PROSPECT: A Randomized, Double-blind, Global Phase 3 Efficacy Trial of PROSTVAC-VF in Men with Metastatic Castration-Resistant Prostate Cancer

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Disclosure Information

I have no personal financial relationships to disclose.

The National Cancer Institute has a CRADA with BN ImmunoTherapeutics (BNIT) for preclinical studies and BNIT has licensed this vaccine for clinical trials.

The therapeutic vaccine I will discuss is experimental and was originally developed within the NCI.
Disease Continuum in Prostate Cancer

Tumor volume

Death

Castration

Local Therapy

2\textsuperscript{nd}-line Hormonal therapy

Symptoms

Asymptomatic

Non-Metastatic

Castration Sensitive

Castration Resistant

Metastatic

Sipuleucel-T*

Docetaxel*

Cabazitaxel*

Abiraterone*

Enzalutamide*

Alpharadin?

Death from Prostate Cancer

Time

*Approved in US and shown to improve OS in CRPC
Recombinant Vaccine Vectors

• Pox vectors
  Vaccinia (rV-) elicits a strong immune response
  – host induced immunity limits its continuous use
  – used in over 1 billion people world-wide for eradication of variola

Avipox (fowlpox rF-, ALVAC)
  – derived from avian species
  – safe; does not replicate
  – can be used repeatedly with little if any host neutralizing immunity

• Can insert multiple transgenes

• Do not integrate into host DNA

• Efficiently infect antigen presenting cells including dendritic cells
Comparison of T-cell Responses in CEA-Transgenic Mice Vaccinated with CEA Protein vs. rV-CEA
T-Cell Dependence on Costimulation

**Signal 1 + Signal 2**
- Antigen Presenting Cell
- MHC
- Costimulatory Molecule
- TCR
- T-Cell
- Activation of Antigen-Specific T-cells

**No Signal 1**
- Antigen Presenting Cell
- MHC
- Costimulatory Molecule
- TCR
- T-Cell
- Clonal Anergy
- Apoptosis
- Ignorance

**No Signal 2**
- Antigen Presenting Cell
- MHC
- Costimulatory Molecule
- TCR
- T-Cell
- Clonal Anergy
- Apoptosis
- Ignorance
Costimulatory Molecule Candidates

- Major Costimulatory Effect must be on the T-cell
- No Overlap of T-cell Ligands
- No Redundancy of Costimulatory Mechanisms

### Costimulatory Molecule Candidates

**APC**
- MHC + Peptide
  - Costimulatory Molecule
    - B7-1 (CD80)
    - ICAM-1 (CD54)
    - LFA-3 (CD58)

**T-Cell**
- TCR
  - Ligand
    - CD28
    - CTLA-4
  - Costimulatory Mechanism
    - IL-2-R upregulation, IL-2 secretion
    - Tyrosine Kinase, Phospholipase C
    - Tyrosine Kinase, Ca\(^{2+}\) Mobilization
    - cAMP Production

### T-cell Activation (CPM x 10\(^5\))

<table>
<thead>
<tr>
<th>Costimulatory Molecule</th>
<th>None</th>
<th>LFA-3</th>
<th>ICAM-1</th>
<th>B7-1 TRICOM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T-Cell</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PROSTVAC-VF
Proposed Mode of Action

Tumor antigen gene  Costimulatory molecule genes

PSA  LFA-3  ICAM-1  B7-1

(TRIad of COstimulatory Molecules)

Induction of tumor-specific immune responses (T-cells)

Vaccines:
PROSTVAC-V
PROSTVAC-F

Developed within the NCI
--Preclinical (Schlom et al.)
--Clinical (Gulley et al.)
How Pox viral vaccines activate TAA specific T-cells

Tarassoff, ...Gulley *The Oncologist*, 2006
T-cell mediated killing of Tumor cells

Cell death via caspase cascade

Tumor cells

T-cell

Granzymes

FAS

MHC

TCR

FAS-L

ICAM

LFA-1

Antigen
Antigen “spreading”

Improved clinical outcomes associated with antigen spreading


• Hardwick N, et al. Epitope spreading contributes to effective immunotherapy in metastatic melanoma patients. *Immunotherapy* 2011


