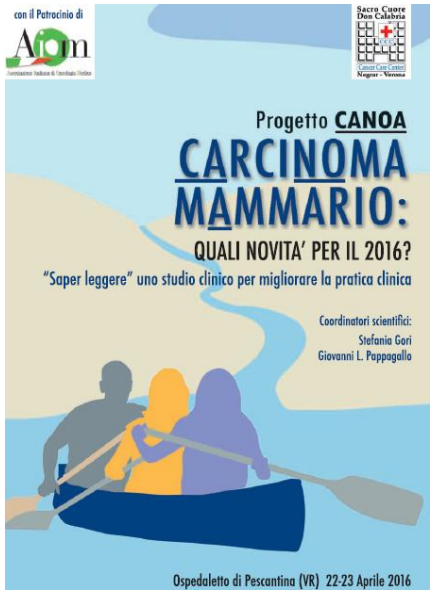


) **L'interpretazione delle curve di sopravvivenza negli studi clinici**
Le domande del clinico - Stefania Gori
Le risposte del metodologo - Giovanni L. Pappagallo

L'interpretazione delle curve di sopravvivenza negli studi clinici: le domande del clinico

Stefania Gori
U.O.C. Oncologia Medica
Cancer Care Center "Sacro Cuore-Don Calabria" Negrar- VERONA

Presidente eletto AIOM

Associazione Italiana
Oncologia Medica

Sacro Cuore
Don Calabria
CCC
Cancer Care Center
Negrar - Verona

Goals of Clinical Trials in Patients with Metastatic Breast Cancer

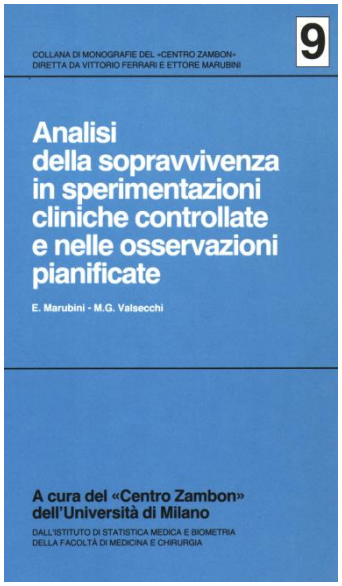
- Improve treatment options for women with advanced disease to:
  - Prolong survival
  - Maximize QOL by minimizing disease and treatment-related symptoms
- "Testing ground" for adjuvant setting

VARIABILE DI RISPOSTA

- di tipo **quantitativo**
  - assume uno spettro continuo di valori e viene misurata in riferimento a una scala a intervalli costanti.
- di tipo **qualitativo**
  - esprime categorie di risposta del tipo successo / insuccesso (di un trattamento somministrato).
- del tipo "**tempo a evento**"
  - rappresenta il tempo trascorso fino al verificarsi (o meno) di un evento.

VARIABILE “TEMPO A EVENTO”

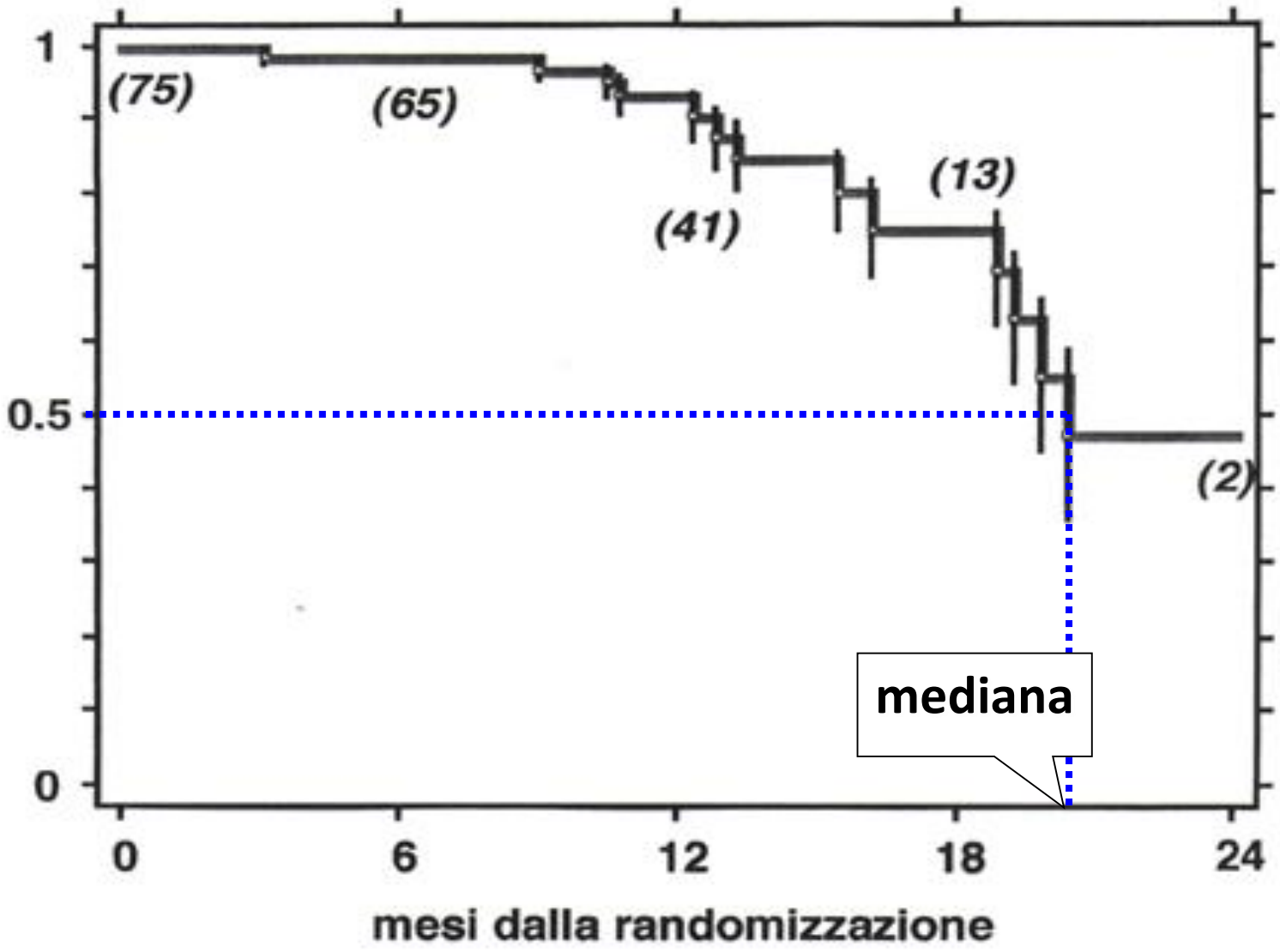
- **Apparentemente assimilabile a una variabile di tipo quantitativo (intervallare).**
- **Ma il verificarsi o meno di un evento la rende assimilabile a una variabile di tipo qualitativo (nominale)**
- **In alcuni soggetti inoltre l’evento di interesse potrebbe non essersi ancora verificato al momento della analisi**
- **Tali risultati vengono quindi meglio rappresentati come stima della funzione di sopravvivenza:**
  - **probabilità di sopravvivere oltre un determinato tempo, misurato dalla data di inizio dell'osservazione.**



Tempi di risposta $t_{(j)}$	Tempi troncati* t^*	N° soggetti esposti a rischio n_j	N° eventi terminali d_j	Rischio istantaneo di "morte" $\hat{\lambda}(t_{(j)})$	Probabilità cumulativa di sopravvivere $t_{(j)}$ $\hat{P}_j$
9		20	1	1/20 = .050	(1 – 1/20) × 1 = .9500
13		19	1	1/19 = .053	(1 – 1/19) × .9500 = .8996
20		18	1	1/18 = .055	(1 – 1/18) × .8996 = .8501
26		17	1	1/17 = .059	(1 – 1/17) × .8501 = .7999
27		16	1	1/16 = .062	(1 – 1/16) × .7999 = .7503
28		15	1	1/15 = .067	(1 – 1/15) × .7503 = .7000
30		14	1	1/14 = .071	(1 – 1/14) × .7000 = .6503
32		13	2	2/13 = .154	(1 – 2/13) × .6503 = .5502
75		11	1	1/11 = .091	(1 – 1/11) × .5502 = .5001
79		10	1	1/10 = .100	(1 – 1/10) × .5001 = .4501
91		9	1	1/9 = .111	(1 – 1/9) × .4501 = .4001
	177*	8	0	0/8 = .0	(1 – 0/8) × .4001 = .4001
193		7	1	1/7 = .143	(1 – 1/7) × .4001 = .3429
541		6	1	1/6 = .167	(1 – 1/6) × .3429 = .2856
1129		5	1	1/5 = .200	(1 – 1/5) × .2856 = .2285
	1499*	4	0	0/4 = .0	(1 – 0/4) × .2285 = .2285
1585		3	1	1/3 = .333	(1 – 1/3) × .2285 = .1524

TABELLA 10.
Calcolo secondo Kaplan e Meier della curva di sopravvivenza del rene trapiantato nei pazienti di tabella 6.

CURVA DI SOPRAVVIVENZA



Indicatori riassuntivi di effetto di variabili tempo-a-evento

- **Differenza tra stime della mediana di sopravvivenza (KM)**
- **Differenza media di sopravvivenza (*restricted means*)**
- **Differenza tra stime di sopravvivenza (KM) al tempo x**
- **Hazard Ratio (KM+Cox)**

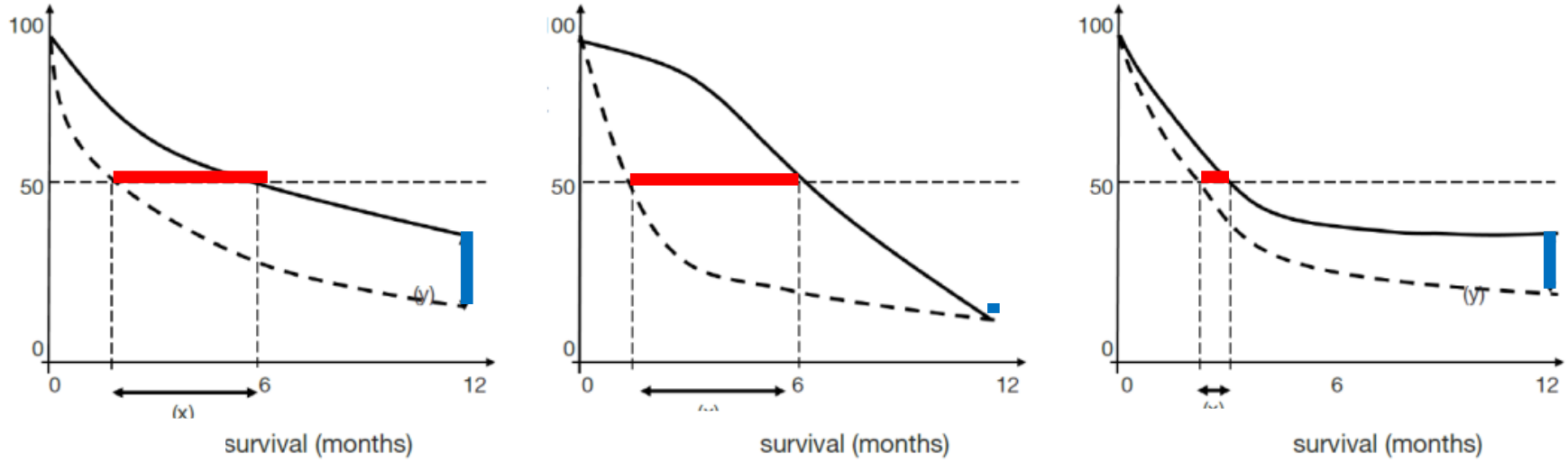
DOMANDA n.1

Le curve di OS negli studi clinici: cosa devo prendere in considerazione?

Le curve di OS nei trials clinici

Typical survival curves (Kaplan-Meier model) observed in clinical trials

(x) difference in median survival;
(y) 12-month difference in survival rate.



Pilotto S et al, TLCR 2015

Le curve di OS nei trials clinici

Typical survival curves (Kaplan-Meier model) observed in clinical trials

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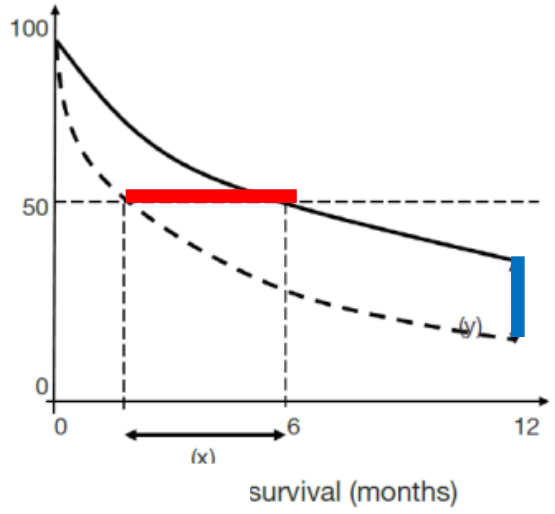

