Therapy of Cancer With Anti-PD-1 Strategies and Combinations

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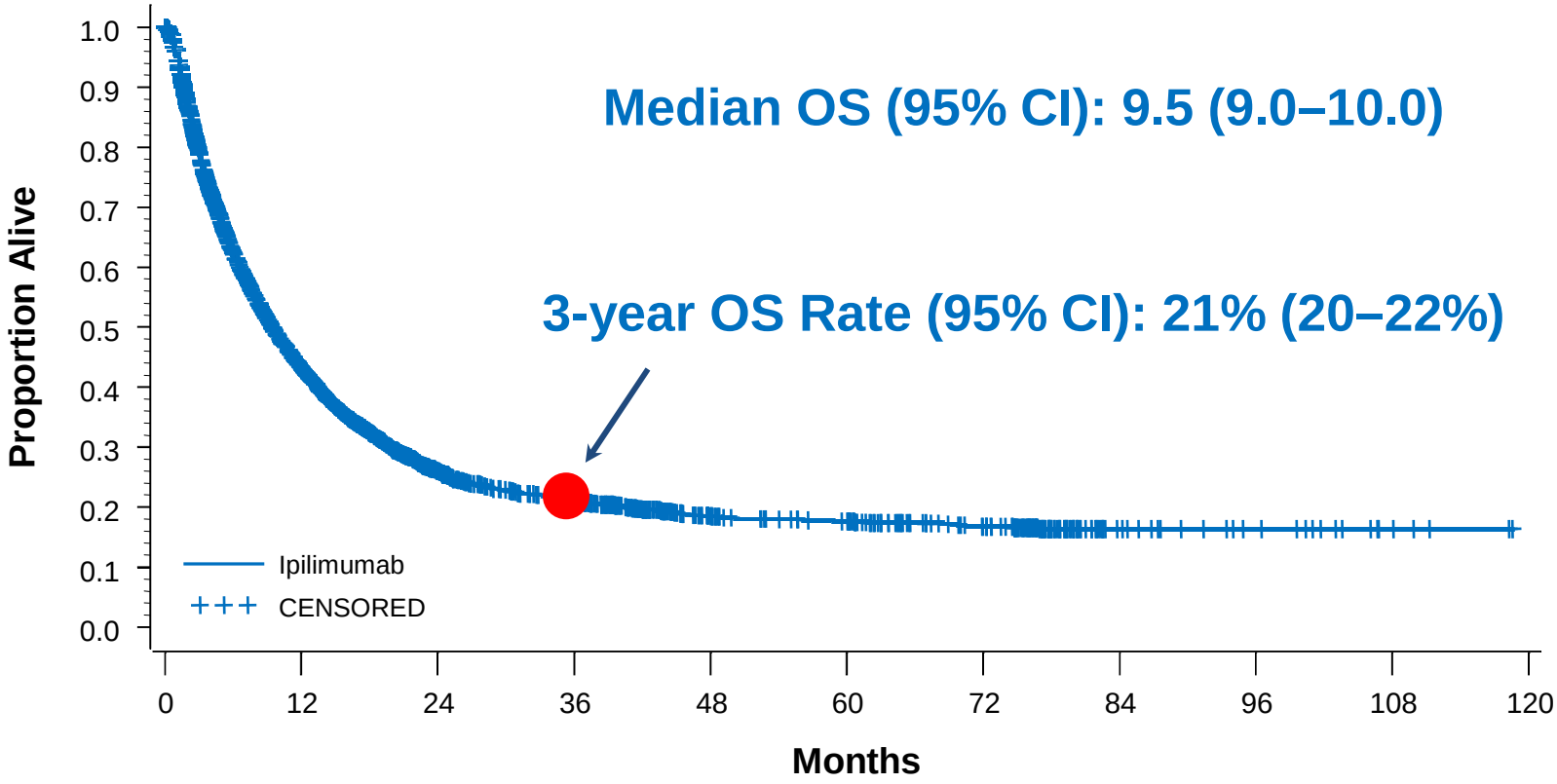
LUDWIG CANCER RESEARCH

Pooled OS Analysis Including EAP Data: 4846 Patients



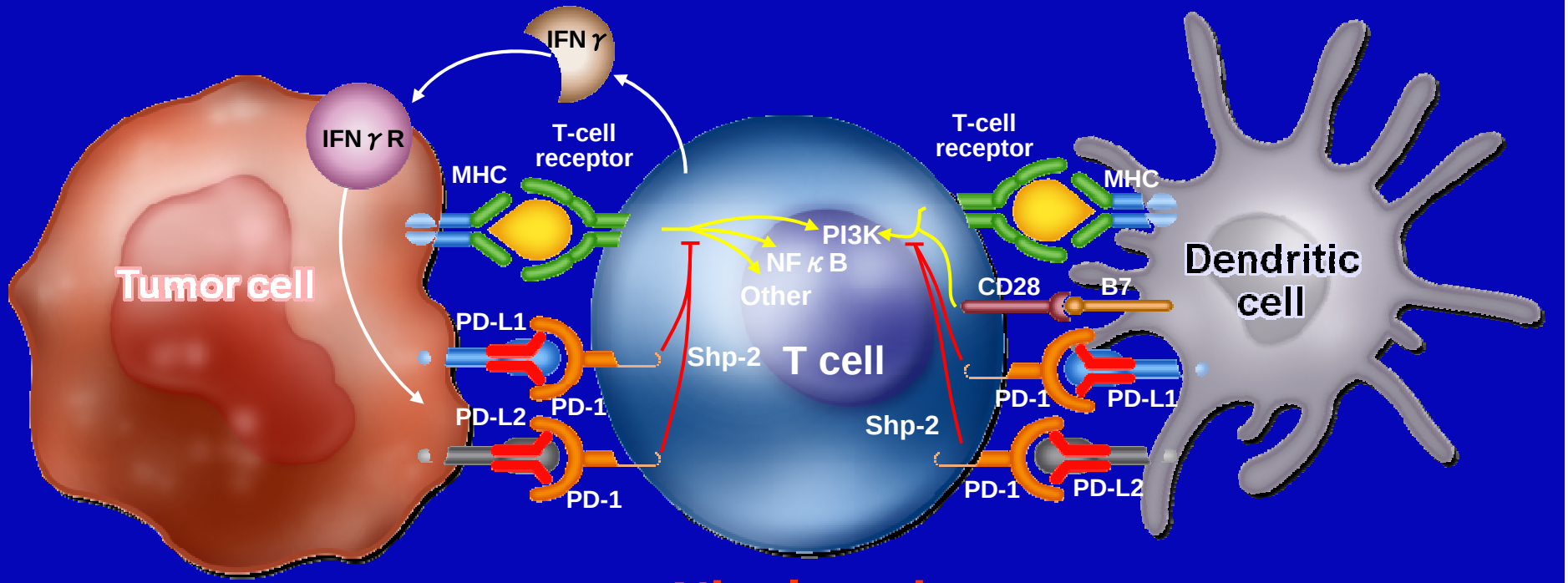
Patients at Risk

Ipilimumab	4846	1786	612	392	200	170	120	26	15	5	0

Role of PD-1 Pathway in Suppressing Anti-tumor Immunity

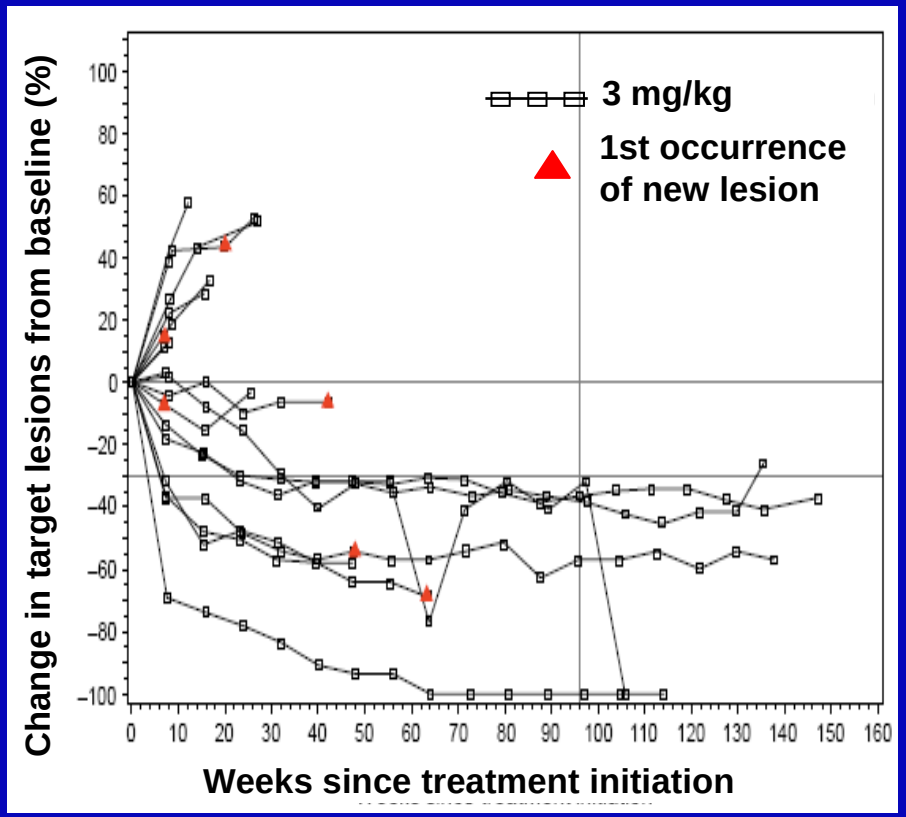
Recognition of tumor by T cell through MHC/antigen interaction mediates IFN γ release and PD-L1/2 up-regulation on tumor

Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells

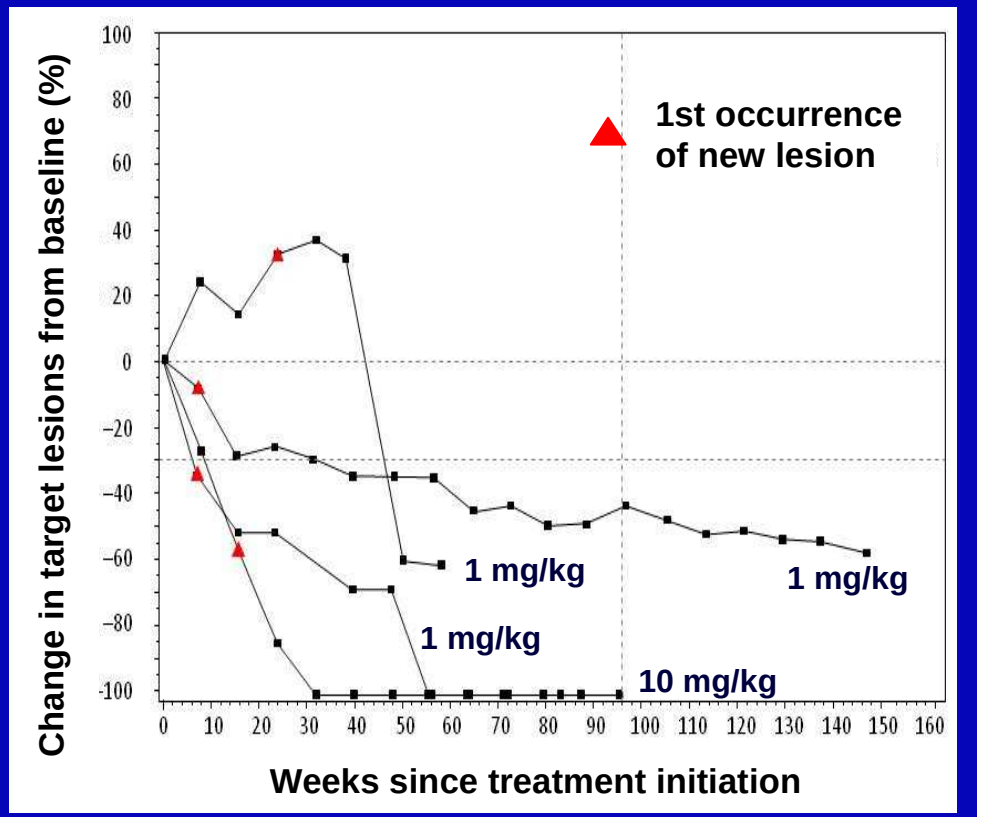


Nivolumab
PD-1 Receptor Blocking Ab

Changes in Tumor Burden in Patients with Melanoma Receiving Nivolumab 3 mg/kg



All Mel patients treated with 3 mg/kg nivolumab



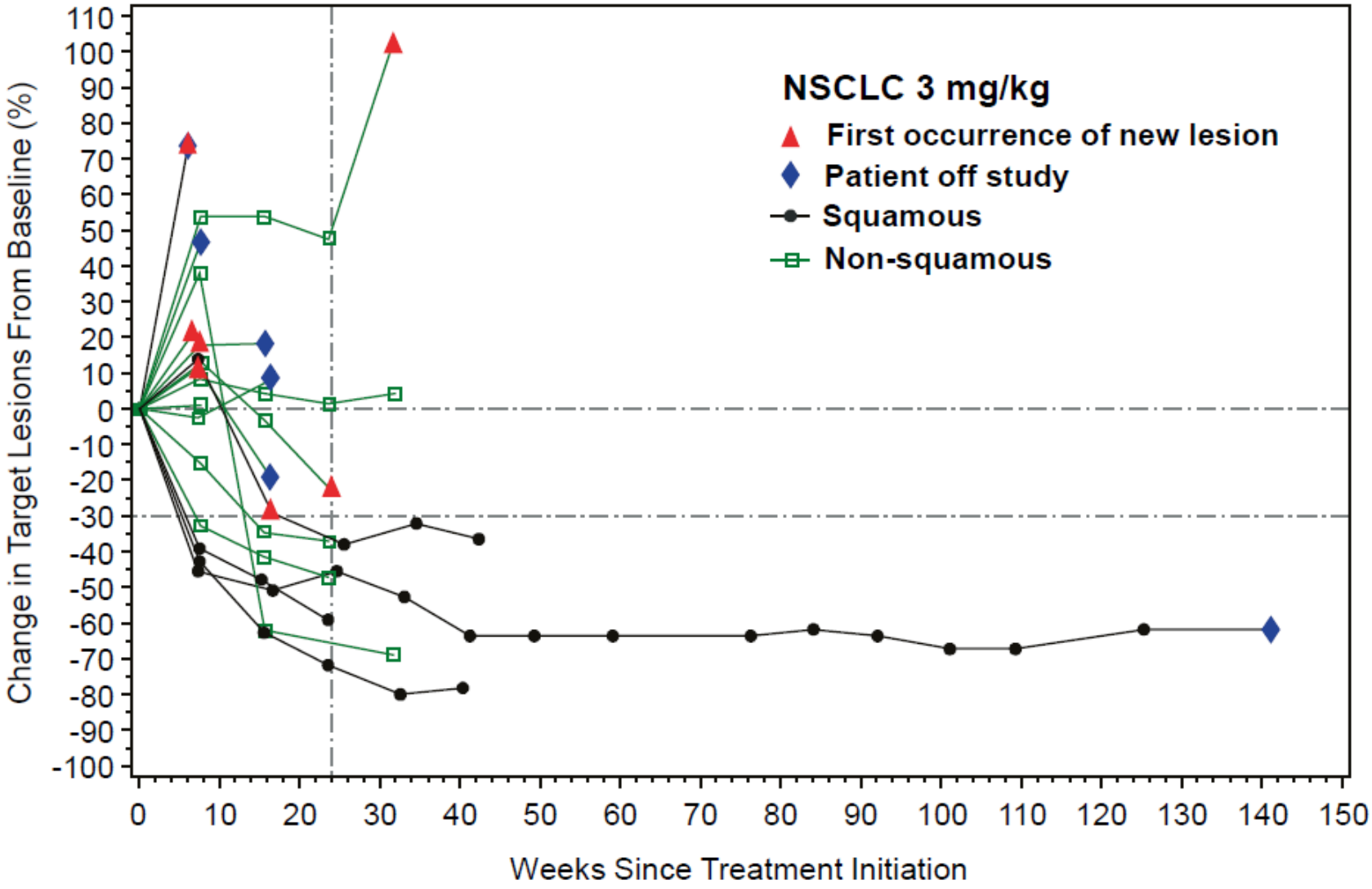
4 Mel patients treated with unconventional responses from nivolumab

Vertical line at 96 weeks = maximum duration of continuous nivolumab therapy

Horizontal line at −30% = threshold for defining objective response (partial tumor regression) in absence of new lesions or non-target disease according to RECIST

Unconventional response = response patterns that did not meet RECIST criteria (e.g., persistent reduction in target lesions in the presence of new lesions, or regression following initial progression)

Changes in Target Lesions Over Time in NSCLC Patients

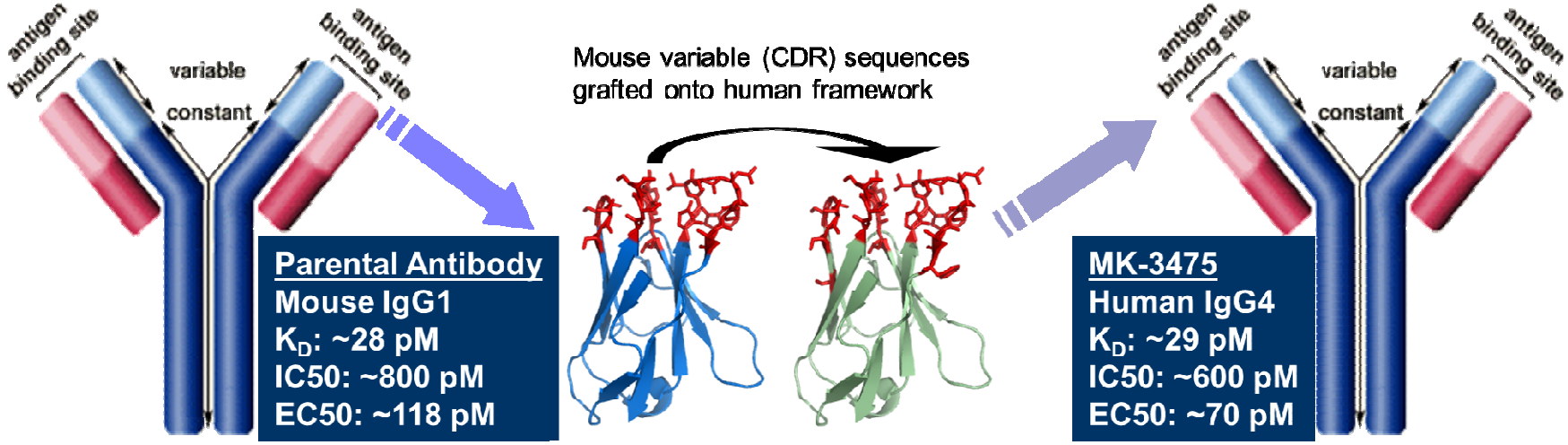


Select Drug-Related Adverse Events (≥1%) Occurring in Melanoma Patients Treated with Nivolumab

- Select AE: AE with potential immunologic etiologies that require more frequent monitoring and/or unique intervention
- All patients have ≥1 year of follow-up

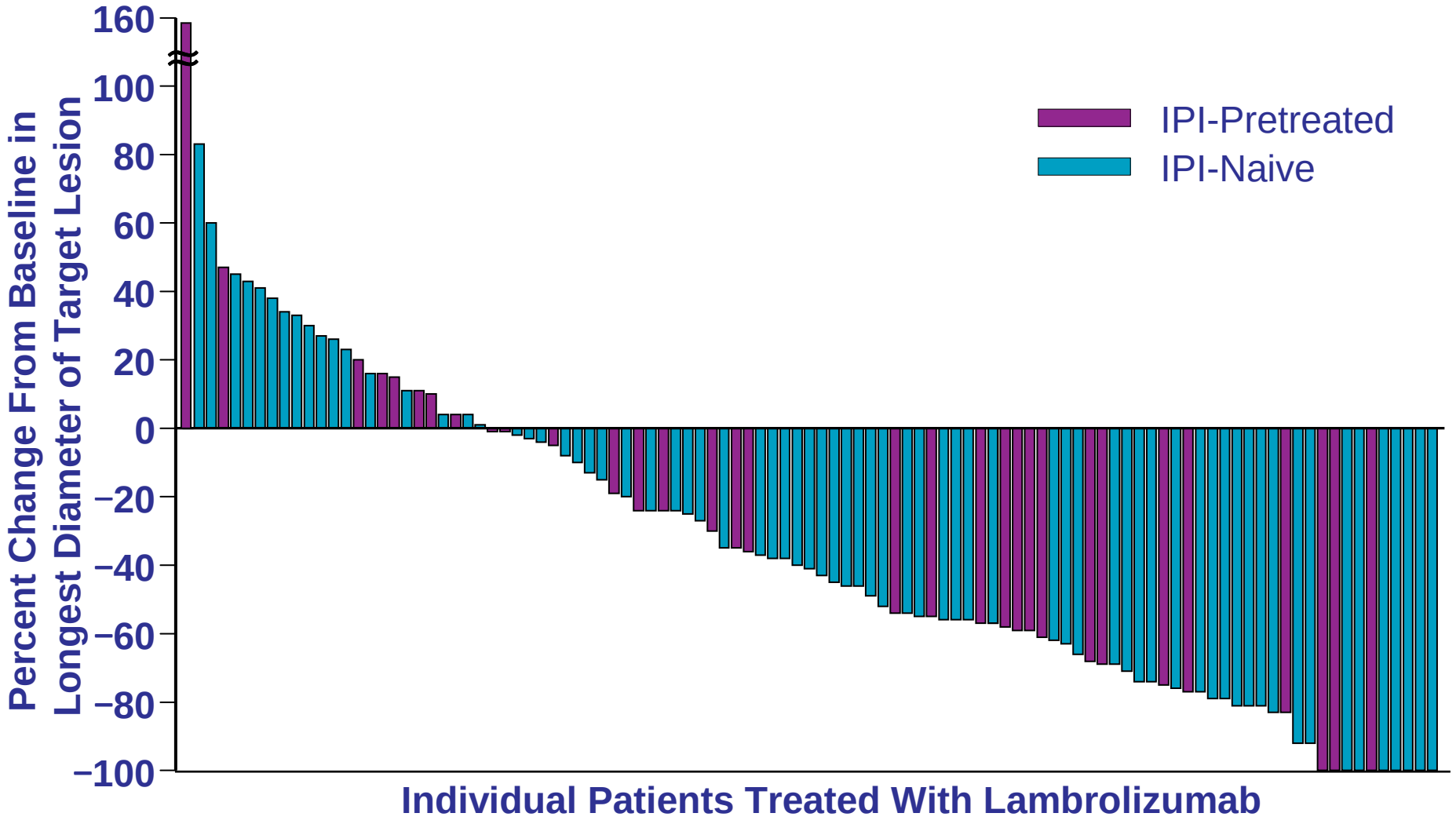
Category	Any Grade % (n)	Grade 3-4 % (n)
Any select AE	54 (58)	5 (5)
Skin	36 (38)	2 (2)
Gastrointestinal	18 (19)	2 (2)
Endocrinopathies	13 (14)	2 (2)
Hepatic	7 (7)	1 (1)
Infusion reaction	6 (6)	0
Pulmonary	4 (4)	0
Renal	2 (2)	1 (1)

