THERAPEUTIC VACCINES IN PROSTATE CANCER

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DISCLOSURE SLIDE

• I have no relevant personal financial disclosures
• The NCI has Collaborative Research and Development Agreements with multiple companies that include money for preclinical and clinical development of immunotherapy agents.
Virus associated cancer
Mutation associated neoantigens

Adapted from Padmanee Sharma, and James P. Allison Science 2015;348:56-61
Working Model for T-cell infiltration and Immunotherapy Implications

Example:

- Melanoma
- Some NSCLC

"Inflamed" Tumor (Presence of T-cells)

anti-PD-L1

Release brakes on T-cells

Tumor Cell Lysis

- Colorectal Carcinoma
- Prostate Cancer

"Non-Inflamed" Tumor (Absence of T-cells)

anti-PD-L1

Vaccine

Tumor Growth
Presence of T-cells

anti-PD-L1

Release brakes on T-cells

Tumor Cell Lysis
Requirements for Effective Immunotherapy

Generation of Immune Response  Functional Effector Cells within the Tumor

Bilusic M, Madan RA, Gulley JL Clin Ca Res 2017
Anti-tumor Immune Response More Efficient with **Vaccine** (Prostvac) vs. SOC

<table>
<thead>
<tr>
<th></th>
<th>Cancer-free controls (n = 15)</th>
<th>AS (n = 9)</th>
<th>EBRT (no vaccine; n = 8)</th>
<th>EBRT + ADT (n = 15)</th>
<th>EBRT+Vaccine (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Western blot</strong></td>
<td>0 (0%)</td>
<td>1 (11.1%)</td>
<td>1 (12.5%)</td>
<td>3 (20.0%)</td>
<td>15 (45.5%)</td>
</tr>
<tr>
<td><strong>Antigen array</strong></td>
<td>0 (0%)</td>
<td>1 (11.1%)</td>
<td>0 (0%)</td>
<td>2 (13.3%)</td>
<td>7 (21.2%)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>0 (0%)</td>
<td>1 (11.1%)</td>
<td>1 (12.5%)</td>
<td>3 (20.0%)</td>
<td>17 (51.5%)</td>
</tr>
</tbody>
</table>

Nesslinger... Schlom, Gulley et al, *Clin Ca Res*, 2010
APC Vaccine: Sipuleucel-T (Provenge)

Day 1
Leukapheresis

Day 2-3
sipuleucel-T is manufactured

Day 3-4
Patient is infused

Apheresis Center

Company
(Dendreon)

Doctor’s Office
Sipuleucel-T: IMPACT trial

P = 0.032 (Cox model)
HR = 0.775 [95% CI: 0.614, 0.979]

Median Survival Benefit = 4.1 Mos.

Sipuleucel-T (n = 341)
Median Survival: 25.8 Mos.

Placebo (n = 171)
Median Survival: 21.7 Mos.

Kantoff et al., NEJM 2010
Sipuleucel-T
- Use early, in less aggressive disease
PROSTVAC-VF (PSA-TRICOM)

Vaccines:
- PROSTVAC-V
- PROSTVAC-F

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)

Developed with the CCR, NCI
--Preclinical (Schlom et al.)
--Clinical (Gulley et al.)
Overall Survival Results

<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>

Significantly extended overall survival

\( \Delta 8.5 \) months

Hazard ratio

0.56 (95% CI 0.37–0.85)

\( p=0.0061 \)

Kantoff (Dahut, Schlm, Gulley) et al. J Clin Oncol 2010
Asymptomatic/minimally symptomatic mCRPC patients

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

PROSTVAC-VF (n = 400)

Vector Placebo (n = 400)

Treatment Phase (5 mo)*

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

Prime

Boosts

Weeks

Pi: Gulley

*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
PROSTVAC CANCER IMMUNOTHERAPY
PHASE 3 FINAL DATA ANTICIPATED IN 2017

The PROSPECT Study:

A Randomized, Double-blind, Global Phase 3 Efficacy Trial of PROSTVAC in Metastatic Castration-Resistant Prostate Cancer

Randomization by region (N=1,297)

- 25.7% Rest of World (n=333)
- 18.4% North America Oncology (n=239)
- 38.2% Western Europe (n=497)
- 17.7% North America Urology (n=229)

Injections

- Average was 6.1 injections
- Randomized Phase 2 trial (n=122) had average of 5.4 injections
- An increased number of injections is expected to improve the clinical outcome for patients receiving the active drug.

