Drug Utilisation of Radium-223 Under Routine Clinical Practice (DIRECT) in Europe: A Post-authorisation Safety Study

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DISCLOSURES

Bayer AG provided the financial support for the study. RTI Health Solutions, an independent nonprofit research organisation, received funding under a research contract with Bayer AG to conduct this study and provide poster support. This research also was supported by the CAPRI foundation, registered at the Dutch Chamber of Commerce in December 2019; this nonprofit organisation aims to serve as the data source on metastatic prostate cancer in the Netherlands and is sponsored by pharmaceutical companies (AAA Novartis, Astellas, Bayer, and MSD/AstraZeneca). These companies had no role in the design and conduct of the study; collection, management, analysis, interpretation of data; and preparation, review, or approval of the abstract. RW, JF, and DM are full-time employees of RTI Health Solutions. BK and UH are employees of BIPS, Bremen, Germany, an independent nonprofit research organisation. AK and VE are employees of Aarhus University and Aarhus University Hospital, which provides research services via institutional research grants to multiple public and private stakeholders, including regulators, governmental agencies, contract research organisations, and pharmaceutical companies. PI is a nuclear medicine specialist employed at Aarhus University Hospital and is responsible for treatment with radium-223 at the Nuclear Medicine Department. JM is a full-time employee of Rigshospitalet and is responsible for treatment with radium-223 at the Nuclear Medicine Department. DB received speaker honoraria from MSD. MK is a radiation-oncologist in training at Maastro and board member of the CAPRI Foundation. FP and ZV are employees of Bayer and hold shares and/or stock options in the company.

BACKGROUND

- Over 90% of patients with metastatic castration-resistant prostate cancer (mCRPC) have bone metastases, which are a major cause of impaired quality of life and death in these patients.[1]
- Radium-223 is an alpha particle–emitting agent indicated for the treatment of adults who (1) have mCRPC with symptomatic bone metastases and no known visceral metastases and (2) experience progression after ≥ 2 prior lines of systemic mCRPC therapy (except luteinising hormone–releasing hormone [LHRH] analogues) or are ineligible for any other systemic mCRPC therapies; radium-223 is contraindicated for concomitant use with abiraterone acetate and prednisone/prednisolone.[2]
- The second indication criteria and the contraindication criterion listed above were added to the radium-223 European Medicines Agency (EMA) label in 2018, following the results of the ERA-223 randomised controlled trial, which observed more fractures and deaths in the arm treated with radium-223 in combination with abiraterone acetate and with prednisone/prednisolone versus the control arm.[3]

OBJECTIVES

- Because use of radium-223 in real-world clinical practice may vary, the aim of this study was to determine the proportion of patients who received radium-223 in compliance with the new 2018 EMA label before and after the label change.

