Pharmacologie médicale

Bordeaux PharmacoEpi
CIC Bordeaux CIC1401

Therapeutic strategy in metastatic castration-resistant prostate cancer: target population and changes between 2012 and 2014.

Two sequential cohorts within the French nationwide claims and hospital database

Protocol

Version V2.1, 26 January 2018

BORDEAUX PHARMACOEPI
Plateforme de recherche en pharmaco-épidémiologie
Service de Pharmacologie médicale, INSERM CIC1401
Université de BORDEAUX – CHU de Bordeaux – Adera
Bâtiment Le Tondu – case 41
146 rue Léo Saignat – 33076 Bordeaux Cedex - France

GENERAL INFORMATION

Title	Therapeutic strategy in metastatic castration-resistant prostate cancer: target population and changes between 2012 and 2014. Two sequential cohorts within the French nation-wide claims and hospital database (CAMERRA)
Protocol version identifier	Version 2.1
Date of last version of protocol	26 January 2018
IMPACT study number	NA
EU PAS register number	NA
Active substance	1st-line treatment of metastatic castration-resistant prostate cancer : abiraterone acetate (ATC code L02BX03); enzalutamide (ATC code L02BB04), docetaxel (ATC code L01CD02).
Medicinal product	Zytiga® 250 mg (CIP: 2174974); Xtandi® 40mg (CIP: 3400927432484); Taxotère® 20mg/1ml CIP 3400957656874, 80mg/4ml CIP 3400957657765, 160mg/8ml CIP 3400957756741
Product reference	Zytiga® 250 mg: EU/1/11/714/001; Xtandi® 40mg: EU/1/13/846/001; Taxotère®: 20mg/1ml EU/1/95/002/003, 80mg/4ml EU/1/95/002/004, 160mg/8ml EU/1/95/002/005
Procedure number	NA
Marketing authorisation holder(s)	Janssen-Cilag; Astellas Pharma; Sanofi-Aventis
Joint PASS	No
Research question and objectives	The research question is to assess the therapeutic strategy changes for metastatic castration-resistant prostate cancer (mCRPC) between 2012 and 2014, as well as the size of the population and healthcare use over three years. The main objective is to describe first-line treatment for patients with mCRPC in 2012 and 2014 and then subsequent treatments-lines during a 3-year follow-up.
Country(-ies) of study	France
Author	Dr Patrick BLIN, Scientific and medical director Bordeaux PharmacoEpi (BPE), Service de Pharmacologie médicale, INSERM CIC1401 Université de Bordeaux – CHU de Bordeaux – Adera Bâtiment Le Tondu – case 41 146 rue Léo Saignat – 33076 Bordeaux Cedex, France ☎ +33 (0)557 574 675 - Fax: +33 (0)557 574 740 patrick.blin@u-bordeaux.fr

SPONSOR

Sponsor	Janssen-Cilag 1, rue Camille Desmoulins 92787 Issy-Les-Moulineaux – France
Medical Advisor Oncology	Bruno SCHOENTJES

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
ARO	Academic Research Organization
ATC	Drug classification (*Anatomique, Thérapeutique et Chimique*)
BPE	Bordeaux PharmacoEpi, the Pharmacoepidemiology research platform of the University of Bordeaux - INSERM CIC1401
CNAMTS	French national health insurance fund for salaried worker (*Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés*)
CNIL	French data protection commission (*Commission Nationale de l'Informatique et des Libertés*)
DEP	Data Extraction Plan
DRG	Diagnosis-Related Groups (*or GHM for Groupes Homogènes de Malades*)
EGB	1/97th random sample of the national health insurance database (*Echantillon Généraliste de Bénéficiaires*)
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FRANCIM	French network of cancer registries, *Réseau français des registres de cancer*
HAS	*Haute Autorité de Santé*
HIFU	High Intensity Focused Ultrasound
ICD	International Classification of Diseases
INDS	National Institute of Health Data (*Institut National des Données de Santé*)
LHRH	Luteinising hormone releasing hormone
LTD	Long-Term Disease (registration for major chronic diseases with full insurance coverage of all claims related to disease)
mCRPC	Metastatic castration-resistant prostate cancer
PMSI	National hospital discharge summary database (*Programme de Médicalisation des Systèmes d'Information*)
SAP	Statistical Analysis Plan
SAR	Statistical Analysis Report
SmPC	Summary of product characteristics
SNDS	National healthcare data system (*Système National des données de Santé*)
SNIIRAM	National healthcare insurance system database (*Système National d'Information Inter-Régimes de l'Assurance Maladie*)
out of T2A	Specific hospital record of innovative and expensive products not included in DRG cost
SRG	Stay-Related Groups (*or GHS for Groupes Homogènes de Séjours*)

3. RESPONSIBLE PARTIES

SCIENTIFIC COMMITTEE	
Dr Marine Gross-Goupil Medical oncologist	CHU de Bordeaux Hôpital Saint André, Service d'oncologie médicale 1 rue Jean Burguet, 33075 Bordeaux cedex, France ☎ 33 (0)556 795 808 marine.gross-goupil@chu-bordeaux.fr
Dr Thibaud Haaser Radiotherapist	CHU de Bordeaux Hôpital Haut Lévèque, Service de radiothérapie Avenue Magellan, 33600 Pessac, France ☎ +33 (0)556 556 565 thibaud.haaser@chu-bordeaux.fr
Pr Gérard de Pouvourville Health economist	ESSEC Business School Avenue Bernard Hirsch, BP 50105 , 95021 Cergy Pontoise cedex, France ☎ 33 (0)134 433 000 pouvourville@essec.fr
Dr Xavier Rébillard Urologist	Clinique BeauSoleil 119, avenue de Lodève, 34070 Montpellier, France ☎ 33 (0)467 759 735 xavier.rebillard@wanadoo.fr
Pr Michel Soulié Urologist	CHU de Toulouse Hôpital Rangueil, 1 avenue du Pr Jean Poulhès - TSA 50032 - 31059 Toulouse cedex 9 ☎ 33 (0)561 322 996 soulie.m@chu-toulouse.fr

COORDINATING CENTRE	
Bordeaux PharmacoEpi (BPE) **INSERM CIC1401** **Service de Pharmacologie médicale**	**Université de Bordeaux – CHU de Bordeaux – Adera** Bâtiment Le Tondu – case 41 146 rue Léo Saignat – 33076 Bordeaux cedex – France ☎ +33 (0)557 574 675 - Fax: +33 (0)557 574 740 http://www.pharmacoepi.eu
Pr Nicholas Moore Head of BPE	☎ +33 (0)557 571 560 nicholas.moore@u-bordeaux.fr
Dr Patrick Blin Scientific and medical director	☎ +33 (0)557 579 563 patrick.blin@u-bordeaux.fr
Cécile Droz-Perroteau Chief operating officer	☎ +33 (0)557 574 737 cecile.droz@u-bordeaux.fr
Nicolas Thurin Scientific and medical advisor	☎ +33 (0)557 579 209 nicolas.thurin@u-bordeaux.fr
Magali Rouyer Project manager	☎ +33 (0)557 574 767 magali.rouyer@u-bordeaux.fr
Régis Lassalle Chief Statistician & Data-manager	☎ +33 (0)557 574 764 regis.lassalle@u-bordeaux.fr
Jérémy Jové Referent Statistician	☎ +33 (0)557 571 446 jeremy.jove@u-bordeaux.fr

SPONSOR	
Janssen-Cilag	1, rue Camille Desmoulins 92787 Issy-Les-Moulineaux – France http://www.janssen.com/france/
Bruno Schoentjes Medical Advisor Oncology	☎ +33 (0)155 004 003 bschoent@its.jnj.com
Ludovic de Beaucoudrey Medical Affairs Oncology	☎ +33 (0)155 003 023 ldbeauc1@its.jnj.com
Julien Thevenon Real Word Manager	☎ +33 (0)155 004 118 jtheveno@its.jnj.com
Marie-Laure Bazil Market Access Director	☎ +33 (0)155 004 356 mbazil@its.jnj.com
Camille Capone Health Economy Analyst	☎ +33 (0)155 003 909 ccapone3@its.jnj.com

4. ABSTRACT

TITLE

CAMERRA: Therapeutic strategy in metastatic castration-resistant prostate cancer: target population and changes between 2012 and 2014. Two sequential cohorts within the French nationwide claims and hospital database.

