IMMUNOTHERAPY OF MELANOMA

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Tampa, Florida
December 10, 2016

Disclosures

- **Dr. Sondak is a compensated consultant for Merck, BMS, GSK, Novartis, and Provectus**

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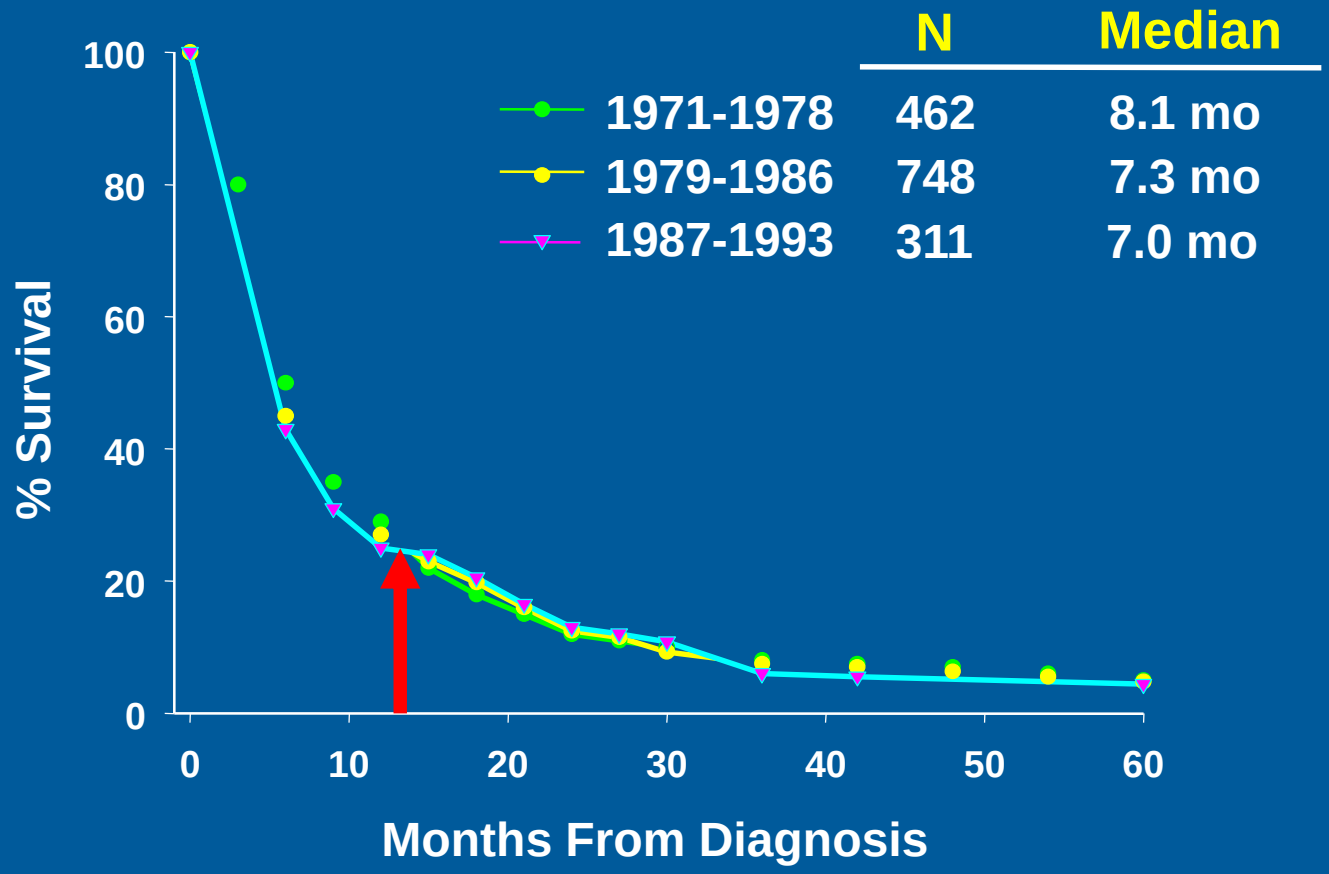
- ***I will be discussing non-FDA approved treatments during my presentation today.***

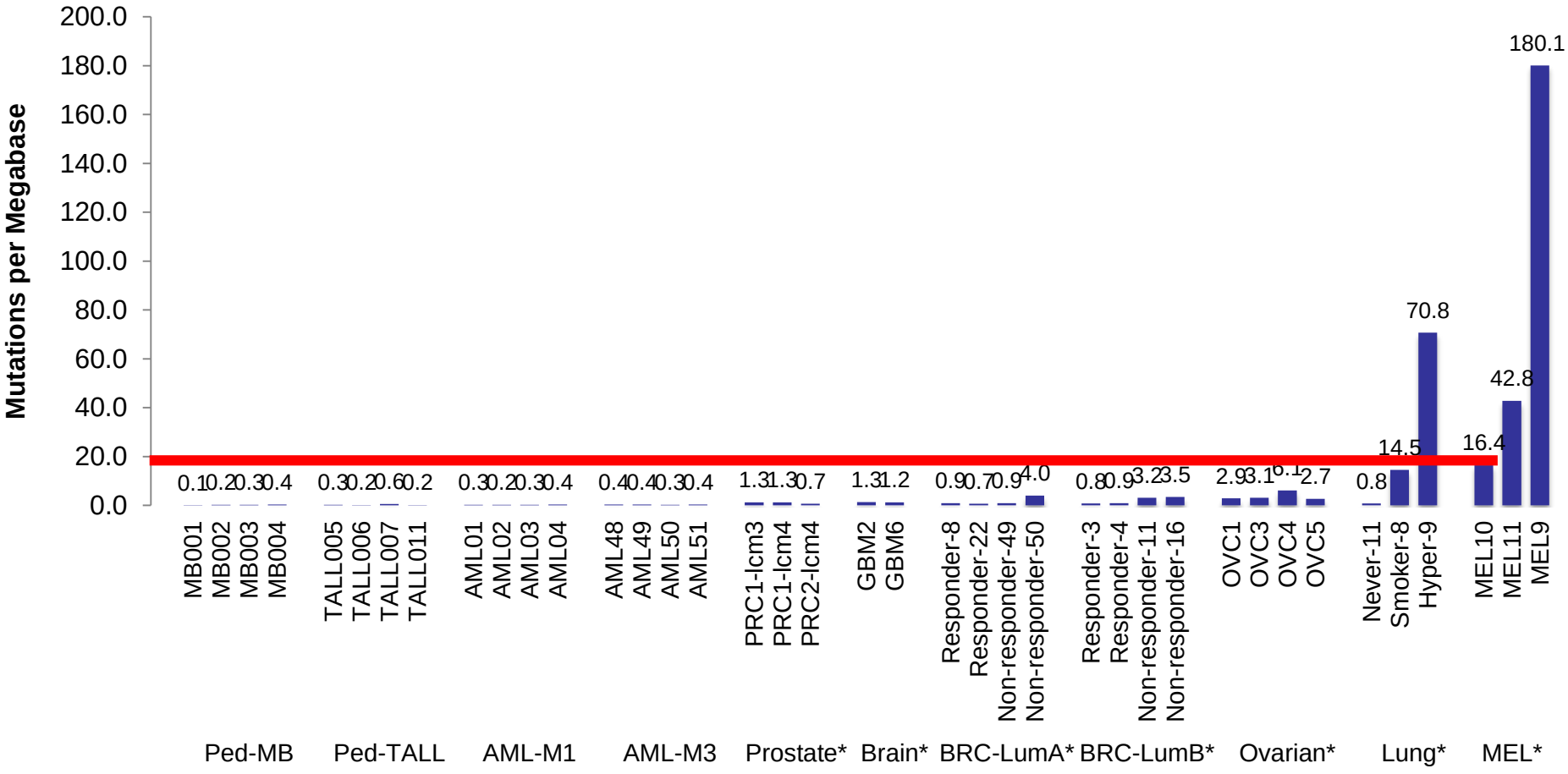
Overall Survival for Metastatic Melanoma



There had been no significant improvement in overall survival for metastatic melanoma in three decades

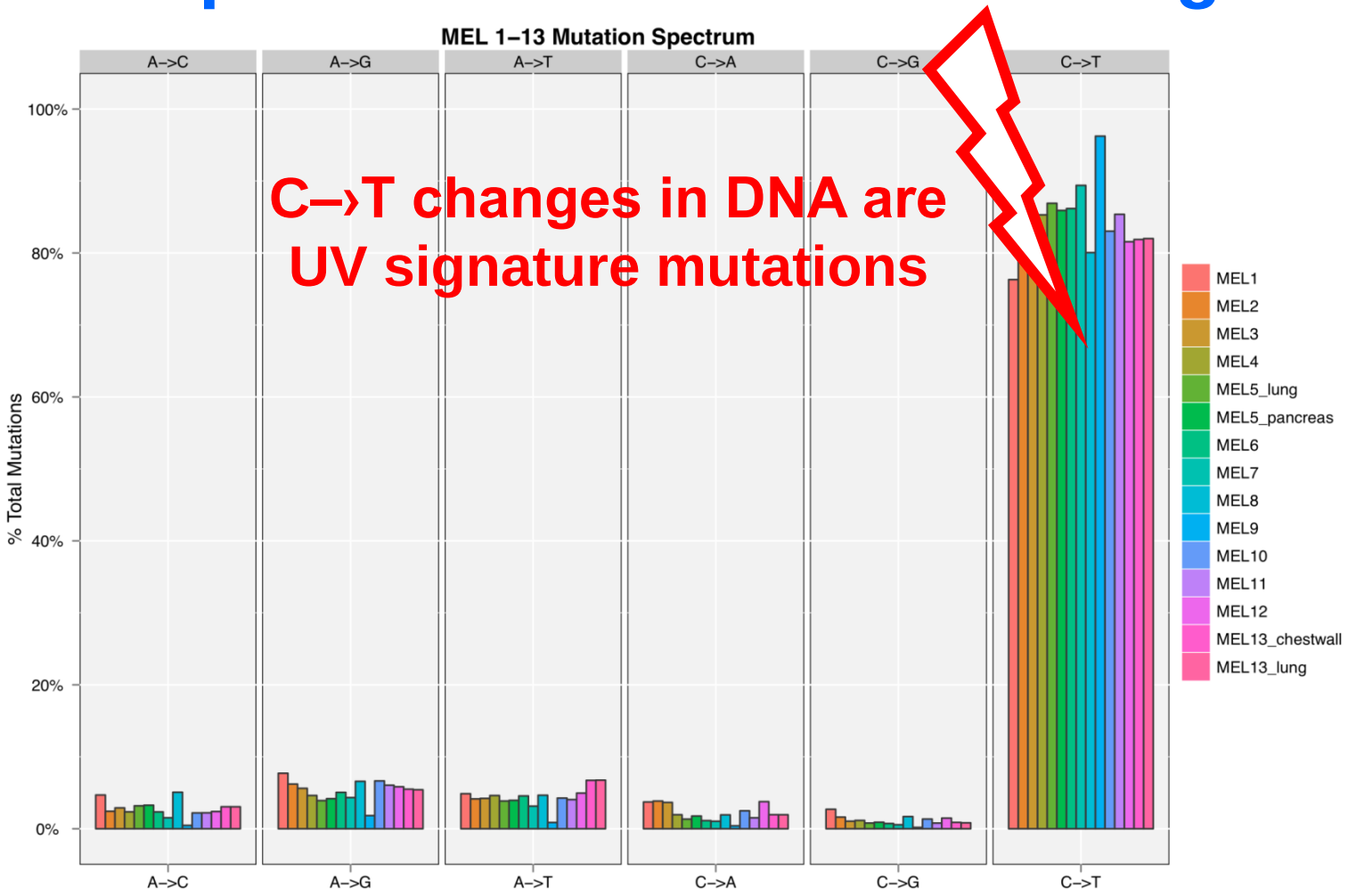
Barth, *J Am Coll Surg* 1995;181:193

Melanomas Have More Mutations Than Any Other Cancer!



In collaboration with the Genome Laboratory, Washington University, St Louis

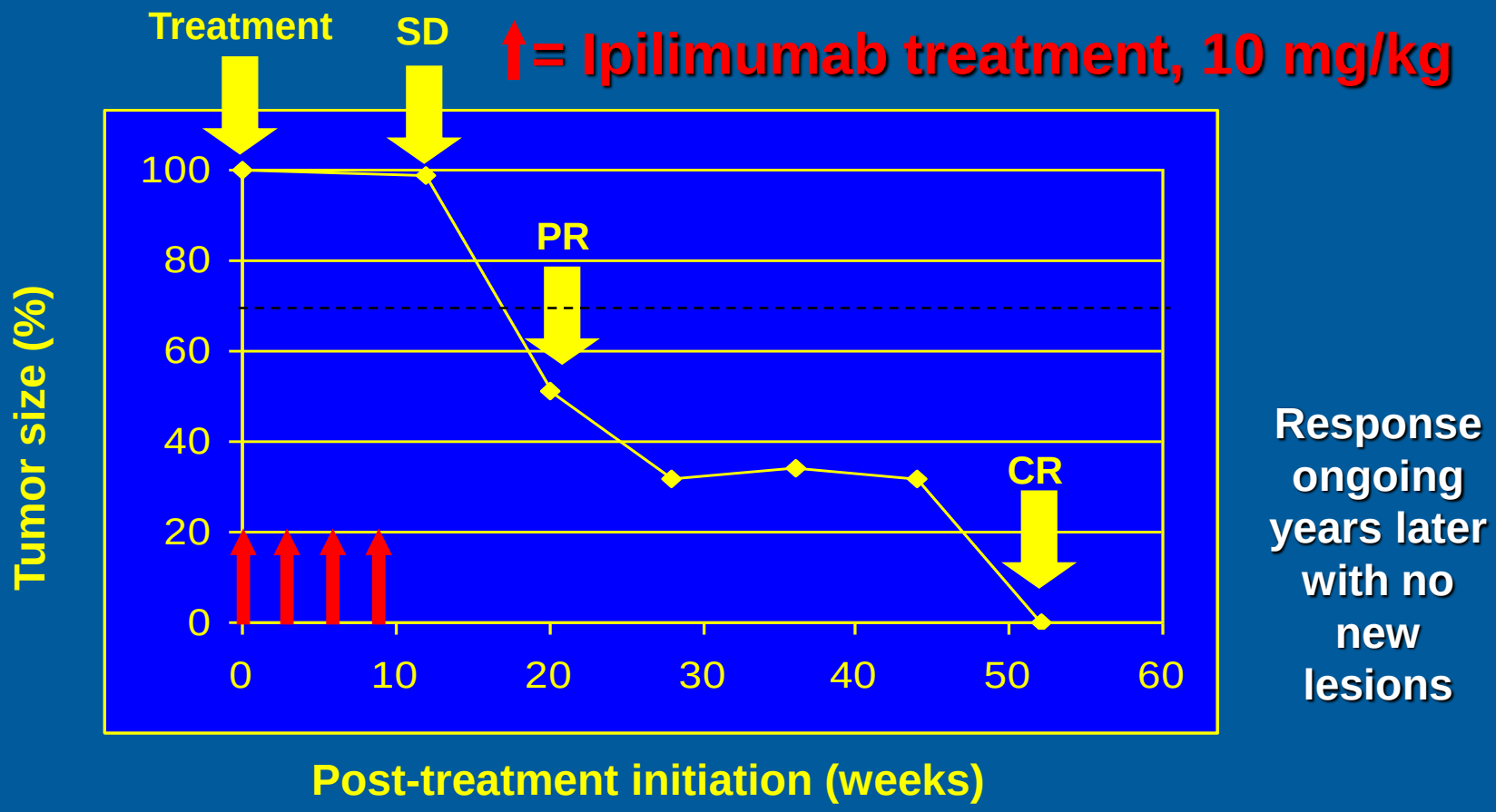
Those Melanoma Mutations Are Caused By UV Exposure And Create Neoantigens



