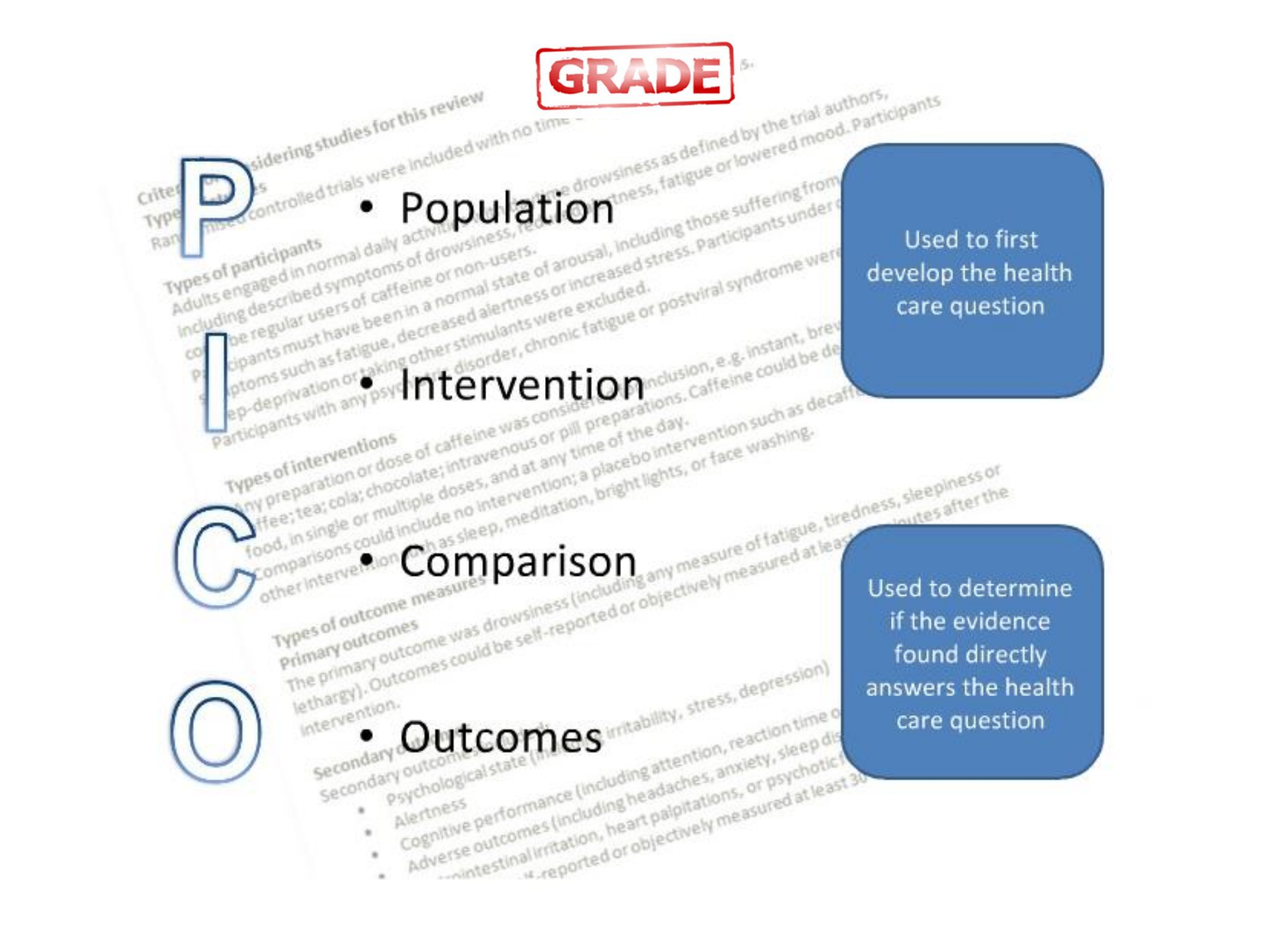
Criteri di valutazione negli studi clinici di immunoterapia

