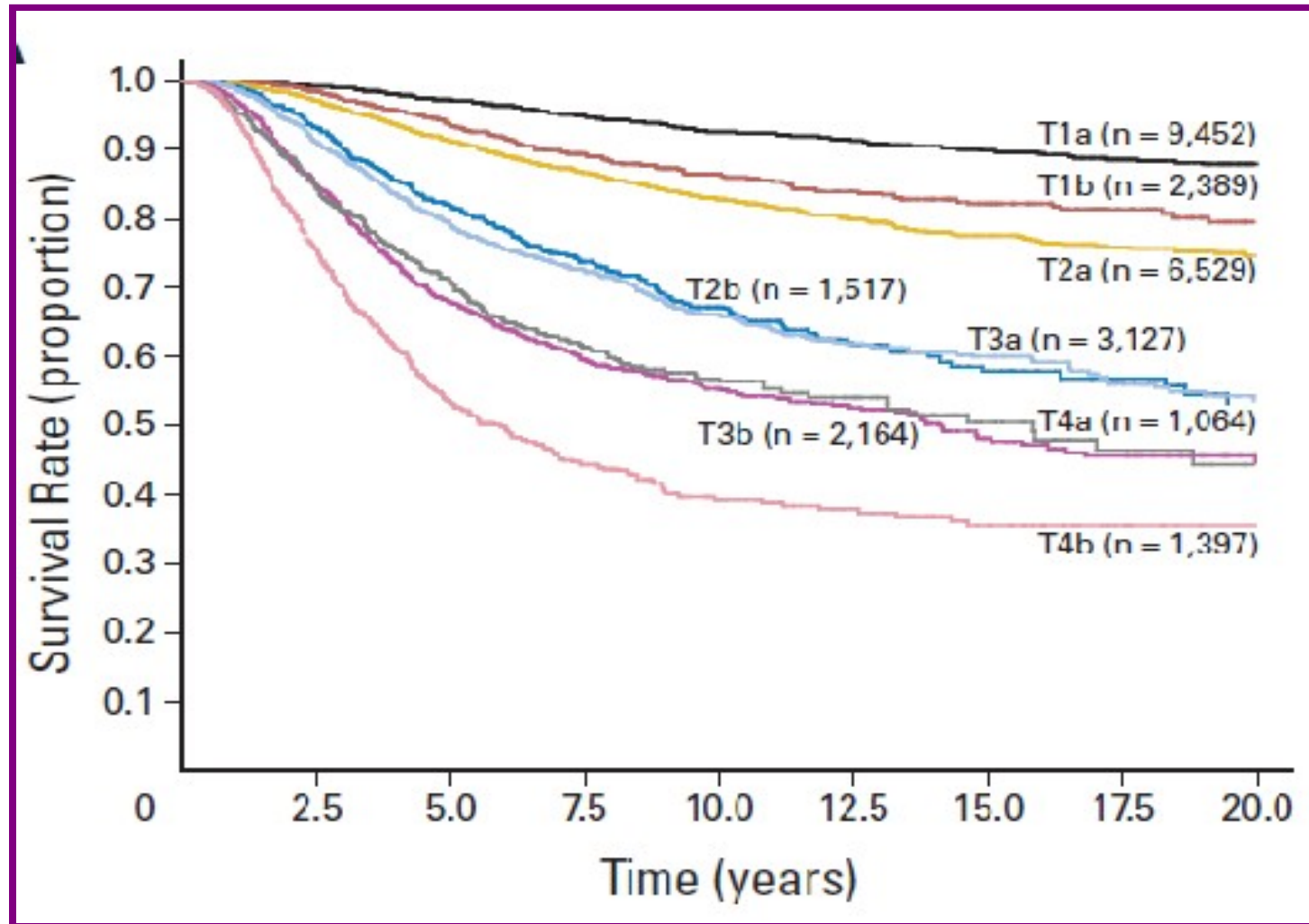


Trattamento medico del melanoma : stato dell'arte

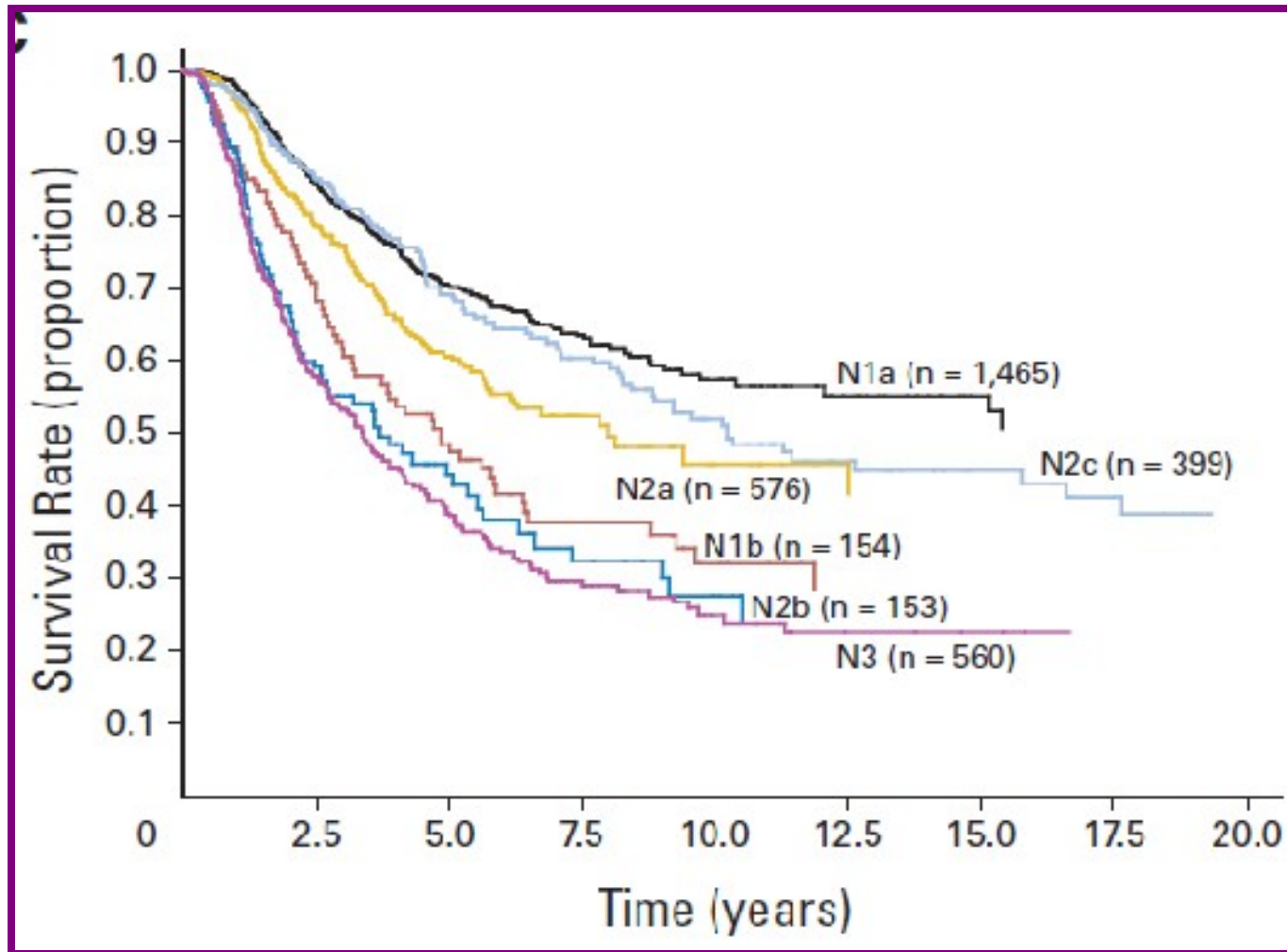
Torino 5 Dicembre 2011

Vanna Chiarion Sileni
Oncologia Medica 2
IOV-IRCCS, Padova

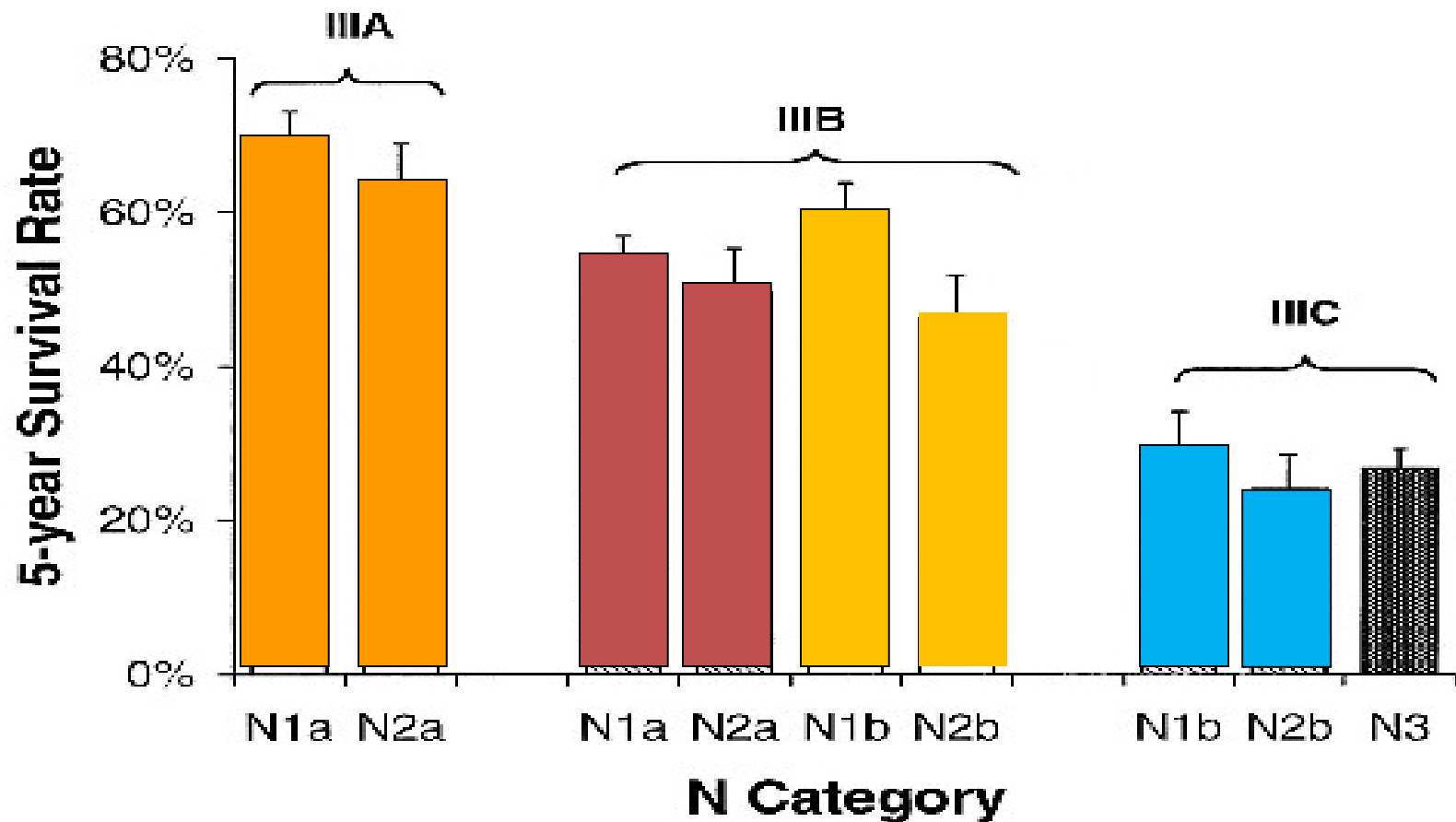
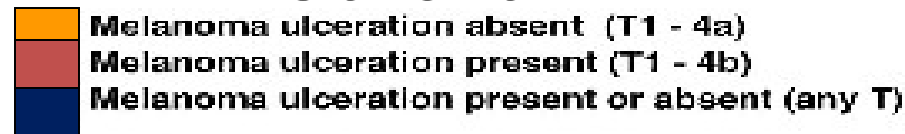
2009 AJCC Melanoma staging



