The Development of Sipuleucel-T (Provenge®) for Active Cellular Immunotherapy for Prostate Cancer

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Forward Looking Statements

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Presenter Disclosure Information

David L. Urdal

The following relationships exist related to this presentation:

• I am employed by Dendreon
• I own stock in Dendreon
• I will be discussing development of a Dendreon product candidate
The Sipuleucel-T Experience

- Introduction to Prostate Cancer and Sipuleucel-T
- Development
  - Clinical results
  - Regulatory milestones
- Conclusions
Natural History of Prostate Cancer

- **Castration**
- **Local Therapy**
- **Chemotherapy**
- **Death**

- **Tumor volume & activity**
  - **Asymptomatic**
    - **Non-Metastatic**
      - Androgen Dependent
    - **Metastatic**
      - Androgen Independent
  - **Symptomatic**
Androgen-Independent (Hormone-Refractory) Prostate Cancer Remains Unmet Medical Need

- Deadly disease
- Modest survival advantage seen with docetaxel-based regimens
- Majority of patients reject chemotherapy due to QOL impact
- Novel treatment approaches with acceptable safety profiles are needed
Sipuleucel-T is an autologous investigational active cellular immunotherapy product that activates the immune system against prostate cancer.
Sipuleucel-T: Patient-Specific Product

Day 1
Leukapheresis

Day 2-3
sipuleucel-T is manufactured

Day 3-4
Patient is infused

Apheresis Center

Dendreon

Doctor’s Office

COMPLETE COURSE OF THERAPY:
Weeks 0, 2, 4
Pre-Clinical Rationale

- Antigen-loaded APCs isolated from peripheral blood showed clinical promise in lymphoma
- Prostatic acid phosphatase (PAP) highly expressed in prostate tissue
- Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) activates APCs
- Rat APCs, loaded with PAP+GM-CSF fusion protein, induced prostatitis

Sipuleucel-T is Active in a Preclinical Model of Autoimmune Prostatitis

Sipuleucel-T: autologous APC cultured with PAP-cytokine fusion protein

Recombinant Prostatic Acid Phosphatase (PAP) antigen combines with resting antigen presenting cell (APC)

APC takes up the antigen

Antigen is processed and presented on surface of the APC

Fully activated, the APC is now sipuleucel-T

INFUSE PATIENT

T-cells proliferate and attack cancer cells

Sipuleucel-T activates T-cells in the body

The precise mechanism of sipuleucel-T in prostate cancer has not been established.
Key Product Components and Attributes

- Mononuclear Cells
  - Total nucleated cell (TNC) count
  - CD54 positive cells take up antigen
  - CD54 positive cells present antigen to PAP specific T cells
  - CD54 upregulates during culture with antigen

- Recombinant Antigen
  - Specified concentration in culture
  - Manufactured under GMP conditions
  - Well characterized biologic
The Sipuleucel-T Experience

- Introduction to Prostate Cancer and Sipuleucel-T
- Development
  - Clinical results
  - Regulatory milestones
- Conclusions
Results: Sipuleucel-T Phases 1 & 2 Trials (Mayo Clinic and UCSF)

Safety
• No dose limiting toxicities
• Treatment well tolerated

Immune Responses
• Regimen: maximum immune responses reached after 3 infusions
• T cell responses were specific [not increased to recall flu antigen or KLH]

Phase 1 and 2 Trials-- Clinical Effects

- PSA decline of > 50% in 6/62 (10%) of AIPCa patients
- Objective (bidimensional mass) response observed
- Immune responses correlated with prolonged time to objective progression
- Prolongs PSADT in ADPC

Burch PA, et al., Clin Cancer Res 6:2175, 2000


Burch PA, et al., Prostate 60:197, 2004

The Phase 3 Plan

• Two identical Phase 3 multi-center, double-blind, randomized, placebo controlled trials
  – D9901
  – D9902A
• Target population: asymptomatic, metastatic androgen independent prostate cancer
• Well-defined manufacturing process
• Potency and other release specifications established
Randomized, Double Blind, Placebo-Controlled Trials, Studies D9901 and D9902