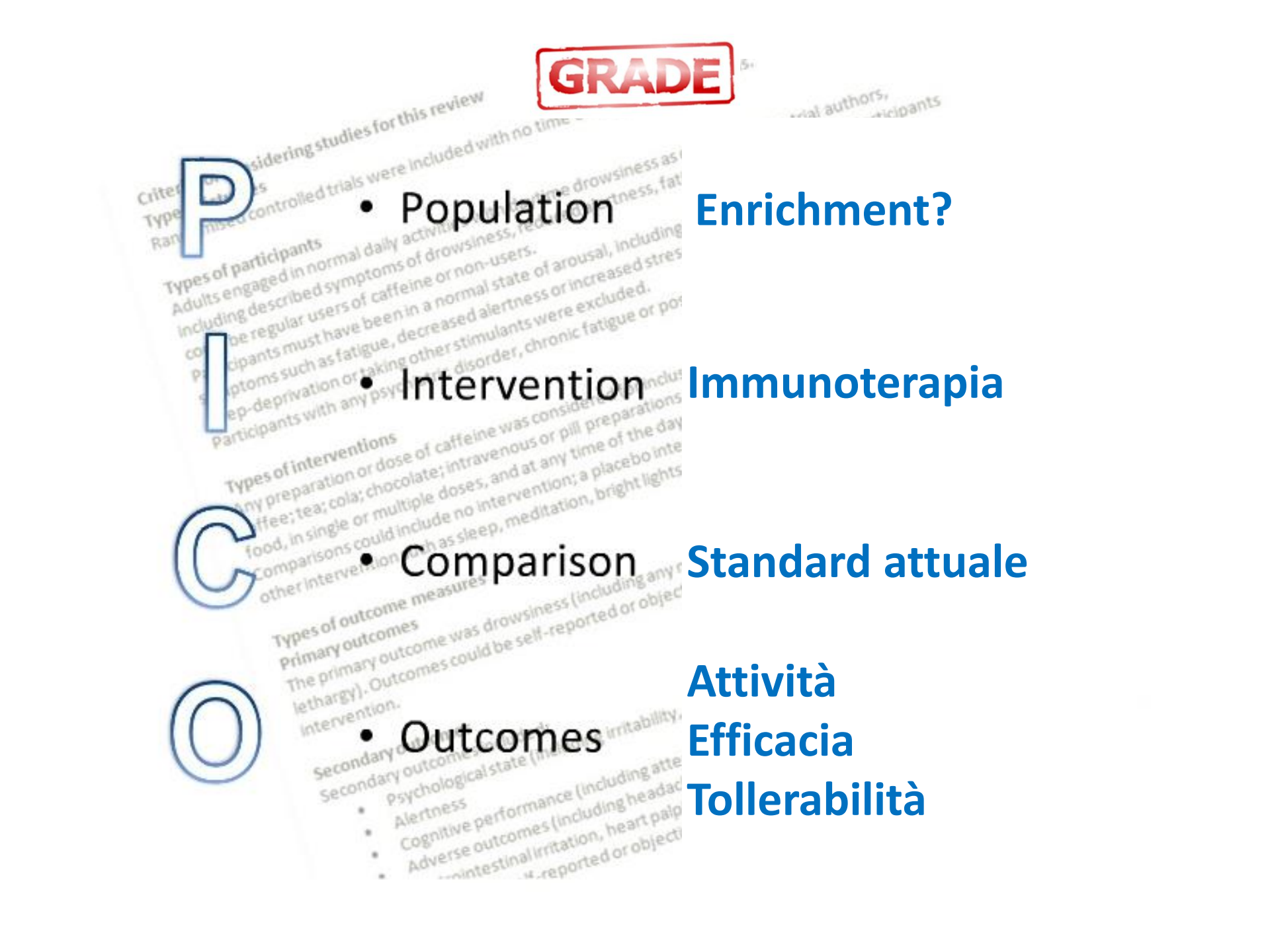
Giovanni L. Pappagallo

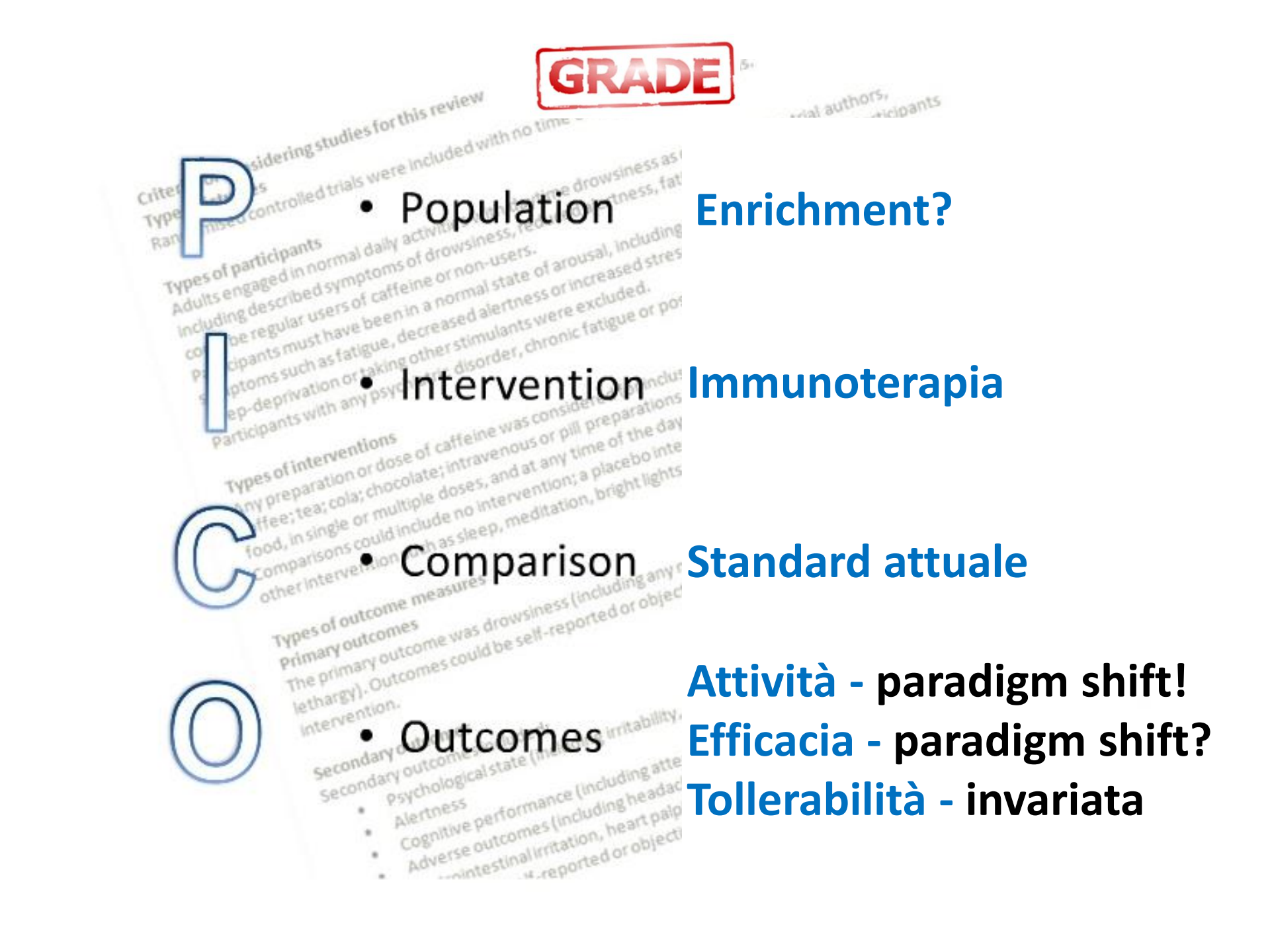
ULSS3 SERENISSIMA

AIOM

SIUrO


GRADE
P
• Population
I
• Intervention
C
• Comparison
O
• Outcomes
Used to first develop the health care question
Used to determine if the evidence found directly answers the health care question


GRADE
P
• Population
Enrichment?
I
• Intervention
Immunoterapia
C
• Comparison
Standard attuale
O
• Outcomes
Attività
Efficacia
Tollerabilità


GRADE
P
• Population
Enrichment?
I
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Immunoterapia
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• Comparison
Standard attuale
O
• Outcomes
Attività - paradigm shift!
Efficacia - paradigm shift?
Tollerabilità - invariata

Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria

Jedd D. Wolchok,[1] Axel Hoos,[2] Steven O'Day,[3] Jeffrey S. Weber,[4] Omid Hamid,[3] Celeste Lebbé,[5] Michele Maio,[6] Michael Binder,[7] Oliver Bohnsack,[8] Geoffrey Nichol,[9] Rachel Humphrey,[2] and F. Stephen Hodi[10]

(Clin Cancer Res 2009;15(23):7412–20)

- Immunotherapeutic agents produce antitumor effects by inducing cancer specific immune responses or by modifying native immune processes.
- Resulting clinical response patterns extend beyond those of cytotoxic agents and can manifest after an initial increase in tumor burden or the appearance of new lesions (progressive disease).
- RECIST or WHO criteria, designed to detect early effects of cytotoxic agents, may not provide a complete assessment of immunotherapeutic agents.
- Novel criteria for the evaluation of antitumor responses with immuno-therapeutic agents are required.

Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria

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(Clin Cancer Res 2009;15(23):7412–20)

Table 1. Comparison between WHO criteria and the irRC

	WHO	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

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 (*Milestone* Survival)
- Hazard Ratio (KM+Cox)

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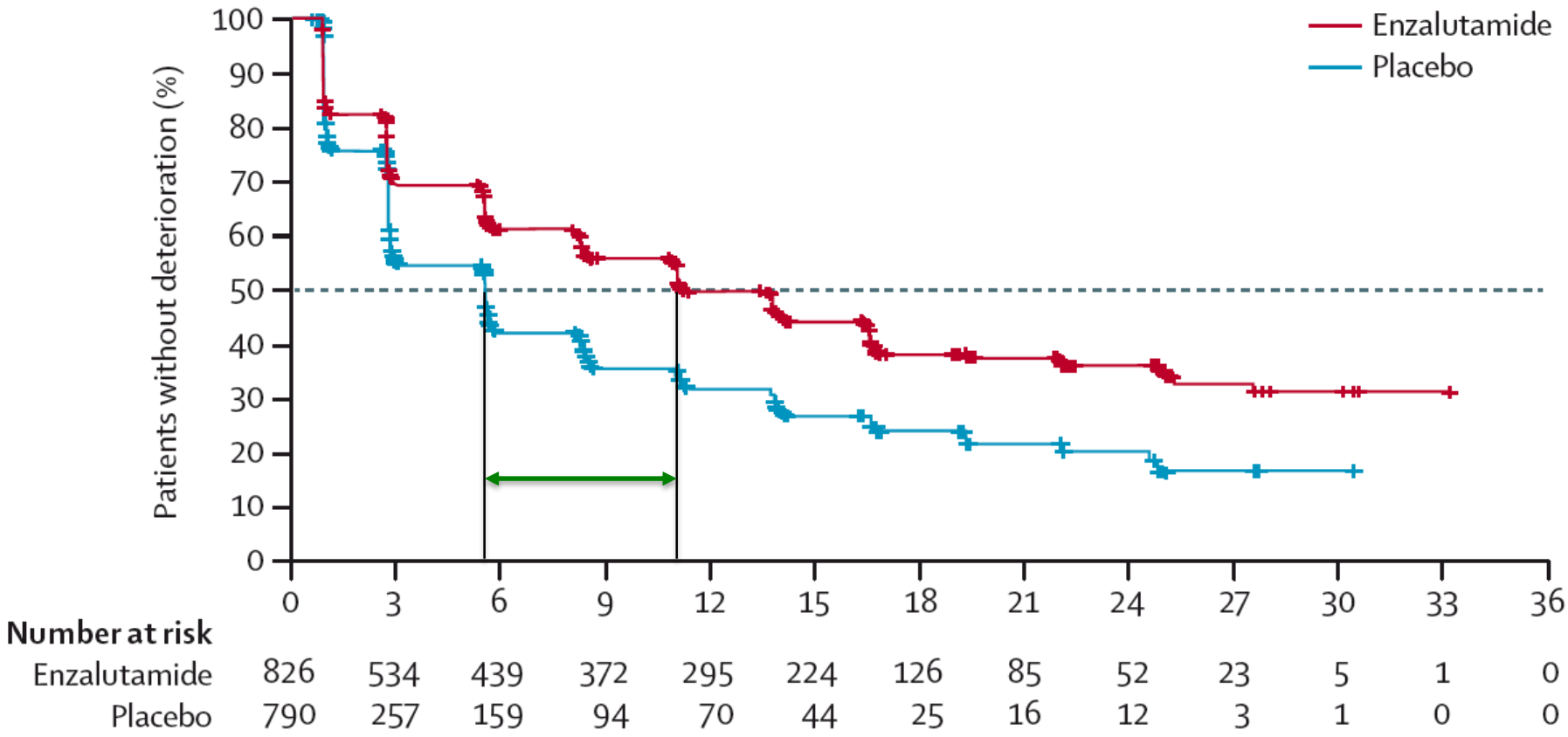
Differenza tra stime della mediana di sopravvivenza



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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

