IRCCS Sacro Cuore Don Calabria
Cancer Care Center Negrar - Verona

ESMO Designated Centers of Integrated Oncology and Palliative Care

Con il Patrocinio di

AIOM Associazione Italiana di Oncologia Medica
RAO
SICO
Società Italiana di Psico-Oncologia

STUDI CLINICI: METODOLOGIA

Coordinatore
Dr.ssa Stefania Gori

Evento ECM MODULO 2

FORMAZIONE AVANZATA

NEGRAR
8/9 Marzo
2019

Centro Formazione
IRCCS Ospedale Sacro Cuore
Don Calabria

Verifica della Rilevanza Clinica

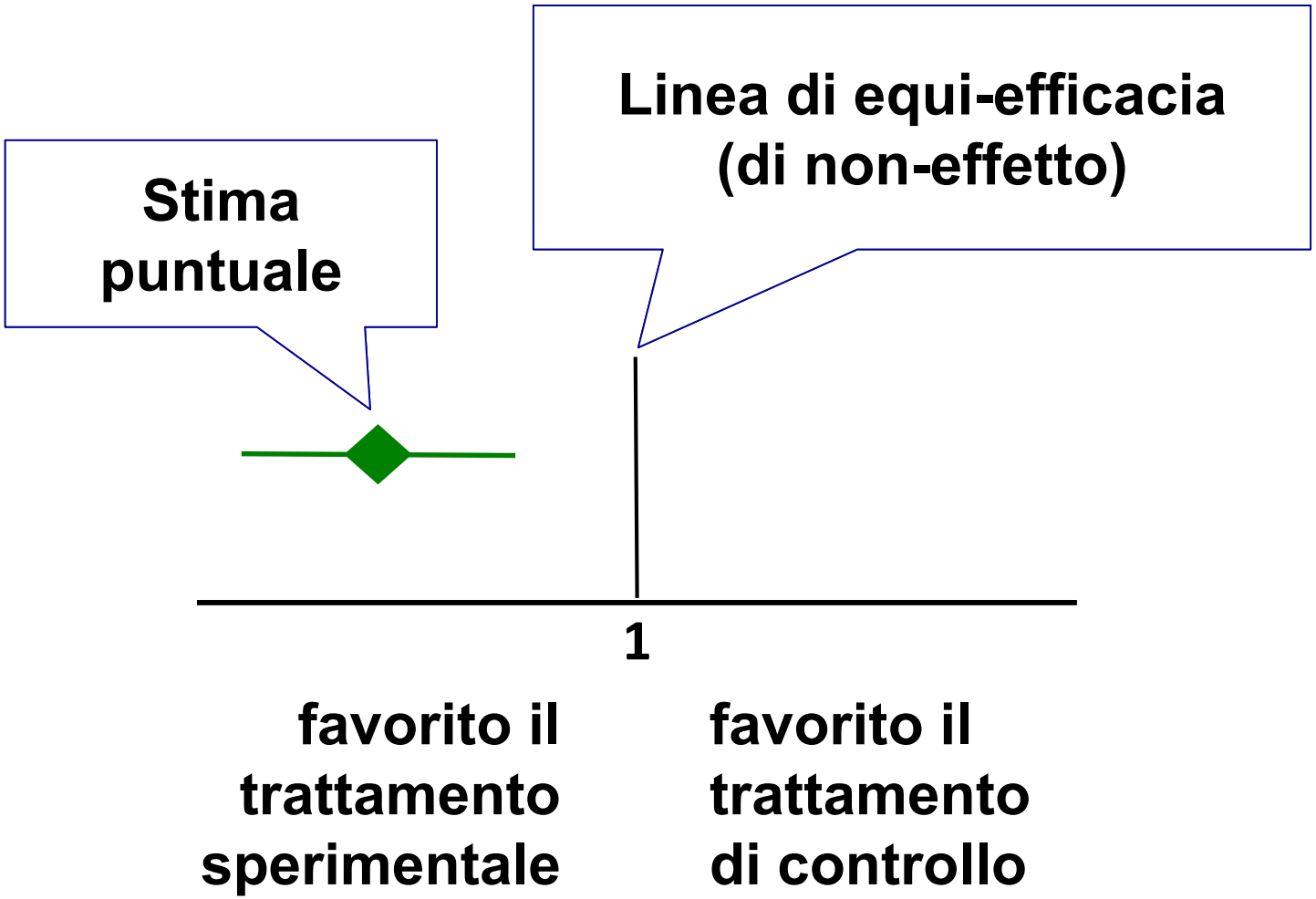
Interpretazione degli studi clinici mediante Forest (Forrest?) Plot

Why a forest plot?

The plot was not called a "forest plot" in print for some time, and the origins of this title are obscured by history and myth. At the September 1990 meeting of the breast cancer overview, Richard Peto jokingly mentioned that the plot was named after the breast cancer researcher Pat Forrest, and, at times, the name has been spelt "forrest plot." However, the phrase actually originates from the idea that the typical plot appears as a forest of lines.

BMJ VOLUME 322 16 JUNE 2001

Interpretazione degli studi clinici mediante Forest (Forrest?) Plot



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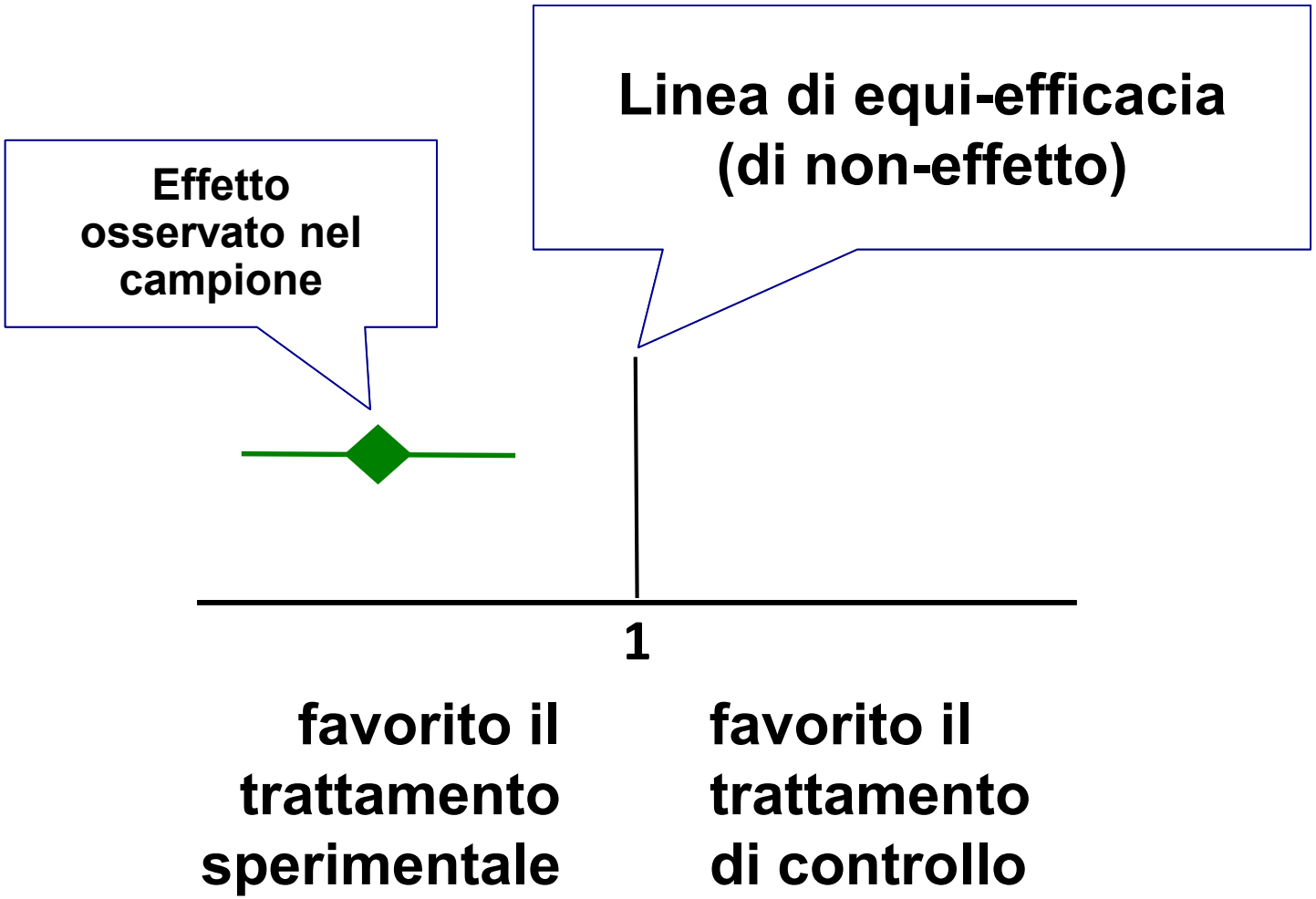
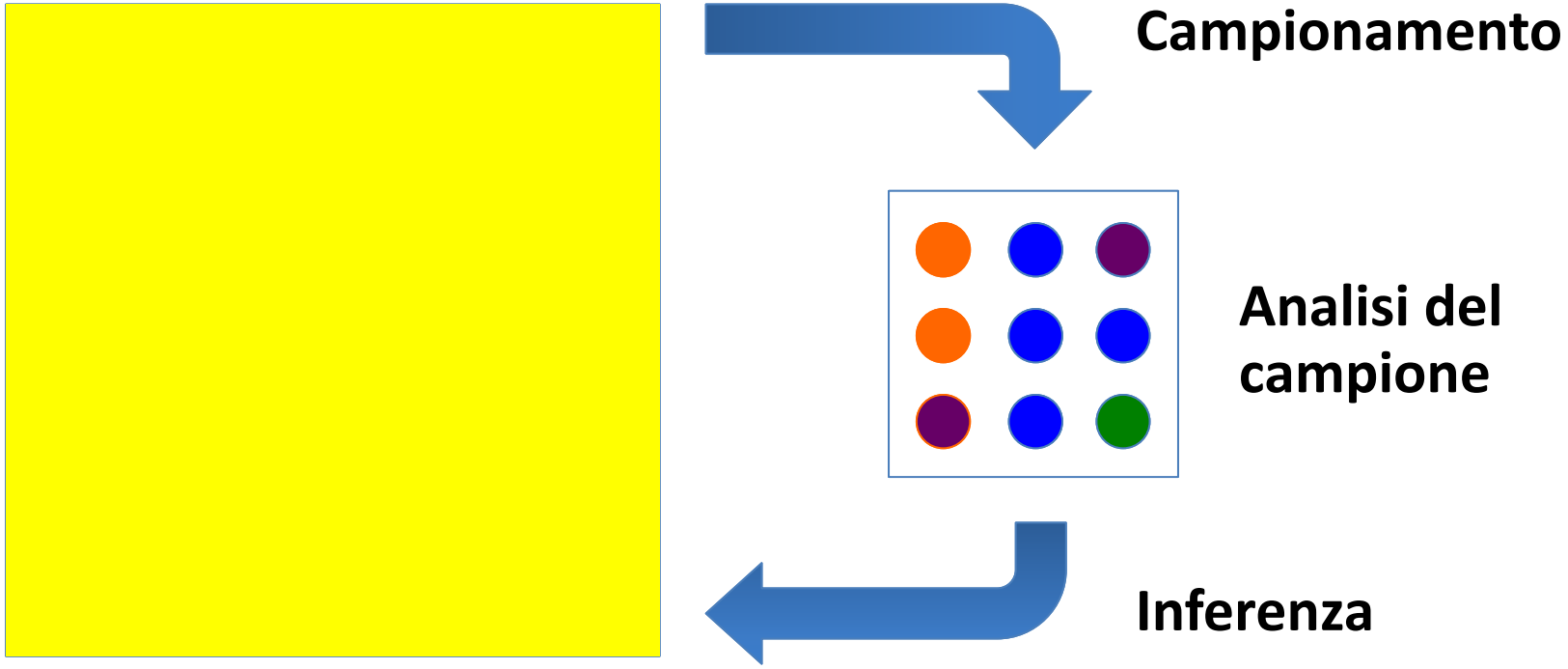
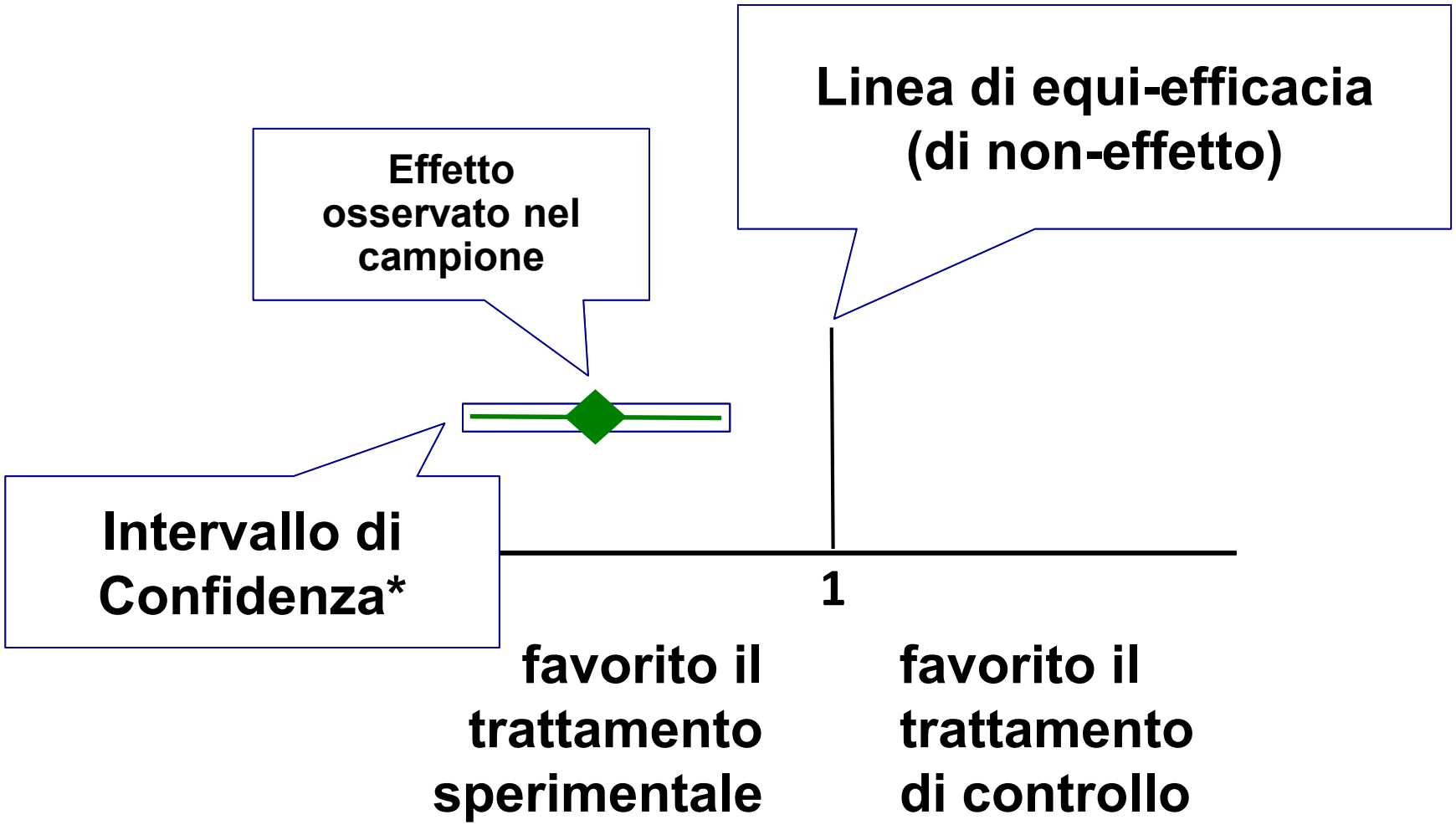


