Harnessing the Immune System via Checkpoint Blockade

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Disclosures

- Bristol Myers Squibb
  - Advisory Board member – uncompensated
  - Institutional Research Support
- Merck
  - Advisory Board member - compensated
Regulation of T Cell Responses Via Multiple Co-Stimulatory and Inhibitory Interactions

- T cell response to antigen is mediated by peptide-MHC recognized by TCR (first signal – specificity)
- B7 family of membrane-bound ligands bind both co-stimulatory and inhibitory receptors (second co-stimulatory signal)

CTLA-4 vs. PD-1: Distinct Immune Checkpoints

Naïve/resting T cell

T cell priming

CTLA-4

Topalian et al., Curr Opin Immunol 2012
Comparison of CTLA-4 versus PD-1

**CTLA-4 Pathway**
- Exclusively on T cells
- Ligands – CD 80 & 86
- Ligands only expressed on APCs
- CTLA-4 deficient mice suffer early, fatal autoimmune syndrome
- Blockade enhances proliferation of CD4 and CD8 T cells with increase in ratio to regulatory T cells

**PD-1 Pathway**
- On T, B and NK cells
- Ligands - PD-L1 & PD-L2
- Ligand expressed on APCs and tumor cells
- PD-1 deficient mice develop strain-specific autoimmune late in life
- Blockade enhances CD8 T cells greater than CD4 with increase of CD8 to Tregs & cytotoxicity of CD8

Blocking the Immune Checkpoint
CTLA-4 - Ipilimumab

Signal 1

HLA

B7.1/2 (CD80/86)

Signal 2

CD28

CTLA-4

T Cell Receptor

T cell

α-CTLA4

antigen
Phase 3 Trial of Ipilimumab in Patients with Previously Treated Melanoma

HLA-A*0201
Unresectable stage 3 or 4 melanoma
One prior Rx

RANDOMIZE

IPI 3mg/kg IV + gp100 vaccine q 3 wk x 4
N=403

IPI 3mg/kg IV q 3 wk x 4
N=137

gp100 vaccine q 3 wk x 4
N=136

If PD after CR/PR/ SD for ≥ 3 mo

REINDUCTION

IPI 3mg/kg IV + gp100 vaccine q 3 wk x 4
N=8

IPI 3mg/kg IV q 3 wk x 4
N=23

gp100 vaccine q 3 wk x 4
N=1

Hodi et al NEJM 2010
Phase 3 Trial of Ipilimumab in Patients with Previously Treated Melanoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BORR</th>
<th>Median OS</th>
<th>2 yr OS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipi + gp 100</td>
<td>5.7%</td>
<td>10 mo</td>
<td>21.6%</td>
<td>0.68 p&lt;0.001 to gp100</td>
</tr>
<tr>
<td>Ipi</td>
<td>10.9%</td>
<td>10.1 mo</td>
<td>23.5%</td>
<td>0.66 p=0.003 to gp 100</td>
</tr>
<tr>
<td>gp100</td>
<td>1.5%</td>
<td>6.4 mo</td>
<td>13.7%</td>
<td></td>
</tr>
</tbody>
</table>

- Most common toxicities – Rash and diarrhea
- Grade 3 / 4 immune related toxicities – 10-15%
- 14 deaths, 7 due to immune related toxicities

BORR – best overall response rate, OS=overall survival

Hodi et al NEJM 2010
Ipilimumab: Survival Benefit in Metastatic Melanoma

Hodi et al. NEJM 2010
Phase 3 Trial of DTIC +/- Ipilimumab in Patients with Advanced Melanoma

Unresectable stage 4 melanoma
No prior Rx
No Brain Met

Randomize 1:1

IPI 10mg/kg IV q 3 wk x 4 + DTIC 850 mg/m² q 3 wk x 8
N=250

If CR/PR/SD

Placebo q 3 wk x 4
DTIC 850 mg/m² q 3 wk x 8
N=252

MAINTENANCE

IPI 10mg/kg IV q 12 wk x 4
Placebo q 12 wk x 4

Robert et al NEJM 2011
Phase 3 Trial of DTIC +/- Ipilimumab in Patients with Melanoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BORR</th>
<th>Median OS</th>
<th>2 yr OS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTIC + Ipi</td>
<td>15.2%</td>
<td>11.2 mo</td>
<td>28.5%</td>
<td>0.72 p&lt;0.001</td>
</tr>
<tr>
<td>DTIC</td>
<td>10.3%</td>
<td>9.1 mo</td>
<td>17.9%</td>
<td></td>
</tr>
</tbody>
</table>

