

PSMA-TARGETING RADIOLIGAND TREATMENT REGIMEN**CROSS-REFERENCE TO RELATED APPLICATIONS**

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This application is related to U.S. Provisional Application No. 63/514,849 filed July 21, 2023. The contents of this application are hereby incorporated by reference in its entirety.

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FIELD

This disclosure relates to radiopharmaceuticals targeting prostate specific membrane antigen (PSMA), and their use in the treatment of PSMA-expressing cancers, such as, *e.g.*, metastatic castration resistant prostate cancer (mCRPC).

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BACKGROUND

Prostate cancer (PC) is a leading cause of cancer-related death among men around the world, with an estimated 1.4 million new cases and 375,000 deaths in 2020 (Wang et al. 2022, Prostate Cancer Incidence and Mortality: Global Status and Temporal Trends in 89 Countries From 2000 to 2019. *Frontiers in Public Health*). The tumors of 10-20% of prostate cancer patients become refractory to androgen-deprivation therapy by pharmaceutical or surgical castration, and progress as metastatic castration-resistant prostate cancer (mCRPC) (Juzeniene et al. 2021, Preclinical and Clinical Status of PSMA-Targeted Alpha Therapy for Metastatic Castration-Resistant Prostate Cancer. *Cancers*).

During the past decade, new therapeutic options such as novel antihormonal therapies, PARP inhibitors, radiopharmaceuticals, immunotherapies, and chemotherapies have been approved for mCRPC patients. Despite these developments, mCRPC remains incurable, which may be explained, in part, by the inter- and intra-patient heterogeneity of the disease. Thus, there is an urgent need for personalized, highly effective targeted therapies for mCRPC patients.

Targeted radioligand therapy (RLT) offers the possibility to treat cancer lesions in a specific and tumor-selective manner by exploiting cell surface receptors that are mainly expressed in malignant cells, such as, *e.g.*, prostate specific membrane antigen (PSMA). PSMA is an attractive target for prostate cancer therapy because, while it is highly expressed in cancerous cells, including mCRPC cells, it has much lower expression in normal tissues. Accordingly, PSMA has the potential to be a viable target for RLT with minimized radioactivity-related side effects. Specifically, RLT that utilizes radiolabeled small-molecule inhibitors of PSMA, which bind to PSMA with high affinity resulting in internalization and retention within the targeted PSMA-expressing cells (*i.e.*, malignant cells), may be used to identify and treat PSMA-positive mCRPC lesions.

SUMMARY

In an aspect, the present disclosure provides a method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a PSMA-binding ligand, wherein the PSMA-binding ligand is radiolabeled with an alpha-emitting radionuclide,

the radiolabeled PSMA-binding ligand is administered at a dose from about 6 MBq to about 8 MBq, and

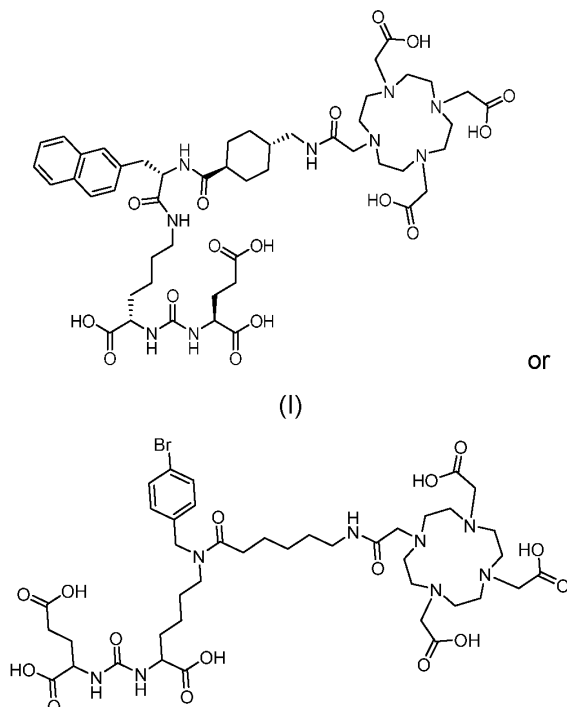
the subject has received prior chemotherapeutic treatment.

In another aspect, the present disclosure provides a method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a PSMA-binding ligand, wherein the PSMA-binding ligand is radiolabeled with an alpha-emitting radionuclide,

the radiolabeled PSMA-binding ligand is administered at a dose from about 6 MBq to about 8 MBq, and

the subject has not received prior chemotherapeutic treatment.

In another aspect, the present disclosure provides a method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a compound of formula (I) or (II):



wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,

(II)

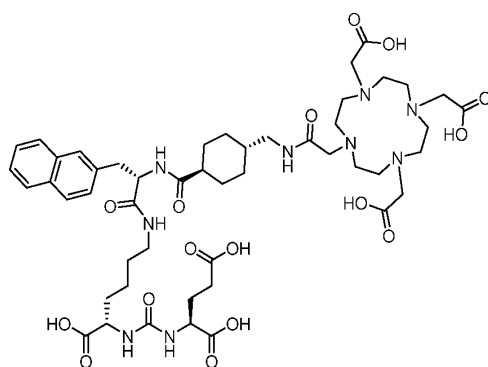
wherein:

the compound of formula (I) or (II) is radiolabeled with an alpha-emitting radionuclide,

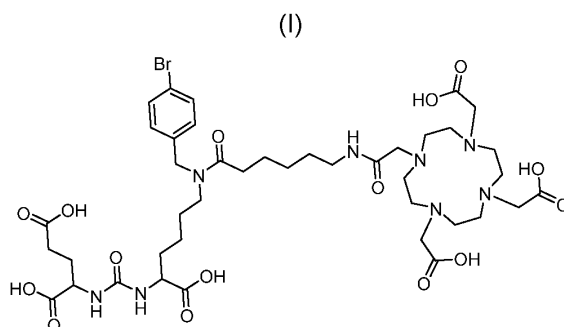
5 the radiolabeled compound of formula (I) or (II) is administered at a dose from about 6 MBq to about 8 MBq, and

the subject has received prior chemotherapeutic treatment.

In another aspect, the present disclosure provides a method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering
10 to the subject a compound of formula (I) or (II):



or



wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,

15 (II),

wherein:

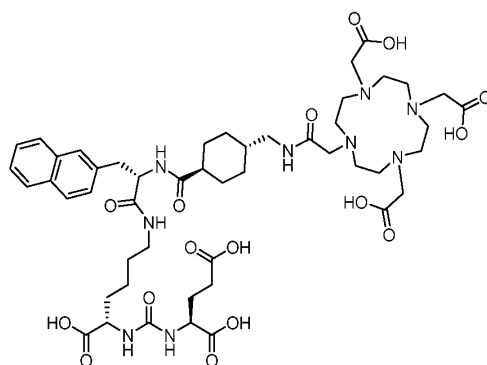
the compound of formula (I) or (II) is radiolabeled with an alpha-emitting radionuclide,

the radiolabeled compound of formula (I) or (II) is administered at a dose from about
20 6 MBq to about 8 MBq, and

the subject has not received prior chemotherapeutic treatment.

In yet another aspect, the present disclosure provides a method of treating prostate cancer in a subject in need thereof, comprising administering to the subject a

radiopharmaceutical at a dose of from about 6 MBq to about 8 MBq, wherein the radiopharmaceutical is a compound of formula (I):

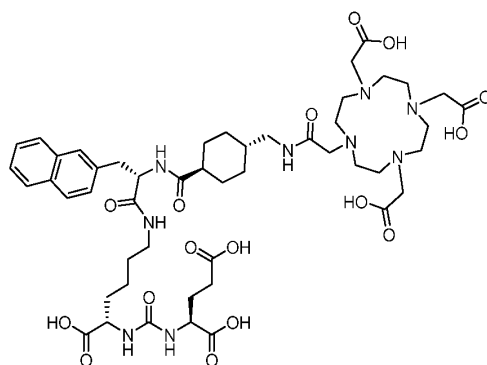


(I),

- 5 wherein the compound of formula (I) is radiolabeled with ^{225}Ac , and wherein the subject has received prior chemotherapeutic treatment.

In still another aspect, the present disclosure provides a method of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical at a dose of from about 6 MBq to about 8 MBq, wherein the

- 10 radiopharmaceutical is a compound of formula (I):



(I)

wherein the compound of formula (I) is radiolabeled with ^{225}Ac , and wherein the subject has not received prior chemotherapeutic treatment.

15

In another aspect, the present disclosure provides a method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a PSMA-binding ligand, wherein the PSMA-binding ligand is radiolabeled with an alpha-emitting radionuclide,

- 20 the radiolabeled PSMA-binding ligand is administered at a dose from about 6 MBq to about 14 MBq, and

the subject has received prior chemotherapeutic treatment.

In another aspect, the present disclosure provides a method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a PSMA-binding ligand, wherein the PSMA-binding ligand is radiolabeled with an alpha-emitting radionuclide.

the radiolabeled PSMA-binding ligand is administered at a dose from about 6 MBq to about 14 MBq, and

the subject has not received prior chemotherapeutic treatment.

In another aspect, the present disclosure provides a method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a PSMA-binding ligand, wherein the PSMA-binding ligand is radiolabeled with an alpha-emitting radionuclide,

the radiolabeled PSMA-binding ligand is administered at a dose from about 8 MBq to

about 10 MBq, and

the subject has received prior chemotherapeutic treatment.

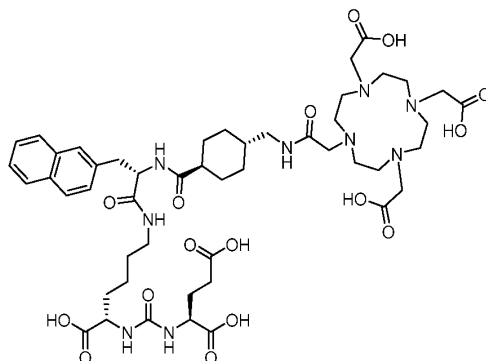
In another aspect, the present disclosure provides a method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a PSMA-binding ligand, wherein the PSMA-binding ligand is radiolabeled with an alpha-emitting radionuclide.

the radiolabeled PSMA-binding ligand is administered at a dose from about 8 MBq to

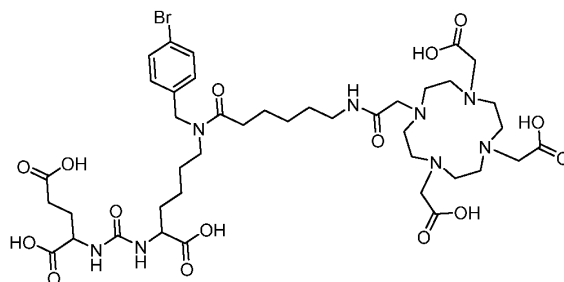
about 10 MBq, and

the subject has not received prior chemotherapeutic treatment.

In another aspect, the present disclosure provides a method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a compound of formula (I), (II), or (IV):



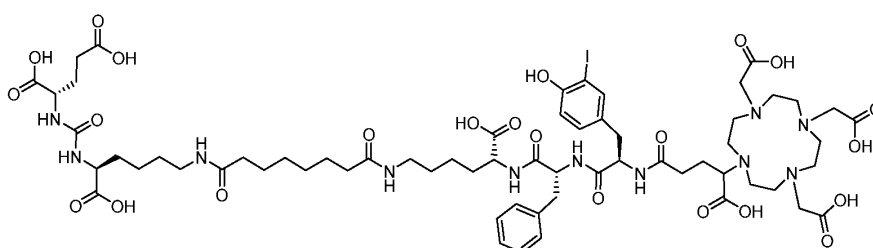
(I)



wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration, or

(II)

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(IV)

wherein:

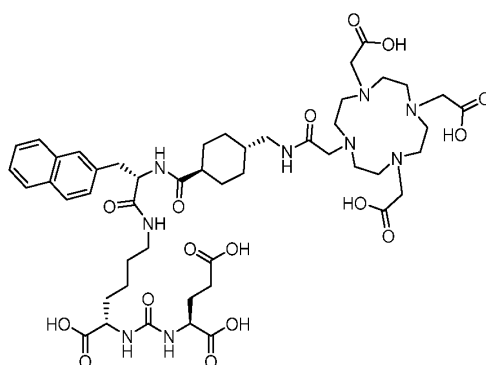
the compound of formula (I), (II), or (IV) is radiolabeled with an alpha-emitting radionuclide,

the radiolabeled compound of formula (I), (II), or (IV) is administered at a dose from about 6 MBq to about 14 MBq, and

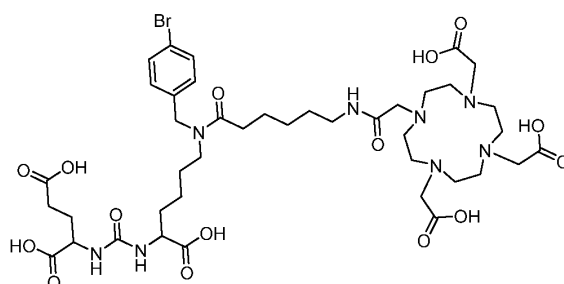
the subject has received prior chemotherapeutic treatment.

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In another aspect, the present disclosure provides a method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a compound of formula (I), (II), or (IV):



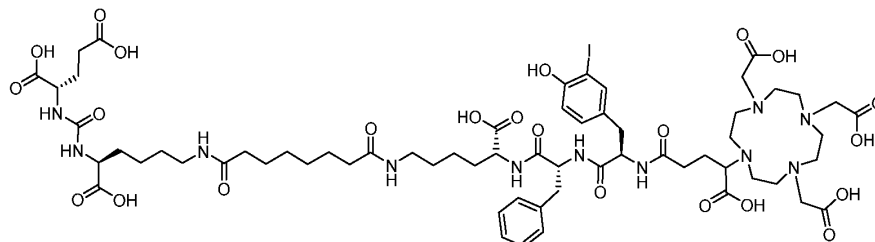
(I)



(II)

wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration, or

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(IV)

wherein:

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the compound of formula (I), (II), or (IV) is radiolabeled with an alpha-emitting radionuclide,

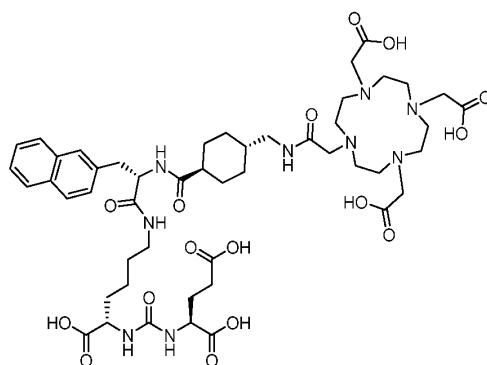
the radiolabeled compound of formula (I), (II), or (IV) is administered at a dose from about 6 MBq to about 14 MBq, and

the subject has not received prior chemotherapeutic treatment.

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In yet another aspect, the present disclosure provides a method of treating prostate cancer in a subject in need thereof, comprising administering to the subject a

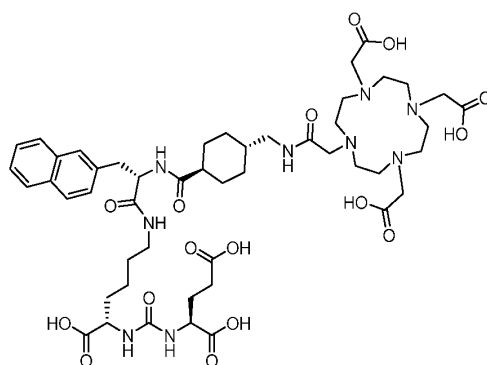
radiopharmaceutical at a dose of from about 8 MBq to about 10 MBq, wherein the radiopharmaceutical is a compound of formula (I):



(I),

- 5 wherein the compound of formula (I) is radiolabeled with ^{225}Ac , and wherein the subject has received prior chemotherapeutic treatment.

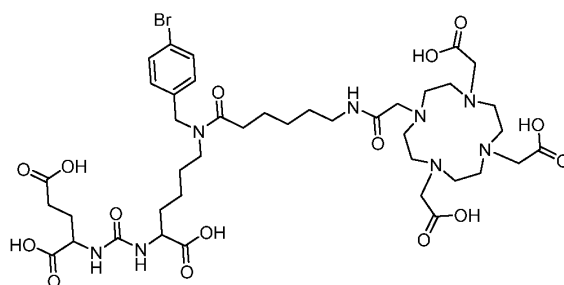
In still another aspect, the present disclosure provides a method of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical at a dose of from about 8 MBq to about 10 MBq, wherein the radiopharmaceutical is a compound of formula (I):



(I)

- 15 wherein the compound of formula (I) is radiolabeled with ^{225}Ac , and wherein the subject has not received prior chemotherapeutic treatment.

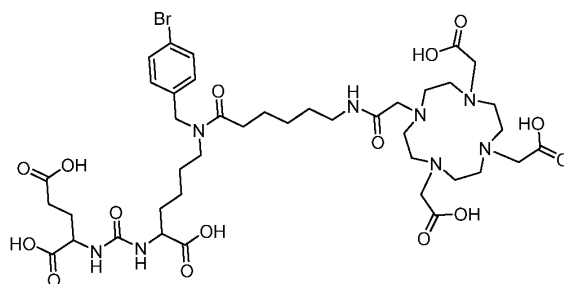
In yet another aspect, the present disclosure provides a method of treating prostate cancer in a subject in need thereof, comprising administering to the subject a radiopharmaceutical at a dose of from about 6 MBq to about 14 MBq, wherein the radiopharmaceutical is a compound of formula (II):



wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,
(II),

wherein the compound of formula (II) is radiolabeled with ^{225}Ac , and wherein the
5 subject has received prior chemotherapeutic treatment.

In still another aspect, the present disclosure provides a method of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical at a dose of from about 6 MBq to about 14 MBq, wherein the
10 radiopharmaceutical is a compound of formula (II):



wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,
(II)

wherein the compound of formula (II) is radiolabeled with ^{225}Ac , and wherein the
15 subject has not received prior chemotherapeutic treatment.

DETAILED DESCRIPTION

PSMA is a transmembrane glycoprotein of about 100 kDA with folate hydrolase, carboxypeptidase, and internalization activities that exhibits low expression in normal
20 prostate tissue, kidneys, duodenum, salivary and lacrimal glands, brain, and intestines. Increased PSMA expression is significantly associated with the degree of differentiation and progression of mCRPC. Accordingly, PSMA-targeting ligands may selectively accumulate in malignant cells, allowing development opportunities for imaging and treating mCRPC. The systemic administration of PSMA-targeted RLT allows the simultaneous treatment of wide-
25 spread bone and extraskeletal metastases, thereby limiting radiotoxicity to healthy tissues.

Currently, ^{177}Lu , a β^- emitting radionuclide, is the most clinically-used radionuclide in RLT for the treatment of PSMA-expressing cancers, e.g., prostate cancer. However, α -particles present significantly higher energies and shorter path lengths (<0.1 mm) than β^- particles and as such, result in a greater probability of generating DNA double-strand breaks upon interaction with cell nuclei (*i.e.*, have greater cytotoxicity). Thus, there is much interest around the use of α -particles in PSMA-targeted RLT for the treatment of prostate cancers, including mCRPC.

Accordingly, described herein are compounds radiolabeled with an alpha-emitting radionuclide that target PSMA, corresponding pharmaceutical compositions, and their use in methods of treating PSMA-expressing cancer in a subject in need thereof.

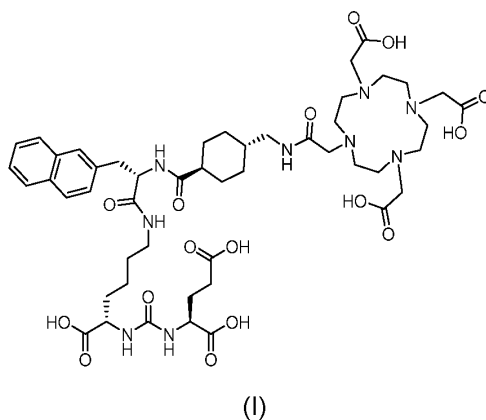
In an aspect, the present disclosure provides a method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a PSMA-binding ligand, wherein the PSMA-binding ligand is radiolabeled with an alpha-emitting radionuclide,

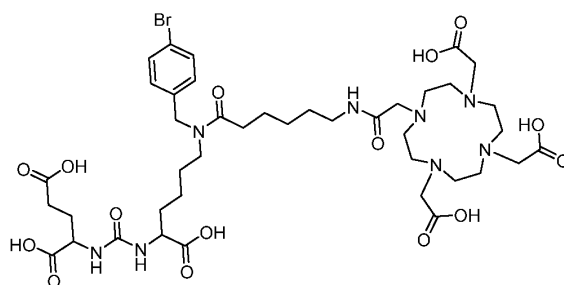
the radiolabeled PSMA-binding ligand is administered at a dose from about 6 MBq to about 14 MBq, such as about 6 MBq to about 8 MBq, or about 8 MBq to about 10 MBq, and the subject has received prior chemotherapeutic treatment.

In another aspect, the present disclosure provides a method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a PSMA-binding ligand, wherein the PSMA-binding ligand is radiolabeled with an alpha-emitting radionuclide,

the radiolabeled PSMA-binding ligand is administered at a dose from about 6 MBq to about 14 MBq, such as about 6 MBq to about 8 MBq, or about 8 MBq to about 10 MBq, and the subject has not received prior chemotherapeutic treatment.

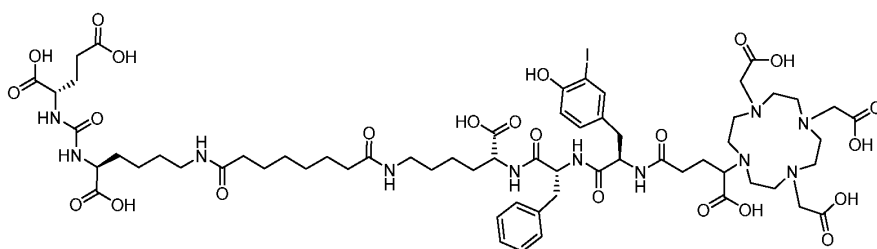
In particular, the present disclosure provides methods for treating a PSMA-expressing cancer in a subject in need thereof, the methods comprising administering to the subject a compound of formula (I), (II), or (IV):





wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration, or

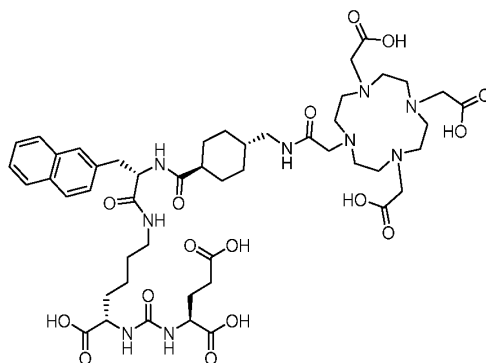
(II)



(IV)

wherein the compound of formula (I), (II), or (IV) is radiolabeled with an alpha-emitting radionuclide.

Also provided herein are methods of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical at a dose of from about 6 MBq to about 10 MBq, such as about 6 MBq to about 8 MBq, or about 8 MBq to about 10 MBq, wherein the radiopharmaceutical is a compound of formula (I):

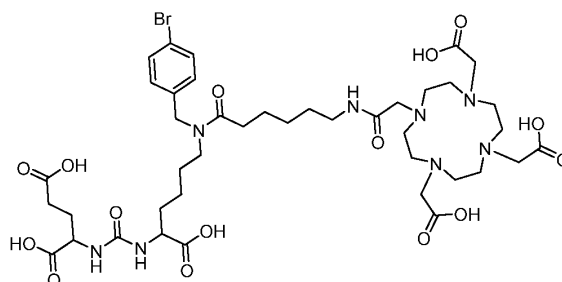


(I)

wherein the compound of formula (I) is radiolabeled with ^{225}Ac .

