

# WHAT'S NEW IN MELANOMA

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# Topics

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- **What does sentinel node biopsy actually do?**
- **Adjuvant therapy with interferon – where are we now?**
- **Will we be seeing some new agents for treatment of metastatic melanoma anytime soon?**



# Rationale for Sentinel Node Biopsy

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- Enhance accuracy of staging
- Improve regional disease control
- Improve odds of survival
- Does sentinel node biopsy:
  - Reliably identify patients at high risk of metastasis and death?
  - Reliably identify patients who would have needed a lymph node dissection eventually anyway?
  - Increase time to disease recurrence?
  - Increase survival for patients with positive nodes?
  - **Improve overall survival?**
  - **Allow earlier, more effective adjuvant therapy?**

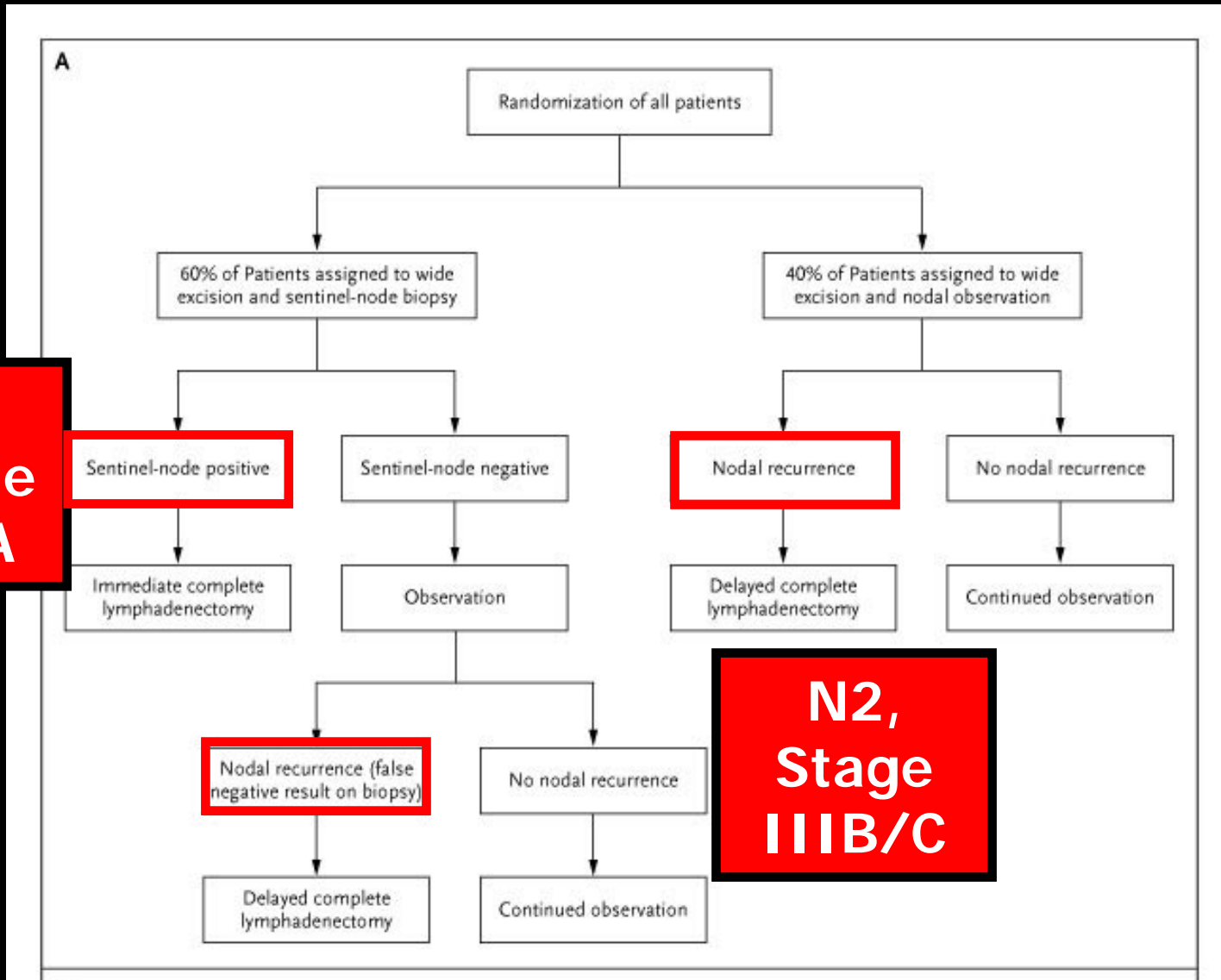


# Sentinel-Node Biopsy or Nodal Observation in Melanoma

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

- 2001 patients randomized between January 1994 and March 2002
- Of these, 1347 had melanomas 1.2 - 3.5 mm in thickness and comprised the “primary stratum” that is described in the NEJM article
- 654 patients had melanomas <1.2 but Clark’s level IV or >3.5 mm in thickness
- The data for all 2001 patients was presented at ASCO 2005

# MSLT-1 Trial Design



## Prognosis and Sentinel Node Status

- 5-year disease-free survival
  - 83.2% if the sentinel node was negative
  - 53.4% if the sentinel node was positive ( $p < 0.001$ )
- 5-year melanoma-specific survival
  - 90.2% if the sentinel node was negative
  - 72.3% if the sentinel node was positive ( $p < 0.001$ )

**Does sentinel node biopsy reliably predict recurrence and death?**

**YES**

## Relapse-free Survival Rates

- Median follow-up 59.8 months
- 134 patients (**26.8%**) on observation arm with relapse at any site
- 159 patients (**20.7%**) on sentinel node biopsy arm with relapse at any site
- **5-year disease-free survival 73.1% vs 78.3%, p=0.009**

**Does sentinel node biopsy increase time to disease recurrence?**

**YES**

## Melanoma-specific Survival Rates

- Median follow-up 59.8 months
- **5-year melanoma-specific survival 86.6% vs 87.1%, p=0.58**

**Does sentinel node biopsy increase overall survival for all patients subjected to the procedure?**

**NO**

## MSLT-1 Results

# Presence of Nodal Metastases

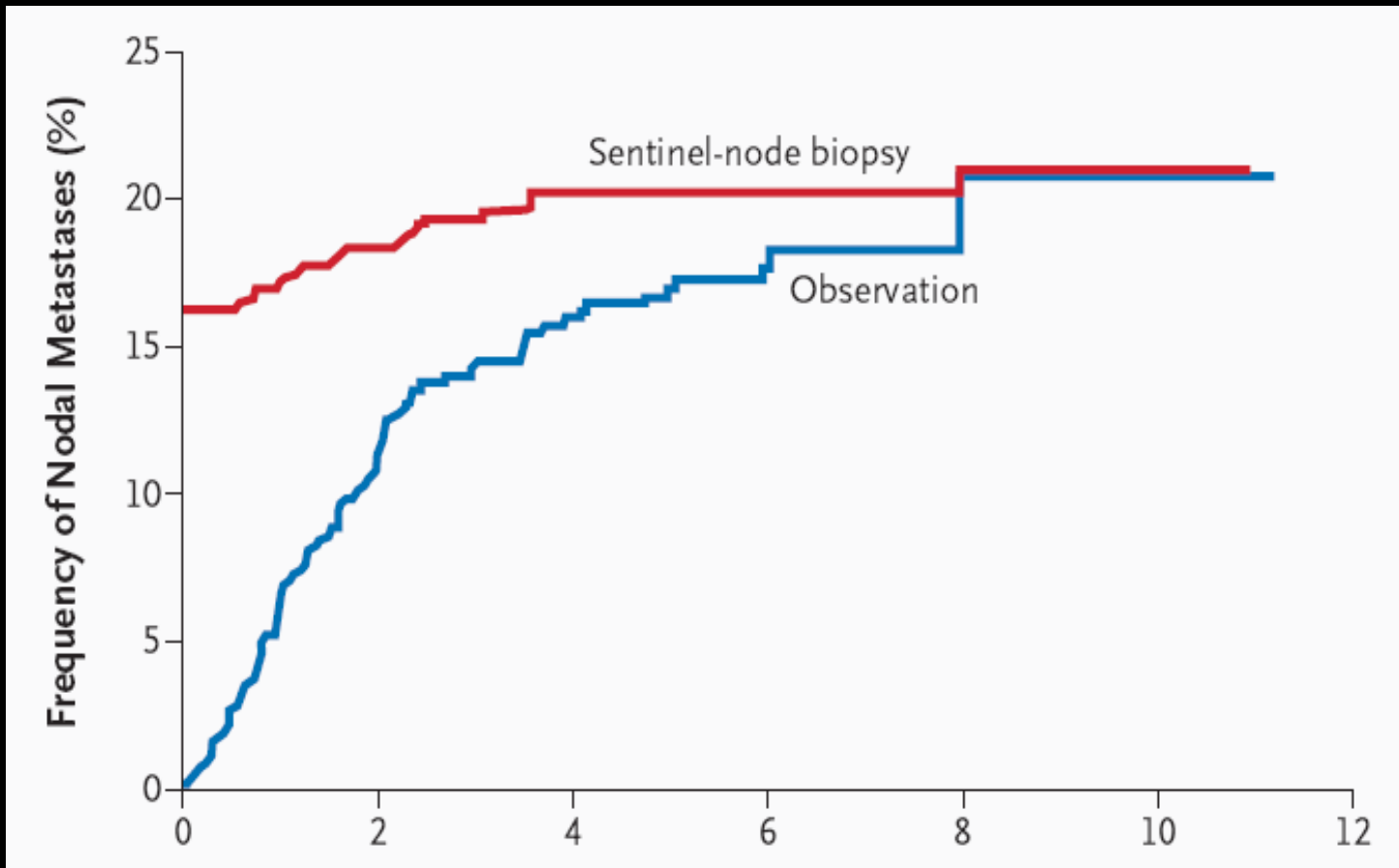
- 78 patients (15.6%) on observation arm with nodal relapse
  - Median time to detection of relapse 1.33 years
- Predicted cumulative incidence of nodal relapse at 8 years 18.5%
- 122 patients (15.8%) on sentinel node biopsy arm with positive sentinel node
- 26 patients (3.4%) on sentinel node biopsy arm with nodal relapse

**Does sentinel node biopsy identify patients who would require a complete node dissection anyway?**

**YES, it seems to...**

## MSLT-1 Results UPDATE

# Cumulative Incidence of Nodal Metastases



**Does sentinel node biopsy identify patients who would require a complete node dissection anyway?**

**YES!**

## Nodal Metastases and Survival

- Prognostic factors well-balanced between observation and sentinel node biopsy arm
  - Age was slightly older for patients developing nodal relapse than for those with positive sentinel nodes
- Median follow-up 48.4 months
- 32/122 patients (26.2%) with positive sentinel node have died of melanoma
- 38/78 patients (48.7%) with nodal relapse on observation arm have died of melanoma (HR for death 0.51,  $p=0.007$ )

**Does sentinel node biopsy increase the chance of survival if the sentinel node is positive?**

**YES – Given the significant limitations of a post-hoc analysis**

# Multicenter Selective Lymphadenectomy Trial

Possible benefit of sentinel node-directed early therapeutic node dissection

*Randomization*

SLNB

OBS

Average 1.6 positive nodes

Average 3.4 positive nodes

Patients with nodal relapse after a negative sentinel node had an average of 4.3 positive nodes at lymphadenectomy

