Facciamo il punto su ...
"Immunoterapia nel carcinoma mammario"

I criteri di valutazione degli endpoints negli studi clinici: cosa cambia?

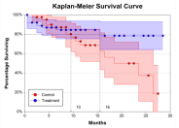
Giovanni L. Pappagallo

CRITERI DI VALUTAZIONE (SPECIFICI PER IMMUNOTERAPIA?)

tipo di variabile		significato clinico
nominale	**RR**	**attività, *surrogato* di efficacia?**
nominale	**pCR**	**attività, *surrogato* di efficacia?**
tempo a evento	**PFS**	**attività, *surrogato* di efficacia? efficacia?**
tempo a evento	**OS**	**efficacia**

DA APPROFONDIRE… (SPECIFICAMENTE PER IMMUNOTERAPIA?)

- Criteri di risposta (irRC ➜ irRECIST ➜ iRECIST *Vs* RECIST)
- **Valutazione delle misure *surrogate* di efficacia**
- **Validità dei fattori proposti quali biomarcatori**
- **Indicatori di effetto per variabili *tempo a evento***



European Journal of Cancer 86 (2017) 257–265

Response rate as a potential surrogate for survival and efficacy in patients treated with novel immune checkpoint inhibitors: A meta-regression of randomised prospective studies

Giandomenico Roviello [a,b,*], Fabrice Andre [c], Sergio Venturini [d], Barbara Pistilli [c], Giuseppe Curigliano [e], Massimo Cristofanilli [f], Pietro Rosellini [g], Daniele Generali [b,h]

Study	Experimental regimen (number)	Control regimen (number)	Site	Design	Primary end-point	System for classifying response
Borghaei *et al.*, 2015	292	290	NSCLC	Nivolumab versus docetaxel	OS	RECIST 1.1
Brahmer *et al.*, 2015	135	137	NSCLC	Nivolumab versus docetaxel	OS	RECIST 1.1
Ferris *et al.*, 2016	240	121	Head & neck	Nivolumab versus methotrexate/ docetaxel/cetuximab	OS	RECIST 1.1
Herbst *et al.*, 2016	344	343	NSCLC	Pembrolizumab versus docetaxel	OS & PFS	RECIST 1.1
Herbst *et al.*, 2016 (2)	346	343	NSCLC	Pembrolizumab versus docetaxel	OS & PFS	RECIST 1.1
Know *et al.*, 2014	399	400	Prostate	Ipilimumab versus placebo	OS	Prostate cancer clinical trials working group's recommendations & RECIST 1.0
Langer *et al.*, 2016	60	63	NSCLC	Pembrolizumab + CHT versus CHT	Objective response	RECIST 1.1
Lynch *et al.*, 2012	68	66	NSCLC	Ipilimumab + CHT versus CHT	irPFS	mWHO & irRC
Lynch *et al.*, 2012 (2)	70	66	NSCLC	Ipilimumab + CHT versus CHT	irPFS	mWHO & irRC
Motzer *et al.*, 2015	410	411	RENAL	Nivolumab versus everolimus	OS	RECIST 1.1
Reck *et al.*, 2013	43	45	SCLC	Ipilimumab + CHT versus CHT	irPFS	mWHO & irRC
Reck *et al.*, 2013 (2)	42	45	SCLC	Ipilimumab + CHT versus CHT	irPFS	mWHO & irRC
Reck *et al.*, 2016	478	476	SCLC	Ipilimumab + CHT versus placebo + CHT	OS	mWHO
Reck *et al.*, 2016 NEJM	154	151	NSCLC	Pembrolizumab versus CHT	PFS	RECIST 1.1
Ribas *et al.*, 2013	328	327	Melanoma	Tremelimumab versus CHT	OS	RECIST 1.1
Ribas *et al.*, 2015	180	179	Melanoma	Pembrolizumab versus CHT	PFS	RECIST 1.1
Ribas *et al.*, 2015 (2)	181	179	Melanoma	Pembrolizumab versus CHT	PFS	RECIST 1.1
Robert *et al.*, 2015 NEJM	210	208	Melanoma	Nivolumab versus dacarbazine	OS	RECIST 1.1
Weber *et al.*, 2015	272	133	Melanoma	Nivolumab versus CHT	Objective response	RECIST 1.1
Bellmunt *et al.*, 2017	270	272	Urothelial	Pembrolizumab versus CHT	OS & PFS	RECIST 1.1
Rittmeyer *et al.*, 2017	425	425	NSCLC	Atezolizumab versus docetaxel	OS	RECIST 1.1

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Response rate as a potential surrogate for survival and efficacy in patients treated with novel immune checkpoint inhibitors: A meta-regression of randomised prospective studies

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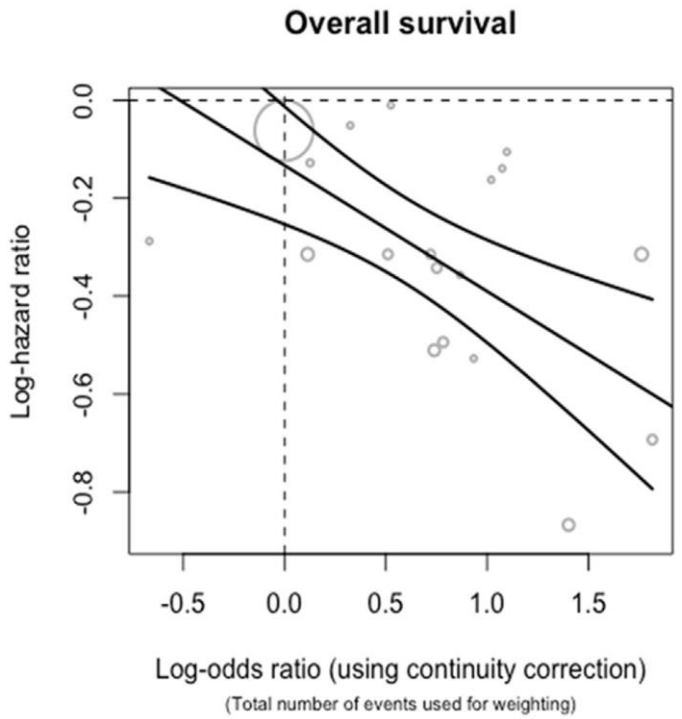


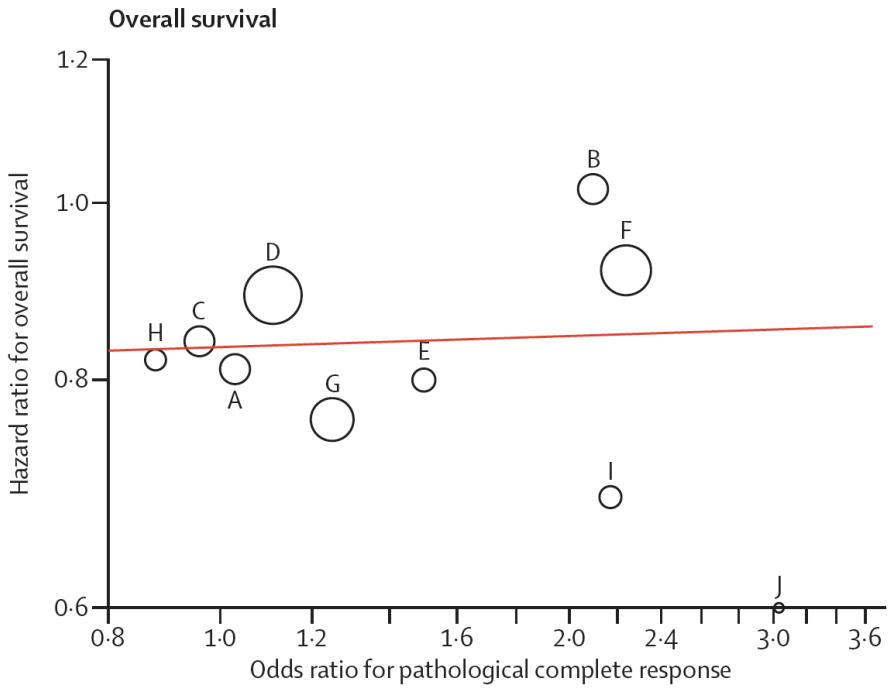
The R2 value of the weighted regression line was 0.47 (95% CI, 0.03-0.77; P = 0.001), indicating that the 47% of the variability among the effects on OS can be explained by the observed effects on RR.

The results of the trial-based meta-regression analysis indicated a weak correlation between RR and OS, supporting future investigations to assess the surrogacy of RR in the patient treated with immune checkpoint inhibitors.

Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis

Patricia Cortazar, Lijun Zhang, Michael Untch, Keyur Mehta, Joseph P Costantino, Norman Wolmark, Hervé Bonnefoi, David Cameron, Luca Gianni, Pinuccia Valagussa, Sandra M Swain, Tatiana Prowell, Sibylle Loibl, D Lawrence Wickerham, Jan Bogaerts, Jose Baselga, Charles Perou, Gideon Blumenthal, Jens Blohmer, Eleftherios P Mamounas, Jonas Bergh, Vladimir Semiglazov, Robert Justice, Holger Eidtmann, Soonmyung Paik, Martine Piccart, Rajeshwari Sridhara, Peter A Fasching, Leen Slaets, Shenghui Tang, Bernd Gerber, Charles E Geyer Jr, Richard Pazdur, Nina Ditsch, Priya Rastogi, Wolfgang Eiermann, Gunter von Minckwitz

Lancet 2014; 384: 164–72

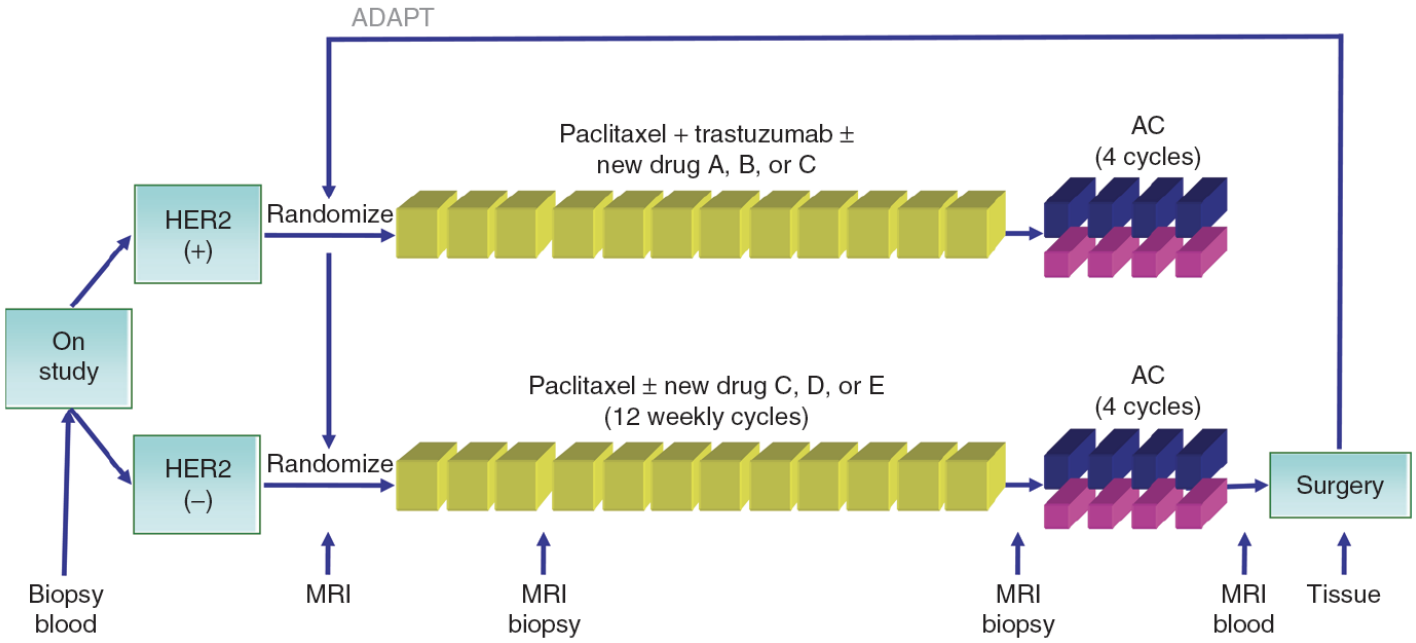


At a trial level, we recorded little association between increases in frequency of pathological complete response and the treatment's effect on OS. The coefficient of determination ($R2$) between improvement in pathologicalcomplete response and OS was 0·24 (0·00–0·70).

