NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	A Real-World Comparison of Clinical Outcomes in Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer (mCRPC) Patients Who Initiated Enzalutamide vs. Abiraterone Acetate (Abiraterone) in Flatiron Electronic Health Record (EHR) database
Protocol number	C3431047
Protocol version identifier	Version 1.0
Date	12 June 2023
Active substance	Enzalutamide
Medicinal product	Xtandi
Research question and objectives	Compare clinical outcomes of enzalutamide vs. abiraterone acetate in chemotherapy-naive mCRPC patients in the Flatiron EHR Primary objective: To compare overall survival (OS) in patients with chemotherapy-naive mCRPC who initiated enzalutamide vs. abiraterone Secondary objective 1: To compare OS in patients with chemotherapy-naive mCRPC who received only enzalutamide without any subsequent therapy vs. abiraterone without any subsequent therapy Secondary objective 2: To compare treatment duration and time to subsequent therapy in chemotherapy-naive mCRPC patients initiating enzalutamide vs. abiraterone CCI [redacted]

	CCI [redacted]
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADT	androgen deprivation therapy
AE	adverse event
ALP	alkaline phosphatase
ASCO	American Society of Clinical Oncology Annual Meeting
BMI	body mass index
CCI	Charlson Comorbidity Index
CI	confidence interval
CPT	current procedural terminology
CRPC	castration-resistant prostate cancer
CSPC	castration-sensitive prostate cancer
ECOG	Eastern Cooperative Oncology Group
EHR	electronic health record
ER	emergency room
FDA	Food and Drug Administration
GPI	Generic Product Identifier
HCPCS	Healthcare Common Procedure Coding System
HR	hazard ratio
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
LDH	lactate dehydrogenase
IPTW	inverse probability of treatment weighting
KM	Kaplan-Meier
LHRH	luteinizing hormone-releasing hormone
LOT	line of therapy
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
NCI	National Cancer Institute
NHT	novel hormone therapy
OS	overall survival
PC	prostate cancer
PCS	procedures
PSA	prostate-specific antigen
RWE	real-world evidence

Abbreviation	Definition
SSDI	Social Security Death Index
US	United States

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Standalone document ANNEX 1.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	01 August 2023
End of data collection	31 December 2023
Final study report	30 November 2024

7. RATIONALE AND BACKGROUND

mCRPC and treatment with enzalutamide and abiraterone

Prostate cancer is the most common cancer (excluding nonmelanoma skin cancer) and the second leading cause of cancer death among men in the United States (US). The American Cancer Society estimates that in 2022 there will be 268,490 new cases and 34,500 deaths from prostate cancer.[1] The majority of men with newly diagnosed prostate cancer present with localized disease and undergo active surveillance, radical prostatectomy and/or radiation therapy. While the long-term outlook is favorable for early-stage prostate cancer, survival rates drastically decrease once the disease has spread beyond the prostate gland or when the disease becomes castration resistant.[2,3] For those either with more advanced disease or whose tumor recurs after treatment, the standard first-line systemic therapy is androgen deprivation therapy (ADT).[4] Prostate cancer previously untreated by or responding to ADT is called castration-sensitive prostate cancer (CSPC). Over time, men with advanced disease may stop responding to ADT and develop castration-resistant prostate cancer (CRPC). CRPC is prostate cancer that progresses clinically, radiographically or biochemically despite maintaining castrate levels of serum testosterone.[5] Median time to mCRPC among patients with metastatic castration-sensitive prostate cancer (mCSPC) treated with ADT alone has been estimated to be 11.7 months, with approximately 80% of patients progressing to mCRPC within 3 years.[6] Estimates of median OS from time of mCRPC diagnosis vary based on treatment received and treatment setting and range from 13 to 35 months across studies.[7-10]

Over the past decade, several therapies for mCRPC that show an increase in OS have gained regulatory approval in the US, including novel hormone therapies (NHTs) abiraterone acetate (hereafter referred to as abiraterone[11,12]) and enzalutamide,[7,13] chemotherapies (eg, docetaxel,[10] cabazitaxel[14]), immunotherapies (eg, sipuleucel-T[15]), and radiotherapies (eg, radium-223[16]). Olaparib and rucaparib are poly(ADP-ribose) polymerase (PARP) inhibitors approved for adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC who have disease progression on NHTs.[17,18] NHTs, particularly enzalutamide and abiraterone, have shown strong efficacy in the mCRPC setting. Enzalutamide was initially approved by the Food and drug administration (FDA) in 2012 for chemotherapy-experienced mCRPC,[19] while

abiraterone was approved in 2011 for the same indication.[20] Enzalutamide and abiraterone were subsequently approved for chemotherapy-naive mCRPC (10 September 2014 for enzalutamide; 10 December 2012 for abiraterone) and are the only approved NHTs in this indication. Both drugs were also subsequently approved for use in mCSPC (16 December 2019 for enzalutamide; 07 February 2018 for abiraterone); however, evidence supporting the efficacy of abiraterone in mCSPC was disseminated at the American Society of Clinical Oncology Annual Meeting (ASCO) between 02-06 June 2017. Both treatments target the androgen axis with different mechanisms of action: enzalutamide inhibits the androgen receptor, subsequently reducing nuclear translocation of the androgen receptor complex and DNA binding, whereas abiraterone blocks cytochrome P450-17 to inhibit androgen synthesis.

Both enzalutamide and abiraterone provide improved OS in patients with mCRPC in both chemotherapy-naive[7,9] and chemotherapy-experienced settings. In the setting of chemotherapy-naive mCRPC, the PREVAIL (N = 1717) study demonstrated that patients receiving enzalutamide with ongoing ADT had a statistically significant improvement in OS (median OS of 35.3 months vs. 31.3 months; HR 0.77; 95% CI 0.67-0.88; p = 0.0002; 01 June 2014 data cutoff) compared to patients receiving placebo.[7] Similarly, the COU-AA-302 (N = 1088) trial of patients with mCRPC who were chemotherapy-naive also showed statistically significant improvement in OS for patients receiving abiraterone and prednisone with ongoing ADT compared to patients only receiving prednisone with ongoing ADT (34.7 months vs. 30.3 months, HR 0.81; 95% CI 0.70-0.93; p = 0.003; 31 March 2014 data cutoff).[9] On the strength of this evidence, the National Comprehensive Cancer Network guidelines recommend both enzalutamide and abiraterone as Category 1, preferred treatment options for men in both pre-docetaxel and post-docetaxel mCRPC populations.[5]

Enzalutamide and abiraterone are the most commonly used NHTs in patients with chemotherapy-naive mCRPC in real-world clinical practice. A study of patients with mCRPC in the US using the Flatiron EHR data (2013Q1 - 2017Q4) reported that over half of patients on mCRPC treatment received either abiraterone or enzalutamide in the first and second-line settings (abiraterone first-line: 37%, second-line: 20%; enzalutamide first-line: 28%, second-line: 34%).[21]