RATIONAL AND BACKGROUND

Prostate cancer is the most common cancer in men and represents more than 57,000 new cases each year in France. For patients diagnosed at the localised and locally advanced stage, 20% and 40% respectively develop metastasis disease within 5 years, while 10% of patients are diagnosed at metastatic stage; nodes and bones being the most frequent localisations.

Several therapeutic options are available at metastatic stage.

Since 2004, docetaxel has been the first-line treatment of metastatic castration-resistant prostate cancer (mCRPC). Since 2011, several drugs (cabazitaxel, abiraterone, enzalutamide) successively received European market authorisation as second-line treatment and then as a first-line treatment for the last two.

In this context, changes in therapeutic strategies have a major impact on care for mCRPC patients. The Marketing Authorisation Holder of abiraterone has entrusted the Bordeaux PharmacoEpi platform, CIC Bordeaux CIC1401 of the University of Bordeaux, with a study to assess the therapeutic strategy, and target population in mCRPC for patients in 2012 and 2014 (i.e. in line with the French Marketing Authorizations of abiraterone: February 2012 as 2nd-line treatment and June 2013 as 1st-line treatment), using the SNDS nation-wide claims and hospital database.

During the regulatory process for SNDS access, a preliminary analysis will be performed using the EGB database (1/97th permanent random sample of the SNDS database) to optimize the SNDS analysis.

RESEARCH QUESTION AND OBJECTIVES

Research question: To assess the therapeutic strategy changes for mCRPC between 2012 and 2014, as well as the size of the population and healthcare use over three years.

Main objective

- To describe first-line treatment for patients with mCRPC in 2012 and 2014 and then subsequent treatment-lines during a 3-year follow-up.

Secondary objectives

- To estimate the number of mCRPC patients initiating a mCRPC first-line treatment in 2012 and 2014;
- To describe characteristics of mCRPC patients initiating a mCRPC first-line treatment: demographics, comorbidities, and prostate cancer history;
- To estimate overall survival for all patients and according to the first-line treatment;
- To describe the complications that could be related to mCRPC treatments
- To describe 3-year healthcare resource use and costs for all patients and according to first-line treatment.

STUDY DESIGN

Two cohorts of mCRPC patients initiating a first treatment for mCRPC and a 3-year follow-up within the French nationwide claims and hospital database:

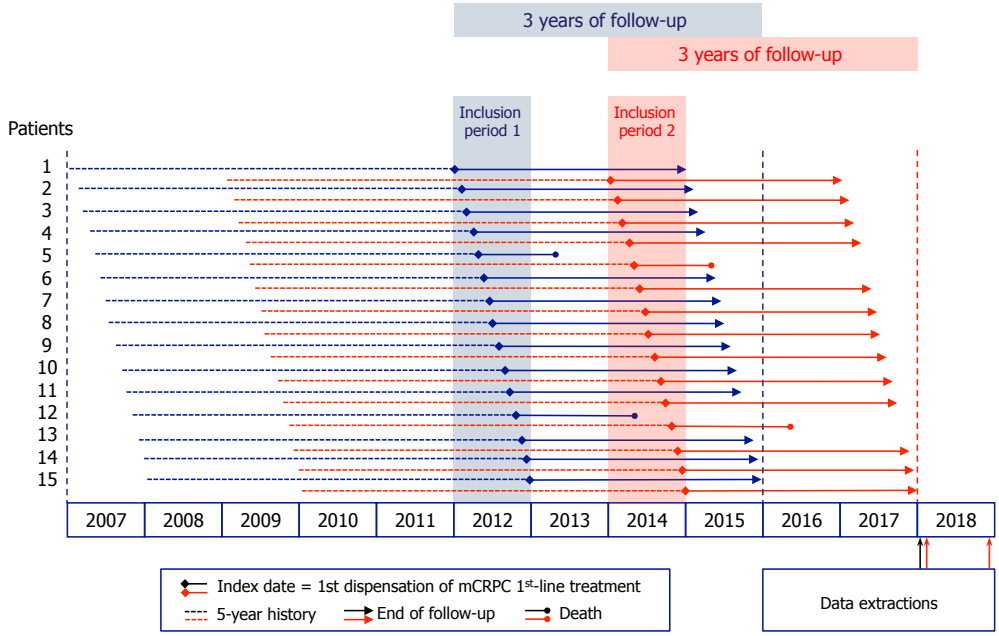
- The index date will be the date of the mCRPC first-line treatment initiation

during the inclusion period:

- Cohort 2012: from 1 January 2012 to 31 December 2012.
- Cohort 2014: from 1 January 2014 to 31 December 2014.

- The follow-up period will start on the study index date and will end three years later.
- All patients will have a 5-year database history before index date.
- Data will be extracted from 2007 to 2017, with two successive data extractions for interim analyses:
  - First extraction (Q1 2018): for the period 2007 to 31 December 2016, i.e. description of patients included in the 2012 and 2014 cohorts, 3-year follow-up of the 2012 cohort and 2-year follow-up of the 2014 cohort.
  - Second extraction (Q4 2018): update for the 2017 period of the 2014 cohort (3-year follow-up).

The overall design of the study is presented in the following figure.



POPULATION

Inclusion criteria for the population of mCRPC patients initiating a first-line treatment for mCRPC

- Men of 40 years old and over, alive on the first day of the inclusion period,
- And affiliated to the healthcare insurance system "*Régime Général*" during the study period,
- And having mCRPC during the inclusion period,
- And initiating a first mCRPC specific treatment during the inclusion period,
- And without any mCRPC specific treatment during the 5-year history before.

VARIABLES

Disease

- **Prostate Cancer**: patients with LTD registration or hospitalisation for

prostate cancer (primary, associated and linked ICD-10 code diagnosis), or hospitalisation with surgical or medical procedure specific of prostate cancer, or specific treatment for local disease, or drug dispensing specific for non-metastatic prostate cancer or for mCRPC.

- **mCRPC**: patients with a prostate cancer and defined as
    - Metastatic, based on hospitalisation for metastases (primary, associated and linked ICD-10 code diagnosis), or specific treatment for metastases (e.g. radiofrequency), or metastases specific drug dispensing (e.g. denosumab)
    - And castration-resistant according to drug dispensing specific for prostate cancer (androgen deprivation), castration-resistant prostate cancer (estramustine) and mCRPC (abiraterone, cabazitaxel, enzalutamide).

Treatment

- mCRPC treatments: i) hospitalisation with chemotherapy for prostate cancer (i.e. docetaxel ± estramustine dispensing included in the DGR), ii) hospitalisation with cabazitaxel (not included in the DRG), iii) dispensing of abiraterone, iv) dispensing of enzalutamide.
- mCRPC 1st-line treatments: first mCRPC treatment during the inclusion period and 5-year history.
- mCRPC 2nd-line, 3rd-line, Nth-line treatments: switch to another mCRPC treatment after a mCRPC treatment line N-1.
- Adjuvant therapy for bone metastases: bone targeted therapy with one of the beta or alpha particle emitting radionuclides (i.e. strontium-89, samarium-153, radium-223), or pharmacy dispensing of bisphosphonates (i.e. zoledronic acid or clodronic acid), or denosumab.
- Supplementation on vitamin D or calcium.
- Androgen deprivation therapy (ADT) for prostate cancer.
- Corticotherapy.
- Radiotherapy (type and number of courses), tumour or metastasis surgery (i.e. vertebroplasty).
- Treatment duration and co-medication, discontinuation, switch to a subsequent treatment-line.

Baseline characteristics

- Age at study index date.
- Comorbidities and Charlson comorbidity index estimated using LTD and hospitalisations during 5-year database history.

Prostate cancer history

- Date of diagnosis estimation using LTD registration and specific exam (i.e. MRI, CT scan, prostate biopsy, quantitative computed tomography, bone scintigraphy, lab test with PSA dosage, plasma testosterone, *etc.*) during the 5-year database history.
- Prostate cancer treatments using 5-year history: surgery, external beam radiotherapy, cryotherapy, brachytherapy, high intensity focused

ultrasound (HIFU), ADT.

- Concomitant treatments using 5-year history (ATC codes and hospitalisations).
- Hospitalisation with prostate cancer diagnosis.

