Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic urothelial bladder cancer (UBC)

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Disclosures

- Dr. Joaquim Bellmunt
  - Consultant: Genentech, Merck, Oncogenex, Pierre Fabre, Astellas, BMS, J&J
Metastatic UBC

- High unmet need with no FDA-approved therapies for relapse after platinum chemo
  - Vinflunine approved in EU with no significant OS benefit in ITT population
- Median OS ≈ 7 months; PFS ≈ 3 months for 2L UBC¹
- Patients tend to be elderly with impaired renal function
- High mutational complexity rates due to tobacco/environmental carcinogen exposure²⁻⁴
- Potential for many neo-antigens to be seen as foreign by host immune system²⁻⁴

MPDL3280A is an Engineered Anti-PD-L1 Antibody That Inhibits the Binding of PD-L1 to PD-1 and B7.1

- Inhibiting PD-L1/PD-1 and PD-L1/B7.1 interactions can restore antitumor T-cell activity and enhance T-cell priming

- MPDL3280A leaves the PD-L2/PD-1 interaction intact, maintaining immune homeostasis and potentially preventing autoimmunity

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PD-L1 Prevalence in Solid Tumors (Pre-screened Patients)

<table>
<thead>
<tr>
<th>Indication</th>
<th>PD-L1+ Tumor-Infiltrating Immune Cells (ICs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UBC (n = 205)</td>
<td>27%</td>
</tr>
<tr>
<td>RCC (n = 88)</td>
<td>25%</td>
</tr>
<tr>
<td>NSCLC (n = 184)</td>
<td>26%</td>
</tr>
<tr>
<td>Melanoma (n = 59)</td>
<td>36%</td>
</tr>
</tbody>
</table>

Based on staining of archival tumor tissue from patients prescreened in MPDL3280A Phase Ia study.
PD-L1+: IHC 3 (≥ 10% of ICs PD-L1+) or IHC 2 (≥ 5% but < 10% of ICs PD-L1+).
PD-L1−: IHC 1 (≥ 1% but < 5% ICs PD-L1+) or IHC 0 (<1% ICs PD-L1+).
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MPDL3280A Phase Ia

Phase Ia Expansion Ongoing

- RCC
  1. All-comers
  2. PD-L1+ patients

- Melanoma
  All-comers

- NSCLC
  1. All-comers
  2. PD-L1+ patients

- Other Tumor Types
  1. PD-L1+ patients
  2. All-comers

- UBC (15 mg/kg)
  1. PD-L1+ patients
  2. All-comers

MPDL3280A administered by IV q3w for up to 16 cycles

Key Eligibility Criteria

Measurable disease per RECIST v1.1
ECOG PS 0 or 1

^ Primarily recruited PD-L1–negative patients.
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## MPDL3280A: UBC Baseline Characteristics

*Efficacy-evaluable population with UBC in Phase I expansion*

<table>
<thead>
<tr>
<th>Characteristics of Patients With UBC</th>
<th>PD-L1+ (IC) (n = 33)</th>
<th>PD-L1– (IC) (n = 36)</th>
<th>All (n = 70^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>67 y (42-89)</td>
<td>63 y (36-81)</td>
<td>65 y (36-89)</td>
</tr>
<tr>
<td>(\geq 65)</td>
<td>67%</td>
<td>44%</td>
<td>56%</td>
</tr>
<tr>
<td>Male</td>
<td>85%</td>
<td>61%</td>
<td>73%</td>
</tr>
<tr>
<td>ECOG PS 0/1</td>
<td>50%/50%(^b)</td>
<td>39%/61%</td>
<td>43%/57%(^c)</td>
</tr>
<tr>
<td>Site of primary tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>88%</td>
<td>78%</td>
<td>81%</td>
</tr>
<tr>
<td>Renal pelvis</td>
<td>3%</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Ureter</td>
<td>3%</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>Urethra</td>
<td>6%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral/liver</td>
<td>64%/30%</td>
<td>83%/33%</td>
<td>74%/33%</td>
</tr>
<tr>
<td>Prior treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystectomy or nephroureterectomy</td>
<td>76%</td>
<td>61%</td>
<td>69%</td>
</tr>
<tr>
<td>Platinum-based chemotherapy</td>
<td>94%</td>
<td>89%</td>
<td>91%</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>91%</td>
<td>67%</td>
<td>79%</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>21%</td>
<td>44%</td>
<td>33%</td>
</tr>
<tr>
<td>(\leq 3) months from last chemo</td>
<td>29%(^d)</td>
<td>53%(^b)</td>
<td>41%(^e)</td>
</tr>
<tr>
<td>Hemoglobin level &lt; 10 g/dL</td>
<td>6%(^b)</td>
<td>26%(^f)</td>
<td>16%(^g)</td>
</tr>
<tr>
<td>GFR &lt; 60 mm/min</td>
<td>30%</td>
<td>40%(^f)</td>
<td>36%(^c)</td>
</tr>
</tbody>
</table>

