Clinical Development:

Prostate and Kidney 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
  – Novartis
  – Pfizer
  – Potenza
  – Roche

• Patents Licensed: AZ / Medimmune, Potenza

• ProstVac VF, AGS-003, Ipilimumab (Anti-CTLA-4) and Nivolumab (anti-PD-1) are experimental agents, and are not FDA approved for use in prostate or kidney cancer
Cancer Vaccines:
- FDA-Approved (Sipuleucel-T) for Prostate Cancer
- Vaccinia – Based Vaccine In Phase III
- Two Vaccines in Phase III in RCC

Immune Checkpoint Blockade:
- Anti-CTLA-4 (Ipilimumab) a Near Miss in Prostate Cancer
- PD-1 Phase III Completed Enrollment in Kidney Cancer

Combination Immunotherapy in the Clinic
Vaccines
Cancer Vaccine Goal ....
Dendritic Cells Traffic and Present Antigen To Specific CD4 and CD8 T Cells in the Draining Lymph node

CD4 T Cell

TCR

Class II MHC

Cytokines

CD8 T Cell

TCR

Class I MHC
A “Dendritic Cell” Vaccine: Sipuleucel T

Harvested leukocytes

Density-gradient centrifugation

Enriched monocytes

Short-term culture (36–44 hours)

PAP

GM-CSF

Fusion protein

Patient with prostate cancer

**IMPACT Overall Survival: Primary Endpoint**

**Intent**
To Treat Population

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**Survival (Months)**

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

- Placebo (n = 171)

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**P = 0.032 (Cox model)**

**HR = 0.775 [95% CI: 0.614, 0.979]**

**Median Survival Benefit = 4.1 Mos.**
A "Vector" Vaccine For Cancer: ProstVac VF

Drake C., *Nature Reviews Immunology*, 2011
Prost Vac VF In Patients

Intradermal administration

Patient with prostate cancer

Epithelial cells

Infection

Necrosis

Cellular debris (including PSA)

Infection

CD4+ T cell

Cytokine help

Lysis

Prostate tumour

CD8+ T cell

PSA peptide

MHC class II

Activated APC

MHC class I

Maturation

Antigen uptake

Immature APC

ProstVac Survival Data

Hazard Ratio = 0.56 (95% CI, 0.37 to 0.85)

<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 VF</td>
<td>82</td>
<td>65</td>
<td>25.1</td>
</tr>
</tbody>
</table>

Kantoff et al JCO 2010, Epub 1/25/2010
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

SURVIVAL

PRIMARY ENDPOINT: Overall Survival
Using RNA to Load Dendritic Cells: Argos AGS-003

- Kidney Cancer Sample
- Leukapheresis Product
- Tumor RNA Isolation
- Load DC With RNA and Activate (AGS-003)
- Cryopreserve
- DC Manufacture
- Intranodal Injection
**ADAPT:**

**Autologous Dendritic Cell Immunotherapy with AGS-003 Plus Sunitinib for the Treatment of Advanced RCC**

- **Primary end point:** PFS (30% increase)
- **Secondary end point:** ORR, OS, Safety

**Randomize**

- Metastatic, unfavorable risk clear cell RCC
- **N= 600**

1 Cycle Sutent (6 wks) → AGS-003 5 doses Q 3 wks → AGS-003 Q 3 months

1 Cycle Sutent (6 wks) → Placebo 5 doses Q 3 wks → Placebo Q 3 months

Ongoing Sutent (4 wks on, 2 wks off)
Immune Checkpoint Blockade: CTLA-4
CTLA-4 Prevents Normal T Cell Activation

Signal 1

T Cell Receptor

Antigen

Signal 2

HLA

B7.1/2

CD28

CTLA-4

Antigen Presenting Cell

T cell
Ipilimumab (Anti-CTLA-4) Blocks the CTLA-4 Checkpoint, Restoring T Cell Activation
## Phase I/II Evidence for Anti-CTLA-4 Activity In Prostate Cancer

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ipilimumab dose</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 mg/kg</td>
<td>5 mg/kg</td>
<td>10 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−XRT (n = 8)</td>
<td>+XRT (n = 7)</td>
<td>−XRT (n = 6)</td>
<td>+XRT (n = 34; %)</td>
</tr>
<tr>
<td>PSA-evaluable patients</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>16 (100)</td>
</tr>
<tr>
<td>PSA decline by day 85</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3 (19)</td>
</tr>
<tr>
<td>PSA decline at any time</td>
<td>2</td>
<td>2</td>
<td>4(27)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Tumor-evaluable patients</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Partial response</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response (unconfirmed)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (25)</td>
</tr>
</tbody>
</table>

*PSA decline of ≥50% from baseline (day 85 and at any time) and tumor response (at any time) were confirmed by a second assessment at least 28 days after the initial assessment.

XRT, external-beam radiotherapy; PSA, prostate-specific antigen.

