THE FUTURE OF VACCINES

ASCO ANNUAL MEETING
JUNE 4, 2016
Welcome and Introduction to Bavarian Nordic’s Cancer immunotherapy Programs

Paul Chaplin, Ph.D.
President & Chief Executive Officer, Bavarian Nordic

A Clinical Overview of PROSTVAC as Monotherapy and Combination Therapy

James L. Gulley, M.D., Ph.D.
Chief, Genitourinary Malignancies Branch, Head, Immunotherapy Section, Director, Medical Oncology Service, CCR Office of the Clinical Director, National Cancer Institute

Brachyury: A Novel Target with First in Man Data. Presentation of Clinical Data, Lessons Learned, and Potential Pathways Forward

Christopher R. Heery, M.D.
Associate Research Physician, Laboratory of Tumor Immunology and Biology, Director, Clinical Trials Group, National Cancer Institute
A CLINICAL OVERVIEW OF PROSTVAC AS MONOTHERAPY AND COMBINATION THERAPY

JAMES L. GULLEY, M.D., PH.D.
CHIEF, GENITOURINARY MALIGNANCIES BRANCH, HEAD, IMMUNOTHERAPY SECTION, DIRECTOR, MEDICAL ONCOLOGY SERVICE, OFFICE OF THE CLINICAL DIRECTOR, NATIONAL CANCER INSTITUTE
Challenges and Opportunities for Immunotherapy in Prostate Cancer

James L. Gulley M.D., Ph.D., F.A.C.P.
Head, Immunotherapy Section
Chief, Genitourinary Malignancies Branch &
Director, Medical Oncology Service
Center for Cancer Research
National Cancer Institute, NIH
Prostate cancer in the US

2016 US estimates: Cancer statistics in men

**Estimated new cases**

- Prostate: 180,890 (21%)
- Lung & bronchus: 117,920 (14%)
- Colon & rectum: 70,820 (8%)
- Urinary bladder: 58,950 (7%)
- Melanoma of the skin: 46,870 (6%)
- Non-Hodgkin lymphoma: 40,170 (5%)
- Kidney & renal pelvis: 39,650 (5%)
- Oral cavity & pharynx: 34,780 (4%)
- Leukemia: 34,090 (4%)
- Liver & intrahepatic bile duct: 28,410 (3%)
- All sites: 841,390 (100%)

**Estimated deaths**

- Lung & bronchus: 85,920 (27%)
- Prostate: 26,120 (8%)
- Colon & rectum: 26,020 (8%)
- Pancreas: 21,450 (7%)
- Liver & intrahepatic bile duct: 18,280 (6%)
- Leukemia: 14,130 (4%)
- Esophagus: 12,720 (4%)
- Urinary bladder: 11,820 (4%)
- Non-Hodgkin lymphoma: 11,520 (4%)
- Brain & other nervous system: 9,440 (3%)
- All sites: 314,290 (100%)

1 in 7 lifetime risk of incident prostate cancer

1 in 38 lifetime risk of death from prostate cancer

Siegel 2016, CA Cancer J Clin.
Why Immunotherapy for Prostate Cancer?

- Compared to other cancers is relatively indolent
- Neoadjuvant setting allows for tumor sampling
- Serum PSA
  - Doubling time/velocity as a marker for therapeutic benefit
  - Can detect recurrent disease years before metastasis
- Well described prostate specific targets
- Nomogram (Halabi) at metastatic disease
  - Can predict survival
- However, often not a T-cell inflamed tumor
The prevalence of somatic mutations across human cancer types.

