17 July 2018
EMA/540557/2018
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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

Invented name: Xofigo

INN/active substance: radium Ra223 dichloride

Procedure number: EMEA/H/A-20/1459/C/002653/0028

Note:

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

Analyses of uncleaned preliminary data of a clinical trial evaluating Xofigo (radium Ra223 dichloride) in a patient population with asymptomatic or mildly symptomatic prostate cancer (ERA-223 [1]), found that the incidences of treatment emergent fractures and deaths were increased in the treatment arm (radium-223 dichloride plus abiraterone acetate and prednisone/prednisolone) compared to the control arm (placebo plus abiraterone acetate and prednisone/prednisolone).

In view of the significance of the findings of the ERA-223 clinical trial, it was considered that they should be thoroughly reviewed in the context of all available data related to radium-223 dichloride in order to assess their potential impact on the benefit-risk balance of Xofigo in the authorised indication of the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

On 30 November 2017 the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of Xofigo (radium Ra223 dichloride) and to issue a recommendation on whether the marketing authorisation of this product should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Xofigo is a radiopharmaceutical containing radium Ra223 dichloride (also radium-223 herein) as active substance. It is indicated for the treatment of adults with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastases. Marketing authorisation was granted in the European Union (EU) on 13 November 2013. The dose regimen of radium-223 is an activity of 55 kBq per kg body weight, given at 4-week intervals for 6 injections.

Since the first marketing authorisation (United States [US], 15/05/13) until 30 November 2017, it is estimated that cumulatively, approximately 41,262 patients have been exposed to the marketed product worldwide, of which 15,251 patients are from EU Member States. Cumulative exposure to radium-223 in clinical studies until 30 November 2017 is approximately 4,828 subjects (2,762 in on-going studies and 2,066 from completed studies).

Radium-223 mimics calcium and, after systemic administration, selectively targets bone by forming complexes with the bone mineral hydroxyapatite. The high linear energy transfer of alpha emitters (80 keV/µm) leads to a high frequency of double-strand deoxyribonucleic acid (DNA) breaks in adjacent tumour cells, resulting in a potent cytotoxic effect. Additional effects on the tumour microenvironment including osteoblasts and osteoclasts also contribute to the in vivo efficacy.

Radium-223 is an alpha particle-emitter with a half-life of 11.4 days. The six-stage decay of radium-223 to lead-207 occurs via short-lived daughters, and is accompanied by a number of alpha, beta and gamma emissions with different energies and emission probabilities. The fraction of energy emitted from radium-223 and its daughters as alpha-particles is 95.3% (energy range of 5.0−7.5 MeV). The fraction emitted as beta-particles is 3.6% (average energies are 0.445 MeV and 0.492 MeV), and the fraction emitted as gamma-radiation is 1.1% (energy range of 0.01−1.27 MeV).

[1] Study 15396 (ERA-223); NCT02043678; A phase III randomised, double-blind, placebo-controlled trial of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic castration-resistant prostate cancer (CRPC)

The alpha particle range from radium-223 is less than 100 µm (less than 10 cell diameters) which minimises damage to the surrounding normal tissue. However, bone marrow toxicity, including thrombocytopenia and neutropenia are recognised adverse drug reactions. In addition, a potential signal of a risk of fractures was raised by non-clinical data during the initial marketing authorisation application; the clinical relevance of these findings was considered unknown at the time. Fractures had then not been identified as a risk of treatment with radium-223 and therefore such risk was not identified as a safety concern in the risk management plan (RMP). However, the summary of product characteristics (SmPC) for Xofigo specified under warning and precautions that in patients with untreated imminent or established spinal cord compression, treatment with standard of care, as clinically indicated, should be completed before starting or resuming treatment with Xofigo and further, in patients with bone fractures, orthopaedic stabilisation of fractures should be performed before starting or resuming treatment with Xofigo.

On 17 November 2017, the EMA was notified by the marketing authorisation holder (MAH) that Study 15396 (ERA-223) had been un-blinded early based on the recommendation of the Independent Data Monitoring Committee (IDMC) because of significant imbalances in fractures and deaths between the two treatment groups. These initial data had been released prior to a survival sweep and data cleaning. Emerging analyses from ERA-223 initially triggered a signal review (EPITT 19132), as an outcome of which, the PRAC agreed on the wording of a "direct healthcare professional communication" (DHPC) together with a communication plan for relevant health care professionals (HCPs) to be informed of the preliminary results and be advised not to treat patients with radium-223 in combination with abiraterone acetate and prednisone/prednisolone with metastatic castration-resistant prostate cancer. Concomitantly, an Article 20 procedure was initiated to review the findings of the ERA-223 clinical trial in the context of all available relevant data related to radium-223 in order to assess their potential impact on the benefit-risk balance of Xofigo in the authorised indication of the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

Whilst the potential impact of these findings on the benefit-risk balance of Xofigo was not fully elucidated, based on the preliminary information available in March 2018, the PRAC considered that provisional measures were necessary in order to protect public health while the issue was being further reviewed [2]. The PRAC recommended provisional amendments to the product information to contraindicate the use of radium-223 in combination with abiraterone acetate and prednisone/prednisolone and reflect the preliminary results of ERA-223. In addition, in the absence of definite evidence that the results observed were specific to the combination with abiraterone acetate and prednisone/prednisolone, the PRAC considered that healthcare professionals and patients should be warned that the safety and efficacy of radium-223 in combination with second generation androgen receptor antagonists including enzalutamide have not been established. These provisional contraindication and warnings were communicated with a DHPC. The European Commission issued a decision on the provisional measures on 19 March 2018.

The PRAC considered all data submitted by the MAH. This included an updated interim analysis of Study 15396 (ERA-223) and data from the pivotal ALSYMPCA clinical trial [3]. In addition, the MAH provided available results from a number of completed and ongoing clinical randomised and non-randomised studies including, non-interventional studies, investigator-initiated studies (Table 1) and data from publications.

[2] More information is available in the published assessment report on provisional measures
[3] A Phase III Study of radium-223 dichloride in patients with symptomatic hormone refractory prostate cancer with skeletal metastases (ALSYMPCA, 15245/BC1-06)

Table 1. Overview of the studies for which data was considered in this procedure

Study number	Tumor type/ Phase	Protocol title	Number of treated patients
Clinical Phase 2 and Phase 3 Studies			
15396 (ERA-223)	Prostate/ Phase 3	Radium-223 & abiraterone combo study in chemotherapy-naïve patients with bone predominant metastatic CRPC	786
15245 (ALSYMPCA; BC1-06)	Prostate/ Phase 3	ALSYMPCA - -A double-blind, randomized, multiple dose, Phase 3, multicenter study of radium-223 dichloride solution for injection in the treatment of patients with symptomatic hormone-refractory prostate cancer with skeletal metastases	901
15397[a]	Prostate / Phase 3	Radium-223 dichloride in the treatment of patients with Castration-Resistant Prostate Cancer (CRPC) with Bone Metastasis	226
16506	Prostate / Phase 2	A retreatment safety study of radium-223 dichloride in subjects with CRPC with bone metastases who received an initial course of six doses of radium-223 dichloride 55 kBq/kg every four weeks	44
16507	Prostate / Phase 2	A three arm randomized open-label Phase II study of Ra 223 50 kBq/kg vs. 80 kBq/kg, and vs. 50kBq/kg in an extended dosing schedule in subjects with castration-resistant prostate cancer metastatic to the bone[b]	370
15280 (BC1-02	Prostate / Phase 2	A Phase 2 placebo controlled multicenter studying prostate cancer patients with bone metastases to evaluate the efficacy and safety of repeated injections of radium 223 dichloride	64
15304 (BC1 04)	Prostate / Phase 2	A double blind, randomized, dose response, repeat dose, Phase 2, multicenter study of radium 223 dichloride for the treatment of patients with hormone refractory prostate cancer and skeletal metastases	122
16544	Prostate/ Phase 2a	A randomized open label Phase IIa study evaluating quantified bone scan response following treatment with radium 223 dichloride alone or in combination with abiraterone acetate or enzalutamide in subjects with CRPC who have bone metastases	63
Expanded Access Program			
16216	Prostate / Phase 3b	Radium-223 dichloride in CRPC patients with bone metastasis	708
Single-arm Interventional and Non-Interventional			
16913 (REASSURE)	Prostate/ Phase 4	REASSURE (Radium-223 alpha Emitter Agent in Safety Study in metastatic CRPC popUlation for long-teRm Evaluation)	1439
17550 (PARABO)	Prostate/ Phase 4	PARABO - Pain evaluation in Radium-223 (Xofigo®) treated mCRPC patients with bone metastases – a non-interventional study in nuclear medicine centers	333

A summary of the most relevant information is included below.

2.2. Study 15396 (ERA-223) raising a signal of increased risk of fractures and mortality

ERA-223 is an on-going, randomised, double blind, phase III study, which started on 30 March 2014. Enrolment was completed in September 2016, the last patient last radium-223 injection was in February 2017 and the analysis as per protocol on the final database lock of 8 June 2018 was ongoing during this procedure with only (OS) overall survival and general fracture analysis available.

The MAH has provided updated analyses as of 15 February 2018 after the survival sweep was completed. All death-related analyses included death events up to the cut-off date of 24 November 2017, which is the starting date of the survival sweep. Most of the additional death events occurred before the death cut-off date of 24 November 2017. Any other analyses included all data up to 15 February 2018.Analyses of clinical data including clinical response markers (e.g. prostate-specific antigen [PSA] / alkaline phosphatase [ALP]), time to non-bone progression, treatment emergent adverse events leading to any treatment discontinuation/dose modifications, treatment duration of bone health agents (BHAs), and lab abnormalities were not available at the time of this report.

2.2.1.1. Patients

The study enrolled asymptomatic or mildly symptomatic, chemotherapy-naïve patients with bone predominant metastatic castrate-resistant prostate cancer (mCRPC). Asymptomatic was defined as a

worst pain score (WPS) of 0 on the World Health Organisation (WHO) Brief Pain Inventory-Short Form (BPI-SF) Question #3 (worst pain in last 24 hours) and mildly symptomatic was defined as a WPS of 1-3; 46% of patients in the study were mildly symptomatic patients. Maintenance of testosterone to castrate levels (< 50 ng/dL) was required through medical (luteinizing hormone-releasing hormone [LHRH] analogues) or surgical castration. Patients with known visceral metastases were excluded.

Baseline characteristics such as baseline haemoglobin, PSA and Eastern Cooperative Oncology Group score (ECOG) appear to be generally well balanced between treatment groups (not shown) despite some minor differences (e.g. Gleason score, lactate dehydrogenase).

2.2.1.2. Study design

This is a Phase III, double-blind, randomized, placebo-controlled, parallel group study. The study period consisted of screening/randomization 1:1, treatment period, active follow-up with clinic visits, active follow-up without clinic visits and long-term follow-up phases.

The treatment period consisted of two phases:

- Treatment with up to 6 cycles of intravenous (IV) administrations of radium-223 55 kBq/kg body weight (Arm A) or placebo (Arm B), each separated by an interval of 4 weeks, plus abiraterone acetate 1000 mg every day plus prednisone/prednisolone 5 mg twice daily. Radium-223 /placebo treatment was started on the same day as the abiraterone/prednisone treatment and used concurrently.
- Ongoing treatment with abiraterone plus prednisone/prednisolone. After completion of treatment with radium-223 (Arm A) or placebo (Arm B), all randomized subjects continued to receive abiraterone acetate 1000 mg every day plus prednisone/prednisolone 5 mg twice daily until an on-study symptomatic skeletal event (SSE) occurs (or other withdrawal criteria are met).

All SSE fractures were reported throughout the treatment and follow-up phases. During the treatment period, all non-SSE fractures were reported, regardless of causality. During the post-treatment follow-up period, only non-SSE fractures that were thought to be related to treatment (as judged by the investigator) were reported.

The use of bone health agents (BHAs) in the form of bisphosphonates or denosumab was allowed only if patients were on the medication prior to randomization.

2.2.1.3. Key results

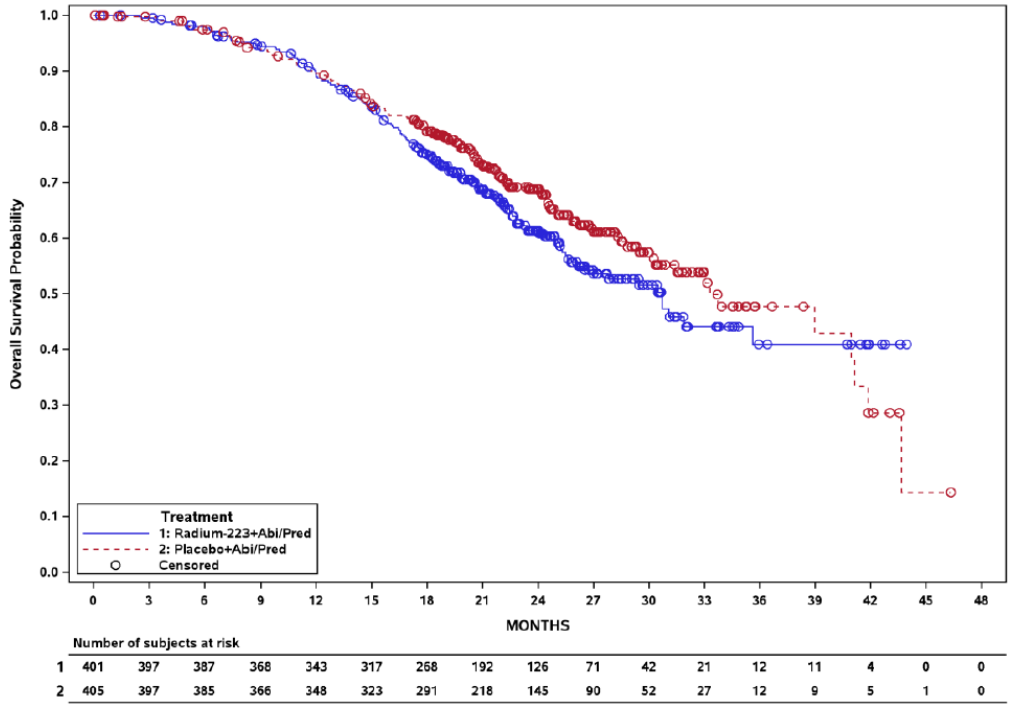
The occurrence of fractures was increased and median OS reduced in the radium-223 plus abiraterone/prednisone treatment arm compared to the placebo arm (Table 2, Figure 1).

Table 2. Fractures and deaths (Study 15396 [ERA-223]; database lock 8 June 2018)

	Arm A (Radium-223) + abiraterone + prednisone/prednisolone	**Arm B (placebo)** + abiraterone + prednisone/prednisolone
Fractures (SAS) (No of patients with≥1 fracture)	28.6% (112/392)	11.4% (45/394)
Survival analysis		
Deaths (SAS)	38.5% (151/392)	35.5% (140/394)
Overall survival (ITT) HR (95% CIs) / 2-sided p-value	1.195 (0.950, 1.505) 0.128	
Median OS (months) (95% CIs)	30.7 (25.8, A)	33.3 (30.2, 41.1)

SAS = safety analysis set; SSE-FS = symptomatic skeletal event-free survival; ITT = intent-to-treat

Figure 1. Kaplan-Meier curve for overall survival (Study 15396 [ERA-223]; ITT analysis; database lock 8 June 2018)



2.3. Data on safety

2.3.1. Deaths

2.3.1.1. Data on deaths in ERA-223

Progressive disease

As of 15 February 2018, the main primary cause of death reported was progressive disease (109 [27.8%] patients in the radium-223 arm vs. 99 [25.1%] patients in the placebo arm). Death with prior radiological bone progression was similar in the radium-223 and placebo groups (7.1% vs 8.9%, respectively). However, 14.5% of patients in the radium-223 group vs 7.4% in the placebo group died with a report of a prior radiological non-bone progression, i.e. visceral metastasis related to prostate cancer, mainly lymph node and liver metastases. Types of first disease progression are described in Table 3.

