Observational Study Information

Title	Incidence of Second Primary Malignancies in Patients With Castration-Resistant Prostate Cancer: An Observational Retrospective Cohort Study in the US
Protocol version identifier	Version 1
Date of last version of protocol	09 March 2016
Active substance	None
Medicinal product	None
Product reference	None
Procedure number	Not applicable
Marketing authorization holder(s)	Bayer Healthcare Pharmaceuticals Inc.
Research question and objectives	The primary objective of this study is to provide population-based estimates of the incidence rates of second primary malignancies among patients with castration-resistant prostate cancer. These estimates will provide additional perspective for the second primary malignancy incidence rates to be estimated in a separate prospective cohort study to evaluate the long-term safety of Xofigo ("REASSURE").
Country of study	United States
Author	[redacted]

The study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

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2. List of abbreviations

ALSYMPCA	Alpharadin in Symptomatic Prostate Cancer Patients
BIPS	Leibniz Institute for Prevention Research and Epidemiology (formerly the Bremen Institute for Prevention Research and Social Medicine)
CMS	Centers for Medicare and Medicaid Services
CPT-4	Current Procedural Terminology, version 4
CRPC	Castration-Resistant Prostate Cancer
dL	Deciliter
DME	Durable Medical Equipment
EMA	European Medicine Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GePaRD	German Pharmacoepidemiological Research Database
HCPCS	Healthcare Common Procedure Coding System
HMO	Health Maintenance Organization
ICD-9-CM	International Classification of Diseases, 9th Edition, Clinical Modification
ICD-O-3	International Classification of Diseases for Oncology, Third Edition
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
MedPAR	Medicare Provider Analysis and Review
NCI	National Cancer Institute
PASS	Post-Authorization Safety Study
PSA	Prostate-Specific Antigen
REASSURE	Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
RECIST	Response Evaluation Criteria in Solid Tumors
RTI-HS	RTI Health Solutions
SAP	Statistical Analysis Plan

SEER	Surveillance, Epidemiology, and End Results
SOP	Standard Operating Procedure
US	United States

3. Responsible parties

[redacted]

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4. Abstract

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

Version 1, January 2016, James Kaye, RTI Health Solutions

Rationale and background

Xofigo (radium-223 dichloride) is approved in the United States (US) and the European Union (EU) for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases, and no known visceral metastatic disease. Its mechanism of action involves induction of double-strand DNA breaks. 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. Nonclinical studies of Xofigo in rats showed an increased risk of neoplasms. The overall incidence of new malignancies in the randomized clinical trial of Xofigo—"Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA)"; ClinicalTrials.gov NCT00699751 (ClinicalTrials.gov, 2015a; Parker et al., 2013)—was lower on the Xofigo arm (< 1%) than on placebo (2%) (Bayer HealthCare Pharmaceuticals Inc., 2013), and no cases of Xofigo-induced cancer have been reported in clinical trials in follow-up of up to 3 years (Bayer Pharma AG, 2013). However, as noted in the Xofigo Food and Drug Administration (FDA) product information, the expected latency period for the development of secondary malignancies exceeds the duration of follow-up available in clinical trials (Bayer HealthCare Pharmaceuticals Inc., 2013).

As a postmarketing requirement, Bayer is conducting a single-arm, noninterventional, 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)," as per ClinicalTrials.gov NCT02141438 (ClinicalTrials.gov, 2015b). 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 (Surveillance, Epidemiology, and End Results)-Medicare linked database is a suitable data resource for providing such estimates. The present study will provide this perspective for an interim analysis of the first 600 patients in the REASSURE study, which is planned by Bayer to be conducted by the end of 2016.

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 in 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). The study in Sweden will be conducted using the Swedish register databases. The present study protocol describes the US component of this epidemiology program.

Research question and objectives

The primary objective of this study is to estimate the population-based incidence rates of selected second primary malignancies among patients with CRPC similar to those treated with Xofigo. The study will be conducted in two phases: in phase 1, RTI Health Solutions (RTI-HS) will calculate the collective incidence rate of all second primary malignancies among men with CRPC. In phase 2, RTI-HS will calculate the individual incidence rates of selected second primary malignancies that will be determined in collaboration with Bayer based on findings from the REASSURE study and other scientific considerations such as the observed number of cases in the present study.

The secondary study objectives are to estimate the proportion of men with CRPC who have evidence of bone metastases (as indicated by a diagnosis and/or treatment), to estimate the proportion of men with CRPC and Medicare Part D coverage who received only oral androgen deprivation therapy, and to estimate overall survival from the time of cohort eligibility. Information related to the first two secondary objectives may be used to inform the analyses for the primary objective in phase 2.

Study design

This is a retrospective, observational cohort study of men in the US aged 65 years or older with CRPC. A diagnosis of prostate cancer and receipt of medical androgen deprivation therapy or surgical castration will be documented in SEER and Medicare data, respectively. Evidence of treatment with a second-line systemic therapy in Medicare data will be taken to indicate castration resistance. There is no internal comparison group for this study, although ultimately these rates will be used to provide perspective on rates found in the REASSURE study.

Population

The study period is 01 January 2006 through the latest year of available Medicare data (2013). The cohort entry date is the day on which the patient is identified as having CRPC and begins follow-up for the occurrence of a second (nonprostate) cancer. After documentation of castration (either surgical castration or androgen deprivation therapy) for prostate cancer, the cohort entry date will be defined operationally as the date on which the patient first received one of the therapies representing a second-line systemic treatment for prostate cancer that progressed after castration. Study follow-up time for each patient will continue until the earliest occurrence of death, discontinuation of Part A or Part B Medicare coverage, enrollment in a health maintenance organization, claim for Xofigo, or the end of the study period.

