Adv Ther (2022) 39:2515–2532
https://doi.org/10.1007/s12325-022-02085-6

ORIGINAL RESEARCH

Real-World Effectiveness of Sipuleucel-T on Overall Survival in Men with Advanced Prostate Cancer Treated with Androgen Receptor-Targeting Agents

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Received: December 31, 2021 / Accepted: February 10, 2022 / Published online: March 30, 2022

ABSTRACT

Introduction: The treatment landscape for metastatic castration-resistant prostate cancer (mCRPC) continues to evolve. Sipuleucel-T was the first immunotherapy approved by the US Food and Drug Administration (FDA) to treat asymptomatic or minimally symptomatic mCRPC. The androgen receptor-targeting agents (ARTAs) abiraterone acetate and enzalutamide were initially approved to treat mCRPC. Looking at chemotherapy-naïve men with mCRPC, we compared survival outcomes between the sipuleucel-T + ARTA cohort (men who received either sipuleucel-T or an ARTA in the first line, and then the other in the second line within 6 months) and the ARTA monotherapy cohort (men who only received ARTA monotherapy).

Methods: This retrospective cohort analysis used longitudinal, adjudicated claims data from the US Medicare Fee-for-Service 100% research identifiable dataset that includes both urologic and oncologic practice settings. Eligible men started their first mCRPC treatment with either sipuleucel-T or ARTA in either 2014 or 2015 and had continuous Medicare Parts A, B, and D eligibility for the subsequent 3 years. A multivariable Cox proportional hazards regression model was used to analyze overall survival (OS), both overall and by index year, and to control for differences.

Results: The sipuleucel-T + ARTA and ARTA monotherapy cohorts comprised 773 and 4642 men, respectively, with different characteristics at treatment start. The most commonly used ARTAs were enzalutamide in the former and abiraterone in the latter cohort. Median OS was 30.4 and 14.3 months in the sipuleucel-T + ARTA and ARTA monotherapy cohorts, respectively, with the sipuleucel-T + ARTA cohort having a 28.3% lower risk of death than the ARTA monotherapy cohort (hazard ratio 0.717; 95% CI 0.648, 0.793; $p < 0.01$).

Conclusions: This real-world study of mCRPC treatment indicates that men receiving sipuleucel-T and ARTAs had a longer median OS than patients receiving treatment with an ARTA

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-022-02085-6.

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alone, suggesting that leveraging mechanisms of action can be beneficial in treating patients with mCRPC.

PLAIN LANGUAGE SUMMARY

The treatment landscape for metastatic castration-resistant prostate cancer (mCRPC) continues to evolve. There are multiple treatments for mCRPC, including sipuleucel-T, the first US Food and Drug Administration (FDA)-approved immunotherapy, and the androgen receptor-targeting agents (ARTAs) abiraterone acetate and enzalutamide. Although sipuleucel-T uses a unique mechanism of action that may be useful in developing a treatment strategy for mCRPC, an optimal treatment algorithm for prostate cancer remains undefined. Therefore, survival was compared in men with mCRPC who received sipuleucel-T and an ARTA in the first 6 months of treatment with those who received only ARTA monotherapy. A retrospective longitudinal study was conducted using the US Medicare Fee-for-Service 100% research identifiable dataset linked to the National Death Index. Eligible men started their first mCRPC treatment with either sipuleucel-T or ARTA in either 2014 or 2015 and had continuous Medicare eligibility for the subsequent 3 years. Men who received treatment with both sipuleucel-T and an ARTA had a longer median survival (30.4 months) than men who received an ARTA without sipuleucel-T (14.3 months). This represents a 28% reduced risk of death with sipuleucel-T. This real-world study of mCRPC treatment indicates that men receiving sipuleucel T and an ARTA survive longer than men who only receive an ARTA, suggesting that changing the mechanism of action can be beneficial in treating patients with mCRPC.

Keywords: Immunotherapy; Observational; Prostate cancer; Real-world evidence; Sequencing; Treatment

Key Summary Points

Real-world evidence data, such as the Medicare Fee-for-Service 100% research identifiable dataset linked to the National Death Index, can provide insight into the outcomes of different treatments for metastatic castration-resistant prostate cancer (mCRPC) because it includes data across both urologic and oncologic treatment settings.

There are multiple treatments for advanced prostate cancer, including sipuleucel-T, the first FDA-approved immunotherapy, and the androgen receptor-targeting agents (ARTAs) abiraterone acetate and enzalutamide.

We examined survival outcomes in men with mCRPC, comparing men who received sipuleucel-T and an ARTA, in either order, in the first 6 months of treatment with men who received only ARTA monotherapy (i.e., no sipuleucel-T).

Men who received treatment with both sipuleucel-T and an ARTA, in either order, exhibited a median overall survival of 30.4 months compared with men who received ARTA without sipuleucel-T (14.3 months). This represents a 28% reduced risk of death with sipuleucel-T (hazard ratio 0.717 [95% CI 0.648, 0.793]; $p < 0.01$) based on a multivariate Cox regression modeling analysis.

INTRODUCTION

Each year, prostate cancer represents approximately 26% of new cancer cases and approximately 11% of cancer-related deaths in men [1]. Metastatic castration-resistant prostate cancer (mCRPC), an advanced form of prostate cancer, is a universally lethal disease [2].

Diagnosis of prostate cancer may occur at any stage of disease; the treatment options available at any given stage are different given

the various levels of evidence available at each stage [3]. Further, these options continue to expand as agents leveraging different mechanisms of action become available. Yet, few studies have studied optimizing the algorithm for prostate cancer treatment, including which sequences and combinations are best or worst for balancing survival and tolerability. Several guidelines for the treatment of prostate cancer explore these questions through hypothesis or evidence examination [3, 4]. Two treatments with demonstrated effectiveness are sipuleucel-T (approved for asymptomatic or minimally symptomatic mCRPC) and androgen receptor-targeting agents (ARTAs) like enzalutamide and abiraterone acetate (approved for use across multiple stages of prostate cancer) as illustrated in McKay et al. [5].

Sipuleucel-T is an autologous antigen-presenting cell-based immunotherapy approved for use by the US Food and Drug Administration (FDA) in 2010 on the basis of its prolongation of overall survival (OS) in patients with asymptomatic or minimally symptomatic mCRPC [6, 7]. A single course of treatment with sipuleucel-T, typically lasting 4–6 weeks, mobilizes the immune system to target and destroy prostate cancer cells [8] with a potential for long-term effectiveness (evidence of effectiveness as long as a median of 8.9 years [9]). A median OS of 30.7 months from the date of the first sipuleucel-T infusion was demonstrated in the PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data (PROCEED), a large registry of men with mCRPC who received sipuleucel-T after FDA approval between 2011 and 2017 [10].

