Protocol

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Research protocol to identify progression and death amongst patients with metastatic hormone-sensitive prostate cancer treated with available treatments: PIONEER IMI's "big data for better outcomes" program

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Abstract

Androgen deprivation therapy-based with or without first-generation anti-androgens, was the standard of care for patients with metastatic hormone-sensitive prostate cancer (mHSPC) for decades. However, the development of docetaxel chemotherapy and new androgen receptor-targeted agents, abiraterone acetate and prednisolone, apalutamide , enzalutamide and darolutamide (in combination with docetaxel chemotherapy) has proven that combination of treatments is more effective. Recently, intensification therapy, so-called "triplets", have emerged in the armamentarium of mHSPC treatment. Metastatic disease is a clinical state that remains poorly understood. The optimal diagnostic and management of patients with mHSPC are changing thanks to the development of new imaging techniques and therapies. The primary objective of this study is to develop and validate a predictive model for the occurrence of symptomatic progression, initiation of new treatments and death amongst patients with mHSPC treated with one of the approved treatment plans, on characteristics present at admission.

Keywords: androgen deprivation therapy, big data, chemotherapy, new androgen receptor-targeted agents, PIONEER, prostate cancer, metastasis, predictive model

Introduction

Background

Approximately 10% of the new prostate cancer (PCa) cases diagnosed worldwide have M1 disease, and globally from all PCa diagnoses, 1/5 patients will reach the M1 stage during the natural history of the disease[1,2]. Incidence rates of M1 PCa have increased slowly during the last 10 years in the United States[3]. In 1988, Soloway and colleagues observed that patients who had a limited number of lesions on bone scans had improved survival

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outcomes compared to those who presented with a high volume of disease[4,5]. This data was corroborated by Ost *et al*.[6] patients who presented with a single M1 site had significantly improved 5-year survival compared to those with multiple site M1 disease. It has been demonstrated that as the number of lymph nodes and distant metastases increases, the prognosis is worse, as well as patients with high-volume M1 PCa have worst outcomes compared to low-volume M1 PCa[7].

Computed tomography Scan (CT) and bone scan are the most used imaging tools for the diagnosis of M1 disease. The sensibility and specificity of CT are less than 40% and 98% and of the bone scan are 79% and 82%, respectively. Nowadays, PET/CT is used for PCa recurrence setting[8]. Still, even though these new imaging techniques have higher sensitivity and specificity than conventional ones, the clinical benefit of detecting metastases remains unclear. Moreover, their prognosis and management are unknown in patients diagnosed as M1 by more sensitive staging procedures[9–16].

Currently the European Association of Urology (EAU) guidelines recommend combination therapy as the standard of care (SOC) for patients with metastatic hormone-sensitive prostate cancer (mHSPC) unless co-morbidities or life expectancy prevent it[17]. Various studies tested new treatments, chemotherapy agents or androgen receptor-targeted agent (ARTA). The randomized phase III trials CHAARTED, GETUG-AFU and STAMPEDE (arm C) investigated the effect of adding docetaxel chemotherapy (DOC) to androgen deprivation therapy (ADT) in the treatment of mHSPC[18–20]. CHAARTED results revealed significantly longer overall survival (OS) than treatment with ADT alone. The median OS was 13.6 months longer with ADT plus DOC than ADT alone. However, this survival benefit was only significantly achieved in high-volume patients after a median follow-up of 53.7 months. No OS benefit was demonstrated in low-volume disease. Of note, the trials were not powered for this analysis. Subsequently, results from the multi-arm STAMPEDE trial were published, showing a survival benefit in the M1 subgroup of arm C, in which DOC was added to SOC. In addition, patients had better survival after the addition of DOC, after a median follow-up of 78.2 months, with a longer analysis showing no difference between low or high volume. On the other hand, the results of the GETUG-AFU 15 trial were published in 2013 and showed no survival benefit from the addition of DOC to ADT. Of patients who received DOC, 32% developed metastases. The definition of high or low-volume disease was based on the stratification of CHAARTED trial using conventional imaging (CT and bone scan). A nonsignificant 20% reduction in the risk of death in the high-volume group was reported by adding DOC, after a median follow-up of 83.9 months. No survival improvement was observed in the low-volume subgroup. It is difficult to know why patients with low-volume disease mHSPC had a benefit from adding DOC to ADT in the STAMPEDE trial but not in CHAARTED and GETUG-AFU studies. However, patients with low-volume metachronous mHSPC have favourable outcomes compared with low-volume synchronous mHSPC. This fact leads to fewer events, and no statistical difference in the outcome might be seen. This could be because most patients in the STAMPEDE trial had synchronous M1 disease, and in CHAARTED and GETUF-AFU, metachronous OMPC was ~50% and 30%, respectively. With these data, it was concluded that DOC with ADT should be considered a valid treatment option in patients with synchronous mHSPC. However, it is unclear in patients with metachronous mHSPC.

