Criteri di valutazione negli studi clinici di immunoterapia

Giovanni L. Pappagallo

Attività

Efficacia

Tollerabilità

Criteri di valutazione negli studi clinici di immunoterapia

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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 200

I Criteri di Risposta Immunocorrelati
(Giuseppe Lorusso)
Oggi, ore 12.15

Table 1. Comparison between WHO criteria and the irRC

	WHO	
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	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

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Immune-related adverse events with immune checkpoint blockade: a comprehensive review

J.M. Michot [a,b,c,*,1], C. Bigenwald [a,1], S. Champiat [b], M. Collins [d,e], F. Carbonnel [d,e], S. Postel-Vinay [b], A. Berdelou [a], A. Varga [b], R. Bahleda [b], A. Hollebecque [b], C. Massard [b], A. Fuerea [a,b], V. Ribrag [a,b], A. Gazzah [b], J.P. Armand [b], N. Amellal [b], E. Angevin [b], N. Noel [c,e,f,g], C. Boutros [a,b,c], C. Mateus [a,b,c], C. Robert [a,b,c], J.C. Soria [b], A. Marabelle [b], O. Lambotte [c,e,f,g]

European Journal of Cancer 54 (2016) 139–148

Severity CTCAE grade	Type of patient care	Steroids	Other immunosuppressive drugs	Immunotherapy and subsequent approach
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids or systemic steroids oral 0.5–1 mg/kg/d	Not recommended	Suspend** temporarily
3	Hospitalisation	Systemic steroids oral or IV 1–2 mg/kg/d for 3 d then reduce to 1 mg/kg/d	To be considered for patients with unresolved symptoms after 3–5 d of steroid course Organ specialist advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalisation consider the intensive care unit	Systemic steroids IV methylprednisolone 1–2 mg/kg/d for 3 d and then reduce to 1 mg/kg/d	To be considered for patients with unresolved symptoms after 3–5 d of steroid course Organ specialist advised	Discontinue permanently

** Outside skin or endocrine disorders, where immunotherapy can be maintained.

The overall management approach and actions to be implemented for IRAEs associated with immune checkpoint blockade, according to the Common Terminology Criteria for Adverse Events (CTCAE) severity grade

Current Diagnosis and Management of Immune Related Adverse Events (irAEs) Induced by Immune Checkpoint Inhibitor Therapy

*Vivek Kumar[1], Neha Chaudhary[2], Mohit Garg[1], and Abhinav B. Chandra[3]**

Frontiers in Pharmacology | www.frontiersin.org

Grading of irAEs may be cha trary distinctions between grade 2 and 3 t nber of stools in a day, may be affecte recall bias. Thus, this system of grading may not be entirely suitable to grade ICIs toxicities.

Therefore, it is prudent to use clinical judgment rather than strictly adhering to the guidelines. We have outlined several general principles that should be followed irrespective of affected organs.

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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)

Indicatori riassuntivi di effetto di variabili tempo-a-evento

- Differenza tra stime della mediana di sopravvivenza (KM)
- D… …za (*restricted* …
- D… …enza (KM) al tempo … *…nestone* Survival)
- **Hazard Ratio** (KM+Cox)

Rapporto tra *hazard rate* dei trattamenti a confronto

Hazard Rate = **probabilità di evento nell'unità di tempo considerata**

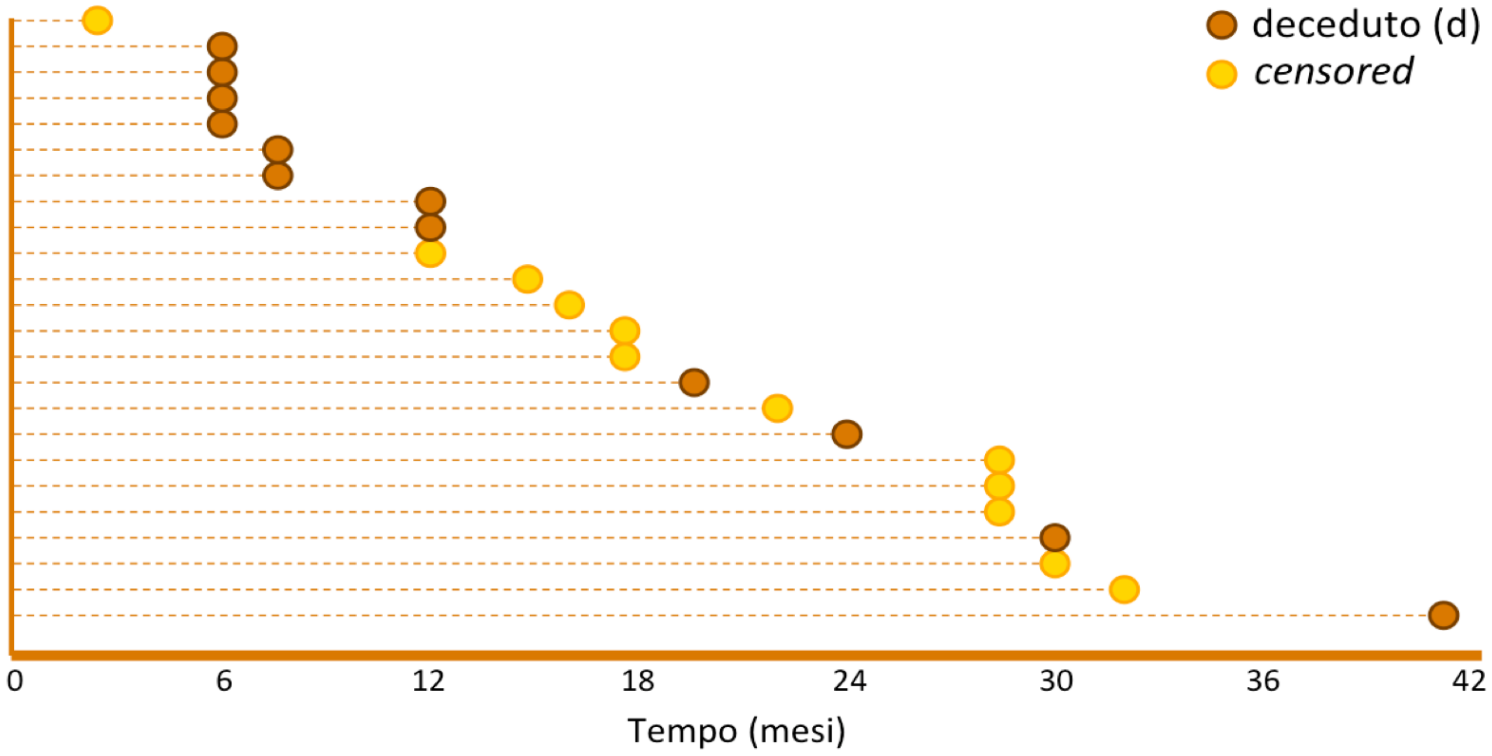
$$\lambda = \frac{d}{f + F}$$

dove:

d = numero di eventi

f = somma della lunghezza dei follow-up nei pazienti con l'evento

F = somma della lunghezza dei follow-up nei pazienti censored



d = 12

f = 6+6+6+6+8+8+12+12+20+24+30+42 = 180

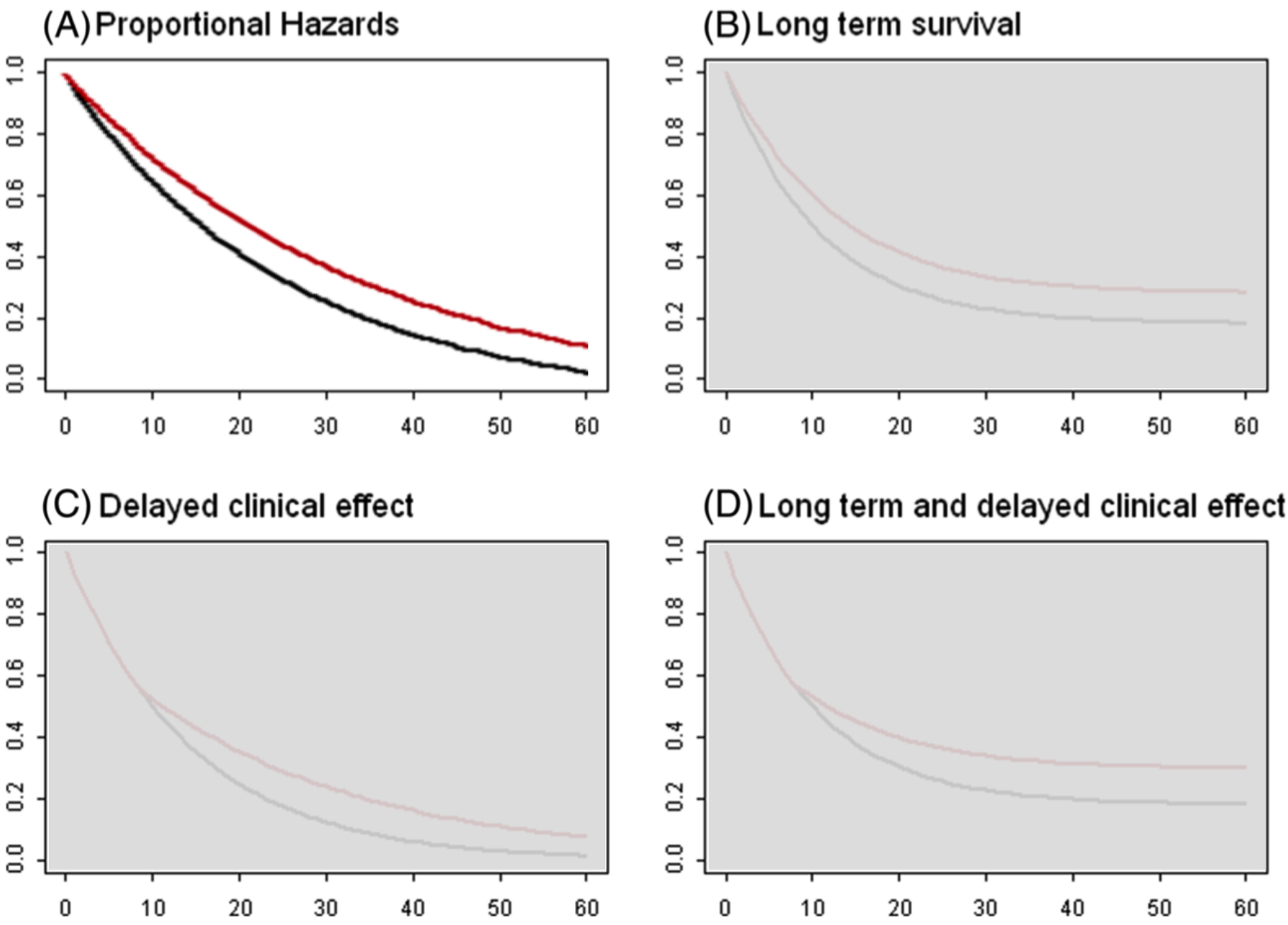
F = 3+12+15+16+18+18+22+28+28+28+30+33 = 251

$$\lambda = \frac{12}{431} = 0.0278$$

Indicatori riassuntivi di effetto di variabili tempo-a-evento

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

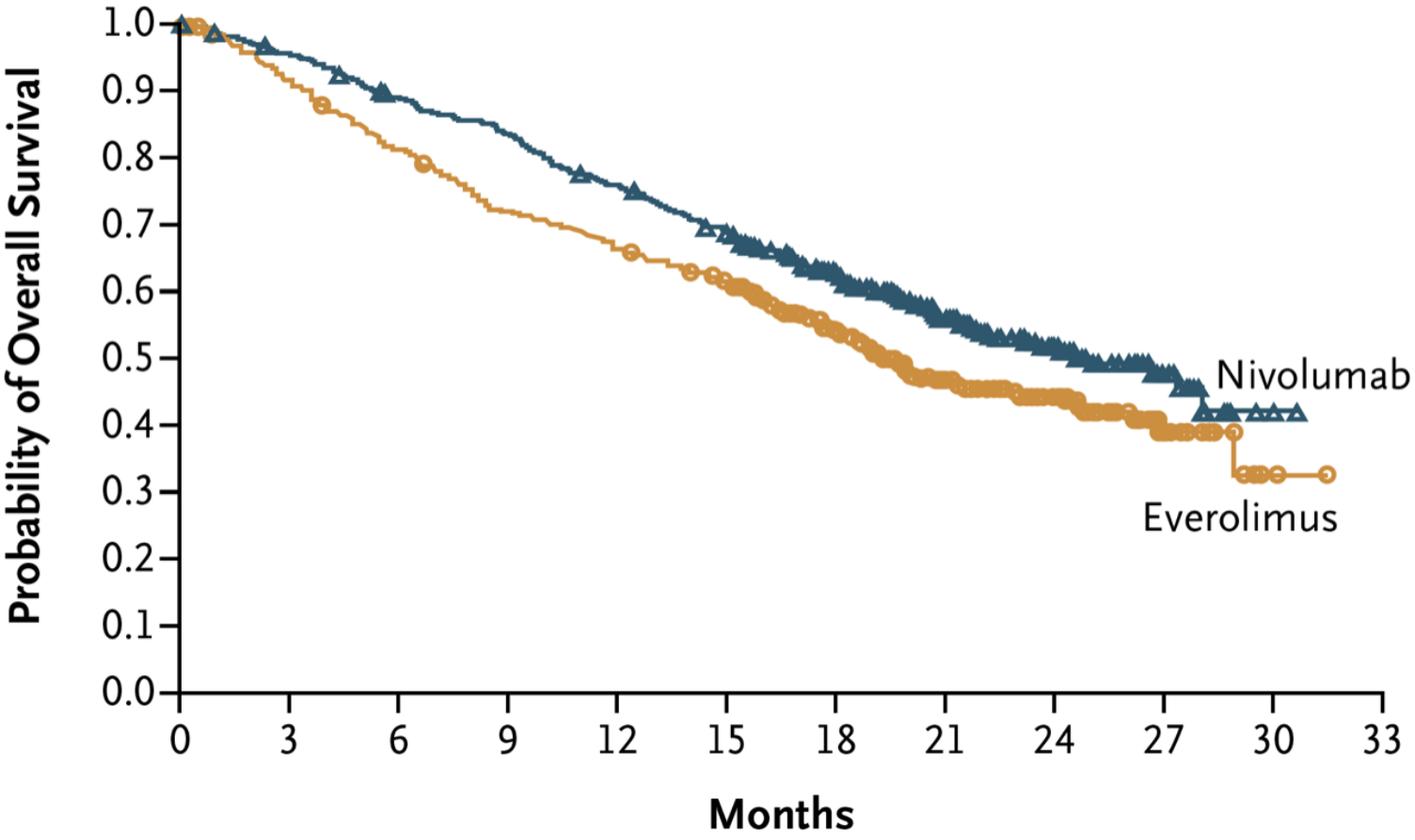
Appropriato quando il rapporto tra gli *hazard* dei due gruppi si mantiene (relativamente) costante