Androgen receptor pathway-targeting agents are also used to treat men with mCRPC. Abiraterone is a CYP17 inhibitor that interferes with the production of testosterone to prevent prostate cancer cell growth. Enzalutamide is a next-generation androgen receptor (AR) inhibitor that prevents testosterone from binding to the androgen receptor in addition to having other cellular inhibitory mechanisms. Sometimes referred to as ARTAs or androgen receptor signaling pathway inhibitors, these orally administered agents are approved for use in multiple prostate cancer states by the FDA, with initial approvals in the post-docetaxel setting and then in the chemotherapy-naïve mCRPC setting [11–14]. Although ARTAs are the most frequently administered treatments for mCRPC, likely because of the ease of oral administration and availability, patients eventually exhibit disease progression [3]. ARTAs can have a high attendant cost because of the need for continued administration to achieve effect while increasing the likelihood for side effects [4].

An optimal treatment algorithm for prostate cancer remains undefined because studies evaluating the appropriate sequences and combinations have been limited. Although there are several guidelines for the treatment of prostate cancer [12, 14], there is a lack of randomized head-to-head clinical trials and real-world evidence to compare and contrast treatments. Various factors may be considered when choosing among treatment options, including patient characteristics, the potential for adverse events, mechanisms of action, costs, and patient preference [12, 13].

Several factors can be considered when deciding whether to use sipuleucel-T or an ARTA. Sipuleucel-T employs a unique mechanism of action that may be useful in developing a treatment strategy for mCRPC, but because it is immunotherapy, it requires a functional immune system. ARTAs do not appear to impact the immune system. Two studies provide evidence that the use of ARTAs, before or concomitantly with sipuleucel-T, did not impair the immune response generated by sipuleucel-T [15, 16]. The different mechanism of action also gives sipuleucel-T a different safety profile, with the most common adverse events being related to infusion reactions. Further, sipuleucel-T has a lower attendant cost than the ARTAs [4].

In the absence of clinical trials comparing these sipuleucel-T and ARTAs, real-world evidence can provide useful insight into clinical outcomes. We recently reported results from a retrospective observational analysis of adjudicated claims of Medicare beneficiaries who started de novo treatment for mCRPC in 2014 [5]. This analysis reported a median OS of 35.2 months for patients who received sipuleucel-T (first through fourth lines) vs 20.7 months for those who did not receive

sipuleucel-T but who did receive one or more ARTA, with an incremental survival benefit of 14.5 months with sipuleucel-T (adjusted hazard ratio [HR] 0.59 [95% CI 0.527–0.651]) [5]. That paper provided a broad view as to the nature of treatment sequencing in advanced prostate cancer.

The current study differs from the prior analysis in two ways. First, we added patients who started mCRPC treatment in 2015 to the analysis set, resulting in an analysis set that includes those who started mCRPC treatment in either 2014 or 2015 [5]. Second, the earlier study established the benefit of adding sipuleucel-T at any time over the course of the analysis period. In this analysis, we focused on specific treatment sequences to examine whether adding a mechanism of action early on in therapy has benefits compared with receipt of one type of therapy. Specifically, in this study, we compare OS between patients who received sipuleucel-T and an ARTA within 6 months of each other, some of whom received concomitant treatment and some concurrent, and those who received monotherapy with an ARTA (Fig. 1).

METHODS

The methodology used here is similar to that described elsewhere by McKay et al. [5].

Study Design

This retrospective observational claims study used the Medicare Fee-for-Service 100% research identifiable dataset that has patient-level linkage to the National Death Index and spans both urologic and oncologic practice settings where prostate cancer may be treated in US eligible men who started their first mCRPC treatment with either sipuleucel-T or ARTA in either 2014 or 2015. Eligible men had to have a known outcome in the next 36 months (Fig. 2). Men were analyzed on the basis of the treatments that they received.

Data Sources

The longitudinal Medicare dataset contains deidentified information on patient demographics and claims data (dates of service, diagnosis codes [International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM, respectively)] as well as procedure codes [current procedural terminology codes]) from hospitals and other institutional and noninstitutional providers. To protect patient privacy, outputs reflecting between 1 and 11 beneficiaries (inclusive) were censored from the outputs delivered by the Centers for Medicare & Medicaid Services.

This data was linked at a patient level to the National Death Index, a central computerized index of death record information collected from state vital statistics offices across the USA [17]. It contains dates and causes of death as reported on death certificates.

Dendreon Pharmaceuticals LLC (Seal Beach, CA) and Milliman Inc. (New York, USA) had permission to access and perform analytics on these datasets; however, they never had possession of the patient-level data. This research is exempt from institutional review board approval.

Study Population

Eligible patients were identified by applying a sequential set of prespecified selection criteria (Fig. 3) to Medicare beneficiaries who participated in the index years. These criteria include codes found within the adjudicated claims data; a list is provided in Supplemental Table 1. Eligible male beneficiaries had to have been continuously enrolled in Medicare Parts A, B, and D, and claims data had to indicate a diagnosis of mCRPC. In addition, eligible patients had to have received their first mCRPC treatment in one of the index years. Beneficiaries who died during the study period and thus lost their eligibility were included in the study to ensure that mortality rate bias was not introduced for beneficiaries who elected to enroll in a Medicare Advantage plan.

