Survival Outcomes of Sipuleucel-T
Phase 3 Studies: Impact of Control Arm Cross-over to Salvage Immunotherapy

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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 3 sipuleucel-T trials were offered, in non-randomized 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 vs. control adjusted for APC8015F treatment (iterative parameter estimation model). Median time to first APC8015F infusion was 5.2 months (range: 1.8–33.1) post-randomization and 2.2 months (0.5-14.6) post-progression. After disease progression, median survival was longer for APC8015F-treated vs. control-only treated patients (20.0 vs. 9.8 months; hazard ratio [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, age, and number of bone metastases as potential (P<0.1) independent predictors of post-progression 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 benefit for sipuleucel-T vs. 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 APC8015F treatment
may have extended patient survival, suggesting the sipuleucel-T OS advantage in CRPC may be more robust than previously estimated.
Introduction

Sipuleucel-T (Provenge®; Dendreon Corporation, Seattle, WA) is an autologous cellular immunotherapy for treatment of men with asymptomatic/minimally symptomatic metastatic castrate-resistant prostate cancer (CRPC) (1). Three randomized, double-blind, controlled, phase 3 sipuleucel-T trials were conducted in CRPC (Figure 1) (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-arm 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 non-randomized 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. Co-primary 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 enrolment was well underway 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 (hazard ratio [HR]=0.78 [95% confidence interval (CI): 0.61, 0.98]; P=0.03) (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 3 studies.

**Materials and Methods**

**Study Design**

Three phase 3 sipuleucel-T trials were conducted: D9901 (Jan 2000-Sept 2004; clinicaltrials.gov NCT00005947), D9902A (May 2000-May 2005; NCT01133704), and IMPACT (Aug 2003-Apr 2009; primary analysis data cut-off: Jan 2009; NCT00065442; Figure 1) (2-4). Two open-label phase 2 APC8015F salvage studies were conducted: D9903 (May 2000-Oct 2004, for D9901/D9902A; NCT00065442) and PB01 (Apr 2004-June 2009, for IMPACT; NCT00849290). Trials were conducted in accordance with the Declaration of Helsinki and conformed to applicable guidelines for good clinical practice and FDA rules and guidelines. Institutional Review Boards approved study protocols. Patients provided written informed consent before any study procedures were performed.
Patients

Detailed eligibility criteria for phase 3 studies were previously described; patients had metastatic CRPC, serum testosterone <50 ng/dL, and Eastern Cooperative Oncology Group (ECOG) scores <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, >4), number of bone metastases (≤5, 6-10, >10), and bisphosphonate use for IMPACT. Whether/when to initiate APC8015F treatment or other anti-cancer interventions following disease progression was at investigator discretion; patients were not randomly assigned and APC8015F could be administered before or after other interventions.

Additional inclusion criteria for D99903/PB01 included: ≥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 \textit{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 (Figure 1).

Control infusions included one-third of cells from each leukapheresis. Remaining cells were cryopreserved for subsequent APC8015F preparation, utilizing the same activation procedure 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 post-activation/pre-activation CD54 molecules on APCs) (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 (Figure 1).

**Outcome Measures**

Disease progression endpoints for D9901/D9902A included progression of measurable or evaluable disease, spinal cord compression or pathologic fracture, requirement for radiation therapy, 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 since randomization was 34.1 months [range: 0–64.8]) (3). All anti-cancer interventions were collected between randomization and protocol-defined disease progression. After disease progression, first non-study anti-cancer 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: 1) unadjusted Cox regression, stratified by salvage protocol (D9903/PB01); 2) stratified Cox regression adjusted for log-transformed baseline PSA, LDH, and alkaline phosphatase levels and baseline hemoglobin and ECOG score; and 3) 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). Post-progression APC8015F and docetaxel use were fit as time-dependent covariates accounting for the exact timing of use and retained in models 3a and 3b while APC8015F was fit as a yes/no variable for models 1 and 2 which 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 iterative parameter estimation (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 crossover 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., Cary, NC).

