The PD-1/PD-L1 Pathway as a Target in Tumor Immunotherapy

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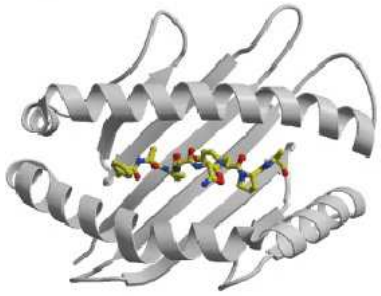
SEATTLE CANCER CARE ALLIANCE

Fred Hutchinson Cancer Research Center
UW Medicine
Seattle Children's

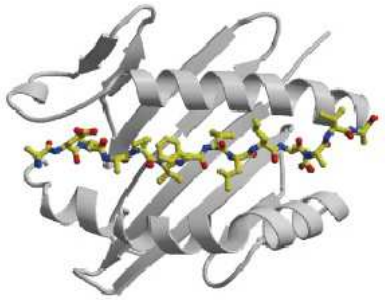
Learning Objectives

- Review the biology of the PD-1 / PD-L1 pathway as it relates to tumor immunity
- Review safety and efficacy data for the lead therapeutic blocking antibodies targeting PD-1 and PD-L1
  - Anti-PD-1 (nivolumab)
  - Anti-PD-L1 (MPDL3280A)
- Discuss available evidence for on-target mechanism of action and biomarker development.