Lambrolizumab (MK3475) Is a Humanized IgG4, High-Affinity Anti-PD-1 Blocking Antibody



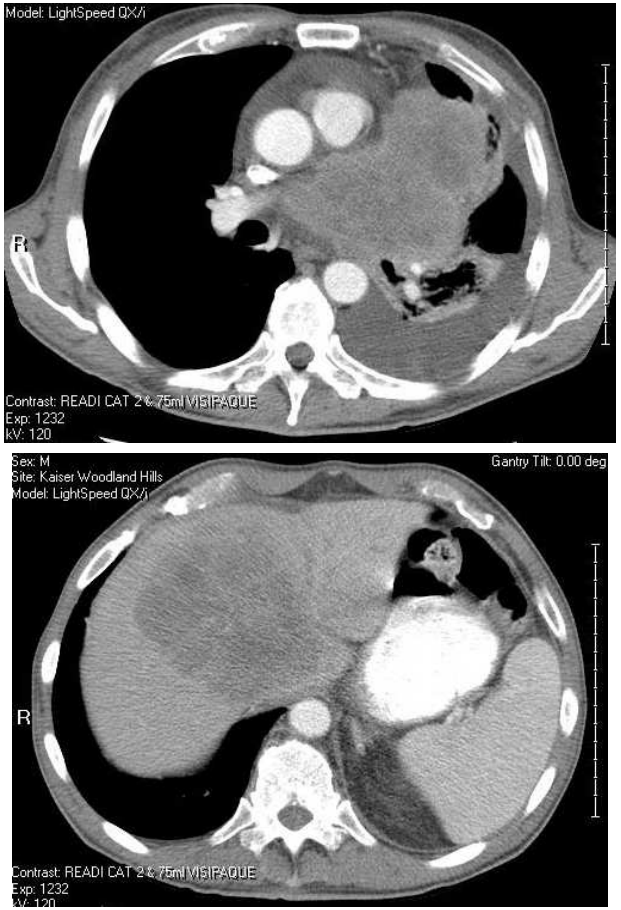
- No cytotoxic (ADCC/CDC) activity
- Pharmacokinetics supportive of dosing every 2 weeks (Q2W) or every 3 weeks (Q3W)
- Low occurrence of anti-drug antibodies and no impact on pharmacokinetics

Part B: Maximum Change From Baseline in Tumor Size (Independent Central Review per RECIST 1.1)

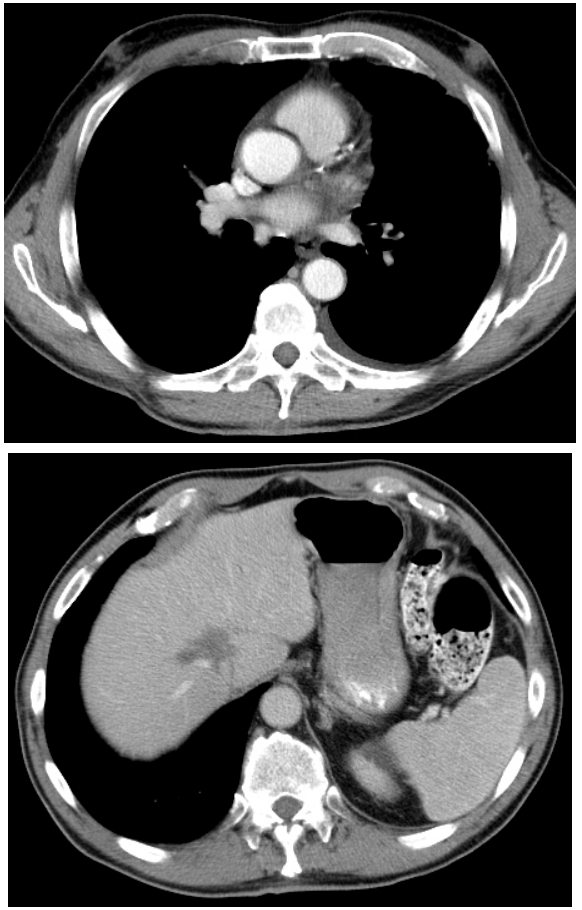


Clinical Activity, Patient 015-105

Baseline: April 13, 2012



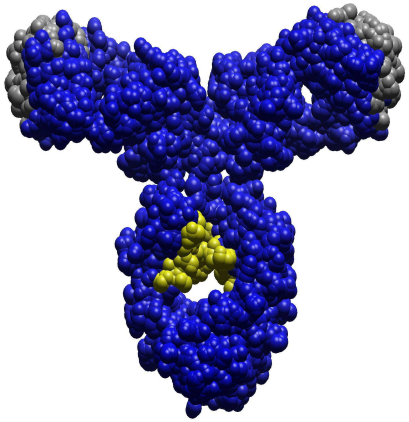
April 9, 2013



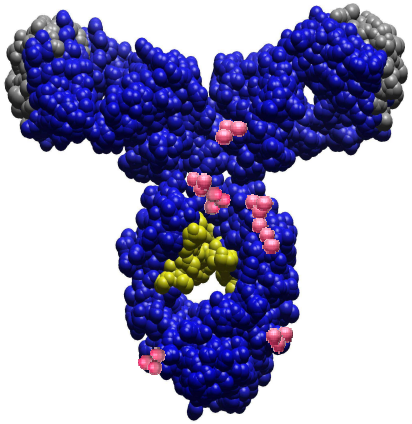
72-year-old male with symptomatic progression after bio-chemotherapy, HD IL-2, and ipilimumab

Images courtesy of A. Ribas, UCLA.

MPDL3280A: *Engineered* Anti-PD-L1 Antibody

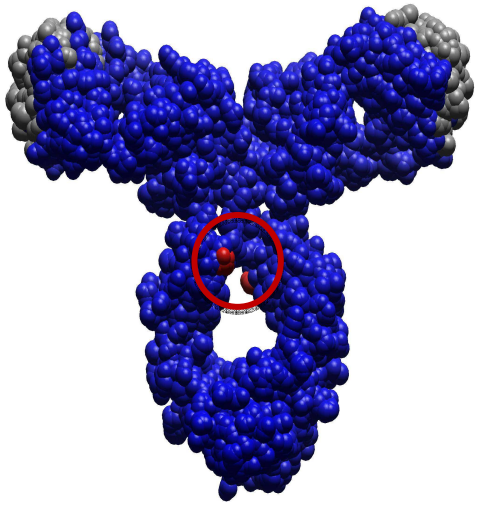


IgG1 Wt



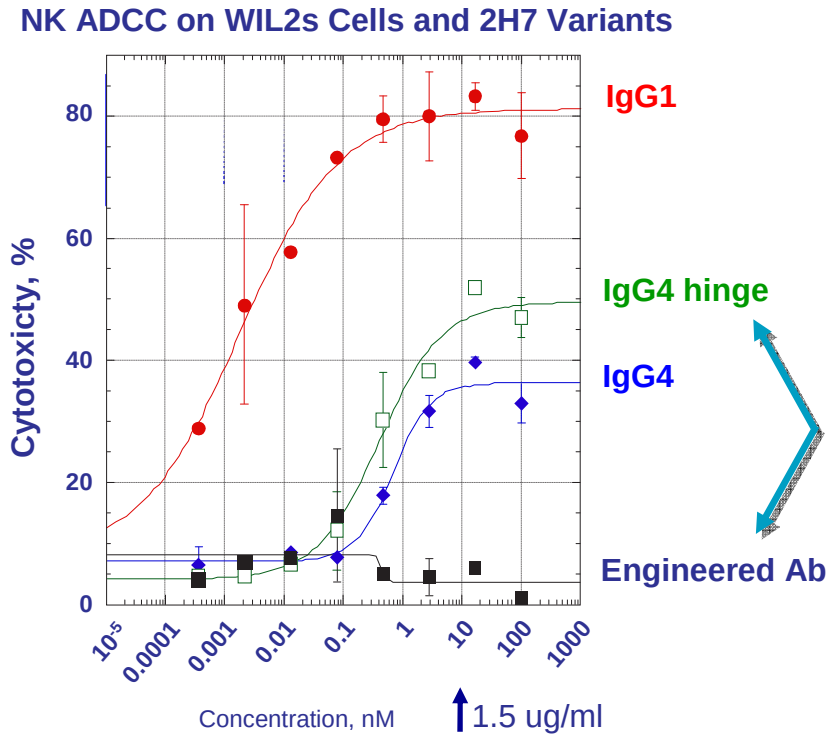
IgG4 hinge mutant

MPDL3280A:
Engineered to remove ADCC function



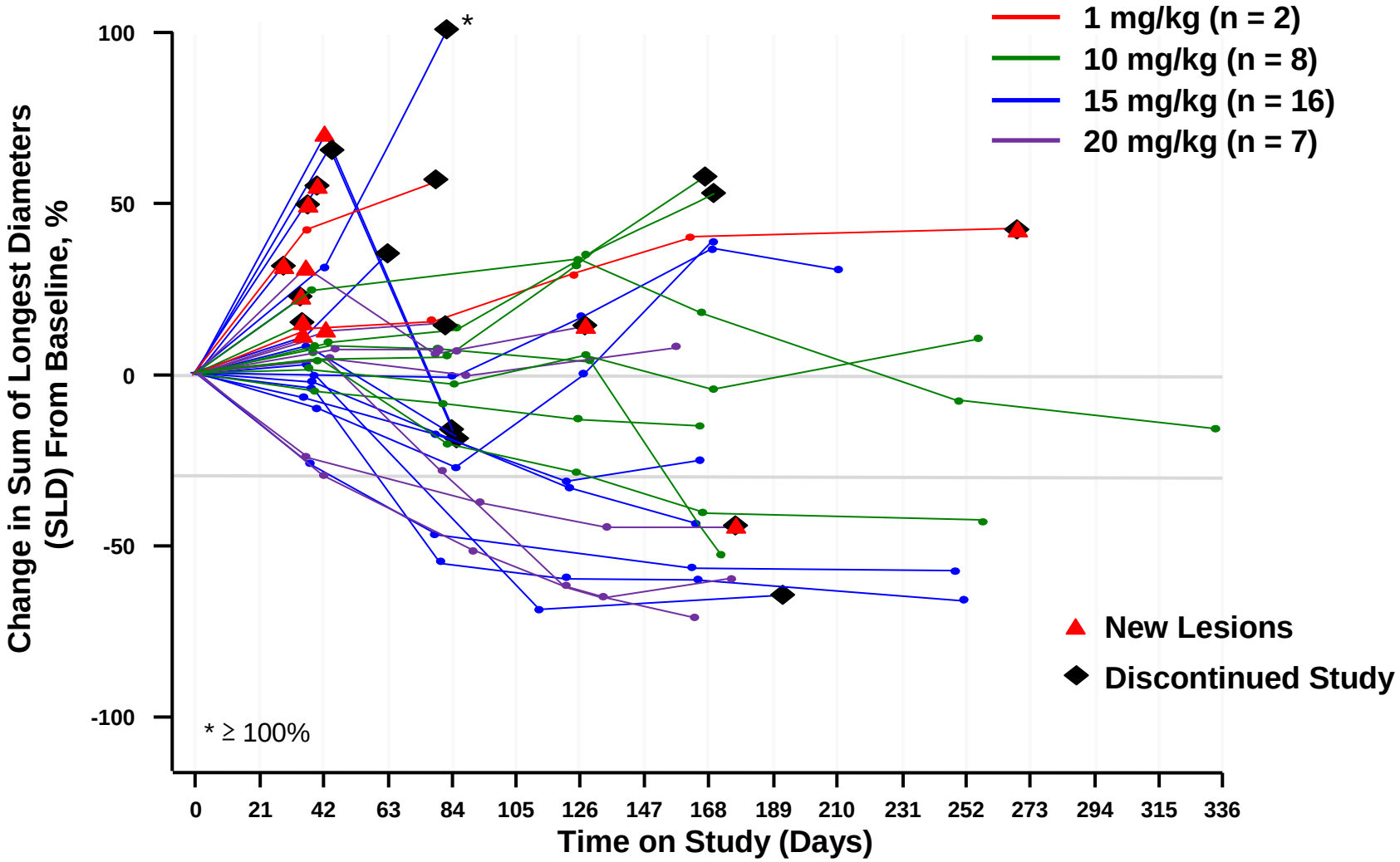
IgG1 Engineered

- Activated T cells express high levels of PD-L1 and PD-1
- MPDL3280A engineered specifically to avoid killing of activated T cells



* ADCC, antibody-dependent cell-mediated cytotoxicity.

