Future Directions in Immunotherapy

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Ipilimumab: Pooled Survival Analysis from Phase II/III Trials in Advanced Melanoma

## Clinical Development of Inhibitors of PD-1 Immune Checkpoint

<table>
<thead>
<tr>
<th>Target</th>
<th>Antibody</th>
<th>Molecule</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLA-4</td>
<td>Ipilimumab</td>
<td>Human IgG1</td>
<td>MEL 2011</td>
</tr>
<tr>
<td></td>
<td>Tremelimumab</td>
<td>Human IgG2</td>
<td>Phase III</td>
</tr>
<tr>
<td>PD-1</td>
<td>Nivolumab</td>
<td>Human IgG4</td>
<td>MEL, NSCLC, RCC 2015</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Humanized IgG4</td>
<td>MEL, PD-L1 + NSCLC 2015</td>
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<tr>
<td></td>
<td>PDR001</td>
<td>Humanized IgG4</td>
<td>Phase I</td>
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<tr>
<td></td>
<td>REGN2810</td>
<td>Human IgG4</td>
<td>Phase I</td>
</tr>
<tr>
<td>PD-L1</td>
<td>MEDI-4736</td>
<td>Engineered human IgG1</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>MPDL-3280A</td>
<td>Engineered human IgG1</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>MSB0010718C</td>
<td>Human IgG1</td>
<td>Phase III</td>
</tr>
</tbody>
</table>
Spectrum of PD-1/PD-L1 Antagonist Activity

**Active**

- Melanoma
- Renal cancer (clear cell and non-clear cell)
- NSCLC (adenocarcinoma and squamous cell) and SCLC
- Squamous head and neck
- Gastric/GE junction
- Mismatch repair deficient tumors
- Bladder cancer
- Triple-negative breast cancer
- Ovarian cancer
- Glioblastoma
- HCC
- Thymic carcinoma
- Mesothelioma
- Cervical cancer
- Merkel cell
- Hodgkin lymphoma
- DLBCL, FL
- T-cell NHL

**Minimal to no activity**

- Prostate cancer
- MMR + colon cancer
- Myeloma
- Pancreatic cancer
- ER+ breast cancer
Nivolumab: Duration of Response and OS

NSCLC Responders by Histology

Squamous

Nonsquamous

Time Since Treatment Initiation, mos

Overall Survival (%)

All Treated Subjects With NSCLC
(n = 129)

Died/Treated | Median, mos | 95% CI
-------------|-------------|----------
99/129       | 9.9         | 7.8 -12.4

1 yr, 42%
2 yr, 24%
3 yr, 18%

# Immune Checkpoint Blockade Activity

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
<th>MEDI4736</th>
<th>MPDL3280A</th>
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</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>35%</td>
<td>27%</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>NSCLC</td>
<td>19%</td>
<td>21%</td>
<td>16%</td>
<td>23%</td>
</tr>
<tr>
<td>RCC</td>
<td>25%</td>
<td></td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td>24%</td>
<td></td>
<td>26%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>23%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td>19%</td>
<td></td>
<td>33%</td>
</tr>
<tr>
<td>Gastric</td>
<td></td>
<td>31%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCCHN</td>
<td>20%</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Response Rates Vary by Tumor Type

Gap to bridge
Expanded population of I/O respondents

~20% (Average)
PD-L1 Selection to Bridge the Gap?

PD-L1 = 0% positive
Negative

PD-L1 = 2% positive
Weak Positive
(1%-49%)

PD-L1 = 100% positive
Strong Positive
(50%-100%)
Neoantigens

MHC class 1: CD8+ T-cells usually bind 9 to 10 amino acid sequences

MHC class 2: CD4+ T-cells usually bind larger amino acid sequences. Length is less clear ~12 to 14

Self antigens: Nonmutant proteins to which tolerance is incomplete

Neoantigens: Epitopes that arise as a consequence of tumor-specific mutations

Cancer Immunotherapy Based on Mutation-Specific CD4+ T Cells in a Patient with Epithelial Cancer

Eric Tran,1 Simon Turcotte,1* Alena Gros,1 Paul F. Robbins,1 Yong-Chen Lu,1 Mark E. Dudley,1† John R. Wunderlich,1 Robert P. Somerville,1 Katherine Hogan,1 Christian S. Hinrichs,1 Maria R. Parkhurst,1 James C. Yang,1 Steven A. Rosenberg1†