I-SPY 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy

AD Barker[1], CC Sigman[2], GJ Kelloff[1], NM Hylton[3], DA Berry[4] and LJ Esserman[3]

Clin Pharmacol Ther. 2009 Jul;86(1):97-100



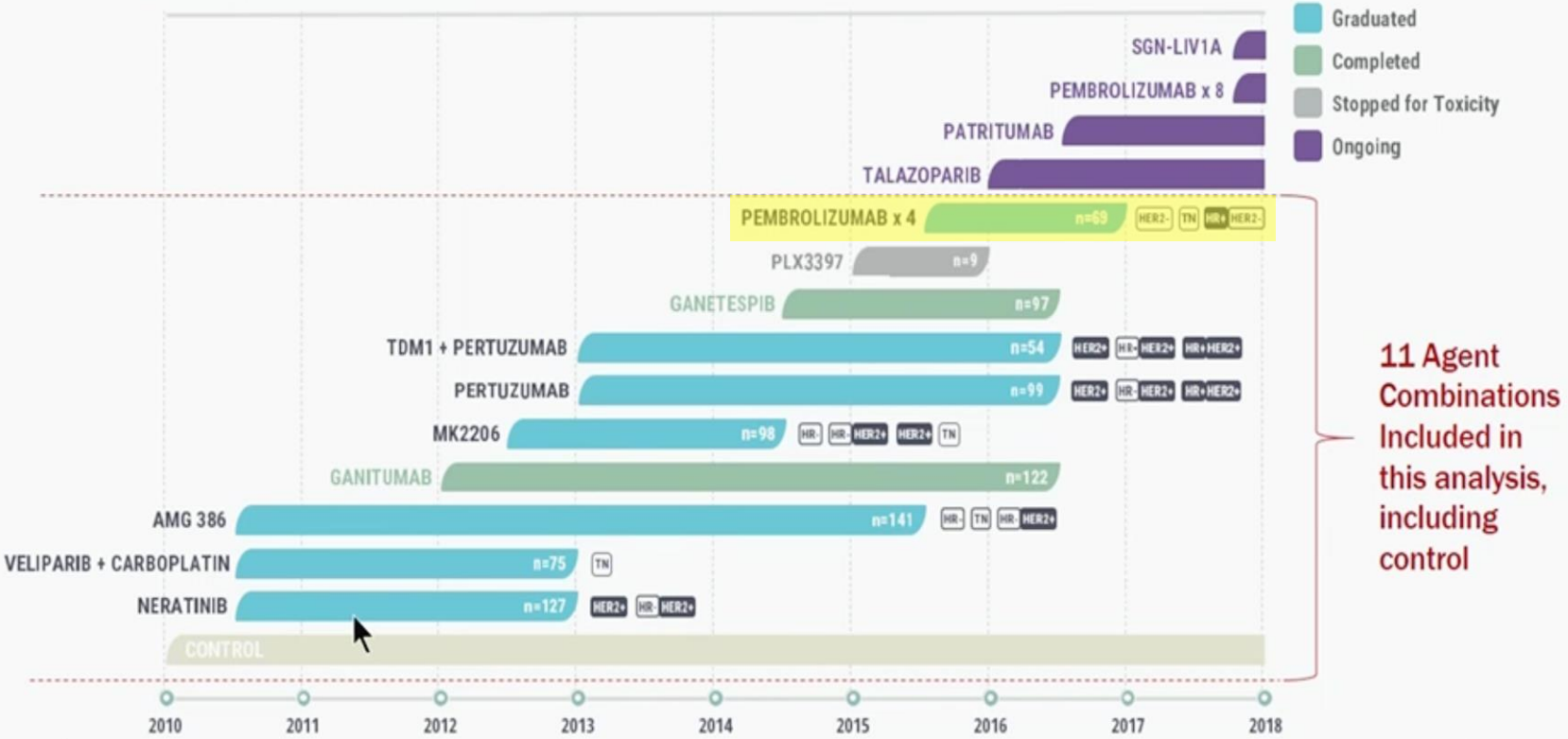
Regimens that show a high Bayesian predictive probability of being more effective than standard therapy will graduate from the trial with their corresponding biomarker signature(s)

I-SPY 2 (investigation of serial studies to predict your therapeutic response with imaging and molecular analysis 2)

Pathological Complete Response Predicts Event-Free and Distant Disease Free Survival in the I-SPY 2 TRIAL

Douglas Yee, MD
Masonic Cancer Center, University of Minnesota

Agent Timeline



I-SPY 2 Results Reporting

- The I-SPY 2 Bayesian model generates predictive probability distributions of pCR rates by signature
  - Estimated pCR rates
  - Actual pCR rates not reported; biased by the adaptive randomization
- Format of results presented
  - Estimated mean pCR rates by signature
  - Probability that experimental arm is superior to the control for a given signature
  - Predicted probability of success in a 1:1 randomized 300 patient phase 3 trial

Signature	Estimated pCR rate (95% probabilty interval)		Probability pembro is superior to control	Predictive probability of success in phase 3
	Pembro	Control		
All HER2-	**0.46** (0.34 – 0.58)	**0.16** (0.06 – 0.27)	**> 99%**	**99%**
TNBC	**0.60** (0.43 – 0.78)	**0.20** (0.06 – 0.33)	**>99%**	**>99%**
HR+/HER2-	**0.34** (0.19 – 0.48)	**0.13** (0.03 – 0.24)	**>99%**	**88%**

Presented By Rita Nanda at 2017 ASCO Annual Meeting

Pathological Complete Response Predicts Event-Free and Distant Disease Free Survival in the I-SPY 2 TRIAL

Douglas Yee, MD
Masonic Cancer Center, University of Minnesota

I-SPY2 EFS Hazard Ratio for pCR/non-pCR compared to FDA meta-analysis and cooperative group results

	I-SPY 2	Cortazar Meta-analysis	Cooperative Group CALGB 40603
Overall	0.20 (0.11-0.36)	0.48 (0.43-0.54)	
*HR+HER2-	0.21 (0.05-0.85)	0.49 (0.33-0.71)	
HER2+	0.21 (0.08-0.55)	0.39 (0.31-0.50)	
HR-HER2-	0.17 (0.07-0.39)	0.24 (0.18-0.33)	0.30 (0.19-0.45)

*Mammaprint low patients excluded

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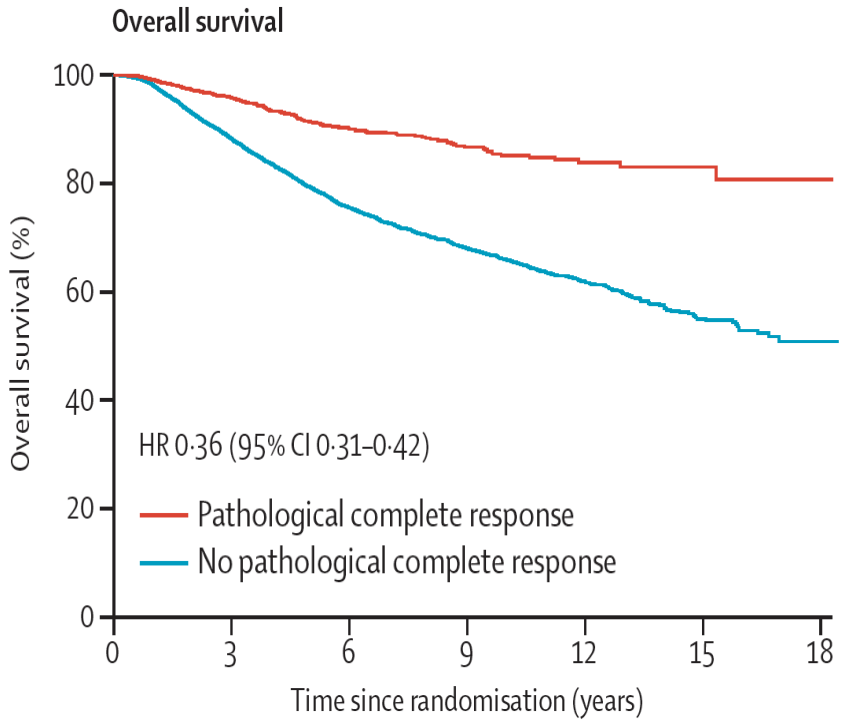
Lancet 2014; 384: 164–72



Patient level analyses predict improved survival for patients who attain pathological complete response. Because these responder analyses are independent of the treatment group, they are not useful for comparisons of treatments at a trial level.