Popolazione Vs Campione

(ovvero: perché è consigliato non fidarsi…)

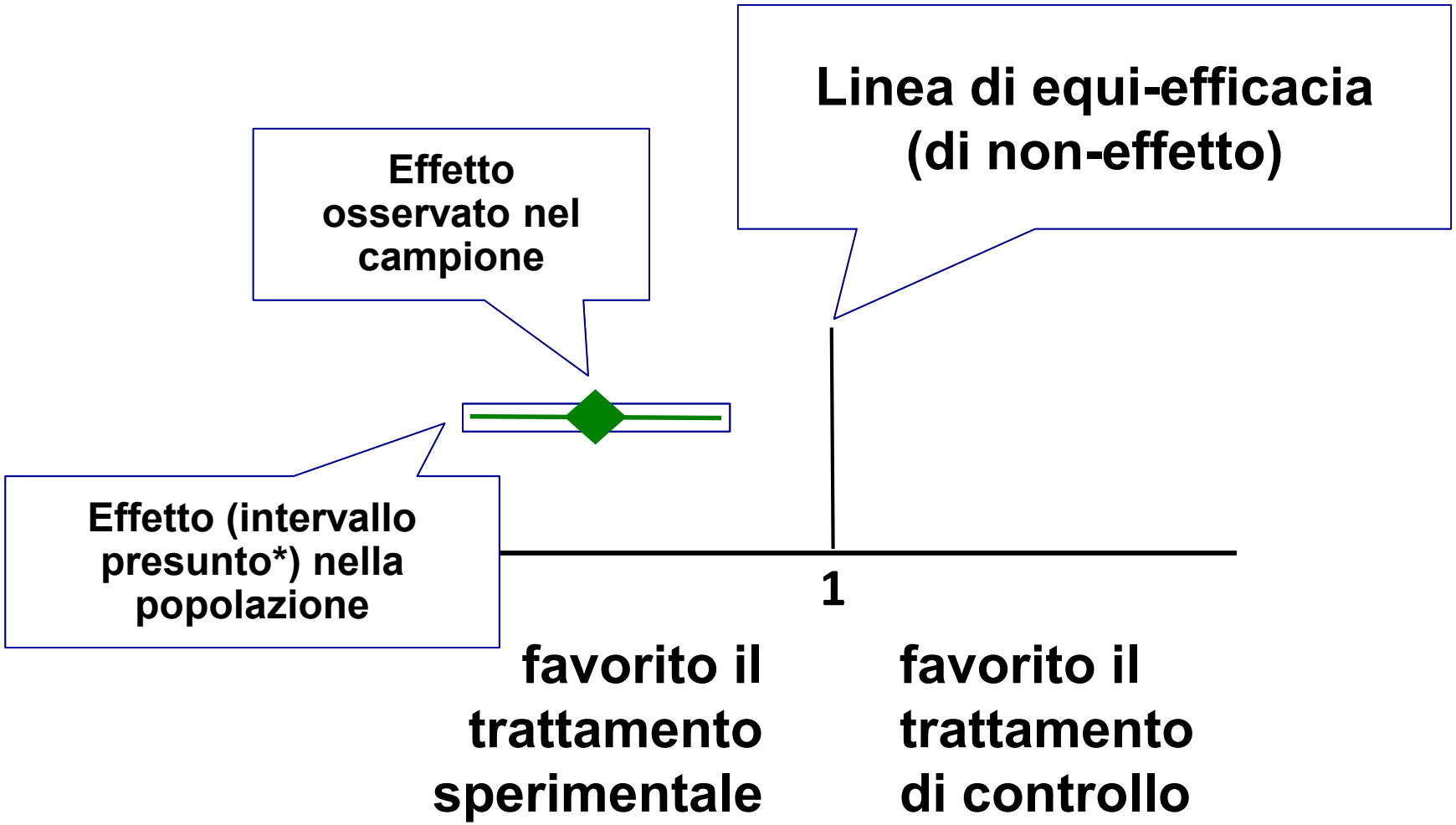


Interpretazione degli studi clinici mediante Forest (Forrest?) Plot



* convenzionalm. 95%

Interpretazione degli studi clinici mediante Forest (Forrest?) Plot



* convenzionalm. 95%

Statistical Vs Clinical Significance

- **Statistical Significance**

  "Is an observed difference likely to be real"

  ✓ dependent on the magnitude of the number of patients and/or the **magnitude of the difference** NOT on whether the difference is meaningful for patients

Interferon Alfa-2a in Advanced Renal Cell Carcinoma: Treatment Results and Survival in 159 Patients With Long-Term Follow-Up

By Lori M. Minasian, Robert J. Motzer, Lisa Gluck, Madhu Mazumdar, Vaia Vlamis, and Susan E. Krown

