

Treatment Patterns and Outcomes in Patients With Metastatic Castration-resistant Prostate Cancer in a Real-world Clinical Practice Setting in the United States

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Abstract

Information on real-world treatment of advanced prostate cancer is limited. We used a database of electronic medical records from over 2500 patients with metastatic castration-resistant prostate cancer to identify real-world treatment patterns and demonstrate areas for improvement in guideline adherence to help health care professionals make decisions on how best to treat prostate cancer to improve outcomes.

Background: Clinical trials have demonstrated the efficacy of several life-prolonging therapies for metastatic castration-resistant prostate cancer (mCRPC); however, real-world data on their use, survival effect, and safety are limited. Using electronic health record data from the Flatiron Health database, we studied real-world treatment patterns and health outcomes in patients with mCRPC. **Patients and Methods:** We conducted a retrospective, non-interventional cohort analysis of electronic health record data of patients with confirmed mCRPC between January 2013 and September 2017. The primary objective was to describe real-world treatment patterns, including treatment type, duration, and sequencing. Secondary objectives included describing patient characteristics and clinical outcomes. **Results:** Of 2559 patients with mCRPC, 1980 (77%) received at least 1 line of life-prolonging therapy (abiraterone, enzalutamide, docetaxel, cabazitaxel, sipuleucel-T, or radium-223). Of patients receiving first-line therapy, 49% received second-line therapy, and of these, 43% received third-line therapy. Abiraterone/prednisone and enzalutamide accounted for 65% of first-line therapies and 54% of second-line therapies. Docetaxel was the most common third-line therapy (24%). Back-to-back use of abiraterone/prednisone and enzalutamide was common. Radium-223 monotherapy use was 2% in the first-line setting, 3% in the second-line setting, and 8% in the third-line setting. The median overall survival was longer in patients who received life-prolonging therapies (23.7 months; 95% confidence interval: 22.3-25.1 months) than in those who did not (10.1 months; 95% confidence interval: 9.1-11.5 months). **Conclusion:** These real-world insights on over 2500 patients with mCRPC supplement findings from randomized controlled trials and may help to inform clinical trial design, treatment guidelines, and clinical decision-making.

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Introduction

Until 2010, docetaxel was the only agent available for the treatment of metastatic castration-resistant prostate cancer (mCRPC) that showed an increase in overall survival (OS) compared with standard of care.¹ Over the past 9 years, several other life-prolonging therapies (sipuleucel-T, cabazitaxel, abiraterone, enzalutamide, and radium-223) have received regulatory approval for mCRPC in the United States (US).¹

Clinical trials provide convincing evidence of the efficacy of these therapeutic options,²⁻¹⁰ but real-world data (RWD) on the use and effect on survival and safety of these agents are limited. Although clinical trials play a fundamental role in assessing the efficacy and safety of new treatment options,¹¹ they are often performed in specialized centers and enroll highly selected patients who are not necessarily representative of the real-world patient population.^{11,12} Strict inclusion and exclusion criteria generally do not permit the enrollment of patients with poor performance status, comorbidities, and significant organ dysfunction. In the US, only 3% of patients participate in clinical trials, with patient groups such as low-income patients, certain ethnic minorities, and the elderly continuing to be under-represented.¹³

RWD can overcome some of the limitations of clinical trials^{12,14} and are increasingly being used by regulatory bodies to support decision-making in health care.¹⁵ For example, the US Food and Drug Administration (FDA) uses RWD to assess the safety of therapeutics in the post-marketing setting and to guide regulatory decisions.¹⁵ Importantly, RWD can be used to validate and expand on the findings of clinical trials (eg, by studying a particular treatment in underrepresented patient populations or investigating long-term safety)^{12,14} and can also shed light on the patterns of care and possible limitations in the use of newer therapies.¹⁴

The Flatiron Health database is a longitudinal demographically and geographically diverse database derived from quality-controlled, real-world electronic health record (EHR) data. It includes data from over 280 community oncology clinics and academic centers (approximately 800 sites of care) throughout the US, representing more than 2 million active US patients with cancer that are available for analysis. Flatiron Health works closely with the FDA, which collects real-world outcomes from patients with cancer with the aim of further understanding newly approved therapies,¹⁶ and has published RWD studies across different cancer types, including prostate cancer.^{17,18}

This retrospective cohort study used the Flatiron Health database to investigate real-world treatment patterns and health outcomes in patients with mCRPC. This article describes the methodology underlying the database, and the study of real-world treatment patterns and OS for patients with mCRPC in the Flatiron Health database.

Materials and Methods

Overview of the Flatiron Health Database

As of September 2019, the Flatiron Health database contained EHR data from over 2 million patients with cancer in the US (from over 280 cancer clinics). The database comprises both structured and unstructured elements that are extracted and processed as per Flatiron Health's EHR data processing pipeline to generate patient-level longitudinal data. Structured data (including demographics,

performance status, laboratory results, and medication administrations) are harmonized and normalized across different source systems. Unstructured data (ie, clinic data, treatment history, reason[s] for treatment discontinuation, and adverse events) are processed according to a modular, technology-enabled chart abstraction methodology supplemented by a manual review (by experienced oncology nurses and tumor registrars, with oncologist oversight), the combination of which significantly enhances the quality and efficiency of the data-extraction process.

