NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Novel Hormonal Therapy (NHT) for Treating Patients with Metastatic Castration-Sensitive Prostate Cancer (mCSPC): An Analysis of National Veterans Affairs Health Care Network Data
Protocol number	C3431052
Protocol version identifier	1.0
Date	06 November 2023
Active substance	Enzalutamide
Medicinal product	Xtandi
Research question and objectives	The main research question is to identify men with mCSPC from the Veterans Affairs Health Care Network Data who were treated with NHT, including abiraterone (ABI), apalutamide (APA), or enzalutamide (ENZ), in the first line (1L) setting and describe clinical outcomes of interest. CCI [redacted] More specifically, the study objectives include: • Primary objective: Describe duration of therapy (DOT) among patients with mCSPC who initiated NHT in 1L • Secondary objective: Describe time to next therapy (TTNT) among patients with mCSPC who initiated NHT in 1L • Exploratory objectives: 1. Describe patient baseline characteristics overall CCI [redacted] CCI [redacted]

	CCI [redacted] 4. Describe time to deep prostate-specific antigen (PSA) response and time to undetectable PSA overall CCI [redacted] 5. Describe time to progression overall CCI [redacted] 6. Describe the distribution of next therapy regimens overall CCI [redacted]
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABI	abiraterone acetate
ADT	Androgen Deprivation Therapy
AE	adverse event
APA	apalutamide
CCI	Charlson Comorbidity Index
CDW	Corporate Data Warehouse
CI	confidence interval
CRPC	castration-resistant prostate cancer
CSPC	castration-sensitive prostate cancer
DOT	duration of treatment
EC	Ethics Committee
ENZ	enzalutamide
FDA	United States Food and Drug Administration
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
IPTW	Inverse probability treatment weighting
IRB	Institutional Review Board
KM	Kaplan-Meier
mCRPC	metastatic CRPC
mCSPC	metastatic CSPC
NCI	National Cancer Institute

Abbreviation	Definition
NHT	Novel Hormonal Therapy
NSAA	non-steroidal anti-androgen
PC	prostate cancer
PH	proportional hazards
PSA	prostate-specific antigen
PFS	progression-free survival
SAS	Statistical Analysis System
SLVHCS	Southeast Louisiana Veterans Health Care System
SMD	Standardized Mean Difference
TTNT	time to next therapy
VA	Veterans' Affairs
VHA	Veterans' Health Administration

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title: Novel Hormonal Therapy (NHT) for Treating Patients with Metastatic Castration-Sensitive Prostate Cancer (mCSPC): An Analysis of National Veterans Affairs Health Care Network Data

Version: 1.0

Date of Protocol: 06 November 2023

Author:

PPD

Rationale and Background: Prostate cancer is the most common cancer and the second leading cause of cancer death among men in the United States. While the long-term outlook is positive for early-stage prostate cancer, survival rates drastically decrease once the disease has spread beyond the prostate gland. Metastatic castration-sensitive prostate cancer (mCSPC) is form of metastatic prostate cancer among men who have never received or are sensitive to androgen deprivation therapy (ADT). Conventional therapy for mCSPC has been ADT, however, mCSPC treated with ADT might eventually transition to castration-resistant prostate cancer (CRPC) stage with a median survival of approximately 3 years. Upfront intensified treatment with NHTs, including abiraterone acetate (ABI), apalutamide (APA), and enzalutamide (ENZ), added to a backbone of ADT, has substantially improved survival in clinical trials. Due to relatively recent approval of NHTs in mCSPC there is limited information on real-world duration of treatment and time to next treatment with these therapies. The current study proposes to use the Veterans Health Administration (VHA) database to describe outcomes of patients with NHT use in mCSPC.

Objectives: The study objectives include:

- **Primary objective:** Describe duration of therapy (DOT) among patients with mCSPC who initiated NHT in the first line (1L)
- **Secondary objective:** Describe time to next therapy (TTNT) among patients with mCSPC who initiated NHT in 1L
- **Exploratory objectives:**
  1. Describe patient baseline characteristics overall CCI [redacted]

CCI [redacted]

[redacted]

4. Describe time to deep prostate-specific antigen (PSA) response and time to undetectable PSA overall CCI [redacted]

5. Describe time to progression overall CCI [redacted]

6. Describe the distribution of next therapy regimens overall CCI [redacted]

Study Design: This is a retrospective, observational study using the VHA data. Patients with mCSPC who initiated NHT in 1L during January 2020 – December 2022 will be selected based on diagnosis history, treatment history, PSA measurements, age, and continuous enrollment. CCI [redacted]. Patients will be required to have 365 days of continuous enrollment in the National Veterans' Affairs (VA) Health Care Network prior to their index date, during which baseline characteristics will be assessed. The follow-up period will be defined as the time from the index date to the end of continuous enrollment, the end of the data availability, or death, whichever comes first. During the follow-up period, the outcome measures (ie, DOT, TTNT, time to deep PSA response, time to undetectable PSA, time to progression, and the distribution of next treatment) will be assessed.