Tandem Minigene Approach (1)

Isolate genomic DNA and RNA

Whole exome and transcriptome sequencing to identify mutations

Synthesize mutated tandem minigenes (TMGs) that encode 25mers containing all mutations and/or peptides

Introduce TMGs into APCs
Pulse peptides onto APCs

Expand TIL (IL-2)

Peptides

Autologous antigen presenting cells (APC), e.g., dendritic cells

Co-culture

1) IFN-γ ELISPOT
2) Flow cytometry for 4-1BB/OX40 upregulation

Rosenberg SA, personal communication.
Tandem Minigene Approach (2)

Tumor Regression After Infusions of CD4+ Expanded TILs Reactive to \textit{ERBB2IP}^{E805G} Mutation, Restricted by HLA-DQ

MEKi Blocks Naïve T-Cell Priming But Inhibits T-Cell Exhaustion

- Likely explains increase in intratumoral T cells
- No effect on CTL killing of tumor cells

PD-L1 and MEK Inhibition: A Rational Combination

- MEK inhibition alone can result in intratumoral T-cell accumulation and MHC I upregulation, and synergizes with an anti-PDL1 agent to promote durable tumor regression.¹

MHC, major histocompatibility complex; ND, no drug (vehicle alone).
CT26 (KRASmt) CRC models.

**Biomarkers: CD8 T-cell Accumulation and MHC I Expression**

**KRAS mutant respondera (mCRC cohort)**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Cobi+Atezo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8</td>
<td>0.03%</td>
</tr>
<tr>
<td>pERK</td>
<td>H=151</td>
</tr>
</tbody>
</table>

- Increased intratumoral CD8 T-cell infiltration and MHC I expression were observed with cobimetinib alone
- Further enhancement seen with cobimetinib + atezolizumab

**Clear cell sarcoma patientb (Solid tumors serial biopsy cohort)**

<table>
<thead>
<tr>
<th>Archival</th>
<th>Cobi</th>
<th>Cobi+Atezo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8</td>
<td>0.08%</td>
<td>12.3%</td>
</tr>
<tr>
<td>MHCI</td>
<td>H=60</td>
<td>H=300</td>
</tr>
<tr>
<td>PD-L1</td>
<td>IC0</td>
<td>IC0</td>
</tr>
</tbody>
</table>

- Similar results were seen in 75% of patients in the biopsy cohort

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aSarah Cannon Research Institute/Tennessee Oncology (J. Bendell).
bPrincess Margaret Cancer Center (J. Lewin, L. Siu).

## Efficacy: Confirmed Objective Response

<table>
<thead>
<tr>
<th>Confirmed Response per RECIST v1.1</th>
<th>KRAS Mutant CRC Cohort n = 20</th>
<th>All CRC Patients N = 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>20% (5.7, 43.7)</td>
<td>17% (5.0, 38.8)</td>
</tr>
<tr>
<td>PR</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>SD</td>
<td>20%</td>
<td>22%</td>
</tr>
<tr>
<td>PD</td>
<td>50%</td>
<td>52%</td>
</tr>
<tr>
<td>NE</td>
<td>10%</td>
<td>9%</td>
</tr>
</tbody>
</table>

- Response did not correlate with PD-L1 status: IC0 (n = 2), IC1 (n = 1) and IC3 (n = 1)

NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.


Efficacy: Change in Tumor Burden Over Time

- Median duration of response was not reached (range: 5.4 to 11.1+ mo)
- Responses are ongoing in 2 of 4 responding patients

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\(^a\)Confirmed per RECIST v1.1. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. Efficacy-evaluable patients. 2 patients missing or unevaluable are not included. Data cut-off February 12, 2016.

Immune-Modulatory Receptors

Turning Up The Activating

Activating receptors
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Activating antibodies

Blocking the Inhibiting

Inhibitory receptors
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Blocking antibodies

Activating T-cell stimulation

Anti–CTLA-4 and Anti–PD-1 Antibodies in Murine Tumor Models

MC38 Colon Cancer
Antibody Rx Only\textsuperscript{1,2}

- mlgG: 0/12 tumor free
- anti-PD-1: 1/12 tumor free

B16BL6 Melanoma
Antibody Rx + Cellular Vaccine\textsuperscript{3}

- Anti–CTLA-4: 0/12 tumor free
- Anti–PD-1 + anti–CTLA-4: 9/12 tumor free

Response of a Large Chest-Wall Melanoma Metastasis to One Dose of Ipilimumab Plus Nivolumab