All datasets are subject to statistical and scientific review, as well as rigorous quality-control standards, which encompass themes such as demographics, treatment duration and dosage, and include both medical (eg, expectations based on published literature and clinical practice) and data (eg, stability from prior months) considerations. Additional indication-specific, quality-control processes are also implemented, with any issues subsequently being logged, prioritized, investigated, and resolved. Algorithms have been developed to enrich for missing data elements in patient records, the occurrence of which can affect the statistical validity of real-world studies.¹⁹

The methodology used in cohort selection combines these structured and unstructured data to select patients with the relevant diagnosis. Patients are initially selected based on diagnostic (International Classification of Diseases, Ninth/Tenth Revisions) codes,^{20,21} with a subsequent manual review performed to confirm the selection criteria of interest. In this study, initial datasets were enriched with castration-resistant prostate cancer (CRPC) data by means of an algorithm that used other information about the patients captured in the database. This additional information included explicit documentation of CRPC status in the patient chart from the physician, which could have been reported as castration-resistant, hormone-resistant or -refractory, or androgen-sensitive or -independent prostate cancer; the use of corresponding abbreviations (such as CRPC, HRPC [hormone-refractory prostate cancer], AIPC [androgen-independent prostate cancer]); or a report that the patient was no longer responding to androgen deprivation therapy alone. Other information included evidence of the patient becoming refractory to their first second-generation androgen receptor axis-targeted therapy (abiraterone/prednisone or enzalutamide), as documented by an increase in prostate-specific antigen (PSA) levels and treatment change, an increased PSA value of ≥ 2 ng/mL over baseline, and at least 1 higher subsequent PSA value while on hormone therapy. Thus, all of the following conditions relating to PSA values had to be met: (1) the patient had a PSA measurement at the start of, or on, hormone therapy; (2) there was a subsequent PSA measurement that was higher by ≥ 2 ng/mL; and (3) there was a subsequent higher PSA measurement within 3 months. The 3-month time period was considered a reasonable time frame in which to confirm an increase in PSA levels.

Lines of Therapy

In this study, treatment patterns were analyzed by line of therapy, defined as the first eligible agent for mCRPC plus other drugs given within 28 days of starting the first agent in that line setting. The name of the 'regimen' for that line of therapy was the combination of therapies in that line, unless otherwise noted. The first line was defined as the treatment line that began after diagnosis of mCRPC.

Real-world Treatment Patterns in mCRPC

Treatment lines for each patient were counted relative to their index date (date of mCRPC diagnosis); these were defined as cohort treatment lines and form the basis of this study. Within a line of therapy, the addition of radium-223 ≤ 3 months after the start of the regimen did not require the line of therapy number to be advanced, whereas this was required with the addition of radium-223 > 3 months after the start of the regimen. If a treatment was discontinued for > 3 months, the line of therapy was advanced. For the most recent line of therapy, the end date was defined as the earliest of either: (1) the most recent administration, visit date, or confirmed receipt of a therapy, or (2) the date of death (if applicable). For all other lines, the end date was defined as the day before the start date of the next line of therapy.

The use of bone health agents (BHAs [denosumab or bisphosphonates]) was also recorded. Concomitant use of BHAs was defined as any use between the start and end dates of each line of therapy, regardless of the start/end dates of the BHA. Patients using multiple BHAs were counted once when calculating the number of patients with any BHA use.

Study Overview

This study was a retrospective, non-interventional cohort analysis that used records from January 2013 to September 2017 from the Flatiron Health database for patients with mCRPC. The primary objective was to provide a description of real-world treatment patterns in patients with mCRPC, including the type of treatment, treatment duration, and treatment sequencing. Secondary objectives included the description of patient characteristics and clinical outcomes, including OS.

Patient Selection

Patients with metastatic prostate cancer with ≥ 2 documented clinical visits on or after January 1, 2013, who developed castration resistance over the follow-up period in the database and had accompanying dates of diagnosis for both metastatic disease and CRPC were included in the study. A confirmed diagnosis of CRPC required all 3 of the following criteria to be met: (1) date of CRPC diagnosis recorded by the physician (explicit documentation); (2) date of the second increase in PSA level (PSA levels increase by ≥ 2 ng/mL after initial hormone therapy, followed by at least 1 further rise ≤ 3 months after the first increase); and (3) date recorded by the physician of a documented increase in PSA level or PSA progression on the first line of hormone therapy, with a change in treatment. In instances when multiple sources of evidence were available, the earliest time point was recorded as the date of CRPC diagnosis. Patients whose castration resistance status was unclear, who did not have a date of onset of resistance, or who were enrolled in a clinical trial were excluded from the study.

Patient Baseline Characteristics

Baseline characteristics at initial prostate cancer diagnosis included disease stage, tumor/node/metastasis (TNM) stage, and Gleason score. Baseline characteristics at index date included patient age, ethnicity, race, PSA values, total alkaline phosphatase, hemoglobin, and lactate dehydrogenase levels. Further patient information not reported here is available in the Flatiron Health database, including payer category, practice type (community or academic),

State, performance status, time since prostate cancer diagnosis (and time since onset of castration resistance), histology, and treatment received at index date.

Definition of Outcomes

The current study assessed treatment patterns, duration of follow-up, and OS. Treatment patterns included: (1) the number of patients who received first-, second-, and third-line life-prolonging therapies (abiraterone, enzalutamide, docetaxel, cabazitaxel, sipuleucel-T, and radium-223); (2) the number of patients who received specific therapies and the duration of each line of therapy; and (3) the number of patients who received agents of particular interest, including duration of treatment. The date of death was presented as month and year (ie, not a precise date) to avoid potential breaches of patient confidentiality. Calculations presumed that deaths occurred on the 15th of the month. This assumption was not anticipated to cause a major bias.

