Turning Tundra Tumor into a Destination Brimming with Hungry T-cells

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Chief, Genitourinary Malignancies Branch &
Director, Medical Oncology Service
Center for Cancer Research
National Cancer Institute, NIH
Tundra vs. tropical island

Barren, cold
Tumor: No T-cells

Teeming with life, hot
Tons of activated T-cells
Requirements for Effective Immunotherapy

Generation of Immune Response "Initiation"  
Functional Effector Cells within the Tumor "Facilitation"

Bilusic M, Madan RA, Gulley JL Clin Ca Res 2017
PD-1/PD-L1 inhibition
Rapid, deep, durable responses
Across a wide range of tumors
Seen in a subset of patients
Not seen in #ProstateCancer

- **Urothelial:** atezolizumab
  Powles T et al. Nature 2014

- **Urothelial:** durvalumab
  Massard C et al. JCO 2016

- **NSCLC (squamous only):** nivolumab
  Rizvi NA et al. Lancet Oncol 2015

- **HNSCC:** pembrolizumab
  Seiwert TY et al. Lancet Oncol 2016

- **NSCLC:** avelumab
  Gulley JL et al. Lancet Oncol 2017

- **MSI hi CRC:** nivolumab
  Overman MJ et al. Lancet Oncol 2017

- **Urothelial:** avelumab
  Apolo AB et al. J Clin Oncol 2017

Rapid, deep, durable responses
Across a wide range of tumors
Seen in a subset of patients
Not seen in #ProstateCancer
Yarchoan et al., 2017
The prevalence of somatic mutations across human cancer types

MSI Hi Prostate Cancer

- Approval with pembrolizumab
- Incidence
  - Localized PC ~2%
  - Autopsy series of mCRPC ~12%
    - Pritchard et al., *Nature Com* 2014
  - Ongoing testing suggests 5-6% of mCRPC
- Suggests all patients with mCRPC should be tested

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### Pembrolizumab Response Rate by Tumor Type

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. of Tumors</th>
<th>Patients with a Response</th>
<th>Range of Response Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td></td>
<td>mo</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>90 (36)</td>
<td>32 (36)</td>
<td>1.6+ to 22.7+</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>14 (36)</td>
<td>5 (36)</td>
<td>4.2+ to 17.3+</td>
</tr>
<tr>
<td>Biliary cancer</td>
<td>11 (27)</td>
<td>3 (27)</td>
<td>11.6+ to 19.6+</td>
</tr>
<tr>
<td>Gastric or gastroesophageal junction</td>
<td>9 (56)</td>
<td>5 (56)</td>
<td>5.8+ to 22.1+</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>6 (83)</td>
<td>5 (83)</td>
<td>2.6+ to 9.2+</td>
</tr>
<tr>
<td>Small-intestine cancer</td>
<td>8</td>
<td>3 (38)</td>
<td>1.9+ to 9.1+</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2 (100)</td>
<td>2 (100)</td>
<td>7.6 to 15.9</td>
</tr>
<tr>
<td><strong>Prostate cancer</strong></td>
<td><strong>2</strong></td>
<td><strong>1 (50)</strong></td>
<td><strong>9.8+</strong></td>
</tr>
<tr>
<td>Other cancers</td>
<td>7</td>
<td>3 (43)</td>
<td>7.5+ to 18.2+</td>
</tr>
</tbody>
</table>

*Response was as defined by RECIST. “Other cancers” includes one patient each with the following tumor types: bladder, esophageal, sarcoma, thyroid, retroperitoneal, small-cell lung cancer, and renal cell cancer (includes two patients who could not be evaluated and were considered not to have had a response). A + sign indicates that the response was ongoing at the time of data cutoff.*

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Lemery et al., *NEJM* 2017
Easy Pickin’ is Over
What’s left?

Immune Recognition*

Clinical Response to ICI

+ Melanoma
  + Lung
  + Bladder

- N/A

*In part based on recognition of immune relevant mutations
What’s left?