- Most common toxicities – Rash, diarrhea, and elevated LFTs
- Grade 3 / 4 immune related toxicities – 38.1% vs 4.4%
- Most common grade 3 /4 immune related toxicity - Hepatitis
- Drug related discontinuation rate – 34% vs 4%
- No deaths

BORR – best overall response rate, OS=overall survival

Robert et al NEJM 2011
Ipilimumab Toxicity Management

- **Grade 1** – supportive care & close observation

- **Symptomatic Grade ≥ 2** – hold treatment
  - Consider moderate dose steroids (prednisone 0.5 to 1.0 mg/kg)
  - Taper over 4 weeks
  - Retreat if ≤ grade 1, prednisone tapered to ≤ 7.5 mg

- **Grade ≥ 3**
  - Permanently stop ipilimumab (except dermatologic)
  - Consider high dose steroids (prednisone 1-2 mg/kg or methylprednisone 1g IV daily)
  - Supportive care, specialist consultation
  - Additional immunosuppressive therapy – infliximab or mycophenolate

*Weber JS et. al. JCO 30:2691-7, 2012,
Kaehler KC et. al. Seminars in Oncology, 37(5), October 2010*
E1609 Schema

Stratify Patients with surgically resected
- IIIB
- IIIC
- M1a
- M1b

RANDOMIZE

Schema

Arm A: Ipilimumab
Induction Phase
Ipilimumab: 10 mg/kg I.V. infusion every three weeks for four doses.

Maintenance Phase
Ipilimumab: 10 mg/kg I.V. infusion every 12 weeks (3 months), beginning at week 24, for a maximum of 4 doses (week 24, 36, 48, 60)

Arm B: HDI
Induction Phase
Interferon Alfa-2b: 20 MU/m²/d I.V. for 5 consecutive days out of 7 (e.g., M-F) every week for 4 weeks.

Maintenance Phase
Interferon Alfa-2b: 10 MU/m²/d Subcutaneous every other day (e.g., M,W,F) 3 times each week for 48 weeks.

Accrual = 1,000
Randomized, Double-Blind, Phase III Trial Comparing Ipilimumab vs. Placebo Following Radiotherapy in Subjects with Castration Resistant Prostate Cancer that Have Received Prior Treatment with Docetaxel (CA184-043)

**SCREENING**

**INDUCTION**

**MAINTENANCE**

**CRPC Prior Docetaxel N = 800**

ICF, Baseline Assessments

Day -28 to Day -2

Radiotherapy (8 gy) to bone mets day -2 or -1

Ipilimumab 10 mg/kg wks 1, 4, 7, 10

Ipilimumab 10 mg/kg every 12 wks

Placebo wks 1, 4, 7, 10

Placebo every 12 wks

TA: wks 12 and 24 PSA: wks 7, 12, 18, 24 OA: wks 7, 10, 12, 18, 24

TA: every 12 wks PSA: every 6 wks OA: every 12 wks

Day -2 to Week 24

Wk 24 to Wk 48+

Completed Accrual 1/2012

TA = tumor assessment
PSA = prostate specific antigen
OA = outcome assessment
Ongoing Phase III Trials of Ipilimumab in Lung Cancer

Squamous cell Subtype only

- Carbo–paclitaxel*-placebo
- Carbo–paclitaxel*-Ipilimumab

Small cell lung cancer

- Carbo–etoposide - placebo
- Carbo-etoposide - ipilimumab

*Carboplatin (AUC 6); paclitaxel (175 mg/m2); ipilimumab (10 mg/kg q3w)
Role of PD-1 in Suppressing Antitumor Immunity

Activation
(cytokines, lysis, prolif., migration)

APC  \( \rightarrow \)  MHC-Ag  \( \rightarrow \)  T cell

\( \text{TCR Signal 1} \)
\( \text{B7.1} \)
\( \text{CD28} \)

\( \text{(+)} \text{ Signal 2} \)

Tumor

Role of PD-1 in Suppressing Antitumor Immunity

Activation
(cytokines, lysis, prolif., migration)

Inhibition
(nergy, exhaustion, death)

