Cancer Vaccine Combination with Conventional Therapies

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The following relationships exist related to this presentation:

No Relationships to Disclose
STRATEGIC PLAN

Cancer Vaccine Development:
– Focus on human carcinoma
– Focus on development of vaccines that can be widely evaluated

Ultimate Use:
– Early in disease process/low tumor burden
– Survival as the endpoint
– Minimal toxicity

Immuno-Oncology Platform:
– Combination immune therapies
  ➢ immune stimulation strategies
  ➢ reduction of immune inhibitory entities

– Combination Therapies: Vaccine plus:
  ➢ conventional therapies
  ➢ conventional therapies in novel strategies
  ➢ other experimental therapies
Recombinant Vaccine Vectors

- **Pox vectors**
  - Vaccinia (rV-) elicits a strong immune response
    - host induced immunity limits its continuous use
    - MVA (replication defective)
  - 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
T-Cell Dependence on Costimulation

**Signal 1 + Signal 2**
- Antigen Presenting Cell
- MHC
- TCR
- Costimulatory Molecule

Activation of Antigen-Specific T-cells

**No Signal 1**
- Antigen Presenting Cell
- MHC
- TCR
- Costimulatory Molecule

Clonal Anergy
Apoptosis
Ignorance

**No Signal 2**
- Antigen Presenting Cell
- MHC
- TCR

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

- **CD2** (Region 1)
- **CD28**
- **CTLA-4**
- **LFA-1**
- **Tyrosine Kinase**
- **Ca\(^{2+}\) Mobilization**
- **cAMP Production**
- **IL-2-R upregulation**
- **IL-2 secretion**

<table>
<thead>
<tr>
<th>APC</th>
<th>T-Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MHC + Peptide</strong></td>
<td><strong>TCR</strong></td>
</tr>
<tr>
<td><strong>Costimulatory Molecule</strong></td>
<td><strong>Ligand</strong></td>
</tr>
<tr>
<td>B7-1 (CD80)</td>
<td><strong>CD28</strong></td>
</tr>
<tr>
<td>ICAM-1 (CD54)</td>
<td><strong>CTLA-4</strong></td>
</tr>
<tr>
<td>LFA-3 (CD58)</td>
<td><strong>LFA-1</strong></td>
</tr>
<tr>
<td><strong>Costimulatory Mechanism</strong></td>
<td><strong>Tyrosine Kinase, Phospholipase C</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Tyrosine Kinase, Ca(^{2+}) Mobilization, cAMP Production</strong></td>
</tr>
<tr>
<td></td>
<td><strong>IL-2-R upregulation, IL-2 secretion</strong></td>
</tr>
</tbody>
</table>

T-cell Activation (CPM x 10⁵)

- None
- LFA-3
- ICAM-1
- B7-1
- TRICOM

Costimulatory Molecule
TRICOM Vaccines

Tumor Antigen Gene  Co-stimulatory molecule genes

<table>
<thead>
<tr>
<th>TAA</th>
<th>B7-1</th>
<th>LFA-3</th>
<th>ICAM-1</th>
</tr>
</thead>
</table>

(TRiad of Co-stimulatory Molecules)

Vaccines:
(rV-TAA-TRICOM)
(rF-TAA-TRICOM)

Induction of Tumor specific immune responses (T-cells)

Vaccine
### TRICOM
TRIad of COstimulatory Molecules

<table>
<thead>
<tr>
<th>Costimulatory Molecule</th>
<th>Ligand on T cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>B7-1 (CD80)</td>
<td>CD28/CTLA-4</td>
</tr>
<tr>
<td>ICAM-1 (CD54)</td>
<td>LFA-1</td>
</tr>
<tr>
<td>LFA-3 (CD58)</td>
<td>CD2</td>
</tr>
</tbody>
</table>