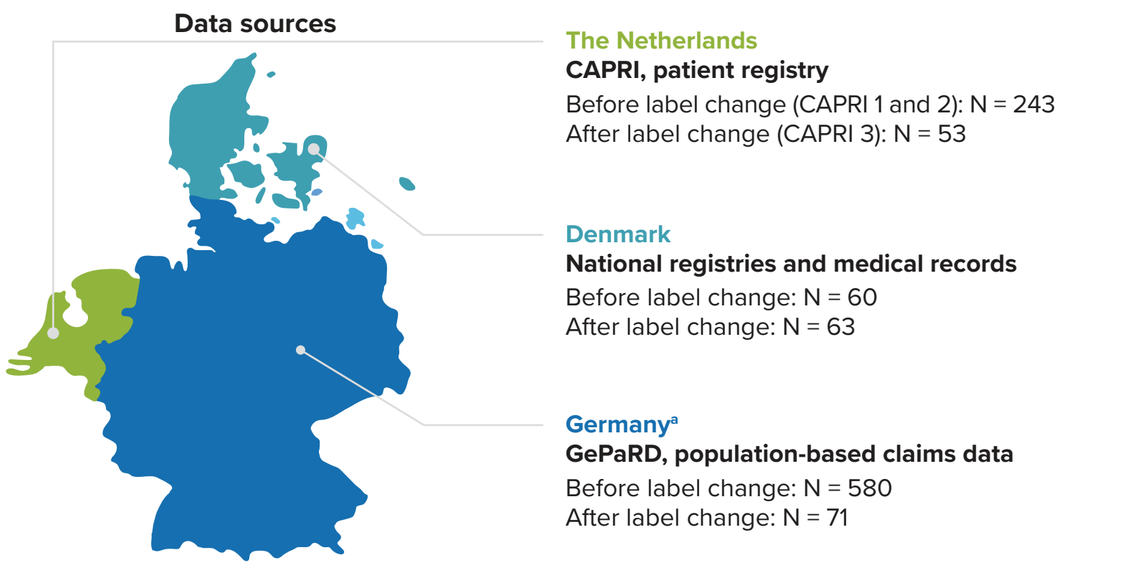
METHODS

- This was an observational, prospective, cohort drug utilisation study (EUPAS37163, EMA study ID 46942[4]), including patients with mCRPC who were new users of radium-223 (Figure 1).
- Data from secondary sources in the Netherlands, Germany, and Denmark before and after the label change (including ≥ 6 months of potential follow-up) were analysed using descriptive statistics.

Figure 1. Study Design

Study population

Men of any age with mCRPC who were new users of radium-223 during the study periods captured in each data source



CAPRI = Castration-Resistant Prostate Cancer Registry; F.u. = follow-up; GePaRD = German Pharmacoepidemiological Research Database; SHI = statutory health insurance.

Notes: CAPRI 1 and 2 data were from 20 hospitals, CAPRI 3 data were from 6 hospitals, GePaRD data were from 4 SHI providers (2 large providers and 2 small providers), and data from Denmark were from 2 large hospitals. For GePaRD, detailed data on the prior use of systemic mCRPC therapies were not available from all SHI providers; thus, analyses of the second and third objectives were conducted using data from only 1 large SHI provider (i.e., "restricted sample").

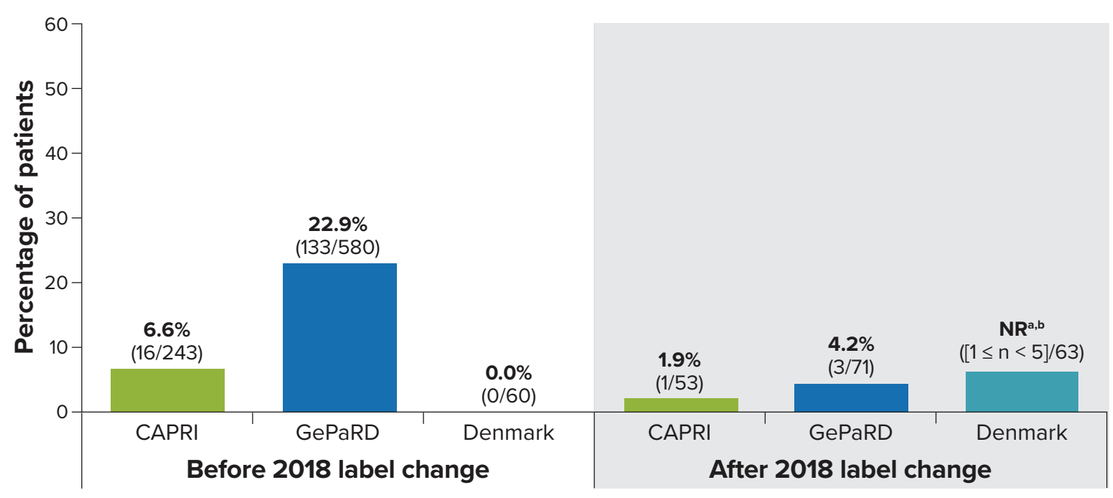
[a] In the restricted sample, there were 245 patients in the period before the label change and 34 patients in the period after the label change.

