g., for parenteral administration. Compositions may contain pharmaceutically acceptable auxiliary substances to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting
30 agents, or detergents, among others. In some embodiments, compositions are formulated for oral delivery; for example, compositions may contain inert ingredients such as binders or fillers for the formulation of a unit dosage form, such as a tablet or a capsule. In some embodiments, compositions are formulated for local administration; for example, compositions may contain inert ingredients such as solvents or emulsifiers for the formulation of a cream, an ointment, a gel, a paste, or an eye drop.

Compositions may be sterilized, e.g., by conventional sterilization techniques, or sterile filtered. Aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the preparations typically will be between 3 and 11, more preferably between 5 and 9 or between 6 and 8, and most preferably between 6 and 7, such as 6 to 6.5. In some embodiments, compositions in solid form are packaged in multiple single dose units, each containing a fixed amount of the above-mentioned agent or agents, such as in a sealed package of tablets or capsules. In some embodiments, compositions in solid form are packaged in a container for a flexible quantity, such as in a squeezable tube designed for a topically applicable cream or ointment.

Other agents

In some embodiments, disclosed methods further include administering an antiproliferative agent, radiation sensitizer, or an immunoregulatory or immunomodulatory agent.

By “antiproliferative” or “antiproliferative agent,” as used interchangeably herein, is meant any anticancer agent, including those antiproliferative agents listed in Table 2, any of which can be used in combination with a radioimmunoconjugate to treat a condition or disorder. Antiproliferative agents also include organo-platinum derivatives, naphtoquinone and benzoquinone derivatives, chrysophanic acid and anthroquinone derivatives thereof.

By “immunoregulatory agent” or “immunomodulatory agent,” as used interchangeably herein, is meant any immuno-modulator, including those listed in Table 2, any of which can be used in combination with a radioimmunoconjugate.

As used herein, “radiation sensitizer” includes any agent that increases the sensitivity of cancer cells to radiation therapy. Radiation sensitizers may include, but are not limited to, 5-fluorouracil, analogs of platinum (e.g., cisplatin, carboplatin, oxaliplatin), gemcitabine, EGFR antagonists (e.g., cetuximab, gefitinib), farnesyltransferase inhibitors, COX-2 inhibitors, bFGF antagonists, and VEGF antagonists.

Table 2

Alkylating agents	Busulfan dacarbazine ifosfamide hexamethylmelamine thiotepa dacarbazine lomustine cyclophosphamide	Chlorambucil procarbazine altretamine estramustine phosphate mechlorethamine streptozocin temozolomide Semustine
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Table 2		
Platinum agents	spiroplatin tetraplatin ormaplatin iproplatin picoplatin oxaliplatin carboplatin	lobaplatin (Aeterna) satraplatin (Johnson Matthey) BBR-3464 (Hoffmann-La Roche) Miriplatin AP-5280 (Access) cisplatin
Antimetabolites	azacytidine Floxuridine 2-chlorodeoxyadenosine 6-mercaptopurine 6-thioguanine cytarabine 2-fluorodeoxy cytidine methotrexate tomudex fludarabine raltitrexed	trimetrexate deoxycoformycin pentostatin hydroxyurea decitabine (SuperGen) clofarabine (Bioenvision) irofulven (MGI Pharma) DMDC (Hoffmann-La Roche) ethynylcytidine (Taiho) gemcitabine capecitabine
Topoisomerase inhibitors	amsacrine epirubicin etoposide teniposide or mitoxantrone 7-ethyl-10-hydroxy-camptothecin dexrazoxanet (TopoTarget) pixantrone (Novuspharma) rebeccamycin analogue (Exelixis) BBR-3576 (Novuspharma) rubitecan (SuperGen) irinotecan (CPT-11) topotecan	exatecan mesylate (Daiichi) quinamed (ChemGenex) gimatecan (Sigma-Tau) diflomotecan (Beaufour-Ipsen) TAS-103 (Taiho) elsamitucin (Spectrum) Edotecarin Cositecan Belotecan hydroxycamptothecin (SN-38)
Antitumor antibiotics	valrubicin therarubicin idarubicin rubidazole plicamycin porfiromycin mitoxantrone (novantrone) amonafide	azonafide anthrapyrazole oxantrazole losoxantrone Sabarubicin Epirubicin mitoxantrone doxorubicin

Table 2		
Antimitotic agents	colchicine vinblastine vindesine dolastatin 10 (NCI) rhizoxin (Fujisawa) mivobulin (Warner-Lambert) cemadotin (BASF) RPR 109881A (Aventis) TXD 258 (Aventis) epothilone B (Novartis) T 900607 (Tularik) T 138067 (Tularik) cryptophycin 52 (Eli Lilly) vinflunine (Fabre) auristatin PE (Teikoku Hormone) BMS 247550 (BMS) BMS 184476 (BMS) BMS 188797 (BMS) taxoprexin (Protarga) SB 408075 (GlaxoSmithKline) Vinorelbine Trichostatin A	E7010 (Abbott) PG-TXL (Cell Therapeutics) IDN 5109 (Bayer) A 105972 (Abbott) A 204197 (Abbott) LU 223651 (BASF) D 24851 (ASTAMedica) ER-86526 (Eisai) combretastatin A4 (BMS) isohomohalichondrin-B (PharmaMar) ZD 6126 (AstraZeneca) AZ10992 (Asahi) IDN-5109 (Indena) AVLB (Prescient NeuroPharma) azaepothilone B (BMS) BNP-7787 (BioNumerik) CA-4 prodrug (OXiGENE) dolastatin-10 (NIH) CA-4 (OXiGENE) docetaxel vincristine paclitaxel
Aromatase inhibitors	aminoglutethimide atamestane (BioMedicines) letrozole anastrozole	YM-511 (Yamanouchi) formestane exemestane
Thymidylate synthase inhibitors	pemetrexed (Eli Lilly) ZD-9331 (BTG)	nolatrexed (Eximias) CoFactor™ (BioKeys)
DNA antagonists	trabectedin (PharmaMar) glufosfamide (Baxter International) albumin + 32P (Isotope Solutions) thymectacin (NewBiotics)	edotreotide (Novartis) mafosfamide (Baxter International) apaziquone (Spectrum Pharmaceuticals) O6 benzyl guanine (Paligent)
Farnesyltransferase inhibitors	arglabin (NuOncology Labs) lonafarnib (Schering-Plough) BAY-43-9006 (Bayer)	tipifarnib (Johnson & Johnson) perillyl alcohol (DOR BioPharma)
Pump inhibitors	CBT-1 (CBA Pharma) tariquidar (Xenova) MS-209 (Schering AG)	zosuquidar trihydrochloride (Eli Lilly) biricodar dicitrate (Vertex)
Histone acetyltransferase inhibitors	tacedinaline (Pfizer) SAHA (Aton Pharma) MS-275 (Schering AG)	pivaloyloxymethyl butyrate (Titan) depsipeptide (Fujisawa)

