Ipilimumab in Melanoma: Indications and Clinical Management in Melanoma

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Case Presentaiton

65 yo male with a history of a 3.5 mm ulcerated melanoma of the arm with a palpable axillary LN in 2012. He underwent wide excision and concurrent complete lymph node dissection. The excision had negative margins and 2/15 lymph nodes were positive.

He now presents on surveillance imaging to have multiple hypermetoblic lung lesions and biopsy confirms metastatic melanoma and has palpable recurrence on his back. His tumor is found to be BRAF WT and MR of the brain is negative.

What are your choices?

- Ipilimumab
- HDIL2
- Chemotherapy
- Ipilimumab + DTIC
- Clinical Trials

Case Presentation

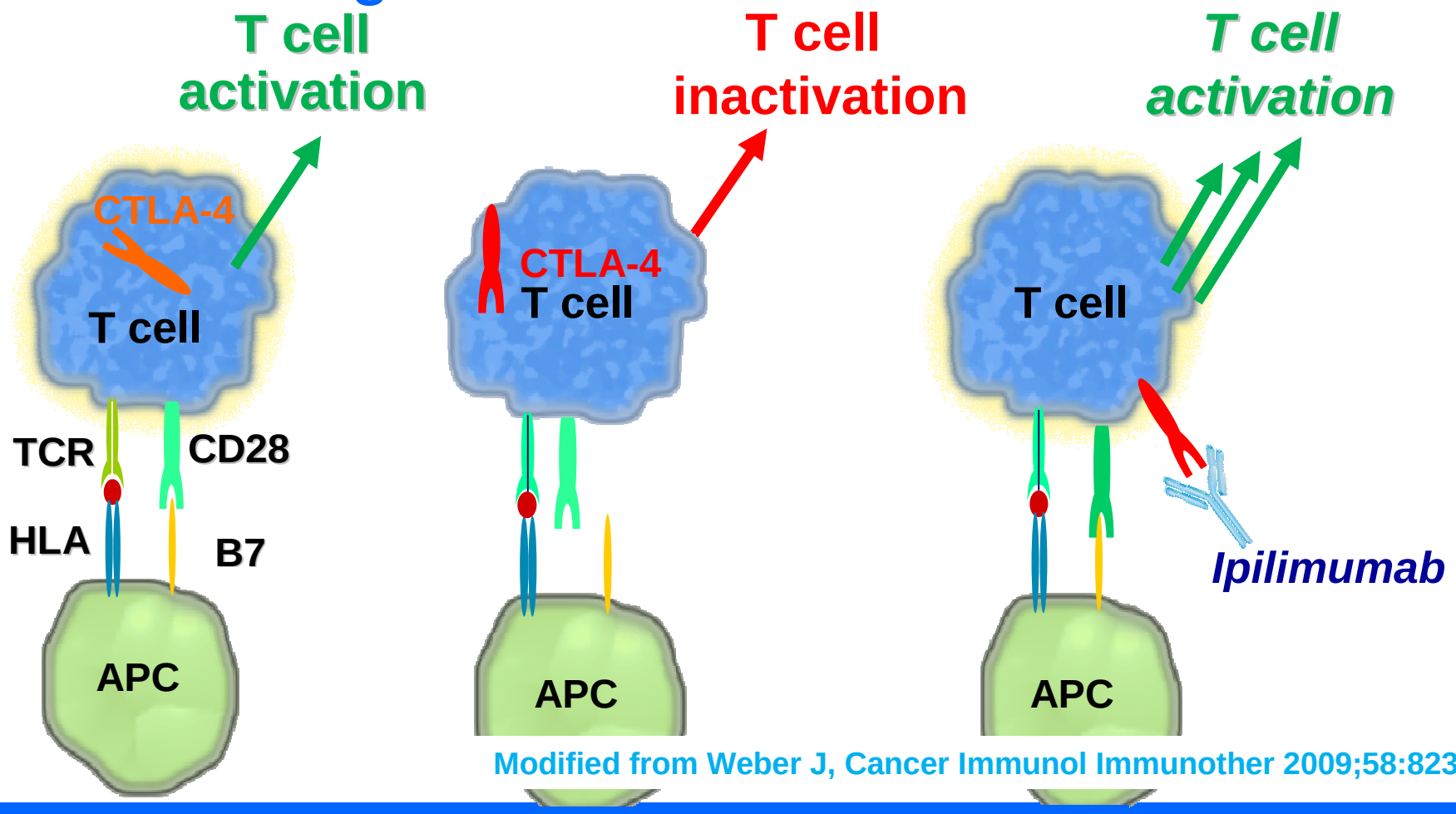
- You choose Ipilimumab at 3mg/kg x 4 doses
- Would you choose differently if the patient's tumor was BRAF mutated?

