Memorial Sloan Kettering Cancer Center

LUDWIG CANCER RESEARCH

Understanding Checkpoint Inhibitors: Approved Agents, Drugs in Development and Combination Strategies

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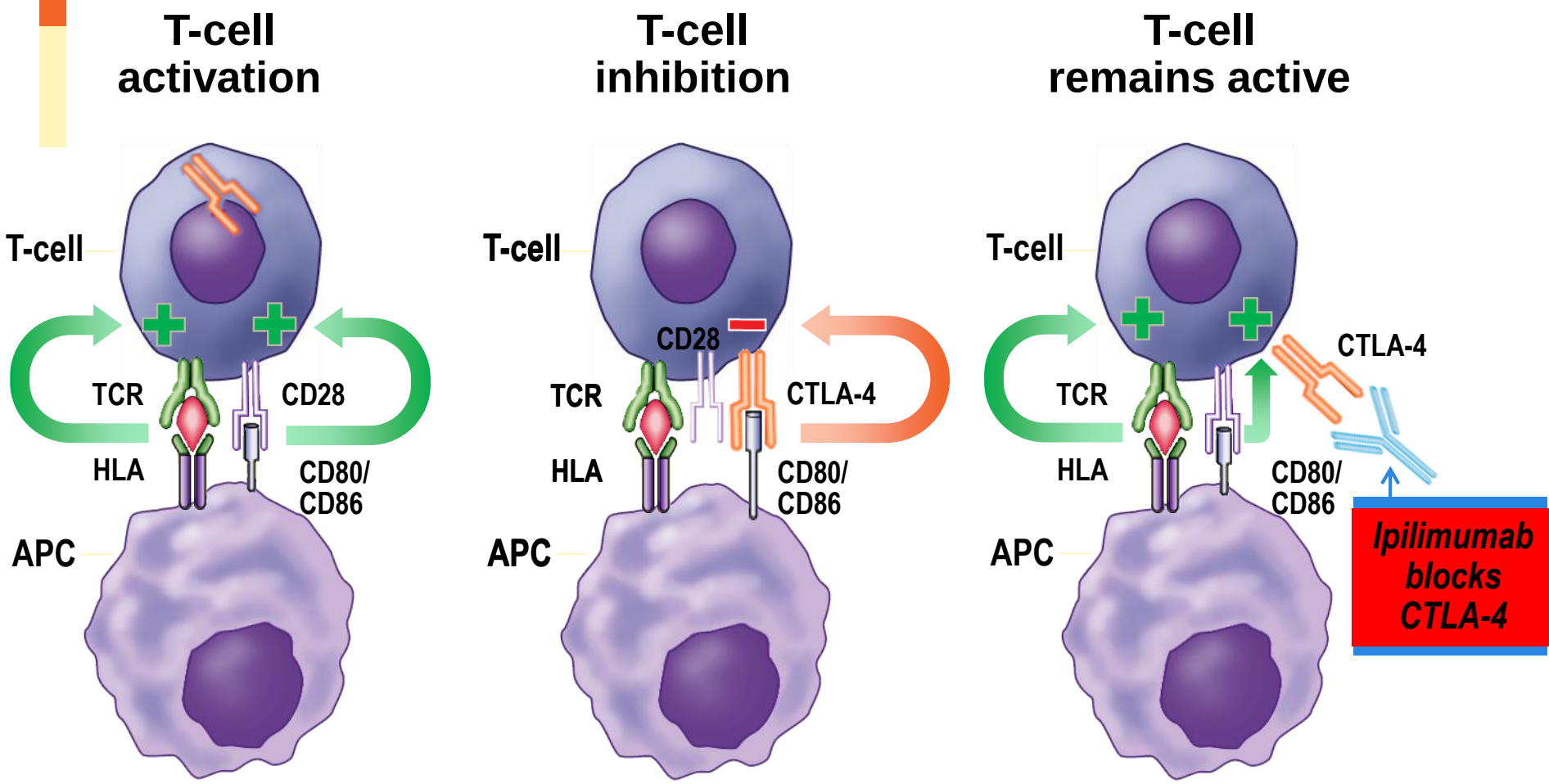
Ludwig Center at MSKCC

SITC ACI-NJ

It's Been A Long Journey…..

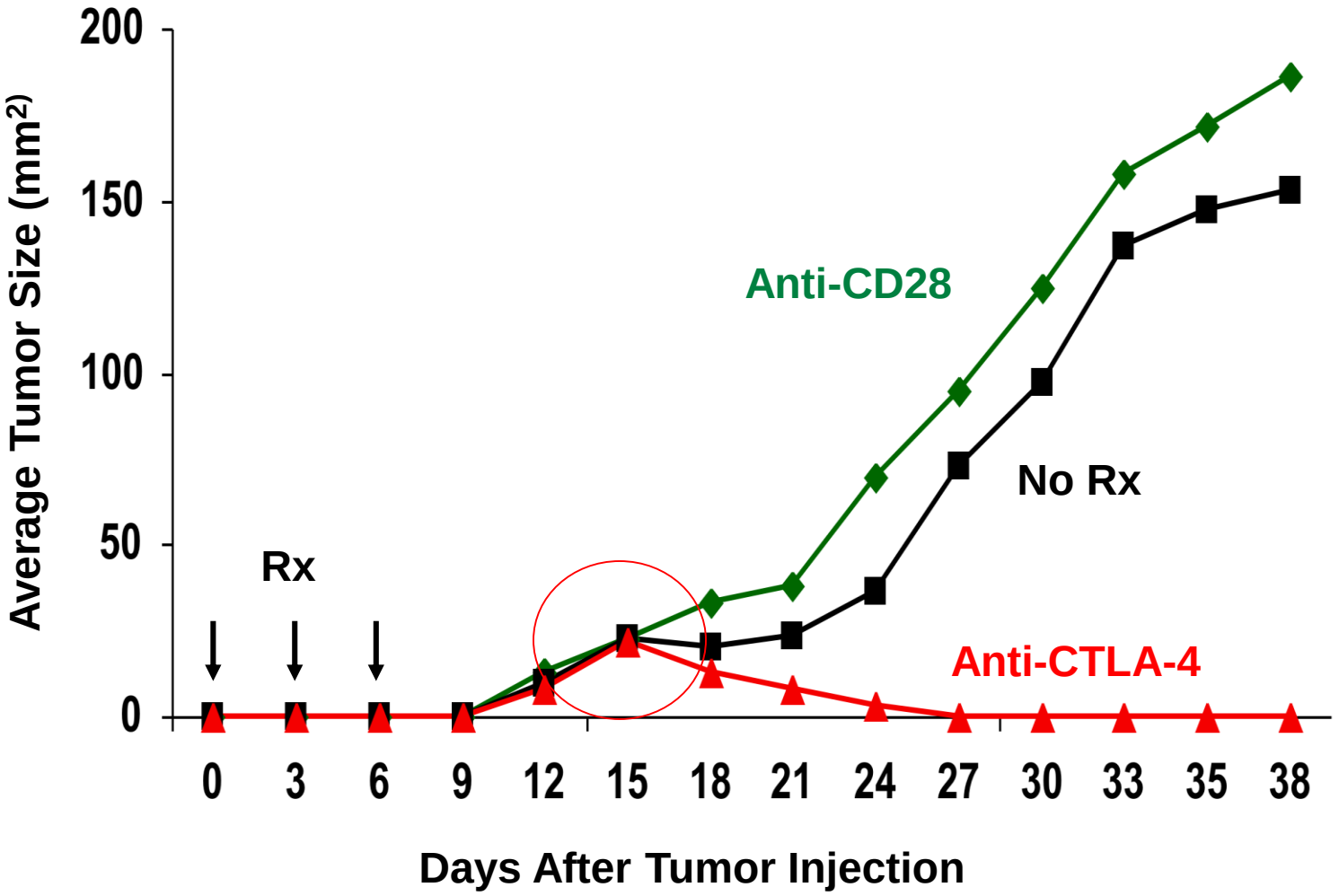
Lewis Thomas, MD: the beginning of immune surveillance

Ipilimumab Augments T-Cell Activation and Proliferation



Adapted from O'Day et al. Plenary session presentation, abstract #4, ASCO 2010.

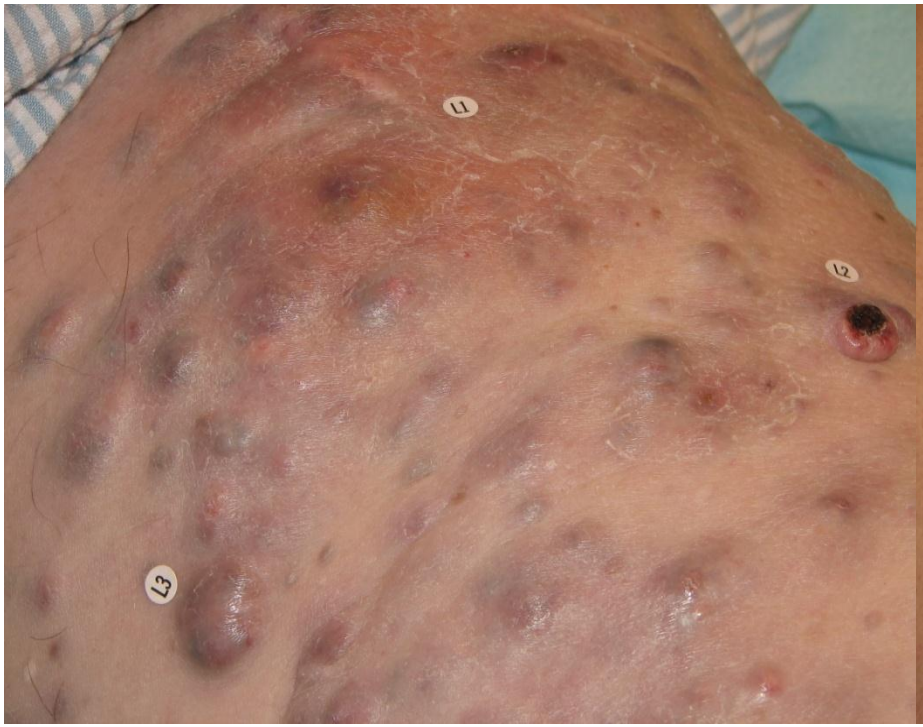
Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma

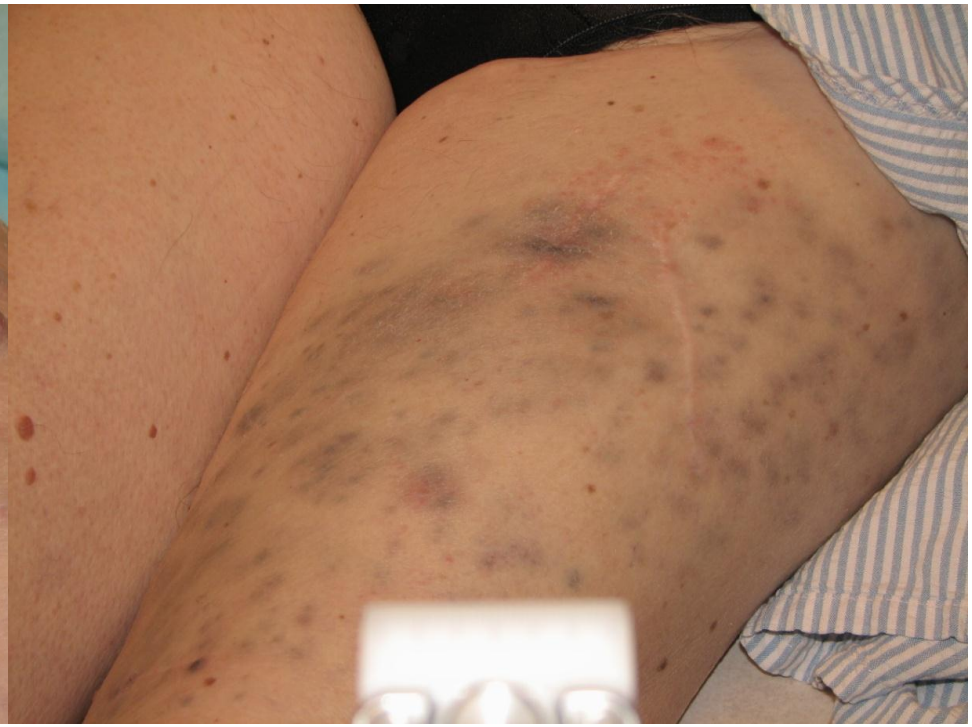


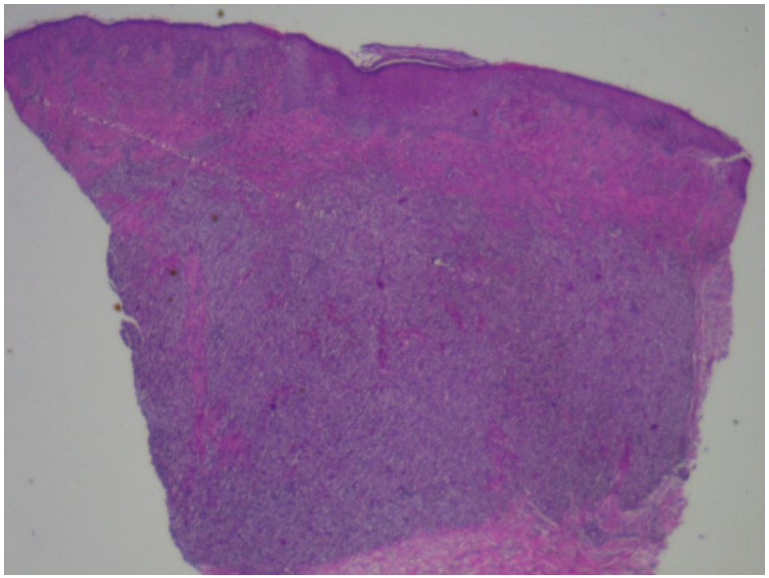
Leach DR et al., Science, 1996

Rapid Clinical Response to Ipilimumab

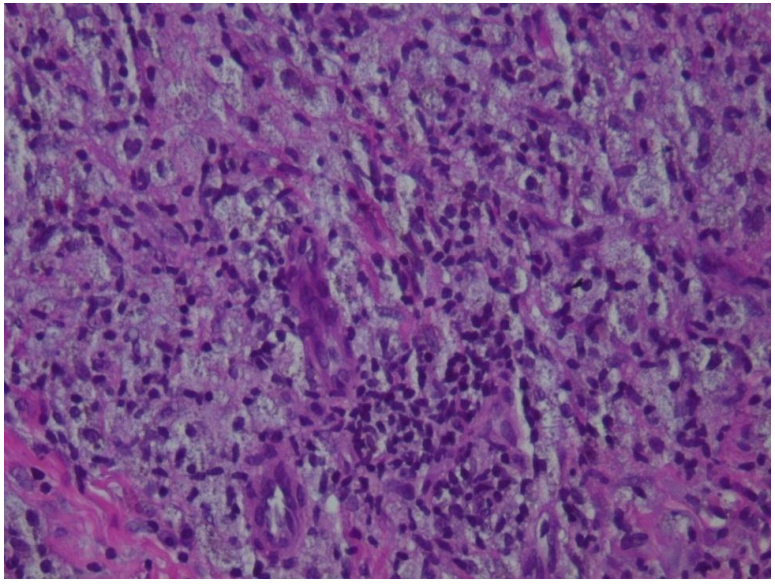
11/28/06 **1/9/07**





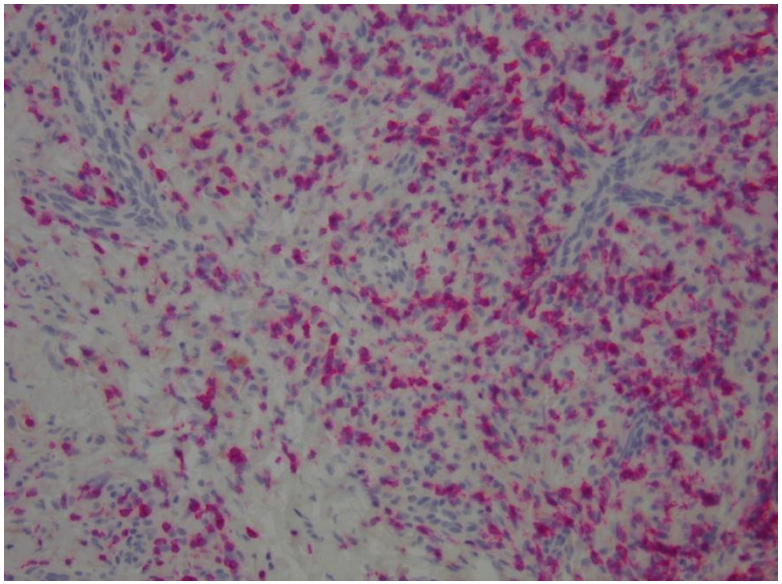


Tumorous nodule with melanin pigment (macrophages and lymphocytes; no melanocytes)

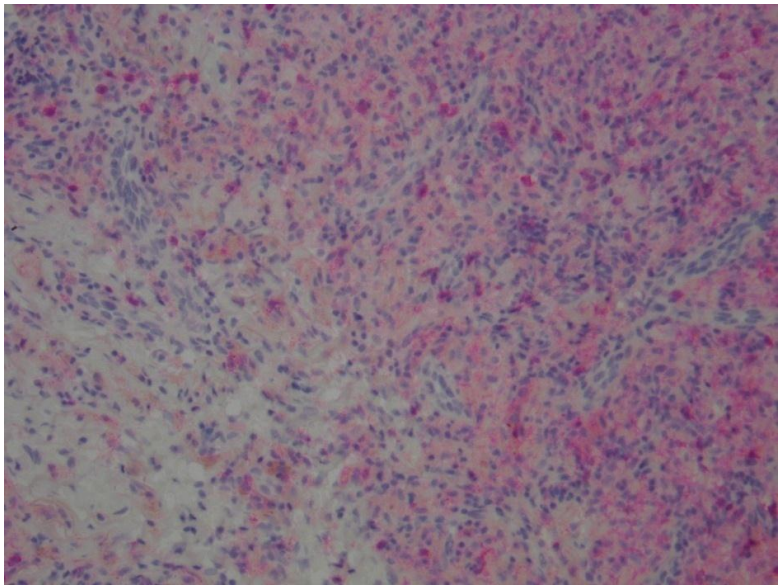


Macrophages and lymphocytes are present, but no tumor cells

Klaus Busam, MSKCC Dermatopathology

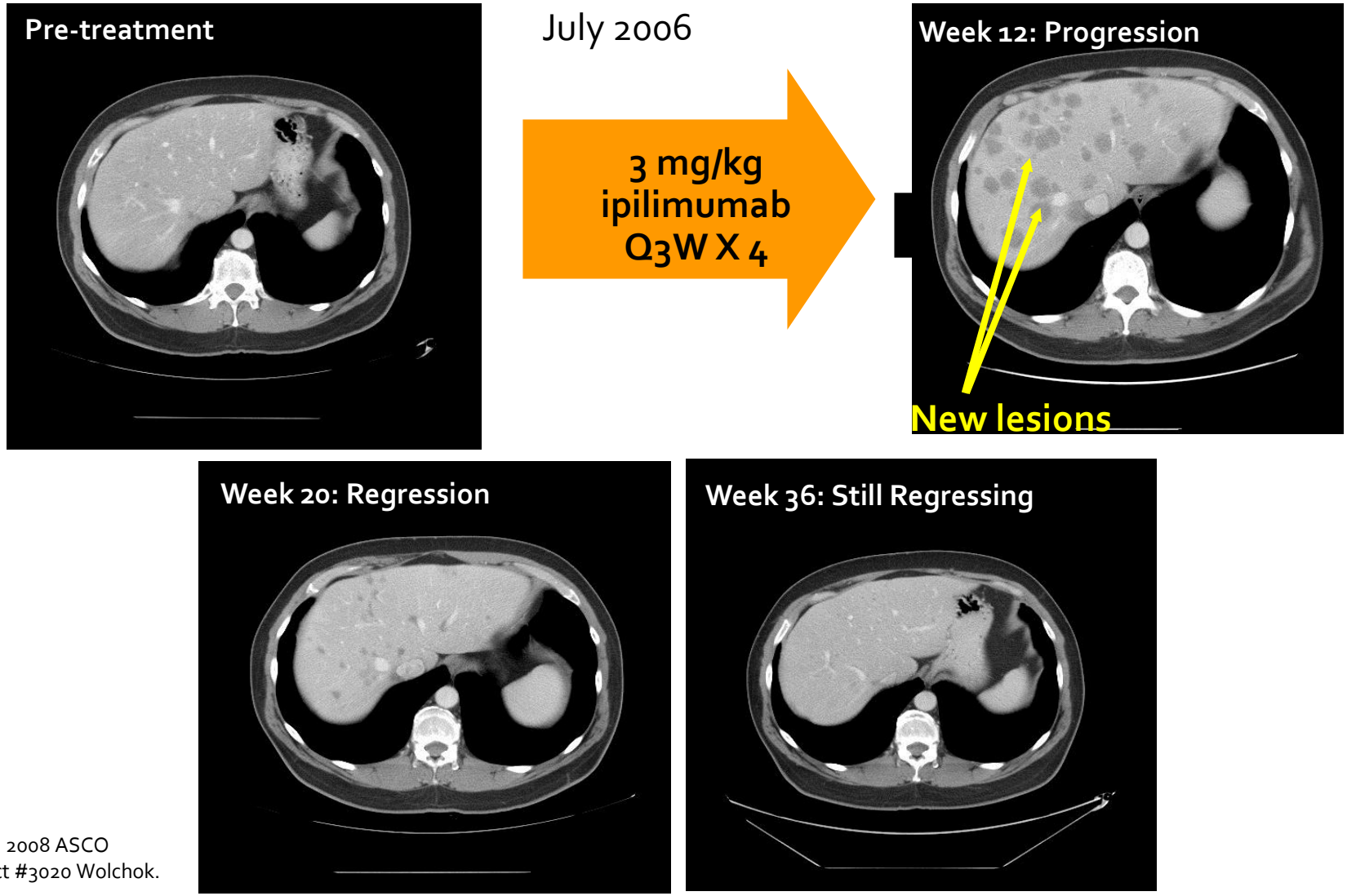


CD8-positive T-cells



CD4-positive T-cells
(macrophages are also weakly pos for CD4)

Ipilimumab Pattern of Response: Responses After the Appearance and Subsequent Disappearance of New Lesions



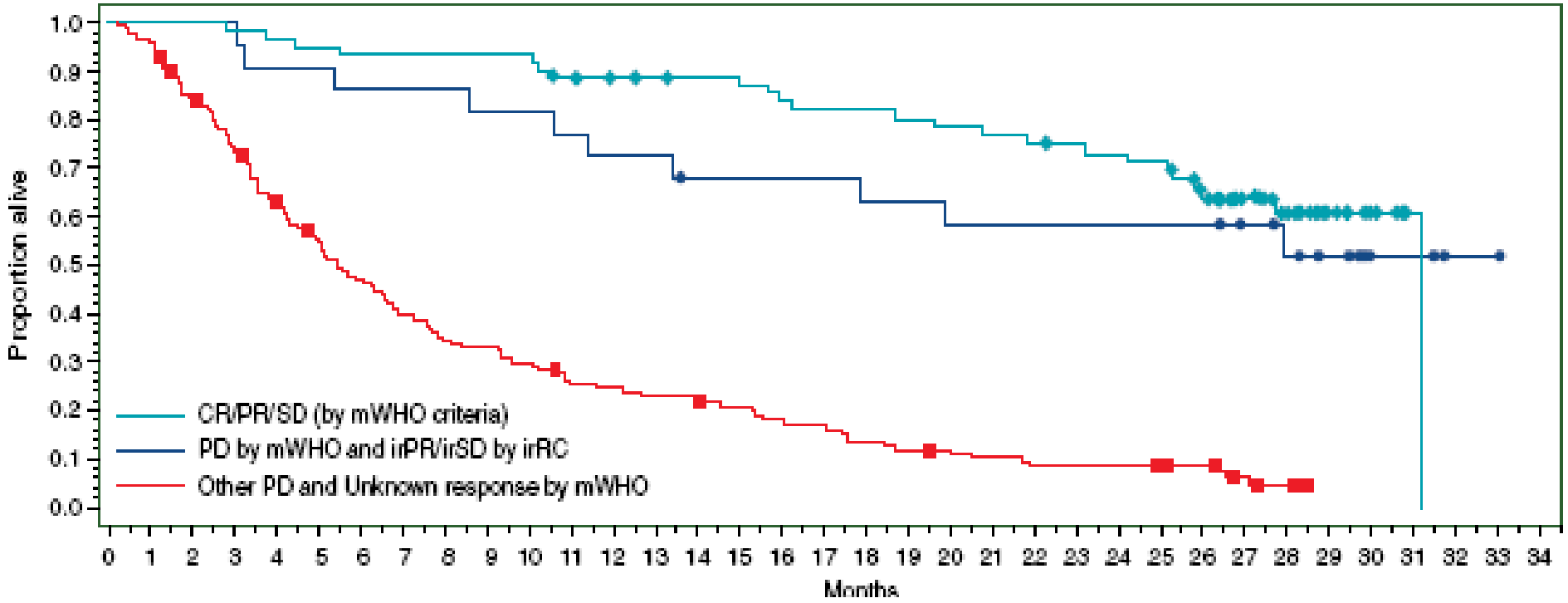
Source: 2008 ASCO Abstract #3020 Wolchok.