Mortality Data

Missing mortality data were addressed as described previously.²² In brief, EHRs were enriched using death data external to the study database from the US Social Security Death Index and a commercial death dataset that mines data from obituaries, funeral homes, and other sources. A deterministic matching algorithm was used to link these external datasets to the EHR data. As part of this process, incorrect data (eg, death dates that occurred prior to abstracted diagnosis dates) were removed from the dataset. Date of death was determined using a hierarchical approach, in which preference was based on comparative analyses, with the US National Death Index as the gold standard.

Ethical Considerations

This was a retrospective study based on anonymized data from a secondary database. Data were reported at the aggregated level rather than at the patient level. The study was exempt from Institutional Review Board approval.

Statistical Analysis

Electronic datasets provided by Flatiron Health (multiple structured and linked text files) were analyzed using SAS (Enterprise Guide Version 7.12). All statistics were descriptive; continuous variables are described using the mean, standard deviation, median, and minimum/maximum values; binary variables (eg, CRPC status) are described as the number of patients with the outcome observed relative to the number of patients in whom the variable could be measured. The time-to-event analysis (eg, OS) used the Kaplan-Meier method. Standard errors and confidence intervals (CIs) are only presented for the time-to-event analysis.

Quality Control and Missing Data

The analyses performed were subject to rigorous quality-control procedures, including checks for data quality (eg, data errors or missing data) and validation of SAS programs.

Results

Patient Demographics and Baseline Characteristics

The December 2017 version of the Flatiron Health database contained a randomly selected sample of 4187 patients (data cutoff

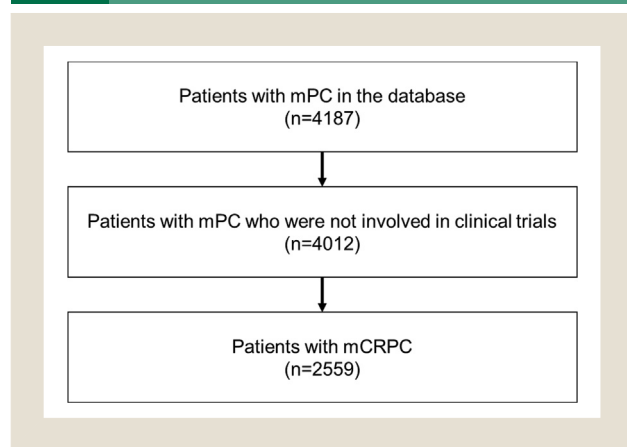
date, September 2017). A total of 4012 patients were diagnosed with metastatic disease, of whom 2559 had mCRPC (Figure 1). Most (93%) patients included in this study were treated in a community practice setting. The remaining patients were treated at academic centers. Patient demographics and baseline characteristics are presented in Table 1. The mean age of patients in the study population at index date was 74 years. The majority (61%) of patients were white, 25% were non-white, and 14% had missing data. Among patients with a known Gleason score at diagnosis, 45% had a score > 7. The disease stage at initial diagnosis was stage IV in 39% of patients and unknown for 51% of patients (Table 1). The median PSA level at initial diagnosis, as assessed in 70% of patients (n = 1784), was 22.3 µg/L. Median PSA values at initial diagnosis for the remaining 30% of patients were either not assessed or were missing (Table 1).

Treatment Patterns

Of the 2559 patients with mCRPC, 1980 (77%) received at least 1 line of systemic therapy for mCRPC, mainly life-prolonging therapies such as abiraterone, enzalutamide, docetaxel, cabazitaxel, sipuleucel-T, or radium-223, either alone or in combination. A small number of patients received other therapies, such as carboplatin. Patients who did not receive life-prolonging therapies or these other agents could have received other standard care (eg, castration, radiotherapy, steroids, or symptomatic treatment). Of patients who received first-line therapy, 49% received second-line therapy, and of these patients, 43% received third-line therapy as of the data cutoff date (Figure 2).

The second-generation androgen receptor axis-targeted therapies, abiraterone/prednisone and enzalutamide, were the most common treatments administered to patients with mCRPC, accounting for 65% of first-line therapies and 54% of second-line therapies. Docetaxel was the most common third-line therapy (received by 24% of patients), with enzalutamide and abiraterone/prednisone being used for 16% and 14% of patients, respectively. Cabazitaxel represented 1%, 6%, and 11%, respectively, of first-, second-, and third-line therapies. Sipuleucel-T accounted for 7%, 2%, and 3% of treatment choices in the first-, second-, and third-line settings, respectively (Figure 3). Combination therapy was administered to 7%, 17%, and 18% of patients in the first-, second- and third-line

Figure 1 Patient Flow



Abbreviations: mCRPC = metastatic castration-resistant prostate cancer; mPC = metastatic prostate cancer.