Table 3. Types of first disease progression in patients with death (Study 15396 [ERA-223], Safety Analysis Set (SAS); cut-off date 15 Feb 2018)

	Radium-223+Abi/Pred N=392 (100%)	Placebo+Abi/Pred N=394 (100%)
Number (%) of deaths due to any reason	**151 (38.5%)**	**137 (34.8%)**
Death without any progression (clinical or radiological)	39 (9.9%)	42 (10.7%)
Death with prior clinical progression only	28 (7.1%)	35 (8.9%)
Death with prior radiological bone progression only	27 (6.9%)	31 (7.9%)
Death with prior radiological non-bone progression	57 (14.5%)	29 (7.4%)
Progression due to new non-bone lesions	46 (11.7%)	20 (5.1%)
Location of new lesions:		
Abdominal Cavity	2 (0.5%)	0
Adrenal Gland	2 (0.5%)	0
Bladder	1 (0.3%)	0
Brain	1 (0.3%)	0
External Iliac Lymph Node	1 (0.3%)	1 (0.3%)
Head	0	1 (0.3%)
Hilar Lymph Node	1 (0.3%)	0
Iliac Lymph Node	4 (1.0%)	2 (0.5%)
Kidney	0	1 (0.3%)
Liver	19 (4.8%)	7 (1.8%)
Lung	8 (2.0%)	3 (0.8%)
Lymph Node	20 (5.1%)	4 (1.0%)
Para-Aortic Lymph Node	3 (0.8%)	0
Parirectal Lymph Nodes	0	1 (0.3%)
Penis	1 (0.3%)	0
Peritoneum	0	1 (0.3%)
Pleural Effusion	1 (0.3%)	0
Prostate	0	1 (0.3%)
Renal Artery	0	1 (0.3%)
Spinal Cord	1 (0.3%)	0
Upper Lobe Lung	1 (0.3%)	0
Ureter	1 (0.3%)	0

Progression is not the progression that necessarily lead to death. Note: Subjects may have more than one location of new lesion
Number of deaths include subjects who began new anti-cancer therapy

Treatment-emergent adverse events as secondary cause of death

An assessment of potential temporal association of adverse events (AEs) with death due to progressive disease shows that among the 170 AEs reported in the 90-day period preceding death due to progressive disease, 100 AEs (58.8%) were in the radium-223 arm and 70 AEs (41.2%) in the placebo arm. The most commonly reported AEs, with at least 4 events in total (both arms combined) were: pathological fracture (9 events reported in 4 patients in the placebo arm compared to 2 events reported in 2 patients in the radium-223 arm), anaemia, fatigue, nausea, bone pain, constipation, cancer pain, musculoskeletal chest pain, weight decreased and decreased appetite.

Influence of fractures and bone health agent (BHA) on mortality

Subgroup analysis were conducted for patient with prior fracture (106 patients in the radium-223 arm vs. 37 in the placebo arm): hazard ratio (HR)=1.170; 95% CI [0.635, 2.155]; 2-sided p =0.6145. Subgroup analysis was also conducted for patients without prior fracture (HR =1.284; 95% CI [0.986, 1.672]; 2-sided p = 0.0624). Landmark analyses were provided to assess a potential association of fracture and death (Table 4).

Table 4. Landmark Analysis and Time-dependent Cox Model of OS (Study 15396 [ERA-223])

ERA-223	**Treatment (radium-223 vs placebo)**		**Fracture (Y vs N)**	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Time-dependent Cox	1.12 (0.88, 1.42)	0.367	1.39 (1.02, 1.90)	0.039
6 months	1.15 (0.90, 1.48)	0.270	1.58 (1.03, 2.42)	0.037
9 months	1.24 (0.95, 1.62)	0.117	1.22 (0.83, 1.80)	0.306
12 months	1.25 (0.93, 1.67)	0.134	0.93 (0.61, 1.42)	0.748

The OS HR with BHA vs without BHA within each treatment arm was numerically lower in the radium-223 arm (HR: 0.85 vs. 0.98, placebo) (multivariate analysis final model).

2.3.1.2. Data on deaths in ALSYMPCA

In the updated analysis of the pivotal ALSYMPCA trial (see section 2.4.1.) with the cut-off date 15 July 2011 (before any patients treated with placebo crossed over to radium-223), the proportion of subjects in the safety population who died was lower in the radium-223 group compared to the placebo group (54.5% vs 63.5%) and this was mainly due to a higher incidence of non-prostate cancer related deaths in the placebo group (Table 5).

Table 5. Summary of deaths, safety analysis set (Study 15245 [ALSYMPCA], 2011)

	Radium-223 chloride N = 600	**Placebo** N = 301
Patients who died	327 (54.5%)	191 (63.5%)
During treatment period	26 (4.3%)	22 (7.3%)
During 3-year follow-up period	301 (50.2%)	169 (56.1%)
Prostate cancer-related death	289 (48.2%)	149 (49.5%)
Skeletal metastases	244 (40.7%)	135 (44.9%)
Liver metastases	24 (4.0%)	8 (2.7%)
Lung metastases	10 (1.7%)	2 (0.7%)
Lymph metastases	27 (4.5%)	5 (1.7%)
Brain metastases	15 (2.5%)	5 (1.7%)
Other metastases	35 (5.8%)	13 (4.3%)
Non-prostate cancer-related death	34 (5.7%)	41 (13.7%)

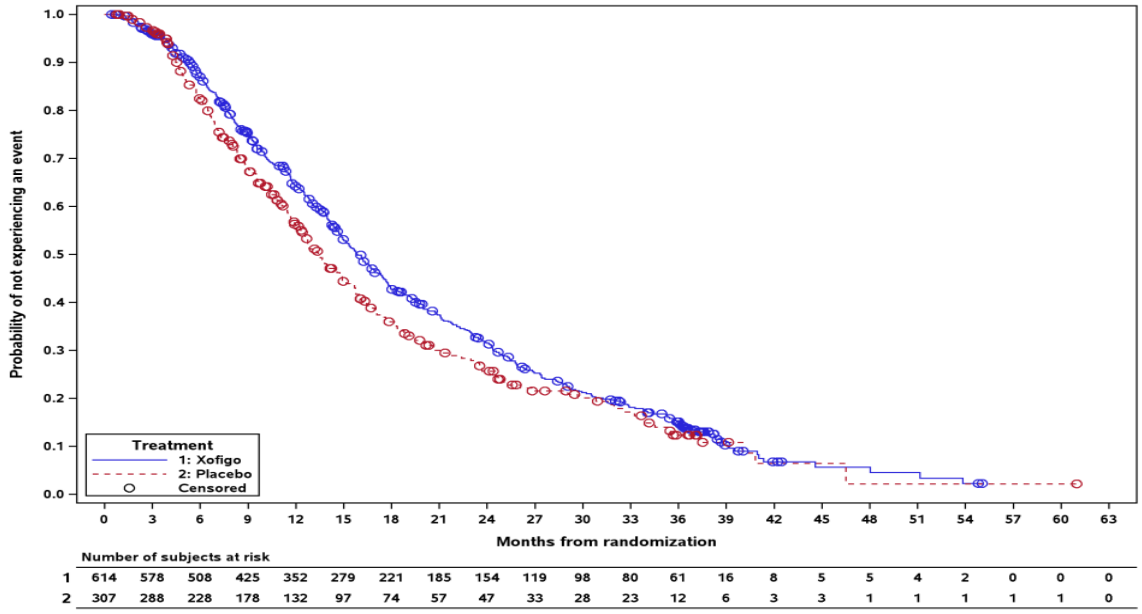
In addition, the final clinical study report addendum for ALSYMPCA presented all safety data collected for the entire study period (treatment period and follow-up period) up to the database lock of 10 October 2014. In this analysis, both prostate cancer-related death and non-prostate cancer-related death were increased in the radium-223 arm, and a trend for increased risk of non-bone progression was observed in the radium-223 arm (Table 6). However, despite imbalances in the proportion of death cases, increased median overall survival considering time-to-event analyses for patients treated with radium-223 was confirmed in the 2014 final database with median survival of 14.6 months in patients treated with radium-223 compared to 11.4 months in patients treated with placebo (HR = 0.747, 95% CI [0.641, 0.870]; p = 0.0002).

Table 6. Summary of deaths, safety analysis set (Study 15245 [ALSYMPCA], 2014)

	Radium-223 dichloride N=600	Placebo N=301
Subjects who died	**520 (86.7)**	**251 (83.4)**
During treatment period	24 (4.0)	22 (7.3)
During 3-year follow-up period	479 (79.8)	224 (74.4)
Prostate cancer-related death	**465 (77.5)**	**205 (68.1)**
Skeletal metastases	397 (66.2)	182 (60.5)
Liver metastases	38 (6.3)	17 (5.6)
Lung metastases	19 (3.2)	5 (1.7)
Lymph metastases	40 (6.7)	9 (3.0)
Brain metastases	20 (3.3)	10 (3.3)
Other metastases	53 (8.8)	15 (5.0)
Missing metastases	7 (1.2%)	0
Missing relationship to prostate cancer	3	1
Non-prostate cancer-related death	**52 (8.7)**	**45 (15.0)**

Increased median overall survival was also confirmed in the subgroup of patients with prostate cancer-related deaths by an analysis of the time to prostate cancer related death based on the March 2014 database (Figure 2).

Figure 2. Time to Prostate Cancer Related Deaths (Study 15245 [ALSYMPCA], 2014)



Note: All subjects are from main study. Crossover subjects are censored at last assessment date before crossover phase starts.
Bayer: /by-sasp/patdb/projects/888223/15245/stat/prod_query29/pgms/t_os_km_surv2014_pcrel.sas ggdtq 20APR2018 18:07

2.3.2. Fractures

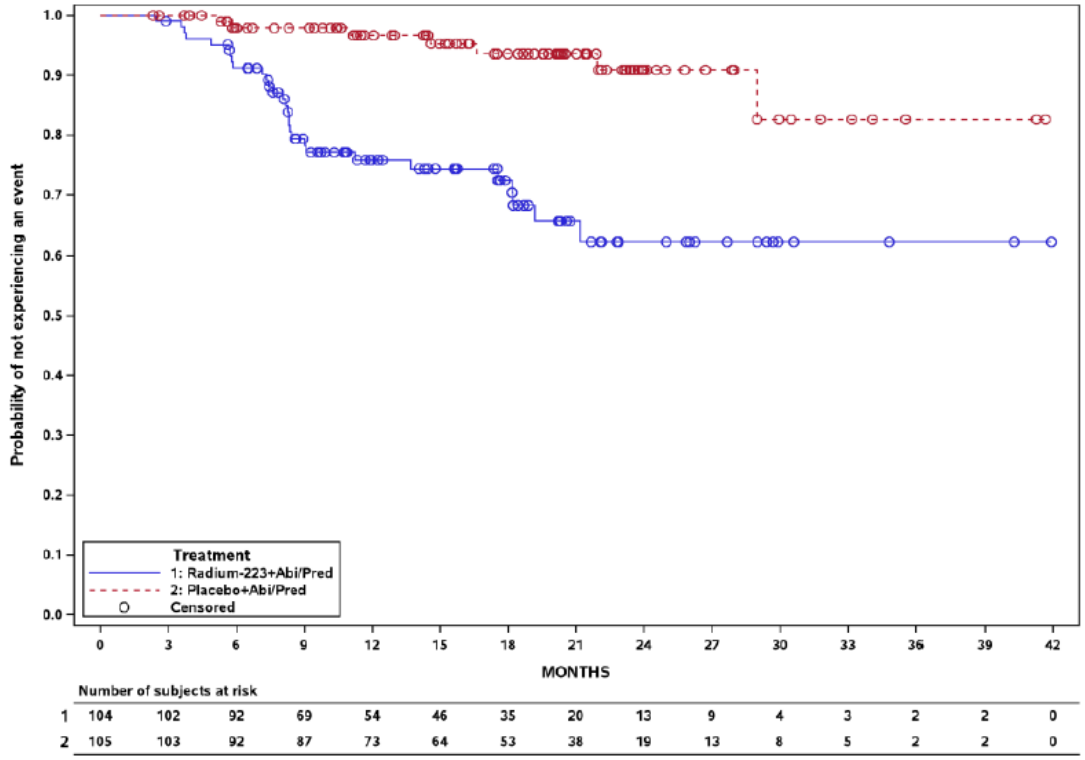
2.3.2.1. Data on fractures from ERA-223 and ALSYMPCA

In the safety analysis set of ERA-223, a higher proportion of patients in the radium-223 group had at least 1 fracture than in the placebo group (112/392 [28.6%] vs 45/394 [11.4%], updated analysis; database lock 08 June 2018). Out of the fractures that occurred as treatment-emergent adverse events in 101 patients in the radium-223 group 79% (n=80) were symptomatic and immobilisation was indicated (n=46) or resulted in severe symptoms (n=33) or were life-threatening (n=1); while 21% (n=21) were asymptomatic.

Median time to fracture was 7.06 months in the radium-223 arm and 10.18 months in the placebo arm. The Kaplan-Meier figures of time to fracture are shown below (Figure 3 and Figure 4).

In ALSYMPCA 2014 database, the incidence of fractures was similar in the radium-223 arm vs. placebo arms was 8.50% vs. 7.97% for pathological and 2.67% vs. 1.66% for non-pathological fractures. In a published *post-hoc* analysis the effect of radium-223 on time to any bone fracture (pathological or otherwise) was not significant (HR=0.80; 95% CI [0.50–1.30]) (Sartor, 2014 [4]).

