

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CURIUM US LLC,

Petitioner,

v.

**UNIVERSITÄT HEIDELBERG AND THE EUROPEAN ATOMIC
ENERGY COMMUNITY (EURATOM), REPRESENTED BY THE
EUROPEAN COMMISSION,**

Patent Owners

Case No. IPR2025-01582

Patent No. 10,980,901 B2

DECLARATION OF CLEMENS KRATOCHWIL, M.D.

1. I, Clemens Kratochwil, M.D., submit this declaration in the above-referenced proceeding in support of Patent Owners' Brief Requesting Discretionary Denial of Institution, Patent Owners' Preliminary Response Pursuant to 37 C.F.R. § 42.107, and any subsequent filings by Patent Owners in this matter.
2. I have personal knowledge of the facts in this declaration and, if called as a witness, could and would testify concerning the information in this declaration
3. I am an inventor on U.S. Patent No. 10,980,901 and was involved in the development of the claimed invention.
4. I am not being separately compensated for my work preparing this declaration. I am a full-time physician and researcher at Heidelberg University Hospital, and my statements are based on my education, training, experience, and personal knowledge unless otherwise indicated.
5. My current contact information is as follows:

Department of Nuclear Medicine, University Hospital Heidelberg (UKHD), Im Neuenheimer Feld 400, 69120 Heidelberg, Germany; email:

clemens.kratochwil@med.uni-heidelberg.de.

I. PERSONAL BACKGROUND

6. I am a nuclear medicine professional with advanced expertise in the therapy of oncological diseases using various alpha- and beta-particle emitting radiopharmaceuticals. My clinical practice and research are based at the

Department of Nuclear Medicine at University Hospital Heidelberg in Heidelberg, Germany.

7. I studied medicine at the University of Ulm from 1999 to 2006 and worked on my research thesis (“ ^{18}F -FLT for Monitoring Treatment Response”) in 2007 at the University of Ulm. I received my Doctor of Medicine degree (MD) from the University of Ulm in 2008.
8. Following medical school, I completed residency training in Nuclear Medicine at the Department of Nuclear Medicine at University Hospital Ulm (2006–2007) and University Hospital Heidelberg (2007–2010), including a three-month visiting residency at the Department of Nuclear Medicine, Technical University of Munich (2008), under Prof. Schwaiger.
9. I joined the Department of Nuclear Medicine at Heidelberg University Hospital under Prof. Uwe Haberkorn as a resident in 2007 and subsequently as a fellow/consultant from 2010 to 2013. I have served as the supervising physician of the radioisotope ward at Heidelberg University Hospital since 2013.
10. I became a board-certified specialist in nuclear medicine in Germany in 2012. I have served as a Nuclear Medicine Radiation Safety Officer at University Hospital Heidelberg since 2010.
11. I have been certified to conduct clinical trials as principal investigator (PI) for pharmacological medicines (since 2010) and for medical devices (since 2013). I

also serve as an educational instructor for the nuclear medicine board examination in the state of Baden-Württemberg, Germany (2016–present).

12. The focus of my clinical research is on targeted beta- and alpha-emitter therapy and precision radiopharmaceutical theranostics, including the development and clinical translation of PSMA-ligand-based agents and surrogate imaging approaches. This research resulted in U.S. Patent No. 10,980,901.

13. My work on the patented technology has been recognized internationally, including the EANM Marie Curie Award (2017) and the Therapy Award of the German Society of Nuclear Medicine (2018) for work related to ^{225}Ac -PSMA.

14. I have coauthored more than 180 peer-reviewed scientific articles spanning preclinical and clinical nuclear medicine, with an emphasis on nuclear medicine, including beta- and alpha-emitter-based therapy, PSMA-directed radioligands, and oncologic applications of molecular imaging and therapy.

15. I currently practice and conduct research at Heidelberg University Hospital, Department of Nuclear Medicine, and collaborate closely with institutional and international partners on the clinical translation of novel radiopharmaceuticals.