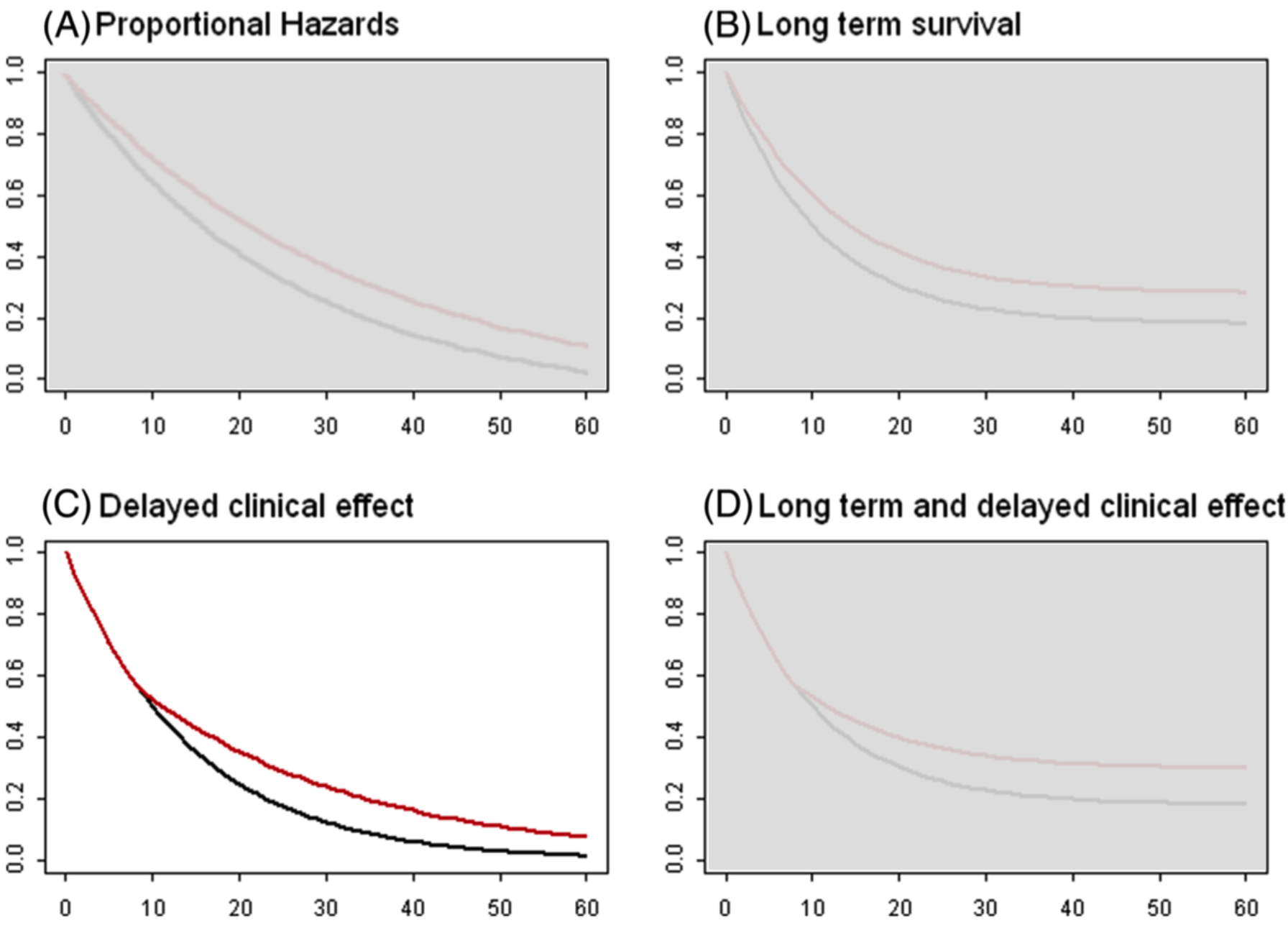

(A) Proportional Hazards
(B) Long term survival
(C) Delayed clinical effect
(D) Long term and delayed clinical effect
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
60

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




(A) Proportional Hazards
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0.0
0.2
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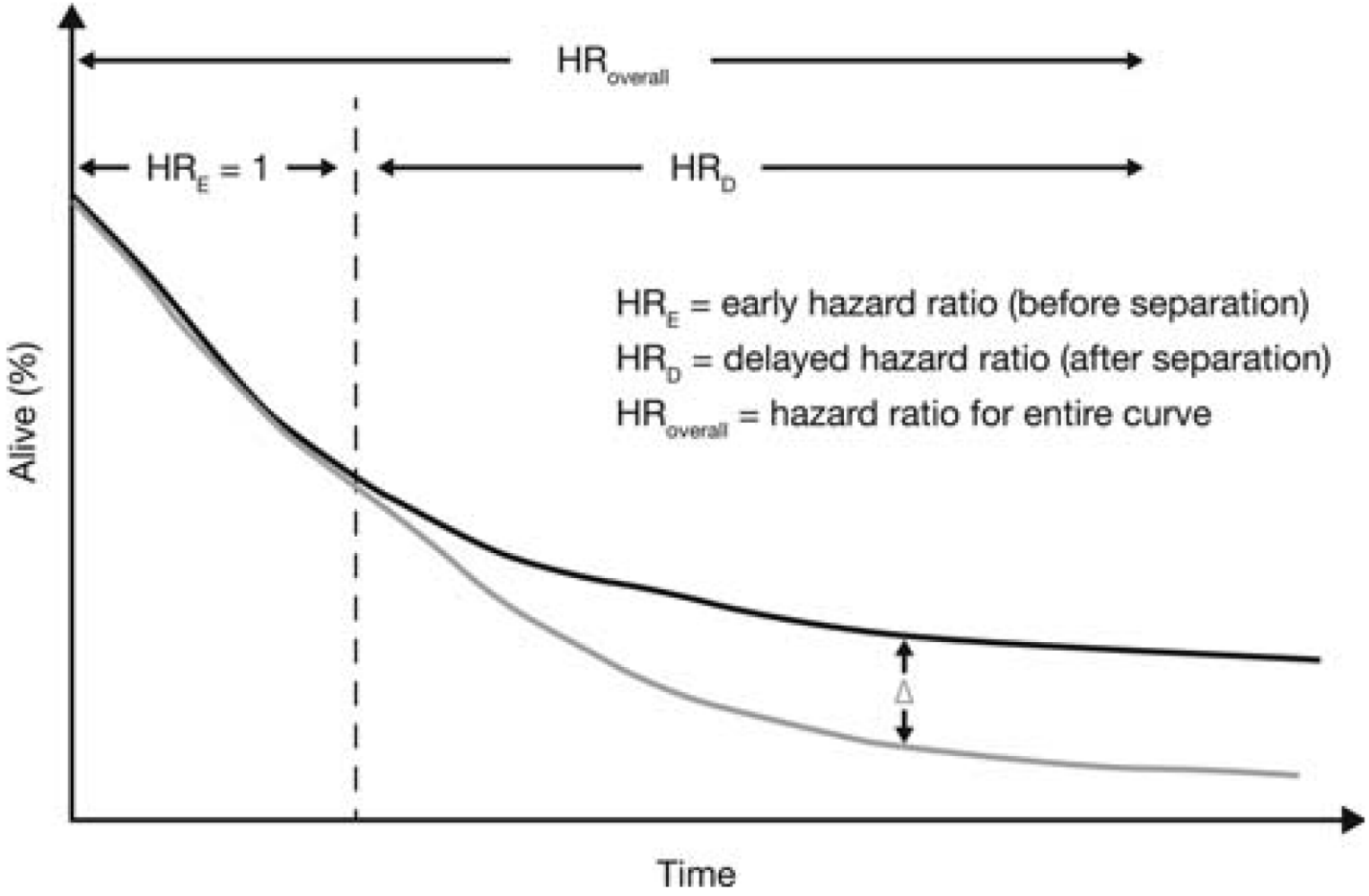
10
20
30
40
50
60