Early TLND

65% 7-year survival

Delayed TLND

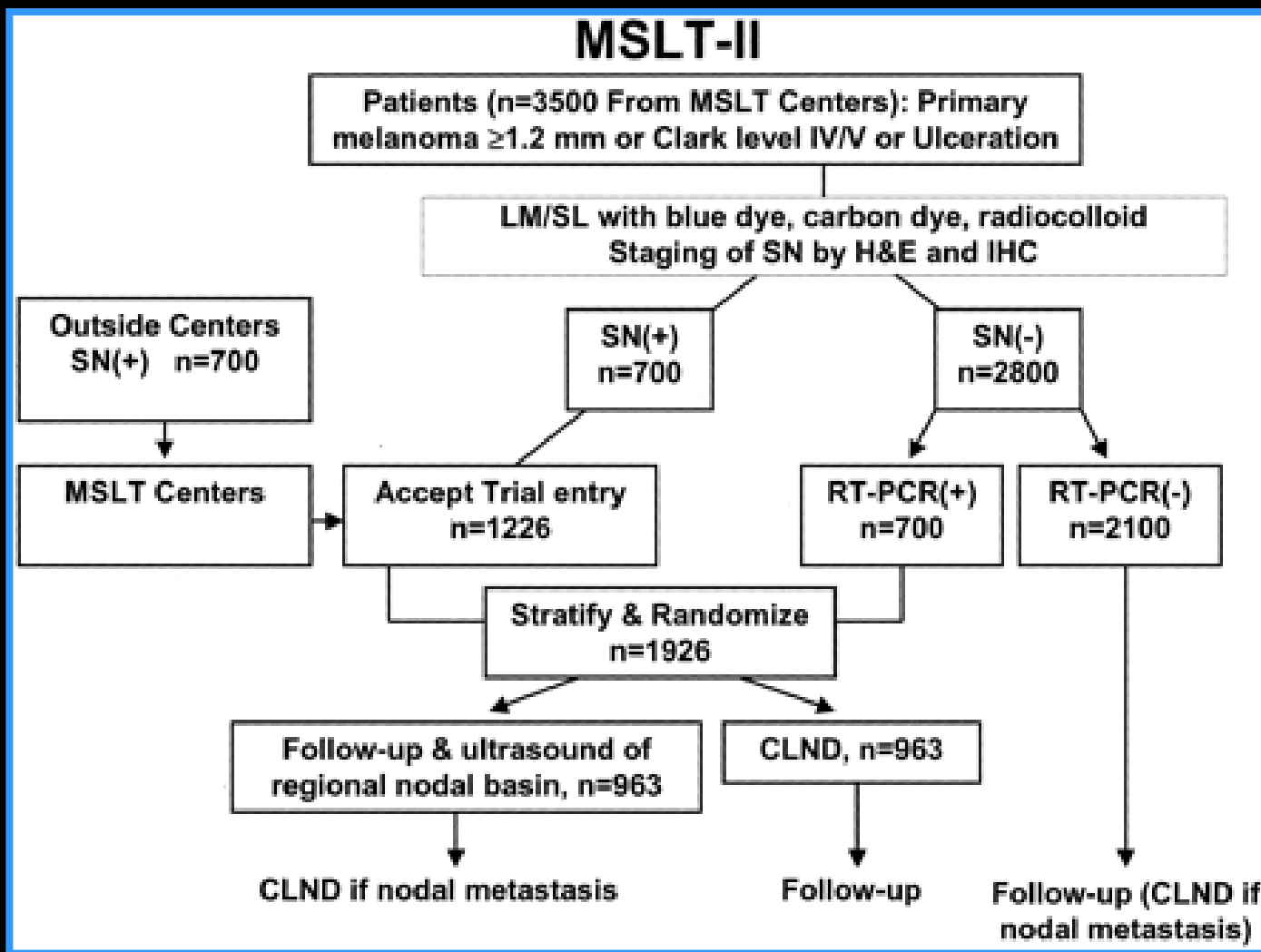
52% 7-year survival

**P= 0.0125**

multivariate model adjusted for known prognostic factors

Morton et al, ASCO 2005 abstract 7501

# Multicenter Selective Lymphadenectomy Trial-II



# ADJUVANT THERAPY WITH INTERFERON

## Where are we now?

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- No therapy consistently prolongs survival once metastatic disease is clinically evident
- Death and relapse risk are accurately predicted by microscopic analysis of the primary and the sentinel node
- **Adjuvant therapy is the best *potential* way to alter the natural history of high-risk patients**
  - High risk = Primary >4mm or Positive Nodes



# Is interferon alfa the standard?

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- Does interferon work?
- Is it worth it?
- What about lower-dose regimens and/or vaccines?



# Does interferon improve recurrence-free survival?

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Five randomized trials with high-dose interferon- $\alpha$  have shown a recurrence-free survival advantage

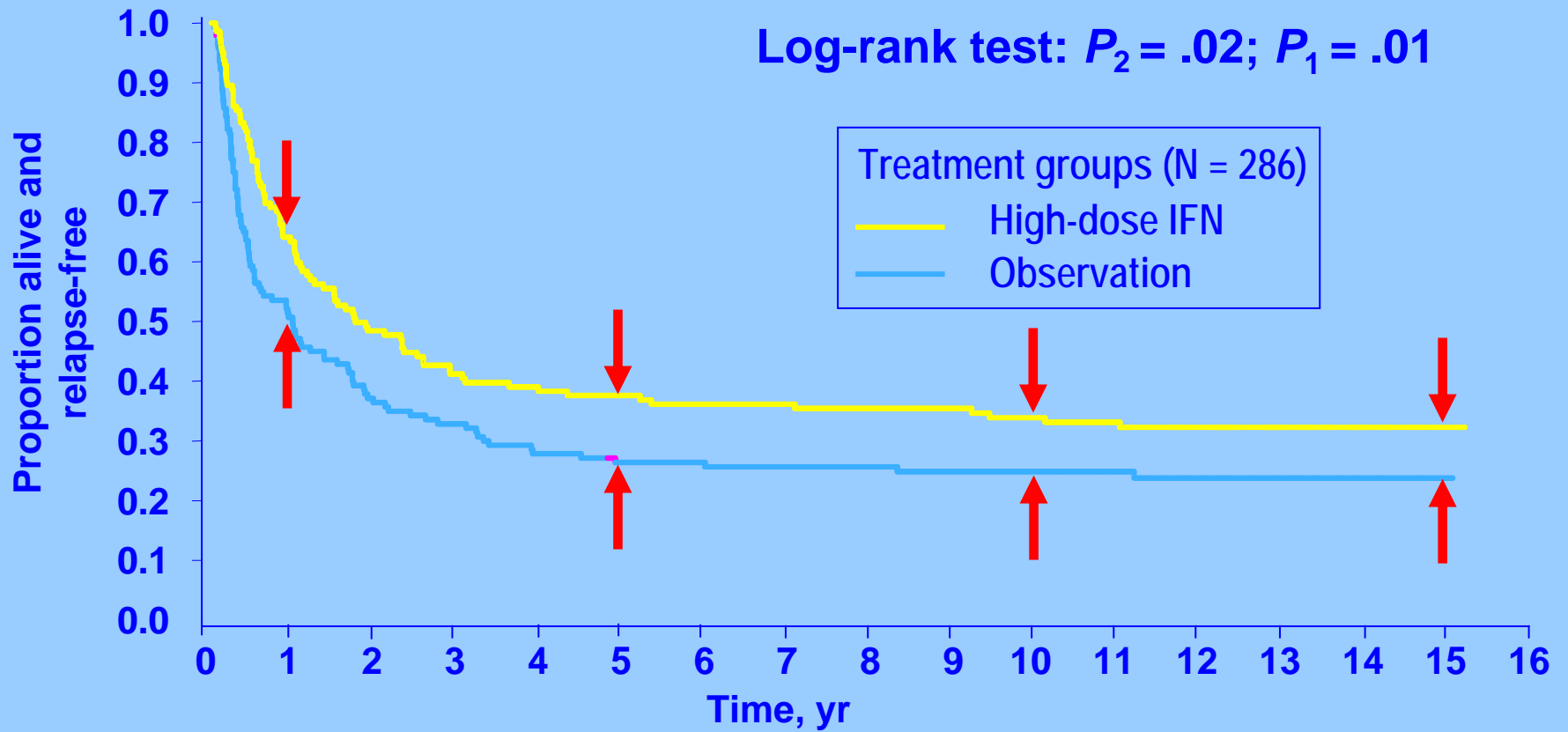
- **ECOG 1684**
- **ECOG 1690**
- **ECOG 1694**
- **ECOG 2696**
  - 20 MU/m<sup>2</sup> iv x 4 weeks, 10 MU/m<sup>2</sup> sc tiw x 11 months
- **NCCTG 83-7052**
  - 20 MU/m<sup>2</sup> im tiw x 3 months



E1684

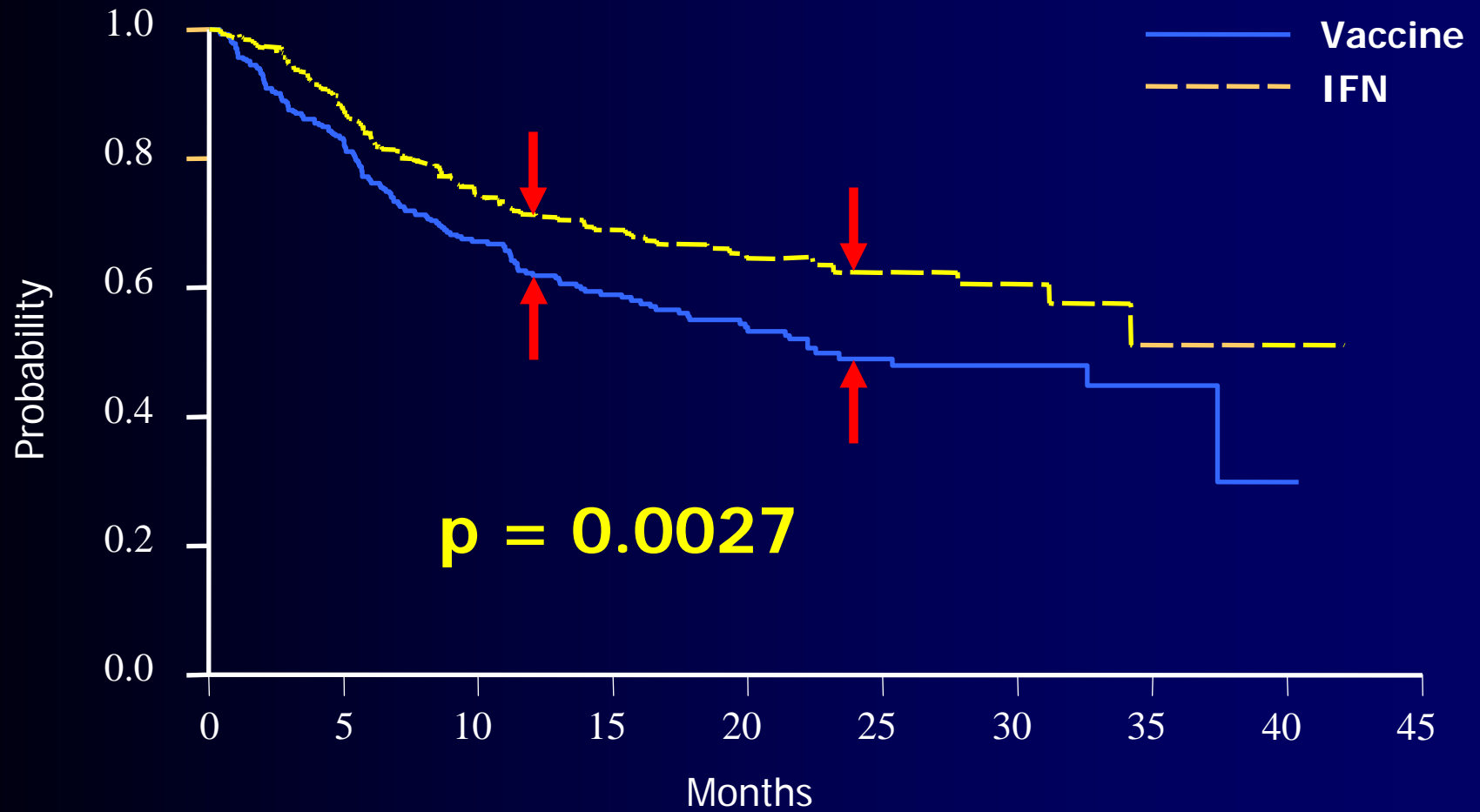
# Relapse-free survival

## Extended follow-up



# E1694

## Relapse-free Survival



# Does interferon improve overall survival?

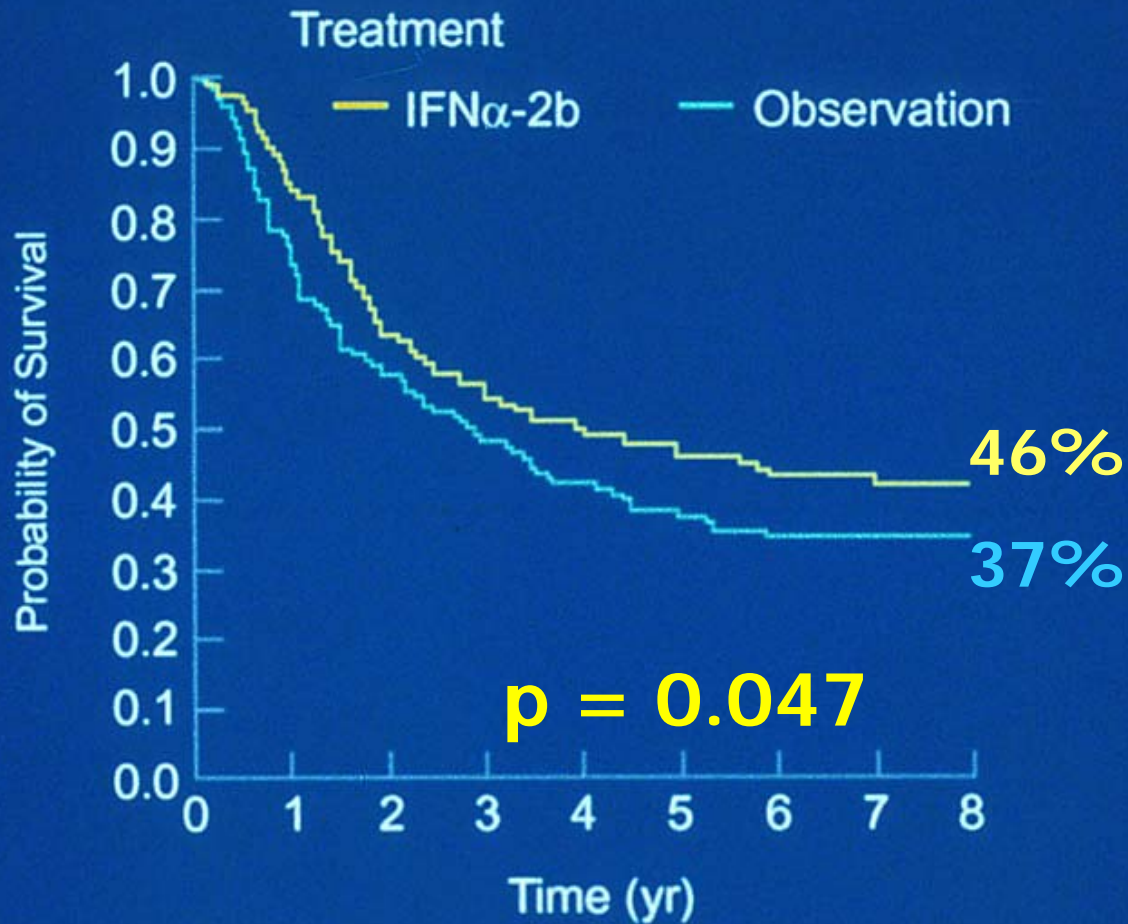
Two randomized trials with high-dose interferon- $\alpha$  have shown an overall survival advantage