J Clin Oncol 11:1368-1375. © 1993

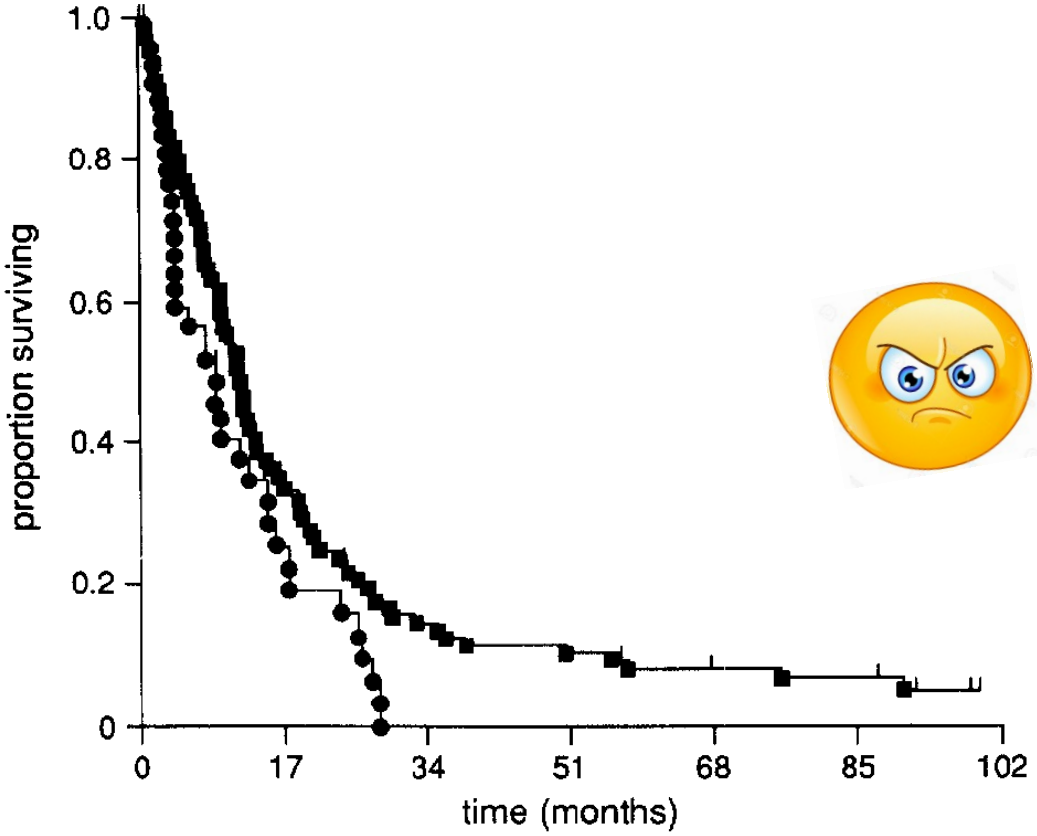


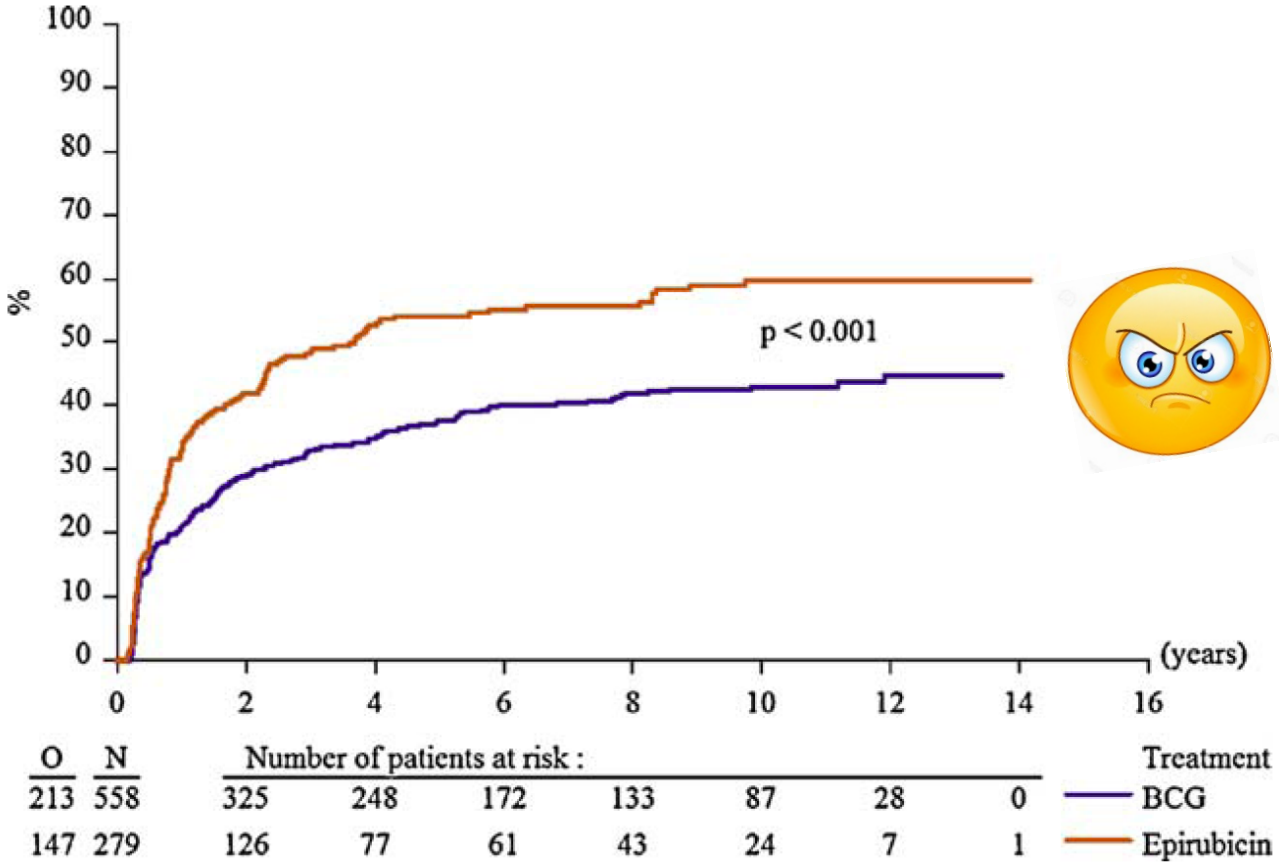
Fig 2. Overall survival for those patients with a prior nephrectomy (■; n = 114; 18 censored) as compared with those without a prior nephrectomy (●; n = 34; 8 censored). Tick mark indicates last follow-up.

EUROPEAN UROLOGY 57 (2010) 766–773

Long-Term Efficacy Results of EORTC Genito-Urinary Group Randomized Phase 3 Study 30911 Comparing Intravesical Instillations of Epirubicin, Bacillus Calmette-Guérin, and Bacillus Calmette-Guérin plus Isoniazid in Patients with Intermediate- and High-Risk Stage Ta T1 Urothelial Carcinoma of the Bladder

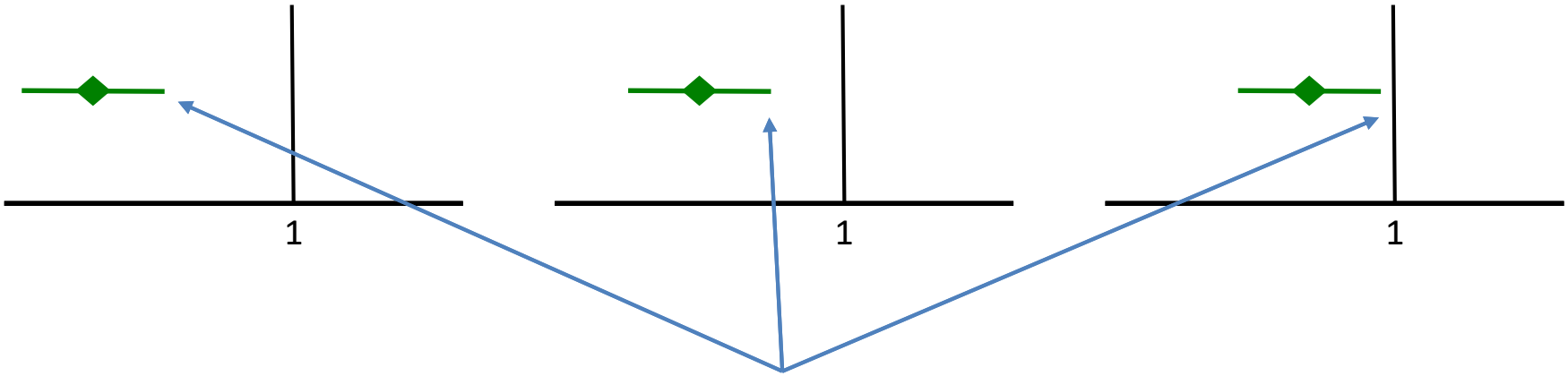
Richard J. Sylvester[a,*], *Maurizio A. Brausi*[b], *Wim J. Kirkels*[c], *Wolfgang Hoeltl*[d], *Fernando Calais Da Silva*[e], *Philip H. Powell*[f], *Stephen Prescott*[g], *Ziya Kirkali*[h], *Cees van de Beek*[i], *Thierry Gorlia*[a], *Theo M. de Reijke*[j]

EORTC Genito-Urinary Tract Cancer Group



Interpretazione statistica di uno Studio di Superiorità

Tutti e tre gli esempi indicano una differenza statisticamente significativa



L'estremo dx dell'intervallo di confidenza NON interseca la linea di non-effetto (P<0.05)

Statistical Vs Clinical Significance

- **Statistical Significance**

  "Is an observed difference likely to be real"

  ✓ dependent on the magnitude of the number of patients and/or the **magnitude of the difference** NOT on whether the difference is meaningful for patients

- **Clinical Significance**

  "Is an observed difference likely to be meaningful for patients"

  ✓ dependent on the **magnitude of the difference** NOT the number of patients

Rilevanza Clinica

Si ritiene che il trattamento in esame "A" abbia le potenzialità per migliorare il trattamento standard "B" almeno di una quantità Δ