Ipilimumab:
Taking the Brakes Off T Cell Activation

Reinventing Immunotherapy

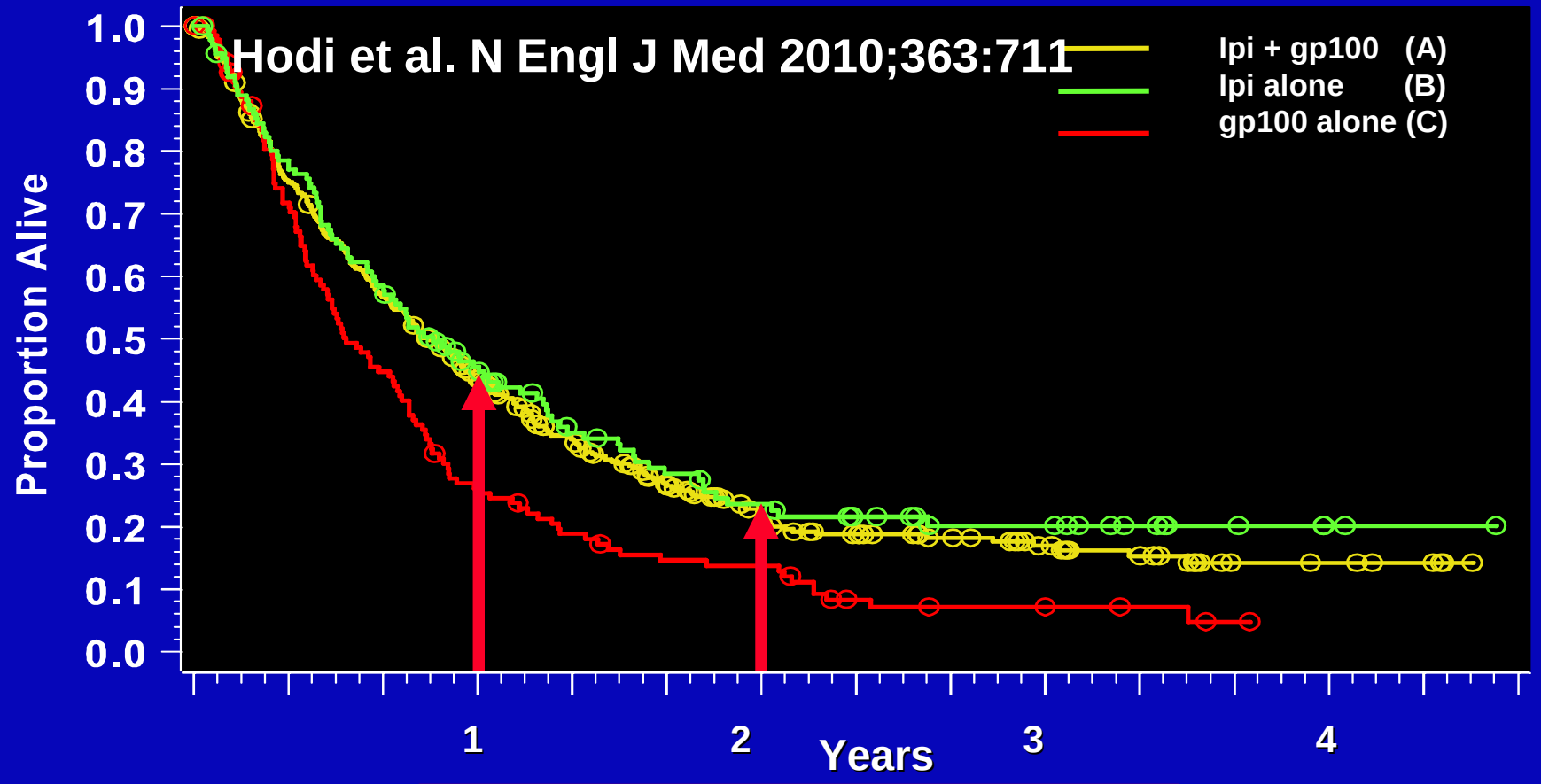
CTLA4 Blockade

Taking the Brakes Off T Cell Activation



Modified from Weber J, Cancer Immunol Immunother 2009;58:823

Ipilimumab (3 mg/kg x 4) Improves Overall Survival in Previously Treated Stage IV Melanoma



Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

IPILIMUMAB ± gp100 VS gp100 ALONE

	Ipi Alone	Ipi+gp100	gp100	Korn
PFS (median)	2.9 mos*#	2.8 mos*	2.8 mos	1.7 mos
PFS @ 6 mos	24%*	16%	10%	15%
OS (median)	10.1 mos*	10.0 mos*	6.4 mos	6.2 mos
OS @ 12 mos	46%*	44%*	25%	26%
Responses	10.9%*#	5.7%*	1.5%	---

* $p<0.05$ compared to gp100 + placebo arm

\# $p<0.05$ compared to ipilimumab + gp100 arm

O'Day et al. *Proc ASCO* 2010

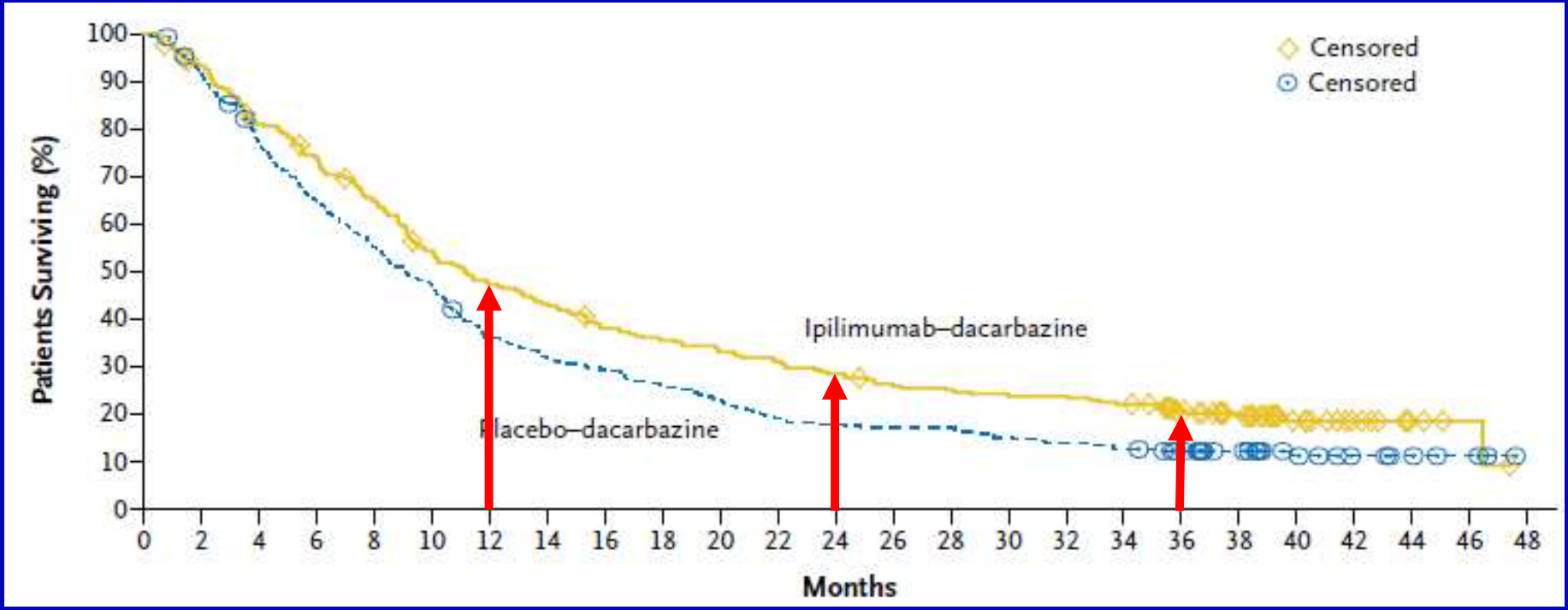
Korn et al. *J Clin Oncol* 2008;26:527-534

IPI + DTIC Study 024

- 502 untreated patients, about 55% M1c disease

- Randomized:
  - IPI 10mg/kg q3w x 4 + DTIC 850mg/m2 q3w x8, followed by IPI 10mg/kg q12w
  - Placebo + DTIC 850mg/m2 x8, Placebo q12w