Role of PD-1 in Suppressing Antitumor Immunity

TCR Signal 1

APC

MHC-Ag

B7.1

CD28

T cell

TCR Signal 1

Activation
(cytokines, lysis, prolif., migration)

(+ ) Signal 2

PD-1

PD-L1

Inhibition
( anergy, exhaustion, death)

Anti-PD-1

Tumor

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

<table>
<thead>
<tr>
<th>Target</th>
<th>Antibody</th>
<th>Molecule</th>
<th>Company</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>Nivolumab/BMS-936558/MDX-1106/ONO-4538</td>
<td>Fully human IgG4 mAb</td>
<td>Bristol-Myers Squibb</td>
<td>Phase III multiple tumors</td>
</tr>
<tr>
<td></td>
<td>Pidilizumab CT-011</td>
<td>Humanized IgG1 mAb</td>
<td>CureTech</td>
<td>Phase II multiple tumors</td>
</tr>
<tr>
<td></td>
<td>Lambrolizumab MK-3475</td>
<td>Humanized IgG4 mAb</td>
<td>Merck</td>
<td>Phase I-II</td>
</tr>
<tr>
<td>PD-L1</td>
<td>BMS-936559/MDX-1105</td>
<td>Fully human IgG4 mAb</td>
<td>Bristol-Myers Squibb</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>MedI-4736</td>
<td>Fully human IgG1 mAb</td>
<td>MedImmune</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>MPDL-3280A</td>
<td>Fully human IgG1 mAb</td>
<td>Genentech</td>
<td>Phase I-II</td>
</tr>
</tbody>
</table>
Nivolumab Study Design: Phase I Multi-Dose Regimen

Eligibility: Advanced MEL, RCC, NSCLC, CRC, or CRPC with PD after 1-5 systemic therapies

Topalian S et al NEJM 2012
Safety of Nivolumab-Multi-dose Phase I Trial

- 220 (72%) patients experienced drug-related AEs
  - Fatigue (26%), rash (14%), diarrhea (12%), and pruritus (10%) were the most common
  - Grade 3–4 AEs were experienced by 15% of patients
  - 18/304 (6%) patients discontinued treatment because of drug-related AEs

- AEs of special interest (AEOSI), defined as AEs with a potential immune-related etiology, were observed in 138 (45%) of study patients
  - Majority of AEOSI were low grade; 6% Grade 3–4
  - The most common AEOSI of any grade included rash (14%), diarrhea (12%), and pruritus (10%)
    - AEOSI occurring in ≤1% of patients included colitis, hepatitis, hypophysitis, and thyroiditis

- There were 3 (1%) deaths in patients with pneumonitis (2 NSCLC, 1 CRC)
### Clinical activity of Nivolumab

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Dose (mg/kg)</th>
<th>No. of Patients</th>
<th>ORR (CR/PR) No. of Patients (%)</th>
<th>SD ≥24 Weeks No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEL</td>
<td>0.1–10</td>
<td>106</td>
<td>33 (31)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>1–10</td>
<td>122</td>
<td>20 (16)</td>
<td>11 (9)</td>
</tr>
<tr>
<td>RCC</td>
<td>1 or 10</td>
<td>34</td>
<td>10 (29)</td>
<td>9 (27)</td>
</tr>
</tbody>
</table>

- 28 responses (16 MEL, 6 RCC, and 6 NSCLC) lasted ≥1 year among 54 patients with treatment initiation prior to 1 year
- 13 patients (4 MEL, 6 NSCLC, 3 RCC) demonstrated non-conventional patterns of response but were not included as responders
Partial regression of metastatic RCC (Nivolumab, 1 mg/kg)

Case studies
- 57-year-old male patient
- Developed progressive disease following radical surgery and treatment with sunitinib, temsirolimus, sorafenib, and pazopanib

RCC = renal cell cancer

McDermott D ESMO 2012
Response of Metastatic NSCLC (Nivolumab, 10mg/kg)

- 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 (trial for T790 mutation), and lastly pemetrexed.
Preliminary molecular marker studies: Correlation of PD-L1 expression in pretreatment tumor biopsies with clinical response to anti-PD-1.

Proportion of patients:

- **PD-L1(+)**: 18/31
- **PD-L1(-)**: 0/18

49 patients include 20 with melanoma, 13 NSCLC, 7 colon, 6 kidney, and 3 prostate cancer.