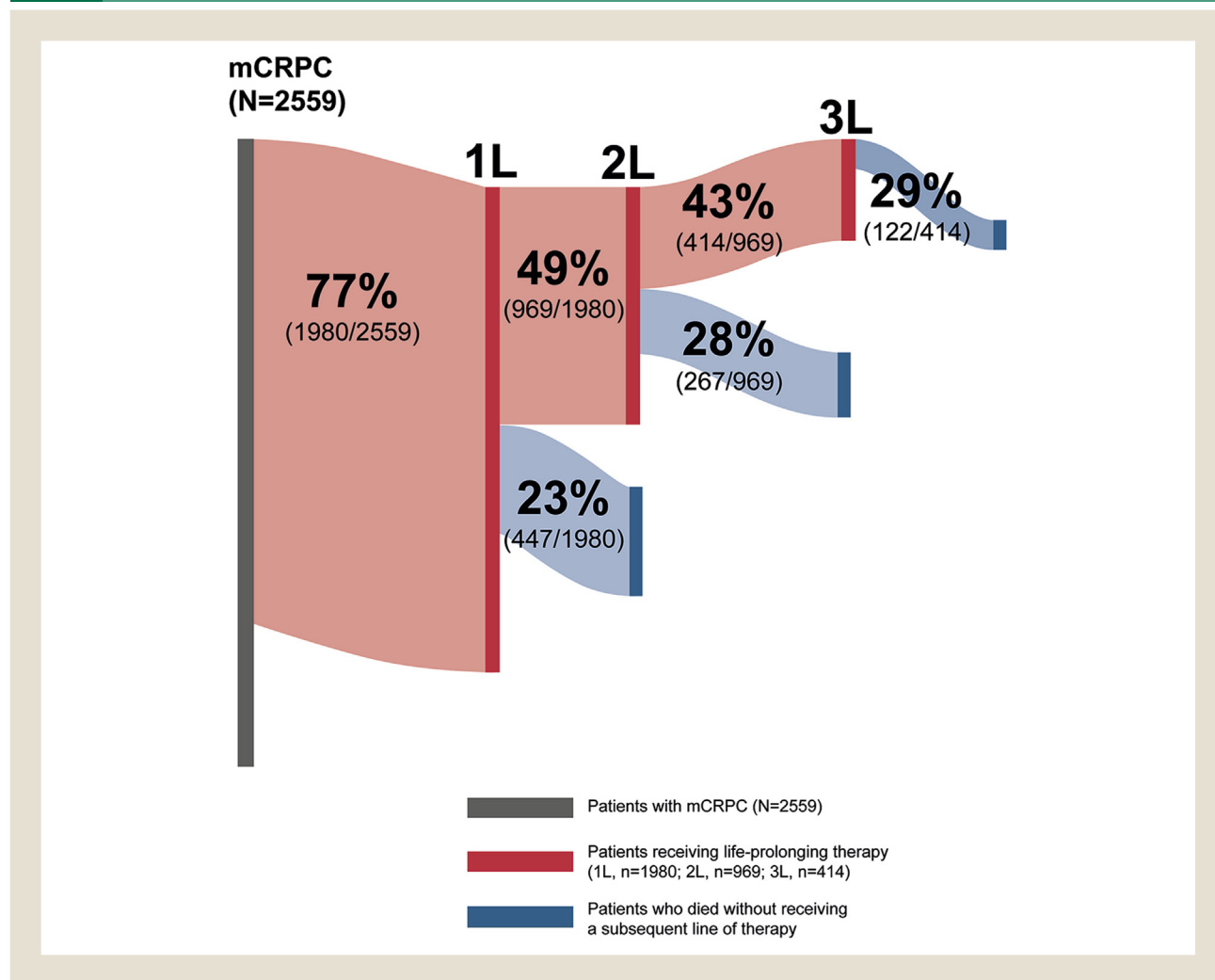
Table 1 Patient Demographics and Baseline Characteristics

Characteristic	Patients With mCRPC (N = 2559)
Mean age (SD), y	74 (9)
Race, n (%)	
White	1558 (61)
Asian	48 (2)
African-American	267 (10)
Other	322 (13)
Missing	364 (14)
Disease stage at initial diagnosis, n (%)	
I	14 (1)
II	139 (5)
III	93 (4)
IV	1003 (39)
Unknown	1310 (51)
T stage at initial diagnosis, n (%)	
0	2 (<1)
1	174 (7)
2	331 (13)
3	315 (12)
4	63 (2)
TX	74 (3)
Unknown	1600 (63)
N stage at initial diagnosis, n (%)	
0	485 (19)
1	201 (8)
NX	157 (6)
Unknown	1716 (67)
M stage at initial diagnosis	
0	813 (32)
1 (including a, b, and c)	899 (35)
Unknown	847 (33)
Gleason score at initial diagnosis	
≤ 7	631 (25)
> 7	1151 (45)
Unknown	777 (30)
Laboratory values, median (min-max)	
ALP, U/L (n = 1827)	98 (0-6272)
PSA, µg/L (n = 1784)	22.3 (0-2,853,000)
Hb, g/dL (n = 1915)	12.3 (4.4-18.6)
LDH, U/L (n = 563)	197 (96-4384)

Baseline characteristics were collected on the index date when mCRPC was diagnosed, except for disease stage, Gleason score, and PSA.

Abbreviations: ALP = alkaline phosphatase; Hb = hemoglobin; LDH = lactate dehydrogenase; mCRPC = metastatic castration-resistant prostate cancer; NX = lymph nodes could not be assessed; PSA = prostate-specific antigen; SD = standard deviation; TX = tumor could not be assessed.

settings, respectively. A wide range of combination regimens were reported. Abiraterone-containing regimens were the most common combinations in the first line (4% of patients) and second line (10%); whereas enzalutamide-containing regimens were the most common combinations in the third line (10%). Overall, 60% of

Figure 2 The Proportion of Patients With mCRPC Receiving Life-Prolonging Anticancer Therapies in the 1L, 2L, and 3L Settings

