Downloaded from jnm.snmjournals.org by Weill Cornell Medical Library on August 8, 2016. For personal use only.
Journal of Nuclear Medicine, published on July 28, 2016 as doi:10.2967/jnumed.116.178673

^{225}Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer

Clemens Kratochwil*[1], Frank Bruchertseifer*[2], Frederik L. Giesel[1], Mirjam Weis[2], Frederik A. Verburg[3], Felix Mottaghy[3], Klaus Kopka[4], Christos Apostolidis[2], Uwe Haberkorn[1], and Alfred Morgenstern[2]

[1]Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany; [2]European Commission, Joint Research Centre, Institute for Transuranium Elements, Karlsruhe, Germany; [3]Department of Nuclear Medicine, RWTH University Hospital Aachen, Aachen, Germany; and [4]Division of Radiopharmaceutical Chemistry, German Cancer Research Center, Heidelberg, Germany

Prostate-specific membrane antigen (PSMA) is a promising target in prostate cancer. Recently, we started the first-in-human treatment with an α-radionuclide–labeled PSMA ligand. Although the case series is still ongoing, we here report in advance about two patients in highly challenging clinical situations who showed a complete response to ^{225}Ac-PSMA-617 therapy. **Methods:** ^{68}Ga-PSMA-11 PET/CT validated the presence of the PSMA-positive tumor phenotype. A 100-kBq activity of ^{225}Ac-PSMA-617 per kilogram of body weight was administered bimonthly. Prostate-specific antigen response and hematologic toxicity were measured at least every 4 wk. Restaging was performed with ^{68}Ga-PSMA-11 PET/CT. **Results:** Both patients experienced a prostate-specific antigen decline to below the measurable level and showed a complete response on imaging. No relevant hematologic toxicity was observed. Xerostomia was the only mentionable clinical side effect. **Conclusion:** Targeted α-therapy with ^{225}Ac-PSMA-617, although still experimental, obviously has strong potential to significantly benefit advanced-stage prostate cancer patients.

Key Words: PSMA; ^{225}Ac; alpha-therapy

J Nucl Med 2016; 57:1–4
DOI: 10.2967/jnumed.116.178673

After the introduction of prostate-specific membrane antigen targeting ^{68}Ga-labeled PSMA-11 as a new PET tracer for prostate cancer (*1*), PSMA-617, a ligand with optimized tumor cell internalization and lowered kidney uptake containing the more universal DOTA chelator, was developed for PSMA-targeted radioligand therapy (*2,3*). For therapy of metastatic castration-resistant prostate cancer (mCRPC), various centers confirmed ^{177}Lu-PSMA-617 to have a favorable dosimetry (*4–6*) and a convincing response in terms of both serum prostate-specific antigen (PSA) level and radiologic findings (*4,7*). Nevertheless, about 30% of patients do not respond to ^{177}Lu-labeled PSMA ligands, and despite good tolerability in general, diffuse red marrow infiltration has been suggested as a risk factor for developing relevant hematologic toxicity (*4*). It has already been demonstrated that targeted α-radiation therapy with ^{213}Bi-DOTATOC could break radioresistance to β-emitters while simultaneously reducing hematologic toxicity in patients with diffuse red marrow infiltration of neuroendocrine tumors (*8*).

Here, we report our initial experience with targeted ^{225}Ac-PSMA-617 α-therapy in one patient in whom treatment with β-emitters was contraindicated (patient A) and one patient resistant to ^{177}Lu-PSMA-617 (patient B).

MATERIALS AND METHODS

Because these cases concern retrospective reports on findings in regular clinical care but not a systematic clinical trial, ethical approval was not needed. The patients were informed about the experimental nature of this therapy and gave written informed consent to receive it; both agreed to the publication of their individual patient history.

Patients

^{225}Ac-PSMA-617 was offered as salvage therapy in accordance with paragraph 37, "Unproven Interventions in Clinical Practice," of the updated Declaration of Helsinki and in accordance with German regulations, which include priority of approved treatments and confirmation of the indication by a nuclear medicine physician and an expert in urologic oncology. Patient A presented with diffuse red marrow infiltration of mCRPC, which was considered a contraindication for treatment with β-emitters, and patient B presented with peritoneal carcinomatosis and liver metastases that were progressive under ^{177}Lu-PSMA-617 therapy. Both patients had undergone extensive pretreatment (Table 1).

