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CTLA-4 Blockade: Indications and Clinical Management

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Disclosures

- Earle A. Chiles Research Institute accepted grants from BMS, MedImmune, Prometheus and Merck to cover costs of clinical trials.
- EACRI has sponsored research agreements with BMS and MedImmune
- I am neither employed nor do I have equity interests in any company or entity whose products/drugs will be discussed today.
- Consulting and advisory boards: Leidos, TRM Oncology, BMS, MedImmune, Cure Tech
- Speakers Bureaus: BMS, CMM Global

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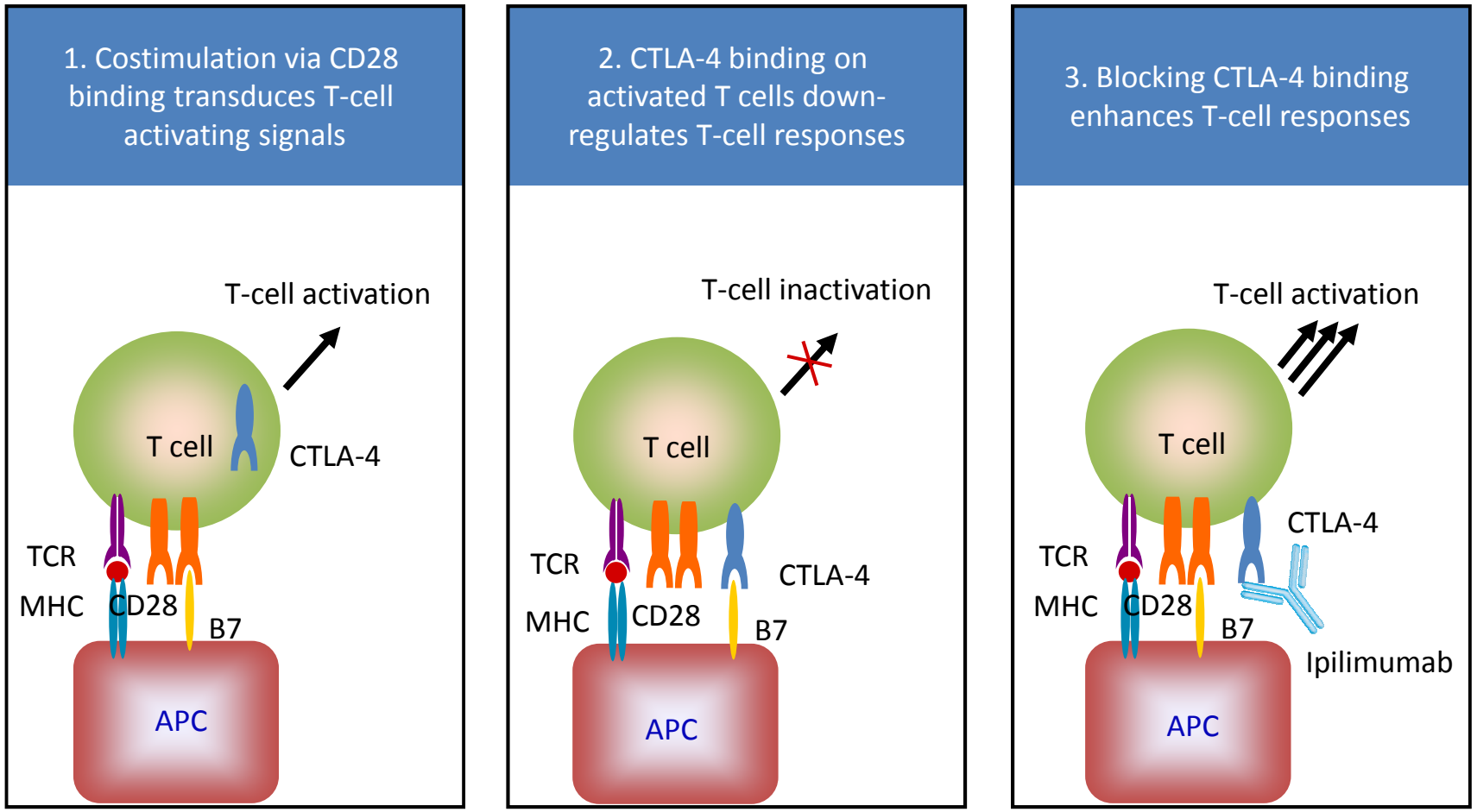
Anti-CTLA-4 : Novel Class of Immunotherapeutic Abs



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T Cell Mechanics

T-cell receptor: antigen/MHC

CD28 B7

CTLA-4 B7

Vaccine?

CTLA-4 Antagonistic mAbs

Antibody Name	Former Names	Type of Antibody	Ig Subtype	Plasma Half-life
Ipilimumab	MDX010	Fully human	IgG1	12-14 days
Tremelimumab	CP-675,206 ticilimumab	Fully human	IgG2	22 days

	IgG1	IgG2	IgG3	IgG4
Antibody-dependent Cellular Cytotoxicity	+++	±	+++	+
Complement Fixation	++	+	+++	–
Plasma Half-life	23 days	23 days	9 days	23 days

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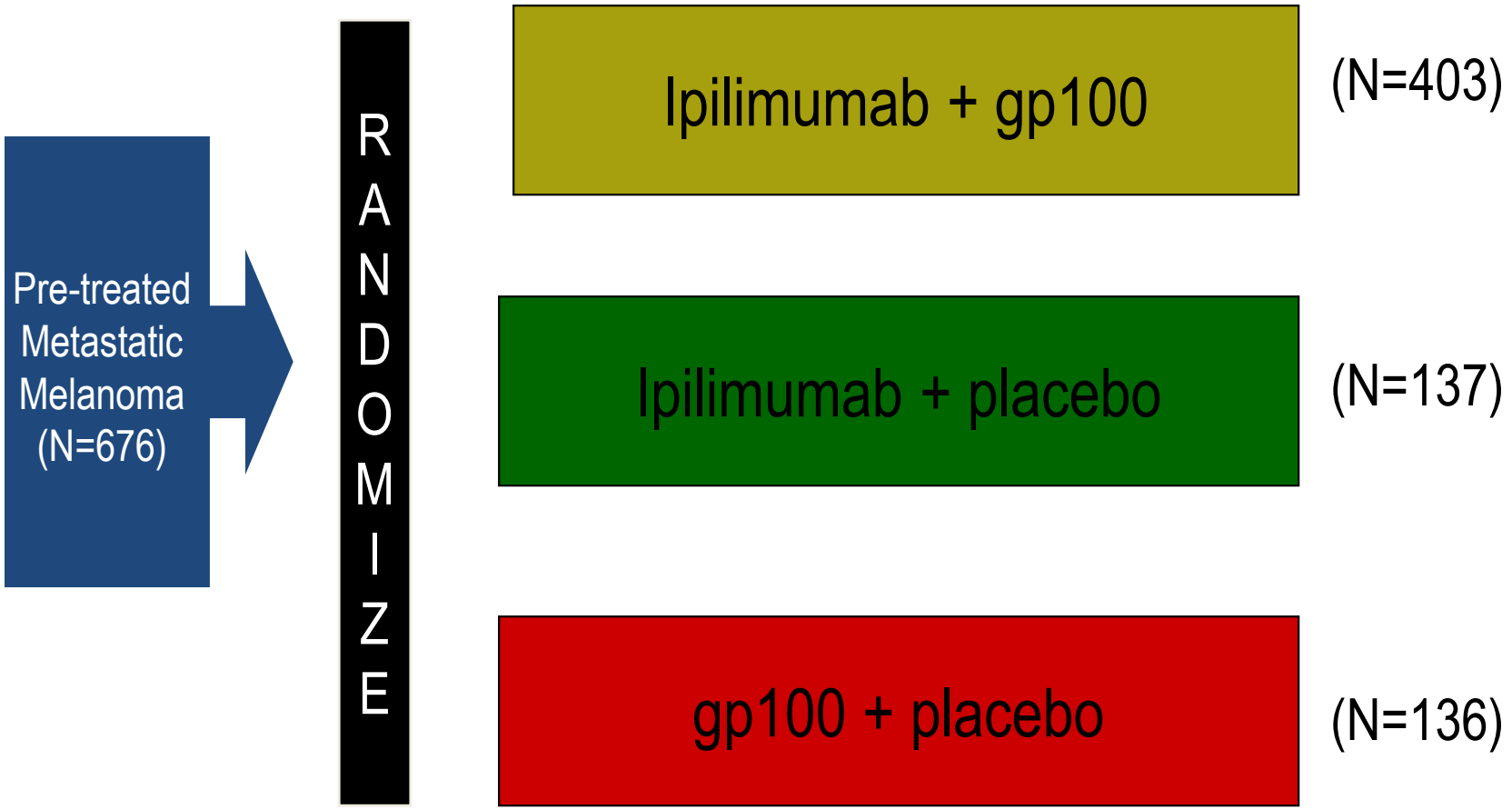
Ribas. *J Clin Oncol*. 2005; Benjamini *et al, 2000*; Paul, et al, 1999; Korman. *Adv Immunol*. 2006;90:297.

MDX010-20: Study Design



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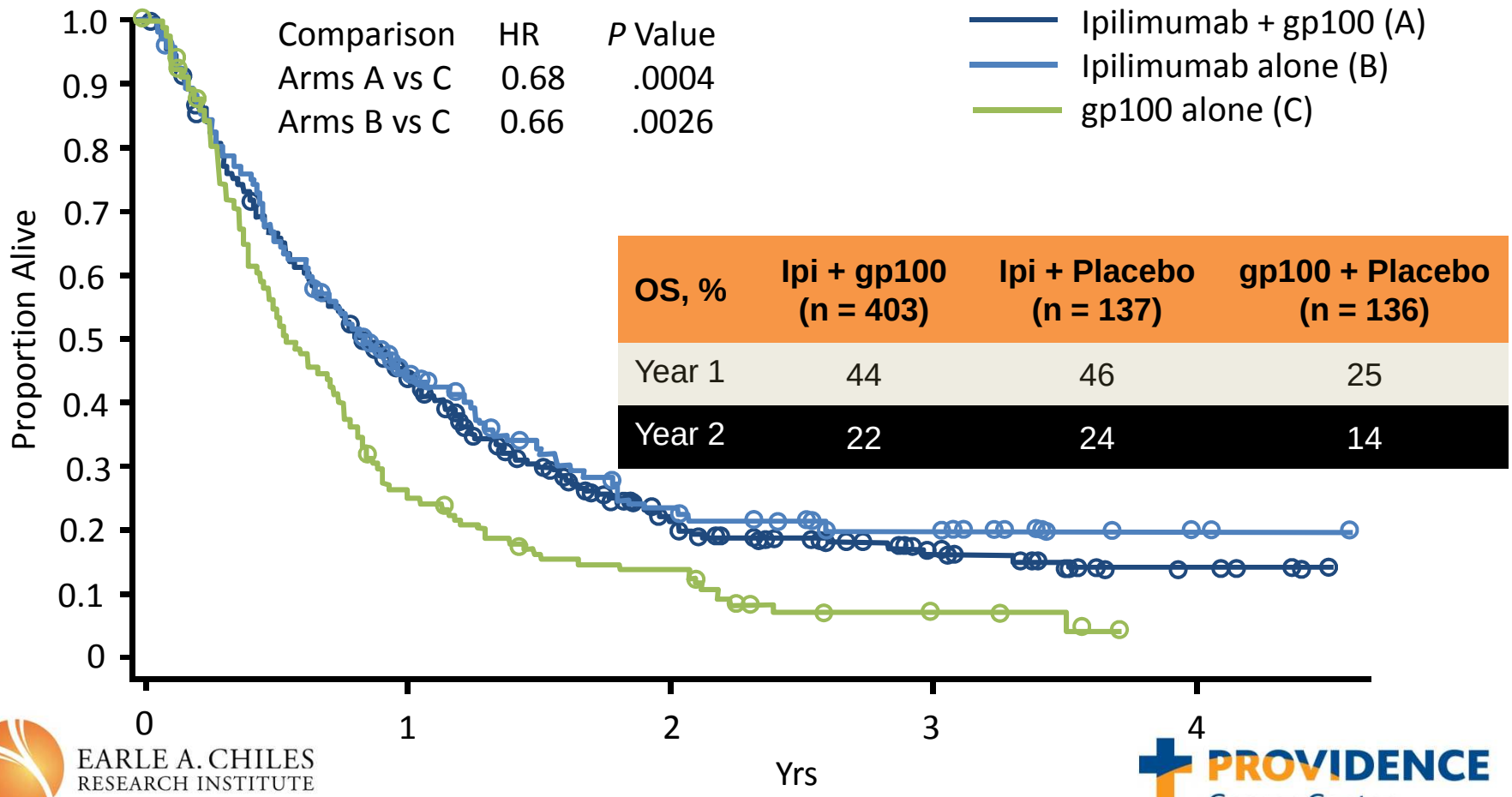
Hodi et al, NEJM;2010

Ipilimumab, gp100, or both (MDX010-20): Survival



OS, %	Ipi + gp100 (n = 403)	Ipi + Placebo (n = 137)	gp100 + Placebo (n = 136)
Year 1	44	46	25
Year 2	22	24	14

