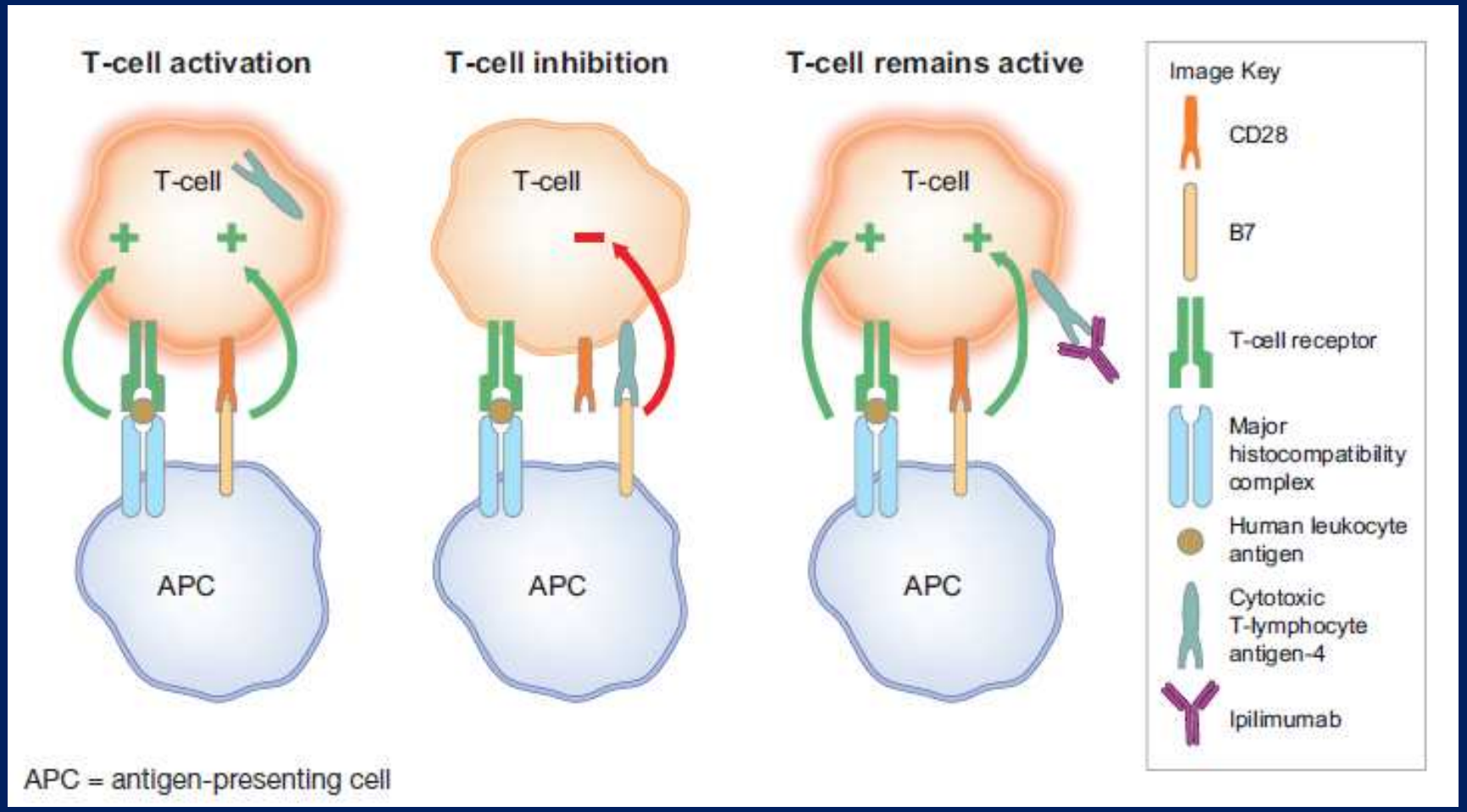
Ipilimumab: clinical benefits and management of toxicity



Heller et al ASCO 2011 Annual Meeting

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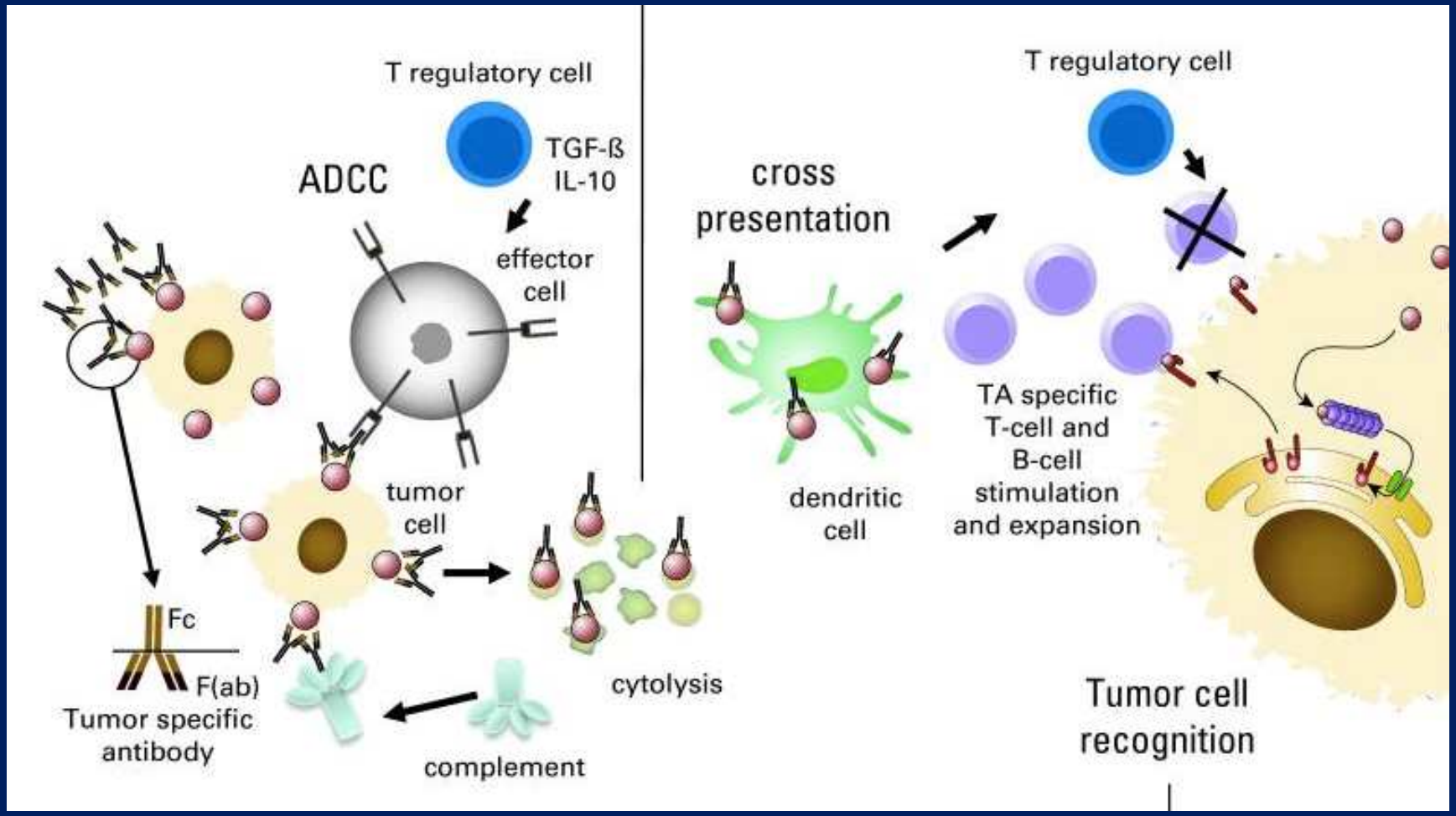
mAbs in Oncology:

1. Block signaling in oncogenic pathways
2. May lead to cell lysis through ADCC
    1. Is antigen expressed on tumor? good
    2. Is antigen expressed on regulatory cell? good
    3. Is antigen expressed on immune effector cell? Not so good

mAbs and ADCC:



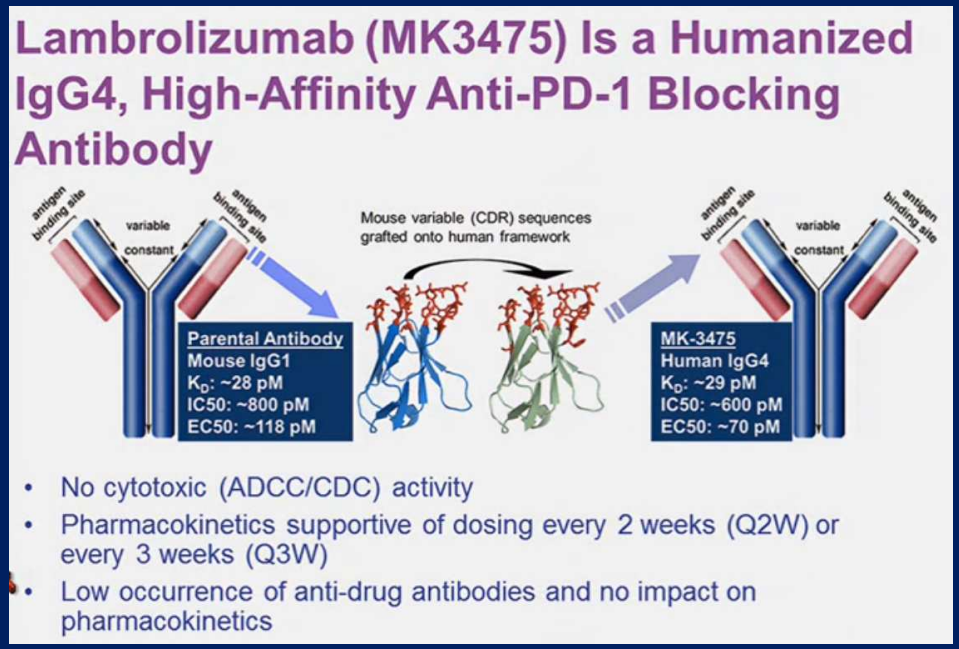
mAb opsonized cell recognition mediated via the FcγRIII (CD16) expressed on NK cells and FcγRIIa on monocytes, DC, and others

Adapted from Ferris et al. JCO. 2010.

