Presenter Disclosure Information

James L. Gulley MD PhD FACP

The following relationships exist related to this presentation:

The NCI has a Collaborative Research and Development Agreement (CRADA) with BN ImmunoTherapeutics (Mountain View, CA):

- PROSTVAC (PSA-TRICOM)
- PANVAC (CVAC-301)

I have no financial interests to disclose
Combining Vaccines with other therapeutics:
A strategy to accelerate proof of concept studies?

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& Principal Investigator, Medical Oncology Branch
Center for Cancer Research
National Cancer Institute, NIH
Monotherapy

• Randomized controlled studies of immunotherapies alone have suggested that TTP may not be a discriminatory endpoint for clinical trials.
  – Sipuleucel-T (2 phase III studies)
  – Ipilimumab (phase III study)*
  – PROSTVAC (phase II study)

*no improved median TTP
Pox Vector Vaccine: PSA TRICOM (PROSTVAC)

Developed at NCI CRADA with BNIT
PSA-TRICOM Significantly Extended Overall Survival in a Multicenter Phase II Study

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Deaths</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>40</td>
<td>37</td>
<td>16.6</td>
</tr>
<tr>
<td>PROSTVAC</td>
<td>82</td>
<td>65</td>
<td>25.1</td>
</tr>
</tbody>
</table>

Δ 8.5 months

Hazard ratio:
0.56 (95% CI 0.37–0.85)

p=0.0061

Kantoff (Schlam, Gulley) et al. J Clin Oncol 2010
## Therapeutic vaccines vs. Conventional therapy

<table>
<thead>
<tr>
<th></th>
<th>Conventional Therapy</th>
<th>Therapeutic Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Tumor or its microenvironment</td>
<td>Immune system</td>
</tr>
<tr>
<td><strong>Pharmacodynamics</strong></td>
<td>Often immediate action</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>Memory Response</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>Toxicity</td>
<td>Requires adequate immune system function (both systemically and at tumor site)</td>
</tr>
</tbody>
</table>
Tumor Growth Rate

PROSTVAC – Interesting Case History

Gleason grade: 4 + 3 = 7

Doubling time | PSA would equal 1000
--- | ---
5.8 months | 65 years
9.6 months | 75 years
28.6 months | 93 years
27 years |
Decrease in growth rate (PSA) over time following therapeutic vaccination

PROSTVAC treatment starting Day 0 and continued for 6 months, n=50
DiPaola et al, ASCO GU 2009 (E9802)
Combination Studies

- **Rationale:** added therapy
  - Kill in an immunologic manner (boosting anti-cancer immune responses)
  - Phenotypically alter tumor cell \(\Rightarrow\) more amenable to immune mediated killing
    - **Killing**
      - Fas, improved T-cell binding (ICAM)
    - **Recognition**
      - MHC, TAA
    - Augment immune effectors / decrease immune regulators
Tumor Growth Rate

## Combination Studies

<table>
<thead>
<tr>
<th></th>
<th>Preclinical Studies</th>
<th>Immune Endpoint</th>
<th>Clinical Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td>✓</td>
<td>✓</td>
<td>ongoing</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>✓</td>
<td>✓</td>
<td>ongoing</td>
</tr>
<tr>
<td>Hormonal Manipulation</td>
<td>✓</td>
<td>✓</td>
<td>ongoing</td>
</tr>
<tr>
<td>Small Molecule</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune Checkpoint inhibition</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

LTIB Studies, Hodge, Schlom et al.
Potential Multiple Effects of Local Irradiation of Tumors

Hodge ...Gulley et al., Oncology 22:1064-70.
QUADRAMET is a therapeutic agent consisting of radioactive samarium (\textsuperscript{153}Sm) and chelator.

It preferentially binds to osteoblastic metastatic tumor deposits in bone.

\textsuperscript{153}Sm is currently FDA approved and clinically utilized for palliation of bone metastasis in multiple tumor histologies.
Treatment of LnCaP prostate cancer cells with palliative doses of $^{153}$Sm results in the upregulation of MHC class I and Fas.

