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Melanoma: The poster child for immunotherapy

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SITC Immunotherapy CME - August 30th, 2015

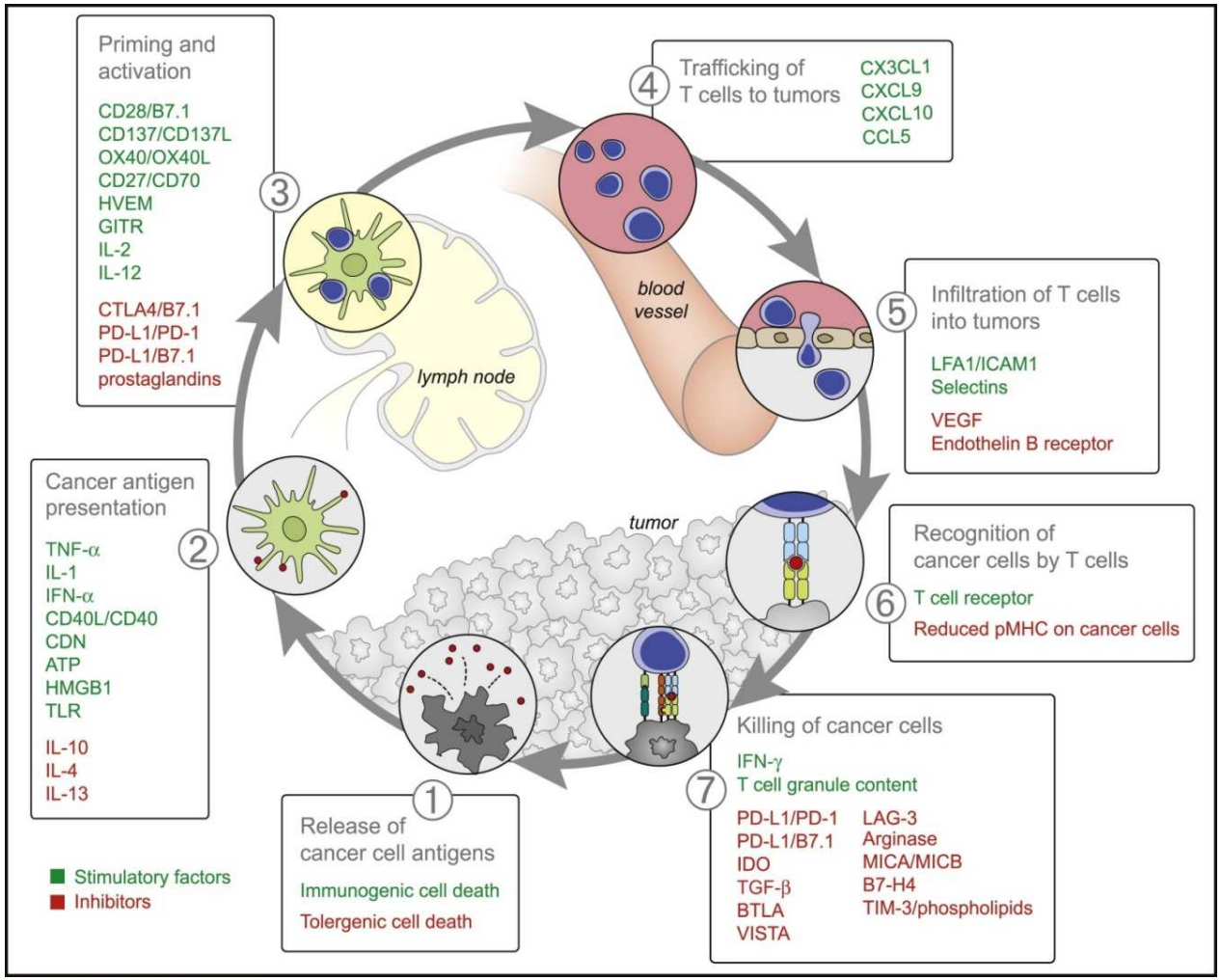
Disclosures

- Consultancy:
  - Amgen
- I will discuss the investigational use of ipilimumab, nivolumab, pembrolizumab, TVEC, dabrafenib, trametinib, and vemurafenib as well as some investigational compounds

Learning objectives

- To describe the available forms of immunotherapy for melanoma
- To describe mechanism of action and management of adverse events with immune-checkpoint immunotherapy
- To discuss the future of immunotherapy for melanoma and all cancer

What are immunotherapy treatments?
The "Cancer Immunity Cycle"



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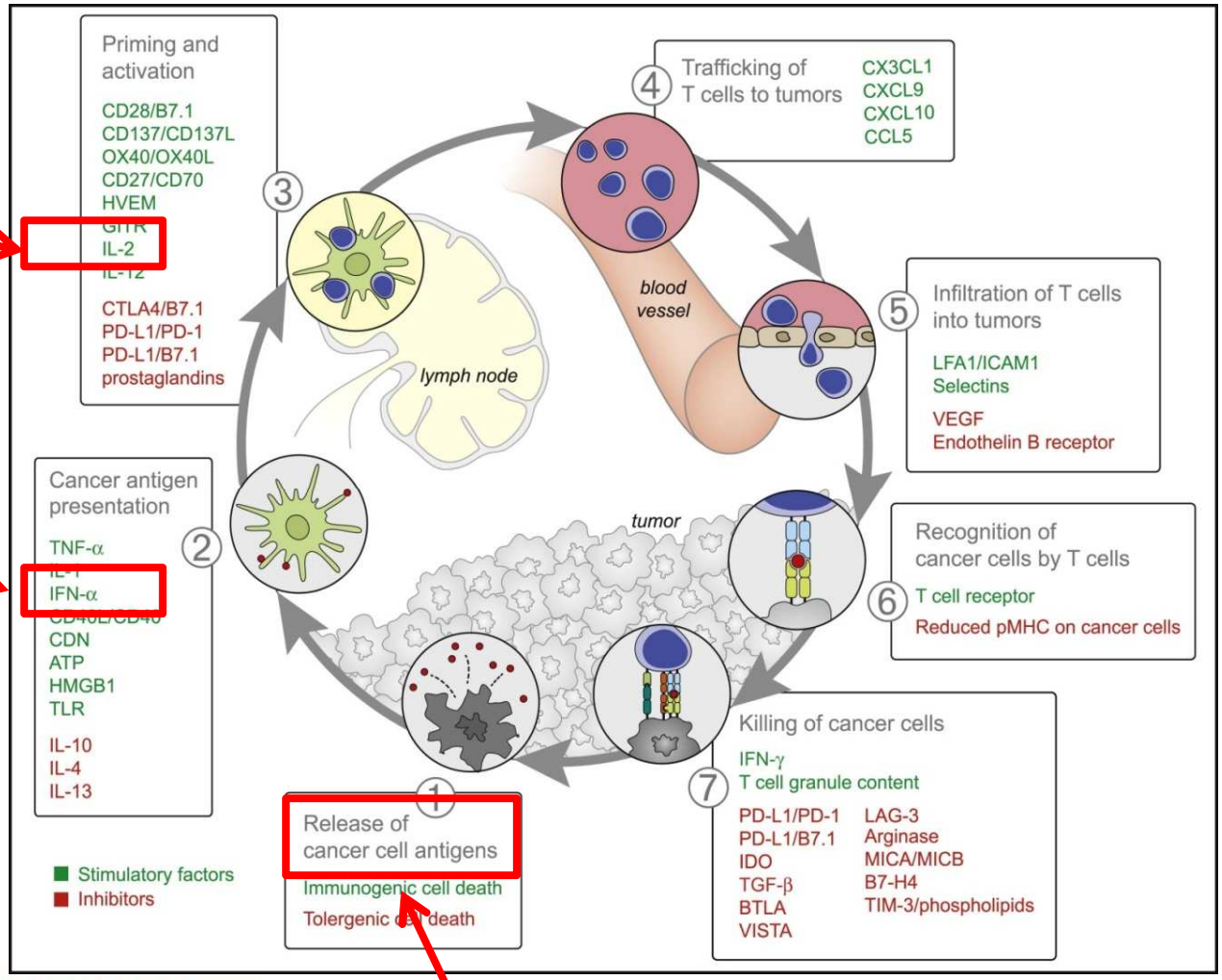
Chen et al. Immunity. 2013

Cytokines and Oncolytic Viruses

Interleukin-2

Interferon-α



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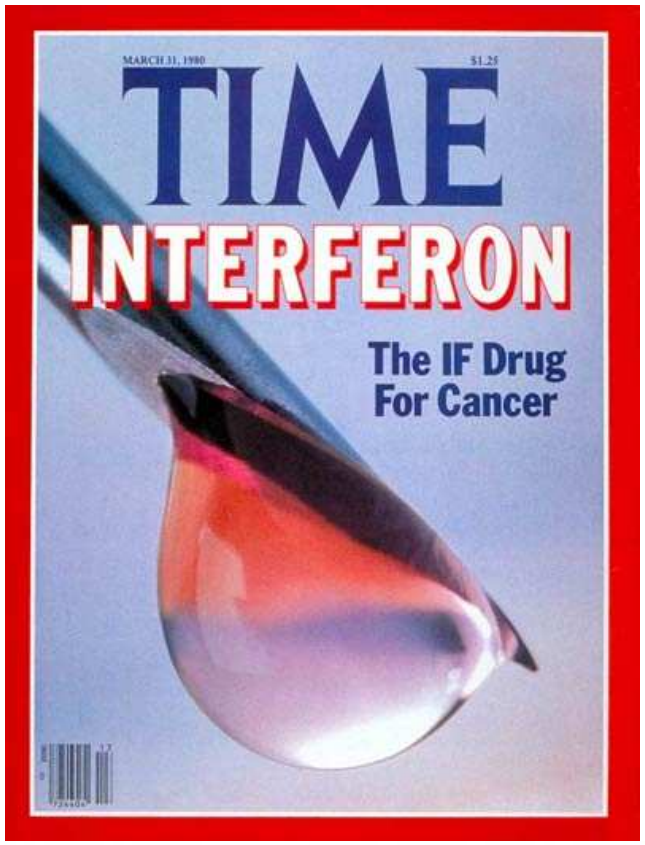
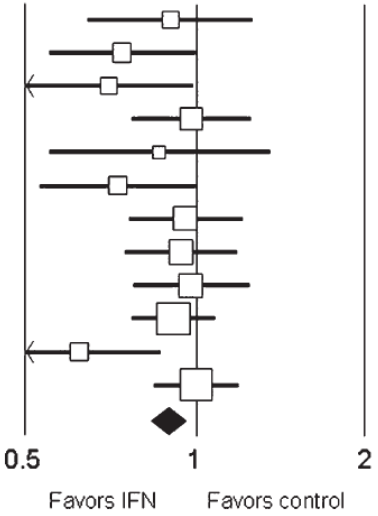
Talimogene Laherparepvec (T-VEC)

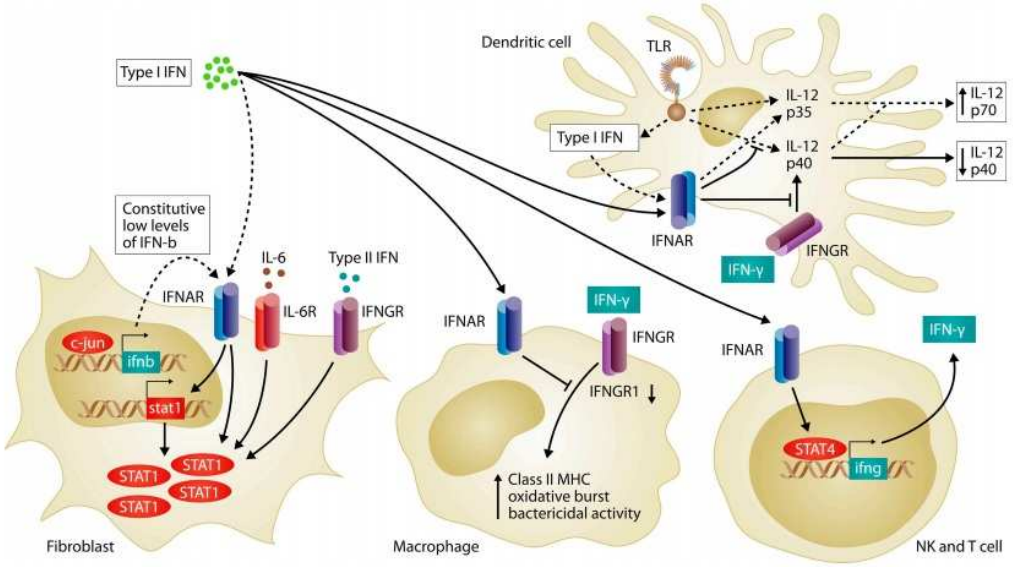
Chen et al. Immunity. 2013

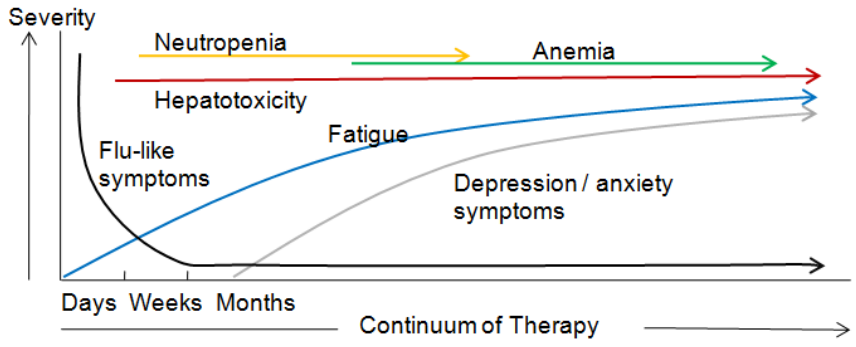
Adjuvant Interferon-α



	HR	LL	UL	SE	Patients	Events (IFN/control)
NCCTG (Creagan, 1995)	0.90	0.64	1.25	0.17	264	68/72
E1684 (Kirkwood, 1996)	0.73	0.54	0.99	0.15	287	81/90
FCGM (Grob, 1998)	0.70	0.49	0.98	0.17	499	59/76
E1690 (Kirkwood, 2000)	0.98	0.76	1.24	0.12	642	194/186
SMG (Cameron, 2001)	0.86	0.54	1.35	0.23	96	31/36
E1694 (Kirkwood, 2001)	0.72	0.52	0.99	0.16	880	52/81
WHO (Cascinelli, 2001)	0.95	0.76	1.20	0.12	444	146/138
UKCCCR (Hancock, 2004)	0.94	0.74	1.17	0.12	674	151/156
EORTC18871 (Kleeberg, 2004)	0.98	0.77	1.23	0.12	484	137/202
EORTC18952 (Eggermont, 2005)	0.91	0.76	1.07	0.09	1388	534/292
DeCOG (Garbe, 2008)	0.62	0.44	0.86	0.17	296	65/88
EORTC18991 (Eggermont, 2008)	1.00	0.84	1.18	0.09	1256	256/257
	0.89	0.83	0.96	0.04		



