

TO THE EDITOR:

What Does an Imaging “Selection” Claim Actually Mean?

I applaud the clear description of the development of imaging “selection” criteria for the Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer (VISION) 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 (PET agents) in selecting patients for ^{177}Lu -PSMA-617 therapy (RLT). I refer to: 1) tenuous clinical logic in claiming that an imaging test “selects” patients for a therapy, and 2) 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 (FDA). The claim is based entirely on VISION clinical trial results (1, 2). VISION demonstrated improved survival for patients with metastatic castration-resistant prostate cancer (mCRPC) who received RLT (3). For VISION enrollment, imaging “selection” criteria integrated CT anatomical information with PET findings (PET/CT). The criteria were developed using professional opinion and vetting of trial logistical considerations (1). The usefulness of the criteria was not piloted in clinical trials prior to their use in VISION (4).

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 due to the criteria. Based on imaging selection criteria, 126 of 995 patients were excluded from enrollment in the trial (3). These exclusion determinations were made by a single image reader (5, 6). Still, imaging criteria were not the main patient “selection” determiners for VISION. Among 1179 patients assessed for trial eligibility, 176 patients were excluded prior to PET/CT imaging, whereby most of these non-selected patients did not meet the protocol’s clinical eligibility determiners (e.g., performance status, prognosis, etc.) (3, 5).

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 ⁶⁸Ga-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 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, ⁶⁸Ga-PSMA-11 drug labeling includes a Warning that emphasizes the risk for unreliability in single reader interpretations using VISION PET/CT selection criteria (for example, reader unanimity for negative image interpretation was 34% across a pool of four readers) (1). This concern is reflected in the FDA ¹⁷⁷Lu-PSMA-617 approval letter, which

describes a post-marketing commitment to study effects of RLT among patients who would have been excluded from VISION due to the imaging criteria (7).

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/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, imaging drug marketing relies upon 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, in the extreme prioritizing 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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