Observational Study Information

Title	Incidence of Second Primary Malignancies in Patients With Castration-Resistant Prostate Cancer: An Observational Retrospective Cohort Study in the US
Version identifier of the final study report	
Date of last version of the final study report	5 May 2017
EU PAS register number	EUPAS13602
Active substance	Radium-223
Product	Xofigo
Product reference	
Procedure number	
Marketing authorization holder(s)	Bayer AG
Joint PASS	NA

Research question and objectives	The primary objective of this study was to estimate population-based incidence rates of second primary malignancies among patients with castration-resistant prostate cancer (CRPC) similar to those treated with Xofigo. RTI Health Solutions (RTI-HS) analyzed the collective incidence rate of all second primary malignancies (other than non-melanoma skin cancer), as well as specific groups of second primary malignancies, among men with CRPC similar to those treated with Xofigo. Secondary objectives aimed to provide further information about the following topics: • The proportion of men with CRPC who have a history of bone metastases as documented by use of diagnostic codes in Medicare data and/or treatment/prescription codes for bone-directed therapies. • Among the cohort patients who were continuously enrolled in Part D for the entire period between initial diagnosis of prostate cancer and the cohort entry date, the proportion who met the definition of castration based solely on receiving androgen deprivation therapy as documented in the Prescription Drug Event data file (i.e., would not have been met the castration definition and been included in the study cohort if Part D data were not available). • The overall survival of men with CRPC.
Country(-ies) of study	United States
Author	[redacted]

Study Description		
Study Sponsor:	Bayer AG	
Study Number:	18673	NCT00000000
Study Phase:		
Official Study Title:	Incidence of Second Primary Malignancies in Patients With Castration-Resistant Prostate Cancer: An Observational Retrospective Cohort Study in the US	
Therapeutic Area:		
Product		
Name of observed Product:	N/A	
Name of Active Ingredient:	N/A	
Dose and Mode of Administration:	N/A	
Reference Therapy		
Reference Therapy:	N/A	
Dose and Mode of Administration:	N/A	
Duration of Treatment:	N/A	
Studied period:	Date of first enrolment	01-Jan-2000
	Date last completed	31-Dec-2013
Study Center(s):	United States	

Methodology:	This was a retrospective, observational cohort study of men in the US aged 65 years or older with CRPC. There was no internal comparison group for this study.
Indication/ Main Inclusion Criteria:	The study cohort included men aged 65 years or older who were enrolled in both Medicare Parts A and B for at least 1 year before the cohort entry date and continuously between the date of initial diagnosis of prostate cancer and the cohort entry date, had a primary site code of prostate cancer, underwent surgical castration or received androgen deprivation therapy after prostate cancer diagnosis, and had evidence that the prostate cancer was resistant to surgical castration or androgen deprivation therapy. Excluded were men who were enrolled in an HMO during the year before cohort entry, had a diagnosis of any other cancer (except melanoma) on or before the cohort entry date, had any diagnostic code for metastases (other than bone or lymph node metastases) on or before the cohort entry date, had any claim for treatment with radium Ra-223 on or before the cohort entry date, or had a claim for any second-line systemic therapy on or before the earliest date of surgical castration or androgen deprivation therapy. All patients who met study eligibility criteria were included in the final study cohort of 2,234 patients.
Study Objectives:	Primary: The primary objective of this study was to estimate the population-based incidence rate of second primary malignancies among patients with CRPC similar to those treated with Xofigo. Secondary: Secondary objectives were to identify the proportion of men with CRPC who had a history of bone metastases, determine the proportion of men who met the definition of castration based solely on receiving androgen deprivation therapy as documented in the Medicare Prescription Drug Event file, and estimate overall survival for men with CRPC. Safety: None
Evaluation Criteria:	Primary objective(s): None Secondary objective(s): None Safety: None Other: None
Statistical Methods:	Descriptive analyses of the data were performed using summary statistics for continuous and categorical data. Continuous data were described by the number of non-missing values, mean and standard deviation, median, quartiles, and ranges. Selected continuous variables were categorized in a clinically meaningful way. Tables with frequencies and percentages were generated for categorical data, but due to SEER restrictions, data were

	suppressed or categories were combined to avoid reporting any cell counts less than 11, as required by the SEER-Medicare Data Use Agreement. As there is no study treatment, premature discontinuation is not an issue for this study. If during follow-up patients disenrolled in either Medicare Part A or Part B or enrolled in an HMO, then some or all of their medical claims data might be missing from that point forward; thus, they were censored on that date for the survival analyses and they did not contribute any additional follow-up time or events for incidence rate calculations. Primary objective(s): Crude incidence rate estimates were calculated by dividing the count of patients in the study cohort who had a second primary cancer by the person-years at risk among all patients and multiplying by 100 to express rates per 100 person-years. Because there were so few second primary malignancies, we report rates to two significant digits to avoid the appearance of more precision than the data provide. Adjusted incidence rates were calculated through direct standardization to the age distribution of the interim analysis population of the REASSURE study aged 65 years or older at entry, using the five age categories 65-69, 70-74, 75-79, 80-84, > 85 years. Because events were rare, the Poisson distribution was used to estimates 95% confidence intervals (CIs) for the crude rates, and the gamma method was used to estimate CIs for standardized rates. Secondary objective(s): The proportion of patients with a history of bone metastasis at cohort entry was calculated by dividing the number of patients with bone metastasis (identified by diagnosis code) or bone-directed treatment (identified by a drug or treatment code) by the total number of patients in the study population. Safety: N/A Other: For all patients with CRPC, Kaplan-Meier methods were used to calculate the survival function. Plots of the survival function along with tables showing 1-, 3-, and 5-year overall survival rates and 95% CIs are presented. Survival time was measured from the date of diagnosis of CRPC to death. Patients who did not die before the end of follow-up were censored on the last day of the study period. Missing data were treated as missing. For indicator variables (e.g., presence or absence of a characteristic), if the patient was not recorded as having a given characteristic, the characteristic was assumed in the analysis not to be present in that patient. There was no ability to query to resolve missing values in the SEER-Medicare data, and no data imputations were performed. Counts of missingness were reported when summarizing categorical variables, and relative frequencies were based on all patients, including those with missing values. Because the reliability of Medicare claims data to identify second primary cancer outcomes in men with CRPC is uncertain, sensitivity analyses were

	conducted to assess the effect on the estimated incidence rates of not including second primary cancer events that were identified only in Medicare data.
Number of Participants:	NCI supplied data on 564,491 individuals diagnosed with prostate cancer since the year 2000. Applying the inclusion and exclusion criteria resulted in a final cohort of 2,234 patients.
Early Termination:	N/A
Substantial Protocol Changes:	None.

Study Results

NCI supplied data on 564,491 individuals diagnosed with prostate cancer since the year 2000. Applying the inclusion and exclusion criteria resulted in a final cohort of 2,234 patients. The great majority of patients in the study cohort (80.4%) had a history of bone metastases recorded in their Medicare claims data.

SEER data and Medicare claims data identified 172 cases of second primary malignancies, yielding a crude incidence rate of 5.9 per 100 person-years (95% CI, 5.0-6.8). The incidence rate standardized to the age distribution of the REASSURE study population (5.8 per 100 person-years; 95% CI, 4.9-6.7) was similar to the crude incidence rate. The most common cancers were lung/bronchus (n = 29), urinary bladder (n = 22), colon/rectum (n = 21), non-prostate, non-bladder genitourinary tract (n = 18), and non-colorectal gastrointestinal (n = 17). When limited to the 1,797 patients with bone metastases, the incidence was 5.6 per 100 (95% CI, 4.6-6.7).

Among the 172 patients with CRPC who developed a second primary cancer, the mean time between meeting the study definition of incident CRPC and a diagnosis of the second cancer was 1.0 year.

Three-quarters of the patients in the study died during follow-up. The median survival time after cohort entry for the 2,234 patients was 1.18 years (95% CI, 1.12-1.26), and the survival probabilities at 1, 3, and 5 years were 56%, 17%, and 9%, respectively.

Results Summary — Patient Disposition and Baseline

The study cohort was primarily white (83.6%), with the remainder black (9.8%), Asian (2.1%), Hispanic (2.1%), and other or unknown (2.5%) (patients with unknown race made up less than 0.5% of the cohort.) The mean age at cohort entry was 76.6 years (median, 76 years), with 74.8% of patients aged 70 to 84 years, 13.3% aged 65 to 69 years, and 11.9% aged 85 or more years (Table SD-1).

Table SD-1 Demographic characteristics of study cohort (N = 2,234)

Variable	No. of patients (%)
Race	
White	1,867 (83.6)
Black	218 (9.8)
Asian	46 (2.1)
Hispanic	48 (2.1)
Other or unknown[a]	55 (2.5)
Age at cohort entry, years	
Mean (SD)	76.6 (6.2)
5 number summary (minimum-Q1-median-Q3-maximum)	65-72-76-81-100
Age group	
65-69	297 (13.3)
70-74	625 (28.0)
75-79	595 (26.6)
80-84	451 (20.2)
85+	266 (11.9)

Q1 = first quartile, Q3 = third quartile; SD = standard deviation.
[a] Categories were combined to avoid reporting a count of < 11.

The numbers and percentages of patients and follow-up time are stratified by year of cohort entry in Table SD-2. Year of cohort entry ranged from 2000 through 2013, with the first 4 years contributing a lower proportion of patients and person-time of follow-up than subsequent years. The proportion of patients entered each year gradually increased over time, with the last 3 years each contributing more than 10% of the cohort.

Table SD-2 Study patients and follow-up years, by cohort entry year (N = 2,234)

Cohort entry year	Patients n (%)	Follow-up, years n (%)	Follow-up years per patient	
			Mean (SD)	Five-number summary (min-Q1-median-Q3-max)
2000	10 (0.4)	40 (1.4)	4.00 (5.15)	0.14 - 0.54 - 1.57 - 4.40 - 13.45
2001	41 (1.8)	49 (1.7)	1.19 (2.10)	0.03 - 0.26 - 0.53 - 1.35 - 12.95
2002	67 (3.0)	120 (4.1)	1.78 (2.94)	0.00 - 0.35 - 0.72 - 1.71 - 11.98
2003	84 (3.8)	114 (3.9)	1.36 (1.81)	0.01 - 0.41 - 0.90 - 1.58 - 10.90
2004	118 (5.3)	198 (6.8)	1.68 (1.99)	0.07 - 0.46 - 1.01 - 1.87 - 9.35
2005	179 (8.0)	319 (10.9)	1.78 (2.19)	0.03 - 0.53 - 0.97 - 2.02 - 8.91
2006	173 (7.7)	257 (8.8)	1.49 (1.53)	0.00 - 0.46 - 1.06 - 1.72 - 7.99
2007	188 (8.4)	309 (10.6)	1.65 (1.62)	0.03 - 0.52 - 1.00 - 2.19 - 6.80
2008	164 (7.3)	232 (7.9)	1.41 (1.35)	0.00 - 0.52 - 1.05 - 1.84 - 5.99
2009	192 (8.6)	281 (9.6)	1.47 (1.24)	0.02 - 0.55 - 0.95 - 2.19 - 4.82
2010	192 (8.6)	239 (8.2)	1.24 (0.98)	0.01 - 0.50 - 1.00 - 1.56 - 3.94
2011	256 (11.5)	335 (11.5)	1.31 (0.86)	0.02 - 0.53 - 1.21 - 2.07 - 2.98
2012	292 (13.1)	295 (10.1)	1.01 (0.53)	0.02 - 0.53 - 1.12 - 1.43 - 1.99
2013	278 (12.4)	134 (4.6)	0.48 (0.29)	0.00 - 0.22 - 0.46 - 0.74 - 0.99

max = maximum; min = minimum; SD = standard deviation.

Clinical characteristics

The following clinical characteristics were assessed at the time of initial prostate cancer diagnosis unless otherwise stated (Table SD-3). The mean age at diagnosis was 73.1 years (median, 72 years), with 2.0% aged less than 65 years and 3.7% 85 years or older. The majority of patients' tumors (72.5%) were grade 3, 15.9% were grade 1 or 2, 1.0% were grade 4, and 10.6% were of unknown grade. Less than 0.5% of tumors were grade 1, so the categories for grades 1 and 2 were collapsed to prevent reporting a cell count less than 11.

Table SD-3 Clinical characteristics of study cohort (N = 2,234)

Variable	Number of patients[a] (%)
Characteristics at initial prostate cancer diagnosis	
Age, years	
Mean (SD)	73.1 (5.9)
Five-number summary (minimum-Q1-median-Q3-maximum)	58-68-72-77-97
Age group	
< 65	45 (2.0)
65-69	678 (30.3)
70-74	676 (30.3)
75-79	482 (21.6)
80-84	271 (12.1)
85+	82 (3.7)
Year of initial prostate cancer diagnosis	
2000	218 (9.8)
2001	201 (9.0)
2002	225 (10.1)
2003	205 (9.2)
2004	201 (9.0)
2005	183 (8.2)
2006	190 (8.5)
2007	185 (8.3)
2008	174 (7.8)
2009	160 (7.2)
2010	162 (7.3)
2011	130 (5.8)
Grade	
Grade 1 or 2 (well differentiated; moderately or intermediately differentiated; differentiated, NOS)[b]	356 (15.9)
Grade 3 (poorly differentiated)	1,619 (72.5)
Grade 4 (undifferentiated/anaplastic)	23 (1.0)
Not determined	236 (10.6)
Stage (derived group)[c]	
Stage I or II[b]	543 (24.3)
Stage III	107 (4.8)
Stage IV	583 (26.1)
Unknown	1,001 (44.8)
Gleason score	
6 or 7[b]	47 (2.1)
8	79 (3.5)
9	162 (7.3)
10	30 (1.3)
Not collected	986 (44.1)
Not performed	69 (3.1)
Unknown	861 (38.5)
Characteristics on or before cohort entry date	
Comorbidities[d]	
Chronic pulmonary disease	947 (42.4)
Diabetes without chronic complications	920 (41.2)
Peripheral vascular disease	830 (37.2)
Cerebrovascular disease	681 (30.5)
Congestive heart failure	636 (28.5)
Mild liver disease	512 (22.9)

Table SD-4 Treatments (N = 2,234)

Variable	Number of patients (%)
Treatment(s) at initial workup or first course of therapy (from SEER)	
Surgery	
Yes	440 (19.7)
No	1,759 (78.7)
Unknown	35 (1.6)
Radiation	
Yes	750 (33.6)
No	1,418 (63.5)
Unknown	66 (3.0)
Castration method	
Surgical	52 (2.3)
Medical	2,106 (94.3)
Surgical and medical	76 (3.4)
Treatment recorded on or after date of initial diagnosis but before or on cohort entry date (from Medicare)	
Chemotherapy, hormonal therapy, or immunotherapy	2,234 (100.0)
Radiation therapy	1,161 (52.0)
Radiopharmaceuticals (strontium-89 or samarium-153)	30 (1.3)
Treatment recorded after cohort entry date (from Medicare)	
Chemotherapy	2,121 (94.9)
Radiation therapy	725 (32.5)
Radiopharmaceuticals (strontium-89 or samarium-153)	103 (4.6)

SEER = Surveillance, Epidemiology, and End Results program of the US National Cancer Institute.