T-cell Poor?
Target Self Ag

T-cell inflamed?
Target neoantigens

Identification of immunogenic neo-antigens

- 1,019 AA changes identified (exome), only two confirmed to be presented by tumor cells (mass spec) and only one immunogenic

Kalaora (Rosenberg) et al., *Oncotarget*, 2016
PROSTVAC-VF
Proposed Mode of Action

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

Tumor antigen gene  Costimulatory molecule genes
PSA  LFA-3  ICAM-1  B7-1
(TRIad of COstimulatory Molecules)

Vaccines:
PROSTVAC-V
PROSTVAC-F

Developed within the CCR, NCI
--Preclinical (Schlom et al.)
--Clinical (Gulley et al.)
Immune Impact Induced by PROSTVAC (PSA-TRICOM), a Therapeutic Vaccine for Prostate Cancer

James L. Gulley¹, Ravi A. Madan¹, Kwong Y. Tsang¹, Caroline Jochems¹, Jennifer L. Marté¹, Benedetto Farsaci¹, Jo A. Tucker¹, James W. Hodge¹, David J. Liewehr², Seth M. Steinberg², Christopher R. Heery¹, and Jeffrey Schlam³

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Specific Immune response</td>
<td>56.7% (59/104)</td>
<td>28 days after last vaccine</td>
</tr>
<tr>
<td>--Median fold increase in PSA specific immune response</td>
<td>5X</td>
<td># of PSA specific T-cells identical to flu T-cells</td>
</tr>
<tr>
<td>Antigen Cascade</td>
<td>67.9% (19/28)</td>
<td></td>
</tr>
<tr>
<td>Anti-PSA Ab</td>
<td>0.57% (2/349)</td>
<td></td>
</tr>
</tbody>
</table>
Antigen Spreading and the Tumor Immunity Cycle

A. Tumor expresses different immunogenic targets

B. Dendritic cell phagocytoses tumor cell along with a transfer of tumor-specific antigens

C. Mature dendritic cells present tumor-specific antigens to T-cells

D. Newly activated tumor-specific T cells form in greater concentration and variation

E. Fully activated T cell destroys tumor cells
## Antigen Cascade

Improved clinical outcomes associated with antigen cascade (aka antigen spreading)

<table>
<thead>
<tr>
<th>Modality</th>
<th>Immune Readout</th>
<th>Clinical Correlation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>T-cell</td>
<td>OS</td>
<td>Disis et al., 2009</td>
</tr>
<tr>
<td>Vaccine</td>
<td>T-cell</td>
<td>ORR</td>
<td>Corbiere, 2011</td>
</tr>
<tr>
<td>Vaccine</td>
<td>T-cell</td>
<td>OS</td>
<td>Walter, 2012</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Ab</td>
<td>OS</td>
<td>Thakurta, 2015</td>
</tr>
<tr>
<td>ACT</td>
<td>T-cell</td>
<td>OS</td>
<td>Chapuis, 2016</td>
</tr>
</tbody>
</table>

Retrospective studies

Gulley JL. Therapeutic vaccines: The ultimate personalized therapy? *Hum Vaccin Immunother*, 2012
PROSTVAC - Phase 2 RCT Trial Design

Asymptomatic
Minimally symptomatic
Metastatic
Castration Resistant
Prostate Cancer

PROSTVAC-V/F + GM-CSF

1º Endpoint

Treated at physician discretion

Crossover PV

Treated at physician discretion

2º Endpoint

Empty Vector (V/F) + Placebo

Kantoff (Dahut, Schlom, Gulley) et al. J Clin Oncol 2010
No Impact on Short-term Progression-free Survival

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>40</td>
<td>30</td>
<td>3.7</td>
</tr>
<tr>
<td>PROSTVAC</td>
<td>82</td>
<td>58</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Hazard ratio: 0.88 (95% CI 0.57–1.38)

Kantoff (Dahut, Schlom, Gulley) et al. *J Clin Oncol* 2010
Overall Survival Results

Significantly extended overall survival

- Control: 16.6 months
- PROSTVAC: 25.1 months

Hazard ratio: 0.56 (95% CI 0.37–0.85)

p = 0.0061

Kantoff (Dahut, Schlom, Gulley) et al. J Clin Oncol 2010
OS but not PFS

<table>
<thead>
<tr>
<th>Δ mOS</th>
<th>HR (p value)</th>
<th>Δ mPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5 months</td>
<td>HR = 0.59 (p=0.01)</td>
<td>0.4 months</td>
</tr>
<tr>
<td>4.1 months</td>
<td>HR = 0.78 (p=0.032)</td>
<td>0.1 months</td>
</tr>
<tr>
<td>8.5 months</td>
<td>HR = 0.56 (p=0.006)</td>
<td>0.1 months</td>
</tr>
</tbody>
</table>

