Clinical Activity and Safety of Anti-Programmed Death-1 (PD-1) (BMS-936558/MDX-1106/ONO-4538) in Patients (pts) With Previously Treated, Metastatic Renal Cell Carcinoma (mRCC)

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Disclosures

- **Advisory Board Participation**
  - Bristol-Myers Squibb
  - Prometheus Labs
  - Genentech
  - Pfizer

- **Research Funding**
  - Prometheus Labs
# Six Years of Impressive Progress

<table>
<thead>
<tr>
<th>Setting</th>
<th>Phase III</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st-Line Therapy</strong></td>
<td>Good or Intermediate Risk*</td>
<td>Sunitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pazopanib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bevacizumab + IFNα</td>
</tr>
<tr>
<td>Poor Risk*</td>
<td>Temsirolimus</td>
<td>Sunitinib</td>
</tr>
<tr>
<td><strong>2nd-Line Therapy</strong></td>
<td>Prior Cytokine</td>
<td>Sorafenib</td>
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<tr>
<td></td>
<td></td>
<td>Sunitinib or</td>
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<tr>
<td></td>
<td></td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Prior VEGFR Inhibitor</td>
<td>Everolimus Axitinib</td>
<td>Clinical Trials</td>
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<tr>
<td>Prior mTOR Inhibitor</td>
<td></td>
<td>Clinical Trials</td>
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</table>

*Does Immunotherapy have any role?*
There are positive and negative signal pathways that regulate T cells. The Programmed Death (PD)-1/PD-L1 ligand pathway is an immune checkpoint that suppresses activated T cells and promotes tolerance. 

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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, PD-L1 expression has been shown to be associated with adverse clinical/pathologic features, including\(^3\):
  - More aggressive disease
  - Shorter survival

Anti-PD-1: Blocking T cell Suppression

Activation (cytokines, proliferation, migration)

Suppression
- Anergy
- Exhaustion
- T cell death

BMS-936558 (MDX-1106/ONO-4538)

- Fully human IgG4 anti-human PD-1-blocking Ab\(^1\)
- No known Fc function (ADCC, CDC)
- High affinity for PD-1 (KD ~3 nM), blocks binding of both PD-L1 (B7-H1) and PD-L2 (B7-DC)
- In the first-in-human, single-dose, dose-escalation study, BMS-936558 exhibited a manageable safety profile and preliminary evidence of clinical activity in patients with treatment-refractory solid tumors\(^1\)

Study Design: Phase I Multi-dose Regimen

8-wk treatment cycle

- Rapid PD or clin. deterioration → Off Study
- Unacceptable toxicity → Follow-up every 8 wks x 6 (48 wks)
- CR/PR/SD or PD but clinically stable → Treat to confirmed CR, worsening PD, unacceptable toxicity, or 12 cycles (96 wks)

* Dose administered IV Q2wk

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

- Primary
  - Assessment of safety and tolerability of BMS-936558

- Secondary/Exploratory objectives include preliminary efficacy of BMS-936558 and pharmacokinetics

- Accrual completed Dec. 2011; patient assessment ongoing (N=304)

- 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

- Antitumor activity was seen in NSCLC, melanoma and RCC

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RCC Cohorts

- **Dose Expansion**
  - 16 patients enrolled at 10 mg/kg followed by
  - 18 patients enrolled at 1 mg/kg
  - Assessment of antitumor activity
  - Assessment of safety and tolerability of BMS-936558

- **Current analysis for patients as of July 3, 2012**
  - Safety results are presented for the overall (N=304) and RCC (n=34) populations
  - Clinical activity is presented for the RCC population
Baseline Characteristics of RCC Patients

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>n=34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, (range), yr</td>
<td>58 (35-74)</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>26 (76)</td>
</tr>
<tr>
<td>ECOG PS, no. (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13 (38)</td>
</tr>
<tr>
<td>1</td>
<td>21 (62)</td>
</tr>
<tr>
<td>Lesions at baseline, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Liver</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Lung</td>
<td>30 (88)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>28 (82)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (59)</td>
</tr>
</tbody>
</table>

- >40% received 3 or more prior therapies
- >70% received anti-angiogenic therapy
## BMS-936558-Related Adverse Events