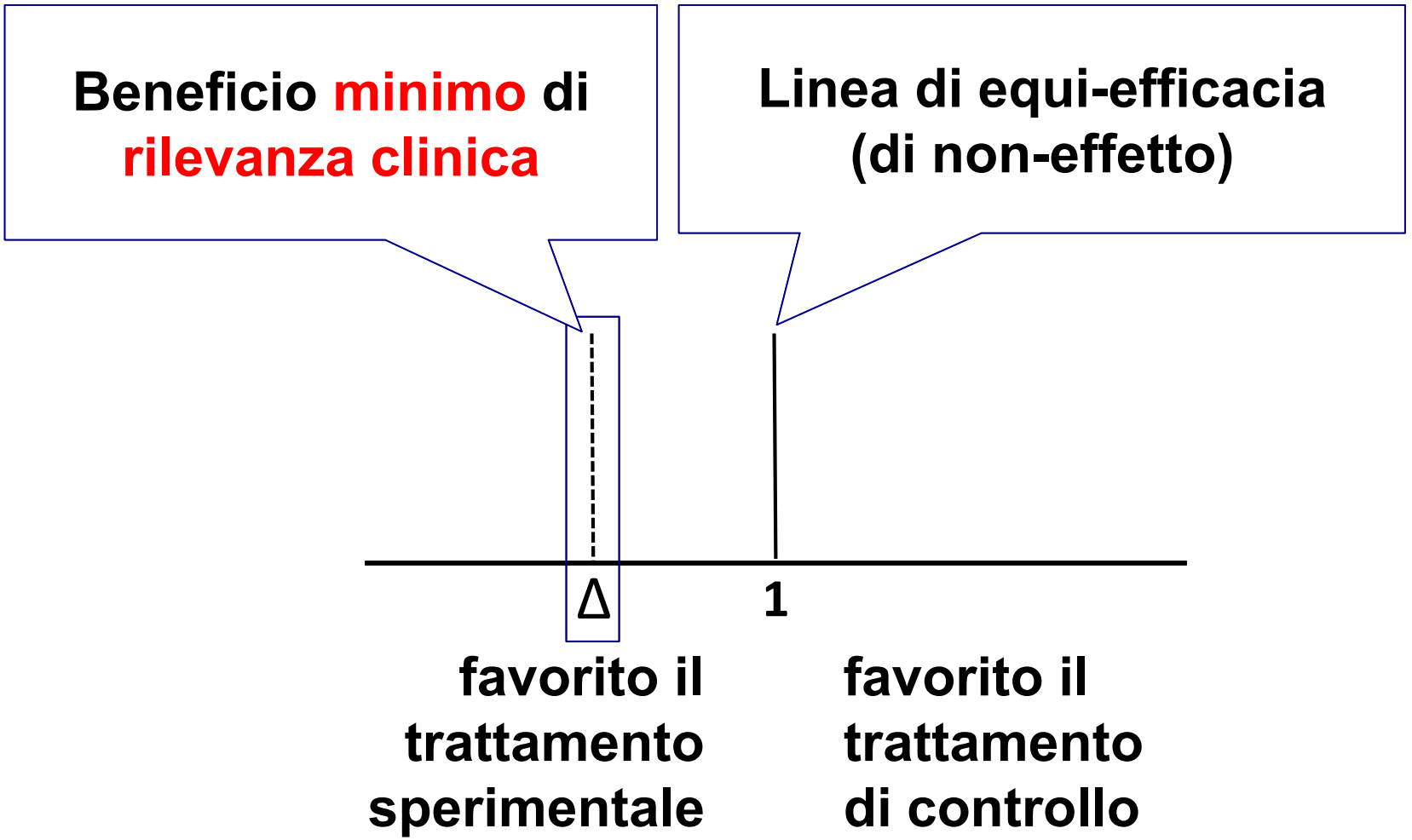
studio di superiorità

A > B di una quantità Δ di interesse clinico

studio di non inferiorità

A < B non oltre una quantità M di rilevanza clinica

Interpretazione degli studi clinici mediante Forest (Forrest?) Plot



When Are "Positive" Clinical Trials in Oncology Truly Positive?

Alberto Ocana, Ian F. Tannock

J Natl Cancer Inst 2011;103:16–20

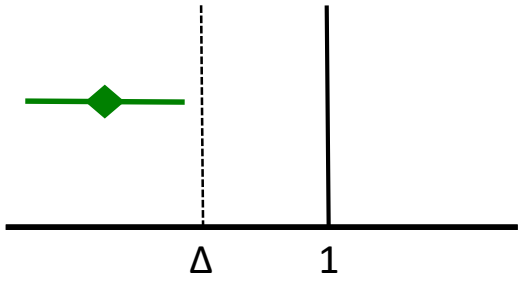
in an endpoint that directly reflects benefit (mainly OS or quality of life) to patients

Consistent with a recent commentary suggesting the need to increase the value of *delta* in future clinical trials, we provide an estimate of *delta* that would be generally accepted as representing a minimum clinically important difference in the primary endpoint: approximately 3 months increase in median OS for patients with advanced metastatic solid tumors (usually corresponding to an hazard ratio of approximately 0.75).

Interpretazione clinica di uno Studio di Superiorità

Effetto (sempre) clinicamente rilevante?

(dato uno specifico Δ di interesse)



RILEVANTE e
(del tutto) **AFFIDABILE**

Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: Results of a 24 week, double-blind, randomized Phase 3 trial

Eli M. Roth [a,*], Marja-Riitta Taskinen [b], Henry N. Ginsberg [c], John J.P. Kastelein [d], Helen M. Colhoun [e], Jennifer G. Robinson [f], Laurence Merlet [g], Robert Pordy [h], Marie T. Baccara-Dinet [i]

International Journal of Cardiology 176 (2014) 55–61

A sample size of 45 patients per treatment arm was calculated to have 95% power to detect a [redacted] in LDL-C percent change from baseline to week 24 using a 2-sided *t*-test with 5% significance, assuming a common standard deviation (SD) of 25% based on a previous alirocumab trial [1] and with an expected rate of exclusion of 5%.

Percent change in LDL-C from baseline to week 24 (ITT and on-treatment analysis).

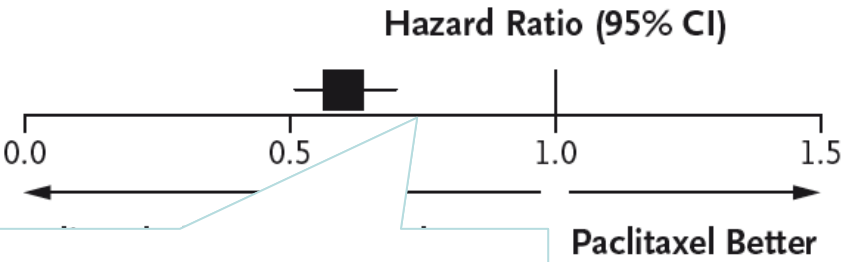
LDL-C	Alirocumab versus ezetimibe		
	LS mean difference (SE) %	95% CI	*p*-Value
ITT			
LS mean (SE) change from baseline (%)	[redacted] (4.3)	−40.2 to [redacted]	<0.0001[a]

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.

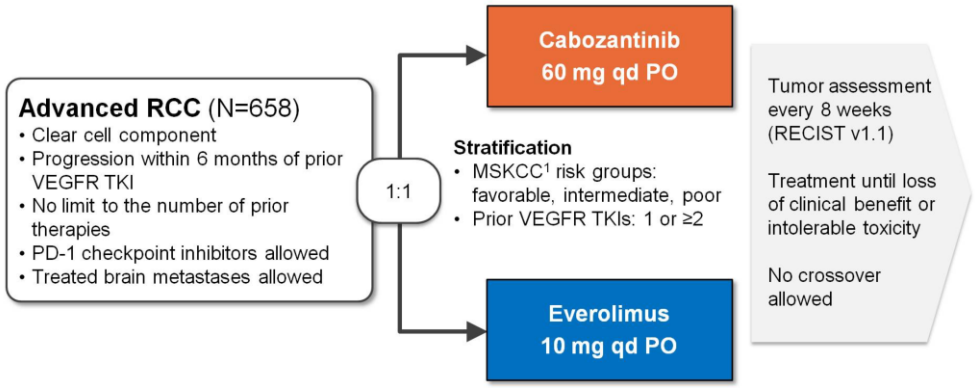
N Engl J Med 2007;357:2666-76.

Progression-free Survival (mo)		Hazard Ratio (95% CI)
Paclitaxel	Paclitaxel plus Bevacizumab	
5.9	11.8	0.60 (0.51-

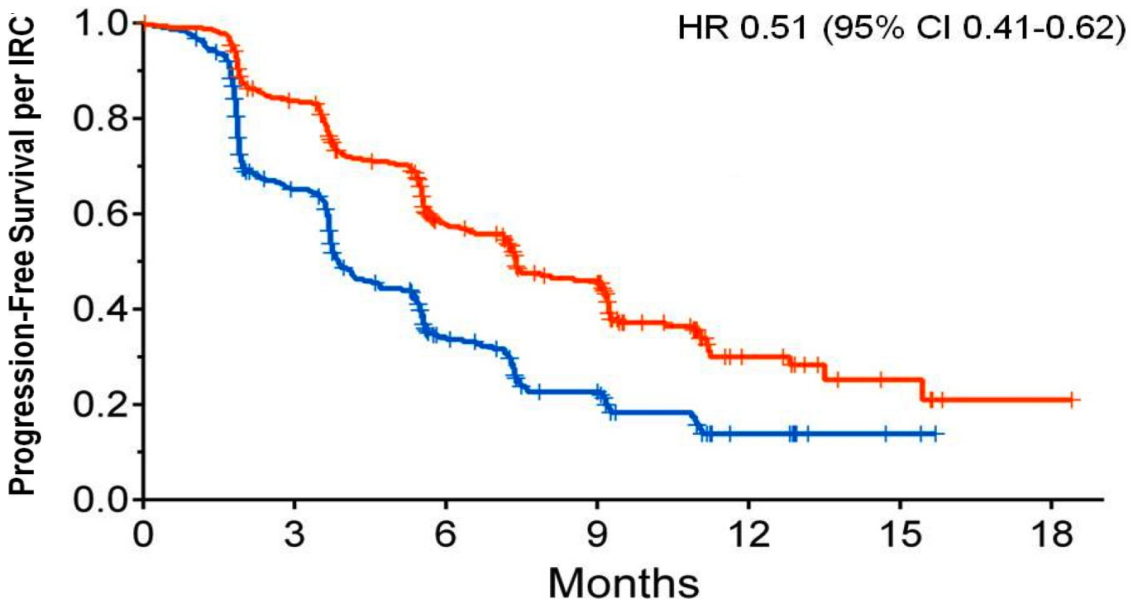


Beneficio minimo preordinato (*Target* Δ) = 0.75

METEOR Study Design



Hypothesized hazard ratio for PFS: 0.667



Presented By Toni Choueiri at 2016 ASCO Annual Meeting

Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy

Howard I. Scher, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Mary-Ellen Taplin, M.D., Cora N. Sternberg, M.D., Kurt Miller, M.D., Ronald de Wit, M.D., Peter Mulders, M.D., Ph.D., Kim N. Chi, M.D., Neal D. Shore, M.D., Andrew J. Armstrong, M.D., Thomas W. Flaig, M.D., Aude Fléchon, M.D., Ph.D., Paul Mainwaring, M.D., Mark Fleming, M.D., John D. Hainsworth, M.D., Mohammad Hirmand, M.D., Bryan Selby, M.S., Lynn Seely, M.D., and Johann S. de Bono, M.B., Ch.B., Ph.D., for the AFFIRM Investigators*

N Engl J Med 2012;367:1187-97.

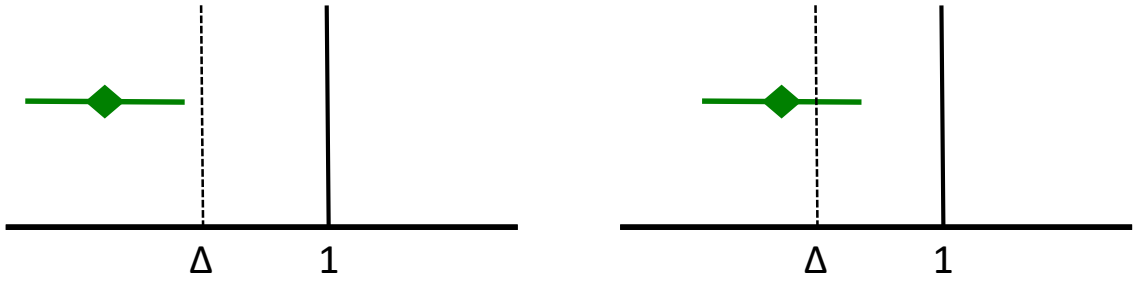
The study was designed to have a power of 90% to detect a hazard ratio of [redacted] for death in the enzalutamide group, as compared with the placebo group, with a two-sided type I error rate of 0.05. We planned to

At the time of the prespecified interim analysis, the use of enzalutamide resulted in a 37% reduction in the risk of death, as compared with placebo (hazard ratio for death, [redacted] 95% CI, 0.53 to [redacted] P<0.001).