Primary endpoint: Time to Disease Progression
- Radiographic, Clinical or Pain
- Not PSA

Planned analysis: Overall Survival
D9901 Primary Efficacy Analysis (ITT)
Time from Randomization to Disease Progression

Sipuleucel-T Overall 3-Year Survival Intent-to-Treat Study D9901

- p-value = 0.01 (log rank)
- HR = 1.7
- Median Survival Benefit = 4.5 months

Placebo (n=45)
- 34% survival

Sipuleucel-T (n=82)
- Median Survival: 25.9 mos.
- 11% survival

Phase 3 Study Key Findings
Study D9901

- 31% delay in time to progression
  \( (p\text{-value} = 0.052; \text{HR} = 1.45) \)
- 41% overall reduction in risk of death
- Median survival benefit: 4.5 months
  \( (p\text{-value} = 0.01; \text{HR} = 1.70) \)
Sensitivity Analyses to Test Survival Result Robustness

- Balance and consistency in study subpopulations
- Adjustment for baseline prognostic factors
- Assessment of chemotherapy use and timing following study treatment
- Prostate cancer-specific survival
## Balance of Treatment Arms
### Halabi Analysis, Study D9901

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Predicted Survival (months)(^+)</th>
<th>Observed Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipuleucel-T</td>
<td>82</td>
<td>20.1</td>
<td>25.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>45</td>
<td>19.9</td>
<td>21.4</td>
</tr>
</tbody>
</table>

+ Median of predicted survivals, as calculated using model of Halabi et al., JCO 2003

Source: Small, EJ, Prostate Cancer Foundation Scientific Retreat, 2006
Treatment Effect Consistent Across Subpopulations

Favors sipuleucel-T

- Age (Above Median)
- (Below Median)
- Alk. Phos. (Above Median)
- (Below Median)
- PSA (Above Median)
- (Below Median)
- LDH (Above Median)
- (Below Median)
- Hemoglobin (Above Median)
- (Below Median)
- Weight (Above Median)
- (Below Median)
- Loc. Dis.-Bone Only or ST Only
- Bone and ST
- Met. Lesions (≤10)
- (>10)

Hazard Ratio (95% Confidence Interval)
Adjustment for Multiple Prognostic Factors

- LDH
- PSA
- # bone metastases
- Weight
- Localization of disease
Survival Benefit Confirmed by Adjustment for Multiple Prognostic Factors

Comparison of Hazard Ratios:

- **Unadjusted**:
  - Hazard Ratio: 1.71
  - Treatment Effect: Favors sipuleucel-T
  - p-value: p = 0.010

- **Adjusted**:
  - Hazard Ratio: 2.16
  - Treatment Effect: Favors sipuleucel-T
  - p-value: p = 0.002
Chemotherapy Use Following Study Treatment Does Not Explain Survival Benefit

- No evidence of a difference in docetaxel use

<table>
<thead>
<tr>
<th>sipuleucel-T</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>56%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>37%</td>
</tr>
</tbody>
</table>

- No evidence of a delay in time to docetaxel initiation in placebo arm

- Treatment effect remained strong:
  - In study subpopulations based on docetaxel use
  - After adjustment for docetaxel use
Prostate Cancer Specific Survival Study D9901

- Sipuleucel-T (n=82)
- Placebo (n=45)

P = 0.002 (log rank)

HR = 2.04 [95% CI: 1.30, 3.19]
Survival Results Confirmed by Multiple Sensitivity Analyses

- Survival
- Adj. for prognostic factors
- Adj. for docetaxel
- PCa-specific survival

Hazard Ratio (95% Confidence Interval)

- Favors sipuleucel-T
  - 1.71
  - 2.16
  - 1.54
  - 2.04

Favors sipuleucel-T
Clinically Significant and Statistically Persuasive Overall Survival Benefit

