Intratumoral characteristics of tumor and immune cells at baseline and on-treatment correlated with clinical responses to MPDL3280A, an engineered antibody against PD-L1

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[1] Stanford University Cancer Institute, [2] Genentech Inc., [3] Yale School of Medicine, [4] Carolina BioOncology Institute, [5] Vanderbilt-Ingram Cancer Center, [6] Vall d'Hebron University Hospital, [7]Dana-Farber Cancer Institute

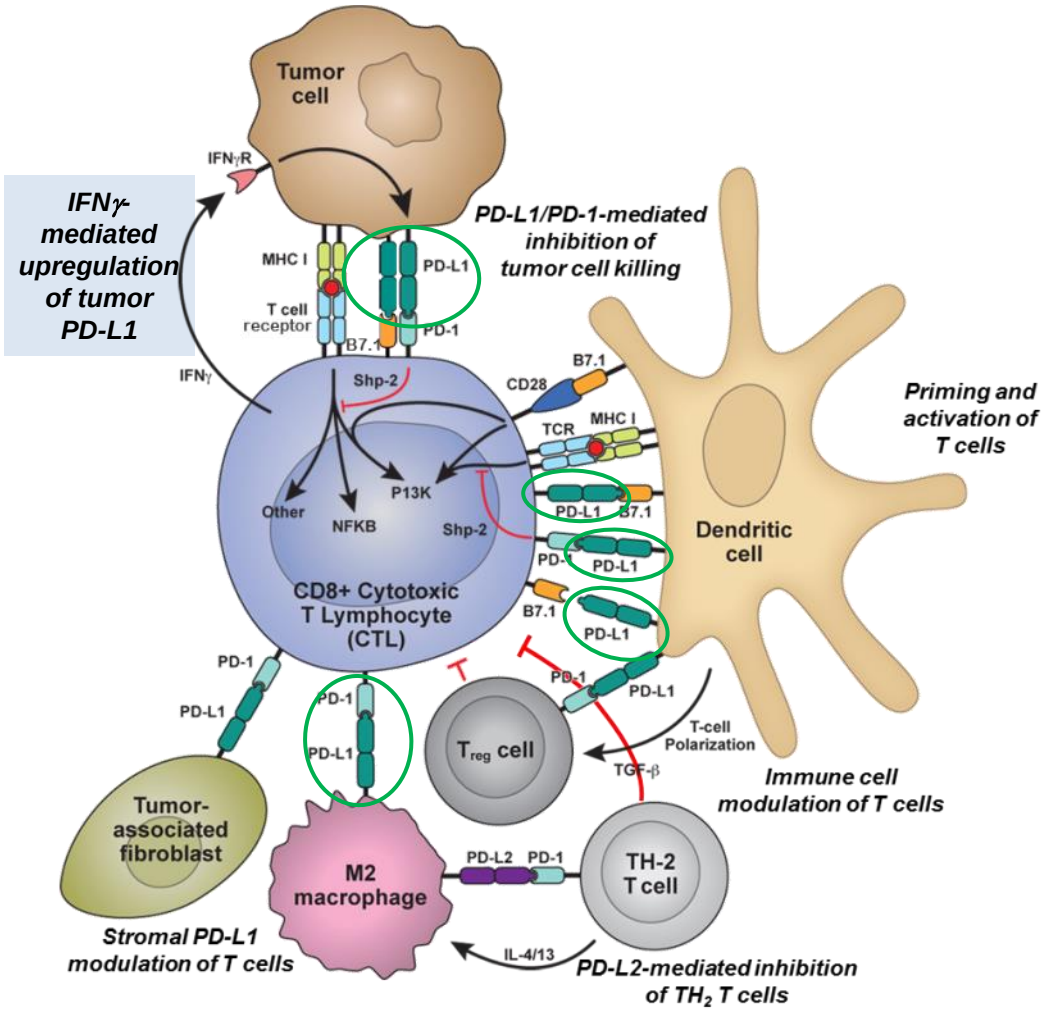
Kohrt et al. SITC, 2013.

Disclosures

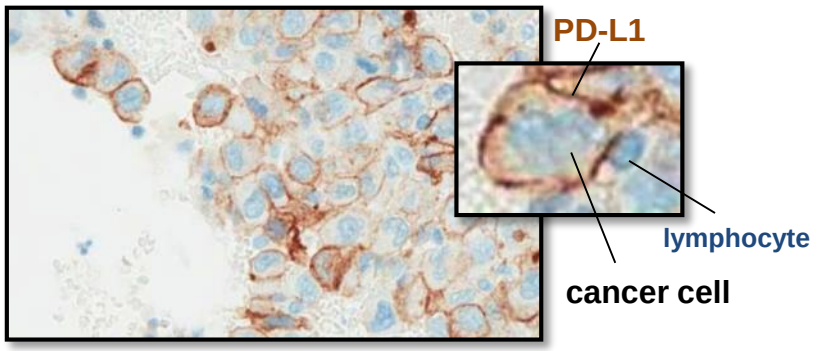
Holbrook Kohrt

- No disclosures

PD-L1 Plays an Important Role in Dampening the Antitumor Immune Response



Chen DS, Irving BA, Hodi FS. *Clin Cancer Res.* 2012.



Presence of intratumoral T cells may lead to adaptive immune resistance

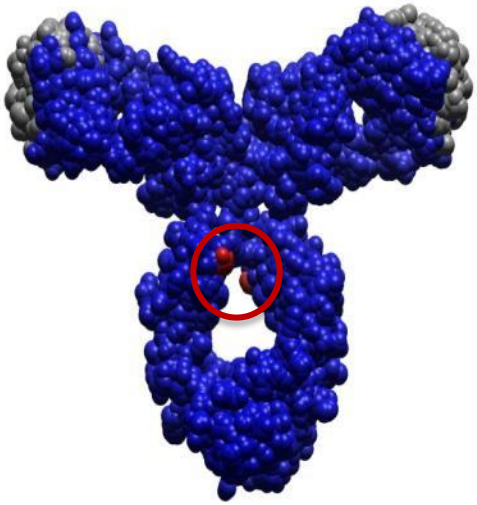
PD-L1 expression in the tumor microenvironment can inhibit antitumor T-cell activity:

1. PD-L1 expression by tumor-infiltrating ***immune cells***
2. PD-L1 expression by ***cancer cells***

Kohrt et al. SITC, 2013.