Population: The population for the primary and secondary objectives will consist of patients with mCSPC who initiated NHT in 1L and who meet all the sample selection criteria. CCI [redacted]

Variables: Baseline demographic and clinical characteristics will include age, race, geographic regions, index year, treatment history, diagnosis history, prognostic variables, Charlson Comorbidity Index score, and individual comorbidities. Outcomes will include DOT, TTNT, time to deep PSA response, time to undetectable PSA, and time to progression.

Data Sources: VHA Medical Statistical Analysis System datasets.

Study Size: All eligible patients available for the analysis will be included.

Data Analysis: In the primary and secondary analyses, DOT and TTNT will be described in the overall sample of patients with mCSPC who initiated 1L NHT using Kaplan-Meier (KM) analysis. The number at risk table and the median time to event and its 95% confidence interval will be reported. In the exploratory analyses, patient baseline characteristics will be described in the overall sample CCI [redacted]. Means, standard deviations, medians, and interquartile range will be e ous variables; counts and percentages will be estimated for categorical variables. CCI [redacted] KM analysis will be conducted to describe time to deep PSA response, time to

undetectable PSA, and time to progression in the overall sample [redacted] Data analysis will be executed using statistical software SAS version 9.4 (Cary, NC).

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Start of data collection	21 November 2023
End of data collection	31 October 2024
Final study report	31 December 2024

7. RATIONALE AND BACKGROUND

Prostate cancer is the most common cancer and the second leading cause of cancer death among men in the United States. The National Cancer Institute estimates that in 2022 there will be 268,490 new cases of prostate cancer (PC) and 34,500 deaths due to PC.[8] While the long-term outlook is positive for early-stage prostate cancer, survival rates drastically decrease once the disease has spread beyond the prostate gland.[9]

Metastatic castration-sensitive prostate cancer (mCSPC) is form of metastatic prostate cancer among men who have never received or are sensitive to ADT.[5] Conventional therapy for mCSPC has been ADT, however, mCSPC treated with ADT might eventually transition to CRPC stage with a median survival of approximately 3 years.[11]

Several NHTs have been approved for treatment in mCSPC together with ADT. ABI and ENZ were initially approved by the United States Food and Drug Administration (FDA) for metastatic CRPC patients with prior chemotherapy in April 2011 and August 2012, respectively, and for chemotherapy-naïve patients in December 2012 and September 2014, respectively. ABI was later approved in February 2018, followed by ENZ in December 2019, for the treatment of mCSPC.[1,2] One of the most recent NHTs, apalutamide (APA) was approved by the FDA in September 2019 for patients with mCSPC.[3]

Upfront intensified treatment with NHTs in mCSPC, including ABI, APA, and ENZ, added to a backbone of ADT, has substantially improved survival.[4,6,10] With the rapidly expanding treatment landscape, there have been limited studies describing clinical outcomes with NHTs in mCSPC.

The current study proposes to use the VHA database to describe outcomes of patients with NHT use in in mCSPC.

8. RESEARCH QUESTION AND OBJECTIVES

The main research question is to identify men with mCSPC from the VHA database who were treated with NHT, including ABI, APA, and ENZ, in the 1L setting and describe clinical outcomes of interest. CCI

More specifically, the study objectives include:

- **Primary objective:** Describe DOT among patients with mCSPC who initiated NHT in 1L
- **Secondary objective:** Describe TTNT among patients with mCSPC who initiated NHT in 1L

- **Exploratory objectives:**

    1. Describe patient baseline characteristics overall [redacted]

    4. Describe time to deep PSA response and time to undetectable PSA overall [redacted]

    5. Describe time to progression overall and [redacted]

    6. Describe the distribution of next therapy regimens overall [redacted]

9. RESEARCH METHODS

9.1. Study Design

This is a retrospective, observational study using the VHA data. Patients with mCSPC who initiated NHT in 1L during January 2020 – December 2022 will be selected based on diagnosis history, treatment history, PSA measurements, age, and continuous enrollment. [redacted]. Patients will be required to have one year of continuous enrollment in the National VA Health Care Network prior to their index date, during which patient baseline characteristics will be assessed. The time period (January 2020 – December 2022) to identify NHT initiation reflects the recency of NHT approvals, and the baseline period allows us to capture any potential comorbidities and characteristics that may be confounders to the outcomes. The follow-up period will be defined as the time from the index date to the end of continuous enrollment, the end of the data availability, or death, whichever comes first. During the follow-up period, the outcome measures (ie, DOT, TTNT, time to deep PSA response, time to undetectable PSA, time to progression, and the distribution of next treatment) will be assessed. The follow-up period is chosen to maximally capture any potential outcomes among patients with mCSPC who initiated NHT in 1L.