T Cell Specificity:
TCR Recognition of HLA + Antigenic Peptide



HLA Class I

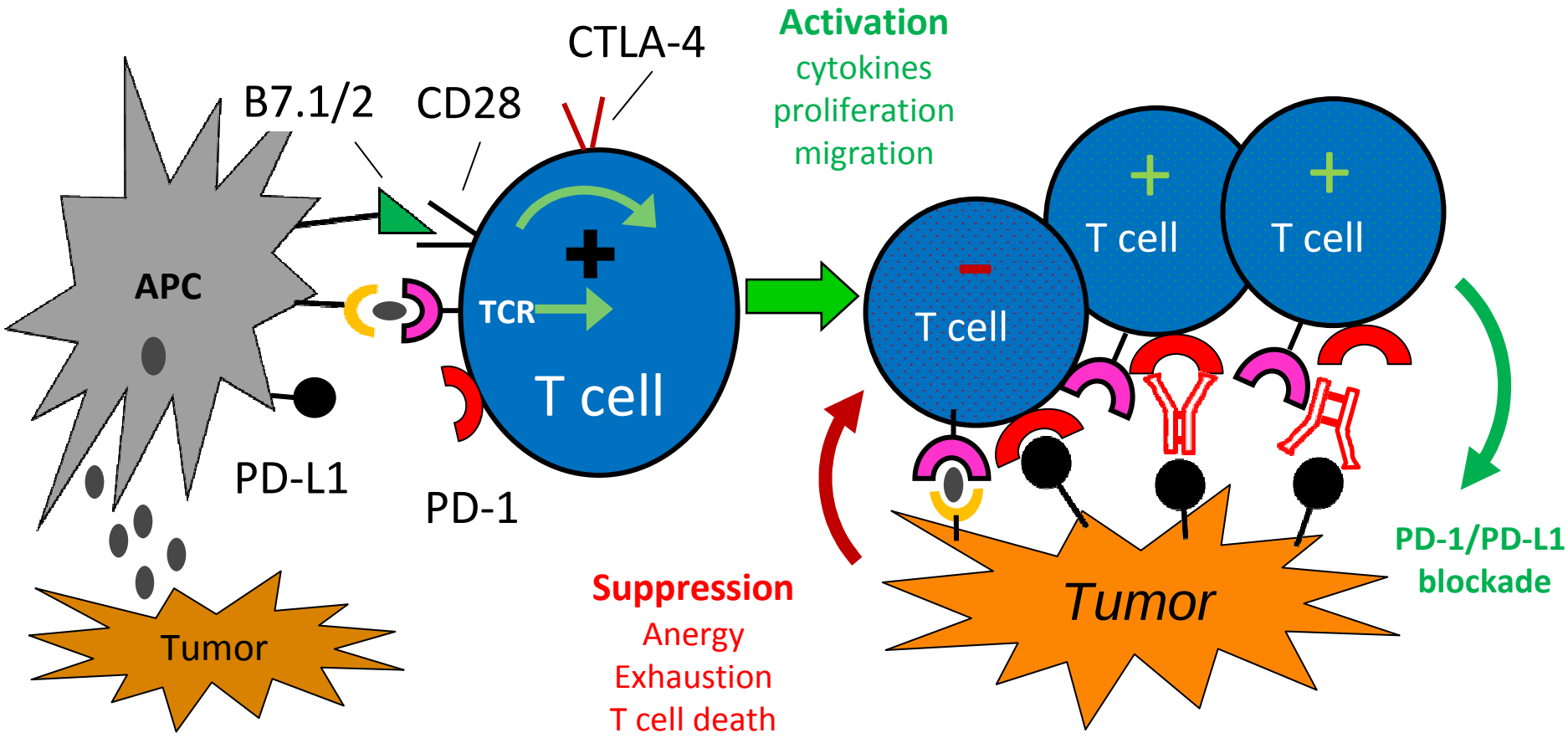


HLA Class II

<u>HLA-Associated Peptide Antigens</u>

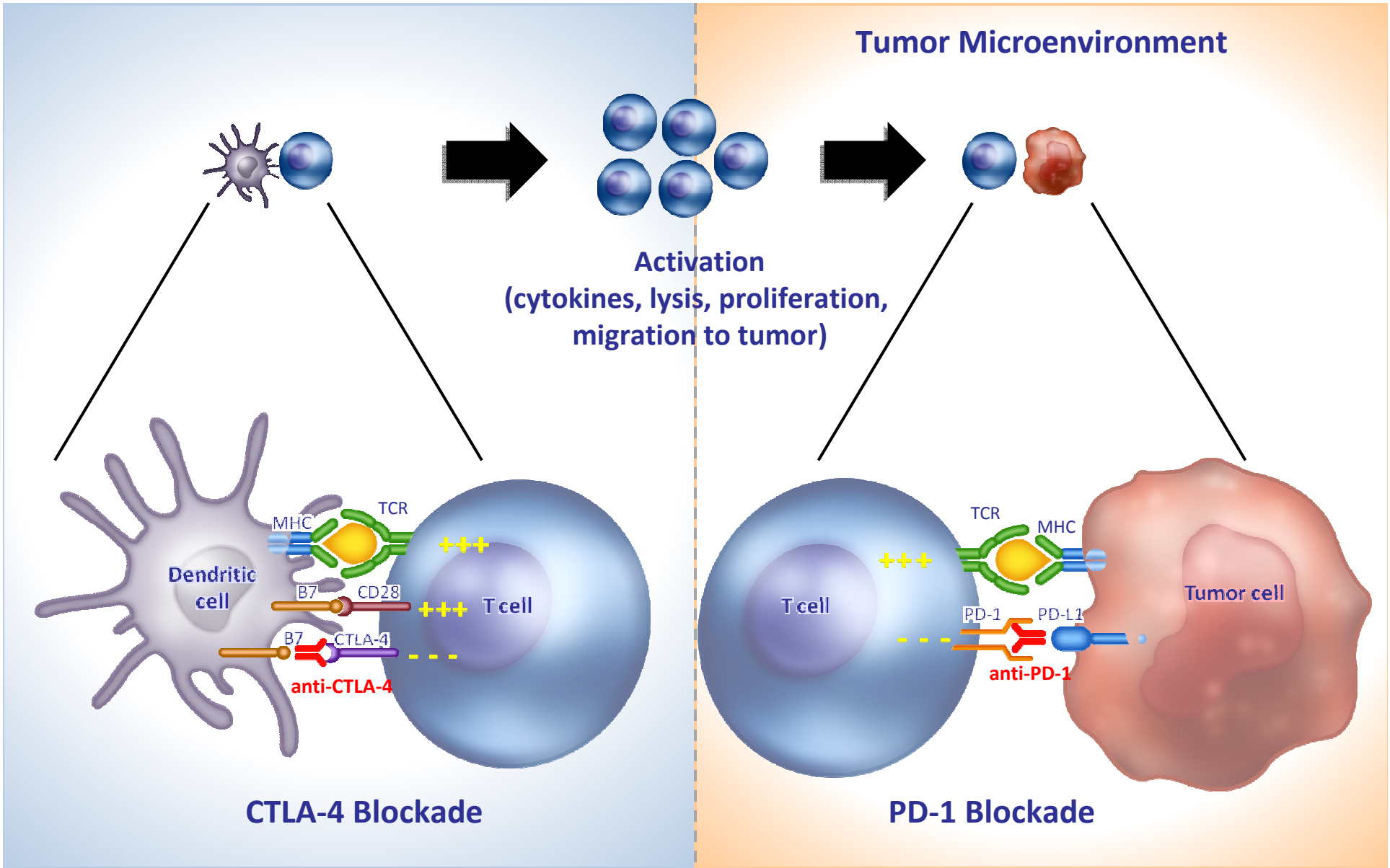
- Normal cell proteins
- Tumor-specific mutated proteins – *"the mutanome"*
- Tumor-associated viral proteins

PD-1/PD-L1 Blockade:
An Emerging Strategy for Cancer Immunotherapy

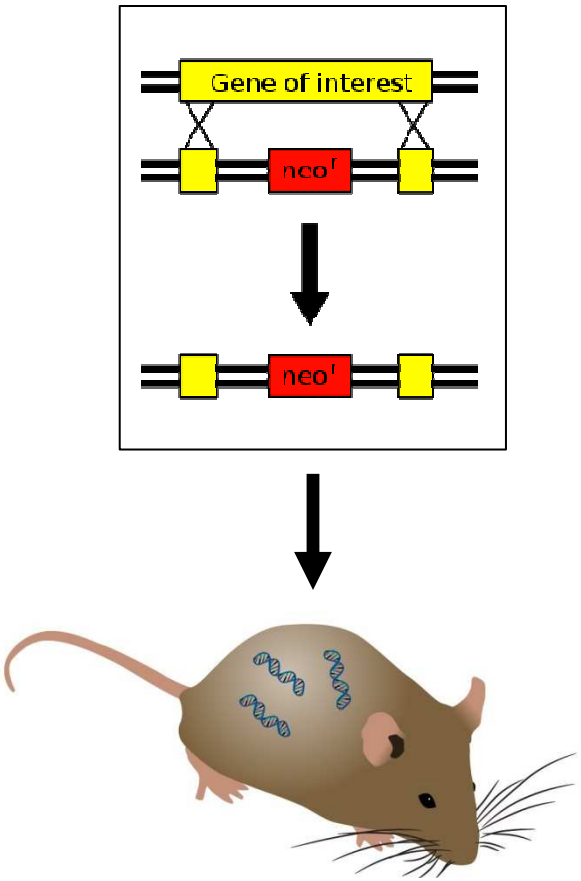


Keir, ME *et al*. Annu Rev Immunol (2008) 26:677. Pardoll, DM. Nat Rev Cancer (2012) 12:252.

CTLA-4 vs PD-1: Distinct Immune Checkpoints



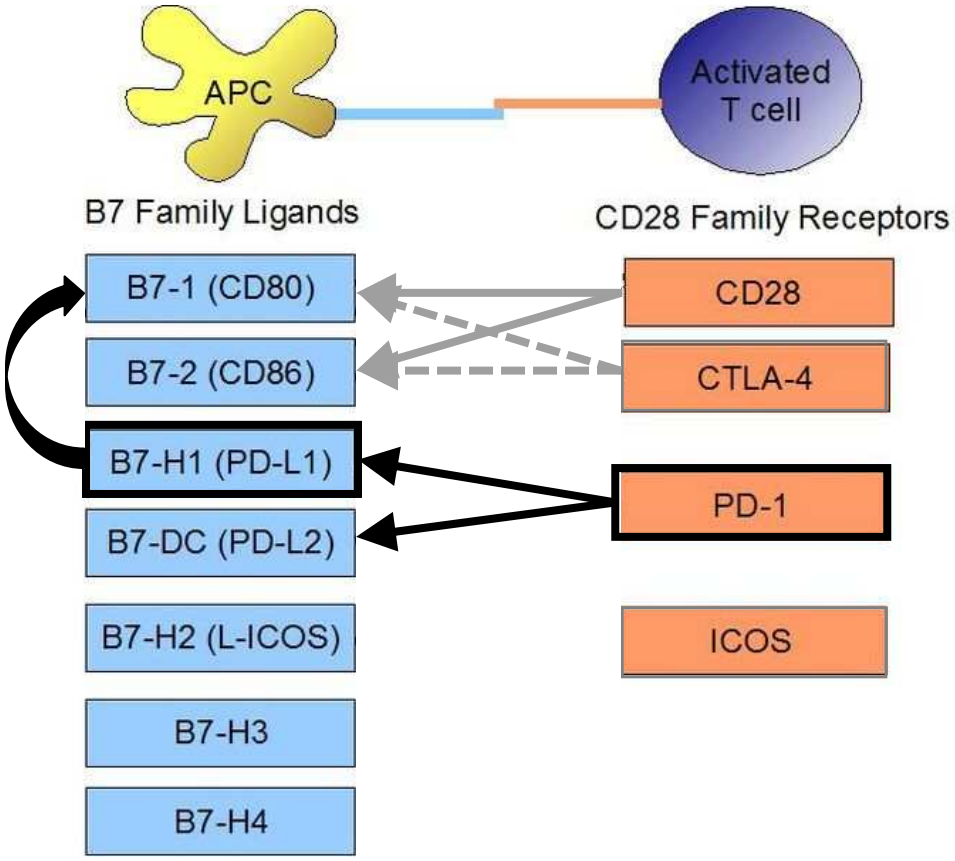
Immune Checkpoint Function Revealed by Murine Knockout Studies



