NASDC
NCI Awardee Skills Development Consortium

Checkpoint Blockade Immunotherapy

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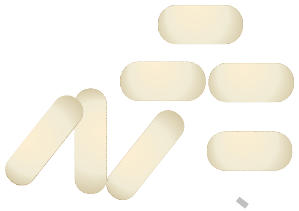
Associate Director, Ludwig Center for Cancer Immunotherapy

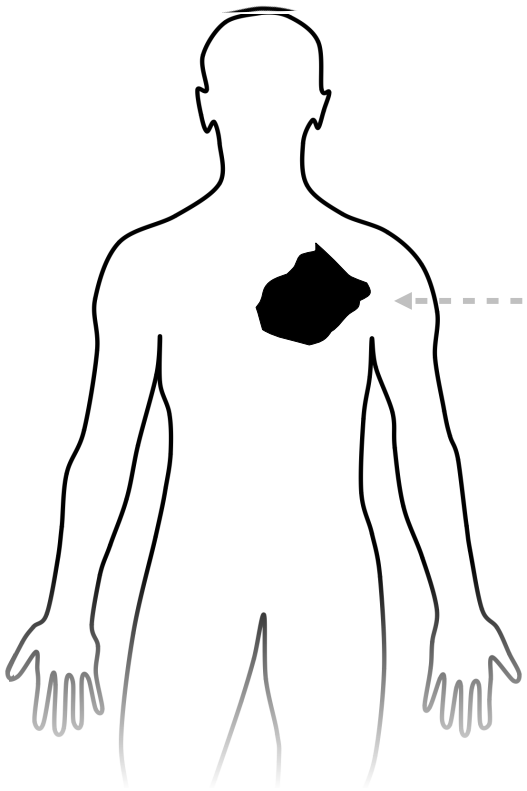
Memorial Sloan Kettering
Cancer Center

Is there an immune response to cancer?

Can the immune system reject cancer?

Foreign Infectious Pathogen

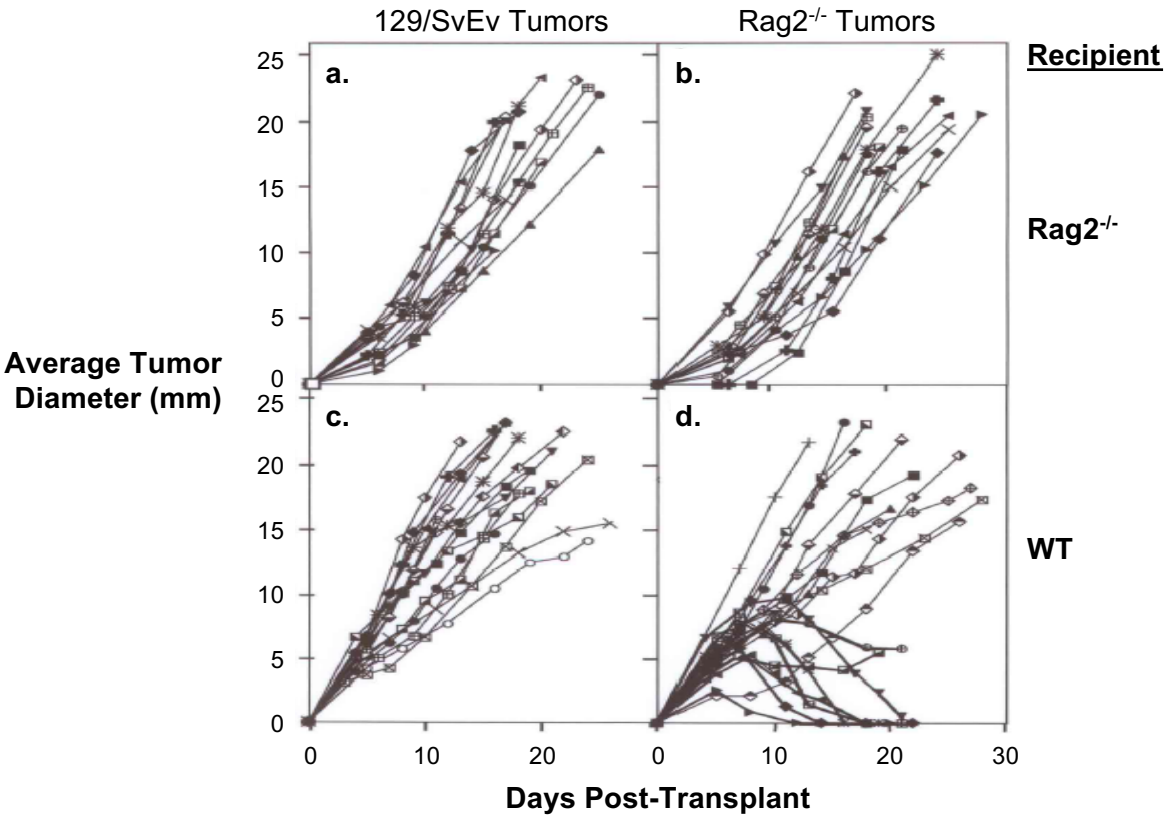




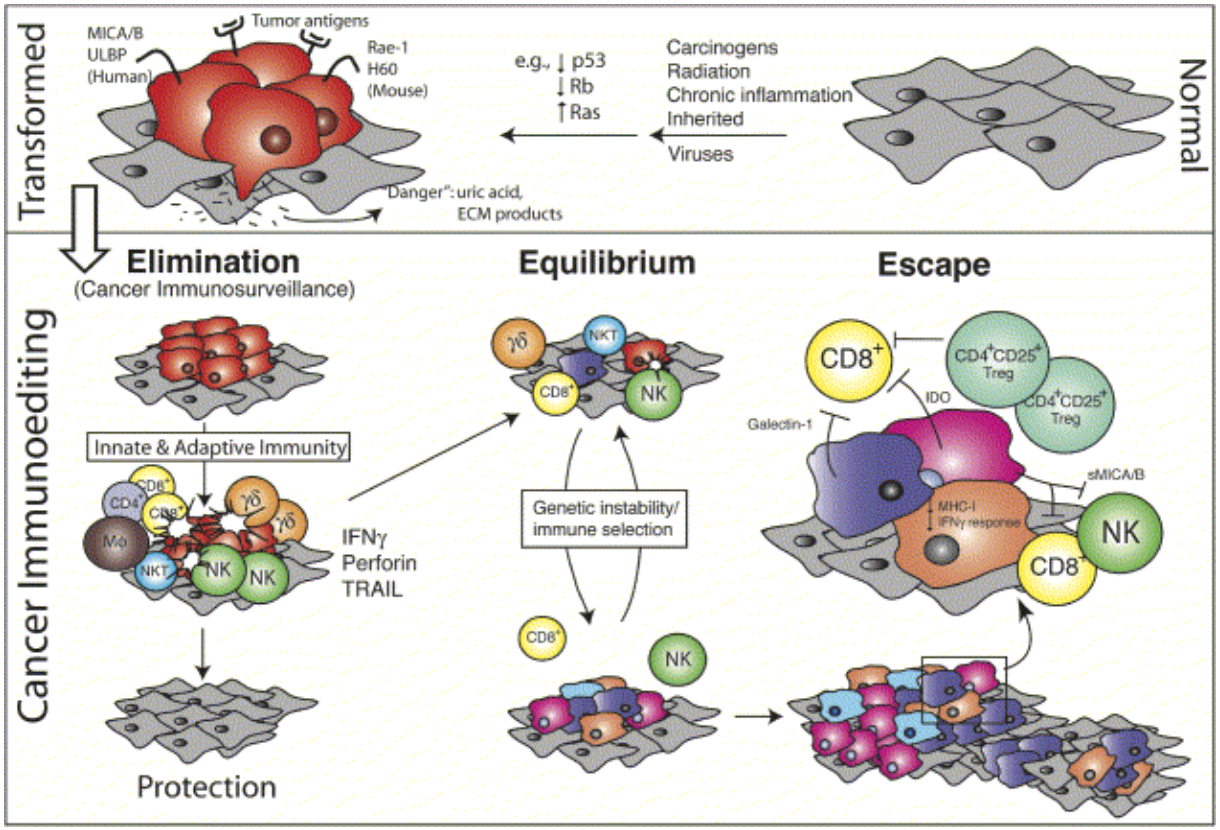
Cancer – Foreign or Self ?

Immune Surveillance

- Proposed: L Thomas and M Burnet
- Disproved: O Stutman
- Resurrected: R Schreiber and LJ Old