Indicatori riassuntivi di effetto di variabili tempo-a-evento

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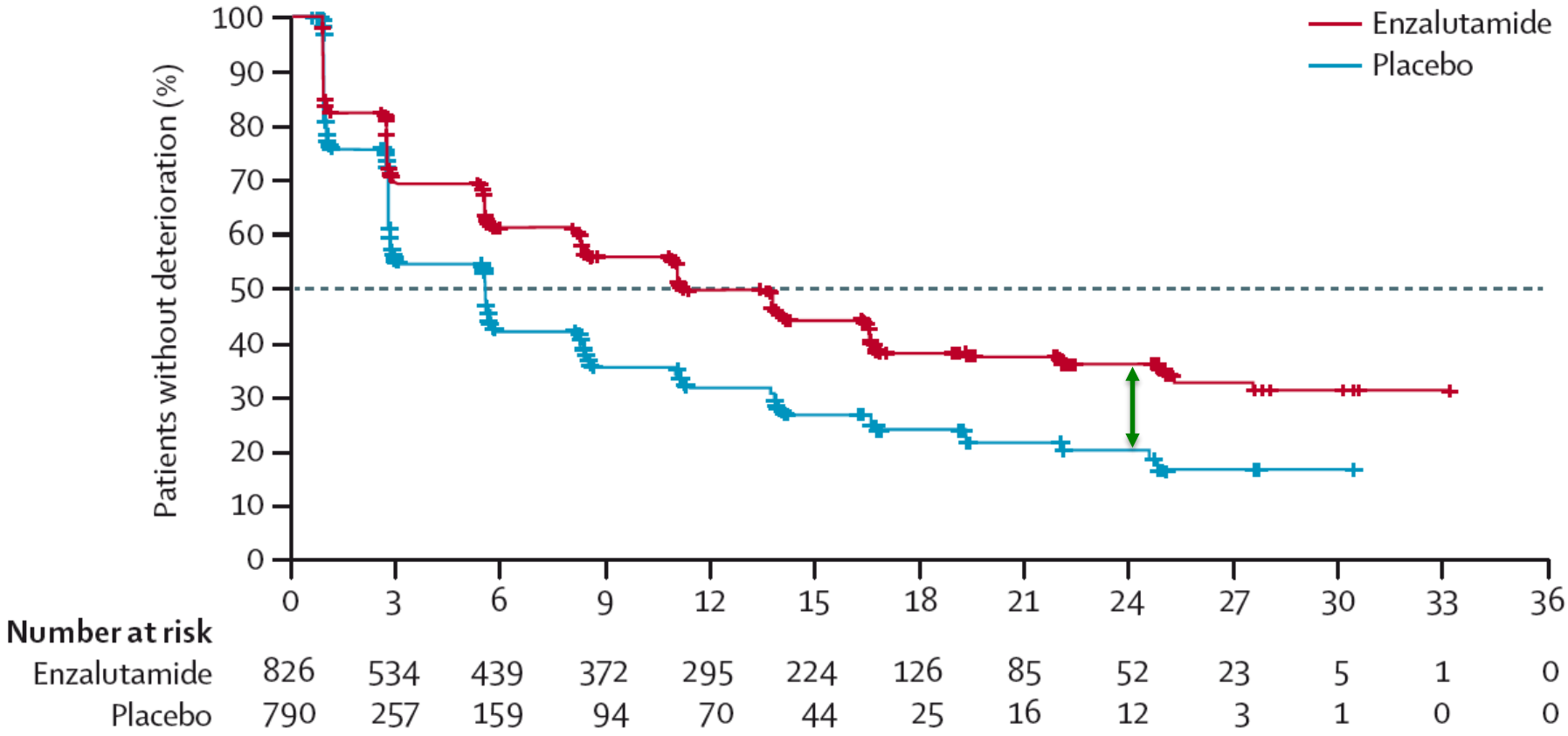
Differenza tra stime di sopravvivenza (KM) al tempo x



Indicatori riassuntivi di effetto di variabili tempo-a-evento

- Differenza tra stime della mediana di sopravvivenza (KM)
- za (*restricted*
- venza (KM) al tempo *Milestone* Survival)
- **Hazard Ratio** (KM+Cox)

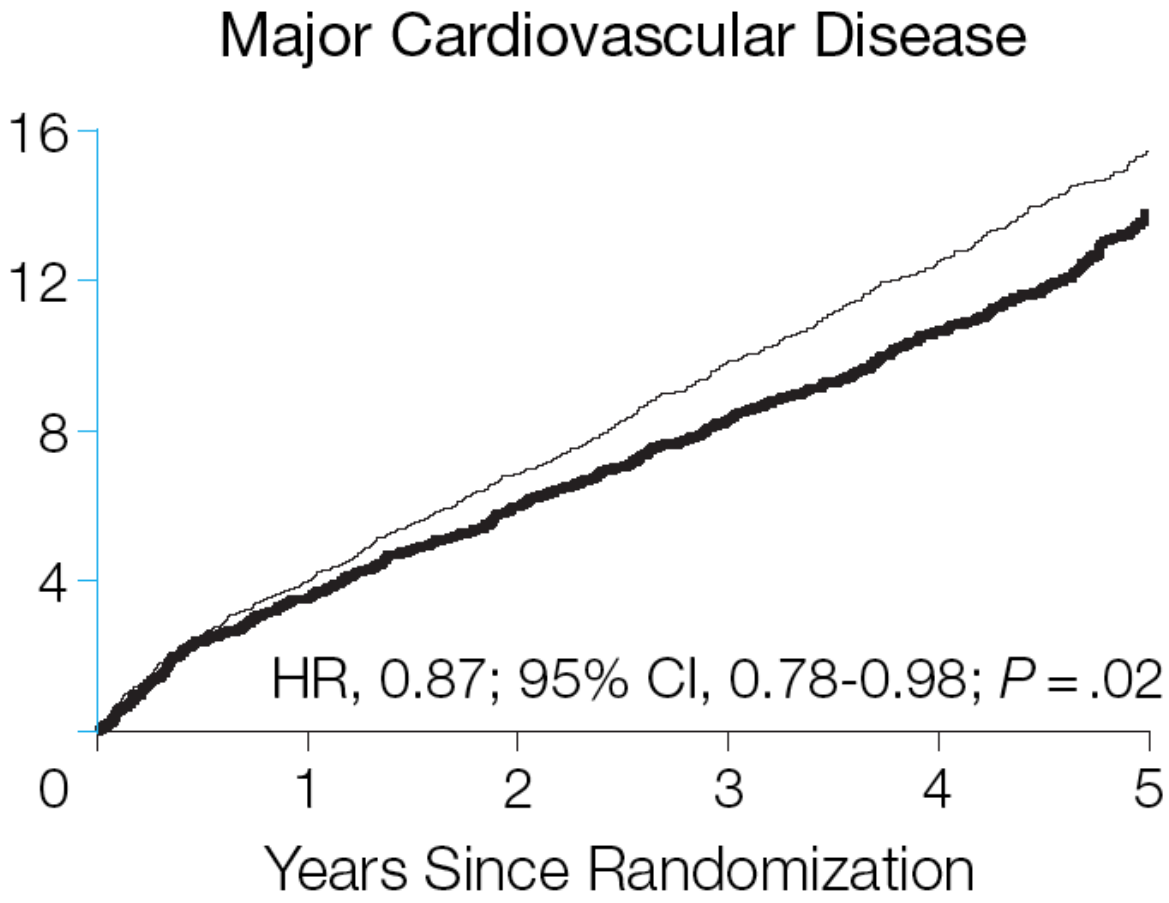
Rapporto tra *hazard rate* dei trattamenti a confronto

Indicatori riassuntivi di variabili tempo-a-evento

- Differenza tra stime della mediana di
- *ricted*
- M) al tempo *estone* Survival)
- **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