Staging 2009 AJCC Melanoma

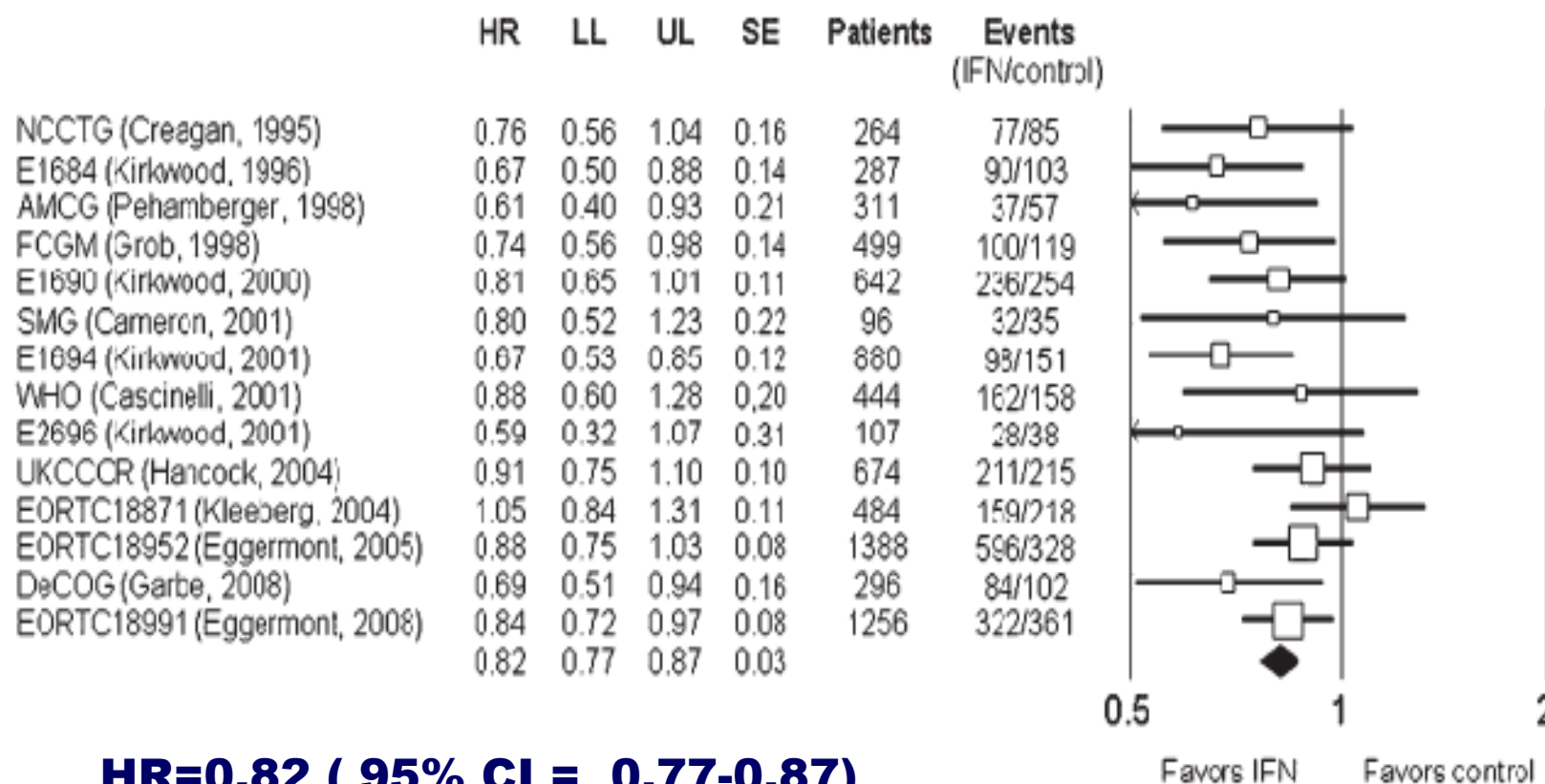


5-y survival rates from the AJCC melanoma staging database comparing N categories and stage groupings for stage III melanoma



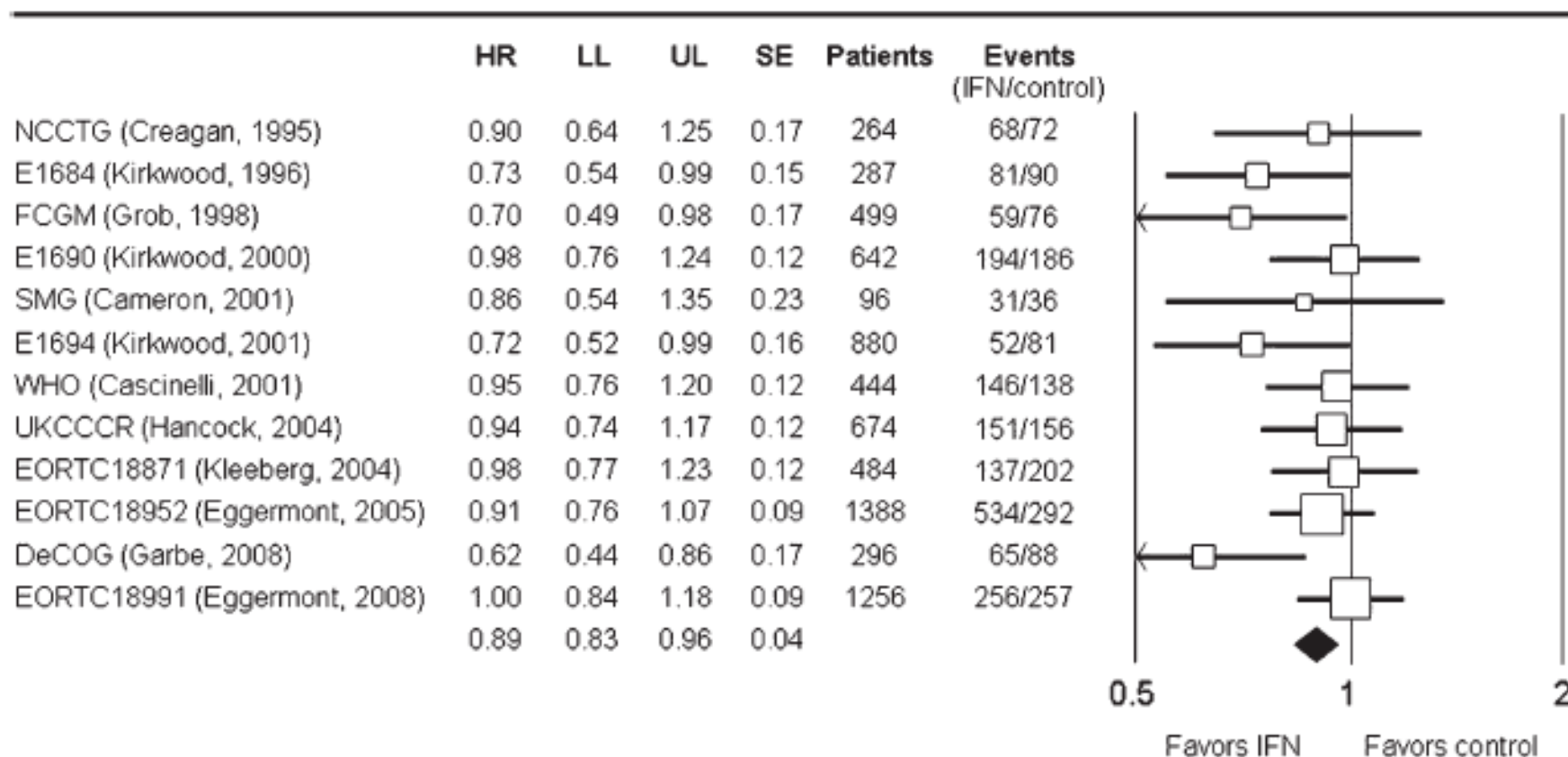
Interferon Alpha Adjuvant Therapy in Patients With High-Risk Melanoma: A Systematic Review and Meta-analysis

Disease Free Survival



Interferon Alpha Adjuvant Therapy in Patients With High-Risk Melanoma: A Systematic Review and Meta-analysis

Overall Survival



HR=0.89(95% CI= 0.83-0.96)

What is IFN benefit in 'high-risk' melanoma?

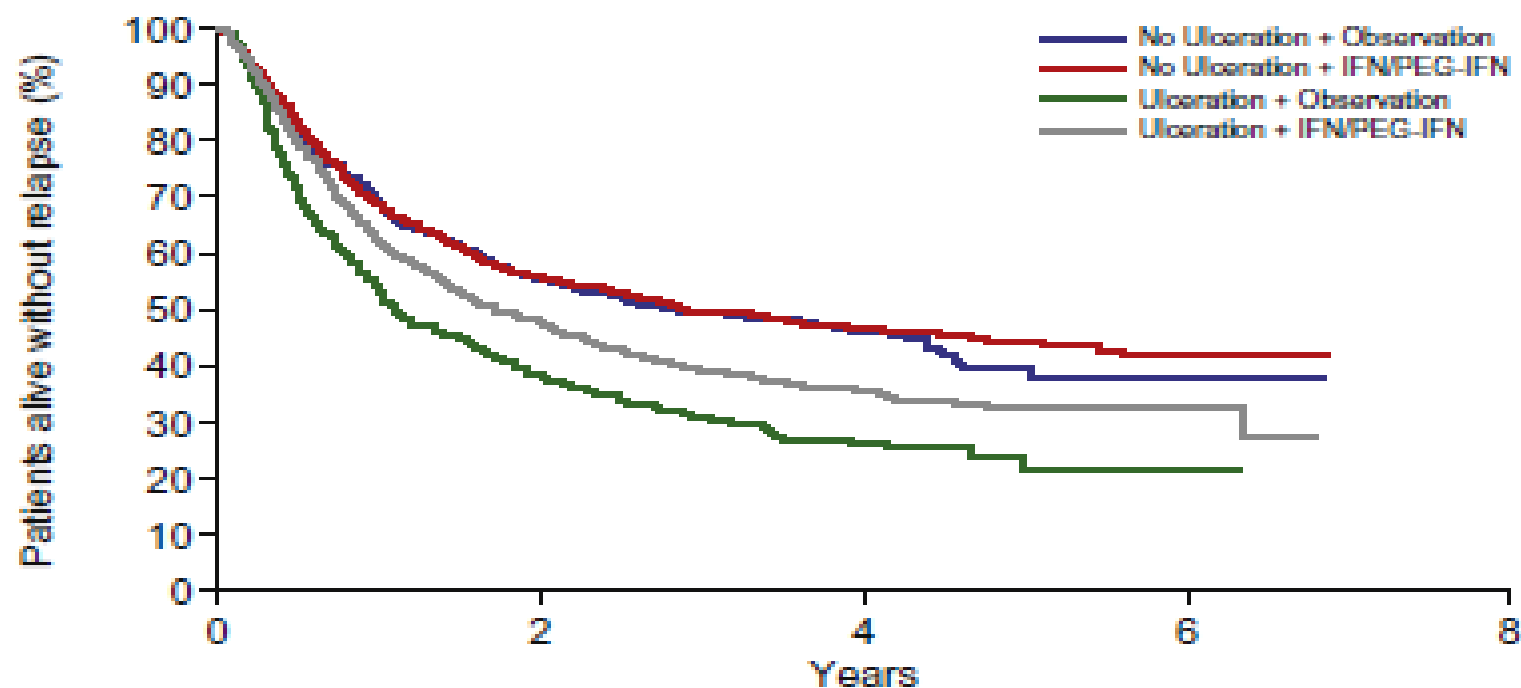
- Prof. K. Wheatley meta-analysis (n=6066, 13 trials)
- 'High-risk' is 'stage II and stage III'
- Relapse-free survival risk reduction
 - Any IFN: 13%
 - High-dose interferon (HDI): 17%
 - Intermediate or low-dose (ID, LD): 12% (NS), 13%
- Overall survival risk reduction
 - Any IFN: 10%
 - Any single regimen (HDI, ID, LD): 10% (NS)

Mela trial

median FU 7.2 y

	RFS		OS
HDI	IHDI	HDI	IHD
5-year rates	46.3	45.4	60.4
Median(yrs)	4	3.3	7.4

2A Relapse-free survival

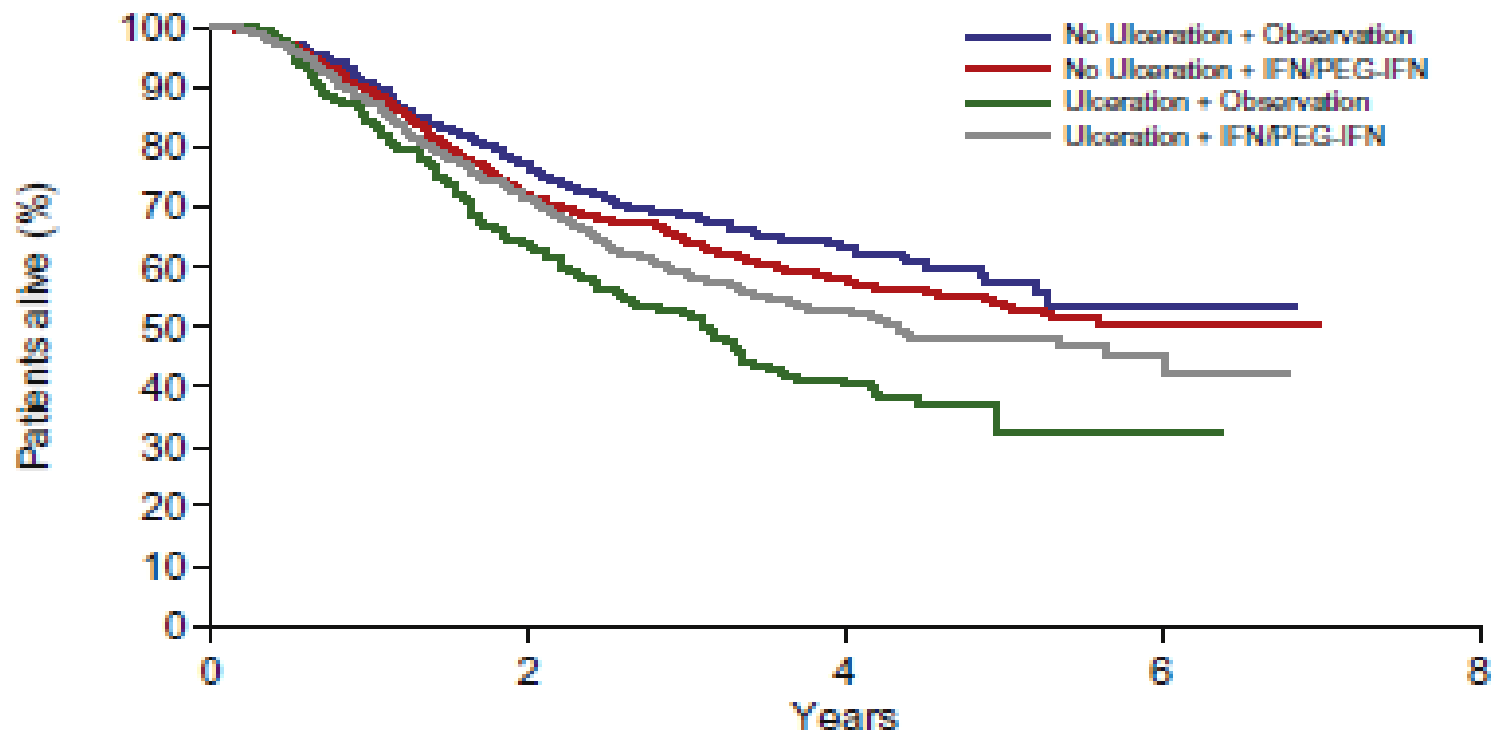


O	N	Number at risk			
256	473	257	94	8	
461	863	477	222	29	
209	287	108	37	1	
363	562	265	120	10	

No ulceration: HR 0.92 (99% CI 0.74–1.14), $p=0.30$.

