Nuclear Medicine Beyond VISION

Wolfgang P. Fendler[1], Ken Herrmann[1], and Matthias Eiber[2]

[1]*Department of Nuclear Medicine, University of Duisburg–Essen and German Cancer Consortium–University Hospital Essen, Essen, Germany; and* [2]*Department of Nuclear Medicine, Technical University of Munich, Munich, Germany*

In March 2021, Novartis announced a positive result for both primary endpoints of the randomized phase III VISION study on ^{177}Lu-PSMA-617 radioligand therapy (RLT). ^{177}Lu-PSMA-617 RLT and the best standard of care improved both overall and radiographic progression-free survival when compared with the best standard of care alone in patients with metastatic castration-resistant prostate cancer (mCRPC) who had already been exposed to taxane-based chemotherapy and novel androgen-axis drugs. The success of VISION is perhaps the most significant event in nuclear medicine of the past few decades and a major advance in the management of metastatic prostate cancer.

How did the vision of novel theranostics become a reality? Radiolabeled somatostatin receptor ligands have been successfully applied by European investigators since the late 1990s. Decades later, an international randomized phase III study proved the unprecedented efficacy of somatostatin receptor–directed peptide-receptor radionuclide therapy of metastatic neuroendocrine tumors (*1*). Fueled by the early clinical success of peptide-receptor radionuclide therapy, researchers at Johns Hopkins and later Heidelberg University developed PSMA-directed theranostic probes, among which were ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 for PET imaging and RLT, respectively (*2*). Long before VISION became a reality, academia with patient support developed a vision of PSMA theranostics. Nuclear medicine teams in Europe and Australia initiated access to PSMA RLT through clinical trials or compassionate use. Early compassionate access, often criticized for impeding approval (*3*), in fact contributed retrospective evidence critically needed for trial design and to leapfrog phase I and II studies. Despite limited public funding, several retrospective and prospective investigator-initiated trials were completed. Hallmark trials were led by researchers of the Peter MacCallum Cancer Centre in Melbourne. Among those numerous initiatives, the randomized TheraP study recently demonstrated a superior prostate-specific antigen response rate, time to progression, and safety for ^{177}Lu-PSMA-617 when compared with cabazitaxel in patients with advanced prostate cancer (*4*). VISION now proves survival benefit, clearing a path to regulatory approval and widespread use.

Anticipated ^{177}Lu-PSMA-617 and recent ^{68}Ga-PSMA-11 approvals herald global expansion of radiotheranostics for prostate cancer (*5*). More important, PSMA targeting rolls in as a platform solution with numerous compounds and radiolabels beyond the VISION framework. More than 20 clinical studies assess the efficacy of PSMA-directed RLT across all relevant stages of prostate cancer, using different ligands and nuclides. The anticipated rapid expansion of PSMA RLT comes with imminent challenges and opportunities for our health systems, and particularly the nuclear medicine and urooncology communities.

A recent study of the German mCRPC target population estimates eligibility for more than 38,000 PSMA RLT cycles each year (*6*). Assuming equal mCRPC prevalence, patients in the United States and the European Union combined would be eligible for more than 350,000 PSMA RLT applications annually. Such unprecedented expansion of radiopharmaceutical applications pushes clinic operations to their capacity limit and beyond. The nuclear medicine infrastructure needs to gear up at warp speed to meet this demand. This means that health systems with strong nuclear medicine services need to reorganize resources for fast access. More importantly, countries with declining or faded nuclear medicine therapeutic programs need to rebuild clinics and rejuvenate independent physician-training programs. PSMA RLT will succeed only in an independent nuclear medicine environment (*7,8*).

Second, the VISION design underlines a fundamental change in nuclear medicine practice: PSMA RLT will be integrated into the best standard of care along with bone agents, external radiation, or novel androgen-axis drugs. Combination treatment with immunotherapy or inhibitors of DNA damage response, including poly(adenosine diphosphate-ribose)polymerase, are being explored in early clinical trials to leverage potential additive effects. In consequence, nuclear medicine needs to join forces with urooncology for optimal management of PSMA RLT candidates. To be accepted as equal clinical partners, nuclear medicine physicians need to advance their clinical knowledge and skills in treating late-stage cancer.

Third, ^{177}Lu-PSMA-617 is part of a versatile platform of PSMA radioligands. More than 10 different compounds are under phase II or III clinical investigation for therapy, surgical guidance, or various forms of prostate cancer imaging. Among these, unlicensed compounds such as PSMA-11 or PSMA-I&T offer free access for industry and academia (*9*). PSMA-I&T RLT is under phase III investigation (NCT04647526). Exchangeable α- to γ-emitting radiolabels enable modular efficacy and a reliable supply. This basket of free and commercial PSMA radioligands under clinical investigation is unparalleled and will catalyze treatment optimization and availability through competition. Not surprisingly, ^{177}Lu-PSMA-617 RLT has moved to earlier lines, with assessment in prechemotherapy mCRPC (NCT04689828) or castration-sensitive prostate cancer patients (NCT047201579) under way.