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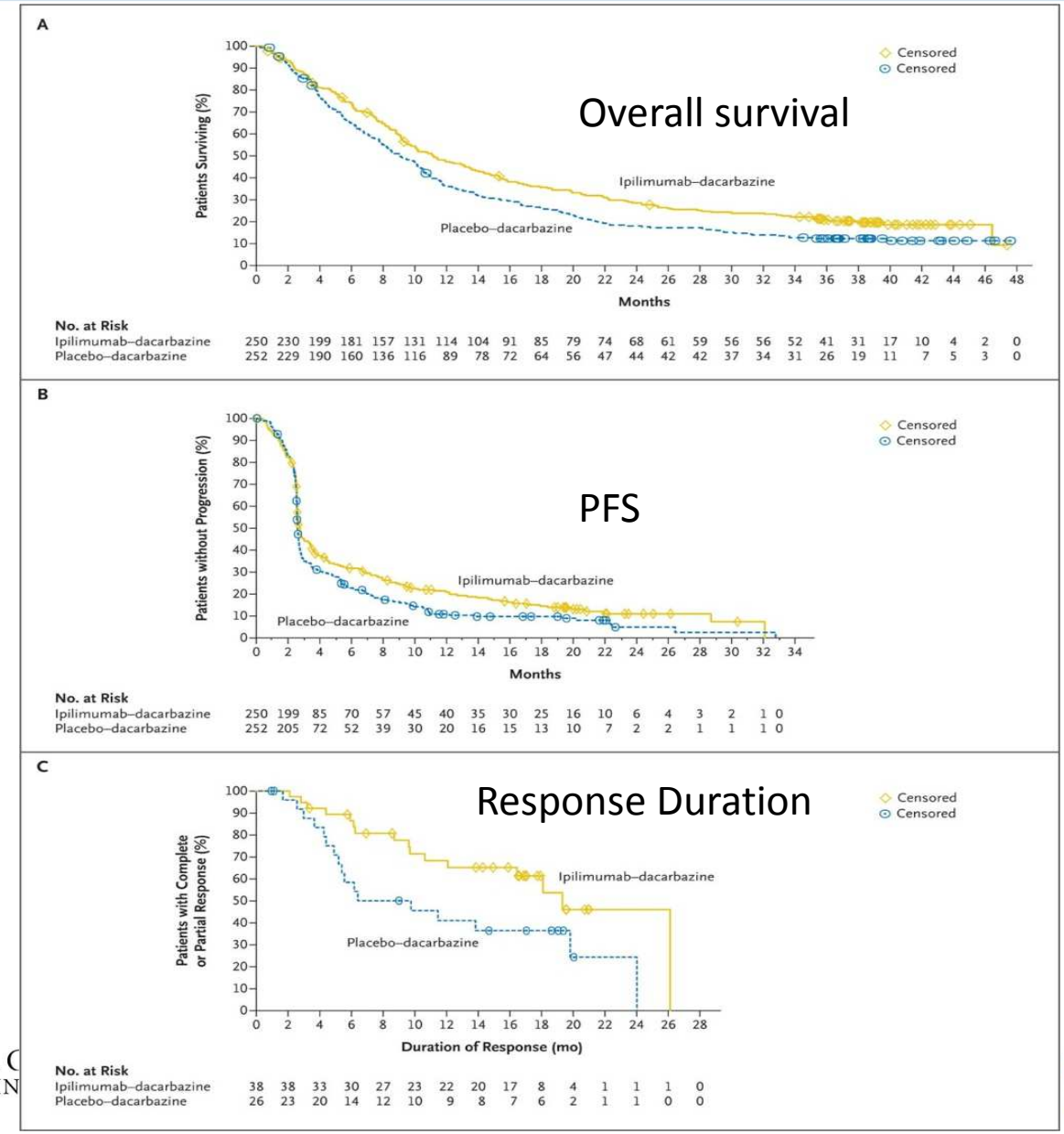
Hodi FS, et al. N Engl J Med. 2010;363:711-723.

Overall Survival, Progression-free Survival, and Duration of Response.



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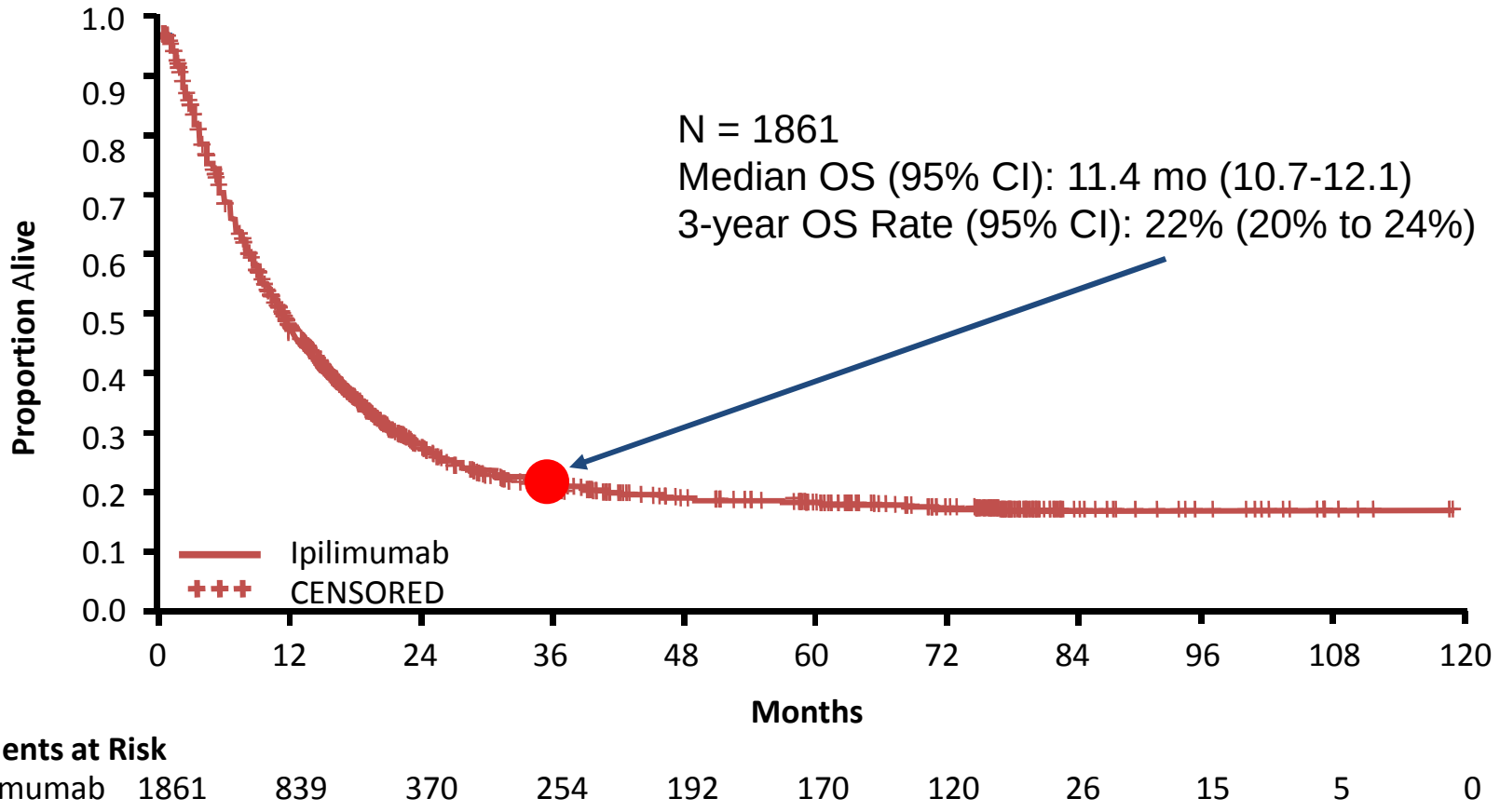
Robert C et al. N Engl J Med 2011;364:2517-2526

Ipilimumab: Pooled Survival Analysis from Phase II/III Trials



Patients at Risk

Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

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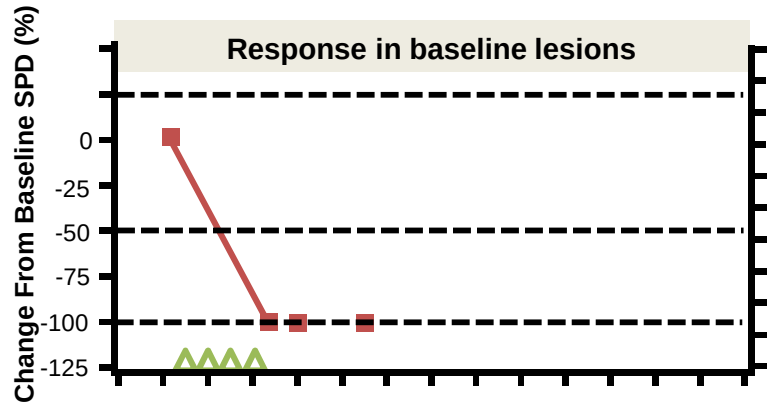
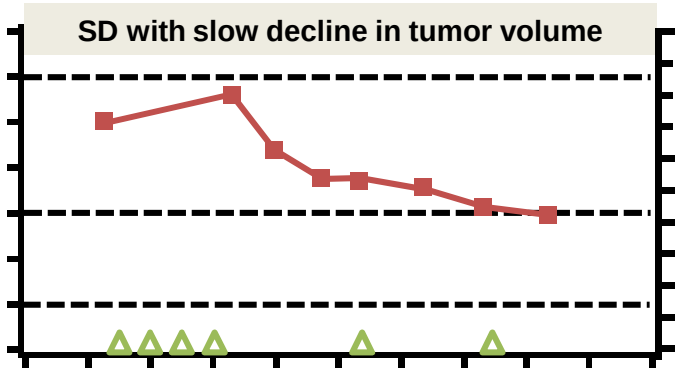
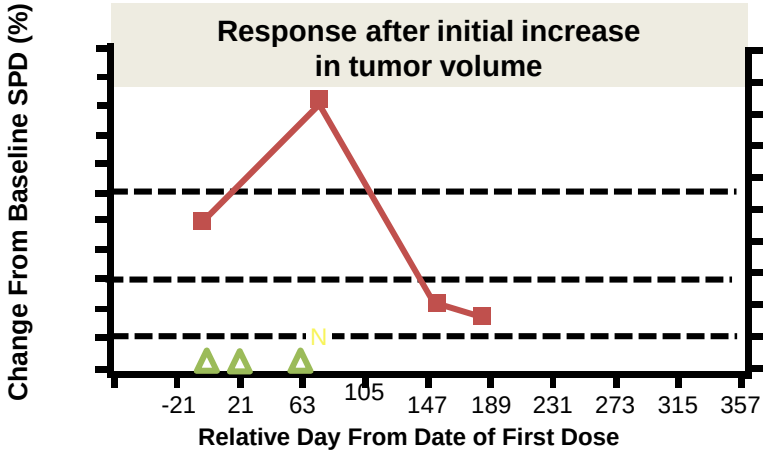
Hodi S, et al. 2013 European Cancer Congress. Abstract LBA 24.

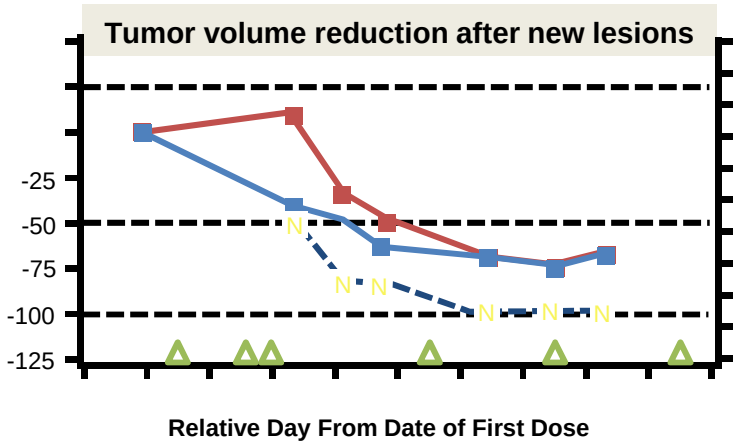
Ipilimumab Immunotherapy in Melanoma: Heterogeneous Response Patterns

- 4 distinct response patterns associated with favorable OS









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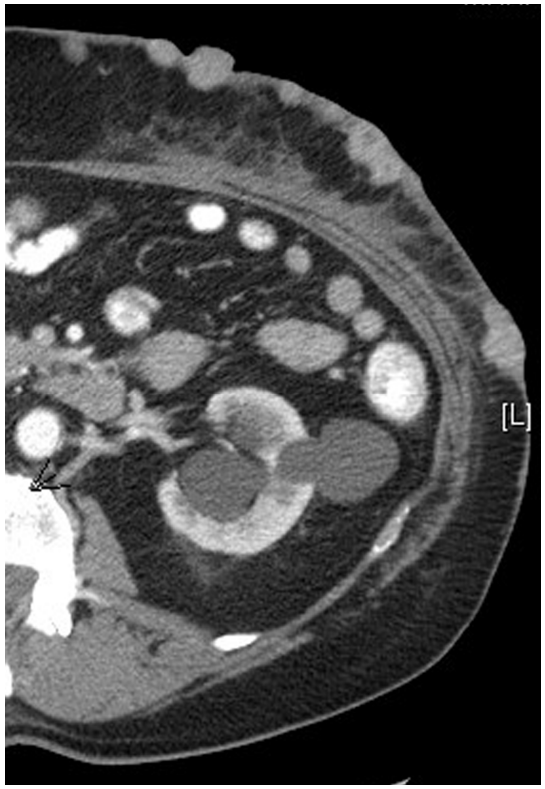
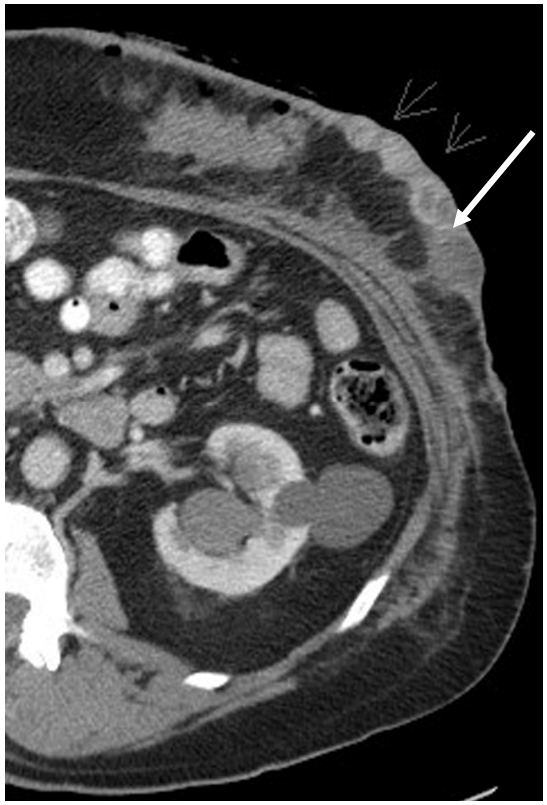
Wolchok JD, et al. Clin Cancer Res. 2009;15:7412-7420.

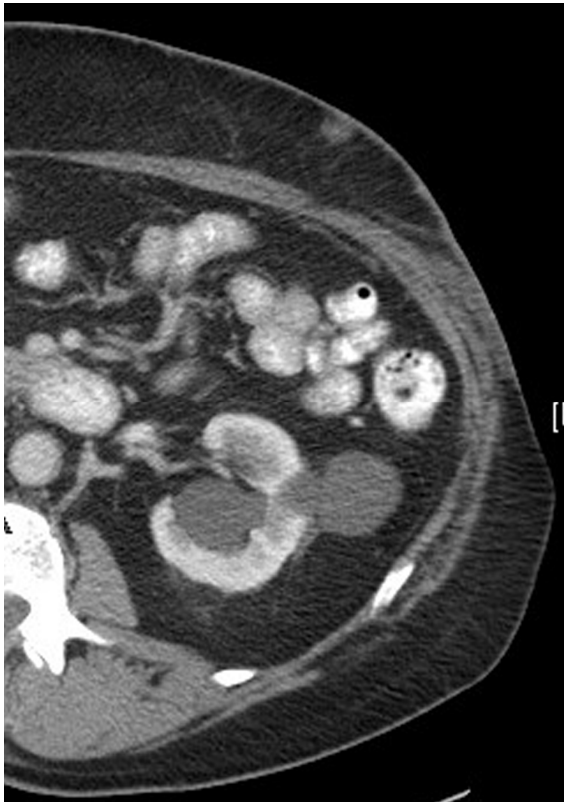
Anti-CTLA4 : Disease Can Get Worse Before It Gets Better



Baseline



3 weeks



4 months

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Images courtesy of J Wolchok, MD, PhD, MSKCC.

