Post-Progression Treatment with APC8015F may have Prolonged Survival of Subjects in the Control Arm of Sipuleucel-T Phase 3 Studies

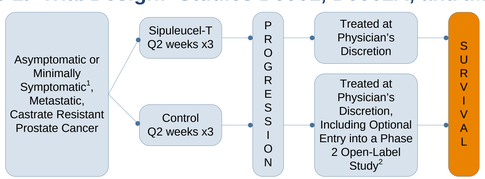
L.G. Gomella[1], C. Nabhan[2], J.B. Whitmore[3], M.W. Frohlich[3], and D.J. George[4] ([1]Jefferson Medical College, Philadelphia PA, [2]Advocate Lutheran General Hospital, Park Ridge IL, [3]Dendreon Corp., Seattle WA, [4]Duke Univ., Durham NC)

Introduction

Sipuleucel-T is an autologous cellular immunotherapy FDA approved for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer (mCRPC). Integrated results from 3 randomized, double blind, controlled Phase 3 studies provided evidence of survival prolongation in the study population (HR=0.735 [95% CI: 0.613, 0.882]; P<0.001). Control was non-activated, autologous peripheral blood mononuclear cells. Subjects with disease progression following participation in the control arm of these 3 studies could participate in a Phase 2, open-label study and receive APC8015F, an autologous immunotherapy made from cells cryopreserved at the time of control generation. Here we report an analysis of the APC8015F treatment effect across the 3 studies.

Methods

Figure 1. Trial Design: Studies D9901, D9902A, and IMPACT



Endpoints for D9901 and D9902A
Primary:Time to Disease Progression
Planned Analysis: Overall Survival

Endpoints for IMPACT
Primary: Overall Survival
Secondary: Time to Objective Disease Progression

[1]Studies D9901 and D9902A enrolled only asymptomatic subjects
[2] Treatment with APC8015F under salvage protocol D9903 for subjects from studies D9901 and D9902A, and salvage protocol PB01 for subjects from the IMPACT study

Analysis of APC8015F Treatment Effect Across Studies D9901, D9902A, and IMPACT

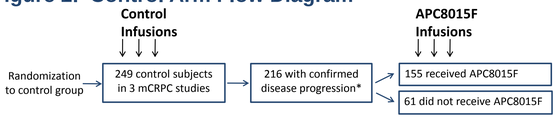
- APC8015F is an autologous immunotherapy made from cells cryopreserved at the time of control generation and required to meet the same potency specifications (CD54 upregulation) as sipuleucel-T
- Disease progression was evaluated by imaging studies (bone scan and CT) and confirmed by independent, blinded review committees
- Following disease progression, subjects in the control arms of D9901, D9902A, and IMPACT were offered 3 infusions of APC8015F
- Baseline characteristics and adverse events (AEs) were reported in the APC8015F group for any subject who received at least one infusion of APC8015F whether or not disease progression was confirmed
- APC8015 treatment effect analyses were performed using data from control subjects with confirmed disease progression

Statistical Analyses of Overall Survival Following Disease Progression

- Unadjusted analysis based on Cox model (stratified by study D9903 or PB01) and the log-rank test
- Stratified Cox regression model adjusted for baseline PSA and LDH
- Stratified Cox regression model adjusted for baseline age, PSA, LDH, and post-randomization docetaxel use (yes/no)
- Model-based analysis using backward selection to identify significant (P<0.10) baseline prognostic variables. Post-randomization APC8015F treatment and docetaxel use were fit as time dependent co-variates, and were retained in the model

Results

Figure 2. Control Arm Flow Diagram



*10 control subjects did not have confirmed disease progression and were treated with APC8015F

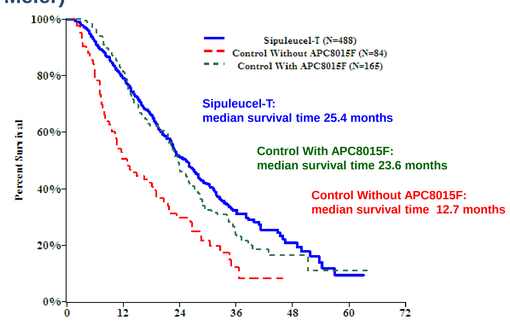
- **Median time from randomization to first APC8015F infusion was 5.2 months (range 1.8-33.1)**
- **Median time from disease progression to first APC8015F infusion was 2.2 months (range 0.5-14.6)**

Table 1. Baseline Characteristics

Characteristic	Control (N=84)	APC8015F (N=165)	Sipuleucel-T[1] (N=488)
Age, median (range, years)	71 (53-89)	70 (40-87)	72 (47-91)
Weight ,median (range, lbs)	186 (135-300)	191 (132-282)	194 (116-384)
Race, Caucasian, n (%)	78 (92.9)	151 (91.5)	437 (89.5)
ECOG Performance Status = 0, n (%)	59 (70.2)	140 (84.8)	393 (80.5)
Gleason Sum, n (%)			
≤ 7	56 (66.7)	115 (69.7)	351 (72.0)
≥ 8	28 (33.3)	49 (29.7)	136 (27.9)
Number of bone metastases, n (%)			
0-5	33 (39.3)	79 (47.9)	206 (42.2)
6-10	10 (11.9)	29 (17.6)	67 (13.7)
> 10	40 (47.6)	57 (34.5)	211 (43.2)
Baseline Laboratory Results			
Alkaline phosphatase, median (U/L)	117.0	97.0	103 .0
Hemoglobin, median (g/dL)	12.6	12.9	12.9
Lactate dehydrogenase, median (U/L)	196.0	184.0	190.0
Serum PSA, median (ng/mL)	62.1	40.8	51.5

[1]Baseline characteristics are reported for all randomized subjects from the 3 mCRPC studies.

