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 the 100% Medicare Fee-For-Service (FFS) Data (2009-2020)
Protocol number	C3431046
Protocol version identifier	Version 1
Date	09 August 2022
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 100% Medicare data 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]
Author	PPD [redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABI	Abiraterone acetate
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
CMS	Centers for Medicare and Medicaid Services
CPT	Current procedural terminology
CrI	Credible interval
CRPC	Castration-resistant prostate cancer
CSPC	Castration-sensitive prostate cancer
ECOG	Eastern cooperative oncology group
ENZA	Enzalutamide
EHR	Electronic health record
ER	Emergency room
FFS	Fee-for-service
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

Abbreviation	Definition
OS	Overall survival
PCS	Procedures
PSA	Prostate specific antigen
rPFS	Radiographic progression-free survival
RRB	Railroad Retirement Board
RWE	Real-world evidence
SSA	Social security administration
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title: A Real-world Comparison of Clinical Outcomes in Chemotherapy-naive mCRPC Patients Who Initiated Enzalutamide vs. Abiraterone Acetate (Abiraterone) in the 100% Medicare FFS Data (2009-2020).

Version: 1

Date of Protocol: 09 August 2022

Authors:

PPD

Rationale and Background: Prostate cancer is the most common malignancy diagnosed among men in the United States (US) and continues to pose a high burden to public health. Enzalutamide and abiraterone acetate (hereafter referred to as abiraterone) are the most commonly used novel hormonal therapies (NHTs) in real-world clinical practice to treat chemotherapy-naive mCRPC patients. However, there is no phase 3 clinical trial comparing enzalutamide and abiraterone, and conflicting evidence exists regarding the relative effectiveness of enzalutamide vs. abiraterone for the treatment of mCRPC in the real-world setting. Therefore, this retrospective study aimed to leverage a large dataset (the 100% FFS Medicare data) to compare OS in patients with chemotherapy-naive mCRPC who initiated enzalutamide vs abiraterone. This study involves data that exist in anonymized structured format and contain no patient personal information.

Objectives:

The current study will be a retrospective data analysis to compare the OS in patients with chemotherapy-naive mCRPC who initiated enzalutamide vs. abiraterone. More specifically, we will address the following objectives:

Primary objective: To compare 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]

Study Design: The current study will be a retrospective data analysis to compare the OS in patients with chemotherapy-naive mCRPC who initiated enzalutamide vs. abiraterone using 100% FFS Medicare claims data. Patients with chemotherapy-naïve mCRPC (aged ≥18 years) who initiated enzalutamide or abiraterone (index date) within 90 days prior to the metastasis date or on or after the metastasis date and between 10 September 2014 and 31 May 2017 will be included in the study. Patients will be required to have continuous health plan enrollment for at least 365 days prior to the index date. The follow-up period will be from the index date to the earliest of death or the end of data availability (i.e., 2020 Q4). CCI [redacted]

Population: Patients meeting all the sample selection criteria will be categorized into the following cohorts based on the treatment received on the index date:

- Enzalutamide cohort: mCRPC patients initiating enzalutamide between 10 September 2014 and 31 May 2017
- Abiraterone cohort: mCRPC patients initiating abiraterone between 10 September 2014 and 31 May 2017

Variables: Baseline characteristics will include variables such as age, race/ethnicity, geographic regions, index year, previous treatment, chronic corticosteroid use, radiation therapy, National cancer institute (NCI) Charlson comorbidity index (CCI), treatment history, baseline comorbidities, and metastatic site.

Study period variables include OS, treatment duration of the index treatment, time to subsequent treatment, and treatment sequences.

Primary outcome of interest will be OS defined as the time from the initiation of enzalutamide or abiraterone (i.e., index date) to the date of death. Patients who do not die will be censored at their last available follow-up, which will be defined as the earlier of disenrollment from Medicare or end of data availability.

Treatment duration of the index treatment will be defined as the time from the initiation of enzalutamide or abiraterone (i.e., index date) to the discontinuation date. Discontinuation will be defined as the earlies of 1) death, 2) last observed administration plus day of supply associated with last administration, or 3) day before the start of next line of therapy (LOT). Death, a gap of 90 days or more after the last observed prescription date + day of supply, and initiation of next LOT will be considered as discontinuation events. Patients who do not

discontinue will be censored at their last available follow-up, which will be defined as the earlier of disenrollment from Medicare or end of data availability.

