RADIOPHARMACEUTICAL TREATMENT METHODS AND USE

CROSS REFERENCE TO RELATED APPLICATION

This Application claims the benefit of U.S. Provisional Application 63/283,999 filed on November 29, 2021. The entire contents of U.S. Provisional Application 63/283,999 are incorporated herein by reference in its entirety.

Field

In one aspect, therapeutic use and methods of treatment comprising ^{177}Lu-PSMA I&T are provided for subjects exhibiting prostate cancer progression following administration with one or more androgen receptor inhibitor agents.

Background

Radiopharmaceuticals have been used for a variety of therapeutic and diagnostic indications. Among others, radiolabeled molecules have been useful to treat various malignant tumors.

Certain androgen receptor inhibitors have been utilized or treatment of prostate cancer. These agents are not however consistently effective. See, for instance, Watson et al., *Nature Reviews Cancer*, volume 15, pages 701-711 (2015).

It thus would be desirable to have new anti-cancer therapies. It would be particularly desirable to have new therapies that would be utilized against tumors that are not effectively treated with androgen receptor inhibitors.

SUMMARY

In a first aspect of the present disclosure, there is provided a use of a lutetium-177 labeled PSMA-targeted radioligand agent in the manufacture of a medicament for treating a subject suffering from prostate cancer, comprising:

a) identifying a human subject i) exhibiting prostate cancer progression during or after treatment with one or more androgen receptor inhibitor agents, and ii) being chemotherapy-naïve before treatment with the one or more androgen receptor inhibitor agents; and wherein

b) the lutetium-177 labeled PSMA-targeted radioligand agent providing from a 4 to 10 Gbq dose is to be administered to the identified human subject, which human subject is to be dosed at least four times, at four week or longer intervals between doses, with the lutetium-177 labeled PSMA-targeted radioligand agent.

In another aspect of the present disclosure, there is provided a use of ^{177}Lu-PSMA I&T in the manufacture of a medicament for treating a subject suffering from prostate cancer, comprising: a) identifying a subject exhibiting prostate cancer progression during treatment with one or more androgen receptor inhibitor agents; and wherein b) the ^{177}Lu-PSMA I&T is to be administered to the identified subject.

In yet another aspect of the present disclosure, there is provided a use of ^{177}Lu-PSMA I&T in the manufacture of a medicament for treating a subject suffering from cancer, comprising: a) one or more androgen receptor inhibitor agents is to be administered to the subject; b) identifying the subject as exhibiting cancer progression following the administration of the one or more androgen reception inhibitor agents; and thereafter c) the ^{177}Lu-PSMA I&T is to be administered to the identified subject.

In a further aspect of the present disclosure, there is provided a kit, comprising:

a pharmaceutical preparation of a lutetium-177 labeled PSMA-targeted radioligand agent suitable for intravenous administration to a subject, and in an amount sufficient to provide from a 4 to 10 Gbq dose; and

a package insert containing instructions for use of the agent in the treatment of a subject exhibiting prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who has previously been treated with androgen receptor (AR) pathway inhibition but which subject is taxane chemotherapy-naïve or taxane chemotherapy adverse.

We now provide new therapeutic uses of a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA (^{177}Lu-PSMA I&T).

In particular examples, methods are provided for treating a subject suffering from cancer, comprising: a) identifying a subject exhibiting cancer progression during treatment

with one or more androgen receptor inhibitor agents; and b) administering to the identified subject an effective amount of a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA.

Methods are also provided for treating a subject suffering from cancer, comprising: a) administering to the subject a therapeutically effective amounts of one or more androgen receptor inhibitor agents; b) identifying the subject as exhibiting cancer progression following administering the one or more androgen reception inhibitor agents; and thereafter c) administering to the identified subject an effective amount of a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA to patient.

In further examples, methods are provided for treating a subject suffering from prostate cancer, comprising: a) identifying a subject i) exhibiting prostate cancer progression during or after treatment with one or more androgen receptor inhibitor agents, and ii) being chemotherapy-naïve before treatment with one or more androgen receptor inhibitor agents; b) administering to the identified subject an amount of a lutetium-177 labeled PSMA-targeted radioligand agent to provide from a 4 to 10 Gbq dose, which subject is dosed at least four times, at four week or longer intervals between doses, with the lutetium-177 labeled PSMA-targeted radioligand agent. In preferred examples, the lutetium-177 labeled PSMA-targeted radioligand agent is a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA, particularly ^{177}Lu-PSMA I&T.

