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A VISION of ALSYMPCA

TO THE EDITOR: I just read the 2 editorials written by Hofman (*1*) and by Czernin and Calais (*2*) commenting on the use of ^{177}Lu-PSMA-617 therapy in patients with metastatic castration-resistant prostate cancer (mCRPC), mainly on the results of the VISION trial (*3*). ^{177}Lu-PSMA-617 together with ^{68}Ga- or ^{18}F-labeled PSMA ligands are doubtless important theranostic technologies that provide a new perspective on mCRPC treatment, as stated in another recent editorial by Srinivas and Iagaru (*4*). However, I miss in the VISION trial a comparison with the results of another study performed a few years ago that analyzed the use of ^{223}Ra in the treatment of mCRPC patients, the ALSYMPCA trial (*5*). Although ^{223}Ra is used to treat patients with exclusive bone metastases, this group represents most patients with mCRPC. In some studies, the percentage of patients with bone metastatic disease, with or without concomitant lymph node disease but without visceral (lung and liver) disease, represents around 70% of cases (*6*), and in this group the presence of concomitant lymph node disease does not appear to change the overall survival (this high percentage was also confirmed in the VISION trial, in which 91% of patients had bone metastases, 50% had lymph node metastases, 9% had lung metastases, and 12% had liver metastases) (*6*). Therefore, ^{223}Ra could represent an adequate option to treat most patients with mCRPC. In this sense, it will be useful if the authors of the VISION study, as well as of other future studies on this issue, also present the survival results for the distinct groups of metastatic lesions or, at least, separate the results of the ones with bone metastatic disease without visceral disease from the group with visceral disease. This separation would be useful to indirectly compare the effects of ^{177}Lu-PSMA-617 with the effects of ^{223}Ra in the group without visceral metastases and also to assess the effect of ^{177}Lu-PSMA-617 in the group of patients with visceral metastases, who certainly are not candidates for ^{223}Ra therapy.

In this line of reasoning, it is interesting to note that median survival differences between groups receiving or not receiving the radionuclide therapy are similar in both trials: 4 mo (15.3 mo vs. 11.3 mo for patients receiving or not receiving the therapy, respectively) in VISION and 3.6 mo (14.9 mo vs. 11.3 mo) in ALSYMPCA. Besides, although the authors of the VISION study did not present the results of subgroups with and without visceral metastases, in the supplementary appendix of the study (*3*) the authors presented the survival results in subgroups with and without liver metastases and showed that there is no statistically significant difference in overall survival in the subgroup with liver metastases. These findings, in my opinion, are worrisome and suggest that the main effect of ^{177}Lu-PSMA-617 in overall survival could be due to its action on bone metastases and not on visceral metastases.

Therefore, presentation of the survival results by subgroups will be essential to define the patients who would most benefit from ^{177}Lu-PSMA-617 therapy and to further establish the best theranostic algorithm to treat these patients (e.g., patients with exclusive bone disease would first receive ^{223}Ra, and patients with visceral disease would first receive ^{177}Lu-PSMA-617). Last, it is important to say that ^{223}Ra therapy is already a reality in several places around the world whereas ^{177}Lu-PSMA-617 is a distant vision; thus, to move from ALSYMPCA to VISION, VISION has to show where it is really effective.

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Reply: A VISION of ALSYMPCA

REPLY: Dr. Duarte urges an analysis of the VISION trial in an effort to ascertain results in subsets of men with bone and visceral disease. He then suggests an indirect comparison between ^{177}Lu-PSMA-617 and ^{223}Ra.

I agree with the first point but disagree with the second. The VISION trial (*1*) can be analyzed in a multiplicity of new ways. Right now, just the prespecified primary analyses have been published (*1*). There are many analyses that will follow that include not only the distribution of the disease (as suggested by Duarte) but also the various biomarkers that are known to be prognostic in other settings. These biomarkers might include hemoglobin, neutrophil-to-lymphocyte ratio, prostate-specific antigen, alkaline phosphatase, lactate dehydrogenase, performance status, age, time since diagnosis, pain, and others. As it turns out, the dataset from VISION is rich and there is much more to explore.

On the second point, there is disagreement. The ALSYMPCA trial with ^{223}Ra (*2*) was conducted in a long-ago era, before the use of novel hormones such as abiraterone and enzalutamide and before the widespread use of cabazitaxel. Further, patients enrolled in ALSYMPCA were not required to progress after docetaxel (but approximately half did). All patients enrolled in VISION had progressed after either

abiraterone or enzalutamide. Further, all patients in VISION had progressed after docetaxel and approximately 40% had progressed after cabazitaxel. Thus, the patient populations of ALSYMPCA and VISION are completely distinct. Indirect comparisons between phase III trials are always fraught with difficulty. In this case, because the populations are so distinct, comparisons would be particularly problematic.