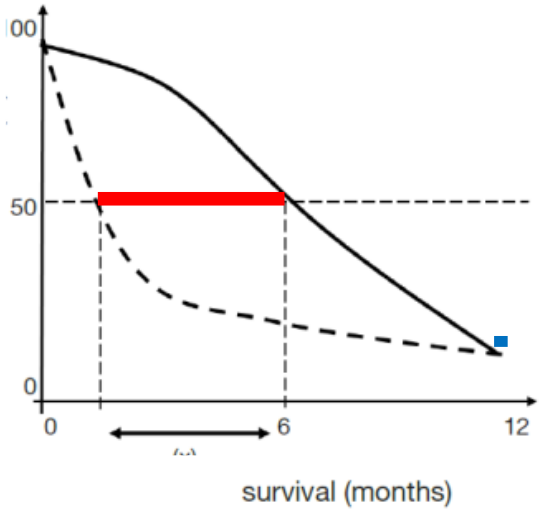

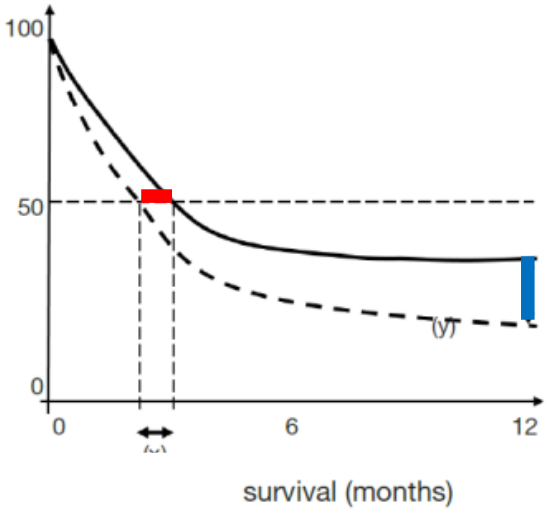

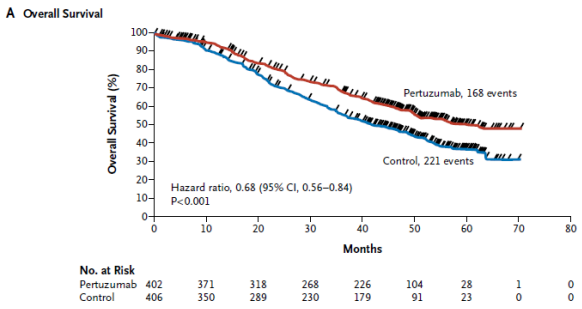

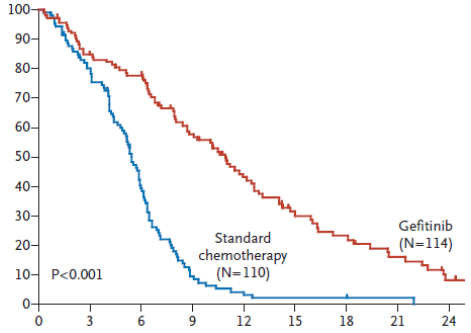

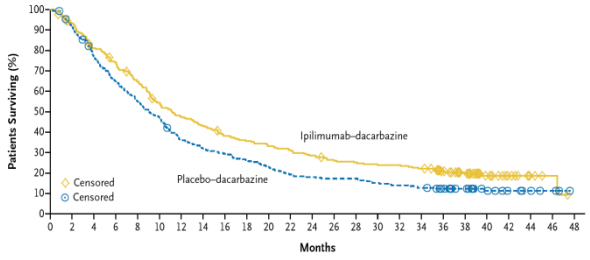

Le curve di OS nei trials clinici

Typical survival curves (Kaplan-Meier model) observed in clinical trials

(x) difference in median survival;
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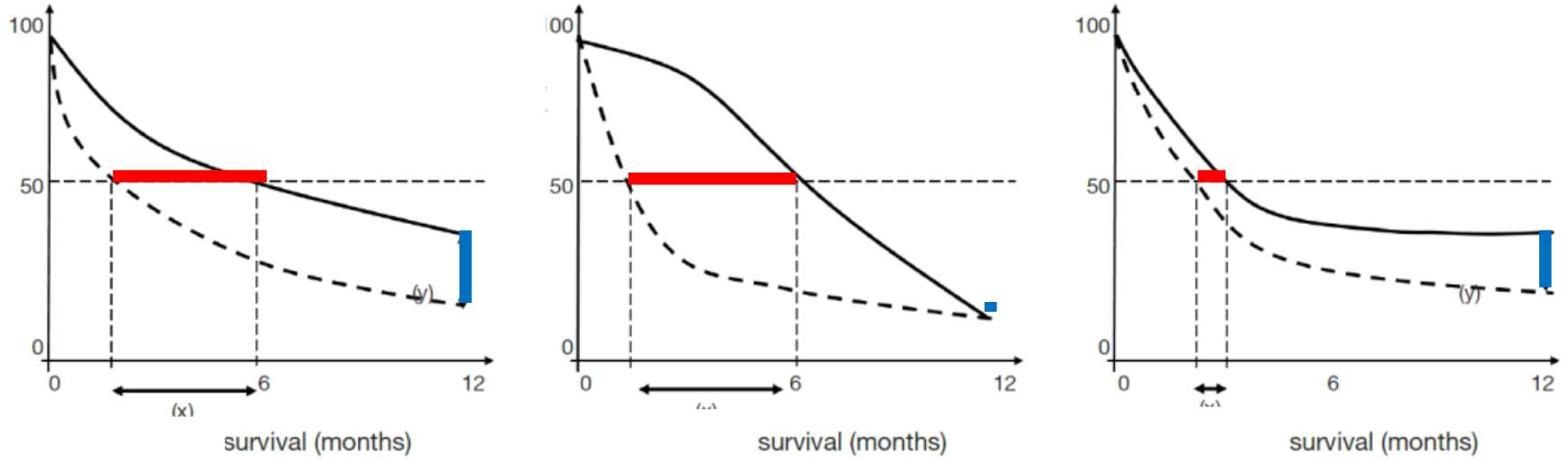
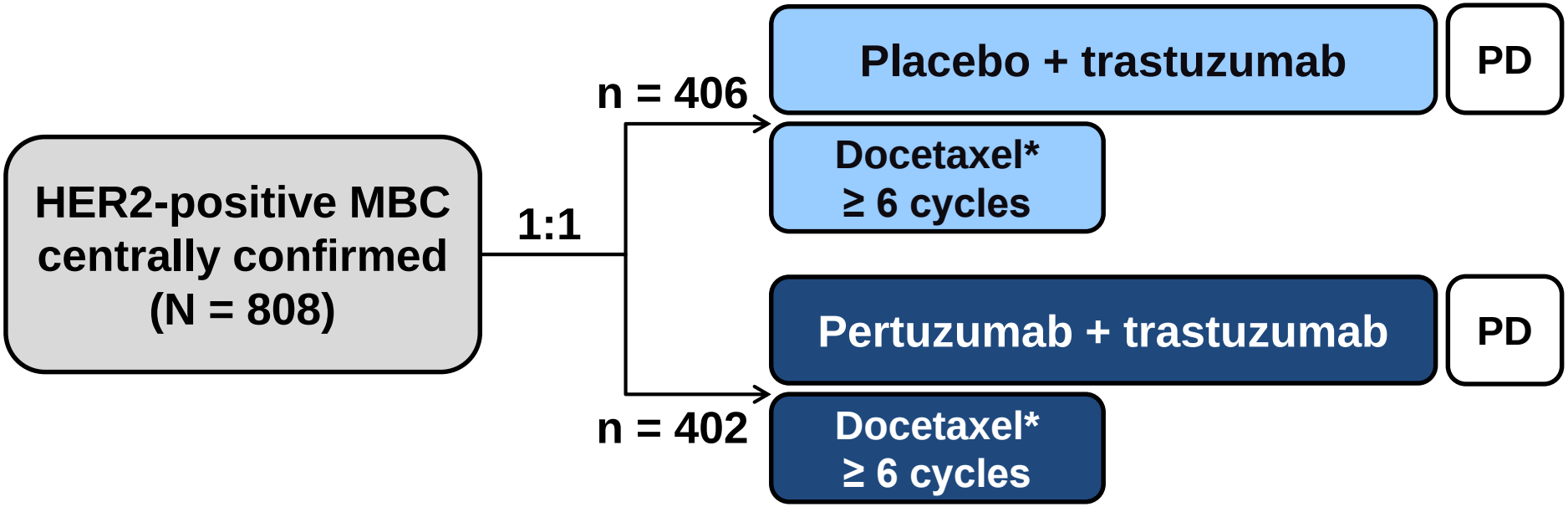


Mediana o differenza a 12 mesi?

CLEOPATRA Study Design



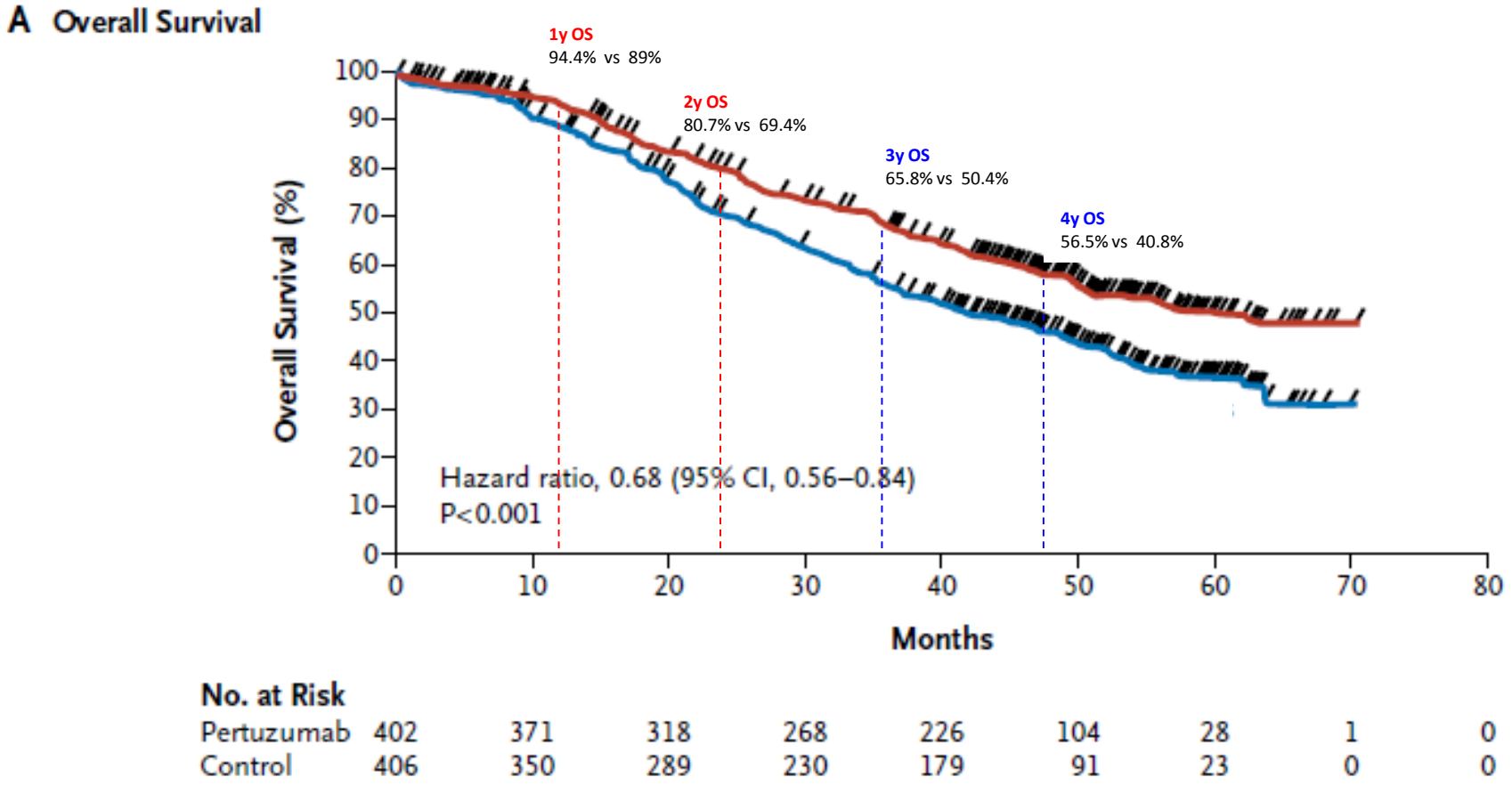
- **Randomization stratified by geographic region and neo/adjuvant chemotherapy**
- **Study dosing q3w:**
  - **Pertuzumab/placebo: 840 mg loading → 420 mg maintenance**
  - **Trastuzumab: 8 mg/kg loading → 6 mg/kg maintenance**
  - **Docetaxel: 75 mg/m^2 → 100 mg/m^2 escalation if tolerated**

* < 6 cycles allowed for unacceptable toxicity or PD; > 6 cycles allowed at investigator discretion.
HER2, human epidermal growth factor receptor 2;
MBC, metastatic breast cancer;
PD, progressive disease.

Baselga J, *et al*. *N Engl J Med* 2012; **366:**109–119.

Final OS Analysis

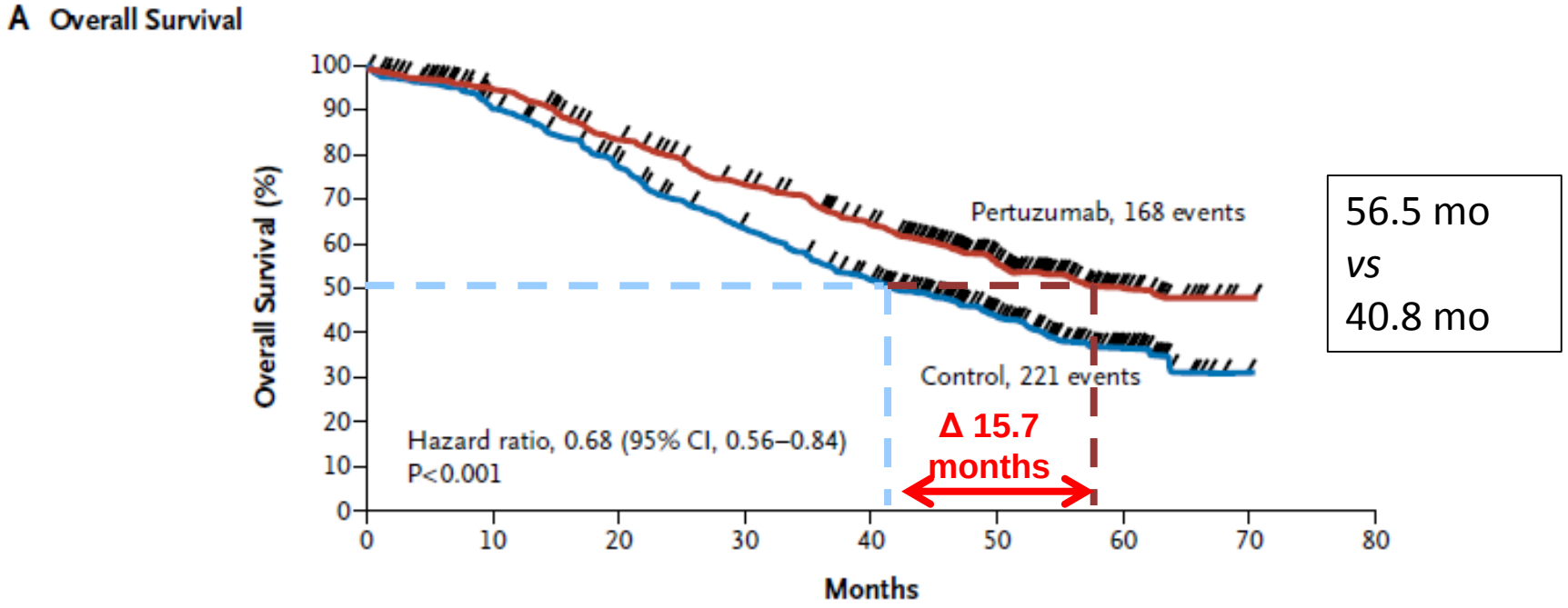
Median follow-up 50 months (range 0–70 months)



Swain, NEJM 2015

Final OS Analysis

Median follow-up 50 months (range 0–70 months)



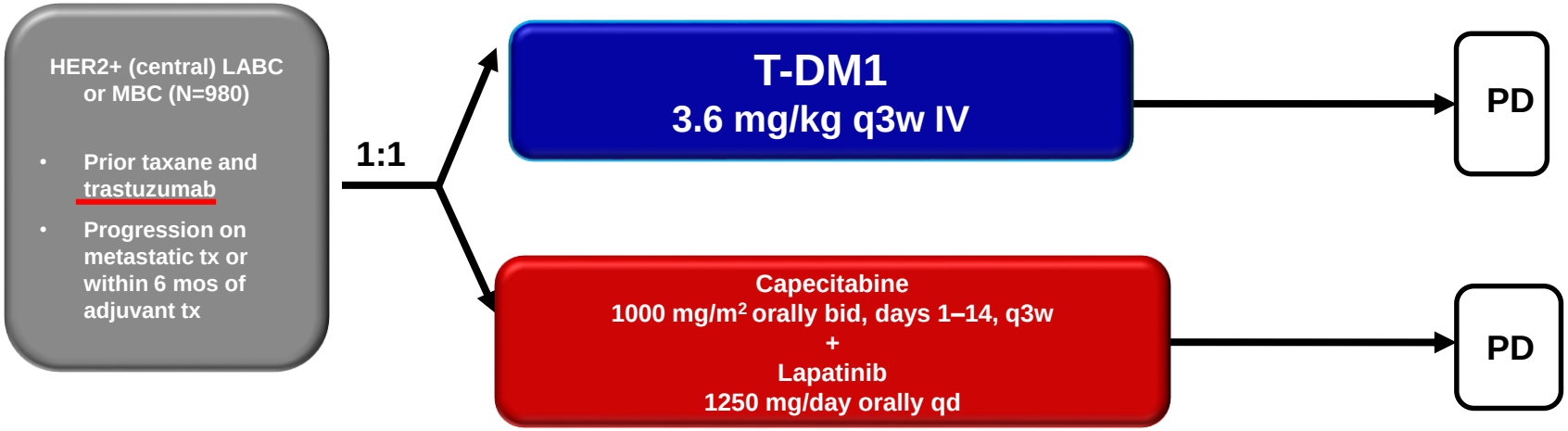
56.5 mo
vs
40.8 mo

- **Valuto la mediana?**
- **Valuto la % di pts vive ad 1 anno, 2 anni, 3 anni, 4 anni?**
- **Valuto l'HR?**

- ITT population. Stratified by geographic region and neo/adjuvant chemotherapy

EMILIA: T-DM1 after disease progression

- **EMILIA Study Design**

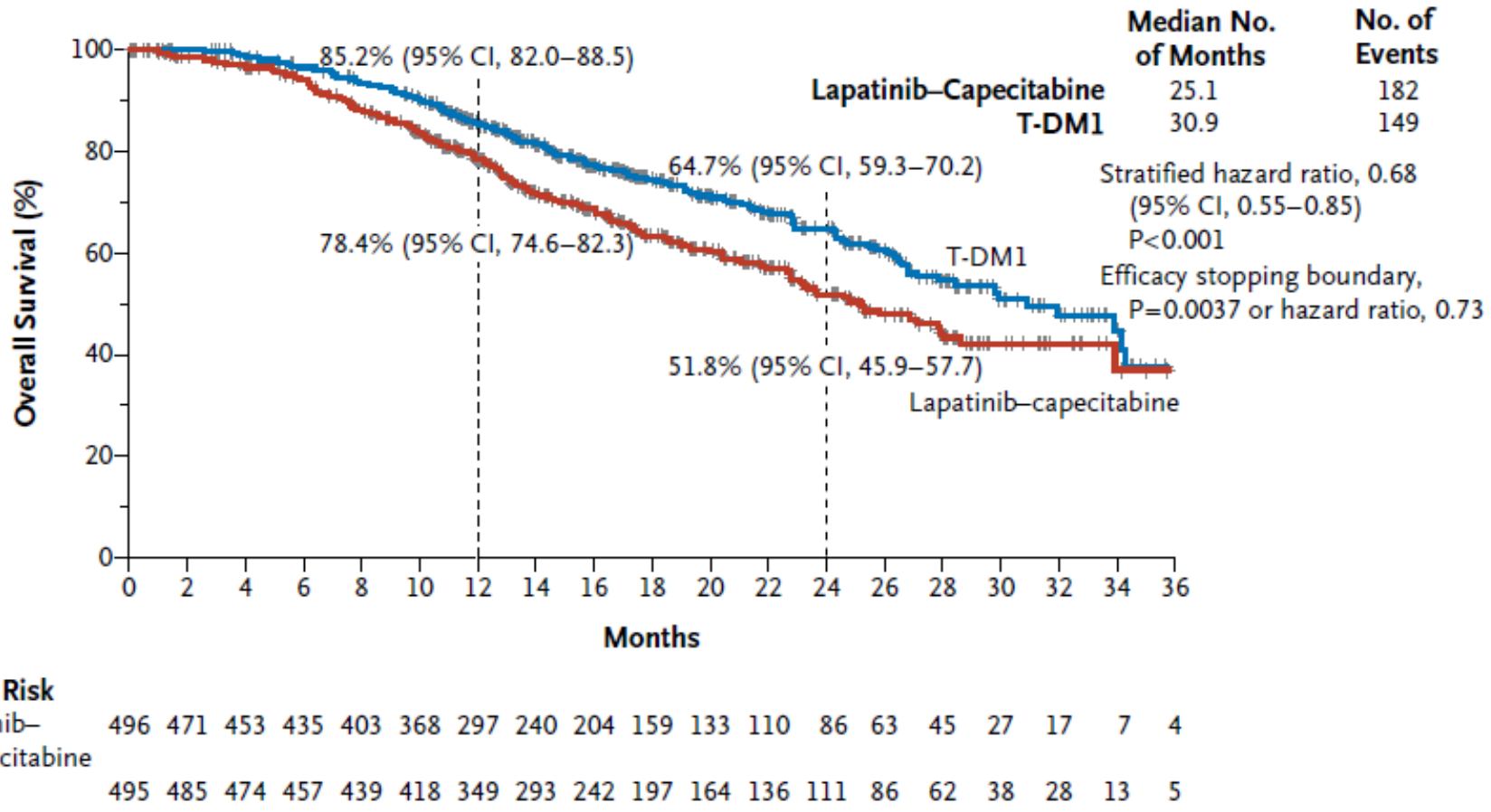


- **Primary endpoints:** PFS by independent review, OS, and safety

Outcome	T-DM1	Lap +Cap	HR (95%CI); p value
Median PFS	9.6 mo	6.4 mo	0.65 (0.55-0.77); p <.001
Median OS	30.9 mo	25.1 mo	0.68 (0.55-0.85); p <.001