Results Summary — Primary [and Secondary] Objectives

In the study cohort of 2,234 patients with CRPC identified in SEER-Medicare data, the crude incidence rate of second primary malignancies was 5.9 per 100 person-years (95% CI, 5.0-6.8). The majority of men with CRPC (80.4%) had a history of bone metastases, and 84.5% either had a history of bone metastases or were prescribed a bone-targeting therapy. For most patients in our cohort (89.6%), medical castration was identified by both Part D and non–Part D data. Fewer than 11 of 412 patients were identified *only* in Part D as having castration, which allowed extension of the study period to the years before Medicare Part D was introduced in order to increase the cohort size and the precision of incidence rate estimates. Three-quarters of the patients in the study died during follow-up. Median survival time was 1.18 years (95% CI, 1.12-1.26), and the survival probabilities at 1, 3, and 5 years were 56%, 17%, and 9%, respectively.

Results Summary — Safety

N/A

[Results Summary — Other]

N/A	
Conclusion(s) The incidence of all second primary malignancies among men with CRPC identified in SEER-Medicare data is 5.9 per 100 person-years (95% CI, 5.0-6.8).	
Publication(s):	Kaye JA, Saltus CW, Calingaert B, Harris DH, Hunter S, Zong J, Brobert GP, Soriano-Gabarro M, Andrews EB. Incidence of second primary malignancies (SPM) in men with castration-resistant prostate cancer (CRPC) in SEER-Medicare database. J Clin Oncol 2017;35 (suppl; abstr e13080)
Date Created or Date Last Updated:	5 Jul 2017

Table of Contents

1. Abstract

Title

Incidence of Second Primary Malignancies in Patients With Castration-Resistant Prostate Cancer: An Observational Retrospective Cohort Study in the US

Protocol Version 1, 09 March 2016

[redacted]

Keywords

castration-resistant, oncology, prostate

Rationale and background

Xofigo (radium-223 dichloride) is approved in the United States (US) and the European Union for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases, and no known visceral metastatic disease. Long-term cumulative radiation exposure may be associated with an increased risk of cancer, and Xofigo may contribute to a patient's overall long-term cumulative radiation exposure.

Research question and objectives

The primary objective of this study was to estimate the population-based incidence rate of second primary malignancies among patients with CRPC similar to those treated with Xofigo.

Secondary objectives were to identify the proportion of men with CRPC who had a history of bone metastases, determine the proportion of men who met the definition of castration based solely on receiving androgen deprivation therapy as documented in the Medicare Prescription Drug Event file, and estimate overall survival for men with CRPC.

Study design

This was a retrospective, observational cohort study of men in the US aged 65 years or older with CRPC. There was no internal comparison group for this study.

Setting

The study period was 01 January 2000 through the latest year of available Medicare data (2013). Cohort entry date in this study was defined as the day on which the patient was identified as having CRPC and began follow-up for the occurrence of a second (non-prostatic) cancer. After documentation of castration (either surgical castration or androgen deprivation therapy, i.e., "medical castration") for prostate cancer, the cohort entry date was defined as the date on which the patient first received a therapy representing a second-line systemic treatment for prostate cancer. For each patient, follow-up began on the day after the cohort entry date and continued until the earliest occurrence of death, discontinuation of coverage, claim for Xofigo treatment, or end of the study period.

Follow-up for a second primary cancer began on the day after the cohort entry date and continued until the earlier of end of study follow-up or occurrence of a second primary cancer.

Subjects and study size, including dropouts

The study cohort included men aged 65 years or older who were enrolled in both Medicare Parts A and B for at least 1 year before the cohort entry date and continuously between the date of initial diagnosis of prostate cancer and the cohort entry date, had a primary site code of prostate cancer, underwent surgical castration or received androgen deprivation therapy after prostate cancer diagnosis, and had evidence that the prostate cancer was resistant to surgical castration or androgen deprivation therapy.

Excluded were men who were enrolled in an HMO during the year before cohort entry, had a diagnosis of any other cancer (except melanoma) on or before the cohort entry date, had any diagnostic code for metastases (other than bone or lymph node metastases) on or before the cohort entry date, had any claim for treatment with radium Ra-223 on or before the cohort entry date, or had a claim for any second-line systemic therapy on or before the earliest date of surgical castration or androgen deprivation therapy.

All patients who met study eligibility criteria were included in the final study cohort of 2,234 patients.

Variables and data sources

The SEER-Medicare linked database administered by the US National Cancer Institute (NCI) was the source of data for this study.

The following variables were assessed: age, race, surgical castration, medical castration, time from initial diagnosis to development of CRPC, stage, grade, Gleason score, Charlson comorbidity index, history of bone or lymph node metastasis, history of bone-directed therapy, injectables, and treatments (surgery, radiation, chemotherapy), second primary cancer event and date, history of bone metastases, occurrence and date of death.

Results

NCI supplied data on 564,491 individuals diagnosed with prostate cancer since the year 2000. Applying the inclusion and exclusion criteria resulted in a final cohort of 2,234 patients. The great majority of patients in the study cohort (80.4%) had a history of bone metastases recorded in their Medicare claims data.

SEER data and Medicare claims data identified 172 cases of second primary malignancies, yielding a crude incidence rate of 5.9 per 100 person-years (95% CI, 5.0-6.8). The incidence rate standardized to the age distribution of the REASSURE study population (5.8 per 100 person-years; 95% CI, 4.9-6.7) was similar to the crude incidence rate. The most common cancers were lung/bronchus (n = 29), urinary bladder (n = 22), colon/rectum (n = 21), non-prostate, non-bladder genitourinary tract (n = 18), and non-colorectal gastrointestinal (n = 17). When limited to the 1,797 patients with bone metastases, the incidence was 5.6 per 100 (95% CI, 4.6-6.7).

Among the 172 patients with CRPC who developed a second primary cancer, the mean time between meeting the study definition of incident CRPC and a diagnosis of the second cancer was 1.0 year.

Three-quarters of the patients in the study died during follow-up. The median survival time after cohort entry for the 2,234 patients was 1.18 years (95% CI, 1.12-1.26), and the survival probabilities at 1, 3, and 5 years were 56%, 17%, and 9%, respectively.

Discussion

This study provides more precise estimates of second primary malignancy risks in older men with CRPC than other available US data resources. Several cancers that occur with relatively high incidence in the general population (e.g., lung/bronchus and colorectal cancers) also occurred relatively commonly in the study population. Restriction to patients with documented bone metastases had little effect on the observed incidence of second primary malignancies. The frequency of bladder and other genitourinary cancers in this study suggests the possibility that local spread of advanced prostate cancer may in some instances be diagnosed as a second primary malignancy. Overall, the prognosis of patients with CRPC is poor.

Marketing Authorization Holder(s)

Names and affiliations of principal investigators

2. List of abbreviations

AJCC	American Joint Committee on Cancer
BIPS	Leibniz Institute for Prevention Research and Epidemiology – BIPS (Germany)
CI	Confidence Interval
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
CRPC	Castration-Resistant Prostate Cancer
CS SSF	Collaborative Stage Site-Specific Factor
DME	Durable Medical Equipment
EU PAS register	European Union electronic register of postauthorization studies
GePaRD	German Pharmacoepidemiological Research Database
HCPCS	Healthcare Common Procedure Coding System
HMO	Health Maintenance Organization
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
ICD-O-3	*International Classification of Diseases for Oncology, Third Edition*
MEDPAR	Medicare Provider Analysis and Review (file)
NCI	National Cancer Institute
PEDSF	Patient Entitlement and Diagnosis Summary File
RTI-HS	RTI Health Solutions
SAP	Statistical Analysis Plan
SEER	Surveillance, Epidemiology, and End Results (program of the United States National Cancer Institute)
US	United States

3. Investigator

[redacted]

4. Other responsible parties

N/A

5. Milestones

The SEER*-Medicare data used in this study were collected from 01 January 2000 through 30 June 2016. In the phase 1 analysis, estimated crude incidence rates for all second primary cancers combined were estimated. In the phase 2 analysis, the incidence rates for selected specific second primary cancers were estimated, and incidence rates were standardized to the age distribution of the REASSURE interim analysis population. The study was not a post-authorization safety study (PASS), but was registered in the EU PAS register, an electronic register of post-authorization studies maintained by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), registration number: EUPAS13602.

Table 1 Milestones

Milestone	Planned date	Actual date	Comments
Start of SEER-Medicare data	01 January 2006	01 January 2000	None
End of SEER-Medicare data	30 June 2016	30 June 2016	None
Report of phase 1 analysis	11 Oct 2016	11 Oct 2016	None
Final report with all analyses	Q1 2017	15 Mar 2017	

Q*n* = quarter of a calendar year; SEER = Surveillance, Epidemiology, and End Results (program of the United States National Cancer Institute).

6. Rationale and background

Xofigo (radium-223 dichloride) is approved in the United States (US) and the European Union for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases, and no known visceral metastatic disease. Long-term cumulative radiation exposure may be associated with an increased risk of cancer [1], and Xofigo may contribute to a patient's overall long-term cumulative radiation exposure. While nonclinical studies of Xofigo in rats showed an increased risk of neoplasms, no cases of Xofigo-induced cancer have been reported in clinical trials in follow-up of up to 3 years [2]. However, as noted in the Food and Drug Administration product information for Xofigo, the expected latency period for the development of secondary malignancies exceeds the duration of follow-up available in clinical trials [3].

* SEER = Surveillance, Epidemiology, and End Results (program of the United States National Cancer Institute).

As a postmarketing requirement, Bayer is conducting a single-arm, non-interventional, prospective cohort study, "REASSURE—Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation," also known as "Observational Study for the Evaluation of Long-term Safety of Radium-223 used for the Treatment of Metastatic Castration Resistant Prostate Cancer (REASSURE)," which is registered at ClinicalTrials.gov (number NCT02141438). This study will evaluate the long-term safety profile of Xofigo, including the incidence of second primary malignancies in patients with CRPC receiving Xofigo in routine clinical practice settings. For additional perspective on incidence rates to be estimated in the REASSURE study, Bayer requires population-based estimates of the background rates of second primary malignancies among patients with CRPC similar to those who are treated with Xofigo. The SEER*-Medicare linked database is a suitable data resource for providing such estimates. The present study provides this perspective for an entire program of observational studies using population-based databases (described below) and the REASSURE study .

Following a feasibility assessment by Bayer of appropriate external secondary data sources, an epidemiology program has been established that consists of three observational studies using population-based databases in Europe (Germany and Sweden) and the US. The study in Germany is planned to be performed using the German Pharmacoepidemiological Research Database (GePaRD) via the Leibniz Institute for Prevention Research and Epidemiology – BIPS (BIPS). The study in Sweden will be conducted using the Swedish Prostate Cancer Database (PCBaSe). The present report describes the US component of this epidemiology program.

7. Research question and objectives

The primary objective of this study was to estimate the population-based incidence rate of second primary malignancies among patients with CRPC similar to those treated with Xofigo. This rate will provide context for incidence rates of second primary malignancies from the REASSURE study.

RTI Health Solutions (RTI-HS) analyzed the collective incidence rate of all second primary malignancies (other than non-melanoma skin cancer), as well as the individual incidence rates of selected specific second primary malignancies, among men with CRPC similar to those treated with Xofigo. The selection of the specific malignancies to evaluate was initially to be determined in collaboration with Bayer based on findings from the REASSURE study; however, the selection was ultimately driven by the number of cases of various cancers in the present study and reporting limits set by the SEER-Medicare Data Use Agreement. Per the data use agreement, no cell counts less than 11 can be reported; thus, specific malignancies selected had to have at least 11 occurrences. The agreement also prohibited provision of information from which a cell count less than 11 could be calculated. Therefore, in order to provide as much information as possible, some specific malignancies that occurred at lower frequency were grouped together, and results are presented for the groups of malignancies.

Secondary objectives were as follows:

- Identify the proportion of men with CRPC who had a history of bone metastases, as documented by the use of diagnostic codes and/or treatment or prescription codes for bone-directed therapies in Medicare data.

* SEER = Surveillance, Epidemiology, and End Results (program of the United States National Cancer Institute).

- Among cohort patients who were continuously enrolled in Medicare Part D for the entire period between the initial diagnosis of prostate cancer and the cohort entry date, determine the proportion who met the definition of castration based solely on receiving androgen deprivation therapy as documented in the Prescription Drug Event data file (i.e., would not have met the castration definition and been included in the study cohort if Part D data were not available).[*]

- Estimate the overall survival function of men with CRPC.

8. Amendments and updates

None.

9. Research methods

9.1 Study design

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* of the International Society for Pharmacoepidemiology (ISPE) [4].

This was a retrospective, observational cohort study of men in the US aged 65 years or older with CRPC. The study definition of CRPC required that patients had a diagnosis of prostate cancer in SEER data and received medical androgen deprivation therapy or surgical castration as documented in Medicare data. Additionally, after surgical castration or initiation of medical castration, evidence of treatment with a second-line systemic therapy (other than Xofigo) in Medicare data was required.