Also provided herein are methods of treating prostate cancer in a subject in need thereof, comprising administering to the subject a radiopharmaceutical at a dose of from

about 6 MBq to about 14 MBq, wherein the radiopharmaceutical is a compound of formula (II):



wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,
(II),

wherein the compound of formula (II) is radiolabeled with ^{225}Ac .

The details of the disclosure are set forth in the accompanying description below.

Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

Definitions

Unless specific definitions are provided, the nomenclature used in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Standard techniques may be used for chemical synthesis, and chemical analysis. Certain such techniques and procedures may be found for example in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa., 21st edition, 2005, which is hereby incorporated by reference for any purpose. Where permitted, all patents, applications, published applications and other publications and other data referred to throughout in the disclosure are incorporated by reference herein in their entirety.

As used herein, the terms "alpha-emitting radionuclide" and "alpha-emitter" include radionuclides that decay primarily via α decay (e.g., ^{225}Ac) and radionuclides that decay via branching decay (e.g., ^{213}Bi , which decays via β^- and α decay).

The term “radiopharmaceutical” is used herein to refer to pharmaceutical compounds, e.g., peptides, oligonucleotides, small molecules, and antibodies, that are radiolabeled with a radionuclide. A radiopharmaceutical may be a radioligand. In some embodiments, radiopharmaceutical refers to a radiolabeled compound of the present disclosure (i.e., a compound of formula (I) (II) or (IV) (above) or a compound of formula (III) or (V) (below). In other embodiments, radiopharmaceutical refers to a radiolabeled compound known in the art.

The term “beta-minus-emitting radiopharmaceutical” as used herein refers to a radiopharmaceutical that is radiolabeled with a β^- emitting radionuclide. β^- emitting radionuclides are radionuclides that, during the process of natural decay, emit β^- particles. Exemplary β^- emitting radionuclides that can be comprised in a beta-minus-emitting radiopharmaceutical include, but are not limited to, ^{177}Lu , ^{161}Tb , ^{131}I , ^{90}Y , ^{67}Cu , and ^{47}Sc .

The phrase “pharmaceutically acceptable” as employed herein refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, the term “treat,” “treatment,” or “treating” means decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disorder or disease.

As used herein, the term “prevent” or “prevention” means no disorder or disease development if none had occurred, or no further disorder or disease development if there had already been development of the disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the disorder or disease.

The terms “administer,” “administering,” and “administration” refer to the giving of a compound disclosed herein, or another indicated compound, to a patient by any appropriate route. In particular, the compounds disclosed herein may be administered by oral or parenteral route, preferably by parenteral route, such as by injection or infusion, wherein the injection or infusion may be made intravenously, intramuscularly, intra-arterially, subcutaneously, intra-dermally, intraperitoneally, etc. Depending on the administration route, the compounds of the present disclosure may be administered in a pharmaceutical composition that further comprises appropriate constituents, such as carriers, solvents, and excipients generally known in the art. The term “pharmaceutical composition” is defined herein to refer to a mixture (e.g., a solution or an emulsion) containing at least one active ingredient or therapeutic agent to be administered to a subject, e.g., a human, in order to prevent or treat a particular disease or condition affecting the subject.

The term “radiolabeled” (or “chelated,” or “complexed”) as used herein means that a non-radioactive compound is labeled with a radioisotope. Radiolabeling can be achieved, e.g., via chelation or complexation of a chelator with an appropriate radionuclide.

Radiolabeling can also refer to chemically substituting one group on a compound for a radionuclide, such as, e.g., in the case of ^{18}F .

Furthermore, it is intended that within the scope of the present invention, any element, in particular when mentioned in relation to a compound of the disclosure, shall comprise all isotopes and isotopic mixtures of said element, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. For example, a reference to hydrogen includes within its scope ^1H , ^2H (*i.e.*, deuterium or D), and ^3H (*i.e.*, tritium or T). In some embodiments, the compounds described herein include a ^2H (*i.e.*, deuterium) isotope. By way of example, the group denoted $-\text{C}_{(1-6)}\text{alkyl}$ includes not only $-\text{CH}_3$, but also CD_3 ; not only CH_2CH_3 , but also CD_2CD_3 , *etc.* Similarly, references to carbon and oxygen include within their scope respectively ^{12}C , ^{13}C and ^{14}C and ^{15}O and ^{16}O and ^{17}O and ^{18}O . The isotopes may be radioactive or non-radioactive. Radiolabelled compounds of the disclosure may include a radioactive isotope selected from the group comprising ^3H , ^{11}C , ^{18}F , ^{35}S , ^{122}I , ^{123}I , ^{125}I , ^{131}I , ^{75}Br , ^{76}Br , ^{77}Br and ^{82}Br . In some embodiments, the radioactive isotope is selected from the group of ^3H , ^{11}C and ^{18}F .

As used herein, the term “carrier” or “pharmaceutically acceptable carrier” includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289-1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

Unless otherwise specified, conventional definitions of terms control and conventional stable atom valences are presumed and achieved in all formulas and groups.

As used herein, the term “about” will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. As used herein when referring to a measurable value such as an amount, a temporal duration, and the like, the term “about” is meant to encompass variations of $\pm 10\%$, including $\pm 5\%$, $\pm 1\%$, and $\pm 0.1\%$ from the specified value, as such variations are appropriate to perform the disclosed methods.

The articles “a” and “an” are used in this disclosure to refer to one or more than one (e.g., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

5 Compounds

The present disclosure provides radiopharmaceuticals for the treatment or prevention of PSMA-expressing cancers, comprising a PSMA-binding ligand radiolabeled with an alpha-emitting radionuclide.

In some embodiments of the present disclosure, the PSMA-binding ligand is selected from the group consisting of PSMA-617, PSMA I&T (PSMA I&T (zadavotide guraxetan) means the “cold” ligand (ligand without radionuclide) of [177Lu]Lu-PSMA I&T (INN: lutetium (177Lu) zadavotide guraxetan), and is commercially available by ABX, Radeberg, Germany), PSMA-R2, MIP-1095, MIP-1545, MIP-1555, MIP-1557, MIP-1558, CTT1403, FC705, BAY-2315497, BAY-2315487, TLX591, TLX592, PSMA-TCC, rhPSMA, rhPSMA-7, rhPSMA-7.3, rhPSMA-10.1, Ludotadipep, PNT2001, PNT2002, PSMA-7, EB-PSMA-617, PSMA-ALB-02, PSMA-ALB-053, PSMA-ALB-056, P16-093, PSMA-93, PSMA-62, PSMA-1, PSMA-1-DOTA, SAR-bis-PSMA, ITM-22, ITM-24D, PMI-21, DOTA-h11B6, FPI-1434, pelgifatamab, NG001, ADVC001, RPS-072, and RPS-074.

In some embodiments, the PSMA-binding ligand is selected from the group consisting of PSMA-617, PSMA I&T, PSMA-62, PSMA-1-DOTA, and PSMA-R2. In certain embodiments, the PSMA-binding ligand is selected from the group consisting of PSMA-617, PSMA I&T, and PSMA-R2.

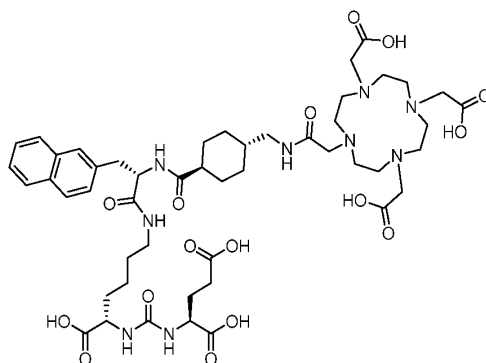
As will be understood by one with skill in the art, the above mentioned PSMA-binding ligands may be radiolabeled with beta-minus-, positron- or alpha-emitting radionuclides, as in, e.g., the following radiopharmaceutical compounds: 64Cu/225Ac-DOTA-TLX592, made by Telix, 67Cu-SAR-bisPSMA, made by Clarity, 212Pb-NG001, made by ART BIO, 212Pb-ADVC001 made by AdvanCell, 225Ac-RPA-074, 225Ac-pelgifatamab, and 227Th-Carboxy-HOPO-PSMA made by Bayer, 225Ac-ITM-22 (Ac-PSMA-TTM*), made by ITM, and 225Ac-PSMA-R2 made by Novartis.

In various embodiments of the present disclosure, the radiopharmaceutical comprising a PSMA-binding ligand radiolabeled with an alpha-radionuclide is selected from the group consisting of [177Lu]Lu-PSMA-617 (lutetium (177Lu) vipivotide tetraxetan), [177Lu]Lu-EB-PSMA-617 (Evans Blue modified [177Lu]Lu-PSMA-617), and [177Lu]Lu-PSMA I&T (lutetium (177Lu) zadavotide guraxetan), [161Tb]Tb-PSMA-617 (terbium (161Tb) vipivotide tetraxetan), [161Tb]Tb-EB-PSMA-617 (Evans Blue modified [161Tb]Tb-PSMA-617), and [161Tb]Tb-PSMA I&T (terbium (161Tb) zadavotide guraxetan), preferably [177Lu]Lu-PSMA-617 (lutetium (177Lu) vipivotide tetraxetan) or [161Tb]Tb-PSMA-617

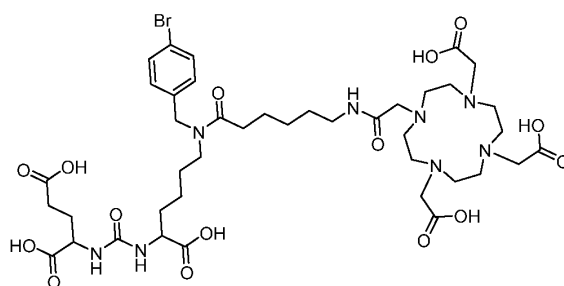
(terbium (^{161}Tb) vipivotide tetraxetan), more preferably [^{177}Lu]Lu-PSMA-617 (lutetium (^{177}Lu) vipivotide tetraxetan), wherein ^{177}Lu and ^{161}Tb are replaced with ^{225}Ac .

The present disclosure also provides radiopharmaceuticals for the treatment of PSMA-expressing cancer, wherein the radiopharmaceuticals are compounds of formulae (I),

(II), (III), (IV), and (V):

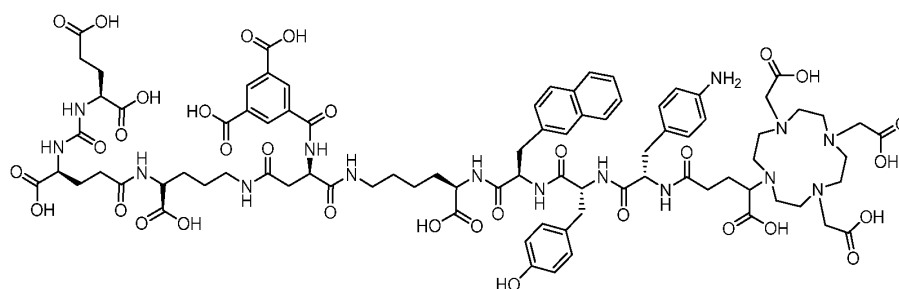


(I)

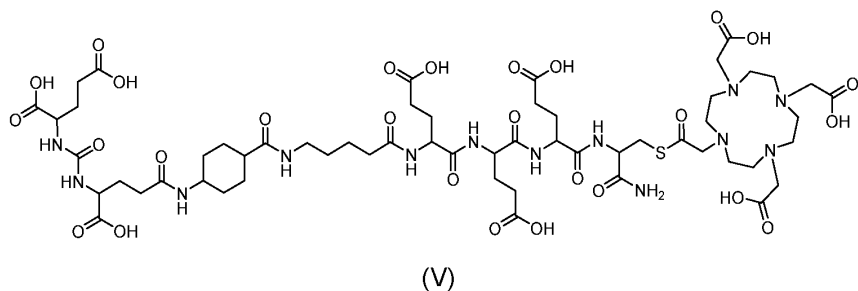
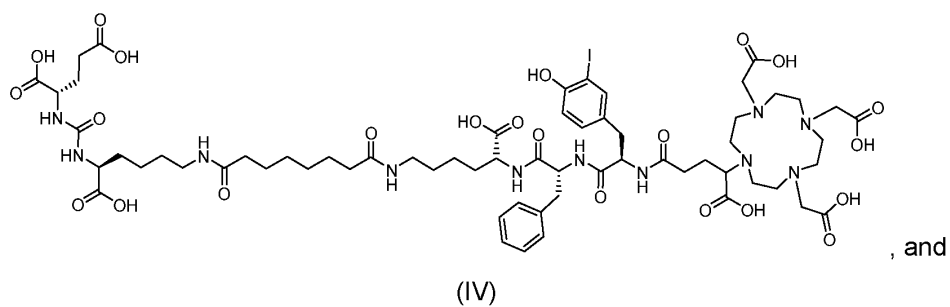


(II)

wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,

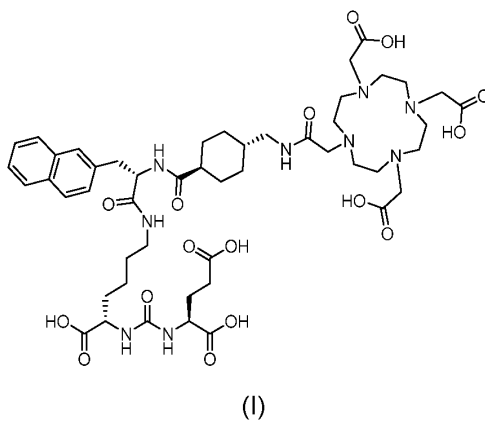


(III)

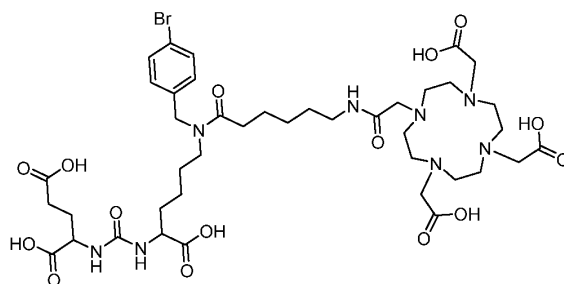


- 5 wherein the compounds of formulae (I), (II), (III), (IV), and (V) are radiolabeled with an alpha-emitting radionuclide.

In some embodiments, the radiopharmaceuticals are compounds of formulae (I), (II), and (IV):

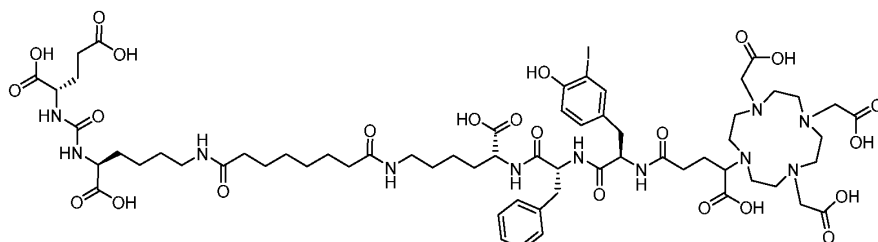


10



wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration, and

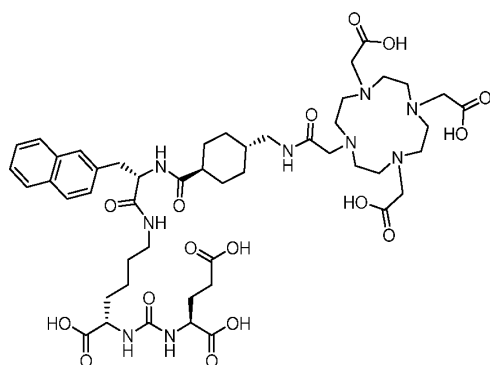
(II)



(IV)

5 wherein the compounds of formulae (I), (II), and (IV) are radiolabeled with an alpha-emitting radionuclide.

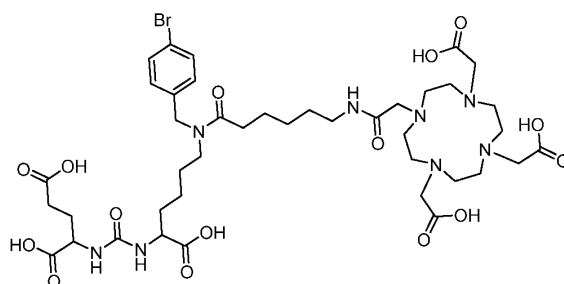
In some embodiments, the radiopharmaceuticals are compounds of formulae (I) and (II):



and

(I)

10



wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,

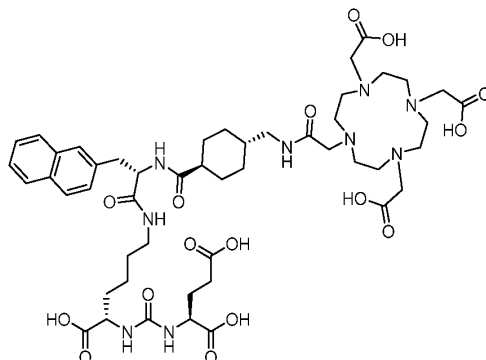
(II)

15 wherein the compounds of formulae (I) and (II) are radiolabeled with an alpha-emitting radionuclide.

In some embodiments, the alpha-emitting radionuclide is selected from the group consisting of ^{225}Ac , ^{211}At , ^{213}Bi , ^{212}Bi , ^{212}Pb , ^{223}Ra , ^{224}Ra , ^{149}Tb , and ^{227}Th . In further

embodiments, the alpha-emitting radionuclide is selected from the group consisting of ^{225}Ac , ^{212}Pb , and ^{227}Th . In still further embodiments, the alpha-emitting radionuclide is ^{225}Ac .

In certain embodiments, the radiopharmaceutical is a compound of formula (I):



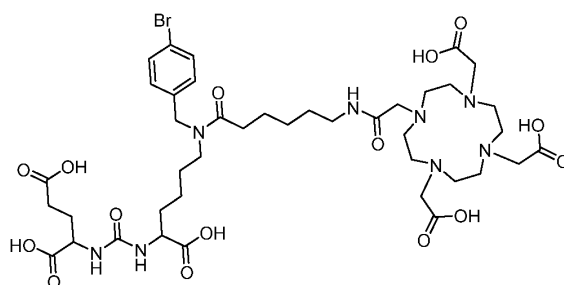
5

(I)

wherein the compound of formula (I) is radiolabeled with ^{225}Ac .

Methods of making and using the compound of formula (I) can be found, for example, in U.S. Patent No. 10,398,791, which is incorporated herein by reference in its entirety.

In certain embodiments, the radiopharmaceutical is a compound of formula (II):



10

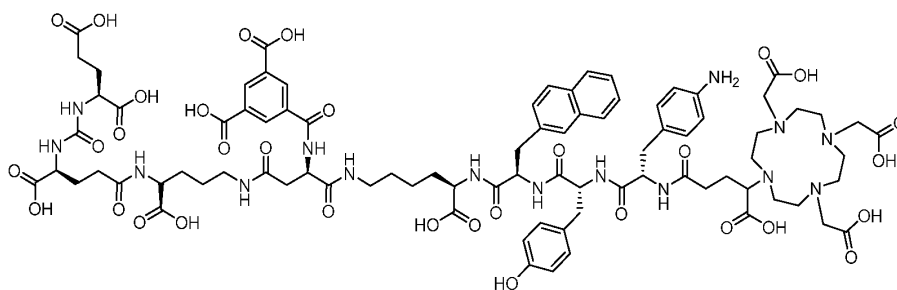
(II)

wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,

wherein the compound of formula (II) is radiolabeled with ^{225}Ac .

15 Methods of making and using the compound of formula (II) can be found, for example, in the Examples of the instant application, see, *e.g.*, Examples 1 and 3.

In certain embodiments, the radiopharmaceutical is a compound of formula (III):

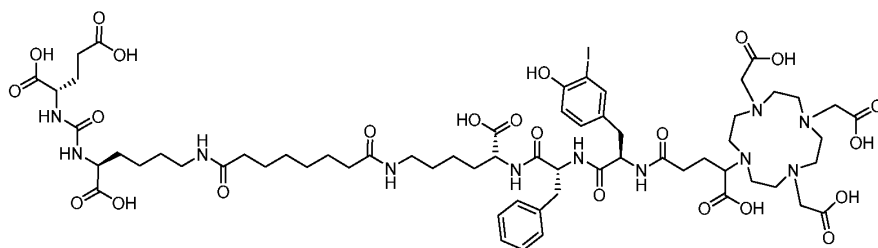


(III)

wherein the compound of formula (III) is radiolabeled with ^{225}Ac .

Methods of making and using the compound of formula (III) can be found, for example, in WO 2019/115547 (compound of formula (III) is therein referred to PSMA-62 and DOTAGA-F(4-NH₂)y-2-nal-k(d[N⁵-orn-C⁴-EuE]-TMA)), which is incorporated herein by reference in its entirety.

In certain embodiments, the radiopharmaceutical is a compound of formula (IV):

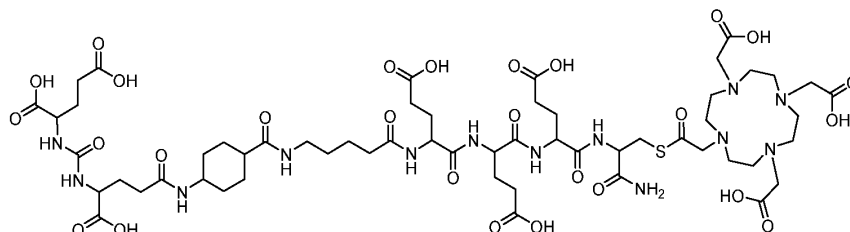


(IV)

wherein the compound of formula (IV) is radiolabeled with ^{225}Ac .

Methods of making and using the compound of formula (IV) can be found, for example, in Weineisen et al. J Nucl Med 2015; 56:1169-1176; and Chatalic, Theranostics, 6(6), 849-861 (2016), US 11,129,912, and US 11,491,246, which are incorporated herein by reference in their entireties.

In certain embodiments, the radiopharmaceutical is a compound of formula (V):



(V)

wherein the compound of formula (V) is radiolabeled with ^{225}Ac .

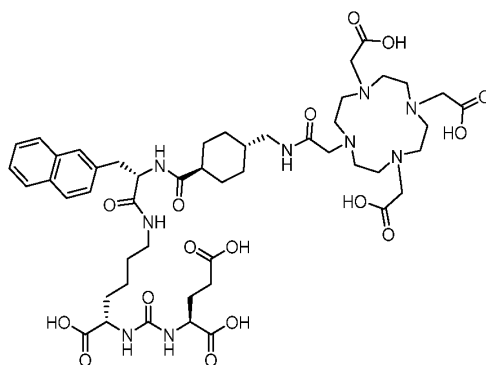
Methods of making and using the compound of formula (V) can be found, for example, in Wang et al. Small Molecule-Based Prodrug Targeting Prostate Specific Membrane Antigen for the Treatment of Prostate Cancer. Cancers (Basel). 2021 13(3):417, and WO 2023/086833, paragraph [00132], which is incorporated herein by reference in its entirety.