Four Patterns of Response to Ipilimumab Therapy Observed

- 2 conventional:
  - Response in baseline lesions
  - 'Stable disease' with slow, steady decline in total tumor volume
- 2 novel:
  - Response after initial increase in total tumor volume
  - Response in index plus new lesions at or after the appearance of new lesions

irRC Identifies Survivors in Patients with Progressive Disease by mWHO

Pooled data from phase II studies CA184-008 and CA184-022: ipilimumab monotherapy 10 mg/kg (N=227)



Wolchok et al, *Clin Cancer Res*, 2009

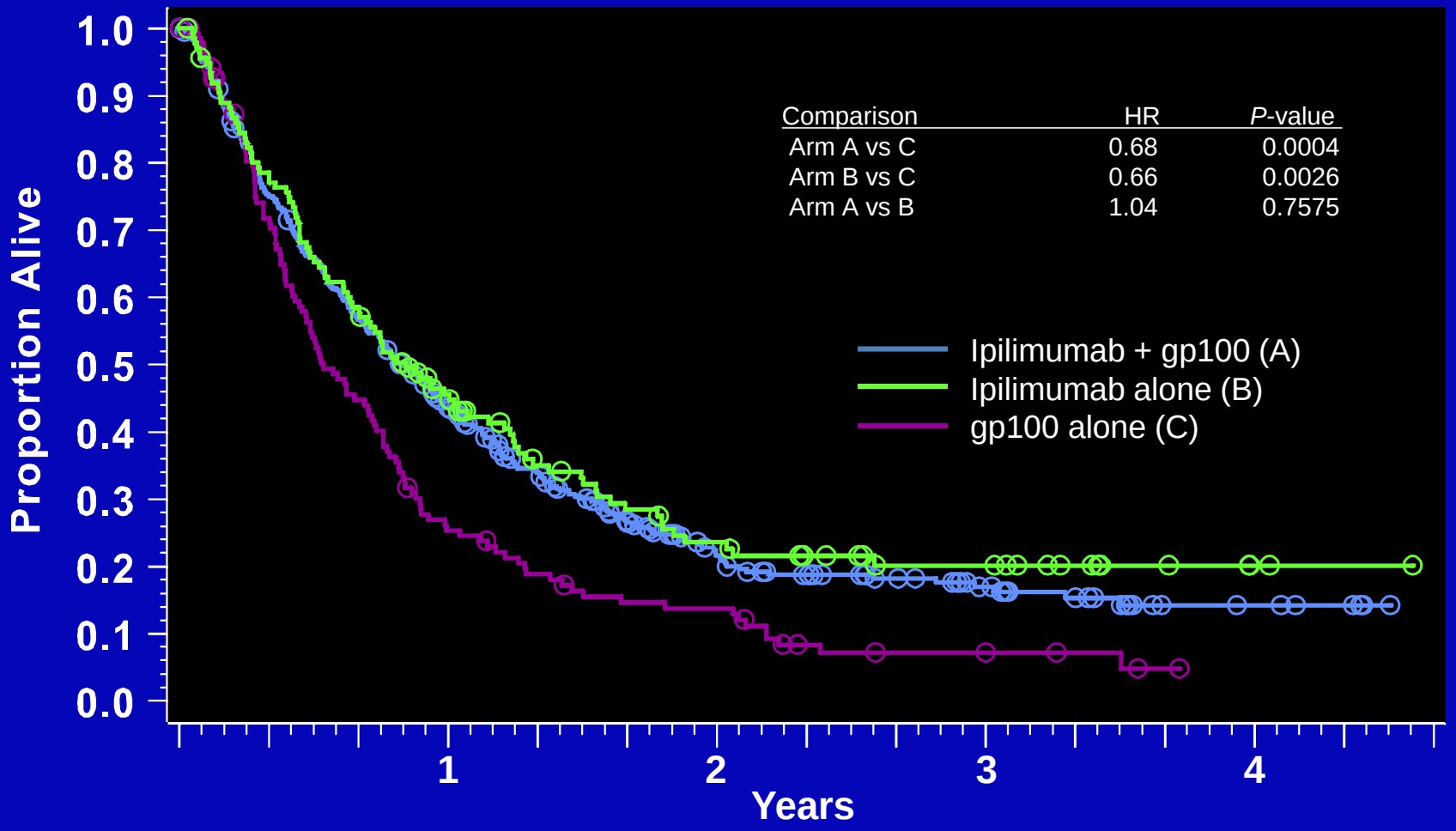
Immune-Related Adverse Events

- Rash (approx 20%)
- Colitis/enteritis (approx 15%)
- Elevated AST/ALT (approx 10%)
- Endocrinopathies: Thyroiditis, Hypophysitis, Adrenal insufficiency(2-5%)

Severity is inversely related to vigilance of surveillance.
If detected early, most are easily treated and reversible.

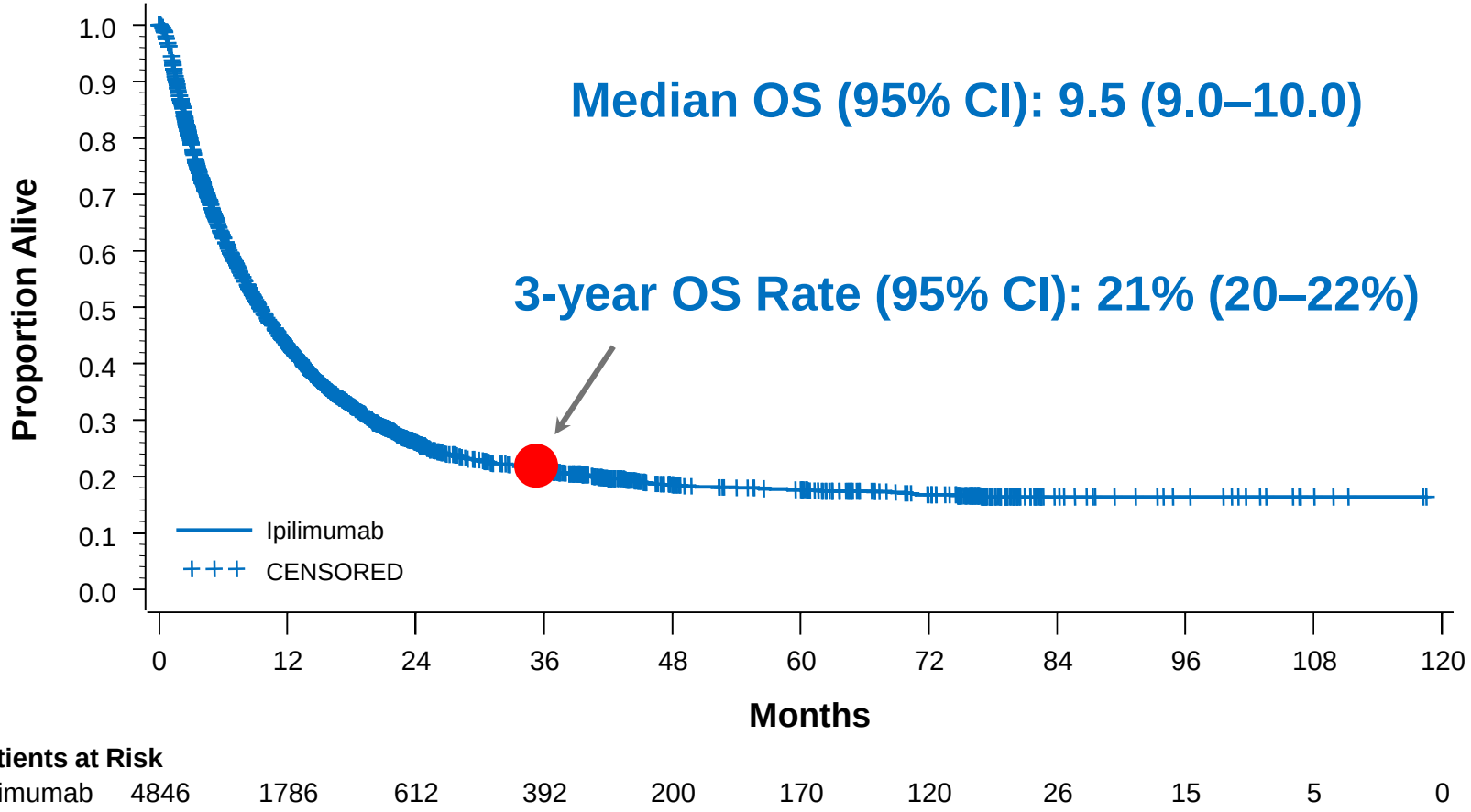
Kaplan-Meier Analysis of Survival

MDX-010-20: Hodi et al, *NEJM*, 2010



Survival Rate	Ipilimumab + gp100	Ipilimumab alone	gp100 alone
1-year	44%	46%	25%
2-year	22%	24%	14%

Ipilimumab Long Term Pooled Survival Analysis: 4846 Patients

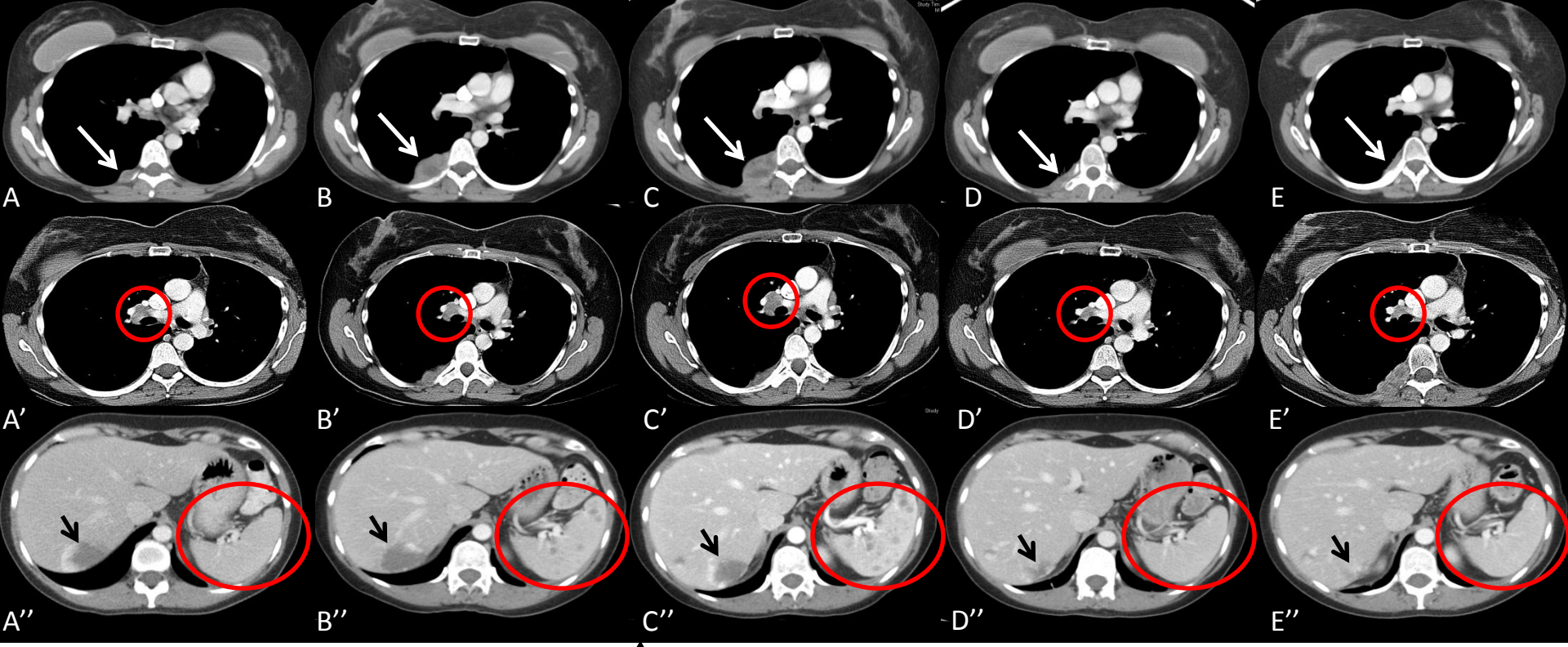


Schadendorf, Hodi Wolchok, ESMO, 2013

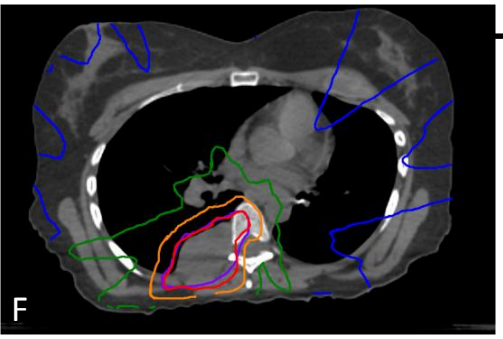
Radiation + Immunotherapy: The Abscopal Effect

