Observational Study Information

Title	Second primary cancers in patients with castration resistant prostate cancer (BOCARP[1])
Protocol version identifier	1.0
Date of last version of protocol	23 February 2016
EU PAS register number	Study not registered
Active substance	NA (external unexposed reference group for Therapeutic Radiopharmaceuticals (V10XX03), radium (223Ra) dichloride)
Medicinal product	NA (external unexposed reference group for Xofigo®)
Product reference	EU/1/13/873/001; NDA 203971
Procedure number	NA
Marketing authorization holder(s)	Bayer Pharma AG, Bayer Healthcare Pharmaceuticals Inc.
Joint PASS	NA (non-PASS)
Research question and objectives	The primary objective is to evaluate the incidence of developing any second primary malignancy (including myelodysplastic syndrome/acute myeloid leukaemia and osteosarcoma) among prostate cancer patients with bone metastases (mPC) and among a subgroup of mPC patients among whom the prostate cancer is castration-resistant (mCRPC). The secondary objectives are • To evaluate separately the incidences of site-specific second primary malignancies among mPC and mCRPC patients, and • To evaluate the overall survival of mPC and mCRPC patients. Information from this study will serve as a historical comparator for an international prospective observational single-arm cohort study in which the occurrence of second primary malignancies in mCRPC patients treated with Radium-223 is studied (The REASSURE study).
Country(-ies) of study	Germany

[1] "Bone metastases in castrate resistant prostate cancer" is the internally used name of the study at BIPS.

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Marketing authorization holder (s)

Marketing authorization holder(s)	Xofigo®: Bayer Pharma AG, Bayer Healthcare Pharmaceuticals Inc.
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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.

1. Table of Contents

2. List of abbreviations

ADT	Androgen deprivation therapy
ATC	Anatomical therapeutic chemical classification system codes
BIPS	Leibniz-Institute for Prevention Research and Epidemiology – BIPS GmbH
CI	Confidence interval
CPR	Central pharmaceutical reference database
CRPC	Castrate-resistant prostate cancer
DDD	Defined daily dose
DMP	Disease Management Programme
EBM	Claim code for outpatient services and procedures ("Einheitlicher Bewertungsmaßstab")
GEP	Good Epidemiological Practice
GePaRD	German Pharmacoepidemiological Research Database
GnRH	Gonadotropin-Releasing-Hormone
GPP	Good Pharmacoepidemiology Practice
GPS	Good Practice of Secondary Data Analysis
ICD	International Classification of Diseases
ICD-10-GM	German Modification of the International Classification of Diseases 10th Revision
LHRH	Luteinizing hormone-releasing hormone
mCRPC	(Bone) metastasized castrate-resistant prostate cancer
mPC	(Bone) metastasized prostate cancer
OPS	Claim code for inpatient services and procedures ("Operationen- und Prozedurenschlüssel")
PC	Prostate cancer
PSA	Prostate specific antigen
PZN	Central pharmaceutical number
SAP	Statistical Analysis Plan
SGB	Social Security Statute Book

SHI	Statutory health insurance
SIR	Standardized Incidence Ratio

3. Responsible parties

3.1 Bayer HealthCare

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4. Abstract

Title of the study: Second primary cancers in patients with castration resistant prostate cancer (BOCARP)

Rationale: With approximately 1,111,300 estimated incident cases, prostate cancer (PC) was the second most common form of cancer among males worldwide in 2012. The risk for PC is associated with age and increases from 0.5% for patients aged 45 years to 5.9% for those aged 75 years. Androgen deprivation therapies (ADTs) form the mainstay of PC treatment, which delays tumor growth by the suppression of testosterone. Patients with tumor progression after surgical or hormonal ablation are referred to as castration-resistant (CRPC), frequently featuring osseous metastases (mCRPC). Patients with mCRPC have a reduced life expectancy, and 97% will die within five years. The data on the epidemiology of mCRPC is scarce and inconsistent. As there is no cure for mCRPC, available treatment options mainly focus on the management of symptoms and palliative care. Recently, radium223-dichloride (Xofigo®) has been introduced to improve the overall survival in mCRPC patients by selectively targeting bone metastases with short-range alpha-particles. However, as a radioactive agent, radium-223-dichloride needs to be further monitored for safety after the authorization regarding the incidence of second primary malignancies under treatment. As for ethical reasons eligible patients cannot be denied the treatment with radium-223-dichloride, in order to facilitate comparisons with radium-223-dichloride, these safety data must be obtained from historical control groups. Thus, information from this study will serve as a historical comparator for an international prospective observational single-arm cohort study in which the occurrence of second primary malignancies in mCRPC patients treated with radium-223 is studied (The REASSURE study).

Objectives: This study aims at estimating the incidence of second primary malignancies as well as the overall survival among mPC and mCRPC patients not treated with radium-223-dichloride.

Methods: The source of data for this study will be the German Pharmacoepidemiological Research Database (GePaRD) comprising secondary claims data from more than 17 million insurants throughout Germany who are members of German Statutory Health Insurance (SHI) providers. A retrospective cohort study covering the time period from 2004 to 2013 will be

conducted. The study population will comprise CRPC patients developing bone metastases. These patients will be followed up for the occurrence of second primary malignancies, end of study, or death due to any cause. Incidence rates will be calculated stratified e.g. by age. As this study serves as a historical reference group for a single-arm observational study, incidence rates of second primary malignancies obtained from these two studies will be compared by the standardized incidence ratio using results from this study as a reference. The overall survival in the study population will be analysed using the Kaplan Meier method. All analyses will be carried out separately for mPC and mCRPC patients.