Evolution of end points for cancer immunotherapy trials

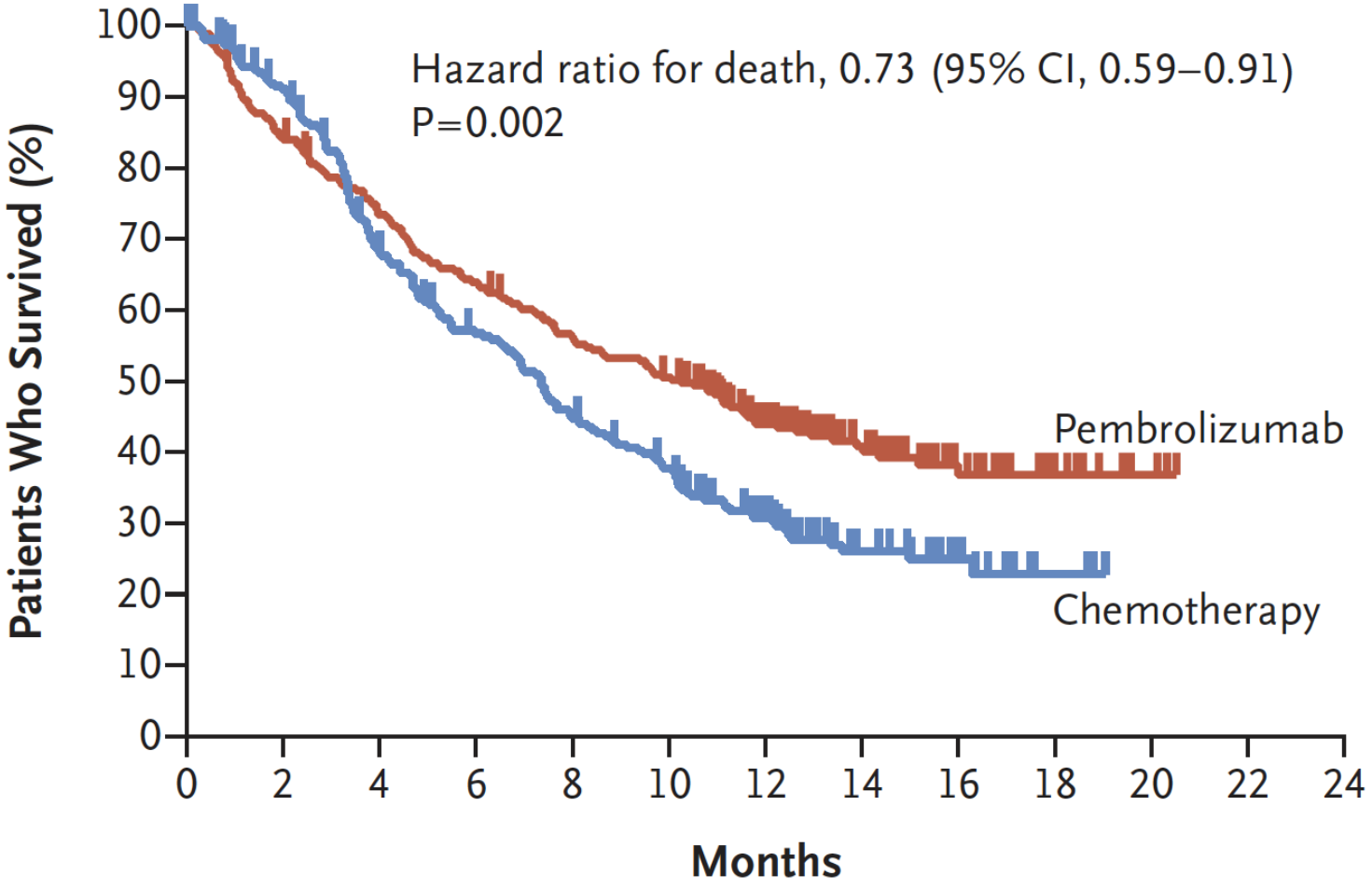
A. Hoos*

Annals of Oncology 23 (Supplement 8): viii47–viii52, 2012



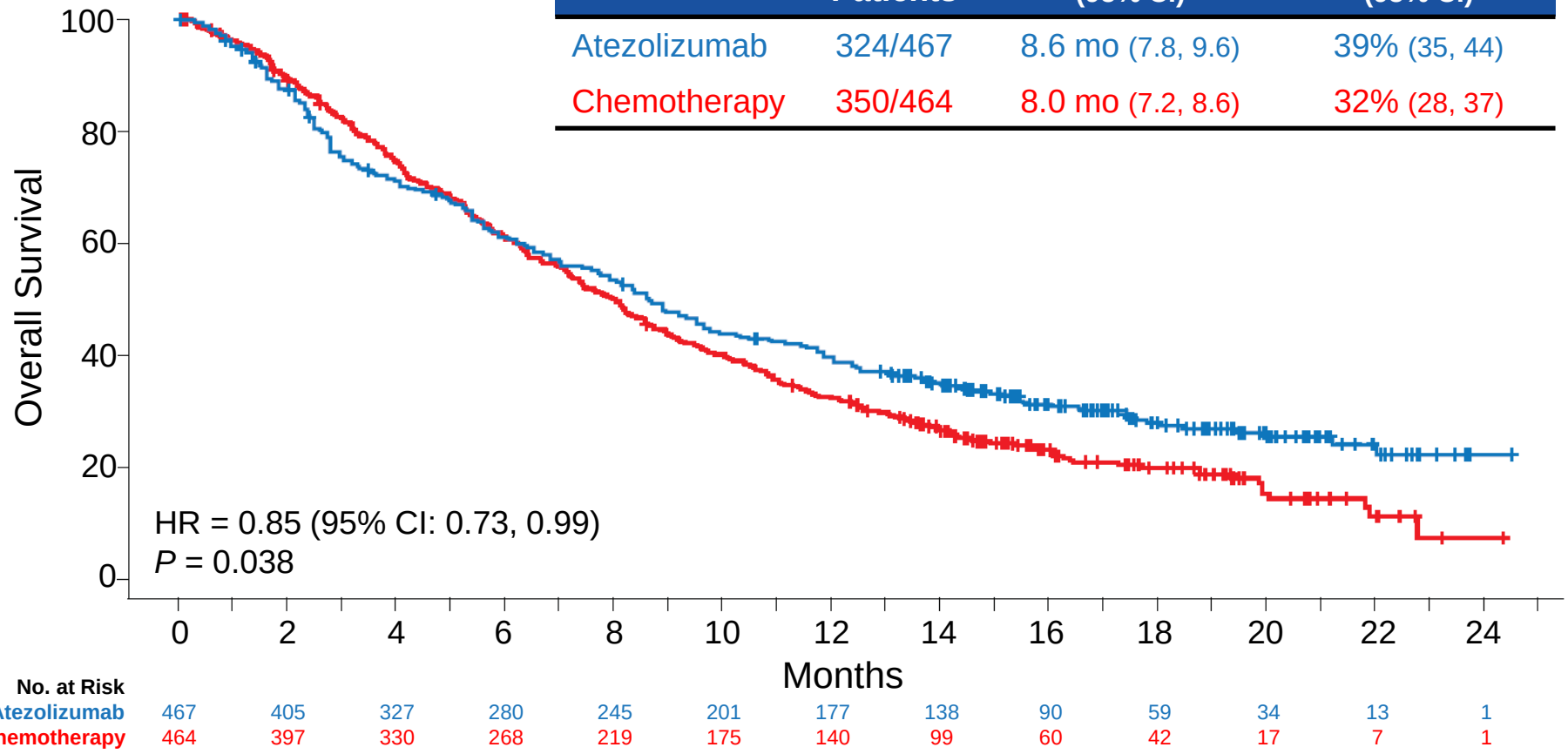
Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

