Anti-PD1 antibodies: The Arrival of Immunotherapy to Lung Cancer

November 10, 2012

Scott Gettinger, MD
Yale Cancer Center
**Tumor antigen**

TUMOR

Dendritic cell

T cell clonal expansion

perforin granzyme

cytokines

Activated T cell

MHC

Resting T cell

TCR

CD28

LYMPH NODE

cytokines

perforin

granzyme

TUMOR

Dendritic cell

T cell clonal expansion

perforin granzyme

cytokines

Activated T cell

MHC

Resting T cell

TCR

CD28

LYMPH NODE

cytokines

perforin

granzyme

TUMOR

Dendritic cell

T cell clonal expansion

perforin granzyme

cytokines

Activated T cell

MHC

Resting T cell

TCR

CD28

LYMPH NODE

cytokines

perforin

granzyme

TUMOR

Dendritic cell

T cell clonal expansion

perforin granzyme

cytokines

Activated T cell

MHC

Resting T cell

TCR

CD28

LYMPH NODE

cytokines

perforin

granzyme

TUMOR

Dendritic cell

T cell clonal expansion

perforin granzyme

cytokines

Activated T cell

MHC

Resting T cell

TCR

CD28

LYMPH NODE

cytokines

perforin

granzyme

TUMOR

Dendritic cell

T cell clonal expansion

perforin granzyme

cytokines

Activated T cell

MHC

Resting T cell

TCR

CD28

LYMPH NODE

cytokines

perforin

granzyme
Ipilimumab – Y

T cell inactivation

T cell activation

LYMPH NODE

Dendritic cell

T cell

CTLA4

MHC

B7

CD28

TCR
Programmed Death Receptor 1 (PD1)/ B7-H1 Pathway

TUMOR

Inflammation (e.g. IFNγ)

PD1

PDL1

T cell inactivation

cytokines

anti-PDL1

anti-PD1
Programmed Death Receptor 1 (PD1)/ B7-H1 Pathway

Inflammation (e.g. IFNγ)

PD1/ PDL1 Blockade in Clinical Trials

Anti-PD1
- BMS-936558
- MK3475
- CT-011
- AMP-224

Anti-PDL1
- BMS-936559
- MPDL3280A
- MEDI4736

TUMOR
TUMOR

Inflammation (e.g. IFNγ)

T Regulatory cell

PDL1

PD1

Cytotoxic T cell

B7

Cytotoxic T cell

T cell inactivation

Natural Killer cell

B cell
PD1 vs. PDL1 Blockade

Tumor cell/ APC

? Anti-apoptotic signal

PDL1

Anti-PD1

B7

PD1

Anti-PDL1

PDL1

PDL2

? Anti-apoptotic signal

T cell
Role of PD-1 Pathway in NSCLC

- PD-1 expression on tumor infiltrating lymphocytes (TILs) in NSCLC has shown decreased cytokine production and decreased effector function\(^1,2\)
- Increase of PD-L1 expression on tumor cells correlated with a decrease in the number of TILs in the same region\(^2,3,4\)
- Preliminary correlation of PD-L1 expression with response to anti-PD-1\(^5\)
- **BMS-936558 (MDX-1106/ONO-4538)**
  - Fully human IgG4 anti-human PD-1 blocking Ab (No ADCC/CDCC)\(^5\)
  - High affinity for PD-1 (\(K_D \sim 3\) nM), blocks binding of both PD-L1 (B7-H1) and PD-L2 (B7-DC)

CA209-003: Phase 1, Multidose Regimen Study

8-wk treatment cycle

Day 1       15         29        43       57

Follow-up every 8 wks x 6 (48 wks)

Rapid PD or clin. deterioration

Unacceptable toxicity

CR/PR/SD or PD but clinically stable

Treat to confirmed CR, worsening PD, unacceptable toxicity, or 12 cycles (96 wks)

Off Study

* Dose administered IV Q2wk

Doses tested for NSCLC: 1, 3, 10 mg/kg

Eligibility: Advanced MEL, RCC, NSCLC, CRC, or CRPC with PD after 1-5 systemic therapies; ECOG 0-1
BMS-936558 (Anti-PD-1): Expansion Cohorts for NSCLC

Eligible NSCLC Pts

Randomized between 3 dose levels

Accrual completed (Dec. 2011)
• Patient assessment ongoing

Current analysis for patients treated through July 2012
– 122 patients with NSCLC were evaluable for clinical activity
## 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&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>NSCLC</td>
</tr>
<tr>
<td><strong>No. (%) of Patients, All Doses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>220 (72)</td>
<td>84 (66)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>78 (26)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Rash</td>
<td>41 (14)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (12)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>31 (10)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (8)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Appetite ↓</td>
<td>24 (8)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Hemoglobin ↓</td>
<td>18 (6)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16 (5)</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

<sup>a</sup>AEs occurring in ≥5% of the total population; protocol algorithms were used to manage AE’s.