- **Rate of grade 3-4 AEs** lower with T-DM1 vs Lapatinib+Capecitabine (41% vs 57%)

Verma S, NEJM 2012; 367:1783-91

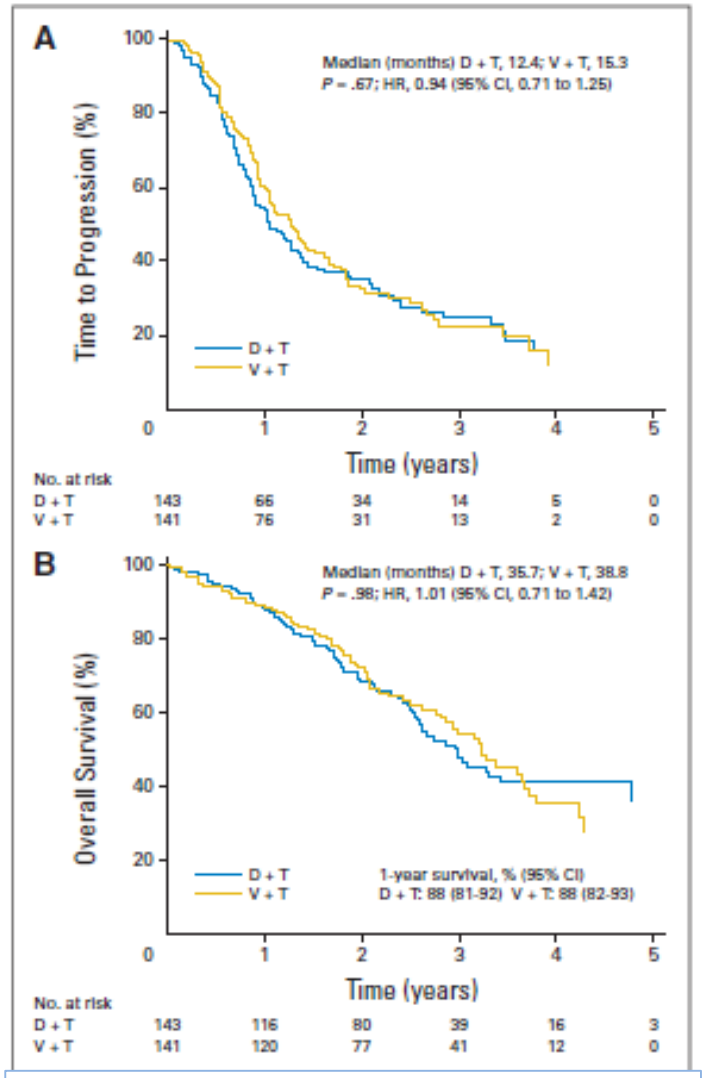


HR, mediana o differenza a 12/24 mesi?

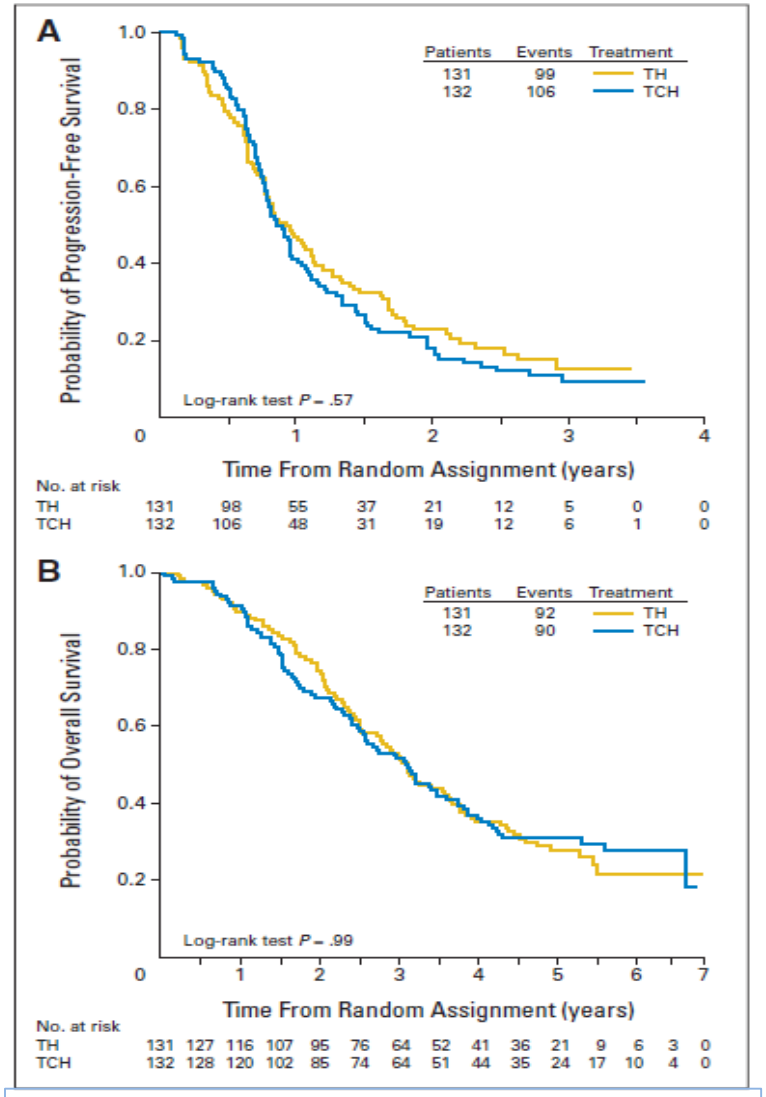
… e le curve che si incrociano alla fine?

Verma S, NEJM 2012; 367:1783-91

Le curve di sopravvivenza che si toccano e alla fine..si incrociano…(??)

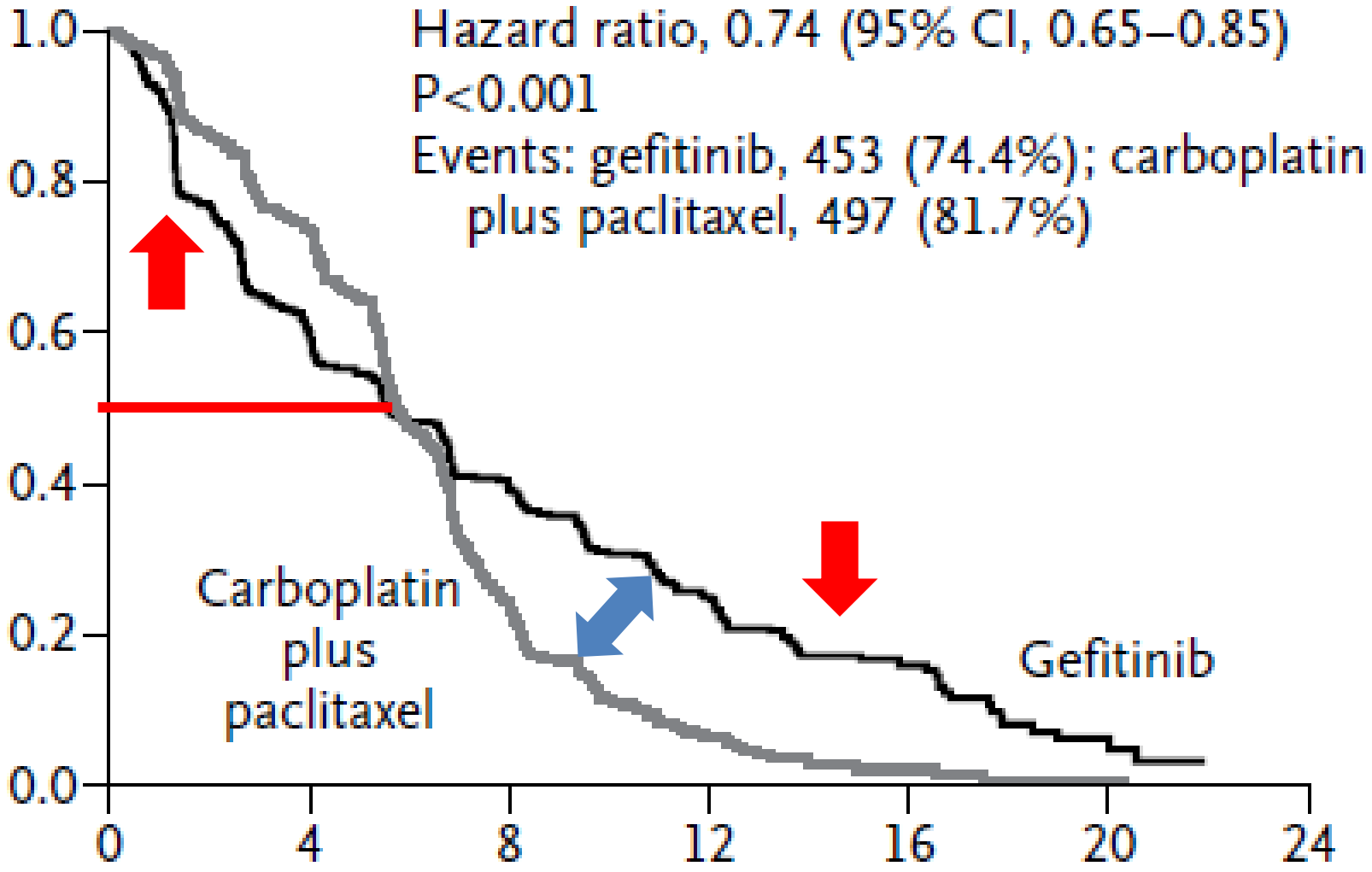


Andersson M:HERNATA study, JCO 2011



Valero V: BCIRG 007 study, JCO 2011

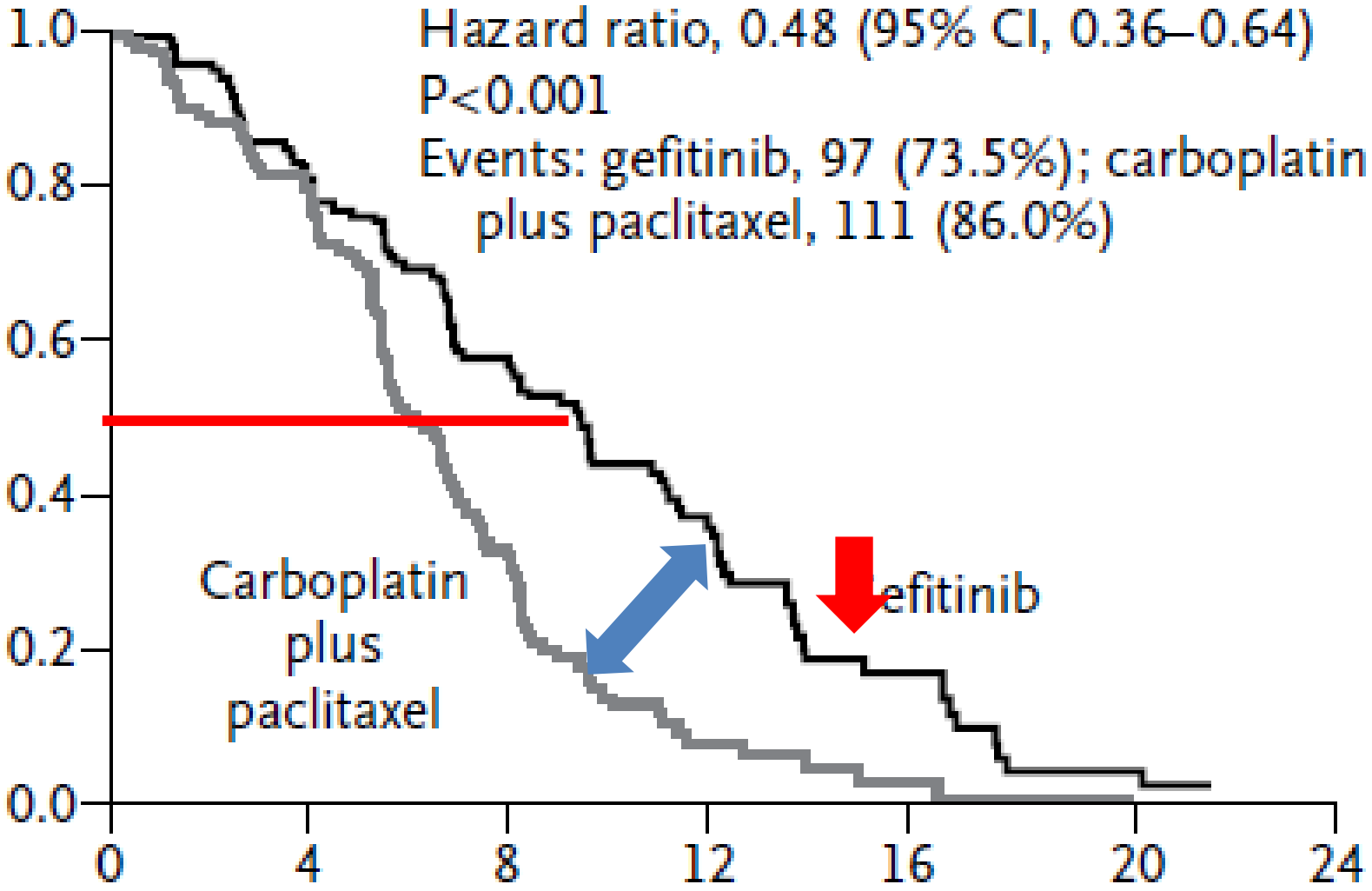
Curves' Crossing



Overall population

Source: Mok et al, NEJM 2009

Curves' Crossing… *anymore*



EGFR-Mutant

Source: Mok et al, NEJM 2009

Median, HR, Mean

- **Median OS is a snapshot comparison of a single timepoint**
  - ✓ **no more statistically or clinically meaningful than any other single time-point**
  - ✓ **value is familiarity and consistency, not clinical utility**
  - ✓ **does not capture long-term survival**

- **The HR compares the slope of the survival curve in two treatment groups**
  - ✓ **Unlike median OS, the HR is not computed at any one timepoint but includes all the data in the survival curve**

- **Mean OS is estimated as the area under the survival curve and is also based upon the entire range of data**

