Immunomodulation with a Focus on the Clinical Development of PD-1/PD-L1 Inhibitors in Non-Small Cell Lung Cancer

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Disclosures

- Consultant/Advisory board member – BMS (Uncompensated), Merck (compensated)
- Institutional Research Support - BMS
Potential Mechanisms for Immune Evasion in Lung Cancer

- Defective antigen presentation
- Immunosuppressive cell infiltrates - T reg and MDSCs
- Upregulation/secretion of immunosuppressive cytokines
- Checkpoint pathways
Immune Checkpoint Pathways

Tumor Cell or Antigen Presenting Cell

- HLA
- Class II MHC
- B7-H1 (PD-L1)

T cell

- CD28
- CTLA-4
- T Cell Receptor
- LAG-3
- PD-1

Others: ICOS, GITR, Tim-3

Signal 1: B7.1/2 (CD80/CD86) with T Cell Receptor (TCR)

Signal 2: B7.1/2 (CD80/CD86) with CD28
PD-1/PD-L1: Pathway: Tumor cells – T cells

T cell priming

- PD-L1 can be expressed on tumor cells either endogenously or induced by association with T cells (adaptive immune resistance)\(^1,2\)
- In RCC, melanoma and other tumors, PD-L1 expression has been shown to be associated with adverse clinical/pathologic features, including\(^3\):
  - More aggressive disease
  - Shorter survival

Potential Differences in PD-1 vs. PD-L1 Blockade

Current Opinion in Immunology

Topalian S et al Curr Opin Immunol 2012
## 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</td>
<td>Fully human IgG4</td>
<td>Bristol-Myers Squibb</td>
<td>Phase III multiple tumors</td>
</tr>
<tr>
<td></td>
<td>Pidilizumab CT-011</td>
<td>Humanized IgG1</td>
<td>CureTech</td>
<td>Phase II multiple tumors</td>
</tr>
<tr>
<td></td>
<td>MK-3475</td>
<td>Humanized IgG4</td>
<td>Merck</td>
<td>Phase I-III</td>
</tr>
<tr>
<td>PD-L1</td>
<td>BMS-936559</td>
<td>Fully human IgG4</td>
<td>Bristol-Myers Squibb</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>MedI-4736</td>
<td>Engineered human IgG1</td>
<td>MedImmune</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>MPDL-3280A</td>
<td>Engineered human IgG1</td>
<td>Genentech</td>
<td>Phase I-III</td>
</tr>
<tr>
<td></td>
<td>MSB0010718C</td>
<td>Human IgG1</td>
<td>EMD Serono</td>
<td>Phase I</td>
</tr>
</tbody>
</table>
# Inhibitors of PD-1 – Phase I Trials

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Molecule</th>
<th>Dose/schedule tested</th>
<th>Eligible patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS-936558</td>
<td>Fully human IgG4 mAb</td>
<td>1,3,10 mg/kg IV once every 2 wks in 8wk cycles</td>
<td>N= 304 MEL, RCC, NSCLC, CRC, Prostate Ca</td>
<td>No MTD identified</td>
</tr>
<tr>
<td>(Nivolumab)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MK-3475</td>
<td>Humanized IgG1 mAb</td>
<td>1,3,10 IV once every 2 or 3 wks in 6 wk cycles</td>
<td>N= 140+ Solid tumors</td>
<td>No MTD identified</td>
</tr>
</tbody>
</table>

Topalian S et al NEJM 2012; Ribas A et al NEJM 2013
Nivolumab (Anti-PD-1) Phase I Trial: Expansion Cohorts for NSCLC

Eligible NSCLC Pts
Randomized between 3 dose levels

Completed accrual Dec 2011

1 mg/kg IV q 2 wks N=32
3 mg/kg IV q 2 wks N=32
10 mg/kg IV q 2 wks N=32

Current analysis for patients treated through July 2012

129 patients with NSCLC were evaluable for safety and clinical activity
### Efficacy of Nivolumab Monotherapy in Patients with NSCLC