HIGHLIGHTS

- PIONEER allows the identification of characteristics that determine the appearance of symptomatic progression, initiation of new treatments and death among patients with metastatic hormone-sensitive prostate cancer.
- PIONEER is the largest cohort of patients with metastatic hormone-sensitive prostate cancer that allows a characterization of the study population, their baseline characteristics and outcomes.
- A cohort of patients with hormone-sensitive prostate cancer will provide results on overall survival, cancer-specific survival, time to symptomatic progression or metastatic castration-resistant prostate cancer at 1, 3 and 5 years.

The LATITUDE and STAMPEDE (arm G) trials support the use of abiraterone acetate and prednisolone (AAP) plus ADT in patients undergoing multimodal therapy[21]. The primary endpoint of both trials was OS and showed a significant OS benefit in both. In LATITUDE, the hazard ratio (HR) in high-risk M1 patients was 0.62. In STAMPEDE, HR in the overall population (M1 and non-M1) and in the subgroup of M1 patients was 0.63 and 0.61, respectively. The LATITUDE trial only included high-risk patients. However, a post hoc analysis from STAMPEDE showed the same benefit regardless of the risk or the volume stratification. The main secondary objectives were PFS, time to radiographic progression, time to pain or time to chemotherapy; all of them were in favour of the combination therapy. No difference in treatment-related deaths was observed with the combination of ADT plus AAP compared to ADT alone. However, in STAMPEDE, 20% of patients discontinued treatment due to adverse effects in the combination arms compared with 12% in the LATITUDE trial.

A meta-analysis of LATITUDE and STAMPEDE trials showed a 38% reduction in the risk of death with AAP plus ADT compared with ADT alone. In addition, an absolute improvement of 14% in 3-year OS and a 28% improvement in 3-year clinical/radiographic progression-free survival (PFS) compared to ADT alone were observed[22]. In summary of these results, AAP combined with ADT should be considered a valid treatment option in patients with "de novo" metastases.

There is a lack of evidence in patients with metachronous mHSPC, so no conclusion can be made in this setting. The ARCHES study included patients diagnosed with mHSPC who were randomized to receive treatment with ADT plus enzalutamide (ENZ) or ADT plus placebo[23]. The percentage of patients with treatment for the primary tumour was 26%, while the rest were M1 debut. The primary endpoint of the study was radiographic PFS, and the secondary objectives were OS, time to treatment with a new antineoplastic agent, time to prostate-specific antigen (PSA) progression, the percentage of patients with undetectable PSA, the rate of patients with an objective response to treatment and time to deterioration of urinary symptoms. The patients were stratified according to tumour volume (according to the criteria defined in the CHAARTED study) and according to whether they had prior treatment with DOC. Treatment with ADT plus ENZ reduced the relative risk of radiological PFS by 61%. This benefit in PFS was

observed in all pre-defined subgroups. Concerning the secondary endpoints, the time to PSA progression time, time to second treatment, % PSA response and % objective response favored the ADT plus enzalutamide group.

