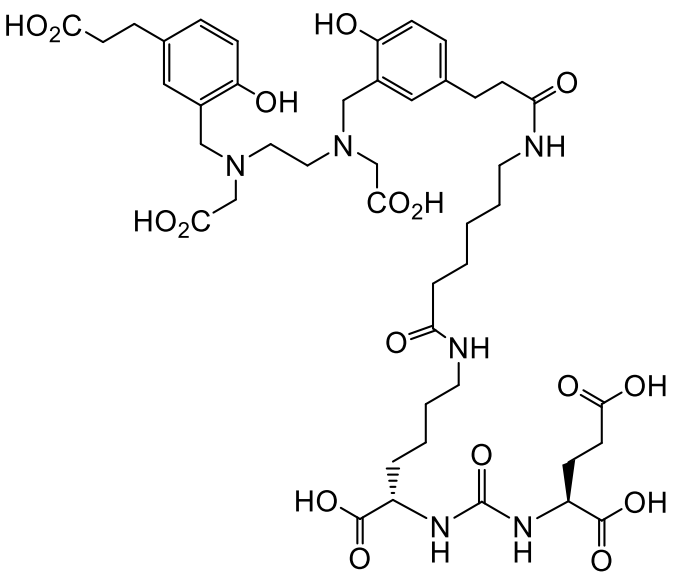
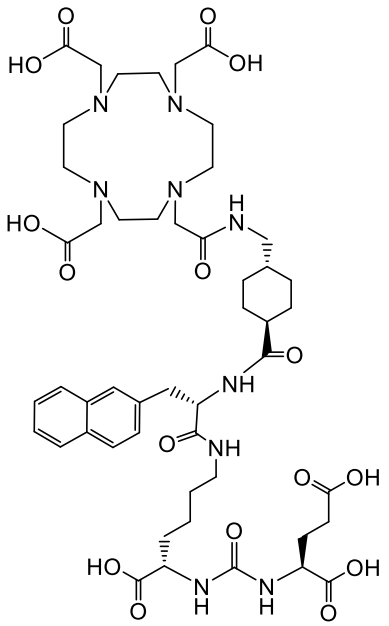


(a.k.a. 4,6,12,19- Tetraazadocosane-1,3,7-tricarboxylic acid, 22-[3-[[[2-[[[5-(2-carboxyethyl)-2-hydroxyphenyl]methyl](carboxymethyl) amino]ethyl](carboxymethyl)amino]methyl]-4-hydroxy-phenyl]-5,13,20- trioxo-,(3S,7S)) wherein ^{68}Ga (or similar radioactive metal isotope) is complexed to the conjugate, useful for the imaging of cancer as described in Eder M, Schafer M, Bauder-Wust U, Hull WE, Wangler C, Mier W, et al. 68Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. Bioconjug Chem. 2012;23:688–97. PSMA imaging conjugate 4 can be prepared according to the methods described in (Eder, 2012), and (Eder, 2012) is incorporated by reference for the preparation of PSMA imaging conjugate 4, as described in the examples.

SUMMARY

In an aspect, there is provided the use of a compound of the formula 1



1

in the manufacture of a medicament for the treatment of cancer in a patient in need of such treatment, wherein the compound is complexed with a radioactive isotope of a metal.

In some examples, the present disclosure provides a method for treating a cancer in a patient in need of such treatment comprising, administering to the patient a therapeutically effective amount of Compound 1.

In some examples, the present disclosure provides use of Compound 1 for treating a cancer in a patient. In some examples, the use comprises administering to the patient a therapeutically effective amount of the Compound 1.

In some examples, the present disclosure provides use of Compound 1 in the preparation of a medicament useful for the treatment of a cancer in a patient. In some examples, the medicament comprises a therapeutically effective amount of Compound 1.

In some examples, the cancer is a PSMA expressing cancer. In some examples, the compound is at least about 98 percent pure. In some examples, the cancer is selected from the group consisting of a glioma, a carcinoma, a

sarcoma, a lymphoma, a melanoma, a mesothelioma, a nasopharyngeal carcinoma, a leukemia, an adenocarcinoma, and a myeloma.