In one example of the above methods, the subject has exhibited cancer progression during treatment with one or more of abiterone, enzalutamide, apalutamide, darolutamide, cimetidine, orteronel, galeterone, seviteronel, topilutamide, bicalutamide, fluamide and/or nilutamide.

In a further example, the subject has exhibited cancer progression during treatment with abiterone, enzalutamide, apalutamide and/or darolutamide.

In certain examples, the subject will be chemotherapy-naïve before administration of any androgen receptor inhibitor agents, and other than the androgen receptor inhibitor therapy, the subject will be chemotherapy-naïve before administration of ^{177}Lu-PSMA

I&T, i.e. the subject will not have received any other chemotherapy (e.g. docetaxel-based chemotherapy or other radiopharmaceutical therapy) for treatment of the subject's cancer.

The subject may be treated with such agents for varying times and under varying conditions. Thus, in certain examples, the subject may be exhibited cancer progression following treatment with one or more androgen receptor inhibitor agents for up to 1, 2, 3 or 4 weeks, or longer periods such as up to 2, 3, 4, 5, 6 months or more.

In certain examples, the subject may be assessed for and identified as exhibiting high or elevated prostate specific membrane antigen (PSMA) expression relative to a healthy subject and that identified subject with elevated PSMA activity is administered a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA.

In certain examples, the present methods and uses include imaging or other assessment of the subject's cancer, including an assessment of PSMA expression. That assessment suitably may occur before administering one or more androgen receptor inhibitor agents and/or before administering a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA (^{177}Lu-PSMA I&T). The cancer assessment preferably includes imaging, for example, SPECT or PET imaging, or immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) imaging. An imaging agent such as the ^{18}F or ^{68}Ga agent (such as agents disclosed in Example 2 below), or ^{64}Cu agents can be administered to the subject to facilitate the cancer analysis.

In one example, a subject is identified for treatment where the subject exhibits a PSMA expression standard uptake value of 1) $(SUV)_{max} \geq 15$ at one site of disease and/or 2) $SUV_{max} > 10$ at all measurable disease sites.

In another example, a subject is identified for treatment where the subject exhibits at least 1 positive lesion $SUV_{max} > 10$.

In a further example, a subject is identified for treatment where the subject has an elevated prostate specific antigen (PSA) level, for example a PSA level of 3 ng/mL, 4 ng/mL, 5 ng/mL or 6 ng/mL or higher.

In certain examples, administration of one or more androgen receptor inhibitor agents is terminated before administering the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA.

In certain examples, the subject is suffering from a prostate specific membrane antigen (PSMA) expressing cancer. In certain examples, the subject has prostate cancer. In particular examples, the subject is suffering from metastatic castration-resistant prostate cancer (mCRPC). In additional examples, the subject is suffering from metastatic castration-resistant prostate cancer (mCRPC) with prostate-specific membrane antigen (PSMA)-avid lesions.

In certain examples, the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA (^{177}Lu-PSMA I&T) is administered parenterally, such as intradermal, subcutaneous, intramuscular , intraperitoneal and/or intravenous. In certain methods, ^{177}Lu-PSMA I&T is administered in a dosage amount (single administration amount or single day amount) of about 1 GBq to about 15 GBq, or about 2 GBq to about 14 GBq, or about 3 or 4 GBq to about 10 or 12 GBq, or about 5 or 6 GBq to about 7, 8 or 9 GBq. A dosage of 6.8 GBq +/- 10% per administration may be particularly preferred for various treatments. ^{177}Lu-PSMA I&T suitably may be administered under varying schedules including multiple times per week, or once every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 or more weeks. In some examples, scheduled ^{177}Lu-PSMA I&T administration may continue for up to 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 24, 26, 28 or 30 months.

^{177}Lu-PSMA I&T is a complex of lutetium (^{177}Lu) and EuK-Sub-kf-iodo-y-DOTAGA. The term “complex” herein generally refers to a union of ^{177}Lu and the ligand EuK-Sub-kf-iodo-y-DOTAGA inclusive of chemical and physical variations that may exist with the joined or associated lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA (designated as ^{177}Lu-PSMA I&T). Also, ^{177}Lu-PSMA I&T and 177Lu-PNT2002 are used interchangeably herein and have the same meaning.