Median, HR, Mean

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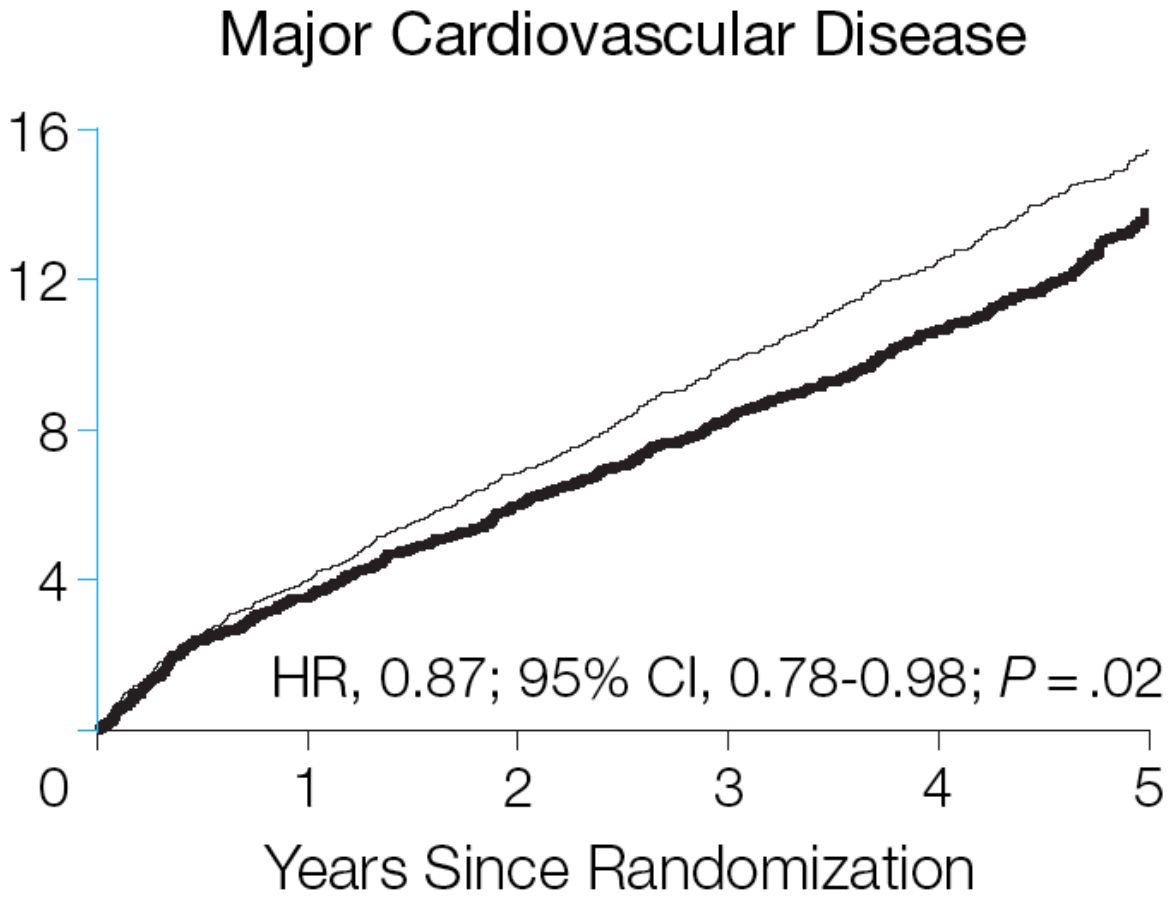
- Mean OS is estimated as the area under the survival curve and is also based upon the entire range of data

Indicatori riassuntivi di variabili tempo-a-evento

- Differenza tra stime della mediana di
- *ricted*
- M) al tempo
- **Hazard Ratio** (KM+Cox)

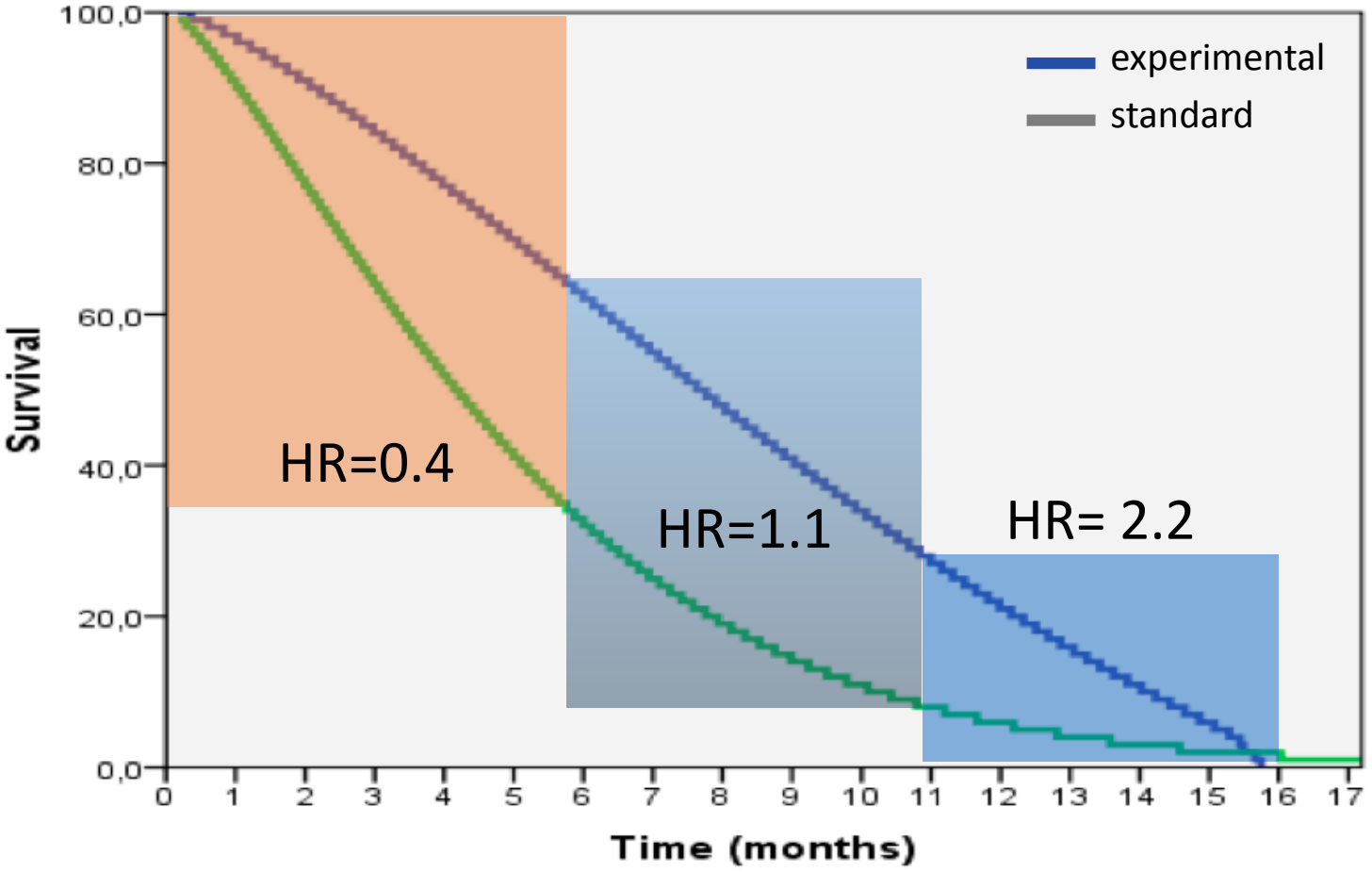
Appropriato quando il rapporto tra gli *hazard* dei due gruppi si mantiene (relativamente) costante

Rapporto tra gli *hazard* dei due gruppi costante nel tempo



Hazard Ratio è la misura di effetto più appropriata

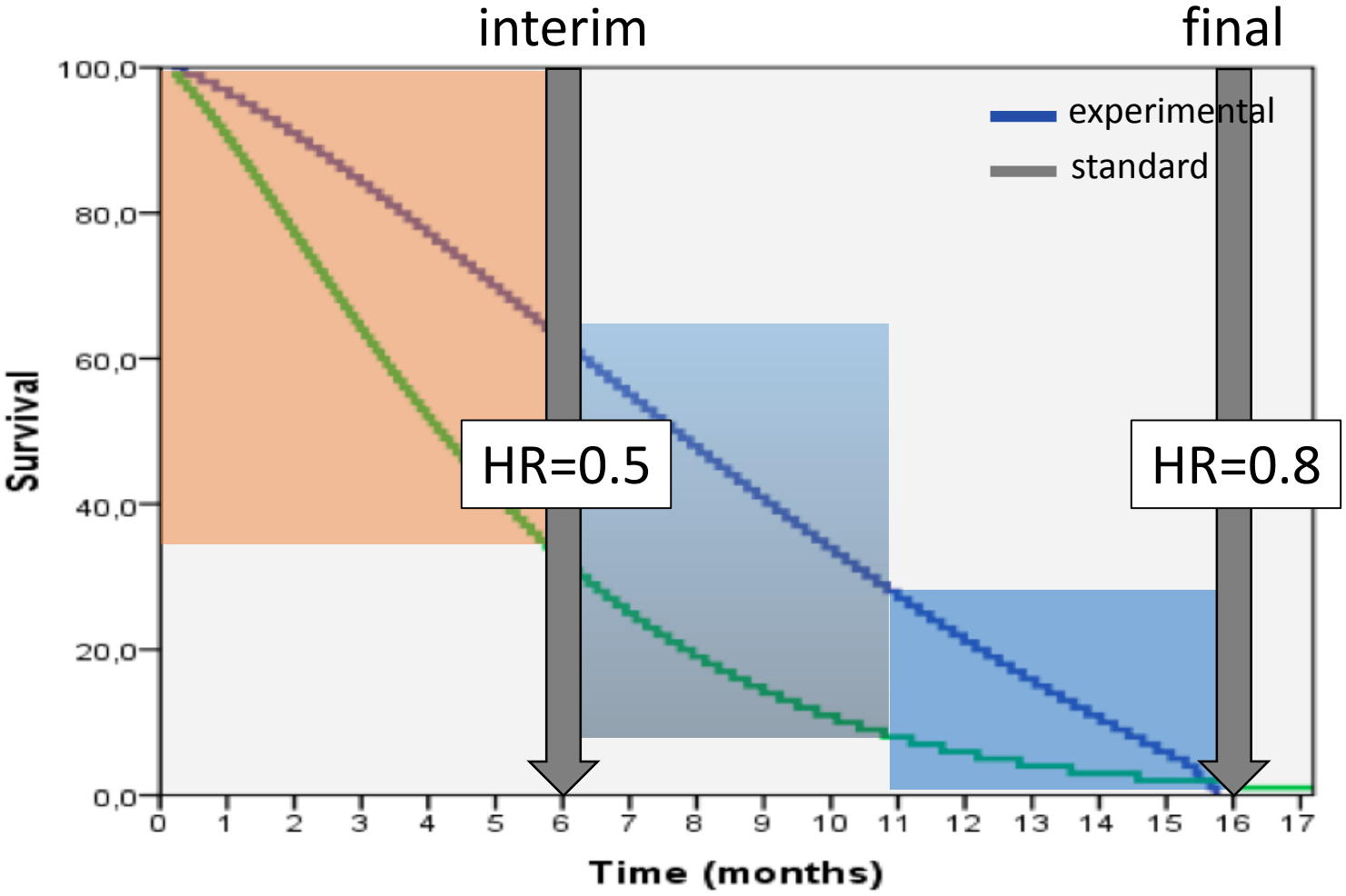
Rapporto tra gli *hazard* dei due gruppi non costante nel tempo – non (pochi) lungo-sopravviventi



Hazard Ratio "globale" =

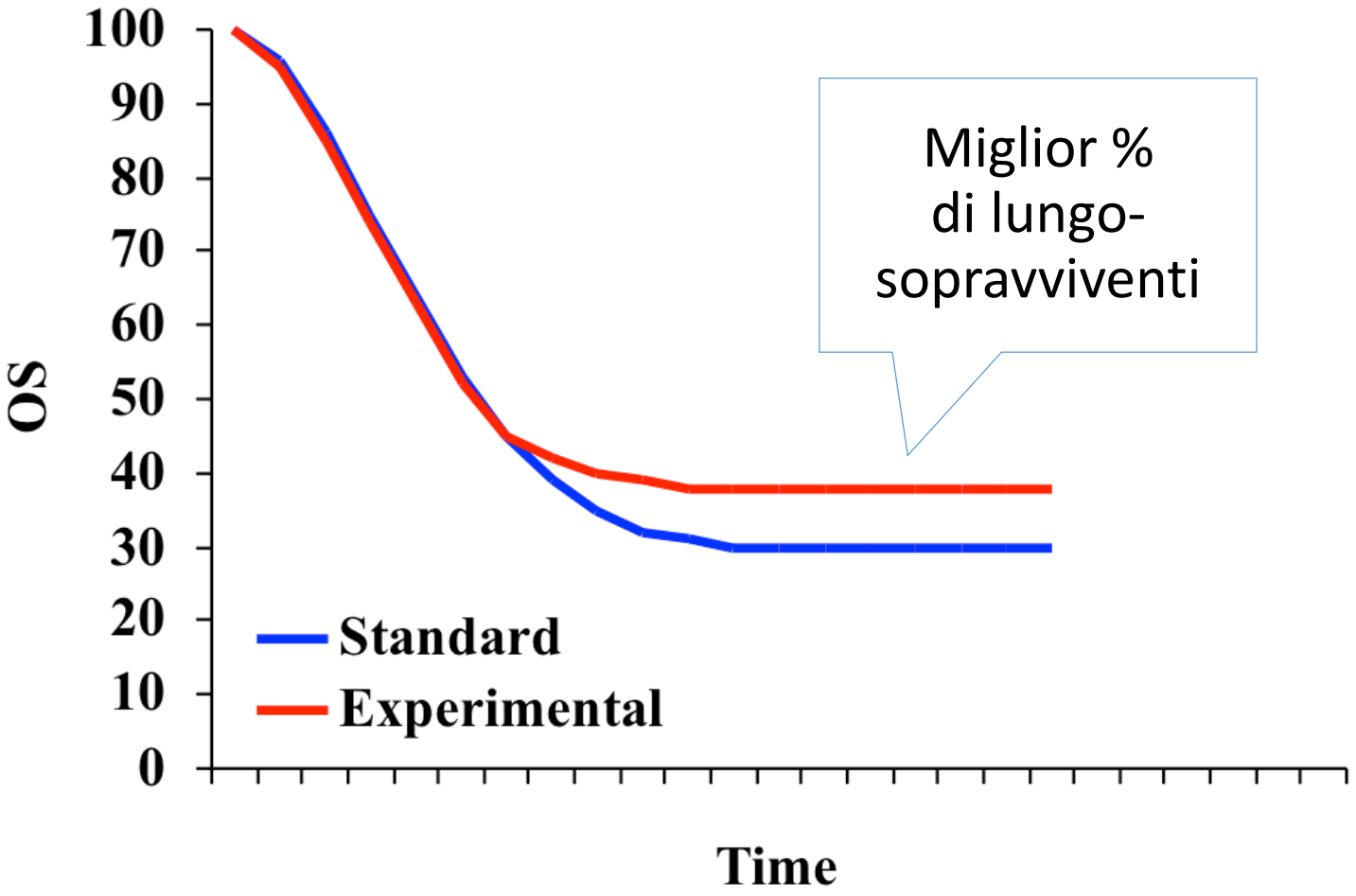
media *pesata* degli HR 'tempo-specifici' (*pesi* = eventi)

Rapporto tra gli *hazard* dei due gruppi non costante nel tempo – non (pochi) lungo-sopravviventi



Se analisi precoce, i pazienti sono troncati (*censored*) nel periodo di inversione del HR, che così va a pesare di meno: HR sovrastimato

Rapporto tra gli *hazard* dei due gruppi non costante nel tempo – presenza di lungo-sopravviventi



Hazard Ratio "globale" = 0.9 (NS)

Median, HR, Mean

- Median OS is a snapshot comparison of a single timepoint
  - ✓ no more statistically or clinically meaningful than any other single time-point
  - ✓ value is familiarity and consistency, not clinical utility
  - ✓ does not capture long-term survival
- The HR compares the slope of the survival curve in two treatment groups
  - ✓ Unlike median OS, the HR is not computed at any one timepoint but includes all the data in the survival curve
- **Mean OS is estimated as the area under the survival curve and is also based upon the entire range of data**

MRC Clinical Trials Unit

Restricted mean survival time

Patrick Royston

- RMST = area under the survival curve up to t^*

Choice of t^*

- t^* should be chosen to cover the follow-up period of clinical interest
- Usually take t^* close to the last observed event time
- In a randomized trial, t^* needs to be pre-specified in the statistical analysis plan

Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome

Patrick Royston* and Mahesh KB Parmar

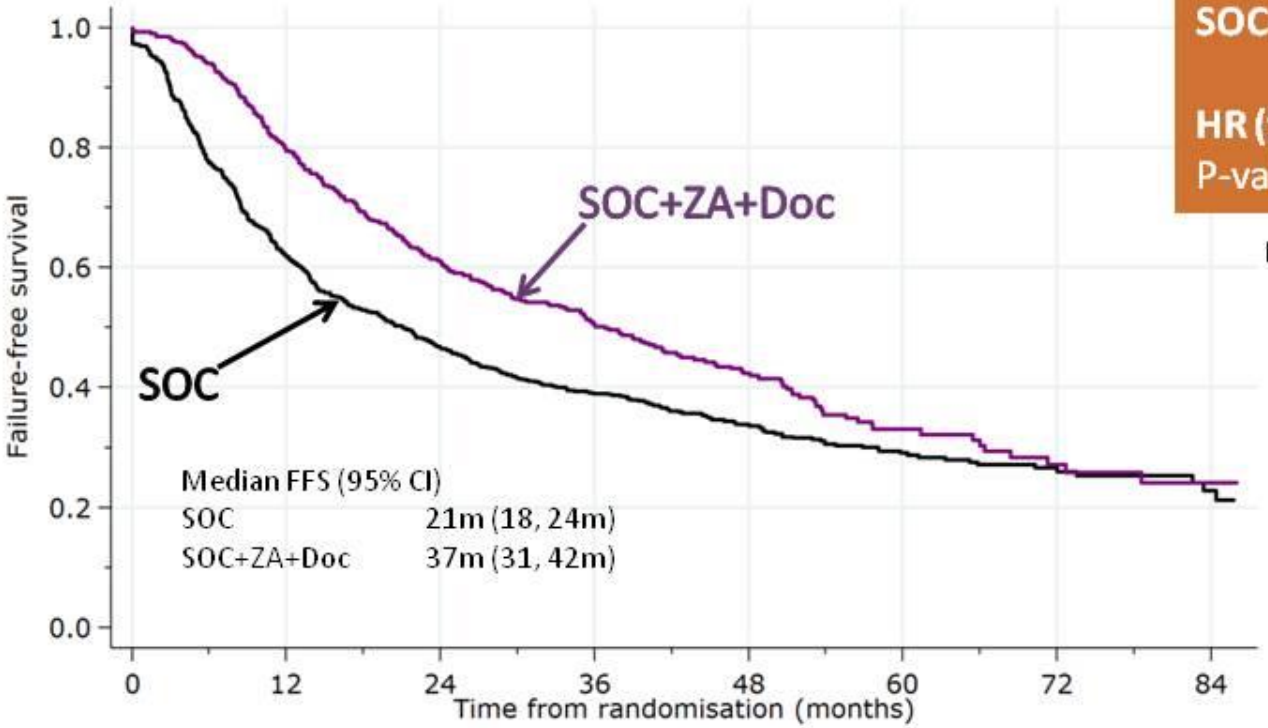
BMC Medical Research Methodology 2013, **13**:152

The restricted mean is a measure of average survival from time 0 to a specified time point, and may be estimated as the area under the survival curve up to that point.