<table>
<thead>
<tr>
<th>Immune Recognition*</th>
<th>Clinical Response to ICI</th>
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<tbody>
<tr>
<td>+</td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
</tr>
<tr>
<td></td>
<td>Bladder</td>
</tr>
<tr>
<td>-</td>
<td>Primary Refractory</td>
</tr>
<tr>
<td></td>
<td>Acquired Resistance</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>prostate</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
</tr>
<tr>
<td></td>
<td>CRC</td>
</tr>
<tr>
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</tr>
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*Next frontier
-Will require combination therapy strategies

*In part based on recognition of immune relevant mutations
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

**Example:**
- Colorectal Carcinoma
- Prostate Cancer

'Non-Inflamed' Tumor (Absence of T-cells)

- anti-PD-L1
- "Vaccine"
- No Activity
- Presence of T-cells
- anti-PD-L1
- Release brakes on T-cells
- Tumor Cell Lysis
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>Western blot</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>Antigen array</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>Overall</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
Developing T-cells to fight

**Therapeutic Vaccine**

**Adoptive Cellular Therapy (ACT)**

Induction of tumor-specific immune responses (T-cells)
What is sufficient to initiate an immune response?

<table>
<thead>
<tr>
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<th>ICI only</th>
<th>Vaccine</th>
<th>ACT</th>
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<tbody>
<tr>
<td></td>
<td>No Ag</td>
<td>Self Ag</td>
<td>Neo Ag</td>
</tr>
<tr>
<td>Logistics</td>
<td></td>
<td>simple</td>
<td></td>
</tr>
<tr>
<td>Needs hot tumor</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target Selection</td>
<td>N/A</td>
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<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>N/A</td>
<td>weak</td>
<td>strong</td>
</tr>
<tr>
<td>Target Selection</td>
<td>N/A</td>
<td></td>
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*Typically only 1 target rather than potential for multiple targets / epitopes in a vaccine. TCR Catch Bond
How to initiate an immune response

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<td>Yes</td>
<td>No</td>
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<td>N/A</td>
<td>weak</td>
<td>strong</td>
</tr>
<tr>
<td>Target Selection</td>
<td>N/A</td>
<td>Immune System</td>
<td>Scientists</td>
</tr>
</tbody>
</table>

*Typically only 1 target rather than potential for multiple targets / epitopes in a vaccine. TCR Catch Bond

Do you need to target a neo-antigen to get a high avidity immune response?
Antigen spreading and the tumor immunity cycle

A. Tumor expresses different immunogenic targets

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

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

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

E. Fully activated T cell destroys tumor cells
Antigen spreading and the tumor immunity cycle
Sipuleucel-T: IMPACT trial

- Median Survival Benefit = 4.1 months
- Survival (Months)
- Percent Survival

P = 0.032 (Cox model)
HR = 0.775 [95% CI: 0.614, 0.979]
Median Survival Benefit = 4.1 months

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

Placebo (n = 171)
Median Survival: 21.7 months

Kantoff et al., NEJM 2010

Sipuleucel-T
- Don't expect PSA decrease or OR
- Use early, in less aggressive disease

Dec 2016
Journal for Immunotherapy of Cancer
The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of prostate carcinoma

- Kantoff et al., NEJM 2010
PROSTVAC-VF
Proposed Mode of Action

Developed within the CCR, NCI
--Preclinical (Schlom et al.)
--Clinical (Gulley et al.)
# Immune Impact Induced by PROSTVAC (PSA-TRICOM), a Therapeutic Vaccine for Prostate Cancer

James L. Gulley, Ravi A. Madan, Kwong Y. Tsang, Caroline Jochems, Jennifer L. Marté, Benedetto Farsaci, Jo A. Tucker, James W. Hodge, David J. Liewehr, Seth M. Steinberg, Christopher R. Heery, and Jeffrey Schlom

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Specific Immune response</td>
<td>56.7% (59/104)</td>
<td>28 days after last vaccine</td>
</tr>
<tr>
<td>--Median fold increase in PSA</td>
<td>5X</td>
<td># of PSA specific T-cells identical to flu T-cells</td>
</tr>
<tr>
<td>specific immune response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antigen Spreading</td>
<td>67.9% (19/28)</td>
<td></td>
</tr>
<tr>
<td>Anti-PSA Ab</td>
<td>0.57% (2/349)</td>
<td></td>
</tr>
</tbody>
</table>
Requirements for Effective Immunotherapy

Initiation

Facilitation

Bilusic M, Madan RA, Gulley JL Clin Ca Res 2017
Importance of PD-1/PD-L1 blockade