Radiopharmaceuticals

Good manufacturing practice–grade PSMA-11 and PSMA-617 were obtained from ABX. ^{225}Ac was produced by radiochemical extraction from ^{229}Th (*9,10*). ^{68}Ga was eluted from a ^{68}Ge/^{68}Ga-generator on site. ^{177}Lu was obtained from ITG. The labeling conditions for ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 have been described previously (*4*).

For radiolabeling of ^{225}Ac-PSMA-617, an aliquot of ^{225}Ac stock solution was added to a microwave vial containing 0.1 M Tris buffer (pH 9) and an appropriate amount of PSMA-617 stock solution. The reaction mixture was heated to 95°C for 5 min using a microwave synthesizer (Biotage Initiator).

Quality control was performed by instant thin-layer chromatography with 0.05 M citric acid (pH 5) as the solvent. After development, the chromatography strip was stored for at least 1 h until radiochemical equilibrium was obtained between ^{225}Ac (half-life [$T_{½}$], 9.9 d) and its daughter nuclide ^{221}Fr ($T_{½}$, 4.8 min). Subsequently, radiochemical purity was determined by measuring the activity of the 218-keV γ-emission of

Received May 25, 2016; revision accepted Jun. 18, 2016.
For correspondence or reprints contact: Clemens Kratochwil, University Hospital Heidelberg, Department of Nuclear Medicine, INF 400, 69120 Heidelberg, Germany.
E-mail: clemens.kratochwil@med.uni-heidelberg.de
*Contributed equally to this work.
Published online ••••••••••••.
COPYRIGHT © 2016 by the Society of Nuclear Medicine and Molecular Imaging, Inc.

Downloaded from jnm.snmjournals.org by Weill Cornell Medical Library on August 8, 2016. For personal use only.

TABLE 1
Overview of Pretreatments

Patient A	Patient B
Leuprorelin	Radical prostatectomy
Zoledronate	Radiotherapy of lymph node metastasis
Docetaxel (50 cycles)	Leuprorelin
Carmustine/epirubicin in hyperthermia	Leuprorelin plus bicalutamide, 150 mg/d
Abiraterone	Docetaxel (11 cycles)
Enzalutamide	Cabazitaxel (10 cycles)
^{223}Ra (6 cycles)	Abiraterone
Abiraterone reexposition	Enzalutamide (not tolerated)
Estramustine	

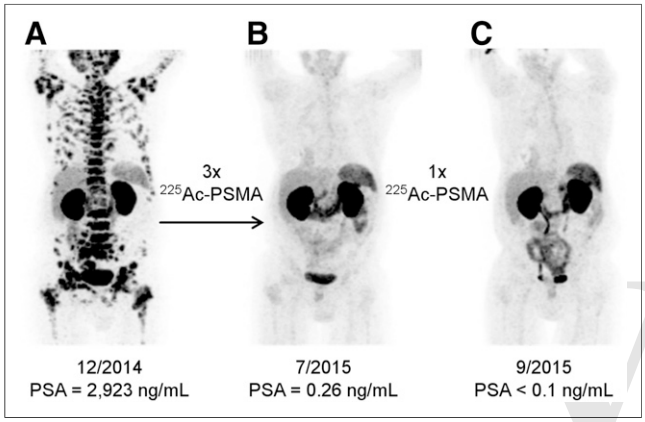

FIGURE 1. ^{68}Ga-PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 mo after third cycle of ^{225}Ac-PSMA-617 (B), and restaging 2 mo after one additional consolidation therapy (C).

