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RESIST-PC: US Academic Foray into PSMA Theranostic Trials

Amir Iravani, MD[1] and Thomas Hope, MD[2]

1. Mallinckrodt Institute of Radiology, Washington University in St Louis, St Louis, MO
2. Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA

Corresponding Author:
Thomas Hope, MD
Associate Professor in Residence
Department of Radiology and Biomedical Imaging
University of California San Francisco
185 Berry Street, Lobby 6, Suite 350
San Francisco, CA 94107
Email: thomas.hope@ucsf.edu

In the accompanying article, Calais et al. from UCLA present the results of their Phase 2 RESIST-PC trial (*1*). This trial pre-dated the VISION trial, and enrolled patients prospectively in a two-arm study intended to compare the efficacy and safety of ^{177}Lu-PSMA-617 dosed at either 6.0 or 7.4 GBq. The study was performed collaboratively between UCLA and Excel Diagnostics, although only the 43 patients enrolled at UCLA are presented in the manuscript. The UCLA team must be commended for the effort in initiating and performing this study without company support. It cannot be understated the effort required to open the first ^{177}Lu - PSMA trial in the United States.

The absence of support for this study required the cost recovery mechanism to be used, something that is not commonly leveraged for therapeutic trials. Unlike in the Australian Phase 2 study (*2*), where the Lutetium-177was provided for free from Australian Nuclear Science and Technology Organization (ANSTO, Sydney, Australia), the study team had to procure Lutetium-177 at cost. It should be noted that prior diagnostic cost-recovery trials have led to the approval of both ^{68}Ga-DOTATOC and ^{68}Ga-PSMA-11 (*3*,*4*). Currently, it may seem odd that there was no corporate support for this study given the large interest in the field we see today, but at the time of trial design, this was not the case. Similar to cost-recovery, many European studies have leveraged compassionate use in the absence of company support (*5*).

Looking at the results presented for the RESIST-PC trial, the PSA response (≥ 50% PSA decline) was 37% which is lower than reported in the LuPSMA (64%) and TheraP (66%) trials (*1*,*2*,*6*). Although the inclusion criterion for PSMA expression was not predefined in RESIST-PC trial, the difference in PSA response may be accounted for by a lower threshold of PSMA PET avidity. The LuPSMA trial required an SUVmax of one and half times above the liver, while the TheraP trial required an SUVmax of 20 at one site with no measurable disease below

SUVmax of 10. In addition, the LuPSMA and TheraP trials used ^{18}F-FDG PET/CT to exclude patients with disease heterogeneity and sites of disease demonstrating low PSMA expression. In the LuPSMA and TheraP trials, 25-30% of patients were excluded, while in RESIST-PC trial only 2 patients (< 5%) were excluded based on PSMA expression. PSMA expression is critical, as shown by Violet et al., who demonstrating a positive correlation between pre-treatment PSMA uptake and post-treatment dosimetry in whole-body scale and further supported by Seifert et al. showing low average PSMA expression is a negative prognostic factor (*7,8*).

The VISION trial used a lower cutoff of a PSMA positive lesion greater than liver with no negative PSMA lesions, which resulted in 13% of patients being excluded, more than twice as many as in the RESIST-PC study (*9*). In the VISION trial, 46% of patients treated with ^{177}Lu-PSMA-617 had a greater than 50% reduction, nearly between the RESIST-PC trial and the TheraP/LuPSMA studies, again supporting the idea that the higher the cutoff for PSMA positivity combined with ^{18}F-FDG imaging, the better the response to treatment (*9*).

While it appears the higher threshold for PSMA avidity would result in a higher response rate, the threshold of PSMA avidity below which the patients may not respond to treatment remains unclear. It is also possible that patients with a limited volume of the discordant ^{18}F-FDG-avid disease may derive some benefit from ^{177}Lu-PSMA, subject to sufficient PSMA expression in other sites and as long as a more intensive therapeutic strategy be adopted. This may support the combination with other oncologic treatments to tackle sites which may have been sub-optimally targeted by ^{177}Lu-PSMA. Multiple phase I/II combinations regimens are underway using immunotherapy (NCT03658447, NCT03805594), PARP inhibitor (NCT03874884), androgen receptor-targeted therapy (NCT04419402), and even tandem treatment with chemotherapy in the castrate-sensitive state (NCT03828838).