Methods of Treatment

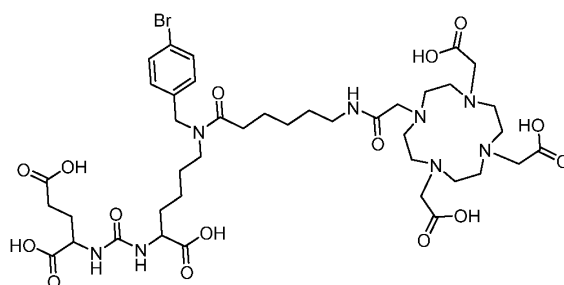
The present disclosure provides methods of treating or preventing a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering

to the subject a radiopharmaceutical comprising a PSMA-binding ligand radiolabeled with an alpha-emitting radionuclide, wherein the radiopharmaceutical is administered at a dose of from about 6 MBq to about 14 MBq, such as about 6 MBq to about 8 MBq, or about 8 MBq to about 10 MBq. The PSMA-binding ligand can be as previously described.

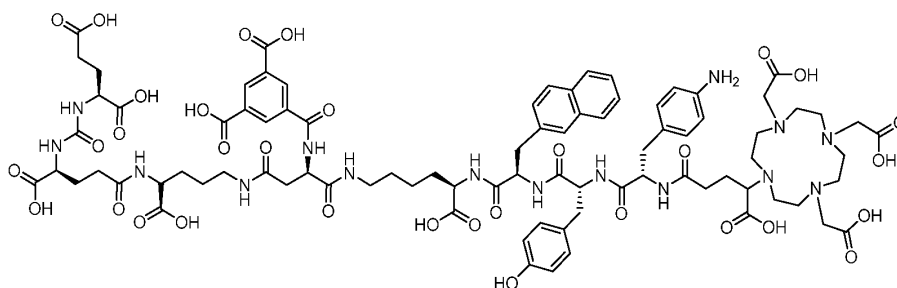
- 5 In some embodiments, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a compound of formula (I), (II), (III), (IV), or (V):



(I)

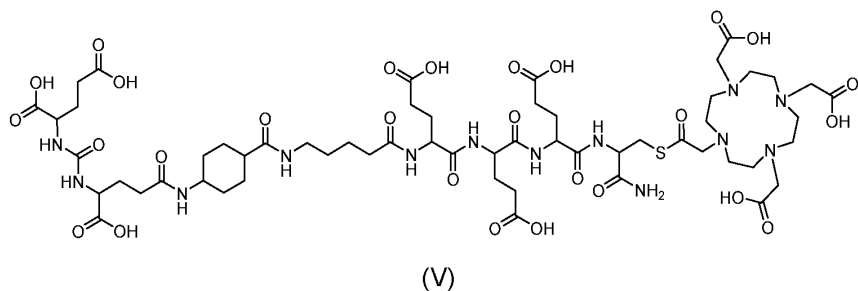
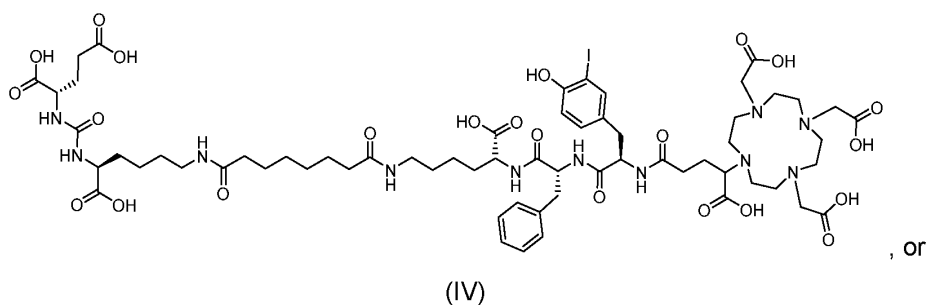


(II)



(III)

wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,

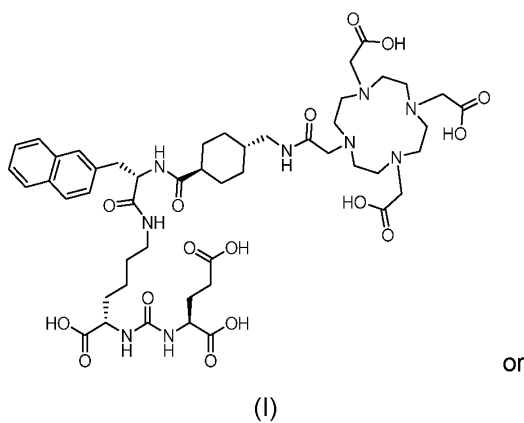


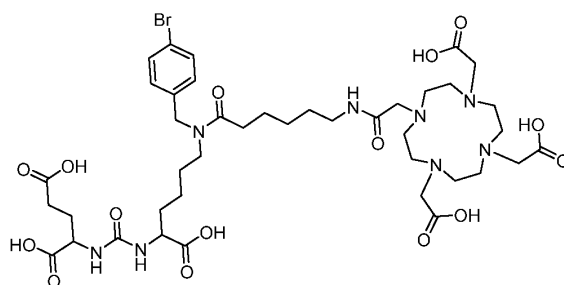
5 wherein:

the compound of formula (I), (II), (III), (IV), or (V) is radiolabeled with an alpha-emitting radionuclide, and

the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose from about 6 MBq to about 10 MBq, such as about 6 MBq to about 8 MBq, or about 8 MBq to about 10 MBq.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a compound of formula (I) or (II):





wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,

(II)

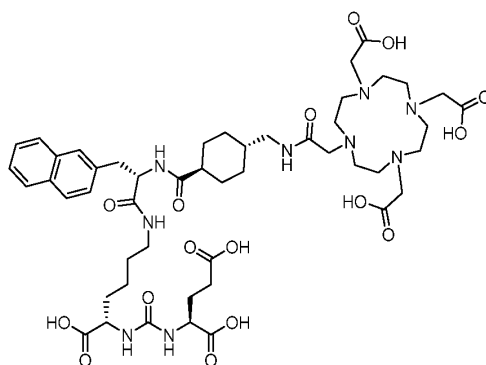
wherein:

- 5 the compound of formula (I), (II), (III), (IV), or (V) is radiolabeled with an alpha-emitting radionuclide, and
- the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose from about 6 MBq to about 10 MBq, such as about 6 MBq to about 8 MBq, or about 8 MBq to about 10 MBq..

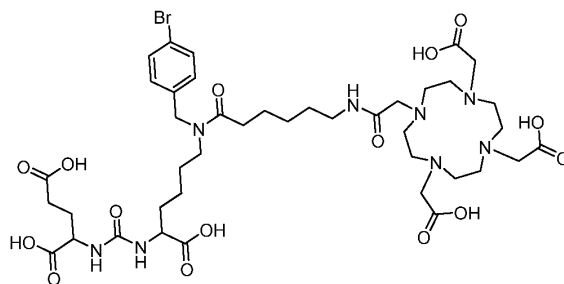
- 10 In some embodiments, the subject has received prior chemotherapeutic treatment. Alternatively, in some embodiments, the subject has not received prior chemotherapeutic treatment.

Accordingly, in one aspect, the present disclosure provides a method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises

- 15 administering to the subject a compound of formula (I), (II), (III), (IV), or (V):

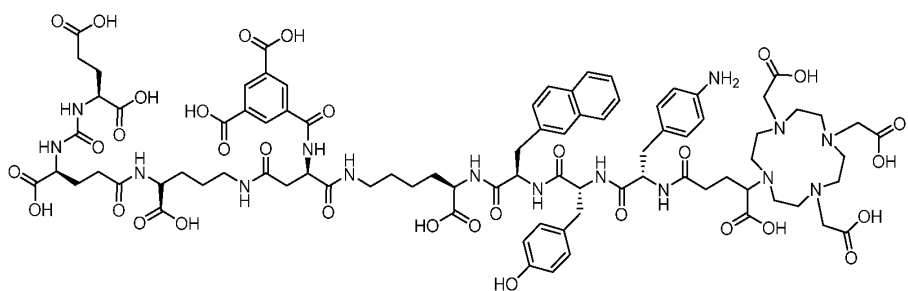


(I)

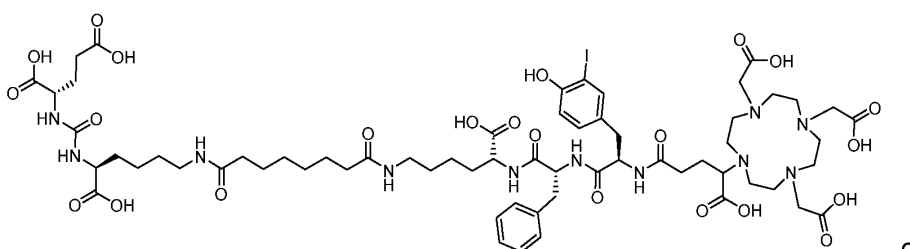


wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,

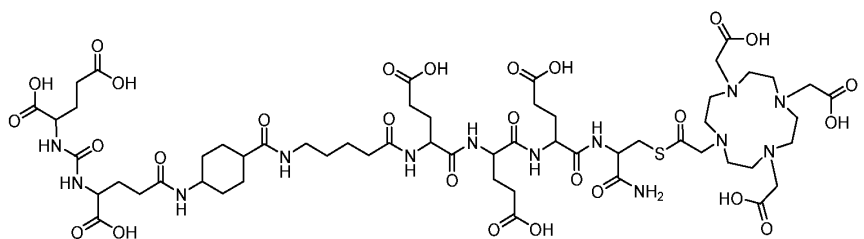
(II)



(III)



(IV)



(V)

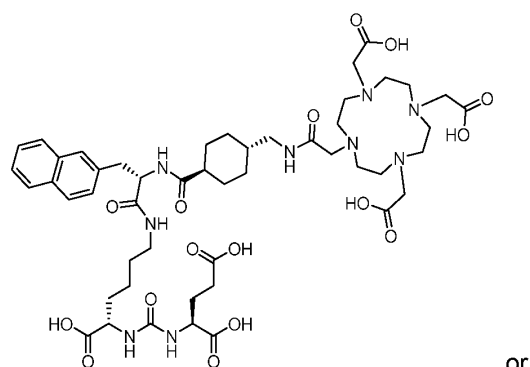
wherein:

the compound of formula (I), (II), (III), (IV), or (V) is radiolabeled with an alpha-emitting radionuclide,

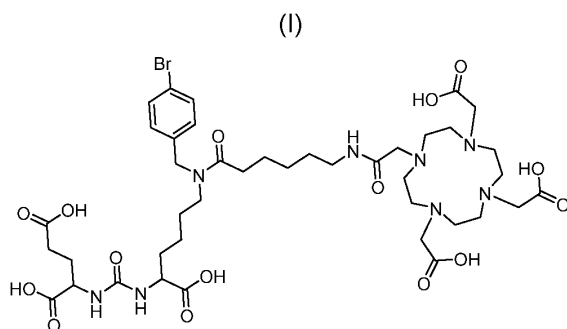
the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6 MBq to about 10 MBq such as about 6 MBq to about 8 MBq, or about 8 MBq to about 10 MBq, and

the subject has received prior chemotherapeutic treatment.

In particular embodiments, the method comprises administering to the subject a compound of formula (I) or (II):



or



wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,

5

(II)

wherein:

the compound of formula (I) or (II) is radiolabeled with an alpha-emitting radionuclide,

the radiolabeled compound of formula (I) or (II) is administered at a dose from about

6 MBq to about 10 MBq, such as about 6 MBq to about 8 MBq, or about 8 MBq to about 10

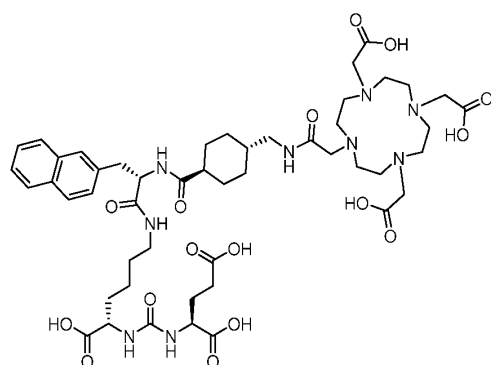
10 MBq, and

the subject has received prior chemotherapeutic treatment.

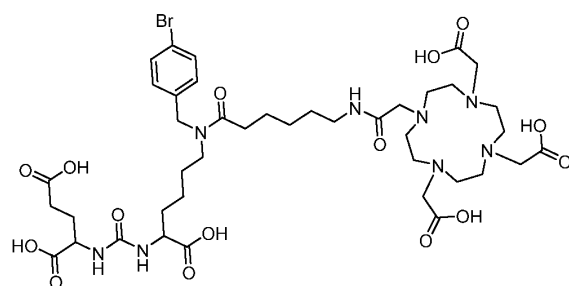
In one or more embodiments, the prior chemotherapeutic treatment comprises administration of taxane.

In another aspect, the present disclosure provides a method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a compound of formula (I), (II), (III), (IV), or (V):

15



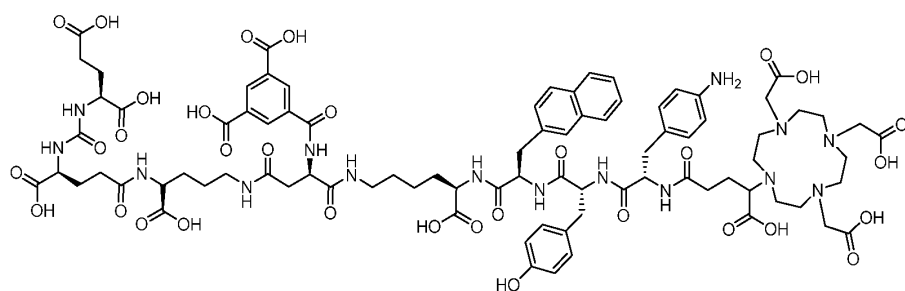
(I)



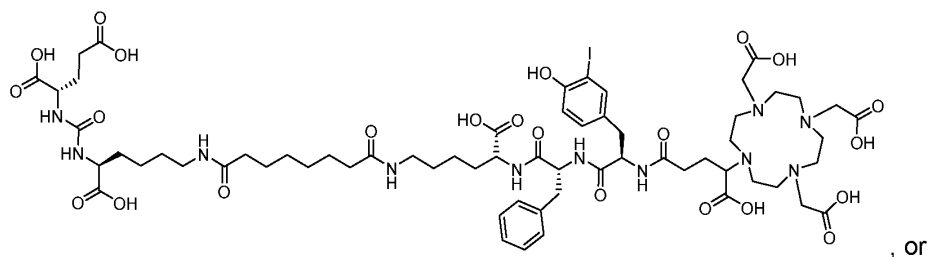
(II)

wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,

5

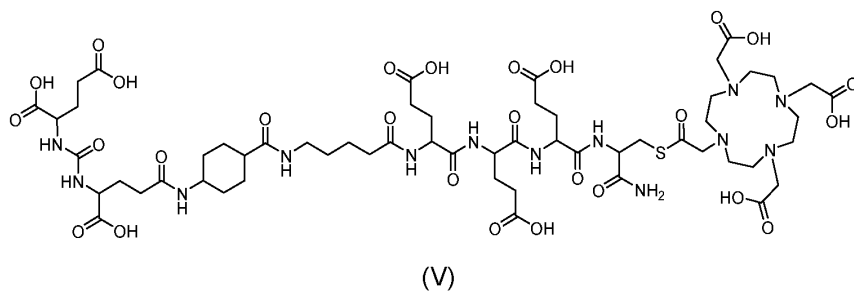


(III)



(IV)

, or



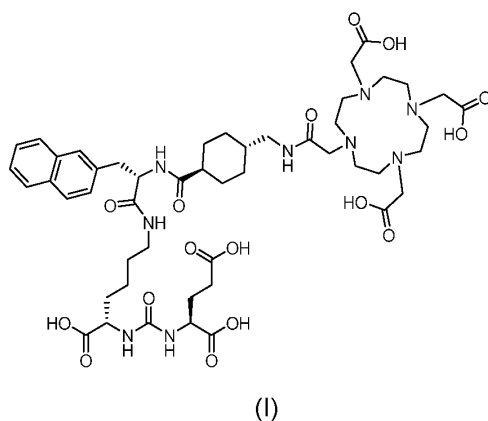
wherein:

the compound of formula (I), (II), (III), (IV), or (V) is radiolabeled with an alpha-emitting radionuclide,

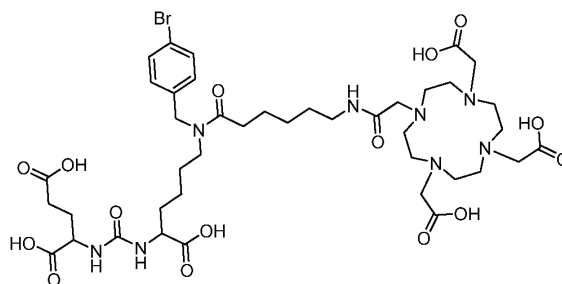
the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose from about 6 MBq to about 14 MBq, such as about 6 MBq to about 8 MBq, or about 8 MBq to about 10 MBq, or 6 MBq, or 7 MBq, or 8 MBq, or 9 MBq, or 10 MBq, or 11 MBq, or 12 MBq, or 13 MBq, or 14 MBq, and

the subject has not received prior chemotherapeutic treatment.

In particular embodiments, the method comprises administering to the subject a compound of formula (I) or (II):



or



wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,

wherein:

the compound of formula (I) or (II) is radiolabeled with an alpha-emitting radionuclide,

the radiolabeled compound of formula (I) or (II) is administered at a dose from about 6 MBq to about 14 MBq, such as about 6 MBq to about 8 MBq, or about 8 MBq to about 10 MB, or 6 MBq, or 7 MBq, or 8 MBq, or 9 MBq, or 10 MBq, or 11 MBq, or 12 MBq, or 13 MBq, or 14 MBq, and

5 the subject has not received prior chemotherapeutic treatment.

In some embodiments, the methods comprise administering to the subject a compound of formula (I). In other embodiments, the methods comprise administering to the subject a compound of formula (II). In yet other embodiments, the methods comprise administering to the subject a compound of formula (III). In still other embodiments, the methods comprise administering to the subject a compound of formula (IV). In still other
10 embodiments, the methods comprise administering to the subject a compound of formula (V).

In some embodiments, the methods comprise administering a compound of formula (I), (II), (III), (IV), or (V), wherein the compound is radiolabeled with an alpha-emitting radionuclide selected from the group consisting of ^{225}Ac , ^{211}At , ^{213}Bi , ^{212}Bi , ^{212}Pb , ^{223}Ra , ^{224}Ra , ^{149}Tb , and ^{227}Th . In further embodiments, the methods comprise administering a compound of formula (I), (II), (III), (IV), or (V), wherein the compound is radiolabeled with an alpha-emitting radionuclide selected from the group consisting of ^{225}Ac , ^{212}Pb , and ^{227}Th . In still further embodiments, the methods comprise administering a compound of formula (I), (II),
15 (III), (IV), or (V), wherein the compound is radiolabeled with an alpha-emitting radionuclide, and the alpha-emitting radionuclide is ^{225}Ac .

Typically, the amount of a radiopharmaceutical, e.g., the radiolabeled compound of formula (I), (II), (III), (IV), or (V), to be administered to a subject in need thereof, is based on the amount of radiation that will be administered to the subject. The amount of radiation may
25 be reflected as a unitary dose (in MBq) or as an amount of radiation per kg bodyweight (in kBq/kg). In the present methods, the radiolabeled compound is administered in a unitary dose of from about 6 MBq to about 14 MBq, such as about 6 MBq to about 8 MBq, or about 8 MBq to about 10 MB, or 6 MBq, or 7 MBq, or 8 MBq, or 9 MBq, or 10 MBq, or 11 MBq, or 12 MBq, or 13 MBq, or 14 MBq.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6.5 MBq to 14 MBq, such as about 6.5 MBq to 10 MBq or 6.5 MBq to 8 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 7 MBq to 8 MBq. In some
30 embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 7.5 MBq to 8 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6 MBq to 7.5 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV),

or (V) is administered at a dose of from about 6 MBq to 7 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6 MBq to 6.5 MBq.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6.5 MBq to 7.5 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 7 MBq to 7.5 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 6 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 7 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 8 MBq.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 7.5 MBq to 10 MBq, such as about 8 MBq to 10 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8.5 MBq to 10 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 9 MBq to 10 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 9.5 MBq to 10 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 7 MBq to 8 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8 MBq to 9.5 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 9 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 10 MBq.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 9.5 MBq to 14 MBq, such as about 10 MBq to 14 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 10.5 MBq to 14 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 11 MBq to 14 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 11.5 MBq to 14 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 10 MBq to 11 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 10 MBq to 11.5 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 10 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 11 MBq. In

some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 12 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 13 MBq. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 14 MBq.

Alternatively, in methods disclosed herein, the radiolabeled compound of formula (I), (II), (III), (IV), or (V), can be administered as a dose of radiation per kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 80 kBq/kg body weight to about 200 kBq/kg body weight, such as about 80 kBq/kg body weight to about 120 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 80 kBq/kg body weight to about 180 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 80 kBq/kg body weight to about 150 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 80 kBq/kg body weight to about 120 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 80 kBq/kg body weight to about 110 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 80 kBq/kg body weight to about 100 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 80 kBq/kg body weight to about 90 kBq/kg body weight.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 90 kBq/kg body weight to about 120 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 100 kBq/kg body weight to about 120 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 110 kBq/kg body weight to about 120 kBq/kg body weight.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 90 kBq/kg body weight to about 180 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 100 kBq/kg body weight to about 180 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 110 kBq/kg body weight to about 180 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 120 kBq/kg body weight to about 180

kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 130 kBq/kg body weight to about 180 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 140 kBq/kg body weight to about 180 kBq/kg body weight.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 85 kBq/kg body weight to about 165 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 85 kBq/kg body weight to about 145 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 85 kBq/kg body weight to about 125 kBq/kg body weight.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 85 kBq/kg body weight to about 115 kBq/kg body weight.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 85 kBq/kg body weight to about 105 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 85 kBq/kg body weight to about 100 kBq/kg body weight.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 90 kBq/kg body weight to about 115 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 100 kBq/kg body weight to about 110 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 100 kBq/kg body weight to about 115 kBq/kg body weight.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 80 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 90 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 100 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 110 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 120 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 130 kBq/kg body weight. In some embodiments, the

radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 140 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 150 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 160 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 170 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 180 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 190 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 200 kBq/kg body weight.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 85 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 95 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 105 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 115 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 125 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 135 kBq/kg body weight. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 145 kBq/kg body weight.

The dose of the radiolabeled compound of formula (I), (II), (III), (IV), or (V), can be administered to the subject about every 4 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 4 to 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 6 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 4 to 5 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 5 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 4 to 7 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 5 to 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 5 to 7 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 6 to 7 weeks.

the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6 MBq to 6.5 MBq about every 6 to 8 weeks.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 7 MBq to 9 MBq about every 6 to 8 weeks. In some
5 embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 7.5 MBq to 9 MBq about every 6 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8.5 MBq to 10 MBq about every 6 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from
10 about 9 MBq to 10 MBq about every 6 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 9.5 MBq to 10 MBq about every 6 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8 MBq to 9.5 MBq about every 6 to 8 weeks. In some embodiments, the radiolabeled compound of
15 formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8 MBq to 9 MBq about every 6 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8 MBq to 8.5 MBq about every 6 to 8 weeks.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V)
20 is administered at a dose of from about 8 MBq to 14 MBq about every 6 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8.5 MBq to 14 MBq about every 6 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 9.5 MBq to 14 MBq about every 6 to 8 weeks. In some
25 embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 10 MBq to 14 MBq about every 6 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 10.5 MBq to 14 MBq about every 6 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from
30 about 10 MBq to 12.5 MBq about every 6 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 10 MBq to 11 MBq about every 6 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 10 MBq to 10.5 MBq about every 6 to 8 weeks.