There was no internal comparison group for this study, although the cancer incidence rates estimated in the present study may be used to provide perspective on cancer incidence rates found in the REASSURE study. Medical claims data from Medicare and cancer information from SEER were used to identify occurrence of second primary cancer subsequent to the date that patients met the CRPC definition. Note, patients who had any non-prostatic cancer any time before they met the CRPC criteria were excluded from the study cohort.

9.2 Setting

9.2.1 Study time frame

- *Time windows:* The study period was 01 January 2000 through the latest year of available Medicare data (2013). Note that SEER data, which was used to identify the initial diagnosis of prostate cancer, were available only through 2011.

- *Cohort entry date:* The cohort entry date in this study was defined as the day on which the patient was identified as having CRPC and began follow-up for the occurrence of a second (non-prostatic) cancer. After documentation of castration (either surgical castration or androgen deprivation therapy, i.e., "medical castration") for prostate cancer, the cohort entry

[*] This secondary objective has been modified from its wording in the protocol, which misstated the intended distinction between Part D prescription data (as oral medications) and procedure code data (as parenteral medications). In fact, some medications administered by both routes are contained in each of the data files.

date was defined as the date on which the patient first received a therapy representing a second-line systemic treatment for prostate cancer.

Follow-up: For each patient in the study cohort, follow-up began on the day after the cohort entry date and continued until the earliest occurrence of one of the following events:

- Death
- Discontinuation of Medicare Part A or Part B coverage or enrollment in a health maintenance organization (HMO), as people enrolled in an HMO do not have details from Medicare claims
- Claim for treatment with Xofigo
- End of study period (31 December 2013)
- *Follow-up for a second primary cancer* began on the day after the cohort entry date and continued until the earlier of end of study follow-up or occurrence of a second primary cancer.

9.2.2 Selection criteria

Inclusion criteria: The study cohort included men who met *all* of the following criteria:

- Enrolled in both Medicare Parts A and B for at least 1 year before the cohort entry date (minimum lookback period for comorbidities and treatments) and continuously between the date of initial diagnosis of prostate cancer and the cohort entry date.
- Had a primary site code of prostate cancer (ICD-O-3* topography code C61.9) in SEER data with behavior code "/3" (malignant).
- Underwent surgical castration (see statistical analysis plan [SAP] Section 6.1.3) or received androgen deprivation therapy after prostate cancer diagnosis. Androgen deprivation therapy is indicated by the use of any of the following drugs: abarelix, bicalutamide, buserelin, cyproterone, degarelix, diethylstilbestrol, estramustine, flutamide, gonadorelin, goserelin, histrelin, leuprolide, medroxyprogesterone, megestrol, nafarelin, nilutamide, polyestradiol, triptorelin.
- Had evidence that the prostate cancer was resistant to surgical castration or androgen deprivation therapy, as indicated by starting one of the following second-line systemic therapies: abiraterone, cabazitaxel, docetaxel, enzalutamide, mitoxantrone, or sipuleucel-T.
- Aged 65 years or older on the cohort entry date.

Exclusion criteria: Men who met *any* of the following exclusion criteria were excluded from the study cohort:

- Enrollment in an HMO in the year before the cohort entry date or at any time between the diagnosis date of the initial prostate cancer identified in SEER and the cohort entry date.
- Diagnosis of any cancer other than prostate cancer or non-melanoma skin cancer on or before the cohort entry date. All of the ICD-9-CM* codes that were used to identify

* ICD-O-3 = *International Classification of Diseases for Oncology, Third Edition*.

exclusions in any of the Medicare files are listed in the SAP in Appendix A; in SEER, exclusions were identified by any cancer site other than prostate in combination with a behavior code indicating that the neoplasm was malignant ("/3").

- Any diagnostic code for metastases other than bone metastases or lymph node metastases on or before the cohort entry date. The applicable ICD-9-CM codes were all codes in categories 197 (secondary malignant neoplasm of respiratory and digestive systems) or 198 (secondary malignant neoplasm of other specified sites) except for 198.2 (secondary malignant neoplasm of skin) and 198.5 (secondary malignant neoplasm of bone and bone marrow).
- Any claim for treatment with radium Ra-223 (Xofigo), identified by HCPCS code A9609, on or before the cohort entry date. [Note: HCPCS code A9606 was assigned to Xofigo on 01 January 2015; before this, Xofigo did not have a specific code and was recorded with a general code, C9399 (Unclassified drugs or biologicals).]
- A claim for any of the second-line systemic therapies (abiraterone, cabazitaxel, docetaxel, enzalutamide, mitoxantrone, or sipuleucel-T) on or before the earliest date of surgical castration or androgen deprivation therapy.

9.2.3 Study population

9.2.3.1 Source

The SEER-Medicare linked database administered by the US National Cancer Institute (NCI) was the source of data for this study. This database combines data from the SEER Program of the US NCI, which collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 30% of the US population [5], and data from Medicare, the US federal health insurance program primarily for people who are aged 65 years or older. The SEER Program collects detailed information for each primary cancer and individual, including the initial diagnosis, first course of treatment, and date of death. The SEER-Medicare data linkage began in 1991 and currently is updated every 2 years. At the time of the most recent update, which was used for this study, the linked database included all Medicare-eligible persons appearing in the SEER data who were diagnosed with cancer through 2011 and all of their available Medicare claims through 2013.

The term "SEER-Medicare data" actually refers to a series of files: one file contains SEER data, while the other files contain Medicare data for specific types of services (e.g., hospital, physician, or outpatient visits). Patient data are linked across the various files using the unique SEER case identification number, an eight-digit case number plus a two-digit cancer registry identification, which, when combined, uniquely identify individuals [6].

The SEER data released as part of the SEER-Medicare linked file are in a customized file known as the Patient Entitlement and Diagnosis Summary File (PEDSF). The PEDSF contains one record per person for individuals in the SEER database who have been matched with Medicare enrollment records. This file contains basic demographic information, death date (when relevant), Medicare eligibility and enrollment dates, and an array of detailed diagnostic information including date of diagnosis, ICD-O-3 site/histology codes, grade, and stage for up to 10 diagnosed primary cancers for each patient.

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[*] ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*.

The Medicare files included in the SEER-Medicare linked database include the following:

- The *inpatient* file (Medicare Provider Analysis and Review [MEDPAR] file) includes all Part A short and long hospital stays and skilled nursing facility stays for each calendar year. The file contains one summarized record per admission, and each record includes up to 25 ICD-9-CM diagnoses and 25 ICD-9-CM procedures provided during the stay.
- The *physician* file (also known as the Physician/Supplier Part B or the Carrier file) contains Part B claims submitted by non-institutional providers, such as physicians, physician assistants, clinical social workers, and nurse practitioners. Claims for other providers, such as free-standing facilities, are also found in the Carrier file. These claims include a principal diagnosis code along with up to 25 additional diagnosis codes, all using ICD-9-CM diagnosis codes. Each claim can also have a procedure code, coded with the Healthcare Common Procedure Coding System (HCPCS). HCPCS codes consist of three types: level I comprises CPT 4 (Current Procedural Terminology, version 4) codes, while levels II and III are used exclusively by the Centers for Medicare and Medicaid Services (CMS) and begin with a letter.
- The *outpatient* file contains all of the Part B claims submitted by institutional outpatient facilities. Each claim includes up to 25 ICD-9-CM diagnosis codes and up to 13 ICD-9-CM procedure codes and 1 HCPCS procedure code.
- The *Home Health Agency* file contains all of the claims for home health services. Each claim contains up to 25 ICD-9-CM diagnosis codes and an HCPCS procedure code.
- The *Hospice* file contains claims submitted by hospice providers. Each claim contains up to 25 ICD-9-CM diagnosis codes and an HCPCS procedure code.
- The *Durable Medical Equipment (DME)* file contains claims submitted by Durable Medical Equipment Regional Carriers. Oral chemotherapeutic agents that are equivalent to intravenous chemotherapies are sometimes captured in the DME file; these are coded with 11-digit National Drug Codes. Additional chemotherapy treatments are found coded with HCPCS J codes in the DME file.
- The *Medicare Part D Enrollment* file contains variables for each year beginning in 2007 to indicate which Medicare beneficiaries are enrolled in Part D (prescription drug coverage) and the dates of coverage.
- The *Prescription Drug Event* file contains information regarding prescription drug utilization. Drugs are recorded within each claim by both brand and generic name.

9.2.3.2 Sampling strategy

The SEER-Medicare data supplied by NCI for this study comprised all records of patients with a SEER diagnosis of prostate cancer between 2000 and 2011. No sampling was applied. All patients who met the eligibility criteria described in Section 9.2.2 were included in the study.

Although patients with pre-existing cancers (other than prostate cancer) are eligible for the REASSURE study, such patients were excluded from the present study (other than those with pre-existing non-melanoma skin cancers) because diagnostic codes related to a pre-existing cancer could have falsely indicated the detection of a “new” malignancy after cohort entry in such patients (for

example, a diagnostic code for "lung cancer" might be recorded when a previously diagnosed rectal cancer metastasizes to the lungs).

9.2.3.3 Representativeness

The SEER-Medicare database population is representative of the general US population, and this database is the largest available source of detailed population-based medical information on men aged 65 years or older with prostate cancer, representing nearly 30% of the US population in this age range. Therefore, this study should provide more precise estimates of second primary malignancy risks in men with CRPC than any other available US data resource. Black males, for whom prostate cancer incidence and mortality rates are higher than for white males in the US, may form a higher proportion of the present study population than of the population in the REASSURE study and we considered adjustment for race (as well as age). Ultimately, after consultation with Bayer, this was deemed not to be necessary as blacks made up less than 10% of the population in the current study and also represent only a small proportion of patients in the REASSURE study.

9.3 Subjects

Please see Section 9.2.2.

9.4 Variables

9.4.1 Patient characteristics

The following demographic characteristics were assessed on or before the cohort entry date and were ascertained from Medicare data:

- Age at cohort entry
- Race: levels were white, black, Asian, Hispanic, other, unknown
- Surgical castration: Indicator variable that patient had been surgically castrated. This was identified by the occurrence of *any* of the following codes in the Medicare data:
    - ICD-9-CM codes 62.41 (removal of both testes at the same operative episode) or 62.42 (removal of remaining testis)
    - CPT/HCPCS code: any of the following codes in conjunction with modifier = 50 (bilateral):
        - 54520: orchiectomy, simple (including subcapsular), with or without testicular prosthesis, scrotal, or inguinal approach
        - 54522: orchiectomy, partial
        - 54690: laparoscopic surgical orchiectomy
        - 56318: laparoscopic surgical orchiectomy (obsolete code as of 2000, replaced by code 54690)
        - 54530: radical inguinal orchiectomy, for tumor
        - 54535: radical inguinal orchiectomy, for tumor, with abdominal exploration
- Medical castration: Indicator variable that the patient had received medical castration. This was identified by the occurrence of specific drug names in Part D data (i.e., abarelix, bicalutamide, buserelin, cyproterone, degarelix, diethylstilbestrol, estramustine, flutamide,

gonadorelin, goserelin, histrelin, leuprolide, medroxyprogesterone, megestrol, nafarelin, nilutamide, polyestradiol, triptorelin) or corresponding HCPCS codes (SAP Appendix C) in any of the other Medicare files. Ketoconazole was not included in this list of drugs because it is rarely used for androgen deprivation therapy in the US, where it is used more commonly as an antifungal agent.

- Evidence that the prostate cancer was resistant to surgical castration or androgen deprivation therapy, as indicated by starting one of the following second-line systemic therapies: abiraterone, cabazitaxel, docetaxel, enzalutamide, mitoxantrone, or sipuleucel-T.
- Time (days) from initial diagnosis of prostate cancer to development of CRPC: This was calculated by subtracting the date of diagnosis from the cohort entry date.

9.4.2 Clinical characteristics

The following clinical characteristics were assessed on or before the cohort entry date unless otherwise specified:

- Stage of prostate cancer at initial diagnosis (from SEER), as defined by the *AJCC Cancer Staging Manual, Sixth Edition* [7].
- Grade of prostate cancer at initial diagnosis (from SEER).
- Gleason score at initial diagnosis, from SEER: collaborative stage site-specific factor (CS SSF) 10 (Gleason's score on prostatectomy/autopsy), if available; otherwise CS SSF 8 (Gleason's score on needle core biopsy/transurethral resection of prostate), if available.