The ENZAMET study included patients diagnosed with mHSPC who were randomized to receive treatment with ADT plus ENZ or ADT plus a first-generation non-steroidal antiandrogen[24]. The percentage of "de novo" patients was 58% and almost half of the patients received DOC as combination therapy according to clinician criteria. The primary endpoint of the study was OS, and the secondary endpoints were PSA PFS and clinical PFS. Treatment with ADT plus ENZ reduced the relative risk of death by 33% in the overall study patients. The OS results were unaffected after adjusting for geographic region, disease volume prior to treatment with DOC, antiresorptive therapy and co-existing conditions. Regarding secondary endpoints, both PSA and clinical PFS were higher in the ADT plus ENZ group than in the control group.

The TITAN study included patients diagnosed with mHSPC who were randomized to treatment with ADT plus apalutamide (APA) or ADT plus placebo[25]. The primary endpoints were OS and radiological PFS, and secondary objectives were the time to initiation of chemotherapy, time to worsening pain, time to initiation of chronic opioid therapy and time to the occurrence of a skeletal-related event (SRE). For subgroup studies, they stratified patients according to tumour volume (defined in the CHAARTED study) and according to prior treatment with DOC. With a follow-up time of 22.7 months, 2-year OS was 82.4% in the apalutamide group and 73.5% in the control group. Treatment with ADT plus APA reduced the relative risk of death by 33%. These results on OS were maintained when we compared patients with high and low tumour volume. 2 years radiological PFS was 68% in the ADT plus apalutamide group and 47.5% in the control group. Treatment with ADT plus APA reduced the relative risk of radiological progression by 52%. These results on PFS were maintained in all stratified subgroups. In relation to secondary endpoints, superiority was observed for treatment with ADT plus apalutamide in time to initiation of chemotherapy.

These three studies allowed the inclusion of patients with previous treatment with DOC. The benefit of ENZ and APA is ultimately independent of tumour volume and whether the PCa is de novo or recurrent, confirming the value of ARTA across the full spectrum of patients with metastatic disease. A meta-analysis has been published in the context of mHSPC[26]. It included seven trials with over 7000 patients and compared six therapeutic alternatives in terms of OS, radiological PFS and adverse events. In this analysis, ABI and APA were the other options that offered the most significant benefit in terms of OS. DOC also improved OS but substantially increased the risk of adverse events. Similarly, a systematic review of the literature and a network meta-analysis showed that patients treated with an ARTA in mHSPC would have a longer OS than those treated with chemotherapy[27].

A four-arm randomized phase III trial testing a combination of DOC and AAP in patients with mHSPC is known as PEACE1[28]. Patients were randomized 1:1:1:1 to SOC (continuous ADT or bilateral orchiectomy, with or without DOC), SOC plus AAP, SOC plus radiation therapy (RT) to the prostate and SOC plus AAP plus RT. A statistically significant improvement in radiographic PFS was observed in the ADT +/- DOC ± RT + AAP arm relative to SOC plus RT without AAP arm. Radiographic PFS improved from a median of 2.2 years to 4.5 years (HR 0.54; 95% CI, 0.46–0.64, P <0.0001). A secondary endpoint was castration-resistant prostate cancer (CRPC) free survival; the addition of AAP conferred an absolute benefit of roughly two years to both groups (ADT ± DOC ± RT and ADT + DOC ± RT). HR for progression to CRPC was 0.40.

Another trial, ARASENS, studies the combination of DARO with DOC in patients with mHSPC[29]. Date reported for the primary analysis showed a risk of death significantly lower in the DARO group (32.5%) than in the placebo group (HR 0.68; 95% CI, 0.57–0.80; $P < 0.001$). Both groups had similar adverse events; the most common incidences were about 10% of patients. In addition, both groups had the highest adverse events during the overlapping DOC treatment period A recent systematic review by Yanaguisawa *et al.*[30], found that the triplet combination therapy improves survival endpoints in mHSPC patients compared with currently available doublet treatment regimens. Still, findings need to be confirmed in further head-to-head trials with longer follow-up and among various patient populations.

Metastatic disease is a clinical state that remains relatively poorly understood. The optimal diagnosis and management of patients with metastatic PCa are changing thanks to the development of new imaging techniques and the emergence of new therapies[31–36].

Aims and objectives

Primary objective

- To prospectively develop and validate a predictive model for the occurrence of symptomatic progression, initiation of new treatments and death amongst patients with mHSPC treated with one of the approved treatment plans, on characteristics present at admission.