Chakraborty, Wansley…Schlom, Hodge, NCI. Clin Cancer Res. 2008

Collaboration with Nuclear Medicine Branch
153\textsuperscript{Sm} +/- PSA-TRICOM

Patient Population: CRPC Metastatic to bone

Randomize

Arm A: PSA-TRICOM + 153\textsuperscript{Sm} (n=34)

Arm B: 153\textsuperscript{Sm} (n=34)

Vaccine: rV-PSA/TRICOM s.c. d 1
rF-PSA/TRICOM s.c. d 15, 29, q 4 wks

153\textsuperscript{Sm}: 1 mCi/kg d 8, may be repeated
q 12 wks upon hematologic recovery.

NCI# 7678  PI Gulley
CINJ (DiPaola) and UC (Stadler)
Preliminary Data: $^{153}\text{Sm} +/- \text{PSA-TRICOM}$

- $^{153}\text{Sm} + \text{PSA-TRICOM}$
  - TTP = 107 days

- $^{153}\text{Sm}$ Alone
  - TTP = 52 days

n=37
Rationale for Vaccine Combined With Androgen Deprivation Therapy (ADT)

- Increase thymic emigrants (naïve immune cells)
- Increased T-cell trafficking to the prostate
- Decreases immune tolerance to tumor antigens

Aragon-Ching JB (Gulley), Front Biosci 2007
ADT+ Flutamide +/- PSA-TRICOM

Patient Population: D0.5 Prostate Cancer

Arm A: PSA-TRICOM + Flutamide 250 mg TID (n=31)
(vaccine given monthly until progression)

Arm B: Flutamide 250 mg TID alone (n=31)

Primary End Point: Time To Progression (PSA rise or mets)

Secondary End Points: Immunologic Response
Preliminary Data: ADT+ Flutamide +/- PSA-TRICOM

- Flutamide + PSA-TRICOM: TTP = 192 days
- Flutamide: TTP = 108 days

Days after Enrollment n=41
Ability of Docetaxel to Alter Tumor-Cell Phenotype: Enhanced Sensitivity to Antigen-Specific T-Cell Lysis

Tumor cell (MC38) Lysis by CEA-Specific T Cells

Human Carcinoma Cells Resistant to Chemotherapy Are Sensitive to CTL Killing After Treatment

Preclinical Data from Hodge et al.
Pox Vector Vaccine: PANVAC

Developed at NCI
CRADA with BNIT
**Docetaxel +/- PANVAC**

*Patient Population:* Metastatic Breast Cancer (Docetaxel Naïve) n=48

- **Arm A:** Weekly Docetaxel + PANVAC
- **Arm B:** Weekly Docetaxel alone

**Primary endpoint:** TTP

NCI 6977: PI, Gulley
MDA (Ibrahim)
Preliminary Data: Docetaxel +/- PANVAC

Median TTP for docetaxel in 2nd line setting is 4 months (Buzdar et al, The Breast 1996)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>TTP (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel alone</td>
<td>9</td>
<td>84</td>
</tr>
<tr>
<td>Docetaxel plus Vaccine</td>
<td>8</td>
<td>265</td>
</tr>
<tr>
<td>Combination</td>
<td>18</td>
<td>274</td>
</tr>
</tbody>
</table>

Remain on study

Days

Time to Progression

Docetaxel alone (n=9)
Median TTP = 84 days

Docetaxel plus Vaccine (n=8)
Median TTP = 265 days
Conclusions

- Immunotherapy monotherapy does not appear to impact PFS
- However, delayed impact on tumor growth kinetics may eventually lead to improved OS
- Rationally designed combination studies
  - may control tumor burden for long enough → optimal immune mediated tumor growth slowing
  - improved PFS for combination arms vs. standard of care
  - This platform may lead to accelerated proof of concept studies and improved patient outcomes
Laboratory of Tumor Immunology and Biology