Comparative effectiveness of enzalutamide and abiraterone

There have only been three, small, head-to-head randomized controlled trials comparing enzalutamide and abiraterone.[22,23,24] A randomized, Phase 3 study from Japan with 203 patients with castration-resistant prostate cancer did not find a statistically significant difference in OS between patients initiating enzalutamide vs. abiraterone (HR 1.17, 95% CI 0.72, 1.88, p=0.53). A randomized, open-label, Phase 2, cross-over trial of 202 patients did not find a statistically significant difference in OS between patients initiating enzalutamide vs. abiraterone (HR 1.27, 95% CI 0.86, 1.85, p = 0.23).[24] The other trial was a single-center, open-label, Phase 4 trial of 170 patients that focused on quality of life, fatigue and metabolic side effects but did not compare OS between.[23]

Comparative effectiveness of enzalutamide and abiraterone in patients with mCRPC in clinical practice has also been evaluated in multiple real-world studies. Six studies had overall sample sizes over 1000 patients and these studies demonstrated favorable OS for enzalutamide compared to abiraterone.[25-30] A population-based study of chemotherapy-naive patients with mCRPC (n = 10308) in the French National Health Data System observed enzalutamide was associated with longer OS compared with abiraterone (HR 0.90; 95% CI 0.85-0.96).[25] A retrospective cohort study based on the Flatiron EHR database of mCRPC patients who received first-line systemic therapy (n = 3808) observed abiraterone was associated with shorter OS compared with enzalutamide among non-Hispanic White men (HR 1.21; 95%CI 1.06-1.38).[28] Two retrospective studies in the VHA database also showed enzalutamide was associated with longer OS than abiraterone.[26,27] In a study of chemotherapy-naive patients with mCRPC (n = 3174), Tagawa et al. found that enzalutamide-treated patients had longer median OS compared to abiraterone-treated patients (median OS of 29.6 vs. 25.9 months; HR 0.84; 95% CI 0.76-0.94; p = 0.0012), after adjustment for baseline differences in age, individual comorbidities and prior use of radiation therapy and corticosteroid therapy between the groups, and irrespective of follow-on therapy for mCRPC.[27] Similar treatment differences were observed in sensitivity analyses additionally adjusting for prostate-specific antigen level, hemoglobin, and alkaline phosphatase (ALP). Analyses in the subgroup of patients who received only first-line treatment without subsequent therapy showed greater OS benefit for enzalutamide vs. abiraterone compared to the OS difference observed in all patients. An independent study by Schoen et al [2022][26] of patients with mCRPC (n = 5822) using a more recent cut of the VHA data also found a similar survival benefit associated with enzalutamide vs. abiraterone (HR 0.89, 95% CI 0.84-0.95) in analyses of all patients, and in the subgroup of patients who received only first-line treatment without subsequent therapy. Two studies using Taiwan National Health Insurance data also showed superior OS with enzalutamide vs abiraterone.[29,30] In a study of 1153 mCRPC patients, Lin et al. found that the enzalutamide treated patients had a lower risk of overall mortality compared with abiraterone [adjusted hazard ratio (aHR) = 0.71, 95% CI: 0.57–0.88, p = 0.002].[29] In a study of 1046 abiraterone and 118 enzalutamide patients with mCRPC, Li et al found that enzalutamide significantly reduced the risk of death for mCRPC when compared with abiraterone aHR = 0.828; 95% CI 0.731-0.938].[30]

Rationale for the current study

As adequately powered, head-to-head, randomized controlled trials comparing OS between these 2 therapies are unlikely to be conducted, real world evidence (RWE) can provide important information to guide treatment decisions, particularly as several years of data on the use of enzalutamide and abiraterone in real-world settings have now accrued. These real-world data may allow for assessment of comparative effectiveness of enzalutamide vs. abiraterone in a larger and more broadly representative population of patients with mCRPC than would be possible in randomized clinical trials, where racial and ethnic minorities and patients with certain comorbidities are often underrepresented. Such comparative evidence is particularly important to patients, prescribers, and healthcare plans, given the advanced stage

of the disease and the imperative to optimize initial treatment choice. Among the large prior RWE studies in this therapeutic area, three of them focused on non-US populations. Two US studies focused on the veterans' population, which may not be generalizable to US population of prostate cancer patients. The Marar et al. US study using Flatiron EHR focused more on the differences of first-line treatment between race/ethnicity groups, included both chemotherapy naïve and patients previously treated with docetaxel, and had a relatively short median follow up of approximately 13 months.[28]

This retrospective RWE study using Flatiron EHR will aim to compare the effectiveness of enzalutamide vs. abiraterone among patients with chemotherapy-naive mCRPC. This study will include more recent data than the study previously published by Marar et al.[28] and will use methodology consistent with that in the published study by Tagawa et al.[27] using VHA data as well as the methodology in an ongoing study in the Medicare population.

8. RESEARCH QUESTION AND OBJECTIVES

Primary objective:

To compare OS in patients with chemotherapy-naive mCRPC who initiated enzalutamide vs. abiraterone.

This objective will be addressed with an intention-to-treat style of analysis comparing OS over the entirety of the study's follow-up period among all eligible patients initiating enzalutamide and abiraterone. This analysis will include all chemotherapy-naive patients initiating first-line enzalutamide vs. abiraterone for mCRPC, irrespective of any subsequent treatment.

Secondary objective 1:

To compare OS in patients with chemotherapy-naive mCRPC who received only enzalutamide without any subsequent therapy vs. abiraterone without any subsequent therapy. Patients receiving only enzalutamide will be defined as patients who initiate enzalutamide without switching to or adding another mCRPC treatment. Patients receiving only abiraterone will be defined as patients who initiate abiraterone without switching to or adding another mCRPC treatment.

The secondary objective will seek to assess the treatment effect attributable to the first NHT received. Given mCRPC is considered an end-stage disease with limited expected survival, the choice of which NHT to initiate first is particularly important. Identifying the treatment effect attributable to the first NHT received is of particular interest because RWE shows that a majority of patients with chemotherapy-naive mCRPC in the US do not receive subsequent therapy. About 51% of patients with mCRPC in a recent EHR-based analysis received only one line of life-prolonging therapies such as NHTs during a mean follow-up time of 14.6 months.[21] Possible reasons for this may include patients being too ill to receive subsequent therapy, patients' refusal of further therapy, death before receiving a second-line therapy, or incomplete recording of post-first line therapies, due to end of study follow-up or

receipt of second-line therapy in another health plan not covered by the database.[21] The VHA studies by Tagawa et al. and Schoen et al. also observed that approximately half of all patients received only enzalutamide or abiraterone without subsequent therapy. Both studies observed there was a larger difference in OS between enzalutamide and abiraterone in this subgroup of patients than among all patients.[26,27]

Secondary objective 2:

To compare treatment duration and time to subsequent therapy in chemotherapy-naive mCRPC patients initiating enzalutamide vs. abiraterone.

This objective will be addressed with an intention-to-treat style of analysis comparing time to discontinuation and time to subsequent therapy over the entirety of the study's follow-up period among all eligible patients initiating enzalutamide and abiraterone. Treatment duration is intended to provide supportive evidence of comparative time on the index therapy. A shorter treatment duration may be indicative of shorter progression free survival or of tolerability issues, and maybe correlated with OS.

