



European Association of Urology



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:e51–2

EMA welcomes this opportunity to comment on the letter from O'Sullivan et al. [1] regarding the recommendation of the European Medicines Agency (EMA) on Xofigo (radium-223 dichloride).

On July 26, 2018, EMA concluded a review of Xofigo following the release of interim results from ERA-223, a placebo-controlled study evaluating the effects of Xofigo combination treatment in asymptomatic or mildly symptomatic chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (mCRPC).

The study population partly overlapped with the patient population for which Xofigo was licensed, with the results indicating a higher risk of mortality and fractures with Xofigo in combination with abiraterone acetate and prednisone/prednisolone than with placebo in combination with abiraterone acetate and prednisone/prednisolone.

The proportion of patients who died with non-bone disease progression (eg, progression in lymph nodes or liver) was notably higher in the Xofigo arm than in the placebo arm (14.5% [57/392] vs 7.4% [29/394]). There appeared to be a higher risk of radiological non-bone progression in the Xofigo arm compared with the placebo arm (hazard ratio 1.376, 95% confidence interval 0.972–1.948; $p = 0.07$), raising concerns that Xofigo promotes visceral and lymph node metastases.

On the basis of the available data, the adverse outcomes in the Xofigo arm cannot be attributed to a mechanism specific to the concurrent use of Xofigo with abiraterone acetate and prednisone/prednisolone. In line with the outcome of a consultation of experts in the field, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) considered these findings relevant for the indication licensed at the time for Xofigo, particularly for patients with low extent of disease or mild symptoms. The PRAC also considered that the results of ERA-223 did not invalidate the

overall improvement in survival seen in the ALSYMPCA study, a benefit that persists after adjusting for major confounding factors. While there are difficulties in extrapolating the trend for higher mortality from ERA-223 to ALSYMPCA, there are also difficulties in reconciling the adverse outcomes observed in ERA-223 with the favourable outcomes in ALSYMPCA, considering that patients in ERA-223 had less advanced mCRPC. The available data therefore raised concerns about the use of Xofigo in early lines of therapy for symptomatic patients.

Having considered all the available data, the PRAC recommended restricting the Xofigo indication to patients who have had two previous systemic treatments for mCRPC or who cannot receive other treatments [2]. The committee also recommended updating the Xofigo product information with warnings and recommendations concerning the risk of fractures and the use in patients who are mildly symptomatic or who have a low level of osteoblastic activity. A number of studies will also be carried out to further characterise the safety and efficacy of Xofigo, including the mechanisms responsible for the higher risk of fracture and the possible risk of visceral and nodal metastases.

Conflicts of interest: The author has nothing to disclose.

References

- [1] O'Sullivan J, Heinrich D, James ND, et al. 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:e51–2.
- [2] European Medicines Agency. PRAC assessment report EMA/540557/2018. www.ema.europa.eu/documents/referral/xofigo-article-20-procedure-prac-assessment-report_en.pdf.

On behalf of EMA*

*Evdokia Korakianiti, European Medicines Agency, 3 Churchill Place, Canary Wharf, London E14 5EU, UK. Tel. +44 20 36606000; Fax. +44 20 36605555. E-mail address: evdokia.korakianiti@ema.europa.eu.

November 28, 2018