9.2. Setting

The study population will include patients with mCSPC who initiated NHT in 1L in the VHA database. Inclusion and exclusion criteria are specified below.

9.2.1. Inclusion Criteria

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

- Males.
- Have at least one claim with a diagnosis code of PC (PC; ICD-10-CM code C61).
- Have documented secondary metastasis codes on or after the initial PC diagnosis (ICD-10 codes C77, C78, C79, C7B).
- Have initiated ABI, APA, or ENZ (1) during the index window of January 2020 – December 2022, and (2) within 90 days prior to or any time after the first claim for metastatic disease. The initiation of date of ABI, APA, or ENZ will be defined as the index date.
    - Index window of January 2020 – December 2022 is selected, as during this period all NHTs were approved for mCSPC, which will help remove early initiator bias (eg, when a product/class of products became available, patients with severe diseases tend to try first). Table 1 lists the approval dates for when each NHT was approved for treating mCSPC.

Table 1. FDA Approval Dates for NHTs in mCSPC

ABI	07 February 2018
APA	17 September 2019
ENZ	16 December 2019

- At least 18 years old at the index date.
- Have continuous enrollment for at least 365 days before the index date.
- Have evidence to be castration sensitive AND have no evidence to be castration resistant. This is tentatively defined as:

Evidence to be castration sensitive:

- No prior surgical castration (ie, bilateral orchiectomy, Appendix Table 1) any time prior to the index date or no medical castration (ie, degarelix, relugolix, goserelin, histrelin, leuprolide, and triptorelin; ≥8 weeks of continuous use; Appendix Table 1) within -90 to -365 days prior to the index date, OR

- Presence of ICD-10-CM diagnosis code indicating hormone sensitive malignancy status (ie, Z19.1, which was introduced on 01 October 2016) within 90 days before the index date

No evidence to be castration resistant:

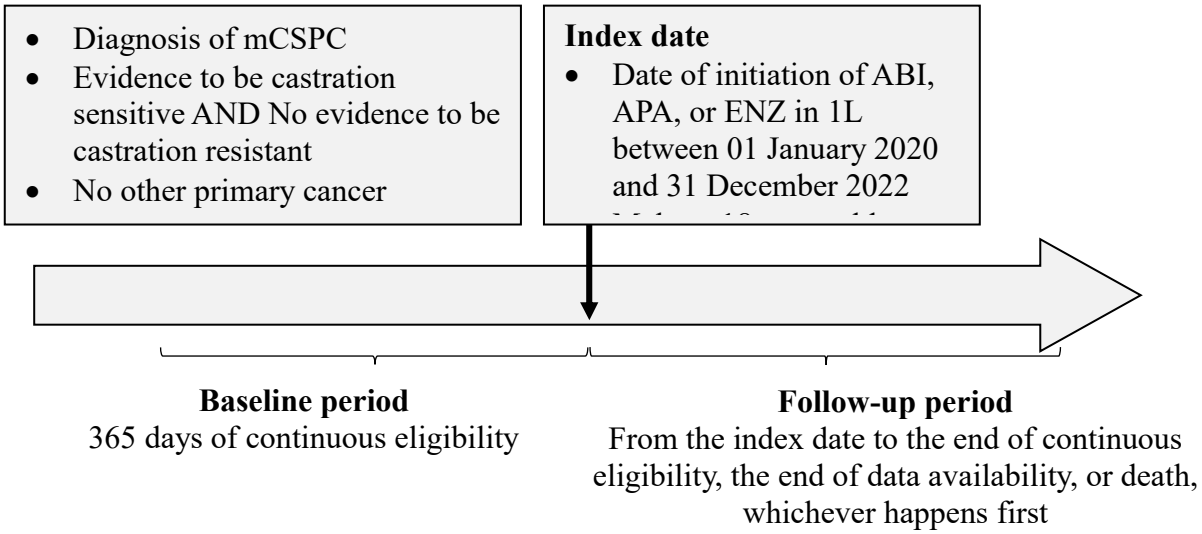
- No evidence of castration resistance any time prior to the index date. Evidence of castration resistance is defined by the following:

  - ICD-10-CM diagnosis code indicating hormone resistance (Z19.2), OR

  - A rise in PSA from the nadir by ≥2 ng/mL after castration (nadir is defined as the lowest PSA since surgical or medical castration and before the index date)

  - Patients with other PC treatment including NHT, non-steroidal anti-androgen (NSAA), chemotherapy, immunotherapy, radium 223, lutetium Lu 177 vipivotide tetraxetan, ketoconazole, niraparib, olaparib, rucaparib, or talazoparib at any time prior to the index date

Figure 1. Study Schema



9.2.2. Exclusion Criteria

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

- Patients with any other primary cancer (excluding non-melanoma skin cancer) prior to the index date
- Participation in clinical trial during the 30 days prior to the index date

CCI [redacted]

9.3. Variables

Table 2. Baseline Demographics and Clinical Characteristics

Variable	Operational Definition
Baseline period	The baseline period will be defined as 365 days prior to the index date.
Age	Age will be defined as of the index date and retained in the dataset as a continuous variable and a categorical variable: 18-49, 50-59, 60-69, 70-79, and ≥80 years old.
Race	Proportion of patients that were Hispanic, non-Hispanic white, black, other, and unknown races will be evaluated.

Variable	Operational Definition
Geographic regions	Proportion of patients that lived in Northeast, Midwest, South and West areas.
Index year	Variable will be created for the index calendar year (from 2020 to 2022).
Treatment history	Proportion of patients who had radical prostatectomy, external radiotherapy, chronic corticosteroid use, hormone therapy, bone protective agents, and pain medication prescribed in the baseline period will be evaluated.
Time from Metastatic Diagnosis Date to Index Date	Time from the first observed metastatic date in the data to the index date will be evaluated.
Time from PC Diagnosis Date to Index Date	Time from the first observed PC date in the data to the index date will be evaluated.
Site of Metastasis	Flags will be created for patients that had a metastatic diagnosis at the following sites: bone only, bone and node only, node only, viscera and other.
PSA Value	Baseline PSA value (if available) will be defined as the PSA value closest to the index date within 180 days prior to index date.
Hemoglobin Value	Baseline hemoglobin value (if available) will be defined as the value closest to the index date within 180 days prior to index date.
Alkaline Phosphatase Value	Baseline alkaline phosphatase value (if available) will be defined as the value closest to the index date within 180 days prior to index date.
Modified National Cancer Institute (NCI) Charlson Comorbidity Index (CCI)	The NCI CCI score excluding cancer will be calculated during the baseline period.
Acute Coronary Syndrome	A binary variable (yes/no) will be created for patients with claims for acute coronary syndrome during the baseline period.
Angina Pectoris	A binary variable (yes/no) will be created for patients with claims for angina pectoris during the baseline period.

Variable	Operational Definition
Arrhythmia	A binary variable (yes/no) will be created for patients with claims for arrhythmia during the baseline period.
Chronic Obstructive Pulmonary Disease	A binary variable (yes/no) will be created for patients with claims for chronic obstructive pulmonary disease during the baseline period.
Congestive Heart Failure	A binary variable (yes/no) will be created for patients with claims for congestive heart failure during the baseline period.
Diabetes	A binary variable (yes/no) will be created for patients with claims for diabetes (types 1 and 2) during the baseline period.
Hyperlipidemia	A binary variable (yes/no) will be created for patients with claims for hyperlipidemia during the baseline period.
Hypertension	A binary variable (yes/no) will be created for patients with claims for hypertension during the baseline period.
Inflammatory Bowel Disease	A binary variable (yes/no) will be created for patients with claims for inflammatory bowel disease (ulcerative colitis, Crohn's disease) during the baseline period.
Lower-extremity Arterial Occlusive Disease	A binary variable (yes/no) will be created for patients with claims for low-extremity arterial occlusive disease during the baseline period.
Myocardial Infarction	A binary variable (yes/no) will be created for patients with claims for myocardial infraction during the baseline period.
Stroke	A binary variable (yes/no) will be created for patients with claims for stroke during the baseline period.