<table>
<thead>
<tr>
<th>Drug-Related Adverse Event</th>
<th>All Grades</th>
<th></th>
<th>Graded 3-4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tot Pop*,†</td>
<td>RCC</td>
<td>Tot Pop</td>
<td>RCC</td>
</tr>
<tr>
<td><strong>No. (%) of Patients, All Doses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>220 (72)</td>
<td>29 (85)</td>
<td>45 (15)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>78 (26)</td>
<td>14 (41)</td>
<td>5 (2)</td>
<td>—</td>
</tr>
<tr>
<td>Rash</td>
<td>41 (14)</td>
<td>9 (27)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (12)</td>
<td>5 (15)</td>
<td>3 (1)</td>
<td>—</td>
</tr>
<tr>
<td>Pruritus</td>
<td>31 (11)</td>
<td>6 (18)</td>
<td>1 (0.3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (8)</td>
<td>2 (6)</td>
<td>1 (0.3)</td>
<td>—</td>
</tr>
<tr>
<td>Appetite ↓</td>
<td>24 (8)</td>
<td>3 (9)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hemoglobin ↓</td>
<td>18 (6)</td>
<td>2 (6)</td>
<td>1 (0.3)</td>
<td>—</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16 (5)</td>
<td>3 (9)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*AEs occurring in ≥5% of the total population.
† 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.
‡ The most common grade 3-4 AEs were respiratory system disorders (2 pts) and hypophosphatemia (2 pts). An additional 10 grade 3-4 drug-related AEs were observed and one or more occurred in a single patient.
Summary of Key Safety Results

● In the total treated patient population across all tumor types:
  – Grade 3-4 drug-related AEs occurred in 15%
  – Discontinuation of treatment due to drug-related AE occurred in 18/304 (6%) of patients
  – Three drug-related deaths occurred in patients with pneumonitis (2 with NSCLC and 1 with CRC)

● In RCC patients:
  – Safety profile was similar to the total treated patient population
  – Grade 3-4 drug-related AEs occurred in 21% of pts
Clinical Activity of BMS-936558 in RCC Patients

<table>
<thead>
<tr>
<th>Population</th>
<th>Dose (mg/kg)</th>
<th>Patients (n)</th>
<th>Median Duration of Response Months (95% CI)</th>
<th>ORR n (%)</th>
<th>SD ≥24 wk n (%)</th>
<th>PFSR at 24 wk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL RCC</td>
<td>1, 10</td>
<td>34</td>
<td>—</td>
<td>10 (29)</td>
<td>9 (27)</td>
<td>58</td>
</tr>
<tr>
<td>RCC</td>
<td>1</td>
<td>18</td>
<td>12.9 (9.2 – NE)</td>
<td>5 (28)</td>
<td>4 (22)</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>16</td>
<td>12.9 (8.4 – NE)</td>
<td>5 (31)*</td>
<td>5 (31)</td>
<td>67</td>
</tr>
</tbody>
</table>

*One CR
NE, currently not estimable by Kaplan-Meier due to insufficient follow-up

- ORR was assessed using modified RECIST v1.0
- 3 additional RCC patients had a nonconventional pattern of response and were not classified as responders by the conventional RECIST
Changes in Target Lesions Over Time in RCC Patients Treated With 1 mg/kg BMS-936558

* line represents the protocol-specified maximum duration of active therapy (96 weeks)

- Shorter study duration in 1 mg/kg cohort is consistent with enrollment occurring after the 10 mg/kg cohort (except for the 2 pts enrolled during dose escalation)
Changes in Target Lesions Over Time in RCC Patients Treated With 10 mg/kg BMS-936558

* line represents the protocol-specified maximum duration of active therapy (96 weeks)
Partial Regression of Metastatic RCC in a Patient Treated with 1 mg/kg BMS-936558

- 57-year-old patient had developed progressive disease after receiving sunitinib, temsirolimus, sorafenib, and pazopanib
- Currently in cycle 6 with ongoing PR

Courtesy of C. Drake, Johns Hopkins Univ
Partial Regression of Metastatic RCC in a Patient Treated with 1 mg/kg BMS-936558: Durable Benefit off Therapy

- 48-year-old patient with low volume but poorly differentiated mRCC
- Developed progressive disease after sunitinib, sorafenib, and thoracic surgery
- Therapy held after 3 cycles due to near CR
- Response has continued for 3 years, while off therapy

Courtesy of M. Sznol, Yale Cancer Center
Correlation of PD-L1 Expression in Pretreatment Tumor Biopsies with Clinical Outcomes

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

- **CR/PR**
- **Non-responders**

* $P=0.006$

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

* 2 pts still under evaluation

Topalian et al NEJM, 2012
Summary

- BMS-936558 can be administered safely in an outpatient setting to pretreated RCC patients, while demonstrating durable clinical benefit

- Blockade of the PD-1 pathway may represent an important, new target for RCC immunotherapy

- Preliminary data correlating PD-L1 expression in pretreatment tumor biopsies with clinical outcomes is being further explored

- Clinical registration trials of BMS-936558 in patients with RCC are planned
Acknowledgments

- The patients and their families
- The study sites enrolling patients to the trial
- Support for this work from Bristol-Myers Squibb and Ono Pharmaceutical Company, Ltd.
- All authors contributed to and approved the presentation; medical writing assistance in the preparation of the slides was provided by StemScientific funded by Bristol-Myers Squibb
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