Complications that could be related to mCRPC treatment

- Severe complications reported in the summary of product characteristics (SmPC) of mCRPC treatments, hospitalisation with main diagnosis of: sepsis, cardiac failure, myocardial infarction, angina pectoris, arrhythmia, atrial fibrillation, tachycardia, deep vein thrombosis, adrenal insufficiency, hepatitis fulminant, acute hepatic failure, acute renal failure, rhabdomyolysis, fractures, neutropenia, febrile neutropenia, anaemia, leukopenia, thrombocytopenia, haemorrhage, posterior reversible encephalopathy syndrome.

Vital status

Healthcare resource use related to prostate cancer

- Hospitalisations related to prostate cancer, drugs for prostate cancer and other non-drug treatments for prostate cancer, specific prostate cancer tests or imaging.
- Medical visits related to the prescription of specific prostate cancer treatment, tests or imaging, transports related to prostate cancer hospitalisation or medical visits.
- Nursing acts, physiotherapy related to prostate cancer hospitalisation or medical visits (defined above).

Other Healthcare resources use

- Other hospitalisations, other medical visits, other drugs, other lab tests, nursing acts, physiotherapy, transport.
- Sick leave daily allowances, pension and disability allowances.

Healthcare resources costs

- Societal perspective using total cost for claims and Diagnosis-related group (DRG) cost for hospitalisations.
- French healthcare insurance perspective using reimbursed cost for claims and Stay-related group (SRG) cost for hospitalisations.

DATA SOURCES

The SNDS includes the national healthcare insurance system database with individual anonymous information on all reimbursed outpatient claims (SNIIRAM) linked to the national hospital-discharge summaries database system (PMSI) and the national death registry, using a unique national pseudonymised identifier. It currently includes 98.8% of the French population, more than 66 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires. The EGB is a permanent 1/97th random sample of the SNDS database. The SNDS and EGB contain individual information on (Tuppin 2010, Moulis 2015):

- General characteristics: sex, year of birth, residence area.
- Date of death for those concerned.
- Long-term disease (LTD) registration (International classification of disease ICD-10 codes with starting and ending date) including prostate

cancer.

- Outpatient reimbursed healthcare expenditures, including drugs, with dates (prescription and dispensing) and codes (but not the corresponding medical indication nor result).
- Hospital-discharge summaries from PMSI: ICD10 diagnosis codes (primary, linked and associated diagnosis) for all medical, obstetric and surgery hospitalisations with the date and duration of hospitalisation, medical procedures and cost coding system (DRG and SRG).

Non-hospital data are updated every month and hospital-discharged summaries are uploaded once a year, at end of Q3 for the previous year. The access to the SNDS is regulated and needs approval from the "*Institut des Données de Santé*" (IDS, Institute of health Data) and the "*Commission Nationale Informatique et Libertés*" (CNIL, the French data protection commission).

STUDY SIZE

The number of new cases of prostate cancer each year in France has been estimated by French national network of cancer registry (*Réseau français des registres de cancer*, FRANCIM) to be more than 57,000 patients, and the national health authorities (HAS) estimated the prevalence of prostate cancers with metastases to be 15,000 patients within a year.

The estimation of the number of patients with a mCRPC in France in 2012 and in 2014 is an objective of the study. A preliminary analysis using the EGB database will be performed to estimate sample size of population expected in the SNDS database.

The first preliminary analysis from EGB database allowed identifying 3,192 prevalent cases with prostate cancer in 2014. Among these 3,192 patients, 137 mCRPC were identified including 29 patients initiating a mCRPC specific treatment. By extrapolation (stratified on age and sex), 20,137 prevalent mCRPC cases in 2014 are expected in the SNDS database including 4,262 patients initiating a mCRPC specific treatment.

DATA ANALYSIS

A Statistical Analysis Plan (SAP) will be developed and will be validated by the Scientific Committee before the analysis. The statistical analysis will be performed using the SAS® software (latest current version), following a detailed statistical analysis plan.

Preliminary EGB database analysis:

- Definition, test and validation of main variables defined above, based on claims, hospitalisation and LTD information, before the availability of the first data extraction from SNDS database;
- Estimation of the sample size expected for 2012 and 2014 SNDS cohorts;
- Definition of an algorithm identifying patients having prostate cancer diagnosis with metastases in order to estimate the prevalence of mCRPC in 2012 and 2014 from the EGB database, including a description of the first-line treatment.

2012 and 2014 SNDS cohorts:

The following analyses will be performed for each cohort using the total population and according to mCRPC first-line treatment:

- Definition of mCRPC stage using preliminary EGB analyses;
- A flow chart depicting the number of patients and sequences of treatment available in the database satisfying the cohort criteria and follow-up

duration;

- Description of baseline characteristics, comorbidities and prostate cancer history;
- Description of first-line treatment for patients with mCRPC in 2012 and 2014 and then subsequent-line treatments during a 3-year follow-up;
- Estimation of overall survival using time to events methods;
- Description of complications that could be related to mCRPC treatment;
- Description of the 3-year healthcare resources use and costs.

MILESTONES		
	Synopsis & Protocol	Q1-Q3 2016
	Regulatory aspects and data extraction follow-up	Q1 2017-Q4 2018
	Statistical Analysis Plan (SAP)	Q4 2016
	EGB data extraction	Q4 2016
	Data management and statistical analysis	Q1-Q4 2017
	Preliminary report	Q1 2018
	First SNDS data extraction	Q1 2018
	Data management and statistical analysis	Q1-Q2 2018
	Interim report	Q3 2018
	Second SNDS data extraction	Q4 2018
	Data management and statistical analysis	Q1 2019
	Final report	Q2 2019

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason

6. MILESTONES

Milestones	Planned Date
Synopsis & Protocol	Q1-Q3 2016
Regulatory aspects and data extraction follow-up with CNAM-TS	Q1 2017- Q4 2018
Statistical Analysis Plan (SAP)	Q4 2016
EGB data extraction	Q4 2016
Data management and statistical analysis	Q1-Q4 2017
Preliminary report	Q1 2018
First SNDS data extraction	Q1 2018
Data management and statistical analysis	Q2-Q3 2018
Interim report	Q3 2018
Second data extraction	Q4 2018
Data management and statistical analysis	Q1 2019
Final report	Q2 2019

7. RATIONAL AND BACKGROUND

Prostate cancer is the most common cancer in men and represents more than 57,000 new cases each year in France (1). It was responsible for 8,876 deaths in 2012 (2, 3). Most prostate cancers are slow growing and it is reported that 70% of cases survive 10 years after diagnosis (4). Although it is one of the most controversial topics in the urological literature (5), screening for prostate cancer usually relies on the measurement of prostate-specific antigen (PSA) and digital rectal examination (6-9), and a prostate biopsy is required to confirm the diagnosis (6-8).

The treatment of prostate cancer is prescribed according to the stage and risk assessment of the disease. After a treatment for local disease such as surgery, active surveillance, radiotherapy, brachytherapy, or high intensity focused ultrasound (HIFU), there is a follow up period with mainly measurement of PSA to detect the disease relapse. The therapeutic strategy at the diagnosis of metastatic prostate cancer includes androgen deprivation therapies (ADT) for hormone-sensitive disease. The majority of patients develop resistance to the ADT, and median time to progression is about 18-24 months (10). For patients diagnosed at the localised and locally advanced stage, 20% and 40% respectively develop metastasis disease within 5 years (metastatic castration-resistant prostate cancer, mCRPC), while 10% of patients are diagnosed with synchronous metastases; nodes and bones being the most frequent localisations.

Since 2004, docetaxel (Taxotere®) in association with prednisone or prednisolone was the standard first-line treatment in mCRPC after showing a significant difference in overall survival compared to mitoxantrone (Novantrone®) (11, 12). Docetaxel can also be associated with estramustine (Estracyt® which has the indication of CRPC since 1979) due to its synergetic effect (13, 14). In March 2011, cabazitaxel (Jevtana®), a new taxane, received a European marketing authorisation, in combination with prednisone or prednisolone, for the treatment of mCRPC patients previously treated with a docetaxel-containing regimen (second-line treatment) (15, 16).