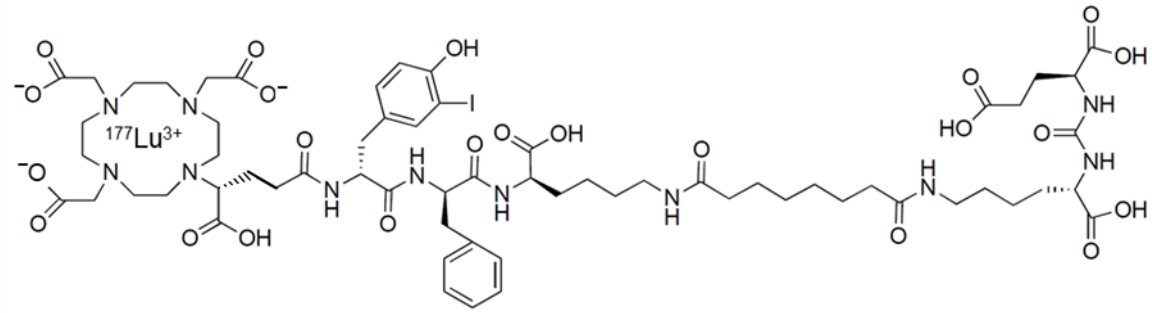
^{177}Lu-PSMA I&T has several possible stereoisomers, including the *R* and *S* isomers of the carbon that is an N-ring substituent of the tetraazacyclotetradecane moiety of the compound. References herein to EuK-Sub-kf-iodo-y-DOTAGA and ^{177}Lu-PSMA

I&T without further limitation includes all possible stereoisomers of each of those compounds and particularly both the noted *R* and *S* isomers.

In certain examples, racemic mixtures of ^{177}Lu-PSMA I&T are utilized in the present pharmaceutical compositions and methods.

In other preferred examples, optically enriched mixtures of ^{177}Lu-PSMA I&T and EuK-Sub-kf-iodo-y-DOTAGA are used in the present methods and pharmaceutical compositions.

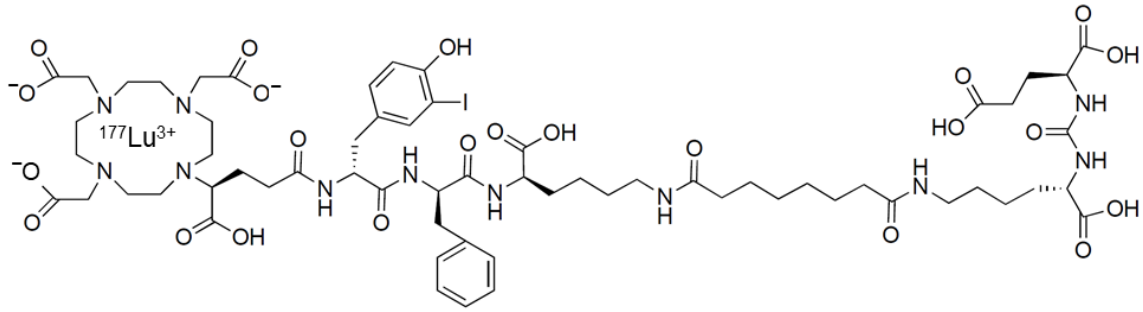
In certain preferred examples, the *R* isomer of ^{177}Lu-PSMA I&T is provided, including for use in the present pharmaceutical compositions and methods. That *R* isomer may be represented by the following structure 2A:



2A

In one example, for use in the present methods and pharmaceutical compositions, generally preferred is ^{177}Lu-PSMA I&T that is substantially optically enriched with the *R* isomer of structure 2A, or is an enantiomerically pure mixture of the *R* isomer of structure 2A.

In another example, the *S* isomer of ^{177}Lu-PSMA I&T is used in the present pharmaceutical compositions and methods. That *S* isomer may be represented by the following structure 2B:



2B

In one example, for use in the present methods and pharmaceutical compositions, generally preferred is ^{177}Lu-PSMA I&T that is substantially optically enriched with the *S* isomer of structure 2B, or is an enantiomerically pure mixture of the *S* isomer of structure 2B.

^{177}Lu-PSMA I&T for use in the present methods preferably has high chemical or radiochemical purities, including greater than 95, 96, 97, 98, 99, 99.5, 99.6, 99.7, 99.8 or 99.9 percent radiochemical purity and/or substantial absence of one or more prior impurities.