Table 3. Outcomes During the Follow-up Period

Variable	Operational Definition
Follow-up period	The follow-up period will be defined as the time from the index date to the end of continuous enrollment, the end of the data availability, or death, whichever comes first.
DOT	Duration of therapy will be defined as the time from the index date to the date of NHT discontinuation for any reason. Discontinuation of the current NHT will be defined as a treatment gap of at least 90 days (the last day with days supply before the gap as discontinuation date), the initiation of a new therapy, or death, whichever comes first. Initiation of a new therapy will be defined by switching to a different NHT, switching to or augmentation with NSAA, chemotherapy, immunotherapy, radium 223, lutetium Lu 177 vipivotide tetraxetan, ketoconazole, niraparib, olaparib, rucaparib, or talazoparib. Patients who do not experience discontinuation will be censored at the end of data availability.
TTNT	Time to next therapy will be defined as the time from the index date to the initiation date of a new therapy (see the definition of a new therapy above). Patients who do not initiate a new therapy will be censored at the end of data availability or death, whichever comes first.
Next therapy regimen	The next therapy regimen will include all therapies noted below initiated within 28 days of the start of the new therapy (different NHT, switching to or augmentation with NSAA, chemotherapy, immunotherapy, radium 223, lutetium Lu 177 vipivotide tetraxetan, ketoconazole, niraparib, olaparib, rucaparib, or talazoparib).
PSA assessment and PSA response description	• The following will be described for patients with a baseline and at least one post baseline PSA value: • The distribution of the number of post baseline PSA assessments • PSA nadir (lowest post-baseline value) • Number and proportion of patients with deep PSA response (≥ 90% decrease in a post-index PSA value

Variable	Operational Definition

	from the baseline PSA value) any time during follow-up
	• Number and proportion of patients with undetectable PSA value post baseline (using different thresholds):
	  • <0.2 ng/mL
	  • <0.1 ng/mL
	  • <0.01 ng/mL

Time to deep PSA response	Time to deep PSA response will be calculated among patients who have baseline PSA value and at least one PSA value after the index date. Time to deep PSA response will be defined as the time from the index date to the date of deep PSA response. Deep PSA response will be defined as ≥90% decrease in a post-index PSA value from the baseline PSA value. Patients who do not experience deep PSA response will be censored at the end of last available PSA assessment.
Time to undetectable PSA	Time to undetectable PSA will be calculated among patients who have baseline PSA value and at least one PSA value after the index date. Time to undetectable PSA will be defined as the time from the index date to the first evidence of undetectable PSA. Undetectable PSA may be defined using different thresholds (eg, <0.2 ng/mL). Patients who do not have undetectable PSA post index will be censored at the end of last available PSA assessment.
Time to progression	Time to progression will be defined as the time from the index date to the first evidence of disease progression. Progression will be defined as PSA progression, initiation of a new therapy, or death, whichever comes first. PSA progression will be defined as an increase of ≥25% and an absolute increase of ≥2ng/mL in PSA from the nadir value post-index. Patients who do not experience disease progression will be censored at the end of data availability.

9.4. Data Sources

Data from the National VA Health Care Network will be used for this study. This network is the U.S.'s largest integrated health care system with over 1,700 sites of care, serving approximately 8.76 million veterans each year. The VA Health System Corporate Data Warehouse (CDW) includes all medical encounter information in the VA, comprised of medical centers, community-based outpatient clinics, community-living centers, veteran centers, and domiciliaries. The VA CDW stores data in separate databases, one for each type of clinical information - inpatient medication, inpatient laboratory, inpatient admission, outpatient medication, outpatient laboratory, outpatient visits, etc. The databases provide demographic information and contain comprehensive services, including primary care, specialty care, inpatient care, rehabilitation, long-term care, home care, and other services, to military veterans. The database also includes date of death. The date of death is extracted from the VA electronic health record systems and verified by official sources, including VA facilities, death certificates, and National Cemetery Administration. Information on CDW, including date of death, is updated on a daily base. Cause of death is not available on CDW.

9.5. Study Size

As no priori hypotheses are specified, sample size calculations are not applicable. The number of patients eligible for the study will be determined in accordance with the sample selection conducted per the criteria described in Section 9.2.

9.6. Data Management

A clean, patient-level dataset will be generated for use throughout the study. This process will entail basic exploratory checks to ensure data integrity; cleaning and reformatting the raw data as needed; and creating variables for all key study measures, including patient characteristics, treatment start and end dates, and classification of treatments and medication. All data will be stored and maintained on National VA Health Care Network and accessed over Southeast Louisiana Veterans Health Care System (SLVHCS) at Tulane University. The data will be made accessible only to individuals working on the current study. No attempt will be made to identify individual patients, hospitals, or physicians. Analyses will be conducted using SAS 9.4 (SAS Institute, Cary NC).

