Adjuvant Immunotherapy For High-risk Melanoma Where Have We Been And Where Are We Going?

Vernon K. Sondak, MD

Chair, Department of Cutaneous Oncology

Moffitt Cancer Center

Tampa, Florida

Society for Immunotherapy of Cancer
Tampa, Florida
December 5, 2014

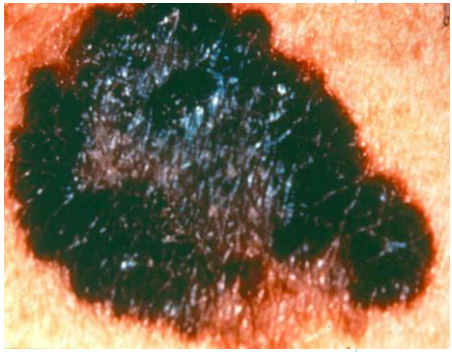
Disclosures

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

  The content of this presentation has been entirely controlled and prepared by Dr. Sondak, who is not acting as an agent or spokesperson for any company. No company had the right of final approval of the content and/or edits of this presentation.

Melanoma: Where are we?
2014 ACS Incidence Predictions

139,870 new cases of melanoma in the US predicted for 2014



- **76,100 invasive cases**
- **5,320 cases predicted in Florida***
- 63,770 noninvasive cases (melanoma in situ)
- 9,710 deaths predicted for US in 2014

* Second-most cases of any state in the US after California, (8,440 cases); New York third (4,240 cases)

Siegel et al, CA Cancer J Clin 2014;64:9

Melanoma: Where are we going? Future Incidence Predictions

76,100 new cases of invasive melanoma in the US predicted for 2014

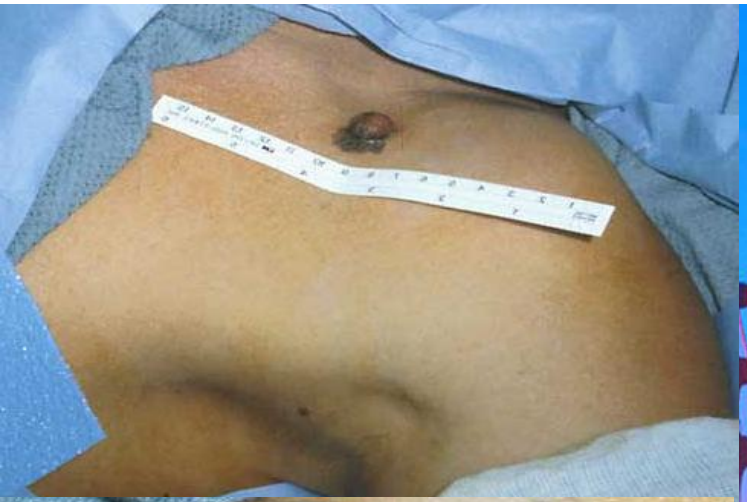
- **2020:** 111,000 invasive cases **+34,900**
- **2030:** 151,000 invasive cases **+74,900**
  - Fifth most common cancer behind breast (294,000), prostate (228,000), lung (225,000), and **thyroid** (183,000)

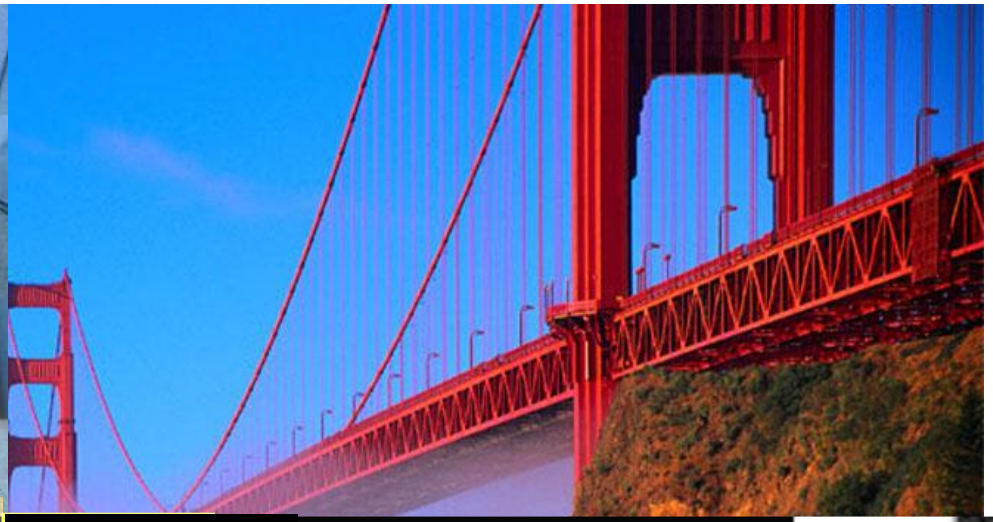
+ = increase compared to 2014 predictions

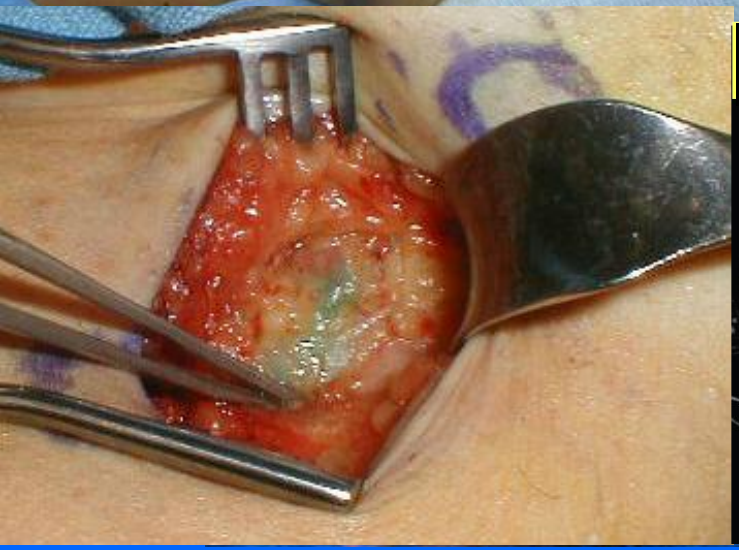
Rahib et al, Cancer Res 2014;74:2913

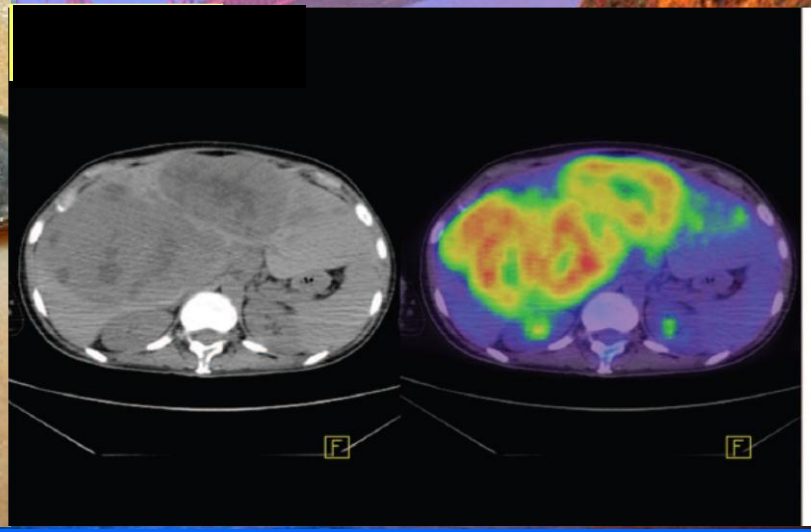
The “Adjuvant Therapy Bridge”

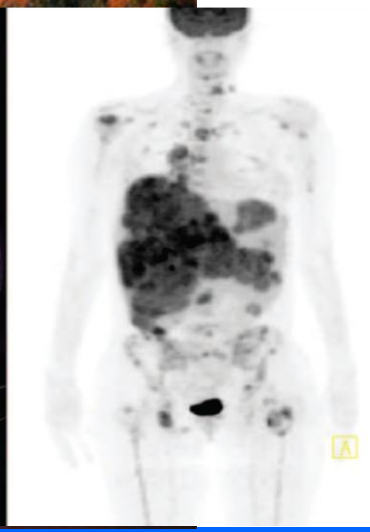
The “Adjuvant Therapy Bridge”