35 In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6.5 MBq to 7.5 MBq about every 6 to 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is

weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6 MBq to 6.5 MBq about every 6 weeks.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8 to 10 MBq about every 6 weeks. In some
5 embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8.5 MBq to 10 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 9 MBq to 10 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 9.5
10 MBq to 10 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8 MBq to 9.5 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8 MBq to 9 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8 MBq to 8.5 MBq about every 6 weeks.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 10 to 14 MBq about every 6 weeks. In some
embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 10.5 MBq to 14 MBq about every 6 weeks. In some embodiments,
20 the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 11 MBq to 14 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 11.5 MBq to 14 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 10 MBq to 11.5 MBq
25 about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 10 MBq to 11 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 10 MBq to 10.5 MBq about every 6 weeks.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6.5 MBq to 7.5 MBq about every 6 weeks. In some
30 embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 7 MBq to 7.5 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 7.5 MBq to 8.5 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8 MBq to 8.5 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8.5 MBq to 9.5 MBq

about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 9 MBq to 9.5 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 10.5 MBq to 11.5 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 11 MBq to 11.5 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 11 MBq to 12.5 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 6 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 7 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 8 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 9 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 10 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 11 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 12 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 13 MBq about every 6 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 14 MBq about every 6 weeks.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6 to 14 MBq, such as about 6 to 8 MBq or about 8 to 10 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6.5 MBq to 8 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 7 MBq to 8 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 7.5 MBq to 8 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6 MBq to 7.5 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6 MBq to 7 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6 MBq to 6.5 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of

formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8.5 MBq to 10 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 9 MBq to 10 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 9.5 MBq to 10 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8 MBq to 9.5 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8 MBq to 9 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8 MBq to 8.5 MBq about every 8 weeks. In a particular embodiment, the ^{225}Ac radiolabeled compound of formula (I) is administered at a dose of from about 8 MBq to 10 MBq about every 8 weeks.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6.5 MBq to 7.5 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 7 MBq to 7.5 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8.5 MBq to 9.5 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 9 MBq to 9.5 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 10.5 MBq to 11.5 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 11 MBq to 11.5 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 11 MBq to 12.5 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 6 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 7 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 8 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 9 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 10 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 11 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is

administered at a dose of about 12 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 13 MBq about every 8 weeks. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 14 MBq about every 8 weeks.

5 As is common with radiation therapy, in order to deliver the total dose of radiation required to eradicate the PSMA-expressing cancer, the method may include administering the radiolabeled compound of formula (I), (II), (III), (IV), or (V), about every 4 to 8 weeks for a number of cycles. For example, the dose of a radiolabeled compound of the present disclosure may be administered about every 4 to 8 weeks for 4 to 6 cycles.

10 In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 4 to 8 weeks for 4 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 4 to 8 weeks for 5 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 4 to 8 weeks for 6 cycles. In some
15 embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 4 to 6 weeks for 4 to 6 cycles.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 6 to 8 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 6 to 8
20 weeks for 4 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 6 to 8 weeks for 5 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 6 to 8 weeks for 6 cycles.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 4 to 5 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 4 to 7
25 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 5 to 8 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 5 to 6 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled
30 compound of formula (I), (II), (III), (IV), or (V) is administered about every 5 to 7 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 6 to 7 weeks for 4 to 6 cycles.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 4 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 5
35 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I),

(II), (III), (IV), or (V) is administered about every 6 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 7 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 8 weeks for 4 to 6 cycles. In a particular embodiment, the ^{225}Ac radiolabeled compound of formula (I) is administered at a dose of from about 8 MBq to 10 MBq about every 8 weeks for 4 to 6 cycles.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 4 weeks for 4 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 4 weeks for 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 6 weeks for 4 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 6 weeks for 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 8 weeks for 4 cycles. In a particular embodiment, the ^{225}Ac radiolabeled compound of formula (I) is administered at a dose of from about 8 MBq to 10 MBq about every 8 weeks for 4 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 8 weeks for 6 cycles. In a particular embodiment, the ^{225}Ac radiolabeled compound of formula (I) is administered at a dose of from about 8 MBq to 10 MBq about every 8 weeks for 6 cycles.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 5 weeks for 4 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 5 weeks for 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 7 weeks for 4 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 7 weeks for 6 cycles.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 4 weeks for 5 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 6 weeks for 5 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 8 weeks for 5 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 5 weeks for 5 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered about every 7 weeks for 5 cycles.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6 to 14 MBq, such as about 6 to 8 MBq or about 8 to 10 MBq about every 4 to 8 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6.5

[illegible]

[illegible]

compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 14 MBq about every 4 to 8 weeks for 4 to 6 cycles.

[illegible]

the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 9 MBq about every 6 to 8 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 10 MBq about every 6 to 8 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 11 MBq about every 6 to 8 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 12 MBq about every 6 to 8 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 13 MBq about every 6 to 8 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 14 MBq about every 6 to 8 weeks for 4 to 6 cycles.

In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6 to 14 MBq, such as about 6 to 8 MBq to about 8 to 10 MBq about every 6 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6.5 MBq to 8 MBq about every 6 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 7 MBq to 8 MBq about every 6 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 7.5 MBq to 8 MBq about every 6 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6 MBq to 7.5 MBq about every 6 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6 MBq to 7 MBq about every 6 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 6 MBq to 6.5 MBq about every 6 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8.5 MBq to 10 MBq about every 6 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 9 MBq to 10 MBq about every 6 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 9.5 MBq to 10 MBq about every 6 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8 MBq to 9.5 MBq about every 6 weeks for 4 to 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of from about 8 MBq to 9 MBq about every 6 weeks for 4 to 6 cycles. In some embodiments, the

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cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 8 MBq about every 8 weeks for 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 9 MBq about every 8 weeks for 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 10 MBq about every 8 weeks for 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 11 MBq about every 8 weeks for 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 12 MBq about every 8 weeks for 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 13 MBq about every 8 weeks for 6 cycles. In some embodiments, the radiolabeled compound of formula (I), (II), (III), (IV), or (V) is administered at a dose of about 14 MBq about every 8 weeks for 6 cycles.

In particular embodiments, the radiolabeled compound of formula (I) is administered at a dose of from 6 to 14 MBq, such as 6 to 8 MBq or 8 to 10 MBq about every 8 weeks for 4 cycles. In particular embodiments, the radiolabeled compound of formula (II) is administered at a dose of from 6 to 8 MBq about every 6 weeks for 4 cycles. In particular embodiments, the radiolabeled compound of formula (II) is administered at a dose of from 6 to 8 MBq about every 6 weeks for 6 cycles. In particular embodiments, the radiolabeled compound of formula (II) is administered at a dose of from 7 to 12 MBq about every 6 weeks for 4 cycles. In particular embodiments, the radiolabeled compound of formula (II) is administered at a dose of from 7 to 12 MBq about every 6 weeks for 6 cycles. In particular embodiments, the radiolabeled compound of formula (II) is administered at a dose of from 10 to 14 MBq about every 6 weeks for 4 cycles. In particular embodiments, the radiolabeled compound of formula (II) is administered at a dose of from 10 to 14 MBq about every 6 weeks for 6 cycles. In particular embodiments, the radiolabeled compound of formula (II) is administered at a dose of from 8 to 10 MBq about every 6 weeks for 4 cycles. In particular embodiments, the radiolabeled compound of formula (II) is administered at a dose of from 8 to 10 MBq about every 6 weeks for 6 cycles.

In the methods described herein, the PSMA-expressing cancer can be any cancer that exhibits high PSMA expression compared to corresponding healthy cells or tissues. For example, in various prostate cancers and salivary gland cancers, the level of PSMA expression of the malignant cells is markedly increased compared to that of healthy cells. In one or more embodiments of the methods described herein, the PSMA-expressing cancer is prostate cancer. In some embodiments, when the PSMA-expressing cancer is prostate cancer, then the prostate cancer is metastatic prostate cancer. In certain embodiments, the metastatic prostate cancer is metastatic castration-resistant prostate cancer (mCRPC).

In various embodiments of the presently disclosed methods, the subject has received prior treatment with at least one of a beta-minus-emitting radiopharmaceutical and an androgen receptor pathway inhibitor (ARPI).

In some embodiments, the subject has received prior treatment with a beta-minus-emitting radiopharmaceutical. In some embodiments, the beta-minus-emitting radiopharmaceutical comprises ^{177}Lu . In some embodiments, the beta-minus-emitting radiopharmaceutical is a ^{177}Lu -PSMA targeting agent. In further embodiments, the beta-minus-emitting radiopharmaceutical is a ^{177}Lu -PSMA targeting agent selected from ^{177}Lu -PSMA-617 or ^{177}Lu -PSMA I&T. In certain embodiments, when the beta-minus-emitting radiopharmaceutical is a ^{177}Lu -PSMA targeting agent, the ^{177}Lu -PSMA targeting agent is ^{177}Lu -PSMA-617. In some embodiments, the subject has received prior treatment with one or more beta-minus-emitting radiopharmaceuticals. In some embodiments, the subject has received treatment with one beta-minus-emitting radiopharmaceutical. In some embodiments, the subject has received prior treatment with two or more beta-minus-emitting radiopharmaceuticals.

In some embodiments, the subject has received prior treatment with an ARPI. Suitable ARPIs that may have been previously administered to the subject include, but are not limited to, ketoconazole, abiraterone, apalutamide, bicalutamide, darolutamide, enzalutamide, flutamide, and nilutamide. In some embodiments, the subject has received prior treatment with one or more, or two or more ARPIs. In some embodiments, the subject has received prior treatment with one ARPI. In some embodiments, the subject has received prior treatment with two different ARPIs. In some embodiments, the subject has received prior treatment with more than two different ARPIs.

In some embodiments, the subject is treatment naïve. In some embodiments, the subject is naïve to beta-minus-emitting pharmaceuticals and ARPIs. In some embodiments, the subject has received prior treatment with a beta-minus-emitting pharmaceutical and an ARPI. In some embodiments, the subject has received prior treatment with a beta-minus-emitting pharmaceutical but has not received prior treatment with an ARPI. In some embodiments, the subject has not received prior treatment with a beta-minus-emitting pharmaceutical but has received prior treatment with an ARPI.

In some embodiments of the methods disclosed herein, the subject did not respond to prior treatment with a beta-minus-emitting radiopharmaceutical and/or an ARPI, or the PSMA-expressing cancer progressed after administration of the prior treatment.

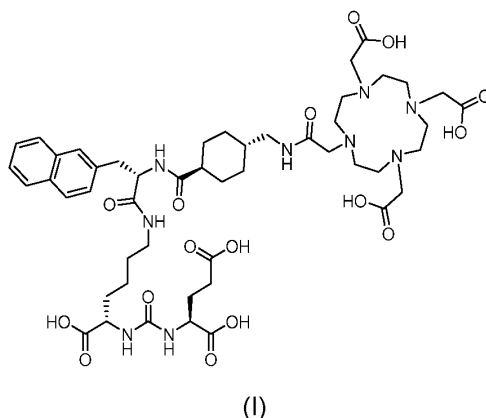
In various embodiments of the presently disclosed methods, the PSMA-expressing cancer has been determined to be resistant to one or more of chemotherapeutic treatment, beta-minus-emitting radiopharmaceuticals, and ARPIs. In some embodiments, the PSMA expressing cancer has been determined to be resistant to chemotherapeutic treatment. In

some embodiments, the PSMA-expressing cancer has been determined to be resistant to beta-minus-emitting radiopharmaceuticals. In some embodiments, the PSMA-expressing cancer has been determined to be resistant to ARPIs. In some embodiments, the PSMA-expressing cancer has been determined to be resistant to chemotherapeutic treatment and beta-minus-emitting radiopharmaceuticals. In some embodiments, the PSMA-expressing cancer has been determined to be resistant to chemotherapeutic treatment and ARPIs. In some embodiments, the PSMA-expressing cancer has been determined to be resistant to beta-minus-emitting radiopharmaceuticals and ARPIs. In some embodiments, the PSMA-expressing cancer has been determined to be resistant to all of chemotherapeutic treatment, beta-minus-emitting radiopharmaceuticals, and ARPIs.

Accordingly, in some embodiments, the methods disclosed herein are used as a first-line treatment, a second-line treatment, a third-line treatment, or a fourth-line treatment for the PSMA-expressing cancer. In some embodiments, the methods disclosed herein are used as a first-line treatment. In other embodiments, the methods disclosed herein are used as a second-line treatment, a third-line treatment, or a fourth-line treatment. In some embodiments, the methods disclosed herein are used as a second-line treatment. In some embodiments, the methods disclosed herein are used as a third-line treatment. In some embodiments, the methods disclosed herein are used as a fourth-line treatment.

Particular Embodiments of the Methods of Treatment

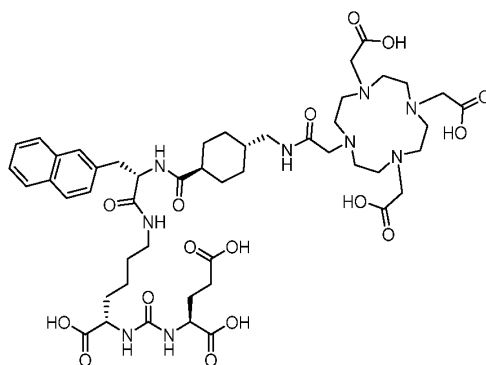
In particular, provided herein are methods of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical at a dose of from about 6 MBq to about 14 MBq, such as about 6 MBq to about 8 MBq or about 8 MBq to about 10 MBq, wherein the radiopharmaceutical is a compound of formula (I):



wherein the compound of formula (I) is radiolabeled with ^{225}Ac .

In some embodiments of the disclosed methods, the subject has received prior chemotherapeutic treatment. Alternatively, in some embodiments, the subject has not received prior chemotherapeutic treatment.

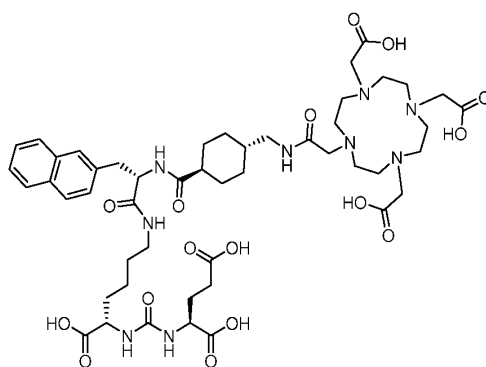
- Accordingly, in some aspects, provided herein is a method of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical at a dose of from about 6 MBq to about 8 MBq, wherein the radiopharmaceutical is a compound of formula (I):



(I)

- wherein the compound of formula (I) is radiolabeled with ^{225}Ac , and wherein the subject has received prior chemotherapeutic treatment.

- In some aspects, provided herein is a method of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical at a dose of from about 8 MBq to about 10 MBq, wherein the radiopharmaceutical is a compound of formula (I):

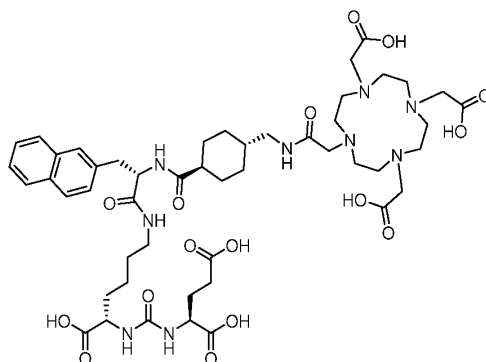


(I)

- wherein the compound of formula (I) is radiolabeled with ^{225}Ac , and wherein the subject has received prior chemotherapeutic treatment.

- In some embodiments, the prior chemotherapeutic treatment comprises the administration of taxane.

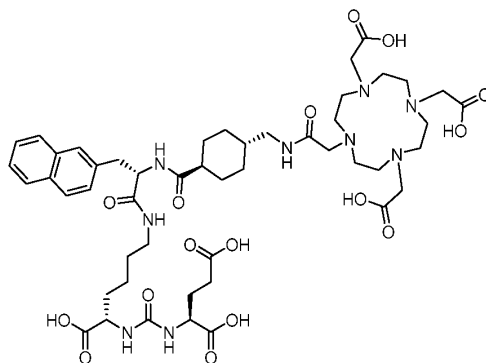
In other aspects, provided herein is a method of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical at a dose of from about 6 MBq to about 8 MBq, wherein the radiopharmaceutical is a compound of formula (I):



(I)

wherein the compound of formula (I) is radiolabeled with ^{225}Ac , and wherein the subject has not received prior chemotherapeutic treatment.

In other aspects, provided herein is a method of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical at a dose of from about 8 MBq to about 10 MBq, wherein the radiopharmaceutical is a compound of formula (I):



(I)

wherein the compound of formula (I) is radiolabeled with ^{225}Ac , and wherein the subject has not received prior chemotherapeutic treatment.

In some embodiments of the methods of treating prostate cancer in a subject in need thereof, the prostate cancer is metastatic prostate cancer. In further embodiments, the metastatic prostate cancer is metastatic castration-resistant prostate cancer (mCRPC).

In some embodiments of the presently described methods, the radiopharmaceutical is administered at a dose of 6 MBq. In some embodiments, the radiopharmaceutical is

administered at a dose of 7 MBq. In some embodiments, the radiopharmaceutical is administered at a dose of 8 MBq. In some embodiments, the radiopharmaceutical is administered at a dose of 9 MBq. In some embodiments, the radiopharmaceutical is administered at a dose of 10 MBq.

5 In some embodiments of the methods described herein, the radiopharmaceutical is administered to the subject about every 4 to 8 weeks. In further embodiments, the radiopharmaceutical is administered about every 6 to 8 weeks. In still further embodiments, the radiopharmaceutical is administered about every 6 weeks. In still further embodiments, the radiopharmaceutical is administered about every 8 weeks.

10 In some embodiments of the presently described methods, the radiopharmaceutical is administered at a dose of 6 to 8 MBq or 8 MBq to 10 MBq about every 4 to 8 weeks. In some embodiments of the presently described methods, the radiopharmaceutical is administered at a dose of 6 MBq about every 6 to 8 weeks. In some embodiments, the radiopharmaceutical is administered at a dose of 7 MBq about every 6 to 8 weeks. In some
15 embodiments, the radiopharmaceutical is administered at a dose of 8 MBq about every 6 to 8 weeks. In some embodiments, the radiopharmaceutical is administered at a dose of 9 MBq about every 6 to 8 weeks. In some embodiments, the radiopharmaceutical is administered at a dose of 10 MBq about every 6 to 8 weeks.

 In some embodiments of the presently described methods, the radiopharmaceutical
20 is administered at a dose of 6 MBq about every 6 weeks. In some embodiments, the radiopharmaceutical is administered at a dose of 7 MBq about every 6 weeks. In some embodiments, the radiopharmaceutical is administered at a dose of 8 MBq about every 6 weeks. In some embodiments, the radiopharmaceutical is administered at a dose of 9 MBq about every 6 weeks. In some embodiments, the radiopharmaceutical is administered at a
25 dose of 10 MBq about every 6 weeks.

 In some embodiments of the presently described methods, the radiopharmaceutical is administered at a dose of 6 MBq about every 8 weeks. In some embodiments, the radiopharmaceutical is administered at a dose of 7 MBq about every 8 weeks. In some
30 embodiments, the radiopharmaceutical is administered at a dose of 8 MBq about every 8 weeks. In some embodiments, the radiopharmaceutical is administered at a dose of 9 MBq about every 8 weeks. In some embodiments, the radiopharmaceutical is administered at a dose of 10 MBq about every 8 weeks.

 The radiopharmaceutical may be administered to a subject in need thereof every 4 to 8 weeks for a number of cycles. For example, in methods of treating prostate cancer
35 described herein, the radiopharmaceutical may be administered about every 4 to 8 weeks for 4 to 6 cycles. In some embodiments, the radiopharmaceutical is administered about every 6 to 8 weeks for 4 to 6 cycles. In some embodiments, the radiopharmaceutical is administered

about every 4 to 8 weeks for 4 cycles. In certain embodiments, the radiopharmaceutical is administered about every 6 to 8 weeks for 4 cycles. In further embodiments, the radiopharmaceutical is administered about every 8 weeks for 4 cycles. In still further embodiments, the radiopharmaceutical is administered about every 6 weeks for 4 cycles.

5 In some embodiments, the radiopharmaceutical is administered about every 4 to 8 weeks for 6 cycles. In some embodiments, the radiopharmaceutical is administered about every 6 to 8 weeks for 6 cycles. In certain embodiments, the radiopharmaceutical is administered about every 6 weeks for 6 cycles. In further embodiments, the radiopharmaceutical is administered about every 8 weeks for 6 cycles.

10 In some embodiments of the presently described methods, the radiopharmaceutical is administered at a dose of 6 to 8 MBq or 8 MBq to 10 MBq about every 4 to 8 weeks for 4 to 6 cycles. In some embodiments of the presently described methods, the radiopharmaceutical is administered at a dose of 6 to 8 MBq or 8 MBq to 10 MBq about every 6 to 8 weeks for 4 to 6 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 6 MBq about every 6 to 8 weeks for 4 to 6 cycles. In some
15 embodiments, the radiopharmaceutical is administered at a dose of 7 MBq about every 6 to 8 weeks for 4 to 6 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 8 MBq about every 6 to 8 weeks for 4 to 6 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 9 MBq about every 6 to 8 weeks for 4 to 6
20 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 10 MBq about every 6 to 8 weeks for 4 to 6 cycles.

 In some embodiments of the presently described methods, the radiopharmaceutical is administered at a dose of 6 to 8 MBq or 8 MBq to 10 MBq about every 6 to 8 weeks for 4 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 6 MBq
25 about every 6 weeks for 4 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 6 MBq about every 8 weeks for 4 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 7 MBq about every 6 weeks for 4 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 7 MBq about every 8 weeks for 4 cycles. In some embodiments, the radiopharmaceutical is
30 administered at a dose of 8 MBq about every 6 weeks for 4 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 8 MBq about every 8 weeks for 4 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 9 MBq about every 6 weeks for 4 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 9 MBq about every 8 weeks for 4 cycles. In some embodiments,
35 the radiopharmaceutical is administered at a dose of 10 MBq about every 6 weeks for 4 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 10 MBq about every 8 weeks for 4 cycles.

In some embodiments of the presently described methods, the radiopharmaceutical is administered at a dose of 6 to 8 MBq or 8 to 10 MBq about every 6 to 8 weeks for 6 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 6 MBq about every 6 weeks for 6 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 6 MBq about every 8 weeks for 6 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 7 MBq about every 6 weeks for 6 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 7 MBq about every 8 weeks for 6 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 8 MBq about every 6 weeks for 6 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 8 MBq about every 8 weeks for 6 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 9 MBq about every 6 weeks for 6 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 9 MBq about every 8 weeks for 6 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 10 MBq about every 6 weeks for 6 cycles. In some embodiments, the radiopharmaceutical is administered at a dose of 10 MBq about every 8 weeks for 6 cycles.

In particular embodiments, the radiopharmaceutical is administered at a dose of from 6 to 8 MBq, 7 to 9 MBq or 8 to 10 MBq about every 8 weeks for 4 cycles. In particular embodiments, the radiopharmaceutical is administered at a dose of from 6 to 8 MBq about every 8 weeks for 4 cycles. In particular embodiments, the radiopharmaceutical is administered at a dose of from 8 to 10 MBq about every 8 weeks for 4 cycles.