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TRICOM = B7-1/ICAM-1/LFA-3  
CEA/TRICOM = CEA/B7-1/ICAM-1/LFA-3  
CEA/MUC-1/TRICOM = CEA/MUC-1/B7-1/ICAM-1/LFA-3 (PANVAC)  
PSA/TRICOM = PSA/B7-1/ICAM-1/LFA-3 (PROSTVAC)

**All vaccines contain:**  
rV- as a prime vaccine  
avipox (fowlpox, rF-) as multiple booster vaccines  
CEA, MUC-1, and PSA transgenes all contain enhancer agonist epitopes
CEA-specific Lymphoproliferation of T Cells from CEA-Tg Mice Vaccinated with TRICOM Vectors

Therapy of 14-Day Established CEA+ Experimental Metastases in CEA-Tg Mice Using CEA/TRICOM Vectors

VAAV Regimen

- CEA
- CEA/TRICOM

All groups with GM-CSF and low dose IL-2

Prostate Cancer and Vaccine Therapy

- Long interval from primary diagnosis to metastatic disease
- Serum PSA (doubling time/velocity) as a surrogate for therapeutic benefit or disease recurrence
- Nomogram (Halabi) at metastatic disease
  - can predict more indolent vs more aggressive disease
Therapies Shown to Improve Overall Survival in Metastatic Castration-Resistant Prostate Cancer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type of therapy</th>
<th>Stop treatment 2° AE</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>chemotherapy</td>
<td>11%</td>
<td>2.4 months</td>
<td>0.76</td>
<td>24%</td>
<td>2004</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>chemotherapy</td>
<td>18%</td>
<td>2.4 months</td>
<td>0.70</td>
<td>30%</td>
<td>2010</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>hormone</td>
<td>19%</td>
<td>3.9 months</td>
<td>0.66</td>
<td>34%</td>
<td>2011</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>vaccine</td>
<td>1.5%</td>
<td>4.1 months</td>
<td>0.78</td>
<td>22%</td>
<td>2010</td>
</tr>
<tr>
<td>Prostvac*</td>
<td>vaccine</td>
<td>~2%</td>
<td>8.5 months</td>
<td>0.56</td>
<td>44%</td>
<td>—</td>
</tr>
</tbody>
</table>

* rV-, rF-PSA-TRICOM – Results of a Phase II randomized, placebo (vector)–controlled, 43-center trial.
PROSTVAC
PSA and a TRIad of COstimulatory Molecules

TAA: PSA: PROSTVAC

Vaccines: (rV-TAA-TRICOM) (rF-TAA-TRICOM)

Induction of Tumor specific immune responses (T-cells)

Tumor Antigen Gene Co-stimulatory molecule genes

TAA B7-1 LFA-3 ICAM-1

(TRiad of COstimulatory Molecules)
PROSTVAC Significantly Extended Overall Survival

<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 (Schlom, Gulley) et al. J Clin Oncol 2010
Observations:

A. Time to Progression: no difference in arms

B. Median survival (at 4 years median follow-up)
   Placebo: 16.6 months
   Vaccine: 25.1 months (p=0.006)

C. 44% reduction in death rate in vaccine arm

NCI Phase II Trial:
   MOS: 26.6 mo
   HPS: 17.4 mo
The Next Frontier: Vaccine Combination Therapies

The use of cancer vaccines in combination with conventional therapies

- Hormone therapy
- Radiotherapy of tumor
- Chemotherapy
Vaccine Combination Therapies

The vaccine induction of a dynamic host immune response can be boosted by

– concomitant or subsequent therapies
Vaccine Combination Therapies

The vaccine induction of a dynamic host immune response can be boosted by

– concomitant or subsequent therapies

(a) can alter the phenotype of tumor cells, rendering them more susceptible to T-cell killing
Vaccine Combination Therapies

The vaccine induction of a dynamic host immune response can be boosted by

– concomitant or subsequent therapies

(a) can alter the phenotype of tumor cells, rendering them more susceptible to T-cell killing

