Meeting the challenges of developing cancer vaccines--APC8015 (Provenge™) as a case study

- Immunogenicity and Breaking Tolerance
- Appropriate endpoints and patient populations
- Survival as an achievable endpoint for active immunotherapy
- Extending to earlier disease and to combination therapy
The challenge of generating a ‘functional’ immune response against a cancer antigen
Immunogenicity and Breaking Tolerance--

Tumor antigens are ignored by the immune system

- **What is a good “tumor antigen”?**
  - Often selected based on a pattern of over-expression relative to normal tissue
  - Typically not expressed in a uniform pattern and not in 100% of cells in a particular tumor
  - Selection of antigen negative variants?
  - Need for cross-priming and/or ‘epitope-spreading’?

- **T cell tolerance and cancer**
  - Central tolerance to tumor antigens
  - Peripheral tolerance and/or Anergy
  - Regulatory T cells

- **Tumor specific effects**
  - Local production of inhibitory cytokines [e.g. TGFβ]
A strong priming response is fundamental to break immune tolerance in cancer
Dendreon’s Cancer Vaccine Platform

- Select well validated and well characterized antigen targets
- Well characterized recombinant protein
- Proprietary Antigen Delivery Cassette™ technology

Prostatic Acid Phosphatase (PAP)  GM-CSF
APC8015 (Provenge™)

Antigen Loading → Antigen Processing → Maturing antigen-loaded APC

Antigen Loading:
- Antigen
- Precursor APC

Antigen Processing:
- Antigen-loaded precursor APC

Maturing antigen-loaded APC

Infuse subject

APC8015

T cells attack tumor cells

In vivo T cell activation
PA2024-FITC Binds to Antigen Presenting Cells
PAP Antigen Presenting Activity is found in CD54+ Cells

![Graph showing APC activity in CD54+ and CD54- cells for Paperino and Papillon](image-url)
Provenge (APC8015) Induces Significant T-cell Mediated Immune Response (Week 0 to Week 8)

Median Stimulation Index Ratio

<table>
<thead>
<tr>
<th></th>
<th>Provenge (n=29)</th>
<th>Placebo (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Stimulation Index Ratio</td>
<td>16.9</td>
<td>1.99</td>
</tr>
</tbody>
</table>

p = 0.0003

Provenge (Mean = 16.9)  Placebo (Mean = 1.99)
Additional immunological data to support mechanism of action

- **From Phase 1 and 2 Studies**
  - T cell response is specific to PA2024 antigen (KLH data)
  - T cell response is associated with IFN\(\gamma\) production (ELISA, ELISPOT)
  - T cell precursor frequency increases from undetectable background

- **From Ongoing Studies**
  - The T cell response is associated with IFN\(\gamma\) production
  - Boosting appears to augment T cell response
  - Intriguing data consistent with ‘epitope spreading’
The Role of Immune Monitoring

- Critical role in early phase clinical studies of cancer vaccines
- Need better definition of tools (CD4, CD8, cytokine response)
- Need to better define whether immune responses are true ‘surrogates’ for clinical activity
The challenge of defining appropriate endpoints in a relevant and meaningful patient population
Dogma of Clinical Development of Cancer Vaccines

- Cancer vaccines would be expected to have more benefit in the context of micro-metastatic and/or ‘minimal residual disease’
- Bulky, metastatic disease might provide a hurdle too high for active immunotherapy
- Not all tumor types would be expected to respond to active immunotherapy (e.g. melanoma/renal better than other solid tumors)
- Long term endpoints such as survival can be prohibitive from a trial perspective
Prostate Cancer offers unique challenges and opportunities for Cancer Vaccines

Androgen Dependent PCa

Primary Therapy
- Radical Prostatectomy
- Brachytherapy
- Radiation Therapy
- Cryotherapy
- Watchful Waiting

Androgen Deprivation
- Lupron
- Zoladex
- Casodex
- Eulexin
- Ketoconazole

Androgen Independent PCa

Asymptomatic
- Palliative Interventions
- Bisphosphonates
  - Taxotere

Symptomatic
- Novantrone
- Emcyt
Phase I and 2 Clinical Development in Androgen-Independent, Metastatic Prostate Cancer
Results
APC8015 (Provenge™) Phases 1 & 2 Studies

**Safety:**
- No dose limiting toxicities
- Treatment well tolerated

**Immunogenicity:**
- Regimen: maximum immune responses reached after 3 infusions
- Dose response: giving more cells (> 100 million) associated with increased immunogenicity

**Effectiveness:**
- Some PSA responses
- One striking objective response
- Immune responses to PAP correlated with Time-to-Progression

What did we know about APC8015 at the end of Phase 2?

