Observational Study Results Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Overall data disclosed, may differ from published or presented data and are a reflection of the limited information provided here. The results from a single study need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

1. Abstract

Acronym/Title	REASSURE - Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Report version and date **Author**	v 1.0, 07 APR 2025 PPD Global Medical and Evidence Targeted Radionuclide Therapies and Xofigo Bayer U.S
GEMSTONE study number	16913
Keywords	Radium-223, alpha emitter radionuclide therapy, mCRPC, bone-predominant prostate cancer
Rationale and background	Prostate cancer is the most common non-cutaneous malignancy in men worldwide. Once prostate cancer becomes metastatic, survival depends on extent of disease and site of metastases. Patients with metastatic castration-resistant prostate cancer (mCRPC) usually suffer from painful bone metastases and complications from other skeletal events. With survival extension, cumulative toxicity may be observed. This study collected and reviewed safety and effectiveness data in the clinical setting.
Research question and objectives	This study aimed to evaluate short- and long-term safety profile of radium-223, which selectively targets bone metastases with high-energy, short-range alpha-particles. Primary objectives : • Assess incidence of all second primary malignancies (SPMs) • Assess incidence of treatment-emergent serious adverse events (SAEs), drug-related adverse events (AEs), and drug-related SAEs • Assess bone marrow suppression Secondary objectives: • Determine overall survival (OS) • Evaluate pain over time using the “Brief pain inventory short form” (BPI-SF) questionnaire

	• Assess incidence of bone fractures and bone-associated events
Study design	International, multicenter, observational, prospective, single-arm cohort study conducted in routine clinical practice settings.
Setting	Sites in Argentina, Austria, Belgium, Canada, Colombia, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Luxembourg, Mexico, Netherlands, Portugal, Spain, Sweden, United Kingdom, United States of America. Patients were enrolled from 2014 to end of 2017. Observation period was time from start of radium-223 therapy to death, withdrawal of consent, loss to follow-up, or end of study (maximum of 7 years after last radium-223 administration).
Subjects and study size, including dropouts	The study enrolled CRPC patients with bone metastasis treated with radium-223. To achieve 1200 evaluable patients, approximately 1334 patients were to be enrolled (expected drop-out rate: around 10%).
Variables and data sources	Data were collected from medical records, routine measurements, other physicians, and patient questionnaires. Primary variables: SPMs, treatment-emergent SAEs, drug-related treatment-emergent AEs, drug-related SAEs, therapeutic/prevention measures for bone marrow suppression, white blood cell count, febrile neutropenia, haemorrhage Secondary variables: OS, worst pain/pain interference/pain severity score on BPI-SF, bone fractures, bone-associated events
Results	Of the 1550 screened patients, 1473 patients (95.0%) were enrolled and 1472 patients were included in the safety analysis set (SAF; i.e., patients who received at least one dose of radium-223). Median time from start of radium-223 to either death or last-known-alive date (LKAD) was 13.97 months. <u>Primary objectives</u> Overall, 24 patients in the SAF (1.6%) experienced 25 **SPMs** (including skin cancer, lung-related SPMs, and gastrointestinal SPMs in 5 patients each, urinary related

	SPMs in 3 patients, and neuroendocrine and hematologic SPMs in 2 patients each). Two (2) SPMs were assessed as related to radium-223 by the investigator, and 7 SPMs were fatal. To contextualize SPM incidence data, three population-based, retrospective cohort studies from Germany, Sweden, and the US were used as reference. The expected number of patients with SPMs in REASSURE as derived from the reference data was 192.176 for the German cohort, 98.881 for the US cohort, and 148.043 for the Swedish cohort. The corresponding Standardized Morbidity Ratios (SMRs) were 0.099, 0.192, and 0.128, respectively, showing that the incidence of SPMs observed over the course of the study was below the incidences in the external references. Regarding **treatment-emergent SAEs**, **treatment-emergent drug-related AEs**, and **drug-related SAEs**, the preferred term (PT) anaemia was among the most common events, across all three types of AEs/SAEs. Anaemia was also commonly reported as prior disease (6.8%) and concomitant disease (6.5%). Treatment-emergent SAEs were reported for 325 patients (22.1%), the most common PTs being anaemia (1.8%), worsening of prostate cancer (PT: prostate cancer; 1.1%), general physical health deterioration (1.0%), pneumonia (1.0%), and spinal cord compression (0.9%). Treatment-emergent drug-related AEs were reported for 537 patients (36.5%), the most common PT being diarrhoea (10.9%), followed by nausea (9.2%), anaemia (8.8%), and fatigue (7.5%). Drug-related SAEs were reported for 88 patients (6.0%), the most common PTs being anaemia (1.6%), thrombocytopenia (0.8%), and platelet count decreased (0.7%). **Bone marrow suppression** relevant treatments up to 6 months after last administration of radium-223 were reported for 339 patients (23.0%). These were blood transfusions (21.5%), erythropoiesis stimulating drugs (1.6%), and colony stimulating factors (1.6%). Post-radium-223 grade 3 or 4 bone marrow suppression relevant events (up to 6 months from last radium-223 administration) were reported for 227 patients (15.42%). The most common reported category was anaemia, defined as Standardized MedDRA Query (SMQ) 'haematopoietic erythropenia (SMQ)' (12.64%), followed by MedDRA Labelling Groupings (MLG): 'thrombocytopenia' (3.87%).

	<u>Secondary objectives</u> Of the 1472 patients in the SAF, 1308 patients (88.9%) died and 164 patients (11.1%) were censored. The median **OS** (from start of radium-223 to death due to any cause) was 15.6 months. The pain severity score of the **BPI-SF** questionnaire was consistently lower on treatment and during follow-up than at baseline. The mean pain severity score was 3.003 at baseline and ranged from 2.760 at treatment 2 to 2.261 at treatment 5. The pain interference score showed similar trends, mean score being 3.283 at baseline and ranging from 2.965 at treatment 2 to 2.358 at treatment 5. Both scores increased slightly at follow-up visits in comparison to post-baseline treatment measurements but remained below the baseline values. The proportion of patients with a clinically meaningful pain response in worst pain item in the SAF increased slightly over treatment time points, ranging from 28.0% at treatment 2 to 34.7% at treatment 5. In a post-hoc analysis restricted to patients with a baseline worst pain score ≥2, the proportion of patients with a clinically meaningful pain response in worst pain item was constantly higher than in the overall SAF. A total of 247 patients (16.8%; Exposure Adjusted Incidence Rate per year: 0.36) had at least one **bone fracture or bone-associated event**. Bone disorders (excl congenital and fractures) occurred in 8.5% and Fractures in 9.7% of patients. In patients with **concomitant bone health agent therapy**, the incidence of bone fractures or bone-associated events was slightly lower than in patients without such therapy (13.9% versus 18.8%).
Discussion	The study provides a robust dataset which demonstrates a low incidence of SPMs and observation of manageable treatment-emergent AEs. Generalizability is supported by the diverse patient population across multiple countries, reflecting real-world clinical settings. Therefore, the study confirms that radium-223 maintains a favorable benefit-risk profile in treatment of mCRPC, reinforcing its role as therapeutic option for patients with bone metastases. No immediate further evidence is deemed necessary to confirm the safety profile. The results do not warrant changes to the known benefit-risk of radium-223 in the authorized indication.

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Names and affiliations of principal investigators	Contact details of the principal and/or coordinating and/or all investigators for each country and site participating in the study are listed in a stand-alone document (see Annex 1).