(b) can lyse populations of tumor cells which, in turn, act as a booster for tumor-specific immune cells
Vaccine Combination Therapies

The vaccine induction of a dynamic host immune response can be boosted by

– concomitant or subsequent therapies

(a) can alter the phenotype of tumor cells, rendering them more susceptible to T-cell killing

(b) can lyse populations of tumor cells which, in turn, act as a booster for tumor-specific immune cells

(c) can kill or inhibit regulatory T cells and thus boost the immune response
The Next Frontier: Vaccine Combination Therapies

The use of cancer vaccines in combination with conventional therapies

- **Hormone therapy**
- **Radiotherapy of tumor**
- **Chemotherapy**
Dosing Regimens of Anti-androgen Therapy

Combination with Testosterone lowering therapy (CAB)

• Flutamide
  – 250 mg three times daily – total 750 mg per day

• Bicalutamide
  – 50 mg daily

• Nilutamide
  – 300 mg once a day for 30 days followed thereafter by 150 mg per day
T cell infiltrate after ADT

12- to 14-week-old NT or ProHA × TRAMP mice were adoptively transferred with $1 \times 10^7$ clonotypic HA targeted CD4 cells 1 week prior to castration. After 1 additional week, animals were challenged with vacc-HA and cells harvested 5 days later.

Cancer Cell, 2005
Vaccine/Androgen Receptor Antagonist Therapy

Patient Population: Androgen Independent Prostate Cancer with Rising PSA and No Radiographic Evidence of Disease (D = 0.5)

Arm A: Vaccine* (n=21)
rV-PSA + rV-B7-1 prime, rF-PSA boosts monthly IL-2 low dose x 5 days, recombinant GM-CSF x 4 days

Arm B: Nilutamide* (n=21)
(Androgen Receptor Antagonist)

*If patient progressed by PSA but still NED radiographically, they could add in the therapy of the other arm

## Time to Treatment Failure

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>PSA 50%</th>
<th>Median Time to Treatment Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>21</td>
<td>1</td>
<td>9.9 months</td>
</tr>
<tr>
<td>Nilutamide</td>
<td>21</td>
<td>10</td>
<td>7.6 months</td>
</tr>
<tr>
<td>Vaccine $\rightarrow$ Vaccine + Nilutamide</td>
<td>12</td>
<td>7</td>
<td>13.9 months (after cross-over)*</td>
</tr>
<tr>
<td>Nilutamide $\rightarrow$ Vaccine + Nilutamide</td>
<td>8</td>
<td>1</td>
<td>5.2 months (after cross-over)</td>
</tr>
</tbody>
</table>

Treatment failure includes progressive disease (radiographic or PSA), or discontinuation due to toxicity.

*Median time to cross-over was 12.0 months.
Overall Survival: Randomized Trial in Patients with Nonmetastatic HRPC Receiving Vaccine (rV-PSA/B7.1, rF-PSA) vs. Androgen Receptor Antagonist (Nilutamide) with Crossover at Progression

Five-Year Overall Survival:

38%: Nilutamide first
59%: Vaccine first
The use of cancer vaccines in combination with conventional therapies

- Hormone therapy
- Radiotherapy of tumor
- Chemotherapy
Potential Multiple Effects of Local Irradiation of Tumors

Hodge et al., Oncology 22:1064-70.
Combination Therapy: Vaccine + External Beam Radiation

Tumor (MC38-CEA+ SQ)

Day 0 8 14 15 22 29

V1 V2 V3 V4

8 Gy (2 Gy x 4)

rV-CEA/TRICOM rF-GM-CSF rf-CEA/TRICOM rF-GM-CSF

Days Post Tumor Transplant

0 7 14 21 28 35 42 49

Tumor volume (mm³)

No Treatment Vaccine Irradiation Vaccine + Irradiation

n=12 n=13 n=12 n=12 12 (36) 11 (41) 66 (435) 54 (415) n=13 n=11 (41) n=9 n=5

% Fas +

Antigen Cascade (Epitope spreading)