- April 2004: 33 woman w/ pT2aNo (Stage IB) melanoma arising in upper back (non-ulcerated, 2mf)
- October 2008: Left pulmonary nodule detected incidentally by CXR with CT scan/PET confirmation (also with additional RLL 3mm nodule)
- December 2008: 2 cycles of Cisplatin, Vinblastine, temozolomide
- February 2009: Left lower lobectomy
- August 2009: Unresectable recurrence

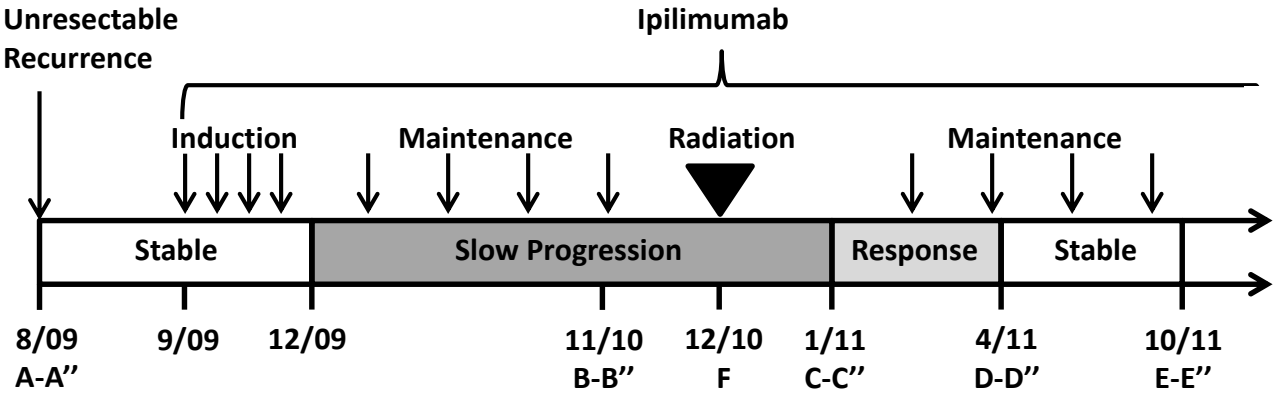
Postow and Callahan, NEJM, 2012



August 2009 | November 2010 | January 2011 | April 2011 | October 2011



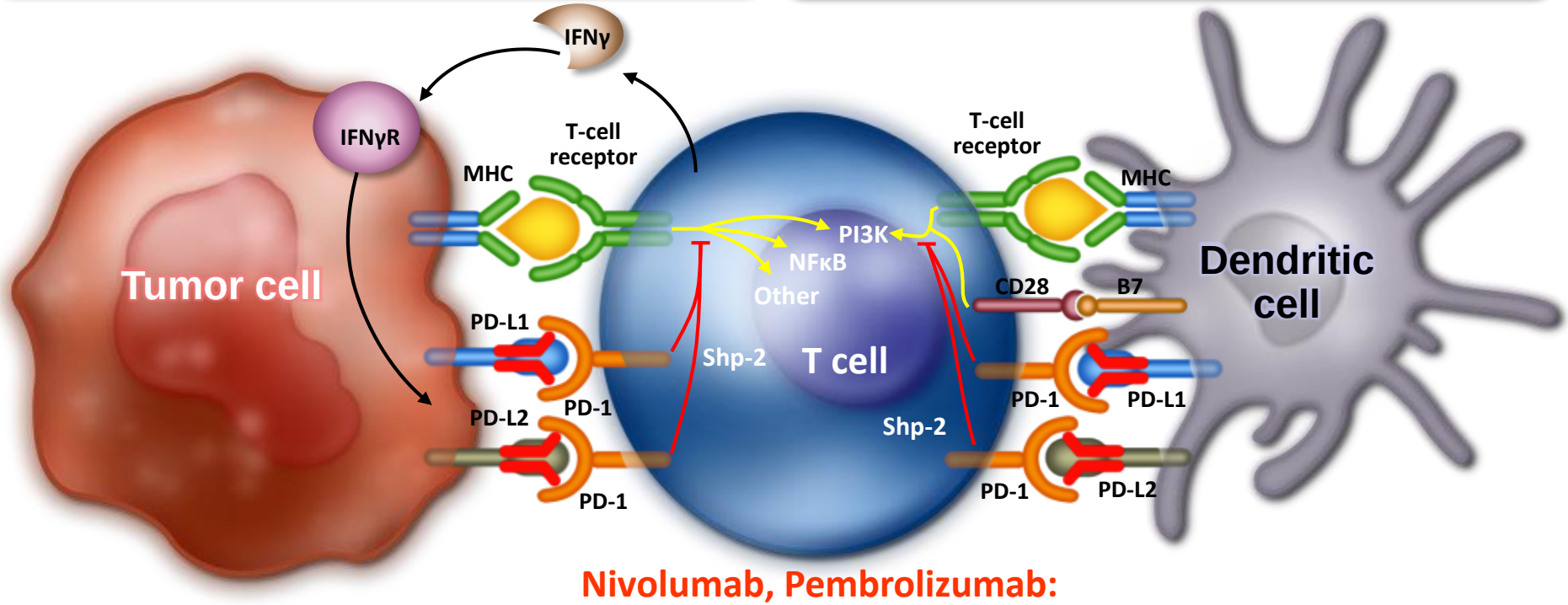
December 2010
Radiation



Role of PD-1 Pathway in Tumor Immunity

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

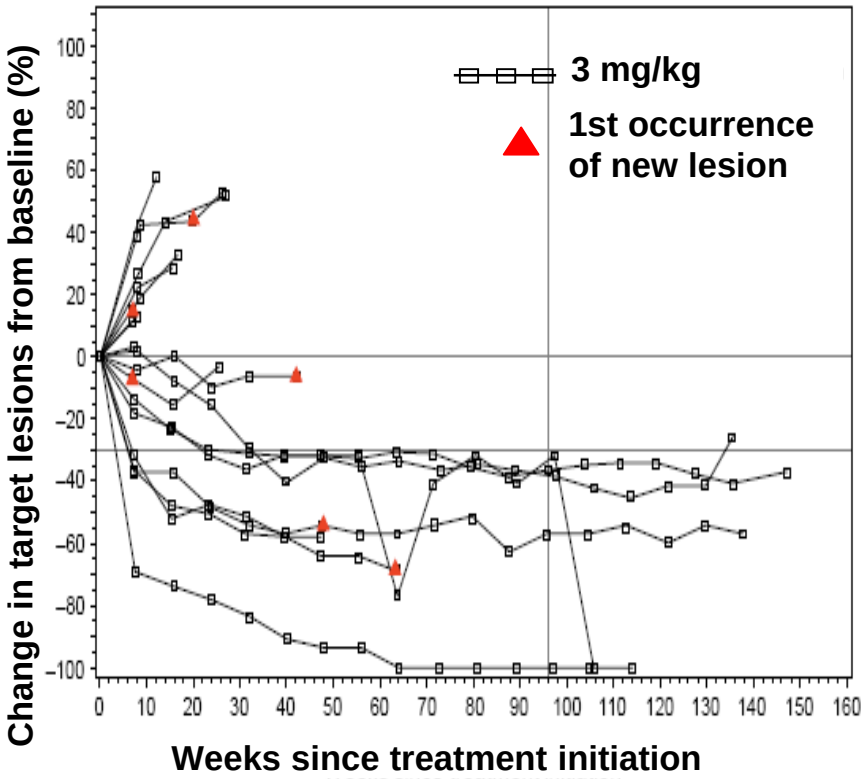
Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells

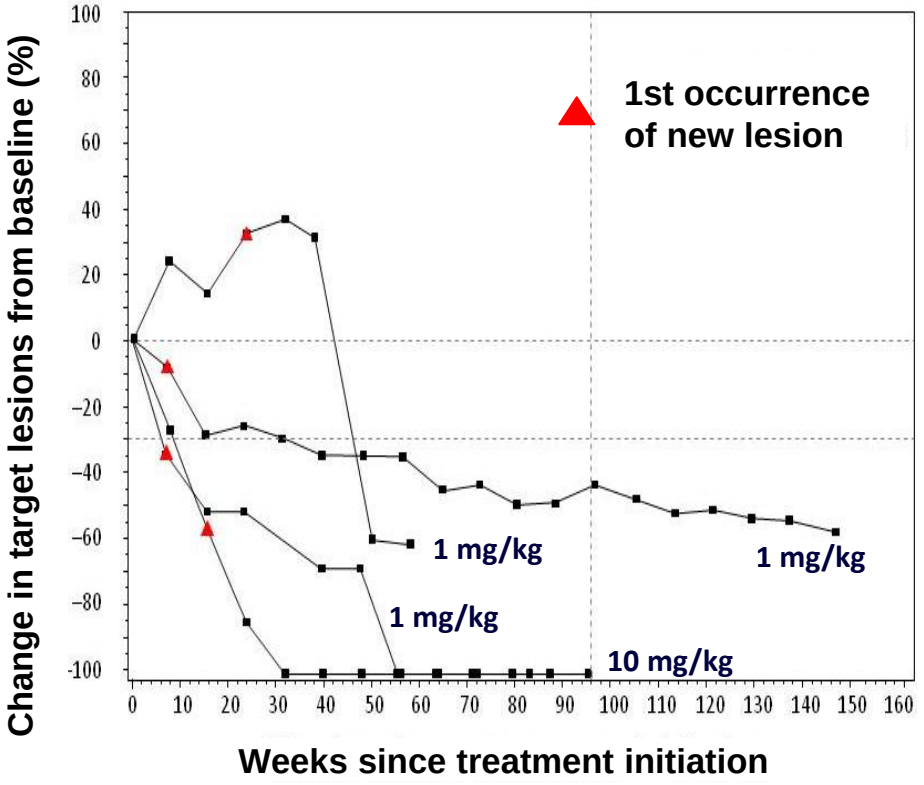


Nivolumab, Pembrolizumab:
PD-1 Receptor Blocking Abs
MPDL-3280A, MEDI-4735:
PD-1L Blocking Abs