In some examples, the cancer is selected from the group consisting of lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head, cancer of the neck, cutaneous melanoma, intraocular melanoma uterine cancer, ovarian cancer, endometrial cancer, rectal cancer, stomach cancer, colon cancer, breast cancer, triple negative breast cancer, metastatic breast cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, non-small cell lung cancer, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic leukemia, acute leukemia, lymphocytic lymphomas, pleural mesothelioma, cancer of the bladder, Burkitt's lymphoma, cancer of the ureter, cancer of the kidney, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, glioma, brain stem glioma, pituitary adenoma, and adenocarcinoma of the gastroesophageal junction. In some examples, the cancer is a primary or secondary brain cancer. In some examples, the cancer is prostate cancer. In some examples, the cancer is metastatic prostate cancer.

In some examples, Compound 1 is administered in a parenteral dosage form. In some examples, the parenteral dosage form is selected from the group consisting of intradermal, subcutaneous, intramuscular, intraperitoneal, intravenous, and intrathecal. In some examples, the therapeutically effective amount is from about 2 GBq to about 13 GBq. In some examples, the therapeutically effective amount is from about 4 GBq to about 11 GBq. In some examples, the therapeutically effective amount is from about 5 GBq to about 10 GBq. In some examples, the therapeutically effective amount is from about 6 GBq to about 9 GBq. In some examples, the therapeutically effective amount is from about 6.5 GBq to about 8.5 GBq. In some examples, the therapeutically effective amount is from about 7 GBq to about 8 GBq. In some examples, the therapeutically effective amount is about 7.4 GBq. In some examples, the total dose ranges from about 15 GBq to about 200 GBq. In some examples, the total dose ranges from about 25 GBq to about 185 GBq. In some examples, the total dose ranges from about 35 GBq to about 150 GBq. In some examples, the total dose ranges from about 40 GBq to about 100 GBq. In some

examples, the total dose is about 44 GBq. In some examples, the maximum duration of treatment of a subject is about 19 to 23 months.

In some examples, the therapeutically effective amount is from 2 GBq to 13 GBq. In some examples, the therapeutically effective amount is from 4 GBq to 11 GBq. In some examples, the therapeutically effective amount is from 5 GBq to 10 GBq. In some examples, the therapeutically effective amount is from 6 GBq to 9 GBq. In some examples, the therapeutically effective amount is from 6.5 GBq to 8.5 GBq. In some examples, the therapeutically effective amount is from 7 GBq to 8 GBq. In some examples, the therapeutically effective amount is 7.4 GBq.

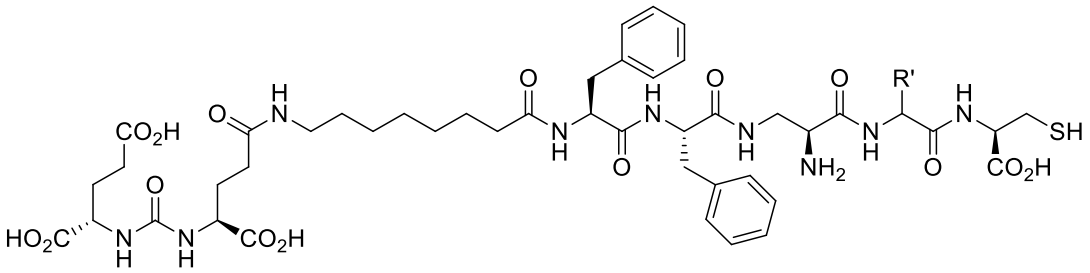
In some examples, the therapeutically effective amount is from about 0.1 mg/m^2 to about 6.0 mg/m^2. In some examples, the therapeutically effective amount is from about 0.1 mg/m^2 to about 5.0 mg/m^2. In some examples, the therapeutically effective amount is from about 0.1 mg/m^2 to about 4.0 mg/m^2. In some examples, the therapeutically effective amount is from about 0.1 mg/m^2 to about 3.5 mg/m^2. In some examples, the therapeutically effective amount is from about 0.1 mg/m^2 to about 3.0 mg/m^2. In some examples, the therapeutically effective amount is from about 0.1 mg/m^2 to about 2.5 mg/m^2. In some examples, the therapeutically effective amount is from about 0.1 mg/m^2 to about 2.0 mg/m^2.