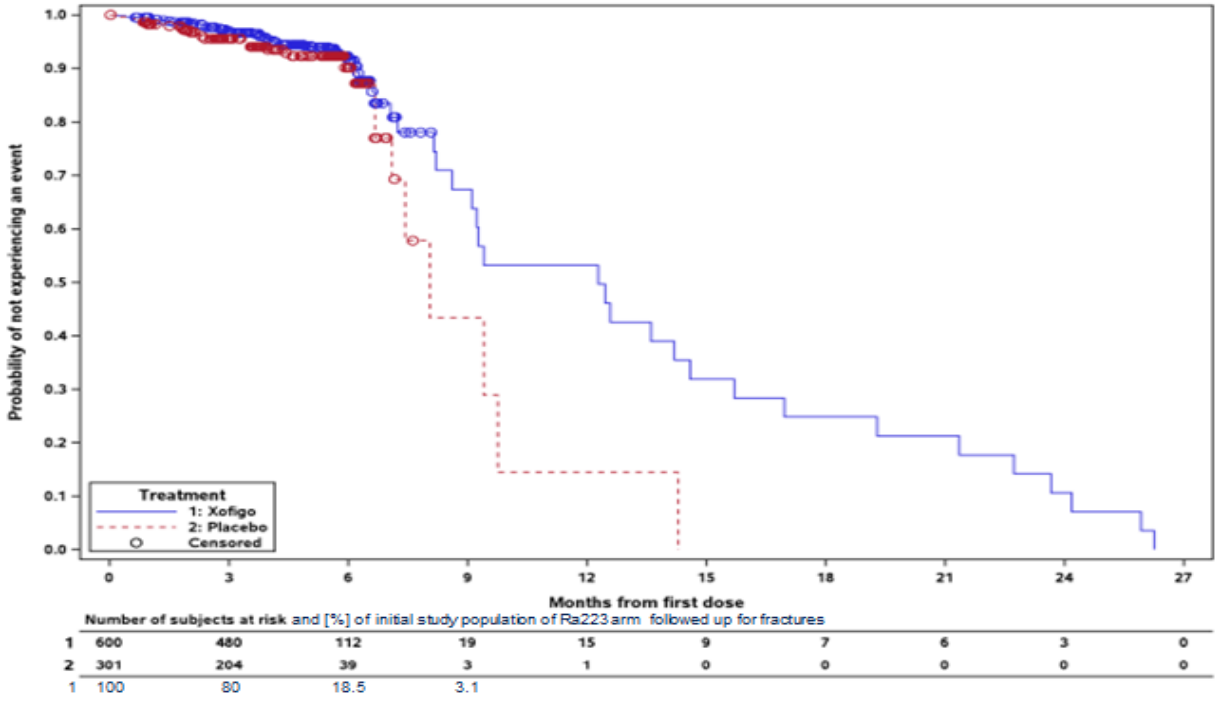
Figure 3. Kaplan-Meier curves of time to first fracture (Study 15396 [ERA-223], database lock 8 June 2018)



In both ERA-223 and ALSYMPCA, non-pathological fractures regardless of causality were only reported during the treatment period. Median duration of exposure to study treatment was significantly longer in ERA-223 (343 days; ~ 11.4 months) (based on the IDMC report dated 26 September 2017) compared to ALSYMPCA (141 days; ~4.7 months). In ALSYMPCA, the number of patients followed-up for all fractures decreased rapidly in the Ra223 arm from 100% of the initial study population at trial initiation to 18.5% and 3.1% at months 6 and 9 after the first dose, respectively (Figure 4).

[4] Sartor O, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. Lancet Oncol 2014; 15: 738–46.

Figure 4. Kaplan-Meier curves of time to fractures (All) (Study 15245 [ALSYMPCA], SAS, 2014)



Timing of fractures

In the radium-223 group of ERA-223, of the 108 patients who had ≥1 fracture (cut-off date 15 February 2018):

- 24 (22%) had a fracture in the treatment period, before or on the last radium-223 dose (including 3 patient who had a SSE fracture).

- 72 (67%) had a fracture in the treatment period, after concurrent treatment with radium-223 plus abiraterone/prednisone and before the last dose of subsequent abiraterone/prednisone treatment (including 25 patient who had a SSE fracture).

- 12 (11%) had a fracture that was reported after the last study dose (radium-223 and/or abiraterone acetate/prednisolone) (including 7 patient who had a SSE fracture).

Location and Type of fractures

At time of this report, fracture imaging data for 107 patients in ERA-223 was available and had underwent independent review. Location and type of fractures is presented in the below table. In most patients there were no bone metastases at the site of the fracture (radium-223 arm 60/76 [79%]). In total, 37 out of 80 fractures (46.3%) were osteoporotic fractures in the radium-223 arm compared to 4 out of 27 fractures (14.8%) in the placebo arm.

Table 7. Summary of the independent reading of the fracture imaging (Study 15396 [ERA-223])

	Radium-223 +Abi/Pred N=392 (100%)	Placebo +Abi/Pred N=394 (100%)
Total number of patients with fracture imaging scans read by independent reviewers	**80 (20.4%)**	**27 (6.9%)**
Total number of patients with at least one fracture	76 (19.4%)	23 (5.8%)
Bone mets at site of fracture	20 (5.1%)	6 (1.5%)
New bone lesion: No	15 (3.8%)	5 (1.3%)
New bone lesion: Yes	6 (1.5%)	1 (0.3%)
No bone mets at site of fracture	60 (15.3%)	17 (4.3%)
Imaging modality of fracture		
CT SCAN	38 (9.7%)	12 (3.0%)
SCINTIGRAPHY TECHNETIUM-99m	47 (12.0%)	10 (2.5%)
X-RAY	0	2 (0.5%)
Type of fracture		
Pathological fracture	19 (4.8%)	6 (1.5%)
Traumatic fracture	27 (6.9%)	13 (3.3%)
Osteoporotic fracture	37 (9.4%)	4 (1.0%)
Indeterminate	1 (0.3%)	0
If Osteoporotic, Osteoporosis at baseline?		
NO	1 (0.3%)	0
NOT ASSESSABLE	2 (0.5%)	0
YES	36 (9.2%)	4 (1.0%)

Subjects with multiple types of fractures or multiple types of imaging modality of fractures are counted in more than one category. If subjects with Osteoporotic fractures in multiple locations have different findings of Osteoporosis at baseline, they are counted in more than one category.

2.3.2.2. Effect of several risk factors on fractures across studies

2.3.2.2.1. BHA, number of metastases at baseline, medical history of osteoporosis

Subgroup analyses on the effect of concurrent use of BHAs (i.e. bisphosphonates and denosumab) on the risk of SSE-FS were conducted (Table 8) as well as on the risk of fractures according to the number of bone metastases (Table 9).

Table 8. SSE-FS events by exposure to BHAs (Study 15396 [ERA-223])

	Radium-223 +Abi/Pred N=401 (100%)		Placebo +Abi/Pred N=405 (100%)	
SSE-FS Event Category	**BHA (N= 155)**	**No BHA (N= 246)**	**BHA (N= 169)**	**No BHA (N= 236)**
Any events	**62 (40.0%)**	**122 (49.6%)**	**71 (42.0%)**	**98 (41.5%)**
Death	53 (34.2%)	86 (35.0%)	48 (28.4%)	63 (26.7%)
External Beam Radiotherapy	25 (16.1%)	65 (26.4%)	32 (18.9%)	52 (22.0%)
Spinal Cord Compression	6 (3.9%)	5 (2.0%)	5 (3.0%)	14 (5.9%)
Symptomatic Pathological Bone Fractures	2 (1.3%)	37 (15.0%)	4 (2.4%)	11 (4.7%)
Tumor-Related Orthopedic Surgical Intervention	1 (0.6%)	9 (3.7%)	2 (1.2%)	4 (1.7%)

BHA = bone health agent. BHAs include bisphosphonates (etidronic acid, clodronic acid, pamidronic acid, alendronic acid, tiludronic acid, Ibandronic acid, risedronic acid, and zoledronic acid) and denosumab.
Note: Patients with multiple types of SSE-FS events are counted in more than one category of events.

Table 9. Risk of fracture according to number of bone metastases (Study 15396 [ERA-223])

	Baseline factor			
	<6 bone metastases		≥6 bone metastases (including Superscan)	
	Radium-223 + Abi/Pred N=133	Placebo + Abi/Pred N=136	Radium-223 + Abi/Pred N=259	Placebo + Abi/Pred N=258
n, % of patients with fractures	50/133 (37.6%)	10/136 (7.4%)	52/259 (20.1%)	22/257 (8.6%)

A number of multivariate analyses were conducted to evaluate the role of possible risk factors in ERA-223 as well as in ALSYMPCA; the most relevant ones are presented below.

Table 10. Multivariate logistic regression analyses of the effect of BHA, number of metastases at baseline and medical history of osteoporosis on fractures in the radium-223 arm (Study 15396 [ERA-223] and Study 15245 [ALSYMPCA])

	ERA-223 Multivariate final model Radium-223 arm	**ALSYMPCA** Multivariate full model Radium-223 arm
Covariates	**Odds ratio (P value)**	
BHA (Y vs N)	0.334 (<0.001)	0.46 (0.029)
Number of metastases at baseline (< 6 vs ≥ 6 metastases)	1.855 (0.016)	1.42 (0.402)
Medical history of osteoporosis (Y vs N)	4.835 (0.001)	Unknown

Odds ratio > 1 = Increased risk; Odds ratio < 1 = decreased risk

In the ERA-223 trial, medical history of osteoporosis and lower number of metastases at baseline (<6 vs. ≥6) was associated with a significantly increased risk of fracture in the radium-223 arm, but not in the placebo arm. Use of BHA was associated with reduced risk of fracture in both the radium-223 and the placebo arm (BHA use radium-223 arm odds ratio = 0.32; p < 0.001; placebo arm odds radio = 0.35; p = 0.016). The number of patients with at least one fracture was lower in patients using BHA in both study arms (radium-223 arm 20/156 [12.8%] vs.82/236 [34.7%]; placebo arm 8/168 [4.8%] vs. 24/226 [10.6%]).

In ALSYMPCA, BHA use was significantly associated with a decreased risk of fracture in the radium-223 arm, but not in the placebo arm (BHA use radium-223 arm odds ratio = 0.46; p = 0.029; placebo arm odds radio = 0.57; p = 0.246). Whilst not statistically significant, the risk of fracture tends to be increased in the radium-223 arm in patients with less than 6 metastases compared to patients with more than 6 metastases (odds ratio: 1.42; p = 0.402), but tends to be lower in the placebo arm (odds ratio: 0.61; p = 0.549).

Of note, in ALSYMPCA, 16.4% of patients had < 6 metastases, whereas in ERA-223 this group corresponded to 33.9% of the ITT population.

Biodistribution of radium-223

Technical issue prevented from determining the fraction of radium-223 activity within the skeleton quantitatively. However data on biodistribution from a phase I study (Study 15303) is presented in the below table, which shows that radium-223 distributes to areas of degenerative joint disease (patient 106).

Table 11. Ratio of counts in bone lesions to normal bone (uncorrected for partial volume effects) (Study 15303)

Subject Number	Hot spot # 1		Hot spot # 2	
	Ratio	Site	Ratio	Site
101	1.01	L humerus	1.55	L femur
102	1.28	R humeral head	1.19	L iliac
103	1.41	L femur	1.42	R humerus
104	3.15	R distal femur	1.36	L humeral head
106	1.18	Sacrum	2.04	Degenerative disease R hip
107	1.41	Upper spine	1.14	L acetabulum
109	2.03	R scapula	1.23	Thoracic spine
110	2.43	Pubic	1.72	L iliac
111	1.74	R humerus		

Source: 15303, Module 5.3.3.2, Report A58798, Section 11.4.2 3.2 Text Table 19

Of note also, in ERA-223 more cases of degenerative bone disease such as osteoporosis and osteoporotic fractures were observed in the radium-223 arm than the placebo arm (5.1% vs. 0.3% and 4.3% vs. 0.3%, respectively).

2.3.2.2.2. Number of doses of radium-223

In ERA-223, 88.0% of patients received the planned 6 doses of treatment in the radium-223 arm and 84.3% in the placebo arm. In a subgroup analysis the hazard ratio for the risk of fractures with radium-223 compared to placebo was 3.721 ($p<0.0001$) in the subgroup having received 5 or more doses (n=709) and 1.866 ($p=0.4195$) in the subgroup having received less than 5 doses (n=77).

In ALSYMPCA, 63.4% of patients received the planned 6 doses of treatment in the radium-223 arm and 47.2% in the placebo arm.

In Study 16507 which compared a standard regimen arm (Arm A=125 patients) with a higher dose arm (Arm B=124 patients) and an extended dose arm of up to 12 doses (Arm C=121 patients), pathological fracture rate ranged from 5% in Arm A to 10.9 % in Arm C. Median time to SSE was shorter in the extended dose arm (Arm C) compared to the standard regimen (9.6 months vs 13.1 months).

2.3.2.2.3. Duration of castration prior radium-223

The percentage of patients with medical castration prior radium-223 treatment was slightly higher in ERA-223 compared to ALSYMPCA (99.0% vs. 90.5% in the radium-223 arm). However, the median duration of castration before treatment was 33.91 months in ERA-223 compared to 49.38 months in ALSYMPCA.

2.3.3. Discussion on safety

Based on the available data from ERA-223, the PRAC considered that in chemotherapy-naïve asymptomatic or mildly symptomatic patients with CRPC, radium-223 in combination with abiraterone acetate and prednisolone/prednisone increases the risk of fractures and tends to decrease overall survival, compared to placebo in combination with abiraterone acetate and prednisone/prednisolone. The impact of these findings on the authorised indication is discussed below.

2.3.3.1. Discussion on the risk of death

For the safety population in ERA-223, the proportion of deaths and median OS in the radium-223 and placebo groups are 151/392 (38.5%) and 30.7 months versus 140/394 (35.5%) and 33.3 months, respectively. Median OS for the placebo plus abiraterone and prednisone/prednisolone group in this

study is similar to that of the abiraterone and prednisone/prednisolone group in study COU-302, conducted in a similar population (Zytiga SmPC). It is acknowledged that the initially observed OS HR imbalance has decreased from 1.347 (95% CI: 1.05 -1.73, p = 0.02) based on the analysis of preliminary, uncleaned data to 1.195 (95% CI: 0.95 -1.51, p = 0.128) based on the analysis further to the database lock on 8 June 2018. However, the HR remains above 1 and the upper 95% CI shows that up to a 50% increase in the risk of death for the radium-223 group cannot be excluded. It is also noted that the reduction in median OS has been maintained at 2.6 months. Baseline characteristics were generally well balanced between treatment groups despite some minor differences, such as in Gleason score. Nonetheless, multivariate analysis were conducted to account for these minor imbalances; after adjusting for confounding factors these analyses suggests no imbalance in OS (HR = 1.06, p = 0.605). This adjusted HR is acknowledged but should be interpreted cautiously because of the *post-hoc* nature of this analysis, which could have had an impact on the variables that were included. In particular, whilst it seems that the same variables as in other multivariate analysis were included, BHA is missing and it could not be confirmed whether the proportional hazards assumption is valid. In addition, in patients who received 5 or 6 injections, the reduction in median OS in the radium-223 arm compared to placebo arm was more pronounced (30.7 months vs 39.0 months ; see section 2.4.2.).

Death due to progressive disease (27.8% in the radium-223 group vs. 25.1% in the placebo group) appears to be the main reason for the imbalance in deaths between the treatment arms. The proportions of death with prior radiological bone progression were similar in the radium-223 and placebo groups (7.1% vs. 8.9%, respectively). However, 14.5% of patients in the radium-223 group vs. 7.4% in the placebo group died with a report of a prior radiological non-bone progression, i.e. visceral metastasis related to prostate cancer, mainly lymph node and liver metastases. Available non-clinical data however indicates that radium-223 inhibits spread from the bone to visceral sites (Suominen, 2017 [5]). In addition, in the overall study population there appears to be an increased risk of radiological non-bone progression in the radium-223 group compared to the placebo group (HR 1.376; 95% CI [0.972, 1.948], p=0.07).

