Original Article

Real-World Outcomes of Sipuleucel-T Treatment in PROCEED, a Prospective Registry of Men With Metastatic Castration-Resistant Prostate Cancer

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BACKGROUND: The large registry, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data (PROCEED) (NCT01306890), evaluated sipuleucel-T immunotherapy for asymptomatic/minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). **METHODS:** PROCEED enrolled patients with mCRPC receiving 3 biweekly sipuleucel-T infusions. Assessments included overall survival (OS), serious adverse events (SAEs), cerebrovascular events (CVEs), and anticancer interventions (ACIs). Follow-up was for ≥3 years or until death or study withdrawal. **RESULTS:** In 2011-2017, 1976 patients were followed for 46.6 months (median). The median age was 72 years, and the baseline median prostate-specific antigen level was 15.0 ng/mL; 86.7% were white, and 11.6% were African American. Among the patients, 1902 had 1 or more sipuleucel-T infusions. The median OS was 30.7 months (95% confidence interval [CI], 28.6-32.2 months). Known prognostic factors were independently associated with OS in a multivariable analysis. Among the 1255 patients who died, 964 (76.8%) died of prostate cancer (PC) progression. The median time from the first infusion to PC death was 42.7 months (95% CI, 39.4-46.2 months). The incidence of sipuleucel-T–related SAEs was 3.9%. The incidence of CVEs was 2.8%, and the rate per 100 person-years was 1.2 (95% CI, 0.9-1.6). The CVE incidence among 11,972 patients with mCRPC from the Surveillance, Epidemiology, and End Results–Medicare database was 2.8%; the rate per 100 person-years was 1.5 (95% CI, 1.4-1.7). One or more ACIs (abiraterone, enzalutamide, docetaxel, cabazitaxel, or radium 223) were received by 77.1% of the patients after sipuleucel-T; 32.5% and 17.4% of the patients experienced 1- and 2-year treatment-free intervals, respectively. **CONCLUSIONS:** PROCEED provides contemporary survival data for sipuleucel-T–treated men in a real-world setting of new life-prolonging agents, which will be useful in discussing treatment options with patients and in powering future trials with sipuleucel-T. The safety and tolerability of sipuleucel-T in PROCEED were consistent with previous findings. ***Cancer* 2019;125:4172-4180**.

KEYWORDS: immunotherapy, overall survival, prostate cancer, safety.

INTRODUCTION

Sipuleucel-T is an autologous cellular immunotherapy for asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). In the pivotal phase 3 trial Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT; NCT00065442), sipuleucel-T significantly reduced the risk of death among patients with mCRPC and improved median overall survival (OS) by 4.1 months versus a placebo.[1] Sipuleucel-T is recommended

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across multiple guidelines[2-7] and as a first-line mCRPC treatment option[2,3,7] (category 1 recommendation by the National Comprehensive Cancer Network). In patients with low baseline prostate-specific antigen (PSA) levels (≤22.1 ng/mL) in IMPACT, retrospective analyses demonstrated a 13-month greater improvement in OS with sipuleucel-T versus a placebo.[8]

Sipuleucel-T was generally well tolerated across several prostate cancer (PC) trials.[1,9-14] The most common adverse events (≥15%) were chills, fatigue, fever, back pain, nausea, joint ache, and headache of mostly mild to moderate severity. Incidences of grade 3 and 4 adverse events were 23.6% and 4.0%, respectively, with sipuleucel-T and 25.1% and 3.3%, respectively, with a placebo. Serious adverse events (SAEs) included acute infusion reactions and cerebrovascular events (CVEs).[14] Data from 4 randomized, double-blind, placebo-controlled clinical trials (D9901 [NCT00005947],[12,13] D9902A [NCT01133704],[13] IMPACT,[1] and PROTECT [NCT00779402][9]) showed that CVEs, excluding transient ischemic attacks (TIAs), occurred in 3.5% (sipuleucel-T) and 2.6% (placebo) of patients (not statistically significant).[14] The clinical significance and causal relationship are uncertain.

The PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data (PROCEED; NCT0136890), evaluated real-world safety data and provided an opportunity to analyze efficacy outcomes of mCRPC management involving sipuleucel-T during a time of rapidly evolving management protocols.

MATERIALS AND METHODS

Study Design and Patients

PROCEED was a multicenter, open-label, observational registry conducted at urology and medical oncology clinics in private practice and at academic sites (see the Supporting Methods section in the supporting information). The primary and secondary objectives were to quantify CVE risk and OS, respectively. SAEs were collected. For a protocol-specified, exploratory objective, the proportion of patients receiving subsequent anticancer interventions (ACIs) was assessed. Both the protocol and its single amendment were approved by each center's Institutional Review Board before patient enrollment. Before participation, patients provided written informed consent.

Treatment

No randomization, blinding, or treatment masking was conducted. Patients underwent a 1.5 to 2.0× blood volume leukapheresis for antigen-presenting cell (APC) isolation with a sipuleucel-T infusion 3 to 4 days later; this was repeated at approximately 2-week intervals for 3 infusions.