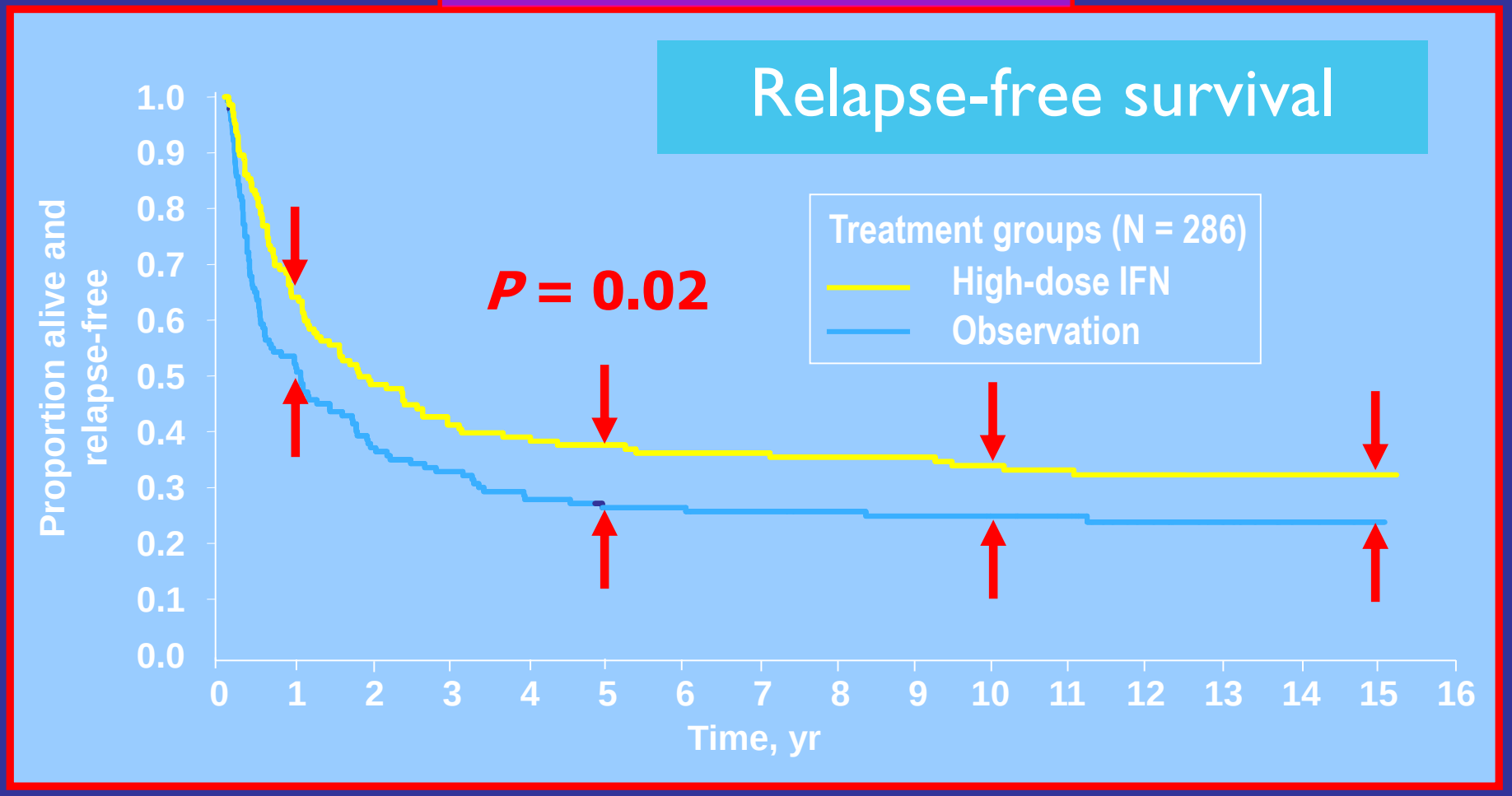




Long-term follow-up

Interferon alfa-2b x 1 year vs observation

E1684



Kirkwood et al Clin Cancer Res 2004;10:1670

Meta-analysis of interferon impact on relapse-free survival

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Agarwala 2011	-0.09 (0.08)		12.8 %	0.91 [0.78, 1.07]
Cameron 2001	-0.228 (0.221)		1.7 %	0.80 [0.52, 1.23]
Cascinelli 2001	-0.133 (0.195)		2.2 %	0.88 [0.60, 1.28]
Creagan 1995	-0.274 (0.158)		3.3 %	0.76 [0.56, 1.04]
Eggermont 2005	-0.128 (0.08)		12.8 %	0.88 [0.75, 1.03]
Eggermont 2008	-0.175 (0.075)		14.6 %	0.84 [0.72, 0.97]
Garbe 2008	-0.371 (0.156)		3.4 %	0.69 [0.51, 0.94]
Grob 1998	-0.301 (0.143)		4.0 %	0.74 [0.56, 0.98]
Hancock 2004	-0.094 (0.098)		8.5 %	0.91 [0.75, 1.10]
Hansson 2011	-0.223 (0.091)		9.9 %	0.80 [0.67, 0.96]
Kirkwood 1996	-0.407 (0.144)		4.0 %	0.67 [0.50, 0.88]
Kirkwood 2000	-0.211 (0.111)		6.7 %	0.81 [0.65, 1.01]
Kirkwood 2001	-0.399 (0.118)		5.9 %	0.67 [0.53, 0.85]
Kirkwood 2001a	-0.528 (0.306)		0.9 %	0.59 [0.32, 1.07]
Kleeberg 2004	-0.49 (0.111)		6.7 %	0.61 [0.49, 0.76]
McMasters 2008	-0.198 (0.278)		1.1 %	0.82 [0.48, 1.41]
Pehamberger 1998	-0.491 (0.211)		1.8 %	0.61 [0.40, 0.93]
Total (95% CI)			**100.0 %**	**0.83 [0.78, 0.87]**

Heterogeneity: Chi² = 18.98, df = 16 (P = 0.27); I² = 16%

Test for overall effect: Z = 6.63 (P < 0.00001)

Test for subgroup differences: Not applicable

0.5 0.7 1 1.5 2

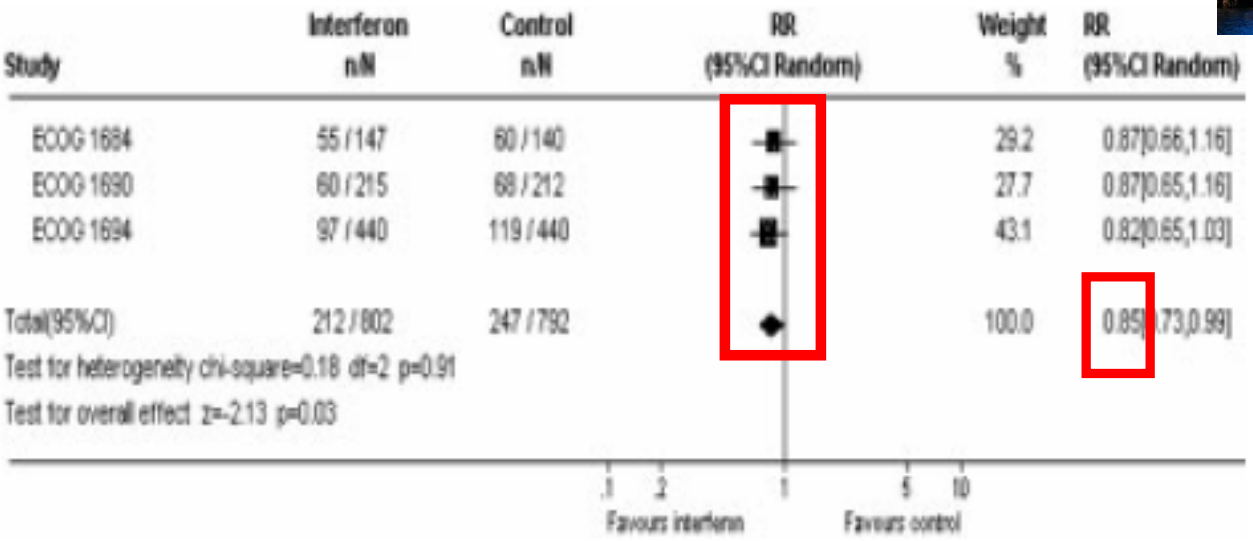
Favours IFN Favours control

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 high-dose interferon impact on survival at 2 years



High dose interferon for one year significantly improved survival at two years

(15% increase, p=0.03)

Verma et al Cancer 2006;106:1431

What difference does a few years make?