Adverse events did not seem to be the reason for differences in mortality between the treatment arms in ERA-223. There was also no clear evidence of consistently contributing secondary causes of death was identified based on the medical review of case narratives. Further, the Kaplan-Meier curve for the overall survival in patients without prior fractures shows an increased risk of death in the radium-223 arm plus abiraterone/prednisone vs. placebo plus abiraterone/prednisone with a HR 1.284 (95% CI[0.986, 1.672]; 2-sided p = 0.0624) which is similar to the HR in the overall population (1.22). Landmark analyses did not show a significantly increased risk of death after fracture, but indicated that an early fracture is associated with an increased risk of death. Although based on subgroup analysis, these data also suggest that fractures are not the main cause of the decreased OS in the radium-223 group.

The use of BHA appears to be associated with a non-significant trend for positive effect on OS in the radium-223 arm, but had no impact on OS in the placebo arm.

In the final safety analysis of ALSYMPCA the proportion of deaths was higher in the radium-223 arm, however this may have been due to a longer follow-up time in the radium-223 arm potentially resulting in a more complete collection of survival information for the radium-223 arm as compared to the control arm. The slightly increased incidence of death in the radium-223 group (86.7% in the radium-223 group vs. 83.4% in the placebo group) seems to be driven by an increase in prostate cancer-related deaths in the radium-223 group compared to placebo (77.5% vs 68.1%), especially

[5] Suominen MI, et al. Radium-223 Inhibits Osseous Prostate Cancer Growth by Dual Targeting of Cancer Cells and Bone Microenvironment in Mouse Models. Clin Cancer Res. 2017 Aug 1;23(15):4335-4346.

skeletal metastases and lymph metastases. Of note, however, prostate-cancer related death was not a pre-specified endpoint and does not change the median overall survival benefit in favour of the radium-223 group in this same final analysis (see section 2.4.). In the final analysis, median overall survival in patients with prostate-cancer related deaths was longer in patients treated with radium-223 compared to patients treated with placebo (+2.4 months, HR = 0.812; 95% CI[0.687, 0.960]; p = 0.015). Whilst this analysis shows a lower risk of prostate cancer death in the radium-223 arm, the treatment curves diverge from about 6 months and start to converge from 21 months to join at just before 30 months, which questions the assumption of proportional hazards. Of those patients who died due to prostate cancer, the proportion who died because of prostate cancer-related visceral (i.e. non-skeletal) metastases was notably higher in the radium-223 arm than the placebo arm (38.1% vs. 27.3%). This imbalance in death due to non-bone progression mirrors the trend seen in ERA-223. Also, the mechanism for the notably lower incidence of non-prostate cancer-related death in the radium-223 group compared to the placebo group (8.7% vs. 15%) is uncertain and may, at least in part, reflect imbalances in baseline with respect to health status, favouring the radium-223 group.

The mechanism(s) for the trend towards an increased risk of death and non-skeletal progression are unclear. Whilst several possible mechanisms were postulated, this uncertainty was also shared by experts of the scientific advisory group on oncology (SAG-O) who was convened at the PRAC request.

2.3.3.2. Discussion on the risk of fractures

In the safety analysis set of ERA-223, a higher proportion of patients in the radium-223 group had at least 1 fracture than in the placebo group (112/392 [28.6%] vs. 45/394 [11.4%]). Median time to fracture was 7.06 months in the radium-223 arm and 10.18 months in the placebo arm, and thus the majority fractures, occurred after the final dose of radium-223. Indeed, the largest absolute difference in the risk of fractures between the radium-223 and placebo groups in study ERA-223 (18.4% [72/392] vs. 6.3% [25/394]) appears to have developed after completion of the [radium-223 or placebo] + abiraterone + prednisone/prednisolone treatment phase, during subsequent abiraterone + prednisolone/prednisone treatment. This delayed occurrence of fractures has been observed with post-radiation therapy fractures, which can occur several months after radiation is administered (Shimoyama, 2017 [6]). The timing of the fractures observed in ERA-223 raises the possibility that patients who receive radium-223 (without abiraterone acetate) are at an increased risk of fractures if they subsequently receive abiraterone acetate or other treatments that adversely affect bone health.

Symptomatic pathological fractures, which are an SSE, had to be reported throughout treatment and follow-up phases of ALSYMPCA and ERA-223. The proportion of patients in the radium-223 group who experienced a symptomatic pathological fracture is only slightly higher in ERA-223 than in ALSYMPCA (8.7% vs. 5.0%). Therefore, it seems that the markedly higher incidence of fractures in ERA-223 compared to ALSYMPCA (26.0% vs. 6.5%) was due to non-SSE fractures (e.g. osteoporotic or traumatic fractures unrelated to the prostate cancer), which had to be reported through the treatment phase of both studies but only in the follow-up phase if they were judged as being related to treatment. Compared to ERA-223, there was a shorter treatment phase in ALSYMPCA and therefore a shorter period during which all AEs (including non-SSE fractures) had to be reported. Further bone/CT scans were undertaken in the treatment phase of ERA-223 but not in ALSYMPCA. In addition, given that fractures appear, in general, to be a delayed event with respect to radium-223 administration, it is possible that the risk of fractures with radium-223 has been under-estimated in ERA-223 (and ALSYMPCA). The PRAC welcomed the MAH's decision to amend the protocols of all ongoing MAH-sponsored trials to ensure all fractures (including non-pathological or unrelated) as well as bone

[6] Shimoyama T, Katagiri H, Harada H et al. Fracture after radiation therapy for femoral metastasis: incidence, timing and clinical features. J Radiat Res. 2017;58:661-668.

associated events (e.g. osteoporosis) are documented not only during the treatment phase, but also in follow-up phase.

2.3.3.2.1. Effect of radium-223 on bone modelling

It is currently assumed that radium-223 mimics calcium and can be taken up into bone by two mechanisms. The first is an active component in which osteoblasts actively insert radium-223 into bone matrix (Suominen, 2013 [7]); therefore, the degree of osteoblastic activity correlates with radium-223 deposition. In addition, there is a passive component through which radium-223 is inserted into hydroxyapatite (anion exchange with calcium). The clinical relevance of an uptake of radium-223 in normal non-tumour bearing bone via a basal activity of osteoblasts and passive anion exchange is not known. However because of their age and previous and concurrent medications, the indicated population is at high risk of osteoporosis and fractures (Bienz & Saad, 2015 [8]). Therefore, any treatment, such as radium-223, which further decreases osteoblastic activity and bone formation is likely to increase the risk of fractures. These patients may have areas of increased osteoblastic activity due to a healing fracture, which in the case of vertebral fractures may be asymptomatic and therefore undiagnosed (Mistry, 2010 [9]). Also, it is of concern that the passive component could become clinically relevant with a higher number of doses of radium-223 or fewer osteoblastic bone metastases.

Non-clinical data from two different animal species raised a signal of fractures. In one study, two out for four dogs developed spontaneous fractures in the context of osteolysis at the clinically recommended activity at the end of their 6-dose course of radium-223. Whilst bone metastases in prostate cancer are generally osteoblastic, it is well recognised they usually have an osteolytic component (Keller & Brown, 2004 [10]). Fractures were also observed in rodents. It is acknowledged that rodents have a higher bone turnover than humans and therefore a higher uptake of radium-223, however there are clinical situations which can increase bone turnover in prostate cancer patients, such as healing of fractures (which may be undiagnosed, especially vertebral fractures), osteoarthritis (Maruotti, 2017 [11]) and concomitant use of statins (Ruan, 2012 [12]).

2.3.3.2.2. Combination with abiraterone and prednisone/prednisolone and possible consequences for combination with other treatments regarding the risk of fracture

The PRAC acknowledged that there might be a synergistic effect of abiraterone, prednisone and radium-223 on osteoblasts leading to increased fracture risk. However, this should in principle apply to all anti-androgens and other medicines commonly used in systemic treatment of prostate cancer up to a certain extent. As is the case with abiraterone and prednisone/prednisolone, an increased risk of fracture (other than pathological fractures) is a known risk of treatment with a number of other anti-androgens including enzalutamide and first-generation androgen receptor antagonists (e.g. flutamide containing products). The markedly higher concurrent use of an anti-androgen in the radium-223 group in ERA-223 compared to ALSYMPCA, is likely to be a factor in the higher rate of fractures observed in the radium-223 group in ERA-223 than in the radium-223 group in ALSYMPCA (28.6 % vs. 10.67 %).

[7] Suominen MI, et al. Survival benefit with radium-223 dichloride in a mouse model of breast cancer bone metastasis. J Natl Cancer Inst 2013;105:908–16.
[8] Bienz M, Saad F. Androgen-deprivation therapy and bone loss in prostate cancer patients: a clinical review. Bonekey Rep 2015;4:716.
[9] Mistry R, Hughes D, Parr NJ, Wadhwa V. Lateral spine radiographs prior to androgen deprivation treatment detect a high incidence of undiagnosed vertebral fragility fractures in advoked prostate cancer. Euro Urol 2010; 3:267.
[10] Keller ET, Brown J. Prostate cancer bone metastases promote both osteolytic and osteoblastic activity. J Cell Biochem 2004;91(4):718-29.
[11] Maruotti N, Corrado A, Cantatore FP. Osteoblast role in osteoarthritis pathogenesis. J Cell Physiol 2017;232:2957-2963.
[12] Ruan F, Zheng Q, Wang J. Mechanisms of bone anabolism regulated by statins. Biosci Rep 2012;32:511-9.

Mechanistically, unlike androgen receptor antagonists which lead to a reduced androgen receptor signalling, the use of abiraterone is associated with two additional potentially bone health impairing factors: circulating levels of bone protecting oestrogens are reduced and the concomitant use of prednisone/prednisolone is needed. This may result in a less pronounced side effect profile of androgen receptor antagonists in the bone compared to abiraterone. However, considering the known pharmacological effects of androgen receptor antagonists on bone, an increased risk of fractures may also occur when radium-223 is combined with these medicinal products. A mechanism proposed by the SAG experts was that abiraterone might downregulate metabolic activity in metastases and surrounding bone by abiraterone resulting in lower uptake of radium-223 in these regions and consequently, increased availability in other tissues. This mechanism would also have implications with other effective treatments, however available data do not confirm this hypothesis. In addition, prednisone/prednisolone is administered in combination with abiraterone as replacement therapy due to decreased steroid synthesis from abiraterone therapy. Therefore, the extent to which prednisone/prednisolone used in combination with abiraterone may have adverse effects on bone is unclear. However, the use of corticosteroids was lower in the treatment phase of ALSYMPCA (43%) than ERA-223 (100 %), which may have contributed to the higher fracture rate observed in ERA-223. In addition, when treating CRPC patients, systemic anti-cancer medicines (inlcuding radium-223) are usually given in combination with LHRH analogues (in patients who are not surgically castrated) to maintain testosterone at castrate levels (e.g. Xtandi and flutamide-containing products SmPC). LHRH analogues substantially reduce oestrogen levels, resulting in adverse effects on bone including osteoporosis and fractures (Wilson, 2015 [13]).The percentage of patients with medical castration was slightly higher in ERA-223 compared to ALSYMPCA but the median duration of castration before treatment was shorter in ERA-223 compared to ALSYMPCA. Differences in type and duration of castration are unlikely to explain the differences in fracture risk observed between the two studies. Also, chemotherapies (e.g. docetaxel) are given in combination with prednisone/prednisolone, which inhibit osteoblastic activity. There are at least two ongoing phase 2 open label studies currently investigating use of radium-223 with other cancer therapies - PEACE-3 (radium-223 and enzalutamide vs. enzalutamide) and DoRa (radium-223 and docetaxel vs. docetaxel). These studies might yield relevant information on the use of radium-223 in combination with enzalutamide and docetaxel. The clinical study reports of studies PEACE-3 and DoRa should be submitted forthwith when available.

Interim data from the observational study REASSURE shows that in clinical practice there is concomitant use with abiraterone (16%), with enzalutamide (19%) and with first-generation androgen receptor antagonists (14%). In addition, robust data on the safety of the combination of radium-223 with other 2nd and 3rd generation anti-androgens are missing, and clinical data on concomitant 1st generation anti-androgens (e.g. bicalutamide) is limited. Whilst the mechanism for the increased risk of fractures and death remain unclear, SAG experts concluded that radium-223 should not be combined with any other effective systemic cancer treatment, including chemotherapy, until the benefits and the risks have been established.

The MAH is conducting non-clinical studies to investigate the mechanism responsible for the increased risk of fracture and death in study ERA-223. Notably, the MAH intends to address the hypothesis of synergistic pro-osteoclastic and anti-osteoblastic effects in ongoing non-clinical experiments in osteoblastic prostate cancer mouse models. Results of these experiments should be reported in upcoming PSURs.

Preliminary biomarker data shows as expected that there is significantly stronger reduction of levels of bone formation markers (e.g. bone ALP [alkaline phosphatase]) by radium-223 in combination with abiraterone and prednisone/prednisolone compared to placebo plus abiraterone plus

[13] Wilson HC, Shah SI, Abel PD et al. Contemporary hormone therapy with LHRH agonists for prostate cancer: avoiding osteoporosis and fracture. Cent European J Urol. 2015;68:165-8.

prednisone/prednisolone (not shown). However, these data do not allow concluding that the substantial increase in the risk of fractures when radium-223 is combined with abiraterone and prednisone reflects a specific synergistic interaction with abiraterone and prednisone/prednisolone in which radium-223 has no inherent risk of fractures. Indeed, in another study in 53 patients with progressing CRPC and ≥ 2 bone metastases, the addition of radium-223 to docetaxel + prednisone also resulted in a greater reduction in levels of bone formation markers (e.g. bone alkaline phosphatase) compared to docetaxel plus prednisone alone (Morris, 2017 [14]). Moreover, the significantly greater reduction in bone markers when radium-223 is added to abiraterone and prednisone/prednisolone would be consistent with radium-223 increasing the risk of fractures as a single agent, especially in patients with risk factors, e.g. osteoporosis or concomitant medication such as corticosteroids or LHRH analogues. Completed bone biomarker data from ERA-223 should be submitted in the next PSUR.

The optimal sequence or combination of radium-223 with other approved agents (abiraterone, enzalutamide, docetaxel) is unknown. In practice, sequencing decisions will be made in the light of the distribution, extent and progression of disease, co-morbidities, patient preferences and drug availability. Hence, the safety of sequential use of radium-223 and abiraterone/prednisone and in particular the time period for safe administration of abiraterone/prednisone treatment after completed radium-223 treatment and vice versa is not established and further data is necessary. In clinical trials a four-week washout period (equivalent to 5 biological half-lives of radium-223 in bone) is currently recommended for radium-223 and subsequent therapy. However, as also noted by the SAG, a washout based on pharmacodynamics (persistent activity on osteoblasts) rather than pharmacokinetic parameters would need to be determined; in particular considering that fractures occurred for several months after end of therapy. The MAH should conduct (non)-clinical studies for adequate washout period, including a pharmacodynamics component, for other systemic mCRPC treatment prior to radium-223 administration and vice versa. In the meantime, based on elimination half-lives, a minimum washout period of 5 days should be respected before initiating radium-223 following treatment with abiraterone and of 30 days after radium-223, before initiation of a subsequent systemic cancer therapy.

2.3.3.2.3. Factors influencing the risk of fracture

Subgroup analyses in ERA-223 suggest that the concurrent use of BHAs was associated with a reduced risk for fracture in both treatment arms. However, the reduction was more pronounced in the radium-223 treatment arm, especially for symptomatic pathological fractures. While the use of BHA was also associated with a reduced risk of fractures, it does not appear to eliminate the risk completely (radium-223 group without BHA use vs with BHA use: 34.7% vs. 12.8%; placebo group (without BHA use vs. with BHA use: 10.6% vs. 4.8%).