- **sipuleucel-T (n=82)**
- **placebo (n=45)**

- \( p = 0.010 \) (log rank)
- \( HR = 1.71 \ [95\% \ CI: 1.13, 2.58] \)

- Median benefit 4.5 months

- 34% for sipuleucel-T
- 11% for placebo
Sipuleucel-T Laboratory/Clinical Correlations

Key product attributes:

• Total nucleated cell count
• CD54 count
• CD54 ‘upregulation’

The precise mechanism of sipuleucel-T in prostate cancer has not been established.
CD54 Upregulation Potency Assay for APCs

APCs cultured with recombinant antigen

CD54

Mean Fluorescence Intensity

Pre-culture

Post-culture
CD54 Upregulation by Treatment Week Phase 3 Manufacturing Data
## Correlation Analysis for Key Product Attributes and Survival, Integrated Studies 1 & 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>p-value</th>
<th>N = 146</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD54 Upregulation</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Total Nucleated Cells</td>
<td>0.018</td>
<td></td>
</tr>
</tbody>
</table>
Survival by Cumulative CD54 Upregulation in Quartiles, Integrated Studies 1 & 2

Percent survival over months for different quartile ranges:
- ≥ 75th percentile
- 50th to 75th percentile
- 25th to 50th percentile
- ≤ 25th percentile
**Correlation analysis for Key Product Attributes and Survival**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted p-value</th>
<th>p-value with Adjustment*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 146</td>
<td>N = 134</td>
</tr>
<tr>
<td><strong>CD54 Upregulation</strong></td>
<td>0.009</td>
<td>0.022</td>
</tr>
<tr>
<td><strong>Total Nucleated Cells</strong></td>
<td>0.018</td>
<td>0.138</td>
</tr>
</tbody>
</table>

*Adjusted for 5 prognostic factors in Cox regression model*
Sipuleucel-T Potency Correlates with Survival

- Biologically relevant product measurement
- Independent of prognostic factors
- May support the efficacy findings
Sipuleucel-T Induces Significant T-cell Mediated Immune Response (Week 0 to Week 8)

Median Stimulation Index Ratio

- Sipuleucel-T (Mean = 16.9)
- Placebo (Mean = 1.99)

p = 0.0003

Presented at ASCO 2003
# Sipuleucel-T is Well Tolerated

<table>
<thead>
<tr>
<th>Event [n(%)]</th>
<th>Sipuleucel-T (n=82)</th>
<th>Placebo (n=45)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
<td>Grade 3-4</td>
<td>Grade 1-2</td>
</tr>
<tr>
<td>Rigors (chills)</td>
<td>45 (54.9)</td>
<td>4 (4.9)</td>
<td>4 (8.9)</td>
</tr>
<tr>
<td>Pyrexia (fever)</td>
<td>22 (26.8)</td>
<td>2 (2.4)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Tremor</td>
<td>8 (9.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Feeling Cold</td>
<td>7 (8.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
The Sipuleucel-T Experience

• Introduction to Sipuleucel-T process and characterization
• Development
  ➢ Clinical results
  ➢ Regulatory milestones
• Conclusions
Sipuleucel-T Proposed Basis for Licensure

- Randomized, double blind, placebo-controlled studies
- Primary Evidence: D9901
  - Survival
    - Statistically robust, internally consistent findings
    - Confirmed in multiple sensitivity analyses
  - Time to disease progression
    - Trend toward a delay
- Supportive evidence
  - Trend in overall survival in D9902A
  - Integrated analyses
  - Survival correlates with product potency
- Demonstrated safety and tolerability
The Center for Biologics Evaluation and Research (CBER)
- Office of Cellular, Tissue and Gene Therapies (OCTGT)

September 2005: Pre-BLA Meeting held with FDA:
- Survival benefit observed in Study D9901
- Supported by D9902A and the absence of significant toxicity
- Will serve as the clinical basis of a BLA for sipuleucel-T

November 2005: FDA granted Fast Track Status for sipuleucel-T
Regulatory Milestones (continued)