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9. RESEARCH METHODS

9.1. Study Design

A retrospective observational cohort design using Flatiron EHR database will be conducted to address the primary and secondary objectives of the study. The study design is summarized in Figure 1 below and described in more detail in the subsequent sections.

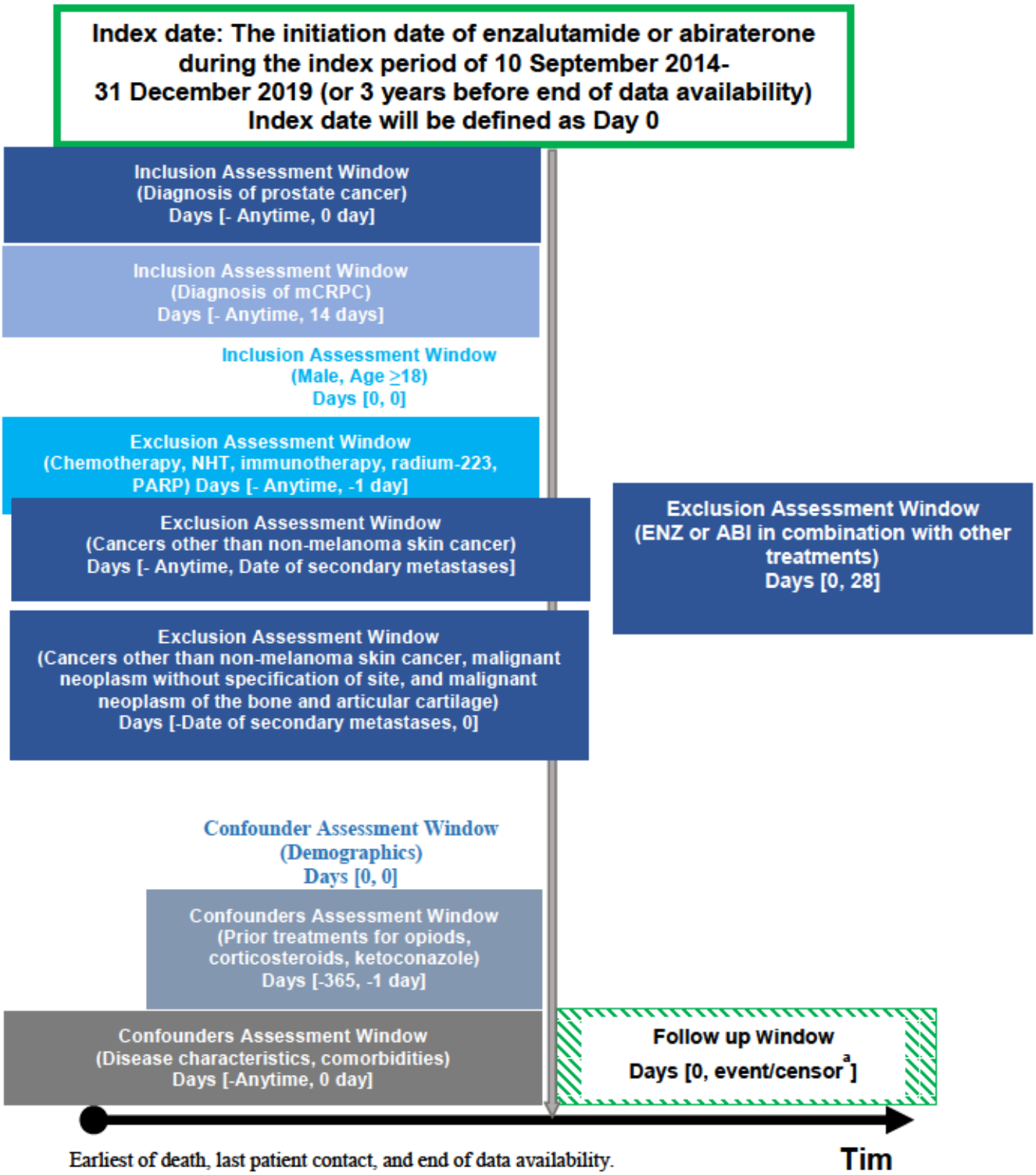
Patients will be classified into either the enzalutamide or abiraterone groups, based on initiation of one of these two drugs during the index period of this study. Patients' index date will be defined as the date of initiation of enzalutamide or abiraterone and their index date is required to occur during the index period.

The proposed index period for this study ranges from 10 September 2014 to 31 December 2019 (or 3 years before the end of data availability in the EHR at the time of analysis start). The start date of the index period, 10 September 2014, is based on the date of FDA approval of enzalutamide in patients with chemotherapy-naive mCRPC. At this time abiraterone had already been approved for use in patients with chemotherapy-naive mCRPC. The end date of 31 December 2019 as the end of the index period allows for the potential of

at least 3 years of follow up until the end of data availability. While clinical trial data about abiraterone use in mCSPC was first presented in June 2017 and patients may have started to use abiraterone in mCSPC after that date, the Flatiron EHR database captures diagnosis of metastasis and CRPC abstracted from unstructured data. These data can be used to ensure that only patients initiating enzalutamide and abiraterone for mCRPC are included in the analyses and that the study does not include patients treated for mCSPC who would have longer survival.

Baseline characteristics including demographics, disease characteristics, comorbidities, and prior treatments will be assessed based on data prior to or on the index date or during the 12-month period prior to the index date. A preliminary list of baseline characteristics to be assessed is included in Section 9.3. Patients will be followed from their index date to the earliest of patient death or end of data availability. Potential duration of follow-up for patients in these data will be more than 3 years for almost all patients given the end of the index period of 31 December 2019 and coverage of the data cut until December 2022. OS over the follow-up period will be compared between enzalutamide and abiraterone groups, adjusting for differences in baseline characteristics between the two groups. This study will be a non-interventional retrospective cohort study that does not impose a treatment protocol, any diagnostic/interventional procedures (PCS), or a visit schedule.

Figure 1. Study Design



[a] Earliest of death, last patient contact, and end of data availability.

9.2. Setting

Patients in the Flatiron EHR database with mCRPC who initiated treatment with enzalutamide or abiraterone and who have not previously received chemotherapy will be selected for this study. The inclusion and exclusion criteria below will be applied to identify patients.

9.2.1. Inclusion Criteria

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

1. Male with a metastatic prostate cancer diagnosis and CRPC diagnosis. The later of (1) date of metastatic diagnosis or (2) the date of diagnosis with castration-resistant prostate cancer will be defined as the mCRPC diagnosis date.

2. Have initiated enzalutamide or abiraterone (1) within 14 days prior to or on or after the mCRPC diagnosis date, and (2) during the index period of 10 September 2014 - 31 December 2019 (or at least 3 years prior to the end of data availability at the time of analysis start). Initiation will be defined as the first ever use of enzalutamide or abiraterone. The initiation date of enzalutamide or abiraterone will be defined as the index date.