Study Procedures

Safety and survival were assessed during normal clinical practice and were reported every 3 months after the final sipuleucel-T infusion. Use of central venous catheters at the physician's discretion was recorded. PROCEED did not require the recording of all PC-related events after sipuleucel-T treatment. ACI use after the first infusion of sipuleucel-T was recorded. Decisions to use further treatment and the choice and timing of ACI use were at the physician's discretion.

All SAEs (according to MedDRA version 19.1) from the first sipuleucel-T infusion through 60 days after the final infusion were captured. Thereafter, SAEs at least possibly related to sipuleucel-T were recorded. All CVE data were collected, regardless of causality, severity, or outcome, throughout PROCEED. CVEs, adjudicated by an independent neurologist, included all strokes (ischemic and hemorrhagic), intracranial hemorrhage, and TIAs (focal neurologic deficit episodes resolving within 24 hours).[15]

Patients were followed for ≥3 years or until death or study withdrawal. The cause of death was reported on a case report form. An end-of-study closeout form was completed to ascertain death. For patients lost to follow-up, sites performed a death-sweep search for obituaries.

Statistical Analyses

The sample size was based on an evaluation of the CVE rate. With ≥1500 patients followed for ≥3 years (4500 person-years), the 95% confidence interval (CI) for estimating the CVE incidence rate per 100 patient-years would have a width of <1 unit as long as the observed rate was <2.8/100 patient-years.[16] For 1500 patients, the probability of observing 1 or more occurrences of a rare event (1 in 1000) would be 0.78. The sample size was increased from 1500 to allow for 4500 person-years of follow-up.

The predefined analysis population was all patients receiving 1 or more full or partial (>0 mL) sipuleucel-T infusions. Endpoints were summarized descriptively unless otherwise stated. All analyses were performed with SAS (versions 9.2 and 9.4; SAS Institute, Inc, Cary, North Carolina).

OS was measured from the date of the first sipuleucel-T infusion for ≥3 years or until the patient had otherwise gone off the study. If death was not reported, patients were censored from the last study visit. OS data were analyzed with Kaplan-Meier methodology; Cox proportional hazards regression was used to calculate hazard ratios and 95% CIs. These were post hoc analyses with *P* values that were not adjusted for multiplicity. Univariable, stepwise Cox modeling and multivariable analysis were performed to assess for independent baseline predictors of OS that had both clinical and statistical relevance. Variables were selected in a stepwise process for the final multivariable analysis model at a .1 significance level (see the Supporting Methods for more details). The association of OS with natural logarithm–transformed sipuleucel-T product parameters (APC activation, APC cell count, and total nucleated cell count) was estimated with a Cox proportional hazards regression model; statistical significance was a 2-tailed *P* value <.05. A post hoc analysis evaluated OS by baseline PSA quartiles; hazard ratios and 95% CIs were calculated by the Cox regression model.

Primary summarization of CVEs excluded TIAs for consistency with how CVE rates had been previously defined.[14] CVEs including TIAs were summarized separately. The PROCEED CVE incidence was compared with a retrospective analysis of the incidence of first-time CVEs in men 65 years old or older with PC, including those with metastatic PC and a castrated state, within the Surveillance, Epidemiology, and End Results (SEER)–Medicare database in 1999-2013 (see the supporting information).

An exploratory analysis described the proportion of patients receiving ACIs after the first sipuleucel-T infusion. The Kaplan-Meier method estimated the proportion of ACI use at 1 and 2 years.

RESULTS

Patients and Treatment

PROCEED was conducted from January 27, 2011 (the first patient registered), to January 17, 2017 (the last patient visit); 1976 consenting patients were enrolled across 192 sites. Overall, 1902 patients received 1 or more sipuleucel-T infusions: 1248 (65.6%) were treated in oncology practices, and 654 (34.4%) were treated in urology practices. Most patients (79.1%) received sipuleucel-T at 140 community clinics; the remainder received it at 52 academic centers (see the Supporting Results in the supporting information for study discontinuation reasons).

Central venous catheters were used in 891 patients (46.8%). Overall, 1813 patients (95.3%) received 3 sipuleucel-T infusions, 57 (3.0%) received 2, and 32 (1.7%) received 1. Reasons for 3 or fewer infusions included an SAE (34 [1.8%]), other (32 [1.7%]), disease progression after the first infusion (22 [1.2%]), patient refusal (16 [0.8%]; including a refusal to transfer location or answer study questions), and venous access problems (4 [0.2%]). Multiple reasons for noninfusion were possible.

Table 1 lists patient characteristics for PROCEED and for IMPACT sipuleucel-T–treated patients for comparison.[1] The median patient age was 72 years; 86.7% were white, and 11.6% were African American. Most patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. The median baseline PSA level was 15.0 ng/mL (interquartile range, 5.2-46.1 ng/mL). Some patients received prior docetaxel, abiraterone, or enzalutamide (commercially or as an investigational agent). Most had bone-dominant metastases with or without lymph node involvement. The metastatic site or status was not reported for 19 patients (1.0%). Supporting Table 1 lists PROCEED baseline CVE risk factors.