In various embodiments of the method of treating a PSMA-expressing cancer in a subject in need thereof described herein, the subject has received prior treatment with at least one of a beta-minus-emitting radiopharmaceutical and an androgen receptor pathway inhibitor (ARPI). In various embodiments, the beta-minus-emitting radiopharmaceutical is a [¹⁷⁷Lu]Lu-PSMA targeted radiopharmaceutical.

In some embodiments, the subject is naïve to beta-minus-emitting pharmaceuticals and ARPIs. In some embodiments, the subject has received prior treatment with a beta-minus-emitting pharmaceutical and an ARPI. In some embodiments, the subject has received prior treatment with a beta-minus-emitting pharmaceutical but has not received prior treatment with an ARPI. In some embodiments, the subject has not received prior treatment with a beta-minus-emitting pharmaceutical but has received prior treatment with an ARPI.

In some embodiments, the subject has received prior treatment with taxane-based chemotherapy, a beta-minus-emitting radiopharmaceutical, and an ARPI.

In some embodiments, the subject did not respond to prior treatment, *i.e.*, with a beta-minus-emitting radiopharmaceutical and/or an ARPI, or the PSMA-expressing cancer

progressed after administration of the prior treatment. In some embodiments, the subject has received prior treatment with taxane-based chemotherapy, an ARPI, and a [¹⁷⁷Lu]Lu-PSMA targeted radiopharmaceutical, and the PSMA-expressing cancer progressed while the subject was being treated with the [¹⁷⁷Lu]Lu-PSMA targeted radiopharmaceutical or recurred
5 after the subject was treated with the [¹⁷⁷Lu]Lu-PSMA targeted radiopharmaceutical.

In various embodiments, the PSMA-expressing cancer has been determined to be resistant to one or more of chemotherapeutic treatment, beta-minus-emitting radiopharmaceuticals, and ARPIs.

In the instantly described method of treating PSMA-expressing cancer in a subject,
10 the subject may experience unwanted side effects, such as, for example, xerostomia. In some embodiments, the subject has experienced up to a Grade 1 xerostomia adverse event, or the subject suffers from up to a Grade 1 xerostomia. In some embodiments of the method, the subject has not previously experienced a Grade ≥ 2 xerostomia adverse event, or the subject does not suffer from a Grade ≥ 2 xerostomia.

In the method of the present disclosure, xerostomia mitigation may be administered to the subject in order to control, prevent, or treat xerostomia. Various types of xerostomia mitigation may be employed, such as, for example those described in Alessandro Villa et al. Diagnosis and management of xerostomia and hyposalivation Therapeutics and Clinical Risk Management 2015:11 45–51 and Yanli Li et al. Diagnosis, Prevention, and Treatment of
20 Radiotherapy-Induced Xerostomia: A Review Hindawi Journal of Oncology Volume 2022, Article ID 7802334, 15 pages, which are incorporated herein by reference in their entireties.

In some embodiments, the subject receives xerostomia mitigation concurrently with the presently described radiopharmaceutical. In some embodiments, the subject receives xerostomia mitigation after receiving the presently described radiopharmaceutical. In some
25 embodiments, the subject receives xerostomia mitigation before receiving the presently described radiopharmaceutical.

In some embodiments, the PSMA-expressing cancer is a PSMA-positive Metastatic Castration-Resistant Prostate Cancer (mCRPC).

In some embodiments, the subject is documented as having heavily pretreated
30 Metastatic Castration-Resistant Prostate Cancer (mCRPC). For example, the heavily pretreated subject can be documented as having at least two prior treatments. In various embodiments, the subject is documented as having a high tumor burden. Tumor burden can be assessed using diagnostic methods such as those described in the Examples (e.g., PET/CT). A subject with a high tumor burden can be documented as having bony metastasis
35 and/or visceral metastasis.

Pharmaceutical Compositions

Also provided herein are pharmaceutical compositions comprising a radiolabeled compound of formula (I), (II), (III), (IV), or (V) and a pharmaceutically acceptable carrier, diluent, or excipient. The pharmaceutically acceptable carrier, diluent or excipient may be a solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type.

The pharmaceutical compositions may be administered parenterally. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous, intradermal and intraarticular injection and infusion. Accordingly, in certain embodiments, the compositions are formulated for delivery by any of these routes of administration. A pharmaceutical composition may be formulated for and administered by parenteral administration. In particular, a pharmaceutical composition of the present disclosure may be formulated for and administered by intravenous administration.

In certain embodiments, pharmaceutical compositions for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders, for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, β -cyclodextrin, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. These compositions may also contain additives such as preservatives, wetting agents, emulsifying agents, chelating agents, buffering agents, and dispersing agents.

In some embodiments, the pharmaceutical composition comprises a chelating agent to sequester internally deposited radionuclides. Any chelating agent known in the art that complexes to alpha-emitting radionuclides may be included in pharmaceutical compositions described herein. In various embodiments, the pharmaceutical composition comprises DTPA. Additional exemplary chelating agents that may be included in pharmaceutical compositions of the present disclosure are described in Holik, et al. "The Chemical Scaffold of Theranostic Radiopharmaceuticals: Radionuclide, Bifunctional Chelator, and Pharmacokinetics Modifying Linker." *Molecules* 27.10 (2022): 3062 and Kostelnik, Thomas I., and Chris Orvig. "Radioactive main group and rare earth metals for imaging and therapy." *Chemical reviews* 119.2 (2018): 902-956, both of which are incorporated herein by reference in their entireties.

Pharmaceutical compositions of the instant disclosure may further comprise a stabilizer, such as, for example, a free radical scavenger, in order to prevent autoradiolysis of the inventive radioligand. Suitable stabilizers for inclusion in the disclosed pharmaceutical compositions include, but are not limited to, 2,5-dihydroxybenzoic acid or salts thereof, ascorbic acid or salts thereof, gentisic acid or salts thereof, methionine, histidine, melatonin, N-acetylmethionine, ethanol, an amino acid infusion solution, or any combination thereof. In some embodiments, the pharmaceutical composition includes a gentisic acid stabilizer. In some embodiments, the pharmaceutical composition includes an ascorbic acid stabilizer. In some embodiments, the pharmaceutical composition include stabilizer including gentisic acid and ascorbic acid.

In some embodiments, the pharmaceutical composition comprises one or more buffering agents to maintain a pH of about 3 to 5. Suitable buffering agents include, but are not limited to acetate, citrate, Tris, lactate, and tartrate, and the acid forms thereof.

The disclosure is further illustrated by the following examples and synthesis schemes, which are not to be construed as limiting this disclosure in scope or spirit. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same or similar results. The compounds of the Examples have demonstrated efficacy in the treatment of prostate cancer, and in particular, metastatic resistance prostate cancer (mCRPC).

EXAMPLES

The radiolabeling of the PSMA-binding ligands and the compounding to a ready to use formulation is exemplified in the following for the PSMA-R2 ligand. Similar labeling conditions and formulations may be applied for other PSMA-binding ligands.

Example 1: Formulation with [225Ac]Ac-PSMA-R2 (Compound of formula (II)) and DTPA

PSMA-R2 was synthesized as described in WO2017/165473 and in WO 2021/001360.

The formulation comprising [225Ac]Ac-PSMA-R2 with DTPA was prepared as a ready to use 1 MBq/ml solution for injection/infusion according to Table 1.

Table 1.

Component	Purpose	Quantity
PSMA-R2	Precursor of active substance	8 µg/mL
[²²⁵ Ac]Ac-PSMA-R2	Drug substance	2.46 ng/mL at EOS*

DTPA	Sequestering Agent	0.03-0.04 mg/mL
Ascorbic acid	Radiolysis protector/anti-oxidant	1.73-2.38 mg/mL
Sodium hydroxide	pH adjuster	0.40-0.54 mg/mL
Tris hydrochloride	Buffering Agent	2.33-0.79 mg/mL
Trometamol	Buffering Agent	1.48-0.50 mg/mL
Water For Injection	Solvent	q.s.**
Sodium chloride (NaCl) 0.9%	Isotonizing agent	6.98-7.72mg/mL

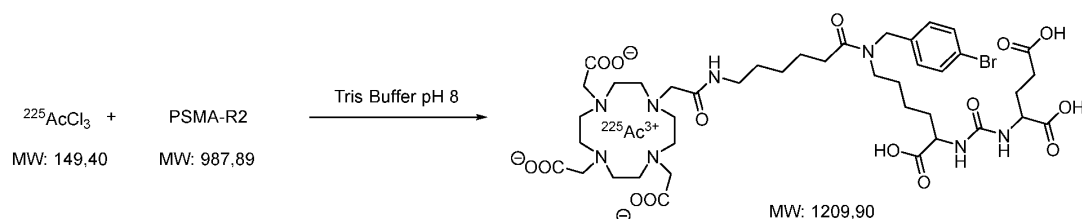
*EOS is the End of Synthesis. Values calculated assuming ^{225}Ac specific activity of 487,7 MBq/nmol at labeling time and a theoretical synthesis yield of 100 % and radiochemical purity ≥ 97 %

**This amount includes as well the water for injections filled in the bulk solution bottle (0.5 ± 0.1 mL) and in the primary packaging (0.20 ± 0.02 mL) during the sterilization process as added amount is considered negligible.

5

Example 2: Formulation with [^{225}Ac]Ac-PSMA-R2 and DMSA

Radiolabeling scheme:



10 PSMA-R2 reconstitution

To a vial containing 1 mg PSMA-R2 was added 1 mL of water to obtain a solution 1000 ppm.

Drug Substance (DS) preparation

Labelling: In a 10 mL glass vial 120 μL of $^{225}\text{AcCl}_3$ 0.1 N HCl (calibration: day 1, 08:00, 91.49 MBq, 1186 μL) was added. Glass vial was crimped and measured at dose calibrator (5.925 MBq, day 7, 14:48). Solution of PSMA-R2 (47 μL) was added then followed by TRIS buffer 0.25 M pH 8 (318 μL). pH of resulting reaction mixture (tot. volume 485 μL) was measured via pH strip (Macherey-Nagel pH-Fix 7.5-9.5): pH 7.9. Reaction mixture was then heated at 95 °C using heating block (Labnet, AccuBlockDigital Dry Bath) for 20 min. Solution was allowed to cool down to ambient temperature over 10 min. Radiolabeling was performed with a ratio mass peptide in microgram to activity in MBq of 8; mass peptide 47.4 microgram; MBq/microgram peptide at time of use 0.125; MBq/microgram peptide (ART) 1.270.

20

Preparation of DMSA solution

1.79 mg of DMSA (meso-2,3-dimercaptosuccinic acid) (Sigma Aldrich) was dispensed in a 1.5 mL centrifuge tube. 0.895 mL of water was added. Suspension was agitated using vortex mixer until complete dissolution to obtain a homogeneous solution of DMSA at 2 mg/mL.

Preparation of Sodium Ascorbate solution

L-ascorbic acid (302.34 mg, 1.7 mmol) and sodium hydroxide (69.85 mg, 1.7 mmol) were dispensed on a pre-tared balance, then transferred to a 50 mL falcon vial. Water (11.72 mL) was added to obtain a solution of Sodium Ascorbate at 26.83 mg/mL.

Drug product (DP) formulation

Sodium ascorbate (596 µL) and DMSA (148 µL) solutions were dispensed via pipette and transferred into a 1.5 mL centrifuge tube. The obtained solution was transferred to a 10 mL reaction vial (containing [²²⁵Ac]Ac-PSMAR2 DS solution) through 1 mL syringe. The syringe was used to transfer 3 x 1 mL of saline (sodium chloride 0.9%) into reaction vial. Finally, 1.695 mL of saline was added to obtain a solution of 1 MBq/mL. The final volume of the formulation was 5.925 mL. The final pH of the formulation was 7.5.

A small aliquot was dispensed (~100 µL) for iTLC analysis (RP-18 F254S, NH₄OAc 5M Aq/ H₂O/ MeOH 3:2:7.5, described in more details below). The acquisition of TLC plate by alpha scanner was carried out at >18 h post development. This time is provided for ²²⁵Ac to reach secular equilibrium, and for migrated daughters to decay. The radio-iTLC analysis indicated >99% radiochemical purity (RCP).

Example 3: Dose Escalation Study for Compound of Formula (II) Radiolabeled with ²²⁵Ac (²²⁵Ac-PSMA-R2)

Overview: A study to determine a safe and efficacious dose of ²²⁵Ac-PSMA-R2 in men with heavily pre-treated PSMA positive metastatic castration resistant prostate cancer (mCRPC) with or without prior ¹⁷⁷Lu-labelled PSMA-targeted radioligand therapy (e.g. Lutetium (¹⁷⁷Lu) vipivotide tetraxetan or Lutetium (¹⁷⁷Lu) zadavotide gaxetan).

Primary Outcome Measures:

Dose Escalation 1: Incidence and severity of Dose Limiting Toxicity (DLTs) during the first cycle of treatment (time frame: up to 6 weeks after the first ²²⁵Ac-PSMA-R2 dose administration). To determine the Recommended Dose for Expansion (RDE) and corresponding regimen for ²²⁵Ac-PSMA-R2 monotherapy in PSMA-positive mCRPC in:

- Group-1: Participants previously treated with 177Lu-labelled PSMA-targeted RLT (post-177Lu).
- Group-2: Participants not treated previously with 177Lu-labelled PSMA-targeted RLT (pre-177Lu)

5 Dose Escalation 2: Incidence and severity of AEs and serious adverse events (SAEs) during the first cycle of treatment (time frame: up to 6 weeks after the first 225Ac-PSMA-R2 dose administration).

- The distribution of adverse events will be done via the analysis of frequencies for treatment emergent Adverse Event (TEAEs), Serious Adverse Event (TESAEs) and Deaths due to AEs, through the monitoring of relevant clinical and laboratory safety parameters.

Dose Expansion 1: Overall Response Rate (ORR) (time frame: from date of the first administration of 225Ac-PSMA-R2 until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to approximately 15 months).

- Overall Response Rate (ORR) is defined as the proportion of participants with best overall response (BOR) of complete response (CR) or partial response (PR) in soft tissue, as per BICR (Blinded Independent Review Committee) and according to Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1 (RECIST: Response Evaluation Criteria In Solid Tumors), in the absence of bone progression as per PCWG3. CR and PR must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Dose Expansion 2: Percentage of participants achieving prostate-specific antigen (PSA) response 50 (PSA50) (time frame: from date of the first administration of 225Ac-PSMA-R2 till 30 days safety follow-up, assessed up to approximately 15 months).

- PSA50 response rate is defined as the proportion of participants who have achieved $\geq 50\%$ decrease in PSA from baseline confirmed by a second PSA measurement ≥ 4 weeks.

Secondary Outcome Measures:

30 Dose Escalation 3: Incidence and severity of AEs and serious adverse events (SAEs) (time frame: up to 6 months after the last 225Ac-PSMA-R2 dose administration).

- The distribution of adverse events will be done via the analysis of frequencies for treatment emergent Adverse Event (TEAEs), Serious Adverse Event (TESAEs) and Deaths due to AEs, through the monitoring of relevant clinical and laboratory safety parameters.

5 Dose Expansion 3: Incidence and severity of AEs and serious adverse events (SAEs) (time frame: from date of the first administration of 225Ac-PSMA-R2 till 30 days safety follow-up, assessed up to approximately 15 months).

- The distribution of adverse events will be done via the analysis of frequencies for treatment emergent Adverse Event (TEAEs), Serious Adverse Event (TESAEs) and Deaths due to AEs, through the monitoring of relevant clinical and laboratory safety parameters.

Dose Escalation & Dose Expansion 1: Frequency of dose interruptions, reductions, discontinuations, and dose intensity by treatment (time frame: cycles 1 to 6 (1 cycle = 6 weeks)).

- Tolerability of study drug will be assessed by summarizing the number of and the reasons for dose delays and dose reductions. Dose intensity will also be tabulated by treatment group.

20 Dose Escalation 4: Overall Response Rate (ORR) (time frame: from date of the first administration of 225Ac-PSMA-R2 until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to approximately 15 months).

- Overall Response Rate (ORR) is defined as the proportion of participants with best overall response (BOR) of complete response (CR) or partial response (PR) in soft tissue, as per BICR and according to Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1, in the absence of bone progression as per PCWG3. CR and PR must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Dose Escalation & Dose Expansion 2: Disease Control Rate (DCR) (time frame: from date of the first administration of 225Ac-PSMA-R2 until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to approximately 15 months).

- Disease control rate (DCR) is defined as the proportion of participants with best overall response (BOR) of complete response (CR), partial response (PR) or stable

disease (SD), as per central and local review and according to PCWG3-modified RECIST v1.1.

5 Dose Escalation & Dose Expansion 3: Best Overall Response (BOR) (time frame: from date of the first administration of 225Ac-PSMA-R2 until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to approximately 15 months).

- Best Overall Response (BOR) is defined to derive Overall Response Rate (ORR) and includes complete response (CR) or partial response (PR). BOR is determined from the sequence of overall responses.

10 Dose Escalation & Dose Expansion 4: radiographic Progression Free Survival (rPFS) (time frame: from date of the first administration of 225Ac-PSMA-R2 until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to approximately 15 months).

- Radiographic progression free survival (rPFS) is defined as the time (in months) from the date of the first administration of 225Ac-PSMA-R2 to the date of radiographic progression as outlined in PCWG3 guideline or death due to any cause.

Dose Escalation & Dose Expansion 5: Overall Survival (OS) (time frame: from date of the first administration of 225Ac-PSMA-R2 until date of death from any cause, assessed up to approximately 15 months).

- Overall survival (OS) is defined as the time (in months) from the date of the first administration of 225Ac-PSMA-R2 to the date of death due to any cause. If a participant is not known to have died, then OS will be censored at the latest date the participant was known to be alive (on or before the cut-off date).

25 Dose Escalation & Dose Expansion 6: Duration of Response (DoR) (time frame: from the date of the first documented response (CR or PR) to the date of first documented progression or death due to any cause, assessed up to approximately 15 months).

- Duration of response (DOR) is defined as the time (in months) from the date of the first documented response (CR or PR) to the date of first documented progression according to PCWG3-modified RECIST v1.1 or death due to any cause, among participants with a confirmed response.

Dose Escalation & Dose Expansion 7: Time to first Symptomatic Skeletal Event (SSE) (time frame: from the date of the first administration of 225Ac-PSMA-R2 until the date of SSE or

date of death from any cause, whichever comes first, assessed up to approximately 15 months).

- 5

 - Time to a first symptomatic skeletal event (SSE) is defined as the time (in months) from the first administration of 225Ac-PSMA-R2 to the date of SSE or death due to any cause. SSE date is date of the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain, or death due to any cause, whichever comes first.
- 10

Dose Escalation & Dose Expansion 8: Percentage of Participants with Biochemical Response time frame: from date of the first administration of 225Ac-PSMA-R2 till 30 days safety follow-up, assessed up to approximately 15 months).

 - Biochemical responses as measured by Prostate Specific Antigen (PSA), Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH).
- 15

During the first cycle of treatment (time frame: Cycle 1 Day 1 (pre-dose (before start of infusion), mid-infusion, just before or at the end of infusion, post-dose (5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h)), Cycle 1 Day 2 (24 h), Cycle 1 Day 3 (48 h), Cycle 1 Day 4 (72 h)) venous whole blood samples will be collected for the following activity-based pharmacokinetics characterizations:
- 20

 - Dose Escalation 4: Area under the serum concentration-time curve from time zero to the time of last quantifiable concentration (AUClast) of 225Ac-PSMA-R2. AUClast will be listed and summarized using descriptive statistics.
 - Dose Escalation 5: Area under the plasma concentration-time curve from time zero to infinity (AUCinf) of 225Ac-PSMA-R2. AUCinf will be listed and summarized using
- 25

 - descriptive statistics.
 - Dose Escalation 6: Maximum plasma concentration (Cmax) of 225Ac-PSMA-R2. Cmax will be listed and summarized using descriptive statistics.
 - Dose Escalation 7: Total systemic clearance for intravenous administration (CL) of 225Ac-PSMA-R2. CL will be listed and summarized using descriptive statistics.
- 30

 - Dose Escalation 8: Time of observed drug concentration occurrence (Tmax) of 225Ac-PSMA-R2. Tmax will be listed and summarized using descriptive statistics.
 - Dose Escalation 9: Volume of distribution during the terminal phase following intravenous elimination (Vz) of 225Ac-PSMA-R2. Vz will be listed and summarized using descriptive statistics.

- Dose Escalation 10: Terminal elimination half-life ($T_{1/2}$) of 225Ac-PSMA-R2. $T_{1/2}$ will be listed and summarized using descriptive statistics.
- Dose Expansion 4: Area under the serum concentration-time curve from time zero to the time of last quantifiable concentration (AUClast) of 225Ac-PSMA-R2. AUClast will be listed and summarized using descriptive statistics.
- Dose Expansion 5: Area under the plasma concentration-time curve from time zero to infinity (AUCinf) of 225Ac-PSMA-R2. AUCinf will be listed and summarized using descriptive statistics.
- Dose Expansion 6: Maximum plasma concentration (C_{max}) of 225Ac-PSMA-R2. C_{max} will be listed and summarized using descriptive statistics.
- Dose Expansion 7: Total systemic clearance for intravenous administration (CL) of 225Ac-PSMA-R2. CL will be listed and summarized using descriptive statistics.
- Dose Expansion 8: Time of observed drug concentration occurrence (T_{max}) of 225Ac-PSMA-R2. T_{max} will be listed and summarized using descriptive statistics.
- Dose Expansion 9: Volume of distribution during the terminal phase following intravenous elimination (V_z) of 225Ac-PSMA-R2. V_z will be listed and summarized using descriptive statistics.
- Dose Expansion 10: Terminal elimination half-life ($T_{1/2}$) of 225Ac-PSMA-R2. $T_{1/2}$ will be listed and summarized using descriptive statistics.

20 *Estimated Enrollment: 100*

Study Groups:

Group 1 – post 177Lu treatment

- 1) Dose Escalation: All eligible participants with mCRPC heavily pre-treated and refractory to 177Lu-labelled PSMA-targeting RLT will receive the starting dose of 7 Megabecquerel (MBq) of 225Ac-PSMA-R2 to determine the Maximum Tolerated Dose/Recommended Dose for Expansion (MTD/RDE) of Group 1.

- 2) Dose Expansion: Once RDE is determined for Group-1, participants being non/partial responders to 177Lu-labelled PSMA-targeted RLT or requiring re-treatment/re-challenge after 177Lu-labelled PSMA-targeted RLT treatment will be enrolled in Group 1 dose expansion.

Group 2 – pre 177Lu treatment

- 1) Dose Escalation: All eligible participants with mCRPC who have received previous treatment with Androgen Receptor Pathway Inhibitors (ARPI) or Computed Tomography (CT) but have never been treated with 177Lu-labelled PSMA-targeted RLT (177Lu-labelled

PSMA-targeted RLT treatment naïve) will receive one level higher than the RDE of Group 1 as the starting dose of 225Ac-PSMA-R2 in order to determine the MTD/RDE of Group 2.

2) Dose Expansion: Once RDE is determined for Group 2, participants naïve to 177Lu-labelled PSMA-targeted RLT with high volume soft tissue and visceral disease and in participants with diffuse bone metastasis will be enrolled in Group 2 dose expansion.

Alternatively, if the RDE1 is not determined, Group 2 will begin the evaluation for the dose escalation at the dose of 7 MBq of 225Ac-PSMA-R2 upon Novartis decision. The early starting of Group 2 will be supported by emerging safety and preliminary efficacy data from Group 1 dose escalation.