Interpretazione clinica di uno Studio di Superiorità

Effetto (sempre) clinicamente rilevante?

(dato uno specifico Δ di interesse)



RILEVANTE e
(del tutto) **AFFIDABILE**

RILEVANTE e
(ragionevolmente) **AFFIDABILE**

Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial

Christian Confavreux, Paul O'Connor, Giancarlo Comi, Mark S Freedman, Aaron E Miller, Tomas P Olsson, Jerry S Wolinsky, Teresa Bagulho, Jean-Luc Delhay, Deborah Dukovic, Philippe Truffinet, Ludwig Kappos, for the TOWER Trial Group†*

Lancet Neurol **2014; 13: 247–56**

We estimated that 370 patients randomly assigned to each treatment group would provide 94% power in annualised relapse rate at the two-tailed significance level of $\alpha=0\cdot05$, assuming an annualised relapse rate of 0·74 in the placebo group.

	Placebo (n=388)	Teriflunomide 7 mg (n=407)	Teriflunomide 14 mg (n=370)
Annualised relapse rate (primary endpoint)			
Adjusted annualised relapse rate* (95% CI)	0·50 (0·43 to 0·58)	0·39 (0·33 to 0·46)	0·32 (0·27 to 0·38)
Relative risk (95% CI)	NA	0·78 (0·63 to 0·96)	0·64 (0·51 to 0·79)
Relative reduction versus placebo, % (95% CI)	NA	22·3% (4·2 to 37·0)	
p value versus placebo	NA	0·0183	0·0001

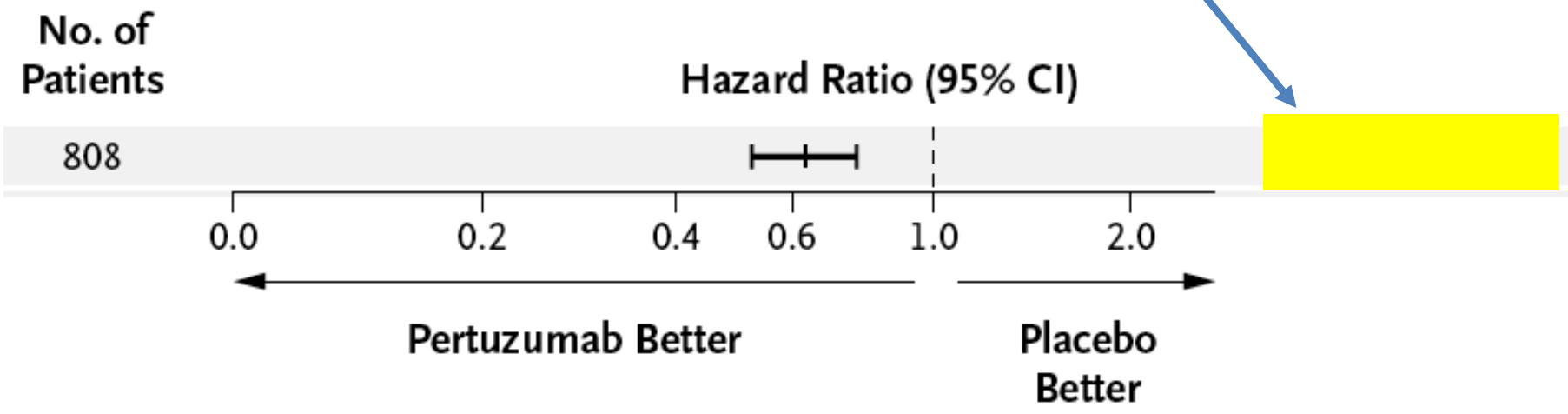
Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D., Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D., Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M., and Sandra M. Swain, M.D., for the CLEOPATRA Study Group*

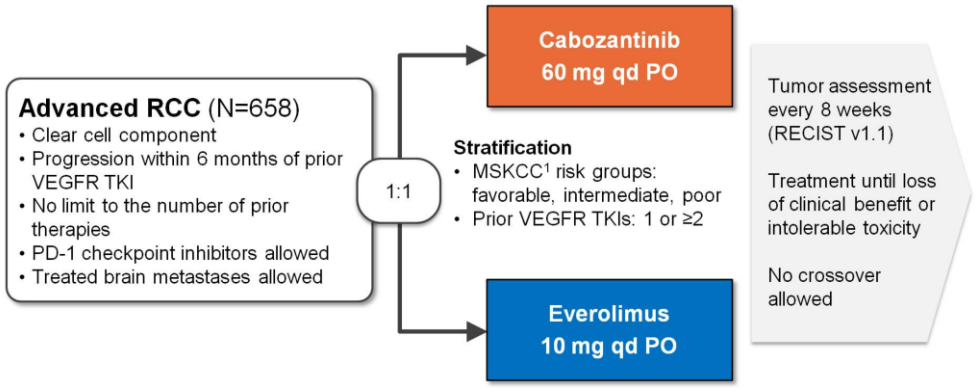
N Engl J Med 2012;366:109-19.

STATISTICAL ANALYSIS

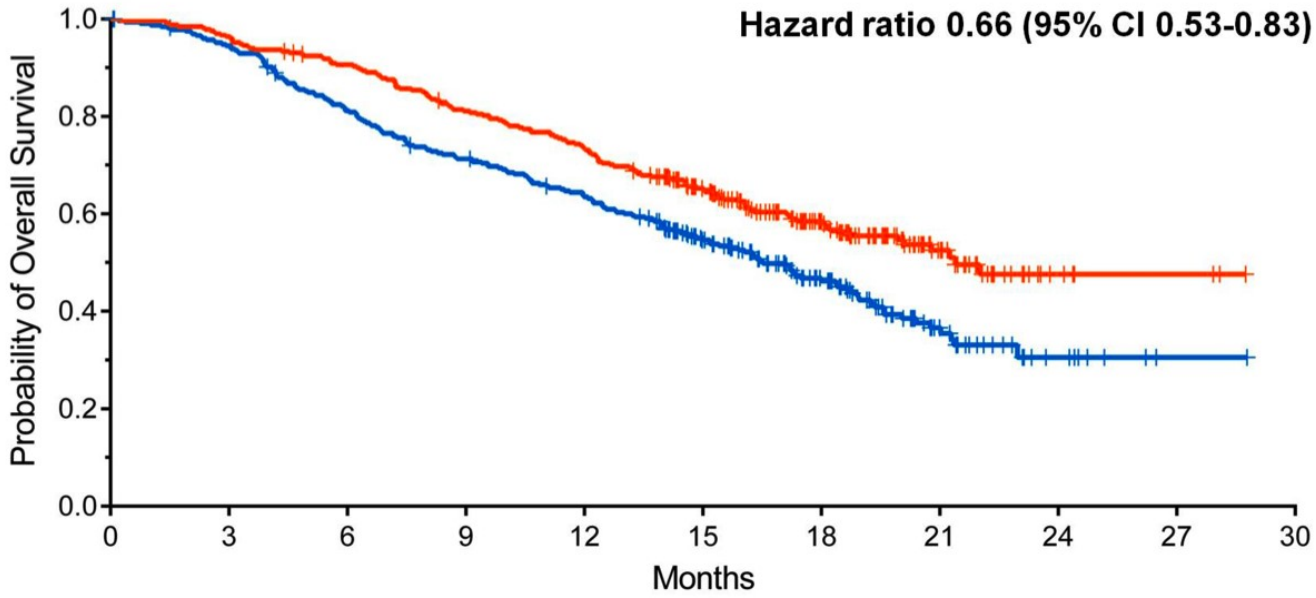
We planned to enroll 800 patients in the study and to perform the primary analysis of progression-free survival after the occurrence of approximately 381 events of independently assessed disease progression or death from any cause within 18 weeks after the last independent assessment of tumors; with that number of events, it was estimated that the study would have 80% power to detect a 33% improvement in median progression-free survival in the pertuzumab group at a two-sided significance level of 5%.



METEOR Study Design



Hypothesized hazard ratio for OS: 0.75



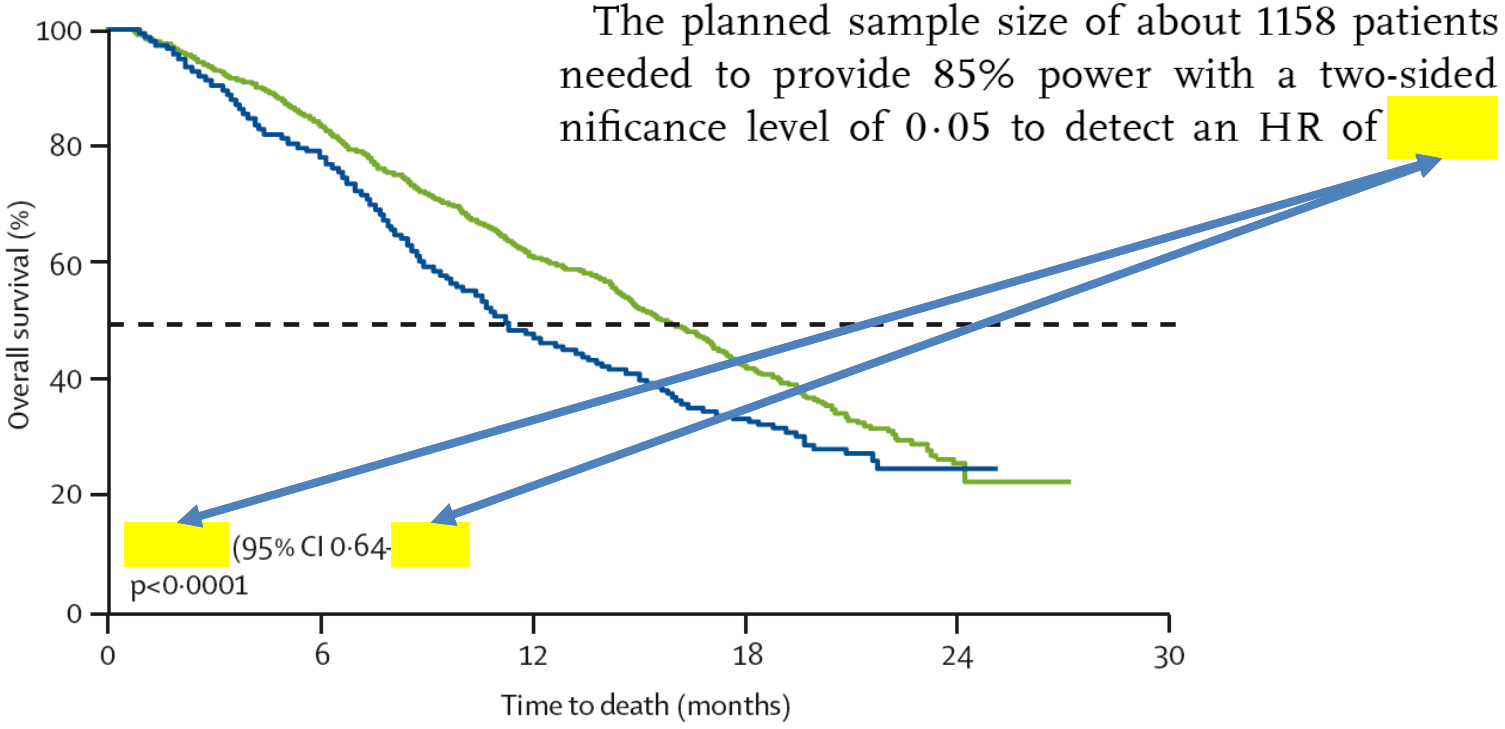
Presented By Toni Choueiri at 2016 ASCO Annual Meeting

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**

The planned sample size of about 1158 patients was needed to provide 85% power with a two-sided significance level of 0·05 to detect an HR of



Interpretazione clinica di uno Studio di Superiorità

Effetto (sempre) clinicamente rilevante?