Overall Survival

The median OS was 30.7 months (95% CI, 28.6-32.2 months; Fig. 1); the median follow-up was 46.6 months. During follow-up, 1255 patients (66.0%) died. Death or survival could not be ascertained for 45 patients. The main cause of death was PC progression (964 of 1255 [76.8%]); the median time to PC-specific death was 42.7 months (95% CI, 39.4-46.2 months). Other causes of death were unknown (154 [12.3%]), other (136 [10.8%]), a cardiac event (42 [3.3%]), a CVE (17 [1.4%]), and a new primary cancer (8 [0.6%]). More than 1 cause of death could be recorded for a patient.

A post hoc analysis indicated that the median OS was longer for patients in the lowest baseline PSA quartile (≤5.27 ng/mL) than patients in the second (>5.27 to ≤15.08 ng/mL), third (>15.08 to ≤46 ng/mL), and fourth quartiles (>46 ng/mL): 47.7 months (95% CI, 43.5-50.7 months), 33.2 months (95% CI, 30.9-35.5 months), 27.2 months (95% CI, 24.1-29.8 months), and 18.4 months (95% CI, 15.9-21.2 months), respectively. The hazard ratios for each quartile versus the lowest quartile were 1.6 (95% CI, 1.3-1.9), 2.0 (95% CI, 1.7-2.4), and 3.0 (95% CI, 2.6-3.6), respectively.

Univariable analyses showed that 15 evaluated baseline characteristics were significant predictors of OS (Supporting Table 2). Eleven characteristics were included in the final primary multivariable analysis. Of these, 10 were associated with OS at a significance level

TABLE 1. Demographics, Baseline Disease Characteristics, and Prior Prostate Cancer Treatments in PROCEED and IMPACT[1]

Parameter	PROCEED Safety Population (n = 1902)	IMPACT Sipuleucel-T–Treated Arm (n = 341)
Age, median (range, min-max), y	72 (42-97)	72 (49-91)
Race, No. (%)		
White	1649 (86.7)	305 (89.4)
Black or African American	221 (11.6)	23 (6.7)
Asian	22 (1.2)	2 (0.6)
Other	10 (0.5)	11 (3.2)
ECOG performance status, No. (%)		
0	1265 (66.5)	280 (82.1)
1	571 (30.0)	61 (17.9)
≥2	42 (2.2)	0
Unknown	24 (1.3)	0
Gleason sum reported, No. (%)		
≤7	790 (41.5)	257 (75.4)
≥8	963 (50.6)	84 (24.6)
Unknown	149 (7.8)	0
Charlson Comorbidity Index, No. (%)		NA
Low (0-1)	1682 (88.4)	
High (≥2)	220 (11.6)	
Bone metastases, No. (%)	n = 1595	
1-10	1117 (70.0)	195 (57.2)
>10	274 (17.2)	146 (42.8)
Unknown	204 (12.8)	0
Disease locations, No. (%)	n = 1883	n = 340
Bone only	1223 (64.3)	173 (50.7)
Bone and lymph nodes	313 (16.5)	143 (41.9)
Lymph nodes only	257 (13.5)	24 (7.0)
Visceral ± bone or lymph nodes	90 (4.7)	0
Liver	21 (1.1)	0
Lung	61 (3.2)	0
Brain	2 (0.1)	0
Visceral site(s) not reported	13 (0.7)	0
Laboratory parameters, median (IQR, Q1-Q3)		
ALP, U/L	82 (63-115) n = 1499	99 (75-146)
Hemoglobin, g/dL	12.8 (11.8-13.7) n = 1794	12.9 (11.7-13.7)
Lactate dehydrogenase, U/L	186 (159-218) n = 644	194 (172-224) n = 340
PSA, ng/mL	15.0 (5.2-46.1) n = 1884	51.7 (22.5-140.3)
Interval from diagnosis to first sipuleucel-T infusion, median (IQR, Q1-Q3), y	5.0 (2.3-9.4) n = 1599	7.1 (4.4-10.7)
Prior local cancer therapy, No. (%)		
No local therapy (systemic therapy only)	429 (22.6)	85 (24.9)
Radical prostatectomy alone	310 (16.3)	46 (13.5)
Radical prostatectomy + radiation	379 (19.9)	73 (21.4)
Radiation therapy alone (external beam/brachytherapy)	564 (29.7)	112 (32.8)
Prior systemic cancer therapy, No. (%)		
Androgen-targeting therapy[a]	1881 (98.1)	279 (81.8)[b]
LHRH antagonist	382 (20.1)	—
LHRH agonist	1566 (82.3)	341 (100)[c]
Abiraterone	157 (8.3)	0
Enzalutamide	54 (2.8)	0
Chemotherapy		
Docetaxel	215 (11.3)	53 (15.5)
Cabazitaxel	32 (1.7)	0
Radium 223	1 (0.1)	0

Abbreviations: ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; IMPACT, Immunotherapy for Prostate Adenocarcinoma Treatment; IQR, interquartile range; LHRH, luteinizing hormone releasing hormone; max, maximum; min, minimum; NA, not applicable; PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data; PSA, prostate-specific antigen; Q1, first quartile; Q3, third quartile.
PROCEED was observational, so calculations were based on values from the number of patients for whom data were available.
[a]Excluded enzalutamide.
[b]Patients received complete androgen blockade treatment.
[c]Patients received an LHRH analogue.