Ipilimumab (10 mg/kg) + DTIC Improves Overall Survival in Previously Untreated Stage IV Melanoma



No. of deaths: 196 versus 218, Hazard ratio 0.72 (0.59–0.87) p<0.001

1 yr survival 47.3% vs 36.3%

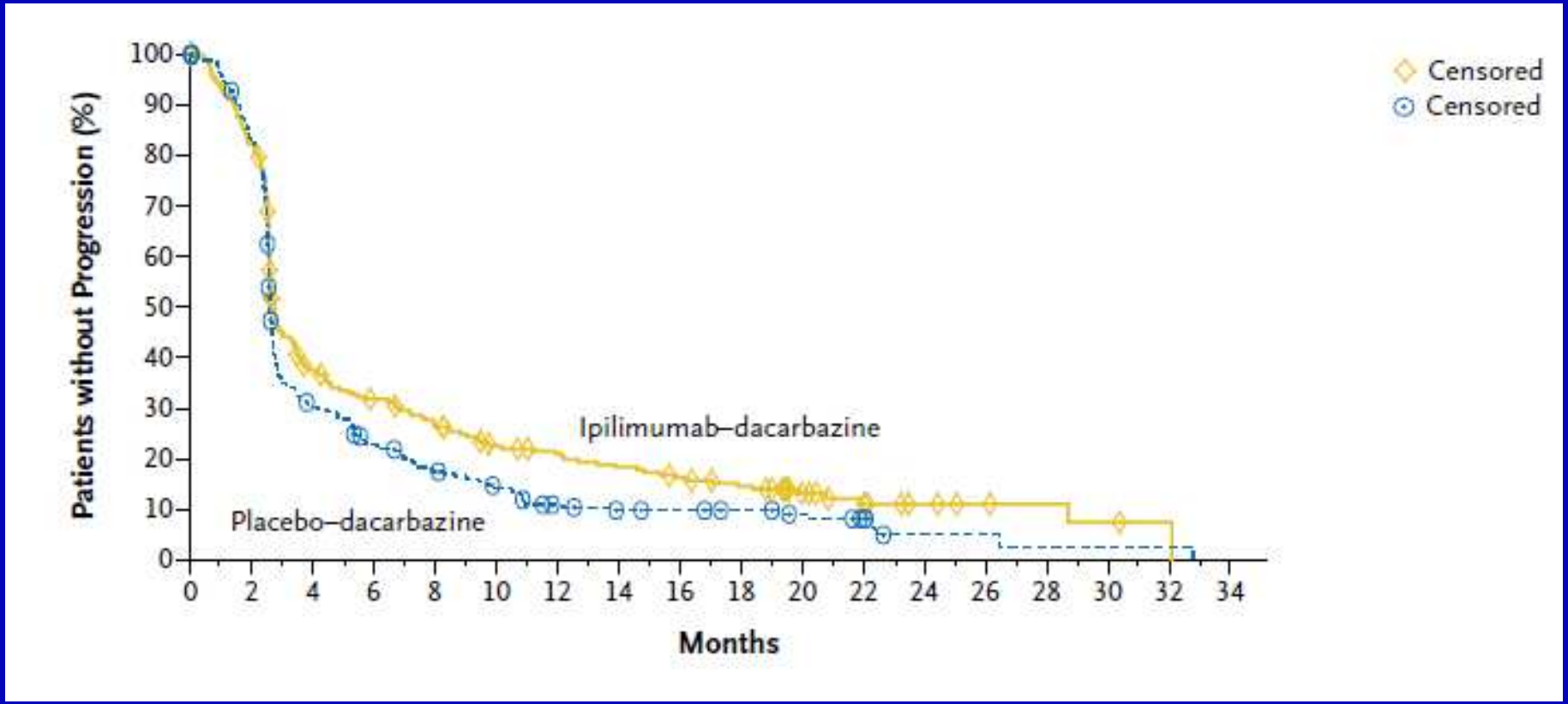
2 yr survival 28.5% vs 17.9%

3 yr survival 20.8% vs 12.2%

Median OS 11.2 vs 9.1 months p 0.0009

Robert et al. N Engl J Med 2011;epub ahead of print

Ipilimumab (10 mg/kg) + DTIC Improves Progression-Free Survival in Previously Untreated Stage IV Melanoma



PFS HR 0.76
Median PFS 2.8 months vs 2.6
P 0.006

Robert et al. N Engl J Med 2011;epub ahead of print

Exposure

- DTIC alone:
  - Median number of doses 4
  - 66% received all 4 doses
  - 1 or more maintenance doses 21.1%
- IPI + DTIC:
  - Median number of dose 3
  - Only 37% had all 4 doses
  - 1 or more maintenance doses 17.4%

Tumor Response

	IPI + DTIC N = 250 N (%)	Placebo + DTIC N = 252 N (%)
Disease Control Rate	83 (33.2)	76 (30.2)
ORR (CR + PR)	38 (15.2)	26 (10.3)
Complete Response	4 (1.6)	2 (0.8)
Partial Response	34 (13.6)	24 (9.5)
Stable disease	45 (18)	50 (19.8)
Progressive disease	111 (44.4)	131 (52.0)
Duration of response, months	19.3	8.1

