

PSMA-TARGETED RADIOPHARMACEUTICALS FOR TREATMENT OF CANCER

BACKGROUND

As a transmembrane glycoprotein, prostate-specific membrane antigen (PSMA) is
5 significantly overexpressed in high grade and advanced stage prostate cancer, thereby making it
an attractive target for diagnostic and therapeutic approaches.

PSMA has also become one of the most promising molecular targets in nuclear medicine.
Various PSMA-targeted radiopharmaceuticals, e.g., radioligand imaging and radioligand
therapy, have been developed and transferred to clinical applications. Among them, ^{225}Ac -
10 labeled PSMA ligands are widely considered to exert better efficacy in treating prostate cancers
due to alpha emission's higher energy, shorter range, and stronger killing effect on tumor cells,
as compared to beta emitters such as ^{177}Lu . However, there are certain toxicities and side effects
associated with the ^{225}Ac -labeled PSMA ligands. For example, xerostomia (or severe dry
mouth) has been the predominant side effect of ^{225}Ac -PSMA ligands in clinical studies, which
15 can have adverse impact on the use of ^{225}Ac -PSMA ligands.

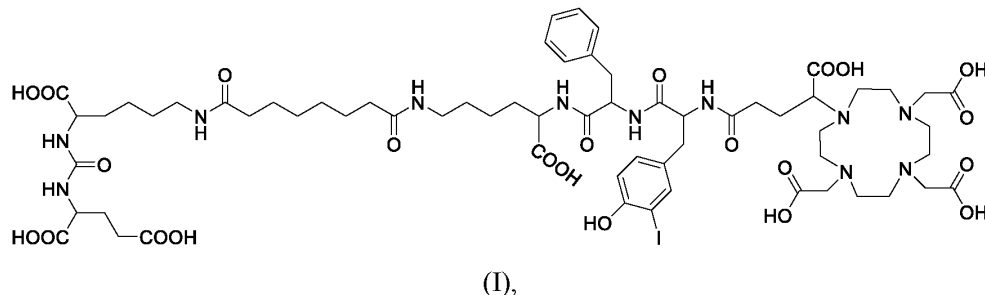
Therefore, there is a need for improved treatment of PSMA-expressing cancers without the
above significant side effects.

SUMMARY

20 The present disclosure encompasses the insight that ^{225}Ac -PSMA ligands, e.g., ^{225}Ac -
PSMA-I&T, at certain dosing regimen may provide a less toxic therapy with improved efficacy.
Radioactive decay can cause direct physical damage (such as single or double-stranded DNA
breaks) or indirect damage (such as by-stander or crossfire effects) to the biomolecules that
constitute a cell. Drugs that deliver radionuclides to cancer cells, i.e., radiopharmaceuticals or
25 radioconjugates, provide a mechanism to generate DNA damage with anti-cancer therapeutic
effect. The present disclosure provides use of ^{225}Ac -radioconjugate, targeting PSMA positive
tumors and using actinium-225 to target cancer cells, at certain specific dosing regimen to treat
or ameliorate cancer, e.g., prostate cancer.

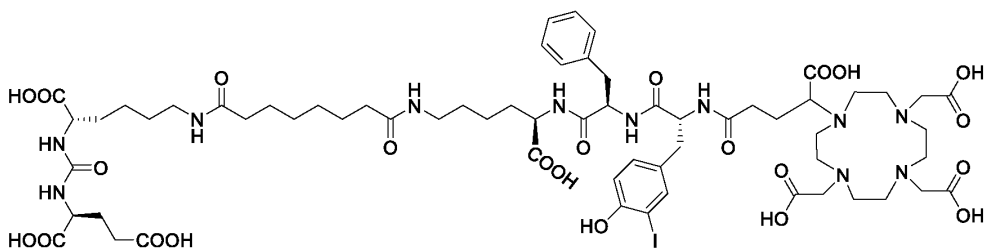
More specifically, provided are methods for treating a patient having cancer expressing
30 PSMA, wherein the method comprises administering to the patient in need thereof a
therapeutically effective amount of an ^{225}Ac -radioconjugate,

wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, a pharmaceutically acceptable salt thereof, or a prodrug thereof:



5 wherein the ^{225}Ac -radioconjugate is administered at a dosage of about 50 kBq/kg to about 75 kBq/kg of body weight of said patient on a dosing schedule of every 4-6 weeks.

In some embodiments, said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure, i.e., ^{225}Ac -PSMA-I&T:



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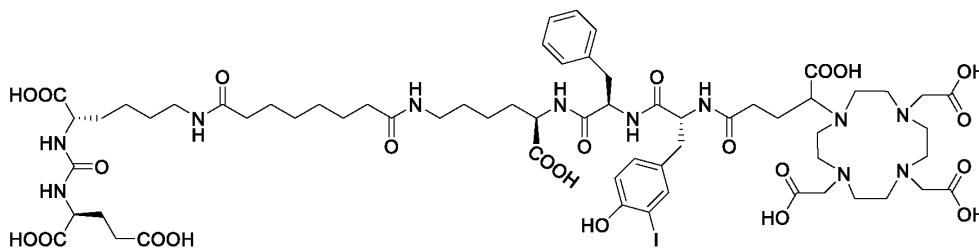
In some embodiments, said ^{225}Ac -radioconjugate is administered at a dosage of 50-75 kBq/kg of body weight of said patient.

In some embodiments, said ^{225}Ac -radioconjugate is administered on a dosing schedule of every 4 or 6 weeks.

15 In some embodiments, said ^{225}Ac -radioconjugate is administered at a dosage of 50 kBq/kg of body weight of said patient on a dosing schedule of every 4 weeks, or a dosage of 75 kBq/kg of body weight of said patient on a dosing schedule of every 6 weeks.

In some embodiments, said ^{225}Ac -radioconjugate is administered at least 4 cycles to said patient.

20 In some embodiments, said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



wherein said ^{225}Ac -radioconjugate is administered at a dosage of 50 kBq/kg of body weight of said patient on a dosing schedule of every 4 weeks, or a dosage of 75 kBq/kg of body weight of said patient on a dosing schedule of every 6 weeks.

5 In some embodiments, said administering results in an absorbed dose of at least 10 Gy per cycle in a tumor of said patient.

In some embodiments, said administering results in a cumulative absorbed dose of at least 30 Gy in a tumor of said patient.

10 In some embodiments, said administering results in an absorbed dose of at most 25 Gy per cycle in the salivary gland of said patient.

In some embodiments, said administering results in a cumulative absorbed dose of at most 100 Gy in the salivary gland of said patient.

15 In some embodiments, the PSMA expressing cancer is selected from the group consisting of prostate cancer, breast cancer, colorectal cancer, renal cell cancer, bladder cancer, testicular cancer, neuroendocrine cancer, and brain tumor. In certain embodiments, the PSMA expressing cancer is prostate cancer, e.g., metastatic castration-resistant prostate cancer (mCRPC).

BRIEF DESCRIPTION OF THE DRAWINGS

20 FIG. 1 is a spider plot showing preliminary Prostate Specific Antigen (PSA) change in Arm 1 as described in Example 6.

FIG. 2 is a spider plot showing preliminary Prostate Specific Antigen (PSA) change in Arm 2 as described in Example 6.

FIG. 3 is a spider plot showing preliminary Prostate Specific Antigen (PSA) change in Arm 3 as described in Example 6.

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DETAILED DESCRIPTION

The present disclosure relates to use of ^{225}Ac -radioconjugate, e.g., ^{225}Ac -PSMA-I&T, at certain dosing regimen for treating PSMA expressing cancer without significant toxicities or side effects associated with ^{225}Ac .

5 Radio-labelled targeting moieties (also known as radiopharmaceuticals or radioconjugates) are designed to target a protein or receptor (e.g., PSMA) that is upregulated in a disease state and/or specific to diseased cells (e.g., tumor cells) to deliver a radioactive payload to damage and kill cells of interest.

^{225}Ac -PSMA-I&T has been used in clinical studies for treating advanced metastatic
10 castration-resistant prostate cancer (mCRPC), yet major side effects such as xerostomia were observed in patients. Xerostomia can be a life-threatening event. Administration of ^{225}Ac -PSMA-I&T at certain dosing regimen, e.g., a lower dose and on a more frequent schedule, may result in an improved benefit/risk profile for patients with fewer adverse events attributable to salivary gland toxicity, which can lead to fewer discontinuations, dosing interruptions and dose
15 reductions due to xerostomia or dry mouth. The improved safety profile may enable delivery of a greater number of cycles which will translate to an improved long-term outcome with respect to progression free survival and overall survival in patients who have been previously treated with a PSMA targeting, beta emitting radiopharmaceutical.

 A dosing regimen that entails more frequent ^{225}Ac -PSMA-I&T administration at lower
20 dose levels provides the theoretic benefit of higher cumulative radiation dose to the target tissue/tumor lesion while limiting toxicities secondary to non-specific binding (e.g., salivary glands) of the radiopharmaceutical. The main reason for using multiple low dose treatments (or so-called “dose fractionation”) is to take advantage of the difference between early-responding and late-responding tissues. The radiation effect on early-responding tissue can be reduced by
25 prolonging the treatment time and dose fractionation (e.g., hypofractionated dose). The radiation effect on late-responding tissues will not be changed significantly if the total cumulative dose is not changed.

 By using ^{225}Ac -PSMA-I&T at certain dosing regimen, e.g., a dosage of about 50 kBq/kg to about 75 kBq/kg of body weight of said patient on a dosing schedule of every 4-6 weeks, the
30 method disclosed herein may decrease the absorbed dose at each administration to the salivary glands resulting in a decreased incidence of xerostomia.

Definitions

Chemical Terms

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

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

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

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

30 *Other terms*

As used herein, the term “about” or “approximately” refers to a $\pm 10\%$ variation from the recited quantitative value (and includes the recited quantitative value itself) unless otherwise indicated or inferred from the context. For example, unless otherwise stated or inferred from the context, a dose of about 75 kBq/kg indicates a dose range of $75 \pm 10\%$ kBq/kg, i.e., from 67.5 kBq/kg to 82.5 kBq/kg, inclusive.

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

The term “cancer” refers to any cancer caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, and lymphomas.

A “solid tumor cancer” is a cancer comprising an abnormal mass of tissue, e.g., sarcomas, carcinomas, and lymphomas. A “hematological cancer” or “liquid cancer,” as used interchangeably herein, is a cancer present in a body fluid, e.g., lymphomas and leukemias.

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

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

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

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

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

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

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

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

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

A “pharmaceutically acceptable excipient,” as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving
30 the active compound) and having the properties of being nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings,

compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluent), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, radioprotectants, sorbents, suspending or dispersing agents, sweeteners, or waters of hydration. Exemplary excipients include, but are not limited to: ascorbic acid, histidine, 5 phosphate buffer, butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, 10 povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

The term “pharmaceutically acceptable salt,” as use herein, represents those salts of the 15 compounds described here that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, or allergic response. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P.H. Stahl and 20 C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting the free base group with a suitable organic acid.

Compounds may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or 25 organic acids or the salts may, in the case of acidic forms of compounds, be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases are well-known in the art, such as hydrochloric, sulphuric, hydrobromic, acetic, lactic, citric, or tartaric acids for forming acid 30 addition salts, and potassium hydroxide, sodium hydroxide, ammonium hydroxide, caffeine,

various amines for forming basic salts. Methods for preparation of the appropriate salts are well-established in the art.

Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, 5 cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, 10 propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, among others. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, and 15 ethylamine.

The term “radiopharmaceutical” or “radioconjugate,” as used herein, refers to any compound or conjugate that includes a radioisotope or radionuclide, such as the radioisotope or radionuclide described herein.