The cohort will include men who are enrolled in both Medicare Parts A and B for at least 1 year before the cohort entry date, have a primary site code of prostate cancer in SEER data, have surgical castration or androgen deprivation therapy after prostate cancer diagnosis, have evidence that prostate cancer was resistant to the castration as indicated by starting a second-line systemic therapy, and have an cohort entry date of 01 January 2006 or later on which they are aged 65 years or older.

Exclusion criteria are having been enrolled in a health maintenance organization during the year before the cohort entry date or having a diagnosis of any cancer other than prostate cancer or nonmelanoma skin cancer on or before the cohort entry date.

All eligible subjects in the SEER-Medicare linked database will be selected (i.e., there will be no sampling). SEER data are representative of the US population, and Medicare data are representative of the US population aged 65 years and older.

Variables

The variables of interest in this study include demographic characteristics (age and race), clinical characteristics (e.g., comorbidities, cancer stage and grade at the time of initial diagnosis, time between diagnosis and progression to CRPC), treatments (e.g., surgical castration, drugs used for medical androgen deprivation, and bone-directed therapies), and the second primary cancer diagnoses that are the study outcomes.

Data sources

This study will use the SEER-Medicare linked database, which combines cancer registry data from the SEER Program of the National Cancer Institute and claims data from Medicare.

Study size

The study will use SEER-Medicare data for all eligible patients who meet study inclusion/exclusion criteria. The study size is therefore based on pragmatic considerations rather than a formal study size calculation.

Data analysis

For the primary objective of calculating incidence rates of secondary primary cancers among patients with CRPC, point estimates will be calculated by dividing cancer events by person-time at risk and presented as estimates with 95% confidence intervals. The cancer incidence rates in phase 2 will be estimated both as crude incidence rates and as standardized incidence rates using as the standard the age distribution of patients in the REASSURE study.

The secondary objectives each focus on calculating the proportion of the study cohort (or, for the third secondary objective, a subgroup) who meet certain criteria. Proportions will be reported as point estimates with 95% confidence intervals.

A separate statistical analysis plan will describe the details of the analysis to be performed, including algorithms used to define study outcomes, drugs, and surgical procedures, as well as how missing data will be handled for specific variables.

Milestones

The SEER-Medicare data used in this study will have been collected from 01 January 2006 through 30 June 2016. The final report of study results from the phase 1 and phase 2 analyses will be submitted on 13 November 2016 and 10 December 2016, respectively. This is not a postauthorization safety study (PASS) and it will not be registered in the EU-PAS register, but the protocol will be listed with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

5. Amendments and updates

None.

6. Milestones

Milestones for the study are listed in Table 1.

Table 1 Milestones

Milestone	Planned date
Start of SEER-Medicare data	01 January 2006
End of SEER-Medicare data	30 June 2016
Final report of study results (from first analysis)	13 November 2016
Updated final report of study results (with results from second analysis)	10 December 2016

* Only if agreed with authorities.

7. Rationale and background

Xofigo (radium-223 dichloride), an alpha particle-emitting pharmaceutical, was approved by the United States (US) Food and Drug Administration (FDA) in May 2013 (Bayer HealthCare Pharmaceuticals Inc., 2013) and by the European Medicines Agency in November 2013 (EMA, 2016) for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases, and no known visceral metastatic disease.

Xofigo may contribute to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may be associated with an increased risk of cancer (Gilbert, 2009). Nonclinical studies of Xofigo in rats showed an increased risk of neoplasms, including osteosarcomas. Genetic toxicology studies have not been conducted with Xofigo, but its mechanism of action involves induction of double-strand DNA breaks, which is a known effect of radiation (Bayer HealthCare Pharmaceuticals Inc., 2013). In the randomized clinical trial of Xofigo—"Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA)," ClinicalTrials.gov NCT00699751 (ClinicalTrials.gov, 2015a; Parker et al., 2013)—the overall incidence of new malignancies was lower on the Xofigo arm (< 1%) than on placebo (2%) (Bayer HealthCare Pharmaceuticals Inc., 2013), and no cases of Xofigo-induced cancer have been reported in clinical trials in follow-up of up to 3 years (Bayer Pharma AG, 2013). However, as noted in the Xofigo FDA product information, the expected latency period for the development of secondary malignancies exceeds the duration of follow-up available in clinical trials (Bayer HealthCare Pharmaceuticals Inc., 2013).

As a postmarketing requirement, Bayer HealthCare Pharmaceuticals, Inc. (Bayer) is conducting a single-arm, noninterventional, prospective cohort study to evaluate the long-term safety profile of Xofigo—"Observational Study for the Evaluation of Long-term Safety of Radium-223 used for the Treatment of Metastatic castration Resistant Prostate Cancer (REASSURE)," ClinicalTrials.gov NCT02141438 (ClinicalTrials.gov, 2015b)—including the incidence of second primary malignancies in patients with CRPC receiving Xofigo in routine clinical practice settings. The study will enroll 1,320 patients who will be followed for up to 7 years.

To provide context for second primary malignancy incidence rates 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.

According to data from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program, there will be an estimated 220,800 new prostate cancer cases diagnosed and an estimated 27,540 deaths due to prostate cancer in the US in 2015. Prostate cancer is most frequently diagnosed among men who are 65 to 74 years of age. Of the new cases diagnosed each year, approximately 4% are diagnosed at a distant stage. Metastatic disease can also develop in men whose prostate cancer presented initially at an earlier stage, and the cases that progress to become metastatic disease after the initial diagnosis account for most of the deaths due to prostate cancer (NCI, 2015a). Bone metastases are by far the most common site of distant disease.