- ECOG 1684
- ECOG 1694
  - Compared to ganglioside vaccine



# E1684

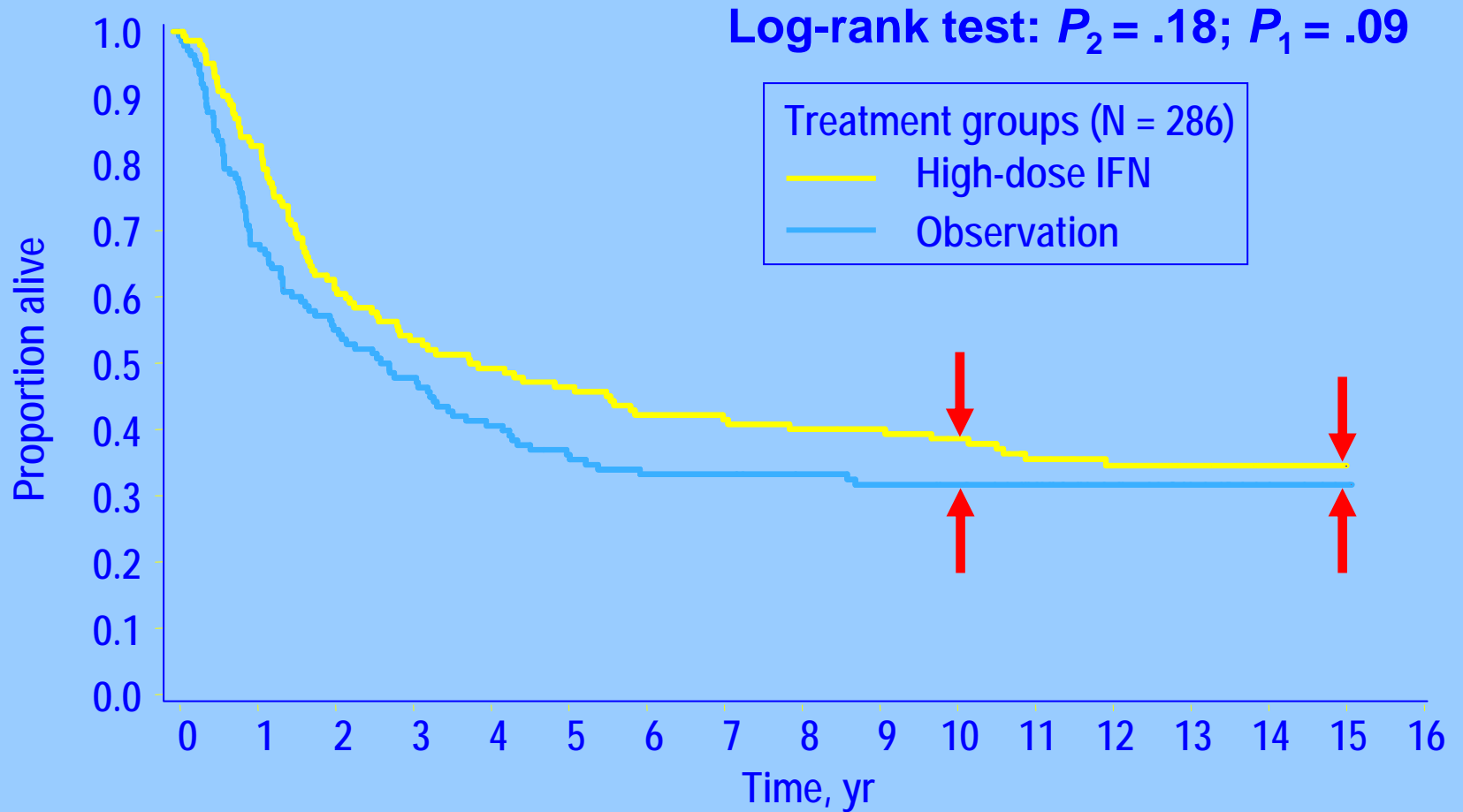
## Overall survival



E1684

# Overall survival

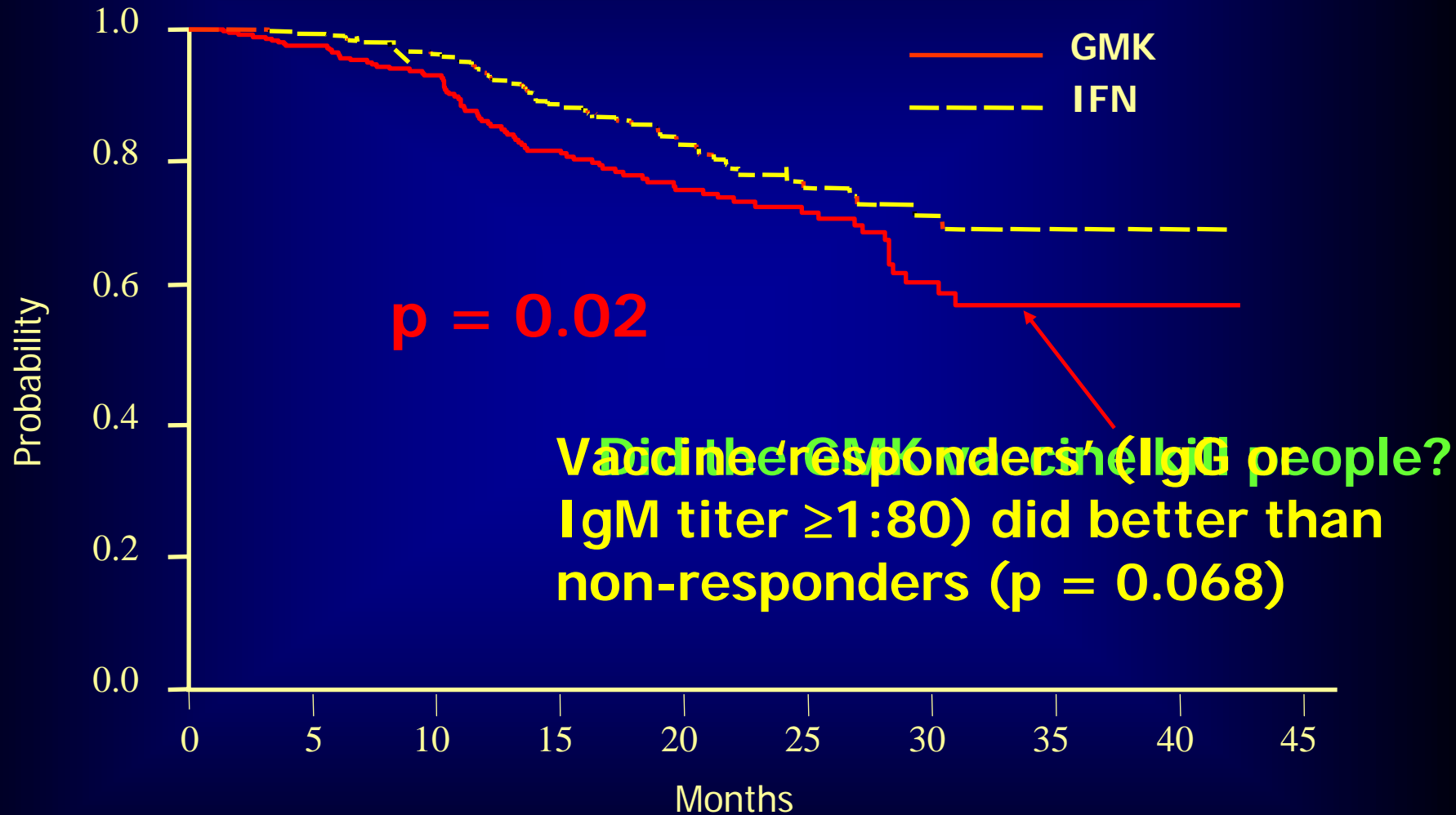
## Extended follow-up



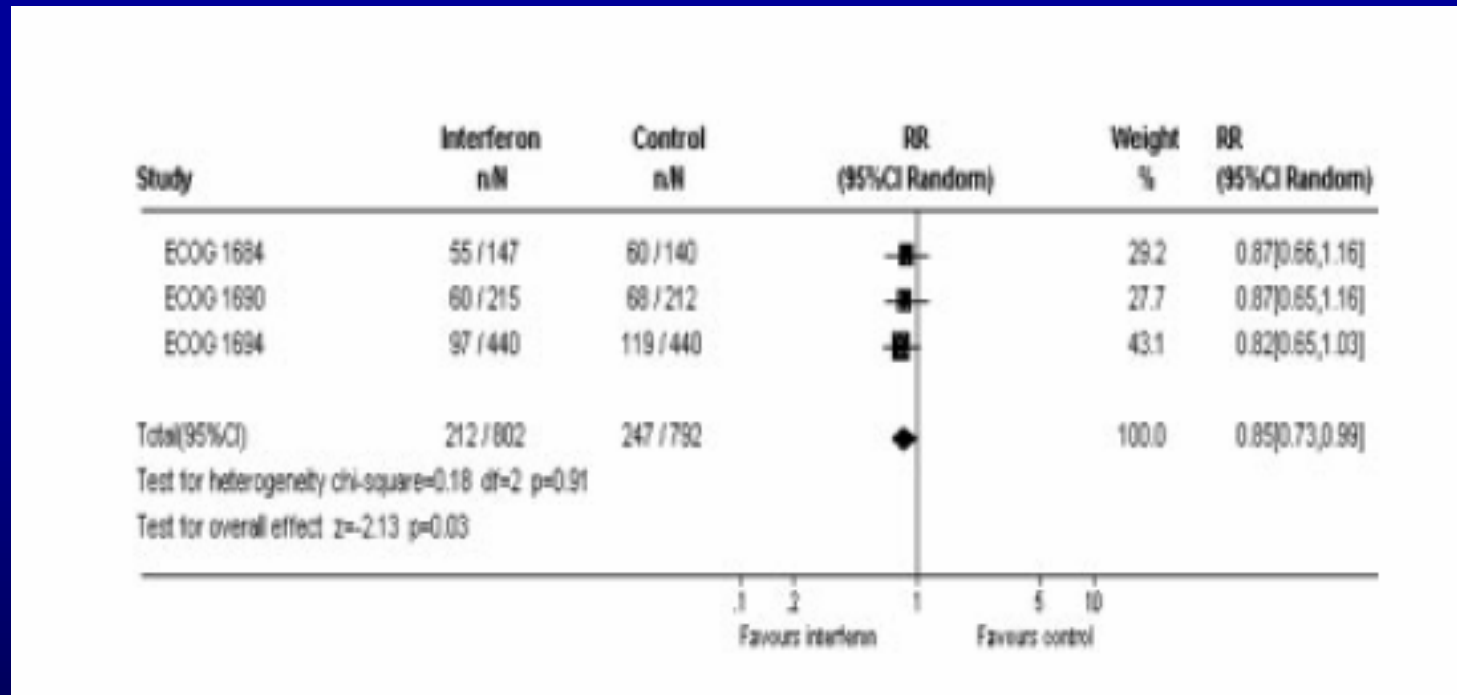
	Total	Dead	Alive	Median
Observation	140	95	45	2.7
High-dose IFN	146	93	53	3.8

# E1694

## Overall Survival



# Does interferon improve overall survival?



High dose interferon for one year significantly improved survival at two years  
(15% increase,  $p=0.03$ )

Verma et al Cancer 2006;106:1431



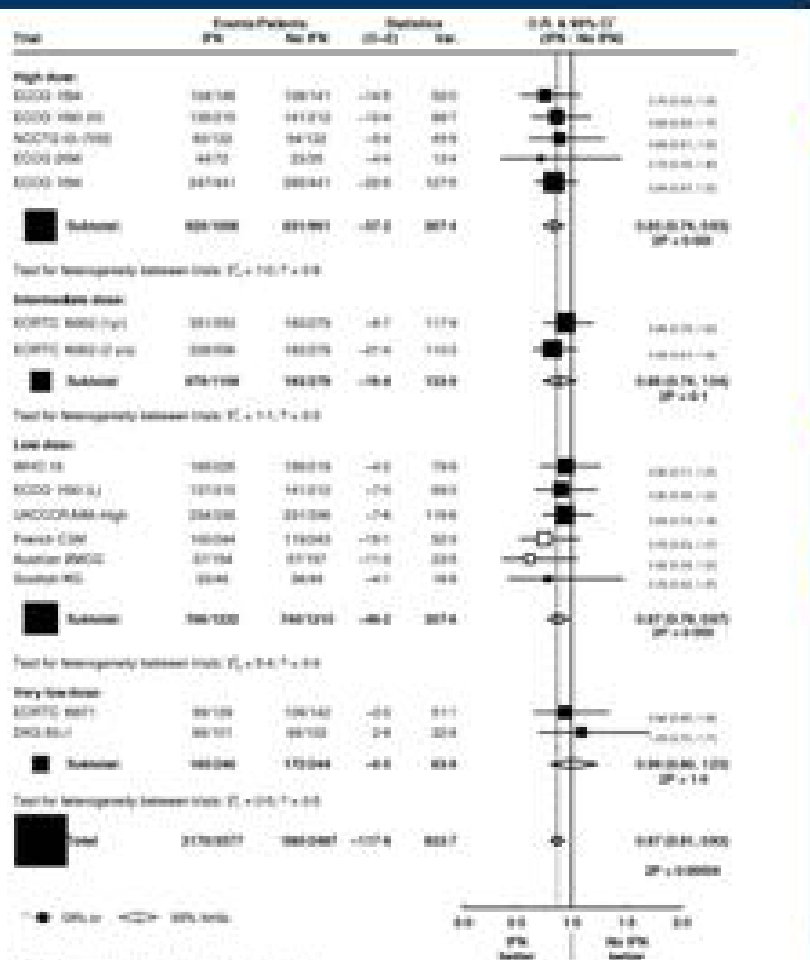
# Does interferon improve overall survival?

