

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

SUPPLEMENTAL DECLARATION OF CLEMENS KRATOCHWIL, M.D.

1. I, Clemens Kratochwil, M.D., submit this supplemental declaration in the above-referenced proceeding in support of Patent Owners' filings 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. My qualifications, background, credentials, and professional experience were set forth in my earlier Declaration dated December 2, 2025, submitted in this proceeding. I incorporate that description by reference and do not repeat it here.
4. I am not being separately compensated for this supplemental 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.

I. IMAGING OF ACTINIUM-225

5. I have been informed that in his deposition, Prof. Zalutsky repeatedly stated that imaging of actinium-225 would not be possible. Prof. Zalutsky is not correct.
6. Multiple independent research groups from around the world have published articles demonstrating imaging of Ac-225 with clinical standard equipment.
7. As one example, Miederer 2008b (Exhibit 1030) discusses in section "3. Physical and chemical properties of ^{225}Ac " that ^{225}Ac decay yields several disintegrations, "from which the ^{213}Bi 440 keV γ emission has been used in imaging drug distribution".
8. In the Kratochwil 2016 paper (Exhibit 1045), we described in the "Imaging" section that we scanned three photopeaks: the 440 keV gamma co-emission of Bi-213, the 218 keV gamma co-emission of Fr-221, and the bremsstrahlung of Pb-209 (which is not a peak but a range around 78 keV). The planar whole-body images of these scans are provided in the supplement to the paper.
9. Thus, the posttherapeutic emission scans do validate that Ac-225 is targeted to the tumor. Not only do they evidence Ac-225 tumor targeting, but they further demonstrate that Ac-225 *as well as its daughter isotopes* are tumor bound. This is important because bismuth-213 is the most critical isotope in the decay chain—if it escapes from the tumor, it could accumulate in the renal cortex.
10. The method suggested by Prof. Zalutsky of scanning for actinium-225 directly in biopsy tissue would be inferior because it would not provide information about the *in vivo* fate of the generated daughter nuclides. Our imaging approach provides direct evidence that the daughter nuclides remain at the tumor sites rather than migrating to the kidneys.

Additionally, Dr. Zalutsky's suggestion is invasive for human patients and would not be able to cover all the locations of metastasis.

II. LEVEL OF EVIDENCE AND RESPONSE TO PROF. ZALUTSKY'S CRITICISMS

11. Even if Ac-225 imaging were not possible (which it is), Prof. Zalutsky sets the bar too high by requiring biopsies to be convinced that it was Ac-225-PSMA-617 that got rid of the tumors. Tissue sampling may be one of the standard approaches in mice studies, but in human patients measuring cancer treatment response is generally performed differently.
12. Evidence of efficacy was also provided by diagnostic Ga-68-PSMA-11 PET/CT imaging before and several months after Ac-225-PSMA-617 treatment. Prof. Zalutsky is a PhD in chemistry who himself disclosed that he has never worked directly with patients. Imaging response and decline of tumor markers are common methods for monitoring anti-tumor activity in early phase trials.
13. The then-valid consensus criteria of experts in the field (the Prostate Cancer Clinical Trials Working Group) recommended PSA waterfall graphs as a good surrogate for anti-tumor activity in early phase studies of novel treatments. See *Scher HI et al., "Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3," J Clin Oncol 34(12) (2016), pp. 1402–18.*
14. I have been informed that in his deposition, Prof. Zalutsky claims that he is "probably not convinced that it was the actinium-225-PSMA-617 that got rid of the tumor". In my opinion, this statement contrasts with his earlier statements that "alpha-particle emitters were known for their potentially improved therapeutic efficacy as compared to beta emitters". In my opinion, this inconsistency demonstrates that the dramatic outcome observed was truly unexpected and not obvious.
15. The follow-up period is sufficient to demonstrate surprisingly long enduring treatment response. In Figure 1 of Kratochwil 2016, the baseline diagnostics were from December 2014, and the complete remission dates to September 2015. In Figure 3, baseline diagnostics date to September 2015, and the last follow-up (in a much improved clinical situation) dates to April 2016. Thus, we demonstrate a duration of imaging-based progression free survival of at least 7 and 9 months, with ongoing remission suggesting an even longer response.