Time to subsequent therapy will be defined as the time from the initiation of enzalutamide or abiraterone (i.e., index date) to the start of next LOT. Patients who do not start a new LOT will be censored at their last available follow-up, which will be defined as the earliest of 1) death, 2) disenrollment from Medicare, and 3) end of data availability.

Treatment sequences will include index treatment i.e., enzalutamide or abiraterone, next treatment following the index treatment (i.e., second treatment), and subsequent treatment following the second treatment if any (i.e., third treatment)

Data Sources: 100% Medicare (representing > 61 million covered lives)

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

Data Analysis: Descriptive analysis will be conducted for baseline demographic and clinical characteristics to compare between enzalutamide and abiraterone patient groups. Means, standard deviations, medians, and interquartile range will be estimated for continuous variables. Counts and percentages will be estimated for categorical variables. Unadjusted comparisons of baseline characteristics will be conducted using appropriate tests (e.g., t-test, Fisher's exact test, chi-square test, and signed rank test) depending on the sample size and the distributions of baseline variables. Kaplan-Meier (KM) curves and Cox proportional-hazards models will be used to evaluate OS outcome. Inverse probability treatment weighting (IPTW) will be used in the main analyses to balance baseline demographic and clinical characteristics when comparing OS outcomes between the two cohorts (enzalutamide vs. abiraterone). Data analysis will be executed using statistical software SAS version 9.4 (Cary, NC).

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Finalized study protocol	03 August 2022
Finalized analytical results	31 October 2022
Finalized study report	30 December 2022

7. RATIONALE AND BACKGROUND

mCRPC and treatment with enzalutamide and abiraterone

Prostate cancer is the most common cancer and the second leading cause of cancer death among men in the US. The American Cancer Society estimates that in 2021 there will be 248 530 new cases and 34 130 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 (e.g., docetaxel [10], cabazitaxel [14]), immunotherapies (e.g., sipuleucel-T [15]), and radiotherapies (e.g., 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 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]. Another study of patients with mCRPC from a multi-country prostate cancer registry in Europe also identified abiraterone and enzalutamide as two of the most common first-line and second-line treatments for mCRPC, along with docetaxel [22].

Comparative effectiveness of enzalutamide and abiraterone

There have only been two, small, head-to-head randomized controlled trials comparing enzalutamide and abiraterone [23,24]. 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 groups [23].

Indirect comparison analyses based on published clinical trial data have indicated that there may be differences in Radiographic progression-free survival (rPFS) and OS between enzalutamide and abiraterone particularly in the chemotherapy-naive mCRPC setting. Three

independent meta-analyses of clinical trials that included PREVAIL and COU-AA-302 suggested better rPFS with enzalutamide vs. abiraterone (McCool et al. 2018: HR 0.59; 95% Credible Interval (CrI) 0.48-0.72; Chopra et al. 2017: HR 0.61; 95% CrI 0.41-0.91; Fang et al. 2017: HR 0.47; 95% CrI not reported, p<0.001) [25-27], and 1 of them revealed better OS for enzalutamide vs. abiraterone (Fang et al.: HR 0.81; 95% CrI not reported; p<0.001) [26]. However, only trial-level summary statistics were used in these studies, and it is possible that unadjusted differences between groups in baseline characteristics may have affected the results of comparative efficacy analyses. Differences between the PREVAIL and COU-AA-302 trials in the rates at which patients subsequently switched to chemotherapy or other treatments could also impact results from indirect comparisons of initial treatments.

Comparative effectiveness of enzalutamide and abiraterone in patients with mCRPC in clinical practice has also been evaluated in real-world studies [22,28-33]. Five RWE studies demonstrated more favorable OS for enzalutamide compared to abiraterone [28-30,32,33]. In a single-center, retrospective study including both chemotherapy-naive and chemotherapy-experienced patients with mCRPC (n=75), Raju et al [2021] found that patients receiving enzalutamide had longer OS compared to abiraterone (median OS of 30 months for enzalutamide vs. 15 months for abiraterone in chemotherapy-naive patients; p=0.002). 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) [29]. A retrospective cohort study based on a nationwide electronic health record (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) [33]. Two retrospective studies in the VHA database also showed enzalutamide was associated with longer OS than abiraterone [30,32]. 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 [32]. 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 [2021] of patients with mCRPC (n=5985) using a more recent cut of the VHA data also found a similar survival benefit associated with enzalutamide vs. abiraterone (HR 0.87, 95% CI 0.82-0.92) in analyses of all patients, and in the subgroup of patients who received only first-line treatment without subsequent therapy.