Chemotherapy	Immunotherapy	Targeted Therapy
Dacarbazine (DTIC) (FDA approved 1975)	Interleukin-2 (FDA approved 1998)	**Vemurafenib** (FDA approved 2011)
Temozolomide*	High-dose Interferon (FDA approved 1995)	**Dabrafenib** (FDA approved 2013)
Carboplatin/Paclitaxel*	**PEG-Interferon** (FDA approved 2011)	**Trametinib** (FDA approved 2013)
	Ipilimumab (FDA approved 2011)	**Dabrafenib+Trametinib** (FDA approved 2014)
	Pembrolizumab (accelerated approval for refractory disease 2014)	Imatinib*
Biochemotherapy* (Cisplatin, DTIC, Vinblastine, IL2, IFN)		

*Off-label use of FDA approved drug(s)

New melanoma drugs approved in past 3 years

ADJUVANT THERAPY OF MELANOMA

Where have we been?

We can delay recurrence with high-dose interferon, but at what cost?

Toxicity is high

Treatment is for a year

Interferon management recommendations

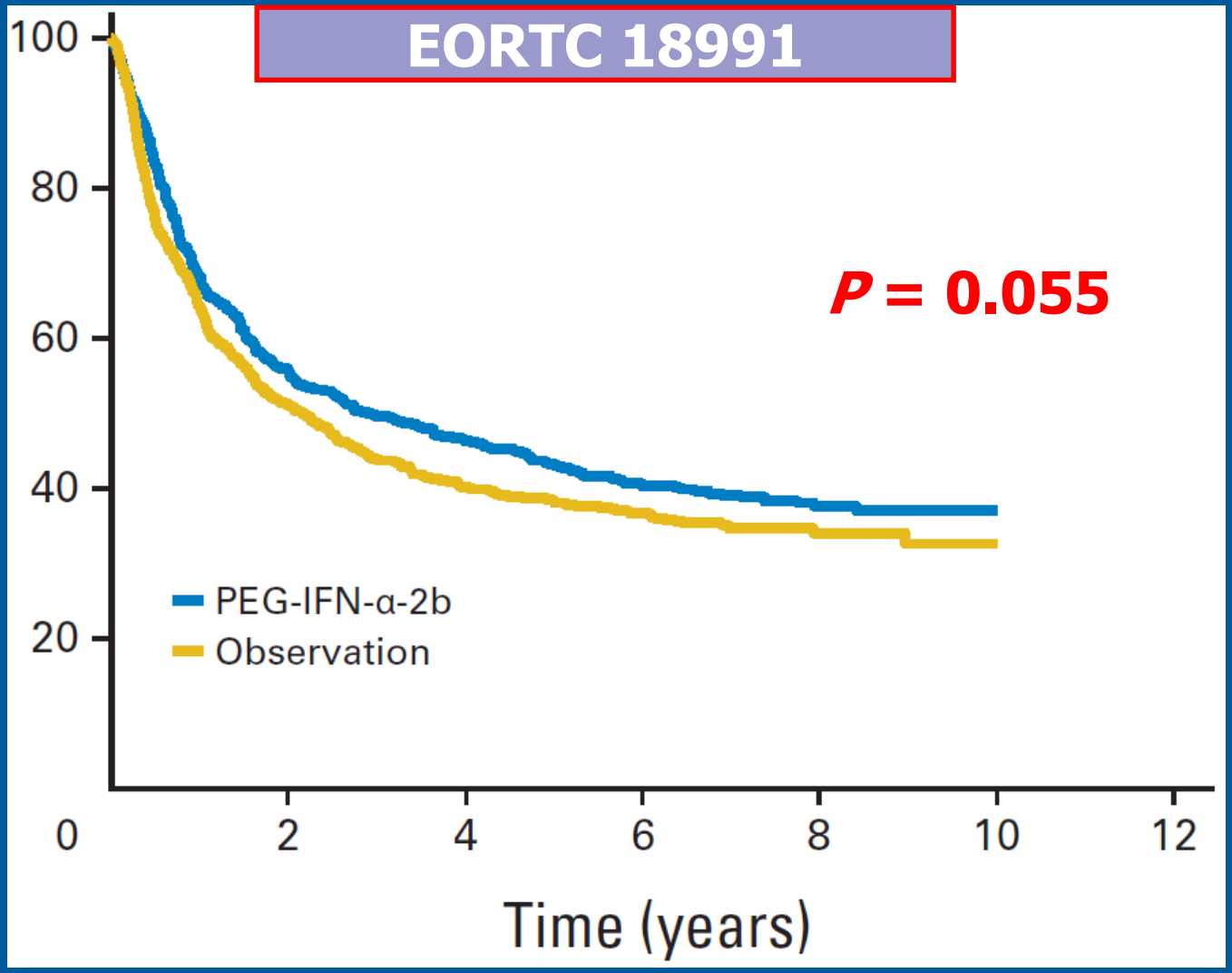
Society for Immunotherapy of Cancer consensus statement on tumour immunotherapy for cutaneous melanoma

Management issue: Treatment of interferon-α2b-related depression

- Can be a significant adverse effect of therapy
- Special attention to history of depression and related disorders before treatment is warranted
- Major depression is a relative contraindication to treatment
- The majority consensus opinion was to use antidepressants in selected patients who develop depression during therapy (45.5%)
- A large minority opinion suggested prophylactic antidepressants should be started at the time of treatment initiation in all patients (31.8%)
- A minority of the panel recommended referral to a psychologist before starting treatment for all patients (13.6%)
- A minority of the panel recommended selective referral to a psychologist only if and when symptoms develop (13.6%)
- Some panel members suggested both antidepressants and psychology referral should be considered

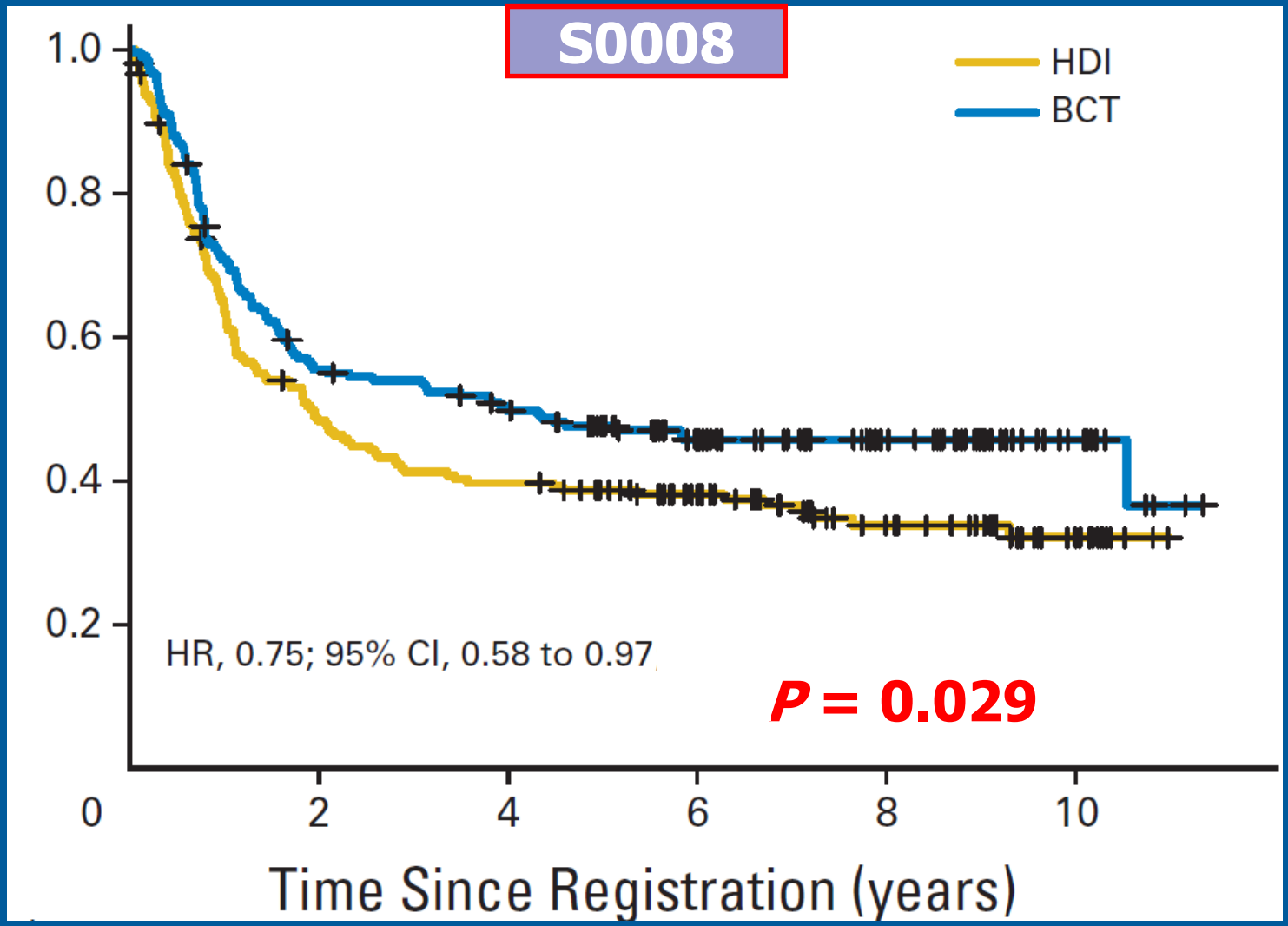
Kaufman et al, Nat Rev Clin Oncol 2013;10:588