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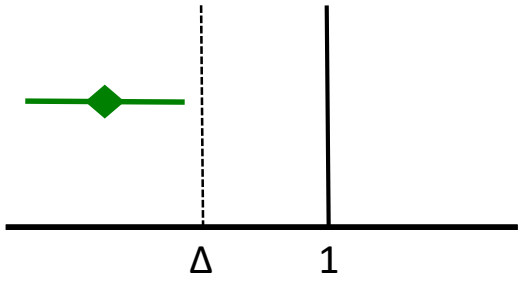
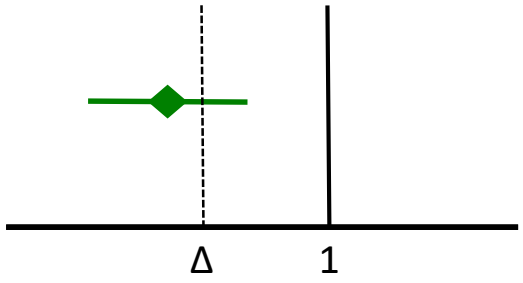


RILEVANTE e
(del tutto) **AFFIDABILE**



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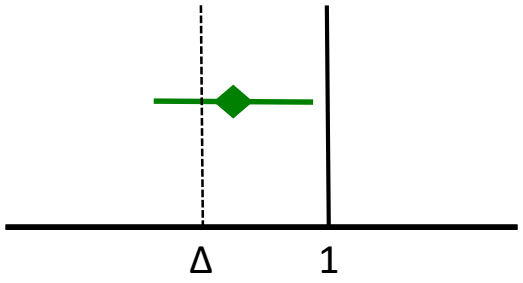

STATISTICAMENTE SIGNIFICATIVO

Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial

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Relative risk (95% CI)	NA	0·78 (0·63 to 0·96)	0·64 (0·51 to 0·79)
Relative reduction versus placebo, % (95% CI)	NA	[redacted]	36·3% (20·7 to 48·8)
p value versus placebo	NA	0·0183	0·0001

JAMA | Original Investigation

Effect of Intravesical Instillation of Gemcitabine vs Saline Immediately Following Resection of Suspected Low-Grade Non–Muscle-Invasive Bladder Cancer on Tumor Recurrence
SWOG S0337 Randomized Clinical Trial

Edward M. Messing, MD; Catherine M. Tangen, DrPH; Seth P. Lerner, MD; Deepak M. Sahasrabudhe, MD; Theresa M. Koppie, MD; David P. Wood Jr, MD; Philip C. Mack, PhD; Robert S. Svatek, MD; Christopher P. Evans, MD; Khaled S. Hafez, MD; Daniel J. Culkin, MD; Timothy C. Brand, MD; Lawrence I. Karsh, MD; Jeffrey M. Holzbeierlein, MD; Shandra S. Wilson, MD; Guan Wu, MD, PhD; Melissa Plets, MS; Nicholas J. Vogelzang, MD; Ian M. Thompson Jr, MD

JAMA. 2018;319(18):1880-1888. doi:10.1001/jama.2018.4657

Gemcitabine Group		Saline Group		
No. With Outcome/ Total No.[a]	4-y Recurrence Rate, % (95% CI)[b]	No. With Outcome/ Total No.[a]	4-y Recurrence Rate, % (95% CI)[b]	Hazard Ratio (95% CI)[c]
67/201	35 (29-42)	91/205	47 (41-54)	0.66 (0.48-0.90)

-12% absolute decrease

Assuming exponential distribution, 2 years of accrual and 2 additional years of follow-up, and a 1-sided $\alpha = .025$ with a stratified log-rank test, there would be 89% power to detect a hazard ratio (HR) of 0.65, which translates into an absolute decrease of 15%in recurrence rates at 4 years.

JAMA | Original Investigation

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JAMA. 2018;319(18):1880-1888. doi:10.1001/jama.2018.4657

EDITORIAL

Simplifying Treatment and Reducing Recurrence for Patients With Early-Stage Bladder Cancer

Samuel D. Kaffenberger, MD; David C. Miller, MD, MPH; Matthew E. Nielsen, MD, MS

Given the potential benefits of these findings, it will be important to educate and mobilize patients with bladder cancer, physicians, advocacy organizations, and health system leaders to facilitate diffusion of this simple, safe, effective, and affordable innovation in the treatment of bladder cancer.

?

?

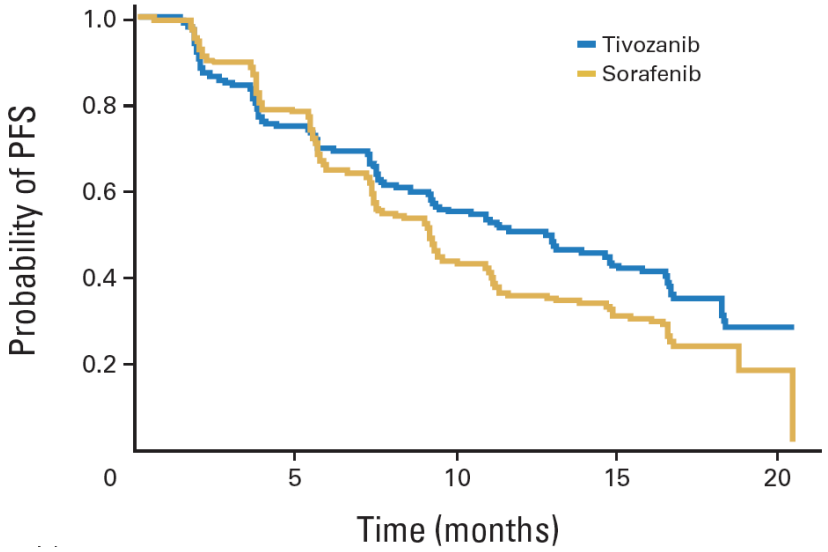
Tivozanib Versus Sorafenib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma: Results From a Phase III Trial

Robert J. Motzer, Dmitry Nosov, Timothy Eisen, Igor Bondarenko, Vladimir Lesovoy, Oleg Lipatov, Piotr Tomczak, Oleksiy Lyulko, Anna Alyasova, Mihai Harza, Mikhail Kogan, Boris Y. Alekseev, Cora N. Sternberg, Cezary Szczylik, David Cella, Cristina Ivanescu, Andrew Krivoshik, Andrew Strahs, Brooke Esteves, Anna Berkenblit, and Thomas E. Hutson

J Clin Oncol 31:3791-3799. © 2013 by American Society of Clinical Oncology

Statistical Methods and Analysis

Target enrollment was 500 patients (250 patients per arm) to observe 310 events (progression or death) yielding 90% power to detect a difference ($P < .05$) between treatment arms with respect to PFS, assuming the median PFS for patients receiving sorafenib and tivozanib was 6.7 months and 9.7 months, respectively (a projected increase of 3 months or 44.8%).



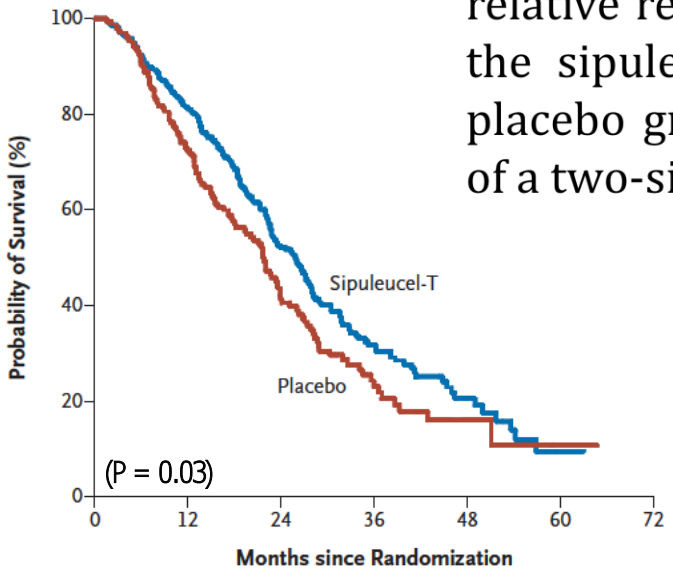
Median PFS, based on independent radiology review, was 11.9 months for tivozanib and 9.7 months for sorafenib (HR, 0.797; 95% CI, 0.639 to 0.993; P .042).

Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer

Philip W. Kantoff, M.D., Celestia S. Higano, M.D., Neal D. Shore, M.D., E. Roy Berger, M.D., Eric J. Small, M.D., David F. Penson, M.D., Charles H. Redfern, M.D., Anna C. Ferrari, M.D., Robert Dreicer, M.D., Robert B. Sims, M.D., Yi Xu, Ph.D., Mark W. Frohlich, M.D., and Paul F. Schellhammer, M.D., for the IMPACT Study Investigators*

N ENGL J MED 363;5 NEJM.ORG JULY 29, 2010

We estimated that we would need to enroll 500 patients in order to analyze 304 deaths, providing a power of at least 88% to detect a relative reduction in the risk of death of 31% in the sipuleucel-T group, as compared with the placebo group (hazard ratio, 0.69) with the use of a two-sided alpha level of 0.05.



