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Invited Perspective, Outcome of patients with PSMA-PET/CT screen failure by VISION criteria and treated with 177Lu- PSMA therapy: a multicenter retrospective analysis

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Selection of patients for treatment with prostate-specific membrane antigen (PSMA) targeted therapy is somewhat controversial. There are those that have suggested that no selection is necessary and those that have suggested that tight imaging-based selection criteria are required. What is optimal, what is required, and what is practical are all different questions.

Given the importance of the VISION trial (the only trial demonstrating overall survival benefit with PSMA targeted therapy), findings in this trial will be examined in some detail.[1] Of note, the VISION trial enrolled patients with ≥1 metastatic lesion present on baseline contrast enhanced CT, MRI, or bone scan imaging obtained ≤28 days prior to beginning study therapy. Thus, metastatic disease on conventional imaging was required. In addition patients must have progressed after one or more androgen axis inhibitors (e.g. abiraterone, enzalutamide, darolutamide, or apalutamide) and at least one taxane-based chemotherapy. Approximately 41% of VISION participants were previously treated with 2 taxane regimens.

What was the eligibility criteria relative to PSMA PET/CT imaging in VISION? First, all patients must have had a centrally read ^{68}GA PSMA-11 PET/CT for trial entry. Second, a metastatic lesion (one or more) that was PSMA PET positive was required. PSMA PET positivity was determined by uptake of the lesion at an intensity level greater than the liver. There was no SUV cut-off requirement; comparisons of potential metastatic lesions in each patient were made relative to liver uptake by centralized PET reading. There was no size criteria for metastatic PSMA-PET positive lesions.

Importantly, the patients screened for the VISION trial had additional imaging-based exclusion criteria. Patients were excluded if there were PSMA PET negative lesions (uptake less than liver) of ≥1 cm in solid organs, or ≥2.5 cm in lymph nodes, or ≥1 cm in a bone lesion with a soft–tissue component. Assessment was done by contrast enhanced CT combined with the PET/CT findings. These negative selection criteria are quite important and helped to exclude patients harboring lesions with low levels of PSMA expression.

During the VISION trial design phase, there was strong desire to avoid using two PET scans as a requirement for trial entry, knowing that the VISION entry criteria would likely be cited by regulatory authorities considering ^{177}Lu PSMA-617 as an approved therapy. In the United States, and many other areas of the world, obtaining reimbursement for two distinct types of PET scans was deemed to be

potentially problematic. Thus for practical reasons, FDG PET scans were not used in the VISION entry criteria.

In the plenary session at the 2021 American Society of Clinical Oncology meeting, the discussant questioned whether or not PSMA-based imaging was required for selection of patients.[2] This discussion followed the initial presentation of the VISION trial. Of the 1003 patients screened with PET/CT scans, 49 (4.9%) had no PSMA positive metastatic lesions. Of the 954 patients with PSMA PET metastatic lesions, 87 patients were excluded because PSMA negative metastases were also detected. All told, only about 13% of patients were excluded because of PET imaging criteria. Given the overall survival (OS) benefit with a hazard ratio (HR) of 0.62 relative to control (HR of 0.62 with 95% confidence intervals 0.52-0.74), it is likely that had the VISION trial been conducted in PSMA-PET unselected patients that the OS benefit would still have been statistically significant, i.e the confidence intervals would not have crossed 1.0. Thus, questioning the requirement for PSMA PET selection for ^{177}Lu PSMA-617 is reasonable.

Have any investigators used PSMA targeted therapies without regard to PSMA PET selection? The answer is yes. Data on PSMA unselected patients have been presented from studies using both ^{177}Lu J591, ^{225}Ac J591, PSMA bispecific antibodies, a PSMA antibody drug conjugate (PSMA ADC), and a PSMA-targted CAR-T. J591 is a monoclonal antibody that binds PSMA and has been used to target either ^{177}Lu or ^{225}Ac.[3,4] The J591 radiopharmaceutical studies have not compared PSMA PET selected and unselected patients, thus it is not possible to determine how important selection might be to patient outcomes. The bispecific antibodies pasotuxizumab (also called AMG 212) and AMG 160 have also been studied in non-PSMA PET selected patients.[5,6] What is clearly noted is that many patients, unselected by PSMA PET, appear to respond to these treatments. Some meaningful responses have also been seen in the PSMA ADC studies[7] and patients treated with Car-T.[8] All in all, given the absence of long term survival data and the absence of PSMA PET selection compared to non-selection, it is speculative to conclude that PSMA PET selection criteria improves outcomes in any of these studies. It is important to note that CAR-T and bispecific antibodies may be very different from radioligands in terms of cellular PSMA expression requirements.

