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

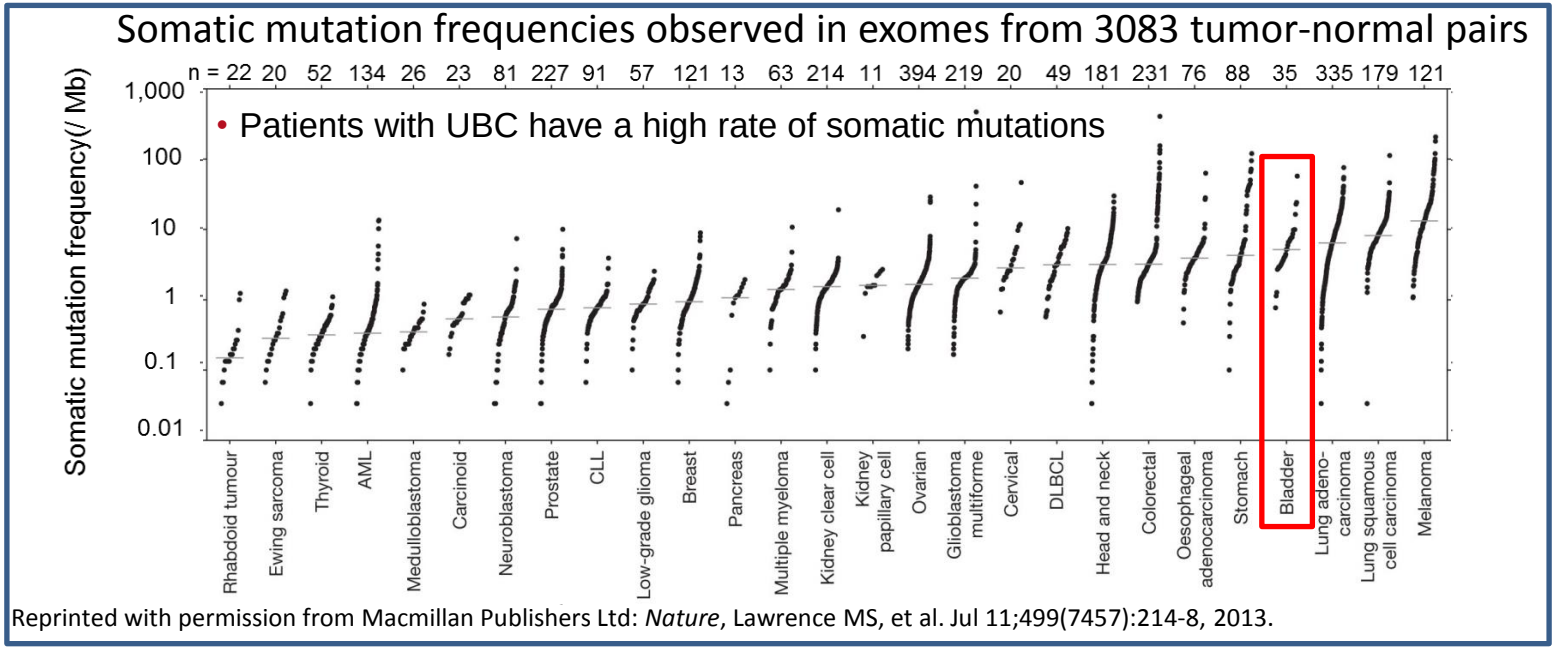
Joaquim Bellmunt,[1] Daniel P. Petrylak,[2] Thomas Powles,[3] Fadi Braiteh,[4] Nicholas J. Vogelzang,[5] Cristina Cruz,[6] Howard A. Burris III,[7] Joseph Paul Eder,[2] Gregg D. Fine,[8] Melinda S.L. Teng,[8] Xiaodong Shen,[8] Jean-Marie Bruey,[8] Zachary S. Boyd,[8] Priti S. Hegde,[8] Daniel S. Chen,[8] Yohann Loriot[9]

[1]Bladder Cancer Center, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA, USA; [2]Yale Cancer Center, New Haven, CT, USA; [3]Barts Cancer Institute, Queen Mary University of London, London, UK; [4]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [5]University of Nevada School of Medicine, Las Vegas, NV, USA and US Oncology/Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [6]Vall d'Hebron University Hospital, Barcelona, Spain; [7]Sarah Cannon Research Institute, Nashville, TN, USA; [8]Genentech, Inc., S. San Francisco, CA, USA; [9]Institut Gustave Roussy, Villejuif, France

