The Role of Immunotherapy in Prostate Cancer: What’s Trending?

Douglas G. McNeel, MD, PhD
University of Wisconsin Carbone Cancer Center
Madison, Wisconsin
Outrline

• Prostate cancer – rationale for immune therapies
• Anti-tumor vaccines
  – Sipuleucel-T
  – Rilimogene galvacirepvec/rilimogene glafolivec
  – Other vaccines in clinical trials
• Other immune therapies
  – Checkpoint inhibitors
  – Chimeric antigen receptor (CAR) T cells and bispecific T-cell engagers (BiTE)
• Integration with medical practice
• Future directions
Prostate Cancer

- Most commonly diagnosed cancer in the US
- Second leading cause of cancer-related death in men
- >180,000 projected new cases in the US in 2016
- >26,000 projected deaths in the US in 2016
Typical Timeline of Prostate Cancer

- **Organ confined**
- **Locally advanced**
- **Rising PSA hormone naïve (D0/M0)**
- **Rising PSA castrate-resistant (D0.5)**
- **Metastatic disease (D2)**
- **Metastatic CR asymptomatic (D3)**
- **Metastatic CR symptomatic**

**Timeline**

- **Docetaxel**
- **Androgen deprivation**
- **Sipuleucel-T**
- **Enzalutamide**
- **Abiraterone**
- **Docetaxel**
- **Enzalutamide**
- **Cabazitaxel**
- **Abiraterone**
- **Mitoxantrone**
- **Radium-223**

**CR**, complete response
Rationale for Immunotherapy of Prostate Cancer

- Significant health problem
- Long natural history
- Currently no “adjuvant” treatment
- The prostate is “expendable”
- Several prostate cancer-associated and tissue-specific proteins are already identified
- Preclinical evidence shows that immune responses to the prostate may be therapeutic
- As a result, much work has been focused on vaccines as treatments
Prostate Cancer Immunotherapy

Major efforts include:

- Supplying/expanding tumor-reactive cells
- Blocking of mechanisms of cytolytic cell regulation
- Disruption of the immunosuppressive tumor microenvironment
Prostate Cancer Immunotherapy: Supplying Tumor-Reactive Cells

Vaccines or cytokines (to expand tumor-reactive T cells or antibodies)

Infuse APCs presenting tumor antigens (to expand tumor-reactive cells or antibodies)

Infusion of tumor-reactive cells (eg, CAR-T cells)

Bispecific antibodies (to force immune cell-tumor contact)

APC, antigen-presenting cell
Prostate Cancer Immunotherapy: Blocking T-Cell Checkpoint Regulation

eg, blocking PD-1 or LAG3 on tumor-reactive T cells, or PD-L1 on tumor cells, to block tumor-associated immune suppression

eg, blocking CTLA-4 on tumor-reactive T cells to permit expansion after activation

Prostate Cancer Immunotherapy: Disrupting Tumor Microenvironment

Agents to disrupt tumor vasculature

Agents to block or deplete Treg or other immunosuppressive cell populations

Tumor Cell

MDSC or Treg

Treg, regulatory T cells; MDSC, myeloid-derived suppressor cells

Types of Anti-Tumor Vaccines

**Cell based**
- Autologous inactivated cells
- Gene-transduced tumor cells
- Dendritic cell (DC)

**Antigen specific**
- Protein/carbohydrates
- Peptide
- Vectors
  - Bacterial
  - Viral
- Nucleic acid
Sipuleucel-T

Source: Dendreon Corporation
Sipuleucel-T


Source: Dendreon Corporation
Sipuleucel-T

- Phase III IMPACT trial – 512 patients with asymptomatic metastatic castration-resistant prostate cancer (mCRPC) randomized to sipuleucel-T vs placebo
- Median overall survival (OS): 25.8 vs 21.7 months
- 36-month survival: 31.7% vs 23%
- No difference in time to progression
- Antibody responses to PAP associated with longer survival
- Most common adverse events included chills, fever, headache
- Approved by FDA in 2010

Sipuleucel-T

• **Approval indications:** Patients with asymptomatic to minimally symptomatic CRPC

• **Dosing:** Collection and infusion every 2 weeks x 3

• **Common adverse reactions:** Chills, fatigue, fever, back pain, nausea, joint aches, headache

• **Warnings:** Infusion reactions, not tested for transmissible infectious diseases, syncope/hypotension, myocardial infarction, thromboembolic events
Who are the best patients for this therapy?