Strengths and Limitations: The main strength of this study will be the underlying large, representative database, covering approximately more than 52 millions of person-years across nine data years. The large sample size allows the estimation of incidence rates and will also enable further stratifications (e. g. by age, or duration of PC). Moreover, the main outcomes relevant for this study are well identifiable in GePaRD. As GePaRD was originally built for reimbursement purposes, not all relevant variables will be in the desired detail. This especially applies to histological parameters or tumour classifications, as results from lab tests are not available in the database. This will be a major flaw of the study as CRPC is understood as disease progression under treatment, usually indicated by rising prostate antigen levels. It should also be noted, however, that a uniform definition of mCRPC is still lacking so far. Considering that bone metastases usually present in 90% of patients with lab confirmed mCRPC, the selected approach in this study can be regarded as an adequate proxy. Moreover, certain treatment procedures that are relevant in the context of CRPC are not analyzable in full detail (e. g. chemotherapy, radiotherapy).

5. Amendments and updates

None.

6. Milestones

Table 1 Milestones

Milestone	Planned date
Start of data collection	Q1 2016
End of data collection	Q2 2016
Final report of study results	Q4 2016

7. Rationale and background

With approximately 1,111,300 estimated incident cases, prostate cancer (PC) was the second most common form of cancer among males worldwide in 2012 (1). PC accounted for 7.8% of all estimated incident non-cutaneous malignant neoplasms, yet varying from 4.4% in developing countries and to up to 12.5% in industrial countries (1). In Germany, the incidence rates of PC have risen from approximately 20,099 cases in 1980 to 65,800 cases in 2010 (2, 3). This growth, however, is also partly due to the simultaneously increased use of early detection measures, e. g. the prostate specific antigen (PSA) test, rather than a real tripling of incidence rates (4). This is also supported by the fact that the introduction of the PSA test has immediately reduced the incidence of progressed tumors by 50-70% (5).

The incidence of PC is clearly associated with age: 90% of all patients are older than 60 years, whereas PC barely occurs in patients below the age of 50. For males aged 45 years, the risk of developing PC within the next ten years is at 0.5% and increases to 5.9% for those aged 75 years (3). Thus, due to demographic ageing, 1.7 million PC incident cases are expected for the year 2030 worldwide (6). It should be noted, however, that beyond epidemiological studies on clinically diagnosed PC, an autopsy study has revealed substantially higher rates, with tumors in more than 75% of males aged ≥85 years, and even in more than 30% of males aged 30 to 40 years (7). This suggests that a substantial proportion of prostate tumors remains asymptomatic and thus does not become clinically significant within the lifespan (5). The relative survival rate is 93% within the first five years following diagnosis, and PC accounted for less than 6% of all cancer-related deaths among men worldwide in 2012 (1, 3). However, once the patient has

reached the symptomatic stage of PC, the prognosis worsens substantially. At that time, 30% of patients present with a locally progressed tumor and metastases, and the mean survival time drops to less than 3 years (8, 9).

Apart from age as an apparent risk factor, the etiology of PC still remains widely unclear. There is evidence obtained from twin studies that genetic predispositions might contribute to the incidence of PC, and it is estimated that up to 40% of prostate tumors might be attributed to genetic factors (10, 11). Epidemiological studies from the United States, however, have shown that PC occurs similar frequently in the second generation of immigrated Asian males like in Caucasian Americans (12). Thus, environmental factors are also assumed to be involved in the evolution of PC but it is unknown which ones are specifically linked with the disease (11). As an example, malnourishment has not been associated with PC (13, 14), while there is evidence for overweight being a moderate risk factor for the disease (15). Mild protective effects have been reported for physical activity (16, 17) and the consumption of lycopene (18, 19).

The dependence of tumor progression on the levels of androgens has already been described in 1941 and was corroborated by molecular biological studies since then. For this reason, aside from chemotherapies, hormone ablation still remains the cornerstone in the treatment of PC (20, 21). The administration of luteinizing hormone-releasing hormones (LHRH) analogs reduces the release of LHRH from the anterior lobe of the pituitary gland, stopping the testicles from further generating testosterone. As this does not affect the androgen synthesis in the adrenal glands, androgen receptor blockers (e. g. flutamide) are additionally utilized to obtain a maximal blockage of androgens. This leads to castrate levels of testosterone and therefore to a retardation of tumor growth.

While this strategy is initially effective, patients will eventually develop a castrate-resistant form of prostate cancer (CRPC), and show up with a further tumor progression even after surgical or hormonal castration. A frequent complication of CRPC is osseous metastases (mCRPC) which are present in 84% of patients at the time of CRPC diagnosis. One third of patients without metastases at that time develops them within two years (22). The progression from PC to CRPC is associated with a shortened life expectancy: 53% of patients die within the first year, and 97% within five years (23). Moreover, CRPC leads to a significant reduction in the quality

of life in patients with pain, nausea and vomiting as strongest impact factors (22, 24). The data on the epidemiology of CRPC is scarce and inconsistent due to different existing definitions in the literature (22). Two studies have estimated the prevalence of CRPC between 19% and 53% (25, 26).