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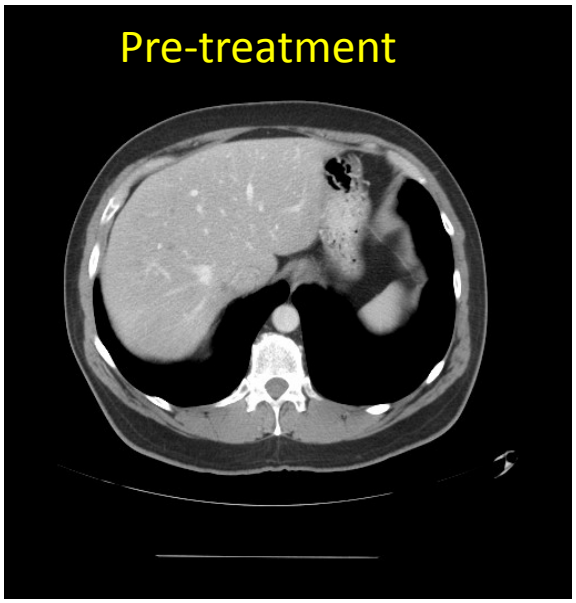
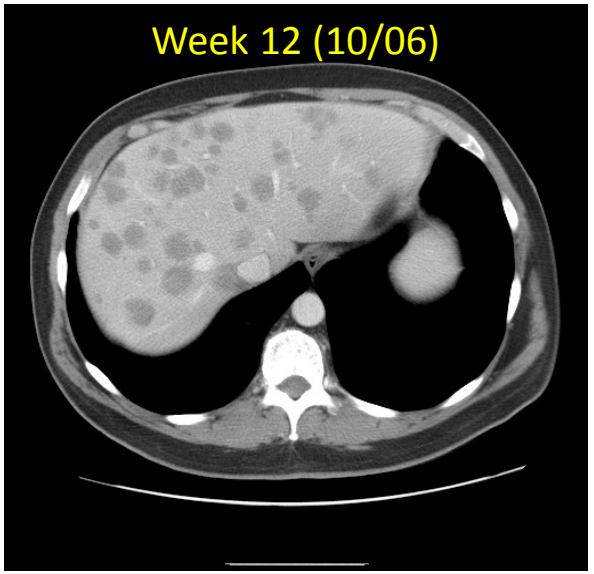
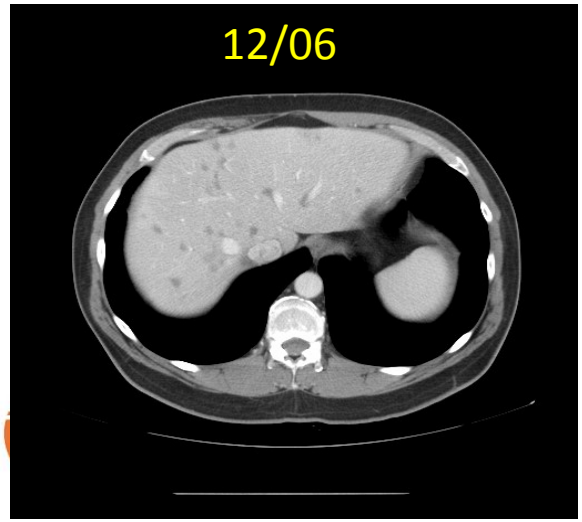
Unique Kinetics of Responses in Pts Treated with Ipilimumab



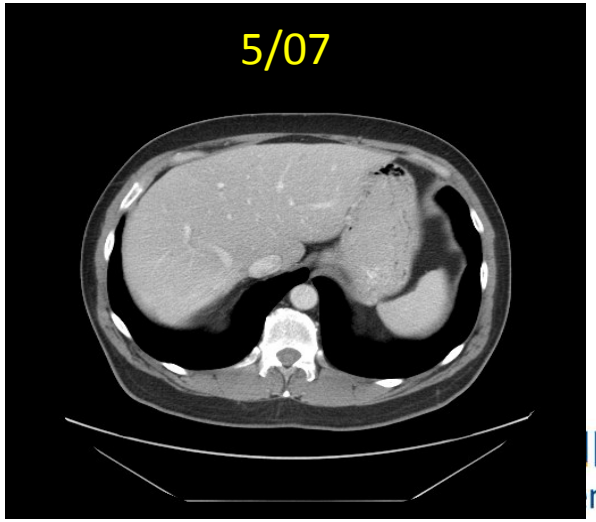
4 blinded doses ipilimumab



No drug



Four 10 mg/kg doses ipilimumab



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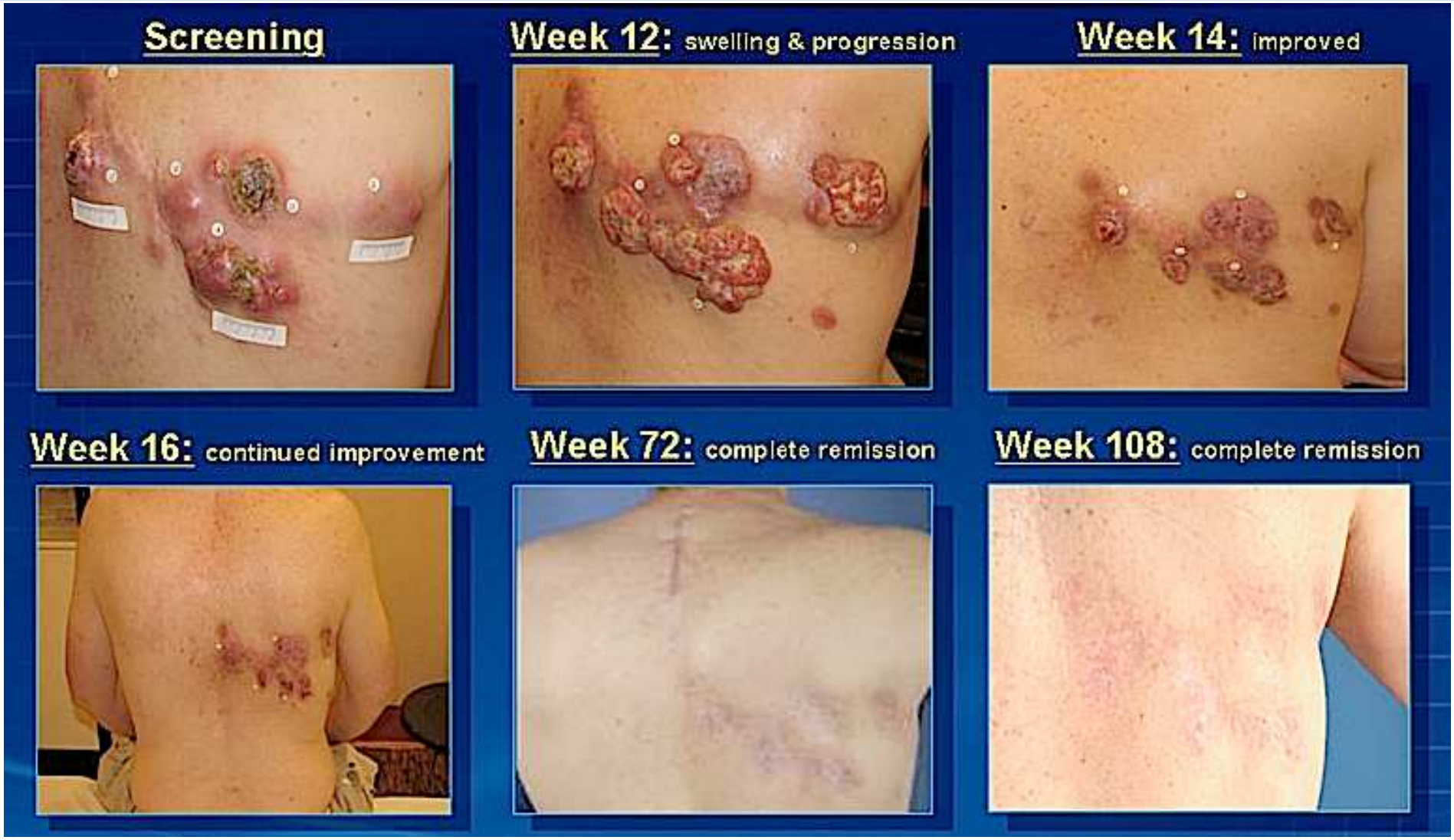
Ipilimumab Patterns of Response



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Response Criteria for Immunotherapy

RECIST 1.1[1]			
CR	PR	SD	PD
Disappearance of all target lesions, reduction in short-axis diameter of pathology LN to < 10 mm	% decrease in sum of longest diameters of target lesions	Neither PR nor PD	absolute increase) in sum of longest diameters, in comparison with smallest sum of longest diameters recorded during treatment
Immune-Related Response Criteria[2]			
irCR	irPR	irSD	irPD
Disappearance of all lesions on 2 consecutive observations ≥ 4 weeks apart	≥ 50% decrease in tumor burden compared with baseline in 2 observations ≥ 4 weeks apart	50% decrease in tumor burden compared with baseline not established, nor 25% increase vs nadir	≥ 25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations ≥ 4 weeks apart

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1. Eisenhauer EA, et al. Eur J Cancer. 2009;45:228-247. 2. Wolchok JD, et al. Clin Cancer Res. 2009;15:7412-7420.

Potential biomarkers to predict outcome after ipilimumab

	Authors' group	Country	Biomarkers				
1	Wolchok	US	ALC				
2	Miao	Italy	ALC	LDH			
3	Neyns	Belgium	ALC	LDH	CRP	WHO-PS	
4	Robert	France	ALC	LDH			
5	Blank	Netherlands	ALC	LDH	ESR	WHO-PS	S100
6	Ascierto	Italy	ALC	LDH	CRP		
7	Hodi	US					VEGF
8	Zitvogel	France					sCD25

Select Immune-related Adverse Reactions

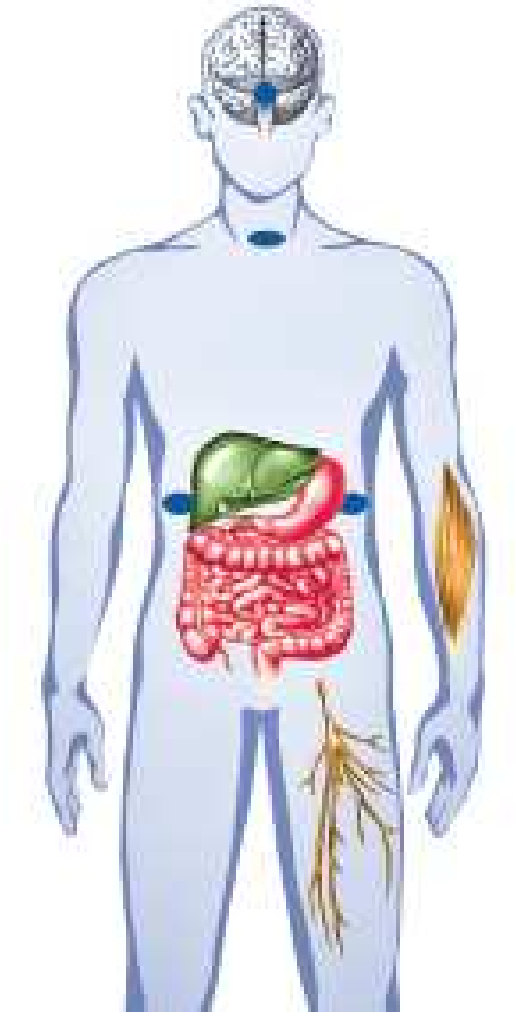
hypophysitis

thyroiditis

adrenal insufficiency

enterocolitis

dermatitis



pneumonitis

hepatitis

pancreatitis

motor & sensory neuropathies

arthritis

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Ipilimumab adverse reaction management guide.

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Ipilimumab, gp100, or Both (MDX010-20): irAEs

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. N Engl J Med. 2010 Aug 19;363(8):711-23

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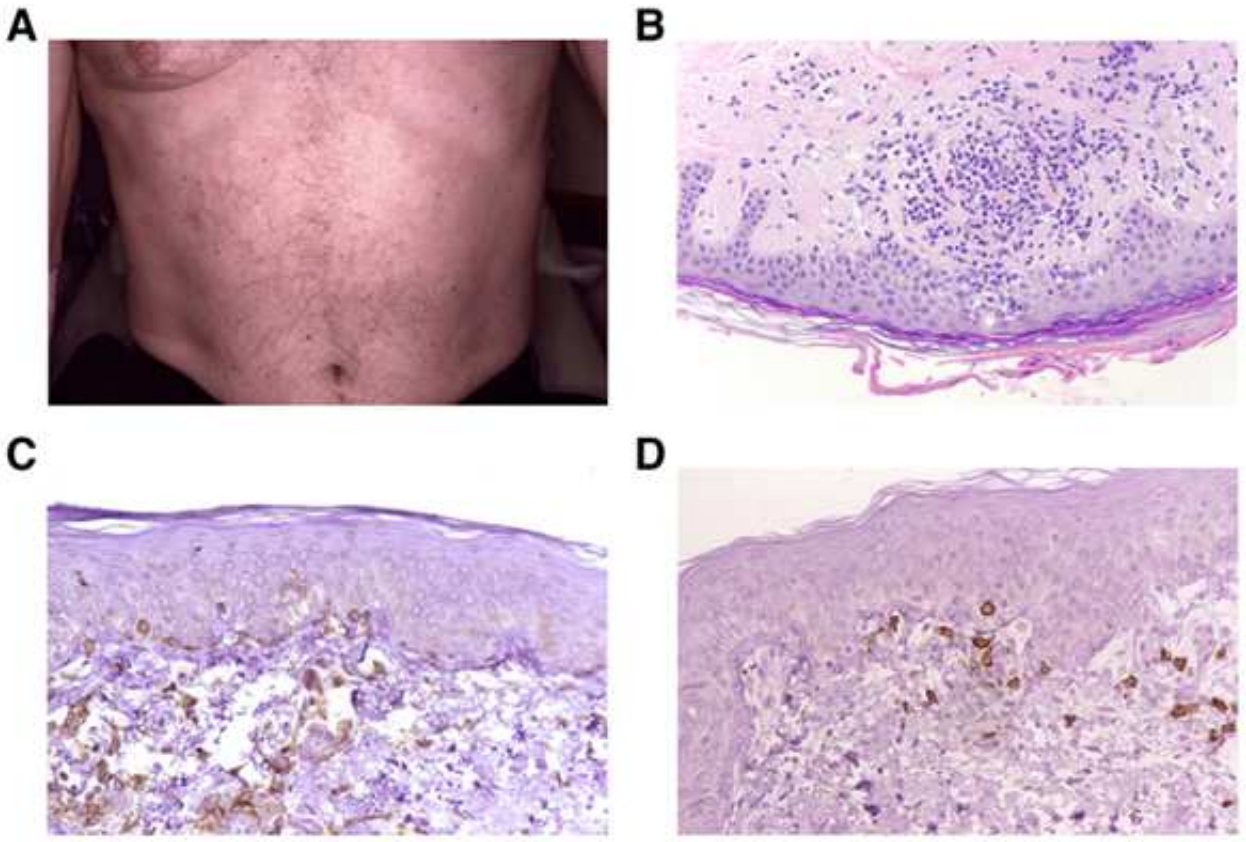
Anti-CTLA-4-Associated Rash

Protocol MDX010CTLA4-02 (Melanoma): MDX-010 3 mg/kg single dose



MDX-CTLA4 stimulated melanocyte immune recognition.