Adapted from: Sznol et al., ASCO, 2013

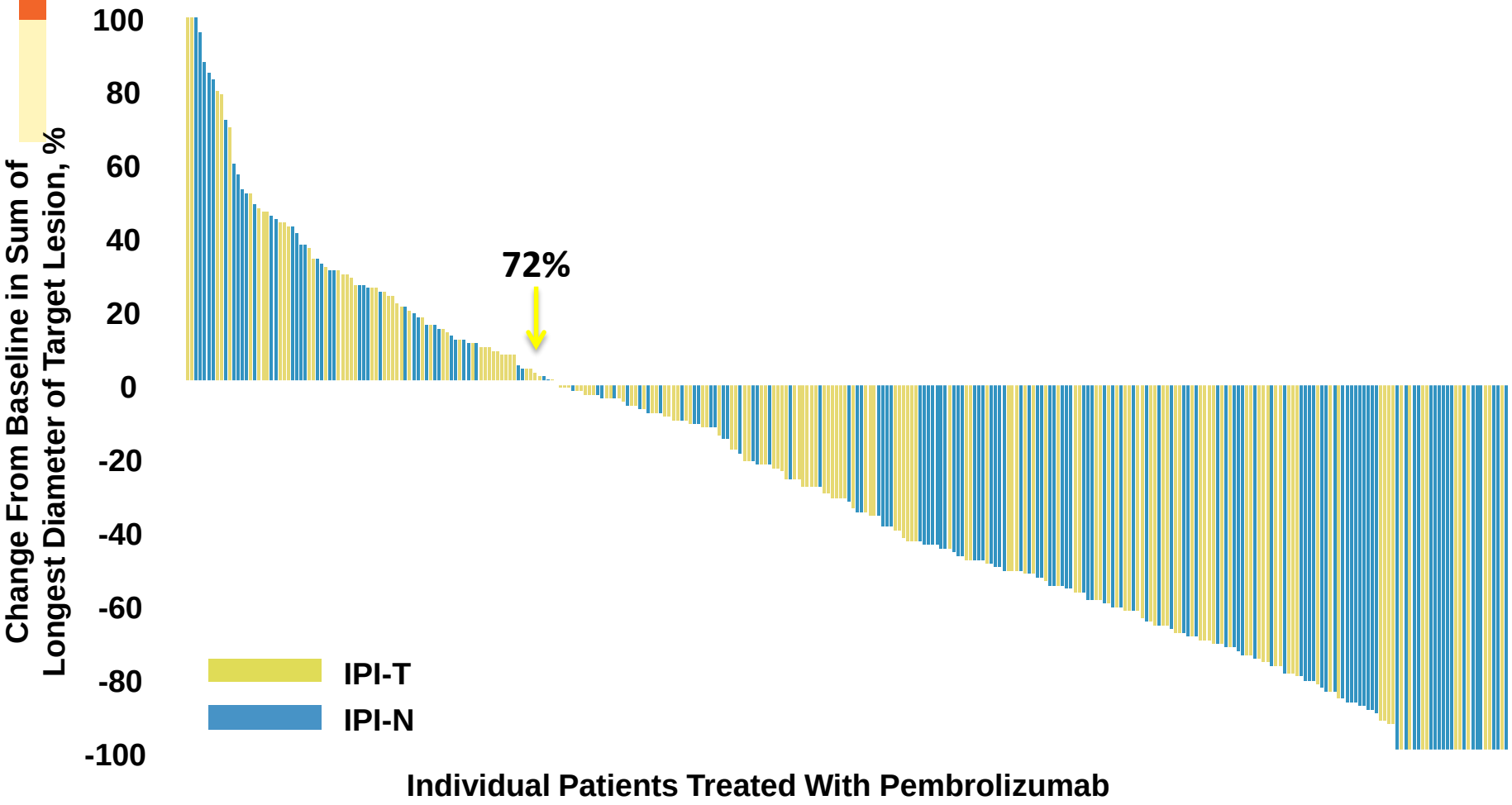
Tumor Burden in Patients with Melanoma Receiving Nivolumab





Sznol et al., ASCO, 2013

Pembrolizumab:
Maximum Percent Change from Baseline in Tumor Size[a]



[a]In patients with measurable disease at baseline by RECIST v1.1 by central review and ≥1 postbaseline assessment (n = 317).
Percentage changes >100% were truncated at 100%.
Analysis cut-off date: October 18, 2013.

Presented by: Antoni Ribas, ASCO, 2014. Robert et al., Lancet, 2014

Treatment-Related AEs With Incidence >5%

Adverse Event, %	Total N = 411	
	Any Grade	Grade 3/4
Fatigue	36	2
Pruritus	24	<1
Rash	20	<1
Diarrhea	16	<1
Arthralgia	16	0
Nausea	12	<1
Vitiligo	11	0
Asthenia	9	0
Cough	9	0

Adverse Event, n (%)	Total N = 411	
	Any Grade	Grade 3/4
Myalgia	9	0
Headache	8	<1
Hypothyroidism	8	<1
Decreased appetite	7	<1
Dyspnea	7	<1
Chills	6	0
Pyrexia	6	0
ALT increased	5	<1
Total	83	12

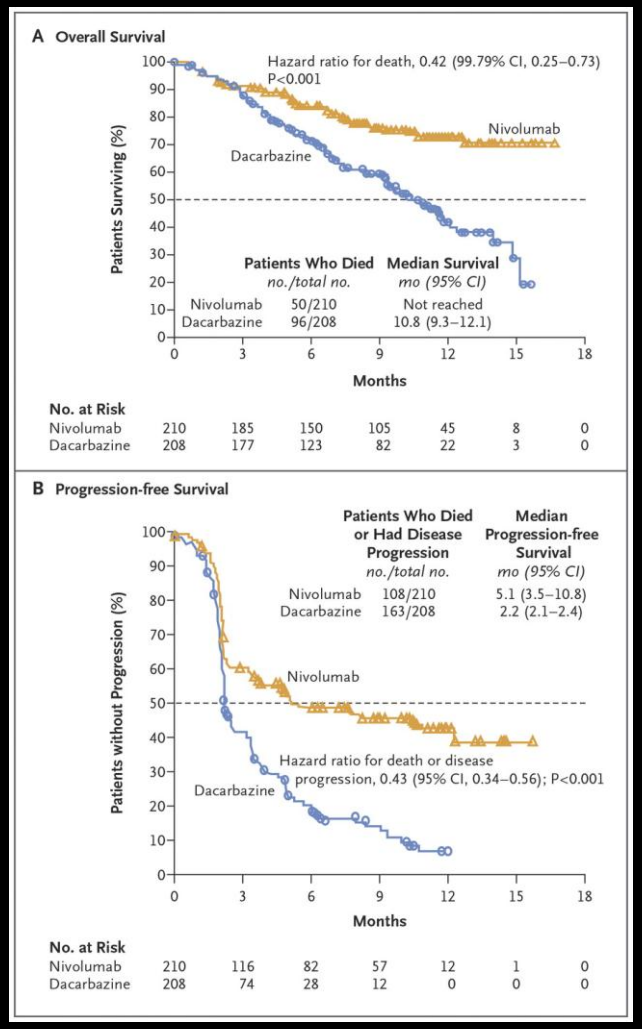
- No treatment-related deaths
- Similar safety profiles in IPI-N and IPI-T patients

Immune-Mediated AEs

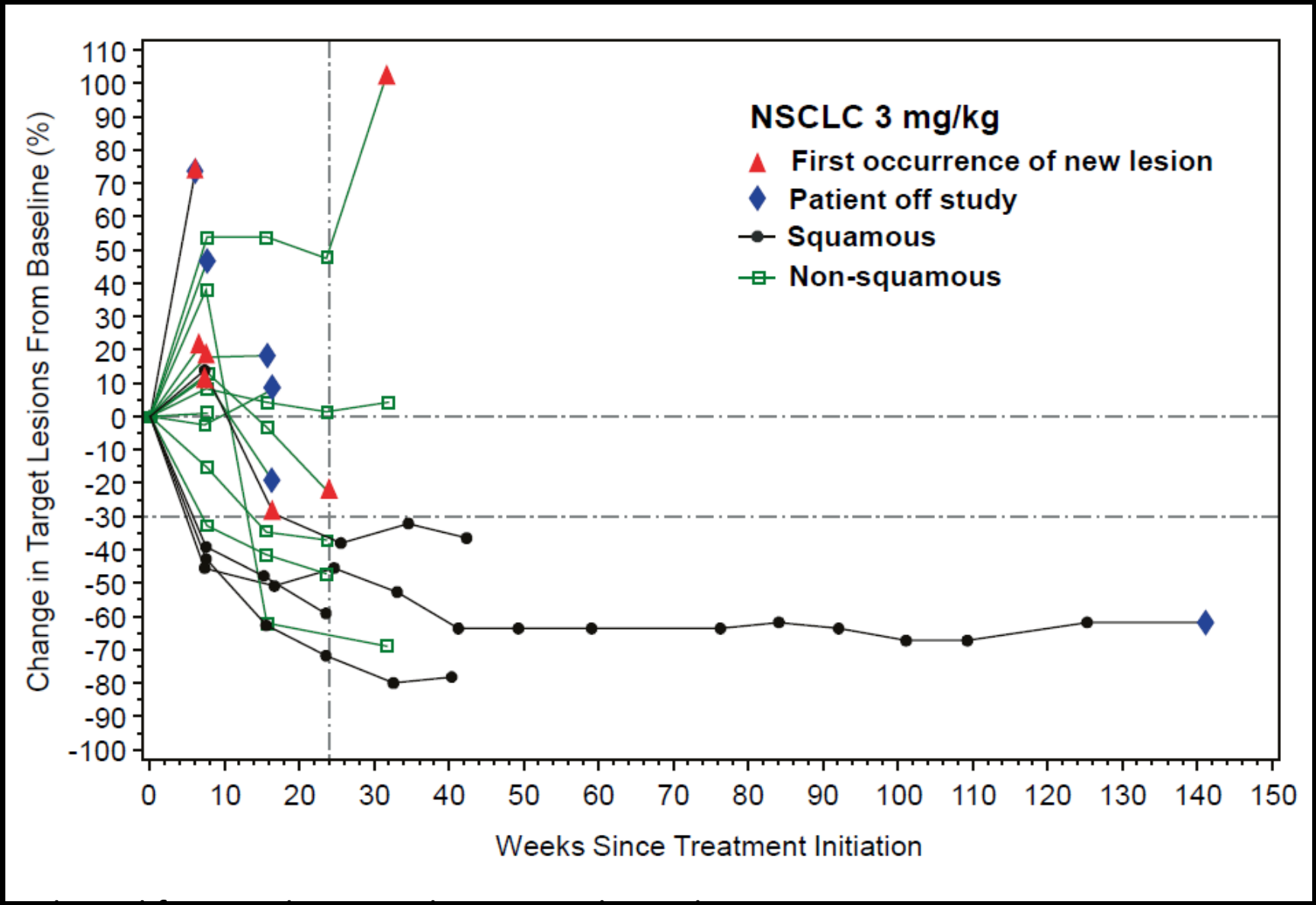
Adverse Event, n (%)	Any Grade	Grade 3-4
Hypothyroidism	32 (8)	1 (<1)
Hyperthyroidism	4 (1)	1 (<1)
Pneumonitis[a]	11 (3)	1 (<1)
Colitis	3 (<1)	2 (<1)
Hepatitis[b]	2 (<1)	1 (<1)

- Some reported skin rashes may have been immune-mediated
- The following potentially immune-mediated AEs were reported in <1% of patients: nephritis, hypophysitis, and uveitis

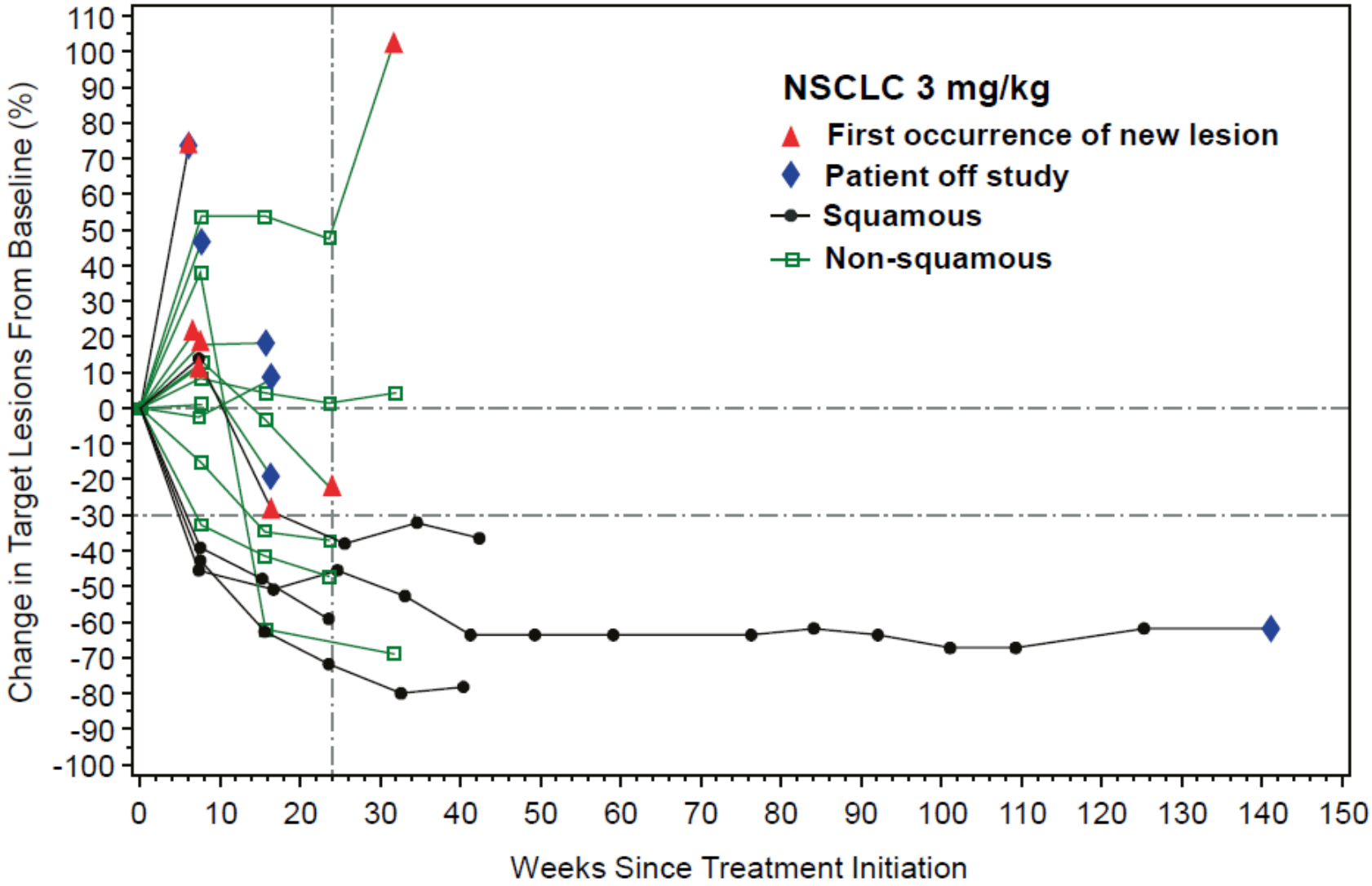
Survival End Points.