Most men with advanced prostate cancer are treated with orchiectomy (castration) or hormonal therapy (also known as “medical castration” or “androgen deprivation therapy”), but eventually the disease can become resistant and progress. Second-line therapy is used in men whose prostate cancer has become “castration resistant” (CRPC).

The SEER Program collects clinical, demographic, and cause-of-death information for patients with cancer, and on a regular basis links its database with the Medicare claims database. The SEER-Medicare linked database is a suitable data resource for providing the estimates required for this study. RTI Health Solutions (RTI-HS) has previously conducted two studies in prostate cancer using these data (Gilsenan et al., 2008; Johannes et al., 2011).

Following a feasibility assessment by Bayer of appropriate external secondary data sources, an epidemiology program has been established by Bayer that consists of three observational studies using population-based databases in Europe (Germany and Sweden) and in 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). The study in Sweden will be conducted using the Swedish register databases. The present study protocol describes the US component of this epidemiology program.

8. Research questions and objectives

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

In phase 1 of the present study, RTI-HS will analyze the collective incidence rate of all second primary malignancies (other than nonmelanoma skin cancer) among men with CRPC. This phase of the study is planned to be completed before the conclusion of the REASSURE study. In phase 2 of the present study, RTI-HS will analyze the individual incidence rates of selected specific second primary malignancies, to be determined in collaboration with Bayer based on findings from the REASSURE study and other scientific considerations such as the number of cases of various cancers in the present study. The present study will provide

context for an interim analysis of the first 600 patients in the REASSURE study, which is planned by Bayer to be conducted by the end of 2016.

Patients with CRPC, as determined by treatment with a second-line systemic therapy after a diagnosis of prostate cancer and treatment with androgen deprivation (i.e., surgical or medical castration) (Unger et al., 2015), will be selected for cohort entry. The study period starts at the time of availability of Medicare Part D (which provides coverage for outpatient prescription drugs) and continues through the end of the current availability of SEER-Medicare follow-up data.

Secondary objectives aim to provide further information about the documentation of bone metastases in Medicare data and the extent of use of only oral androgen deprivation drugs among patients with Medicare Part D coverage, as well as to estimate overall survival of the study population. These include the following questions:

1. What proportion of men with CRPC 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? If the proportion of men with evidence of bone metastases (identified by diagnostic code and/or therapy) is high (e.g., > 85%), RTI-HS will consider restricting the study analyses to patients with CRPC whose bone metastases are thus documented.
2. What proportion of men received *only oral* androgen deprivation therapy (i.e., no *parenteral* androgen deprivation therapy) among those who met the CRPC definition and had Medicare Part D coverage?
3. What is the estimated overall survival of men with CRPC?

Study phases and the research objectives addressed in each phase are illustrated in Figure 1.

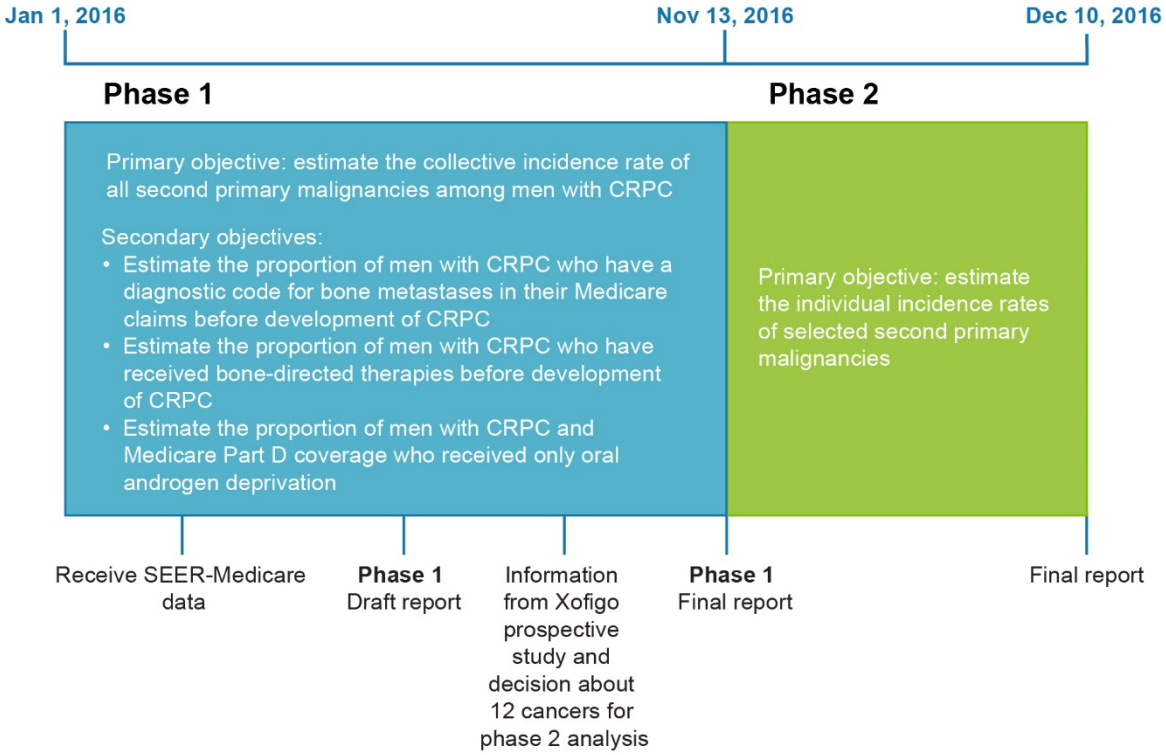

Figure 1. Study Phases and Research Objectives

8.1 Primary objective

The primary objective for phase 1 is to estimate the collective incidence rate of all second primary malignancies (other than nonmelanoma skin cancer) among men with CRPC. The primary objective for phase 2 is to estimate the individual incidence rates of selected second primary malignancies. The cancer incidence rates in phase 2 will be estimated both as crude incidence rates and as standardized incidence rates using as the standard the age distribution of patients in the REASSURE study.