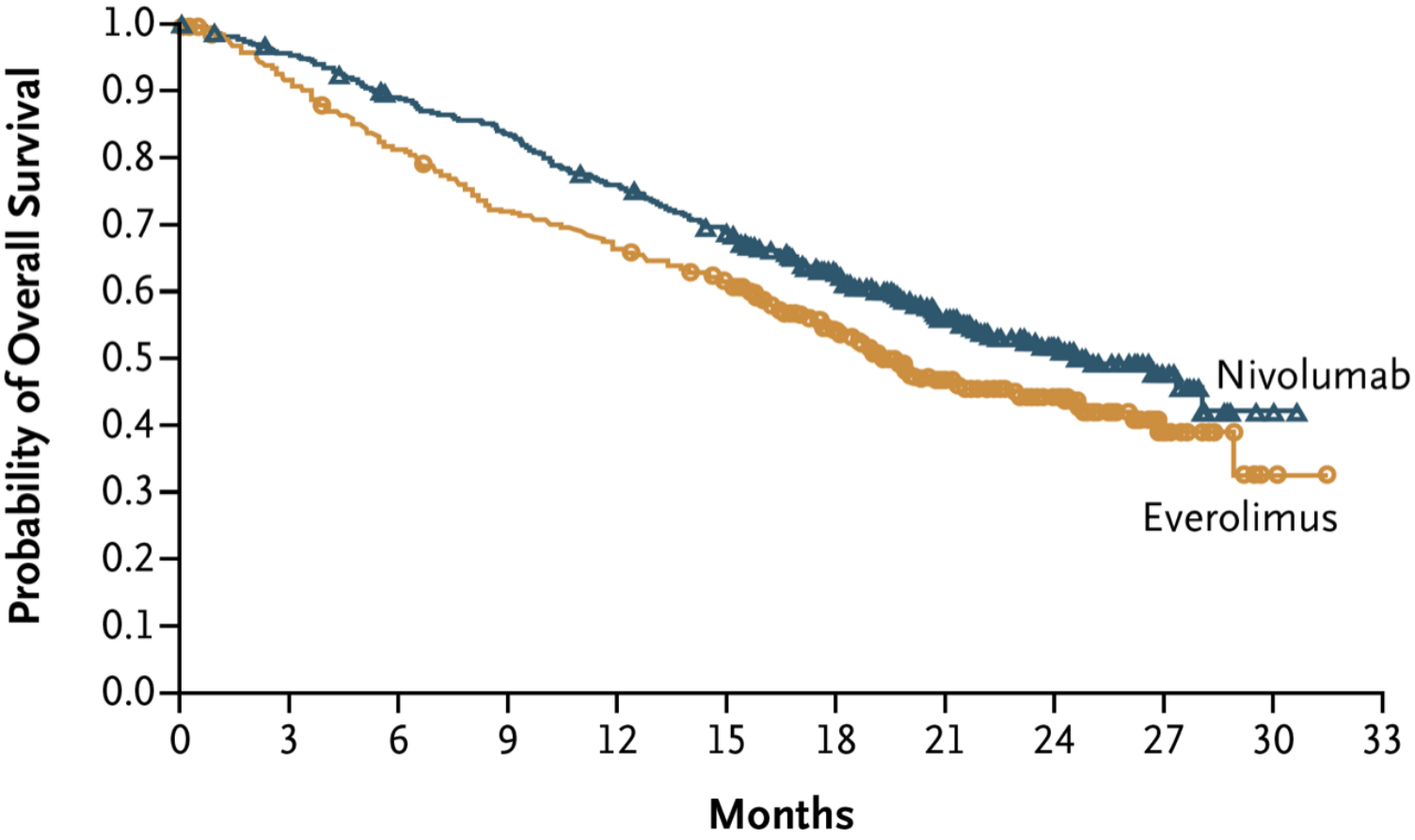


Hazard Ratio è la misura di effetto più appropriata

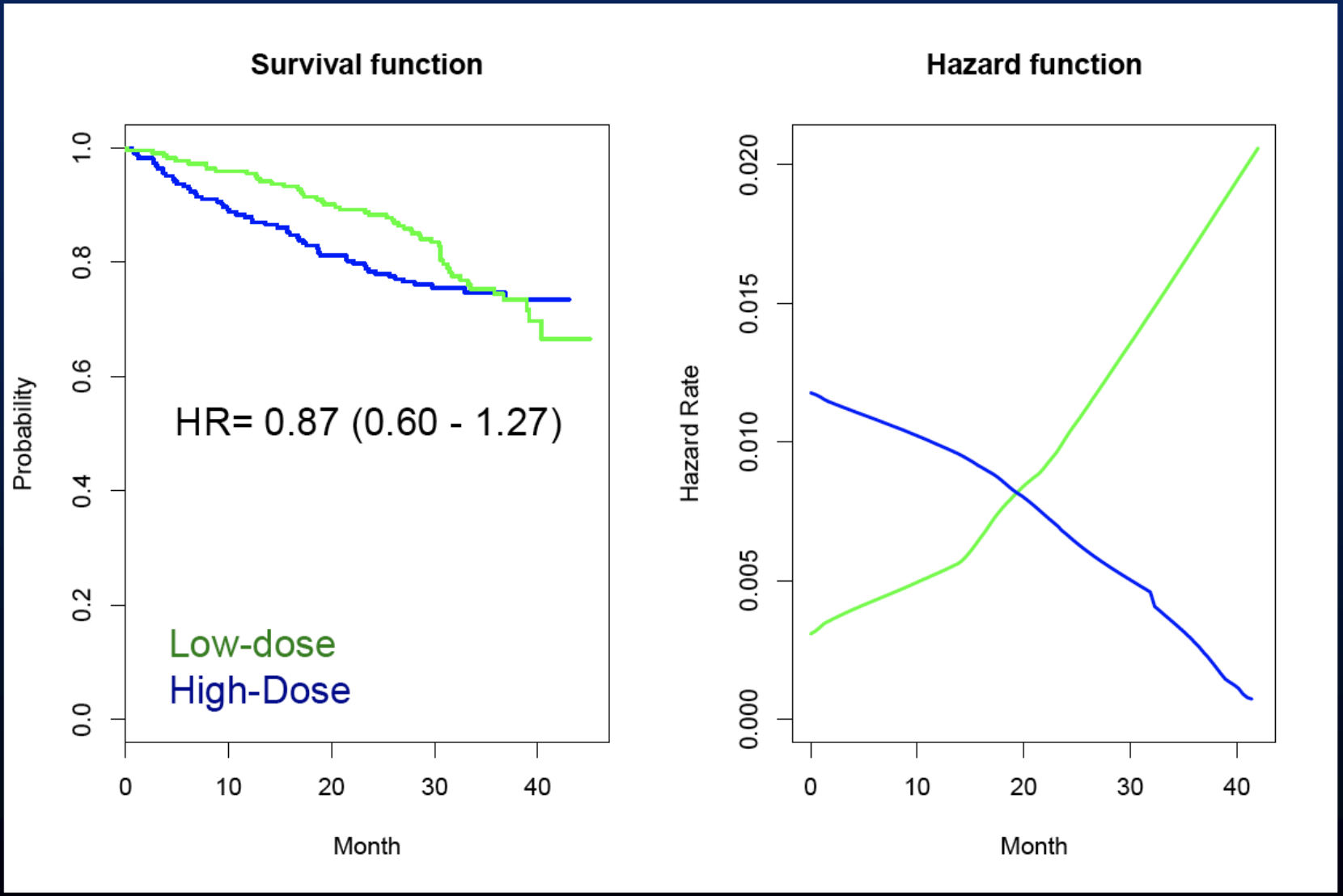
Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