MPDL3280A Phase Ia: Tumor Burden Over Time (Melanoma)



Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012 with at least 1 post-baseline evaluable tumor assessment; data cutoff Feb 1, 2013.

MPDL3280A: Efficacy Summary

Investigator Assessed

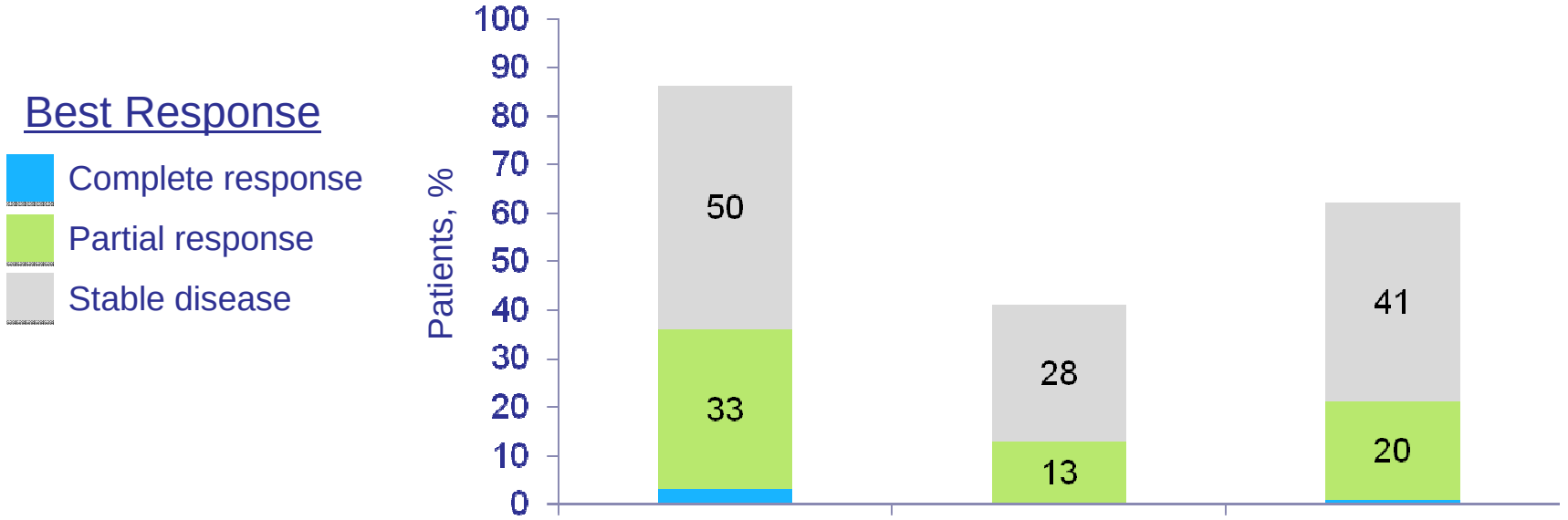
	RECIST 1.1 Response Rate (ORR*)	SD of 24 Weeks or Longer	24-Week PFS
Overall population (N = 140)	**21%**	**16%**	**45%**
NSCLC (n = 41)	22%	12%	46%
Melanoma (n = 38)	29%	5%	43%
RCC (n = 47)	13%	32%	53%

- 26 of 29 responders continued to respond at last assessment
  - Time on study in responders: 3 to 15+ months
- Additional delayed responses not reflected in above ORR
- Other tumor types (14) include CRC (PR in 1/4) and gastric cancer (PR in 1/1)

Patients dosed at 1-20 mg/kg prior to Aug 1, 2012. Data cutoff February 1, 2013.
7 patients who did not have a post-baseline scan were included as non-responders.
* ORR includes unconfirmed PR/CR and confirmed PR/CR.

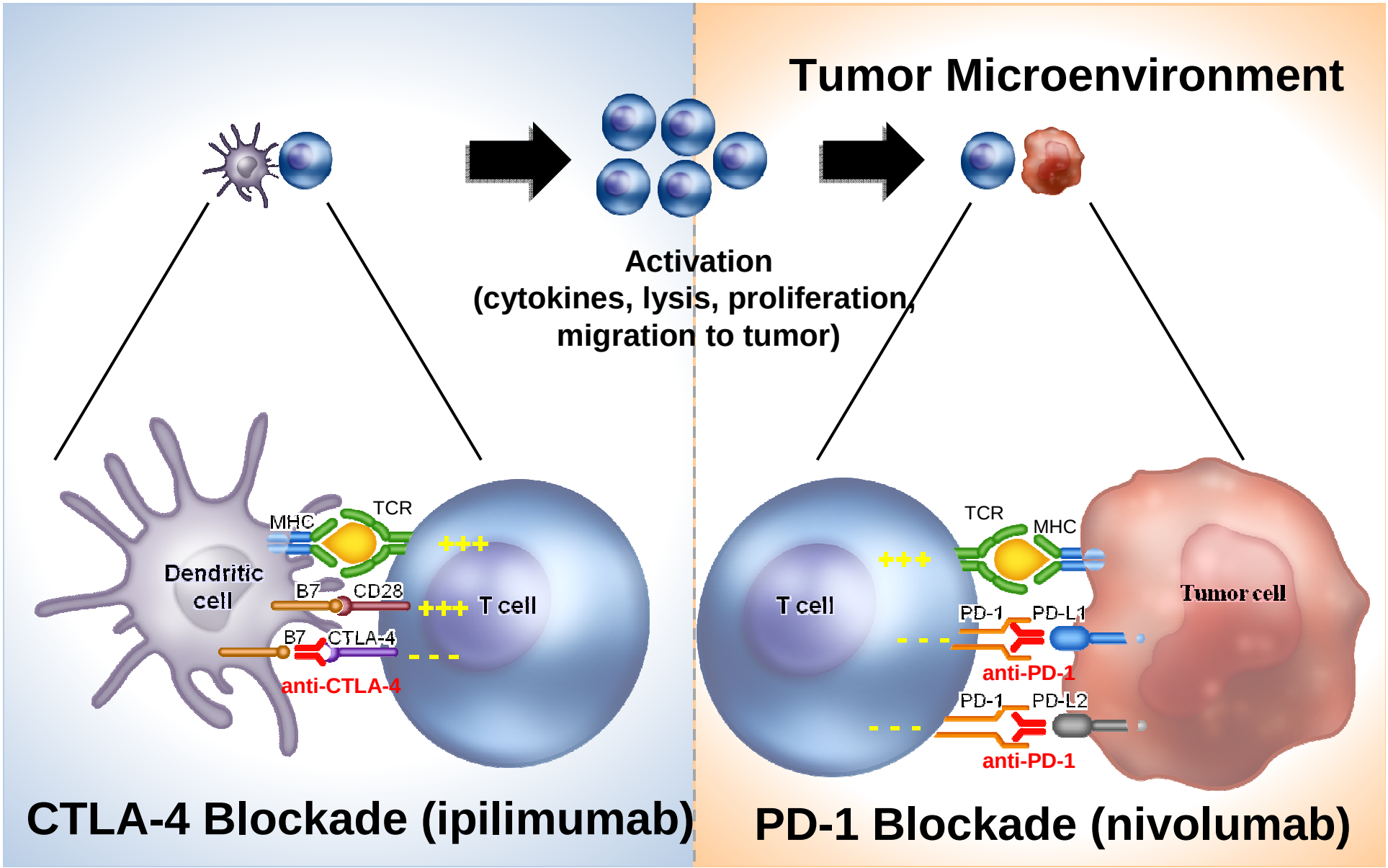
MPDL3280A: Summary of Response by PD-L1 IHC Status

Investigator-Assessed Response Rate (ORR*)			
	PD-L1 Positive	PD-L1 Negative	All†
Overall population (N = 140)	36% (13/36)	13% (9/67)	21% (29/140)



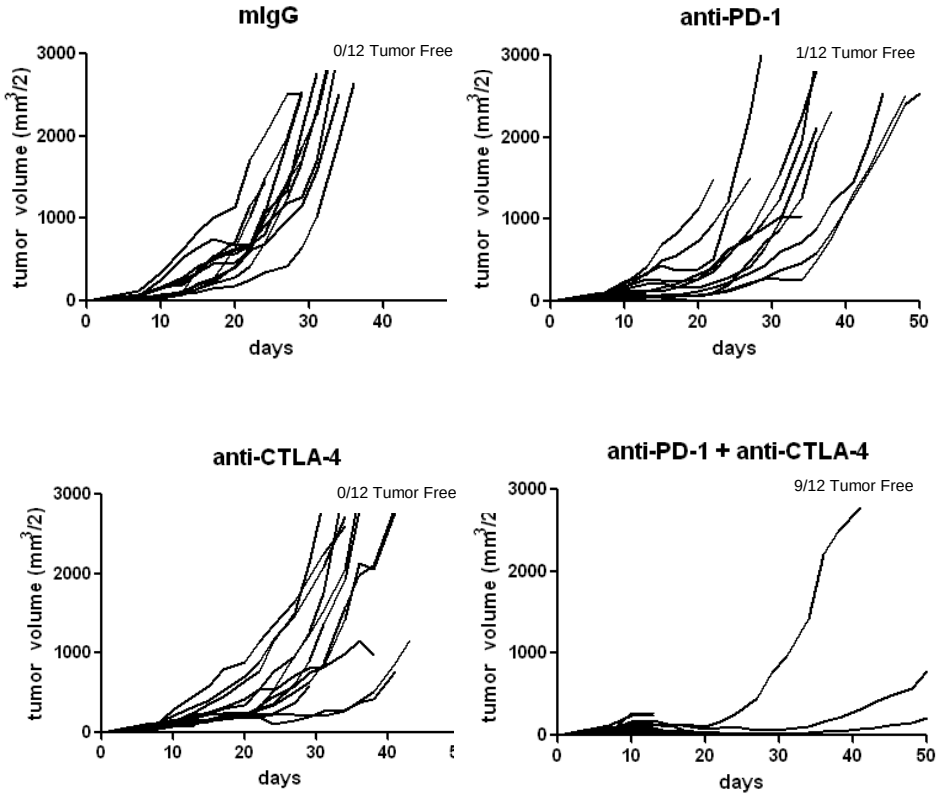
* ORR includes investigator assessed unconfirmed PR/CR and confirmed PR/CR by RECIST 1.1.
†All patients include PD-L1–positive, PD-L1–negative and patients with unknown tumor PD-L1 status.
Patients dosed at 1-20 mg/kg prior to Aug 1, 2012; data cutoff Feb 1, 2013.