J. Bellmunt, R. de Wit, D.J. Vaughn, Y. Fradet, J.-L. Lee, L. Fong, N.J. Vogelzang, M.A. Climent, D.P. Petrylak, T.K. Choueiri, A. Necchi, W. Gerritsen, H. Gurney, D.I. Quinn, S. Culine, C.N. Sternberg, Y. Mai, C.H. Poehlein, R.F. Perini, and D.F. Bajorin, for the KEYNOTE-045 Investigators*



OS Analysis: ITT Population

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	324/467	8.6 mo (7.8, 9.6)	39% (35, 44)
Chemotherapy	350/464	8.0 mo (7.2, 8.6)	32% (28, 37)



- Median follow-up duration in ITT population: 17.3 mo (range, 0 to 24.5 mo)

Powles T, et al. EAS 2017, IMvigor211.

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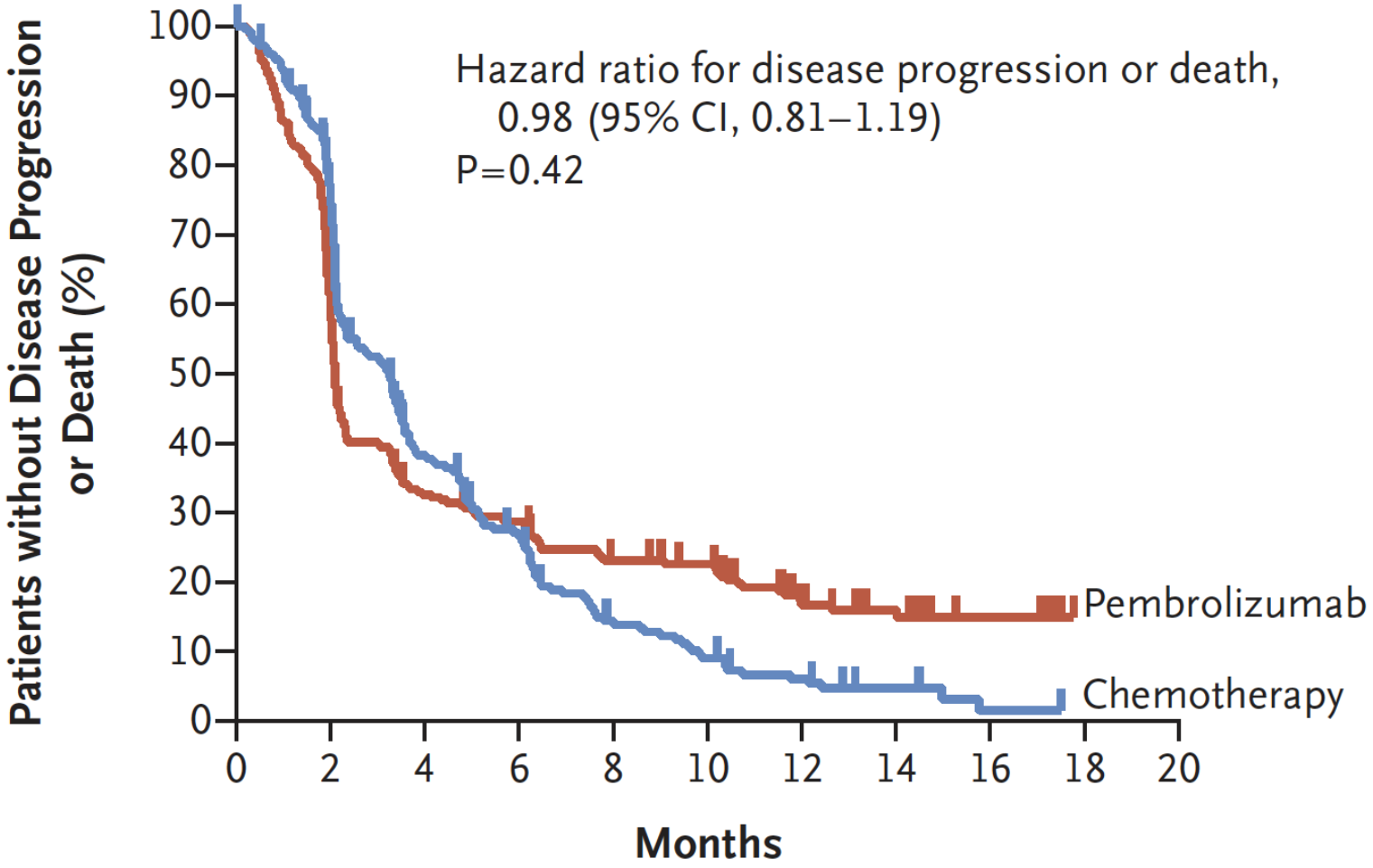