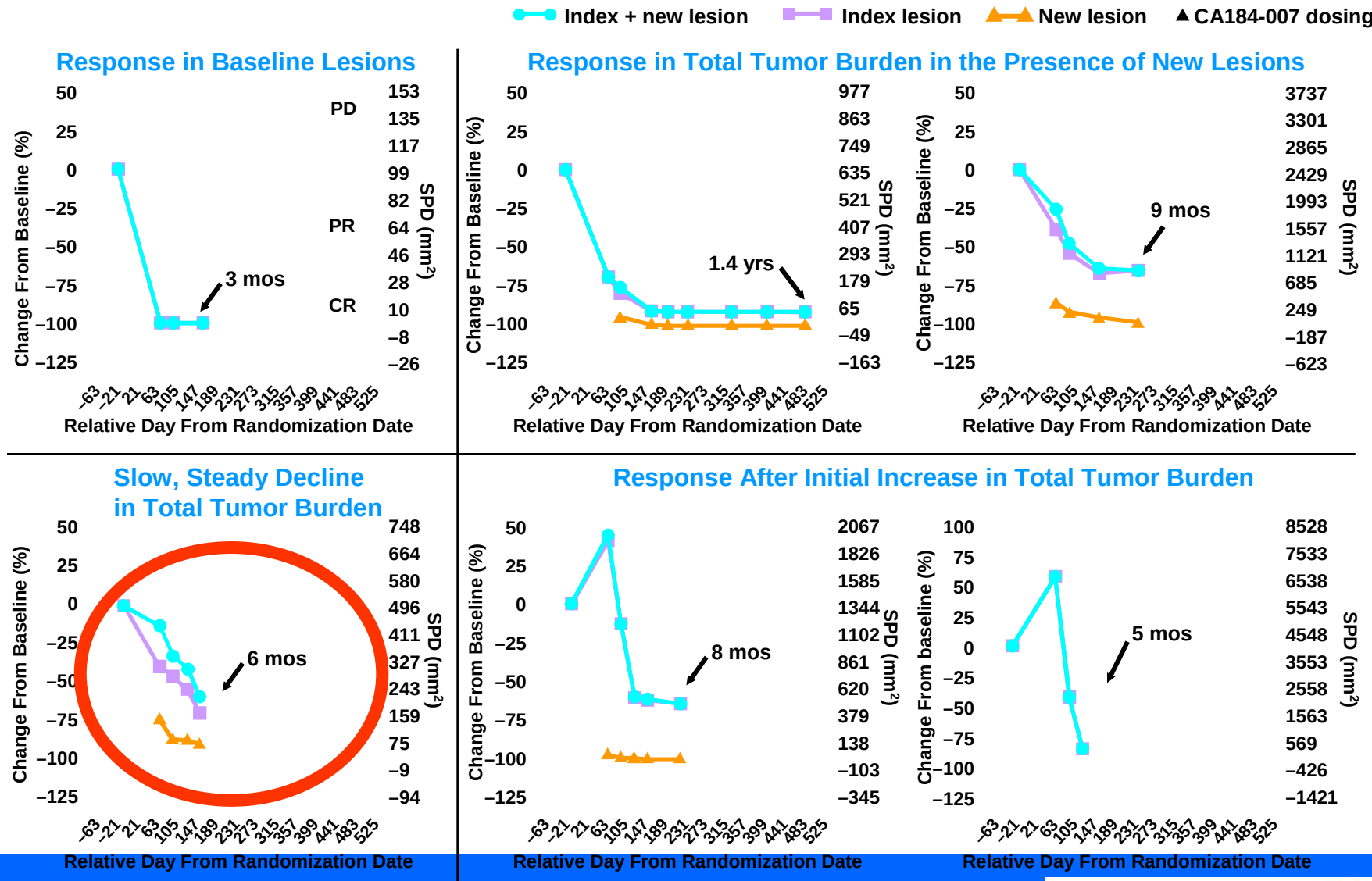
Should IPI + DTIC used over IPI alone for metastatic melanoma patients?

NO

Case Update

- The patient receives 2 doses of the IPI, and comes stating “my tumors are bigger and I need to get another treatment”

CA184-007 Trial: 4 Patterns of Response Observed



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Reproduced with permission from Weber. *ASCO*. 2008 (abstr 9010).

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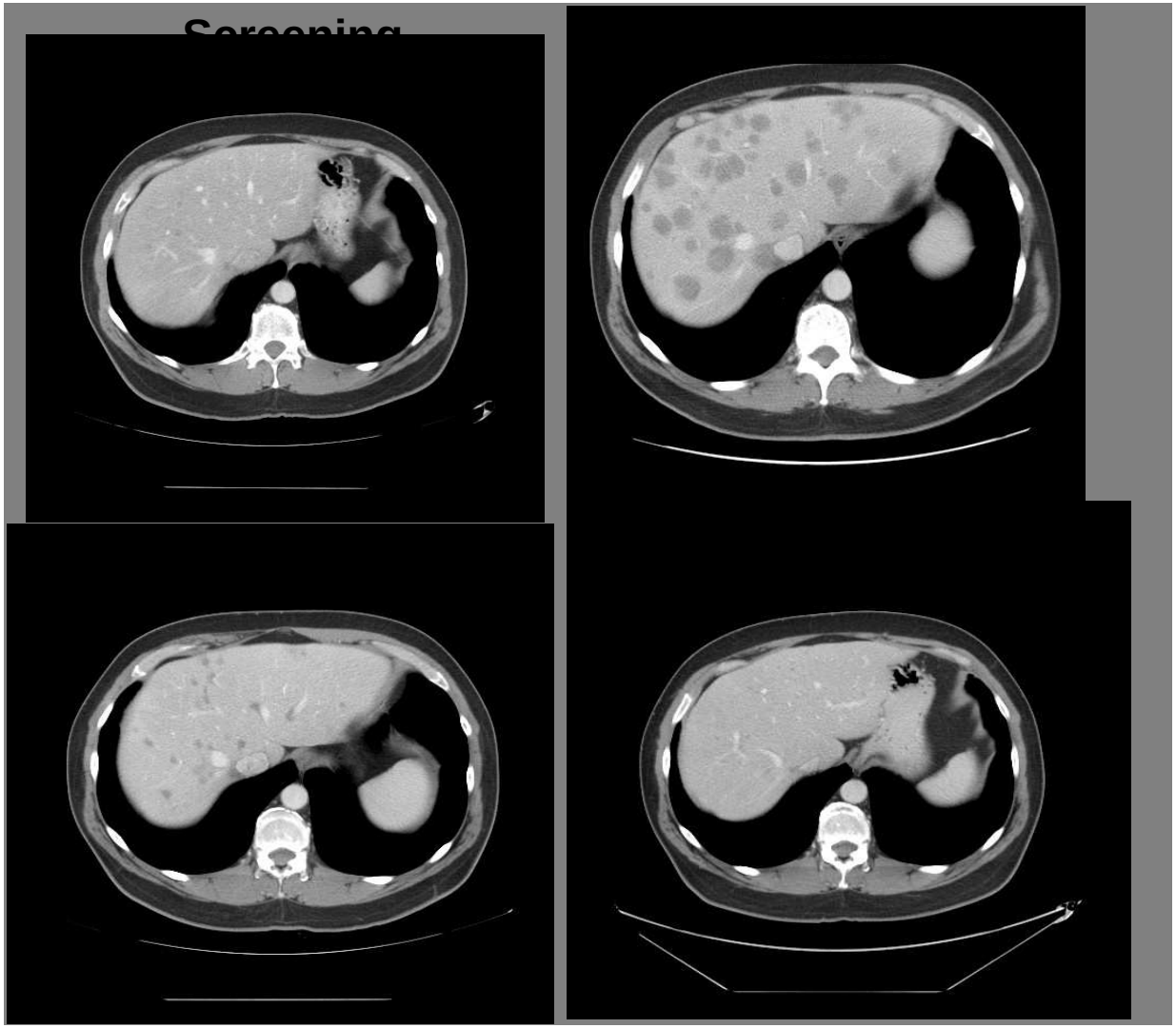
Objective Response to Ipilimumab After Significant Progression With Tumor Volume Increase



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Reproduced with permission from Wolchok. *ASCO*. 2008 (abstr 3020).