Two RWE studies did not find statistically significant differences in OS between these 2 therapies [22,31]. No difference between enzalutamide and abiraterone on OS was seen in the Multicenter Prostate Cancer Registry of chemotherapy-naive patients with mCRPC (n=751) (HR 1.00, 95% CI, 0.79-1.27) [22]. Finally, Soleimani et al [2021] found OS was comparable

between enzalutamide and abiraterone (HR 0.91, 95% CI, 0.70-1.19) in a retrospective study of 278 patients with mCRPC aged ≥80 years.

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 and indirect treatment comparisons have provided suggestive but inconclusive results, RWE can provide important information to guide treatment decisions [34-36], 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 populations 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 five prior RWE studies in this therapeutic area, two of them focused on non-US population with limited sample size. One US study focused more on the differences of first-line treatment between race/ethnicity groups. The other two US studies focused on the veterans' population, which may not be generalizable to US population of prostate cancer patients.

In alignment with FDA's draft Guidance for Industry, Submitting Documents Using Real-World Data and Real-World Evidence (RWE) to FDA for Drugs and Biologics (May 2019) [37], the sponsors propose to conduct a retrospective RWE study based on a pre-specified protocol to compare the effectiveness of enzalutamide vs. abiraterone among patients with chemotherapy-naive mCRPC.

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 enzalutamide vs. abiraterone, irrespective of any subsequent treatment.

In the 100% Medicare data, a beneficiary's date of death is available in the Master Beneficiary Summary File and the Vital Status File. Death information is validated against records from the US Social Security Administration (SSA) agency or the Railroad Retirement Board (RRB), with 99% of death dates been validated[38-41].

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 [30, 32].

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.

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

9. RESEARCH METHODS

9.1. Study design

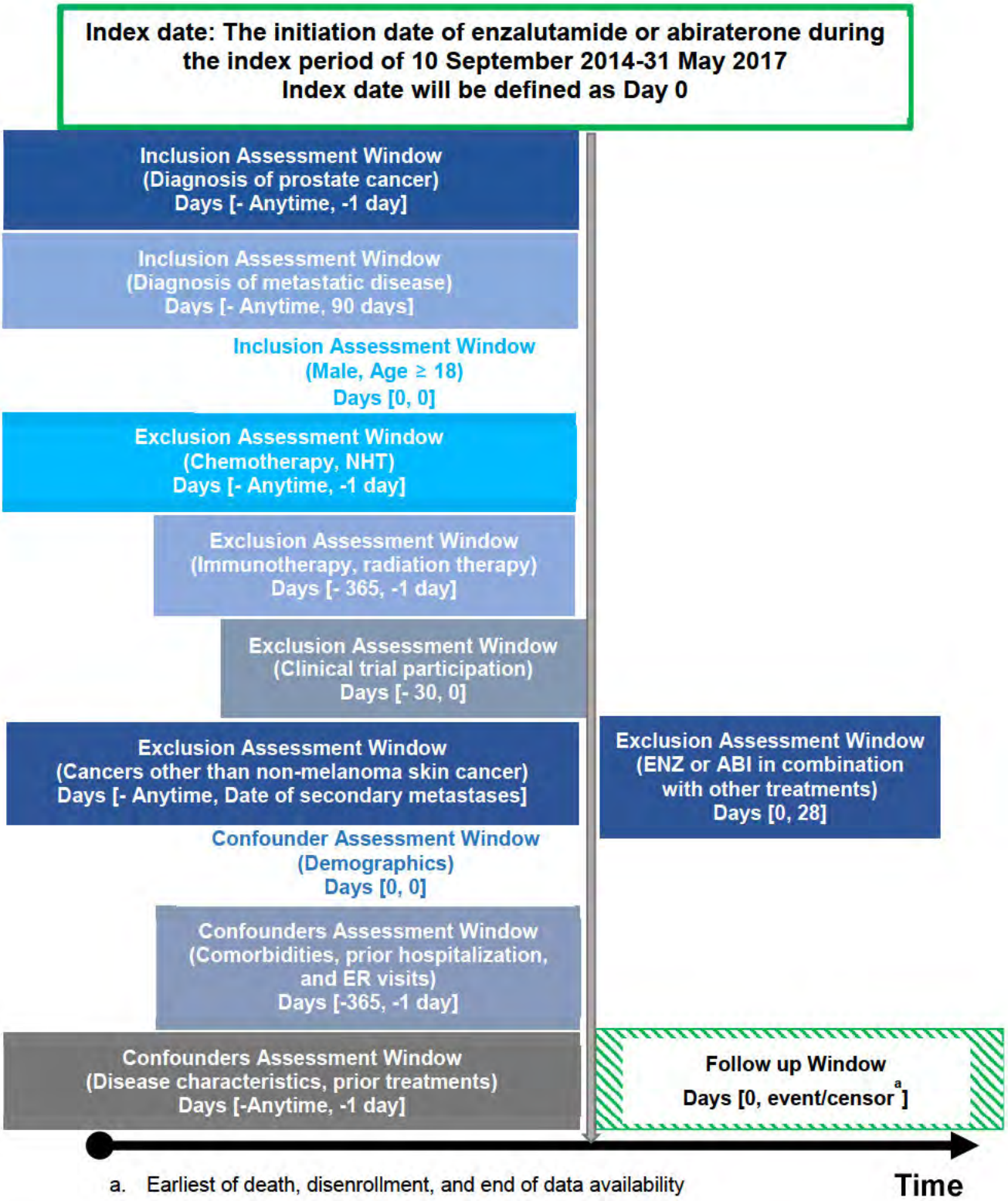
A retrospective observational cohort design using the 100% Medicare data will be conducted to address the primary and secondary objectives of the study. The study design is summarized in Figure 1 below and described in more detail in the subsequent sections.