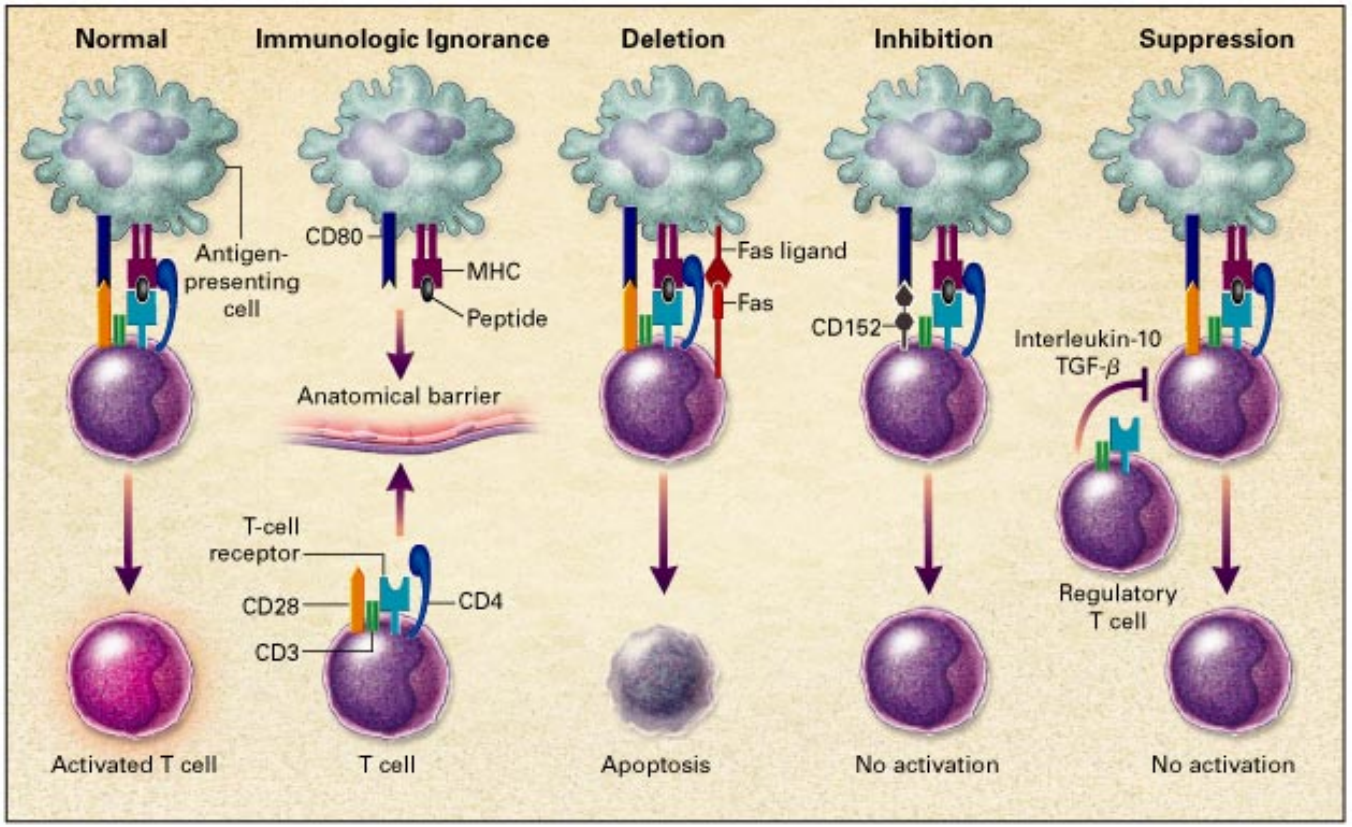

129/SvEv Tumors
Rag2-/- Tumors
Recipient
a.
b.
c.
d.
Rag2-/-
WT
Average Tumor Diameter (mm)
0
5
10
15
20
25
0
10
20
30
Days Post-Transplant

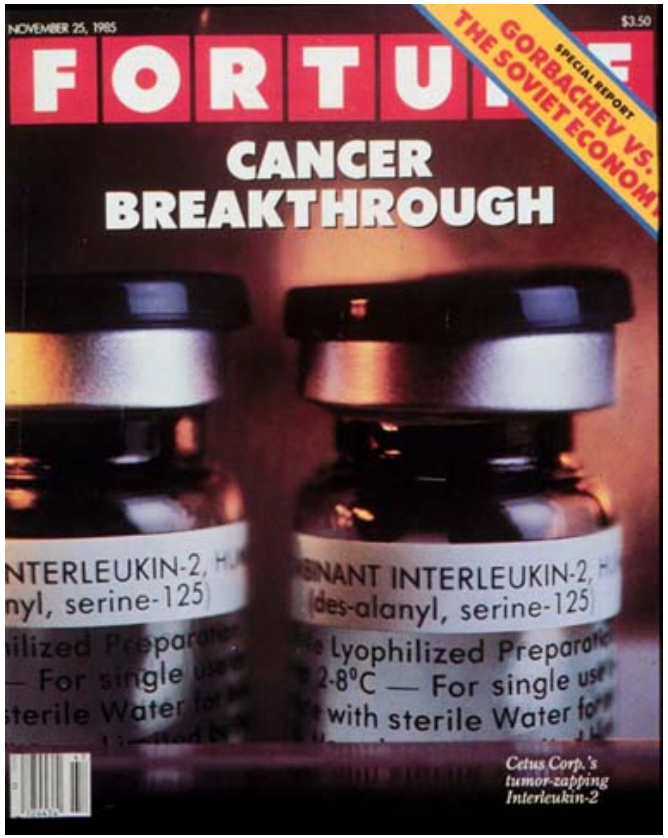
Immune surveillance of cancer



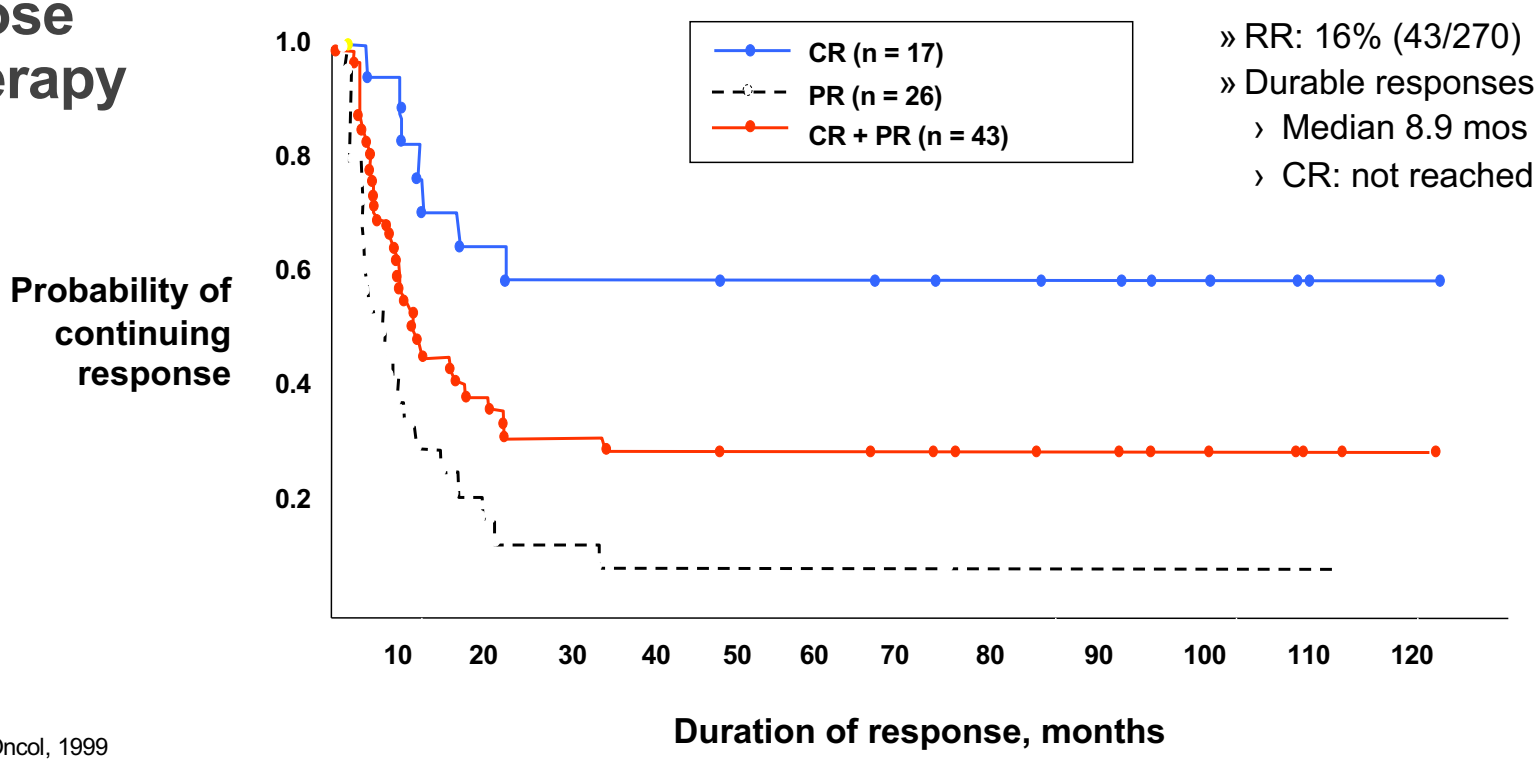
Dunn et al. Immunity 21:137, 2004

Mechanisms of Immune Suppression




NOVEMBER 25, 1985
$3.50
FORTUNE
SPECIAL REPORT
GORBACHEV VS. THE SOVIET ECONOMY
CANCER BREAKTHROUGH
NTERLEUKIN-2,
nyl, serine-125)
ilized Preparat
— For single use
sterile Water for
INANT INTERLEUKIN-2,
(des-alanyl, serine-125)
Lyophilized Preparat
2-8°C — For single use
with sterile Water for
Cetus Corp.'s tumor-zapping Interleukin-2