The use of BHA was lower in ERA-223 (40%) than in ALSYMPCA (42-51%). However in ALSYMPCA information on BHA use was no systematically collected in the follow-up period and therefore these figures may be underestimated. The results from stratified Cox models and logistic regression models for fracture for ALSYMPCA (2014 database) and ERA-223 are relatively consistent, indicating that use of BHAs is strongly associated with a decrease in fracture risk and the time to first fracture in the radium-223 arm in both ERA-223 and ALSYMPCA, and in the placebo arm in ERA-223 but not in the placebo arm in ALSYMPCA. These data highlights that radium-223 seems to carry an inherent risk of fracture independent of concomitant abiraterone and prednisolone use, which appear to be minimized by BHA use. This further supports the need to investigate fracture risk after radium-223 therapy.

[14] Morris MJ, et al. Effects of radium-223 (Ra-223) with docetaxel versus docetaxel alone on bone biomarkers in patients with bone-metastatic castration-resistant prostate cancer (CRPC): A phase I/IIa clinical trial. J Clin Oncol, available from http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.6_suppl.154

Data from a Phase I study on biodistribution (Study 15303 [15]) showed that in most instances the hot spots of radium-223 accumulation corresponded to tumour deposits; however they could also correspond to non-malignant disease e.g. degenerative bone disease as evidenced by one patient. Accumulation at sites of degenerative bone disease may indicate off-target effects of radium-223. When radium-223 accumulates at sites of degenerative bone disease such as osteoporosis, the surrounding tissue of the weakened bone will further be damaged, which in turn increases the risk of fracture. Albeit data was only available for one patient regarding radium-223 accumulation at sites of degenerative bone disease, the effect is clearly relevant for the interpretation of the observed increased fracture rate in ERA-223. This finding is further supplemented by a marked imbalance in AEs observed in ERA-223 between the radium-223 and placebo arm in osteoporosis (5.1% vs. 0.3%) and osteoporotic fracture (4.3% vs. 0.3%). Notably, medical history of osteoporosis is predictive for fracture risk in ERA-223 in the radium-223 arm, but not the placebo arm. Fracture imaging scans for 76 patients in the radium-223 group who experienced at least one fracture were available. These data confirm that for most of these patients (60/76 [79%]), there were no bone metastases at the site of the fracture. The finding that the majority of fractures occurred outside of metastases is of concern and indicates a substantial off-target effect of radium-223 in ERA-223. In this group, the most common fracture was osteoporotic fracture (N=37) and osteoporosis was present at baseline in nearly all these patients with this type of fracture (n=36). Moreover, the number of osteoporotic fractures was higher in the radium-223 arm (37 out of 80 fractures, 46.3%) compared to the placebo arm (4 out of 27 fractures, 14.8%), which further substantiated that radium-223 seems to promote osteoporosis and/or osteoporotic fractures.

Notably, while reviewing this imaging data, a higher number of patients with osteoporosis at baseline (36 patients) were identified than initially based on medical records (23 patients). Updated analysis of an independent review of imaging data for ERA-223 to re-evaluate the risk of osteoporosis in the study population therefore need to be reported in the next PSUR.

In multivariate analyses in ERA-223, medical history of osteoporosis and lower number of metastases at baseline (<6 vs. ≥6) were significantly associated with increased risk of fracture in the radium-223 arm, but not the placebo arm. Patients in the radium-223 arm with less than 6 bone metastases at baseline also tended to have a shorter time-to-first-fracture compared to patients with 6 or more bone metastases, whereas this was not the case for patients in the placebo arm. The small imbalance in baseline characteristics of patients with less than 6 metastases in Gleason score favouring the placebo arm compared to the radium-223 arm is considered of minor relevance as Gleason Score was not among the factors predictive for fracture risk. However, in the same population an imbalance in longer duration of androgen deprivation therapy (ADT) >24 months was observed compared to those with 6 or more metastases especially in the radium-223 arm (78.9% vs. 47.1–59.4%). As ADT therapy not only increases risk of fractures but also osteoporosis, which in turn seems to increased risk of fracture with radium-223, this might partly explain higher fracture risk in patients with less than 6 metastases. In ALSYMPCA, the incidence of fractures in patients with <6 metastases is higher in the radium-223 arm (10/99, 10.1%) than in the placebo group (2/37, 5.41%). In multivariate analyses the risk of fracture tends to be increased in patients with less than 6 bone metastases compared to patients with 6 or more bone metastases in the radium-223 arm (odds ratio: 1.42), but was lower in the placebo arm (odds ratio: 0.61). Whilst this trend does not reach statistical significance, this is still considered relevant as the follow-up of fractures was incomplete and too short in ALSYMPCA. Therefore, the smaller number of patients with < 6 bone metastases in ALSYMPCA (16.5%) compared to ERA-223 (34%) may also, in part, explain why fractures were not identified as a risk in that study. One theory

[15] Phase 1, open label, Single Ascending-dose Study to Assess Safety, Pharmacokinetics, Biodistribution and Radiation Dosimetry of Intravenous Doses of Alpharadin® Injection (radium-223 chloride) in Patients with Hormone Refractory Prostate Cancer and Skeletal Metastases

proposed by the SAG experts was a reduced specific uptake of radium-223 into bone metastasis in case of low disease burden resulting in increased non-specific uptake. However, a definite conclusion cannot be drawn and other theories may also be relevant. Taken together, albeit subgroup analysis should be interpreted cautiously, fracture risk seems to be associated with number of metastases (<6 vs. ≥6 metastases). The correlation between the extent of the disease and the distribution of radium-223 in bone metastases versus sites of impaired bone health (e.g. osteoporosis) versus normal bone structure should be further investigated in a biodistribution study requested by the PRAC.

The PRAC considered that there is compelling evidence from clinical and non-clinical data that radium-223 is likely to decrease bone stability and promote fractures at sites of degenerative bone disease. The PRAC further considered that an increased risk of fractures with radium-223, as observed in study ERA-223, could also be present in patients within the approved target population when risk factors for fractures e.g. pre-existing osteoporosis, chronic concomitant use of corticosteroids or other systemic cancer therapy are present. These views were shared by the SAG which considered that radium-223 should not be given in combination with other systemic prostate cancer therapies.

The majority of the fractures that occurred as treatment-emergent adverse events in the radium-223 group were symptomatic and a minority were asymptomatic, but even these fractures may be clinically relevant. In clinical practice, asymptomatic fractures might not be diagnosed and subsequently become more severe, either from further doses of radium-223 which could be taken up into an area of bone healing that has increased osteoblastic activity or from a fall. There is also evidence that asymptomatic vertebral fractures cause back pain (despite being classed as “asymptomatic”) and increase the number of days in bed, reduce quality of life and increase the risk of future fractures (Lems, 2007 [16], Bandeira, 2015 [17]).

Most patients in ERA-223 received all six doses of study drug, whereas in the pivotal study ALSYMPCA less patients received all six doses (88% vs. 65%). The lower disease burden, better performance status and no prior chemotherapy of the study population in ERA-223 compared to ALSYMPCA, may explain why a higher proportion of patients were able to receive all 6 doses of radium-223 in that study. In study 16507, a higher rate of pathological fractures in the treatment arm with extended (up to 12) dose compared to the treatment arm with standard dose was found (10.9% vs. 5.0%). The number of doses has also been studied in an interventional study (Study 16506), however many limitations were identified and it does not allow to draw robust conclusion on continuous therapeutic efficacy and clinical benefit as well as safety of a second course of treatment with radium-223. A statistically significant increase in the risk of fractures with radium-223 compared to placebo is also observed in the subgroup of patients who received ≥ 5 injections of radium-223 (HR 3.721, p <0.0001). In contrast, a significant increase in fracture risk with radium-223 was not observed in the patient subgroup who received <5 injections, but the sample size for this group is much smaller. Therefore, although the safety and efficacy of the current dosing of radium-223 (55 kBq per kg body weight, given at 4-week intervals for 6 injections) has been established based on data from ALSYMPCA, the PRAC considered that the potential impact of number of doses of radium-223 should be further explored. The PRAC concluded that the correlation between the dose and the distribution of radium-223 in bone metastases versus sites of impaired bone health (e.g. osteoporosis) versus normal bone structure should be further characterized in an imposed a biodistribution study.

[16] Lems WF. Clinical relevance of vertebral fractures. Ann Rheum Dis 2007; 66:2–4.
[17] Bandeira F. Asymptomatic vertebral fracture: a wolf in sheep’s clothing? Arch Endocrinol Metab 2015;59/2.

2.4. Data on efficacy

2.4.1. Data on efficacy from ALSYMPCA

The clinical efficacy of radium-223 in the authorised indication had been established during the initial marketing authorisation application based on the assessment of data from one pivotal Phase III study (15245/BC1-06, ALSYMPCA).

The study was conducted in castration-resistant prostate cancer patients with symptomatic bone metastases. Symptomatic was defined as either regular (not occasional) use of analgesic medication for cancer related bone pain (≥ level 1; WHO ladder for cancer pain), or treatment with EBRT for bone pain (the EBRT should have been within previous 12 weeks before randomisation). Testosterone levels were maintained ≤ 50ng/dL by bilateral orchiectomy or maintenance on androgen ablation therapy with luteinizing hormone-releasing hormone (LHRH) agonist or polyestradiol phosphate throughout the study. The study included 41.9% of mildly symptomatic patients. Patients had to have at least two skeletal metastases on bone scan. Patients with visceral metastases and malignant lymphadenopathy exceeding 3 cm were excluded. Patients had to have received docetaxel (57.3%); not be fit enough to receive docetaxel; not willing to receive docetaxel; or docetaxel was not available to them for other reasons.

Subjects were randomized 2:1 to receive either radium-223 or placebo. Other treatments for prostate cancer, best standard of care (BSC), could be used in accordance with routine clinical practice, at the discretion of the Investigator. BSC included local external beam radiotherapy, bisphosphonates, corticosteroids, oestrogens, estramustine, ketoconazole or anti-androgens (bicalutamide, flutamide and nilutamide). A proportion of 40% of patients were receiving bone health agents at baseline and up to 51% in the follow-up period, however this information was not systematically collected in the follow up period. Approximately 15% of patients received a first-generation anti-androgen (e.g. bicalutamide) in the treatment phase and approximately 40% to 60% received concomitant corticosteroids at different stages of the study. When this study was being conducted, abiraterone acetate and enzalutamide were not authorised.

There were some imbalances at baseline for some prognostic factors in favour of radium-223 (e.g. PSA, extent of disease [<6 metastases] and time between diagnosis of prostate cancer and bone metastasis).

The results of both the interim (14 October 2010) and updated analysis (15 July 2011) had shown that overall survival was significantly longer in patients treated with radium-223 plus BSC compared to patients treated with placebo plus BSC (Table 12 and Figure 5).

Table 12. Survival results (Study 15245 [ALSYMPCA], interim [data lock: 14 October 2010] and updated analysis [data lock: 15 July 2011])

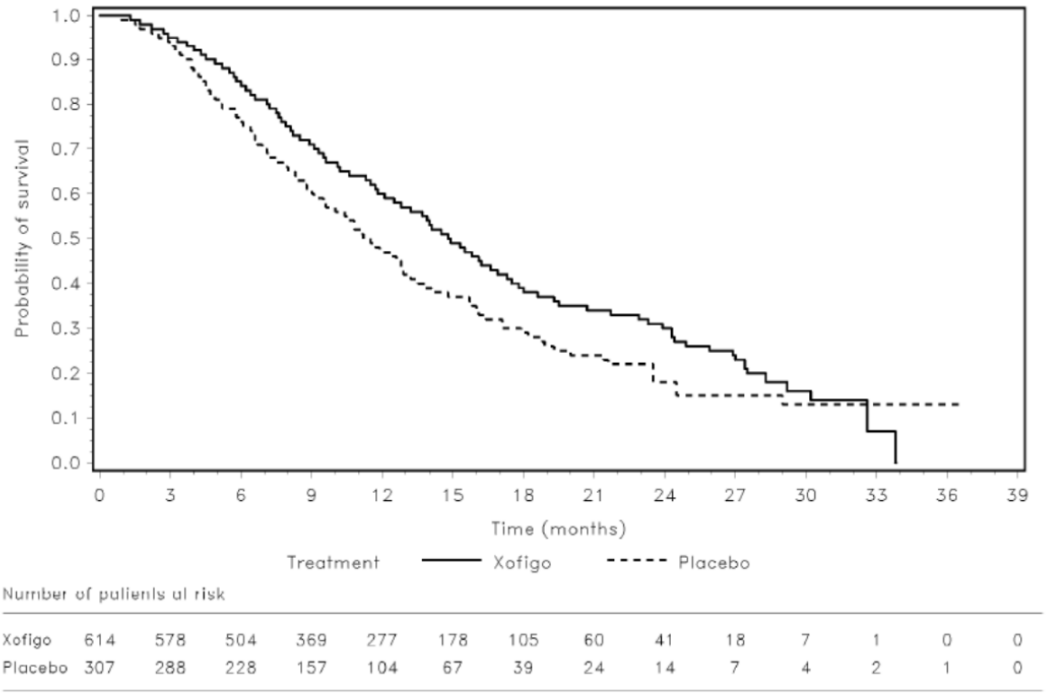
	Xofigo	Placebo
Interim analysis	N = 541	N = 268
Number (%) of deaths	191 (35.3%)	123 (45.9%)
Median overall survival (months) (95% CI)	14.0 (12.1 – 15.8)	11.2 (9.0 – 13.2)
Hazard ratio[b] (95% CI)	0.695 (0.552 – 0.875)	
p-value[a] (2-sided)	0.00185	
Updated analysis	N = 614	N = 307
Number (%) of deaths	333 (54.2%)	195 (63.5%)
Median overall survival (months) (95% CI)	14.9 (13.9 – 16.1)	11.3 (10.4 – 12.8)
Hazard ratio[b] (95% CI)	0.695 (0.581 – 0.832)	

CI = confidence interval

[a] The Phase 3 study ALSYMPCA was stopped for efficacy after the interim analysis. As the updated analysis is provided for descriptive purposes only, a p-value is not provided.

[b] Hazard ratio (Xofigo over placebo) < 1 favours Xofigo.

Figure 5. Kaplan-Meier overall survival curves (Study 15245 [ALSYMPCA], updated analysis)



The Kaplan Meier curve for overall survival in the intention to treat (ITT) population at the 2014 cut-off date curve for ALSYMPCA reports 14.6 months [95% CI 13.77, 15.70] vs 11.4 months [95% CI 10.09, 12.75] for the radium-223 group vs placebo group (HR = 0.747, 95% CI: 0.641,0.870; 2-sided p = 0.0002).

Several subgroup survival analysis were conducted including according to docetaxel treatment, level of symptoms of bone metastases (Table 13), total ALP level (Table 14) and number of bone metastases (Table 15).

