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Letter to the Editor

Reply to Joe O'Sullivan, Daniel Heinrich, Nicholas D. James, et al's Letter to the Editor re: The Case Against the European Medicines Agency's Change to the Label for Radium-223 for the Treatment of Metastatic Castration-resistant Prostate Cancer. Eur Urol 2019;75:e53

I read with great interest the letter by O'Sullivan et al criticizing the recommendation by the European Medicines Agency (EMA) regarding radium-223 (Xofigo) [1] and the subsequent reply on behalf of the EMA [2]. In brief, the former state their disagreement with the recent updated EMA recommendation to use Xofigo only as a third (or higher) treatment line in metastatic castration-resistant prostate cancer (mCRPC). The authors claim that the detrimental effects on bone fractures seen with the combination of abiraterone and Xofigo in the ERA-223 trial merely mandate not using these two drugs concomitantly, but do not necessitate postponing Xofigo to such advanced lines. The response from EMA reveals that the detrimental results of the ERA-223 trial encompass more than the higher rate of fractures observed in the combination arm, and articulates a concern that Xofigo in itself promotes lymph node and visceral progression.

The positive effect of single-agent Xofigo on overall survival (OS) in the ALSYMPCA trial [3] came as a surprise to the prostate cancer community. As opposed to other therapeutics approved during these years for mCRPC (such as abiraterone or enzalutamide), it was shown that Xofigo only improved OS in this single trial. Moreover, Xofigo was given with the "best standard of care" (BSC) at that time, which may have included an active drug such as ketoconazole or prednisone, yet details of what constituted this BSC and whether it was stratified between the two treatment arms were never disclosed. I argue that a retrospective analysis of the subcohorts of patients in ALSYMPCA receiving either Xofigo alone or placebo without any additional pharmaceutical would help in clarifying if single-agent Xofigo truly increases OS. If this were to turn out to be the case, then I would agree with O'Sullivan et al. Conversely, without this data, a cloud continues to hang over single-agent Xofigo at this time.

The ALSYMPCA and ERA-223 trials both included patients with bone-only disease or with bone and lymph node disease up to 3 cm. We have shown that prostate cancer that metastasizes to both these organ sites is prognostically worse than bone-only disease [4]. It also stands to reason that patients with bone and lymph node metastases would be more prone to further disease progression to nodal and visceral sites than patients with metastasis only to bone. Thus, it would be very interesting to see if the cohort of patients with bone-only disease in the ERA-223 trial also showed the worrisome increased tendency to experience progression to visceral or nodal sites on receiving Xofigo versus placebo. If not, then Xofigo could continue to be a legitimate single-agent treatment for prostate cancer patients with bone-only metastases.

Conflicts of interest: The author has received honoraria from MSD, BMS, Roche, and Janssen; advisory/consulting fees from Sanofi, Pfizer, Bayer, Neopharm, and Astellas Medivation; and travel expenses from Pfizer and Janssen.

References

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