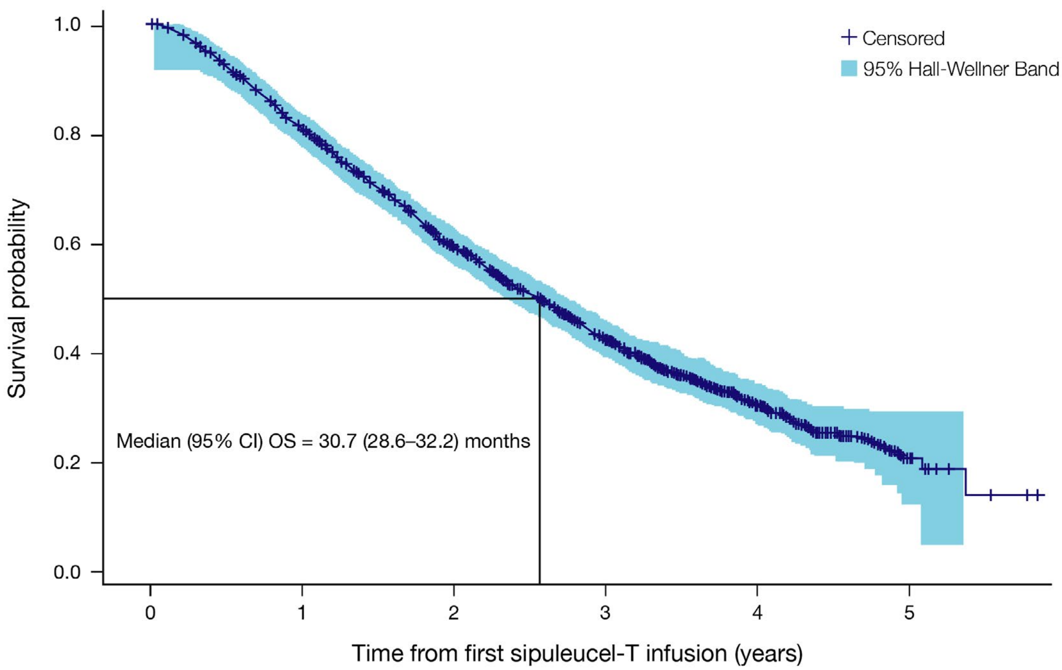

Figure 1. OS in PROCEED as a Kaplan-Meier plot with a 95% Hall-Wellner band. CI indicates confidence interval; OS, overall survival; PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data.

below .05 (Table 2): age, ethnicity, Eastern Cooperative Oncology Group performance status, time since diagnosis, PSA, alkaline phosphatase, hemoglobin, lymph node only metastases, prior abiraterone/enzalutamide, and prior docetaxel/cabazitaxel.

Cumulative sipuleucel-T product parameters (Supporting Table 3) per unit increase correlated with OS.

Safety

All-grade SAEs, regardless of causality, were reported in 260 patients (13.7%); the most common SAEs were disease progression (28 patients), cerebrovascular accident (16 patients), chills (13 patients), syncope (12 patients), and device-related infection (10 patients; Table 3). Seventy-four patients (3.9%) had 1 or more SAEs considered possibly or probably related to the study drug (all grades); the most common were chills (13 [0.7%]), cerebrovascular accident (9 [0.5%]), deep vein thrombosis (4 [0.2%]), device-related infection (4 [0.2%]), pulmonary embolism (4 [0.2%]), and pyrexia (4 [0.2%]). Grade 3 to 5 SAEs, regardless of causality, occurred in 175 patients (9.2%; Table 3). The incidence of grade 4 SAEs was 1.1% (n = 21). Fifty-two patients (2.7%) had grade 5 SAEs, and 22 deaths were due to disease progression. Central venous catheter–related SAEs were reported in 19 patients (1.0%); 13 were grade 3 or 4 with no grade 5 SAEs. Of these 19 patients, 2 and 5 had 1 and 2 sipuleucel-T infusions, respectively.