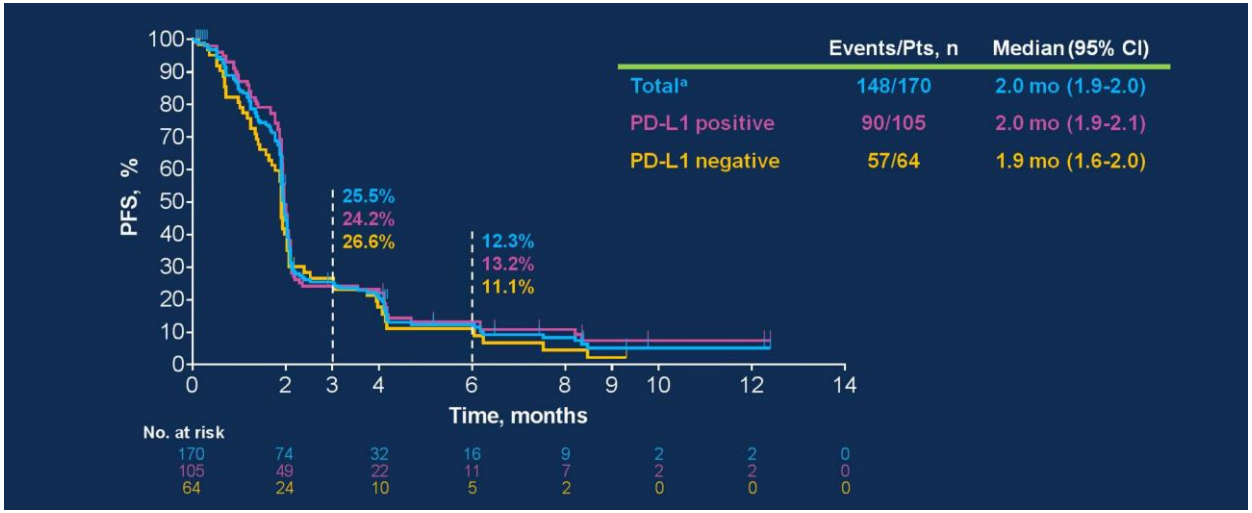
Pathological Complete Response Predicts Event-Free and Distant Disease Free Survival in the I-SPY 2 TRIAL

Douglas Yee, MD
Masonic Cancer Center, University of Minnesota

The Future of I-SPY 2

- Achieving pCR through any therapy for any subtype is a sufficient endpoint ?
- Develop minimally invasive techniques (MRI and biopsy) to identify pCR prior to definitive surgery
  - Validate robust MRI and tissue predictors of pCR
  - Deescalate toxic therapy (AC) if pCR obtained early
- Re-assign patients to new therapies if pCR is not predicted ?
  - Validate robust MRI and tissue predictors of non-PCR
  - Assign new therapies based on molecular profiling of tumor and link to investigational agents

Phase 2 Study of Pembrolizumab Monotherapy for Previously Treated Metastatic Triple-Negative Breast Cancer: KEYNOTE-086 Cohort A



Presented By Sylvia Adams at 2017 ASCO Annual Meeting

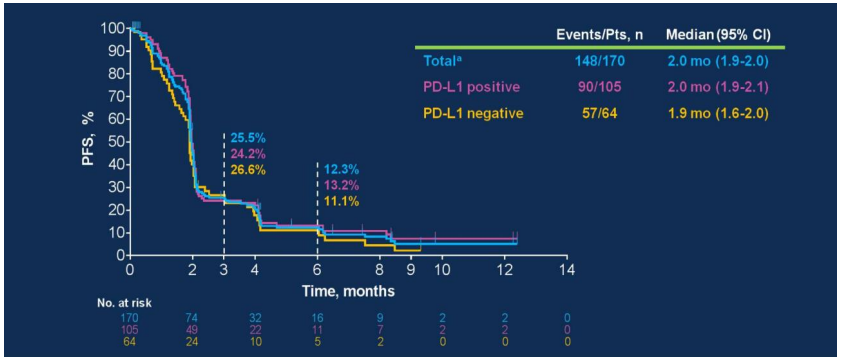
Types of Validation for Prognostic and Predictive Biomarkers

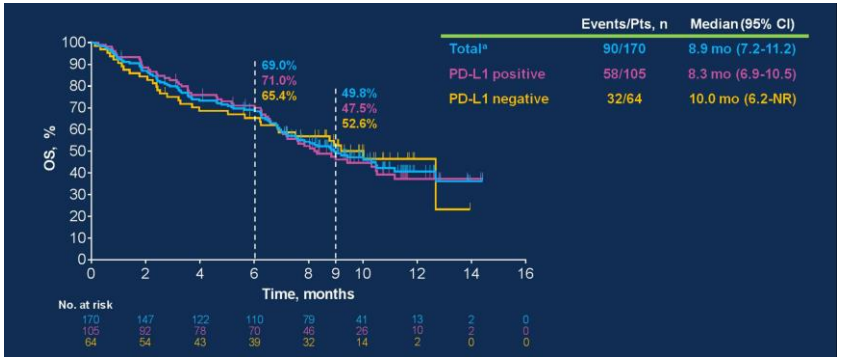
- Analytical validation
  - Pre-analytical and post-analytical robustness

- PD-L1: assessed at a central laboratory
  - Samples: newly obtained core needle or excisional biopsy samples from non-irradiated metastatic lesions or archival samples from the primary tumor
  - Assay: PD-L1 IHC 22C3 pharmDx (Agilent Technologies [formerly Dako])
  - Measure of expression: combined positive score (CPS)
    - Number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) out of the total number of tumor cells × 100
    - PD-L1 positive: CPS ≥1%

Types of Validation for Prognostic and Predictive Biomarkers

- Analytical validation
  - Pre-analytical and post-analytical robustness
- Clinical validation
  - Does the biomarker predict what its supposed to predict for independent data





Types of Validation for Prognostic and Predictive Biomarkers

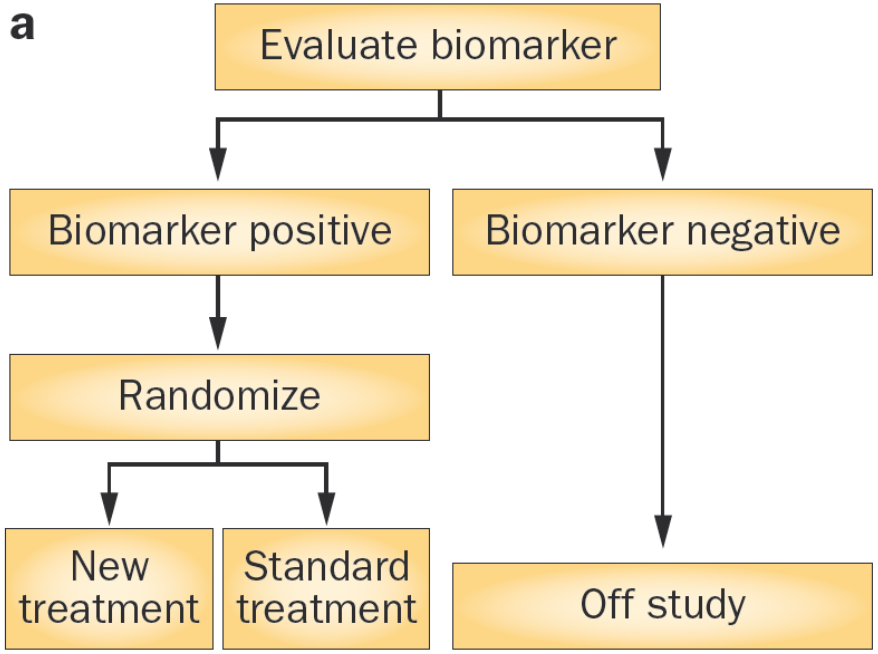
- Analytical validation
  - Pre-analytical and post-analytical robustness
- Clinical validation
  - Does the biomarker predict what its supposed to predict for independent data
- Clinical utility
  - Does use of the biomarker result in patient benefit

Biomarker enrichment strategies: matching trial design to biomarker credentials

Boris Freidlin and Edward L. Korn

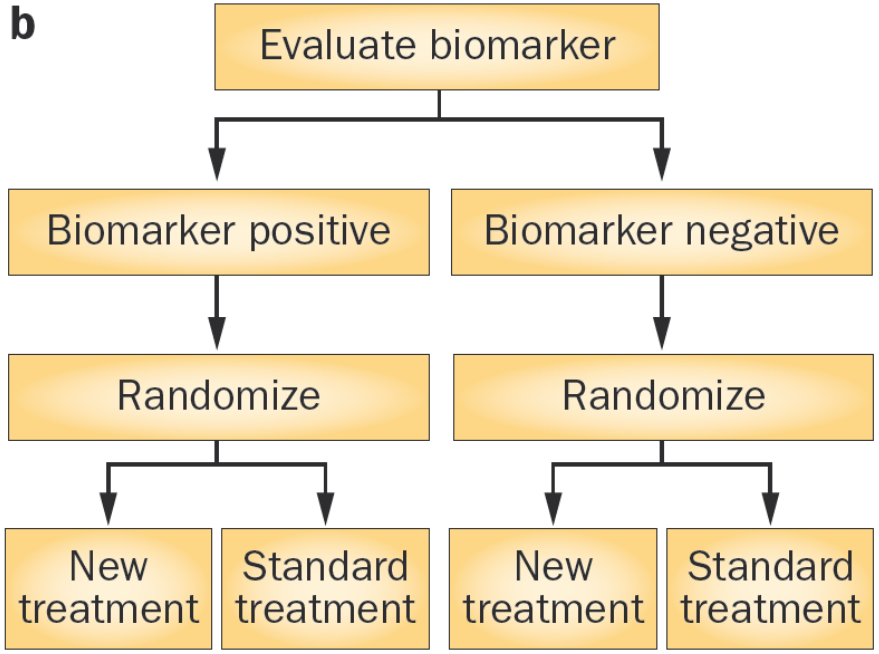
Nat. Rev. Clin. Oncol. **11**, 81–90 (2014)

a

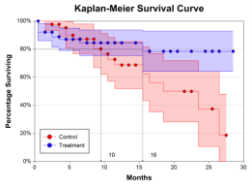


Enrichment designs only evaluate a new treatment in the biomarker-positive subpopulation.

b

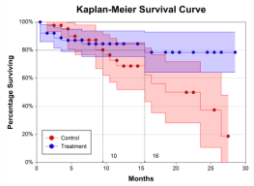


Biomarker-stratified designs randomly assign both biomarker-positive and biomarker-negative patients to the treatment under investigation.



Indicatori riassuntivi di effetto di variabili tempo-a-evento

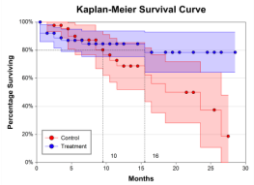
- **Differenza tra stime della mediana di sopravvivenza (KM)**
- **Differenza media di sopravvivenza (*restricted means*) al tempo *t***
- **Differenza tra stime di sopravvivenza (KM) al tempo *t* (*Milestone* Survival)**
- **Hazard Ratio (KM+Cox)**



Indicatori riassuntivi di effetto di variabili tempo-a-evento

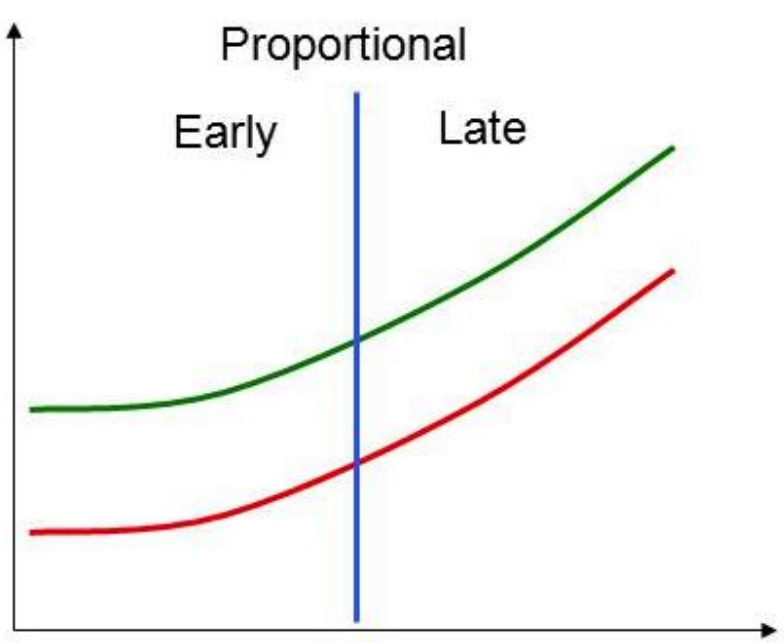
- Differenza tra stime della mediana di s
- D ted *m*
- D al tempo *t* *estone* Survival)
- **Hazard Ratio** (KM+Cox)