Table 2		
Metalloproteinase inhibitors	Neovastat (Aeterna Laboratories) marimastat (British Biotech)	CMT-3 (CollaGenex) BMS-275291 (Celltech)
Ribonucleoside reductase inhibitors	gallium maltolate (Titan) triapine (Vion)	tezacitabine (Aventis) didox (Molecules for Health)
TNF alpha agonists/antagonists	virulizin (Lorus Therapeutics) CDC-394 (Celgene)	revimid (Celgene)
Endothelin A receptor antagonist	atrasentan (Abbott) ZD-4054 (AstraZeneca)	YM-598 (Yamanouchi)
Retinoic acid receptor agonists	fenretinide (Johnson & Johnson) LGD-1550 (Ligand)	alitretinoin (Ligand)
Immuno-modulators	interferon oncophage (Antigenics) GMK (Progenics) adenocarcinoma vaccine (Biomira) CTP-37 (AVI BioPharma) IRX-2 (Immuno-Rx) PEP-005 (Peplin Biotech) synchrovax vaccines (CTL Immuno) melanoma vaccine (CTL Immuno) p21 RAS vaccine (GemVax) MAGE-A3 (GSK) nivolumab (BMS) abatacept (BMS) pembrolizumab (Merck)	dexosome therapy (Anosys) pentrix (Australian Cancer Technology) ISF-154 (Tragen) cancer vaccine (Intercell) norelin (Biostar) BLP-25 (Biomira) MGV (Progenics) β -alethine (Dovetail) CLL therapy (Vasogen) Ipilimumab (BMS), CM-10 (cCam Biotherapeutics) atezolizumab (Genentech)

Table 2		
Hormonal and antihormonal agents	estrogens conjugated estrogens ethinyl estradiol chlortrianisen idenestrol hydroxyprogesterone caproate medroxyprogesterone testosterone testosterone propionate; fluoxymesterone methyltestosterone diethylstilbestrol megestrol bicalutamide flutamide nilutamide	dexamethasone prednisone methylprednisolone prednisolone aminoglutethimide leuprolide octreotide mitotane P-04 (Novogen) 2-methoxyestradiol (EntreMed) arzoxifene (Eli Lilly) tamoxifen toremifene goserelin Leuporelin bicalutamide
Photodynamic agents	talaporfin (Light Sciences) Theralux (Theratechnologies) motexafin gadolinium (Pharmacyclics)	Pd-bacteriopheophorbide (Yeda) Motexafin lutetium hypericin
Kinase Inhibitors	imatinib (Novartis) leflunomide (Sugen/Pharmacia) ZD1839 (AstraZeneca) erlotinib (Oncogene Science) canertinib (Pfizer) squalamine (Genaera) SU5416 (Pharmacia) SU6668 (Pharmacia) ZD4190 (AstraZeneca) ZD6474 (AstraZeneca) vatalanib (Novartis) PKI166 (Novartis) GW2016 (GlaxoSmithKline) EKB-509 (Wyeth) trastuzumab (Genentech) OSI-774 (Tarceva™) CI-1033 (Pfizer) SU11248 (Pharmacia) RH3 (York Medical) Genistein Radicinol Met-MAb (Roche)	EKB-569 (Wyeth) kahalide F (PharmaMar) CEP-701 (Cephalon) CEP-751 (Cephalon) MLN518 (Millenium) PKC412 (Novartis) Phenoxodiol (Novogen) C225 (ImClone) rhu-Mab (Genentech) MDX-H210 (Medarex) 2C4 (Genentech) MDX-447 (Medarex) ABX-EGF (Abgenix) IMC-1C11 (ImClone) Tyrphostins Gefitinib (Iressa) PTK787 (Novartis) EMD 72000 (Merck) Emodin Radicinol Vemurafenib (B-Raf enzyme inhibitor, Daiichi Sankyo)

Table 2

SR-27897 (CCK A inhibitor, Sanofi-Synthelabo) tocladesine (cyclic AMP agonist, Ribapharm) alvocidib (CDK inhibitor, Aventis) CV-247 (COX-2 inhibitor, Ivy Medical) P54 (COX-2 inhibitor, Phytopharm) CapCell™ (CYP450 stimulant, Bavarian Nordic) GCS-100 (gal3 antagonist, GlycoGenesys) G17DT immunogen (gastrin inhibitor, Aphton) efaproxiral (oxygenator, Allos Therapeutics) PI-88 (heparanase inhibitor, Progen) tesmilifene (histamine antagonist, YM BioSciences) histamine (histamine H2 receptor agonist, Maxim) tiazofurin (IMPDH inhibitor, Ribapharm) cilengitide (integrin antagonist, Merck KGaA) SR-31747 (IL-1 antagonist, Sanofi-Synthelabo) CCI-779 (mTOR kinase inhibitor, Wyeth) exisulind (PDE V inhibitor, Cell Pathways) CP-461 (PDE V inhibitor, Cell Pathways) AG-2037 (GARFT inhibitor, Pfizer) WX-UK1 (plasminogen activator inhibitor, Wilex) PBI-1402 (PMN stimulant, ProMetic LifeSciences) bortezomib (proteasome inhibitor, Millennium) SRL-172 (T cell stimulant, SR Pharma) TLK-286 (glutathione S transferase inhibitor, Telik) PT-100 (growth factor agonist, Point Therapeutics) midostaurin (PKC inhibitor, Novartis) bryostatin-1 (PKC stimulant, GPC Biotech) CDA-II (apoptosis promotor, Everlife) SDX-101 (apoptosis promotor, Salmedix) rituximab (CD20 antibody, Genentech) carmustine Mitoxantrone Bleomycin Absinthin Chrysophanic acid Cesium oxides BRAF inhibitors, PD-L1 inhibitors MEK inhibitors bevacizumab angiogenesis inhibitors dabrafenib	ceflatonin (apoptosis promotor, ChemGenex) BCX-1777 (PNP inhibitor, BioCryst) ranpimase (ribonuclease stimulant, Alfacell) galarubicin (RNA synthesis inhibitor, Dong-A) tirapazamine (reducing agent, SRI International) N-acetylcysteine (reducing agent, Zambon) R-flurbiprofen (NF-kappaB inhibitor, Encore) 3CPA (NF-kappaB inhibitor, Active Biotech) seocalcitol (vitamin D receptor agonist, Leo) 131-I-TM-601 (DNA antagonist, TransMolecular) eflornithine (ODC inhibitor, ILEX Oncology) minodronic acid (osteoclast inhibitor, Yamanouchi) indisulam (p53 stimulant, Eisai) aplidine (PPT inhibitor, PharmaMar) gemtuzumab (CD33 antibody, Wyeth Ayerst) PG2 (hematopoiesis enhancer, Pharmagenesis) Immunol™ (triclosan oral rinse, Endo) triacetyluridine (uridine prodrug, Wellstat) SN-4071 (sarcoma agent, Signature BioScience) TransMID-107™ (immunotoxin, KS Biomedix) PCK-3145 (apoptosis promotor, Procyon) doranidazole (apoptosis promotor, Pola) CHS-828 (cytotoxic agent, Leo) trans-retinoic acid (differentiator, NIH) MX6 (apoptosis promotor, MAXIA) apomine (apoptosis promotor, ILEX Oncology) urocidin (apoptosis promotor, Bioniche) Ro-31-7453 (apoptosis promotor, La Roche) brostallicin (apoptosis promotor, Pharmacia) β-lapachone gelonin cafestol kahweol caffeic acid Tyrphostin AG PD-1 inhibitors CTLA-4 inhibitors sorafenib
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Examples

Example 1. In Vivo Synergy Study: [²²⁵Ac]-FPI-1434 + BAY-1895344 – Dosing Schedule 1

An in vivo synergy study was conducted with [²²⁵Ac]-FPI-1434 and BAY-1895344. [²²⁵Ac]-FPI-1434 was given as a single agent at doses sub-optimal for tumor regression (50 nCi) in a Colo-205 (colorectal cancer) xenograft model and (200 nCi) in an A549 (NSCLC) xenograft model. Combination groups (n=5) were dosed with BAY-1895344 (i.p.) 2 days on, 5 days off, using a 20 mg/kg dose for 28 days. The first dose of BAY-1895344 was administered 24 hours following [²²⁵Ac]-FPI-1434 administration. See Figure 1.