II. ROLES OF CERTAIN CO-AUTHORS ON KRATOCHWIL 2016

16. I was the lead author on Kratochwil et al., “ ^{225}Ac -PSMA-617 for PSMA-Targeted α -Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer,” *Journal of Nuclear Medicine*, vol. 57, no. 12: 1941-1944 (2016),

which the Petitioner refers to as Kratochwil 2016. I am also an inventor on U.S. Patent No. 10,980,901, which I will refer to as the '901 Patent. I have personal knowledge as to the roles of inventors in the development of the invention patented in the '901 Patent and the role of the non-inventor co-authors on Kratochwil 2016.

17. The conception of the invention claimed in the '901 Patent and disclosed in Kratochwil 2016—including using ^{225}Ac with PSMA-617 and the dosing reported—resided with the inventors, including myself together with Profs. Giesel and Haberkorn and Drs. Bruchertseifer and Morgenstern. The non-inventor co-authors obtained the information disclosed in the paper from the inventors as explained further below.

18. I worked with Dr. Klaus Kopka and others on the development of the ^{177}Lu -PSMA-617 molecule as a cancer treatment. That molecule is claimed in a separate family of patents which predate the '901 Patent's application.

19. After the patents directed to the PSMA-617 molecule were filed in 2013, Dr. Alfred Morgenstern and I discussed the combination of the PSMA-617 molecule with ^{225}Ac . Dr. Morgenstern had extensive experience working with radionuclides, and he and Dr. Bruchertseifer first prepared ^{225}Ac -PSMA-617. Dr. Morgenstern performed the initial stability work on the molecule in serum to evaluate its suitability for use in radiotherapy. It was known that different

radionuclides could decrease the affinity of targeting ligands, such as the PSMA portion of the molecule, by 50%, and the relative biological efficiency of ^{177}Lu to ^{225}Ac was unknown. So, we were still not certain how effective a new ^{225}Ac -based medicine would be at treating PSMA-positive cancers or how tolerable the effective dosage would be.

20. By March 2014, we started the clinical evaluation this new radiotherapeutic at the University Hospital Heidelberg. I did not discuss this work to Dr. Kopka until after we had begun the clinical studies and had already treated a few patients. The other inventors and I conceived of adding ^{225}Ac to the PSMA-617 molecule at the claimed dosages without Dr. Kopka's input. To the best of my knowledge, Dr. Kopka had not worked with ^{225}Ac at that point. We included him as an author on the Kratochwil 2016 publication because we had a friendly and collaborative relationship and as a recognition of Dr. Kopka being one of the main inventors of the PSMA-617 molecule.

21. In December 2014, that is 9 months after we began our clinical work with ^{225}Ac -PSMA-617, Drs. Verburg and Mottaghy at the RWTH University Hospital Aachen approached me with a patient of theirs. They had determined that this patient had metastatic, PSMA-positive, prostate cancer. They knew that I was working on experimental treatments for PSMA-positive cancers and asked me to include him in my study. We started his treatment in January 2015.

He was the 22nd patient receiving ^{225}Ac -PSMA-617.

22. By the time Drs. Verburg and Mottaghy contacted me, I and the other named inventors had already conceived and created the radiotherapeutic molecule and were determining the dosage based on our work with the patients. Drs. Verburg and Mottaghy had no input on any of the elements of the patented invention. They did not administer the therapeutic agent, did not participate in discussions regarding the dosing regimen, and played no role in designing or deciding any aspects of the use of ^{225}Ac -PSMA-617 described in the paper or any other embodiment of the '901 Patent.

23. All or most of the patient scans in the study were performed at our facility.

Figures 4, 5, 6, and 14 of the '901 Patent are scans performed at the University Hospital Heidelberg. Drs. Verburg and Mottaghy had already done the baseline PET/CT scans for their patient before his referral to our hospital for the experimental treatment, so he returned to them for follow-up scans after his treatment in our study.