Gene Knockout	Phenotype
CTLA-4	▪ lymphoproliferative disease ▪ multi-organ lymphocytic infiltration ▪ death by 3 to 4 weeks
PD-1	▪ strain specific autoimmune syndromes – Arthritis – Glomerulonephritis – dilated cardiomyopathy
PD-L1	▪ No spontaneous autoimmunity

Waterhouse, P *et al*. Science (1995) 270:985. Tivol, EA *et al*. Immunity (1995) 3:541. Nishimura, H *et al*. Immunity (1999) 11:141. Nishimura, H *et al*. Science (2001) 291:319. Latchman, YE *et al*. PNAS (2004) 101:10691.

PD-1/PD-L1 Binding Interactions



PD-L1 (B7-H1, CD274)

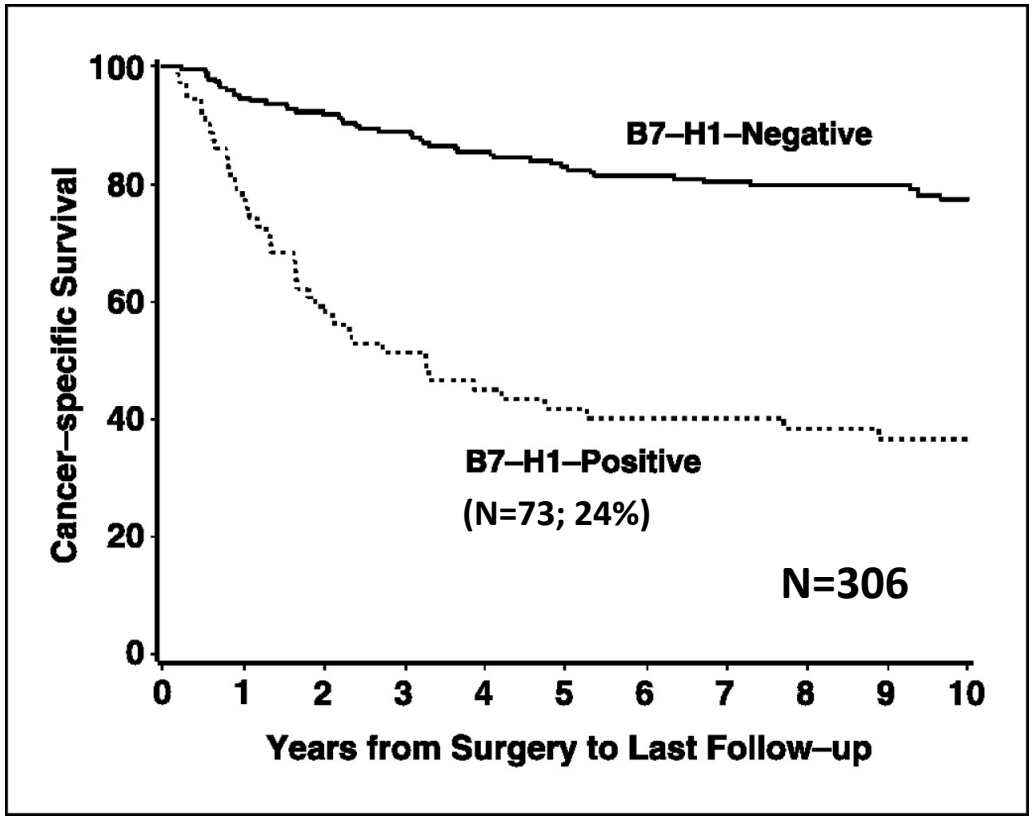
- **Constitutive Expression**
  - Macrophage, DC, B-cell, ?T-cell
- **IFN-γ Inducible**
  - Tumor, normal epithelium

PD-L1 Expression is Common in Solid and Hematopoietic Tumors

Cancer Type	Histology	% PD-L1^{+} Tumors
Solid Tumors	Melanoma	40-100
	NSCLC	35-95
	RCC	15-24
	CRC	53
	Gastric	42
	Ovarian cancer	33-80
	Pancreatic	39
	Breast	31-34
	HCC	45-93
	Urothelial carcinoma	28-100
Hematologic Tumors	Multiple Myeloma	93
	Lymphomas	17-94
	Leukemias	11-42

Adapted from Chen, DS *et al*. Clin Ca Res (2012) 18:6580.

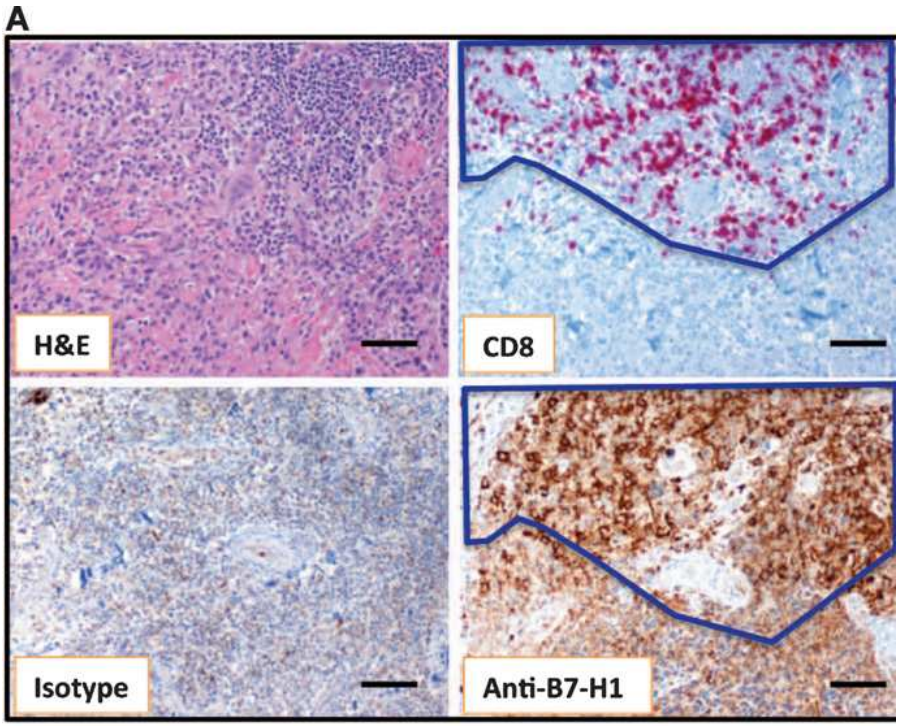
Association of Tumor B7-H1 (PD-L1) Expression with Death from ccRCC