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

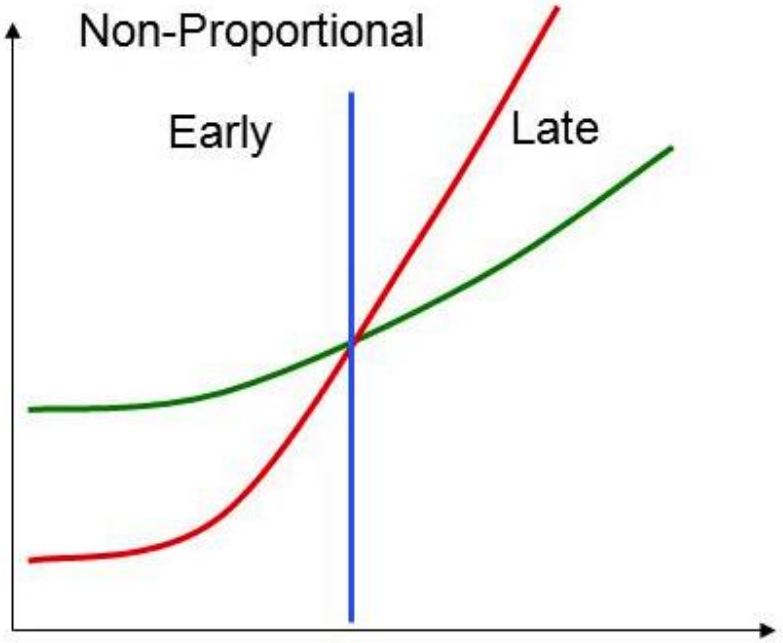


Proportional Hazard Assumption

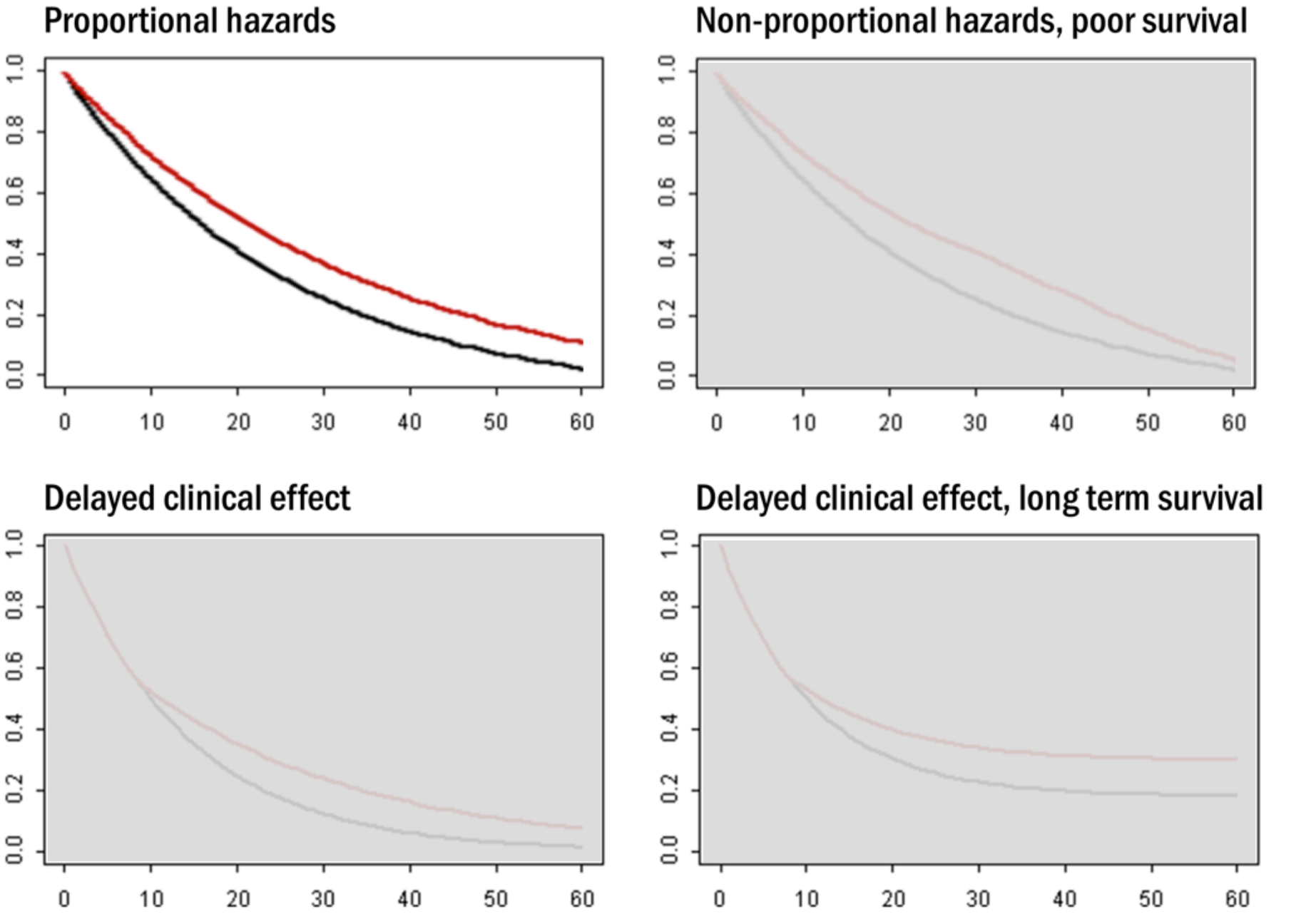
If we are comparing a new treatment with the standard treatment, it is assumed that the ratio of the hazard for an individual on a new treatment to that for an individual on the standard treatment remains constant over time



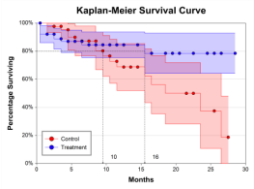
Here, the effect is the same in both time periods



Here, the effect is negative in the early period and positive in the late period



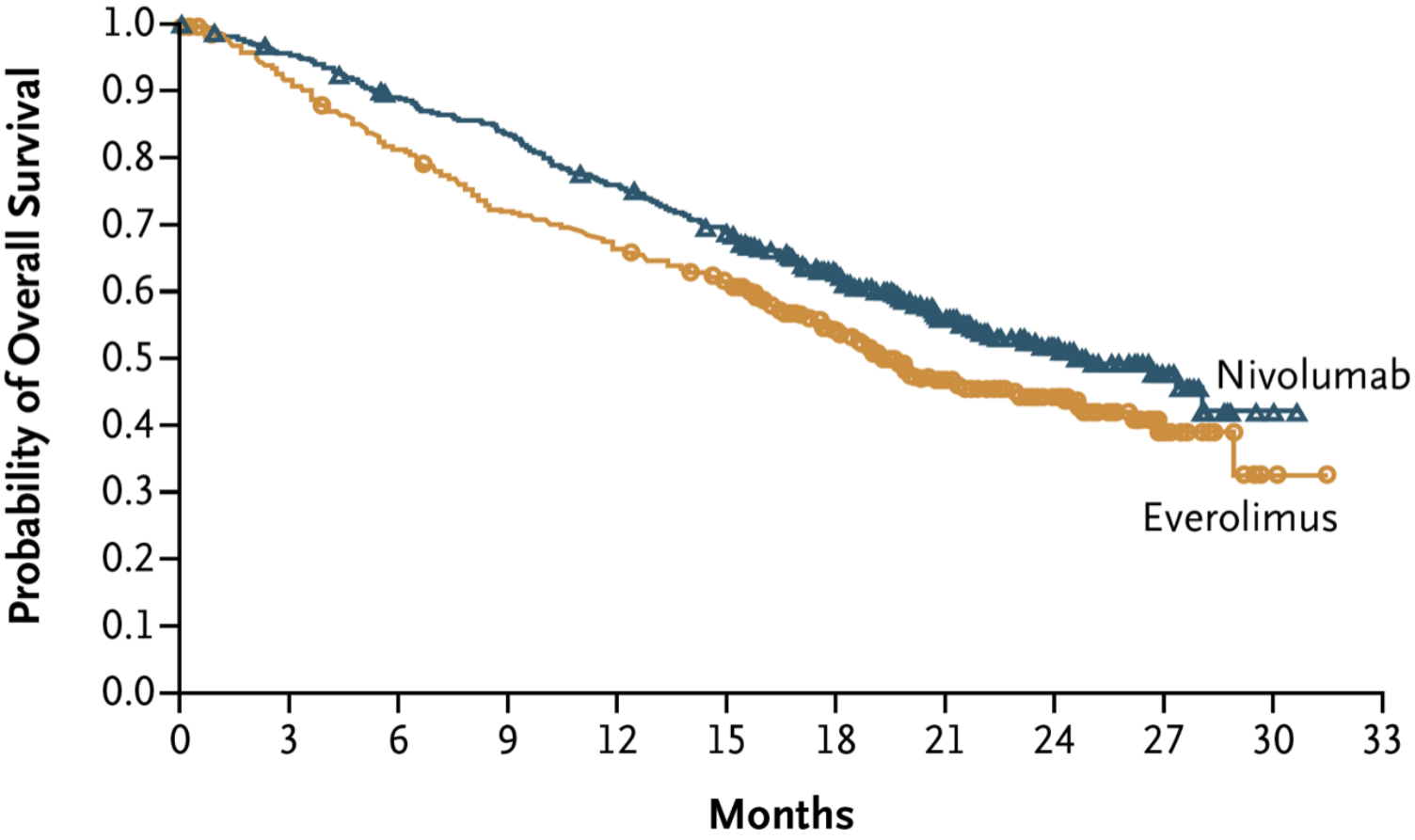
modif. from Chen et al. J Immunother Cancer 2013, 1:18