9.4.3 Comorbidities

- An indicator variable was created to identify a history of each of the following comorbidities (Charlson comorbidity index categories) based on having any record with the corresponding ICD-9-CM code(s) listed below appearing in the Medicare records for the patient at any time on or before the cohort entry date [8]:
  - Myocardial infarction (410, 412)
  - Congestive heart failure (398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428)
  - Peripheral vascular disease (093.0, 437.3, 440, 441, 443.1-443.9, 447.1, 557.1, 557.9, V43.4)
  - Cerebrovascular disease (362.34, 430-438)
  - Dementia (290, 294.1, 331.2)
  - Chronic pulmonary disease (416.8, 416.9, 490-505, 506.4, 508.1, 508.8)
  - Connective tissue disease or rheumatic disease (446.5, 710.0-710.4, 714.0-714.2, 714.8, 725)
  - Peptic ulcer disease (531-534)
  - Mild liver disease (070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570, 571, 573.3, 573.4, 573.8, 573.9, V42.7)
  - Diabetes without chronic complications (250.0-250.3, 250.8, 250.9)

- Diabetes with chronic complications (250.4-250.7)
- Paraplegia and hemiplegia (334.1, 342, 343, 344.0-344.6, 344.9)
- Renal disease (403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582, 583.0-583.7, 585, 586, 588.0, V42.0, V45.1, V56)
- Moderate or severe liver disease (456.0-456.2, 572.2-572.4, 572.8)
- HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome) (042-044)

- History of lymph node metastasis: indicator variable that patient had a record with an ICD-9-CM diagnosis code starting with 196 recorded at some point between the initial prostate cancer diagnosis date and 30 days after cohort entry
- History of bone metastasis: indicator variable that patient had a record with an ICD-9-CM diagnosis code of 198.5 recorded at some point between the initial prostate cancer diagnosis date and 30 days after cohort entry
- History of bone-directed therapy (proxy for bone metastases diagnosis): indicator variable that patient had a record with one of the specific drug names listed below or with one of the corresponding HCPCS codes (SAP Appendix C) recorded at some point between the initial prostate cancer diagnosis date and 30 days after cohort entry.
  - Injectables: denosumab (Prolia and Xgeva), etidronate (Didronel), ibandronate sodium (Boniva), pamidronate (APD, Aredia), zoledronic acid (Reclast and Zometa)
  - Non-injectable bisphosphonates (no HCPCS codes): clodronate (Bonefos, Loron), tiludronate (Skelid), neridronate (Nerixia), olpadronate, alendronate (Fosamax), risedronate (Actonel)

9.4.4 Treatments

- Treatments at the time of the initial prostate cancer diagnosis or during the first course of therapy (from SEER):
  - Surgery: Yes, No, or Unknown
  - Radiation: Yes, No, or Unknown
- Other treatments for prostate cancer (from Medicare):
  - Chemotherapy: indicator variable, received chemotherapy, identified by
    - HCPCS code or drug name:
      - HCPCS codes (SAP, Appendix E)
      - Specific drug name for Part D and DME file (SAP Appendix E)
    - Administration code:
      - ICD-9-CM diagnosis codes V58.1, V58.11
      - ICD-9-CM procedure code 99.25
      - HCPCS codes 964xx, 96400-96549, 51720, Q0083-Q0085

- Radiation therapy: indicator variable received radiation therapy, identified by
  - ICD-9-CM diagnosis codes V58.0, V66.1, V67.1
  - ICD-9-CM procedure codes 92.2x
  - HCPCS codes 77401-77499, 77520, 77523, 77750-77799, G0256, G0261
- Radiopharmaceuticals (strontium-89 or samarium-153): indicator variable received radiopharmaceuticals, identified by
  - HCPCS codes A9600, A9604, A9605
  - Specific name in Part D records

Note, two sets of indicator variables for chemotherapy, radiation therapy, and radiopharmaceuticals were created: one to indicate if treatment was recorded on or after the prostate cancer diagnosis date but before or on the cohort entry date, and one to indicate if treatment was recorded after the cohort entry date but before the end of follow-up.

9.5 Primary outcome variables

Second Primary Cancer Event: indicator variable that patient was diagnosed with a second primary cancer during follow-up. This was ascertained using both SEER data and Medicare data.

- In SEER data, second primary cancer events were identified when there was a diagnosis of a primary cancer other than prostate after cohort entry.
- In Medicare data, second primary cancer events were identified by searching the hospital inpatient, hospital outpatient, and physician files, for primary cancer ICD-9-CM codes for a primary malignancy other than non-melanoma skin cancer or prostate cancer (see SAP Appendix A) associated with encounters that occurred after the date of the initial prostate cancer diagnosis. [Note: Any such diagnosis that occurred before a patient was determined to have CRPC excluded the patient from the study cohort.]
  - In the inpatient file, the first such diagnosis occurring after the date of cohort entry was counted as a second cancer event.
  - In the outpatient file and the physician file, second cancers were identified when a patient had two codes for the cancer occurring on different dates, both after the date of cohort entry and before the end of follow-up.
  - Note: Medicare data are insurance claims, and diagnoses are recorded using ICD-9-CM diagnosis codes. These codes specify whether a cancer diagnosis is a primary cancer or metastatic cancer; if used accurately, these codes will also distinguish primary cancers (whether first or subsequent) from metastases.
  - Note: this strategy of using one inpatient or two outpatient or physician claims is consistent with methodology used by the CMS Chronic Conditions Data Warehouse when it creates the chronic condition variables distributed to researchers [9].

Second Primary Cancer Date: Date that the patient was diagnosed with a second primary cancer during follow-up. For cancers identified in the inpatient file, this was the date of the claim. For cancers identified in the outpatient file or the physician file, this is the date of the first claim of the two with the cancer code. When a second primary was identified in both SEER and Medicare and the dates did not match, the SEER date was used.

9.6 Variables for secondary analyses

- *History of Bone Metastases at Cohort Entry*: indicator variable that the patient met the definition for either history of bone metastasis or history of bone-directed therapy (defined in Section 9.4.3).
- *Castration Based Solely on Part D Data*: indicator variable that the patient met the definition of castration based solely on receiving oral androgen deprivation therapy as documented in the Part D data file.
- *Death*: indicator variable to identify fact of death.
- *Date of Death*: the Medicare death date, if there is one; if not, and there is a SEER death date, then Date of Death is the SEER death date.

9.7 Data sources and measurement

The SEER Program of the NCI is an authoritative source of information on cancer incidence and survival in the US. SEER currently collects and publishes incidence and survival data from population-based cancer registries covering approximately 30% of the US population. SEER is the only comprehensive source of population-based information in the US that includes stage of cancer at the time of diagnosis and patient survival data. Quality improvement has been an integral part of SEER Program activities since its inception in 1973. The quality improvement process is dedicated to improving data quality by performing rigorous quality-control studies and various data assessments [10].

Medicare, which is administrated by CMS, is a US federal health insurance program primarily for people who are aged 65 years or older. The health services utilization, or "claims," data that are included in the Medicare administrative files are derived from reimbursement data used for billing purposes. Therefore, it is expected that information needed to pay the bill, such as procedure codes, medication data, and demographics, will be reasonably accurate and nearly complete. Data files are available in a relatively short time following the end of a calendar year, with utilization files being at least 98% complete by June of the following year [11].

9.8 Bias

According to the published literature, approximately 10% of patients with metastatic prostate cancer do not have bone metastasis [12,13], which is a potential source of selection bias in our study since the aim here is to emulate as closely as possible the clinical status of the REASSURE population (all of whom presumably have bone metastases). As a secondary objective, we estimated the proportion of men in our study who met the operational definition of CRPC and had a diagnostic code recorded for bone metastases and/or evidence of treatment with bone-directed therapies and found that about 80% fell into this category. This supports the warning from the SEER-Medicare data holder that capture of information on cancer metastases is likely incomplete or underrecorded in this data source.

Per our SEER-Medicare Data Use Agreement, we cannot report values less than 11, which is a limitation when counts and rates of individual cancer types are small. This issue led us to combine several cancer types into categories, some of which are only partially justifiable by clinical considerations.

A minor limitation of the SEER data is that for the patients who move outside of the SEER region after diagnosis of their first primary cancer, we will be able to capture second or subsequent primary cancers only in the Medicare claims data. The same is true for cancers diagnosed after the end of the available SEER data but before the end of the available Medicare data. This is a potential source of information bias.

9.9 Study size

No study size calculations were performed. All patients who met study eligibility were included in the study cohort.

9.10 Data transformation

Age at cohort entry was transformed into categories to match the categories in the REASSURE interim analysis.

9.11 Statistical methods

9.11.1 Main summary measures

Descriptive analyses of the data were performed using summary statistics for continuous and categorical data. Continuous data were described by the number of non-missing values, mean and standard deviation, median, quartiles, and ranges. Selected continuous variables were categorized in a clinically meaningful way. Tables with frequencies and percentages were generated for categorical data, but due to SEER restrictions, data were suppressed or categories were combined to avoid reporting any cell counts less than 11, as required by the SEER-Medicare Data Use Agreement.

9.11.2 Main statistical methods

9.11.2.1 Handling of loss to follow-up and premature discontinuation

As there is no study treatment, premature discontinuation is not an issue for this study. If during follow-up patients disenrolled in either Medicare Part A or Part B or enrolled in an HMO, then some or all of their medical claims data might be missing from that point forward; thus, they were censored on that date for the survival analyses and they did not contribute any additional follow-up time or events for incidence rate calculations.

9.11.2.2 Primary outcome

9.11.2.2.1 Incidence rates of second primary cancers

Crude incidence rate estimates were calculated by dividing the count of patients in the study cohort who had a second primary cancer by the person-years at risk among all patients and multiplying by 100 to express rates per 100 person-years. Because there were so few second primary malignancies, we report rates to two significant digits to avoid the appearance of more precision than the data provide. Adjusted incidence rates were calculated through direct standardization to the age distribution of the interim analysis population of the REASSURE study aged 65 years or older at entry, using the five age categories 65-69, 70-74, 75-79, 80-84, > 85 years.

Because events were rare, the Poisson distribution was used to estimates 95% confidence intervals (CIs) for the crude rates, and the gamma method [14] was used to estimate CIs for standardized rates.

9.11.2.3 Secondary outcomes

9.11.2.3.1 Proportion with a history of bone metastasis at cohort entry

The proportion of patients with a history of bone metastasis at cohort entry was calculated by dividing the number of patients with bone metastasis (identified by diagnosis code) or bone-directed treatment (identified by a drug or treatment code) by the total number of patients in the study population.

9.11.2.3.2 Proportion who met the definition of castration based solely on Part D data

This analysis was limited to patients who were continuously enrolled in Medicare Part D for the entire period between their initial diagnosis of prostate cancer and their cohort entry date. In this subset, we divided the number of patients who met the definition of castration based solely on receiving androgen deprivation therapy as documented in the Prescription Drug Event data file by the total count of patients.

9.11.2.3.3 Overall survival

For all patients with CRPC, Kaplan-Meier methods were used to calculate the survival function. Plots of the survival function along with tables showing 1-, 3-, and 5-year overall survival rates and 95% CIs are presented. Survival time was measured from the date of diagnosis of CRPC to death. Patients who did not die before the end of follow-up were censored on the last day of the study period.

9.11.2.3.4 Missing values

Missing data were treated as missing. For indicator variables (e.g., presence or absence of a characteristic), if the patient was not recorded as having a given characteristic, the characteristic was assumed in the analysis not to be present in that patient. There was no ability to query to resolve missing values in the SEER-Medicare data, and no data imputations were performed. Counts of missingness were reported when summarizing categorical variables, and relative frequencies were based on all patients, including those with missing values.

9.11.3 Sensitivity analyses

Because the reliability of Medicare claims data to identify second primary cancer outcomes in men with CRPC is uncertain, sensitivity analyses were conducted to assess the effect on the estimated incidence rates of not including second primary cancer events that were identified only in Medicare data.

9.11.4 Amendments to the statistical analysis plan

Our originally planned study cohort included all patients from SEER-Medicare with a prostate cancer diagnosis between 2006 and 2011. The start date was selected based on the introduction of Medicare Part D in January 2006. However, due to there being a limited number of eligible patients in the originally planned study period, and because we found that few patients were identified as having medical castration on the basis of Medicare Part D data only, we extended the study period to precede the introduction of Medicare Part D. Therefore, in the analyses presented here, men with prostate cancer diagnosed from 2000 to 2011 were included if they met all other eligibility criteria.

9.12 Quality control

All analyses were performed using SAS 9.3 (or higher) statistical software (SAS Institute, Inc., Cary, North Carolina). Programs, logs, and output were reviewed for accuracy according to relevant RTI-HS standard operating procedures. A second programmer reviewed all programs and, in most cases, independently wrote code to reproduce the results generated from the initial programs.

10. Results

10.1 Participants

In response to the study data request for all patients in SEER-Medicare data who had been diagnosed with prostate cancer since the year 2000, NCI supplied data on 564,491 individuals. To limit the study population to patients with CRPC, we eliminated 383,713 with no evidence of either surgical castration or medical castration (androgen deprivation therapy), 376 who either were surgically castrated or started medical castration on or before prostate cancer diagnosis date and 168,388 with no history of second-line therapy after the surgical castration date or start of medical castration, leaving 12,014 patients. Applying the exclusion criteria sequentially led to the exclusion of the following numbers of patients for each criterion:

- Had a diagnosis of any cancer other than prostate cancer or non-melanoma skin cancer on or before the potential cohort entry date (n = 5,543)
- Had exclusionary metastases on or before the potential cohort entry date (n = 1,767)
- Was not aged at least 65 years on the potential cohort entry date (n = 246)
- Did not meet both Parts A and B Medicare enrollment criteria (n = 1,293) or HMO enrollment criteria (n = 931)

The patient selection process described above resulted in a final study cohort of 2,234 patients (Table 2).

Table 2 Cohort selection

Reason for exclusion	No. of patients (%)	Remaining sample
Initial sample of prostate cancer cases from SEER-Medicare	564,491 (100)	564,491
Had no record of surgical or biologic castration	383,713 (67.98)	180,778
Had no record of second-line systemic therapy[a] after the castration date	168,388 (29.83)	12,390
Castration was on or before the prostate cancer diagnosis date	376 (0.07)	12,014
Had a diagnosis of any cancer other than prostate cancer or non-melanoma skin cancer on or before the potential cohort entry date	5,543 (0.98)	6,471
Had a diagnostic code for exclusionary metastases (197X or 198X with exception of 198.2-skin or 198.5-bone) on or before the potential cohort entry date	1,767 (0.31)	4,704
Was not aged at least 65 years on the potential cohort entry date	246 (0.04)	4,458
Was not continuously enrolled in both Parts A and B Medicare coverage between the earlier of (1) 12 months before cohort entry or (2) the month of prostate cancer diagnosis and the cohort entry date	1,293 (0.23)	3,165
Was enrolled in an HMO either (1) in the year before the potential cohort entry date or (2) at some time between the diagnosis date of the initial prostate cancer identified in SEER and the potential cohort entry date	931 (0.16)	2,234
Had any claim for treatment with Xofigo (radium-223 dichloride) on or before the potential cohort entry date	0 (0.00)	2,234

HMO = health maintenance organization; SEER = Surveillance, Epidemiology, and End Results program of the United States National Cancer Institute.

[a] Abiraterone, cabazitaxel, docetaxel, enzalutamide, mitoxantrone, or sipuleucel-T.

10.2 Descriptive data

10.2.1 Demographics

The study cohort was primarily white (83.6%), with the remainder black (9.8%), Asian (2.1%), Hispanic (2.1%), and other or unknown (2.5%) (patients with unknown race made up less than 0.5% of the cohort.) The mean age at cohort entry was 76.6 years (median, 76 years), with 74.8% of patients aged 70 to 84 years, 13.3% aged 65 to 69 years, and 11.9% aged 85 or more years (Table 3).