Assigned Interventions:

- Drug: 225Ac-PSMA-R2 (Compound of Formula (II))
- Radiation: 68Ga-PSMA-R2
- Kit for radiopharmaceutical preparation

Detailed Description:

This is an open label, phase I/II, multi-center study which contains two treatment groups (Group 1 and Group 2). Each group has a dose escalation part, once the Maximum Tolerated Dose/Recommended Dose for Expansion (MTD/RDE) is determined in each of the dose escalation parts, the study will continue with an expansion part in the respective group.

The dose escalation parts will establish the MTD/RDE of the 225Ac-PSMA-R2 guided by the well-established Bayesian Logistic Regression Model (BLRM) method. The adaptive BLRM will be guided by the Escalation with Overdose Control (EWOC) principle to control the risk of DLT in future participants on study. Dose escalation decisions will be performed by the Investigators and Novartis during dose escalation meetings (DEMs) based on safety and tolerability information (BLRM summaries of DLT risk) along with PK and preliminary efficacy information.

The dose expansion parts will assess the anti-tumor activity (Overall Response Rate (ORR) by Prostate Cancer Working Group 3 (PCWG3) modified RECIST 1.1 and Prostate Specific Antigen 50 (PSA50) response rate) as well as further assess the safety, tolerability, and PK of 225Ac-PSMA-R2.

Eligibility:

Ages Eligible for Study: 18 Years and older
Sexes Eligible for Study: Male

Accepts Healthy Volunteers: No

Key Inclusion Criteria:

- Evidence of PSMA-positive disease by 68Ga-PSMA-R2 PET/CT and eligible as determined
5 by central reading
- Documented progressive mCRPC
- Adequate organ function (bone marrow reserve, hepatic, renal)
- Prior orchiectomy and/or ongoing ARPI and taxane-based chemotherapy and should have
10 received prior 177Lu-PSMA-RLT (Group1 dose escalation & expansion) or never received
177Lu-PSMA-RLT (Group 2 dose escalation & expansion).

Key Exclusion Criteria:

- Any other investigational agents within 28 days of the anticipated C1D1 of 225Ac-PSMA-
R2 therapy
- 15 - Any systemic anti-cancer therapy within 28 days of the anticipated C1D1 of 225Ac-PSMA-
R2 therapy
- Uncontrolled pain or incompatibility that may result in participant's lack of ability to comply
with imaging procedures
- History of CNS metastases and symptomatic cord compression, or clinical or radiologic
20 findings indicative of impending cord compression
- Uncontrolled cardiovascular history
- Diagnosis of other malignancies expected to alter life expectancy or may interfere with
disease assessment
- Other protocol-defined inclusion/exclusion criteria may apply.

25

Based on the results of the above-described dose escalation study, the R2PD will be
determined for administering the compound of formula (II) at a dose of 4 MBq, or 5 MBq, or
6 MBq, or at 7 MBq, or at 8MBq, or at 9, or at 10 MBq, or 11 MBq, or 12 MBq, or 13 MBq, or
14 MBq, preferably at a dose of 4, 7, 10, 12, or 14 MBq, more preferably at a dose of 7 or 10
30 MBq, even more preferably at a dose of 7 MBq.

Example 4: Dose Escalation Study for Compound of Formula (I) Radiolabeled with

²²⁵Ac

Overview: A study to determine a safe and efficacious dose of ²²⁵Ac-PSMA-617 in men with
heavily pre-treated PSMA positive metastatic castration resistant prostate cancer (mCRPC)
35 with or without prior 177Lu-labelled PSMA-targeted radioligand therapy (e.g. Lutetium (¹⁷⁷Lu)
vipivotide tetraxetan or Lutetium (¹⁷⁷Lu) zadavotide guraxetan).

Detailed Description:

Approximately 60 patients with PSMA-positive disease (determined by ⁶⁸Ga-PSMA-11 PET/CT) will be assigned to one of three groups (20 patients per group):

- Group A - prior chemotherapy and androgen receptor pathway inhibitors (ARPI) received, no prior ¹⁷⁷Lu-PSMA-targeted agent (in particular, ¹⁷⁷Lu-PSMA-617 or ¹⁷⁷Lu-PSMA I&T);
- Group B – ¹⁷⁷Lu-PSMA-targeted agent treatment naïve; and
- Group C – prior ARPI and ¹⁷⁷Lu-PSMA-targeted agent (in particular, ¹⁷⁷Lu-PSMA-617 or ¹⁷⁷Lu-PSMA I&T).

Enrolled patients will receive intravenous ²²⁵Ac-PSMA-617 once every 8 weeks (±1 week) for a maximum of 6 cycles. Dose escalation will proceed using a Bayesian Logistic Regression Model (Table 2). In each group, ≥ 3 patients will be treated at each dose and evaluated for ≥ 6 weeks before consideration of patient enrolment into the next dose. The maximum tolerated dose will be the dose at which the posterior probability of targeted toxicity exceeds 50% (≥ 6 patients treated at this dose and observed for 6 weeks). Patients may also receive supportive care but cannot receive concurrent anti-cancer therapies. Secondary endpoints are overall safety and tolerability, response according to RECIST v1.1 (overall response rate, duration of response, disease control rate), progression free survival (radiographic disease progression, clinical progression and PSA progression), biochemical response, and health related quality of life (HRQoL). Safety follow-up will be performed approximately 60 days following the final dose of ²²⁵Ac-PSMA-617, or before any subsequent anti-cancer treatment. Long-term follow up will include HRQoL, survival and treatment updates every 3 months (± 1 month) for 12 months.

Table 2.

	Cycle (C) and Day (D) of ²²⁵ Ac-PSMA-617 Administration [‡]					
Dose Level	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1
–1 (2 MBq)*	2	2	2	2	2	2
1 (4 MBq) [†]	4	4	4	4	4	4
2 (6 MBq)	6	6	6	6	6	6
3 (8 MBq)	8	8	8	8	8	8
4 (10 MBq)	10	10	10	10	10	10

*Decrease from starting dose

[†]Starting dose

[‡]Additional and/or intermediate dose levels may be added during the study

Primary Outcome Measures:

1. Recommended Phase 2 Dose (RP2D) (time frame: 6 weeks post C1D1 of each dosing cohort through enrollment completion, an average of 1.5 years to determine RP2D).

- The RP2D for each group (Group A, B and C) is defined as the dose level that is well tolerated (i.e., at or below the MTD) and for which there may be additional findings (e.g., longer term tolerability) effecting the RP2D decision. In the case where an MTD is not identified, even at the highest dose level tested, the RP2D may be determined on the basis of data indicating adequate tolerability and therapeutic effectiveness.

Secondary Outcome Measures:

Percentage of Participants with treatment emergent adverse events - Time Frame: Day 1/Infusion Day up to 60 days post infusion. Safety measured by the percentage of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term).

Overall Response Rate (ORR) - Time Frame: every 8 weeks after first dose of 225Ac-PSMA-617 for the first 24 weeks, then every 12 weeks through the end of treatment visit, on average 2.5 years. Overall Response Rate (ORR) is defined as the proportion of participants with best overall response of Complete Response (CR) or Partial Response (PR) as measured by RECIST v1.1.

Duration of Response (DOR) - Time Frame: every 8 weeks after first dose of 225Ac-PSMA-617 for the first 24 weeks, then every 12 weeks through the end of treatment visit, on average 2.5 years. Duration of Response (DOR) is the time from the date of the first documented response (CR or PR) to the date of the first radiologically documented disease progression or death due to disease according to RECIST v1.1.

Disease Control Rate (DCR) - Time Frame: every 8 weeks after first dose of 225Ac-PSMA-617 for the first 24 weeks, then every 12 weeks through the end of treatment visit, on average 2.5 years. Disease Control Rate (DCR) is the percentage of participants with a best overall response of Complete Response (CR), Partial Response (PR) or Stable Disease (SD) according to RECIST v1.1.

Progression Free Survival (PFS) - Time Frame: every 8 weeks after first dose of 225Ac-PSMA-617 for the first 24 weeks, then every 12 weeks through the end of treatment visit, on average 2.5 years. Progression Free Survival (PFS) is defined as the time from Cycle 1 Day 1 (C1 D1) to the first of radiographic, clinical, or prostate-specific antigen [PSA] progression-free survival, or censorship with events defined as follows:

- Radiographic disease progression as determined from bone scans and contrast CT/MRI as outlined in Prostate Cancer Working Group 3 (PCWG3) and RECIST 1.1
- Unequivocal clinical progression
- PSA progression, defined as the date that a $\geq 25\%$ increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored. Where no decline from baseline is documented, baseline PSA is the nadir. The date of progression is date of first occurrence, not date of confirmation (PCWG3 Guidance).

10 Percentage of Participants with Biochemical Response - as measured by Prostate Specific Antigen (PSA); Time Frame: Baseline, Days 1, 15, 29 and 43 of each Cycle (1 cycle = 8 weeks +/- 1 week), End of Treatment and every 3 months during the 12-month follow-up period. Prostate-specific antigen is a glycoprotein considered as a biomarker for the response to therapy in men with prostate cancer. A 50 percent (%) decline in PSA from

15 Baseline to the PSA level at End of Study was considered as a PSA response.

Notable Changes in Alkaline phosphatase (ALP) levels - Time Frame: Baseline, Cycle 1 and Cycle 2 (Weekly), Cycle 3 to Cycle 6 (Bi-weekly) (1 cycle = 8 weeks +/- 1 week). Safety measured by the notable post-baseline changes in Alkaline phosphatase (ALP) levels

20 compared to baseline.

Notable Changes in Lactate dehydrogenase (LDH) levels - Time Frame: Baseline, Cycle 1 and Cycle 2 (Weekly), Cycle 3 to Cycle 6 (Bi-weekly) (1 cycle = 8 weeks +/- 1 week). Safety measured by the notable post-baseline changes in Lactate dehydrogenase (LDH) levels

25 compared to baseline.

Change from Baseline in European Quality of Life (EuroQoL) - 5 Domain 5 Level scale (EQ-5D-5L); Time Frame: Baseline, Day 1 of each Cycle (1 cycle = 8 weeks +/- week), End of Treatment, on average 2.5 years. EQ-5D-5L is a standardized participant completed

30 questionnaire that measures health-related quality of life and translates that score into an index value or utility score. EQ-5D-5L consists of two components: a health state profile and an optional visual analogue scale (VAS). EQ-5D health state profile is comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1= no problems, 2= slight problems, 3= moderate problems,

35 4= severe problems, and 5= extreme problems. Higher scores indicated greater levels of problems across each of the five dimensions.

- Change from Baseline in Functional Assessment of Cancer Therapy - Prostate (FACT-P) Questionnaire; Time Frame: Baseline, Day 1 of each Cycle (1 cycle = 8 weeks +/- week), End of Treatment, on average 2.5 years. FACT-P assesses symptoms/problems related to prostate carcinoma and its treatment. It is a combination of the FACT- General + the Prostate Cancer Subscale (PCS). The FACT-General (FACT-G) is a 27 item Quality of Life (QoL) measure that provides a total score as well as subscale scores: Physical (0-28), Functional (0-28), Social (0-28), and Emotional Well-being (0-24). The total score range is between 1-108, higher scores indicates better for total score and subscale scores. PCS is a 12-item prostate cancer subscale that asks about symptoms and problems specific to prostate cancer (Range 0-48, higher scores better). The FACT-P total score is the sum of all 5 subscale scores of the FACT-P questionnaire and ranges from 0-156. Higher scores indicate higher degree of functioning and better quality of life.
- 15 Change from Baseline in Brief Pain Inventory - Short Form (BPI-SF) Questionnaire: Pain Severity Score; Time Frame: Baseline, Day 1 of each Cycle (1 cycle = 8 weeks +/- week), End of Treatment, on average 2.5 years. The BPI-SF is a publicly available instrument to assess the pain and includes severity and interference scores. BPI-SF is an 11-item self-report questionnaire that is designed to assess the severity and impact of pain on daily functions of a participant. Pain severity score is a mean value for BPI-SF questions 3, 4, 5 and 6 (questions inquiring about the extent of pain, where the extent is ranked from 0 [no pain] to 10 [pain as bad as you can imagine]). Pain severity progression is defined as an increase in score of 30% or greater from baseline without decrease in analgesic use.
- 25 Change from Baseline in Brief Pain Inventory - Short Form (BPI-SF) Questionnaire: Pain Interference Score; Time Frame: Baseline, Day 1 of each Cycle (1 cycle = 8 weeks +/- week), End of Treatment, on average 2.5 years. The BPI-SF is a publicly available instrument to assess the pain and includes severity and interference scores. BPI-SF is an 11-item self-report questionnaire that is designed to assess the severity and impact of pain on daily functions of a participant. Pain interference score is mean value for the 7 BPI-SF questions (questions inquiring about the extent of interference with activities by pain) where the extent is ranked from 0 (does not interfere) to 10 (completely interferes). Pain interference progression is defined as an increase in score of 50% or greater from baseline without decrease in analgesic use.
- 35 Change from Baseline in Xerostomia-Related Quality of Life Scale (XeQOLS) - Time Frame: Baseline, Day 1 of each Cycle (1 cycle = 8 weeks +/- 1 week), End of Treatment and every 3

months during the 12-month follow-up period. The XeQOLS is a validated patient reported 15-item assessment scale with 4 domains: physical functioning, pain/discomfort, personal/psychologic functioning, and social functioning. The score is the average of all responses of all domains and can range from 0 to 4, with higher scores indicating increased xerostomia burden. A negative change from Baseline indicates an improvement of the xerostomia burden.

Eligibility:

Ages Eligible for Study: 18 Years and older

10 Sexes Eligible for Study: Male

Accepts Healthy Volunteers: No

Key Inclusion Criteria:

- Patients must have the ability to understand and sign an approved ICF.
- 15 - Patients must have the ability to understand and comply with all protocol requirements.
- Patients must be ≥ 18 years of age.
- Patients must have an ECOG performance status of 0 to 2.
- Patients must have had histological, pathological, and/or cytological confirmation of prostate cancer.
- 20 - Patients must have a positive 68Ga-PSMA-11 PET/CT scan performed within 28 days of study entry as described in Imaging Manual).
- Patients must have recovered or stabilized to $\leq$ Grade 2 or baseline from all clinically significant toxicities related to prior prostate cancer therapy.
- Determination of disease progression on treatment prior to enrollment. Progressive
- 25 disease for study entry is defined as any one or more of the following:
 1. PSA progression: minimum of two rising PSA values from a baseline measurement with an interval of ≥ 1 week between each measurement. 2.0 ng/mL is the minimal starting value if PSA rise is only indication of progression.
 2. Soft tissue or visceral disease progression as per RECIST 1.1 criteria: increase $\geq$
 - 30 20% in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions.
 3. Bone progression: ≥ 2 new lesions on bone scan.
- Patients must have adequate organ function (bone marrow reserve, hepatic function and
- 35 renal function).

- Known HIV-positive patients who are healthy and have a low risk of AIDS-related outcomes are eligible. HIV testing is required.
- For patients who have partners of childbearing potential, patient must use a method of birth control with adequate barrier protection, deemed acceptable by the principle investigator
- 5 during the study and for 6 months after last study drug administration.
- Group A Subjects: Patients must have prior orchiectomy and/or ongoing androgen-deprivation therapy, a castrate level of serum testosterone (< 50 ng/dL or < 1.7 nmol/L) and must have received prior cytotoxic chemotherapy and a novel androgen axis drug (e.g., abiraterone or enzalutamide). Patients must also be naïve to prior ¹⁷⁷Lu-PSMA radioligand
- 10 therapy (¹⁷⁷Lu-PSMA-617 or ¹⁷⁷Lu-PSMA I&T)
- Group B Subjects (South-Africa only): Patients must have ongoing androgen deprivation therapy (ADT) and either prior orchiectomy or be medically castrate using LHRH agonists/antagonists in order to achieve adequate suppression of serum testosterone (< 50 ng/dL) but must not have received prior cytotoxic chemotherapy or novel androgen axis
- 15 drugs (e.g., abiraterone or enzalutamide). These patients are naïve to ¹⁷⁷Lu-PSMA radioligand therapy (¹⁷⁷Lu-PSMA-617 or ¹⁷⁷Lu-PSMA I&T).
- Group C Subjects: Patients must have ongoing androgen deprivation therapy (ADT) and either prior orchiectomy or be medically castrate using LHRH agonists/antagonists in order to achieve adequate suppression of serum testosterone (< 50 ng/dL). Patients must have
- 20 been treated with prior ¹⁷⁷Lu-PSMA radioligand therapy (¹⁷⁷Lu-PSMA-617 or ¹⁷⁷Lu-PSMA I&T) for at least one cycle administered greater than 6 weeks from study enrollment, and been evaluated for biochemical and radiological response to therapy. Prior exposure to ARPI and/or chemotherapy is not required.
- 25 *Key Exclusion Criteria:*
- Previous treatment with Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223 or hemi-body irradiation.
- Any investigational agents within 28 days of study enrollment.
- Known hypersensitivity to the components of the study therapy or its analogues.
- 30 - Other concurrent cytotoxic chemotherapy, targeted therapy, biologic agents, immunotherapy, radioligand therapy, or investigational therapy.
- Transfusion for the sole purpose of eligibility into the study.
- Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving
- 35 corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired.

- Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.
- Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, uncontrolled infection, active hepatitis B or C, or other significant
- 5 co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.
- Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. Patients with a prior history of malignancy who have been disease free for more than 3 years are eligible.

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Based on the results of this above-described dose escalation study, the recommended Phase 2 dose (RP2D) for compound of formula (I) radiolabeled with ^{225}Ac is 6 MBq or 8MBq.

15 **Example 5: Phase 2 Trial Design for Compound of Formula (I) Radiolabeled with ^{225}Ac**

Overview: A randomized study of ^{225}Ac -PSMA-617 (Formula (I) radiolabeled with ^{225}Ac) vs the base standard of care (BSoC) in men with mCRPC post treatment with chemotherapy (e.g., taxane).

20 *Enrollment:* 141

Inclusion Criteria:

- Patients with progressive PSMA PET+ mCRPC
- Patients who have received prior ARPI, taxane, Lu-PSMA RLT

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Exclusion Criteria:

- Patients with $\text{gr} \geq 2$ xerostomia

Stratification Factors:

- 30 - Time to radiographical/biochemical progression on prior Lu (≤ 6 mos vs > 6 mos)
- Number of cycles of prior Lu (≤ 4 vs > 4)

Study Details:

- The study is a randomized trial. The ratio of patients who will receive ^{225}Ac -PSMA-617
- 35 (treatment) to patients who receive BSoC (control) is 2:1. Patients in the treatment group will receive ^{225}Ac -PSMA-617 via IV injection at a dose of RP2D (as determined by Example 4) every 8 weeks for 4 cycles.

- All patients will receive PSMA PET imaging after Cycle 2
- All patients will receive xerostomia mitigation per protocol

Primary Endpoint:

- 5 Radiographic progression-free survival (rPFS) per blinded independent central review (BICR) assessment using PCWG3.

Secondary Endpoints:

- Overall survival (OS)
- 10 • Overall response rate (ORR), Disease control rate (DCR), Duration of response (DOR) using PCWG3 modified-RECIST 1.1
- Time to first symptomatic skeletal event (TTSSE)
- Biochemical response
- Safety
- 15 • Health related quality of life (HRQoL)
- Characterize PK by radioactivity in blood during Cycle 1

Exploratory objectives:

- To assess molecular biomarkers associated with response, resistance to treatment and/or safety.
- 20 • To explore the association between imaging with PSMA SPECT and efficacy of treatment with ²²⁵Ac-PSMA-617.

Example 6: Phase 3 Trial Design for Compound of Formula (I) Radiolabeled with ²²⁵Ac

- 25 *Overview:* A randomized study of ²²⁵Ac-PSMA-617 (Formula (I) radiolabeled with ²²⁵Ac) vs the base standard of care (BSoC) in men with mCRPC pre treatment with chemotherapy.

Enrollment: 684

30 *Inclusion Criteria:*

- Patients with progressive PSMA PET+ mCRPC
- Patients who have received prior ARPI and Lu-PSMA RLT

Exclusion Criteria:

- 35
- Patients with gr ≥ 2 xerostomia
 - Patients who have received prior taxane

Stratification Factors:

- Time to radiographical/biochemical progression on prior Lu (≤ 6 mos vs > 6 mos)
- Number of cycles of prior Lu (≤ 4 vs > 4)
- ECOG performance status (0-1 vs 2)

5

Study Details:

The study is a randomized trial. The ratio of patients who will receive 225Ac-PSMA-617 (treatment) to patients who receive BSoC (control) is 2:1. Patients in the treatment group will receive 225Ac-PSMA-617 via IV injection at a dose of RP2D (as determined by Example 4)

10 every 8 weeks for 4 cycles.

- All patients will receive PSMA PET imaging after Cycle 2
- All patients will receive xerostomia mitigation per protocol

Primary Endpoint:

15 Overall Survival

Secondary Endpoints:

- rPFS using PCWG3 criteria
- ORR, DCR, DOR using PCWG3 modified-RECIST 1.1
- 20 • Time to first symptomatic skeletal event (TTSSE)
- Biochemical response
- Safety
- HRQoL
- Characterize PK by radioactivity in blood during Cycle 1

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Exploratory objectives:

- To assess molecular biomarkers associated with response, resistance to treatment and/or safety.
- To explore the association between imaging with PSMA SPECT and efficacy of
- 30 treatment with 225Ac-PSMA-617.

Example 7: Phase 2 Trial Design to Support 10 MBq as the Phase 3 Dose of Compound of Formula (I) Radiolabeled with ^{225}Ac (225Ac-PSMA-617)

35 *Overview:* A study to collect additional information in support of 10 MBq as the phase 3 dose of 225Ac-PSMA-617 (Formula (I) radiolabeled with ^{225}Ac) in men with PSMA-positive mCRPC

cancer post treatment with Androgen Receptor Pathway Inhibitors (ARPI) and chemotherapy (e.g., taxane), and who progressed on or after [177Lu]Lu-PSMA targeted therapy (e.g., Lutetium (¹⁷⁷Lu) vipivotide tetraxetan or Lutetium (¹⁷⁷Lu) zadavotide guraxetan) (See Example 8 for Phase 3 study design).

5

Primary Outcome Measures:

Data Collection: additional data on 225Ac-PSMA-617 at doses of 8 MBq and 10 MBq to support 10 MBq as the phase 3 dose of 225Ac-PSMA-617 in participants with PSMA-positive mCRPC who have had treatments with ARPI and taxane-based chemotherapy, and progressed on or after [177Lu]Lu-PSMA targeted therapy.

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- Prostate Specific Antigen response (PSA50): The proportion of participants who achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
- Safety: Type, incidence and severity of Adverse Events (AEs) and serious adverse events (SAEs), and deaths.
- Tolerability: Dose interruptions, reductions, discontinuation, dose intensity and duration of exposure.

15

Secondary Outcomes Measures:

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Activity assessment: anti-tumor activity of 225Ac-PSMA-617 (8 MBq and 10 MBq).

- Radiographic Progression-Free survival (rPFS): The time from the date of randomization to the date of the first documented radiographic disease progression as assessed by investigator's assessment and according to Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1 criteria (RECIST: Response Evaluation Criteria In Solid Tumors) or death due to any cause, whichever occurs first.
- Progression Free Survival (PFS): The time from date of randomization to first documented progression by investigator's assessment (radiographic progression according to PCWG3-modified RECIST v1.1 criteria, clinical progression, PSA progression per PCWG3) or death due to any cause, whichever occurs first.
- Overall response rate (ORR): The proportion of participants with best overall response (BOR) of confirmed complete response (CR) or partial response (PR) in soft tissue based on tumor response data by investigator's assessment and according to PCWG3-modified RECIST v1.1, in the absence of bone progression as per PCWG3.