Gulley JL. Therapeutic vaccines: The ultimate personalized therapy? *Hum Vaccin Immunother*, 2012
Background and Rationale

Clinical Experience

• Pox-viral PSA-containing vectors have been evaluated in approximately 600 patients, over 300 of these patients have received PROSTVAC-VF
  - In Phase 1 and 2 trials, PROSTVAC-VF was well tolerated\(^1\)-\(^4\)
    - The most common adverse events were Grade 1 and 2 injection site reactions and fatigue\(^1,2\)
  - In a randomized, multicenter phase 2 trial of PROSTVAC-VF in 32 patients with mCRPC, patients with greater PSA-specific T-cell responses showed a trend toward improved survival\(^3\)

PROSTVAC-VF ≥ Gr 2 Adverse Events
PROSTVAC-V: 139 Injections
PROSTVAC-F: 679 Injections

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th># (%) of Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection Site Reaction</td>
<td>230 (28.1)</td>
</tr>
<tr>
<td>Fever</td>
<td>18 (2.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (1.2)</td>
</tr>
<tr>
<td>Myalgias</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Flu-like Syndrome</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Allergic Rhinitis</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

6 NCI Trials, n=145 patients
(NCT00450619, NCT00450463, NCT00113984, NCT00096551, NCT00060528)
PROSTVAC-VF Adverse Events
Local vs. Systemic

Kim…Gulley et al., ASCO GU, 2013
Phase 2 Results: PROSTVAC-VF Significantly Improved Overall Survival

Control | Deaths, n | Median Survival, months
---|---|---
40 | 37 | 16.6
82 | 65 | 25.1

Hazard ratio
0.56 (95% CI: 0.37-0.85)

P=0.0061

## Therapeutic vaccines vs. Conventional therapy

<table>
<thead>
<tr>
<th>Target</th>
<th>Conventional Therapy</th>
<th>Therapeutic Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor or its microenvironment</td>
<td>Tumor or its microenvironment</td>
<td>Immune system</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>Often immediate action</td>
<td>Delayed</td>
</tr>
<tr>
<td>Memory Response</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Tumor Evolution / new mutations</td>
<td>Resistance to therapy</td>
<td>New immunogenic targets</td>
</tr>
<tr>
<td>Limitations</td>
<td>Toxicity</td>
<td>Requires adequate immune system function (both systemically and at tumor site)</td>
</tr>
</tbody>
</table>

Gulley et al., ASCO Education Book, 2013
Tumor Growth Rate

PROSTVAC – Interesting Case History

Gleason grade: 4 + 3 = 7

Trend before radical prostatectomy (■)
5.8 months
65 years

Trend after radical prostatectomy, External beam radiation (■)
9.6 months
75 years

Trend after first vaccine trial (■)
28.6 months
93 years

Trend after second vaccine trial (■)
27 years

Age at which PSA would equal 1000

Rajan…Gulley, Bubley et al. Clin. GU Ca, in press
Decrease in growth rate (PSA) over time following therapeutic vaccination

PROSTVAC treatment starting Day 0 and continued for 6 months, n=50
Gulley…DiPaola et al, ASCO GU 2013 (E9802)
## Current and Emerging Therapies in CRPC

**Phase III data**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of patients</th>
<th>Stop treatment 2º AE</th>
<th>PSA ↓ ≥50%</th>
<th>Improvement in Median OS</th>
<th>Hazard Ratio</th>
<th>Reduction in Death Rate</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>1006</td>
<td>11%</td>
<td>45%</td>
<td>2.4 months</td>
<td>0.76</td>
<td>24%</td>
<td>2004</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>755</td>
<td>18%</td>
<td>39%</td>
<td>2.4 months</td>
<td>0.70</td>
<td>30%</td>
<td>2010</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>512</td>
<td>1.5%</td>
<td>2.6%</td>
<td>4.1 months</td>
<td>0.78</td>
<td>22%</td>
<td>2010</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>1195</td>
<td>19%</td>
<td>38%</td>
<td>3.9 months</td>
<td>0.66</td>
<td>34%</td>
<td>2011</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>1199</td>
<td>8%</td>
<td>54%</td>
<td>4.8 months</td>
<td>0.63</td>
<td>37%</td>
<td>2012</td>
</tr>
<tr>
<td>Alpharadin</td>
<td>922</td>
<td>--</td>
<td>--</td>
<td>2.8 months</td>
<td>0.70</td>
<td>30%</td>
<td>--</td>
</tr>
</tbody>
</table>