Table 13. Overall survival by pain and opiate use at baseline, (Study 15245 [ALSYMPCA], Intent-to-Treat Analysis, 2011)

		Overall survival time (months) Median (95% CI)		Hazard ratio [a] (95% CI)	P-value log rank test
		Radium-223 dichloride	Placebo		
Opiate use	**Not present**	N = 269	N = 139		
Mildly symptomatic	WHO Grade 0, 1	16.4	12.8	0.696	0.01293
		(14.4 – 18.4)	(11.3 – 16.0)	(0.523 – 0.928)	
	Present	N = 345	N = 168		
Symptomatic	WHO Grade 2, 3	13.9	10.4	0.679	0.00116
		(11.9 – 15.4)	(8.7 – 11.6)	(0.537 – 0.859)	

a. Cox proportional hazards model. Hazard ratio < 1 favors radium-223 dichloride.
b. 13/14 patients without baseline pain had a record of prior pain-controlling therapy.
CI = confidence interval; NE = not estimable

Table 14. Overall Survival according to ALP (Study 15245 [ALSYMPCA], ITT, updated analysis)

Factor	Subject with an event N, n, %		Hazard ratio	95% CI	p-value
	Radium-223	Placebo			
ALP					
< 220 U/L	348, 163 (46.8)	169, 86 (50.9)	0.825	0.635-1.072	0.14945
≥ 220 U/L	266, 170 (63.9)	138, 109 (79.0)	0.619	0.486-0.788	0.00009

Table 15. Overall survival according to number of metastases (Study 15245 [ALSYMPCA], 2014)

	N Median number of months (95% CI)		Hazard Ratio (95% CI)	*P* value
	Radium 223	Placebo		
>=6 metastases	510 12.91 (11.86-14.13)	268 10.64 (9.10-11.66)	0.764 (0.634-0.878)	0.0004
<6 metastases	101	38	0.901	
	27.4 (23.43 – 32.82)	25.3 (17.08-34.17)	0.553-1.466	0.6741

Covariate analysis for OS, was carried out as a sensitivity analysis and which included ALP, PSA, LDH, ECOG and age as factors: p = 0.0086; HR = 0.783. A *post-hoc* multivariate analysis including extent of disease (EOD, e.g. <6 vs >=6 metastases) as a factor was also conducted for OS: HR = 0.786, p = 0.778. Sensitivity analysis including baseline Gleason score was also conducted although the scores were missing for 72 of 614 patients in the radium-223 arm, for 37 of 307 in the placebo arm.

In addition, in the final CSR addendum presenting all safety data for the entire study period (2014), while no updated overall survival analysis was performed, as death information for those patients who died was collected as a safety endpoint, median overall survival was 14.6 months in patients treated with radium-223 compared to 11.4 months in patients treated with placebo (HR = 0.747, 95% CI [0.641, 0.870]; p = 0.0002).

The results of the interim analysis and the updated analysis had also shown a significant improvement in all main secondary endpoints in the radium-223 arm compared to the placebo arm, although the effect of delaying median PSA progression (median 0.2 months) was small (Table 16 and Table 17.).

Table 16. Secondary efficacy endpoints (Study 15245 [ALSYMPCA], interim analysis)

			Incidence [no. (%) of patients]		Time-to-event analysis (95% CI) [median no. of months]			
			Xofigo N = 541	Placebo N = 268	Xofigo N = 541	Placebo N = 268	Hazard ratio < 1 favours Xofigo	p-value
Symptomatic skeletal event (SSE)	SSE composite endpoint [a]		132 (24.4%)	82 (30.6%)	13.5 (12.2–19.6)	8.4 (7.2 – NE)[b]	0.610 (0.461 – 0.807)	0.00046
	SSE components	External beam radiation for pain relief	122 (22.6%)	72 (26.9%)	17.0 (12.9–NE)	10.8 (7.9 – NE)	0.649 (0.483 – 0.871)	0.00375
		Spinal cord compression	17 (3.1%)	16 (6.0%)	NE	NE	0.443 (0.223 – 0.877)	0.01647
		Surgical intervention	9 (1.7%)	5 (1.9%)	NE	NE	0.801 (0.267 – 2.398)	0.69041
		Bone fractures	20 (3.7%)	18 (6.7%)	NE	NE	0.450 (0.236 – 0.856)	0.01255
Total ALP progression [c]			79 (14.6%)	116 (43.3%)	NE	3.7 (3.5 – 4.1)	0.162 (0.120 – 0.220)	< 0.00001
PSA progression [d]			288 (53.2%)	141 (52.6%)	3.6 (3.5 – 3.7)	3.4 (3.3 – 3.5)	0.671 (0.546 – 0.826)	0.00015

ALP = alkaline phosphatase; CI = confidence interval; NE = not estimable; PSA = prostate-specific antigen; SSE = symptomatic skeletal event

a Defined as occurrence of any of the following: external beam radiotherapy to relieve pain, or pathologic fracture, or spinal cord compression, or tumor-related orthopedic surgical intervention.

b not estimable owing to insufficient events after the median

c Defined as ≥ 25% increase compared to baseline/nadir.

d Defined as a ≥ 25% increase and an increase in absolute value of ≥ 2 ng/mL compared to baseline/nadir.

Table 17. Relative risk of individual symptomatic skeletal event components (Study 15245 [ALSYMPCA], ITT, updated analysis) (Sartor, 2014 [4])

	Radium-223 (n=614)		Placebo (n=307)		HR (95% CI)	P value*
	No of patients (%)	Median time to first event months (95% CI)	No of patients (%)	Median time to first event months (95% CI)		
Skeletal event components						
External beam radiotherapy	186 (30%)	17.1 (14.1-19.8)	105 (34%)	17.5 (7.9-29.0)	0.67 (0.53-0.85)	0.00117
Symptomatic pathological bone fracture	32 (5%)	NE	20 (7%)	NE	0.62 (0.35-1.09)	0.10
Spinal cord compression	25 (4%)	NE	21 (7%)	NE	0.52 (0.29-0.93)	0.03
Tumour-related orthopaedic surgical intervention	12 (2%)	NE	7 (2%)	NE	0.72 (0.28-1.82)	0.48

In *post-hoc* analysis, a significantly higher percentage of 29.2% of patients receiving radium-223 versus 18.5% of patient receiving placebo experienced meaningful improvement in EQ-5D utility score (*P* = 0.004; odds ratio (OR) = 1.82 [95% confidence interval (CI) 1.21–2.74]). A proportion of 24.6% of patients receiving radium-223 versus 16.1% of patient receiving placebo experienced meaningful improvement in FACT=P score (*P* = 0.020; OR = 1.70 (95% CI 1.08–2.65)) (Nilsson, 2016 [18]).

2.4.2. Data on efficacy from ERA-223

General overall survival data is presented under section 2.2. A subgroup analysis of overall survival in patients having received 5 or 6 injections is presented below.

Table 18. Overall Survival in the subgroup of patients with ≥ 5 injections (Study 15396 [ERA-223], cut-off March 2018)

	Ra-223 + Abiraterone + prednisone N=360	Placebo + Abiraterone + prednisone N=349	Hazard ratio (95% CI) 2-sided p-value
No (%) of subjects who died	129 (35.8%)	108 (30.9%)	1.291 (0.997, 1.627) P=0.0523
Median [95% CI] months	30.7 [27.8, A]	39.0 [33.1, 41.9]	

Interim analysis of the Kaplan Meier curves of time to deterioration in HR quality of life based on the NCCN-FACT FPSI-17 physical disease related symptoms (FPSI-DRS-P) subscale score were also presented (HR=1.079; 95% CI: [0.865. 1.345], p=0.498).

2.4.3. Discussion on efficacy

In the single pivotal Phase III, placebo-controlled study in symptomatic patients with bone metastases from CRPC without visceral metastases, overall survival was longer in the radium-223 group compared to the placebo group by 2.8 months, based on the pre-specified interim analysis (HR 0.695, 95% CI 0.552-0.875, p=0.00185). The OS benefit persisted after correcting for baseline imbalances. Also, treatment of patients with radium-223 delayed the composite endpoint symptomatic skeletal events compared to placebo (median 13.5 months vs 8.4 months). The Kaplan Meier curve for overall survival in the intention to treat (ITT) population at the 2014 cut-off date for ALSYMPCA is consistent with the median overall survival results reported from the interim and updated analysis of ALSYMPCA in 2010 and 2011.

Subgroup survival analysis showed a consistent survival benefit for treatment with radium-223 independent of prior use of docetaxel. CHMP also noted that there appeared to be a better treatment effect for radium-223 in terms of OS in patients with a total ALP ≥ 220 U/L (compared to total ALP < 220 U/L), suggesting greater benefit in patients with higher osteoblastic activity and therefore possibly higher extent of disease. Indeed, a statistically significant overall survival benefit of treatment could not be demonstrated in the subgroup of patients with a baseline total alkaline phosphatase (ALP) < 220 U/L (HR 0.823; 95% CI [0.633 - 1.068], p=0.142). However, there is no scientific consensus on the best threshold of ALP levels to discriminate patients benefitting from treatment to those no benefitting from treatment questioning feasibility to implement baseline ALP levels into clinical practice. Total ALP level thresholds used so far for radium-223 have been total ALP < 220 U/L versus ≥ 220 U/L in ALSYMPCA, total ALP < 90 U/L versus ≥ 90 U/L in ERA-223. A statistically significant overall survival benefit of treatment could not be demonstrated either in the subgroup of

[18] Nilsson S, Cislo P, Sartor O et al. Patient-reported quality-of-life analysis of radium-223 dichloride from the phase III ALSYMPCA study. Annals of Oncology 2016, 27: 868–874.

patients with fewer than 6 metastases (HR for radium-223 to placebo 0.901; 95% CI [0.553 - 1.466], p=0.674). Considering the lack of a statistically significant overall survival benefit in these two subgroups, efficacy may be diminished in patients with a low level of osteoblastic activity from their bone metastases.

At the time of marketing authorisation, several uncertainties about the benefits of radium-223 were recognised, including but not limited to the absence of demonstration of a direct anti-tumour effect (progression-free survival was not included as an endpoint) and to the potential impact of co-medication (e.g. bisphosphonates) on skeletal-related events. CHMP also noted that there was no head-to-head comparison between radium-223 and products for systemic treatment of prostate cancer or to the effect of other bone-targeted radionuclides. In addition, CHMP concluded that optimisation of the dose could be further explored e.g. longer treatment duration, dose adjustments, use of a lower number of doses (including a single-dose as other radiopharmaceuticals) or higher interval between doses (especially because the absorbed radiation dose is likely to change during the treatment period if radium-223 acts on bone metastases). It was concluded that until further dose optimisation data become available, the total number of doses suggested (6 doses over a period of 5 months) was acceptable. The scientific rationale for exposing patients in ERA-223 to more or the same number of doses of radium-223 compared to patients in ALSYMPCA despite a lower extent of target (i.e. osteoblastic bone metastases) is not clear and it cannot be excluded that this may have contributed to the adverse effects observed in ERA-223. Indeed in ERA-223 in patients 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). However, these data have to be interpreted cautiously due to the known bias of longevity.

The PRAC noted that radium-223 was an add-on to BSC in the pivotal clinical trial ALSYMPCA. However, several new medicinal products (e.g. abiraterone, enzalutamide) have been authorised for metastatic CRPC in the meantime, therefore it is difficult to put the beneficial effects of a bone-specific agent into context with current treatment standards.

In addition, the PRAC noted the presented effects on quality of life, however these should be interpreted with caution as they derive from *post-hoc* analyses and only 55% of patients in the radium-223 group at 24 weeks are included in these analyses (Nilsson, 2016 [18]). Indeed, as noted by CHMP at the time of marketing authorisation, compliance with the questionnaires was regarded as critically low during the follow-up period, which is the period during which most fractures were reported in ERA-223. Further, once a patient initiated opioid therapy, significant increases or decreases in pain management could not be accurately assessed. Therefore, it is not possible to make any reliable correlation between the possible effects of radium-223 on quality of life and the risk of fractures with radium-223 in ALSYMPCA. Interim quality of life data was did not show statistical difference between the two arms of ERA-223 and final analysis should be reported in the next PSUR.

3. Expert consultation

The PRAC consulted the oncology scientific advisory group (SAG) which provided advice on a number of issues.

A number of possible mechanisms were discussed for the increased risk of fractures observed when radium-223 is added to abiraterone and prednisone/prednisolone in ERA-223: reduced bone lesion specific uptake of radium-223 in the bone metastasis in case of low disease burden resulting in increased non-specific uptake; downregulation of metabolic activity in bone metastases and surrounding bone by abiraterone resulting again in lower uptake and more availability in other tissues; concomitant morbidities (e.g. skeleton conditions) that may result in higher non-specific uptake; etc.

Such mechanisms, if correct, could have implications for the combination of radium-223 with other effective treatments (e.g. enzalutamide, cytotoxic therapies). Other factors also appear to influence the risk of fractures, such as the use of bone health agents and medical history of osteoporosis.

However, overall, the likely mechanism(s) are currently unclear.

The SAG discussed a number of additional uncertainties about the mechanism of action of radium-223 and potential association with death. The mechanism for the apparent increase in non-bone lesion progression observed across studies with radium-223 is also unclear (perhaps associated to pathological fracture and haematogenous spread of metastases), and the magnitude of this effect raises concerns. Furthermore, the effect on overall survival observed in the pivotal study (ALSYMPCA) was apparently associated with a decrease in cardiovascular deaths and not cancer-related deaths, which is again difficult to explain (and perhaps due to imbalance in baseline risk factors for cardiovascular mortality). Other mechanisms might include adverse drug-drug interactions, persistent chronic toxicity that may impact on the choice of effective subsequent treatments or additional mutation induced by radium-223 to micro-metastases ("genetic hit").

Given the available data, a number of SAG members had serious concerns about the totality of evidence of efficacy and safety suggesting that the observed effect on overall survival in the pivotal study might be due to chance and that ERA-223 might be a more accurate reflection of the effects of the drug, including: lack of a favourable effect on overall survival and perhaps a detrimental effect; excess of non-bone ("visceral") progressions; excess of fractures.

Given the available data and the lack of a good understanding of the mechanisms involved, implications for the combination of radium-223 with any other effective treatments for CRPC (including chemotherapy) cannot be excluded. Use in combination should therefore be avoided unless benefits and risks of the combination can be established. The only combination that seems rational to lower the risk of fractures is that with bone health agents (BHA) for osteoporosis, however there are uncertainties about optimal schedules (see below).

The SAG experts considered that the risk of fractures could definitely be relevant to the authorised indication on the basis of expected common pharmacological action. They agreed that assessing fracture risk using bone densitometry, skeletal scintigraphy and CT scans are valid measures to assess bone health status including fracture risk and should be definitely considered before initiating treatment with radium-223 and when evaluating possible harms associated with radium-223 and the need for BHA. In clinical practice, the use of BHA seems insufficient in prostate cancer patients compared to breast cancer patients. However, also for concomitant use of BHA with radium-223, there are a number of unknowns, such as the safety of concomitant initiation of treatment since some of these compounds decrease osteoclastic activity which may hamper radium uptake.