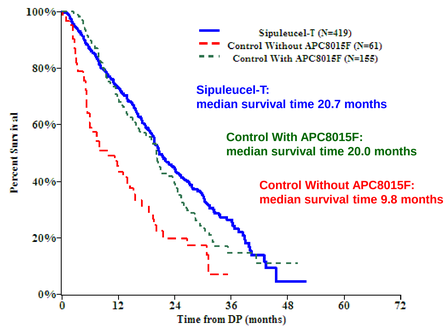
Figure 3. Overall Survival from Randomization (Kaplan-Meier)



To eliminate the effect of variability in time to disease progression (at which point the control subjects became eligible to receive APC8015F), an analysis of survival subsequent to disease progression was undertaken (Figure 4).

Results

Figure 4. Overall Survival Following Disease Progression (Kaplan-Meier)



APC8015F-treated control subjects had improved post-progression survival relative to untreated control subjects. Because APC8015F-treated control subjects had more favorable baseline characteristics, modeling approaches to adjust for baseline and post-progression covariates were therefore undertaken.

Table 2. Modeling Approaches

Post-progression APC8015F effect in control subjects (log rank test, Cox regression)	
Unadjusted	HR=0.52 (95% CI: 0.37, 0.73); P=0.0001
Adjusted for baseline PSA and LDH	HR=0.56 (95% CI: 0.40, 0.80); P=0.001
Adjusted for baseline age, PSA, LDH, and post-randomization docetaxel use	HR=0.55 (95% CI: 0.39, 0.78); P<0.001
Adjusted for independent predictors of overall survival and with APC8015F treatment and docetaxel as time dependent covariates[1]	
APCF8015F 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

[1] Independent baseline predictors were determined by backwards stepwise method, and included lower LDH, alkaline phosphatase, ECOG status, age, number of bone metastases, and higher hemoglobin

Docetaxel was received post-randomization in 78/155 (50.3%) of APC8015F-treated control subjects and in 28/61 (45.9%) of untreated control subjects

Table 3. Cumulative Product Parameters

	Correlation with Overall Survival Subsequent to First APC8015F Infusion[1] (n=155)			
	Median	HR	95% CI	P value
CD54 upregulation (fold)	21.98	0.555	0.322, 0.958	0.03
CD54 counts (x 10^9)	0.50	0.916	0.732, 1.145	0.44
Total nucleated cell count (x 10^9)	1.90	0.751	0.571, 0.987	0.04

[1] HR, 95% CI, and p-value from Cox regression model with log-transformed cumulative product parameter adjusted for log-transformed baseline PSA and LDH, stratified by salvage protocol D9903 or PB01.

Results

Table 4. Incidence of Adverse Events with Onset ≤ 1 Day After Infusion Reported in >2% of APC8015F Subjects

Preferred Term	Control[1] (N=244) n (%)	APC8015F (N=165) n (%)	Sipuleucel-T[1] (N=485) n (%)
Any Subject Reporting an AE	126 (51.6)	71 (43.0)	390 (80.4)
Chills	11 (4.5)	23 (13.9)	254 (52.4)
Nausea	6 (2.5)	13 (7.9)	64 (13.2)
Pyrexia	5 (2.0)	13 (7.9)	114 (23.5)
Fatigue	37 (15.2)	10 (6.1)	88 (18.1)
Back Pain	11 (4.5)	8 (4.8)	20 (4.1)
Constipation	7 (2.9)	6 (3.6)	6 (1.2)
Hypertension	2 (0.8)	6 (3.6)	25 (5.2)
Pain in Extremity	11 (4.5)	6 (3.6)	9 (1.9)
Arthralgia	9 (3.7)	5 (3.0)	21 (4.3)
Dizziness	1 (0.4)	5 (3.0)	22 (4.5)
Musculoskeletal Pain	7 (2.9)	5 (3.0)	7 (1.4)
Vomiting	2 (0.8)	5 (3.0)	41 (8.5)
Anorexia	3 (1.2)	4 (2.4)	12 (2.5)
Weight Decreased	3 (1.2)	4 (2.4)	5 (1.0)

[1] AEs from safety population of studies D9901, D9902A, and IMPACT ≤ 1 day after initial infusion of sipuleucel-T or control. Table ordered by APC8015F events.

Summary

- **APC8015F-treated control subjects had improved post-progression survival relative to untreated control subjects, which persisted after adjusting for baseline and post-progression variables**
- **Cumulative CD54 upregulation and TNC count product parameters were correlated with survival in APC8015F-treated control subjects, consistent with correlations observed between product parameters and survival for sipuleucel-T subjects**
- **APC8015F-treated control subjects generally experienced more of the most common AEs than untreated control subjects and fewer of the most common AEs than subjects treated with sipuleucel-T**

Conclusions

- **There is no evidence that treatment with APC8015F adversely affected outcome**
- **APC8015F demonstrated evidence of clinical activity**
  - **Associated with longer survival**
  - **Demonstrated modest treatment-related AEs**
  - **Cumulative CD54 upregulation correlated with prolonged survival**
- **APC8015F may have prolonged survival of the control arm in the three Phase 3 studies of sipuleucel-T, potentially diminishing the observed survival benefit**

Contact: Daniel J. George, MD (daniel.george@duke.edu) PP-1940.00 02JUN11