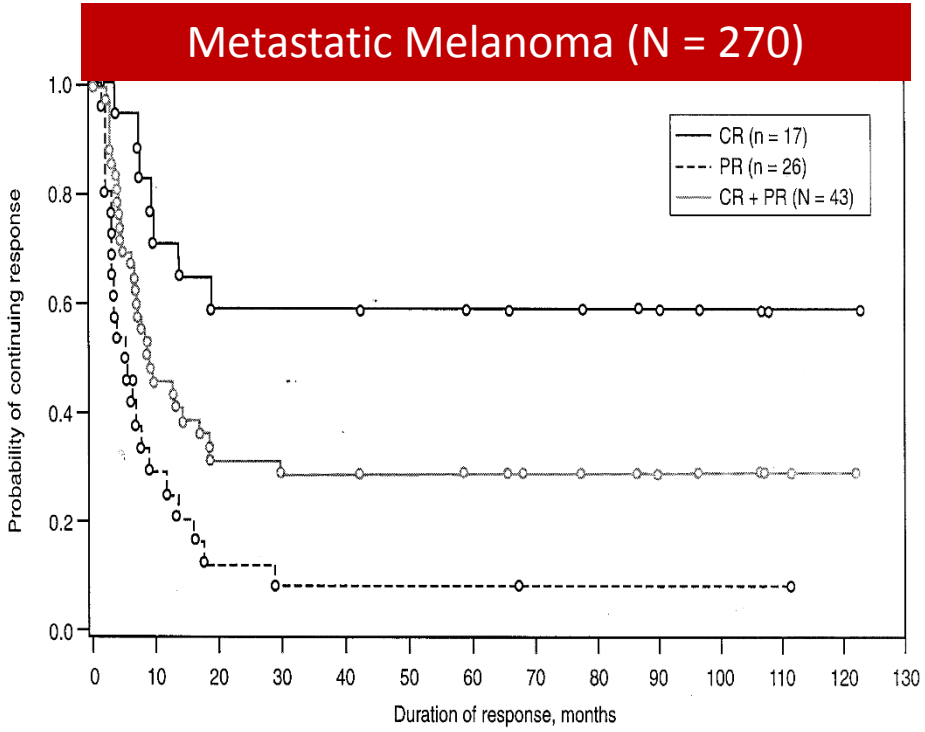




Time Magazine, March 31st, 1980
Trinchieri, J Exp Med. 2010
Mocellin et al. JNCI. 2010
http://www.sinobiological.com/Interferon-Side-Effects-a-6085.html

High Dose Interleukin-2 Therapy (HD IL-2): Durable Responses

- HD IL-2 produces durable responses in 6%-10% of patients with advanced melanoma
- Few relapses in patients responding for over 2.5 years (cured?)
- FDA approval for melanoma in 1997



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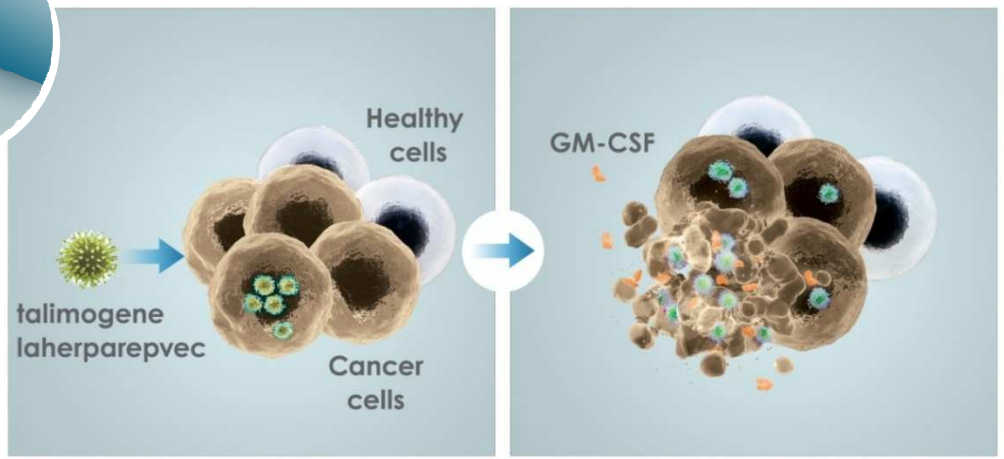
Atkins et al. J Clin Oncol. 1999

HD IL-2 Therapy in Melanoma

- High-dose IL-2 benefits some patients **BUT**
  - Toxic
  - Expensive
  - Inpatient procedure
- Use limited to well-selected patients at experienced centers
- Efforts to better select patients who might benefit from HD IL-2 therapy have not been particularly successful (NRAS?)

T-VEC: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects

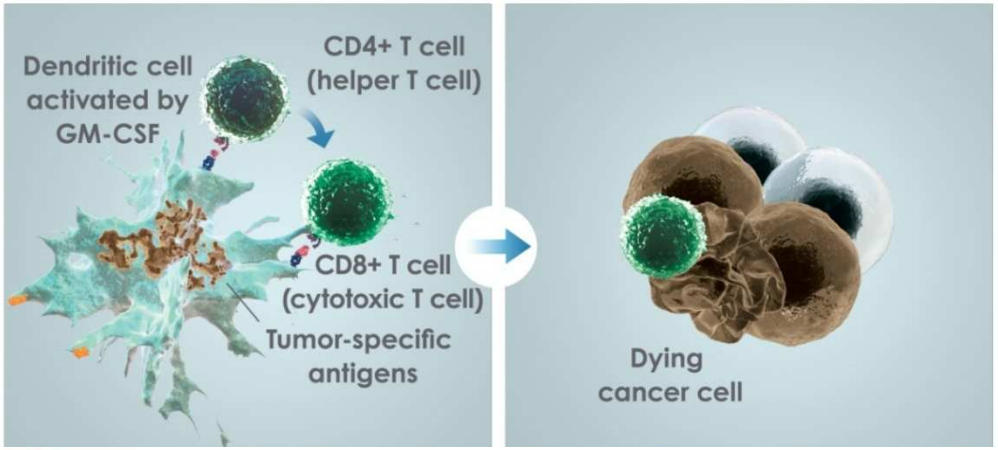
Local Effect:
Virally-Induced Tumor Cell Lysis



Selective viral replication in tumor tissue

Tumor cells rupture for an oncolytic effect

Systemic Effect:
Tumor-Specific Immune Response



Systemic tumor-specific immune response

Death of distant cancer cells

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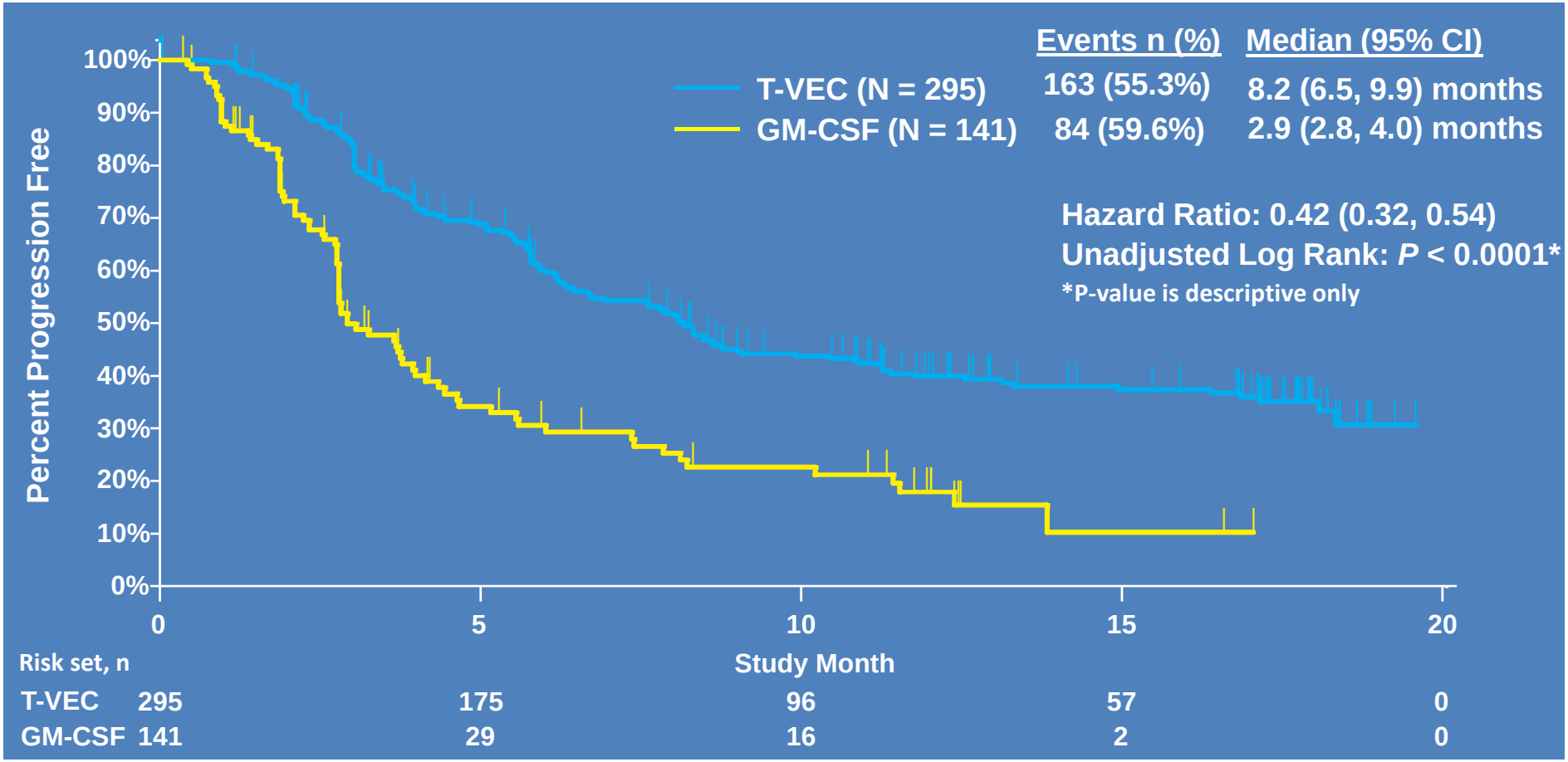
Kaufman et al. ASCO (2014), abstr LBA9008

Phase III trial of T-VEC vs GM-CSF PFS Per Investigator



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Andtbacka et al. ASCO 2013; LBA9008

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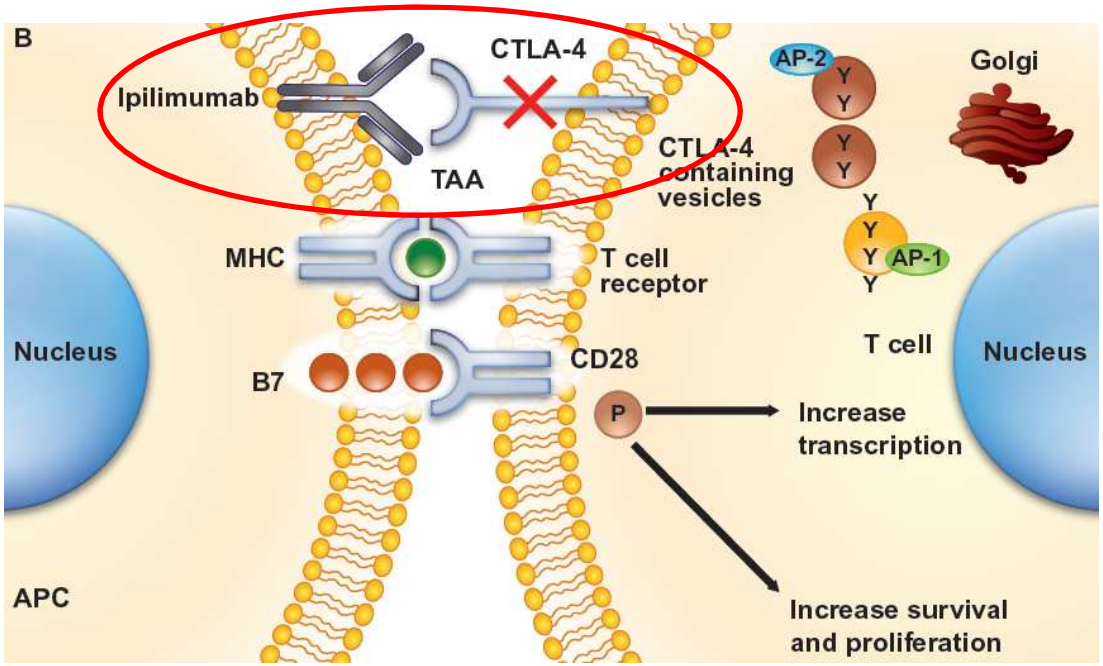
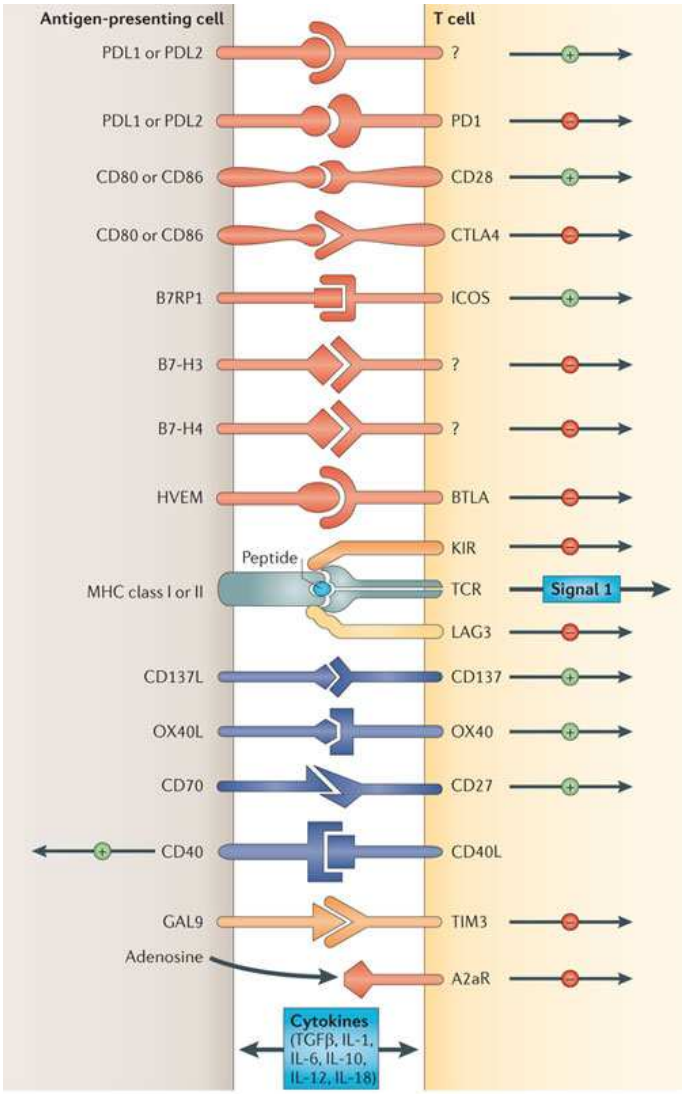
Science Magazine, December 20th, 2013