Table 3 Demographic characteristics of study cohort (N = 2,234)

Variable	No. of patients (%)
Race	
White	1,867 (83.6)
Black	218 (9.8)
Asian	46 (2.1)
Hispanic	48 (2.1)
Other or unknown[a]	55 (2.5)
Age at cohort entry, years	
Mean (SD)	76.6 (6.2)
5 number summary (minimum-Q1-median-Q3-maximum)	65-72-76-81-100
Age group	
65-69	297 (13.3)
70-74	625 (28.0)

Variable	No. of patients (%)
75-79	595 (26.6)
80-84	451 (20.2)
85+	266 (11.9)

Q1 = first quartile, Q3 = third quartile; SD = standard deviation.
[a] Categories were combined to avoid reporting a count of < 11.

The numbers and percentages of patients and follow-up time are stratified by year of cohort entry in Table 4. Year of cohort entry ranged from 2000 through 2013, with the first 4 years contributing a lower proportion of patients and person-time of follow-up than subsequent years. The proportion of patients entered each year gradually increased over time, with the last 3 years each contributing more than 10% of the cohort.

Table 4 Study patients and follow-up years, by cohort entry year (N = 2,234)

Cohort entry year	Patients n (%)	Follow-up, years n (%)	Follow-up years per patient	
			Mean (SD)	Five-number summary (min-Q1-median-Q3-max)
2000	10 (0.4)	40 (1.4)	4.00 (5.15)	0.14 - 0.54 - 1.57 - 4.40 - 13.45
2001	41 (1.8)	49 (1.7)	1.19 (2.10)	0.03 - 0.26 - 0.53 - 1.35 - 12.95
2002	67 (3.0)	120 (4.1)	1.78 (2.94)	0.00 - 0.35 - 0.72 - 1.71 - 11.98
2003	84 (3.8)	114 (3.9)	1.36 (1.81)	0.01 - 0.41 - 0.90 - 1.58 - 10.90
2004	118 (5.3)	198 (6.8)	1.68 (1.99)	0.07 - 0.46 - 1.01 - 1.87 - 9.35
2005	179 (8.0)	319 (10.9)	1.78 (2.19)	0.03 - 0.53 - 0.97 - 2.02 - 8.91
2006	173 (7.7)	257 (8.8)	1.49 (1.53)	0.00 - 0.46 - 1.06 - 1.72 - 7.99
2007	188 (8.4)	309 (10.6)	1.65 (1.62)	0.03 - 0.52 - 1.00 - 2.19 - 6.80
2008	164 (7.3)	232 (7.9)	1.41 (1.35)	0.00 - 0.52 - 1.05 - 1.84 - 5.99
2009	192 (8.6)	281 (9.6)	1.47 (1.24)	0.02 - 0.55 - 0.95 - 2.19 - 4.82
2010	192 (8.6)	239 (8.2)	1.24 (0.98)	0.01 - 0.50 - 1.00 - 1.56 - 3.94
2011	256 (11.5)	335 (11.5)	1.31 (0.86)	0.02 - 0.53 - 1.21 - 2.07 - 2.98
2012	292 (13.1)	295 (10.1)	1.01 (0.53)	0.02 - 0.53 - 1.12 - 1.43 - 1.99
2013	278 (12.4)	134 (4.6)	0.48 (0.29)	0.00 - 0.22 - 0.46 - 0.74 - 0.99

max = maximum; min = minimum; SD = standard deviation.

10.2.2 Clinical characteristics

The following clinical characteristics were assessed at the time of initial prostate cancer diagnosis unless otherwise stated (Table 5). The mean age at diagnosis was 73.1 years (median, 72 years), with 2.0% aged less than 65 years and 3.7% 85 years or older. The majority of patients' tumors (72.5%) were grade 3, 15.9% were grade 1 or 2, 1.0% were grade 4, and 10.6% were of unknown grade. Less than 0.5% of tumors were grade 1, so the categories for grades 1 and 2 were collapsed to prevent reporting a cell count less than 11.

Table 5 Clinical characteristics of study cohort (N = 2,234)

Variable	Number of patients[a] (%)
Characteristics at initial prostate cancer diagnosis	
Age, years	
Mean (SD)	73.1 (5.9)
Five-number summary (minimum-Q1-median-Q3-maximum)	58-68-72-77-97
Age group	
< 65	45 (2.0)
65-69	678 (30.3)
70-74	676 (30.3)
75-79	482 (21.6)
80-84	271 (12.1)
85+	82 (3.7)
Year of initial prostate cancer diagnosis	
2000	218 (9.8)
2001	201 (9.0)
2002	225 (10.1)
2003	205 (9.2)
2004	201 (9.0)
2005	183 (8.2)
2006	190 (8.5)
2007	185 (8.3)
2008	174 (7.8)
2009	160 (7.2)
2010	162 (7.3)
2011	130 (5.8)
Grade	
Grade 1 or 2 (well differentiated; moderately or intermediately differentiated; differentiated, NOS)[b]	356 (15.9)
Grade 3 (poorly differentiated)	1,619 (72.5)
Grade 4 (undifferentiated/anaplastic)	23 (1.0)
Not determined	236 (10.6)
Stage (derived group)[c]	
Stage I or II[b]	543 (24.3)
Stage III	107 (4.8)
Stage IV	583 (26.1)
Unknown	1,001 (44.8)
Gleason score	
6 or 7[b]	47 (2.1)
8	79 (3.5)
9	162 (7.3)
10	30 (1.3)
Not collected	986 (44.1)
Not performed	69 (3.1)
Unknown	861 (38.5)

Variable	Number of patients[a] (%)
Characteristics on or before cohort entry date	
Comorbidities[d]	
Chronic pulmonary disease	947 (42.4)
Diabetes without chronic complications	920 (41.2)
Peripheral vascular disease	830 (37.2)
Cerebrovascular disease	681 (30.5)
Congestive heart failure	636 (28.5)
Mild liver disease	512 (22.9)
Renal disease	487 (21.8)
Myocardial infarction	359 (16.1)
Diabetes with chronic complications	273 (12.2)
Rheumatic disease	183 (8.2)
Peptic ulcer disease	171 (7.7)
Paraplegia and hemiplegia	87 (3.9)
Dementia	83 (3.7)
Moderate or severe liver disease	18 (0.8)
AIDS/HIV	< 11
Metastases[e]	
Lymph node	296 (13.2)
Bone	1,797 (80.4)
Bone-directed therapy[e]	1,326 (59.4)
Either bone metastases or bone-directed therapy	1,887 (84.5)
Time from initial diagnosis to development of CRPC	
Mean (SD), months	42.1 (32.6)
Distribution	
< 6 months	89 (4.0)
6 months to 1 year	251 (11.2)
> 1 to 1.5 years	279 (12.5)
> 1.5 to 2 years	223 (10.0)
> 2 years	1,392 (62.3)

CRPC = castrate-resistant prostate cancer; HIV = human immunodeficiency virus; NOS = not otherwise specified; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

[a] Unless stated otherwise.

[b] Categories were combined to avoid reporting a count of < 11.

[c] Stage according to the *AJCC Staging Manual, Sixth Edition* [7].

[d] Individual patients can have multiple comorbidities; thus, the sum of all comorbidities adds up to more than 100%.

[e] Recorded anytime between initial date of prostate cancer diagnosis and 30 days after the cohort entry date.

Stage information was missing for 44.8% of the patients. Nearly 30% of prostate cancers were stage I/II (24.3%) or stage III (4.8%). (Note, less than 0.5% were stage I, so categories were collapsed to prevent reporting cell counts less than 11.) The remaining cases were stage IV (26.1%) at the time of initial diagnosis. Gleason score was either not collected, not performed, or unknown for 86% of the patients; the remainder had scores of 6 or 7 (2.1%), 8 (3.5%), 9 (7.3%), or 10 (1.3%).

The number of patients diagnosed within each calendar year was fairly evenly distributed across all the study years from 2000-2011 (about 7%-10%, except 2011, which made up only 5.8% of the cohort). The proportion of patients diagnosed in each of the more recent years, 2008-2011, was slightly lower than earlier years since patients diagnosed in recent years had not had as much time to demonstrate castration resistance as patients diagnosed in earlier years.

Most of the patients had a history of other serious medical conditions on or before the cohort entry date. The most common comorbidities (present in > 20% of patients) were chronic pulmonary disease (42.4%), diabetes without chronic complications (41.2%), peripheral vascular disease (37.2%), cerebrovascular disease (30.5%), congestive heart failure (28.5%), mild liver disease (22.9%), and renal disease (21.8%).

History of metastases and bone-directed therapy was assessed through all of the patients' available medical history and up to 30 days after the cohort entry date (to allow diagnostic and therapeutic claims to be counted that closely followed clinical determination of castration resistance). The majority (80.4%) had a history of bone metastases and 59.4% had received bone-directed therapy; 84.5% had a history of either bone metastases or having received bone-directed therapy. Thirteen percent had history of lymph node metastases.

The average time from initial diagnosis of prostate cancer to development of CRPC was 42 months, with only 15% of the cohort developing CRPC within 1 year of the initial diagnosis. The majority (62%) had an interval of over 2 years from initial prostate cancer diagnosis to development of CRPC.

10.2.3 Treatment history

Based on the SEER data, just under 20% of the patients had surgery as their initial diagnostic procedure or first form of therapy for prostate cancer, while 34% had radiation therapy (Table 6). Using patient medical records from the Medicare portion of the data to identify treatments received between the initial diagnosis date and the cohort entry date (the date the patient met the CRPC definition), all patients received chemotherapy (as expected as a consequence of our definition of CRPC), 52.0% received radiation therapy, and 1.3% received radiopharmaceuticals. Treatments received after the cohort entry date included chemotherapy (94.9%), radiation therapy (32.5%) and radiopharmaceuticals (4.6%).

Table 6 Treatments (N = 2,234)

Variable	Number of patients (%)
Treatment(s) at initial workup or first course of therapy (from SEER)	
Surgery	
Yes	440 (19.7)
No	1,759 (78.7)
Unknown	35 (1.6)
Radiation	
Yes	750 (33.6)
No	1,418 (63.5)
Unknown	66 (3.0)
Castration method	
Surgical	52 (2.3)
Medical	2,106 (94.3)
Surgical and medical	76 (3.4)
Treatment recorded on or after date of initial diagnosis but before or on cohort entry date (from Medicare)	
Chemotherapy, hormonal therapy, or immunotherapy	2,234 (100.0)
Radiation therapy	1,161 (52.0)
Radiopharmaceuticals (strontium-89 or samarium-153)	30 (1.3)
Treatment recorded after cohort entry date (from Medicare)	
Chemotherapy	2,121 (94.9)
Radiation therapy	725 (32.5)
Radiopharmaceuticals (strontium-89 or samarium-153)	103 (4.6)

SEER = Surveillance, Epidemiology, and End Results program of the US National Cancer Institute.

10.3 Outcome data: second primary malignancies

Using both SEER data and the Medicare claims data across the entire study period (2000-2013) to identify cases of second primary cancer resulted in 172 cases among the 2,234 patients (Table 7). Using only SEER data to identify cases identified 20 cases of second primary cancers among the cohort; this analysis truncated follow-up on 31 December 2011 because that was the date that SEER data were updated.

Table 7 Crude and standardized incidence rates of second primary cancer, per 100 person-years

Case identification	Patients	Person-years	Cases	Crude rate (95% CI)	Standardized rate (95% CI)
SEER and Medicare	2,234	2,922	172	5.9 (5.0-6.8)	5.8 (4.9-6.7)
Age at cohort entry, years					
65-69	297	551	30	5.4 (3.7-7.8)	
70-74	625	920	63	6.8 (5.3-8.8)	
75-79	595	747	37	5.0 (3.5-6.8)	
> 80[b]	717	704	42	6.0 (4.3-8.1)	
SEER only	1,664	2,055	20	0.97 (0.59-1.5)	0.96 (0.58-1.5)

CI = confidence interval; SEER = Surveillance, Epidemiology, and End Results program of the US National Cancer Institute.

[a] Standardized to the age distribution of the REASSURE study interim analysis population aged 65 years or older.

[b] Categories were combined to avoid reporting a count of less than 11.

Using both SEER and Medicare data yielded a crude incidence rate of 5.9 second primary cancers per 100 person-years (95% CI, 5.0-6.8) (Table 7). There was no trend when rates were compared across age categories. The incidence rate was closely similar when standardized to age distribution of the REASSURE study population (5.8 per 100 person-years; 95% CI, 4.9-6.7) (Table 7). Limiting to the 1,797 patients with bone metastases, the incidence of second primary malignancies was 5.6 per 100 person-years (95% CI, 4.6-6.7). This result is based on 116 cases in 2,070 person-years.

Among the 172 cases identified using SEER and Medicare, the most common cancers were lung/bronchus (n = 29), urinary bladder (n = 22), colon/rectum (n = 21), non-prostate, non-bladder genitourinary tract (n = 18), and non-colorectal gastrointestinal (n = 17) (Table 8). Grouping was performed because of data use restrictions that prohibit reporting cell counts less than 11. Corresponding rates and confidence intervals are also provided in the table. There was no case of myelodysplastic syndromes (MDS) reported in the data as a second primary malignancy; however, the nonspecific neoplasm site “bone marrow” did appear in the data.