9.7. Data Analysis

9.7.1. Data Analysis for Primary Objective: Describe TTNT among patients with mCSPC who initiated NHT in 1L

DOT, as defined in Table 3, will be summarized among the overall sample of patients with mCSPC who initiated NHT in 1L. Kaplan-Meier (KM) analysis will be used to describe DOT, and patients who do not experience treatment discontinuation will be censored at the end of data availability. The number of patients at risk and the number and proportion of individuals experiencing discontinuation during the follow-up period (eg, annually or every 6 months) will be reported. The median DOT and corresponding 95% CI will be reported.

9.7.2. Data Analysis for Secondary Objective: Describe TTNT among patients with mCSPC who initiated NHT in 1L

TTNT, as defined in Table 3, will be summarized among the overall sample of patients with mCSPC who initiated NHT in 1L. KM analysis will be used to describe TTNT, and patients who do not initiate a new therapy will be censored at the end of data availability. The number of patients at risk and the number and proportion of individuals initiating a new therapy during the follow-up period (eg, annually or every 6 months) will be reported. The median TTNT and corresponding 95% CI will be reported.

9.7.3. Data Analysis for Exploratory Objectives

9.7.3.1. Data Analysis for Exploratory Objective 1: Describe patient baseline characteristics overall CCI

Descriptive analysis will be conducted for baseline demographic and clinical characteristics, as defined in Table 2, in the overall sample of patients with mCSPC who initiated NHT in 1L CCI Means, standard deviations, medians, and interquartile range will be estimated for continuous variables. Counts and percentages will be estimated for categorical variables. CCI

CCI

CCI [redacted]

9.7.3.3. Data Analysis for Exploratory Objective 4: Describe time to deep prostate-specific antigen (PSA) response and time to undetectable PSA overall CCI [redacted]

Descriptive analysis will be conducted to describe the distribution of post-baseline PSA assessments, PSA nadir, deep PSA response, and undetectable PSA, as defined in Table 3, in the overall sample of patients with mCSPC who initiated NHT in 1L CCI [redacted]. Means, standard deviations, medians, and interquartile range will be estimated for continuous variables. Counts and percentages will be estimated for categorical variables. CCI [redacted]

Time to deep PSA response and time to undetectable PSA, as defined in Table 3, will be summarized in the overall sample of patients with mCSPC who initiated 1L NHT CCI [redacted]

9.7.3.4. Data Analysis for Exploratory Objective 5: Describe time to progression overall CCI [redacted]

Time to progression, as defined in Table 3, will be summarized in the overall sample of patients with mCSPC who initiated 1L NHT CCI [redacted]

9.7.3.5. Data Analysis for Exploratory Objective 6: Describe the distribution of next therapy regimens overall CCI [redacted]

The number and proportion of patients who initiated a new therapy following the index NHT will be estimated in the overall sample CCI [redacted] Among those who initiated a new therapy, the number and proportion of patients who received different type of regimen for first subsequent therapy will be described. A noted in Table 3, the next therapy regiment will include all therapies noted below initiated within 28 days of the start of the new therapy (different NHT, switching to or augmentation with NSAA, chemotherapy, immunotherapy, radium 223, lutetium Lu 177 vipivotide tetraxetan, ketoconazole, niraparib, olaparib, rucaparib, or talazoparib).

9.8. Quality Control

Best practice guidelines will be followed to ensure project quality, including structured organization of project materials (eg, data extracts, statistical software programs, output tables) and standard internal audit process. The audit process both confirms the validity of the analytical approach and ensures that all programs and results are accurate.

9.9. Limitations of the Research Methods

The analyses conducted as part of this study are subject to the following limitations, which will be addressed in any write-up of the study:

- As this study will be conducted among veterans, its findings may not be generalizable to other populations.
- Also, as we are pulling VA only data, we are not able to capture care that occurs outside the VA which could lead to missing data and misclassification of disease states and treatment groups.
- There are no specific diagnosis codes for CSPC. Assumptions will be made to select patients with CSPC based on clinical input.
- Certain assumptions will be made in order to depict treatment patterns for determining TTNT. However, the definition of treatment patterns will nevertheless be subject to assumptions that may not match up to the prescribing physicians' intent.
- Data are subject to inaccuracies in coding of diagnoses. The presence of a diagnosis code in the data does not necessarily mean the presence of disease. The disease may be incorrectly coded or the code was included as a rule-out criterion.
- The presence of a prescription does not necessarily mean the medication was used as prescribed. In addition, prescriptions filled over the counter or provided as samples by the physician are not included in the data.
- Regression models cannot account for unmeasured factors.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves deidentified/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.

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

This protocol, and any subsequent modifications, will be reviewed and approved by the SLVHCS IRB prior to implementation.