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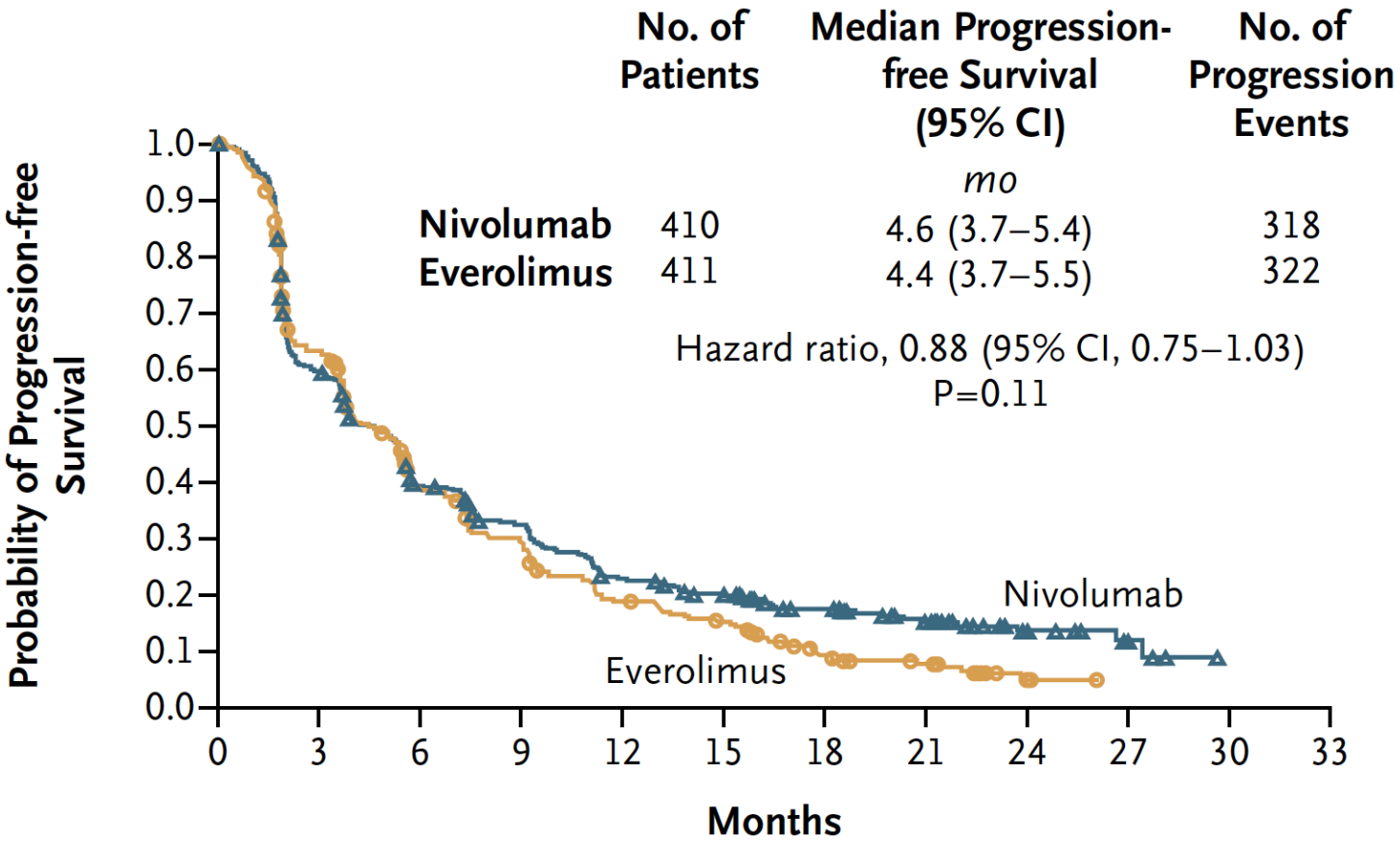

Indicatori riassuntivi di effetto di variabili tempo-a-evento

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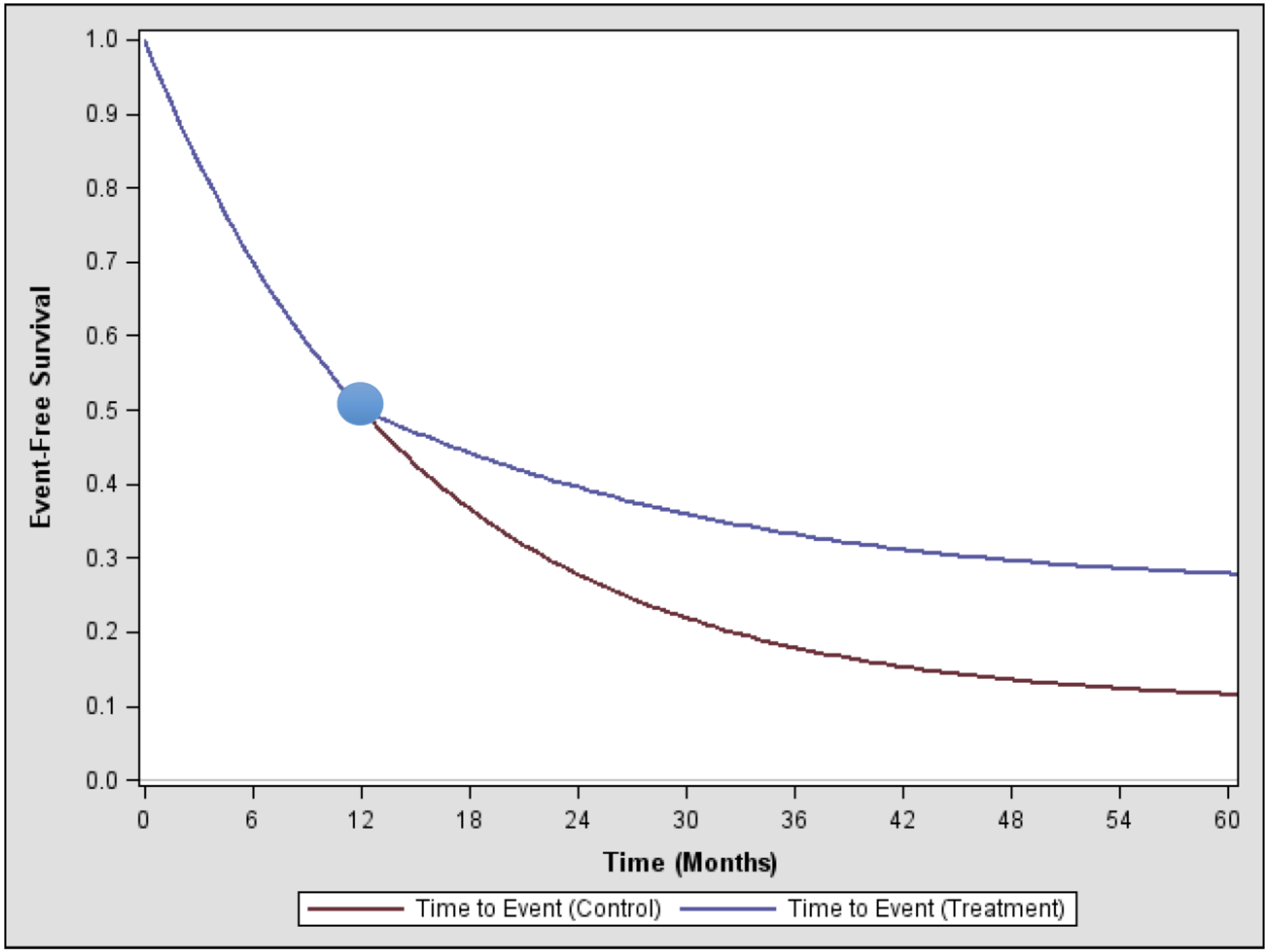

Event-Free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
6
12
18
24
30
36
42
48
54
60
Time (Months)
Time to Event (Control)
Time to Event (Treatment)

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)