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 May 2017. 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 the index period, 31 May 2017, corresponds to a date shortly before the data on the efficacy of abiraterone in mCSPC was made publicly available at ASCO 201– (02 - 06 June 2017) [42]. The index period will end at this point to ensure that patients with mCSPC are excluded from the analysis as their survival is expected to be longer than patients with mCRPC. In the LATITUDE study of patients with mCSPC, median OS for patients receiving abiraterone plus prednisone was 53.3 months (95% CI 48.2-not reached), compared to 36.5 months (95% CI 33.5-40.0) for patients receiving prednisone alone [43].

Baseline characteristics including demographics, disease characteristics, prior treatments, comorbidities, and all-cause healthcare resource use will be assessed based on data prior to the index date and/or during the 12-month period prior to the index date. A preliminary list of baseline characteristics to be assessed is included in Section 8.3. Patients will be followed from their index date to the earliest of patient death, disenrollment, 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 May 2017 and coverage of the data cut until the end of 2020. 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 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, disenrollment, and end of data availability

9.2. Setting

Patients in the 100% Medicare data 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 ≥ 1 diagnosis claim for prostate cancer (ICD-9-CM code 185; or ICD-10-CM code C61)
2. Have documented secondary metastasis code on or after the initial prostate cancer diagnosis (ICD-9-CM codes 196-199.1 or ICD-10 codes C77, C78, C79, C7B). The date of the first secondary metastasis code meeting this criterion will be defined as the date of secondary metastasis.
3. Have initiated enzalutamide or abiraterone (1) within 90 days prior to the metastasis date or on or after the metastasis date, and (2) during the index period of 10 September 2014 - 31 May 2017. 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. To ensure that patients included in the study are those initiating enzalutamide or abiraterone for the treatment of chemotherapy-naive mCRPC but not for mCSPC, patients' index dates will be required to occur during the index period of 10 September 2014 to 31 May 2017.

