Journal of Nuclear Medicine, published on August 26, 2019 as doi:10.2967/jnumed.119.234054

Is the "VISION" of Radioligand Therapy for Prostate Cancer becoming reality?

An Overview of the Phase III trial and the Importance for the Future of Theranostics

Kambiz Rahbar[1] and Michael J. Morris[2]

1. Department of Nuclear Medicine, University Hospital Muenster, Muenster, Germany
2. Department of Genitourinary Oncology Service and Medicine, Memorial Sloan-Kettering Cancer Center, New York, USA

Short title: VISION and the Future of Theranostics
Key words: Prostate Cancer, PSMA targeted therapy, theranostics

Corresponding Author:
Kambiz Rahbar MD
Department of Nuclear Medicine,
University Hospital Muenster
Albert-Schweitzer-Campus 1
D-48149 Münster
Germany
Tel: +49-251-8347362
rahbar@uni-muenster.de

Noteworthy

- PSMA targeted ligands have significantly changed the management of prostate cancer patients.
- Phase III "VISION" trial is needed to prove the benefit of this novel therapeutic according to current oncological standards.
- If "VISION" fails, this would be a draw back for the entire field of theranostics.

The Theranostic approach

Prostate cancer is the most common cancer and the second most common cause of cancer-related death in men (1). Evolving diagnostic and therapeutic strategies for men with advanced stage, metastatic, prostate cancer have revolutionized the field and are of major clinical and economic interest, with the potential to extend survival while maintaining quality of life. One such strategy involves the use of agents that combine diagnostic and therapeutic capabilities. These agents can identify the presence of a target on a patient's cancer and normal tissues, in order to enhance the likelihood of patient benefit and minimize needless exposure or normal organ toxicity. Some term the development of these agents as "theranostics."

One molecular target of intense interest has been prostate specific membrane antigen (PSMA), a transmembrane protein that was discovered over 25 years ago and has been the subject of intense investigation since. (2-11) The ability to identify PSMA expressing prostate cancer cells using a non-invasive imaging-based method, followed by administration of experimental therapy, has led to the development of ^{68}Ga-PSMA-11, a diagnostic compound used to select patients for experimental treatment with ^{177}Lu-PSMA-617 radioligand (3, 12, 13).

Developed by the German Cancer Center in Heidelberg, PSMA-617 labelled with Lutetium-177 (i.e., ^{177}Lu-PSMA-617) has garnered attention as an experimental therapeutic compound showing promising response rates and low toxicity in men with advanced prostate cancer in case reports and published patient series, reported by the German Multicenter Study showing a PSA decline of 50% and an overall response rate of 45% (14-17).

An Australian phase II study led by Michael Hofman treated 30 metastasized castration resistant prostate cancer (mCRPC) patients with significant prior treatment exposures and resulted in significant declines in PSA with minimal toxicity (18). Based upon these promising data, ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 are now being evaluated in a study called VISION, an

international, prospective, open-label, randomized Phase III study in men with PSMA-expressing mCRPC (ClinicalTrials.gov Identifier: NCT03511664).

Phase III VISION Trial

The overall trial design, primary and secondary endpoints are depicted in Figure 1. Patients are randomized on a 2:1 basis to receive either best standard of care (SOC) along with ^{177}Lu-PSMA-617 -or- best SOC alone.

Men with metastatic prostate cancer have an expanding armamentarium of life-prolonging agents, that can be applied early in the clinical course of metastatic disease (e.g., docetaxel, enzalutamide, apalutamide, or abiraterone), or in the context of mCRPC. Indeed, men with mCRPC may have already received chemotherapy and yet still have an intact performance status, be candidates for further treatment, and are appropriate for clinical trials. In recognition of these numerous treatment options for mCRPC, including first- and second-generation androgen receptor axis directed drugs, palliative maneuvers, and other standards of care, VISION was designed knowing that there are many ways to care for the chemotherapy-exposed mCRPC treatment population. Due to safety concerns, chemotherapy and radium were not considered to be standards for this trial population, as the dosing and side effects of tumor-directed radiotherapy in combination with those marrow-toxic agents has not yet been defined. Patients that require or are likely to benefit from second-line chemotherapy are not allowed in the study.