CTLA-4 and PD-1 expression:

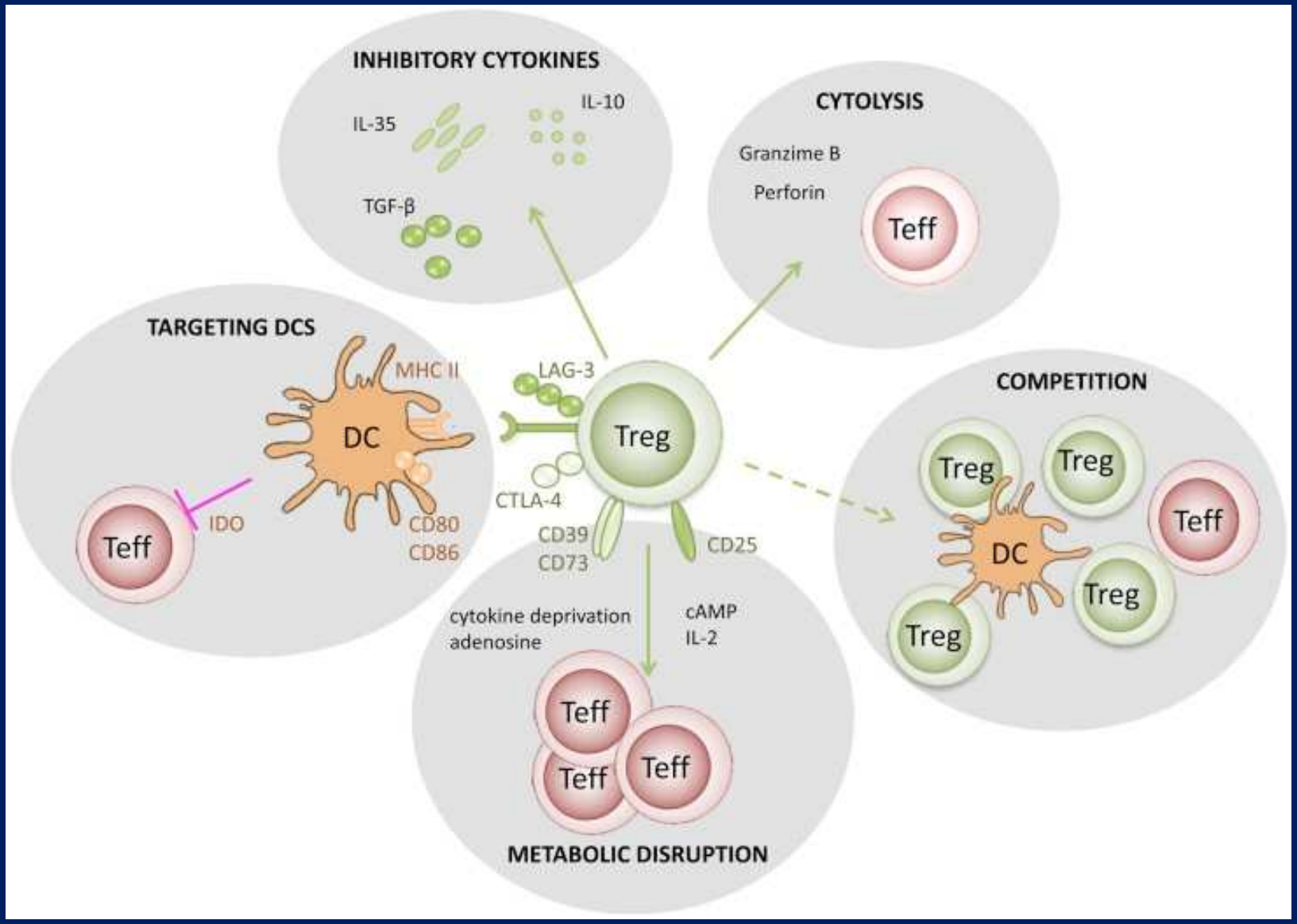
	CTLA-4	PD-1
Receptor	Helper T cells Regulatory T cells	T cells B cells NK cells
Ligand	APCs	APC Tumors

Brahmer. 2012.



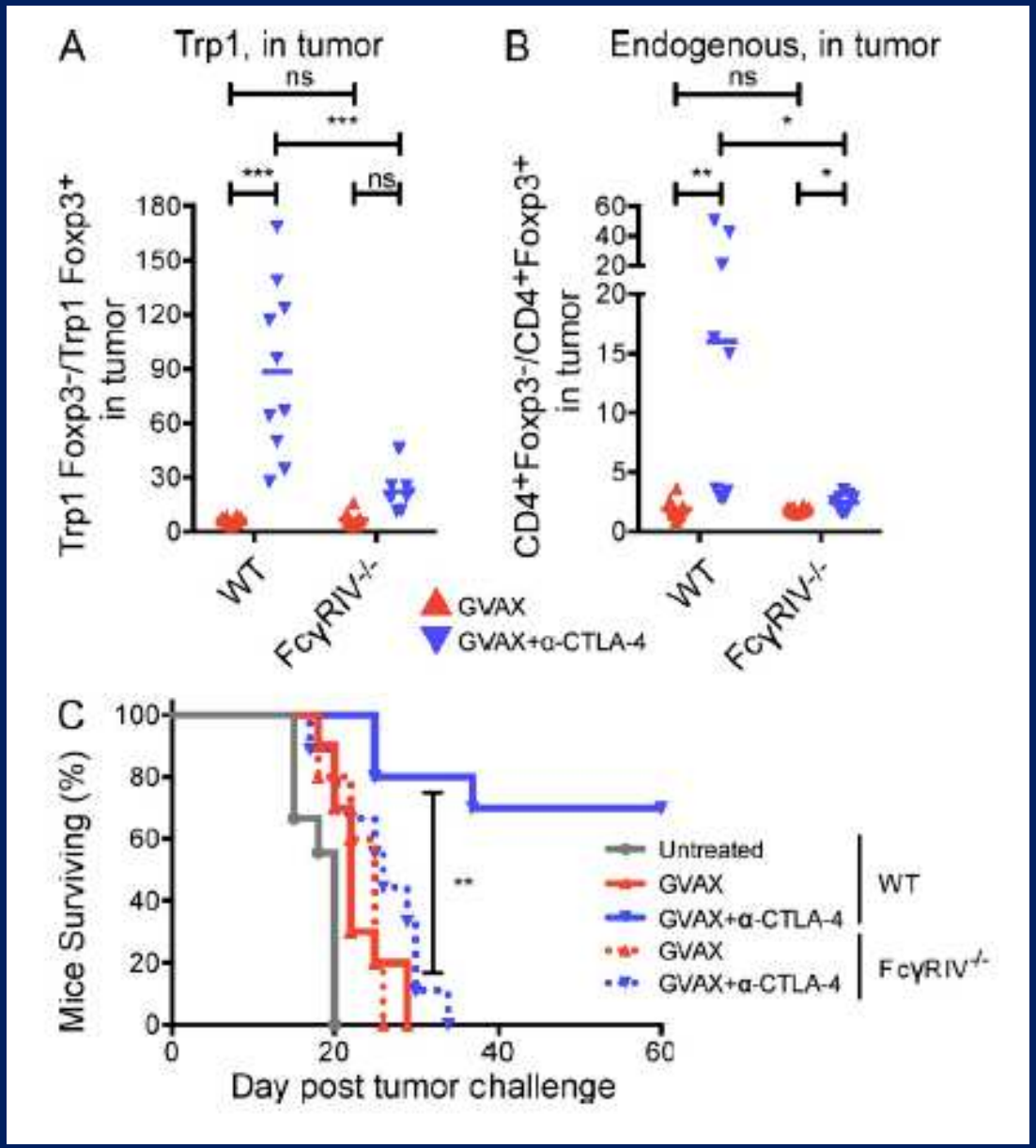
Ribas et al. ASCO. 2013.

Treg mechanisms of action:



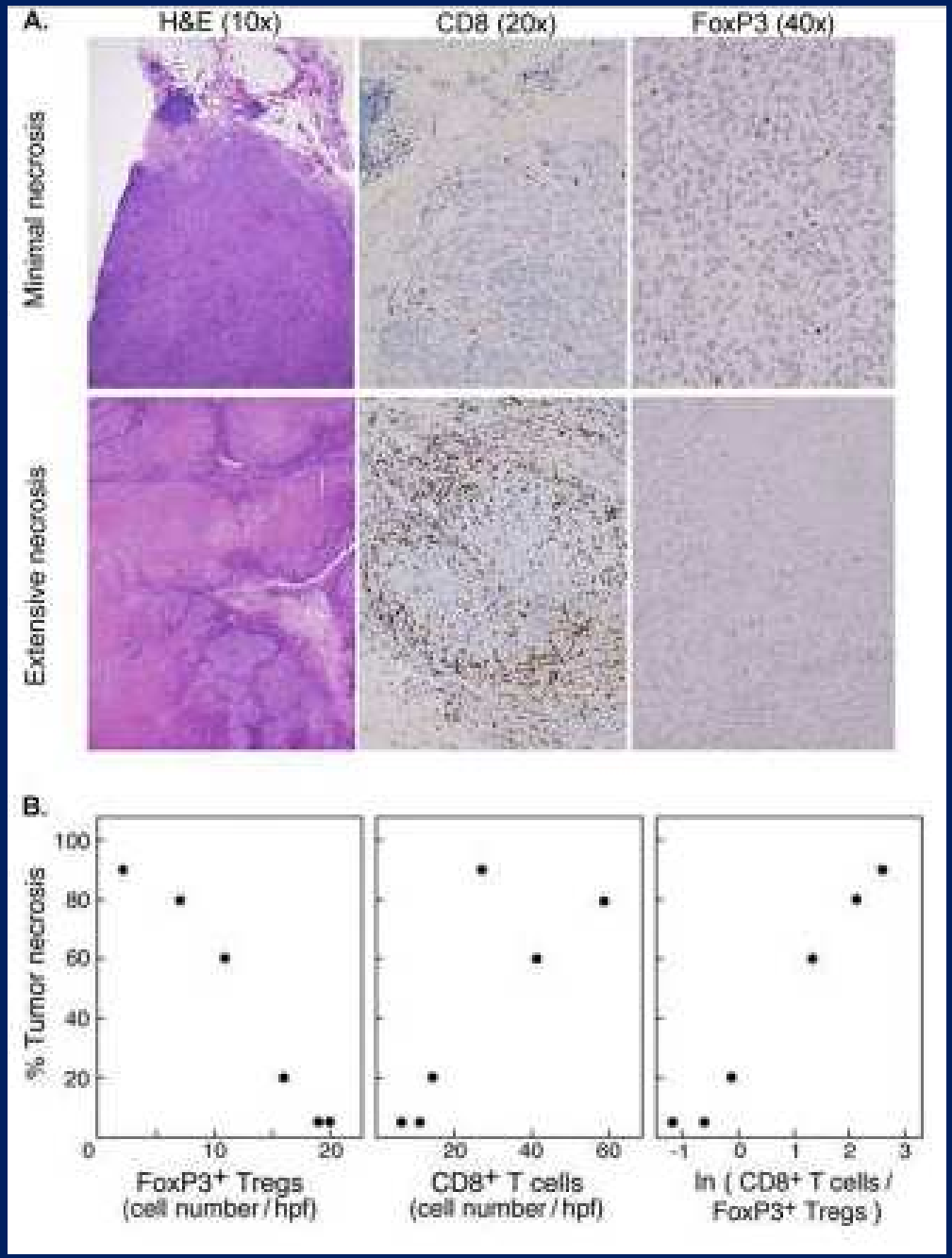
Caridade et al. Front. Immun. 2009.

CTLA-4 Ab mediated Treg depletion: Dependent on FcγRIV



Simpson et al. J Exp Med. 2013.

<u>Ipilimumab:</u> Treg/Teff ratio correlates with tumor necrosis



Oble et al. Cancer Immun. 2009.