MPDL3280A (Anti-PDL1)

MPDL3280A



IgG1 Engineered

- MPDL3280A (anti-PDL1) is engineered to avoid the killing of activated T cells by ADCC

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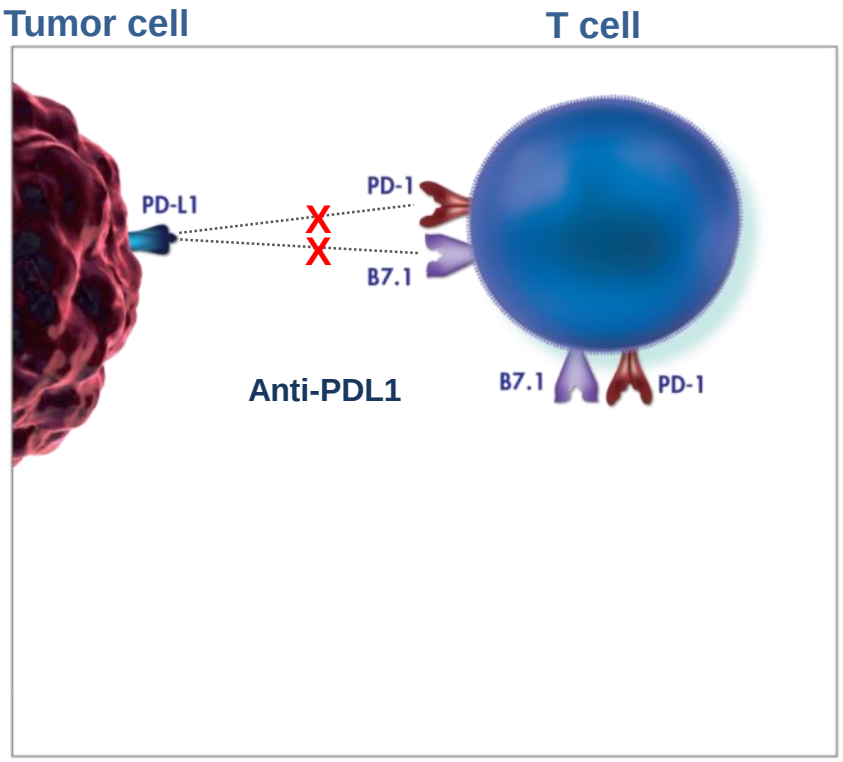
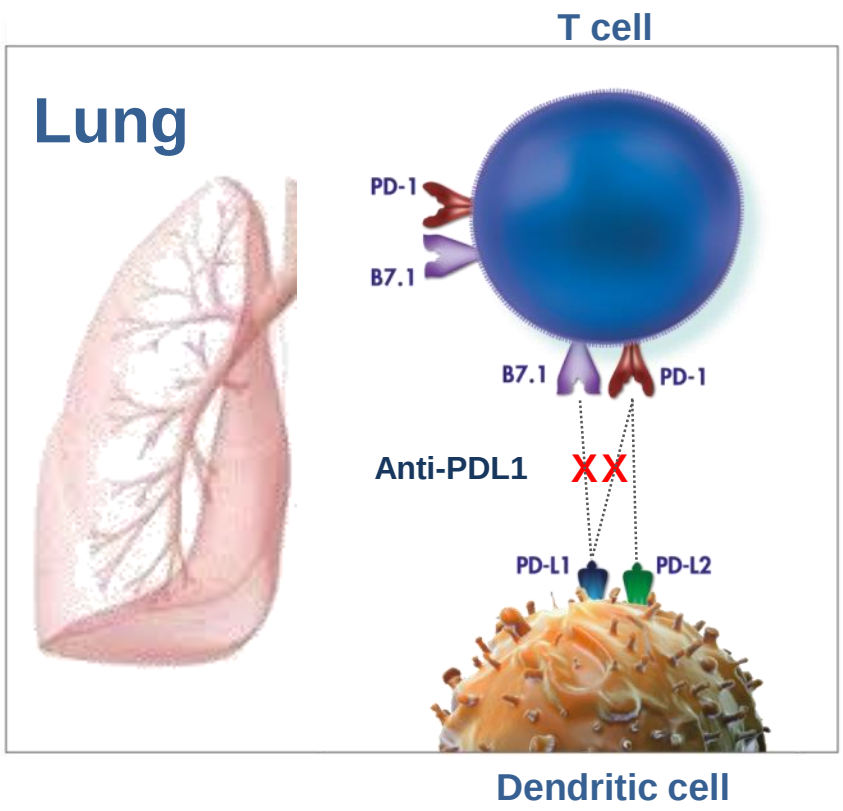
MPDL3280A (Anti-PDL1) Inhibits the Binding of PD-L1 to PD-1 and B7.1





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

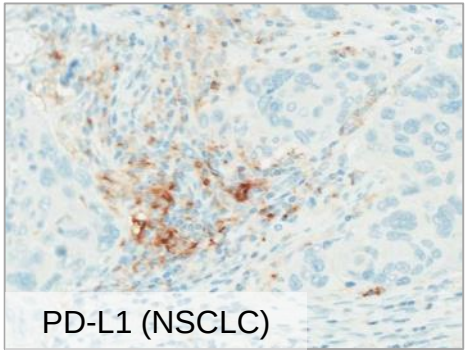
- MPDL3280A leaves the PD-1/PD-L2 interaction intact – maintaining immune homeostasis and potentially preventing autoimmunity

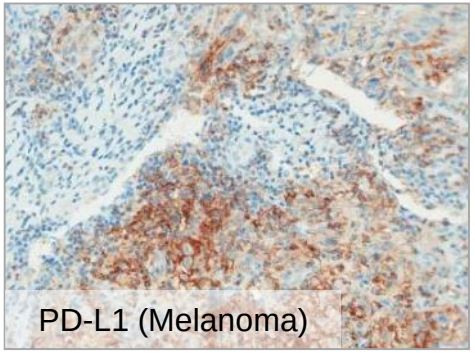
Akbari O, et al. *Mucosal Immunol.* 2010;
Matsumoto K, et al. *Biochem Biophys Res Commun.* 2008.

Kohrt et al. SITC, 2013.

MPDL3280A Target PD-L1 Is Broadly Expressed in Human Cancer

Tumor Type[a]	Estimated PD-L1 Prevalence (non-trial samples),[b] ≈ %
NSCLC (SCC)	50%
NSCLC (adeno)	45%
Colon	45%
Melanoma	40%
Head and neck SCC	25%
Renal	20%


PD-L1 (NSCLC)


PD-L1 (Melanoma)

[a] Surgical tumor specimens (internal Genentech data from non-trial samples). NSCLC samples include collaboration with Ignacio Wistuba (MD Anderson) and David Shames (Genentech).
[b] PD-L1 expression assessed with proprietary Genentech/Roche IHC reagent.

