

COMBINATION THERAPY USING PSMA-TARGETED
RADIOPHARMACEUTICALS AND AN INHIBITOR OF PI3K, AKT,
AND/OR MTOR

FIELD OF THE INVENTION

5 The invention relates to combinations comprising PSMA I&T and an inhibitor of PI3K, AKT, and/or mTOR for the treatment of a disease, preferably a cancer, more preferably a prostate cancer.

RELATED ART

10 Prostate cancer (PCa) is the second most prevalent cancer in men worldwide and the sixth leading cause of death in men. Ilic, D. *et al.*, *Cochrane Database of Systematic Reviews*, 2013, Issue 1. Art. No.: CD004720.

15 Prostate-specific membrane antigen (PSMA) is a well-established target for nuclear imaging and therapy of PCa. Chatalic *et al.*, *Theranostics*, 2016, 6(6), 849-861. Compared to healthy human prostate tissue, in almost all PCa tumors, the expression of PSMA is 10–80 fold higher. Baur *et al.*, *Pharmaceuticals*, 2014, 7, 517-529. PSMA is a peptidase that catalyzes the hydrolysis of N-acetyl-L-aspartyl-L-glutamate (NAAG) into the corresponding N-acetyl-L-aspartate (NAA) and L-glutamate. *Id.* Based on the chemical structure of NAAG, several glutamate-urea-glutamate-based peptides bearing a 2-[3-(1,3-dicarboxypropyl)-ureido]pentanedioic acid (DUPA) moiety have been developed. *Id.* Molecules bearing a
20 DUPA fragment showed high affinity and specific binding to PSMA, as demonstrated in binding studies using PSMA-expressing LNCaP cell lines. *Id.*

 DUPA-bearing fragments can be further conjugated to a dodecane tetraacetic acid (DOTA) fragment capable of chelating a radionuclide. Such DUPA-DOTA containing molecules include PSMA-11, PSMA-617, and PSMA-I&T. Chatalic 2016. Radiolabeled
25 small-molecule PSMA inhibitors comprising DUPA and DOTA fragments are known candidates for PCa theranostics because they rapidly and efficiently localize in tumor lesions. *Id.*

 Despite the use of PSMA-targeted, radiolabeled molecules, morbidity and mortality remain unmet challenges for prostate cancer patients. Thus there is a need for effective
30 treatments of prostate cancer.

SUMMARY OF THE INVENTION

As set forth in the Detailed Description below, the inventive kits of parts, compositions and combinations are effective for the treatment of cancers such as prostate cancer.

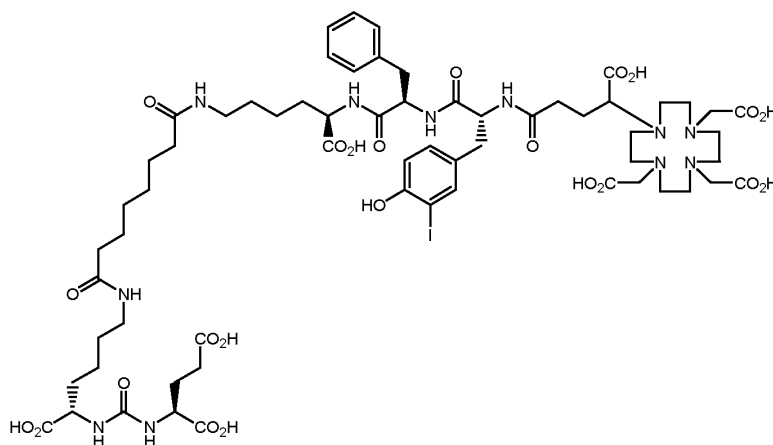
Without wishing to be bound by theory, treatment of cancer cells (e.g., prostate cancer cells) with an inhibitor of PI3K, AKT, and/or mTOR can metabolically exhaust the cancer cells. The addition of the PSMA I&T, preferably a PSMA I&T chelated to a radionuclide such as ^{161}Tb or ^{177}Lu , can further damage the DNA of the cancer cells, causing additional cell death. Thus, in preferred embodiments, the inventive combinations can act synergistically to treat cancers such as prostate cancer.

In one aspect, the present disclosure provides a kit of parts comprising:

- (i) a PSMA-targeted radiopharmaceutical; and
- (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a kit of parts comprising:

- (i) Compound A:



Compound A; and

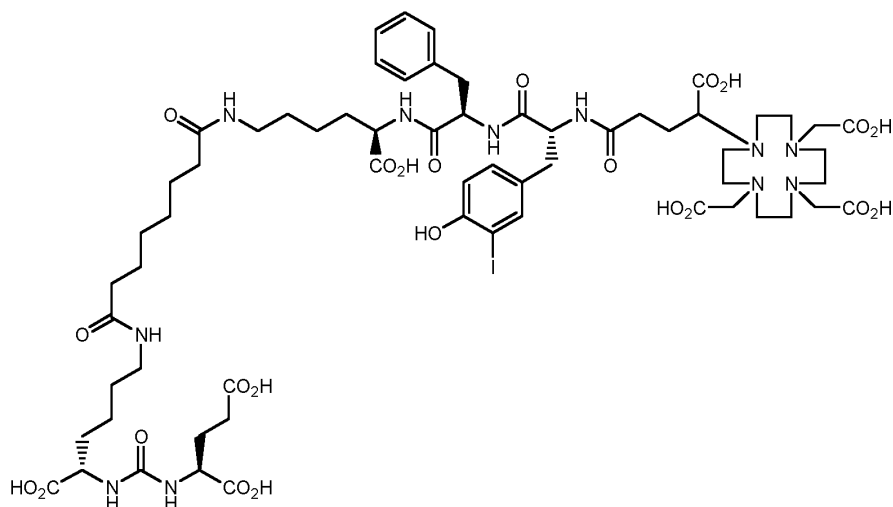
- (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present disclosure provides a composition comprising:

- (i) a PSMA-targeted radiopharmaceutical; and
- (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a composition comprising:

- (i) Compound A:



Compound A; and

(ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention comprises a combination comprising:

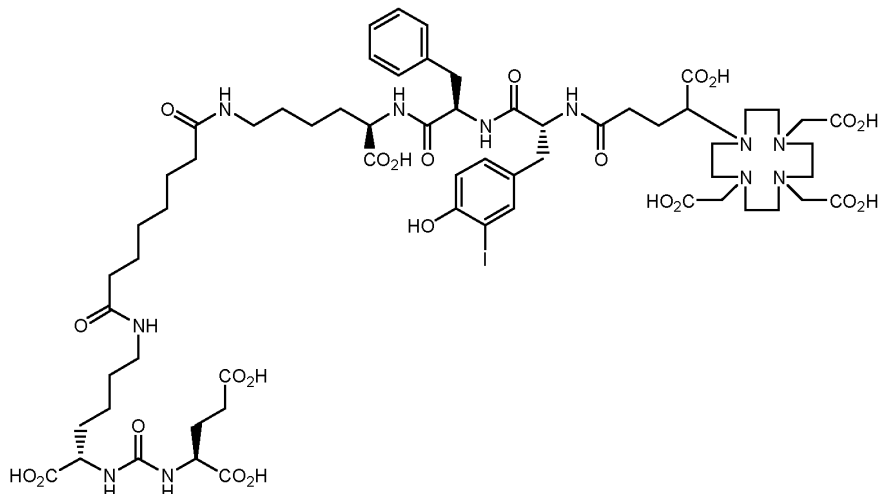
- 5 (i) a composition comprising a PSMA-targeted radiopharmaceutical; and
- (ii) a composition comprising an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention comprises a combination for use in a method of treating a cancer in a subject, said combination comprising:

- 10 (i) a composition comprising a PSMA-targeted radiopharmaceutical; and
- (ii) a composition comprising an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a combination comprising:

- (i) a composition comprising Compound A:



Compound A; and

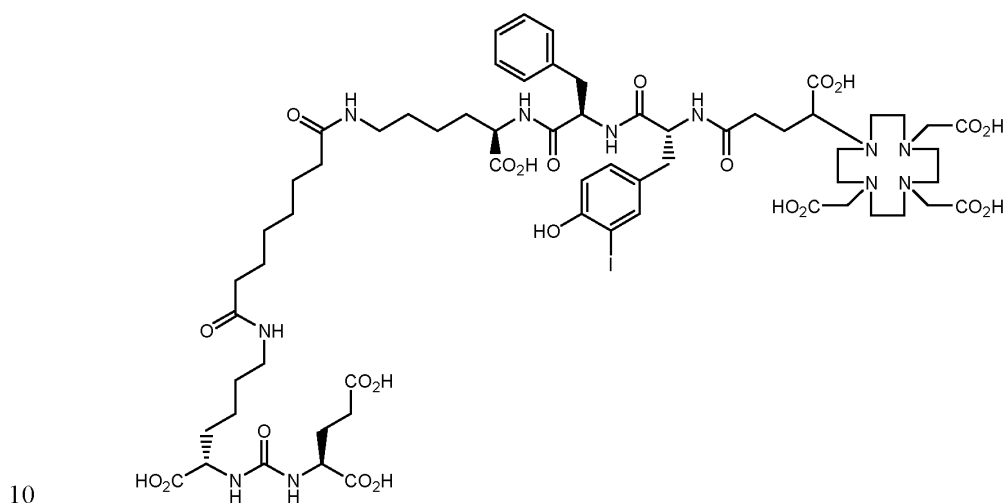
(ii) a composition comprising an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention comprises a combination for use in a method of treating a cancer in a subject, said combination comprising:

- 5 (i) a PSMA-targeted radiopharmaceutical; and
(ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, said combination comprising:

- (i) Compound A:



Compound A; and

- (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a method of treating a cancer in a subject in need thereof, the method comprising: administering to said subject a therapeutically effective amount of (i) a PSMA-targeted radiopharmaceutical; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

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In one aspect, the present disclosure provides an inhibitor of PI3K, AKT, and/or mTOR for use in a method of treating a cancer; wherein said inhibitor of PI3K, AKT, and/or mTOR is administered in combination with a PSMA-targeted radiopharmaceutical.

20 In one aspect, the present disclosure provides a PSMA-targeted radiopharmaceutical for use in a method of treating a cancer; wherein said PSMA-targeted radiopharmaceutical is administered in combination with an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides the use of a combination in the

manufacture of a medicament for treating a cancer, preferably a prostate cancer, wherein said combination comprises: (i) a PSMA-targeted radiopharmaceutical; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

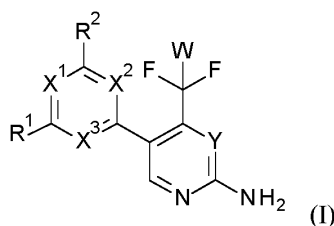
5 In some embodiments, said PSMA-targeted radiopharmaceutical comprises a DUPA targeting group.

In some embodiments, said PSMA-targeted radiopharmaceutical is selected from Compound A, PSMA-617, and PSMA-11.

10 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is a dual PI3K/mTOR inhibitor.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is selected from the group consisting of Compound 1* and Compound 2.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is a compound of Formula (I):



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wherein:

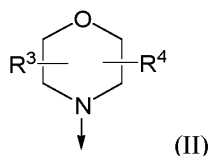
X^1 , X^2 and X^3 are, independently of each other, N or CH; with the proviso that at least two of X^1 , X^2 and X^3 are N;

Y is N or CH;

20 W is H or F; with the proviso that when W is F, then X^1 , X^2 and X^3 are N;

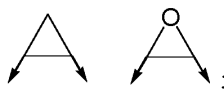
R^1 and R^2 are independently of each other

(i) a morpholinyl of formula (II)



25 wherein the arrow denotes the bond in formula (I); and wherein R^3 and R^4 are independently of each other H, C₁-C₃alkyl optionally substituted with one or two OH, C₁-C₂fluoroalkyl, C₁-C₂alkoxy, C₁-C₂alkoxyC₁-C₃alkyl, CN, or C(O)O-C₁-C₂alkyl; or R^3 and R^4

form together a bivalent residue $-R^5R^6-$ selected from C_1-C_3 alkylene optionally substituted with 1 to 4 F, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures



wherein the arrows denote the bonds in formula (II); or

- 5 (ii) a saturated 6-membered heterocyclic ring Z selected from thiomorpholinyl and piperazinyl, optionally substituted by 1 to 3 R^7 ; wherein R^7 is independently at each occurrence C_1-C_3 alkyl optionally substituted with one or two OH, C_1-C_2 fluoroalkyl, C_1-C_2 alkoxy C_1-C_3 alkyl, C_3-C_6 cycloalkyl; or two R^7 substituents form together a bivalent residue $-R^8R^9-$ selected from C_1-C_3 alkylene optionally substituted with 1 to 4 F, $-CH_2-O-CH_2-$ or $-O-CH_2CH_2-$
- 10 O-;

with the proviso that at least one of R^1 and R^2 is a morpholinyl of formula II;

and prodrugs, metabolites, tautomers, solvates and pharmaceutically acceptable salts thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is bimiralisib, or a

15 pharmaceutically acceptable salt thereof.

In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to a radionuclide.

In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to ^{161}Tb .

20 In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to ^{161}Tb ; and wherein said inhibitor of PI3K, AKT, and/or mTOR is bimiralisib.

In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to ^{177}Lu .

In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to

25 ^{177}Lu ; and wherein said inhibitor of PI3K, AKT, and/or mTOR is bimiralisib.

In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to ^{161}Tb or ^{177}Lu .

In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to ^{161}Tb or ^{177}Lu ; and wherein said inhibitor of PI3K, AKT, and/or mTOR is bimiralisib.

30 In one aspect, the present disclosure provides a kit of parts or a composition as described herein, for use in therapy.

In one aspect, the present disclosure provides a kit of parts, a composition, or a

combination as described herein, for use in the treatment of a cancer. In one aspect, the disclosure provides a method of treatment of cancer in a subject in need thereof.

In some embodiments, said cancer is prostate cancer.

5 In some embodiments, said cancer is prostate cancer, wherein said PSMA-targeted radiopharmaceutical is Compound A, wherein said Compound A is chelated to ^{161}Tb ; and wherein said compound capable of inhibiting PI3K, AKT, and/or mTOR is bimiralisib.

In some embodiments, said cancer is prostate cancer, wherein said PSMA-targeted radiopharmaceutical is Compound A, wherein said Compound A is chelated to ^{177}Lu ; and wherein said compound capable of inhibiting PI3K, AKT, and/or mTOR is bimiralisib.

10 In some embodiments, said cancer is prostate cancer, wherein said PSMA-targeted radiopharmaceutical is Compound A, wherein said Compound A is chelated to ^{161}Tb or ^{177}Lu ; and wherein said compound capable of inhibiting PI3K, AKT, and/or mTOR is bimiralisib.

In some embodiments, said cancer is castration-resistant prostate cancer, wherein said PSMA-targeted radiopharmaceutical is Compound A, wherein Compound A is chelated to ^{161}Tb ; and wherein said compound capable of inhibiting PI3K, AKT, and/or mTOR is bimiralisib.

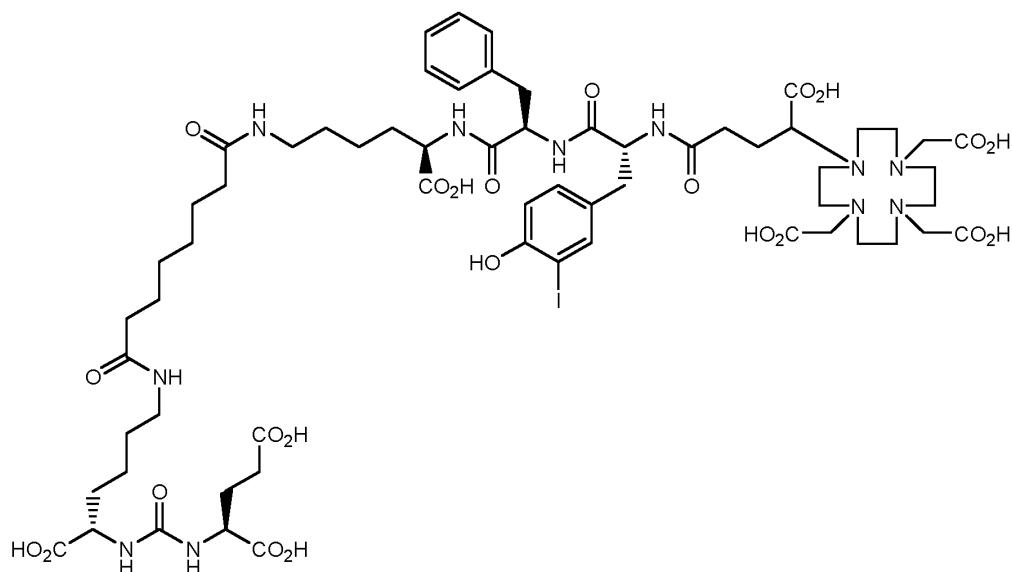
15 In some embodiments, said cancer is castration-resistant prostate cancer, wherein said PSMA-targeted radiopharmaceutical is Compound A, wherein Compound A is chelated to ^{177}Lu ; and wherein said compound capable of inhibiting PI3K, AKT, and/or mTOR is bimiralisib.

20 In some embodiments, said cancer is castration-resistant prostate cancer, wherein said PSMA-targeted radiopharmaceutical is Compound A, wherein Compound A is chelated to ^{161}Tb or ^{177}Lu ; and wherein said compound capable of inhibiting PI3K, AKT, and/or mTOR is bimiralisib.

25 In some embodiments, said (i) PSMA-targeted radiopharmaceutical is Compound A, wherein said Compound A and (ii) said inhibitor of PI3K, AKT, and/or mTOR (preferably bimiralisib) are administered sequentially.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, preferably a prostate cancer, wherein said combination comprises:

30 (i) Compound A:



Compound A; and

(ii) an inhibitor of PI3K, AKT, and/or mTOR.

BRIEF DESCRIPTION OF THE FIGURES

FIG 1 is a plot showing percent survival of 22Rv1 cells treated with different concentrations of Compound 1* and Compound 2 for 7 days relative to untreated cells. IC₅₀ values were determined by non-linear regression analysis. Graphs represent the mean of three replicates $\pm$ SEM. “PQR309” refers to Compound 1* as disclosed herein.

FIG 2A is a plot showing percent survival of 22Rv1 cells treated with different concentrations of Compound 1* and Compound 2 in combination with different doses of ¹⁷⁷Lu-PSMA-617 (0, 0.5, 1, 2.5, 5, 10, or 20 MBq) for 7 days relative to cells treated with respective dose of ¹⁷⁷Lu-PSMA-617 only (i.e., not treated with Compound 1* or Compound 2).

FIG 2B is a synergy analysis of 22Rv1 cells treated with different concentrations of Compound 1* in combination with different doses of ¹⁷⁷Lu-PSMA-617, as described in Example 1. “PQR309” refers to Compound 1* as disclosed herein.

FIG 2C is a synergy analysis of 22Rv1 cells treated with different concentrations of Compound 2 in combination with different doses of ¹⁷⁷Lu-PSMA-617, as described Example 1.

FIG 3A is a plot of body weight in g of female nude mice at start of treatment period

(Study day -1) in the indicated treatment groups as described in Example 2. n=8 per group. “PQR309” refers to Compound 1* as disclosed herein.

FIG 3B is a plot of tumor volume in mm³ at start of treatment period (Study day -1) in the indicated treatment groups as described in Example 2. n=8 per group. “PQR309” refers to
5 Compound 1* as disclosed herein.

FIG 4A is a plot of tumor volume (mm³) over time in mice treated with vehicle; Compound 1*; ¹⁶¹Tb-PSMA-I&T (21.8 MBq); or both Compound 1* and ¹⁶¹Tb-PSMA-I&T (21.8 MBq). Treatment as indicated started at study day 0. Mice received a single injection of ¹⁶¹Tb-PSMA-I&T and/or Compound 1* daily until reaching the endpoint (tumor volume
10 1500 mm³). Data presented as mean $\pm$ SEM. n=8 per group. “PQR309” refers to Compound 1* as disclosed herein.

FIG 4B is a plot of tumor volume (mm³) over time in mice treated with vehicle; Compound 1*; ¹⁶¹Tb-PSMA-I&T (43.7 MBq); or both Compound 1* and ¹⁶¹Tb-PSMA-I&T (43.7 MBq). Treatment as indicated started at study day 0. Mice received a single injection of ¹⁶¹Tb-PSMA-I&T and/or Compound 1* daily until reaching the endpoint (tumor volume
15 1500 mm³). Data presented as mean $\pm$ SEM. n=8 per group. “PQR309” refers to Compound 1* as disclosed herein.

FIG 4C is a plot of tumor volume (mm³) over time in mice treated with vehicle; Compound 1*; ¹⁷⁷Lu-PSMA-617 (30 MBq); or both Compound 1* and ¹⁷⁷Lu-PSMA-617 (30
20 MBq). Treatment as indicated started at study day 0. Mice received a single injection of ¹⁷⁷Lu-PSMA-617 and/or Compound 1* daily until reaching the endpoint (tumor volume 1500 mm³). Data presented as mean $\pm$ SEM. n=8 per group. “PQR309” refers to Compound 1* as disclosed herein.

FIG 4D is a plot of tumor volume (mm³) over time in mice treated with vehicle; Compound 1*; ¹⁷⁷Lu-PSMA-617 (60 MBq); or both Compound 1* and ¹⁷⁷Lu-PSMA-617 (60
25 MBq). Treatment as indicated started at study day 0. Mice received a single injection of ¹⁷⁷Lu-PSMA-617 and/or Compound 1* daily until reaching the endpoint (tumor volume 1500 mm³). Data presented as mean $\pm$ SEM. n=8 per group. “PQR309” refers to Compound 1* as disclosed herein.

FIG 5 is a series of plots of tumor volume (mm³) over time in mice treated with vehicle; Compound 1*; ¹⁶¹Tb-PSMA-I&T (21.8 MBq); ¹⁶¹Tb-PSMA-I&T (43.7 MBq); ¹⁷⁷Lu-PSMA-617 (30 MBq); ¹⁷⁷Lu-PSMA-617 (60 MBq); or both Compound 1* and ¹⁶¹Tb-PSMA-I&T (21.8 MBq) or ¹⁶¹Tb-PSMA-I&T (43.7 MBq) or ¹⁷⁷Lu-PSMA-617 (30 MBq) or ¹⁷⁷Lu-PSMA-
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617 (60 MBq). Treatment as indicated started at study day 0. Mice received a single injection of ^{161}Tb -PSMA-I&T (21.8 MBq) or ^{161}Tb -PSMA-I&T (43.7 MBq) or ^{177}Lu -PSMA-617 (30 MBq) or ^{177}Lu -PSMA-617 (60 MBq) and/or Compound 1* daily until reaching the endpoint (tumor volume 1500 mm³). Data presented as individual tumor volumes. n=8 per group.

- 5 “PQR309” refers to Compound 1* as disclosed herein.

FIG 6 is a plot of days until endpoint (i.e., number of study days from treatment start until tumors reaching >1500 mm³) from all treatment groups as described in Example 2.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

- 10 Each “alkyl” moiety either alone or as part of a larger group such as alkoxy is a straight or branched chain and is preferably C₁-C₃alkyl, more preferably C₁-C₂alkyl. Examples include in particular methyl, ethyl, *n*-propyl and prop-2-yl (*iso*-propyl). Examples of an alkoxy include in particular methoxy, ethoxy, *n*-propoxy and *iso*-propoxy. As described herein, alkoxy may include further substituents such as halogen atoms leading to haloalkoxy moieties.

- 15 The term “alkoxyalkyl” refers to an R-O-R’ moiety in which the R and R’ groups are alkyl groups as defined herein. Examples include methoxymethyl, methoxyethyl, ethoxyethyl and methoxypropyl.

- Each alkylene moiety is a straight or branched chain and is, particularly for example, -CH₂-, -CH₂-CH₂-, -CH(CH₃)-, -CH₂-CH₂-CH₂-, -CH(CH₃)-CH₂-, or -CH(CH₂CH₃)-,
20 preferably -CH₂-, -CH₂-CH₂- or -CH(CH₃)-.

- Each haloalkyl moiety either alone or as part of a larger group such as haloalkoxy is an alkyl group substituted by one or more of the same or different halogen atoms. Haloalkyl moieties include for example 1 to 5 halo substituents, or 1 to 3 halo substituents. Examples include in particular fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl and
25 2,2,2-trifluoro-ethyl.

Each haloalkenyl moiety either alone or as part of a larger group such as haloalkenyloxy is an alkenyl group substituted by one or more of the same or different halogen atoms. Examples include 2-difluoro-vinyl and 1,2-dichloro-2-fluoro-vinyl. Haloalkenyl moieties include for example 1 to 5 halo substituents, or 1 to 3 halo substituents.

- 30 Each cycloalkyl moiety can be in mono- or bi-cyclic form, typically and preferably in mono-cyclic form, and preferably contains 3 to 6 carbon atoms. Preferred examples of monocyclic cycloalkyl groups include in particular cyclopropyl, cyclobutyl, cyclopentyl and

cyclohexyl.

The term "heterocyclic ring" refers to a saturated or partially unsaturated carbocyclic ring containing one to three heteroatoms selected from nitrogen, oxygen and sulfur as ring members. Such rings do not contain adjacent oxygen atoms, adjacent sulfur atoms, or adjacent oxygen and sulfur atoms within the ring. Preferred examples include in particular
5 tetrahydrofuranyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, dioxanyl, morpholinyl, oxazolidinyl and isooxazolidinyl.