Simplified mechanism: Two Ways to Go Faster

Senior faculty:
Purchase Lamborghini

Junior faculty / housestaff:
Disable brakes on Yugo

The checkpoint inhibitor strategy

Nobody wants to take credit for this slide.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

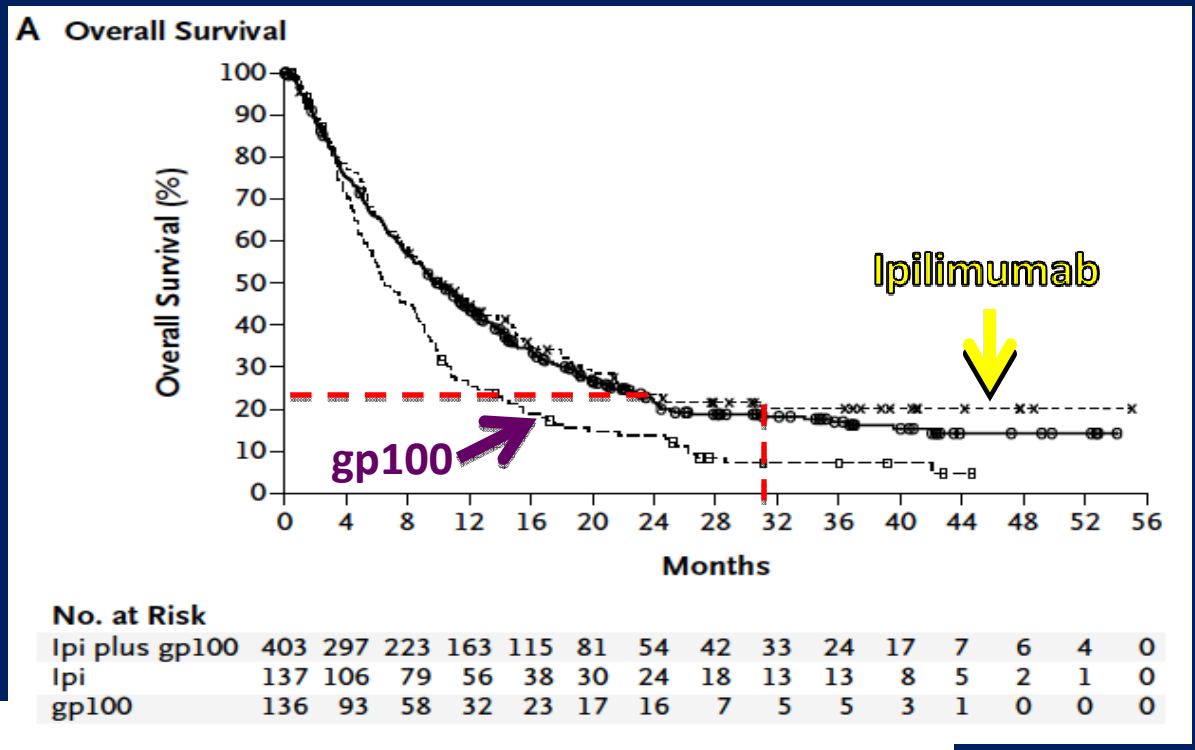
F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

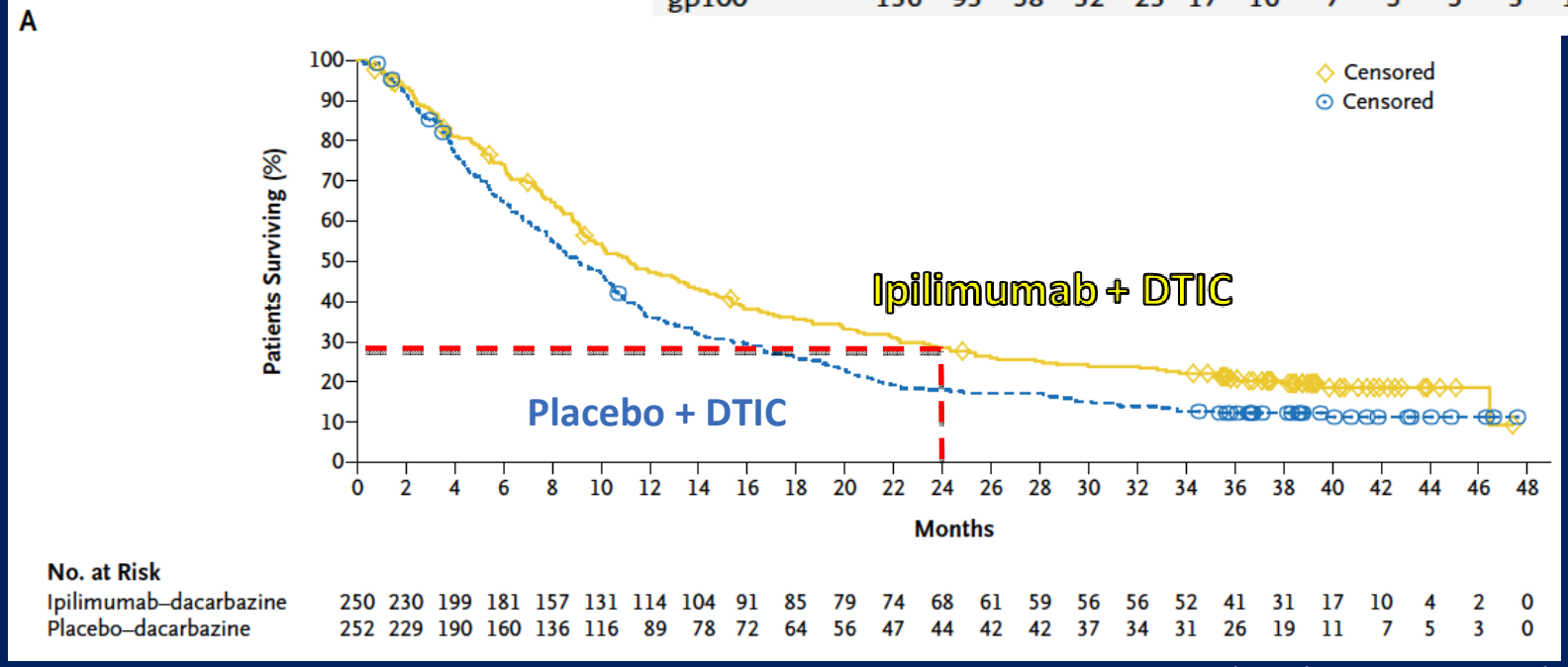
ORIGINAL ARTICLE

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Caroline Robert, M.D., Ph.D., Luc Thomas, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Steven O'Day, M.D., Jeffrey Weber M.D., Ph.D., Claus Garbe, M.D., Celeste Lebbe, M.D., Ph.D., Jean-François Baurain, M.D., Ph.D., Alessandro Testori, M.D., Jean-Jacques Grob, M.D., Neville Davidson, M.D., Jon Richards, M.D., Ph.D., Michele Maio, M.D., Ph.D., Axel Hauschild, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Pere Gascon, M.D., Ph.D., Michal Lotem, M.D., Kaan Harmankaya, M.D., Ramy Ibrahim, M.D., Stephen Francis, M.Sc., Tai-Tsang Chen, Ph.D., Rachel Humphrey, M.D., Axel Hoos, M.D., Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

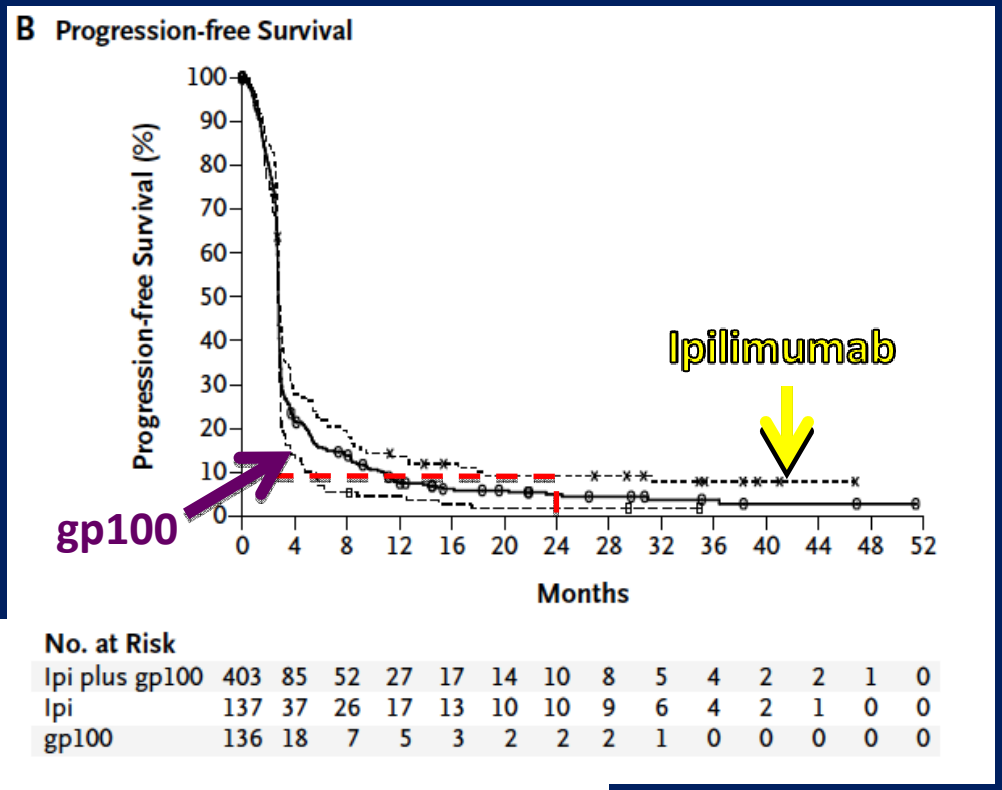
Ipilimumab and Survival

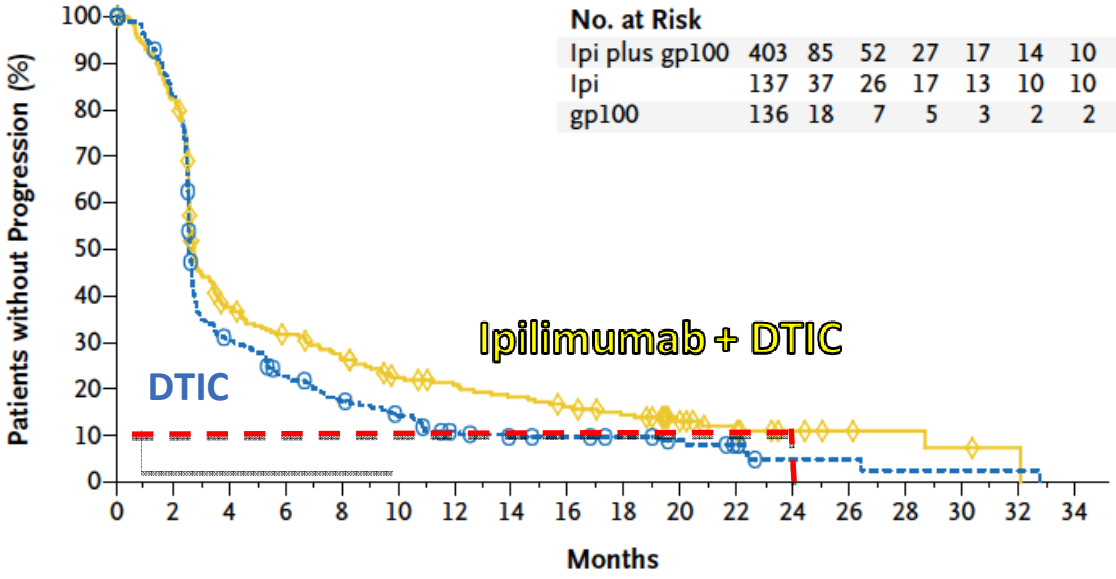




Hodi et al. NEJM. 2010, Robert et al NEJM. 2011.