Secondary objectives

- To describe demographics and clinical characteristics of patients with mHSPC across a distributed network of observational databases.
- To describe what treatments patients with mHSPC were exposed to and in which sequence across a distributed network of observational databases.
- To characterise the clinical outcomes of patients with mHSPC such as overall survival, time to symptomatic progression, time to mCRPC and time to the next treatment across a distributed network of observational databases at 1, 3 and 5 years.

Materials and methods

Data sources

The study will rely on large observational data, namely population-based registries, electronic health records and insurance claims data. The study uses only de-identified data. Confidentiality of patient records will be maintained at all times. Data custodians will remain in full control of executing the analysis and packaging results. There will be no transmission of patient-level data at any time during these analyses. Only aggregate statistics will be shared. Study packages will contain

minimum cell count parameters to obscure any cells which fall below allowable reportable limits.

Study design

The study will be an observational cohort study using routinely collected health data converted to Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

The study period starts from 01/01/2016 and ends at the end of the latest available data for all data sources. The study identification period will be from January 2012 to 365 days prior to the latest available data in each database. This allows for at least 365 days of follow-up data for the last person included in the study.

Target cohorts

There is no diagnosis code for mHSPC. As such, the following operational definitions will be applied.

Two mHSPC subcohorts will be identified: metachronous mHSPC and synchronous mHSPC. Adult male patients with a metastatic disease will be identified. Patients are eligible to be included in either cohort if they have at least 365 days of observation prior to diagnosis of metastatic disease in the data source. Index date is set as the date of first metastasis diagnosis in the patient record.

Patients are included in the metachronous sub-cohort if they have:

(1) At least one diagnosis of prostate cancer prior to or up to 30 days after index date.
(2) No evidence of other primary malignancies (other than non-melanoma skin cancer) prior to index date.
(3) Not undergone orchidectomy prior to index date AND have not received ADT 6 months prior to index date.
(4) Received local therapy (radiotherapy or surgery) any time prior to up to 184 days prior to index date.

Patients are included in the synchronous sub-cohort if they have:

(1) Their first diagnosis of prostate cancer in the database between183 days prior and 30 days after index date.
(2) No evidence of other primary malignancies (other than non-melanoma skin cancer) prior to index.

Treatment-initiated mHSPC

mHSPC patients imitated an ADT-based regimen (ADT monotherapy or combination therapies) as the first line of therapy after diagnosis with mHSPC will be included in either cohort. Index date will be set at the date of initiation of the treatment.

Additionally, the following treatment-initiated mHSPC cohorts will be created according to different treatment options using the same logic:

- mHSPC initiated ADT monotherapy
- mHSPC initiated ADT + ARTA
- mHSPC initiated ADT + ARTA + Chemotherapy
- mHSPC initiated ADT + Chemotherpay

The specific characteristics of each cohort are summarized in Figure 1.

Treatment-related information

(1) ADT: luteinising-hormone-releasing hormone agonists, luteinising-hormone-releasing hormone antagonists or first-generation anti-androgens
(2) ARTA: abiraterone acetate, enzalutamide, apalutamide or darolutamide
(3) Chemotherapy: docetaxel, paclitaxel or capazitaxel
(4) PARPi: olaparib or rucaparib
(5) radium-223
(6) lutetium PSMA
(7) Immunotherapy: sipuleucel-T or pembrolizumab

Prostate cancer-specific treatments standardized to RxNorm (listed in Section Treatment-related information) will be identified. Date of the first drug episode (e.g. first administration or non-cancelled order of ADT) after diagnosis of mHSPC will be considered as the start of the first line of treatment (LoT). Treatments received up to 183 days after the of the initiation of the first ingredient will be considered a part of the first LoT. Addition of a new treatment 183 days after the initiation of the first ingredient is considered a treatment switch. The date patient discontinues LoT will be considered the end date of the first LoT. Discontinuation will be defined as having a subsequent treatment after the first LoT; having a gap of more than 30 days with no prostate cancer related therapy following the last administration; or having a date of death while on the regimen. Patients will be censored at their last known usage within the database or end of follow-up. Receipt of a new treatment after the end of the first LoT will initiate a subsequent LoT.