In multivariate analysis, PD-L1 expression (≥ 5%) on RCC tumor cells was an independent risk factor for death

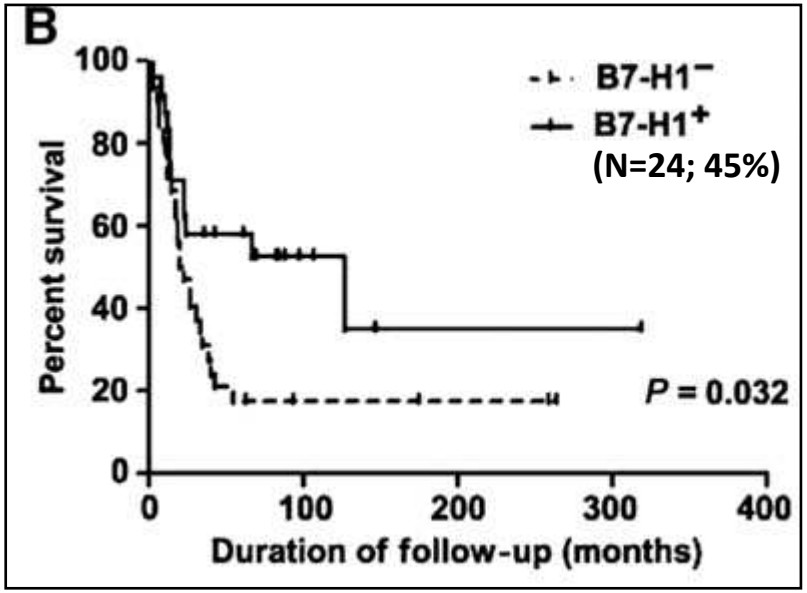
Thompson, RH *et al*. Cancer Res (2006) 66:3381-3385.

Strong Association of PD-L1 Expression in Melanoma with Immune Cell Infiltration



- PD-L1 and TIL co-localize
- TIL may trigger their own inhibition by IFN-γ mediated PD-L1 induction

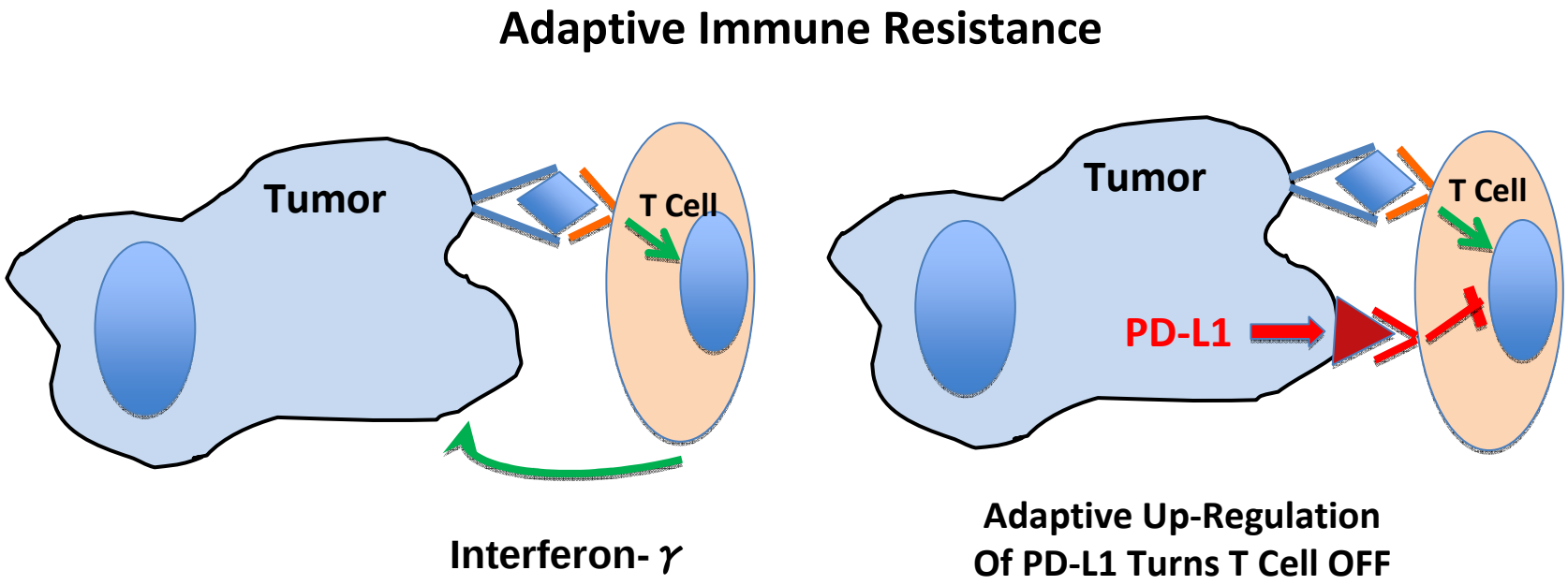
Metastatic Melanoma (N=53)



PD-L1 expression (≥ 5%) on melanocytes was positively associated with survival

Taube, JM *et al*. Sci Transl Med (2012) 4:ra37.

Tumor Immune Escape by "Adaptive Resistance"



Taube, JM *et al*. Sci Transl Med (2012) 4:ra37.

PD-1 Targeted Drugs in Development 2013

PD-1 Blockade

Drug	Developer	Composition	Development Phase
Nivolumab (BMS-936558)	Bristol-Myers Squibb	fully human IgG4 mAb	phase III
MK-3475	Merck	humanized IgG4 mAb	phase III
CT-011	CureTech / Teva	humanized IgG1 mAb	phase II
AMP-224	Amplimmune / GlaxoSmithKline	PD-L2 / IgG1 fusion protein	phase I