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Anti-PDL1 (MPDL3280A) Phase Ia Ongoing

Phase Ia Expansion Ongoing

NSCLC		RCC		Melanoma		Mandatory Serial Tumor Biopsies	Other Tumor Types	
All-comers	PD-L1+ patients	All-comers	PD-L1+ patients	All-comers	PD-L1+ patients	All- comers	All-comers	PD-L1+ patients

Patients enrolled at 10, 15 and 20 mg/kg

MPDL3280A administered by IV q3w for up to 16 cycles

Key Eligibility Criteria

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

277 patients have been dosed at 1-20 mg/kg by October 1, 2012

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MPDL3280A Phase Ia: Summary of Baseline Demographics

Characteristics	N = 277
Median age (range), y	61 (21-88)
Sex, male / female, n (%)	63% / 37%
Tumor type, n (%)	
Melanoma	45 (16%)
Renal cell carcinoma (RCC)	68 (25%)
NSCLC	85 (31%)
Other[a]	79 (29%)
ECOG PS, 0 / 1, n (%)	140 (50%) / 137 (50%)
Prior radiotherapy, n (%)	129 (47%)
Prior systemic regimens[b], n (%)	
0	33 (12%)
1	57 (21%)
2	61 (22%)
≥ 3	126 (45%)

[a] Including sarcoma, ovarian, head and neck, cervical, breast, colorectal, malignant lymphoma, multiple myeloma, pancreatic, gastric, uterine, neuroendocrine and pancreatoduodenal.
[b] Systemic regimens administered in the metastatic, adjuvant or neoadjuvant setting; data cutoff April 30, 2013.

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Most Common Treatment-Related Adverse Events *Investigator Assessed*

- No maximum tolerated dose or dose-limiting toxicities
- The majority of adverse events (AEs) were Grade 1 - 2 and did not require intervention
- No Grade 3 - 5 pneumonitis observed
- One treatment-related death (cardiorespiratory arrest)[a] in a patient with preexisting sinus thrombosis and cardiac/great vessel invasion by tumor at baseline
- Immune-related[b] Grade 3 - 4 AEs observed in 3 patients (1%)[c]

Adverse Event	Treatment-Related, n (%) N = 277	
	Any Grade	Grade 3 - 4
Any AE	194 (70%)	35 (13%)
Fatigue	67 (24%)	5 (2%)
Decreased appetite	33 (12%)	0
Nausea	32 (12%)	1 (< 1%)
Pyrexia	32 (12%)	0
Diarrhea	29 (11%)	0
Rash	29 (11%)	1 (< 1%)
Pruritus	23 (8%)	0
Arthralgia	22 (8%)	0
Headache	21 (8%)	1 (< 1%)
Chills	19 (7%)	0
Influenza-like illness	16 (6%)	1 (< 1%)

[a] Event suspected to be caused by treatment, disease under study and concurrent illness. [b] Investigator assessed.
[c] Events included increased AST or ALT, colitis, diabetes mellitus; 1 immune-related AE led to discontinuation of MPDL3280A treatment (elevated ALT and AST).
Data cutoff April 30, 2013; AEs occurred in ≥ 16 patients.

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MPDL3280A Phase Ia: Efficacy Summary
Investigator Assessed

	RECIST 1.1 Response Rate (ORR[a])
Overall population (N = 175)	21%
NSCLC (n = 53)	23%
Melanoma (n = 43)	30%
RCC (n = 56)	14%

- Thirty of 36 responders (83%) continued to respond as of the data cutoff date
- Additional delayed responses not reflected in above RECIST ORR
- Objective responses observed include NSCLC, melanoma, RCC, CRC, gastric cancer and HNSCC

[a] ORR includes unconfirmed and confirmed PR/CR.
Patients first dosed at 1-20 mg/kg by October 1, 2012; data cutoff April 30, 2013.
Six patients overall who did not have a postbaseline scan were included as nonresponders.

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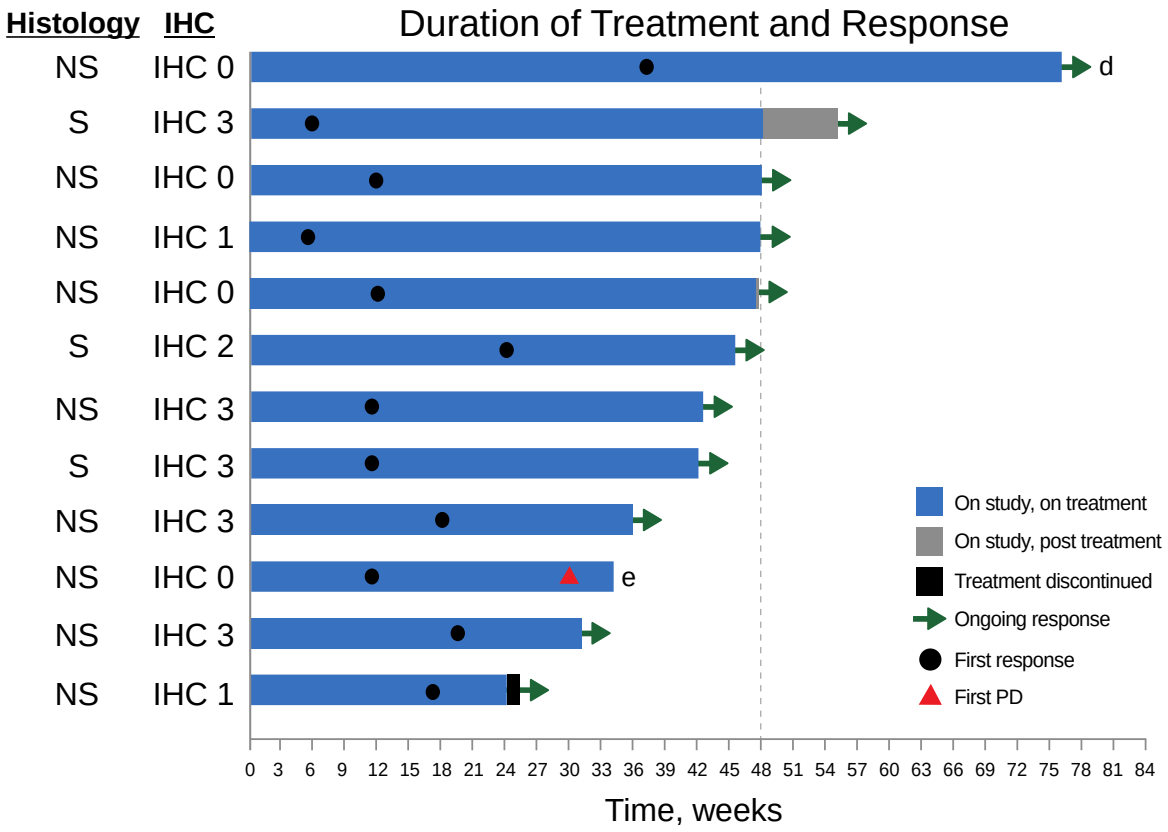
MPDL3280A Phase Ia: NSCLC Experience With Diagnostic and Duration of Response

PD-L1 Status[a] (n = 53)	RECIST 1.1 ORR[b]	PD Rate[c]
IHC 3 (n = 6)	**83%** (5/6)	**17%** (1/6)
IHC 2 and 3 (n = 13)	**46%** (6/13)	**23%** (3/13)
IHC 1/2/3 (n = 26)	**31%** (8/26)	**38%** (10/26)
All patients (IHC 0/1/2/3 and 7 patients with diagnostic unknown; n = 53)	**23%** (12/53)	**40%** (21/53)



- 11 of 12 NSCLC responders continue to respond on or off treatment

Soria et al. ECC, 2013.

