Immunotherapy for Metastatic Castrate Resistant Prostate Cancer

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Complete Disclosure

• **Consulting:**
  Bayer, BMS, F-Star, Genocea, Janssen, Merck, Merck-Serono, Pfizer, Pierre Fabre, Roche / Genentech, Shattuck Labs

• **Patents (held by Johns Hopkins University)**
  Amplimmune, BMS, Janssen

• **Options**
  Harpoon, Kleo, Tizona, Werewolf
Outline

• Sipuleucel-T

• Patient Selection
  – Microsatellite Instability (MSI)
  – CDK12
  – DRD

• Combinations
  – Next Gen Anti-Androgens
  – Chemotherapy

• Could immunotherapy be more active in the CS setting?
IMmunotherapy for Prostate AdenoCarcinoma Treatment (IMPACT)

Kantoff et al, NEJM 2010
Anti-PD-1 (Pembrolizumab) is US FDA Approved for MSI+ Tumors

Activity of PD-1 Blockade in MSI+ Prostate Cancer

- 1300 PC pts with genomic testing - MSK IMPACT Panel
- MSI Incidence = 2%
- 5/10 treated pts with evidence of activity (SD or PR)

Wasim Abida et al, JAMA Oncology 2018
CDK12 and Potential Response to PD-1 Blockade

IMmunotherapy in PAtients With Metastatic Cancers and CDK12 MuTations (IMPACT)

NCCT: NCT03570619
PI: Ajjai Alva, MD
N = 40

STARVE-PC: Biomarker-Driven Phase-2 Study of Ipilimumab plus Nivolumab for AR-V7-Expressing Metastatic Castration-Resistant Prostate Cancer

Nivolumab 3mg/kg + ipilimumab 1mg/kg - given every 3 weeks for 4 doses, followed by nivolumab 3mg/kg alone every 2 weeks (for up to 1 year)

Boudadi K, Drake CG, Antonarakis E. *Oncotarget* 2018
2/8 RECIST Evaluable Pts With PR to Anti-PD-1 + Anti-CTLA-4 (note – BOTH had DRD)

Boudadi K, Drake CG, Antonarakis. *Oncotarget* 2018
Adding PD-1 Blockade To Enzalutamide

Pembrolizumab 200 mg IV every 3 weeks x 4

Continued Enzalutamide Treatment

Courtesy of J. Graff OSHU
## Objective Responses to PD-1 Blockade in mCRPC

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Date of cycle 1</th>
<th>PSA (ng/ml) baseline to nadir</th>
<th>Measurable Disease at Baseline</th>
<th>Best Radiologic Response</th>
<th>MSI</th>
<th>Prior Treatment for mCRPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>April 2015</td>
<td>70.65 → 0.08</td>
<td>Yes</td>
<td>PR</td>
<td>present</td>
<td>abi, enz</td>
</tr>
<tr>
<td>7</td>
<td>October 2015</td>
<td>46.09 → 0.02</td>
<td>No</td>
<td>N/A</td>
<td>n/a</td>
<td>abi, enz</td>
</tr>
<tr>
<td>10</td>
<td>January 2016</td>
<td>2502.75 → &lt; 0.01</td>
<td>Yes</td>
<td>PR</td>
<td>absent</td>
<td>enz</td>
</tr>
</tbody>
</table>

* All responding patients remain on study.
PR – partial response; N/A – not applicable (i.e. no baseline biopsy done); MSI – microsatellite instability; abi – abiraterone; enz – enzalutamide

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Oncotarget 2016 (Update coming!)
**IMbassador250: A Phase III Trial in Patients With Metastatic Castration-Resistant Prostate Cancer Comparing Atezolizumab Plus Enzalutamide vs Enzalutamide Alone**

**Key Eligibility Criteria**
- Histologically confirmed mCRPC
- Progressed on an androgen synthesis inhibitor
- Failure of, ineligible for or refused a taxane regimen