Peginterferon alfa-2b x 5 years vs observation



Eggermont et al, J Clin Oncol 2012;30:3810

Biochemotherapy x 3 months vs interferon alfa-2b x 1 year

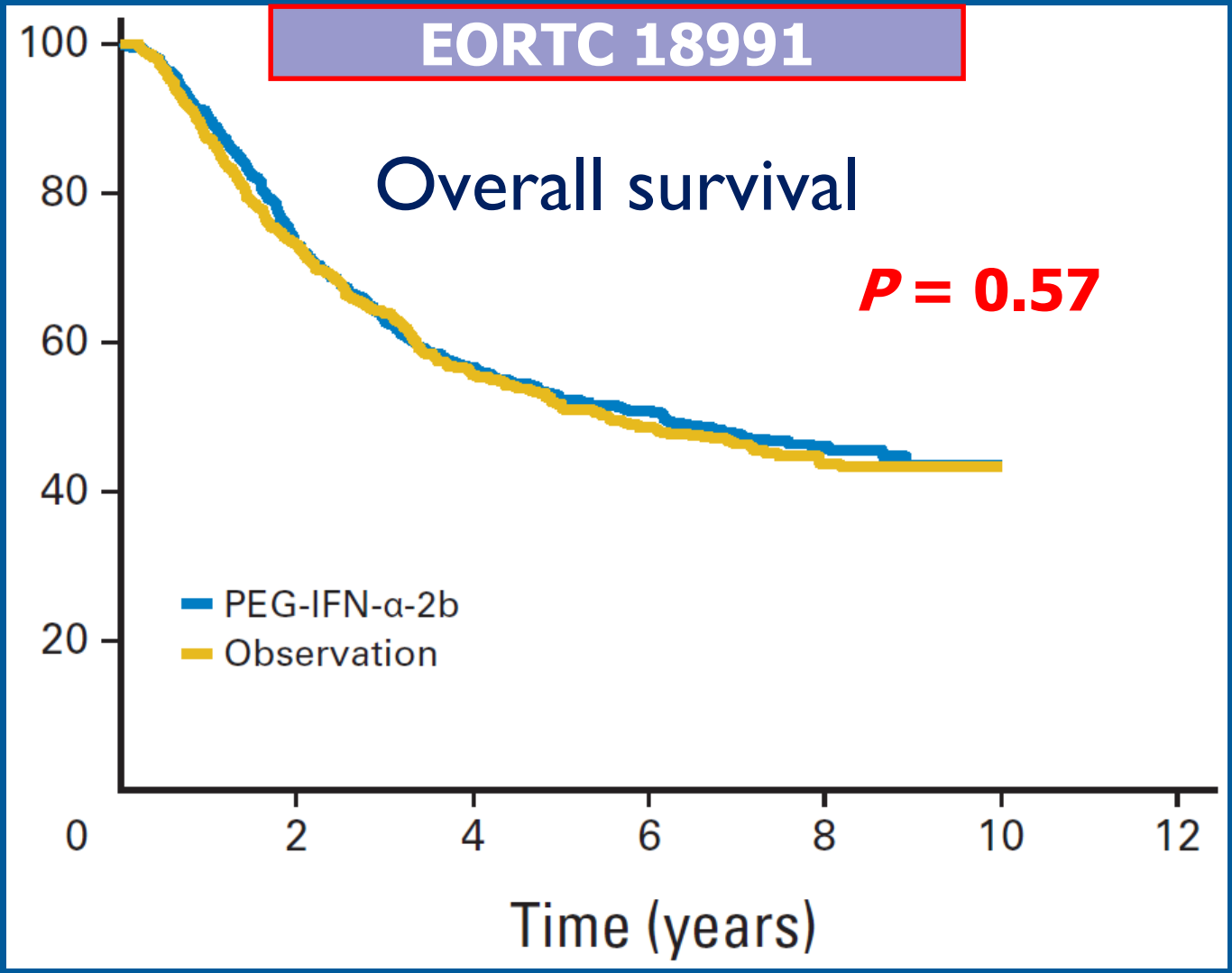


Flaherty et al, J Clin Oncol 2014; epub

Where have we been?

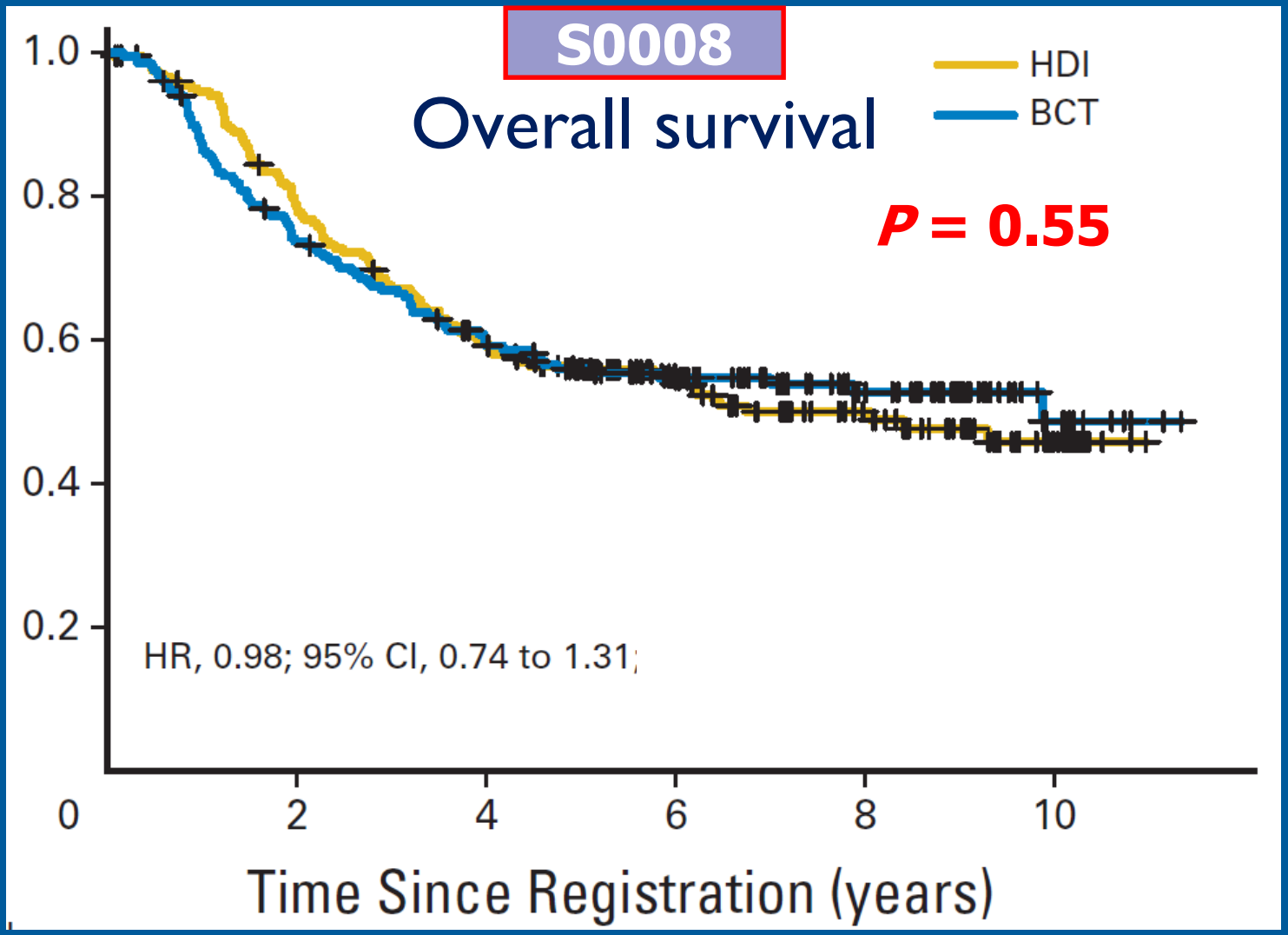
We can delay recurrence with high-dose or pegylated interferon or with biochemotherapy, but can we improve survival?