In further examples, treatment kits are provided. In a preferred example, a kit may comprise a) a pharmaceutical preparation of lutetium-177 labeled PSMA-targeted radioligand agent suitable for intravenous administration to a patient, and in an amount sufficient to provide from a 4 to 10 Gbq dose; and b) a package insert containing instructions for use of the agent in the treatment of a subject exhibiting prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have previously been treated with androgen receptor (AR) pathway inhibition but which patient is taxane chemotherapy-naïve or taxane chemotherapy adverse (i.e., ineligible or averse to chemotherapeutic treatment options).

Uses of a lutetium-177 labeled PSMA-targeted radioligand agent to treat a subject (such as human) suffering from cancer including prostate cancer are also provided, wherein a) a subject is identified as i) exhibiting prostate cancer progression during or after treatment with one or more androgen receptor inhibitor agents, and ii) being chemotherapy-naïve before treatment with the one or more androgen receptor inhibitor agents; b) an amount of a lutetium-177 labeled PSMA-targeted radioligand agent is administered providing from a 4 to 10 Gbq dose, which subject is dosed at least four times, at four week or longer intervals between doses, with the lutetium-177 labeled PSMA-targeted radioligand therapy . In preferred examples, the lutetium-177 labeled PSMA-targeted radioligand agent is a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA.

Other examples of the disclosure are disclosed *infra*.

Definitions

As used herein, the term "a," "an," "the" and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

The language "and/or" is used herein as a shorthand notation to represent the expression "and," describing the combination of items, as well as "or," describing the items in the alternative form.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

The term "about", as used herein, means an acceptable margin of error for a particular value, which depends in part on how the value is measured or determined. In certain embodiments, "about" as used herein will be understood by persons of ordinary

What is claimed is:

1. Use of a lutetium-177 labeled PSMA-targeted radioligand agent in the manufacture of a medicament for treating a subject suffering from prostate cancer, comprising:

a) identifying a human subject i) exhibiting prostate cancer progression during or after treatment with one or more androgen receptor inhibitor agents, and ii) being chemotherapy-naïve before treatment with the one or more androgen receptor inhibitor agents; and wherein

b) the lutetium-177 labeled PSMA-targeted radioligand agent providing from a 4 to 10 Gbq dose is to be administered to the identified human subject, which human subject is to be dosed at least four times, at four week or longer intervals between doses, with the lutetium-177 labeled PSMA-targeted radioligand agent.

2. The use of claim 1, wherein the lutetium-177 labeled PSMA-targeted radioligand agent is a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA.

3. The use of claim 1 or 2 wherein the human subject has exhibited cancer progression during treatment with one or more of:

(a) abiraterone, enzalutamide, apalutamide, darolutamide, cimetidine, orteronel, galeterone, seviteronel, topilutamide, bicalutamide, fluamide and/or nilutamide; or

(b) abiraterone, enzalutamide, apalutamide and/or darolutamide; or

(c) abiraterone, apalutamide and/or darolutamide.

4. The use of any one of claims 1 through 3 wherein the human subject has exhibited cancer progression following at least month of treatment with one or more androgen receptor inhibitor agents.

5. The use of any one of claims 1 through 4 wherein the human subject is identified by:

(a) imaging PSMA expression of the cancer; or

(b) based on radiological assessment of cancer progression during treatment with one or more androgen receptor inhibitor agents.

6. The use of any one of claims 1 through 5 wherein administration of one or more androgen receptor inhibitor agents is terminated before the administration of the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA.

7. The use of any one of claims 1 through 6 wherein the human subject is suffering from:

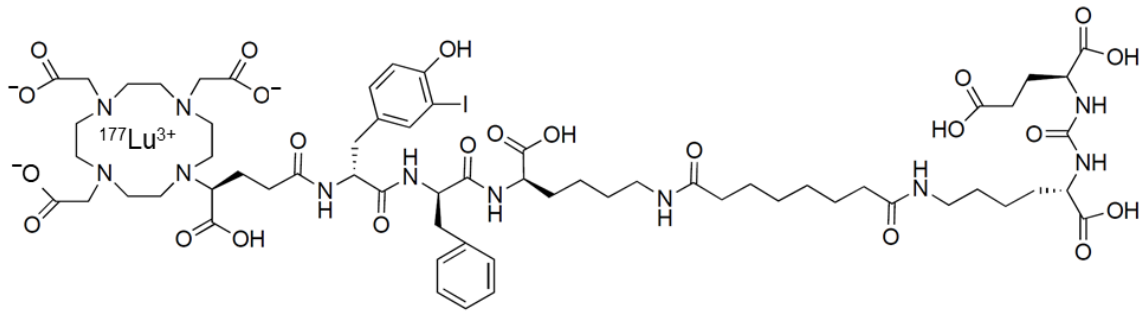
(a) a PSMA expressing cancer; or

(b) prostate cancer; or

(c) metastatic castration-resistant prostate cancer (mCRPC); or

(d) metastatic castration-resistant prostate cancer (mCRPC) with prostate-specific membrane antigen (PSMA)-avid lesions.