MRC Clinical Trials Unit

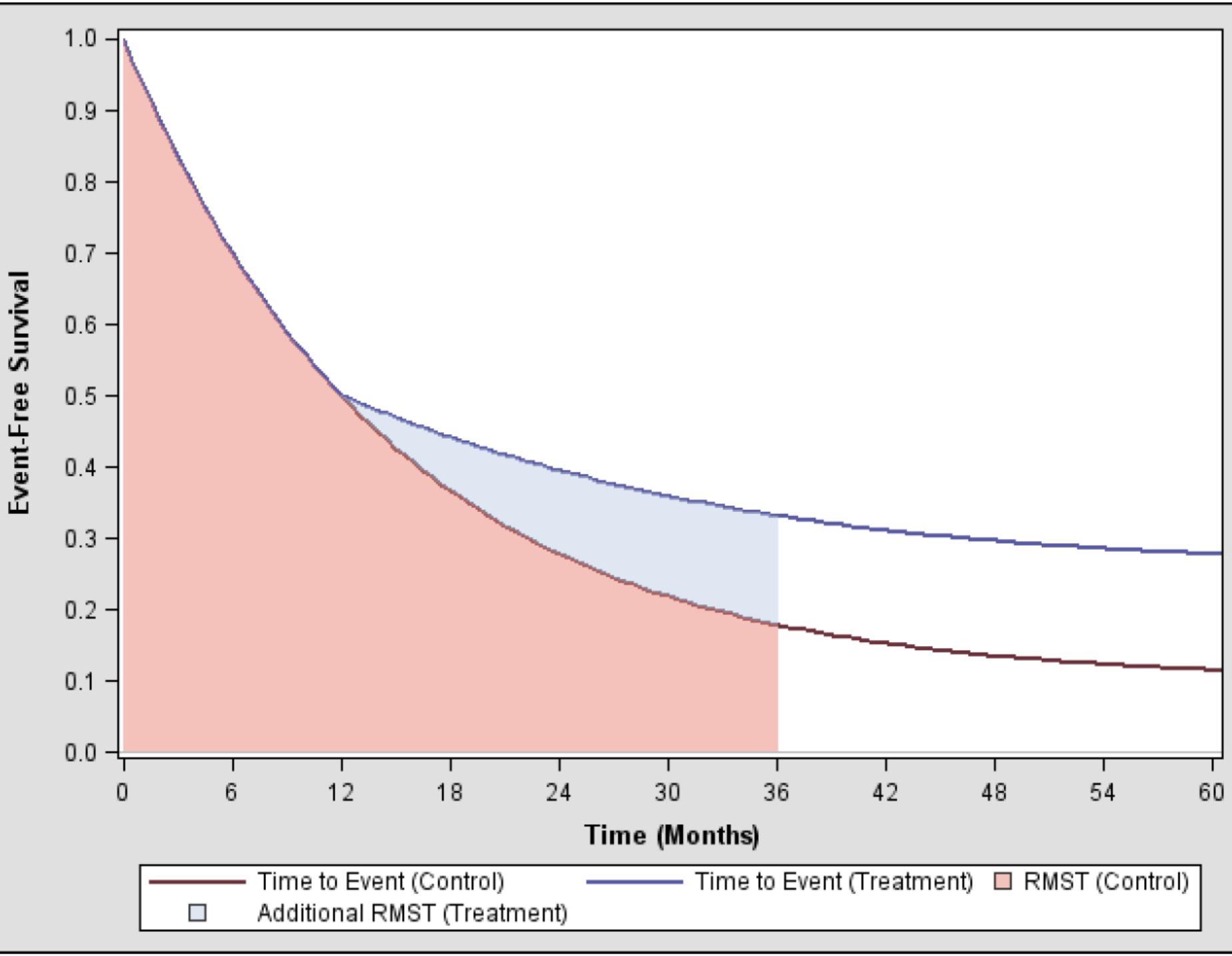
Restricted mean survival time

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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0.5
0.4
0.3
0.2
0.1
0.0
0
6
12
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.

Statistical issues and challenges in immuno-oncology

Tai-Tsang Chen[1,2]

Journal for ImmunoTherapy of Cancer 2013, **1**:18

When designing randomized clinical studies with immunotherapies, the simulation study indicated that the conventional study design with exponential assumption could lead to an underestimation of either statistical power or study duration in the presence of delayed clinical effect or long term survival.

The necessity and timing of superiority or futility interim analysis also required careful consideration due to decreasing true positive rate or increasing false negative rate.

Moving Beyond the Hazard Ratio in Quantifying the Between-Group Difference in Survival Analysis

Hajime Uno, Brian Claggett, Lu Tian, Eisuke Inoue, Paul Gallo, Toshio Miyata, Deborah Schrag, Masahiro Takeuchi, Yoshiaki Uyama, Lihui Zhao, Hicham Skali, Scott Solomon, Susanna Jacobus, Michael Hughes, Milton Packer, and Lee-Jen Wei

J Clin Oncol 32:2380-2385. © 2014 by American Society of Clinical Oncology

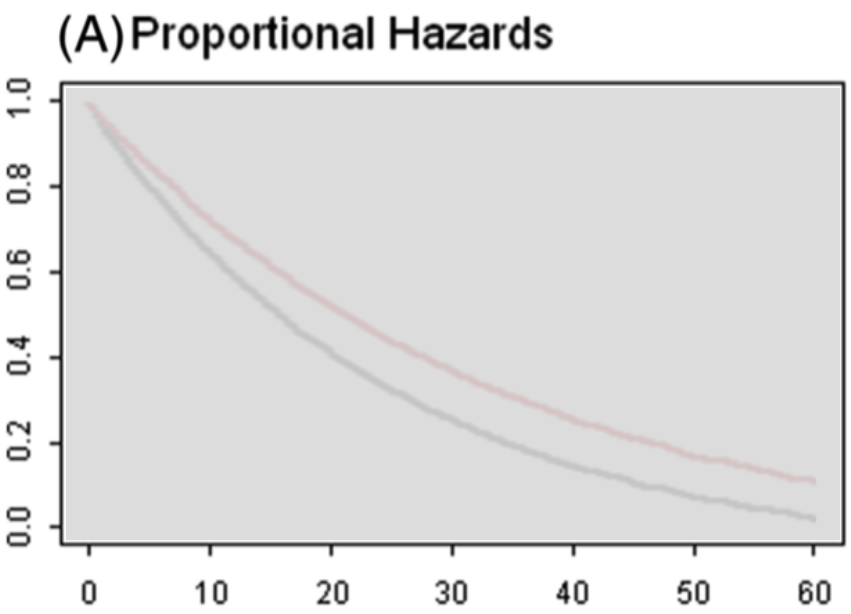
When there is not sufficient information about the profile of the between-group difference at the design stage of the study, we encourage practitioners to consider a prespecified, clinically meaningful, model-free measure for quantifying the difference.
The ratio of the estimated RMSTs would be a clinically meaningful global summary of the group difference.

Some statistical considerations in the clinical development of cancer immunotherapies

Bo Huang

Pharmaceutical Statistics. 2017;1–12.

Weighted log-rank test assigns unequal weights to events, with the choice of weight function being the number of patients at risk, function of time, or a function of the survival distribution.
The benefit of using the weighted log-rank test for late separation by putting more weights on the curve tails is that it will potentially yield higher statistical power.