Peginterferon alfa-2b x 5 years vs observation



Eggermont et al, J Clin Oncol 2012;30:3810

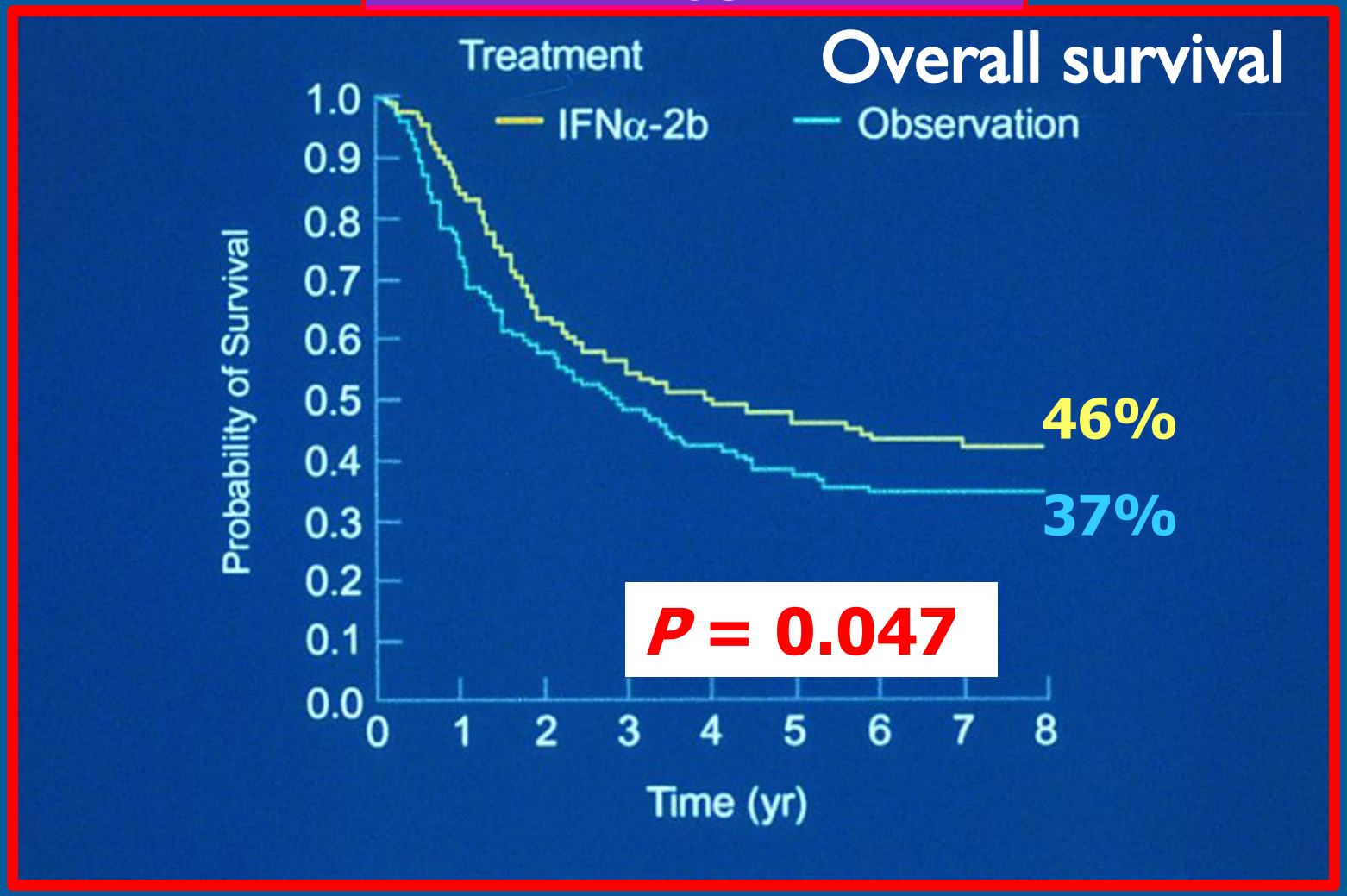
Biochemotherapy x 3 months vs interferon alfa-2b x 1 year