(A) Reticular erythematous rash.

(B) Peri-vascular lymphocyte infiltrate extending into epidermis.

(C) CD4+ T cells apposed to dying melanocytes.

(D) CD8+ T cells apposed to dying melanocytes.

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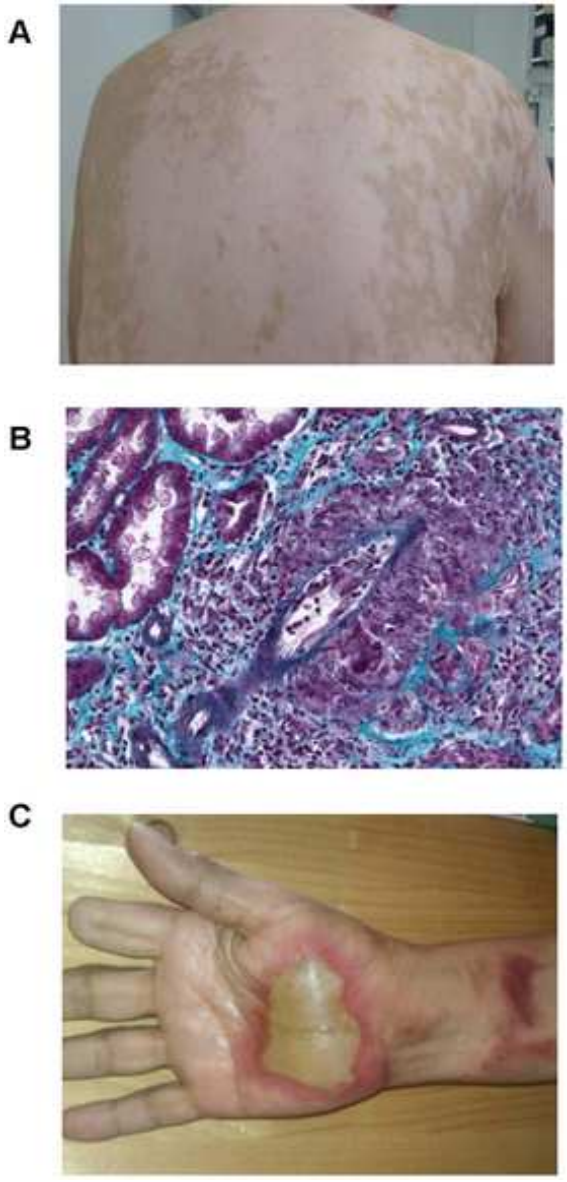
Hodi *et al.* PNAS. 2003 Apr;100(8):4712-4717

Ipilimumab-induced skin reactions and nephritis



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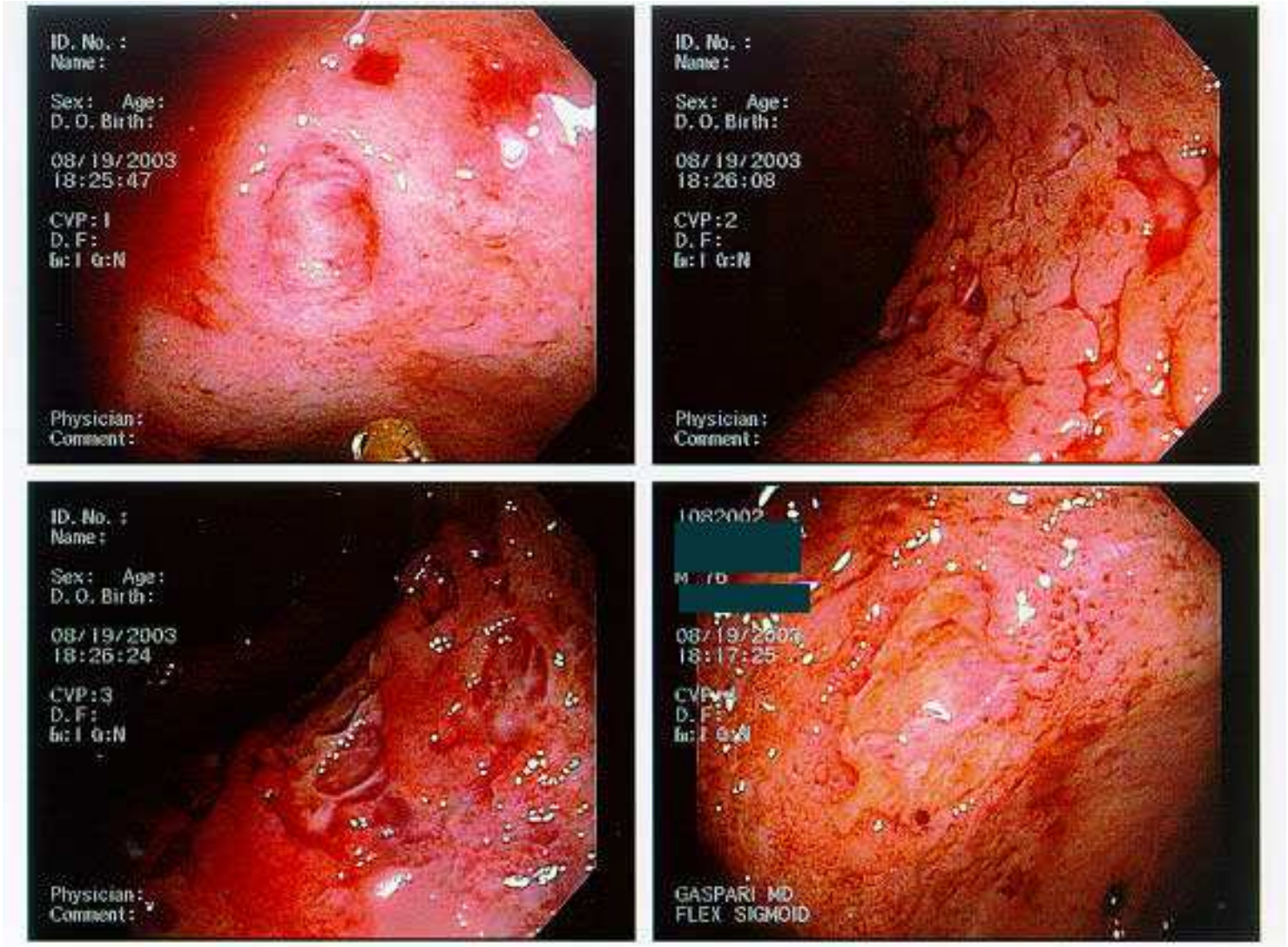
Voskens CJ, Goldinger SM, Loquai C, Robert C, et al. (2013) PLoS ONE 8(1): e53745.

Endoscopic Appearance of Colitis



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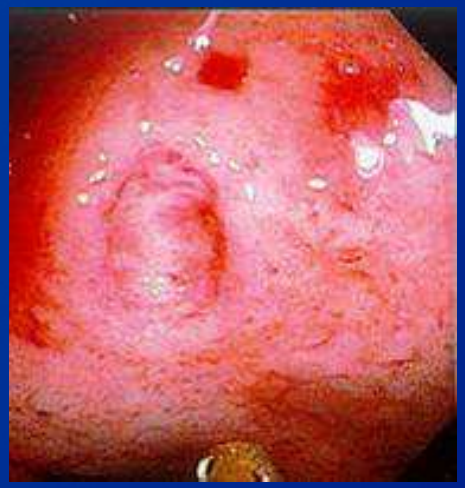
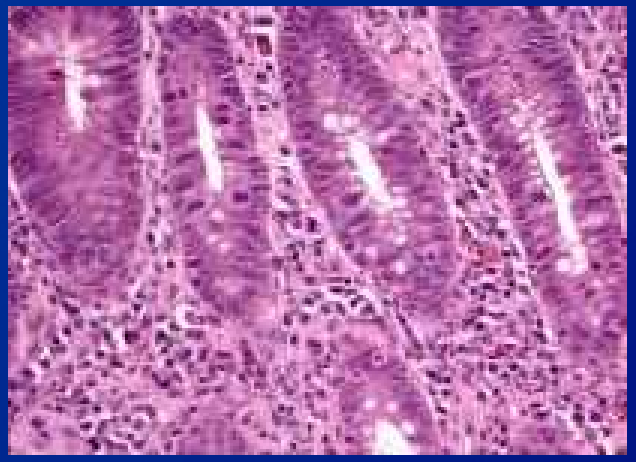
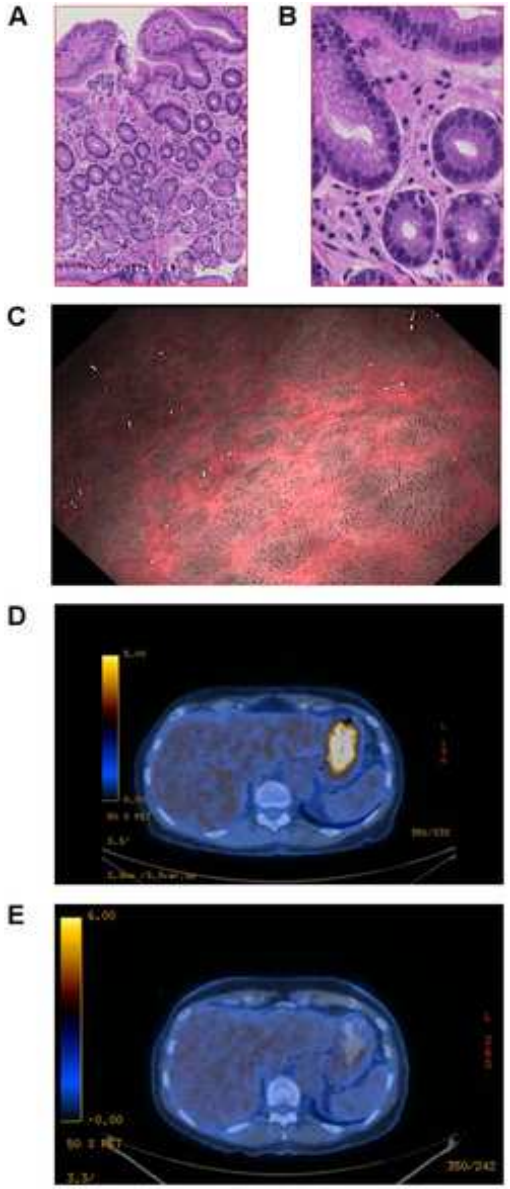
Ipilimumab-Induced Colitis Resembles IBD and Usually Resolves Without Sequela With Appropriate Therapy





Robinson et al, 2004; Phan et al, 2003.

Ipilimumab-induced ischemic gastritis



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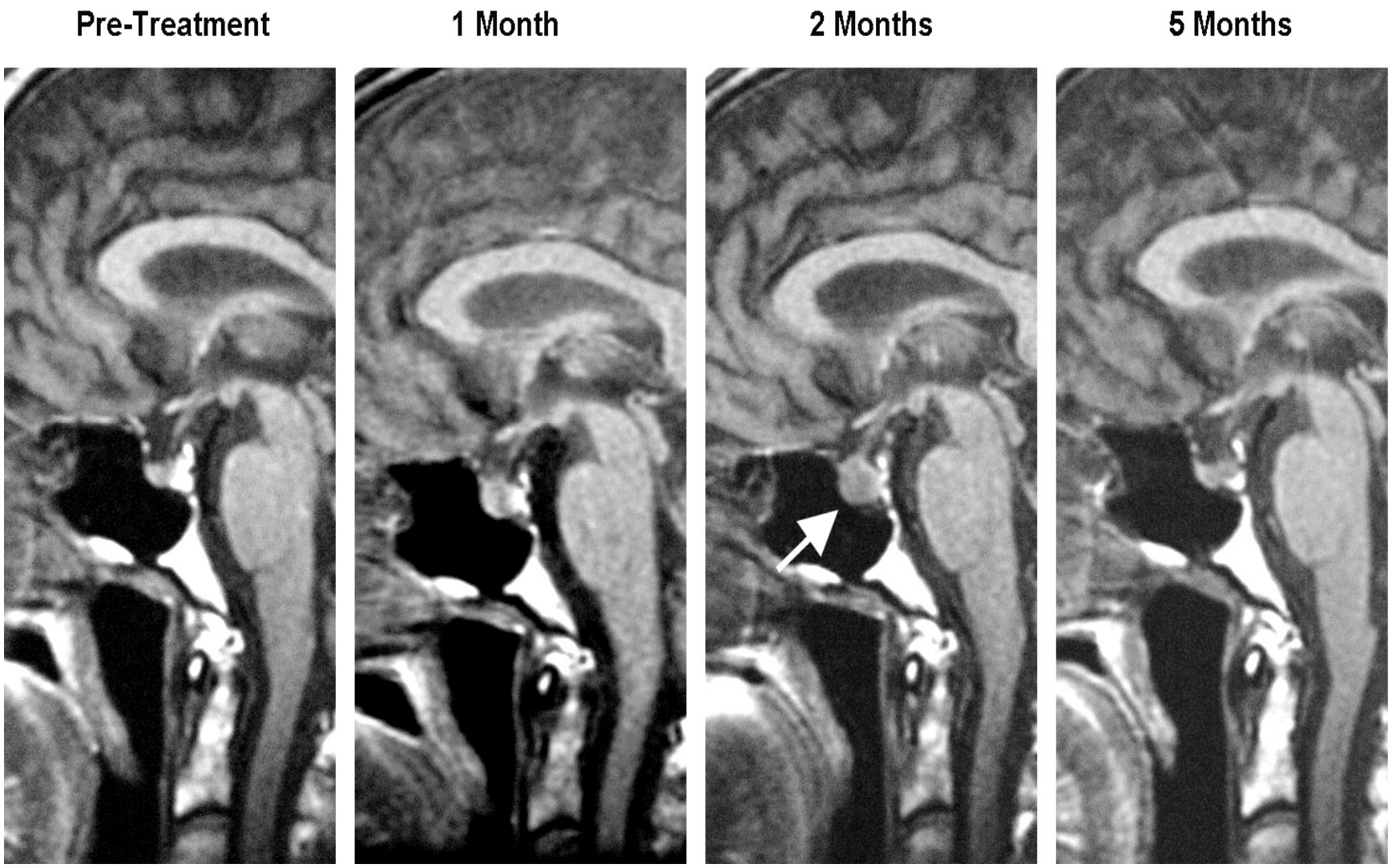
Voskens CJ, Goldinger SM, Loquai C, Robert C, et al. (2013) PLoS ONE 8(1): e53745.