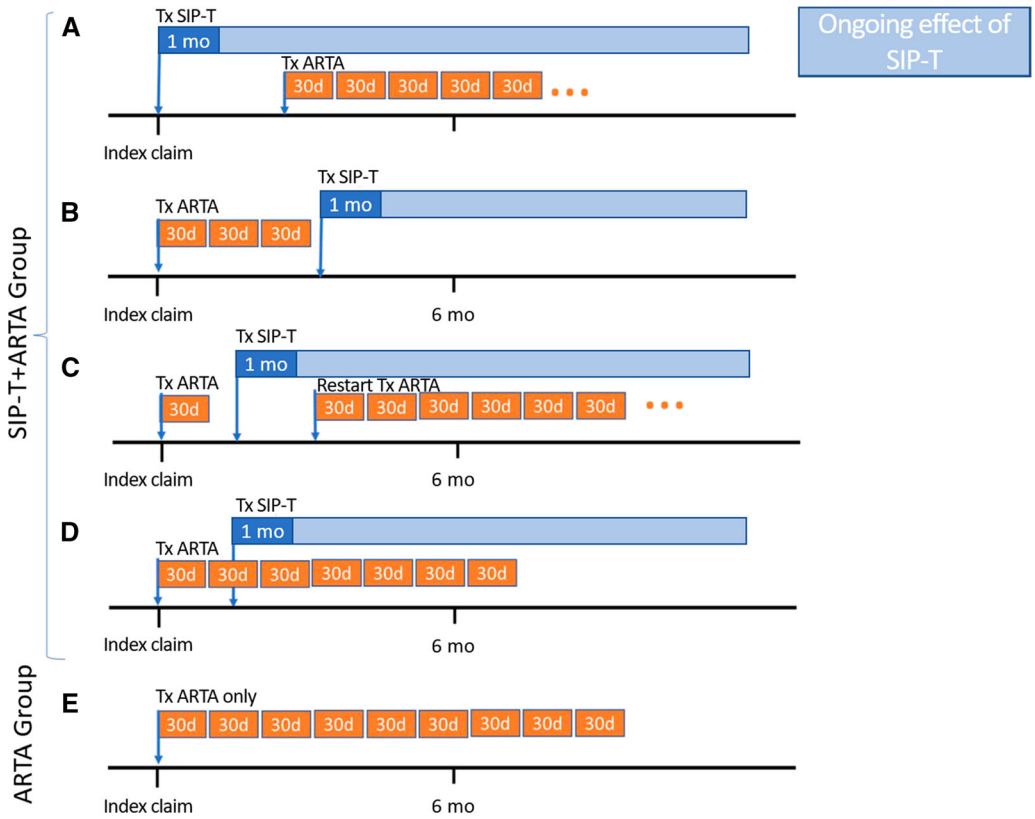


Fig. 1 Illustration of the analysis cohorts used in this study. The action of sipuleucel-T persists after the infusion is finished (light blue bars). The sipuleucel-T + androgen receptor-targeting agent (ARTA) cohort comprised patients who had one of these treatment patterns (**A–D**). **A** Initiation of ARTA therapy within 6 months of initiating sipuleucel-T as first-line therapy; sipuleucel-T treatment may be continuing or completed when patients initiate ARTA therapy. **B** Initiation of sipuleucel-T therapy within 6 months of initiating ARTA as first-line therapy; ARTA treatment completed for 90 days before initiating sipuleucel-T therapy. **C** Initiation of sipuleucel-T therapy within 6 months of initiating ARTA therapy; ARTA treatment completed for 30 days before initiation of sipuleucel-T therapy. Treatment with sipuleucel-T followed by reinitiation of ARTA therapy; sipuleucel-T treatment may be continuing or completed when patients initiate ARTA therapy. Most patients reinitiate therapy with the same ARTA (abiraterone or enzalutamide) as the initial ARTA. **D** Initiation of sipuleucel-T within 6 months of initiating ARTA therapy; ARTA treatment completed for at least 30 days before initiation of sipuleucel-T therapy. **E** ARTA group comprised patients who initiated ARTA therapy and continued to receive ARTA treatment throughout the study period

Patients were excluded if they had a claim for an mCRPC treatment in the previous 12 months; this time frame was chosen based on the typical disease course (Fig. 3). Patients who were enrolled in a Medicare Advantage plan were also excluded because these plans provide additional treatment options compared with the base plan and could introduce bias. Patients whose data indicated enrollment in Medicare's end-stage renal disease special needs program in the month of index therapy were also excluded because the nature of their treatment would introduce additional confounding factors.

Treatment Groups

The selection of treatment groups was based on observations of frequency of use in the Medicare dataset and the lack of head-to-head

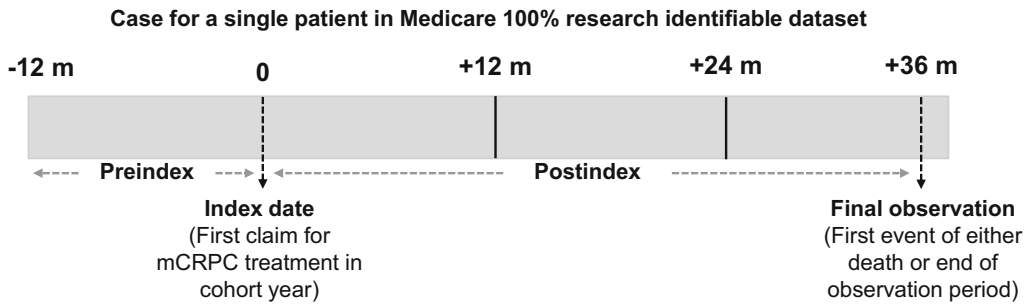


Fig. 2 Illustration of the study design. Patients with their first claim for an mCRPC treatment in either of the index years (2014 or 2015) were identified. They could not have received treatment for mCRPC in the previous 12 months (look back) and had to have a known outcome during the observation period of up to 36 months (look forward for either death or survival at 36 months). *mCRPC* metastatic castration-resistant prostate cancer

clinical trials between many agents in the prostate cancer space. Our previous study reported that among men who started treatment for mCRPC in 2014, 5878 patients received an ARTA in any line (43% of these received ARTA monotherapy) and 906 patients received sipuleucel-T in any line during the observation period [5]. Given the frequency of use of ARTA monotherapy, we used this as the comparison in the current study.

The patients with mCRPC were analyzed by cohort based on treatment received, sipuleucel-T + ARTA and ARTA monotherapy cohorts. The sipuleucel-T + ARTA cohort included men who received sipuleucel-T and an ARTA, in either order, in the first 6 months of treatment. The ARTA monotherapy cohort included men who received only ARTA monotherapy (i.e., no sipuleucel-T).

Study Variables

The primary outcome variable was OS, defined as the time from the index date to the date of death or the end of the observation period. The independent variable was treatment (i.e., sipuleucel-T + ARTA versus ARTA monotherapy). Covariates used in these analyses included sociodemographic variables and clinical factors, as described previously [17]. The list and descriptions of the covariates are provided in Supplemental Table 2.

Statistical Analyses

Fisher's exact test and *t* test statistics were generated to see if the observed differences in individual covariates were statistically meaningfully different between model cohorts. Survival was analyzed in two ways. First, Kaplan–Meier survival curves were generated on the basis of unadjusted analyses. Second, the multivariable Cox proportional hazards model from our previous study [5] was used to compare survival outcomes because many of the inherent assumptions about the patient populations were carried forward into this expanded population.

Stepwise regression was used to test for significant variables across the McKay model covariates in the current study. During this process, both time to second-line therapy and number of lines of therapy were determined to not be significant covariates. In other words, whatever effect these covariates might have on the outcome was being effectively controlled for by other covariates in the model. Therefore, these two factors were removed from the final model. The covariates included in the final multivariate model are described in Supplemental Table 2. Outcomes are reported for each index year and the two index years combined.