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- Disease control rate (DCR): The proportion of participants with BOR of confirmed CR, PR, stable disease (SD) or Non-CR/Non-progressive disease (PD) in soft tissue based on tumor response data by investigator's assessment and according to PCWG3-modified RECIST v1.1, in the absence of bone progression as per PCWG3.
- Overall survival (OS): The time from the date of randomization to the date of death due to any cause.

225Ac-PSMA-617 Safety: characterize the safety profile of 225Ac-PSMA-617 at 8 MBq and 10 MBq.

- Other safety endpoints: changes in laboratory values, vital signs, and ECGs.
-

Exploratory Objectives:

1. To characterize salivary gland function due to the effect of 225Ac-PSMA-617 (8 MBq and 10 MBq).
2. To assess patient reported disease related symptoms and health-related quality of life (HRQoL) with 225Ac-PSMA-617 (8 MBq and 10 MBq).
3. To assess change in patient-reported pain severity with 225Ac-PSMA-617 (8 MBq and 10 MBq).
4. To characterize molecular biomarkers of 225Ac-PSMA-617 (8 MBq and 10 MBq).
5. To evaluate the effect of 225Ac-PSMA-617 (8 MBq and 10 MBq) on the QTc interval including concentration/QT assessment.
6. To assess radiation dosimetry of 225Ac-PSMA-617 (8 MBq and 10 MBq) to further evaluate the dose to critical organs (e.g., kidney, bone marrow and salivary glands) and tumors.
7. To characterize pharmacokinetic profile of 225Ac-PSMA-617 (8 MBq and 10 MBq).
8. To characterize the biodistribution of 225Ac-PSMA-617 (8 MBq and 10 MBq).

Detailed Description:

This Example describes the phase 2 part of a 2-arm randomized, open-label, international, multicenter, phase 2/3 study to assess the efficacy and safety of 225Ac-PSMA-617 compared with investigator's choice of best standard of care (BSoC) in adult participants with PSMA-positive mCRPC who had treatments with ARPI and taxane-based chemotherapy, and progressed on or after [¹⁷⁷Lu]Lu-PSMA targeted therapy.

At least 12 eligible participants will be randomized using a ratio of 1:1 to receive 225Ac-PSMA-617 at either 8 MBq (Arm 1) or 10 MBq (Arm 2). Randomization will not be stratified. Participants will be treated with an intravenous dose of 225Ac-PSMA-617 (1 MBq/mL unit dose strength) as per the assigned treatment arm once every 8 weeks for 4 cycles (1 cycle = 8 weeks) and may be allowed to receive an additional 2 cycles of treatment for up to a total of 6 cycles, referred to as 4 (+2) cycles. The primary analysis will be conducted after at least 12 participants have at least one dose administered, have been followed up for 12 weeks, and underwent single timepoint imaging. The objective of this primary analysis is to collect additional information to support 10 MBq as the phase 3 dose of 225Ac-PSMA-617. The phase 3 dose will be assessed based on all available efficacy, safety, and tolerability data, including data from Example 4 (phase 1 study (published as Clinical Trial ID NCT04597411 "AcTION" study)) and Example 5 (phase 2 study). A safety follow up will be performed approximately 56 days following the final dose of 225Ac-PSMA-617, or before any subsequent anti-cancer treatment. Participants receiving the study treatment 225Ac-PSMA-617 will continue to be followed for safety every 12, 24, and 48 weeks during the long-term follow-up period (LTFU) year 1-2, year 3 and year 4-5 respectively. During this long term follow up, AEs of xerostomia, xerophthalmia, myelosuppression related to study treatment, AEs of renal toxicity and second primary malignancy regardless of causality and any serious AEs (SAEs) causally related to study treatment will be recorded, and optionally survival, treatment updates, hematology, chemistry, PSA and other biomarkers, weight, estimated glomerular filtration rate based on creatinine and cystatin C, and patient reported outcomes (PROs) information will be collected.

Eligibility:

The study will enroll adult male participants (≥ 18 years of age) with PSMA-positive mCRPC cancer who had treatments with ARPI and taxane-based chemotherapy, and progressed on or after [177Lu]Lu-PSMA targeted therapy.

Key Inclusion Criteria:

- Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
- Histopathological and/or cytological confirmation of adenocarcinoma of the prostate.
- Documented progressive mCRPC.
- Participants must have PSMA-positive disease as assessed by PSMA PET/CT scan using an approved PSMA imaging agent as protocol instructed, with eligibility being determined by the sponsor's central reading rules.
- A castrate level of serum/plasma testosterone (< 50 ng/dL or < 1.7 nmol/L).

- Prior treatments with ARPI and taxane-based chemotherapy, and progressed on or after [177Lu]Lu-PSMA targeted therapy. ARPI and taxane-based chemotherapy previous treatment exposures in the metastatic hormone sensitive prostate cancer (mHSPC) setting are acceptable.

- 5
 - Participants must have ≥ 1 metastatic lesion that is present on screening/baseline CT, MRI, or bone scan imaging obtained ≤ 28 days prior to randomization.
 - All clinically significant toxicities related to prior therapies (i.e., prior chemotherapy, radiation, etc.) except alopecia must have recovered to $\leq$ Grade 2.
 - Adequate organ function (bone marrow reserve, hepatic, renal).

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Key Exclusion Criteria

- Previous treatment with any of the following within 6 weeks of randomization: Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation, ^{177}Lu -PSMA and ^{177}Lu -DOTA targeted therapies.
- 15
 - Any investigational agents within 28 days prior to the day of randomization.
 - Any ^{225}Ac -based investigational compound used prior to the day of randomization.
 - Known hypersensitivity to any of the study treatments or to drugs of similar classes.
 - A history of CNS metastases who are neurologically unstable, symptomatic, or receiving corticosteroids for the purpose of maintaining neurologic integrity and symptomatic cord compression, clinical or radiologic findings indicative of impending cord compression.
- 20
 - History or current diagnosis of ECG abnormalities which present significant risk of safety.
 - Concurrent serious acute or chronic nephropathy (based on Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2024) KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int; 25
 - 105(4S):S117-S314 (KDIGO 2024 guideline)).
 - Concurrent serious uncontrolled infection determined by the principal investigator that in his/her opinion would be considered an impairment to study participation or cooperation.
 - Diagnosis with other active malignancies that are expected to alter life expectancy or may interfere with disease assessment in the past 3 years.
- 30
 - Baseline xerostomia $\geq$ Grade 2 by Common Terminology Criteria for Adverse Events v.5 (CTCAE v.5).

Other protocol-defined inclusion/exclusion criteria may apply.

- 35

Based on the results of the above-described study, the dose of Formula (I) radiolabeled with ^{225}Ac will be 8 MBq or 10 MBq in the phase 3 part of the study. For example, if the incoming data suggest that the benefit/risk profile of 10 MBq of ^{225}Ac -PSMA-617 is

acceptable, then a dose of 10 MBq will be considered for phase 3. If the incoming data suggest that the benefit/risk profile of 8 MBq of 225Ac-PSMA-617 is more acceptable, then a dose of 8 MBq will be considered for phase 3.

5 **Example 8: Phase 3 Study of Compound of Formula (I) Radiolabeled with 225Ac**
(225Ac-PSMA-617) versus Best Standard of Care

Overview:

10 A phase 3, open-label, international, multi-center, randomized study of 225Ac-PSMA-617 versus best standard of care (BSoC) in the treatment of adult participants with PSMA-positive metastatic castration-resistant prostate cancer who progressed on or after [¹⁷⁷Lu]Lu-PSMA targeted therapy.

Primary Outcome Measures:

- 15 1. To determine whether treatment with 225Ac-PSMA-617 prolongs radiographic progression-free survival (rPFS) as assessed by PCWG3-modified RECIST v1.1 in participants with PSMA-positive mCRPC who had treatments with ARPI and taxane-based chemotherapy, and progressed on or after [¹⁷⁷Lu]Lu-PSMA targeted therapy compared to participants treated with investigator's choice of best standard of care
- 20 (BSoC).
- rPFS: The time from the date of randomization to the date of the first documented radiographic disease progression as assessed by blinded independent central review (BICR) and Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1 criteria or death due to any cause, whichever occurs first.
- 25
2. To determine whether treatment with 225Ac-PSMA-617 prolongs overall survival (OS) in participants with PSMA-positive mCRPC who had treatments with ARPI and taxane-based chemotherapy, and progressed on or after [¹⁷⁷Lu]Lu-PSMA targeted therapy compared to participants treated with investigator's choice of BSoC.
- 30
- OS: The time from the date of randomization to the date of death due to any cause.

Secondary Outcome Measures:

- 35 1. To evaluate the radiographic progression-free survival by PSMA PET imaging (rPFS-PET) in participants treated with 225Ac-PSMA-617 and investigator's choice of BSoC.

- rPFS-PET: The time from date of randomization to the date of the first documented radiographic disease progression by PSMA PET imaging or death due to any cause, whichever occurs first.
- 5 2. To evaluate the progression free survival (PFS) in participants treated with 225Ac-PSMA-617 and investigator's choice of BSoC.
- PFS: The time from date of randomization to first documented progression by investigator's assessment (radiographic progression according to PCWG3-modified RECIST v1.1 criteria, clinical progression, PSA progression per
- 10 PCWG3) or death due to any cause, whichever occurs first.
3. To evaluate the overall response rate (ORR) in participants treated with 225Ac-PSMA-617 and investigator's choice of BSoC.
- ORR: The proportion of participants with best overall response (BOR) of
- 15 confirmed complete response (CR) or partial response (PR) in soft tissue based on tumor response data per BICR assessment and according to PCWG3-modified RECIST v1.1, in the absence of bone progression as per PCWG3. Additionally, ORR in soft tissue only according to PCWG3-modified RECIST v1.1 will be analyzed.
- 20
4. To evaluate the disease control rate compared (DCR) in participants treated with 225Ac-PSMA-617 and investigator's choice of BSoC.
- DCR: The proportion of participants with BOR of confirmed CR, PR, stable disease (SD) or Non-CR/Non-progressive disease (PD) in soft tissue based on
- 25 tumor response data per BICR assessment and according to PCWG3-modified RECIST v1.1, in the absence of bone progression as per PCWG3.
5. To evaluate the duration of response (DoR) in participants treated with 225Ac-PSMA-617 and investigator's choice of BSoC.
- DoR: The duration of time between the date of first documented response (CR or PR) according to PCWG3-modified RECIST v1.1, in the absence of bone progression as per PCWG3, based on tumor response data per BICR and the date of first documented radiographic progression in soft tissue or death due to any cause, whichever occurs first.
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- 35

6. To evaluate the time to first radiographic soft tissue progression (TTSTP) in participants treated with 225Ac-PSMA-617 and investigator's choice of BSoC.
- TTSTP: The time from the date of randomization to the date of radiographic soft tissue progression per soft tissue rules of PCWG3-modified RECIST v1.1 as assessed by BICR.
7. To evaluate the time to first symptomatic skeletal event (TTSSE) in participants treated with 225Ac-PSMA-617 and investigator's choice of BSoC.
- TTSSE: The time from the date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain, or death due to any cause, whichever occurs first.
8. To evaluate the biochemical response as detected by Prostate specific antigen (PSA) halving (PSA50) in participants treated with 225Ac-PSMA-617 and investigator's choice of BSoC.
- PSA50: The proportion of participants who achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
9. To assess patient reported disease related symptoms and health-related quality of life (HRQoL) in both treatment arms.
- Change from baseline on FACT-P Prostate Cancer Subscale (PCS).
 - Time to worsening on the FACT-P total score defined as the time from randomization to the first occurrence of worsening on the score of at least 10 points decrease from baseline or death due to any cause, whichever occurs first.
10. To assess change in patient-reported pain severity in both treatment arms.
- Time to worsening on the Worst Pain: The time from randomization to the first occurrence of worsening on the Worst Pain item (BPI-SF) of at least 30% of baseline or minimum of 2 points increase from baseline, or death due to any cause, whichever occurs first.
11. To assess the safety and tolerability of Formula (I) Radiolabeled with 225Ac.
- Safety endpoints: Incidence and severity of AEs and serious adverse events (SAEs), changes in laboratory values, vital signs, and ECGs.

- Tolerability endpoints: dose interruptions, dose reductions, dose discontinuation, dose intensity, and duration of exposure.

Exploratory Objectives:

1. To characterize pharmacokinetic profile of 225Ac-PSMA-617.
2. To assess radiation dosimetry of 225Ac-PSMA-617 to further evaluate the dose to critical organs (e.g., kidney, bone marrow and salivary glands) and tumors.
3. To assess molecular and imaging biomarkers associated with response or resistance to treatment.
4. To assess the effects of 225Ac-PSMA-617 and BSoC on the PSMA expression in salivary glands (SG) and kidneys (KD).
5. To explore health-related quality of life and other patient reported outcomes (PROs) in both treatment arm.
6. To investigate renal safety biomarker and early detection of renal impairment with 225Ac-PSMA-617 vs. BSoC.
7. To characterize salivary gland function due to the effect of 225Ac-PSMA-617 vs. BSoC considering the known ADR of xerostomia.
8. To assess the relationship between exposure/dosimetry and relevant clinical efficacy and/or safety endpoints.

Detailed Description:

This Example describes the phase 3 part of a 2-arm randomized, open-label, international, multicenter, phase 2/3 study to assess the efficacy and safety of 225Ac-PSMA-617 compared with investigator's choice of best standard of care (BSoC) in adult participants with PSMA-positive mCRPC who had treatments with ARPI and taxane-based chemotherapy, and progressed on or after [¹⁷⁷Lu]Lu-PSMA targeted therapy. A total of 420 eligible participants will be randomized using a ratio of 2:1 to receive either 225Ac-PSMA-617 (Investigational Arm) or investigator's choice of BSoC (Control Arm), respectively. Randomization will be stratified by time to progression on prior [¹⁷⁷Lu]Lu-PSMA targeted therapy (≤ 6 months vs. > 6 months), prior therapy with cabazitaxel (yes vs. no) and presence of liver metastases (yes vs. no). These stratification factors were chosen based on their association with OS and PFS and are relevant prognosis factors in mCRPC.

Investigational arm: Participants randomized to receive 225Ac-PSMA-617 will be treated with 10 MBq of 225Ac-PSMA-617 once every 8 weeks for 4 cycles (1 cycle = 8 weeks) and may be allowed to receive an additional 2 cycles of treatment for up to a total of 6 cycles, referred to as 4 (+2) cycles, under investigator's discretion. If in the case that

incoming data suggest that the benefit/risk profile of 8 MBq of 225Ac-PSMA-617 is more acceptable, then a dose of 8 MBq will be considered for phase 3.

- Control Arm: Participants randomized to investigator's choice of BSoC (Control Arm) will be treated with the investigator chosen BSoC (ARPIs, taxanes, carboplatin, radium-223 dichloride and sipuleucel-T as detailed in Table 3) with a total treatment period depending on the chosen regimen and investigator's considerations. Since BSoC treatment regimen may differ from 225Ac-PSMA-617, the PSMA PET/CT scan schedule will be based on weeks to align with the investigational arm, i.e., the PSMA PET/CT scan will be performed every 16 weeks for a maximum of 3 times depending on treatment completion. BSoC arm conventional imaging assessments will be done every 8 weeks from baseline independent of the investigator chosen regimen.

Table 3 – Best Standard of Care

*Treatment	Description	Form (Route)	Unit Dose Strength(s)	Dosage Levels
Enzalutamide	Anti-androgen	Tablet/ Capsule (Oral)	40 mg	160 mg enzalutamide (four 40 mg soft capsules) as a single oral daily dose
Apalutamide	Anti-androgen	Tablet (Oral)	60 mg	240 mg (four 60 mg tablets) as an oral single daily dose
Darolutamide	Anti-androgen	Tablet (Oral)	300 mg	600 mg darolutamide (two tablets of 300 mg) taken twice daily
Abiraterone	Other hormone antagonists and related agents	Tablet (Oral)	Various	As per locally approved label or institutional practice
Cabazitaxel	Taxane	Solution for infusion (Intravenous)	Various	20-25 mg/m ² IV over one-hour every three weeks. Use in combination with oral prednisone 10 mg once a day. Dose is based on calculation of the Body Surface Area (BSA).
Docetaxel	Taxane	Solution for infusion (Intravenous)	Various	75 mg/m ² IV over 1 hour every 3 weeks; prednisone 5 mg orally 2 times a day is administered continuously. Dose is based on calculation of the Body Surface Area (BSA).
Sipuleucel-T	Immuno-stimulating agent - tumor vaccine	Dispersion for infusion (Intravenous)	> 50 million autologous CD54+ activated cells/dose solution for infusion	> 50 million autologous CD54+ activated cells/dose IV (median dosing interval, 2 week; for a total of 3 doses)
Radium-223 dichloride	Radio-pharmaceutical	Solution for injection (Intravenous)	1100 kBq/ml solution for injection	55 kbq per kg body weight, given at 4-week intervals for 6 injections

Carboplatin	Platinum compound – Alkylating Agent	Solution for injection (Intravenous)	10 mg/ml	Target AUC 5 - 7 mg/ml/min at d1 q21d cycle for previously untreated patients. For previously treated, AUC 5 at day 1 q21d cycle regimens. For weekly injections (d1, d8, d15) at q28d cycle regimens, AUC 2 is suggested to either treated or untreated participant.). AUC is based on CrCl. Modified according to CrCl. No dose reduction if CrCl > 60 ml/min.
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*All BSoCs are used as comparators, have IMP, are provided centrally by the sponsor or locally by the study site, subsidiary, or designee; and will be provided in packaging as locally available, and labelled as required per country requirements (if applicable). CrCl = Creatinine Clearance

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After completion of treatment of 225Ac-PSMA-617 or selected BSoC, radiographic progression per BICR, or discontinuation of study treatment for any reason; participants will have an End of Treatment (EoT) visit and enter the post-treatment follow-up (including the 56-day Safety follow-up period and the long-term follow-up (LTFU) period for up to 5 years after EoT). Efficacy assessment for the primary endpoint of rPFS will be conducted every 8 weeks (± 7 days) after the first dose of study treatment during the first 24 weeks, then every 12 weeks until confirmation of radiographic progression per BICR to control biases that might result from errors in progression assessments (Dodd et al 2008). Crossover to the 225Ac-PSMA-617 arm will not be allowed for any participant randomized to the control arm.

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Eligibility:

The study will enroll adult male (≥ 18 years of age) participants with PSMA-positive mCRPC cancer who had treatments with ARPI and taxane-based chemotherapy, and progressed on or after [177Lu]Lu-PSMA targeted therapy.

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Key Inclusion Criteria:

- An ECOG performance status of 0 to 2.
- Histopathological and/or cytological confirmation of adenocarcinoma of the prostate.
- Documented progressive mCRPC.
- Participants must have PSMA-positive disease as assessed by PSMA PET/CT scan using an approved PSMA imaging agent as protocol instructed, with eligibility being determined by the sponsor's central reading rules.
- A castrate level of serum/plasma testosterone (< 50 ng/dL or < 1.7 nmol/L).
- Prior treatments with ARPI and taxane-based chemotherapy, and progressed on or after [177Lu]Lu-PSMA targeted therapy. ARPI and taxane-based chemotherapy previous

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treatment exposures in the metastatic hormone sensitive prostate cancer (mHSPC) setting are acceptable.

- Participants must have ≥ 1 metastatic lesion that is present on screening/baseline CT, MRI, or bone scan imaging obtained ≤ 28 days prior to randomization.
- 5 • All clinically significant toxicities related to prior therapies (i.e., prior chemotherapy, radiation, etc.) except alopecia must have recovered to $\leq$ Grade 2.
- Adequate organ function (bone marrow reserve, hepatic, renal).

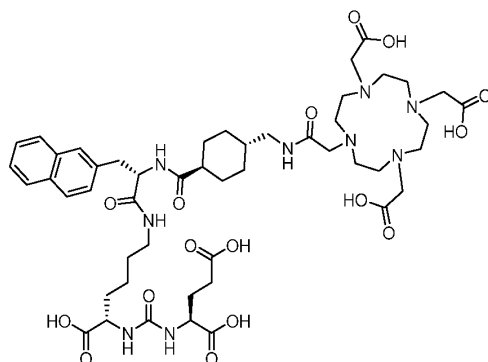
Key Exclusion Criteria

- 10 • Previous treatment with any of the following within 6 weeks of randomization: Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation, ^{177}Lu -PSMA and ^{177}Lu -DOTA targeted therapies.
- Any investigational agents within 28 days prior to the day of randomization.
- Any ^{225}Ac -based investigational compound used prior to the day of randomization.
- 15 • Known hypersensitivity to any of the study treatments or to drugs of similar classes.
- History of CNS metastases and Symptomatic cord compression, clinical or radiologic findings indicative of impending cord compression.
- History or current diagnosis of ECG abnormalities which present significant risk of safety.
- Concurrent serious acute or chronic nephropathy (based on the KDIGO 2024 guideline).
- 20 • Concurrent serious uncontrolled infection determined by the principal investigator that in his/her opinion would be considered an impairment to study participation or cooperation.
- Diagnosed with other active malignancies that are expected to alter life expectancy or may interfere with disease assessment in the past 3 years.
- Baseline xerostomia $\geq$ Grade 2 by CTCAE v.5
- 25 • Uncontrolled cardiovascular history

Other protocol-defined inclusion/exclusion criteria may apply.

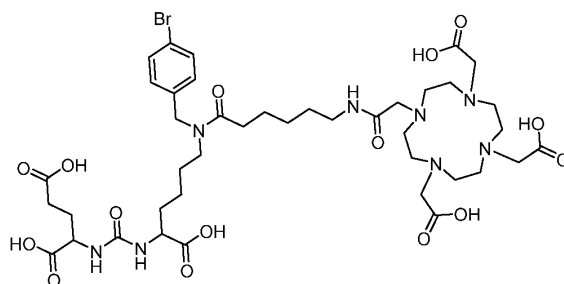
CLAIMS

1. A method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a compound of formula (I) or (II):



or

(I)

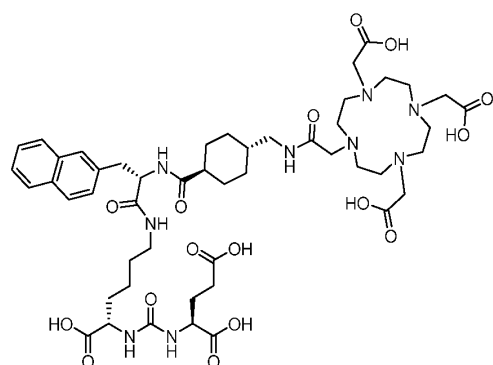


wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,

(II)

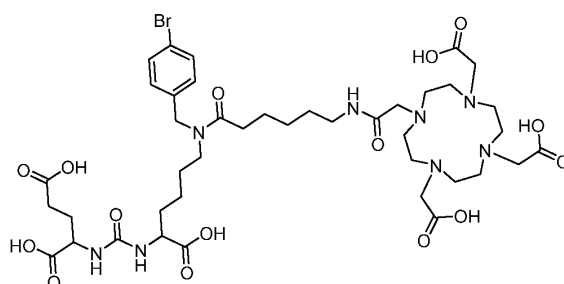
- wherein:
 the compound of formula (I) or (II) is radiolabeled with an alpha-emitting radionuclide,
 the radiolabeled compound of formula (I) or (II) is administered at a dose from about 6 MBq to about 8 MBq, and
 the subject has received prior chemotherapeutic treatment.