A separate issue with ^{177}Lu-PSMA therapy, is that the optimal treatment schedule is not well understood, including administered activity per cycle, the interval between treatments and the number of treatments/cumulative activity (*10*). The choice of fixed administered activity between 6-8 GBq and up to six cycles is predominantly based on the limits of normal organ absorbed dose and thresholds extrapolated from external beam radiotherapy, ignoring fundamental differences of radiobiology of radiopharmaceutical therapies. One of the most interesting aspects of RESIST-PC, was that it attempted to determine the difference in efficacy and toxicity between two different doses of ^{177}Lu-PSMA-617, although the narrow difference between the doses and the premature closure of the study prevented the team from determining which dose was superior. Determination of the appropriate number of cycles, dose per cycle and timing between cycles still remains an art form in radioligand therapy. Attempts are being made to study this, for example, Weill Cornell is studying two higher dose cycles (up to 11.1 GBq) given two weeks apart (NCT03042468).

It seems self-evident that straying from the rigid treatment plans used in these trials would be beneficial. For example, one could continue therapy beyond six cycles in a subset of patients that continues benefit from treatment, increase intervals beyond 6-8 weeks in early responders, or rechallenge treatment at the time of progression subject to sufficient target expression have to be considered (*11*). Furthermore, incorporating post-treatment dosimetry will enhance our understanding of differences in absorbed doses in tumor and critical organs and how it impacts patient outcome. While the oversimplified approach of “one size fits all” would expedite the approval and increase the accessibility of this treatment, this should not hinder exploiting the fundamental strengths of this treatment modality which allows individualizing the

treatment based on the patient's characteristics and tumor biology as well as dynamically modifying the treatment schedule based on response to treatment and post-treatment dosimetry.

It is unfortunate that the completion of the RESIST-PC study was halted when the VISION trial started enrollment, as evaluating the difference in two different doses would have provided valuable information for the community. As we patiently await the approval of ^{177}Lu-PSMA-617 in light of the positive overall survival data from the VISION study, we would like to encourage members of the nuclear medicine community to develop and engage in multi-institutional trials as well as participate in NCI cooperative groups, similar to what has proven successful in Australia.

DISCLOSURES

TAH is a consultant for Curium, and he received fees from Blue Earth Diagnostics and Ipsen outside of the submitted work.

REFERENCES

1. Calais J, Gafita A, Eiber MR, et al. Prospective phase 2 trial of PSMA-targeted molecular RadiothErapy with ^{177} Lu-PSMA-617 for metastatic Castration-reSISTant Prostate Cancer (RESIST-PC): Efficacy results of the UCLA cohort. *J Nucl Med*. May 2021:jnumed.121.261982.

2. Hofman MS, Sandhu S, Eu P, et al. Lutetium-177 PSMA (LuPSMA) theranostics phase II trial: Efficacy, safety and QoL in patients with castrate-resistant prostate cancer treated with LuPSMA. *Ann Oncol*. 2017;28.

3. Sartor O, Hope TA, Calais J, Fendler WP. Oliver Sartor Talks with Thomas A. Hope, Jeremie Calais, and Wolfgang P. Fendler About FDA Approval of PSMA. *J Nucl Med*. 2021;62:146-148.

4. Sunderland JJ. The Academic NDA: Justification, Process, and Lessons Learned. *J Nucl Med*. 2020;61:jnumed.119.238287-487.

5. Rahbar K, Ahmadzadehfar H, Kratochwil C, et al. German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. *J Nucl Med*. 2017;58:85-90.

6. Hofman MS, Goh JC, Tan TH, et al. [177Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *The Lancet*. 2021;351:1502-106.

7. Seifert R, Seitzer K, Herrmann K, et al. Analysis of PSMA expression and outcome in patients with advanced Prostate Cancer receiving ^{177} Lu-PSMA-617 Radioligand Therapy. *Theranostics*. 2020;10:7812-7820.

8. Violet J, Jackson P, Ferdinandus J, et al. Dosimetry of 177Lu-PSMA-617 in Metastatic Castration-Resistant Prostate Cancer: Correlations Between Pretherapeutic Imaging and Whole-Body Tumor Dosimetry with Treatment Outcomes. *J Nucl Med*. 2019;60:517-523.

9. Sartor O, de Bono J, Chi KN, et al. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med*. June 2021:NEJMoa2107322.

10. Iravani A, Violet J, Azad A, Hofman MS. Lutetium-177 prostate-specific membrane antigen (PSMA) theranostics: practical nuances and intricacies. *Prostate Cancer Prostatic Dis*. 2020;23:38-52.

11. Violet J, Sandhu S, Iravani A, et al. Long term follow-up and outcomes of re-treatment in an expanded 50 patient single-center phase II prospective trial of Lutetium-177 (177Lu) PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. *J Nucl Med*. November 2019.