P-value: p=0.002

* Normal renal glomerulus

Topalian S and Taube J personal communication 2013
Correlation of PD-L1 expression with tumor type in 49 patients treated with anti-PD-1

Patients were “PD-L1+” if ≥5% of tumor cells in any tumor biopsy expressed cell surface PD-L1, using mAb 5H1 and manual staining technique.

Responders/total: 8/20 3/13 2/6 0/7 0/3

Topalian S and Taube J personal communication 2013
Nivolumab Ongoing Phase 3 Trials

- **NSCLC**
  - Nivolumab vs. Docetaxel in the 2\(^{nd}\) line setting in patients with squamous cell carcinoma
  - Nivolumab vs. Docetaxel in the 2\(^{nd}\) or 3rd line setting in patients with non-squamous cell

- **RCC**
  - Nivolumab vs. Everolimus who have received prior anti-angiogenic therapy

- **Melanoma**
  - Nivolumab vs. Nivo + Ipi vs. Ipi in untreated pts
  - Nivolumab vs. Physicians’ Choice (taxol/carbo or dacarbazine) after Ipi progression
  - Nivolumab vs. Dacarbazine in untreated (outside-US)
MK-3475: Phase I Trial Design

MK-3475 - Humanized IgG4 antibody binds to PD-1

Part A – Dose escalation
- 3+3 design 1, 3, and 10 mg/kg
  - Administered every 2 or 3 weeks
- Advanced solid tumors

Part B – Melanoma expansion cohort
- Single arm, open label
- 2 mg/kg and 10 mg/kg
  - Administered every 2 or 3 weeks
- Advanced Melanoma
  - Naïve to Ipilimumab (IPI)
  - Previously treated with IPI

Hamid O et al Society of Melanoma 2012
MK-3475: Summary of Dose Escalation Phase

- MK-3475 is well tolerated at all dose levels tested - (1mg/kg, 3mg/kg, and 10 mg/kg; administered every 2 or 3 weeks):
  - No DLTs
  - Majority of AEs are Grade 1-2
    - Common AEs were fatigue, pruritus, dyspnea, and nausea

- Early evidence of anti-tumor activity
  - Two melanoma patients with confirmed partial responses by RECIST 1.1 at 3 mg/kg and 10 mg/kg
  - One NSCLC patient with unconfirmed partial response by RECIST 1.1 at 1 mg/kg

Hamid O et al Soc of Melanoma 2012
MK-3475: Preliminary Best Overall Response in Advanced Melanoma Patients

<table>
<thead>
<tr>
<th></th>
<th>Complete Response (N, 95% CI)</th>
<th>Objective Response (N, 95% CI)</th>
<th>Disease Control Rate (N, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All MEL N=83</strong></td>
<td>5% (4; 2%-13%)</td>
<td>47% (39; 34%-56%)</td>
<td>60% (50; 48% - 70%)</td>
</tr>
<tr>
<td><strong>IPI Naïve N=58</strong></td>
<td>7% (4; 2%-18%)</td>
<td>50% (29; 35%-61%)</td>
<td>67% (39; 51%-76%)</td>
</tr>
<tr>
<td><strong>IPI Treated N=25</strong></td>
<td>0%</td>
<td>40% (10; 17%-59%)</td>
<td>44% (11; 24%-68%)</td>
</tr>
</tbody>
</table>

- All patients were dosed at 10 mg/kg
- 7 Grade 3 / 4 immune related events including thyroid disease, pneumonitis, nephritis etc
- Disease control rate = objective response + stable disease

Randomized phase II trial for 2nd line therapy enrolling – High dose vs. low dose vs. chemo

Hamid O et al Soc of Melanoma 2012
Potential Differences in PD-1 vs. PD-L1 Blockade

Topalian S et al Curr Opin Immunol 2012
Study Design: First-in-Human Trial of BMS-936559 (anti-PD-L1 Ab)

6-wk Treatment Cycle

Dose administered IV, Q2wk in 6 wk cycles

Eligibility: Advanced MEL, NSCLC, RCC, CRC, Ovarian, Pancreatic, Breast, Gastric Cancers with PD; No previous T-cell therapy (CTLA-4, Anti-PD-1/L1)

