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Title:
Nuclear Medicine beyond VISION

Editorial

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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 best standard of care improved both overall and radiographic progression-free survival when compared with best standard of care alone in patients with metastatic castration-resistant prostate cancer (mCRPC) who have already been exposed with taxane-based chemotherapy and novel androgen axis drugs. VISION success is perhaps the most significant event in Nuclear Medicine of the past decades and a major advance in the management of metastatic prostate cancer.

How did the vision of novel theranostics become reality? Radiolabeled somatostatin receptor (SSTR) ligands were successfully applied by European investigators since the late 1990ies. Decades later an international randomized phase III study proved unprecedented efficacy of SSTR-directed peptide-receptor radionuclide therapy (PRRT) of metastatic neuroendocrine tumors (*1*). Fueled by the early clinical success of PRRT, Johns Hopkins and later Heidelberg University researchers developed PSMA-directed theranostic probes, among these ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 for PET imaging and radioligand therapy, respectively (*2*). Long before VISION became 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/II studies. Despite limited public funding several retrospective and prospective investigator-initiated trials (IIT) 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 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-PSMA11 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 Uro-Oncology 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 US and EU combined would be eligible for more than 350.000 PSMA RLT applications annually. Such unprecedented expansion of radiopharmaceutical applications pushes clinic operations and supply chains to their capacity limit and beyond. The Nuclear Medicine infrastructure needs to gear-up at warp speed to meet this demand. This means, health systems with strong Nuclear Medicine service 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 only succeed 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 best standard of care along with bone agents, external radiation, and/or novel androgen axis drugs. Combination treatment with immunotherapy or inhibitors of DNA damage response, including PARP, are explored in early clinical trials to leverage potential additive effects. In consequence, Nuclear Medicine needs to join forces with Uro-Oncology 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 ten different compounds are under Phase II/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 3 investigation (NCT04647526 among others). Exchangeable alpha to gamma-emitting radiolabels enable modular efficacy and 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 surprising, ^{177}Lu-PSMA-617 RLT moves to earlier lines with assessment in pre-chemotherapy CRPC (NCT04689828) or castration-sensitive prostate cancer patients (NCT047201579) underway.

Successful translation of SSTR- and now PSMA-directed therapy sends clear signals to academia and industry. Radiotheranostic development yields high mid- and long-term returns. Not surprising 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 (FAP), 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 enzalutamide pre-treatment 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 ^{177}Lu-PSMA-617 for each cycle. However, preliminary data demonstrate feasibility of up to 22 GBq ^{177}Lu-PSMA-617 in a single cycle without excess toxicity (*12*). Intratherapeutic dosimetry reveals individual organ dose limits for guidance. Patients with higher risk for non-response, fast disease progression, or intermediate tumoral PSMA expression level 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 an ever-increasing volume of radioligand applications. PSMA RLT will be applied by a new generation of Nuclear 'Theranosticians' as part of interdisciplinary cancer care.

Conflict of Interest

Wolfgang Fendler is a consultant for Endocyte and BTG, and he received fees from RadioMedix, Bayer, and Parexel outside of the submitted work.
Ken Herrmann reports personal fees from Bayer SIRTEX, Adacap, Curium, Endocyte, IPSEN, Siemens Healthineers, GE Healthcare, Amgen, Novartis, and ymabs, personal fees and other from Sofie Biosciences, non-financial support from ABX, grants and personal fees from BTG, outside the submitted work.
Matthias Eiber reports an advisory role for Blue Earth Diagnostics, Point Biopharma, Telix and Janssen and patent application for rhPSMA.

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