Blocking CTLA-4 and PD-1

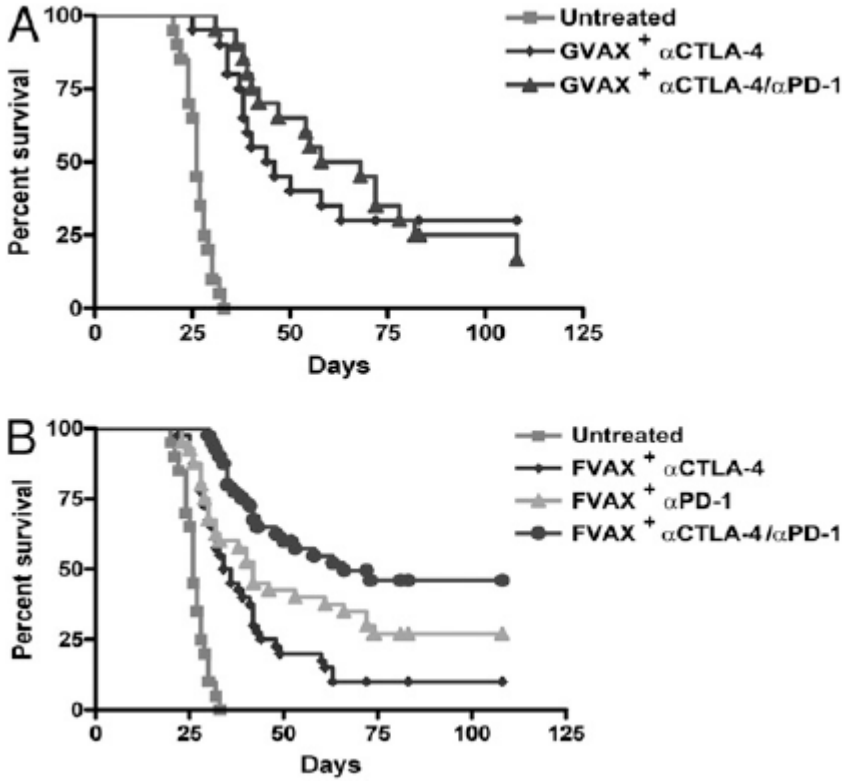


Antitumor Activity of Anti-CTLA-4 and Anti-PD-1 Antibodies in Murine Tumor Models

MC38 Colon Cancer
Antibody Rx Only [1, 2]



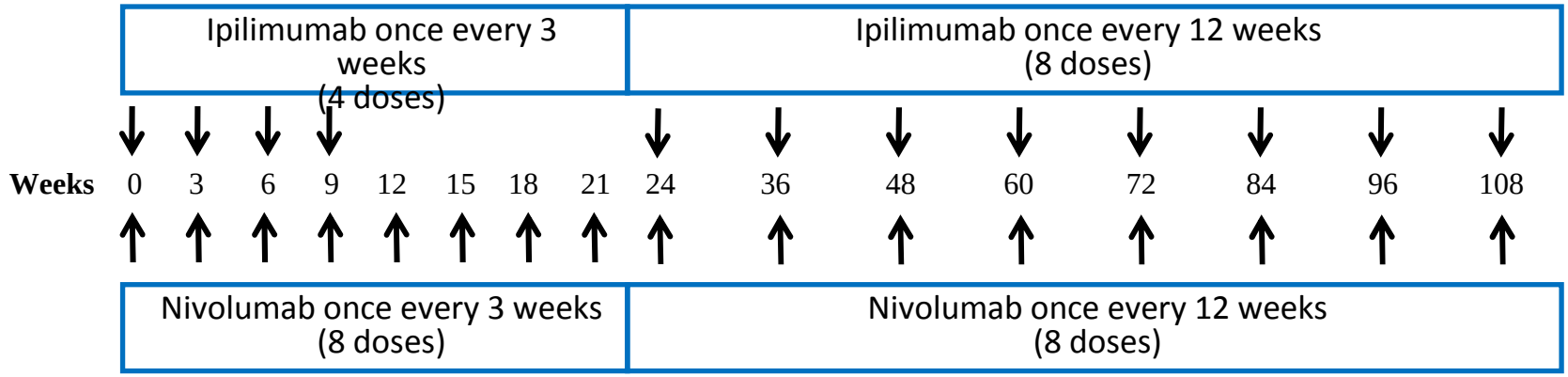
B16BL6 Melanoma
Antibody Rx + Cellular Vaccine[3]



[1]Korman et al. J Immunol. 2007;178:48.37. [2]Selby et al. ASCO 2013, abs 3061. [3]Curran et al. Proc Natl Acad Sci. 2010;107:4275.

Phase I Study: Schedule

Concurrent Cohorts

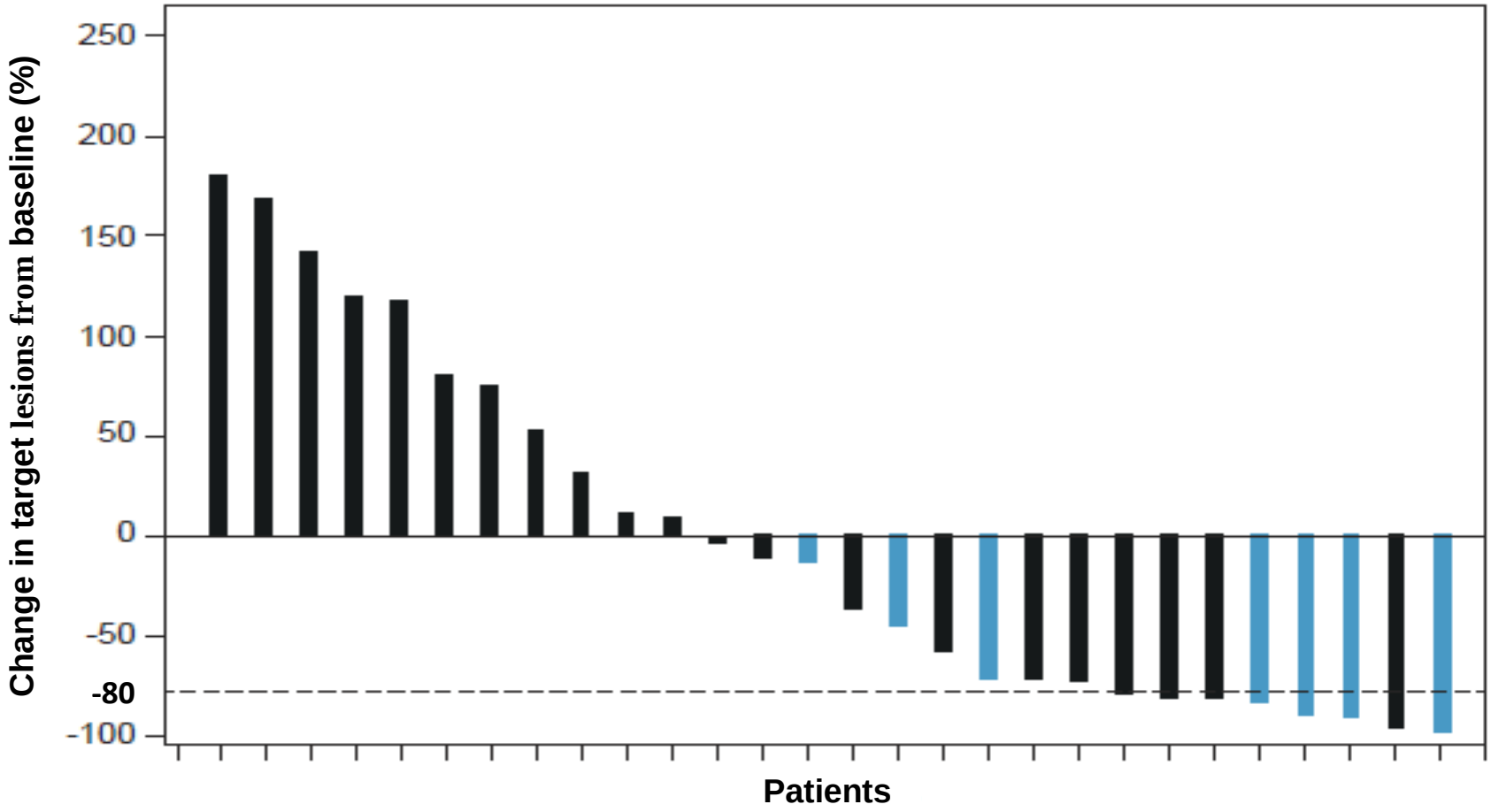


- First tumor assessment at 12 weeks

Sequenced Cohorts

- Following prior ipilimumab, patients received nivolumab every
  2 weeks for a maximum of 48 doses
- First tumor assessment at 8 weeks
  - **Tumor assessments by mWHO and immune-related response criteria**
  - **Data as of Feb 2013 for 86 patients**

Best Responses in All Evaluable Patients in Sequenced Cohorts

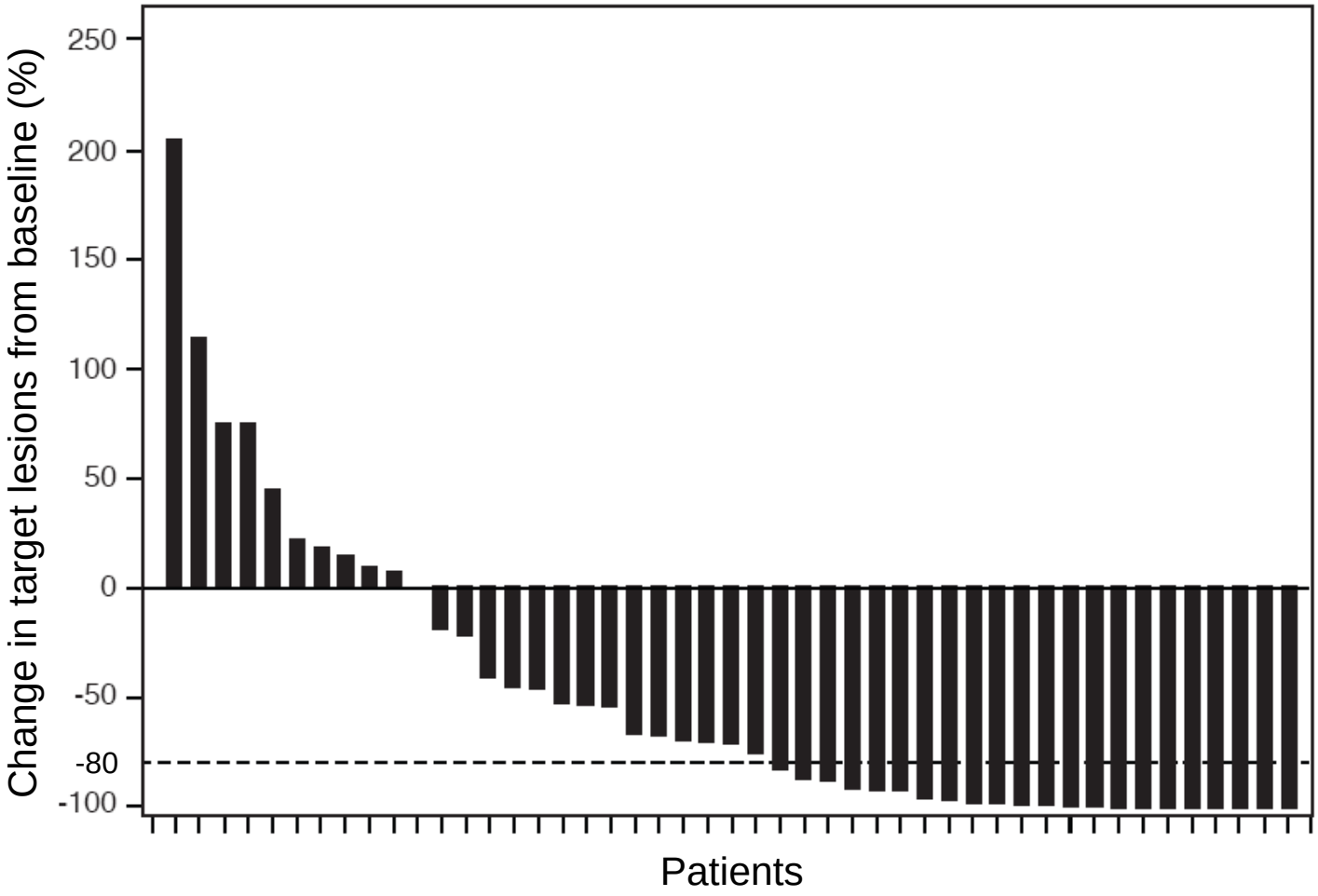


■ Patients who had radiographic progression with prior ipilimumab treatment.