Model success was measured by the concordance (*C*) statistic; the closer the *C* value is to 1, the better the concordance. The *C* statistic was 0.7975. Direct adjusted survival functions were calculated and graphed for the models comparing treatments. A priori statistical

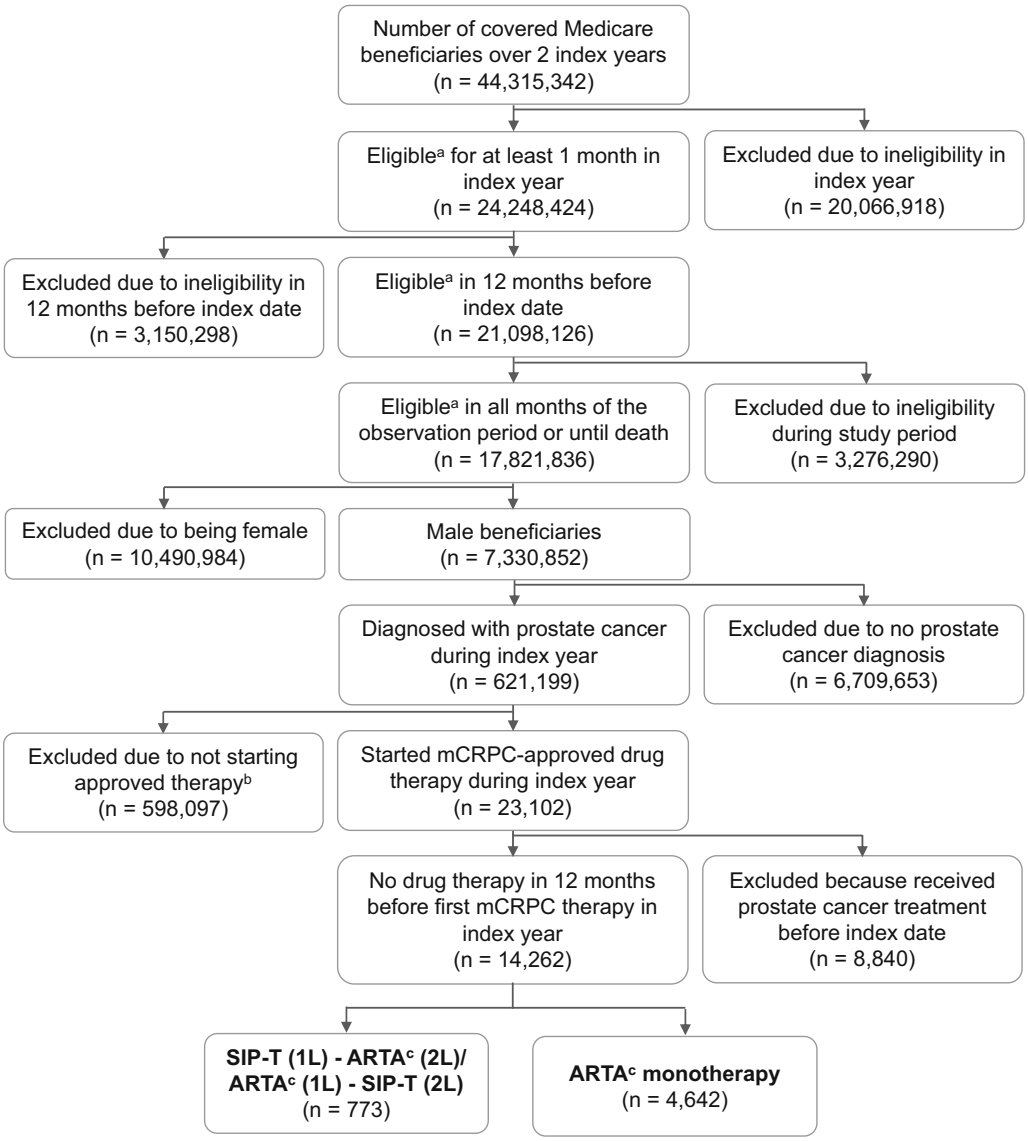


Fig. 3 Flowchart shows how eligible patients were identified in the Medicare Fee-for-Service 100% research identifiable dataset with the number of patients at each stage. To be eligible, patients had to have continuous Medicare Part A, B, and D eligibility and could not be enrolled in a health maintenance organization. Patients could have received androgen-deprivation treatment. [a]Eligibility requirements were having continuous Part A, B, and D eligibility and no health maintenance organization (HMO) enrollment; [b]Patients could have received androgen deprivation treatment; [c]ARTA treatments include abiraterone acetate or enzalutamide. *mCRPC* metastatic castration-resistant prostate cancer

significance in this study was set at $p < 0.05$. All reported p values are two-sided. No adjustments for multiple testing were made because it was determined that the benefits of such an adjustment did not outweigh the cost to the power of the study. Analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Figure 3 illustrates how we identified the 5415 patients who met our base eligibility criteria across both index years, including 773 men in the sipuleucel-T + ARTA cohort and 4642 men in the ARTA monotherapy cohort. Inclusion

Table 1 Baseline characteristics by treatment cohort for Medicare patients with metastatic castration-resistant prostate cancer

Characteristic	Sipuleucel-T + ARTA (n = 773)[a]	ARTA monotherapy (n = 4642)[a]	p value
1L, n (%)			< 0.01
Abiraterone	72 (9.3%)	2619 (56.4%)	
Enzalutamide	104 (13.5%)	2023 (43.6%)	
Sipuleucel-T	597 (77.2%)	0 (0.0%)	
2L, n (%)			< 0.01
Abiraterone	290 (37.5%)	0 (0.0%)	
Enzalutamide	307 (39.7%)	0 (0.0%)	
Sipuleucel-T	176 (22.8%)	0 (0.0%)	
Age distribution, n (%)			
Average age, years	75.9	80.2	< 0.01
Median age, years	75.0	81.0	
< 65	12 (1.6%)	90 (1.9%)	< 0.01
65–69	114 (14.7%)	345 (7.4%)	
70–74	229 (29.6%)	717 (15.4%)	
75–79	195 (25.2%)	930 (20.0%)	
80–84	141 (18.2%)	1066 (23.0%)	
85–89	68 (8.8%)	968 (20.9%)	
90+	14 (1.8%)	526 (11.3%)	
Dual/nondual, n (%)[b]			
Dual	62 (8.0%)	813 (17.5%)	< 0.01
Nondual	711 (92.0%)	3829 (82.5%)	
Race, n (%)			
Black	66 (8.5%)	549 (11.8%)	< 0.01
White	683 (88.4%)	3864 (83.2%)	
Other	24 (3.1%)	229 (4.9%)	
Urban/rural, n (%)			
Urban	604 (78.1%)	3321 (71.5%)	< 0.01
Rural	169 (21.9%)	1321 (28.5%)	
mCRPC lines of therapy, n (%)			
Average no. of lines	3.3	1.0	< 0.01
Median no. of lines	3.0	1.0	