Checkpoint Inhibitor Immunotherapy

- **T cells have ‘checkpoints’ that suppress the immune response, and melanoma hijacks these checkpoints to evade immune destruction**
- **Antibodies that inhibit these checkpoints, despite possessing no inherent antitumor activity, are capable of inducing long-lasting tumor regression and possibly even cure of metastatic melanoma**

Targeting T cells with Ipilimumab (Anti-CTLA4 Antibody) Leads to Durable Response

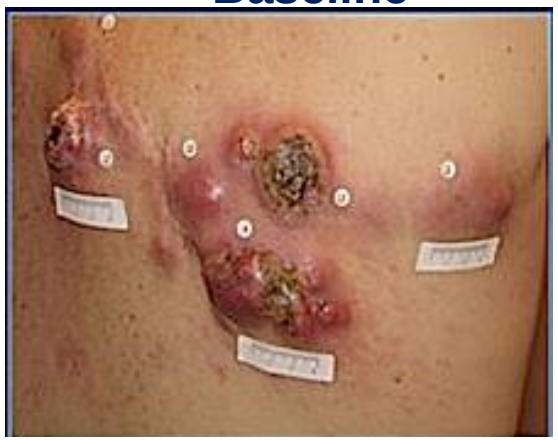


Response ongoing years later with no new lesions

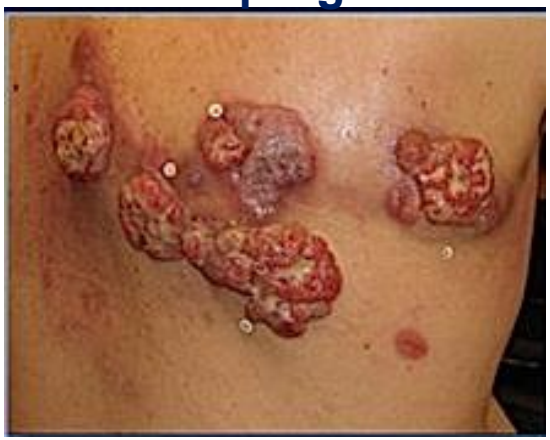
Weber J, *Oncologist* 2008;13(supp4):16

Progression Followed by Response in Melanoma Patient Treated with Ipilimumab

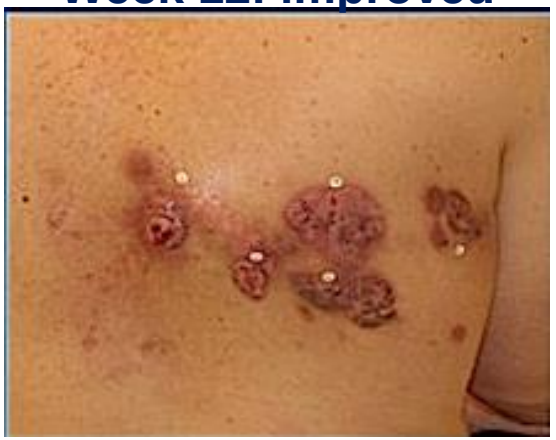
Baseline



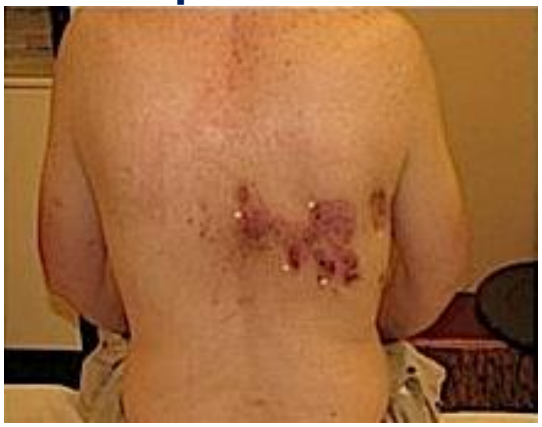
Week 8: "progression"