10.4. 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 Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2015; 25:2-10. https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3891.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Based on the analysis results and discussions with Pfizer, a study report summarizing the background, objectives, methods, results, and conclusion of the study will be prepared. The study report may be disseminated within Pfizer but is not expected to be externally communicated.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant 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.

13. REFERENCES

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2. US Food and Drug Administration. FDA approves enzalutamide for metastatic castration-sensitive prostate cancer 2019 [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-enzalutamide-metastatic-castration-sensitive-prostate-cancer].

3. US Food and Drug Administration. FDA approves apalutamide for metastatic castration-sensitive prostate cancer 2019 [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-apalutamide-metastatic-castration-sensitive-prostate-cancer].

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Appendix Table 1. Codes for Treatments

Hormonal therapy	GPI	HCPCS/CPT	ICD
Androgen deprivation therapy			
Bilateral orchiectomy *Identified by having at least one procedure code for bilateral orchiectomy, having unilateral procedure codes for both testicles (left and right), or having two unilateral orchiectomy procedures (location unspecified) on different dates*		CPT 54520, 54522, 54530, 54535, 54690	ICD-9-CM V45.77 ICD-10-CM Z90.79 ICD-9-PCS 623, 6241, 6242 ICD-10-PCS 0V590ZZ, 0V593ZZ, 0V594ZZ, 0V5B0ZZ, 0V5B3ZZ, 0V5B4ZZ, 0V5C0ZZ, 0V5C3ZZ, 0V5C4ZZ, 0VT90ZZ, 0VT94ZZ, 0VTB0ZZ, 0VTB4ZZ, 0VTC0ZZ, 0VTC4ZZ
LHRH agonists/antagonists			
Degarelix	2140552510	J9155	
Relugolix	21405570000320 24993503800320		
Goserelin	21405005	J9202	
Histrelin	2140500710	J1675, J9225, J9226, S0133	
Leuprolide	21405010	J1950, J9217, J9218, J9219, Q0057	
Triptorelin	21405050	J3315	
Novel hormonal therapy			
Apalutamide	2140241000		
Abiraterone	2140601020		
Darolutamide	2140242500		
Enzalutamide	2140243000		
Non-steroidal anti-androgens			
Bicalutamide	2140242000		
Flutamide	2140244000		
Nilutamide	2140246000		

Hormonal therapy	GPI	HCPCS/CPT	ICD
Definitive therapy	**GPI**	**HCPCS**	**ICD**
Radical prostatectomy		55831, 55840, 55842, 55845, 55866	ICD-9-PCS 6021, 6029, 603, 604, 605, 6061, 6062, 6069 ICD-10-PCS 0VT00ZZ, 0VT04ZZ, 0VT07ZZ, 0VT08ZZ, 0VB00ZZ, 0VB03ZZ, 0VB04ZZ, 0VB07ZZ, 0VB08ZZ, 0V500ZZ, 0V503ZZ, 0V504ZZ, 0V507ZZ, 0V508ZZ
External beam radiation treatment		CPT 77401-77416 HCPCS G6003-G6014	
Brachytherapy		CPT 7761-77763, 77767-77768, 77770-77772, 77778, 77789, 77750, 77790 HCPCS 0394T-0395T	
Chemotherapy	**GPI**	**HCPCS**	**ICD**
Taxane Chemotherapy			
Cabazitaxel	2150000300	C9276, J9043	
Docetaxel	2150000500	J9170, J9171	
Other Chemotherapy			
Carboplatin	2110001500	J9045	
Cisplatin	2110002000	J9060, J9062	
Oxaliplatin	2110002800	J9263	
Mitoxantrone	2120005500	J9293	
Immunotherapy	**GPI**	**HCPCS**	**ICD**
Pembrolizumab	21357953002	J9271, C9027	
Sipuleucel-T	2165107000	Q2043, C9273	
Radium	**GPI**	**HCPCS**	**ICD**
Radium-223	2160005500	A9606	
Others	**GPI**	**HCPCS**	**ICD**
Lutetium Lu 177 vipivotide tetraxetan	21600045802020	A9607	
Olaparib	21535560		
Rucaparib	21535570		
Niraparib	21535550200,		