Relative tumor volume was evaluated up to 28 days after administration. In the both Colo-205 xenograft model and the A549 xenograft model, BAY-1895344 alone did not demonstrate any reduction in reduction in tumor volume over time relative to Vehicle controls. In both models, treatment with [²²⁵Ac]-FPI-1434 alone demonstrated significant reduction in tumor volume relative to Vehicle controls and treatment with BAY-1895344 alone. There did not appear to be any additional benefit, when [²²⁵Ac]-FPI-1434 and BAY-1895344 were administered as a combination therapy using the dosing schedule in Figure 1 as compared to either treatment being administered alone. See Figures 2a and 2b.

Example 2. In Vivo Synergy Study: FPI-1434 + BAY-1895344 – Dosing Schedule 2

An in vivo synergy study was conducted with [²²⁵Ac]-FPI-1434 and BAY-1895344 using a second dosing schedule. FPI-1434 was given as a single agent at doses sub-optimal for tumor regression (50 nCi) in a Colo-205 (colorectal cancer) xenograft model. Combination groups (n=5) were dosed with BAY-1895344 three times a week starting with a 40 mg/kg dose. The dose was gradually reduced to 20 mg/kg due to transient animal somnolence at the higher doses. The first dose of BAY-1895344 was administered 24 hours following FPI-1434 administration. See Figure 3.

Relative tumor volume was evaluated up to 28 days after administration. Both [²²⁵Ac]-FPI-1434 and BAY-1895344 alone demonstrated some reduction in tumor volume over time, with [²²⁵Ac]-FPI-1434 being more effective at reducing tumor volume compared to BAY-1895344 alone. When [²²⁵Ac]-FPI-1434 and BAY-1895344 were administered as a combination therapy using the dosing schedule in Figure 3, animals demonstrated significantly lower tumor volumes when compared with either treatment alone. See Figure 4.

Example 3. In Vivo Efficacy of Olaparib as a Single Agent

An in vivo efficacy study was conducted with olaparib alone as a single agent. Olaparib was given as a single agent at different doses in a Colo-205 (colorectal cancer) xenograft model and in an A549 (NSCLC) xenograft model. Groups of animals (n=5) were dosed with olaparib (i.p.) 5 days on, 2 days off using 10-100 mg/kg doses. See Figure 5.

Olaparib showed modest efficacy as a single agent in both models (Figure 6A and 6B). There did not appear to be a dose response for either model, and immunohistochemical analysis of γ -H2AX foci showed no increase in DSB formation after olaparib treatment.

Example 4. In Vivo Synergy Study: FPI-1434 + Olaparib – Dosing Schedule 1

- 5 An in vivo synergy study was conducted with [^{225}Ac]-FPI-1434 and olaparib. [^{225}Ac]-FPI-1434 was given as a single agent at doses sub-optimal for tumor regression (50 nCi) in a Colo-205 (colorectal cancer) xenograft model and (200 nCi) in an A549 (NSCLC) xenograft model. Combination groups (n=5) were dosed with olaparib (i.p.) 5 days on, 2 days off, using a 50 mg/kg dose for 28 days. Animals were pre-dosed with olaparib 3 times prior to the [^{225}Ac]-FPI-1434 administration. See Figure 7.
- 10 Relative tumor volume was evaluated up to 28 days after administration. In the Colo-205 xenograft model, both [^{225}Ac]-FPI-1434 and olaparib alone demonstrated some reduction in tumor volume over time, with [^{225}Ac]-FPI-1434 being more effective at reducing tumor volume compared to olaparib alone. There did not appear to be any additional benefit, when [^{225}Ac]-FPI-1434 and olaparib were administered as a combination therapy using the dosing schedule in Figure 7 as compared to either treatment being
- 15 administered alone. See Figure 8a.

In the A549 xenograft model, there was no apparent difference in tumor volume over time with treatment of olaparib alone when compared to animals who had received no treatment. [^{225}Ac]-FPI-1434 had significantly reduced tumor volume when compared to vehicle treated animals, and olaparib treated animals. There did not appear to be any addition benefit, when [^{225}Ac]-FPI-1434 and olaparib were

20 administered as a combination therapy using the dosing schedule in Figure 7 as compared to either treatment being administered alone. See Figure 8b.

Example 5. In Vivo Synergy Study: FPI-1434 + Olaparib – Dosing Schedule 2

- An in vivo synergy study was conducted with [^{225}Ac]-FPI-1434 and olaparib using a second dosing schedule. FPI-1434 was given as a single agent at doses sub-optimal for tumor regression (50 nCi) in a
- 25 Colo-205 (colorectal cancer) xenograft model. Combination groups (n=5) were dosed with olaparib (i.p.) 5 days on, 2 days off, using a 50 mg/kg dose for 28 days. The first dose of olaparib was administered 24 hours following FPI-1434 administration. See Figure 9.

Relative tumor volume was evaluated up to 28 days after administration. Both [^{225}Ac]-FPI-1434 and olaparib alone demonstrated significant reduction in tumor volume over time, with [^{225}Ac]-FPI-1434 being

30 more effective at reducing tumor volume compared to olaparib alone. When [^{225}Ac]-FPI-1434 and olaparib were administered as a combination therapy using the dosing schedule in Figure 9, animals demonstrated significantly lower tumor volumes when compared with either treatment alone. See Figure 10.

Example 6. In vivo synergy study: FPI-1434 + olaparib combination therapy at multiple dose levels

An in vivo study was conducted with [^{225}Ac]-FPI-1434 and olaparib in a Colo-205 (colorectal cancer) xenograft model, with [^{225}Ac]-FPI-1434 administered at a dose of 20 nCi, 50 nCi, or 100 nCi. In combination groups (n=5), animals were dosed with olaparib (i.p.) starting at 24 hours after [^{225}Ac]-FPI-1434 administration according to a 5 days on, 2 days off schedule using 25 or 50 mg/kg doses until day 30 after [^{225}Ac]-FPI-1434 administration ("day 0"). See Figure 11.

Relative tumor volume was evaluated at various time points after administration. Figure 12 shows results using lower effective doses of [^{225}Ac]-FPI-1434 (20 nCi) and olaparib (25 mg/kg). Whereas no or limited therapeutic effect was observed with either [^{225}Ac]-FPI-1434 or olaparib alone, animals that received the combination therapy demonstrated significantly lower tumor volumes when compared with animals that received either treatment alone. Figure 13A-13C show results using 20 nCi (Figure 13A), 50 nCi (Figure 13B), or 100 nCi (Figure 13C) [^{225}Ac]-FPI-1434 with olaparib (25 mg/kg or 50 mg/kg). The strongest combination effects were observed at the lowest single agent doses. See Figure 13A.