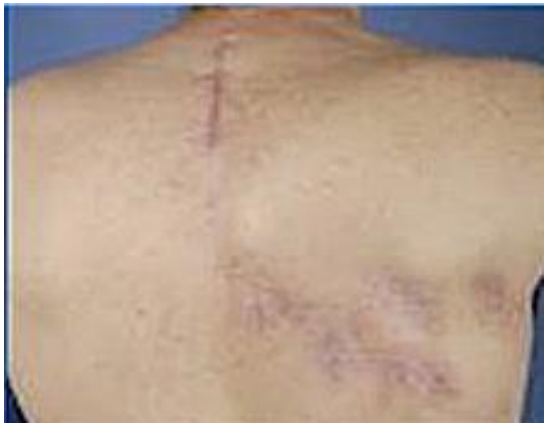
Week 12: improved



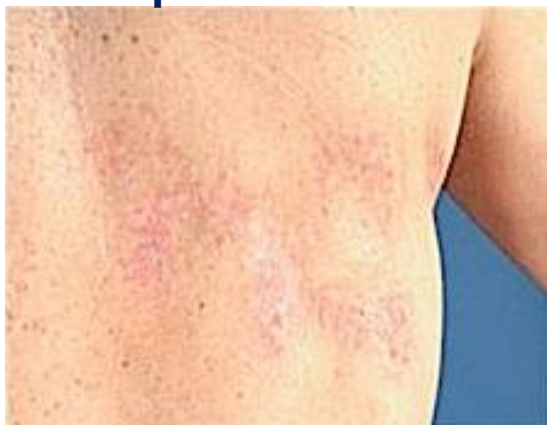
Week 16: continued improvement



Week 72: complete remission



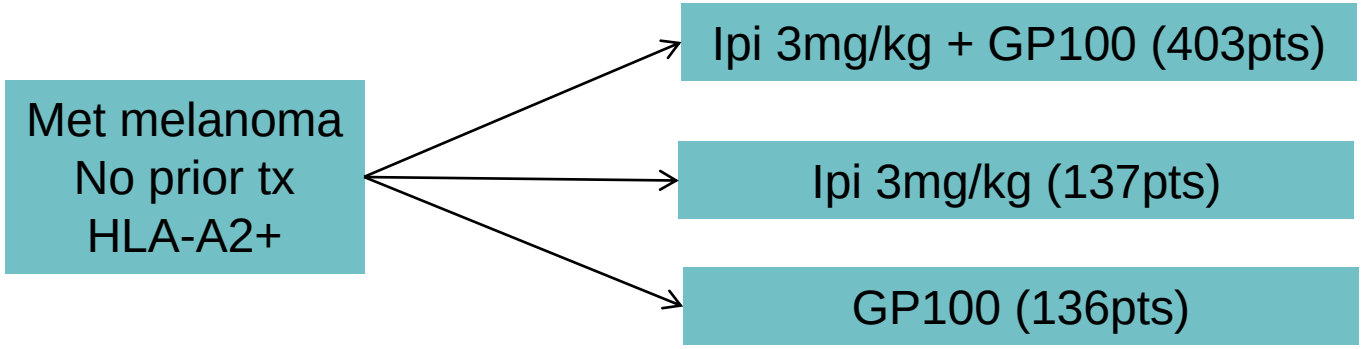
Week 108: still in complete remission



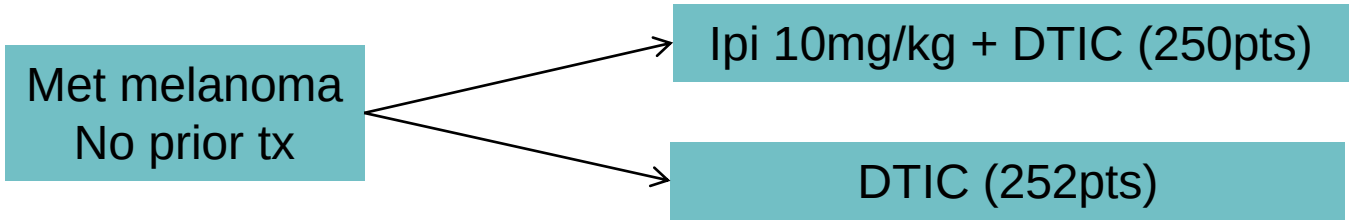
Images courtesy of Jedd Wolchok, MD

Ipilimumab Phase III Trials

Hodi et al, *N Engl J Med*, 2010

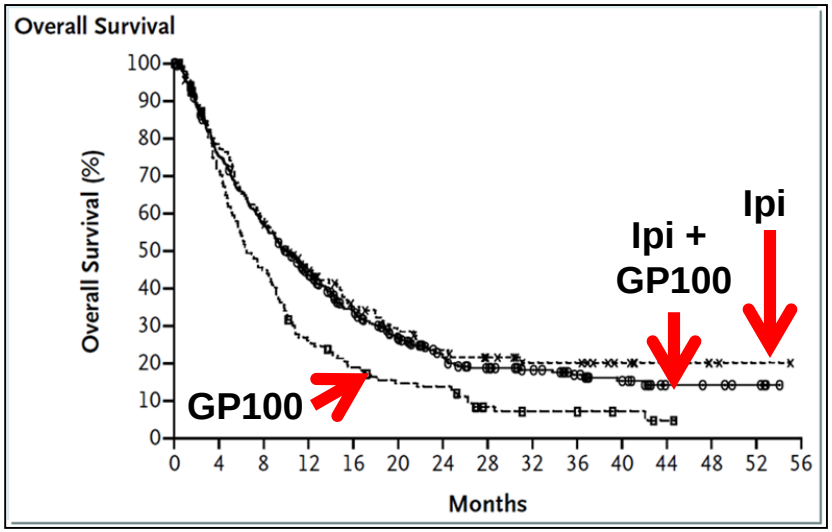


Robert et al, *N Engl J Med*, 2011



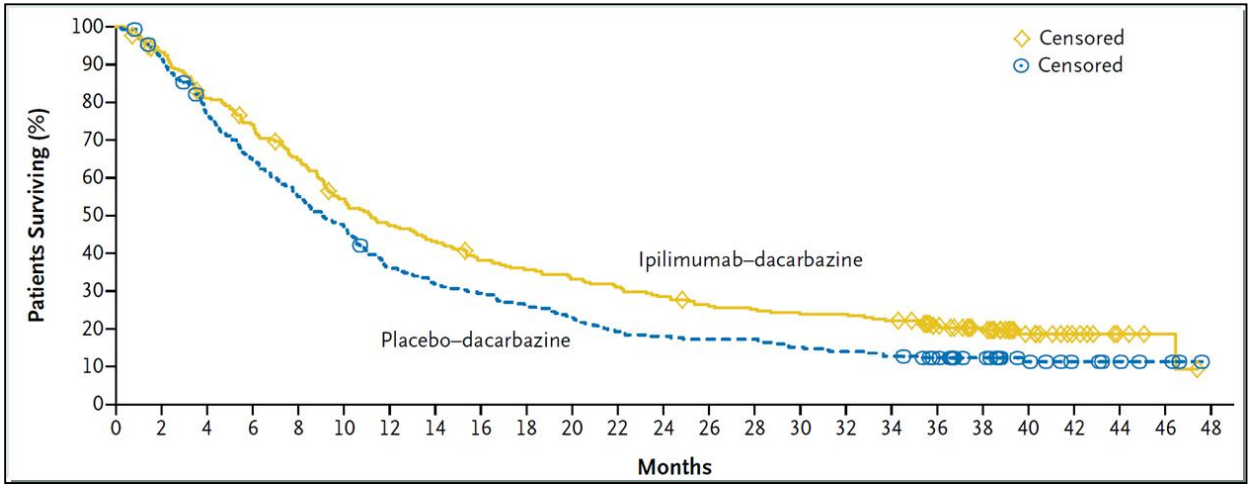
Survival Advantage with Ipilimumab

Ipilimumab 3mg/kg
Hodi et al, *N Engl J Med*, 2010

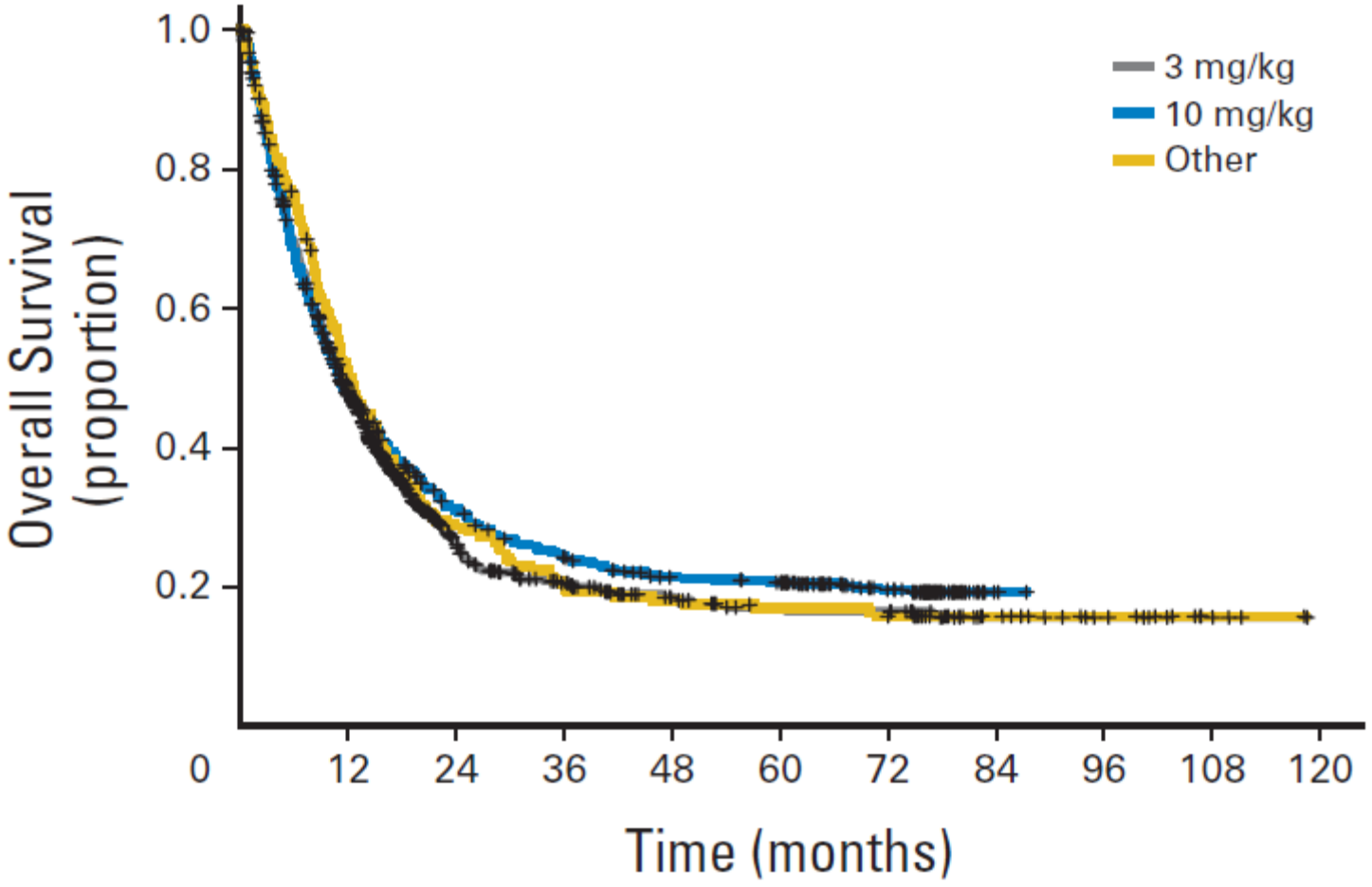


	ORR
Ipi 3ug/kg	11.0%
Ipi 3ug/kg + GP100	5.7%
Ipi 10ug/kg + DTIC	15.2%

Ipilimumab 10mg/kg
Roberts et al, *N Engl J Med*, 2011



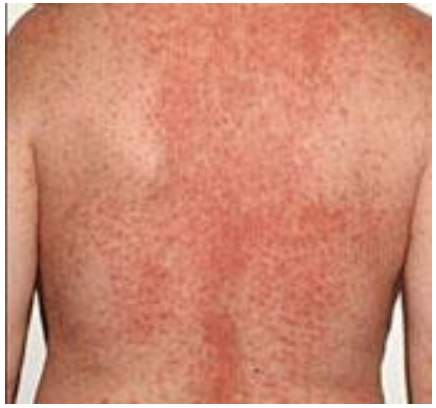
Durable Survival Impact with Ipilimumab

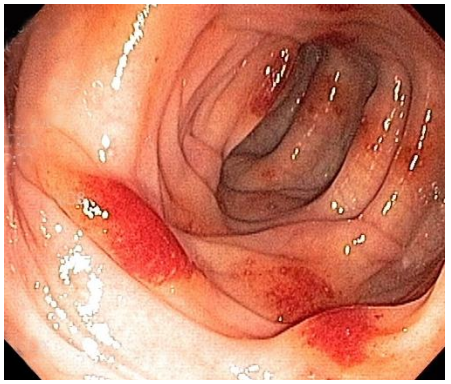


Schadendorf et al, *J Clin Oncol* 2015;33:1889

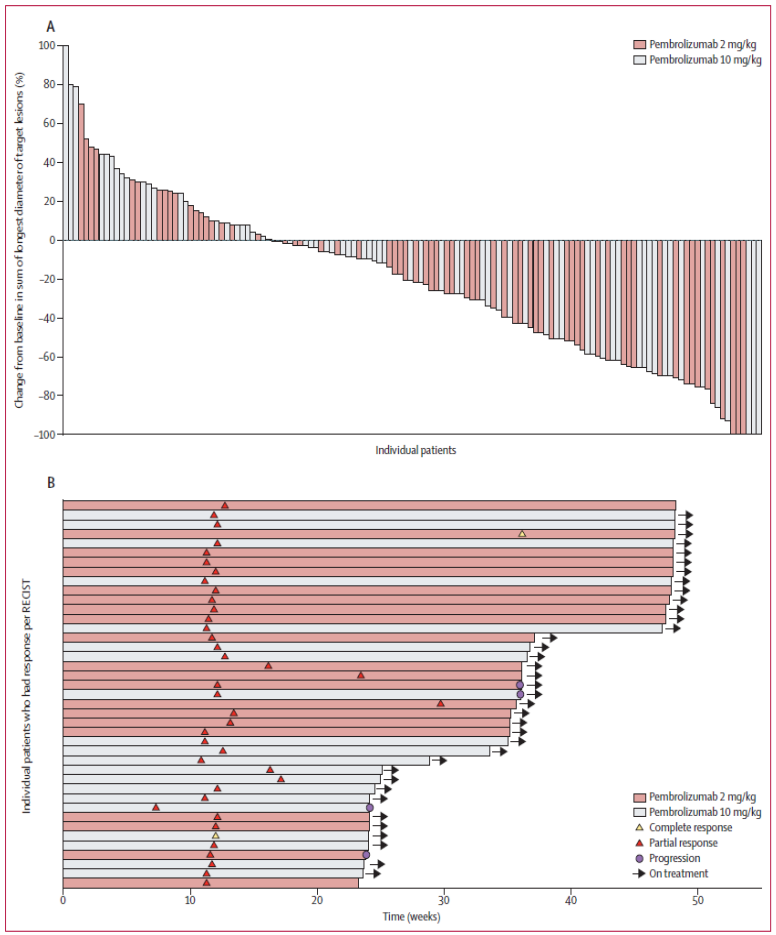
Ipilimumab Immune-related Toxicities

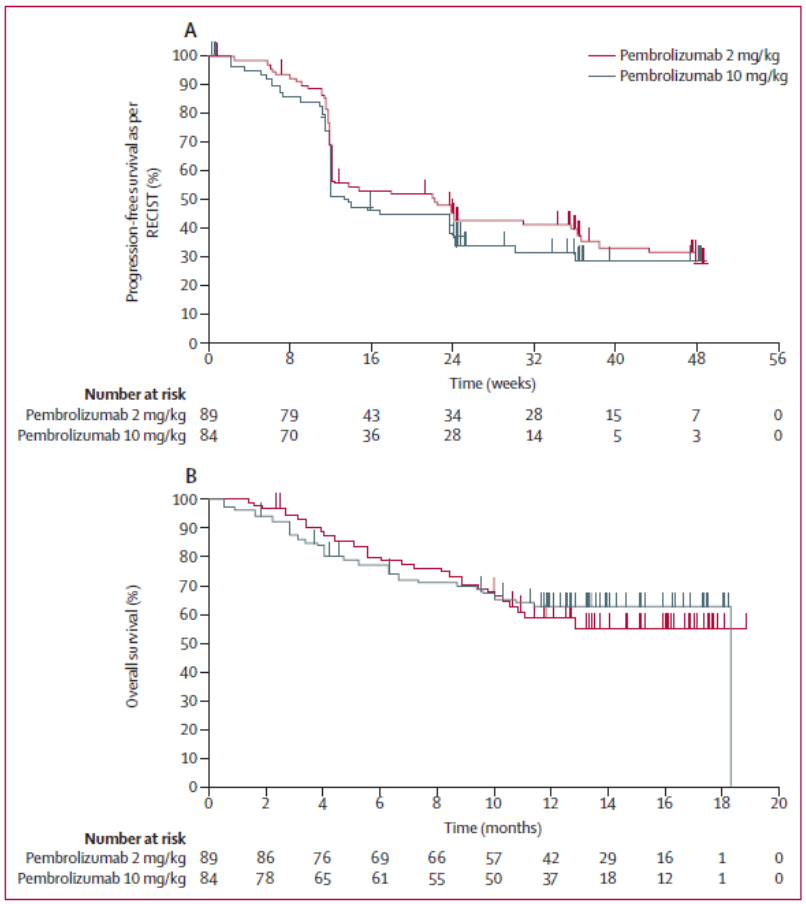
- Common autoimmune adverse events include:
  - Dermatitis
  - Hepatitis
  - Endocrinopathies/pituitary dysfunction
  - Enterocolitis
- Diarrhea is often the first manifestation of autoimmune toxicity, and requires prompt and aggressive treatment
  - Antidiarrheal agents (loperamide or diphenoxylate/atropine)
  - Oral budesonide
  - Intravenous and/or oral corticosteroids
  - Infliximab (anti-TNFα antibody)
  - Surgery in extreme cases (<1%)





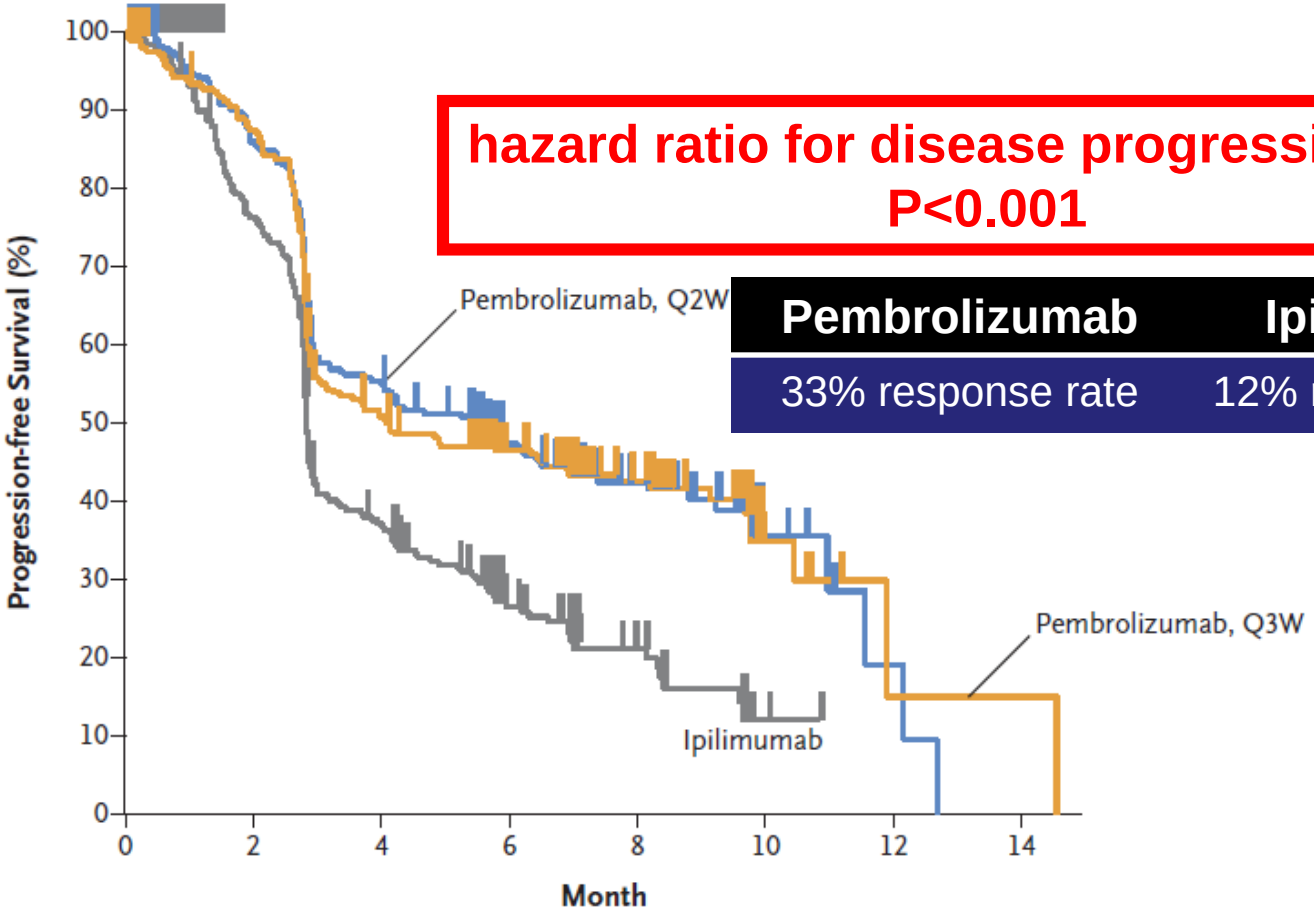
Pembrolizumab (Anti-PD1 Antibody) Leads To Rapid Responses and Prolongs Progression-free and Overall Survival Durably





Robert et al, *Lancet* 2014;384:1109

Pembrolizumab (Anti-PD1 Antibody) Leads To More Responses and Prolongs Progression-free Survival vs Ipilimumab