Pituitary Enlargement Following Anti-CTLA-4



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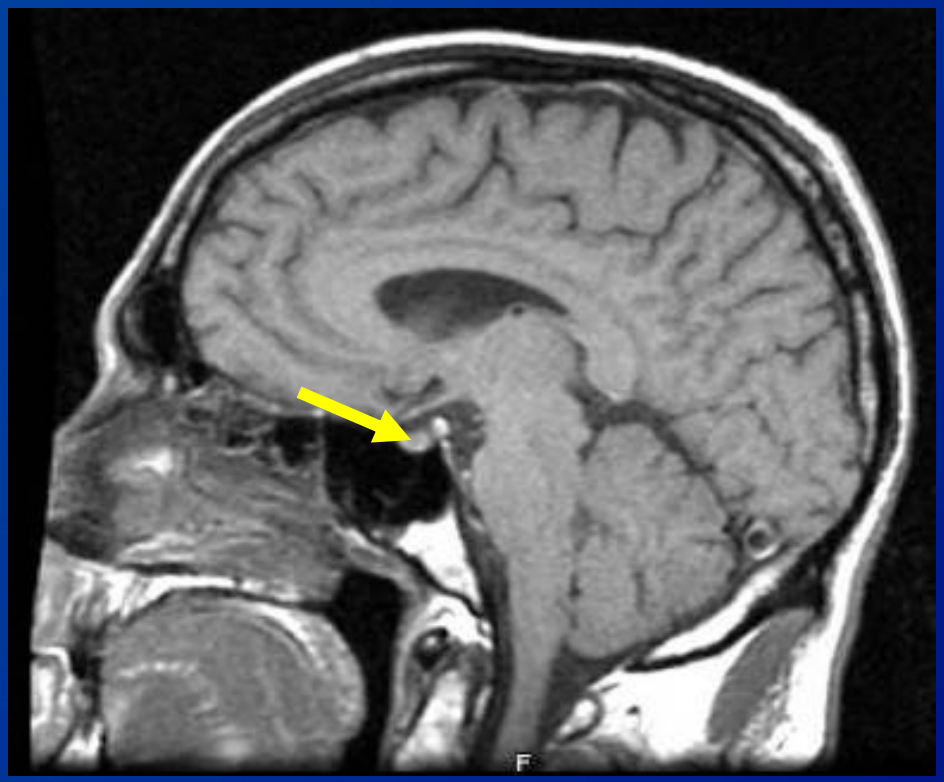
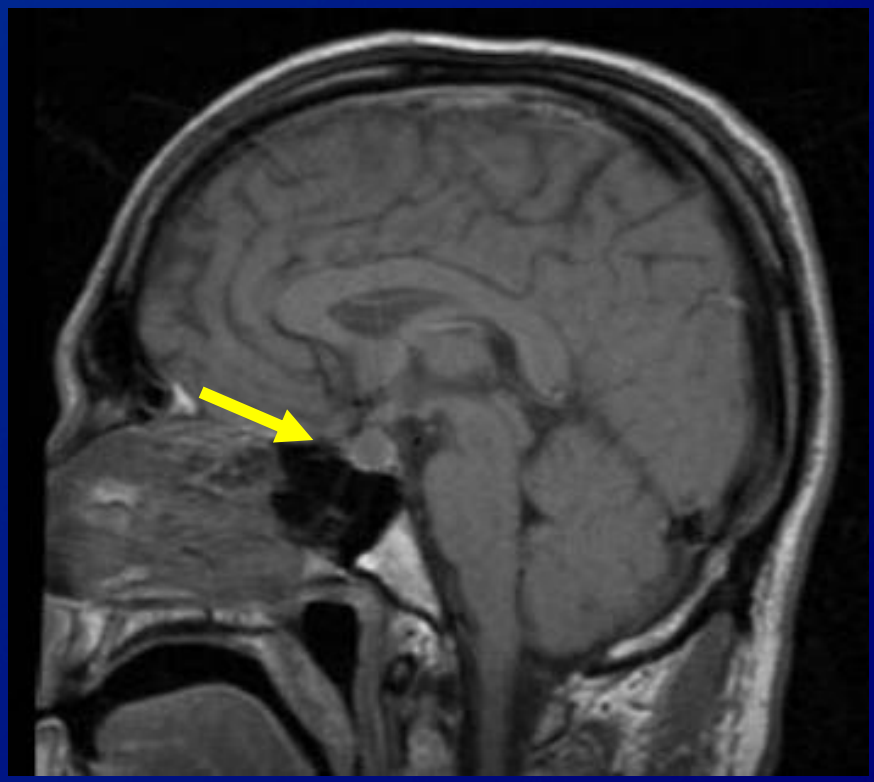
Ipilimumab-Related Pituitary Swelling and Dysfunction



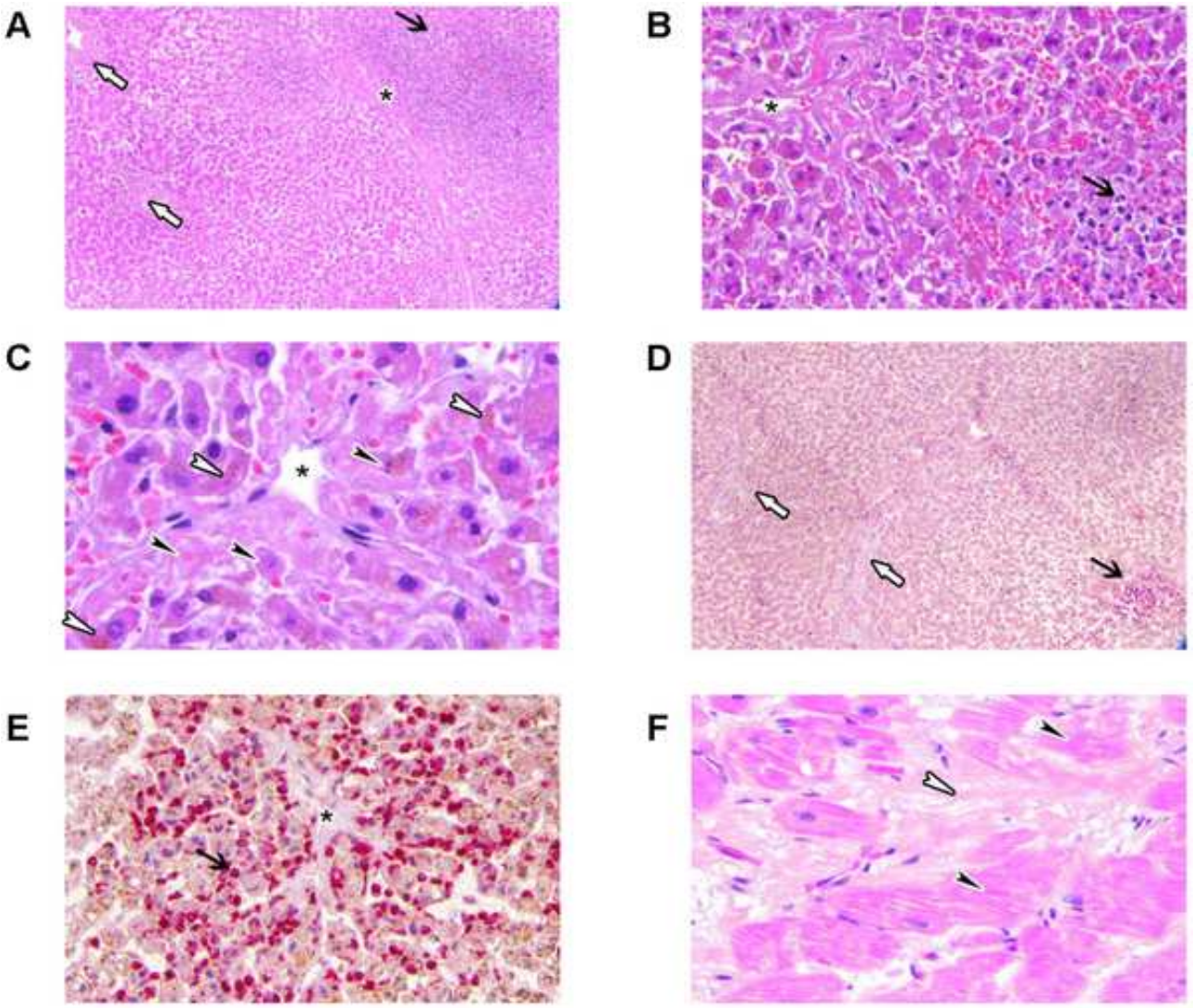
6/30/04 Baseline (4.5 mm)



12/3/04 Headache/fatigue after 5 doses (10.8 mm)

Blansfield et al, 2005.

Ipilimumab-induced myocardial fibrosis in conjunction with hepatotoxicity



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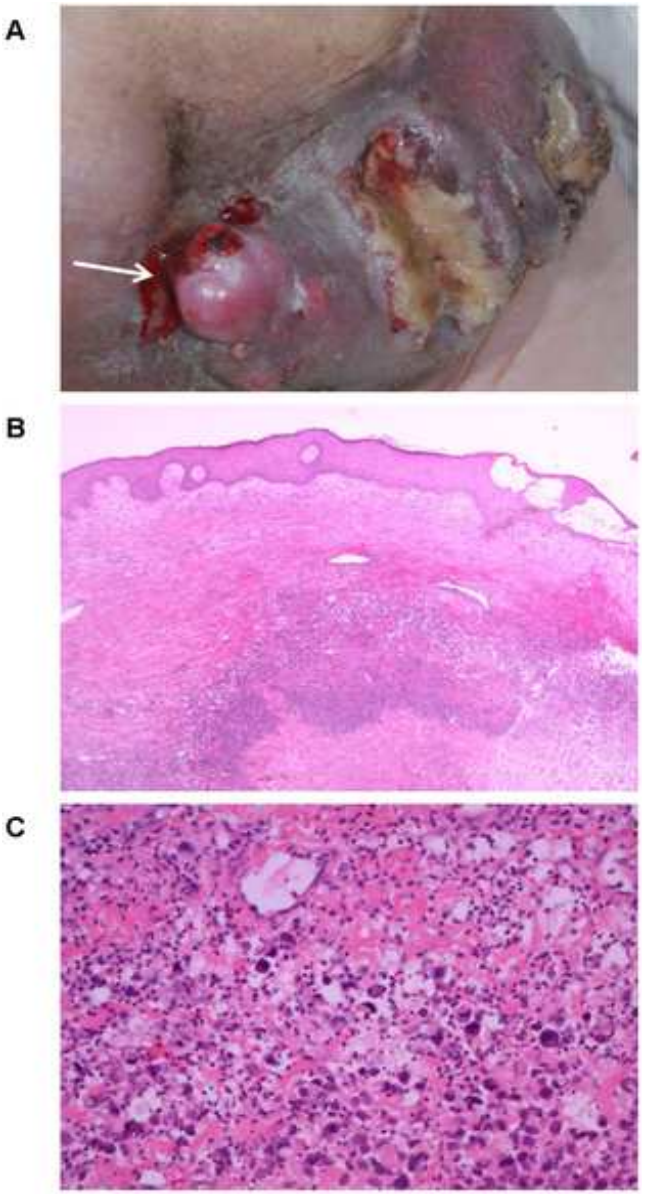
Voskens CJ, Goldinger SM, Loquai C, Robert C, et al. (2013) PLoS ONE 8(1): e53745.

Ipilimumab-induced tumor mass liquefication



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Voskens CJ, Goldinger SM, Loquai C, Robert C, et al. (2013) PLoS ONE 8(1): e53745.