Disclosures

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

Metastatic UBC



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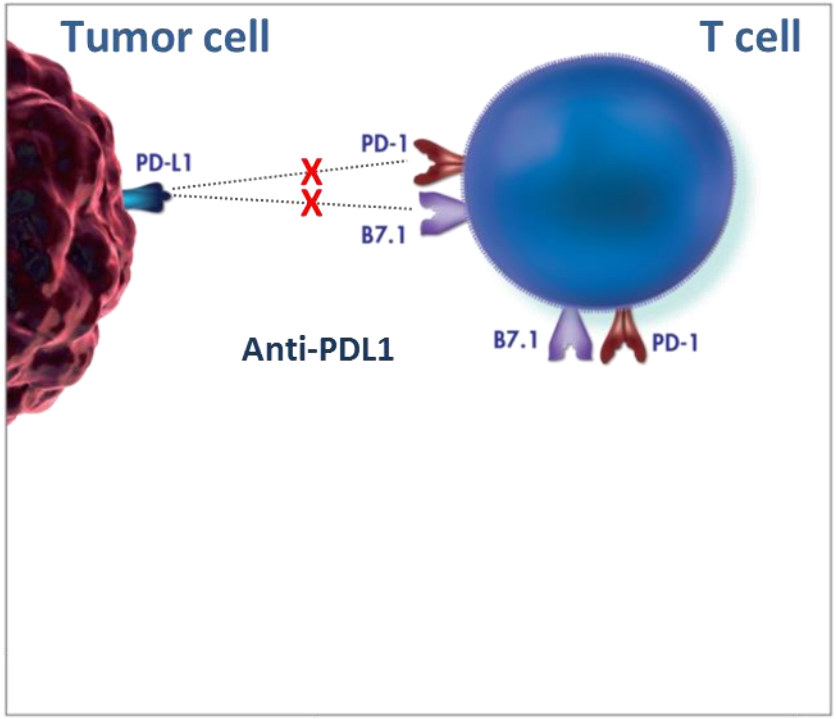
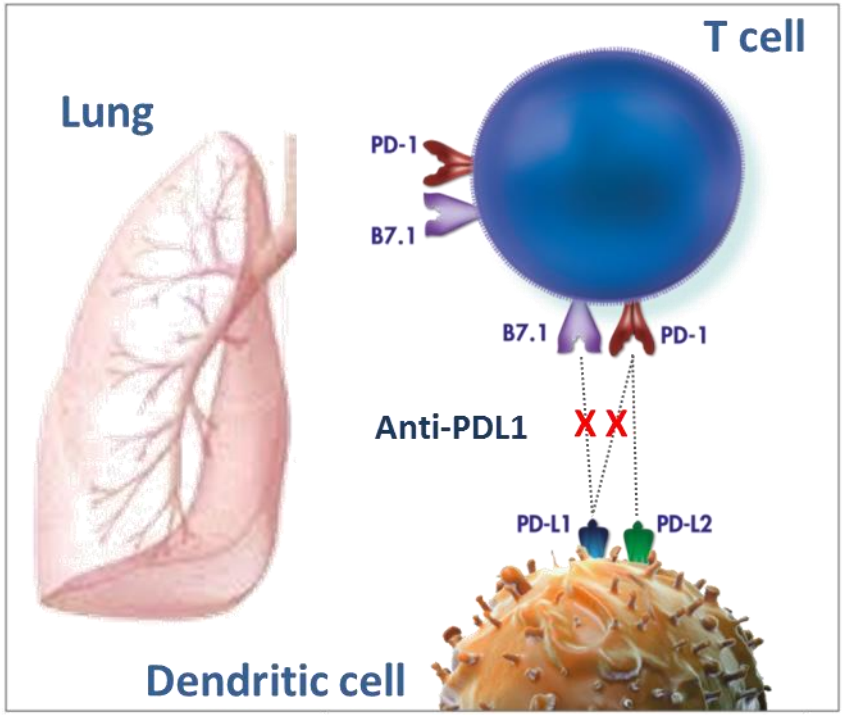
- High unmet need with no FDA-approved therapies for relapse after platinum chemo
  - Vinflunine approved in EU with no significant OS benefit in ITT population
- Median OS ≈ 7 months; PFS ≈ 3 months for 2L UBC[1]
- Patients tend to be elderly with impaired renal function
- High mutational complexity rates due to tobacco/environmental carcinogen exposure[2-4]
- Potential for many neo-antigens to be seen as foreign by host immune system[2-4]