RESULTS

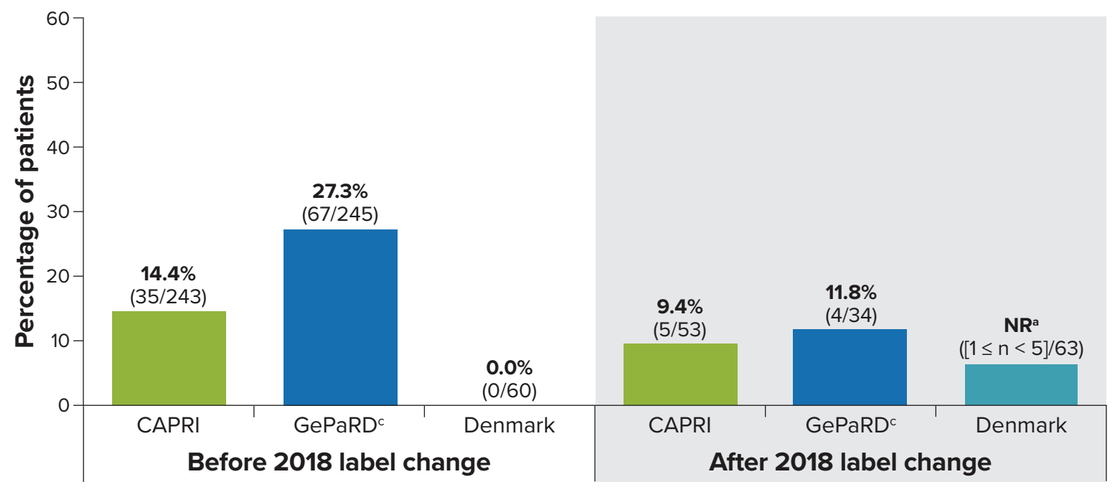
- This study included 1,070 patients (Figure 1); key patient characteristics are listed in Supplemental Table 1 (accessed via the QR code below).
- Overall, use of radium-223 with abiraterone acetate or other systemic therapies for mCRPC was very limited (Figures 2A and 2B). In the Netherlands and Germany, the prevalence of these outcomes decreased after the label change. In Denmark, no outcomes were identified before the label change, and use in combination after the label change was rare—although it should be noted that changes in treatment after starting radium-223 may have been registered as combined use and these results may be an artefact of recording.
- Similarly, use of radium-223 without having received ≥ 2 prior lines of systemic mCRPC therapy decreased in all countries after the label change despite remaining relatively common in the Netherlands and Germany (Figure 2C).

Figure 2. Primary Outcomes

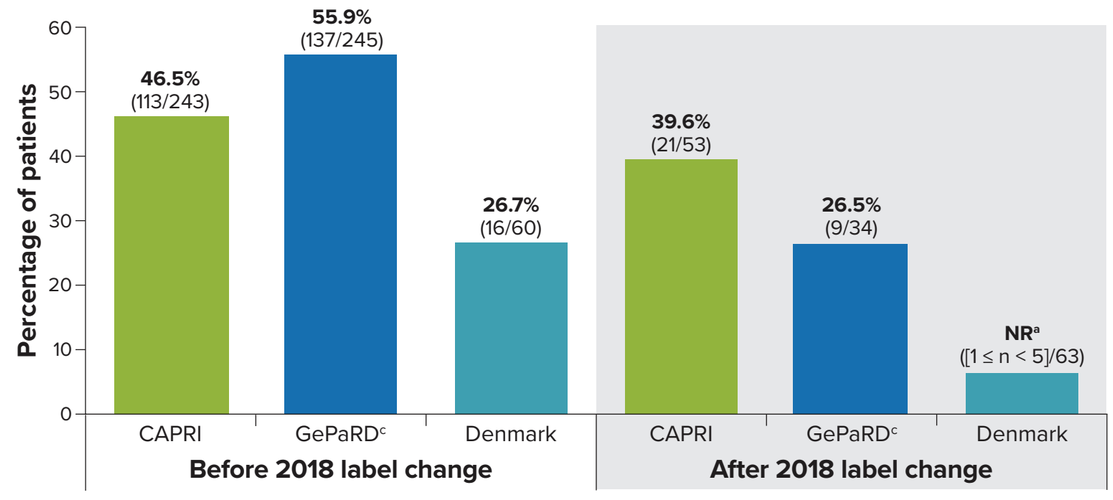
A) Use of Radium-223 in Combination With Abiraterone Acetate



B) Use of Radium-223 in Combination With Other Systemic mCRPC Therapies Except LHRH Analogues



C) Use of Radium-223 Without Having Received ≥ 2 Prior Lines of Systemic mCRPC Therapy Except LHRH Analogues



NR = not reportable.

Notes: Results are visually split by label change periods (i.e., before and after the 2018 label change). The "use of radium-223 in combination with abiraterone acetate" was defined as a patient having ≥ 1 administration of abiraterone acetate 5 days prior to, on the same date as, or within 30 days after an administration of radium-223. The "use of radium-223 in combination with other systemic mCRPC therapies" was defined as a patient having ≥ 1 administration of systemic mCRPC therapy other than abiraterone acetate on the same date or within 30 days after a radium-223 administration. For Figure 2C, "systemic therapy for mCRPC" was defined as any use of abiraterone acetate, enzalutamide, docetaxel, cabazitaxel, sipuleucel-T, or pembrolizumab (each drug substance counted as a prior line irrespective of the number of administrations of the specific drug substance).