[a] IHC 3: ≥ 10% tumor immune-infiltrating cells positive for PD-L1 (IC+); IHC 2 and 3: ≥ 5% tumor immune-infiltrating cells positive for PD-L1; IHC 1/2/3: ≥ 1% tumor immune-infiltrating cells positive for PD-L1; IHC 0/1/2/3: all patients with evaluable PD-L1 tumor IC status.

[b] ORR includes investigator-assessed unconfirmed and confirmed PR per RECIST 1.1.

[c] Best response of PD.

[d] Patient received more than 1 year of MPDL3280A due to intrapatient dose escalation from 1-20 mg/kg during treatment course.

[e] Patient experiencing ongoing benefit per investigator.

Patients first dosed at 1-20 mg/kg by October 1, 2012. Data cutoff April 30, 2013.

NS, nonsquamous.
S, squamous.

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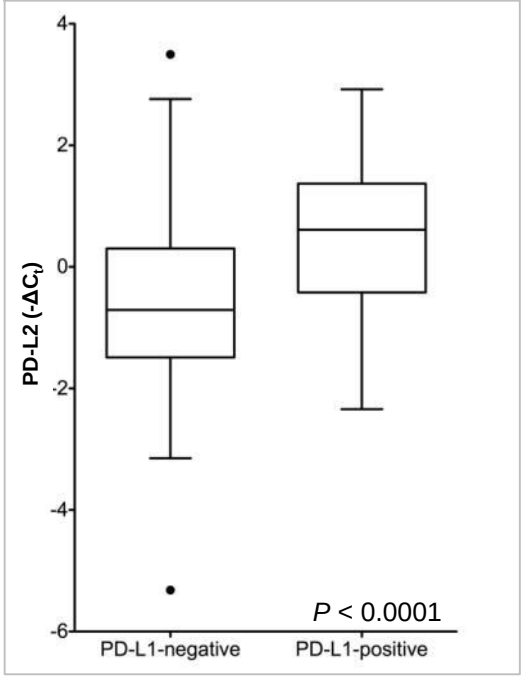
PD-L2 Status Is Not Associated With Progression on MPDL3280A in Phase Ia

PD-L2 Expression (qPCR) in Baseline Tumor Samples From Phase Ia Patients



Summary of Best Response by PD-L2 Status

	RECIST 1.1 ORR[a]	PD rate
PD-L2 high[b]	20% (13/66)	35% (23/66)
PD-L2 low[b]	19% (12/63)	46% (29/63)
All[c]	21% (36/175)	37% (65/175)

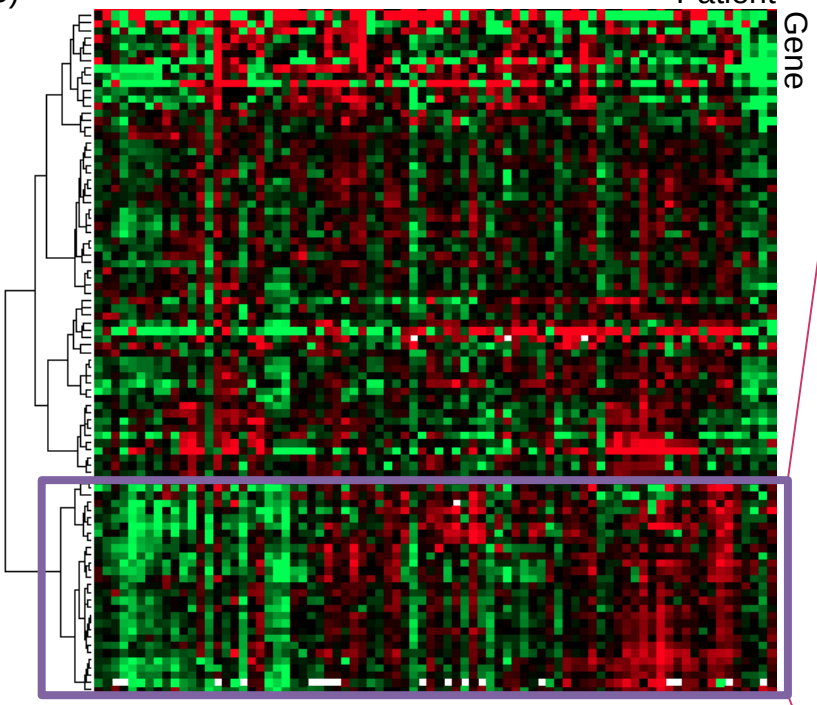
- Tumor PD-L2 expression appears higher in PD-L1–positive tumors compared with PD-L1–negative tumors
- High tumor PD-L2 expression does not appear to be associated with progression on MPDL3280A

[a] ORR includes investigator-assessed unconfirmed and confirmed PR/CR by RECIST 1.1.
[b] PD-L2 low is defined as patients with tumor PD-L2 level lower than the median PD-L2 level in all patients; PD-L2 high is defined as patients with tumor PD-L2 level equal to or higher than the median PD-L2 level in all patients.
[c] All patients include PD-L2–high patients, PD-L2–low patients and patients with unknown tumor PD-L2 status.
Patients first dosed at 1-20 mg/kg prior to October 1, 2012; data cutoff April 30, 2013.

Kohrt et al. SITC, 2013.

Anti-tumor Response to MPDL3280A Is Associated With Markers Related to T-Cell Biology