As there is no cure for CRPC, the treatment of patients at this stage focuses on the management of symptoms by palliative care, radiotherapies, and chemotherapy (27, 28). For the treatment of bone metastases in PC, radium223-dichloride (Xofigo®) has been introduced to the US and the European market. This drug selectively targets bone metastases with high-energy, short-range alpha-particles and has been shown to significantly improve the overall survival in patients (median, 14.0 months vs. 11.3 months) (29-31). However, as a radiopharmaceutical agent, post-authorization monitoring of radiation associated second malignancies was requested. As for ethical reasons eligible patients cannot be denied the treatment with radium-223-dichloride, in order to build a control group to patients who are treated with radium-223-dichloride, these safety data must be obtained from historical control groups. Following feasibility assessment on appropriate external secondary data sources, an epidemiology program was established which consists of three observational studies using population-based databases in Europe (Germany and Sweden/Nordic country) and US. The study in Germany would be performed using GePaRD via the Leibniz Institute for Prevention Research and Epidemiology (BIPS). The study in Sweden will be conducted using the Swedish register databases. The US study is planned to be conducted using the US Surveillance, Epidemiology and End Results (SEER) and Medicare linked database. The current study protocol is part of this epidemiology program and will thus serve as a historical comparator for an international prospective observational single-arm cohort study in which the occurrence of second primary malignancies in mCRPC patients treated with radium-223 is studied (The REASSURE study).

8. Research questions and objectives

8.1 Primary objective

The primary objective of this study is to estimate the incidence of any second primary malignancy (including myelodysplastic syndrome/acute myeloid leukaemia and osteosarcoma) among patients with PC and bone metastases (mPC), as well as among a subgroup of patients for whom the PC can be regarded as castration-resistant (mCRPC).

8.2 Secondary objective(s)

The secondary objective of this study is the evaluation of the overall survival of mPC and mCRPC patients. Furthermore, the incidence of site-specific second primary malignancies will be evaluated.

This study does not aim at testing apriori hypothesis. Information from this study will serve as a historical comparator for an international prospective observational single-arm cohort study in which the occurrence of second primary malignancies in mCRPC patients treated with radium-223 is studied (The REASSURE study).

9. Research methods

9.1 Study design

This is an observational retrospective cohort study that uses claims data from three health insurance companies from Germany.

9.2 Setting

This is an observational retrospective cohort study, based on German secondary claims data obtained from the GePaRD database as depicted in section 9.4 of this study protocol. Patients with prostate cancer and with metastases will be identified using ICD-10-GM codes as recorded in the GePaRD. Treatments based on anatomical therapeutic chemical classification system (ATC) codes will serve as a proxy for mCRPC. Information on cancer diagnoses and time of death will be used as main outcome variables.

9.2.1 Study period

The study period covers all data years between January 1, 2004 and December 31, 2013. Hereof, the first data year (January 1, 2004 to December 31, 2004) will be used as the baseline period. The enrolment period for patients with mPC or mCRPC will take place from January 1, 2005 to December 31, 2011. The last two data years (January 1, 2012 to December 31, 2013) will serve as the follow-up period. This period, when no further patients are included, ensures that all enrolled patients have the possibility of at least two years of follow-up time before the study period ends.

9.2.2 Study population

According to the study objectives as defined above the study population will consist of mPC patients and a subgroup of patients who can be regarded as mCRPC patients.

Inclusion criteria

Members of the **mPC** cohort will have to fulfill all of the following criteria:

1. Valid information on sex, age and the region of residence
2. A period of at least 12 months of continuous insurance preceding cohort entry
3. Diagnosis of PC (ICD-10 Code C61) in the study period (January 1, 2004 – December 31, 2011)
4. Diagnosis of bone metastases (ICD-10 Code C79.5) in the enrolment period (January 1, 2005 – December 31, 2011)

In addition to the criteria of the mPC cohort, members of the **mCRPC** cohort will additionally have to fulfill:

5. One of the following in the enrolment period and before or at the same time with bone metastases
    a. Discontinuation of the initial chemical castration (see Table 2), change of the agent or modality of the ADT, or start of treatment for advanced PC after the primary ADT (see Table 3).
    b. Surgical castration and initiation of ADT treatment (see Table 3)

c. Treatment with medication specific to mCRPC (see Table 3)

Table 2. Identification of castration therapies.