- Meta-analysis of 6067 patients treated with interferon in a variety of doses or control (observation, placebo or vaccine) in randomized trials
- Interferon treatment (any dose) significantly improved relapse-free survival (18% increase,  $p=0.00006$ ) and overall survival (3% increase,  $p=0.008$ )
- No statistical evidence of an effect for dose of interferon or stage of disease

Wheatley et al Proc ASCO 2007 abstract 8526



## EVENT-FREE SURVIVAL – BY DOSE OF IFN

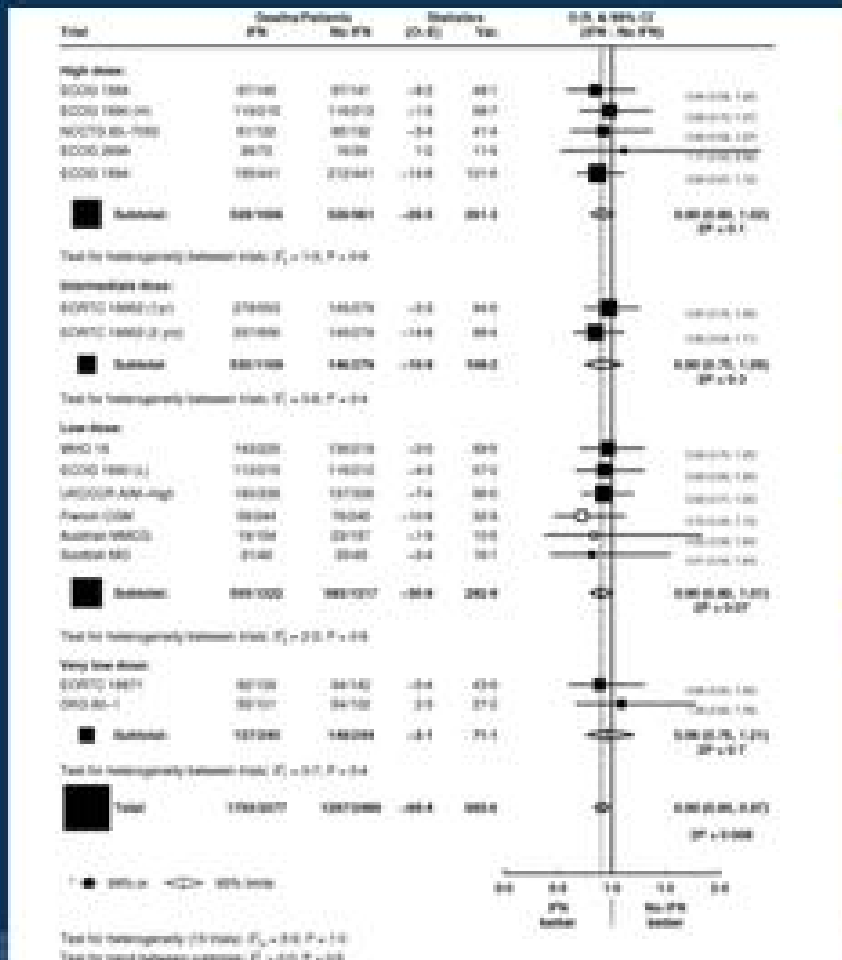


- There was a statistically significant benefit for IFN for EFS (p=0.00004)

- OR=0.87, CI=0.81-0.93

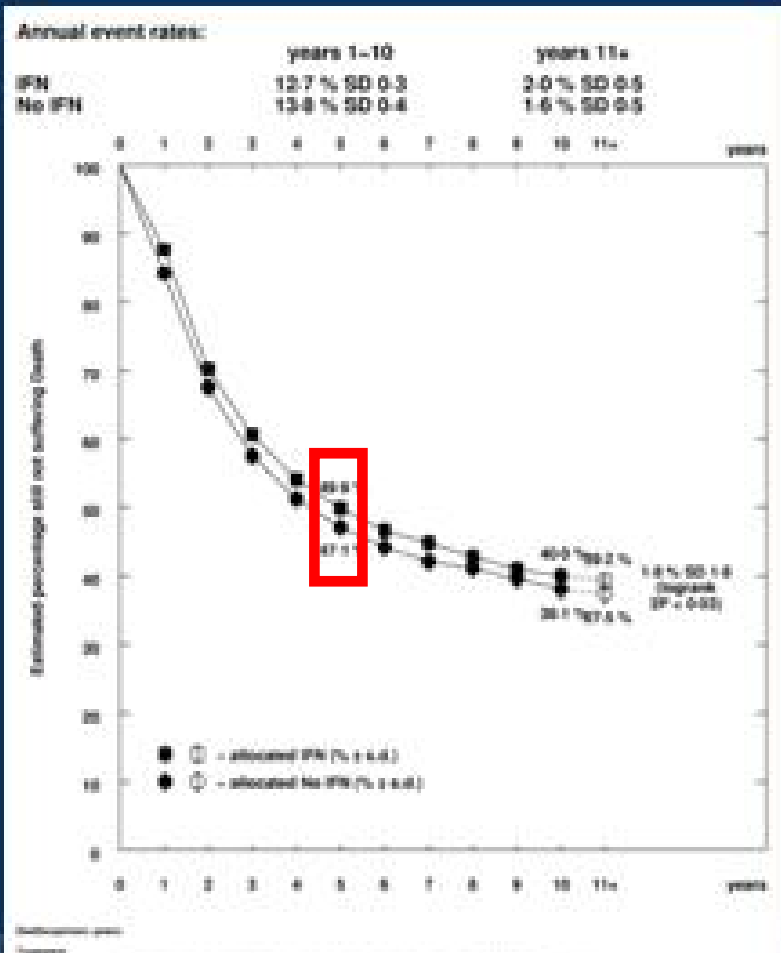
- With no evidence of difference according to dose (test for trend: p=0.2)

## OVERALL SURVIVAL – BY DOSE OF IFN



- There was also a statistically significant benefit for IFN for OS (p=0.008)
- OR=0.9, CI=0.84-0.97
- With no evidence of difference according to dose (test for trend: p=0.8) or duration of IFN (test for trend: p=0.9)

## OVERALL SURVIVAL – IPD DATA ONLY



- This proportional survival advantage translates into an absolute benefit of about 3% (CI 1%-5%) at 5 years

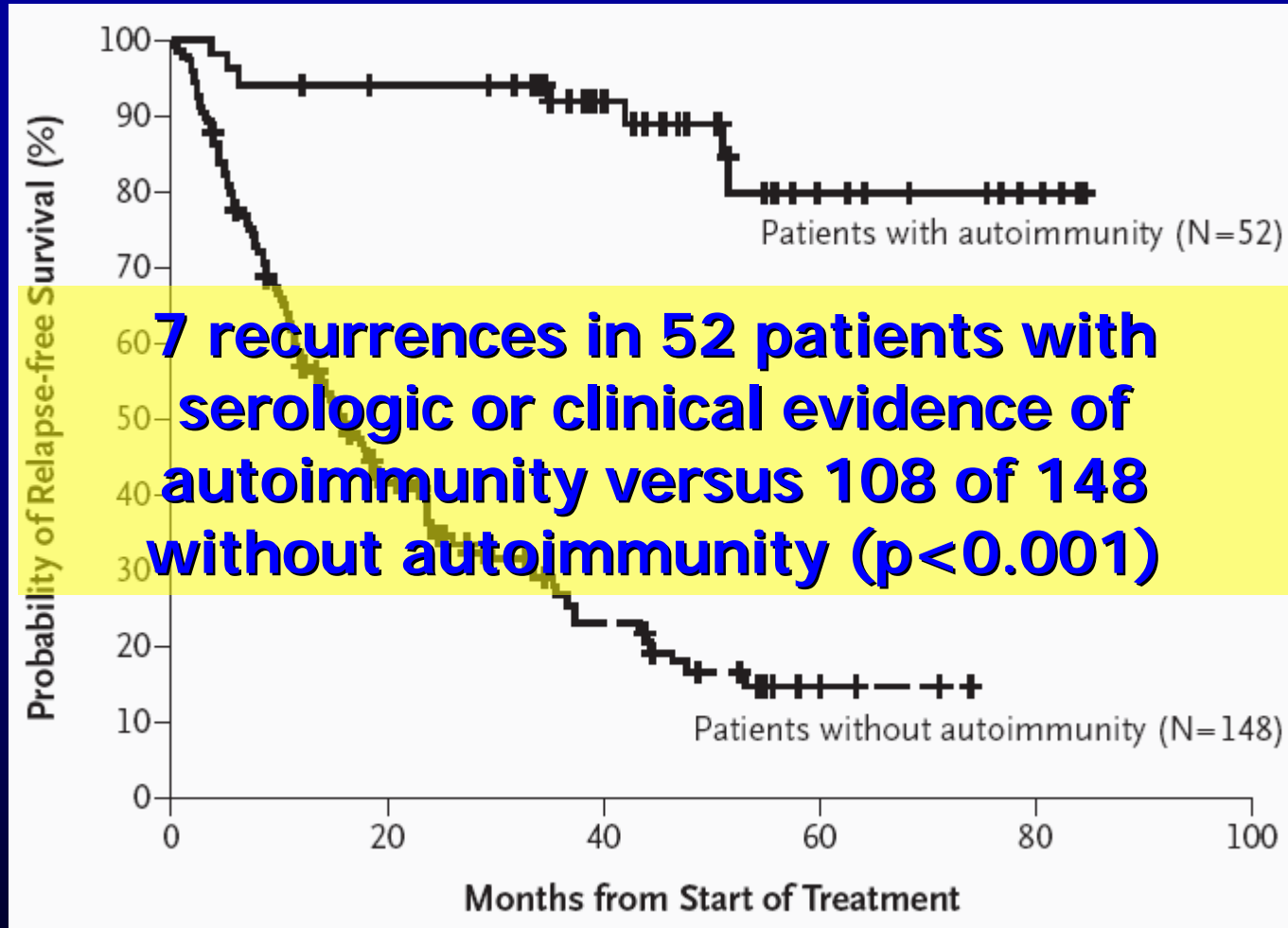
# How does it work?

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- By an immune-mediated effect that promotes the breaking of tolerance to self-antigens?????