Thus, the present Example demonstrates that the combination of [^{225}Ac]-FPI-1434 and olaparib, each at lower effective doses, resulted in a synergistic efficacy.

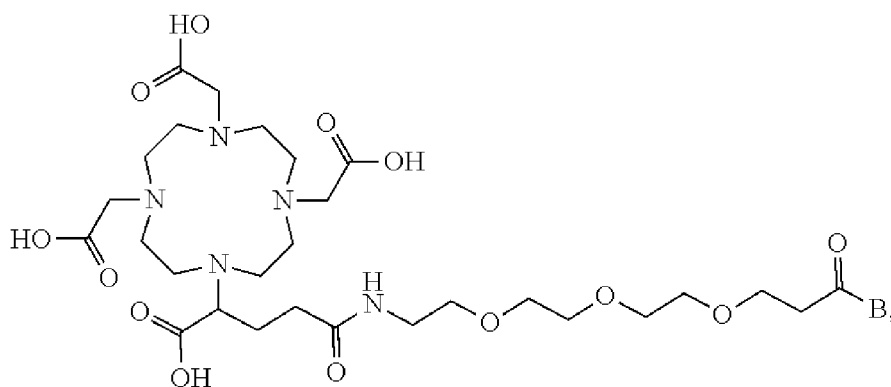
Equivalents/ other embodiments

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

1. A method for treating or ameliorating cancer, said method 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.
2. The method of claim 1, said method comprising administering to a mammal a DDRi, wherein the mammal has received or is receiving a radioimmunoconjugate.
3. The method of claim 1 or 2, wherein the DDRi is administered in a lower effective dose.
4. The method of any one of claims 1-3, wherein the radioimmunoconjugate is administered in a lower effective dose.
5. The method of claim 1, wherein the radioimmunoconjugate comprises (i) a targeting moiety, (ii) a linker, and (iii) a chelating moiety or a metal complex of a chelating moiety.
6. The method of claim 5, wherein the targeting moiety is capable of binding to a tumor-associated antigen.
7. The method of claim 6, wherein the tumor-associated antigen is a tumor-specific antigen.
8. The method of claim 6 or 7, wherein the targeting moiety is an antibody or an antigen-binding fragment thereof.
9. The method of claim 8, wherein the antibody or antigen-binding fragment thereof is an IGF1-R antibody or an antigen-binding fragment thereof.
10. The method of claim 8, wherein the antibody or antigen-binding fragment thereof is an endosialin (TEM-1) antibody or an antigen-binding fragment thereof.
11. The method of any one of claims 5-10, wherein the radioimmunoconjugate comprises a metal complex of a chelating moiety.

12. The method of claim 11, wherein the metal complex comprises a radionuclide.
13. The method of claim 12, wherein the radionuclide is an alpha emitter.
14. The method of claim 13, wherein the radionuclide is 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).
15. The method of claim 14, wherein the radionuclide is ^{225}Ac .
16. The method of any one of claims 5-15, wherein the radioimmunoconjugate comprises the following structure:



wherein B is the targeting moiety.

17. The method of any one of claims 1-16, wherein the DDRi is a PARP inhibitor.
18. The method of claim 17, wherein the PARP inhibitor is a small molecule PARP inhibitor.
19. The method of claim 18, wherein the small molecule PARP inhibitor is selected from the group consisting of niparib, niraparib, olaparib, talazoparib, pamiparib, rucaparib (camsylate), and veliparib, or an analog thereof.
20. The method of claim 19, wherein the small molecule PARP inhibitor is olaparib or an analog thereof.
21. The method of any one of claims 1-16, wherein the DDRi is an ATR inhibitor.
22. The method of claim 21, wherein the ATR inhibitor is a small molecule ATR inhibitor.

23. The method of claim 22, wherein the small molecule 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.
24. The method of claim 23, wherein the ATR inhibitor is BAY-1895344 or an analog thereof.
25. The method of any one of claims 1-16, wherein the DDRi is a WEE1 inhibitor, a Chk1 inhibitor, or a Chk2 inhibitor.
26. The method of any one of claims 1-16, wherein the DDRi is a DNA-protein kinase (DNA-PK) inhibitor.
27. The method of any one of claims 1-26, wherein the mammal is a human.
28. The method of any one of claims 1-27, wherein the mammal is diagnosed with cancer.
29. The method of any one of claims 1-28, wherein 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.
30. The method of any one of claims 1-29, wherein the mammal has at least one solid tumor.
31. The method of any one of claims 1-30, wherein said administering results in a therapeutic effect.
32. The method of claim 31, wherein said therapeutic effect comprises a decrease in tumor volume, a stable tumor volume, or a reduced rate of increase in tumor volume.
33. The method of claim 31 or 32, wherein said therapeutic effect comprises a decreased incidence of recurrence or metastasis.