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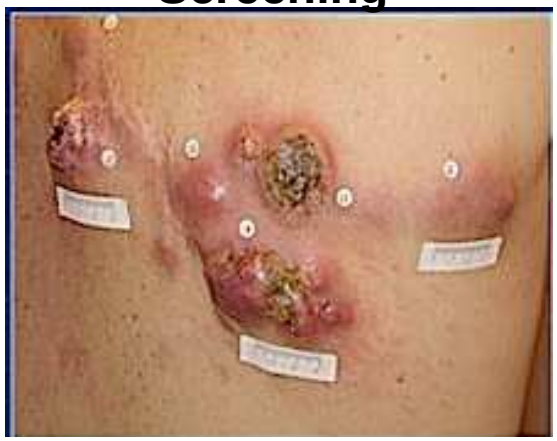
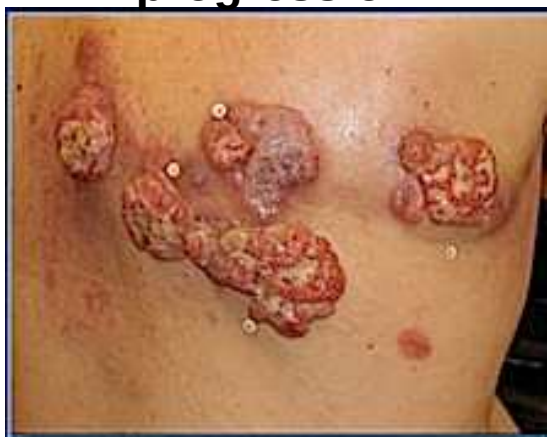
Unique Kinetics of Response in Patients Treated With Ipilimumab