1) Subjects who have completed study treatment phase or have completed 7th dosing visit. N=1,279
2) Kantoff et al., Journal of Clinical Oncology, January 2010
Recruitment timing and Follow-up Maturation

Recruitment duration = 38 months

Minimum potential follow-up by the end of Sept 2017:

First patient in = 69 m.

T 1-2
T 2-3

Last patient in = 32 m.
Median Survival = 33.9 months

BLINDED OVERALL SURVIVAL (ALL GROUPS)
**Median (months)**

<table>
<thead>
<tr>
<th>REGION</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>33.9</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>24.0</td>
</tr>
<tr>
<td>North America</td>
<td>36.9</td>
</tr>
<tr>
<td>Rest of World</td>
<td>35.9</td>
</tr>
</tbody>
</table>

**Reference OS in mCRPC (pre-chemo)**

- **Abiraterone**
  - NR (>27.2 months)
  - Placebo 27.2 months
  - COU-AA-302 Ryan et al. NEJM 2013

- **Enzalutamide**
  - 32.4 months
  - Placebo 30.2 months
  - PREVAIL Beer et al., NEJM 2014

- **Ipilimumab**
  - 28.7 months
  - Placebo 29.8 months
  - CA184-0495 Beer et al., JCO 2016
Antigen spreading and the tumour immunity cycle

A. Tumour expresses different immunogenic targets
- Neoepitope #2 to 1,000
- Neoepitope #1
- MUC-1
- PSA
- Dying tumour cells

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

C. Mature dendritic cell presents tumour-specific antigens to T cells

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

E. Fully activated T cell destroys tumour cells

Neoepitope #1
MUC-1
PSA
Antigen spreading and the tumour immunity cycle
Multi-layered immunosuppression

- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can "peel back" the layers of local immune suppression, thereby restoring the capacity of T cells to eradicate the tumor
QuEST (Quick Efficacy Seeking Trial)*

1) MVA/rF-Brachyury TRICOM + anti-PDL1 / TGF-β Trap
   - Cohort 1
     - n=12
     - Expand to n=35
     - + signal in ≥ 2
     - + signal in ≥ 6
     - Further study

2) MVA/rF-Brachyury TRICOM + anti-PDL1 / TGF-β Trap + ALT-803
   - Cohort 2
     - n=12
     - Expand to n=35
     - + signal in ≥ 2
     - + signal in ≥ 6

3) MVA/rF-Brachyury TRICOM + anti-PDL1 / TGF-β Trap + ALT-803 + Epacadostat
   - Cohort 3
     - n=12
     - Expand to n=35
     - + signal in ≥ 2
     - Further study

ALT-803 Dose-finding Safety Cohort (fixed dose M7824)
- n = 6-12

Signal:
- ≥ 30% PSA decline or Objective Response or PFS ≥ 6 mo

*NCI sponsored concept in review
CONCLUSIONS

• T-cell poor tumors may require a “spark” to get the immune system to recognize and seek to destroy the tumor.

• One of the most efficient ways of doing this is with vaccine

• Sipuleucel-T is approved in the US and unblinded data from the study of PSA-TRICOM is anticipated soon.

• The tumor immunity cycle is an ongoing iterative process that may lead to an individualized evolution of the immune response to focus on targets most immunologically relevant for a given patient (e.g., neoantigens) (#PrecisionMedicine #PersonalizedMedicine #ImmuneSculpting)

• Approaches that both steer the immune system and allow effector cells to get to and remain functional within the TME will be optimal