Flaherty et al, J Clin Oncol 2014; epub

Interferon alfa-2b x 1 year vs observation

E1684

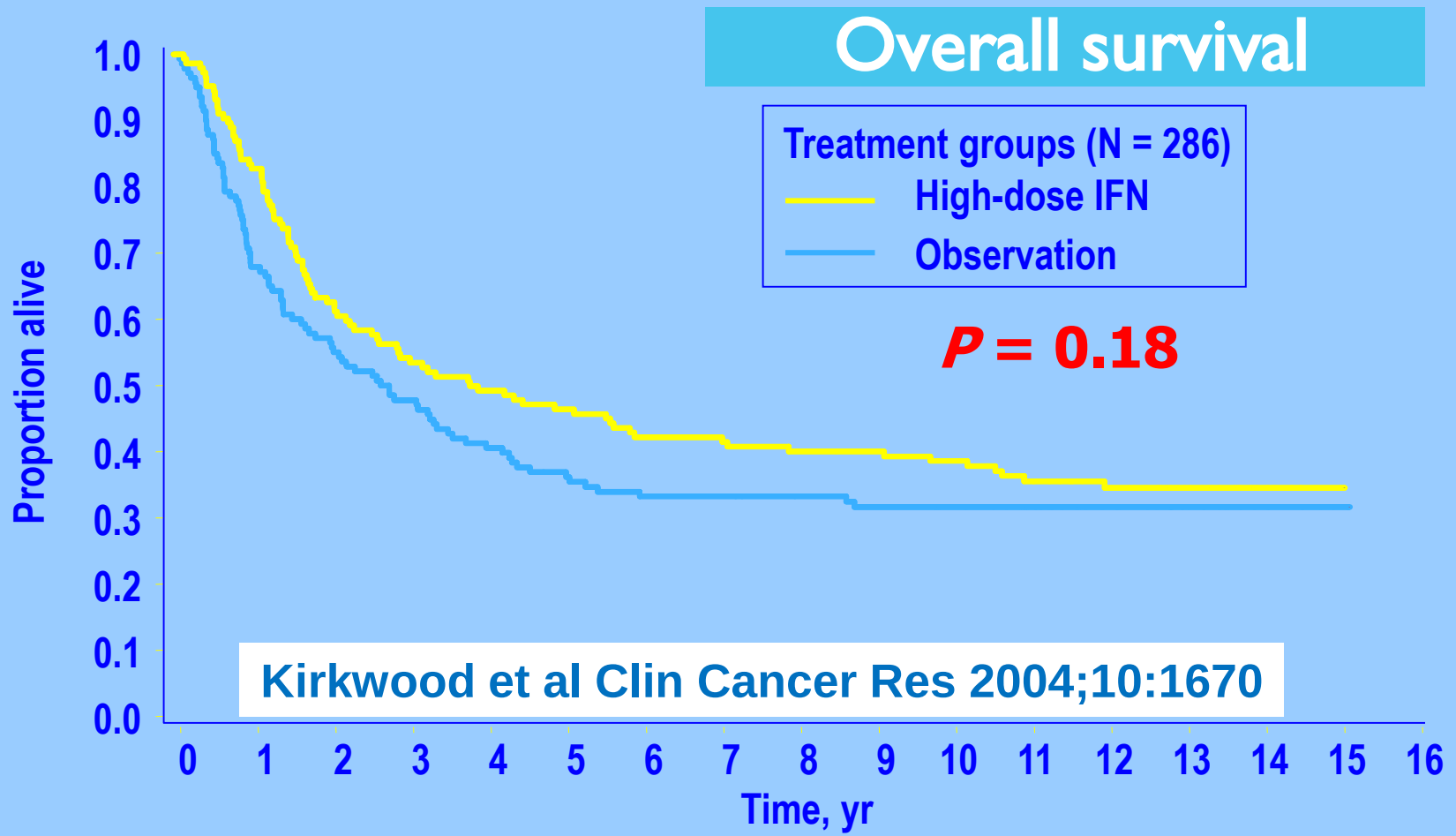


Kirkwood et al J Clin Oncol 1996;14:7

Long-term follow-up

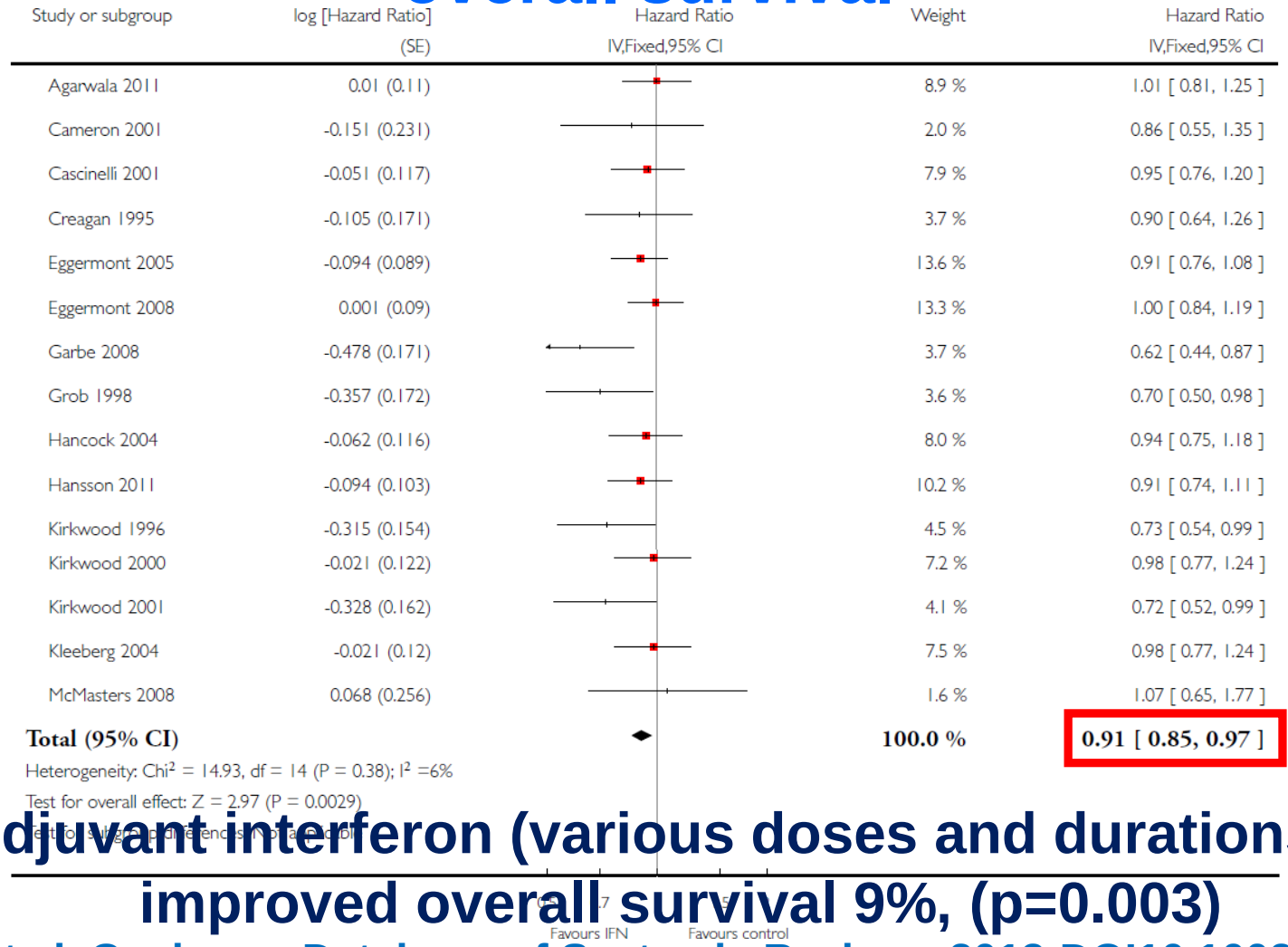
Interferon alfa-2b x 1 year vs observation

E1684



	Total	Dead	Alive	Median
Observation	140	95	45	2.7
High-dose IFN	146	93	53	3.8

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

How many patients can interferon cure?

Interferon alpha compared with treatment other than interferon (including observation) for the adjuvant treatment of melanoma

Patient o
Settings:
Intervent
Compari

Outcome

evidence

First recu

Death

Until better selection methods or more effective therapies are available, the findings of the present meta-analysis lend support to the use of interferon in the routine clinical setting to provide patients with the best chance of survival. Moreover, we must remember that other well-established adjuvant treatments, such as those routinely administered to people with breast, colorectal, and ovarian carcinomas, are associated with risk reductions very similar to those found in this meta-analysis for those with high-risk melanoma treated with interferon (Ascierto 2008). Therefore, the need for better therapeutic strategies is an urgent issue for virtually all tumour types.

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

Why would there be a RFS benefit without OS improvement?

- **Crossover effect**
  - Currently relevant for E1690 only
  - Likely to significantly impact adjuvant trials of ipilimumab, targeted therapy
- **Delayed recurrence by elimination of "nonlethal" tumor cells**
- **Rescue or salvage therapy**

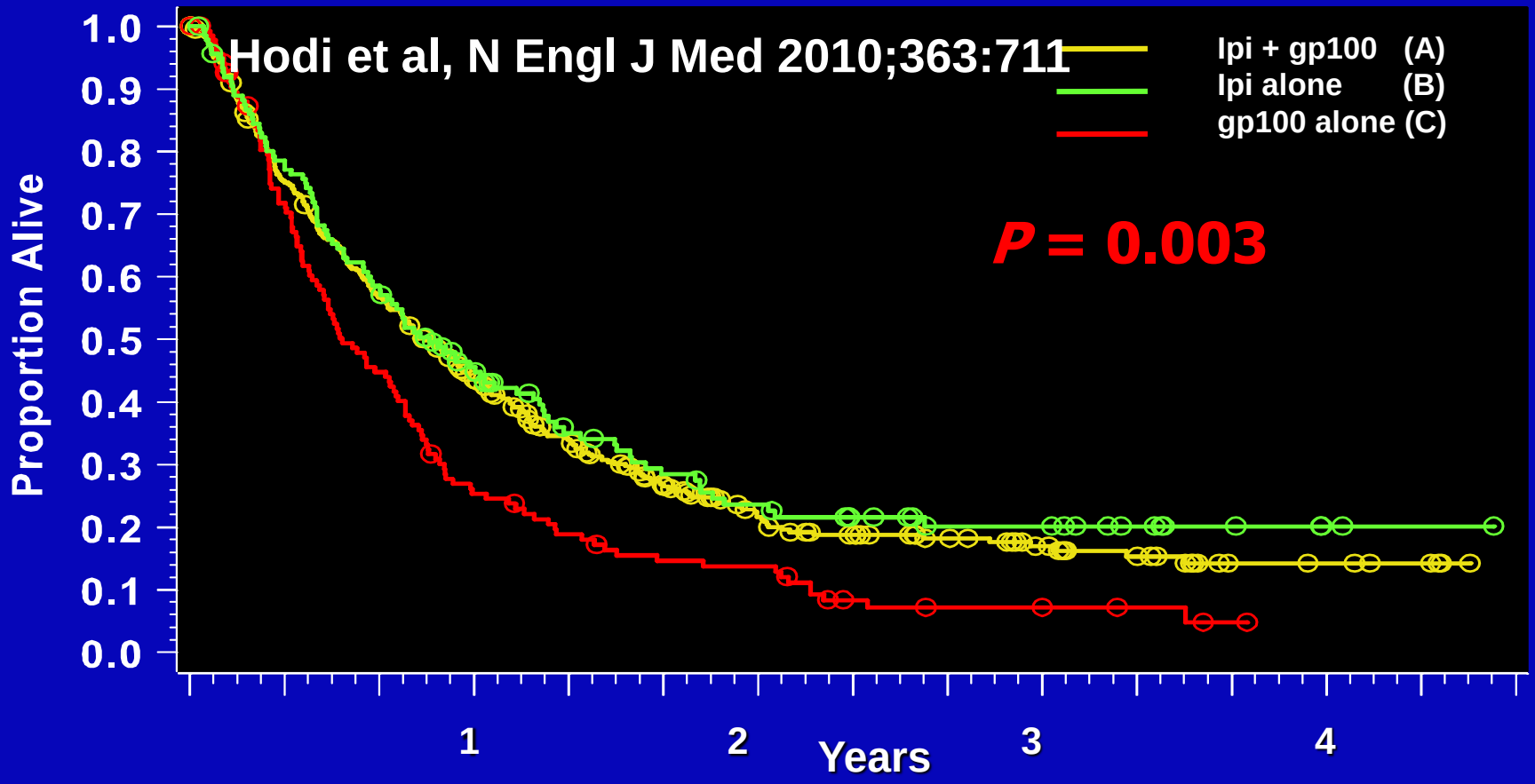
Rescue or Salvage?

