What Does an Imaging "Selection" Claim Actually Mean?

TO THE EDITOR: I applaud the clear description of the development of imaging "selection" criteria for the VISION (^{177}Lu-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer) clinical trial, as published in this journal (*1*). Accordingly, I highlight a risk for misinterpreting the use of ^{68}Ga-PSMA-11 PET imaging agents in selecting patients for ^{177}Lu-PSMA-617 radioligand therapy (RLT). I refer to, first, tenuous clinical logic in claiming that an imaging test selects patients for a therapy and, second, the lack of clinical data assessing whether PET agents alone are useful in predicting which patients are and are not likely to respond to RLT.

The patient selection claim is described in labeling for the PET and RLT drugs, which have been approved by the U.S. Food and Drug Administration. The claim is based entirely on VISION clinical trial results (*1–3*). VISION demonstrated improved survival for patients with metastatic castration-resistant prostate cancer who received RLT (*4*). For VISION enrollment, imaging selection criteria integrated CT anatomic information with PET/CT findings. The criteria were developed using professional opinion and vetting of trial logistic considerations (*1*). The usefulness of the criteria was not piloted in clinical trials before their use in VISION (*5*).

Clinical practice has long recognized that selection of a therapy for a patient is generally a decision-making process integrating patient choice with the caregiver's clinical expertise and insight regarding therapeutic options. In short, no test selects the patient for a specific therapy. Instead, a therapy is selected for the patient.

The VISION trial was not designed to determine whether the PET/CT imaging criteria were useful in predicting the response to RLT, a design limitation particularly important for patients who might be excluded from the trial because of the criteria. On the basis of imaging selection criteria, 126 of 995 patients were excluded from enrollment in the trial (*4*). These exclusions were determined by a single image-reader (*6,7*). Still, imaging criteria were not the main patient selection determiners for VISION. Among 1,179 patients assessed for trial eligibility, 176 were excluded before PET/CT imaging, whereby most of these nonselected patients did not meet the protocol's clinical eligibility determiners (e.g., performance status and prognosis) (*4,6*).

Considering the assumptions and limitations surrounding the PET/CT selection for RLT, I was concerned when I heard one of the presenters at the recent Society of Nuclear Medicine and Medical Imaging annual meeting state that ^{68}Ga-PSMA-11 helps physicians determine whether patients should or should not be considered for RLT. The implication was that VISION verified no reasonable likelihood of treatment benefit among patients with negative PET/CT results. Unfortunately, there is a disconnect between VISION data and a clinical understanding that a selection claim for a PET/CT imaging agent means the test predicts who is likely to respond to RLT as well as who is not likely to respond.

Given the magnitude of benefit observed in VISION and the limitations associated with using a single image-interpreter, some patients may have been inadvisably excluded from VISION. Indeed, ^{68}Ga-PSMA-11 drug labeling includes a warning that emphasizes the risk for unreliability in single-reader interpretations using VISION PET/CT selection criteria (e.g., reader unanimity for negative image interpretation was 34% across a pool of 4 readers) (*1*). This concern is reflected in the Food and Drug Administration ^{177}Lu-PSMA-617 approval letter, which describes a postmarketing commitment to studying the effects of RLT among patients who would have been excluded from VISION because of the imaging criteria (*8*).

Concern about the selection claim for ^{68}Ga-PSMA-11 does not lessen the profound usefulness of the imaging agent in evaluating the distribution of PSMA-positive or -negative lesions among men with prostate cancer. This information may be essential to optimize treatment option considerations. Misunderstanding the selection claim may limit patient access to RLT, particularly if imaging reimbursement or clinical practice administrative factors require strident compliance with VISION selection criteria. Further, marketing of imaging drugs relies on information in drug labeling. Hence, an imaging drug manufacturer's claim that the test selects patients for RLT may ultimately change how we think about caring for our patients—with the extreme being a prioritization of the selection test results over patients themselves. This risk may be lessened with updated drug labeling that briefly describes the strengths and limitations of PSMA PET imaging information in helping select RLT for men with prostate cancer.

