Immune Checkpoint Blockade in Cancer Therapy: New Insights and Opportunities

Charles G. Drake MD, PhD
Associate Professor: Oncology, Immunology and Urology
Johns Hopkins Sidney Kimmel Cancer Center
Relevant Disclosures

• BMS – paid consultant, patent royalties

• I am NOT Jim Allison
Immune Checkpoint Blockade

• New Insights:
  – Recent sequencing data in RCC
  – Immune checkpoint blockade
    • Objective responses in multiple tumor types
    • Some responses durable (and complete)
  – PD-L1 expression as a POTENTIAL biomarker

• New Opportunities:
  – Combining multiple immune checkpoint blocking antibodies
  – Combining immune checkpoint blockade with epigenetic modulators
Metastatic RCC: An Array of Diverse and Moving Targets

Swanton et. al. *NEJM* 2012
Despite Significant Heterogeneity: Immune Checkpoint Blockade is Active in RCC

- 57-year-old patient had developed progressive disease after receiving sunitinib, temsirolimus, sorafenib, and pazopanib
- Rx with Nivolumab (anti-PD-1) at 1 mg/kg q 2 wks.
- Currently in cycle 6 with ongoing PR
CTLA-4
Two Signals Are Required for a T Cell Response

Signal 1:
- HLA
- T Cell Receptor
- Antigen

Signal 2:
- CD28
- B7.1/2

T cell

Antigen Presenting Cell
In Tumor Microenvironment (and Gut):
CTLA-4 Prevents Normal T Cell Activation

T cell

HLA

CD28

B7.1/2

Antiogen

CTLA-4

Signal 1

Signal 2

Antigen Presenting Cell
Ipilimumab (Anti-CTLA-4) Blocks the CTLA-4 Checkpoint, Restoring T Cell Activation
Ipilimumab in Melanoma: The First “Drug” EVER to Show a Survival Benefit in a Randomized Phase III Clinical Trial

Hodi et. al. *NEJM* 2010
About 20 Interactions That Regulate T Cell Immune Responses
PD-1
Two Phase I Clinical Trials of anti-PD-1 (BMS-936558) in Patients with Advanced Solid Tumors

1st Treatment Cycle

Follow Up or Additional Treatment Cycle(s)
OR or PD: stop Ab

Day 1
Dose 0.3-10 mg/kg
Day 57
Scans
Day 85
Scans
2 years or until CR/PR or PD

1st Treatment Cycle

Follow Up or Additional Treatment Cycle(s)
OR or SD: continue Ab

Days 1, 15, 29, 43
Dose 0.1-10 mg/kg
Day 57
Scans
2 years or until CR or PD

Eligible patients: treatment-refractory metastatic melanoma, kidney, lung, colon, or prostate cancer
Anti-PD1: Phase I Data

- 39 pts treated
- Median age 62 years (42-84)
- Diagnoses: CRC (14), MEL (10), CRPC (8), NSCLC (6), RCC (1)
- Toxicities: generally mild and manageable

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Pts (no.)</th>
<th>Total Number of Doses</th>
<th>Best Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>6</td>
<td>6 0 0 0 0 0 0</td>
<td>none</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>3 1 1 1 1 0</td>
<td>1 MR (NSCLC)</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>3 0 2 1 0</td>
<td>1 CR (CRC)</td>
</tr>
<tr>
<td>10</td>
<td>21</td>
<td>15 1 4 0 1</td>
<td>2 PR (MEL, RCC), 1 MR (MEL)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>39</strong></td>
<td><strong>27 2 7 2 1</strong></td>
<td><strong>1 CR, 2 PR, 2 MR</strong></td>
</tr>
</tbody>
</table>

Brahmer et al, JCO 2010
Two Phase I Clinical Trials of anti-PD-1 (BMS-936558) in Patients with Advanced Solid Tumors

1st Treatment Cycle
- Day 1: Dose 0.3-10 mg/kg
- Day 57: Scans

Follow Up or Additional Treatment Cycle(s)
OR or PD: stop Ab

Day 85: Scans
2 years or until CR/PR or PD

1st Treatment Cycle
- Days 1, 15, 29, 43: Dose 0.1-10 mg/kg
- Day 57: Scans

Follow Up or Additional Treatment Cycle(s)
OR or SD: continue Ab

2 years or until CR or PD

Eligible patients: treatment-refractory metastatic melanoma, kidney, lung, colon, or prostate cancer
Phase Ib: Response of Metastatic NSCLC