Anti-CD137 + Anti–PD-1

Targeting IDO in the Microenvironment

- IDO1 is a tryptophan-catabolizing enzyme that is overexpressed in many cancers\textsuperscript{1-3} and induces immune tolerance by suppressing T-cell responses\textsuperscript{4}
  - IDO1 is expressed in human tumors and in dendritic cells within tumor-draining lymph nodes\textsuperscript{5}
  - IDO1 expression is associated with more rapid tumor progression and reduced survival\textsuperscript{5}
  - IDO1 inhibition exhibits antitumor activity through the reactivation of effector T-cells\textsuperscript{3} and is synergistic with PD-1 blockade\textsuperscript{6}

### Epacadostat + Pembrolizumab: Best ORR by RECIST 1.1—Melanoma

<table>
<thead>
<tr>
<th>Efficacy-Evaluable Patients, n (%)</th>
<th>Melanoma n = 19</th>
<th>25 mg BID n = 2</th>
<th>50 mg BID n = 12</th>
<th>100 mg BID n = 4</th>
<th>300 mg BID n = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR + PR)</td>
<td>10 (53)</td>
<td>1 (50)</td>
<td>5 (42)</td>
<td>4 (100)</td>
<td>0</td>
</tr>
<tr>
<td>CR</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>7</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>DCR (CR + PR + SD)</td>
<td>14 (74)</td>
<td>2 (100)</td>
<td>7 (58)</td>
<td>4 (100)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (26)</td>
<td>0</td>
<td>5 (42)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- In patients who were treatment-naïve for advanced/metastatic melanoma (n = 16)
  - ORR 56%
  - DCR 75%

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*By data cut-off for efficacy (October 1, 2015), patients had at least 1 post-baseline scan or discontinued or died before the first post-baseline scan.*

Epacadostat + Pembrolizumab: Best ORR by RECIST 1.1

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Melanoma n = 20</th>
<th>RCC n = 11</th>
<th>NSCLC n = 10</th>
<th>TCC n = 5</th>
<th>EA n = 5</th>
<th>TNBC n = 3</th>
<th>SCCHN n = 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evaluable</strong></td>
<td>19</td>
<td>8</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>ORR (CR + PR)</strong></td>
<td>10 (53)</td>
<td>2 (25)</td>
<td>3 (38)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>0</td>
<td>1 (50)</td>
</tr>
<tr>
<td>CR</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>SD</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1b</td>
<td>1</td>
</tr>
<tr>
<td><strong>DCR (CR + PR + SD)</strong></td>
<td>14 (74)</td>
<td>7 (88)</td>
<td>5 (63)</td>
<td>2 (50)</td>
<td>1 (25)</td>
<td>1 (50)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (26)</td>
<td>0</td>
<td>1 (13)</td>
<td>1 (25)</td>
<td>3 (75)</td>
<td>1 (50)</td>
<td>0</td>
</tr>
</tbody>
</table>

*a By data cut-off for efficacy (October 1, 2015), patients had at least 1 post-baseline scan or discontinued or died before the first post-baseline scan. b Patient achieved an SD but discontinued for a DLT (grade 3 rash) prior to the protocol required minimum observation (56 days).

NOTE: All percentages are calculated based on number of evaluable patients.

T-VEC: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects

**Local Effect:**
Virally-Induced Tumor Cell Lysis

- Selective viral replication in tumor tissue
- Tumor cells rupture for an oncolytic effect

**Systemic Effect:**
Tumor-Specific Immune Response

- Systemic tumor-specific immune response
- Death of distant cancer cells

Talimogene Laherparepvec Plus Ipilimumab in Advanced Melanoma

Personalized Combination Strategies

Co-stimulatory mAbs targeting:
- CD137
- OX40
- CD40
- G1TR

Conventional agents inducing immunogenic cell death:
- Chemotherapy
- Radiotherapy
- Anti-angiogenics
- Targeted therapies

Other checkpoint inhibitory molecules:
- CTLA4
- LAG3
- TIM3
- BTLA
- TIGIT

Cancer vaccines considering individual neoantigens

Functional modification of immunosuppressive enzymes such as:
- IDO1
- iNOS

T_{Reg} cell targeting or inhibition

Adoptive cell therapy

Myeloid cell modulation

PD1 or PD1L blockade