Table 1 continued

Characteristic	Sipuleucel-T + ARTA (n = 773)[a]	ARTA monotherapy (n = 4642)[a]	p value
One	0 (0.0%)	4642 (100.0%)	< 0.01
Two	236 (30.5%)	0 (0.0%)	
Three	237 (30.7%)	0 (0.0%)	
Four	170 (22.0%)	0 (0.0%)	
Five	108 (14.0%)	0 (0.0%)	
Six	22 (2.8%)	0 (0.0%)	
Time to mCRPC second-line therapy (months)			
Average	2.8	0.0	< 0.01
25th percentile	1.6	0.0	
50th percentile	2.8	0.0	
75th percentile	4.1	0.0	
Corticosteroid use within 6 months after index date (patients with abiraterone steroid use not counted)			
< 0.2	764 (98.8%)	4460 (96.1%)	< 0.01
0.2–0.4	–	47 (1.0%)	
0.4–0.6	–	39 (0.8%)	
0.6–0.8	–	18 (0.4%)	
> 0.8	–	78 (1.7%)	
Charlson Comorbidity Index[c]			
0–3	203 (26.3%)	1261 (27.2%)	< 0.01
4–7	85 (11.0%)	684 (14.7%)	
8–11	414 (53.6%)	1940 (41.8%)	
12–15	66 (8.5%)	654 (14.1%)	
16–19	–	98 (2.1%)	
20–24	0 (0.0%)	–	
Opioid use around index date[d]			
Chronic use	71 (9.2%)	862 (18.6%)	< 0.01
No chronic use	702 (90.8%)	3780 (81.4%)	
Multiple metastases[e,f]			
Multiple (yes or no)	140 (18.1%)	1003 (21.6%)	0.03
Skeletal-related events around index date			
Radiation therapy[g]	48 (6.2%)	571 (12.3%)	< 0.01
Bone fracture[h]	28 (3.6%)	385 (8.3%)	< 0.01

Table 1 continued

Characteristic	Sipuleucel-T + ARTA (n = 773)[a]	ARTA monotherapy (n = 4642)[a]	p value
Spinal cord compression[h]	58 (7.5%)	333 (7.2%)	0.71
Bone surgery[h,i]	–	85 (1.8%)	0.20
Any	121 (15.7%)	1054 (22.7%)	< 0.01
Corticosteroid proportion of days covered[h] within 6 months after index date (excluding use in patients with abiraterone-related steroid use)			
< 0.2	766 (99.1%)	4550 (98.0%)	0.04
0.2–0.4	–	92 (2.0%)	
Regression "drops"			
ESRD	–	96	
Unknown race	–	23	
Unknown urban/rural designation	0	–	
Unique patients to be excluded from regression development because of missing variables[j]	–	122	

ARTA androgen receptor-targeting agent, *ESRD* end-stage renal disease, *1L* first-line, *2L* second-line, *mCRPC* metastatic castration-resistant prostate cancer

[a]"–" indicates that numbers are masked because of suppression requirements for showing cohorts with fewer than 11 beneficiaries by Centers for Medicare & Medicaid Services

[b]Nondual refers to Medicare eligibility only. Dual refers to both Medicare and Medicaid eligibility

[c]Charlson Comorbidity Index assigned on the basis of claims in the year before the index date. A score of 0 indicates that no comorbidities were found; the level of comorbidity is indicated by higher scores, and the maximum score possible is 33

[d]Chronic opioid use is defined as two or more prescription claims within 30 days, both claims identified within 60 days before and 60 days after the index date

[e]One or more claims in the year before the index date for each main body region: lung, visceral, bone, lymph nodes, liver, and other

[f]Multiple metastasis counts include all patients who reported metastases in at least two of the sites of interest

[g]One or more claims in the 60 days before and 60 days after the index date

[h]One or more claims in the 90 days before and 90 days after the index date

[i]Excludes evidence of high impact fractures

[j]Patients with unknown values for race, dual/nondual status, or urban/rural designation will be excluded from the regression development process

and exclusion criteria are provided for eligible patients by index year (2014 and 2015) in Supplemental Table 3.

Patient Characteristics

Table 1 presents baseline patient characteristics for the treatment cohorts, most of which were used as covariates in the Cox proportional

hazards model. Most were significantly different.

Treatments

In the sipuleucel-T + ARTA cohort, enzalutamide was the most frequently used ARTA in either first-line (13.5%) or second-line (39.7%) treatment, whereas in the ARTA monotherapy cohort, abiraterone (56.4%) was the most frequently used ARTA.

Most men who reinitiated ARTA (Fig. 1c) received the same ARTA that they received as first-line therapy, and a few switched to the other ARTA. Ninety-eight of the 106 (93%) men who received abiraterone after sipuleucel-T and 140 of 165 (85%) men who received enzalutamide after sipuleucel-T received the same agent as first-line therapy. These results suggest that some patients received sipuleucel-T during a planned course of ARTA, either concomitantly or during a break in ARTA treatment.

Only men in the sipuleucel-T + ARTA cohort received more than one line of therapy. Of these, 31% received only the two lines of therapy and 69% received three or more lines of treatment (Table 1).