8.2 Secondary objective(s)

- Estimate the proportion of men with CRPC who have a diagnostic code for bone metastases in their Medicare claims before development of CRPC, and estimate the proportion of men with CRPC who have received bone-directed therapies before development of CRPC
- Estimate the proportion of men with CRPC and Medicare Part D coverage who received only oral androgen deprivation therapy
- Estimate overall survival of men with CRPC

9. Research methods

9.1 Study design

This is a retrospective, observational cohort study of US men aged 65 years and older with CRPC. A diagnosis of prostate cancer will be established using SEER data. Medical androgen deprivation therapy or surgical castration will be documented in Medicare data. Evidence in Medicare data for treatment with a second-line systemic therapy (other than Xofigo) will be taken to indicate castration resistance. The overall rate of second primary malignancies (other than nonmelanoma skin cancer) and selected specific second primary malignancies will be estimated for this population. There is no internal comparison group for this study, although ultimately these rates will be used to provide perspective on incidence rates found in the REASSURE study.

9.2 Setting

9.2.1 Study time frame

The different time periods of the study are defined as follows:

- *Study period*: The study period will be 01 January 2006 through the latest year of available Medicare data (2013). Note that SEER data, which will be used to identify cases of prostate cancer, are available only through 2011.
- *Cohort entry date:* The cohort entry date in this study is the day on which the patient is identified as having CRPC and begins follow-up for the occurrence of a second (nonprostate) cancer. After documentation of castration (either surgical castration or androgen deprivation therapy, i.e., “medical castration”) for prostate cancer, the cohort entry date will be defined operationally as the date on which the patient first received a therapy representing a second-line systemic treatment for prostate cancer (other than Xofigo).
- *Follow-up:* Study follow-up time for each patient will continue 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

Note: for the overall cancer analysis, the person-time at risk will stop at the earlier of end of study follow-up or first occurrence of cancer. For the analysis of specific cancers, person-time at risk will stop at the earlier of end of study follow-up or the occurrence of the specific cancer, but not at the occurrence of other cancers.

9.2.2 Selection criteria

The study cohort includes men aged 65 and older in the US enrolled in Medicare with castrate resistant prostate cancer identified after January 1, 2006. The specific inclusion criteria are described below.

Inclusion criteria: The study cohort will include men who meet *all* of the following inclusion 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)
- Primary site code of prostate cancer (International Classification of Diseases for Oncology, Third Edition [ICD-O-3][1] topography code C61.9) in SEER data
- Surgical castration or androgen deprivation therapy after prostate cancer diagnosis; androgen deprivation therapy will be 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
- Evidence that prostate cancer was resistant to surgical castration or androgen deprivation therapy ("castration-resistant prostate cancer"), as indicated by starting one of the following second-line systemic therapies (cohort entry date): abiraterone, cabazitaxel, docetaxel, enzalutamide, mitoxantrone, or sipuleucel-T
- Cohort entry date 01 January 2006 or later
- Age 65 years or older on the cohort entry date

Exclusion criteria: Men who meet *any* of the following exclusion criteria will be excluded from the study cohort:

- Enrollment in an HMO in the year before the cohort entry date
- Diagnosis of any cancer other than prostate cancer or nonmelanoma skin cancer on or before the cohort entry date
- Any diagnostic code for metastases other than bone metastases or lymph node metastases on or before the cohort entry date
- Any claim for treatment with Xofigo on or before the cohort entry date

9.2.2.1 Identifying Patients With Castration-Resistant Prostate Cancer

"Castration resistant" refers to patients who show evidence of prostate cancer progression despite medical or surgical castration. According to Heidenreich et al. (2014), several groups have published recommendations for defining CRPC in clinical practice. The key defining factors of these definitions include castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either (1) biochemical progression—three consecutive rises of prostate-specific antigen (PSA), 1 week apart, resulting in two 50% increases over the nadir, with PSA > 2 ng/mL, or (2) radiological progression—the appearance of two or more bone lesions on bone scan or

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

enlargement of a soft tissue lesion using Response Evaluation Criteria in Solid Tumors (RECIST).

Although using this definition for a study such as the present one would be ideal, information regarding serum testosterone levels, PSA measurements, and results of bone imaging studies are not available in Medicare claims data. Therefore, the present study will use a pragmatic approach to defining CRPC based on second-line treatments administered after surgical or medical castration to indicate that progression has occurred despite castration. Specifically, SEER data will be used initially to identify all men in the study population diagnosed with prostate cancer. Algorithms specifying orchiectomy that were created for a previous study (Johannes et al., 2011) will be used to identify surgical castration (bilateral orchiectomy). A list of drugs described in the American Urological Association Guidelines (Cookson et al., 2015), modified by further information provided by Bayer, will be used to identify medical castration (androgen deprivation therapy). Use of second-line systemic treatments (other than Xofigo) will be taken to indicate castrate resistance (Cookson et al., 2015; Heidenreich et al., 2014; Unger et al., 2015). We will not use treatment with Xofigo to define CRPC because the present study is intended to provide context for cancer incidence rates that will be estimated in the REASSURE study of patients treated with Xofigo, and patients treated with Xofigo before cohort entry will be excluded from the present study. For patients who initiate treatment with Xofigo after cohort entry, second primary cancer events (and person-time of follow-up) that occur before the start of Xofigo will be included in the estimation of incidence rates, but second primary cancer events (and person-time of follow-up) that occur on the day of or after the start of Xofigo will be censored.