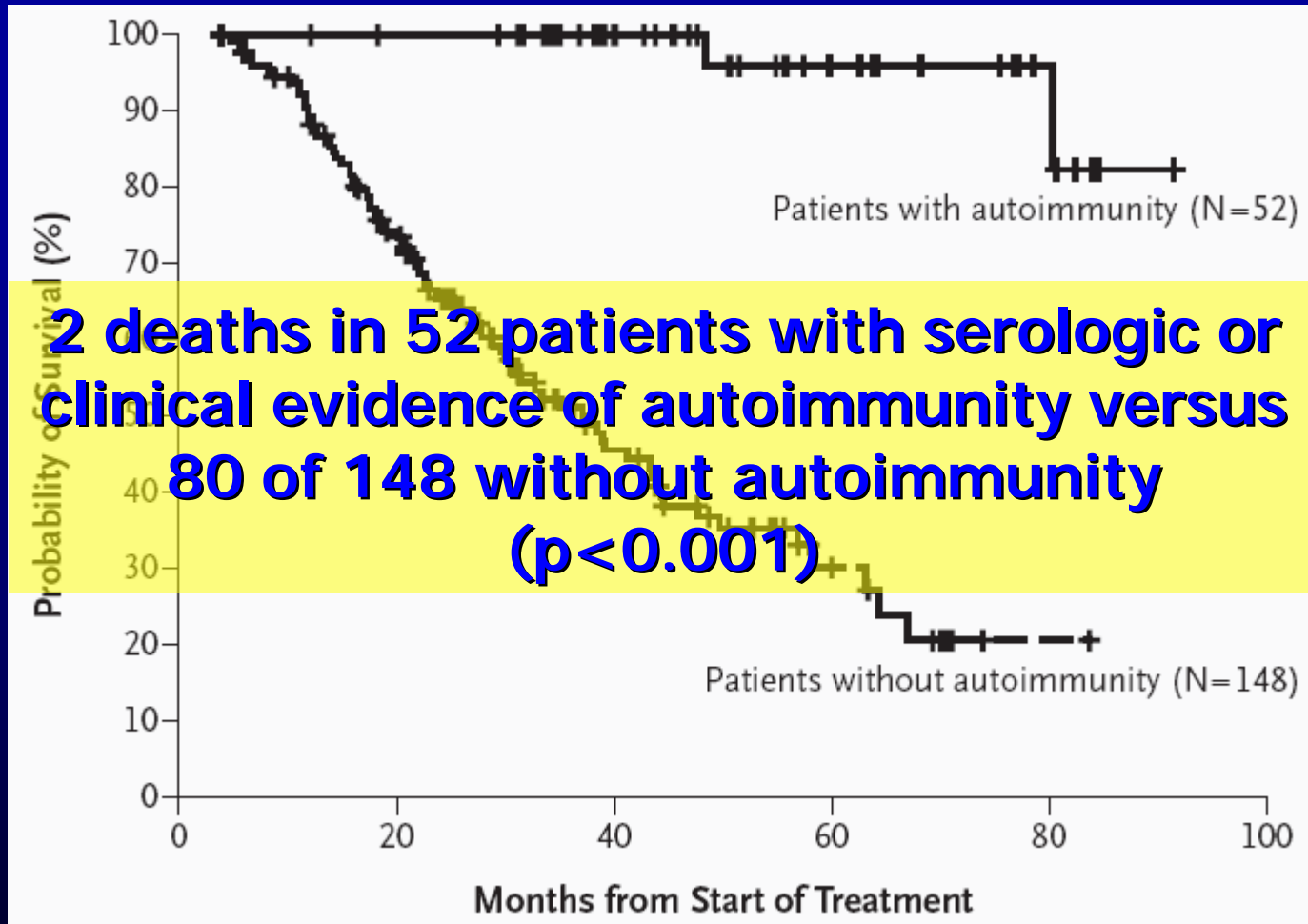


# Autoimmunity Correlates with Interferon Efficacy



Gogas et al, N Engl J Med 2006;354:710

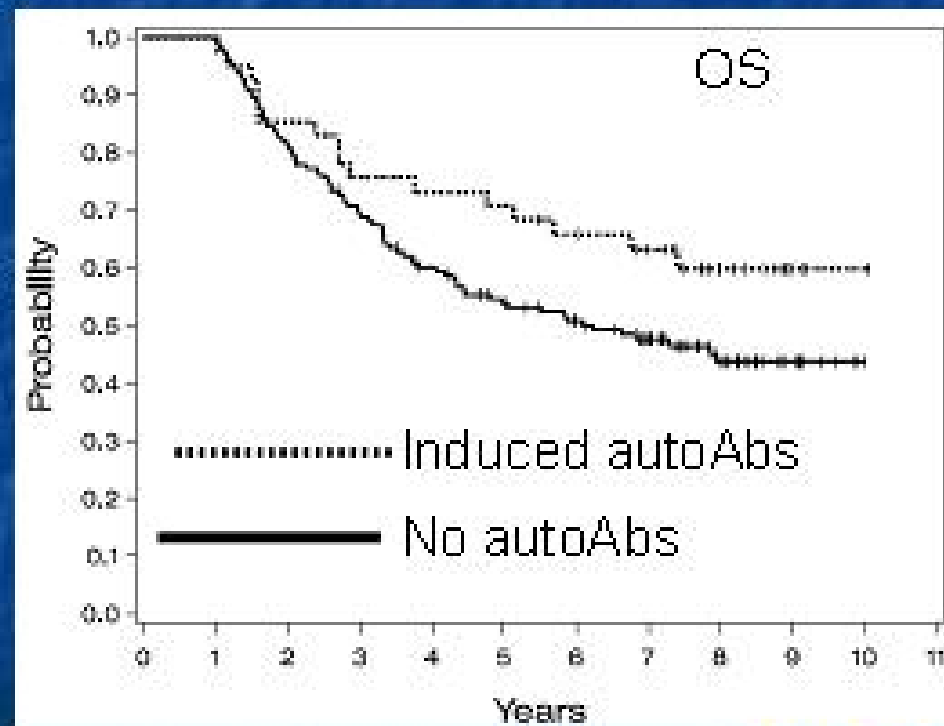
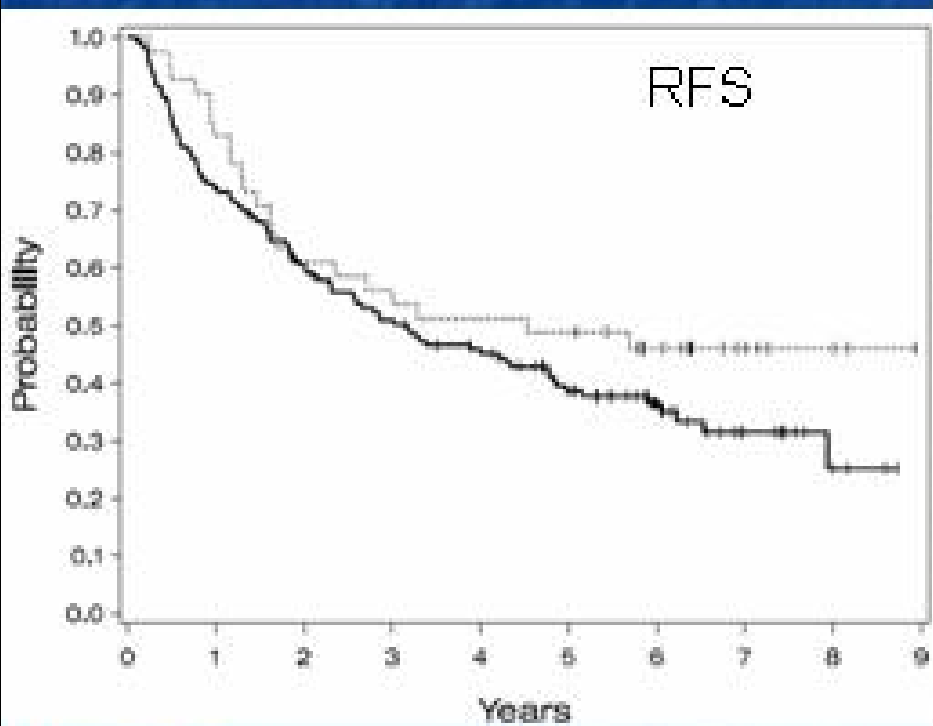
# Autoimmunity Correlates with Interferon Efficacy



Gogas et al, N Engl J Med 2006;354:710

# HDI only patients

RFS		Multivariate Analysis (adjusting for treatment)	OS	
HR	P-value		HR	P-value
1.38	.176		1.58	.091



Stuckert et al Proc ASCO 2007 abstract 8506



E1684

## Is the cost of interferon justified?

End Point	7 Years		Benefit
	IFN	No IFN	
<b>Survival</b>			
Mean survival (years)	3.99	3.47	0.52
Mean discounted survival* (years)	3.66	3.20	0.46
Quality-adjusted survival* (years)	3.04	2.69	0.35
Relapse-free survival (%)	32.8	23.1	9.7
Average survival (%)	35.8	26.5	9.3
<b>Cost-effectiveness</b>			
Costs associated with IFN (\$)	28,636	0	28,636
Total costs of care (\$)	91,656	76,580	15,076
Cost per year of life saved*† (\$‡)	32,600		
Cost per quality-adjusted year of life saved*‡ (\$)	43,200		

\*Costs and benefits discounted at 3% annual rate. Cost-effectiveness ratios rounded to nearest \$100.

†No quality-of-life adjustment for time receiving IFN or survival after melanoma recurrence.

‡Quality of life for time receiving IFN or survival after melanoma recurrence according to Table 2.

Hillner et al, J Clin Oncol 1998;16:2351

HIGH-DOSE IFN $\alpha$ -2b

## Is the cost of interferon justified?

### COST PER YEAR OF LIFE SAVED

- **HIGH DOSE INTERFERON**      \$43,000
- SEAT BELTS/AIR BAGS      \$400,000
- CARDIAC TRANSPLANTATION      \$200,000
- RENAL HEMODIALYSIS      \$30,000
- SCREENING FOR MELANOMA      \$29,170
- MD "Quit Smoking" MESSAGE      \$60

2002 Cost estimates adapted from Phillipe Autier, Center for Research in Epidemiology and Health Information Systems, Luxembourg

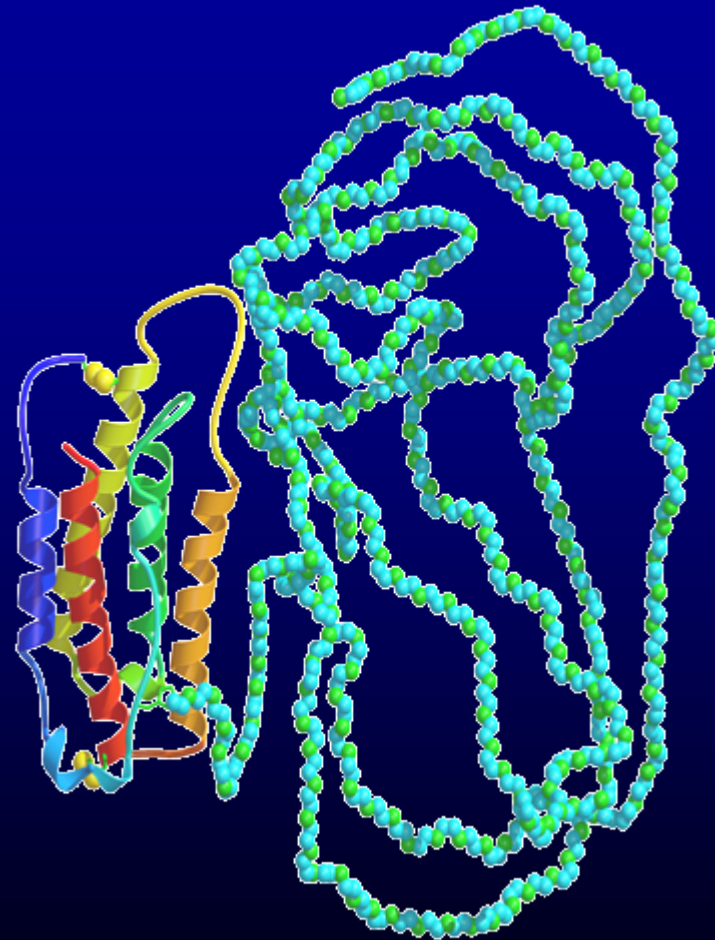
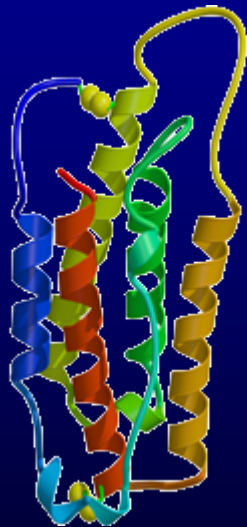


ALTERNATIVES TO HIGH DOSE IFN

# Low-dose, long-duration Pegylated-IFN

PEG-IFN  $\alpha$ -2b

IFN  $\alpha$ -2b



## ALTERNATIVES TO HIGH DOSE IFN

# Low-dose, long-duration Pegylated-IFN

EORTC 18991

- Randomized phase III trial of 1256 patients with stage III melanoma randomized to Peg-IFN (6  $\mu\text{g}/\text{kg}/\text{wk}$  x 8 wks then 3  $\mu\text{g}/\text{kg}/\text{wk}$  x 5 years) versus observation
- Stratified by N1 (microscopic) versus N2 (palpable) nodal disease
- Median follow-up 3.8 years
- 251 patients (40%) stopped Peg-IFN before 5 years due to toxicity or patient refusal