■ Patients who had stable disease with prior ipilimumab treatment.

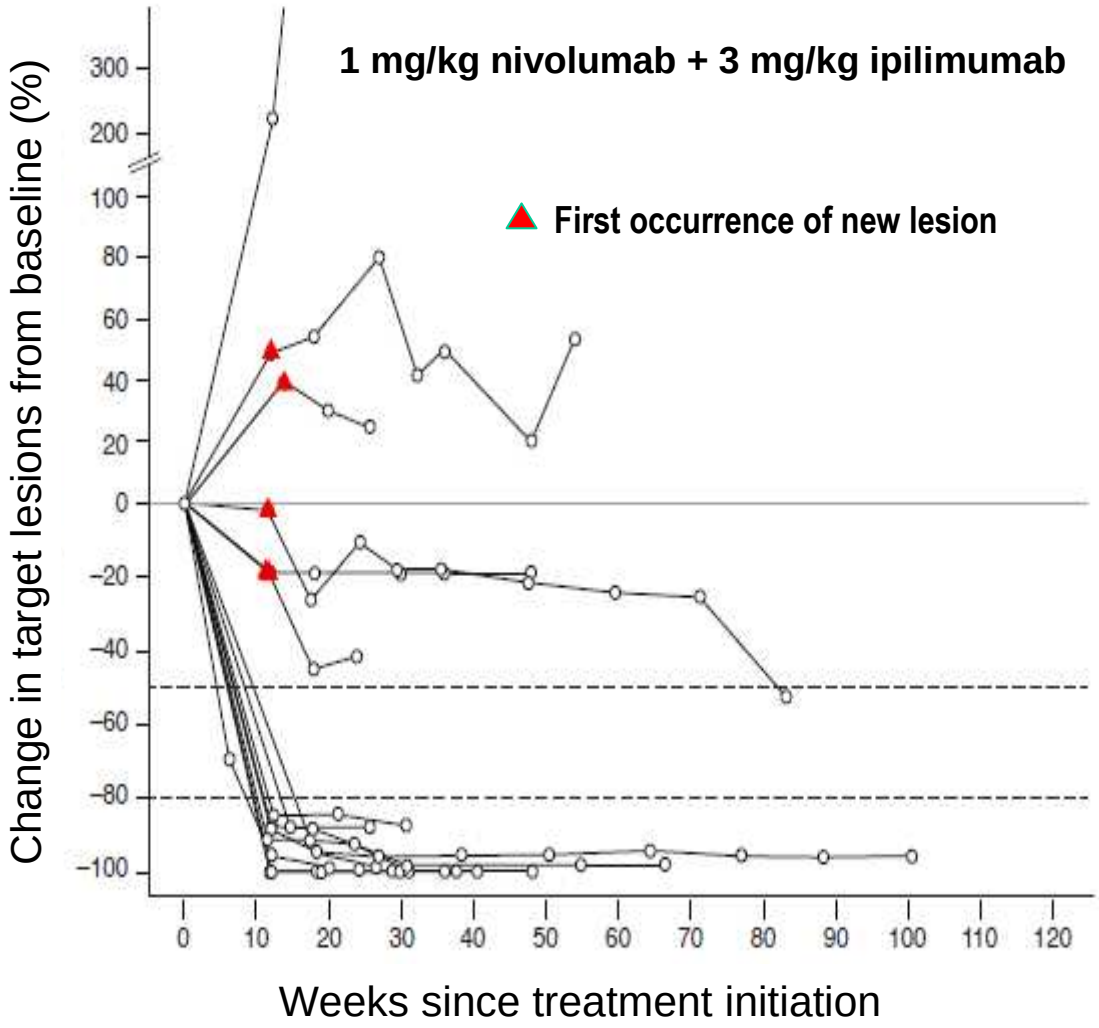
Presented by: Jedd D. Wolchok, MD, PhD

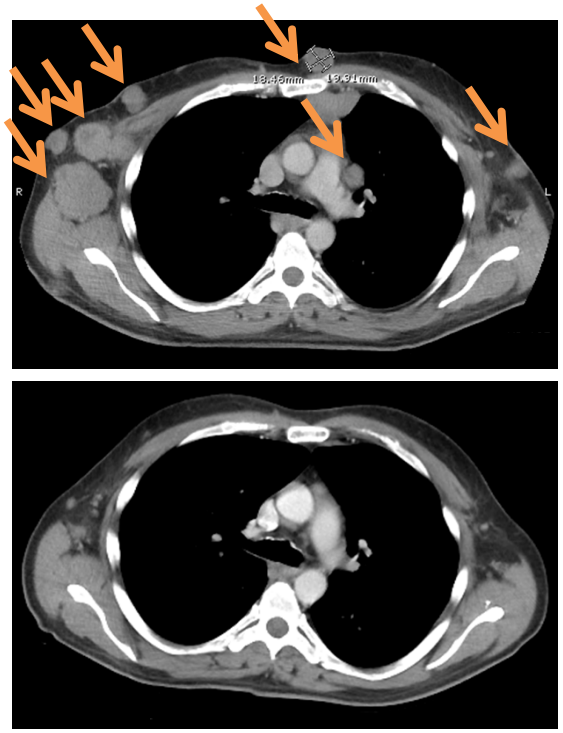
Best Responses in All Evaluable Patients in Concurrent Cohorts



After ~13 months of follow-up, for all concurrent cohorts, 90% of all responding patients continue to respond as of Feb 2013.