The Importance of VISION

The study design contains a subtle, but critical, feature. Namely, it *does not* compare SOC to treatment with ^{177}Lu-PSMA-617. VISION compares SOC+^{177}Lu-PSMA-617 *against* SOC. Thus, all therapeutic options, with the exception of cytotoxic, bone-targeted radiotherapy, or other investigational treatment can be used in either arm of the VISION study. This leads to a critical issue. Patients who are on both arms of the trial must have expert care in the administration of systemic therapy for mCRPC, and the management of side effects of both the disease and the standard systemic treatments, but is especially relevant for the patients on the control arm. In order for the study to succeed, investigators must have a facile knowledge of SOC options

available to VISION patients; the ability to manage end-stage prostate cancer patients using the SOC options; the ability to have a frank and open discussion with study candidates regarding their expectations if assigned to the SOC-only arm. In addition, since many patients have seen data available on the internet suggesting ^{177}Lu-PSMA-617 can have an anti-tumor effect, investigators must have a clear understanding that ^{177}Lu-PSMA-617 has not, to date, shown *any survival advantage* or other metric of clinical benefit over SOC.

This last point is especially important. The VISION study is the first international, randomized study testing the hypotheses that OS is increased after treatment with ^{177}Lu-PSMA-617 in men with advanced stage prostate cancer. VISION also contains an alternate primary endpoint of rPFS whose integrity requires that patients assigned to the control arm continue receiving SOC until such time as a clinical or radiographic progression-free survival event occurs. Upon the occurrence of an rPFS event, these patients can then receive any and all options available to them, including other experimental therapy, but not ^{177}Lu-PSMA-617. Maintaining control arm patients in the study until the point of an rPFS event correlates with the speed in which VISION reaches the rPFS alternate primary endpoint; the more the integrity of the study remains intact, the faster the answer of whether ^{177}Lu-PSMA-617 will fulfil its potential as a new therapeutic option.

If VISION succeeds, it establishes a new line of therapy for prostate cancer that becomes the developmental paradigm for theranostics; the ability to use ^{68}Ga-PSMA-617-based imaging to identify patients for treatment with ^{177}Lu-PSMA-617. If successful, it may become impossible to conduct any subsequent study testing whether the VISION target population benefits from ^{177}Lu-PSMA-617 in terms of overall survival. Alternatively, if VISION fails, meaning that the largest well-designed and executed study of a theranostic pair has failed, this would be a draw back for the entire field of theranostics. Independent of the activity of the drug, success or failure is in the hands of the clinical investigators and their ability to maintain the integrity of the VISION study as it is designed.

Disclosures:

Kambiz Rahbar reports being compensated consultant for ABX. Michael J. Morris reports being uncompensated consultant for Astellas, Bayer, Endocyte and compensated consultant for Advanced Accelerator Applications, Blue Earth Diagnostics, and Tokai and having institutional