The SAG experts were all concerned about using radium-223 in patients with low number of bone metastases or mildly symptomatic ones or in combination with other anticancer treatments. The experts were split on the general use of this product. Some experts questioned if there is a place for radium-223 in any indication, based on the current conflicting evidence and lack of understanding about the mechanisms of action. Others agreed that as monotherapy, in highly symptomatic patients, this could be a useful "last-line" option when no other available treatments are preferred (including chemotherapy). It was noted that in ALSYMPCA forest plot showed no difference in efficacy between patients treated with radium-223 as a first line option compared to those having received previous docetaxel treatment. However, fewer treatment options were available at the time the study was conducted, in particular second generation anti-androgens were not available. Personal experiences from experts were also shared of reports of clear improvement of patients' symptoms after start of treatment. Even with the current unknowns about survival benefits or excess progression in non-bone

sites, this may be a useful option for some patients. Still, even in this situation, careful measures for allowing sufficient washout of prior therapy, based on pharmacodynamics (persistent activity on osteoblasts) rather than pharmacokinetic parameters, is needed.

With regards to studies that could further characterise the benefits and risks of treatment with radium-223, the SAG commented that non-clinical models generally do not translate well in terms of effects on both skeletal and non-skeletal metastases. However for fractures existing osteoporosis models (e.g. mice) could be more promising. In addition, models can be used for testing pharmacodynamic drug-drug interactions.

For SAG experts who considered that there are serious doubts about the balance of benefits and harms of the product, further randomized controlled trial(s) to establish efficacy and safety are needed. Possible comparators could be other radioisotopes or best standard of care (which would need to be predefined) in the setting of treatment after failure of at least two prior lines of therapy for metastatic disease. Such studies should be particularly convincing in order to overcome the uncertainties and conflicting information of the available evidence from the two available randomized trials. State of the art bone imaging should be implemented throughout. However, the feasibility and interest in further randomized trials of this kind was seriously questioned in view of the rapid development of new agents and the availability of other radioisotopes.

All SAG members agreed that intensive monitoring of ongoing studies (safety reviews, interim efficacy analyses) should be considered in the light of the available evidence, to protect trial subjects and to obtain further meaningful data, in agreement with the competent authorities. The apparent association with fractures and increase progression in non-bone lesions and perhaps death should clearly be communicated to patients in clinical studies.

All experts agreed that registry data should be looked into and the company reported the intent to explore the Swedish registry. Results from such study should be available in a timely fashion (and not two years as currently foreseen). Such data could confirm any excess in harms if there is a strong signal but are unlikely to be able to overturn the current concerns about the harms associated with the product.

4. Benefit-risk balance

Xofigo (radium-223 dichloride) is a centrally authorised product indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

The PRAC considered interim data analyses from a randomized, placebo-controlled, multicentre phase III study (15396/ERA-223) in chemotherapy-naïve patients with asymptomatic or mildly symptomatic castration resistant prostate cancer with bone metastases (CRPC). The PRAC also considered data from the pivotal phase III clinical trial ALSYMPCA (15245/BC1-06) which supported the marketing authorisation of Xofigo, as well as data from other completed and ongoing studies which became available since the marketing authorisation.

The clinical efficacy of radium-223 in the authorised indication was established during the initial marketing authorisation application based on the assessment of data from one pivotal study (ALSYMPCA), in which an improved overall survival and delayed symptomatic skeletal events were observed. At the time of marketing authorisation, based on the data from that pivotal clinical trial, radium-223-related adverse events were considered manageable and of lower intensity than those associated with the use of cytostatic drugs also used in the target population.

The PRAC noted that ERA-223 included chemotherapy-naïve adults with castration-resistant prostate cancer, no known visceral metastases and of which 46% had mildly symptomatic bone metastases. These characteristics are consistent with the authorised indication. Based on the available data, it cannot be demonstrated that the adverse outcomes in ERA-223 are due to mechanism specific to the concurrent use with abiraterone acetate and prednisone/prednisolone. In line with the SAG outcome, PRAC therefore considered that these findings are relevant for the authorised indication.

Considering all available data from clinical, non-clinical studies and the literature, the PRAC, concluded that the use of radium-223 is associated with an increased risk of fracture during and after treatment, in the authorised indication. This view was also shared by the SAG. The magnitude of this risk is however not fully elucidated since in all studies available, as also noted by the SAG, significant limitations were identified regarding data collection on fractures, including lack of systematic follow-up of risk of fracture and lack of intensive monitoring of skeletal health. It remains that in ERA-223 all fractures were to be reported for a longer period of time than in ALSYMPCA and bone/computed tomography (CT) scan were performed in the treatment phase.

Subgroup analyses in ERA-223 suggest that the use of bisphosphonates and denosumab ("bone health agents" [BHA]) reduced the risk of "symptomatic skeletal event-free survival" events, in particular symptomatic pathological fractures, the reduction was more pronounced in the radium-223 group. The use of these medicines also reduced the risk of all fractures in both treatment arms but did not eliminate the increased risk in the radium-223 arm compared to placebo arm. The results from stratified Cox models and logistic regression models for fracture for ALSYMPCA and ERA-223 are relatively consistent, indicating that use of BHAs is strongly associated with a decrease in fracture risk and the time to first fracture in the radium-223 arm, and in the placebo arm in ERA-223, but not in the placebo arm in ALSYMPCA. This indicates that the use of these medicines can minimize the risk of fractures associated with radium-223, including as single systemic cancer therapy.

In available imaging data the most common type of fracture was osteoporotic fractures and nearly all the patients with these fractures had osteoporosis at baseline. The finding that the majority of fractures occurred outside of metastases is of concern and indicates a substantial off-target effect of radium-223 in ERA-223. Data from a biodistribution study showed that in most instances the hot spots of radium-223 accumulation corresponded to tumour deposits; however they can also correspond to non-malignant disease e.g. degenerative bone disease. Xofigo is believed to accumulate at sites of high bone turnover such as sites of degenerative bone disease (osteoporosis) or recent (micro-)fracture, increasing the risk of fractures. In multivariate analyses in ERA-223, medical history of osteoporosis and lower number of metastases at baseline (<6 vs. ≥6) was significantly associated with increased risk of fracture in the radium-223 arm, but not the placebo arm. In addition, in ERA-223 patients with less than 6 bone metastases at baseline experienced more fractures and had a shorter time-to-first-fracture compared to those who had 6 or more bone metastases; this might be partly explained by baseline imbalance in the length of prior androgen deprivation therapy. In ALSYMPCA the incidence of fractures in patients with less than 6 bone metastases was approximately two-fold compared to the placebo group. In multivariate analyses the risk of fracture tended to be increased in patients with less than 6 bone metastases compared to patients with 6 or more bone metastases in the radium-223 arm. In conclusion, medical history of osteoporosis and lesser extent of disease at baseline seem to be key contributing factors for occurrence of fractures and time to first fracture in the radium-223 arm with both a history of osteoporosis and having fewer than 6 bone metastases being associated with an increased risk of fractures in *post-hoc* analyses.

Based on the aforementioned observations, the PRAC considered that prior to starting radium-223 treatment bone status should be assessed using for example scintigraphy and bone mineral density measurement as well as the baseline risk of fractures of patients, based on the known risk factors and

those identified in this procedure (e.g. osteoporosis, less than 6 bone metastases, medication increasing fracture risk and low body mass index). Other factors such as concomitant use of steroids may further increase the risk of fracture. In view of the delayed risk of fractures observed, these two aspects should be closely monitored for at least 24 months after treatment initiation. In addition, preventive measures such as the use of bisphosphonates or denosumab should be considered before starting or resuming treatment with Xofigo. Further, in patients with a high baseline risk of fracture, the benefit of treatment should be carefully assessed to outweigh the risk.

The PRAC noted that in ERA-223, the proportion of patients who have died with non-bone progression (e.g. progression in lymph nodes or liver) was notably higher in the radium-223 arm compared to the placebo group (14.5% [57/392] vs. 7.4% [29/394]). In the overall population, an increased risk of radiological non-bone progression in the radium-223 group compared to the placebo group (HR 1.376; 95% CI [0.972, 1.948], p=0.07) was also observed, raising concerns that radium-223 promotes visceral and lymph node metastases. A similar trend was observed in ALSYMPCA, where in patients who died due to prostate cancer, the proportion of death due to prostate cancer-related non-skeletal metastasis was higher in the radium-223 arm than the placebo arm (38.1% vs. 27.3%). The PRAC noted concerns raised at time of the initial marketing authorisation that the incidence of non-prostate cancer-related death in the radium-223 group was lower compared to the placebo group, which could indicate health status imbalance favouring the radium-223 group. Other concerns had been raised such as the absence of demonstration of direct anti-tumour effect and the potential impact of co-medication such a bisphosphonates. However, unlike some of the SAG experts, the PRAC considered that the results of ERA-223, did not affect the overall validity of the overall survival improvement observed in ALSYMPCA in the radium-223 group compared to the placebo group and noted that the overall survival benefit persisted after adjusting for major confounding factors. Further, whilst no direct anti-tumour effect had been demonstrated, as also noted at the time of authorisation, other endpoints were supportive of a benefit of radium-223. Less patients in the radium-223 group experienced skeletal-related events (SRE) and time to first skeletal-related event was clinically significantly longer with six months difference. All aspects of the composite endpoint SRE were referring to clinically relevant aspects and there was a consistent beneficial effect in three of four parameters of the composite endpoint in favour of radium-223, with external beam radiation therapy (EBRT) being the dominant component.

Therefore, whilst there are limitations to extrapolate the trend for increased mortality from ERA-223 to ALSYMPCA, but 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 metastatic CRPC, the available data raise concerns about the use of radium-223 in early lines of therapy for symptomatic patients.

In ALSYMPCA, patients were either post-docetaxel, unfit for docetaxel, unwilling to receive docetaxel or docetaxel was not available to them for other reason. Consequently, the chemotherapy-naïve patient population included in the ALSYMPCA trial was not well defined and the extent and characteristics of the different subpopulations is unknown. ERA-223 was exclusively conducted in chemotherapy-naïve patients, which adds further concern to treat chemotherapy-naïve metastatic prostate cancer patients with radium-223. Since the authorisation of radium-223, abiraterone and enzalutamide have been authorised for chemotherapy-naïve and post-docetaxel prostate cancer patients based on robust data showing OS benefit. Chemotherapy and to a certain extent abiraterone and enzalutamide are capable of targeting nodal and visceral metastasis (Drake, 2014 [19]; Conteduca, 2015 [20]; Loriot, 2017

[19] Drake CG. Visceral metastases and prostate cancer treatment: 'die hard,' 'tough neighborhoods,' or 'evil humors'? Oncology (Williston Park). 2014;28:974-80.
[20] Conteduca V, et al. Impact of visceral metastases on outcome to abiraterone after docetaxel in castration-resistant prostate cancer patients. Future Oncol. 2015;11(21):2881-91. doi: 10.2217/fon.15.158.

[21]). The mode of action of radium-223 is limited to the bone environment and a significant proportion of men with CRPC have soft-tissue (nodal and/or visceral) disease, some of which might remain undetected prior treatment initiation. Further, median ALP (an approximate measure of osteoblastic activity) of patients in the ALSYMPCA study was 211 U/L, which is relatively high. In example, median ALP was notably lower in a Phase III study investigating treatment benefit of enzalutamide in post-docetaxel patients (115 U/L) or abiraterone in chemotherapy-naïve patients (91 U/L). Therefore, other patient population including a post-docetaxel group of patients does not automatically replicate the type of patients enrolled in ALSYMPCA in terms of extent of disease.

Overall, the PRAC considered that Xofigo should only be used as monotherapy, or in combination with a luteinising hormone releasing hormone (LHRH) analogue, for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment. This view was supported to a certain extent by some SAG experts who considered radium-223 a useful 'last-line' option when no other available treatments are preferred and recommended the conduct of a randomised controlled trial in patients in progression after at least two prior lines of therapy for metastatic disease. Restricting radium-223 beyond third line of treatments was however not supported by the PRAC in view of the known safety issues with subsequent lines of chemotherapy regimens and as there is limited data on sequencing of therapy in this patient population. In addition, a number of published studies indicate cross-resistances of abiraterone and enzalutamide or docetaxel in the post-abiraterone setting (Noonan, 2013 [22]; Loriot, 2013 [23]).

Whilst a majority of patients in ALSYMPCA had received prior docetaxel therapy, data is lacking for the use of radium-223 after further lines of treatment. In addition, results of the two completed randomised controlled trials are not consistent in terms of overall survival. The PRAC, in line with the advice of some of the SAG experts, therefore recommended to impose as a condition to the marketing authorisation of Xofigo the conduct of a randomised double-blind multicentre study, in order to further characterise the safety and efficacy, in particular the risk of fractures and the risk of formation of visceral and nodal metastases in the settings of the restricted indication. In addition, in order to obtain further data in a timely manner, in line with the SAG advice, the PRAC also recommended that the conduct of a non-interventional post-authorisation safety study is imposed to further characterise its safety.

As the dataset evolved during this procedure, it is noted that the statistically significant mortality imbalance observed in the interim analysis of ERA-223 at the time of the provisional measures (HR 1.347; 95% CI [1.047, 1.732] p=0.02) was no longer statistically significant in the analysis after the database lock on 8 June 2018 (HR 1.195; 95% CI [0.950, 1.505] p=0.128). However, this trend is still of concern. In addition, approximately three times as many patients experienced fractures in the radium-223 arm compared to the placebo arm. Abiraterone is known to increase the risk of fractures, as well as prednisone/prednisolone and a synergistic effect of the triple combination cannot be excluded. Observational data reported that radium-223 is used in clinical practice in combination with abiraterone (16% based on interim data from the observational study REASSURE). Overall, the PRAC considered that the contraindication introduced at the time of provisional measures for the use of radium-223 in combination with abiraterone and prednisone/prednisolone should be maintained.

[21] Loriot Y, Fizazi K, de Bono JS et al. Enzalutamide in castration-resistant prostate cancer patients with visceral disease in the liver and/or lung: Outcomes from the randomized controlled phase 3 AFFIRM trial. Cancer. 2017 Jan 1;123(2):253-262.
[22] Noonan KL, et al. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol. 2013;24:1802–7.
[23] Loriot Y, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100) Ann Oncol. 2013;24:1807–12.

Whilst mechanistically abiraterone could potentially have a more negative effect on bone health than androgen receptor antagonists, considering the known pharmacological effects of this class of medicines on bone, a further increased risk of fractures may also occur when radium-223 is combined with these medicinal products. The interim data from REASSURE also indicate concomitant use with enzalutamide (22%). Similarly as chemotherapy is authorised for the treatment of mCPRC in combination with prednisone/prednisolone also known to adversely affect bones, a further increased risk cannot be excluded. In addition, whilst a small proportion of patients received in a first-generation anti-androgen in the radium-223 treatment phase in ALSYMPCA, there are currently no data establishing the safety and efficacy of radium-223 in combination with cancer therapies other than LHRH analogues. The PRAC also noted the concerns of the SAG regarding combination with any other effective treatments (including chemotherapy) and the combination of radium-223 with any other cancer therapies should be avoided unless benefits and risks of the combination can be established. It was acknowledged that LHRH analogues can also adversely affect bone via reduction of bone mineral density, however on balance, LHRH are part of the gold standard treatment for metastatic prostate cancer (Cornford, 2017 [24]). It is therefore considered critical that testosterone levels are maintained at castrate level in patients with mCRPC. Further, in ALSYMPCA, 83.9% of patients were administered LHRH analogues during treatment with radium-223. In conclusion, the PRAC recommended against the combination of radium-223 with other systemic cancer therapies other than LHRH analogues.