Table 8 Crude and standardized incidence rates of second primary cancer found using SEER and Medicare, by broad groupings, per 100 person-years

		Rate (95% CI)	
Cancer type	**Cases**	**Crude**	**Standardized[a]**
Lung/bronchus	29	0.99 (0.66 - 1.4)	0.97 (0.65 - 1.4)
Urinary bladder	22	0.75 (0.47 - 1.1)	0.73 (0.45 - 1.1)
Colon/rectum	21	0.72 (0.44 - 1.1)	0.73 (0.44 - 1.1)
Non-prostate, non-bladder genitourinary tract[b]	18	0.62 (0.37 - 0.97)	0.56 (0.33 - 0.90)
Non-colorectal gastrointestinal[c]	17	0.58 (0.34 - 0.93)	0.56 (0.32 - 0.90)
Non-Hodgkin lymphoma and myeloma	15	0.51 (0.29 - 0.85)	0.50 (0.28 - 0.83)
Brain	14	0.48 (0.26 - 0.80)	0.45 (0.25 - 0.76)
Miscellaneous or unspecified	13	0.44 (0.24 - 0.76)	0.43 (0.23 - 0.75)
Meninges, head, neck, and endocrine	12	0.41 (0.21 - 0.72)	0.43 (0.22 - 0.77)
Melanoma, breast, and nipple	11	0.38 (0.19 - 0.67)	0.42 (0.20 - 0.75)

[a] Standardized to the age distribution of the REASSURE study analysis population.
[b] Non-prostate, non-bladder genitourinary tract represents cancers of the kidney, ureters, urethra, and testis.
[c] Non-colorectal gastrointestinal represents cancers of the esophagus, stomach, small intestine, liver, biliary tract, and pancreas.

10.4 Other main results

Limiting the population to the subset who had bone metastases identified within their Medicare claims (n = 1,997) resulted in a slightly lower crude rate of 5.6 per 100 person-years (95% CI, 4.6-6.7) based on 116 second primaries identified in 2,070 person-years of follow-up.

Using only SEER data yielded an incidence rate of 0.97 second primary cancers per 100 person-years (95% CI, 0.59-1.5) (Table 7).

10.5 Other analyses

10.5.1 Part D data to identify medical castration

To explore the contribution of Part D data (prescription drug claims) to identification of medical castration, records on all patients continuously enrolled in Part D between initial prostate cancer diagnosis date and date of cohort entry (n = 412) were examined to determine the data file source in which medical castration was identified. Less than 11 of these patients were identified by only Part D data as having castration; most patients (89.6%) were identified by both Part D data and non–Part D data (Table 9). These results provided support to the decision to extend the study entry period to include the years before the introduction of Medicare Part D.

Table 9 Distribution by source used to identify castration among patients enrolled in Part D continuously between diagnosis and cohort entry date (N = 412)

Source in which castration was identified	Number of patients (%)
Only non–Part D or Only Part D[a]	43 (10.4)
Both Part D and non–Part D	369 (89.6)

[a] Categories “Only non–Part D” and “Only Part D” were combined to avoid reporting a count less than 11 in the “Only Part D” category.

10.5.2 Survival

Of the 2,234 patients in the cohort, 1,689 died during follow-up. The median survival time after cohort entry (i.e., after meeting the study CRPC definition) was 1.2 years, and the survival probabilities at 1, 3, and 5 years were 56%, 17%, and 9%, respectively (Table 10).

Table 10 Median survival and survival at 1 year, 3 years, and 5 years after cohort entry

Number at risk	Died n (%)	Median survival, years (95% CI)	Survival probability		
			1 Year (95% CI)	3 Years (95% CI)	5 Years (95% CI)
2,234	1,689 (75.6)	1.18 (1.12-1.26)	0.56 (0.54-0.58)	0.17 (0.15-0.18)	0.09 (0.07-0.11)

CI = confidence interval.
Note: Survival estimates were calculated using the Kaplan-Meier method.

10.5.3 Time from cohort entry to developing second cancer

Among the 172 patients with CRPC who developed a second primary cancer, the mean time between developing CRPC and the second cancer was 1.0 year (Table 11). About one-fifth (22%) of patients who developed second primary cancers did so within 3 months; in about 15%, the interval was more than 2 years; the remaining 64% developed their second primary cancer between 3 months and 2 years after developing CRPC.

Table 11 Years from cohort entry to second cancer (N = 172)

Variable	n (%)
Years to second cancer, mean (SD)	1.02 (1.08)
Years to second cancer, distribution	
0 - 0.25	37 (21.5)
> 0.25 to 0.50	31 (18.0)
> 0.50 to 0.75	21 (12.2)
> 0.75 to 1.00	24 (14.0)
> 1.00 to 2	34 (19.8)
> 2	25 (14.5)

SD = standard deviation

10.6 Adverse events/adverse reactions

Not applicable.

11. Discussion

11.1 Key results

In the study cohort of 2,234 patients with CRPC identified in SEER-Medicare data, the crude incidence rate of second primary malignancies was 5.9 per 100 person-years (95% CI, 5.0-6.8). The majority of men with CRPC (80.4%) had a history of bone metastases, and 84.5% either had a history of bone metastases or were prescribed a bone-targeting therapy. For most patients in our cohort (89.6%), medical castration was identified by both Part D and non–Part D data. Fewer than 11 of 412 patients were identified *only* in Part D as having castration, which allowed extension of the study period to the years before Medicare Part D was introduced in order to increase the cohort

size and the precision of incidence rate estimates. Three-quarters of the patients in the study died during follow-up. Median survival time was 1.18 years (95% CI, 1.12-1.26), and the survival probabilities at 1, 3, and 5 years were 56%, 17%, and 9%, respectively.

11.2 Limitations

We used second-line treatment (after surgical castration or medical androgen deprivation therapy) to define CRPC because the biochemical and diagnostic radiologic data necessary to diagnose castration resistance in routine clinical practice are not available in claims data (see Section 20.1 in Mottet et al. [15]). There are likely additional patients who are diagnosed with CRPC (i.e., meet biochemical and clinical criteria for CRPC) in the SEER-Medicare database who were not eligible for this study because they did not receive a second-line systemic treatment. Although this may be seen as a limitation, it could also be considered a strength of the chosen study design given that the results of this study are intended to provide context for estimates of second primary malignancy incidence rates among patients with CRPC treated with Xofigo. Men in the SEER-Medicare database with CRPC who were eligible for the present study (because they were selected to receive second-line systemic treatment) are more likely to be comparable to those treated with Xofigo than men in the SEER-Medicare database with biochemical and clinical evidence of CRPC who declined or were otherwise not considered to be candidates for treatment with second-line systemic therapies.

Another potential limitation of this study was that several of the drugs used to identify medical castration are oral therapies that might have been identifiable only among patients who had Medicare Part D coverage. This would have resulted in some potentially eligible patients not being included in the study cohort. However, our analysis found that almost 90% of patients were identified both by Part D and non–Part D data, and only a small proportion were identified only by Part D data.

In addition, a limitation of using SEER-Medicare data is that the data use agreement prohibits releasing cell counts less than 11, which results in a need to aggregate some forms of cancer in the analyses in this report more than would be necessary otherwise.

Finally, although the underlying purpose of the present study was to provide context for incidence rates from the REASSURE study, the population in the present study may not be fully comparable in all respects to the REASSURE study population. Although we provided estimates of cancer incidence rates standardized by age to the population aged 65 years or older of REASSURE, methods to further adjust for other potential differences between study populations are unlikely to be applicable because there will not be as detailed or reliable clinical information in the SEER-Medicare data about other prognostic factors (e.g., performance status, number of metastatic lesions, or clinical response to prior therapies) as may be available for the REASSURE population.

11.3 Interpretation

Our study provides a reasonable estimate of the crude incidence rate of second primary malignancies in the population identified. In our study, 84.5% of men had a diagnostic code recorded for bone metastases and/or evidence of treatment with bone-directed therapies, which is close to the approximately 90% reported in the published literature [12,13]. However, only 80.4% had a recorded diagnostic code for bone metastases, which suggests confirmation of the admonishment from the National Cancer Institute that capture of information on metastases is incomplete or underrecorded in the SEER-Medicare data [16].

Very few cases (20) were found by using SEER data alone. Although we have no direct evidence to understand the reasons for this number being so low in relation to number of cases found using both SEER and Medicare data, we can speculate about several possibilities:

- Patients may have moved out of a SEER reporting region and therefore had follow-up information only in the Medicare data.
- Some second primary malignancies found in the Medicare data may be false positives (not true second malignancies)—for example, a "bladder" cancer could represent invasion of the bladder by an adjacent prostate cancer.
- There could be some underreporting of second primary malignancies to cancer registries, particularly for patients who are diagnosed with a second primary malignancy on a clinical basis (without pathological confirmation), perhaps because they have advanced prostate cancer or other comorbidities that prompt a less aggressive approach to diagnosis.
- The SEER data have a shorter follow-up time than the Medicare data (by about 2 years); however, judging from the proportion of second primary malignancy cases identified in the last 2 years of the study (n = 42), it can be estimated that this would account for at most approximately 25% of the case deficit in SEER data.

The SEER-Medicare Data Use Agreement prohibited us from reporting cell counts less than 11 or even providing information (e.g., person-years and rates) that could allow the calculation of event numbers less than 11. We examined the distribution of second cancers among patients in our study, but were limited in what information could be included in this report due to the constraints of the data use agreement. As a workaround to these restrictions and to maximize the amount of useful information we could provide, we grouped cancers to yield reportable numbers; however, this may not make it possible to directly compare results with rates of some specific cancers identified in the REASSURE study and instead may require that a similar aggregation of cases be performed on the REASSURE data to make comparison possible.

Of the patients we identified as having castration, only a small proportion were identified *only* in Part D data. Therefore, having Part D was not essential for our study, but did provide a few additional patients who had continuous enrollment during the follow-up period and whose cohort entry and would not have been identified via non–Part D data.

Median survival time in our cohort was short (1.2 years), which is expected in this population. Among patients with metastatic prostate cancer in the ALSYMPCA phase 3 clinical trial, median survival was 14 months in the treatment group and 11.2 months in the placebo group [17].

11.4 Generalizability

The SEER-Medicare database population is considered to be representative of the general US population, and this database is the largest available source of detailed population-based medical information on men aged 65 years or older with prostate cancer, representing nearly 30% of the US population in this age range. Therefore, this study provides more precise estimates of second primary malignancy risks in men with CRPC than other available US data resources. Given that prostate cancer incidence and mortality rates are higher for black males than for white males in the US, we considered adjustment for race as well as for age; however, in the present study and in the REASSURE study, blacks represented only a small proportion of patients in the study population and the adjustment was not deemed necessary.

12. Other information

None.

13. Conclusion

The incidence of all second primary malignancies among men with CRPC identified in SEER-Medicare data is 5.9 per 100 person-years (95% CI, 5.0-6.8).

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15. Appendices

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1		11 October 2016	Statistical analysis plan

Annex 2. Signature Pages

Observational Study Information

Title	Addendum to Report "Incidence of Second Primary Malignancies in Patients With Castration-Resistant Prostate Cancer: An Observational Retrospective Cohort Study in the US" *Assessment of Skeletal-Related Events*
Date of last version of the final study report	9 May 2018
EU PAS register number	EUPAS13602
Active substance	Radium-223
Product	Xofigo
Marketing authorization holder(s)	Bayer AG
Joint PASS	NA
Research question and objectives	For the addendum analysis reported here, RTI Health Solutions explored the risk of fractures and other skeletal-related events (bone surgery, radiation therapy, and spinal cord compression) in the previously identified cohort of men with CRPC in the SEER-Medicare data.
Country(-ies) of study	United States
Author of addendum report	[redacted]

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1. Abstract

Acronym/Title	Addendum to Report "Incidence of Second Primary Malignancies in Patients With Castration-Resistant Prostate Cancer: An Observational Retrospective Cohort Study in the US" *Assessment of Skeletal-Related Events*
Report version and date **Author**	9 May 2018
Keywords	Skeletal-related events, castration-resistant prostate cancer, SEER-Medicare data
Rationale and background	Xofigo (radium-223 dichloride) is marketed in Europe and the United States (US) for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases, and no known visceral metastases. The European Medicines Agency recently issued a communication regarding an increased risk of death and fractures reported in an ongoing clinical trial of Xofigo in combination with abiraterone acetate and prednisone/prednisolone.
Research question and objectives	Bayer has requested that RTI Health Solutions explore the risk of fractures and other skeletal-related events (SREs) (bone surgery, radiation therapy, and spinal cord compression) in the previously identified cohort of men with CRPC in the SEER-Medicare data.
Study design	This analysis used a retrospective cohort of men in the US aged 65 years or older with evidence of CRPC that was previously identified in SEER-Medicare data (N = 2,234) and was used to assess rates of second primary malignancies.
Setting	Please see project report
Subjects and study size, including dropouts	Please see project report

Variables and data sources	Please see project report for a description of SEER-Medicare data. The primary outcome was SREs, defined broadly as fracture, bone surgery, radiation therapy, or spinal cord compression. Among eligible patients, the first occurrence of any code for an SRE after the date of cohort entry was counted as an event. Skeletal-related events were identified with diagnosis or procedure codes using the Medicare Provider Analysis and Review (MEDPAR), Outpatient, and Carrier files. The algorithm for SREs included codes for both traumatic and pathologic fractures, since pathologic fractures could be miscoded as traumatic fractures. Additional analyses were conducted (1) restricting the outcome to fractures (as indicated by ICD-9 diagnosis codes for pathologic or traumatic fractures) and (2) restricting the outcome to pathologic fracture (as indicated by ICD-9 diagnosis code 733.1 or 733.1x). We calculated overall incidence rates of SREs and incidence rates stratified by history of SRE prior to cohort entry (using the same definition as that used for the primary outcome) and by use of bone-targeted agents. Both crude incidence rates of SREs and incidence rates standardized to the age distribution of the REASSURE study population were estimated, although age adjustments had minimal impact on the results.
Results	*Descriptive data* As described previously in the study report, the cohort was primarily white (83.6%) and the mean age at cohort entry was 76.6 years (median, 76 years), with 13.3% aged 65 to 69 years, 74.8% aged 70 to 84 years, and 11.9% aged 85 or more years. More than half of the cohort (56.0%) had a history of SRE prior to cohort entry. Use of a bone-targeted agent in the cohort was common, with initial use before cohort entry in 54.3% of patients, initial use after cohort entry in 14.6% of patients, and no use in 31.1% of patients. Mean length of follow-up was 10.6 months, with 69.4% of patients having 1 year or less of follow-up. Mean time from cohort entry to first SRE was 9 months, with 74.3% of patients developing the first SRE within the first year after cohort entry.