<sup>b</sup>Pneumonitis occurred in <5% of the total population.

<sup>c</sup>Drug-related renal failure/nephritis occurred in 1% of the total population, with no grade 3-4 drug-related events based on an analysis on July 3, 2012.

<sup>d</sup>The most common grade 3-4 AEs were fatigue, pneumonitis, and elevated AST (2 pts each). An additional 16 grade 3-4 drug-related AEs were observed and 1 or more occurred in a single patient.
Clinical Activity of BMS-936558 in NSCLC Patients

<table>
<thead>
<tr>
<th>Pop</th>
<th>Dose (mg/kg)</th>
<th>Pts n</th>
<th>ORR n (%)</th>
<th>Median DOR months (95%CI) [Individual pt response]</th>
<th>SD ≥24 wk n (%)</th>
<th>PFSR at 24 wk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL NSCLC</td>
<td>1-10</td>
<td>122</td>
<td>20 (16)</td>
<td>NE Range:1.9+ to 30.8+</td>
<td>11 (9)</td>
<td>33</td>
</tr>
<tr>
<td>NSCLC</td>
<td>1</td>
<td>31</td>
<td>1 (6)</td>
<td>NE [11.0+]</td>
<td>3 (10)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>33</td>
<td>9 (27)</td>
<td>NE [2.3 +, 3.7+, 5.5+, 6.7+, 9.2+, 9.4+, 13.3+, 15.8, 30.8+]</td>
<td>3 (9)</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>58</td>
<td>10 (17)</td>
<td>9.8 (4.2 – NE) [1.9+, 1.9+, 3.7, 4.2, 5.6+, 6.7, 7.4+, 9.8, 13.0+, 18.5 +]</td>
<td>5 (9)</td>
<td>31</td>
</tr>
</tbody>
</table>

- ORR was assessed using modified RECIST v1.0
- 6 NSCLC patients showed a non-conventional pattern of response and were not classified as responders by the conventional RECIST

DOR = duration of response; NE = not currently estimable by Kaplan-Meier due to insufficient follow-up; SD = stable disease; ORR = objective response rate; PFSR = progression-free survival rate; PR = partial response
Changes in Target Lesions Over Time in NSCLC Patients Treated with 3 mg/kg BMS-936558
Response of Metastatic NSCLC (BMS-936558, 10mg/kg)

- Initial progression of pulmonary lesions in a patient with EGFR mutant (del19, T790M) NSCLC, followed by regression
- Prior treatment with gemcitabine/carboplatin, erlotinib, erlotinib + LBH589, and pemetrexed
- 58 y/o ex smoker with squam NSCLC
- 4 prior tx for Stage IV disease
- Left flank pain resolved within 2 mos

- Response Ongoing after completing 2 years of BMS-936558 in June 2012
## Clinical Activity by Histology

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BMS-936558 Dose, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td><em><em>ORR, No. patients</em> (%)</em>*</td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>0 (0%) n=13</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>1 (6%) n=18</td>
</tr>
<tr>
<td><strong>SD ≥24 wk, No. patients (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>1 (6%)</td>
</tr>
<tr>
<td><strong>PFSR at 24 wk, (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>37</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>19</td>
</tr>
</tbody>
</table>

*1 patient of unknown histology who received 1mg/kg had an OR.
Correlation of PD-L1 Expression in Pretreatment Tumor Biopsies with Clinical Outcomes

Percentage of Patients

<table>
<thead>
<tr>
<th></th>
<th>CR/PR</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 (+)</td>
<td>9/25</td>
<td>16*/25</td>
</tr>
<tr>
<td>PD-L1 (-)</td>
<td>0/17</td>
<td>17/17</td>
</tr>
</tbody>
</table>

* 2 pts still under evaluation

P = 0.006

Patient samples: 18 MEL, 10 NSCLC, 7 CRC, 5 RCC, 2 CRPC

- 1 PR out 5 pts with PD-L1+ NSCLC
- No responses for 5 pts with PD-L1- NSCLC

PD-L1 expression by IHC in 61 pretreatment tumor biopsies across tumor types from 42 pts

NSCLC
Phase 3 Study of Anti-PD-1 Compared to Docetaxel in 2nd-Line Advanced/Metastatic Squamous Cell NSCLC (CA209-017/NCT01642004)

Primary Endpoints
- ORR
- OS

Secondary Endpoints
- PFS
- ORR and OS in PD-L1+ vs PD-L1− subgroups
- Duration of OR
- Time to OR
- Proportion of patients exhibiting disease-related symptom progression per Lung Cancer Symptom Scale