TABLE 2. Final Primary Multivariable Analysis of Overall Survival in PROCEED

Baseline Covariate	HR (95% CI)	P^{a}
Log PSA (ng/mL)	1.22 (1.16-1.27)	<.001
Hemoglobin, per g/dL increase	0.87 (0.83-0.91)	<.001
ECOG performance status, >0 vs 0	1.22 (1.05-1.42)	.009
Log ALP (U/L)	1.60 (1.42-1.81)	<.001
Age (y), >median vs ≤median	1.30 (1.12-1.50)	<.001
Race, white vs all others	1.64 (1.30-2.06)	<.001
Time since diagnosis (y), >median vs ≤median	0.72 (0.62-0.83)	<.001
Lymph node only metastases, yes vs no	0.79 (0.63-0.99)	.044
Visceral metastases, any vs none	1.30 (0.95-1.78)	.098
Prior docetaxel/cabazitaxel, yes vs no	1.54 (1.25-1.90)	<.001
Prior abiraterone/enzalutamide, yes vs no	1.53 (1.16-1.27)	<.001

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data; PSA, prostate-specific antigen.
[a]Multivariable Cox modeling.

The overall incidence of adjudicated CVEs (excluding TIAs) in PROCEED was 2.8% (n = 54), and the rate per 100 person-years was 1.2 (95% CI, 0.9-1.6; Supporting Table 4). In the SEER-Medicare data analyses of men with PC at diagnosis who were metastatic at

TABLE 3. Overall Summary of All-Grade SAEs and Grade 3 to 5 SAEs Occurring in 3 (0.2%) or More Patients (in the All-Grade List) Regardless of Causality (n = 1902) in PROCEED

	No. (%)	
SAE	All Grades	Grades 3-5
Any SAE	260 (13.7)	175 (9.2)
Disease progression	28 (1.5)	25 (1.3)
Cerebrovascular accident	16 (0.8)	11 (0.6)
Chills	13 (0.7)	0 (0)
Syncope	12 (0.6)	7 (0.4)
Device-related infection	10 (0.5)	7 (0.4)
Acute kidney injury	8 (0.4)	7 (0.4)
Deep vein thrombosis	8 (0.4)	2 (0.1)
Pulmonary embolism	8 (0.4)	7 (0.4)
Anemia	7 (0.4)	2 (0.1)
Dyspnea	7 (0.4)	6 (0.3)
Chest pain	6 (0.3)	2 (0.1)
Myocardial infarction	6 (0.3)	5 (0.3)
Pyrexia	6 (0.3)	2 (0.1)
Subdural hematoma	6 (0.3)	6 (0.3)
TIA	6 (0.3)	1 (0.1)
Cerebral hemorrhage	5 (0.3)	5 (0.3)
Pneumonia	5 (0.3)	3 (0.2)
Cerebral infarction	4 (0.2)	4 (0.2)
Congestive cardiac failure	4 (0.2)	3 (0.2)
Dehydration	4 (0.2)	3 (0.2)
Device-related sepsis	4 (0.2)	3 (0.2)
Intracranial hemorrhage	4 (0.2)	2 (0.1)
Nausea	4 (0.2)	1 (0.1)
Spinal cord compression	4 (0.2)	4 (0.2)
Vomiting	4 (0.2)	4 (0.2)
Asthenia	3 (0.2)	1 (0.1)
Atrial fibrillation	3 (0.2)	1 (0.1)
Back pain	3 (0.2)	2 (0.1)
Bacteremia	3 (0.2)	1 (0.1)
Confusional state	3 (0.2)	1 (0.1)
Constipation	3 (0.2)	2 (0.1)
Fall	3 (0.2)	3 (0.2)
Hematuria	3 (0.2)	1 (0.1)
Hypotension	3 (0.2)	2 (0.2)
Infusion-related reaction	3 (0.2)	2 (0.2)
Presyncope	3 (0.2)	1 (0.1)

Abbreviations: PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data; SAE, serious adverse event; TIA, transient ischemic attack.

follow-up and in a castrated state (n = 11,972), the CVE incidence (excluding TIAs) was 2.8%, and the rate per 100 person-years was 1.5 (95% CI, 1.4-1.7; Supporting Table 5).

Subgroup analyses of CVEs (excluding TIAs) showed higher CVE rates in older patients, African Americans, patients with more advanced PC, and those with preexisting conditions associated with CVEs (Supporting Table 6). Nine patients had a TIA (3 concurrent with another CVE and 6 in isolation). Thus, 60 PROCEED patients (3.2%) had CVEs, including TIAs, and the rate per 100 person-years was 1.3 (95% CI, 1.0-1.7; Supporting Table 4). The observed median time to a CVE (including TIAs) from the last sipuleucel-T infusion was

TABLE 4. Proportion of Patients Receiving an Overall Survival–Prolonging ACI After Sipuleucel-T Treatment

Posttreatment ACI	Safety Population (n = 1902)	Patients Who Died During PROCEED (n = 1255)
No. of posttreatment ACIs, No. (%)		
0	419 (22.0)	287 (22.9)
1	565 (29.7)	329 (26.2)
2	462 (24.3)	326 (26.0)
3	319 (16.8)	216 (17.2)
4	126 (6.6)	87 (6.9)
5	11 (0.6)	10 (0.8)
Specific posttreatment ACI, No. (%)		
Abiraterone	1036 (54.5)	663 (52.8)
Enzalutamide	831 (43.7)	514 (41.0)
Docetaxel	739 (38.9)	553 (44.1)
Cabazitaxel	309 (16.2)	236 (18.8)
Radium 223	90 (4.7)	61 (4.9)

Abbreviation: ACI, anticancer intervention; PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data.