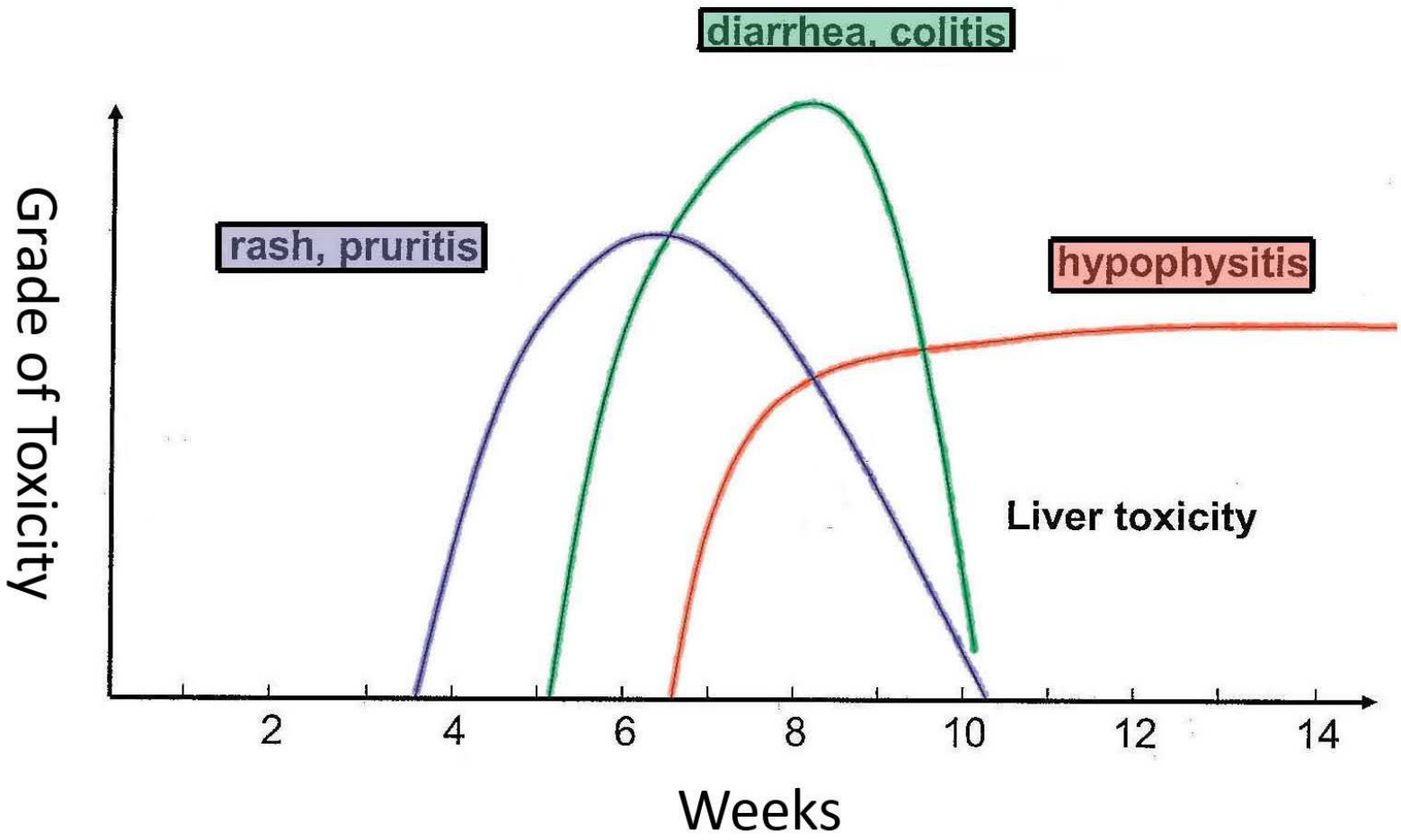
Less Common Immune-related Adverse Events

- Hematologic (hemolytic anemia, thrombocytopenia)
- Cardiovascular (myocarditis, pericarditis, vasculitis)
- Ocular (blepharitis, conjunctivitis, iritis, scleritis, uveitis)
- Renal (nephritis)

Ipilimumab: neurologic complications

- Inflammatory myopathy
- Aseptic meningitis
- Posterior reversible encephalopathy syndrome
- Guillain-Barre syndrome
- Myasthenia gravis-type syndrome
- Sensorimotor neuropathy
- Inflammatory enteric neuropathy
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Transverse myelitis

Ipilimumab: (irAEs)



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Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.

Ipilimumab: Managing Immune-Related Adverse Events

System	Symptoms	Management
GI tract	Diarrhea Abdominal pain Dark, bloody stools	Moderate enterocolitis: hold ipilimumab, administer antidiarrheal. Persistent diarrhea (> 1 wk): systemic corticosteroids. 7+ stools/day: start methylprednisone, permanently discontinue ipilimumab. Consider infliximab for corticosteroid-refractory patients
Skin	Rash (± itching) Blistering/peeling Oral sores	Moderate/nonlocalized rash: hold ipilimumab, start topical or systemic corticosteroids. Severe dermatitis: permanently discontinue ipilimumab, start corticosteroids
Liver	Jaundice Nausea/vomiting	Assess ALT/AST, bilirubin, and thyroid function before each dose and as necessary. Hold ipilimumab if ALT/AST > 2.5 x but ≤ 5 x ULN; permanently discontinue if AST/ALT > 5 x ULN or bilirubin > 3 x ULN. The immunosuppressant mycophenolate can be used for hepatotoxicity in corticosteroid-refractory patients
CNS	Weakness in extremities Numbness/tingling Sensory changes	Moderate neuropathy: hold ipilimumab. New or worsening neuropathy: permanently discontinue ipilimumab. Consider corticosteroids
Endocrine	Headaches Fatigue Behavior/mood changes Menstruation changes Dizziness/light-headedness	Moderate endocrinopathy: hold ipilimumab, start corticosteroids. Endocrine abnormalities can be difficult to detect, due to nonspecific symptoms. Consider having an endocrinologist follow the patient
Eyes	Vision problems Irritation	Monitor for redness suggesting uveitis, treat with topical steroidal eye drops

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Ipilimumab adverse reaction management guide.

General Principles of irAE Management

Generally based on severity of symptoms

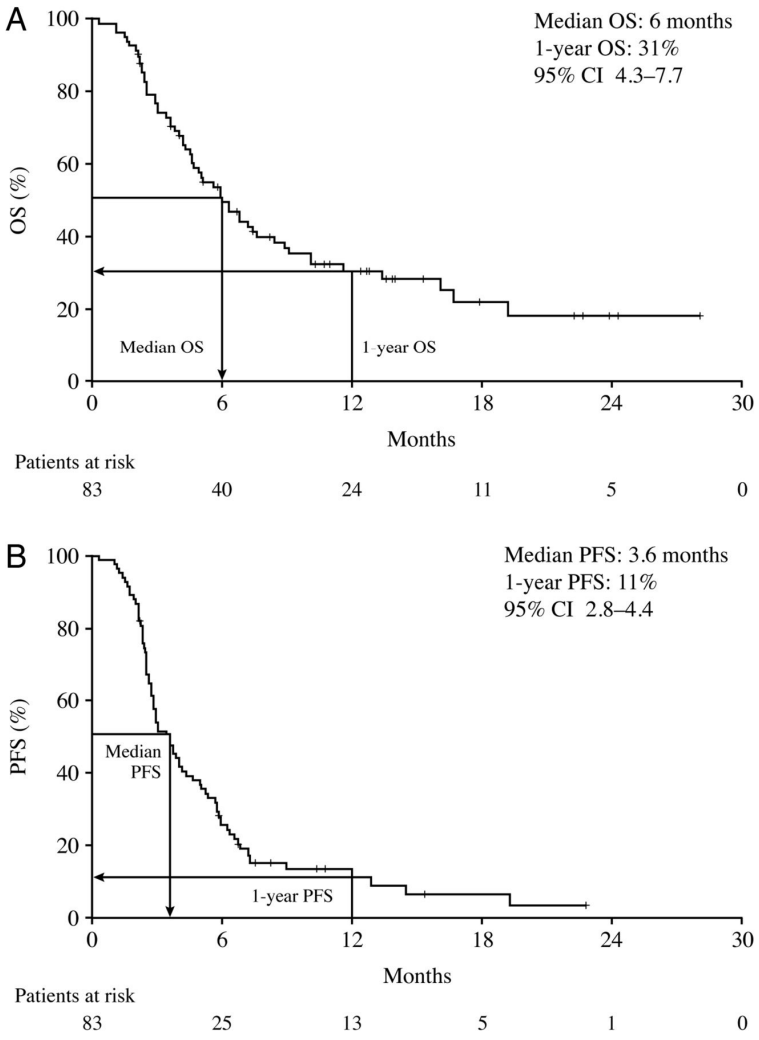
- Grade 1: supportive care; +/- withhold drug
- Grade 2: withhold drug, consider re-dose if toxicity resolves to ≤ Grade 1. Low dose corticosteroids (prednisone 0.5mg/kg/day or equivalent) if symptoms do not resolve within a week
- Grade 3-4: discontinue drug; high dose corticosteroids (prednisone 1-2mg/kg/day or equivalent) tapered over ≥ 1 month once toxicity resolves to ≤ Grade 1.

Ipilimumab in special populations

- Uveal melanoma
- Mucosal melanomas
- Patients with brain metastases

Uveal melanoma: (A) Overall and (B) progression-free survival

N = 83
RR = 5%
DCR (CR+PR+SD) = 34%



Maio M et al. Ann Oncol 2013;24:2911-2915

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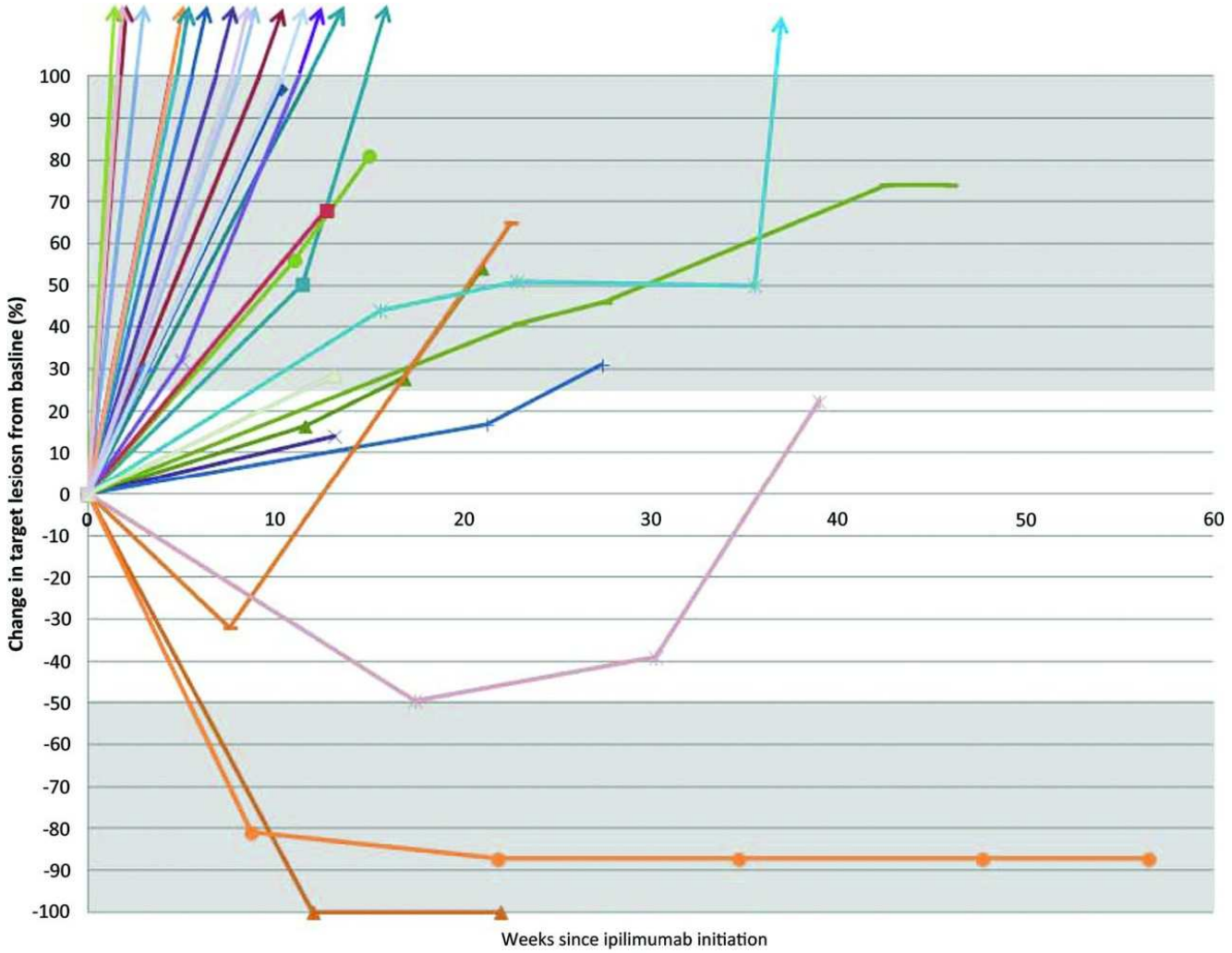
Mucosal Melanoma: changes in tumor burden after ipilimumab

N=33
1CR
1PR
6SD



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Postow M A et al. The Oncologist 2013;18:726-732

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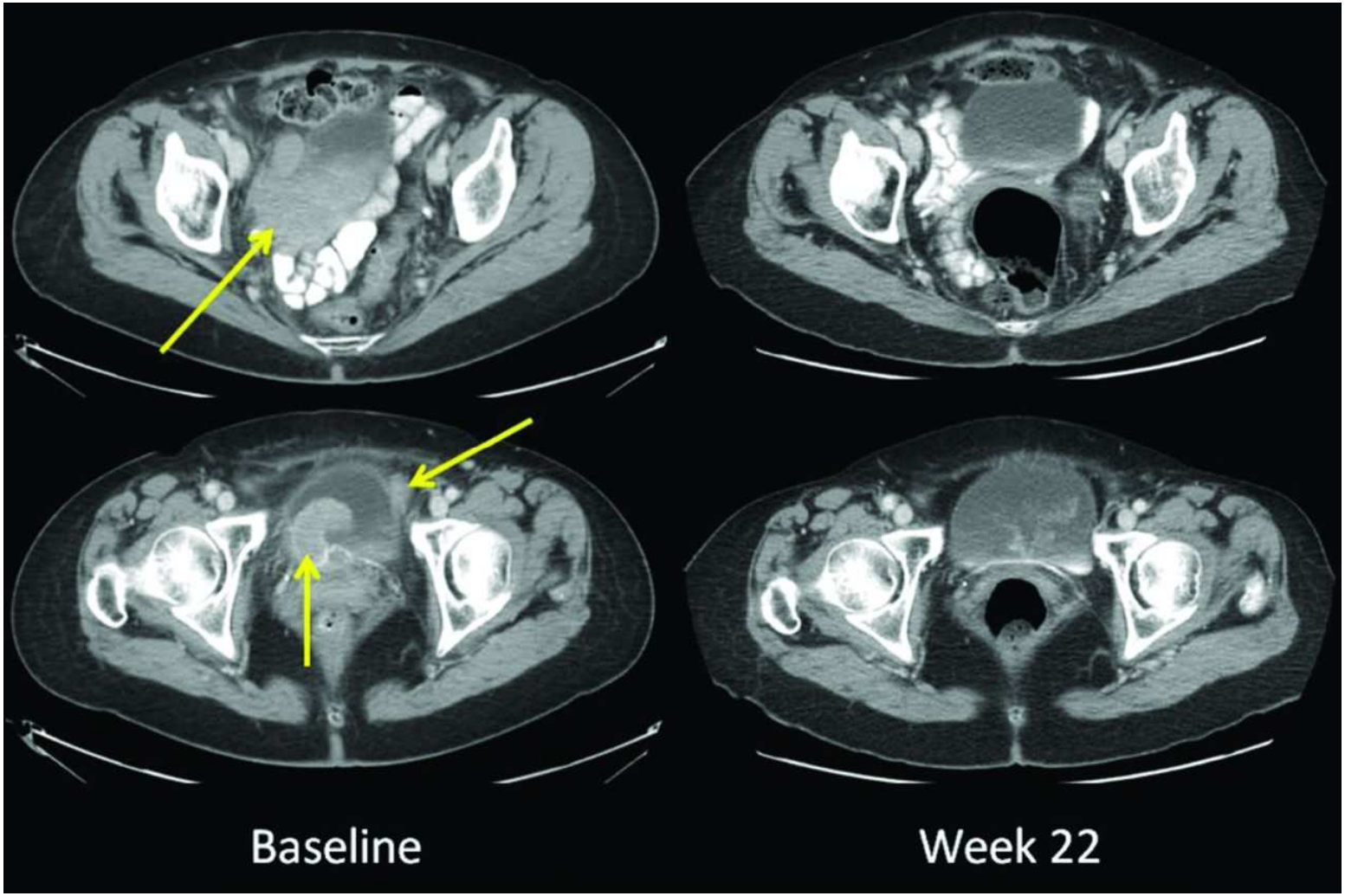
Mucosal melanoma patient who achieved a CR after ipilimumab



