Cancer vaccines for prostate cancer

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(Cha and Fong, JCO 2011)
Sipuleucel-T (Provenge)

Sipuleucel-T: an autologous cellular immunotherapy targeting prostate cancer

Sipuleucel-T improves overall survival in patients with asymptomatic or minimally symptomatic mCRPC

*PAP/GM-CSF = “PA2024”
Sipuleucel-T improves overall survival for mCRPC

Overall Survival

PFS

(Small JCO 2006, Kantoff NEJM 2010)
Sipuleucel-T Clinical Indication

Asymptomatic or minimally mCRPC
Before or after chemotherapy
No visceral metastasis
Slowly progressing disease with “enough time” (6 weeks)

Challenges
Clinical responses, including PSA responses, are rare (<5%)
Cost
How do we sequence with other therapies?
How does a treatment improve survival but not impact time to progression?
What is its mechanism of action?
Does treatment alter the immune response within the tumor microenvironment?
Prostatic Acid Phosphatase (PAP) can be immunogenic

PAP is a 354 aa glycoprotein

Specifically expressed in prostate tissue

Vaccinating rats with recombinant vaccinia virus expressing human PAP induces inflammation.

(Fong et al., JI 1997)
Sipuleucel-T treatment recruits T cells to the prostate

Leukapheresis

PBMC co-incubated with PAP/GM-CSF fusion

Sipuleucel-T x 3

Radical Prostatectomy

Immunohistochemistry

Blood

T Cell responses (ELISPOT)

(Fong et al, JNCI 2014)
Quantitative Tissue Analysis

Immunohistochemical staining: FFPE sections stained with Dako Autostainer

Digital microscopy: slide scanning with Aperio ScanScope

Image field selection: 5 fields randomly selected from classified tissues for each tissue type (n≈4800)

Image analysis: Zeiss Axiovision

 Quantify parameters of interest:
Areas of epithelium, stroma and lumen
Number of total and stained nucleated cells/area
Sip-T treatment recruits T cells to the tumor interface

(Fong et al, JNCI 2014)
Sipuleucel-T can broaden immune responses to other antigens

(Zambrena and Fong, in press 2014)
Conclusions

Neoadjuvant Sip-T recruits CD3 T cells to the tumor interface.

These are comprised of effector CD4 and CD8 T cells.

Immune responses to immunotherapy can be quantitated in the tissue.

Neoadjuvant trials could be used to examine
• Mechanism of action
• Relative potency of an immunotherapy
Challenges

• Clinical responses, including PSA responses, are rare (<5%).
• Costly
• Other therapies
• How does a treatment improve survival but not impact time to progression?
• Sip-T contains very few if any dendritic cells. What is its mechanism of action?
• Does treatment alter the immune response within the tumor microenvironment?
Sipuleucel-T Combination Trials

Sipuleucel-T/abiraterone acetate
Sipuleucel-T/ipilimumab
Sipuleucel-T/IL-7

Sipuleucel-T/ADT
Sipuleucel-T/DNA vaccine
Sipuleucel-T + Abiraterone Combination Trial

PA2024

Week
0 2 4 6 10 14 26
Stimulation Index
0.5 1.0 5.0 10.0 50.0 100.0
Concurrent Arm
Sequential Arm

(Small et al. PASCO 2013)
Tumor Immune Recognition

(Cha and Fong, JCO 2011)
Poxvirus-based Cancer Vaccine: PROSTVAC

TAA: tumor associated antigen

Full-length protein expressed as target tumor antigen

BN's dual poxvirus vectors “prime/boost” regimen

Ready-to-use with subcutaneous administration

TRICOM (TRIad of COstimulatory Molecules)

Facilitate T cell/APC interaction

Strengthen the anticancer immune response
PROSTVAC-VF Phase 3 Treatment Schedule

1 PRIME
Subcutaneous Administration

6 BOOSTS
Subcutaneous Administration

5 Months

Adjuvant low-dose GM-CSF (100 µg) or placebo (subcutaneous) Day 1-4 for each PROSTVAC-VF administration.
Randomized Phase 2: Progression-Free Survival

**Graph:**
![Graph showing progression-free survival](Image)

**Table:**
<table>
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<tr>
<th></th>
<th>N</th>
<th>Events</th>
<th>Median PFS (months)</th>
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<tbody>
<tr>
<td>PROSTVAC</td>
<td>82</td>
<td>58</td>
<td>3.8</td>
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<tr>
<td>Control</td>
<td>40</td>
<td>30</td>
<td>3.7</td>
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</table>

**HR = 0.88 (95% CI 0.57–1.38)**

(Kantoff PW, et al. 2010 *J Clin Oncol*.)
PROSTVAC Phase 2 Increases in Survival in mCRPC

- Median OS (months)
  - PROSTVAC: 25.1 (82 patients, 65 deaths)
  - Control: 16.6 (40 patients, 37 deaths)

Survival (% of subjects) vs. Time (months)

- 8.5 months improvement in OS
  - HR=0.56 (95% CI 0.37–0.85), P=.0061

(Kantoff PW, et al. 2010 J Clin Oncol.)
Phase 3 clinical study plan agreed upon with FDA under SPA
PROSTVAC treatment regimen is the same as used in phase 2
Primary Efficacy Endpoint:
Overall survival

Secondary Efficacy Endpoint:
The proportion of event-free subjects (radiological progression, pain progression, chemotherapy initiation, or death at six months (or early termination) compared to placebo

Safety Endpoint:
Number of adverse events compared to placebo

Exploratory Endpoints:
Model secondary radiological progression (6 months post end-of-treatment vs. end-of-treatment)
Asses any role of subsequent anti-cancer therapies as alternative explanation for observed survival differences
Overall survival and event-free at 6 months analysis in HLA-A2 expressing subset
PSA specific immune response, and immune response to non-vaccine containing prostate antigens (antigen spread); and assess whether immune responses are prognostic and/or predictive
Evaluate baseline biomarkers with are prognostic and/or predictive of survival
Effect on circulating tumor cell (CTC) levels (US site only)
PROSTVAC + Ipilimumab Combination

PROSTVAC Phase 2 study

NCI Phase 1 PROSTVAC + Ipilimumab

**PROSTVAC 40** 37 25.1
**Control** 82 65 16.6

HR=0.56 (0.37–0.85), logrank P=0.0061

(Madan et al., Lancet Oncol 2012)
Neoadjuvant PROSTVAC Study design

PROSTVAC-V/F (n=12)
V  F  F  F  F

PROSTVAC-V/F + Ipilimumab (n=12)
V  F  F  F  F

Radical Prostatectomy
Day 78

Follow up
Days 120 and 162

Post-treatment
Every 6 months up to 12 months

(Zambrena, Kim and Fong)

V = PROSTVAC-V
F = PROSTVAC-F
Ipilimumab (Ipilimumab)
Antigen-Specific DNA Vaccines
Phase I Trial – DNA Vaccine Encoding PAP Study Design

Patients with stage D0/M0 prostate cancer

<table>
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* Leukaphereses

Timepoints for which PBMC available for immune monitoring

Dose Escalation Schedule

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<tr>
<th>Dose Level</th>
<th>pTVG-HP</th>
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<tr>
<td>1</td>
<td>100 µg</td>
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<tr>
<td>2</td>
<td>500 µg</td>
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<tr>
<td>3</td>
<td>1500 µg</td>
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(McNeel et al., JCO 2009)
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