Rapid PD or Clinical deterioration

Off Study

Unacceptable toxicity

Follow-up

CR/PR/SD or PD but clinically stable

Treat to 16 cycles (96 wk total)

On-study follow-up for 12 mo

Optional: Retreatment at original dose for ≤12 mo if PD during follow-up

Brahmer J et al NEJM 2012
BMS 936559 - Safety

- A maximum tolerated dose was not identified at doses up to 10 mg/kg
- There was no apparent relationship between drug dose and AE frequency in all treated patients
- Median duration of therapy was 12 weeks (range 2.0–111.1 weeks)
- 12 of 207 (6%) patients discontinued treatment due to a BMS-936559-related adverse event (AE)
- Drug-related AEs in 126 of 207 patients (61%)
  - Most AEs were low grade (grade 1/2 in 107 of 207 patients, 52%)
  - Grade 3/4 drug-related AEs in 19 of 207 patients (9%)
- No drug-related deaths

Brahmer J et al NEJM 2012
Clinical activity of BMS-936559 in 160 response-evaluable patients

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Dose (mg/kg)</th>
<th>No. Patients (N=160)</th>
<th>ORR&lt;sup&gt;c&lt;/sup&gt; No. Patients (%)</th>
<th>Duration of Response Range, Months</th>
<th>SD≥24 Weeks No. Patients (%)</th>
<th>PFSR at 24 Weeks (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>0.3-10</td>
<td>52</td>
<td>9 (17)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.8-23.5+</td>
<td>14 (27)</td>
<td>42</td>
</tr>
<tr>
<td>NSCLC</td>
<td>1-10</td>
<td>49</td>
<td>5 (10)</td>
<td>2.3+-16.6+</td>
<td>6 (12)</td>
<td>31</td>
</tr>
<tr>
<td>All Squamous</td>
<td></td>
<td>13</td>
<td>1 (8)</td>
<td>-</td>
<td>3 (23)</td>
<td>43</td>
</tr>
<tr>
<td>All Non-squamous</td>
<td></td>
<td>36</td>
<td>4 (11)</td>
<td>-</td>
<td>3 (8)</td>
<td>26</td>
</tr>
<tr>
<td>RCC</td>
<td>10</td>
<td>17</td>
<td>2 (12)</td>
<td>4-17</td>
<td>7 (41)</td>
<td>53</td>
</tr>
<tr>
<td>Ovarian</td>
<td>3 and 10</td>
<td>17</td>
<td>1 (6)</td>
<td>1.3+</td>
<td>3 (18)</td>
<td>22</td>
</tr>
</tbody>
</table>

<sup>a</sup> Response-evaluable patients who initiated treatment by August 1, 2011

<sup>b</sup> To date there have been no objective responses in patients with colorectal or pancreatic cancer; no patients with gastric or breast cancer were evaluable as of the date of data analysis

<sup>c</sup> ORR was assessed using modified RECIST v1.0 criteria

<sup>d</sup> Includes 3 CRs
MPDL3280A, Anti-PD-L1: Phase I Schema

Pre-screen/Screening
MPDL3280A IV q3 weeks x 16 cycles (≈ 1 y)

Follow-up
Patients with CR/PR/SD followed every 12 weeks until PD

Response assessed by CT scan (RECIST v1.1 and irRC) every 6 weeks for 6 months, then every 12 weeks

Key Eligibility Criteria
- Incurable or metastatic solid tumor or hematologic malignancy
- Measureable disease per RECIST v1.1
- ECOG PS 0 or 1

Gordon M et al AACR 2013
MPDL3280A: Phase I trial

- MPDL3280A safety and PK profile
  - Generally well tolerated
    - Most common side effects: fatigue, nausea and diarrhea
    - No dose-limiting toxicities up to 20 mg/kg
  - No MTD identified
- Activity observed in multiple solid tumor types, with responses continuing in all responders
- Expansion phases in NSCLC, melanoma, RC and other tumor types are ongoing
- Phase Ib trials in combination with bevacizumab, chemotherapy and vemurafenib are ongoing
- Phase II trials in NSCLC initiated
Conclusions

- Checkpoint inhibitors have promising anti-tumor activity
  - Ipilimumab is the first checkpoint inhibitor approved for use in cancer
- Checkpoint inhibitors have a unique set of side effects consistent with the immune mechanism of action
- Patient selection (biomarker) are being sought
- Phase 3 trials are ongoing