\(^a\) 1 pt has unknown IHC (IC) status; \(^b\) \(n = 32\); \(^c\) \(n = 69\); \(^d\) \(n = 31\); \(^e\) \(n = 64\); \(^f\) \(n = 35\); \(^g\) \(n = 68\).

PD-L1+: IHC (IC) 2/3; PD-L1–: IHC (IC) 0/1.

Patients dosed by Jan 27, 2014 (\(\geq 12\)-wk follow-up) with measurable disease at baseline. Clinical data cutoff was Apr 21, 2014.

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# MPDL3280A: Treatment-Related AEs

*Safety-evaluable population with UBC in Phase I expansion*

<table>
<thead>
<tr>
<th>Patients With UBC</th>
<th>All Grade n (%)</th>
<th>Grade 3-4(^a) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>48 (65%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (15%)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>9 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 (7%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Chills</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Lethargy</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Additional treatment-related grade 3/4 AEs: One patient experienced an increase in alanine aminotransferase (grade 3), aspartate aminotransferase (grade 3) and gamma-glutamyltransferase (grade 4). Two additional patients (one each) experienced either thrombocytopenia (grade 3) or decreased blood phosphorus (grade 3). Clinical data cutoff was April 21, 2014. Includes events occurring in ≥ 3 patients.

- Median treatment duration 95 days (5.5 cycles)
- MPDL3280A well tolerated in patients with UBC
  - No discontinuations due to treatment-related AEs
  - No investigator-assessed immune-related toxicities reported as of the clinical cutoff
- MPDL3280A not observed to be associated with renal toxicity
- No treatment-related grade 5 AEs
### MPDL3280A: Summary of ORR in UBC

**Efficacy-evaluable population with UBC in Phase I expansion**

<table>
<thead>
<tr>
<th>PD-L1 IHC (IC)</th>
<th>ORR, Best Response % (95% CI)</th>
<th>PD-L1+ vs PD-L1− ORR, Best Response % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC 3 (n = 10)</td>
<td>60% (27, 85)</td>
<td></td>
</tr>
<tr>
<td>IHC 2 (n = 23)</td>
<td>48% (27, 68)</td>
<td>52% (34, 69)</td>
</tr>
<tr>
<td>IHC 1 (n = 24)</td>
<td>17% (6, 37)</td>
<td>14% (6, 28)</td>
</tr>
<tr>
<td>IHC 0 (n = 12)</td>
<td>8% (0, 35)</td>
<td></td>
</tr>
</tbody>
</table>

- 3 CRs (1 IHC 2, 2 IHC 3)
- Median follow-up was 6 months (range, 1+ to 12) for PD-L1+ patients and 4 months (range, 1+ to 7) for PD-L1− patients

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*Investigator-assessed ORRs (unconfirmed) per RECIST v1.1.*

1 patient with unknown IHC status not included in table.

PD-L1+: IHC (IC) 2/3; PD-L1−: IHC (IC) 0/1.

Patients dosed by Jan 27, 2014 (≥ 12-wk follow-up) with measurable disease at baseline. Clinical data cutoff was Apr 21, 2014.