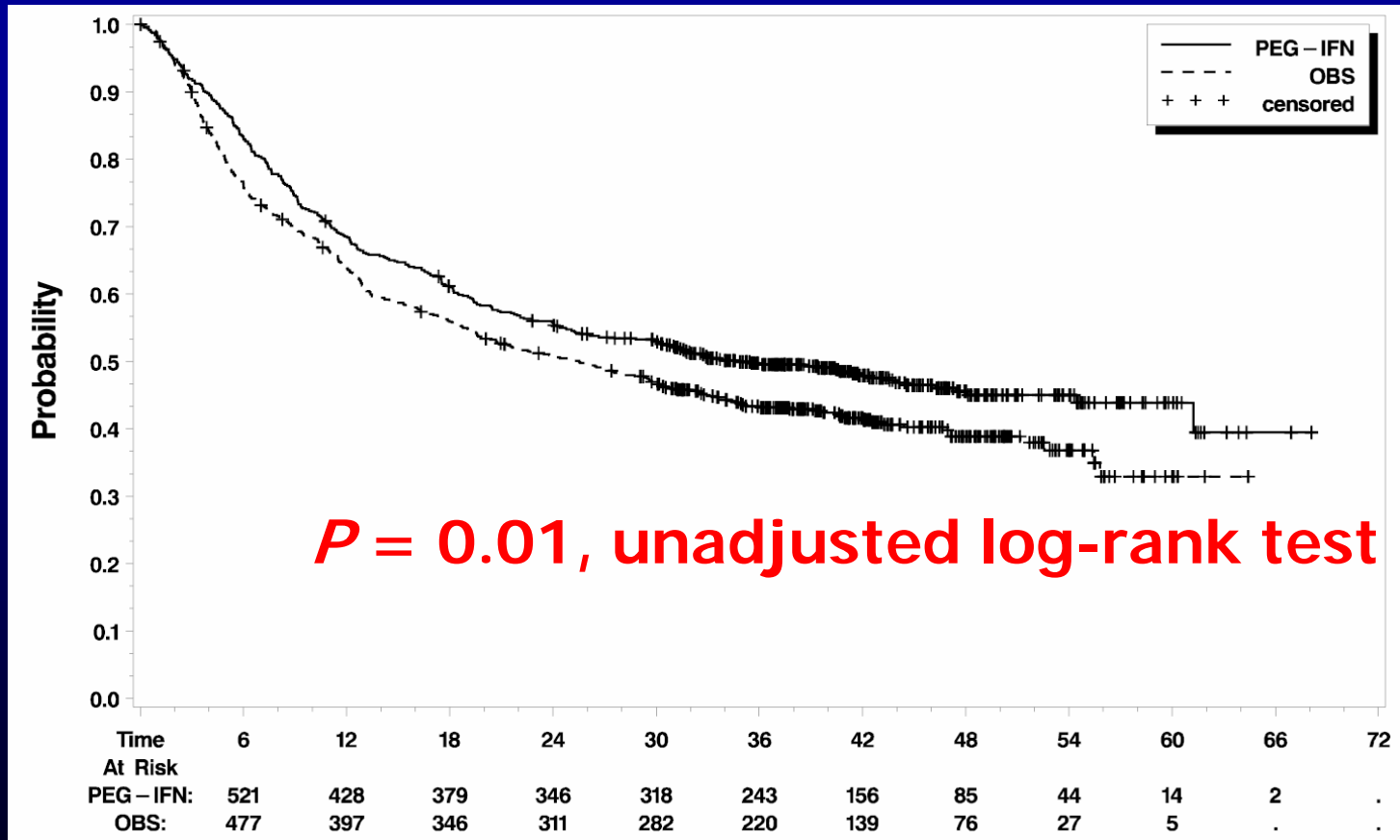
Eggermont et al Proc ASCO 2007 abstract 8504

## ALTERNATIVES TO HIGH DOSE IFN

# Low-dose, long-duration Pegylated-IFN

EORTC 18991

## Relapse-free survival



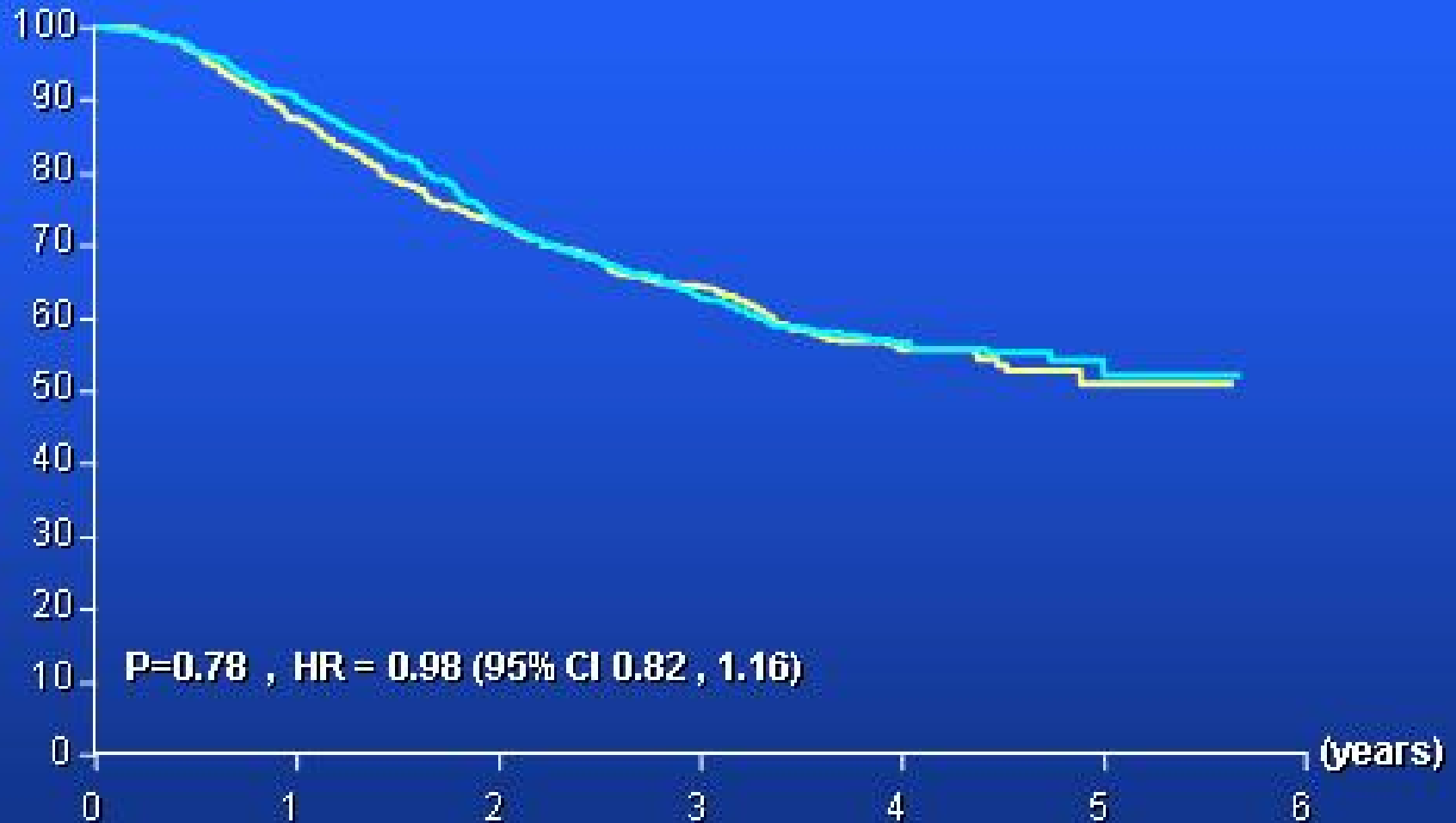
Eggermont et al Proc ASCO 2007 abstract 8504

# DMFS (ITT)



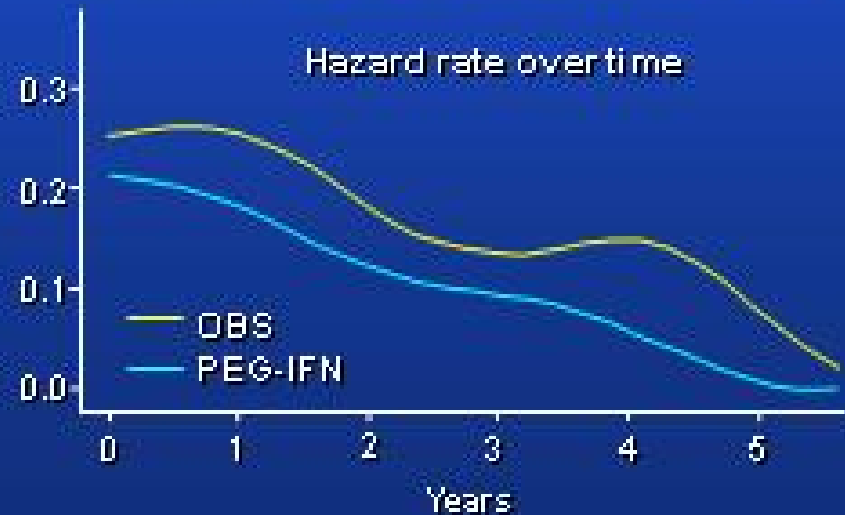
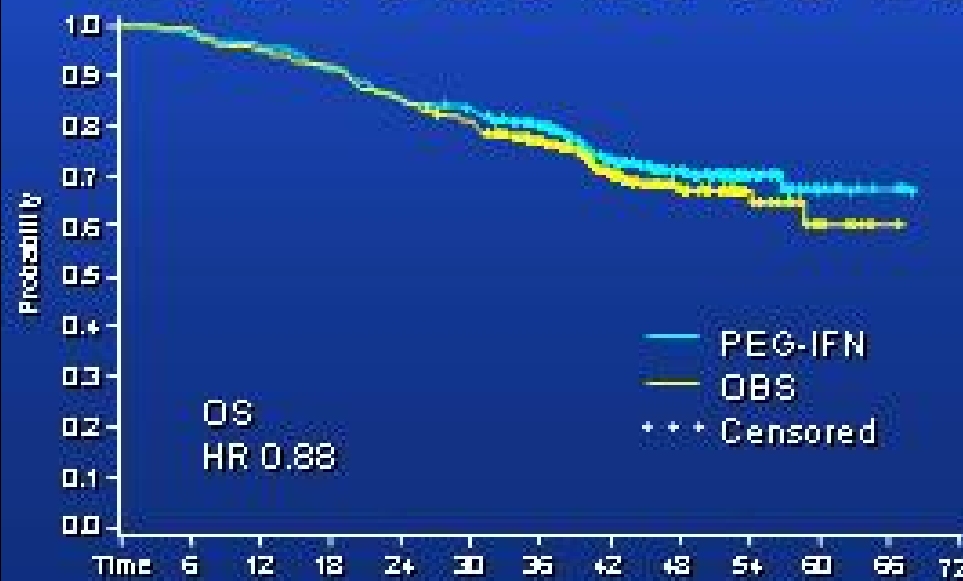
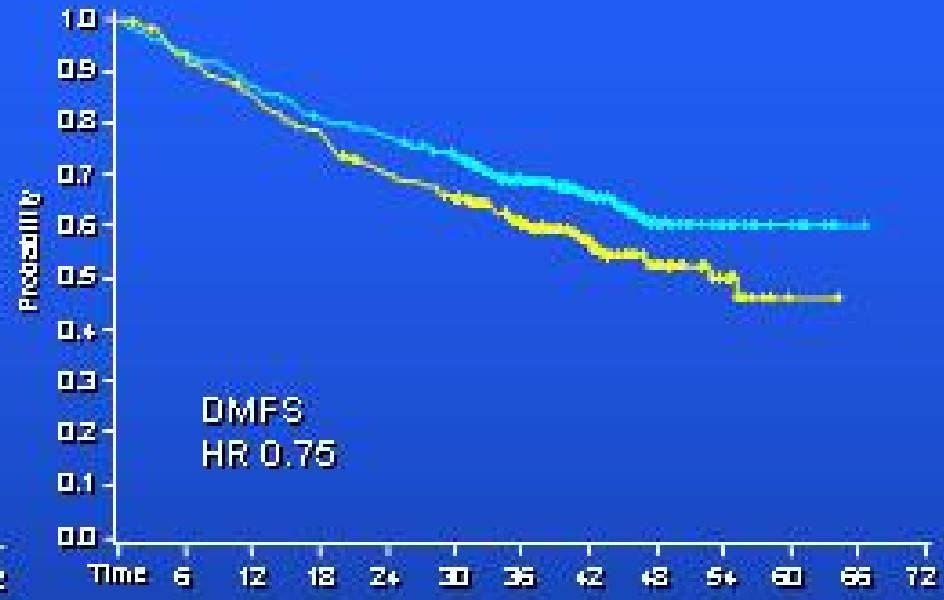
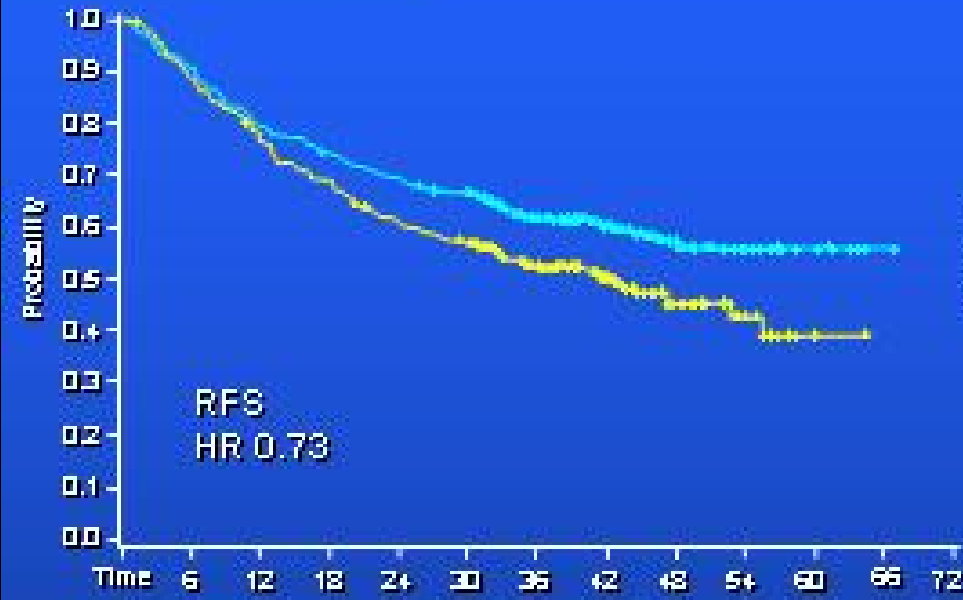
<b>O</b>	<b>N</b>	<b>Number of patients at risk :</b>						
		0	1	2	3	4	5	
304	627	476	384	267	91	17		— Peg-IFN alfa-2b
325	629	446	354	255	92	6		— Observation