More than 90% of patients with metastatic prostate cancer have bone metastases (with or without metastases in other organs) (Bubendorf et al., 2000), but bone metastases may not be recorded reliably in insurance claims data. Selecting patients who receive a second-line systemic treatment after surgical castration or androgen deprivation therapy is expected to have a high predictive value for selecting those with CRPC and bone metastases because of the high prevalence of bone metastases among men with metastatic prostate cancer. The alternative strategy of relying on a specific International Classification of Diseases (ICD) code for bone metastasis in claims data would be expected to substantially underascertain the population of interest. For example, in a SEER-Medicare study of patients with metastatic prostate cancer (all of whom were diagnosed initially with stage IV disease), the sensitivity of the International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) code for bone metastases (198.5) recorded in the Medicare data within the period from one month before to one month after the month of diagnosis in which bone metastases were documented in the SEER data was 58.8% (Onukwugha et al., 2012). Moreover, experts at the Healthcare Delivery Research Program in the Division of Cancer Control & Population Sciences at the US NCI advise, in general, that metastases occurring after a diagnosis of cancer in the SEER-Medicare data cannot be determined reliably from diagnostic codes (NCI, 2015b). Therefore, to avoid unnecessarily reducing the size of the eligible study population, we define study eligibility by the recorded use of second-line treatments rather than by a diagnostic code for bone metastases. However, the frequency of recording of the diagnostic code for bone metastases and treatment codes for bone-directed therapies will be explored in secondary objectives, with the possibility of restricting the study cohort to patients whose records contain these codes as evidence of bone metastases if the proportion

of men with CRPC and a history of documented bone metastases by either of these criteria is high (e.g., > 85%).

9.2.3 Study population

The following features define the study population (see also Figure 2):

- *Source:* See Section 9.4, Data sources.
- *Sampling strategy:* All eligible subjects will be selected; there will be no sampling.
- *Representativeness:* SEER data are representative of the US population, and Medicare data are representative of the US population aged 65 years and older, as almost all of this population is covered. Thus, the study population should be representative of the US population aged 65 years and older with CRPC.

Although patients with pre-existing cancers (other than prostate cancer) are eligible for the REASSURE study, such patients will be excluded from the present study (other than those with pre-existing nonmelanoma skin cancers) because diagnostic codes related to a pre-existing cancer may falsely indicate 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). RTI-HS will report the number of patients excluded from the study cohort for this reason.

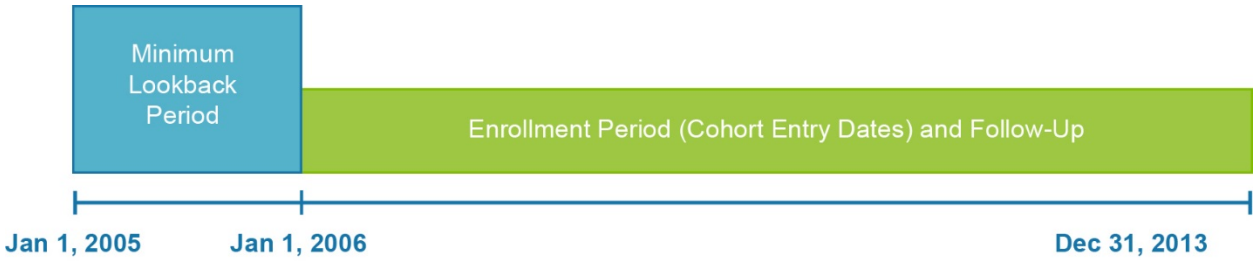

Figure 2. Study Schema

9.3 Variables

9.3.1 Baseline characteristics

Unless otherwise stated, the following characteristics will be assessed at on or before cohort entry date and will be ascertained from Medicare data:

Demographics characteristics:

- Age (65-69, 70-74, 75-79, 80-85, 85+ years) at cohort entry
- Race (white, black, Asian, Hispanic, native American, other, unknown)

Clinical characteristics:

- Stage and grade of prostate cancer at initial diagnosis (from SEER)
- Time from initial diagnosis of prostate cancer to development of CRPC
- Comorbidities (as per Charlson or NCI comorbidity index)
- History of visceral metastasis

- Bone metastasis diagnosis
- Bone-directed therapies (proxy for bone metastases diagnosis) including alendronate, clodronate, denosumab, ibandronate, pamidronate, risedronate, and zoledronate

Treatments:

- Surgical castration
- Drugs used for medical androgen deprivation
- Primary treatments at the time of initial prostate cancer diagnosis per SEER: surgery (yes/no/unknown); radiation (yes/no/unknown) (from SEER)
- Other treatments for prostate cancer
  - Chemotherapy
  - Radiation therapy
  - Radiopharmaceuticals

9.3.2 Exposure

There is no study exposure in this protocol. Follow-up begins with CRPC as defined by second-line systemic treatment, but cancer incidence rates will be estimated only for the whole study cohort (without regard to subsequent drug treatments).