24. Drs. Verburg and Mottaghy reached out to me again after seeing the results and were very surprised and excited at the quality of the results. They had not expected the complete remission that we obtained with their patient. We had also been obtaining unexpectedly good results with our patients. Drs. Verburg and Mottaghy were so excited that they asked if we could publish the results as

a case report right away. So, rather than waiting for the completion of the full study, we published the Brief Communication in the *Journal of Nuclear Medicine*, which is Kratochwil 2016. We used images from Drs. Verburg's and Mottaghy's patient and one from one of our patients and the safety data that we had been developing. Because we used Drs. Verburg's and Mottaghy's patient's image, we included them in the authorship of Kratochwil 2016. Furthermore, I considered it advantageous if two independent and unbiased physicians from another renowned university hospital, who had examined the patient before and after our treatment with ^{225}Ac -PSMA-617, would confirm the critical baseline condition and the achieved complete remission; otherwise, I would have doubted that other nuclear oncologists would believe the inventors about this extraordinary therapeutic success. However, neither of them had any control over or input in the study and the elements of the invention, such as the molecule and the dosage, which had been determined before they were involved.

25. Mirjam Weis was an employee of the other inventors, Drs. Morgenstern and Bruchertseifer. My interaction with her was primarily in the exchange and management of regulatory information involved in the shipping and sharing of radioactive materials. She was not involved in any of the clinical aspects of the study. To the best of my knowledge, she was not involved in selecting or

determining the dosing regimen and did not contribute to the conception of using ^{225}Ac with PSMA-617 at the claimed dosage levels.

III. INVENTORS' CLINICAL STUDIES ON THE PATENTED TECHNOLOGY

26. Since March 2014, I and the other inventors have been using ^{225}Ac -PSMA-617 in patients and determining efficacy, safety, dosage, etc. This work was done under Article 37 of the Declaration of Helsinki entitled "Unproven Intervention in Clinical Practice" and the related German regulations (widely equivalent of the U.S. Emergency Investigational New Drug application of the FDA), which limits the compassionate use of ^{225}Ac -PSMA-617 to those patients for whom the approved options are inadequate or ineffective, and usually the patients are close to death. Only patients in critical need are allowed to participate in compassionate use studies because experimental treatments may be dangerous and cause unknown side effects or worsen patients' conditions rather than help them.

27. Dr. Giesel, Dr. Haberkorn, and I were the responsible treating physicians in the testing of ^{225}Ac -PSMA-617. Drs. Bruchertseifer and Morgenstern produced the radiopharmaceuticals.

28. After a decade, we had expanded our efforts to treat a total of 233 patients who otherwise had no place else to turn. The results of this ongoing study represent

thousands of hours of work on the part of the inventors and later contributors.

They required the coordinated multidisciplinary efforts across nuclear medicine, radiochemistry, and medical physics. This work is represented by over a dozen publications, some of which are listed below:

²²⁵Ac-PSMA-617 Publications
Kratochwil, C, <i>et al.</i> , ²²⁵ Ac-PSMA-617 for PSMA-Targeted α -Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer, <i>J Nucl Med.</i> 2016 Dec;57(12):1941-1944.
Kratochwil, C, <i>et al.</i> , Targeted α -Therapy of Metastatic Castration-Resistant Prostate Cancer with ²²⁵ Ac-PSMA-617: Dosimetry Estimate and Empiric Dose Finding, <i>J Nucl Med.</i> 2017 Oct;58(10):1624-1631.
Kratochwil, C, <i>et al.</i> , Targeted α -Therapy of Metastatic Castration-Resistant Prostate Cancer with ²²⁵ Ac-PSMA-617: Swimmer-Plot Analysis Suggests Efficacy Regarding Duration of Tumor Control, <i>J Nucl Med.</i> 2018 May;59(5):795-802.
Rathke, H, <i>et al.</i> , Initial clinical experience performing sialendoscopy for salivary gland protection in patients undergoing ²²⁵ Ac-PSMA-617 RLT, <i>Eur J Nucl Med. Mol Imaging.</i> 2019 Jan;46(1):139-147.
Sathekge, M, <i>et al.</i> , ²²⁵ Ac-PSMA-617 in chemotherapy-naïve patients with advanced prostate cancer: a pilot study, <i>Eur J Nucl Med Mol Imaging.</i> 2019 Jan;46(1):129-138.
Sathekge, M, <i>et al.</i> , Treatment of brain metastases of castration-resistant prostate cancer with ²²⁵ Ac-PSMA-617, <i>Eur J Nucl Med Mol Imaging.</i> 2019 Jul;46(8):1756-1757.
Scheiser, HH, <i>et al.</i> , DNA damage in human whole blood caused by radiopharmaceuticals evaluated by the comet assay, <i>Mutagenesis.</i> 2019 Sep 20;34(3):239-244.
Sathekge, M, <i>et al.</i> , Predictors of Overall and Disease-Free Survival in Metastatic Castration-Resistant Prostate Cancer Patients Receiving ²²⁵ Ac-PSMA-617 Radioligand, <i>Therapy, J Nucl Med.</i> 2020 Jan;61(1):62-69.