1. Bellmunt. *Ann Oncol.* 2013; 2. TCGA. *Nature.* 2014; 3. Lawrence. *Nature.* 2013; 4. Kandoth. *Nature.* 2013.

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



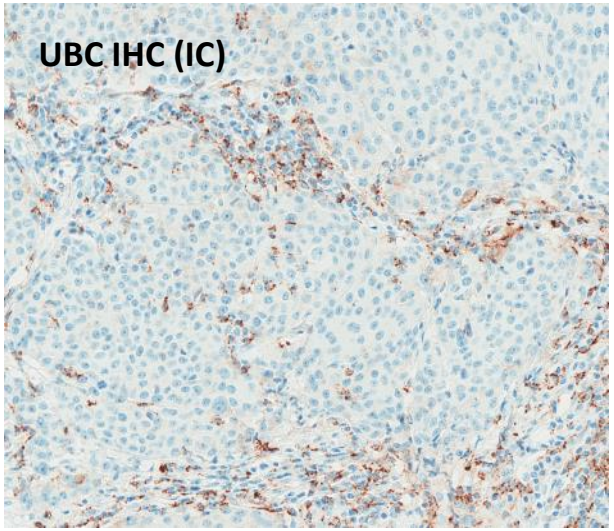


- Inhibiting PD-L1/PD-1 and PD-L1/B7.1 interactions can restore antitumor T-cell activity and enhance T-cell priming
- MPDL3280A leaves the PD-L2/PD-1 interaction intact, maintaining immune homeostasis and potentially preventing autoimmunity

Akbari. *Mucosal Immunol.* 2010; Matsumoto. *Biochem Biophys Res Commun.* 2008.

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

Indication	PD-L1+ Tumor-Infiltrating Immune Cells (ICs)
UBC (n = 205)	**27%**
RCC (n = 88)	25%
NSCLC (n = 184)	26%
Melanoma (n = 59)	36%



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+).
Powles T, et al. ASCO, 2014.

MPDL3280A Phase Ia

Phase Ia Expansion Ongoing

RCC		Melanoma	NSCLC		Other Tumor Types		UBC (15 mg/kg)	
1. All-comers	2. PD-L1+ patients	All-comers	1. All-comers	2. PD-L1+ patients	1. PD-L1+ patients	2. All-comers	1. PD-L1+ patients	2. All-comers[a]

MPDL3280A administered by IV q3w for up to 16 cycles

Key Eligibility Criteria

Measurable disease per RECIST v1.1

ECOG PS 0 or 1

[a] Primarily recruited PD-L1–negative patients.

MPDL3280A: UBC Baseline Characteristics

Efficacy-evaluable population with UBC in Phase I expansion

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

[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 (≥ 12-wk follow-up) with measurable disease at baseline. Clinical data cutoff was Apr 21, 2014.

Bellmunt et al., 26-30 September 2014, Madrid, Spain

MPDL3280A: Treatment-Related AEs

Safety-evaluable population with UBC in Phase I expansion

Patients With UBC N = 74	All Grade n (%)	Grade 3-4[a] n (%)
All	48 (65%)	4 (5%)
Fatigue	11 (15%)	0
Decreased appetite	9 (12%)	0
Nausea	8 (11%)	0
Pruritus	7 (9%)	0
Pyrexia	7 (9%)	0
Asthenia	5 (7%)	1 (1%)
Chills	3 (4%)	0
Dry skin	3 (4%)	0
Influenza-like illness	3 (4%)	0
Lethargy	3 (4%)	0
Rash	3 (4%)	0

- 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

[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.

