Will Immunotherapy Change Your Prostate Cancer Treatment Path?

Lawrence Fong, MD
Efim Guzik Distinguished Professor in Cancer Biology
Division of Heme/Onc, Department of Medicine
Co-director, Parker Institute for Cancer Immunotherapy @UCSF
Leader, Cancer Immunotherapy Program
Helen Diller Family Comprehensive Cancer Center
### The Clinical States Model of Prostate Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Cases/yr</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diagnosis: Clinically Localized Disease</td>
<td>186,320</td>
<td>RP, XRT + ADT, ADT alone</td>
</tr>
<tr>
<td>2</td>
<td>Biochemical Recurrence Castration-Sensitive</td>
<td>~30,000</td>
<td>Salvage XRT, Salvage RP, ADT alone</td>
</tr>
<tr>
<td>3a</td>
<td>Clinical Metastasis Castration-Sensitive (mCSPC)</td>
<td>28,660</td>
<td>ADT, Chemo, Radium-223, Immunotherapy, Clinical Trials</td>
</tr>
<tr>
<td>3b</td>
<td>Biochemical Recurrence Castration-Resistant (nmCRPC)</td>
<td></td>
<td>ADT +/- Chemo</td>
</tr>
</tbody>
</table>

**Clinical Trials**
- ADT
- Chemo
- Radium-223
- Immunotherapy
- Clinical Trials
Cancer Immunity Cycle

(Chen and Mellman, Immunity 2013)
Immunotherapy has transformed how we treat cancer patients

**Enhancing endogenous immunity**
- Blocking inhibitors
- Stimulating effectors
- Vaccines
- Anti-PD-1

**Redirecting immune effectors**
- Engineering cellular specificities
- Colocalizing effectors to tumors
- Anti-CD19 CART
- Anti-CD19 x anti-CD3
SIPULEUCEL-T
First approved prostate cancer immunotherapy

- Autologous cellular immunotherapy that works as a vaccine
- Targets prostatic acid phosphatase (PAP)
- Induces T and B cell responses that correlate with outcomes

Fong J Immunol 1997
Kantoff NEJM 2010
Schellhammer Urology 2013
SIPULEUCEL-T
First approved prostate cancer immunotherapy

- Improved OS without PFS or PSA responses
- Longer OS in patients with lower baseline PSAs

Fong J Immunol 1997
Kantoff NEJM 2010
Schellhammer Urology 2013
Neoadjuvant sipuleucel-T induces intratumoral T cells in prostate tumors

- Induction of Th1 immunity
- Induction of CTLA-4 and TIGIT (not PDL1, VISTA)
CHALLENGES IN PROSTATE CANCER

Another cancer vaccine

- Negative phase III randomized of Prostvac-VF
Balancing Immune Checkpoints

Antigen recognition via T cell receptor

<table>
<thead>
<tr>
<th>Antigen presenting cell</th>
<th>T cell</th>
<th>Clinical results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDL1 or PDL1</td>
<td>PD1</td>
<td>Huge Success</td>
</tr>
<tr>
<td>FDL1 or PDL1</td>
<td>PD1</td>
<td>Toxic</td>
</tr>
<tr>
<td>CD80 or CD95</td>
<td>CD80</td>
<td>Combination with anti-PD1</td>
</tr>
<tr>
<td>CD80 or CD95</td>
<td>CTLA4</td>
<td>No toxicity, no activity</td>
</tr>
<tr>
<td>B7-H1</td>
<td>ICOS</td>
<td>No toxicity, activity as an ADC</td>
</tr>
<tr>
<td>B7-H2</td>
<td>BTLA</td>
<td>Halted in pre-clinical</td>
</tr>
<tr>
<td>B7-H4</td>
<td>KIR</td>
<td>No efficacy</td>
</tr>
<tr>
<td>HVEM</td>
<td>Peptide</td>
<td>Multiple neoantigen trials</td>
</tr>
<tr>
<td>MHC class I or II</td>
<td>TCR</td>
<td>Limited efficacy in LAG3+ tumors</td>
</tr>
<tr>
<td>CD137</td>
<td>LAG3</td>
<td>No toxicity, no activity, ? Combo with anti-PD1</td>
</tr>
<tr>
<td>OX40L</td>
<td>CD137</td>
<td>Toxicity, no activity</td>
</tr>
<tr>
<td>CD70</td>
<td>OX40</td>
<td>No toxicity, no activity</td>
</tr>
<tr>
<td>CD40</td>
<td>CD27</td>
<td>Toxicity, limited efficacy</td>
</tr>
<tr>
<td>GAL.9</td>
<td>CD40L</td>
<td>No toxicity, no activity</td>
</tr>
<tr>
<td>Adenosine</td>
<td>TIM3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A20R</td>
<td></td>
</tr>
</tbody>
</table>