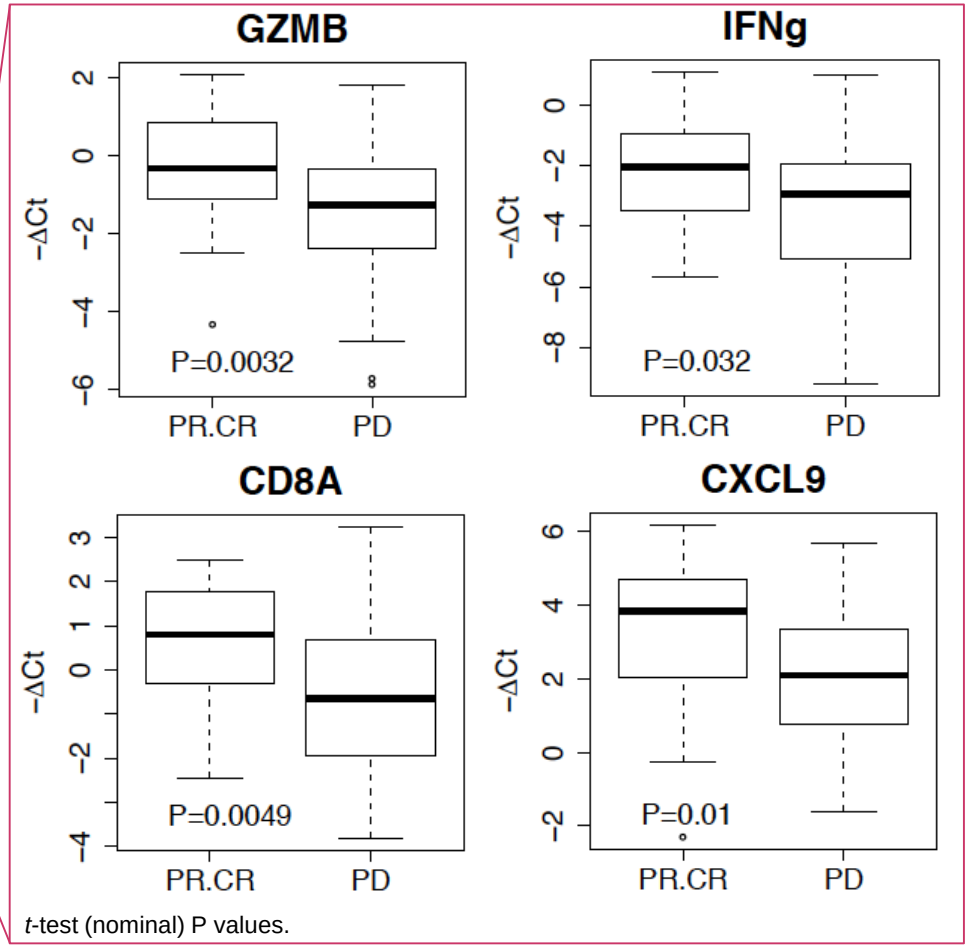
Hierarchical clustering of Phase Ia samples (n = 125)



Up-regulation

Down-regulation

Baseline tumor samples, n = 125 (MPDL3280A, Phase Ia). Data for samples available as of June 1, 2013. Patients first dosed at 1-20 mg/kg by October 1, 2012; data cutoff April 30, 2013. Includes investigator-assessed unconfirmed and confirmed PR/CR by RECIST 1.1

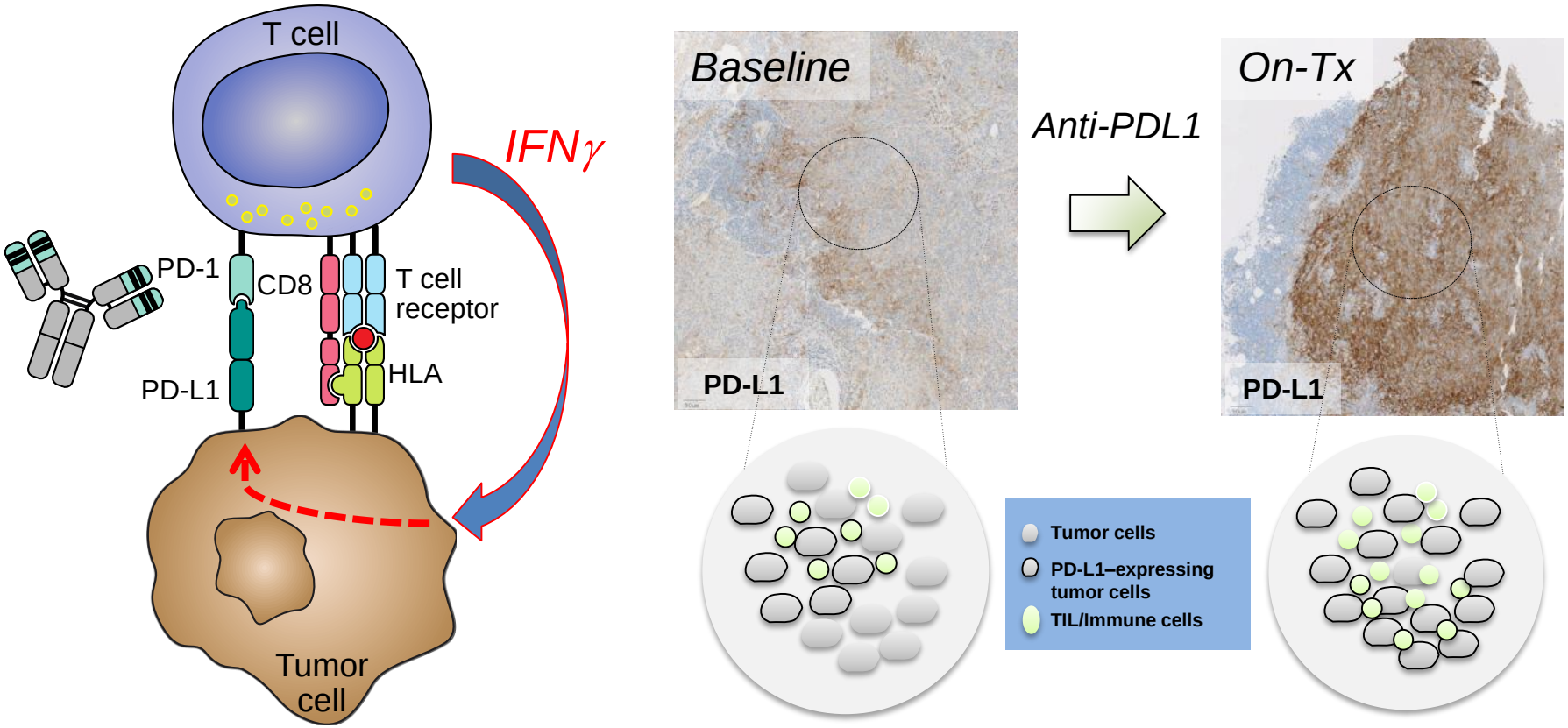


t-test (nominal) P values.

- Higher expression of cytotoxic Th1, IFNg and T-cell trafficking markers in tumor tissue at baseline is associated with MPDL3280A activity

Kohrt et al. SITC, 2013.