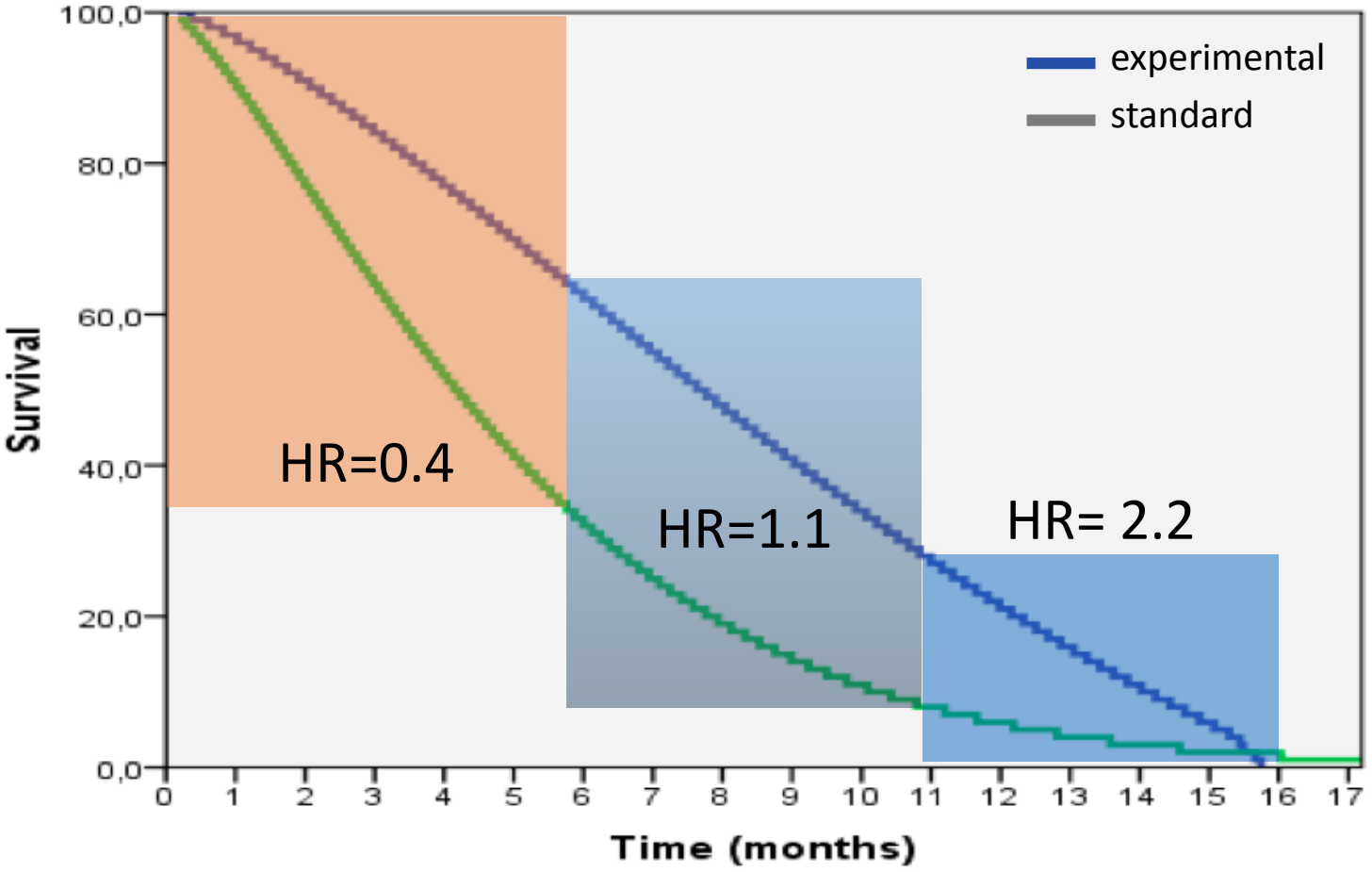
N Engl J Med 2015;373:1803-13



How hazard functions looked like?



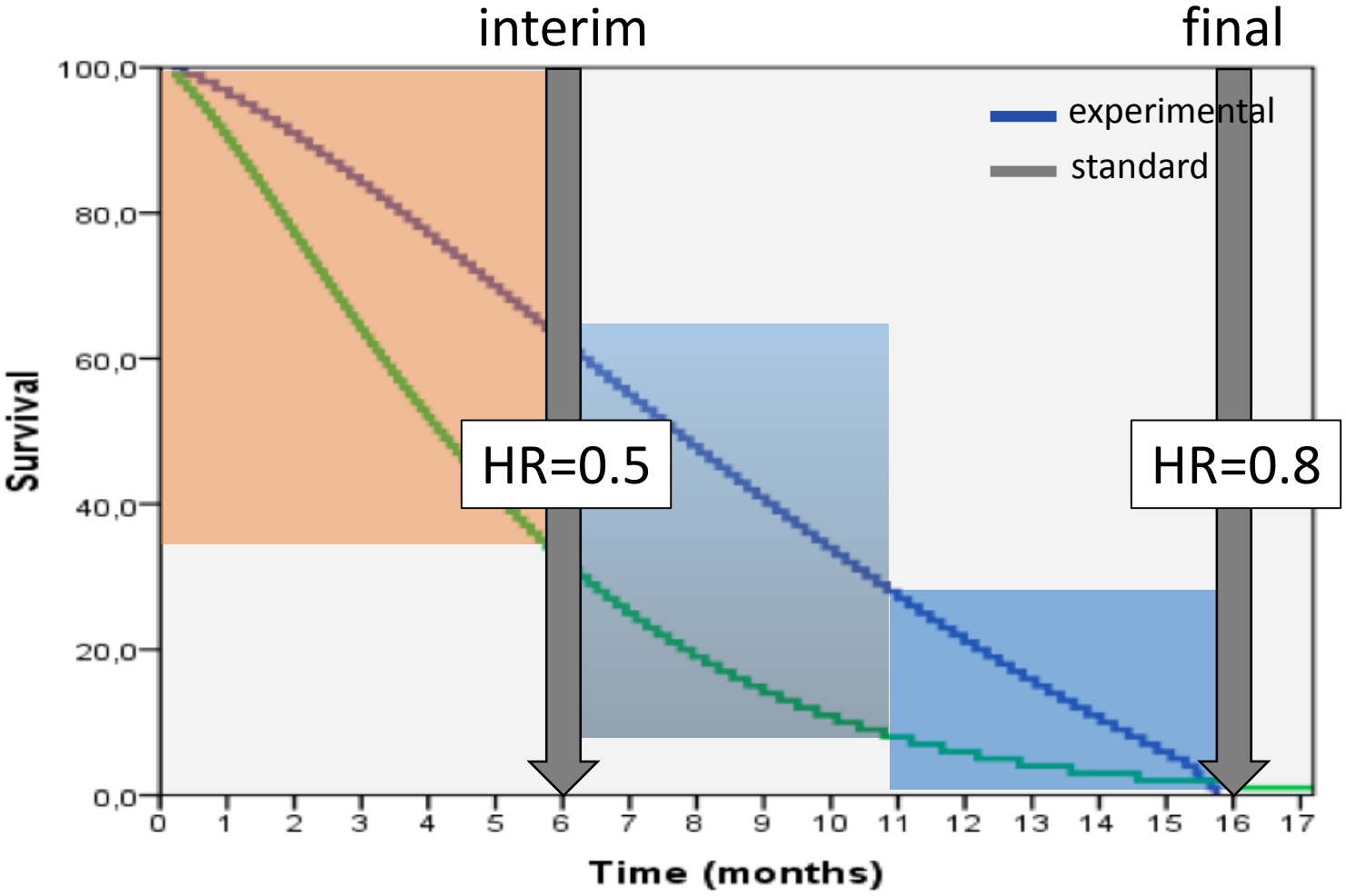
Rapporto tra gli *hazard* dei due gruppi non costante nel tempo – non (pochi) lungo-sopravviventi



Hazard Ratio "globale" =

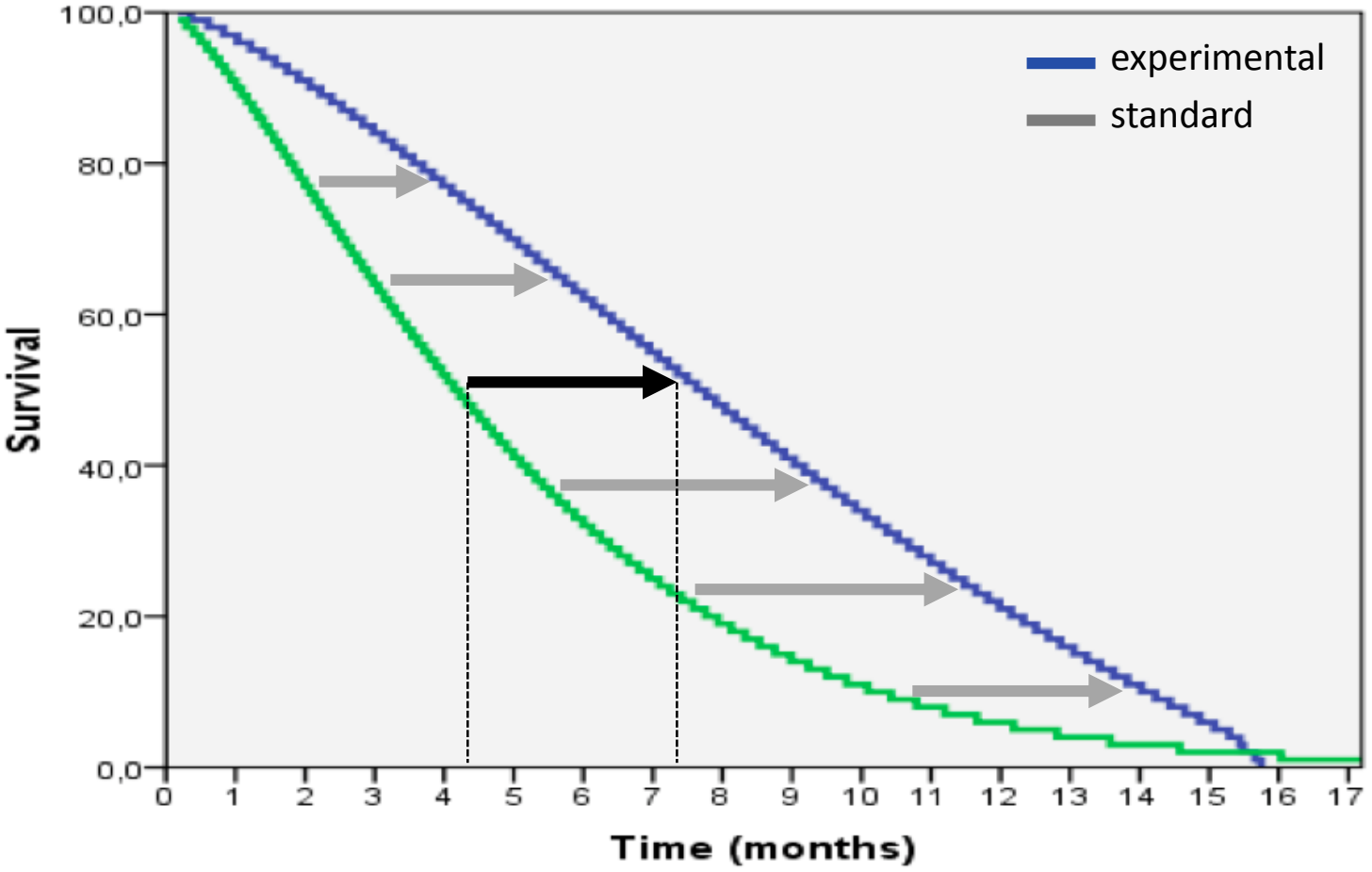
media *pesata* degli HR 'tempo-specifici' (*pesi* = eventi)