Since 2012, therapeutic strategy in mCRPC has continued to change with the arrival of new generation antiandrogen: at first, abiraterone (Zytiga®) obtained a European marketing authorization for the treatment of mCRPC patients previously treated with a docetaxel-containing regimen (17, 18), followed in June 2013 by enzalutamide (Xtandi®) (19, 20). Then, in December 2012 and November 2014, abiraterone and enzalutamide saw their indication extended to the first-line treatment of mCRPC patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (20-23). A prostate cancer vaccine Sipuleucel-T (Provenge®), obtained a European marketing authorization in September 2013 for patients with asymptomatic or minimally symptomatic mCRPC, but the product was withdrawn in May 2015 for commercial reasons (24). Moreover, other new molecules are being developed in the indication of mCRPC, including other hormonotherapies and targeted therapies. The figure 1 illustrates the chronology of the main drugs in treatment for mCRPC and their approval from the French regulatory authority, and the figure 2 illustrates the drugs used until 2014 according to the current guideline for treatment of prostate cancer.

Several drugs have the indication of adjuvant therapy for the pain of bone metastases: bisphosphonates (i.e. zoledronic acid or clodronic acid), and radionuclides (samarium-153 [Quadramet®], strontium-89 [Metastron®], radium-223 [Xofigo®], the two latter being specific of bone metastases secondary to prostate cancer). Denosumab (Xgeva®), meanwhile, has the indication of prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with

bone metastases from solid tumours (25). Among these adjuvant therapies, only radium-223 was demonstrated to improve survival in mCRPC (26, 27).

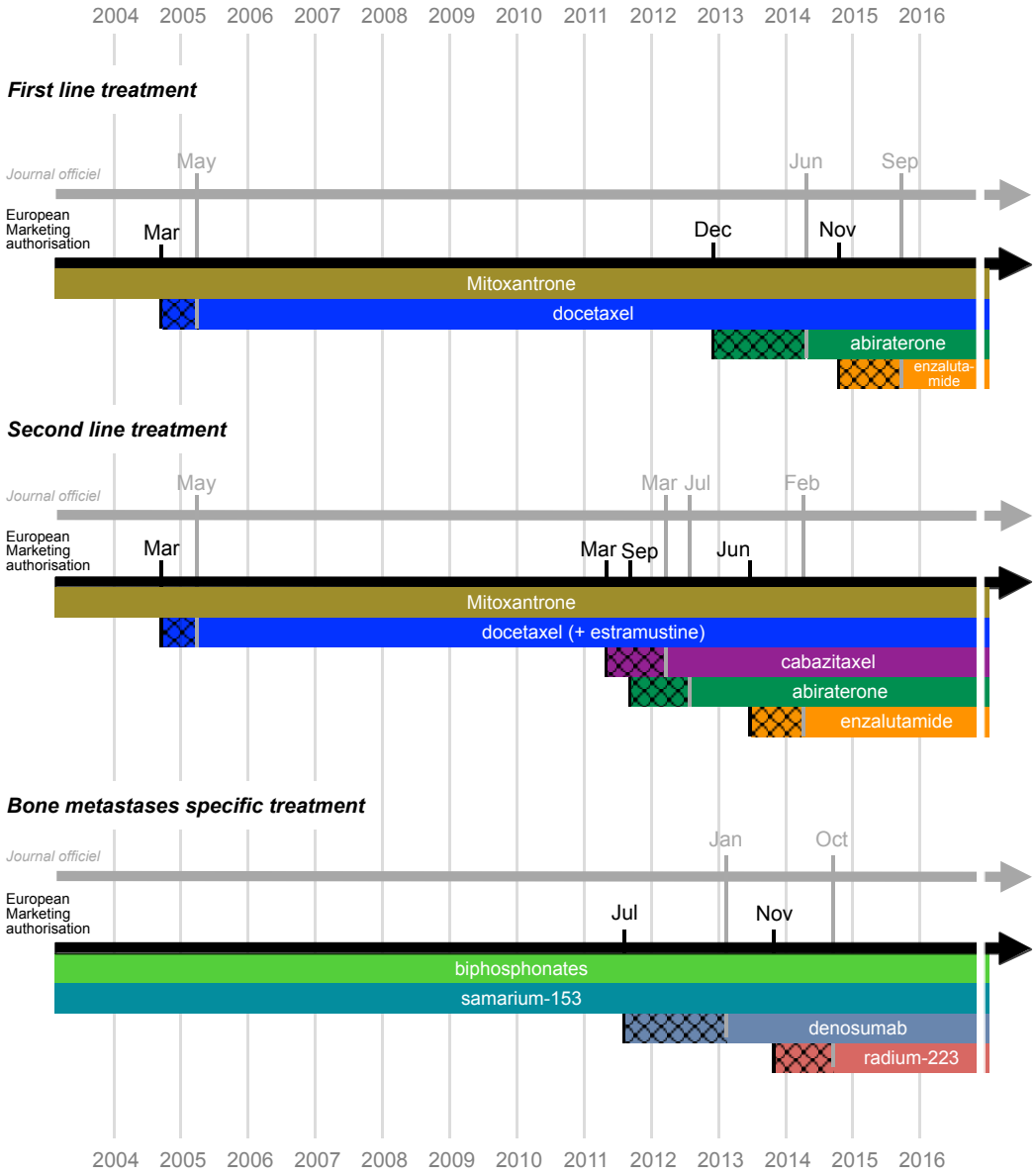


Figure 1: Drugs in treatment for mCRPC and their approval from the French regulatory authorities.

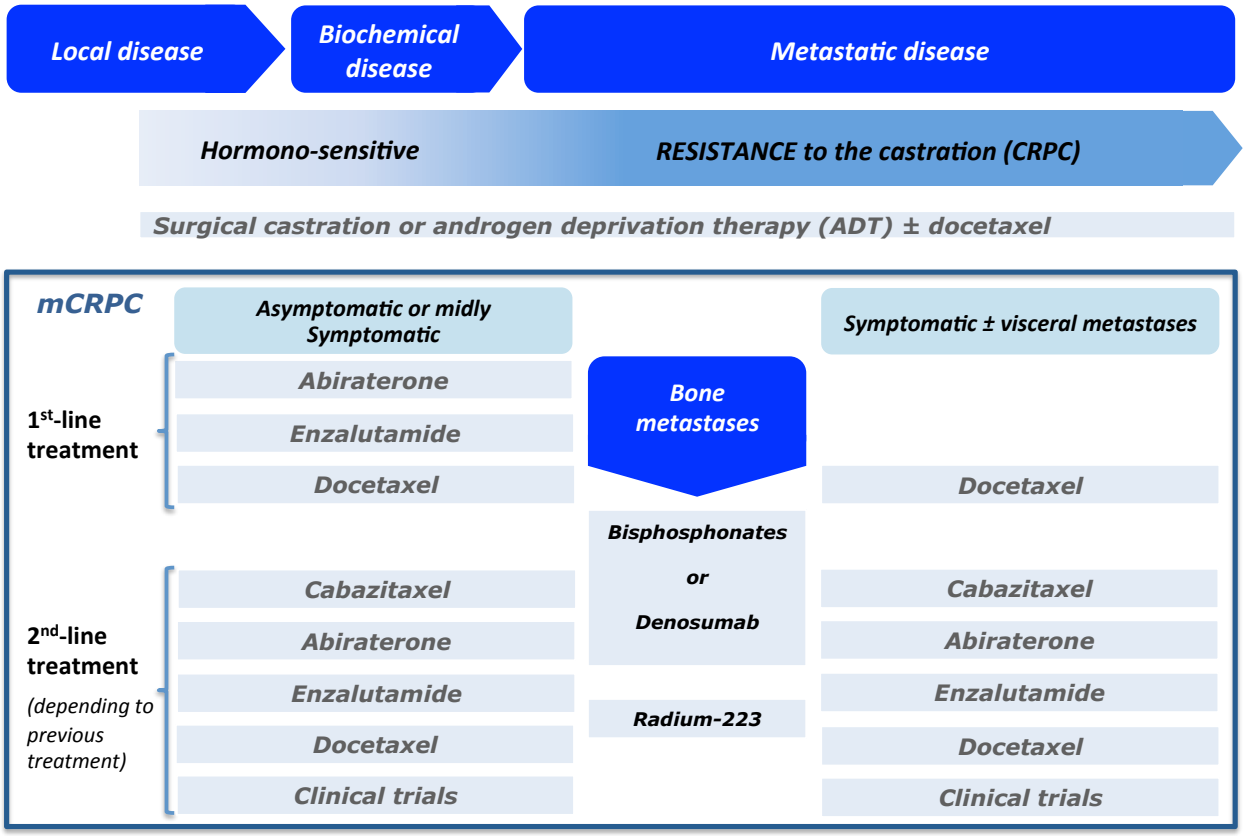


Figure 2: Drugs used until 2014 according to the current guideline for treatment of prostate cancer

In this context, changes in therapeutic strategies have a major impact on care for mCRPC patients. The Marketing Authorization Holder of abiraterone has entrusted the Bordeaux PharmacoEpi platform, CIC Bordeaux CIC1401 of the University of Bordeaux, with a study to assess the therapeutic strategy and target population in mCRPC for patients in 2012 and 2014, using the SNDS nation-wide claims and hospital database.