In some examples, the therapeutically effective amount is from 0.1 mg/m^2 to 6.0 mg/m^2. In some examples, the therapeutically effective amount is from 0.1 mg/m^2 to 5.0 mg/m^2. In some examples, the therapeutically effective amount is from 0.1 mg/m^2 to 4.0 mg/m^2. In some examples, the therapeutically effective amount is from 0.1 mg/m^2 to 3.5 mg/m^2. In some examples, the therapeutically effective amount is from 0.1 mg/m^2 to 3.0 mg/m^2. In some examples, the therapeutically effective amount is from 0.1 mg/m^2 to 2.5 mg/m^2. In some examples, the therapeutically effective amount is from 0.1 mg/m^2 to 2.0 mg/m^2.

In other examples, the methods and uses described herein further comprise imaging PSMA expression by the cancer. In some examples, the step of imaging occurs before the step of administering. In some examples, the imaging is performed by imaging wherein the imaging is selected from the group consisting of SPECT

imaging, PET imaging, IHC, and FISH. In some examples, the imaging is performed by SPECT imaging.

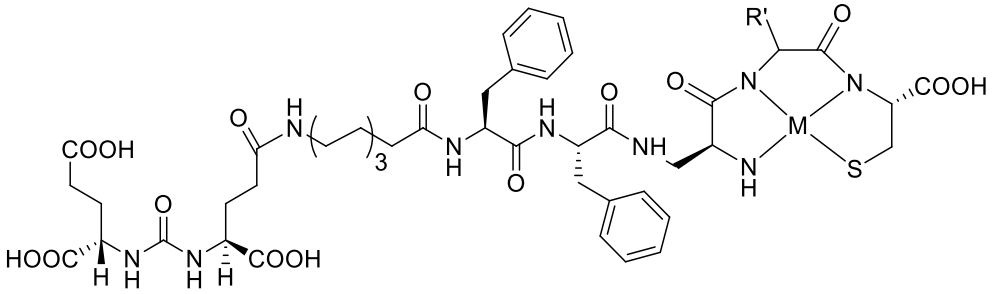
In some examples, the step of imaging comprises administering to the patient a PSMA ligand-imaging conjugate of the formula 2



2

or a pharmaceutically acceptable salt thereof, wherein R' is hydrogen, or R' is selected from the group consisting of alkyl, aminoalkyl, carboxyalkyl, hydroxyalkyl, heteroalkyl, aryl, arylalkyl and heteroarylalkyl, each of which is optionally substituted, and wherein a radionuclide is bound to the conjugate.

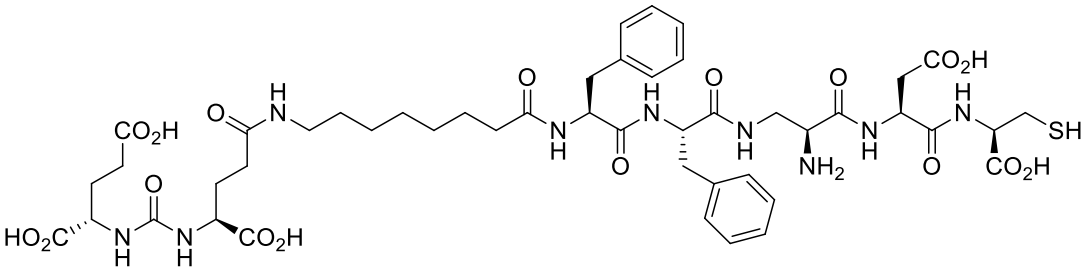
In some examples, the step of imaging comprises administering a PSMA ligand-imaging conjugate of the formula 3



3

or a pharmaceutically acceptable salt thereof, wherein R' is hydrogen, or R' is selected from the group consisting of alkyl, aminoalkyl, carboxyalkyl, hydroxyalkyl, heteroalkyl, aryl, arylalkyl and heteroarylalkyl, each of which is optionally substituted, and wherein M is a cation of a radionuclide. In some examples, M in the conjugate, or a pharmaceutically acceptable salt thereof, is selected from the group consisting of an isotope of gallium, an isotope of indium, an isotope of copper, an isotope of technetium, and an isotope of rhenium. In some examples, M in the conjugate, or a pharmaceutically acceptable salt thereof, is an isotope of technetium.