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MPDL3280A: Summary of ORR in UBC

Efficacy-evaluable population with UBC in Phase I expansion

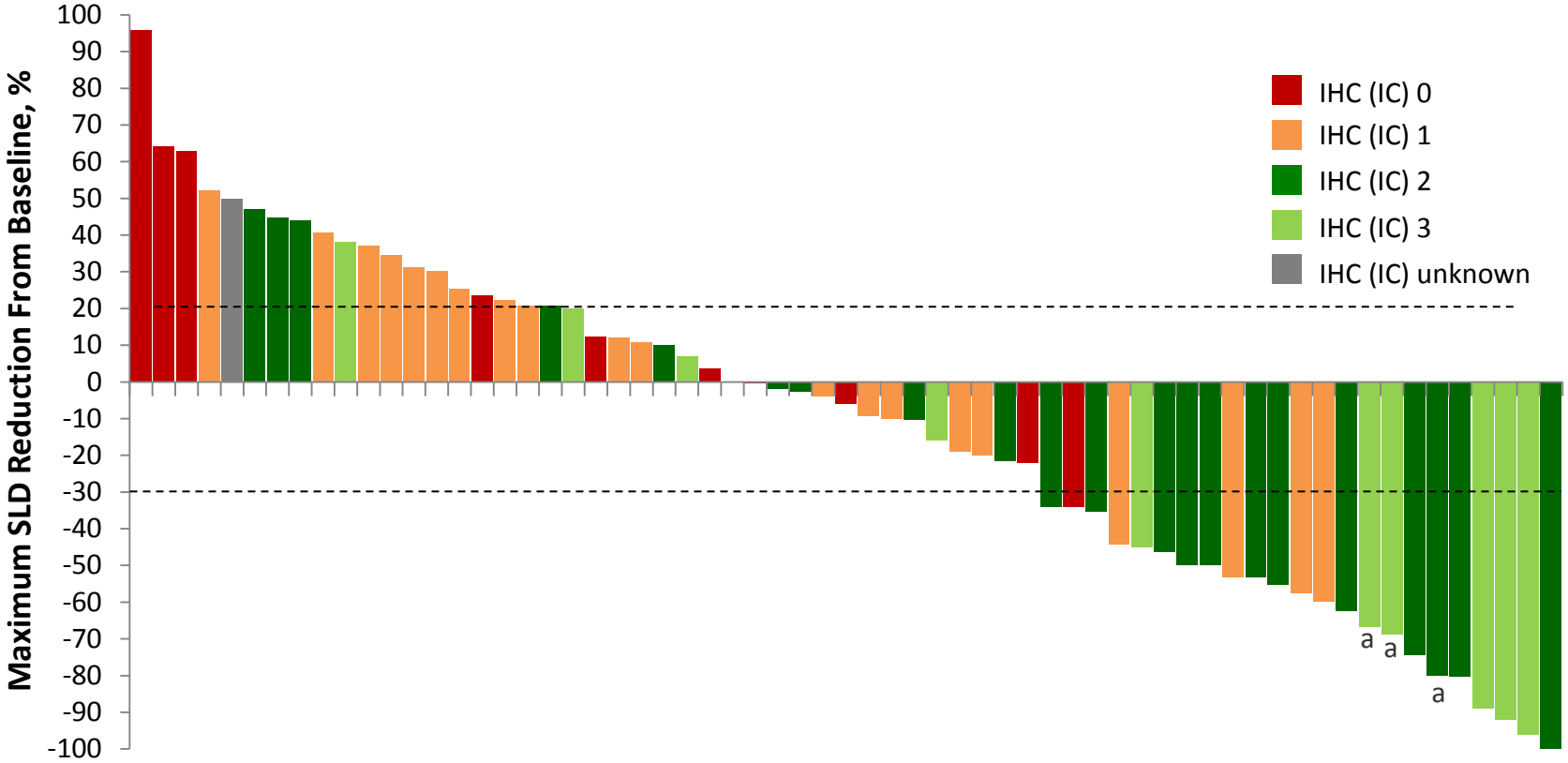
PD-L1 IHC (IC)	ORR, Best Response % (95% CI)	PD-L1+ vs PD-L1− ORR, Best Response % (95% CI)
IHC 3 (n = 10)	60% (27, 85)	52% (34, 69)
IHC 2 (n = 23)	48% (27, 68)	
IHC 1 (n = 24)	17% (6, 37)	14% (6, 28)
IHC 0 (n = 12)	8% (0, 35)	

- 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

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.