Ipilimumab and Immune Check-Point Blockade



Luke et al, Oncologist 2013



Pardoll, Nat Rev Can 2012

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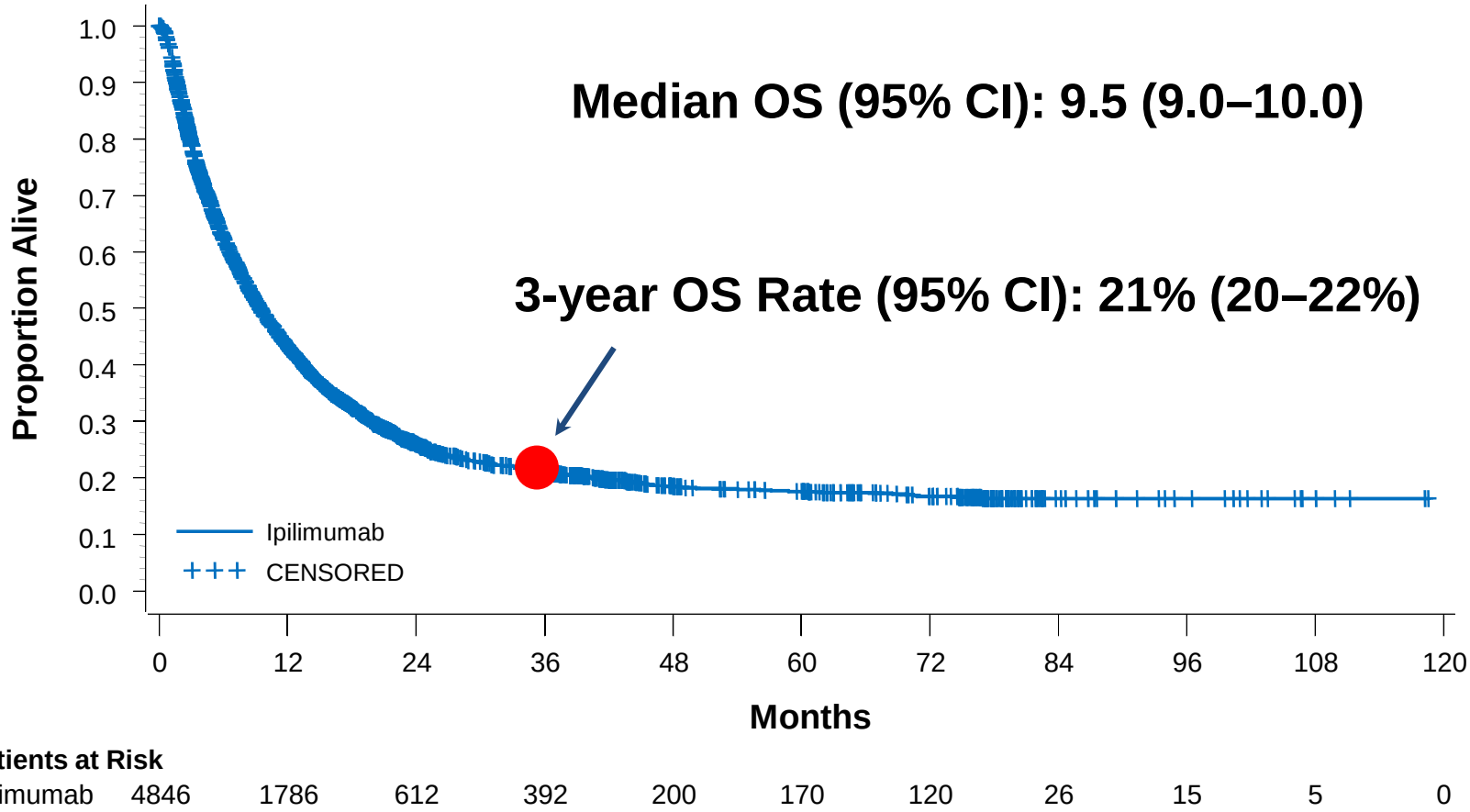
Pooled Overall Survival Analysis of 4846 Patients treated with ipilimumab



Patients at Risk

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

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Schadendorf et al. ECCO (2013) (abstract LBA24)

Ipilimumab Immune-Related Adverse Events From Phase III Trial

irAE, %	All grades (Gr 3/4)		
	Ipi + gp100 N=380	Ipi +pbo N=131	gp100 + pbo N=132
Any	57 (9.7/0.5)	60 (12.2/2.3)	32 (3.0/0)
Dermatologic	39 (2.1/0.3)	42 (1.5/0)	17 (0/0)
GI	31 (5.3/0.5)	28 (7.6/0)	14 (0.8/0)
Endocrine	3 (1.1/0)	8 (2.3/1.5)	2 (0/0)
Hepatic	2 (1.1/0)	3 (0/0)	4 (2.3/0)

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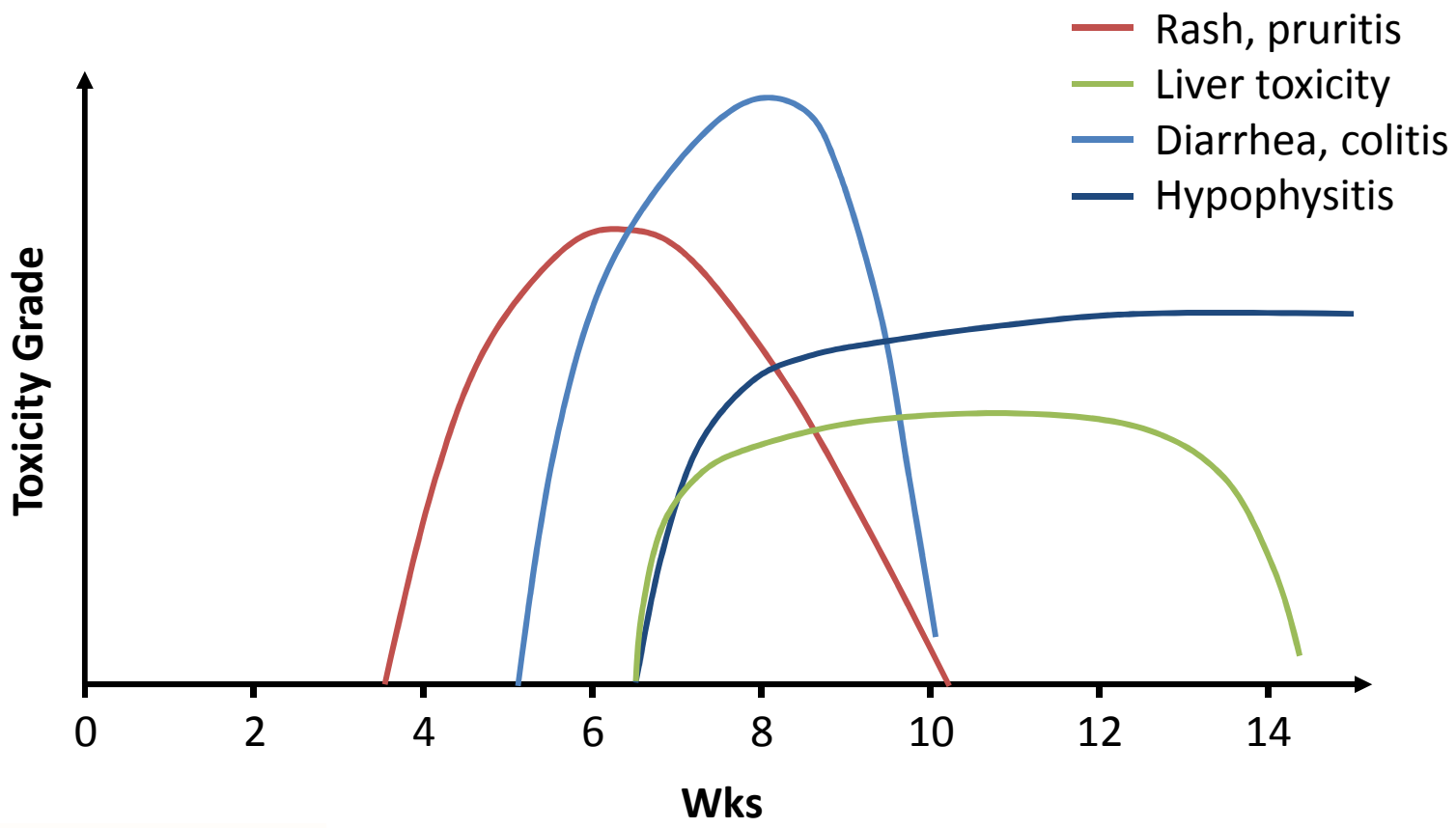
Hodi et al, NEJM 2010

Kinetics of Appearance of irAEs with Ipilumumab



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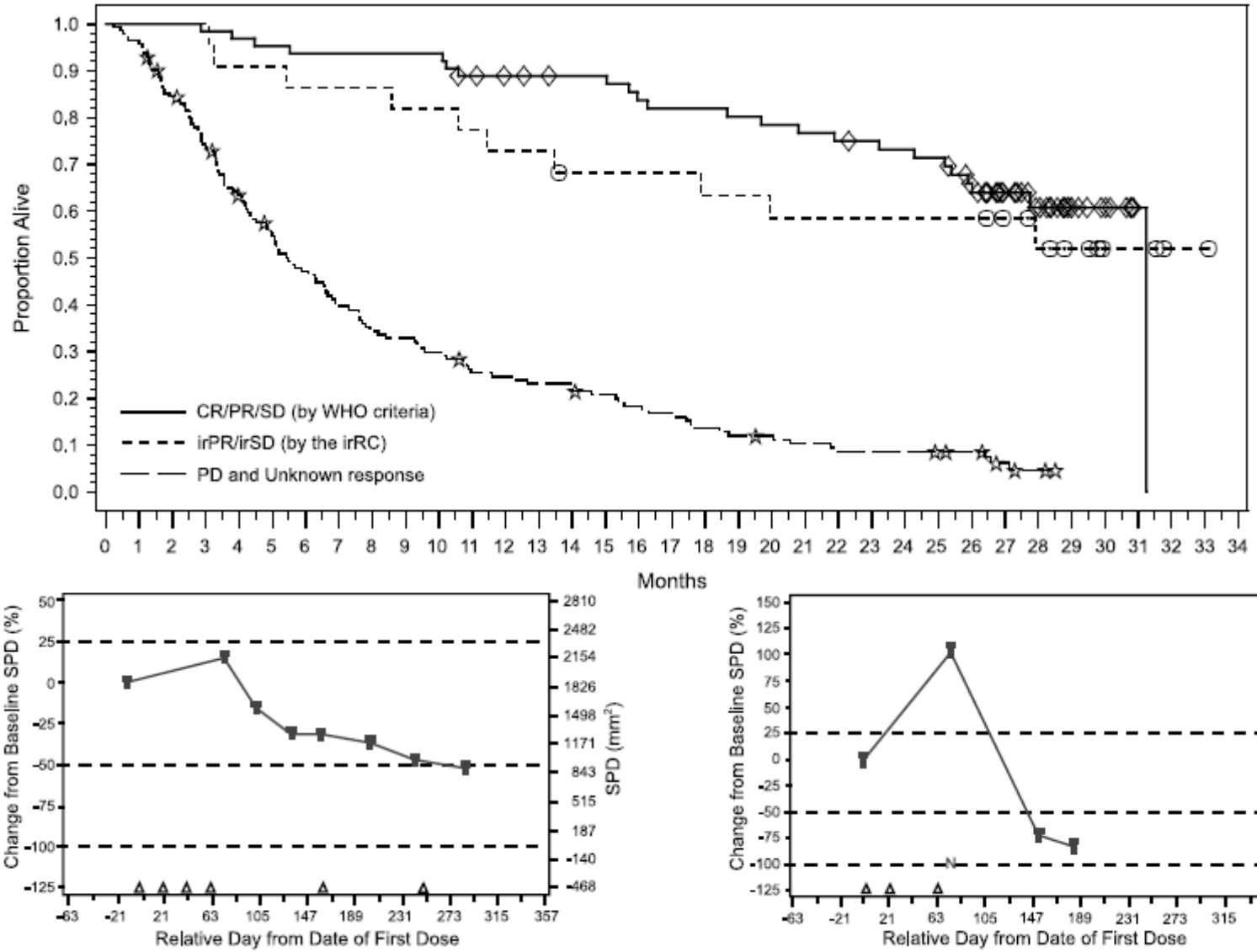
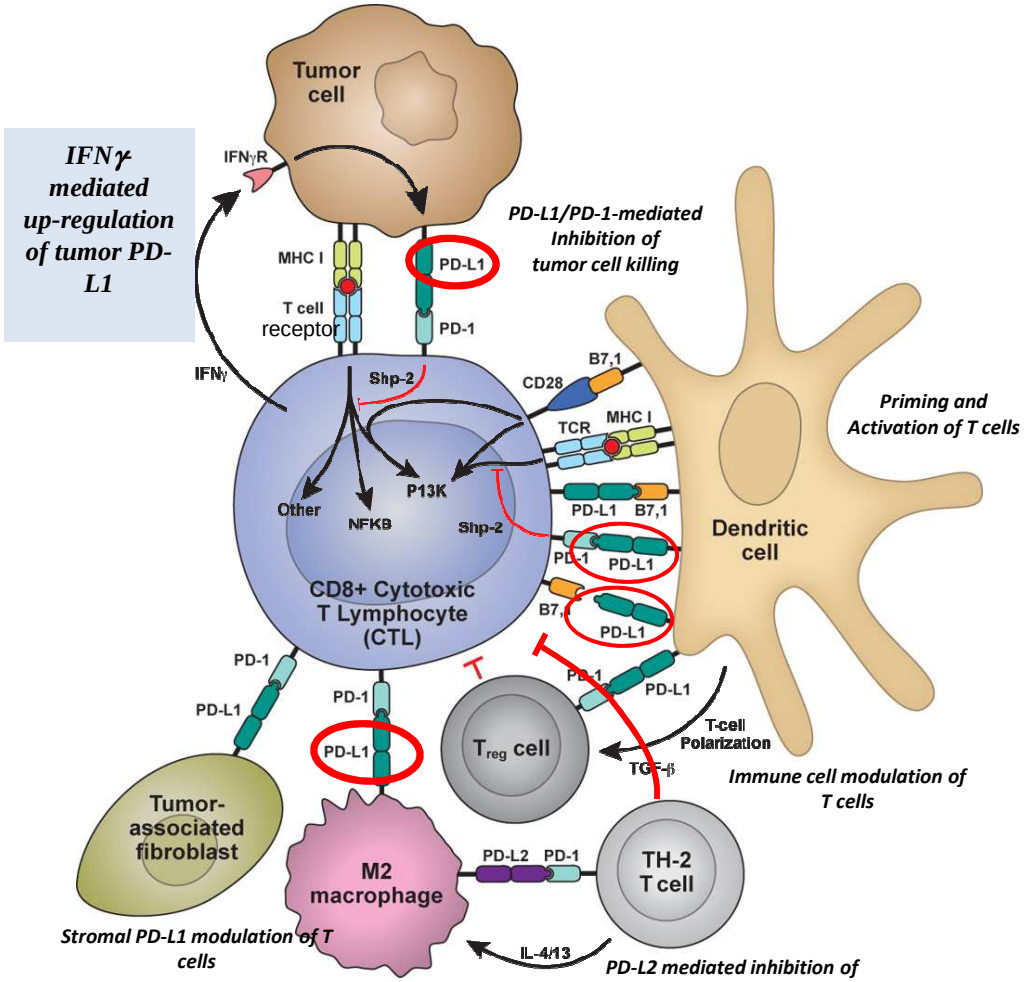
Weber et al. J Clin Oncol. 2012