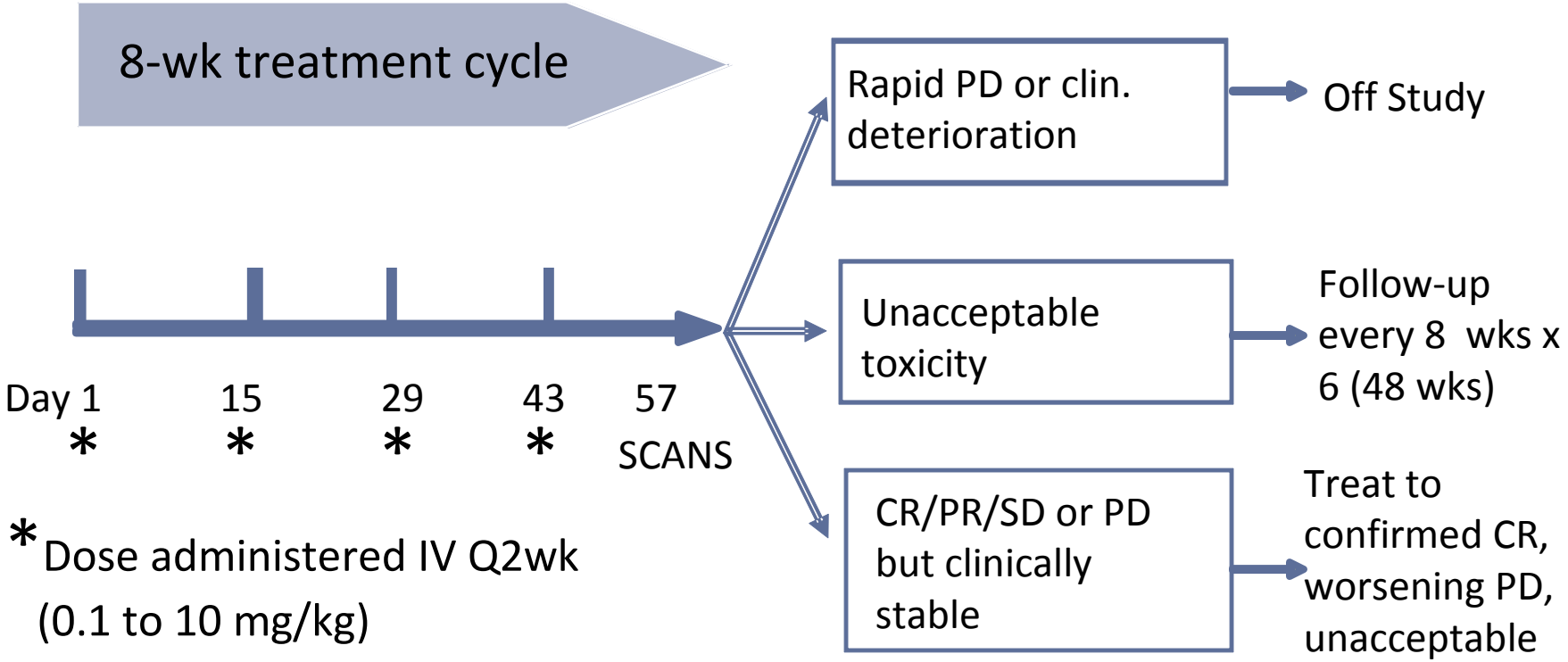
Abbreviations: mAb - monoclonal antibody

Anti-PD1 Monoclonal Antibody Nivolumab (BMS-936558, MDX-1106)

- Fully human IgG4 anti-human PD-1-blocking Ab
- No known Fc function (ADCC, CDC)
- High affinity for PD-1 (K_D ~3 nM)
- Preliminary results of a phase Ib dose-escalation study with nivolumab published June 2012
- 296 patients in total with melanoma, RCC, NSCLC, colorectal cancer, or prostate cancer

Topalian, SL *et al*. New Engl J Med (2012) 366:2443

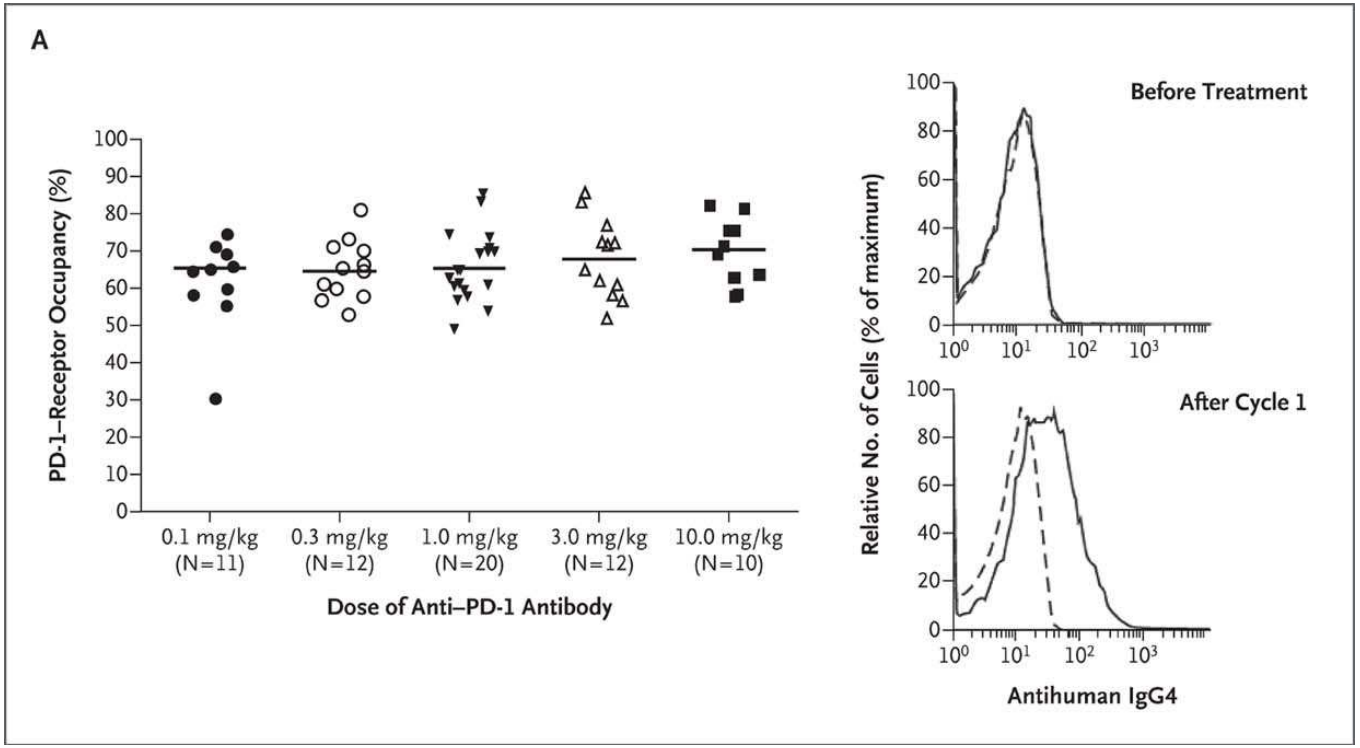
Nivolumab Study Design: Phase Ib Multi-dose Regimen



*Dose administered IV Q2wk (0.1 to 10 mg/kg)