	Outcome data A total of 896 of the 2,234 patients in the cohort (40%) had an SRE during follow-up. The most common types of SREs were radiation (n = 609, 27.3% of the cohort) and fracture (n = 266, 11.9% of the cohort). Spinal cord compression and bone surgery were less common, and each was identified in less than 2% of the cohort. *Main results* Overall, the age-standardized incidence rate of SREs was 3.78 (95% confidence interval [CI], 3.53-4.04) per 100 person-months. The age-standardized incidence rate before any bone-targeted agent use was 4.17 (95% CI, 3.71-4.67) per 100 person-months, and after any bone-targeted agent use it was 3.62 (95% CI, 3.32-3.93) per 100 person-months. *Additional results* Among 982 patients *without* SREs before cohort entry, 385 had an SRE during 11,549 person-months of follow-up, and the age-standardized incidence rate was 3.33 (95% CI, 3.01-3.69) per 100 person-months. Among 1,252 patients *with* SREs before cohort entry, 511 patients had an SRE during 12,167 person-months of follow-up, and the age-standardized incidence rate was 4.30 (95% CI, 3.90-4.72) per 100 person-months. In the entire study cohort, 363 patients had a *fracture* during 31,257 person-months of follow-up, and the age-standardized incidence rate of fractures was 1.18 (95% CI, 1.06-1.31) per 100 person-months. A total of 176 patients had a *pathologic fracture* during 33,635 person-months of follow-up, and the age-adjusted incidence rate of pathologic fractures was 0.52 (95% CI, 0.45-0.61) per 100 person-months.
Discussion	We observed an age-standardized incidence rate of SREs of 3.78 per 100 person-months. The age-standardized incidence rate of fractures was 1.18 per 100 person-months, and the age-standardized incidence rate of pathologic fractures was 0.52 per 100 person-months. While the incidence rates appeared slightly lower following any use of bone-targeted agents, we are unable to make any causal interpretations regarding bone-targeted agents and risk of SREs because of likely confounding by indication.

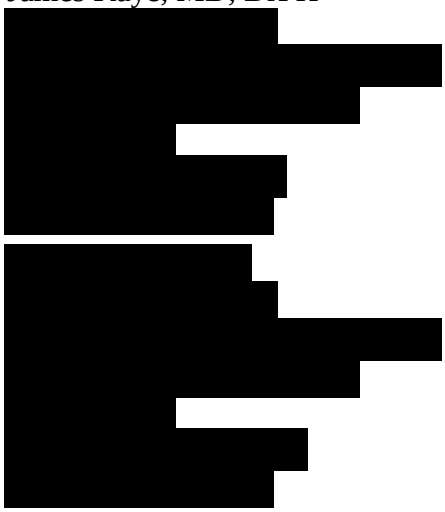
Marketing Authorization Holder(s)	Bayer AG
Names and affiliations of principal investigators	[redacted]

2. List of abbreviations

CI	confidence interval
CRPC	castration-resistant prostate cancer
MEDPAR	Medicare Provider Analysis and Review
Q1, Q3	first and third quartiles
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results
SRE	skeletal-related event
US	United States

3. Investigators

James Kaye, MD, DrPH



4. Other responsible parties

None

5. Milestones

Table 1 Milestones

Milestone	Planned date	Actual date	Comments
Draft results tables for addendum analysis	06 April 2018	06 March 2018	None
Draft report addendum	27 April 2018	24 April 2018	None
Final report addendum	11 May 2018	9 May 2018	None

6. Rationale and background

Xofigo (radium-223 dichloride) is marketed in Europe and the United States (US) for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases, and no known visceral metastases (Bayer HealthCare Pharmaceuticals Inc., 2013; Bayer Pharma AG, 2013). The European Medicines Agency recently issued a communication regarding an increased risk of death and fractures reported in an ongoing clinical trial of Xofigo in combination with abiraterone acetate and prednisone/prednisolone (European Medicines Agency, 2017).

7. Research question and objectives

Bayer has requested that RTI Health Solutions explore the risk of fractures and other skeletal-related events (SREs) (bone surgery, radiation therapy, and spinal cord compression) in the previously identified cohort of men with CRPC in the SEER[1]-Medicare data. We report here on the results of the analysis of all SREs in the SEER-Medicare cohort.

8. Amendments and updates

None

9. Research methods

9.1 Study design

This analysis used a retrospective cohort of men in the US aged 65 years or older with evidence of CRPC that was previously identified in SEER-Medicare data (N = 2,234) and was used to assess rates of second primary malignancies. The data source and methods used to identify the cohort were described previously in the project report, "Incidence of Second Primary Malignancies in Patients With Castration-Resistant Prostate Cancer: An Observational Retrospective Cohort Study in the US" and are summarized in the following text.

9.2 Setting

The cohort was formed using data from 01 January 2000 through the latest year of available Medicare data (2013). The cohort included men who were enrolled in both Medicare Parts A and B for at least 1 year before the cohort entry date, had a primary site code of prostate cancer in SEER data, had surgical castration or androgen deprivation therapy after prostate cancer diagnosis, and had evidence that prostate cancer was resistant to the castration or androgen deprivation therapy (as indicated by starting a second-line systemic therapy). We excluded patients if they were enrolled in a health maintenance organization during the year before the cohort entry date, had a diagnosis of any cancer other than prostate cancer or non-melanoma skin cancer on or before the cohort entry date, or had a diagnostic code for metastases (other than bone or lymph node metastases) on or before the cohort entry date. Patients were excluded if they received second-line systemic therapies on or before the earliest date of surgical castration or androgen deprivation therapy. We also planned to exclude patients who had received Xofigo, although no use was actually identified among the patients considered for cohort entry.

Similar to prior analyses, patients entered the cohort on the date they were identified as first receiving a therapy representing a second-line systemic treatment for prostate cancer. On this cohort entry date, follow-up began for the occurrence of an SRE. Follow-up time for each patient continued until the earliest occurrence of an SRE, death, second primary malignancy, discontinuation of Part A or Part B Medicare coverage, enrollment in a health maintenance organization, or the end of the study period. We also planned to discontinue follow-up after Xofigo use, but no use was observed after cohort entry.

[1] SEER = Surveillance, Epidemiology, and End Results program of the United States National Cancer Institute.

9.3 Subjects

Please see Section 9.2**.**

9.4 Variables

9.4.1 Primary outcome variable

The primary outcome was SREs, defined broadly as fracture, bone surgery, radiation therapy, or spinal cord compression. Among eligible patients, the first occurrence of any code for an SRE after the date of cohort entry was counted as an event. Skeletal-related events were identified as any diagnosis or procedure code listed in Annex 1 or 2 of the protocol addendum, using the Medicare Provider Analysis and Review (MEDPAR), Outpatient, and Carrier files. Together, these files contain all Part A short and long hospital stays and skilled nursing facility stays and Part B claims submitted by institutional outpatient facilities and non-institutional providers, such as physicians, physician assistants, clinical social workers, and nurse practitioners. The algorithm for SREs included codes for both traumatic and pathologic fractures, since pathologic fractures could be miscoded as traumatic fractures (Aly et al., 2015).

Two differences are worth noting in the outcome definition between our claims-based study and clinical trials conducted to evaluate drugs intended to decrease the risk of SREs. First, because of the eventual interest in SREs as a safety concern rather than an efficacy endpoint, the outcome in this study was incident SREs (i.e., first SRE occurrence in a patient) rather than also including subsequent SREs as might be done in an efficacy evaluation. Consequently, the endpoint analyzed was the first occurrence of any claim with a code for an SRE. Because only a patient's first SRE code was used in the analysis, grouping a series of claims or codes representing a single clinical event (e.g., pathologic fracture followed by radiation therapy to the fractured bone) together as an "episode" of SRE to avoid double-counting was not necessary. Second, because claims data are collected primarily for administrative and billing purposes and lack explicit confirmatory clinical and radiologic data, the outcome definitions for this analysis are likely to be more sensitive and less specific than is feasible with more rigorous criteria in clinical trials.

9.4.2 Secondary outcome variables

Two additional analyses were conducted restricting the outcome to fractures (as indicated by ICD-9[2] diagnosis codes in Annex 1 of the protocol addendum, which includes codes for both pathologic and traumatic fractures) and, separately, to pathologic fracture (as indicated by ICD-9 diagnosis code 733.1 or 733.1x). Note that in these restricted analyses, the first qualifying SRE code in a patient's claim record may not be the same code as the one counted as the outcome for the same patient in the overall analysis of any SRE.

9.4.3 Additional variables of interest

We calculated overall rates and rates stratified by history of SRE prior to cohort entry (using the same definition as that used for the primary outcome) and by use of bone-targeted agents. Bone-targeted agents included injectables and non-injectable bisphosphonates as listed in the study report.

[2] ICD-9 = *International Classification of Diseases, 9th Revision*.

9.5 Data sources and measurement

Please see the study report for this information.

9.6 Bias

Please see Section 9.4 for this information.

9.7 Study size

Please see the study report for this information.

9.8 Data transformation

Please see the study report for this information.

9.9 Statistical methods

9.9.1 Main summary measures

Descriptive analyses of the data were performed using summary statistics for continuous and categorial data. Continuous data were described by the number of non-missing values, mean and standard deviation, median, quartiles, and ranges. Select continuous variables were categorized in a clinically meaningful way.

9.9.2 Main statistical methods

Both crude incidence rates of SREs and incidence rates standardized to the age distribution of the REASSURE study population were estimated. Rates (per 100 person-months) were calculated in all eligible person-time and separately among person-time before and after first use of any bone-targeted agent (other than Xofigo, as there was no such use in the study population). We did not conduct any formal hypothesis testing or calculate any measures of association to compare rates.

Rates of overall SRE (defined broadly as any fracture, use of radiation therapy, surgery on bone, or spinal cord compression) were first estimated. Additional analyses were conducted as follows: (1) stratifying by whether patients had any SRE prior to the cohort entry date, (2) restricting the outcome to fractures (as indicated by ICD-9 diagnosis codes in Annex 1), and (3) restricting the outcome to pathologic fracture (as indicated by ICD-9 diagnosis code 733.1 or 733.1x).

9.9.3 Missing values

Please see the study report for this information.

9.9.4 Sensitivity analyses

None

9.9.5 Amendments to the statistical analysis plan

None

9.10 Quality control

All analyses were performed using SAS 9.3 (or higher) statistical software (SAS Institute, Inc., Cary, North Carolina). Programs, logs, and output were reviewed for accuracy according to relevant RTI Health Solutions standard operating procedures. A second programmer reviewed all programs and, in most cases, independently wrote code to reproduce the results generated from the initial programs.

10. Results

10.1 Participants

Please see the study report for this information.

10.2 Descriptive data

The study cohort of men with CRPC consisted of 2,234 patients (Table 1). As described previously in the study report, the cohort was primarily white (83.6%) and the mean age at cohort entry was 76.6 years (median, 76 years), with 13.3% aged 65 to 69 years, 74.8% aged 70 to 84 years, and 11.9% aged 85 or more years.

More than half (56.0%) of the cohort had a history of SRE prior to cohort entry. Bone-targeted agent use in the cohort was common, with initial use before cohort entry in 54.3% of patients, initial use after cohort entry in 14.6% of patients, and no use in 31.1% of patients. Mean length of follow-up was 10.6 months, with 69.4% of patients having 1 year or less of follow-up, 21.0% having more than 1 year and up to 2 years of follow-up, and 9.6% having more than 2 years of follow-up. Mean time from cohort entry to first SRE was 9 months, with 74.3% of patients developing the first SRE within the first year after cohort entry, 18.3% within the second year after cohort entry, and 7.4% more than 2 years after cohort entry.

Table 2: Demographic and clinical characteristics of study cohort (N = 2,234)

Variable	Number of patients (%)
Race	
White	1,867 (83.6)
Black	218 (9.8)
Asian	46 (2.1)
Hispanic	48 (2.1)
Other or unknown[a]	55 (2.5)
Age at cohort entry, years	
Mean (SD)	76.6 (6.2)
Min, Q1, Median, Q3, Max	65, 72, 76, 81, 100
Age distribution, years	
65-69	297 (13.3)
70-74	625 (28.0)
75-79	595 (26.6)
80-84	451 (20.2)
85+	266 (11.9)
SRE prior to cohort entry[b]	1,252 (56.0)
First use of bone-targeted agent prior to cohort entry[c]	1,213 (54.3)
First use of bone-targeted agent after cohort entry	326 (14.6)
No use of bone-targeted agents	695 (31.1)
Length of follow-up, months	
Mean (SD)	10.6 (11.6)
Distribution	
< 6 months	960 (43.0)
6 months to 1 year	590 (26.4)
> 1 to 1.5 years	317 (14.2)
> 1.5 to 2 years	152 (6.8)
> 2 years	215 (9.6)
Time from cohort entry to first SRE, months	
Mean (SD)	9 (10.1)
Distribution	
< 6 months	449 (50.1)
6 months to 1 year	217 (24.2)
> 1 to 1.5 years	117 (13.1)
> 1.5 to 2 years	47 (5.2)
> 2 years	66 (7.4)

Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation; SRE = skeletal-related event.
[a] Categories were combined to avoid reporting a count of < 11.
[b] Defined as any code in Annex 1 or Annex 2 of the protocol addendum identified in the Medicare Provider Analysis and Review file, Carrier claims, or Outpatient claims between the initial date of prostate cancer diagnosis and the cohort entry date.
[c] Defined as any code in Appendix C of version 1.1 of the statistical analysis plan, recorded any time between the initial date of prostate cancer diagnosis and the cohort entry date.

10.3 Outcome data

A total of 896 of the 2,234 patients in the cohort (40%) had an SRE during follow-up (Table 2). No substantial differences were observed in the race distribution of patients with and without SREs. Patients with SREs tended to be younger than those without SREs (mean age 75.5 years vs. 77.3 years); 74.5% of patients with SREs were younger than 80 years, as compared to 63.5% of patients without SREs.