Immune Related Response Criteria

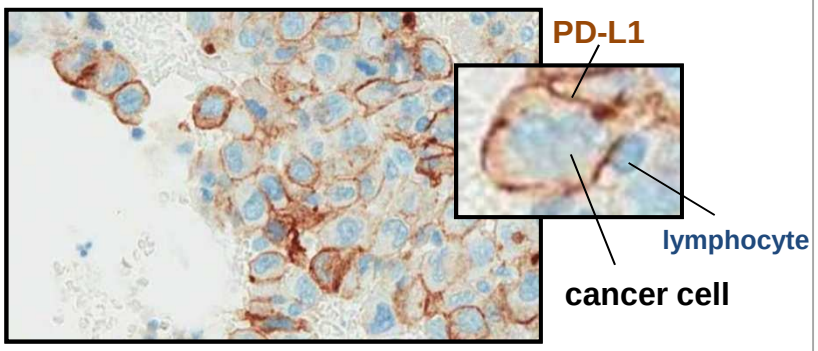


Wolchok et al, Clin Can Res 2010

PD-L1 dampens the anti-tumor immune response



Chen DS, Irving BA, Hodi FS. Clin Cancer Res. 2012;18:6580.



Presence of intratumoral T-cells may lead to adaptive immune resistance

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

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

Powderly et al. ASCO (2013) Abstract 9010

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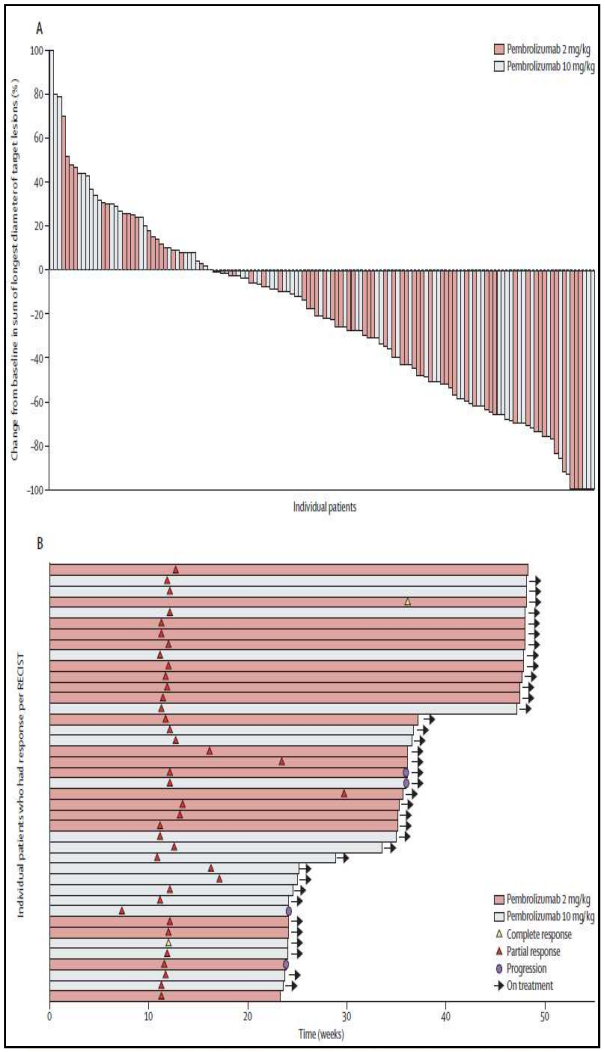
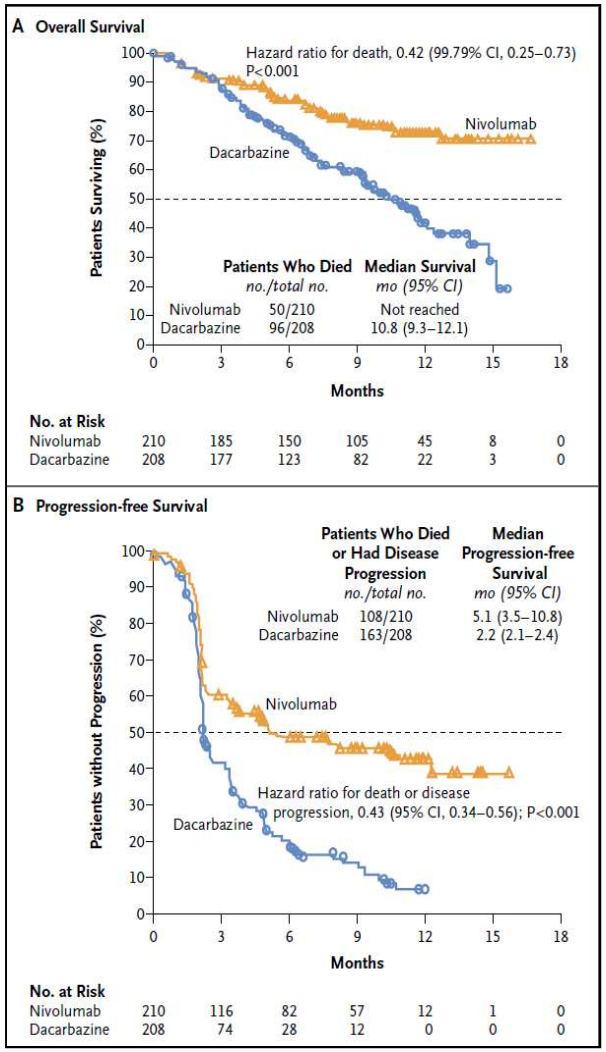
Anti-PD1 (pembrolizumab) *after* ipilimumab in Melanoma



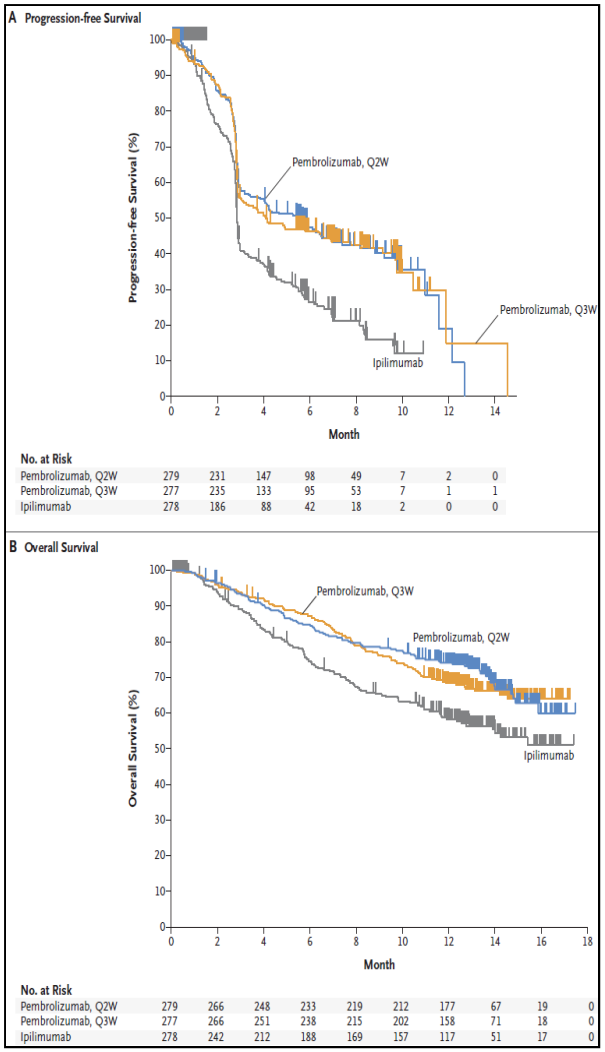
Robert et al, NEJM 2015

Front-line anti-PD1 (nivolumab) vs. DTIC in Melanoma(BRAF WT)



Robert et al, Lancet 2014

Front-line anti-PD1 (pembrolizumab) vs. ipilimumab in Melanoma



Robert et al, NEJM 2015

Pembrolizumab-Related Adverse Events

Adverse Event	All Grades, n (%)	Grade 3-4, n (%)
Any	107 (79.3)	17 (12.6)
Fatigue	41 (30.4)	2 (1.5)
Rash	28 (20.7)	3 (2.2)
Pruritus	28 (20.7)	1 (0.7)
Diarrhea	27 (20.0)	1 (0.7)
Myalgia	16 (11.9)	0
Headache	14 (10.4)	0
Increased AST	13 (9.6)	2 (1.5)
Asthenia	13 (9.6)	0
Nausea	13 (9.6)	0
Vitiligo	12 (8.9)	0
Hypothyroidism	11 (8.1)	1 (0.7)
Increased ALT	11 (8.1)	0
Cough	11 (8.1)	0
Pyrexia	10 (7.4)	0
Chills	9 (6.7)	0
Abdominal pain	7 (5.2)	1 (0.7)

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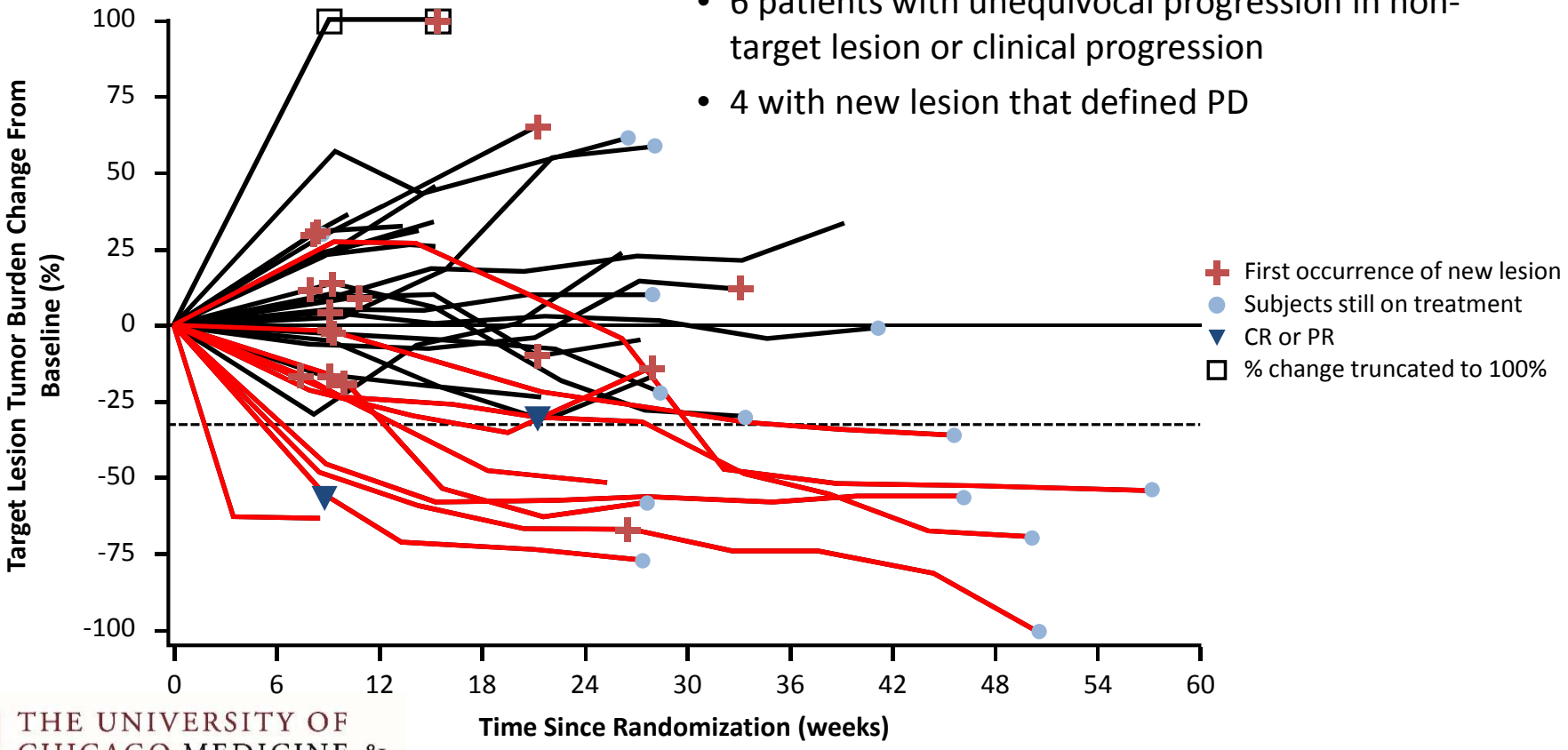
Observed in >5% of Patients (N = 135)

Ribas A, et al. ASCO 2013. Abstract 9009.

