Advances in Immunotherapy for Prostate Cancer

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The following relationships exist relevant to this presentation:

- Dr Kantoff has served on the Scientific Advisory Board or is an advisor to Sanofi, Novartis, Amgen, BN-IT, Dendreon, Janssen, Bellicum and Bayer.
Immunotherapeutic Approaches

• Provenge (Sipuleucel-T)

• PROSTVAC-VF Tricom

• Ipilimumab
• Sipuleucel-T (Provenge)
Sipuleucel-T: Mechanism of Action

Antigen (PAP-GMCSF) is exposed to an 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 and is collected

INFUSE PATIENT

T-cells proliferate and attack cancer cells

sipuleucel-T activates T-cells in the body
Sipuleucel-T: Logistics of Therapy

**Day 1**
Leukapheresis

**Day 2-3**
Sipuleucel-T is manufactured

**Day 3-4**
Patient is infused

Apheresis Center

Central Processing

Doctor’s Office

**COMPLETE COURSE OF THERAPY:**
Weeks 0, 2, 4
Randomized Phase III Trial of Sip-T in CRPC (D9901)

Asymptomatic metastatic CRPC (N=127)

- Placebo q2wks x 3 (N=45)
- Sip-T q2wks x 3 (N=82)

Primary endpoint - TTP

Progression:
- APC8015F q2wks x 3
- Long-term follow-up

Small et al. JCO 2006
Results: Time to Objective Progression

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

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

Small et al. JCO 2006
Results: Overall Survival

- APC8015 (N=82)
- Placebo (N=45)

\[ P = 0.01 \text{ (log-rank)} \]
\[ \text{HR} = 1.7 \]
\[ (95\% \text{ CI: 1.126, 2.563}) \]
Randomized Phase 3 IMPACT Trial
(IMmunotherapy Prostate AdenoCarcinoma Treatment)

Asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer (N = 512)

2:1

Sipuleucel-T Q 2 weeks x 3

Treated at physician discretion

Placebo Q 2 weeks x 3

Treated at physician discretion and/or salvage protocol

Primary endpoint: Overall survival
Secondary endpoint: Objective disease progression

Kantoff et al NEJM 2010
IMPACT Overall Survival
Final Analysis (349 events)

36.5 mo median f/u
HR = 0.759 (95% CI, 0.606, 0.951)
$P = 0.017$ (Cox model)
Median survival benefit = 4.1 months

Sipuleucel-T (n = 341)
Median survival: 25.8 mo.
36 mo. survival: 32.1%

Placebo (n = 171)
Median survival: 21.7 mo.
36 mo. survival: 23.0%

Kantoff et al NEJM 2010
Unresolved Issues

• Adoption has been slower than expected
  – Controversial MOA with few PSA declines
  – Predicting who will benefit
  – Lack of markers of benefit
  – Other agents with of MOAs have been developed

• What is appropriate timing?
  – Most appropriate patient has very early mCRPC asymptomatic and slowly progressing
Time to Disease Related Pain

Survival rate estimate (95% CI)

<table>
<thead>
<tr>
<th>Group</th>
<th>Survival Rate</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Sipuleucel-T</td>
<td>37.0%</td>
<td>(27.8, 46.3)</td>
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<tr>
<td></td>
<td>32.7%</td>
<td>(23.3, 42.1)</td>
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<tr>
<td></td>
<td>21.3%</td>
<td>(10.9, 31.6)</td>
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<td></td>
<td>7.1%</td>
<td>(0.0, 15.8)</td>
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<tr>
<td>Control</td>
<td>37.2%</td>
<td>(24.4, 49.9)</td>
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<tr>
<td></td>
<td>14.5%</td>
<td>(3.9, 25.2)</td>
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<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Small et al. (submitted)
Hazard ratios for treatments with different MOAs

Kantoff et al.
ESMO 2012
Does sipuleucel-T activate the immune system?
IMPACT Trial: APC Activation Increases after Initial Sipuleucel-T Treatment

Sheikh et al Cancer Immunology and Investigation 2012
IMPACT Trial: Sipuleucel-T Induces Proliferative Responses to PA2024* and PAP

*PA2024 = PAP-GM-CSF recombinant antigen
IMPACT Trial: Sipuleucel-T Generates Persistent Antigen-specific Humoral Responses

Sheikh et al. Cancer Immunology and Investigation 2012
Development of PROSTVAC VF-Tricom

- **Vaccinia**
  - Potent immunological priming agent

- **Fowlpox**
  - Minimally/non-cross-reactive with vaccinia
  - Enables boosting

- **Slightly altered PSA transgene**
  - Modified HLA-A2 epitope. Increased HLA-A2 binding and immunogenicity.