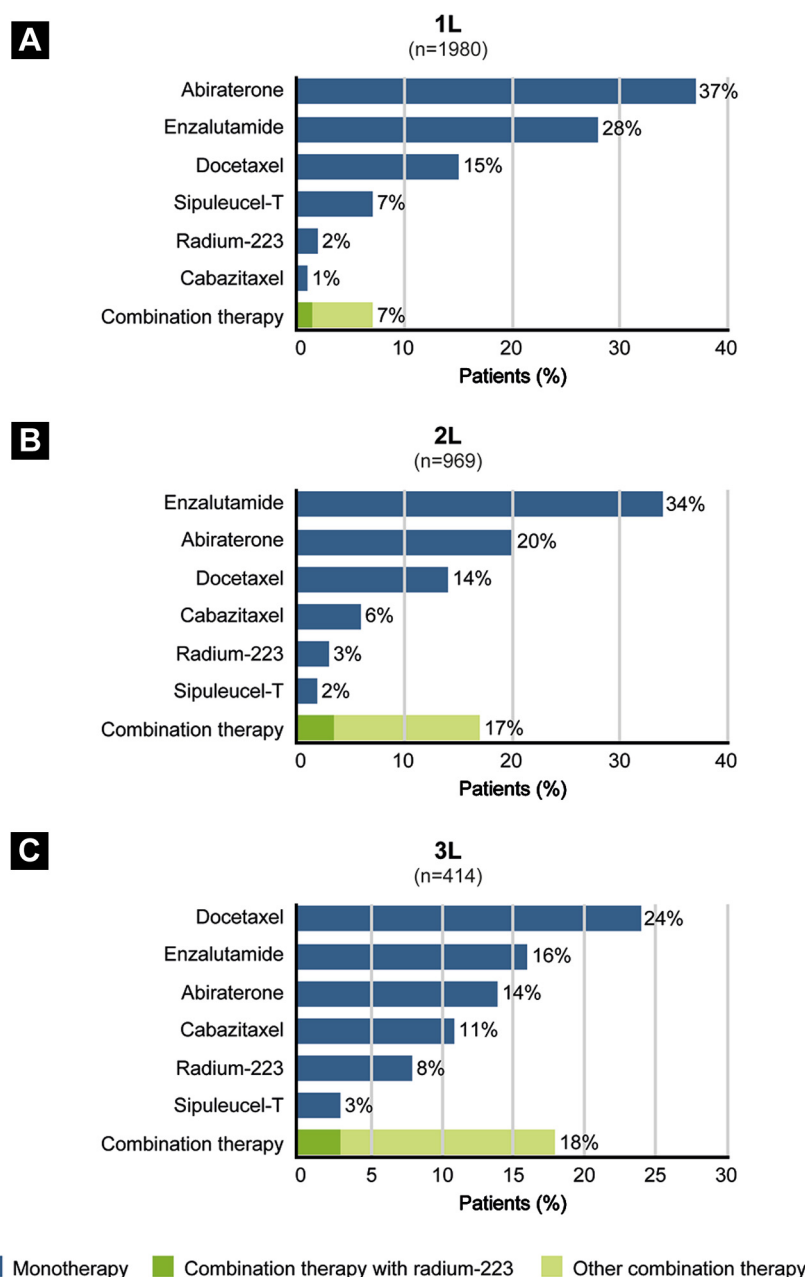
A total of 23%, 28%, and 29% of patients did not receive a subsequent line of therapy after 1L, 2L, and 3L therapy, respectively. In this Sankey diagram, a node to the right illustrates patients with mCRPC (gray) transitioning to a subsequent line of therapy (pink) or death without receiving a subsequent line (blue). Abbreviations: 1L = first line; 2L = second line; 3L = third line; mCRPC = metastatic castration-resistant prostate cancer.

patients received one or more BHAs (denosumab, 43%; zoledronic acid, 21%). The median duration of treatment for each agent by line of therapy is shown in Table 2.

Treatment patterns are shown in Figure 4A. Patients who received abiraterone/prednisone or enzalutamide as first-line therapy were most likely to switch to enzalutamide or abiraterone/prednisone, respectively, if treated in the second-line setting. Patients who received first-line docetaxel (15% of all patients) were most likely to receive enzalutamide (20% of patients) in the second-line setting, whereas cabazitaxel was given to 13% of patients in this setting (Figure 4B). Patients who received second-line abiraterone/prednisone were most likely to receive enzalutamide (15% of patients) if treated in the third-line setting, and patients treated with second-line enzalutamide most frequently received docetaxel (17%) if treated in the third-line setting. Patients who received second-line docetaxel were most likely to receive cabazitaxel (17%) if treated with a third-line therapy (Figure 4C).

The percentage of patients treated with radium-223 monotherapy increased over subsequent lines of therapy, from 2% in the first-line setting to 3% and 8% in the second- and third-line settings, respectively. The use of radium-223 as part of combination therapy also increased in the second and third lines of treatment (Figure 3). The most frequently prescribed therapies after radium-223 were second-generation androgen receptor axis-targeted therapies, received by 34% and 19% of patients in the second- and third-line settings, respectively. Similar proportions of patients received radium-223 subsequent to taxanes (3% and 4% in the second- and third-line settings, respectively) and second-generation androgen receptor axis-targeted therapies (2% and 4% in the second- and third-line settings, respectively).

More than one-half (51%) of patients received no subsequent mCRPC-targeted therapy after their first-line treatment, and 47% of patients who had a second line of therapy had no third-line treatment during the study period. Of patients who received first-

Figure 3 Patients With Metastatic Castration-resistant Prostate Cancer Receiving Various Life-Prolonging Therapies in the 1L (A), 2L (B), and 3L (C) Settings

Abbreviations: 1L = first line; 2L = second line; 3L = third line.

second-, and third-line therapies, 23%, 28%, and 29%, respectively, died without receiving a subsequent line of therapy (Figure 2). The arithmetic median time from the end of last therapy to death was < 2 months.