Survival Analysis

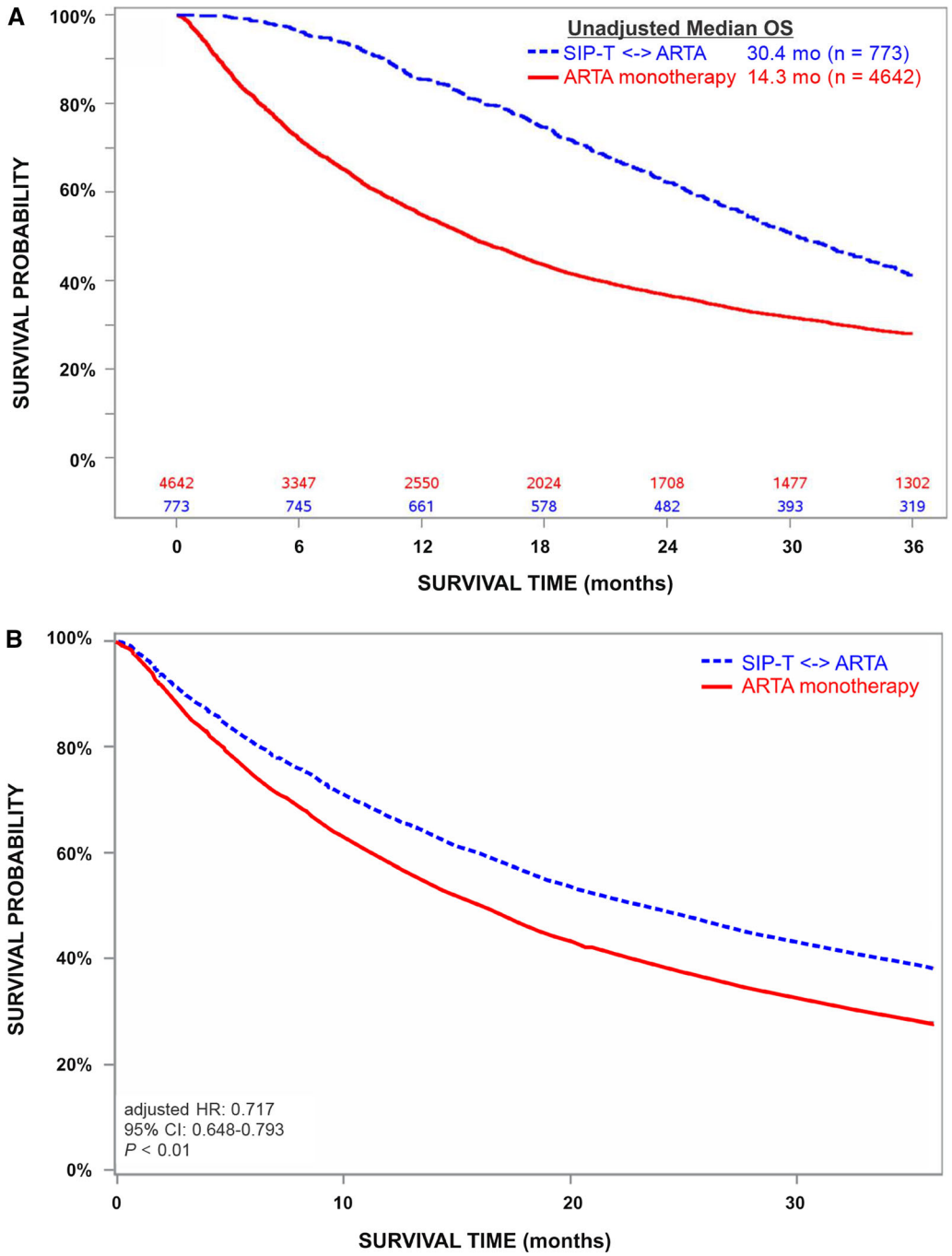
Survival outcomes with the sipuleucel-T + ARTA and ARTA monotherapy cohorts are presented in Fig. 4a and Supplemental Table 4 for the unadjusted Kaplan-Meier analyses and in Fig. 4b for the multivariate Cox proportional hazards model analyses. Among the covariates included in the multivariate model, all were significant at the $p < 0.05$ level (Fig. 5).

Across the two index years combined, the survival benefit with sipuleucel-T + ARTA was 16.1 months. Similarly, the survival benefit with sipuleucel-T + ARTA was 14.8 and 17.3 months for the index years 2014 and 2015, respectively. Patients in the sipuleucel-T + ARTA cohort had a 28.3% lower risk of death than did the patients in the ARTA monotherapy cohort (HR 0.717 [95% CI 0.648, 0.793; $p <$ 0.01) (Fig. 5).

DISCUSSION

We studied beneficiaries included in the Medicare Fee-For-Service 100% research identifiable longitudinal claims dataset that is linked to the National Death Index for survival outcomes. In the current study, we compared two cohorts: one that received both sipuleucel-T and an ARTA in either order (sipuleucel-T + ARTA cohort) and one in which only ARTA monotherapy without sipuleucel-T (ARTA monotherapy cohort) was received (Fig. 1). Median OS was 30.4 months in men with mCRPC who received sipuleucel-T and an ARTA and 14.3 months in men who only got ARTA monotherapy, a 16.1-month difference. After adjustment for significant prognostic covariates, patients in the sipuleucel-T + ARTA cohort had improved survival benefits over those in the ARTA monotherapy cohort, with a 28% reduced risk of death at 36 months. These findings highlight the survival benefit of using sipuleucel-T and an ARTA. Given there is a possibility that men receiving sipuleucel-T as second-line therapy received it in combination with the first-line ARTA, we looked at the claims for mCRPC agents after sipuleucel-T. Most men received the same ARTA that they received as first-line therapy. A few switched to the other ARTA.

Multivariate analysis was used to assess the relative impact on outcomes between the sipuleucel-T + ARTA cohort and the ARTA monotherapy cohort. All assessed covariates were significant at the $p < 0.05$ level. This is not unexpected given most are based on prognostic indicators of worse disease (Table 2) [18]. The results shown here suggest that sipuleucel-T added to treatment with an ARTA, administered in sequence or in combination, exhibited incremental survival benefits, compared with ARTA monotherapy, in men with mCRPC who were eligible for Medicare or Medicaid. That said, real-world data such as these may reflect treatment bias because the choice of treatments for these patients reflects decisions made by the treating physician and patients were not randomly assigned. The clinical context in which


A
Unadjusted Median OS
SIP-T <-> ARTA 30.4 mo (n = 773)
ARTA monotherapy 14.3 mo (n = 4642)
SURVIVAL PROBABILITY
100%
80%
60%
40%
20%
0%
4642 3347 2550 2024 1708 1477 1302
773 745 661 578 482 393 319
0 6 12 18 24 30 36
SURVIVAL TIME (months)
B
SIP-T <-> ARTA
ARTA monotherapy
SURVIVAL PROBABILITY
100%
80%
60%
40%
20%
0%
adjusted HR: 0.717
95% CI: 0.648-0.793
P < 0.01
0 10 20 30
SURVIVAL TIME (months)

◀**Fig. 4** Impact of the use of sipuleucel-T (SIP-T) in combination with androgen receptor-targeting agent (ARTA) treatment on overall survival by analysis cohort. Median overall survival outcomes were calculated by analysis group. Patients either received sipuleucel-T in combination with ARTA treatment or ARTA only. Patients in the sipuleucel-T + ARTA combination cohort are indicated by a dashed blue line and those in the ARTA monotherapy cohort are indicated by a solid red line. **A** Graph of Kaplan–Meier estimates of overall survival. This graph illustrates the univariate analysis of overall survival as well as the numbers of patients at risk by treatment cohort and the estimates of unadjusted median overall survival by treatment cohort. **B** Graph of direct adjusted survivor functions. This graph illustrates the estimates of survival using a direct adjusted survivor function based on the Cox multivariable model. The respective estimates of adjusted median overall survival are also presented. *HR* hazard ratio

these decisions were made is missing from this dataset.