2. A method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a compound of formula (I) or (II):



or

(I)



(II)

wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration,

5

wherein:

the compound of formula (I) or (II) is radiolabeled with an alpha-emitting radionuclide,

the radiolabeled compound of formula (I) or (II) is administered at a dose from about

6 MBq to about 8 MBq, and

10

the subject has not received prior chemotherapeutic treatment.

3. The method of claim 1 or 2, wherein the alpha-emitting radionuclide is selected from the group consisting of ^{225}Ac , ^{211}At , ^{213}Bi , ^{212}Bi , ^{212}Pb , ^{223}Ra , ^{224}Ra , ^{149}Tb , and ^{227}Th .

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4. The method of claim 3, wherein the alpha-emitting radionuclide is ^{225}Ac .

5. The method of any one of claims 1-4, wherein the dose is about 6 MBq.

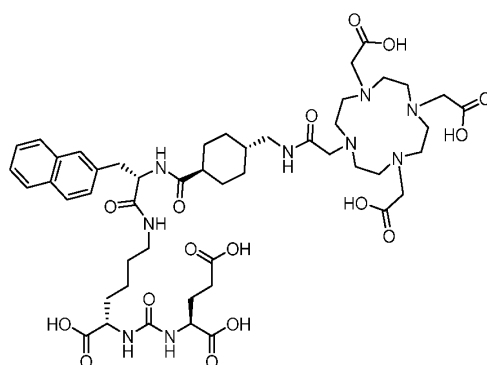
6. The method of any one of claims 1-4, wherein the dose is about 8 MBq.

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7. The method of any one of claims 1-6, wherein the dose of the compound of formula (I) or (II), (III), (IV), or (V) is administered to the subject about every 4 to 8 weeks.

8. The method of any one of claims 1-7, wherein the dose of the compound of formula (I), (II), (III), (IV), or (V) is administered to the subject about every 6 to 8 weeks.
9. The method of claim 8, wherein the dose of the compound of formula (I), (II), (III), (IV), or (V) is administered to the subject about every 6 weeks.
10. The method of claim 8, wherein the dose of the compound of formula (I), (II), (III), (IV), or (V) is administered to the subject about every 8 weeks.
11. The method of any one of claims 1-9, wherein the dose of the compound of formula (I), (II), (III), (IV), or (V) is administered to the subject about every 4 to 8 weeks for 4 to 6 cycles.
12. The method of claim 11, wherein the dose of the compound of formula (I), (II), (III), (IV), or (V) is administered to the subject about every 6 to 8 weeks for 4 to 6 cycles.
13. The method of claim 11, wherein the dose of the compound of formula (I), (II), (III), (IV), or (V) is administered to the subject about every 4 to 8 weeks for 4 cycles.
14. The method of claim 13, wherein the dose of the compound of formula (I), (II), (III), (IV), or (V) is administered to the subject about every 6 to 8 weeks for 4 cycles.
15. The method of claim 14, wherein the dose of the compound of formula (I), (II), (III), (IV), or (V) is administered to the subject about every 6 weeks for 4 cycles.
16. The method of claim 14, wherein the dose of the compound of formula (I), (II), (III), (IV), or (V) is administered to the subject about every 8 weeks for 4 cycles.
17. The method of any one of claims 1-9, wherein the dose of the compound of formula (I), (II), (III), (IV) or (V) is administered to the subject about every 4 to 8 weeks for 6 cycles.
18. The method of claim 17, wherein the dose of the compound of formula (I), (II), (III), (IV), or (V) is administered to the subject about every 6 to 8 weeks for 6 cycles.
19. The method of claim 18, wherein the dose of the compound of formula (I), (II), (III), (IV), or (V) is administered to the subject about every 6 weeks for 6 cycles.

20. The method of any one of claims 1-19, wherein the PSMA-expressing cancer is prostate cancer.
21. The method of claim 20, wherein the prostate cancer is metastatic prostate cancer.
22. The method of claim 21, wherein the metastatic prostate cancer is metastatic castration resistant prostate cancer (mCRPC).
23. The method of any one of claims 1-22, wherein the prior chemotherapeutic treatment comprises administration of taxane.
24. The method of any one of claims 1-23, wherein the subject has received prior treatment with a beta-minus-emitting radiopharmaceutical.
25. The method of claim 24, wherein the beta-minus-emitting radiopharmaceutical is a ¹⁷⁷Lu-PSMA targeting agent.
26. The method of claim 25, wherein the ¹⁷⁷Lu-PSMA targeting agent is ¹⁷⁷Lu-PSMA-617 or ¹⁷⁷Lu-PSMA I&T.
27. The method of claim 26, wherein the ¹⁷⁷Lu-PSMA targeting agent is ¹⁷⁷Lu-PSMA-617.
28. The method of any one of claims 1-27, wherein the subject has received prior treatment with an androgen receptor pathway inhibitor (ARPI).
29. The method of any one of claims 1-28, wherein the PSMA-expressing cancer has been determined to be resistant to one or more of chemotherapeutic treatment, beta-minus-emitting radiopharmaceuticals, and ARPIs.
30. The method of any one of claims 1 and 3-28, wherein the subject did not respond to the prior chemotherapeutic treatment, or the PSMA-expressing cancer progressed after administration of the prior chemotherapeutic treatment.
31. A method of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical at a dose of from about 6 MBq to about 8 MBq, wherein the radiopharmaceutical is a compound of formula (I):

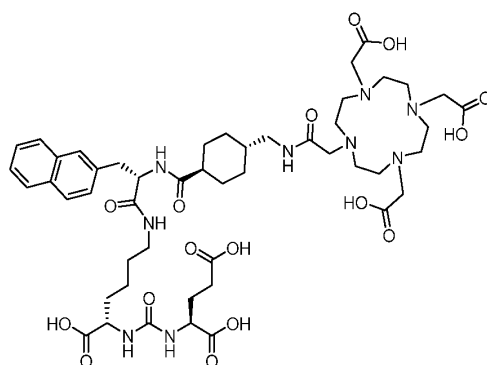


(I),

wherein the compound of formula (I) is radiolabeled with ^{225}Ac , and wherein the subject has received prior chemotherapeutic treatment.

5

32. A method of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical at a dose of from about 6 MBq to about 8 MBq, wherein the radiopharmaceutical is a compound of formula (I):



(I)

wherein the compound of formula (I) is radiolabeled with ^{225}Ac , and wherein the subject has not received prior chemotherapeutic treatment.

10

33. The method of claim 31 or 32, wherein the prostate cancer is metastatic prostate cancer.

15

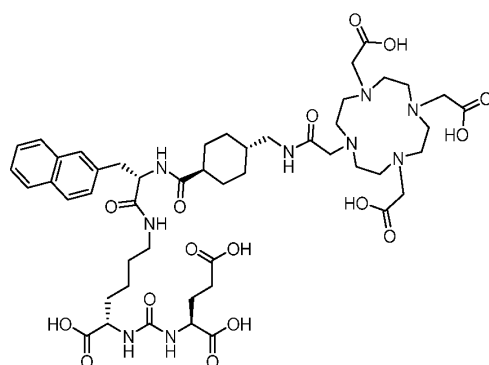
34. The method of claim 33, wherein the metastatic prostate cancer is metastatic castration resistant prostate cancer (mCRPC).

35. The method of any one of claims 31-34, wherein the prior chemotherapeutic treatment comprises administration of taxane.

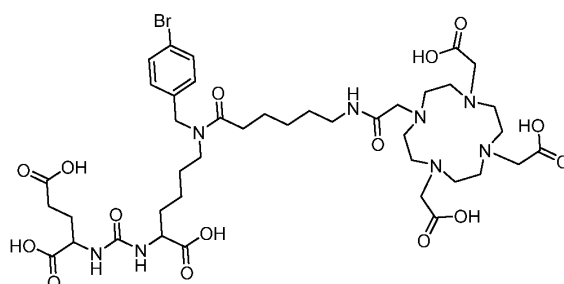
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36. The method of any one of claims 31-35, wherein the radiopharmaceutical is administered at a dose of about 6 MBq.
37. The method of any one of claims 31-35, wherein the radiopharmaceutical is administered at a dose of about 8 MBq.
38. The method of any one of claims 31-37, wherein the radiopharmaceutical is administered about every 4 to 8 weeks.
39. The method of claim 38, wherein the radiopharmaceutical is administered about every 6 to 8 weeks.
40. The method of claim 39, wherein the radiopharmaceutical is administered about every 6 weeks.
41. The method of claim 39, wherein the radiopharmaceutical is administered about every 8 weeks.
42. The method of any one of claims 31-38, wherein the dose of the radiopharmaceutical is administered to the subject about every 4 to 8 weeks for 4 to 6 cycles.
43. The method of claim 42, wherein the dose of the compound of formula (I) is administered to the subject about every 6 to 8 weeks for 4 to 6 cycles.
44. The method of claim 42, wherein the dose of radiopharmaceutical is administered to the subject about every 4 to 8 weeks for 4 cycles.
45. The method of claim 44, wherein the dose of the compound of formula (I) is administered to the subject about every 6 to 8 weeks for 4 cycles.
46. The method of claim 45, wherein the dose of the compound of formula (I) is administered to the subject about every 6 weeks for 4 cycles.
47. The method of claim 45, wherein the dose of the compound of formula (I) is administered to the subject about every 8 weeks for 4 cycles.

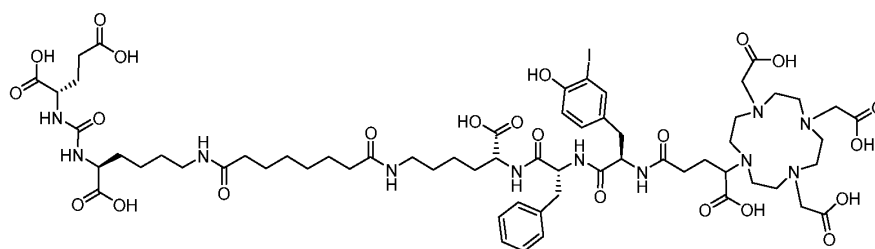
48. The method of any one of claims 31-38, wherein the dose of radiopharmaceutical is administered to the subject about every 4 to 8 weeks for 6 cycles.
49. The method of claim 48, wherein the dose of the compound of formula (I) is administered to the subject about every 6 to 8 weeks for 6 cycles.
50. The method of claim 49, wherein the dose of the compound of formula (I) is administered to the subject about every 6 weeks for 6 cycles.
51. The method of any one of claims 31-50, wherein the subject has received prior treatment with at least one of a radiopharmaceutical or an androgen receptor pathway inhibitor (ARPI).
52. The method of any one of claims 31-51, wherein the PSMA-expressing cancer has been determined to be resistant to one or more of chemotherapeutic treatment, radiopharmaceuticals, and ARPIs.
53. The method of claim 51, wherein the subject did not respond to the prior treatment, or the PSMA-expressing cancer progressed after administration of the prior treatment.
54. The method of any one of claims 1-53, wherein the subject has not previously experienced a Grade ≥ 2 xerostomia adverse event, or the subject does not suffer from a Grade ≥ 2 xerostomia.
55. The method of any one of claims 1-54, wherein the subject receives xerostomia mitigation concurrently.
56. A method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a compound of formula (I), (II), or (IV):



(I)



(II)

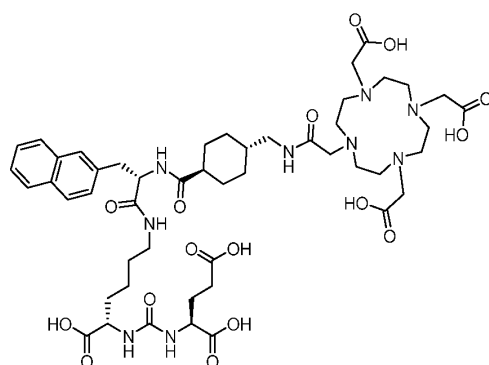


(IV)

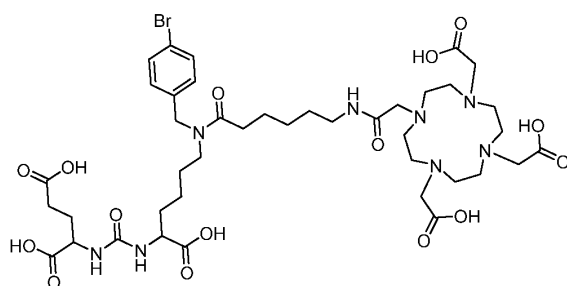
wherein:

- the compound of formula (I), (II), or (IV) is radiolabeled with an alpha-emitting radionuclide,
- the radiolabeled compound of formula (I), (II), or (IV) is administered at a dose from about 6 MBq to about 14 MBq, and
- the subject has received prior chemotherapeutic treatment.

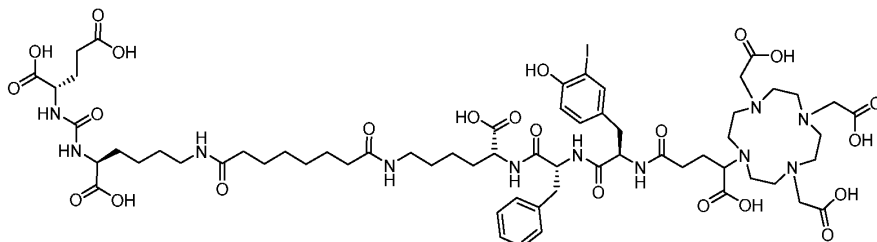
57. A method of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a compound of formula (I), (II), or (IV):



(I)



(II)



(IV)

wherein the glutamic acid and the lysine adjacent to the urea are in the L-configuration, or

5

10

wherein:

the compound of formula (I), (II), or (IV) is radiolabeled with an alpha-emitting radionuclide,

the radiolabeled compound of formula (I), (II), or (IV) is administered at a dose from about 6 MBq to about 14 MBq, and

15

the subject has not received prior chemotherapeutic treatment.

58. The method of claim 56 or 57, wherein the alpha-emitting radionuclide is selected from the group consisting of ^{225}Ac , ^{211}At , ^{213}Bi , ^{212}Bi , ^{212}Pb , ^{223}Ra , ^{224}Ra , ^{149}Tb , and ^{227}Th .

59. The method of any one of claims 56-58, wherein the dose of formula (I), (II), or (IV) is about 6 MBq, about 8 MBq, about 9 MBq, about 10 MBq, about 11 MBq, about 12 MBq, about 13 MBq, or about 14 MBq.

5

60. The method of claim 58, wherein the alpha-emitting radionuclide is ^{225}Ac .

61. The method of claim 60, wherein the radiolabeled compound of formula (I) is administered at a dose from about 8 MBq to about 10 MBq.

10

62. The method of claim 60, wherein the radiolabeled compound of formula (II) is administered at a dose from about 6 MBq to about 14 MBq.

63. The method of claim 60, wherein the radiolabeled compound of formula (IV) is administered at a dose from about 6 MBq to about 14 MBq.

15

64. The method of any one of claims 56-63, wherein the dose of the compound of formula (I), (II), or (IV) is administered to the subject about every 4 to 8 weeks.

65. The method of any one of claims 56-64, wherein the dose of the compound of formula (I), (II), or (IV) is administered to the subject about every 6 to 8 weeks.

20

66. The method of claim 65, wherein the dose of the compound of formula (I), (II), or (IV) is administered to the subject about every 6 weeks.

25

67. The method of claim 65, wherein the dose of the compound of formula (I), (II), or (IV) is administered to the subject about every 8 weeks.

68. The method of any one of claims 56-63, wherein the dose of the compound of formula (I), (II), or (IV) is administered to the subject about every 4 to 8 weeks for 4 to 6 cycles.

30

69. The method of claim 68, wherein the dose of the compound of formula (I), (II), or (IV) is administered to the subject about every 6 to 8 weeks for 4 to 6 cycles.

35

70. The method of claim 68, wherein the dose of the compound of formula (I), (II), or (IV) is administered to the subject about every 4 to 8 weeks for 4 cycles.

71. The method of claim 69, wherein the dose of the compound of formula (I), (II), or (IV) is administered to the subject about every 6 to 8 weeks for 4 cycles.
- 5 72. The method of claim 71, wherein the dose of the compound of formula (I), (II), or (IV) is administered to the subject about every 6 weeks for 4 cycles.
73. The method of claim 71, wherein the dose of the compound of formula (I), (II), or (IV) is administered to the subject about every 8 weeks for 4 cycles.
- 10 74. The method of any one of claims 56-63, wherein the dose of the compound of formula (I), (II), or (IV) is administered to the subject about every 4 to 8 weeks for 6 cycles.
75. The method of claim 74, wherein the dose of the compound of formula (I), (II), or (IV) is administered to the subject about every 6 to 8 weeks for 6 cycles.
- 15 76. The method of claim 75, wherein the dose of the compound of formula (I), (II), or (IV) is administered to the subject about every 6 weeks for 6 cycles.
- 20 77. The method of any one of claims 56-76, wherein the PSMA-expressing cancer is prostate cancer.
78. The method of claim 77, wherein the prostate cancer is metastatic prostate cancer.
- 25 79. The method of claim 78, wherein the metastatic prostate cancer is metastatic castration resistant prostate cancer (mCRPC).
80. The method of claim 79, wherein the subject is documented as having a high tumor burden.
- 30 81. The method of any one of claims 56-80, wherein the prior chemotherapeutic treatment comprises administration of taxane.
82. The method of any one of claims 56-81, wherein the subject has received prior treatment with a beta-minus-emitting radiopharmaceutical.
- 35

83. The method of claim 82, wherein the beta-minus-emitting radiopharmaceutical is a ¹⁷⁷Lu-PSMA targeting agent.

84. The method of claim 83, wherein the ¹⁷⁷Lu-PSMA targeting agent is ¹⁷⁷Lu-PSMA-
5 617 or ¹⁷⁷Lu-PSMA I&T.

85. The method of any one of claims 56-84, wherein the subject has received prior treatment with an androgen receptor pathway inhibitor (ARPI).

10 86. The method of any one of claims 56-85, wherein the PSMA-expressing cancer has been determined to be resistant to one or more of chemotherapeutic treatment, beta-minus-emitting radiopharmaceuticals, and ARPIs.

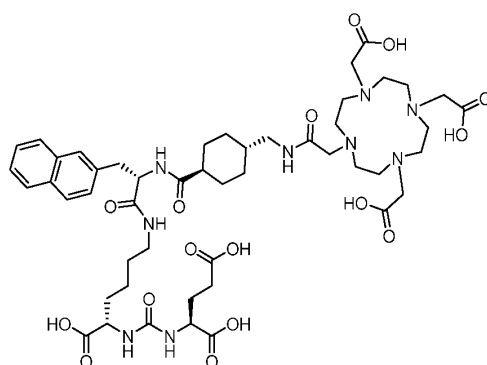
15 87. The method of any one of claims 56 and 58-86, wherein the subject has received prior treatment with a taxane-based chemotherapy, a beta-minus-emitting radiopharmaceutical, and an ARPI.

88. The method of claim 87, wherein the beta-minus-emitting radiopharmaceutical is a [¹⁷⁷Lu]Lu-PSMA targeted radiopharmaceutical.

20 89. The method of claim 88, wherein the PSMA-expressing cancer progressed while the subject was being treated with the [¹⁷⁷Lu]Lu-PSMA targeted radiopharmaceutical or the PSMA-expressing cancer recurred after the subject was treated with the [¹⁷⁷Lu]Lu-PSMA targeted radiopharmaceutical.

25 90. The method of any one of claims 56 and 57-89, wherein the subject did not respond to the prior chemotherapeutic treatment, or the PSMA-expressing cancer progressed after administration of the prior chemotherapeutic treatment.

30 91. A method of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical at a dose of from about 8 MBq to about 10 MBq, wherein the radiopharmaceutical is a compound of formula (I):

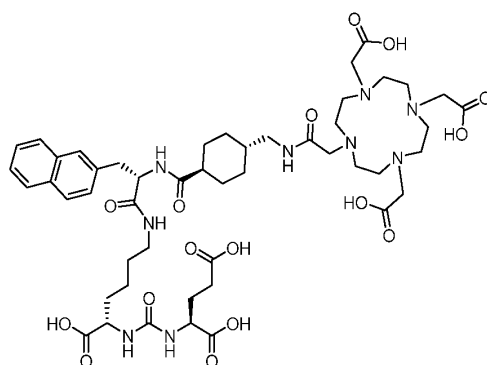


(I),

wherein the compound of formula (I) is radiolabeled with ^{225}Ac , and wherein the subject has received prior chemotherapeutic treatment.

5

92. A method of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical at a dose of 8 MBq to about 10 MBq, wherein the radiopharmaceutical is a compound of formula (I):



(I),

wherein the compound of formula (I) is radiolabeled with ^{225}Ac , and wherein the subject has not received prior chemotherapeutic treatment.

10

93. The method of claim 91 or 92, wherein the prostate cancer is metastatic prostate cancer.

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94. The method of claim 93, wherein the metastatic prostate cancer is metastatic castration resistant prostate cancer (mCRPC).

95. The method of claim 94, wherein the subject is documented as having heavily pretreated mCRPC.

20

96. The method of claim 94 or 95, wherein the subject is documented as having a high tumor burden.

97. The method of any one of claims 91-96, wherein the prior chemotherapeutic
5 treatment comprises administration of taxane.

98. The method of any one of claims 91-97, wherein the radiopharmaceutical is administered about every 4 to 8 weeks.

10 99. The method of claim 98, wherein the radiopharmaceutical is administered about every 6 to 8 weeks.

100. The method of claim 99, wherein the radiopharmaceutical is administered about every 6 weeks.

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101. The method of claim 99, wherein the radiopharmaceutical is administered about every 8 weeks.

102. The method of any one of claims 91-97, wherein the dose of the radiopharmaceutical
20 is administered to the subject about every 4 to 8 weeks for 4 to 6 cycles.

103. The method of claim 102, wherein the dose of the compound of formula (I) is administered to the subject about every 6 to 8 weeks for 4 to 6 cycles.

25 104. The method of claim 102, wherein the dose of radiopharmaceutical is administered to the subject about every 4 to 8 weeks for 4 cycles.

105. The method of claim 102, wherein the dose of the compound of formula (I) is administered to the subject about every 6 to 8 weeks for 4 cycles.

30

106. The method of claim 105, wherein the dose of the compound of formula (I) is administered to the subject about every 6 weeks for 4 cycles.

107. The method of claim 105, wherein the dose of the compound of formula (I) is
35 administered to the subject about every 8 weeks for 4 cycles.

108. The method of any one of claims 91-97, wherein the dose of radiopharmaceutical is administered to the subject about every 4 to 8 weeks for 6 cycles.

109. The method of claim 108, wherein the dose of the compound of formula (I) is
5 administered to the subject about every 6 to 8 weeks for 6 cycles.

110. The method of claim 109, wherein the dose of the compound of formula (I) is administered to the subject about every 6 weeks for 6 cycles.

10 111. The method of claim 103, wherein the dose of the compound of formula (I) is administered to the subject about every 8 weeks for 4 to 6 cycles.

112. The method of any one of claims 91-111, wherein the subject has received prior treatment with at least one of a radiopharmaceutical and an androgen receptor pathway
15 inhibitor (ARPI).

113. The method of any one of claims 91-112, wherein the prostate cancer has been determined to be resistant to one or more of chemotherapeutic treatment, radiopharmaceuticals, and ARPIs.

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114. The method of claim 112, wherein the subject did not respond to the prior treatment, or the prostate cancer progressed after administration of the prior treatment.

115. The method of any one of claims 91-114, wherein the subject has not previously
25 experienced a Grade ≥ 2 xerostomia adverse event, or the subject does not suffer from a Grade ≥ 2 xerostomia.

116. The method of any one of claims 91-114, wherein the subject receives xerostomia mitigation concurrently.

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