Outcomes

The complete list of outcomes taken into account is shown in Table 1.

Time to initiation of the next line of treatment: Time from the index date in the treatment-initiated mHSPC cohorts to the date the patient received their next treatment or to their date of death if death occurs prior to having another treatment. Patients will be censored at their last activity within the database or end of follow-up.

Time to symptomatic progression: Time from the index date in the treatment-initiated mHSPC and mCRPC cohorts to the date the patient experiences symptomatic progression or to their date of death if death occurs prior to having another treatment. Patients will be censored at their last activity within the database or end of follow-up.

Time to discontinuation of the initial treatment: Time from the index date in the treatment-initiated mHSPC cohorts to the date the patients discontinue their initial treatment because of adverse events or to their date of death if death occurs prior to having another treatment. Patients will be censored at their last activity within the database or end of follow-up.

Follow-up

Patients are followed up from index date until death, diagnosed with another malignancy (except for non-melanoma skin cancer), or end of the observation period, whichever occurs first.

Stratifications

Each target cohort will be analyzed in full and stratified on factors based on the baseline characteristics shown in Table 2 assessed

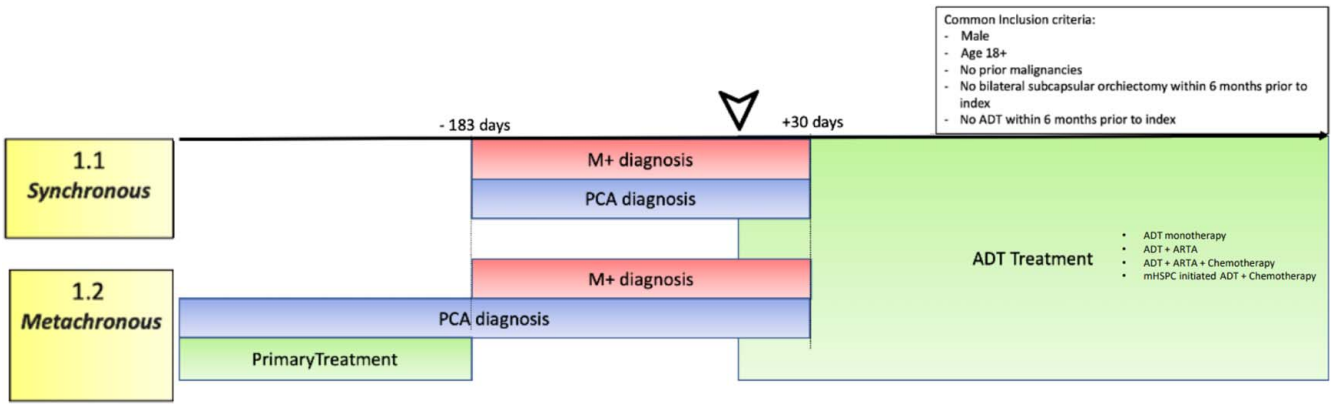

Figure 1. Definition of study cohorts. The inclusion criteria common to all cohorts are listed in the upper right box. The Index event is indicated by the upper arrow: for cohort 1 the diagnosis of metastasis (synchronous to the diagnosis of Prostate cancer for cohort 1.1 and metachronous for cohort 1.2), for cohort 2 the start of androgen deprivation therapy (synchronous to the diagnosis of Prostate cancer for cohort 2.1 and metachronous for cohort 2.2). ADT, androgen deprivation therapy; ARTA, androgen receptor-targeted agent; M+, metastatic; PCa, prostate cancer.

for the 1 year pre-index period, all strata are pending meeting minimum reportable cell counts (as specified by data owners).

Study size

This study will use routinely collected data. Therefore, all patients meeting the eligibility criteria outlined in Fig. 1 will be included.

Table 1

The complete list of outcomes taken into consideration for the drafting of the concept sets.