Where a group is said to be optionally substituted, preferably there are optionally 1-3 substituents, more preferably optionally 1-2 substituents.

10 Certain compounds of formula (I) may contain one or two or more centers of chirality and such compounds may be provided as pure enantiomers or pure diastereoisomers as well as mixtures thereof in any ratio. The compounds of the invention also include all tautomeric forms of the compounds of formula (I).

As used herein, the terms "overexpression" or "overexpressed" refer to the abnormal
15 or artificial expression of a gene or protein in increased quantity, e.g., as compared to wild-type cells. In some embodiments, the expression of the overexpressed gene or protein can be, e.g., 10% higher than the expression of the same gene or protein in a corresponding wild-type cell, as measured by standard techniques used in the art for quantification of gene expression. In some embodiments, the expression of the overexpressed gene or protein can be, e.g., 50%
20 higher, 100% higher, ten times higher, 100 times higher, or 1,000 times higher or more than the expression of the same gene in a corresponding wild-type cell.

As used herein, the term "PSMA" is understood to mean prostate specific membrane antigen. In preferred embodiments, PSMA is a type II membrane protein and is expressed in all forms of prostate tissue, including carcinoma. PSMA is described by Chang, Rev. Urol.,
25 2004 6(Suppl. 10): S13-S18.

As used herein, the term "measurable quantities", typically and preferably when used in the context of one or both of the inhibitor of PI3K, AKT and/or mTOR and the PSMA-targeted radiopharmaceutical, is understood to mean that such compound(s) can be measured in a given sample (e.g., a blood or serum sample obtained from the subject) using techniques
30 known to one of skill in the art. For example, a "measurable quantity" of, e.g., an inhibitor of PI3K, AKT and/or mTOR in a blood sample obtained from a subject is a quantity that is above the lower limit of quantitation (LLOQ) for a given analytical technique used to measure said inhibitor, and thus able to be quantified using that technique. Suitable analytical techniques

are known to one of skill in the art and include but are not limited to, e.g., ELISA, HPLC-MS, and the like.

As used herein, the term “simultaneous” is understood to mean “at the same time as”, and the two terms are used interchangeably herein. Accordingly, in preferred embodiments, when an inhibitor of PI3K, AKT and/or mTOR is administered “simultaneously” with a PSMA-targeted radiopharmaceutical, it is understood that the inhibitor of PI3K, AKT and/or mTOR is administered at the same time as the a PSMA-targeted radiopharmaceutical. For example, if the inhibitor of PI3K, AKT and/or mTOR is administered over a period of hours or minutes (e.g., from about 1 to about 90 minutes, e.g., by intravenous administration), said PSMA-targeted radiopharmaceutical can be administered during the time period in which the inhibitor of PI3K, AKT and/or mTOR is administered. Likewise, the inhibitor of PI3K, AKT and/or mTOR can be administered during the time period in which the PSMA-targeted radiopharmaceutical is administered.

As used herein, the term “[has] previously been treated” is understood to refer to situations in which a subject, preferably a subject who is to be treated with one of an inhibitor of PI3K, AKT and/or mTOR or a PSMA-targeted radiopharmaceutical, has earlier been treated with one of an inhibitor of PI3K, AKT and/or mTOR or a PSMA-targeted radiopharmaceutical. In preferred embodiments, said subject who is to be treated with one of (i) an inhibitor of PI3K, AKT and/or mTOR or (ii) a PSMA-targeted radiopharmaceutical has earlier been treated with the other of (i) an inhibitor of PI3K, AKT and/or mTOR or (ii) a PSMA-targeted radiopharmaceutical.

Although the term “[has] previously been treated” encompasses embodiments in which a subject was previously treated with either of a (i) an inhibitor of PI3K, AKT and/or mTOR or (ii) a PSMA-targeted radiopharmaceutical at any point in the future, in preferred embodiments, said “previous treatment” with either of the (i) inhibitor of PI3K, AKT and/or mTOR or (ii) PSMA-targeted radiopharmaceutical is administered during the course of a combination therapy as described herein. Preferably, when the two active ingredients (i.e., the (i) inhibitor of PI3K, AKT and/or mTOR and the (ii) PSMA-targeted radiopharmaceutical) are administered sequentially, the active ingredients are administered within such a time period that the two active ingredients can exert an additive, preferably synergistic effect within the body of a subject. Preferably, when a subject has “previously been treated” with one of the active ingredients described herein, said active ingredient is still present in measurable quantities in the blood of the subject (as determined by one of skill in the art) when the second

of the active ingredients is administered to said subject.

In some preferred embodiments, said inhibitor of PI3K, AKT and/or mTOR is administered to a subject prior to administration of said PSMA-targeted radiopharmaceutical, wherein measurable quantities of said inhibitor of PI3K, AKT and/or mTOR are still present
5 in the blood of said subject upon administration of said PSMA-targeted radiopharmaceutical.

In some preferred embodiments, said PSMA-targeted radiopharmaceutical is administered to a subject prior to administration of said inhibitor of PI3K, AKT and/or mTOR, wherein measurable quantities of said PSMA-targeted radiopharmaceutical are still present in the blood of said subject upon administration of said inhibitor of PI3K, AKT and/or mTOR.

10 Thus, in some embodiments, said “previous treatment” with either of (i) the inhibitor of PI3K, AKT and/or mTOR or (ii) the PSMA-targeted radiopharmaceutical has occurred within one month of the treatment with the other of the inhibitor of PI3K, AKT and/or mTOR or the PSMA-targeted radiopharmaceutical. In preferred embodiments, said “previous treatment” with either of (i) the inhibitor of PI3K, AKT and/or mTOR or (ii) the PSMA-
15 targeted radiopharmaceutical has occurred within two weeks; preferably within seven days; more preferably within one day of the treatment with the other of the inhibitor of PI3K, AKT and/or mTOR or the PSMA-targeted radiopharmaceutical. In some embodiments, said “previous treatment” with either of (i) the inhibitor of PI3K, AKT and/or mTOR or (ii) the PSMA-targeted radiopharmaceutical has occurred within 12 hours; e.g., within six hours; e.g.,
20 within three hours of the treatment with the other of the inhibitor of PI3K, AKT and/or mTOR or the PSMA-targeted radiopharmaceutical.

As used herein, the term “in combination with”, preferably when used in the context of administering an inhibitor of PI3K, AKT and/or mTOR and a PSMA-targeted radiopharmaceutical to a subject, is understood to encompass both simultaneous
25 administration (as defined herein) and to situations wherein said subject has previously been treated with (as defined herein) either said inhibitor of PI3K, AKT and/or mTOR or a PSMA-targeted radiopharmaceutical prior to treatment with the other of said inhibitor of PI3K, AKT and/or mTOR and a PSMA-targeted radiopharmaceutical. Accordingly, as used herein, the term “in combination with” is understood to encompass any embodiment in which: (i) a subject
30 is administered a PSMA-targeted radiopharmaceutical, wherein the subject has previously been treated with an inhibitor of PI3K, AKT, and/or mTOR; (ii) a subject is administered an inhibitor of PI3K, AKT, and/or mTOR, wherein the subject has previously been treated with a PSMA-targeted radiopharmaceutical; or (iii) a subject is administered an inhibitor of PI3K,

AKT, and/or mTOR at the same time as said subject is administered a PSMA-targeted radiopharmaceutical.

In some preferred embodiments, the term “in combination with” refers to situations in which: (i) a subject is administered a PSMA-targeted radiopharmaceutical, wherein the subject
5 has previously been treated with an inhibitor of PI3K, AKT, and/or mTOR; (ii) a subject is administered an inhibitor of PI3K, AKT, and/or mTOR, wherein the subject has previously been treated with a PSMA-targeted radiopharmaceutical; or (iii) a subject is administered an inhibitor of PI3K, AKT, and/or mTOR at the same time as said subject is administered a PSMA-targeted radiopharmaceutical.

10 In some preferred embodiments, the term “in combination with” refers to situations in which: a subject is administered a PSMA-targeted radiopharmaceutical, wherein the subject has previously been treated with an inhibitor of PI3K, AKT, and/or mTOR.

In some preferred embodiments, the term “in combination with” refers to situations in which: a subject is administered an inhibitor of PI3K, AKT, and/or mTOR, wherein the subject
15 has previously been treated with a PSMA-targeted radiopharmaceutical.

In some preferred embodiments, the term “in combination with” refers to situations in which: a subject is administered an inhibitor of PI3K, AKT, and/or mTOR at the same time as said subject is administered a PSMA-targeted radiopharmaceutical.

Thus, a therapeutically effective amount of each of the active ingredients (i.e., the (i)
20 inhibitor of PI3K, AKT and/or mTOR and the (ii) PSMA-targeted radiopharmaceutical) as described herein may be administered simultaneously or sequentially and in any order, and the active ingredients may be administered separately or as a fixed combination. For example, the method of treatment of diseases (e.g., prostate cancer) according to the invention may comprise (i) administration of the first active ingredient in free or pharmaceutically acceptable
25 salt form and (ii) administration of the second active ingredient in free or pharmaceutically acceptable salt form, simultaneously or sequentially in any order, in jointly therapeutically effective amounts, preferably in synergistically effective amounts, e.g. in daily dosages corresponding to the amounts described herein. The individual active ingredients of the inventive combinations can be administered separately at different times during the course of
30 therapy or concurrently in divided or single combination forms.

The present invention also provides combinations for use in the treatment of a cancer, wherein said combination comprises: (i) a PSMA-targeted radiopharmaceutical; and (ii) an inhibitor of PI3K, AKT, and/or mTOR. The term “combination for use” is understood to

encompass both simultaneous administration (as defined herein) and to situations wherein said subject has previously been treated with (as defined herein) either said inhibitor of PI3K, AKT and/or mTOR or a PSMA-targeted radiopharmaceutical prior to treatment with the other of said inhibitor of PI3K, AKT and/or mTOR and a PSMA-targeted radiopharmaceutical.

- 5 Accordingly, a “combination for use” is understood to encompass any embodiment in which:
(i) a subject is administered a PSMA-targeted radiopharmaceutical, wherein the subject has previously been treated with an inhibitor of PI3K, AKT, and/or mTOR; (ii) a subject is administered an inhibitor of PI3K, AKT, and/or mTOR, wherein the subject has previously been treated with a PSMA-targeted radiopharmaceutical; or (iii) a subject is administered an
10 inhibitor of PI3K, AKT, and/or mTOR at the same time as said subject is administered a PSMA-targeted radiopharmaceutical.

Accordingly, in some embodiments, the present disclosure provides a combination for use in a method of treating a cancer in a subject, said combination comprising:

- (i) a composition comprising a PSMA-targeted radiopharmaceutical; and
15 (ii) a composition comprising an inhibitor of PI3K, AKT, and/or mTOR;
wherein (i) said subject is administered a PSMA-targeted radiopharmaceutical, wherein the subject has previously been treated with an inhibitor of PI3K, AKT, and/or mTOR; (ii) said subject is administered an inhibitor of PI3K, AKT, and/or mTOR, wherein the subject has previously been treated with a PSMA-targeted radiopharmaceutical; or (iii) said subject is
20 administered an inhibitor of PI3K, AKT, and/or mTOR at the same time as said subject is administered a PSMA-targeted radiopharmaceutical.

In some embodiments, the present disclosure provides a combination for use in a method of treating a cancer in a subject, said combination comprising:

- (i) a composition comprising a PSMA-targeted radiopharmaceutical; and
25 (ii) a composition comprising an inhibitor of PI3K, AKT, and/or mTOR;
wherein (i) said subject is administered a PSMA-targeted radiopharmaceutical, wherein the subject has previously been treated with an inhibitor of PI3K, AKT, and/or mTOR.

In some embodiments, the present disclosure provides a combination for use in a method of treating a cancer in a subject, said combination comprising:

- (i) a composition comprising a PSMA-targeted radiopharmaceutical; and
30 (ii) a composition comprising an inhibitor of PI3K, AKT, and/or mTOR;
wherein (ii) said subject is administered an inhibitor of PI3K, AKT, and/or mTOR, wherein the subject has previously been treated with a PSMA-targeted radiopharmaceutical.

In some embodiments, the present disclosure provides a combination for use in a method of treating a cancer in a subject, said combination comprising:

- (i) a composition comprising a PSMA-targeted radiopharmaceutical; and
- (ii) a composition comprising an inhibitor of PI3K, AKT, and/or mTOR;

5 wherein (iii) said subject is administered an inhibitor of PI3K, AKT, and/or mTOR at the same time as said subject is administered a PSMA-targeted radiopharmaceutical.

Said inhibitor of PI3K, AKT, and/or mTOR and said PSMA-targeted radiopharmaceutical can be packaged, produced and/or stored separately. In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR and said PSMA-targeted radiopharmaceutical can be produced by different, e.g. independent vendors.

Without wishing to be bound by theory, in preferred embodiments said inhibitor of PI3K, AKT, and/or mTOR is stable (e.g., shelf-stable) and can be stored for an indefinite period (e.g., a year or more), e.g., in a clinical (e.g., hospital) setting. In contrast, said PSMA-targeted radiopharmaceutical can comprise a radionuclide with a half-life that is insufficient to allow long-term storage, and thus cannot be stored indefinitely (e.g., cannot be stored for more than a week; cannot be stored for more than a day) without losing efficacy. Accordingly, in some embodiments, an inhibitor of PI3K, AKT, and/or mTOR is stored in a clinical setting (e.g., at a hospital), and a PSMA-targeted radiopharmaceutical is delivered to and/or freshly prepared at said clinical setting (e.g., hospital) shortly before administration of said PSMA-targeted radiopharmaceutical to said subject. Such embodiments are encompassed within “combinations for use” and methods of treatment wherein an inhibitor of PI3K, AKT, and/or mTOR is administered “in combination with” a PSMA-targeted radiopharmaceutical as those terms are used herein, including in situations in which said inhibitor of PI3K, AKT, and/or mTOR and said PSMA-targeted radiopharmaceutical are packaged, produced and/or stored separately.

As a non-limiting example, a combination for use in a method of treating a cancer in a subject, e.g., a prostate cancer can comprise situations in which a clinician has in her possession one or more (therapeutically effective) doses of said inhibitor of PI3K, AKT, and/or mTOR, and wherein said clinician further requests (e.g., from an outside vendor), one or more (therapeutically effective) doses of said PSMA-targeted radiopharmaceutical. In some embodiments said PSMA-targeted radiopharmaceutical can be delivered to said clinician shortly before (e.g., within 6 hours) of administration of said PSMA-targeted radiopharmaceutical to said subject.

The phrase “therapeutically effective amount” means an amount of one or more compounds of the present invention that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein. In the case of cancer, the therapeutically effective amount of the drug may be reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the drug combinations described herein may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy can be measured, for example, by assessing the time to disease progression (TTP) and/or determining the response rate (RR).

The terms “treatment”/“treating” as used herein include: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a subject that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition; (2) inhibiting the state, disorder or condition (e.g. arresting, reducing or delaying the development of the disease, or a relapse thereof in case of maintenance treatment, of at least one clinical or subclinical symptom thereof); and/or (3) relieving the condition (i.e. causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms). The benefit to a patient to be treated is either statistically significant or at least perceptible to the patient or to the physician. However, it will be appreciated that when a medicament is administered to a patient to treat a disease, the outcome may not always be effective treatment. In one embodiment, the terms “treatment”/“treating” as used herein, refer to a therapeutic treatment. In another embodiment, the terms “treatment”/“treating” as used herein, refer to a prophylactic treatment.

The term "mammal" includes, but is not limited to, humans, mice, rats, guinea pigs, monkeys, dogs, cats, horses, cows, pigs, and sheep. The term "mammal", as used herein, preferably refers to humans.

The terms "individual," "subject" or "patient" are used herein interchangeably. In a preferred embodiment, the subject is a human.

As used herein, the term "systemic administration" refers to administration of a

compound according to the invention, e.g., the inhibitor of PI3K, AKT, and/or mTOR and/or the PSMA-targeted radiopharmaceutical, such that the compound becomes widely distributed in the body in significant amounts and has a biological effect, e.g. its desired effect, in the blood and/or reaches its desired site of action via the vascular system. Typical systemic routes of administration include administration by (1) introducing the compound directly into the vascular system or (2) oral, pulmonary, or intramuscular administration wherein the compound is adsorbed, enters the vascular system, and is carried to one or more desired site(s) of action via the blood.

The terms "oral", "orally", and "oral administration", as used herein, refer to orally ingesting a compound of the present invention.

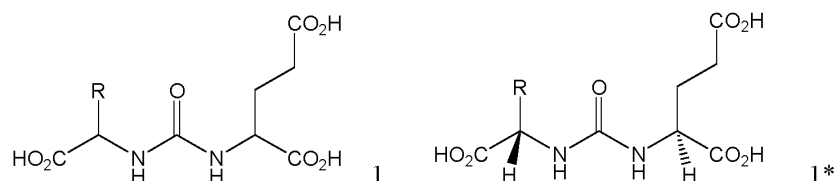
The term "parenteral" as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

PSMA-Targeted Radiopharmaceuticals

As used herein, the term "PSMA-targeted radiopharmaceutical" is understood as a radiopharmaceutical that is targeted in vivo or in vitro to PSMA. A "radiopharmaceutical" is understood as a pharmaceutical drug containing a radioactive isotope (also known as a radionuclide as defined herein). In preferred embodiments, the PSMA-targeted radiopharmaceutical comprises a chelating group to chelate the radionuclide. In some embodiments, the chelating group comprises a DOTA chelator or a DOTA residue. In preferred embodiments, the PSMA-targeted radiopharmaceutical comprises a PSMA-targeting fragment. In some embodiments, said targeting fragment is a dipeptide urea based PSMA-targeting fragment, preferably DUPA.

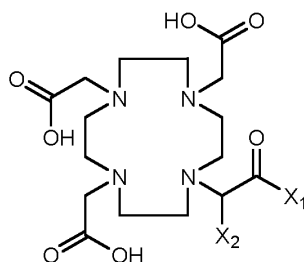
In preferred embodiments, the PSMA-targeted radiopharmaceuticals of the present disclosure are administered to a subject internally, e.g., via intravenous (IV) administration. In some embodiments, the PSMA-targeted radiopharmaceutical is administered systemically. Accordingly, in preferred embodiments, radiation from a PSMA-targeted radiopharmaceutical as described herein is not administered externally, e.g., as a beam of energy (e.g., X-rays, proton radiation, gamma knife radiation and the like) to the subject.

As used herein, a "DUPA" is understood to mean a glutamate-urea moiety of formula 1, preferably of formula 1*:



and enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof; wherein R is preferably substituted or unsubstituted alkyl, substituted or unsubstituted aryl, and any combination thereof; more preferably R is C₁₋₆-alkyl, preferably C₂₋₄-alkyl, substituted one or more times, preferably one time with OH, SH, NH₂, or COOH, wherein one of said NH₂, OH or SH or COOH group serve as the point of covalent attachment to the PSMA-targeted radiopharmaceutical. In preferred embodiments, R is -C₄alkylene-NH-, wherein said -NH- forms an amide bond with the remainder of the PSMA-targeted radiopharmaceutical.

A “DOTA” chelator, also known as “tetraxetan”, as used herein is understood as a complexing agent with the formula (CH₂CH₂NCH₂CO₂H)₄, or a residue thereof. In some preferred embodiments, the DOTA chelator, or residue thereof, has the structure below, wherein said DOTA chelator is connected to the remainder of the PSMA-targeted radiopharmaceutical at the position X₁ or X₂:



In some embodiments, the DOTA chelator is connected to the remainder of the PSMA-targeted radiopharmaceutical at position X₂, and X₁ is -OH. In such embodiments, the DOTA chelator is referred to as a “DOTAGA” chelator.

In some embodiments, the DOTA chelator is connected to the remainder of the PSMA-targeted radiopharmaceutical at position X₁, e.g., by an amide linkage wherein X₁ is -NHR-, wherein “R” is the remainder of the PSMA-targeted radiopharmaceutical. In preferred embodiments, X₂ is a C₁-C₆ alkyl or -H, preferably X₂ is -H.

In preferred embodiments, the PSMA-targeted radiopharmaceutical is selected from the group consisting of PSMA-I&T (i.e., “Compound A”), PSMA-617, PSMA-11, PSMA-62, PSMA-R2, PSMA-ALB-56, EB-PSMA-617, CTT1403, PSMA-617, HTK01169, L1, L14, and SibuDAB. In preferred embodiments, the PSMA-targeted radiopharmaceutical is selected

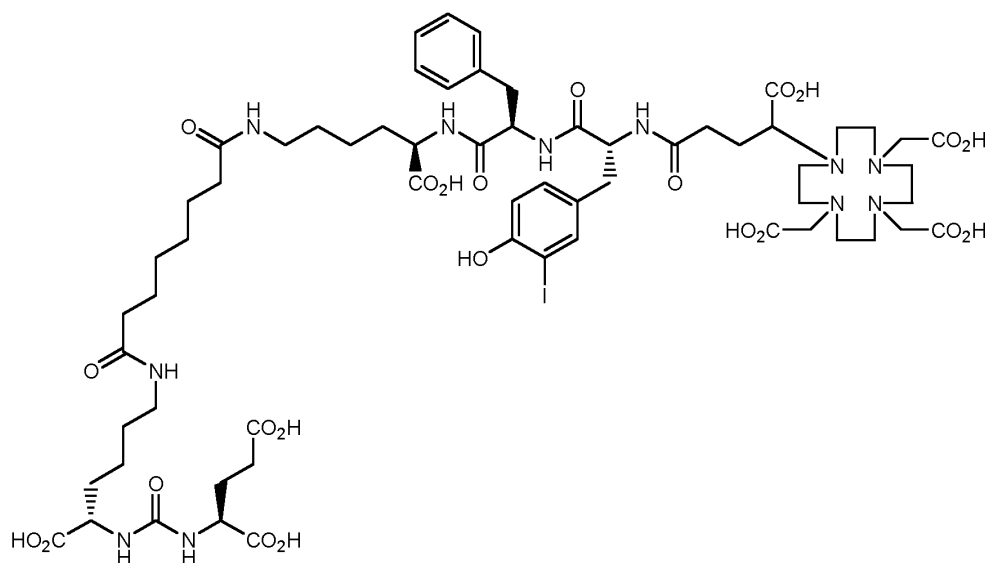
from the group consisting of PSMA-I&T (i.e., “Compound A”), PSMA-617, and PSMA-11.

In preferred embodiments, the PSMA-targeted radiopharmaceutical is PSMA-I&T (i.e., “Compound A”). In some embodiments, the PSMA-targeted radiopharmaceutical is PSMA-617. In some embodiments, the PSMA-targeted radiopharmaceutical is PSMA-11. In some embodiments, the PSMA-targeted radiopharmaceutical is PSMA-62. In some embodiments, the PSMA-targeted radiopharmaceutical is PSMA-R2. In some embodiments, the PSMA-targeted radiopharmaceutical is PSMA-ALB-56. In some embodiments, the PSMA-targeted radiopharmaceutical is EB-PSMA-617. In some embodiments, the PSMA-targeted radiopharmaceutical is CTT1403. In some embodiments, the PSMA-targeted radiopharmaceutical is PSMA-617. In some embodiments, the PSMA-targeted radiopharmaceutical is HTK01169. In some embodiments, the PSMA-targeted radiopharmaceutical is L1. In some embodiments, the PSMA-targeted radiopharmaceutical is L14. In some embodiments, the PSMA-targeted radiopharmaceutical is SibuDAB.

The structures for PSMA-I&T (i.e., Compound A), PSMA-617, and PSMA-11 are described below and by Chatalic et al., *Theranostics*, (2016), 6(6): 849-861.

Compound A (PSMA-I&T)

As used herein, “Compound A” has the structure below:

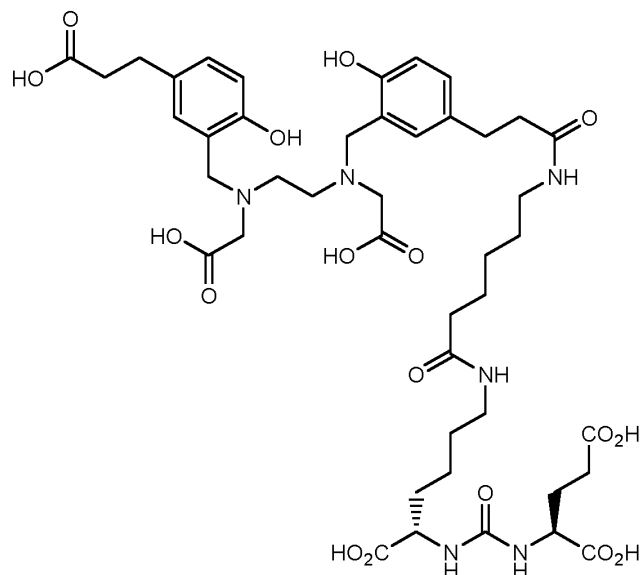


Compound A can also be referred to herein as “PSMA I&T”, and has the CAS number 2192281-54-0.

