Survival Outcomes of Sipuleucel-T Phase III Studies: Impact of Control-Arm Cross-Over to Salvage Immunotherapy

Daniel J. George¹, Chadi Nabhan², Todd DeVries³, James B. Whitmore³, and Leonard G. Gomella⁴

Abstract

Sipuleucel-T is an autologous cellular immunotherapy for asymptomatic/minimally symptomatic metastatic castrate-resistant prostate cancer (CRPC). After disease progression, control-arm patients on three double-blind, randomized phase III sipuleucel-T trials were offered, in nonrandomized open-label protocols, APC8015F, an autologous immunotherapy made from cells cryopreserved at the time of control manufacture. These exploratory analyses evaluated potential effects on survival outcomes associated with such treatment. Of 249 control-treated patients, 165 (66.3%) received APC8015F. We explored the effects of APC8015F on the overall survival (OS; Cox regression) of control-arm patients and treatment effects of sipuleucel-T versus control adjusted for APC8015F treatment [iterative parameter estimation model (IPE)]. The median time to first APC8015F infusion was 5.2 months (range, 1.8–33.1) after randomization and 2.2 months (0.5–14.6) after progression. After disease progression, median survival was longer for APC8015F-treated versus control-only treated patients [20.0 vs. 9.8 months; HR, 0.53; 95% confidence interval (CI), 0.38–0.74; P < 0.001]; however, baseline characteristics were more favorable for APC8015F-treated patients. Multivariate regression analyses identified lactate dehydrogenase, alkaline phosphatase, hemoglobin, ECOG status, age, and number of bone metastases as potential (P < 0.1) independent predictors of postprogression survival. After adjusting for these predictors, APC8015F (HR, 0.78; 95% CI, 0.54–1.11; P = 0.17) treatment trended toward improved survival. Estimated median OS benefited sipuleucel-T versus control adjusted for APC8015F treatment was 3.9 months if APC8015F had no effect and was 8.1 months if APC8015F was equally as effective as sipuleucel-T. Exploratory analyses indicate that APC8015F treatment may have extended patient survival, suggesting the sipuleucel-T OS advantage in CRPC may be more robust than previously estimated. Cancer Immunol Res; 3(9); 1063–9. ©2015 AACR.

Introduction

Sipuleucel-T (Provenge; Dendreon Corporation) is an autologous cellular immunotherapy for the treatment of men with asymptomatic/minimally symptomatic metastatic castrate-resistant prostate cancer (CRPC; ref. 1). Three randomized, double-blind, controlled, phase III sipuleucel-T trials were conducted in CRPC (Fig. 1; refs. 2–4). Sipuleucel-T-arm patients underwent leukapheresis procedures followed by infusion of an activated cellular product designed to stimulate an immune response to prostate cancer. To preserve anonymity of the study arms, control patients also underwent leukapheresis procedures, and then received an infusion of a product appearing identical to sipuleucel-T, except containing a portion of their unstimulated cells; remaining cells were cryopreserved (2). After disease progression, control patients were eligible, on a separate nonrandomized open-label protocol, to receive salvage treatment with APC8015F, an autologous immunotherapy made using the same procedure as sipuleucel-T, except the process was initiated with the cryopreserved cells.

The primary endpoint for the D9901 and D9902A studies was time to disease progression, with overall survival (OS) a planned analysis. Coprimary endpoints for the D9902B (IMPACT) study were initially time to disease progression and time to disease-related pain. After reviewing OS results from D9901/D9902A, the IMPACT primary endpoint was changed to OS. Because enrollment was well under way at the time, “cross-over” to salvage treatment with APC8015F was continued to maintain consistency in trial design. Results provided evidence of prolonged OS after sipuleucel-T treatment; for example, median OS in the IMPACT trial was 4.1 months longer for sipuleucel-T than control [HR, 0.78; 95% confidence interval (CI), 0.61–0.98; P = 0.03; ref. 3].

Approximately two thirds of control patients received APC8015F, which had not been previously administered to patients. We report here exploratory analyses evaluating how APC8015F treatment may have influenced OS findings in the three phase III studies.

Materials and Methods

Study design

Three phase III sipuleucel-T trials were conducted: D9901 (January 2000–September 2004; clinicaltrials.gov NCT00005947), D9902A (May 2000–May 2005; NCT01133704), and IMPACT.
Patients
Detailed eligibility criteria for phase III studies were previously described; patients had metastatic CRPC, serum testosterone <50 ng/dL, and Eastern Cooperative Oncology Group (ECOG) score ≤2 (2–4). D9901/D9902A included asymptomatic patients. IMPACT initially included asymptomatic patients with Gleason scores ≤7; a subsequent amendment included patients with minimally symptomatic disease and any Gleason score (3).