    - 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.
    - 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. To account for the possibility that physicians could have begun prescribing abiraterone for mCSPC after this meeting, the date of 31 May 2017, a date shortly before the ASCO 2017 meeting, is selected as the end date of the index period.
4. Have evidence of surgical or medical castration with ADT before the index date
    - Surgical castration any time prior to the index date will be considered
    - Medical castration will be defined as having LHRH agonists/antagonists lasting ≥ 8 weeks within 1-year prior to index date

5. At least 18 years old at the index date
6. Continuous eligibility for ≥ 12 months prior to the index date

9.2.2. Exclusion criteria

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

1. Received chemotherapy at any time prior to the index date
2. Received NHTs (i.e., enzalutamide or abiraterone) at any time prior to the index date
3. Received Radium 223 and/or immunotherapy during the baseline period
4. Received another NHT/ chemotherapy/ immunotherapy/ radium 223/ ketoconazole/ olaparib/ rucaparib within 28 days of the index date
5. Had a prior history of other cancers except for non-melanoma skin cancer prior to or on the date of secondary metastasis
6. 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 secondary metastasis and the index date
7. Enrolled in clinical trials during the period from 30 days pre-index to 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 and 3:

- **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:

- **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

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 variables

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 non-Hispanic White, Black, Hispanic, and other/unknown 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.
Socioeconomic status	Proportion of patients using Medicaid dual enrollment status or eligibility for Medicare Part D Low-income subsidy
Site of Metastasis	Flags will be created for patients that had a metastatic diagnosis 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 observed secondary 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.
Time between ADT and index date	Time from the first observed claim for medical or surgical castration used to identify eligibility in the study to index date
Radical prostatectomy	A binary variable (yes/no) will be created for patients with a claim for radical prostatectomy during the baseline period.
First-generation anti-androgens (bicalutamide, flutamide, nilutamide)	A binary variable (yes/no) will be created for patients with prescription claim for first-generation anti-androgens during the baseline period.
Chronic corticosteroid use	A binary variable (yes/no) will be created for patients with chronic corticosteroid use, defined as having one of the following: • Continuous use for at least 90 days without a gap of more than 30 days, between consecutive pharmacy claims (per Part D data), during the baseline period

Table 1. Baseline demographic and clinical characteristic variables

Variable	Operational definition
	• At least two corticosteroid procedure claims (per Part B data) with at least 90 days apart during the baseline period
Opioid analgesics	A binary variable (yes/no) will be created for patients with prescription claim for opioid analgesics during the baseline period.
Ketoconazole	A binary variable (yes/no) will be created for patients with prescription claim for ketoconazole during the baseline period.
Modified NCI CCI Score	The NCI version of the CCI score will be created during the baseline period. 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 claims for hypertension during the baseline period.
Stroke	A binary variable (yes/no) will be created for patients with claims for stroke 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.
Arrhythmia	A binary variable (yes/no) will be created for patients with claims for arrhythmia 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.
Congestive Heart Failure	A binary variable (yes/no) will be created for patients with claims for congestive heart failure during the baseline period.
Hyperlipidemia	A binary variable (yes/no) will be created for patients with claims for hyperlipidemia 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.
Type 2 Diabetes	A binary variable (yes/no) will be created for patients with claims for type 2 diabetes 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.

Table 1. Baseline demographic and clinical characteristic variables

Variable	Operational definition
Inflammatory Bowel Disease	A binary variable (yes/no) will be created for patients with claims for inflammatory bowel disease during the baseline period.
Anemia	A binary variable (yes/no) will be created for patients with claims for anemia during the baseline period.
Seizures	A binary variable (yes/no) will be created for patients with claims for seizures during the baseline period.
Urinary tract infection	A binary variable (yes/no) will be created for patients with claims for urinary tract infection during the baseline period.
Renal disease	A binary variable (yes/no) will be created for patients with claims for renal disease during the baseline period.
Liver disease	A binary variable (yes/no) will be created for patients with claims for liver disease during the baseline period.
Rheumatologic disease	A binary variable (yes/no) will be created for patients with claims for rheumatologic disease during the baseline period.
Hemiplegia	A binary variable (yes/no) will be created for patients with claims for hemiplegia during the baseline period.
Paralysis	A binary variable (yes/no) will be created for patients with claims for paralysis during the baseline period.
Peptic ulcer disease	A binary variable (yes/no) will be created for patients with claims for peptic ulcer disease during the baseline period.
AIDs	A binary variable (yes/no) will be created for patients with claims for AIDS during the baseline period.
Impotence	A binary variable (yes/no) will be created for patients with claims for impotence during the baseline period.
All-cause hospitalizations	The number of hospital inpatient (IP) admissions and IP days for all-cause hospitalizations and the proportion of patients with ≥ IP visit during the 1 year pre-index will be reported.
All-cause ER visits	The number of all-cause emergency room (ER) visits and the proportion of patients with ≥ 1 ER visit during the baseline period will be reported.
PC-related hospitalizations	The number of hospital inpatient (IP) admissions and IP days for PC-related hospitalizations and the proportion of patients with ≥ PC-related IP visit during the baseline period will be reported.