Adaptive Increase in Tumor PD-L1 Expression May Be an Indicator of Local TILs Attacking Tumor

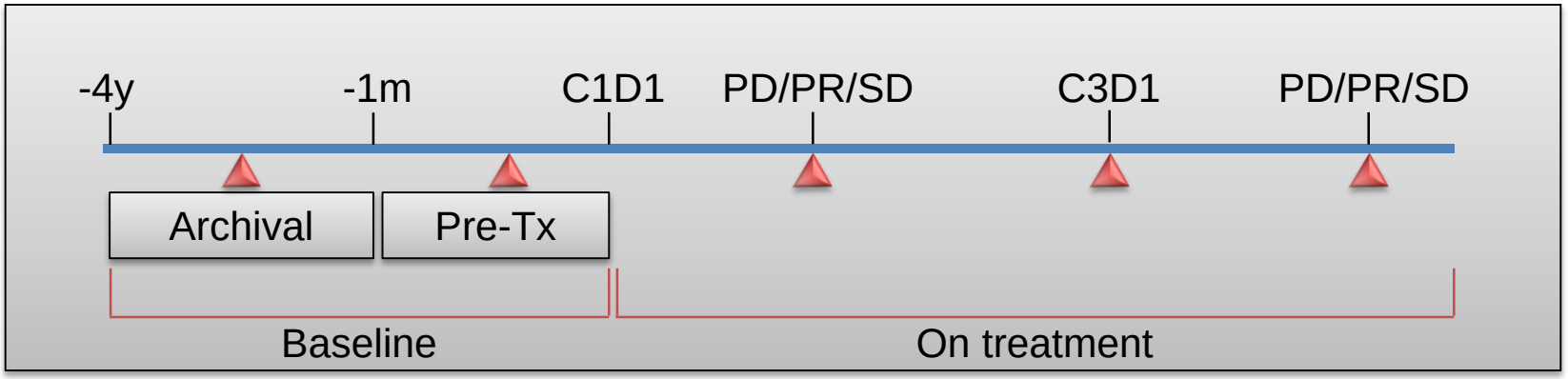


- Demonstration of pharmacodynamic MPDL3280A activity in humans: Adaptive increase in PD-L1 expression in tumor cells

Kohrt et al. SITC, 2013.

Serial Pre-/On-Treatment Tumor Biopsies Collected on MPDL3280A Phase Ia Study to Characterize Immune Biology

Baseline tumor samples available for 154 patients



▲ - approx. time of biopsy

Paired Serial Biopsy Tumor Samples[a]	N = 31
Indications:	
Melanoma	16
RCC	5
NSCLC	5
Head and neck	2
Other (CRC, gastric, breast)	3 (1 each)

[a] Paired tumor samples that contained tumor tissue.

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Adaptive Increase in PD-L1 Expression Is Prominent in Patients Responding to MPDL3280A

Summary of responses to MPDL3280A in paired biopsies:

Max SLD Decrease[a]	Increase in Tumor PD-L1,[b] n/N (%)
> 30% reduction	5/7[c] (71%)
0-30% reduction	4/9 (44%)
0-20% increase	2/10 (20%)
> 20% increase	0/4 (0%)
Unevaluable SLD (due to tumor excision[d])	1/1 (100%)

[a] At any time point in study.
[b] Number of patients with increased PD-L1 expression in tumor cells following tx with MPDL3280A; increase in tumor PD-L1 as measured by Genentech/Roche PD-L1 IHC.
[c] Includes sterilized tumor with residual ghost tumor cells and PD-L1–positive immune cells. Majority of tumors show increase also in PD-L1 expression in immune cells following tx with MPDL3280A.
[d] Excision of responding tumor for purposes of biomarker analysis rendered the patient unevaluable for max SLD change.

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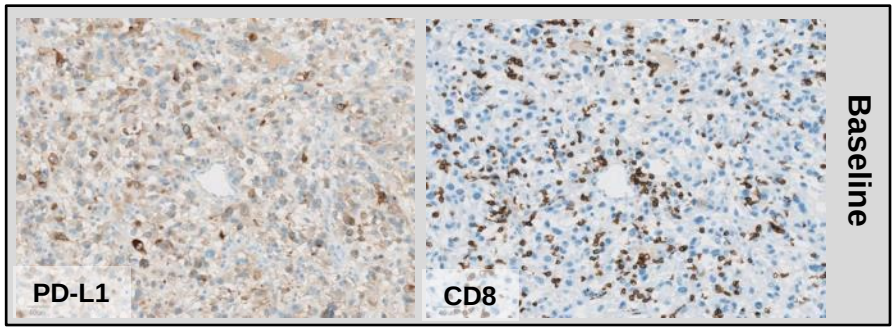
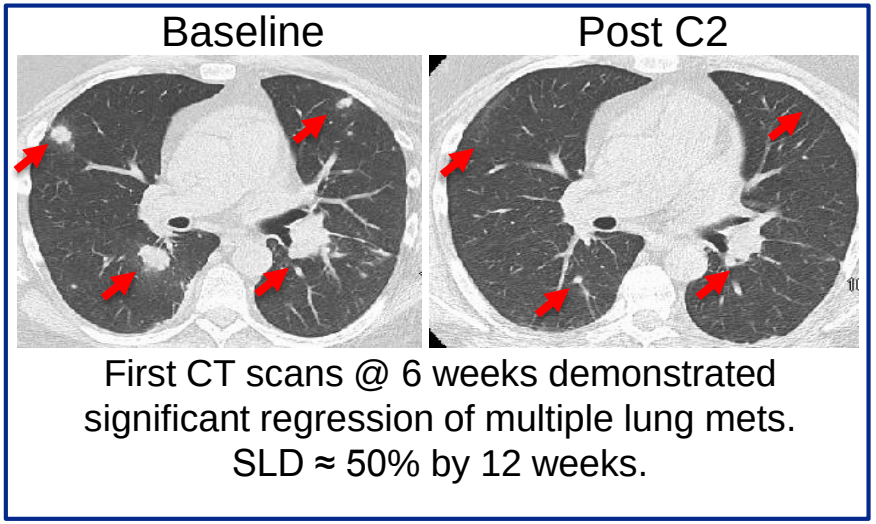
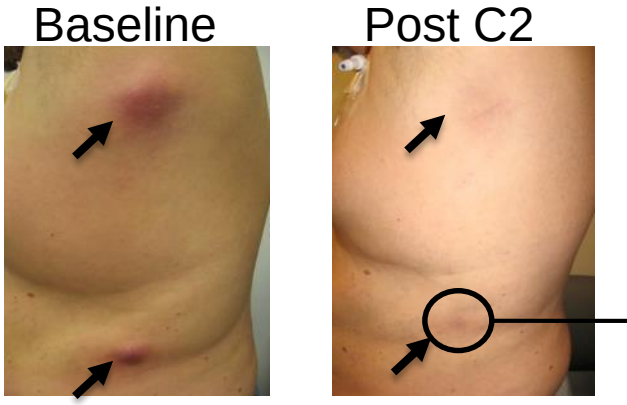
Serial Biopsy in a PD-L1–Positive RCC Patient With a Rapid Response to MPDL3280A