Ulceration: HR 0.75 (99% CI 0.59–0.95), $p=0.001$.

2C Survival



O	N	Number at risk			
176	473	362	144	8	
370	863	612	300	36	
167	287	180	59	2	
273	562	394	186	16	

No ulceration: HR 1.11 (99% CI 0.86–1.41), $p=0.20$.

Ulceration: HR 0.72 (99% CI 0.55–0.93), $p=0.001$.

The current opportunity

Intergroup E1609 Phase III trial: HD-Ipilimumab vs. HDI

S
U
R
G
E
R
Y

Patients with
resectable
IIIB, IIIC
M1a, M1b

N=800

Chair: A Tahrini, UPCI

Endpoints

OS, RFS (Co-primary)

QOL

Immunological correlates of RFS, OS

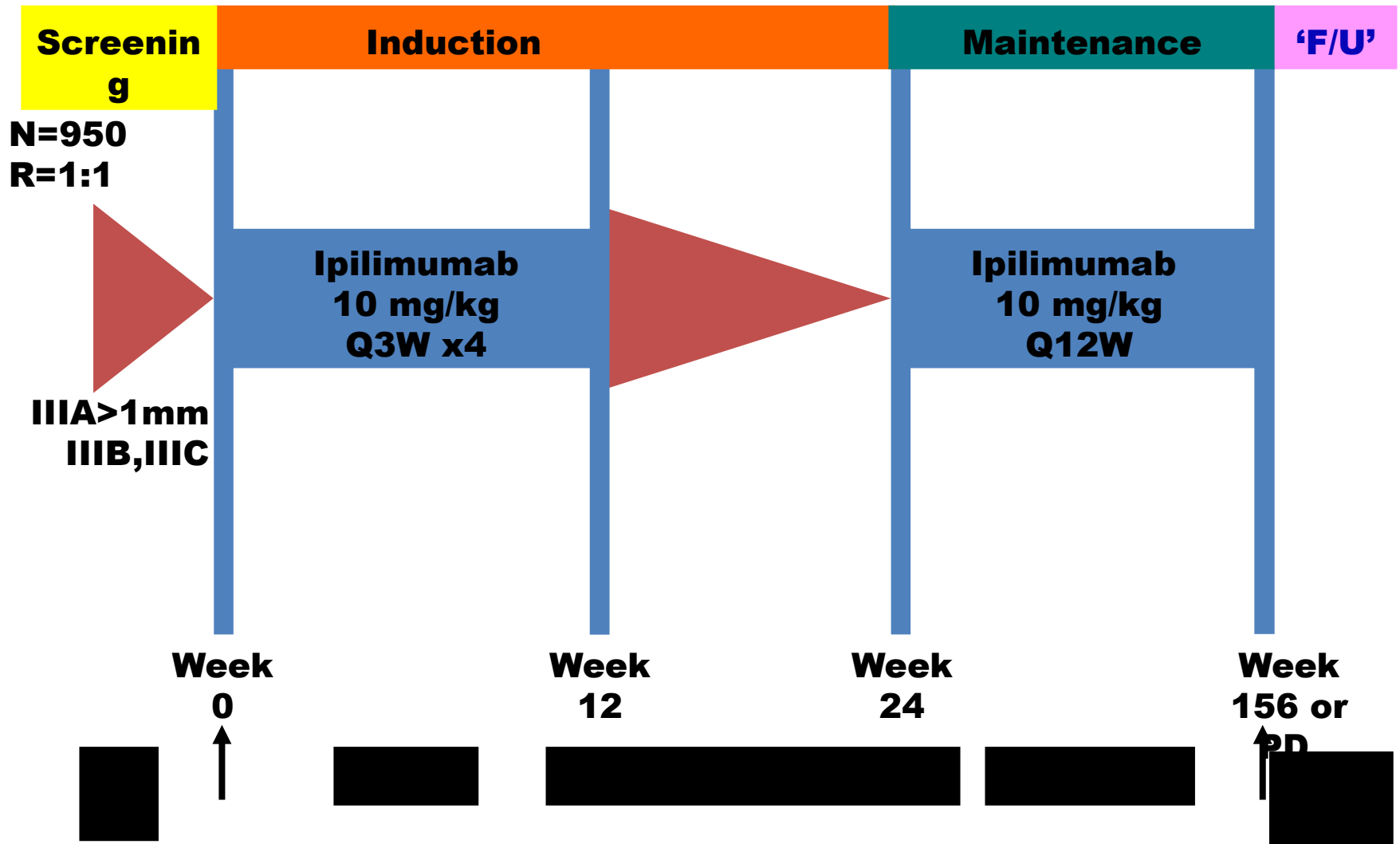
- serial blood serum and lymphocytes
- baseline tissue blocks

Ipilimumab 10 mg/kg q 21 x 4
then 10 mg/kg q 3 mos x 3 for
1 year

HDI 20 MiU/m² IV x 20
then 10 MiU/m² SC TIW
for 1 year

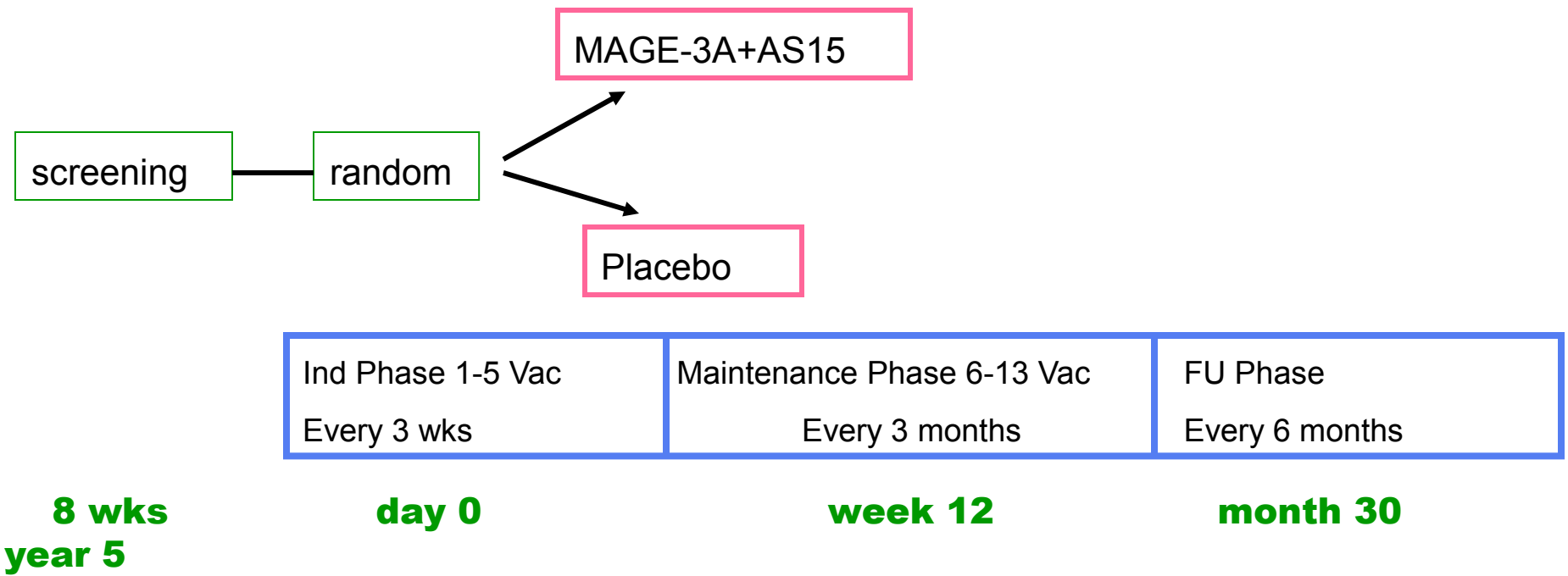


CA184-029: Study Design



'FU' = follow-up after end or PD every 24 wks ; TA = tumor assessment

DERMA STUDY (GSK 2132231A)

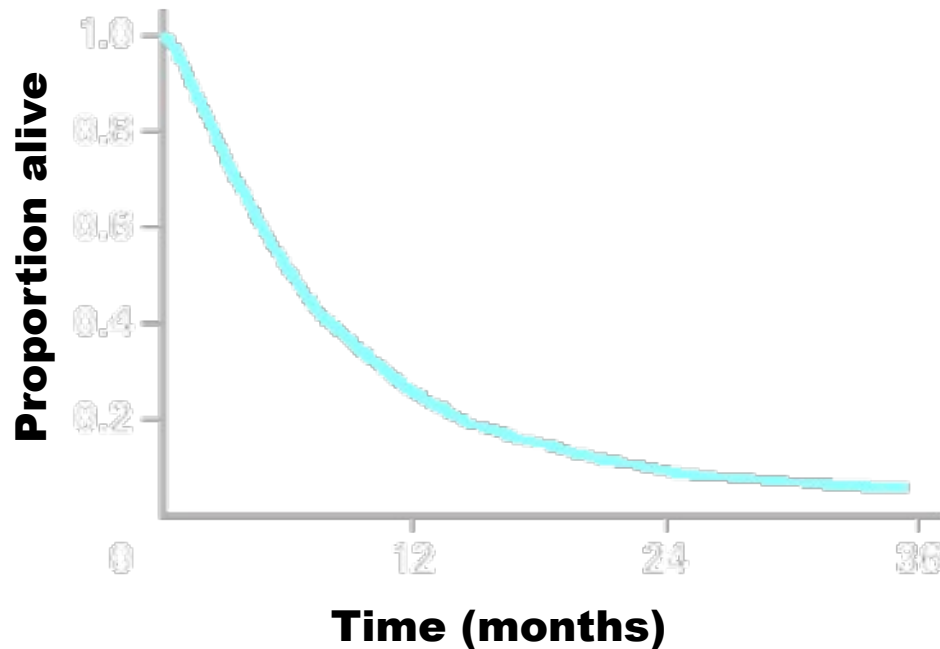


Interim analysis (420 events) Final (701 events): median DFS from 13 to 16.9 mos

Raccomandazioni per il trattamento adiuvante del melanoma

- Stadio IIA : trattamento non raccomandato
- Stadio IIB: LDI
- Stadio IIC: LDI/HDI
- Stadio IIIA: LDI/HDI/PegIFN
- Stadio IIIB: LDI/HDI/PegIFN
- Stadio IIIC: HDI
- Stadio IV(R0): assenza di dati

Overall Survival for Metastatic Melanoma



Adapted from Korn 2008

Survival data from 42 Phase II trials with over 2,100 stage IV patients¹:

12 month OS: 25.5 %, median OS: 6.2 months (stage IV melanoma including patients with brain metastases)

Due to the lack of efficacious therapy, the preferred treatment for metastatic melanoma remains the inclusion in a clinical trial²

¹Korn EL et al. J Clin Oncol 2008;26(4):527-34.

²Dummer R, Hauschild A, Jost L. Cutaneous malignant melanoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19 Suppl 2:ii86-8.