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Postow M A et al. The Oncologist 2013;18:726-732

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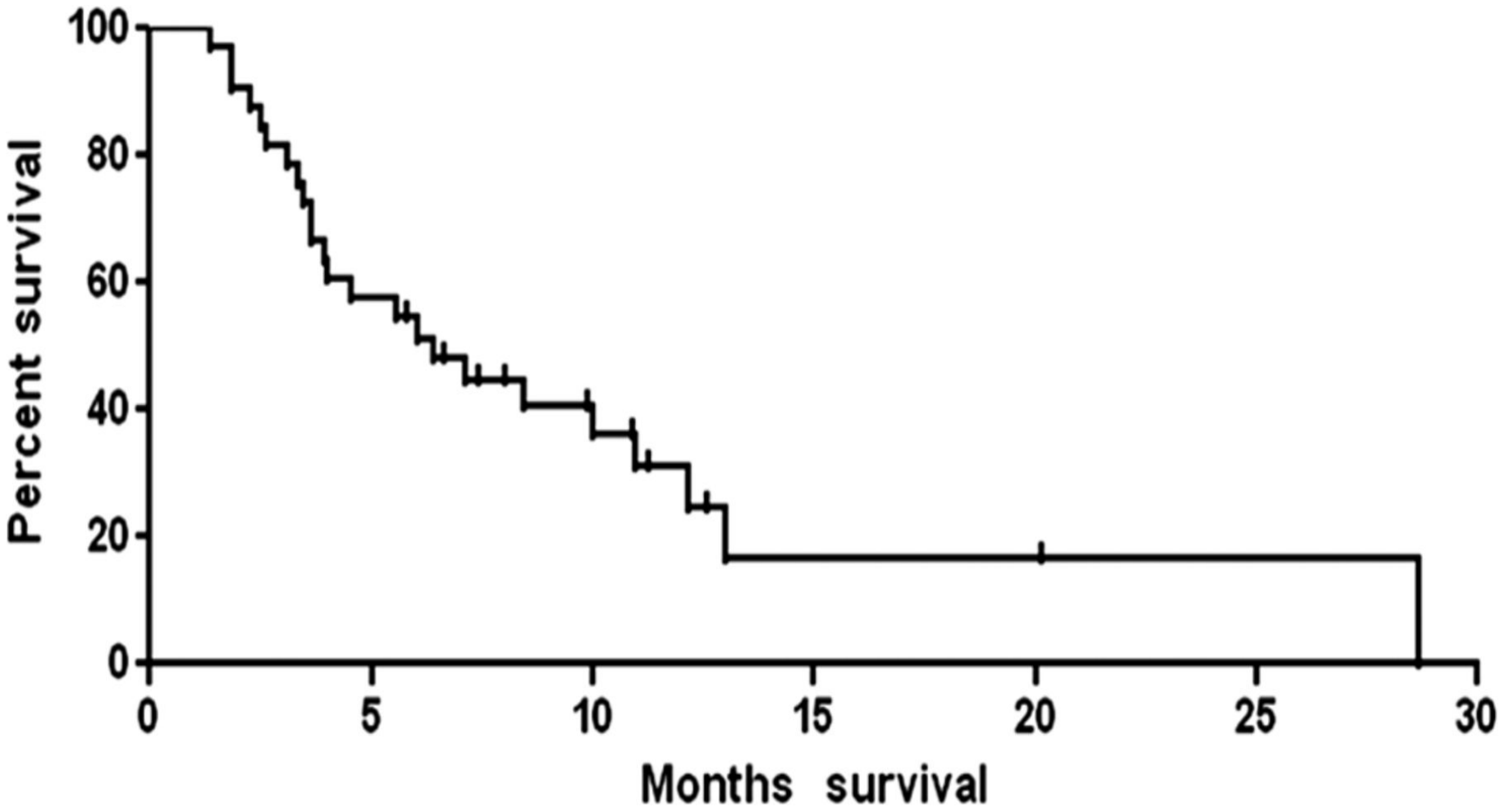
Mucosal melanoma : Overall survival (n = 33)



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Postow M A et al. The Oncologist 2013;18:726-732

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Treatment of Brain Metastases with Ipilimumab

	Cohort A (*n* = 51)		Cohort B (*n* = 21)	
	mWHO	irRC	mWHO	irRC
Global				
CR	0	0	0	0
PR	5 (10%)	5 (10%)	1 (5%)	1 (5%)
SD	4 (8%)	8 (16%)	0	1 (5%)
PD	40 (78%)	36 (71%)	20 (95%)	19 (90%)
Unknown	2 (4%)	2 (4%)	0	0
CNS				
CR	0	0	1 (5%)	1 (5%)
PR	8 (16%)	8 (16%)	0	0
SD	4 (8%)	5 (10%)	1 (5%)	1 (5%)
PD	39 (76)%)	38 (75%)	19 (90%)	19 (90%)
Unknown	0	0	0	0
Non-CNS				
CR	0	0	0	0
PR	7 (14%)	7 (14%)	1 (5%)	1 (5%)
SD	7 (14%)	10 (20%)	0	1 (5%)
PD	35 (69%)	32 (63%)	20 (95%)	19 (90%)
Unknown	2 (4%)	2 (4%)	0	0

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Margolin K, et al. Lancet Oncol. 2012;13(5):459-465.

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Ipilimumab in the adjuvant setting

Ipilimumab Versus Placebo After Complete Resection of Stage III Melanoma: Initial Efficacy and Safety Results from the EORTC 18071 Phase III Trial

Eggermont AM,[1] Chiarion-Sileni V,[2] Grob JJ,[3] Dummer R,[4] Wolchok JD,[5] Schmidt H,[6] Hamid O,[7] Robert C,[1] Ascierto PA,[8] Richards JM,[9] Lebbé C,[10] Ferraresi V,[11] Smylie M,[12] Weber JS,[13] Maio M,[14] Konto C,[15] Karra Gurunath R,[16] de Pril V,[17] Suciu S,[16] Testori A[18]

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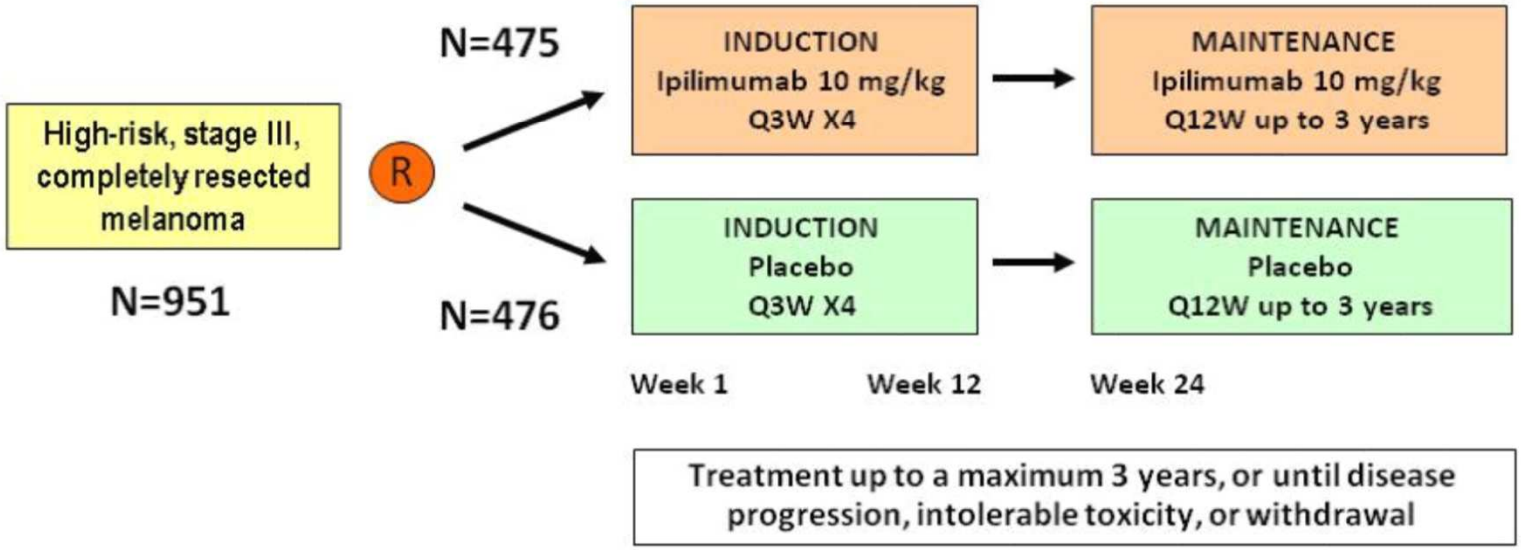
Presented By Alexander Eggermont at 2014 ASCO Annual Meeting

EORTC 18071/CA184-029: Study Design



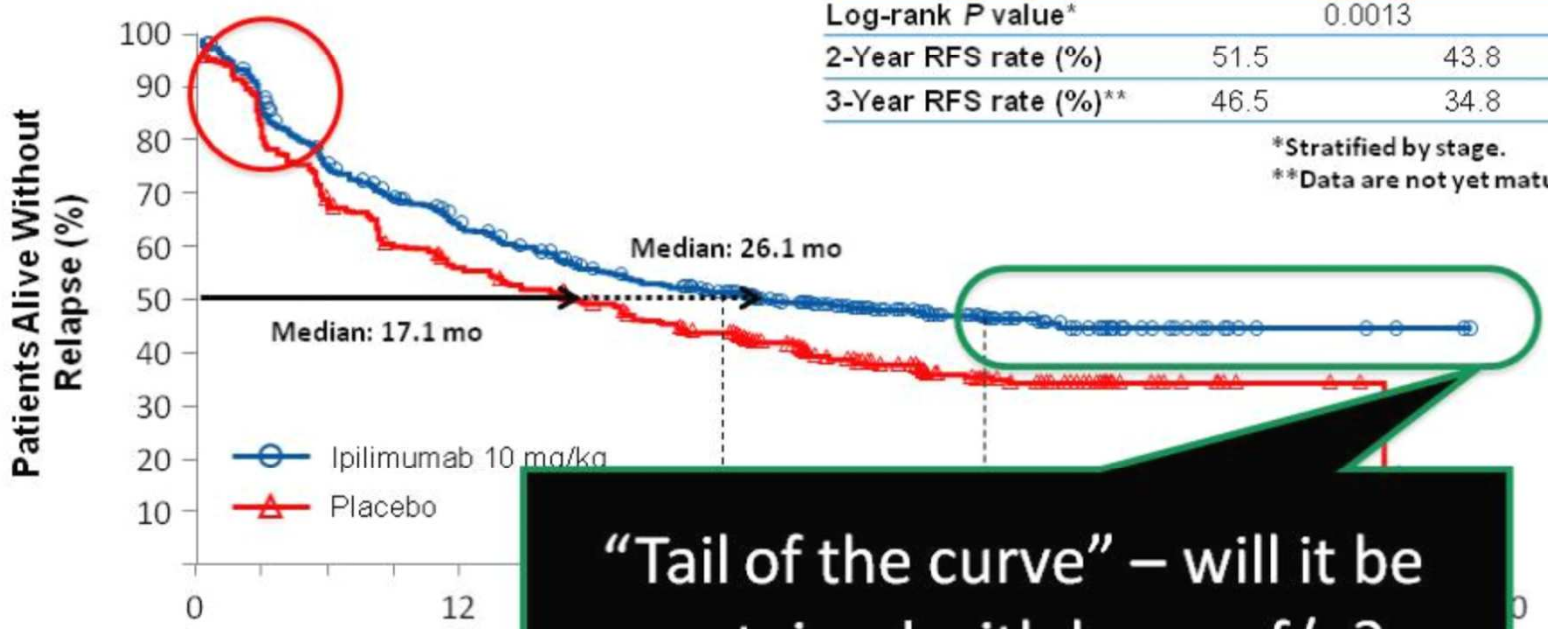
Stratification factors:

- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries and Australia)

Primary Endpoint: Recurrence-free Survival

	Ipilimumab	Placebo
Events/patients	234/475	294/476
HR (95% CI)*	0.75 (0.64 – 0.90)	
Log-rank *P* value*	0.0013	
2-Year RFS rate (%)	51.5	43.8
3-Year RFS rate (%)**	46.5	34.8

*Stratified by stage.
**Data are not yet mature.