Nivolumab Immune-Related Response

- Of 120 nivolumab-treated subjects in the treated population
  - 37 continued treatment beyond RECIST 1.1-defined progression
  - 10 (8%) subsequently experienced a ≥30% reduction in target lesion tumor burden ("immune-related, unconventional response pattern")
    - 6 patients with unequivocal progression in non-target lesion or clinical progression
    - 4 with new lesion that defined PD



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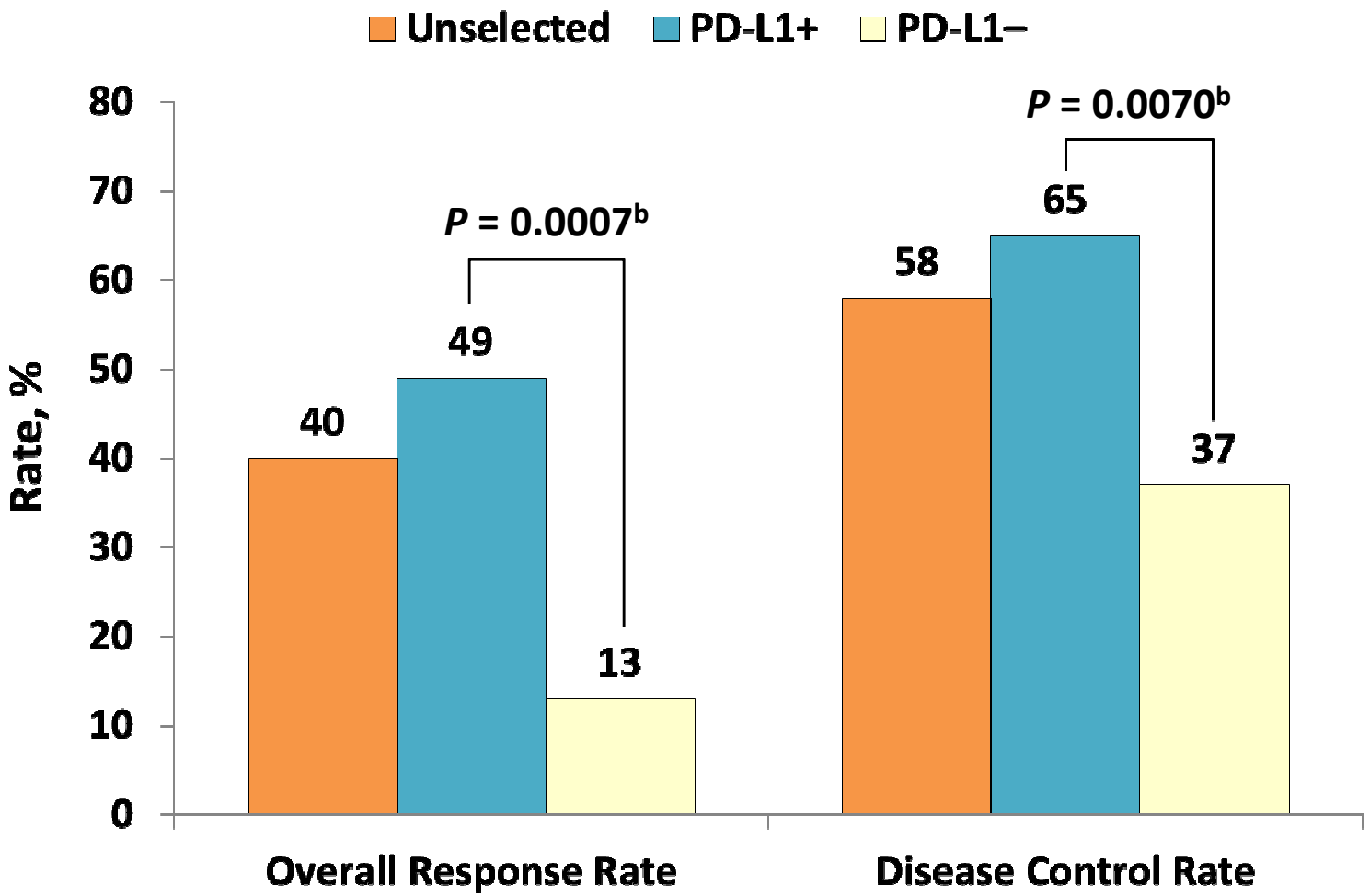
Weber et al. ESMO (2014) LBA3_PR/Abstract #7218

Response to Pembrolizumab Based on Tumor PD-L1 Expression: RECIST v1.1

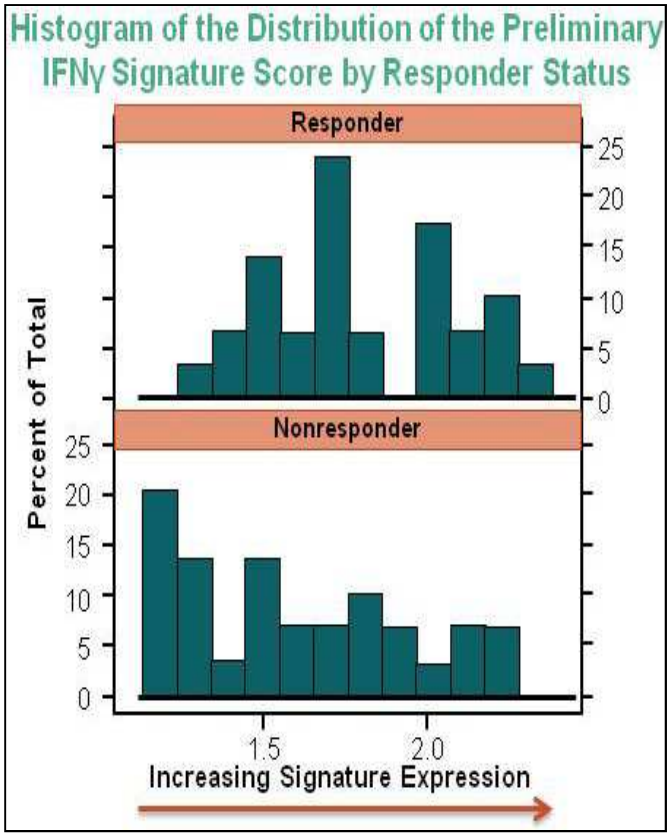
PD-L1 and Radiologically Evaluable Patients (n = 113),[a] Independent Central Review

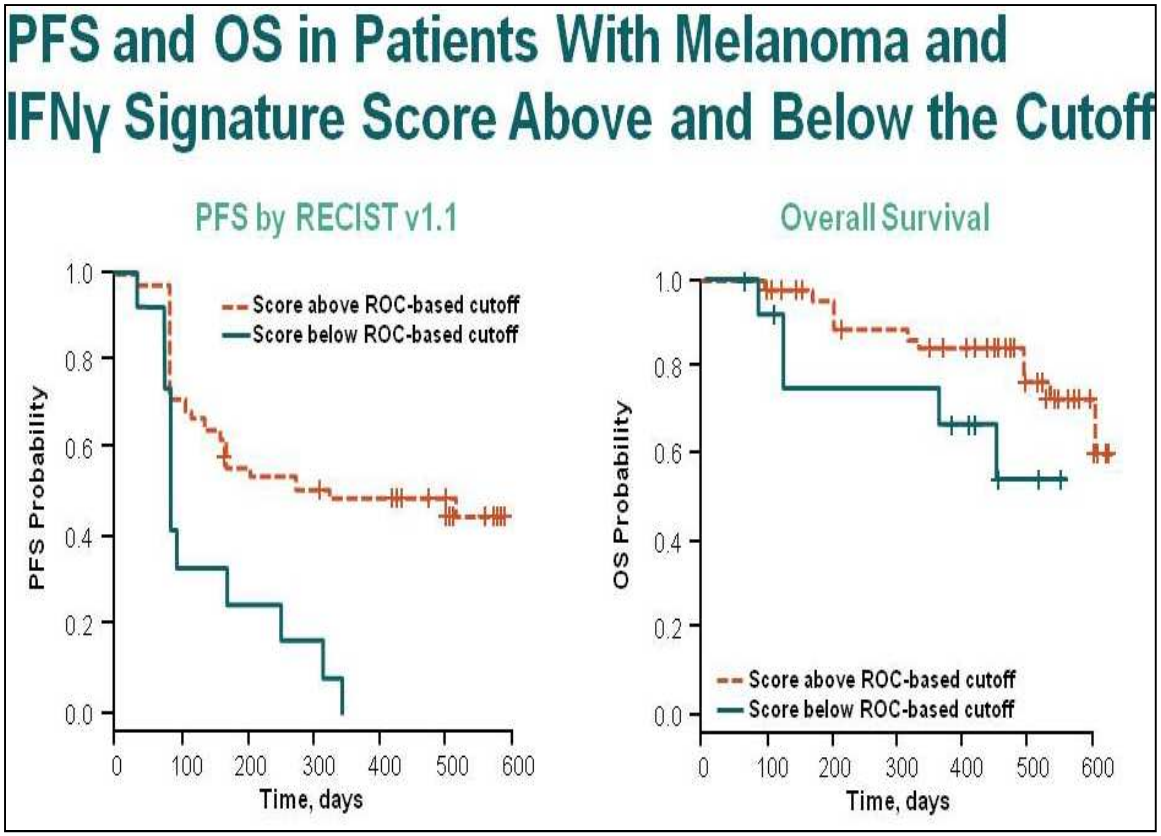


PD-L1 positivity defined as staining in ≥1% of tumor cells.
Analysis cutoff date: 18 October 2013.
[a]Evaluable patients were those patients in the training set with evaluable tumor PD-L1 expression who had measurable disease at baseline per central review.
[b]1-sided *P* values calculated by logistic regression, adjusting for dose/schedule.