When Compound A is chelated to a radionuclide such as ^{161}Tb , said chelate is referred to as, e.g., “ ^{161}Tb -PSMA I&T”

PSMA-11

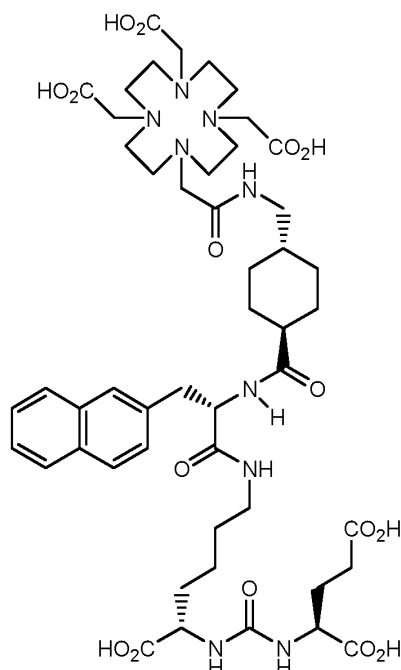
As used herein, “PSMA-11” has the structure below:



When PSMA-11 is chelated to a radionuclide such as ¹⁶¹Tb, said chelate is referred to
5 as, e.g., “¹⁶¹Tb-PSMA-11”. PSMA-11 has the CAS number 1366302-52-4.

PSMA-617

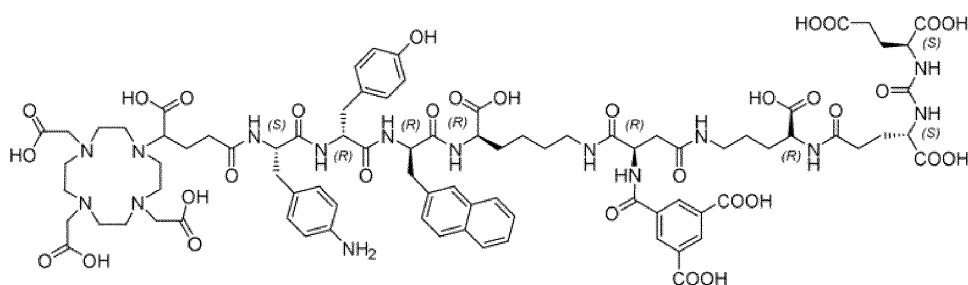
As used herein, “PSMA-617” has the structure below:



When PSMA-617 is chelated to a radionuclide such as ^{161}Tb , said chelate is referred to as, e.g., “ ^{161}Tb -PSMA-617”. PSMA-617 has the CAS number 1702967-37-0.

PSMA-62

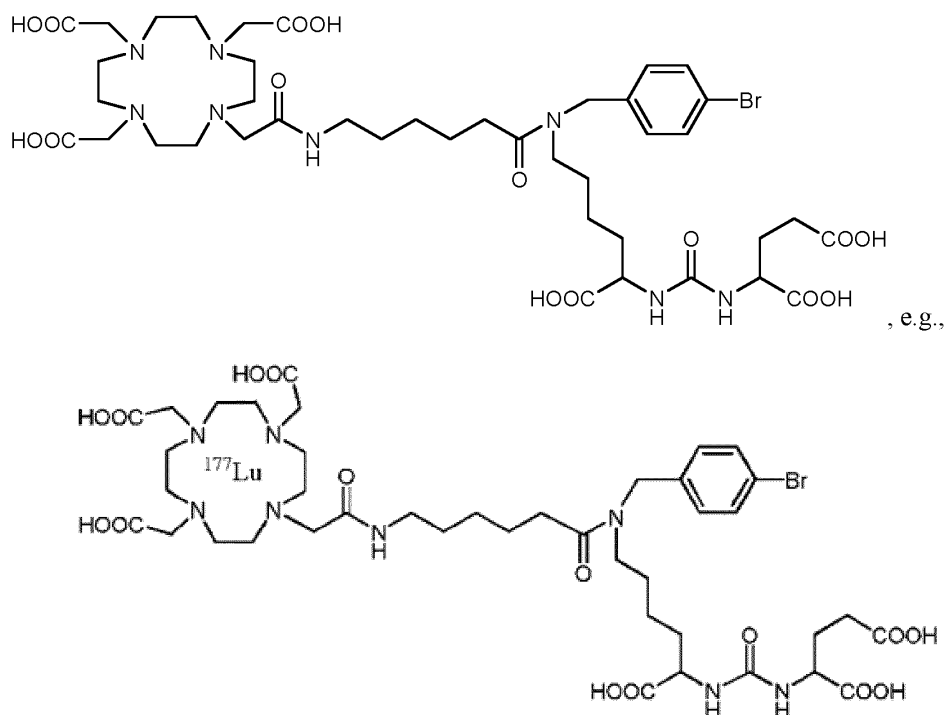
5 As used herein, “PSMA-62” has the structure below:



The structure of PSMA-62 is also described by Schmidt, A. (2017). *Structural modifications of PSMA ligands to optimize their pharmacokinetics*. [Doctoral Dissertation, Technischen Universität München], <https://d-nb.info/1170872573/34>.

10 PSMA-R2

As used herein, “PSMA-R2” has the structure below:



The structure of PSMA-R2 is also described in WO 2021/001360.

In some embodiments, the PSMA-targeted radiopharmaceutical comprises an albumin-binding fragment. In preferred embodiments, the PSMA-targeted radiopharmaceutical comprising an albumin-binding fragment is selected from the group consisting of PSMA-ALB-56, EB-PSMA-617, CTT1403, PSMA-617, HTK01169, L1, L14, and SibuDAB. The structures of PSMA-ALB-56, EB-PSMA-617, CTT1403, PSMA-617, HTK01169, L1, and L14, are described by Boinapally, S. et al., *Molecules*, **2023**, 28, 6158; see also Choy et al, *Theranostics*, 2017, 7(7): 1928-1939. The structure of SibuDAB is described by Tschan et al., *Journal of Nuclear Medicine* July 2023, jnumed.123.265524; DOI: <https://doi.org/10.2967/jnumed.123.265524>.

In preferred embodiments, the PSMA-targeted radiopharmaceutical is selected from the group consisting of Compound A, PSMA-617, and PSMA-11.

Radionuclides

As used herein, a “radionuclide” is understood as a nuclide that has excess nuclear energy, making it unstable. The excess energy can be (i) emitted from the nucleus as gamma radiation; (ii) transferred to one of its electrons to release it as a conversion electron; or (iii)

used to create and emit a new particle (e.g., an alpha particle or a beta particle) from the nucleus.

In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to a radionuclide. In some embodiments, said radionuclide is selected from: ^{11}C , ^{13}N , ^{15}O , ^{18}F , ^{43}Sc , ^{44}Sc , ^{47}Sc , ^{61}Cu , ^{64}Cu , ^{67}Cu , ^{68}Cu , ^{68}Ga , ^{89}Sr , ^{89}Zr , ^{90}Y , $^{99\text{m}}\text{Tc}$, ^{123}I , ^{125}I , ^{131}I , ^{153}Sm , ^{149}Pm , ^{149}Tb , ^{152}Tb , ^{155}Tb , ^{161}Tb , ^{165}Dy , ^{166}Ho , ^{169}Er , ^{177}Lu , ^{188}Re , ^{198}Au , ^{203}Pb , ^{212}Pb , ^{211}At , ^{212}Bi , ^{213}Bi , ^{223}Ra , ^{225}Ac , and ^{227}Th . In some embodiments, said radionuclide is selected from: ^{43}Sc , ^{44}Sc , ^{47}Sc , ^{61}Cu , ^{64}Cu , ^{67}Cu , ^{68}Cu , ^{68}Ga , ^{89}Sr , ^{89}Zr , ^{90}Y , $^{99\text{m}}\text{Tc}$, ^{123}I , ^{125}I , ^{131}I , ^{153}Sm , ^{149}Pm , ^{149}Tb , ^{152}Tb , ^{155}Tb , ^{161}Tb , ^{165}Dy , ^{166}Ho , ^{169}Er , ^{177}Lu , ^{188}Re , ^{198}Au , ^{203}Pb , ^{212}Pb , ^{211}At , ^{212}Bi , ^{213}Bi , ^{223}Ra , ^{225}Ac , and ^{227}Th . In some embodiments, said radionuclide is selected from: ^{161}Tb , ^{177}Lu , and ^{225}Ac .

In some embodiments, said radionuclide is a beta-emitter. In some embodiments, said radionuclide is a long-range beta emitter, e.g., wherein said long-range beta emitter is selected from the group consisting of ^{90}Y , ^{32}P , $^{186}\text{Re}/^{188}\text{Re}$, ^{166}Ho , $^{76}\text{As}/^{77}\text{As}$, ^{89}Sr , and ^{153}Sm . In some embodiments, said radionuclide is a medium range beta-emitter, e.g., wherein said medium range beta-emitter is selected from the group consisting of ^{131}I , ^{177}Lu , ^{67}Cu , ^{161}Tb , and ^{105}Rh . In some embodiments, said radionuclide is a low-energy beta-emitter, e.g., wherein said low-energy beta-emitter is selected from the group consisting of ^{45}Ca and ^{35}S . In some embodiments, said radionuclide is a conversion or Auger-emitter, e.g., wherein said conversion or Auger-emitter is selected from the group consisting of ^{51}Cr , ^{67}Ga , $^{99\text{m}}\text{Tc}$, ^{111}In , $^{114\text{m}}\text{In}$, ^{123}I , ^{125}I , and ^{201}Tl . In some embodiments, said radionuclide is an alpha emitter, e.g., wherein said alpha emitter is selected from the group consisting of ^{212}Bi , ^{213}Bi , ^{223}Ac , ^{225}Ac , ^{212}Pb , ^{255}Fm , ^{223}Ra , ^{149}Tb and ^{221}At .

In some embodiments, said radionuclide is selected from: ^{161}Tb , and ^{177}Lu .

In some embodiments, said radionuclide is ^{11}C . In some embodiments, said radionuclide is ^{13}N . In some embodiments, said radionuclide is ^{15}O . In some embodiments, said radionuclide is ^{18}F . In some embodiments, said radionuclide is ^{43}Sc . In some embodiments, said radionuclide is ^{44}Sc . In some embodiments, said radionuclide is ^{47}Sc . In some embodiments, said radionuclide is ^{64}Cu . In some embodiments, said radionuclide is ^{67}Cu . In some embodiments, said radionuclide is ^{68}Ga . In some embodiments, said radionuclide is ^{89}Sr . In some embodiments, said radionuclide is ^{89}Zr . In some embodiments, said radionuclide is ^{90}Y . In some embodiments, said radionuclide is $^{99\text{m}}\text{Tc}$. In some embodiments, said radionuclide is ^{123}I . In some embodiments, said radionuclide is ^{131}I . In some embodiments,

said radionuclide is ^{153}Sm . In some embodiments, said radionuclide is ^{149}Tb . In some embodiments, said radionuclide is ^{152}Tb . In some embodiments, said radionuclide is ^{155}Tb . In preferred embodiments, said radionuclide is ^{161}Tb . In some embodiments, said radionuclide is ^{165}Dy . In some embodiments, said radionuclide is ^{166}Ho . In some embodiments, said radionuclide is ^{169}Er . In preferred embodiments, said radionuclide is ^{177}Lu . In some embodiments, said radionuclide is ^{188}Re . In some embodiments, said radionuclide is ^{198}Au . In some embodiments, said radionuclide is ^{203}Pb . In some embodiments, said radionuclide is ^{212}Pb . In some embodiments, said radionuclide is ^{211}At . In some embodiments, said radionuclide is ^{212}Bi . In some embodiments, said radionuclide is ^{213}Bi . In some embodiments, said radionuclide is ^{223}Ra . In some embodiments, said radionuclide is ^{225}Ac . In some embodiments, said radionuclide is ^{227}Th .

In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to a radionuclide, and said inhibitor of PI3K, AKT, and/or mTOR is bimiralisib.

In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to a radionuclide selected from ^{161}Tb and ^{177}Lu . In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to ^{161}Tb . In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to ^{177}Lu . In some preferred embodiments, said PSMA-conjugated radiopharmaceutical is chelated to ^{225}Ac .

In some embodiments, said Compound A is chelated to a radionuclide selected from ^{161}Tb and ^{177}Lu . In some embodiments, said Compound A is chelated to ^{161}Tb . In some embodiments, said Compound A is chelated to ^{177}Lu . In some preferred embodiments, said Compound A is chelated to ^{225}Ac .

Inhibitors of PI3K, AKT, and/or mTOR

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is a dual PI3K/mTOR inhibitor. In some embodiments, the inhibitor of PI3K, AKT, and/or mTOR is selected from: Buparlisib (NVP-BKM120; BKM120), CH5132799 (PA-79), Pifaralisib (XL147; SAR245408), ZSTK474, Sonolisib (PX-866), Pictilisib (GDC-0941; RG7321), Copanlisib (BAY 80-6946; Aliqopa), B591, TG-100-115, RIDR-PI-103, BYL719 (Alpelisib; Piqray), Serabelisib (INK-117; MLN-117; TAK-117), GSK2636771, Idelalisib (GS-1101; CAL-101; Zydelig), Zandelisib (ME-401; PWT-143), AMG 319, YY-20394 (Linerlisib), INCB050465 (Parsaclisib; IBI-376), Umbralisib (TGR-1202; RP5264), Tenalisib (RP6530), Taselisib/GDC-0032/RG-7604, AZD8186, AZD8835, IPI-145/Duvelisib/INK1197,

Leniolisib (CDZ173), Eganelisib (IPI-549), Dactolisib (BEZ-235; NVP-BEZ235), Apitolisib (GDC-0980, RG7422), Gedatolisib (PF-05212384; PKI-587, SF1126, Omipalisib (GSK458; GSK2126458), Samotolisib (LY3023414), Bimiralisib (PQR309), Paxalisib (GDC-0084; RG7666), XL765 (Voxtalisib; SAR245409), GNE-493, GNE-477, PF-04691502, WJD008, BGT226, MK-2206, miransertib (ARQ 092), ARQ 751, BAY1125976, uprosertib (GSK2141795), GSK690693, LY2780301, ipatasertib (GDC-0068), capivasertib (AZD5363), edelfosine, perifosine (KRX-0401), afuresertib (GSK2110183), rapamycin, temsirolimus (CCI-779), everolimus (RAD001), ridaforolimus (AP23573; deforolimus; MK-8669), 32-deoxorapamycin (SAR943), Zotarolimus (ABT-578), PP242, PP30, WAY-600, WYE-687, WYE-354, KU0063794, AZD8055, OSI-027, AZD2014, INK128, Torin 1, curcumin, resveratrol, epigallocatechin gallate (EGCG), genistein, 3,3-diindolylmethane (DIM), and caffeine; or a pharmaceutically acceptable salt thereof.

In some embodiments, the inhibitor of PI3K, AKT, and/or mTOR is an inhibitor of PI3K. In some embodiments, said inhibitor of PI3K is selected from: Buparlisib (NVP-BKM120; BKM120), CH5132799 (PA-79), Pilaralisib (XL147; SAR245408), ZSTK474, Sonolisib (PX-866), Pictilisib (GDC-0941; RG7321), Copanlisib (BAY 80-6946; Aliqopa), B591, TG-100-115, RIDR-PI-103, BYL719 (Alpelisib; Piqray), Serabelisib (INK-117; MLN-117; TAK-117), GSK2636771, Idelalisib (GS-1101; CAL-101; Zydelig), Zandelisib (ME-401; PWT-143), AMG 319, YY-20394 (Lipnerlisib), INCB050465 (Parsaclisib; IBI-376), Umbralisib (TGR-1202; RP5264), Tenalisib (RP6530), Taselisib/GDC-0032/RG-7604, AZD8186, AZD8835, IPI-145/Duvelisib/INK1197, Leniolisib (CDZ173), Eganelisib (IPI-549), Dactolisib (BEZ-235; NVP-BEZ235), Apitolisib (GDC-0980, RG7422), Gedatolisib (PF-05212384; PKI-587, SF1126, Omipalisib (GSK458; GSK2126458), Samotolisib (LY3023414), Bimiralisib (PQR309), Paxalisib (GDC-0084; RG7666), XL765 (Voxtalisib; SAR245409), GNE-493, GNE-477, PF-04691502, WJD008, and BGT226; or a pharmaceutically acceptable salt thereof.

In some embodiments, the inhibitor of PI3K is: a pan-PI3K inhibitor; an isoform-specific PI3K inhibitor; or a dual PI3K/mTOR inhibitor. In some embodiments, the inhibitor of PI3K is a pan-PI3K inhibitor.

In some embodiments, said pan-PI3K inhibitor is selected from: Buparlisib (NVP-BKM120; BKM120), CH5132799 (PA-79), Pilaralisib (XL147; SAR245408), ZSTK474, Sonolisib (PX-866), Pictilisib (GDC-0941; RG7321), Copanlisib (BAY 80-6946; Aliqopa), B591, TG-100-115, and RIDR-PI-103; or a pharmaceutically acceptable salt thereof.

In some embodiments, the inhibitor of PI3K is an isoform-specific PI3K inhibitor. In some embodiments, said isoform-specific PI3K inhibitor is selected from: BYL719 (Alpelisib; Piqray), Serabelisib (INK-117; MLN-117; TAK-117), GSK2636771, Idelalisib (GS-1101; CAL-101; Zydelig), Zandelisib (ME-401; PWT-143), AMG 319, YY-20394 (Linerlisib),
5 INCB050465 (Parsaclisib; IBI-376), Umbralisib (TGR-1202; RP5264), Tenalisib (RP6530), Taselisib/GDC-0032/RG-7604, AZD8186, AZD8835, IPI-145/Duvelisib/INK1197, Leniolisib (CDZ173), and Eganelisib (IPI-549); or a pharmaceutically acceptable salt thereof.

In some embodiments, the inhibitor of PI3K is a dual PI3K/mTOR inhibitor. In some embodiments, said dual PI3K/mTOR inhibitor is selected from: Dactolisib (BEZ-235; NVP-
10 BEZ235), Apatolisib (GDC-0980, RG7422), Gedatolisib (PF-05212384; PKI-587, SF1126, Omipalisib (GSK458; GSK2126458), Samotolisib (LY3023414), Bimiralisib (PQR309), Paxalisib (GDC-0084; RG7666), XL765 (Voxtalib; SAR245409), GNE-493, GNE-477, PF-04691502, WJD008, and BGT226; or a pharmaceutically acceptable salt thereof.

In preferred embodiments, the inhibitor of PI3K, AKT, and/or mTOR is a dual
15 PI3K/mTOR inhibitor. In preferred embodiments, said dual PI3K/mTOR inhibitor is bimiralisib, or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is an inhibitor of AKT. In some embodiments, said inhibitor of AKT is selected from: MK-2206, miransertib (ARQ 092), ARQ 751, BAY1125976, uprosertib (GSK2141795), GSK690693, LY2780301,
20 ipatasertib (GDC-0068), capivasertib (AZD5363), edelfosine, perifosine (KRX-0401), and afuresertib (GSK2110183); or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of AKT is an allosteric inhibitor of AKT, or an ATP-competitive inhibitor of AKT.

In some embodiments, said inhibitor of AKT is an allosteric inhibitor of AKT. In some
25 embodiments, said allosteric inhibitor of AKT is selected from: MK-2206, miransertib (ARQ 092), ARQ 751, and BAY1125976; or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of AKT is an ATP-competitive inhibitor of AKT. In some embodiments, said ATP-competitive inhibitor of AKT is selected from: uprosertib (GSK2141795), GSK690693, LY2780301, ipatasertib (GDC-0068), and capivasertib
30 (AZD5363); or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of AKT is selected from: edelfosine, perifosine (KRX-0401), and afuresertib (GSK2110183); or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is an inhibitor of mTOR. In some embodiments, said inhibitor of mTOR is selected from: rapamycin, temsirolimus (CCI-779), everolimus (RAD001), ridaforolimus (AP23573; deforolimus; MK-8669), 32-deoxorapamycin (SAR943), Zotarolimus (ABT-578), PP242, PP30, WAY-600, 5 WYE-687, WYE-354, KU0063794, AZD8055, OSI-027, AZD2014, INK128, Torin 1, curcumin, resveratrol, epigallocatechin gallate (EGCG), genistein, 3,3-diindolylmethane (DIM), and caffeine; or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Buparlisib (NVP-BKM120; BKM120) or a pharmaceutically acceptable salt thereof.

10 In some embodiments, the inhibitor of PI3K, AKT, and/or mTOR is CH5132799 (PA-79) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Pilaralisib (XL147; SAR245408) or a pharmaceutically acceptable salt thereof.

15 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is ZSTK474 or a pharmaceutically acceptable salt thereof.

In some embodiments, said compound capable of inhibiting PI3K, AKT, and/or mTOR is Sonolisib (PX-866) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Pictilisib (GDC-0941; RG7321) or a pharmaceutically acceptable salt thereof.

20 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Copanlisib (BAY 80-6946; Aliqopa) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is B591 or a pharmaceutically acceptable salt thereof.

25 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is TG-100-115 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is RIDR-PI-103 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is BYL719 (Alpelisib; Piqray) or a pharmaceutically acceptable salt thereof.

30 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Serabelisib (INK-117; MLN-117; TAK-117) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is GSK2636771 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Idelalisib (GS-1101; CAL-101; Zydelig) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Zandelisib (ME-401; PWT-143) or a pharmaceutically acceptable salt thereof.

5 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is AMG 319 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is YY-20394 (Linerlisib) or a pharmaceutically acceptable salt thereof.

10 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is INCB050465 (Parsaclisib; IBI-376) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Umbralisib (TGR-1202; RP5264) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Tenalisib (RP6530) or a pharmaceutically acceptable salt thereof.

15 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Taselisib/GDC-0032/RG-7604 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is AZD8186 or a pharmaceutically acceptable salt thereof.

20 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is AZD8835 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is IPI-145/Duvelisib/INK1197 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Leniolisib (CDZ173) or a pharmaceutically acceptable salt thereof.

25 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Eganelisib (IPI-549) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Dactolisib (BEZ-235; NVP-BEZ235) or a pharmaceutically acceptable salt thereof.

30 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Apatolisib (GDC-0980, RG7422) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Gedatolisib (PF-05212384; PKI-587) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is SF1126 or a

pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Omipalisib (GSK458; GSK2126458) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Samotolisib
5 (LY3023414) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Bimiralisib (PQR309; also identified herein as Compound 1*) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Paxalisib (GDC-
10 0084; RG7666) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is XL765 (Voxtalisib; SAR245409) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is GNE-493 or a pharmaceutically acceptable salt thereof.

15 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is GNE-477 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is PF-04691502 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is WJD008 or a
20 pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is BGT226 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is MK-2206 or a pharmaceutically acceptable salt thereof.

25 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is miransertib (ARQ 092) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is ARQ 751 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is BAY1125976 or
30 a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is uprosertib (GSK2141795) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is GSK690693 or

a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is LY2780301 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is ipatasertib (GDC-
5 0068) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is capivasertib (AZD5363) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is edelfosine or a pharmaceutically acceptable salt thereof.

10 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is perifosine (KRX-0401) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is afuresertib (GSK2110183) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is rapamycin or a
15 pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is temsirolimus (CCI-779) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is everolimus (RAD001) or a pharmaceutically acceptable salt thereof.

20 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is ridaforolimus (AP23573; deforolimus; MK-8669) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is 32-deoxorapamycin (SAR943) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Zotarolimus
25 (ABT-578) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is PP242 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is PP30 or a pharmaceutically acceptable salt thereof.

30 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is WAY-600 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is WYE-687 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is WYE-354 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is KU0063794 or a pharmaceutically acceptable salt thereof.

5 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is AZD8055 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is OSI-027 or a pharmaceutically acceptable salt thereof.

10 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is AZD2014 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is INK128 or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is Torin 1 or a pharmaceutically acceptable salt thereof.

15 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is curcumin or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is resveratrol or a pharmaceutically acceptable salt thereof.

20 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is epigallocatechin gallate (EGCG) or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is genistein or a pharmaceutically acceptable salt thereof.

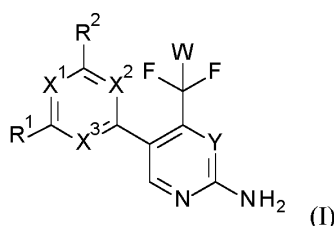
In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is 3,3-diindolylmethane (DIM) or a pharmaceutically acceptable salt thereof.

25 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is caffeine or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is FB214, or a pharmaceutically acceptable salt thereof.