- August – November 2006: Submit rolling BLA
- January 2007: BLA accepted for Priority Review
- March 2007: FDA’s Cell, Tissue and Gene Therapies Advisory Committee
Cell, Tissue and Gene Therapy Advisory Committee

• Key Questions to the Committee
  – Is sipuleucel-T reasonably safe for the intended patient population?
    17 yes – 0 no
  – Has substantial evidence of efficacy been established?
    13 yes – 4 no
The Preliminary Outcome

- Request for additional clinical and CMC information
### Sipuleucel-T Studies in Prostate Cancer

#### Androgen Dependent

<table>
<thead>
<tr>
<th>Study</th>
<th>D9905</th>
<th>P-16</th>
<th>P-11</th>
<th>D9901</th>
<th>D9902A</th>
<th>D9902B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Phase 2</td>
<td>Phase 2</td>
<td>Phase 3</td>
<td>Phase 3</td>
<td>Phase 3</td>
<td>Phase 3</td>
</tr>
<tr>
<td>No. of Subjects</td>
<td>19</td>
<td>22</td>
<td>~175</td>
<td>127</td>
<td>98</td>
<td>500</td>
</tr>
<tr>
<td>Results</td>
<td>Sipuleucel-T may lead to improved PSADT</td>
<td>Sipuleucel-T plus Avastin™ increased PSADT</td>
<td>Data suggest a potential role for sipuleucel-T in ADPC</td>
<td>4.5 month median survival benefit for men who received sipuleucel-T</td>
<td>3.3 month median survival benefit for men who received sipuleucel-T</td>
<td>Patient accrual complete in 2007</td>
</tr>
<tr>
<td>Complete</td>
<td>√</td>
<td>√</td>
<td>Preliminary</td>
<td>√</td>
<td>√</td>
<td>Enrolled</td>
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</table>

#### Androgen Independent

- **Patient accrual complete in 2007**
- **4.5 month median survival benefit for men who received sipuleucel-T**
- **3.3 month median survival benefit for men who received sipuleucel-T**

**Note:** PSADT = Prostate Specific Antigen Density Time.
**IMPACT Phase 3 Study (D9902B)**

**IMmunotherapy for Prostate AdenoCarcinoma Treatment**

- Randomized 2:1, double-blind, placebo-controlled
- ~500 men with minimally symptomatic, metastatic AIPC
- Enrolling at ~70 sites in North America
- Primary endpoint: Survival
- Secondary endpoint: Time to objective disease progression
- Special Protocol Assessment
- Positive interim or final survival analysis sufficient to amend BLA
Sipuleucel-T Phase 3 Study: Conclusions

• An ITT analysis of survival demonstrated that compared with Placebo, sipuleucel-T:
  – Provided a survival advantage of 4.5 months
  – Resulted in a significantly greater percentage of patients alive at 36 months (34% vs 11%)

• There is a trend towards improved median time to progression in asymptomatic AIPC patients treated with sipuleucel-T, compared with placebo ($P = 0.052$, Hazard Ratio = 1.45)
Sipuleucel-T Phase 3 Study: Conclusions

- Survival results represent mature data set
- Survival data not explained by differences in:
  - Non-prostate cancer related deaths
  - Imbalance in baseline prognostic factors
  - Subsequent chemotherapy use or timing following treatment
- Potency may correlate with survival outcome
- Consistent results between studies
Sipuleucel-T Phase 3 Study: Conclusions

- Rapid tumor progression prior to onset of immune effect may explain discordance between effect of sipuleucel-T on time to progression and its effect on overall survival

- TTP may not be the most appropriate endpoint for clinical studies in patients treated with immunotherapy agents like sipuleucel-T

- Sipuleucel-T is well tolerated and has a favorable toxicity profile

- Sipuleucel-T results in a significant T cell mediated immune response

- Sipuleucel-T represents the first non-chemotherapeutic agent that may provide a survival advantage in AIPC patients
Active Cellular Immunotherapy: A Potential New Treatment for Prostate Cancer

Immunotherapies (sipuleucel-T)
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