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

PD-1–receptor occupancy by anti–PD-1 antibody



Topalian, SL *et al*. New Engl J Med (2012) 366:2443

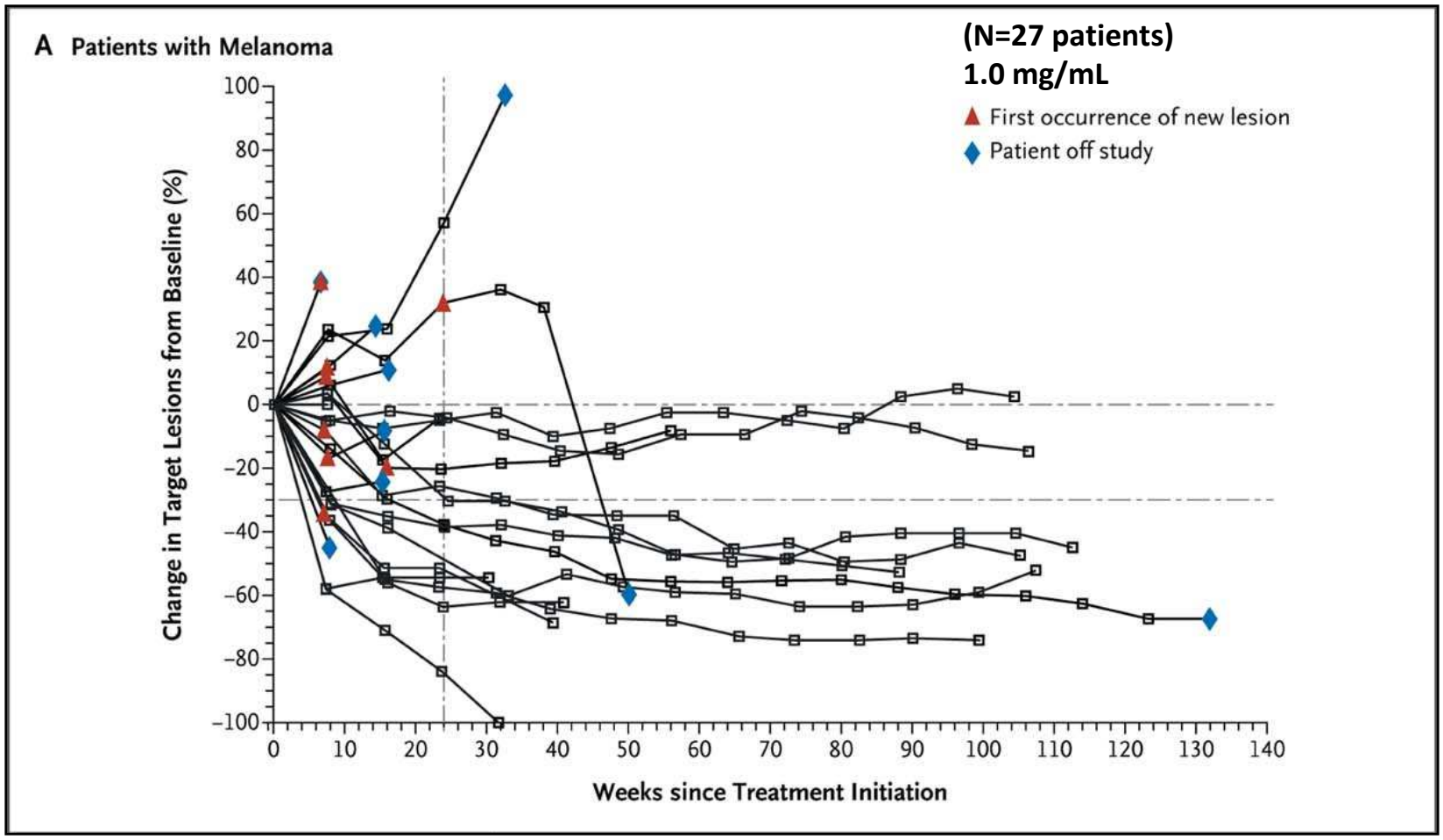
Clinical Activity of Nivolumab in 236 Patients; (All Doses)

Tumor Type		Patients	ORR (%)	SD ≥24 weeks (%)	PFSR at 24 Weeks (%)
Melanoma		94	28	6	41
NSCLC	*Squamous*	18	33	0	33
	Nonsquamous	56	12	9	22
RCC		33	27	27	56

- **ORR was assessed using modified RECIST v1.0 criteria**
- **ORR = objective response rate; PFSR = progression-free survival rate; SD = stable disease**
- **8 additional pts with reduction in tumor measurements, but in presence of new lesions – Immune related response pattern**

Topalian, SL *et al*. New Engl J Med (2012) 366:2443

Changes in Melanoma Tumor Burden with Nivolumab Treatment



Topalian, SL *et al*. New Engl J Med (2012) 366:2443

Immune-related Adverse Events (irAE) Associated with Nivolumab (anti-PD1)

Adverse Event	Any Event (%)	Grade 3/4 (%)
Any	41	6
Dermatologic Prutitis Rash	21	1
Gastrointestinal Diarrhea	11	1
Hepatic	4	1
Endocrine Hypothyroid Hypophysitis Adrenal insufficiency	3	1
Pulmonary	3	1*

- Data from 296 pts (all histologies entered on phase Ib study)
- *Includes 3 deaths from pneumonitis

Topalian, SL *et al*. New Engl J Med (2012) 366:2443

PD-L1 Targeted Drugs in Development 2013

PD-L1 Blockade

Drug	Developer	Composition	Development Phase
MPDL3280A (RG7446)	Genetech	IgG1 mAb with a modified Fc domain	phase II
BMS-936559	Bristol-Myers Squibb	fully human IgG4 mAb	phase I
MEDI4736	MedImmune / AstraZeneca	fully human mAb	phase I

Abbreviations: mAb - monoclonal antibody

MPDL3280A: Anti-PD-L1

- IgG1 anti-human PD-L1 blocking Ab
- Fc domain engineered to remove ADCC function and avoid killing activated T cells
- Inhibits PD-L1 binding to PD-1 or B7-1 in vitro

Herbst, RS *et al*. JCO (2013) 31:abstr 3000.

MPDL3280A - Phase Ia Experience (N=171)

- Administered iv q3 weeks x maximum of 16 doses (~ 1 yr)
- Doses ranging from 0.01 mg/kg to 20 mg/kg;

(162/171 patients treated at doses ≥ 3mg/kg)

- Primary Objectives:
  - Evaluate safety and tolerability
  - Determine MTD and recommended phase II dose

Tumor Type	N (Total = 171)
Melanoma	**44 (26%)**
RCC	**55 (32%)**
NSCLC	**52 (30%)**
Other 10 histologies included CRC (4), gastric	**20 (12%)**

Herbst, RS *et al*. JCO (2013) 31:abstr 3000.