The term “prodrug,” as used herein, refers to a pharmacologically inactive compound or 20 medication that is administered in its inactive form, and it is converted into a pharmacologically active drug inside the body through metabolism or other chemical reactions.

As used herein, and as well understood in the art, “to treat” a condition or “treatment” of the condition (e.g., the conditions described herein such as cancer) is an approach for obtaining beneficial or desired results, such as clinical results. Beneficial or desired results can include, 25 but are not limited to, alleviation or amelioration of one or more symptoms or conditions; diminishment of extent of disease, disorder, or condition; stabilized (i.e., not worsening) state of disease, disorder, or condition; preventing spread of disease, disorder, or condition; delay or slowing the progress of the disease, disorder, or condition; amelioration or palliation of the disease, disorder, or condition; and remission (whether partial or total), whether detectable or 30 undetectable. In the context of cancer treatment, “ameliorating” may include, for example, reducing incidence of metastases, reducing tumor volume, reducing tumor vascularization and/or

reducing the rate of tumor growth. “Palliating” a disease, disorder, or condition means that the extent and/or undesirable clinical manifestations of the disease, disorder, or condition are lessened and/or time course of the progression is slowed or lengthened, as compared to the extent or time course in the absence of treatment.

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Subjects

In the methods disclosed herein, the ^{225}Ac -radioconjugate is administered to a patient having PSMA-expressing cancer or at risk of developing such cancer.

In some embodiments, the patient may have been diagnosed with cancer. The cancer
10 may be a primary cancer or a metastatic cancer. The patient may have any stage of cancer, e.g., stage I, stage II, stage III, or stage IV with or without lymph node involvement and with or without metastases. Provided methods may prevent or reduce further growth of the cancer and/or otherwise ameliorate the cancer (e.g., prevent or reduce metastases). In some
15 embodiments, the patient does not have cancer but has been determined to be at risk of developing PSMA-expressing cancer, e.g., because of the presence of one or more risk factors such as environmental exposure, presence of one or more genetic mutations or variants, family history, etc.

In some embodiments, the PSMA expressing cancer is selected from the group consisting of prostate cancer, breast cancer, colorectal cancer, renal cell cancer, bladder cancer, testicular
20 cancer, neuroendocrine cancer, and brain tumor.

In some embodiments, the cancer is prostate cancer, e.g., metastatic castration-resistant prostate cancer (mCRPC).

Administration and dosage

25 *Effective or therapeutically effective doses*

In some embodiments, the ^{225}Ac -radioconjugate, or a pharmaceutical composition comprising the same, as disclosed herein is administered to a subject in a manner (e.g., dosing amount and timing) sufficient to cure or at least partially arrest the symptoms of the disorder and its complications. In the context of a single therapy (a “monotherapy”), an amount adequate to
30 accomplish this purpose is defined as a “therapeutically effective amount,” an amount of a compound sufficient to substantially improve at least one symptom associated with the disease or

a medical condition. The “therapeutically effective amount” typically varies depending on the therapeutic. For known therapeutic agents, the relevant therapeutically effective amounts may be known to or readily determined by those of skill in the art.

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

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

Single or multiple administrations of an ^{225}Ac -radioconjugate or a composition (e.g., a pharmaceutical composition comprising a therapeutic agent or an ^{225}Ac -radioconjugate) can be carried out with dose levels and pattern being selected by the treating physician. The dose and administration schedule can be determined and adjusted based on the severity of the disease or condition in the subject, which may be monitored throughout the course of treatment according to the methods commonly practiced by clinicians or those described herein.

In some embodiments, the ^{225}Ac -radioconjugate is administered in a single dose. In some embodiments, the ^{225}Ac -radioconjugate is administered more than once, i.e., multiple doses.

When the ^{225}Ac -radioconjugate is administered more than once, the dose of each administration may be the same or different.

Pharmaceutical compositions comprising an ^{225}Ac -radioconjugate can be formulated for use in accordance with disclosed methods and systems in a variety of drug delivery systems.

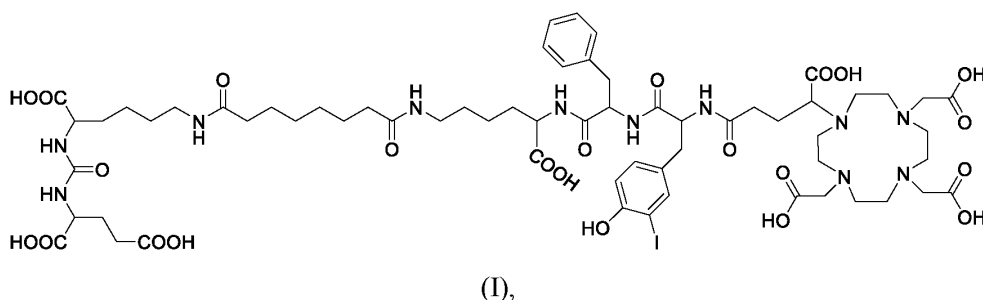
- 5 One or more physiologically acceptable excipients or carriers can also be included in the composition for proper formulation. Examples of suitable formulations are found in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Philadelphia, PA, 17th ed., 1985. For a brief review of methods for drug delivery, see, e.g., Langer (*Science* 249:1527-1533, 1990).

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Administration of ^{225}Ac -radioconjugate

The present disclosure provides methods for treating a patient having cancer expressing PSMA. The method comprises administering to the patient in need thereof a therapeutically effective amount of an ^{225}Ac -radioconjugate,

- 15 wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, a pharmaceutically acceptable salt thereof, or a prodrug thereof:



- 20 wherein the ^{225}Ac -radioconjugate is administered at a dosage of about 50 kBq/kg to about 75 kBq/kg of body weight of said patient on a dosing schedule of every 4-6 weeks.

- As set forth above, a dose of about 75 kBq/kg indicates a dose range of $75 \pm 10\%$ kBq/kg, i.e., from 67.5 kBq/kg to 82.5 kBq/kg, inclusive. Similarly, a dose of about 50 kBq/kg indicates a dose range of $50 \pm 10\%$ kBq/kg, i.e., from 45 kBq/kg to 55 kBq/kg, inclusive. Thus, the ^{225}Ac -radioconjugate can be administered at a dosage of 45 kBq/kg, 46 kBq/kg, 47 kBq/kg, 48 kBq/kg, 49 kBq/kg, 50 kBq/kg, 51 kBq/kg, 52 kBq/kg, 53 kBq/kg, 54 kBq/kg, 55 kBq/kg, 56 kBq/kg, 57 kBq/kg, 58 kBq/kg, 59 kBq/kg, 60 kBq/kg, 61 kBq/kg, 62 kBq/kg, 63 kBq/kg, 64 kBq/kg, 65 kBq/kg, 66 kBq/kg, 67 kBq/kg, 68 kBq/kg, 69 kBq/kg, 70 kBq/kg, 71 kBq/kg, 72 kBq/kg, 73

kBq/kg, 74 kBq/kg, 75 kBq/kg, 76 kBq/kg, 77 kBq/kg, 78 kBq/kg, 79 kBq/kg, 80 kBq/kg, 81 kBq/kg, or 82 kBq/kg, or any dosage therebetween.

In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 74 to 76 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 72 to 77 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 70 to 80 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 68 to 82 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 65 to 85 kBq/kg of body weight of a patient.

In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 65 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 67 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 69 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 71 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 73 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 75 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 77 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 79 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 81 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 83 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 85 kBq/kg of body weight of a patient.

In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 50 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 45-55 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 40-60 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 50 kBq/kg of body weight of a patient Q4W. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 45-55 kBq/kg of body weight of a patient Q4W. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 40-60 kBq/kg of body weight of a patient Q4W.

In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 75 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 70-80 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 65-85

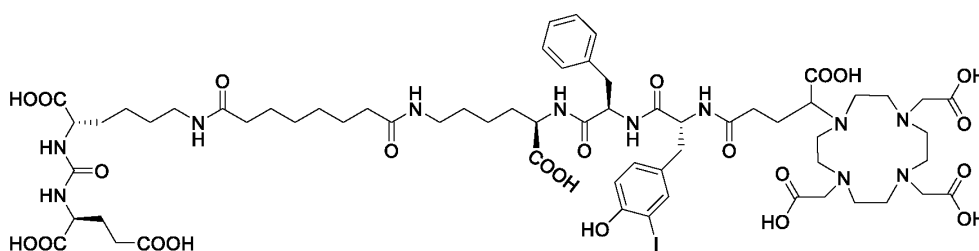
kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 75 kBq/kg of body weight of a patient Q6W. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 70-80 kBq/kg of body weight of a patient Q6W. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 65-85 kBq/kg of body weight of a patient Q6W.

5 In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 100 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 95-105 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 90-110 kBq/kg of body weight of a patient. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is about 100 kBq/kg of body weight of a patient Q8W. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 95-105 kBq/kg of body weight of a patient Q8W. In some embodiments, a dosage of a ^{225}Ac -radioconjugate is 90-110 kBq/kg of body weight of a patient Q8W.

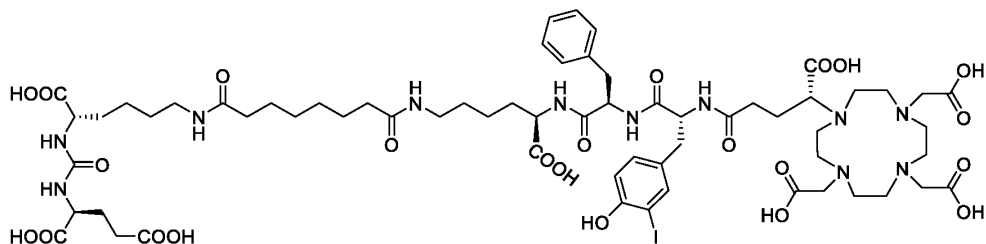
As used herein, the term “cycle” refers to a period of treatment optionally followed by a period of rest. Cycles may be repeated on a regular schedule. In some embodiments, a cycle is 4-8 weeks. In some embodiments, a cycle is 4-6 weeks. In some embodiments, a cycle is about 4 weeks. In some embodiments, a cycle is about 5 weeks. In some embodiments, a cycle is about 6 weeks. In some embodiments, a cycle is about 7 weeks. In some embodiments, a cycle is about 8 weeks. The ^{225}Ac -radioconjugate can be administered on a dosing schedule of every 4-6 weeks, e.g., every 4 weeks, every 5 weeks, or every 6 weeks.

Compounds of Formula I include all their stereoisomers (e.g., diastereomers or enantiomers) and prodrugs (e.g., an ester prodrug, an amide prodrug, or a phosphate prodrug).

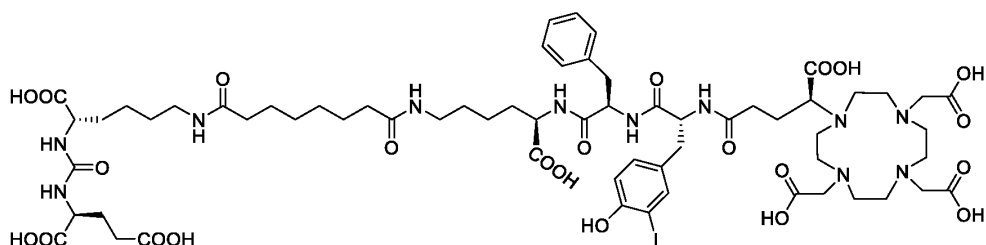
In some embodiments, said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure, i.e., ^{225}Ac -PSMA-I&T:



25 In certain embodiments, said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure, i.e., PSMA-I&T in (*R*)-enantiomeric form with respect to the stereocenter on the carbon adjacent to the DOTA:



In certain embodiments, said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure, i.e., PSMA-I&T in (*S*)-enantiomeric form with respect to the stereocenter on the carbon adjacent to the DOTA:



In some embodiments, said ^{225}Ac -radioconjugate is administered at a dosage of 50-75 kBq/kg of body weight (inclusive) of said patient on a dosing schedule of every 4 or 6 weeks.