    - Enzalutamide and abiraterone were approved for chemotherapy-naive mCRPC at different times (10 September 2014 for enzalutamide; 10 December 2012 for abiraterone). Therefore, 10 September 2014 is selected as the start date of the index period, as at this date both enzalutamide and abiraterone became potential treatment choices for patients with chemotherapy-naïve mCRPC. The end date 31 December 2019 was selected to allow for at least 3 years of potential follow up before the end of data availability.

3. At least 18 years old at the index date.

4. Initial patient contact in the EHR (which could be recording of vital information, visit, a medication administration, or a laboratory test/result being reported, last abstracted oral therapy date, or last clinically-relevant abstracted date [eg, for specimen collection, procedure]) at least 180 days before the index date to ensure that patients were treated at the practice, have treatment information before the index date, and that the index date is the initiation of first-line abiraterone or enzalutamide for mCRPC.

5. Evidence of contact with patient in the EHR within 180 days after the index date to ensure that the patient was actively engaged in care at the data providing institution.

9.2.2. Exclusion Criteria

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

1. Received chemotherapy, NHT (ie, abiraterone, apalutamide, darolutamide, or enzalutamide), radium 223 and/or immunotherapy, olaparib/ rucaparib at any time prior to the index date.
    - CCI [redacted]
2. Received another NHT/chemotherapy/immunotherapy/radium 223/ketoconazole/olaparib/ rucaparib within 28 days on/after the index date.
3. Had a prior history of other cancers except for non-melanoma skin cancer prior to the date of metastasis diagnosis.
4. Had a prior history of other cancers except for non-melanoma skin cancer, malignant neoplasm without specification of site, and malignant neoplasm of the bone and articular cartilage between the date of metastasis diagnosis and the index date.

Relevant diagnosis, procedure and drug codes needed to operationalize the criteria above are included in Appendix 1.

9.2.3. Treatment regimens

Not applicable.

9.2.4. Cohort creation

Cohorts (or treatment cohorts) for primary objective, secondary objective 2 CCI [redacted]

- **Enzalutamide cohort:** mCRPC patients who initiated enzalutamide on the index date
- **Abiraterone cohort:** mCRPC patients who initiated abiraterone on the index date

Cohorts for secondary objective 1 CCI [redacted]:

- **Enzalutamide only cohort:** mCRPC patients who initiated enzalutamide on the index date and did not receive subsequent systemic anti-neoplastic therapy
- **Abiraterone only cohort:** mCRPC patients who initiated abiraterone on the index date and did not receive subsequent systemic anti-neoplastic therapy

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9.3. Variables

9.3.1. Baseline Characteristics Variables

Baseline variables (Table 1) will be measured for the 365 days prior to the index date unless otherwise specified.

Table 1. Baseline Demographic and Clinical Characteristic Vvariables

Variable	Operational definition
Age	Age will be defined as of the index date and retained in the dataset as a continuous variable and a categorical variable: ≤64, 65-69, 70-74, 75-79, 80-84, ≥85 years old.
Race/ethnicity	Proportion of patients that were Asian, Black or African American, Hispanic or Latino, White, Other Race will be evaluated.
Index year	Variable will be created for the index calendar year.
Geographic Regions	Proportion of patients that lived in Northeast, Midwest, South, West areas, and other/unknown created based on patient state of residence and US Census Region definitions.

Table 1. Baseline Demographic and Clinical Characteristic Vvariables

Variable	Operational definition
Insurance	Proportion of patients with Medicaid, Medicare, Commercial Health Plan, Workers Compensation, Other Government Program, Patient Assistance Program, Self Pay, Other Payer - Type Unknown based on the patient's latest recorded payer category
Practice type	Proportion of patients treated in academic and community practice
Social determinants of health (SES quintile)	Proportion of patients in different SES Index quintiles for a patient's block group based on 2015-2019 Census data.
Gleason score at initial diagnosis	Variable will be created for Gleason score at initial diagnosis: Less than or equal to 6, 4 + 3 = 7, 3 + 4 = 7, 7 (when breakdown not available), 8, 9, 10, Unknown / Not documented.
Site of Metastasis	Flags will be created for patients that had a metastatic diagnosis any time prior to or on the index date at the following sites: viscera, bone only, node only, bone and node only, and other.
Time from Metastatic Diagnosis Date to Index Date	Time from the first metastatic diagnosis 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.
Time from PC Diagnosis to mCRPC Diagnosis Date	Time from the first observed PC diagnosis to mCRPC diagnosis date will be evaluated.
Time from mCRPC Diagnosis Date to Index Date	Time from the first mCRPC diagnosis date in the data to the index date will be evaluated.
CRPC diagnosis before first Metastatic Diagnosis	Proportion of patients who had CRPC diagnosis before first metastatic diagnosis.
Time between ADT and index date	Time from the first observed record for medical or surgical castration to index date.
Radical prostatectomy	A binary variable (yes/no) will be created for patients with a claim for radical prostatectomy before index date.
First-generation anti-androgens (bicalutamide, flutamide, nilutamide)	A binary variable (yes/no) will be created for patients with use of first-generation anti-androgens within a year before index date (from Enhanced_MetPC_Orals.
Docetaxel use	A binary variable (yes/no) will be created for patients with docetaxel use prior to mCRPC CCI [redacted].
Chronic corticosteroid use	A binary variable (yes/no) will be created for patients with chronic corticosteroid use within a year prior to index date, defined as having one

Table 1. Baseline Demographic and Clinical Characteristic Vvariables

Variable	Operational definition
	of the following: • At least two corticosteroid medication orders with at least 90 days apart within a year prior to index date • At least two corticosteroid administrations with at least 90 days apart within a year prior to index date
Opioid analgesics	A binary variable (yes/no) will be created for patients with medication order for opioid analgesics within a year prior to index date.
Ketoconazole	A binary variable (yes/no) will be created for patients with use of ketoconazole within a year prior to index date (from Enhanced_MetPC_Orals).
Modified NCI CCI Score	The NCI version of the CCI score will be created based on diagnoses any time prior to or on the index date. As a note EHR data may capture only date of first diagnosis or may have multiple records for the same diagnosis at different times. Binary variables (yes/no) will be created to flag patients who have claims for each of the individual comorbidities within the NCI. Cancer will be excluded from CCI score.
Hypertension	A binary variable (yes/no) will be created for patients with diagnosis for hypertension before or on the index date.
Stroke	A binary variable (yes/no) will be created for patients with diagnosis for stroke before or the index date.
Acute Coronary Syndrome	A binary variable (yes/no) will be created for patients with claims for acute coronary syndrome before or on the index date.
Angina Pectoris	A binary variable (yes/no) will be created for patients with claims for angina pectoris before or on the index date.
Arrhythmia	A binary variable (yes/no) will be created for patients with claims for arrhythmia before or on the index date.
Myocardial Infarction	A binary variable (yes/no) will be created for patients with claims for myocardial infraction before or on the index date.
Congestive Heart Failure	A binary variable (yes/no) will be created for patients with claims for congestive heart failure before or on the index date.
Hyperlipidemia	A binary variable (yes/no) will be created for patients with claims for hyperlipidemia before or on the index date.
Lower-extremity Arterial Occlusive Disease	A binary variable (yes/no) will be created for patients with claims for low-extremity arterial occlusive disease before or on the index date.