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 – non (pochi) lungo-sopravviventi

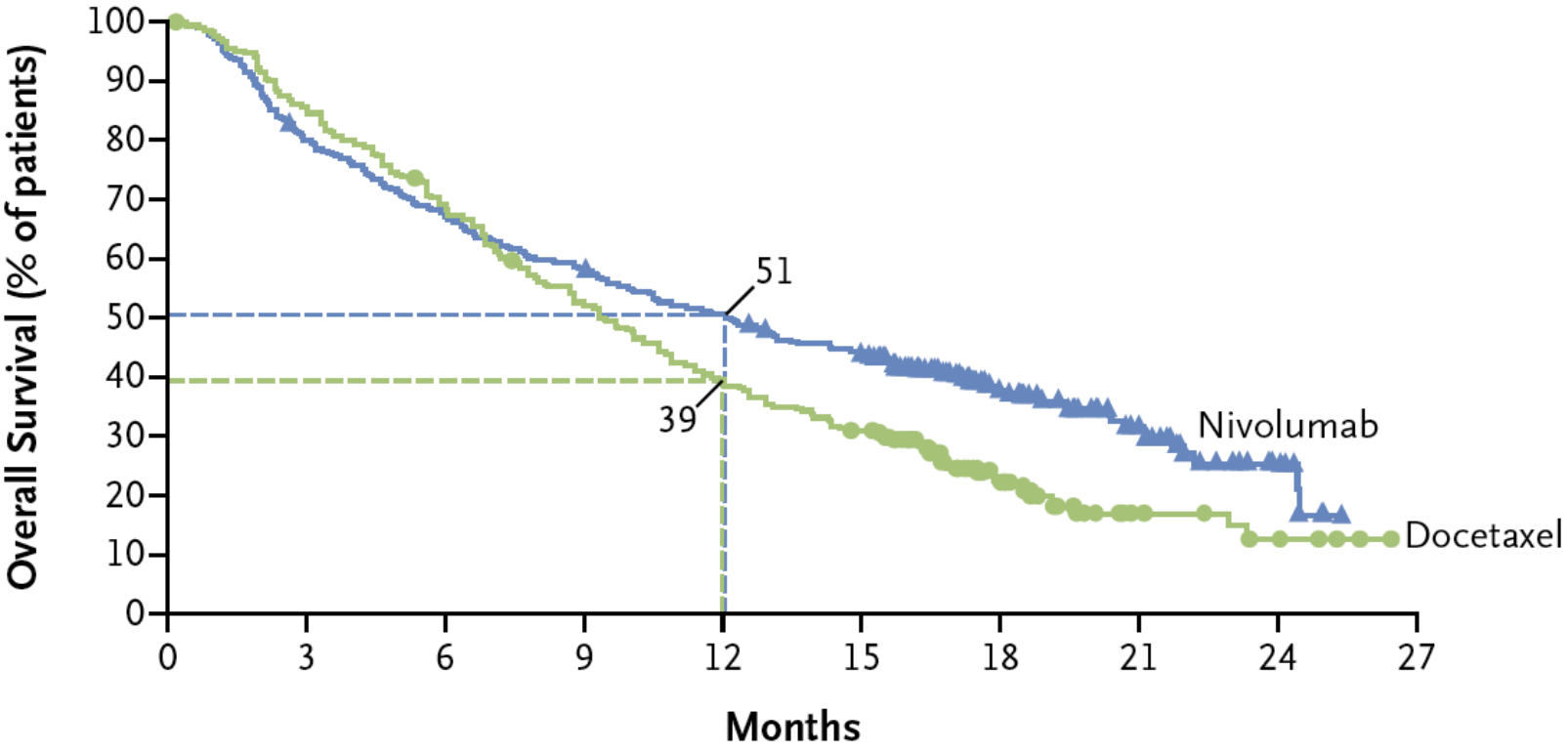


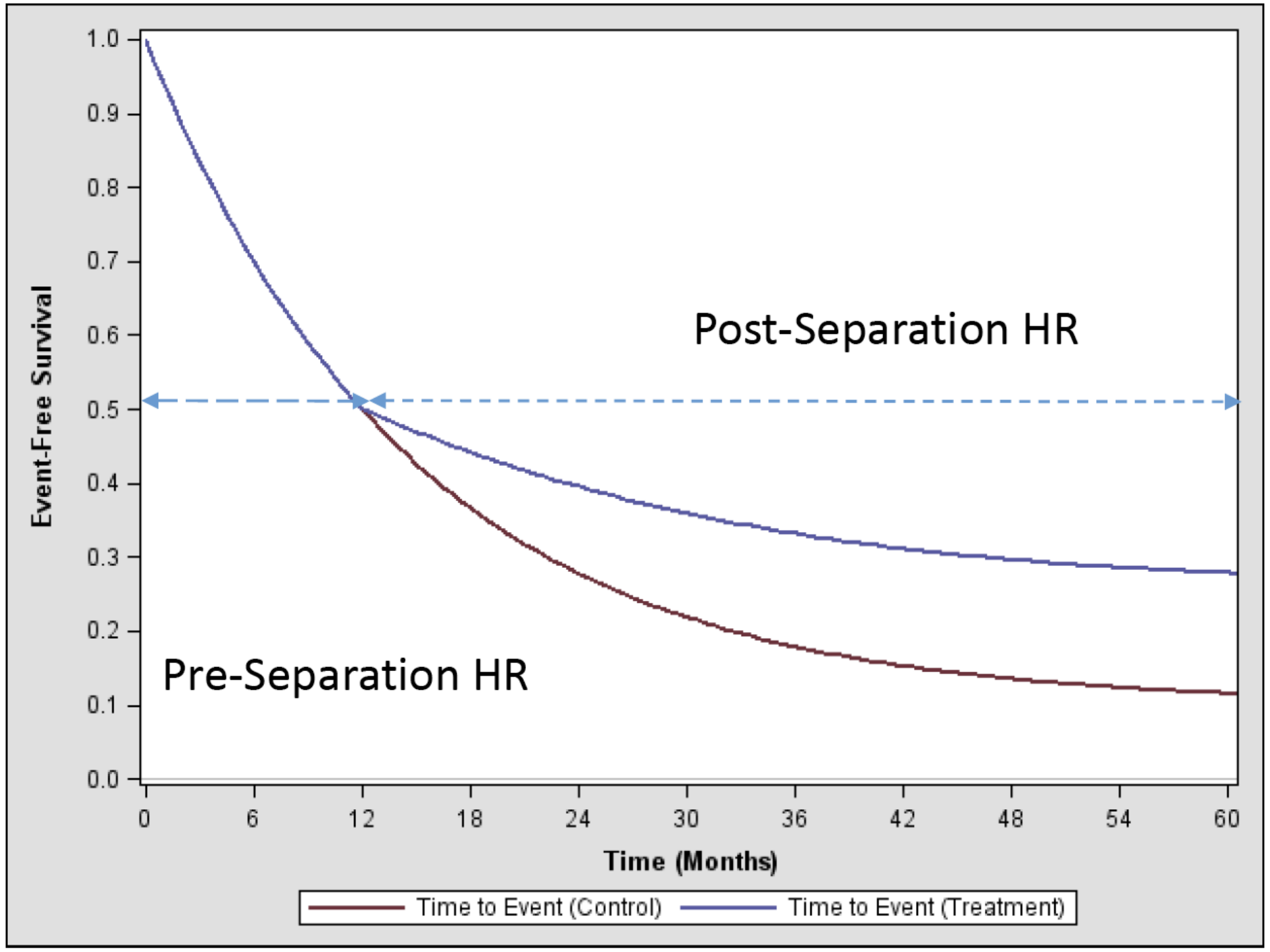
Differenza tra mediane: spesso interpretata come beneficio medio per ogni paziente (di solito questo è minore del 20-30%)