30 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is JBL200, or a pharmaceutically acceptable salt thereof.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is AF030, or a pharmaceutically acceptable salt thereof. In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is a compound of Formula (I):



wherein:

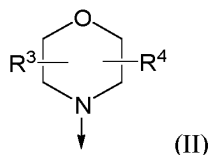
X^1 , X^2 and X^3 are, independently of each other, N or CH; with the proviso that at least two of X^1 , X^2 and X^3 are N;

5 Y is N or CH;

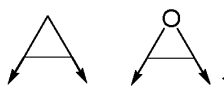
W is H or F; with the proviso that when W is F, then X^1 , X^2 and X^3 are N;

R^1 and R^2 are independently of each other

(i) a morpholinyl of formula (II)



10 wherein the arrow denotes the bond in formula (I); and wherein R^3 and R^4 are independently of each other H, C₁-C₃alkyl optionally substituted with one or two OH, C₁-C₂fluoroalkyl, C₁-C₂alkoxy, C₁-C₂alkoxyC₁-C₃alkyl, CN, or C(O)O-C₁-C₂alkyl; or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from C₁-C₃alkylene optionally substituted with 1 to 4 F, $-\text{CH}_2\text{-O-CH}_2-$, $-\text{CH}_2\text{-NH-CH}_2-$, or any of the structures



15

wherein the arrows denote the bonds in formula (II); or

(ii) a saturated 6-membered heterocyclic ring Z selected from thiomorpholinyl and piperazinyl, optionally substituted by 1 to 3 R^7 ; wherein R^7 is independently at each occurrence C₁-C₃alkyl optionally substituted with one or two OH, C₁-C₂fluoroalkyl, C₁-C₂alkoxyC₁-C₃alkyl, C₃-C₆cycloalkyl; or two R^7 substituents form together a bivalent residue $-R^8R^9-$ selected from C₁-C₃alkylene optionally substituted with 1 to 4 F, $-\text{CH}_2\text{-O-CH}_2-$ or $-\text{O-CH}_2\text{CH}_2\text{-O-}$;

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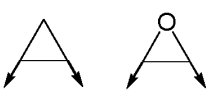
with the proviso that at least one of R^1 and R^2 is a morpholinyl of formula II;

and prodrugs, metabolites, tautomers, solvates and pharmaceutically acceptable salts

25 thereof.

In some embodiments of Formula I, R^3 and R^4 denote two independent substitutions and substituents, as defined herein, of said morpholinyl of formula (II) which are either both on the same carbon atom of said morpholinyl of formula (II) or on different carbon atoms of said morpholinyl of formula (II), and, hereby further, either on the same carbon-carbon bridge or on different carbon-carbon bridges linking the heteroatoms of said morpholinyl of formula (II).

Typically and preferably, when R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from C_1 - C_3 alkylene optionally substituted with 1 to 4 F, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures

, wherein the arrows denote the bonds in formula (II), then said bivalent residue $-R^5R^6-$ and said bonds denoted by said arrows are linked to carbon atoms located on different carbon-carbon bridges linking the heteroatoms of said morpholinyl of formula (II).

In a preferred embodiment, (i) said X^1 and said X^2 are N, and said X^3 is CH; (ii) said X^1 and said X^3 are N, and said X^2 is CH; or (iii) said X^2 and said X^3 are N, and said X^1 is CH, and preferably tautomers, solvates and pharmaceutically acceptable salts thereof.

In some embodiments, (i) said X^1 and said X^2 are N, and said X^3 is CH; or (ii) said X^2 and said X^3 are N, and said X^1 is CH, and preferably tautomers, solvates and pharmaceutically acceptable salts thereof.

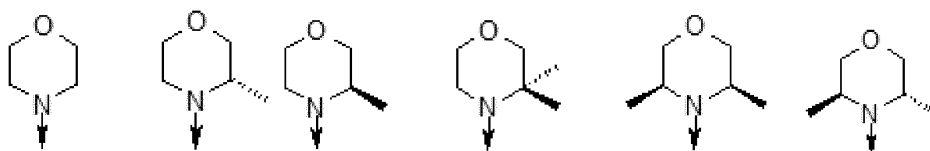
In a preferred embodiment, said X^1 and said X^3 are N, and said X^2 is CH; and preferably tautomers, solvates and pharmaceutically acceptable salts thereof.

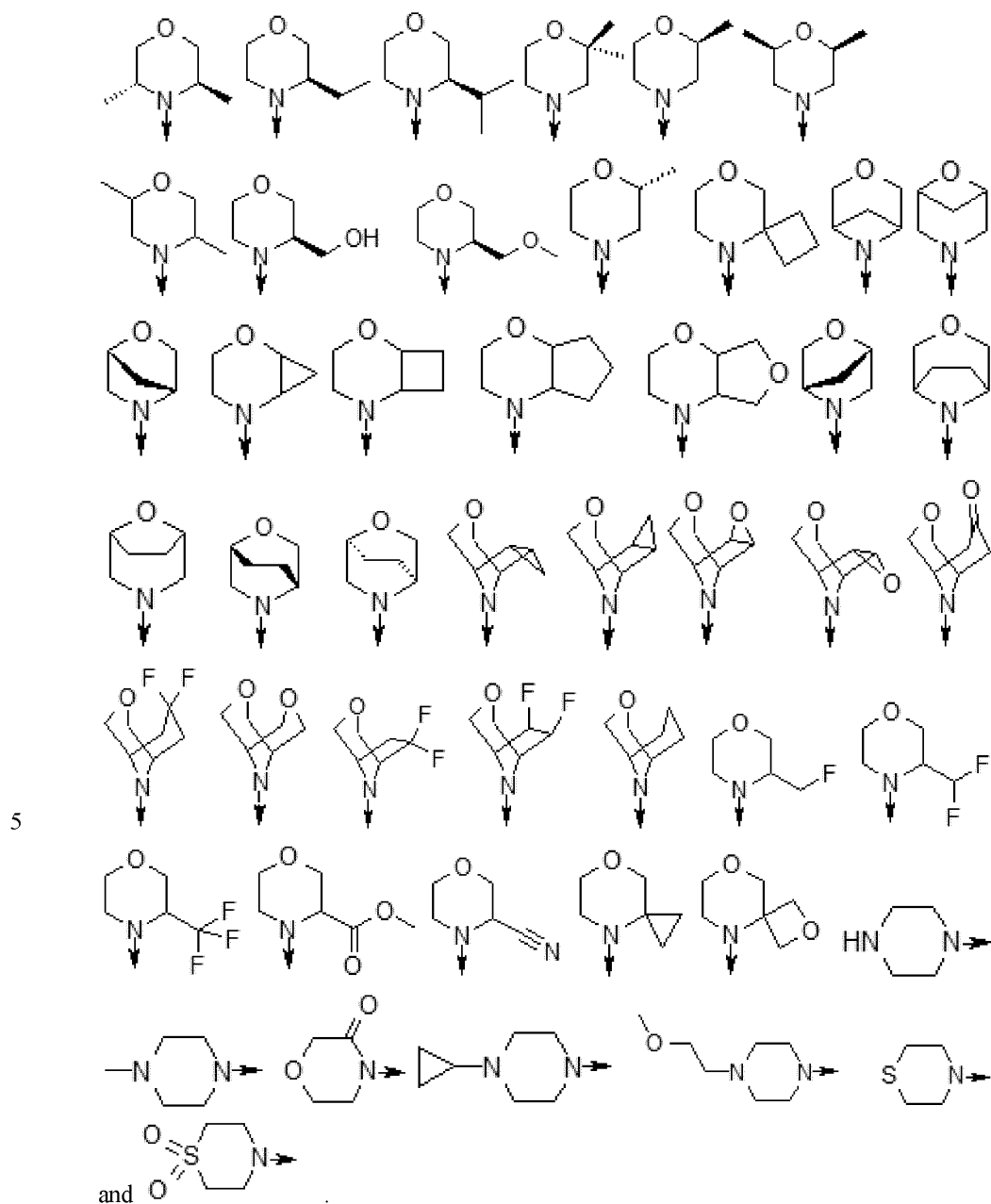
In a preferred embodiment, W is H.

In a preferred embodiment, W is F.

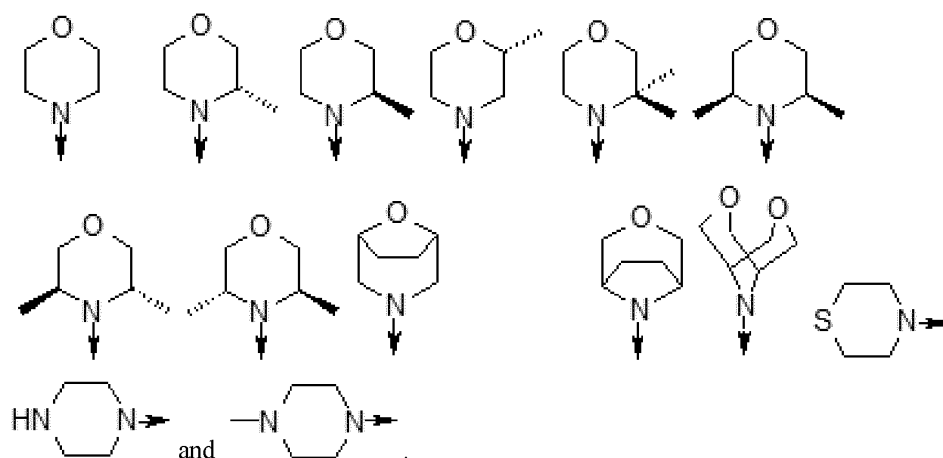
In another preferred embodiment, said Y is N, and preferably tautomers, solvates and pharmaceutically acceptable salts thereof. In another preferred embodiment, said Y is CH, and preferably tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said R^1 and said R^2 are independently of each other selected from:



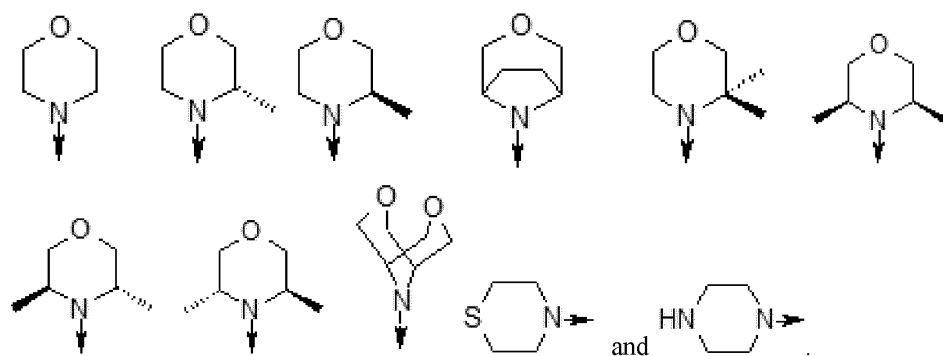


In another preferred embodiment, said R¹ and said R² are independently of each other
 10 selected from:

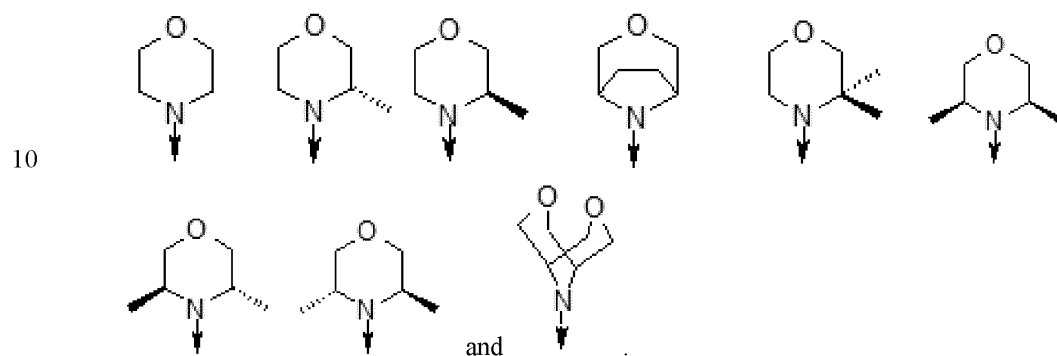


In another preferred embodiment, said R^1 and said R^2 are independently of each other selected from:

5 other selected from:



In another preferred embodiment, said R^1 and said R^2 are independently of each other selected from:



10

In another preferred embodiment, said compound is selected from 1, 1*, 2, 2*, 3, 4, 5, 6, 6*, 7, 7*, 8, 8*, 9, 9*, 10, 11, 12, 12*, 13, 13*, 14, 15, 16, 17, 18, 19, 20, 20*, 21, 21*, 22,

23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 37, 38, 39, 40, 41, 42, 44, 45, 46, 47, 50, 51, 52, 53, 54, 55, 56, 66, 67, 68, 69, 70, 71, 77, 78, 79, 80, 82, 83, 84, 85, 86 and 88, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said compound is selected from 1, 1*, 2, 2*, 3, 4, 5, 6, 6*, 7, 7*, 8, 8*, 9, 9*, 10, 11, 12, 12*, 13, 13*, 14, 15, 16, 17, 18, 19, 20, 20*, 21, 21*, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 37, 38, 39, 40, 41, 42, 44, 45, 46, 47, 82, 83, 84, 85, 86 and 88, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said compound is selected from 1, 1*, 2, 2*, 3, 4, 6*, 7, 7*, 8, 8*, 9, 9*, 12*, 13, 13*, 20*, 21*, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 82, 83, 84, 85, 86 and 88; and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said compound is selected from 1, 2, 3, 4, 7, 8, 9, 13, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 82, 83, 84, 85, 86 and 88, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said compound is selected from 1, 1*, 2, 2*, 3, 4, 6*, 7, 7*, 8, 8*, 9, 9*, 12*, 13, 13*, 20*, 21* and 44, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said compound is selected from 1, 1*, 2, 2*, 3, 4, 6*, 7, 7*, 8, 8*, 9, 9*, 12*, 13, 13*, 20*, 21*, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said compound is selected from 1, 2, 3, 4, 7, 8, 9, 13 and 44, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said compound is selected from:

1: 4-(difluoromethyl)-5-(4,6-dimorpholino-1,3,5-triazin-2-yl)pyridin-2-amine;

2: 4-(difluoromethyl)-5-(4,6-dimorpholino-1,3,5-triazin-2-yl)pyrimidin-2-amine;

3: 5-(4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-1,3,5-triazin-2-yl)-4-(difluoromethyl)pyridin-2-amine;

4: 5-(4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-morpholino-1,3,5-triazin-2-yl)-4-(difluoromethyl)pyridin-2-amine;

5: 5-(4,6-bis((S)-3-methylmorpholino)-1,3,5-triazin-2-yl)-4-(difluoromethyl)pyrimidin-2-amine;

8: (S)-4-(difluoromethyl)-5-(4-(3-methylmorpholino)-6-morpholino-1,3,5-triazin-2-yl)pyridin-2-amine;

9: (S)-4-(difluoromethyl)-5-(4-(3-methylmorpholino)-6-morpholino-1,3,5-triazin-2-

yl)pyrimidin-2-amine;

13: 4-(difluoromethyl)-5-(4-morpholino-6-(piperazin-1-yl)-1,3,5-triazin-2-yl)pyrimidin-2-amine; and

44: 4-(difluoromethyl)-5-[4-[(3*R*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-[(3*R*)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]pyridin-2-amine.

In another preferred embodiment, said compound is selected from 1, 2, 3, 4, 7, 8, 9 and 13, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said compound is selected from 1*, 2*, 6*, 7*, 8*, 9*, 12*, 13*, 20* and 21*, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said compound is selected from 1*, 2*, 6*, 7*, 8*, 9* and 20*, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said compound is selected from:

- 1*: 5-(4,6-dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine;
15 2*: 5-(4,6-dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyrimidin-2-amine;
6*: 5-[4,6-bis[(3*S*)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]-4-(trifluoromethyl)pyridin-2-amine;
7*: 5-[4,6-bis[(3*S*)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]-4-(trifluoromethyl)pyrimidin-2-amine;
20 8*: 5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-morpholino-1,3,5-triazin-2-yl]-4-(trifluoromethyl)pyridin-2-amine;
9*: 5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-morpholino-1,3,5-triazin-2-yl]-4-(trifluoromethyl)pyrimidin-2-amine; and
25 20*: 5-(4-morpholino-6-thiomorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine.

In another preferred embodiment, said compound is selected from 1*, 2; 2*, 3; 6*, 7*, 8; 8*, 9*, 20* and 44, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said compound is selected from 1*, 2; 2*, 3; 6*, 7*, 8; 8*, 9*, 12*, 13*, 20* and 21*, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said compound is selected from 2, 3, 8 and 44, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said compound is selected from 2, 3, and 8, and

tautomers, solvates and pharmaceutically acceptable salts thereof.

In another very preferred embodiment, said compound is selected from 3, 8 and 44, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another very preferred embodiment, said compound is selected from 3 and 8; and
5 tautomers, solvates and pharmaceutically acceptable salts thereof.

In another very preferred embodiment, said compound is selected from 3, 8, 44 and 1*; and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another very preferred embodiment, said compound is selected from 3, 8, and 1*; and tautomers, solvates and pharmaceutically acceptable salts thereof.

10 In another very preferred embodiment, said compound is selected from 3, 44 and 1*, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another very preferred embodiment, said compound is selected from 3 and 1*, and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another very preferred embodiment, said compound of formula (I) is 2.

15 In another very preferred embodiment, said compound of formula (I) is 2; and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another very preferred embodiment, said compound of formula (I) is 3.

In another very preferred embodiment, said compound of formula (I) is 3; and tautomers, solvates and pharmaceutically acceptable salts thereof.

20 In another very preferred embodiment, said compound of formula (I) is 8.

In another very preferred embodiment, said compound of formula (I) is 8; and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another very preferred embodiment, said compound of formula (I) is 44.

In another very preferred embodiment, said compound of formula (I) is 44; and
25 tautomers, solvates and pharmaceutically acceptable salts thereof.

In another very preferred embodiment, said compound of formula (I) is 1*.

In another very preferred embodiment, said compound of formula (I) is 1*; and tautomers, solvates and pharmaceutically acceptable salts thereof.

In another preferred embodiment, said R^1 and R^2 are independently of each other a morpholinyl of formula (II). In one preferred embodiment, said R^1 is equal to R^2 . In another preferred embodiment, said R^1 is not equal to R^2 .
30

In another preferred embodiment, said W is H, and said R^1 and R^2 are independently of each other a morpholinyl of formula (II). In one preferred embodiment, said R^1 is equal to

R^2 . In another preferred embodiment, said R^1 is not equal to R^2 .

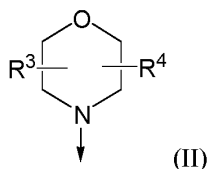
In another preferred embodiment, said W is F, said R^1 and R^2 are independently of each other a morpholinyl of formula (II). In one preferred embodiment, said R^1 is equal to R^2 . In another preferred embodiment, said R^1 is not equal to R^2 .

5 In another preferred embodiment, said R^1 and R^2 are independently of each other a morpholinyl of formula (II) and said saturated 6-membered heterocyclic ring Z.

In another preferred embodiment, said W is H, and said R^1 and R^2 are independently of each other a morpholinyl of formula (II) and said saturated 6-membered heterocyclic ring Z.

10 In another preferred embodiment, said W is F, and said R^1 and R^2 are independently of each other a morpholinyl of formula (II) and said saturated 6-membered heterocyclic ring Z.

In another preferred embodiment, within said morpholinyl of formula (II)

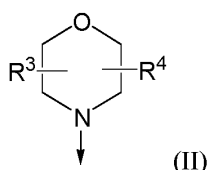


R^3 and R^4 are independently of each other H, C_1 - C_3 alkyl optionally substituted with one or two OH, C_1 - C_2 fluoroalkyl, C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl; or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from C_1 - C_3 alkylene optionally substituted with 1 to 4 F, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures



; wherein the arrows denote the bonds in formula (II).

In another preferred embodiment, within said morpholinyl of formula (II)



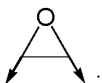
20 R^3 and R^4 are independently of each other H, C_1 - C_2 alkyl, preferably methyl, optionally substituted with one or two, preferably one, OH; C_1 - C_2 fluoroalkyl, C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl; or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from C_1 - C_3 alkylene optionally substituted with 1 to 4 F, $-CH_2-O-CH_2-$, $-CH_2-$
 25 $NH-CH_2-$, or any of the structures



; wherein the arrows denote the bonds in formula (II).

In the instance that R³ and R⁴ together form a bivalent residue and are bound to vicinal carbon atoms annulated morpholinyl substituents are formed. In the instance that R³ and R⁴ together form a bivalent residue and are spanning across the morpholine ring bridged morpholinyl substituents are formed. In the instance that R³ and R⁴ together form a bivalent residue and are bound to the same carbon atom of the morpholine, spiro morpholinyl substituents are formed.

In a preferred embodiment, R³ and R⁴ form together a bivalent residue –R⁵R⁶– selected from C₁-C₃alkylene optionally substituted with 1 to 4 F, -CH₂-O-CH₂-, -CH₂-NH-CH₂-, or any of the structures



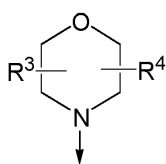
and forming a bridged morpholinyl substituent.

In another preferred embodiment, said R¹ and R² are independently of each other a morpholinyl of formula (II), wherein R³ and R⁴ form together a bivalent residue leading to a bridged morpholinyl, wherein R³ and R⁴ form together a bivalent residue –R⁵R⁶– selected from C₁-C₃alkylene, preferably C₁-C₂alkylene, -CH₂CF₂-, -CHFCHF-, -CH₂CF₂CH₂-, -CH₂-O-CH₂-, -CH₂-NH-CH₂-, or any of the structures



; wherein the arrows denote the bonds in formula (II).

In a further preferred embodiment, said morpholinyl of formula (II)



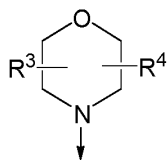
(II)

is independently of each other a morpholinyl of said formula (II), wherein R³ and R⁴ are independently of each other H, C₁-C₃alkyl, CH₂OH, CH₂CH₂OH, CH₂F, CHF₂, CF₃, CH₂CF₃, C₁-C₂alkoxy, C₁-C₂alkoxyC₁-C₃alkyl, CN, or C(O)O-C₁-C₂alkyl; or R³ and R⁴ form together a bivalent residue –R⁵R⁶– selected from C₁-C₃alkylene, preferably C₁-C₂alkylene, -CH₂CF₂-, -CHFCHF-, -CH₂CF₂CH₂-, -CH₂-O-CH₂-, -CH₂-NH-CH₂-, or any of the structures



; wherein the arrows denote the bonds in formula (II).

In a further preferred embodiment, said morpholinyl of formula (II)



(II)

is independently of each other a morpholinyl of said formula (II), wherein R^3 and R^4 are independently of each other H, C_1 - C_2 alkyl, preferably methyl; CH_2OH , CH_2CH_2OH , CH_2F , CHF_2 , CF_3 , CH_2CF_3 , C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl; or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from C_1 - C_3 alkylene, preferably C_1 - C_2 alkylene, $-CH_2CF_2-$, $-CHFCHF-$, $-CH_2CF_2CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures



10

; wherein the arrows denote the bonds in formula (II).

In a further preferred embodiment, said morpholinyl of formula (II) is independently of each other a morpholinyl of said formula (II), wherein R^3 and R^4 are independently of each other H or CH_3 .

In a further preferred embodiment, said morpholinyl of formula (II) is independently of each other a morpholinyl of said formula (II), wherein R^3 and R^4 are independently of each other C_1 - C_2 alkyl, preferably methyl; CH_2OH , CH_2CH_2OH , CH_2F , CHF_2 , CF_3 , CH_2CF_3 , C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl; or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from $-CH_2-$ or C_3 alkylene, preferably $-CH_2-$, $-CH_2CF_2-$, $-CHFCHF-$, $-CH_2CF_2CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures

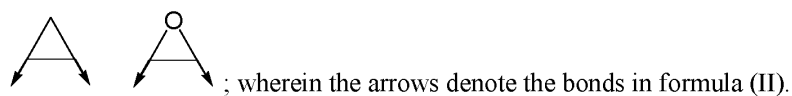


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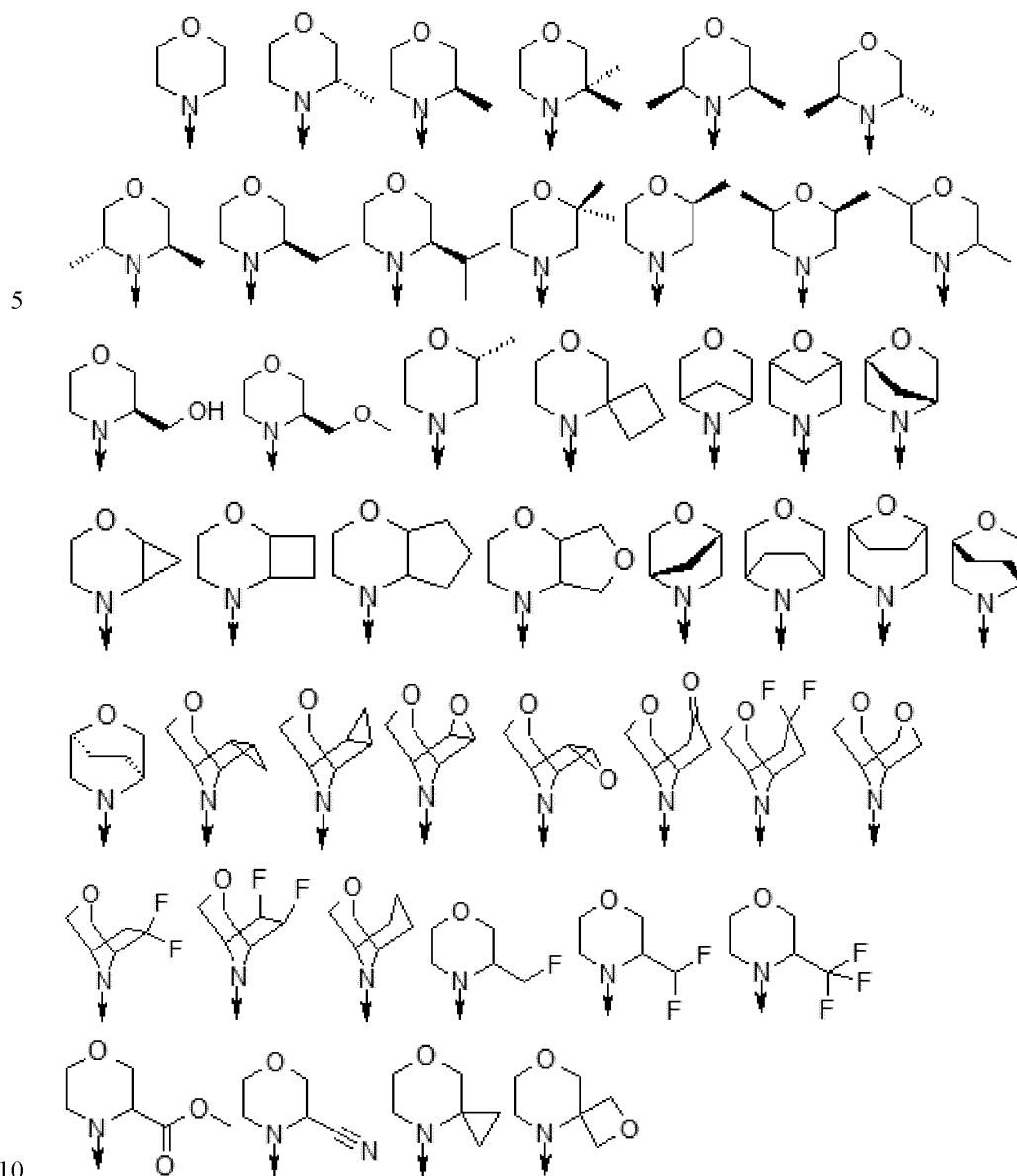
; wherein the arrows denote the bonds in formula (II).