MPDL3280A: Summary of ORR in UBC

Efficacy-evaluable population with UBC in Phase I expansion



[a] 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.

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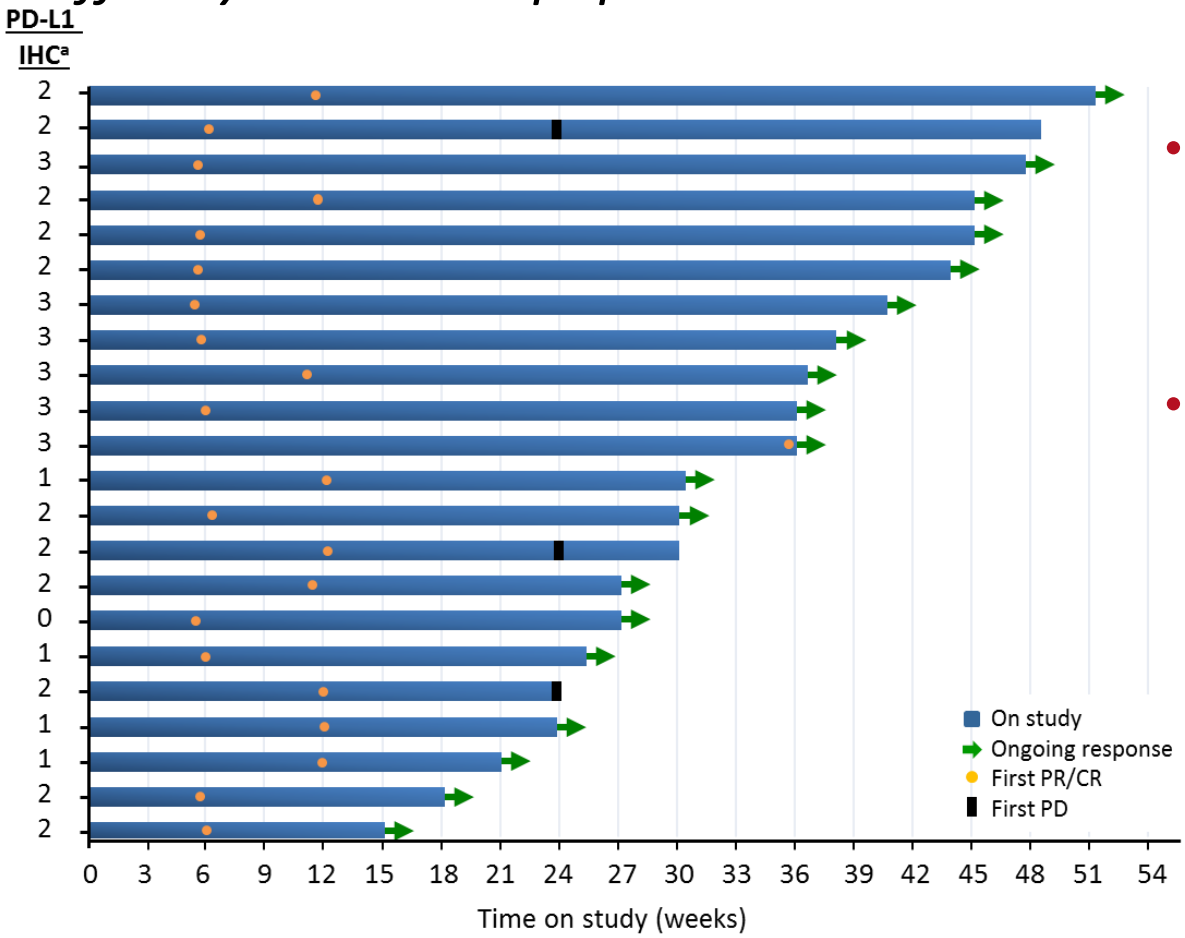
MPDL3280A: Duration on Study, Treatment and Response in Responding Patients

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

[a] 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.