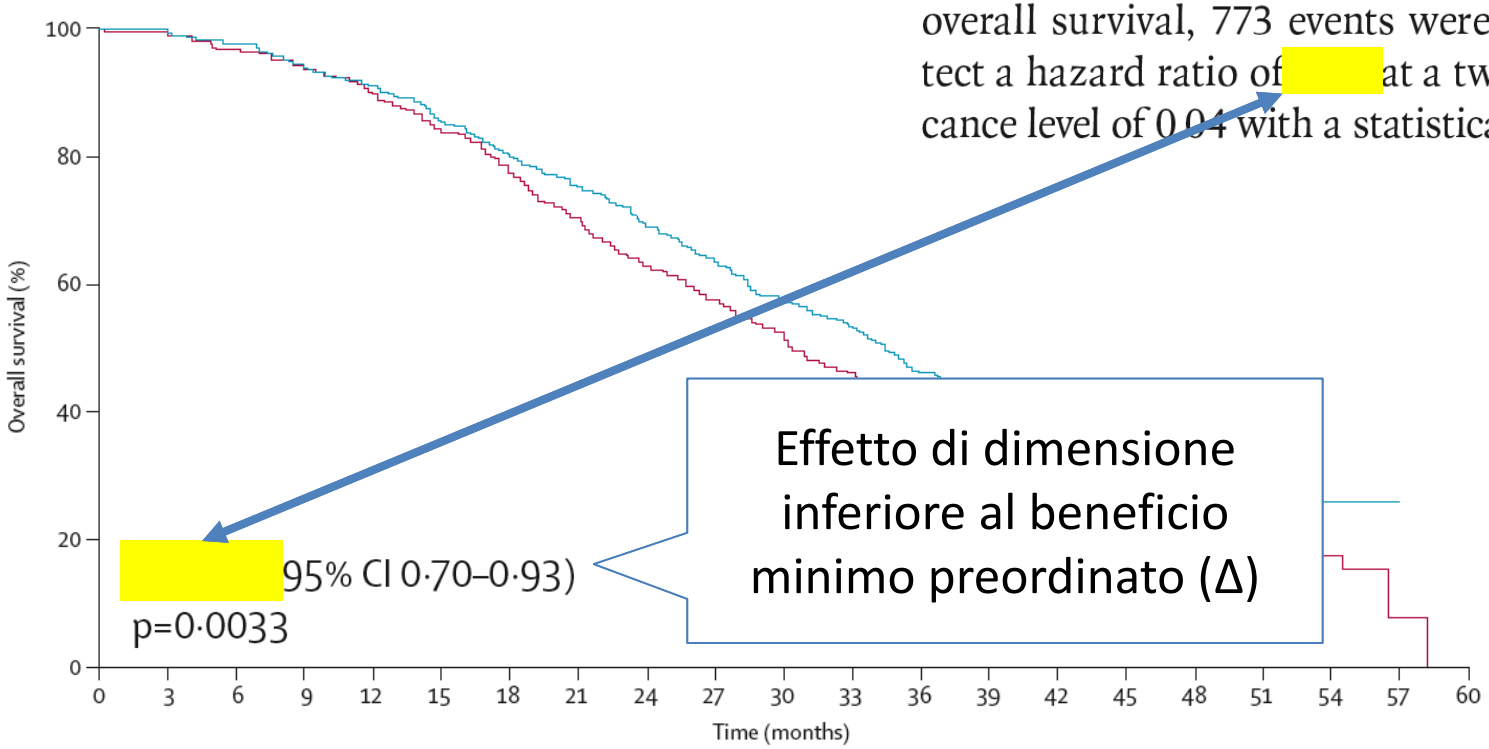
For men in the sipuleucel-T group, as compared with those in the placebo group, the adjusted hazard ratio for death was 0.78 (95% CI, 0.61 to 0.98).

Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study

*Charles J Ryan, Matthew R Smith, Karim Fizazi, Fred Saad, Peter F A Mulders, Cora N Sternberg, Kurt Miller, Christopher J Logothetis, Neal D Shore, Eric J Small, Joan Carles, Thomas W Flaig, Mary-Ellen Taplin, Celestia S Higano, Paul de Souza, Johann S de Bono, Thomas W Griffin, Peter De Porre, Margaret K Yu, Youn C Park, Jinhui Li, Thian Kheoh, Vahid Naini, Arturo Molina, Dana E Rathkopf, for the COU-AA-302 Investigators**

***Lancet Oncol* 2015; 16: 152–60**

For the coprimary end point of overall survival, 773 events were required to detect a hazard ratio of [redacted] at a two-tailed significance level of 0·04 with a statistical power of 85%.



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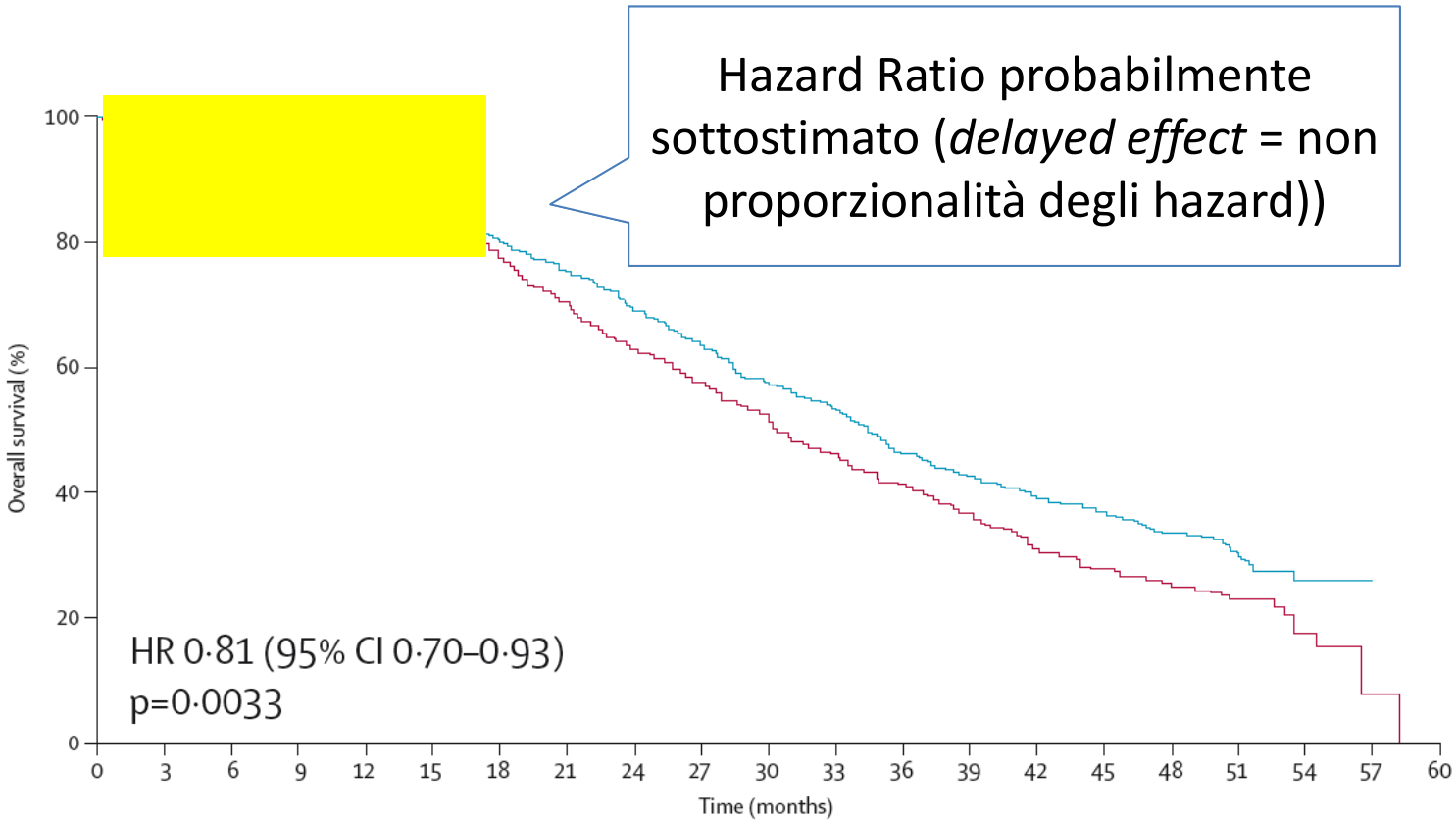
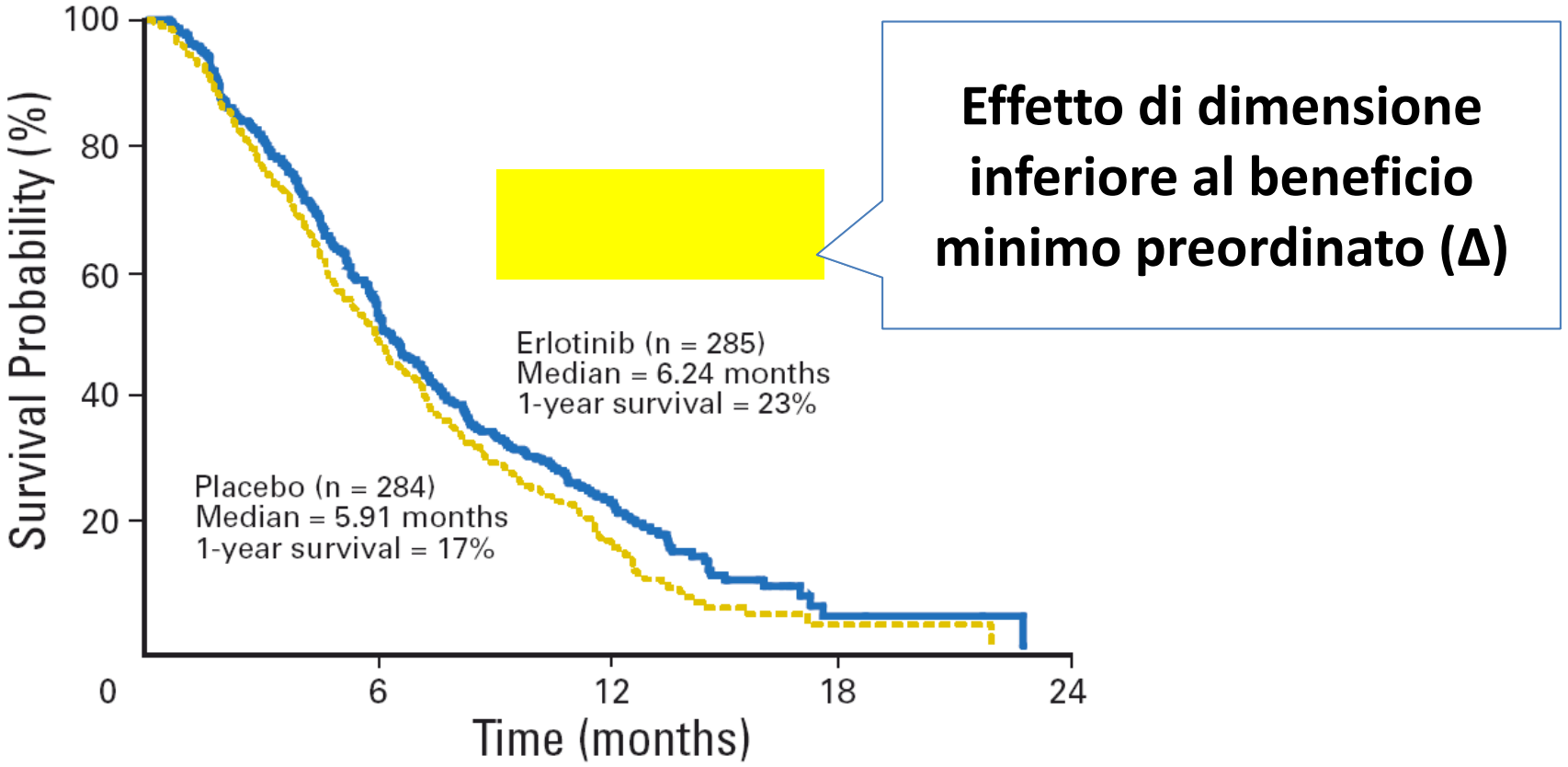