Ipilimumab and Progression



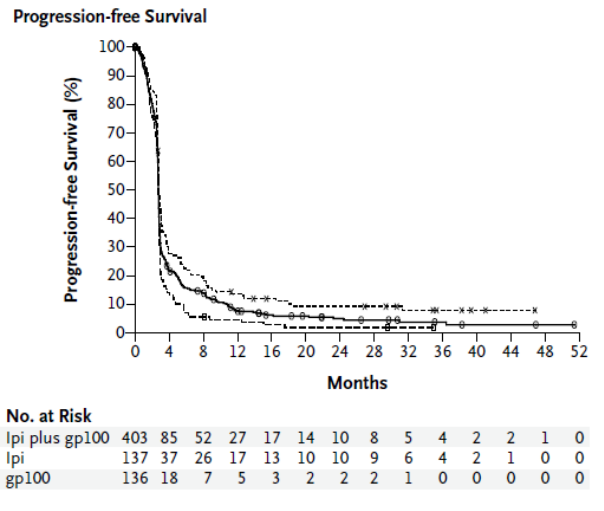


No. at Risk

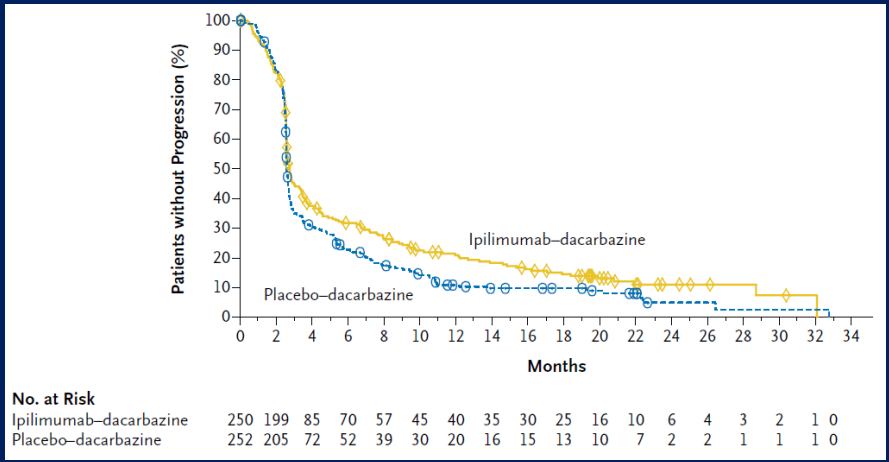
Ipilimumab–dacarbazine	250	199	85	70	57	45	40	35	30	25	16	10	6	4	3	2	1	0
Placebo–dacarbazine	252	205	72	52	39	30	20	16	15	13	10	7	2	2	1	1	1	0

Hodi et al. NEJM. 2010, Robert et al NEJM. 2011.

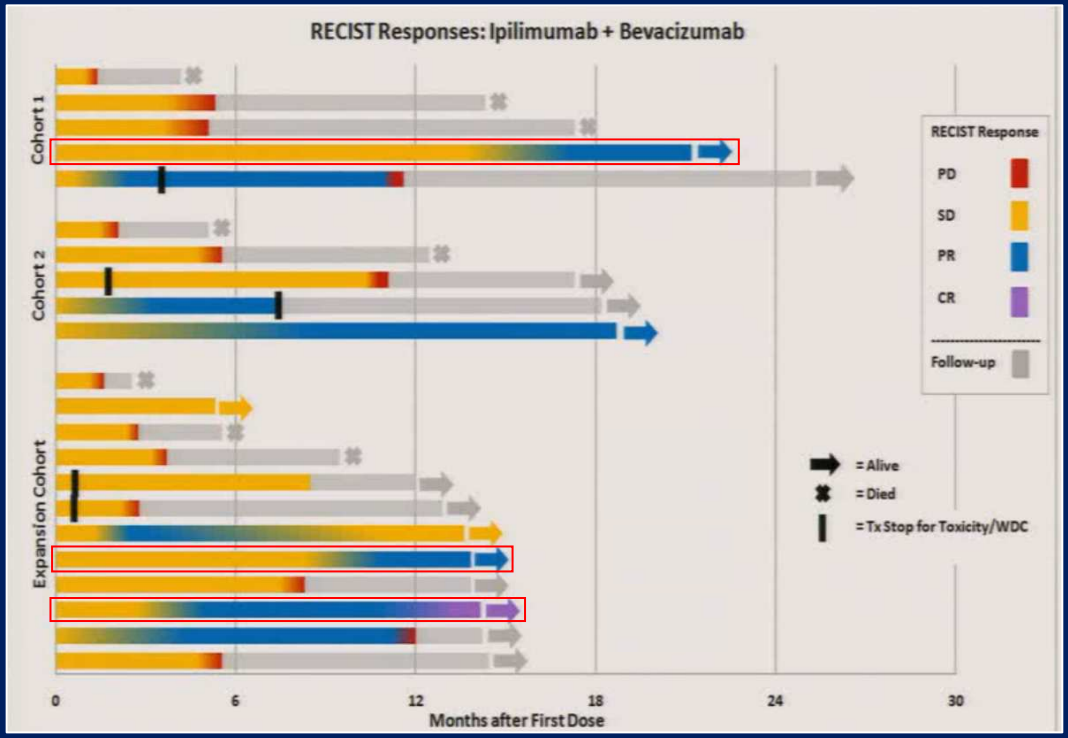
Ipilimumab: latent responses are common



NEJM 363(8):711-23

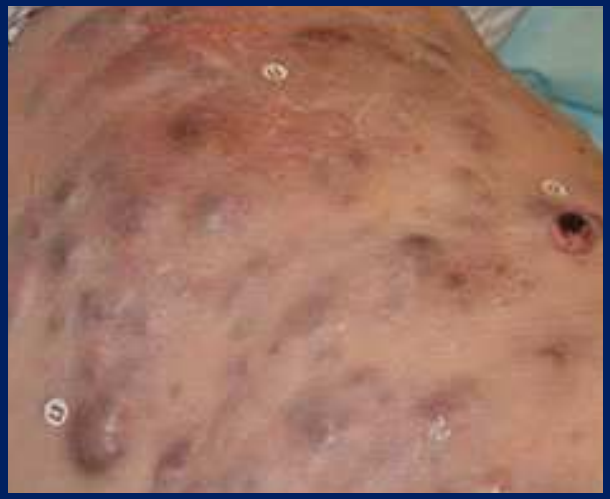


NEJM 364(26):2517-26



Hodi et al 2011 ASCO Annual Meeting

A response to ipilimumab:

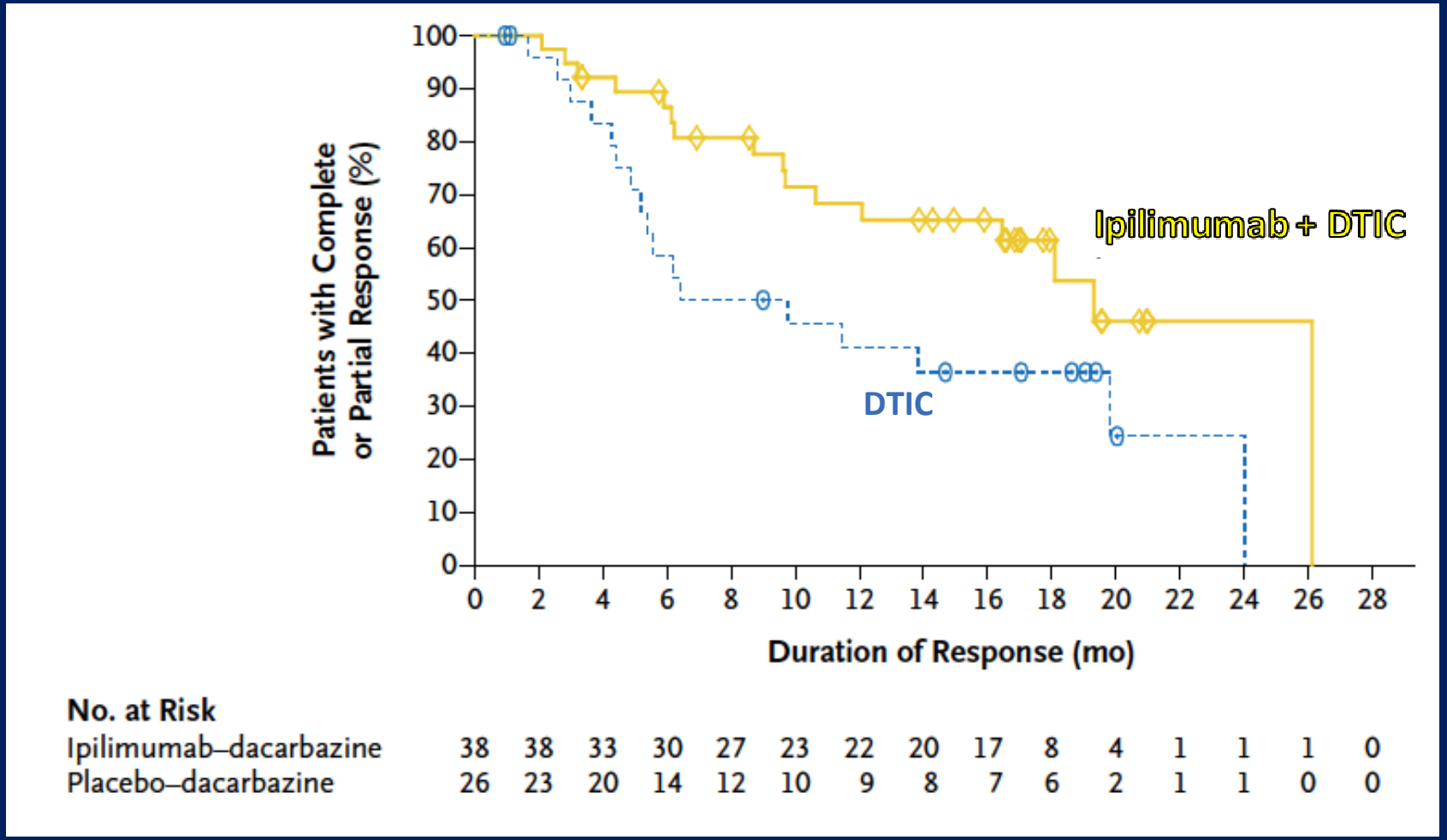


Baseline

After 12 weeks ipilimumab

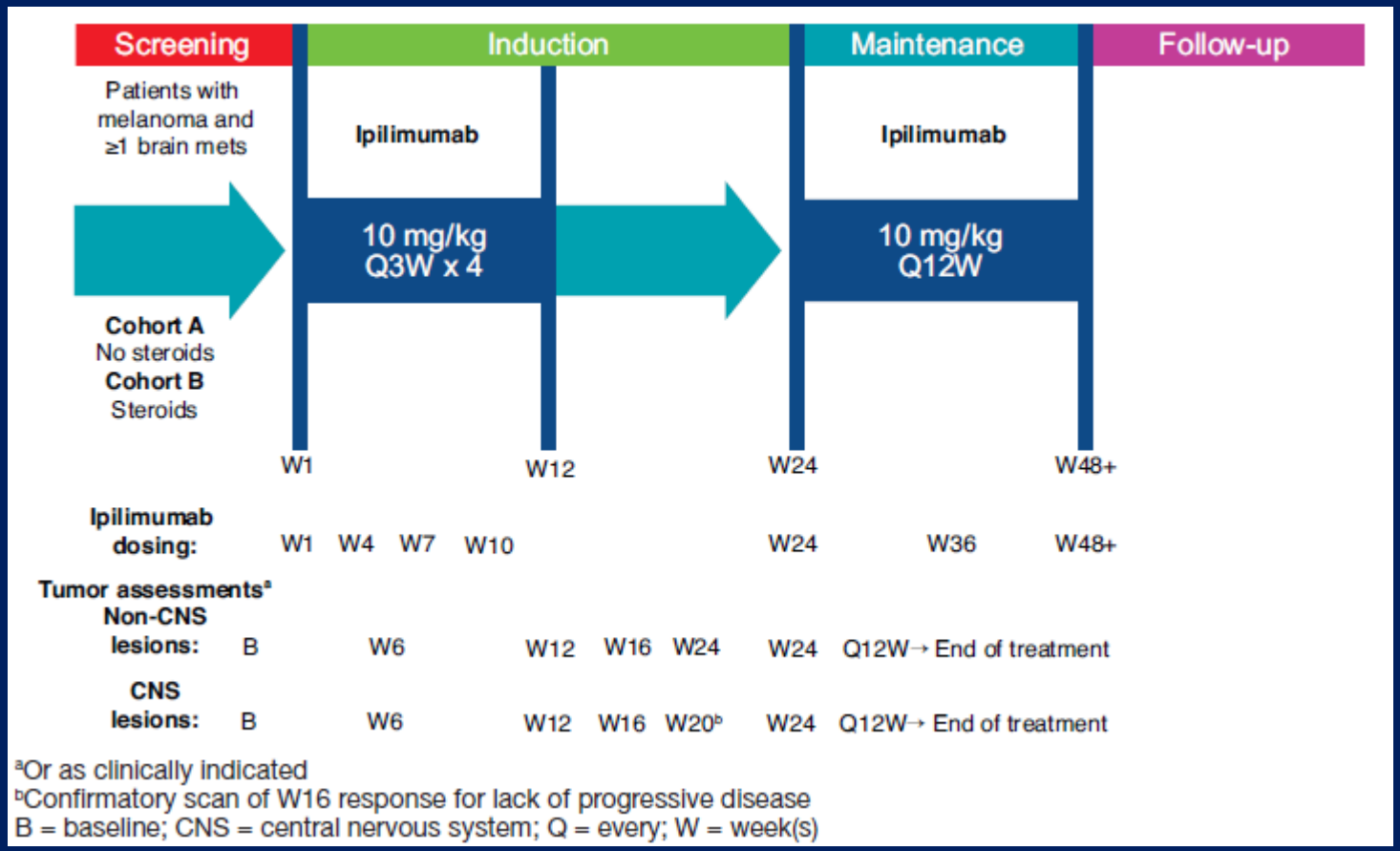
Cancer immunity. 8(1). 2008.

Ipilimumab and Response Duration



Robert et al NEJM. 2011.

Ipilimumab therapy in patients with stable asymptomatic brain metastases



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Population

Key Inclusion Criteria	CA184-042: Cohort A	CA184-045
Signed, written informed consent from patient or legal representative	✓	✓
Male or female ≥16 years of age	✓	✓
Stage III (unresectable) or Stage IV melanoma and ≥1 brain mets (1 lesion 0.5–3 cm or ≥2 lesions)	✓	-
Stage III (unresectable) or Stage IV melanoma	-	✓
Asymptomatic patients, no steroids within 10 days of starting ipilimumab	✓	-
Failed ≥1 systemic therapy for malignant melanoma or intolerance to ≥1 prior systemic treatment	-	✓
Prior treatment with anti-CTLA-4 agent allowed	-	✓
ECOG-PS of 0 or 1	✓	-
ECOG-PS of 0, 1, or 2	-	✓

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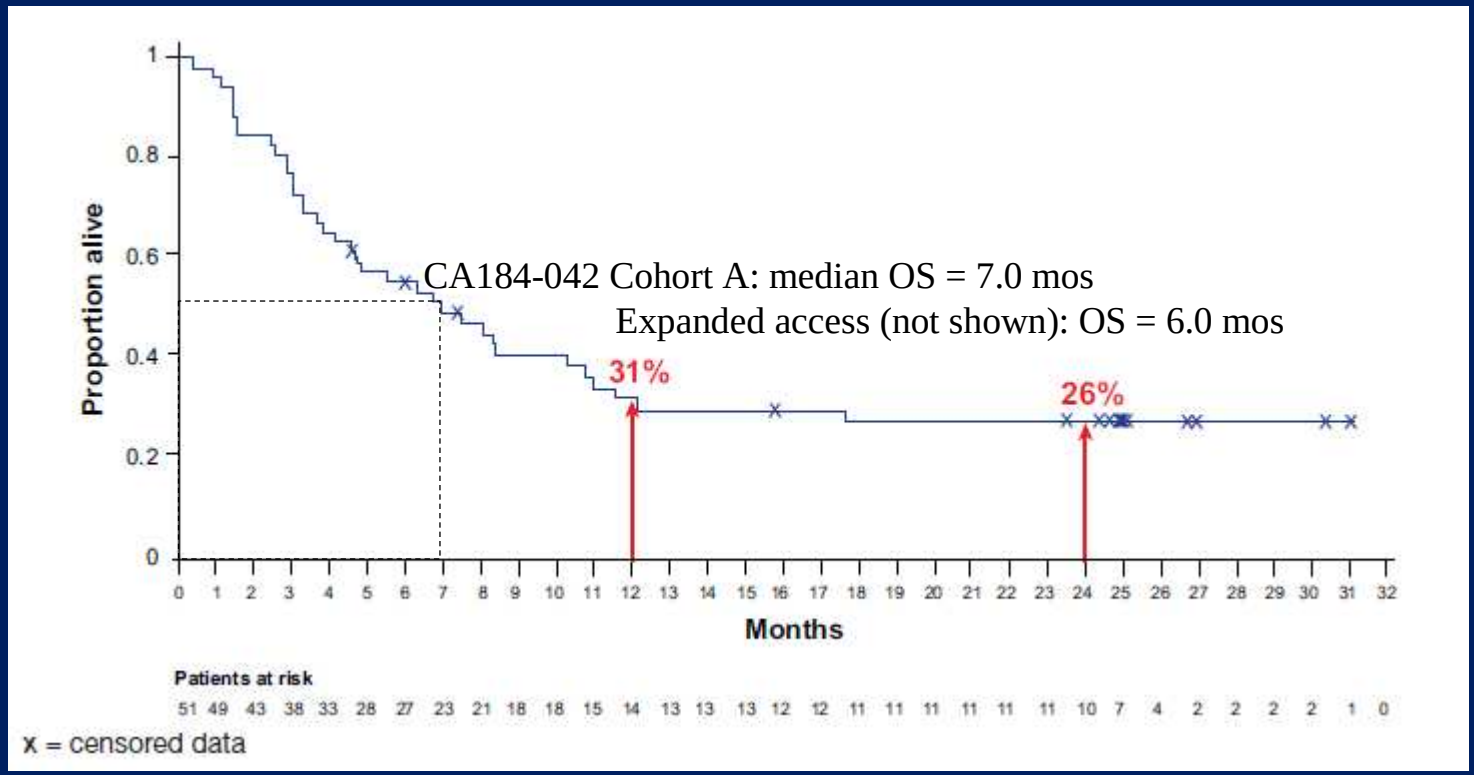
CA184-042: Prospective, phase II +/- clinical need for corticosteroids
CA184-045: Expanded access trial – subpopulation with brain metastases

Overall Survival



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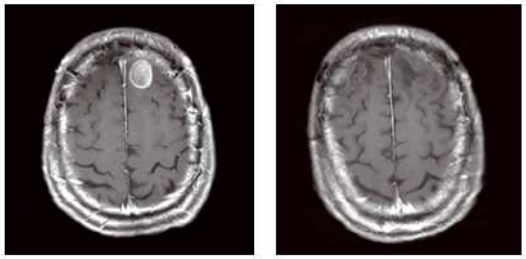
Ipilimumab:

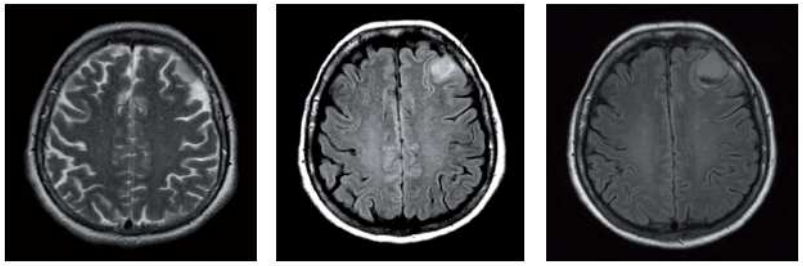
Advantage: durable CNS responses

A: Partial response (PR) in brain and PR in total tumor burden, duration 11+ months

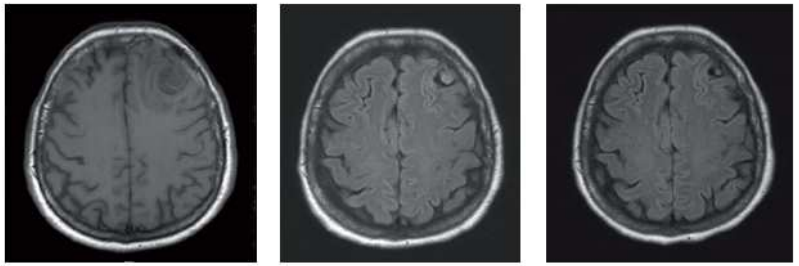


Baseline Week 16

B: Durable response (24+ months) after evidence of progressive disease (PD)



Baseline Week 6 (PD) Week 12 (PD)