- Generation of T-cell responses to antigens not in vaccine

Tumor Therapy Model

- Antigen cascade T-cell responses greater in responders (tumor cure) vs. non-responders (tumor growth)

* Cascade antigen T-cell responses
  - can be more potent than those directed against antigen in vaccine
    - clinical implications

Kudo-Saito C, Schlom J, Camphausen K, Coleman CN, and Hodge JW. Clin Cancer Res. 11:4533-4544, 2005
Chakraborty M, Abrams SI, Coleman CN, Camphausen K, Schlom J, and Hodge JW. Cancer Res. 64:4328-4337, 2004
Trial: Radiotherapy ± Vaccine

Background: ~1/3 have PD after radiation therapy, often 2º to occult metastasis. Perhaps this could be improved with a well tolerated systemic therapy (vaccine). The addition of vaccines to radiation → minimal risk of toxicity, potential synergy.

Hypothesis: Immune responses can be raised to TAA despite local RT.

Gr. A ↓ □ = Prime: rV-PSA + rV-B7.1
Gr. B No vaccine ↓ □ = Boost: rF-PSA

↓ □ = Blood for ELISPOT

All vaccines given with GM-CSF and IL-2

Immune response

• **13 of 17** evaluable patients in the vaccine arm had increases of their PSA-specific T-cells of at least 3-fold following vaccination as measured by ELISPOT assay.

• **None of 8** evaluable patients tested on the radiation only arm had any measurable increase in their PSA-specific T-cells (*p*<0.0005).

• **Hypothesis:** Effective immune mediated killing $\rightarrow$ induction of immune response to prostate cancer antigens not in the vaccine (prior to RT).

• **6/8 pts** tested had $\geq$2-fold increase in immune response to PAP, PSMA, PSCA and / or MUC-1.

• Cells isolated from a pt who had both MUC-1 and PSA responses could specifically lyse PSA or MUC-1 containing tumors.

## Antigen Cascade

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sample</th>
<th>PSA3</th>
<th>PSMA</th>
<th>PAP</th>
<th>PSCA</th>
<th>MUC-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt 3</td>
<td>pre vac</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>post 3</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pt 6</td>
<td>pre vac</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>post 3</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Pt 7</td>
<td>pre vac</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>post 3</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pt 8</td>
<td>pre vac</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>post 3</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>Pt 11</td>
<td>pre vac</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>post 3</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Pt 12</td>
<td>pre vac</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>post 3</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

**Controls:**
- Flu
- HIV
- No peptide
The use of cancer vaccines in combination with conventional therapies

- Hormone therapy
- Radiotherapy of tumor
- Chemotherapy
Mode of Action of Vaccine Combination Therapies

- Exploitation of the phenomenon of homeostatic proliferation of T cells post-chemotherapy
  — certain effector immune cell subsets can be expanded more rapidly vs. regulatory cells

- Evidence of non-coordinate lytic susceptibility of tumor cells
  — tumor cells have shown differential susceptibilities to killing by chemotherapy/radiation vs. T cells
Human Carcinoma Cells Resistant to Chemotherapy Are Sensitive to CTL Killing After Treatment
Patient Population: Metastatic Androgen Independent Prostate Cancer (AIPC)

Primary endpoint: Fold change in PSA specific T-cell precursors post-vaccine

Secondary endpoints: Change in PSA velocity after 3 months, median time to disease progression

Arm A: Vaccine + Docetaxel (n=14)

Arm B: Vaccine alone (n=14)*

Vaccine: rV-PSA + rV-B7.1 prime on day 1; rF-PSA boosts on days 15, 30, and 58

*At time of PD, vaccine could be stopped and docetaxel added.