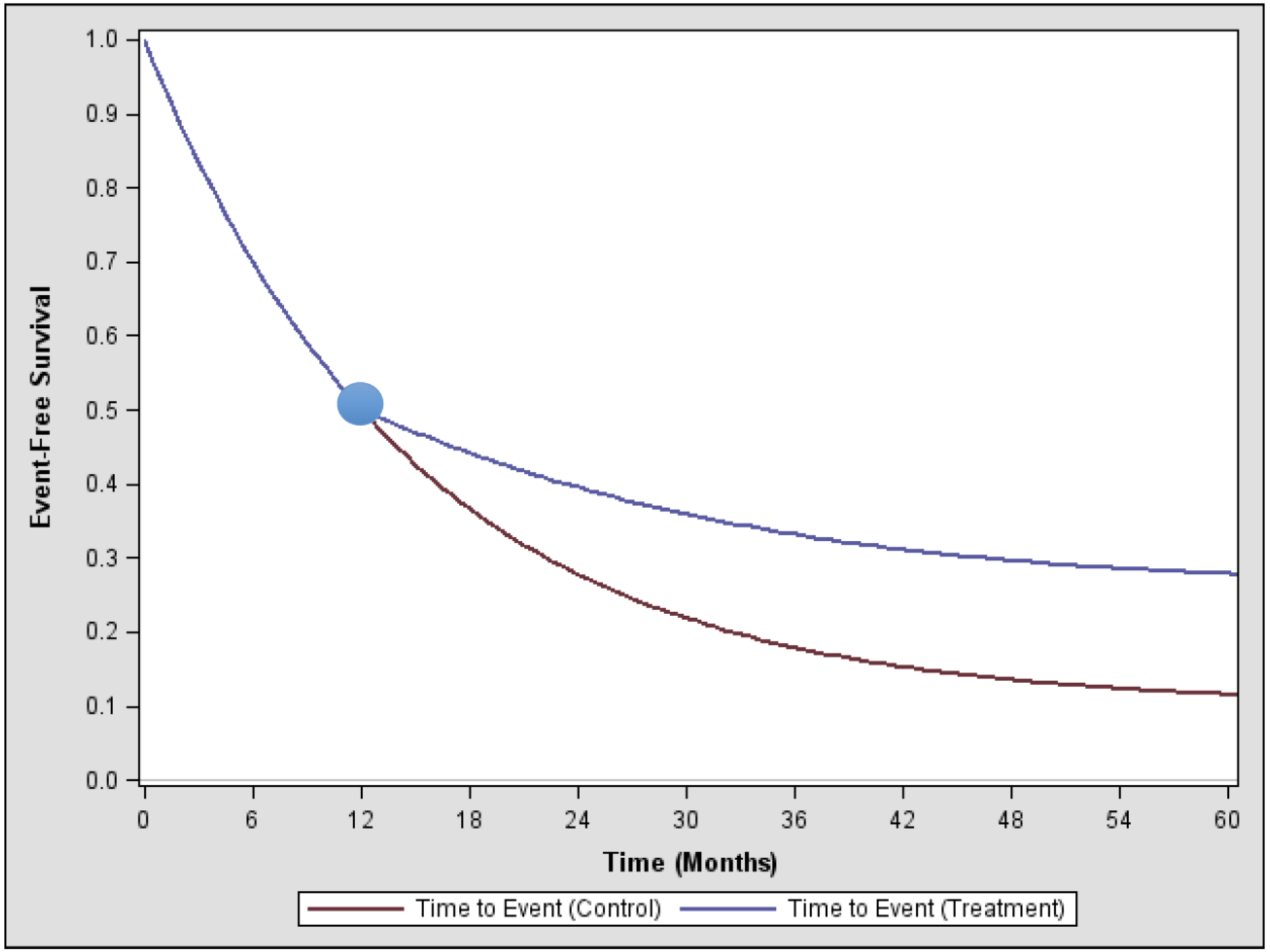
Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, and J.R. Brahmer

N Engl J Med 2015;373:1627-39




Event-Free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Post-Separation HR
Pre-Separation HR
0
6
12
18
24
30
36
42
48
54
60
Time (Months)
Time to Event (Control)
Time to Event (Treatment)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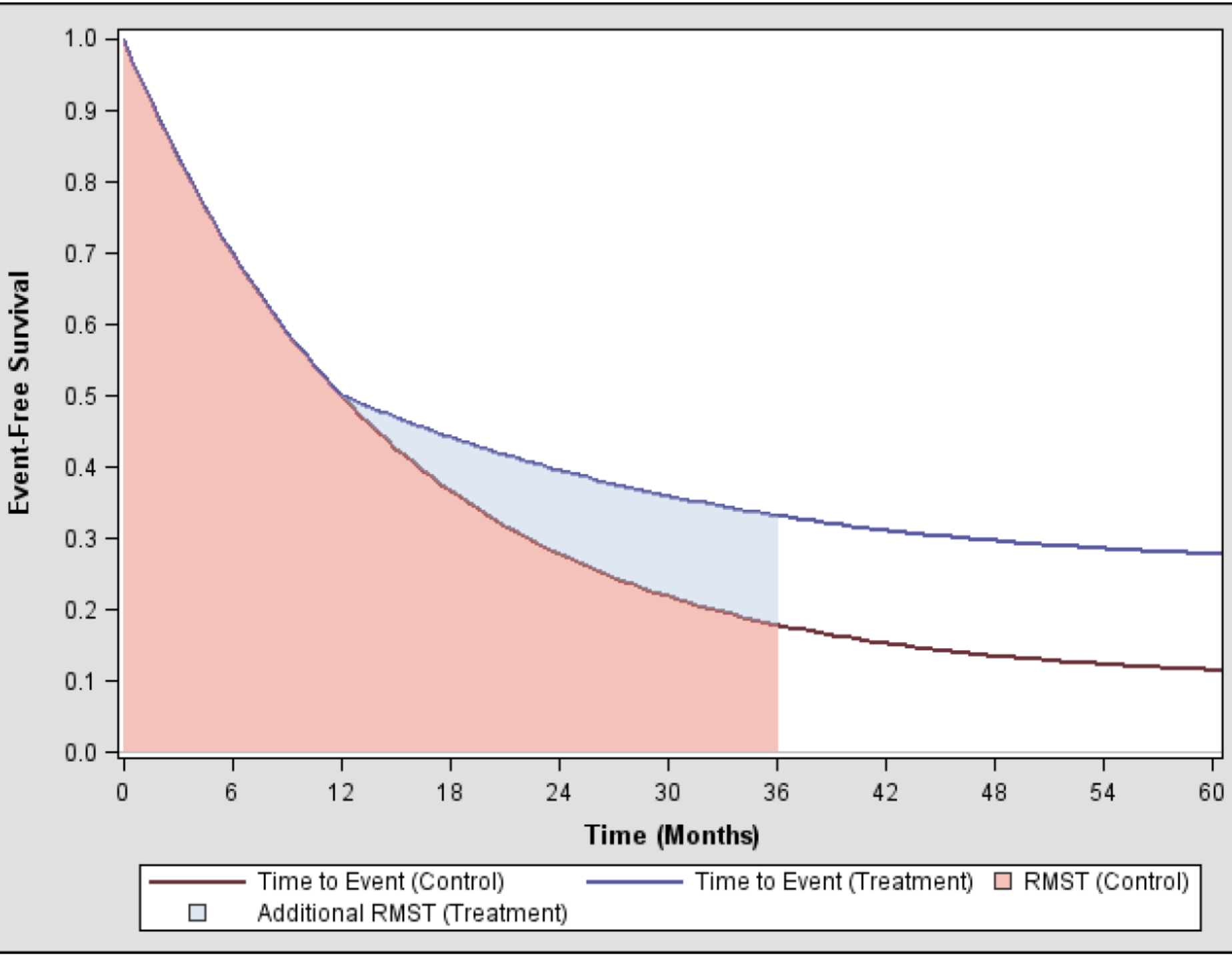
Time (Months)
Time to Event (Control)
Time to Event (Treatment)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6
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18
24
30
36
42
48
54
60
Time (Months)
Time to Event (Control)
Time to Event (Treatment)
RMST (Control)
Additional RMST (Treatment)

