Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Procedure No: EMEA/H/A-20/1459/C/002653/0028

Xofigo (INN: radium Ra223 dichloride)

Divergent statement

Based on a review of all available data provided during the Article 20 procedure, the following CHMP Members consider that the benefit risk ratio of Xofigo is not favourable based on the following grounds:

1. Concerns over the effect of radium-223 on overall survival and disease progression in the indicated population

The single pivotal phase III study, ALSYMPCA, does not provide convincing evidence of a beneficial effect of radium-223 on overall survival (OS) because of limitations of the study, including differences between the treatment arms in the baseline risk of cardiovascular events and in the exposure to anti-cancer treatments during the treatment phase. Indeed, the OS benefit was driven by an increased incidence of non-prostate cancer deaths in the placebo arm, suggesting the placebo arm had worse health status at baseline and/or experienced more treatment toxicity. The absence of a progression-free survival endpoint to provide supportive evidence for a beneficial effect on disease progression further highlights the uncertainties about the OS benefit, especially considering that there is not a clear rationale for a bone-specific agent to affect OS.

In addition, study 15396 has shown decreased survival in the radium-223 arm compared with the placebo arm, especially in patients who received 5-6 injections (median overall survival 30.7 months vs 39 months). Furthermore, the risk of dying with non-bone progression was twice as high in the radium-223 arm as the placebo arm (11.7% [46/392] vs 5.1% [20/394]), raising concerns that radium-223 promotes visceral and lymph node metastases. The results of study 15396 are relevant to the authorised indication because approximately half the patients in study 15396 (46%) had mildly symptomatic bone metastases, a group of patients which fall within the indicated population for radium-223.

These concerns were shared by some of the SAG Oncology members who considered that the OS effect in ALSYMPCA might be due to chance and that study 15396 might more accurately reflect the effects of radium-223.

2. The lack of reliable data to determine whether the recommended posology (i.e. 6 doses) is appropriate for all symptomatic metastatic CRPC patients

The available data do not answer the question as to whether a lower number of cycles of radium-223 would be more appropriate in patients with a lower extent of bone disease. It cannot be excluded that the number of doses received relative to the extent of disease may have contributed to the adverse effects observed in study 15396. Indeed, in those patients in study 15396 who received 5 or 6 doses of treatment (placebo or radium-223), the median OS was notably lower in the radium-223 group than the placebo group (30.7 months vs 39.0 months). Data from a randomised study of three different dosing regimens showed a higher incidence of symptomatic skeletal events (including symptomatic pathological fractures) in patients who received doses at a higher activity than standard, or who were given up to 12 doses. Both these findings are suggestive of dose-related toxicity. The question of whether patients with a low extent of bone metastases require fewer doses remains unanswered. Given the nature of the product (an alpha emitter which produces lethal DNA breaks) that is not

specific for its target (bone metastases), the lack of data to reliably characterise the posology for the revised indication, which is likely to contain patients with differing extent of bone metastases, is considered unacceptable.

3. The lack of reliable data to inform decisions on how best to sequence therapy with radium-223 in relation to life-extending treatments (particularly abiraterone).

The washout period from the last injection to subsequent treatment with other anti-cancer therapies is not known and the effects of radium-223 on bone may persist for many months, into the next line of treatment. In addition, there is considerable inter-patient variability in the skeletal retention of radium-223 (Pratt et al 2018). It is considered unacceptable to have to delay subsequent anti-cancer therapy for many weeks given the uncertainties over the benefit of radium-223. The revised indication in patients who have received at least two lines of prior therapy or are ineligible for other therapies is expected to limit the use of other life-extending treatments after radium-223, but will not exclude patients being treated with abiraterone after radium-223. Moreover, the effects of radium-223 used after life-extending treatments are also not known.

4. Risk of sub-optimal treatment

As well as the possibility of promoting non-bone progression, it is likely that treatment with radium-223 monotherapy will be sub-optimal in some patients because of its selective effects on the skeletal system, which means that it is not indicated in patients with visceral metastases. To minimise the risk of non-bone progression it is essential to ensure that patients are free from visceral metastases prior to starting radium-223, since radium-223 is not expected to have anti-tumour effects on these metastases. This is problematic given that visceral micro-metastases may be present and undetectable at the time that radium-223 is initiated.

Indeed, a study of metastatic CRPC patients found that radiological non-bone progression occurred in 46% (57/124) of patients with available CT data at 3 and/or 6 months (Keizman D et al 2017).

Unlike study 15396, these observations do not originate from randomised controlled studies, nevertheless, they further highlight that initiating radium-223 as monotherapy is probably unnecessarily exposing some patients to an earlier risk of disease progression. These concerns could potentially be overcome by combining radium-223 with an effective anti-cancer therapy. However, based on the results of study 15396, and in line with the advice of SAG Oncology experts, radium-223 should not be combined with anti-cancer therapies (other than LHRH analogues) until further data from randomised controlled trials are available to determine the benefits and the risks.

5. Lack of data to support an indication in patients who have received prior, effective treatments

There are no reliable prospective data from randomised controlled data to support an indication after previous lines of therapies currently used in clinical practice. Although 57% of patients in ALSYMPCA had previously used docetaxel, abiraterone, enzalutamide and cabazitaxel were not available at the time ALSYMPCA was started. Therefore, any proposal to restrict the indication based on prior lines of therapy is not based on robust data and does not address the serious concerns regarding radium-223, outlined in points 1-4 above. It is also noted that the SAG Oncology was split on the general use of this product, with some experts questioning if there is a positive benefit risk balance for radium-223 in any indication at all, based on the current conflicting evidence and lack of understanding about the mechanisms of action.

References

Keizman D, Fosboel MO, Reichegger H et al. Imaging response during therapy with radium-223 for castration-resistant prostate cancer with bone metastases-analysis of an international multicenter database. Prostate Cancer Prostatic Dis 2017;20:289-293.

Pratt BE, Hindorf C, Chittenden SJ et al. Excretion and whole-body retention of radium-223 dichloride administered for the treatment of bone metastases from castration resistant prostate cancer. Nucl Med Commun 2018: 39:125-130.

CHMP Members expressing a divergent opinion:

- Alexandre Moreau (FR)
- Daniela Melchiorri (IT)
- Concepcion Prieto Yerro (ES)
- Jayne Crowe (IE)
- Greg Markey (UK)
- Johann Lodewijk Hillege (NL)
- Robert James Hemmings (Co-opted Member)
- Sol Ruiz (Co-opted Member)

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CHMP Members expressing a divergent opinion:

- Svein Rune Andersen (NO)