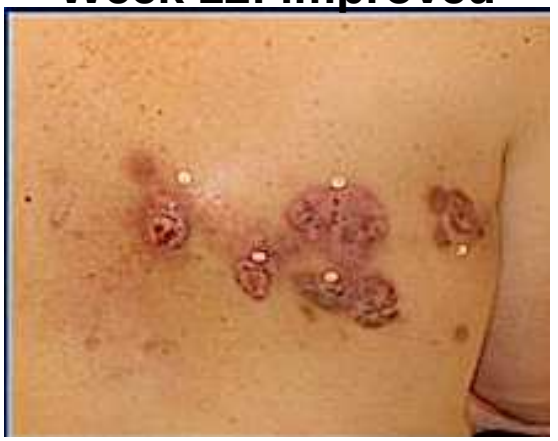
Screening



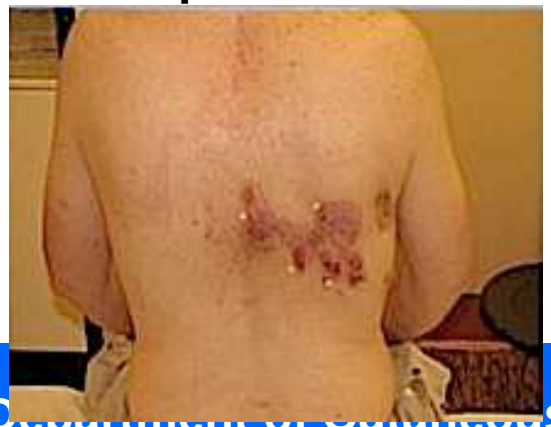
Week 12: swelling and progression



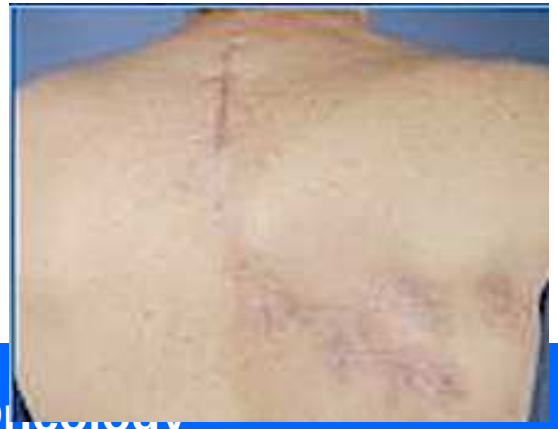
Week 12: improved



Week 16: continued improvement



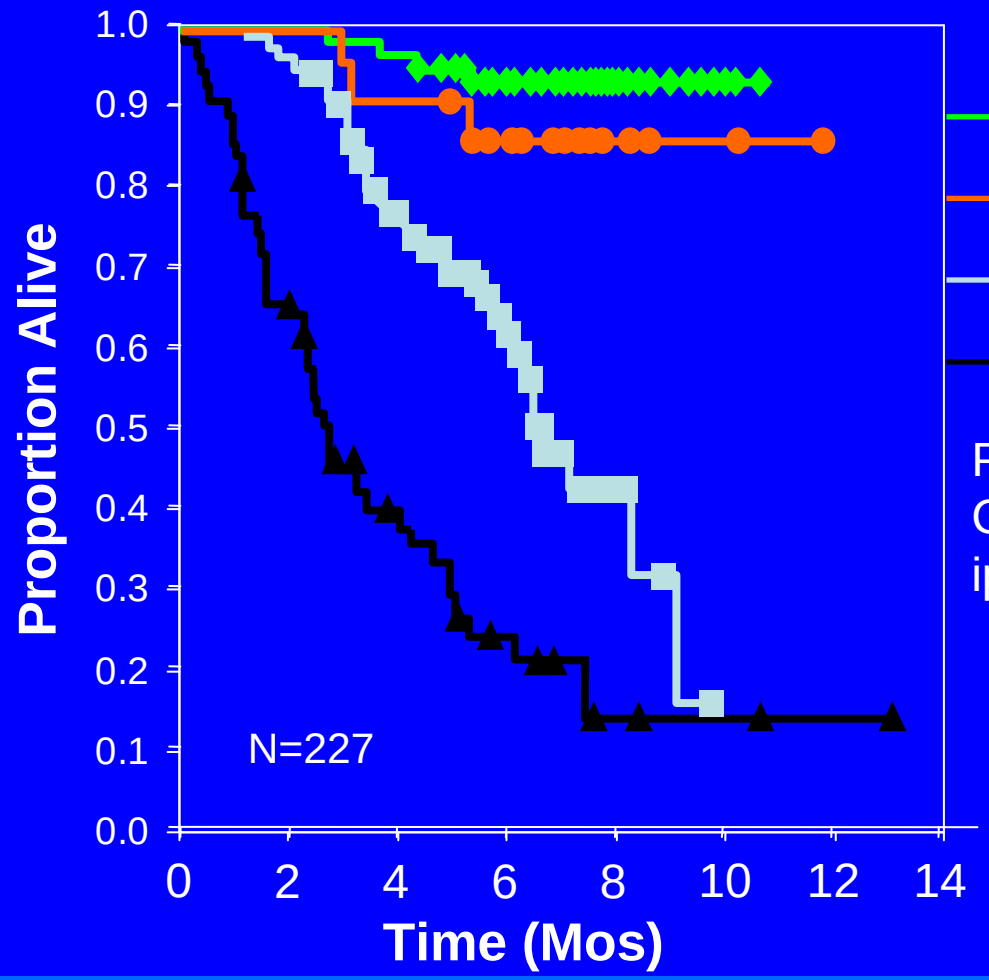
Week 72: complete remission



Week 108: complete remission

Images courtesy of Jedd D. Wolchok, MD.

irRC Identifies Survivors With Otherwise mWHO PD



- **mWHO: CR/PR/SD (28%)**
- **irRC: CR/PR/SD with mWHO PD (10%)**
- **PD under both criteria (38%)**
- **Early PD without follow-up (25%)**

Pooled data from CA184-008 and CA184-022 phase II trials: ipilimumab 10 mg/kg alone

irRC=immune-related response criteria; mWHO=modified World Health Organization.

Hodi. *ASCO*. 2008 (abstr 3008); Wolchok. *Clin Cancer Res.* In press.

So when do I scan the patient to evaluate for response?

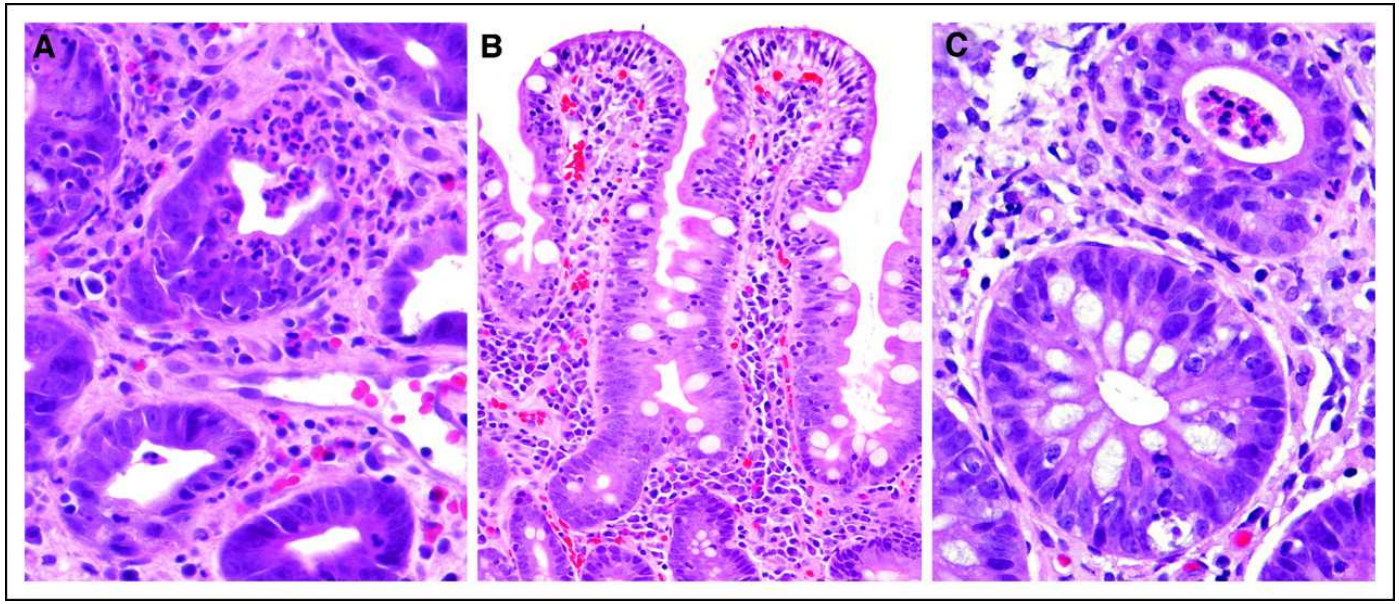
Case Update

Following the patients third dose, he calls your clinic with 12 nonbloody loose stools in the last 24 hours despite lomotil.

What is the best next step in management?

a. Call in a 1 week steroid taper, such as a medrol dose pack
b. Hold further ipilimumab, the diarrhea will resolve on its own without further intervention as long as no additional treatment is given
c. Hold further ipilimumab, treat with steroids and taper over 4-6 weeks if improved. Restart ipilumimab once diarrhea is resolved
d. Discontinue ipilumimab. Start 1mg/kg of steroids and consider hospital admission.

Fig 3. Representative photomicrographs of histopathologic features of enterocolitis



Beck, K. E. et al. J Clin Oncol; 24:2283-2289 2006

Case Update

- Your patient is started on 1mg/kg daily of steroids but continues to have abdominal pain and diarrhea after 2 days of steroids and bowel rest
- What do you do next?

  Infliximab 5mg/kg

GI irAEs: Overview

- Diarrhea is a frequent irAE
  - Most cases are mild or moderate
  - Biopsy demonstrates inflammatory colitis and T-cell infiltrates
  - Most cases respond to either symptomatic treatment or steroids
  - Can rarely lead to GI perforation (<1%) requiring surgery

