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	DIRECT: **D**rug Utilisat**I**on Study of **R**adium-223 Under Routin**E** **C**linical Prac**T**ice in Europe
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Keywords	Xofigo, radium-223, drug utilisation study
Rationale and background	Radium-223 is a radioactive agent indicated for the treatment of adults with metastatic castration-resistant prostate cancer (mCRPC). The randomised controlled trial ERA-223 was unblinded in November 2017 per an independent data monitoring committee's recommendation due to the observation of an imbalance of more fractures and deaths in the study arm treated with radium-223 and abiraterone acetate and prednisone/prednisolone than in the control arm. This outcome resulted in a change in the European Union (EU) product information in 2018, with the contraindication of the use of radium-223 "in combination with abiraterone acetate and prednisone/prednisolone" and the restriction to use among patients who are in progression after at least 2 prior lines of systematic therapy for mCRPC (other than luteinising hormone–releasing hormone analogues) or who are ineligible for any other available systemic mCRPC treatment. Bayer performed this drug utilisation study (DUS) in Europe to evaluate the effectiveness of the risk minimisation measures by assessing compliance with the new indication and contraindications set after the 2018 EU label change.
Research question and objectives	This DIRECT post-authorisation safety study (PASS) was intended to answer the following question, "What proportion of users of radium-223 receive it in compliance with the new indication and contraindication introduced in October 2018?" To answer this question, the **primary objectives** of the DIRECT PASS were to estimate the following among the population of patients receiving radium-223 during the period *after* the 2018 European Medicines Agency (EMA) label change: (1) the proportion

	who receive radium-223 in combination with abiraterone acetate, (2) the proportion who receive radium-223 in combination with other systemic therapies for mCRPC, and (3) the proportion who receive radium-223 without at least 2 prior lines of systemic therapy for mCRPC. The **secondary objectives** are to (4) estimate the difference before and after the label change in the proportions estimated in the primary objectives and (5) characterise the population of new users of radium-223, irrespective of combination with other systemic therapies for castration-resistant prostate cancer (CRPC) at treatment start for both study periods.
Study design	This was an observational, European prospective cohort DUS of new users of radium-223 in the Netherlands, Denmark, and Germany. The study used existing data sources (secondary data collection) through electronic medical records and medical record abstraction in the Netherlands, a combination of routinely collected data from national registries and data from electronic medical record abstraction in Denmark, and claims data from a population-based database in Germany. A period before the label change was assessed as a reference for a period after the label change. Compliance with the indication and contraindication introduced in the October 2018 EU label change was measured during these 2 periods. A common study design, protocol, and statistical analysis plan were followed in all 3 participating data sources. Each country-specific data source was managed, and country-specific data were analysed locally.
Setting	The study population included new users of radium-223 during the study periods captured in each data source. The study period included time periods before and after the label change. The “before” period started in November 2013, the month of radium-223 approval, and ended in November 2017, the month when the first Direct Healthcare Professional Communication letter was sent. The “after” period included an enrolment phase during which patients initiating radium-223 in each data source were identified. The enrolment phase started in April 2019 (6 months after the label change) and continued through a follow-up phase of at least 6 months after the last new user of radium-223 was identified. A 6-month follow-up allowed for the evaluation of radium-223 in combination with abiraterone acetate or other systemic therapies for mCRPC after the last radium-223 new user was identified, so that this patient could be followed during the approximately 6-month duration of radium-223 treatment.

Subjects and study size, including dropouts	For the main study period (i.e., the period after the 2018 EU label change for Xofigo [after–label change period]), a total of 184 patients exposed to radium-223 were included: 53 in the Netherlands, 68 in Germany, and 63 in Denmark. For the reference period before the label change, a total of 883 patients were included: 243 in the Netherlands, 580 in Germany, and 60 in Denmark.
Variables and data sources	The study was conducted using the following existing secondary data sources: • Electronic medical record data of all new users of radium-223 from an existing register of patients with CRPC in the Netherlands (CAPRI). CAPRI 1 and 2 were used to identify users of radium-233 before the label change from 20 hospitals, and CAPRI 3, to which 6 hospitals contributed data, was used after the label change. Users of radium-223 were identified through drug substance or product names identified in the electronic medical records of patients in CAPRI 2 and 3 from participating hospitals. • Data abstracted from existing medical records of all new users of radium-223 in 2 treating hospitals in Denmark. Initially, users of radium-223 were identified using the treatment code for "isotope therapy with radium-223 dichloride" as recorded in the Danish National Patient Registry (DNPR), a population-based administrative database, which contains information on all hospital encounters in Denmark since 1977 and is updated continually. Once potential users of radium-223 were identified, data from hospital medical records for these patients were retrieved by trained employees of the Aarhus University Hospital. To supplement data from the medical record abstraction, additional data on comorbidities, cancer, and comedications were obtained through linkage to the DNPR and Danish Cancer Registry. Linkage to all Danish registries is possible via the centralised Civil Registration System that allows for personal identification of each person in the entire Danish population (5.78 million). • Claims data from all new users of radium-223 were captured in the German Pharmacoepidemiological Research Database (GePaRD), which is a population-based claims database. Users of radium-223 were identified based on dispensations of radium-223 recorded in the database. GePaRD covers approximately 15 to 17 million individuals per year from 4 statutory health insurance providers (SHIs) in Germany (2 large SHIs and 2 small SHIs) and provides data on hospital diagnoses and procedures, ambulatory care diagnoses and

	procedures, and ambulatory prescriptions, including date of prescription and date of pharmacy dispensing. Ultimately, reliable data on the prior use of systemic therapies for mCRPC were available from only 1 (large SHI) of the 4 participating SHIs. Therefore, the analyses of the second and third objectives were conducted in a restricted sample including only patients from this large SHI. Data on abiraterone use were available for all 4 SHIs.
Results	A total of 1 patient (1.9%) in the Netherlands, 3 patients (4.2%) in Germany, and $1 \leq n < 5$ patients in Denmark (exact number masked due to local privacy regulations) used radium-223 in combination with abiraterone in the after–label change period. A total of 5 patients (9.4%) in the Netherlands, 4 (11.8%) in Germany, and $1 \leq n < 5$ in Denmark used radium-223 in combination with other systemic therapies for mCRPC in the after–label change period. Use of radium-223 without at least 2 prior lines of systemic therapy for mCRPC occurred in 21 patients (39.6%) in the Netherlands, 9 (26.5%) in Germany, and $1 \leq n < 5$ in Denmark in the after–label change period.
Discussion	In patients covered by the participating data sources in the Netherlands, Germany, and Denmark, use of radium-223 with abiraterone or with other systemic therapies for mCRPC was very limited, in line with the prescription limitations imposed by the 2018 EU label change. In addition, many of the patients with combination use received abiraterone or other systemic therapies only at the last cycle, likely at the end of the treatment course with radium-223. Use of radium-223 without at least 2 prior lines of systemic therapy for mCRPC remained relatively common in the period after the 2018 EU label change in the Netherlands and Germany, but was uncommon in Denmark. It is important to note that the eligibility of patients to receive other systemic therapies for mCRPC could not be determined in this study; therefore, this finding reflects, at least in part, the proportion of patients in whom other systemic therapies were contraindicated. The relatively small number of patients enrolled in the after–label change period makes findings reported in this report prone to random variation.
Marketing Authorisation Holder(s)	Bayer AG