Patients at Risk

	O	N					
Ipilimumab	234	475	276	205	67	5	0
Placebo	294	476	260	193	62	4	0

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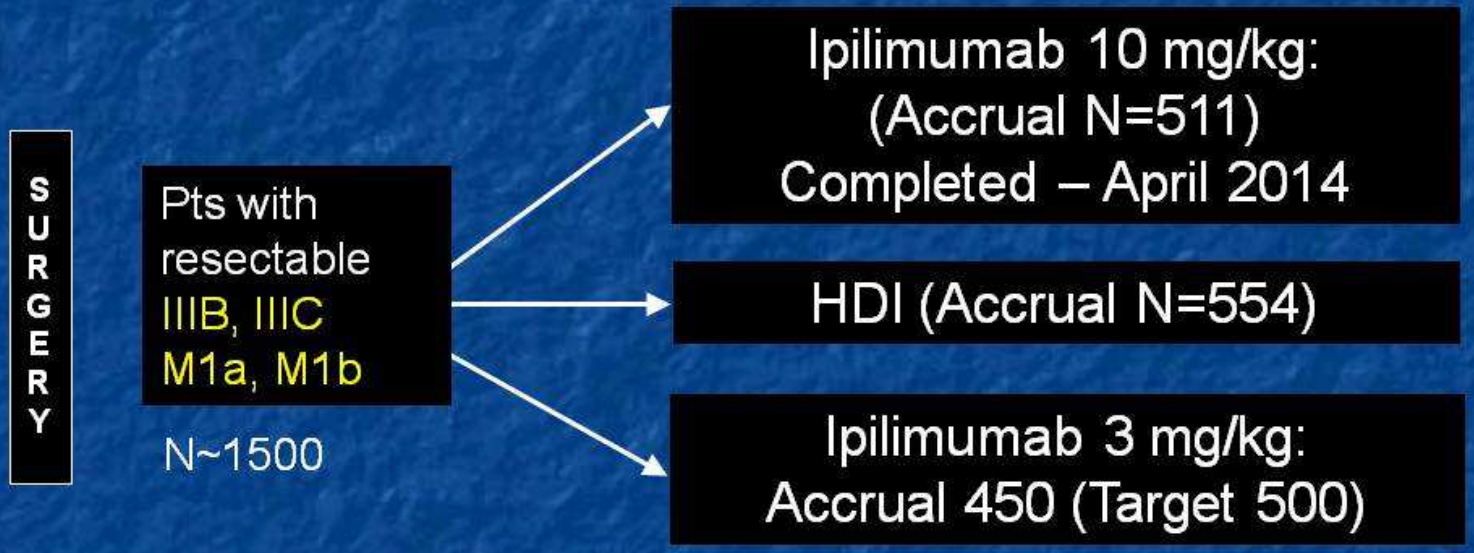
Presented By Jeffrey Gershenwald at 2014 ASCO Annual Meeting

Deaths Related to Study Drug

- Five patients (1.1%) died due to drug-related AEs in the ipilimumab group:
  - Three patients with colitis (2 with gastrointestinal perforations)
  - One patient with myocarditis
  - One patient with Guillain-Barré syndrome
- No deaths related to study drug were reported in the placebo group

U.S. Intergroup E1609 Adjuvant Phase III trial: Ipilimumab (10 mg/kg or 3 mg/kg vs. HDI) - Design and Current Accrual



- Co-primary endpoints: OS and RFS
- Secondary endpoints: QOL, Biomarkers: RFS, OS, toxicity
- **Completion of accrual anticipated Summer 2014**

Courtesy A. Tarhini and JM Kirkwood,

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Ipilimumab in Other Malignancies

Population	Phase	Treatment	Primary Endpoint	Status
NSCLC, squamous	III (NCT01285609)	Ipi + Carboplatin/Paclitaxel vs Carboplatin/Paclitaxel	OS	Recruiting
SCLC	III (NCT01450761)	Ipi + Etoposide/platinum vs etoposide/platinum	OS	Recruiting
Prostate Cancer	III (NCT00861614, NCT01057810)	Ipi vs placebo	OS	Active
CRPC	I/II (NCT01688492)	Ipi + abiraterone acetate	Safety, PFS	Recruiting
Urothelial carcinoma	II (NCT01524991)	Ipi + Gem/Cis	1-yr OS rate	Recruiting
Ovarian, recurrent	II (NCT01611558)	Ipi	Safety, BORR	Recruitingq

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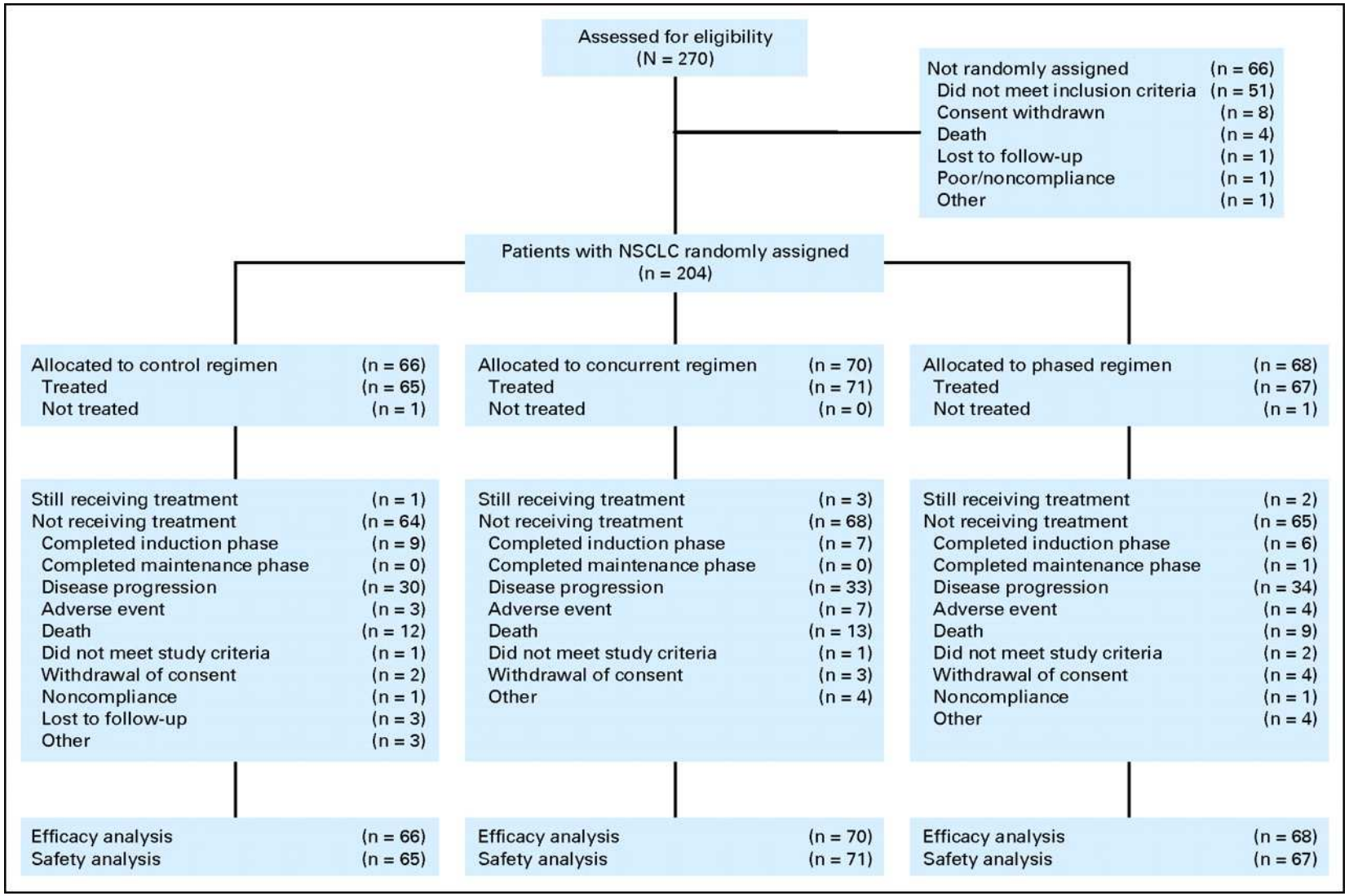
Ipilimumab in Other Malignancies

Population	Phase	Treatment	Response Rate	Source
Pancreas	II	Ipilimumab	0/27	Royal et al.
NHL	I	Ipilimumab	2/18	Ansell et al.
Mesothelioma	II	Tremelimumab	2/29	Calabro et al.
Breast Cancer	I	Tremelimumab + Exemestane	0/26	Vonderheide et al.

Ipilimumab for non–small-cell lung cancer (NSCLC) :CA184-041



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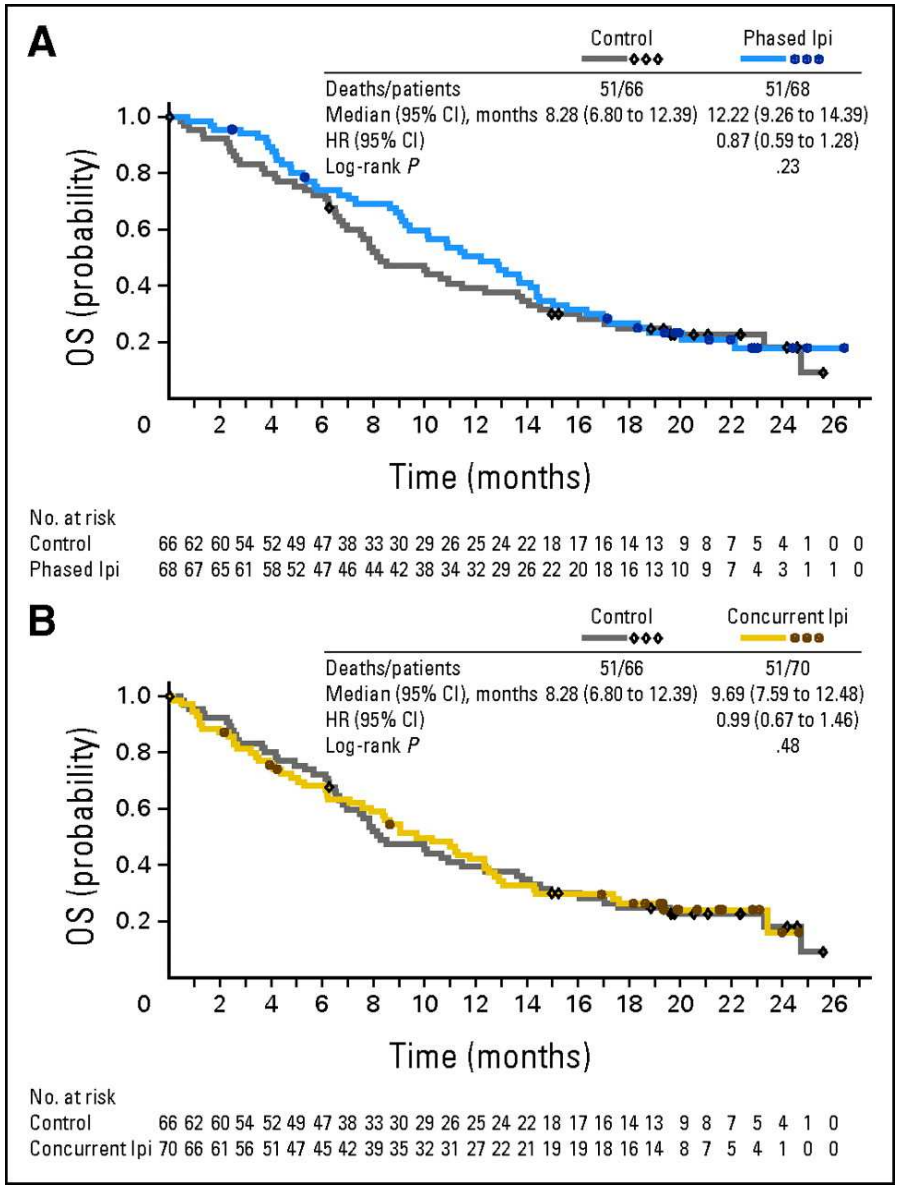
Lynch T J et al. JCO 2012;30:2046-2054

Ipilimumab for non–small-cell lung cancer (NSCLC) :CA184-041 overall survival (OS)



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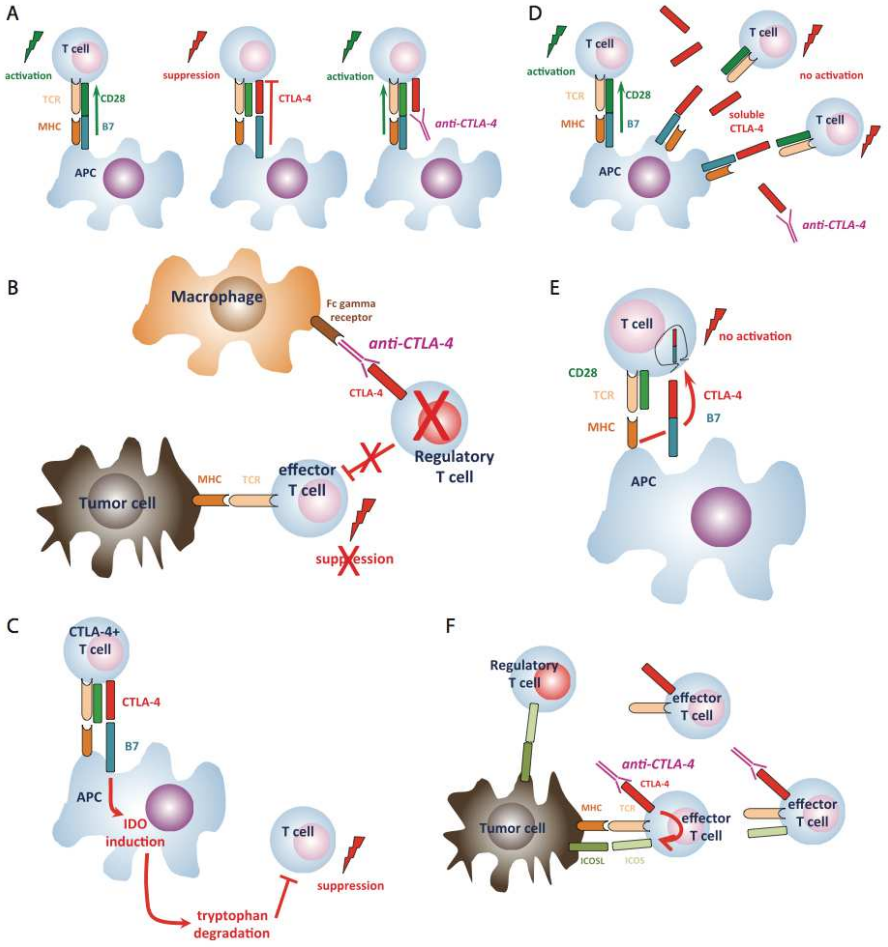
Lynch T J et al. JCO 2012;30:2046-2054

Preclinical studies suggest that anti-CTLA-4 treatment results in effector T cell activation

Increased CD28-B7 engagement

Treg depletion

Inhibit Tryptophan degradation



Neutralizing Soluble CTLA-4

Activation of Effector T cells

Increased ICOS Expression in Teff Leads to expansion Of Teff over Treg

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Blank and Enk. 2014. Int Immunol.

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Ipilimumab in Melanoma: Current Issues

- Dose: 3 mg/kg or 10 mg/kg?
  - Phase III in pts metastatic melanoma done(NCT01515189)
- Schedule: Maintenance therapy or not?
- Role in the adjuvant setting
  - EORTC 18071[1]
  - E1609 (NCT01274338)
- Role in patients with brain metastases, uveal and mucosal primaries
- Proper sequencing with targeted therapy and other immunotherapies
- In combinations
  - Bevacizumab, targeted therapy, other immunotherapies (GM-CSF, IFN, IL-2, **PD-1:PD-L1 blockade, and T-Vec**), and radiation therapy
  - High toxicity when combined with BRAF inhibitor in one trial[2]

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Eggermont A, et al. ASCO 2014. LBA9008. Ribas A, et al. N Engl J Med. 2013;368:2861365-1366