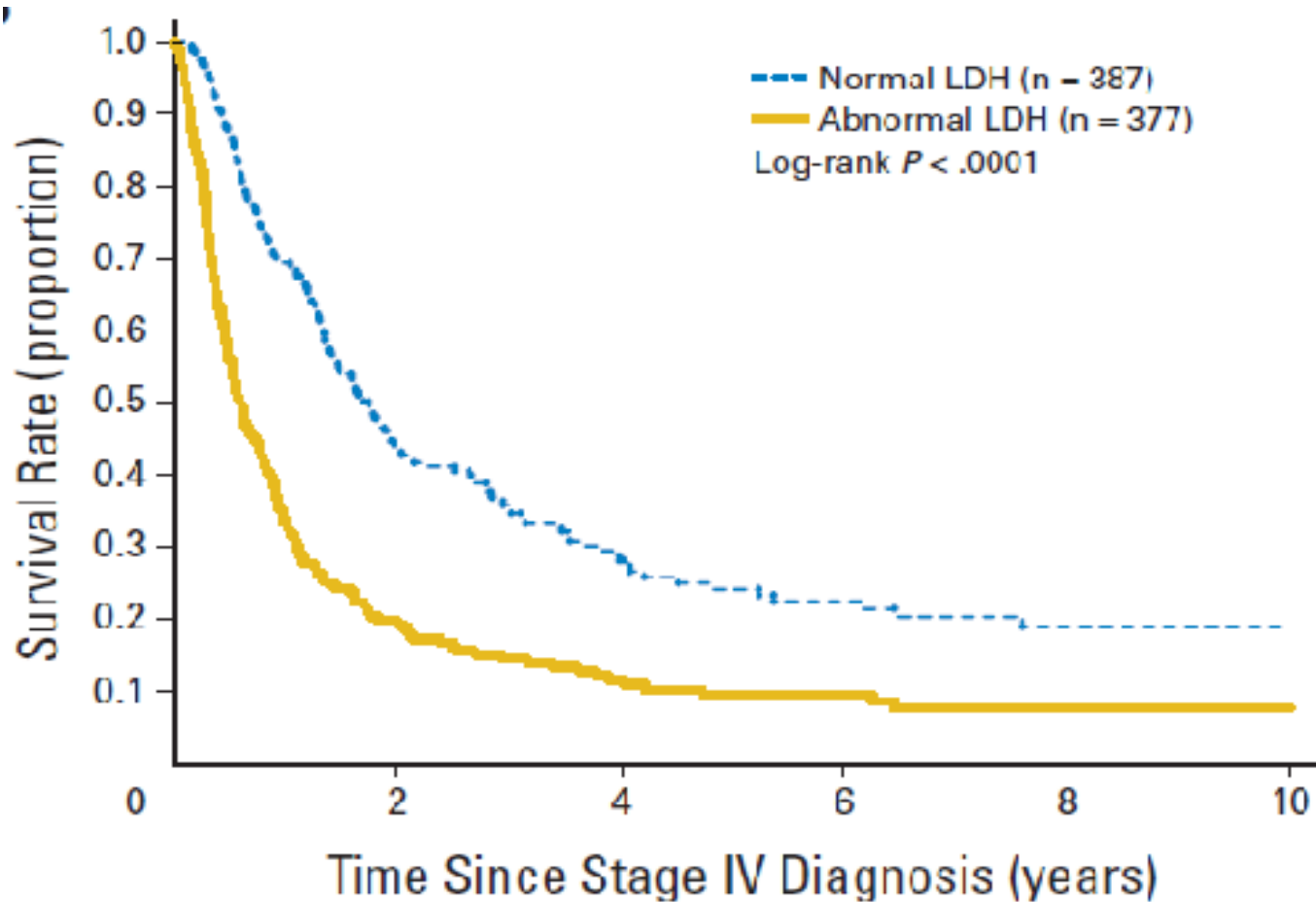
Prognostic factors in metastatic melanoma

1362 pts enrolled in 8 studies ECOG in the last 25 years

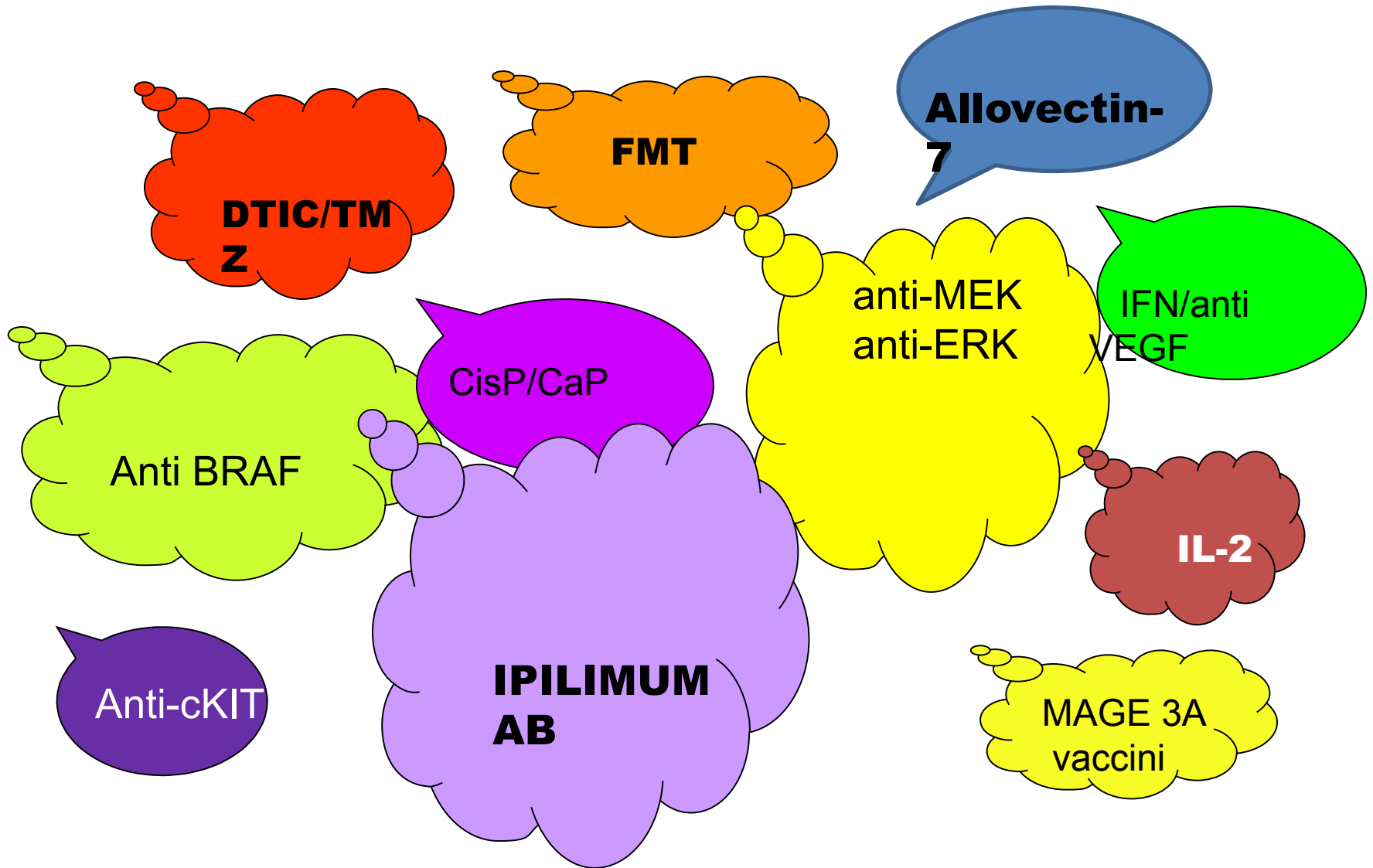
Median OS 6.4 months (CI 6.1-6.9)

- **Multiple metastases RR= 1.3**
- **ECOG PS >1 RR = 1.49**
- **GI metastases RR =1.49**
- **Liver metastases = 1.44**
- **Pleural metastases RR =1.35**
- **LDH ↑ RR = 1.89**
- **FAL ↑ RR = 1.76**
- **Previous immunotherapy RR = 0.84**

LDH remains the most important prognostic factor

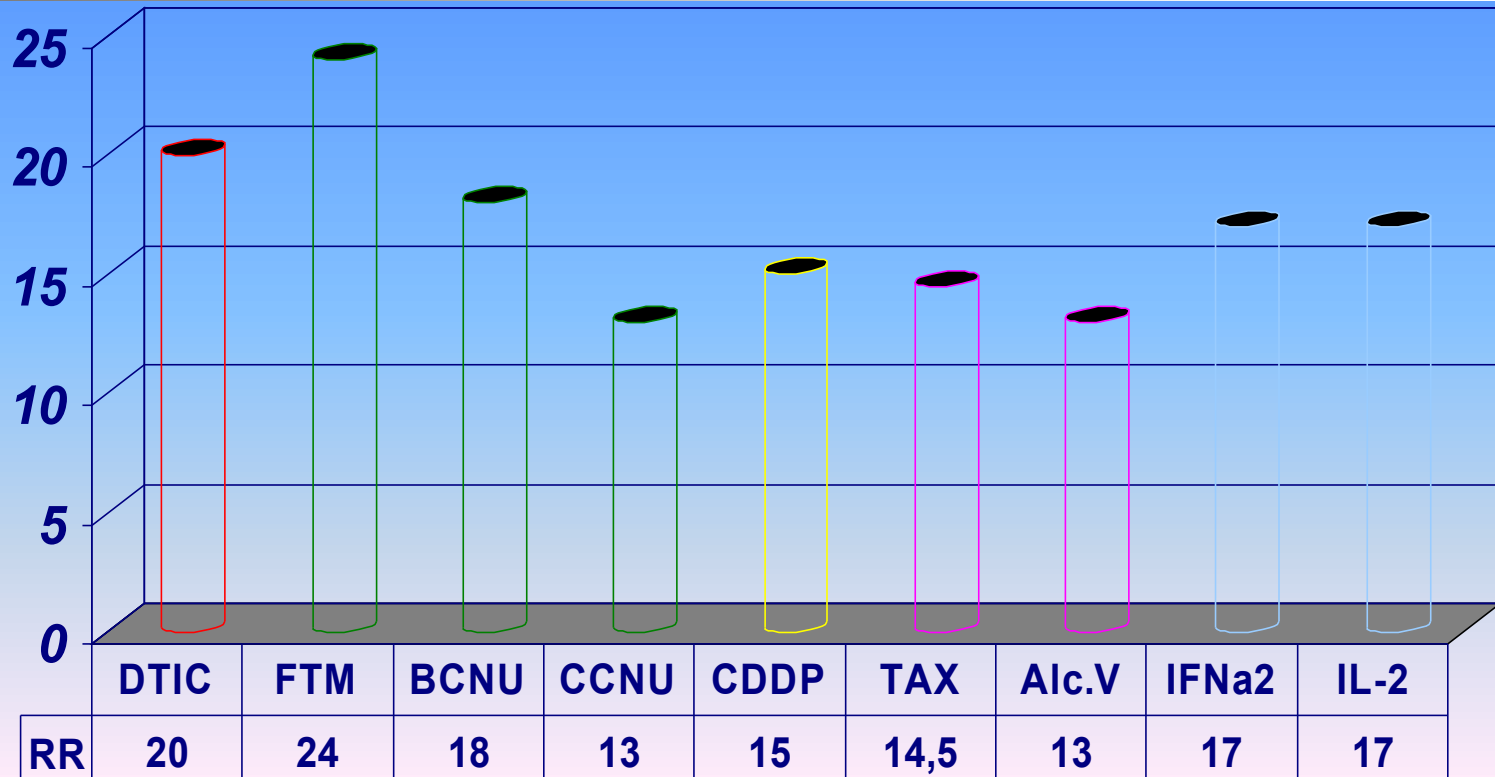


Scelte terapeutiche possibili



Metastatic Melanoma : Single Agent Options

Overall responses with monotherapy



CRT con DTIC

Chapman JCO 17; 2745,1999: OR 10 % OS 6.3 ms

Middleton JCO 18; 158, 2000: OR 12.1 % PFS 1.5 ms

Chiarion-Sileni Melanoma Res 11; 189,2001: OR 5%, PFS 2 ms

Avril JCO 22;1118,2004:OR 6.8% PFS 1.9 ms

Millward ASCO 7505,2004: OR 6.8 % PFS 49 d

Schadendorf ASCO 7508,2004: OR 5.5 % PFS ?

DTIC alternatives ?