Type of treatment	Identifier
Non-steroidal antiandrogenes	
Bicalutamide	ATC: L02BB03
Flutamide	ATC: L02BB01
Nilutamide	ATC: L02BB02
LHRH-Agonists/Antagonists	
Abarelix	ATC: L02BX01[a]
Buserelin	ATC: L02AE01, H01CA06
Degarelix	ATC: L02BX02[b]
Gonadorelin	ATC: H01CA01
Goserelin	ATC: L02AE03, H01CA05
Histrelin	ATC: L02AE05[c]
Leuprorelin	ATC: L02AE02, H01CA04
Nafarelin	ATC: H01CA02
Triptorelin	ATC: L02AE04, H01CA07
Other	
Cyproterone acetate	ATC: G03HA01, G03HB01[f]
Medroxyprogesterone acetate	ATC: L02AB02, G03AC06, G03DA02, G03FA12[f], G03FB06[f], G03AA08[f]
Estramustine	ATC: L01XX11[d]
Fosfestrol	ATC: L02AA04[g]
Polyestradiol phosphate	ATC: L02AA02[e]
Diethylstilbestrol	ATC: L02AA01[e]
Ethinylestradiol, mono	ATC: L02AA03, G03CA01
Estradiol	ATC: G03CA03, G03CC07, G03CA53[f], G03CD53[f]
Estrogens, conjugated	ATC: G03CA57
Estriol	ATC: G03CA04, G03CC06[f]
Surgical procedures	
Bilateral orchiectomy	OPS: 5-622

[a] available since 02/2008; [b] available since 06/2009; [c] available since 07/2009; [d] only identifiable if administered as capsules; [e] not available in Germany for the study period,[f] combination preparation containing the respective drug; [g]available in Germany until 1/2006

Discontinuation of treatment such as chemical castration is defined as the absence of any new exposure (e. g. new dispensation or new treatment in a hospital) for the same treatment or class of treatments within the duration of the previous exposure plus an additional grace period. Duration of exposure will be based on dates and amounts of drugs purchased or received in a pharmacy (or hospital, if available), and will be specified in the statistical analysis plan.

Table 3. Identification of treatments for advanced PC

Type of treatment	Identifier
Treatment for advanced PC	
Docetaxel	ATC: L01CD02[a]
Cabazitaxel	ATC: L01CD04[a, b]
Mitoxantrone	ATC: L01DB07[a]
Sipuleucel-T	ATC: L03AX17[f]
Ketoconazole	ATC: J02AB02
Treatment for mCRPC	
Abiraterone	ATC: L02BX03[c]
Enzalutamide	ATC: L02BB04[d]
Bone-directed treatments	
Bisphosphonates (e.g.):	
Clodronate	ATC: M05BA02
Ibandronic acid	ATC: M05BA06
Pamidronate	ATC: M05BA03
Zoledronic acid	ATC: M05BA08
Other:	
Denosumab	ATC: M05BX04[e]

[a]Specific chemotherapies cannot be identified in GePaRD since these are reimbursed by generic pharmaceutical reference numbers for logistic reasons; [b]available in Germany since 3/2011; [c]available in Germany since 10/2011; [d] available in Germany since 9/2013; [e]available in Germany since 7/2010; [f]available in Germany since 10/2014 and therefore not during the study period

For both study populations, cohort entry will be defined as the date of first bone metastases during the enrolment period.

Cohort exit will be defined as:

- End of study period (December 31, 2013)
- End of insurance coverage
- Death

Exclusion criteria

Patients will be excluded from the mPC and from the mCRPC populations if they meet any of the following criteria:

1. First PC diagnosis later than 2 months after the diagnosis of bone metastases, or
2. Use of any radiopharmaceuticals for bone metastases (e.g., samarium, strontium, rhenium, radium).

PC and bone metastases, visceral metastases (see Table 5) and any other cancer will be identified using hospital main discharge diagnoses and hospital secondary diagnoses. The admission date of the respective hospitalization will be defined as the date of the diagnosis.

9.3 Variables

9.3.1 Characteristics and other variables

Variables listed in Table 4 and Table 5 will be used primarily to characterize the cohort or to identify criteria variables.

Table 4: Identification of other treatments

Type of treatment	Identifier
Other cancer-related treatments	
[^{153}Sm] Samarium lexidronam	ATC: V10BX02[a]
[^{89}Sr] Strontium chloride	ATC: V10BX01[a]
[^{186}Re] Rhenium etidronate	ATC: V10BX03[a]
Estramustine	ATC: L01XX11
Radiotherapy	OPS: 8-52; EBM: 2533, 2534, 25214
Inpatient therapy with radionuclides	OPS: 8-530.1
Outpatient therapy with radionuclides	EBM: 17372, 40562
Other chemotherapy	ATC: L01
Additional treatments	
Dexamethasone	ATC: H02AB02
Prednisolone	ATC: H02AB06
Prednisone	ATC: H02AB07
Non-steroidal inflammatory drugs	ATC: M01A
Other analgetics and antipyretics	ATC: N02B
Opioids	ATC: N02A
Radical prostatectomy	OPS: 5-604
Other operations for prostate	OPS: 5-600-5-603, 5-605, 5-607, 5-609

[a] not available in GePaRD in detail, since these radiopharmaceuticals are not dispensed by pharmacies (only depicted as procedure – see "[…] therapy with radionuclides"); OPS: Code for the reimbursement of inpatient procedures; EBM: Code for the reimbursement of outpatient procedures.