9.3.3 Outcome measures

Bayer requires population-based estimates of the background rates of second primary malignancies. In phase 1, we will estimate the collective incidence rate of any second primary cancer (other than nonmelanoma skin cancer) in men with CRPC. This analysis is planned to be completed before the conclusion of the REASSURE study. In phase 2, we will estimate incidence rates for selected specific cancers of interest, as determined by the REASSURE study and other scientific considerations such as the number of cases of various cancer types observed in the present study.

Second primary cancer events will be ascertained using both SEER data and Medicare data. Specific codes for primary malignancies (not metastatic) from SEER and Medicare data sets will be used for second primary malignancy ascertainment. Details on specific codes will be described in the statistical analysis plan (SAP). SEER is the most reliable population-based source of information available in the US on cancer incidence, and SEER data are commonly used to estimate the incidence of first malignancies, as well as second or subsequent malignancies, in population-based studies; for example, see Berrington de Gonzalez et al. (2010). The SEER data contain information about all primary cancers a person may develop regardless of whether it is their first or a subsequent primary malignancy. Basic SEER diagnostic information (including month and year of diagnosis) is available for up to 10 primary cancers for each person, with ICD-O-3 topography codes recorded in the variables site1-site10 to identify the anatomic site in which each primary tumor originated. Additionally, SEER data contain variables indicating how many primary tumors have been diagnosed for each patient and the chronological sequence number for each primary tumor.

Data regarding metastases from a previously registered primary malignancy, if reported to SEER, are included in a variable field that is separate from that used to specify primary tumors (whether first or subsequent). As part of the information on stage, metastases are routinely captured when present at the time of the initial diagnosis of a primary tumor. However, metastases occurring subsequently (i.e., in a patient who initially presented with a more limited stage of cancer but subsequently experienced disease progression) may or may not be captured.

Identifying second primary cancers in Medicare data is not as precise as in SEER data. 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 so, if used accurately, these codes will also distinguish primary cancers (whether first or subsequent) from metastases. Although there is no coding of the number of primary cancers diagnosed in a particular patient or their sequence, a second primary cancer can be identified in Medicare data as the first new primary cancer documented in a patient with only one previous primary cancer diagnosis. Second primary cancers will be identified in Medicare data by searching the MedPAR (hospital inpatient), Outpatient (hospital outpatient), and Carrier (physician) claims files for primary cancer ICD-9-CM codes associated with encounters that occur after the date of the initial prostate cancer diagnosis. Any such diagnosis occurring before a patient is determined to have CRPC will exclude the patient from the study cohort. Among eligible patients, the first such diagnosis occurring after the date of cohort entry will be counted as an event for the analysis of second cancer incidence rates.

Since the reliability (sensitivity, specificity, positive predictive value, and negative predictive value) of Medicare claims data to identify second primary cancer outcomes in men with CRPC is uncertain, sensitivity analyses will be conducted to assess the effect on the estimated incidence rates of not including second primary cancer events identified only in the Medicare data.

9.4 Data sources

The SEER-Medicare Linked Database has been selected for this study. This combines data from the SEER Program of the NCI, which collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 30 percent of the US population (NCI, 2015c), 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, the first course of treatment, and date of death. The SEER-Medicare data linkage began in 1991 and currently is updated every 2 years. As of the most recent update in November 2014, the linked database included all Medicare eligible persons appearing in the SEER data who were diagnosed with cancer through 2011 and all of their 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). For the cancer cases, patients may be 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 (NCI, 2015d).

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.

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

- Medicare Provider Analysis and Review (MedPAR): the MedPAR file includes all Part A short stay, long stay, 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.
- Carrier claims (also known as the Physician/Supplier Part B): the Carrier file contain Part B claims submitted by noninstitutional 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 includes 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 Procedure 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.
- Outpatient claims: 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 HCPCS procedure codes.
- Home Health Agency claims: 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 a HCPCS procedure code.
- Hospice claims: the hospice file contains claims submitted by hospice providers. Each claim contains up to 25 ICD-9-CM diagnosis codes and a HCPCS procedure code.
- Durable Medical Equipment (DME) claims: the 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.
- Medicare Part D data: the Part D enrollment file contains variables for each year beginning in 2006 to indicate which Medicare beneficiaries are enrolled in Part D and the dates of coverage. Information regarding prescription drug utilization is obtained from the Prescription Drug Event file. Drugs are recorded within each claim by both brand and generic name.