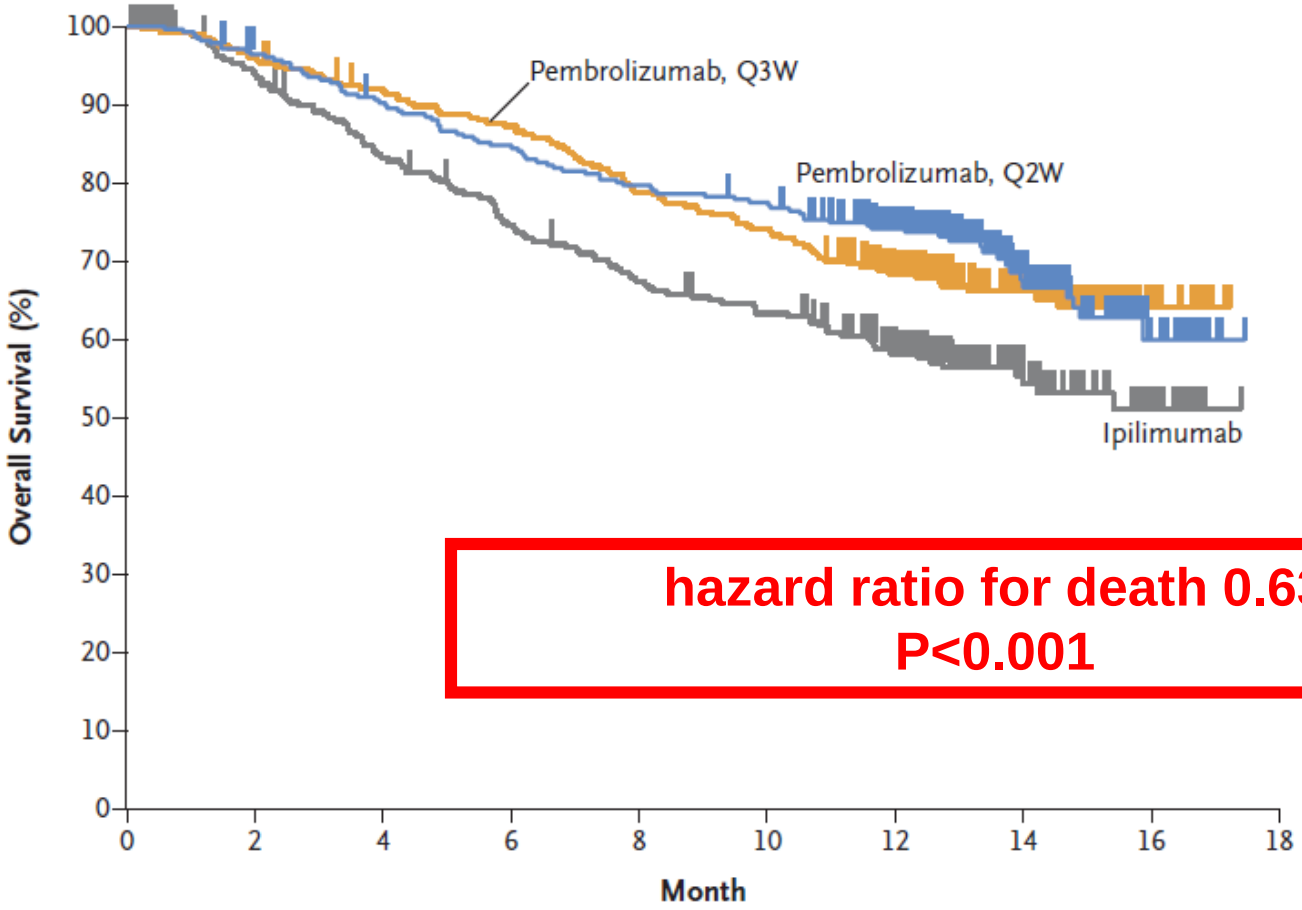


hazard ratio for disease progression 0.58
P<0.001

Pembrolizumab	Ipilimumab
33% response rate	12% response rate

Robert et al, *N Engl J Med* 2015;372:2521

Pembrolizumab (Anti-PD1 Antibody) Prolongs Overall Survival vs Ipilimumab



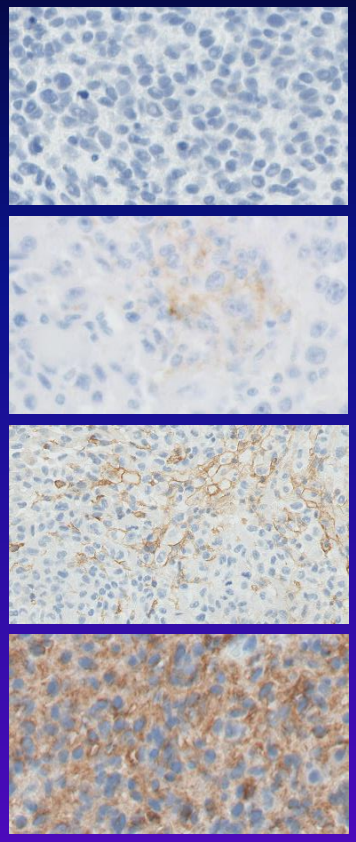
hazard ratio for death 0.63
P<0.001

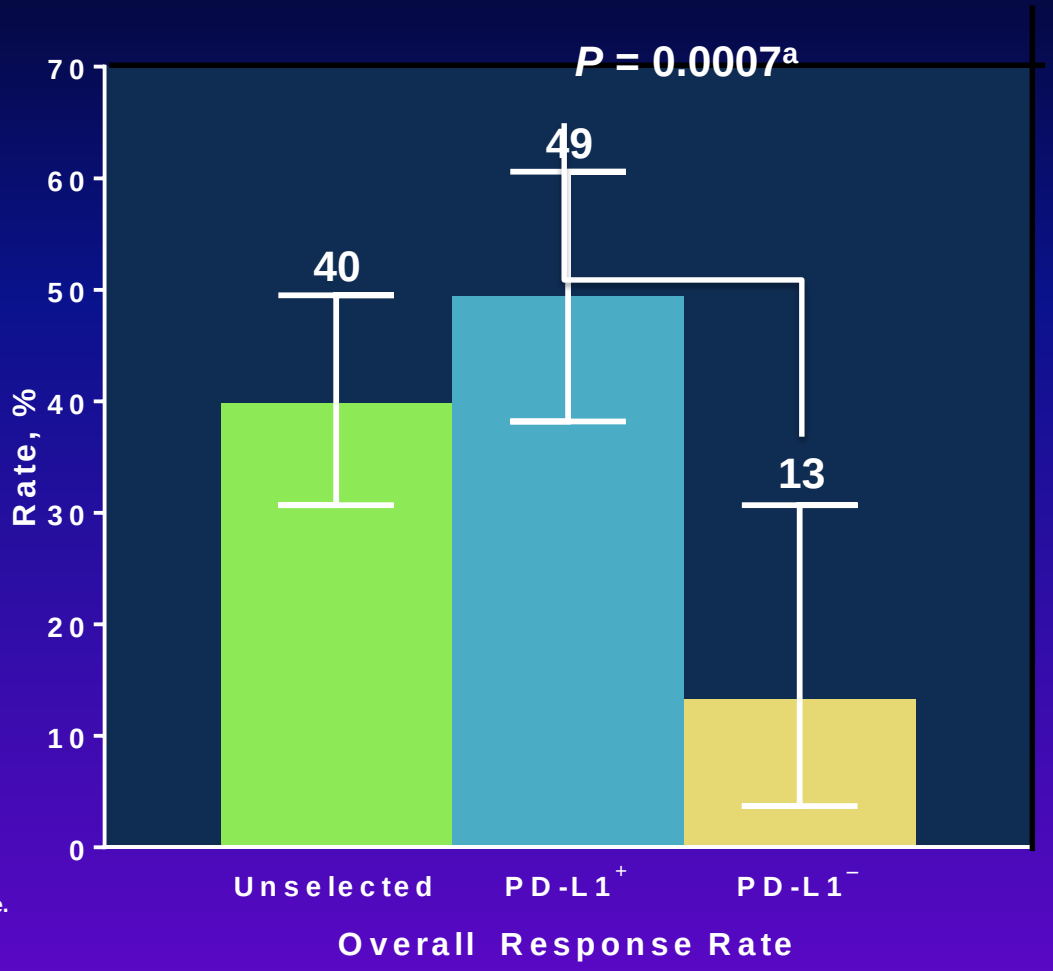
Robert et al, *N Engl J Med* 2015;372:2521

Unanswered Questions

- **Can we predict who will benefit from immune checkpoint antibody immunotherapy?**

Is Tumor PD-L1 Expression a Potential Biomarker of Response to Anti-PD1 Therapy?





[a]1-sided *P* values calculated by logistic regression, adjusting for dose/schedule.
PD-L1 positivity defined as staining in ≥1% of tumor cells.
125 patients were evaluable for PD-L1 expression.
Analysis cut-off date: October 18, 2013.
Daud A et al. Presented at: 2014 Annual AACR Meeting; April 5-9, 2014; San Diego, CA.

Presented by: Antoni Ribas

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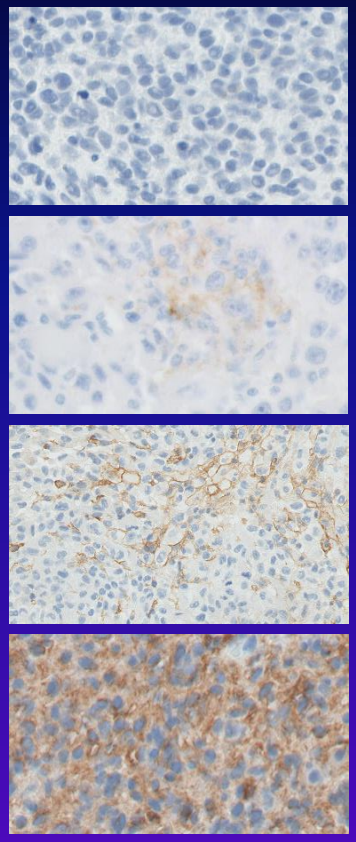

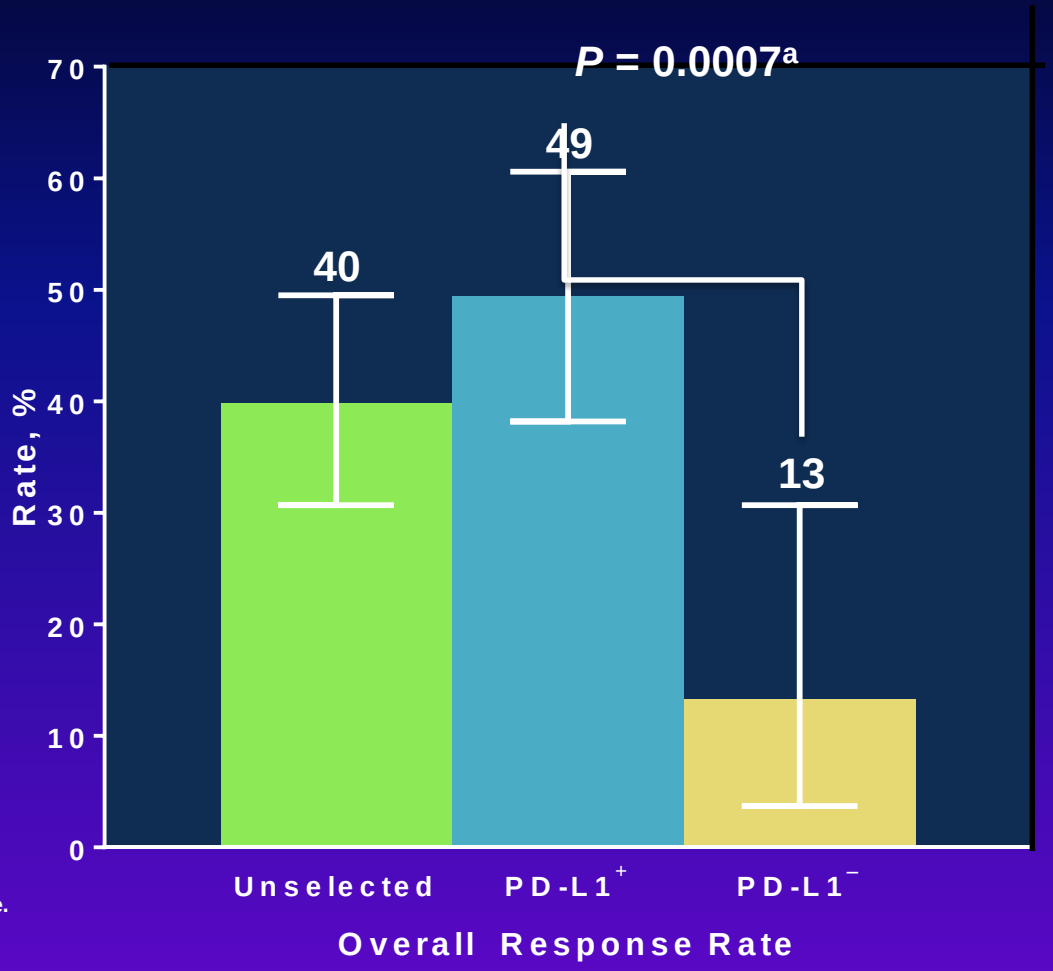

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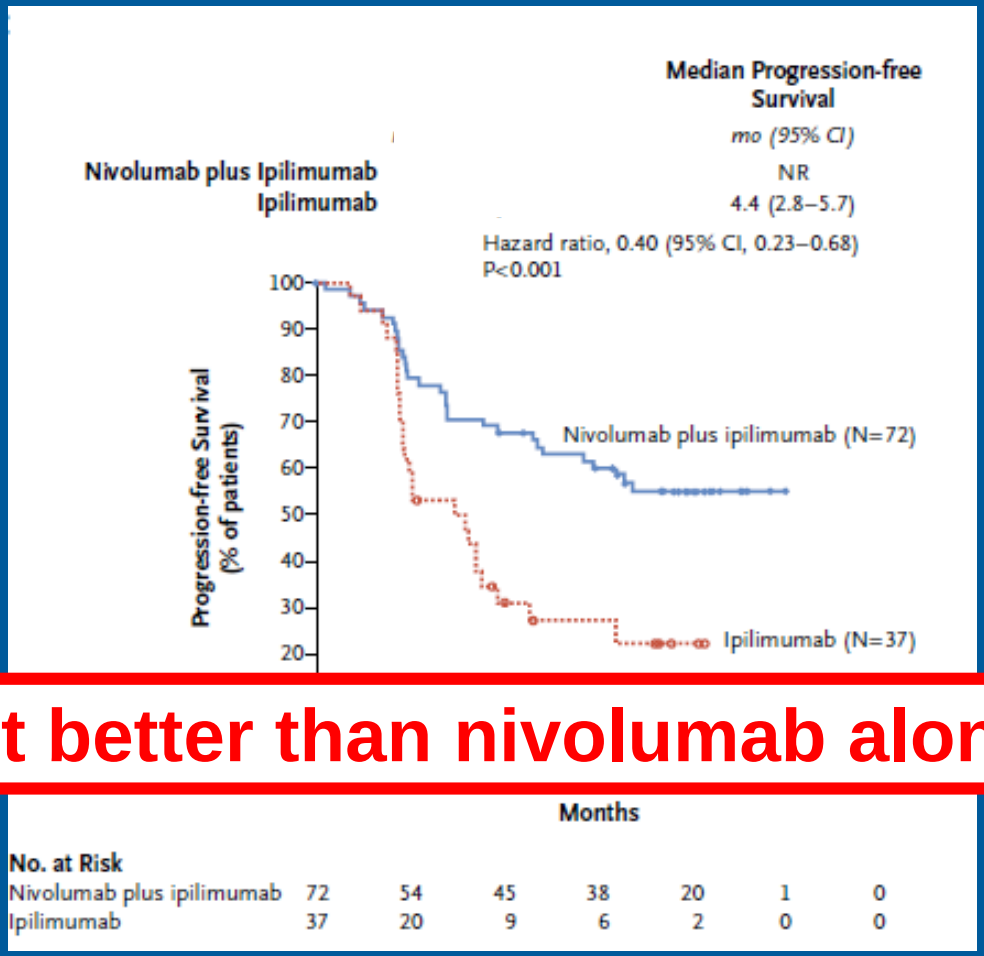
Unanswered Questions