Findings from the current study, however, are consistent with the published literature for survival outcomes with sipuleucel-T among patients with advanced prostate cancer. Both clinical trials and observational studies have consistently demonstrated that sipuleucel-T can improve survival among patients with advanced prostate cancer [6, 10, 19]. The current study provides further insights into the use of sipuleucel-T that were first identified by McKay et al. [5]. With the increased size of the analysis population, the current study saw a similar pattern of results, with an incremental survival benefit in men who received sipuleucel-T in addition to ARTA treatment compared with an ARTA alone. Both the current and prior studies examined patient populations that started their treatment for mCRPC when the only treatment

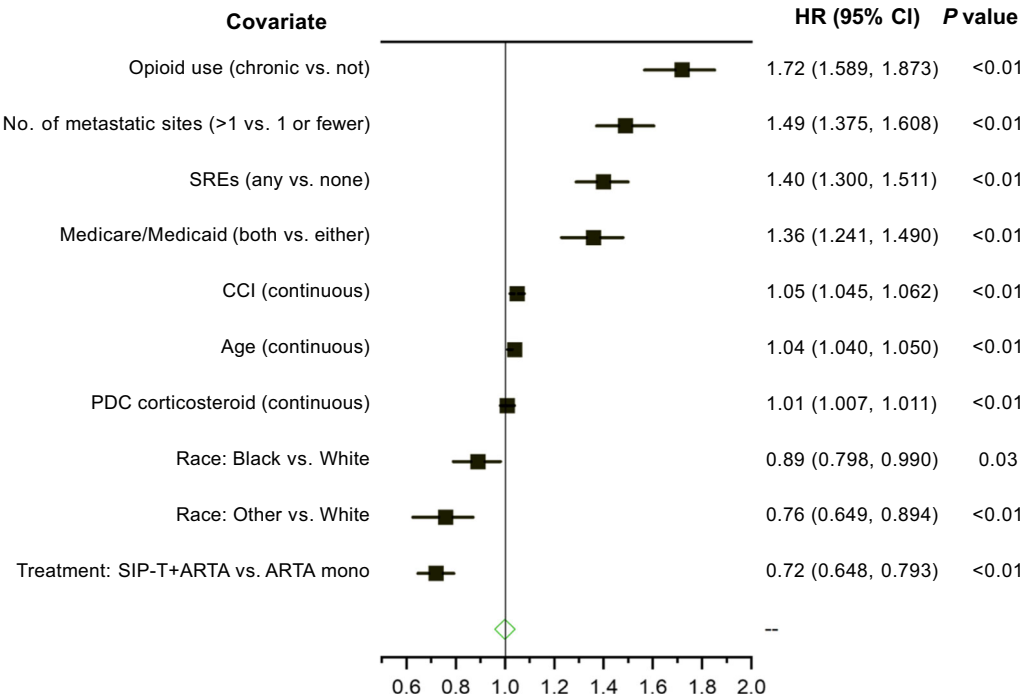


Fig. 5 Forest plot illustrating the impacts of the covariates used in the Cox proportional hazards model. The hazard ratios (HRs) and 95% confidence intervals (95% CIs) for each of the covariates used in the final model are presented here. See Table 1 for additional information on covariates. *ARTA* androgen receptor-targeting agent, *CCI* Charlson Comorbidity Index, *continuous* continuous variable, *mono* monotherapy, *PDC* proportion of days covered, *SIP-T* sipuleucel-T, *SREs* skeletal-related events

Table 2 Final multivariable model of overall survival in all patients by treatment cohort

Covariate	HR (95% CI)	*P* value
Treatment: sipuleucel-T + ARTA[a] vs ARTA monotherapy[b]	0.72 (0.648, 0.793)	< 0.01
Age: continuous variable	1.04 (1.040, 1.050)	< 0.01
Race: Black vs White	0.89 (0.798, 0.990)	0.03
Race: other vs White	0.76 (0.649, 0.894)	< 0.01
Medicare and Medicaid: both vs either	1.36 (1.241, 1.490)	< 0.01
Charlson Comorbidity Index[c]: continuous variable (0–8)	1.05 (1.045, 1.062)	< 0.01
Opioid use around index date[d]: chronic vs not chronic	1.72 (1.589, 1.873)	< 0.01
Number of metastatic sites: > 1 vs ≤ 1	1.49 (1.375, 1.608)	< 0.01
Skeletal-related events around index date: any vs none	1.4 (1.300, 1.511)	< 0.01
Corticosteroid proportion of days covered[e] within 6 months after index date[f]: continuous variable (calculated, 0–1)	1.01 (1.007, 1.011)	< 0.01

ARTA androgen receptor-targeting agent, *CI* confidence interval, *HR* hazard ratio

[a]Patients received sipuleucel-T followed by an ARTA or an ARTA followed by sipuleucel-T (Fig. 3). The switch occurred within 6 months of starting the first treatment

[b]Patients received ARTA monotherapy

[c]Charlson Comorbidity Index score was assigned on the basis of claims in the year before the index date. A score of 0 indicates that no comorbidities were found; worse comorbidities are indicated by higher scores, with a maximum possible score of 33

[d]Chronic opioid use is defined as two or more 30-day prescriptions within 60 days before or after the index date

[e]Proportion of days covered refers to the number of days of supply of corticosteroids divided by the difference in the number of days alive in the study and the number of days spent in an inpatient or skilled nursing facility care

[f]Excludes corticosteroid use concomitant with abiraterone

options for chemotherapy-naïve men with mCRPC were docetaxel, sipuleucel-T, and the ARTAs. ARTAs were approved for use in the postchemotherapy setting, but not yet for treatment in hormone-sensitive disease for this analysis set. The current study also looked more carefully at the nature of the first- and second-line treatments, observing that most patients who receive an ARTA as first-line therapy continue the same ARTA after sipuleucel-T has been administered. As immunotherapy stimulates the immune system to target prostate cancer cells, the benefits of sipuleucel-T persist beyond the period of its administration [8, 9].