Overall Survival

The mean ($\pm$ standard deviation) time from index date (date of mCRPC diagnosis) to the end of the follow-up period for these 2559 patients was 14.6 ± 11.7 months. The median OS from index

date for patients with mCRPC was 21.2 months (95% confidence interval [CI]: 19.6-22.5 months) (Figure 5). The median OS was longer in patients who received life-prolonging therapies (23.7 months; 95% CI: 22.3-25.1 months) compared with those who did not (10.1 months; 95% CI: 9.1-11.5 months).

Discussion

The large sample size and wide geographic coverage within the US in the Flatiron Health database suggest that this is a

Table 2 Duration of Metastatic Castration-resistant Prostate Cancer Treatment by Line of Therapy for 1L, 2L, and 3L Therapies

Treatment	Treatment Duration, months ^a					
	1L		2L		3L	
	n	Median (Min-Max)	n	Median (Min-Max)	n	Median (Min-Max)
Docetaxel	293	4.6 (0.03-28.9)	137	3.8 (0.03-37.2)	101	4.1 (0.03-20.8)
Abiraterone	742	5.4 (0.03-47.5)	193	4.8 (0.03-53.4)	59	4.2 (0.3-17.5)
Enzalutamide	552	5.8 (0.03-48.6)	326	5.4 (0.03-36.5)	68	4.0 (0.03-27.2)
Other combination	107	4.7 (0.27-28.6)	112	4.3 (0.03-24.0)	51	4.9 (0.03-28.4)
Sipuleucel-T	140	3.5 (0.03-51.4)	16	2.5 (0.03-6.8)	14	2.8 (0.03-13.2)
Cabazitaxel	22	2.2 (0.03-6.3)	61	2.6 (0.03-26.3)	46	3.1 (0.03-24.5)
Radium overall	94	6.0 (0.03-34.4)	85	5.0 (0.03-22.7)	56	4.4 (0.03-13.1)
Radium-223	47	4.7 (0.03-16.1)	32	4.9 (0.03-13.3)	33	5.1 (0.03-11.0)
Radium combination	47	7.3 (0.7-34.4)	53	5.2 (0.4-22.7)	23	4.1 (0.8-13.1)
Other	30	1.9 (0.03-18.4)	39	1.9 (0.03-22.9)	19	1.7 (0.4-12.9)

Abbreviations: 1L = first line; 2L = second line; 3L = third line.

^aIn cases in which patients were treated with combination therapy, the duration of therapy was defined as the period between the first and last administration of any agent(s) in the combination.

representative sample of US practice patterns. As such, these data provide real-world insights into the treatment patterns and outcomes in patients with mCRPC in the US, and demonstrates the utility of information captured in such databases. This real-world study in a predominantly community-based setting showed that among the 77% of patients who received a life-prolonging therapy in the mCRPC setting, approximately one-half received a subsequent life-prolonging therapy during the study period. Abiraterone/prednisone, enzalutamide, and docetaxel were the most frequently prescribed life-prolonging therapies in the first-, second-, and third-line settings, respectively. Combination therapies administered to 7%, 17%, and 18% of patients in the first-, second- and third-line settings, respectively, reveal that most patients are treated with sequential monotherapy, following national treatment guidelines and prescribing information. However, the common practice of back-to-back use of abiraterone/prednisone and enzalutamide represents a deviation from these guidelines, given the lack of prospective phase III randomized clinical trials of this approach, and in spite of reported cross-resistance and limited clinical benefit with short duration of response.²³⁻²⁵ Overall, 60% of patients with mCRPC received BHAs, which may represent a modest underutilization in a patient population expected to harbor bone metastases in more than 80% of patients.²⁶ Contraindications may exist to limit the use of these agents in some patients, especially given the relatively lower OS observed. Life-prolonging therapies that may have been administered to patients for de novo metastatic hormone-sensitive disease were not considered in this analysis.