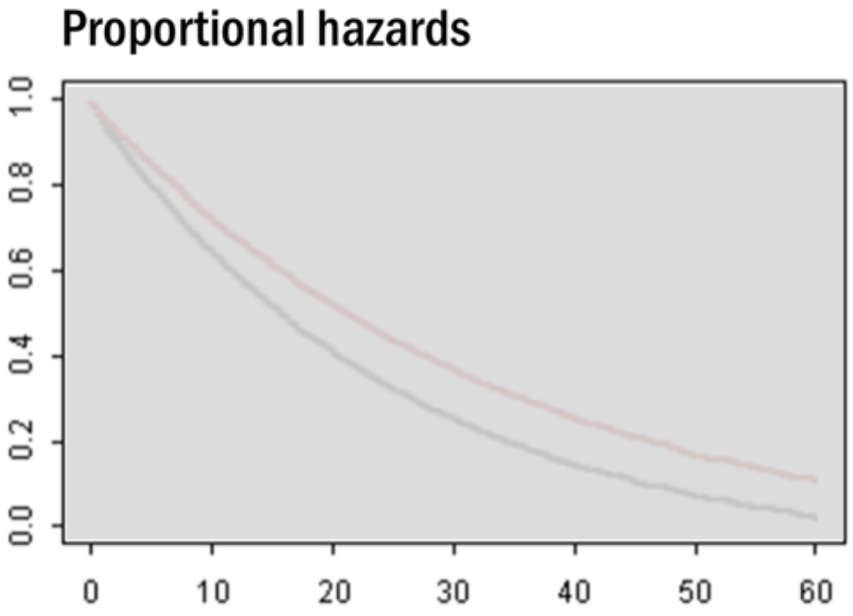


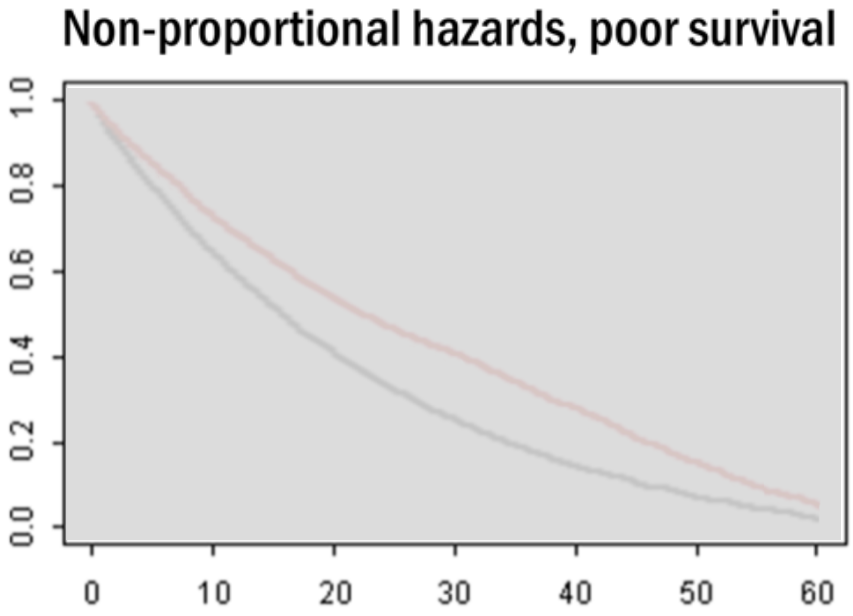
Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

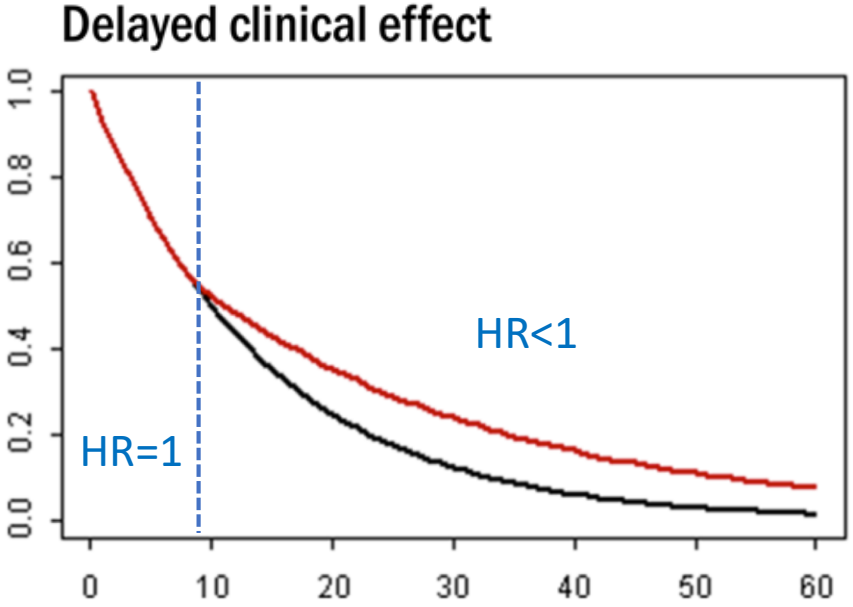
R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S.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

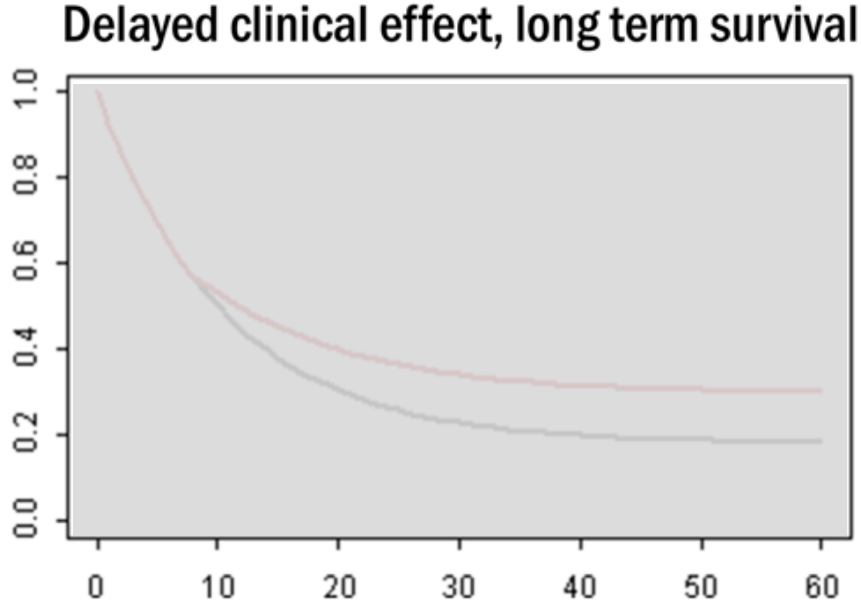
N Engl J Med 2015;373:1803-13











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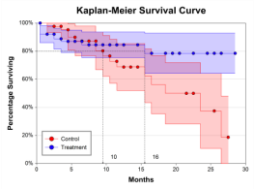

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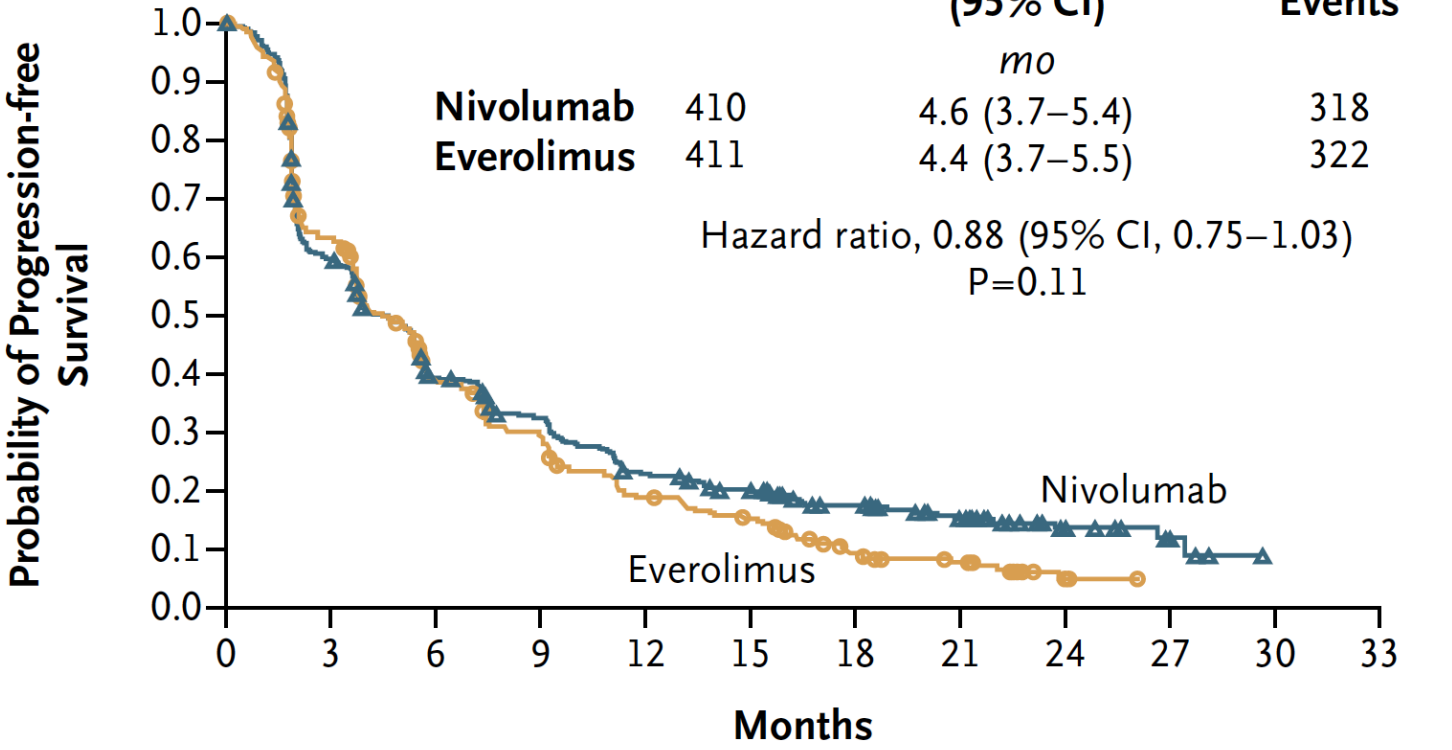
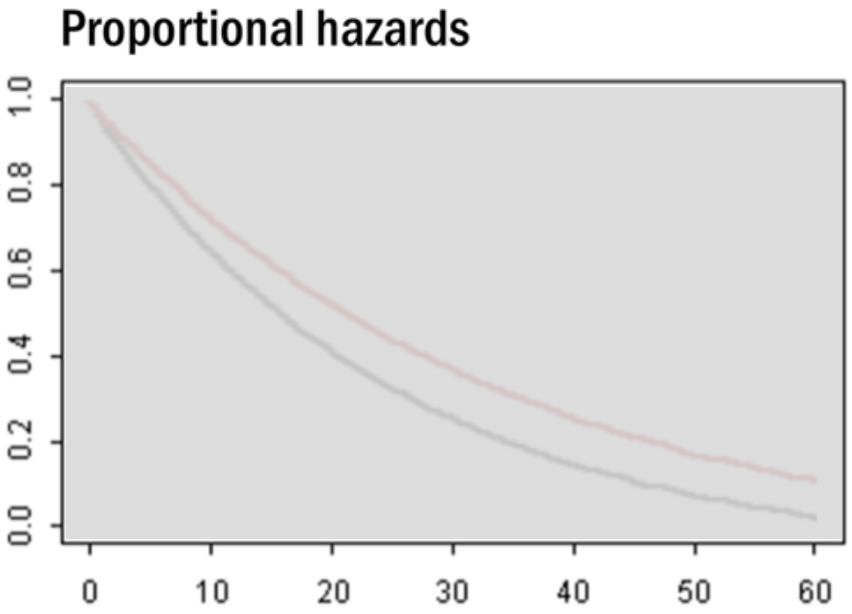
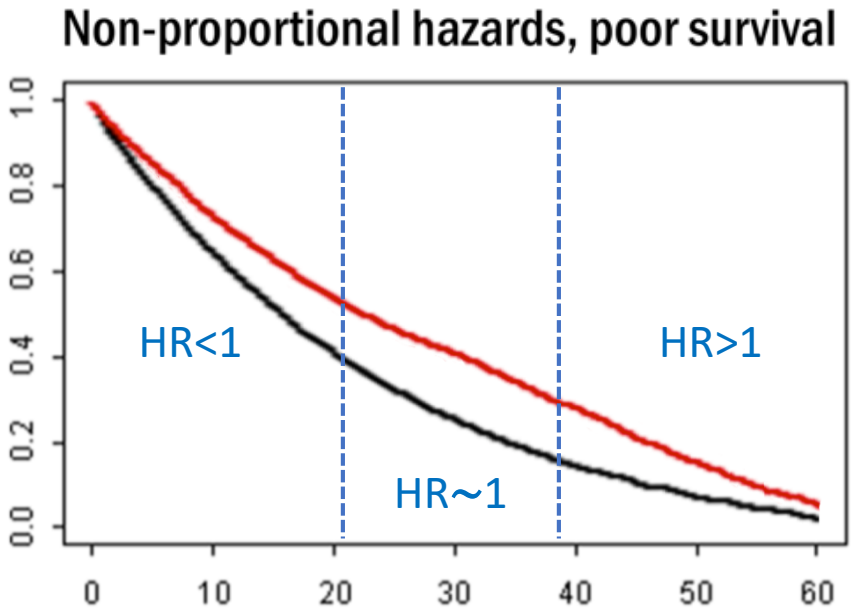
N Engl J Med 2015;373:1803-13