- Safe and well tolerated
- Highly immunogenic resulting in antigen-specific T cell responses
- 3 dose regimen sufficient
- A statistically significant effect on PSA or objective response rate would be unlikely
- Early signal in delaying time to disease progression
- Unmet clinical need in metastatic AIPC
- Long term effect on survival not assessed
Goal:
To develop an active immuno-therapeutic agent with evidence of clinical benefit in men with metastatic, AIPC with a favorable toxicity profile
Provenge® Phase 3 Development Program (c.1999)

Two identical Phase 3 studies (D9901 & D9902)

- 2:1 randomization (active vs. placebo)
- Open-label salvage protocol available for those who progress on placebo
- Population: asymptomatic, metastatic, hormone refractory
- Primary Endpoint: Time to Progression
  - Each study of n=120 powered for TTP
  - Assumed Asymptomatic men progress more slowly than Symptomatic men
  - First scan at 8 weeks
- Secondary Endpoint: Delay in onset of cancer related pain
  - Both studies to be pooled (n=240) for pain endpoint
- 36 month follow-up for survival on every subject explicitly stated in protocol and statistical analysis plan
D9901 Time to Objective Progression
Intent-to-Treat Population

Time to Objective Disease Progression (weeks)

Percent Without Progression

APC8015 (n=82)
APC-Placebo (n=45)

$P = 0.061$ (log rank)
$HR = 1.43$ (95% CI: 0.98, 2.09)*

* HR and CI are based on proportional hazards model.
Time-to-Progression (TTP) as a Primary Endpoint—Hindsight is 20:20

• Kinetics of immune induction make delaying TTP difficult
• Need alternate approaches/definitions for TTP/PFS for active immunotherapy products (subject of subsequent Workstreams)
• TTP is particularly challenging in a rapidly progressive disease in the context of clinical heterogeneity
Why is Survival the “Gold Standard”? 

• Survival offers a clear, meaningful benefit that can be appreciated by both the physician and the patient
• Assessment of survival is not subject to significant bias

Is demonstration of a statistically significant survival benefit with a cancer vaccine possible in late-stage cancer?!?
D9901 Overall Survival
Intent-to-Treat Population

- APC8015 (n=82)
- APC-Placebo (n=45)

Survival (months)

Percent Survival

$P = 0.010$ (log rank)
HR = 1.71 [95% CI: 1.13, 2.58] *

* HR and CI are based on proportional hazards model.
## D9901 Overall Survival
### Intent-to-Treat Population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Subjects</th>
<th>Deaths</th>
<th>Alive at 36 months</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC8015</td>
<td>82</td>
<td>54</td>
<td>28 (34%)</td>
<td>25.9</td>
</tr>
<tr>
<td>APC-Placebo</td>
<td>45</td>
<td>40</td>
<td>5 (11%)</td>
<td>21.4</td>
</tr>
</tbody>
</table>

Phase 3 Trial #D9901
Various factors can influence a survival analysis including imbalances and the effect of concurrent or subsequent therapy.
## D9901 Chemotherapy Use Following Treatment
### Intent-to-Treat Population

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>APC8015 (n = 78)</th>
<th>APC-Placebo (n = 41)</th>
<th>p-value (Fisher’s Exact)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>29 (37.2%)</td>
<td>20 (48.8%)</td>
<td>0.244</td>
</tr>
<tr>
<td>Chemotherapy other than taxanes</td>
<td>36 (46.2%)</td>
<td>13 (31.7%)</td>
<td>0.170</td>
</tr>
<tr>
<td>Taxane-based chemotherapy</td>
<td>34 (43.6%)</td>
<td>22 (53.7%)</td>
<td>0.337</td>
</tr>
<tr>
<td>Any chemotherapy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44 (55.7%)</td>
<td>27 (62.8%)</td>
<td>0.565</td>
</tr>
</tbody>
</table>

<sup>a</sup> For any chemotherapy, APC8015 (n=79) and APC-Placebo (n=43)
Adjustments for Prognostic Factors – Methodology

- 20 prognostic factors considered
- Evaluated the significance of each of the 20 prognostic factors by use of a Cox regression model using a single prognostic factor as a covariate
- Used all significant prognostic factors as simultaneous covariates in a Cox regression model
- Determined the treatment effect adjusted for the covariates in the final model
## D9901 Proportional Hazards Regression Model for Survival Intent-to-Treat Population