In a further preferred embodiment, said morpholinyl of formula (II) is independently of each other a morpholinyl of said formula (II), wherein R^3 and R^4 are independently of each other C_2 - C_3 alkyl, CH_2OH , CH_2CH_2OH , CH_2F , CHF_2 , CF_3 , CH_2CF_3 , C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl; or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from $-CH_2-$ or C_3 alkylene, preferably $-CH_2-$, $-CH_2CF_2-$, $-CHFCHF-$, $-CH_2CF_2CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures

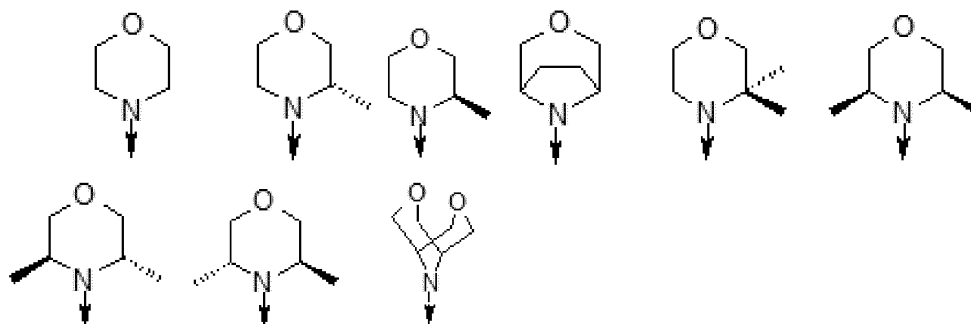
25



In a further preferred embodiment, said morpholinyl of formula (II) is independently of each other selected from

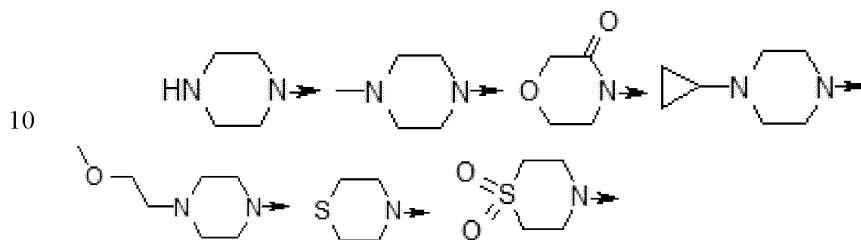


In a further preferred embodiment, said morpholinyl of formula (II) is independently of each other selected from

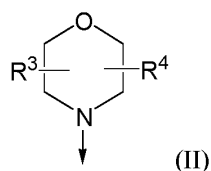


In a further preferred embodiment, said heterocyclic ring Z is a saturated 6-membered heterocyclic ring Z selected from thiomorpholinyl and piperazinyl, optionally substituted by 1 to 3 R^7 ; wherein R^7 is independently at each occurrence C_1 - C_3 alkyl, CH_2OH , CH_2CH_2OH , CH_2F , CHF_2 , CF_3 , CH_2CF_3 , C_1 - C_2 alkoxy C_1 - C_3 alkyl, C_3 - C_6 cycloalkyl; or two R^7 substituents form together a bivalent residue $-R^8R^9-$ selected from C_1 - C_3 alkylene optionally substituted with 1 to 4 F, $-CH_2-O-CH_2-$ or $-O-CH_2CH_2-O-$;

In a further preferred embodiment, said heterocyclic ring Z is selected from



In another preferred embodiment of the present invention, said R^1 and said R^2 are independently of each other a morpholinyl of formula (II)



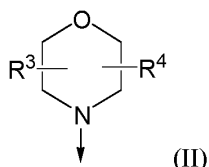
wherein the arrow denotes the bond in formula (I); and

wherein R^3 and R^4 are independently of each other H, C_1 - C_3 alkyl optionally substituted with one or two OH, C_1 - C_2 fluoroalkyl, C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl; or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from C_1 - C_3 alkylene optionally substituted with 1 to 4 F, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures



wherein the arrows denote the bonds in formula (II).

In another preferred embodiment of the present invention, said R^1 and said R^2 are independently of each other a morpholinyl of formula (II)



5 wherein the arrow denotes the bond in formula (I); and

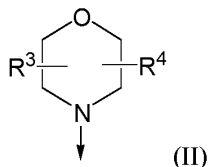
wherein R^3 and R^4 are independently of each other H, C_1 - C_2 alkyl, preferably methyl, optionally substituted with one or two, preferably one, OH; C_1 - C_2 fluoroalkyl, C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl; or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from C_1 - C_3 alkylene optionally substituted with 1 to 4 F, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures

10 , $-CH_2-NH-CH_2-$, or any of the structures



wherein the arrows denote the bonds in formula (II).

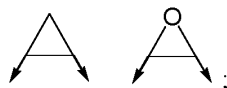
In a further preferred embodiment, said R^1 is equal to said R^2 , and said R^1 and said R^2 are independently of each other a morpholinyl of formula (II)



15 wherein the arrow denotes the bond in formula (I); and

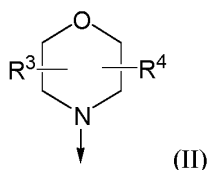
wherein R^3 and R^4 are independently of each other H, C_1 - C_3 alkyl optionally substituted with one or two OH, C_1 - C_2 fluoroalkyl, C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl; or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from C_1 - C_3 alkylene optionally substituted with 1 to 4 F, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures

20 optionally substituted with 1 to 4 F, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures



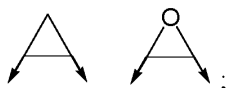
wherein the arrows denote the bonds in formula (II).

In a further preferred embodiment of the present invention, said R^1 and said R^2 are independently of each other a morpholinyl of formula (II)



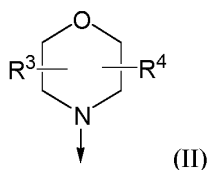
wherein the arrow denotes the bond in formula (I); and

- wherein R^3 and R^4 are independently of each other H, C_1 - C_3 alkyl, CH_2OH , CH_2CH_2OH , CH_2F , CHF_2 , CF_3 , CH_2CF_3 , C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl;
 5 or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from C_1 - C_3 alkylene, preferably C_1 - C_2 alkylene, $-CH_2CF_2-$, $-CHFCHF-$, $-CH_2CF_2CH_2-$,
 $-CH_2OCH_2-$, $-CH_2NHCH_2-$, or any of the structures



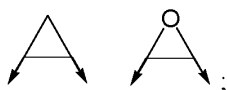
wherein the arrows denote the bonds in formula (II).

- 10 In a further preferred embodiment of the present invention, said R^1 and said R^2 are independently of each other a morpholinyl of formula (II)



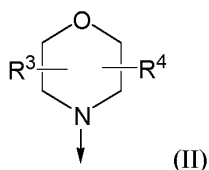
wherein the arrow denotes the bond in formula (I); and

- wherein R^3 and R^4 are independently of each other H, C_1 - C_2 alkyl, preferably methyl;
 15 CH_2OH , CH_2CH_2OH , CH_2F , CHF_2 , CF_3 , CH_2CF_3 , C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl; or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from C_1 - C_3 alkylene, preferably C_1 - C_2 alkylene, $-CH_2CF_2-$, $-CHFCHF-$, $-CH_2CF_2CH_2-$,
 $-CH_2OCH_2-$, $-CH_2NHCH_2-$, or any of the structures



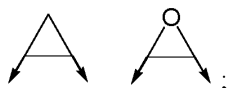
- 20 wherein the arrows denote the bonds in formula (II).

In a further preferred embodiment of the present invention, R^1 is equal to R^2 , and said R^1 and said R^2 are a morpholinyl of formula (II)



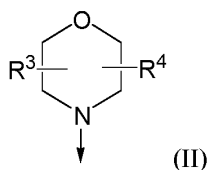
wherein the arrow denotes the bond in formula (I); and

- wherein R^3 and R^4 are independently of each other H, C_1 - C_3 alkyl, CH_2OH , CH_2CH_2OH , CH_2F , CHF_2 , CF_3 , CH_2CF_3 , C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl;
 5 or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from C_1 - C_3 alkylene, preferably C_1 - C_2 alkylene, $-CH_2CF_2-$, $-CHFCHF-$, $-CH_2CF_2CH_2-$,
 $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures



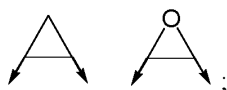
wherein the arrows denote the bonds in formula (II).

- 10 In a further preferred embodiment of the present invention, R^1 is equal to R^2 , and said R^1 and said R^2 are a morpholinyl of formula (II)



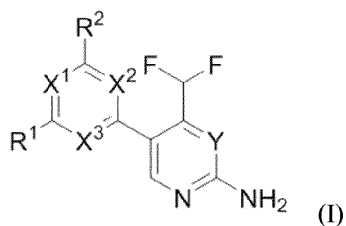
wherein the arrow denotes the bond in formula (I); and

- wherein R^3 and R^4 are independently of each other H, C_1 - C_2 alkyl, preferably methyl;
 15 CH_2OH , CH_2CH_2OH , CH_2F , CHF_2 , CF_3 , CH_2CF_3 , C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl; or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from C_1 - C_3 alkylene, preferably C_1 - C_2 alkylene, $-CH_2CF_2-$, $-CHFCHF-$, $-CH_2CF_2CH_2-$,
 $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures



- 20 wherein the arrows denote the bonds in formula (II).

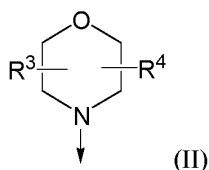
In some embodiments, the inhibitor of PI3K, AKT, and/or mTOR is a compound of Formula (I):



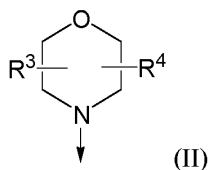
wherein

X^1 , X^2 and X^3 are, independently of each other, N or CH; with the proviso that at least two of X^1 , X^2 and X^3 are N; Y is N or CH; and wherein

5 R^1 and R^2 are independently of each other a morpholinyl of formula (II)



wherein the arrow denotes the bond in formula (I); and R^1 is not equal to R^2 , and at least one of said R^1 and said R^2 are a morpholinyl of formula (II),

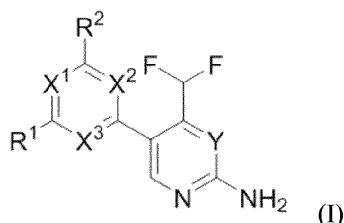


10 wherein R^3 and R^4 are independently of each other C_2 - C_3 alkyl, CH_2OH , CH_2CH_2OH , CH_2F , CHF_2 , CF_3 , CH_2CF_3 , C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl; or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from $-CH_2-$ or C_3 alkylene, preferably $-CH_2-$, $-CH_2CF_2-$, $-CHFCHF-$, $-CH_2CF_2CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures



15 ; wherein the arrows denote the bonds in formula (II).

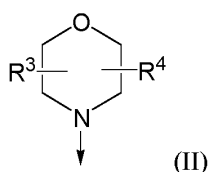
In another aspect and preferred embodiment, the inhibitor of PI3K, AKT, and/or mTOR is a compound of Formula (I):



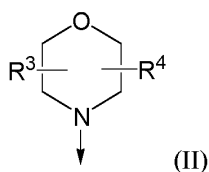
wherein

X^1 , X^2 and X^3 are, independently of each other, N or CH; with the proviso that at least two of X^1 , X^2 and X^3 are N; Y is N or CH; and wherein

5 R^1 and R^2 are independently of each other a morpholinyl of formula (II)



wherein the arrow denotes the bond in formula (I); and R^1 is not equal to R^2 , and at least one of said R^1 and said R^2 are a morpholinyl of formula (II),



10 wherein R^3 and R^4 are independently of each other C_1 - C_2 alkyl, preferably methyl; CH_2OH , CH_2CH_2OH , CH_2F , CHF_2 , CF_3 , CH_2CF_3 , C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl; or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from $-CH_2-$ or C_3 alkylene, preferably $-CH_2-$, $-CH_2CF_2-$, $-CHFCHF-$, $-CH_2CF_2CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures



15 ; wherein the arrows denote the bonds in formula (II).

Preferably, said R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from $-CH_2-$ or C_3 alkylene, preferably $-CH_2-$, $-CH_2CF_2-$, $-CHFCHF-$, $-CH_2CF_2CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures



20 In another preferred embodiment, R^1 is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, 3,5-dimethyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-

acceptable salts thereof.

In a further preferred embodiment, R¹ is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, 3,5-dimethyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl or 3-aza-8-oxabicyclo[3.2.1]oct-3-yl; and R² is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl, 3-aza-8-oxabicyclo[3.2.1]oct-3-yl, 4-piperazin-1-yl, 4-methylpiperazin-1-yl, or 4-thiomorpholinyl, and X¹ and X³ are N, and X² is CH; and tautomers, solvates and pharmaceutically acceptable salts thereof. In a further preferred embodiment, R¹ is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl or 3-aza-8-oxabicyclo[3.2.1]oct-3-yl; and R² is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl, 3-aza-8-oxabicyclo[3.2.1]oct-3-yl, 4-piperazin-1-yl, 4-methylpiperazin-1-yl, or 4-thiomorpholinyl, and X¹ and X³ are N, and X² is CH; and tautomers, solvates and pharmaceutically acceptable salts thereof. Preferably Y is N or CH; R¹ is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, 3,5-dimethyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl or 3-aza-8-oxabicyclo[3.2.1]oct-3-yl; and R² is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl, 3-aza-8-oxabicyclo[3.2.1]oct-3-yl, 4-piperazin-1-y, 4-methylpiperazin-1-yl, or 4-thiomorpholinyl; and tautomers, solvates and pharmaceutically acceptable salts thereof. Preferably Y is N or CH; R¹ is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl or 3-aza-8-oxabicyclo[3.2.1]oct-3-yl; and R² is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl, 3-aza-8-oxabicyclo[3.2.1]oct-3-yl, 4-piperazin-1-y, 4-methylpiperazin-1-yl, or 4-thiomorpholinyl; and tautomers, solvates and pharmaceutically acceptable salts thereof.

In a preferred embodiment, R¹ is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, 3,5-dimethyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl or 3-aza-8-oxabicyclo[3.2.1]oct-3-yl; and R² is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl, 3-aza-8-oxabicyclo[3.2.1]oct-3-yl, 4-piperazin-1-yl, 4-methylpiperazin-1-yl, or 4-thiomorpholinyl, and X¹ and X² are N, and X³ is CH; and

tautomers, solvates and pharmaceutically acceptable salts thereof. In a preferred embodiment, R¹ is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl or 3-aza-8-oxabicyclo[3.2.1]oct-3-yl; and R² is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl, 3-aza-8-oxabicyclo[3.2.1]oct-3-yl, 4-piperazin-1-yl, 4-methylpiperazin-1-yl, or 4-thiomorpholinyl, and X¹ and X² are N, and X³ is CH; and tautomers, solvates and pharmaceutically acceptable salts thereof. Preferably, Y is N or CH; R¹ is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, 3,5-dimethyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl or 3-aza-8-oxabicyclo[3.2.1]oct-3-yl; and R² is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl, 3-aza-8-oxabicyclo[3.2.1]oct-3-yl, 4-piperazin-1-yl, 4-methylpiperazin-1-yl, or 4-thiomorpholinyl; and tautomers, solvates and pharmaceutically acceptable salts thereof. Preferably, Y is N or CH; R¹ is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl or 3-aza-8-oxabicyclo[3.2.1]oct-3-yl; and R² is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl, 3-aza-8-oxabicyclo[3.2.1]oct-3-yl, 4-piperazin-1-yl, 4-methylpiperazin-1-yl, or 4-thiomorpholinyl; and tautomers, solvates and pharmaceutically acceptable salts thereof.

20 In a preferred embodiment, R¹ is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, 3,5-dimethyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl or 3-aza-8-oxabicyclo[3.2.1]oct-3-yl; and R² is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl, 3-aza-8-oxabicyclo[3.2.1]oct-3-yl, 4-piperazin-1-yl, 4-methylpiperazin-1-yl, or 4-thiomorpholinyl, and X² and X³ are N, and X¹ is CH; and tautomers, solvates and pharmaceutically acceptable salts thereof. In a preferred embodiment, R¹ is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl or 3-aza-8-oxabicyclo[3.2.1]oct-3-yl; and R² is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl, 3-aza-8-oxabicyclo[3.2.1]oct-3-yl, 4-piperazin-1-yl, 4-methylpiperazin-1-yl, or 4-thiomorpholinyl, and X² and X³ are N, and X¹ is CH; and tautomers, solvates and pharmaceutically acceptable salts thereof. Preferably, Y is N or CH; R¹ is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, 3,5-dimethyl-

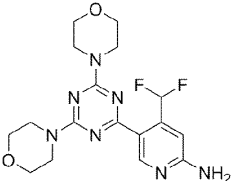
4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl or 3-aza-8-oxabicyclo[3.2.1]oct-3-yl; and R² is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl, 3-aza-8-oxabicyclo[3.2.1]oct-3-yl, 4-piperazin-1-yl, 4-methylpiperazin-1-yl, or 4-thiomorpholinyl;
 5 and tautomers, solvates and pharmaceutically acceptable salts thereof. Preferably, Y is N or CH; R¹ is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl or 3-aza-8-oxabicyclo[3.2.1]oct-3-yl; and R² is 4-morpholinyl, 2-methyl-4-morpholinyl, 3-methyl-4-morpholinyl, octadeuterio-4-morpholinyl, 8-aza-3-oxabicyclo[3.2.1]oct-8-yl, 3-aza-8-oxabicyclo[3.2.1]oct-3-yl, 4-piperazin-1-yl, 4-methylpiperazin-1-yl, or 4-thiomorpholinyl;
 10 and pharmaceutically acceptable salts thereof.

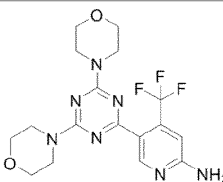
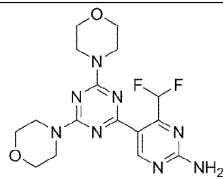
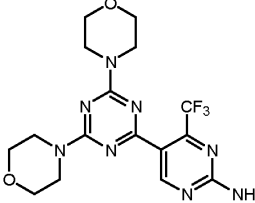
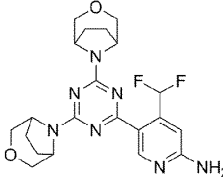
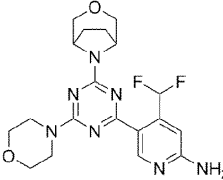
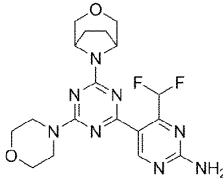
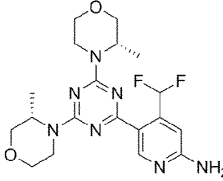
In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is selected from the group consisting of Compound 1*, and Compound 2, and Compound 8, and pharmaceutically acceptable salts thereof.

15 In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is selected from the group consisting of Compound 1* and Compound 2, and pharmaceutically acceptable salts thereof.

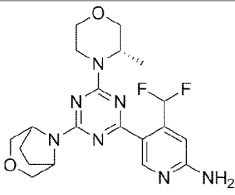
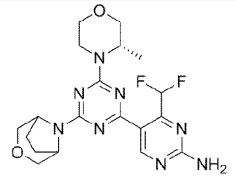
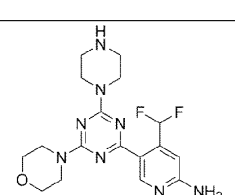
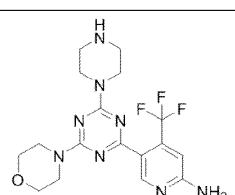
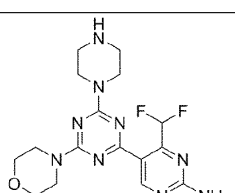
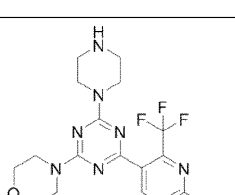
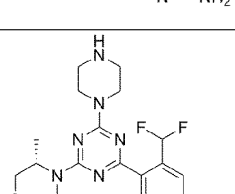
In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is bimiralisib, or a pharmaceutically acceptable salt thereof.

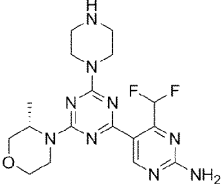
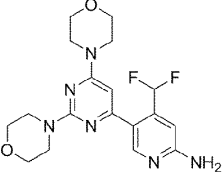
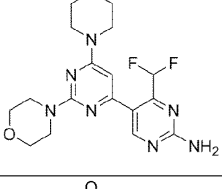
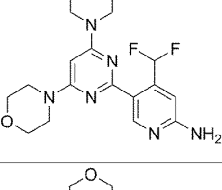
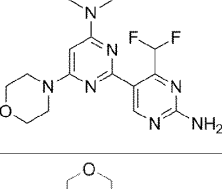
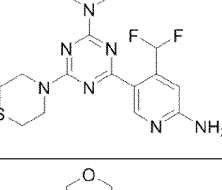
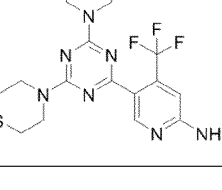
20 Most preferred for the present invention are the following compounds with the chemical structures shown below. The names of the corresponding structures were produced using ChemDraw Ultra, version 13.0.1 as well as lower and upper software versions thereof, CambridgeSoft Corp., Cambridge MA.