Robert C et al. N Engl J Med 2015;372:320-330.


NSCLC 3 mg/kg
First occurrence of new lesion
Patient off study
Squamous
Non-squamous
Change in Target Lesions From Baseline (%)
Weeks Since Treatment Initiation
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

Anti-PD-L1 (BMS-936559) in NSCLC



Adapted from Brahmer et al., *New Engl J Med*, 2012

Abstract #3462

Phase II Study of Nivolumab (anti-PD-1) in Patients with Advanced, Refractory Squamous Non-Small Cell Lung Cancer

Suresh S. Ramalingam,[1] Julien Mazières,[2] David Planchard,[3] Thomas E. Stinchcombe,[4] Grace K. Dy,[5] Scott J. Antonia,[6] Leora Horn,[7] Herve Lena,[8] Elisa Minenza,[9] Bertrand Mennecier,[10] Gregory A. Otterson,[11] Luis T. Campos,[12] David R. Gandara,[13] Benjamin P. Levy,[14] Suresh G. Nair[15], Gerard Zalcman,[16] Juergen Wolf,[17] Christine Baudelet,[18] Brian J. Lestini,[19] and Naiyer A. Rizvi[20]

Email: suresh.ramalingam@emory.edu

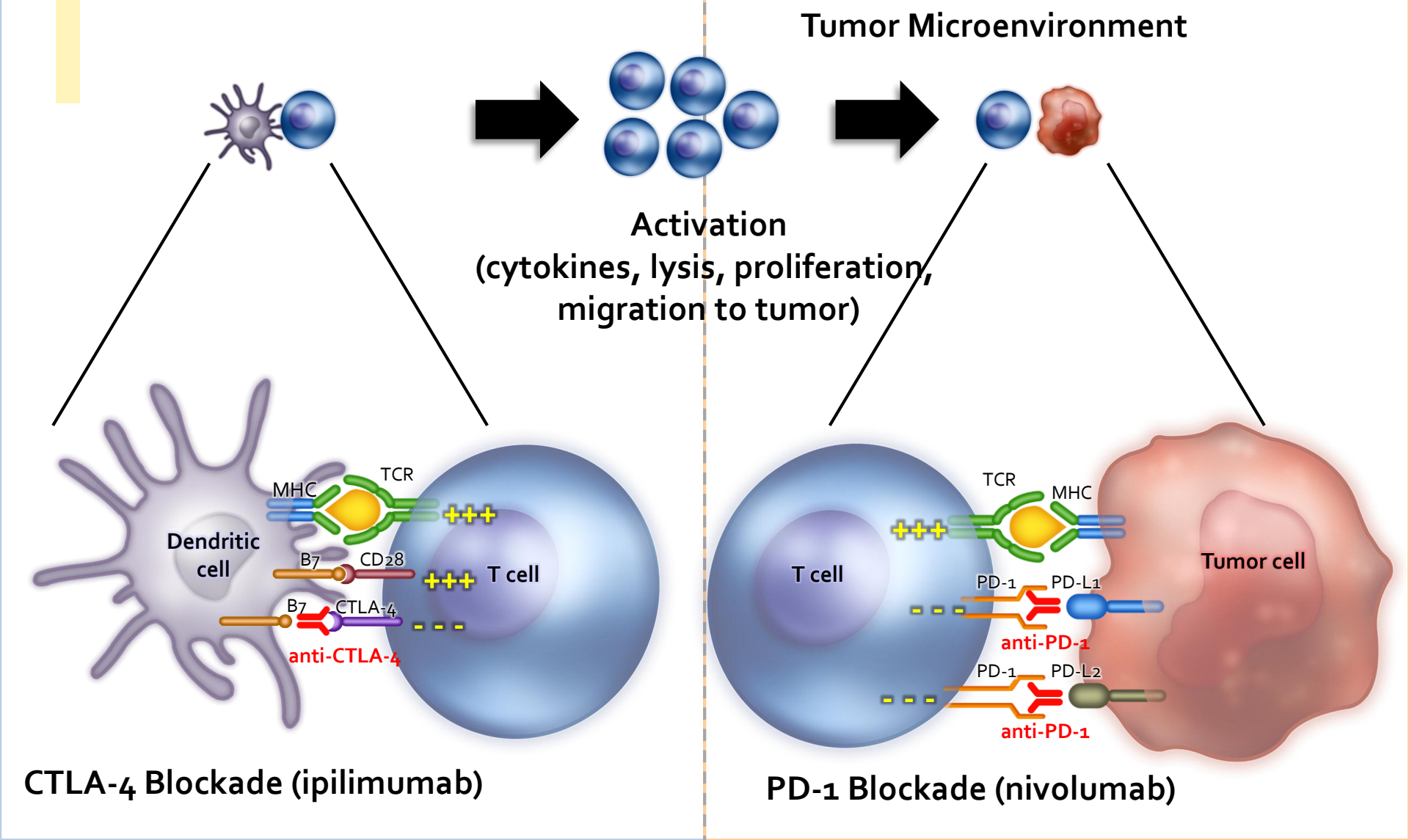
Clinical Activity of Nivolumab

	IRC Assessed (per RECIST 1.1)[a]
ORR, % (n) [95% CI]	15 (17) [9, 22]
Disease control rate, % (n)	40 (47)
Median DOR, months (range)	NR (2+, 12+)
Ongoing responders, % (n)	59 (10)
Median time to response, months (range)	3 (2, 9)
Median PFS, months (95% CI)	1.9 (2, 3)
PFS rate at 1-year, % (95% CI)	20 (13, 29)

[a]July 2014 DBL
NR = not reached; ORR = objective response rate; DOR = duration of response; PFS = progression free survival

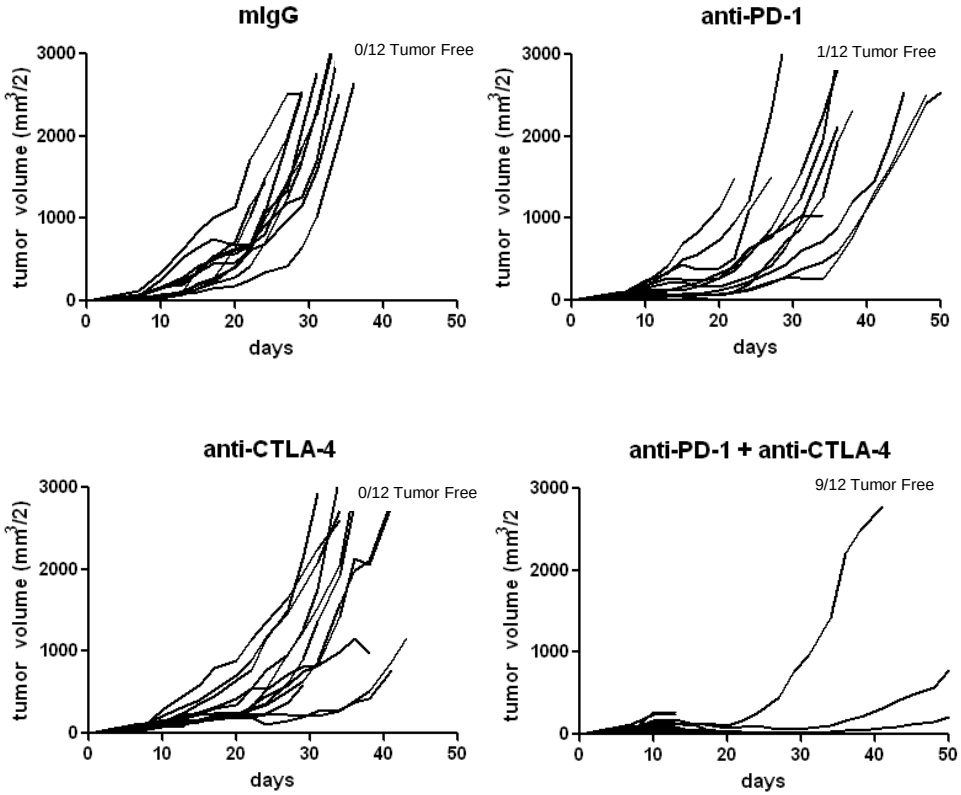
- Investigator-assessed ORR was 13% (95% CI, 7, 20)
  - Concordance between IRC and investigator assessed responders was 92% (based on March 2014 DBL)

Blocking CTLA-4 and PD-1

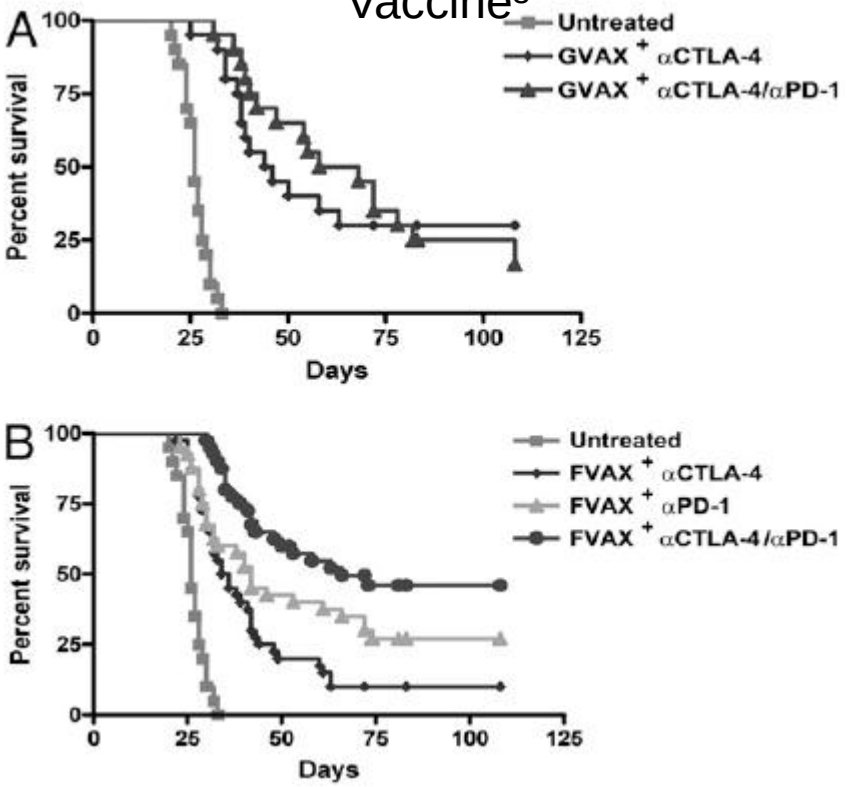


Activity of Anti-CTLA-4 and Anti-PD-1 Antibodies

MC38 Colon Cancer
Antibody Rx Only [1, 2]