- **Can we improve on the results of immunotherapy by combining antibodies concurrently or sequentially?**

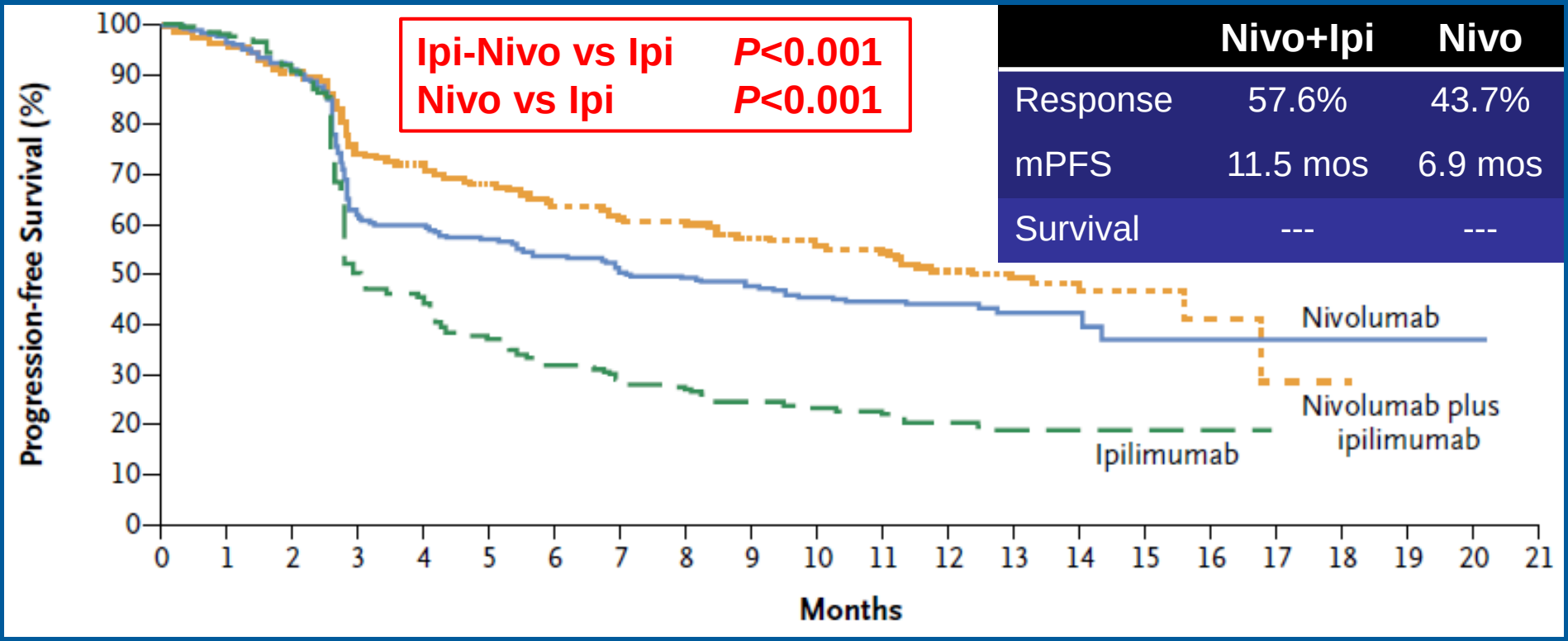
Combining nivolumab and ipilimumab is better than ipilimumab alone



But is it better than nivolumab alone????

Postow et al, *N Engl J Med* 2015;372:2006

Combining nivolumab and ipilimumab may be better than nivolumab alone



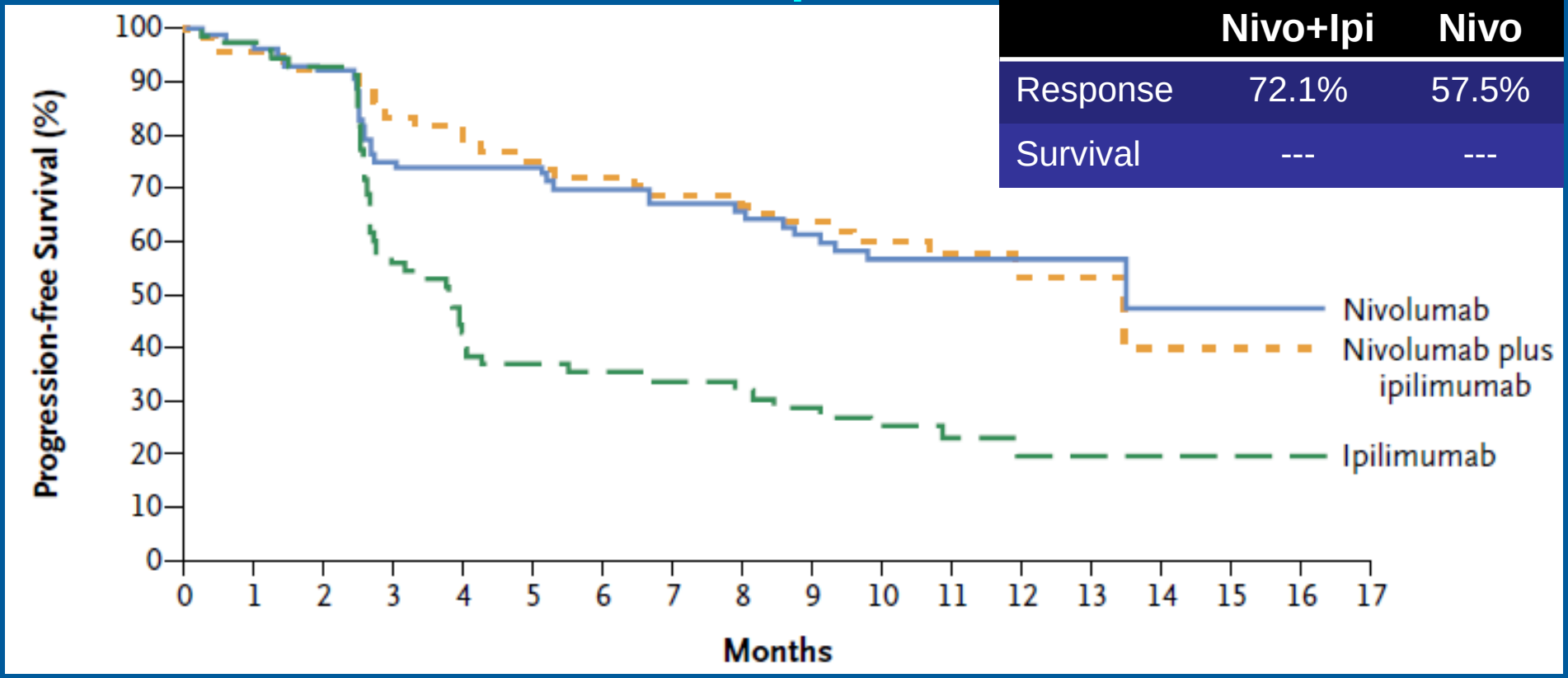
	Nivo+Ipi	Nivo
Response	57.6%	43.7%
mPFS	11.5 mos	6.9 mos
Survival	---	---

Larkin et al, *N Engl J Med* 2015;373:23

Combining nivolumab and ipilimumab may be better than nivolumab alone

Tumors with ≥5% PD-L1 expression (24% of patients)

	Nivo+Ipi	Nivo
Response	72.1%	57.5%
Survival	---	---

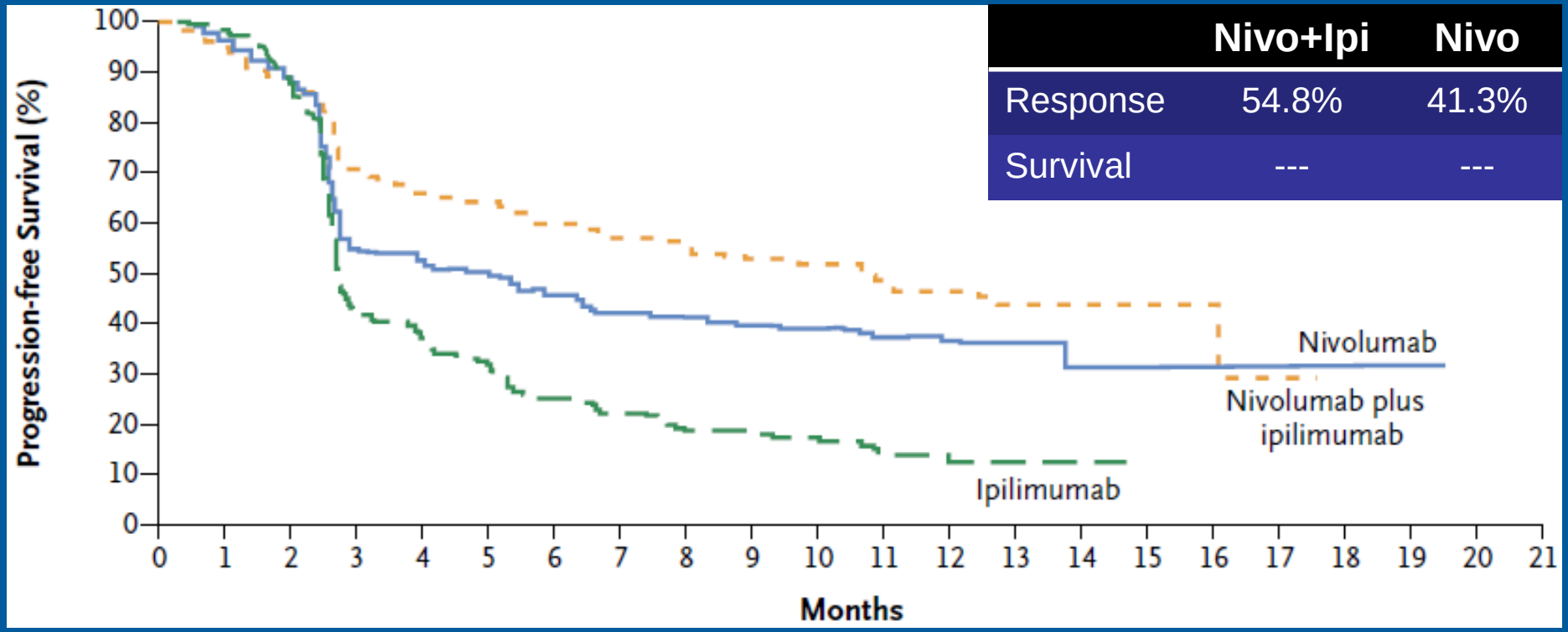


Larkin et al, *N Engl J Med* 2015;373:23

Combining nivolumab and ipilimumab may be better than nivolumab alone

Tumors with <5% PD-L1 expression (66% of patients)

	Nivo+Ipi	Nivo
Response	54.8%	41.3%
Survival	---	---



Larkin et al, *N Engl J Med* 2015;373:23

Combining nivolumab and ipilimumab is more toxic than ipilimumab alone

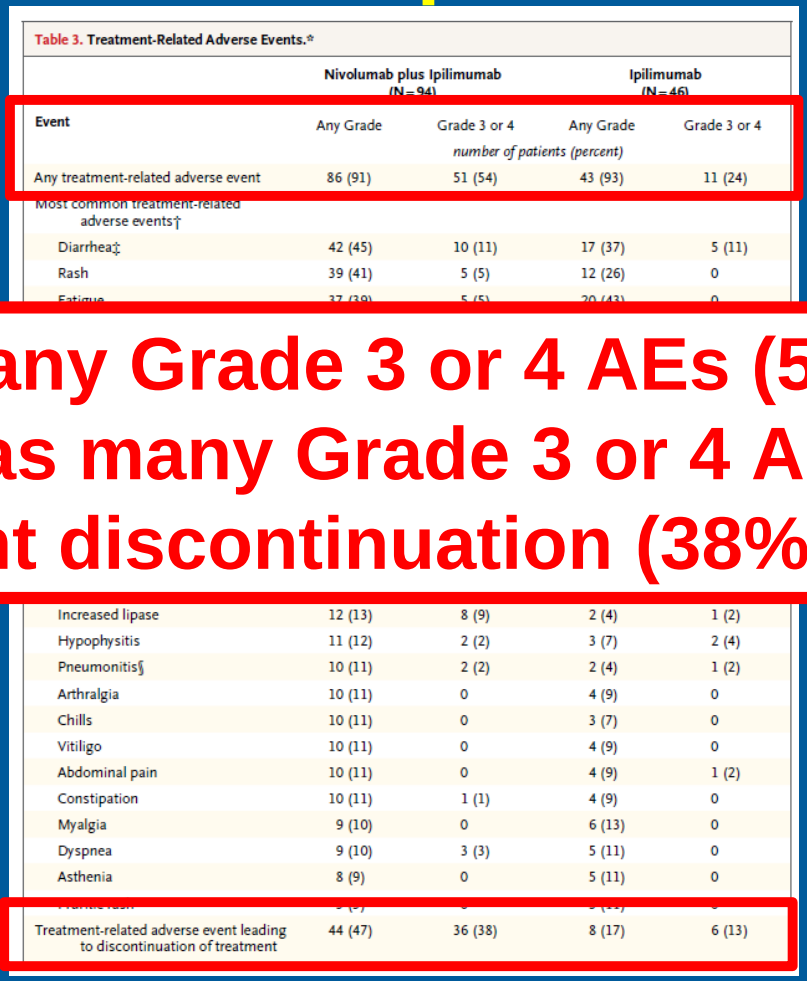


Table 3. Treatment-Related Adverse Events.*

Event	Nivolumab plus Ipilimumab (N=94)		Ipilimumab (N=46)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any treatment-related adverse event	86 (91)	51 (54)	43 (93)	11 (24)
Most common treatment-related adverse events†				
Diarrhea‡	42 (45)	10 (11)	17 (37)	5 (11)
Rash	39 (41)	5 (5)	12 (26)	0
Fatigue	37 (39)	5 (5)	20 (43)	0
Increased lipase	12 (13)	8 (9)	2 (4)	1 (2)
Hypophysitis	11 (12)	2 (2)	3 (7)	2 (4)
Pneumonitis§	10 (11)	2 (2)	2 (4)	1 (2)
Arthralgia	10 (11)	0	4 (9)	0
Chills	10 (11)	0	3 (7)	0
Vitiligo	10 (11)	0	4 (9)	0
Abdominal pain	10 (11)	0	4 (9)	1 (2)
Constipation	10 (11)	1 (1)	4 (9)	0
Myalgia	9 (10)	0	6 (13)	0
Dyspnea	9 (10)	3 (3)	5 (11)	0
Asthenia	8 (9)	0	5 (11)	0
Pruritic rash	5 (5)	0	5 (11)	0
Treatment-related adverse event leading to discontinuation of treatment	44 (47)	36 (38)	8 (17)	6 (13)