Patients were randomized to sipuleucel-T or control (2:1), stratified by study center and bisphosphonate use (yes/no) for D9901/D9902A and by primary Gleason grade (≤3, >3), number of bone metastases (≤5, 6–10, >10), and bisphosphonate use for IMPACT. Whether/when to initiate APC8015F treatment or other anticancer interventions following disease progression was at investigator discretion; patients were not randomly assigned, and APC8015F could be administered before or after other anticancer interventions following disease progression. Whether/when to initiate APC8015F treatment or other anticancer interventions following disease progression was at investigator discretion; patients were not randomly assigned, and APC8015F could be administered before or after other anticancer interventions following disease progression. Whether/when to initiate APC8015F treatment or other anticancer interventions following disease progression was at investigator discretion; patients were not randomly assigned, and APC8015F could be administered before or after other anticancer interventions following disease progression.

Additional inclusion criteria for D9993/PB01 were as follows: ≥4 weeks since previous therapies (PB01: ≥2 weeks), ECOG score ≤2 (PB01: <2), and life expectancy ≥16 weeks (PB01: ≥24 weeks).

Treatment
Sipuleucel-T consisted of autologous peripheral blood mononuclear cells (PBMC), including antigen-presenting cells (APC), activated for approximately 2 days in vitro with PA2024 (prostatic acid phosphatase linked to granulocyte-macrophage colony stimulating factor), as previously reported (2–4). A dose included all the sipuleucel-T prepared from a single leukapheresis procedure. Control was an autologous cell product, collected identically to sipuleucel-T, but not activated with PA2024 or cultured. Thus, all patients would undergo identical procedures until disease progression: 3 leukapheresis procedures and 3 infusions were planned for each patient, with 2 weeks between treatments (Fig. 1).

Control infusions included one third of cells from each leukapheresis. Remaining cells were cryopreserved for subsequent APC8015F preparation, utilizing the same activation procedure as used for sipuleucel-T. APC8015F was assayed for total nucleated cell (TNC) and APC counts (APCs = large CD54+ cells), and APC activation (increased ratio of postactivation/preactivation CD54 molecules on APCs; ref. 5). Cumulative product parameters were calculated by summing values for all infusions for each patient. Each dose was administered via single intravenous infusion: 3 APC8015F infusions were planned for each patient, with approximately 2 weeks between treatments (Fig. 1).

Outcome measures
Disease progression endpoints for D9901/D9902A included progression of measurable or evaluable disease, spinal cord compression or pathologic fracture, requirement for radiotherapy, or other clinically significant events, including disease-related pain or other symptoms. For IMPACT, the disease progression endpoint included only objective disease progression (progression of measurable or evaluable disease confirmed by independent, blinded review). Serum prostate-specific antigen (PSA) increases were not used to measure disease progression.

Patients were followed for survival for 3 years after randomization (D9901/D9902A) or until study termination (IMPACT; reported median time after randomization was 34.1 months; range, 0–64.8; ref. 3). All anticancer interventions were collected between randomization and protocol-defined disease progression. After disease progression, first non-study anticancer interventions/first chemotherapies were collected.

Statistical analyses
Survival after disease progression and OS from randomization were summarized (Kaplan–Meier methods). Survival after disease progression was analyzed using the following models to evaluate the effect of APC8015F use: (i) unadjusted Cox regression, stratified by salvage protocol (D9903/PB01); (ii) stratified Cox regression adjusted for log-transformed baseline PSA, LDH, and alkaline phosphatase levels and baseline hemoglobin and ECOG score; and (iii) Cox regression using backward selection to identify (a) independent (P < 0.10) baseline prognostic variables and (b) independent prognostic variables, using the most recently collected values (prior to/within 28 days of progression). Postprogression APC8015F and docetaxel use were fit as time-dependent covariates accounting for the exact timing of use and retained in models iiiia and iiiib, while APC8015F was fit as a yes/no variable for models 1 and 2 that...
does not account for the exact timing of use. Effects of APC8015F product characteristics on survival after disease progression were assessed using stratified Cox regression models with log-transformed cumulative product parameters adjusted for the last PSA collected prior to the first APC8015F infusion.