Table 1. Baseline demographic and clinical characteristic variables

Variable	Operational definition
PC-related ER visits	The number of PC-related ER visits and the proportion of patients with ≥ 1 PC-related ER visit during the baseline period will be reported.

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, disenrollment from Medicare, or the end of data availability (i.e., 2020 Q4)
OS (time to death)	Time to death will be defined as the time from the initiation of enzalutamide or abiraterone (i.e., index date) to the date of death. Patients who do not die will be censored at their last available follow-up, which will be defined as the earlier of disenrollment from Medicare or end of data availability.
Line of therapy (LOT) start date	• The start date for the first LOT is the index date • The start date for the second and later LOTs will be defined as the date of the first claim for a treatment of interest following the end of the preceding LOT
LOT regimen	A LOT will include all treatments of interest 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
LOT end date	A LOT will end when one of the following occurs: • A new treatment of interest 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 • More than 90 days pass without a new claim for a treatment in the LOT regimen from the later of 1) the last observed prescription + day of supply for the last oral medication in the regimen, 2) the claim date for the last infused/injectable medication in the regimen LOT end date will be defined as the earliest of 1) death, 2) last observed administration plus day of supply associated with last administration, 3) day before the start of next LOT, 4) disenrollment from Medicare, and 5) end of data availability

Table 2. Study period variables

Variable	Operational definition
Treatment duration (time to discontinuation)	Treatment duration of the index treatment will be defined as the time from the initiation of enzalutamide or abiraterone (i.e., index date) to the discontinuation date. Discontinuation will be defined as the earliest of 1) death, 2) last observed administration plus day of supply associated with last administration, or 3) day before the start of next LOT. Death, a gap of 90 days or more after the last observed prescription date + day of supply, and initiation of next LOT will be considered as discontinuation events. Patients who do not discontinue will be censored at their last available follow-up, which will be defined as the earlier of disenrollment from Medicare or end of data availability.
Time to subsequent therapy	Time to subsequent therapy will be defined as the time from the initiation of enzalutamide or abiraterone (i.e., index date) to the start of next LOT. Patients who do not start a new LOT will be censored at their last available follow-up, which will be defined as the earliest of 1) death, 2) disenrollment from Medicare, and 3)end of data availability.
Treatment sequence	Treatment sequences will include index treatment i.e., enzalutamide or abiraterone, next treatment regimen following the index treatment (i.e., second treatment), and subsequent treatment regimen following the second treatment if any (i.e., 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

Administrative claims data available from the Centers for Medicare and Medicaid Services (CMS) will be used for this study to address the primary and secondary objectives listed above. These data capture Medicare FFS beneficiaries' healthcare encounters including medications, PCS and healthcare resource use[44]. In particular, beneficiary-level information is available on demographics, enrollment and claims history including Medicare Part A (i.e., claims for services provided in inpatient, outpatient, skilled nursing facilities, home, or hospice), Medicare Part B (i.e., claims for physician services and durable medical equipment), and Medicare Part D (i.e., prescription drug claims). The data for this study will

include analytical datasets drawn from a 100% sample of Medicare FFS Part A, B and D claims files. The data covers approximately 20 million enrollees per year. The data cut used will cover the period from 2009 until the end of 2020.

The majority of patients with mCRPC are aged 65 years and above [7,12,13,45,46], and most US patients with mCRPC are expected to be enrolled in Medicare. Further, the 100% Medicare data will also include broad representation of racial minorities and patients with comorbidities. These data therefore provide a large and representative source of data for patients with mCRPC in the US for comparison of OS between enzalutamide and abiraterone.

Date of death in the 100% Medicare data has been verified against records from the U.S. SSA agency or the RRB [38-41]. A beneficiary's date of death is available in the Master Beneficiary Summary File and the Vital Status File. Death information is based on death reports from various sources such as information used to administer the Medicare program collected from the SSA and the RRB, Medicare claims data, and date of death edits submitted by family members. Evidence of death, such as death certificate, relevant SSA forms, or death data based on an Electronic Death Registration report, is collected to determine the death date. If conflicts exist in the evidence, all the available evidence is examined, and a most reasonable date of death is determined based on an order of evidence for proof of death. Because of the variation in sources of information, sometimes only the month and year of death are reported, and the exact day of death is not known. Overall, 99% of death dates have been validated[38,39]. However, the vast majority of deaths are known to Medicare within 2-3 months.