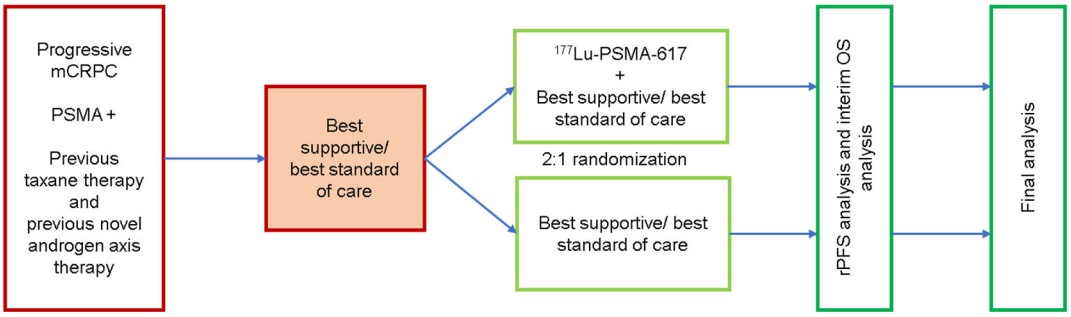
research contracts with Bayer, Sanofi, Endocyte, Progenics, Corcept, and Roche and has received travel grants from Bayer, Endocyte and Fujifilm. No other potential conflict of interest relevant to this article was reported.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015;65(1):5-29.
2. Afshar-Oromieh A, Babich JW, Kratochwil C, et al. The Rise of PSMA Ligands for Diagnosis and Therapy of Prostate Cancer. *J Nucl Med.* 2016;57(Suppl 3):79S-89S.
3. Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al. Diagnostic performance of (68)Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. *Eur J Nucl Med Mol Imaging.* 2017;44(8):1258-68.
4. Rahbar K, Ahmadzadehfar H, Boegemann M. (177)Lu-PSMA-617 radioligand therapy in mCRPC: ready for phase III trial? *Eur J Nucl Med Mol Imaging.* 2018;45(3):513-4.
5. Israeli RS, Powell CT, Corr JG, Fair WR, Heston WD. Expression of the prostate-specific membrane antigen. *Cancer Res*. 1994;54(7):1807-11.
6. Afshar-Oromieh A, Hetzheim H, Kratochwil C, et al. The Theranostic PSMA Ligand PSMA-617 in the Diagnosis of Prostate Cancer by PET/CT: Biodistribution in Humans, Radiation Dosimetry, and First Evaluation of Tumor Lesions. *J Nucl Med.* 2015;56(11):1697-705.
7. Kratochwil C, Giesel FL, Eder M, et al. 177-Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. *Eur J Nucl Med Mol Imaging*. 2015;42(6):987-8.
8. Kratochwil C, Giesel FL, Stefanova M, et al. PSMA-Targeted Radionuclide Therapy of Metastatic Castration-Resistant Prostate Cancer with 177Lu-Labeled PSMA-617. *J Nucl Med.* 2016;57(8):1170-6.
9. Fendler WP, Kratochwil C, Ahmadzadehfar H, et al. [177Lu-PSMA-617 therapy, dosimetry and follow-up in patients with metastatic castration-resistant prostate cancer]. *Nuklearmedizin*. 2016;55(3):123-8.
10. O'Keefe DS, Bacich DJ, Huang SS, Heston WDW. A Perspective on the Evolving Story of PSMA Biology, PSMA-Based Imaging, and Endoradiotherapeutic Strategies. *J Nucl Med.* 2018;59(7):1007-13.
11. Baum RP, Kulkarni HR, Schuchardt C, et al. 177Lu-Labeled Prostate-Specific Membrane Antigen Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy. *J Nucl Med.* 2016;57(7):1006-13.
12. Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. E*ur J Nucl Med Mol Imaging.* 2015;42(2):197-209.
13. Fendler WP, Calais J, Eiber M, et al. Assessment of 68Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial. *JAMA Oncol.* 2019.
14. Ahmadzadehfar H, Rahbar K, Kurpig S, et al. Early side effects and first results of radioligand therapy with (177)Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Res.* 2015;5(1):114.
15. Rahbar K, Bode A, Weckesser M, et al. Radioligand Therapy With 177Lu-PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. *Clin Nucl Med.* 2016;41(7):522-8.
16. Rahbar K, Schmidt M, Heinzel A, et al. Response and Tolerability of a Single Dose of 177Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis. *J Nucl Med.* 2016;57(9):1334-8.

17. Kessel K, Seifert R, Schäfers M, et al.Second line chemotherapy and visceral metastases are associated with poor survival in patients with mCRPC receiving 177Lu-PSMA-617. *Theranostics.* 2019;9(17):4841-8.
18. Hofman MS, Violet J, Hicks RJ, et al. [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol.* 2018;19(6):825-33.

Figure 1



Stratification Factors

- Serum lactate dehydrogenase (LDH) (≦260 IU/L vs. >260 IU/L)
- Presence of liver metastases (yes vs. No)
- ECOG score (0-1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care (yes vs. No)

Alternative Primary Endpoints

- Overall survival
- Radiografic progression-free survival (rPFS)

Key Secondary Endpoints (with α control)

- RECIST response
- Time to first symptomatic skeletal event (SSE)

Additional Secondary Endpoints

- Safety and tolerability
- Health-related quality of life (HRQoL; EORTC QLQ-C30 and Brief Pain Inventory – Short Form (PI-SF))
- Health Economics
- Progression-free survival (PFS) (radiological, clinical or PSA progression)
- Biochemical response: PSA levels, alkaline phosphotase levels and lactate dehydrogenase levels