<table>
<thead>
<tr>
<th>Dose mg/kg</th>
<th>ORR&lt;sup&gt;a,b&lt;/sup&gt; % (n/N)</th>
<th>Estimated Median DOR Weeks (Range)</th>
<th>Stable Disease Rate ≥24 Wks % (n/N)</th>
<th>Median PFS Months (95% CI)</th>
<th>Median OS Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All doses</td>
<td>17.1 (22/129)</td>
<td>74.0 (6.1+, 133.9+)</td>
<td>10.1 (13/129)</td>
<td>2.3 (1.9, 3.7)</td>
<td>9.9 (7.8, 12.4)</td>
</tr>
<tr>
<td>1</td>
<td>3.0 (1/33)</td>
<td>63.9 (63.9, 63.9)</td>
<td>15.2 (5/33)</td>
<td>1.9 (1.8, 3.6)</td>
<td>9.2 (5.3, 11.1)</td>
</tr>
<tr>
<td>3</td>
<td>24.3 (9/37)</td>
<td>74.0 (16.1+, 133.9+)</td>
<td>8.1 (3/37)</td>
<td>1.9 (1.7, 12.5)</td>
<td>14.9 (7.3, NE)</td>
</tr>
<tr>
<td>10</td>
<td>20.3 (12/59)</td>
<td>83.1 (6.1+, 132.7+)</td>
<td>8.5 (5/59)</td>
<td>3.6 (1.9, 3.8)</td>
<td>9.2 (5.2, 12.4)</td>
</tr>
</tbody>
</table>

CI = confidence interval; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

<sup>a</sup>Tumors and responses were assessed after each cycle per modified RECIST v1.0.

<sup>b</sup>All efficacy analyses based on data collected as of September 2013

- Durable responses were observed; responses are ongoing in 45% of patients (10/22)
- Higher ORRs observed at 3 and 10 mg/kg nivolumab doses relative to 1 mg/kg dose
- Rapid responses; 50% of patients (11/22) demonstrating response at first assessment (8 weeks)
- 7/16 responders who discontinued for reasons other than disease progression responded for ≥16 wks; 6/7 remain in response
- Similar response rates in both squamous and nonsquamous histologies
- 6 patients with unconventional “immune-related” responses were not included as responders
Response of Metastatic NSCLC (Nivolumumab, 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

S Antonia, Moffitt Cancer Center
Nivolumab in NSCLC: Duration of Response and Overall Survival

NSCLC Responders\textsuperscript{a,b} by Histology

- Squamous
- Non-squamous

Time (Week)

0 8 16 24 32 40 48 56 64 72 80 88 96 104 112 120 128 136 144 152 160

Vertical line at 96 weeks = maximum duration of continuous nivolumab therapy

\textsuperscript{a}Responses were assessed by modified RECIST v1.0
\textsuperscript{b}All efficacy analyses based on data collected as of September 2013

All Treated Subjects with NSCLC

<table>
<thead>
<tr>
<th>Died/Treated</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>94/129</td>
<td>9.90 (7.80,12.40)</td>
</tr>
</tbody>
</table>

Median OS: 9.9 Months (7.8, 12.4)

1 year OS Rate 42\% (48 pts at risk)

2 year OS Rate 24\% (20 pts at risk)

Proportion Survival

Subjects at Risk

Total 129 111 82 66 48 35 28 20 9 4 3 3 3 2 1 1 1 0 0

Months Since Initiation of Treatment

Duration of response up to discontinuation of therapy
Ongoing response
Time to response
Response duration following discontinuation of therapy
MK-3475: Phase I Trial

MK-3475 - antibody binds to PD-1

Part A – Dose escalation

- 3+3 design 1, 3, and 10 mg/kg
  - IV every 2 or 3 wks
- Advanced solid tumors
- Well tolerated – No Dose Limiting Toxicities, low grade fatigue, itching, breathlessness
- Activity – 2 Partial Responses (PR) melanoma, 1 PR NSCLC

Part B – NSCLC expansion cohort

- 10 mg/kg q 3 wks
- 33 pts
- Response Rate – 21%
- Similar for squamous and nonsquamous

Ribas A et al ASCO 2013, Garon E et al WCLC 2013
MK-3475: NSCLC Clinical Activity

Characteristics- 42% Male, 58% ECOG 1, 66% Former and Current smokers, 16% Squamous, 61% PD-L1 positive tumors