To correct for possible effects of APC8015F salvage treatment on OS of control-arm patients, OS was estimated with the IPE model, which is a parametric form of the rank-preserving structural failure time (RPSFT) model (6, 7). This model’s approach provided a randomization-based estimate of treatment effect, assuming that the treatment effect on survival was multiplicative and that the survival times follow a Weibull distribution, and allowed estimation of the control OS curve had no cross-over to APC8015F occurred. Uncertainty in the true treatment effect of APC8015F on OS was incorporated by running the model under varying levels of assumed APC8015F effectiveness, defined as the proportion of the sipuleucel-T treatment effect (0%, no effect of APC8015F; 100%, APC8015F equally effective as sipuleucel-T).

All statistical analyses were performed using SAS (Version 9.2; SAS Institute Inc.).

Results

Patient disposition

These exploratory analyses included pooled data for 737 patients from three randomized, controlled, double-blind, phase III trials (sipuleucel-T: 488; control: 249; Fig. 2). Overall, 165 control-arm patients received APC8015F; 155 of 165 patients met the protocol-defined disease progression endpoint prior to APC8015F treatment, and 10 patients (on IMPACT) had initial evidence of disease progression, not subsequently confirmed by an independent committee.

The median time to first APC8015F infusion was 5.2 months (range, 1.8–33.1) from randomization for all APC8015F-treated patients (n = 165) and 2.2 months (0.5–14.6) from disease progression for APC8015F-treated patients with protocol-defined disease progression (n = 155).

Patient characteristics

Patient characteristics were comparable for sipuleucel-T (n = 488) and control (n = 249) arms (Table 1). Baseline characteristics appeared more favorable for survival for control-arm patients who received APC8015F than for those who did not; e.g., baseline median alkaline phosphatase, LDH, and PSA levels were lower for APC8015F-treated control-arm patients.

Survival estimates

Kaplan–Meier estimates of median OS from randomization were 25.4 months for sipuleucel-T–treated patients (n = 488), 23.6 months for APC8015F–treated control patients (n = 165), and 12.7 months for control patients not receiving APC8015F (n = 84). Patients were not eligible to receive APC8015F before disease progression. To reduce variability associated with time from randomization to disease progression, analyses of survival from protocol-defined disease progression were also performed; median survival estimates were 20.7 months for sipuleucel-T–treated patients (n = 419), 20.0 months for APC8015F–treated control patients (n = 155), and 9.8 months for control patients not receiving APC8015F (n = 61). Comparing control patients who did/did not receive APC8015F, the unadjusted HR for death was 0.53 (95% CI, 0.38–0.74), representing a 47% reduction in risk of death associated with APC8015F treatment (P < 0.001; Table 2).

Because patients were not randomized to APC8015F salvage treatment, there were likely selection differences between patients who did/did not receive APC8015F, as suggested by differences in baseline characteristics (Table 1). To account for potential differences in outcome resulting from patient selection, the model was adjusted for baseline PSA, LDH, alkaline phosphatase, hemoglobin, and ECOG status, parameters previously identified as associated with survival in the IMPACT study (8); the results (HR, 0.54; 95% CI, 0.38–0.76; P < 0.001; Table 2; Supplementary Table S1) were comparable with the unadjusted model. To more comprehensively adjust for potential differences in baseline characteristics,

Figure 2.

Patient disposition.


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Table 1. Baseline characteristics

<table>
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<th>Overall study population</th>
<th>Patients with protocol-defined disease progression</th>
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<td></td>
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<td>With subsequent (N = 155)</td>
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<tr>
<td></td>
<td></td>
<td>With no subsequent (N = 94)</td>
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<td></td>
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<td>Sipuleucel-T (N = 488)</td>
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<td>Sipuleucel-T (N = 419)</td>
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<td>71 (53–89)</td>
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NOTE: Data missing for: a. 1 patient; b. 2 patients; c. 5 patients; d. 4 patients; e. 5 patients.

Table 2. Statistical modeling approaches to survival subsequent to disease progression for control-arm patients

All control patients with protocol-defined disease progression

Cox regression model, stratified by study (D9903/P801; n = 216)

APC8015F treatment effect (unadjusted)

HR: 0.53; 95% CI: 0.38–0.74; P < 0.001

Adjusted for baseline PSA and LDH

HR: 0.56; 95% CI: 0.40–0.80; P = 0.001

Cox regression model, adjusted for baseline values for patient characteristics (n = 215)★

APC8015F treatment effect

HR: 0.78; 95% CI: 0.54–1.11; P = 0.17

Docetaxel effect

HR: 0.86; 95% CI: 0.60–1.22; P = 0.40

Control patients on IMPACT study with protocol-defined disease progression

Cox regression model, adjusted for most recent collected values for patient characteristics (n = 141)★

APC8015F treatment effect

HR: 0.81; 95% CI: 0.53–1.30; P < 0.39

Docetaxel effect

HR: 0.71; 95% CI: 0.45–1.10; P = 0.32

★Model terms considered but not included in the final model due to lack of statistical significance were baseline PSA, study, prior docetaxel usage, Gleason sum, primary Gleason grade, and bisphosphonate usage. One subject was excluded from the analysis due to a missing baseline covariate.