Table 1. Baseline Demographic and Clinical Characteristic Vvariables

Variable	Operational definition
Type 2 Diabetes	A binary variable (yes/no) will be created for patients with claims for type 2 diabetes before or on the index date.
Chronic Obstructive Pulmonary Disease	A binary variable (yes/no) will be created for patients with claims for chronic obstructive pulmonary disease before or on the index date.
Inflammatory Bowel Disease	A binary variable (yes/no) will be created for patients with claims for inflammatory bowel disease before or on the index date.
Anemia	A binary variable (yes/no) will be created for patients with claims for anemia before or on the index date.
Seizures	A binary variable (yes/no) will be created for patients with claims for seizures before or on the index date.
Urinary tract infection	A binary variable (yes/no) will be created for patients with claims for urinary tract infection before or on the index date.
Renal disease	A binary variable (yes/no) will be created for patients with claims for renal disease before or on the index date.
Liver disease	A binary variable (yes/no) will be created for patients with claims for liver disease before or on the index date.
Rheumatologic disease	A binary variable (yes/no) will be created for patients with claims for rheumatologic disease before or on the index date.
Hemiplegia	A binary variable (yes/no) will be created for patients with claims for hemiplegia before or on the index date.
Paralysis	A binary variable (yes/no) will be created for patients with claims for paralysis before or on the index date.
Peptic ulcer disease	A binary variable (yes/no) will be created for patients with claims for peptic ulcer disease before or on the index date.
AIDs	A binary variable (yes/no) will be created for patients with claims for AIDS before or on the index date.
Impotence	A binary variable (yes/no) will be created for patients with claims for impotence before or on the index date.
Body mass index (BMI)	Body mass index (weight in kg/(height in meters)^2) will be calculated based on most recent measure of height and weight prior to or on index date. BMI will be calculated as a continuous variable and for the following categories:<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40,

Table 1. Baseline Demographic and Clinical Characteristic Vvariables

Variable	Operational definition
	and ≥40.
ECOG	Variable will be created for ECOG based on the most recent assessment prior to or on index date. ECOG will be reported as a categorical variable: 0, 1, 2, 3, 4, unknown.
Prostate-specific antigen (PSA)	PSA will be calculated based on the most recent assessment prior to or on the index date and retained in the dataset as a continuous variable. Depending on completeness of available PSA at index, a categorial variable for PSA may be created based on PSA distribution with a category for unknown PSA at index.
Albumin	Variable will be created for albumin based on the most recent assessment prior to or on the index data and will be retained as a continuous variables or categorical variable based on cutoffs for normal range in the data.
ALP	Variable will be created for ALP based on the most recent assessment prior to or on the index data and will be retained as a continuous variables or categorical variable based on cutoffs for normal range in the data.
Hemoglobin	Variable will be created for hemoglobin based on the most recent assessment prior to or on the index data and will be retained as a continuous variables or categorical variable based on cutoffs for normal range in the data.
Lactate dehydrogenase (LDH)	Variable will be created for LDH based on the most recent assessment prior to or on the index data and will be retained as a continuous variables or categorical variable based on cutoffs for normal range in the data.

9.3.2. Study Period Variables

Study period variables (Table 2) are summarized below.

Table 2. Study Period Variables

Variable	Operational definition
Follow-up time	The follow-up period will be defined as the time from the index date to the earliest of death, end of data availability (eg, 2022 Q4), or last patient contact defined as the date of most recent contact in the data, which could be recording of vital information, visit, a medication administration, or a laboratory test/result being reported, last abstracted oral therapy date, or last clinically-relevant abstracted date (eg, for specimen collection, procedure).
OS (time to death)	Time to death will be defined as the time from the initiation of enzalutamide or abiraterone (ie, index date) to the date of death. Patients

Table 2. Study Period Variables

Variable	Operational definition
	who do not die will be censored at their last available follow-up, which will be defined as the earlier of end of data availability or last patient contact. Date of death. In most Flatiron deliverables, death data is delivered with a month granularity. Date of death is a consensus variable across the three data sources (EHR, Social Security Death Index (SSDI) and obituary data). Flatiron generates the variable according to the following rules and hierarchy (preference is based on comparative analyses with the National Death Index as the gold standard): Use abstracted dates over structured dates when the abstracted date granularity is at the day level. Use the following rules when there are multiple structured dates of death: If all three dates are in agreement, that date of death is selected If any two dates are in agreement, that date of death is selected If none of the dates are in agreement, then the rank order to which the date of death is selected is: SSDI→Obituary data→EHR
Line of therapy (LOT) start date	• The index date and the start date for the first LOT is the initiation of enzalutamide or abiraterone within 14 days before or on or after the mCRPC diagnosis date. • The start date for the second and later LOTs will be defined as the date of the first claim for a systemic treatment following the end of the preceding LOT.
LOT regimen	A LOT will include all systemic treatments started within 28 days of the LOT start date. This group of treatments started within 28 days of the start date will be referred to as the LOT regimen. As a note, this study will follow Flatiron mPC regimen rules and will exclude the following from the regimens: radiation and surgery, luteinizing hormone-releasing hormone (LHRH) agonists/antagonists, bicalutamide, nilutamide, flutamide, denosumab, zoledronic acid, megestrol, and megestrol acetate.
LOT end date	Generally this study will use the Flatiron LOT definition rules for mPC. A LOT will end when one of the following occurs: • A new systemic treatment is started more than 28 days after the LOT start date Exception for radium-223[21] o Starting radium-223 within 90 days of the LOT start date does not end a LOT o Starting radium-223 more than 90 days after the LOT start date does end a LOT • Addition of select beta emitters (Strontium-89, Samarium-153, Rhenium-188) to a regimen does not advance the LOT. Addition of

Table 2. Study Period Variables

Variable	Operational definition
	lutetium 177 vipivotide tetraxetan to a regimen >28 days after the start of the regimen does advance the LOT. • When a gap in drug episodes of more than 90 days occurs, the line number is advanced. LOT end date will be defined as the earliest of 1) death, 2) last patient contact, 3) day before the start of next LOT, 4) end of data availability
Treatment duration (time to discontinuation)	Treatment duration of the index treatment will be defined as the time from the initiation of enzalutamide or abiraterone (ie, index date) to the discontinuation date. Discontinuation will be defined as the earliest of 1) death, 2) abstracted end date for last enzalutamide or abiraterone drug episode that starts within the index treatment LOT (drug episodes for abstracted oral therapies from the Flatiron Drug Episode table), or 3) day before the start of next LOT. Patients who do not discontinue will be censored at their last available follow-up, which will be defined as the earlier of end of data availability or last patient contact. The treatment duration definition follows Flatiron's guidance on "Strategies for Estimating Real-World Time to Treatment Discontinuation (rwTTD) Using Abstracted Discontinuation Information" available through Flatiron Knowledge Center.
Time to subsequent therapy	Time to subsequent therapy will be defined as the time from the initiation of enzalutamide or abiraterone (ie, index date) to the start of next LOT. Patients who do not start a new LOT will be censored at the earliest of 1) death, 2) end of data availability or 3) last patient contact.
Treatment sequence	Treatment sequences will include index treatment ie, enzalutamide or abiraterone, next treatment regimen following the index treatment (ie, second treatment), and subsequent treatment regimen following the second treatment if any (ie, third treatment). The following agents will be considered as subsequent treatment regimen post enzalutamide or abiraterone: • NHT • Chemotherapy • Immunotherapy • Radium-223 • Ketoconazole • Olaparib • Rucaparib ADT and anti-androgen (bicalutamide, flutamide, nilutamide) will not be considered as subsequent treatment regimens post enzalutamide or abiraterone