Outcome	Defined as
Initiation of other therapies	RT following symptoms of pain and or/haematuria
	Placement of ureteral stent or nephrostomy for acute kidney failure
	Colostomy
	Chronic foley catheter placement
	Pelvectomy (Total pelvic exenteration)
	Suprapubic catheter placement
	Haemostatic TUR
Symptomatic progression	Skeletal-related events
	Urinary retention
	Hydronephrosis and acute kidney failure
	Bowel occlusion/obstruction
	Opioid use
Adverse events	Convulsions
	Fatigue
	Diarrhoea
	Hot flushes
	Anaemia
	Thrombocytopenia
	Neutropenia
	Haematuria
	Constipation
	Hypokalemia
	Hypertension
	OEdema
	Arrhythmia
	Myocardial infarction
Death	

RT, radiation therapy; TUR, transurethral resection.

All strata are pending meeting minimum reportable cell count of greater than 10 persons.

Analysis

This is a descriptive study without any formal hypothesis testing. Each target cohort will be characterized by a series of demographic, comorbidity and medication features (defined in Section Materials and methods). Categorical covariates are summarized as counts and percentages (%), while continuous covariates are summarized by median and interquartile range (Fig. 2), minimum and maximum. Standardized mean differences will be calculated comparing demographic and clinical characteristics between the target cohorts.

Prior to analysis, the definitions of mHSPC cohorts will be evaluated using the Observational Health Data Sciences and Informatics (OHDSI) R package *CohortDiagnostics*[37]. *CohortDiagnostics* produces the following metrics: cohort counts in the database, incidence rates (by calendar year and age), baseline characteristics and cohort attrition. Following execution of diagnostics, the cohort definitions will be reviewed to determine if alterations need to be made to improve the data capture capability of the definitions for the target population. We place particular focus on the inclusion rules to assess how well these algorithms work in various data sources. The study team will review the diagnostic results and refine the cohort. Data analysis will be initiated only if the database and cohort diagnostics results pass CDM and cohort diagnostics.

Patient demographic and clinical characteristics (co-morbidities) at baseline (using 1 year of prior observation) will be described for each target cohort. The concept-based co-morbidities use condition group eras within 365 days before index, where the condition groups are defined by Systematized Nomenclature of Medicine—Clinical Terms (SNOMED-CT) hierarchy. The concept-based drug classes use drug group eras within 365 days before index, where the drug groups are defined by Anatomical Therapeutic Chemical (ATC) hierarchy. Concept-based co-morbidities and drug classes are characterized using optimized scripts from the *FeatureExtraction* package from OHDSI[38].

Treatment patterns will be described for both mHSPC and visualized using Sankey diagrams. Pathways with at least 30

Table 2

List of factors, divided in subgroups and its specific definition used during the construction of concept sets.

Type of factor	Factors	Defined as
Demographics baseline	Age at index	< 60 years / 60–69 years / 70–79 years / ≥ 80 years
	Charlson Comorbidity Index	CCI = 0 / CCI = 1 / CCI ≥ 2
	ECOG PS	ECOG = 0 / ECOG = 1 / ECOG ≥ 2
	Type of comorbidity	Obesity, hypertension, cardiovascular events, type 2 diabetes, venous thromboembolic events (VTE), anxiety, psychological distress, respiratory disease
	Race/ethnic groups	Caucasian, African-American, Jew Askenazi.
	Smoking	Smokers, non-smokers
	Family history of cancer	PCa, breast cancer, ovarian cancer, bowel, pancreatic cancer or BRCA mutation
	Physical therapy	
Baseline disease status	Metastatic stage	M1a / M1b / M1c
	Index imaging procedures	Multiparametric MRI of prostate, bone scan, abdominal CT scan, chest CT scan, PET/CT imaging
	PSA at diagnosis	
	Grade group (Gleason score)	(3 + 3), 2 (3 + 4) , 3 (4 + 3), 4 (4 + 4 OR 3 + 5 OR 5 + 3), 5 (5 + 5 OR 4 + 5 OR 5 + 4)
	EAU risk group	low-risk, intermediate-risk, high-risk
Treatment	ADT only	Luteinising-hormone-releasing hormone agonists, Luteinising-hormone-releasing hormone antagonists, or First-generation anti-androgens
	ARTA only	AAP, APA, DARO or ENZA
	Chemotherapy only	DOC
	Doublets	ADT + DOC, ADT + ARTA
	Triplets	ADT + DOC + ARTA