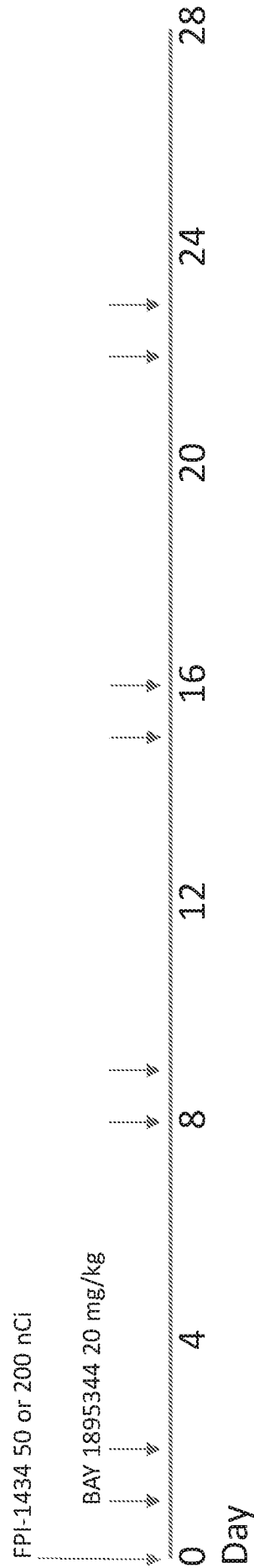


Figure 1

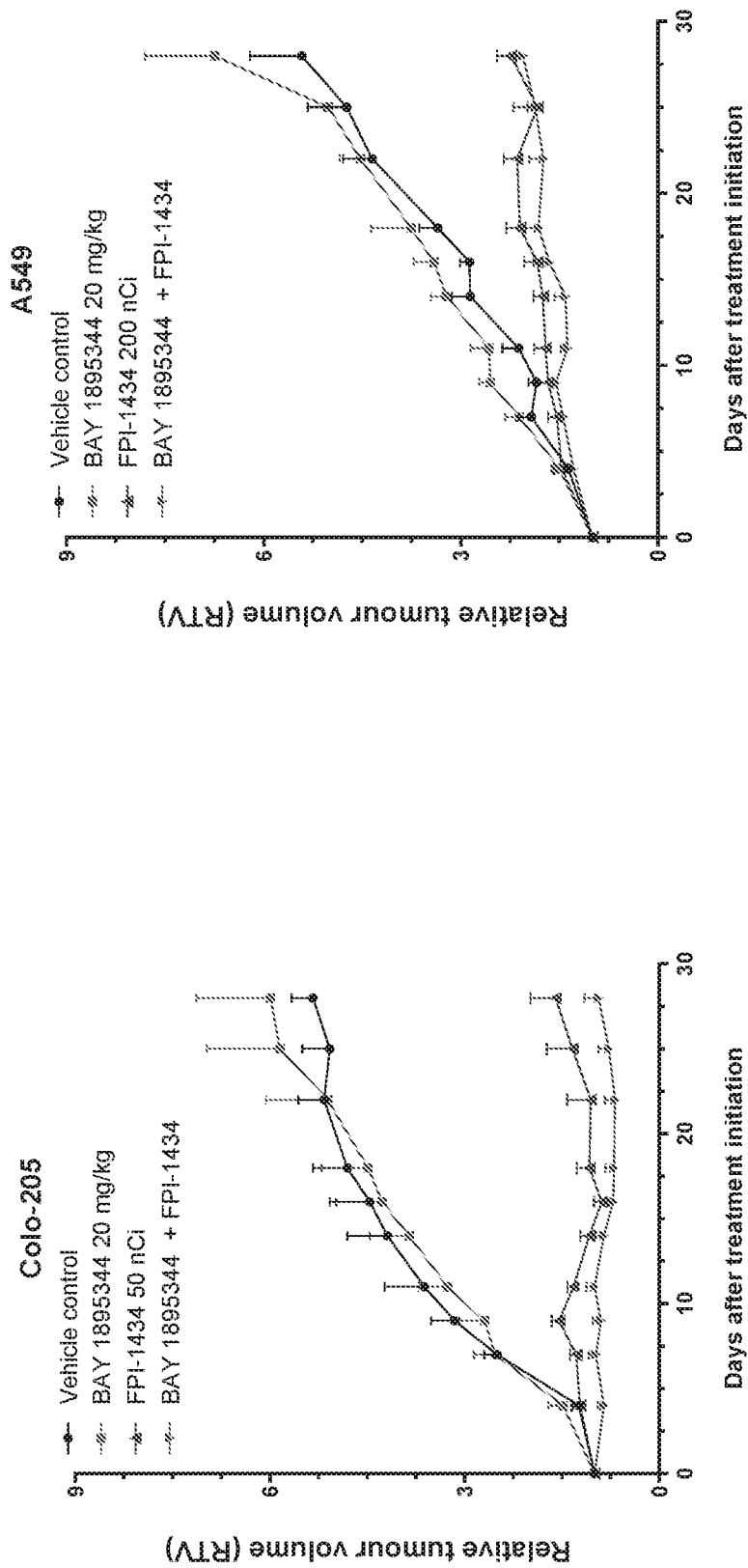


Figure 2B

Figure 2A

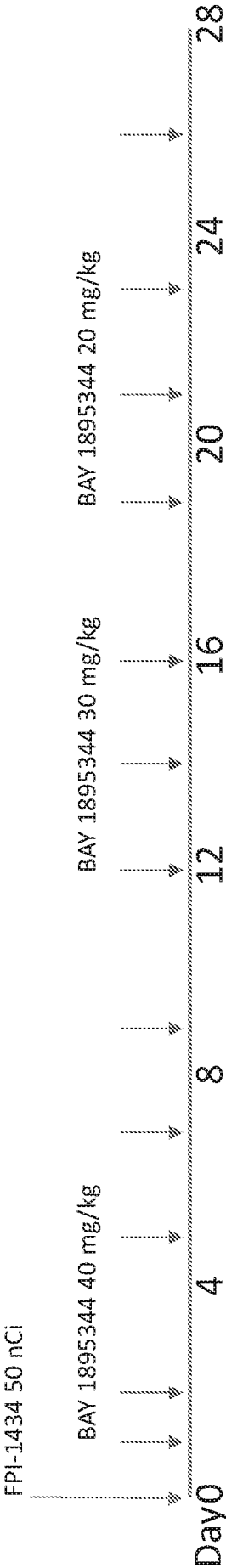


Figure 3

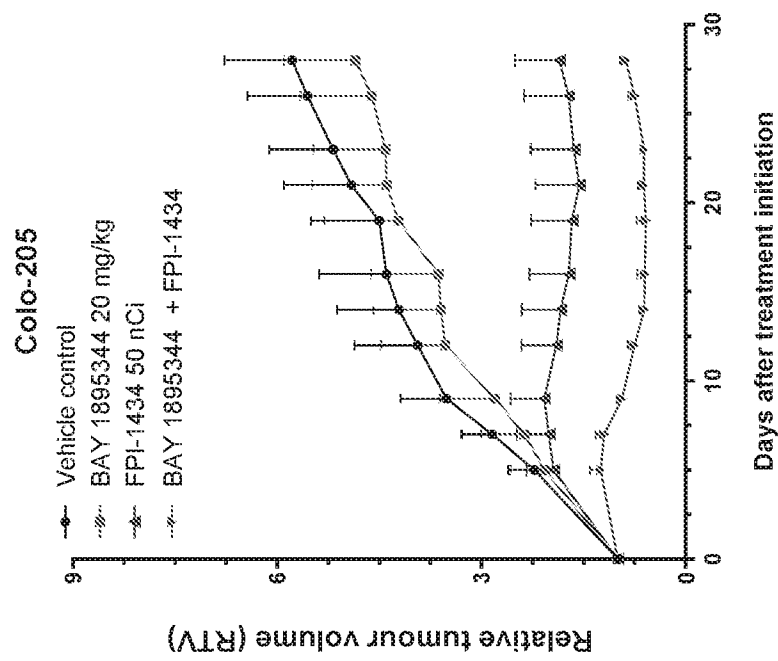


Figure 4

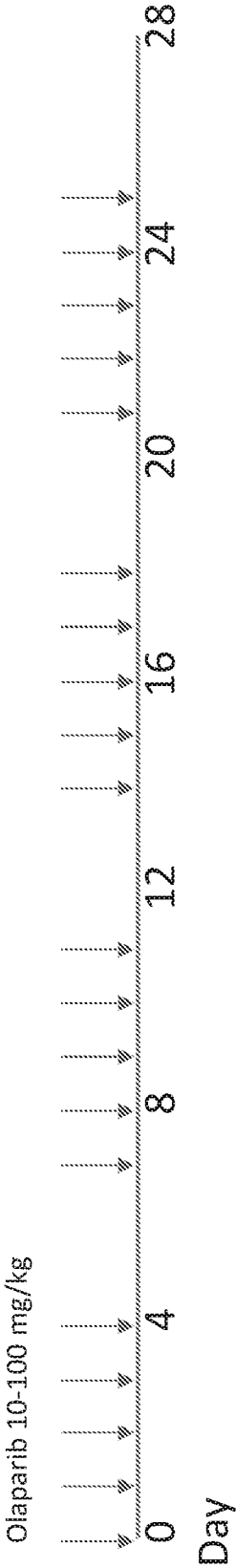


Figure 5

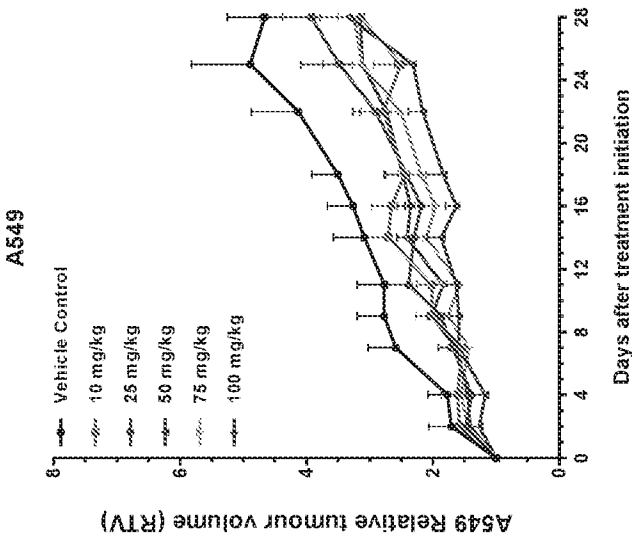


Figure 6B

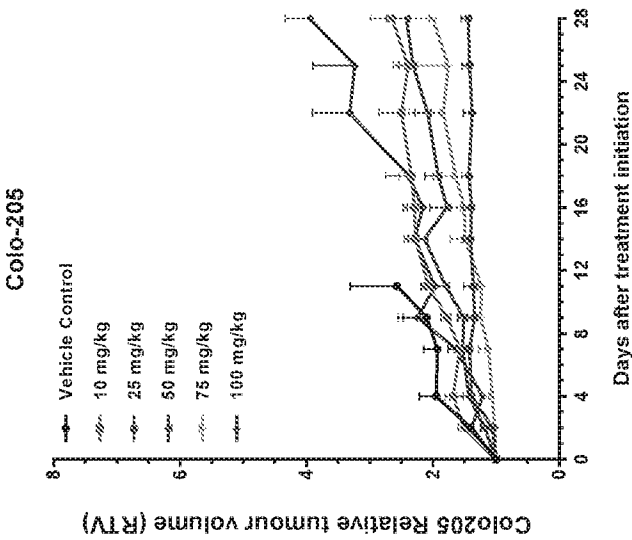


Figure 6A

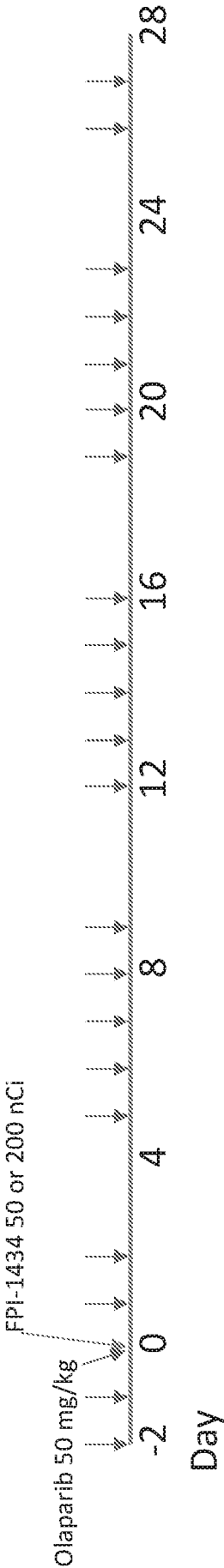


Figure 7

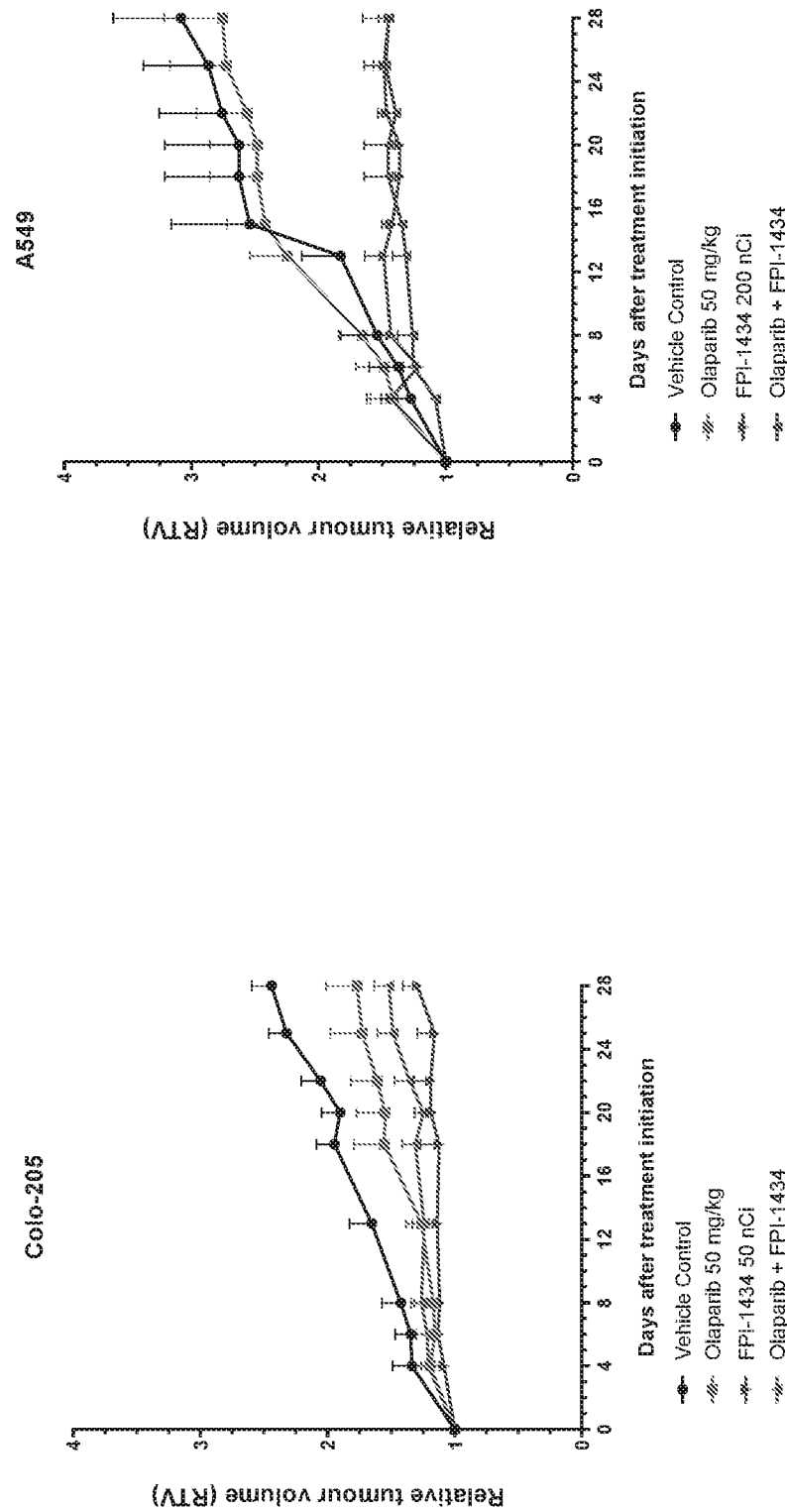


Figure 8A

Figure 8B

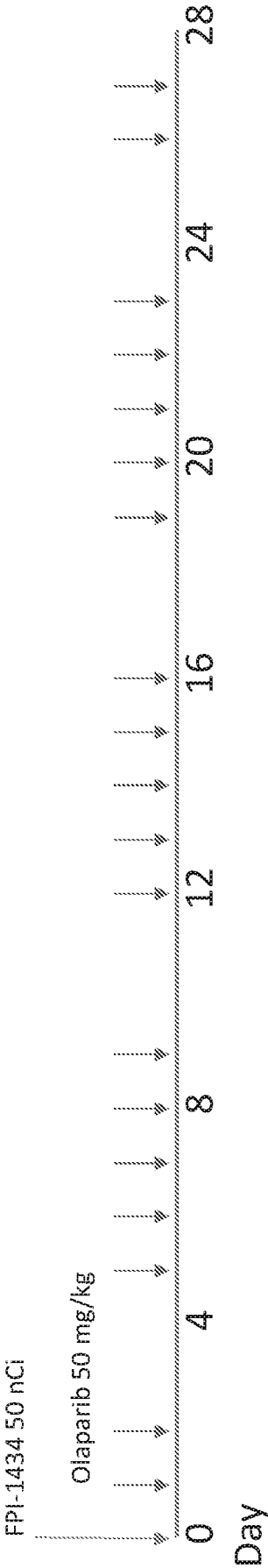


Figure 9

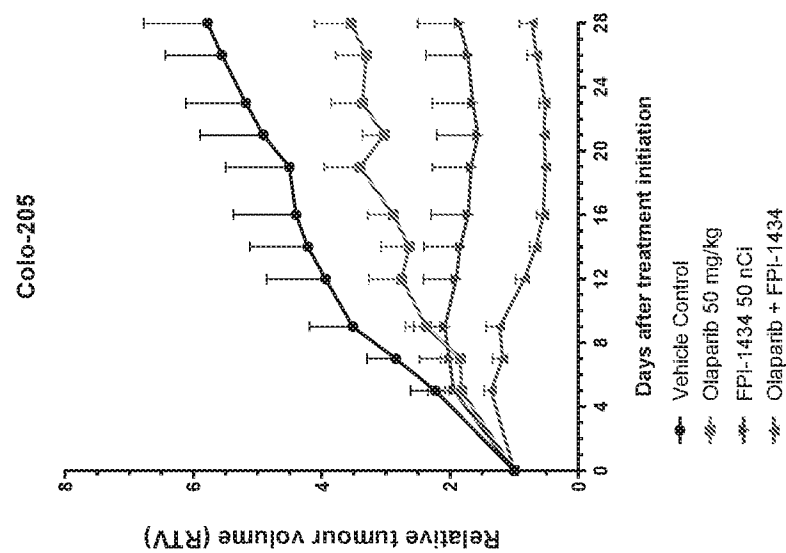


Figure 10

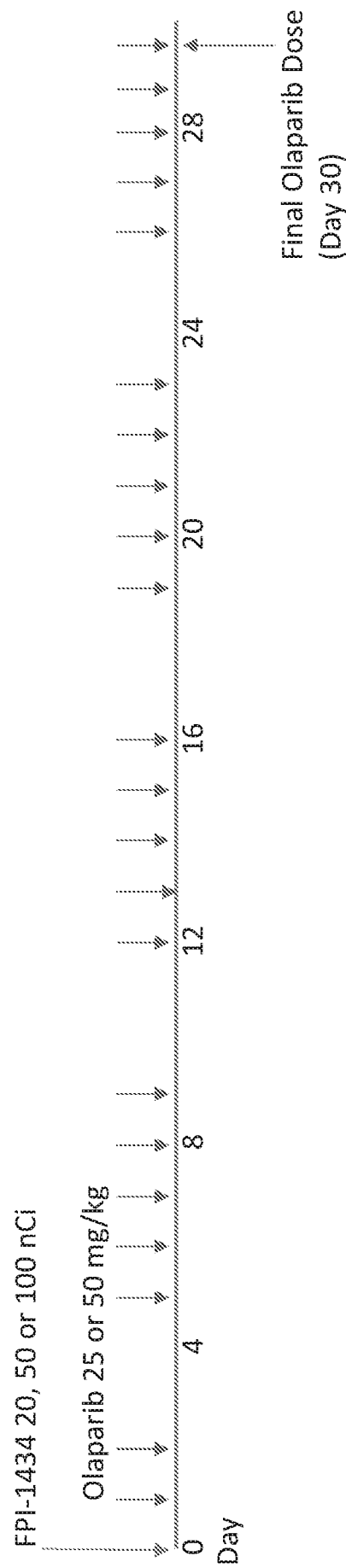


Figure 11

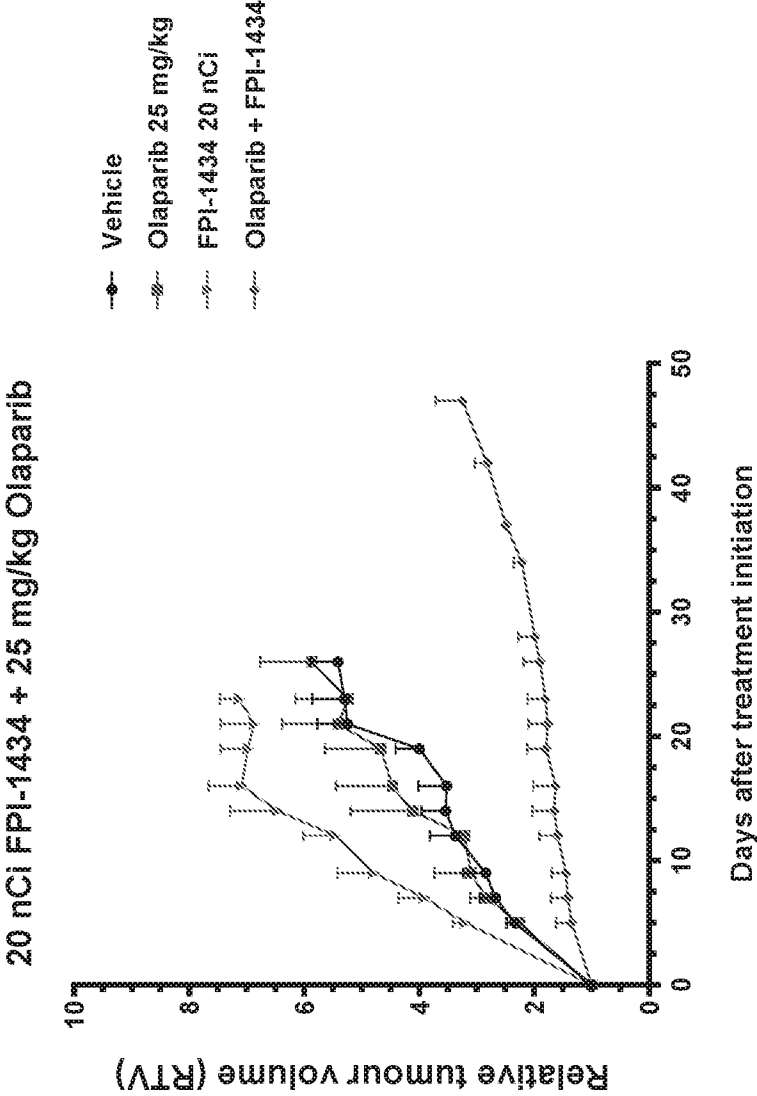


Figure 12

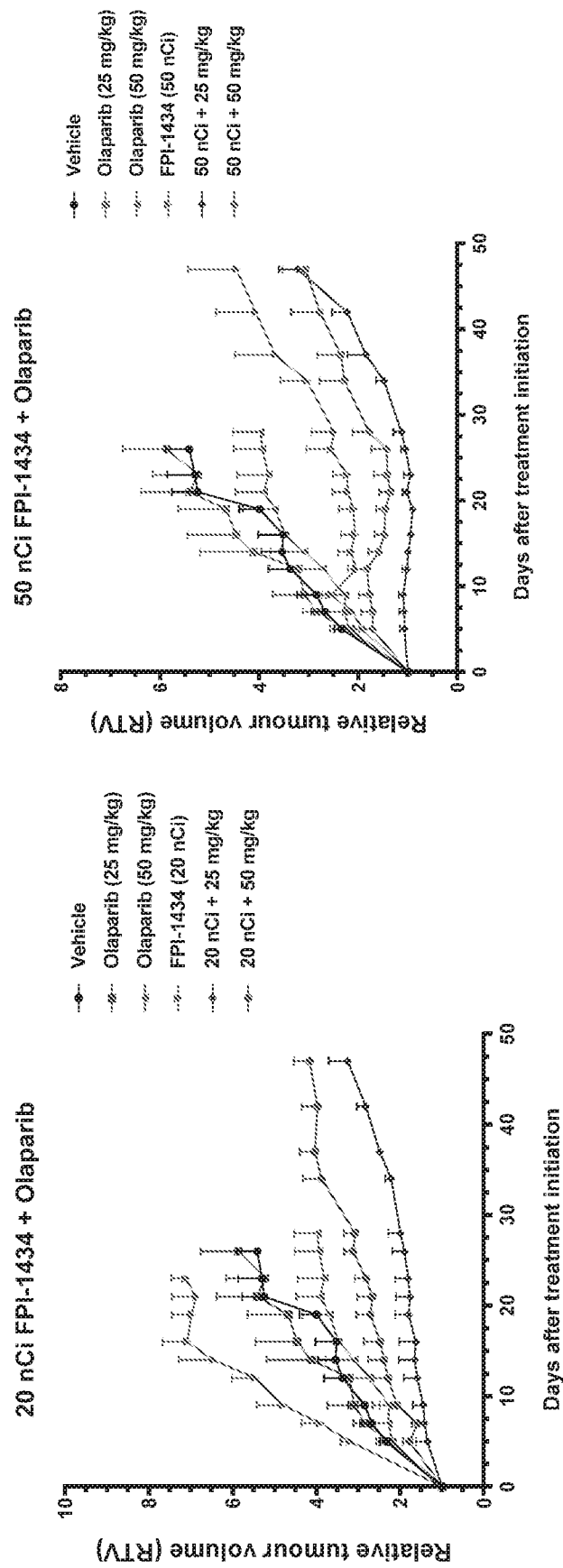


Figure 13B

Figure 13A

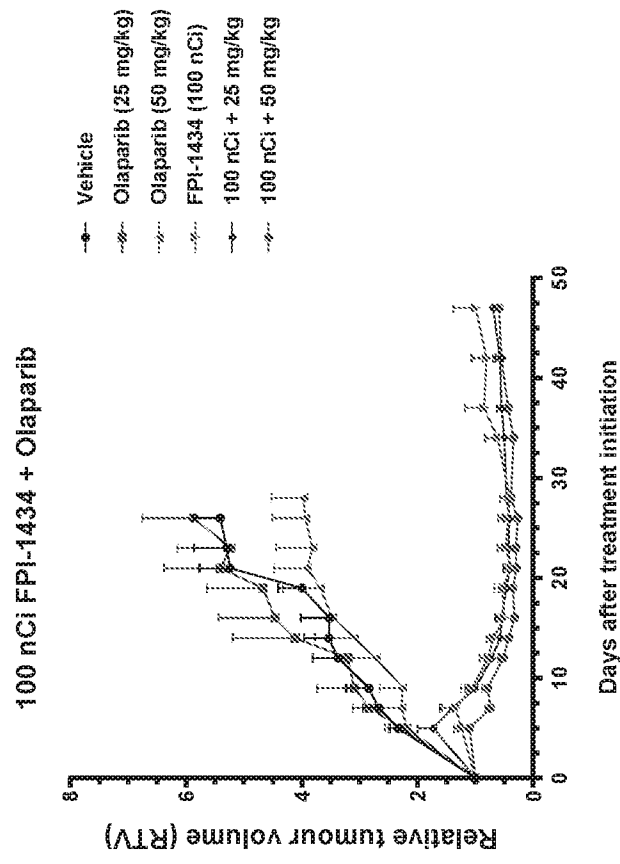


Figure 13C