In some embodiments, said ^{225}Ac -radioconjugate is administered at a dosage of 50 kBq/kg of body weight of said patient on a dosing schedule of every 4 weeks, or a dosage of 75 kBq/kg of body weight of said patient on a dosing schedule of every 6 weeks.

The ^{225}Ac -radioconjugate can be administered for multiple cycles (e.g., 2 cycles, 3 cycles, 4 cycles, 5 cycles, 6 cycles, or more) with each cycle being 4-6 weeks long.

In some embodiments, said ^{225}Ac -radioconjugate is administered at least 4 cycles to said patient. For example, said ^{225}Ac -radioconjugate is administered at a dosage of 50 kBq/kg of body weight of said patient on a dosing schedule of every 4 weeks for at least 4 cycles (e.g., 4 cycles, 5 cycles, or 6 cycles). For example, said ^{225}Ac -radioconjugate is administered at a dosage of 75 kBq/kg of body weight of said patient on a dosing schedule of every 6 weeks for at least 4 cycles (e.g., 4 cycles, 5 cycles, or 6 cycles).

In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 7-9 MBq. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 7-9 MBq. In some

embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 7-9 MBq at Q6W. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of about 8 MBq. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of about 8 MBq at Q6W. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 7-9 MBq per cycle.

- 5 In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of about 8 MBq per cycle. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 7-9 MBq per cycle, wherein a cycle is 6 weeks. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of about 8 MBq per cycle, wherein a cycle is 6 weeks.

- In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 9-11 MBq.
- 10 In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 9-11 MBq. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 9-11 MBq at Q6W. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of about 10 MBq. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of about 10 MBq at Q6W. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 9-11 MBq
- 15 per cycle. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of about 10 MBq per cycle. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 9-11 MBq per cycle, wherein a cycle is about 6 weeks. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of about 10 MBq per cycle, wherein a cycle is about 6 weeks.

- 20 In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 11-13 MBq. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 11-13 MBq. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 11-13 MBq at Q6W. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of about 12 MBq. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of about 12
- 25 MBq at Q6W. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 11-13 MBq per cycle. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of about 12 MBq per cycle. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of 11-13 MBq per cycle, wherein a cycle is about 6 weeks. In some embodiments, an ^{225}Ac -radioconjugate is administered at a dosage of about 12 MBq per cycle, wherein a cycle is
- 30 about 6 weeks.

In some embodiments, an ^{225}Ac -radioconjugate is administered for at least 4 cycles of treatment, at a dosage of about 12 MBq per cycle for cycles 1 and 2, and at a dosage of about 8 MBq per cycle for cycles 3 and 4. In some embodiments, an ^{225}Ac -radioconjugate is administered for at least 4 cycles of treatment, at a dosage of about 12 MBq at Q6W for cycles 1 and 2, and at a dosage of about 8 MBq at Q6W for cycles 3 and 4. In some embodiments, an ^{225}Ac -radioconjugate is administered for at least 4 cycles of treatment, at a dosage of about 12 MBq per cycle for cycles 1 and 2, and at a dosage of about 8 MBq per cycle for cycles 3 and 4, wherein a cycle is about 6 weeks. In some embodiments, an ^{225}Ac -radioconjugate is administered for at least 4 cycles of treatment, at a dosage of about 12 MBq at Q6W for cycles 1 and 2, and at a dosage of about 8 MBq at Q6W for cycles 3 and 4, wherein a cycle is about 6 weeks. In some embodiments, said administering results in an absorbed dose of at least 10 Gy per cycle (e.g., at least 12 Gy per cycle, at least 14 Gy per cycle, at least 16 Gy per cycle, at least 18 Gy per cycle, or at least 20 Gy per cycle) in a tumor of said patient.

In some embodiments, said administering results in a cumulative absorbed dose of at least 30 Gy (e.g., at least 35 Gy, at least 40 Gy, at least 45 Gy, at least 50 Gy, at least 55 Gy, at least 60 Gy, at least 65 Gy, at least 70 Gy, at least 75 Gy, or at least 80 Gy) in a tumor of said patient.

In some embodiments, said administering results in an absorbed dose of at most 25 Gy per cycle (e.g., at most 20 Gy per cycle, at most 15 Gy per cycle, or at most 10 Gy per cycle) in the salivary gland of said patient.

In some embodiments, said administering results in a cumulative absorbed dose of at most 100 Gy (e.g., at most 95 Gy, at most 90 Gy, at most 85 Gy, at most 80 Gy, at most 75 Gy, at most 70 Gy, at most 65 Gy, at most 60 Gy, at most 55 Gy, or at most 50 Gy) in the salivary gland of said patient.

Formulations

Pharmaceutical compositions may be formulated for parenteral, intranasal, topical, oral, or local administration, such as by a transdermal means, for prophylactic and/or therapeutic treatment. Pharmaceutical compositions can be administered parenterally (e.g., by intravenous, intramuscular, or subcutaneous injection), or by oral ingestion, or by topical application or intraarticular injection at areas affected by the vascular or cancer condition. Examples of

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

Compositions may be sterilized, e.g., by conventional sterilization techniques, or sterile filtered. Aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the preparations typically will be between 3 and 11, more preferably between 5 and 9 or between 6 and 8, and most preferably between 6 and 7, such as 6 to 6.5.

Effects

A therapeutic effect refers to the desirable or beneficial effect of a medication or medical treatment in treating a disease, condition, or symptom. It is the intended effect that a medication or treatment is designed to produce in order to improve the health or well-being of a patient.

The therapeutic effect of a medication, or a pharmaceutical composition as disclosed herein, may include relieving symptoms, treating or curing a disease, preventing a condition from getting worse, or improving overall health and quality of life.

The therapeutic effect for cancer patients depends on the type of cancer and the stage of the disease. The goal of cancer treatment is to eliminate or control the cancer cells while

minimizing harm to normal, healthy cells in the body. In some embodiments, the therapeutic effect comprises a decrease in tumor volume, a stable tumor volume, or a reduced rate of increase in tumor volume. In some embodiments, the therapeutic effect comprises a decreased incidence of recurrence or metastasis.

5 In some embodiments, a therapeutic effect of a method of the present disclosure is reduction in tumor volume. In some embodiments, tumor volume is reduced by about 5% as compared to volume prior to treatment with a method of the present disclosure. In some
10 embodiments, tumor volume is reduced by about 10% as compared to volume prior to treatment with a method of the present disclosure. In some embodiments, tumor volume is reduced by about 20% as compared to volume prior to treatment with a method of the present disclosure. In
15 some embodiments, tumor volume is reduced by about 30% as compared to volume prior to treatment with a method of the present disclosure. In some embodiments, tumor volume is reduced by about 40% as compared to volume prior to treatment with a method of the present
20 disclosure. In some embodiments, tumor volume is reduced by about 50% as compared to volume prior to treatment with a method of the present disclosure. In some embodiments, tumor volume is reduced by about 60% as compared to volume prior to treatment with a method of the
25 present disclosure. In some embodiments, tumor volume is reduced by about 70% as compared to volume prior to treatment with a method of the present disclosure. In some embodiments, tumor volume is reduced by about 80% as compared to volume prior to treatment with a method
30 of the present disclosure. In some embodiments, tumor volume is reduced by about 90% as compared to volume prior to treatment with a method of the present disclosure.

In some embodiments, tumor volume is reduced by about 5-10% as compared to volume prior to treatment with a method of the present disclosure. In some embodiments, tumor volume is reduced by about 10-30% as compared to volume prior to treatment with a method of the
25 present disclosure. In some embodiments, tumor volume is reduced by about 30-50% as compared to volume prior to treatment with a method of the present disclosure. In some
30 embodiments, tumor volume is reduced by about 50-70% as compared to volume prior to treatment with a method of the present disclosure. In some embodiments, tumor volume is reduced by about 70-90% as compared to volume prior to treatment with a method of the present
disclosure. In some embodiments, tumor volume is reduced by about 90-100% as compared to volume prior to treatment with a method of the present disclosure.

In some embodiments, tumor volume is measured about 1 week after treatment with a method of the present disclosure. In some embodiments, tumor volume is measured about 4 weeks after treatment with a method of the present disclosure. In some embodiments, tumor volume is measured about 3 months after treatment with a method of the present disclosure. In some embodiments, tumor volume is measured about 6 months after treatment with a method of the present disclosure. In some embodiments, tumor volume is measured about 1 year after treatment with a method of the present disclosure. In some embodiments, tumor volume is measured about 2 years after treatment with a method of the present disclosure. In some embodiments, tumor volume is measured about 3 years after treatment with a method of the present disclosure.

In some embodiments, a patient having received treatment from a method of the present disclosure does not develop one or more metastases after about 1 week after treatment. In some embodiments, a patient having received treatment from a method of the present disclosure does not develop one or more metastases after about 4 weeks after treatment. In some embodiments, a patient having received treatment from a method of the present disclosure does not develop one or more metastases after about 3 months after treatment. In some embodiments, a patient having received treatment from a method of the present disclosure does not develop one or more metastases after about 6 months after treatment. In some embodiments, a patient having received treatment from a method of the present disclosure does not develop one or more metastases after about 1 year after treatment. In some embodiments, a patient having received treatment from a method of the present disclosure does not develop one or more metastases after about 2 years after treatment. In some embodiments, a patient having received treatment from a method of the present disclosure does not develop one or more metastases after about 3 years after treatment.

In some embodiments, xerostomia can be measured using a clinical grading scale. For example, radiation-induced xerostomia can be classified into 3 grades using CTCAE Version 3.0 modified criteria:

Grade	Characteristic
1, Mild	Symptomatic (dry or thick saliva) without significant dietary alteration
2, Moderate	Symptomatic or significant oral intake alteration (e.g. copious water, other lubricants, diet limited to purees and/or soft moist foods)

3, Severe	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or parenteral nutrition indicated
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In some embodiments, a patient having received treatment using a method of the present disclosure comprising administering to the patient a radiopharmaceutical experience a lower grade radiation-induced xerostomia as compared to a patient receiving treatment using a higher dose of the radiopharmaceutical. In some embodiments, a patient having received treatment using a method of the present disclosure comprising administering to the patient a radiopharmaceutical do not experience radiation-induced xerostomia. In some embodiments, a patient having received treatment using a method of the present disclosure comprising administering to the patient a radiopharmaceutical experience grade 1 radiation-induced xerostomia. In some embodiments, a patient having received treatment using a method of the present disclosure comprising administering to the patient a radiopharmaceutical experience grade 2 radiation-induced xerostomia.

Other agents

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

By “antiproliferative” or “antiproliferative agent,” as used interchangeably herein, is meant any anticancer agent, including those antiproliferative agents listed in Table 1, any of which can be used in combination with a radiopharmaceutical (e.g., ²²⁵Ac-radioconjugate) disclosed herein to treat a condition or disorder. Antiproliferative agents also include organo-platinum derivatives, naphtoquinone and benzoquinone derivatives, chrysophanic acid and anthroquinone derivatives thereof.

By “immunoregulatory agent” or “immunomodulatory agent,” as used interchangeably herein, is meant any immuno-modulator, including those listed in Table 1, any of which can be used in combination with a radiopharmaceutical provided herein.