Where are we going?

Can we use the new active agents for treating metastatic melanoma to improve survival in the adjuvant setting?

Ipilimumab

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



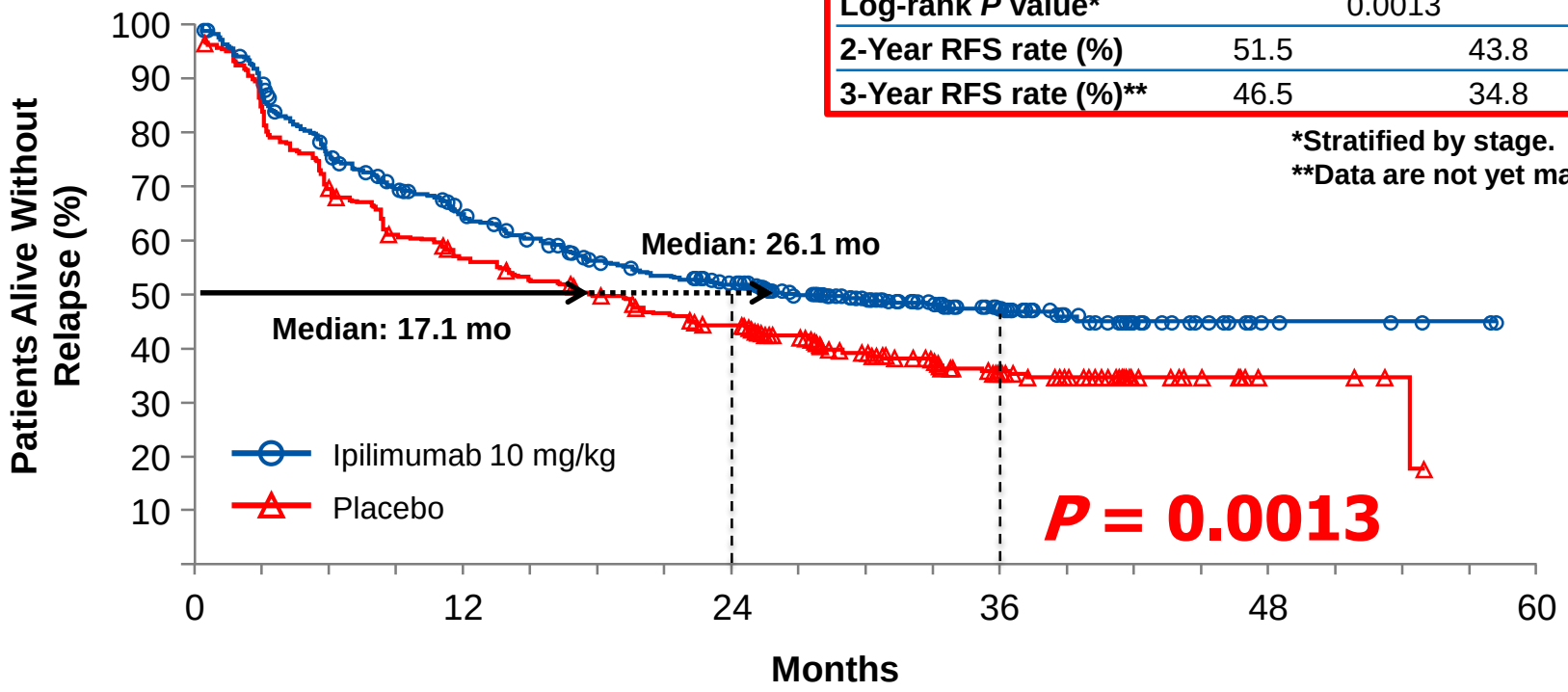
Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

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

EORTC 18071

	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.



Eggermont et al, Proc ASCO 2014; LBA9008

EORTC

The future of cancer therapy

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, Proc ASCO 2014; LBA9008

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, Proc ASCO 2014; LBA9008

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, Proc ASCO 2014; LBA9008

Where are we going?

Can we use the new active agents for treating metastatic melanoma to improve survival in the adjuvant setting?

Ipilimumab

E1609 Ipilimumab 10 mg/kg or 3 mg/kg vs high-dose interferon alfa-2b

Study closed to accrual, results not anticipated for several years

Where are we going?

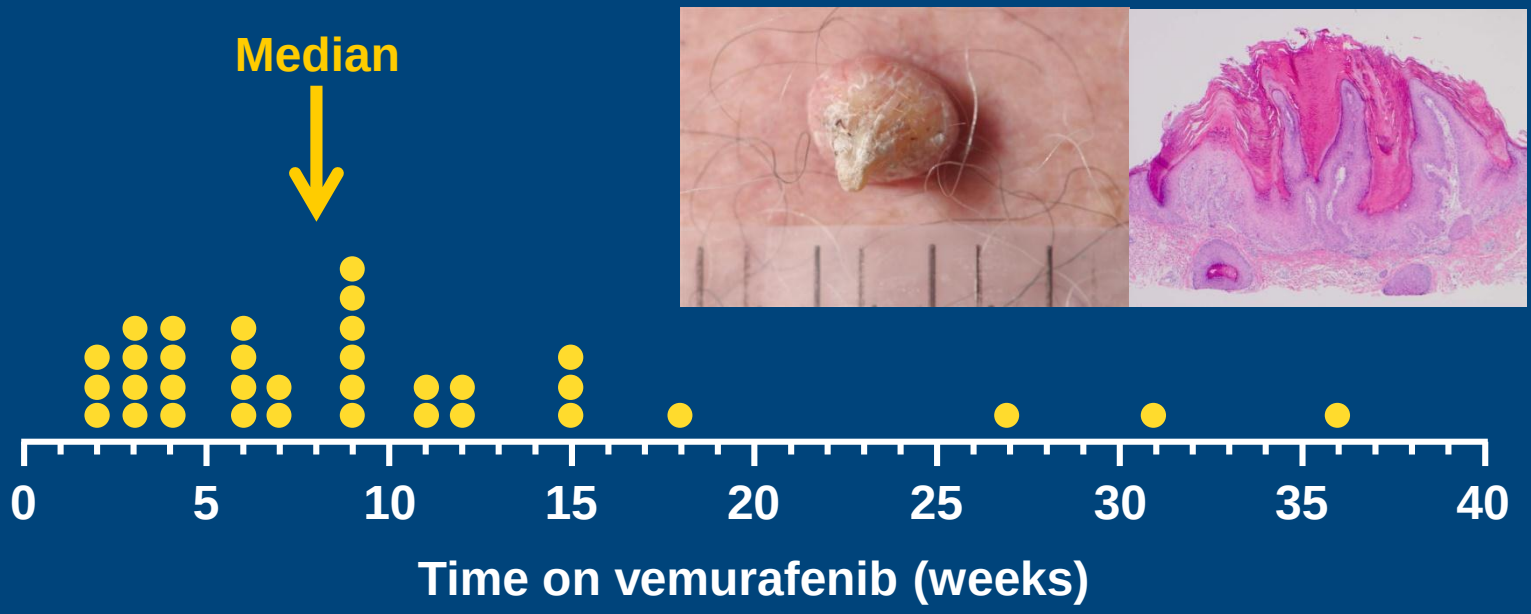
Can we use the new active agents for treating metastatic melanoma to improve survival in the adjuvant setting?

BRAF±MEK inhibitors

Several studies underway, results not anticipated for several years

Adjuvant therapy with BRAF inhibitors

Will second-primary cancers be a limiting factor?