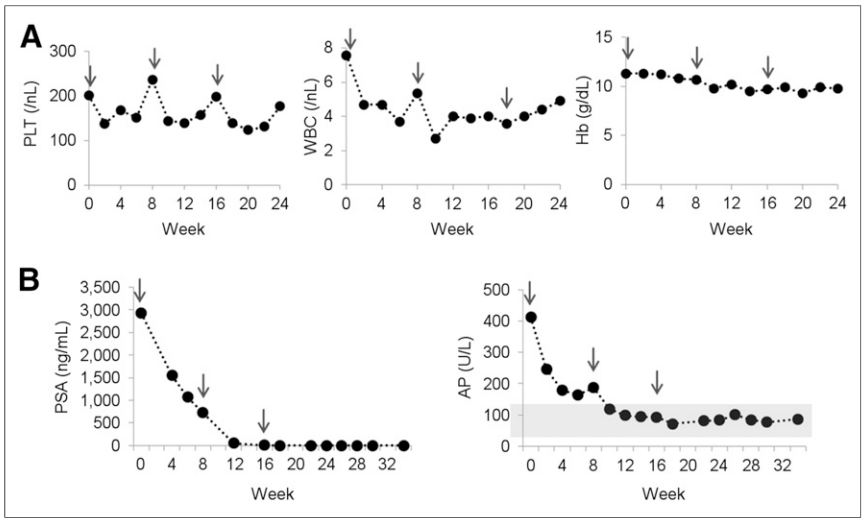

FIGURE 2. Laboratory test follow-up of patient A. Arrows indicate administration of treatment cycles. (A) Blood cell count demonstrates moderate hematologic toxicity. (B) Decline of tumor markers to none measurable or reference range correlates with imaging response. AP = alkaline phosphatase; Hb = hemoglobin; PLT = platelets; WBC = white blood cells.

^{221}Fr on the upper and lower parts of the strip using high-resolution γ-spectrometry (Ortec). The mean radiochemical purity (±SD) of the radiolabeled peptide was 98.8% ± 0.8% at a specific activity of 0.17 ± 0.05 MBq/nmol.

After synthesis, an aliquot of ascorbic acid was added to the reaction mixture (to minimize radiolytic degradation of ^{225}Ac-PSMA-617) together with an aliquot of diethylenetriaminepentaacetic acid (to scavenge free radiometals). The final pH of the formulation was 7.4. Sterility was ensured via sterile filtration.

Imaging

^{68}Ga-PSMA-11 PET/CT and ^{177}Lu-PSMA-617 emission scans were performed as described previously (*1,6*).

Posttherapy ^{225}Ac-PSMA-617 scans were acquired using the 440-keV γ-coemission of ^{213}Bi (26% emission probability), the 218-keV γ-coemission of ^{221}Fr (12%), and the bremsstrahlung of ^{209}Pb with a scan speed of 10 cm/min on a 2.54-cm-crystal (1-in) γ-camera (Hawkeye; GE Healthcare) equipped with a high-energy collimator.

RESULTS

Clinical Course of Patient A

After exhausting conventional therapies (Table 1), imaging with PSMA PET/CT was suggestive of diffuse red marrow infiltration (Fig. 1A). This was considered a contraindication for ^{177}Lu-PSMA-617 therapy. Therefore, patient A was treated with 3 cycles of 9–10 MBq (100 kBq per kilogram of body weight) of ^{225}Ac-PSMA-617 at bimonthly intervals. Posttherapeutic emission scans validated sufficient tumor targeting (Supplemental Fig. 1; supplemental materials are available at http://jnm.snmjournals.org). Two months later, all previously PSMA-positive lesions had visually disappeared on PSMA PET/CT (Fig. 1B) and, accordingly, the PSA level had dropped from more than 3,000 ng/mL to 0.26 ng/mL. The patient received an additional 6 MBq of ^{225}Ac-PSMA-617 as consolidation therapy, resulting in a further PSA decline to less than 0.1 ng/mL along with a complete imaging response (Fig. 1C). [Fig. 1]

After each cycle, the blood cell count and alkaline phosphatase level were checked every 2 wk. The platelet level never dropped below 100/nL (grade 1 according to the Common Terminology Criteria for Adverse Events, version 4.0), the total white blood cell count never dropped below 2.5/nL (grade 1), and the hemoglobin level never dropped below 9.5 g/dL (grade 2) (Fig. 2A). Moderate but enduring xerostomia was the only clinically reported side effect. A concordant decline in PSA level and alkaline phosphatase level (Fig. 2B) further underlined the excellent treatment response. [Fig. 2]

Clinical Course of Patient B

Conventional treatments were also exhausted for patient B, who had peritoneal carcinomatosis and liver infiltration (Fig. 3A) at the time that ^{177}Lu-PSMA-617 (7.4 GBq per cycle) was offered as salvage therapy. The initial PSA level was 294 ng/mL. Despite sufficient tumor targeting as demonstrated by posttherapeutic emission scans (Supplemental Fig. 2), after cycle 2 the PSA level increased to 419 ng/mL and most lesions demonstrated tumor progression on PSMA PET/CT (Fig. 3B). Therapy was changed to [Fig. 3]

Downloaded from jnm.snmjournals.org by Weill Cornell Medical Library on August 8, 2016. For personal use only.