During the regulatory process for SNDS access, a preliminary analysis will be performed using the EGB database (1/97th permanent random sample of the SNDS database) to optimize the SNDS analysis.

8. RESEARCH QUESTION AND OBJECTIVES

The research question is to assess the therapeutic strategy changes for mCRPC between 2012 and 2014, as well as the size of the population and healthcare use over three years.

The main study objective is to describe first-line treatment for patients with mCRPC in 2012 and 2014 and then subsequent treatment-lines during a 3-year follow-up.

Secondary objectives are the following:

- To estimate the number of mCRPC patients initiating a mCRPC first-line treatment in 2012 and 2014.
- To describe characteristics of mCRPC patients initiating a mCRPC first-line treatment: demographics, comorbidities, and prostate cancer history.

- To estimate overall survival for all patients and according to the first-line treatment.
- To describe the complications that could be related to mCRPC treatments
- To describe 3-year healthcare resource use and costs for all patients and according to first-line treatment.

9. RESEARCH METHODS

9.1. STUDY DESIGN

The design is two successive cohort studies of mCRPC patients initiating a first treatment for mCRPC and a 3-year follow-up within the French nationwide claims and hospital database. The index date will be the date of the mCRPC first-line treatment initiation during the inclusion period:

- Cohort 2012: from 1 January 2012 to 31 December 2012,
- Cohort 2014: from 1 January 2014 to 31 December 2014.

The overall design of the study is presented in figure 2: the follow-up period will start on the study index date and will end three years later, and each patient will have a 5-year database history before index date.

Data will be extracted from 1 January 2007 to 31 December 2017, with two successive data extractions for interim analyses:

- First extraction (Q1 2018): for the period from 1 January 2007 to 31 December 2016 for the description of patients included in the two cohorts (2012 and 2014), the 3-year follow-up of the Cohort 2012 and the 2-year follow-up of the Cohort 2014.
- Second extraction (Q4 2018): update for the 2017 period of the 2014 cohort.

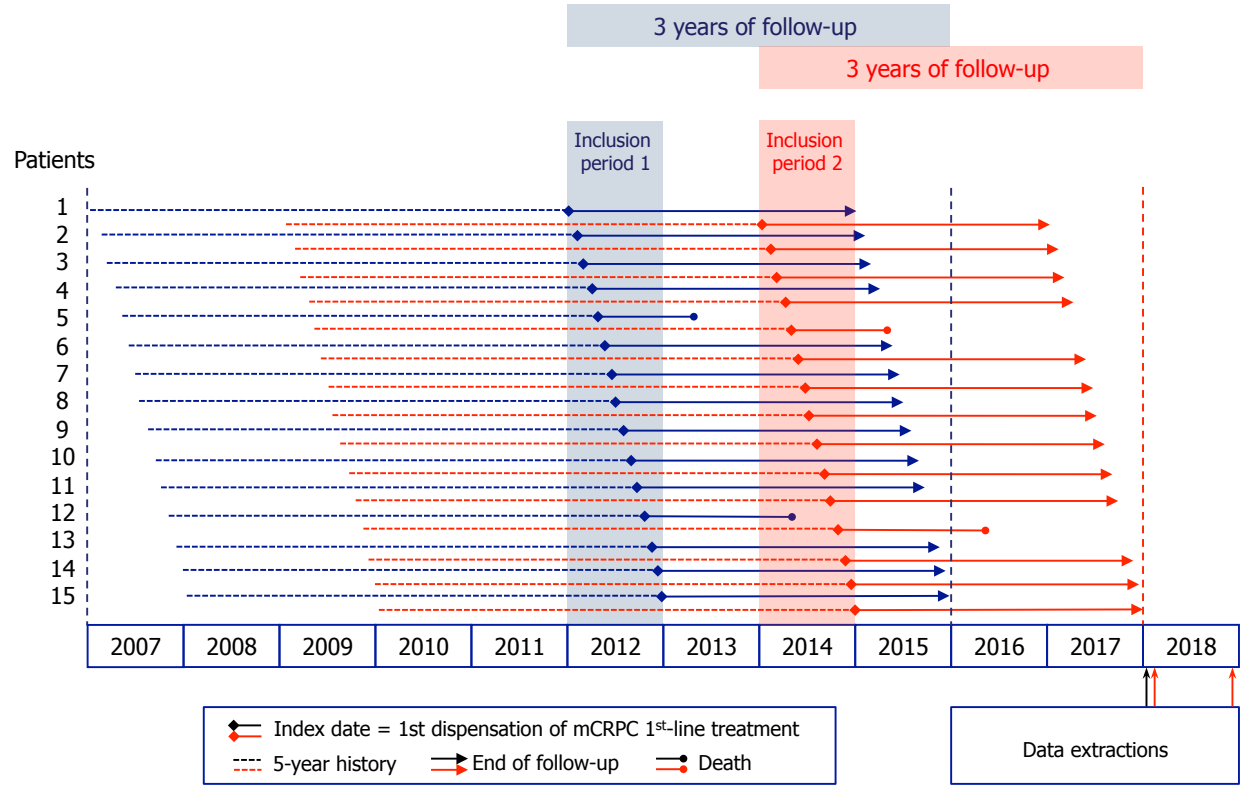


Figure 3: Study design

The SNDS database is one of the best ways to analyse therapeutic strategy and healthcare resources reimbursed. However, it usually represents some challenges to define clinical information such as diagnosis, stage and history of disease; for this, specific and sensitive definition will be used to identify medical conditions. Limits of this database analysis are discussed in Section 9.9 (Limitations of the research methods).

9.2. SETTING

This is a study of mCRPC patients with a first mCRPC treatment in current practice, identified and followed in the French nationwide claims and hospital database (SNDS).

The **population of mCRPC patients with a first mCRPC specific treatment** will be defined with the following inclusion criteria:

- Men of 40 years old and over, alive on the first day of the inclusion period,
- And affiliated to the healthcare insurance system “Régime Général” during the study period,
- And having mCRPC during the inclusion period,
- And initiating a first mCRPC specific treatment during the inclusion period,
- And without mCRPC specific treatment during the 5-year history before index date.

9.3. VARIABLES

9.3.1. Disease

Disease definition will use the following variables:

- **Prostate cancer**: patients with LTD registration or hospitalisation for prostate cancer (primary, associated and linked ICD-10 code diagnosis, i.e. C61), or hospitalisation with medical or surgical procedure specific of prostate cancer (prostate biopsy, vesiculo-prostatectomy, testicular pulpectomy), or specific treatment for local disease (external beam radiotherapy, brachytherapy, HIFU, cryotherapy), or drug dispensing specific for non-metastatic prostate cancer (androgen deprivation therapy) or for mCRPC (abiraterone, cabazitaxel, enzalutamide).
- **mCRPC**: patients with a prostate cancer and defined as
  - Metastatic, based on hospitalisation for metastases (primary, associated and linked ICD-10 code diagnosis), or specific treatment for metastases (e.g. radiofrequency), or metastases specific drug dispensing (e.g. denosumab)
  - And castration-resistant according to drug dispensing specific for prostate cancer (androgen deprivation), castration-resistant prostate cancer (estramustine) and mCRPC (abiraterone, cabazitaxel, enzalutamide).