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

Table 1		
Alkylating agents	Busulfan dacarbazine ifosfamide hexamethylmelamine thiotepa dacarbazine lomustine cyclophosphamide	Chlorambucil procarbazine altretamine estramustine phosphate mechlorethamine streptozocin temozolomide Semustine
Platinum agents	spiroplatin tetraplatin ormaplatin iproplatin picoplatin oxaliplatin carboplatin	lobaplatin (Aeterna) satraplatin (Johnson Matthey) BBR-3464 (Hoffmann-La Roche) Miriplatin AP-5280 (Access) cisplatin

Table 1		
Antimetabolites	azacytidine Floxuridine 2-chlorodeoxyadenosine 6-mercaptopurine 6-thioguanine cytarabine 2-fluorodeoxy cytidine methotrexate tomudex fludarabine raltitrexed	trimetrexate deoxycoformycin pentostatin hydroxyurea decitabine (SuperGen) clofarabine (Bioenvision) irofulven (MGI Pharma) DMDC (Hoffmann-La Roche) ethynylcytidine (Taiho) gemcitabine capecitabine
Topoisomerase inhibitors	amsacrine epirubicin etoposide teniposide or mitoxantrone 7-ethyl-10-hydroxy-camptothecin dexrazoxanet (TopoTarget) pixantrone (Novuspharma) rebeccamycin analogue (Exelixis) BBR-3576 (Novuspharma) rubitecan (SuperGen) irinotecan (CPT-11) topotecan	exatecan mesylate (Daiichi) quinamed (ChemGenex) gimatecan (Sigma-Tau) diflomotecan (Beaufour-Ipsen) TAS-103 (Taiho) elsamitrucin (Spectrum) Edotecarin Cositecan Belotecan hydroxycamptothecin (SN-38)
Antitumor antibiotics	valrubicin therarubicin idarubicin rubidazone plicamycin porfiromycin mitoxantrone (novantrone) amonafide	azonafide anthrapyrazole oxantrazole losoxantrone Sabarubicin Epirubicin mitoxantrone doxorubicin

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

Table 1		
Histone acetyltransferase inhibitors	tacedinaline (Pfizer) SAHA (Aton Pharma) MS-275 (Schering AG)	pivaloyloxymethyl butyrate (Titan) depsipeptide (Fujisawa)
Metalloproteinase inhibitors	Neovastat (Aeterna Laboratories) marimastat (British Biotech)	CMT-3 (CollaGenex) BMS-275291 (Celltech)
Ribonucleoside reductase inhibitors	gallium maltolate (Titan) triapine (Vion)	tezacitabine (Aventis) didox (Molecules for Health)
TNF alpha agonists/antagonists	virulizin (Lorus Therapeutics) CDC-394 (Celgene)	revimid (Celgene)
Endothelin A receptor antagonist	atrasentan (Abbott) ZD-4054 (AstraZeneca)	YM-598 (Yamanouchi)
Retinoic acid receptor agonists	fenretinide (Johnson & Johnson) LGD-1550 (Ligand)	alitretinoin (Ligand)
Immuno-modulators	interferon oncophage (Antigenics) GMK (Progenics) adenocarcinoma vaccine (Biomira) CTP-37 (AVI BioPharma) IRX-2 (Immuno-Rx) PEP-005 (Peplin Biotech) synchrovax vaccines (CTL Immuno) melanoma vaccine (CTL Immuno) p21 RAS vaccine (GemVax) MAGE-A3 (GSK) nivolumab (BMS) abatacept (BMS) pembrolizumab (Merck)	dexosome therapy (Anosys) pentrix (Australian Cancer Technology) ISF-154 (Tragen) cancer vaccine (Intercell) norelin (Biostar) BLP-25 (Biomira) MGV (Progenics) β -alethine (Dovetail) CLL therapy (Vasogen) Ipilimumab (BMS), CM-10 (cCam Biotherapeutics) atezolizumab (Genentech)

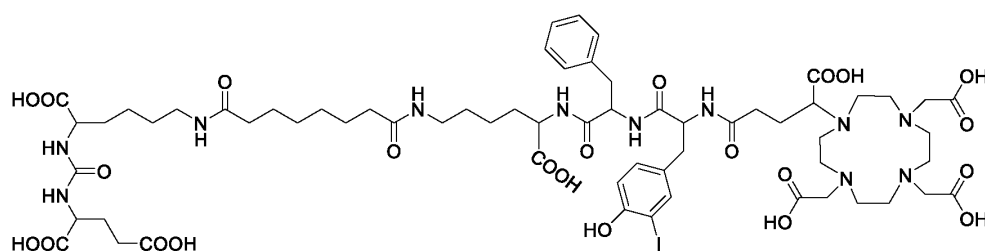
Table 1		
Hormonal and antihormonal agents	estrogens conjugated estrogens ethinyl estradiol chlortrianisen idenestrol hydroxyprogesterone caproate medroxyprogesterone testosterone testosterone propionate; fluoxymesterone methyltestosterone diethylstilbestrol megestrol bicalutamide flutamide nilutamide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

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

Enumerated Embodiments

1. A method for treating a patient having cancer expressing Prostate Specific Membrane Antigen (PSMA), wherein the method comprises administering to the patient in need thereof a therapeutically effective amount of an ^{225}Ac -radioconjugate,

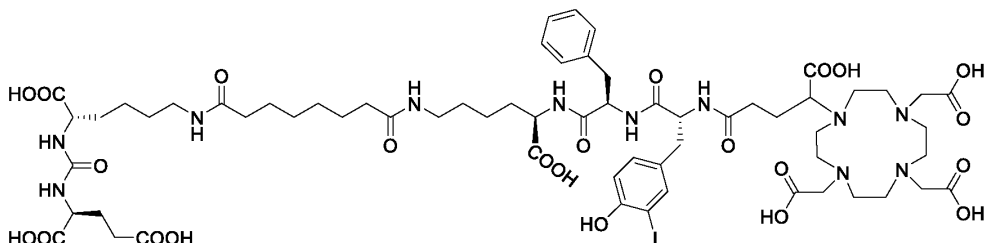
5 wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, or a prodrug thereof:



(I),

10 wherein the ^{225}Ac -radioconjugate is administered at a dosage of about 75 kBq/kg of body weight of said patient on a dosing schedule of every 4-6 weeks.

2. The method of embodiment 1, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



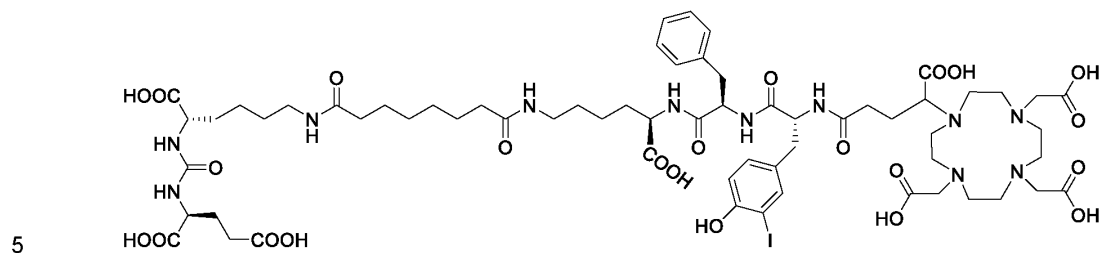
15 3. The method of embodiment 1 or 2, wherein said ^{225}Ac -radioconjugate is administered at a dosage of 75 kBq/kg of body weight of said patient.

4. The method of any one of the preceding embodiments, wherein said ^{225}Ac -radioconjugate is administered on a dosing schedule of every 4 or 6 weeks.

20 5. The method of any one of the preceding embodiments, wherein said ^{225}Ac -radioconjugate is administered at a dosage of 75 kBq/kg of body weight of said patient on a dosing schedule of every 6 weeks.

6. The method of any one of the preceding embodiments, wherein said ^{225}Ac -radioconjugate is administered at least 4 cycles to said patient.

7. The method of any one of the preceding embodiments, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



wherein said ^{225}Ac -radioconjugate is administered at a dosage of 75 kBq/kg of body weight of said patient on a dosing schedule of every 6 weeks.

8. The method of any one of the preceding embodiments, wherein said administering results in an absorbed dose of at least 10 Gy per cycle in a tumor of said patient.

10 9. The method of any one of the preceding embodiments, wherein said administering results in a cumulative absorbed dose of at least 30 Gy in a tumor of said patient.

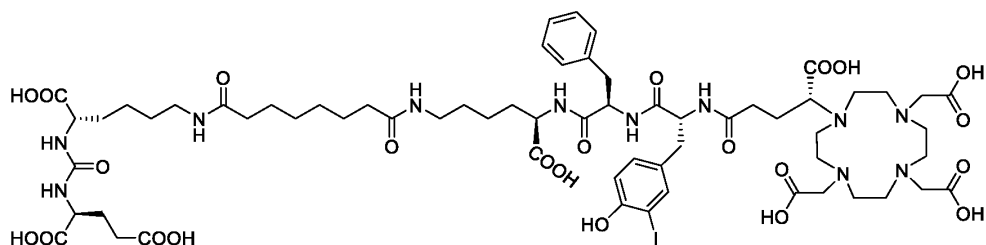
10. The method of any one of the preceding embodiments, wherein said administering results in an absorbed dose of at most 25 Gy per cycle in the salivary gland of said patient.

15 11. The method of any one of the preceding embodiments, wherein said administering results in a cumulative absorbed dose of at most 100 Gy in the salivary gland of said patient.

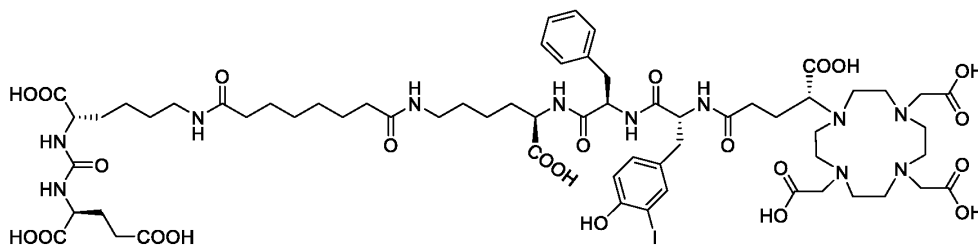
12. The method of any one of the preceding embodiments, wherein the PSMA expressing cancer is prostate cancer.

13. The method of any one of the preceding embodiments, further comprising administering an antiproliferative agent, a radiation sensitizer, or an immunomodulatory agent.

20 14. The method of any one of the preceding embodiments, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



15. The method of any one of the preceding embodiments, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



5 wherein said ^{225}Ac -radioconjugate is administered at a dosage of 75 kBq/kg of body weight of said patient on a dosing schedule of every 6 weeks.

Examples

Materials:

The compounds used in the methods described herein are made from commercially available chemicals and/or from compounds described in the chemical literature, following standard organic synthesis techniques known to those skilled in this art. “Commercially available chemicals” can be obtained from standard commercial sources including, but not limited to, ABX advanced biochemical compounds GmbH (Radeberg, Germany), Acros Organics (Pittsburgh, Pa.), Apin Chemicals Ltd. (Milton Park, U.K.), Avidity Science (U.S.A.), Avocado Research (Lancashire, U.K.), BDH, Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chem Service Inc. (West Chester, Pa.), Crescent Chemical Co. (Hauppauge, N.Y.), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, N.Y.), Fisher Scientific Co. (Pittsburgh, Pa.), Frontier Scientific (Logan, Utah), ICN Biomedicals, Inc. (Costa Mesa, Calif.), ITM (Munich, Germany), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, N.H.), Parish Chemical Co. (Orem, Utah), Pfaltz & Bauer, Inc. (Waterbury, Conn.), Polyorganix (Houston, Tex.), Pierce Chemical Co. (Rockford, Ill.), Sigma-Aldrich (U.S.A.), Spectrum Quality Product, Inc. (New Brunswick, N.J.), TCI America (Portland, Oreg.), Trans World Chemicals, Inc. (Rockville, Md.), VWR (Radnor, Pa., USA), Wako Chemicals USA, Inc. (Richmond, Va.), and Wuxi-Apptech Inc. (Shanghai, China).