9.4. Data Sources

De-identified patient-level data from patients with mPC will be extracted from the Flatiron Health Electronic Health Record database. The Flatiron database consists of nationally representative real-world data from community practices and academic medical centers from 2013 through the present and contains structured and unstructured data curated via technology-enabled abstraction and supplemented with third-party death information.

9.5. Study Size

Table 3 below shows sample sizes needed to detect a range of hazard ratios (HR) for OS from 0.80 to 0.90 between enzalutamide and abiraterone with 80% power and a one-sided alpha level of 0.025, varying the percentage of deaths during the study follow-up period (50%, 55% and 60%). Calculations are based on the method by Schoenfeld (1983).[31] In the published Marar et al.[28] Flatiron study, there were 2785 mCRPC patients initiating first-line treatment with single agent enzalutamide or abiraterone, and approximately 2500 were chemotherapy-naïve. Our study will use more recent data and have longer follow up and may have a larger sample of patients. If we have a similar number of patients we expect that we will be able to detect at HR ≤0.85 with 80% power.

Table 3. Sample Sizes to Detect a Range of OS HRs for Enzalutamide vs Abiraterone with 80% Power

	1:1 ratio of patients receiving enzalutamide to abiraterone			2:3 ratio of patients receiving enzalutamide to abiraterone		
HR	**50% deaths**	**55% deaths**	**60% deaths**	**50% deaths**	**55% deaths**	**60% deaths**
0.80	1262	1147	1052	1314	1195	1095
0.81	1416	1287	1180	1474	1340	1228
0.82	1596	1451	1330	1662	1511	1385
0.83	1810	1645	1508	1884	1713	1570
0.84	2066	1878	1722	2152	1956	1793
0.85	2378	2162	1982	2478	2253	2065
0.86	2762	2511	2302	2876	2615	2397
0.87	3238	2944	2698	3374	3067	2812
0.88	3844	3495	3203	4004	3640	3337
0.89	4624	4204	3853	4816	4378	4013
0.90	5658	5144	4715	5892	5356	4910

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 a secure encrypted non-cloud-based server and accessed over a secure internal private wide area network. 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. Primary Analysis

The primary analysis, addressing the primary objective, will compare OS in patients with chemotherapy-naive mCRPC in Flatiron initiating enzalutamide vs. abiraterone, adjusting for baseline confounders using IPTW as described below.

9.7.1.1. Summary of Baseline Characteristics and OS

Baseline characteristics including demographics, insurance status, race, disease characteristics, time from first PC diagnosis to mCRPC diagnosis, time from mCRPC diagnosis to index date, time from first ADT to index date, ECOG, baseline lab values, prior prostate cancer treatments, and comorbidities will be compared between enzalutamide and abiraterone groups.

Summary statistics for baseline characteristics will be reported, including frequencies and percentages for categorical variables, and means, standard deviations, and medians for continuous variables.

Descriptive analyses of OS will be done using KM analyses to describe the probability of survival over time in each cohort. The median follow-up time, number of deaths and median OS (and 95% CI) will be reported for each group. Unadjusted Cox proportional hazard models will also be fit for descriptive purposes only.

9.7.1.2. Comparative analysis of OS for the primary objective, adjusting using IPTW

The primary analysis, addressing the primary objective, will compare OS in chemotherapy-naive mCRPC patients initiating enzalutamide vs. abiraterone adjusting for confounding as described below. IPTW will be used to adjust for differences between the two treatment cohorts on the pre-specified confounding factors listed in Appendix 2 Table 1. These potential confounding factors were based on published articles reporting prognostic factors for OS. IPTW will be based on propensity scores estimated as described below.

Propensity score calculation

Propensity scores will be obtained based on a logistic regression model that includes treatment group (enzalutamide or abiraterone) as the dependent variable, and the pre-specified set of confounders listed in Appendix 2 Table 1 as independent variables. A propensity score, defined as the probability of initiating enzalutamide as opposed to abiraterone, conditional on baseline characteristics, will be estimated from this model for each patient. The distribution of propensity scores in the two treatment cohorts will be compared using density plots to ensure adequate overlap.

IPTW

Patients' weights will be a function of the propensity score: weights for enzalutamide patients will be 1/(probability of initiating enzalutamide), whereas weights for abiraterone patients will be 1/(1- probability of initiating enzalutamide). To address the possibility of extreme weight values, patients' weights will be stabilized by the marginal probability of being in their treatment group.[32] The distribution of the stabilized weights will be examined, and if needed, extreme weights may be truncated such that weights exceeding a particular threshold are each set to that threshold.[33]

Balance of the baseline characteristics between enzalutamide and abiraterone groups in the weighted sample will be assessed using standardized differences. Baseline characteristics will be considered to be adequately balanced if the absolute value of standardized differences is less than 0.1.[34] If imbalances remain, additional covariates may be included in the subsequent IPTW-adjusted Cox proportional hazards regression model.

Kaplan-Meier analysis and Cox proportional-hazards model

OS will be compared between enzalutamide and abiraterone-treated patients in the weighted sample using weighted KM analyses. To compare the hazard of death between patients who initiated enzalutamide and patients who initiated abiraterone, a weighted Cox proportional hazards model with an independent variable for treatment group will be fitted, using a robust variance estimator. HRs with corresponding 95% CIs and p-values will be reported.

9.7.2. Secondary Analysis 1

9.7.2.1. Comparative Analysis of OS for the Secondary Objective 1, Adjusting Using IPTW

The secondary analysis will focus on the subgroup of patients who received enzalutamide or abiraterone without subsequent therapy (ie, including only patients who did not switch to or add another mCRPC treatment). Patient characteristics and OS will be summarized for this subgroup as done in the primary analysis, described in Section 9.7.1.1. OS between these two groups will be compared using an IPTW-adjusted analysis. Propensity scores and balance of pre-specified confounders in this subgroup of patients will be assessed. If substantial imbalances exist, propensity scores may be re-estimated for this subgroup of patients, using

the same pre-specified confounders and propensity score estimation method as described for the primary analysis in Section 9.7.1.2.