III. KRATOCHWIL 2016 RESULTS AND PRIOR STUDIES

16. In the statement “Thus, radioligand therapy with ^{225}Ac -PSMA-617 ideally matches the theoretic considerations for targeted α -therapy of mCRPC” at the end of page 1943 of Kratochwil 2016, “theoretic considerations” referred to our theoretic considerations for the properties that an optimal radiopharmaceutical would have for treating mCRPC.
17. My previous work with alpha emitter Bi-213, which I cite in Kratochwil 2016 as “demonstrating that targeted α -radiation therapy with ^{213}Bi -DOTATOC could break radioresistance to β -emitters” did not support this optimal treatment. While it did have an effect on the cancer, it had to be given at high levels of radioactivity in the 3.3-10.5 GBq dosage range to achieve only partial responses. This is in dramatic contrast with the Kratochwil 2016 paper that achieved complete remission with over a thousand times lower dosage of three treatments with 6.4 MBq.
18. The results of ^{225}Ac -DOTATOC were also not impressive. That is why we published the final results of the ^{225}Ac -DOTATOC dose escalation MTD without ever publishing efficacy data.
19. At the time, there was significant skepticism about the clinical use of actinium-225. Among my physician peer group, actinium-225 was considered a preclinical radionuclide. More widespread clinical use was not a significant topic of discussion. After I made my presentation on my work on ^{225}Ac -DOTATOC, I received comments that more long-term follow-up would be needed regarding late toxicity such as chronic kidney disease or myelodysplastic syndrome, and that it was too early to state that our dosage of ^{225}Ac -DOTATOC would be safe. So there was significant doubt as to the safety of ^{225}Ac .
20. It was known that the radionuclide inside the chelator can influence pharmacokinetics, binding affinity, and eventually internalization. However, at the time, a log *KML* value for ^{225}Ac (which Prof. Zalutsky agreed is important to predict chelator-metal-complex stability) had not yet been measured, and it was still questionable whether the geometry of actinium DOTA chelates is identical to lutetium DOTA chelates. It was unpredictable how ^{225}Ac labeling would affect, for example, the overall charge of ^{225}Ac -PSMA-617 in comparison to ^{177}Lu -PSMA-617.
21. It was already known that if the ^{225}Ac daughter Bi-213 is generated in the bloodstream, it can accumulate in the renal cortex and do damage there. It was also known that due to the recoil of the ^{225}Ac alpha decay, the Bi-213 escapes the chelator. There was a good chance it would do damage to the kidneys.
22. The work on the internalization on PSMA-targeting molecules had been done *in vitro*, which is not the same as *in vivo* human studies. *In vitro* cell studies combine the cells with the radiopharmaceutical so they can attach and be internalized easily. But in the

body, there can be additional complications. The radiopharmaceutical can be metabolized, or not find its target because it does not have access, or be fully absorbed by healthy tissue, or not have the same binding or internalization because the micro environment (the local pH or ionic strength) cause it to work differently from cell culture.

23. This is why, as part of our study, we wanted to demonstrate sufficient tumor targeting on page 1942 of the Kratochwil 2016 paper.
24. Our results then demonstrated that the in vivo characteristics of Ac-225-PSMA-617 were a perfect match to these theoretical requirements. The statement in Kratochwil 2016 concerning theoretical considerations was noting that we had accomplished something very unlikely by marking all the boxes. Something like: “mission accomplished.”
25. This is why we published early and wrote in the first paragraph of the discussion section of Kratochwil 2016: “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.” This shows how impressive we considered the Ac-225-PSMA-617 results to be.

V. COMPASSIONATE USE UNDER THE DECLARATION OF HELSINKI

26. The clinical studies were conducted under Article 37 of the Declaration of Helsinki (2013 version), which governs “Unproven Interventions in Clinical Practice.” Article 37 states:

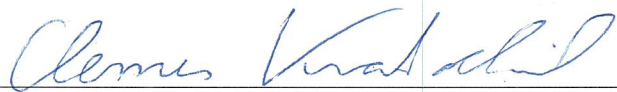
“In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.”

27. The Declaration of Helsinki requires that “in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering.” The Declaration of Helsinki is not directly binding law; participating nations agree to translate its content into their respective national regulations to become binding law.
28. This treatment was used precisely because the patients had exhausted all approved options and the physician didn’t reasonably expect that other known therapies would provide effective treatment. These were patients with nothing left to lose. The treatment

was administered because, in my physician's judgment, it offered hope – but hope differs from expectation. There were too many unknowns and risks associated to have an expectation that the treatment would work. The results we actually obtained belonged more in the category of what a physician can dream of rather than expect.

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

Date: 21. August 2026

A handwritten signature in blue ink, reading "Clemens Kratochwil", written over a horizontal line.

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