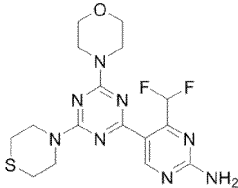
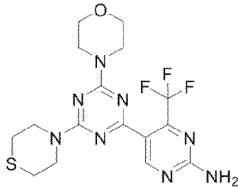
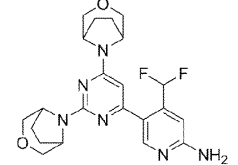
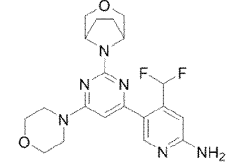
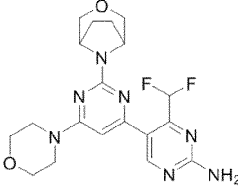
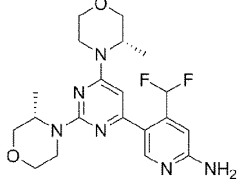
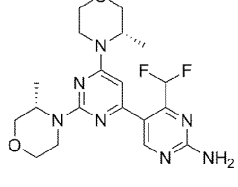
Compound		
1		4-(difluoromethyl)-5-(4,6-dimorpholino-1,3,5-triazin-2-yl)pyridin-2-amine

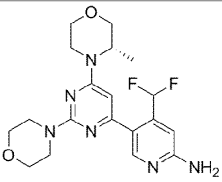
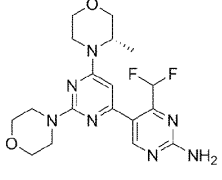
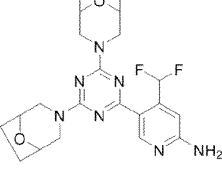
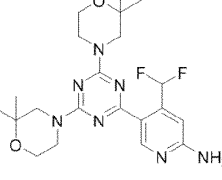
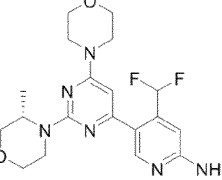
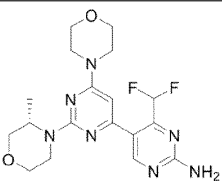
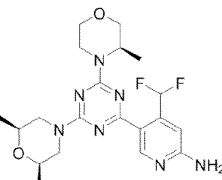
1*		5-(4,6-dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine
2		4-(difluoromethyl)-5-(4,6-dimorpholino-1,3,5-triazin-2-yl)pyrimidin-2-amine
2*		5-(4,6-dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyrimidin-2-amine
3		5-(4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-1,3,5-triazin-2-yl)-4-(difluoromethyl)pyridin-2-amine
4		5-(4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-morpholino-1,3,5-triazin-2-yl)-4-(difluoromethyl)pyridin-2-amine
5		5-(4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-morpholino-1,3,5-triazin-2-yl)-4-(difluoromethyl)pyrimidin-2-amine
6		5-(4,6-bis((S)-3-methylmorpholino)-1,3,5-triazin-2-yl)-4-(difluoromethyl)pyridin-2-amine

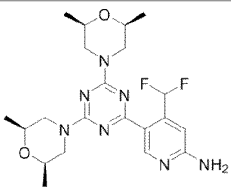
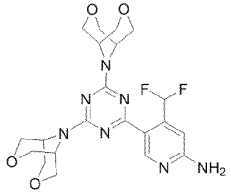
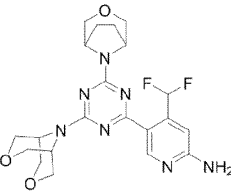
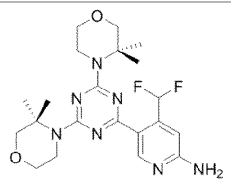
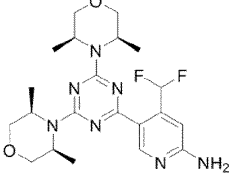
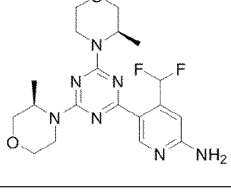
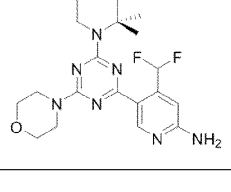
6*		5-[4,6-bis[(3S)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]-4-(trifluoromethyl)pyridin-2-amine
7		5-(4,6-bis[(S)-3-methylmorpholino]-1,3,5-triazin-2-yl)-4-(difluoromethyl)pyrimidin-2-amine
7*		5-[4,6-bis[(3S)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]-4-(trifluoromethyl)pyrimidin-2-amine
8		(S)-4-(difluoromethyl)-5-(4-(3-methylmorpholino)-6-morpholino-1,3,5-triazin-2-yl)pyridin-2-amine
8*		5-[4-[(3S)-3-methylmorpholin-4-yl]-6-morpholino-1,3,5-triazin-2-yl]-4-(trifluoromethyl)pyridin-2-amine
9		(S)-4-(difluoromethyl)-5-(4-(3-methylmorpholino)-6-morpholino-1,3,5-triazin-2-yl)pyrimidin-2-amine
9*		5-[4-[(3S)-3-methylmorpholin-4-yl]-6-morpholino-1,3,5-triazin-2-yl]-4-(trifluoromethyl)pyrimidin-2-amine

10		5-(4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-((S)-3-methylmorpholino)-1,3,5-triazin-2-yl)-4-(difluoromethyl)pyridin-2-amine
11		5-(4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-((S)-3-methylmorpholino)-1,3,5-triazin-2-yl)-4-(difluoromethyl)pyrimidin-2-amine
12		4-(difluoromethyl)-5-(4-morpholino-6-(piperazin-1-yl)-1,3,5-triazin-2-yl)pyridin-2-amine
12*		5-(4-morpholino-6-piperazin-1-yl)-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine
13		4-(difluoromethyl)-5-(4-morpholino-6-(piperazin-1-yl)-1,3,5-triazin-2-yl)pyrimidin-2-amine
13*		5-(4-morpholino-6-piperazin-1-yl)-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyrimidin-2-amine
14		(S)-4-(difluoromethyl)-5-(4-(3-methylmorpholino)-6-(piperazin-1-yl)-1,3,5-triazin-2-yl)pyridin-2-amine

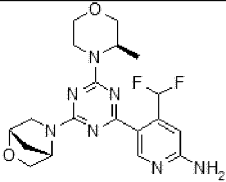
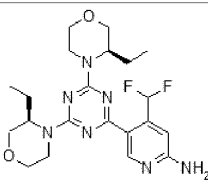
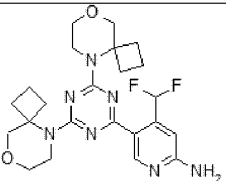
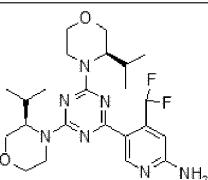
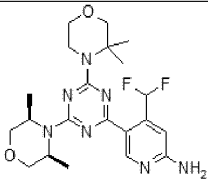
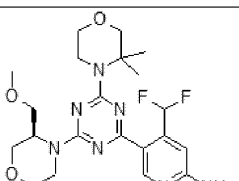
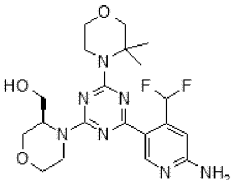
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16		4-(difluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine
17		4'-(difluoromethyl)-2,6-dimorpholino-[4,5'-bipyrimidin]-2'-amine
18		4-(difluoromethyl)-5-(4,6-dimorpholinopyrimidin-2-yl)pyridin-2-amine
19		4'-(difluoromethyl)-4,6-dimorpholino-[2,5'-bipyrimidin]-2'-amine
20		4-(difluoromethyl)-5-(4-morpholino-6-thiomorpholino-1,3,5-triazin-2-yl)pyridin-2-amine
20*		5-(4-morpholino-6-thiomorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine

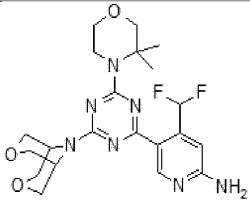
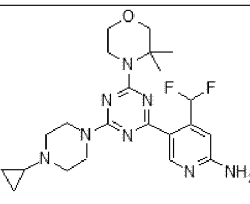
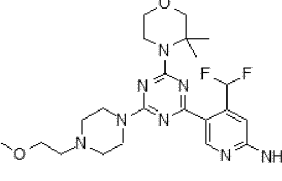
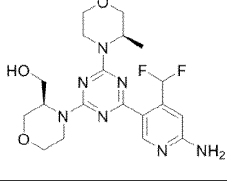
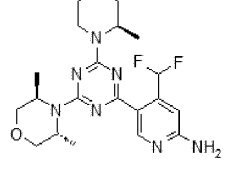
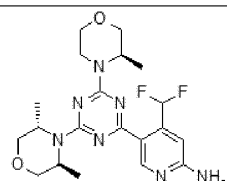
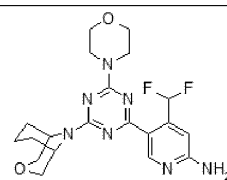
21		4-(difluoromethyl)-5-(4-morpholino-6-thiomorpholino-1,3,5-triazin-2-yl)pyrimidin-2-amine
21*		5-(4-morpholino-6-thiomorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyrimidin-2-amine
22		5-(6-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-2-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)pyrimidin-4-yl)-4-(difluoromethyl)pyrimidin-2-amine
23		5-(2-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-morpholinopyrimidin-4-yl)-4-(difluoromethyl)pyrimidin-2-amine
24		2-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-4'-(difluoromethyl)-6-morpholino-[4,5'-bipyrimidin]-2'-amine
25		5-(2,6-bis((S)-3-methylmorpholino)-pyrimidin-4-yl)-4-(difluoromethyl)pyrimidin-2-amine
26		4'-(difluoromethyl)-2,6-bis((S)-3-methylmorpholino)-[4,5'-bipyrimidin]-2'-amine

27		(S)-4-(difluoromethyl)-5-(6-(3-methylmorpholino)-2-morpholinopyrimidin-4-yl)pyridin-2-amine
28		(S)-4'-(difluoromethyl)-6-(3-methylmorpholino)-2-morpholino-[4,5'-bipyrimidin]-2'-amine
29		5-(4-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)-6-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-1,3,5-triazin-2-yl)-4-(difluoromethyl)pyridin-2-amine
30		5-[4,6-bis(2,2-dimethylmorpholin-4-yl)-1,3,5-triazin-2-yl]-4-(difluoromethyl)-pyridin-2-amine
31		(S)-4-(difluoromethyl)-5-(2-(3-methylmorpholino)-6-morpholinopyrimidin-4-yl)pyridin-2-amine
32		(S)-4'-(difluoromethyl)-2-(3-methylmorpholino)-6-morpholino-[4,5'-bipyrimidin]-2'-amine
33		4-(difluoromethyl)-5-[4-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-6-[(3R)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]pyridin-2-amine

34		5-[4,6-bis[(2R,6S)-2,6-dimethylmorpholin-4-yl]-1,3,5-triazin-2-yl]-4-(difluoromethyl)pyridin-2-amine
37		5-[4,6-bis(3,7-dioxo-9-azabicyclo[3.3.1]nonan-9-yl)-1,3,5-triazin-2-yl]-4-(difluoromethyl)pyridin-2-amine
38		4-(difluoromethyl)-5-[4-(3,7-dioxo-9-azabicyclo[3.3.1]nonan-9-yl)-6-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-1,3,5-triazin-2-yl]pyridin-2-amine
39		5-[4,6-bis(3,3-dimethylmorpholin-4-yl)-1,3,5-triazin-2-yl]-4-(difluoromethyl)pyridin-2-amine
40		5-[4,6-bis[(3R,5S)-3,5-dimethylmorpholin-4-yl]-1,3,5-triazin-2-yl]-4-(difluoromethyl)pyridin-2-amine
41		5-[4,6-bis[(3R)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]-4-(difluoromethyl)pyridin-2-amine
42		4-(difluoromethyl)-5-[4-(3,3-dimethylmorpholin-4-yl)-6-morpholino-1,3,5-triazin-2-yl]pyridin-2-amine

44		4-(difluoromethyl)-5-[4-[(3 <i>R</i> ,5 <i>S</i>)-3,5-dimethylmorpholin-4-yl]-6-[(3 <i>R</i>)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]pyridin-2-amine
45		4-(difluoromethyl)-5-[4-(3,3-dimethylmorpholin-4-yl)-6-[(3 <i>R</i>)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]pyridin-2-amine
46		4-(difluoromethyl)-5-[4-[(3 <i>R</i>)-3-(methoxymethyl)morpholin-4-yl]-6-[(3 <i>R</i>)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]pyridin-2-amine
47		4-(difluoromethyl)-5-[4-(3,7-dioxo-9-azabicyclo[3.3.1]nonan-9-yl)-6-[(3 <i>R</i>)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]pyridin-2-amine
50		4-(difluoromethyl)-5-[4-[(3 <i>R</i>)-3-methylmorpholin-4-yl]-6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)-1,3,5-triazin-2-yl]pyridin-2-amine
51		4-(difluoromethyl)-5-[4-[(3 <i>R</i>)-3-methylmorpholin-4-yl]-6-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)-1,3,5-triazin-2-yl]pyridin-2-amine
52		4-(difluoromethyl)-5-[4-[(3 <i>R</i>)-3-methylmorpholin-4-yl]-6-[(1 <i>R</i> ,4 <i>R</i>)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-1,3,5-triazin-2-yl]pyridin-2-amine

53		4-(difluoromethyl)-5-[4-[(3 <i>R</i>)-3-methylmorpholin-4-yl]-6-[(1 <i>S</i> ,4 <i>S</i>)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-1,3,5-triazin-2-yl]pyridin-2-amine
54		5-[4,6-bis[(3 <i>R</i>)-3-ethylmorpholin-4-yl]-1,3,5-triazin-2-yl]-4-(difluoromethyl)pyridin-2-amine
55		5-[4,6-bis(8-oxa-5-azaspiro[3.5]nonan-5-yl)-1,3,5-triazin-2-yl]-4-(difluoromethyl)pyridin-2-amine
56		5-[4,6-bis[(3 <i>R</i>)-3-isopropylmorpholin-4-yl]-1,3,5-triazin-2-yl]-4-(difluoromethyl)pyridin-2-amine
66		4-(difluoromethyl)-5-[4-(3,3-dimethylmorpholin-4-yl)-6-[(3 <i>R</i> ,5 <i>S</i>)-3,5-dimethylmorpholin-4-yl]-1,3,5-triazin-2-yl]pyridin-2-amine
67		4-(difluoromethyl)-5-[4-(3,3-dimethylmorpholin-4-yl)-6-[(3 <i>R</i>)-3-(methoxymethyl)morpholin-4-yl]-1,3,5-triazin-2-yl]pyridin-2-amine
68		[(3 <i>R</i>)-4-[4-[6-amino-4-(difluoromethyl)-3-pyridyl]-6-(3,3-dimethylmorpholin-4-yl)-1,3,5-triazin-2-yl]morpholin-3-yl]methanol

69		4-(difluoromethyl)-5-[4-(3,3-dimethylmorpholin-4-yl)-6-(3,7-dioxo-9-azabicyclo[3.3.1]nonan-9-yl)-1,3,5-triazin-2-yl]pyridin-2-amine
70		5-[4-(4-cyclopropylpiperazin-1-yl)-6-(3,3-dimethylmorpholin-4-yl)-1,3,5-triazin-2-yl]-4-(difluoromethyl)pyridin-2-amine
71		4-(difluoromethyl)-5-[4-(3,3-dimethylmorpholin-4-yl)-6-[4-(2-methoxyethyl)piperazin-1-yl]-1,3,5-triazin-2-yl]pyridin-2-amine
77		[(3R)-4-[4-[6-amino-4-(difluoromethyl)-3-pyridyl]-6-[(3R)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]morpholin-3-yl]methanol
78		4-(difluoromethyl)-5-[4-[(3R,5R)-3,5-dimethylmorpholin-4-yl]-6-[(3R)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]pyridin-2-amine
79		4-(difluoromethyl)-5-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-[(3R)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]pyridin-2-amine
80		4-(difluoromethyl)-5-[4-morpholino-6-(3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)-1,3,5-triazin-2-yl]pyridin-2-amine

82		4-(difluoromethyl)-5-[4-(3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl)-6-(3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)-1,3,5-triazin-2-yl]pyridin-2-amine
83		5-[4,6-bis[(3 <i>S</i> ,5 <i>S</i>)-3,5-dimethylmorpholin-4-yl]-1,3,5-triazin-2-yl]-4-(difluoromethyl)pyridin-2-amine
84		4-(difluoromethyl)-5-[4-(3,7-dioxa-9-azabicyclo[3.3.1]nonan-9-yl)-6-morpholino-1,3,5-triazin-2-yl]pyridin-2-amine
85		4-(difluoromethyl)-5-[4-[(3 <i>S</i>)-3-ethylmorpholin-4-yl]-6-[(3 <i>R</i>)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]pyridin-2-amine
86		4-(difluoromethyl)-5-[4-[(3 <i>R</i>)-3-ethylmorpholin-4-yl]-6-[(3 <i>R</i>)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]pyridin-2-amine
88		4-(difluoromethyl)-5-[4-[(3 <i>R</i>)-3-methylmorpholin-4-yl]-6-(8-oxa-5-azaspiro[3.5]nonan-5-yl)-1,3,5-triazin-2-yl]pyridin-2-amine

In some embodiments, one or more atoms of the PI3K, AKT, and/or mTOR inhibitor can be a radionuclide. In some embodiments, one or more of the F atoms in the PI3K, AKT, and/or mTOR inhibitor (e.g., bimiralisib) can be ^{18}F . In some embodiments, one or more of the C atoms in the PI3K, AKT, and/or mTOR inhibitor (e.g., bimiralisib) can be ^{11}C . In some

embodiments, one or more of the N atoms in the PI3K, AKT, and/or mTOR inhibitor (e.g., bimiralisib) can be ^{13}N . In some embodiments, one or more of the O atoms in the PI3K, AKT, and/or mTOR inhibitor (e.g., bimiralisib) can be ^{15}O .

5 Preparation of compounds of the invention

 The compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. Moreover, the synthesis of compounds of the present invention and the intermediates used for said synthesis of compounds of the present invention have
10 already been described in WO 2016/075130; in the application PCT/EP2017/025137 filed on May 17, 2017 and published as WO/2017/198347 on Nov. 23, 2017; and in the application PCT/EP2018/082211 filed on November 22, 2018 and published as WO/2019/101853 on May 31, 2019. The starting materials are generally available from commercial sources or are readily prepared using methods well known to those skilled in the art.

15 In preparing compounds of the invention, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups include *tert*-butyloxycarbonyl (BOC), bis-*tert*-butyloxycarbonyl or dimethylaminomethylenyl. The need for such protection is
20 readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1991.

Methods of separation

 In the methods of preparing the compounds of this invention, it may be advantageous to
25 separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps are separated and/or purified to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods
30 including, for example: reverse-phase and normal phase; high, medium and low-pressure liquid chromatography methods and apparatus; small scale analytical; and preparative thin or thick layer chromatography, as well as techniques of small-scale thin layer and flash chromatography.

Selection of appropriate methods of separation depends on the nature of the materials involved, for example, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

5

Kits of Parts, Compositions, Combinations, and Methods of Treatment

As used herein, the term "for use" as used in "composition for use in treatment of a disease" or "combination for use in the treatment of a disease" shall disclose also the corresponding method of treatment of a human subject and the corresponding use of the composition or combination for the manufacture of a medicament for the treatment of a disease. Accordingly, embodiments disclosed herein are understood to related to compositions, kits of parts, combinations, compositions for use, combinations for use, methods of treatment, and the use of a composition or combination as described herein for the manufacture of a medicament.

15 In one aspect, the present disclosure provides a kit of parts comprising:

- (i) a PSMA-targeted radiopharmaceutical; and
- (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a kit of parts comprising:

- 20 (i) Compound A; and
- (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a kit of parts comprising:

- (i) PSMA-11; and
- (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a kit of parts comprising:

- 25 (i) PSMA-617; and
- (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In preferred embodiments, said kit of parts further comprises instructions for administering said Compound A, said PSMA-11, or said PSMA-617 and said inhibitor of PI3K, AKT, and/or mTOR to treat cancer, preferably prostate cancer, in a subject in need thereof.

30

In one aspect, the present disclosure provides a composition comprising:

- (i) a PSMA-targeted radiopharmaceutical; and
- (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a composition comprising:

- (i) Compound A; and
- (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a composition comprising:

- 5 (i) PSMA-11; and
- (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a composition comprising:

- (i) PSMA-617; and
- (ii) an inhibitor of PI3K, AKT, and/or mTOR.

10 In some embodiments, said kit of parts or said composition comprises said (i) PSMA-targeted radiopharmaceutical and (ii) said inhibitor of PI3K, AKT, and/or mTOR as a combined dosage form. In some embodiments, said kit of parts or said composition comprises said (i) Compound A and (ii) said inhibitor of PI3K, AKT, and/or mTOR as separate dosage forms.

15 In some embodiments, said kit of parts or said composition comprises said (i) Compound A and (ii) said inhibitor of PI3K, AKT, and/or mTOR as a combined dosage form. In some embodiments, said kit of parts or said composition comprises said (i) Compound A and (ii) said inhibitor of PI3K, AKT, and/or mTOR as separate dosage forms.

20 In some embodiments, said kit of parts or said composition comprises said (i) PSMA-11 and (ii) said inhibitor of PI3K, AKT, and/or mTOR as a combined dosage form. In some embodiments, said kit of parts or said composition comprises said (i) PSMA-11 and (ii) said inhibitor of PI3K, AKT, and/or mTOR as separate dosage forms.

25 In some embodiments, said kit of parts or said composition comprises said (i) PSMA-617 and (ii) said inhibitor of PI3K, AKT, and/or mTOR as a combined dosage form. In some embodiments, said kit of parts or said composition comprises said (i) PSMA-617 and (ii) said inhibitor of PI3K, AKT, and/or mTOR as separate dosage forms.

In one aspect, the present invention comprises a combination (e.g., a combination for use) comprising:

- (i) a composition comprising a PSMA-targeted radiopharmaceutical; and
- 30 (ii) a composition comprising an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a combination (e.g., a combination for use) comprising:

- (i) a composition comprising Compound A; and

(ii) a composition comprising an inhibitor of PI3K, AKT, and/or mTOR.

In some embodiments, said combination (e.g., said combination for use) comprises said (i) composition comprising said PSMA-targeted radiopharmaceutical and (ii) said composition comprising an inhibitor of PI3K, AKT, and/or mTOR as a combined dosage form.

5 In some embodiments, said combination (e.g., said combination for use) comprises said (i) composition comprising Compound A and (ii) said composition comprising an inhibitor of PI3K, AKT, and/or mTOR as a combined dosage form.

In some embodiments, said combination (e.g., said combination for use) comprises said (i) composition comprising Compound A and (ii) said composition comprising an
10 inhibitor of PI3K, AKT, and/or mTOR as separate dosage forms.

In one aspect, the present invention provides a combination (e.g., a combination for use) comprising:

(i) a composition comprising PSMA-11; and

(ii) a composition comprising an inhibitor of PI3K, AKT, and/or mTOR.

15 In some embodiments, said combination (e.g., said combination for use) comprises said (i) composition comprising PSMA-11 and (ii) said composition comprising an inhibitor of PI3K, AKT, and/or mTOR as a combined dosage form.

In some embodiments, said combination (e.g., said combination for use) comprises said (i) composition comprising PSMA-11 and (ii) said composition comprising an inhibitor
20 of PI3K, AKT, and/or mTOR as separate dosage forms.

In one aspect, the present invention provides a combination (e.g., a combination for use) comprising:

(i) a composition comprising PSMA-617; and

(ii) a composition comprising an inhibitor of PI3K, AKT, and/or mTOR.

25 In some embodiments, said combination (e.g., said combination for use) comprises said (i) composition comprising PSMA-617 and (ii) said composition comprising an inhibitor of PI3K, AKT, and/or mTOR as a combined dosage form.

In some embodiments, said combination (e.g., said combination for use) comprises said (i) composition comprising PSMA-617 and (ii) said composition comprising an inhibitor
30 of PI3K, AKT, and/or mTOR as separate dosage forms.

In some embodiments, said PSMA-targeted radiopharmaceutical comprises a DUPA targeting group. In some embodiments, the PSMA-targeted radiopharmaceutical is selected from the group consisting of PSMA-11, PSMA-617, and PSMA I&T. In some embodiments,

the PSMA-targeted radiopharmaceutical is PSMA I&T. In some embodiments, the PSMA-targeted radiopharmaceutical is PSMA-11. In some embodiments, the PSMA-targeted radiopharmaceutical is PSMA-617.

In one aspect, the present invention provides a kit of parts comprising: (i) Compound A; wherein said Compound A is chelated to ^{161}Tb ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a kit of parts comprising: (i) Compound A; wherein said Compound A is chelated to ^{177}Lu ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a kit of parts comprising: (i) Compound A; wherein said Compound A is chelated to ^{225}Ac ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a composition comprising: (i) Compound A; wherein said Compound A is chelated to ^{161}Tb ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a composition comprising: (i) Compound A; wherein said Compound A is chelated to ^{177}Lu ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a composition comprising: (i) Compound A; wherein said Compound A is chelated to ^{225}Ac ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) Compound A; wherein said Compound A is chelated to ^{161}Tb ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) Compound A; wherein said Compound A is chelated to ^{177}Lu ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) Compound A; wherein said Compound A is chelated to ^{225}Ac ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to ^{161}Tb ; and said inhibitor of PI3K, AKT, and/or mTOR is bimiralisib.

In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to

¹⁷⁷Lu; and said inhibitor of PI3K, AKT, and/or mTOR is bimiralisib.

In some embodiments, said PSMA-conjugated radiopharmaceutical is chelated to ²²⁵Ac; and said inhibitor of PI3K, AKT, and/or mTOR is bimiralisib.

In one aspect, the present invention provides a kit of parts comprising: (i) Compound A; wherein said Compound A is chelated to ¹⁶¹Tb; and (ii) bimiralisib.

In one aspect, the present invention provides a kit of parts comprising: (i) Compound A; wherein said Compound A is chelated to ¹⁷⁷Lu; and (ii) bimiralisib.

In one aspect, the present invention provides a kit of parts comprising: (i) Compound A; wherein said Compound A is chelated to ²²⁵Ac; and (ii) bimiralisib.

In one aspect, the present invention provides a composition comprising: (i) Compound A; wherein said Compound A is chelated to ¹⁶¹Tb; and (ii) bimiralisib.

In one aspect, the present invention provides a composition comprising: (i) Compound A; wherein said Compound A is chelated to ¹⁷⁷Lu; and (ii) bimiralisib.

In one aspect, the present invention provides a composition comprising: (i) Compound A; wherein said Compound A is chelated to ²²⁵Ac; and (ii) bimiralisib.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) Compound A; wherein said Compound A is chelated to ¹⁶¹Tb; and (ii) bimiralisib.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) Compound A; wherein said Compound A is chelated to ¹⁷⁷Lu; and (ii) bimiralisib.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) Compound A; wherein said Compound A is chelated to ²²⁵Ac; and (ii) bimiralisib.