**Safety Run-In**
- Atezolizumab 1200 mg IV q3w + Enzalutamide 160 mg oral qd
- N = 10

**Randomisation 1:1**
- Atezolizumab 1200 mg IV q3w + Enzalutamide 160 mg oral qd
- Enzalutamide 160 mg oral qd

**Key Stratification Factors**
- Prior taxane-containing regimen for mCRPC
- Presence of liver metastases

**Primary efficacy objective**: overall survival (OS)

**Key secondary objectives**: landmark 1-year and 2-year OS rates, time to cancer-related pain progression, time to first SSE, investigator-assessed radiographic PFS and ORR per PCWG3 criteria, PSA response rate, time to PSA progression, safety and tolerability

IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; PCWG3, Prostate Cancer Working Group 3; PFS, progression-free survival; PSA, prostate specific antigen; qd, daily; q3w, every 3 weeks; SSE, symptomatic skeletal event.

T Powles PI
ADT Increases Infiltration With Regulatory T Cells (Treg)

**Murine Model**

**NeoAdjuvant Trial in Patients**

<table>
<thead>
<tr>
<th></th>
<th>Cohort C (Control) N=20</th>
<th>Arm A (ADT) N=15</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8+ T cell density (mean, 95%CI)</td>
<td>96 (72–120)</td>
<td>205 (121–289)</td>
<td>0.03 (A vs C)</td>
</tr>
<tr>
<td>Treg cell density (mean, 95%CI)</td>
<td>29 (21–36)</td>
<td>59 (34–85)</td>
<td>0.02 (A vs C)</td>
</tr>
<tr>
<td>CD8+ / Treg ratio (mean, 95%CI)</td>
<td>3.7 (2.9–4.6%)</td>
<td>4.0 (2.7–5.3%)</td>
<td>0.68 (A vs C)</td>
</tr>
</tbody>
</table>

Shen and Drake *Prostate Cancer Neoplastic Disease* 2017
Neo-RED-P: Neoadjuvant Trial of Regulatory t cell Depletion

**Key Eligibility**
- Confirmed prostate cancer
- Localized prostate cancer
- Gleason grade \( \geq 4+3=7 \)
- Physically fit for radical prostatectomy

**N=12/arm**

**Randomize**

**Degarelix** → **Radical Prostatectomy** → **Degarelix + CTLA4-nf (BMS-986218)**

**Primary Outcomes**
- Feasibility
- Safety

**Secondary Outcomes**
- Difference in Treg density
- Differences in CD8 density and CD8/Treg ratio
- Pathological complete response (pCR) rate
- Time to PSA relapse
- PSA response rate

**Exploratory Immune profiling:** sc-RNA-seq, CyTOF, qmIF, cytokine analysis
IL-8 Drives PMN-MDSC Recruitment

CRISPR IL-8 KO Human Cell Line

mCherry

PC3 Cells

IL-8

Neo

Cas9

PMN-MDSCs

Cells/mg

WT

IL-8 KO

Lopez Bujanda Z.A. et al., in revision.
**MAximizing ADT ImmunoGenicity With Anti-IL-8 (MAGIC-8)**

**Patients**
- Recurrent prostate cancer
- PSADT<12 mos
- Previous local therapy

Randomize 1:1 (30/group)

**Exploratory Endpoints:**
- Immune cell subsets
- Immune gene signatures
- Cytokines
- TCR repertoire

**Primary Endpoints:**
- Safety
- Rate of PSA relapse

**Secondary Endpoints:**
- Relapse-free survival (RFS)
- Time to testosterone recovery
- RFS after recovery of testosterone
- Time to PSA >5.0ng/mL
- Rate of metastatic progression at 10 months
- PSA response rate after immunotherapy alone

*Labs:* Safety, PSA, testosterone (screening; monthly during treatment; every 2 months for year 1 follow up; every 3 months year 2 follow up)
*Imaging:* CT c/a/p and bone scan (screening; 6 months; 10 months)
*Sera/PBMCs:* C1D1, C3D1, EOT, 10 months, 14 months, 18 months

Open and Accruing: NCCT03689699
Ongoing

- Immunotherapy Combinations in CRPC Phase III
  - + Chemo
  - + ADT
  - + PARPi

- Anxiously awaiting data
  - Not soon
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