MPDL3280A: Summary of Progression Free Survival

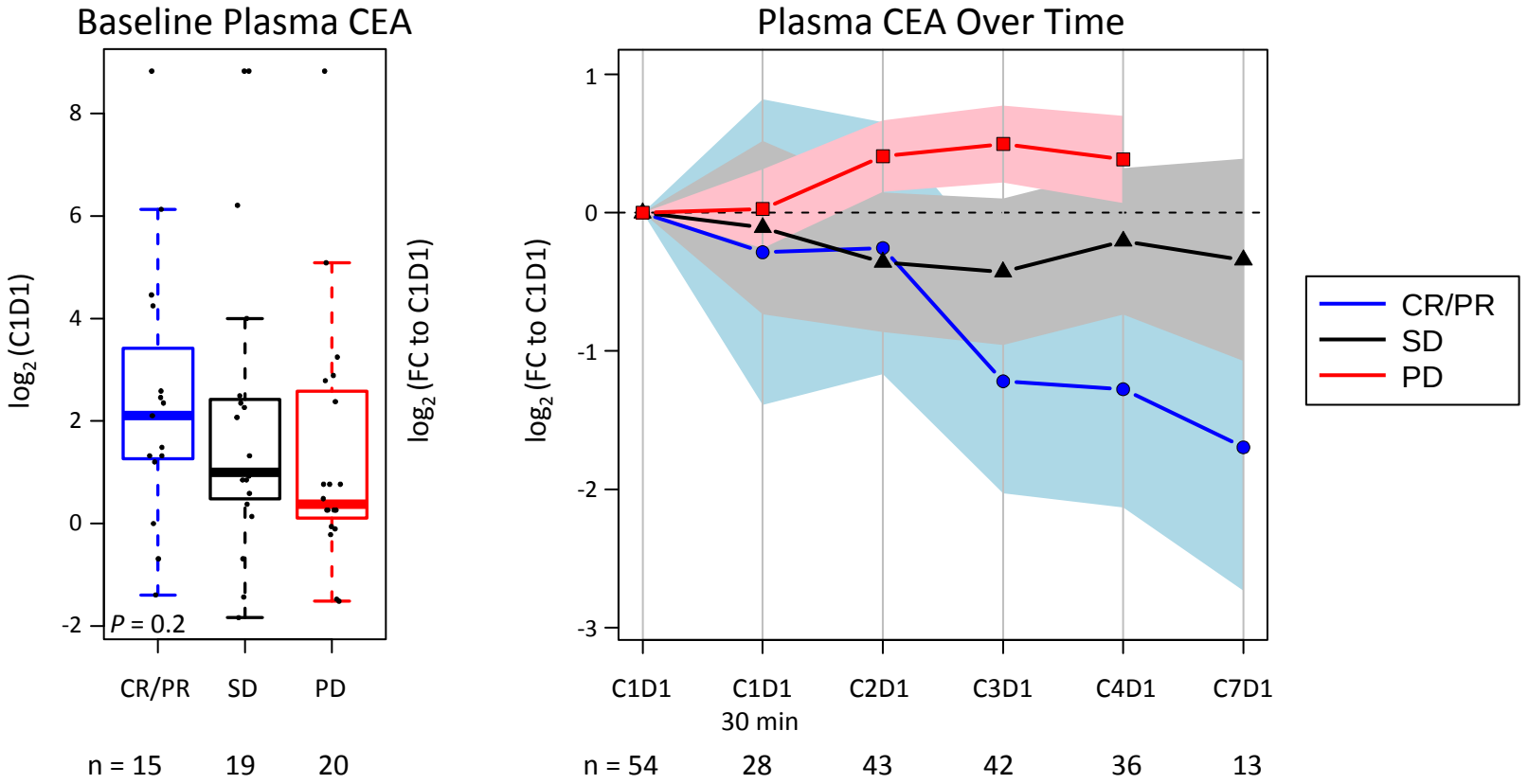
Efficacy-evaluable population with UBC in Phase I expansion

PD-L1 IHC (IC)	Median PFS (range), weeks	PD-L1+ vs PD-L1– Median PFS (range), weeks
IHC 3 (n = 10)	Not reached (5 to 48+)	24 (5 to 50+)
IHC 2 (n = 23)	24 (5 to 50+)	
IHC 1 (n = 24)	11 (0.1+ to 30+)	8 (0.1+ to 30+)
IHC 0 (n = 12)	7 (5 to 24+)	

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

Investigator-assessed PFS per RECIST v1.1.
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.

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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  - Only 5% of patients experienced Grade 3/4 treatment-related AEs
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  - 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)

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