Kratochwil, C, <i>et al.</i> , ^{225}Ac -PSMA-617 for Therapy of Prostate Cancer, <i>Semin Nucl Med.</i> 2020 Mar;50(2):133-140.
Kratochwil, C, <i>et al.</i> , Patients Resistant Against PSMA-Targeting α -Radiation Therapy Often Harbor Mutations in DNA Damage-Repair-Associated Genes, <i>J Nucl Med.</i> 2020 May;61(5):683-688.
Feuerecker, B, <i>et al.</i> , Activity and Adverse Events of Actinium-225-PSMA-617 in Advanced Metastatic Castration-resistant Prostate Cancer After Failure of Lutetium-177-PSMA, <i>Eur Urol.</i> 2021 Mar;79(3):343-350.
Van der Doelen, MJ, <i>et al.</i> , Clinical outcomes and molecular profiling of advanced metastatic castration-resistant prostate cancer patients treated with ^{225}Ac -PSMA-617 targeted alpha-radiation therapy, <i>Urol Oncol.</i> 2021 Oct;39(10): 729.e7-729.e16. NCT01855477
Lawal, IO, <i>et al.</i> , Hematologic toxicity profile and efficacy of [^{225}Ac]Ac-PSMA-617 α -radioligand therapy of patients with extensive skeletal metastases of castration-resistant prostate cancer, <i>Eur J Nucl Med Mol Imaging.</i> 2022 Aug;49(10):3581-3592.
Sathekge, M, <i>et al.</i> , mCRPC Patients Receiving ^{225}Ac -PSMA-617 Therapy in the Post-Androgen Deprivation Therapy Setting: Response to Treatment and Survival Analysis, <i>J Nucl Med.</i> 2022 Oct;63(10):1496-1502.
Sathekge, M, <i>et al.</i> , ^{225}Ac -PSMA-617 radioligand therapy of de novo metastatic hormone-sensitive prostate carcinoma (mHSPC): preliminary clinical findings, <i>Eur J Nucl Med Mol Imaging.</i> 2023 Jun;50(7):2210-2218.
Feuerecker, B, <i>et al.</i> , Comparative Analysis of Morphological and Functional Effects of ^{225}Ac - and ^{177}Lu -PSMA Radioligand Therapies (RLTs) on Salivary Glands, <i>Int J Mol Sci.</i> 2023 Nov 28;24(23):16845.
Sathekge, M, <i>et al.</i> , Actinium-225-PSMA radioligand therapy of metastatic castration-resistant prostate cancer (WARMTH Act): a multicentre, retrospective study, <i>Lancet Oncol.</i> 2024 Feb;25(2):175-183.
Rathke, H, <i>et al.</i> Deescalated ^{225}Ac -PSMA-617 Versus $^{177}\text{Lu}/^{225}\text{Ac}$ -PSMA-617 Cocktail Therapy: A Single-Center Retrospective Analysis of 233 Patients, <i>J Nucl Med.</i> 2024 Jul 1;65(7):1057-1063.

29. At the time of our clinical studies, there was no evidence that ^{225}Ac would work better than ^{177}Lu and it could have been much worse. While we were hopeful that it would do as well as ^{177}Lu , we did not, and could not, expect the level of remission that we achieved.

30. I understand that the '901 Patent has been licensed by both Fusion Pharmaceuticals and Novartis Pharmaceuticals, who are also preparing for or have performed clinical studies with molecules claimed by the '901 Patent. I also understand that Dr. Morgenstern is overseeing additional prospective clinical trials in South Africa.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed this 2 day of December, 2025.



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