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Example 1. Synthesis of Radiopharmaceuticals Comprising Compound of Formula I

Compounds of Formula I are small molecule antagonists targeting PSMA, which can be radiolabeled with a radionuclide such as Actinium-225 (^{225}Ac) to form radionuclide-chelated radiopharmaceuticals. The synthesis of compound of Formula I, or corresponding radionuclide-chelated radiopharmaceuticals, can be referred to the following documents: Weineisen M, et al. *EJNMMI Research*, 2014, 4:63; Weineisen M, et al. *J Nucl Med* 2015, 56:1169–1176; US 11,129,912 B1; and WO 2018/108287 A1.

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Example 2. Preparation of Pharmaceutical Compositions Comprising ^{225}Ac -radioconjugate

Pharmaceutical compositions comprising an ^{225}Ac -radioconjugate of Formula I can be prepared by following or referencing to the protocols set forth below.

1.0 Preparation of 0.001 M HCl Solution: 4.4 μL of concentrated hydrochloric acid (TraceSelect or equivalent) is added into 40 mL of Water (TraceSelect), followed by mixing the solution until completely homogeneous.

2.0 Preparation of 0.05 M HCl Solution: 220 μL of concentrated hydrochloric acid (TraceSelect or equivalent) is added into 40 mL of Water (TraceSelect), followed by mixing the solution until completely homogeneous.

3.0 Preparation of Sodium Acetate – Gentisic Acid Buffer Solution: 0.09–0.11 g of 2,5-dihydroxybenzoic acid (Gentisic acid) is added to a weighing boat using a disposable spatula. The Gentisic acid is quantitatively transferred to a 150 mL Biotainer. 3.9–4.3 g of sodium acetate is transferred to the 150 mL Biotainer. 50 mL of Water (TraceSelect) is added to the Biotainer using an appropriately sized disposable serological pipette. The Biotainer is closed and the resulting solution is swirled until completely homogeneous.

4.0 Preparation of Ascorbate-DTPA Formulation Buffer Solution: 0.0055–0.0065 g of DTPA is transferred to a 150 mL Biotainer. 5.94–6.06 g of sodium ascorbate is transferred to the 150 mL Biotainer. 100 mL of Water (TraceSelect) is added to the Biotainer using an appropriately sized disposable serological pipette. 2.5 mL of 0.05 M hydrochloric acid is added to the biotainer using an appropriately sized disposable serological pipette. The Biotainer is closed and the resulting solution is swirled until completely homogeneous. A pH paper is used to check the pH value of the buffer solution to be 6.0–7.0.

5.0 Preparation of 0.045 M NaOH Solution: 0.06–0.08 g (M1) Sodium Hydroxide Pellets are added to a 50 mL conical tube. The volume of Water (TraceSelect) to add (M2 mL) is calculated using the following equation: $M2 = 1000 \times (M1/1.8)$. M2 mL of Water (TraceSelect) is added to the conical tube using an appropriately sized serological pipette. The solution is mixed until completely homogeneous.

6.0 Reconstitution of Ac-225/Ac-227 Accelerator and Ac-225 Generator Vials: A 1 mL syringe with 21 G 2" needle is used to transfer 0.5 mL of 0.001 M HCl solution to a v-vial containing [Ac-225]. Another 1 mL syringe with 21 G 2" needle is used to transfer 0.5 mL of 0.001 M HCl solution to a v-vial containing [Ac-227]. A minimum of 14 hours is allowed to

elapse before proceeding to the next step. The [Ac-225] vial is assayed, with the radioactivity value being recorded in unit of μCi . The [Ac-227] radioactivity from the appropriate CoA is also recorded in unit of μCi . Reconstitution of Ac-225 and Ac-227 is performed using 0.001 M HCl (1 mL total volume) such that it comprises 0.43 mCi of Ac-225 and 0.035 mCi of Ac-227.

7.0 Preparation of PSMA I&T buffer solution: A 1.0 mL of Sodium Acetate – Gentisic Acid buffer solution is transferred to a precursor vial containing 0.5 mg of PSMA I&T. The concentration of the resulting solution in the precursor vial is determined in unit of $\mu\text{g/mL}$.

The vial is swirled for thirty seconds, inverted several times, until the entire contents are dissolved, and a homogeneous solution is obtained.

8.0 Radiolabeling: The PSMA I&T buffer solution described above is transferred to a 15 mL “reaction” tube containing Ac-225. The contents of the “reaction” tube are gently swirled for 30 seconds to ensure adequate mixing. The “reaction” tube is heated on a thermomixer at 90 °C for 25 minutes. Thereafter, the “reaction” tube is transferred to a lead pig and allowed to sit at room temperature to cool for 5-10 minutes.

9.0 Final Product formation: The entire contents of the “reaction” tube are transferred using a 5 mL syringe to a final product vial labeled as “Ac-225-PSMA-I&T Bulk Product”. The solution is slowly and carefully swirled for 30 seconds to ensure that the solution in the “Ac-225- PSMA-I&T Bulk Product” vial is fully mixed. The “Ac-225- PSMA-I&T Bulk Product” vial is stored in a lead pig labelled “Ac-225- PSMA-I&T Bulk Product Vial” at room temperature for a minimum of 14 hours before use. The “Ac-225- PSMA-I&T Bulk Product” vial is assayed in the dose calibrator. The radioactivity value of the final product is recorded in unit of μCi .

Example 3. Evaluation of the Stability of Compositions

The stability of the pharmaceutical composition is evaluated according to the protocol set forth below.

- 5 The bulk final drug product comprising ^{225}Ac -PSMA-I&T described above is used in a stability test, in a glass or plastic container.

The test sample is evaluated for stability by inverting in a shielded container at the appropriate storage temperature.

The storage location, date and time is recorded corresponding to the batch number.

At least six (6) hours prior to date and time of expiry (at least 72 hours), the test sample is removed for testing from storage location and allowed to reach room temperature for a minimum of 30 minutes. The sample removal date and time are recorded corresponding to the
5 batch number.

The temperature monitoring data is attached to this protocol for the relevant time period of the storage location for the test sample; also, it is verified that there are no temperature excursions.

The stability of the test sample will be evaluated based on the quality attributes shown in
10 Table 2 below.

Table 2. Quality attributes of the stability of pharmaceutical compositions

Quality Attributes	Method
Appearance	Visual inspection
pH	pH indicator strip
Radiochemical purity by TLC	TLC-radiometric detector
Sterility	Direct inoculation
Chemical content	HPLC-UV
Chemical impurities	HPLC-UV

Example 4. Administration of Compositions in Treatment of Cancer

15 The pharmaceutical composition comprising an ^{225}Ac -radioconjugate is administered to patient having PSMA expressing cancer according to the protocols set forth below.

Dose Preparation

Each dose is individually prepared prior to dosing. The dose calibrator used for
20 participant administration measurement should be the same machine that is utilized during the dose calibrator calibration process during study start-up.

Dose is prepared aseptically for administration under site's standard environmental conditions and standard operating procedures (SOPS). The below procedures are followed for preparing for administration: The vial containing the investigational medicinal product (IMP) is

allowed in the lead pig to thaw on the bench at room temperature. Thaw time is estimated to take 1 hour, but sites can use their own judgement when thawing to ensure the IMP has come to room temperature prior to administration.

5 The area of preparation is ensured to be clean prior to dispensing. Prior to donning gloves, operator hands shall be washed or sanitized using an alcohol-based hand sanitizer. Once gloves are donned, it is recommended that they are sprayed with 70% isopropyl alcohol (IPA). The vial septum shall be wiped with a sterile IPA pad. The wiped septum is allowed to dry before piercing the septum.

10 A sterile disposable syringe and needle shall be used to prepare the injection and shall be assembled immediately before preparing the injection. Syringes shall be assembled with needles in a clean environment (or aseptic environment if possible). Aseptic connections shall not be handled directly.

15 Radioactivity concentration of the product at the time of calibration (TOC). TOC is the date and time when the supplied radionuclide corresponds to the stated activity of the radionuclide. After the TOC, the radioactivity is decreased. The radioactivity concentration, and time and date of calibration, are stated on the Certificate of Analysis (CoA). Decay correction factor ^{225}Ac is used to correct for physical decay to the nearest hour.

For ^{225}Ac -PSMA-I&T administration, the actual body weight from the participant's general screening visit shall be used to calculate the ^{225}Ac -PSMA-I&T dose.

20 The estimated volume of ^{225}Ac -PSMA-I&T to be administered to a participant in need thereof is calculated as follows:

Volume (mL) = [Dose Level (kBq/kg) x Body weight in kg] / [Decay Correction Factor ^{225}Ac * Activity Concentration at TOC (kBq/mL)]

25 *Dose Administration*

Administration of the pharmaceutical composition follows the below procedures for administering ^{225}Ac -PSMA-I&T to the participant.

30 The IMP should not be diluted or administered with any other IV fluids, combined with other drugs, or administered through an infusion set used at the same time for any purpose other than the current IMP administration.

The IMP is administered by slow intravenous injection (IV, 2-5 minutes). For ^{225}Ac -PSMA-I&T, the dose to be administered depends on participant weight and study cohort assignment.

5 The injection may be administered via a peripheral vein (preferred) or a central vein. The use of a 3-way stopcock is recommended during injection to ensure intravenous delivery of the products and to ensure proper priming and flushing. After administration, the line will be thoroughly flushed with normal saline to ensure delivery of full dose.

Following administration, the injection line should be removed from the participant and not used for any other procedures. The syringe and all contaminated tubing should be assayed in
10 the same dose calibrator to determine the net dose administered. The volume injected, time of administration, and participant net dose should be recorded.

Example 5. Dosing of ^{225}Ac -PSMA-I&T

Based on the acceptable safety profile associated with ^{177}Lu -PSMA RLT administered
15 Q8W, shorter treatment intervals have been explored. The tolerability and efficacy of ^{177}Lu -PSMA-617 has also been demonstrated with a Q6W dosing schedule. Results of two Phase 2 studies in 30 and 14 patients with mCRPC treated with Lu-PSMA were reported by Hofman and Emmett, respectively. In both studies, patients had been previously treated with second generation anti-androgens (abiraterone and/or enzalutamide) and taxane-based chemotherapy.
20 Hofman reported a PSA50 response in 17 (57%) patients. Findings included high response rates, low toxic effects, and pain reduction. Overall, ^{177}Lu -PSMA-617 treatment was well tolerated with predominantly Grade 1 treatment-related toxicities which were largely self-limiting and easily managed. The most common treatment-related toxic effect was dry mouth which was exclusively reported as Grade 1. The occurrence of treatment-related Grade 3 to 4 hematological
25 toxicity was low (Hofman et al, 2018; Emmett et al, 2019).

In a study of 54 patients, ^{177}Lu -PSMA-617 (7400 MBq) was administered Q4W. This dosing schedule was safe with only two cases of Grade 3 leukocytopenia, one case of Grade 3 anemia, and no Grade 3 thrombocytopenia. A PSA decline of ≥ 50 and $\geq 80\%$ were observed in 58% and 35% of patients, respectively. Median OS was 119 weeks; median PFS was 25 weeks.
30 Patients presenting with any PSA decline had significantly longer PFS (27 vs 15 weeks, $p < 0.0001$) and OS (median survival not reached vs 52 weeks, $p < 0.001$) than patients without any

PSA reduction. It was concluded that an intense ^{177}Lu -PSMA RLT regimen with cycles administered Q4W was well tolerated and provided a favorable response rate, PFS and survival (Rasul et al, 2020).