Received Apr. 14, 2021; revision accepted Apr. 15, 2021.

For correspondence or reprints, contact Wolfgang P. Fendler (wolfgang.fendler@uk-essen.de).

DOI: 10.2967/jnumed.121.262441

Successful translation of somatostatin receptor- and now PSMA-directed therapy sends clear signals to academia and industry. Radiotheranostic development yields high mid- and long-term returns. Thus, many initiatives are currently exploring ways to expand theranostics beyond prostate cancer to other high-incidence tumors (*10*). Novel targets such as fibroblast activation protein, integrins, or bombesin receptors are under investigation worldwide. Meanwhile, clinicians need to leverage unique advantages of PSMA RLT over conventional systemic therapy: target modulation and dosimetry guidance should be assessed in clinical trials.

Enzalutamide was associated with enhanced PSMA expression in vitro, in vivo, and in clinical trials (*11*). Thus, short pretreatment with enzalutamide may lead to higher efficacy of PSMA RLT through improved radiation delivery. Other approaches aim at reduced radioligand uptake of physiologic organs, foremost the salivary glands.

VISION implemented a standard activity of 7.4 GBq of ^{177}Lu-PSMA-617 for each cycle. However, preliminary data demonstrate the feasibility of using up to 22 GBq of ^{177}Lu-PSMA-617 given within a short time interval without excess toxicity (*12*). Intratherapeutic dosimetry reveals individual-organ dose limits for guidance. Patients with a higher risk of nonresponse, fast disease progression, or an intermediate level of tumoral PSMA expression might benefit from high-activity therapy guided by individual patient dosimetry.

Taken together, VISION clears a path to ^{177}Lu-PSMA-617 approval and widespread clinical implementation for patients with mCRPC. PSMA RLT expansion leads to improved prostate cancer outcomes and fuels growing interest in theranostic technology, personalized dosimetry, and combination therapy. Nuclear medicine needs to gear up for a rapidly increasing volume of radioligand applications. PSMA RLT will be applied by a new generation of nuclear theranosticians as part of interdisciplinary cancer care.

DISCLOSURE

Wolfgang Fendler is a consultant for Endocyte and BTG, and he received fees from RadioMedix, Bayer, and Parexel outside the submitted work. Ken Herrmann receives personal fees from Bayer SIRTEX, Adacap, Curium, Endocyte, IPSEN, Siemens Healthineers, GE Healthcare, Amgen, Novartis, and ymabs; personal fees and other from Sofie Biosciences; nonfinancial support from ABX; and grants and personal fees from BTG, outside the submitted work. Matthias Eiber has an advisory role with Blue Earth Diagnostics, Point Biopharma, Telix, and Janssen and a patent application for rhPSMA. No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med.* 2017;376:125–135.
2. Benešová M, Schafer M, Bauder-Wust 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. Paschalis A, Tombal B, de Bono JS. Prostate-specific membrane antigen theranostics for prostate cancer care: a need to prove clinical utility. *Eur Urol Focus.* 2021;7:231–233.
4. Hofman MS, Emmett L, Sandhu S, et al. [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet.* 2021;397:797–804.
5. 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.
6. Zippel C, Giesel FL, Kratochwil C, et al. PSMA radioligand therapy could pose infrastructural challenges for nuclear medicine: results of a basic calculation for the capacity planning of nuclear medicine beds in the German hospital sector [in German]. *Nuklearmedizin.* February 2, 2021 [Epub ahead of print].
7. Czernin J, Herrmann K. The disappearance act of nuclear medicine in The Netherlands: just a new trick by the great Harry Houdini? *J Nucl Med.* March 12, 2021 [Epub ahead of print].
8. Velleman T, Noordzij W, Dierckx R, Ongena Y, Kwee TC. The new integrated nuclear medicine and radiology residency program in the Netherlands: why do residents choose to subspecialize in nuclear medicine and why not? *J Nucl Med.* March 12, 2021 [Epub ahead of print].
9. Notni J. PSMA-targeted therapeutics: a tale about law and economics. *J Nucl Med.* March 31, 2021 [Epub ahead of print].
10. Langbein T, Weber WA, Eiber M. Future of theranostics: an outlook on precision oncology in nuclear medicine. *J Nucl Med.* 2019;60(suppl):13S–19S.
11. Emmett L, Yin C, Crumbaker M, et al. Rapid modulation of PSMA expression by androgen deprivation: serial ^{68}Ga-PSMA-11 PET in men with hormone-sensitive and castrate-resistant prostate cancer commencing androgen blockade. *J Nucl Med.* 2019;60:950–954.
12. Tagawa ST, Osborne JR, Hackett A, et al. Preliminary results of a phase I/II dose-escalation study of fractionated dose ^{177}Lu-PSMA-617 for progressive metastatic castration resistant prostate cancer (mCRPC) [abstract]. *Ann Oncol.* 2019;30:V329–V330.