★Model terms considered but not included in the final model due to lack of statistical significance were prior docetaxel usage, the most recently collected hemoglobin and PSA velocity values, baseline values for Gleason sum, primary Gleason grade, current bisphosphonate use, and number of bone metastases.
to 141 IMPACT patients with protocol-defined disease progression. Trends toward increased postprogression survival were observed for APC8015F (HR, 0.81; 95% CI, 0.51–1.30; \( P = 0.39 \)) and postprogression docetaxel (HR, 0.71; 95% CI, 0.45–1.10; \( P = 0.12 \)) treatments (Table 2; Supplementary Table S1). The final model included most recently collected values for PSA, LDH, and alkaline phosphatase, ECOG status (0/1 vs. 2/3), and age. Variables not included were prior docetaxel use, the most recently collected hemoglobin and PSA velocity values, and baseline values for Gleason sum, primary Gleason grade, current bisphosphonate use, and number of bone metastases.

Extent of exposure

Of 165 patients receiving \( \geq 1 \) APC8015F infusion, 146 (88.5%) received three infusions; 137 of 155 (88.4%) patients with protocol-defined disease progression received three infusions. PB01 patients could undergo another leukapheresis procedure if their cryopreserved cells were inadequate for manufacturing three APC8015F infusions; 19 of 109 patients underwent additional leukapheresis procedures and 11 received sipuleucel-T infusions instead of APC8015F prepared from frozen cells (1 infusion: \( n = 5 \); 2 infusions: \( n = 5 \); 3 infusions: \( n = 1 \)). These 11 patients were included in the APC8015F treatment group for analysis.

We explored correlations between cumulative exposure and OS in patients receiving APC8015F. After adjusting for the last PSA value collected prior to the first APC8015F infusion, a positive association with subsequent survival was observed for cumulative APC activation (HR, 0.52; 95% CI, 0.31–0.89; \( P = 0.02 \)), but not for cumulative TNC counts (HR, 0.77; 95% CI, 0.57–1.05; \( P = 0.09 \)) or cumulative APC counts (HR, 0.98; 95% CI, 0.77–1.24; \( P = 0.84 \)).

Adverse events

Chills, nausea, and pyrexia were the most common adverse events reported within 1 day of APC8015F infusions (Table 3). Incidences of these events after APC8015F infusions were greater than those observed after control infusions, but fewer than incidences observed after sipuleucel-T infusions (3, 4).

Survival estimates for sipuleucel-T, after correction for APC8015F treatment

Post hoc analysis from three phase III trials, a 3.9-month median OS difference was observed between sipuleucel-T and control arms. However, 66.3% of control-arm patients (\( n = 165/249 \)) received APC8015F. Using IPE modeling, the control group OS curve was reconstructed as if APC8015F treatment had not occurred; the estimated sipuleucel-T treatment effect on median OS was between 3.9 months (if APC8015F had no effect) and 8.1 months (if APC8015F and sipuleucel-T were equally effective; Fig. 3). For the IMPACT study alone, 63.7% of control-arm patients received APC8015F, and the estimated sipuleucel-T treatment effect on median OS was between 4.1 and 7.8 months.

Discussion

The results of three randomized controlled trials of sipuleucel-T versus control in metastatic CRPC demonstrating an OS benefit for active immunotherapy represented a paradigm shift in the treatment landscape of patients with advanced prostate cancer. After patients experienced disease progression, the trials tested the option for control-arm patients to receive salvage treatment with APC8015F, an autologous cellular immunotherapy made from cells cryopreserved at the time of control manufacture. Because of this trial design feature, we evaluated subsequent outcomes of control patients to characterize APC8015F effects. Although our results are confounded by the randomized nature of treatment decisions after progression and the imbalance of prognostic characteristics, we found that the control-treated patients in sipuleucel-T phase III trials were comparable with those experienced following sipuleucel-T infusions, albeit at lower incidences (9). In addition, survival after APC8015F treatment correlated with cumulative APC activation. These findings are consistent with those for sipuleucel-T: APC activation is a sipuleucel-T potency measure and correlates with OS in sipuleucel-T–treated patients (4, 10). Taken together, these results suggest that APC8015F may have prolonged survival of patients in the control arms in the phase III sipuleucel-T trials, potentially understimating the observed differences in OS between the control and sipuleucel-T arms.
Although not all subsequent anticancer interventions were for other postprogression treatments were not performed. Postprogression docetaxel treatment was included as a time-only broadly available treatment with a known survival benefit. The assumption that APC8015F is equally as effective as sipuleucel-T is 0.78 is the same as the hazard ratio point estimate for sipuleucel-T. The assumption that APC8015F treatment had not occurred. The estimated sipuleucel-T treatment effect on median OS was 3.9 months if APC8015F had no effect on survival and was as high as 8.1 months if APC8015F was equally as effective as sipuleucel-T. The assumption that APC8015F is equally as effective as sipuleucel-T cannot be assessed, but it is not an unreasonable assumption given the estimated hazard ratio for APC8015F of 0.78 is the same as the hazard ratio point estimate for sipuleucel-T observed in the IMPACT trial (3).