- Initial progression in pulmonary lesions of a NSCLC patient with non-squamous histology was followed by regression
- Dx '04, EGFR mutation +; Rx Gem/carbo, erlotinib, erlotinib + LBH589, Pemetrexed
Phase Ib: Clinical activity of Anti-PD1 (BMS 936558, Novlumab)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Dose (mg/kg)</th>
<th>No. pts</th>
<th>ORR (CR/PR) No. pts (%)</th>
<th>SD ≥24 wk No. pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEL</td>
<td>0.1-10</td>
<td>94</td>
<td>26 (28)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>1-10</td>
<td>76</td>
<td>14 (18)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>RCC</td>
<td>1 or 10</td>
<td>33</td>
<td>9 (27)</td>
<td>9 (27)</td>
</tr>
</tbody>
</table>

- 236 patients starting therapy before 07/2011 were evaluated for response as of 02/24/2012
- 20/31 responses lasted ≥1 year in patients with ≥1 year follow-up
- No ORs were observed in 19 CRC or 13 CRPC patients

Topalian et al, NEJM 2012
Changes in Target Lesions Over Time in RCC Patients Treated With 10 mg/kg BMS-936558
# Anti-PD1 (BMS 936558) Related Adverse Events

<table>
<thead>
<tr>
<th>Drug-Related Adverse Event</th>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tot Pop*</td>
<td>RCC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>220 (72)</td>
<td>29 (85)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>78 (26)</td>
<td>14 (41)</td>
</tr>
<tr>
<td>Rash</td>
<td>41 (14)</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (12)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>31 (11)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (8)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Appetite †</td>
<td>24 (8)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Hemoglobin †</td>
<td>18 (6)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16 (5)</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

* AEs occurring in ≥5% of the total population.
† The most common grade 3-4 AEs were respiratory system disorders (2pts) and hypophosphatemia (2 pts). An additional 10 grade 3-4 drug-related AEs were observed and one or more occurred in a single patient.
I would reference the topalian NEJM article here

dmcdermo; 12/09/2012
Long-Term F/U From the First Phase I Trial

Pt 2-2013
CR Stop Rx

0 1 yr 2 yr 3 yr 4 yr

Pt 1-4033
Stop Rx Best resp. (PR)

0 1 yr 2 yr 3 yr 4 yr

? new brain met on MRI resected: no viable tumor

Sustained PR

Latest evaluation: CR

Latest evaluation: CR

Lipson et al in submission
Differential Role of CTLA-4 vs PD-1 in Anti-tumor Immunity

**T cell**
- **TCR Signal 1**
- **B7.1/2**
- **CD28**

**APC**
- **MHC-Ag**

**Tumor or Vaccine**

**Inhibition**
- PD-1
- PD-L1

**Tumor**

**Activation**
- (cytokines, lysis, prolif., migration)

**Traffic to tumor**

(-) Signal 2 dominates
PD-L1
Geographic co-localization of TIL With Tumor Cells Expressing Membrane PD-L1

Taube et al *Science Translational Medicine* 2012
In Melanocytic Lesions:
PD-L1+ Cases = Lymphocyte Enriched

- 150 lesions including 40 benign nevi, 54 primary melanomas (in situ or invasive), and 56 metastases

Taube et al., *Science Translational Med* 2012)
Innate Immune Resistance

MHC + Peptide → Tumor → Oncogenic Pathway → PD-1

Oncogene-Driven PD-L1 Expression (i.e. Pten loss)

Adaptive Immune Resistance

Interferon γ → Tumor → Adaptive Up-Regulation Of PD-L1 Turns T Cell OFF
Data From the Phase 1b trial:

Lack of PD-L1 Expression Correlates Lack of Response to PD-1 Blockade

42 pts include 18 MEL, 10 NSCLC, 7 CRC, 5 RCC, and 2 CRPC.

Topalian, S. et al NEJM 2011
Therapeutic Implications

**Strong endogenous anti-tumor immune response**

PD-L1 up-regulation in tumor

RESPONSE

**Weak endogenous anti-tumor immune response**

No PD-L1 up-regulation in tumor

1. Inducer of anti-tumor immunity (targeted therapy, vaccine, radiation therapy)

2. **Anti-PD-1 monotherapy**

Endogenous anti-tumor immune response

PD-L1 expression in tumor

RESPONSE
Friends
Approach to Identification of “Tolerance” Genes

**In vitro**
- Anergy Specific Genes
  - PD-1
  - LAG-3
  - A2a receptor
  - Neuritin

**In vivo**
- Tolerance Specific Genes

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### Experiments

**Jonathan Powell**
- Cyt C-specific T cell clone
  - ACTIVATION
    - $\alpha$CD3 + $\alpha$CD28
  - GENE EXPRESSION PROFILE