(accessed August 2017)
**Prostvac + Ipi or Nivo or Comb.**

*Patient Population:* Localized Prostate Cancer, candidates for RP

**Cohort 1:** Vaccine + Ipi + Nivo (n=10, mCRPC)

**Cohort 2:** Vaccine + Nivo (n=16)

**Cohort 3:** Vaccine + Ipi (n=16)

**Cohort 4:** Vaccine + Ipi + Nivo (n=16)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 0</th>
<th>Week 2</th>
<th>Week 5</th>
<th>Week 8</th>
<th>Week 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>Prostvac-V</td>
<td>Prostvac-F</td>
<td>Prostvac-F</td>
<td>Prostvac-F</td>
<td>RP</td>
</tr>
<tr>
<td></td>
<td>Ipiilimumab</td>
<td>Ipiilimumab</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nivolumab</td>
<td>Nivolumab</td>
<td>Nivolumab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ipilimumab 1 mg/kg, Nivolumab 240 mg

(NCT02933255) PI Gulley
**Patient Population:** Localized Prostate Cancer, candidates for RP

- **Cohort 1:** Vaccine + Ipi + Nivo (n=10, mCRPC)
- **Cohort 2:** Vaccine + Nivo (n=16)
- **Cohort 3:** Vaccine + Ipi (n=16)
- **Cohort 4:** Vaccine + Ipi + Nivo (n=16)

Primary analysis: Immune infiltrate by IHC
Secondary: Safety
  - Imaging
  - Peripheral immune analysis
**In depth analysis of change in tumor microenvironment post immunotherapy**
  - RNA Seq, multiplex IF, TCR Seq, NGS assays for MSI etc.
**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
Requirements for Effective Immunotherapy

**Initiation**
- Vaccine (brachyury)
- IL-15 (NK and T-cells)

**Facilitation**
- PD-L1
- TGF-beta
- IDO

Bilusic M, Madan RA, Gulley JL *Clin Ca Res* 2017
Brachyury Makes Cancer Cells Behave Badly

- Transcription Factor Important in Embryogenesis
  - Master Driver of Metastatic Process (EMT)
  - Involved in Drug Resistance
  - Associated with Stem-like Properties
Brachyury in Prostate Cancer

Overexpressed in cancer vs. normal (protein and mRNA)
Correlates with aggressive tumors, invasion
Phase I Study of a Poxviral TRICOM-Based Vaccine Directed Against the Transcription Factor Brachyury

Christopher R. Heery¹, Claudia Palena¹, Sheri McMahon², Renee N. Donahue¹, Lauren M. Lepone¹, Italia Grenga¹, Ulrike Dirmeier³, Lisa Cordes², Jenn Marté², William Dahut², Harpreet Singh², Ravi A. Madan², Romaine I. Fernando¹, Duane H. Hamilton¹, Jeffrey Schlom¹, and James L. Gulley²

- Well tolerated (no DLT)
- 28 of 34 (82%) patients developed brachyury-specific CD4 and/or CD8 T-cell responses after vaccination
**M7824**

- M7824 is an innovative first-in-class bifunctional fusion protein
- Phase I dose escalation data presented at ASCO 2017
  - n=19
  - Well tolerated
  - Sequesters all activated TGF-beta in plasma throughout dosing period
- Promising clinical activity
  - 1 CR
  - 3 PRs

*Clin Ca Res in press*
QuEST (Quick Efficacy Seeking Trial)*

Cohort 1 (any solid tumor)

Arm 1.1: M7824+ ALT-803
n = 9-18

Cohort 2 (mCRPC)

Arm 2.1A: BN-Brachyury
+ M7824
n=13

if safety in Arm 2.1A

Arm 2.2A: BN-Brachyury
+ M7824
+ ALT-803
n=13

if safety in Arm 2.2A

Arm 2.3A: BN-Brachyury
+ M7824
+ ALT-803
+ Epacadostat
n=13

Signal:
Sustained ≥ 30% PSA decline or Objective response

if + signal in ≥ 2 in Arm 2.1A

if + signal in ≥ 2 in Arm 2.2A

if + signal in ≥ 2 in Arm 2.3A

RANDOMIZE

Arm 2.1B:
BN-Brachyury
+ M7824
Expand n=25

Arm 2.2B:
BN-Brachyury
+ M7824
+ ALT-803
Expand to n=25

Arm 2.3B:
BN-Brachyury
+ M7824
+ ALT-803
+ Epacadostat
Expand to n=25

*NCI sponsored trial in review, FDA “May Proceed” last Friday (19 Jan 2018)
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
• There are some MSI hi prostate cancers (2-10% of mCRPC) that may respond to PD-1/PDL-1 inhibition (MSI testing)
• 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 (e.g., vaccine) and allow effector cells to get to and remain functional within the TME (e.g., immune checkpoint blockade) will be optimal
  • Ongoing trials should help determine the utility of this approach