Criterion	Measure		
	log HR	Median[a]	RMST[a]
1. Is easily interpreted	no	yes	yes
2. Does not assume proportional hazards	no	yes	yes
3. Reflects entire survival history	yes	no	yes
4. Is a measure of survival time	no	yes	yes
5. Can be used with all models	no	yes	yes
6. Can be calculated in any dataset	yes	no	yes
7. Does not require a time point to be specified	yes	yes	no
8. Does not change with extended follow-up	no	yes	yes
9. Is routinely associated with a clinically meaningful time point	no	no	yes

[a]The measure is the difference in the given statistic between trial arms.

Zoledronic acid + docetaxel: Failure-free survival



SOC	750 FFS events
SOC+ZA+Doc	371 FFS events
HR (95%CI)	0.62 (0.54, 0.71)
P-value	<0.0000000001*a

Non-PH p-value <0.0000000001*b

Restricted mean FFS time

SOC	35.3m
SOC+ZA+Doc	43.5m
Diff (95%CI)	8.2m (5.5, 11.1m)

Group
At risk (events)

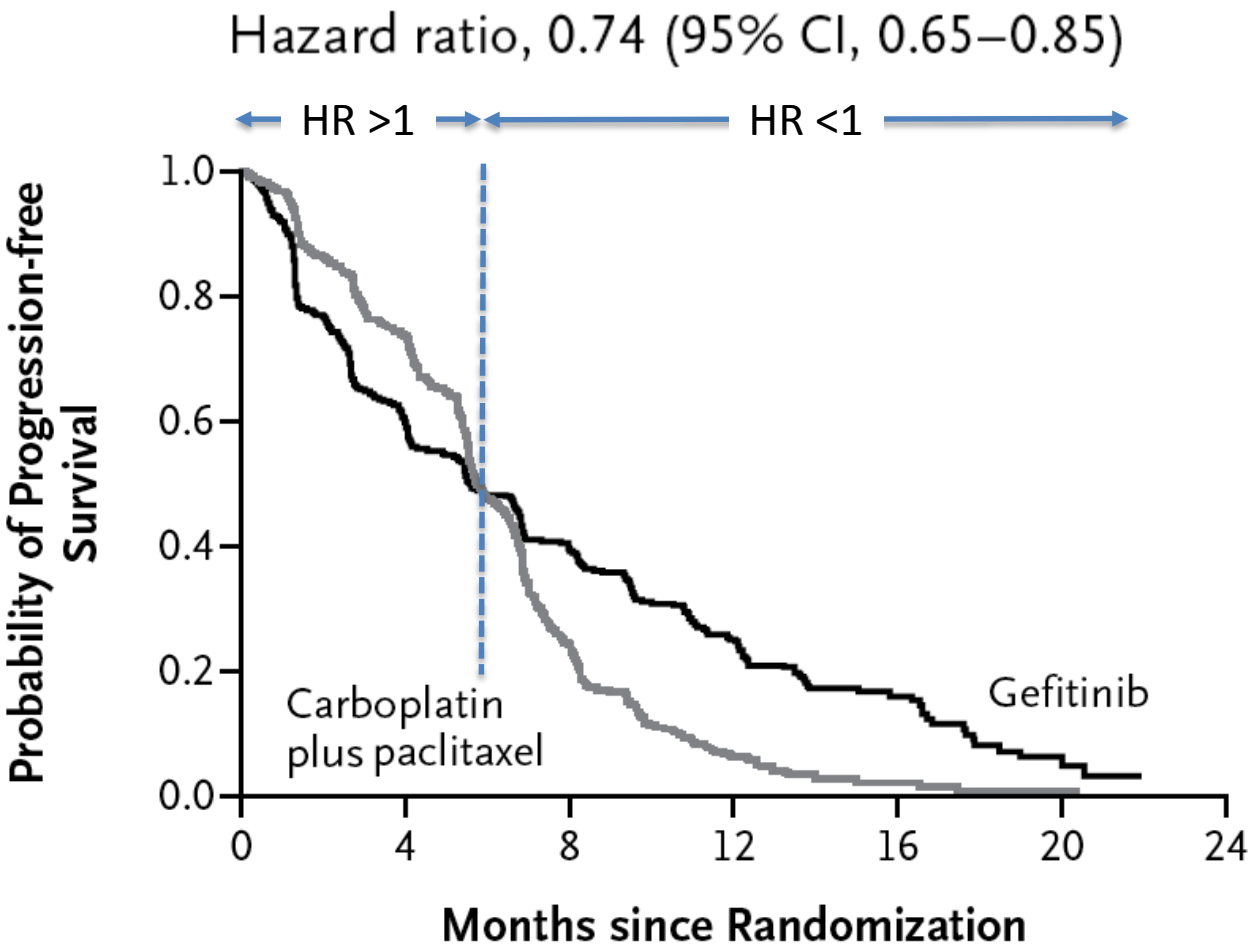
SOC	1184	(446)	713	(173)	488	(70)	287	(31)	161	(19)	84	(6)	45	(4)	17
SOC+ZA+Doc	593	(116)	448	(102)	303	(45)	180	(24)	103	(19)	42	(6)	20	(2)	13

*aexact HR p-value 0.0000000000005038
*bexact non-PH p-value 0.000000010376

Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

Tony S. Mok, M.D., Yi-Long Wu, M.D., F.A.C.S., Sumitra Thongprasert, M.D., Chih-Hsin Yang, M.D., Ph.D., Da-Tong Chu, M.D., Nagahiro Saijo, M.D., Ph.D., Patrapim Sunpaweravong, M.D., Baohui Han, M.D., Benjamin Margono, M.D., Ph.D., F.C.C.P., Yukito Ichinose, M.D., Yutaka Nishiwaki, M.D., Ph.D., Yuichiro Ohe, M.D., Ph.D., Jin-Ji Yang, M.D., Busyamas Chewaskulyong, M.D., Haiyi Jiang, M.D., Emma L. Duffield, M.Sc., Claire L. Watkins, M.Sc., Alison A. Armour, F.R.C.R., and Masahiro Fukuoka, M.D., Ph.D.

N Engl J Med 2009;361:947-57.



The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt

Patrick Royston*† and Mahesh K. B. Parmar

Statist. Med. ***2011,*** 30 2409–2421

Restricted mean survival time has great potential as a meaningful and sensitive outcome measure in the analysis of trial data with a time-to-event outcome. We recommend it as the primary outcome measure when we cannot be confident that the PH assumption holds and therefore doubt that a single HR is appropriate.

				Restricted mean survival time	
Trial	HR	95 per cent CI	t^*	Diff.	95 per cent CI
IPASS	0.73	(0.65, 0.82)	18 months	0.90	(0.38, 1.42)

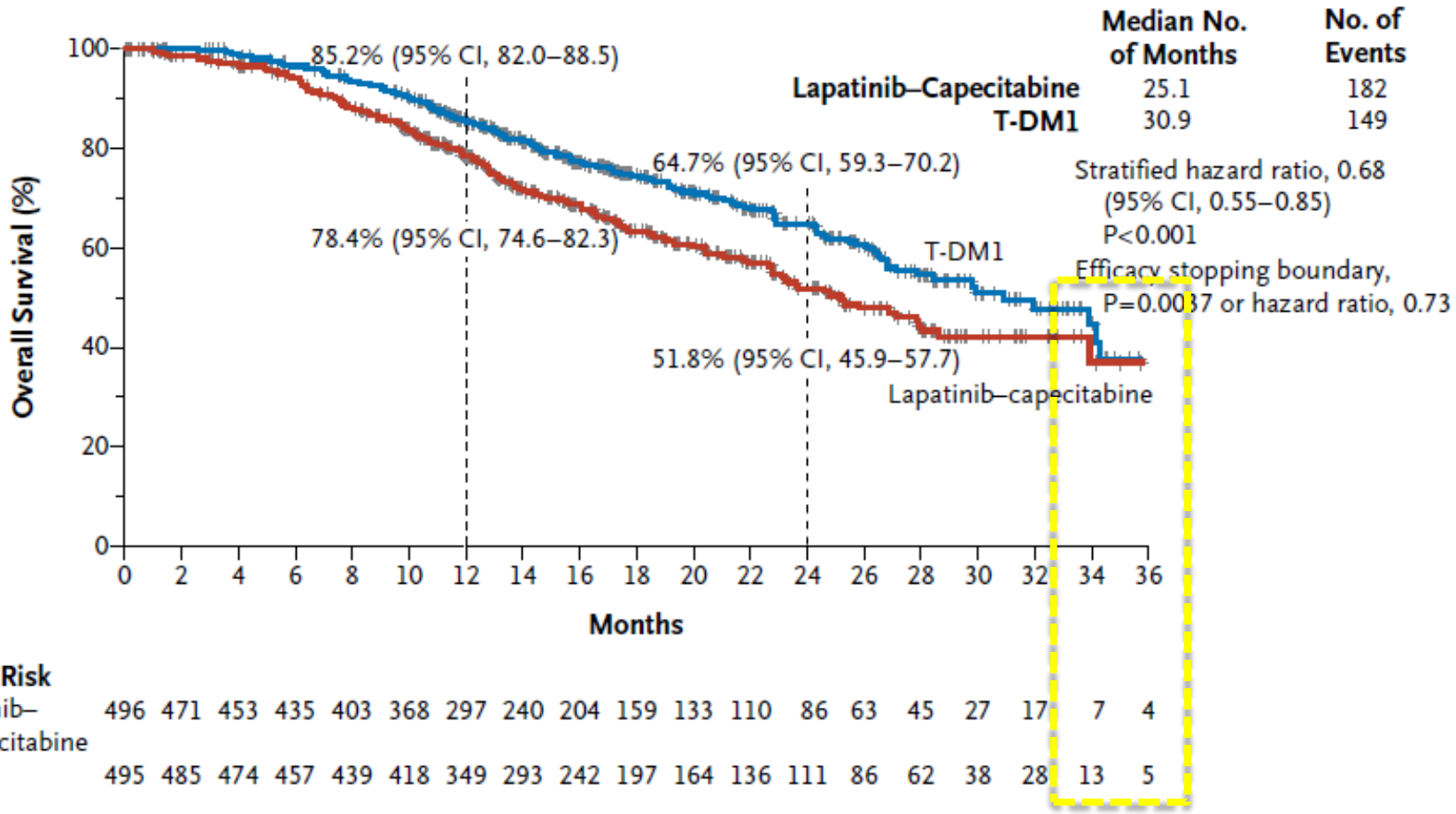


Figure 2. Second Interim Analysis of Overall Survival

Show … to world … al vs. nonv … O'Bri … ths (rang …

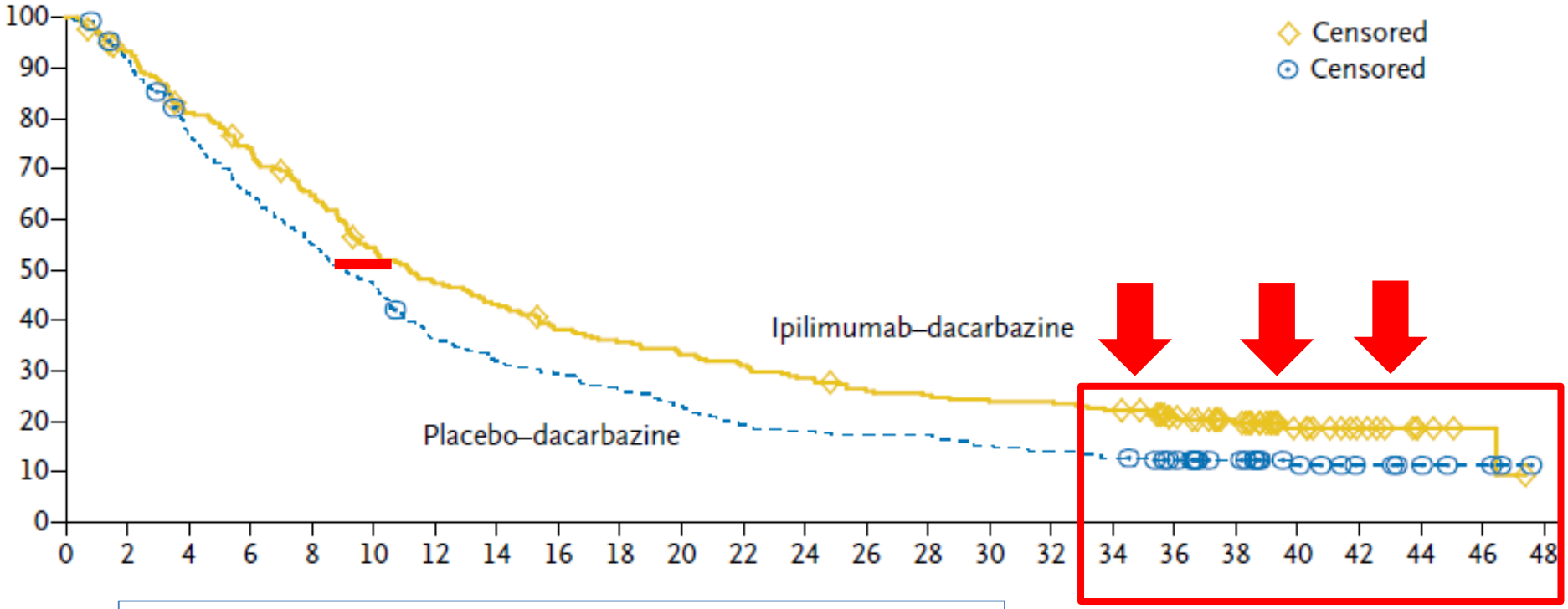
… l'incrocio delle curve avviene quando i pazienti (ancora) a rischio di evento sono in numero molto basso

Verma S, NEJM 2012; 367:1783-91

DOMANDA n. 2

Le code delle curve

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma



Domanda:

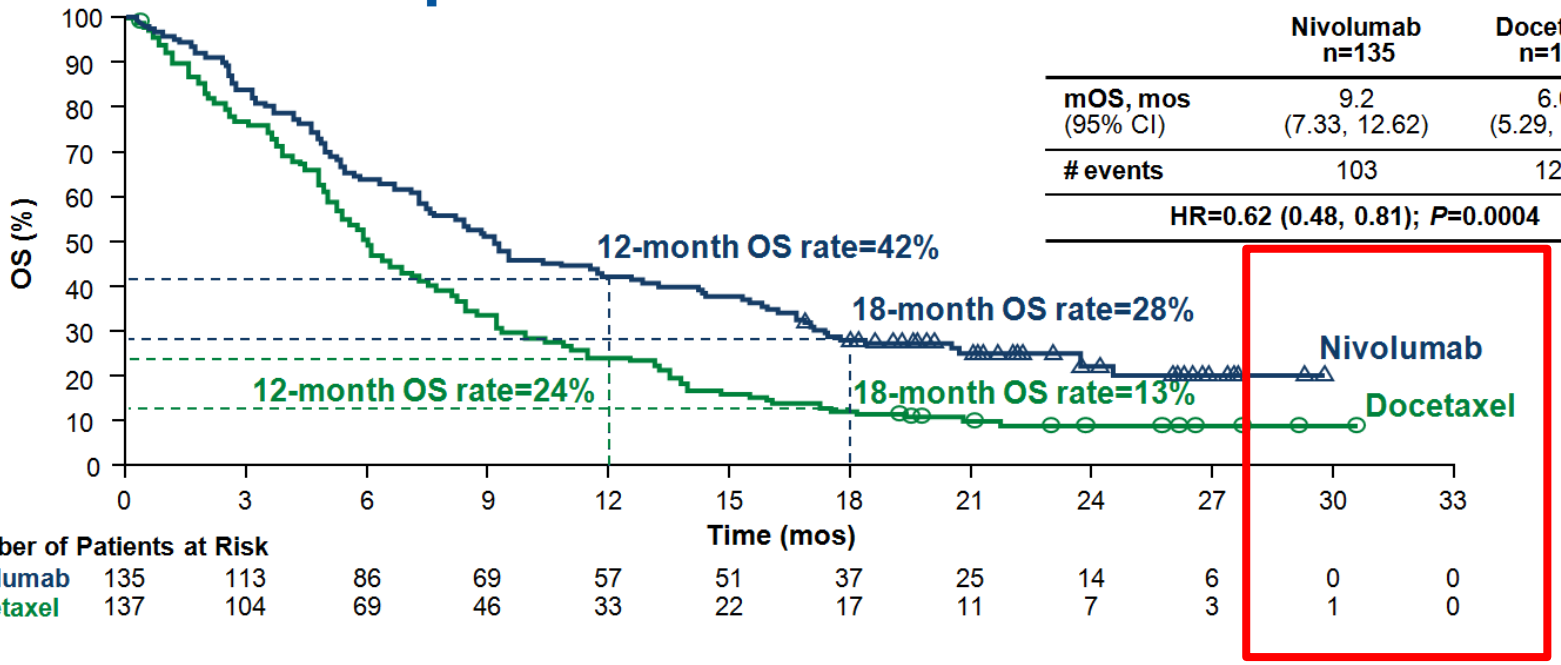
- **quale significato dare alle code delle curve?**