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>irRC, Investigator Review</th>
<th>RECISt v1.1, Independent Review</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ORR, n (%) [95% CI]</td>
<td>Median PFS, wk (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR, * (%) [95% CI] Median PFS, wk (95% CI) Median OS, wk (95% CI)</td>
</tr>
<tr>
<td>All</td>
<td>38</td>
<td>9 (24%) [11%, 40%] 9.1 (8.3, 17.4)</td>
<td>7 (21%) [9%, 39%] 9.7 (7.6, 17) 51 (14, NR)</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>31</td>
<td>7 (23%) [10%, 41%] 9.1 (8.3, 17.0)</td>
<td>4 (16%) [4%, 35%] 10.3 (7.6, 17) 35 (14, NR)</td>
</tr>
<tr>
<td>Squamous</td>
<td>6</td>
<td>2 (33%) [4%, 78%] 23.5 (2.7, NR)</td>
<td>2 (33%) [4%, 78%] 15.2 (1.4, NR) NR (2.7, NR)</td>
</tr>
</tbody>
</table>
MK-3475 Responders Have Prolonged Duration of Response

- 7/9 responders on treatment at time of analysis
- Median PFS of responders not reached at 62 weeks
- AN 179: stopped MK for local therapy to brain metastasis; MK resumed based on continued systemic response
- AN 169: after 1 dose, MK stopped for unrelated grade 4 hypercalcemia; response maintained without further treatment; per protocol, follow-up ceased at 39 weeks

Garon E et al WCLC 2013
Potential Differences in PD-1 vs. PD-L1 Blockade

Current Opinion in Immunology

Topalian S et al Curr Opin Immunol 2012
Inhibitors of PD-L1 – Activity in NSCLC

<table>
<thead>
<tr>
<th>Antibody</th>
<th># of evaluable NSCLC</th>
<th>RR (%)</th>
<th>SD rate at 24 wks</th>
<th>PFS rate at 24 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS-936559</td>
<td>49</td>
<td>10%*</td>
<td>12%</td>
<td>31%</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>36</td>
<td>11%</td>
<td>8%</td>
<td>26%</td>
</tr>
<tr>
<td>Squamous</td>
<td>13</td>
<td>8%</td>
<td>23%</td>
<td>43%</td>
</tr>
<tr>
<td>MPDL-3280A</td>
<td>53</td>
<td>23%^</td>
<td>17%</td>
<td>45%</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>42</td>
<td>21%</td>
<td>17%</td>
<td>44%</td>
</tr>
<tr>
<td>Squamous</td>
<td>11</td>
<td>27%</td>
<td>18%</td>
<td>46%</td>
</tr>
</tbody>
</table>

^Recist 1.1 used, *Recist 1.0 used

Clinical Activity of MPDL3280A in NSCLC (Adeno)

62-year-old male, pretreated including carboplatin + paclitaxel, bevacizumab + erlotinib, pemetrexed, PD-L1 positive

Spigel D, et al ASCO 2013
MPDL-3280A: Duration of Response

Histology | IHC
---|---
Nonsquamous | IHC 0
Squamous | IHC 3
Nonsquamous | IHC 0
Nonsquamous | IHC 1
Nonsquamous | IHC 0
Squamous | IHC 2
Nonsquamous | IHC 3
Squamous | IHC 3
Nonsquamous | IHC 3
Nonsquamous | IHC 0
Nonsquamous | IHC 3
Nonsquamous | IHC 1

* Patient experiencing ongoing benefit per investigator.

Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.
MPDL-3280A: Response by Smoking History in NSCLC Patients

Maybe due to the fact that people with a smoking history have a higher mutation rate which could be associated with increased immune recognition or response.