321 days (10.5 months; interquartile range, 79-689 days or 2.6-22.6 months). For patients with a CVE (including TIAs), the number and percent of patients with CVE onset within ≤30, 31-60, 61-180, and >181 days of the most recent sipuleucel-T infusion were 10 (16.7%), 4 (6.7%), 9 (15.0%) and 37 (61.7%), respectively. No appreciable differences in the CVE ± TIA incidence or rate were observed between patients with or without a central venous catheter (Supporting Table 7).

Protocol-Specified, Exploratory Analysis: ACIs

Three hundred thirty-eight patients (17.8%) received an OS-prolonging ACI (abiraterone, enzalutamide, docetaxel, cabazitaxel, or radium 223) before sipuleucel-T. Approximately one-third of the patients (32.5%) did not receive any OS-prolonging ACI at 1 year, and 17.4% did not at 2 years after sipuleucel-T treatment. Of these patients, 9.5% and 7.4% had received an ACI before sipuleucel-T; thus, most of these patients had sipuleucel-T as first-line mCRPC therapy. Among patients in the lowest baseline PSA quartile (≤5.27 ng/mL), 44.1% and 25.8% did not receive an ACI at 1 and 2 years, respectively. Of these, 94.3% and 95.0% received sipuleucel-T before any other ACI.

During PROCEED, 1483 of all patients (78.0%) received 1 or more OS-prolonging ACIs, and 48.3% received 2 or more lines of treatment after sipuleucel-T (Table 4). The most commonly used OS-prolonging ACIs after sipuleucel-T treatment were abiraterone (1036 [54.5%]), enzalutamide (831 [43.7%]), and docetaxel

(739 [38.9%]; Table 4). Having sipuleucel-T as the only OS-prolonging treatment in PROCEED was reported in 22.0% of the patients (n = 419).

Similar patterns of ACI use were observed in patients who died during PROCEED (n = 1255), with 968 patients (77.1%) receiving 1 or more OS-prolonging ACIs and 50.9% receiving 2 or more lines of treatment after sipuleucel-T (Table 4). The most common OS-prolonging ACIs reported in those who died were abiraterone (52.8%), docetaxel (44.1%) and enzalutamide (41.0%; Table 4). Sipuleucel-T was the only OS-prolonging ACI prescribed in PROCEED for 22.9% of these patients (n = 287).

DISCUSSION

Since the conduct of the phase 3 IMPACT trial[1] with sipuleucel-T (2003-2007), mCRPC treatments[17-22] and guidelines[2-7] have rapidly evolved. The PROCEED study (2011-2017), which includes the largest mCRPC patient population treated with sipuleucel-T and prospectively followed in a real-world setting, offers interesting observations about patients with mCRPC, sipuleucel-T use, and the use of other ACIs since IMPACT. The baseline characteristics of PROCEED patients reveal clinical practice changes (Table 1). Although the median age was similar, the median baseline PSA level was much lower in PROCEED versus IMPACT (15.0 vs 51.7 ng/mL); this is noteworthy because a previous analysis of IMPACT showed a much greater OS benefit from sipuleucel-T versus a placebo in patients with lower baseline PSA levels.[8] Most PROCEED patients had a good performance status, although in comparison with IMPACT, the performance status was somewhat worse (likely because randomized clinical trials have more stringent eligibility criteria). The Gleason score was also higher in PROCEED. PROCEED enrolled a higher proportion of African American patients than IMPACT (11.6% vs 6.7%), and this is notable because this population is often underrepresented in clinical trials. Visceral metastases, an IMPACT exclusion criterion, were reported in 4.7% of PROCEED patients. Furthermore, PROCEED spanned a period of unprecedented progress in mCRPC management as 4 life-extending therapies became available: abiraterone acetate,[17,18] enzalutamide,[19,20] cabazitaxel,[21] and radium 223.[22] Thus, in PROCEED, the median OS (30.7 months) likely, in part, reflects use of these life-prolonging drugs with sipuleucel-T in contrast to the IMPACT (median OS, 25.8 months[1]) era, in addition to the use of sipuleucel-T in patients with lower PSA levels.