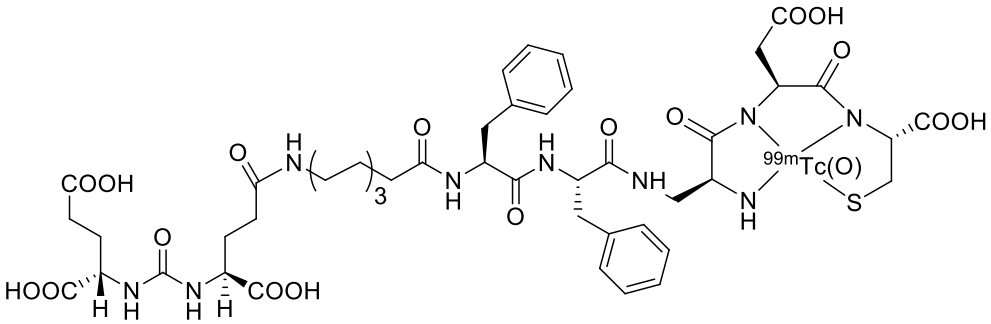
In some examples, the PSMA ligand-imaging conjugate is of the formula 2a



2a

or a pharmaceutically acceptable salt thereof, wherein a radionuclide is bound to the conjugate.

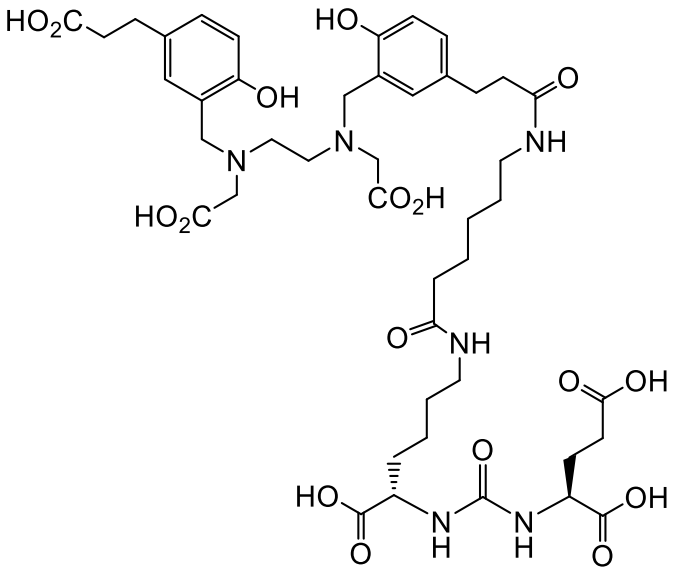
In some examples, the PSMA ligand-imaging conjugate is of the formula 3a



3a

or a pharmaceutically acceptable salt thereof.

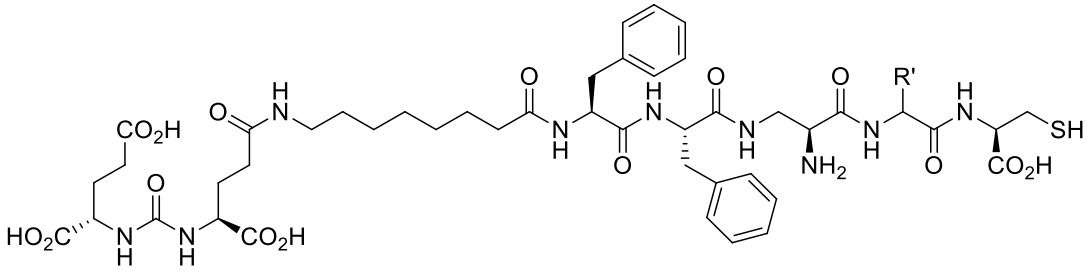
In some examples, the step of imaging comprises administering to the patient a PSMA ligand-imaging conjugate of the formula 4



or a pharmaceutically acceptable salt thereof, wherein a radionuclide is bound to the conjugate. In some examples, the radionuclide is ^{68}Ga.