The TheraP Australian trial is a large phase II trial assessing PSA responses to cabazitaxel or ^{177}Lu PSMA-617.[9] The prior therapies administered to TheraP patients and the dosing of ^{177}Lu PSMA-617 was distinct as compared to VISION. The TheraP trial utilized a double PET/CT selection using ^{68}Ga PSMA-11 and 2-flourine-18 [^{18}F] fluoro-2-deoxy-D-gluycose PET/CT scans (18F FDG) criteria. PSMA-positive metastatic disease required a maximum standardized uptake value (SUVmax) of at least 20 at a disease site and greater than 10 at all other measurable sites of metastatic disease. In addition, FDG PET positivity must be concordant. Patients with FDG PET positive lesions that were discordant by PSMA PET were deemed not eligible for ^{177}Lu PSMA-617 treatment.

The data from TheraP suggest a high rate of PSA response to ^{177}Lu PSMA-617 treatments; unconfirmed PSA decline of $\geq$50% occurred in 66% of patients. Direct comparisons of the PSA response rate between TheraP and VISION can be made but the patient populations are distinct in a number of ways. Not only was imaging entry criteria distinct but prior treatments were distinct (no cabazitaxel pretreatments were allowed in TheraP) and doses of ^{177}Lu PSMA-617 differed between the two trials. Thus direct comparisons of PSA response rate in TheraP and VISION are problematic.

It is possible to be compare exclusion rates between TheraP and VISION. As noted previously approximately 13% of patients were excluded from VISION because of imaging issues. For TheraP, 291

patients were screened and 29 (10%) were excluded because of PSMA uptake was insufficient and 51 (18%) were excluded because of imaging discordance between the FDG PET and the PSMA PET findings. Thus, together a total of 28% of the patients screened in TheraP were not treated because of PSMA PET criteria. Clearly this exclusion rate was higher than VISION.

Investigators had previously treated a number of patients on various protocols with ^{177}Lu PSMA-617.[10] These clinical trials had entry criteria distinct from VISION but all patients had undergone a baseline ^{68}Ga PSMA PET/CT scan. A retrospective analysis of these findings is now available for analysis. There was a higher percentage of visceral disease in those not meeting VISION criteria (58.6% versus 25.4%). Their findings indicated that treating patients that were excluded by using VISION criteria lead to a lower PSA response rate (PSA decline of $\geq$50%) and a longer time to PSA progression. These data were striking in that PSA $\geq$50% decline rate was 50.3% versus 20.7%. Survival analyses were not properly powered and thus were not informative (however survival trended favorably among those meeting VISION entry criteria). These data help to support the validity of the VISION criteria in patient selection and represent the only published experience addressing this issue.

What is optimal PSMA PET criteria for selection of patients? This question is important for radioligands (both betas and alphas), bispecific antibodies, antibody drug conjugates, and/or CAR-T cells. Answers to this question are not yet clear and trials with overall survival as an endpoint will likely be best to assess this question. It is intuitive to say that higher PSMA expression is better but the different PSMA targeted approaches may yield different answers. What is required? One can create an argument that no PSMA PET imaging is required for patient selection when using PSMA targeted therapy. Little data are available to date. That said, administration of expensive therapies with potential toxicities to patients who stand little chance of benefit seems unwise. What is practical? Practicality depends of perspective and geography and economics. What is practical in one region may not be practical in another. In many respects, what is practical is what the regulators allow. There is much work to do before we can be definitive in our conclusions, especially not that PSMA targeted therapy has many iterations.

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