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

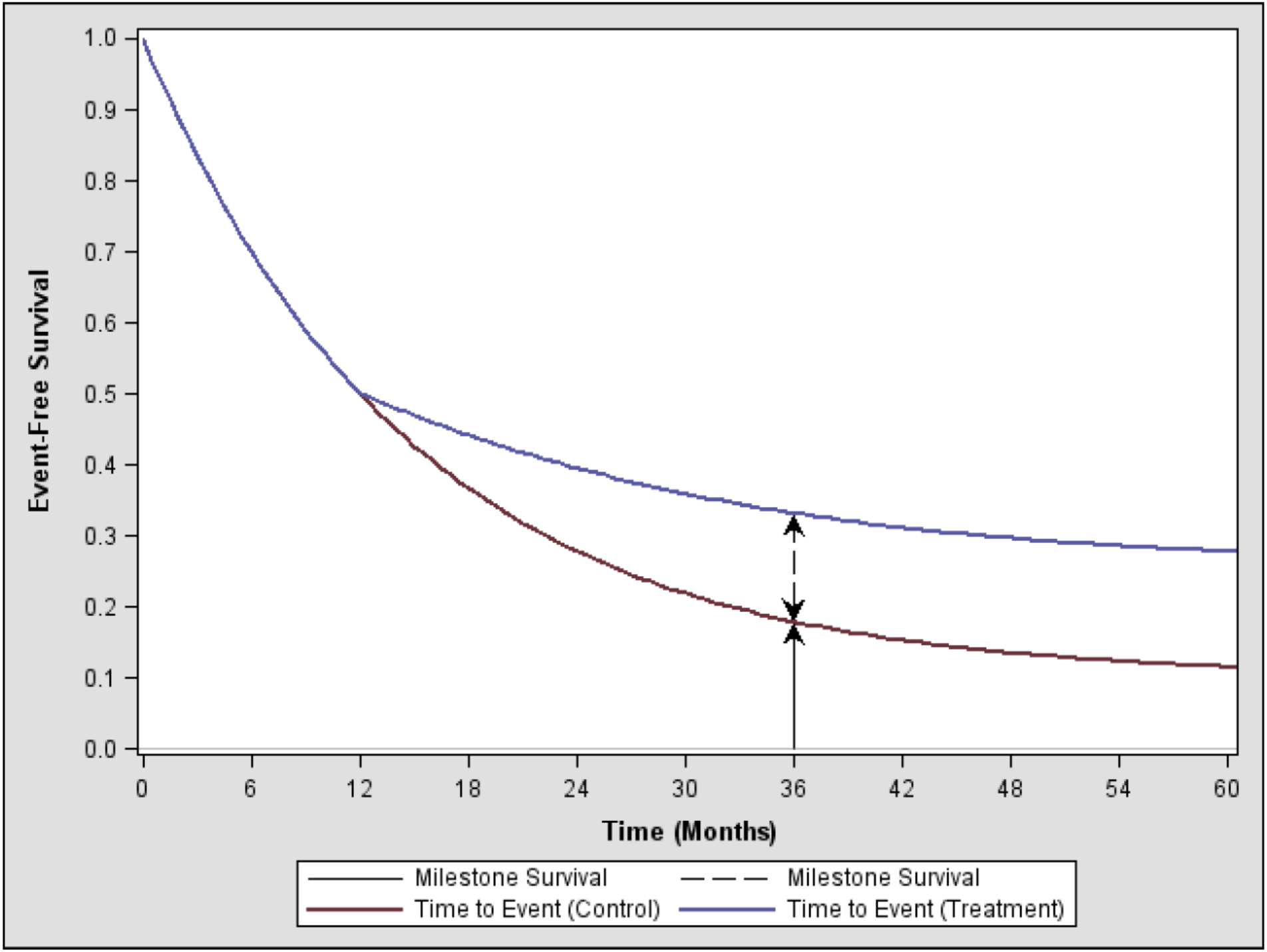
Patrick Royston* and Mahesh KB Parmar

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.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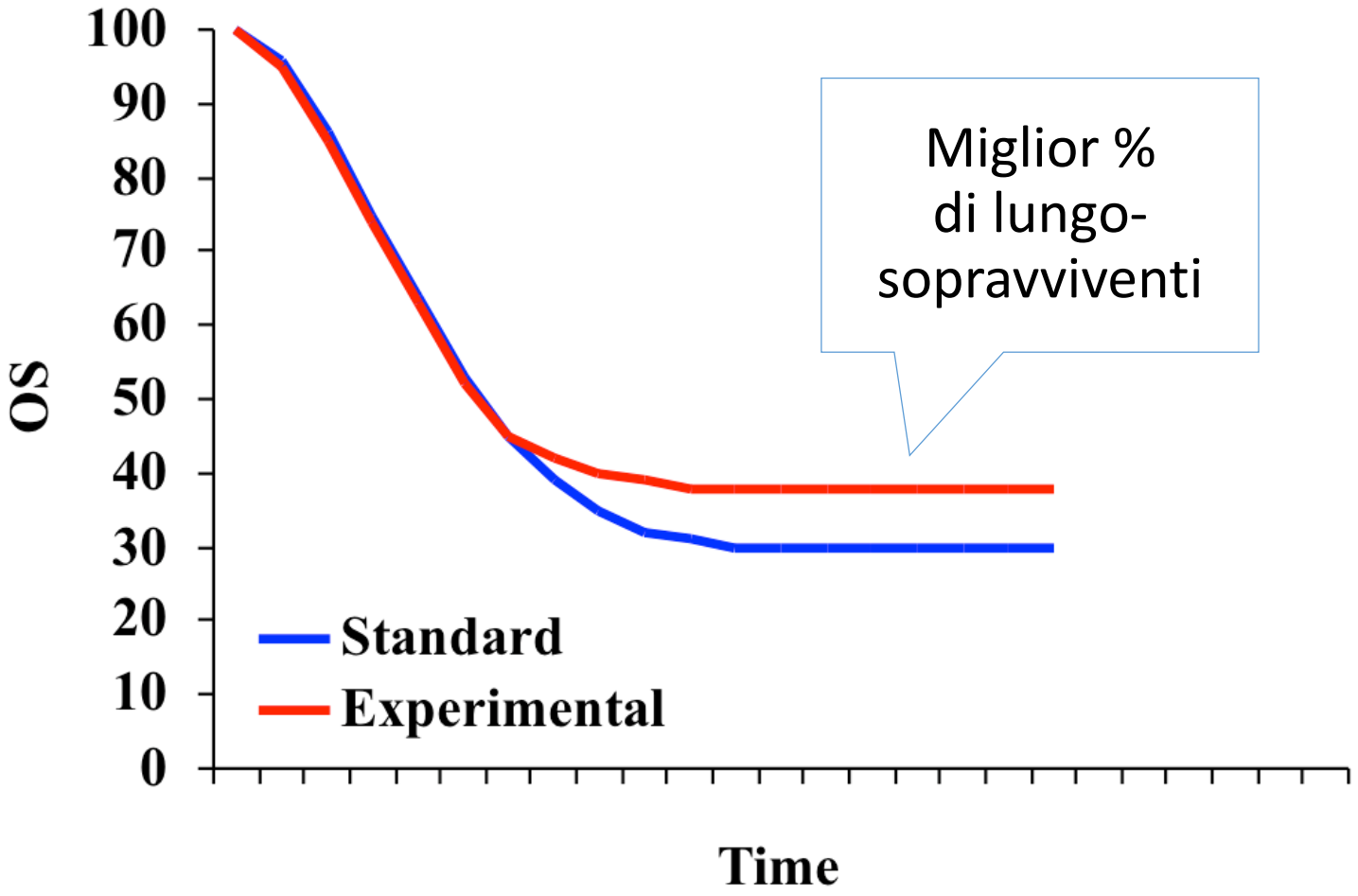
Time (Months)
Milestone Survival
Time to Event (Control)
Milestone Survival
Time to Event (Treatment)

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



Hazard Ratio "globale" = 0.9 (NS)

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Caroline Robert, M.D., Ph.D., Luc Thomas, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Steven O'Day, M.D., Jeffrey Weber M.D., Ph.D., Claus Garbe, M.D., Celeste Lebbe, M.D., Ph.D., Jean-François Baurain, M.D., Ph.D., Alessandro Testori, M.D., Jean-Jacques Grob, M.D., Neville Davidson, M.D., Jon Richards, M.D., Ph.D., Michele Maio, M.D., Ph.D., Axel Hauschild, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Pere Gascon, M.D., Ph.D., Michal Lotem, M.D., Kaan Harmankaya, M.D., Ramy Ibrahim, M.D., Stephen Francis, M.Sc., Tai-Tsang Chen, Ph.D., Rachel Humphrey, M.D., Axel Hoos, M.D., Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

N ENGL J MED 364;26 JUNE 30, 2011