Hormonal therapy	**GPI**	**HCPCS/CPT**	**ICD**
Talazoparib	21409902120 215355804001		
Ketoconazole	1140404000, 9630106400, 9015404500		
Radiation therapy	**GPI**	**HCPCS**	**ICD**
Brachytherapy		CPT 7761-77763, 77767-77768, 77770-77772, 77778, 77789, 77750, 77790 HCPCS 0394T-0395T	
External beam radiation treatment		CPT 77401-77416 HCPCS G6003-G6014	
Intensity modulated radiation therapy		G6015-G6016 CPT: 77385-77386	
Proton beam therapy		CPT: 77520-77525	
Stereotactic body radiation therapy		CPT: 77373	
Bone protective agents	**GPI**	**HCPCS**	**ICD**
Denosumab	3004453000	J0897, C9272	
Ibandronate	3004204810	J1740, C9229	
Zoledronic acid	3004209000	J3489, Q2051, J3487, J3488, Q4095	ICD-9-PCS V58.68 ICD-10-PCS Z79.83
Pamidronate disodium	3004206010	J2430	
Corticosteroids	**GPI**	**HCPCS**	**ICD**
Corticosteroids	22, 8910, 8915	C9256, J0702, J0704, J1020, J1030, J1040, J1094, J1100, J1700, J1710, J1720, J2650, J2920, J2930, J3300, J3301, J3302, J3303, J7312, J7506, J7509, J7510, J7512, J8540	
Pain medications (analgesics)			
Non-narcotics	64		

Hormonal therapy	GPI	HCPCS/CPT	ICD
Opioids	65		
Anti-inflammatory medications	66		

Appendix Table 2. Diagnosis Codes for Comorbidities

Conditions and comorbidities	ICD-9-CM	ICD-10-CM
Charlson comorbidity index (CCI)[1]		
HIV/AIDS	042–044	B20–B22, B24
Cerebrovascular disease	362.34, 430–438	G45, G46, H34.0, I60–I69
Chronic pulmonary disease	416.8, 416.9, 490–505, 506.4, 508.1, 508.8	I27.8, I27.9, J40–J47, J60–J67, J68.4, J70.1, J70.3
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43, I50, P29.0
Dementia	290, 294.1, 331.2	F00–F03, F05.1, G30, G31.1
Diabetes with chronic complication	250.4–250.7	E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7
Diabetes without chronic complication	250.0–250.3, 250.8, 250.9	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Hemiplegia or paraplegia	334.1, 342, 343, 344.0–344.6, 344.9	G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0–G83.4, G83.9
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570, 571, 573.3, 573.4, 573.8, 573.9, V42.7	B18, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73, K74, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4
Moderate or severe liver disease	456.0–456.2, 572.2–572.8	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Myocardial infarction	410, 412	I21, I22, I25.2
Peptic ulcer disease	531–534	K25–K28
Peripheral vascular disease	093.0, 437.3, 440, 441, 443.1–443.9, 447.1, 557.1, 557.9, V43.4	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582, 583.0–583.7, 585, 586, 588.0, V42.0, V45.1, V56	I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18, N19, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
Rheumatic disease	446.5, 710.0–710.4, 714.0–714.2, 714.8, 725	M05, M06, M31.5, M32–M34, M35.1, M35.3, M36.0
Individual conditions		
Hypertension	362.11, 401.xx-405.xx, 437.2	H35.039, I10–I13, I15–I16, I67.4
Stroke	430-434, 436, 362.31-362.34	I60, I61, I62, I64, I65, I67, H34.1, H34.23, H34.21, H34.0
Acute Coronary Syndrome	411.x, 410.xx	I24, I21
Angina Pectoris	413	I20
Arrhythmia	427.1, 427.4, 427.41, 427.42, 427.5, 427.69, 427.2, 427.60,	I47.0, I47.2, I49.0, I46, I49.3, I49.49, I47.9, I49.40, I49.5, I49.8, I49.9

Conditions and comorbidities	ICD-9-CM	ICD-10-CM
	427.8, 427.89, 427.9	
Myocardial Infarction	410, 412	I21, I22, I25.2
Congestive Heart Failure	428.xx	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0
Hyperlipidemia	272.0-272.4	E78.00, E78.01, E78.1, E78.2, E78.3, E78.41, E78.49, E78.5
Low-extremity Arterial Occlusive Disease	444.22	I74.3, I74.4
Type II Diabetes	250.0-250.3, 250.7	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Chronic Obstructive Pulmonary Disease	490-492, 494, 496	J40, J41, J42, J43, J47, J44.9
Inflammatory bowel disease		
Crohn's disease	555	K50
Ulcerative Colitis	556	K51
Other cancers	140-172, 174-184, 186-195, 199-209	C00-C43, C45-C60, C62, C63, C67-C76, C80-C96, C7A, C7B

Abbreviations: HIV: human immunodeficiency virus; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification

[1] Source: Quan, Hude, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical care (2005): 1130-1139.

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