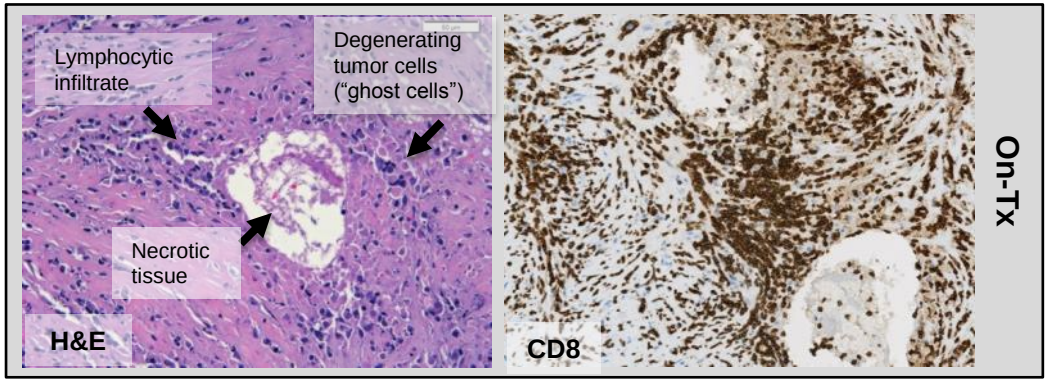
Biomarkers at baseline:
PD-L1 positive
CD8+ T cells present



First CT scans @ 6 weeks demonstrated significant regression of multiple lung mets.
SLD ≈ 50% by 12 weeks.



Surgical resection of responding mass, 0.75 x 0.75cm at time of resection



Multiple subcutaneous mets started resolving days after initiating anti-PDL1.

Biomarkers at week 4 post C1D1:
Dense CD8+ T-cell infiltrate
No viable tumor cells seen

Carolina BioOncology Institute (Powderly). MPDL3280A Phase Ia.

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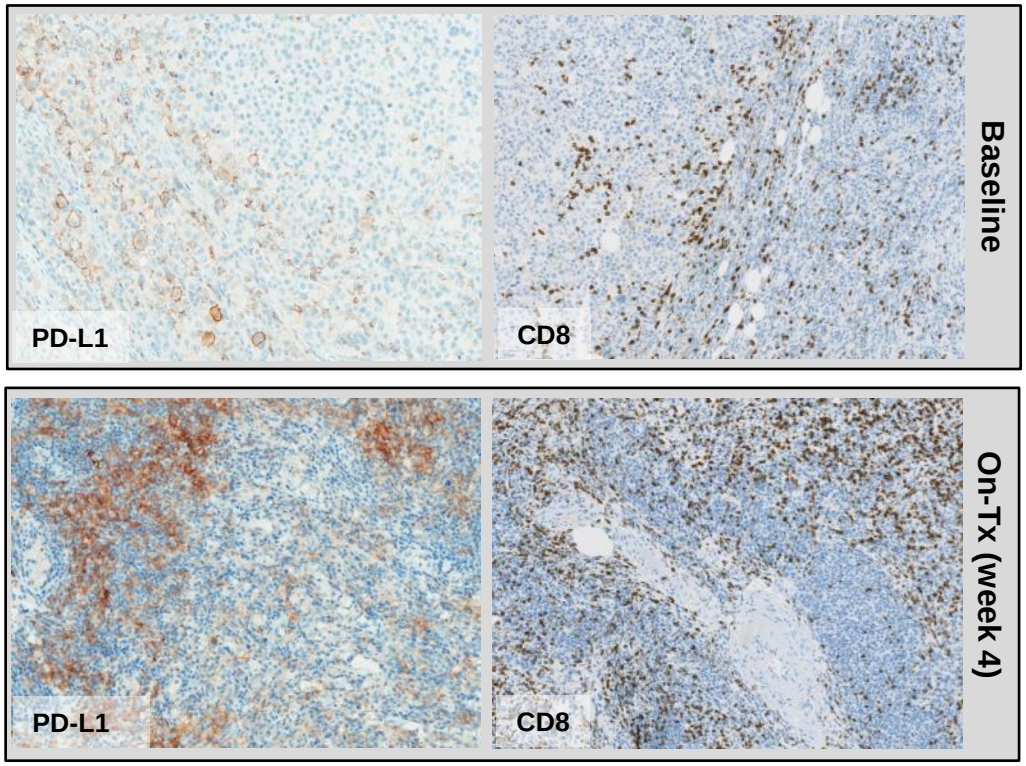
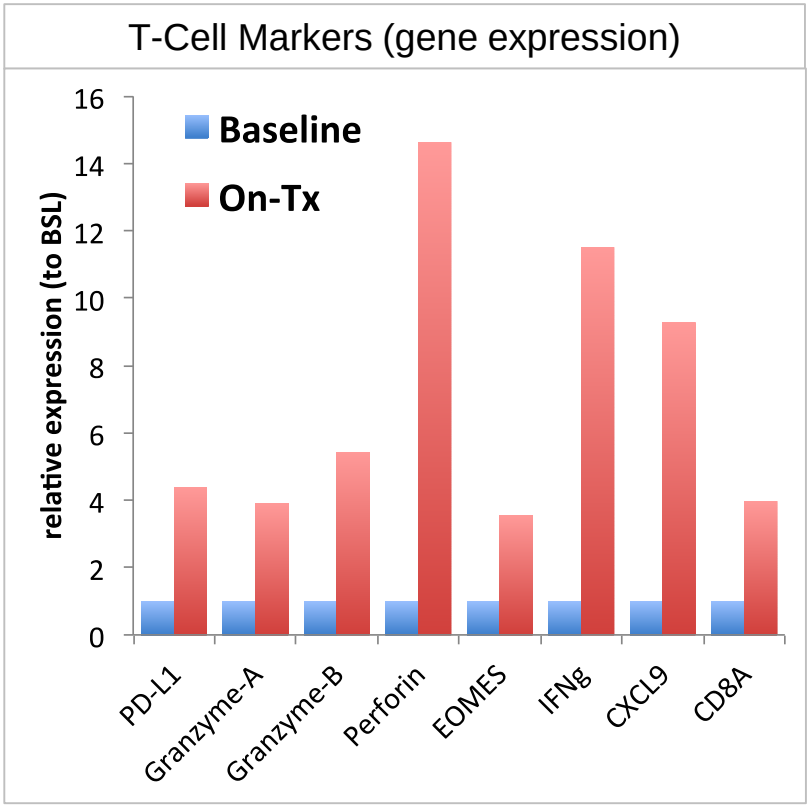
MPDL3280A Leads to Increased T-Cell Activation in PD-L1–Positive Patient Responding to Treatment





Possible MoA of response to MPDL3280A:

- Pre-existing intratumoral CD8+ T cells
- Increased trafficking or proliferation of intratumoral CD8+ cells
- Increased T-cell activation and cytotoxicity (e.g., granzymes and perforin production)

Yale Cancer Center (Kluger/Herbst).
MPDL3280A Phase Ia.