In other examples, the methods and uses described herein further comprise determining the PSMA status of the patient by imaging. In some examples, the imaging is SPECT imaging. In some examples, the PSMA status of the patient correlates with a clinical benefit to the patient. In some examples, the clinical benefit is selected from the group consisting of inhibition of tumor growth, stable disease, a partial response, and a complete response. In some examples, the clinical benefit is stable disease. In some examples, the PSMA positive lesions indicate functionally active PSMA.

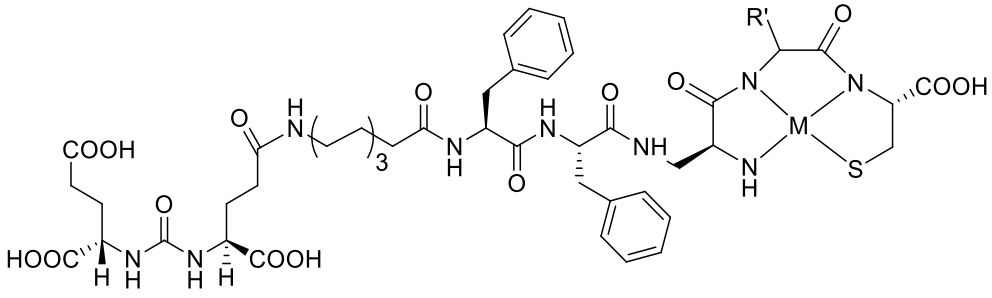
In some examples, the step of determining comprises administering to the patient a PSMA ligand-imaging conjugate of the formula 2



2

or a pharmaceutically acceptable salt thereof, wherein R' is hydrogen, or R' is selected from the group consisting of alkyl, aminoalkyl, carboxyalkyl, hydroxyalkyl, heteroalkyl, aryl, arylalkyl and heteroarylalkyl, each of which is optionally substituted, and wherein the conjugate is bound to a radionuclide.

In some examples, the step of determining comprises administering a PSMA ligand-imaging conjugate of the formula 3

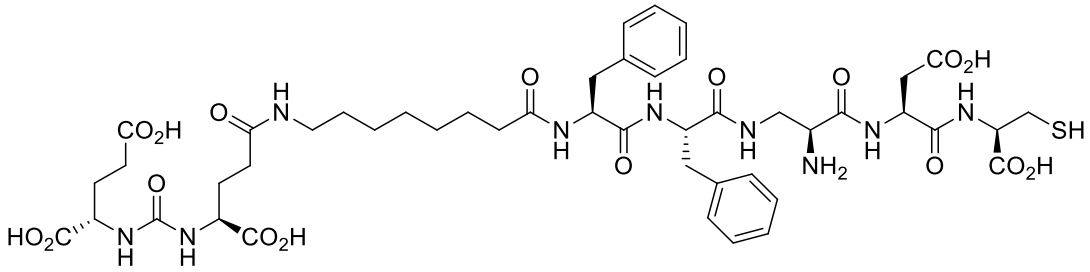


3

or a pharmaceutically acceptable salt thereof, wherein R' is hydrogen, or R' is selected from the group consisting of alkyl, aminoalkyl, carboxyalkyl, hydroxyalkyl, heteroalkyl, aryl, arylalkyl

and heteroarylalkyl, each of which is optionally substituted, and wherein M is a cation of a radionuclide.

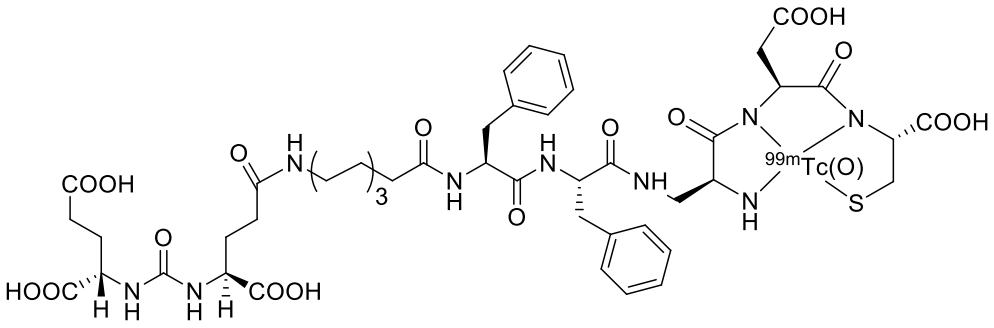
In some examples, M in the conjugate, or a pharmaceutically acceptable salt thereof, is selected from the group consisting of an isotope of gallium, an isotope of indium, an isotope of copper, an isotope of technetium, and an isotope of rhenium. In some examples, M in the conjugate, or a pharmaceutically acceptable salt thereof, is an isotope of technetium. In some examples, the PSMA ligand-imaging conjugate is of the formula 2a