[a] Per Danish data privacy requirements, if the number of individuals in a cell is from 1 to 4, or would allow back-calculation of cells to lead to a result of 1 to 4, the value is shown as a range (1.6%-6.3%).

[b] All of these patients received abiraterone acetate ≥ 20 days after the last cycle of radium-223.

[c] Analysed in the restricted sample, including only patients from 1 large SHI provider.

CONCLUSIONS

- Use of radium-223 in combination with abiraterone acetate or other systemic mCRPC therapies largely aligned with the 2018 EMA label.
- Use of radium-223 without ≥ 2 prior lines of systemic mCRPC therapy remained common in the Netherlands and Germany after the label change.
  - Because clinical guidelines before the label change recommended radium-223 as a first-line treatment for mCRPC in frail patients (who may be ineligible for other therapies), doctors still may be considering it for first-line use in these cases.
  - We could not assess patients' eligibility for other systemic mCRPC therapies. Therefore, our findings partly reflect radium-223 use in accordance with the 2018 label in patients for whom other systemic therapies were contraindicated.

REFERENCES

1. Parker C, et al. N Engl J Med. 2013 Jul 18;369(3):213-23. doi:http://dx.doi.org/10.1056/NEJMoa1213755.
2. Bayer AG. 2020. https://www.ema.europa.eu/en/documents/product-information/xofigo-epar-product-information_en.pdf. Accessed 9 January 2024.
3. EMA. European Medicines Agency. EMA restricts use of prostate cancer medicine Xofigo. 2018.
4. EMA. European Medicines Agency. https://catalogues.ema.europa.eu/node/3081/administrative-details#darwin-regulatory. Accessed 20 June 2024.

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Scan the QR code to access an online version of the poster with Supplemental Table 1

Table 1. Key Patient Characteristics and Duration of Follow-up

	Period before the 2018 EMA label change			Period after the 2018 EMA label change		
	The Netherlands (CAPRI 1& 2)	Germany (GePaRD)	Denmark	The Netherlands (CAPRI 3)	Germany (GePaRD)	Denmark
Baseline characteristics						
Age, mean (SD), years	73.1 (8)	72.4 (7.9)	71.9 (7.8)	73.9 (8.0)	74.2 (8.5)	71.9 (6.3)
Time since first prostate cancer diagnosis, median (Q1, Q3), months	59.3 (39, 101)	57 (28, 108)	59.8 (31.2, 102.0)	52.2 (32, 108)	50 (28, 94)	55.0 (32.9, 96.5)
Patients who underwent surgical castration, n (%)	29 (11.9%)	11 (1.9%)	N/A	9 (17.0%)	0	N/A
Prior use of therapies for CRPC, n (%)[a]	238 (97.9)	572 (98.6%)	N/A	50 (94.3)	71 (100%)	N/A
Follow-up, N, months	**1,304**	**3,248**	**340**	**251.1**	**390.5**	**345**
Median (Q1, Q3), months	6.0 (6.0, 6.0)	6 (6, 6)	5.9 (5.7, 6.0)	4.6 (4.6, 5.7)	6 (6, 6)	5.7 (5.5, 6.0)
Number of radium-223 cycles, N	**989**	**2,551**	**276**	**257**	**281**	**246**
Median (Q1, Q3), per patient	5 (2, 6)	5 (3, 6)	6 (3, 6)	6 (3.5, 6)	4 (3, 6)	3 (3, 6)

N/A = not available; Q1, Q3 = first and third quartiles; SD = standard deviation.

Note: In Denmark, due to constraints on the chart abstraction process imposed by the COVID-19 pandemic, not all baseline characteristics—like previous surgical castration or prior use of therapies—could be obtained.

[a] In GePaRD, because castration-resistant status was not available, all systemic therapies were assumed to have been administered for CRPC. Prior use of therapies (i.e., cytotoxic medications, immunotherapies, antiandrogens, LHRH agonists/analogues, LHRH antagonists, and corticosteroids) was defined as having ≥ 1 administration at any time before the index date.