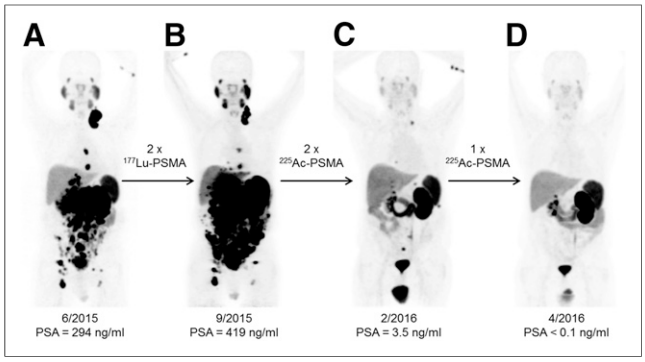

FIGURE 3. ^{68}Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting ^{177}Lu-PSMA-617 presented progression (B). In contrast, restaging after second (C) and third (D) cycles of α-emitting ^{225}Ac-PSMA-617 presented impressive response.

^{225}Ac-PSMA-617, and the patient received 3 cycles of 6.4 MBq (100 kBq per kilogram of body weight) at bimonthly intervals. Restaging based on the PSMA PET/CT results finally indicated a partial response after 2 cycles (Fig. 3C) and a complete remission after 3 cycles (Fig. 3D). Laboratory tests revealed no relevant hematologic toxicity; PSA dropped to below the measurable level [**Fig. 4**] (<0.1 ng/mL) (Fig. 4). However, spray substitution of saliva had to be prescribed after the last cycle because of severe xerostomia.

DISCUSSION

Here, we present a novel treatment concept for patients with mCRPC that is progressive under conventional therapy or β-emitting ^{177}Lu-PSMA-617. Two patients in a clinically critical situation experienced remarkable benefit from targeted α-therapy with ^{225}Ac-PSMA-617. This early observation from our study is of such high interest for scientists and clinicians in the field that we wanted to share it as a brief communication in advance of the full report.

PSMA radioligand therapy with ^{177}Lu-PSMA-617, itself an investigational treatment, has already demonstrated promising results (*6,7*). However, radioligand therapies based on β-particle emitters can have typical shortcomings, especially during treatment of patients with late-stage cancer.

One challenge is that the dose contribution of β-particles arising from bone metastases to the red marrow cannot be modeled sufficiently. If only a limited number of solid bone metastases are present, it is possible to neglect this dose contribution because the 498-keV β-energy of ^{177}Lu corresponds to a tissue range of only 1.5 mm and the red marrow dose is typically estimated by sampling of peripheral blood. However, the blood-dose–based models are valid only if specific red marrow uptake of the radiopharmaceutical can be excluded; in the case of diffuse tumor infiltration, the red marrow self-dose can become the limiting factor. In this setting, targeted α-therapy can be beneficial because the 50- to 100-μm range of an α-particle (2–3 cell diameters) translates into a much more cell-specific radiotherapy (*11*). In analogy, targeting myeloblasts with a β-labeled ^{131}I-CD33 antibody translates into bone marrow ablation (*12*), whereas an α-labeled ^{213}Bi-CD33 antibody can eliminate myeloblasts cell-selectively with tolerable hematologic toxicity (*13*). Therefore, the remarkable low hematologic toxicity observed after treatment of patient A is reasonable.

In the available reports about ^{177}Lu-labeled PSMA ligands, approximately 30% of the patients were refractory a priori (*6,7*). In patients with neuroendocrine tumors refractory to ^{177}Lu-labeled somatostatin analogs, it has already been demonstrated that targeted α-therapy can break radioresistance to β-radiation (*8*). In mCRPC, the α-emitting $^{223}RaCl_2$ but not its β-emitting analog $^{89}SrCl_2$ was demonstrated to improve survival (*14*). Therefore, it seems comprehensible that patient B, despite being refractory to ^{177}Lu-radioligand therapy, could still be treated successfully with ^{225}Ac-targeted α-therapy.