Results

Patient Disposition

These exploratory analyses included pooled data for 737 patients from 3 randomized, controlled, double-blind, phase 3 trials (sipuleucel-T: 488; control: 249; Figure 2). Overall, 165 control-arm patients received APC8015F; 155/165 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 independent committee. 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 favourable 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 1) were comparable to the unadjusted model. To more comprehensively adjust for potential differences in baseline characteristics, independent predictors for post-progression survival were identified and incorporated in the model. Lower LDH and alkaline phosphatase levels, lower ECOG status (0 vs. 1), younger age (<65 vs. ≥65 years), fewer bone metastases (≤10 vs. >10), and higher hemoglobin levels were identified as independent variables with significant effects on post-progression survival (P<0.10). PSA values, study (D9903/PB01), previous docetaxel use (yes/no), Gleason sum (≤ 7, ≥8), primary Gleason grade (≤3, ≥4), and bisphosphonate use (yes/no) were not significant predictors. In addition to adjusting for independent predictors of post-progression survival, APC8015F and post-progression docetaxel treatments were included as time-dependent covariates in the model, given that initiating these therapies may also have influenced OS. Approximately half the control-treated patients received post-progression docetaxel (control with APC8015F:...
n=78/155, 50.3% [docetaxel before APC8015F treatment for 5 patients]; control with no APC8015F: n=28/61, 45.9%). Neither APC8015F nor docetaxel were significant predictors of post-progression survival in the multivariate model accounting for the exact timing of usage, but the point estimates are suggestive of increased survival; APC8015F (HR=0.78; 95%CI: 0.54, 1.11, p=0.17), post-progression docetaxel (HR=0.86; 95%CI: 0.60, 1.22, p=0.40) (Table 2, Supplementary Table 1). Importantly, 162 of the 216 subjects died, and this number of deaths provided 80% power to detect a HR of 0.61 for APC8015F and 0.64 for docetaxel; thus, the lack of statistical significance in the multivariate modelling could be related to power.

Changing patient characteristics after randomization may have influenced treatment decisions, so an additional model was created to include the most recent values for potential prognostic variables (collected prior to or within 28 days after disease progression). Only a subset of variables was collected post-baseline for D9901/D9902A, so the analysis was limited to 141 IMPACT patients with protocol-defined disease progression. Trends toward increased post-progression survival were observed for APC8015F (HR=0.81; 95%CI: 0.51, 1.30, p=0.39) and post-progression docetaxel (HR=0.71; 95%CI: 0.45, 1.10, p=0.12) treatments (Table 2, Supplementary Table 1). 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 ≥1 APC8015F infusion, 146 (88.5%) received 3 infusions; 137/155 (88.4%) patients with protocol-defined disease progression received 3 infusions. PB01 patients could undergo another leukapheresis procedure if their cryopreserved cells were inadequate for manufacturing 3 APC8015F infusions; 19/109 patients underwent additional leukapheresis procedure(s) 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 less than incidences observed after sipuleucel-T infusions (3, 4).

Survival Estimates for Sipuleucel-T, After Correction for APC8015F Treatment
Pooling data from three phase 3 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 modelling, 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; Figure 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 vs. control in metastatic CRPC demonstrating an OS benefit for active immunotherapy represented a paradigm shift in the treatment landscape of advanced prostate cancer patients. After patients experienced disease progression, the trials included 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. While our results are confounded by the non-randomized nature of treatment decisions after progression and the imbalance of prognostic characteristics, we found that the control-treated patients in sipuleucel-T phase 3 trials who received treatment with APC8015F had improved survival relative to control-treated patients not receiving APC8015F. Selection bias likely contributed to some of the difference in outcomes. A variety of modelling approaches were undertaken to assess the effectiveness of APC8015F on post-progression survival. The most comprehensive model accounted for the timing and usage of APC8015F and docetaxel and adjusted for differences in patient characteristics significantly associated with post-progression survival. This model showed trends toward improved post-progression survival with APC8015F (HR = 0.78, p=0.17), but this trend did not reach statistical significance.

Supportive evidence for the biologic activity of APC8015F was provided by the adverse events commonly experienced during the day following APC8015F.
infusions, which were comparable to 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 3 sipuleucel-T trials, potentially underestimating the observed differences in OS between the control and sipuleucel-T arms.

IPE modelling was used to explore what the sipuleucel-T treatment effect on OS might have looked like if ACP8015F salvage treatment had not occurred. This approach has been shown to be robust and produce minimal bias in comparison to other adjustment methods (11); it provided a framework for estimating control-arm outcomes, assuming 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 this 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 herein, post-progression docetaxel treatment was included as a time-dependent covariate during statistical modelling. Adjustments for other post-progression treatments were not performed. While not all subsequent anti-cancer 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 employ 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 non-compliance with dosing (26). Using these models will require collecting patient characteristics and subsequent anti-cancer interventions throughout the time period during which survival is assessed.