Prostate

Melanoma

Gulley, Drake *Clin Ca Res*, 2012
## 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>Tumor Evolution / new mutations</strong></td>
<td>Resistance to therapy</td>
<td>New immunogenic targets</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>
Time

Tumor Burden

Tumor Growth Rate

Vaccine

Cytotoxic Therapy

Stein (Gulley, Dahut) et al., *Clin Ca Res*, 2011

Madan (Gulley, Dahut) et al., *Oncologist*, 2010
Prostvac: PSA Kinetics in a Patient with D0 Prostate Cancer

Rojan (Gulley) et al. *Clin. GU Ca*, 2013
E9802: Decrease in growth rate (PSA) over time following therapeutic vaccination

PROSTVAC treatment starting Day 0 and continued for 6 months, n=50

Gulley et al, ASCO GU 2013
DiPaola (Gulley) et al, Eur Urol, 2014

PSA DT
5.3 → 7.7 months at 6 months
p=0.02
## Therapies in Metastatic Prostate Cancer

### Phase III data

<table>
<thead>
<tr>
<th>Therapy</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><strong>1.5%</strong></td>
<td>&lt;5%</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>Ra-223</td>
<td>922</td>
<td>--</td>
<td>(47% PAP)</td>
<td>2.8 months</td>
<td>0.70</td>
<td>30%</td>
<td>2013</td>
</tr>
</tbody>
</table>

### Phase II PROSTVAC data

<table>
<thead>
<tr>
<th>Therapy</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>Multi-Center</td>
<td>125</td>
<td><strong>~2%</strong></td>
<td>&lt;5%</td>
<td>8.5 months</td>
<td>0.56</td>
<td>44%</td>
<td>---</td>
</tr>
</tbody>
</table>

N=191 treated with Prostvac at NCI with no side effects requiring stopping vaccine
PROSPECT Trial Design

Asymptomatic/minimally symptomatic mCRPC patients

PROSTVAC-V/F + GM-CSF**
(n = 400)

Vector Placebo
(n = 400)

Treatment Phase
(5 mo)*

Long-term Follow-up
(every 6 mo for 5 yr)

Prime Boosts

Weeks

Enrollment of 1,298
Completed in Jan 2015

*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 administration

PI: Gulley
## PSA-TRICOM Clinical Trials

<table>
<thead>
<tr>
<th>Disease State</th>
<th>New Diagnosis</th>
<th>New Diagnosis</th>
<th>Nonmetastatic ↑PSA (D0)</th>
<th>Nonmetastatic CRPC (D0.5)</th>
<th>Metastatic CRPC (pre-chemo)</th>
<th>Metastatic CRPC</th>
<th>Metastatic CRPC (post-chemo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Treatment</td>
<td>Active surveillance</td>
<td>Surgery</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;-line hormonal therapy (Gn-RH agonist)</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;-line hormonal therapy (ARA)</td>
<td>Enzalutamide</td>
<td>Docetaxel</td>
<td>Cabazitaxel Ra-223</td>
</tr>
<tr>
<td>Clinical Study</td>
<td>Phase II vaccine vs. placebo</td>
<td>Phase II EBRT + vaccine</td>
<td>Phase II ECOG VFFF vs. FFFF vs. FFFFV</td>
<td>Phase II Nilutamide vs. vaccine</td>
<td>Phase II Vaccine alone</td>
<td>Phase II Vaccine ± docetaxel</td>
<td>Phase II Quadramet ± vaccine</td>
</tr>
<tr>
<td></td>
<td>Phase II Neoadjuvant PSA-TRICOM</td>
<td>Phase II ECOG Vaccine alone</td>
<td>Phase II Flutamide ± vaccine</td>
<td>Phase II Multicenter trial vaccine vs. placebo</td>
<td>Phase II Vaccine→ docetaxel (ECOG)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase II Metastatic castration-sensitive prostate cancer Docetaxel + ADT ± PSA-TRICOM</td>
<td>Phase I Intraprostatic vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase II Anti-CTLA4 + vaccine</td>
</tr>
<tr>
<td></td>
<td>Phase I/II Neoadjuvant PSA-TRICOM, ipilimumab, and nivolumab</td>
<td>Phase II Enzalutamide ± PSA-TRICOM</td>
<td></td>
<td></td>
<td>Phase II Enzalutamide ± PSA-TRICOM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase II PSA-TRICOM vs. observation then PSA-TRICOM</td>
<td></td>
<td></td>
<td>Phase III Vaccine vs. placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Key**
- Published
- Recently completed
- Ongoing
- Planned
Phase I Study: Intraprostatic Vaccine