- Lower volume disease
- Not rapidly growing; can wait for 6 weeks of therapy
- (Probably not) neuroendocrine tumors

Special considerations:

- When to proceed on to next therapy
- No defined measure of benefit – “adjuvant” therapy for metastatic disease
Rilimogene Galvacirepvec/
Rilimogene Glafolivec

Rilimogene Galvacirepvec/ Rilimogene Glafolivec

- Randomized phase II trial: 125 patients with minimally symptomatic mCRPC
- Primary endpoint: Progression-free survival

International, randomized phase III trial currently underway

# Other Prostate Cancer Vaccines in Phase II / III Evaluation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Description</th>
<th>Current Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCVAC</td>
<td>Autologous APCs loaded with LNCaP tumor cell lysate</td>
<td>III</td>
</tr>
<tr>
<td>Ad/PSA</td>
<td>Adenovirus-based vaccine encoding PSA</td>
<td>II</td>
</tr>
<tr>
<td>pTVG-hPAP</td>
<td>DNA vaccine encoding PAP</td>
<td>II</td>
</tr>
<tr>
<td>Natural DCs</td>
<td>Autologous DC loaded with NY-ESO-1 and MUC1 peptides</td>
<td>II</td>
</tr>
<tr>
<td>ME TARP</td>
<td>Autologous DC loaded with TARP peptides</td>
<td>II</td>
</tr>
<tr>
<td>GX301</td>
<td>Synthetic multi-peptide vaccine targeting telomerase</td>
<td>II</td>
</tr>
<tr>
<td>Tecemotide</td>
<td>Synthetic lipopeptide vaccine targeting MUC-1</td>
<td>II</td>
</tr>
<tr>
<td>UV1/hTERT2012P</td>
<td>Synthetic peptide vaccine</td>
<td>II</td>
</tr>
<tr>
<td>RNActive</td>
<td>mRNA vaccine targeting multiple antigens</td>
<td>II</td>
</tr>
</tbody>
</table>

### Other Prostate Cancer Vaccines in Phase II / III Evaluation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Description</th>
<th>Current Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCVAC</td>
<td>Autologous <strong>APCs</strong> loaded with LNCaP tumor cell lysate</td>
<td>III</td>
</tr>
<tr>
<td>Ad/PSA</td>
<td>Adenovirus-based vaccine encoding PSA</td>
<td>II</td>
</tr>
<tr>
<td>pTVG-hPAP</td>
<td>DNA vaccine encoding PAP</td>
<td>II</td>
</tr>
<tr>
<td>Natural DCs</td>
<td>Autologous DC loaded with NY-ESO-1 and MUC1 peptides</td>
<td>II</td>
</tr>
<tr>
<td>ME TARP</td>
<td>Autologous DC loaded with TARP peptides</td>
<td>II</td>
</tr>
<tr>
<td>GX301</td>
<td>Synthetic multi-peptide vaccine targeting telomerase</td>
<td>II</td>
</tr>
<tr>
<td>Tecemotide</td>
<td>Synthetic <strong>lipopeptide</strong> vaccine targeting MUC-1</td>
<td>II</td>
</tr>
<tr>
<td>UV1/hTERT2012P</td>
<td>Synthetic peptide vaccine</td>
<td>II</td>
</tr>
<tr>
<td>RNActive</td>
<td>mRNA vaccine targeting multiple antigens</td>
<td>II</td>
</tr>
</tbody>
</table>

T-cell Checkpoint Blockade

Tumor cell or APC

CTLA4-specific antibody

T cell

CD80 or CD86

CD28

CTLA4

LAG3

Signal 2

Signal 1

B7-H1

MHC class I

MHC class II

TCR

PD1

PD1-specific antibody

T cell activation

Ipilimumab

- Phase III trial: 799 patients with mCRPC after docetaxel therapy randomized to ipilimumab vs placebo + bone-directed radiation therapy (XRT) (NCT00861614)
- Primary endpoint: OS