# Overall Survival (ITT)



<u>O</u>	<u>N</u>	<u>Number of patients at risk :</u>						
262	627	564	457	343	143	28	<span style="color: red;">—</span> Peg-IFN alfa-2b	
263	629	547	457	349	139	23	<span style="color: blue;">—</span> Observation	

# N1: RFS DMFS OS hazard/time



# EORTC 18952 (1388 pts): Efficacy in IIB > N1 > N2

RFS: HR estimate	13-month interferon alfa-2b (1 mos 10MU – 12 mos 10MU)			25-month interferon alfa-2b (4wk 10MU – 24 mos 5 MU)		
	IIB	III N1	III N2	IIB	III N1	III N2
n subjects (test+ obs)	214	209	409	<b>215</b>	<b>212</b>	408
DMFI	0.78	0.89	1.01	<b>0.54</b>	<b>0.66</b>	0.90
DMFS	0.76	0.96	1.02	<b>0.58</b>	<b>0.69</b>	0.92

**Does sentinel node biopsy allow for earlier, more effective use of adjuvant therapy?**

**YES!**

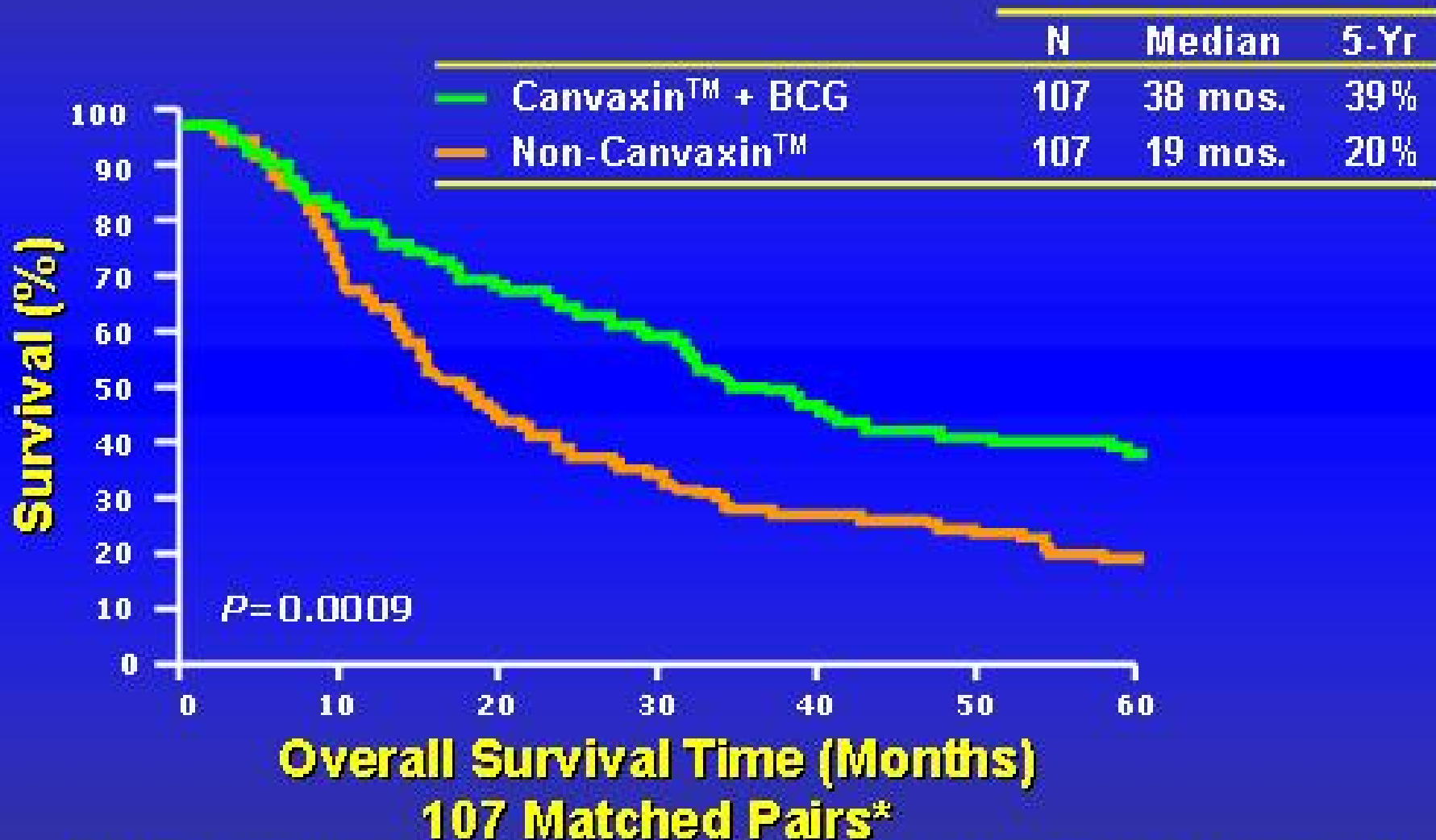
# What about vaccines?

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- Autologous tumor vaccines
- Defined antigen vaccines
  - **Gangliosides**
  - Peptides
- Dendritic cell-based vaccines
- Genetically modified tumor vaccines
- **Allogeneic, polyvalent vaccines**

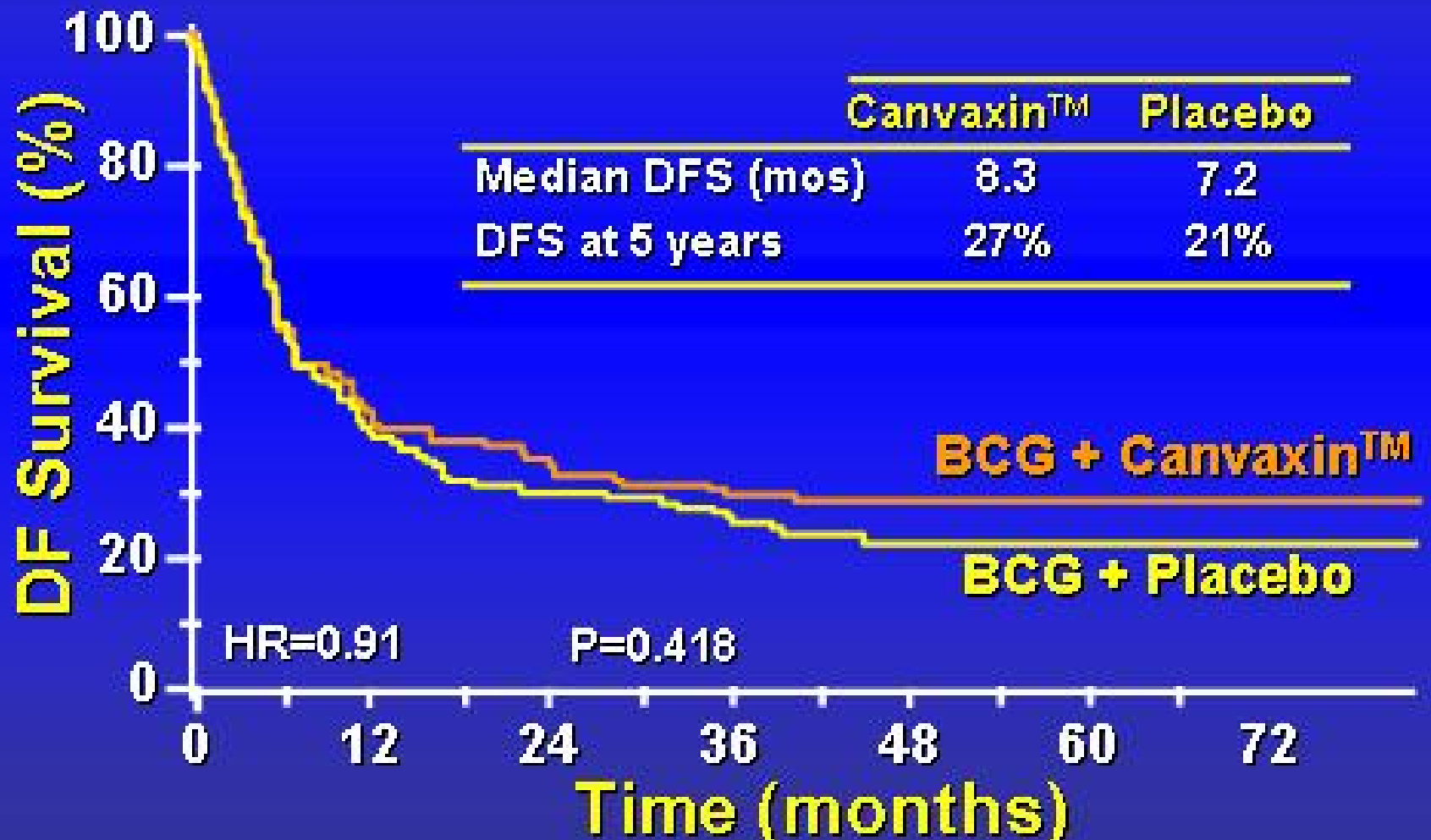


# Phase II Matched Pair Results of Adjuvant Canvaxin™ in Stage IV Melanoma: Overall Survival



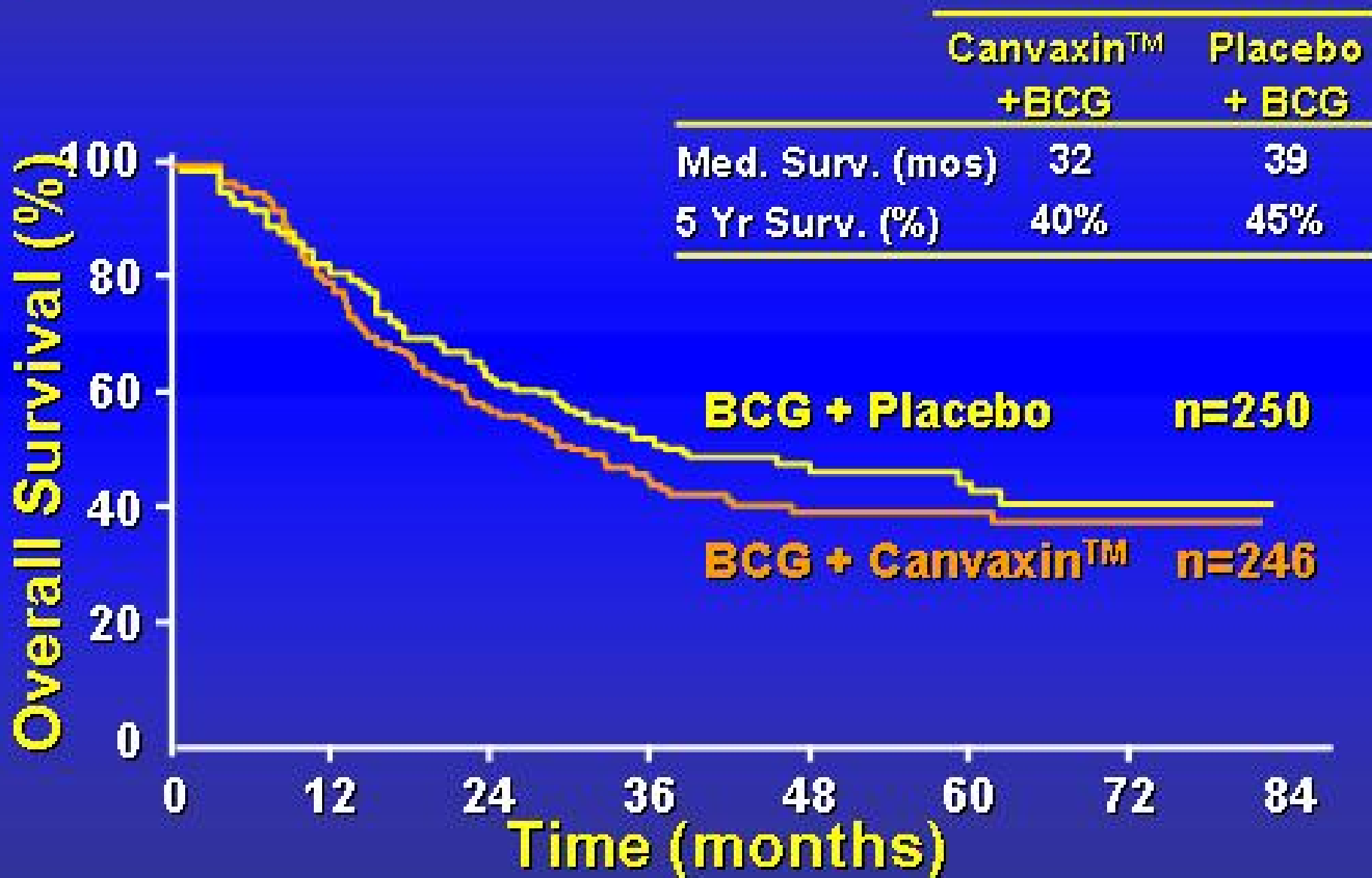
\*Matched according to site of metastasis, number of organs involved, and gender.