9.5 Study size

This study will use SEER-Medicare data for all eligible patients with cohort entry dates after 01 January 2006. The study size is therefore based on pragmatic considerations rather than a formal study size calculation. Based on the assumptions and calculations described below, we estimate that approximately 15,750 eligible patients will be identified in the SEER-Medicare database. The incidence count of CRPC in the US in 2006-2011 is assumed to be approximately equal to the total mortality count for prostate cancer in the US in those years, 176,190 (American Cancer Society, 2006-2011). Since approximately 90% of prostate cancer deaths occur among patients aged 65 years or older at the time of death (NCI, 2015a), we assume that 85% of patients who develop CRPC were aged 65 years or older at the time of their initial diagnosis. This reduces the potential study population to approximately 150,000 (176,190 x 0.85). Since the study is limited to patients enrolled in Medicare Parts A and B and not enrolled in an HMO during the year prior to their diagnosis, we further reduce this estimate by a factor of 0.78—average of the percentage aged 65 years and over enrolled in fee-for-service (not HMO) ranging from approximately 85% in 2005 (CMS, 2007) to 73% in 2011 (CMS, 2012a)—and by an additional factor of 0.90—among the fee-for-service enrollees, about 90% of which were enrolled in both Part A and Part B (CMS, 2012b)—yielding a potential sample of approximately 105,000 (150,000 x 0.78 x 0.9). Approximately 30% of the US population lives in a region contributing to SEER (NCI, 2015c), reducing the estimated number of men with CRPC who would be eligible for the study if they received second-line treatment to approximately 31,500 (105,000 x 0.3). Finally, we estimate that approximately 50% of such patients actually receive second-line systemic treatment—a somewhat higher proportion than the 41.7% of men with CRPC who received chemotherapy during the year before death as reported by Abdollah et al. (2015), since all the patients in that study were diagnosed initially with metastatic prostate cancer. Patients in the present study will be a mix of patients diagnosed with metastatic disease and patients diagnosed with earlier stages of disease but progressed to metastatic disease while under medical observation. We assume that men who progress to metastatic disease while under medical observation will tend to be younger and have less extensive metastases than those diagnosed initially with metastatic disease, and therefore will be more likely to be considered candidates for further systemic treatment after failure of androgen deprivation therapy. This reduces the estimated study size to approximately 15,750 (31,500 x 0.5).

9.6 Data management

Data received from SEER will be checked for accuracy and completeness per RTI-HS standard operating procedures (SOPs) and stored on a secure server in a location where access is limited to the appropriate project staff. Creation of the analysis data sets and analysis of the data will be performed using SAS software release 9.3 or higher run on the Windows and/or Linux platforms. There is no ability to query missing values in the SEER-Medicare data.

RTI-HS will retain all study analytic programs, results, and related project materials for 15 years in accordance with the contractual agreement between Bayer HealthCare Pharmaceuticals, Inc., and RTI-HS to conduct this study, and subject to the license agreement for use of SEER-Medicare data, which permits retention of SEER-Medicare data files for a maximum of 5 years unless the NCI grants permission for a longer retention period.

9.7 Data analysis

For the primary objective of estimating incidence rates of secondary primary cancers among patients with CRPC, outcome events will be ascertained as the first recorded second primary cancer in SEER data or as the first recorded ICD-9-CM code for an inpatient or outpatient encounter in the Medicare data. Incidence rate estimates will be calculated by dividing cancer events by person-time at risk and presented as point estimates with 95% confidence intervals based on the Poisson distribution. The cancer incidence rates in phase 2 will be estimated both as crude incidence rates and as standardized incidence rates using as the standard the age distribution of patients in the REASSURE study. Consideration will also be given to standardization by race, in addition to age, since a substantial proportion of men in the US are black (and this proportion may be higher than that in the Xofigo study), and there is evidence that the epidemiology of prostate cancer varies between blacks and whites in the US. (The incidence rates of prostate cancer in the US in 1975-2012 among men age 65 years or older were approximately 881 per 100,000 among whites and 1,305 per 100,000 among blacks, a nearly 1.5-fold difference (Howlader et al., 2015, Table 23.5); the mortality rates of prostate cancer in the same population during this period were approximately 210 among whites and 461 among blacks, a 2.2-fold difference (Howlader et al., 2015, Table 23.6). Therefore, it is possible that the incidence of second primary malignancies may also vary between black and white patients with CRPC.

The secondary objectives each focus on calculating proportions of the cohort (or, for the third secondary objective, a subgroup) who meet certain criteria. Proportions will be reported as point estimates with 95% confidence intervals.

The number of patients excluded from the study because of a prior diagnosis of malignancy will be reported.

A detailed description of the analysis to be performed will be included in a separate SAP. The SAP will also include descriptions of algorithms (including code lists) to be used to define study outcomes, drugs, and surgical procedures, as well as how missing data will be handled for specific variables.

9.8 Quality control

In accordance with relevant SOPs, the initial programmer(s) will review all program log files for errors messages, messages about unexplained variables, and warning messages and will retain electronic copies of all final program log files in the project folder. The programmer will account for the number of observations reported at each executed data step and make note in the program code when the number of observations increases or decreases. Listings of observations/results from intermediate and final data sets will be output and reviewed. A quality control (QC) analyst(s) will perform quality-control review for all programs written by the initial programmer(s). The strategy for validation of SAS programs will be defined at the level of the individual program by the project analyst, if necessary in consultation with the project director, after each program is completed and the level of complexity of the program has been identified.

All study reports will undergo senior scientific, quality control, and editorial review. Documentation of these reviews will be maintained in accordance with relevant SOPs.

9.9 Limitations of the research methods

We will use second-line treatment (after surgical castration or medical androgen deprivation therapy) to define CRPC. There will likely be other (untreated) patients who meet biochemical and clinical criteria for CRPC in the SEER-Medicare database who are not eligible for this study. Although this may seem to be a limitation, it is more likely 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 with CRPC who are eligible for the present study because they have been selected for 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 decline or are not considered to be candidates for treatment with second-line systemic therapies.

A minor limitation of the present study is that approximately 10% of patients with metastatic prostate cancer do not have bone metastasis (Bubendorf et al., 2000). This is a potential source of selection bias. However, since diagnostic codes for bone metastases may be underrecorded in claims data, relying on the presence of such a code might reduce the size of the study population to a greater extent than is necessary. As secondary objectives, we will estimate the proportion of men who meet the operational definition of CRPC who have a diagnostic code recorded for bone metastases and/or evidence of treatment with bone-directed therapies. If this proportion is high (e.g., 90%), we will consider restricting the study population to patients with recorded bone metastases and/or bone-directed therapies when the phase 2 analysis is conducted.