In one aspect, the present invention provides a kit of parts comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ¹⁶¹Tb; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a kit of parts comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ¹⁷⁷Lu; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a kit of parts comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ²²⁵Ac; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a composition comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{161}Tb ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a composition comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{177}Lu ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a composition comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{225}Ac ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{161}Tb ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{177}Lu ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{225}Ac ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a kit of parts comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{161}Tb ; and (ii) bimiralisib.

In one aspect, the present invention provides a kit of parts comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{177}Lu ; and (ii) bimiralisib.

In one aspect, the present invention provides a kit of parts comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{225}Ac ; and (ii) bimiralisib.

In one aspect, the present invention provides a composition comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{161}Tb ; and (ii) bimiralisib.

In one aspect, the present invention provides a composition comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{177}Lu ; and (ii) bimiralisib.

In one aspect, the present invention provides a composition comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{225}Ac ; and (ii) bimiralisib.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{161}Tb ; and (ii) bimiralisib.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{177}Lu ; and (ii) bimiralisib.

5 In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{225}Ac ; and (ii) bimiralisib.

In one aspect, the present invention provides a kit of parts comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{161}Tb ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

10 In one aspect, the present invention provides a kit of parts comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{177}Lu ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a kit of parts comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{225}Ac ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a composition comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{161}Tb ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

15 In one aspect, the present invention provides a composition comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{177}Lu ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a composition comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{225}Ac ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

20 In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{161}Tb ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{177}Lu ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

25 In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{225}Ac ; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a kit of parts comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{161}Tb ; and (ii) bimiralisib.

30 In one aspect, the present invention provides a kit of parts comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{177}Lu ; and (ii) bimiralisib.

In one aspect, the present invention provides a kit of parts comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{225}Ac ; and (ii) bimiralisib.

In one aspect, the present invention provides a composition comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{161}Tb ; and (ii) bimiralisib.

In one aspect, the present invention provides a composition comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{177}Lu ; and (ii) bimiralisib.

5 In one aspect, the present invention provides a composition comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{225}Ac ; and (ii) bimiralisib.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{161}Tb ; and (ii) bimiralisib.

10 In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{177}Lu ; and (ii) bimiralisib.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, comprising: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{225}Ac ; and (ii) bimiralisib.

15 In some embodiments, the present invention provides a kit of parts or a composition of as described herein, for use in the treatment of a cancer.

In one aspect, the present invention provides a method of treating a cancer in a subject in need thereof, the method comprising: administering to said subject a therapeutically effective amount of (i) a PSMA-targeted radiopharmaceutical; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

20 In one aspect, the present invention provides a method of treating a cancer in a subject in need thereof, the method comprising: administering to the subject a therapeutically effective amount of (i) a PSMA-targeted radiopharmaceutical in combination with (ii) an inhibitor of PI3K, AKT, and/or mTOR.

25 In one aspect, the present disclosure provides a method of treating a cancer in a subject in need thereof, said method comprising:

(i) administering to said subject a therapeutically effective amount of a PSMA-targeted radiopharmaceutical, wherein said subject has previously been treated with an inhibitor of PI3K, AKT, and/or mTOR;

30 (ii) administering to said subject a therapeutically effective amount of an inhibitor of PI3K, AKT, and/or mTOR, wherein said subject has previously been treated with a PSMA-targeted radiopharmaceutical; or

(iii) administering to said subject a therapeutically effective amount of an inhibitor of PI3K, AKT, and/or mTOR at the same time as administering to said subject a therapeutically effective amount of a PSMA-targeted radiopharmaceutical.

In one aspect, the present disclosure provides a method of treating a cancer in a subject
5 in need thereof, said method comprising: administering to said subject a therapeutically effective amount of a PSMA-targeted radiopharmaceutical, wherein said subject has previously been treated with an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present disclosure provides a method of treating a cancer in a subject
10 in need thereof, said method comprising: administering to said subject a therapeutically effective amount of an inhibitor of PI3K, AKT, and/or mTOR, wherein said subject has previously been treated with a PSMA-targeted radiopharmaceutical.

In one aspect, the present disclosure provides a method of treating a cancer in a subject
15 in need thereof, said method comprising: administering to said subject a therapeutically effective amount of an inhibitor of PI3K, AKT, and/or mTOR at the same time as administering to said subject a therapeutically effective amount of a PSMA-targeted radiopharmaceutical.

In one aspect, the present disclosure provides an inhibitor of PI3K, AKT, and/or mTOR
for use in a method of treating a cancer in a subject; wherein said inhibitor of PI3K, AKT,
and/or mTOR is administered in combination with a PSMA-targeted radiopharmaceutical.

20 In one aspect, the present disclosure provides a PSMA-targeted radiopharmaceutical for use in a method of treating a cancer in a subject; wherein said PSMA-targeted radiopharmaceutical is administered in combination with an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present disclosure provides an inhibitor of PI3K, AKT, and/or mTOR
25 for use in a method of treating a cancer in a subject; wherein said inhibitor of PI3K, AKT, and/or mTOR is to be administered in combination with a PSMA-targeted radiopharmaceutical.

In one aspect, the present disclosure provides a PSMA-targeted radiopharmaceutical
30 for use in a method of treating a cancer; wherein said PSMA-targeted radiopharmaceutical is to be administered in combination with an inhibitor of PI3K, AKT, and/or mTOR.

In some embodiments of any of the above-aspects, said cancer is prostate cancer. In some embodiments, said prostate cancer is castration-resistant prostate cancer. In some embodiments, said prostate cancer is metastatic castration-resistant prostate cancer. In some

embodiments, said prostate cancer is hormone-sensitive prostate cancer. In some embodiments, said prostate cancer is hormone naïve prostate cancer (e.g., anti-hormone therapy naïve prostate cancer). In some embodiments, said prostate cancer is high-risk localized prostate cancer (HRCaP). In some embodiments, said prostate cancer is node-
5 positive prostate cancer (N1M0). In some embodiments, said prostate cancer is oligometastatic prostate cancer.

In some embodiments, said cancer is prostate cancer. In some embodiments, said prostate cancer is PSMA-positive prostate cancer. In some embodiments, said prostate cancer is characterized by overexpression of PSMA.

10 In some embodiments, said cancer is prostate cancer, said PSMA-targeted radiopharmaceutical is Compound A, wherein said Compound A is chelated to ^{161}Tb ; and said compound capable of inhibiting PI3K, AKT, and/or mTOR is bimiralisib.

In one aspect, the present invention provides a kit of parts, a composition for use, or a combination for use in the treatment of a prostate cancer, wherein said kit of parts,
15 composition, or combination for use comprises: (i) Compound A; wherein said Compound A is chelated to ^{161}Tb ; and (ii) bimiralisib.

In one aspect, the present invention provides a kit of parts, a composition for use, or a combination for use in the treatment of a prostate cancer, wherein said kit of parts,
20 composition, or combination for use comprises: (i) Compound A; wherein said Compound A is chelated to ^{177}Lu ; and (ii) bimiralisib.

In one aspect, the present invention provides a kit of parts, a composition for use, or a combination for use in the treatment of a prostate cancer, wherein said kit of parts,
composition, or combination for use comprises: (i) Compound A; wherein said Compound A is chelated to ^{225}Ac ; and (ii) bimiralisib.

25 In some embodiments, said cancer is castration-resistant prostate cancer, wherein said Compound A is chelated to ^{161}Tb ; and wherein said compound capable of inhibiting PI3K, AKT, and/or mTOR is bimiralisib.

In one aspect, the present invention a kit of parts, a composition for use, or a combination for use in the treatment of a castration-resistant prostate cancer, wherein said kit
30 of parts, composition, or combination for use comprises: (i) Compound A; wherein said Compound A is chelated to ^{161}Tb ; and (ii) bimiralisib.

In one aspect, the present invention a kit of parts, a composition for use, or a combination for use in the treatment of a castration-resistant prostate cancer, wherein said kit

of parts, composition, or combination for use comprises: (i) Compound A; wherein said Compound A is chelated to ^{177}Lu ; and (ii) bimiralisib.

In one aspect, the present invention a kit of parts, a composition for use, or a combination for use in the treatment of a castration-resistant prostate cancer, wherein said kit
5 of parts, composition, or combination for use comprises: (i) Compound A; wherein said Compound A is chelated to ^{225}Ac ; and (ii) bimiralisib.

In some embodiments, said (i) PSMA-targeted radioligand is Compound A, wherein said Compound A is chelated to ^{161}Tb ; and (ii) said inhibitor or PI3K, AKT and/or mTOR is bimiralisib.

10 In some embodiments, said: (i) PSMA-targeted radioligand is Compound A; wherein said Compound A is chelated to ^{177}Lu ; and (ii) said inhibitor or PI3K, AKT and/or mTOR is bimiralisib. In some embodiments, said (i) PSMA-targeted radioligand is Compound A, wherein said Compound A is chelated to ^{161}Tb ; and (ii) said inhibitor or PI3K, AKT and/or mTOR is bimiralisib.

15 In some embodiments, said: (i) PSMA-targeted radioligand is Compound A; wherein said Compound A is chelated to ^{225}Ac ; and (ii) said inhibitor or PI3K, AKT and/or mTOR is bimiralisib.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A and (ii) said an inhibitor of PI3K, AKT, and/or mTOR are administered
20 sequentially.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A and (ii) said inhibitor of PI3K, AKT, and/or mTOR are administered simultaneously.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably
25 Compound A and (ii) said inhibitor of PI3K, AKT, and/or mTOR are administered as a combined dosage form.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A and (ii) said inhibitor of PI3K, AKT, and/or mTOR are administered simultaneously as a combined dosage form.

30 In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A and (ii) said inhibitor of PI3K, AKT, and/or mTOR are provided in separate dosage forms.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably

Compound A and (ii) said inhibitor of PI3K, AKT, and/or mTOR are provided in separate dosage forms, wherein said separate dosage forms comprise separate packaging.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A and (ii) said inhibitor of PI3K, AKT, and/or mTOR are provided in separate
5 dosage forms, and are administered simultaneously.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A and (ii) said inhibitor of PI3K, AKT, and/or mTOR are provided in separate dosage forms, and are administered sequentially.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably
10 Compound A is administered prior to said (ii) inhibitor of PI3K, AKT, and/or mTOR.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 1 minute. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A is first administered to a subject, and said (ii)
15 inhibitor of PI3K, AKT, and/or mTOR is administered within about 15 minutes. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 30 minutes. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A is first administered to a subject, and said (ii) inhibitor of PI3K, AKT,
20 and/or mTOR is administered within about 60 minutes. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 2 hours. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered
25 within about 6 hours. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 12 hours. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 24 hours. In some
30 embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 2 days. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A is first administered to a subject, and said (ii) inhibitor of PI3K, AKT,

and/or mTOR is administered within about 5 days. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably Compound A is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 7 days.

In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered
5 prior to said (i) PSMA-targeted radiopharmaceutical, preferably Compound A. In some
embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject,
and said (i) PSMA-targeted radiopharmaceutical, preferably Compound A is administered
within about 1 minute. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR
is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably
10 Compound A is administered within about 15 minutes. In some embodiments, said (ii)
inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-
targeted radiopharmaceutical, preferably Compound A is administered within about 30
minutes. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first
administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably
15 Compound A is administered within about 60 minutes. In some embodiments, said (ii)
inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-
targeted radiopharmaceutical, preferably Compound A is administered within about 2 hours.
PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted
radiopharmaceutical, preferably Compound A is administered within about 6 hours. In some
20 embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject,
and said (i) PSMA-targeted radiopharmaceutical, preferably Compound A is administered
within about 12 hours. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR
is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably
Compound A is administered within about 24 hours. In some embodiments, said (ii) inhibitor
25 of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted
radiopharmaceutical, preferably Compound A is administered within about 2 days. In some
embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject,
and said (i) PSMA-targeted radiopharmaceutical, preferably Compound A is administered
within about 5 days. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is
30 first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably
Compound A is administered within about 7 days.

In one aspect, the present invention provides a combination for use in a method of
treating a cancer in a subject, preferably a prostate cancer, wherein said combination

comprises: (i) a PSMA-targeted radiopharmaceutical; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, preferably a prostate cancer, wherein said combination
5 comprises: (i) Compound A; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a method of treating a cancer, preferably a prostate cancer, in a subject in need thereof, the method comprising: administering to said subject a combination comprising (i) a PSMA-targeted radiopharmaceutical; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

10 In one aspect, the present invention provides a method of treating a cancer, preferably a prostate cancer, in a subject in need thereof, the method comprising: administering to said subject a combination comprising (i) Compound A; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In preferred embodiments, as used herein the steps of administering to said subject (i)
15 a PSMA-targeted radiopharmaceutical; and/or (ii) an inhibitor of PI3K, AKT, and/or mTOR preferably comprises administering to said subject a therapeutically effective amount of said (i) a PSMA-targeted radiopharmaceutical; and/or (ii) said inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides the use of a combination in the
20 manufacture of a medicament for treating a cancer, preferably a prostate cancer, wherein said combination comprises: (i) a PSMA-targeted radiopharmaceutical; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides the use of a combination in the manufacture of a medicament for treating a cancer, preferably a prostate cancer, wherein said
25 combination comprises: (i) Compound A; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is any of those described herein. Preferably said inhibitor of PI3K, AKT, and/or mTOR is a dual PI3K/mTOR inhibitor. More preferably, said inhibitor of PI3K, AKT, and/or mTOR is bimiralisib.

In some embodiments, said Compound A is chelated to a radionuclide as described
30 herein. In some preferred embodiments, said Compound A is chelated to ¹⁶¹Tb. In some preferred embodiments, said Compound A is chelated to ¹⁷⁷Lu. In some preferred embodiments, said Compound A is chelated to ²²⁵Ac.

In some embodiments, said cancer is prostate cancer, wherein said PSMA-11 is

chelated to ^{161}Tb , ^{177}Lu , or ^{225}Ac ; and said compound capable of inhibiting PI3K, AKT, and/or mTOR is bimiralisib.

In one aspect, the present invention provides a kit of parts, a composition for use, or a combination for use in the treatment of a prostate cancer, wherein said kit of parts,
5 composition, or combination for use comprises: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{161}Tb ; and (ii) bimiralisib.

In one aspect, the present invention provides a kit of parts, a composition for use, or a combination for use in the treatment of a prostate cancer, wherein said kit of parts,
10 composition, or combination for use comprises: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{177}Lu ; and (ii) bimiralisib.

In one aspect, the present invention provides a kit of parts, a composition for use, or a combination for use in the treatment of a prostate cancer, wherein said kit of parts,
15 composition, or combination for use comprises: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{225}Ac ; and (ii) bimiralisib.

In some embodiments, said cancer is castration-resistant prostate cancer, wherein said PSMA-11 is chelated to ^{161}Tb ; and wherein said compound capable of inhibiting PI3K, AKT,
and/or mTOR is bimiralisib.

In some embodiments, said cancer is castration-resistant prostate cancer, wherein said PSMA-11 is chelated to ^{177}Lu ; and wherein said compound capable of inhibiting PI3K, AKT,
20 and/or mTOR is bimiralisib.

In some embodiments, said cancer is castration-resistant prostate cancer, wherein said PSMA-11 is chelated to ^{225}Ac ; and wherein said compound capable of inhibiting PI3K, AKT,
and/or mTOR is bimiralisib.

In one aspect, the present invention a kit of parts, a composition for use, or a combination for use in the treatment of a castration-resistant prostate cancer, wherein said kit
25 of parts, composition, or combination for use comprises: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{161}Tb ; and (ii) bimiralisib.

In one aspect, the present invention a kit of parts, a composition for use, or a combination for use in the treatment of a castration-resistant prostate cancer, wherein said kit
30 of parts, composition, or combination for use comprises: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{177}Lu ; and (ii) bimiralisib.

In one aspect, the present invention a kit of parts, a composition for use, or a combination for use in the treatment of a castration-resistant prostate cancer, wherein said kit

of parts, composition, or combination for use comprises: (i) PSMA-11; wherein said PSMA-11 is chelated to ^{225}Ac ; and (ii) bimiralisib.

In some embodiments, said (i) PSMA-targeted radioligand is PSMA-11, wherein said Compound A is chelated to ^{161}Tb ; and (ii) said inhibitor or PI3K, AKT and/or mTOR is
5 bimiralisib.

In some embodiments, said: (i) PSMA-targeted radioligand is PSMA-11; wherein said Compound A is chelated to ^{177}Lu ; and (ii) said inhibitor or PI3K, AKT and/or mTOR is bimiralisib.

In some embodiments, said: (i) PSMA-targeted radioligand is PSMA-11; wherein said
10 Compound A is chelated to ^{225}Ac ; and (ii) said inhibitor or PI3K, AKT and/or mTOR is bimiralisib.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 and (ii) said an inhibitor of PI3K, AKT, and/or mTOR are administered sequentially.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably
15 PSMA-11 and (ii) said inhibitor of PI3K, AKT, and/or mTOR are administered simultaneously.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 and (ii) said inhibitor of PI3K, AKT, and/or mTOR are administered as a combined
20 dosage form.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 and (ii) said inhibitor of PI3K, AKT, and/or mTOR are administered simultaneously as a combined dosage form.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably
25 PSMA-11 and (ii) said inhibitor of PI3K, AKT, and/or mTOR are provided in separate dosage forms.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 and (ii) said inhibitor of PI3K, AKT, and/or mTOR are provided in separate dosage forms, wherein said separate dosage forms comprise separate packaging.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably
30 PSMA-11 and (ii) said inhibitor of PI3K, AKT, and/or mTOR are provided in separate dosage forms, and are administered simultaneously.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably

PSMA-11 and (ii) said inhibitor of PI3K, AKT, and/or mTOR are provided in separate dosage forms, and are administered sequentially.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is administered prior to said (ii) inhibitor of PI3K, AKT, and/or mTOR.

5 In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 1 minute. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 15 minutes. In some
10 embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 30 minutes. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 60 minutes. In some embodiments, said (i) PSMA-
15 targeted radiopharmaceutical, preferably PSMA-11 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 2 hours. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 6 hours. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 12 hours. In some embodiments, said (i) PSMA-
20 targeted radiopharmaceutical, preferably PSMA-11 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 24 hours. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 2 days. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 5 days. In some embodiments, said (i) PSMA-
25 targeted radiopharmaceutical, preferably PSMA-11 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 7 days.

In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered prior to said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject,

and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is administered within about 1 minute. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is administered within about 15 minutes. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is administered within about 30 minutes. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is administered within about 60 minutes. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is administered within about 2 hours. PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is administered within about 6 hours. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is administered within about 12 hours. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is administered within about 24 hours. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is administered within about 2 days. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is administered within about 5 days. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-11 is administered within about 7 days.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, preferably a prostate cancer, wherein said combination comprises: (i) PSMA-11; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a method of treating a cancer, preferably a prostate cancer, in a subject in need thereof, the method comprising: administering to said subject a combination comprising (i) PSMA-11; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides the use of a combination in the

manufacture of a medicament for treating a cancer, preferably a prostate cancer, wherein said combination comprises: (i) PSMA-11; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is any of those described herein. Preferably said inhibitor of PI3K, AKT, and/or mTOR is a dual PI3K/mTOR
5 inhibitor. More preferably, said inhibitor of PI3K, AKT, and/or mTOR is bimiralisib.

In some embodiments, said PSMA-11 is chelated to a radionuclide as described herein. In some preferred embodiments, said PSMA-11 is chelated to ¹⁶¹Tb. In some preferred
embodiments, said PSMA-11 is chelated to ¹⁷⁷Lu. In some preferred embodiments, said
PSMA-11 is chelated to ²²⁵Ac.

10 In some embodiments, said cancer is prostate cancer, wherein said PSMA-617 is
chelated to ¹⁶¹Tb, ¹⁷⁷Lu, or ²²⁵Ac; and said compound capable of inhibiting PI3K, AKT, and/or
mTOR is bimiralisib.

In one aspect, the present invention provides a kit of parts, a composition for use, or a
combination for use in the treatment of a prostate cancer, wherein said kit of parts,
15 composition, or combination for use comprises: (i) PSMA-617; wherein said PSMA-617 is
chelated to ¹⁶¹Tb; and (ii) bimiralisib.

In one aspect, the present invention provides a kit of parts, a composition for use, or a
combination for use in the treatment of a prostate cancer, wherein said kit of parts,
composition, or combination for use comprises: (i) PSMA-617; wherein said PSMA-617 is
20 chelated to ¹⁷⁷Lu; and (ii) bimiralisib.

In one aspect, the present invention provides a kit of parts, a composition for use, or a
combination for use in the treatment of a prostate cancer, wherein said kit of parts,
composition, or combination for use comprises: (i) PSMA-617; wherein said PSMA-617 is
chelated to ²²⁵Ac; and (ii) bimiralisib.

25 In some embodiments, said cancer is castration-resistant prostate cancer, wherein said
PSMA-617 is chelated to ¹⁶¹Tb; and wherein said compound capable of inhibiting PI3K, AKT,
and/or mTOR is bimiralisib.

In some embodiments, said cancer is castration-resistant prostate cancer, wherein said
PSMA-617 is chelated to ¹⁷⁷Lu; and wherein said compound capable of inhibiting PI3K, AKT,
30 and/or mTOR is bimiralisib.

In some embodiments, said cancer is castration-resistant prostate cancer, wherein said
PSMA-617 is chelated to ²²⁵Ac; and wherein said compound capable of inhibiting PI3K, AKT,
and/or mTOR is bimiralisib.

In one aspect, the present invention a kit of parts, a composition for use, or a combination for use in the treatment of a castration-resistant prostate cancer, wherein said kit of parts, composition, or combination for use comprises: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{161}Tb ; and (ii) bimiralisib.

5 In one aspect, the present invention a kit of parts, a composition for use, or a combination for use in the treatment of a castration-resistant prostate cancer, wherein said kit of parts, composition, or combination for use comprises: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{177}Lu ; and (ii) bimiralisib.

10 In one aspect, the present invention a kit of parts, a composition for use, or a combination for use in the treatment of a castration-resistant prostate cancer, wherein said kit of parts, composition, or combination for use comprises: (i) PSMA-617; wherein said PSMA-617 is chelated to ^{225}Ac ; and (ii) bimiralisib.

15 In some embodiments, said (i) PSMA-targeted radioligand is PSMA-617, wherein said Compound A is chelated to ^{161}Tb ; and (ii) said inhibitor or PI3K, AKT and/or mTOR is bimiralisib.

In some embodiments, said: (i) PSMA-targeted radioligand is PSMA-617; wherein said Compound A is chelated to ^{177}Lu ; and (ii) said inhibitor or PI3K, AKT and/or mTOR is bimiralisib.

20 In some embodiments, said: (i) PSMA-targeted radioligand is PSMA-617; wherein said Compound A is chelated to ^{225}Ac ; and (ii) said inhibitor or PI3K, AKT and/or mTOR is bimiralisib.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 and (ii) said an inhibitor of PI3K, AKT, and/or mTOR are administered sequentially.

25 In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 and (ii) said inhibitor of PI3K, AKT, and/or mTOR are administered simultaneously.

30 In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 and (ii) said inhibitor of PI3K, AKT, and/or mTOR are administered as a combined dosage form.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 and (ii) said inhibitor of PI3K, AKT, and/or mTOR are administered simultaneously as a combined dosage form.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 and (ii) said inhibitor of PI3K, AKT, and/or mTOR are provided in separate dosage forms.

5 In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 and (ii) said inhibitor of PI3K, AKT, and/or mTOR are provided in separate dosage forms, wherein said separate dosage forms comprise separate packaging.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 and (ii) said inhibitor of PI3K, AKT, and/or mTOR are provided in separate dosage forms, and are administered simultaneously.

10 In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 and (ii) said inhibitor of PI3K, AKT, and/or mTOR are provided in separate dosage forms, and are administered sequentially.

In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is administered prior to said (ii) inhibitor of PI3K, AKT, and/or mTOR.

15 In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 1 minute. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 15 minutes. In some
20 embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 30 minutes. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 60 minutes. In some embodiments, said (i) PSMA-
25 targeted radiopharmaceutical, preferably PSMA-617 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 2 hours. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 6 hours. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 12 hours. In some
30 embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 24 hours. In some

embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 2 days. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 5 days. In some embodiments, said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is first administered to a subject, and said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered within about 7 days.

In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is administered prior to said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is administered within about 1 minute. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is administered within about 15 minutes. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is administered within about 30 minutes. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is administered within about 60 minutes. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is administered within about 2 hours. PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is administered within about 6 hours. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is administered within about 12 hours. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is administered within about 24 hours. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is administered within about 2 days. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject, and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is administered within about 5 days. In some embodiments, said (ii) inhibitor of PI3K, AKT, and/or mTOR is first administered to a subject,

and said (i) PSMA-targeted radiopharmaceutical, preferably PSMA-617 is administered within about 7 days.

In one aspect, the present invention provides a combination for use in a method of treating a cancer in a subject, preferably a prostate cancer, wherein said combination
5 comprises: (i) PSMA-617; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In one aspect, the present invention provides a method of treating a cancer, preferably a prostate cancer, in a subject in need thereof, the method comprising: administering to said subject a combination comprising (i) PSMA-617; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

10 In one aspect, the present invention provides the use of a combination in the manufacture of a medicament for treating a cancer, preferably a prostate cancer, wherein said combination comprises: (i) PSMA-617; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.