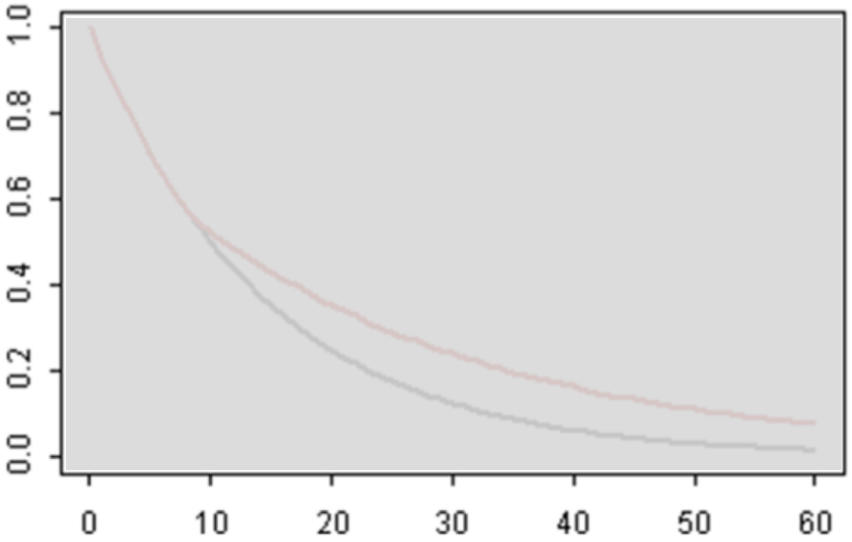
	No. of Patients	Median Progression-free Survival (95% CI)	No. of Progression Events
		mo	
Nivolumab	410	4.6 (3.7–5.4)	318
Everolimus	411	4.4 (3.7–5.5)	322

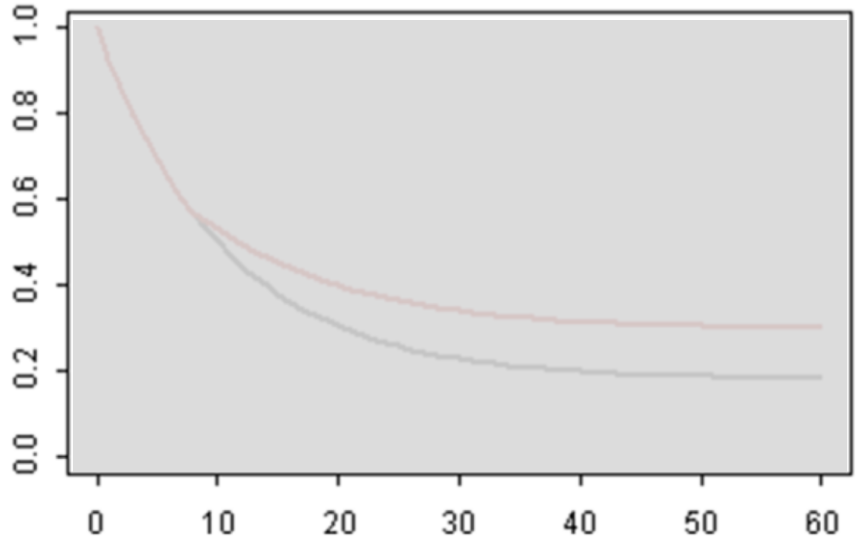
Hazard ratio, 0.88 (95% CI, 0.75–1.03)
P=0.11



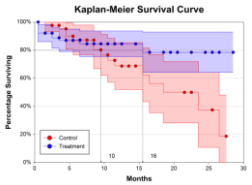








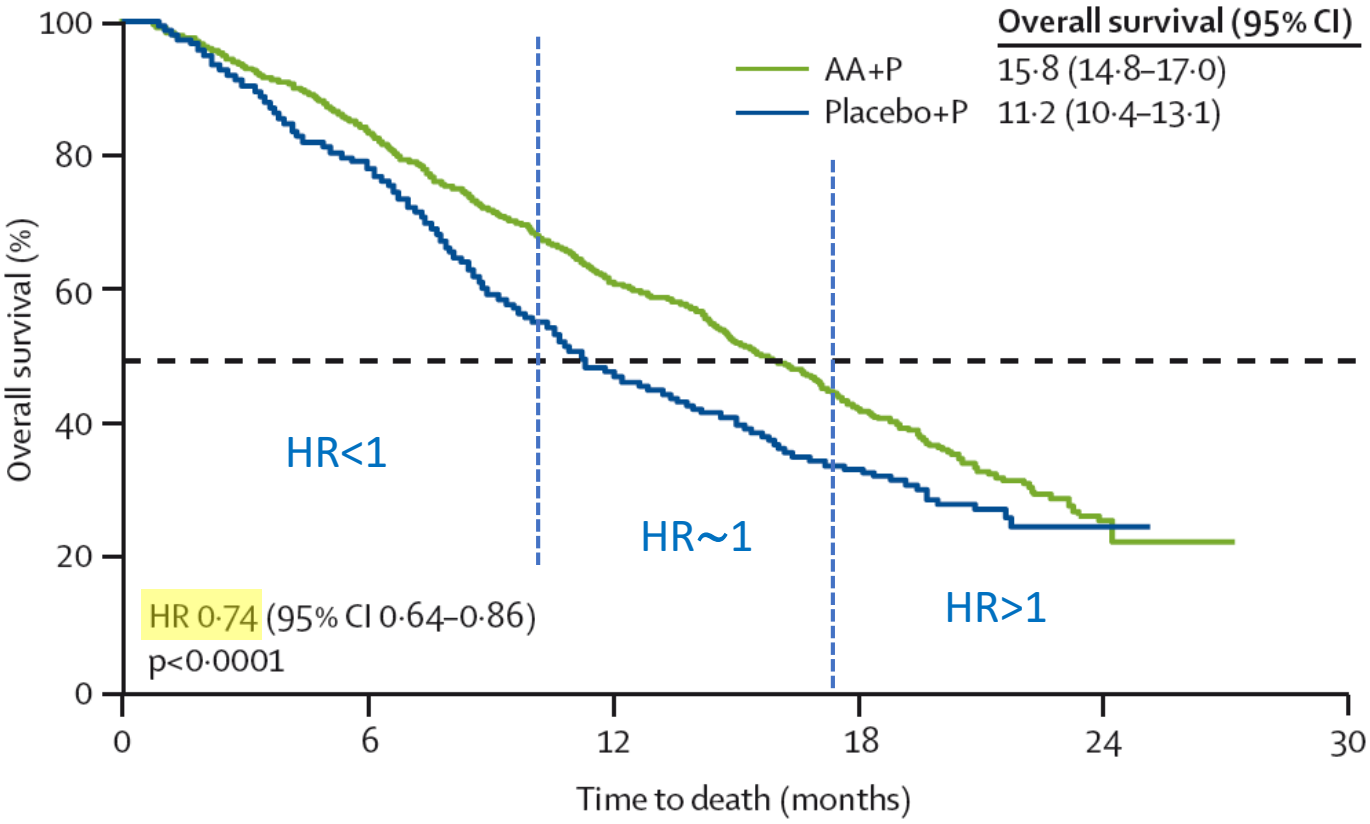
modif. from Chen et al. J Immunother Cancer 2013, 1:18

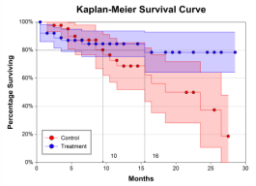


Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study

*Karim Fizazi, Howard I Scher, Arturo Molina, Christopher J Logothetis, Kim N Chi, Robert J Jones, John N Staffurth, Scott North, Nicholas J Vogelzang, Fred Saad, Paul Mainwaring, Stephen Harland, Oscar B Goodman Jr, Cora N Sternberg, Jin Hui Li, Thian Kheoh, Christopher M Haqq, Johann S de Bono, for the COU-AA-301 Investigators**