Table 3: Demographic characteristics of patients with and without skeletal-related events during follow-up (N = 2,234)

Variable	Number of patients with SRE (%) (N = 896)	Number of patients without SRE (%) (N = 1,338)
Race		
White	769 (85.8)	1,098 (82.1)
Black	72 (8.0)	146 (10.9)
Asian	16 (1.8)	30 (2.2)
Hispanic	12 (1.3)	36 (2.7)
Other or unknown[a]	27 (3.0)	28 (2.1)
Age at cohort entry, years		
Mean (SD)	75.5 (5.9)	77.3 (6.3)
Min, Q1, Median, Q3, Max	65, 71, 75, 80, 96	65, 72, 77, 82, 100
Age distribution, years		
65-69	143 (16.0)	154 (11.5)
70-74	293 (32.7)	332 (24.8)
75-79	231 (25.8)	364 (27.2)
80-84	156 (17.4)	295 (22.0)
85+	73 (8.1)	193 (14.4)

Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation; SRE = skeletal-related event.
[a] Categories were combined to avoid reporting a count of < 11.

Table 3 shows the number of cases of first SREs by type. The most common types of SREs were radiation (n = 609, 27.3% of the cohort) and fracture (n = 266, 11.9% of the cohort). Spinal cord compression and bone surgery were less common, and each was identified in less than 2% of the cohort (1.7% and 1.0% of the cohort, respectively).

Table 4: Number of cases of first skeletal-related events

Skeletal-related event	Cases (% of total cohort)
Fracture	266 (11.9)
Bone surgery	22 (1.0)
Radiation	609 (27.3)
Spinal cord compression	37 (1.7)
Total	896 (40.1)

SRE = skeletal-related event.
Note: Skeletal-related events on the date of the initial SRE during follow-up were counted. The sum of the cases of fracture, bone surgery, radiation, and spinal cord compression is greater than the total number of SRE cases, as patients may have had more than one type of SRE on the date of the first SRE.

10.4 Main results

10.4.1 Incidence rates of skeletal-related events, overall and by bone-targeted agent use

Table 4 shows crude and age-standardized incidence rates of SREs overall and in person-time before and after use of any bone-targeted agent. Crude incidence rates were closely similar to those standardized to the age distribution of the REASSURE study population. Overall, the age-standardized incidence rate of SREs was 3.78 (95% confidence interval [CI], 3.53-4.04) per 100 person-months. The age-standardized incidence rate before any bone-targeted agent use was 4.17 (95% CI, 3.71-4.67) per 100 person-months, and after any bone-targeted agent use was 3.62 (95% CI, 3.32-3.93) per 100 person-months.

Table 5: Crude and standardized incidence rates of skeletal-related events (per 100 person-months)

Person-time included	Patients	Person-months	Cases	Crude rate (95% CI)	Standardized[a] rate (95% CI)
All person-time	2,234	23,716	896	3.78 (3.53-4.03)	3.78 (3.53-4.04)
Person-time before use of any bone-targeted agent[b]	1,021	7,429	309	4.16 (3.71-4.65)	4.17 (3.71-4.67)
Person-time after use of any bone-targeted agent[c]	1,539	16,287	587	3.60 (3.32-3.91)	3.62 (3.32-3.93)

CI = confidence interval.

Note: Cases identified using Medicare Provider Analysis and Review file, Carrier claims (Physician/Supplier Part B), and Outpatient claims.

[a] Standardized to the age distribution of the REASSURE study population.

[b] Includes (1) all eligible person-time in patients without any use of bone-targeted agent after the initial prostate cancer diagnosis and (2) person-time prior to exposure to a bone-targeted agent in patients with any use of bone-targeted agent only after cohort entry.

[c] Includes person-time following first use of a bone-targeted agent in patients with use of a bone-targeted agent at any time after the initial prostate cancer diagnosis.

10.4.2 Incidence rates of skeletal-related events by history of skeletal-related events

Table 5 shows crude and age-standardized incidence rates of SREs in patients with or without a history of SRE before cohort entry, overall and stratified by person-time before and after use of any bone-targeted agent. Again, crude incidence rates were very close to those standardized to the age distribution of the REASSURE study population.

Among 982 patients without SREs before cohort entry, 385 had an SRE during 11,549 person-months of follow-up and the age-standardized incidence rate was 3.33 (95% CI, 3.01-3.69) per 100 person-months. Among the patients without SREs before cohort entry, the age-standardized incidence rate before any bone-targeted agent use was 3.69 (95% CI, 3.09-4.38) per 100 person-months, and after any bone-targeted agent use it was 3.17 (95% CI, 2.79-3.60) per 100 person-months.

Among 1,252 patients with SREs before cohort entry, 511 patients had an SRE during 12,167 person-months of follow-up and the age-standardized incidence rate was 4.30 (95% CI, 3.90-4.72) per 100 person-months. Among the patients with skeletal-related events before cohort entry, the age-adjusted incidence rate of SREs before any bone-targeted agent use was 4.76 (95% CI, 4.02-5.59) per 100 person-months, and after any bone-targeted agent use it was 4.10 (95% CI, 3.63-4.61) per 100 person-months.

10.5 Other analyses: fractures and pathologic fractures

Table 6 shows crude and age-standardized incidence rates of fractures and pathologic fractures.

Crude incidence rates were again quite similar to those standardized to the age distribution of the REASSURE study population.

A total of 363 patients had a fracture during 31,257 person-months of follow-up, and the age-standardized incidence rate of fractures in all person-time was 1.18 (95% CI, 1.06-1.31) per 100 person-months. The age-adjusted incidence rate of fractures before any bone-targeted agent use was 1.50 (95% CI, 1.26-1.77) per 100 person-months, and after any bone-targeted agent use it was 1.03 (95% CI, 0.89-1.18) per 100 person-months.

A total of 176 patients had a pathologic fracture during 33,635 person-months of follow-up, and the age-adjusted incidence rate of pathologic fractures in all person-time was 0.52 (95% CI, 0.45-0.61) per 100 person-months The age-adjusted incidence rate of pathologic fractures before any bone-targeted agent use was 0.77 (95% CI, 0.60-0.96) per 100 person-months, and after any bone-targeted agent use it was 0.41 (95% CI, 0.33-0.51) per 100 person-months.

Table 6: Crude and standardized incidence rates of skeletal-related events (per 100 person-months), among patients without or with a skeletal-related event before cohort entry

Person-time included	Patients	Person-months	Cases	Crude rate (95% CI)	Standardized[a] rate (95% CI)
Patients without SRE before cohort entry					
All person-time	982	11,549	385	3.33 (3.01-3.68)	3.33 (3.01-3.69)
Person-time before use of any bone-targeted agent[b]	467	3,814	138	3.62 (3.04-4.27)	3.69 (3.09-4.38)
Person-time after use of any bone-targeted agent[c]	670	7,735	247	3.19 (2.81-3.62)	3.17 (2.79-3.60)
Patients with SRE before cohort entry					
All person-time	1,252	12,167	511	4.20 (3.84-4.58)	4.30 (3.90-4.72)
Person-time before use of any bone-targeted agent[b]	554	3,615	171	4.73 (4.05-5.50)	4.76 (4.02-5.59)
Person-time after use of any bone-targeted agent[c]	869	8,553	340	3.98 (3.56-4.42)	4.10 (3.63-4.61)

CI = confidence interval; SRE = skeletal-related event.
Note: Cases identified using Medicare Provider Analysis and Review file, Carrier claims (Physician/Supplier Part B), and Outpatient claims.
[a] Standardized to the age distribution of the REASSURE study population.
[b] Includes (1) all eligible person-time in patients without any use of bone-targeted agent after the initial prostate cancer diagnosis and (2) person-time prior to exposure to a bone-targeted agent in patients with any use of bone-targeted agent only after cohort entry.
[c] Includes person-time following first use of a bone-targeted agent in patients with use of a bone-targeted agent at any time after the initial prostate cancer diagnosis.

Table 7: Crude and standardized incidence rates of fractures and pathologic fractures, per 100 person-months

Person-time included	Patients	Person-months	Cases	Crude rate (95% CI)	Standardized[a] rate (95% CI)
Fractures[b]					
All person-time	2,234	31,257	363	1.16 (1.04-1.29)	1.18 (1.06-1.31)
Person-time before use of any bone-targeted agent[c]	1,021	10,189	148	1.45 (1.23-1.71)	1.50 (1.26-1.77)
Person-time after use of any bone-targeted agent[d]	1,591	21,068	215	1.02 (0.89-1.17)	1.03 (0.89-1.18)
Pathologic fractures[e]					
All person-time	2,234	33,635	176	0.52 (0.45-0.61)	0.52 (0.45-0.61)
Person-time before use of any bone-targeted agent[c]	1,021	10,887	80	0.73 (0.58-0.91)	0.77 (0.60-0.96)
Person-time after use of any bone-targeted agent[d]	1,606	22,748	96	0.42 (0.34-0.52)	0.41 (0.33-0.51)

CI = confidence interval; ICD-9 = *International Classification of Diseases, 9th Revision*.
Note: Cases identified using Medicare Provider Analysis and Review file, Carrier claims (Physician/Supplier Part B), and Outpatient claims.
[a] Standardized to the age distribution of the REASSURE study population.
[b] As indicated by ICD-9 diagnosis codes in Annex A of the protocol addendum.
[c] Includes (1) all eligible person-time in patients without any use of bone-targeted agent after the initial prostate cancer diagnosis and (2) person-time prior to exposure to a bone-targeted agent in patients with any use of bone-targeted agent only after cohort entry.
[d] Includes person-time following first use of a bone-targeted agent in patients with use of a bone-targeted agent at any time after the initial prostate cancer diagnosis.
[e] As indicated by ICD-9 diagnosis code 733.1 or 733.1x.

10.6 Safety data (Adverse events/adverse reactions)

Not applicable

11. Discussion

11.1 Key results

In a cohort of 2,234 patients with CRPC identified in SEER-Medicare data with a mean follow-up of 10.6 months, the cumulative incidence of SREs was 40%. Standardized to the age distribution of the REASSURE study population, the incidence rate of SREs was 3.78 per 100 person-months. The age-standardized incidence rate of fractures was 1.18 per 100 person-months, and the age-standardized incidence rate of pathologic fractures was 0.52 per 100 person-months.

To our knowledge, no studies on the incidence *rates* of SREs in men with CRPC have been published. However, a number of observational studies have estimated the *cumulative incidence* of SREs in cohorts of men with metastatic CRPC or prostate cancer with bone metastases. The cumulative incidence of SREs in a small cohort of men with bone metastatic CRPC identified from two Veterans Administration Medical Centers was 38% (Klaassen et al., 2017), which is similar to our estimate in the cohort of men with CRPC identified in SEER-Medicare data (40%). Compared with our findings, the cumulative incidence estimate was also similar in another cohort of men with prostate cancer and bone metastases identified in SEER-Medicare data (McDougall et al., 2016). However, higher cumulative incidences were reported in cohorts of men with prostate cancer and bone metastases identified in the Danish National Patient Registry (1 year cumulative incidence of 46%) and in the Thomson MedStat MarketScan Commercial Claims and Encounter database (overall cumulative incidence of 53%) (Hagiwara et al., 2013; Norgaard et al., 2010). The differences in estimates of cumulative incidence of SREs in those studies versus ours could be due to differences in data sources, outcome definitions, length of follow-up, and/or study populations. Notably, our cohort included men with castration-resistant prostate cancer (CRPC) regardless of whether they were known to have bone metastasis, although estimates in the literature report that approximately 90% of patients with metastatic prostate cancer have bone metastasis (Bubendorf et al., 2000; Fahrbach et al., 2016). As described previously in the project report, 80.4% of the cohort of patients with CRPC identified in SEER-Medicare data had a history of bone metastases, and 84.5% had either bone metastases or bone-directed therapy (Kaye, 2017).

Incidence rates of SREs appeared to be slightly lower among patients without a history of SREs before cohort entry and among person-time following bone-targeted agent use. However, we did not estimate any measures of association or conduct formal hypothesis testing because of the descriptive nature of this analysis. Also, because this was an observational study with no attempt to adjust for differences in patient characteristics between subgroups, any comparison of rates before and after initial use of a bone-targeted agent would likely be biased from confounding by indication, as patients at greater risk for an SRE are more likely to be prescribed a bone-targeted agent. We therefore cannot make any causal interpretations regarding bone-targeted agents and risk of SREs.

11.2 Strengths

A strength of this analysis is the use of the SEER-Medicare database, which is considered to be representative of the elderly population in the US and is the largest available source of detailed population-based medical information on men aged 65 years or older with prostate cancer. Another strength of this analysis is the ability to use available data for the previously identified cohort of patients with CRPC to assess the additional outcome of interest (i.e., SREs).

11.3 Limitations

As described in the initial report, we used second-line treatment (after surgical or medical androgen deprivation therapy) to define CRPC because biochemical and radiologic data that would directly indicate disease progression despite androgen deprivation therapy are not available in claims data. Another limitation is the use of diagnosis and procedure code algorithms in Medicare claims data to identify SREs. For this analysis of SREs that may inform an eventual safety analysis, we selected a relatively simple algorithm that we consider likely to be more sensitive and possibly less specific than would be used in clinical trials, which use prospectively collected radiologic and clinical data and can define outcomes more rigorously in a study protocol using such information. Notably, claims codes for radiation do not specify the anatomic target (Aly et al., 2015), so it is possible that some radiation therapy outcomes analyzed in this study were not bone directed. Furthermore, codes for fractures may capture fractures due to causes other than pathologic processes (including trauma or osteoporosis) (Aly et al., 2015). Because of potential bias due to confounding by indication, we did not perform any hypothesis testing or calculate any measures of association comparing rates before and after bone-targeted agent use.

11.4 Interpretation

Please see Section 11.1 for this information.

11.5 Generalizability

Please see the study report for this information.

12. Other information

None

13. Conclusion

This analysis provides estimates of incidence rates of SREs, fractures, and pathologic fractures in a cohort of men with CRPC identified in SEER-Medicare data. We observed an age-standardized incidence rate of SREs of 3.78 per 100 person-months. The age-standardized incidence rate of fractures was 1.18 per 100 person-months, and the age-standardized incidence rate of pathologic fractures was 0.52 per 100 person-months. While the incidence rates appeared slightly lower following any use of bone-targeted agents, we are unable to make any causal interpretations regarding bone-targeted agents and risk of SREs because of likely confounding by indication.

14. References

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Appendices

Annex 1 Signature Pages