9.5. Study size

The inclusion/exclusion criteria defined above were applied to the 100% Medicare data cut currently available to estimate the number of patients expected. Based on these counts, a total of 8173 patients are expected (3951 patients initiating enzalutamide and 4222 patients initiating abiraterone).

Table 3 and Table 4 below show power to detect a hazard ratio (HR) of 0.84 for OS between enzalutamide and abiraterone (based on Tagawa et al [2021]), using a Cox proportional hazards regression analysis, assuming a two-sided alpha-level of 5%, an R-squared of 0.25 between predictors and treatment cohort, and different estimates for the percentage of patients in each treatment cohort (40%, 50% and 60%) and the percentage of deaths during the study follow-up period (50%, 55% and 60%). Power calculations are based on the method proposed by Hsieh [2000]. Based on the estimated sample size of 8000 (Table 3) and 9000 (Table 4) patients, there will be ample power to compare the treatments in the 100% Medicare data.

Table 3. Power to detect an HR of 0.84 for enzalutamide vs. abiraterone with n=8000

Percentage of patients receiving enzalutamide	Percentage of patients receiving abiraterone	Percentage of deaths during follow-up period	Power*
40%	60%	50%	99.7%
50%	50%	50%	99.8%
60%	40%	50%	99.7%
40%	60%	55%	99.8%
50%	50%	55%	99.9%
60%	40%	55%	99.8%
40%	60%	60%	>99.9%
50%	50%	60%	>99.9%
60%	40%	60%	>99.9%

*two-sided alpha of 0.05, R-squared between treatment cohort and covariates of 0.25 is used

Table 4. Power to detect an HR of 0.84 for enzalutamide vs. abiraterone with n=9000

Percentage of patients receiving enzalutamide	Percentage of patients receiving abiraterone	Percentage of deaths during follow-up period	Power*
40%	60%	50%	99.9%
50%	50%	50%	>99.9%
60%	40%	50%	>99.9%
40%	60%	55%	>99.9%
50%	50%	55%	>99.9%
60%	40%	55%	>99.9%
40%	60%	60%	>99.9%
50%	50%	60%	>99.9%
60%	40%	60%	>99.9%

*two-sided alpha of 0.05, R-squared between treatment cohort and covariates of 0.25 is used

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 100% Medicare data 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, disease characteristics, prior prostate cancer treatments, comorbidities, and resource use will be compared between enzalutamide and abiraterone groups.

The following steps were taken to identify a list of patient characteristics to adjust for when comparing outcomes between the two treatment cohorts. First, a targeted literature review was conducted to identify prognostic factors for OS in patients with mCRPC. A total of 31 articles reporting prognostic factors for OS were identified during 01 January 2008 to 28 June 2021. Prognostic factors reported in at least 2 articles were considered as candidate confounders. This candidate confounder list was further reviewed and updated based on input from clinical experts in prostate cancer. Availability of these confounders in the 100% Medicare data was further assessed. Alternative measures were proposed for confounders not available in 100% Medicare data based on clinical input. Based on this process, the list of confounders proposed for adjustment in the 100% Medicare data is summarized in Appendix 2 Table 1.

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. Unadjusted Cox proportional hazard models will also be fit for descriptive purposes only. The median follow-up time, number of deaths and median OS (and 95% confidence interval [CI]) will be reported for each group.

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. The list of confounding factors will be finalized based on discussion with Pfizer. IPTW will be based on propensity scores estimated as described below.

Propensity score matching

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 [47]. 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 [48].

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 10% [49]. 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 (i.e., 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 8.7.1.1. 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 8.7.1.2.

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 8.7.1.2.