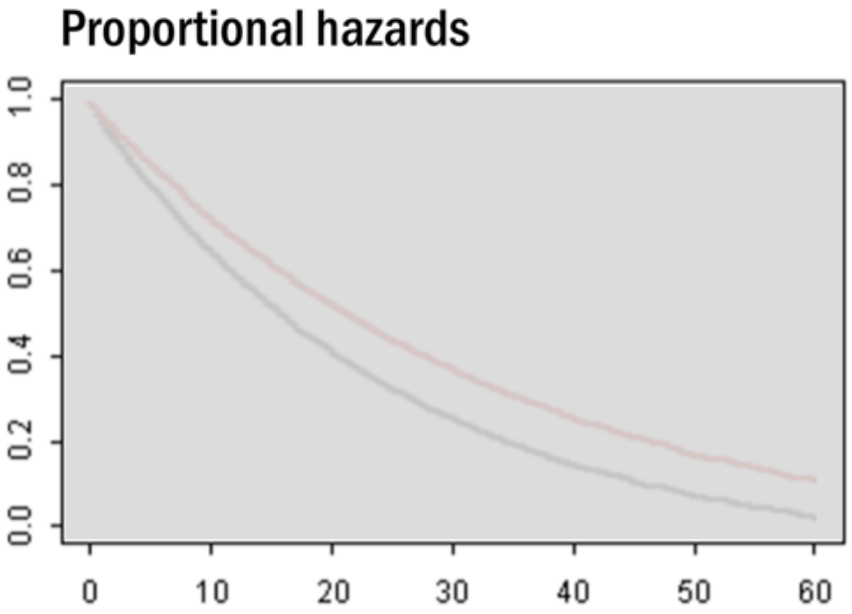
***Lancet Oncol* 2012; 13: 983–92**

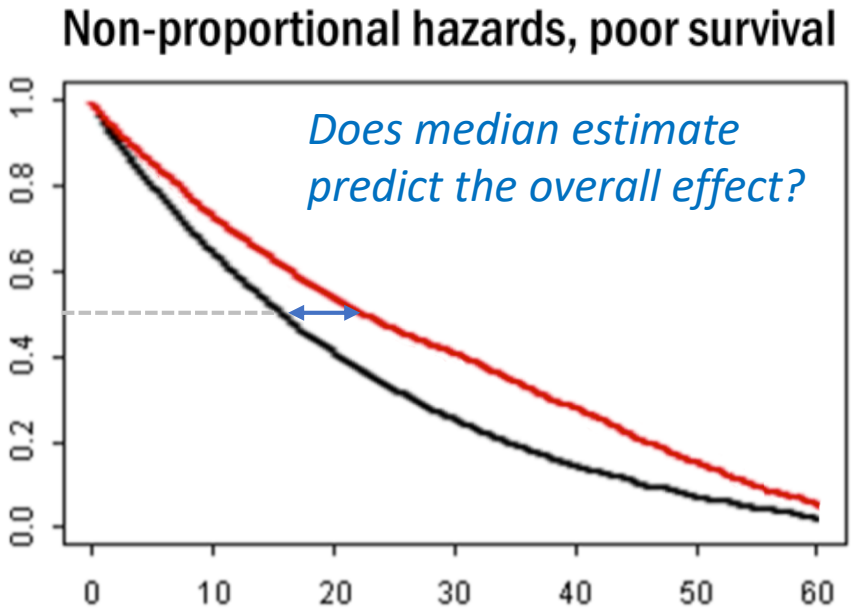


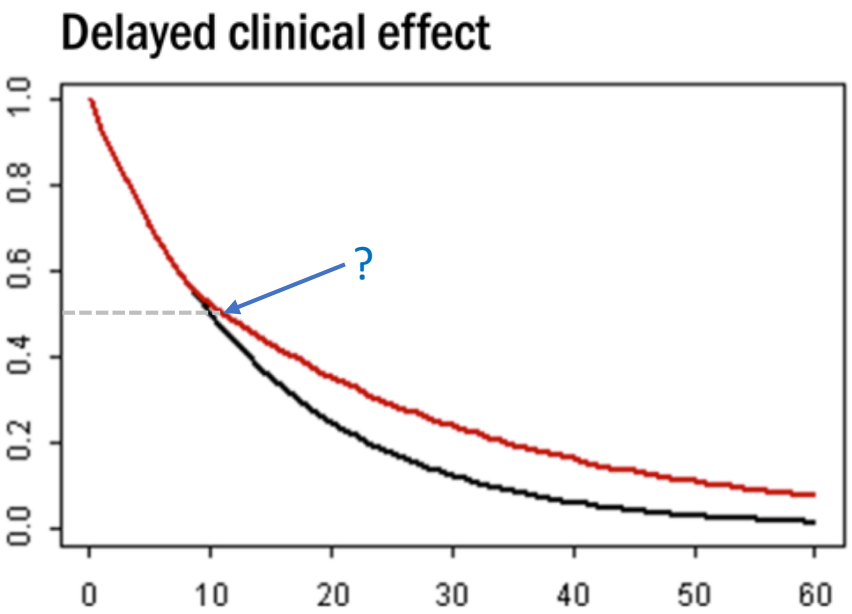


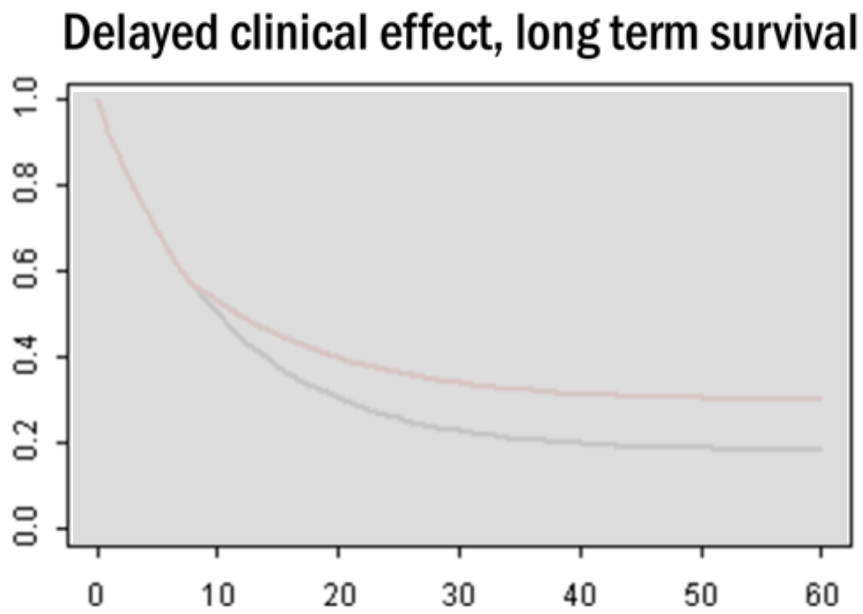
Indicatori riassuntivi di effetto di variabili tempo-a-evento

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









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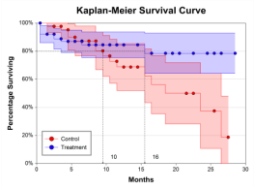

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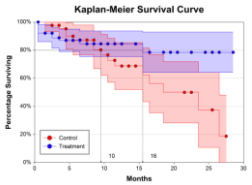


MRC Clinical Trials Unit

Restricted mean survival time

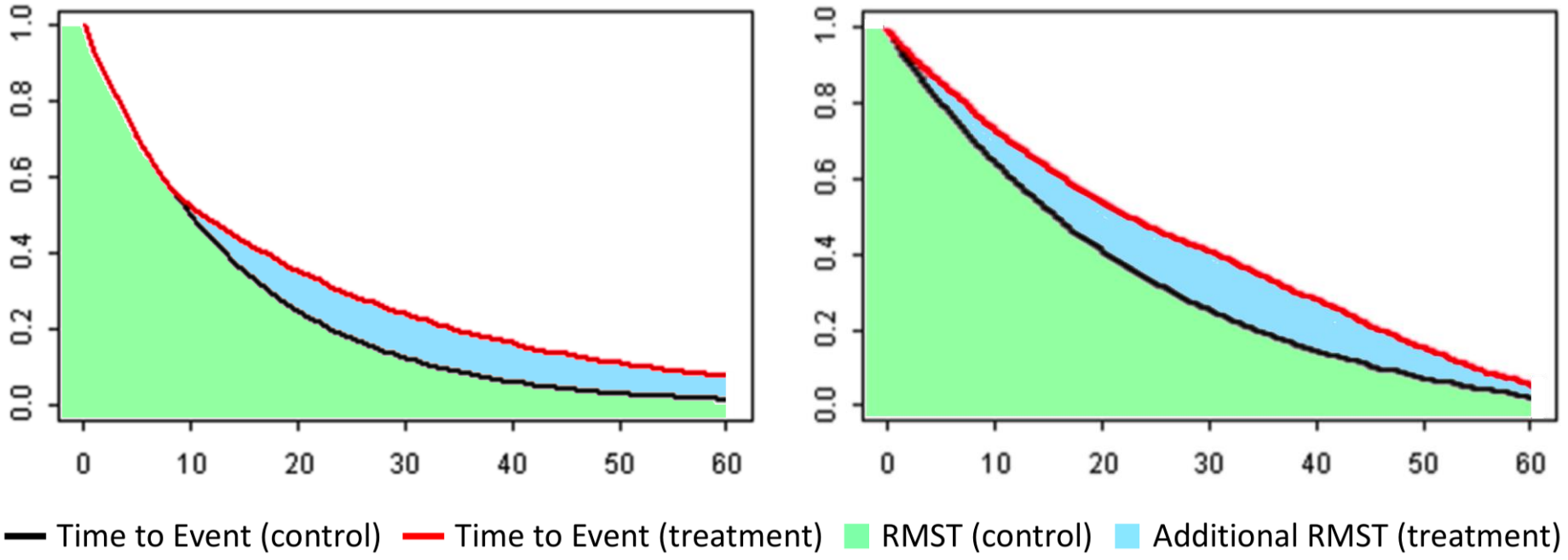
Patrick Royston

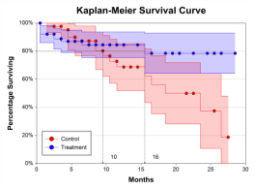
- RMST = area under the survival curve up to t^*

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

Flexible parametric survival models workshop, Stockholm, November 2011

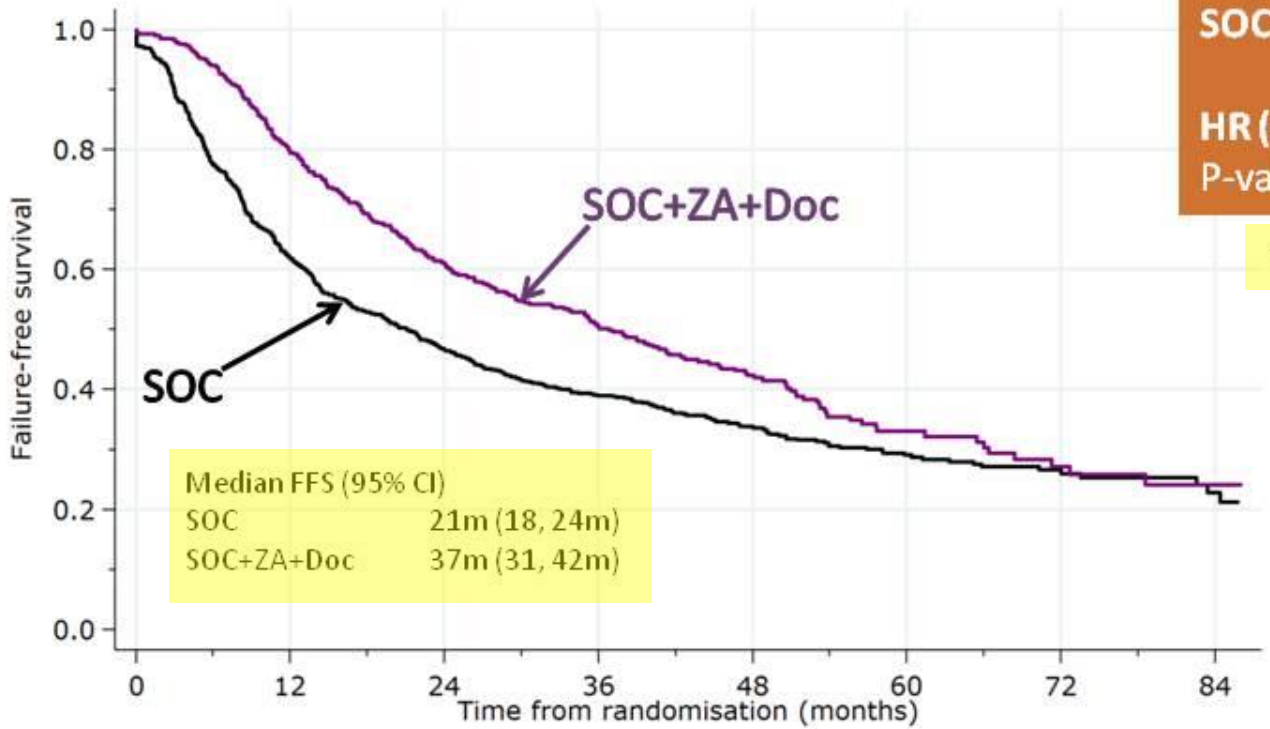




Zoledronic acid + docetaxel: Failure-free survival

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



Median FFS (95% CI)