Daud et al. AACR Annual Meeting. Abstract CT104. 2014

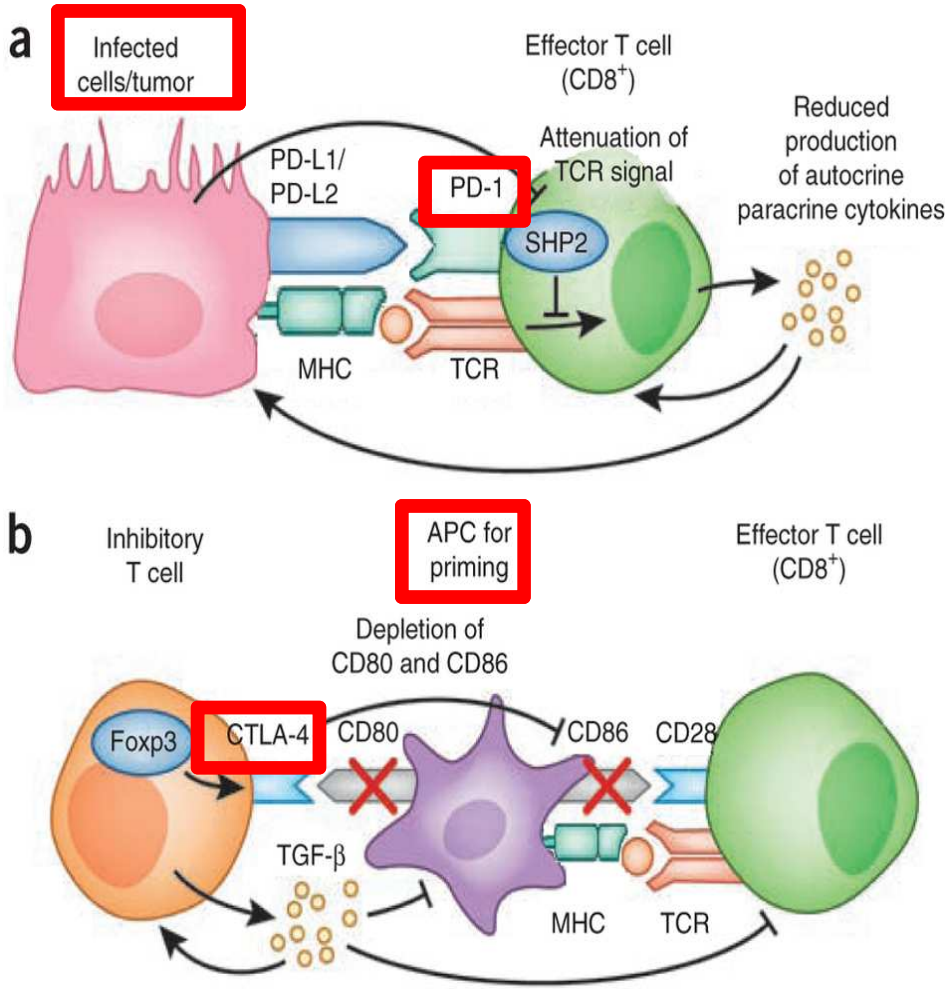
Interferon-ɣ gene signature

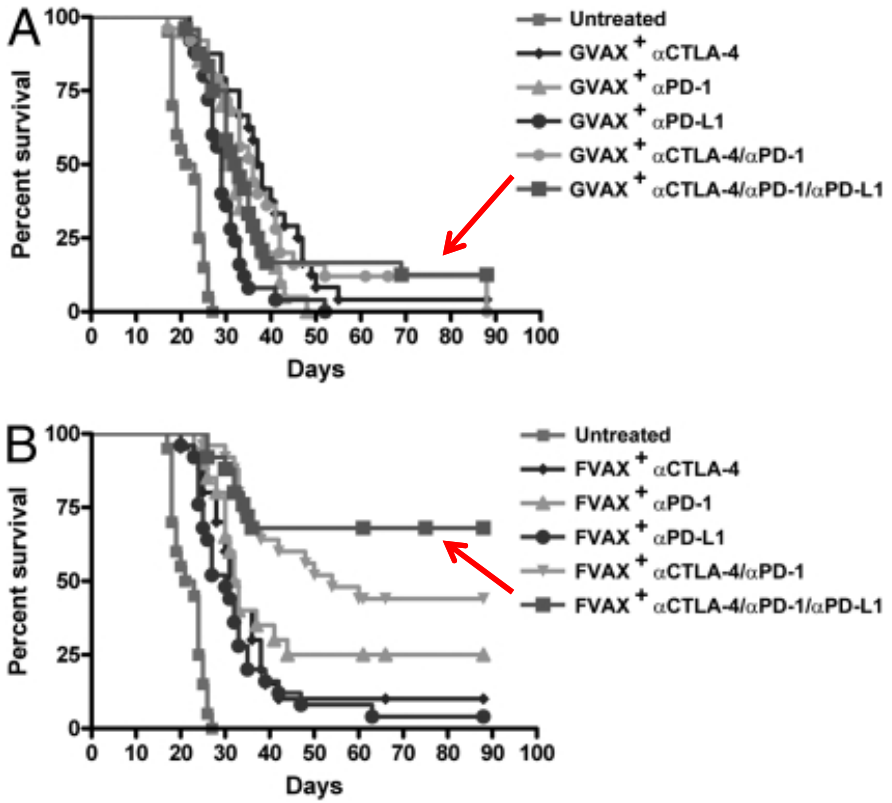




Presented By Antoni Ribas at 2015 ASCO Annual Meeting - J Clin Oncol 33, 2015 (suppl; abstr 3001)

Combining Anti-CTLA4 and Anti-PD1 Antibodies





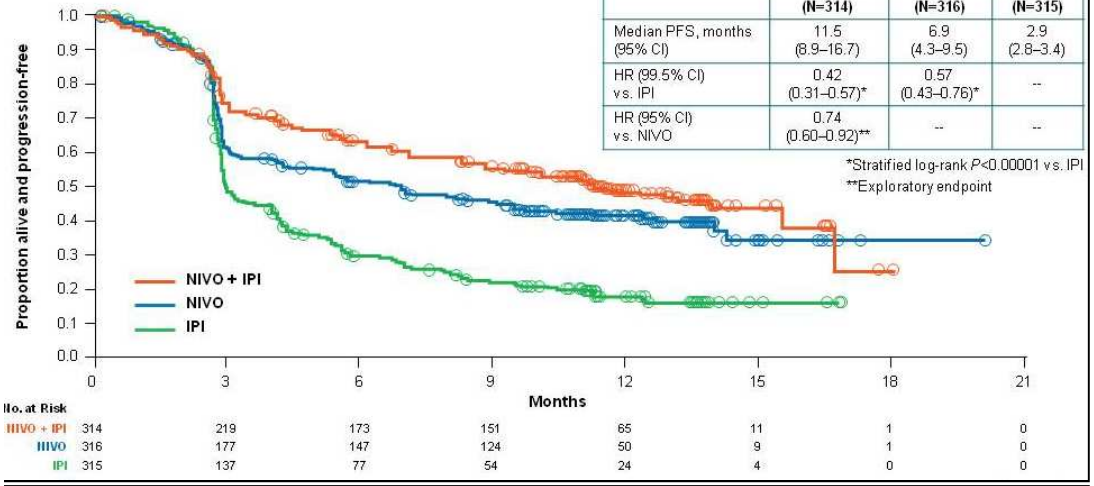
Okazaki et al, Nature Immunology 2013

Curran et al, PNAS 2010

CHECKMATE 067 – Ipi+Nivo vs. Ipi or Nivo vs. Ipi in Melanoma

Wolchok et al. J Clin Oncol 33, 2015 (suppl; abstr LBA1)

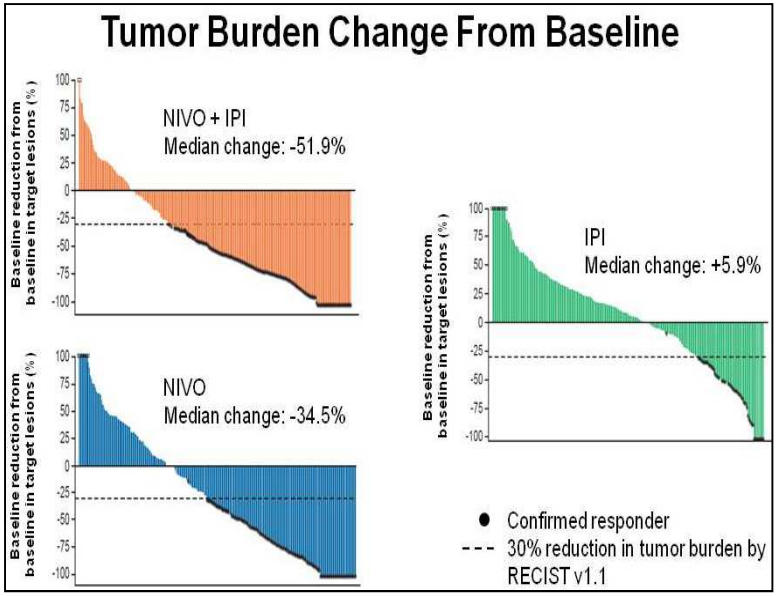
PFS (Intent-to-Treat)



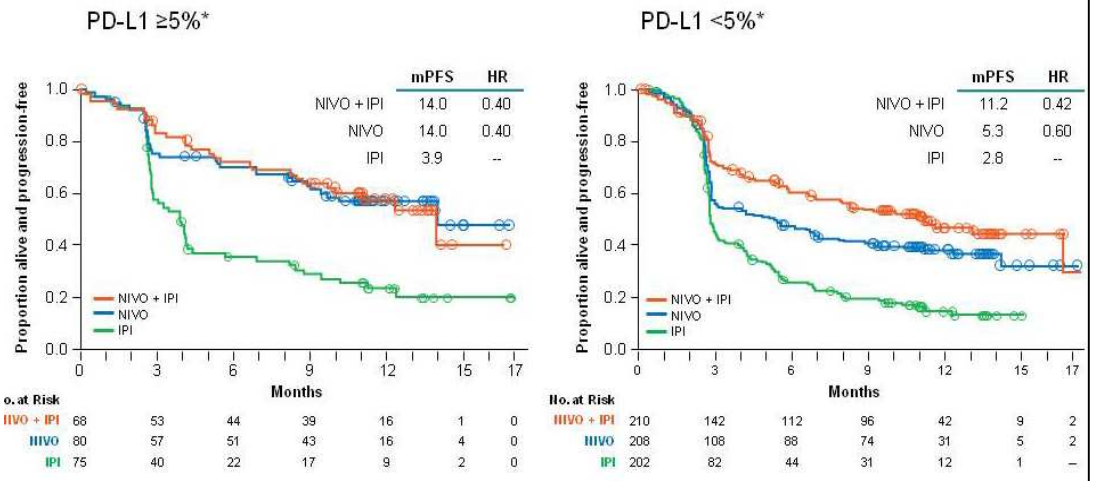
	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

*Stratified log-rank $P<0.00001$ vs. IPI
**Exploratory endpoint

Tumor Burden Change From Baseline



PFS by PD-L1 Expression Level (5%)



*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

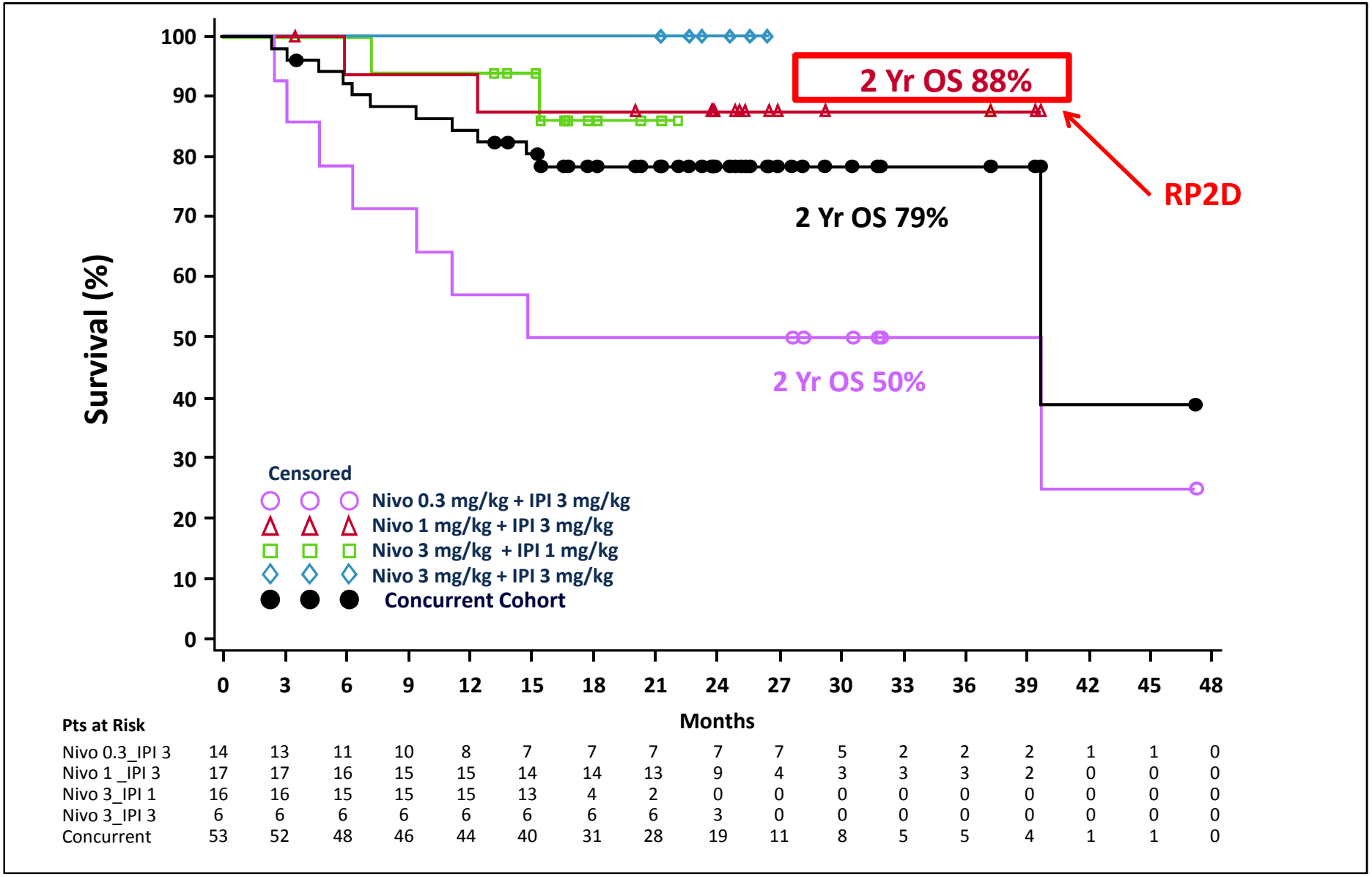
Safety Summary

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 adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death*	0		0.3		0.3	

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response

Overall Survival for Concurrent Therapy by Dose Cohort

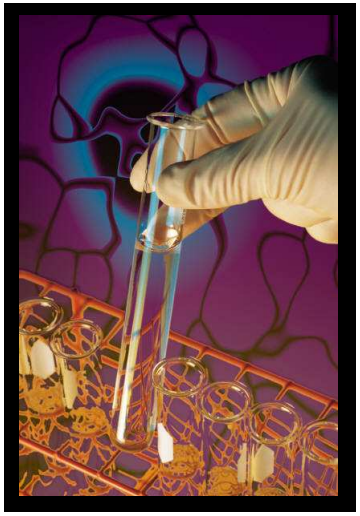


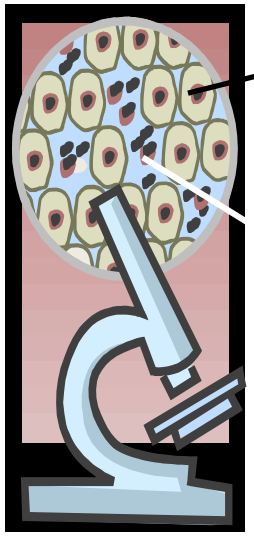
Pts at Risk																	
Nivo 0.3_IPI 3	14	13	11	10	8	7	7	7	7	7	5	2	2	2	1	1	0
Nivo 1 _IPI 3	17	17	16	15	15	14	14	13	9	4	3	3	3	2	0	0	0
Nivo 3_IPI 1	16	16	15	15	15	13	4	2	0	0	0	0	0	0	0	0	0
Nivo 3_IPI 3	6	6	6	6	6	6	6	6	3	0	0	0	0	0	0	0	0
Concurrent	53	52	48	46	44	40	31	28	19	11	8	5	5	4	1	1	0