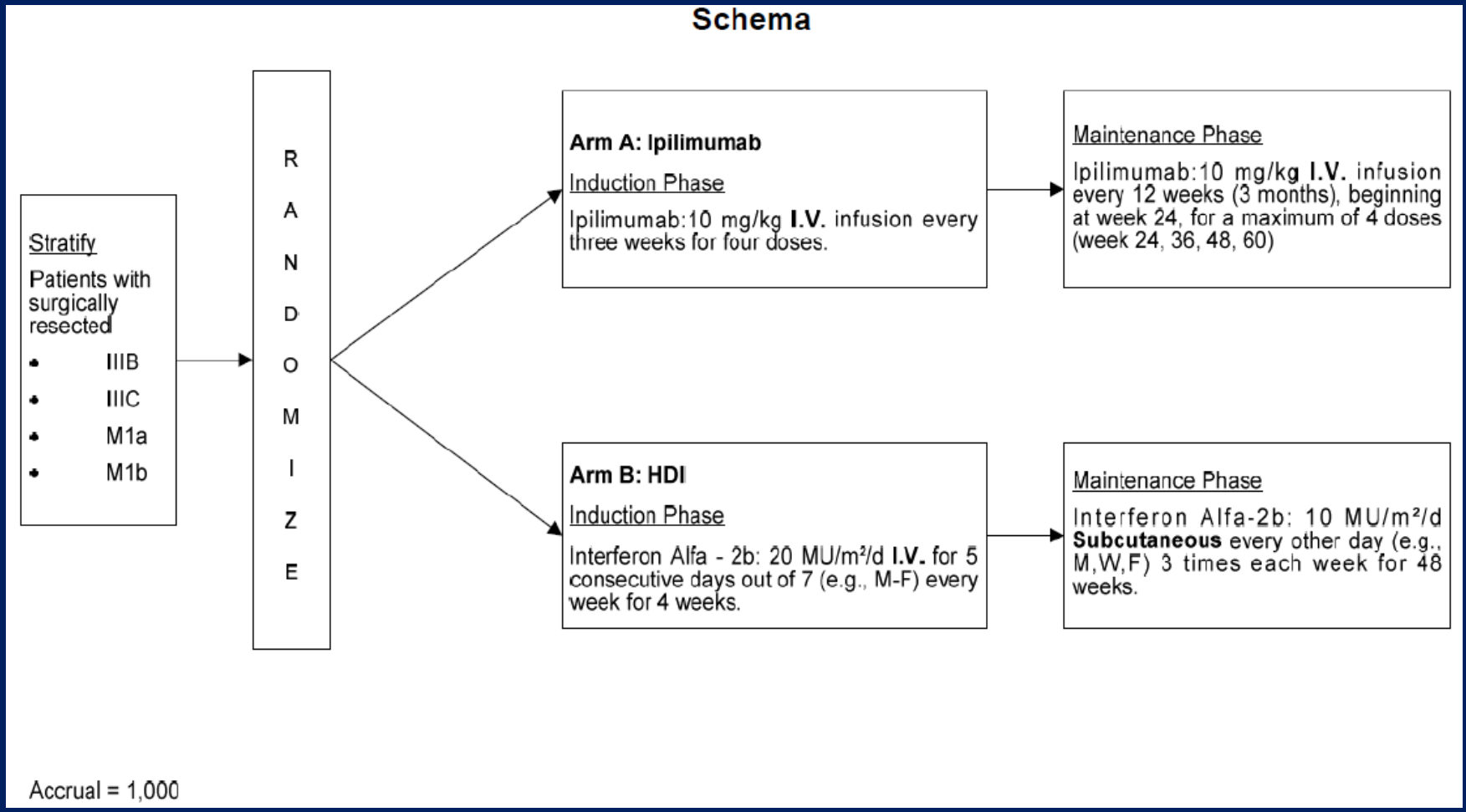
Week 16 (PR) Week 20 (PR) Week 24 (PR)

Heller et al ASCO 2011 Annual Meeting

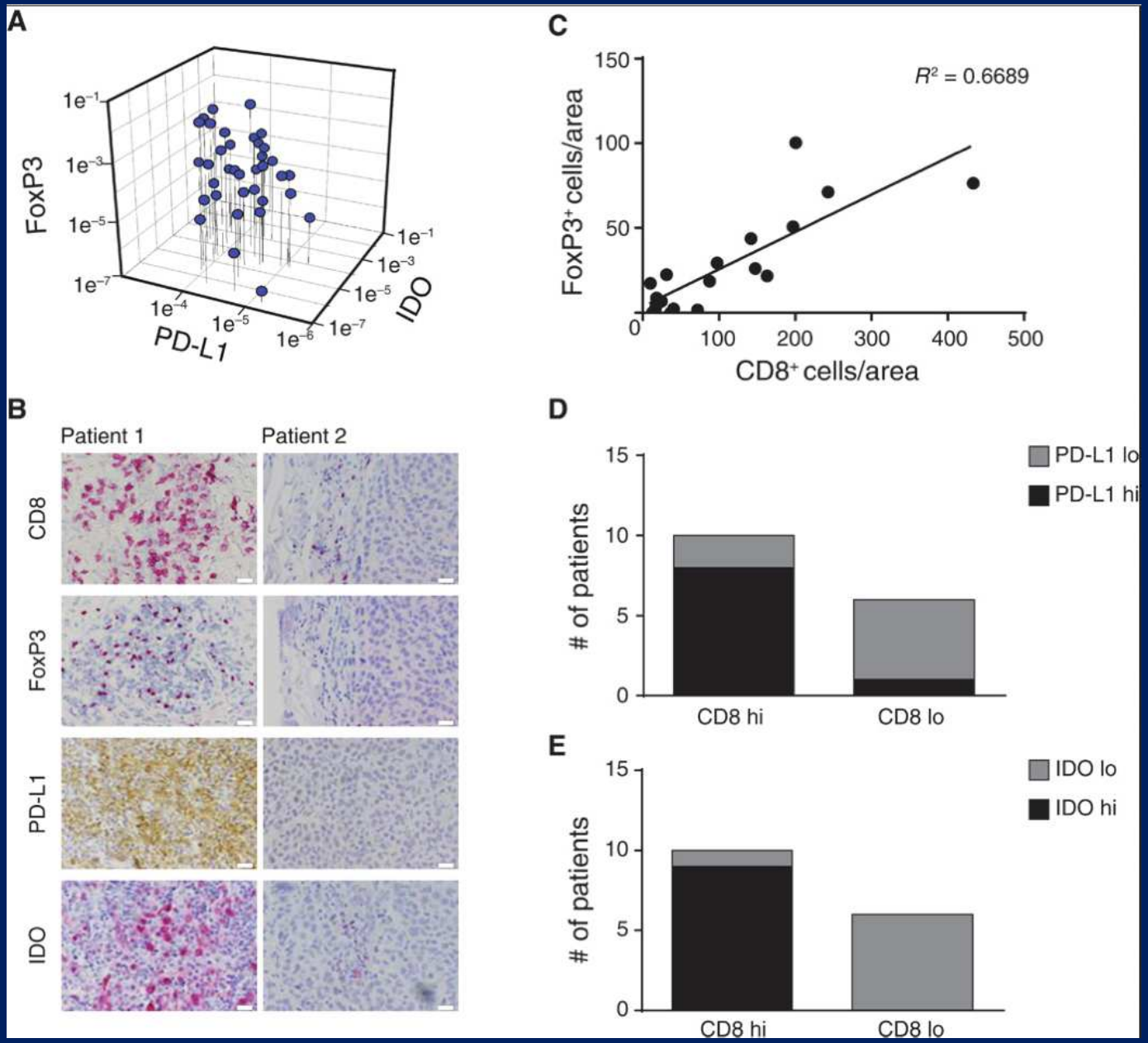
Disadvantages:

- ✓*Slow*
- ✓*Poor with steroids for edema*
- ✓*ORR = 11%, CBR ~ 30%*
- ✓*Autoimmunity*