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 29</th>
<th>Day 57</th>
<th>Day 85</th>
<th>Day 113</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>Priming Vaccination</td>
<td>Booster Vaccination</td>
<td>Booster Vaccination</td>
<td>Booster Vaccination</td>
<td>Biopsy</td>
</tr>
<tr>
<td></td>
<td>s.c.</td>
<td>intraprostatic</td>
<td>intraprostatic</td>
<td>intraprostatic</td>
<td></td>
</tr>
</tbody>
</table>

Dose escalation study in patients with biopsy proven local recurrence following RT (n=21)

Digital analysis of biopsy (pre vs. post)

NCT 00096551  
PI Gulley  
Urologist Pinto
TILs significantly increased after vaccination

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased</td>
<td>10/10</td>
<td>100%</td>
</tr>
<tr>
<td>Unchanged</td>
<td>0/10</td>
<td>0%</td>
</tr>
<tr>
<td>Decreased</td>
<td>0/10</td>
<td>0%</td>
</tr>
</tbody>
</table>

- **CD4+CD8**
  - Increased: 10/10 (100%)
  - Unchanged: 0/10 (0%)
  - Decreased: 0/10 (0%)

- **CD4**
  - Increased: 12/12 (100%)
  - Unchanged: 0/12 (0%)
  - Decreased: 0/12 (0%)

- **CD8**
  - Increased: 12/13 (92%)
  - Unchanged: 1/13 (8%)
  - Decreased: 0/13 (0%)
PROSTVAC:
Robust Immune Responses within Target Organ

- 21 pts. with local recurrence after radiation, hormone-naive
- Intra-prostatic PROSTVAC (VFFF)
- Biopsies (13 pts.) taken before and after PROSTVAC (day 113)

TILs significantly increased after PROSTVAC

T\text{reg} proportion significantly decreased after PROSTVAC


Neoadjuvant study using a s.c. PROSTVAC regimen nearing completion
Phase II: Neoadjuvant Vaccine

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 0</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>Prostvac-V</td>
<td>Prostvac-F</td>
<td>Prostvac-F</td>
<td>Prostvac-F</td>
<td>RP</td>
</tr>
</tbody>
</table>

Single arm phase II (n=27)
Enrolled 26
IHC of tissue (pre vs. post)

Immune analysis
- Peripheral: 123 subsets, ICC, cascade
- Tumor: PerkinElmer vs. GE vs. IHC
- HTG Molecular (RNA)
- Definians “Tissue Phenomics”

PI Pinto; Al Gulley
T cell recognition of tumor cell

Tumor cells

T-cell

APM

MHC

Antigen

TCR
T cell function at tumor cell: to kill

**Immunogenic Modulation**
- ↑ APM/MHC
- ↑ TAA
- ↑ Fas
- ↑ Adhesion Molecules

Modalities: RT, Chemo, TKI, ADT
Hodge et al., NCI
Tumor Growth Rate

Tumor Burden

Time

Vaccine
Cytotoxic Therapy
Combination

Potential Multiple Effects of Local Irradiation of Tumors
QUADRAMET is a therapeutic agent consisting of radioactive samarium ($^{153}$Sm) and chelator.