Another potential limitation of this study is that several of the drugs used to identify medical castration are oral therapies that will be identifiable only among patients who have Medicare Part D coverage (approximately 40% of the subjects). This could result in some potentially eligible subjects not being included in the study cohort. The proportion of men whose only hormonal therapy is oral (and therefore found only in Part D data) will be estimated as a secondary objective, and a decision will be made whether to modify the protocol to require Part D data for all subjects for the phase 2 analysis. However, it is anticipated that the proportion of patients with only oral androgen deprivation treatment will be small.

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 is expected to provide more precise estimates of second primary malignancy risks in men with CRPC than other available US data resource. However, 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. If so, consideration will be given to adjustment for race (as well as age) in the analyses of the present study data.

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. These are potential sources of information bias.

Finally, although the underlying purpose of the present study is 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 plan to estimate age- and possibly age-race-standardized cancer incidence rates, methods to adjust for other potential differences between study populations, such as propensity score stratification or regression modeling, may be considered in the future. If a decision is made to pursue such methods, they would be described in a separate comparative analysis plan. Such a decision would likely not be made until results from the REASSURE study are available.

9.10 Other aspects

This is not a postauthorization safety study (PASS), but the protocol will be listed with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

10. Protection of human subjects

For use of the SEER-Medicare data, it is required that institutional review board (IRB) review and approval be obtained before an application to use Medicare data can be approved. RTI International's[2] Office of Research Protection holds a Federal-Wide Assurance from the Department of Health and Human Services Office for Human Research Protections (FWA #3331, effective until 05 February 2019) that allows RTI to review and approve human subjects protocols through its internal IRB committees. The Federal-Wide Assurance requires IRB review for all studies conducted by RTI-HS that involve human subjects, regardless of the funding source, and all approved studies must undergo a continuing review by the IRB at once per year. RTI-HS study staff will manage the completion and submission of all forms and the tracking of updates or changes that need to be reported to the IRB.

The SEER-Medicare data are available to outside investigators for research purposes. Although personal identifiers for all patient and medical care providers have been removed from the SEER-Medicare data, there remains the remote risk of re-identification (given the large amount of data available). Therefore, the SEER-Medicare data are not public use data files. Investigators are required to obtain approval for specific research questions to obtain the data to ensure the confidentiality of the patients and providers in SEER areas (NCI, 2015e).

RTI-HS will prepare and submit the required documents to obtain SEER-Medicare data, including the application form, the SEER-Medicare data use agreement, IRB approval, and the request form for any restricted variables (if necessary).

11. Management and reporting of adverse events/adverse reactions

As per the European Medicine Agency (EMA) Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for noninterventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required (EMA, 2014). Reports of adverse events/reactions will be summarized in the study report in aggregated form, if applicable.

[2] RTI Health Solutions is a business unit of RTI International.

12. Plans for disseminating and communicating study results

The investigators will prepare a study report that will include a description of the study design, methodology, results, and interpretation.

At this time there are no plans for dissemination of study results beyond the study report.

13. List of references

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Annex 1. Code lists

Bilateral orchiectomy:

- ICD-9-CM:
  - 62.4x: bilateral orchiectomy; either removal of both testes at same operative episode or removal of remaining testis
- Current Procedure Terminology (CPT)/ Healthcare Common Procedure Coding System (HCPCS) code; used only when 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
  - 54690: laparoscopic surgical orchiectomy (since the year 2000)

Intravenous second-line systemic treatments will be identified with HCPCS codes. Oral second-line systemic treatments use will be identified in Medicare Part D data by drug name:

- Cabazitaxel (C9276 and J9043)
- Docetaxel (J9170, J9171)
- Mitoxantrone (J9293)
- Sipuleucel-T (C9273)
- Abiraterone
- Enzalutamide

Annex 2. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013; Doc.Ref. EMA/540136/2009

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

Study reference number:
[add reference number here]

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[3]	☒	☐	☐	9
1.1.2 End of data collection[4]	☒	☐	☐	9
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register	☐	☐	☒	9
1.1.6 Final report of study results	☒	☐	☐	9

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	9-10
2.1.2 The objectives of the study?	☒	☐	☐	10-12
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	10-12

[3] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[4] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 if applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	13
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	17
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	21-21

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	14-16
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	14
4.2.2 Age and sex?	☒	☐	☐	14
4.2.3 Country of origin?	☒	☐	☐	14
4.2.4 Disease/indication?	☒	☐	☐	14
4.2.5 Co-morbidity?	☒	☐	☐	14
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☒	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☒	17
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	17
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	17
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	17
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	16

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	16
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	18-20
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	16-18
8.1.3 Covariates?	☒	☐	☐	16-18
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	17
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	17
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	17
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	14
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	14-16

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	14-16
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	18

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	20-20

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	20-20
10.3 Are descriptive analyses included?	☒	☐	☐	20-20
10.4 Are stratified analyses included?	☒	☐	☐	20-20
10.5 Does the plan describe the methods for adjusting for confounding?	☐	☐	☒	20-20
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	21-21

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	20
11.3 Are methods of quality assurance described?	☒	☐	☐	21
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	22-23
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	22-23
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	22-23
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	20
12.3 Does the protocol address other limitations?	☒	☐	☐	22-23

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/ Institutional Review Board approval been described?	☒	☐	☐	23
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	23-23

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	9

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	24
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	24

Comments:

Name of the main author of the protocol: [redacted]

Date: dd/Month/year

Signature: _____

Annex 3. Signature pages