Dr. Duarte also raises the issue that the liver metastasis patients do not have improved survival in VISION and suggests that the positive effects of ^{177}Lu-PSMA-617 may be predominantly on patients with bone metastases. Although these points are well taken, the overanalysis of small data subsets can at times be erroneous. The number of patients in the VISION trial with liver metastases was far smaller than optimal for a conclusive analysis. There is much more to learn before a definitive conclusion can be drawn. Further, we would all agree that there is considerable heterogeneity for those with liver metastases and that more analyses may potentially yield interesting findings. Perhaps the patients with higher PSMA PET SUVs may be distinct from those with lower PSMA PET SUVs. Perhaps those with more than 20 liver metastases may be distinct from those having just one. Simply stated, there is much more to learn before categoric statements can be made regarding analyses of underpowered subsets.

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On Semiquantitative Methods for Assessing Vascular ^{18}F-FDG PET Activity in Large-Vessel Vasculitis

TO THE EDITOR: In a series of 95 large-vessel vasculitis patients investigated with ^{18}F-FDG PET imaging, Dashora et al. recently tested the performance of qualitative (PET vascular activity score [PETVAS]) and semiquantitative (SUV and tissue-to-background ratio [TBR] relative to liver and blood activity) scoring methods (*1*). Regarding the latter methods, 9 territories were created in each patient by segmenting the aorta and branch arteries. A territory score was calculated by averaging the SUV_{max} assessed in each axial region of interest that was manually drawn across the territory, and a global summary, SUV_{Artery}, was then calculated by averaging all territory scores. Liver TBR (TBR_{Liver}) and blood TBR (TBR_{Blood}) were computed by dividing SUV_{Artery} by a mean liver and blood SUV, respectively. The performance of each metric was assessed in association with reader interpretation of vascular PET activity and with physician assessment of clinical disease activity, including the area under the receiver-operating-characteristic curve. Tables 2 and 3 by Dashora reported the metrics performance against the 2 reference standards; this performance was poor–poor for SUV_{Artery} (area under receiver-operating-characteristic curve, 0.67–0.59) and good–poor for TBR_{Liver} and PETVAS (areas under receiver-operating-characteristic curve, 0.85–0.66 and 0.87–0.65, respectively) (*1*). TBR_{Blood} had slightly lower performance than TBR_{Liver}.

Since TBR_{Liver} involves SUV_{Artery}, which results from SUV_{max} averaging, we suggest that instead of using SUV_{Artery}, we use an averaged SUV_{max} obtained from N hottest voxels ($SUV_{max\text{-}N}$) irrespective of their location within the 9 vascular territories (*2*). Both SUV_{Artery} and $SUV_{max\text{-}N}$ take into consideration the heterogeneity of the vessel-wall uptake, but N can actually be much greater than the total number of regions of interest used by Dashora et al. for calculating SUV_{Artery}. Since the greater the N number, the lower the $SUV_{max\text{-}N}$ variability, a more reliable TBR_{Liver} can thus be provided than with SUV_{Artery} (*2*,*3*). A previous assessment of treatment response in a Takayasu arteritis patient illustrates the possible magnitude of N, with $SUV_{max\text{-}N}$ pooling $N = 4{,}100$ and 515 voxels, corresponding to a hottest volume V = 100 and 12.6 mL, respectively (*4*). $SUV_{max\text{-}V}$ might be preferred to $SUV_{max\text{-}N}$, for the voxel volume depends on the PET system at a given center. For assessing response to treatment in a large-vessel vasculitis patient, it has been previously shown that V (or N) should be set in the scan showing the lowest total ^{18}F-FDG–positive volume, which is expected to be posttreatment one (*4*). For assessing the severity of large-vessel vasculitis inflammation as in the study of Dashora et al., we suggest that standard $SUV_{max\text{-}V}$–based TBR_{Liver} metrics might be relevant, using an arbitrary value of V defined by expert consensus (e.g., of 10 cm^3). Additionally, we suggest that the hottest volume V corresponding to a standard value of $SUV_{max\text{-}V}$–based TBR_{Liver} could also be investigated by Dashora et al. as a further metric. This TBR_{Liver} standard value should be greater than 1, as is consistent with the qualitative territory score of 3 used in PETVAS (arterial uptake > liver uptake). The standard might be set at 1.33 according to TBR_{Liver} data reported in Table 3 by Dashora et al. for physician assessment of clinical disease activity, that is, between the clinical-active range and the clinical-remission range ($1.33 = 1.27 + 1.96 \times 0.03 \approx 1.46–1.96 \times 0.06$) (*1*). A similar line of argument provides a TBR_{Blood} standard value of 2.43 (from Table 3 of Dashora et al. (*1*)).

To conclude, we fully agree with the authors that qualitative metrics for assessing large-vessel vasculitis inflammation severity with ^{18}F-FDG PET, such as PETVAS, are attractive in clinical practice because of ease of implementation and ease of interpretation. However, we believe that $SUV_{max\text{-}V}$–based TBR_{Liver} (or $SUV_{max\text{-}V}$–based TBR_{Blood}) could also be used daily if manufacturers are encouraged to make $SUV_{max\text{-}V}$ (or $SUV_{max\text{-}N}$) easier to assess than currently (*2*–*4*).

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