In another small, retrospective study, ^{177}Lu -PSMA RLT was administered Q4W with a fixed dose (about 7400 MBq). Results showed that the regimen was safe and effective, in terms of producing a significant PSA decrease. A substantial number of patients [almost 60% (N=10)], had a significant PSA decline of more than 50%, which was associated with better OS and PFS. The median overall OS was 1.6 years. It was concluded that a shorter treatment interval may broaden the therapeutic window among mCRPC patients with high volume disease and rapidly rising PSA (Kemppainen et al, 2022).

^{225}Ac -PSMA-I&T Dosing Regimen Justification

The acute toxicities associated with ^{225}Ac -based radiopharmaceuticals can be predominantly hematologic with dose-dependent thrombocytopenia and leukocytopenia that require time for recovery between treatment cycles with some agents (Kratochwil 2020). The hematologic profile of ^{225}Ac -PSMA-I&T and ^{225}Ac -PSMA-617 has been demonstrated through various retrospective studies in which patients were treated with either radiopharmaceutical. In the collective patient experience across these studies, more than 150 patients with mCRPC have been treated at a dose of 100 kBq/kg Q8W. Clinically significant myelosuppression associated with ^{225}Ac -PSMA-I&T and ^{225}Ac -PSMA-617 administered Q8W was generally not observed or was very low and has not been life threatening, suggesting ^{225}Ac -PSMA-I&T may be safely administered at shorter than Q8W dosing frequency (Ling 2022).

Safety, biodistribution, and dosimetry of ^{177}Lu -PSMA-I&T and ^{177}Lu -PSMA-617 were compared in patients with mCRPC (Schuchardt et al, 2022). The effective half-life of ^{177}Lu -PSMA-I&T was determined in whole-body (35 hours), kidneys (33 hours), lacrimal glands (25 hours) and parotid glands (23 hours). The effective half-life of ^{225}Ac -PSMA-I&T is estimated to be ~24 to 38 hours in these organs, by accounting for longer physical decay half-life of ^{225}Ac (9.92 days) compared to Lu-177 (6.7 days). Based on this estimated effective half-life, ^{225}Ac -PSMA-I&T is anticipated to be nearly completely eliminated from the body within four weeks of administration. Thus, accumulation of radiation absorbed dose to these organs is not anticipated upon administration of multiple cycles at Q4W or Q6W dosing frequency. In this study, safety, biodistribution, and dosimetry were found to be comparable between ^{177}Lu -PSMA-I&T and

¹⁷⁷Lu-PSMA-617. Population PK dosimetry model using imaging data of ¹⁷⁷Lu-PSMA-617 in prostate cancer patients has been published by Siebinga et al. (Siebinga 2023). Based on comparable biodistribution between ¹⁷⁷Lu-PSMA-I&T and ¹⁷⁷Lu-PSMA-617 in mCRPC patients, ²²⁵Ac-PSMA-I&T whole-body radioactivity was simulated with the model parameters of ¹⁷⁷Lu-PSMA-617. The results of this simulation also support lack of apparent accumulation of radiation absorbed doses upon administration of multiple cycles at Q4W or Q6W dosing frequency.

²²⁵Ac-PSMA-I&T Weight-Based Dosing Justification

The lower dose per cycle of ²²⁵Ac-PSMA-I&T (²²⁵Ac-PSMA-I&T) may mitigate toxicity without impacting efficacy when administered at similar dose density (e.g., 50 kBq/kg Q4W or 75 kBq/kg Q6W).

Dosimetry estimates for ²²⁵Ac-PSMA-I&T were extrapolated from the ²²⁵Ac-PSMA-617 calculations by Kratochwil (Kratochwil et al, 2017) based on time-activity curves derived from serially obtained ¹⁷⁷Lu-PSMA-617 scans extrapolated to the physical half-life of ²²⁵Ac. Assuming a relative biologic effectiveness of 5, dosimetry estimates of ²²⁵Ac-PSMA-617 revealed mean doses of 0.74 Sv/ MBq for kidneys. In study ²²⁵Ac-PSMA-I&T-202, ²²⁵Ac-PSMA-I&T will be administered at 100 kBq/kg once every eight weeks up to four cycles or 75 kBq/kg once every six weeks up to six cycles and 50 kBq/kg once every four weeks up to nine cycles. Assuming 70 kg body weight of the participant, anticipated cumulative kidney dose is ~23 Gy from ²²⁵Ac-PSMA-I&T administration. In this study, patients with ≥ Grade 2 renal impairment (creatinine clearance < 60 mL/min) are excluded. Additionally, kidney function will be monitored throughout the study and management of potential toxicities while on ²²⁵Ac-PSMA-I&T treatment is provided to ensure participant safety.

The proposed regimens will deliver comparable cumulative dose of ²²⁵Ac-PSMA-I&T with a similar dose intensity and a limit of 450 kBq/kg will not be exceeded in any treatment regimen.

Shorter treatment intervals may broaden the therapeutic window and improve the outcome of RL T, especially among mCRPC patients with high volume disease and rapidly rising PSA.

Of note, another alpha-emitting radiopharmaceutical, radium 223 dichloride (Xofigo) is FDA approved at a dose of 55 kBq/kg administered Q4W for up to six cycles in men with prostate cancer who have bone metastases.

²²⁵Ac-PSMA-I&T Flat Dosing Justification

5 To ensure more consistent drug exposure and minimize variability due to weight differences, flat dosing regimens in the range of 5-12 MBq, administered every 4 or 6 weeks (Q4W or Q6W) will be evaluated in Part B of the study. This approach aims to enhance the reliability of results by reducing the impact of body weight variability, while maintaining exposure levels that align with those achieved by body weight-based dosing.

10 Both Lutathera (Lutetium Lu 177 Dotatate) and Pluvicto (Lutetium Lu 177 Vipivotide Tetraxetan) are approved by the FDA as flat-dose therapies rather than body weight-adjusted doses with following dosing schedules:

- Lutathera is administered at a fixed dose of 7.4 GBq (200 mCi) per infusion, given every eight weeks for a total of four cycles. This fixed dosing approach simplifies administration and has been shown to be effective across a range of patients (Lutathera FDA Multi-Discipline Review and Evaluation 2018).
- Pluvicto is also administered as a flat dose, typically 7.4 GBq (200 mCi) per cycle, every six weeks until disease progression or unacceptable toxicity (Pluvicto FDA Multi-Discipline Review and Evaluation 2018).

20 To determine the appropriate flat dose for ²²⁵Ac-PSMA-I&T, a body weight (BW) distribution assessment was conducted based on baseline BW data from 16 participants. Both Non Compartmental Analysis (NCA) and population pharmacokinetic (popPK) analyses demonstrated that ²²⁵Ac-PSMA-I&T exhibits linear radiolabeled plasma pharmacokinetics, with dose-proportional exposures across tested dose ranges (50 kBq/kg-100 kBq/kg).

25 Furthermore, using the popPK model, simulation of 500 patients per dosing group (BW range from 50-120 kg with median BW of 91 kg) were performed to compare flat doses of ²²⁵Ac-PSMA-I&T with equivalent BW-based doses, ensuring similar exposure levels. The comparison of ²²⁵Ac-PSMA-I&T exposures (AUC₀₋₇₂ and C_{max}) across different dosing approaches showed overlapping simulated exposure at any dose levels and confirming appropriateness of flat based dosing. Table 1 summarizes the exposure (AUC₀₋₇₂) for ²²⁵Ac-PSMA-I&T in the simulated

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population following the flat doses, confirming near-complete overlap with that achieved by the BW-based doses. While flat doses may result in higher exposures in lighter patients and lower exposures in heavier patients compared to BW-based dosing, the overall exposure across the BW range remained in comparable to safe, tolerable dose observed with the highest tested BW-based dose of 100 kBq/kg in the ²²⁵Ac-PSMA-I&T clinical trial.

A high dose of 12 MBq will be administered during the first two cycles, followed by a dose reduction to 8 MBq for the final two cycles. This strategy is supported by literature findings, which show a decrease in tumour uptake across cycles. Specifically, when patients were treated with ¹⁷⁷Lu--PSMA-I&T, a significant decrease in tumour uptake rates during later cycles was identified (compared to cycle 1 uptake decreased to 73%, 50% and 44% in cycles 2, 3 and 4–7, respectively) (Siebinga et al 2024). This approach allows for more precise targeting, delivering the higher dose only when it is likely to be effective, thus enhancing therapeutic efficacy while simultaneously managing and reducing the likelihood of adverse side effects.

Table 1: ²²⁵Ac-PSMA-I&T Exposure in Simulated Population PK Model

AUC ₀₋₇₂ (H·kBq/mL)						
Dosing Group	Doses	BW Group*	Median	Min	Max	SD
Proposed Flat Dosing ARMs	8MBq	BW<91	3.077	1.558	5.709	0.766
		BW>=91	2.641	1.408	5.329	0.663
	10MBq	BW<91	3.94	2.1	7.182	0.987
		BW>=91	3.236	1.675	5.818	0.784
	12MBq	BW<91	4.603	2.357	8.482	1.076
		BW>=91	3.959	1.984	7.065	0.937
*Equivalent BW-based doses	88kBq/kg	BW<91	2.834	1.342	4.821	0.625
		BW>=91	2.922	1.59	5.082	0.672
	110kBq/kg	BW<91	3.37	1.73	6.674	0.837
		BW>=91	3.601	1.819	6.506	0.881
	132kBq/kg	BW<91	4.205	2.415	7.383	0.989
		BW>=91	4.316	1.846	7.469	0.965

* Equivalent doses calculated based on the median body weight of 91 kg from the population BW in the study
PopPK-predicted AUC_{0-72h} (h.kBq/mL) exposure after the first ²²⁵Ac-PSMA-I&T dose in cycle 1 in patients given 88kBq/kg equivalent to 8 MBq, 110 kBq/kg equivalent to 10 MBq, and 132 kBq/kg equivalent to 12 MBq.

In the Phase 3 segment, the dosing regimen selected from the Phase 2 segment for continued study will be based on recommendations from the DSMB, which will review safety, efficacy, and study drug exposure findings from the Phase 2 segment.

5 Example 6. Safety and Efficacy of ²²⁵Ac-PSMA-I&T

²²⁵Ac-PSMA-I&T was tested in an open-label, randomized, multicenter study consisting of a Phase 2 part investigating the safety, tolerability, and antitumor activity of three dosing regimens of ²²⁵Ac-PSMA-I&T with a subsequent Phase 3 part evaluating efficacy of ²²⁵Ac-PSMA-I&T versus standard of care in patients with PSMA-positive mCRPC who have been previously treated with [177Lu]-PSMA-617 or another [177Lu]-PSMA radioligand therapy. In Phase 2, approximately 60 patients (20 per dose regimen) will be randomized (1:1:1) to receive ²²⁵Ac-PSMA-I&T at one of three different dosing regimens:

- Arm 1: 50 kBq/kg ²²⁵Ac-PSMA-I&T IV Q4W (± three days);
- Arm 2: 75 kBq/kg ²²⁵Ac-PSMA-I&T IV Q6W (± five days);
- 15 • Arm 3: 100 kBq/kg ²²⁵Ac-PSMA-I&T IV every eight weeks (Q8W) (± seven days).

Patient Disposition and Prior Treatment

	Arm 1: 50 kBq/kg n (%) N = 3	Arm 2: 75 kBq/kg n (%) N = 2	Arm 3: 100 kBq/kg n (%) N = 2	Overall: n (%) N = 7
Randomized	5	5	5	15
Treated/Safety Population	3 (100.0)	2 (100.0)	2 (100.0)	7 (100.0)
Phase 2 Efficacy- Evaluable Population	2 (66.7)	0	2 (100.0)	4 (57.1)
Currently on Treatment	3 (100.0)	2 (100.0)	2 (100.0)	7 (100.0)
Discontinued Treatment	0	0	0	0

The Safety Analysis Population includes all patients who receive at least one dose of study treatment. Patients will be grouped according to the treatment and dose regimen received.