- **Tricom**
  - Lymphocyte function-associated antigen LFA-3 (CD58)
  - Intercellular adhesion molecule ICAM-1 (CD54)
  - Costimulatory molecule for the T-cell receptor B7.1 (CD80)
Construction of a Recombinant Cancer Vaccine

1. Gene(s) for Tumor-Associated Antigen(s) (TAA)
2. Genes for Three Costimulatory Molecules
3. Attenuated Vaccine Vector
4. Transfection
5. Infection

Stimulation of Anti-Tumor Immune Response

Proposed Mechanism of Action

1. T-Lymphocyte Recognition of TAA
2. Tumor Cell Destruction
3. Activation and Clonal Expansion of TAA-Specific T-Lymphocytes
4. Cytokine Release

SUBCUTANEOUS INJECTION OF THERAPEUTIC VACCINE

HOST CELL

Recombinant Vaccine Containing TAA(s) and Three Costimulatory Molecules

Three Lymphocytes

Antigen Presenting Cell

Helper T-Cell

Activated T-Lymphocytes
Randomized Phase II Study

Asymptomatic or Minimally Symptomatic Metastatic Castration Resistant Prostate Cancer (N=125)

Primary endpoint: Progression Free Survival
Secondary endpoint: Overall Survival

2:1

PROSTVAC-VF Tricom + GM

Treated at physician discretion

Treated at physician discretion and/or Salvage Protocol

Empty Vector + placebo

Kantoff et al. J Clin Oncol 2010
Progression Free Survival

Hazard Ratio = 0.88 (95% CI 0.57 to 1.38)

P = 0.60 (stratified logrank)

Months

Control

N: 40
Events: 30
Median: 3.7

PROSTVAC

N: 82
Events: 58
Median: 3.8

Kantoff et al. J Clin Oncol 2010
Hazard Ratio = 0.56 (95% CI 0.37 to 0.85)

P = 0.006 (stratified logrank)

**Control**
- N: 40
- Deaths: 37
- Median: 16.6

**PROSTVAC**
- N: 82
- Deaths: 65
- Median: 25.1

Kantoff et al. J Clin Oncol 2010
Non/minimally symptomatic metastatic castration resistant prostate cancer N=1200

- PROSTVAC-(V)(F) TRICOM + low dose adjuvant GM-CSF
- PROSTVAC-(V)(F) TRICOM Adjuvant placebo
- Vector Placebo Adjuvant placebo
- Standard of Care
- No cross Over

Gulley J and Kantoff P
Ipilimumab
Phase I/II CRPC Treatment Schema

**Design:**
- Phase 1 – Dose escalation: 3, 5 or 10 mg/kg Ipi, then 3 or 10 mg/kg Ipi ± XRT (single dose of 8 Gy/lesion, up to 3 lesions per patient)
- Phase 2 – Cohort expansion: 10 mg/kg ± XRT cohorts

**Endpoints:**
- Safety
- PSA response at Day 85, overall PSA response, and tumor response by RECIST

**Response assessments:**
- PSA: Days 22, 43, 64, 85, then monthly
- Tumor: Day 85, then every 3 months

Slovin et al submitted 2011
PSA Waterfall Plot on Day 85

Slovin et al submitted 2011
Ipilimumab Randomized Phase II in advanced CaP

- 108 patients with advanced CaP were randomized to ADT alone (54 patients) or to ADT plus 3 mg/kg ipilimumab
- Primary endpoints were safety and efficacy as measured by PSA and clinical response
- No baseline differences between the treatment groups.
- Percent decline in testosterone level was > 97% in both arms
- Patients treated with ipilimumab + ADT were more likely to have an undetectable PSA by 3 months (55% vs. 38%)

Tollefson et al. 2010 GU Cancers Symp
Bone metastatic CRPC after docetaxel (N = 800)

XRT

XRT + IPI x4 every 3 weeks followed by IPI maintenance

Asymptomatic, minimally symptomatic CRPC, no prior docetaxel (N = 600)

Placebo

IPI x4 every 3 weeks followed by IPI maintenance

OS
Conclusions on Immunotherapy Approaches

- Proof of concept that immunotherapy provides clinical benefit in prostate cancer
  - Sipuleucel-T in prostate cancer

- Potential for further advances in prostate cancer in next few years
  - PROSTVAC VF-Tricom
  - Ipilimumab
  - Combination therapies