Enteritis Induced by Ipilimumab

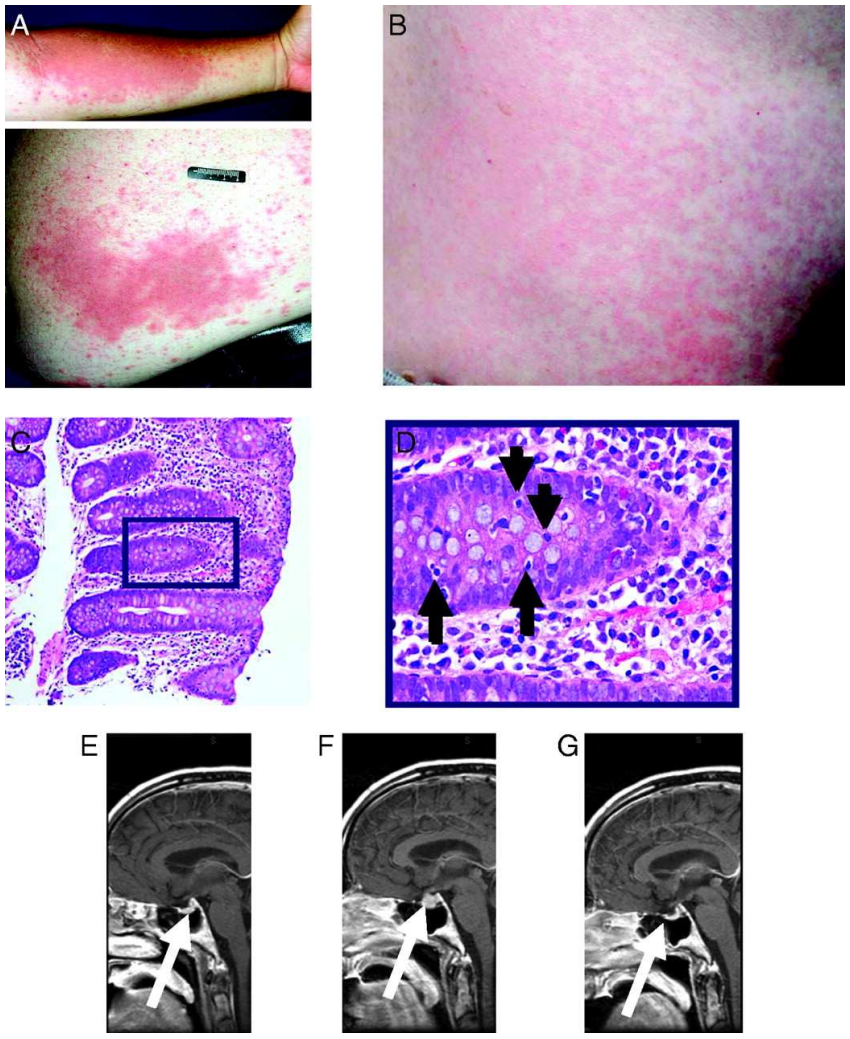
- Inflammation can be anywhere in GI tract (eg, mucositis and gastritis, but most commonly colitis)
- Diarrhea: requires attention
  - New and watery
  - Increased frequency >50% baseline
  - Duration
  - Bloody
- Grade 1 and 2
  - Treat symptomatically
  - Rule out other causes
  - No need for systemic steroids; can use budesonide
  - Follow closely for resolution

Weber. *Cancer Immunol Immunother*. 2009;58:823; Weber. *Oncologist.* 2007;12:864; Ledezma. *Oncol Nurs* Forum. 2009;36:97.

Management of IRAEs

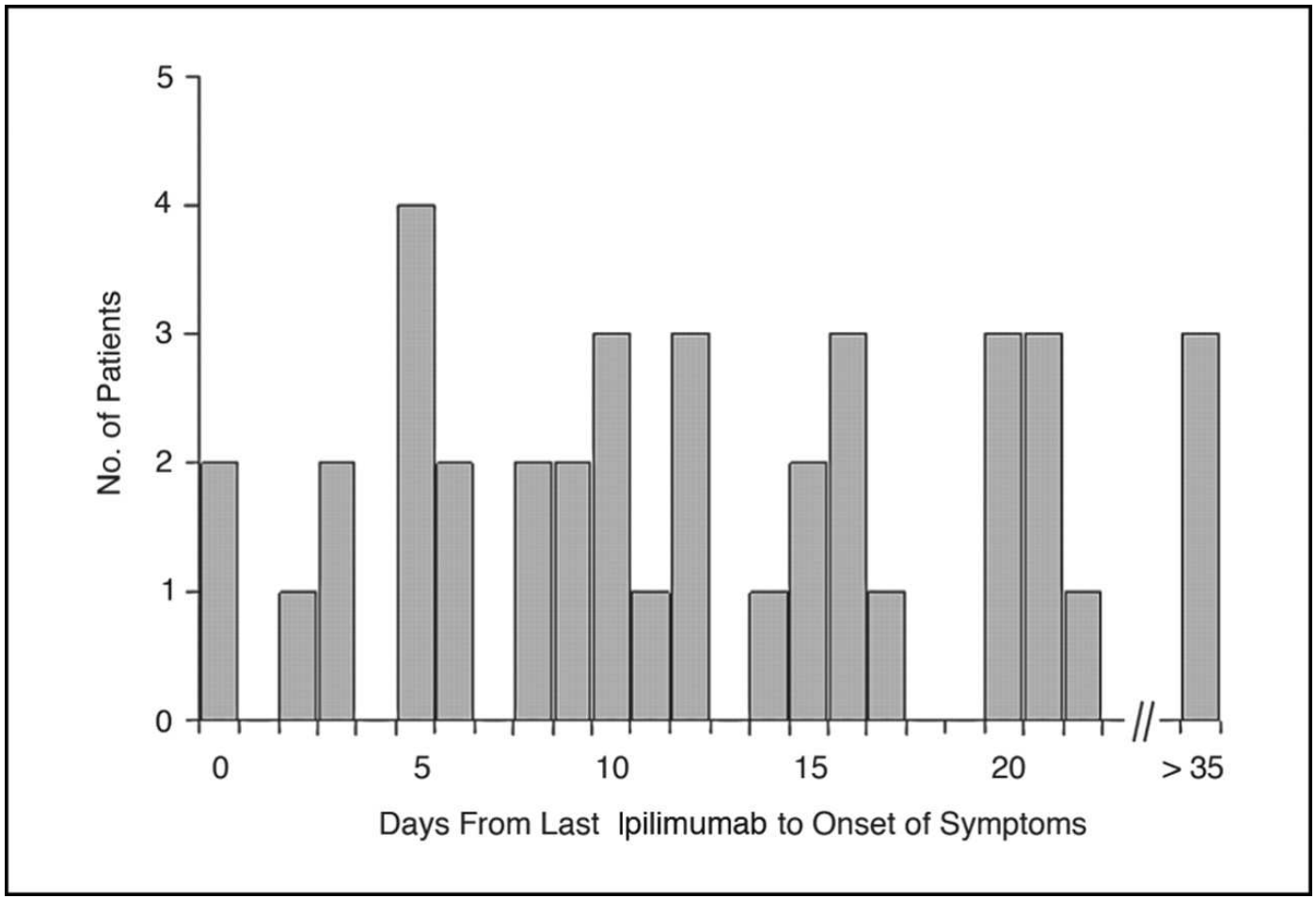
- Hepatotoxicity
- Pituitary Dysfunction
- Rash/Pruitis
- Diarrhea
  - Immodium/Lomotil
  - Oral Budesonide
  - Predisone
  - Remicade
- Do you retreat?