20 The Phase 2 Efficacy Evaluable Population includes all patients who are randomized, receive at least one dose of study treatment, have a baseline PSA measurement, and have at least one post-baseline PSA measurement or have discontinued early due to disease progression, unacceptable toxicity, or treatment- or disease-related death

Treatment-Emergent Adverse Events (TEAE) is defined as any Adverse Event (AE) that occurs or worsens during the treatment period (after the first dose of ²²⁵Ac-PSMA-I&T and ≤1 month following the last dose of ²²⁵Ac-PSMA-I&T) or AEs that have possible attribution to

²²⁵Ac-PSMA-I&T and occur within 24 months of the last treatment with ²²⁵Ac-PSMA-I&T. Four patients (57.1%) have reported at least one TEAE, one each at the 50-kBq/kg and 75-kBq/kg dose level and two patients at the 100 kBq/kg dose level. Hematologic and non-hematologic AEs are being recorded according to NCI CTCAE.

- 5 TEAEs and serious TEAEs reported by the seven patients are presented by system organ class, preferred term, and severity in Table 2. With the exception of one patient with Grade 3 pelvic pain, there have been no $\geq$ Grade 3 TEAEs reported.

MedDRA System Organ Class MedDRA Preferred Term Worst Severity	Arm 1: 50 kBq/kg (N = 3) n (%) Y	Arm 2: 75 kBq/kg (N = 2) n (%) Y	Arm 3: 100 kBq/kg (N = 2) n (%) Y	Overall (N = 7) n (%) Y
Number of Patients (% of Patients) Number of Events				
Number of patients with at least one TEAE	1 (33.3) 3	1 (50.0) 2	2 (100.0) 5	4 (57.1) 10
Gastrointestinal disorders	0	1 (50.0) 1	2 (100.0) 4	3 (42.9) 5
Nausea	0	0	2 (100.0) 2	2 (28.6) 2
Grade 1	0	0	1 (50.0) 1	1 (14.3) 1
Grade 2	0	0	1 (50.0) 1	1 (14.3) 1
Diarrhoea	0	0	1 (50.0) 1	1 (14.3) 1
Grade 1	0	0	1 (50.0) 1	1 (14.3) 1
Dry mouth	0	1 (50.0) 1	0	1 (14.3) 1
Grade 1	0	0	0	0
Grade 2	0	1 (50.0) 1	0	1 (14.3) 1
Vomiting	0	0	1 (50.0) 1	1 (14.3) 1
Grade 1	0	0	1 (50.0) 1	1 (14.3) 1
General disorders and administration site conditions	1 (33.3) 1	1 (50.0) 1	0	2 (28.6) 2
Fatigue	1 (33.3) 1	1 (50.0) 1	0	2 (28.6) 2
Grade 1	1 (33.3) 1	0	0	1 (14.3) 1
Grade 2	0	1 (50.0) 1	0	1 (14.3) 1
Injury, poisoning and procedural complications	0	0	1 (50.0) 1	1 (14.3) 1
Fall	0	0	1 (50.0) 1	1 (14.3) 1
Grade 1	0	0	1 (50.0) 1	1 (14.3) 1
Reproductive system and breast disorders	1 (33.3) 2	0	0	1 (14.3) 2
Pelvic pain	1 (33.3) 2	0	0	1 (14.3) 2
Grade 1	0 (0.0) 1	0	0	0 (0.0) 1
Grade 2	0	0	0	0
Grade 3	1 (33.3) 1	0	0	1 (14.3) 1

As shown in Fig. 1, Arm 1 received 50 kilobecquerels per kg of bodyweight dosed at every 4 weeks (Q4W). Each line represents the percentage change in individual patient's prostate specific antigen (PSA) serum levels which is measured serially in a four-week interval which is measured serially in a four-week interval. The dotted line represents the 50% reduction threshold (PSA50). This threshold needs to be passed to indicate biochemical response activity. Of the 9 patients represented by the 9 different lines, only one passes through the PSA50 threshold. This indicates preliminary biochemical response activity at this dose and schedule for ²²⁵Ac-PSMA-I&T.

As shown in Fig. 2, Arm 2 received 75 kilobecquerels per kg of bodyweight dosed at every 6 weeks (Q6W). Each line represents the percentage change in individual patient's prostate specific antigen (PSA) serum levels which is measured serially in a four-week interval. The dotted line represents the 50% reduction threshold (PSA50). This threshold needs to be passed to indicate biochemical response activity. Of the 9 patients represented by the 9 different lines, none passes through the PSA50 threshold. This suggests the preliminary lack of biochemical response activity at this dose and schedule for ²²⁵Ac-PSMA-I&T.

As shown in Fig. 3, Arm 3 received 100 kilobecquerels per kg of bodyweight dosed at every 8 weeks (Q8W). Each line represents the percentage change in individual patient's prostate specific antigen (PSA) serum levels which is measured serially in a four-week interval. The dotted line represents the 50% reduction threshold (PSA50). This threshold needs to be passed to indicate biochemical response activity. Of the 9 patients represented by the 9 different lines, two pass through the PSA50 threshold. This indicates preliminary biochemical response activity at this dose and schedule for ²²⁵Ac-PSMA-I&T.

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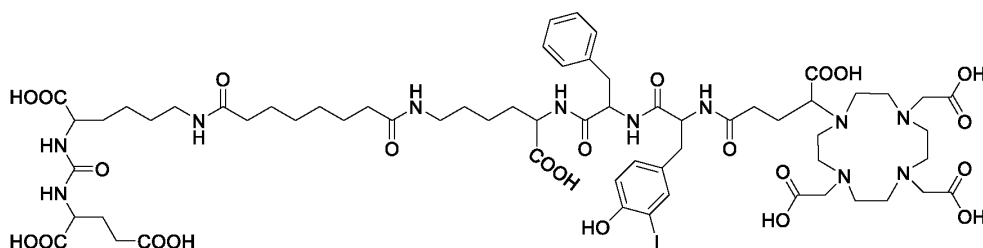
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- 25

OTHER EMBODIMENTS

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

CLAIMS

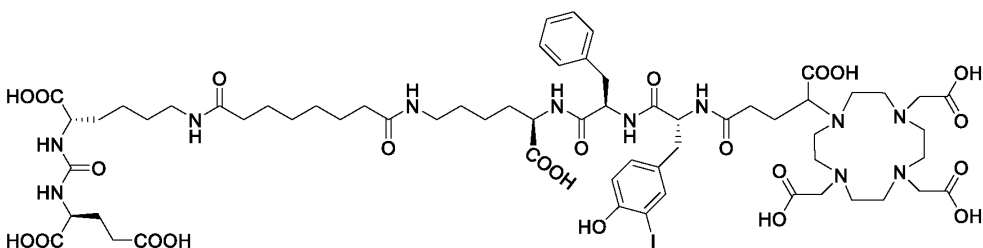
1. A method for treating a patient having cancer expressing Prostate Specific Membrane Antigen (PSMA), wherein the method comprises administering to the patient in need thereof a therapeutically effective amount of an ^{225}Ac -radioconjugate, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, a pharmaceutically acceptable salt thereof, or a prodrug thereof:



(I),

wherein the ^{225}Ac -radioconjugate is administered at a dosage of about 50 kBq/kg to about 75 kBq/kg of body weight of said patient on a dosing schedule of every 4-6 weeks.

2. The method of claim 1, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



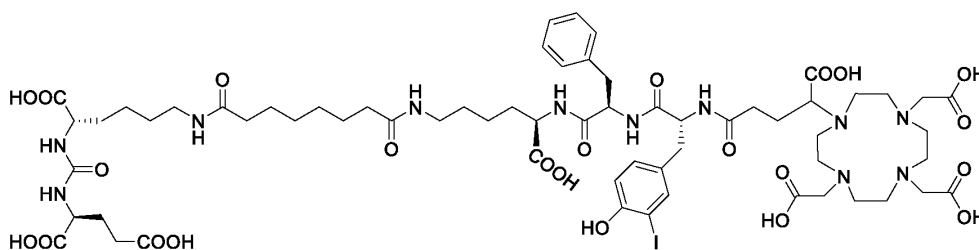
3. The method of claim 1 or 2, wherein said ^{225}Ac -radioconjugate is administered at a dosage of 50-75 kBq/kg (inclusive) of body weight of said patient.

4. The method of any one of the preceding claims, wherein said ^{225}Ac -radioconjugate is administered on a dosing schedule of every 4 or 6 weeks.

5. The method of any one of the preceding claims, wherein said ^{225}Ac -radioconjugate is administered at a dosage of 50 kBq/kg of body weight of said patient on a dosing schedule of every 4 weeks, or a dosage of 75 kBq/kg of body weight of said patient on a dosing schedule of every 6 weeks.

6. The method of any one of the preceding claims, wherein said ^{225}Ac -radioconjugate is administered at least 4 cycles to said patient.

7. The method of any one of the preceding claims, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



wherein said ^{225}Ac -radioconjugate is administered at a dosage of 50 kBq/kg of body weight of said patient on a dosing schedule of every 4 weeks, or a dosage of 75 kBq/kg of body weight of said patient on a dosing schedule of every 6 weeks.

8. The method of any one of the preceding claims, wherein said administering results in an absorbed dose of at least 10 Gy per cycle in a tumor of said patient.

9. The method of any one of the preceding claims, wherein said administering results in a cumulative absorbed dose of at least 30 Gy in a tumor of said patient.

10. The method of any one of the preceding claims, wherein said administering results in an absorbed dose of at most 25 Gy per cycle in the salivary gland of said patient.

11. The method of any one of the preceding claims, wherein said administering results in a cumulative absorbed dose of at most 100 Gy in the salivary gland of said patient.

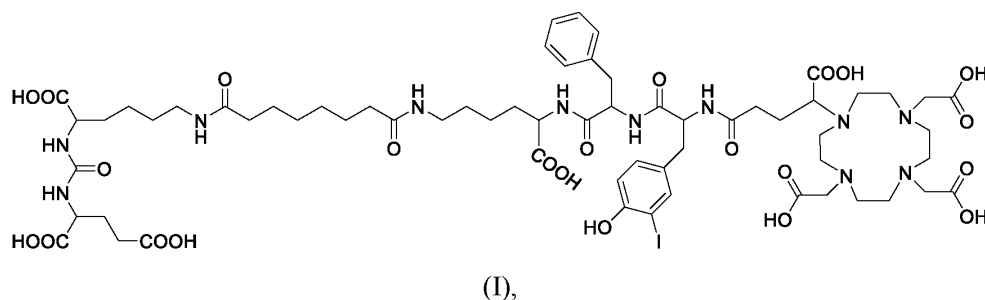
12. The method of any one of the preceding claims, wherein the PSMA expressing cancer is selected from the group consisting of prostate cancer, breast cancer, colorectal cancer, renal cell cancer, bladder cancer, testicular cancer, neuroendocrine cancer, and brain tumor.

13. The method of any one of the preceding claims, wherein the PSMA expressing cancer is prostate cancer.

14. The method of any one of the preceding claims, further comprising administering an antiproliferative agent, a radiation sensitizer, or an immunomodulatory agent.