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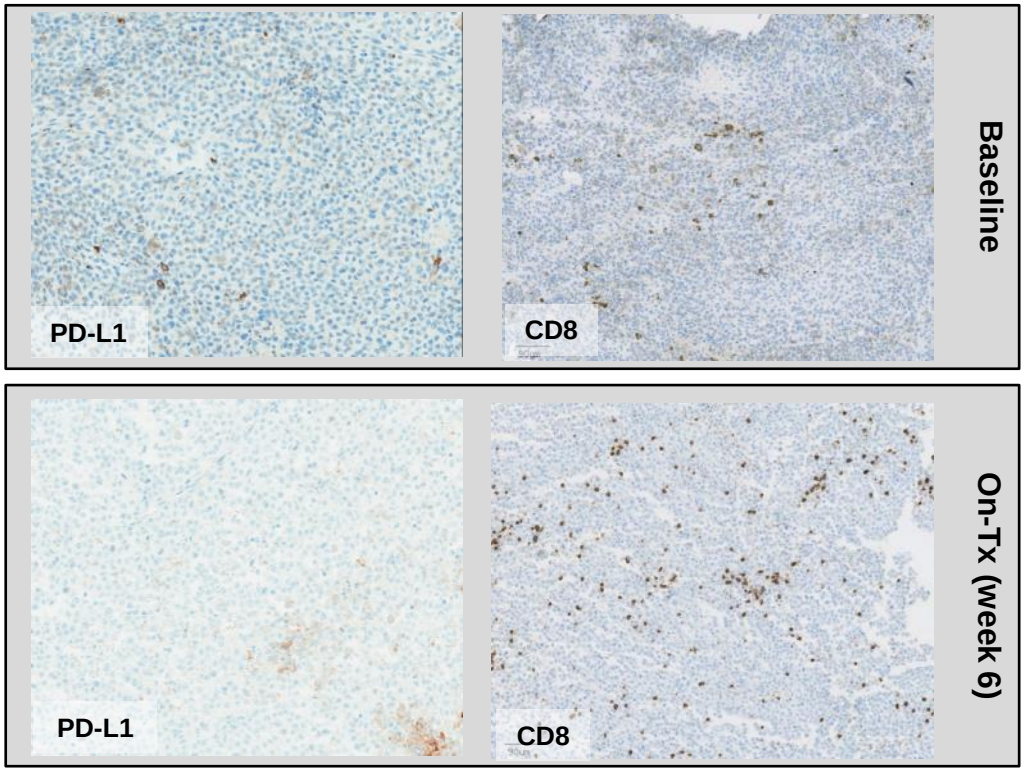
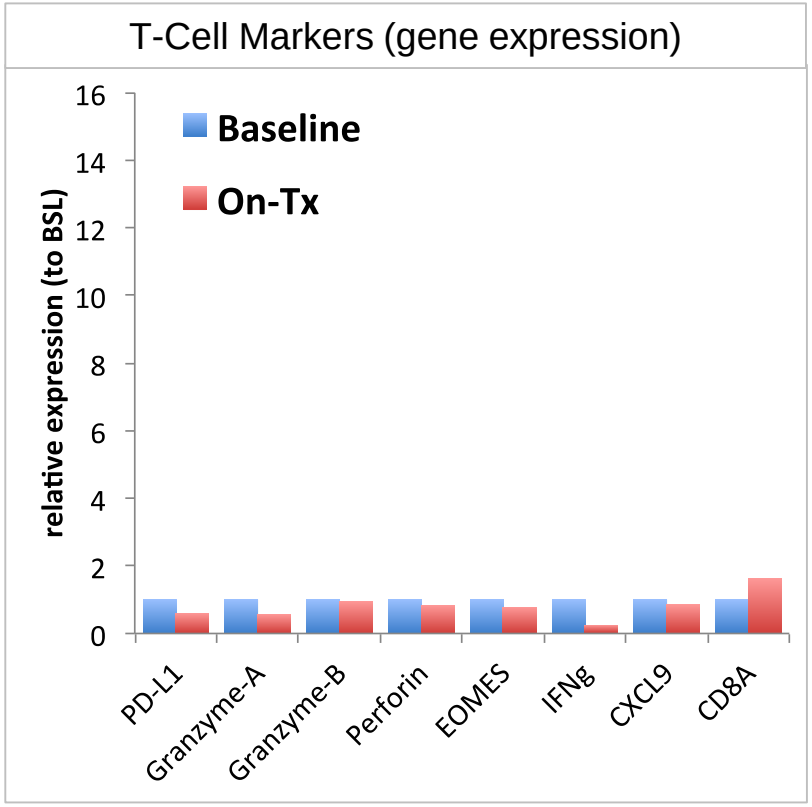
PD-L1–Negative Patient Not Responding to MPDL3280A Exhibits Low Frequency of Intratumoral T Cells





Possible MoA of lack of response to MPDL3280A:

- Low frequency of intratumoral CD8+ T-cells
- Impaired T-cell trafficking
- No increase in T-cell cytotoxicity

The Angeles Clinic (Hamid).
MPDL3280A Phase Ia.

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Conclusions

- Preliminary biomarker data suggest tumor PD-L1 IHC status in the tumor microenvironment may be associated with antitumor response to MPDL3280A
- Tumor PD-L2 expression does not appear to confer resistance to MPDL3280A activity
- Patients with higher baseline expression of cytotoxic Th1, IFNg and T-cell trafficking markers appear to respond favorably to MPDL3280A in initial analysis
- MPDL3280A therapy appears to restore antitumor immunity in responders
  - Evidence of adaptive PD-L1 tumor expression and active immune infiltration in responders
- These data provide mechanistic insights into anti-PDL1 biology and immunotherapy
- The relationship between PD-L1 status and OS on MPDL3280A is being prospectively studied

Kohrt et al. SITC, 2013.

Acknowledgments

The patients and their families

Participating Centers:

The Angeles Clinic and Research Institute (Hamid)

Barts Cancer Institute (Powles)

Beth Israel Deaconess Medical Center (Cho)

Carolina BioOncology (Powderly)

Centre Léon-Bérard (Cassier)

Comprehensive Cancer Centers of Nevada (Braiteh)

Dana-Farber Cancer Institute (Hodi)

Institut Claudius Regaud (Delord)

Gustave Roussy (Bahleda)

Massachusetts General Hospital (Lawrence)

Moffitt Cancer Center (Antonia)

New York Oncology Hematology (Garbo)

Pinnacle Oncology Hematology (Gordon)

Sarah-Cannon Research Institute (Burris)

Stanford University (Kohrt)

Vall d'Hebron University Hospital (Tabernero)

Vanderbilt-Ingram Cancer Center (Sosman)

Virginia Oncology Associates, US Oncology (Conkling)

Yale School of Medicine (Herbst)

Our colleagues at Genentech, a member of the Roche group