MPDL3280A Efficacy Summary (N=140)

Tumor Type	Patients	ORR (%)	SD ≥24 weeks (%)	PFSR at 24 Weeks (%)
Melanoma	38	29	5	43
NSCLC	41	22	12	46
RCC	47	13	32	53

- **ORR was assessed using modified RECIST v1.1 criteria**
- **ORR = objective response rate; PFSR = progression-free survival rate; SD = stable disease**
- **Additional delayed responses not reflected in ORR**
- **Other responses included CRC (PR 1/4) and gastric (PR in 1/1)**

Herbst, RS *et al*. JCO (2013) 31:abstr 3000.

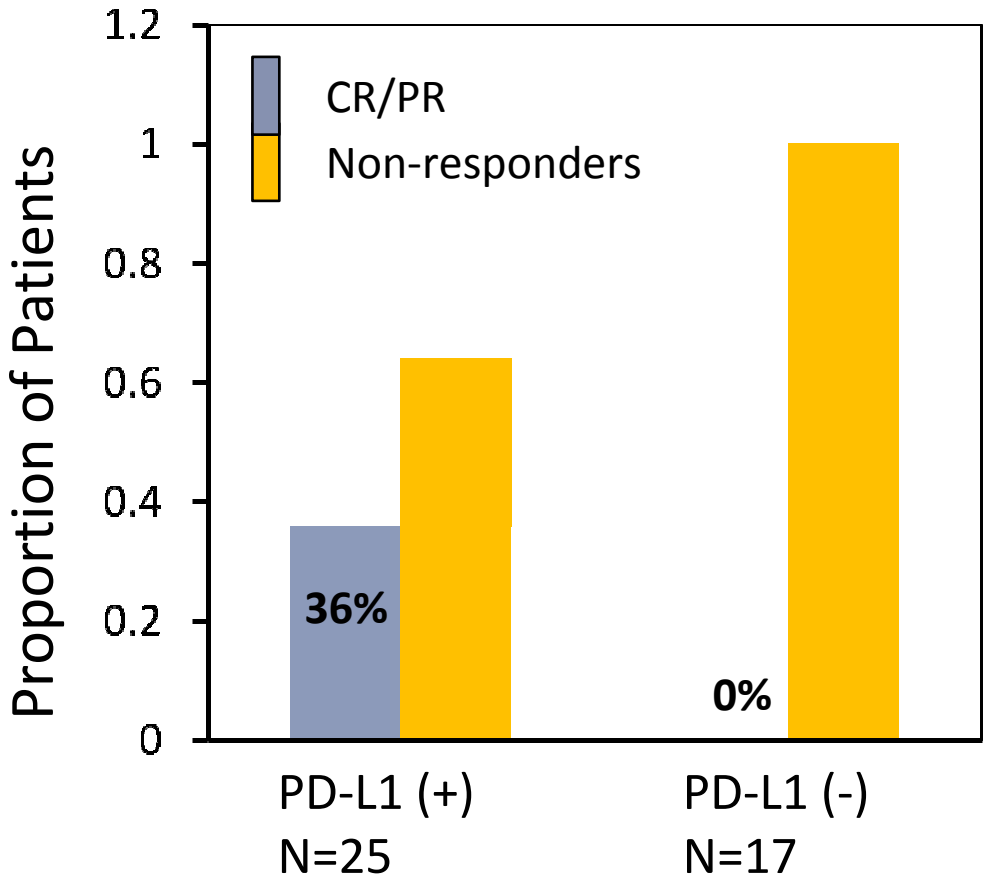
MPDL3280A Phase Ia Safety – Immune-related AE

Adverse Event	Grade 3/4 N (%)
Any	4 (2)
Dermatologic Prutitis Rash	0
Gastrointestinal Diarrhea	1 (0)
Hepatic	2 (1)
Endocrine Hyperglycemia	1 (0)
Pulmonary	0*

- No Treatment related deaths
- No Grade 3-5 pneumonitis
- No MTD identified at doses tested

Herbst, RS *et al*. JCO (2013) 31:abstr 3000.

Correlation of PD-L1 Expression in Pretreatment Tumor Biopsies with Responses to Nivolumab



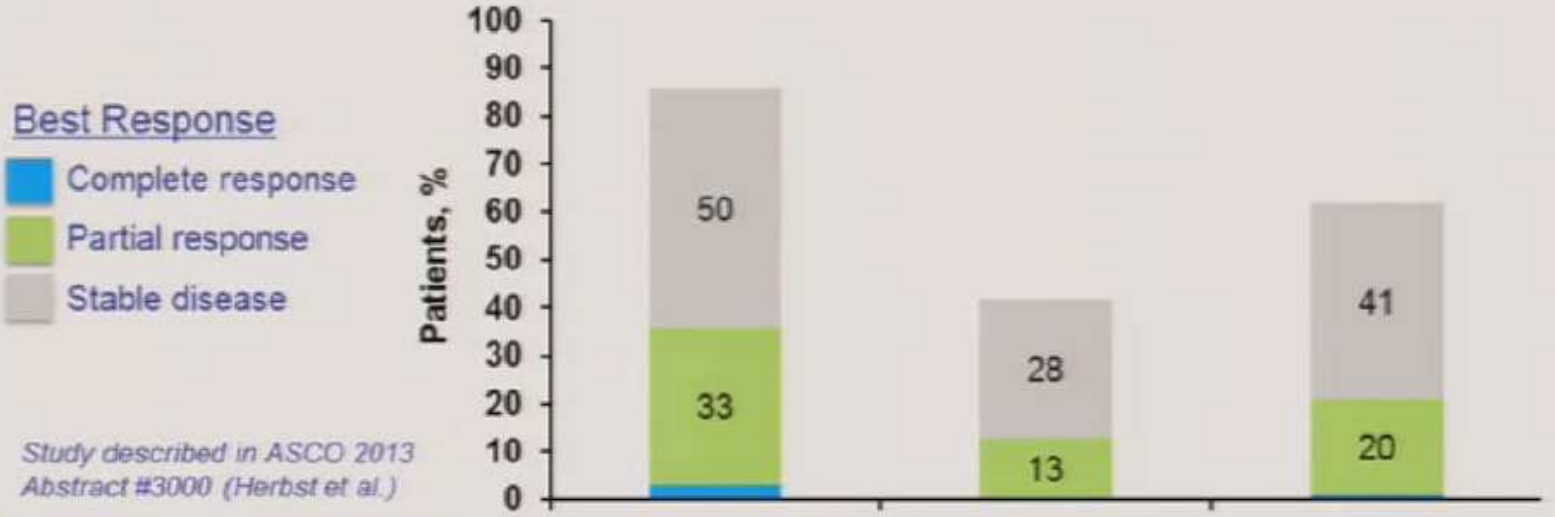
- PD-L1 expression in pretreatment tumor biopsies across tumor types from 42 pts
- Positive defined as ≥ 5% tumor cells PD-L1^{+}
- *P=0.006*