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2019/001292

A. CLASSIFICATION OF SUBJECT MATTER

IPC: *A61K 51/10* (2006.01), *A61K 31/502* (2006.01), *A61K 31/5377* (2006.01), *A61P 35/00* (2006.01), *A61P 35/04* (2006.01), *C07D 237/32* (2006.01) *C07D 471/04* (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Not searched by classification

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

Canadian Patent Database, Scopus, Google Scholar, Google Patent

Keywords: DNA damage inhibition, ATR kinase inhibitor, BAY 1895344, tumor, cancer, targeted alpha therapy, radioimmunoconjugate, Ac225, antibody, authors names, Fusion Pharmaceuticals

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, Y	WO2018153975A1 (CUTHBERTSON A.) 30 August 2018 (30-08-2018)	1 - 33
Y	FUSION PHARMACEUTICALS, "A Phase 1 Study of [225Ac]-FPI-1434 Injection". ClinicalTrial.gov, 19 November 2018 (19-11-2018), [online] [retrieved on 13 April 2020 (13-04-2020)]. Retrieved from the Internet: < https://clinicaltrials.gov/ct2/show/NCT03746431 >	1 - 33
Y	WENGER et AL, "ATR inhibitor BAY 1895344 shows potent anti-tumor efficacy in monotherapy and strong combination potential with the targeted alpha therapy Radium-223 dichloride in preclinical tumor models". AACR Annual Meeting 2017, July 2017 (07-2017), Vol. Vol. 77, Is.13 Supplement, pp. Abstract 836, (abstract) [online] [retrieved on 13 April 2020 (13-04-2020)]. Retrieved from the Internet: < https://cancerres.aacrjournals.org/content/77/13_Supplement/836 >	1 - 33

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* "A" "D" "E" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance document cited by the applicant in the international application earlier application or patent but published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	"T" "X" "Y" "&"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family
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Date of the actual completion of the international search
13 April 2020 (13-04-2020)

Date of mailing of the international search report
30 April 2020 (30-04-2020)

Name and mailing address of the ISA/CA
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Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 819-953-2476

Authorized officer

Henrietta Bor (819) 639-7761

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/IB2019/001292

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2018153975A1	30 August 2018 (30-08-2018)	CA3054248A1 EP3585436A1 TW201840341A US2020016283A1	30 August 2018 (30-08-2018) 01 January 2020 (01-01-2020) 16 November 2018 (16-11-2018) 16 January 2020 (16-01-2020)