(Pardoll. Nat Rev Can 2012)
CTLA-4 blockade in mCRPC

Phase 3 of ipilimumab

(Fong et al, Can Res 2009; Kwek et al, Can Imm Res, 2015)

(Kwon et al Lancet Oncology 2014)

(Beer et al JCO 2016)
PD-1/PD-L1 blockade for mCRPC

(Sweeney et al. AACR 2020)

Lawrence Fong

(Antonarakis et al. JCO 2020)

(Sweeney et al. AACR 2020)
**PD-1 + CTLA-4 blockade for mCRPC**

<table>
<thead>
<tr>
<th></th>
<th>Pre-Chemotherapy</th>
<th>Post-Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response (measurable disease only)</strong></td>
<td>Cohort 1 (N = 32)</td>
<td>Cohort 2 (N = 30)</td>
</tr>
<tr>
<td>Confirmed ORR, n (%)</td>
<td>8 (25.0)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>95% CI</td>
<td>11.5–43.4</td>
<td>2.1–26.5</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>2 (6.3)b</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Partial response</td>
<td>6 (18.8)c</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13 (40.6)</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>9 (28.1)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>2 (6.3)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Median time to response, months (Q1–Q3)</td>
<td>1.9 (1.9–2.8)</td>
<td>2.1 (1.9–7.4)</td>
</tr>
</tbody>
</table>

| **PSA response (measurable/unmeasurable disease in patients with baseline and ≥1 post-baseline PSA result)** | Cohort 1 (N = 34) | Cohort 2 (N = 40) |
| Confirmed PSA response rate, n (%) | 6 (17.6)         | 4 (10.0)          |
| 95% CI               | 6.8–34.5         | 2.8–23.7          |
| Patients with PSA <0.2 ng/mL, n (%) | 5 (14.7)         | 2 (5.0)           |
| Median time to confirmed PSA response, months (Q1–Q3) | 1.4 (0.8–1.4) | 1.2 (0.8–1.4) |

**Median rPFS, months (95% CI)**
- TMB high: 7.4 (6.5–NE)
- TMB low: 2.4 (1.8–3.9)

**40-50% Grade 3-4 AEs**

(Sharma et al. ASCO GU 2019)
IMMUNOSUPPRESSIVE TUMOR MICROENVIRONMENT IN PROSTATE CANCER

[Diagram of immune cells and their interactions in the tumor microenvironment]

Stultz and Fong. Prostate Can Prostatic Dis 2021
TGF-β in the “excluded” phenotype

(Mariaithasan et al, Nature 2018)
Targeting myeloid cells with cabozantinib + atezolizumab in mCRPC

(Agarwal N et al, ASCO 2020)
Targeting the adenosine axis for cancer immunotherapy

(Fong et al. Can Discov 2019)

M2 polarization
↑ Adenosine Signature

↑ PD-1 expression
↓ IL-2 & IFNγ production
↓ Proliferation

Tumor response in refractory kidney cancer to A2ARi

(Fong et al. Can Discov 2019)
Clinical activity of ciforadenant + atezolizumab

- Treatment Start (May-2017)
- Last dose (Oct-17)
- Before (5.7cm)
- After (1.71cm)
Ciforadenant and Atezo in mCRPC

Patient Characteristics:
- Median age 68
- Visceral metastases 46%
- Hormone refractory 96%
- Chemo failures 16%
VACCINE COMBINATIONS