Conclusions

In conclusion, determining the impact of post-progression 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 3 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.
Acknowledgments

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References

1. PROVENGE® (sipuleucel-T) Suspension for Intravenous Infusion prescribing information. 2011.


### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Study Population</th>
<th>Patients with Protocol-Defined Disease Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control N=249</td>
<td>Sipuleucel-T N=488</td>
</tr>
<tr>
<td></td>
<td>With subseqnt APC8015F</td>
<td>With no subseqnt APC8015F</td>
</tr>
<tr>
<td></td>
<td>N=165</td>
<td>N=84</td>
</tr>
<tr>
<td></td>
<td>With subseqnt APC8015F</td>
<td>With no subseqnt APC8015F</td>
</tr>
<tr>
<td></td>
<td>N=155</td>
<td>N=61</td>
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<tr>
<td>Age, years; median (range)</td>
<td>71 (40, 89)</td>
<td>71 (40, 87)</td>
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<tr>
<td>Weight, pounds; median (range)</td>
<td>189(^a)</td>
<td>191(^a)</td>
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<tr>
<td></td>
<td>(132, 300)</td>
<td>(132, 282)</td>
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<tr>
<td>Race, Caucasian; n (%)</td>
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<td>151(^a)</td>
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<td></td>
<td>(92.0)</td>
<td>(91.5)</td>
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<td>ECOG status, 0; n (%)</td>
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<td>131 (84.5)</td>
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<td>Primary Gleason grade; n (%)</td>
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<td>a</td>
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<tr>
<td>≤3</td>
<td>116 (46.6)</td>
<td>74 (47.7)</td>
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<tr>
<td>≥4</td>
<td>133 (53.4)</td>
<td>81 (52.3)</td>
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<td>Gleason score; n (%)</td>
<td>a</td>
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<tr>
<td>≤7</td>
<td>171 (68.7)</td>
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<tr>
<td>≥8</td>
<td>77 (30.9)</td>
<td>47 (30.3)</td>
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<td>Number of bone metastases, n (%)</td>
<td>a</td>
<td>a</td>
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<tr>
<td></td>
<td>0 to 5</td>
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<td>27 (17.4)</td>
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<td>&gt;10</td>
<td>27 (17.4)</td>
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<td>51 (32.9)</td>
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<td>Prior use of docetaxel, yes; n (%)</td>
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<td>11 (7.1)</td>
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<td>Baseline laboratory results; median</td>
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<tr>
<td>Alkaline phosphatase, U/L</td>
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<td>98</td>
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<td>Hemoglobin, g/dL</td>
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<td>12.9</td>
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<tr>
<td>Lactate dehydrogenase, U/L</td>
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<td>184.0(^b)</td>
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<tr>
<td>PSA, ng/mL</td>
<td>46.6</td>
<td>49.9(^b)</td>
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</table>

Data missing for: a. 1 patient; b. 2 patients; c. 3 patients; d. 4 patients; e. 5 patients

ECOG=Eastern Cooperative Oncology Group; PSA=prostate specific antigen
Table 2. Statistical Modeling Approaches to Survival Subsequent to Disease Progression for Control-Arm Patients

<table>
<thead>
<tr>
<th>All Control Patients With Protocol-Defined Disease Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cox regression model, stratified by study (D9903, PB01; n=216)</strong></td>
</tr>
<tr>
<td>APC8015F treatment effect (unadjusted) HR=0.53 (95%CI: 0.38, 0.74); P&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for baseline PSA and LDH HR=0.56 (95%CI: 0.40, 0.80); P=0.001</td>
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</table>

<table>
<thead>
<tr>
<th>Control Patients On Impact Study With Protocol-Defined Disease Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cox-regression model, adjusted for most recently collected values for patient characteristics (n=141)</strong></td>
</tr>
<tr>
<td>APC8015F treatment effect HR=0.81 (95%CI: 0.51, 1.30); P=0.39</td>
</tr>
<tr>
<td>Docetaxel effect HR=0.71 (95%CI: 0.45, 1.10); P=0.12</td>
</tr>
</tbody>
</table>

1 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.