Autore	farmaco	No Pts	MS	PFS	RR TBrP	ToxN/Plt
Middleton1	TMZ	156	7.7	1.9	13.5	
	DTIC	149	6.4	1.5*	12,1	
Avril2	FMT	110	7.3	1.9	15.5 22.7	51/43
	DTIC	111	5.6	1.8	7.2 7.2	5/6

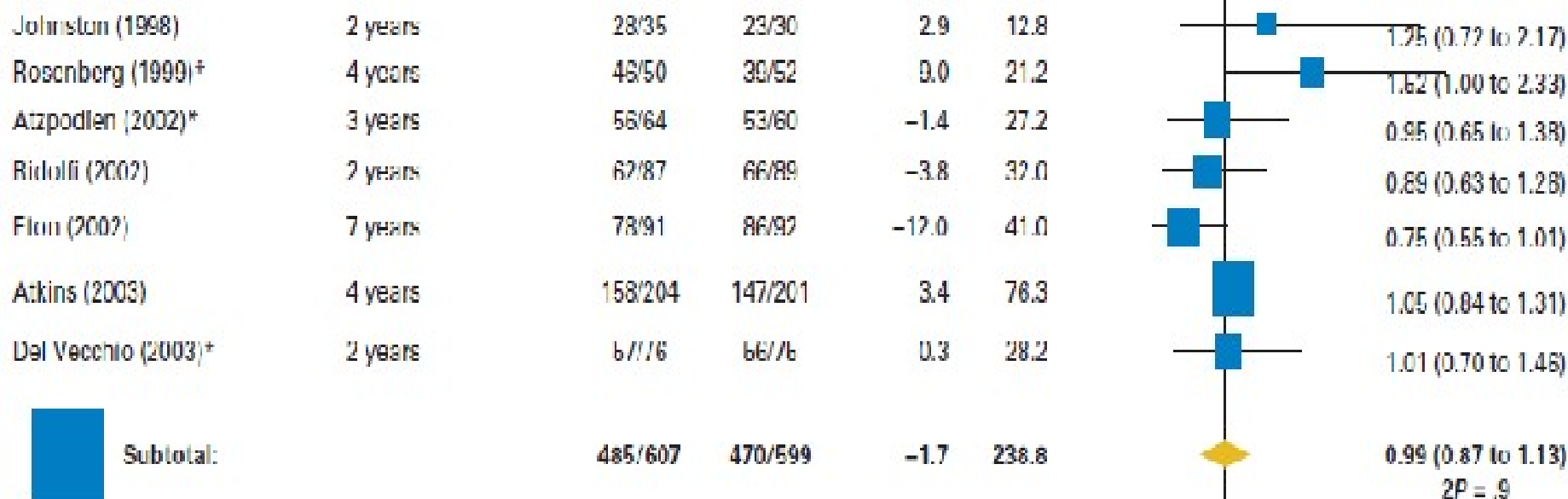
1= End point: MS □ di 3 mesi (da 6 a 9 = 50 %)

2= “ “ : RR □ del 17 % (DTIC 13 %)

* p= 0.12

Chemotherapy Compared With Biochemotherapy for the Treatment of Metastatic Melanoma: A Meta-Analysis of 18 Trials Involving 2,621 Patients

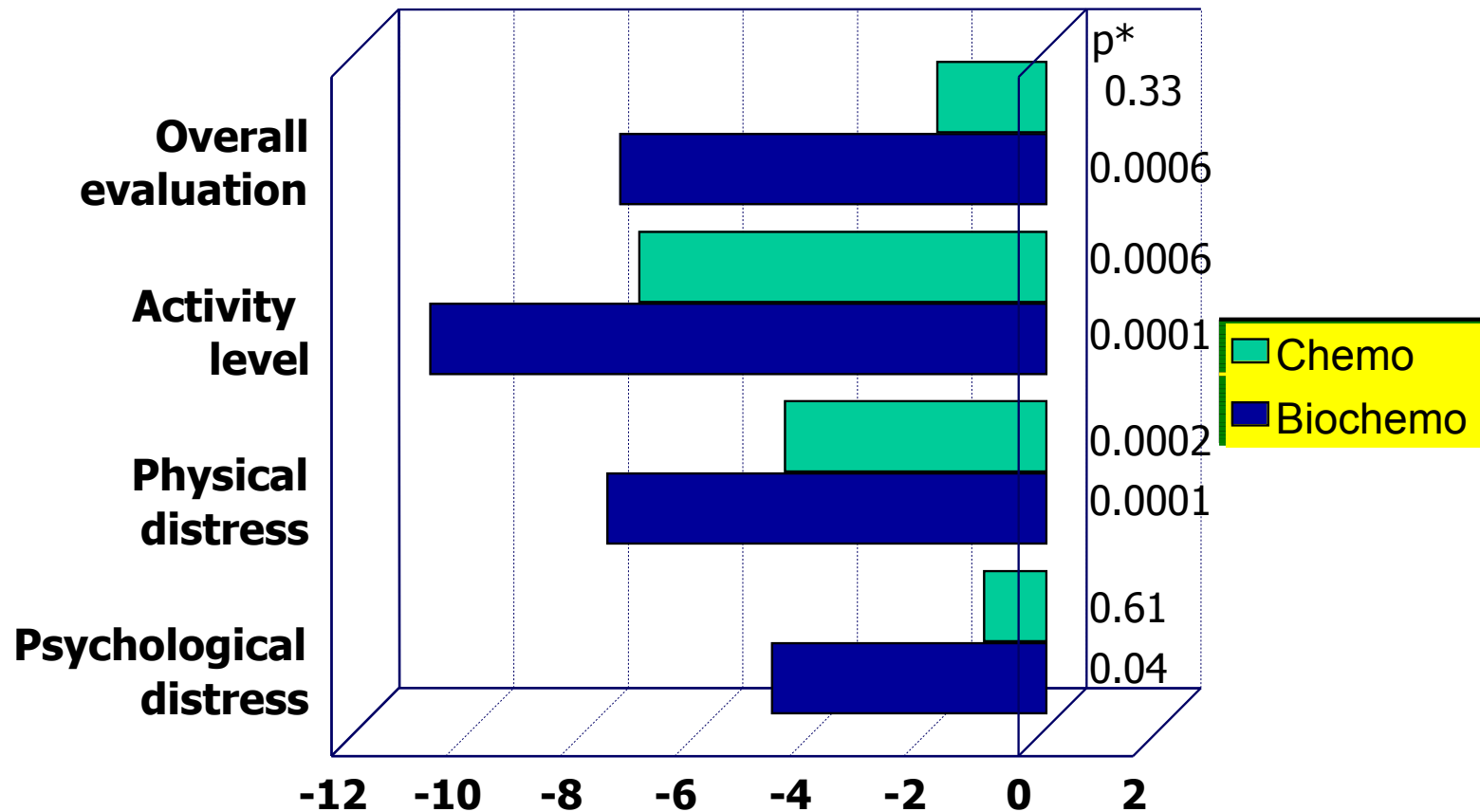
Chemotherapy +/- IFN and IL-2:



Test for heterogeneity between trials: $\chi^2_6 = 8.6$; $P = .2$

Randomized trial of chemotherapy vs biochemotherapy for advanced melanoma

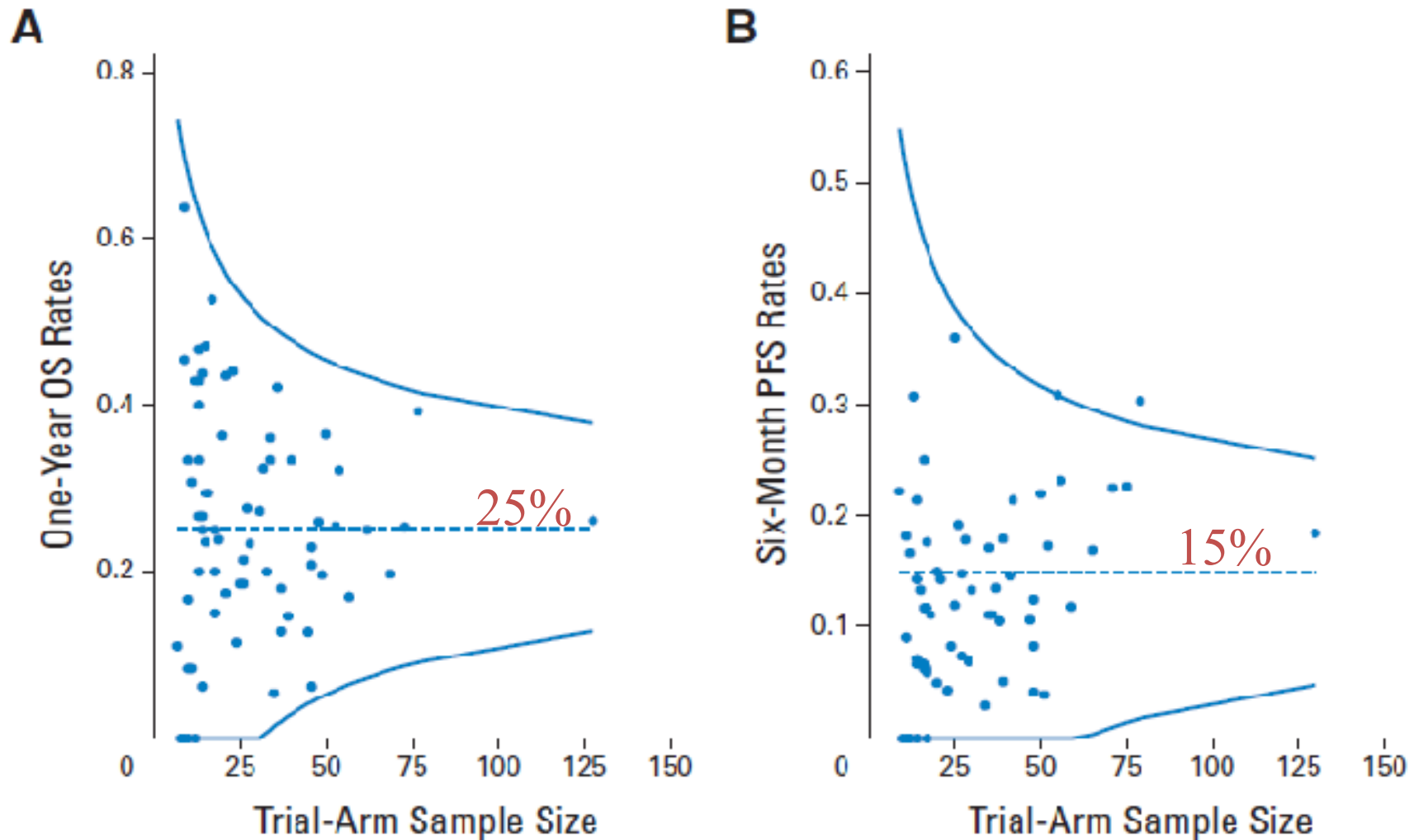
Mean difference between baseline and cycle scores by treatment



*Analysis of Variance fo repeated measures

Chiarion-Sileni EJC 39; 1577, 2003

Meta-Analysis of Phase II Cooperative Group Trials in Metastatic Stage IV Melanoma to Determine Progression-Free and Overall Survival Benchmarks for Future Phase II Trials