In some embodiments, said inhibitor of PI3K, AKT, and/or mTOR is any of those described herein. Preferably said inhibitor of PI3K, AKT, and/or mTOR is a dual PI3K/mTOR
15 inhibitor. More preferably, said inhibitor of PI3K, AKT, and/or mTOR is bimiralisib.

In some embodiments, said PSMA-617 is chelated to a radionuclide as described herein. In some preferred embodiments, said PSMA-617 is chelated to ¹⁶¹Tb. In some preferred embodiments, said PSMA-617 is chelated to ¹⁷⁷Lu. In some preferred embodiments, said PSMA-617 is chelated to ²²⁵Ac.

EXAMPLES

The invention will now be illustrated by way of the following non-limiting examples. While particular embodiments of the invention are described below, a skilled person will appreciate that various changes and modifications can be made. References to preparations
5 carried out in a similar manner to, or by the general method of, other preparations, may encompass variations in routine parameters such as time, temperature, workup conditions, minor changes in reagents amounts, and the like.

10 EXAMPLE 1: CO-TREATMENT OF ¹⁷⁷LU-PSMA-617 AND COMPOUND 1* (PQR309; BIMIRALISIB) OR COMPOUND 2 IN 22RV1 HUMAN PROSTATE CANCER CELLS

This study determined the anti-proliferative effects of ¹⁷⁷Lu-PSMA-617 in combination with Compound 1* (PQR309; bimiralisib) and Compound 2 (see, e.g., Borsari et al., Preclinical Development of PQR514, a Highly Potent PI3K Inhibitor Bearing a
15 Difluoromethyl-Pyrimidine Moiety, *ACS Med. Chem. Lett.*, 10(10): 1473-1497 (2019)) on cell survival in the human prostate cancer cell line 22Rv1.

Cell culture: 22Rv1 cells (Sigma Aldrich) were cultured according to standard procedures (growth medium: RPMI-160 ATCC modified supplemented with 10% (v/v) FBS, 2 mM L-glutamine, and 1% (v/v) Pen/Strep; growth at 37 °C with 5 % CO₂) and harvested
20 when cells were between 70-90 % confluent.

Determination of IC₅₀ of Compound 1* (PQR309; bimiralisib) and Compound 2, in 22Rv1 cells: 9,000 22Rv1 cells per well were seeded in opaque-walled clear bottom 96-well plates in growth medium and incubated overnight prior to treatment. Triplicates were seeded for each condition. The next day, medium was replaced with warm medium containing
25 Compound 1* or Compound 2 at different concentrations (10, 3, 1, 0.3, 0.1, 0.03, 0.01, 0.003, 0.001, and 0 μM) and cells were incubated for 7 days. After 7 days, a CellTiter-Glo assay was performed as per manufacturer's instructions. Luminescence was measured on a Spectramax i3x multi-mode microplate reader and the dose-response curves were determined by non-linear regression analysis in GraphPad Prism, including calculation of the IC₅₀. A plot of percent
30 survival of 22Rv1 cells as a function of concentration of Compound 1* or Compound 2 is shown in FIG 1, and the IC₅₀s are given in Table 1, below.

Table 1: IC₅₀s of Compound 1* and Compound 2, in 22Rv1 Cells (μM)

	Compound 1*	Compound 2
IC ₅₀ (μM)	0.5218	0.1616

Compound 1* and Compound 2 dose-dependently inhibited survival of 22Rv1 cells.

5 Cell survival of 22Rv1 cells treated with ¹⁷⁷Lu-PSMA-617, Compound 1, or
Compound 2, as single agents or treated with combinations of ¹⁷⁷Lu-PSMA-617 and
Compound 1* or Compound 2: Different doses of ¹⁷⁷Lu-PSMA-617 (0 (vehicle), 0.5, 1, 2.5,
5, 10, and 20 MBq/mL; Table 2) were added to tubes containing 22Rv1 cells (final volume of
2.5 mL) and then incubated under constant agitation at 37 °C with 5 % CO₂ for 4 hours. After
10 incubation, the cells were washed twice with PBS and cells were seeded in opaque-walled
clear bottom 96-well plate with 9 000 cells per well. Triplicates (3 wells) were seeded for each
treatment (Table 2). Compound 1* and Compound 2 were added at the concentrations
indicated in Table 2 (i.e., these concentrations corresponded to the IC₈₀, IC₆₀, IC₅₀, IC₄₀, IC₃₀,
IC₂₀ determined in the previous experiment above). Cells were incubated at 37 °C with 5 %
15 CO₂ for 7 days. After incubation, CellTiter-Glo was added to all wells as per the
manufacturer’s instructions. The plates were placed on a shaker to induce cell lysis and
incubated at room temperature to stabilize the signal. Luminescence was measured on a
Spectramax i3x multi-mode microplate reader and the dose-response curve was determined by
non-linear regression analysis.

20

Table 2: Dosage Combinations for Survival Assay with Compound 1* or Compound 2 and ¹⁷⁷Lu-PSMA-617

Concentrations of PI3K/mTOR inhibitors (μM)			combined with	Concentrations of ¹⁷⁷ Lu- PSMA-617 (MBq/mL)
Compound 1*	Compound 2	IC _x		
1.17	0.58	IC ₈₀		20
0.66	0.24	IC ₆₀		10
0.52	0.16	IC ₅₀		5
0.41	0.11	IC ₄₀		2.5
0.32	0.07	IC ₃₀		1
0.23	0.04	IC ₂₀		0.5

vehicle			vehicle
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Cell survival decreased with increasing concentrations of Compound 1* (PQR309) or Compound 2 (FIG 2A). Treatment of cells with ¹⁷⁷Lu-PSMA-617 in combination with Compound 1* (PQR309) or Compound 2 further decreased survival (FIG 2A). To assess the effect of the combination of ¹⁷⁷Lu-PSMA-617 with Compound 1* (PQR309) or Compound 2, the Bliss synergy score was calculated using SynergyFinder (<https://synergyfinder.fimm.fi/synergy/20241025144228237071/>). A Bliss synergy score above 10 indicates synergy between two drugs. Combination of ¹⁷⁷Lu-PSMA-617 with both Compound 1* (PQR309) or Compound 2 was synergistic as evidenced by a Bliss synergy score of 11.145 (FIG 2B) and 12.158 (FIG 2C), respectively.

EXAMPLE 2: CO-ADMINISTRATION OF ¹⁶¹Tb-PSMA-I&T OR ¹⁷⁷Lu-PSMA-617 AND COMPOUND 1* (PQR309; BIMIRALISIB) IN NUDE MICE BEARING 22RV1 TUMORS

This study evaluated and compared the anti-tumor efficacy of ¹⁶¹Tb-PSMA-I&T and ¹⁷⁷Lu-PSMA-617 as single treatment and in combination with Compound 1* in female NMRI nude mice bearing subcutaneous human prostate carcinoma established with the cell line 22Rv1.

Study outline and procedures: 8-week-old female NMRI nude mice (80 mice required for the experiment plus extra mice in reserve) from Janvier (France) were implanted with 3x10⁶ 22Rv1 cells (Sigma Aldrich; cultured as described in Example 1) in PBS:Matrigel (1:1) by subcutaneous injection using a 27G needle and a total injection volume of 100 µL at the flank above the right limb on day -16 (relative to start of treatment, defined as study day 0). On day -1 (i.e., 15 days post-implantation), the mice were randomized based on tumor size and body weight to ensure similar average and variation of the groups. Mice were distributed to the treatment and control groups (8 mice per group). FIG 3A is a plot of average body weight of mice at day -1, and FIG 3B is a plot of tumor volume of mice at day -1. Average body weight was 29 g (range from 25.5 to 33.4 g; FIG 3A) and average tumor volume was 175 mm³ (range from 76 to 347 mm³; FIG 3B) for all groups.

Treatments with radioligands (¹⁶¹Tb-PSMA-I&T and ¹⁷⁷Lu-PSMA-617) and Compound 1* were initiated on study day 0. Study groups and treatment details are outlined in Table 3.

¹⁶¹Tb-PSMA-I&T was intravenously (IV) administered once at a target dose of 21.8 MBq or at a target dose of 43.7 MBq. ¹⁷⁷Lu-PSMA-617 was intravenously administered once

at a target dose of 30 MBq or at a target dose of 60 MBq. The doses of 21.8 MBq and 43.7 MBq ^{161}Tb -PSMA-I&T correspond to the same dose (in Gy) of 30 MBq and 60 MBq ^{177}Lu -PSMA-617. IV injections were carried out at an injection volume of 100-200 μL at the lateral tail vein.

- 5 Compound 1* was intraperitoneally (IP) administered at 7 mg/kg daily (QD) for 45 days or until mice reached a humane endpoint (see below). Control mice were IV administered with vehicle once. All injections were performed at a dosing volume of 5 mL/kg. Compound 1* was formulated weekly in 7.5% (v/v) SBECd at pH 7.

10 Table 3. Study Groups and Treatment Details

Treatment	n	Radionuclide	Target Dose (MBq)	Dose (mg/kg)	Route of Administration	Frequency
Vehicle	8	N/A	N/A	N/A	IV	Single
Compound 1	8	N/A	N/A	7	IP	Daily
^{161}Tb -PSMA-I&T	8	^{161}Tb	21.8	N/A	IV	Single
^{161}Tb -PSMA-I&T	8	^{161}Tb	43.7	N/A	IV	Single
^{177}Lu -PSMA-617	8	^{177}Lu	30	N/A	IV	Single
^{177}Lu -PSMA-617	8	^{177}Lu	60	N/A	IV	Single
^{161}Tb -PSMA-I&T + Compound 1	8	^{161}Tb	21.8	-	IV	Single
		-	-	7	IP	Daily
^{161}Tb -PSMA-I&T + Compound 1	8	^{161}Tb	43.7	-	IV	Single
		-	-	7	IP	Daily
^{177}Lu -PSMA-617 + Compound 1	8	^{177}Lu	30	-	IV	Single
		-	-	7	IP	Daily
^{177}Lu -PSMA-617 + Compound 1	8	^{177}Lu	60	-	IV	Single
		-	-	7	IP	Daily

- 15 Mice were checked daily and adverse clinical reactions noted. Animal body weight and tumor size were assessed twice a week. Animals were euthanized at the end of the experiment or upon reaching humane endpoints as listed in Table 4. Euthanasia was performed by cervical dislocation.

Table 4. Humane endpoints

Humane Endpoint	Comments
Tumor weight $\geq$ 1.5 g (1500 mm ³)	Tumor weight based on tumor volume calculated by the formula*: $\text{Tumor volume} = 0.52(\text{length} \times \text{width}^2)$ *Assuming a tissue density of 1.0 g/cm ³ , converted to tumor weight. Width refers to the shorter of the two axes.
Tumor burden $\geq$ 10% of animal body weight	Tumor burden calculated by the formula: $\text{Tumor burden} = \text{tumor weight} / (\text{animal weight} - \text{tumor weight}) \times 100$
Body weight loss of 20%	Body weight loss calculated by the formula*: $\text{Body weight loss (\%)} = (\text{animal weight} - \text{tumor weight} - \text{normal weight}) / (\text{normal weight}) \times 100$ *Normal weight defined as weight at inclusion
Tumor ulceration	Ulcerations are treated with Fucidin® or Dexem™. Animals were euthanized if any of the following endpoints were reached: • Tumor wound caused by excessive tumor growth • Tumor wound with an open area or diameter $\geq$ 8 mm • Tumor wound with cavity formation or damaged basement membrane • Tumor wound where no sign of regression or reduction is observed for 5 days • Distress and impairment of movement due to tumors or tumor wound
Distress and impairment of movement due to tumors	

Tumor size was measured by caliper 2x every week and on the day of stratification.

All treatments were tolerated well and no mice had to be sacrificed before reaching the endpoint of the tumor volume being as big as or bigger than 1500 mm³.

- 5 Treatment with (a) Compound 1* alone; (b) 21.8 MBq ¹⁶¹Tb-PSMA-I&T alone; and (c) both 30 and 60 MBq of ¹⁷⁷Lu-PSMA-617 alone did not reduce tumor growth as single agents up to study day 15 (i.e., the last day on which all mice were still alive, allowing all

conditions to be compared directly) compared to treatment with vehicle (FIG 4A, 4C, 4D). All mice that were treated with vehicle alone or Compound 1* alone reached a tumor volume of 1500 mm³ by or shortly after day 15 and thus were euthanized on or shortly after day 15.

In contrast, the combination of Compound 1* with either 21.8 MBq ¹⁶¹Tb-PSMA-I&T (FIG 4A) or 30 or 60 MBq ¹⁷⁷Lu-PSMA-617 (FIG 4C and FIG 4D respectively) reduced tumor growth compared to treatment with vehicle or single agents alone. Treatment with 43.7 MBq ¹⁶¹Tb-PSMA-I&T alone reduced tumor growth (FIG 4B) compared to vehicle or monotherapy with Compound 1*. Moreover, the combination of 43.7 MBq ¹⁶¹Tb-PSMA-I&T with Compound 1* led to a greater reduction in tumor growth after study day 15 compared to treatment with ¹⁶¹Tb-PSMA-I&T alone (FIG 4B).

Some of the mice treated with ¹⁶¹Tb-PSMA-I&T or ¹⁷⁷Lu-PSMA-617 alone reached the endpoint of tumor volume >1500 mm³ after study day 15 (i.e., the day on which most mice in the vehicle group and Compound 1* monotherapy treatment group reached a tumor volume of >1500 mm³) and several mice treated with Compound 1* in combination with ¹⁶¹Tb-PSMA-I&T or ¹⁷⁷Lu-PSMA-617 did not exhibit a tumor volume > 1500 mm³ until on or after study day 20. Individual tumor volumes are shown in Figure 5. Based on these individual tumor data, the number of days-until-endpoint was calculated for each mouse (i.e., the number of days from treatment start to reaching a tumor volume of >1500 mm³) (FIG 6). Tumors of mice treated with a combination of ¹⁶¹Tb-PSMA-I&T or ¹⁷⁷Lu-PSMA-617 and Compound 1* reached the endpoint significantly later than mice treated with vehicle, Compound 1*, ¹⁶¹Tb-PSMA-I&T or ¹⁷⁷Lu-PSMA-617 alone (p<0.05).

EXAMPLE 3: CO-ADMINISTRATION OF ²²⁵AC-PSMA OR ²¹²PB-PSMA AND COMPOUND 1* (PQR309; BIMIRALISIB) OR COMPOUND 2 IN NUDE MICE BEARING 22RV1 TUMORS

The purpose of this study will be to evaluate and compare the anti-tumor efficacy of ²²⁵Ac-PSMA- and ²¹²Pb-PSMA-targeting radioligand therapy (RLT; e.g., PSMA-617 or PSMA-I&T), as single treatment and in combination with dual PI3K/mTOR inhibitors (such as Compound 1* (PQR309; bimiralisib) or Compound 2 in mice (e.g., female NMRI nude mice) bearing subcutaneous human prostate carcinoma (established with cell lines such as 22Rv1, LNCaP, or PC3-PIP).

Mice (e.g., 8-week-old female NMRI nude mice) will be implanted with cells (e.g.,

3x10⁶ 22Rv1 cells in PBS:Matrigel (1:1)) by subcutaneous injection (e.g., using a 27G needle and a total injection volume of 100 µL, e.g., at the flank above the right limb). A sufficient number of mice per treatment group will be implanted (e.g., 8 mice per group plus extra mice as described in Example 2). When subcutaneous tumors reach a certain volume (e.g., 100, 150, or 200 mm³), the mice will be randomized based on tumor size and body weight to ensure similar average and variation of the groups. Mice will be distributed to the treatment and control groups (e.g., 8 mice per group).

In a first experiment, sub-optimal doses of ²²⁵Ac-PSMA- and ²¹²Pb-PSMA-targeting RLT will be determined by treating tumor-bearing mice with different target doses (e.g., 50, 75, 150, 200, and 300 kBq). ²²⁵Ac-PSMA- and ²¹²Pb-PSMA-targeting RLT or vehicle will be administered once by IV. In parallel, sub-optimal doses of dual PI3K/mTOR inhibitors (such as Compound 1* or Compound 2) will be determined by treating tumor-bearing mice with different target doses (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg/kg). The dual PI3K/mTOR inhibitors will be administered (e.g., by IP injection) multiple times (e.g., daily, every 2nd day, or every 3rd day). Mice will be checked daily and adverse clinical reactions will be noted. Animal body weight and tumor size will be assessed twice a week. Animals will be euthanized (e.g., by cervical dislocation) at the end of the experiment or upon reaching humane endpoints (e.g., as listed above in Table 4). Tumor size will be measured by caliper (e.g., 2x every week and on the day of stratification). The tumor volume will be estimated with a formula such as: 0.52(length × width²). Tumor volumes over time (i.e., study days) will be displayed and used to estimate sub-optimal treatment doses for each agent. A sub-optimal dose of ²²⁵Ac-PSMA- and ²¹²Pb-PSMA-targeting RLT and dual PI3K/mTOR inhibitors (such as Compound 1* or Compound 2) is defined as a dose which is not capable of inhibiting or only capable of moderately inhibiting tumor growth (e.g., a dose leading to an inhibition of 10, 20, 30, 40, 50, or 60% compared to vehicle).

In a second experiment, sub-optimal doses of ²²⁵Ac-PSMA- and ²¹²Pb-PSMA-targeting RLT will be combined with sub-optimal doses of dual PI3K/mTOR inhibitors (such as Compound 1* or Compound 2). ²²⁵Ac-PSMA- and ²¹²Pb-PSMA-targeting RLT or vehicle will be administered once by IV. Dual PI3K/mTOR inhibitors will be administered (e.g., by IP injections) multiple times (e.g., daily, every 2nd day, or every 3rd day). Mice will be checked and tumor volumes will be measured and analyzed (e.g., as described in Example 2). Additive or synergistic effects of ²²⁵Ac-PSMA- and ²¹²Pb-PSMA-targeting RLT with dual PI3K/mTOR inhibitors (such as Compound 1* or Compound 2) will be calculated using methods described

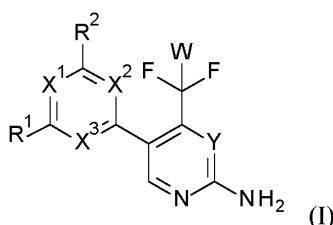
in the art, such as SynergyFinder
(<https://synergyfinder.fimm.fi/synergy/20241025144228237071/>).

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CLAIMS

1. A combination for use in a method of treating a cancer in a subject, said combination comprising:
 - 5 (i) a composition comprising a PSMA-targeted radiopharmaceutical; and
 - (ii) a composition comprising an inhibitor of PI3K, AKT, and/or mTOR.
2. A method of treating a cancer in a subject in need thereof, the method comprising: administering to said subject a therapeutically effective amount of (i) a PSMA-targeted radiopharmaceutical; and (ii) an inhibitor of PI3K, AKT, and/or mTOR.
- 10 3. The method or combination for use of claim 1 or claim 2, wherein said PSMA-targeted radiopharmaceutical comprises a DUPA targeting group.
- 15 4. The method or combination for use of any of the preceding claims, wherein said inhibitor of PI3K, AKT, and/or mTOR is a dual PI3K/mTOR inhibitor.
5. The method or combination for use of any of the preceding claims, wherein said inhibitor of PI3K, AKT, and/or mTOR is a compound of Formula (I):



wherein:

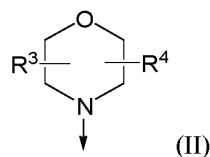
X^1 , X^2 and X^3 are, independently of each other, N or CH; with the proviso that at least two of X^1 , X^2 and X^3 are N;

Y is N or CH;

W is H or F; with the proviso that when W is F, then X^1 , X^2 and X^3 are N;

R^1 and R^2 are independently of each other

(i) a morpholinyl of formula (II)



wherein the arrow denotes the bond in formula (I); and wherein R^3 and R^4 are independently of each other H, C_1 - C_3 alkyl optionally substituted with one or two OH, C_1 - C_2 fluoroalkyl, C_1 - C_2 alkoxy, C_1 - C_2 alkoxy- C_1 - C_3 alkyl, CN, or $C(O)O$ - C_1 - C_2 alkyl; or R^3 and R^4 form together a bivalent residue $-R^5R^6-$ selected from C_1 - C_3 alkylene optionally substituted with 1 to 4 F, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, or any of the structures



wherein the arrows denote the bonds in formula (II); or

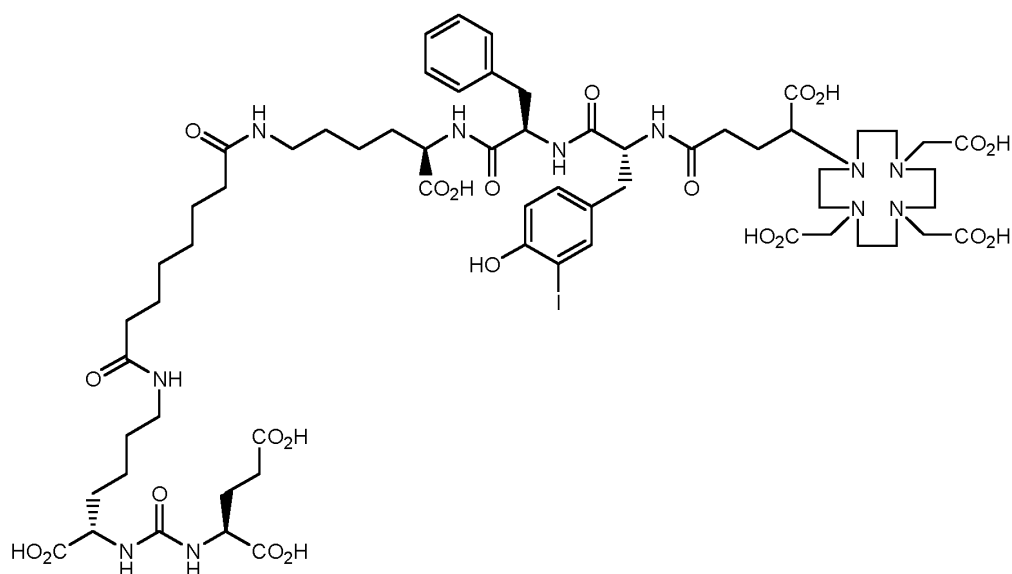
(ii) a saturated 6-membered heterocyclic ring Z selected from thiomorpholinyl and piperazinyl, optionally substituted by 1 to 3 R^7 ; wherein R^7 is independently at each occurrence C_1 - C_3 alkyl optionally substituted with one or two OH, C_1 - C_2 fluoroalkyl, C_1 - C_2 alkoxy- C_1 - C_3 alkyl, C_3 - C_6 cycloalkyl; or two R^7 substituents form together a bivalent residue $-R^8R^9-$ selected from C_1 - C_3 alkylene optionally substituted with 1 to 4 F, $-CH_2-O-CH_2-$ or $-O-CH_2CH_2-O-$;

with the proviso that at least one of R^1 and R^2 is a morpholinyl of formula II;

and prodrugs, metabolites, tautomers, solvates and pharmaceutically acceptable salts thereof.

6. The method or combination for use of any of the preceding claims, wherein said inhibitor of PI3K, AKT, and/or mTOR is bimiralisib, or a pharmaceutically acceptable salt thereof.
7. The method or combination for use of any of the preceding claims, wherein said PSMA-conjugated radiopharmaceutical is chelated to a radionuclide.
8. The method or combination for use of any of the preceding claims, wherein said PSMA-conjugated radiopharmaceutical is chelated to ^{161}Tb or ^{177}Lu .

9. The method or combination for use according to any of the preceding claims, wherein said PSMA-conjugated radiopharmaceutical is chelated to ^{161}Tb or ^{177}Lu ; and wherein said inhibitor of PI3K, AKT, and/or mTOR is bimiralisib.
- 5 10. The method or combination for use according to any of the preceding claims, wherein said cancer is prostate cancer.
11. The method or combination for use of any the preceding claims, wherein said cancer is prostate cancer, said PSMA-targeted radiopharmaceutical is Compound A, wherein
10 said Compound A is chelated to ^{161}Tb or ^{177}Lu ; and wherein said compound capable of inhibiting PI3K, AKT, and/or mTOR is bimiralisib.
12. The method or combination for use of any of the preceding claims, wherein said cancer is castration-resistant prostate cancer, wherein said PSMA-targeted
15 radiopharmaceutical is Compound A, wherein said Compound A is chelated to ^{161}Tb or ^{177}Lu ; and wherein said compound capable of inhibiting PI3K, AKT, and/or mTOR is bimiralisib.
13. The method or combination for use of any of the preceding claims, wherein said (i)
20 PSMA-targeted radiopharmaceutical is Compound A, wherein said Compound A and (ii) said an inhibitor of PI3K, AKT, and/or mTOR are administered sequentially.
14. A combination for use in a method of treating a cancer in a subject, preferably a prostate cancer, wherein said combination comprises:
25 (i) Compound A:



Compound A; and

(ii) an inhibitor of PI3K, AKT, and/or mTOR.

- 5 15. A composition or a kit of parts comprising:
- (i) a PSMA-targeted radiopharmaceutical; and
 - (ii) an inhibitor of PI3K, AKT, and/or mTOR.