Table 5. Identification of visceral metastases

Diagnoses	ICD-10 code
Secondary malignant neoplasms of respiratory and digestive organs	C78
Secondary malignant neoplasms of kidney and renal pelvis	C79.0
Secondary malignant neoplasms of bladder and other unspecified urinary organs	C79.1
Secondary malignant neoplasms of brain and cerebral meninges	C79.3
Secondary malignant neoplasms of other and unspecified part of nervous system	C79.4

9.3.2 Outcome measures

The primary outcome of this study will be the incidence of any second primary malignancy (ICD-10 codes: C00-C76, C81-C96, D00-D09, D37-D48). Hospital main discharge diagnoses as well as hospital secondary diagnoses will be considered to identify patients with any cancer. The admission date of the respective hospitalization will be defined as the date of the diagnosis.

The secondary outcome will be the overall survival of mPC and mCRPC patients which will be identified using the reason for the end of the insurance period and the reason for discharge from hospital.

9.4 Data sources

9.4.1 Database description

The source of data for this study will be the German Pharmacoepidemiological Research Database (GePaRD), which has been built by the Leibniz-Institute for Prevention Research and Epidemiology – BIPS GmbH for assessing the utilization and safety of drugs in pharmacoepidemiological studies. GePaRD comprises secondary claims data from more than 17 million insurants throughout Germany who are members of German SHI providers. The database covers all SHI members, who have been enrolled in one of the four SHIs since 2004. The population contained in this database represents more than 20 percent of the German population of 82.4 million inhabitants. The data are representative with respect to age, sex, prescriptions and hospital diagnoses (32, 33).

The database contains core data, hospitalization data (§301 Social Security Statute Book (SGB) V), outpatient prescription data (§300 SGB V), and outpatient care data/diagnoses starting at January 1st, 2004 (amendment: §295 SGB V). Membership in an SHI is compulsory in Germany for employees with an annual income up to a certain limit (approximately 47,000 € in 2004 and approximately 50,000 € in 2011).

This study will be based on data of three of the SHIs contributing to GePaRD, since one SHI refused to participate. Therefore, data of ~10 million insurants will be available for this study.

The structure of GePaRD and the central pharmaceutical reference database (CPR) are displayed in Table 6. Information from the CPR is linked to the SHI database via the central pharmaceutical number (PZN).

Table 6. German Pharmacoepidemiological Research Database (GePaRD): Structure and content of data files from statutory health insurances (SHI) and central pharmaceutical reference database (CPR)

SHI				**CPR**
Core data (socio-demographic)	Hospital data	Outpatient data[$]	Prescription data[$$]	Pharmaceutical information
Pseudonymized subject ID No. Birth year Sex SHI code Region of residence Nationality (German/other) Dates of insurance coverage (entry and exit) Occupational code Reasons for exit (e.g. death) Insurance status (self/relative-spouse/child) Family ID No. Participation in Disease Management Program (DMP)	Pseudonymized subject ID No. Pseudonymized hospital ID No. Day of admission/ discharge Admission diagnosis* Reason for admission Discharge diagnoses* Secondary and ancillary diagnoses* OPS-code (Diagnostic and surgical/medical procedures) Reasons for discharge (incl. death, roughly 50% of all deaths occur in hospital) Day of delivery Weight of infants less than 1 year old * All diagnoses: ICD-10-GM, at least 4 digits	Pseudonymized subject ID No. Pseudonymized physician ID No. Physician specialty Diagnoses* (quarterly**) Types and dates of treatment / diagnostic procedures (EBM code) [$] Provided to SHIs by Regional Associations of Statutory Health Insurance Physicians *All diagnoses: ICD-10-GM, at least 4 digits ** Diagnoses refer to a period of three months, as physicians' services are settled quarterly	Pseudonymized subject ID No. Central pharmaceutical No. (PZN) Pseudonymized pharmacy ID No. Date of prescription Date of dispensation Pseudonymized physician ID No. Physician specialty Quantity prescribed [$$] Provided to SHIs by pharmacies' electronic data processing centers	Central pharmaceutical No. (PZN) Generic name Brand Manufacturer Packaging size Strength Defined daily dose (DDD) Pharmaceutical formulation ATC GM code*** *** Anatomical Therapeutic Chemical Classification System

** Hospital and outpatient diagnoses are coded using the International Classification of Diseases, version 10 - German Modification (ICD-10-GM) with at least 4 digits*
*** Outpatient diagnoses refer to a period of three months, as physicians' services are settled quarterly (i.e. the four quarters of a year: January-March, April-June, July-September, October-December)*
[#] *Diagnostic and surgical/medical procedures are coded using the Operations and Procedures Coding System (OPS)*
[##] *Outpatient treatment / diagnostic procedures are coded using claim codes for outpatient services and procedures („Einheitlicher Bewertungsmaßstab", EBM)*
[###] *Anatomical Therapeutic Chemical Classification System, German Modification*
[$] *Provided to SHIs by Hospitals*

9.4.2 Legal restrictions

Access to the data is only possible in the context of approved projects. Thus, preliminary investigations regarding the number of prescriptions of a specific drug or the number of patients diagnosed with a specific disease are not allowed.

Approval of a project is based on the endorsement of the project by the SHIs and their responsible authority (e.g. the German Federal Insurance Authority for nationwide operating SHIs). To gain approval, a proposal is written and sent to each SHI. If they endorse the project, they ask approval from their responsible authority, which will be granted according to §75 of the SGB X if the public health interest in the project outweighs the data privacy concerns.