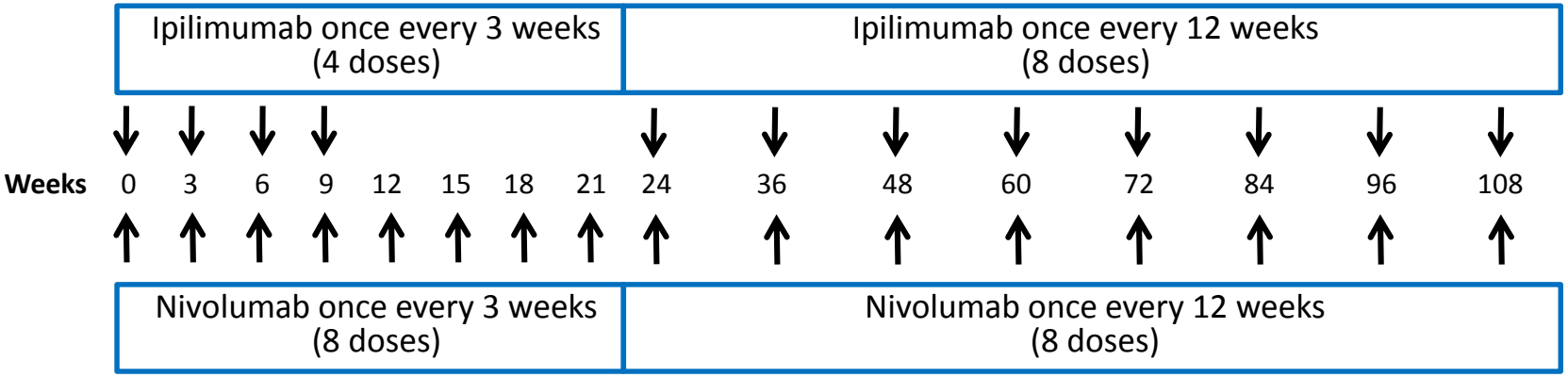
B16BL6 Melanoma
Antibody Rx + Cellular Vaccine[3]



[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



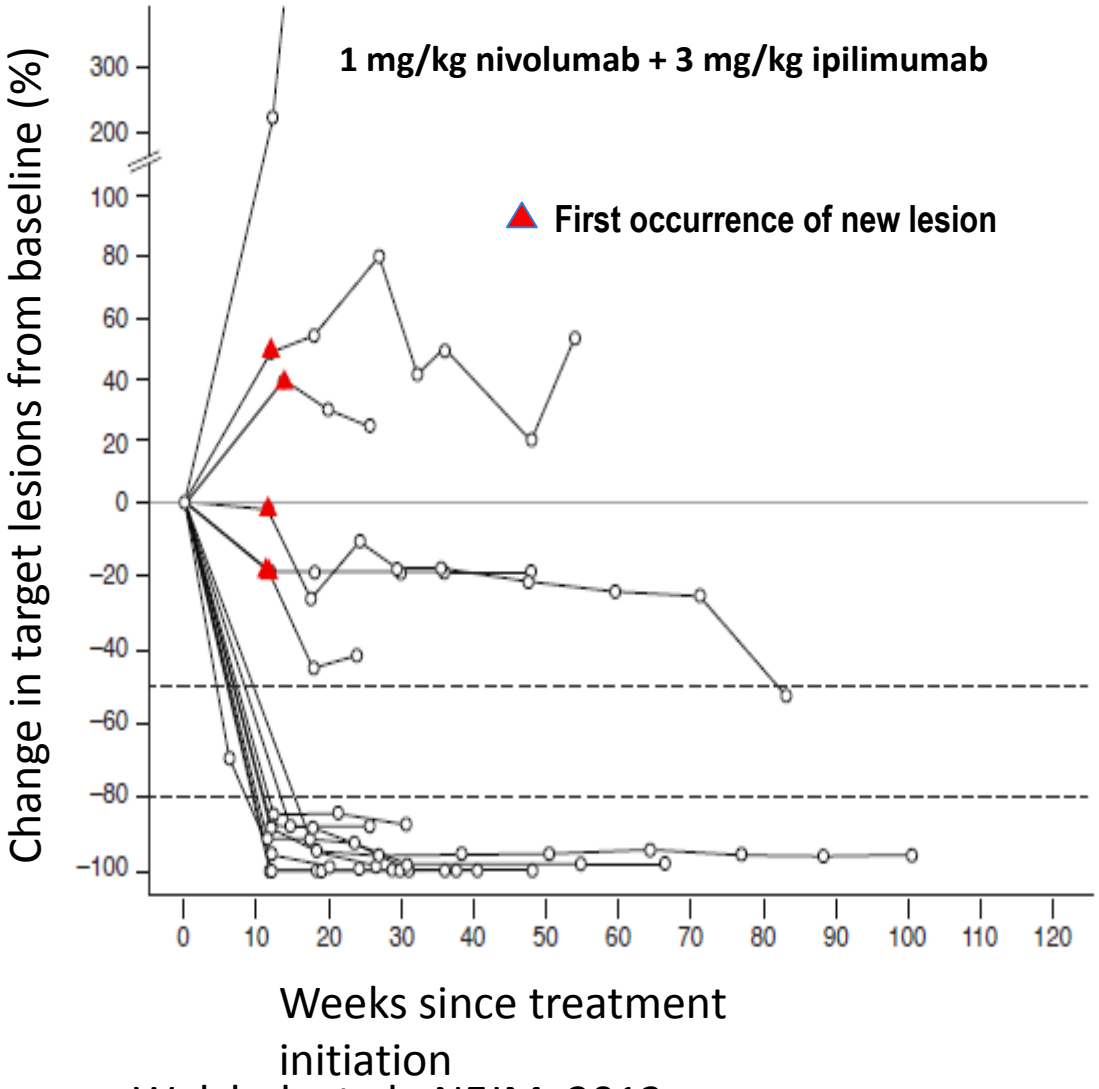
- First tumor assessment at 12 weeks

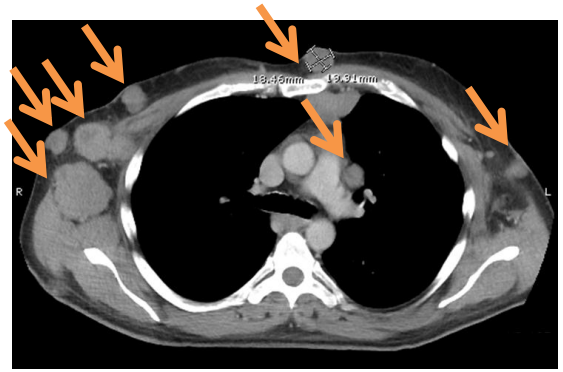
Sequenced Cohorts

- Following prior ipilimumab, patients received nivolumab every 2 weeks for a maximum of 48 doses
- First tumor assessment at 8 weeks

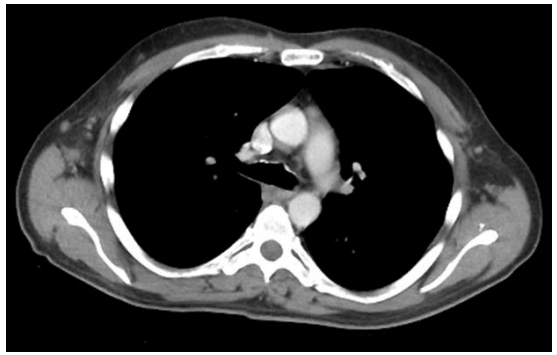
- **Tumor assessments by mWHO and immune-related response criteria**

Rapid and Durable Changes in Target Lesions





Pre-treatment

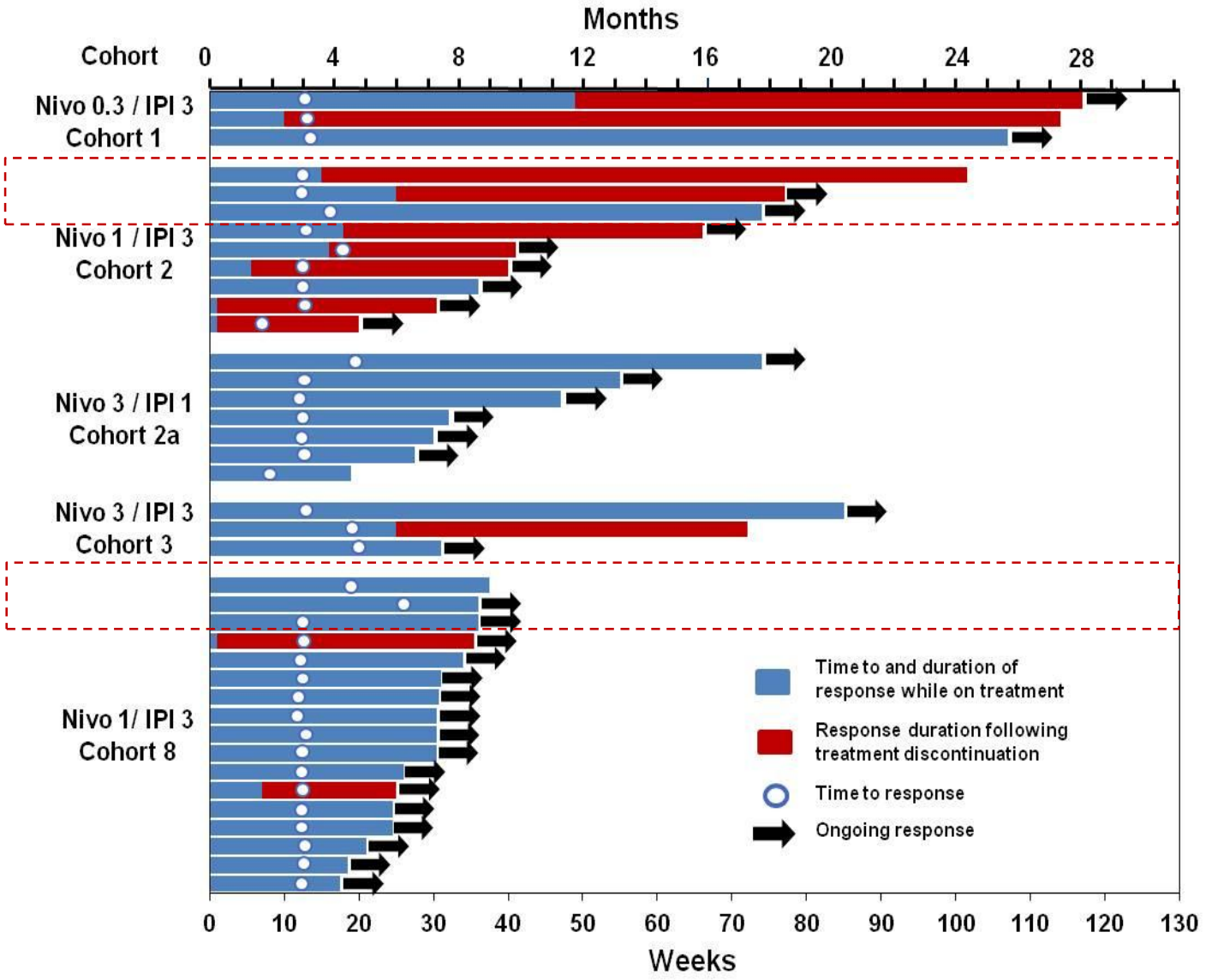


12 weeks

- 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

Wolchok et al., NEJM, 2013

Characteristics of Response



- Median duration of response in Cohorts 1-3 and cohort 8 not reached
- 18/22 responses ongoing