Topalian, SL *et al*. New Engl J Med (2012) 366:2443

MPDL3280A Phase Ia: Response by PD-L1 IHC Status (N=103/140)

Investigator-Assessed Overall Response Rate (ORR*); % (n/n)

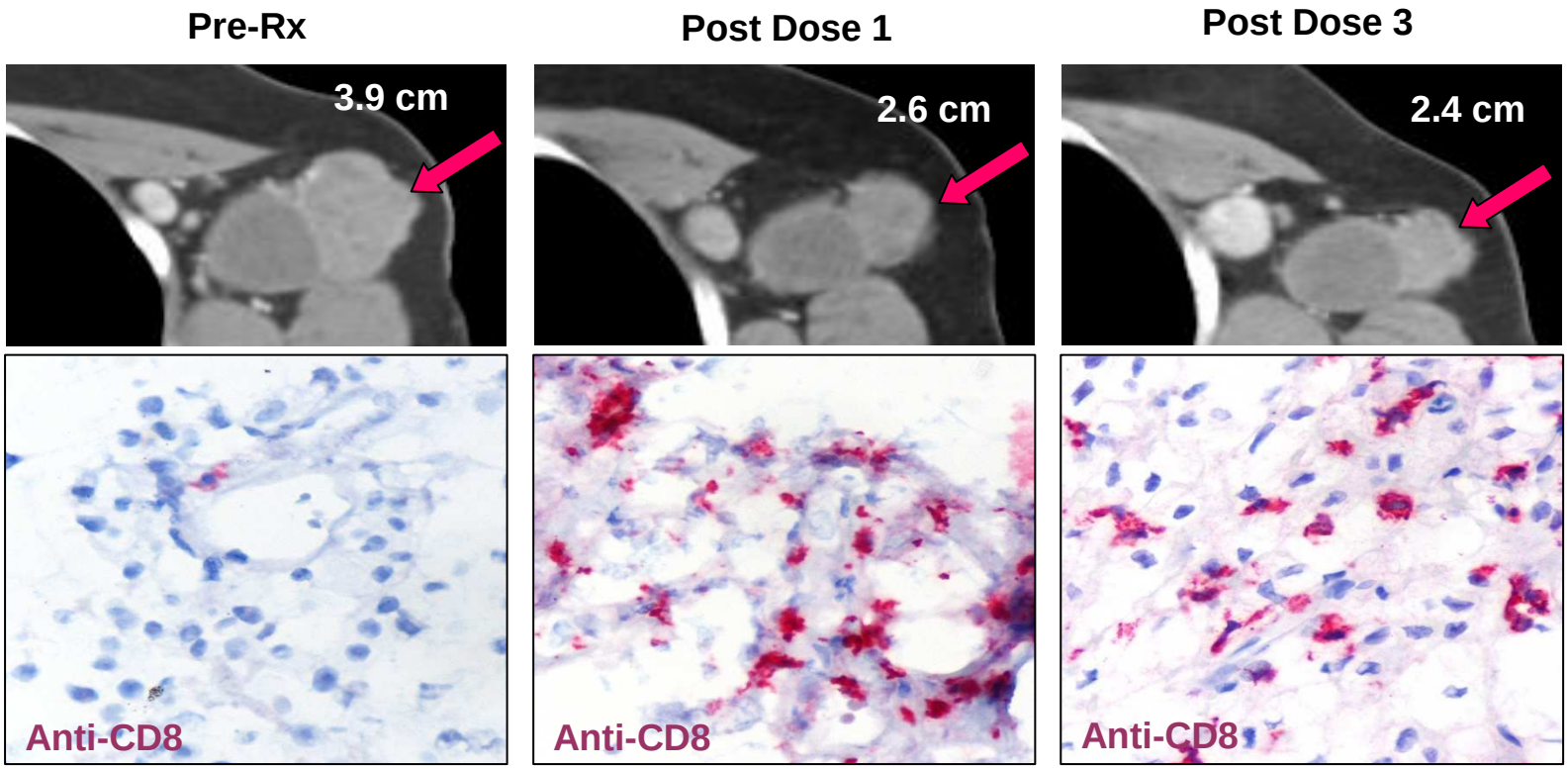
	PD-L1 Positive	PD-L1 Negative	All†
Overall population (N = 140)	36% (13/36)	13% (9/67)	21% (29/140)



- *PD-L1 positive* defined as tumors with infiltrating immune cells that stain for PD-L1 using Genentech/Roche Dx IHC
- Further assessment of PD-L1 Dx ongoing

Herbst, RS *et al*. JCO (2013) 31:abstr 3000.

PD-1 Blockade: Increased CD8+ T Cells in a Regressing Melanoma Tumor Treated with Nivolumab



Brahmer, JR *et. al*. JCO (2010) 28:3167

MPDL3280A Phase Ia: PD-L1 IHC Status in Paired Tumor Biopsies

Summary of responses to MPDL3280A in paired biopsies

Max SLD Decrease*	Increase in tumor PD-L1†
> 30% reduction	4/4 (100%)
Unevaluable SLD (due to tumor excision¶)	2/2 (100%)
0-30% reduction	2/6 (33%)
0-20% increase	1/10 (10%)
> 20 increase	0/4 (0%)

* Best response; SLD = sum of linear dimensions.

† PD-L1 expression measured by proprietary Genetech/Roche IHC Assay for PD-L1 expression on infiltrating immune cells.

¶ Excision of responding tumor for marker analysis. Patient not evaluable for max SLD change.

Powderly, JD *et al*. JCO (2013) 31:abstr 3001.

Anti-PD1/PDL1 Cancer Immunotherapy: Summary and Conclusions

- Spontaneous and durable anti-tumor effects in a subset of patients with continuous treatment (q 2-3 weeks)
- Similar efficacy with PD-1 versus PD-L1 blockade
- Side effects are autoimmune in nature
  - Manageable in early testing
  - Similar spectrum of autoimmune phenomena with PD1 vs CTLA4
  - *frequency and severity of pneumonitis worse with PD1 vs CTLA4 blockade
- Ongoing evaluation of the association of pretreatment tumor expression of PD-L1 with clinical outcome.

Advanced Phase Clinical Trials Pipeline for Anti-PD1/PDL1 Therapies

Target	Diagnosis	Phase	Drug and Format	
PD-1	Melanoma	III	Nivolumab	- 1L vs Ipi or Combo - 1L vs dacarbazine - ≥ 2L vs chemo (Ipi +/- BRAF failure)
			MK-3475	- 1L vs Ipi
	NSCLC	III	Nivolumab	- 2L vs standard chemo (SSC and non-SSC)
			MK-3475	- 2L vs chemo
	RCC	III	Nivolumab	- 2L randomized vs everolimus
PD-L1	NSCLC Melanoma (RCC)	II	MPDL3280A	- (multiple studies)

www.clinicaltrials.gov