PROCEED provides further evidence of sipuleucel-T safety and tolerability in a real-world setting. Particularly in an elderly patient population, the safety profile of a treatment deserves careful consideration in decision making. Importantly, the SAE incidence in PROCEED was low and was comparable to that documented during IMPACT.[1] A previous analysis of pooled data from 4 phase 3 trials reported CVE rates (excluding TIAs) of 3.5% (sipuleucel-T) and 2.6% (placebo).[14] The causal relationship of sipuleucel-T with CVEs is unclear. Men with mCRPC are typically elderly with multiple comorbidities that increase the risk of cardiovascular events and CVEs. In PROCEED, a CVE rate of 2.8% was reported. Incidentally, the CVE rate was 2.8% in a SEER-Medicare database analysis with more than 10,000 patients with metastatic PC in a castrated state. Furthermore, subgroup analyses by baseline factors in PROCEED demonstrated that older patients and those with baseline CVE factors had higher rates of CVEs (Supporting Table 6), and this was consistent with published findings.[23-25] Moreover, although central venous catheter use (which varied greatly by site) for leukapheresis was high in PROCEED, overall, this practice did not increase CVE risk (Supporting Table 7).

PROCEED also offers confirmation of correlative findings noted in prior phase 3 studies. Patients in the lowest baseline PSA quartile (PSA ≤ 5.27 ng/mL) had significantly longer OS (median survival, 47.7 months) than those in higher PSA quartiles. Similar findings were seen in the post hoc analysis of IMPACT, which demonstrated a greater OS benefit in lower baseline PSA quartiles versus higher baseline PSA quartiles and also suggested that sipuleucel-T was superior to a placebo in each quartile.[8] Likewise, similar correlations with immune parameters and OS were seen in both PROCEED and IMPACT; in vitro indicators of immune activation and product potency (cumulative APC activation, APC count, and total nucleated cell count in the product) were significantly correlated with OS (Supporting Table 3).[26,27]

PROCEED also exhibited 10 baseline characteristics that were independent predictors of OS in PROCEED (Table 2). The examined covariates were selected on the basis of those previously observed to be clinically and statistically relevant in this population. Our findings, though broadly consistent with the Halabi model,[28] also differ in terms of which significant predictors were identified, potentially because of the treatment being received (chemotherapy in the population used for the Halabi nomogram and sipuleucel-T for the current study), the data coming from a clinical trial versus a registry, the time periods during which the various studies informing these analyses were conducted and the changes in available therapies and PSA levels guiding treatment, and so on. One notable observation is the emergence of race as a statistically significant predictor, and this potentially reflects the relatively high enrollment of African Americans in PROCEED (12%). Further research is warranted to explore these findings.

Another notable finding in PROCEED is that a substantial number of patients experienced a long interval between sipuleucel-T and subsequent therapy with abiraterone, enzalutamide, docetaxel, cabazitaxel, or radium 223. Approximately one-third and one-sixth of the patients had not received any of these agents 1 and 2 years, respectively, after sipuleucel-T. For most of these patients, sipuleucel-T was their first OS-prolonging mCRPC therapy; having a long treatment-free interval after sipuleucel-T may reflect patient selection as well as the clinical benefit of sipuleucel-T. Interestingly, 22% of the overall PROCEED population received sipuleucel-T as their only OS-prolonging treatment for mCRPC. The reasons for this are unclear. However, the long median time to death from PC of 42.7 months observed provides further evidence for the early use of sipuleucel-T for mCRPC followed by other ACIs, as recommended by the National Comprehensive Cancer Network and other guidelines.[2-4,7]

PROCEED has several limitations. Although OS was prospectively determined, there was no comparator group, so a survival benefit could not be determined. Nonetheless, this observation gives an accurate picture of expected OS with sipuleucel-T plus other life-prolonging drugs that were not available when IMPACT was conducted. Similar reasoning applies to SAE and CVE risk in that there was no placebo arm; hence, the results are descriptive.

PROCEED provides a real-world portrait of the safety profile of sipuleucel-T and defines the expected OS after sipuleucel-T in patients with mCRPC in the modern era of 5 additional life-prolonging agents. This information may be useful in powering future combination trials with sipuleucel-T, and studying the sequencing of therapies in this large population may shed light on optimal treatment approaches.

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CONFLICT OF INTEREST DISCLOSURES