Fig 1. Toxic events during CP-675,206 administration



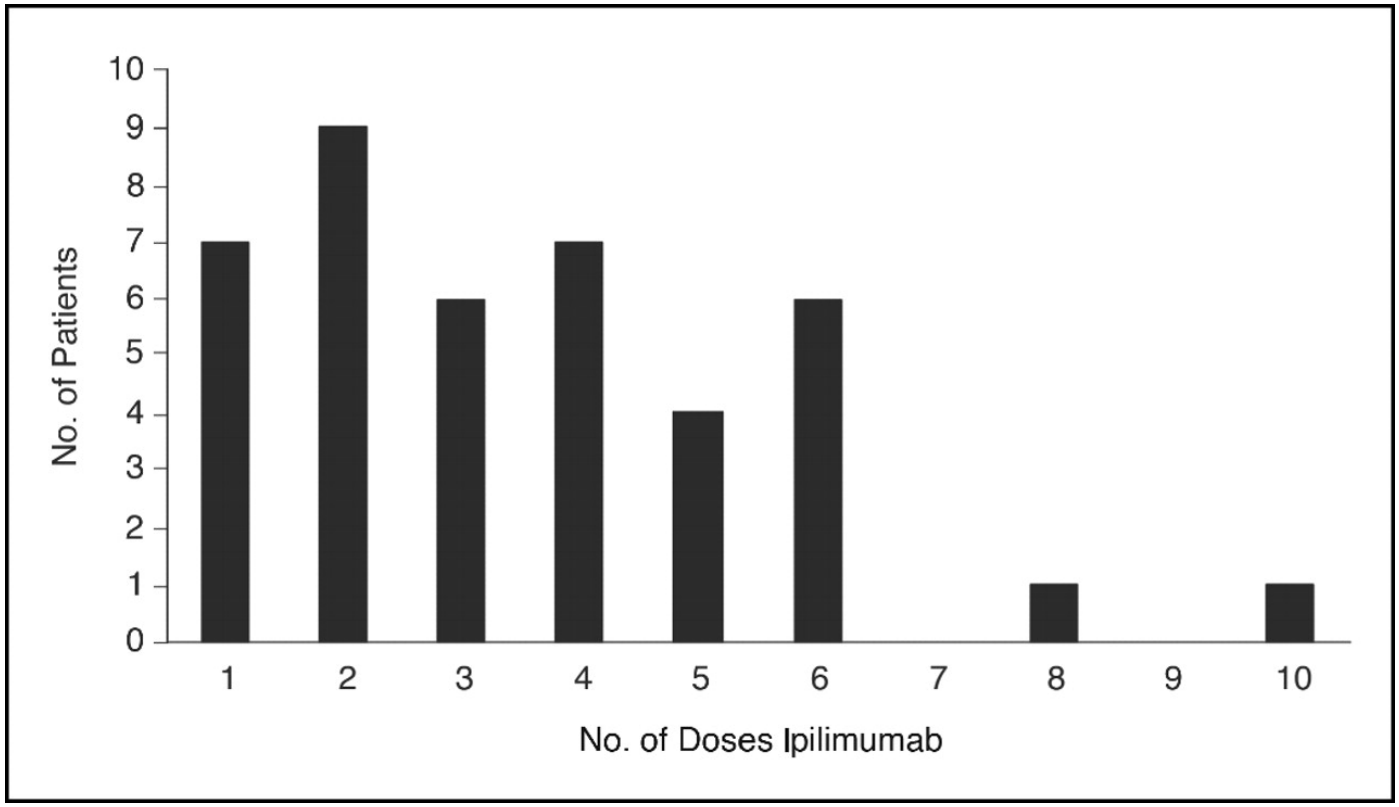
Ribas, A. et al. J Clin Oncol; 23:8968-8977 2005

The interval from last dose of ipilimumab to the onset of symptoms of enterocolitis



Beck, K. E. et al. J Clin Oncol; 24:2283-2289 2006

The number of doses of ipilimumab given before the onset of symptoms of enterocolitis



Beck, K. E. et al. J Clin Oncol; 24:2283-2289 2006

Dermatologic irAEs: Overview

- Common irAEs
  - Mostly low grade
  - Rash, pruritus, and vitiligo
  - Resolves with symptomatic therapy or corticosteroids
  - Frequently associated with T-cell infiltrate

Hodi. *ASCO*. 2008 (abstr 3008); Beck. *J Clin Oncol*. 2006;24:2283 Attia. *J Clin Oncol*. 2005;23:6043

Endocrinopathy irAEs: Overview

- Symptoms: fatigue, nausea, amenorrhea, impotence, hypotension, hyponatremia, hypoglycemia, and eosinophilia
  - If strong suspicion for adrenal crisis (dehydration and hypotension), start stress-dose steroids
  - If suspect hypophysitis, head MRI with pituitary cuts; visual field testing
  - Hormone replacement; consider trial of high-dose steroids

- Can you retreat?

Beck. *J Clin Oncol*. 2006;24:2283

Management of irAEs

- Patient education for early recognition of irAEs
- Aggressive work-up and management for moderate/severe events
- Nonspecific complaints might reflect endocrine (eg, pituitary) toxicity

Management of IRAEs

- Hepatotoxicity
- Pituitary Dysfunction
- Rash/Pruitis
- Diarrhea
  - Immodium/Lomotil
  - Oral Budesonide
  - Predisone
  - Infliximab
- Do you retreat?

The Future of Ipilimumab

- **Activity against non-cutaneous melanomas**
  - Different biology, ? Different immunology
  - Very low responses with IPI seen in ocular melanomas

- **IPI + Drug X**
  - Toxicity may be variable
  - Combination studies are on-going
    - Nivolumab
    - Pegylated interferon
    - IDO-inhibitor
    - Bevacizumab
    - Chemotherapy

- **Adjuvant Therapy**
  - EORTC IPI vs placebo now closed
  - ECOG 1609 IPI vs alpha IFN in high risk patients

Conclusions

- Ipilimumab improves overall survival in treatment naïve and refractory metastatic melanoma
- Immune-related adverse events are serious, but manageable in most cases
- Despite low overall response rates, durable survival is seen in 15-30% of patients treated