SOC	21m (18, 24m)
SOC+ZA+Doc	37m (31, 42m)

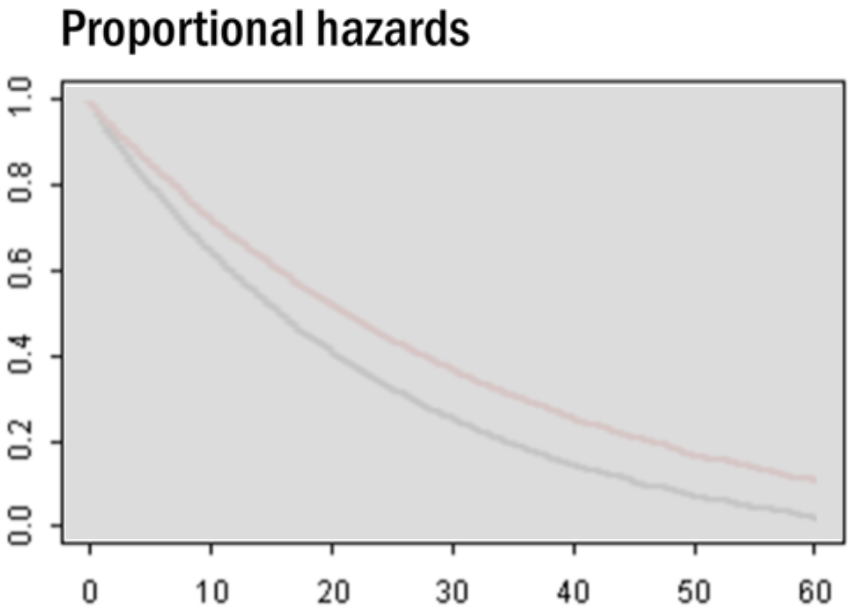
Restricted mean FFS time

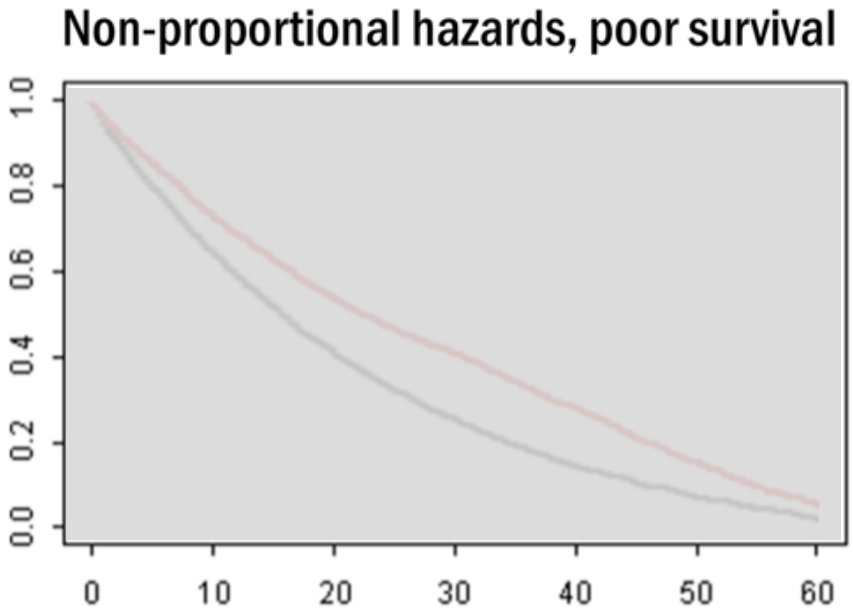
SOC	35.3m
SOC+ZA+Doc	43.5m
Diff (95%CI)	8.2m (5.5, 11.1m)

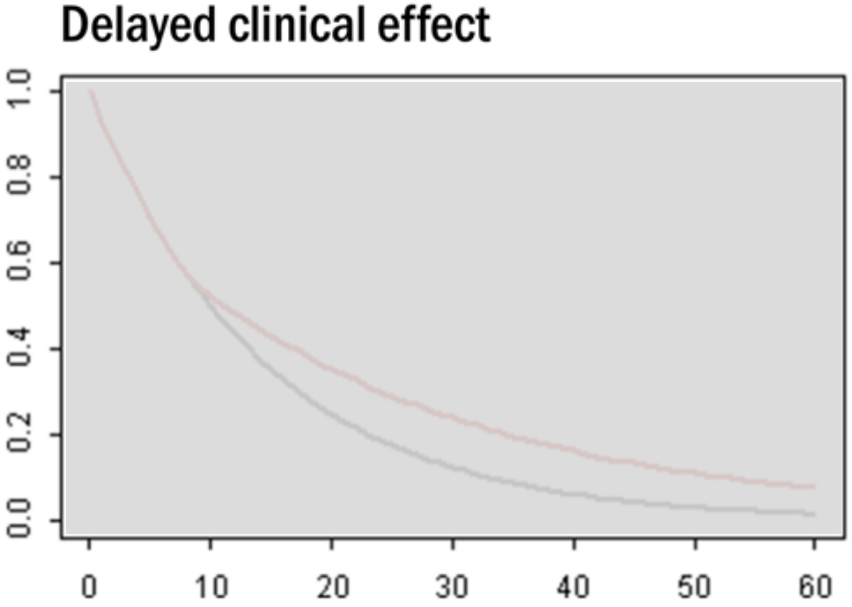
Group At risk (events)															
SOC	1184	(446)	713	(173)	488	(70)	287	(31)	161	(19)	84	(6)	45	(4)	17
SOC+ZA+Doc	593	(116)	448	(102)	303	(45)	180	(24)	103	(19)	42	(6)	20	(2)	13

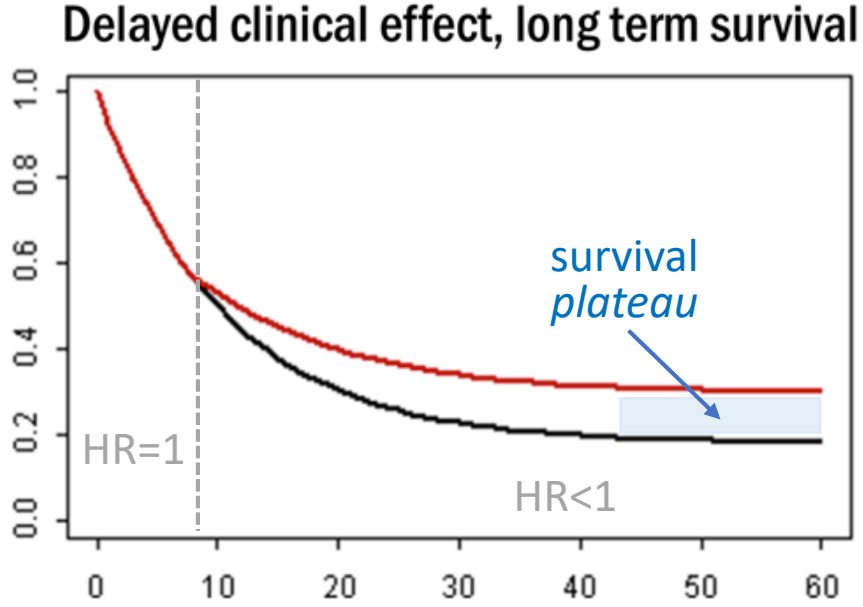
*a exact HR p-value 0.0000000000005038

*b exact non-PH p-value 0.000000010376









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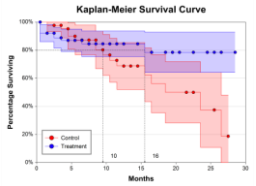

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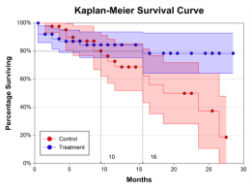
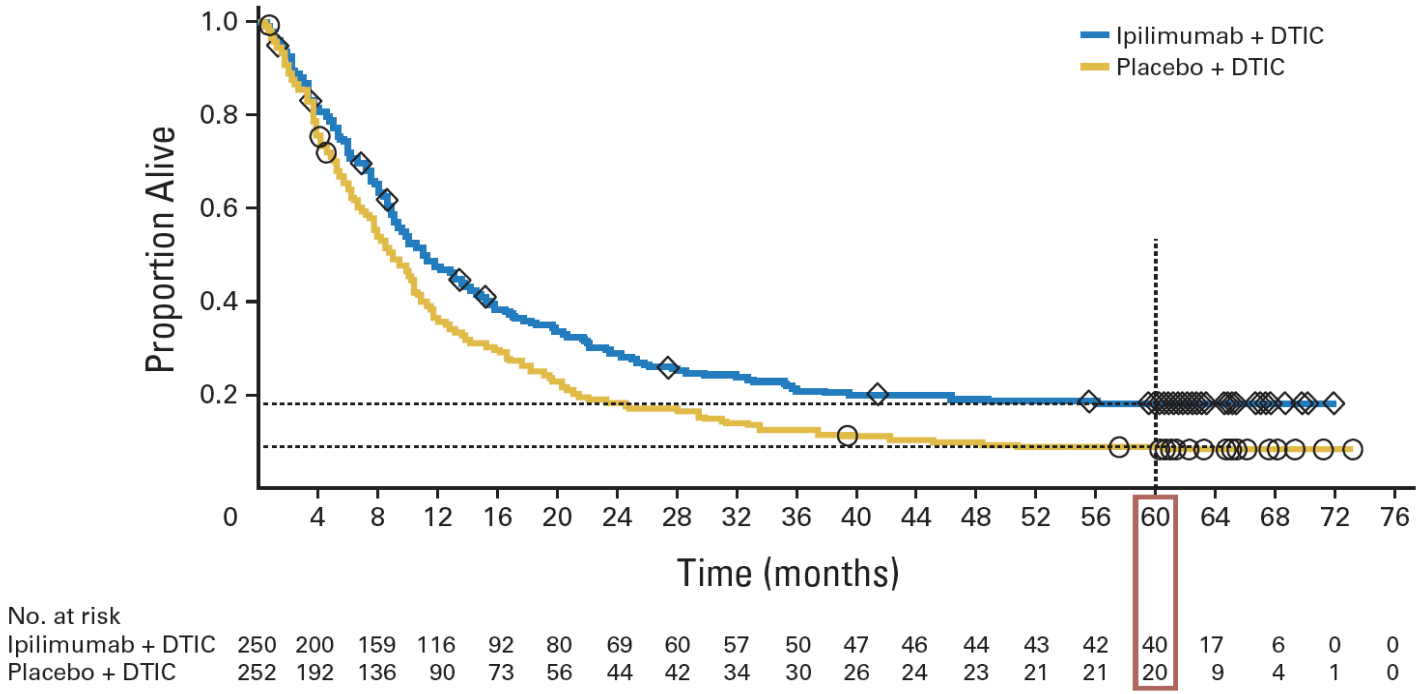


Milestone Survival: A Potential Intermediate Endpoint for Immune Checkpoint Inhibitors

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.



J Clin Oncol 33:1191-1196. © 2015 by American Society of Clinical Oncology