Although prolongation of survival is still the primary intent of cancer treatment, it is important to consider multiple strategies when determining treatment options. One strategy aims to interrupt disease progression by using different cancer treatments and their different mechanisms of action, hopefully preventing the development of resistance in cancer cells and thereby theoretically prolonging patient survival. Currently, multiple agents are available for the treatment of prostate cancer, some of which are approved or have evidence of benefit in multiple prostate cancer settings. While the National Comprehensive Cancer Network has developed regularly updated evidence-based guidelines [3], the evidence is still maturing. Although ARTAs are approved for use across multiple treatment settings, including mCRPC as well as earlier settings such as metastatic hormone-sensitive prostate cancer, there is an increasing possibility that physicians may prescribe sequential courses of ARTAs despite

evidence suggesting poor outcomes with their use [20–24]. The use of ARTAs in earlier disease stages leads to an increased possibility of resistance developing, requiring new options for treatment to be considered. Given the nature of treatment resistance, changing the mechanism of action that is being leveraged in the treatment can be beneficial [25]. Real-world evidence, both in the current study and in the study by McKay et al., indicates that the use of sipuleucel-T and ARTAs in patients with advanced prostate cancer is more beneficial than treatment with either alone [5].

This study, which adds to the current literature on treatment patterns for advanced prostate cancer in real-world clinical practice, examined the impact of including sipuleucel-T as part of the treatment protocol. The scope and quality of the Medicare Fee-for-Service 100% research identifiable dataset, the large size of the study population, and the multivariate analysis with the Cox proportional hazards model provide a robust study population. Further, the consistency of our results with the results of previously published studies provides confidence in our analysis and results. The use of ARTA alone may have limited efficacy in patients with prostate cancer who had disease progression and is generally not recommended by clinical experts and RADAR II guidelines [26, 27]. Yet, it was a very common regimen used in this population (43% in McKay et al.) [5].

The current study provides important information that can be contextualized to clinical practice with further validation. This analysis also provides a framework for future studies on understanding the preferred treatment approach for mCRPC in other populations in a real-world setting. As additional years of data become available for research in the Medicare dataset, it would be helpful to expand on this research to develop a broader understanding of treatment approaches for prostate cancer as new agents and expanded use of ARTA are reflected in the dataset. Specifically, future work should begin to address issues that would help clarify whether agents should be considered specifically for certain stages of the disease and possibly in certain sequences and combinations to optimize their impact.

Limitations

This study has limitations. First, the Medicare dataset has limited clinical information and lacks information including factors known to be associated with survival, such as Eastern Cooperative Oncology Group performance status and laboratory test data (e.g., lactate dehydrogenase, albumin, hemoglobin, prostate-specific antigen, and alkaline phosphatase levels) [18]. As such, we could not control for these variables directly in the regression models and used surrogates based on claims codes. Our ability to extrapolate our findings to patient-level care decisions is limited. As such, this research is intended to inform physician decision-making. Second, there is the possibility of selection bias because the choice of treatments used in the patients in our study was influenced by physician- and patient-related factors not reflected in the data. We attempted to address this, at least in part, through the use of multivariate Cox proportional hazards modeling and the application of a common set of eligibility criteria. Third, the findings may not be generalizable to younger men because the Medicare dataset predominantly includes patients who are 65 years and older. Fourth, patient selection focused on identifying patients who matched both the approved indication for sipuleucel-T and the approved indications for ARTAs in 2014 and 2015, namely mCRPC. As such, the ARTA monotherapy population does not fully represent the population of patients who are treated with ARTAs in 2022. That said, this is still some of the most current observational data allowing examination of outcomes between different treatments. Therefore, the results should be considered with this context, as informative rather than prescriptive. Finally, there is a possibility that the patient eligibility criteria used to minimize the bias that might arise from excessive censoring may inadvertently lead to differential disqualification by race. Despite these limitations, the findings from this study add to the available literature by providing real-

world evidence on treatment patterns in patients with mCRPC.

CONCLUSIONS

Real-world evidence indicates that the use of sipuleucel-T and ARTAs in patients with advanced prostate cancer is more beneficial than treatment with an ARTA alone. This study adds to the body of evidence to inform more defined treatment protocols and supports the concept that considering changing mechanisms of action can be beneficial for treating patients with mCRPC.

ACKNOWLEDGEMENTS

Funding. Dendreon Pharmaceuticals LLC., funded the analyses by Milliman Inc, the medical writing assistance by Global Outcomes Group, and the journal's Rapid Service and Open Access fees.

Medical Writing and Other Assistance. The authors thank Steven Metz of Milliman Inc. for his biostatistical contribution, and they also thank Ishveen Chopra and Thomas Drake of the Global Outcomes Group for medical writing support.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All authors contributed to the study conception and design. Data analysis methodology was developed by Christine Ferro, Scott C Flanders, Matt Harmon, and Helen M Wilfehrt. Data analysis and investigation were performed by Helen M Wilfehrt and Christine Ferro. All stages of writing and visualization development were the responsibility of Helen Wilfehrt. All authors critically reviewed and edited the manuscript. All authors gave their permission for submission of the paper. Project administration was the responsibility of Helen M Wilfehrt with support by Christine Ferro. Funding acquisition and provision of resources were done by Helen M Wilfehrt and Scott C Flanders (as Dendreon Employee).

Disclosures. Jason M Hafron reports personal fees from Amgen Inc, Bayer, and Blue Earth Diagnostics; grants and personal fees from Dendreon Pharmaceuticals LLC, Janssen Biotech Inc, Myriad Genetics Inc, Pfizer Inc, Astellas Pharma Inc, and Merck & Co. Inc.; and grants from Nucleix and Cellay Inc. outside the submitted work. Helen M Wilfehrt is an employee of Dendreon Pharmaceuticals LLC. Christine Ferro is an employee of Milliman Inc. Ms. Ferro reports that her employer received fees from Dendreon Pharmaceuticals LLC., for data acquisition and analysis of data during the conduct of the study. Matt Harmon is an employee of Dendreon Pharmaceuticals LLC. Scott C Flanders was an employee of Dendreon Pharmaceuticals LLC when this work was initiated. He is currently an employee of Myovant Sciences. Rana R McKay received research funding from Bayer, Pfizer, and Tempus; serves on advisory boards for AstraZeneca, Bayer, Bristol Myers Squibb, Calithera, Exelixis, Janssen, Merck, Novartis, Pfizer, Sanofi, and Tempus; is a consultant for Dendreon, Myovant, Sorrento Therapeutics, and Vividion; and serves on the molecular tumor board at Caris Life Sciences.

Compliance with Ethics Guidelines. This retrospective study used the secondary databases, the Medicare Fee-for-Service 100% research identifiable dataset, and the National Death Index, which is based on anonymized patient claims data. Dendreon and Milliman had permission to access and use these data. This research is exempt from institutional review board approval.

Data Availability. Patient-level data remain in the possession of the Centers for Medicare & Medicaid Services and are not in the possession of either Dendreon or Milliman. Questions

regarding the analysis methodology and outputs may be sent to Jason Hafron, MD (hafronj@michiganurology.com) or Dendreon via the Medical Information group (mac@dendreon.com).

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