Twice as many Grade 3 or 4 AEs (54% vs 24%)
Three times as many Grade 3 or 4 AEs leading to treatment discontinuation (38% vs 13%)

Postow et al, *N Engl J Med* 2015;372:2006

Combining nivolumab and ipilimumab is much more toxic than nivolumab alone

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

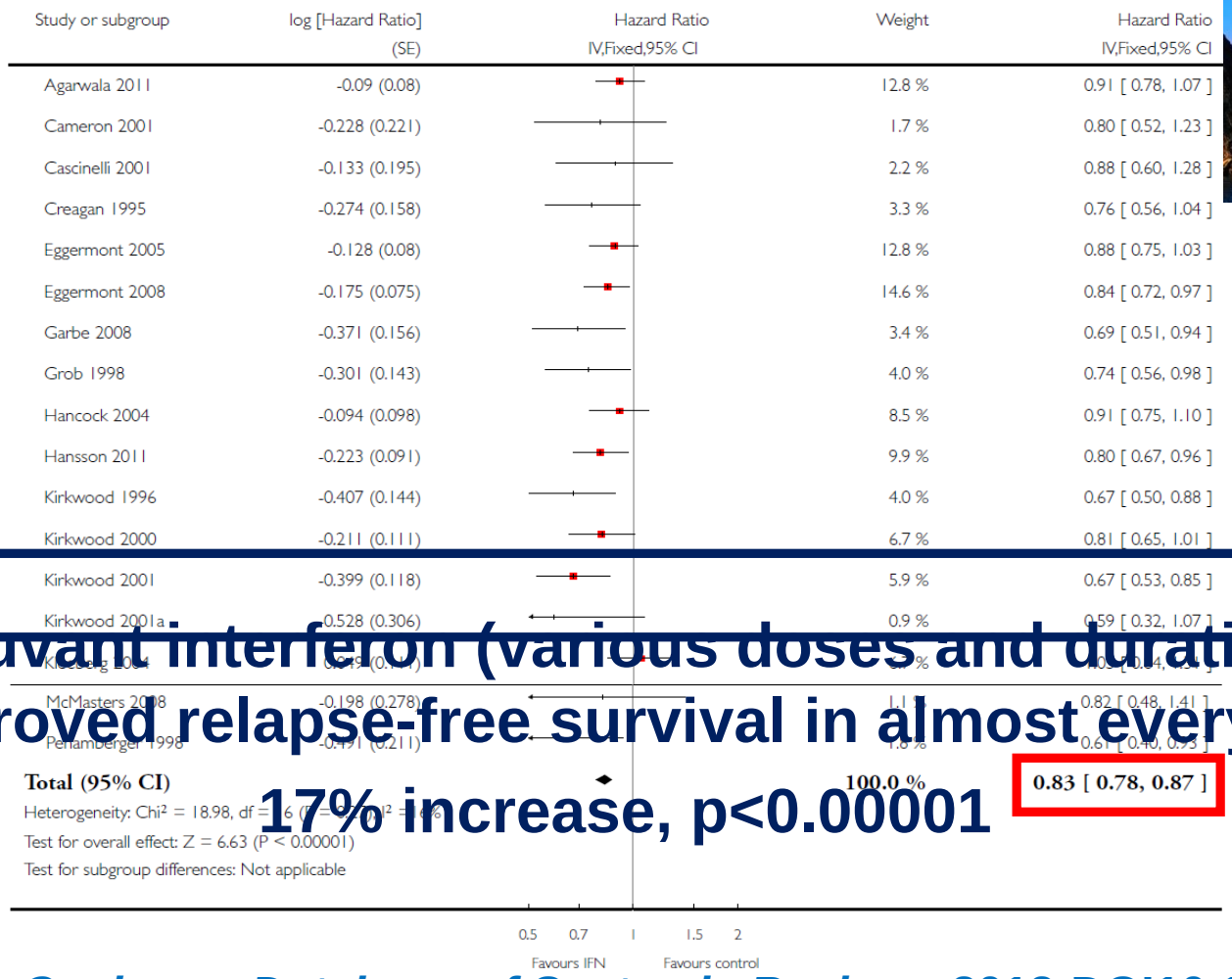
More Grade 3 or 4 AEs (69% vs 44%)
Six times as many Grade 3 or 4 AEs leading to treatment discontinuation (30% vs 5%)

Larkin et al, *N Engl J Med* 2015;373:23

Unanswered Questions

- **Can we introduce these new agents for advanced disease into the adjuvant setting?**

Meta-analysis of interferon impact on relapse-free survival

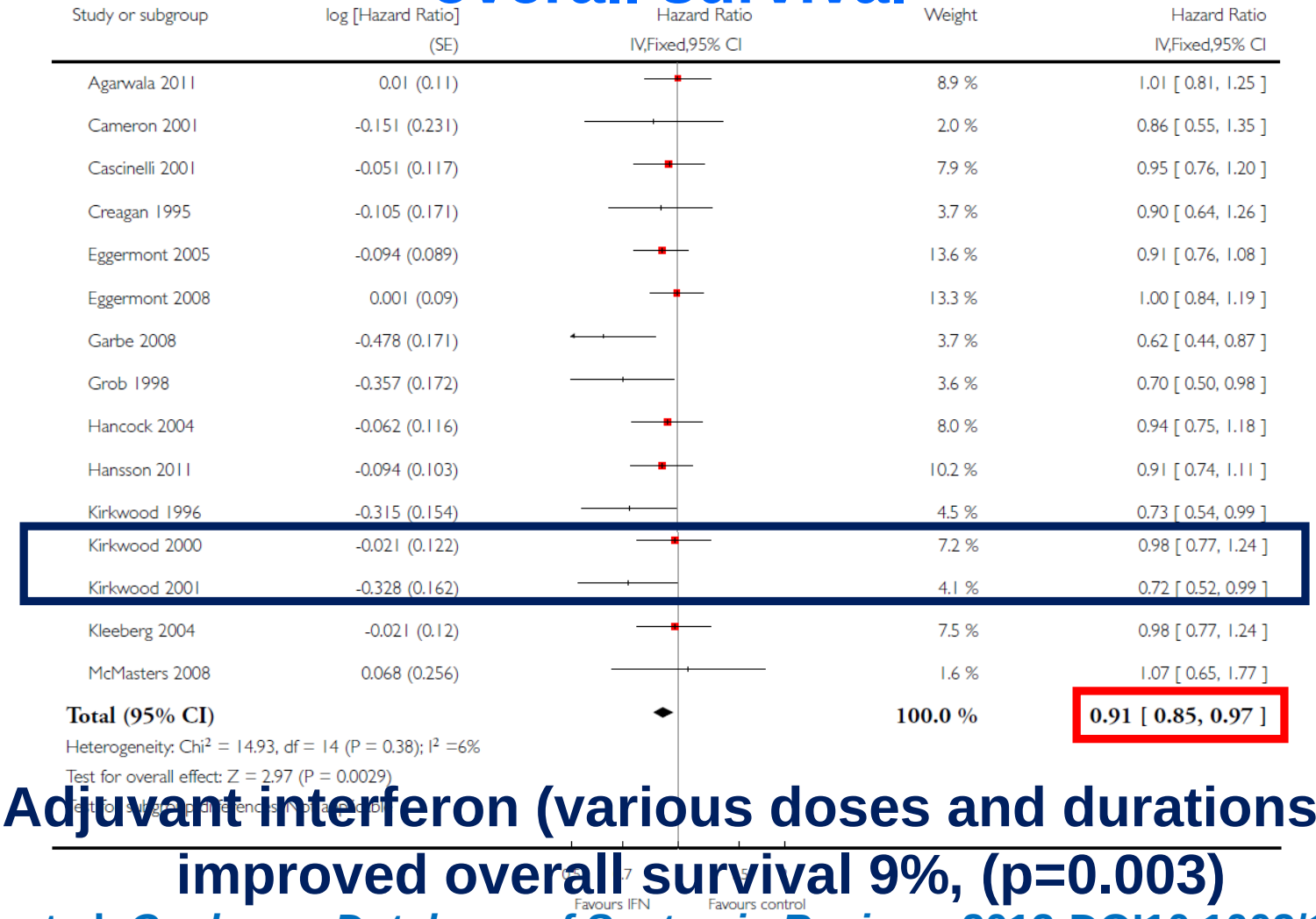


Adjuvant interferon (various doses and durations) improved relapse-free survival in almost every study

17% increase, p<0.00001

Mocellin et al, *Cochrane Database of Systemic Reviews* 2013;DOI10.1002/14651858

Meta-analysis of interferon impact on overall survival



Study or subgroup	log [Hazard Ratio] (SE)	Weight	Hazard Ratio IV,Fixed,95% CI
Agarwala 2011	0.01 (0.11)	8.9 %	1.01 [0.81, 1.25]
Cameron 2001	-0.151 (0.231)	2.0 %	0.86 [0.55, 1.35]
Cascinelli 2001	-0.051 (0.117)	7.9 %	0.95 [0.76, 1.20]
Creagan 1995	-0.105 (0.171)	3.7 %	0.90 [0.64, 1.26]
Eggermont 2005	-0.094 (0.089)	13.6 %	0.91 [0.76, 1.08]
Eggermont 2008	0.001 (0.09)	13.3 %	1.00 [0.84, 1.19]
Garbe 2008	-0.478 (0.171)	3.7 %	0.62 [0.44, 0.87]
Grob 1998	-0.357 (0.172)	3.6 %	0.70 [0.50, 0.98]
Hancock 2004	-0.062 (0.116)	8.0 %	0.94 [0.75, 1.18]
Hansson 2011	-0.094 (0.103)	10.2 %	0.91 [0.74, 1.11]
Kirkwood 1996	-0.315 (0.154)	4.5 %	0.73 [0.54, 0.99]
Kirkwood 2000	-0.021 (0.122)	7.2 %	0.98 [0.77, 1.24]
Kirkwood 2001	-0.328 (0.162)	4.1 %	0.72 [0.52, 0.99]
Kleeberg 2004	-0.021 (0.12)	7.5 %	0.98 [0.77, 1.24]
McMasters 2008	0.068 (0.256)	1.6 %	1.07 [0.65, 1.77]
Total (95% CI)		**100.0 %**	**0.91 [0.85, 0.97]**

Heterogeneity: Chi² = 14.93, df = 14 (P = 0.38); I² =6%

Test for overall effect: Z = 2.97 (P = 0.0029)

Test for subgroup differences: Not applicable

0.7 1 1.5

Favours IFN Favours control

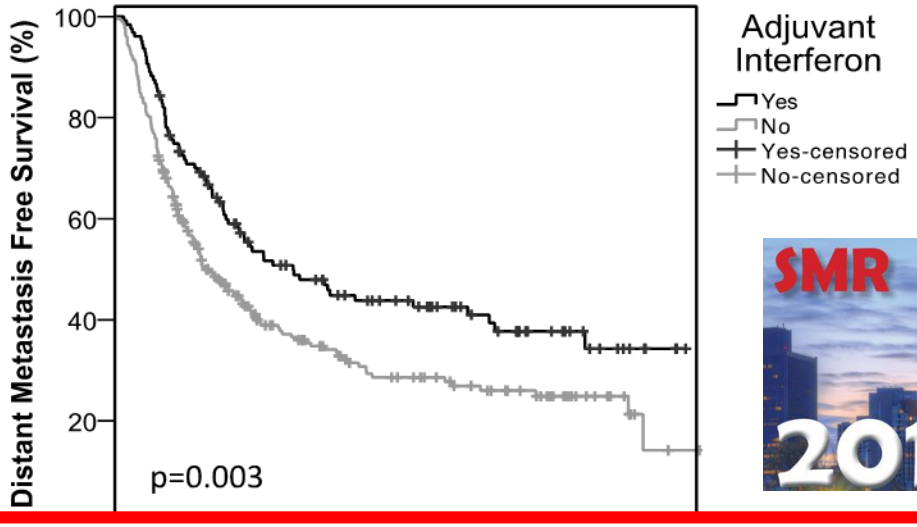
Adjuvant interferon (various doses and durations) improved overall survival 9%, (p=0.003)