- Listeria vaccine (LADD) + CPI
- KEYNOTE-046: ADXS-PSA +/- pembrolizumab
- Part B: 72% SD, 38% PSA responses, 27% PSA30
VACCINE COMBINATIONS

- Neoantigen vaccines + CPI
- mHSPC after tumor burden reduction with docetaxel + ADT
- NCT03532217
RADIOIMMUNOTHERAPY

- Sipuleucel-T +/- radium-223 (NCT02463799):
  - Improved PSA50 responses (33% vs 0%), PFS/OS
  - Decreased peripheral immune responses

- Radium-223 + atezolizumab (NCT02814669)

- Ongoing: Radium-223 + avelumab + peposertib (M3814) (NCT04071236)
Immunotherapy has transformed how we treat cancer patients

Enhancing endogenous immunity
- Blocking inhibitors
- Stimulating effectors
  - Vaccines
  - Anti-PD-1

Redirecting immune effectors
- Engineering cellular specificities
- Colocalizing effectors to tumors
  - Anti-CD19 CART
  - Anti-CD19 x anti-CD3
T CELL BASED

- T cell bi-specifics
  - AMG-160: 34.3% PSA50
  - AMG-509: anti-STEAP

- CAR T-PSMA-TGFβRDN (NCT04227275)

- Will the lack of existing T cells or impedance of trafficking limit efficacy?
- Will toxicity be limiting?
Interim results from a phase 1 study of AMG 160, a half-life extended (HLE), PSMA-targeted, bispecific T-cell engager (BiTE®) immune therapy for metastatic castration-resistant prostate cancer (mCRPC)

Ben Tran, MBBS, FRACP, 1 Lisa Horvath, PhD, MBBS, FRACP, 2 Tanya Dorff, MD, 3 Matthew Rettig, MD, 4 Martijn P. Lolkema, MD, PhD, 5 Jean-Pascal Machiels, MD, 6 Sylvie Rottey, MD, PhD, 7 Karen Autio, MD, 8 Richard Greil, MD, 9 Nabil Adra, MD, MSc, 10 Charlotte Lemech, MD, FRACP, 11 Mukul Minocha, PhD, 12 Fu-Chih Cheng, PhD, 12 Hosein Kouros-Mehr, MD, PhD, 12 Karim Fizazi, MD, PhD 13

1Peter MacCallum Cancer Centre, Melbourne, Australia; 2Chris O'Brien Lifehouse, Camperdown, Australia; 3City of Hope, Duarte, CA, USA; 4University of California, Los Angeles, CA, USA; 5Erasmus MC Cancer Institute, Rotterdam, Netherlands; 6Cliniques Universitaires Saint-Luc, Brussels, Belgium; 7Drug Research Unit, Ghent University, Ghent, Belgium; 8Memorial Sloan Kettering Cancer Center, New York, NY, USA; 9Paracelsus Medical University Salzburg, Salzburg Cancer Research Institute-CCCIT and Cancer Cluster, Salzburg, Austria; 10Indiana University School of Medicine, Indianapolis, IN, USA; 11Scientia Clinical Research, Randwick, Australia; 12Amgen Inc., Thousand Oaks, CA, USA; 12Gustave Roussy, University of Paris Saclay, Villejuif, France

Presented at European Society of Medical Oncology 2020 Virtual Congress, September 19-21, 2020

Provided September 21, 2020, as part of an oral presentation and is qualified by such, contains forward-looking statements, actual results may vary materially; Amgen disclaims any duty to update.
AMGEN BITE® (BISPECIFIC T-CELL ENGAGER) IMMUNOTHERAPY

AMG 160

- **BiTE®** molecules engage a patient’s own T cells to attack and eradicate cancer cells
  - T-cell activation induces transient cytokine release and tumor killing
- Blinatumomab (BLINCYTO®, Amgen Inc.) is the first and only bispecific immunotherapy approved in oncology worldwide
- **AMG 160** is a half-life extended PSMA x CD3 BiTE® immunotherapy for mCRPC

PSA reductions (best response) were dose dependent and occurred in 24/35 (68.6%) evaluable patients (20 July 2020)