Rapid and Durable Changes in Target Lesions



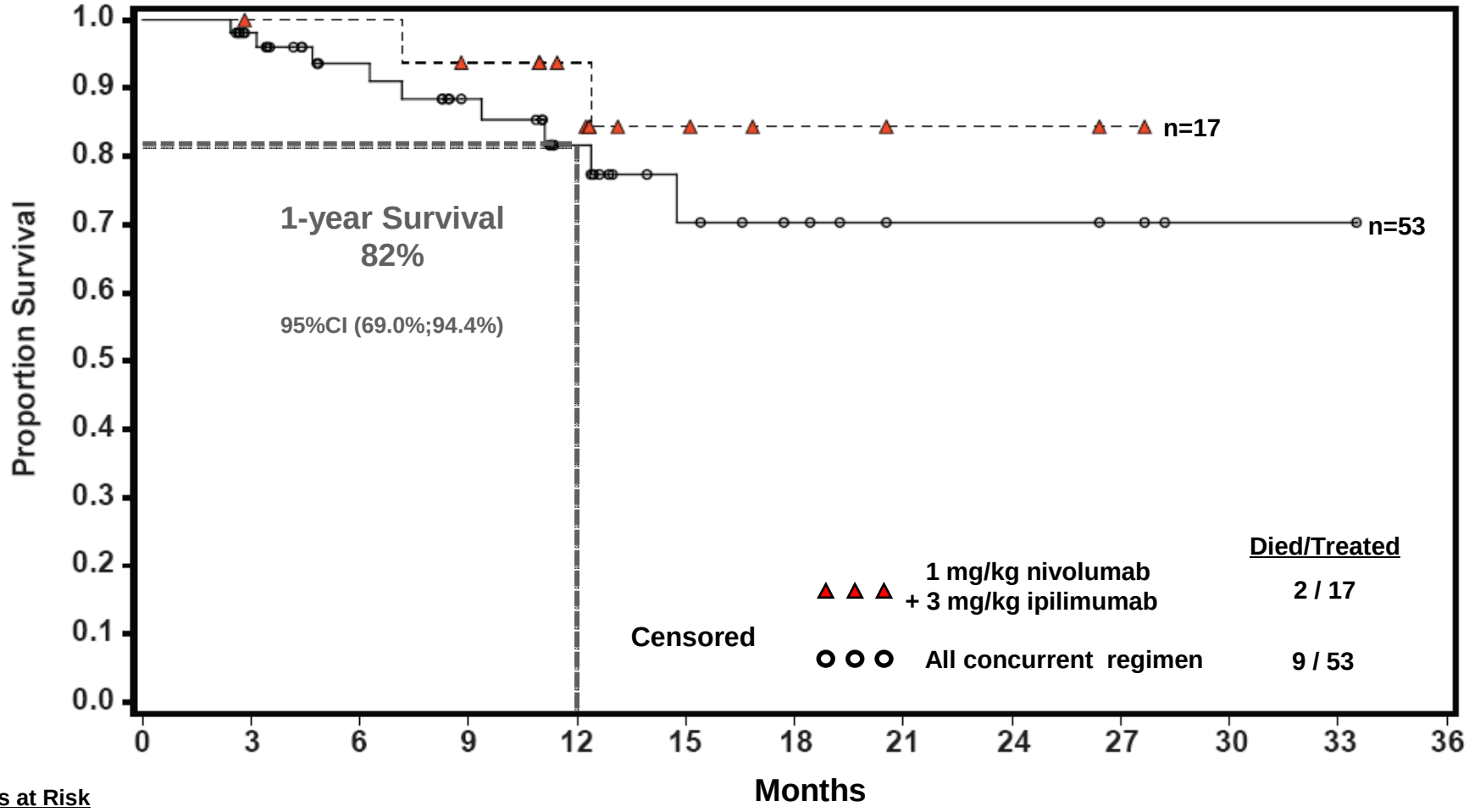


Pre-treatment

12 weeks

- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown

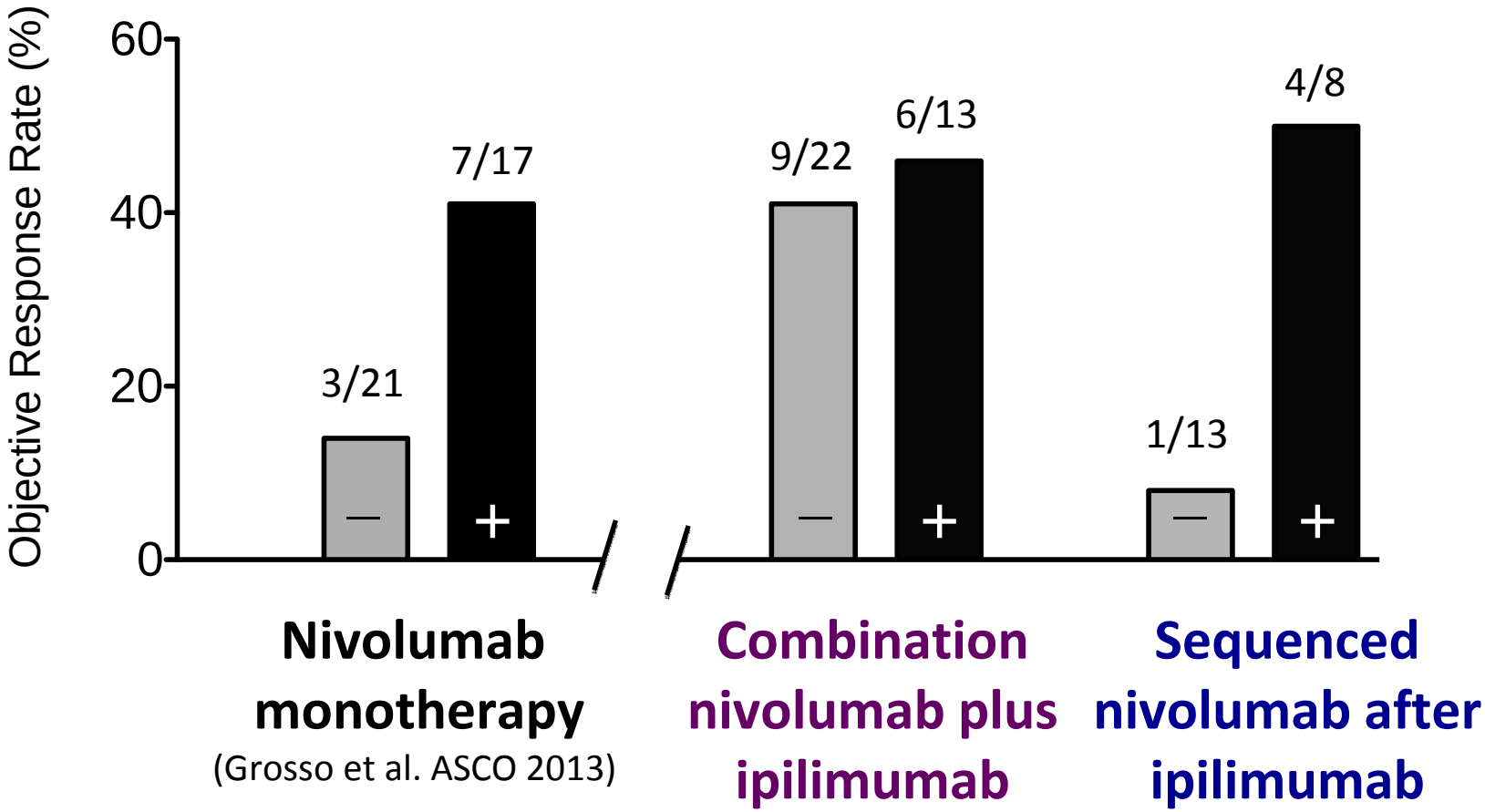
Preliminary Survival of Patients Treated with the Concurrent Regimen



Patients at Risk

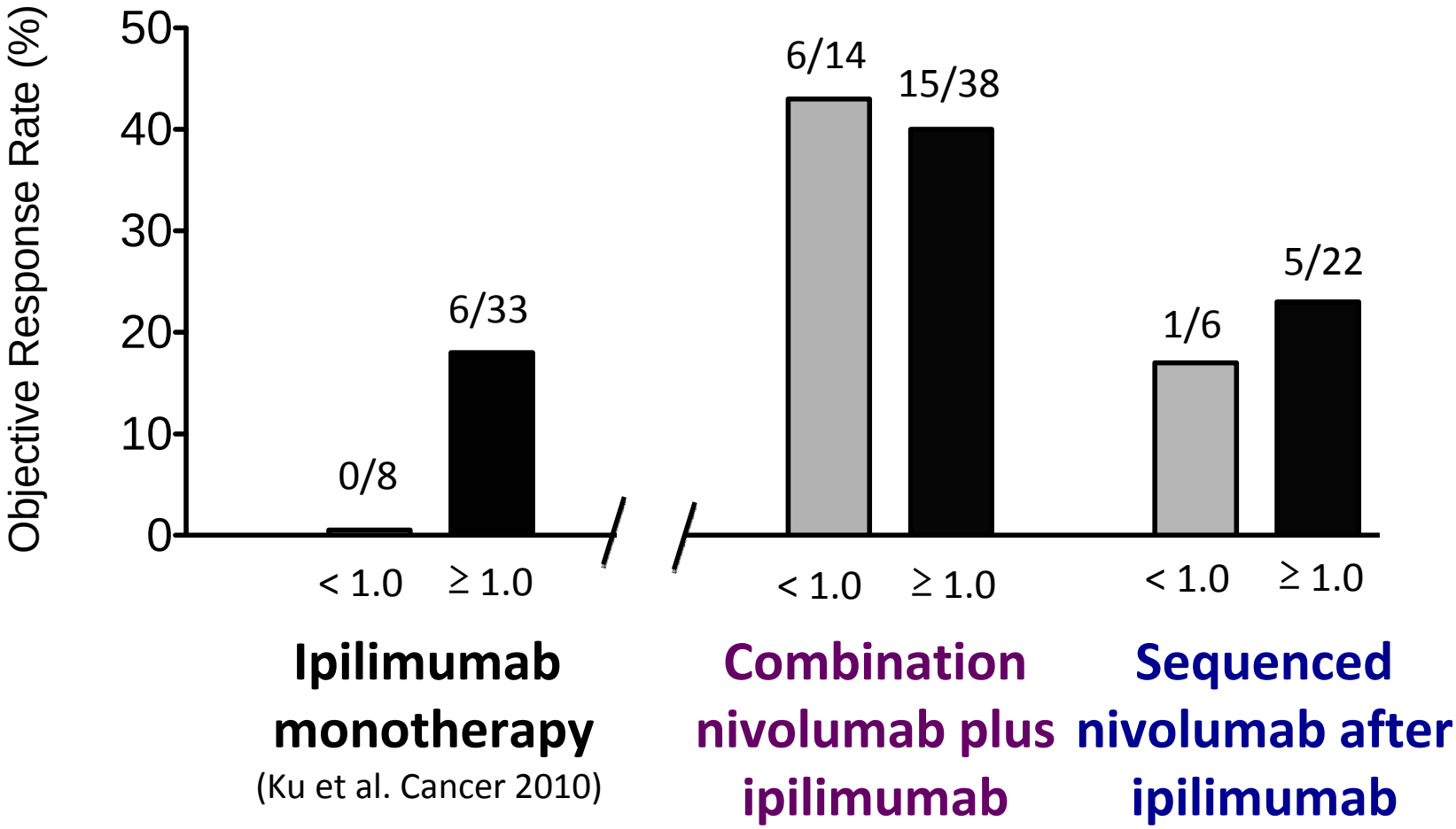
1 mg + 3 mg	17	16	16	14	10	5	3	2	2	1	0	0	0
All concurrent	53	47	36	29	19	10	7	4	4	3	1	1	0

Evaluating PD-L1 status as a candidate biomarker



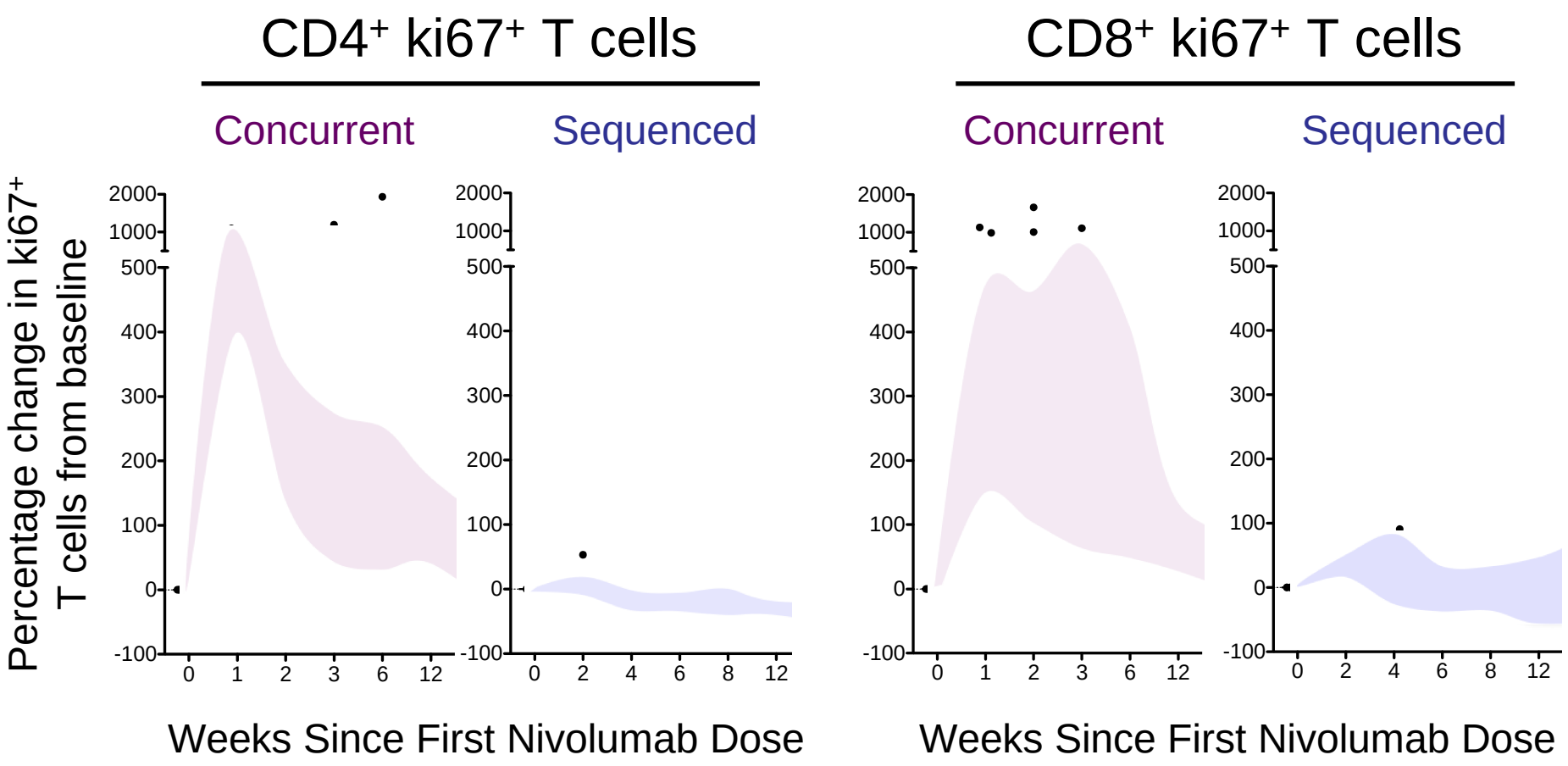
Positivity rate = 45% (17/38, monotherapy), 37% (13/35, combination therapy), and 38% (8/21, sequenced therapy)

Evaluating ALC as a candidate biomarker



Low ALC rate = 20% (8/41, monotherapy), 27% (14/52, combination therapy), and 21% (6/28, sequenced therapy)