8. The use of any one of claims 1 through 7 wherein the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA comprises the following structure:



9. Use of ^{177}Lu-PSMA I&T in the manufacture of a medicament for treating a subject suffering from prostate cancer, comprising: a) identifying a subject exhibiting prostate cancer progression during treatment with one or more androgen receptor inhibitor agents; and wherein b) the ^{177}Lu-PSMA I&T is to be administered to the identified subject.

10. Use of ^{177}Lu-PSMA I&T in the manufacture of a medicament for treating a subject suffering from cancer, comprising: a) one or more androgen receptor inhibitor agents is to be administered to the subject; b) identifying the subject as exhibiting cancer progression following the administration of the one or more androgen reception inhibitor agents; and thereafter c) the ^{177}Lu-PSMA I&T is to be administered to the identified subject.

11. A kit, comprising:

a pharmaceutical preparation of a lutetium-177 labeled PSMA-targeted radioligand agent suitable for intravenous administration to a subject, and in an amount sufficient to provide from a 4 to 10 Gbq dose; and

a package insert containing instructions for use of the agent in the treatment of a subject exhibiting prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who has previously been treated with androgen receptor (AR) pathway inhibition but which subject is taxane chemotherapy-naïve or taxane chemotherapy adverse.

12. The kit of claim 11, wherein:

(a) the instructions of the package insert include guidance for dosing the patient with the lutetium-177 labeled PSMA-targeted radioligand therapy at least four times and at four week or longer intervals between doses; and/or

(b) the package insert further includes an indication that the shelf life for the lutetium-177 labeled PSMA-targeted radioligand is 120 hours from end of synthesis and formulation of the pharmaceutical preparation of the lutetium-177 labeled PSMA-targeted radioligand for use in the kit; and/or

(c) the package insert further includes instructions for selecting patients using a PSMA-targeted imaging agent; and/or

(d) the package insert further includes instructions for ensuring patients increase oral fluid intake and advise patients to void as often as possible to reduce bladder radiation.

13. The kit of either claim 11 or 12, wherein the lutetium-177 labeled PSMA-targeted radioligand agent is a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA.

14. The kit of claim 13, wherein lutetium-177 EuK-Sub-kf-iodo-y-DOTAGA complex is provided in a single dose form sufficient to provide 6.8 GBq +/- 10% within shelf-life.

15. The kit of either claim 13 or 14, wherein the pharmaceutical preparation includes Sodium Ascorbate at a concentration of 55-75 mg/mL and Sodium Gentisate at a concentration of 16 - 36 mg/mL, and has a pH in the range of 5.0 - 7.0.

16. The kit of any of claims 13-15, wherein the pharmaceutical preparation has a radioactive concentration (RAC) of 0.5 to 1.2 GBq/mL, more preferably 0.79 - 0.86 GBq/mL ± 10%, at end of synthesis and formulation of the pharmaceutical preparation.

17. The kit of any one of claims 13-16, wherein the pharmaceutical preparation has a total peptide content of less than or equal to 250 μg (sum of EuK-Sub-kf-iodo-y-DOTAGA and lutetium-177 EuK-Sub-kf-iodo-y-DOTAGA complex), preferably a total peptide content in the range of 180-250 μg.

18. The kit of any of claims 11-17, wherein the package insert further includes instructions for patient eligibility, including that patients must have progressive mCRPC at the time of consent based on one or more of the following criteria:

a) Serum/plasma PSA progression defined as increase in PSA greater than 25% and >2 ng/mL above nadir;

b) Progression on previous treatment with one ARAT in either the CSPC or CRPC setting;

c) PSMA-PET scan (i.e., 68Ga-PSMA-11 or 18F-DCFPyL) positive;

d) Castrate circulating testosterone levels (<1.7 nmol/L or <50 ng/dL); and/or.

e) Adequate bone marrow, renal and liver organ function.