2a

or a pharmaceutically acceptable salt thereof, wherein a radionuclide is bound to the conjugate.

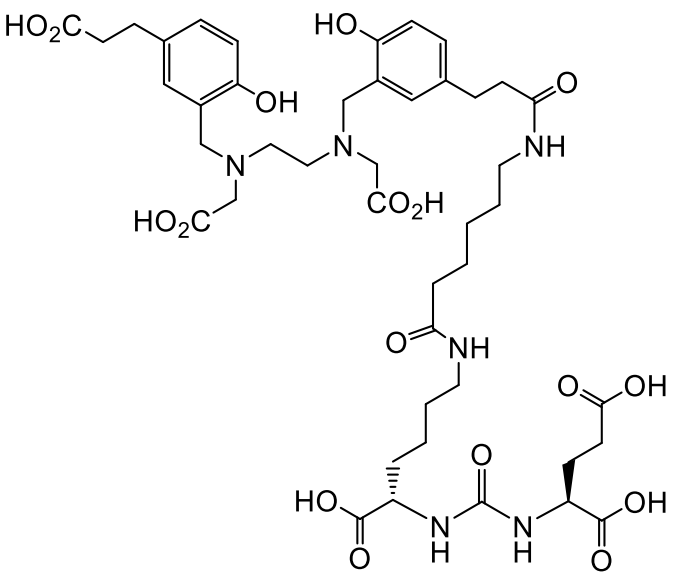
In some examples, the PSMA ligand-imaging conjugate is of the formula 3a



3a

or a pharmaceutically acceptable salt thereof.

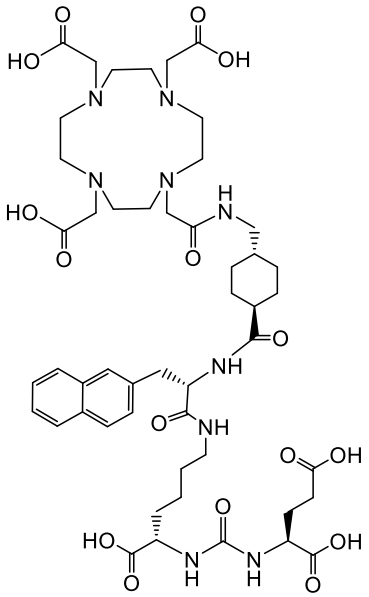
In some examples, the step of determining comprises administering to the patient a PSMA ligand-imaging conjugate of the formula 4



4

or a pharmaceutically acceptable salt thereof, wherein a radionuclide is bound to the conjugate. In some examples, the radionuclide is ^{68}Ga.

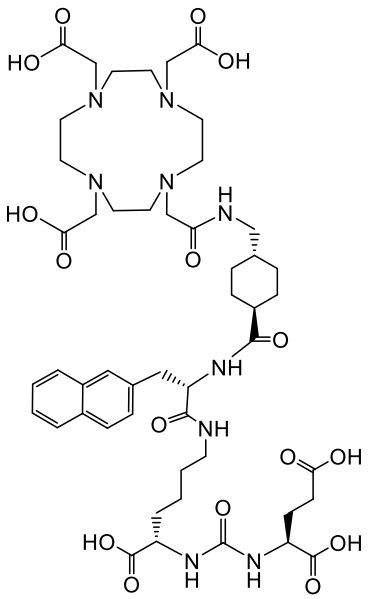
In other examples, the present disclosure provides a method of treating a cancer in a patient in need of such treatment comprising, administering to the patient a therapeutically effective amount of a Compound 1



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wherein ^{177}Lu is complexed to the Compound 1, wherein stable disease results after the Compound 1, or a pharmaceutically acceptable salt thereof, is administered.