Key Eligibility Criteria
- ≥ 18 years of age
- Stage IIIB/IV squamous cell NSCLC or recurrent disease following RT or surgical resection
- Prior Pt-containing chemotherapy
- ECOG PS ≤ 1
- Formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation

Start Date: August, 2012
Estimated Study Completion Date: August 2014
Estimated Primary Completion Date: August 2014
Status: Not yet recruiting
Study Director: BMS
Phase 3 Study of Anti-PD-1 Compared to Docetaxel in 2nd/3rd-Line Advanced/Metastatic Non-Squamous Cell NSCLC
(CA209-057/NCT01673867)

Phase 3 Trial
Stage IIIB/IV non-squamous NSCLC
N=574

Docetaxel
75 mg/m² IV Q3W

Anti-PD-1
3 mg/kg IV Q2W

Treat until progression or unacceptable toxicity or withdrawal of consent

Overall Survival (OS)

Primary Endpoints
• OS

Secondary Endpoints
• PFS
• ORR
• QoL

Key Eligibility Criteria
• ≥ 18 years of age
• Stage IIIB/IV non-squamous NSCLC
• Prior Pt-containing chemotherapy (2nd-line) required: additional TKI therapy allowed (3rd-line)
• Patient may have received continuous or switch maintenance with pemetrexed, erlotinib or bevacizumab post Pt-containing chemotherapy
• ECOG PS ≤ 1
• Formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation

Start Date: TBD
Estimated Study Completion Date: TBD
Estimated Primary Completion Date: TBD
Status: TBD
Study Director: BMS

ECOG PS, Eastern Cooperative Oncology Group Performance Status; ORR, Objective response rate;
OS, Overall survival; PFS, Progression-free survival; Pt, Platinum; QoL, Quality of life; TKI, Tyrosine kinase inhibitor
Phase 1 Multi-arm Safety Study of Anti-PD-1 in Combination With Chemotherapy or as Monotherapy in Patients With Stage IIIB/IV NSCLC: ARMS A-C (CA209-012/ NCT01454102)

**Primary Endpoints**
- Safety and tolerability

**Secondary Endpoints**
- ORR
- PFS Rate

**Key Eligibility Criteria**
- ≥ 18 years of age
- Stage IIIB/IV NSCLC
- Chemotherapy treatment-naïve; Prior use of EGFR TKI is acceptable
- ECOG PS ≤ 1
- Collection of tumor tissue (archival or recent)

**Start Date:** April 2011
**Estimated Study Completion Date:** December 2013
**Estimated Primary Completion Date:** December 2013
**Status:** Currently Recruiting Participants
**Study Director:** BMS

---

CARB, Carboplatin; CIS, Cisplatin; D, Day; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, Epidermal growth factor receptor; GEM, Gemcitabine; ORR, Objective response rate; PAC, Paclitaxel; PEM, Pemetrexed; PFS, Progression-free survival; TKI, Tyrosine kinase inhibitor
Phase 1 Multi-arm Safety Study of Anti-PD-1 in Combination With Chemotherapy or as Monotherapy in Patients With Stage IIIB/IV NSCLC: ARMS D-F (CA209-012/ NCT01454102)

Phase 1 Trial
Stage IIIB/IV NSCLC
N= 108 (across all arms of trial)

ARM D
BEV maintenance
15 mg/kg IV
D1 Cycle 1 then
Q3W Until PD or
discontinuation due
to toxicity
Anti-PD-1
5 mg/kg IV
D1 Q3W Until PD or
discontinuation due
to toxicity

ARM E
ERL 150 mg/day
Until PD or
discontinuation due
to toxicity
Anti-PD-1
3 mg/kg IV Q2W
Until PD or
discontinuation due
to toxicity

ARM F
Anti-PD-1
3 mg/kg IV Q2W
Until PD or
discontinuation due
to toxicity

Primary Endpoints
- Safety and tolerability

Secondary Endpoints
- ORR
- PFS Rate

Key Eligibility Criteria
- ≥ 18 years of age
- Stage IIIB/IV NSCLC
- Chemotherapy treatment-naïve (except Arm D); Prior use of EGFR TKI is acceptable
- ECOG PS ≤ 1
- Collection of tumor tissue (archival or recent)

Start Date: April 2011
Estimated Study Completion Date: December 2013
Estimated Primary Completion Date: December 2013
Status: Currently Recruiting Participants
Study Director: BMS

BEV, Bevacizumab, CARB, Carboplatin; CIS, Cisplatin; D, Day; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, Epidermal growth factor receptor; ERL, Erlotinib; ORR, objective response rate; PD, Progressive disease; PFS, progression-free survival; TKI, tyrosine kinase inhibitor
Study Design: First-in-Human Trial of BMS-936559 (anti-PD-L1 Ab)