Mocellin et al, *Cochrane Database of Systemic Reviews* 2013;DOI10.1002/14651858

ADJUVANT THERAPY OF MELANOMA

Moffitt Experience

Adjuvant Interferon Off Protocol

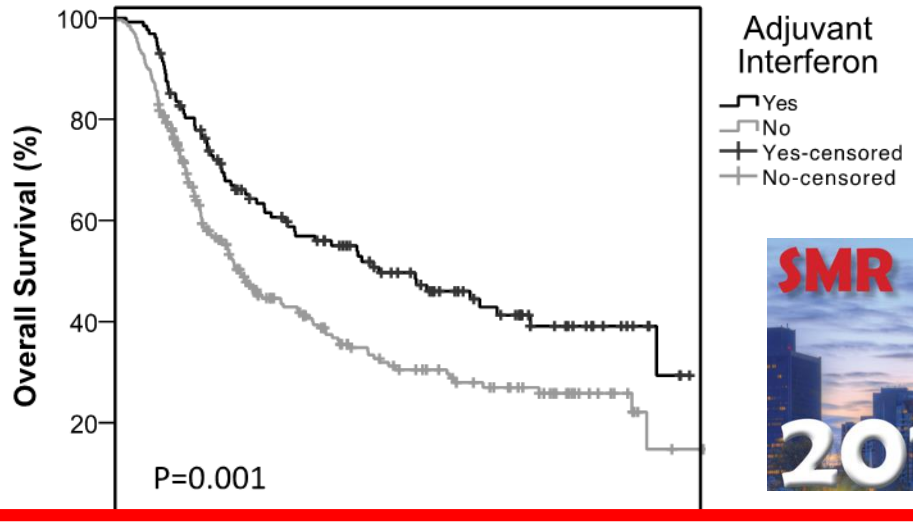


Adjuvant interferon in our non-randomized experience significantly improved Distant Metastasis-Free Survival (5-year estimate: 47.9% vs. 35.4%; hazard ratio 0.59) p=0.003

ADJUVANT THERAPY OF MELANOMA

Moffitt Experience

Adjuvant Interferon Off Protocol



Adjuvant interferon in our non-randomized experience significantly improved Overall Survival (5-year estimate: 56.9% vs. 40.6%; hazard ratio 0.61) P=0.001

ADJUVANT THERAPY OF MELANOMA

Ipilimumab 10 mg/kg

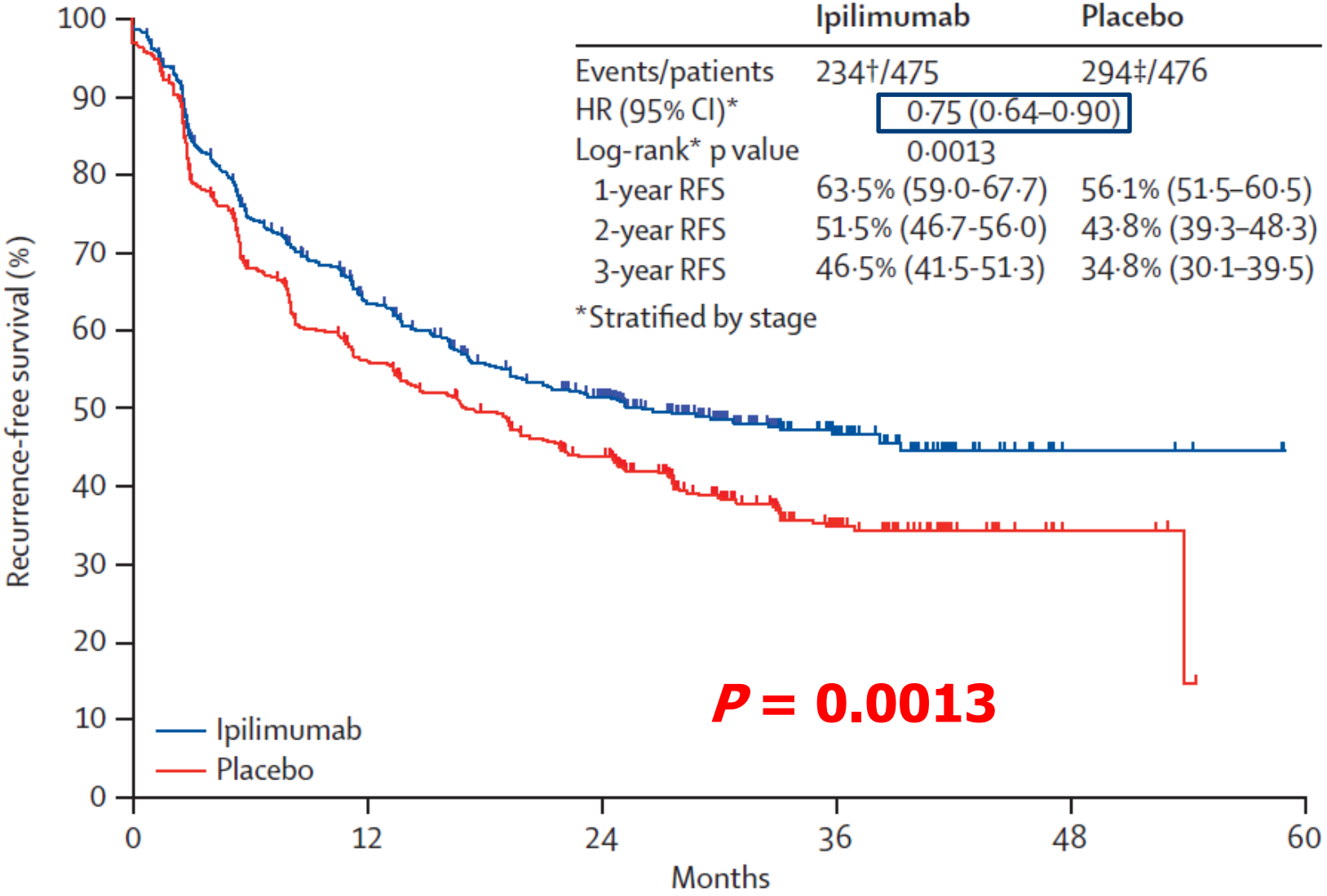
We can delay recurrence and improve survival with high-dose ipilimumab, but at a significant cost

Toxicity is very high

Treatment is for up to three years (if you get through four doses)

Crossover occurred in ~25% of placebo arm patients

Ipilimumab (10 mg/kg) x 3 years vs placebo

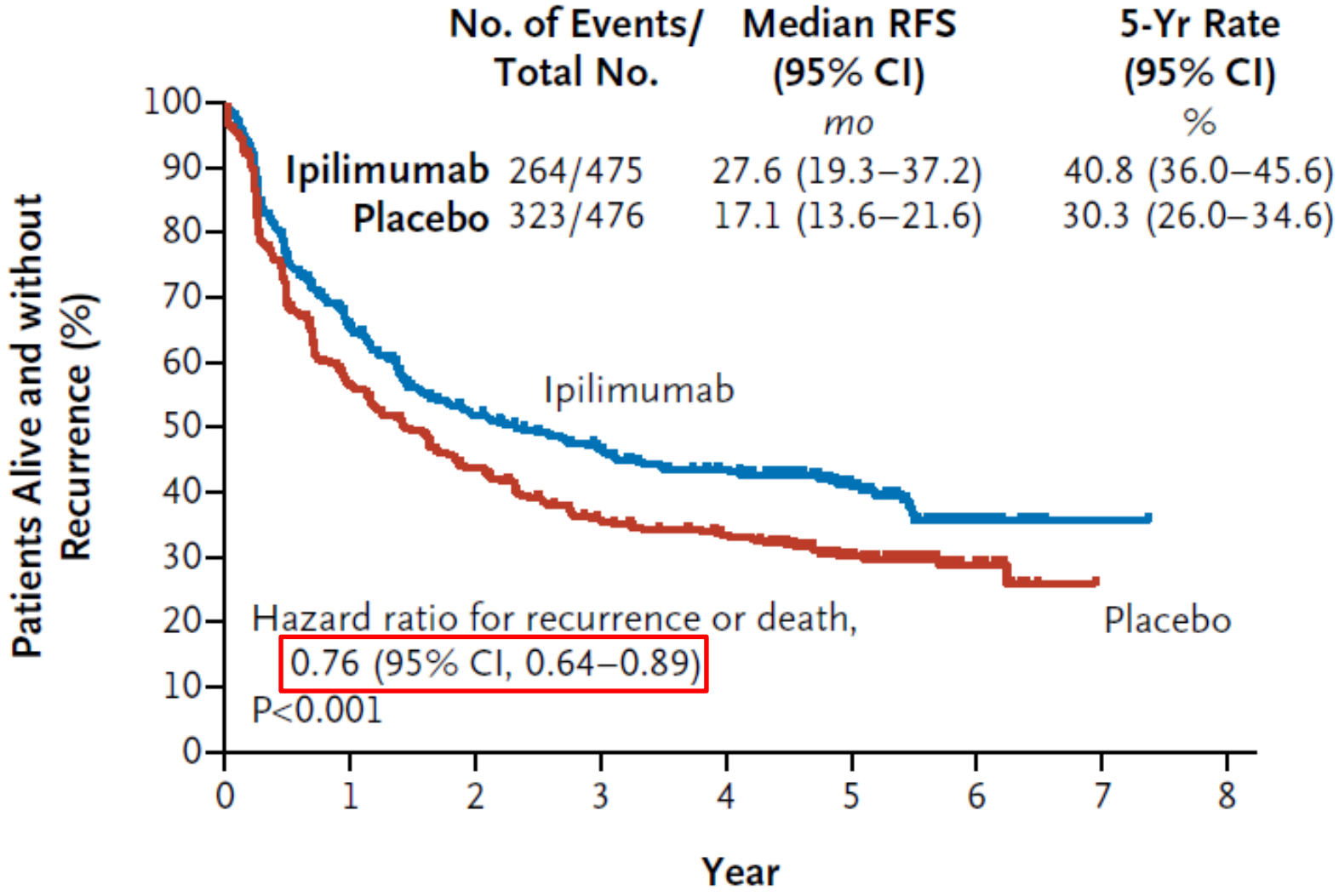


	Ipilimumab	Placebo
Events/patients	234†/475	294‡/476
HR (95% CI)*	0·75 (0·64–0·90)	
Log-rank* p value	0·0013	
1-year RFS	63·5% (59·0-67·7)	56·1% (51·5–60·5)
2-year RFS	51·5% (46·7-56·0)	43·8% (39·3–48·3)
3-year RFS	46·5% (41·5-51·3)	34·8% (30·1–39·5)

*Stratified by stage

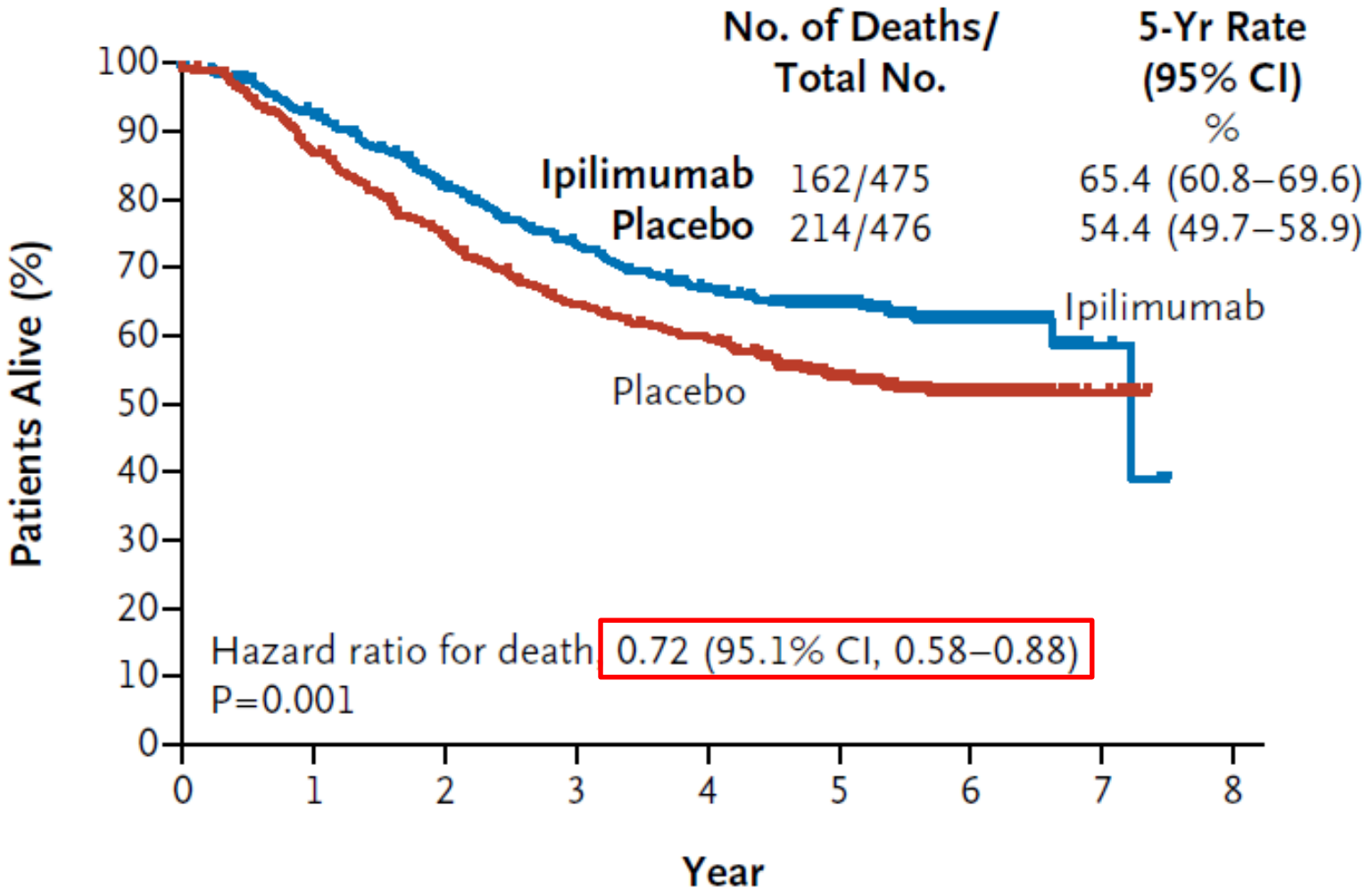
Eggermont et al, *Lancet Oncol* 2015;16:522

Ipilimumab (10 mg/kg) x 3 years vs placebo



Eggermont et al, *N Engl J Med* 2016;375:1845

Ipilimumab (10 mg/kg) x 3 years vs placebo



Eggermont et al, *N Engl J Med* 2016;375:1845

Immune-related Adverse Events

Ipilimumab (10 mg/kg) x 3 years vs placebo

	% Patients					
	Ipilimumab (n=471)			Placebo (n=474)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Any irAE	90.4	36.5	5.5	38.6	2.3	0.2
Dermatologic	63.3	4.5	0	20.9	0	0
Rash	34.4	1.3	0	11.0	0	0
Gastrointestinal	46.3	14.9	1.1	17.7	0.6	0.2
Diarrhea	41.4	9.6	0	16.7	0.4	0
Colitis*	15.9	6.8	0.8	1.3	0.2	0
Endocrine	37.6	7.9	0.6	6.5	0	0
Hypophysitis	18.3	4.7	0.4	0.4	0	0
Hypothyroidism	8.9	0.2	0	0.8	0	0
Hepatic	25.1	7.9	2.8	4.4	0.2	0
LFT increase	19.7	3.8	1.5	4.0	0	0
Neurologic	4.5	1.1	0.8	1.9	0	0
Other	23.6	7.4	0.4	4.4	1.7	0

LFT=liver function test.*Gastrointestinal perforations: ipilimumab, 6 related (1.3%); placebo, 3 unrelated (0.6%).