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Slovin S et. al. *Annals Oncology.* 2013
**Phase 3 Study of Ipilimumab in Post-Docetaxel mCRPC (CA184-043): Study Design**

- **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.

Drake CG, et al GU ASCO 2014
Phase 3 Study of Ipilimumab in Post-Docetaxel mCRPC (CA184-043)\(^1\)

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) &amp; Stratified log-rank (P)</td>
<td>0.85 (0.72-1.00) &amp; 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.
## Presence of Visceral Metastases Appears to Interact With Treatment Effect*

<table>
<thead>
<tr>
<th>Prognostic Feature</th>
<th>P Value**</th>
<th>HR (95% CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;70 years, ≥70 years)</td>
<td>0.6764</td>
<td>1.073 (0.772-1.491)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>0.1655</td>
<td>1.271 (0.906-1.782)</td>
</tr>
<tr>
<td>ALP</td>
<td>0.3304</td>
<td>1.178 (0.847-1.637)</td>
</tr>
<tr>
<td>Gleason score</td>
<td>0.4971</td>
<td>0.888 (0.631-1.250)</td>
</tr>
<tr>
<td>LDH</td>
<td>0.3778</td>
<td>1.214 (0.789-1.870)</td>
</tr>
<tr>
<td><strong>Visceral metastases</strong></td>
<td><strong>0.0056</strong></td>
<td><strong>1.644 (1.157-2.336)</strong></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.3257</td>
<td>0.842 (0.597-1.187)</td>
</tr>
<tr>
<td>Average daily worst pain (&lt;4, ≥4)</td>
<td>0.7645</td>
<td>1.057 (0.735-1.519)</td>
</tr>
<tr>
<td>Log PSA</td>
<td>0.4105</td>
<td>0.951 (0.845-1.071)</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>0.8077</td>
<td>0.954 (0.655-1.391)</td>
</tr>
<tr>
<td>Bone regions with metastases</td>
<td>0.4526</td>
<td>1.156 (0.792-1.689)</td>
</tr>
</tbody>
</table>

*No multiplicity adjustment.

**For descriptive purposes only.

Presented at the Genitourinary Cancers Symposium
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>
PD-1
Tumor Cell or Antigen Presenting Cell

- HLA
- Class II MHC
- B7-H1 (PD-L1)

T cell

- CD28
- CTLA-4
- T Cell Receptor
- LAG-3
- PD-1

Signal 1

- B7.1/2

Signal 2
66 year old with RCC
2001 - nephrectomy at JHU = (T3b, NX, MX)

2003 – CT Scan = Multiple Pulmonary Nodules
    Multiple treatments, including clinical trials

2007 – CT Scan = Progressive Disease (Pulmonary mets, soft tissue disease, bone dz)

2008 – First dose (10 mg/kg) MDX-1106 on 1/29

01/15/08 (pre-Rx) 03/25/08 04/22/08 07/22/08

- Received 2 additional on-study treatments (10 mg/kg)
- Stable PR -> off study

US-guided biopsy: No viable tumor
Update: Phase I Nivolumab: RCC cohort (n=34)

- Generally tolerable: fatigue, rash, pruritus, diarrhea
  - 3 deaths: pneumonitis (non-RCC)

- Preliminary efficacy in heavily pre-treated patients:
  - 29% objective responses
  - Median PFS 7.3 months

Phase III Study of Anti-PD-1 vs Everolimus in Patients With Previously Treated mRCC (NCT01668784)

Metastatic clear-cell RCC
N = 822

Primary Endpoints
• OS

Secondary Endpoints
• PFS
• ORR
• Duration of objective response
• Duration of overall survival
• Safety
• Disease related symptom progression rate

Key Eligibility Criteria
• Confirmed RCC with clear-cell component
• 1/2 prior anti-angiogenic therapies in advanced / metastatic setting
• ≤ 3 prior systemic treatment regimens and evidence of progression on or after last treatment and within 6 months of enrollment
• Karnofsky Performance Score ≥ 70%
• No CNS metastasis

Everolimus
10 mg/d PO

Anti-PD-1
3 mg/kg IV Q2W

Treat until progression or unacceptable toxicity or withdrawal of consent

Overall Survival (OS)
Summary

- There is ONE cancer vaccine that is US FDA-approved for in the treatment setting (Sipuleucel-T)
- Ongoing Phase III Vaccine Trials in Prostate and Kidney Cancer:
  - ProstVac VF in prostate cancer
  - Argos RNA-loaded DC vaccine in kidney cancer
  - Immatics peptide vaccine in kidney cancer
- Immune Checkpoint Blockade is NOT FDA-approved to treat either prostate OR kidney cancer
  - Phase III trial of anti-CTLA-4 a “near miss” in post-chemotherapy 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
  - Phase III trial of anti-PD-1 completed enrollment in kidney cancer
- Earlier Phase Combination trials ongoing (lots !)
  - Toxicity a concern