These conclusions are subject to a number of caveats. The studies were not powered to conduct comparisons within subsets of control arms. Patients were not randomly assigned to APC8015F treatment, and the process by which investigators chose which patients to enroll in APC8015F studies may have varied. Only specific patient characteristics were collected, and therefore included in the statistical models to adjust for effects of selection bias. Not all characteristics were collected throughout the studies, and additional variables may have affected survival (12). Statistical models can only adjust for measured variables and cannot fully account for all patient differences.

At the time these studies were conducted, docetaxel was the only broadly available treatment with a known survival benefit for patients with CRPC (13, 14). In the analyses described here, postprogression docetaxel treatment was included as a time-dependent covariate during statistical modeling. Adjustments for other postprogression treatments were not performed. Although not all subsequent anticancer interventions were collected, agents recently demonstrated to prolong OS, including cabazitaxel, abiraterone, enzalutamide, and alpharadin, were not generally available at the time these trials were conducted, and were therefore not likely to have influenced the findings (15–18).

Endpoints based on disease progression have the advantage of avoiding confounding effects of treatments administered after disease progression. However, the clinical significance of such endpoints is controversial; e.g., effects on progression-free survival have not reliably correlated with effects on OS, particularly in advanced prostate cancer (2, 19–21). OS therefore remains the most clinically meaningful endpoint in oncology clinical trials (22), and the potential for subsequent therapies to influence it requires careful assessment. Assessing OS in future clinical trials may need to use sophisticated statistical analyses, such as marginal structural models, in which prognostic variables that may also inform treatment decisions (e.g., ECOG status or PSA) are allowed to vary over time (23–25). More sophisticated models could also account for patient discontinuations that are dependent on treatment assignment and patient noncompliance with dosing (26). Using these models will require collecting patient characteristics and subsequent anticancer interventions throughout the time period during which survival is assessed.

Conclusions

In conclusion, determining the impact of postprogression therapies is difficult; however, these analyses indicate that APC8015F treatment was not associated with a detrimental outcome and may have extended patient survival on the control arms of the sipuleucel-T phase III trials. If so, the OS advantage for sipuleucel-T in metastatic CRPC may be more robust than previously estimated. Although treatment with APC8015F may have imparted some clinical benefit, a randomized trial would be required to obtain definitive evidence of its efficacy. With the recent studies demonstrating the efficacy of new agents in metastatic CRPC, including cabazitaxel, abiraterone, enzalutamide, and alpharadin (15–18), demonstrating improvements in OS may become increasingly difficult, and more sophisticated methods for understanding potential impacts of subsequent therapies will be needed.

Disclosure of Potential Conflicts of Interest

D.J. George reports receiving speakers bureau honoraria from Dendreon Pharmaceuticals, Inc., for which he also serves as a consultant/advisory board member. C. Nabhan is a consultant/advisory board member for Dendreon Pharmaceuticals, Inc. T. DeVries has ownership interest (including patents) in Dendreon Pharmaceuticals, Inc. J.B. Whitmore is VP, Biometrics at Dendreon Pharmaceuticals, Inc. for which he also has ownership interests, including patents. L.G. Gomella reports receiving commercial research support from Astellas, Dendreon Pharmaceuticals, Inc., and Janssen and is a consultant/advisory board member for Dendreon Pharmaceuticals, Inc.

Authors’ Contributions

Conception and design: D.J. George, C. Nabhan, T. DeVries, J.B. Whitmore

Development of methodology: D.J. George, T. DeVries, J.B. Whitmore

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Nabhan, L.G. Gomella

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D.J. George, C. Nabhan, T. DeVries, J.B. Whitmore, L.G. Gomella

Writing, review, and/or revision of the manuscript: D.J. George, C. Nabhan, T. DeVries, J.B. Whitmore, L.G. Gomella

Study supervision: L.G. Gomella
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