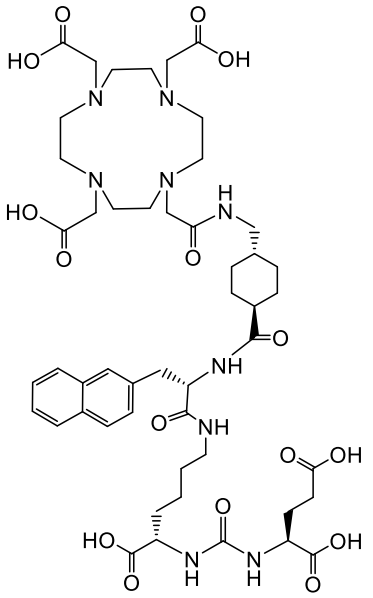
In other examples, the present disclosure provides use of a Compound 1



1

wherein ^{177}Lu is complexed to the Compound 1, wherein stable disease results after the Compound 1, or a pharmaceutically acceptable salt thereof, is administered. In some examples, the use comprises administering to the patient a therapeutically effective amount of the Compound 1.

In other examples, the present disclosure provides use of a Compound 1



1

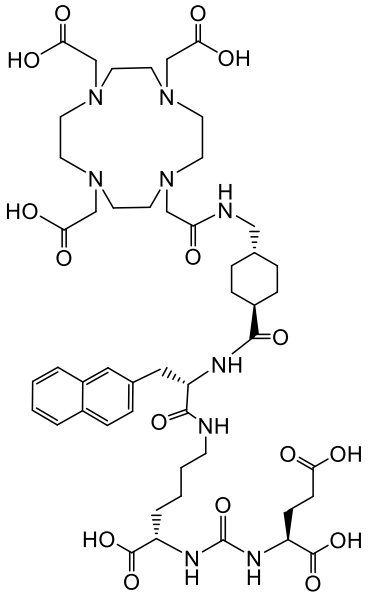
wherein ^{177}Lu is complexed to the Compound 1, in the preparation of a medicament useful for the treatment of a cancer in a patient, wherein stable disease results after the Compound 1, or a

pharmaceutically acceptable salt thereof, is administered. In some examples, the medicament comprises a therapeutically effective amount of the Compound 1, or a pharmaceutically acceptable salt thereof.

In some examples, the patient has been treated with at least one prior treatment. In some examples, the at least one prior treatment is selected from the group consisting of an androgen axis systemic treatment, a chemotherapeutic agent, surgery, radiation therapy, immunotherapy, photodynamic therapy, stem cell therapy, and hyperthermia. In some examples, the at least one prior treatment is a systemic treatment. In some examples, the systemic treatment is selected from the group consisting of palifosfamide, 5-fluorouracil, capecitabine, pemetrexed, cisplatin, carboplatin, gemcitabine, paclitaxel, vinorelbine, eribulin, docetaxel, cyclophosphamide, doxorubicin, regorafinib, and combinations thereof. In some examples, the cancer is a PSMA expressing cancer. In some examples, the compound is at least about 98 percent pure.

Examples of the disclosure are further described by the following enumerated clauses:

1. A method for treating a cancer in a patient in need of such treatment comprising, administering to the patient a therapeutically effective amount of a compound of the formula 1 or 2



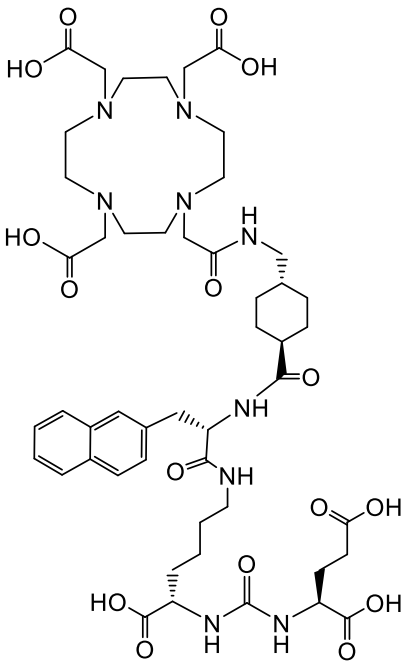
1

wherein the compound is complexed with a metal.