E1609: Adjuvant therapy for resected melanoma

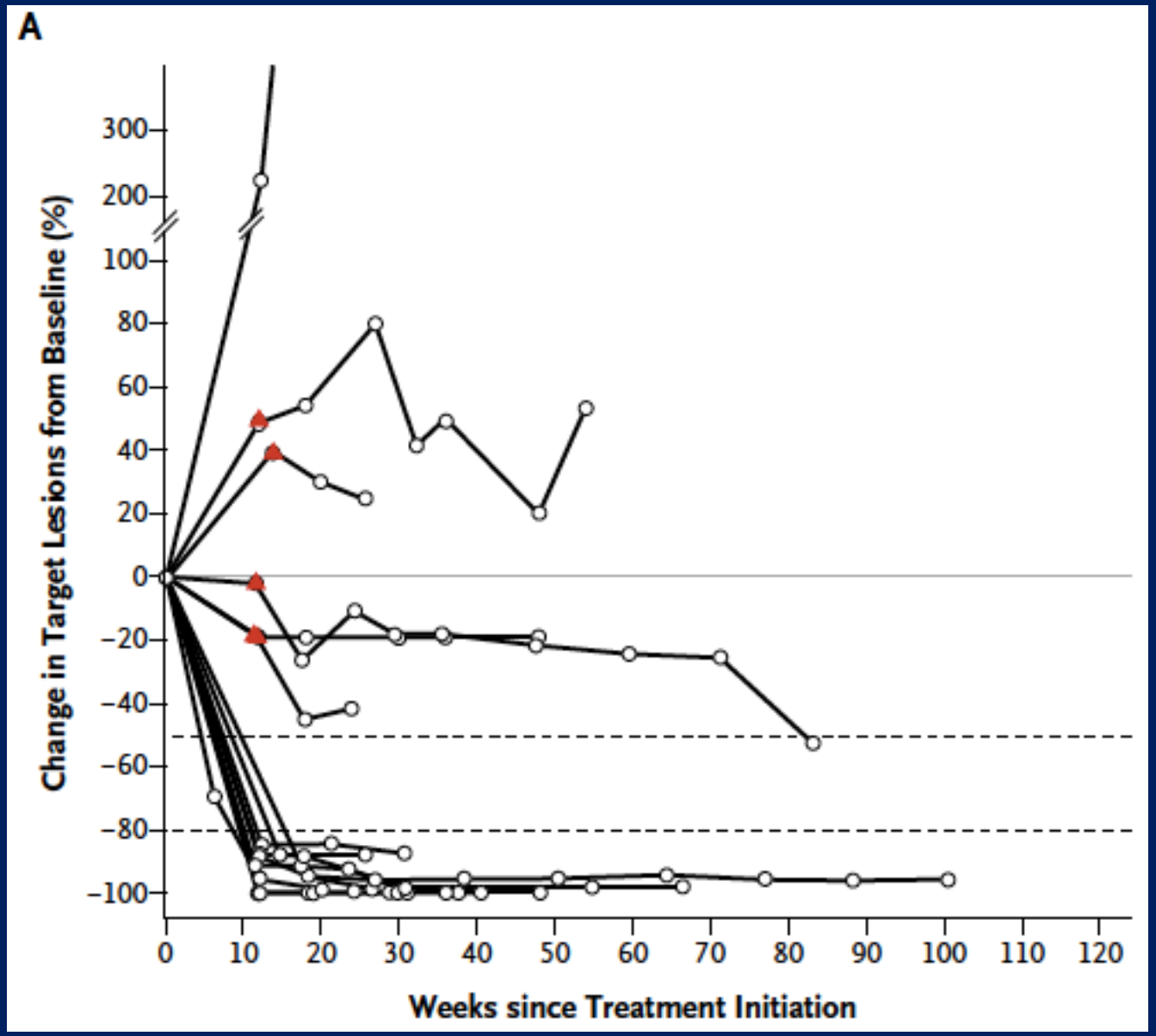


Ipilimumab combination candidates



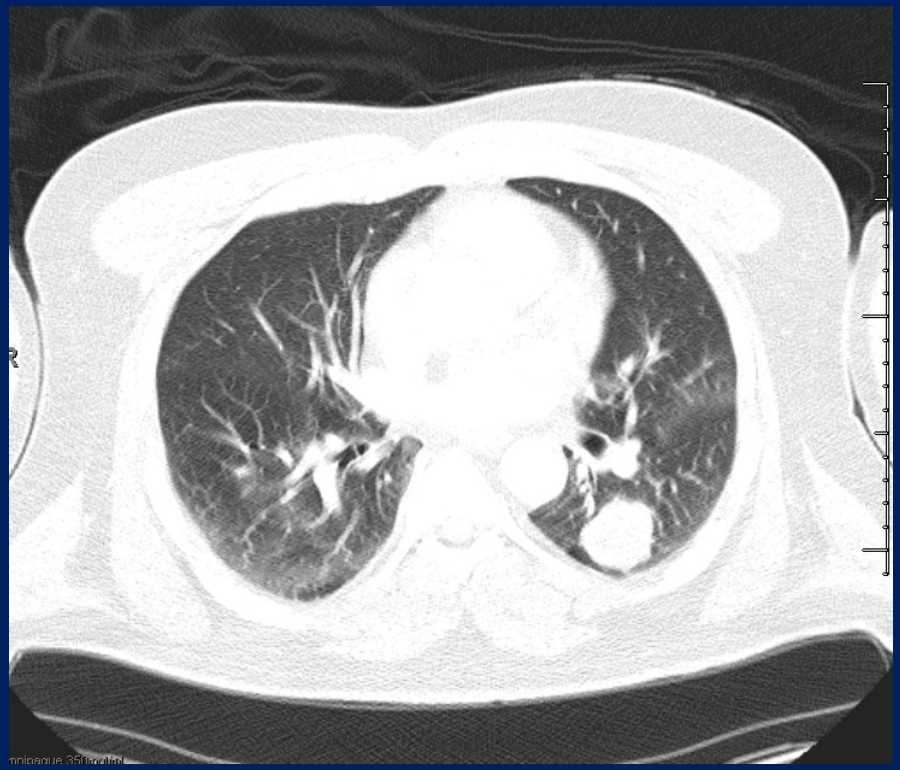
Spranger et al. Sci Transl Med. 2013

Nivolumab + ipilimumab – deep early responses

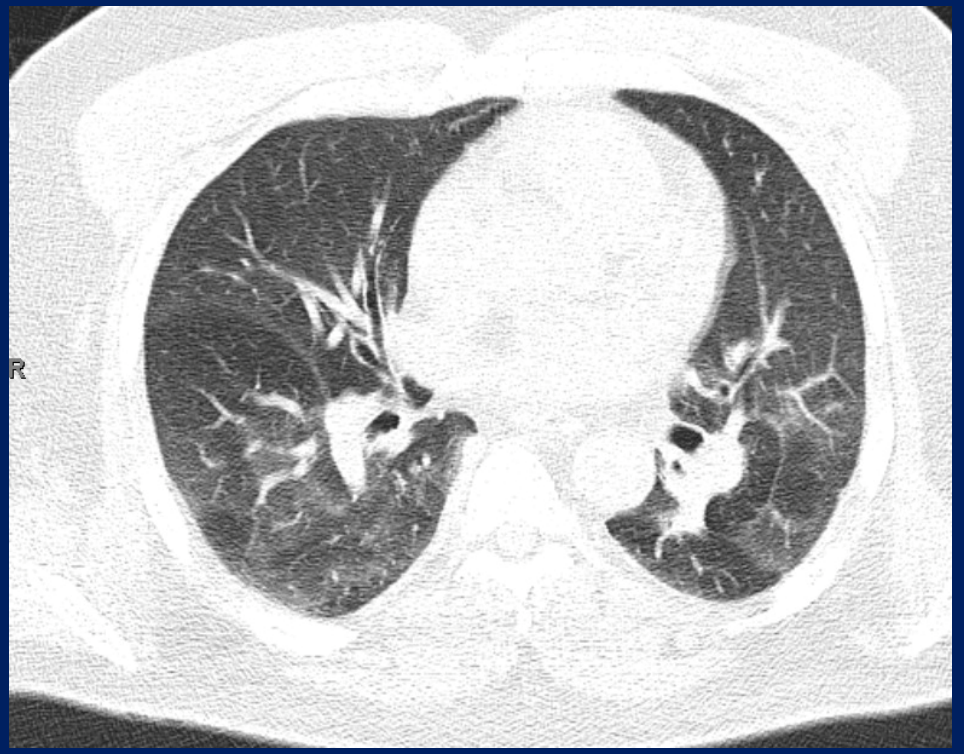


Wolchok et al. NEJM. 2013

Ipilimumab + Radiation



May 2011



November 2013

Ipilimumab toxicity – taking the brakes off (part 2):

Ipilimumab toxicity reflects a disinhibited immune system

Adverse Event	Ipilimumab plus gp100 (N=380)			Ipilimumab Alone (N=131)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
	number of patients (percent)					
Any event	374 (98.4)	147 (38.7)	26 (6.8)	127 (96.9)	49 (37.4)	11 (8.4)
Any drug-related event	338 (88.9)	62 (16.3)	4 (1.1)	105 (80.2)	25 (19.1)	5 (3.8)
Any immune-related event	221 (58.2)	37 (9.7)	2 (0.5)	80 (61.1)	16 (12.2)	3 (2.3)
Dermatologic	152 (40.0)	8 (2.1)	1 (0.3)	57 (43.5)	2 (1.5)	0
Pruritus	67 (17.6)	1 (0.3)	0	32 (24.4)	0	0
Rash	67 (17.6)	5 (1.3)	0	25 (19.1)	1 (0.8)	0
Vitiligo	14 (3.7)	0	0	3 (2.3)	0	0
Gastrointestinal	122 (32.1)	20 (5.3)	2 (0.5)	38 (29.0)	10 (7.6)	0
Diarrhea	115 (30.3)	14 (3.7)	0	36 (27.5)	6 (4.6)	0
Colitis	20 (5.3)	11 (2.9)	1 (0.3)	10 (7.6)	7 (5.3)	0
Endocrine	15 (3.9)	4 (1.1)	0	10 (7.6)	3 (2.3)	2 (1.5)
Hypothyroidism	6 (1.6)	1 (0.3)	0	2 (1.5)	0	0
Hypopituitarism	3 (0.8)	2 (0.5)	0	3 (2.3)	1 (0.8)	1 (0.8)
Hypophysitis	2 (0.5)	2 (0.5)	0	2 (1.5)	2 (1.5)	0
Adrenal insufficiency	3 (0.8)	2 (0.5)	0	2 (1.5)	0	0

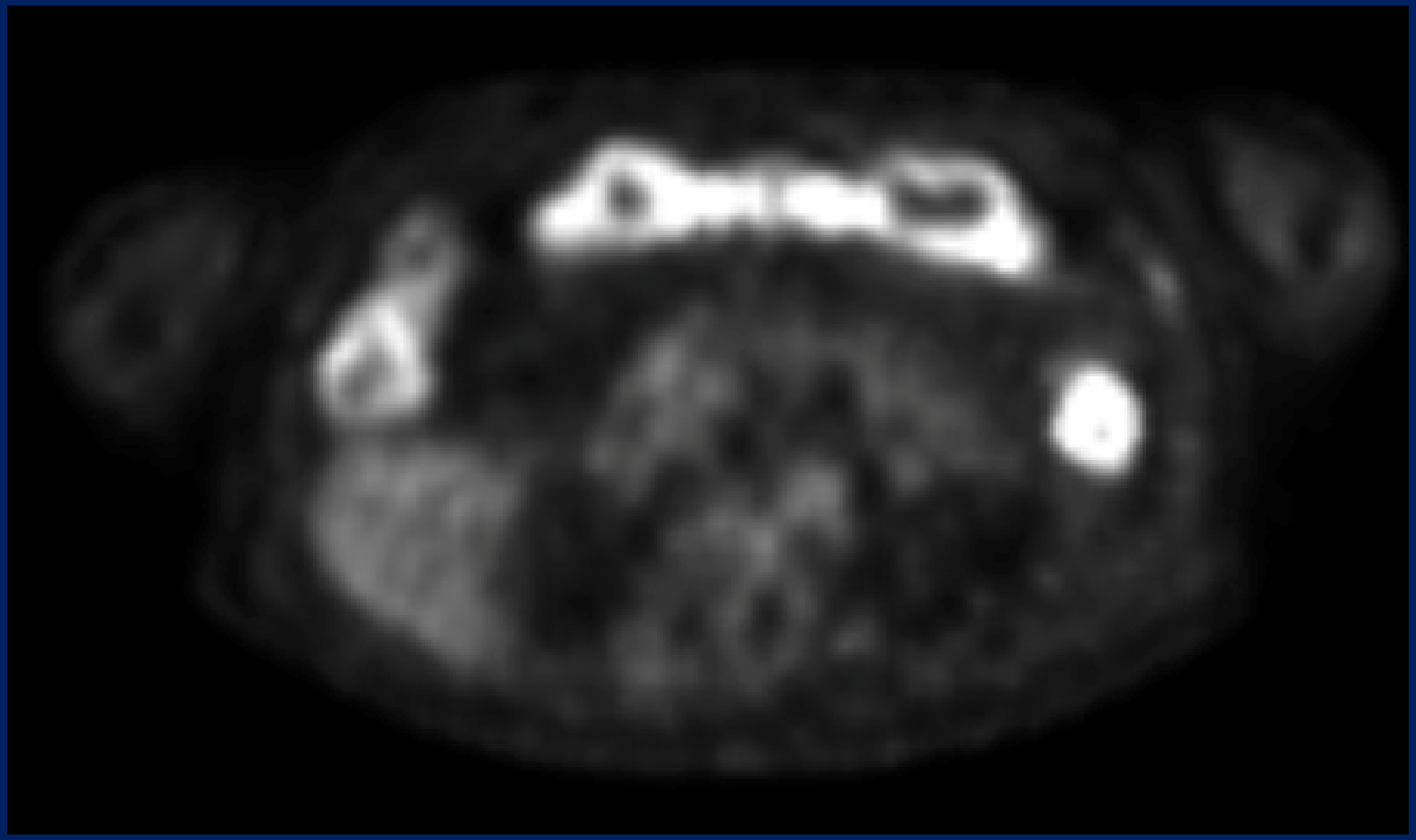
Nivolumab + ipilimumab – toxicity

Table 2. Highest Grade of Selected Treatment-Related Adverse Events That Occurred in at Least One of the Patients Who Received the Concurrent Regimen.*