Soria J et al ECC 2013
Summary of PD-1/PD-L1 blockade immune-mediated toxicities

- **Common:**
  - Fatigue
  - Rash – maculopapular and pruritus
    - topical treatments
  - Diarrhea/colitis
    - initiate steroids early, taper slowly
  - Hepatitis/liver enzyme abnormalities
  - Infusion reactions
  - Endocrinopathies – Thyroid, adrenal, hypophysitis

- **Infrequent** – pneumonitis

- **Grade 3 and 4 toxicities uncommon**

## PD-1 Checkpoint Inhibition - Toxicities

<table>
<thead>
<tr>
<th>Agent &amp; Population, N</th>
<th>Rx related AE - All &amp; Grade 3/4</th>
<th>Most common Rx related AE</th>
<th>Select AE All Grade &amp; Grade 3/4</th>
<th>Pneumonitis rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab NSCLC - 129</td>
<td>71% 14%</td>
<td>Fatigue - 24%</td>
<td>53% 5%</td>
<td>All – 6% Gr 3/4 - 2% 2 deaths</td>
</tr>
<tr>
<td>MK3475 NSCLC - 38</td>
<td>53% 2%</td>
<td>Rash – 21% Pruritis – 18% Fatigue – 16%</td>
<td>NR</td>
<td>All – 2% (1-grade 2) No Grade 3-5</td>
</tr>
<tr>
<td>BMS-936559 Phase I -207</td>
<td>61% 9%</td>
<td>Fatigue -16% Infusion rxn – 10% Diarrhea – 9%</td>
<td>39% 5%</td>
<td>All – 1% No Grade 3-5</td>
</tr>
<tr>
<td>MPDL-3280A NSCLC - 85</td>
<td>66% 11%</td>
<td>Fatigue – 20% Nausea – 14% ↓ appetite – 10%</td>
<td>NR 1%</td>
<td>All – NR No Grade 3-5</td>
</tr>
</tbody>
</table>

Slight differences may be due to mechanism of action OR trial maturity and number of treated patients

Current Trials of PD-1 Pathway Inhibitors

- MPDL-3280A – PD-L1 positive disease
- MPDL-3280A – PD-L1 antibody versus taxotere in the second line treatment setting
- MK-3475 – Taxotere versus anti-PD-1 antibody in the second line treatment setting
- MK-3475 – Single agent
- Nivolumab – First line trial in metastatic disease
- Other Phase I trials – MEDI-4736, Combination trials
- Phase 3 trials of Nivolumab vs. Taxotere have completed enrollment
PD-L1 testing

Positive PD-L1 staining in lung cancer (GNE/Roche PD-L1 IHC)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Estimated PD-L1 Prevalence (≈ %)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC (SCC)</td>
<td>50</td>
</tr>
<tr>
<td>NSCLC (adenocarcinoma)</td>
<td>45</td>
</tr>
</tbody>
</table>
Expression of PD-L1: Required for Clinical Response to PD-1 Blockade

B7-H1 staining patterns (clone 5H1)

- Negative
  - 0/1 responders

- Cytosolic
  - 0/4 responders

- Membranous
  - 3/4 responders

MDX-1106-01: 9 JHU pts with pre-Rx biopsies

J. Taube and S. Topalian, Brahmer J et al JCO 2010
## Objective Response Rates by PD-L1 Expression in Patients with Solid Tumors

<table>
<thead>
<tr>
<th>Rx Antibody</th>
<th>Testing Method</th>
<th>N</th>
<th>PD-L1 Positive RR</th>
<th>PD-L1 Negative RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>Manual staining – 5H1 5% cutoff Tumor staining</td>
<td>49</td>
<td>13/31 42%</td>
<td>0/18 0%</td>
</tr>
<tr>
<td>Topalian 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Dako automated 5% cutoff Tumor staining</td>
<td>38</td>
<td>7/17 41%</td>
<td>3/21 14%</td>
</tr>
<tr>
<td>Grosso 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPDL3280A</td>
<td>Automated Genentech Roche Dx IHC 1% cutoff Tumor immune cell staining</td>
<td>103</td>
<td>13/36 36%</td>
<td>9/67 13%</td>
</tr>
<tr>
<td>Herbst 2013</td>
<td></td>
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</tr>
</tbody>
</table>

### MPDL-3280A Phase I – NSCLC PD-L1 Staining and Response

<table>
<thead>
<tr>
<th>Diagnostic Population(^a) (n = 53)</th>
<th>ORR(^b) % (n/n)</th>
<th>PD Rate % (n/n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC 3</td>
<td>83% (5/6)</td>
<td>17% (1/6)</td>
</tr>
<tr>
<td>IHC 2 and 3</td>
<td>46% (6/13)</td>
<td>23% (3/13)</td>
</tr>
<tr>
<td>IHC 1/2/3</td>
<td>31% (8/26)</td>
<td>38% (10/26)</td>
</tr>
<tr>
<td>All Patients(^c)</td>
<td>23% (12/53)</td>
<td>40% (21/53)</td>
</tr>
</tbody>
</table>