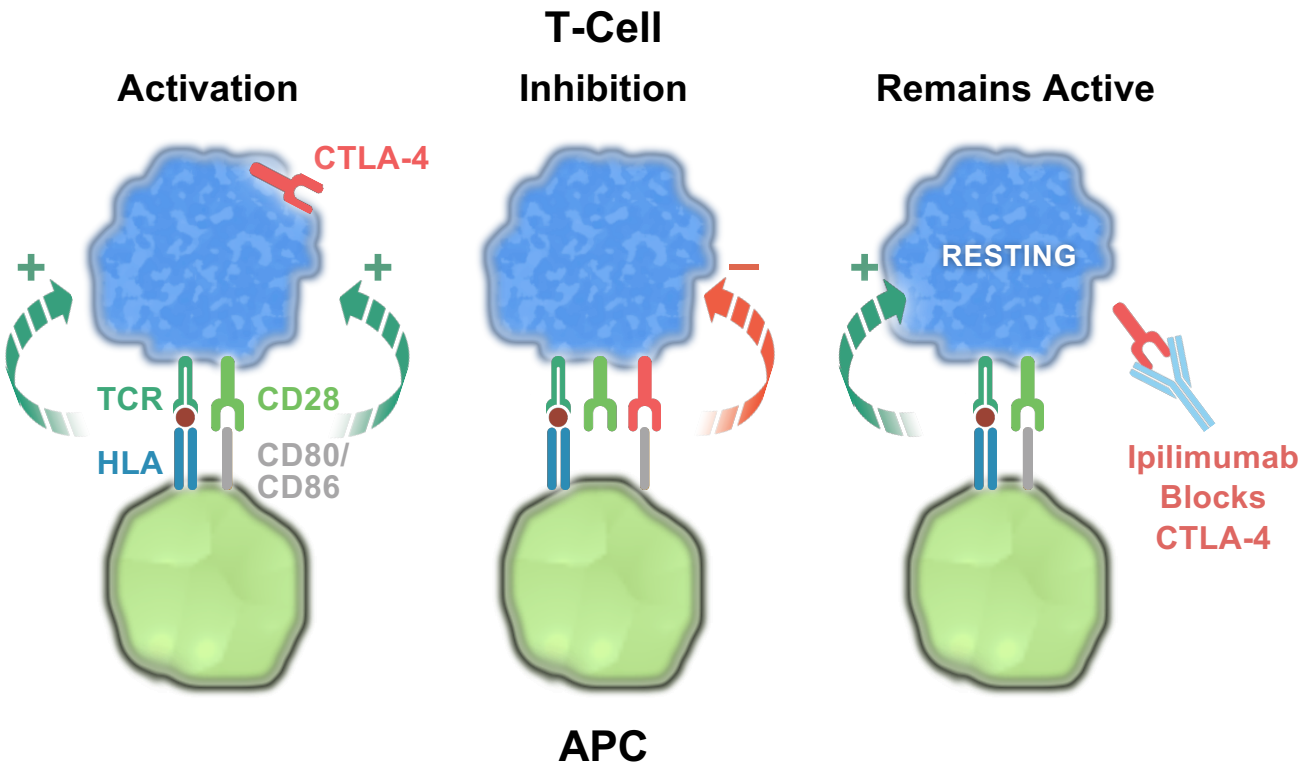
High-Dose IL-2 Therapy



» RR: 16% (43/270)
» Durable responses
› Median 8.9 mos
› CR: not reached

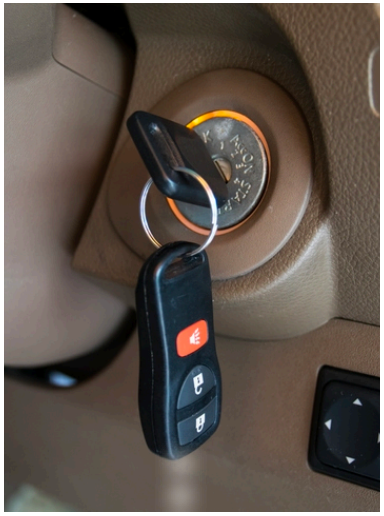
Atkins et al., J Clin Oncol, 1999

Ipilimumab Augments T-Cell Activation and Proliferation

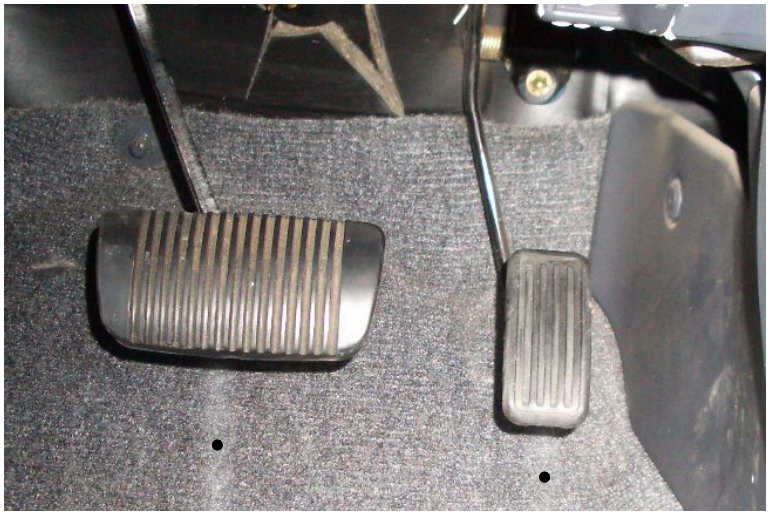


Adapted from O'Day et al.
Plenary session presentation,
abstract #4, ASCO 2010.

‘Driving’ An Immune Response



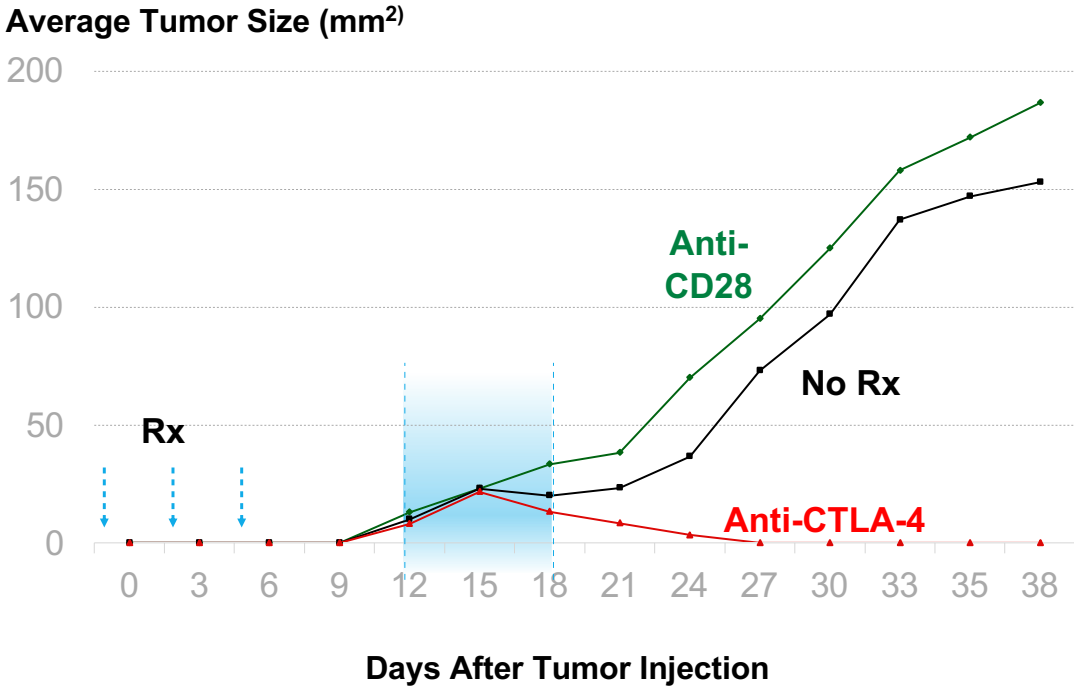
T-cell receptor: Antigen-MHC



CTLA-4:B7 **CD28:B7**

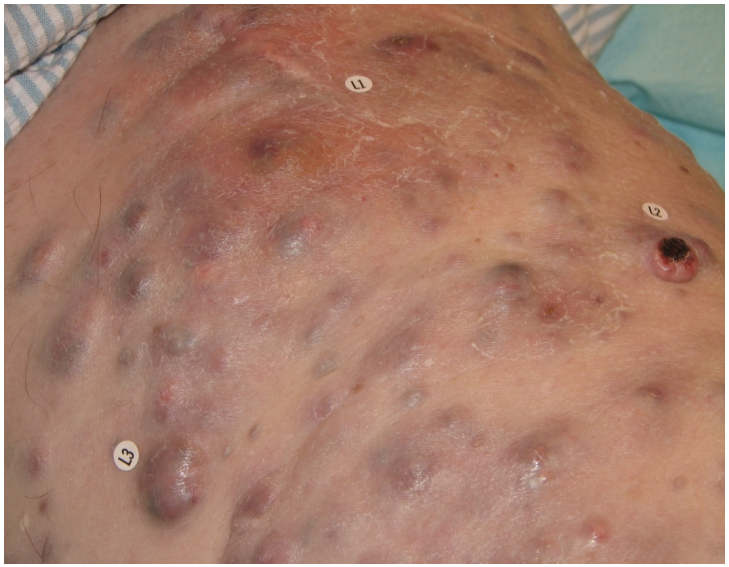
Vaccine?

Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma

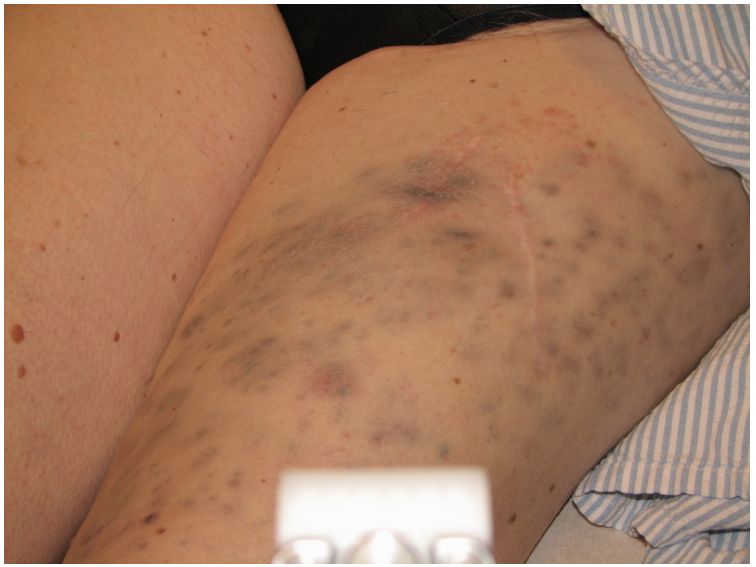


Leach DR et al., Science, 1996

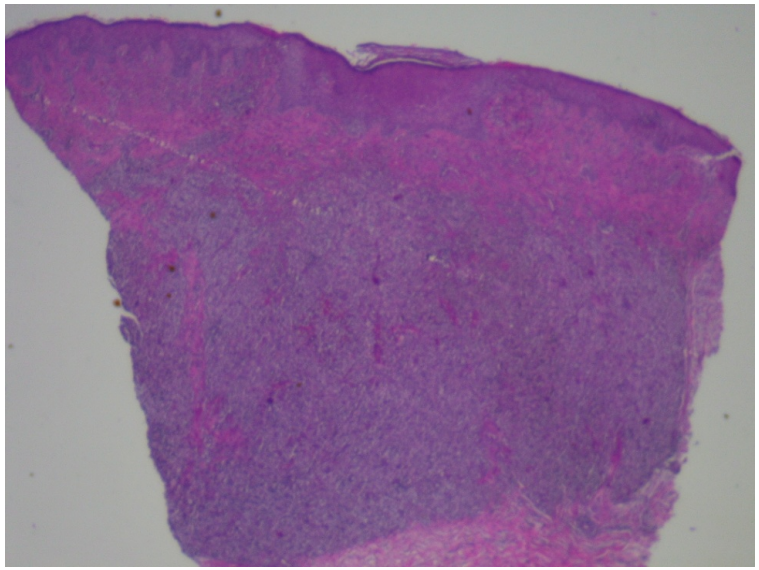
Clinical Response in Melanoma



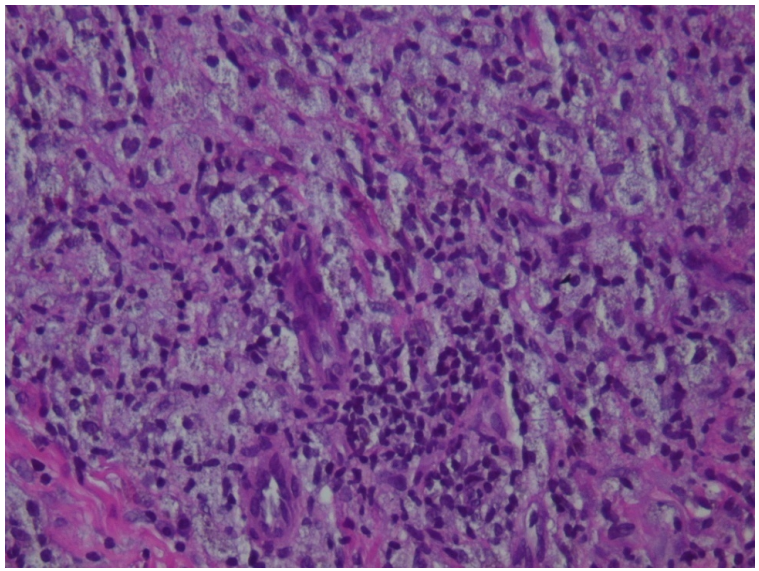
Nov 28, 2006



Jan 9, 2007

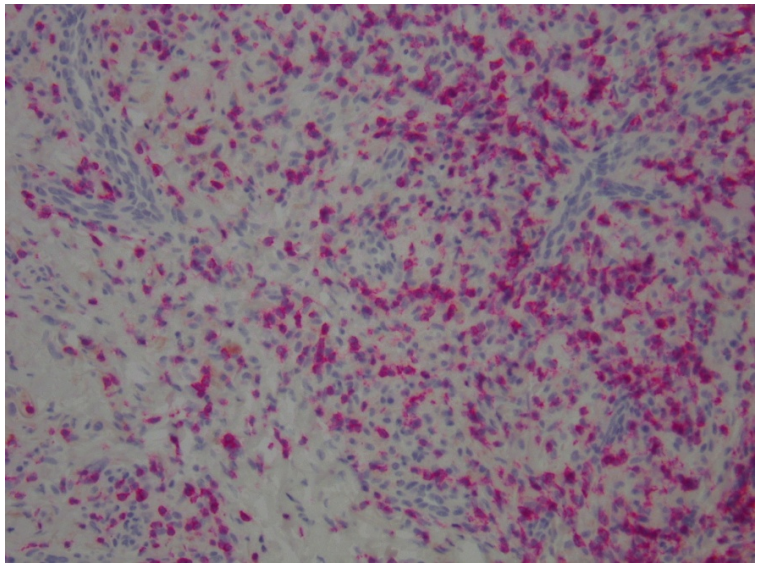


Tumorous nodule with melanin pigment (macrophages and lymphocytes; no melanocytes)

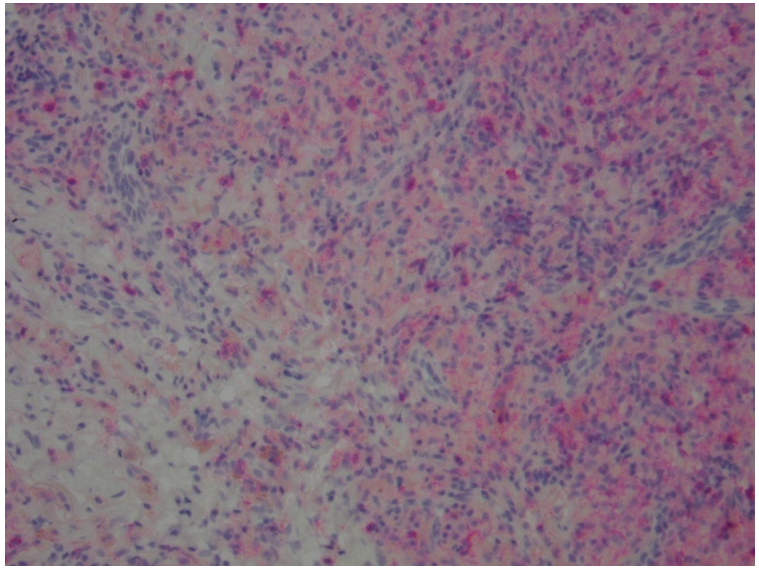


Macrophages and lymphocytes are present, but no tumor cells

Klaus Busam, MSKCC Dermatopathology



CD8-positive T-cells



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

Klaus Busam, MSKCC Dermatopathology

Immune-Related Adverse Events


SECTIONS HOME SEARCH The New York Times GIVE THE TIMES jeddkaren0

HEALTH

Immune System, Unleashed by Cancer Therapies, Can Attack Organs

By MATT RICHTEL DEC. 3, 2016

- 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.

Immune-mediated Adverse Reactions

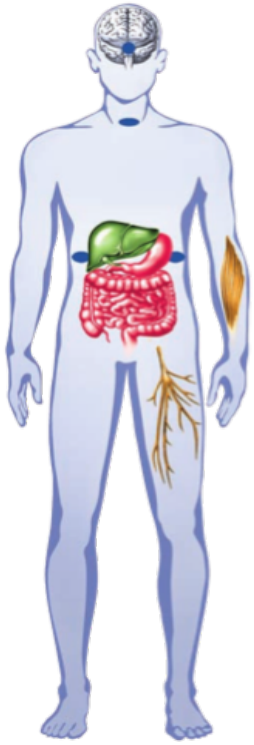
- Result from increased or excessive immune activity
- Can be severe or life-threatening, affecting various organs

Follow color code to appropriate management guide section.

GASTROINTESTINAL
GO TO PAGE 6
Signs and symptoms such as
- Diarrhea
- Abdominal pain
- Blood or mucus in stool
- Bowel perforation
- Peritoneal signs
- Ileus

LIVER
GO TO PAGE 8
Signs such as
- Abnormal liver function tests (eg, AST, ALT) or total bilirubin

SKIN
GO TO PAGE 10
Symptoms such as
- Pruritus
- Rash



NEUROLOGIC
GO TO PAGE 12
Symptoms such as
- Unilateral or bilateral weakness
- Sensory alterations
- Paresthesia

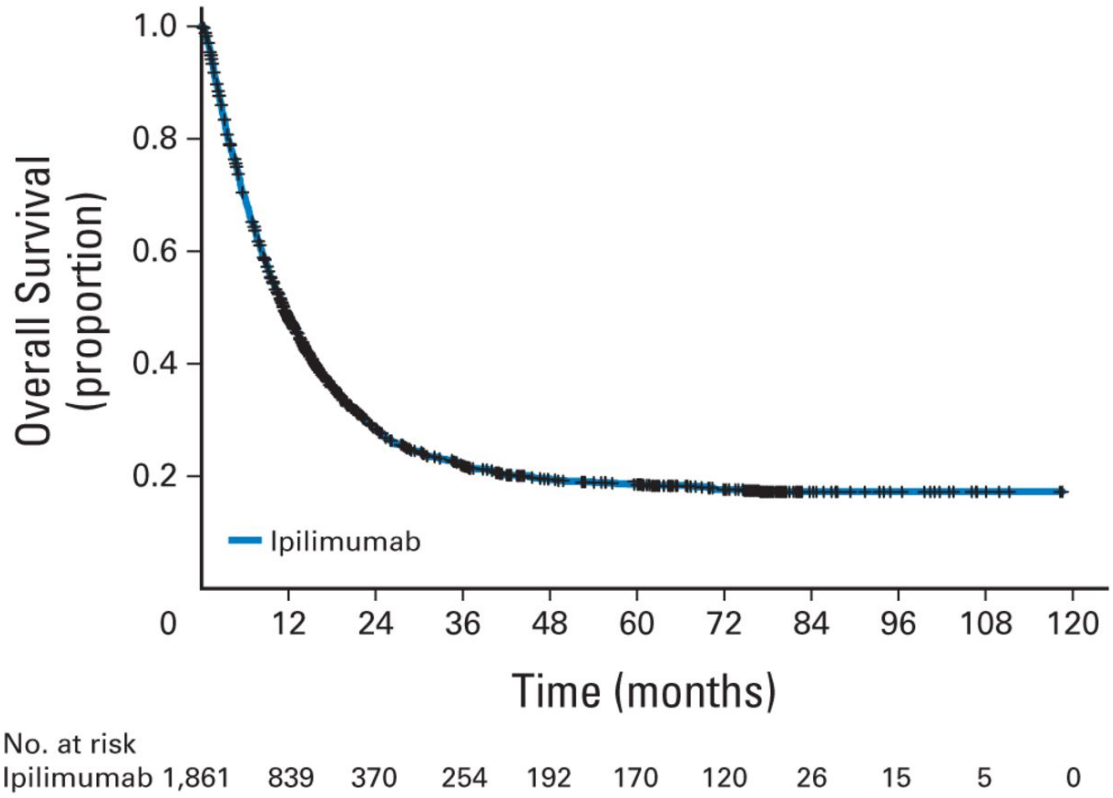
ENDOCRINE
GO TO PAGE 14
Signs and symptoms such as
- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries

OTHER ADVERSE REACTIONS, including ocular manifestations
GO TO PAGE 16

Please see each organ system section for related guidance.