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95.0% CI for HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Treatment with APC8015</td>
<td>2.122</td>
<td>1.310</td>
<td>3.438</td>
</tr>
<tr>
<td>Baseline PSA (ln)</td>
<td>1.320</td>
<td>1.094</td>
<td>1.594</td>
</tr>
<tr>
<td>Lesion count (0-5 lesions, 6-10 lesions, &gt;10 lesions)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion count: 0-5 lesions versus 6-10 lesions</td>
<td>1.695</td>
<td>0.907</td>
<td>3.167</td>
</tr>
<tr>
<td>Lesion count: 0-5 lesions versus &gt;10 lesions</td>
<td>2.161</td>
<td>1.289</td>
<td>3.623</td>
</tr>
<tr>
<td>Localization of Disease (bone and soft only versus both)</td>
<td>1.539</td>
<td>0.962</td>
<td>2.461</td>
</tr>
<tr>
<td>LDH (ln)</td>
<td>4.880</td>
<td>2.011</td>
<td>11.844</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>0.992</td>
<td>0.985</td>
<td>0.999</td>
</tr>
</tbody>
</table>

N = 127: Events =85, Censored = 32, and Cases with Missing Values = 10
Cancer Vaccines are well tolerated
D9901 Safety: Adverse Events Occurring at a Significantly Higher Frequency with APC8015 Compared with APC-Placebo

<table>
<thead>
<tr>
<th>Events</th>
<th>APC8015</th>
<th>APC-Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1 or 2</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Any Adverse Event, n (%)</td>
<td>59 (72.0)</td>
<td>23 (28.0)</td>
</tr>
<tr>
<td>Events More Frequent with APC8015:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>47 (57.3)</td>
<td>4 (4.9)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>26 (31.7)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Tremor</td>
<td>8 (9.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (17.1)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Percent of subjects with adverse events: APC8015 (n=82) and APC-Placebo (n=45)
Dendreon is filing a Biologics License Application (BLA) for APC8015 in Metastatic AIPC

- **Significant, unmet medical need**
  - Only one available therapy shown to prolong survival in metastatic AIPC and it is associated with significant toxicity

- **D9901 demonstrates survival advantage in asymptomatic metastatic AIPC**
  - 25.9 months vs 21.4 months [unadj. HR 1.71; P=0.01 log rank]
  - 28 subjects (APC8015) vs 5 subjects (placebo) remaining alive at the 36 month cutoff
  - Delay in development of objective disease progression

- **D9902A provides supportive evidence of clinical benefit**

- **Highly favorable safety profile**
  - Most common AEs in Provenge treated subjects are chills, fever, tremor, asthenia and headache
Expanding the study of APC8015 (Provenge™) to earlier stage Prostate Cancer and to combination therapy
The Prostate Cancer Continuum

**Androgen Dependent PCa**

**Primary Therapy**
- Radical Prostatectomy
- Brachytherapy
- Radiation Therapy
- Cryotherapy
- Watchful Waiting

**Androgen Deprivation**
- Lupron
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- Casodex
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**Androgen Independent PCa**

**Asymptomatic**

**Symptomatic**
- Palliative Interventions
- Bisphosphonates
- Taxotere
- Novantrone
- Emcyt

Early Stage  Advanced Stage
APC8015 Provenge: P-11 (PROTECT)
Phase 3 Study in Early Stage Prostate Cancer

Double Blind, Placebo Controlled

Treatment at Weeks

- Trial in androgen dependent prostate cancer
- Evaluating men with biochemical recurrence following prostatectomy
- Over 170 patients enrolled at 19 sites in the U.S.

- Composite endpoints of biochemical and clinical progression
- Enrollment completed; data available in 1H 2006
Possible Combinations with APC8015 (Provenge™)

- Modulators of APC function
  - Toll-like receptor agonists
  - Anti-VEGF
- Modulators of T regulatory cell activity
- Modulators of T cell activation
- Chemotherapy
- Hormonal Therapy
APC8015 Provenge: P-16*
Phase 2 Study in Early Stage Prostate Cancer

- APC8015 combined with bevacizumab in androgen dependent prostate cancer
- Evaluating men with serologic progression after primary therapy
- 26 patients enrolled

* NCI-sponsored study

Endpoints: safety, immune response, PSA response

Results presented at 2005 Multidisciplinary Prostate Cancer Symposium
## PSA Summary Data

<table>
<thead>
<tr>
<th>PSA Reduction</th>
<th>Number of Patients (n=22)</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50%</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>&gt; 25%</td>
<td>3</td>
<td>14%</td>
</tr>
<tr>
<td>Any</td>
<td>9</td>
<td>41%</td>
</tr>
</tbody>
</table>

**PSADT (n=21)**

- Median pre-treatment: 6.7 months
- Median post-treatment: 12.7 months
- Increase in median PSADT: 6.0* months

* \( P = 0.004 \)

*Presented at 2005 Multidisciplinary Prostate Cancer Symposium*
Conclusions

• We have developed an autologous active immunotherapy (APC8015, Provenge™) that is:
  – Highly immunogenic
  – Well tolerated
  – Capable of providing a meaningful, statistically significant survival benefit in men with metastatic AIPC
  – Derived from a consistent, defined manufacturing process that is scaleable

• These data support the belief that cancer vaccines will be an important and feasible treatment option in a variety of settings