For most of the patients who experienced a fracture in ERA-223, it occurred after their final dose of radium-223. Therefore, it is likely that the risk of fractures with radium-223 persists beyond the last injection and may further increase in patients who subsequently receive abiraterone or other medicines that can also cause osteoporosis and fractures. There are no clinical data to support a recommendation on a washout period between the last injection of radium-223 and abiraterone, although in clinical trials a four-week washout period is currently recommended for radium-223 and subsequent therapy. The PRAC acknowledged the view of the SAG that sufficient washout periods, including of prior therapies, should be established based on pharmacodynamics and not only pharmacokinetics. In the absence of clinical data, the PRAC considered that healthcare professionals should be advised to allow for a treatment-free interval based on elimination half-lives, of at least 5 days after abiraterone before initiating treatment with radium-223 and of at least 30 days after the last dose of radium-223 before a subsequent systemic cancer treatment is administered.

The definition of mildly symptomatic bone metastases has evolved since ALSYMPCA was conducted. However, given that there are significant concern regarding overall survival and fracture risk in asymptomatic patients from ERA-223 trial and no substantial data from ALSYMPCA or other trials indicating a benefit of radium-223 in these patients, Xofigo is not authorised in this subpopulation and the benefit-risk balance is regarded as negative. It is noted that a proportion of clinicians may however consider it appropriate to extrapolate the results of ALSYMPCA to certain asymptomatic patients with bone metastases (St. Gallen Advanced Prostate Cancer Consensus Conference (APCCC) in 2015). Consequently, the PRAC recommended to include a warning in the product information to emphasise that the use of Xofigo is not recommended in this patient population.

As noted above, patients with fewer than 6 bone metastases had an increased risk of fractures both in ERA-223 and in ALSYMPCA. Further, in ALSYMPCA a statistically significant overall survival benefit of treatment could not be demonstrated in the subgroups of patients with fewer than 6 bone metastases (HR for radium-223 to placebo 0.901; 95% CI [0.553 - 1.466]. Further, as noted at the time of initial marketing authorisation, in ALSYMPCA a better radium-223 effect was demonstrated in patients having total ALP ≥220 U/L and thus in those patients having a high osteoblastic activity and probably higher extent of disease. Indeed a statistically significant overall survival benefit of treatment could not be

[24] Cornford P, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol. 2017 Apr;71(4):630-642.

demonstrated either in the subgroup of patients with a baseline total alkaline phosphatase (ALP) < 220 U/L (HR 0.823; 95% CI [0.633 - 1.068], p=0.142). Interim data from an observational study showed that amongst patients who used radium-223 after at least two lines of therapy 12% had < 6 bone metastases and the median ALP of this group was lower than that of the ALSYMPCA population (167 U/L compared with 211 U/L) (Higano, 2017 [25]). Therefore, it was noted that the restricted indication does not clearly exclude treatment of patients a low level of osteoblastic bone metastases. Considering this possibility, in view of the newly identified risk of fracture, of the mechanism of action of radium-223 and the lower expected efficacy, the PRAC concluded that in patients with a low level of osteoblastic bone metastases radium-223 is not recommended.

Some of the SAG experts were of the view that radium-223 could be a useful option as monotherapy only in patients with highly symptomatic bone metastases. In ALSYMPCA, radium-223 significantly prolonged overall survival in the group of non-opioids users (HR = 0.70; 95% CI [0.52–0.93]; p = 0.013), however, there were baseline differences in favour of radium-223. As the classification for pain severity has evolved since conduct of ALSYMPCA, there are some uncertainties whether reviewed ALSYMPCA data adequately defines patients classified as mildly symptomatic. While there is an overlap with ERA-223 in the study population defined as mildly symptomatic, differences in term of previous chemotherapy and treatment combination during the study make it difficult to extrapolate the negative results of ERA-223 to the authorised population. The PRAC considered that in adults with CRPC and mildly symptomatic bone metastases the benefit of treatment should be carefully assessed to outweigh the risks considering that high osteoblastic activity is likely to be required for treatment benefit.

In ERA-223, the median overall survival was reduced by 8.6 months in the group of patients who received 5 or 6 doses of radium-223, compared to those who received 5 or 6 doses of placebo. In addition, a statistically significant increase in the risk of fractures with radium-223 compared to placebo was observed in the subgroup of patients who received ≥5, but no statistical differences was reached in the subgroup who received less doses - the sample size in this latter group was however much smaller. The PRAC considered that whilst not allowing to question the benefit risk balance of the currently established posology, the hypothesis that dosing is one of the factors that may have contributed to the increased risk of fracture and mortality should be further investigated.

In view of the above the PRAC recommended that the conduct of a biodistribution study should be imposed as a condition to the marketing authorisation of Xofigo in order to further characterize correlation between the extent of the disease, the dose and the distribution of radium-223 in bone metastases versus sites of impaired bone health (e.g. osteoporosis) versus normal bone structure.

In addition, in order to assess the effectiveness of the above risk minimisation measures, the MAH should conduct a drug utilisation study.

The PRAC concluded that the benefit-risk balance remained positive, provided that Xofigo (radium Ra223 dichloride) is only used as monotherapy or in combination with LHRH analogue for the treatment of adult patients with mCRPC, symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment and that changes are implemented in the product information to minimise the risk of fracture. In addition, as a condition to the marketing authorisation, the efficacy and safety of radium-223 must be further characterised via the conduct of a randomised controlled trial, a non-interventional post-authorisation safety study and a biodistribution study.

[25] Celestia S. Higano, et al. Patient (pt) characteristics and treatment patterns in the radium (Ra)-223 REASSURE observational study.Journal of Clinical Oncology 2017 35:15_suppl, 5042-5042.

5. Risk management

The MAH should operate a risk management system described in a Risk Management Plan which has been endorsed as part of the current review procedure. The PRAC considered that “fracture” should be added as an important identified risk, “increased formation of visceral and nodal metastases” should be included as an important potential risk and “safety in patients with insufficient wash-out period” as well as “safety of radium-223 with other cancer therapy apart from therapy for maintenance of castration-level” should be added as missing information.

5.1. Pharmacovigilance activities

5.1.1. PSUR monitoring

The PSURs for Xofigo are currently under a yearly submission frequency. The PRAC considered that this frequency should be maintained. In future PSURs, the MAH should report notably on the quality of life data and bone biomarker analyses from ERA-223, the non-clinical studyies on mechanism responsible for increased risk of fractures and death in ERA-223 and on the updated analysis of an independent review of imaging data for ERA-223 to re-evaluate the risk of osteoporosis in the study population.

5.1.2. Clinical trials

The MAH shall conduct and submit the results of a phase IV randomised double-blind multicentre clinical study according to an agreed protocol in order to further characterise the safety and efficacy, in particular the risk of fractures, the risk of formation of visceral and nodal metastases of radium-223 in the authorised indication. The protocol should foresee a stratified randomization of patients according to bone ALP levels. The MAH is encouraged to seek scientific advice to the relevant competent authorities to design this study. This study is imposed as a condition to the terms of the marketing authorisation and is reflected as category 1 in the RMP. The protocol shall be submitted to EMA for assessment within 6 months following the notification of the European Commission Decision.

The MAH shall conduct and submit the results of a phase IV biodistribution study according to an agreed protocol in order to further characterize correlation between the extent of the disease, the dose and the distribution of radium-223 in bone metastases versus sites of impaired bone health (e.g. osteoporosis) versus normal bone structure. This study is imposed as a condition to the marketing authorisation and should be reflected as category 1 in the RMP. The protocol shall be submitted to EMA for assessment within 6 months following the notification of the European Commission Decision.

The submission of the final study reports of the ongoing EORTC sponsored phase III randomized clinical trial PEACE-3 investigating the combination use of radium-223 with enzalutamide in asymptomatic and mildly symptomatic CRPC patients and PCCTC sponsored phase III randomized clinical trial “DoRa” investigating the combination use with docetaxel in CRPC patients is already included in the RMP as category 3 and should be maintained. Final clinical study reports are respectively expected in April 2021 and by the end of 2023.

The MAH should conduct (non)-clinical studies to define the adequate washout period, including a pharmacodynamics component, for other systemic mCRPC treatment prior to radium-223 administration and vice versa. This(ese) study(ies) is(are) reflected as category 3 in the RMP. The study(ies) protocol(s) (pending feasibility assessment) shall be submitted to EMA for assessment within 6 months following the notification of the European Commission Decision.

5.1.3. Non-interventional studies

The MAH shall conduct and submit the results of a non-interventional post-authorisation safety study (PASS) based on the data from the Prostate Cancer Data Base Sweden (PCBaSe) and other relevant Scandinavian cancer registers or other suitable data sources, in order to further characterise the safety of radium-223 in the authorised indication. The MAH is encouraged to seek scientific advice to the relevant competent authorities to design this study. This study is imposed as a condition to the marketing authorisation and should be reflected as category 1 in the RMP. The protocol shall be submitted to EMA for assessment within 3 months following the notification of the European Commission Decision.

In order to assess the effectiveness of the risk minimisation measures implemented, the MAH should conduct a drug utilisation study. This study is introduced as category 3 in the RMP. The protocol shall be submitted to EMA for assessment within 4 months following the notification of the European Commission Decision.

5.2. Risk minimisation measures

5.2.1. Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to further minimise the risk of fractures associated with the use of Xofigo (radium-223). These changes complemented and further refined those implemented in the provisional measures in March 2018[1] and include amendments to sections 4.1, 4.3, 4.4, 4.8 and 5.1 of the SmPC.

The indication was restricted to monotherapy or use in combination with luteinising hormone releasing hormone (LHRH) analogue, for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment.

In addition, the PRAC confirmed the provisional measure that Xofigo should be contraindicated in combination with abiraterone acetate and prednisone/prednisolone.

Further warnings and precautions of use were implemented relating to the risk of fracture associated with the use of Xofigo including risk factors, possible risks of increased mortality in combination use with systemic cancer therapies other than LHRH analogue and patients with a low level of osteoblastic bone metastases and only asymptomatic metastases.

The Package Leaflet was amended accordingly.

5.2.2. Direct Healthcare Professional Communications and Communication plan

A DHPC was disseminated in Mach 2018 based on the preliminary data available to inform HCPs of the recommended provisional contraindication and warnings regarding radium-223. A further DHPC was considered warranted to communicate the outcome of the review. Therefore the PRAC adopted the wording of a DHPC, to inform HCPs of the increased risk of fracture and possible increased risk of mortality with Xofigo and associated risk minimisation measures including the restriction of the indication. The PRAC also agreed on a communication plan.

6. Conditions the marketing authorisations

The MAH shall complete, within the stated timeframe, the below measures:

The MAH shall conduct and submit the results of a phase IV randomised double-blind multicentre study according to an agreed protocol in order to further characterise the efficacy and safety, in particular the risk of fractures, the risk of formation of visceral and nodal metastases of radium-223 in the authorised indication. The protocol should foresee a stratified randomization of patients according to bone ALP levels.	Q2 2024
The MAH shall conduct and submit the results of a non-interventional post-authorisation safety study (PASS) based on the data from the Prostate Cancer Data Base Sweden (PCBaSe) and other relevant Scandinavian cancer registers or other suitable data sources, in order to further characterise the safety of radium-223 in the authorised indication.	Q1 2020
The MAH shall conduct and submit the results of a phase IV biodistribution study according to an agreed protocol in order to further characterize correlation between the extent of the disease, the dose and the distribution of radium-223 in bone metastases versus sites of impaired bone health (e.g. osteoporosis) versus normal bone structure.	Q3 2020

In addition, in accordance with Article 23 of Regulation (EC) No 726/2004, in view of the above mentioned imposed PASS, Xofigo (radium-223) will remain included in the list of products for additional monitoring. The relevant information as well as the pictogram (black triangle) is already reflected in the product information.

7. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Xofigo (radium Ra223 dichloride).
- The PRAC reviewed the preliminary data analyses of Study ERA-223 that showed an increased risk of fracture and a trend for an increased risk of mortality compared to placebo when radium-223 treatment was combined with abiraterone acetate and prednisone/prednisolone treatment. The PRAC also considered all other available data, including data from the ALSYMPCA clinical trial which supported the initial marketing authorisation, in relation to the potential impact of the results of Study ERA-223 on the benefit-risk balance of radium-223 in the authorised indication. The PRAC also considered the views expressed by the scientific advisory group on oncology.
- The PRAC noted that the use of radium-223 in ERA-223 took place in chemotherapy-naïve patients at earlier stages of the disease, albeit partially overlapping with that included in the authorised indication. Considering all available data, the PRAC concluded that radium-223 is associated with an increased risk of fracture, during treatment and for several months after the end of treatment.

- The PRAC considered that the results of ERA-223 added to the uncertainties regarding the extent of benefit noted in ALSYMPCA at the time of initial marketing authorisation, in particular in patients with a lower disease burden and on the potential for radium-223 to promote non-bone disease progression. The PRAC thus considered that measures are needed to minimise these risks including preventing the use of the product in similar settings to that of ERA-223.
- As a consequence, the PRAC recommended that the indication of radium-223 is restricted to use as monotherapy or in combination with luteinising hormone releasing hormone (LHRH) analogue, for the treatment of adults patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment. The PRAC further considered that radium-223 should be contraindicated in combination with abiraterone acetate and prednisone/prednisolone.
- In addition, considering the increased risk of fracture and as an increase in mortality is possible, the PRAC recommends not to use radium-223 in patients with only asymptomatic bone metastases or in combination with other systemic active cancer therapies. Treatment-free intervals before and after treatment with radium-223 are recommended.
- In view of the increased risk of fracture, the uncertainties raised, and the absence of significant evidence that the benefits observed in ALSYMPCA apply to patients with a low level of osteoblastic bone metastases, the PRAC recommends not to use radium-223 in these patients, and, in patients with mildly symptomatic bone metastases, to use radium-223 only if the benefits are expected to outweigh the risks.
- Further, the PRAC considered that in order to minimise the risk of fracture, healthcare professionals should assess bone status and baseline risk of fracture for all patients prior to initiating radium-223 and monitor patients for at least 24 months. The use of bisphosphonates or denosumab should be considered. In patients at high risk of fracture, radium-223 should only be initiated if the expected benefits are considered to outweigh the risks associated with the treatment.
- Finally, the PRAC recommended imposing as conditions to the marketing authorisation of Xofigo the conduct of a randomised controlled clinical trial, a non-interventional post-authorisation safety study and a biodistribution study, in order to further characterise the safety and efficacy of radium-223, including the mechanisms responsible for the increased risk of fracture, and possible risk of increased mortality reported in ERA-223.

In view of the above, the Committee considers that the benefit-risk balance of Xofigo (radium Ra223 dichloride) remains favourable subject to the agreed conditions to the marketing authorisation, and taking into account the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Xofigo (radium Ra223 dichloride).

Appendix 1

Divergent positions

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 PRAC 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.

PRAC Members expressing a divergent opinion:

- Ghania Chamouni (FR)
- Amelia Cupelli (IT)
- Dolores Montero (ES)
- Adam Przybylkowski (PL)
- Almath Spooner (IE)
- Julie Williams (UK)
- Sabine Straus (NL)

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 PRAC Members consider that the benefit risk ratio of Xofigo is not favourable based on the following grounds:

6. 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.

7. 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.

8. 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.

9. 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.

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PRAC Members expressing a divergent opinion:

- Karen Pernille Harg (NO)