9.7.3. Secondary Analysis 2

9.7.3.1. Comparative Analyses of Treatment Duration and Time to Subsequent Treatment Therapy for the Secondary Objective 2, Adjusting Using IPTW

The secondary analysis 2, addressing the secondary objective 2, will compare treatment duration of the index treatment and time to subsequent therapy in patients with chemotherapy-naive mCRPC initiating enzalutamide vs. abiraterone, adjusting for baseline confounders using IPTW as described in Section 9.7.1.2.

CCI

[redacted]

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:

- Flatiron data collects patient information mostly from community oncology centers.
- Certain covariates may have been incompletely coded due to inconsistent electronic health record documentation (eg, comorbidities), and information about some variables affecting prognosis and outcomes were not available in the database.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

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

10.1. Patient Information

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

10.2. 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.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The IRB approval of this observational study with secondary data use from an existing EHR database is covered by IRB approval on Flatiron parent protocol. Data provided by Flatiron to third parties were de-identified and provisions were in place to prevent re-identification in order to protect patients' confidentiality. This study is exempt from institutional review board approval because it is retrospective, non-interventional, and will use anonymized data provided by Flatiron.

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 2016; 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 this data source, 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, 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 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. Upon study completion and finalization of the study report, the results of this non-interventional study will be submitted for publication or conference presentation, pending on discussion and agreement of all parties involved in the analysis.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Section 4	12 June 2023	Abstract

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Appendix 1.

Appendix 1 Table 1. Administrative codes for relevant treatments

Hormonal therapy	GPI	HCPCS/CPT	ICD
ADT			
Orchiectomy		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	
Goserelin	21405005	J9202	
Histrelin	2140500710	J1675, J9225, J9226, S0133	
Leuprolide	21405010	J1950, J9217, J9218, J9219, Q0057	
Triptorelin	21405050	J3315	
NHT			
Apalutamide	21402410		

Appendix 1 Table 1. Administrative codes for relevant treatments

	00		
Abiraterone	21406010 20		
Darolutamide	21402425 00		
Enzalutamide	21402430 00		
First generation anti-androgens			
Bicalutamide	21402420 00		
Flutamide	21402440 00		
Nilutamide	21402460 00		
Chemotherapy	**GPI**	**HCPCS**	**ICD**
Taxane Chemotherapy			
Cabazitaxel	21500003 00	C9276, J9043	
Docetaxel	21500005 00	J9170, J9171	
Other Chemotherapy			
Carboplatin	21100015 00	J9045	
Cisplatin	21100020 00	J9060, J9062	
Oxaliplatin	21100028 00	J9263	
Mitoxantrone	21200055 00	J9293	
Immunotherapy	**GPI**	**HCPCS**	**ICD**
Sipuleucel-T	21651070 00	Q2043, C9273	
Pembrolizumab	21357953 00	J9271, C9027	
Radium	**GPI**	**HCPCS**	**ICD**
Radium-223	21600055 00	A9606	
Radiation therapy	**GPI**	**HCPCS**	**ICD**
Brachytherapy		0394T-0395T CPT: 77761-77763, 77767-77768, 77770-77772, 77778, 77789, 77750, 77790	

Appendix 1 Table 1. Administrative codes for relevant treatments

Conventional external beam radiation treatment delivery		G6003-G6014 CPT: 77401-77416,	
Intensity modulated radiation therapy		G6015-G6016 CPT: 77385-77386	
Proton beam therapy		CPT: 77520-77525	
Stereotactic body radiation therapy		CPT: 77373	
Bone targeting 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	
Surgery	**GPI**	**HCPCS/CPT**	**ICD**
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
Fracture and skeletal-related events[1]	**GPI**	**HCPCS**	**ICD**
Bone surgery		27187, 27235, 27236, 27244, 27245, 27248, 27269, 27495, 27506, 27507, 27509, 27511, 27513, 27514, 23615, 23616,	ICD-9-PCS: 7815, 7845, 7855, 7915, 7925, 7935, 7995, 7812, 7842,

Appendix 1 Table 1. Administrative codes for relevant treatments

		23630, 24498, 24515, 24516, 24538, 24545, 24546, 24566, 24575, 24579, 24582, 24586, 24587, 24635, 24665, 24666, 24685, 25490, 25491, 25492, 25515, 25525, 25526, 25545, 25606, 25607, 25608, 25609, 27535, 27536, 27745, 27756, 27758, 27759, 27766, 27769, 27784, 27792, 27826, 27827, 22325, 22326, 22327, 22328, 22520, 22521, 22522, 22532, 22533, 22534, 22548, 22550, 22554, 22555, 22556, 22558, 22565, 22585, 22590, 22595, 22600, 22610, 22612, 22614, 22615, 22625, 22630, 22632, 20982, 23490, 23515, 23585, 27215, 27216, 27217, 27218, 27226, 27227, 27228, 27524, 27540, 22523, 22524, 22525, 22526, 22527, 25574, 25575	7852, 7911, 7921, 7931, 7991, 7813, 7843, 7853, 7912, 7922, 7932, 7992, 7817, 7847, 7857, 7916, 7926, 7936, 7996, 0353, 8102, 8103, 8104, 8105, 8106, 8107, 8108, 7810, 7811, 7816, 7819, 7840, 7841, 7846, 7849, 7850, 7851, 7856, 7859, 7910, 7919, 7920, 7929, 7930, 7939, 7990, and 7999
Bone palliative radiotherapy		A9600, A9604, A9605, C9401, J3005, 77401, 77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416, 77418, 79005, 79101, 79200, 79300, 79400, 79403, 79440, 79445, 79999	ICD-10-PCS: DP000ZZ-DP0C6ZZ ICD-9-CM: 9223, 9224, 9229
Pathologic fracture			ICD-9-CM: 733.1 ICD-10-CM: M84.5
Spinal cord compression		63050, 63051, 22551, 22552, 63064, 63066, 61343, s2348, 63075-8, s2350, s2351, 63195, 63197, 63199, 63001, 63003, 63005, 63011, 63015, 63016, 63017, 63170, 63012, 63045, 63046, 63047, 63048, 63040, 63042, 63043, 63044, 63020, 63030, 63035, 22224, 22222, 22214, 22212, 22207, 22206, 0274t, 0275t, c9729, 0202t, 22865, 0164t, 0094t, 0097t, 63057, 63056, 63055, 63081,	ICD-9-CM: 336.3, 336.8, 336.9 ICD-10-CM: G55, G95.2, G99.2

Appendix 1 Table 1. Administrative codes for relevant treatments

		63082, 63087, 63088, 63101, 63102, 63103, 63090, 63091, 63086, 63085	
Other prostate cancer drugs	**GPI**	**HCPCS**	**ICD**
Ketoconazole	11404040 00 96301064 00		
Olaparib	21535560		
Rucaparib	21535570 20		
Other baseline period medications	**GPI**	**HCPCS**	**ICD**
Corticosteroids	**22, 8910, 8915**		
Pain medications (analgesics)			
Non-narcotics	64		
Opioids	65		
Anti-inflammatory medications	66		