2. The method of clause 1, wherein the cancer is a PSMA expressing cancer.

WHAT IS CLAIMED IS:

1. Use of a compound of the formula 1



1

in the manufacture of a medicament for the treatment of cancer in a patient in need of such treatment, wherein the compound is complexed with a radioactive isotope of a metal.

2. The use of claim 1, wherein the cancer is a PSMA expressing cancer.

3. The use of claim 1, wherein the cancer is prostate cancer, or metastatic castration-resistant prostate cancer.

4. The use of any one of the preceding claims, wherein the medicament is to be administered in a parenteral dosage form.

5. The use of claim 4, wherein the parenteral dosage form is selected from the group consisting of intradermal, subcutaneous, intramuscular, intraperitoneal, intravenous, and intrathecal.

6. The use of any one of claims 1 to 5, wherein the medicament comprises from about 2 GBq to about 13 GBq, or about 4 GBq to about 11 GBq, or about 5 GBq to about 10 GBq, or about 6

GBq to about 9 GBq, about 6.5 GBq to about 8.5 GBq, or about 7 GBq to about 8 GBq of the radioactive isotope of the metal.

7. The use of any one of claims 1 to 5, wherein the medicament comprises about 7.4 GBq of the radioactive isotope of the metal.

8. The use of any one of claims 1 to 5, further comprising PSMA expression by the cancer of the patient to be imaged.

9. The use of claim 8, wherein the PSMA expression is to be imaged before the medicament is to be administered.

10. The use of claim 9, wherein the PSMA expression is to be imaged by imaging and wherein the imaging is selected from the group consisting of SPECT imaging, PET imaging, IHC, and FISH.

11. The use of any one of claims 1 to 10, further comprising the PSMA status of the patient to be determined by imaging.

12. The use of claim 11, wherein the imaging is SPECT imaging.

13. The use of claim 12, wherein at least one PSMA positive lesion indicates functionally active PSMA.

14. The use of any one of claims 1 to 13, wherein the patient has been treated with at least one prior treatment selected from the group consisting of an androgen axis systemic treatment, chemotherapeutic agent, surgery, radiation therapy, immunotherapy, photodynamic therapy, stem cell therapy, and hyperthermia.

15. The use of claim 14, wherein the at least one prior treatment is selected from the group consisting of abiraterone, orteronel, galeterone, seviteronel, apalutamide, enzalutamide, and combinations thereof.

16. The use of claim 14, wherein the at least one prior treatment is selected from the group consisting of palifosfamide, 5-fluorouracil, capecitabine, pemetrexed, cisplatin, carboplatin, gemcitabine, paclitaxel, vinorelbine, eribulin, docetaxel, cyclophosphamide, doxorubicin, regorafinib, and combinations thereof.

17. The use of any one of claims 1 to 16, wherein the medicament is to be administered in combination with a second treatment.

18. The use of claim 17, wherein the second treatment is an androgen axis systemic treatment.

19. The use of claim 18, wherein the androgen axis systemic treatment is selected from the group consisting of abiraterone, orteronel, galeterone, seviteronel, apalutamide, enzalutamide, and combinations thereof.

20. The use of claim 17, wherein the second treatment is radiation therapy.

21. The use of claim 20, wherein the radiation therapy is external beam radiation therapy (EBRT).

22. The use of any one of the claims 1 to 21, wherein the medicament is to be administered on a schedule of once per every 4 to 6 weeks.

23. The use of claim 22, wherein the medicament is to be administered for about 2 to 8 cycles of the schedule, or about 3 to 7 cycles of the schedule, or about 4 to 6 cycles of the schedule.

24. The use of any one of the preceding claims, wherein the radioactive isotope of a metal is selected from the group consisting of ^{90}Y, ^{177}Lu, ^{64}Cd, ^{153}Gd, ^{155}Gd, ^{157}Gd, ^{213}Bi, and ^{225}Ac.

25. The use of claim 24, wherein the radioactive isotope of a metal is ^{177}Lu.

26. The use of claim 24, wherein the radioactive isotope of a metal is ^{225}Ac.