9.3.2. Treatment strategy

Treatment strategy will correspond to drugs exposure from index date until 3-years follow-up, and definitions will use the following variables:

- **mCRPC treatments** will be defined by: i) hospitalisation with chemotherapy for prostate cancer (i.e. for docetaxel ± estramustine dispensing included in the hospital stay cost), ii) hospitalisation with cabazitaxel prescription (over and above the hospital stay cost), iii) dispensing of abiraterone, iv) dispensing of enzalutamide.
- **mCRPC 1st-line treatments** will be defined as a first mCRPC treatment during the inclusion period and 5-year history.
- **mCRPC 2nd-line, 3rd-line, Nth-line treatments** will be defined as a switch to another mCRPC treatment after a mCRPC treatment line N-1.
- **Adjuvant therapy for bone metastases**: bone targeted therapy with one of the beta particle emitting radionuclides (i.e. strontium-89, samarium-153, radium-223), or pharmacy dispensing of bisphosphonate (zoledronic acid and clodronic acid) or denosumab,
- Supplementation on vitamin D or calcium.
- **Radiotherapy** (type and number of courses).
- **Androgen deprivation therapy for prostate cancer**: LHRH analogues (busereline, triptoreline, leuproreline, gosereline), LHRH antagonists (degarelix), non-steroidal antiandrogen agents (nilutamide, bicalutamide, flutamide), steroidal antiandrogen agents (cyproterone), and non-steroidal estrogen (diethylstilbestrol).
- **Corticosteroids**: prednisone and prednisolone.
- **Surgery**: bilateral testicular pulpectomy, prostatectomy and other surgical procedure for complication or metastases (e.g. vertebroplasty).
- First-line treatment duration and co-medication.
- Switch to a subsequent treatment line duration and co-medication (mCRPC treatment, other anti-cancer drugs such as taxanes…).

9.3.3. Baseline characteristics

Baseline characteristics will be:

- Age at study index date.
- Comorbidities and Charlson comorbidity index (28) estimated using LTD and 5-year history of hospitalisations.

9.3.4. Prostate cancer history

Disease history for prostate cancer will correspond to LTD, specific exams and treatments during the 5-years history before index date using the following variables:

- Estimation of the date of diagnosis using the 5-year database history and LTD registration;
- Specific exam during the 5-year database history: MRI, CT scan, prostate biopsy, quantitative computed tomography, bone scintigraphy, lab test with PSA dosage, plasma testosterone, *etc*;
- Prostate cancer treatments using 5-year history: active surveillance, watchful waiting, surgery, external beam radiotherapy, cryotherapy, brachytherapy, HIFU, ADT;
- Concomitant treatments using 5-year history (ATC codes and hospitalisations);
- Hospitalisation with prostate cancer diagnosis.

9.3.5. Complications

The severe complications reported in the summary of product characteristics (SmPC) of mCRPC treatments will be investigated (29-32), hospitalisation with main diagnosis of: sepsis, cardiac failure, myocardial infarction, angina pectoris, arrhythmia, atrial fibrillation, tachycardia, deep vein thrombosis, adrenal insufficiency, hepatitis fulminant, acute hepatic failure, acute renal failure, rhabdomyolysis, fractures, neutropenia, febrile neutropenia, anaemia, leukopenia, thrombocytopenia, haemorrhage, posterior reversible encephalopathy syndrome.

9.3.6. Vital status

Vital status will be defined with the date of death (cause of death not available in the database).

9.3.7. Healthcare resource use

Healthcare resource use related to prostate cancer will be defined as:

- Hospitalisations related to prostate cancer;
- Drugs and other non-drug treatments for prostate cancer;
- Specific prostate cancer tests or imaging;
- Medical visits related to the prescription of specific prostate cancer treatment, tests or imaging;
- Transport related to prostate cancer hospitalisation or medical visits;

Other Healthcare resources use will be classified as:

- Other hospitalisations;
- Other medical visits;
- Other drugs;
- Other lab tests;
- Physiotherapy;
- Nursing acts;
- Transport;
- Sick leave daily allowances;
- Pension and disability allowances;
- Other.

9.3.8. Healthcare resource cost

Healthcare resource cost will be estimated for both perspectives:

- Societal perspective using total costs for claims and Diagnosis-related group (DRG) cost for hospitalisations.
- French healthcare insurance perspective using reimbursed cost for claims and Stay-related group (SRG) hospital costs.

9.4. DATA SOURCES

The SNDS database includes the national healthcare insurance system database with individual anonymous information on all reimbursed outpatient claims (SNIIRAM) linked to the national hospital-discharge summaries database system (PMSI) and the national death registry, using a unique national pseudonymised identifier. It currently includes 98.8% of the French population, more than 66 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires. The EGB is a permanent 1/97 random sample of the SNDS, with free and full access to certain entities fixed by ministerial order, including accredited INSERM unit. The SNDS and EGB contain individual information on (33, 34):

- General characteristics: gender, year of birth, affiliation scheme, area of residence.
- Month and year of death.
- Long-term disease (LTD, or ALD in French, and associated ICD-10 codes) with starting and ending date. There is a list of 30 LTD for a total of 3448 available ICD-10 codes, which includes most of chronic diseases with long term and/or expensive treatment; e.g. a disease such as malignant tumours is specified by the ICD-10 code within LTD. Registration with a LTD is obtained at the request of a patient's general practitioner and must be validated by the health insurance system physician. Once registered, patients receive full (i.e. 100%) reimbursement for expenditure related to the LTD, as defined by the health authorities. The LTD information is specific for the diagnosis (very low risk of false positives), but not sensitive because not all patients with the disease ask to benefit from a LTD.
- Outpatient reimbursed healthcare expenditures: visits, medical procedures, medical imageries, lab tests (e.g. PSA test), drugs with dosage and number of boxes dispensed, medical devices, transports, sick leaves, etc., with prescriber and professional caregiver information (medical or paramedical specialty, private/public practice), dates (prescription and dispensing), and codes (e.g. ATC codes for drugs), but not the medical indication nor result.
- Hospital-discharge summaries from the PMSI: ICD-10 diagnosis codes (primary, linked and associated diagnosis) for all medical, obstetric and surgery hospitalisations, with the date and duration, medical procedures, expensive drugs over and above the hospital stay cost and cost coding system (DRG and SRG). The hospital discharge summary includes the medical unit summaries when the patient is hospitalised successively in several medical units.

  Primary diagnosis is the health problem that motivated the admission in the hospital. It is determined at hospital discharge. For patients hospitalised successively in several medical units, the primary diagnosis of the hospitalisation, as well as all medical unit primary diagnosis, are generally taken into account to define the occurrence of an outcome in a pharmacoepidemiology study.

  A linked diagnosis can exist only if the primary diagnosis is a care procedure with a code Z of the ICD-10 classification (e.g. chemotherapy session) for a chronic or LTD disease. It indicates the pathology at the origin of the care procedure. Linked diagnoses can be used to define chronic diseases but are generally not taken into account to define the occurrence of an outcome in a pharmacoepidemiology study (many being false positives for the studied outcome).

  Associated diagnoses are specified if they represent specific healthcare resources. They are mainly underlying chronic diseases. Associated diagnoses can be used to define chronic diseases but are generally not taken into account to define the

occurrence of an outcome in a pharmacoepidemiology study (many being false positives for the studied outcome).

The CNAMTS proposes algorithms to define 56 diseases, including prostate cancer (35). Furthermore, algorithms for identification of prostate cancer incident cases based on ICD-10 code in the SNDS, procedure or drug specific to prostate cancer was recently published (36, 37) and guidelines (38, 39).

Several anticancer drugs, and notably chemotherapy such as docetaxel and cabazitaxel should be confined to units specialised in the administration of cytotoxics and it should only be administered under the supervision of a physician experienced in the use of anticancer chemotherapy (i.e. in hospital). Moreover, some anticancer drugs are registered on a specific hospital record of innovative and expensive products compared to the cost of hospital stay (out of T2A, *« liste des médicaments facturables en sus des prestations d'hospitalisation »*). The availability of data is summarized in the following table 1:

Table 1: Identification of drugs used in mCRPC according to data source

DCI	French expanded access	French Marketing authorisation	Outpatient dispen-sation	Specific hospital record (out of T2A)	Included in hospital stay
Docetaxel		2004		From 10 May 2005 to 1 Mar 2012	From 1 Mar 2012
Abiraterone	2010	2011	✓		
Enzalutamide	2012	2013	✓		
Cabazitaxel	2010	2011		From 22 July 2013	
Estramustine		1979	✓		
Mitoxantrone		2003			✓
Radium-223		2013			✓
Strontium-89		1993		From 10 May 2005 to 1 Mar 2015	
Samarium-153		1998		From 10 May 2005 to 1 Mar 2015	From 1 Mar 2015
Denosumab		2011	✓		
Zoledronic acid		2001	✓		
Clodronic acid		1989	✓		

Non-hospital data are updated every month and hospital-discharge summaries yearly at end of Q3 for the previous year. Access to SNDS is regulated and needs approval from Institute of Health Data (*Institut National des Données de Santé* - INDS) and French data protection commission (*Commission Nationale de l'Informatique et des Libertés* - CNIL).