Event	Cohort 1 (N=14)		Cohort 2 (N=17)		Cohort 2a (N=16)		Cohort 3 (N=6)		All Patients in Concurrent-Regimen Group (N=53)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	number of patients (percent)									
Pneumonitis	1 (7)	0	2 (12)	1 (6)	0	0	0	0	3 (6)	1 (2)
Endocrinopathy	1 (7)	0	3 (18)	0	1 (6)	0	2 (33)	1 (17)	7 (13)	1 (2)
Hypothyroidism	0	0	2 (12)	0	0	0	0	0	2 (4)	0
Hypophysitis	0	0	1 (6)	0	0	0	1 (17)	1 (17)	2 (4)	1 (2)
Thyroiditis	0	0	1 (6)	0	1 (6)	0	1 (17)	0	3 (6)	0
Adrenal insufficiency	0	0	2 (12)	0	0	0	0	0	2 (4)	0
Hyperthyroidism	0	0	1 (6)	0	0	0	1 (17)†		2 (4)†	0
Thyroid-function results abnormal	1 (7)	0	0	0	0	0	0	0	1 (2)	0
Hepatic disorder	4 (29)	3 (21)	5 (29)	3 (18)	2 (12)	1 (6)	1 (17)	1 (17)	12 (23)	8 (15)
Aspartate aminotransferase increased	4 (29)	3 (21)	4 (24)	2 (12)	2 (12)	1 (6)	1 (17)	1 (17)	11 (21)	7 (13)
Alanine aminotransferase increased	3 (21)	2 (14)	5 (29)	3 (18)	2 (12)	0	1 (17)	1 (17)	11 (21)	6 (11)
Gastrointestinal disorder	5 (36)	1 (7)	6 (35)	2 (12)	6 (38)	2 (13)	3 (50)	0	20 (38)	5 (9)
Diarrhea	5 (36)	0	5 (29)	1 (6)	5 (31)	2 (13)	3 (50)	0	18 (34)	3 (6)
Colitis	1 (7)	1 (7)	2 (12)	1 (6)	1 (6)	0	1 (17)	0	5 (9)	2 (4)
Renal disorder	1 (7)	1 (7)	1 (6)	1 (6)	1 (6)	1 (6)	0	0	3 (6)	3 (6)
Blood creatinine increased	1 (7)	1 (7)	1 (6)	1 (6)	1 (6)	1 (6)	0	0	3 (6)	3 (6)
Acute renal failure	0	0	1 (6)	1 (6)	1 (6)	1 (6)	0	0	2 (4)	2 (4)
Renal failure	0	0	1 (6)	1 (6)	0	0	0	0	1 (2)	1 (2)
Tubulointerstitial nephritis	1 (7)	0	0	0	0	0	0	0	1 (2)	0
Skin disorder	10 (71)	1 (7)	14 (82)	0	10 (62)	1 (6)	3 (50)	0	37 (70)	2 (4)
Rash	8 (57)	1 (7)	11 (65)	0	7 (44)	1 (6)	3 (50)	0	29 (55)	2 (4)
Pruritus	6 (43)	0	11 (65)	0	7 (44)	0	1 (17)	0	25 (47)	0
Urticaria	0	0	0	0	1 (6)	0	0	0	1 (2)	0
Blister	0	0	1 (6)	0	0	0	0	0	1 (2)	0
Infusion-related reaction	0	0	1 (6)	0	0	0	0	0	1 (2)	0

Wolchok et al. NEJM. 2013

Ipilimumab toxicity with reinduction



Ipilimumab toxicity:

Like most veterinary students, Doreen breezes through chapter 9.

Grade 1 – supportive care / observation

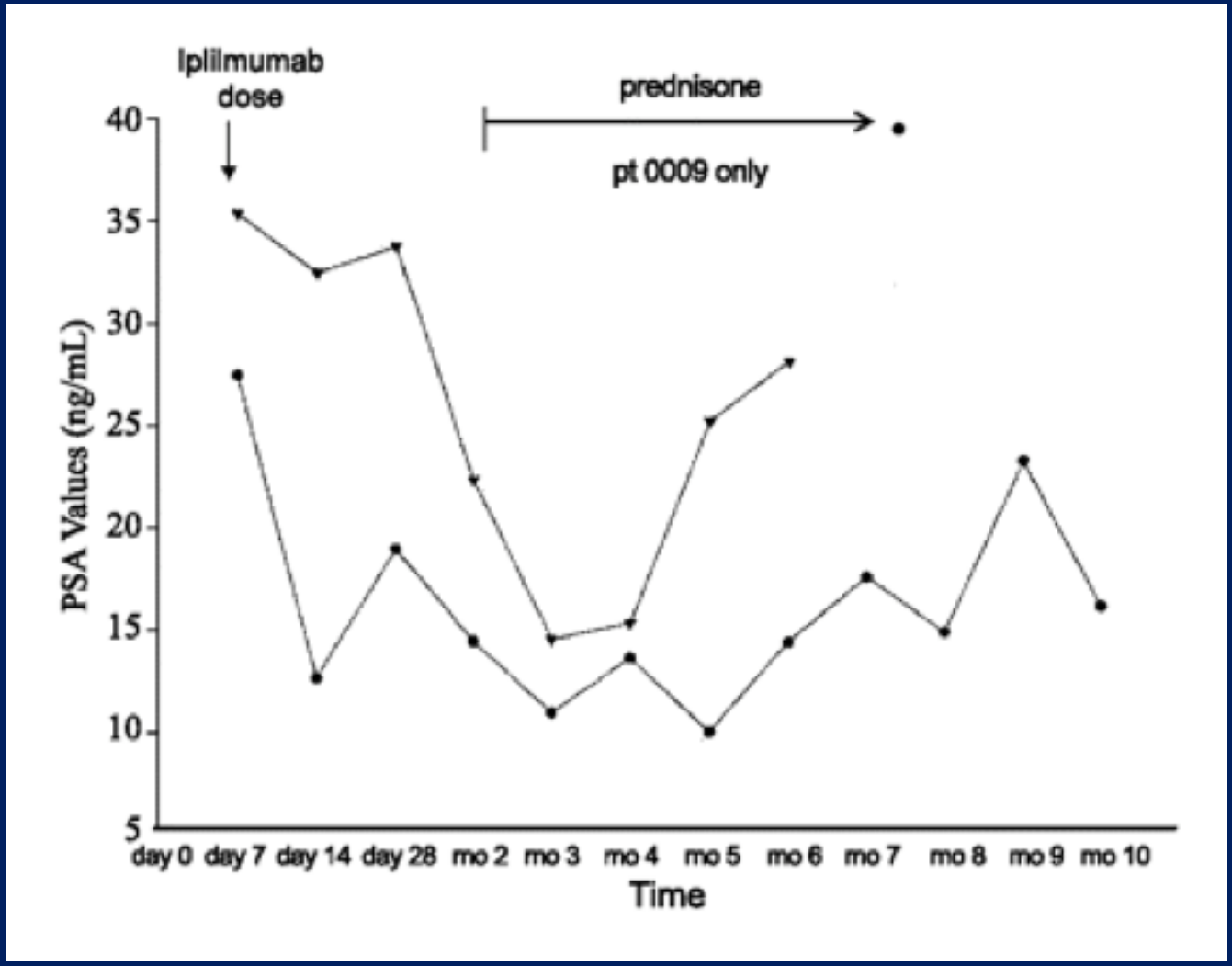
Grade 2 – give steroids (+/-)
- hold treatment
- prednisone 0.5 to 1.0 mg/kg
- taper over 4 weeks
- retreated if gr 1, < 7.5 mg pred

Grade 3+ – give more steroids
- d/c ipilimumab
- prednisone 1 – 2 mg/kg
- supportive care, consults

Steroid refractory –
- intensify immune suppression
  - colitis – infliximab
  - hepatitis – mycophenolate

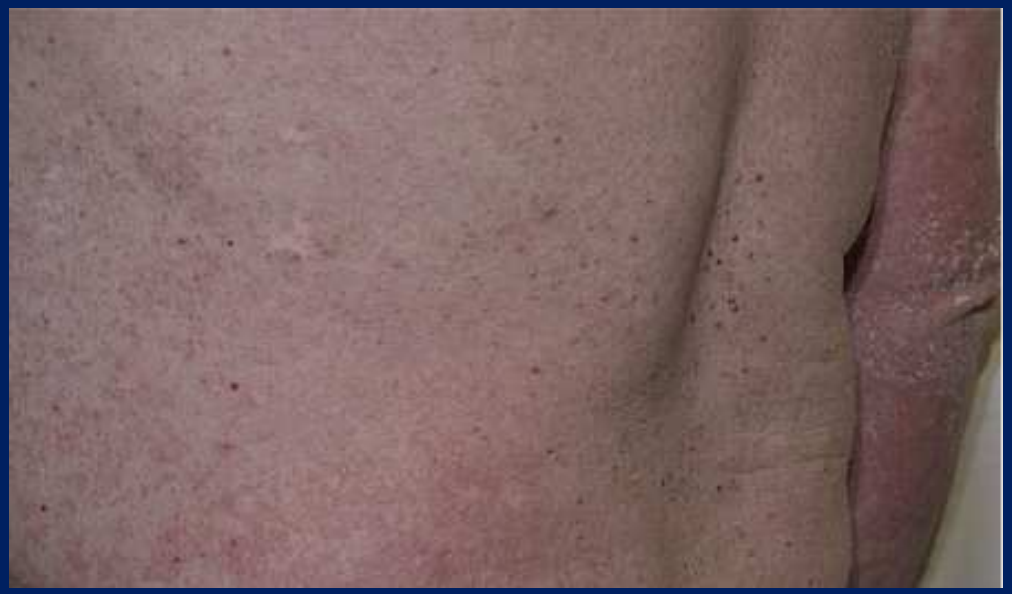
Weber et al, JCO, 2012
Kaehler et al, Seminars in Oncology, 2012

Steroids and efficacy



Small et al. CCR. 2007

Ipilimumab toxicity: Rash



Minkis et al. J Acad Derm. 2012.

Skin and subcutaneous tissue disorders			
	Grade		
Adverse Event	**1**	**2**	**3**
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.			

Ipilimumab toxicity: Ipilimumab with GM-CSF

Grade 3-4 Tox	Ipilimumab + GM-CSF (N=118)	Ipilimumab (N = 120)	Proposed explanation
GI	16.1%	26.7%	• GM-CSF involved in mucosal homeostasis • GM-/- mice develop colitis rescued by GM administration • Some Crohn's patients have GM neutralizing Abs or decreased receptors • GM-CSF benefits some with Crohn's
Pulmonary	0%	7.5%	• GM-CSF involved in pulmonary homeostasis • GM-/- mice develop lymphoid hyperplasia around airways and vasculature
Any	44.9%	58.3%	

Hodi et al. ASCO. 2013.

Conclusions:

1. Ipilimumab may work by decreasing co-stimulation of effector pathways or by depletion of regulatory elements

2. Ipilimumab improves survival compared to “no-cebo” gp100 vaccination and when added to DTIC

3. Low response rates, slow, durable

4. Toxicity is a concern, but can be managed

5. Combinations may be synergistic

6. Combinations may impact toxicity

Thanks!

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Call me!

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