Ipilimumab Phase II and III Data

Primary analysis of pooled overall survival (OS) data

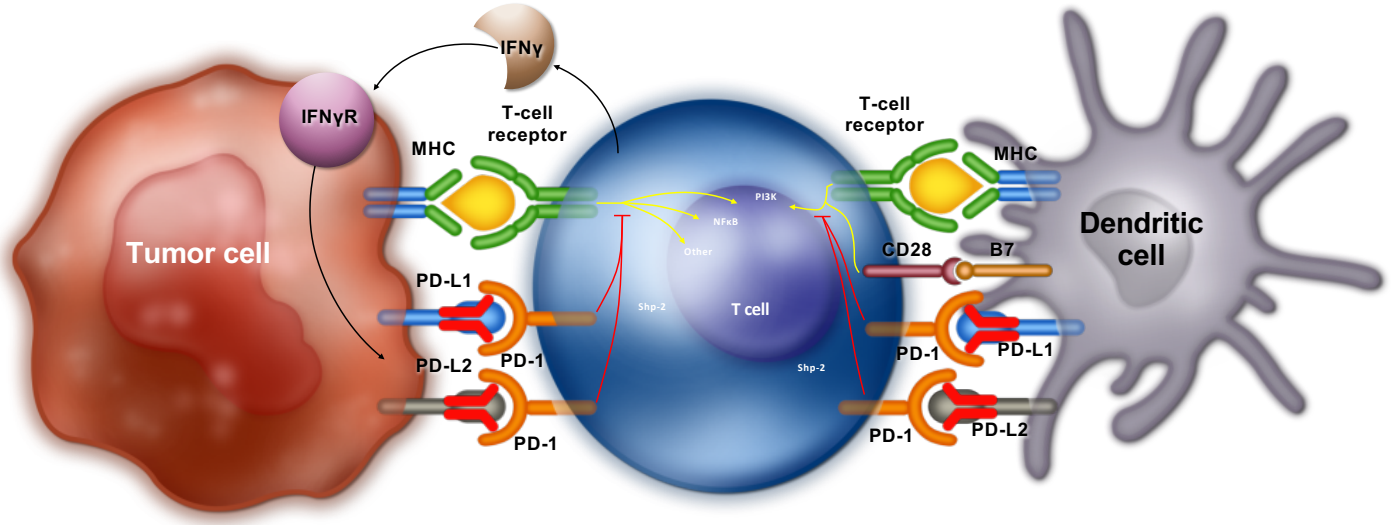


Dirk Schadendorf et al. JCO 2015;33:1889-1894

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

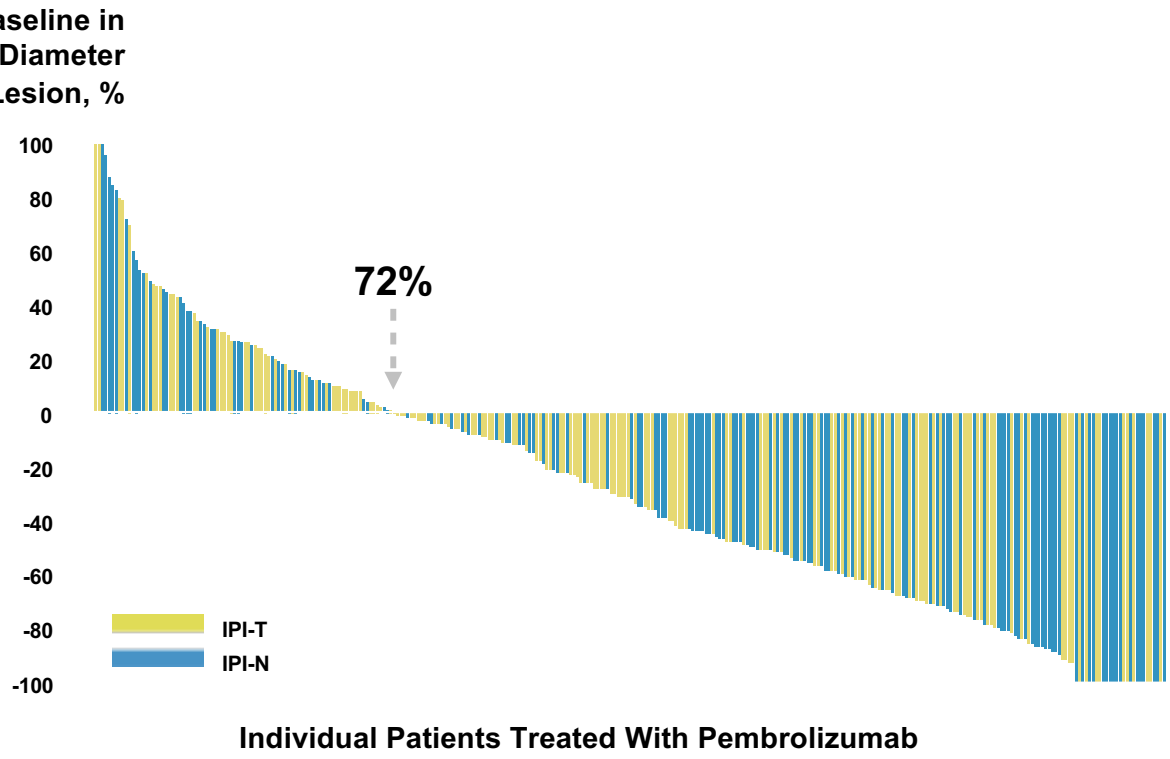
Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells



Nivolumab, Pembrolizumab, Cemiplimab:PD-1 Receptor Blocking Abs
Atezolizumab, Avelumab, Durvalumab: PD-L1 Blocking Abs

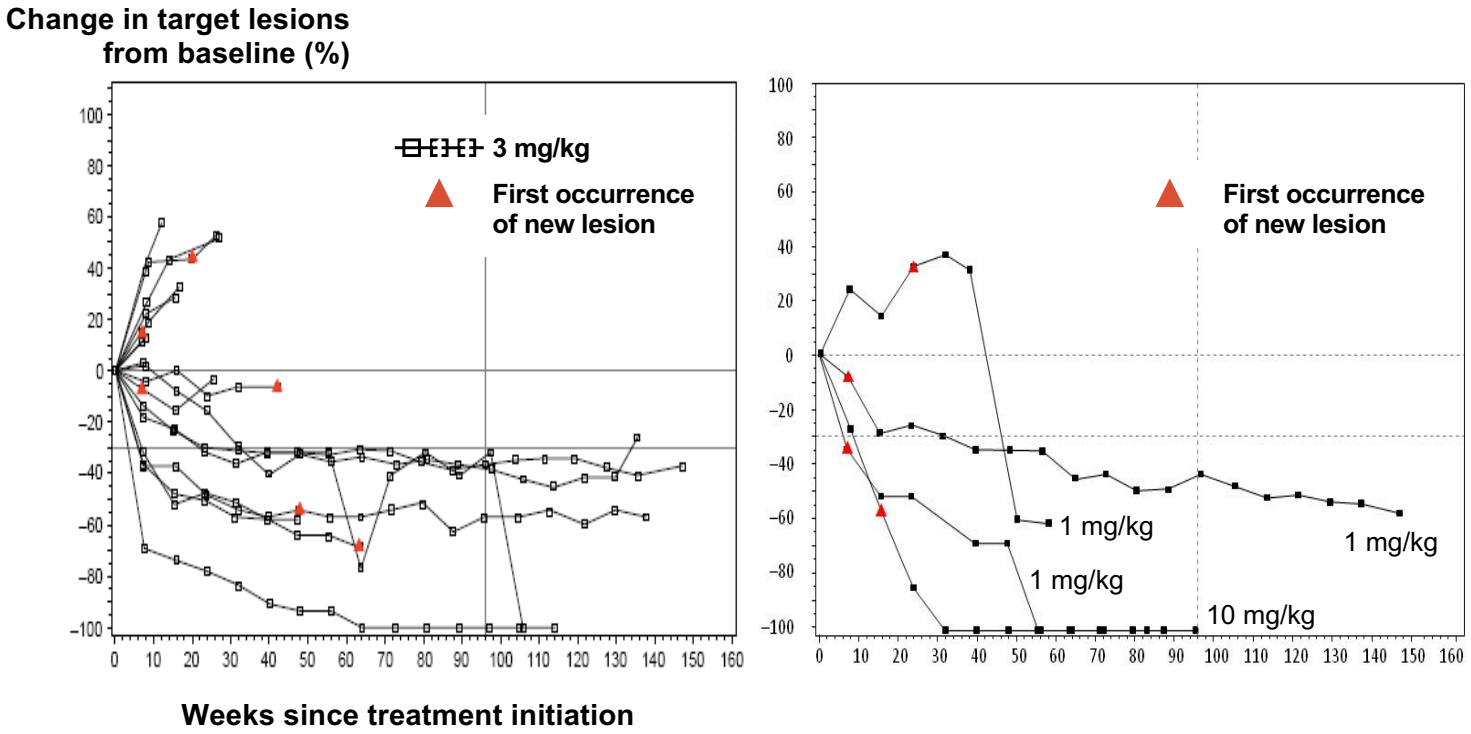
Sznol et al., ASCO, 2013

Maximum Percent Change from Baseline in Tumor Sizea (Central Review, RECIST v1.1)



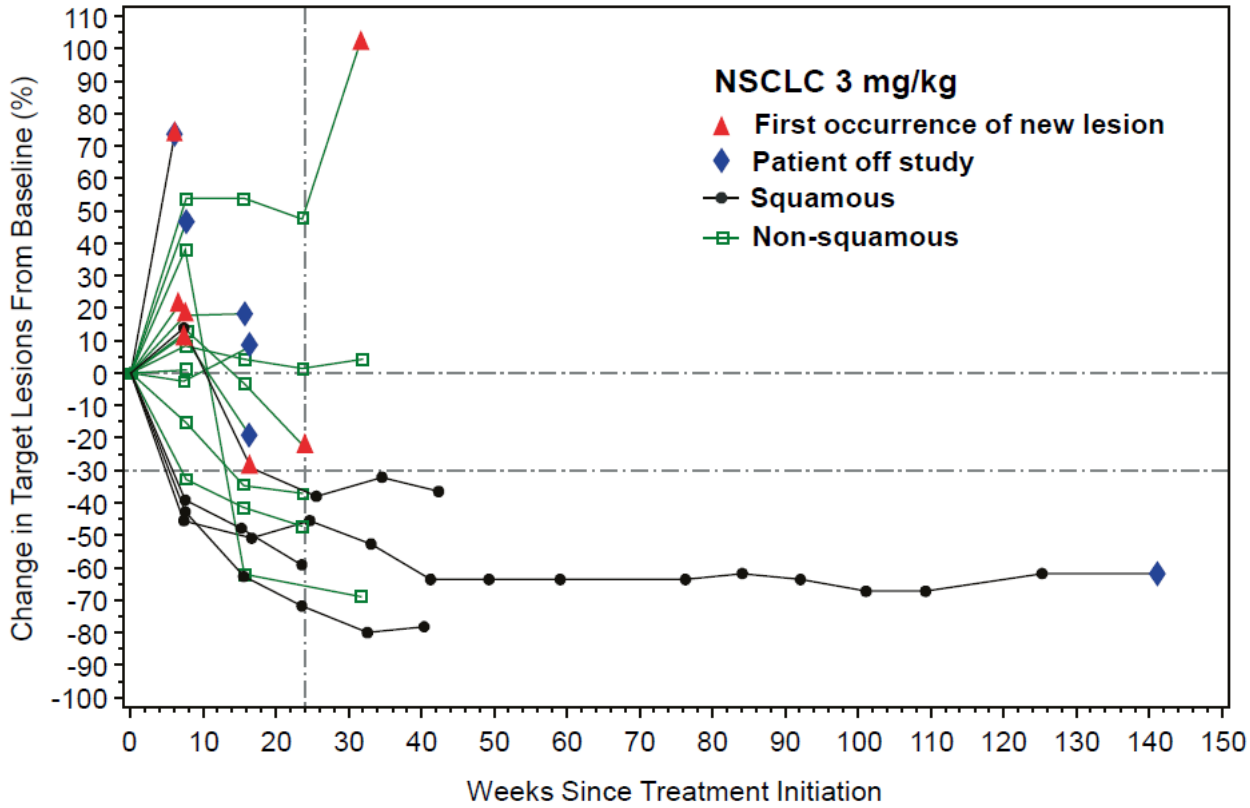
[a]In patients with measurable disease at baseline by RECIST v1.1 by central review and ≥1 postbaseline assessment (n = 317).
Percentage changes >100% were truncated at 100%.
Analysis cut-off date: October 18, 2013.