The NEW ENGLAND JOURNAL of MEDICINE

Robert et al NEJM 2011

CheckMate 017: Updated OS Data

Updated Overall Survival



	Nivolumab n=135	Docetaxel n=137
mOS, mos (95% CI)	9.2 (7.33, 12.62)	6.0 (5.29, 7.39)
# events	103	122
HR=0.62 (0.48, 0.81); *P*=0.0004		

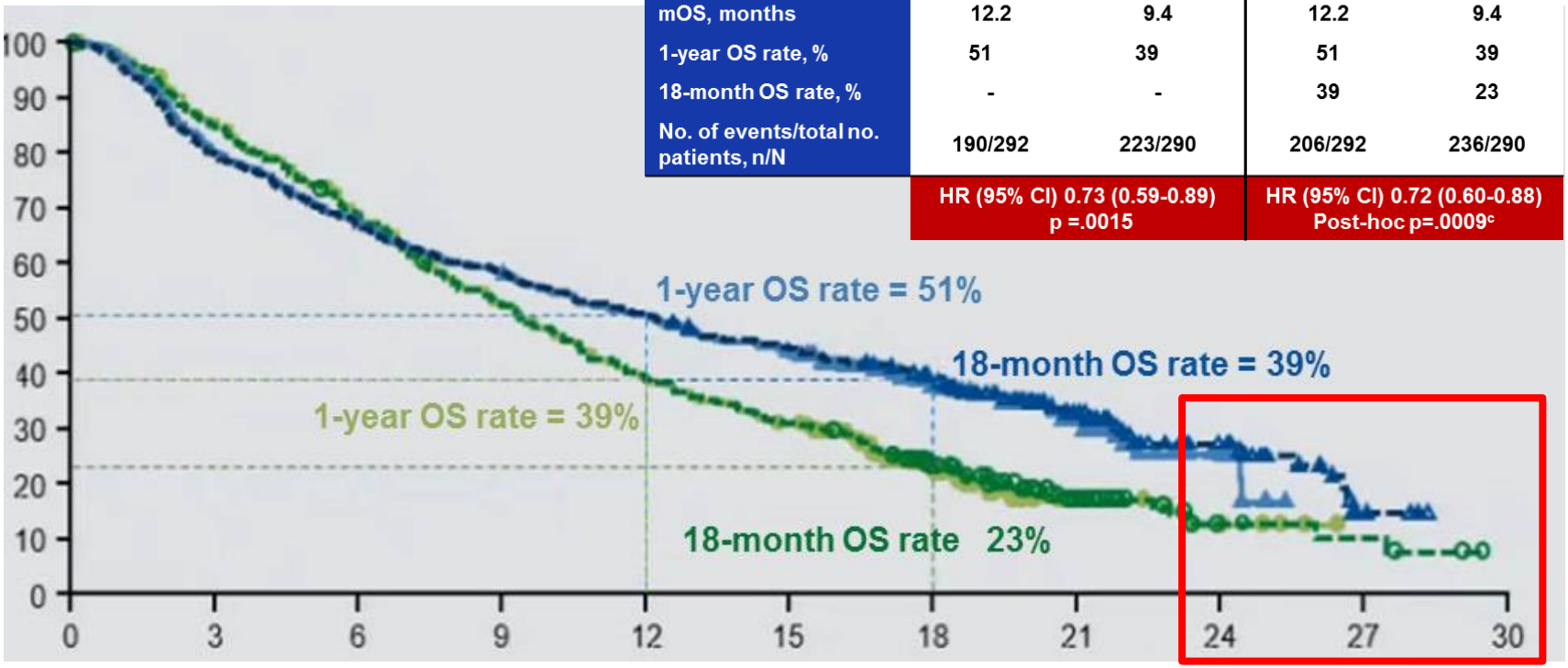
Minimum follow-up for survival: 18 months

Based on August 2015 DBL.
Symbols refer to censored observations.

Reckamp K et al, WCLC 2015

CheckMate 057: Updated OS Data

	12-month OS[a]		18-month OS[b]	
	Nivo (n=292)	Doc (n=290)	Nivo (n=292)	Doc (n=290)
mOS, months	12.2	9.4	12.2	9.4
1-year OS rate, %	51	39	51	39
18-month OS rate, %	-	-	39	23
No. of events/total no. patients, n/N	190/292	223/290	206/292	236/290
	HR (95% CI) 0.73 (0.59-0.89) p =.0015		HR (95% CI) 0.72 (0.60-0.88) Post-hoc p=.0009[c]	

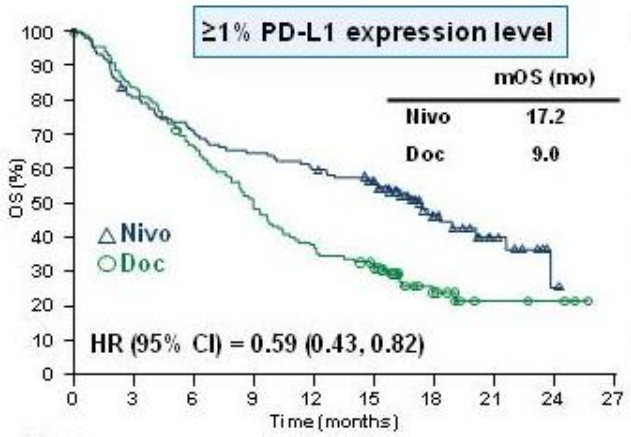


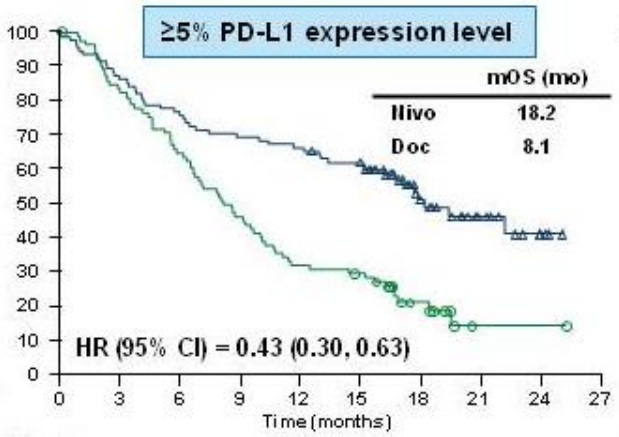
No. at risk (12-month OS)[a]											
Nivolumab	292	232	194	169	146	123	62	32	9	0	0
Docetaxel	290	244	194	150	111	88	34	10	5	0	0
No. at risk (18-month OS)[b]											
Nivolumab	292	233	195	171	148	128	107	55	27	4	0
Docetaxel	290	244	194	150	111	89	61	23	6	4	0

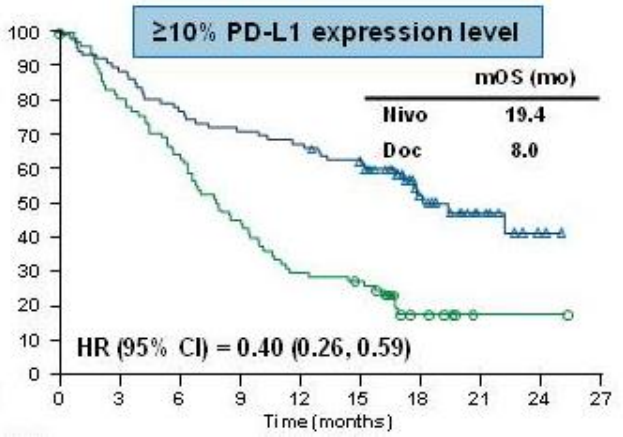
Minimum F.U. for 12-month OS rate, 13.2 months; for 18-month OS rate, 17.1 months

Horn L, et al, ECC 2015

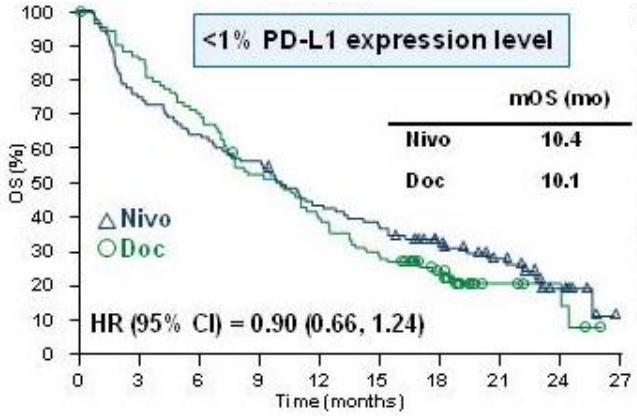
CheckMate 057: OS According to PD-L1

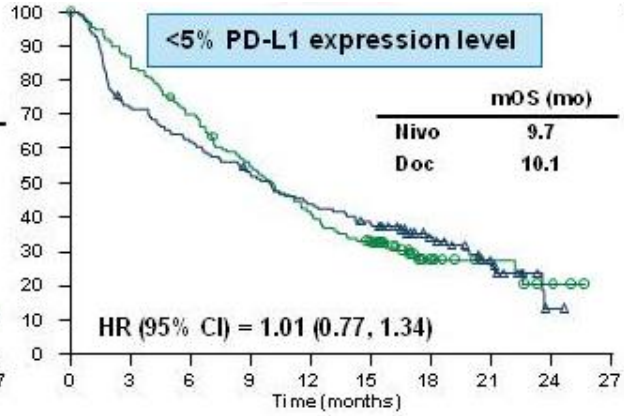


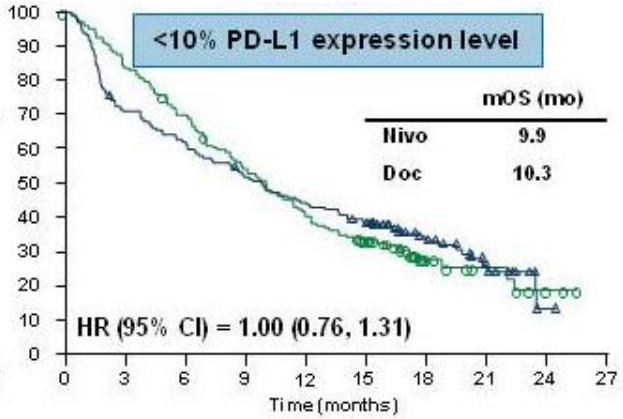




HR 0.59 **HR 0.43** **HR 0.40**







HR 0.90 **HR 1.01** **HR 1.00**

Paz-Ares L et al, ASCO 2015

DOMANDA n.3

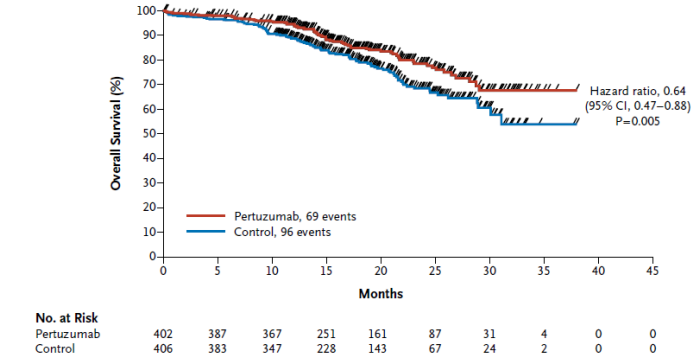
La maturità dei dati

Curve di sopravvivenza e maturità dei dati

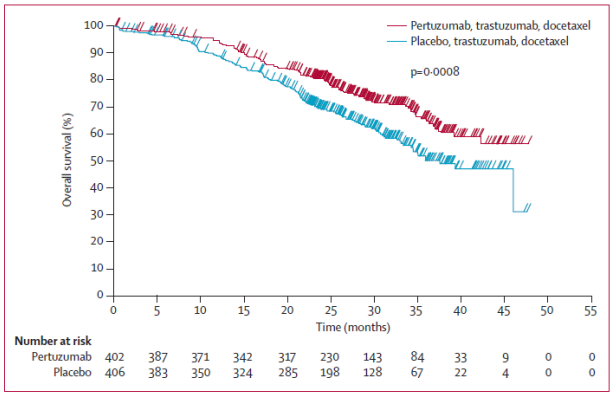
	Median F. up	Events (deaths)	HR (95%CI) p	Median OS
Baselga NEJM 2012	19 mo	165 (=43% of the 385 prespecified)	0.64 (0.47–0.88) p=0.005	The hazard ratio was 0.64 (95% CI, 0.47 to 0.88; P = 0.005), which did not meet the O'Brien–Fleming stopping boundary of the Lan–DeMets alpha spending function for this interim analysis of overall survival (hazard ratio, ≤0.603; P≤0.0012) and was therefore not significant.
Swain Lancet Oncol 2013	30 mo	267 (=69%)	0.66 (0.52-0.84) p=0.0008	NR *vs* 37.6 mo
Swain NEJM 2015	50 mo	389 (>100%)	0.68 (0.56-0.84) p< 0.01	56.5 mo *vs* 40.8 mo

Curve di sopravvivenza e maturità dei dati

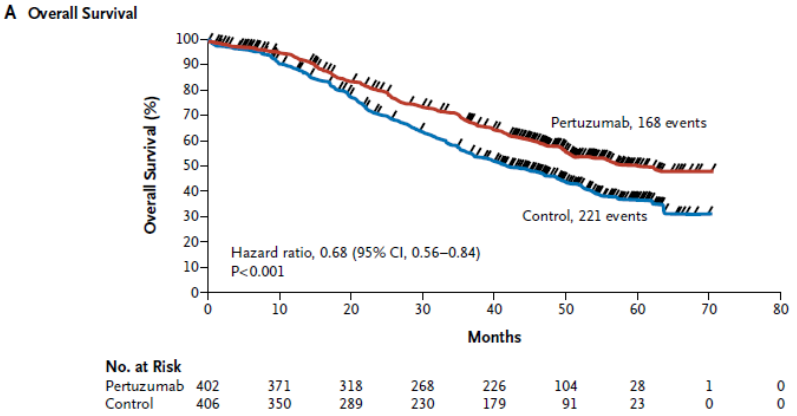
	Median F. up	Events (deaths)	HR (95%CI)	Median OS
Baselga NEJM 2012	19 mo	165 (=43% of the 385 prespecified)		
Swain Lancet Oncol 2013	30 mo	267 (=69%)		
Swain NEJM 2015	50 mo	389 (>100%)		



This HR valuedid not crossed the O'Brien-Fleming stopping boundary threshold; therefore, the interim result is not statistically significant and is deemed exploratory



This HR value crossed the O'Brien-Fleming stopping boundary for this **second interim analysis** (HR≤0.739 and p value ≤0.0138). **This benefit in OS must be considered statistically significant.**



E2100

A Randomized Phase III Trial of Paclitaxel versus Paclitaxel plus Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

KD Miller, M Wang, J Gralow, M Dickler, MA Cobleigh, EA Perez, TN Shenkier, NE Davidson

Indiana University Cancer Center, Dana Farber Cancer Institute, Pudget Sound Oncology Consortium, Memorial Sloan Kettering Cancer Center, Rush University Medical Center, Mayo Clinic, British Columbia Cancer Agency, Vancouver Cancer Center, Johns Hopkins Oncology Center

Study Design

Stratify:

- DFI $\leq$ 24 mos. vs. > 24 mos.
- < 3 vs. $\geq$ 3 metastatic sites
- Adjuvant chemotherapy yes vs. no
- ER+ vs. ER- vs. ER unknown

Paclitaxel + Bevacizumab

Paclitaxel

28-day cycle:

Paclitaxel 90 mg/m^2 D1, 8 and 15

Bevacizumab 10 mg/kg D1 and 15

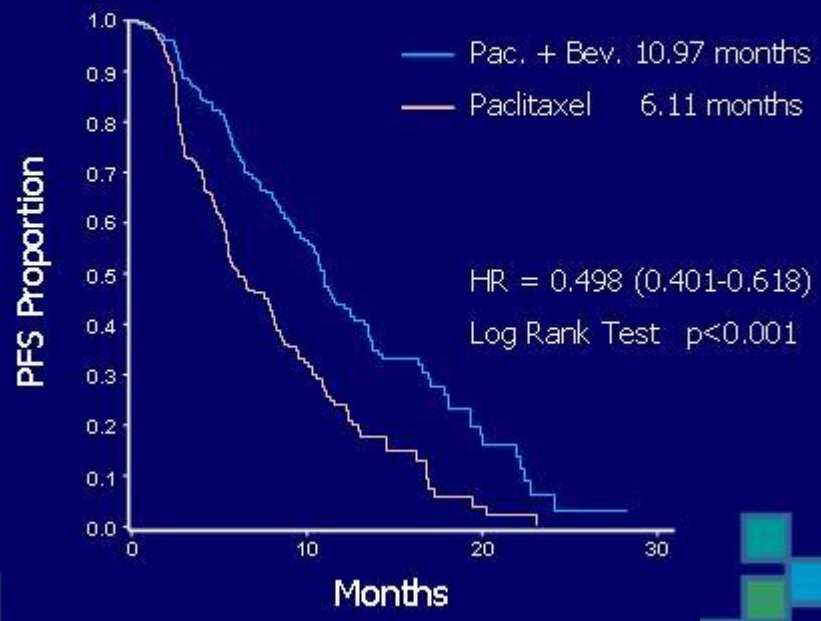
Statistical Design - Efficacy

- Primary endpoint: Progression-Free Survival
  - 85% power for a 33% improvement
    - 6 vs. 8 months
  - One-sided type I error ≅ 2.5%
  - Requires 650 eligible patients
- Final analysis after 546 PFS events
  - Interim analyses after 270 and 425 events
  - Asymmetric boundaries to stop early either for demonstrated benefit or for lack of benefit
  - O-Brien-Fleming boundaries and repeated confidence interval analyses at each interim

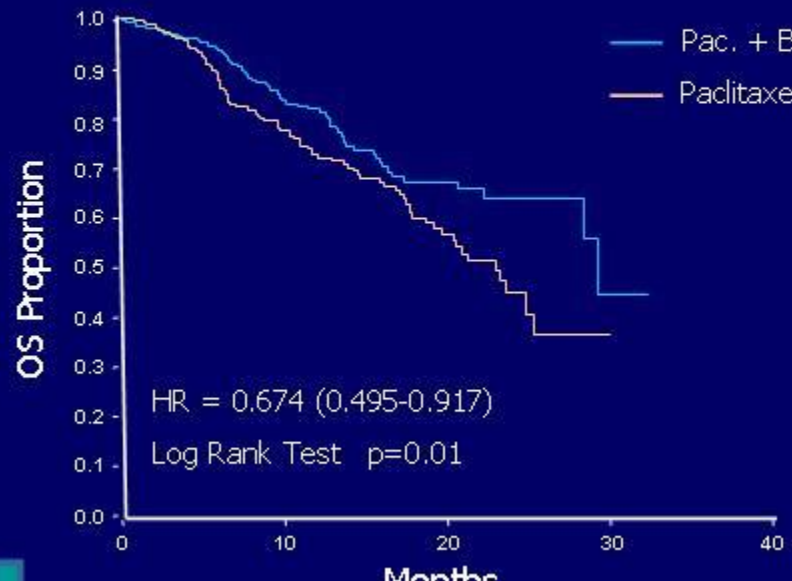
Current Analysis

- Study activated Dec 21, 2001
- Closed March 24, 2004
  - 715 eligible patients
- First planned interim analysis
- Data cut-off February 9, 2005
- 355 events
  - Progression – 291
  - Death without documented progression - 64

Progression Free Survival



Overall Survival



Paclitaxel plus Bevacizumab versus Paclitaxel Alone for Metastatic Breast Cancer

Kathy Miller, M.D., Molin Wang, Ph.D., Julie Gralow, M.D., Maura Dickler, M.D., Melody Cobleigh, M.D., Edith A. Perez, M.D., Tamara Shenkier, M.D., David Cella, Ph.D., and Nancy E. Davidson, M.D.

N ENGL J MED 357;26 WWW.NEJM.ORG DECEMBER 27, 2007

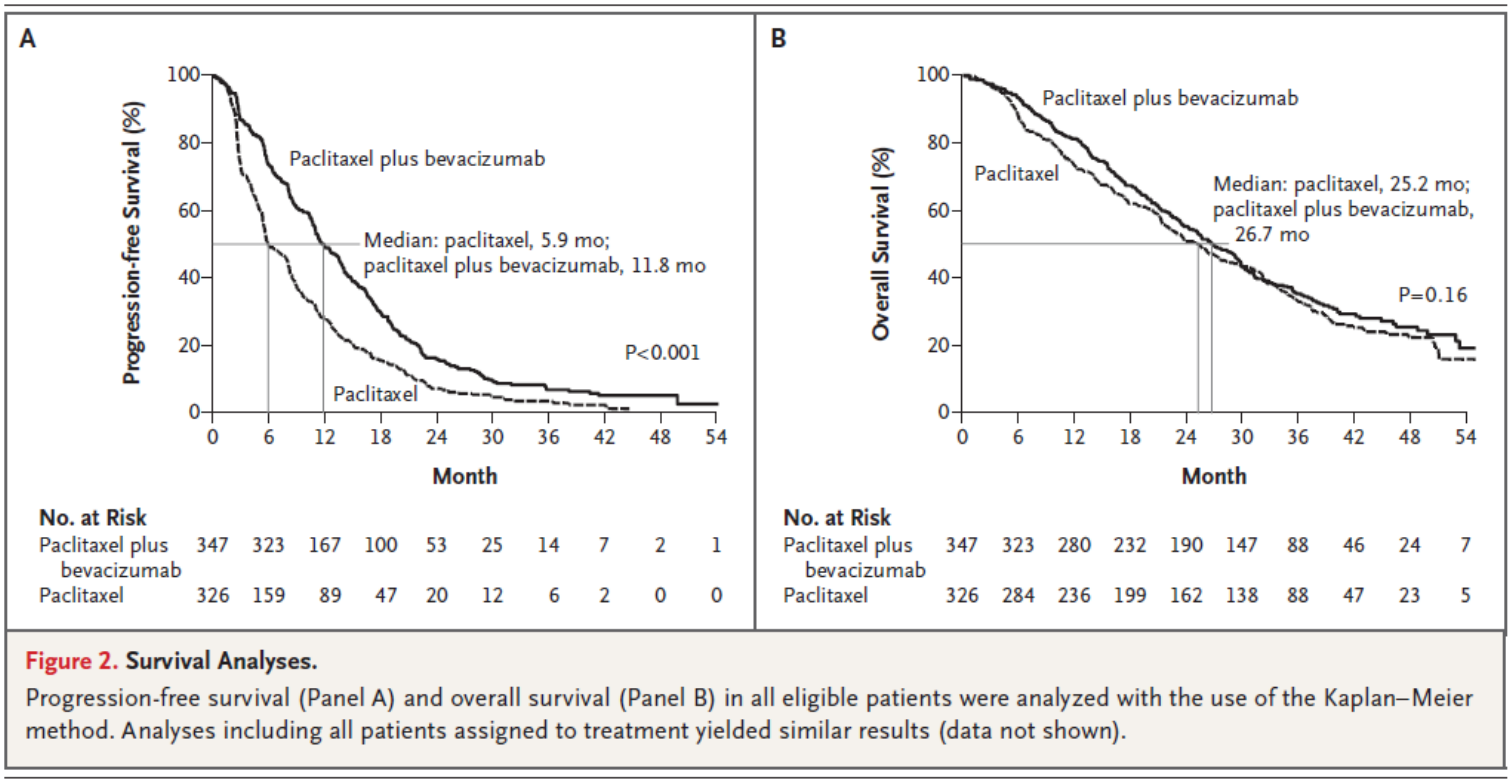


Figure 2. Survival Analyses.

Progression-free survival (Panel A) and overall survival (Panel B) in all eligible patients were analyzed with the use of the Kaplan–Meier method. Analyses including all patients assigned to treatment yielded similar results (data not shown).

DOMANDA n.4

Il crossover

The New England
Journal of Medicine

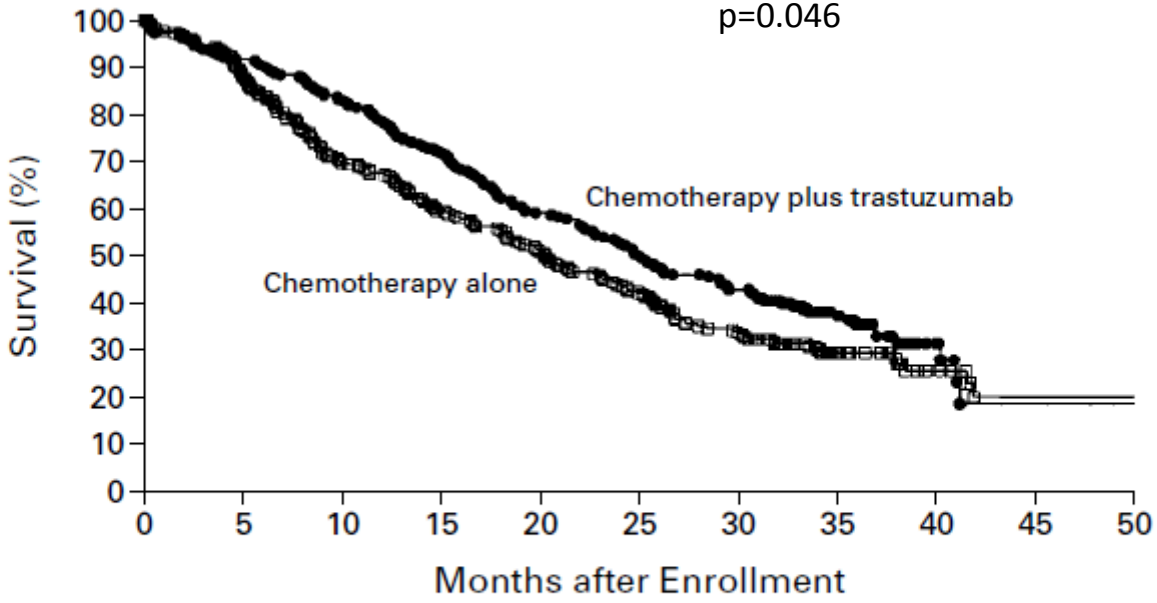
VOLUME 344 MARCH 15, 2001 NUMBER 11

USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

Median OS:
25.1 mo *vs* 20.3 mo
HR=….
p=0.046

A



NO. AT RISK

Chemotherapy plus trastuzumab	235	214	192	165	134	114	96	47	11
Chemotherapy alone	234	205	160	136	116	97	76	37	13

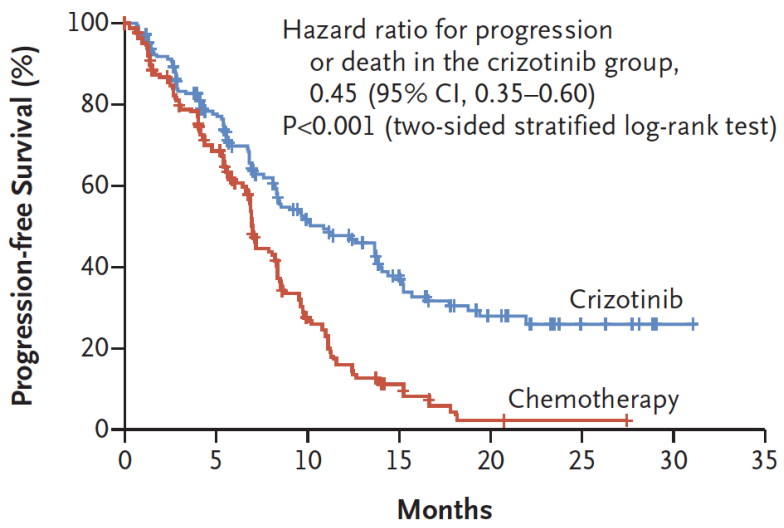
Upfront crizotinib: PROFILE 1014

Median follow up: ~ 17 mo

Table 2. Response to Treatment in the Intention-to-Treat Population.*

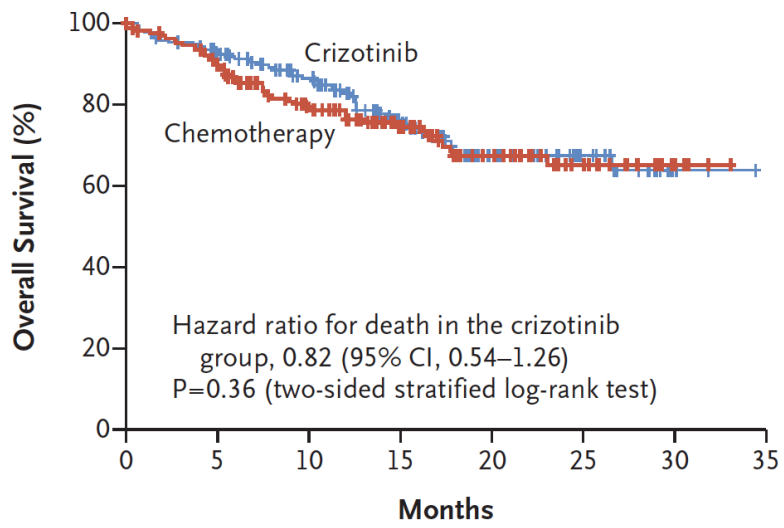
Response	Crizotinib (N = 172)	Chemotherapy (N = 171)
Duration of response — mo ‖		
Median	11.3	5.3
95% CI	8.1–13.8	4.1–5.8

A Progression-free Survival



No. at Risk								
Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

B Overall Survival



No. at Risk								
Crizotinib	172	152	123	80	44	24	3	0
Chemotherapy	171	146	112	74	47	21	4	0

Solomon BJ, NEJM 2014

Table S2. Summary of Systemic Anticancer Therapies at Follow-Up Among Patients with Progressive Disease.*

Therapy	Crizotinib (n=89)	Chemotherapy (n=132)
	no. of patients (%)	
Any systemic therapy	38 (43)	118 (89)†
Alectinib	1 (1)	3 (2)
Bevacizumab	2 (2)	0
Carboplatin	15 (17)	3 (2)
Ceritinib	6 (7)	2 (2)
Cisplatin	13 (15)	1 (1)
Crizotinib	1 (1)	114 (86)†
Cyclophosphamide	0	1 (1)
Denosumab	0	1 (1)
Docetaxel	3 (3)	6 (5)
Doxorubicin	0	1 (1)
Gefitinib	1 (1)	1 (1)
Gemcitabine	6 (7)	1 (1)
Icotinib	1 (1)	0
Investigational drug (unspecified)	3 (3)	3 (2)
Paclitaxel	1 (1)	2 (2)
Pemetrexed	25 (28)	3 (2)
Tegafur/gimeracil/oteracil	1 (1)	0
Vinblastine	0	1 (1)
Vinorelbine	3 (3)	0
Other therapeutic products	1 (1)	0

* By independent radiologic review; patients may have received more than one therapy.

† Including crizotinib taken by crossover patients on study or outside of the study.

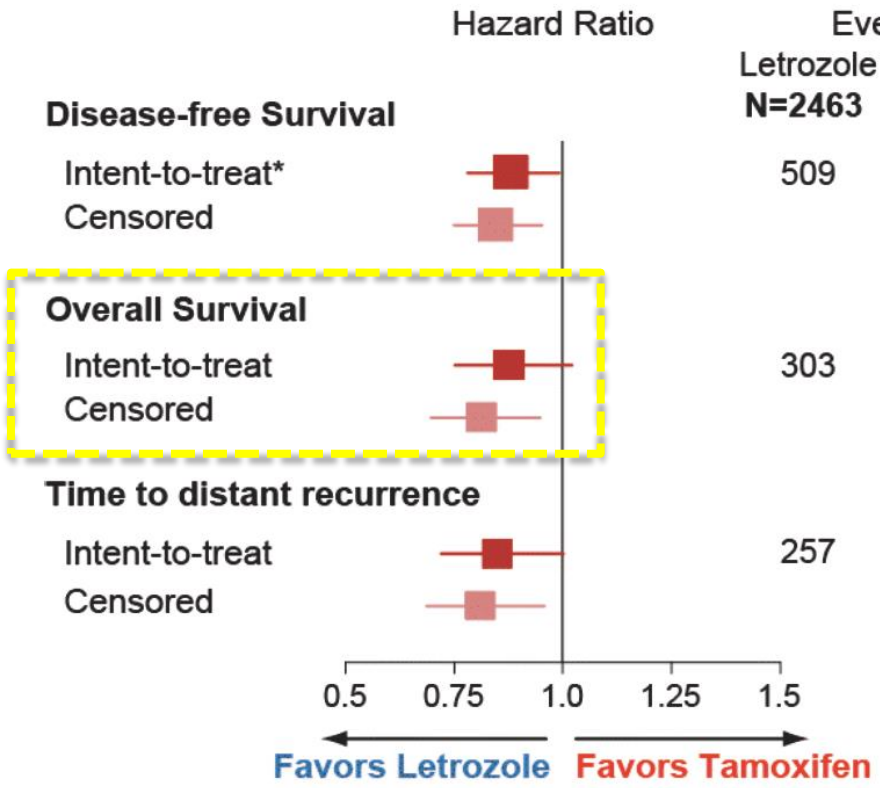
- Il cross over può determinare una mancata differenza in OS: devo quindi leggere con attenzione i risultati degli studi clinici?