Snzol et al. ASCO 2014 Abstract 9003

Future: Adoptive Cell Therapy (ACT) with Antigen Specific T-cells

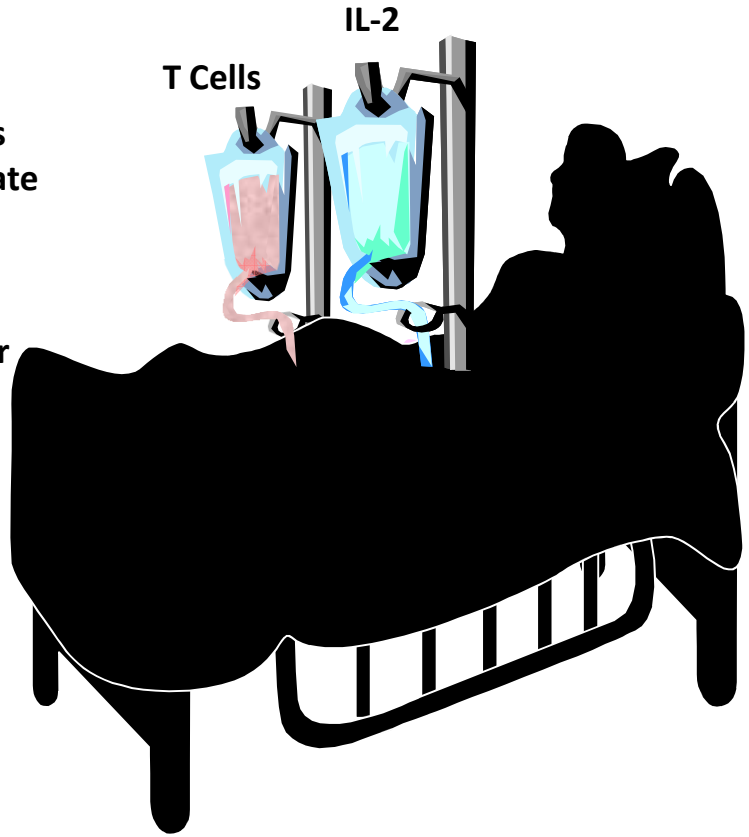
Single Cell Suspension
Incubated with IL-2





T Cells
Proliferate

Cancer
Cells
Die



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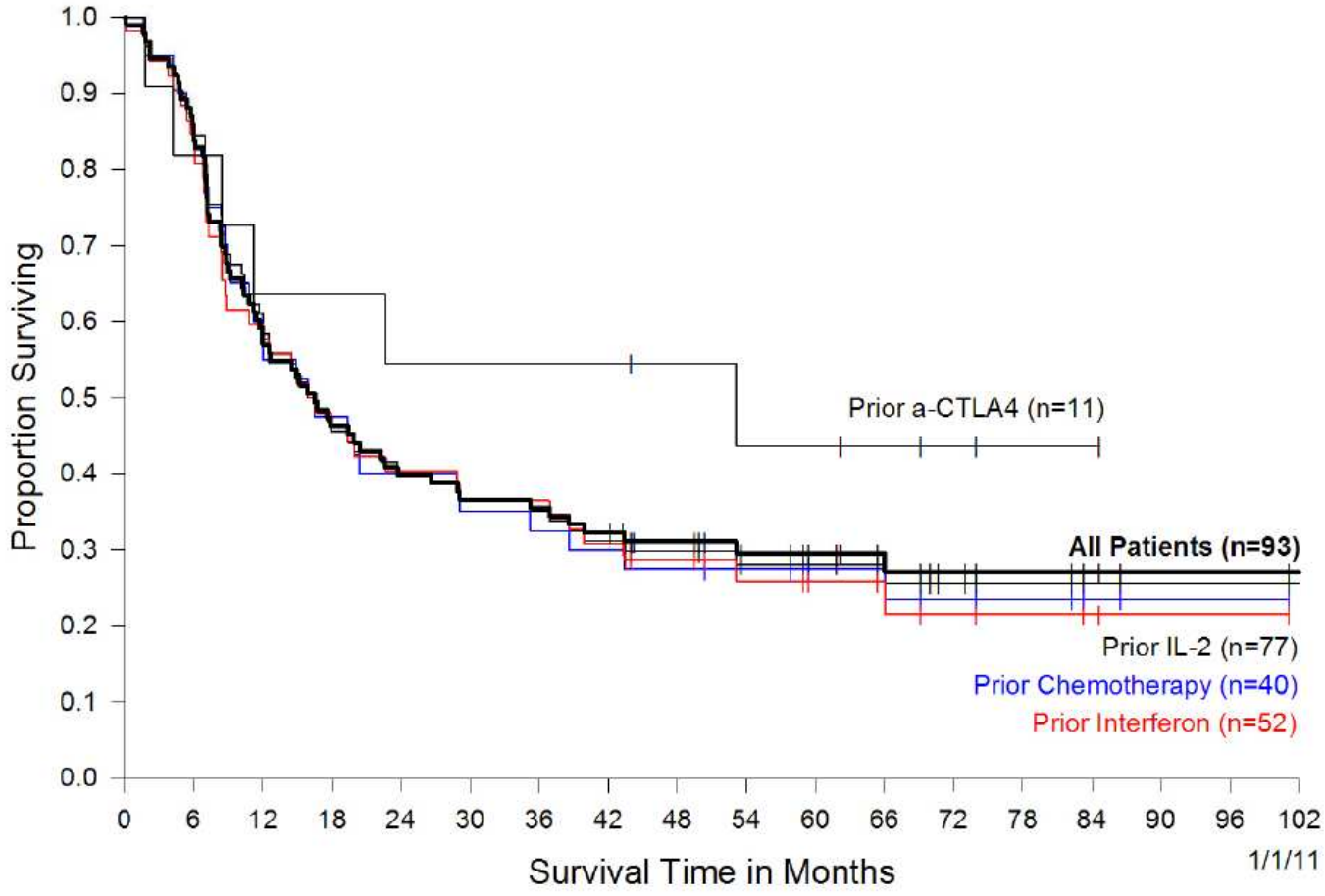
Courtesy of Patrick Hwu MD, PhD – MD Anderson Cancer Center

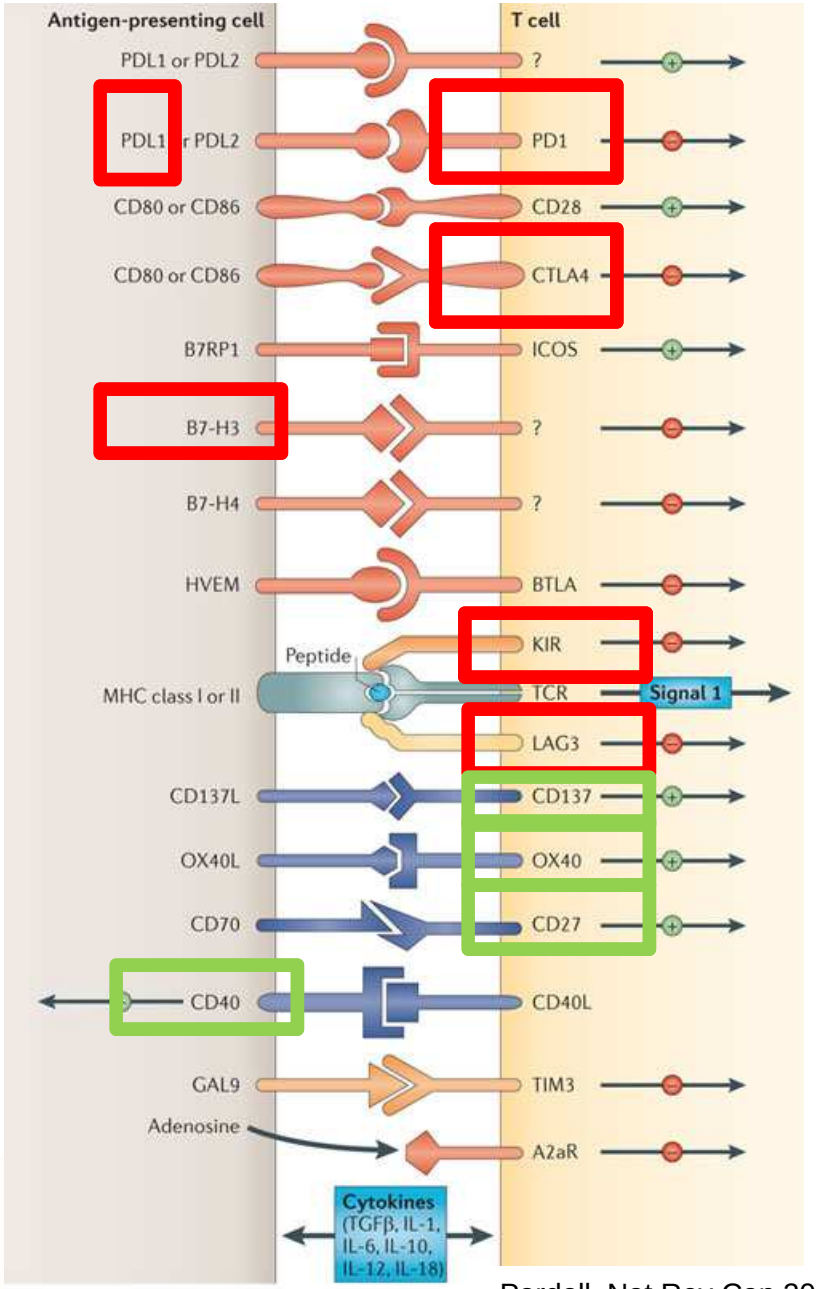
Effect of Prior Treatment Regimens on Survival of Patients Treated with Autologous TILs and IL-2 NIH Experience

Durable Remission Rates Regardless of Use of Other Therapies



Rosenberg et al. Clin Cancer Res 2011

What is the future: **COMBINATIONS!**



Pardoll, Nat Rev Can 2012

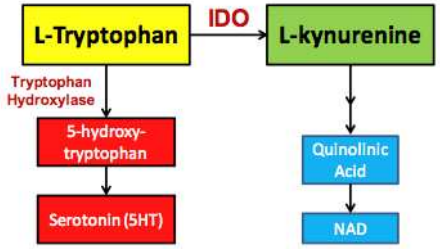
Other interesting immune approaches

- **Metabolic**
  - IDO inhibitor
- **Cytokines**
  - IL-2, IL-12 etc
- **Oncolytic Viruses**
  - TVEC
- **Targeted therapy**
  - BRAF, VEGF etc.
- **Chemotherapy**
  - Gemcitabine, Cisplatin
- **Radiation**

IDO inhibitor epacadostat plus ipilimumab

Indoleamine Dioxygenase-1 (IDO1)

- IDO1 is a heme-containing monomeric oxidoreductase that metabolizes tryptophan to kynurenine

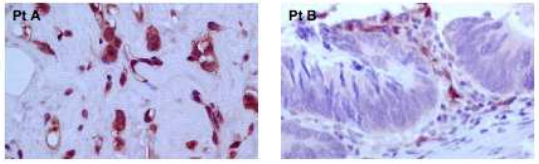


- IDO1 is expressed by antigen presenting cells as well as tumor cells
- IDO1 activity is upregulated in response to infection and tissue inflammation in response to IFN-γ

PRESENTED BY: Gregory L. Beatty PRESENTED AT: ASCO Annual '12 Meeting

Indoleamine Dioxygenase-1 as a Target for Therapy

- IDO1 is expressed in the tumor microenvironment of many cancers



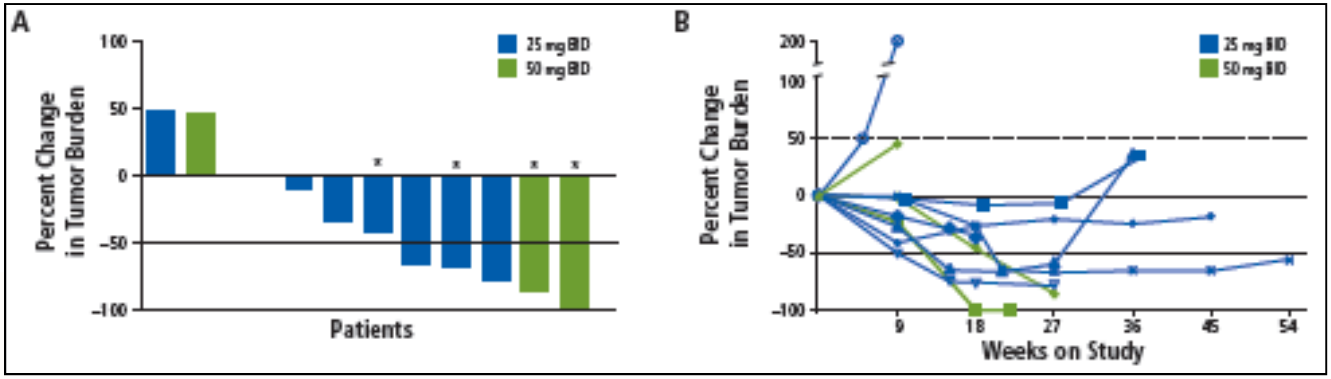
Breast Colon

- IDO1 expression in human tumors is associated with decreased survival
- IDO1 activity can suppress host anti-tumor immunity
- Inhibition of IDO1 in preclinical models of cancer slows tumor growth and restores anti-tumor immunity
- IDO1 inhibition synergizes with cytotoxic agents, vaccines, and cytokines to induce potent anti-tumor activity in preclinical models of cancer

PRESENTED BY: Gregory L. Beatty PRESENTED AT: ASCO Annual '12 Meeting

Beatty et al. ASCO (2012) Abstract 2500^

Preliminary Results From a Phase 1/2 Study of INCB024360 Combined with Ipilimumab in Patients With Melanoma