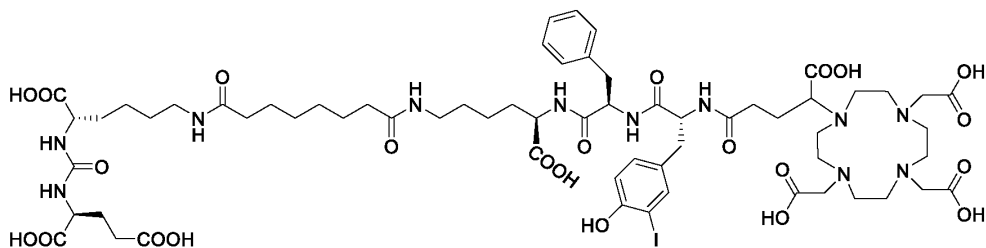
15. A method for treating a patient having cancer expressing Prostate Specific Membrane Antigen (PSMA), wherein the method comprises administering to the patient in need thereof a therapeutically effective amount of an ^{225}Ac -radioconjugate,

wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, a pharmaceutically acceptable salt thereof, or a prodrug thereof:



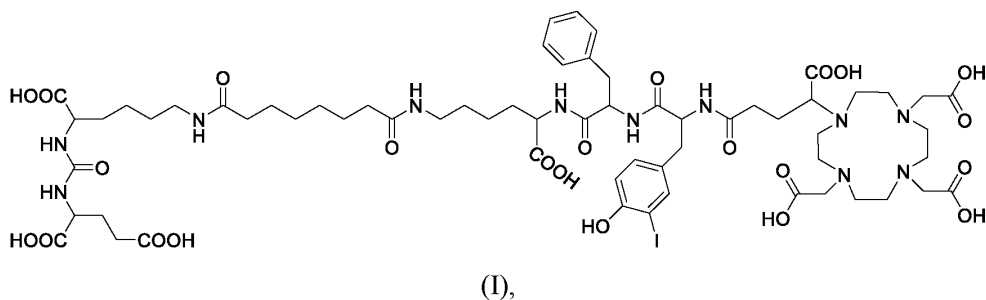
wherein the ^{225}Ac -radioconjugate is administered at a dosage of about 8 MBq at Q6W.

16. The method of claim 15, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



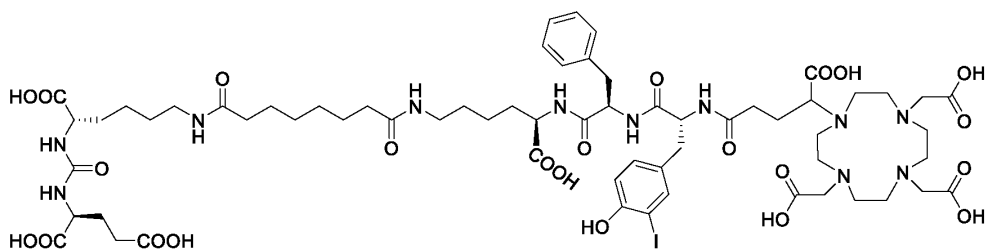
17. A method for treating a patient having cancer expressing Prostate Specific Membrane Antigen (PSMA), wherein the method comprises administering to the patient in need thereof a therapeutically effective amount of an ^{225}Ac -radioconjugate,

wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, a pharmaceutically acceptable salt thereof, or a prodrug thereof:



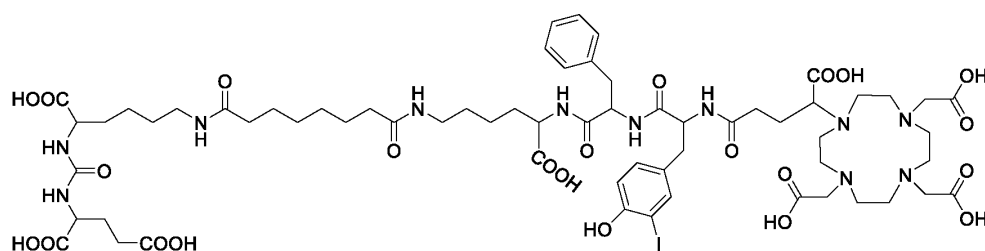
wherein the ^{225}Ac -radioconjugate is administered at a dosage of about 10 MBq at Q6W.

18. The method of claim 17, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



19. A method for treating a patient having cancer expressing Prostate Specific Membrane Antigen (PSMA), wherein the method comprises administering to the patient in need thereof a therapeutically effective amount of an ^{225}Ac -radioconjugate,

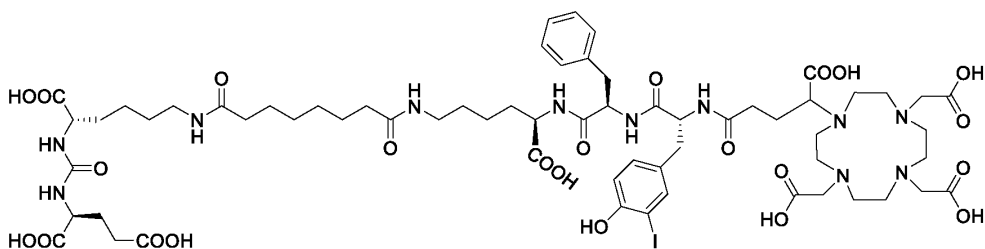
wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, a pharmaceutically acceptable salt thereof, or a prodrug thereof:



(I),

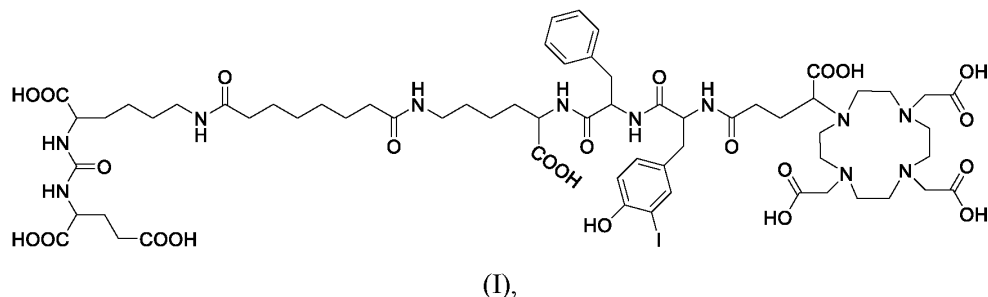
wherein the ^{225}Ac -radioconjugate is administered for at least 4 cycles of treatment,
 at a dosage of about 12 MBq at Q6W for cycles 1 and 2, and
 at a dosage of about 8 MBq at Q6W for cycles 3 and 4,
 wherein a cycle is about 6 weeks.

20. The method of claim 19, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



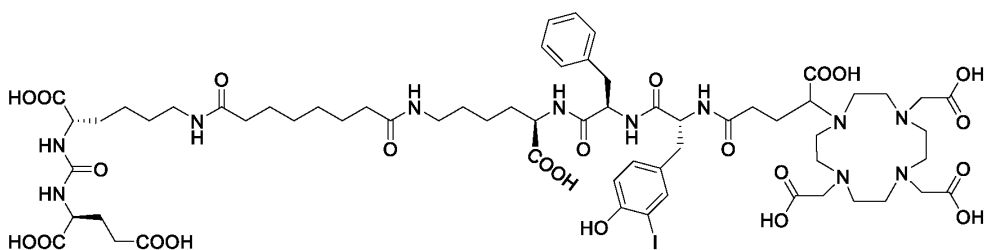
21. A method for treating a patient having cancer expressing Prostate Specific Membrane Antigen (PSMA), wherein the method comprises administering to the patient in need thereof a therapeutically effective amount of an ^{225}Ac -radioconjugate,

wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, a pharmaceutically acceptable salt thereof, or a prodrug thereof:



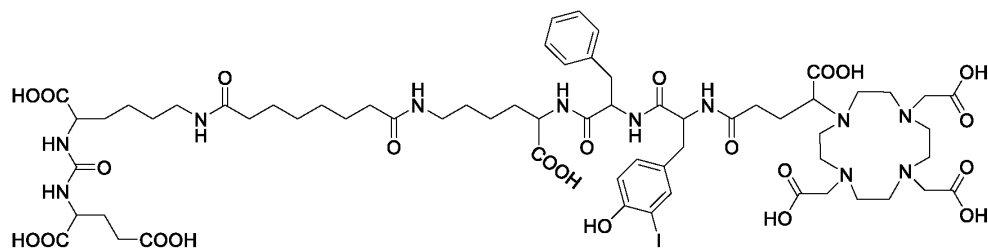
wherein the ^{225}Ac -radioconjugate is administered at a dosage of about 8 MBq per cycle.

22. The method of claim 21, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



23. A method for treating a patient having cancer expressing Prostate Specific Membrane Antigen (PSMA), wherein the method comprises administering to the patient in need thereof a therapeutically effective amount of an ^{225}Ac -radioconjugate,

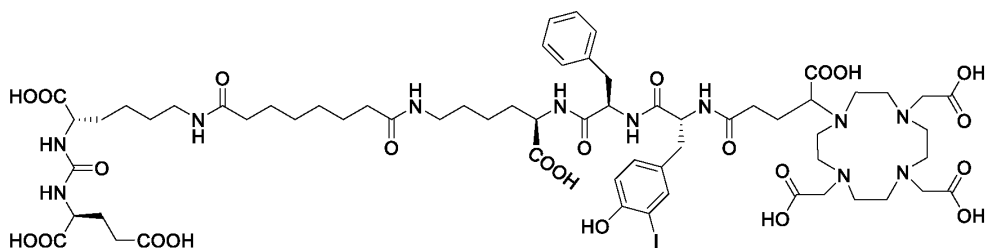
wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, a pharmaceutically acceptable salt thereof, or a prodrug thereof:



(I),

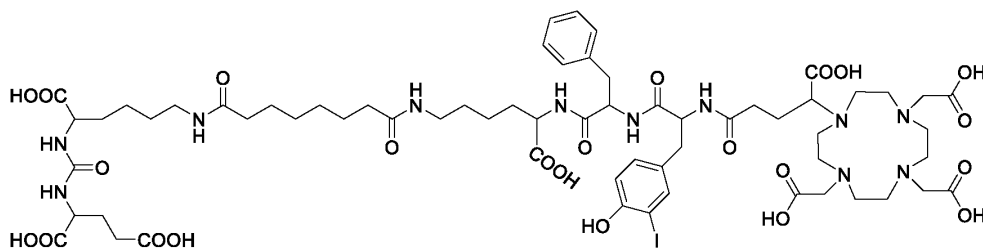
wherein the ^{225}Ac -radioconjugate is administered at a dosage of about 10 MBq per cycle.

24. The method of claim 23, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



25. A method for treating a patient having cancer expressing Prostate Specific Membrane Antigen (PSMA), wherein the method comprises administering to the patient in need thereof a therapeutically effective amount of an ^{225}Ac -radioconjugate,

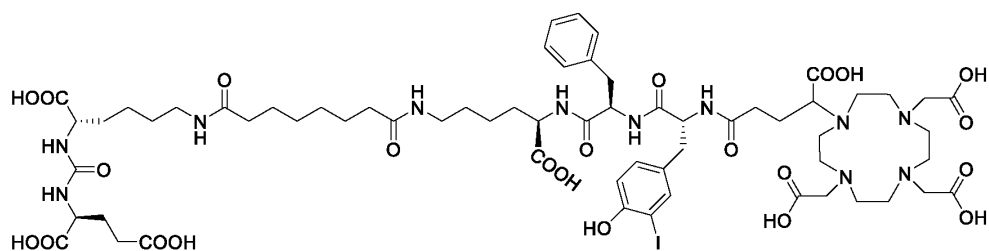
wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, a pharmaceutically acceptable salt thereof, or a prodrug thereof:



(I),

wherein the ^{225}Ac -radioconjugate is administered for at least 4 cycles of treatment, at a dosage of about 12 MBq per cycle for cycles 1 and 2, and at a dosage of about 8 MBq per cycle for cycles 3 and 4.

26. The method of claim 25, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



27. The method of any of claim 21-26, wherein a cycle is about 6 weeks.