It preferentially binds to osteoblastic metastatic tumor deposits in bone.

$^{153}$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 $^{153}\text{Sm}$ 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>
</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 $^{153}\text{Sm}$ results in increased sensitivity to multiple CTLs.
**Patient Population:** CRPC Metastatic to bone

Randomize

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

Arm B: $^{153}$Sm (n=34)

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

**$^{153}$Sm:**
- 1 mCi/kg d 8, may be repeated
- q 12 wks upon hematologic recovery.

NCT00450619; PI Gulley
CINJ (DiPaola) and UC (Stadler)
Final Data: $^{153}\text{Sm} +/- \text{PSA-TRICOM}$

- $^{153}\text{Sm Alone}$
  - TTP = 1.7 months

- $^{153}\text{Sm+PSA-TRICOM}$
  - TTP = 3.7 months

$P_2 = 0.03$

$n=44$

Heery ... Gulley, ASCO GU 2013
Enzalutamide Mediates Immunogenic Modulation in TRAMP-C2 Prostate Cells

MHC Increased ~5-Fold

Fas Increased ~1.7-

## Enzalutamide/PSA-TRICOM Phase 2 Combo studies

### Protocol

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>M0 hormone-naive PC</th>
<th>mCRPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in tumor re-growth rate (PSA kinetics) after 3 months of enzalutamide</td>
<td>Time to progression</td>
<td></td>
</tr>
</tbody>
</table>

### Study Design (open label)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Arm A: Enzalutamide (n = 17)</th>
<th>Arm A: Enzalutamide (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm B: Enzalutamide + PSA-TRICOM (n = 17)</td>
<td>Arm B: Enzalutamide + PSA-TRICOM (n = 36)</td>
<td></td>
</tr>
</tbody>
</table>

### NCT Numbers

- M0 hormone-naive PC: NCT01875250
- mCRPC: NCT01867333

PI: Ravi Madan
Combination with Docetaxel
Human Carcinoma Cells Resistant to Chemotherapy Are Sensitive to CTL Killing After Treatment

Hodge et al., *Int J Ca*, 2013
Docetaxel Modulates Phenotype of Human Tumors *in vivo*

Prostate: LNCaP (MUC-1)

Hodge et al., *Int J Ca*, 2013
Changes in Teff:Tregs Ratios andSuppressive Activity of Tregs During Therapy with Docetaxel in Patients with Hormone Refractory Prostate Cancer

Roselli (Gulley, Schlom) et al. OncolImmunology, 2013
Rationale to Combine Docetaxel and Vaccine – *in vivo* Studies

- Docetaxel and vaccine has enhanced anti-tumor activity in a transgenic self-antigen mouse model.

- Docetaxel and vaccine induces *antigen spreading* greater than either treatment alone in transgenic mice.

Garnett et al. *Int. Clin Cancer Res* 2008
Patient Population: Metastatic Breast Cancer (Docetaxel Naïve) n=48

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

Primary endpoint: Progression-Free Survival (PFS)
Figure 2. Progression-Free Survival in the 2 Treatment Arms

The combination treatment group underwent a median of 5 treatment cycles over 7.9 months; the docetaxel group, 3 cycles over 3.9 months (1-sided \( P = .09 \), which met the predefined statistical definition of \( P \leq .10 \)); hazard ratio, 0.65 (95% CI, 0.34-1.14). Median potential follow-up was 42.8 months.