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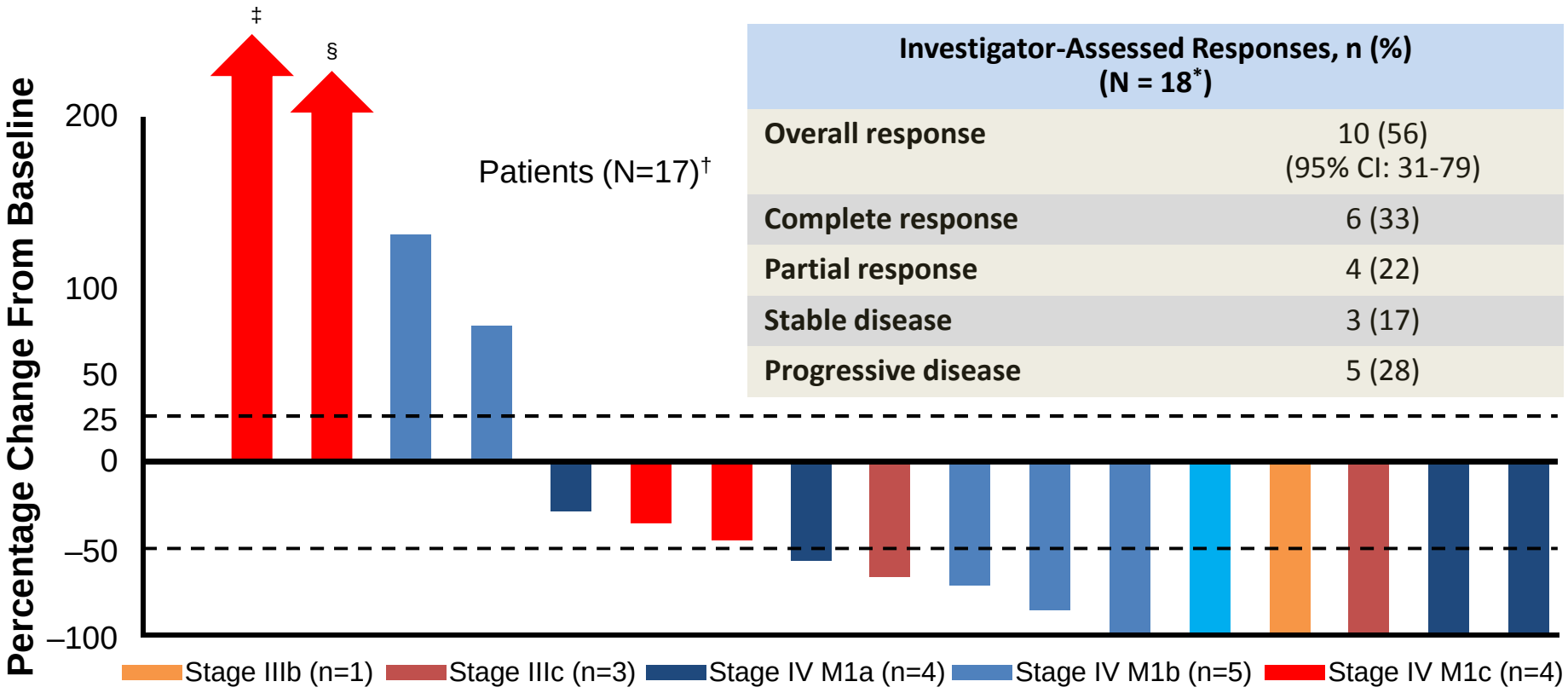
Gibney et al. ASCO (2014). Abstract TPS9117

T-Vec + Ipi in Unresected Stage IIIB-IV Melanoma: Max Change in Tumor Burden



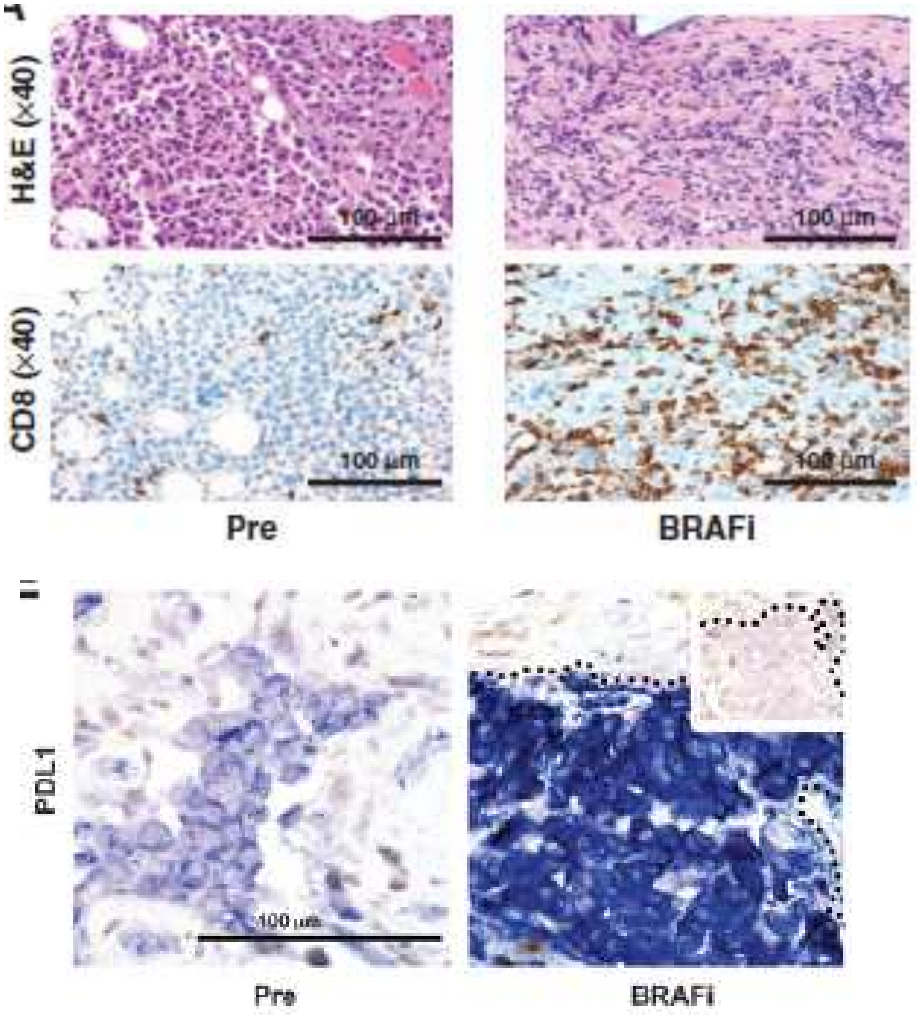
Investigator-Assessed Responses, n (%) (N = 18*)	
Overall response	10 (56) (95% CI: 31-79)
Complete response	6 (33)
Partial response	4 (22)
Stable disease	3 (17)
Progressive disease	5 (28)

*Only patients who received both T-Vec and ipilimumab. CR, CRu, and PD included.
† One patient with PD not shown in the plot because tumor burden could not be accurately calculated (missing post-baseline data)
‡ Percentage change from baseline: 538
§ Percentage change from baseline: 265

Puzanov et al. ASCO (2014) suppl; abstr 9029^

What about Targeted Therapy – Immunotherapy Combos?

- BRAF inhibitor associated with increase CD8+ T-cell infiltrate
- Resistance to BRAF inhibitors leads to up regulation of PD-L1



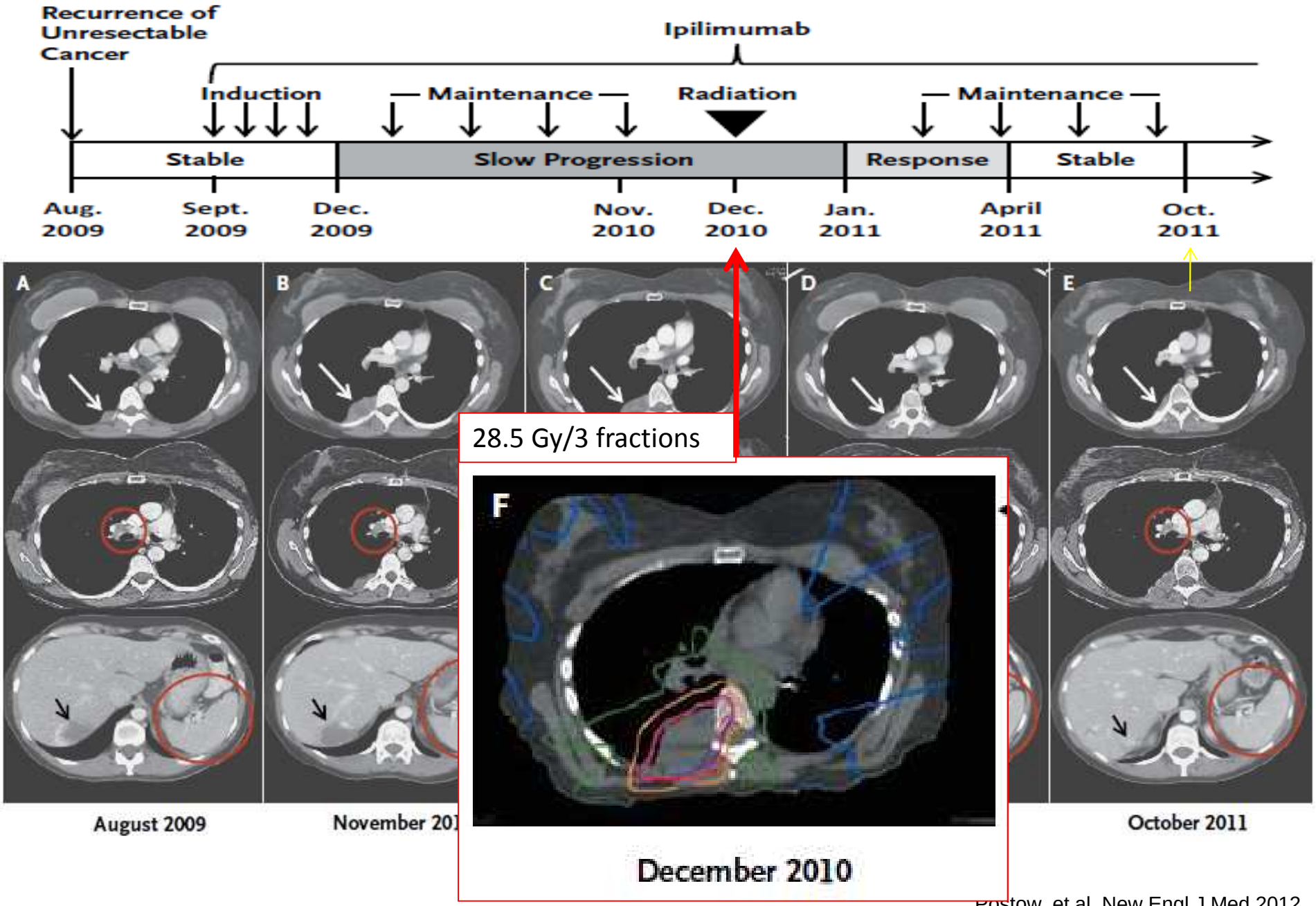
Frederick et al, Clin Can Res 2013

What about Targeted Therapy – Immunotherapy Combos?

- Phase I ipilimumab + vemurafenib
  - **Stopped for hepatic toxicity**
- Phase I ipilimumab + dabrafenib + trametinib
  - **Stopped for colitis/perforation toxicity**
- On-going studies of BRAF and MEK inhibitors with anti-PD1/L1 antibodies
  - **First report suggests no gain in response rate and substantial toxicity with combo**

Ribas et al, NEJM 2013
Puzanov et al. ASCO (2014) abstr 2511
Ribas et al. ASCO (2015) abstr 3003

Synergy between immunotherapy and radiation?



Postow, et al. New Engl J Med 2012

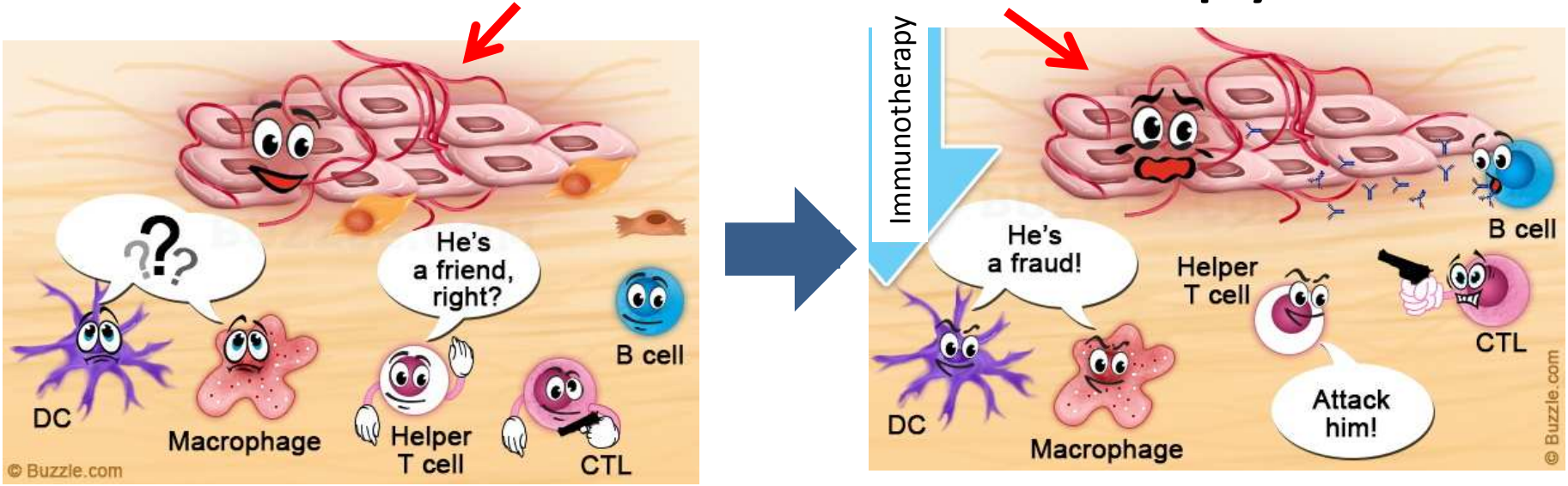
Conclusions

- Immunotherapy is standard of care in melanoma
  - Likely first and second line in most patients
- Understanding mechanisms of action important
  - Manage side effects, understand long-term benefit
- Immunotherapy combinations are likely the future
  - For melanoma and likely all cancers!

Thanks!

- Q's?
  - Jason Luke, MD FACP – jluke@medicine.bsd.uchicago.edu

Cancer Immunotherapy



http://goldenprague.us/strategies-for-cancer-vaccine-development/