(A) Proportional Hazards
0.0
0.2
0.4
0.6
0.8
1.0
0
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30
40
50
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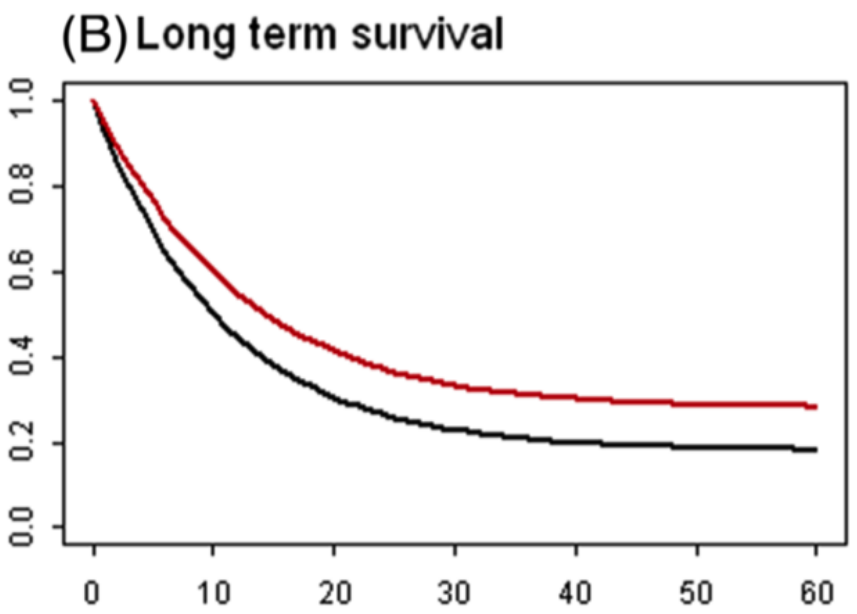
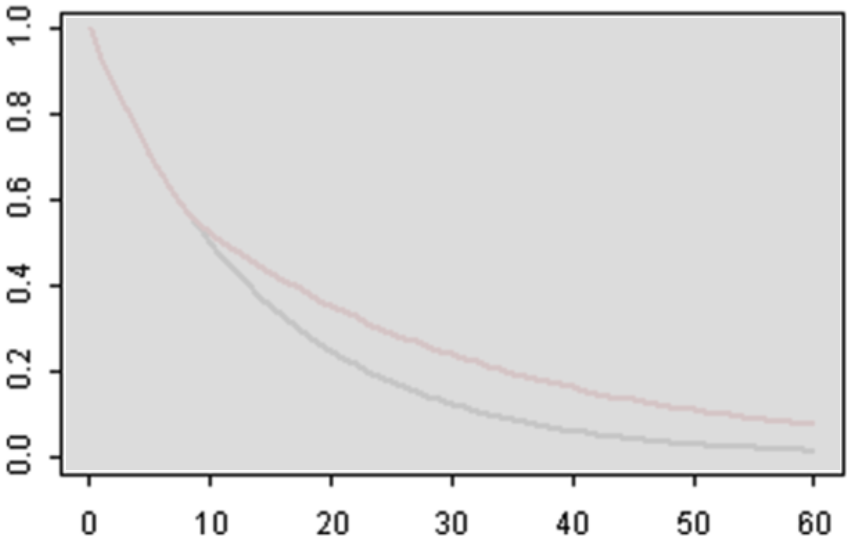
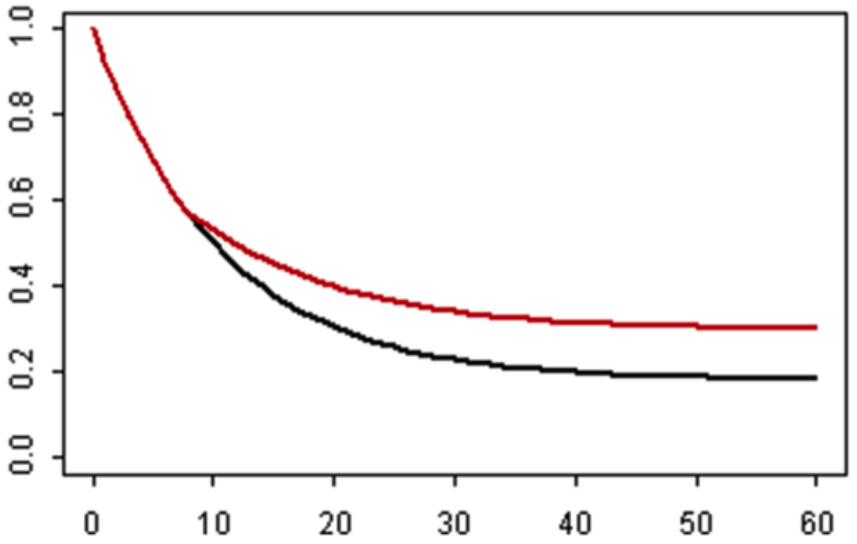

(B) Long term survival
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
60


(C) Delayed clinical effect
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
60


(D) Long term and delayed clinical effect
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
60

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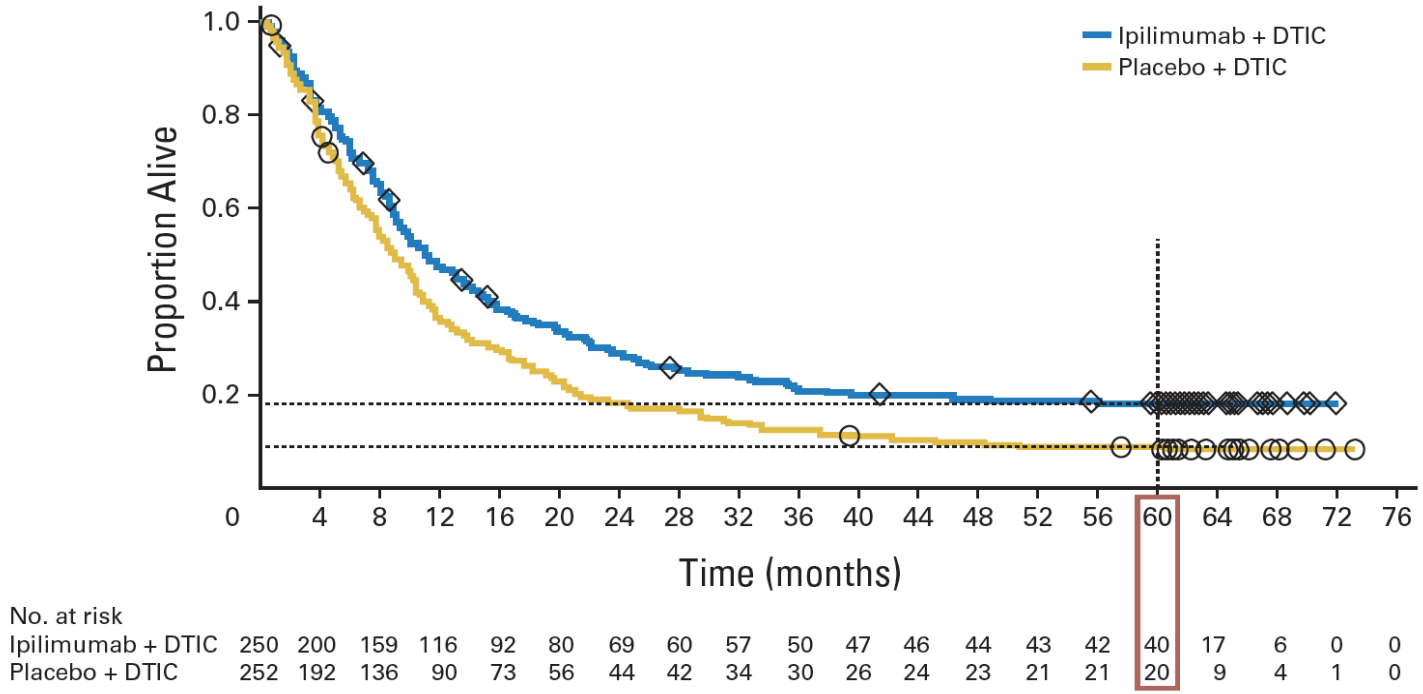
Milestone Survival: A Potential Intermediate Endpoint for Immune Checkpoint Inhibitors

Tai-Tsang Chen

JNCI J Natl Cancer Inst (2015) 107(9): djv156

Milestone overall survival was proposed for the evaluation of cancer immunotherapies to take into account the possibility of delayed treatment effect and to better characterize the clinical activity profile of such agents.



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ULSS3 SERENISSIMA · Aiom · SIUrO · RAO · SIU Società Italiana di Urologia Fondata nel 1908