In accordance with §75 SGB X, informed consent of the insurants is not required. Since the study will be based on routinely collected pseudonymized data and persons will not be contacted, ethical approval is not needed.

Access to data is only allowed for BIPS employees. It is not possible to give access or analysis data sets to a third party.

9.5 Study Size

The five-year prevalence of PC during the study period in Germany was 0.7% (about 281,000 patients). Assuming that 10-20% of these patients will develop CRPC and ~90% of CRPC patients will develop mCRPC, a study size of ~1,400 - ~2,800 mCRPC patients can be expected (see Table 7).

Table 7: Expected size of the study population in GePaRD based in the five-year prevalence of prostate cancer in Germany (2010)

	Expected size of study population					
	0-44	*45-54*	*55-64*	*65-74*	*≥75*	*All*[b]
PC cases in Germany[a]	349	8,858	50,288	129,462	91,720	280,677
GePaRD coverage of Germany in %	8.0	8.0	8.0	6.0	3.0	~7.0
PC cases in GePaRD (3 SHIs)	28	709	4,023	7,768	2,752	15,279
CRPC cases in GePaRD max	6	142	805	1,554	550	3,056

	min	3	71	402	777	275	1,528
mCRPC cases in GePaRD	max	5	128	724	1,398	495	2,750
	min	3	64	362	699	248	1,375

[a]Source: Zentrum für Krebsregisterdaten im Robert Koch-Institut, www.krebsdaten.de/abfrage
[b]Sum of all age groups

9.6 Data management

Data management and statistical analyses will be conducted using SAS 9.3 (SAS Institute 9.3).

9.7 Data analysis

9.7.1 Characteristics of the study population

The study populations will be described regarding social demographic factors, relevant comorbidity, diagnostic procedures as well as drug treatment and other treatments. Respective information will be obtained from the one-year-insurance period preceding cohort entry. Categorical variables will be described by proportion of patients in each category and continuous variables with the relevant summary statistics.

9.7.2 Incidence of second primary malignancies

The incidence of second primary malignancies will be calculated by dividing the number of incident cases by the accumulated person-time in the cohort (until outcome occurred, death, end of insurance period or end of study period, whichever comes first) stratified by e.g. age. Corresponding 95% confidence intervals (CI) of the incidence rate will be calculated based on the Poisson distribution (34). The calculation of the incidence of second primary malignancies will be carried out separately for the mPC and mCRPC cohort. Furthermore, the incidence of second primary malignancies will be calculated by several variables including but not limited to sociodemographic variables or treatment regimes. Stratification will be described in more detail in the Statistical Analysis Plan (SAP).

As this study serves as a historical reference group for the "Observational Study for the Evaluation of Long-term Safety of Radium-223 Used for the Treatment of Metastatic Castration Resistant Prostate Cancer (REASSURE-study)", incidence rates of second primary malignancies obtained from these two studies will be compared by the standardized incidence ratio (SIR) using results from this study as a reference. Age will be considered as a stratification variable in the calculation of the SIR. The calculation of the SIR will be described in more detail in the SAP. Corresponding 95% confidence intervals will be calculated according to the method proposed by Vandenbroucke (35). These analyses will be repeated with selected site-specific second primary malignancies.

The SIR will be calculated separately for the GePaRD data in comparison to the pooled data of the REASSURE-study. Pooling of the different register data does not seem reasonable due to e.g. different processes of data compilation, different information comprised by the databases as well as different incentives for documentation of e.g. diagnoses in the databases. In the REASSURE study respective differences are not presumed due to the standardized protocol.

9.7.3 Overall survival

The overall survival will be defined as time from cohort entry to death, due to any cause. Summary of the survival time in the population will be described with mean, median, 1st and 3rd quartiles, range and standard deviation. Furthermore, overall survival will be analyzed using the Kaplan Meier method. Patients alive at cohort exit will be censored at the date of the cohort exit. Kaplan Meier survival curves will be calculated stratified e.g. by age. Differences between the age groups will be evaluated using the log rank test ($p<0.05$). The age-standardized mortality rates will be provided to investigate the effect of death as a competing risk in the SIR comparison against the REASSURE study.

9.7.4 Sensitivity analyses

It is likely that second primary malignancies are diagnosed with delay in routine care when compared to patients participating in a prospective observational study, since in routine care patients probably have to wait longer for an appointment at the hospital, where the diagnosis is

confirmed based on imaging techniques. Therefore, when using secondary data for incidence estimations, more person time might be accumulated during follow up leading to a lower incidence rate and an overestimation of the standardized incidence ratio. To study the impact of this potential limitation, a sensitivity analysis will be conducted in which also outpatient diagnoses will be considered for the identification of second primary malignancies. The date of the outpatient diagnosis will be defined as the first physician contact within the respective treatment case which might lead to an earlier date of diagnosis and thus less accumulated person time during follow up and higher incidence of second primary malignancies.

Furthermore, the analyses will be repeated as described below:

1. To verify that diagnoses are recorded completely in the patient register, the following proxies will be used:
    a. Initiation of prostate cancer treatment as a proxy for the date of PC diagnosis.
    b. Bone-directed treatments as a proxy for bone metastases diagnosis.
2. To test the sensitivity of results for the definition of mCRPC proxy: in addition to the other inclusion criteria, those who have had at least 6 months since the initiation of ADT treatment before the diagnosis of bone metastases are included in the mCRPC population.