**Phase II PROSTVAC data**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Stop treatment</th>
<th>PSA ↓</th>
<th>Improvement in OS</th>
<th>Hazard Ratio</th>
<th>Reduction in Death Rate</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-Center</td>
<td>125</td>
<td>~2%</td>
<td>1%</td>
<td>8.5 months</td>
<td>0.56</td>
<td>44%</td>
<td>--</td>
</tr>
<tr>
<td>NCI</td>
<td>145</td>
<td>0%</td>
<td>3.1%</td>
<td>--</td>
<td>--</td>
<td>--</td>
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</tr>
</tbody>
</table>
Phase 3 PROSPECT Trial Design

Asymptomatic/minimally symptomatic mCRPC patients

Randomization

<table>
<thead>
<tr>
<th>Treatment Phase (5 mo)*</th>
<th>Long-term Follow-up (every 6 mo for 5 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROSTVAC-VF + GM-CSF**</td>
<td></td>
</tr>
<tr>
<td>(n = 400)</td>
<td></td>
</tr>
<tr>
<td>PROSTVAC-VF (n = 400)</td>
<td></td>
</tr>
<tr>
<td>Vector Placebo (n = 400)</td>
<td></td>
</tr>
<tr>
<td>Prime</td>
<td></td>
</tr>
<tr>
<td>Boosts</td>
<td></td>
</tr>
<tr>
<td>Vaccination Weeks</td>
<td></td>
</tr>
</tbody>
</table>

*at the end of the 5 month treatment phase, use of other therapies for mCRPC is at the discretion of the investigator

**low-dose adjuvant (100 µg) SC days 1-4 of each vaccination

Gulley JL, Global PI
## Key Eligibility Criteria for PROSPECT

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≥18 years with asymptomatic or minimally symptomatic mCRPC</td>
<td>• Scheduled opioid narcotics for cancer-related pain</td>
</tr>
<tr>
<td>• PSA or radiological progression during androgen-suppression</td>
<td>• Metastasis to organs other than lymph nodes and/or bone</td>
</tr>
<tr>
<td>• ECOG Performance Score of 0 or 1</td>
<td>• Rapidly progressing disease</td>
</tr>
<tr>
<td>• Life expectancy ≥1 year</td>
<td>• Contraindications for vaccinia immunization</td>
</tr>
<tr>
<td>• Chemotherapy-naïve</td>
<td></td>
</tr>
</tbody>
</table>

- mCRPC: Metastatic Castration Resistant Prostate Cancer
- ECOG: Eastern Cooperative Oncology Group
- PSA: Prostate Specific Antigen
• **Primary:** Overall survival PROSTVAC VF with and without GM-CSF compared with placebo

• **Secondary:** Proportion of patients who remain event-free (radiological or pain progression, initiation of chemotherapy or death) at 6 months

• **Key Exploratory:**
  • Immune response to immunizing antigen, non-vaccine–contained prostate antigens, tumor-associated antigens; changes in baseline biomarker levels and circulating tumor cell levels; and characterization of T-cell subpopulations

The Phase 3 PROSPECT trial is open for enrollment

Website for more information: www.continueyourfight.com
Tumor Growth Rate

Does tumor volume matter for vaccine strategies?

Hypothesis:

– The subset of patients with less aggressive disease / lower tumor burdens are more likely to benefit from vaccine therapy.