AAP, abiraterone acetate and prednisolone; ADT, androgen deprivation therapy; APA, apalutamide; ARTA, androgen receptor-targeted agent; BRCA, breast cancer gene; CCI, Charlson Comorbidity Index; CT, computed tomography; DARO, darolutamide; DOC, docetaxel chemotherapy; EAU, European Association of Urology; ECOG, Eastern Cooperative Oncology Group; ENZA, enzalutamide; PCa, prostate cancer; PSA, prostate-specific antigen.

patients will only be considered in the analysis. Counts (%) of patients receiving different treatment regimens for first line treatment of mHSPC. Median (95% CI) time to treatment discontinuation and time to initiation of next treatment will be estimated using Kaplan–Meier methodology. Analysis will be conducted for all target cohorts and will be further stratified to assess patients' characteristics and treatment variations by predefined stratum.

Analyses will be conducted in each database separately using R[39] and Redshift Structures Query Language (SQL).

Timeframe

The study period starts from 1 January 2016 and end at latest available date for all data sources.

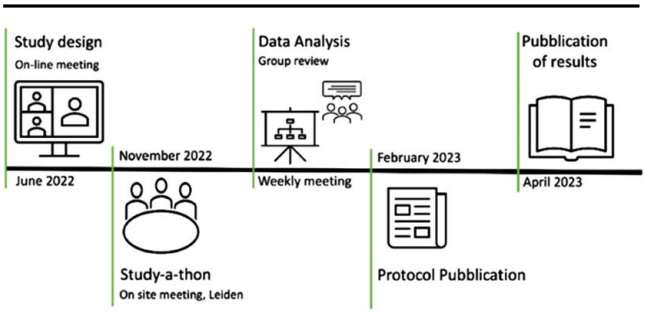

Figure 2. The image shows the timeline of the study: the study design started in June 2022, the Study-a-thon held in Leiden in November 2022, the data analysis and group review, the protocol publication, and the future publication of results.

Strengths and limitations

Strengths

The study is anticipated to be the largest patient-level cohort of metastatic PCa patients, thus allowing characterization of relatively uncommon outcomes, otherwise not identifiable in smaller datasets. Data will be obtained from multiple centres and providers. This enables comprehensive characterization of the study population, key baseline characteristics, outcomes. Lastly, the use of routinely collected data from multiple sources maximizes the external validity and generalizability of the findings.

Limitations

This study is carried out using data recorded in a collection of electronic health record, claims and cancer registries. As with any healthcare database used for secondary data analysis, the patient records might be incomplete in many respects and may have had erroneous entries, leading to misclassification of study variables. Data regarding diagnosis of metastatic PCa, treatments, pathology, imaging and laboratory results or baseline covariates prior to enrolment within the database may not be available. Clinical progression based on the radiological imaging is limited by the data collection.

Pca specific characteristics such as stage, grade at diagnosis or the extent of the disease are not readily available in most her and claims databases. Treatment provided in hospitals or any other setting outside each participating institution is not included.

Medical conditions may be underestimated as they will be based on the presence of condition codes, with the absence of such a record taken to indicate the absence of a disease. Meanwhile, medication records indicate that an individual was prescribed or dispensed a particular drug, but this does not

necessarily mean that an individual took the drug as originally prescribed or dispensed.

Ethical approval

NIL.

Consent

NIL.

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Author contribution

Conceptualization: J.G.R., J.N., N.M., A.M., A.G.; Formal analysis: A.G., B.d.M., Writing—original draft preparation: J.G.R., R.N., L.I., P.P.W., T.M.; Supervision: M.J.R., R.C., M.G.; Project administration: C.S., S.E.A. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest disclosure

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Research registration unique identifying number (UIN)

NIL.

Guarantor

Dr. Juan Gómez Rivas.

Data availability statement

Not applicable.

Provenance and peer review

This paper was not invited.

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