All proxies in 1. and 2. will be used together in one sensitivity analysis and, if the results differ substantially from the original analyses, the effect of each proxy will be subsequently determined by re-performing the analyses using one proxy at a time.

3. To further investigate the sensitivity of results for the definition of mCRPC proxy: castration-resistant PC will be defined solely through medication specific to either CRPC or mCRPC.
4. To investigate the temporal relation of mCRPC proxy and bone-metastases diagnosis, the mPC population who fulfill the mCRPC proxy criterion only after entering the cohort will be described.
5. To verify that the results from this study concern population with bone metastases from PC and not from other cancers: patients who have ever been diagnosed with cancer other than PC before bone metastases diagnosis will be excluded.

6. To provide general information on the possible effect of visceral metastases on the study results (overall survival in particular): patients with visceral metastases will be excluded.
7. To exclude the possibility that the results could be affected by exposure to radium-223, the two last months (1.11.2013 – 31.12.2013) will be removed from the follow-up time.
8. Patients receiving radiopharmaceuticals for bone metastases will not be excluded.

9.7.5 Missing data

For study variables, if a variable is totally missing from a database, it will be excluded from the analysis. If a variable is missing for only some of the patients a missing data category will be added and used in the analysis.

9.8 Quality control

The study will be conducted according to the Guidelines for Good Pharmacoepidemiology Practice (GPP), Good Practice of Secondary Data Analysis (GPS), the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, as well as Good Epidemiological Practice (GEP). SHI data are checked by numerous plausibility checks before they are entered into GePaRD.

All programs will be programmed according to agreed coding standards and will be validated by double programming or source code review with second programmer involvement.

Main project documents (study protocol, statistical analysis plan, reports, etc.) are stored electronically in the project folder. Older versions are stored there, too, and version control is managed by a page in the respective document. Backups are made on a regular basis. The executive project leader also stores printed hard copies of the main versions of the project documents in his office.

The project team has project specific access to the database (e.g. regarding years or SHIs). All analysis datasets are stored in project specific data set schemas to which only the project team has access. After completion of the project, the datasets will be archived for ten years.

Only validated software (SAS) will be used for the statistical analyses.

9.9 Limitations of the research methods

The main strength of this study will be the expected underlying large database, covering approximately more than 52 millions of person-years across nine data years. The representativeness of these data for Germany have been previously reported (32, 33), and the feasibility of long-term follow-ups is constituted by the stability of statutory health insurance (SHI) memberships. In a pilot database of more than 3.5 million inhabitants from three SHIs, membership was stable in about 75 percent of all subjects over four years (36). However, patients leaving a specific SHI and entering one of the other 3 participating SHIs cannot be identified as the same individual (synonym error). The large sample size allows the estimation of incidence rates especially for rare events and will also enable further stratifications (e. g. by age, or duration of PC). Moreover, the main outcomes relevant for this study are well depictable since malignancies are ICD-10 codeable and mortality has recently been proven to be accurately recorded in GePaRD (37).

The limitations of this study stem mainly from the nature of secondary data. Since the data in GePaRD represent health claims information, i. e. were originally generated for reimbursement purposes rather than scientific aims, not all relevant variables are available in the desired detail. As an example, results from lab tests are not available in the database, and therefore histological parameters or tumour classifications cannot be assessed. This can be regarded as the major flaw of the study as the state of castration-resistance is understood as disease progression under androgen depriving treatment, usually indicated by rising PSA levels (38). It should also be noted, however, that a unique definition of mCRPC is still lacking so far (22, 39). Considering that bone metastases are usually present in 90% of patients with lab confirmed mCRPC, the selected approach in this study can be regarded as an adequate proxy (40, 41).

This uncertainty also applies to certain treatment procedures that are relevant in the context of CRPC. For radiotherapy, which can be used as treatment against PC as well as pain therapy, only the type of radiotherapy but not the site of irradiation is available in GePaRD. Chemotherapy as a treatment can be identified in GePaRD but not the specifically administered cytostatic drugs, e. g. whether docetaxel has been used, since these are reimbursed by generic pharma-

ceutical reference numbers for logistic reasons. Radiopharmaceuticals are generally not dispensed by pharmacies and therefore not presentable, at least in particular. However, procedure codes indicating therapy with radionuclides do exist. Furthermore, only quarterly dates but no exact dates of outpatient diagnoses are available in GePaRD. This is, however, expected to have only minor impact on the incidence estimations since both the occurrence of bone metastases as well as further malignancies are usually confirmed in the hospital, where exact dates are available.

It should be kept in mind that the results might be biased by misclassifications due to the left truncation of data years available in GePaRD. For example, patients who were diagnosed with PC prior to the baseline (e.g. 2002 or 2003) would erroneously not be identified as PC patients during the study period if not coded continuously. Since PC is a chronic disease which requires ongoing treatment, we assume that continued coding will usually occur, limiting the amount of misclassification. Similarly, as a matter of nature of health claims data, GePaRD does not capture persons with present but still undiagnosed PC, potentially leading to an underestimation of the number of patients with PC. Yet as previously discussed, bone metastases usually present in patients at the symptomatic stage of the disease which requires specific treatments. Thus, it can be assumed that this underestimation will be very low.