BIG 1-98 Monotherapy Update

- 2005 results of Let superiority led to unblinding of Tam-alone arm
- 619 (25.2%) patients selectively crossed over to Let
  - Mostly in years 3-5
  - Median duration Let after crossover 18 mos.
- This complicates comparisons with Tam alone
- The comparison of Tam vs. Let was done by
  - Intent-to-treat (ITT)
  - Censoring at crossover

BIG 1-98 Monotherapy Update

Median Follow-up 76 months



	Events Letrozole N=2463	Events Tamoxifen N=2459	Hazard Ratio (95% CI)	ITT P-value
Disease-free Survival				
Intent-to-treat*	509	565	0.88 (0.78–0.99)	0.03
Censored			0.84 (0.74–0.95)	
Overall Survival				
Intent-to-treat	303	343	0.87 (0.75–1.02)	0.08
Censored			0.81 (0.69–0.94)	
Time to distant recurrence				
Intent-to-treat	257	298	0.85 (0.72–1.00)	0.05
Censored			0.81 (0.68–0.96)	

International Breast Cancer Study Group
IBCSG SABCS 2008

*Let:Tam: breast cancer events, 321:363
second (non breast) malignancy, 101:115
deaths without prior cancer event, 87:87

BIG
BREASTINTERNATIONALGROUP

Adjusting overall survival for treatment switches: commonly used methods and practical application

Claire Watkins,[a]* Xin Huang,[b] Nicholas Latimer,[c] Yiyun Tang,[b] and Elaine J. Wright[d]

Pharmaceut. Statist. ***2013,*** 12 348–357

There are several statistical methods available to adjust long-term time-to-event endpoints for treatment switch. None is universally suitable in all situations, and different methods make different assumptions.

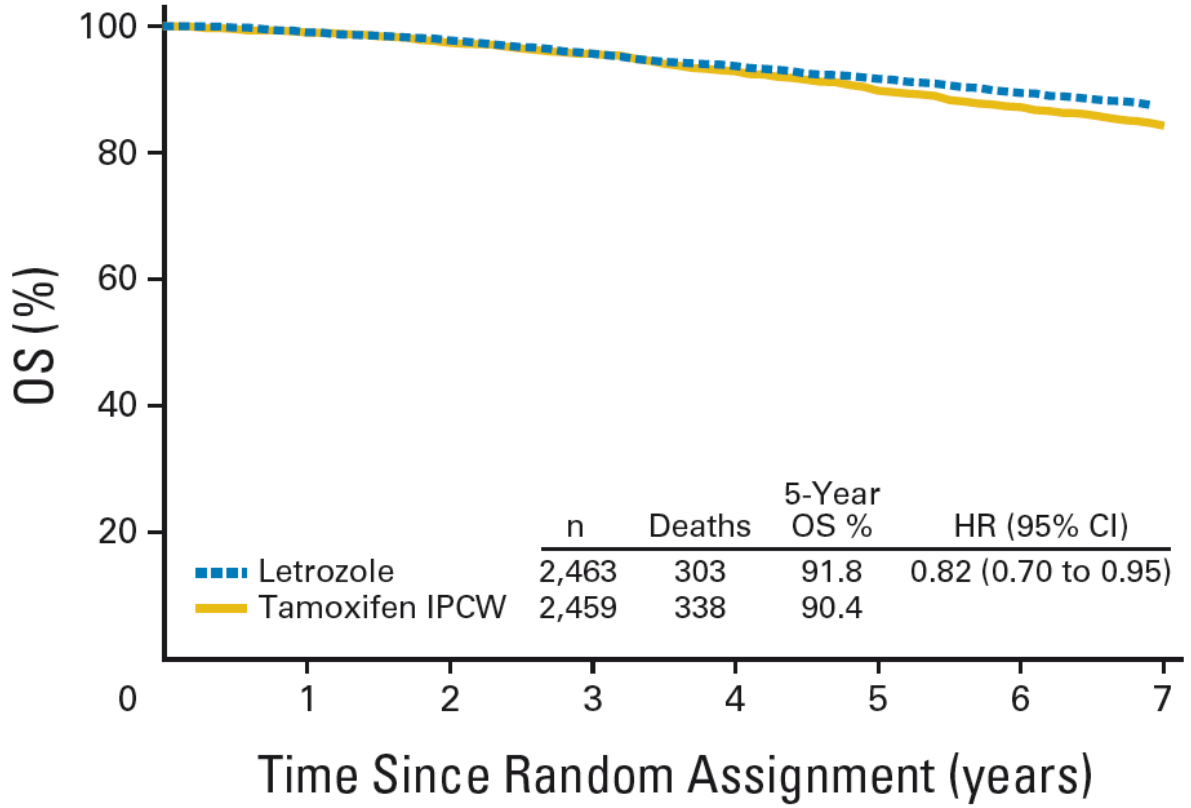
Inverse Probability of Censoring Weighting. The IPCW method assign weights to individuals that do not drop out. Weights recreate the population you would have seen with no drop-out.

Rank-Preserving Structural Failure Time / Iterative Parameter Estimation. The RPSFT and IPE methods maintain the original randomised group definition and thus preserve the validity of between-group comparisons.

Analyses Adjusting for Selective Crossover Show Improved Overall Survival With Adjuvant Letrozole Compared With Tamoxifen in the BIG 1-98 Study

Marco Colleoni, Anita Giobbie-Hurder, Meredith M. Regan, Beat Thürlimann, Henning Mouridsen, Louis Mauriac, John F. Forbes, Robert Paridaens, István Láng, Ian Smith, Jacquie Chirgwin, Tadeusz Pienkowski, Andrew Wardley, Karen N. Price, Richard D. Gelber, Alan S. Coates, and Aron Goldhirsch

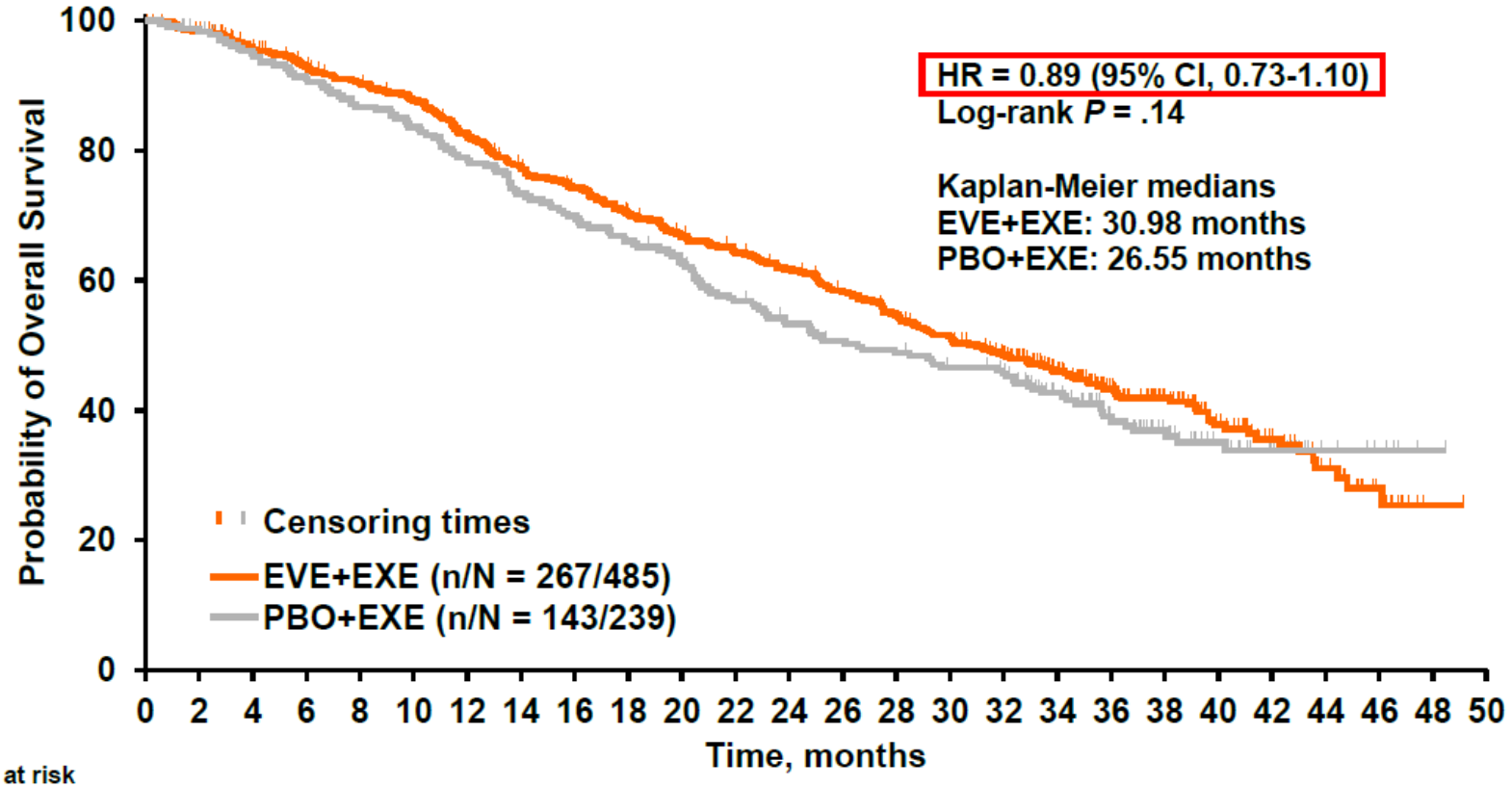
J Clin Oncol 29.



DOMANDA n.5

Differenza statisticamente NON significativa …ma clinicamente interessante

BOLERO-2 (39-mo): Final OS Analysis



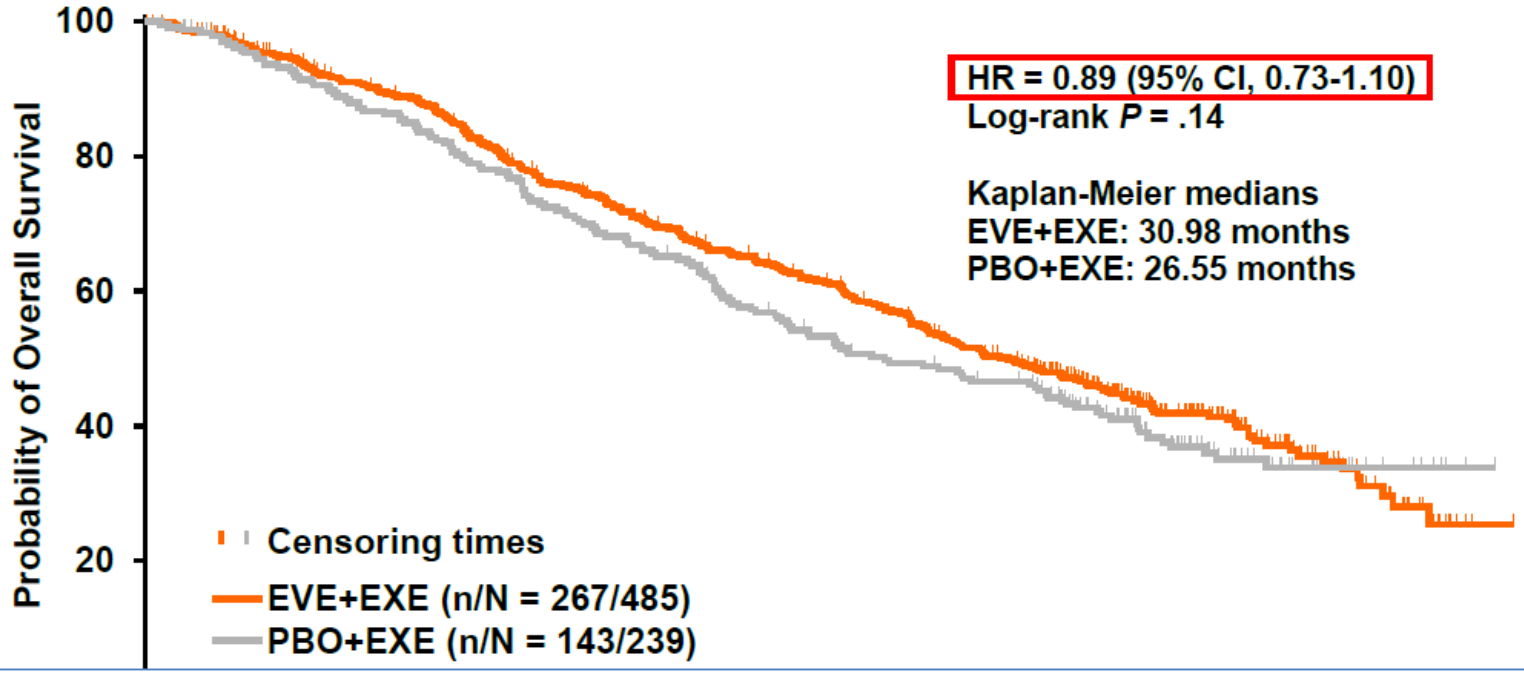
No. at risk

EVE+EXE	485	471	448	429	414	399	373	347	330	311	292	279	266	248	232	216	196	154	118	91	58	39	23	11	1	0
PBO+EXE	239	232	220	211	201	194	182	170	162	153	145	130	120	113	109	102	98	77	56	41	28	18	8	5	1	0

- At 39 months' median follow-up, 410 deaths had occurred (data cutoff date: 03 October 2013)
  - 55% deaths (n = 267) in the EVE+EXE arm vs 60% deaths (n = 143) in the PBO+EXE arm

Piccart M, Presented at EBCC-9; 19–21 March 2014; Glasgow, Scotland. Abstract 1LBA.

BOLERO-2 (39-mo): Final OS Analysis



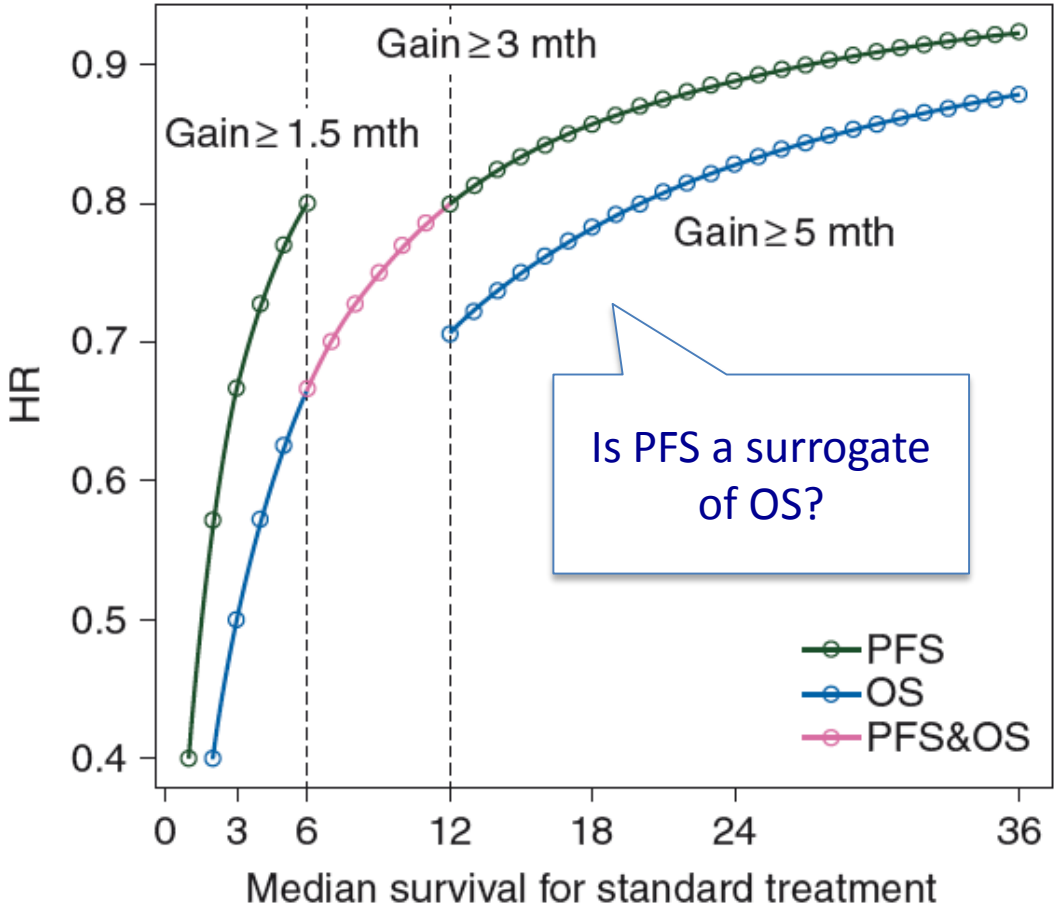
- Non c'è differenza statisticamente significativa ma clinicamente è una differenza importante: come valutare questo dato?

Piccart M, Presented at EBCC-9; 19–21 March 2014; Glasgow, Scotland. Abstract 1LBA.

A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

N. I. Cherny[1*], R. Sullivan[2], U. Dafni[3], J. M. Kerst[4], A. Sobrero[5], C. Zielinski[6], E. G. E. de Vries[7] & M. J. Piccart[8,9]

Annals of Oncology 26: 1547–1573, 2015



The correspondence between an HR value and the minimum absolute gain in months considered as beneficial according to the ESMO-MCBS by median survival (OS or PFS) for control

THANK YOU !

Sacro Cuore Don Calabria
CCC
Cancer Care Center
Negrar - Verona

CANCER CARE CENTER

Sacro Cuore -Don Calabria

Negrar-VERONA