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

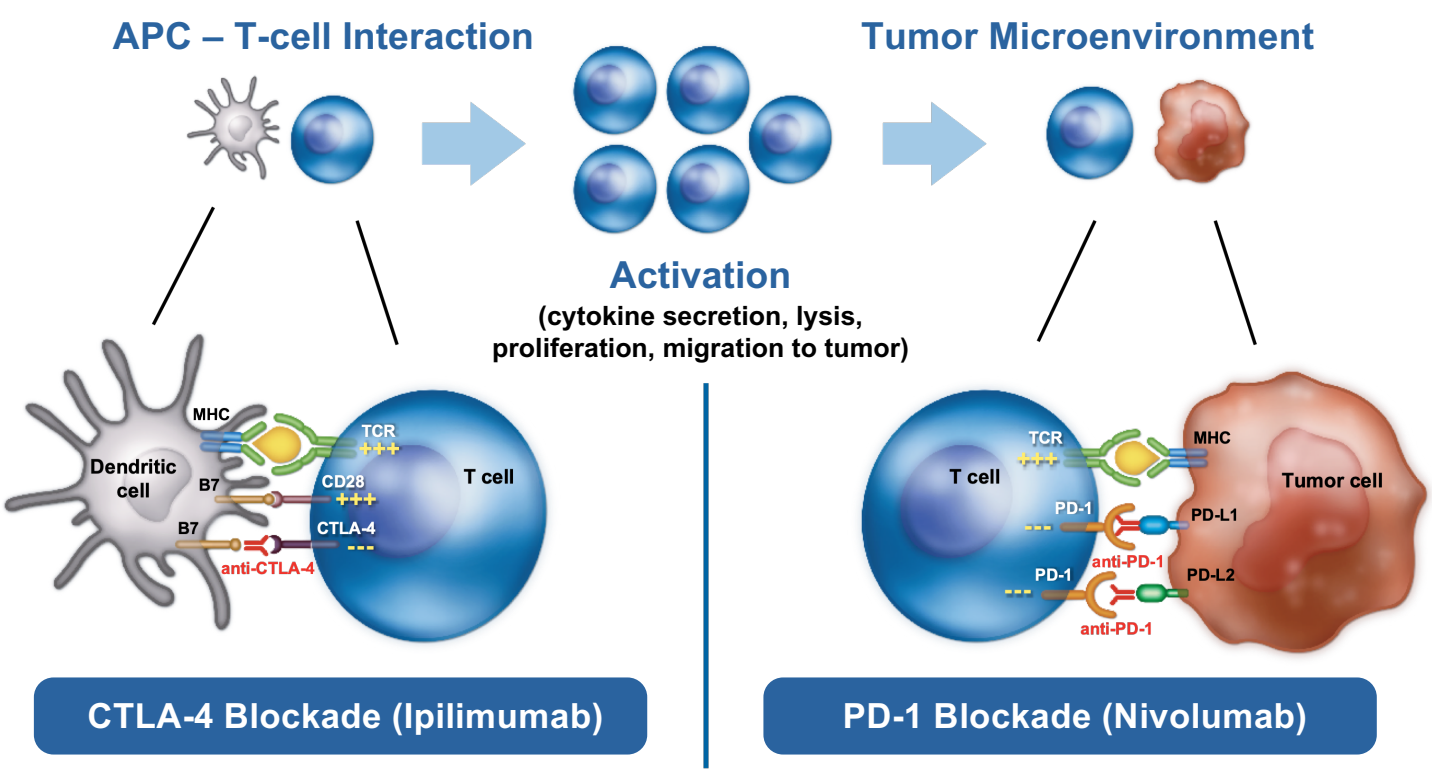


Sznol et al.,
ASCO, 2013

Changes in Target Lesions Over Time in NSCLC

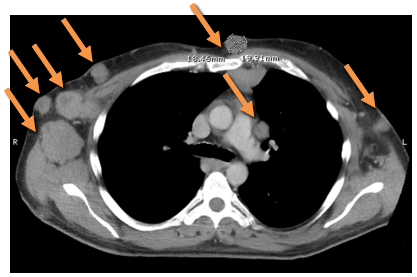


Blocking CTLA-4 and PD-1

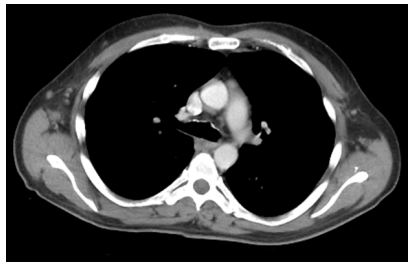


Rapid and Durable Changes in Target Lesions

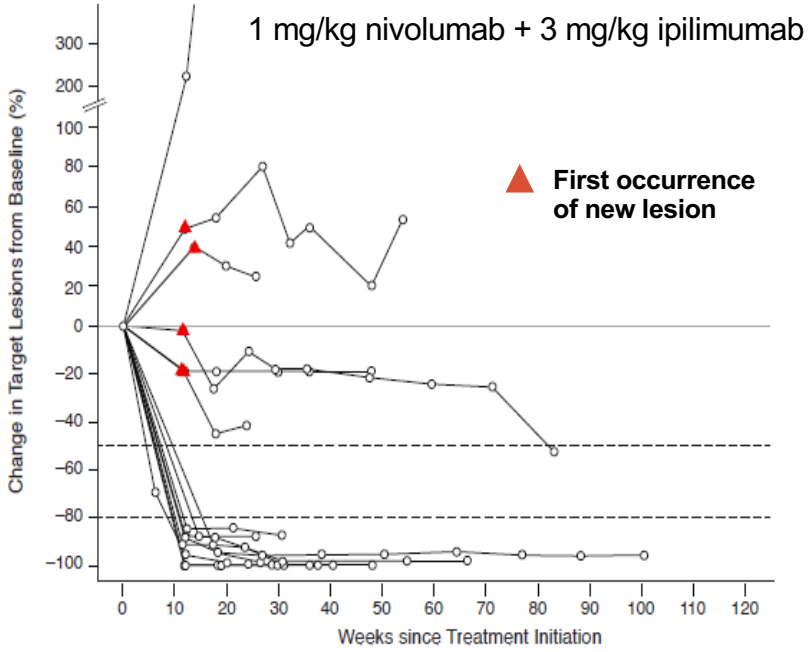
- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown



Pre-treatment



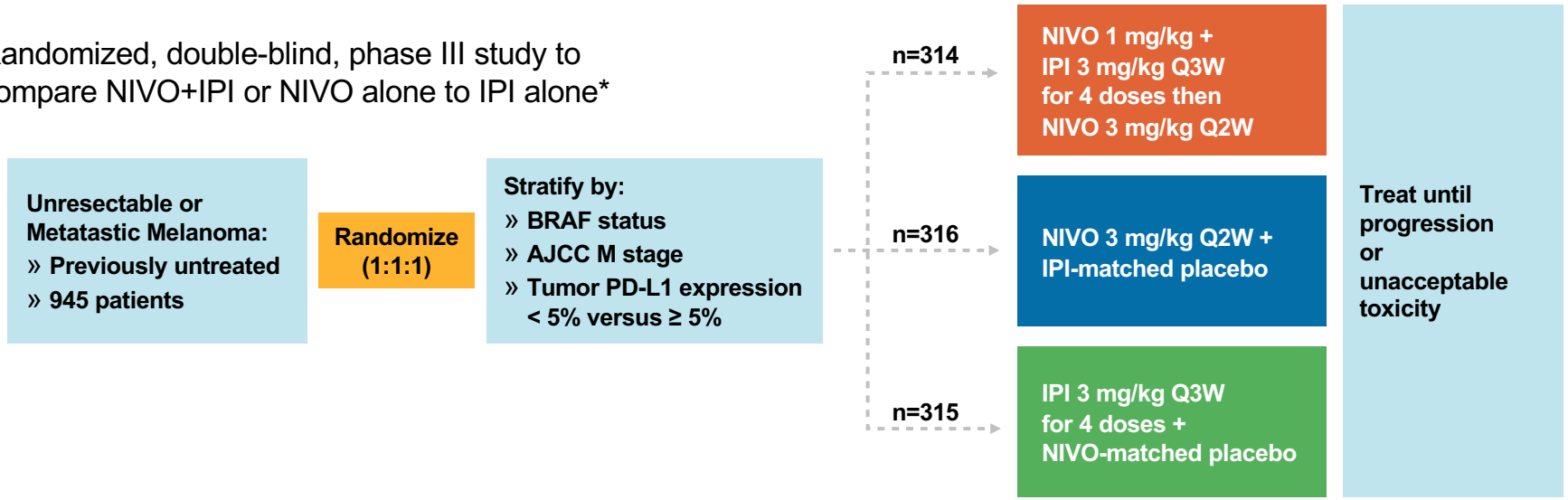
12 weeks



Wolchok et al., NEJM, 2013

CheckMate 067: Study Design

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone*



Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

*The study was not powered for a comparison between NIVO and NIVO+IPI

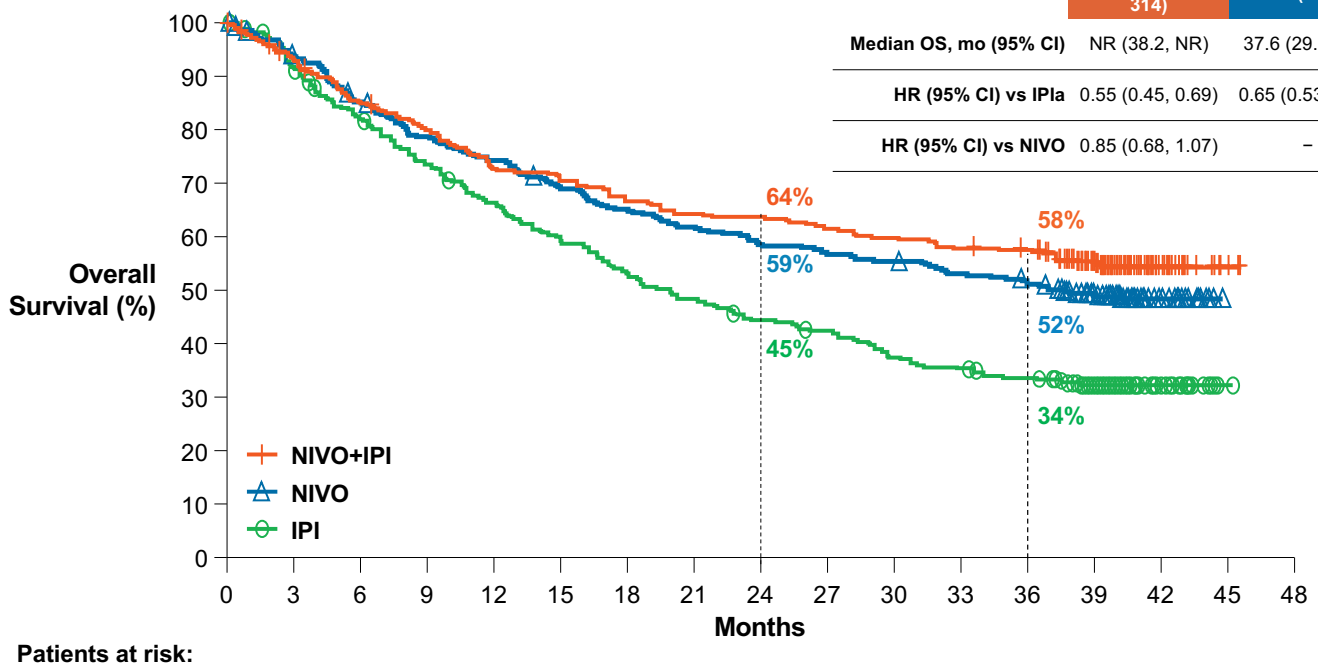
Updated Response Data

	NIVO + IPI	NIVO	IPI
ORR, % (95% CI)[a]	58.3 (52.6, 63.8)	44.3 (38.7, 50.0)	18.7 (14.6, 23.5)
Best overall response, %			
Complete response	19.4	16.5	5.1
Partial response	38.9	27.8	13.7
Median DOR, months (95% CI)	NR	NR (36.3, NR)	19.3 (8.3, NR)

[a]By RECIST v1.1
CI = confidence interval; NR = not reached
Database lock: May 24, 2017. Median follow-up of approximately 36 months in both NIVO-containing arms

OS: Intent-to-treat

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	37.6 (29.1, NR)	19.9 (16.9, 24.6)
HR (95% CI) vs IPIa	0.55 (0.45, 0.69)	0.65 (0.53, 0.80)	–
HR (95% CI) vs NIVO	0.85 (0.68, 1.07)	–	–



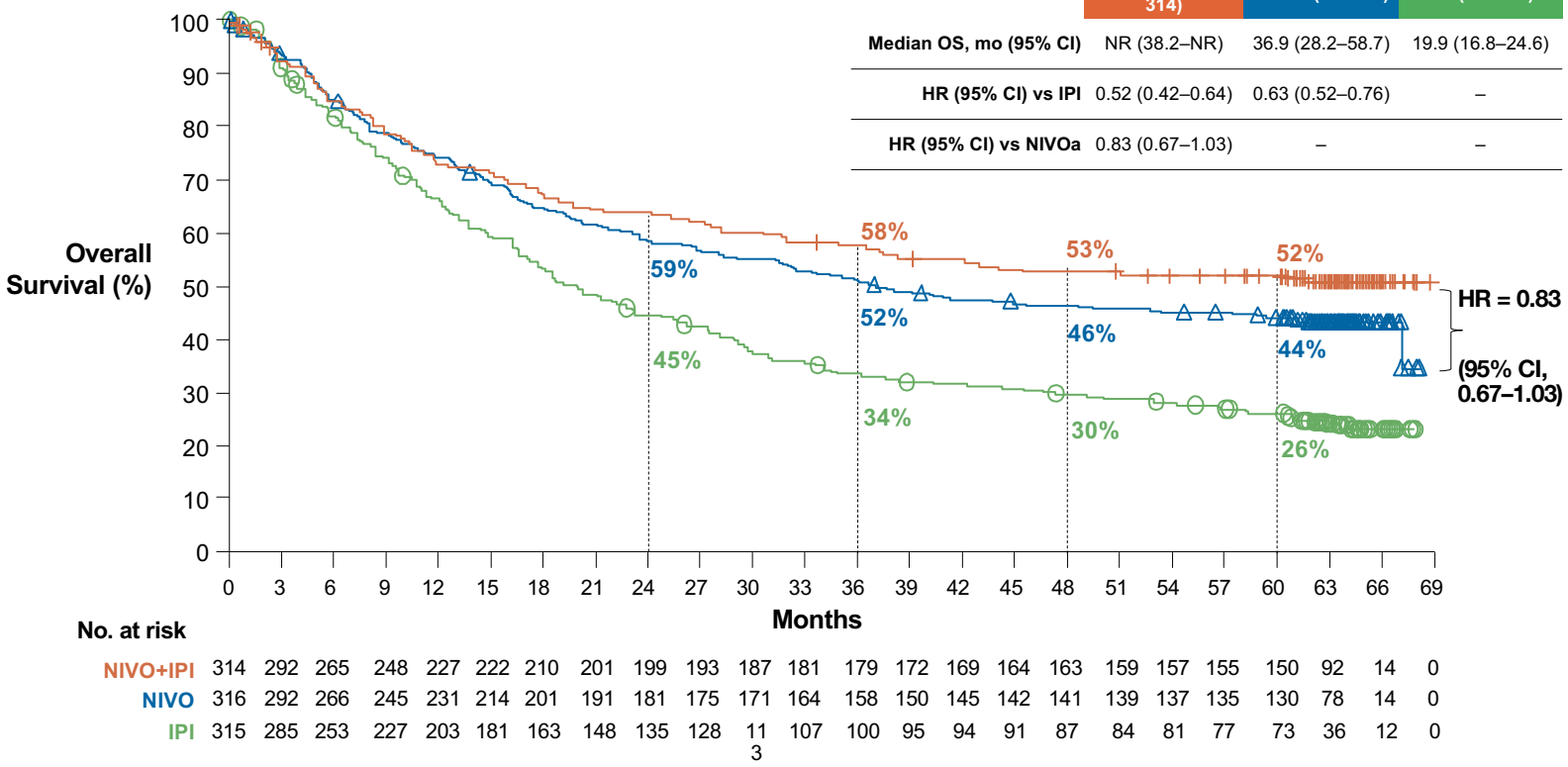
Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
NIVO	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	68	20	2	0

CI = confidence interval;
NR = not reached
Database lock: May 24, 2017. Minimum follow-up of 36 months

Improved OS with NIVO+IPI and NIVO vs IPI over 5 years

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVOa	0.83 (0.67–1.03)	–	–



[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. N Engl J Med 2017;377:1345–1356; 2. Hodi FS, et al. Lancet Oncol 2018;19:1480–1492.
Larkin et al, NEJM, 2019

Safety Summary

Patients reporting event, %	NIVO + IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AE	95.8	58.8	86.3	21.4	86.2	27.7
Treatment-related AE leading to discontinuation	39.3	30.4	11.8	7.7	15.8	13.8
Treatment-related death, n (%)	2 (0.6)[a]		1 (0.3)[b]		1 (0.3)[c]	

[a]Cardiomyopathy (NIVO+IPI, n = 1); liver necrosis (NIVO+IPI, n = 1). Both deaths occurred >100 days after the last treatment
[b]Neutropenia (NIVO, n = 1)
[c]Colon perforation (IPI, n = 1)