9.5. STUDY SIZE

The number of new cases of prostate cancer each year in France has been estimated by the French national network of cancer registry (*Réseau français des registres de cancer*, FRANCIM) to be more than 50,000 patients (3), and the national health authorities (HAS) estimated the prevalence of prostate cancers with metastases to be 15,000 patients within a year (40, 41).

The estimation of the number of patients with a mCRPC in France in 2012 and in 2014 is an objective of the study. A preliminary analysis using the EGB database will be performed to estimate sample size of population expected in the SNDS database.

The first preliminary analysis from EGB database allowed identifying 3,192 prevalent cases with prostate cancer in 2014. Among these 3,192 patients, 137 mCRPC were identified including 29 patients initiating a mCRPC specific treatment. By extrapolation (stratified on age and sex), 20,137 prevalent mCRPC cases in 2014 are expected in the SNDS database including 4,262 patients initiating a mCRPC specific treatment.

9.6. DATA MANAGEMENT AN DATA STORAGE

Database extraction criteria will be described in a Data Extraction Plan (DEP) approved prior to initiating extraction. Data extraction will be done by the CNAMTS. The BPE data manager in charge of the project will validate the population extracted by the CNAMTS using the EGB data extraction.

Data transformation, including decision rules, disease definition, exposure definition, outcomes, risk factors, healthcare resources and calculated variables will be detailed in a statistical analysis plan (SAP).

Data will be stored on a secured server with logical and physical restricted access. Back-ups will be made twice a day and held in different sites.

9.7. DATA ANALYSIS

9.7.1. Generalities

Statistical analysis will be performed using SAS® software (SAS Institute, latest current version, North Carolina, USA). A Statistical Analysis Plan (SAP) will be developed and will be validated by the Scientific Committee before the analysis.

During the regulatory process for SNDS access, a preliminary analysis will be performed using the EGB database (1/97th permanent random sample of the SNDS) to optimize the SNDS analysis as well as to investigate an algorithm to define patients having prostate cancer diagnosis with metastases. Sensitive analyses will complete the SAP using more or less sensitive algorithms, or more or less specific algorithms in order to define mCRPC patients. External validations could be considered in partnership with other databases such as *ad hoc* clinical database or French regional registries that include an exhaustive record of prostate cancer, and histological, clinical and biological parameters for history disease.

The following analyses will be performed for each cohort 2012 and 2014 for the overall population and according the first line treatment. Other specific statistical analyses could be performed with protocol amendment.

9.7.2. Population description

- A flow chart depicting the number of patients available in the database satisfying the cohort criteria.
- Description of baseline characteristics, comorbidities and prostate cancer history.

9.7.3. Treatment strategy

- Description of first-line mCRPC specific treatment for patients with mCRPC in 2012 and 2014 and then subsequent-line treatments during a 3-year follow-up, especially second and third line therapy and time of switch using Kaplan-Meier methods.
- Description of complications that could be related to mCRPC treatment.
- Estimation of overall survival using Kaplan-Meier methods.

9.7.4. Healthcare resources use and costs

- Description of healthcare resources use for mCRPC and their related costs during the follow-up.

9.8. QUALITY CONTROL

The BPE, INSERM CIC1401, has implemented a quality management system for all its activities. CNAMTS data extraction will be validated using the expected population size estimated using the EGB. An independent double programming will be performed for main criteria and analysis, and the results compared for validation. All statistical logs are kept and can be provided. In the case of interim analysis, the database for the interim analysis is locked and kept for ulterior validation if needed. The statistical analysis report (SAR) is included in the final study report.

9.9. LIMITATIONS OF THE RESEARCH METHODS

The SNDS includes the national healthcare claims database linked to the national hospital discharge summaries database that now covers about 99% of the French population. It provides a unique opportunity to identify all subject treated for mCRPC from January 2009 to December 2017, with exhaustive information about reimbursed outpatient healthcare resources including reimbursed drugs, as well as all public and private hospitalisations. Furthermore, the SNDS has the advantage of any study that uses patient records from an existing database that are not impacted by the study, such as most of field studies.

This is also the main limit of this claims and hospitalisation database that was built for administrative and reimbursement purposes with a lack of clinical data and biological results, including severity or stage of the disease (e.g. TNM classification or Gleason score), or some risk factors such as smoking status, body mass index, blood pressure.

Selection bias: Since all subjects identified will be extracted from a national database, there is no study selection bias, nor attrition bias, except very rare withdrawals for emigrant people.

Information bias:

- mCRPC population will be identified through their metastatic and castration-resistant status. Even though TNM classification and Gleason score are not available, metastatic status and localisation could be defined as a proxy from hospital diagnosis, medical procedure, drugs and exams, with more or less specific-sensitive definitions.

- mCRPC patients newly treated with a mCRPC specific drug will be identified among mCRPC population using their treatments. All specific mCRPC drugs dispensed through community pharmacy will be identified and taken into account. For in hospital treatment, all those over and above the hospital stay cost will also be identified and taken into account, and those included in the hospital stay cost will be identified through the main diagnosis code Z for chemotherapy and linked diagnosis of prostate cancer. Drugs used before Market Authorization with ATU (temporary authorisation of use, a French specific procedure) can also be identified and taken into account (hospital pharmacy dispensing). However, drugs provided by the sponsor during clinical trial are also not recorded (of the study), and the patients concerned could not be identified, that could concern about 8 to 10% of patients according to centres.
-

9.10. OTHER ASPECTS

None.

10. PROTECTION OF HUMAN SUBJECTS

This project is a database analysis with individual anonymous information for which subject informed consent is not required. Data extraction from the SNDS is regulated and needs approval from National Institute of Health Data (*Institut des Données de Santé* - IDS) and French data protection commission (*Commission Nationale de l'Informatique et des Libertés* - CNIL).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This project is a database analysis using anonymous individual information without any spontaneous reporting. Study outcomes will be reported in aggregate in the final study report, and no individual or expedited reporting is required, according to the EMA Guideline on good pharmacovigilance practices cited above (GVP IV*), as well as the ENCePP Guide on Methodological Standards in Pharmacoepidemiology.

* The latest revision of the Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1) from EMA (coming into effect 16 Sept 2014) specifies: *For Non-interventional post-authorisation studies based on secondary use of data (VI.C.1.2.1.b): "The design of such studies is characterised by the secondary use of data previously collected from consumers or healthcare professionals for other purposes. Examples include medical chart reviews (including following-up on data with healthcare professionals), analysis of electronic healthcare records, systematic reviews, meta-analyses. For these studies, the reporting of suspected adverse reactions in the form of ICSRs is not required. Reports of adverse events/reactions should be summarised as part of any interim safety analysis and in the final study report unless the protocol provides for different reporting*".

12. PLANS FOR DISSEMINATING AND COMMUNATING STUDY RESULTS

This database analysis will be performed by the BPE, INSERM CIC1401, an academic research organisation (ARO), for which scientific communication and publication is a major component of its activities. Study methods and results will be submitted to scientific meetings and for publication in international scientific journals.

13. REFERENCES

1. Tuppin P, Leboucher C, Samson S, Peyre-Lanquar G, Gabach P, Rébillard X. Vers une évolution des pratiques de détection et de prise en charge du cancer de la prostate chez les hommes de 40 ans et plus en France (2009-2014) ? Bull Epidémiol Hebd. 2016 (9):156-63.

2. Grosclaude P, Belot A, Daubisse Marliac L, Remontet L, Leone N, Bossard N, et al. [Prostate cancer incidence and mortality trends in France from 1980 to 2011]. Progres en urologie : journal de l'Association francaise d'urologie et de la Societe francaise d'urologie. 2015 Jul;25(9):536-42. PubMed PMID: 26043950. Le cancer de la prostate, evolution de l'incidence et de la mortalite en France entre 1980 et 2011.

3. Binder-Foucard F, Bossard N, Delafosse P, Belot A, Woronoff AS, Remontet L, et al. Cancer incidence and mortality in France over the 1980-2012 period: solid tumors. Revue d'epidemiologie et de sante publique. 2014 Apr;62(2):95-108. PubMed PMID: 24613140.

4. Institut National du Cancer. Prévalence et survie nationales du cancer de la prostate 2015 [updated 03 Apr; cited 2016 04 May]. Available from: http://lesdonnees.e-cancer.fr/les-fiches-de-synthese/1-types-cancer/10-cancer-prostate/18-prevalence-survie-france-cancer-prostate.html.

5. Loeb S. Guideline of guidelines: prostate cancer screening. BJU international. 2014 Sep;114(3):323-5. PubMed PMID: 24981126.

6. Salomon L, Azria D, Bastide C, Beuzeboc P, Cormier L, Cornud F, et al. Recommandations en Onco-Urologie 2010 : Cancer de la prostate. Progrès en Urologie. 2010;20:S217-S51.

7. Salomon L, Bastide C, Beuzeboc P, Cormier L, Fromont G, Hennequin C, et al. Recommandations en onco-urologie 2013 du CCAFU : Cancer de la prostate. Progrès en Urologie. 2013;23:S69-S101.

8. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. European urology. 2016 Aug 25. PubMed PMID: 27568654.

9. l'Assurance Maladie. Cancer de la prostate : se faire dépister ? 2016 [updated 24 Mar; cited 2016 04 May]. Available from: http://www.ameli-sante.fr/cancer-de-la-prostate/depistage-du-cancer-de-la-prostate.html.

10. Denis LJ, Keuppens F, Smith PH, Whelan P, de Moura JL, Newling D, et al. Maximal androgen blockade: final analysis of EORTC phase III trial 30853. EORTC Genito-Urinary Tract Cancer Cooperative Group and the EORTC Data Center. European urology. 1998;33(2):144-51. PubMed PMID: 9519355.

11. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. The

New England journal of medicine. 2004 Oct 7;351(15):1502-12. PubMed PMID: 15470213.

12. Haute Autorité de Santé. Avis de la Commission de la Transparence du 6 juillet 2005 - TAXOTERE 20 mg TAXOTERE 80 mg. 2005.

13. Haute Autorité de Santé. Avis de la Commission de la Transparence du 16 novembre 2005 - ESTRACYT 140 mg. 2005.

14. Machiels JP, Mazzeo F, Clausse M, Filleul B, Marcelis L, Honhon B, et al. Prospective randomized study comparing docetaxel, estramustine, and prednisone with docetaxel and prednisone in metastatic hormone-refractory prostate cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008 Nov 10;26(32):5261-8. PubMed PMID: 18794543.

15. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010 Oct 2;376(9747):1147-54. PubMed PMID: 20888992.

16. Haute Autorité de Santé. Avis de la Commission de la Transparence du 17 octobre 2012 - JEVTANA 60 mg. 2012.

17. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. The New England journal of medicine. 2011 May 26;364(21):1995-2005. PubMed PMID: 21612468. Pubmed Central PMCID: 3471149.

18. Haute Autorité de Santé. Avis de la Commission de la Transparence du 29 février 2012 - ZYTIGA 250 mg. 2012.

19. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. The New England journal of medicine. 2012 Sep 27;367(13):1187-97. PubMed PMID: 22894553.

20. Haute Autorité de Santé. Avis de la Commission de la Transparence du 20 novembre 2013 - XTANDI 40mg. 2013.

21. Basch E, Autio K, Ryan CJ, Mulders P, Shore N, Kheoh T, et al. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. The Lancet Oncology. 2013 Nov;14(12):1193-9. PubMed PMID: 24075621.

22. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. The New England journal of medicine. 2014 Jul 31;371(5):424-33. PubMed PMID: 24881730. Pubmed Central PMCID: 4418931.

23. Haute Autorité de Santé. Avis de la Commission de la Transparence du 12 juin 2013 - ZYTIGA 250 mg. 2013.

24. European Medicines Agency. Provenge - autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (sipuleucel-T) 2015 [updated 19 May; cited 2016 10 May]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002513/human_med_001680.jsp&mid=WC0b01ac058001d124.

25. Haute Autorité de Santé. Avis de la Commission de la Transparence du 11 avril 2012 - XGEVA 120 mg. 2012.

26. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. The New England journal of medicine. 2013 Jul 18;369(3):213-23. PubMed PMID: 23863050.

27. Haute Autorité de Santé. Avis de la Commission de la Transparence du 02 avril 2014 - XOFIGO 1000 kBq/ml. 2014.

28. Bannay A, Chaignot C, Blotiere PO, Basson M, Weill A, Ricordeau P, et al. The Best Use of the Charlson Comorbidity Index With Electronic Health Care Database to Predict Mortality. Medical care. 2016 Feb;54(2):188-94. PubMed PMID: 26683778.

29. EMA. Jevtana® SmPC. Available from: http://ec.europa.eu/health/documents/community-register/2011/2011031798490/anx_98490_en.pdf.

30. EMA. Xtandi® SmPC. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002639/WC500144996.pdf.

31. EMA. Zytiga® SmPC. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002321/WC500112858.pdf.

32. EMA. Taxotere® SmPC. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000073/WC500035264.pdf.

33. Tuppin P, de Roquefeuil L, Weill A, Ricordeau P, Merliere Y. French national health insurance information system and the permanent beneficiaries sample. Revue d'epidemiologie et de sante publique. 2010 Aug;58(4):286-90. PubMed PMID: 20598822.

34. Moulis G, Lapeyre-Mestre M, Palmaro A, Pugnet G, Montastruc JL, Sailler L. French health insurance databases: What interest for medical research? La Revue de medecine interne / fondee par la Societe nationale francaise de medecine interne. 2015 Jun;36(6):411-7. PubMed PMID: 25547954.

35. l'Assurance Maladie. Les 56 fiches par pathologie sont réparties en 13 grands groupes de pathologies. Cancer de la prostate actif. Année 2013 2013. Available from: http://www.ameli.fr/fileadmin/user_upload/documents/Cancer_de_la_prostate_actif_2013.pdf.

36. Tuppin P, Samson S, Fagot-Campagna A, Lukacs B, Alla F, members Csb, et al. Prostate cancer outcomes in France: treatments, adverse effects and two-year mortality. BMC urology. 2014;14:48. PubMed PMID: 24927850. Pubmed Central PMCID: 4067687.

37. Doat S, Samson S, Fagot-Campagna A, Tuppin P, Menegaux F. Estimation of breast, prostate, and colorectal cancer incidence using a French administrative database (general sample of health insurance beneficiaries). Revue d'epidemiologie et de sante publique. 2016 Jun;64(3):145-52. PubMed PMID: 27238161.

38. Institut National du Cancer, Haute Autorité de Santé. Liste des actes et prestations : Affection de Longue Durée, ALD n°30 - Cancer de la prostate. Révision janvier 2012 [cited 2016]. Available from: http://www.e-cancer.fr/Professionnels-de-sante/Recommandations-et-outils-d-aide-a-la-pratique/Cancers-uronephrologiques.

39. Institut National du Cancer, Haute Autorité de Santé. Guide, Affection de Longue Durée, ALD n°30 : Cancer de la prostate. Révision janvier 2012 [cited 2016]. Available from: http://www.e-cancer.fr/Professionnels-de-sante/Recommandations-et-outils-d-aide-a-la-pratique/Cancers-uronephrologiques.

40. Haute Autorité de Santé. Avis de la Commission de la Transparence du 04 mars 2015 - XTANDI 40 mg. 2015.

41. Haute Autorité de Santé. Avis de la Commission de la Transparence du 17 juin 2015 - ZYTIGA 250 mg. 2015.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHEKLIST FOR STUDY PROTOCOLS

The ENCePP Checklist will be completed when the protocol will be validated.

ANNEX 3. ADDITIONAL INFORMATION

None.