Celestia S. Higano has served in an advisory role for Aptevo, Asana, Astellas, Bayer, Blue Earth Diagnostics, Churchill Pharma, Clovis Oncology, Dendreon, Endocyte, Ferring, Medivation, Orion Corporation, and Pfizer; she has also participated in sponsored research for Aptevo, Bayer, Aragon Pharma, Astellas, AstraZeneca, Dendreon, Genentech, Hoffman-LaRoche, Medivation, Sanofi, and Pfizer, and her spouse was in a leadership role for CTI Biopharma. Andrew J. Armstrong has received grants and personal fees from Dendreon, Pfizer/Astellas, Janssen, Bayer, and Sanofi-Aventis during this study as well as grants from Novartis, Gilead, Bristol-Myers Squibb, and Genentech/Roche outside the submitted work. A. Oliver Sartor has served as a consultant for and received personal fees from Advanced Accelerator Applications, Astellas, AstraZeneca, Bavarian-Nordic, Bayer, Bellicum, Blue Earth Diagnostics, Celgene, Constellation, Dendreon, EMD Serono, Endocyte, Johnson & Johnson, Bristol-Myers Squibb, Myovant, Pfizer, Progenics, Sanofi, Teva, and Hinova during this study; he has also received grants from AstraZeneca, Bayer, Constellation, Dendreon, Endocyte, Johnson & Johnson, Bristol-Myers Squibb, Progenics, Sanofi, Innocrin, Invitae, Merck, Roche, and Sotio. Philip W. Kantoff has received personal fees from Astellas, Bayer, Bellicum, BIND Biosciences, Bavarian Nordic Immunotherapies, DRGT, Genentech/Roche, Ipsen Pharmaceuticals, Janssen, Metamark, Merck, Millennium/Prometrika, MTG, Omnitura, OncoCell MDx, OncoGenex, Progenity, Sanofi, Tarveda Pharmaceuticals, Thermo Fisher, GE Healthcare, Context Therapeutics, New England Research Institutes, SEER Biosciences, and Placon; he also has investment interests in DRGT, Tarveda Pharmaceuticals, Context Therapeutics, SEER Biosciences, and Placon. Christopher M. Pieczonka has received personal fees as a consultant for Dendreon, Bayer, Janssen, and Pfizer and as an investigator for Dendreon, Bayer, Janssen, Pfizer, Merck, AstraZeneca, Taiho, Innocrin, and Myovant outside the submitted work. David F. Penson has received personal fees from Dendreon and Janssen as well as a grant from the Vanderbilt University Research Center. Neal D. Shore has served as a consultant for and received personal fees from Ferring, Bayer, Amgen, Janssen, Dendreon, Tolmar, Astellas, Pfizer, AstraZeneca, Genentech/Roche, Myovant Sciences, Merck, Bristol Meyers Squibb, and Nymox outside the submitted work. Raoul S. Concepcion has served in an advisory role for Dendreon and received personal fees outside the submitted work. David I. Quinn has been involved in payments to the University of Southern California for trial conduct with Dendreon; he has also acted as an advisor for and received personal fees from Dendreon, Bayer, Janssen, Pfizer, Astellas, Genzyme, Clovis, and AstraZeneca. Vahan Kassabian has served as a consultant or speaker for Dendreon, Amgen, Astellas, Pfizer, Janssen, Bayer, UroGPO, Tolmar, and Genomic Health outside the submitted work and is a shareholder of UroGPO. Matt Harmon reports stock ownership in Amgen. Robert C. Tyler has been an employee of Janssen, Dendreon, Medivation, Pfizer, and Innocrin. Nancy N. Chang was a full-time employee of Dendreon at the time of the analyses and drafting of this manuscript. Hong Tang was a full-time employee of Dendreon at the time of the analyses and drafting of the manuscript; is a nonexecutive director of OnQuality Pharmaceuticals; and owns stock in BeiGene, Nektar, Sangamo Therapeutics, Tesaro, Verastem, Editas Medicine, and CVS Health Corporation. Matthew R. Cooperberg has received personal fees from Dendreon in relation to a PROCEED trial steering committee and has served in an advisory or consultancy role for Bayer, MDx Health, and Myriad Genetics; he has also participated in a registry steering committee for Astellas. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Celestia S. Higano: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, visualization, writing–original draft, and writing–review and editing. **Andrew J. Armstrong:** Conceptualization, investigation, methodology, project administration, resources, supervision, writing–original draft, and writing–review and editing. **A. Oliver Sartor:** Conceptualization, data curation, formal analysis, investigation, methodology, supervision, writing–original draft, and writing–review and editing. **Nicholas J. Vogelzang:** Investigation, writing–original draft, and writing–review and editing. **Philip W. Kantoff:** Conceptualization, investigation, and writing–review and editing. **David G. McLeod:** Writing–original draft and writing–review and editing. **Christopher M. Pieczonka:** Investigation and writing–review and editing. **David F. Penson:** Investigation, methodology, and writing–review and editing. **Neal D. Shore:** Formal analysis, investigation, and writing–review and editing. **Jeffrey Vacirca:** Data curation, investigation, project administration, resources, software, supervision, validation, and visualization. **Raoul S. Concepcion:** Investigation and writing–review and editing. **Ronald F. Tutrone:** Data curation, investigation, and writing–review and editing. **Luke T. Nordquist:** Investigation and writing–review and editing. **David I. Quinn:** Investigation and writing–review and editing. **Vahan Kassabian:** Investigation, validation, visualization, and writing–review and editing. **Mark C. Scholz:** Investigation, supervision, and writing–review and editing. **Matt Harmon:** Data curation, methodology, software, visualization, and writing–review and editing. **Robert C. Tyler:** Conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, and writing–review and editing. **Nancy N. Chang:** Visualization, writing–original draft, and writing–review and editing. **Hong Tang:** Funding acquisition, resources, supervision, and writing–review and editing. **Matthew R. Cooperberg:** Conceptualization, methodology, supervision, visualization, and writing–review and editing.

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