Sznol et al., ASCO, 2014

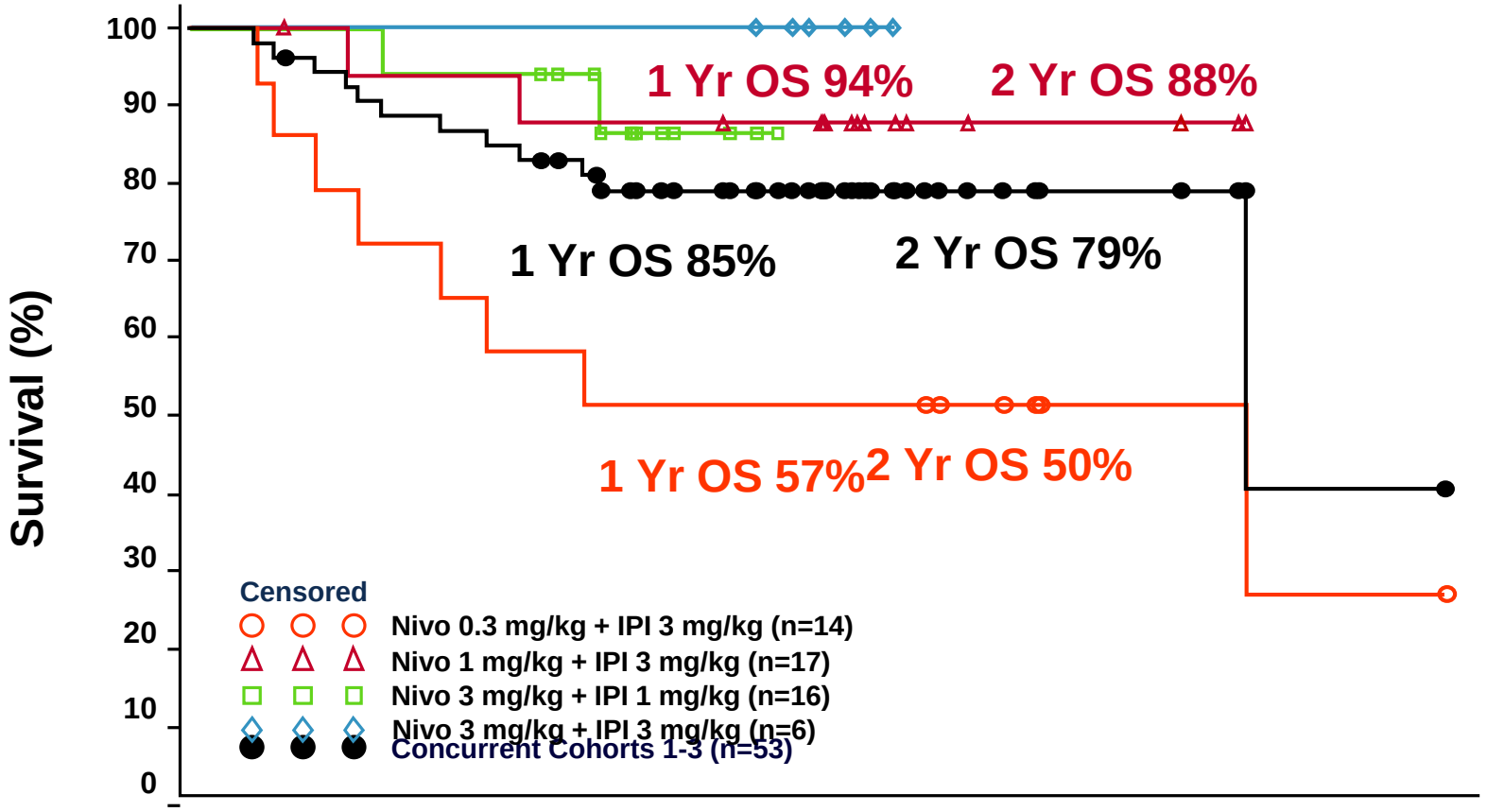
Safety Overview

AE, %	Concurrent Cohorts 1-3 n=53		Cohort 8 n = 41		All Concurrent n=94	
	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4
All Related AEs	**96**	**62**	**95**	**61**	**96**	**62**
Select AEs						
Gastrointestinal	43	9	34	20	39	14
Hepatic	30	15	12	12	22	14
Skin	79	4	73	15	77	9
Endocrine	17	4	22	2	19	3
Renal	6	6	0	0	3	3
Other						
Uveitis	6	4	2	2	4	3
Pneumonitis	6	2	2	2	4	2
Lipase increased	26	19	15	10	21	15
Amylase increased	21	6	12	7	17	6

- No new safety signals with 22 months of follow-up for the initial concurrent cohorts
- 22/94 (23%) patients discontinued treatment due to treatment-related adverse events
- 1/94 drug-related death in trial; fatal multi-organ failure (as a result of colitis) in cohort 8

Sznol et al., ASCO, 2014

Overall Survival for Concurrent Therapy by Dose Cohort

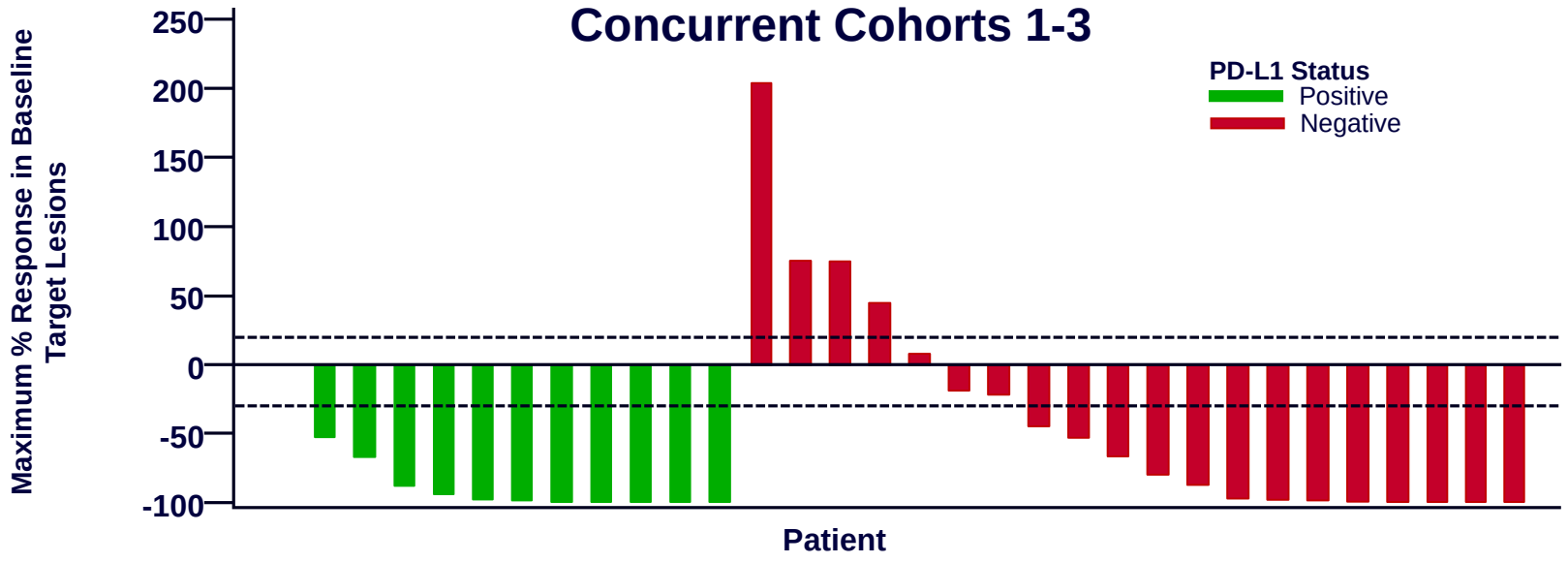


Pts at Risk																	
Nivo 0.3_IPI 3	14	13	11	10	8	7	7	7	7	7	5	2	2	2	1	1	0
Nivo 1 _IPI 3	17	17	16	15	15	14	14	13	9	4	3	3	3	2	0	0	0
Nivo 3_IPI 1	16	16	15	15	15	13	4	2	0	0	0	0	0	0	0	0	0
Nivo 3_IPI 3	6	6	6	6	6	6	6	6	3	0	0	0	0	0	0	0	0
Concurrent	53	52	48	46	44	40	31	28	19	11	8	5	5	4	1	1	0

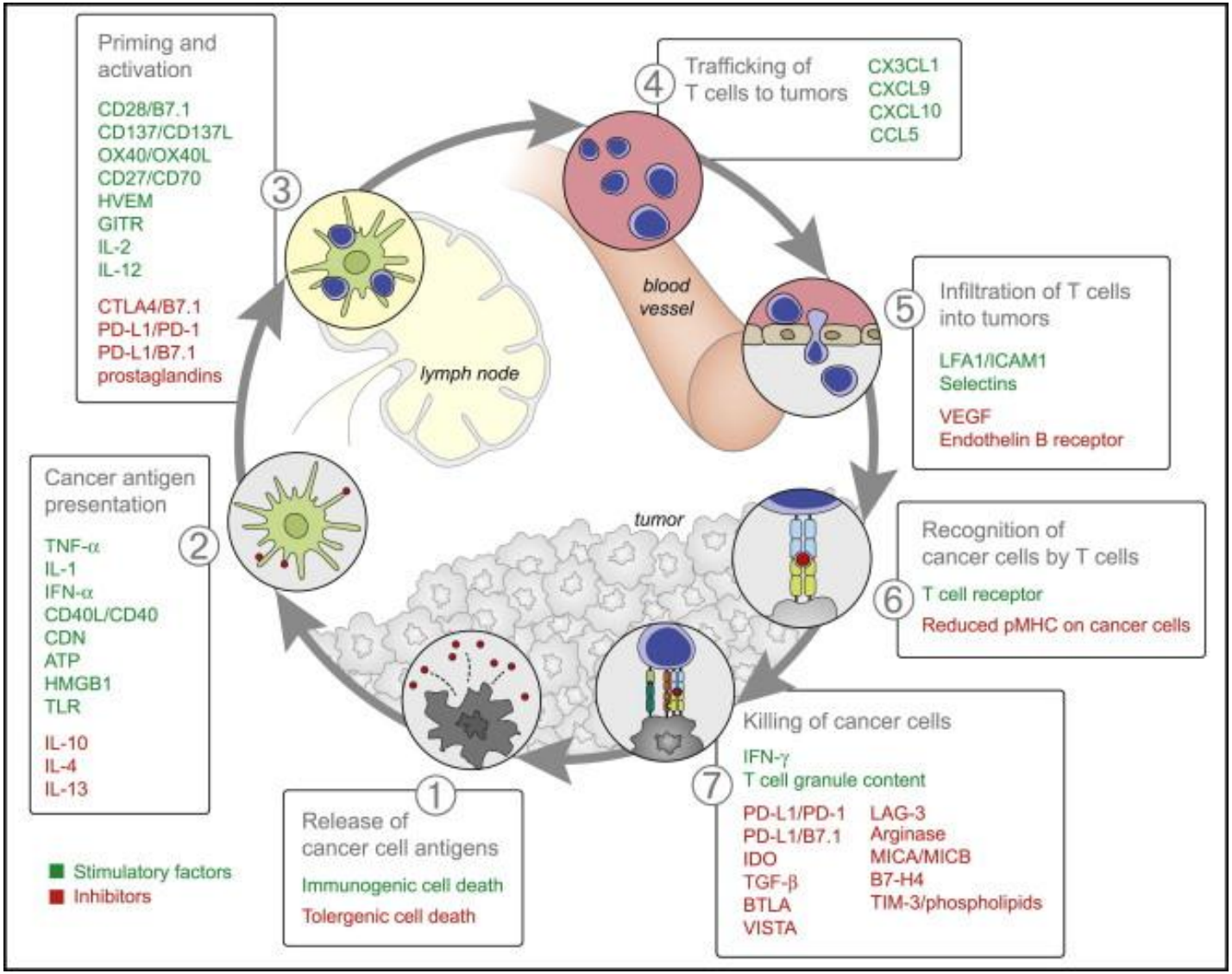
Sznol et al., ASCO, 2014

Response Rate by PD-L1 Status (5% cutoff)

Cohort [n]	Evaluable Samples	ORR, n (%)	
PD-L1 Status		PD-L1+	PD-L1-
Concurrent Cohorts 1-3 [53]	36	8/14 (57)	9/22 (35)
Cohort 8 [41; Nivo1 + IPI3]	20	0/0	8/20 (40)
Sequenced [33]	23	5/8 (63)	3/15 (20)



The Cancer–Immunity Cycle



Chen and Mellman*, Immunity*, Vol 39 (1), 2013, 1 - 10

Summary

- Checkpoint blockade is an effective treatment with durable responses and improvement in overall survival in melanoma and non-small cell lung cancer.
- Promising clinical activity has also been demonstrated, specially for PD-1 pathway blockade in renal cell carcinoma,, urothelial bladder cancer, lymphomas and head/neck cancer.
- Combination therapy will be necessary for immunotherapy to achieve full potential (other immune modulators, oncolytic viruses, vaccines, radiation, chemotherapy, targeted therapy, anti-angiogenic therapy).
- New agents are in early clinical development. These include additional antagonists (LAG-3) as well as agonist agents for costimulatory pathways (GITR, OX40, CD40, CD137) which may be beneficial alone and as part of combinatorial approaches.