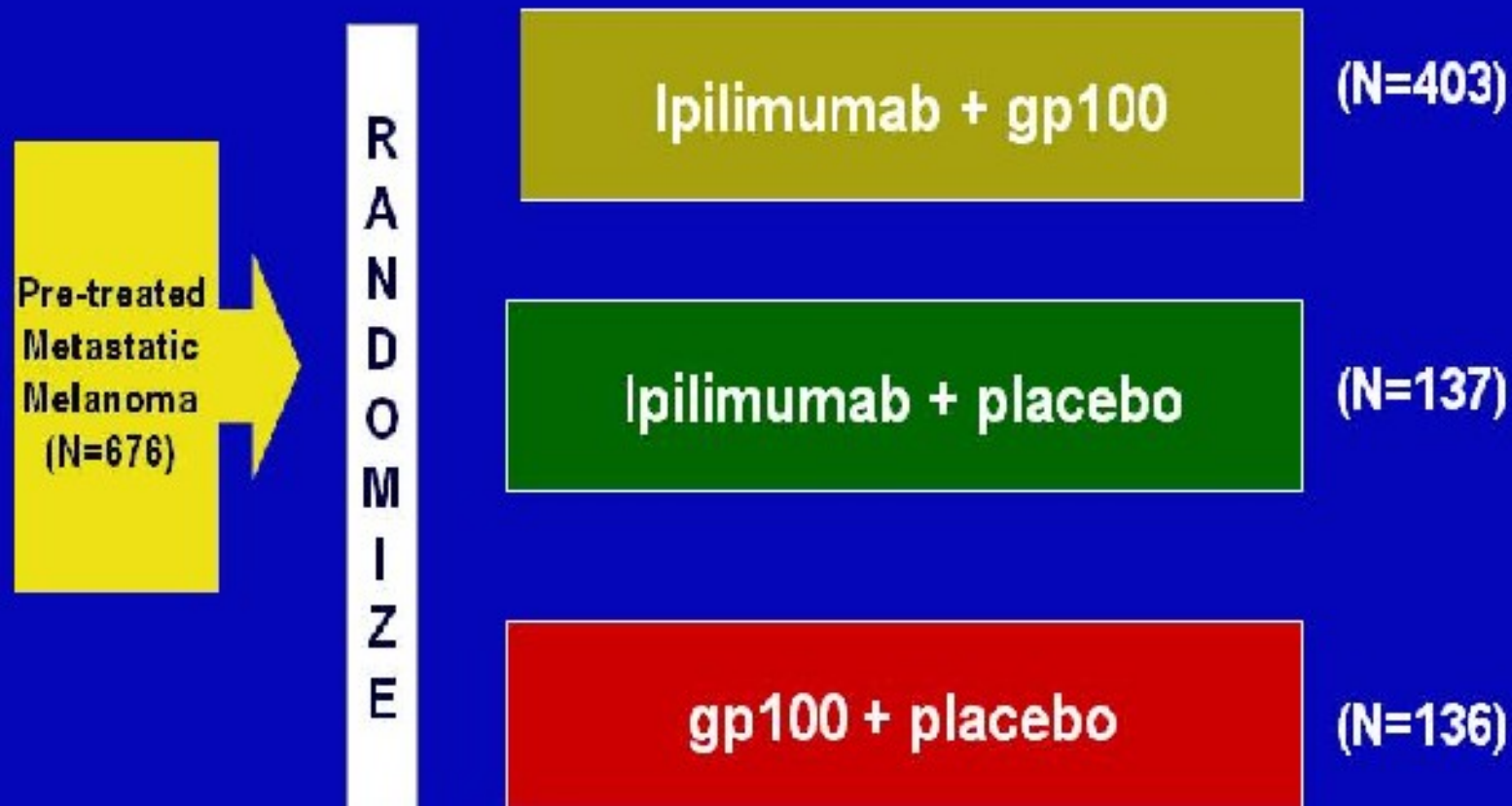




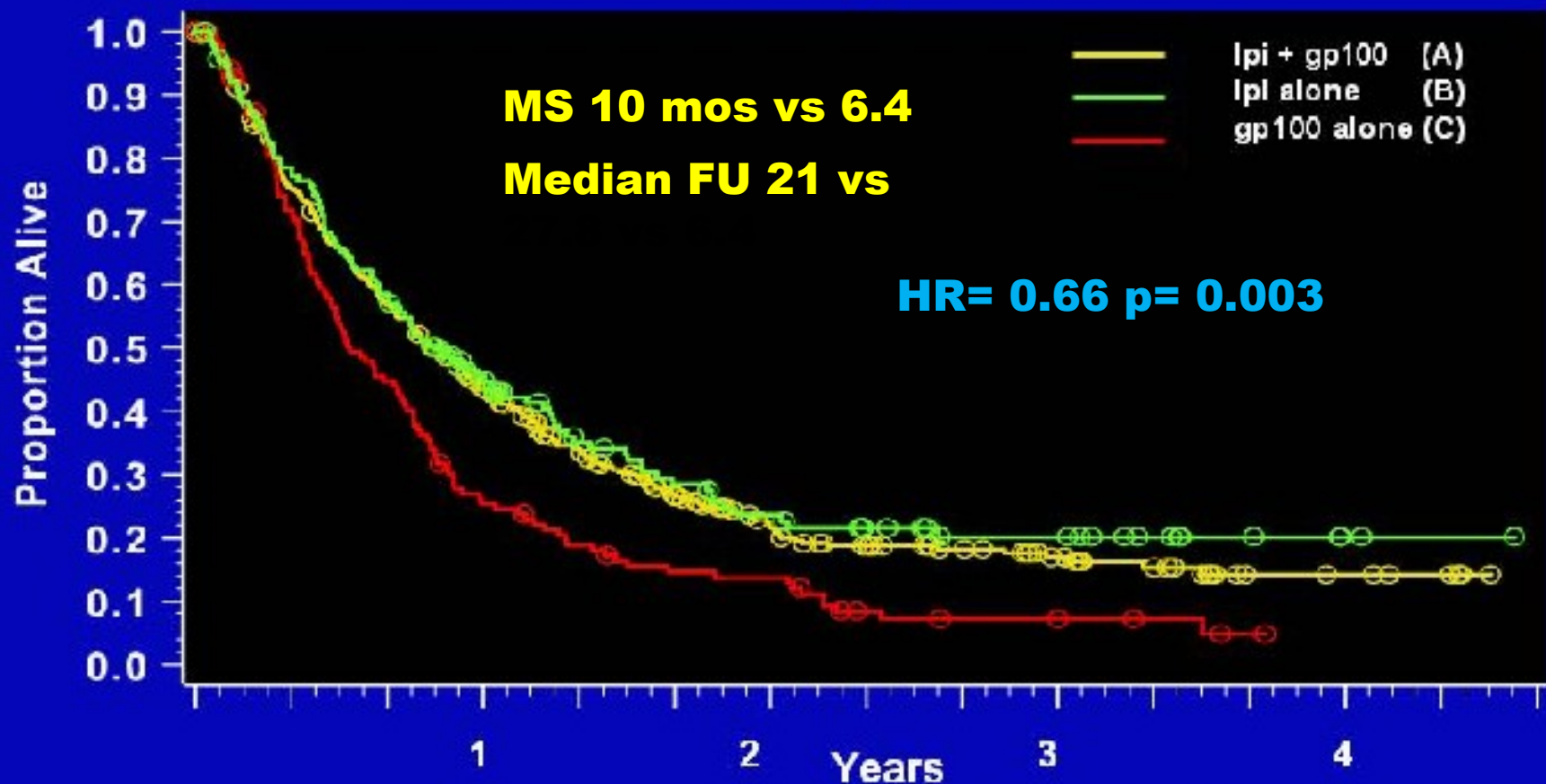
Long lasting
CR in a pt
with multiple
sc lesions
treated with
TMZ and LD-
IFN

V. Chiarion Sileni courtesy

MDX010-20: Study Design

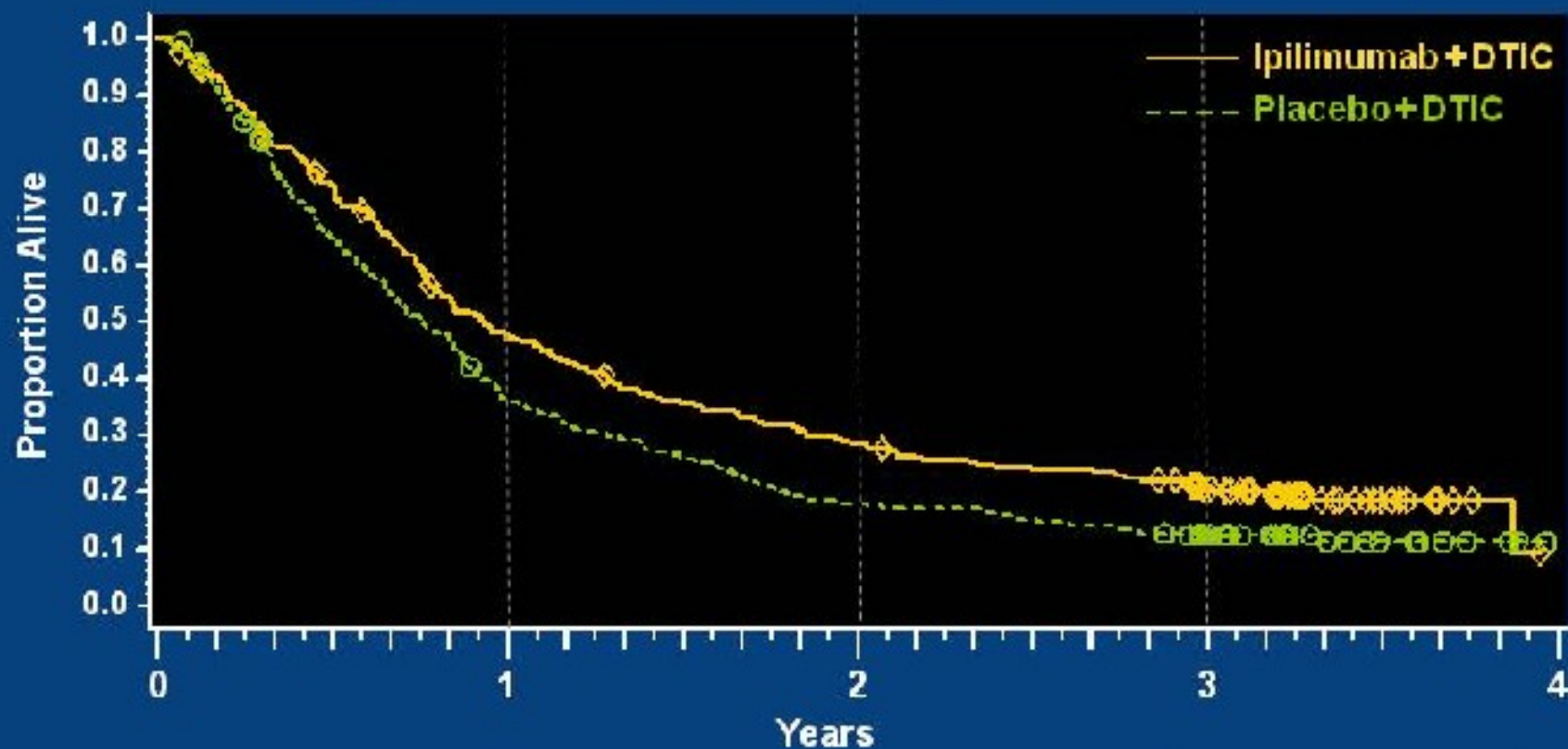


Kaplan-Meier Analysis of Survival



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

Study 024: Overall Survival



Estimated Survival Rate	1 Year	2 Year	3 Year*
Ipilimumab+DTIC n=250	47.3	28.5	20.8
Placebo+DTIC n=252	36.3	17.9	12.2

*3-year survival was a post-hoc analysis

Study 024: Tumor Response

	Ipilimumab + DTIC n=250	Placebo + DTIC n=252
Disease Control Rate, n (%)	83 (33.2)	76 (30.2)
BORR (CR + PR), n (%)	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 (18.0)	50 (19.8)
Progressive disease	111 (44.4)	131 (52.0)
Duration of response, months	19.3	8.1

BORR=Best Overall Response Rate

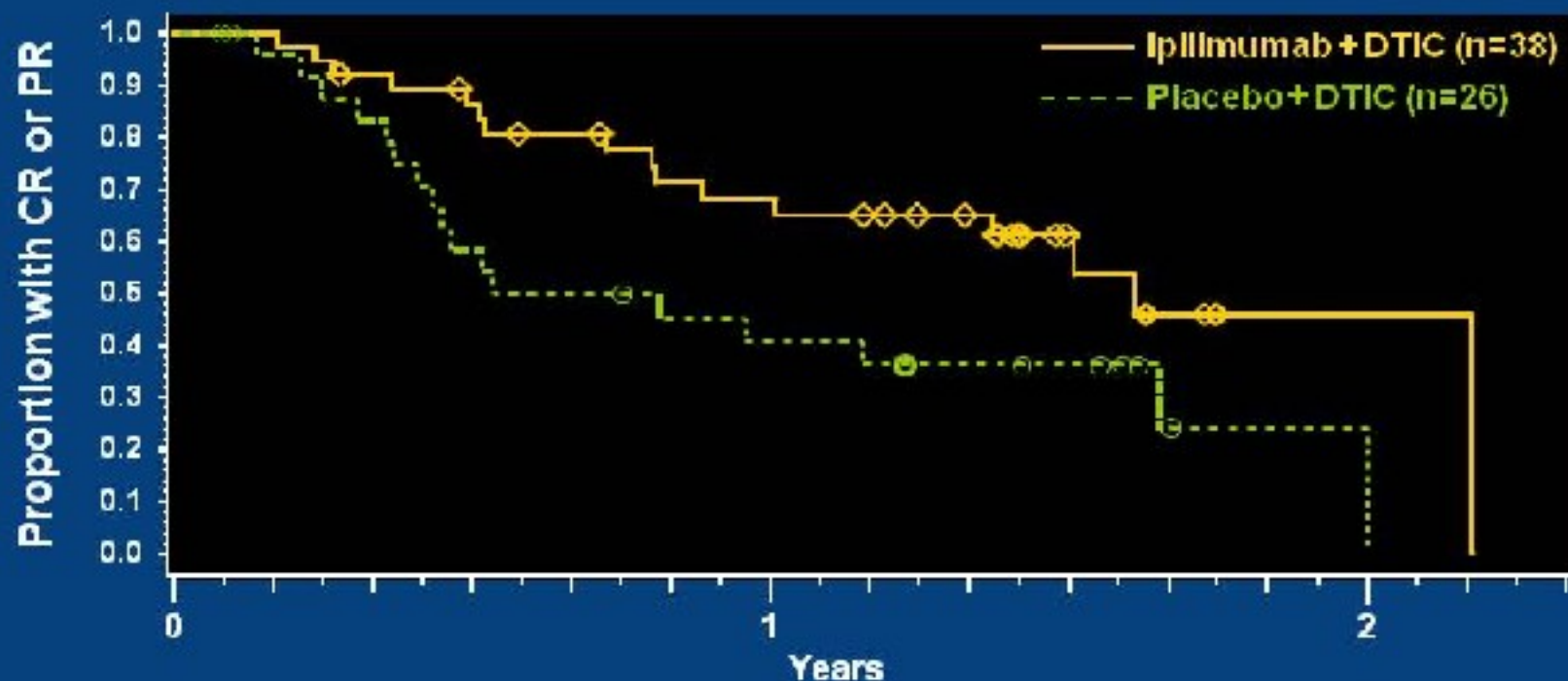
Patients (%) not evaluable for response (no follow-up scans): 56 (22.4) vs 45 (17.9)

PRESENTED AT:



Annual '11
Meeting

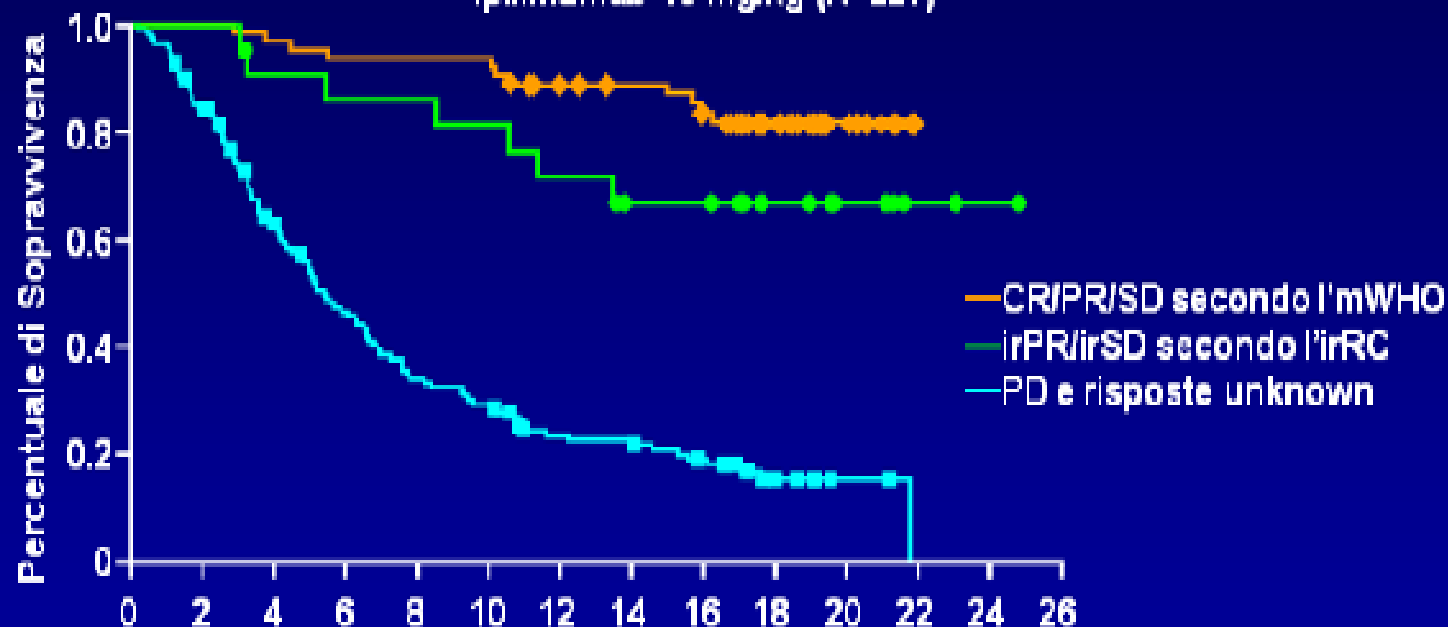
Study 024: Duration of Response



Data shown for patients with a confirmed complete response (CR) or partial response (PR)

Sopravvivenza di pazienti in PD (mWHO)

Dati raccolti dagli studi di fase II CA184-008 e CA184-022:
ipilimumab 10 mg/kg (N=227)



63 CR/PR/SD

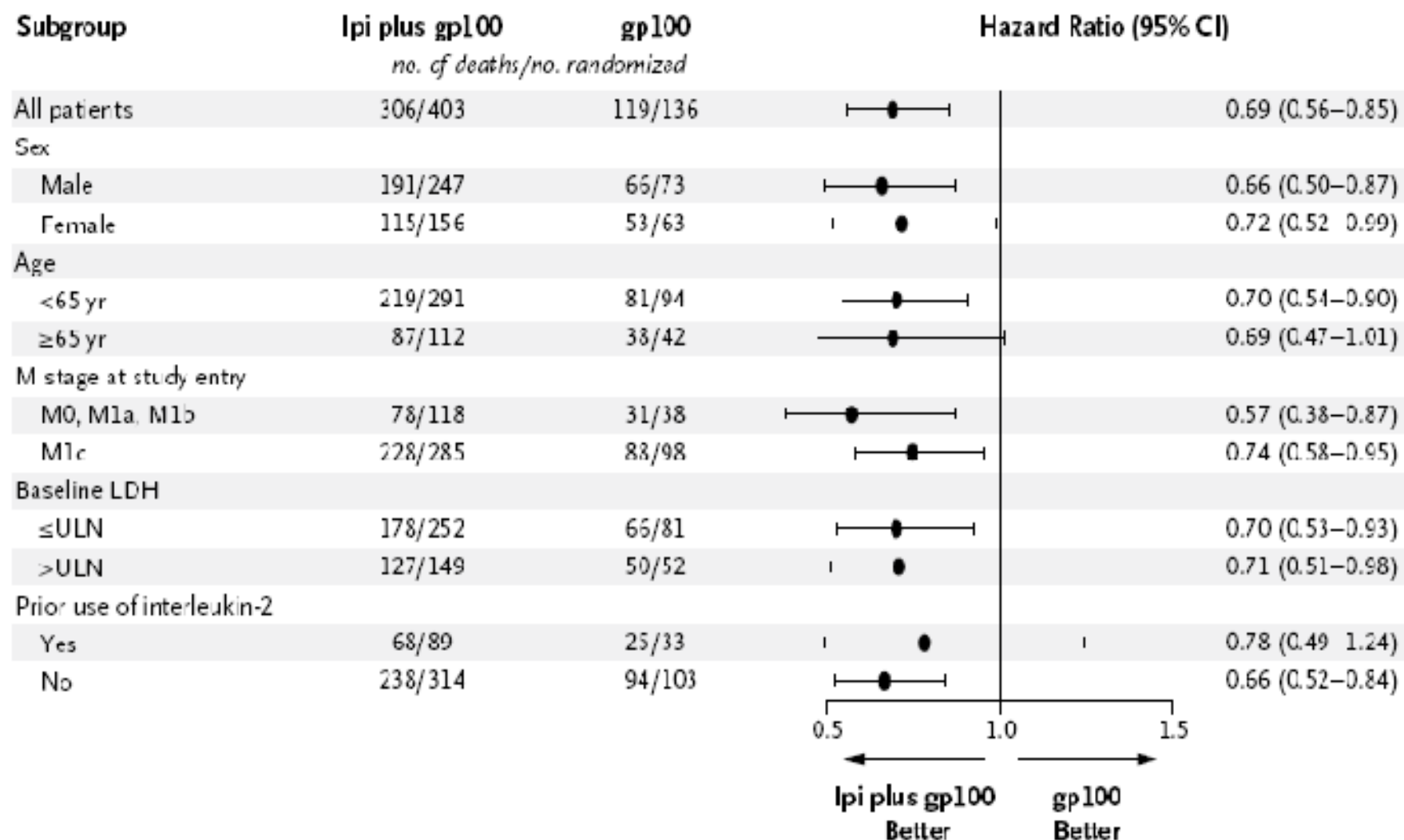
22 IrPR/IrSD

142 PD

9,7% dei pazienti trattati, inizialmente classificati come PD secondo i criteri WHO, sembrano evidenziare una risposta ad ipilimumab

Subgroup analyses of overall survival

A



Melanoma: Multiple Molecular Subsets

Defined by 'Driver' Mutations

PRESENTED AT: ASCO Annual 11 Meeting



Arising from Skin
Without Chronic
Sun Damage



50% BRAF
20% NRAS

0% KIT



Arising from Skin
With Chronic
Sun Damage



10% BRAF
10% NRAS

2% KIT



Arising from
Mucosal
Surfaces



5% BRAF
15% NRAS

20% KIT



Arising from
Acral
Surfaces



15% BRAF
15% NRAS

15% KIT



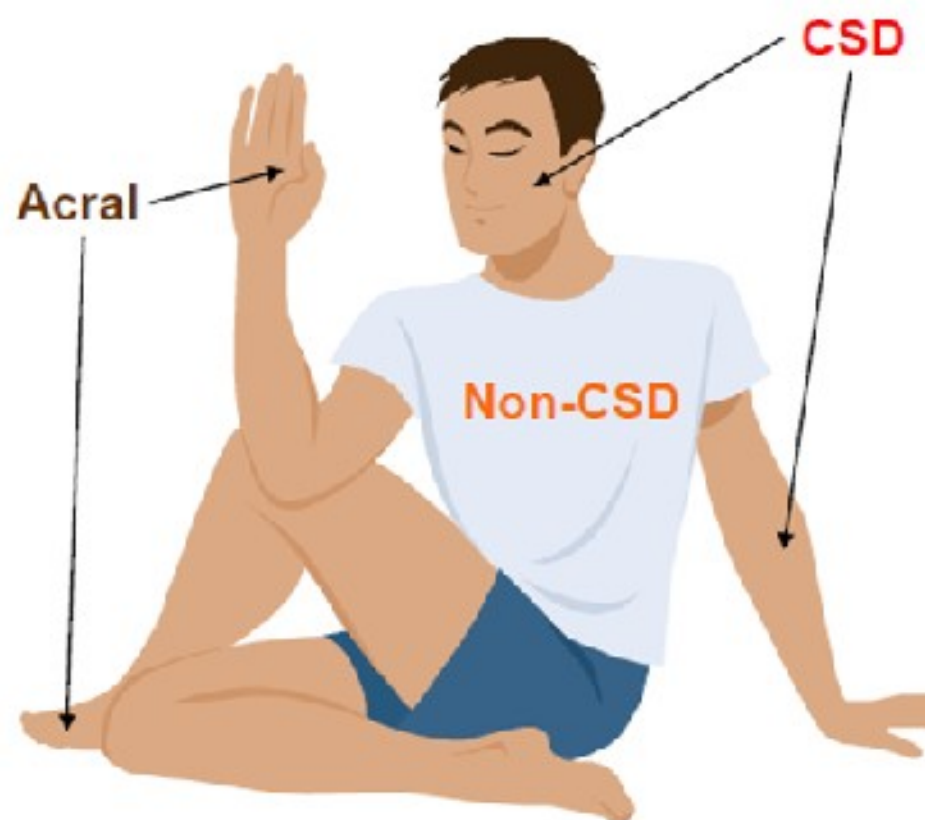
Uveal Melanoma



20-25% GNAQ
55% GNA11

Classification Based on Anatomic and Genomic Information

- The New Classification suggested has four types of melanoma:
- **Chronic sun damaged (CSD)**
- **Non-Chronic sun damaged (non-CSD)**
- **Acral**
- **Mucosal**
- ❖ BRAF and RAS mutations tend to occur in non-CSD populations
- ❖ c-Kit mutations and amplifications in the CSD, acral and mucosal populations



Mucosal: inside mouth, rectum, etc.

(Curtin J et al. J Clin Oncol 200

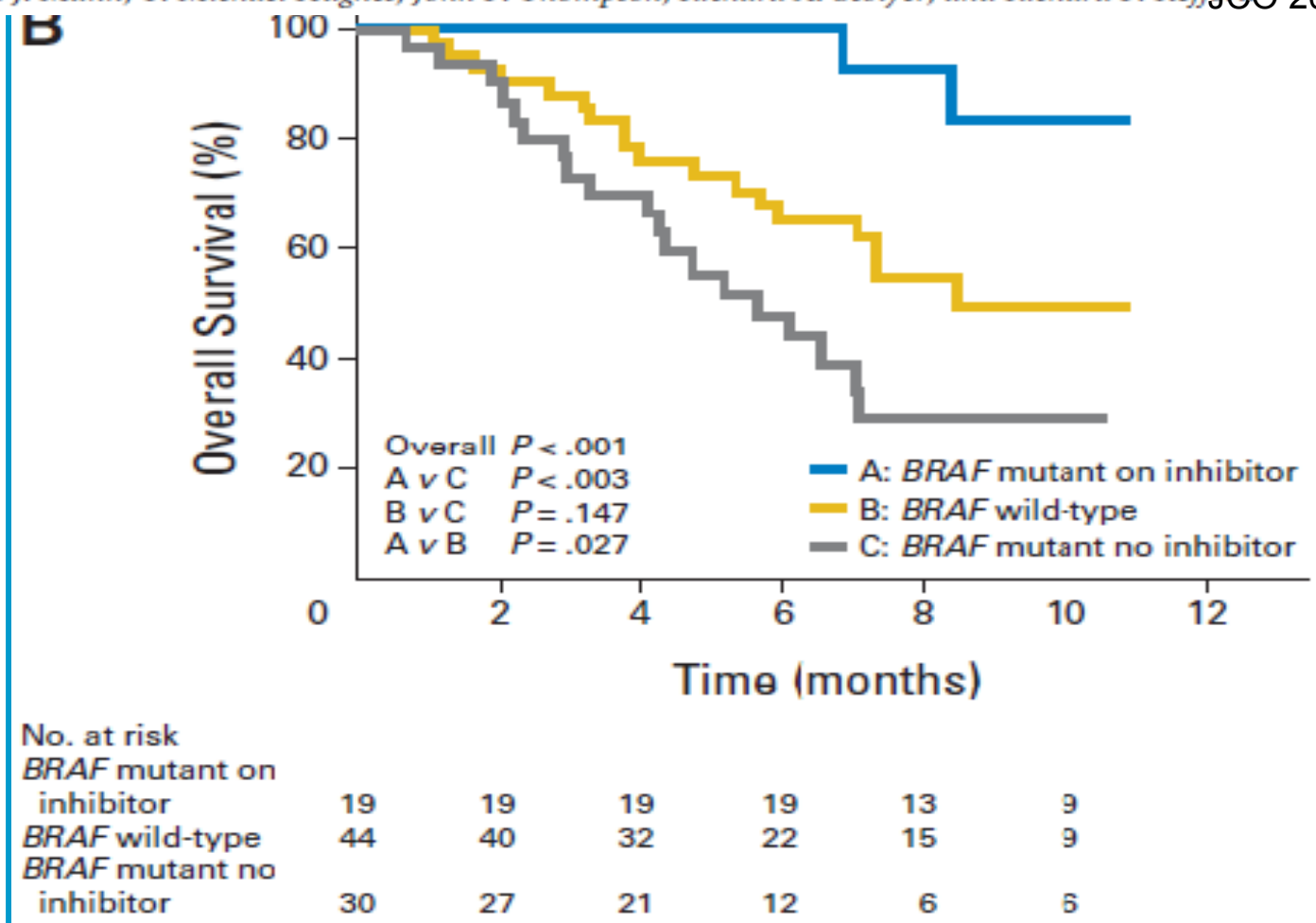
V600E B-Raf Rate Declines with Advancing Age