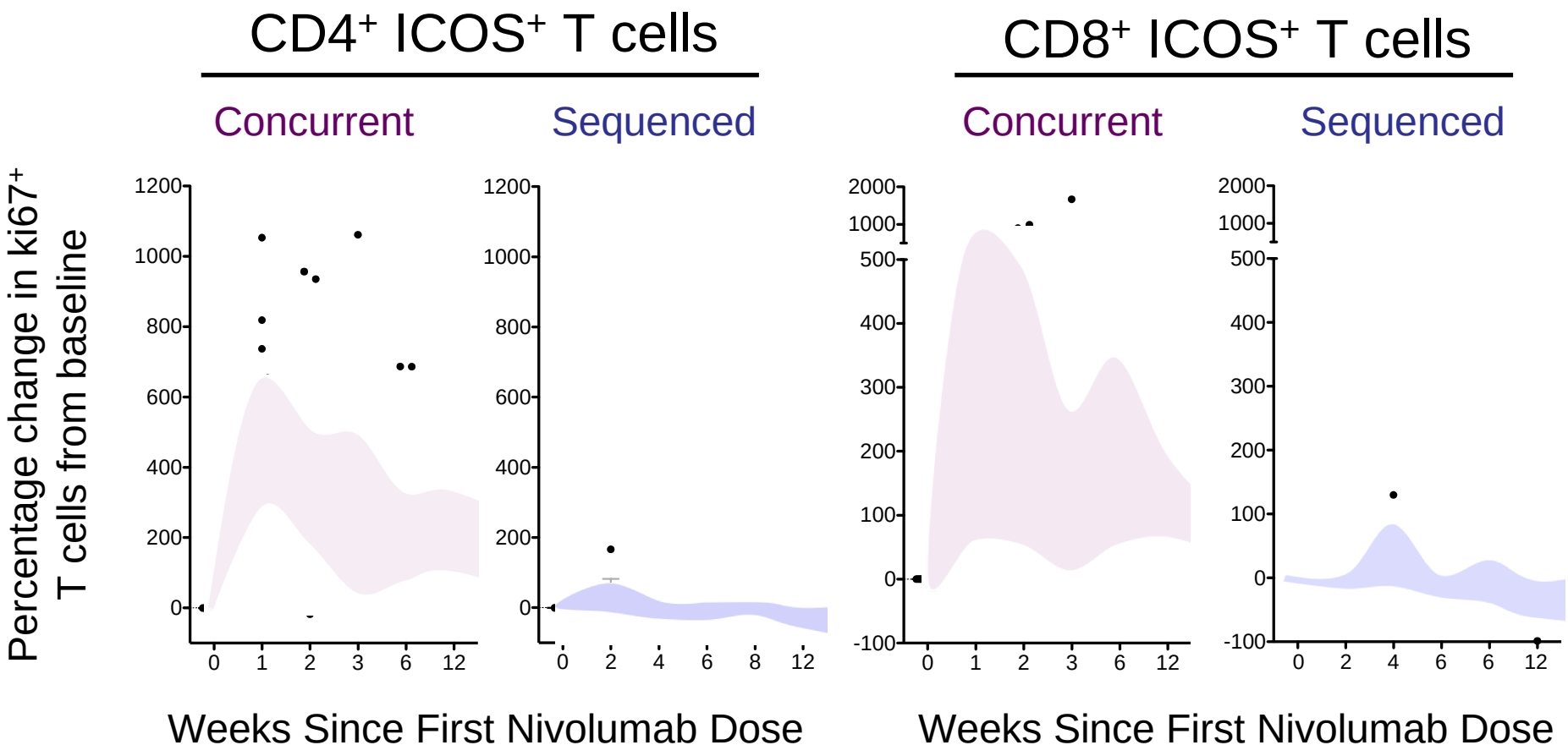
Increased frequency of activated **(ki67$^+$)** CD4$^+$ and CD8$^+$ T cells with concurrent nivolumab + ipilimumab



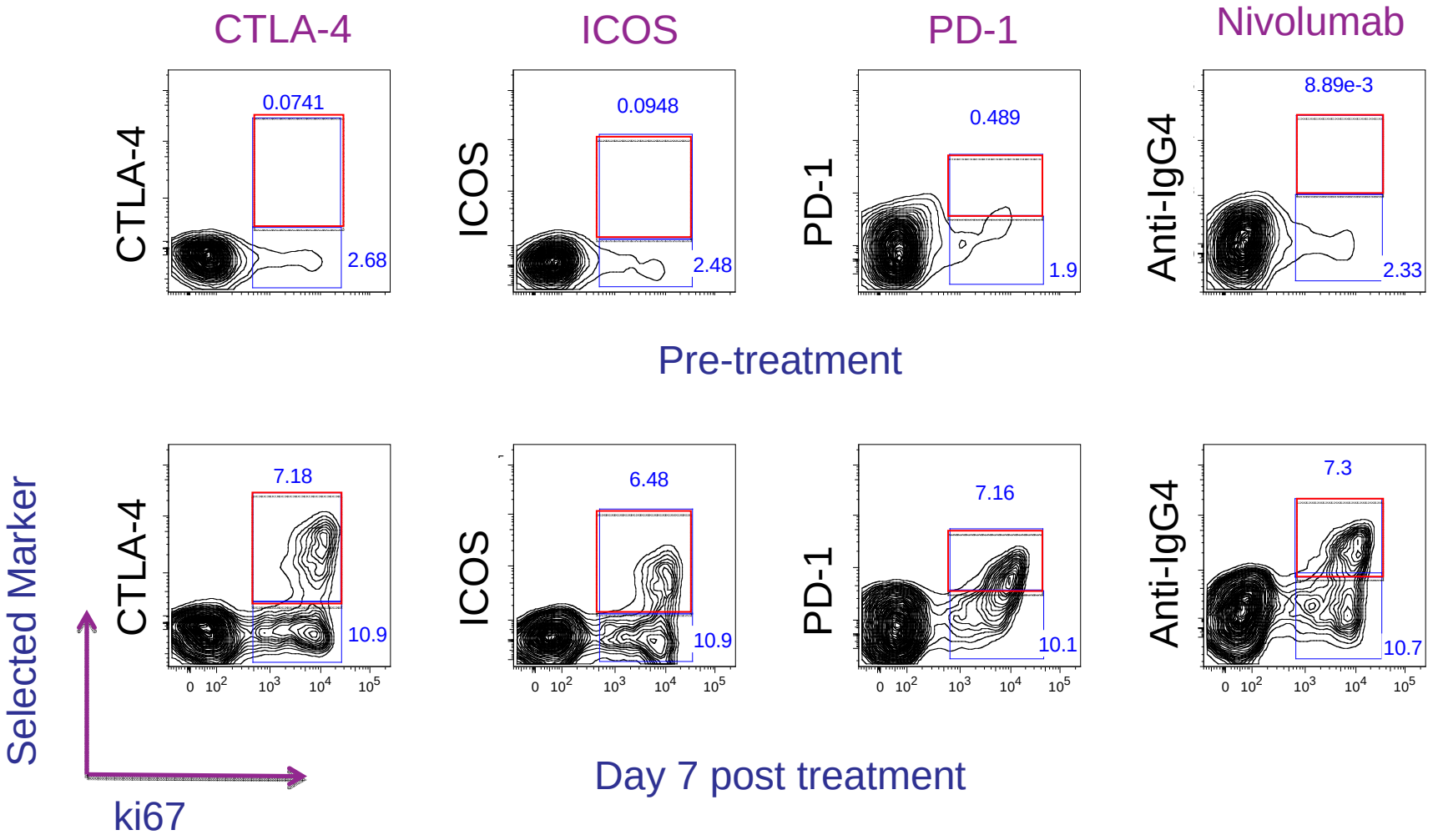
Median with interquartile range

Based upon single institution (MSKCC) analysis of a subset of patients

Increased frequency of activated **(ICOS$^+$)** CD4$^+$ and CD8$^+$ T cells with concurrent nivolumab + ipilimumab



Phenotype of activated peripheral blood CD8+ T cells after combination therapy



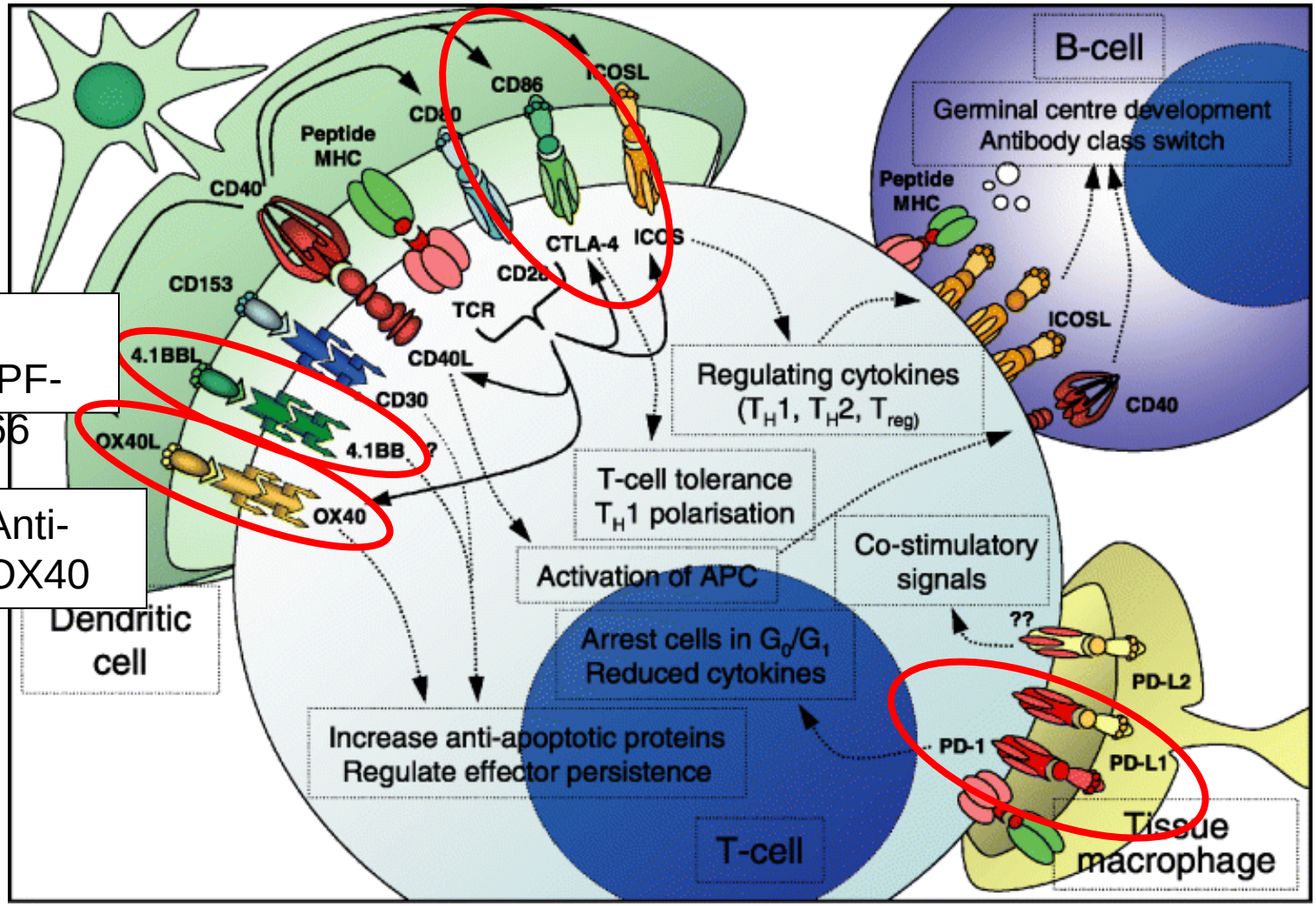
Based upon single institution (MSKCC) analysis of a subset of patients

Positive and Negative Signals Regulate T cell Activation

Ipilimumab, tremelimumab

BMS-663513,PF-05082566

Anti-OX40



CT-011,MDX-1106, MK-3475, RG7446, AMP224

Summary

- Checkpoint blockade is an effective treatment with durable responses.
- Intense study of both predictive and pharmacodynamic biomarkers of response and toxicity will allow for more intelligent patient selection and novel target discovery.
- New and promising immune modulators are in clinical development.
- Combination therapy will be necessary for immunotherapy to achieve full potential (other immune modulators, vaccines, radiation, chemotherapy, targeted therapy, anti-angiogenic therapy).