Eggermont et al, *Lancet Oncol* 2015;16:522

Resolution of Grade 2-4 Immune Adverse Events

	Ipilimumab (n=471)	Placebo (n=474)
Skin irAE		
N with event	129	14
Resolved, n (%)	115 (89.1)	13 (92.9)
Median, wks (95% CI)	5.5 (4.1–8.1)	2.6 (0.1–39.7)
Gastrointestinal irAE		
N with event	144	18
Resolved, n (%)	135 (93.8)	17 (94.4)
Median, wks (95% CI)	4.0 (2.7–5.1)	0.9 (0.4–1.9)
Hepatic irAE		
N with event	77	5
Resolved, n (%)	73 (94.8)	4 (80.0)
Median, wks (95% CI)	5.0 (3.7–8.4)	12.0 (1.1–NR)
Endocrine irAE		
N with event	134	5
Resolved, n (%)	75 (56.0)	4 (80.0)
Median, wks (95% CI)	31.0 (13.9–186.0)	12.6 (3.4–NR)

NR=not reached.

Eggermont et al, *Lancet Oncol* 2015;16:522

Fatal Adverse Events

Ipilimumab (10 mg/kg) x 3 years vs placebo

- 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

Eggermont et al, *Lancet Oncol* 2015;16:522

ADJUVANT THERAPY OF MELANOMA

What we soon will know

Ipilimumab

1. **Does ipilimumab at 3 or 10 mg/kg improve relapse-free survival compared to high-dose interferon?** E1609
2. **Does ipilimumab at 3 or 10 mg/kg improve overall survival compared to high-dose interferon?** E1609
3. **Does ipilimumab at 10 mg/kg improve relapse-free or overall* survival compared to nivolumab?** CheckMate238

Primary endpoint ***Secondary endpoint**

Unanswered Questions

- **Can we introduce these new agents before surgery (neoadjuvant therapy) to improve results from surgery or even avoid surgery entirely?**

Pretreatment PET-CT scan

Unresectable Stage IV melanoma from misdiagnosed primary

BRAF wild type

- **Patient deemed unresectable due to multiple pelvic and possible para-aortic nodes involved and entered onto a trial of sequential nivolumab followed by ipilimumab**
- **Tolerated 4 cycles of each relatively well, developed mild areas of vitiligo**
- **Switched per protocol to maintenance nivolumab every 2 weeks**

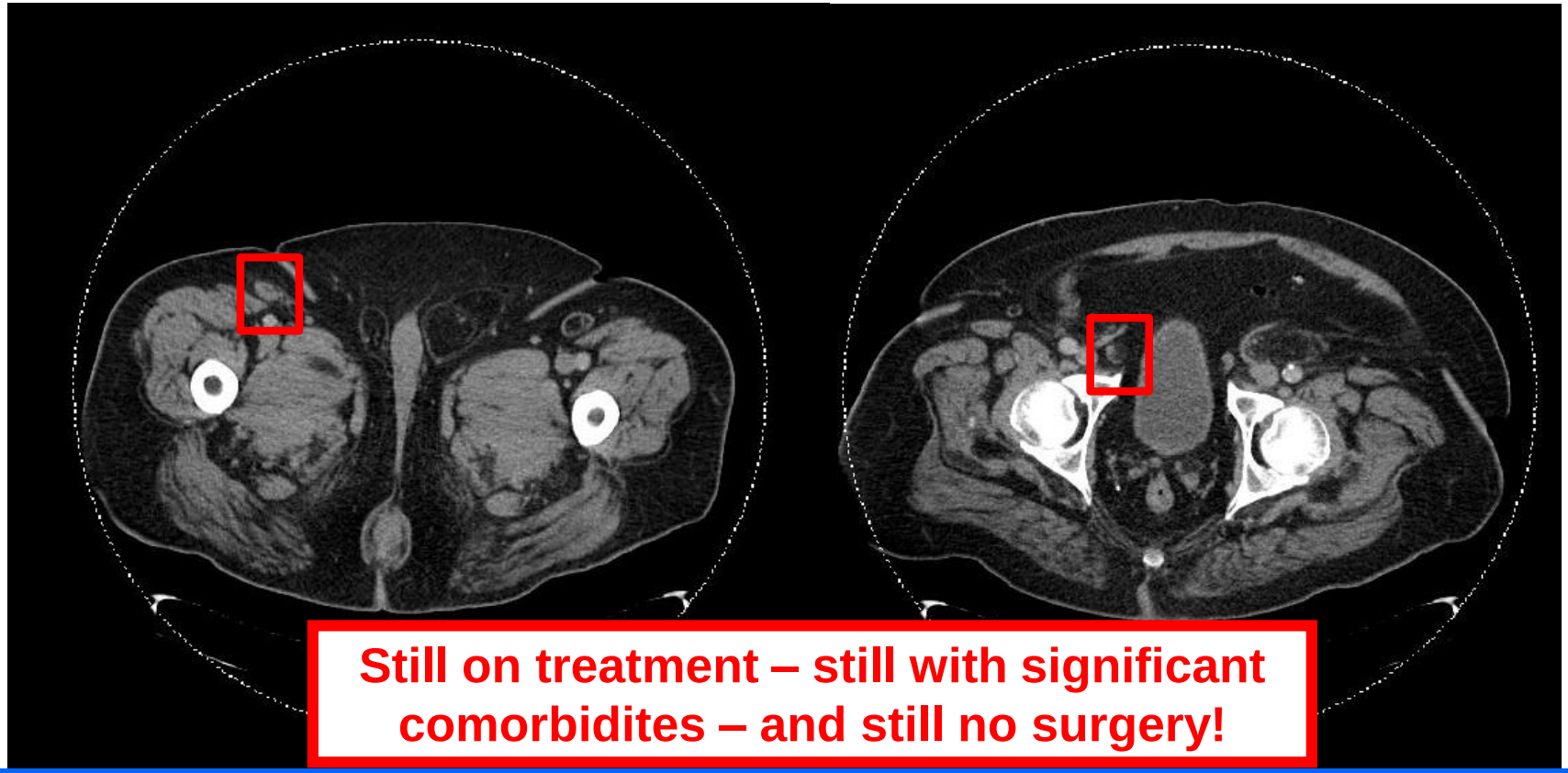
Neoadjuvant Therapy of Regionally Advanced or Metastatic Melanoma

Posttreatment PET-CT scan

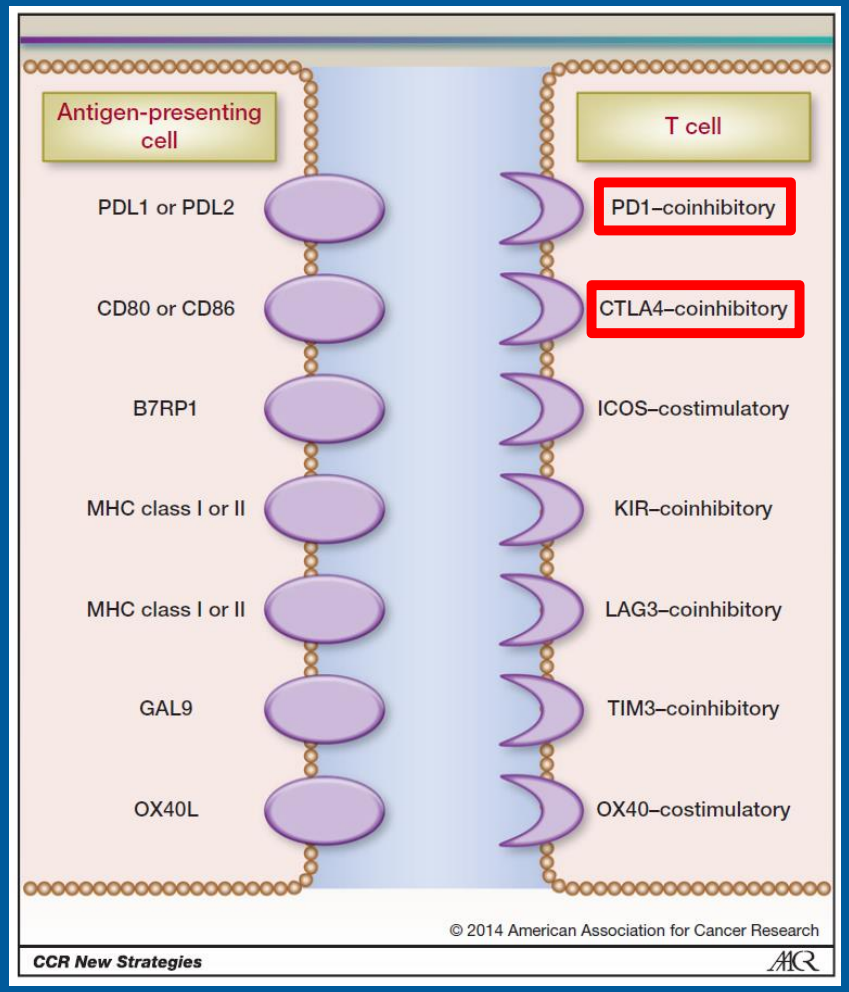
Unresectable Stage III melanoma from misdiagnosed primary

BRAF wild type

Sequential nivolumab>ipilimumab>nivolumab x24 months



PD1 and CTLA4 are not the only targets!



Forde et al, *Clin Cancer Res* 2014;20:1067

The Next Melanoma Revolution
The Right Care to the Right Patient at the Right Time

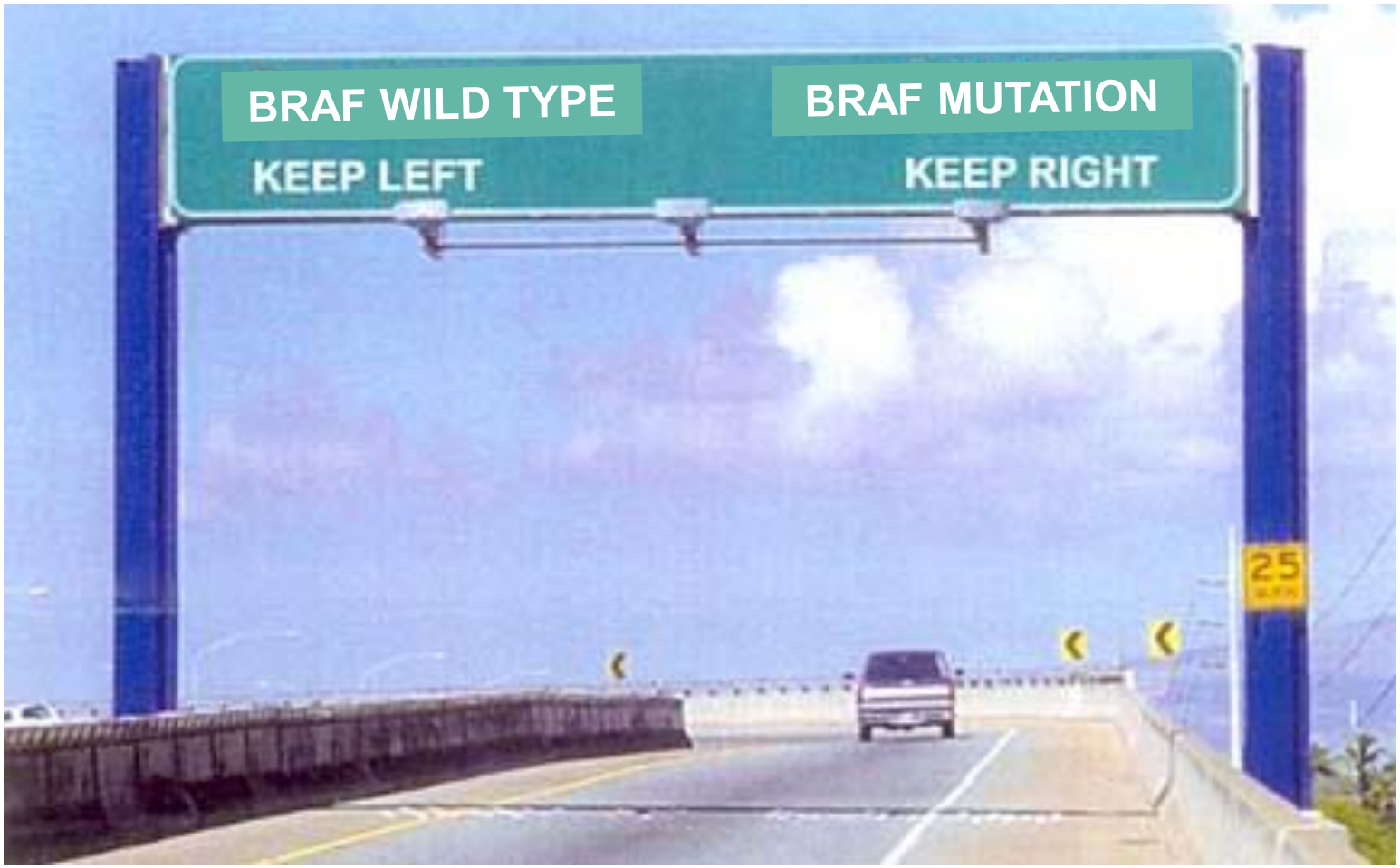
- Which treatment first and for how long?
- How much drug is enough?
- How best to move these drugs into the adjuvant setting?
- **Who's going to pay for all these miracle drugs?**

Ipilimumab $120,000 for four doses, pembrolizumab $12,500 per month, dabrafenib/trametinib $16,000 per month

Immunotherapy of Melanoma
The Bottom Line

- Checkpoint inhibitor therapy has revolutionized the management of advanced melanoma, but we still have many unanswered questions about optimal combinations, timing, doses, schedules and duration of treatment
- Adjuvant therapy with these agents to prevent melanoma recurrence after surgery is promising but associated with higher toxicity than using the same drugs in the advanced disease setting
- **The best treatment is <u>still</u> a clinical trial!**

The Fork in the Melanoma Road



The Fork in the Melanoma Road