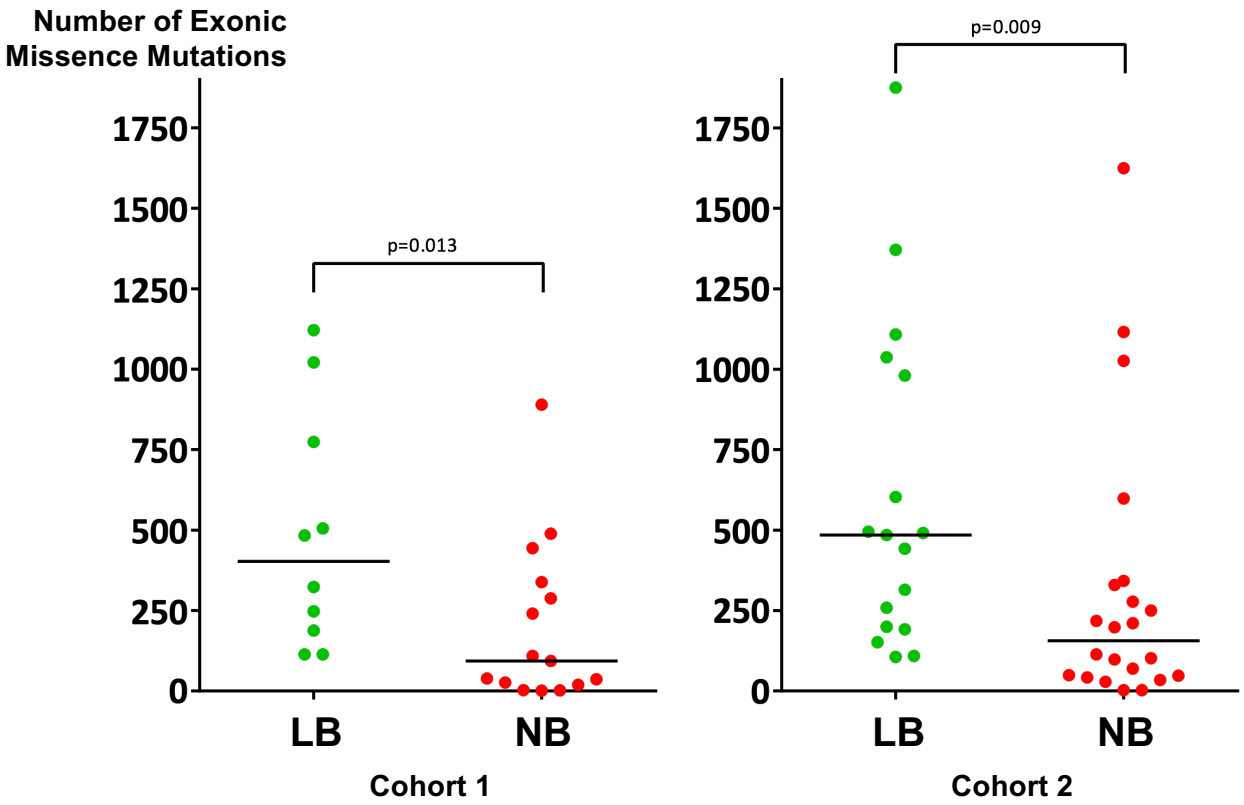
May genomics underlie differential response?

Lawrence et al,
Nature 2013

Mutational Load Correlates with Clinical Outcome: Melanoma

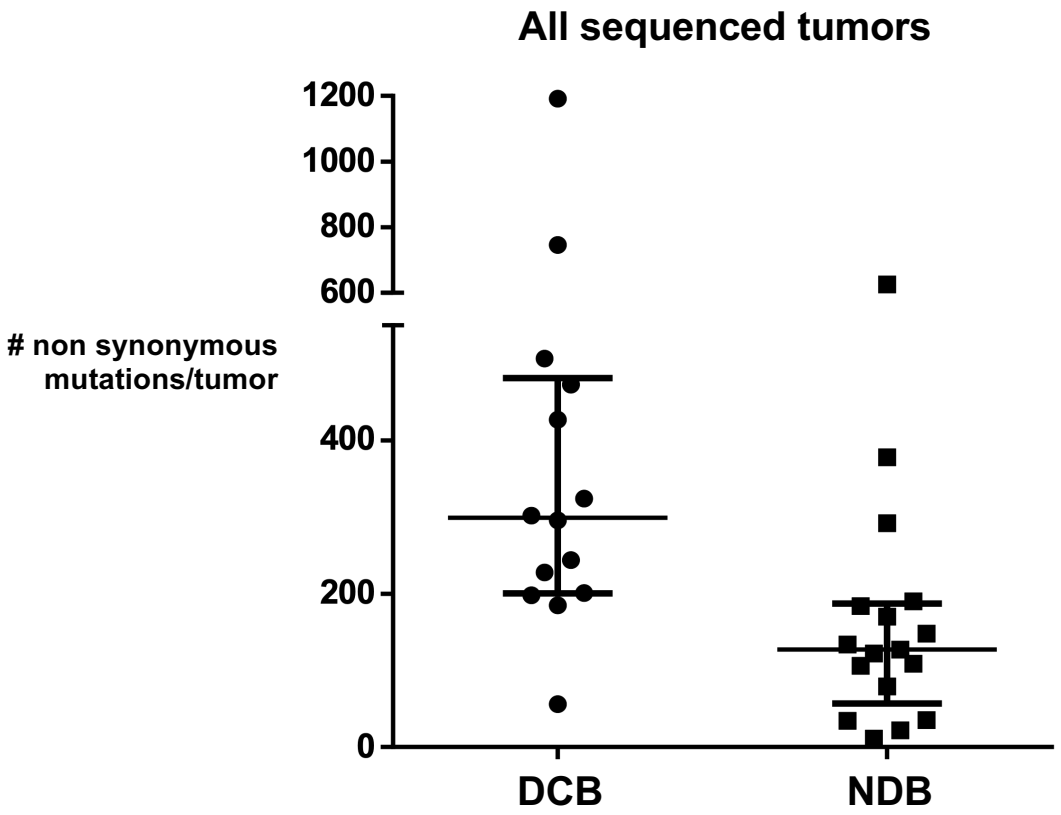
LB, long-term clinical benefit lasting ≥6 months

NB, no durable benefit



Snyder et al., New Engl J Med, 2014

Mutational Burden Correlates With Clinical Outcome: NSCLC



Rizvi, Hellmann, Snyder et al, Science 2015

PD-1 Blockade in Tumors with Mismatch Repair Deficiency

Dung Le, Jennifer Uram, Hao Wang, Bjarne Bartlett, Holly Kemberling, Aleksandra Eyring, Andrew Skora, Brandon Luber, Nilofer Azad, Daniel Laheru, Barbara Biedrzycki, Ross Donehower, Atif Zaheer, George Fisher, Todd Crocenzi, Steven Duffy, James Lee, Richard Goldberg, Albert de la Chapelle, Minori Koshiji, Feriyl Bhaijee, Thomas Huebner, Ralph Hruban, Laura Wood, Nathan Cuka, Drew Pardoll, Nickolas Papadopoulas, Kenneth Kinzler, Shibin Zhou, Toby Cornish, Janis Taube, James Eshleman, Robert Anders, Bert Vogelstein and Luis Diaz Jr.

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
Providence Cancer Center, Portland, OR
Stanford University School of Medicine, Stanford, CA
Bons Secours Cancer Institute, Richmond, VA
University of Pittsburgh, Pittsburgh, PA
Ohio State University Comprehensive Cancer Center, Columbus, OH
Merck & Co., Inc., Kenilworth, NJ

PRESENTED AT: ASCO Annual '15 Meeting

Study Design

Colorectal Cancers		Non-Colorectal Cancers
Cohort A **Deficient in Mismatch Repair (n=25)**	Cohort B **Proficient in Mismatch Repair (n=25)**	Cohort C **Deficient in Mismatch Repair (n=21)**

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Primary endpoint: immune-related 20-week PFS rate and response rate
- Mismatch repair testing using standard PCR-based test for detection of microsatellite instability

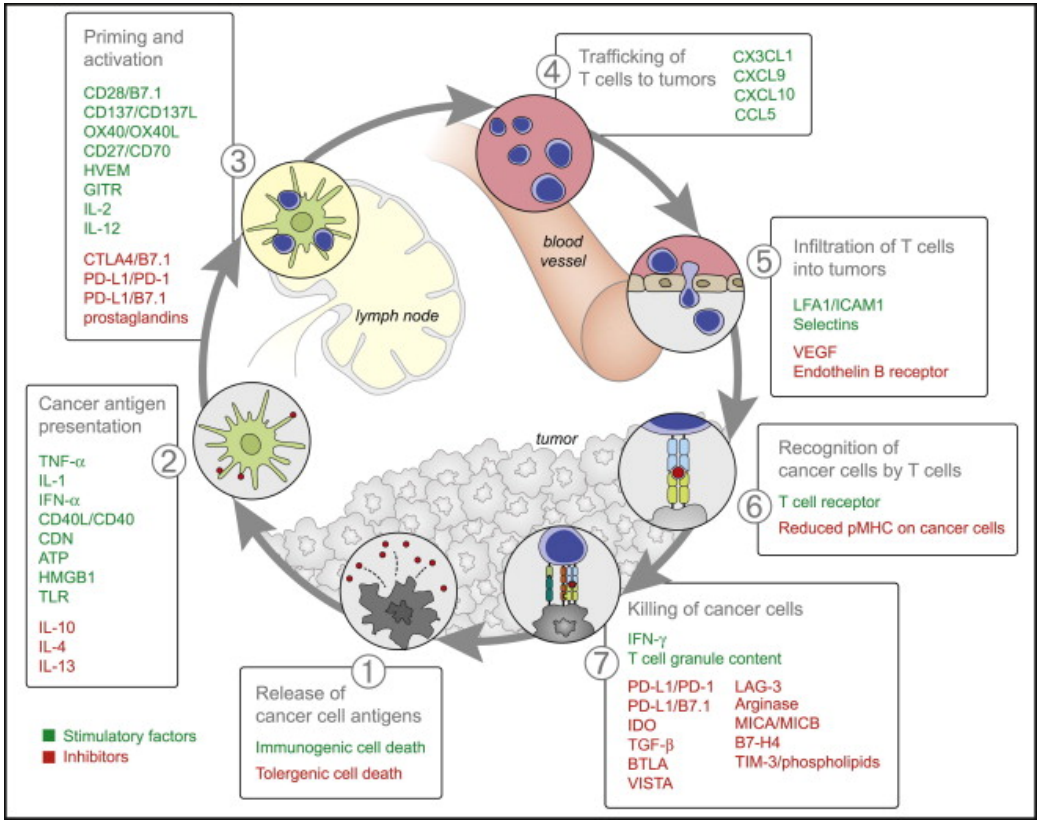
Objective Responses

	MMR-deficient CRC	MMR-proficient CRC	MMR-deficient non-CRC
N	13	25	10
Objective Response Rate	62%	0%	60%
Disease Control Rate	92%	16%	70%

Toward a Central Dogma for Cancer Immunotherapy?

- Mutational landscape fuels baseline immune reactivity
- Primary immune evasion and adaptive resistance restrain therapeutic immunity
- Checkpoint blockade may disinhibit baseline response to achieve regression and antigen spreading, leading to durable disease control in some patients
- Above subject to modulation by numerous factors: suppressive cells, physical barriers to trafficking, deficient antigen presentation/processing, hostile microenvironment, insufficient costimulation. These form basis for next some next steps.

The Cancer–Immunity Cycle



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

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Checkpoint Blockade Immunotherapy

Questions