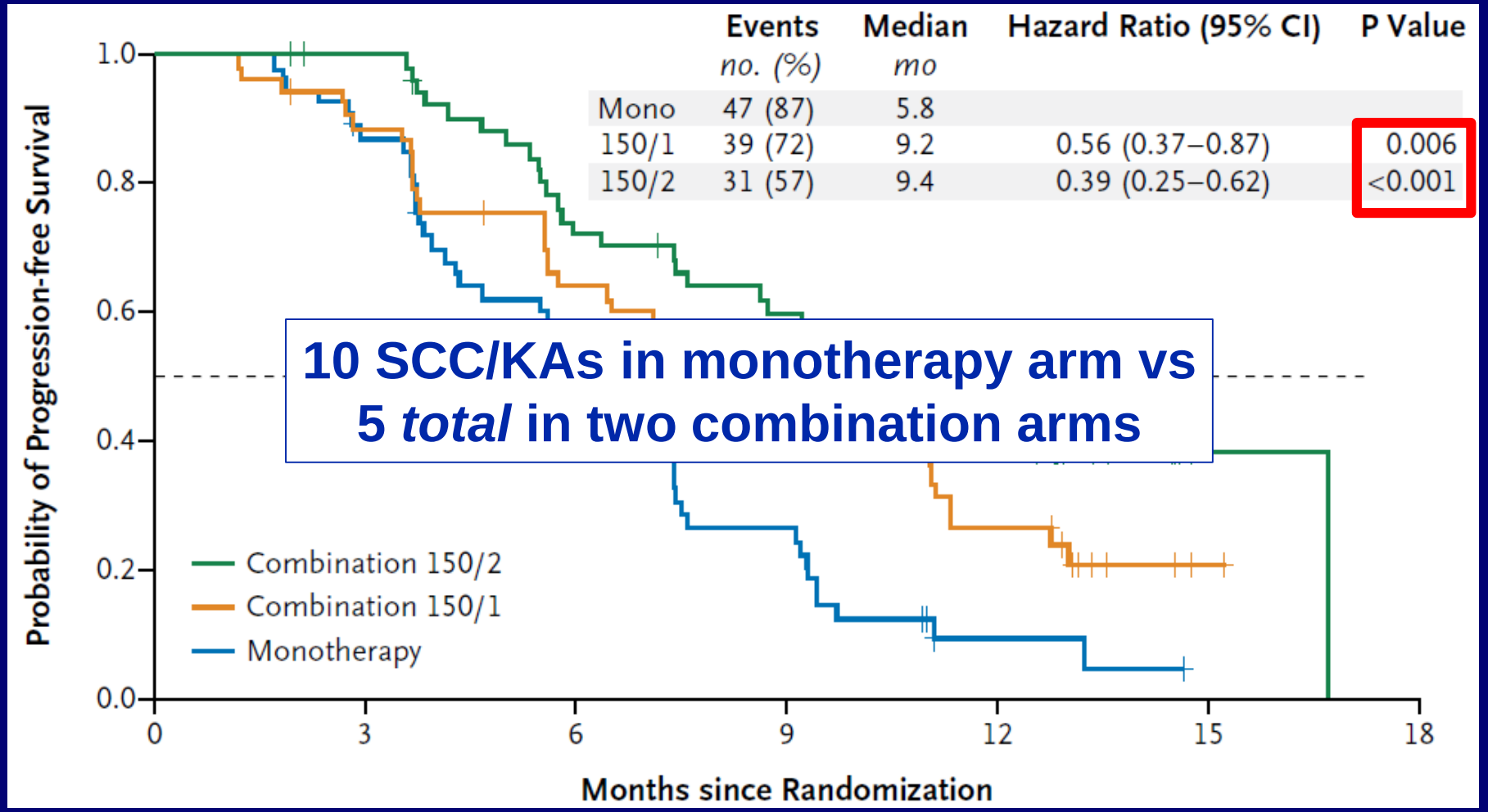
- Median time 8 weeks (range 2–36)
- Each dot represents weeks to development of first lesion

Ribas et al, Proc ASCO 2011; abstract 8509

PRESENTED AT: ASCO Annual '11 Meeting

Adjuvant therapy with BRAF+MEK inhibitors

Will development of resistance be a limiting factor?



Flaherty et al, N Engl J Med 2012;367:1694

Where are we going?

Can we use the new active agents for treating metastatic melanoma to improve survival in the adjuvant setting?

Anti-PD1 antibodies

S1404 Pembrolizumab vs high-dose interferon alfa-2b

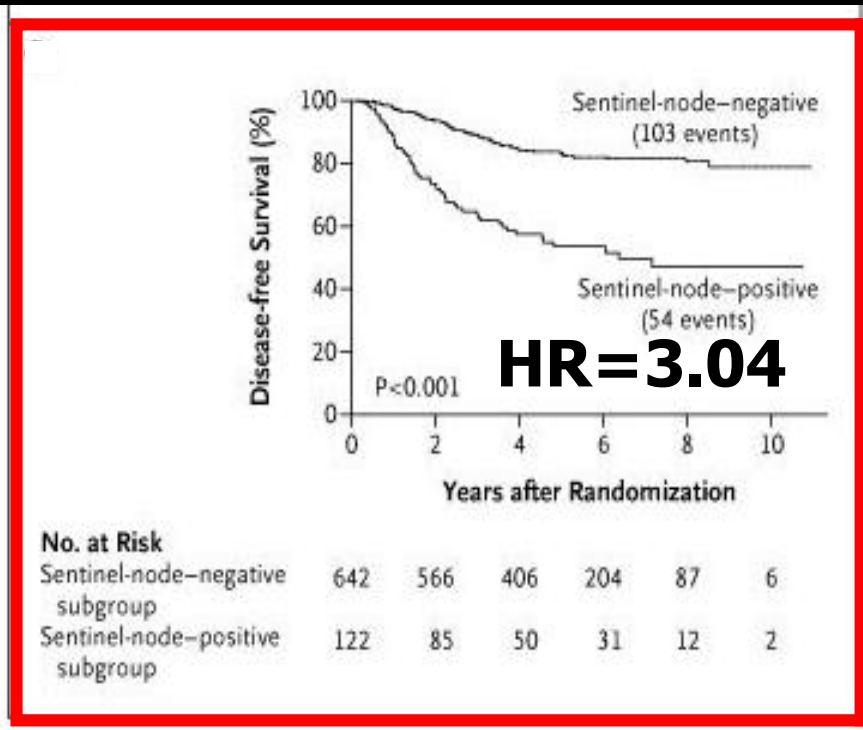
Study anticipated to open January 2015, accrual will take several years

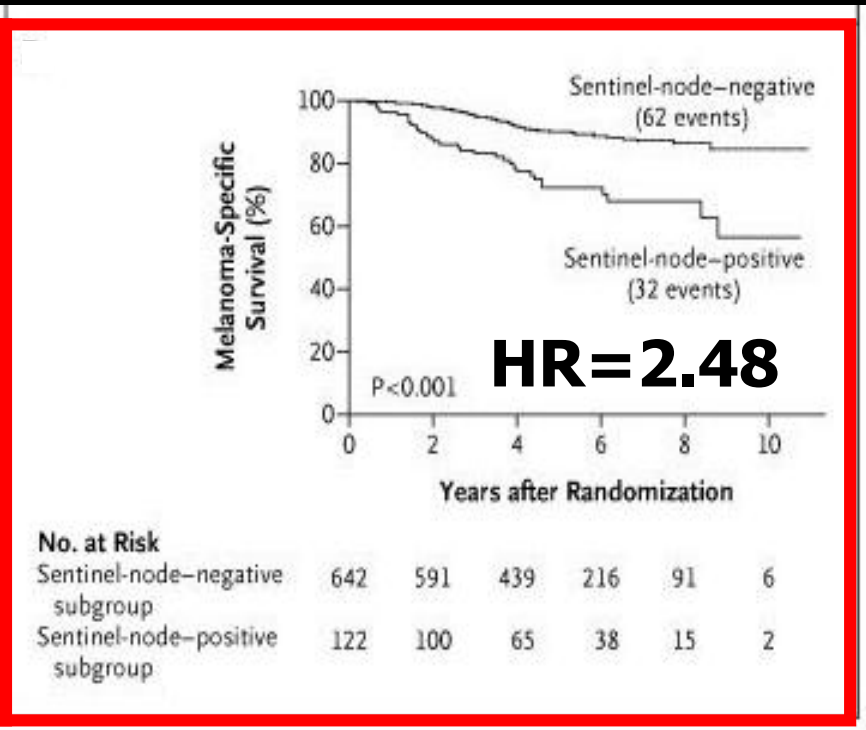
What Do We Need To Get There?

- **We still need better prognostic markers to identify patients at risk of relapse, especially in the sentinel node negative population**

ADJUVANT THERAPY OF MELANOMA

Let's Not Forget The "Low Risk" Groups





Morton D et al. N Engl J Med 2006;355:1307-1317

Sentinel node negative patients outnumber sentinel node positive patients by about 5 to 1

The NEW ENGLAND JOURNAL of MEDICINE

ADJUVANT THERAPY OF MELANOMA