Abbreviations: CM: Clinical Modification; CPT, Current Procedural Terminology; GPI: Generic Product Identifier; HCPCS: Healthcare Common Procedure Coding System; ICD: International Classification of Diseases; LHRH: Luteinizing Hormone-Releasing Hormone; PCS: Procedures
Note:

[1] Source: Aly A, Onukwugha E, Woods C, et al. Measurement of skeletal related events in SEER-Medicare: a comparison of claims-based methods. BMC Med Res Methodol. 2015;15:65. Published 2015 Aug 19. doi:10.1186/s12874-015-0047-5

Appendix 1 Table 2. Administrative codes for site of metastatic disease

Site of metastatic disease	ICD-9-CM	ICD-10-CM
Lymph Node	1960-1963, 1965, 1966, 1968, 1969	C770-C775, C778, C779, C7B01
Visceral		
Respiratory Organs	1970-1973	C7800-C7802, C781, C782, C7830, C7839
Digestive Organs		
Liver	1977	C787, C7B02
Other digestive organs	1974- 1976, 1978	C784-C786, C7880, C7889, C7B04
Bone	1985	C7951, C7952, C7B03
Other Specified Sites	1980-1984, 1986-1987, 19881, 19882, 19889	C7900-C7902, C7910, C7911, C7919, C792, C7931, C7932, C7940, C7949, C7960-C7962, C7970-C7972, C7981, C7982, C7989, C7B03, C7B09, C7B1, C7B8
Without Specification of Site	1990, 1991	C799, C7B09, C7B00

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

Appendix 1 Table 3. Administrative codes for comorbidities

Conditions and comorbidities	ICD-9-CM	ICD-10-CM
NCI comorbidity index[1]		
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

Appendix 1 Table 3. Administrative codes for comorbidities

Conditions and comorbidities	ICD-9-CM	ICD-10-CM
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
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
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, 427.8, 427.89, 427.9	I47.0, I47.2, I49.0, I46, I49.3, I49.49, I47.9, I49.40, I49.5, I49.8, I49.9
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,

Appendix 1 Table 3. Administrative codes for comorbidities

Conditions and comorbidities	ICD-9-CM	ICD-10-CM
		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-C76, C80-C96, C7A, C7B
Anemia	280-285	D50-D53, D55-D59, D60-D64

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

Notes:
[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. Adapted using codes found in NCI Comorbidity Index Overview: https://healthcaredelivery.cancer.gov/seermedicare/considerations/comorbidity.html

Appendix 2 Table 1. Summary of preliminary list of prognostic factors for OS in mCRPC for adjustment in multivariable analysis

Identified from the targeted literature review by at least 2 studies	Factors added based on clinical input	Consolidated list from literature review and clinical input	Adjustable in Flatiron EHR
Demographics			
Age		Age	Yes
	Race/ethnicity	Race/ethnicity	Yes
	Geographic regions	Geographic regions	Yes
	Socioeconomic status	Socioeconomic status	Yes
	BMI	BMI	Yes (subject to completeness)
Site and extent of metastases			
Liver metastasis		Liver metastasis	Yes
Visceral metastasis		Visceral metastasis	Yes
	Lymph node metastasis alone	Lymph node metastasis alone	Yes
Bone metastases/No. of bone metastases		Bone metastases/No. of bone metastases	Yes, for presence of bone metastasis
No. of bone lesions or bone lesion size		No. of bone lesions or bone lesion size	No (not available)
Bone scan lesion area		Bone scan lesion area	No (not available)
PSA			
Baseline PSA		Baseline PSA	Yes (subject to completeness)
Baseline PSADT		Baseline PSADT	No (not available)
Performance status			
Karnofsky		Karnofsky	No (not available)
ECOG		ECOG	Yes (subject completeness)
Disease characteristics			
Time from diagnosis to the index date		Time from diagnosis to the index date	No (overlapping with other time variables below)
	Time from diagnosis to mCRPC	Time from diagnosis to metastasis	Yes
	Time from mCRPC to the index date	Time from metastasis to the index date	Yes
	Time from ADT start to the index date	Time from ADT start to the index date	Yes
Progression type: measurable disease		Progression type: measurable disease	No (not available)
Progression type: bone scan progression		Progression type: bone scan progression	No (not available)
Tumor grade (Gleason)		Tumor grade (Gleason)	Yes
Prior treatments			
Radical prostatectomy		Radical prostatectomy	Yes
Duration on prior hormone therapy (e.g.,		Duration on prior hormone therapy (eg,	Yes (adjusted as "Time from ADT to the index

Appendix 2 Table 1. Summary of preliminary list of prognostic factors for OS in mCRPC for adjustment in multivariable analysis

Identified from the targeted literature review by at least 2 studies	Factors added based on clinical input	Consolidated list from literature review and clinical input	Adjustable in Flatiron EHR
ADT)		ADT)	date")
	Prior ADT	Prior ADT	No (already included in inclusion criteria)
	Prior first-generation anti-androgens (eg, >90 days)	Prior first-generation anti-androgens (eg, >90 days)	Yes
Prior chemotherapy		Prior chemotherapy	No (not relevant due to exclusion criteria)
	Prior chronic corticosteroid use (ie, >90 days)	Prior chronic corticosteroid use (ie, >90 days)	Yes
Pain at baseline		Pain at baseline	No (but will adjust for opioid use)
Opioid analgesic use	Opioid analgesic use	Opioid analgesic use	Yes
Lab measures			
Albumin		Albumin	Yes (subject to completeness)
ALP		ALP	Yes (subject to completeness)
Hemoglobin		Hemoglobin	Yes (subject to completeness)
LDH		LDH	Yes (subject to completeness)
Neutrophil-to-lymphocyte ratio		Neutrophil-to-lymphocyte ratio	No (not available)
Platelet-to-lymphocyte ratio		Platelet-to-lymphocyte ratio	No (not available)
	Circulating Tumor cells	Circulating Tumor cells	No (not available)
C-reactive protein		C-reactive protein	No (not available)
Comorbidities			
	NCI and its components	NCI and its components	Yes
	Diabetes	Diabetes	Yes
	Cardiovascular disease	Cardiovascular disease	Yes
	Anemia	Anemia	Yes
	Concomitant cancer diagnosis (except for non-melanoma skin cancer)	Concomitant cancer diagnosis (except for non-melanoma skin cancer)	No (not relevant due to exclusion criteria)
Prior hospitalization and ER room visits			
	PC-related hospitalization	PC-related hospitalization	No (not available)
	PC-related ER visit	PC-related ER visit	No (not available)
	All-cause hospitalization	All-cause hospitalization	No (not available)
	All-cause ER visit	All-cause ER visit	No (not available)

Note: The completeness/missingness of particular variables is being determined.

Appendix 2 Table 1. Summary of preliminary list of prognostic factors for OS in mCRPC for adjustment in multivariable analysis

Identified from the targeted literature review by at least 2 studies	Factors added based on clinical input	Consolidated list from literature review and clinical input	Adjustable in Flatiron EHR

Abbreviations: ADT: androgen deprivation therapy; ALP: alkaline phosphatase; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; ER: Emergency room; LDH: lactate dehydrogenase; PC: prostate cancer; PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time.

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