On the other hand, radioligand therapies based on α-particle emitters face other challenges. The nuclides suitable for medical application often are either hampered by an unfavorable half-life or decay with multiple unstable daughter nuclides. Because of the recoil of the α-decay and different chemical properties, the daughter nuclides can leave the chelator of the radioconjugate. If this happens on the cell surface, the bloodstream can translocate the activity into nontumor tissue. ^{225}Ac ($T_{½}$, 9.9 d) decays to the daughters ^{221}Fr ($T_{½}$, 4.8 min), ^{217}At ($T_{½}$, 33 ms), and ^{213}Bi ($T_{½}$, 45.6 min); each of these nuclides disintegrates with emission of one α-particle. To ensure that most of the 4 resulting α-emissions are on target, carrier-mediated internalization into the tumor cells is desired for ^{225}Ac-targeted α-therapy.

The ligand PSMA-617 induces fast cellular internalization, with 54% and 75% of the total cell-associated activity internalized after 1 h and 3 h, respectively, of incubation in the LNCaP cell line (*2*). For the PSMA-targeted and then internalized antibody ^{225}Ac-J591, sufficient tumor retention of the ^{225}Ac daughter nuclides has already been demonstrated in vitro (*15*). Thus, radioligand therapy with ^{225}Ac-PSMA-617 ideally matches the theoretic considerations for targeted α-therapy of mCRPC.

Nevertheless, the limited availability of ^{225}Ac is still a key challenge for its clinical translation, and this shortage has to be

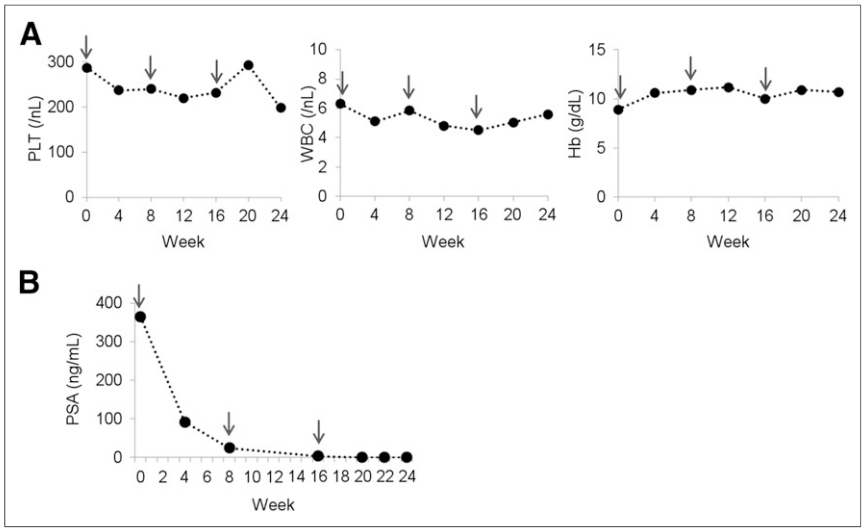

FIGURE 4. Laboratory test follow-up of patient B. Arrows indicate administration of treatment cycles. Blood cell count (A) always stayed in reference range, and tumor marker PSA (B) finally declined to none measurable.

Downloaded from jnm.snmjournals.org by Weill Cornell Medical Library on August 8, 2016. For personal use only.

solved before large studies are feasible. However, several methods of accelerator-driven production of ^{225}Ac have already been described (*16,17*), and routine production of this radionuclide can be realized with manageable effort once a relevant demand is predictable. Our early results already indicate that ^{225}Ac-targeted α-therapy has high potential for the epidemiologically important tumor entity prostate cancer, which presumably will further accelerate the routine availability of ^{225}Ac for systematic clinical trials, for example.