PSA reductions > 50% occurred in 12/35 (34.3%) evaluable patients

PSA50 = PSA decrease of ≥ 50%; Q2W = every 2 weeks; * Best PSA reductions at any time point in evaluable patients included those who had received ≥ 1 dose of AMG 160 and had measurable baseline PSA; † Checkered bars indicate cohorts with optimised cycle 1 priming strategies; ▲ Indicates patient who had failed prior LuPSMA treatment

Provided September 21, 2020, as part of an oral presentation and is qualified by such, contains forward-looking statements, actual results may vary materially; Amgen disclaims any duty to update.
EXAMPLES OF DEEP RESPONSES TO AMG 160

<table>
<thead>
<tr>
<th>Patient</th>
<th>Prior Rx</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>10112001002</td>
<td>Surgery, radiotherapy, docetaxel, enzalutamide, bicalutamide, and talazoparib</td>
<td>4 (0.09 mg with cycle 1 priming)</td>
</tr>
<tr>
<td>10166004005</td>
<td>Surgery, docetaxel, enzalutamide, sipuleucel</td>
<td>4 (0.09 mg with optimised cycle 1 priming)</td>
</tr>
<tr>
<td>10166004006</td>
<td>Radiotherapy, apalutamide, docetaxel, sipuleucel-T, radium-223</td>
<td>5 (0.3 mg with optimised cycle 1 priming)</td>
</tr>
</tbody>
</table>

**PR by 3 Months**

PSMA PET/CT

Baseline

Week 12

**Not RECIST evaluable**

PSMA PET/CT

Baseline

Week 12

**Rapid PSA Drop in 1 Month**

Best PSA reduction: ~98.1%

**Rapid PSA Drop in 1 Month**

Best PSA reduction: ~87.9%

**Rapid PSA Reduction**

Best PSA reduction: ~75.5%

PET/CT = positron emission tomography–computed tomography; PR = partial response; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RECIST = Response Evaluation Criteria in Solid Tumors; u = unconfirmed; * PR (u) response reported after 20 July, 2020 data cutoff

Provided September 21, 2020, as part of an oral presentation and is qualified by such, contains forward-looking statements, actual results may vary materially; Amgen disclaims any duty to update.
CART-PSMA-TGFβRDN:
Lentivirally-transduced modified T cell expressing PSMA CAR and
TGFβ dominant negative receptor transgene
scFv derived from the J591 antibody
3+3 dose escalation design

Study Schema

Confirm mCRPC and
tumor PSMA expression

Study screening, apheresis, T cell manufacture, disease staging

Cy 300 mg/m² + Flu 30 mg/m² x 3 days

CART cell infusion
1-3 x 10⁷/m²
Cohort 1

CART cell infusion
1-3 x 10⁸/m²
Cohort 2

CART cell infusion
MTD
Cohort 3

CART cell infusion
1-3 x 10⁷/m²
Cohort 3

CART cell infusion
1-3 x 10⁷/m²

Follow-up

Day 0 Days 1 3 7 10 14 21
Day 28
CT c/a/p staging, bone scan research studies, PSA
Month 2
Safety and research PSA
Month 3
CT c/a/p staging, bone scan research studies, PSA
Month 6
CT c/a/p staging, bone scan research studies, PSA

Follow-up every 3 months until 2 years; long term follow-up until 15 years

Narayan et al. PCF 2020
PSA waterfall plot of all treated patients

Narayan et al. PCF 2020
Conclusions

• Prostate cancer can respond to immunotherapy
• Immune checkpoint inhibition leads to low rates of response.
  • Phase 3 trials have not show benefit in unselected patients.
  • Responses can be very durable.
• Multiple immune resistance mechanisms are operative in prostate cancer.
Future directions

• Treatment combinations will be needed to address multiple resistance mechanisms.
• Empiric -> rationale combinations must be developed through studying our patients.
• Patient selection
  • Tumor intrinsic (MSI$^\text{hi}$, CDK12-loss)
  • Immune attributes of our patients
• Redirecting T cells (BITE, CART) are showing early signs of clinical activity