\(^a\) IHC 3: ≥ 10% tumor immune cells positive for PD-L1 (IC+); IHC 2 and 3: ≥ 5% tumor immune cells positive for PD-L1 (IC+); IHC 1/2/3: ≥ 1% tumor immune cells positive for PD-L1 (IC+); IHC 0/1/2/3: all patients with evaluable PD-L1 tumor IC status.  
\(^b\) ORR includes investigator-assessed unconfirmed and confirmed PR.  
\(^c\) All patients includes patients with IHC 0/1/2/3 and 7 patients have an unknown diagnostic status. Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.

Soria J et al ECC 2013
Questions Regarding PD-L1 testing

- Assay limitations
  - Requirement to assess membrane B7-H1 protein (IHC)
  - Differing commercially available antibodies
  - What is important? Tumor vs. Stroma or Both?
- Archived versus fresh biopsy – How old of a biopsy is too old?
- Heterogeneity in expression within tumor tissue – Did you biopsy the right spot?
- Is the presence and composition of TILS required?
- Is PD-L1 positivity a Predictor of response and / or Prognostic?
PD-L1 (B7-H1) Expression and Inflammation: Implications for Mechanisms and Therapy

*Implications for combination therapy with other checkpoint inhibitors, chemotherapy, targeted therapy, and vaccines
Combinations with PD-1 Checkpoint Inhibitors

- **Other co-inhibitory pathways**
  - CTLA-4, TIM-3, LAG-3

- **Co-stimulatory pathways**
  - OX40, 4-1BB, GITR

- **Standard of care**
  - Chemotherapy, TKI, XRT

- **Cancer vaccines**

- **Epigenetic therapy**
Combination epigenetic therapy

Normal

Open promoter chromatin (euchromatic state)

p16, VHL, E-cad, etc.

Cancer

Closed promoter chromatin (heterochromatic state)

Synergy

Entinostat

Azacitidine
Epigenetic lung cancer study - trial schema

- Single-arm phase II
- Simon two-stage design
- 5AC dosing = 40 mg/m² SQ daily on days 1-6 and 8-10
- Entinostat dosing = 7 mg PO days 3 & 10
- Cycle length = 28 days
- 3% RR, Median Survival 8.6 months

Juergens R et al Cancer Disc 2011
Synergy between Epigenetic Modulation and PD-1 pathway blockade - Unleashing the Perfect Storm against Tumors

**AZA/HDACi Rx**

**Tumor**

- **De novo antigen expression:** ie C-T Antigens

**T cells**

- **De-repression of γ-IFN promoter in tolerant T cells**

**Intratumoral pro-inflammatory responses:** IL-1, IL-18, IFN pathway, HLA

**Adaptive Resistance:** ↑ PD-L1

**Enhanced Anti-tumor Response**

**PD-1 Blockade**

**↑ PD-1 from promoter demethylation**

**PD-1 Blockade**
Epigenetic Priming Study Design

Study population

Metastatic NSCLC
1 – 2 prior therapies
ECOG PS 0 - 1

Biopsy

Epigenetic priming

Azacitidine 40 mg/m2 SC d 1-6, 8-10
Entinostat 7mg PO
days 3 + 10
28 day cycle × 2

Biopsy

Nivolumab

Nivolumab 3 mg/kg IV q 2 weeks
Until progression

Nivolumab 3 mg/kg IV q 2 weeks
Until progression
Conclusions

- PD-1/PD-L1 checkpoint inhibitors have promising activity in NSCLC
- Checkpoint inhibitors have a unique set of side effects consistent with the immune mechanism of action.
- Patient selection (biomarker) is being evaluated
- Randomized studies are ongoing
- The future of immunotherapy in NSCLC may be in determining the mechanism of immune evasion in each patient
Acknowledgements

PD-1 / PD-L1 Trial Team: Hopkins
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UAD Clinical Research Team