CONCLUSION

The two impressive responses reported here demonstrate the high potential of ^{225}Ac-PSMA-617 to significantly benefit mCRPC patients who are in a clinically critical situation, that is, patients with diffuse red marrow infiltration and resistance to other therapies. Investigation of this therapeutic modality in larger patient cohorts is warranted.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. A patent application for PSMA-617 (regardless of the radiolabeling nuclide) was submitted by Drs. Kopka and Haberkorn. No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the ^{68}Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42:197–209.
2. Benešová M, Schäfer M, Bauder-Wüst U, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med.* 2015;56:914–920.
3. Benešová M, Bauder-Wüst U, Schäfer M, et al. Linker modification strategies to control the prostate-specific membrane antigen (PSMA)-targeting and pharmacokinetic properties of DOTA-conjugated PSMA inhibitors. *J Med Chem.* 2016;59:1761–1775.
4. Delker A, Fendler WP, Kratochwil C, et al. Dosimetry for ^{177}Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43:42–51.
5. Kabasakal L, AbuQbeitah M, Aygün A, et al. Pre-therapeutic dosimetry of normal organs and tissues of ^{177}Lu-PSMA-617 prostate-specific membrane antigen (PSMA) inhibitor in patients with castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42:1976–1983.
6. Kratochwil C, Giesel FL, Stefanova M, et al. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with Lu-177 labeled PSMA-617. *J Nucl Med.* March 16, 2016 [Epub ahead of print].
7. Ahmadzadehfar H, Eppard E, Kürpig S, et al. Therapeutic response and side effects of repeated radioligand therapy with ^{177}Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. *Oncotarget.* 2016;7:12477–12488.
8. Kratochwil C, Giesel FL, Bruchertseifer F, et al. ^{213}Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience. *Eur J Nucl Med Mol Imaging.* 2014;41:2106–2119.
9. Apostolidis C, Molinet R, Rasmussen G, Morgenstern A. Production of Ac-225 from Th-229 for targeted alpha therapy. *Anal Chem.* 2005;77:6288–6291.
10. Zielinska B, Apostolidis C, Bruchertseifer F, Morgenstern A. An improved method for the production of Ac-225/Bi-213 from Th-229 for targeted alpha therapy. *Solvent Extr Ion Exch.* 2007;25:339–349.
11. Sgouros G, Roeske JC, McDevitt MR, et al. MIRD pamphlet no. 22 (abridged): radiobiology and dosimetry of alpha-particle emitters for targeted radionuclide therapy. *J Nucl Med.* 2010;51:311–328.
12. Schwartz MA, Lovett DR, Redner A, et al. Dose-escalation trial of M195 labeled with iodine 131 for cytoreduction and marrow ablation in relapsed or refractory myeloid leukemias. *J Clin Oncol.* 1993;11:294–303.
13. Jurcic JG, Larson SM, Sgouros G, et al. Targeted alpha particle immunotherapy for myeloid leukemia. *Blood.* 2002;100:1233–1239.
14. Rubini G, Nicoletti A, Rubini D, Asabella AN. Radiometabolic treatment of bone-metastasizing cancer: from ^{186}rhenium to ^{223}radium. *Cancer Biother Radiopharm.* 2014;29:1–11.
15. McDevitt MR, Ma D, Lai LT, et al. Tumor therapy with targeted atomic nanogenerators. *Science.* 2001;294:1537–1540.
16. Apostolidis C, Molinet R, McGinley J, Abbas K, Möllenbeck J, Morgenstern A. Cyclotron production of Ac-225 for targeted alpha therapy. *Appl Radiat Isot.* 2005;62:383–387.
17. Weidner JW, Mashnik SG, John KD, et al. ^{225}Ac and ^{223}Ra production via 800 MeV proton irradiation of natural thorium targets. *Appl Radiat Isot.* 2012;70:2590–2595.

Downloaded from jnm.snmjournals.org by Weill Cornell Medical Library on August 8, 2016. For personal use only.

The Journal of NUCLEAR MEDICINE

^{225}Ac-PSMA-617 for PSMA targeting alpha-radiation therapy of patients with metastatic castration-resistant prostate cancer

Clemens Kratochwil, Frank Bruchertseifer, Frederik L Giesel, Mirjam Weis, Frederik A Verburg, Felix Mottaghy, Klaus Kopka, Christos Apostolidis, Uwe Haberkorn and Alfred Morgenstern

J Nucl Med.
Published online: July 7, 2016.
Doi: 10.2967/jnumed.116.178673

This article and updated information are available at:
http://jnm.snmjournals.org/content/early/2016/07/27/jnumed.116.178673

Information about reproducing figures, tables, or other portions of this article can be found online at:
http://jnm.snmjournals.org/site/misc/permission.xhtml

Information about subscriptions to JNM can be found at:
http://jnm.snmjournals.org/site/subscriptions/online.xhtml

JNM ahead of print articles have been peer reviewed and accepted for publication in *JNM*. They have not been copyedited, nor have they appeared in a print or online issue of the journal. Once the accepted manuscripts appear in the *JNM* ahead of print area, they will be prepared for print and online publication, which includes copyediting, typesetting, proofreading, and author review. This process may lead to differences between the accepted version of the manuscript and the final, published version.

The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

© Copyright 2016 SNMMI; all rights reserved.

SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING