NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Real World Evidence study on metastatic prostate cancer patient characteristics, treatment patterns and outcomes in the Pirkanmaa Hospital District in Finland
Protocol number	C3441057
Protocol version identifier	Version 1
Date	13 December 2022
Active substance	Enzalutamide (ATC-code L02BB04) Talazoparib (ATC-code L01XK04)
Medicinal product	Xtandi, Talzenna
Research question and objectives	Current understanding of the epidemiology and disease burden of mPC patients in Finland is lacking. This study will attempt to answer the following questions: • What are the demographic and clinical characteristics of mPC patients? • How are mPC patients currently treated and how effective are these treatments? • How does the development of castration-resistance affect patient outcomes? • What is the economic burden of mPC?
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADT	Androgen deprivation therapy
AE	Adverse event
AJCC	American Joint Committee on Cancer
ATC	Anatomic therapeutic chemical classification system
CI	Confidence Interval
BMI	Body mass index
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOF	End of follow-up
ESMO	European Sociey for Medical Oncology
GnRH	Gonadotropin-releasing hormone
HCRU	Healthcare resource utilization
ICD-10	International Classification of Diseases 10th revision
LOT	Line of treatment
mCRPC	Metastatic castration resistant prostate cancer
mCSPC	Metastatic castration sensitive prostate cancer
mPC	Metastatic prostate cancer
mOS	Median overall survival
nmPC	Non-metastatic prostate cancer
OS	Overall survival
PFS	Progression-free survival

PHD	Pirkanmaa hospital district
PO	Primary Objective
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
RWE	Real-world evidence
RWD	Real-world data
SAP	Statistical analysis plan
SII	Social Insurance Institute
SO	Secondary objective
SSRE	Symptomatic skeletal-related event
TAYS	Tampere University Hospital
TNM	Tumor – Node – Metastasis (classification of malignant tumors)
TTNT	Time to next treatment

3. RESPONSIBLE PARTIES

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4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date
Project kick-off (Item 1)	*June 2022*
Study protocol and statistical analysis plan (SAP) (Items 2,3)	*November 2022*
Study permission (Item 4)	*December 2022*
Start of data collection	*Q1 2023*
Data analysis and quality control (QC) checks (Item 6)	*Q1 2023 – Q2 2023*
End of data collection	*Q1 2023*
Study report draft (Item 7)	*Q1-Q2 2023*
Final study report (Item 8)	*Q2 2023*

6. RATIONALE AND BACKGROUND

Prostate cancer (PC) is the most common cancer type in Finnish men, comprising of 33% of all annual cancer diagnoses. In 2021, over 5100 new cases were diagnosed with the mean age of 70 years at diagnosis. Over 55 000 men are currently living with the disease. In 2020, 928 PC-related deaths were reported, of which 799 were in men >70 years of age (Cancer registry (1)). The current 5-year survival rate is 93 %. However, disease stage, differentiation (Gleason score) and prostate specific antigen (PSA) scores at diagnosis have a significant impact on prognosis. Higher stage, low differentiation (high Gleason score >8) and high PSA levels are indicative of a more aggressive disease and poorer prognosis. Interestingly, 55 % of PC cases have localized disease and 23 % are metastatic at diagnosis. First symptoms may be similar to symptoms of benign prostatic hyperplasia, but they may also be bone pain or pathological bone fractures, indicative of advanced disease (2–4).

Treatment of PC is highly dependent on the severity of symptoms, the disease stage and patient characteristics. Non-metastatic PC (nmPC) can be treated with active surveillance, radical surgery, radiotherapy and/or adjuvant hormone treatment. Prognosis for low-risk patients is excellent even without treatment and if the lifetime probability of cancer progression is considered low due to high age or comorbidities, symptoms are managed with hormonal treatment (3).

Metastatic PC (mPC) treatment options include surgical or chemical castration with gonadotropin releasing hormone (GnRH)-antagonists or GnRH-agonists (such as goserelin) paired with anti-

androgens (such as enzalutamide), depending on the extent of symptoms. Castration and GnRH antagonist is the primary treatment choice for patients with high risk of spinal cord compression, brain metastasis and/or severe pain. Many patients initially respond well to the current treatments, but many cancers develop from castration sensitive PC (CSPC) into castration resistant PC (CRPC) with a significant negative consequence for prognosis. Metastatic PC (mPC) median overall survival (mOS) is 2-3 years, but only 6-18 months for castration resistant mPC (mCRPC) (3,4).

Since the approval of docetaxel for mCRPC in 2004 significantly improved patient outcomes for mCRPC, the improvements in prognosis for mPC have been steady. In clinical trial setting, many novel drugs have demonstrated significant increases in progression-free survival (PFS) and overall survival (OS), but the evidence from real-world evidence (RWE) studies is not as comprehensive. Recent multi-national and RWE studies in USA and Sweden have described treatment practices and outcomes but are not entirely reflective of the Finnish setting and are lacking in terms of drug utilization and long-term outcomes (5–8).

Despite the introduction of novel therapeutic options within the past decades and improvements in prognosis, the overall burden of disease in Finland remains significant with potential for improvement especially in the management of high-risk mPC patients. Thus, it is crucial to understand the epidemiology and disease burden of mPC patients as well as the development of castration resistance. There is a paucity of information on these features in Finland, leading to the need of the proposed RWE study.

This RWE study will provide up to date real-world data (RWD) on Finnish metastatic CSPC (mCSPC) and mCRPC patient characteristics, treatment patterns, incidence and healthcare resource utilization (HCRU) in Pirkanmaa Hospital District (PHD), covering c. 20 % of the Finnish population. These data will provide updated information on real-world mPC patient populations, their current treatment practices and outcomes. This contribution will support the assessment of current treatment practices in Finland and the Nordics and help identify areas in need of improvement in the treatment practice of the highest risk PC patients.

7. RESEARCH QUESTION AND OBJECTIVES

Current understanding of the epidemiology and disease burden of mPC patients in Finland is lacking. This study will address the following questions:

- What are the demographic and clinical characteristics of mPC patients?
- How are mPC patients currently treated and how effective are these treatments?
- How does the development of castration-resistance affect patient outcomes?
- What is the economic burden of mPC?

These questions are addressed in the following study objectives:

7.1. Primary objective

1. Clinically characterize patients with metastatic castration sensitive and/or castration resistant prostate cancer

7.2. Secondary objectives

1. Assess time to disease progression from castration sensitive to castration resistant
2. Assess the factors associated with disease progression to castration resistance
3. Describe treatment lines
4. Assess outcomes by treatment line, treatment sequence and by medication received, as feasible:
    a. time to next treatment
    b. overall survival + changes in survival over time
5. Assess annual incidence of mCRPC
6. Assess the healthcare resource utilization

8. RESEARCH METHODS

8.1. Study design

This study is a non-interventional retrospective registry-based cohort study where all adult patients (age ≥18 years) with PC diagnosis (C61*; '*' indicates any number) between 1.1.2010 and 31.12.2022 will be identified from Pirkanmaa Hospital District (PHD) data lake. All available patient data will be collected as per the variables listed in Subsection 9.3.

The main focus of this study is to characterize patients with either mCSPC or mCRPC, and their treatment patterns and outcomes. Additionally, incidences and HCRU are computed, respectively.

8.2. Setting

The cohort in this study covers all patients with incident mPC diagnosis. All PC patients (patients with ICD-10 diagnosis code C61*) are requested from the PHD data lake. Metastatic patients are identified from these patients according to the inclusion criteria for mPC cohort described in the Subsection 9.2.1. The exclusion criteria are described in the Subsection 9.2.2. Depending on the coverage of the received data, minor modifications to the inclusion and exclusion criteria may be considered when finalizing the study cohort and before the data analysis phase.

The study includes two patient groups, metastatic castration sensitive prostate cancer (mCSPC) patients and metastatic castration resistant prostate cancer (mCRPC) patients. The identification of these patients and the selection of the index date for these patients is described in the Subsection 9.2.3.

The follow-up period for this study is estimated to be 1.1.2014-31.12.2022, but it can be extended or shortened based on data coverage or data collection schedule (e.g. if data is collected before the end of 2022, the study time frame will be shortened).

A patient can be included in both mCSPC and mCRPC cohorts (the scenario visualized in Figure 1) or only one of those cohorts (Figure 2 and Figure 3). The definitions for index and end of follow-up (EOF) dates are described below.

Index

1. Patients diagnosed with metastatic castration sensitive prostate cancer (mCSPC)
   - Date for the first record of metastatic prostate cancer (mPC)
2. Patients diagnosed with metastatic castration resistant prostate cancer (mCRPC)
   - Date for progression to castration resistant (if ≤3 months from castration-sensitive treatment initiation [1st control usually at 3 mo], considered de novo CRPC)

End of follow-up:

1. Patients diagnosed with mCSPC
   - End of study (31.12.2022)
   - Death
   - Moving outside of Pirkanmaa
   - Progression to mCRPC
2. Patients diagnosed with mCRPC
   - End of study (31.12.2022)
   - Death
   - Moving outside of Pirkanmaa

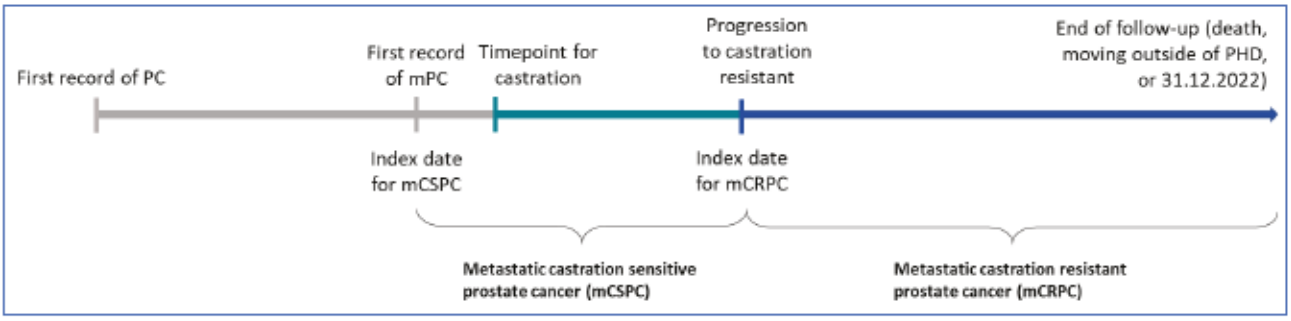

Figure 1. Index definition for a patient who is included *both* in the mCSPC and the mCRPC cohorts.

Figure 2. Index definition for a patient who is included in the mCSPC cohort.

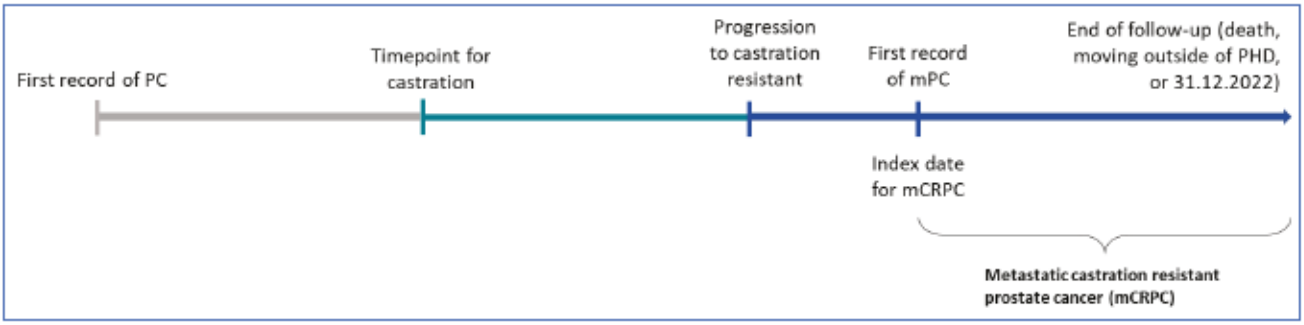

Figure 3. Index definition for a patient who is included in the mCRPC cohort.

8.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Diagnosis of PC (ICD-10: C61) between 1.1.2007 (or as early as possible) - 31.12.2022

2. Resident of Pirkanmaa at index date (diagnosis of mCSPC and/or mCRPC)
3. Detection of mPC

   Any of the following criteria:

   - ICD-10: C77*, C78* or C79* reported with C61*
   - TNM M1 (regular expressions "T1", "T2", "T3", "T4")
   - Initiation of treatment for mPC (Table 1)
   - Procedures: Radiation of metastasis (WF049; Non-English text)
   - Diagnoses: M49.5*C79.5 or M84.4
   - Metastatic cancer recorded in the clinical notes (regular expressions Non-English text)
4. Diagnosis date of mCSPC or mCRPC between 1.1.2014-31.12.2022 (start date can be modified based on data coverage at PHD data lake)

Table 1. List of medications for inclusion of mPC patients.

Active ingredient	ATC code	EMA approval date / SII reimbursement/ ESMO 2020 recommendations (4)
abiraterone	L02BX03	EMA approved 09/05/2011 for mPC; SII: 01/09/2012 (42%) for mCRPC (post-docetaxel); 01/10/2014 for mCRPC (post-docetaxel); 01/02/2018 mCRPC (post-ADT; After 01/11/2021, also for nmCRPC. Recommended for 1.-3. LOTs
enzalutamide	L02BB04	EMA approved 02/07/2013 for mCRPC; 2019 for mCSPC SII: 01/04/2014 (42%) for mCRPC (post-docetaxel); 01/10/2014 for mCRPC (post-docetaxel); After 01/11/2021, also for nmCRPC. Recommended for 1.-3. LOTs
docetaxel	L01CD02	EMA approved 2005 for mPC No SII reimbursement (hospital medicine) Recommended for 1.-2. LOTs
cabazitaxel	L01CD04	EMA Approved 17/03/2011 for mCRPC No SII reimbursement (hospital medicine) Recommended for post-docetaxel/2. LOT
apalutamide	L02BB05	EMA approved 14/01/2019 for nmCRPC; 27/01/2020 for mCSPC

		Recommended for 1. LOT
Radium-223	V10XX03	EMA approved 13/11/2013 for mCRPC Recommended for CRPC, post-docetaxel/3. LOT

Abbreviations: ADT = androgen deprivation therapy; ATC = anatomical therapeutic chemical; EMA = European Medicines Agency; ESMO = European Society for Medical Oncology; LOT = line of treatment, mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive PC; mPC = metastatic PC; nmCRPC = non-metastatic CRPC; SII = Social Insurance Institution

8.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Prevalent mCSPC and mCRPC patients (mCSPC or mCRPC diagnosis date before 1.1.2014)
2. Patient has another cancer diagnosis (all ICD-10 diagnosis codes starting with C* except C61*, or C44 or C77*,C79*), or the patient has received chemotherapy other than docetaxel or cabazitaxel (all L01* ATC codes except L01CD02 and L01CD04) within 2 years of mPC diagnosis.

8.2.3. Patient groups

In this study, all mPC patients meeting the inclusion criteria are split into two patient groups:

1. Patients diagnosed with metastatic castration sensitive prostate cancer (mCSPC)
    1. Detection of mPC
    2. Not progressed to castration resistant
2. Patients diagnosed with metastatic castration resistant prostate cancer (mCRPC)
    1. Detection of mPC
    2. Underwent orchiectomy or receiving/received chemical castration medication
        - Surgical castration: procedure KFC10 (bilateral orchiectomy) or,
        - Chemical castration: ATC codes in Table 2
    3. Castration resistant
        - Received CRPC-specific medication (Table 3) or,
        - Castration resistance recorded in the clinical notes Non-English text or,
        - >1 (or 1 based on data coverage) post-castration testosterone result below castration threshold (<1.73 nmol/l) AND (if feasible) >1 PSA increases of 50% from trough levels (primary care data not available)

Table 2. List of medications for chemical castration.

Active ingredient	ATC code
degarelix	L02BX02
goserelin	L02AE03
leuprorelin	L02AE02
triptorelin	L02AE04

Table 3. List of medications for castration resistant prostate cancer.

Active ingredient	ATC code
abiraterone	L02BX03
enzalutamide	L02BB04
Docetaxel (Until 31.12.2015)	L01CD02
cabazitaxel	L01CD04
darolutamide	L02BB06
Radium-223	V10XX03
Lutetium-177 (177Lu)-Prostate-specific membrane antigen (PSMA) -617	V10XX04

8.3. Variables

The requested variables are listed in Table 4, with associated objectives and operational definitions. Detailed definitions and computations are described in the integrated statistical analysis plan (SAP) outlined in the following sections.

Table 4. List of variables

Variable	Role/Relevant objective	Operational definition
ICD-10 diagnoses	Patient inclusion/exclusion Comorbidities PO1, SO2, SO6	yes/no
Date of birth	Patient inclusion PO1, SO2	Date; age defined at index based on birth date
Date of death	End of follow-up SO2, SO3, SO4	Date
Home municipality	Patient inclusion End of follow-up	Home municipality at each healtcare contact

Weight	PO1	kg
Height	PO1	m
Body mass index (BMI)	PO1	derived from weight and height
Outpatient visits (including emergency room visits)	SO6	All associated data including date, physician's specialty, type of arrival
Hospitalizations	SO6	Start and end dates
Procedures, operations, surgeries, including radiotherapy	Patient inclusion/exclusion SO3, SO4, SO5, SO6	Procedure code, date
Medical imaging	SO1, SO2, SO3, SO4, SO6	Imaging code, date
Medications; including - hospital medications - prescriptions	Patient inclusion/exclusion and index definition PO1, SO1-SO6	Dates, ATC-codes, active substance
Laboratory and pathology tests	PO1, SO1, SO2, SO6	Dates, test id's, **results for specific tests** (PSA, Krea, testosterone, A-fos results especially important)
Tumor-node-metastasis (TNM) classification	Patient inclusion and index definition PO1	TxNxMx T1-T4* c/r/p-prefixes clinical/radiology/pathology; no spaces in text definitions
Text mining: metastatic disease, castration-resistant	Patient inclusion and index definition PO1, SO1	Text mining with relevant phrases: Non-English text
Gleason score	PO1, SO2	Text mining with relevant phrases: "Gleas*"; range from 1-10
ECOG		Text mining "ECOG", "WHO", "Z1-4"

8.4. Data sources

This study is conducted using existing and available electronic health records accessible from Tampere University Hospital (TAYS). The study protocol and associated data request for all data will therefore be submitted to TAYS Research Services for approval.

The data will be collected from electronic health records of Pirkanmaa Hospital District of the patients diagnosed with PC (ICD-10 code C61*). Each of the collected data set will include personal identity code that is unique for every individual in Finland. The identification of the PC cohort and collection of the data with personal identification numbers will be handled solely by the personnel of TAYS Research Services. The identification codes will be removed after linkage so that only pseudonymized data is provided for the analyses.

For the PC patients, all of the following datasets are requested

- Medication data (hospital medication, prescriptions, Non-English text, all other cancer medication sources if applicable)
- Diagnoses, healthcare contacts
- Patient demographics
    - Date of birth, sex, home municipality, date of death, weight, height, BMI
- Laboratory and pathology tests
- Procedures, operations, surgeries, radiation, imaging
- Patient texts with regular expressions of AJCC stage, metastasis, castration resistant or Gleason score

The mCSPC and mCRPC cohorts are formed from the received data (Figure 4). All of the requested data is structured except the patient texts. Text mining of information is performed algorithmically without manual collection, review or validation.

The data quality and validity will be ensured by performing Medaffcon's quality control steps (see 9.8. Quality Control for further information). Due to the retrospective nature of the study, missing and/or incomplete data are expected in some of the medical records. These records will not be excluded because of missing values, and missing data will not be imputed, i.e. the data will be analyzed as they are recorded in the electronic medical records. The proportion of missing values per variable will be reported.

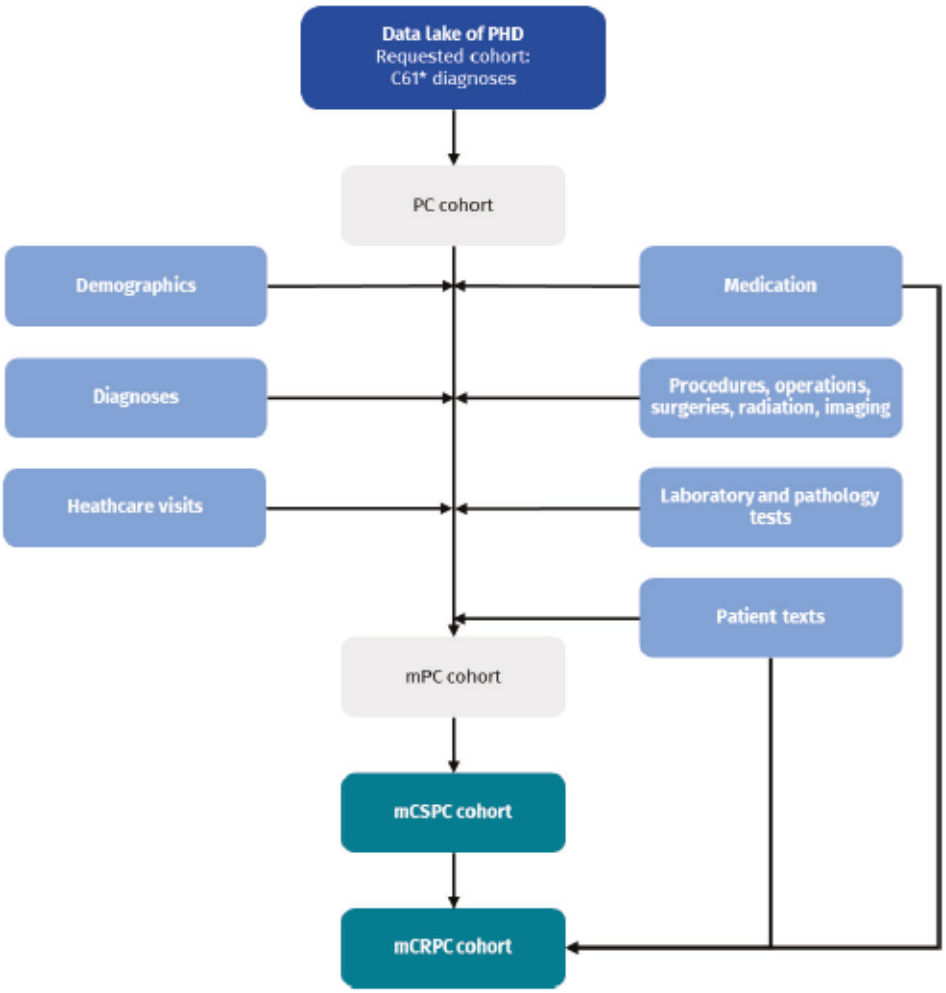

Figure 4. Overview of data sources and cohort formation.

8.5. Study size

Although sample size calculations are not applicable for descriptive studies, based on reported PC nationwide annual incidence of 191 per 100000 inhabitants for 2016-2020 in Finland (from Finnish Cancer Registry), we estimate c. 1021 newly diagnosed PC patients per year in the PHD region (population base of c. 535 000 inhabitants). With a 9 year follow-up period (1.1.2014 – 31.12.2022), we expect c. 9189 cases, of which 5-8% are expected to be metastatic (8). Hence, the de novo metastatic cohort is expected to be 459 – 735 patients.

8.6. Data management

All data collection, storage and handling will be coordinated by Tays Research Services. Tays Research Services collects the required data, pseudonymizes the IDs and releases the row level pseudonymized data to a secure analysis environment maintained by Findata. All data-analyses will be performed by the Medaffcon Oy analytics team in the secure analysis environment using the statistical software R (version 3.6.1. or higher). No patient level data will be transferred outside of this

system. Only aggregate level and/or fully anonymous data and/or summary statistics may be transferred outside this system for reporting and publication purposes. Thus, individual patients cannot be identified from this data set.

8.7. Data analysis

Data will be analyzed using primarily descriptive measures, which include mean and median values for continuous variables and frequencies and proportions for categorical variables. Costs will be estimated using data of outpatient visits, hospitalizations, etc. and utilizing publicly available price listings. For treatment outcomes, Kaplan-Meier estimates and/or corresponding time to event competing risk models will be utilized.

All of the outcome results will be reported for the both mCSPC and mCRPC cohorts when applicable.

Analyses are mostly based on structured data. However, the variables AJCC stage and Gleason score are extracted using text mining. Also, mPC and castration resistant population is supplemented by text mining.

Analyses will be performed using R, a language and environment for statistical computing, in Rstudio-server environment.

8.7.1. Primary objective 1 – Patient characteristics

Demographical and clinical variables of mCSPC and/or mCRPC patients will be summarized at index. Treated and non-treated patients will be both included.

Table 5. Patient characteristics variables

Variable	Description
Age	(index – birth date + 1 day) / 365.25
Body mass index (BMI)	The closest value from 3 months before index
Charlson Comorbidity Index (CCI)	Categories: 1, 2, 3, 4+
PSA at index	The closest value from 3 months before index
Gleason score	Categories: 6-10 The closest value from index
TNM classification	T categories: T1, T2, T3, T4 N categories: N0, N1, N2, NX M categories: M0, M1 The closest value +/- 3 months from index
De novo metastatic	Yes / No (≤2 mo from diagnosis)
Received treatment for mCSPC/mCRPC	Yes / No
Progressed into mCRPC (only for mCSPC)	Yes / No

P-AFOS (alkaline phosphatase)	Lab value (at index)
Orchiectomy performed (KFC10)	Yes / No
Palliative radiology (WF049)	Yes / No
ECOG (Eastern Cooperative Oncology Group) performance status	0-4; Structured or **not**, cost of mining (if feasible) ECOG X (0-4Z..etc)
Symptomatic skeletal-related event (SSRE, ICD-10 M49.5*C79.5, M84.4 and S*2*)	Yes / No
Osteoporosis (ICD-10 M80*, M81*)	Yes / No
Bone medication (denosumab, zoledronic acid)	Yes / No

For categorical variables, the number (N) and the proportion (%) of patients in each class will be reported. For continuous variables mean, standard deviation (SD), median, the 1st and the 3rd quartile will be reported.

8.7.2. Secondary objective 1 – Assess time to disease progression

Assess the time to disease progression for the mCSPC cohort using Aalen-Johansen competing risk time-to-event model. Define the time to event as time from mCSPC index until mCRPC index (event), death (competing event) or end of study (December 31st 2022; censoring event). Visualize the fit by plotting the curves and report the estimates at e.g., 1, 3, 6, 12, 24, 36, 60 month timepoints with 95% confidence intervals (CI), and report the median time with 95% CIs.

8.7.3. Secondary objective 2 – Assess the factors associated with disease progression to castration resistance

For time-to-event model assessing time to disease progression (Secondary objective 1), fit corresponding multistate (or single-event if number of patients is small) extension of Cox-proportional hazard model, with variables described in primary objectives as covariates (e.g. Gleason score, age, CCI, BMI). Use only covariates with complete coverage.

8.7.4. Secondary objective 3 – Describe treatment lines

The treatment lines will be defined using drug administration and prescription data. The treatment options and lines will be visualized using Sankey plots and the number and proportion of patients per treatment type will be reported. For chemotherapy treatment options (docetaxel and cabazitaxel), average number of cycles will be reported.

Treatment line changes when the active substance changes, as the treatments are mainly monotherapies (simultaneous androgen deprivation therapy (ADT) not considered as combination treatment) for both mCSPC and mCRPC treatment options, and only a few options consist of two substances. All of the treatment options for PC and concomitant medications are listed in Table 6.

The treatment lines will be defined *post hoc* using the following process:

- For each active substance, single administrations/prescriptions are merged to treatment continuums.

- To identify whether the treatment is monotherapy or combination of two active substances, the first records of the active substances will be considered

  - if the first records of the two active substances are within 28 days, the treatment is considered as combination therapy of these two medications

  - otherwise the two active substances are considered as two separate treatment lines

The initiation of the treatment line is defined as the date of first record (dosing or prescription) of the active substance, and the end of the treatment line as initation of next treatment line, end of follow-up or diagnosis of palliative care (ICD-10 Z51.5). Additionally, for each active ingredient/treatment option the number and proportion of patients receiving opioids during the treatment is reported. The patient is considered to have received opioids during the treatment, if the patient is prescribed any medication listed in Table 7 from initiation of the treatment until initiation of the next treatment. Number and proportion of patients on ADT per treatment can be additionally reported.

Table 6. Treatment options for PC and concomitant medications

Active ingredient	ATC code	Relevant SII reimbursement code/ date for reimbursement (or estimate)	Treatment Indication (relevant to PC)
degarelix	L02BX02	116 / 2012	chemical castration, ADT
goserelin	L02AE03	116 / 2011	chemical castration, ADT
leuprorelin	L02AE02	116 / 2011	chemical castration, ADT
triptorelin	L02AE04	116 / 1993	chemical castration, ADT
nilutamide	L02BB02	-	**mCSPC**
docetaxel	L01CD02	-	**mPC**
cabazitaxel	L01CD04	-	**mPC**
prednisone, prednisolone	A07EA03, A07EA02	163 / 2014	**PC**
apalutamide	L02BB05	1528, 3031 / 01/08/2020 (40%) for mCSPC and nmCRPC w/high risk for mCRPC 01/11/2021 (40%) for mCSPC w/ ADT 01/05/2022 (100%) for mCSPC and nmCRPC w/high risk for mCRPC	**mCSPC, nmCRPC** from 01/08/2020
bicalutamide	L02BB03	116 / 2011	**mPC**
darolutamide	L02BB06	116, 1525, 3036 /	**nmCRPC**

		SII: 01/12/2020 (40%) for nmCRPC 01/02/2022 (100%) for nmCRPC	
flutamide	L02BB01	116 / 1997	**PC**
Radium-223	V10XX03	-	**mCRPC**
Lutetium-177 (177Lu)-Prostate-specific membrane antigen (PSMA) -617	V10XX04	-	**mCRPC**
mitoxantrone	L01DB07	-	**mCRPC**
zoledronic acid	M05BA08	Basic (40%) / 2011	Bone frailty, pathological bone fractures
denosumab	M05BX04	116 / SII: 01/03/2011 (42%) for hormone-treatment related bone frailty; 01/01/2012 (42%) as per SPC indications	Bone frailty, pathological bone fractures
radiotherapy	Radiation of metastasis (WF049)	-	**mPC**
olaparib	L01XX46, L01XK01 (since 2021)	-	**mCRPC (BRCA mutation)**
abiraterone	L02BX03	163, 352 / SII: 01/09/2012 (42%) for mCRPC (with prednisone/prednisolone, post-docetaxel); 01/10/2014 (100%) for mCRPC (with prednisone/prednisolone, post-docetaxel); 01/02/2018 for mCRPC (with prednisone/prednisolone, post-ADT); After 01/11/2021, also for nmCRPC	**mCRPC, nmCRPC from 01/11/2021**
enzalutamide	L02BB04	163, 352 (1523, 3054 after 01/11/2021) / SII: 01/04/2014 (35%) for mCRPC (post-docetaxel); 01/12/2015 (100%) for mCRPC (post-docetaxel); 01/01/2018 (100%) for mCRPC (post-ADT) 01/11/2021, also for nmCRPC.	**mCRPC, nmCRPC from 01/11/2021**

Abbreviations: ADT = androgen deprivation therapy; ATC = anatomical therapeutic chemical; mPC = metastatic prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; nmCRPC = non-metastatic castration-resistant prostate cancer; PC = prostate cancer; SII = Social insurance institution; SPC = Summary of product characteristics

Table 7. List of strong opioids used in mPC treatment.

Active ingredient	ATC code
morphine	N02AA01
oxycodone	N02AA05
fentanyl	N02AB03
methadone	N07BC02
hydromorphone	N02AA03

8.7.5. Secondary objective 4 – Assess outcomes

The treatment outcomes will be assessed using time-to-event analysis, namely Kaplan-Meier fits or other relevant competing risk models. For each outcome, the time will be defined as follows:

1. Time to next treatment (TTNT)
    - time from initiation of the current treatment line until the initiation of the next treatment line (event), death (event), or end of study (censoring event)
    - maximum number of treatment lines for reporting TTNT is 5
2. Overall survival (OS)
    - time from index until death (event) or end of study (censoring event)
    - The OS will be stratified by
        1. For mCSPC patients with index between 2014-2016 and 2017-2022
        2. For mCRPC Patients with index between 2014-2017 and 2018-2022
        3. De novo metastatic patients and later metastasized patients

The Kaplan-Meier fits will be visualized, and the median survival/TTNT and 95 % confidence intervals for the medians will be reported.

Outcomes analyses will be done in subgroups determined by individual treatment line, major treatment sequence and/or by medication received/prescribed (with main focus on enzalutamide and abiraterone) when feasible based on data coverage.

Additionally, corresponding Cox proportional-hazards model will be fitted, including variables described in primary objectives as covariates (e.g. Gleason score, age). Use only covariates with complete coverage. The hazard ratios, 95% confidence intervals and p-values corresponding to each covariate will be reported.

8.7.6. Secondary objective 5 – Assess annual incidence of mCRPC

1. Incidence of metastatic prostate cancer (mPC)
2. Incidence of metastatic castration sensitive prostate cancer (mCSPC)
3. Incidence of metastatic castration resistant prostate cancer (mCRPC)

Report the number of incident patients (new patients each year between 2014-2022) and calculate incidence by dividing the number of incident patients each year (2014-2022) by the size of background population in Pirkanmaa Hospital District. Additionally, report the overall incidence and compute the yearly age-standardized incidences.

8.7.7. Secondary objective 6 – Assess the healthcare resource utilization

Healthcare resource utilization (HCRU) will be defined as the number of outpatient clinic visits, hospitalization and hospital inpatient days. The prices will be evaluated for each entry using publicly available price listings namely Mäklin et al 2017 (9). Prices will be derived based on specialty and type of visit (9).

The absolute number of each HCRU type and the absolute costs associated will be reported. Additionally, the estimates will be scaled to "per-patient" estimates (by dividing the absolute estimates with the number of contributing patients) and to "per patient year" estimates (by dividing the absolute estimates by the number of contributing patient years).

No statistical testing for difference between groups will be performed and estimates will be descriptive in nature. However, 95% CIs for the estimates will be derived using bootstrapping over the patients.

Additionally, stratify the HCRU analysis by specialty groups

- urology (specialty code 20U)
- oncology (specialty code 65)
- other specialties.

Transitions between urology and oncology contacts will be visualized in Sankey plots if feasible. Alternatively, the number of contacts at urology and oncology can be visualized in mean cumulative functions as a function of length of follow-up.

8.8. Quality control

Internal quality will be assured by consulting clinical experts on the data integrity, the clinical relevance, and the plausibility of the results.

A quality control will be performed, whereby all data will be sanity checked by the allocated data scientist(s). This quality control includes e.g., data coverages, number of individuals and data rows, changes as a function of time and checks for systematic gaps on data coverage and outliers in the data. Additionally, all the results will be sanity checked with a clinical expert and study team for plausibility

and clinical relevance, and especially in case of unexpected results, both analytical methods and data will be discussed and validated with the whole Medaffcon analytics team.

All R scripts to process and analyze the data will be saved, and there is version control and external back-ups for the scripts. At the end of the study, all scripts will be archived to assure analysis reproducibility, and plausible later audits (by client and/or from scientific publication side).

8.9. Limitations of the research methods

All the data is recorded by the hospital during everyday practice and most of the data is stored in structured format. Therefore, rather high quality of the data is expected. However, as with all RWD, it is plausible to have erroneous entries. Also due to the retrospective nature of the study, missing and/or incomplete data is expected in some of the medical records. Patients' records will not be excluded because of missing values, and missing data will not be imputed, i.e. the data will be analyzed as they are recorded in the electronic medical records. The proportion of missing values per variable will be reported.

The treatment lines will be defined based on the medication data from the Pirkanmaa hospital district and therefore, misclassification of treatment lines is possible. However, the start date of each main drug are expected to be recorded rather precisely, and the clinicians will be consulted when constructing the treatment lines. Thus, the majority of the treatment lines are expected to be defined correctly.

Text mining is applied to extract a few variables and supplement the data set. The text mining methods are selected and applied in order to minimize extraction of incorrect information. However, incorrect variable values are possible to exist to a small extent.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information. If automated/algorithmic methods, such as natural language processing, will be used to convert unstructured data to structured data during the implementation of the protocol, no patient personal data will be accessed.

9.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

9.3. Institutional review board (IRB)/Independent ethics committee (IEC)

Per the Act on Secondary Use of Health and Social Data 552/2019 (in Finnish: Non-English text), no institutional review board or independent ethics committee for this retrospective registry study is required.

9.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in:

- Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372 (10).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The detailed results obtained from this study will be made available upon publication. Research results from this study will be published in peer-reviewed scientific journals and/or international scientific congresses. The Authorship of any publications resulting from this study will be determined based on the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.