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A VISION of ALSYMPCA

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Dear sir, I just read the two editorials written by Michael Hofman(*1*) and by Czernim 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*). The ^{177}Lu–PSMA-617 together with ^{68}Ga or ^{18}F labeled PSMA ligands are doubtless very 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 the radium-223 in the treatment of mCRPC patients, the ALSYMPCA trial(*5*). Although radium-223 is used to treat patients with exclusive bone metastases, this group represents the great majority of 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(*6*) (this high percentage is also confirmed in the VISION trial, where 91% of patients presented bone, 50% lymph node, 9% lung and 12% liver metastases). Therefore the radium-223 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 ones of radium-223 in the group without visceral metastases and also to assess the effect of the ^{177}Lu–PSMA-617 in the group of patients with visceral metastases, who certainly are not candidates for radium-223 therapy.

In this line of reasoning, it is interesting to note that median survival differences between groups receiving or not the radionuclide therapy are very similar in both trials: 4 months (15.3 months versus 11.3 months for patients receiving or not the therapy, respectively) in VISION and 3.6 months (14.9 months versus 11.3 months) in ALSYMPCA. Besides, although the authors of the VISION study did not present the results of subgroups with and without visceral metastases, as it was said above, 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 the overall survival in the subgroup with liver metastases. These findings, in my opinion, are worrisome and suggest that the main effect of the ^{177}Lu–PSMA-617 in overall survival could be due to its action on bone metastases and not on visceral metastases.

Therefore, the presentation of the survival results by subgroups will be essential to define the patients that would benefit the most from the ^{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 be first submitted to radium-223 and patients with visceral disease to ^{177}Lu-PSMA-617). Last, it is important to say that radium-223 therapy is already a reality in a number of places around the world while ^{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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