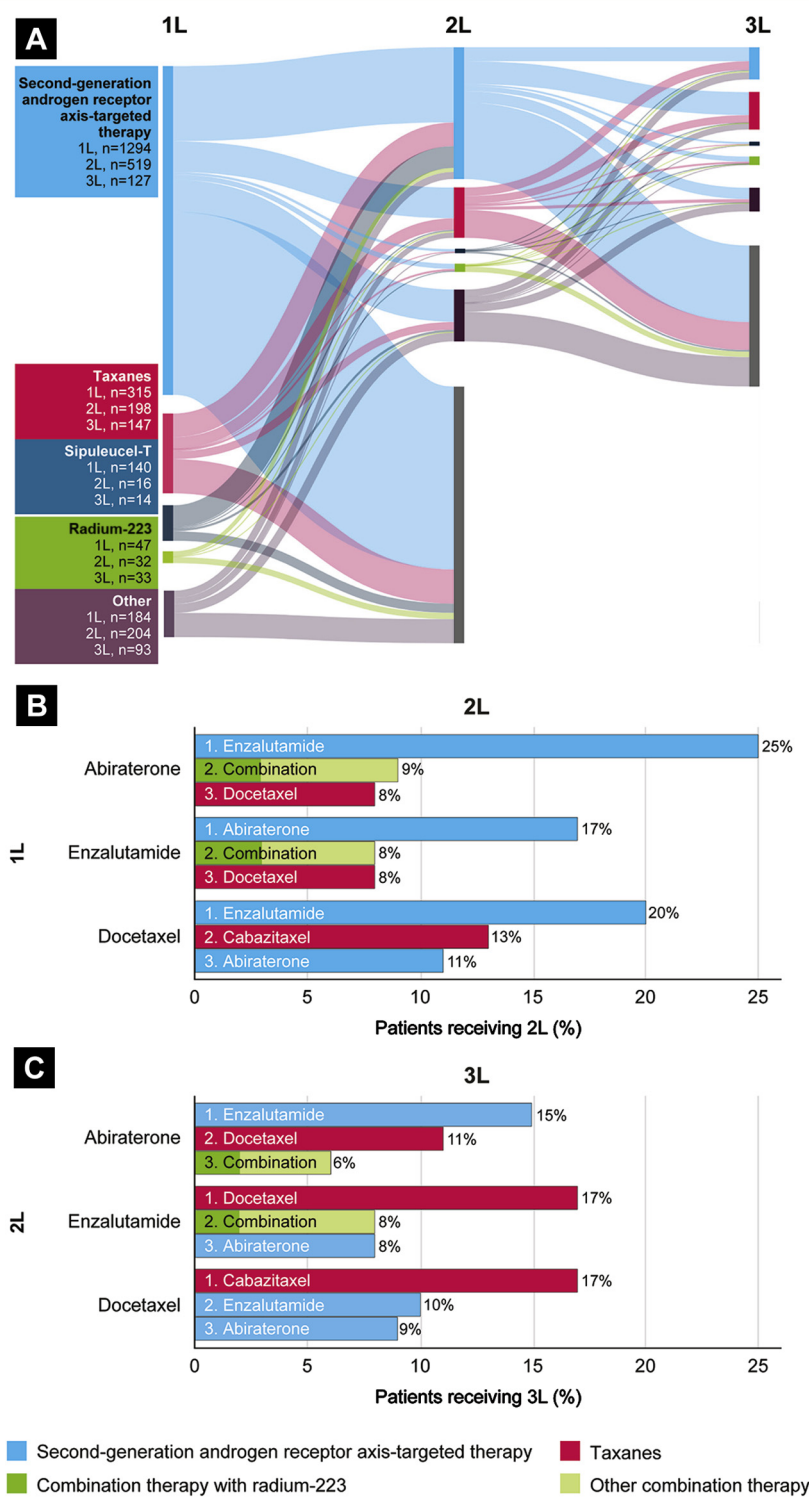
In addition to investigating second-generation androgen receptor axis-targeted therapy, immunotherapy, and chemotherapy treatment patterns, this study examined radium-223 use, which was the latest agent approved by the FDA that provides an OS benefit in patients with mCRPC and symptomatic bone metastases. A similar proportion (~2%-4%) of patients received radium-223 (either as monotherapy or in combination) subsequent to taxanes or second-generation androgen receptor axis-targeted therapy, and second-generation androgen

receptor axis-targeted therapy was the most commonly prescribed therapy following first- or second-line radium-223. Radium-223 was prescribed as both monotherapy and combination therapy, and prescription of both monotherapy and combination therapy increased in the second- and third-line settings. Combination therapies as a whole were more common in the second- and third-line settings. However, overall, radium-223 was likely underutilized in this cohort.

The National Comprehensive Cancer Network (NCCN) prostate cancer guideline recommendations for first-line systemic therapy include abiraterone/prednisone, enzalutamide, docetaxel, sipuleucel-T, and radium-223. Second-line options depend on whether the patient received prior second-generation androgen receptor axis-targeted therapy or docetaxel.²⁷ In the present study, the most common first-line treatment prescribed for patients with mCRPC was abiraterone/prednisone, followed by enzalutamide in the second line and docetaxel in the third line. As noted earlier, current evidence suggests that there is limited benefit to the back-to-back use of second-generation androgen receptor axis-targeted therapies in patients who progress on one agent, and this information may not have been widely known until recently,^{23,24} although this practice is in line with the NCCN prostate cancer guidelines.²⁷ The use of radium-223 in this study was also consistent with published guidelines.^{27,28} The finding that only one-half of patients who received first-line therapy subsequently received second-line therapy during the study period could be owing to several factors, such as a short follow-up period, patients being too ill to receive second-line therapy, or patient refusal of therapy. It is also possible that patients received care outside the network included in the Flatiron Health database or may have received additional treatments after the analysis cutoff date. Moreover, approximately one-quarter of patients who received first-, second-, and third-line therapies died without receiving a subsequent line of therapy.

In this real-world study, the OS for patients was < 2 years from diagnosis of mCRPC, and patients who did not receive life-prolonging therapies during that time had shorter survival

