Title	Incidence of Second Primary Malignancies in Patients With Castration-Resistant Prostate Cancer: An Observational Retrospective Cohort Study in the US
Keywords	Castration-resistant, oncology, prostate 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	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. Bayer also 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.
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. Using the same cohort of men (N = 2,234), the incidence of SREs was estimated. SREs were 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.
Subjects and Study Size, including dropouts	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.
Variables and Data sources	Primary outcome variables: • Incidence rate of second primary malignancy • Incidence rates of skeletal-related events Variables for secondary analyses: • Proportion with a history of bone metastasis at cohort entry • Proportion who met the definition of castration based solely on Part D data • Overall survival
Results	*Primary outcome(s)* 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. 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. 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. There was no trend when rates were compared across age categories. 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). This result is based on 116 cases in 2,070 person-years. 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. 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. Crude incidence rates were closely 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. *Secondary outcome(s)* The majority of men with CRPC (80.4%) in the study cohort had a history of bone metastases, and 84.5% either had a history of bone metastases or were prescribed a bone-targeting therapy. 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. These results provided support to the decision to extend the study entry period to include the years before the introduction of Medicare Part D. 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. *Safety variable(s)* Not applicable

Discussion	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. 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.
Marketing Authorisation Holder(s)	Bayer AG