2 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.
Table 3. Incidence of Adverse Events with Onset of ≤1 Day after Infusion of Control, APC8015F, or Sipuleucel-T

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Control (N=244)</th>
<th>APC8015F (N=165)</th>
<th>Sipuleucel-T (N=485)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>126 (51.6)</td>
<td>71 (43.0)</td>
<td>390 (80.4)</td>
</tr>
<tr>
<td>Chills</td>
<td>11 (4.5)</td>
<td>23 (13.9)</td>
<td>254 (52.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (2.5)</td>
<td>13 (7.9)</td>
<td>64 (13.2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5 (2.0)</td>
<td>13 (7.9)</td>
<td>114 (23.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37 (15.2)</td>
<td>10 (6.1)</td>
<td>88 (18.1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>11 (4.5)</td>
<td>8 (4.8)</td>
<td>20 (4.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (2.9)</td>
<td>6 (3.6)</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (0.8)</td>
<td>6 (3.6)</td>
<td>25 (5.2)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>11 (4.5)</td>
<td>6 (3.6)</td>
<td>9 (1.9)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9 (3.7)</td>
<td>5 (3.0)</td>
<td>21 (4.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (0.4)</td>
<td>5 (3.0)</td>
<td>22 (4.5)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>7 (2.9)</td>
<td>5 (3.0)</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (0.8)</td>
<td>5 (3.0)</td>
<td>41 (8.5)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (1.2)</td>
<td>4 (2.4)</td>
<td>12 (2.5)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>3 (1.2)</td>
<td>4 (2.4)</td>
<td>5 (1.0)</td>
</tr>
</tbody>
</table>

a. Includes events reported for >2 % of APC8015F-treated patients. Control and sipuleucel-T columns include events occurring within 1 day after infusion during phase 3 studies, for safety analysis populations (patients undergoing a leukapheresis procedure). APC8015F column includes events occurring within 1 day after infusions during phase 2 salvage studies, for APC8015F-treated patients.

**Figure Legends** (files are attached separately)

Figure 1. Study Design.

Figure 2. Patient Disposition.

Figure 3. Estimates of Overall Survival, for all Patients on the Sipuleucel-T Phase 3 Trials (N=737), with Adjustment for APC8015F Treatment (IPE Model). Dotted red line assumes 100% effectiveness of APC8015F, compared with sipuleucel-T, and solid red line assumes 0% effectiveness.
**Figure 1**

Asymptomatic or Minimally Symptomatic\(^a\)
Metastatic Castrate-Resistant Prostate Cancer

Sipuleucel-T
Q2 weeks x3

2:1

Control
Q2 weeks x3

PROGRESSION

Treated at Physician’s Discretion

Treated at Physician’s Discretion, Including Optional Phase 2 Open-Label Study with APC8015F

SURVIVAL

\(^a\)D9901/D9902A: asymptomatic patients; IMPACT: both asymptomatic and minimally symptomatic patients
Figure 2

Randomized to sipuleucel-T or control (D9901; D9902A; IMPACT studies): 737

Randomized to sipuleucel-T: 488
  • Underwent leukapheresis: 485<sup>a</sup>

Randomized to control: 249
  • Underwent leukapheresis: 244<sup>a</sup>

Treatment with sipuleucel-T: 476
  • Protocol-defined disease progression: 419
    ▪ Radiographic progression: 400
    ▪ Other measures of progression: 19

Treatment with control: 243
  • Protocol-defined disease progression: 216
    ▪ Radiographic progression: 202
    ▪ Other measures of progression: 14

Received APC8015F (D9903; PB01): 165<sup>a</sup>
  • Protocol-defined disease progression: 155
  • Unconfirmed disease progression: 10

Did not receive APC8015F: 84
  • Protocol-defined disease progression: 61
  • Censored for disease progression: 23

<sup>a</sup>Defined as safety analysis set
The graph compares the percent survival over time from randomization (in months) for two groups: Sipuleucel-T (N=488) and control groups, with and without adjustment for APC8015F (N=249).

The table below summarizes the median overall survival (OS) for each group and the difference in medians:

<table>
<thead>
<tr>
<th>Effectiveness of APC8015F Compared with Sipuleucel-T</th>
<th>Sipuleucel-T Median OS, Months</th>
<th>Control Median OS, Months</th>
<th>Difference in Medians, Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>25.4</td>
<td>21.5</td>
<td>3.9</td>
</tr>
<tr>
<td>25%</td>
<td>25.4</td>
<td>20.5</td>
<td>4.9</td>
</tr>
<tr>
<td>50%</td>
<td>25.4</td>
<td>19.3</td>
<td>6.1</td>
</tr>
<tr>
<td>75%</td>
<td>25.4</td>
<td>18.4</td>
<td>7.0</td>
</tr>
<tr>
<td>100%</td>
<td>25.4</td>
<td>17.3</td>
<td>8.1</td>
</tr>
</tbody>
</table>
Cancer Immunology Research

Survival Outcomes of Sipuleucel-T Phase 3 Studies: Impact of Control Arm Cross-over to Salvage Immunotherapy

Daniel J George, Chadi Nabhan, Todd DeVries, et al.

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