Fold Increase in PSA-specific T Cells post Vaccination for Patients Receiving Vaccine vs. Vaccine plus Docetaxel (plus Steroid)

*\(p = 0.92\) using Wilcoxon Sum Rank Test
# Vaccine/Docetaxel Combination Therapy

## Time to Progression

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>&gt;50% PSA decline</th>
<th>Median time to progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine alone</td>
<td>14</td>
<td>0/14 (0%)</td>
<td>1.8 months</td>
</tr>
<tr>
<td>Vaccine + docetaxel</td>
<td>14</td>
<td>3/14 (21.4%)</td>
<td>3.2 months</td>
</tr>
<tr>
<td>Docetaxel post-progression on vaccine</td>
<td>11</td>
<td>5/11 (45.5%)</td>
<td>6.1 months</td>
</tr>
<tr>
<td>Docetaxel alone*</td>
<td>25</td>
<td>9/24 (37.5%)</td>
<td>3.7 months</td>
</tr>
</tbody>
</table>

*Historical control with same dose and schedule of docetaxel in similar patient population at same institution (Dahut et al., J. Clin. Oncol. 2004)
Chemotherapy vs. Vaccine Followed by Chemotherapy (ECOG Multicenter Trial)

**Patient Population:** Metastatic CRPC (Halabi Predicted Survival $\geq$ 18 months)

**Phase II (n=135)**

**Primary endpoint: OS**

- **Arm A:** PSA-TRICOM vaccine $\rightarrow$ Docetaxel + Prednisone (n=90)
- **Arm B:** Docetaxel + Prednisone (n=45)

Protocol Chair: Doug McNeel
Co-Chair: Gulley
**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

Preclinical Data from Hodge et al.
Tumor Growth Rate

Unique Properties of Therapeutic Cancer Vaccines

- Minimal toxicity

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

- Overall survival vs RECIST or time to progression as the appropriate primary endpoint

- Induction of host immunity is a dynamic process that can persist post-vaccination

- Potential for an enhanced effect on concomitant or subsequent therapies
Translational Research Programmatic Effort

PRECLINICAL STUDIES:
Laboratory of Tumor Immunology and Biology (LTIB)
James Hodge
Claudia Palena
Al Tsang
Jack Greiner
Jianping Huang
Ingrid Fernando
Benedetto Farsaci
Sofia Gameiro

Laboratory of Molecular Biology
Ira Pastan

Vaccine Branch
Jay Berzofsky

CLINICAL STUDIES:
LTIB/Medical Oncology Branch
James Gulley
Mary Pazdur
Ravi Madan

Medical Oncology Branch
William Dahut
William Figg
Marijo Bilusic
Chris Heery
Tito Fojo

Radiation Oncology
Kevin Camphausen
Deborah Citrin

Urologic Oncology
Marston Linehan
Peter Pinto
Gennady Bratslavsky

Biostatistics and Data Management Section
Seth Steinberg

NIH Nuclear Medicine
C.H. Paik

NIH Interventional Radiology
Brad Wood
Translational Research Programmatic Effort

CLINICAL STUDIES — EXTRAMURAL:
Georgetown – John Marshall
Dana Farber Cancer Center – Donald Kufe, Paul Eder, Philip Kantoff
Columbia – Howard Kaufman
Cancer Institute of New Jersey – Edward Lattime, Robert DiPaola
Ohio State – William Carson
Duke – H. Kim Lyerly, Michael A. Morse
Eastern Cooperative Oncology Group (ECOG) – Robert DiPaola

CANCER THERAPY EVALUATION PROGRAM (CTEP):
Howard Streicher Jan Casadei

PRIVATE SECTOR:
GlobeImmune – David Apelian
BN ImmunoTherapeutics – Wayne Godfrey, Reiner Laus, Alain Delcayre
Merck/EMD Serono – Helen Sabzevari, Jens-Oliver Funk

NCI Technology Transfer Center: Kevin Brand, Bob Wagner, Karen Maurey
NIH Office of Technology Transfer: Sabarni Chatterjee, Mojdeh Bahar