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MPDL3280A: Summary of ORR in UBC

Efficacy-evaluable population with UBC in Phase I expansion

Patients with complete responses. Patients with a CR had < 100% reduction of the target lesions due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.

IC; tumor-infiltrating immune cells.

Responses are investigator assessed (unconfirmed). 7 patients are not included due to no post-baseline tumor assessments.

PD-L1+: IHC (IC) 2/3; PD-L1‒: IHC (IC) 0/1.

Patients dosed by Jan 27, 2014 (≥ 12-wk follow-up) with measurable disease at baseline. Clinical data cutoff was Apr 21, 2014.

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MPDL3280A: Duration on Study, Treatment and Response in Responding Patients

**Efficacy-evaluable population with UBC in Phase I expansion**

- 19 of 22 responding patients had ongoing responses at the time of data cutoff
- Median duration of response has not yet been reached
  - PD-L1+ patients (n = 17): range, 0.1+ to 42+ weeks
  - PD-L1− patients (n = 5): range, 6+ to 19+ weeks

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**PD-L1 IHC**

<table>
<thead>
<tr>
<th>IHC</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

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**Time on study (weeks)**

- On study
- Ongoing response
- First PR/CR
- First PD

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*IHC 3, 2, 1, 0: ≥ 10%, < 10% and ≥ 5%, < 5% and ≥ 1% and < 1% tumor-infiltrating immune cells positive for PD-L1, respectively.

Investigator-assessed ORRs (unconfirmed) per RECIST v1.1. Arrow indicates the status of no PD or no death only and has no implication on the timing.

Patients dosed by Jan 27, 2014 (≥ 12-wk follow-up) with measurable disease at baseline. Clinical data cutoff was Apr 21, 2014.

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MPDL3280A: Summary of Progression Free Survival

*Efficacy-evaluable population with UBC in Phase I expansion*

<table>
<thead>
<tr>
<th>PD-L1 IHC (IC)</th>
<th>Median PFS (range), weeks</th>
<th>PD-L1+ vs PD-L1− Median PFS (range), weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC 3 (n = 10)</td>
<td>Not reached (5 to 48+)</td>
<td>24 (5 to 50+)</td>
</tr>
<tr>
<td>IHC 2 (n = 23)</td>
<td>24 (5 to 50+)</td>
<td></td>
</tr>
<tr>
<td>IHC 1 (n = 24)</td>
<td>11 (0.1+ to 30+)</td>
<td>8 (0.1+ to 30+)</td>
</tr>
<tr>
<td>IHC 0 (n = 12)</td>
<td>7 (5 to 24+)</td>
<td></td>
</tr>
</tbody>
</table>

- Median PFS appears to be associated with PD-L1 expression

Investigator-assessed PFS per RECIST v1.1.
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Plasma Tumor Burden Markers and Association With Response to MPDL3280A

- Plasma tumor burden marker carcinoembryonic antigen (CEA) baseline expression not clearly associated with response
- CEA increase at C2D1 associated with PD
- Similar patterns observed with CA125 and CA19-9 (data not shown)
MPDL3280A: Conclusions in UBC

- MPDL3280A had high ORR of 52% observed in mostly platinum-pretreated IHC 2/3 patients with metastatic UBC
  - ORR of 14% observed in IHC 0/1 patients
  - Rapid responses seen
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  - Median PFS was 24 weeks in IHC 2/3 patients and 8 weeks in IHC 0/1 patients
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  - Only 5% of patients experienced Grade 3/4 treatment-related AEs
  - There were no grade 5 treatment-related AEs
  - Renal toxicity has not been observed in MPDL3280A-treated patients to date
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  - Only 5% of patients experienced Grade 3/4 treatment-related AEs
  - There were no grade 5 treatment-related AEs
  - Renal toxicity has not been observed in MPDL3280A-treated patients to date
- On-treatment plasma tumor burden markers, but not baseline markers, associated with response
- Additional studies of MPDL3280A in UBC are planned and ongoing (including NCT02108652)
Acknowledgments

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