Ipilimumab

- Phase III trial: 799 patients with mCRPC after docetaxel therapy randomized to ipilimumab vs placebo + bone-directed XRT (NCT00861614)
- Primary endpoint: OS
- Phase III of ipilimumab vs placebo: Study completed, 600 chemotherapy-naïve patients with mCRPC (NCT01057810)
Other Checkpoint Inhibitors
PD-1/PD-L1 Blockade

• Phase I trials with nivolumab or pembrolizumab: No evidence of single-agent activity in mCRPC
• Phase II trial with pembrolizumab as single agent: Ongoing (NCT02312557)
• Multiple combinations with ipilimumab or PD-pathway inhibitors with vaccines, including sipuleucel-T and rilimogene galvacirepvec/rilimogene glafolivec, and chemotherapy, androgen deprivation, and radiation therapy
BiTE and CAR-T–Cell Approaches

- Phase I trials underway evaluating BiTE specific for CD3 and prostate-specific membrane antigen (PSMA)
- Phase I trial underway evaluating BiTE specific for CD3 and epithelial cell adhesion molecule (EpCAM)
- Phase I trials underway evaluating CAR T cells specific for PSMA
Where are we with prostate cancer in terms of available immunotherapies?

And how does this impact patient care?
Best information to date is with vaccines

Suggests having tumor-reactive T cells is important for this disease

Only FDA-approved therapy to date is sipuleucel-T

Survival benefit at least as great as seen with other approved therapies for mCRPC

Other agents are in advanced stages of clinical testing

Combination treatment approaches are eagerly awaited
Where do we go from here?

What exciting approaches are on the horizon?
Model of Treatment Effect From Vaccine Trials

Timeline and Therapies for Prostate Cancer

Organ confined

Locally advanced

Rising PSA hormone naïve (D0/M0)

Metastatic disease (D2)

Rising PSA castrate-resistant (D0.5)

Metastatic CR asymptomatic (D3)

Metastatic CR symptomatic

Sipuleucel-T
Enzalutamide
Abiraterone
Docetaxel

Androgen deprivation

Docetaxel

Enzalutamide
Cabazitaxel
Abiraterone
Mitoxantrone
Radium-223

Timeline
Clinical Monitoring - PSA Doubling Time

Staging studies (CT, bone scintigraphy):

ARM 1 Vaccine Schedule:

ARM 2 Vaccine Schedule: (Frequency of booster immunizations determined by immune monitoring)

Immunization continuing until evidence of disease progression, 24 immunizations total, or 2 years maximum

Randomized Phase II Clinical Stage D0/MO

• ~100 patients with prostate cancer with quickly rising serum PSA, but no evidence of metastases

• Primary endpoint: Two-year metastasis-free survival

Quantitative Assessment of Disease Burden and Growth Kinetics
DNA Vaccination Elicits PD-L1 Expression in the Tumor

Anti-Tumor Response Using DNA Vaccine With PD-1/PD-L1 Blockade

PDL-1 Expression Can Be Detected on Human Circulating Tumor Cells (CTC) Following Immunization

Clinical Trial NCT02499835: pTVG-HP + Pembrolizumab

<table>
<thead>
<tr>
<th>Week:</th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>-6</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>1</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(§= Pembrolizumab)  
(*)= pTVG-HP)

32 patients with advanced castration-resistant metastatic prostate cancer

- Immune/peripheral blood analyses
- CT scans / bone scans
- Quantitative bone imaging
- Tissue biopsy
The Future of Prostate Cancer Immunotherapy (?)

Vaccines

- T-cell checkpoint inhibitors
- Tumor microenvironment modulators
- Regulatory and immunosuppressive mechanisms

Immunomodulating agents

- OX-40 agonist
- Cytokines
Summary and Conclusions

- Immunotherapy has a role in the treatment of prostate cancer
- Anti-tumor vaccines have been investigated most often
  - Sipuleucel-T is currently the only FDA-approved vaccine approved for the treatment of existing cancer
  - Other prostate cancer vaccines are in advanced stages of clinical testing
- Combination therapies are demonstrating anti-tumor effects
- Larger studies with other agents are anticipated