# MMAIT-IV Disease Free Survival (Intent To Treat)



Morton et al Proc ASCO 2007 abstract 8508

# MMAIT-IV Overall Survival (Intent To Treat)



# MMAIT-III

## DISEASE FREE SURVIVAL

Median DFS (months)

43

>60

DFS at 5 years

47%

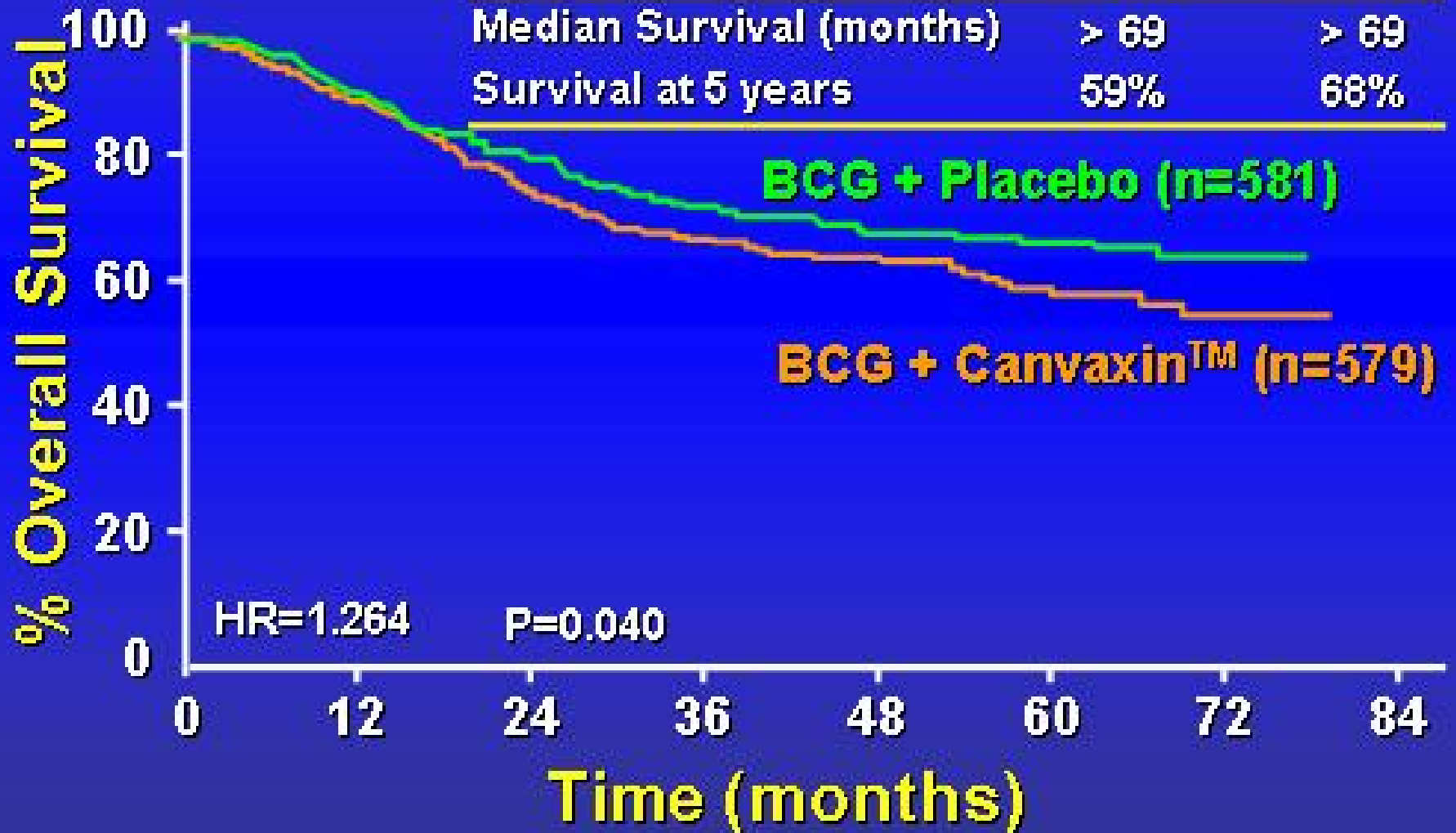
52%



# MMAIT-III

## OVERALL SURVIVAL

	Canvaxin™	Placebo
Median Survival (months)	> 69	> 69
Survival at 5 years	59%	68%

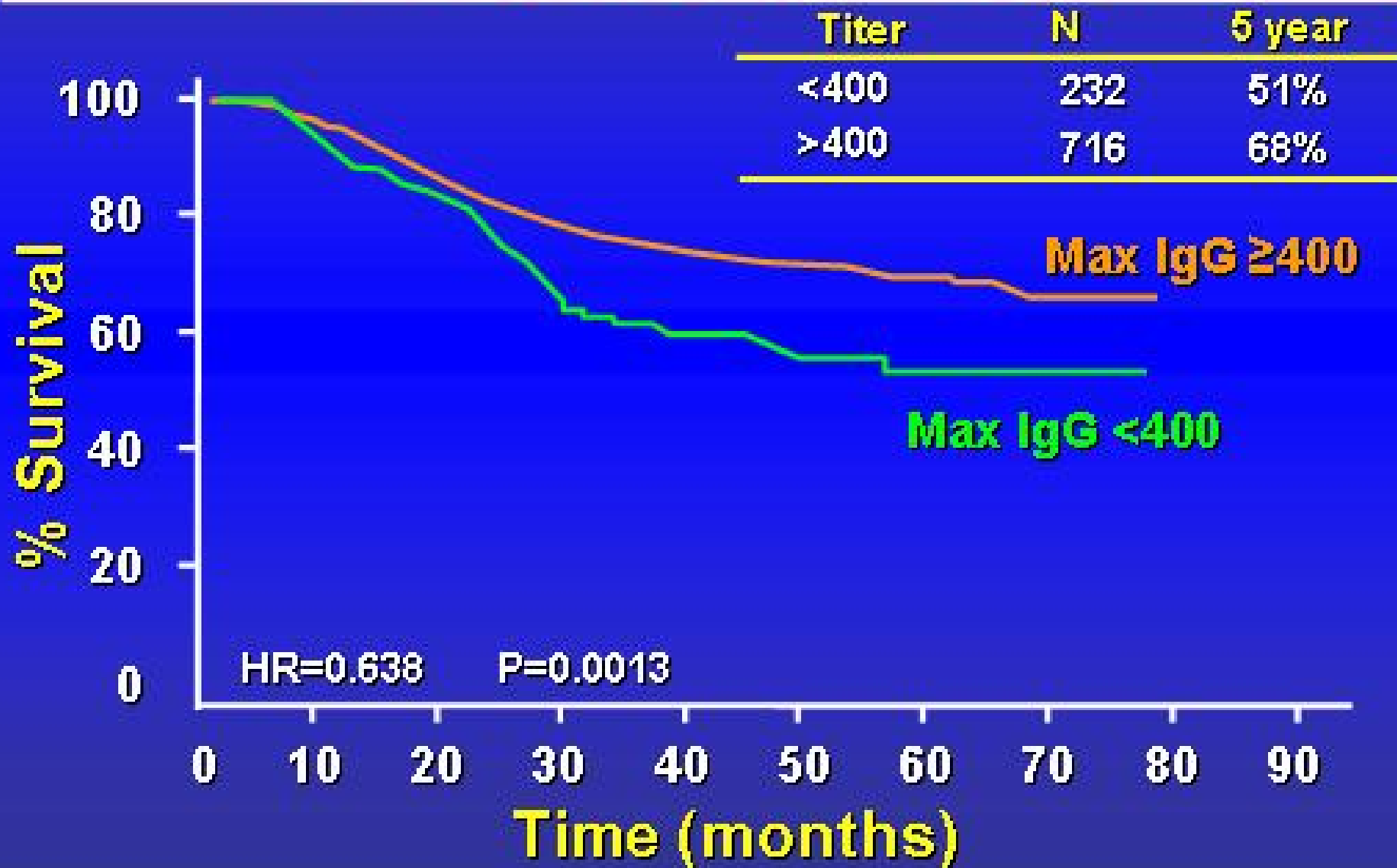


# Overall Survival: Immune Responder Status\* in Stage IV Canvaxin™ Group



\*Immune Responder defined as average DTH induration  $\geq 7$  mm within first 12 wks

# Overall Survival in Relation to UTAA IgG Antibody Response - Stage III



# Topics

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- What does sentinel node biopsy actually do?
- Adjuvant therapy with interferon – where are we now?
- Will we be seeing some new agents for treatment of metastatic melanoma anytime soon?



# CTLA-4: The Brake on T cell Activation

J Wolchok, ASCO 2007 Poster Discussant



T-cell receptor: Antigen-MHC



CD28: B7



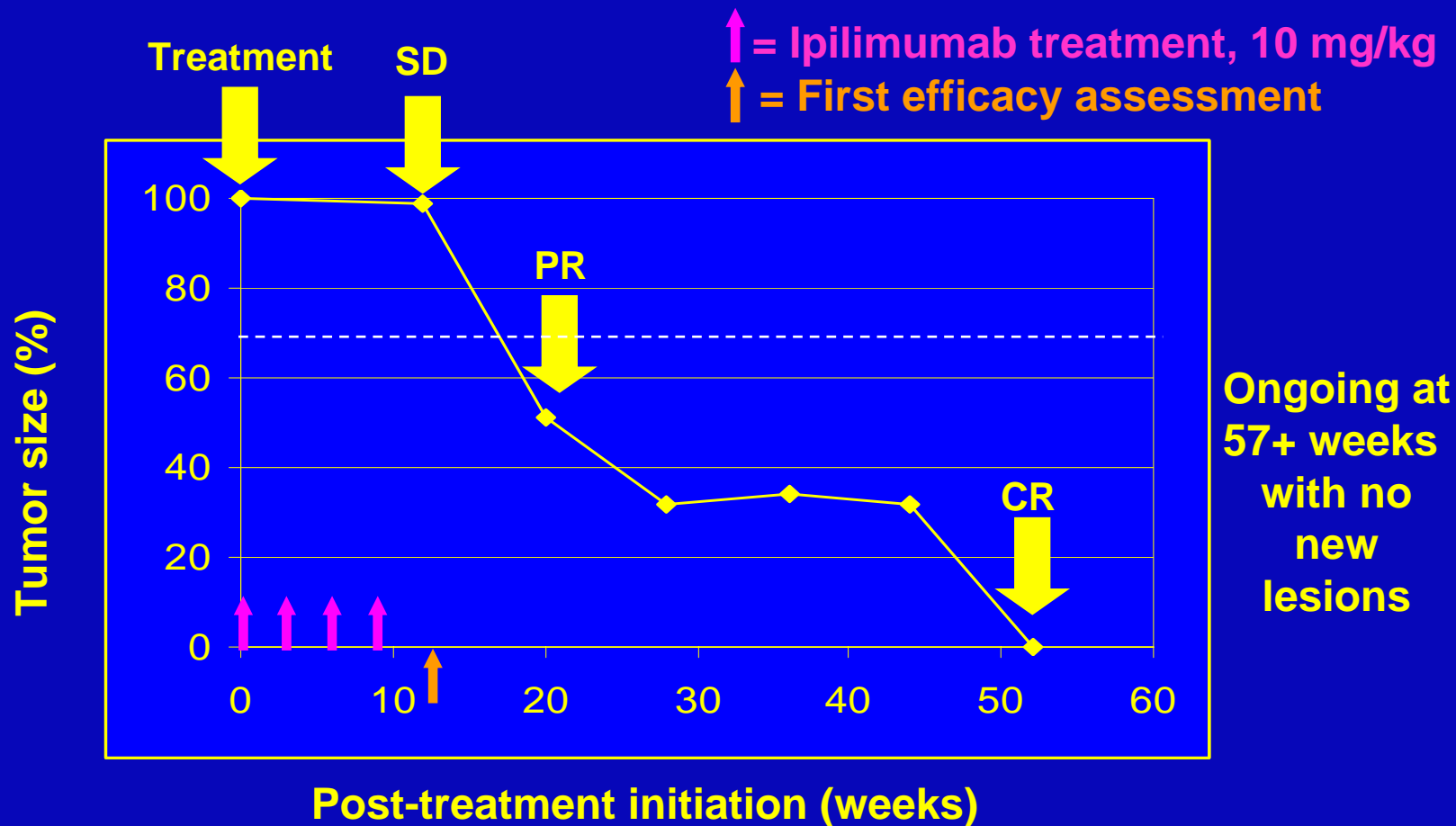
CTLA-4: B7



Vaccine?

Weber et al, Proc ASCO 2007 abstract 8523

# Slow but steady response to Anti-CTLA4 ab



Prior treatment included surgery, interferon alpha, GM-CSF, BCG, IL-2, and an unspecified biologic. irAEs included G1 diarrhea and G1 rash

**When going downhill with no brakes, a steering wheel is a great idea!**



## Sorafenib, STA-4783 and others

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- Melanoma is one of the least responsive cancers to cytotoxic chemotherapy
- Adding targeted therapies like sorafenib (blocks BRAF, VEGF) and chemosensitizers like STA-4783 (increases free radicals in the tumor) are promising approaches in phase III trials in metastatic melanoma



## TREATING METASTATIC MELANOMA

# The Light at the End of the Tunnel

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# The H. Lee Moffitt Cancer Center Cutaneous Oncology Program



**DONALD A. ADAM COMPREHENSIVE CENTER  
FOR MELANOMA RESEARCH**

*"The End Of Melanoma Begins Here"*

Cutaneous Oncology Program

H. LEE  
**MOFFITT**  
Cancer Center & Research Institute





