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

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To the Editor:

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

A multitude of experts took no issue with the word choice of "selection" for the screening criteria PSMA-PET for 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 RLT." Clearly, PET alone is not the only important factor to consider. The VISION trial had non-imaging exclusion criteria. Indeed, Gafita et al. published a retrospective analysis demonstrating many non-imaging factors are important to outcomes (2).

The author criticizes that the 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 word to "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 routinely does not, especially, the longer a drug has been approved and the more trials that have been performed post-approval.

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

At the request of the USFDA, a VISION substudy was designed and conducted to test whether the baseline PSMA-PET could be a prognostic tool for clinical outcomes to [177Lu]Lu-PSMA-617. Higher whole body SUV_{mean} was strongly associated with improved outcomes (overall survival and radiographic progression free survival) to [177Lu]Lu-PSMA-617. Even the patients in the lowest quartile of whole body SUV_{mean} showed greater survival than the standard of care alone arm (3). The analysis of the baseline PSMA-PET scans from the standard of care alone arm is underway. Ultimately, I hope that analyses such as these will allow for more personalized utilization of RLT, particularly as more therapeutic options are approved. Earlier this year, an important retrospective study by Hotta et al. classified patients treated with [177Lu]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. While 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, you need 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.

Disclosures:

P.H. Kuo is an employee of Invicro. He is a consultant and/or speaker for Amgen, Eisai, Endocyte, General Electric Healthcare, Novartis, Invicro, Bayer, Chimerix, Fusion Pharma, and UroToday. He is a recipient of research grants from Blue Earth Diagnostics and General Electric Healthcare.

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