Immuno-Oncology Across Tumor Types:

Prostate Cancer

Charles G. Drake M.D. / Ph.D.
Associate Professor: Medical Oncology, Immunology and Urology
Johns Hopkins Kimmel Cancer Center
Disclosures

- Consulting: Bristol Myers Squibb, Compugen, Dendreon, ImmunExcite, Merck, NexImmune Novartis, Pfizer, Roche

- Research: Aduro Biotech, BMS

- Patents Licensed: AZ / Medimmune, Potenza
Outline

- Prostate Cancer Vaccines:
  - FDA-Approved Therapy (Sipuleucel-T) for Prostate Cancer
  - Vaccinia – Based Vaccine In Phase III

- Immune Checkpoint Blockade:
  - Anti-CTLA-4 (Ipilimumab) a Near Miss in Prostate Cancer

- Combining Immunotherapy with Hormonal Therapy

- Antigen-Spread following Sipuleucel-T Administration
Vaccines
A “Dendritic Cell” Vaccine: Sipuleucel T

IMPACT Overall Survival: Primary Endpoint
Intent-to-Treat Population

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.
Prospect Trial: Design (SPA)
Phase 3 Global (US-CAN-AUS/WE/EE/Latin America)

Non/Minimally symptomatic
Metastatic Castration Resistant Prostate Cancer

PROSTVAC-(V)(F) TRICOM + low dose adjuvant GM-CSF
PROSTVAC-(V)(F) TRICOM Adjuvant placebo
Vector Placebo Adjuvant placebo

Standard of Care
No cross Over

PRIMARY ENDPOINT: Overall Survival
Immune Checkpoint Blockade: CTLA-4
Ipilimumab (Anti-CTLA-4) Blocks the CTLA-4 Checkpoint, Restoring T Cell Activation
Phase 3 Study of Ipilimumumab in Post-Docetaxel mCRPC (CA184-043): Study Design*¹

- **Primary endpoint:** overall survival (OS)
- **Secondary endpoints:** progression-free survival (PFS), safety
- **Exploratory endpoint:** prostate-specific antigen (PSA) response rate

*ClinicalTrials.gov Identifier: NCT00861614.
ALP=alkaline phosphatase; ECOG=Eastern Cooperative Oncology Group; RT=radiotherapy.
Phase 3 Study of Ipilimumab in Post-Docetaxel mCRPC (CA184-043)\textsuperscript{1}

Primary Endpoint: OS (Intent to Treat [ITT] Population)

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab (n=399)</th>
<th>Placebo (n=400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>11.2 (9.5-12.7)</td>
<td>10.0 (8.3-11.0)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.85 (0.72-1.00)</td>
<td></td>
</tr>
<tr>
<td>Stratified log-rank P</td>
<td>0.0530</td>
<td></td>
</tr>
</tbody>
</table>

Safety

- Adverse event (AE) profile was consistent with that previously reported for ipilimumab*  
  - The most frequent severe immune-related AEs were diarrhea and colitis

\*See poster presentation at this meeting: Beer et al. Abstract ID: 52.

\textsuperscript{1}Gerritsen WR et al. Paper presented at: European Cancer Congress 2013; Amsterdam, The Netherlands. Abstract 2850.
OS by the Presence of Visceral Metastases at Baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipi No Visceral Metastases (n=280)</td>
<td>14.4 (11.5-16.4)</td>
</tr>
<tr>
<td>Pbo No Visceral Metastases (n=275)</td>
<td>10.3 (9.6-11.7)</td>
</tr>
<tr>
<td>Pbo Visceral Metastases (n=114)</td>
<td>7.4 (6.1-10.2)</td>
</tr>
<tr>
<td>Ipi Visceral Metastases (n=113)</td>
<td>5.7 (4.7-7.8)</td>
</tr>
</tbody>
</table>
Visceral Mets Don’t Seem to Affect Efficacy Of Abiraterone Acetate

Goodman et. al, PCAN 2014
Antigen Spread
Testing for Antigen Spread

ProtoArray IgG Profiling

Compare serum IgG levels pre- vs. post- Tx

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<thead>
<tr>
<th></th>
<th>WK2</th>
<th>WK10</th>
<th>WK22</th>
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</thead>
<tbody>
<tr>
<td>Sipuleucel-T</td>
<td>56</td>
<td>162</td>
<td>23</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Sipuleucel-T: n=25
Control: n=13

Sipuleucel-T or Control

Serum

Pre-treatment

Post-treatment (WK2, WK10, WK22)

Thakurta et. al. *Cancer Immunology* Research, in submission
IgG Responses to Non-Targeted Antigens

*IgG response against PAP (primary antigen) is shown for reference

Thakurta et. al. *Cancer Immunology Research*, in submission
Responses Overlap

PSA (36)
PAP (69)
KRAS (37)
LGALS3 (26)
LGALS8 (23)
ERAS (39)
LGALS3 (26)
And Correlate With Survival

**PSA**

- ≥ Median (n=47)
- < Median (n=46)

**LGALS3**

- ≥ Median (n=47)
- < Median (n=46)

<table>
<thead>
<tr>
<th>ANTIGEN</th>
<th>HR</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>0.63</td>
<td>0.003**</td>
</tr>
<tr>
<td>LGALS3</td>
<td>0.60</td>
<td>0.035*</td>
</tr>
<tr>
<td>ERAS</td>
<td>0.79</td>
<td>0.075*</td>
</tr>
<tr>
<td>LGALS8</td>
<td>0.83</td>
<td>0.369</td>
</tr>
<tr>
<td>KRAS</td>
<td>0.83</td>
<td>0.218</td>
</tr>
<tr>
<td>KLK2</td>
<td>0.75</td>
<td>0.051*</td>
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Thakurta et. al. *Cancer Immunology* Research, in submission
Summary

- One cancer vaccine that is US FDA-approved for treating prostate cancer

- Ongoing Phase III Vaccine Trials in Prostate Cancer
  - ProstVac VF

- Immune Checkpoint Blockade is not FDA-approved to treat prostate cancer
  - Phase III trial of anti-CTLA-4 (ipliimumab) pre-chemotherapy prostate cancer
  - Not much activity for anti-PD-1 in advanced prostate cancer

- Are visceral mets in prostate cancer immunologically different
  - Resistant to immune attack?
  - Hostile microenvironment?
  - Systemic immune suppression (cytokine-mediated?)

- Antigen Spread