CCI

CCI

- CCI

CCI [redacted]

- CCI [redacted]

9.8. Quality control

Best practice guidelines will be followed to ensure project quality, including structured organization of project materials (e.g., 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:

- Data on clinical covariates important for confounding control (e.g., performance status, laboratory measurements) are not available for adjustment in the 100% Medicare data.
- ICD-9/10-CM diagnosis codes used to identify patients with prostate cancer and baseline comorbidities are billing diagnostic codes, and may not always reflect confirmed clinical diagnoses, resulting in potential inaccuracies.
- Medicare enrollment eligibility requirement and potential enrollment turnover may also result in truncated medical history and left and right censoring biases.
- Pharmacy claims do not indicate whether the medication was taken as prescribed, and misclassification of exposure may occur. However, these inaccuracies and data deficiencies are generally expected to be non-differentially distributed between enzalutamide and abiraterone groups in this study.
- Both enzalutamide and abiraterone are approved for both mCRPC and mCSPC. To ensure that only patients with mCRPC are included, a narrower index period was used to limit the chance of including mCSPC patients in this study. However, in the absence of data to verify patients' diagnoses, this cannot be assured.
- The 100% Medicare data mainly includes patients who are over 65 years of age, thus, it does not reflect patients with mCRPC who are younger. However, this limitation is mitigated by the fact that most patients with mCRPC are above age 65 years.

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)

An IRB waiver was received.

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 issued by the International Society for Pharmacoepidemiology.

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 (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

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

13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

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	21405525 10	J9155	
Goserelin	21405005	J9202	
Histrelin	21405007 10	J1675, J9225, J9226, S0133	
Leuprolide	21405010	J1950, J9217, J9218, J9219, Q0057	
Triptorelin	21405050	J3315	
NHT			
Apalutamide	21402410 00		

Appendix 1 Table 1. Administrative codes for relevant treatments

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	
Conventional external beam radiation treatment delivery		G6003-G6014 CPT: 77401-77416,	

Appendix 1 Table 1. Administrative codes for relevant treatments

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	30044530 00	J0897, C9272	
Ibandronate	30042048 10	J1740, C9229	
Zoledronic acid	30042090 00	J3489, Q2051, J3487, J3488, Q4095	ICD-9-PCS V58.68 ICD-10-PCS Z79.83
Pamidronate disodium	30042060 10	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, 23630, 24498, 24515, 24516, 24538, 24545, 24546, 24566, 24575, 24579, 24582, 24586, 24587, 24635, 24665, 24666,	ICD-9-PCS: 7815, 7845, 7855, 7915, 7925, 7935, 7995, 7812, 7842, 7852, 7911, 7921, 7931, 7991,

Appendix 1 Table 1. Administrative codes for relevant treatments

		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	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,	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

		63081, 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

Appendix 1 Table 3. Administrative codes for comorbidities

Conditions and comorbidities	ICD-9-CM	ICD-10-CM
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-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 100% Medicare data
Demographics			
Age		Age	Yes
	Race/ethnicity	Race/ethnicity	Yes
	Geographic regions	Geographic regions	Yes
	Socioeconomic status	Socioeconomic status	Yes
	BMI	BMI	No (not available)
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	No (not available)
Baseline PSADT		Baseline PSADT	No (not available)
Performance status			
Karnofsky		Karnofsky	No (not available)
ECOG		ECOG	No (not available)
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 metastasis	Time from diagnosis to metastasis	Yes
	Time from metastasis 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)	No (not available)
Prior treatments			
Radical prostatectomy		Radical prostatectomy	Yes
Duration on prior hormone therapy (e.g., ADT)		Duration on prior hormone therapy (e.g., ADT)	Yes (adjusted as "Time from ADT to the index date")
	Prior ADT	Prior ADT	No (already included in inclusion criteria)

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 100% Medicare data
	Prior first-generation anti-androgens (e.g., > 90 days)	Prior first-generation anti-androgens (e.g., > 90 days)	Yes
Prior chemotherapy		Prior chemotherapy	No (not relevant due to exclusion criteria)
	Prior chronic corticosteroid use (i.e., > 90 days)	Prior chronic corticosteroid use (i.e., > 90 days)	Yes
Pain at baseline		Pain at baseline	No (but will adjust for opioid use; vital status has quality of pain but not populated)
Opioid analgesic use	Opioid analgesic use	Opioid analgesic use	Yes
Lab measures			
Albumin		Albumin	No (not available)
ALP		ALP	No (not available)
Hemoglobin		Hemoglobin	No (not available)
LDH		LDH	No (not available)
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	Yes
	PC-related ER visit	PC-related ER visit	Yes
	All-cause hospitalization	All-cause hospitalization	Yes
	All-cause ER visit	All-cause ER visit	Yes

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