6-wk Treatment Cycle

- Rapid PD or Clinical deterioration \(\rightarrow\) Off Study
- Unacceptable toxicity \(\rightarrow\) Follow-up
- CR/PR/SD or PD but clinically stable \(\rightarrow\) Treat to 16 cycles (96 wk total)

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)

BMS-936559 (Anti-PD-L1): Expansion Cohorts for NSCLC

Eligible NSCLC Pts
Randomized between 3 dose levels

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

Accrual ongoing
## BMS-936559-Related Adverse Events

<table>
<thead>
<tr>
<th>Drug-Related Adverse Event *</th>
<th>BMS-936559</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Gr</td>
<td>Gr 3-4</td>
</tr>
<tr>
<td>No. Patients per Cohort (%)</td>
<td>Total (N=207)</td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>126 (61)</td>
<td>19 (9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33 (16)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>21 (10)</td>
<td>1(1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19 (9)</td>
<td>-</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15 (7)</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>14 (7)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (6)</td>
<td>-</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12 (6)</td>
<td>-</td>
</tr>
</tbody>
</table>

* AEs occurring in ≥ 5% of total population
- 12 of 207 (6%) discontinued treatment due to BMS-936559 related AE
- Potential immune-related events in 39% (including rash, hypothyroidism, hepatitis and one case each of sarcoidosis, endophthalmitis, diabetes mellitus and myasthenia gravis)
Clinical Activity of BMS-936559 in NSCLC Subset of the 49 Response-Evaluable Patients

<table>
<thead>
<tr>
<th>Tumor Type*</th>
<th>Dose (mg/kg)</th>
<th>No. Patients (N=49/160)</th>
<th>ORR** 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>NSCLC</td>
<td>1−10</td>
<td>49</td>
<td>5 (10)</td>
<td>9.8 to 16.6+</td>
<td>6 (12)</td>
<td>31</td>
</tr>
<tr>
<td>All Squamous</td>
<td>13</td>
<td>13</td>
<td>1 (8)</td>
<td>-</td>
<td>3 (23.1)</td>
<td>43</td>
</tr>
<tr>
<td>All Non-Squamous</td>
<td>36</td>
<td>36</td>
<td>4 (11)</td>
<td>-</td>
<td>3 (8)</td>
<td>26</td>
</tr>
</tbody>
</table>

**ORR was assessed using modified RECIST v1.0 criteria
ORR = objective response rate; PFSR = progression-free survival rate; SD = stable disease

Patnaik et al, ASCO 2012: Phase I Study of MK-3475 (anti-PD-1) in Patients with Advanced Solid Tumors

<table>
<thead>
<tr>
<th>Dose</th>
<th>Disease</th>
<th>Best Response</th>
<th>Duration on Study (Wks)</th>
<th>Number of Cycles Received</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/kg</td>
<td>Rectal</td>
<td>PD</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>PD</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Carcinoid</td>
<td>SD</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td><strong>NSCLC</strong></td>
<td><strong>uPR</strong></td>
<td>18</td>
<td><strong>7</strong></td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>Rectal</td>
<td>PD</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>cPR**</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Soft tissue sarcoma</td>
<td>SD</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td><strong>NSCLC</strong></td>
<td>SD</td>
<td>22</td>
<td><strong>10</strong></td>
</tr>
<tr>
<td></td>
<td><strong>NSCLC</strong></td>
<td>PD</td>
<td>8</td>
<td><strong>3</strong></td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>SD</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Neuroendocrine</td>
<td>SD</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Colon</td>
<td>PD</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>cPR</td>
<td>24 (on-going)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Karposi’s sarcoma</td>
<td>PD</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>PD</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td><strong>NSCLC</strong></td>
<td>PD</td>
<td>1</td>
<td><strong>1</strong></td>
</tr>
<tr>
<td></td>
<td><strong>NSCLC</strong></td>
<td>PD</td>
<td>4</td>
<td><strong>1</strong></td>
</tr>
</tbody>
</table>

*8 week scan=30% tumor reduction, PD at Wk 16  ** Patient d/c’ed due to AE (unrelated) uPR: unconfirmed PR, cPR: confirmed PR
Future Development: PD1/PDL1 Blockade

- Combination with chemotherapy/ targeted therapies/ other immunotherapies (e.g. vaccines, other immune checkpoint inhibitors)
- First line, salvage, maintenance, adjuvant, radiation
- Need for predictive biomarkers- tumor PDL1 expression, histology, Immunochip, baseline serum tumor antigen reactivity …
- Be prepared for autoimmune toxicity- manageable to date