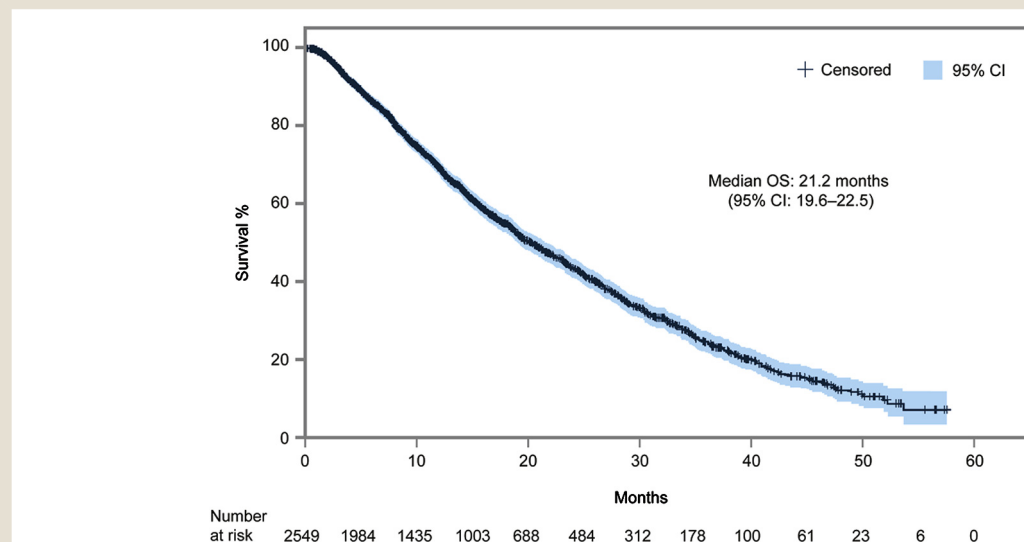
Figure 4 Treatment Patterns in All Patients With mCRPC (A), and in Those Receiving Abiraterone/Prednisone, Enzalutamide, and Docetaxel as 1L (B) and 2L (C) Therapies



In this Sankey diagram (panel A), a node to the right illustrates the transition from the current line to a subsequent line of therapy among patients with mCRPC. 'Second-generation androgen receptor axis-targeted therapy' includes abiraterone and enzalutamide; 'taxanes' include docetaxel and cabazitaxel; 'other' includes combination therapy and other therapies. The gray bar represents patients who did not receive a subsequent line of therapy due to deaths or other reasons.

Abbreviations: 1L = first line; 2L = second line; 3L = third line; mCRPC = metastatic castration-resistant prostate cancer.

Figure 5 Overall Survival (OS) of Patients With mCRPC. OS Was Determined as Time From Index Diagnosis Date of mCRPC. Note that the Effects of Administration of Life-Prolonging Therapies During the Hormone-sensitive Stage (ie, Prior to the Index Date of Diagnosis of mCRPC) are Not Captured in this Analysis. Ten Subjects Were Excluded From Survival Analysis owing to Invalid Survival Data



Abbreviations: CI = confidence interval; mCRPC = metastatic castration-resistant prostate cancer.

compared with those who did. The reason why some patients did not receive life-prolonging therapies is not known from this study, but they may have had poorer Eastern Cooperative Oncology Group performance status or there may have been other medical or non-medical reasons. The relatively short time from last treatment to death (median, < 2 months) would support this conclusion. Similar proportions of patients at each line of therapy died without receiving subsequent therapy (23%, 28%, and 29% after first-, second-, and third-line treatment, respectively).

This real-world OS finding (< 2 years) was lower than the OS reported in chemotherapy-naïve patients in phase III studies of abiraterone/prednisone (34.7 months) and enzalutamide (32.4 months).^{4,9} One reason for this may be that pivotal phase III trials often have strict patient selection criteria, including the selection of patients with a good performance status; adequate hematologic, renal, and liver function; the absence of severe comorbidities^{2-8,26,29}; and the absence of visceral disease or lymphadenopathy of > 3 cm.² In addition, the majority of patients in the Flatiron Health database were treated in a community setting, where patient characteristics and physician practice patterns may differ from those at subspecialty academic centers. Consequently, in the current study, not all patients received a life-prolonging therapy. Moreover, follow-up times vary at the patient level in real-world studies. Some of these factors may also account for the relatively short duration of each line of therapy (typically 4-6 months) in the real-world setting, and for the short time from the end of the last therapy to death (< 2 months). Finally, up to an estimated 10% of patients in this analysis may have received life-prolonging therapies

for de novo metastatic hormone-sensitive disease (ie, prior to the index date of diagnosis of mCRPC), but these data are not captured in this analysis.

This study was not designed to capture longitudinal changes in treatment patterns or health outcomes over time. As such, the study results are limited to the selected observational period in the dataset. However, the database was able to capture the use of different regimens in the metastatic prostate cancer and metastatic hormone-sensitive prostate cancer settings; these will be reported separately. In addition, this was a descriptive study only. A limitation of the Flatiron Health database was that the number of patients selected may have been reduced owing to the stipulation that they must have had 2 prostate cancer visits before being included in the analysis. A further limitation is that the selection criteria did not specify castration levels of testosterone, although this reflects the real-world nature of the study. Another important potential limitation is that the Flatiron Health network does not include urology practices; some patients may have received treatment for mCRPC at a urology practice, which may not have been captured in the database.

Conclusion

The current analysis provides real-world insights on over 2500 patients with mCRPC, demonstrating an underutilization of life-prolonging treatment options. These data may help to inform future clinical trial designs, highlight the need for better adherence to treatment guidelines, and inform clinical decision-making.^{15,16} Further studies of other patient cohorts and outcomes (eg, symptomatic skeletal events) can also be extracted from the

database and will provide valuable additional insights into real-world patient outcomes to help inform and improve clinical decision-making.

Clinical Practice Points

- RWD on the use, effect on survival, and safety of mCRPC therapies are limited.
- The Flatiron Health database contains real-world EHR data from more than 2 million US patients with cancer.
- Of over 2500 patients with mCRPC, three-quarters received at least 1 line of therapy.
- Of patients receiving first-line therapy, 49% received a second line of therapy, and of these, 43% received a third line of therapy.
- Abiraterone/prednisone and enzalutamide were common first- and second-line therapies, frequently used back-to-back.
- The percentage of patients treated with radium-223 monotherapy or in combination increased over subsequent lines of therapy.
- These real-world data may inform clinical trial designs, treatment guidelines, and regulatory health care decisions.

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