The REASSURE study includes a different time period (2013 onwards) compared to this study (2004-2013). As evidence suggests an improved survival during this time period, potential bias should be considered in the interpretation of the results (42). By analogy, death might be also considered as a competing risk when investigating the incidence of second primary malignancies in mCRPC patients in the REASSURE population compared to the historical cohort without alpharadin or other lifetime improving treatment.

There are a number of further limitations, which however can be largely be regarded negligible. For example, consideration of additional variables such as life-style related behaviour (e. g. smoking, diet), which are potential (protective) factors for the occurrence of cancers, is not possible since the required data is not available in the GePaRD (43). However, this limitation is regarded to be very low since PC has been shown to be among the few forms of cancer, which are largely unlinked with these factors (2).

Subjects with higher incomes can choose private health insurance providers instead of an SHI and are probably underrepresented in SHIs. However, some of these higher-income patients are voluntary members of SHIs, most often because SHIs provide free health insurance for unemployed family members (children and spouse) whereas in private health insurance plans all family members have to be paid for. About 70 million people (85% of the German population) are SHI members, including about five million voluntary members, children and patients who are retired or unemployed. There may also be some overrepresentation of patients with middle to higher socio-economic status in the database, since two of the three contributing SHIs are so called 'Ersatzkassen', which are more likely to insure patients of middle to higher socio-economic status. However, the database also includes patients from one AOK (AOK Bremen-Bremerhaven), a SHI which has traditionally insured patients of lower socio-economic status.

9.10 Other aspects

NA

10. Protection of human subjects

In accordance with §75 SGB X, informed consent of the insurants is not required. Since the study will be based on routinely collected pseudonymized data and persons will not be contacted, ethical approval is not needed.

11. Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. If applicable, adverse reactions will be reported in aggregated form in the final report.

12. Plans for disseminating and communicating study results

The findings of the study will be submitted as a report to Bayer Healthcare. In addition, we expect the results of this study to be published in international peer-reviewed scientific journals following guidelines of the selected journal and STROBE checklist (http://www.strobe-statement.org). The principal investigator will ensure that authorship for all publications complies

with the criteria defined by the International Committee of Medical Journal Editors. Each author should have participated sufficiently in the work to take public responsibility for the content (www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

The involved project members of BIPS, the sponsor and individuals acting on their behalf commit to adhere to the rules of the ENCePP Code of Conduct in their entirety. The study protocol will be registered in the ENCePP E-register of Studies (www.encepp.eu/encepp/studiesDatabase.jsp). Study results will also be published in the ENCePP E-register.

13. List of references

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Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	Adopted by the ENCePP Steering Group on 14/01/2013; Doc.Ref. EMA/540136/2009	05 February 2016	**ENCePP Checklist for Study Protocols** (Revision 2, amended)

Annex 2. Signature pages

See following pages

Signature Page - Global Pharmacovigilance and Risk Management

Title	Second primary cancers in patients with castration resistant prostate cancer (BOCARP)
Protocol version identifier	1.0
Date of last version of protocol	23 February 2016
IMPACT study number	18044
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Global Pharmacovigilance and Risk Management
Name	Cinara McCarthy
Title	Global Safety Leader
Address	Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page - Global Medical Affairs

Title	Second primary cancers in patients with castration resistant prostate cancer (BOCARP)
Protocol version identifier	1.0
Date of last version of protocol	23 February 2016
IMPACT study number	18044
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page - Global Regulatory Strategist

Title	Second primary cancers in patients with castration resistant prostate cancer (BOCARP)
Protocol version identifier	1.0
Date of last version of protocol	23 February 2016
IMPACT study number	18044
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page - Global Epidemiology

Title	Second primary cancers in patients with castration resistant prostate cancer (BOCARP)
Protocol version identifier	1.0
Date of last version of protocol	23 February 2016
IMPACT study number	18044
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
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Title	Study Epidemiologist
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page - Global Integrated Analysis

Title	Second primary cancers in patients with castration resistant prostate cancer (BOCARP)
Protocol version identifier	1.0
Date of last version of protocol	23 February 2016
IMPACT study number	18044
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page - Global Epidemiology

Title	Second primary cancers in patients with castration resistant prostate cancer (BOCARP)
Protocol version identifier	1.0
Date of last version of protocol	23 February 2016
IMPACT study number	18044
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page - Global Health Economics and Outcomes Research

Title	Second primary cancers in patients with castration resistant prostate cancer (BOCARP)
Protocol version identifier	1.0
Date of last version of protocol	23 February 2016
IMPACT study number	18044
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page - BIPS

Title	Second primary cancers in patients with castration resistant prostate cancer (BOCARP)
Protocol version identifier	1.0
Date of last version of protocol	23 February 2016
IMPACT study number	18044
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____

Signature Page - BIPS

Title	Second primary cancers in patients with castration resistant prostate cancer (BOCARP)
Protocol version identifier	1.0
Date of last version of protocol	23 February 2016
IMPACT study number	18044
Study type	☒non-PASS ☐ PASS
EU PAS register number	NA
Active substance (medicinal product)	NA
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Executive project leader
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The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: _____, _____