3.9 vs. 7.9 months
Open Clinical Trial in Metastatic Castration-Sensitive Prostate Cancer

Primary Endpoint:
Antigen spreading

Secondary Endpoints
Other immune analysis
Clinical outcomes (PSA, ORR, PFS)

PI: Ravi Madan, 16C0048
anti-PD1 or anti-PD-L1

Lung Cancer

Bladder Cancer

Pancreas Cancer

Ovarian Cancer

Gastric Cancer

Gastroesophageal Cancer

Modified from a Slide Courtesy of “Mac” Cheever
Immunogenic Intensification

Proportion Alive

Months

Ipilimumab
CENSORED

Schadendorf et al., JCO 2015
O'Sullivan et al., JCO 2014
Importance of PD1 / PDL1 blockade
Colocalization of inflammatory response and PDL1 expression

IFN-γ upregulates PDL1 expression in vitro

Taube et al., Sci Trans Med 2012
Prostate Cancer and PDL1

- ORR <10% in unselected patients (nivolumab and others).
- PDL1 highly expressed in enzalutamide resistant prostate cancer
  - Murine cell lines
  - In circ. DC in pts

Bishop et al. Oncotarget, 2014
Requirements for Effective Immunotherapy

Effector Cells Functional within Tumor

Generate Immune Response
## Immunogenic Intensification

<table>
<thead>
<tr>
<th></th>
<th>Median Halabi Predicted Survival* (months)</th>
<th>Median Overall Survival in months (95% CI)</th>
<th>Δ OS (months)</th>
<th>Alive at 24 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostvac alone</strong>  (n=32)(^1)</td>
<td>17.2</td>
<td>26.3</td>
<td>+9.1</td>
<td>53%</td>
</tr>
<tr>
<td><strong>Prostvac + Ipilimumab</strong>  (n=30)(^2)</td>
<td>18.5</td>
<td>34.4 (29.6 - &gt;41)</td>
<td>+15.9</td>
<td>73.3%</td>
</tr>
</tbody>
</table>

\(^*\)Halabi et al., *JCO* 2003
\(^1\)Gulley (Dahut) et al, *Ca Immunol Immunother*, 2010
\(^2\)Madan (Dahut, Gulley) et al, *Lancet Oncology*, 2012
Prostvac plus Ipilimumab Combination: Updated Overall Survival

Singh (Dahut, Gulley), ASCO GU 2015
Effect of Vaccination on Tumor PD-L1 Expression

Effect of vaccination on tumor PD-L1 expression in CEA-Tg mice.

MC38 (CEA) cells s.c. followed by vaccination with rMVA-CEA-mTRICOM or rF-CEA-mTRICOM.

Harvest tumors for IHC.

Similar results with LLC lung carcinoma cells.

Unpublished Courtesy Jack Greiner

Gajewski T et al. Current Opinion in Immunology, 25, 1-9 2013
Prostvac + Ipi or Nivo or Comb.

Patient Population: Localized Prostate Cancer, candidates for RP

Cohort 1: Vaccine + Ipi + Nivo (n=10, mCRPC)
Cohort 2: Vaccine + Nivo (n=16)
Cohort 3: Vaccine + Ipi (n=16)
Cohort 4: Vaccine + Ipi + Nivo (n=16)

Baseline  | Week 0 | Week 2  | Week 5  | Week 8  | Week 9
----------|--------|---------|---------|---------|---------
Biopsy    | Prostvac-V | Prostvac-F | Prostvac-F | Prostvac-F | RP
          | Ipilimumab  | Ipilimumab | Ipilimumab | Ipilimumab | Ipilimumab
          | Nivolumab   | Nivolumab  | Nivolumab  | Nivolumab  | Nivolumab

Ipilimumab 1 mg/kg, Nivolumab 240 mg

PI Gulley
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Cohort 4: Vaccine + Ipi + Nivo (n=16)

Primary analysis: Immune infiltrate by IHC
Secondary: Safety
   Imaging
   Peripheral immune analysis
   In depth analysis of tumor microenvironment
      - EdgeSeq, multiplex IF, tissue phenomics
Requirements for Effective Immunotherapy

Effector Cells Functional within Tumor
- PDL1
- TGF-β
- IDO
- IL-10
- VEGF (MDSC and immature DC)
- Other immune checkpoints

Generate Immune Response
- Vaccine
- ACT
- CTLA4 blockade
- Intratumoral cytokines (NHS-IL12, BCG)
- NK cells (ACT or cytokines)
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