Age	N.	<i>BRAF</i> mut (N.)	<i>BRAF</i> mut (%)
20-30	14	12	86%
31-40	29	23	79%
41-50	42	21	50%
51-60	58	24	41%
61-70	103	49	46%
>70	65	14	22%

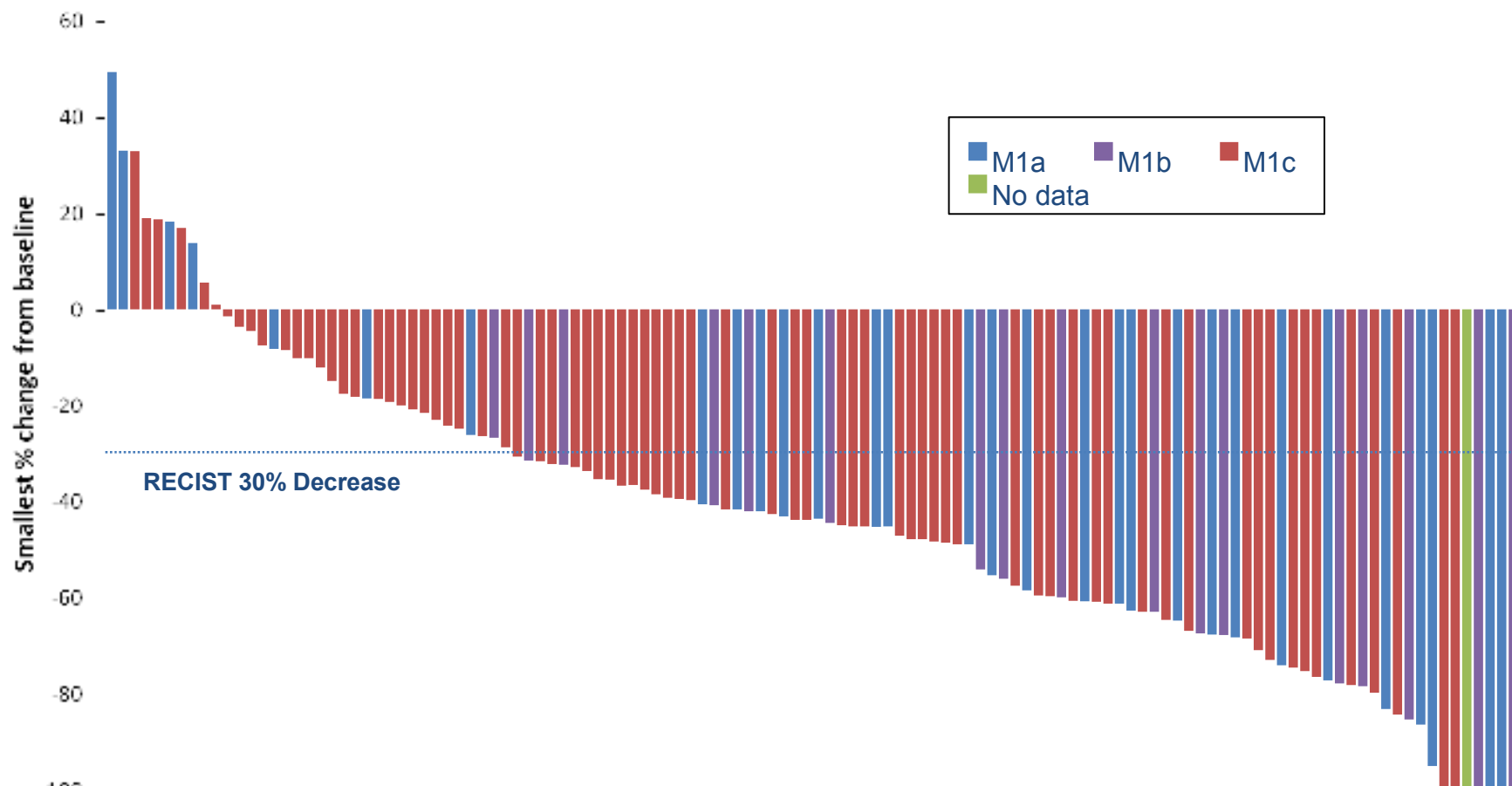
P=0.000

Prognostic and Clinicopathologic Associations of Oncogenic *BRAF* in Metastatic Melanoma

Georgina V. Long, Alexander M. Menzies, Adnan M. Nagrial, Lauren E. Haydu, Anne L. Hamilton, Graham J. Mann, T. Michael Hughes, John F. Thompson, Richard A. Scolyer, and Richard F. Kefford
JCO 2011



BRIM-2—Tumor Regression (Target Lesions) in Most Patients (IRC)12



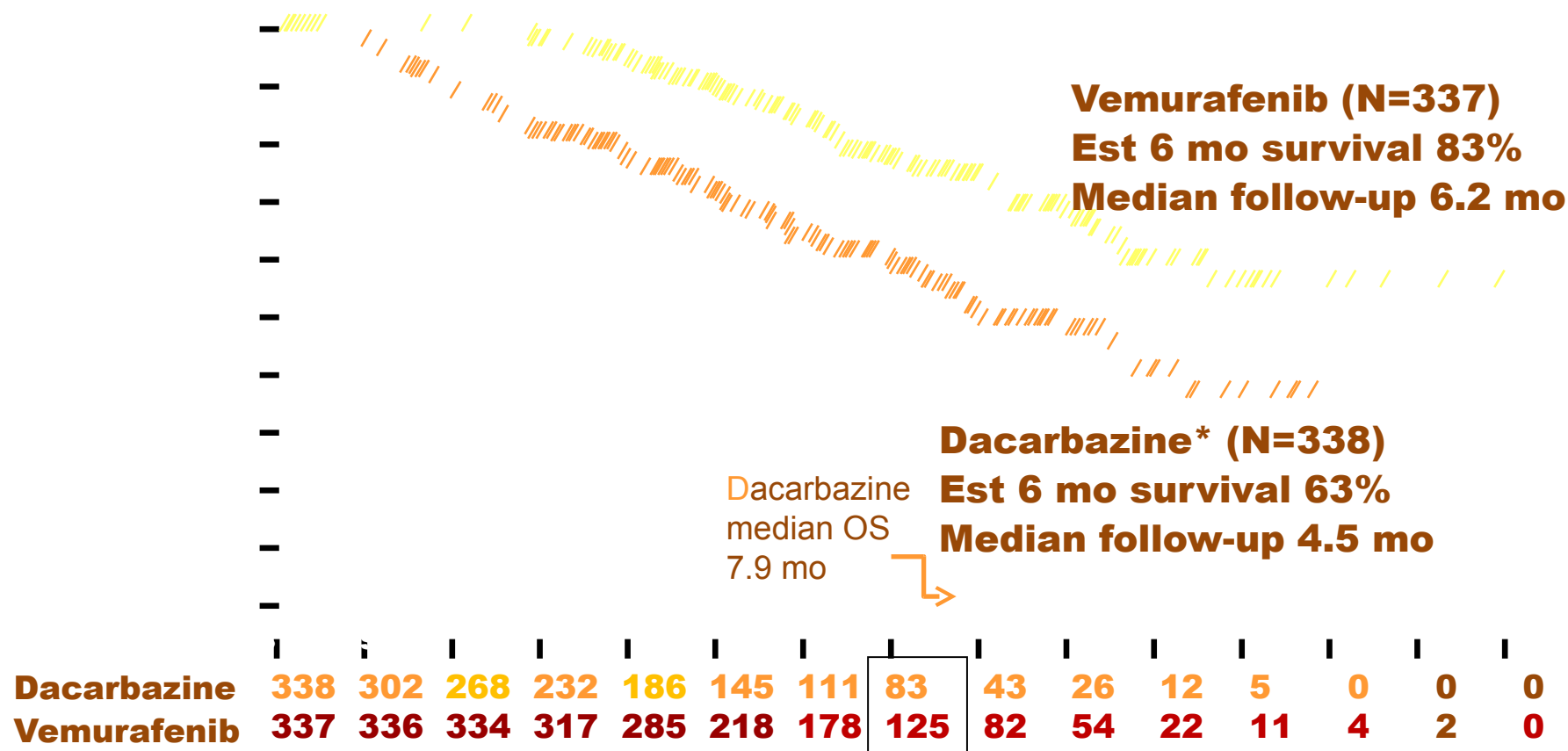
* Seven patients had 100% tumor shrinkage, three of which had confirmed CR; one patient had unconfirmed CR and three patients had

non-target lesions present—122 patients had baseline and ≥ 1 post-baseline scan with measurable disease.

CR = complete response; IRC = independent review committee; RECIST = Response Evaluation Criteria in Solid Tumors.

12. Sosman J, *et al.* Oral presentation at Melanoma 2010 Congress. Available from www.melanoma2010.com (last accessed March 1, 2011).

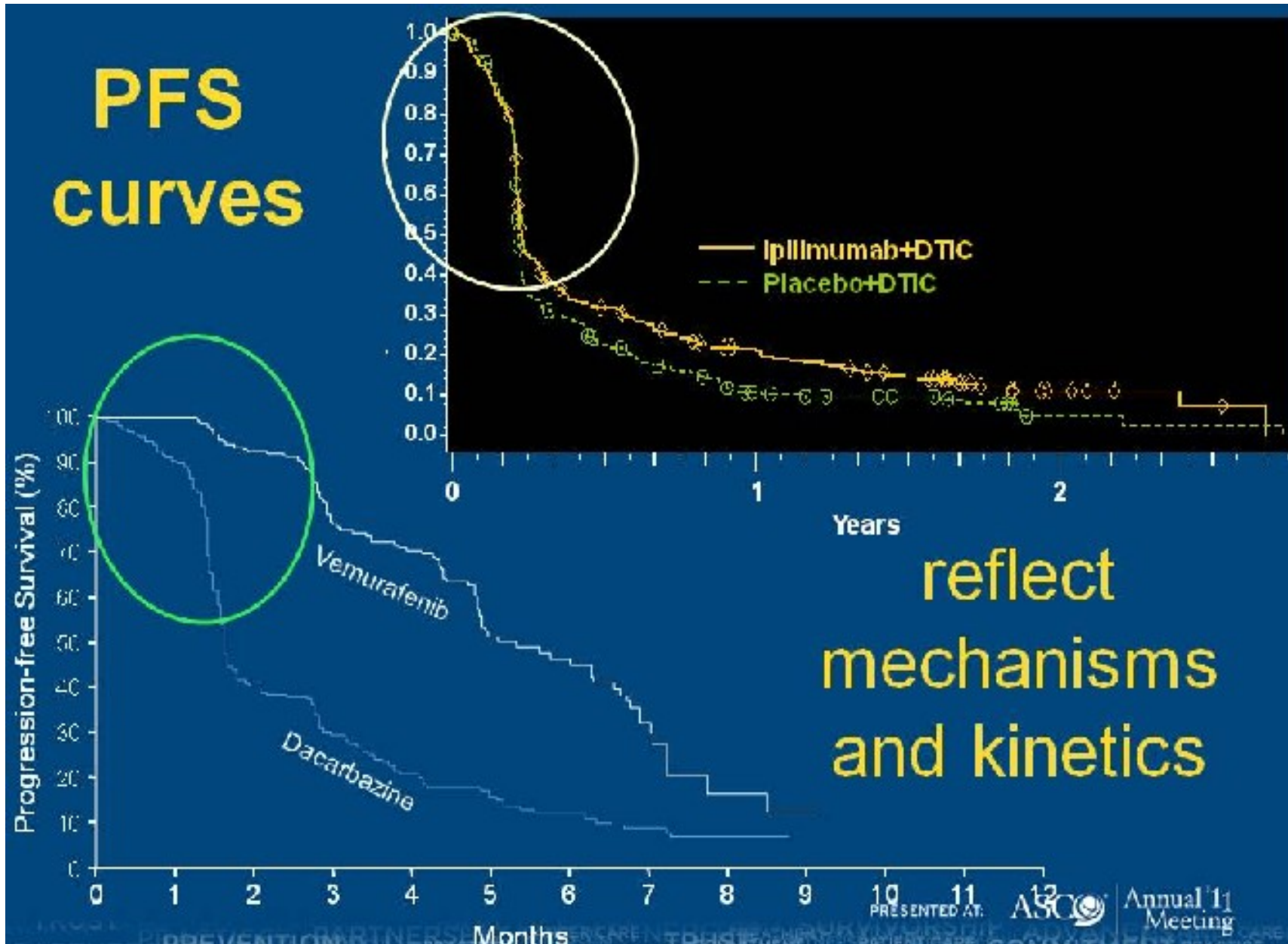
Overall survival (March 31, 2011 cutoff)



Post-progression use of ipilimumab: 17% dacarbazine patients vs 6% vemurafenib patients

*Dacarbazine patients who received vemurafenib after the IA (by DSMB recommendation; N=50) were censored at the date of crossover

PFS curves



reflect
mechanisms
and kinetics

PRESENTED AT:



Annual Meeting

Melanoma Brain Metastases

- **~ 190,000 patients will develop CNS metastases in 2010**
- **Melanoma is the 4th leading cause of CNS metastases**
- **Melanoma ranks 2nd in incidence proportion percentage**
- **If patients with metastatic melanoma live long enough most will develop brain metastases !**

Metastatic Melanoma Management

2010 onward