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Reply: What Does an Imaging "Selection" Claim Actually Mean?

REPLY: Thank you for the opportunity to respond and provide further insight into this complex and rapidly evolving field.

A multitude of experts took no issue with use of the word *selection* for the screening criteria for prostate-specific membrane antigen

(PSMA) PET in the VISION trial (*1*), but I appreciate concerns about the word choice and hope to clarify. *Patient selection* is a commonly used term in typical parlance and written protocols for clinical trials. It was not intended that using *selection* versus some other term would necessitate obtaining some special burden of clinical data or meet some sort of claim, like a legal term. If not *selection,* then what term should we use? My colleagues and I have also used the term *eligibility* or *screening* criteria in discussions and presentations if that would be less controversial or preferable.

I do not understand how the term *selection* would be interpreted to mean that "PET agents alone are useful in predicting which patients are and are not likely to respond to [radioligand therapy (RLT)]." Clearly, PET alone is not the only important factor to consider. The VISION trial had nonimaging exclusion criteria. Indeed, Gafita et al. published a retrospective analysis demonstrating that many nonimaging factors are important to outcomes (*2*).

The author criticizes that the Food and Drug Administration (FDA) label is based on the VISION trial. FDA labels should be based on data and thus strongly influenced by the phase 3 trials used for the drug approval. Conversely, the FDA could have been criticized for not including PSMA PET on the label, as it was criticized for not including amyloid PET initially on the label for aducanumab. In my opinion, using an alternative to the word *selection* would not have changed the FDA's decision, which was based on the trial methodology regardless of the semantics. The practice of medicine need not strictly follow the FDA label, and the longer after a drug has been approved and the more trials that have since been performed, the greater is the likelihood that it routinely does not.

Regarding the point that the "usefulness of the criteria was not piloted in clinical trials before their use in VISION," a phase 3 trial does not need to replicate the methodology of the preceding phase 2 trial. Indeed, one should apply lessons from the phase 2 trial to optimize phase 3. In this case, we used results from phase 2 trials published in the scientific literature to develop this protocol, which (to our knowledge) was the first phase 3 registrational trial for a PSMA-targeted theranostic.

At the request of the FDA, a VISION substudy was designed and conducted to test whether baseline PSMA PET could be a prognostic tool for clinical outcomes from ^{177}Lu-PSMA-617. A higher whole-body SUV_{mean} was strongly associated with improved outcomes (overall survival and radiographic progression-free survival) from ^{177}Lu-PSMA-617. Even the patients in the lowest quartile of the whole-body SUV_{mean} showed greater survival than the arm receiving the standard of care alone (*3*). Analysis of the baseline PSMA PET scans from the standard-of-care–alone arm is under way. Ultimately, I hope that analyses such as these will allow for more personalized use of RLT, particularly as more therapeutic options are approved. Earlier this year, an important retrospective study by Hotta et al. classified patients treated with ^{177}Lu-PSMA using the PSMA PET VISION criteria and found a survival difference between the groups (*4*).

We need more research into the group of patients excluded by the VISION PSMA PET selection or eligibility criteria. Although the VISION trial was not designed to answer many important questions that remain, it has provided us the breakthrough approval of a PSMA-targeted RLT. In my view, criteria are not meant to be static. The VISION selection criteria were not intended to be the only and everlasting criteria for PSMA-targeted trials. If the intention is to maximize benefit, then the criteria should be more restrictive; on the other hand, one needs to loosen the criteria to benefit a greater proportion of the patient population. Criteria need to be adjusted to different patient populations and different pharmaceuticals (*5*). The VISION trial has given us this first phase 3 level of data, and as more large trials give us high-level evidence, the criteria should continue to evolve to serve patients better.

DISCLOSURE

Phillip Kuo is an employee of Invicro. He is a consultant or speaker for Amgen, Eisai, Endocyte, GE Healthcare, Novartis, Invicro, Bayer, Chimerix, Fusion Pharma, and UroToday. He is a recipient of research grants from Blue Earth Diagnostics and GE Healthcare. No other potential conflict of interest relevant to this article was reported.

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