For a review see Gulley et al., *Curr Oncol*. 2011
Tumor

Immune System

SIZE
Sometimes it does matter.
Phase II Study of PSA-TRICOM

- 32 patients with metastatic castration-resistant prostate cancer (CRPC)
- Chemotherapy naive
- Primary endpoint: immune response by ELISPOT
- Secondary / exploratory endpoints: Response, Survival

Gulley et al., Clin Immunol Immunother, 2010
Prognostic Model for Predicting Survival in Men with Hormone-Refractory Metastatic Prostate Cancer

By Susan Halabi, Eric J. Small, Philip W. Kantoff, Michael W. Kattan, Ellen B. Kaplan, Nancy A. Dawson, Ellis G. Levine, Brent A. Blumenstein, and Nicholas J. Vogelzang

*J Clin Oncol.*, 2003

**Conclusion:**
Can predict survival probabilities.
## Halabi Predicted Survival vs. Actual Survival

<table>
<thead>
<tr>
<th>NCI Docetaxel therapy (n=22)</th>
<th>All patients</th>
<th>Patients with Halabi predicted survival &lt; 18 mos</th>
<th>Patients with Halabi predicted survival ≥ 18 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted survival by Halabi score (mos)</td>
<td>16.5</td>
<td>13.0</td>
<td>21.0</td>
</tr>
<tr>
<td>Actual median overall survival (mos)</td>
<td>15.5</td>
<td>15.4</td>
<td>16.9</td>
</tr>
<tr>
<td>Difference (mos)</td>
<td>(-1.0)</td>
<td>2.4</td>
<td>(-4.1)</td>
</tr>
<tr>
<td>Patients survival longer than predicted by Halabi nomogram</td>
<td>11 of 22 (50%)</td>
<td>8 of 13 (62%)</td>
<td>3 of 9 (33%)</td>
</tr>
</tbody>
</table>

Survival Based PSA-Specific T-Cell Response

ELISPOT > 6 Fold Increase

p = 0.055

ELISPOT < 6 Fold Increase
Patient with Metastatic CRPC Treated with PROSTVAC with >6 fold increase in PSA specific T cells

- Pervasive bone disease at enrollment
- Halabi predicted survival 16.8 months
- 5 years on vaccine study
- No subsequent therapy
- Died 7 years after enrolling

Kim, Madan, Gulley, *Clin Genitourinary Ca*, 2011
Combination Studies

- **Rationale**: added therapy
  - Immunogenic cell death (boosting anti-cancer immune responses)
  - Immunogenic modulation \(\rightarrow\) tumor cell more amenable to immune mediated killing
    - Killing
      - Fas, improved T-cell binding (ICAM)
    - Recognition
      - MHC, TAA
  - Augment immune effectors / decrease immune regulators
Treatment of LnCaP prostate cancer cells with palliative doses of $^{153}$Sm results in the upregulation of MHC class I and Fas.

<table>
<thead>
<tr>
<th>Accessory Genes</th>
<th>0 Gy</th>
<th>25 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fas</td>
<td>1</td>
<td>1.96</td>
</tr>
<tr>
<td>MHC-I</td>
<td>0</td>
<td>25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Antigen Genes</th>
<th>0 Gy</th>
<th>25 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>1</td>
<td>2.79</td>
</tr>
<tr>
<td>PSMA</td>
<td>1</td>
<td>4.14</td>
</tr>
<tr>
<td>PAP</td>
<td>1</td>
<td>29.0</td>
</tr>
<tr>
<td>CEA</td>
<td>1</td>
<td>10.3</td>
</tr>
<tr>
<td>MUC-1</td>
<td>1</td>
<td>3.67</td>
</tr>
</tbody>
</table>

Treatment of LnCaP prostate cancer cells with palliative doses of $^{153}$Sm results in increased sensitivity to multiple CTLs.
Tumor Growth Rate

Examples

1. Quadramet +/- vaccine
2. Docetaxel +/- vaccine
3. Flutamide +/- vaccine
Conclusion

■ Minimal toxicity

■ Effect on the host immune system
  — indirect effect on the tumor
  — anti-tumor effects may be delayed

■ Overall survival vs radiographic response (RECIST) or time to progression as the appropriate primary endpoint for vaccine alone studies.

■ Induction of host immunity is a dynamic process that can persist long term post-vaccination
  — immune response may become broader and deeper over time
  — earlier may be better

■ Potential for an enhanced effect on concomitant or subsequent therapies