**C. Drake**
- HA specific TCR transg. T cells
  - Vac-HA infect
  - ACTIVATION
    - GENE EXPRESSION PROFILE
  - Self-HA Transg. mouse
  - TOLERANCE
    - GENE EXPRESSION PROFILE

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151 genes
LAG-3

- CD4 homologue but does not substitute for CD4 in T cell development or helper T cell function
- Binds MHC II with higher affinity than CD4 but at a distinct site from CD4
- Cytoplasmic tail completely different from CD4. Signaling pathways completely different than CD4
LAG-3: Expressed On Prostate-Infiltrating Treg

<table>
<thead>
<tr>
<th>Probe ID</th>
<th>Fold Increase</th>
<th>Gene Definition</th>
<th>Gene Symbol</th>
<th>Cellular Component</th>
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<tbody>
<tr>
<td>TNFSF9</td>
<td>122</td>
<td>Tumor necrosis receptor superfamily, member 9 (41BB)</td>
<td>TNFRSF9</td>
<td>Membrane</td>
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<tr>
<td>234895_at</td>
<td>95</td>
<td>cytotoxic T-lymphocyte-associated protein 4</td>
<td>CTLA4</td>
<td>Membrane</td>
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<tr>
<td>206486_at</td>
<td>86</td>
<td>lymphocyte-activation gene 3</td>
<td>LAG3</td>
<td>Membrane</td>
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<tr>
<td>211269_s_at</td>
<td>58</td>
<td>interleukin 2 receptor, alpha (CD25)</td>
<td>IL2RA</td>
<td>Membrane</td>
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<tr>
<td>223851_s_at</td>
<td>31</td>
<td>tumor necrosis factor receptor superfamily, member 18 (GTHR)</td>
<td>TNFRSF18</td>
<td>Membrane</td>
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<tr>
<td>224211_at</td>
<td>17</td>
<td>forkhead box P3</td>
<td>FOXP3</td>
<td>Nucleus</td>
</tr>
</tbody>
</table>

Table 1: Selected Transcripts Differentially Up-Regulated in Prostate Infiltrating Treg

*Sfanos, Drake, Isaacs 2006*
LAG-3: Co-Expressed With PD-1 on Tumor Infiltrating Lymphocytes

Woo, Goldberg, Drake and Vignali. *Cancer Research* 2012
Combining PD-1 Blockade with LAG-3 Blockade

Day 7 Staged MC38 – Similar Results in Staged SA1N
In Phase I Now: Ipilimumab (anti-CTLA4) + Nivolumab (anti-PD-1)

IMPLANTED MC38 Colon Cancer

Injected on d0 with $2 \times 10^6$ cells
dosing d7,10,13 @ 10 mg/kg
or d6,9,11,13,16,18 @ 10 mg/kg

- **con**
- 9D9
- 4H2
- 9D9+4H2
- CCCPPP
- PPPCCC

*Courtesy of Alan Korman, BMS Inc*
Epigenetics
Serendipity:
Anti-PD-1 After an Epigenetic Trial

**History:**
61-year-old male with stage IV NSCLC refractory to multiple surgeries, RT, 2 multidrug chemotherapy regimens, 5-AZA and entinostat (HDACi).
Hypothesis Generating:
ResponseS* to anti-PD-1 Post RX

* 3 of 4 patients responded to anti-PD-1 after azacytidine /entinostat

Juergens et al, Cancer Discovery 2011
Combining Epigenetic Therapy With PD-1 Blockade

AZA/HDACi

→

Tumor

→

Re-Expression of Hypermethylated Tumor Antigens

→

Enhanced Anti-Tumor Response
Combining Epigenetic Therapy With PD-1 Blockade

AZA/HDACi

T cells

↑ IFN-γ Expression

↑ PD-1 Expression

Enhanced Anti-Tumor Response

PD-1 Blockade
Combining Epigenetic Therapy With PD-1 Blockade

AZA/HDACi
Combining Epigenetic Therapy With PD-1 Blockade

AZA/HDACi

Tumor

Intratumoral
Pro-inflammatory Response:
(IL-1, IL-18, IFN pathway, HLA)

Adaptive Resistance:
↑ PD-L1

Re-Expression of
Hypermethylated
Tumor Antigens

↑ IFN-γ
Expression

↑ PD-1
Expression

Enhanced Anti-Tumor Response

PD-1 Blockade
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- Ros Jurgens
- Malcolm Brock

JHU Fearless Leader
- Drew Pardoll

“A bottle of wine contains more philosophy than all the books in the world.”
L. Pasteur