Erlotinib Plus Gemcitabine Compared With Gemcitabine Alone in Patients With Advanced Pancreatic Cancer: A Phase III Trial of the National Cancer Institute of Canada Clinical Trials Group

Malcolm J. Moore, David Goldstein, John Hamm, Arie Figer, Joel R. Hecht, Steven Gallinger, Heather J. Au, Pawel Murawa, David Walde, Robert A. Wolff, Daniel Campos, Robert Lim, Keyue Ding, Gary Clark, Theodora Voskoglou-Nomikos, Mieke Ptasynski, and Wendy Parulekar

J Clin Oncol 25:1960-1966. © 2007 by American Society of Clinical Oncology

Target Δ: HR erlotinib:placebo = 0.75 (**2 months** OS improvement)
Analysis after **381 events** (450 patients; α 5%, power 80%)



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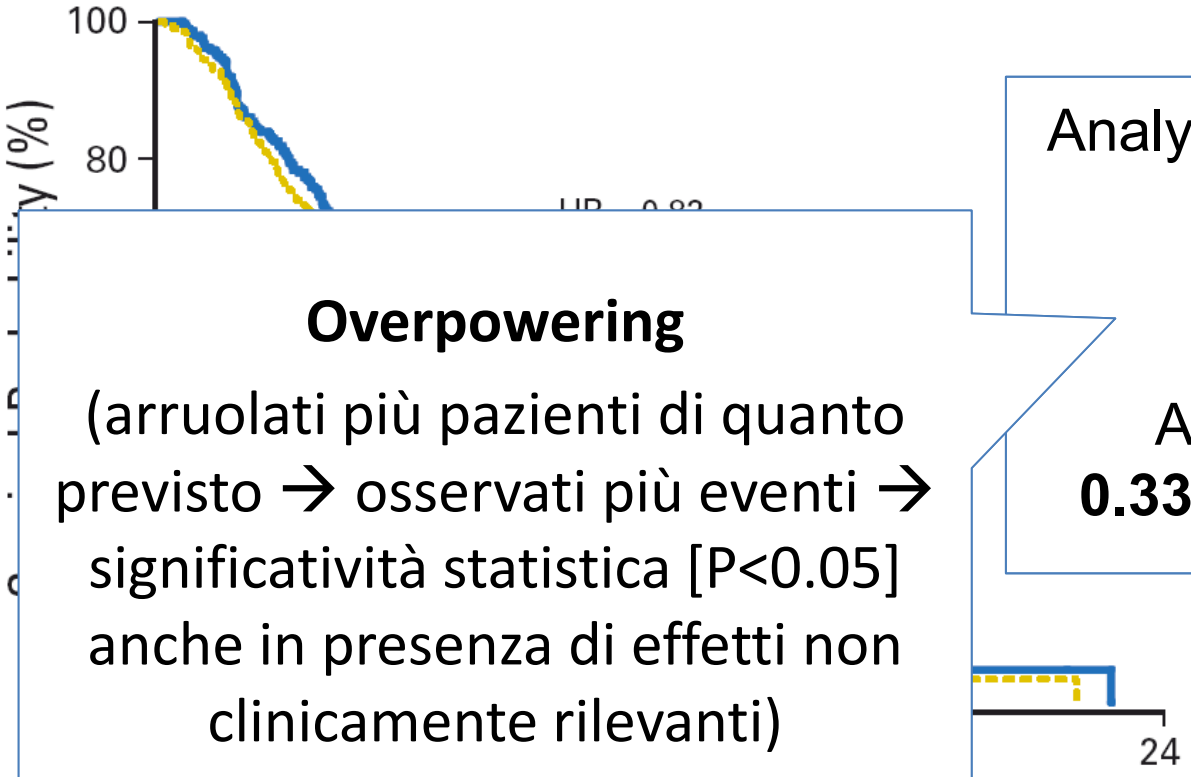

Analysis after **486 events** (569 patients)

Actual difference: **0.33 months** (10 days)

Overpowering

(arruolati più pazienti di quanto previsto → osservati più eventi → significatività statistica [P<0.05] anche in presenza di effetti non clinicamente rilevanti)

Symptom Endpoints (Patient-Reported Outcomes)

- Blinding is often difficult
- Data are often missing or incomplete
- Few validated instruments

Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

Robert J. Motzer, M.D., Thomas E. Hutson, D.O., David Cella, Ph.D., James Reeves, M.D., Robert Hawkins, M.B., B.S., Ph.D., Jun Guo, Ph.D., Paul Nathan, M.B., B.S., Ph.D., Michael Staehler, M.D., Paul de Souza, M.B., B.S., Ph.D., Jaime R. Merchan, M.D., Ekaterini Boleti, M.D., Ph.D., Kate Fife, M.D., Jie Jin, M.D., Robert Jones, Ph.D., Hirotsugu Uemura, M.D., Ph.D., Ugo De Giorgi, M.D., Ulrika Harmenberg, M.D., Ph.D., Jinwan Wang, M.D., Cora N. Sternberg, M.D., Keith Deen, M.S., Lauren McCann, Ph.D., Michelle D. Hackshaw, Ph.D., Rocco Crescenzo, D.O., Lini N. Pandite, M.D., and Toni K. Choueiri, M.D.

N Engl J Med 2013;369:722-31

Table 2. Change in Health-Related Quality of Life during the First 6 Months for 927 Patients Treated in the Study.*

Instrument	Pazopanib	Sunitinib				Effect Size‖
	number of patients					
[redacted]						0.24
FKSI-19**						
Treatment side effects	351	382	0.31	0.03	Pazopanib	0.14
Disease-related physical symptoms	378	407	0.78	0.03	Pazopanib	0.13
Disease-related emotional symptoms	370	402	–0.05	0.41	Neither	–0.04
Functional well-being	378	403	0.31	0.10	Neither	0.09
Total score	377	408	1.41	0.02	Pazopanib	0.14

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N Engl J Med 2013;369:722-31

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Instrument	Pazopanib	Sunitinib	[redacted]	P Value§	Drug Favored According to Significant Difference¶	Effect Size‖
	number of patients					
FACIT-F**	377	403	2.32	<0.001	Pazopanib	0.24
FKSI-19**						
Treatment side effects	3			0.03	Pazopanib	0.14
Disease-related physical symptoms	3			0.03	Pazopanib	0.13
Disease-related emotional symptoms	3			0.41	Neither	–0.04
Functional well-being	378	403	0.31	0.10	Neither	0.09
Total score	377	408	1.41	0.02	Pazopanib	0.14

Rilevanza dell'effetto da rapportare alla M.I.D. specifica

Minimal (Clinical) Interesting Difference (MID / MCID)

the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management

- it’s easily understood by clinicians as a key concept in the interpretability of PRO scores;
- will inform judgments about the success-fulness of an intervention;

The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation

Kimberly Webster, David Cella* and Kathleen Yost

Health and Quality of Life Outcomes 2003, **1**:79

Table 1: Minimally important differences for select FACIT scales

Instrument	Scale/Subscale	MID (points)	Reference
FACT-G	PWB	2–3	[28]
	SWB	NA	
	EWB	2*	[28,29]
	FWB	2–3	[28]
	Total FACT-G	3–7	[27,28,30,31]
FACT-Anemia			[27,31]
	TOI-Fatigue	5	[27]
	TOI-Anemia	6	
	Total FACT-Anemia	7	
FACT-Breast	Breast cancer subscale	2–3	[30]
	TOI-Breast	5–6	
	Total FACT-Breast	7–8	
FACT-Colorectal	Colorectal cancer subscale	2–3	[32]
	TOI-Colorectal	4–6	
	Total FACT-Colorectal	5–8	
FACT-Head & Neck	Total FACT-Head & Neck	6–12	[33]
FACT-Lung	Lung cancer subscale	2–3	[34]
	TOI-Lung	5–6	

*This MID should be considered tentative as it may be revised based on future research.

Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial

Yohann Loriot, Kurt Miller, Cora N Sternberg, Karim Fizazi, Johann S De Bono, Simon Chowdhury, Celestia S Higano, Sarah Noonberg, Stefan Holmstrom, Harry Mansbach, Frank G Perabo, De Phung, Cristina Ivanescu, Konstantina Skaltsa, Tomasz M Beer, Bertrand Tombal

Lancet Oncol 2015 Published Online April 15, 2015

	Enzalutamide	Placebo	Treatment difference*	p value
FACT-P				
FACT-P total score	−5·08 (−6·87 to −3·28)	−10·87 (−13·49 to −8·25)	5·80 (3·18 to 8·41)	<0·0001
EQ-5D				
Utility index	−0·07 (−0·09 to −0·05)	−0·10 (−0·14 to −0·06)	0·03 (−0·00 to 0·07)	0·080
VAS score	−5·19 (−7·14 to −3·23)	−9·76 (−12·61 to −6·92)	4·58 (1·85 to 7·31)	0·0010
BPI-SF				
Worst pain	0·90 (0·64 to 1·17)	1·30 (1·00 to 1·61)	−0·40 (−0·66 to −0·15)	0·0022

	Established MID range	MID used in PREVAIL
(FACT-P) Total score	6–10[22]	10
EQ-5D utility index	0·04–0·14[30]	0·14
EQ-5D VAS	7–11[30]	11
Worst pain	Increase ≥30% and ≥2 points from baseline[31]	Increase ≥30% and ≥2 points from baseline

Minimal Interesting Difference

… the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate a change in the patient's management

Vista la migliore tollerabilità del trattamento in esame “A”, si è disposti ad accettarne una eventuale minore efficacia rispetto al trattamento standard “B” purché questa non vada oltre un margine M

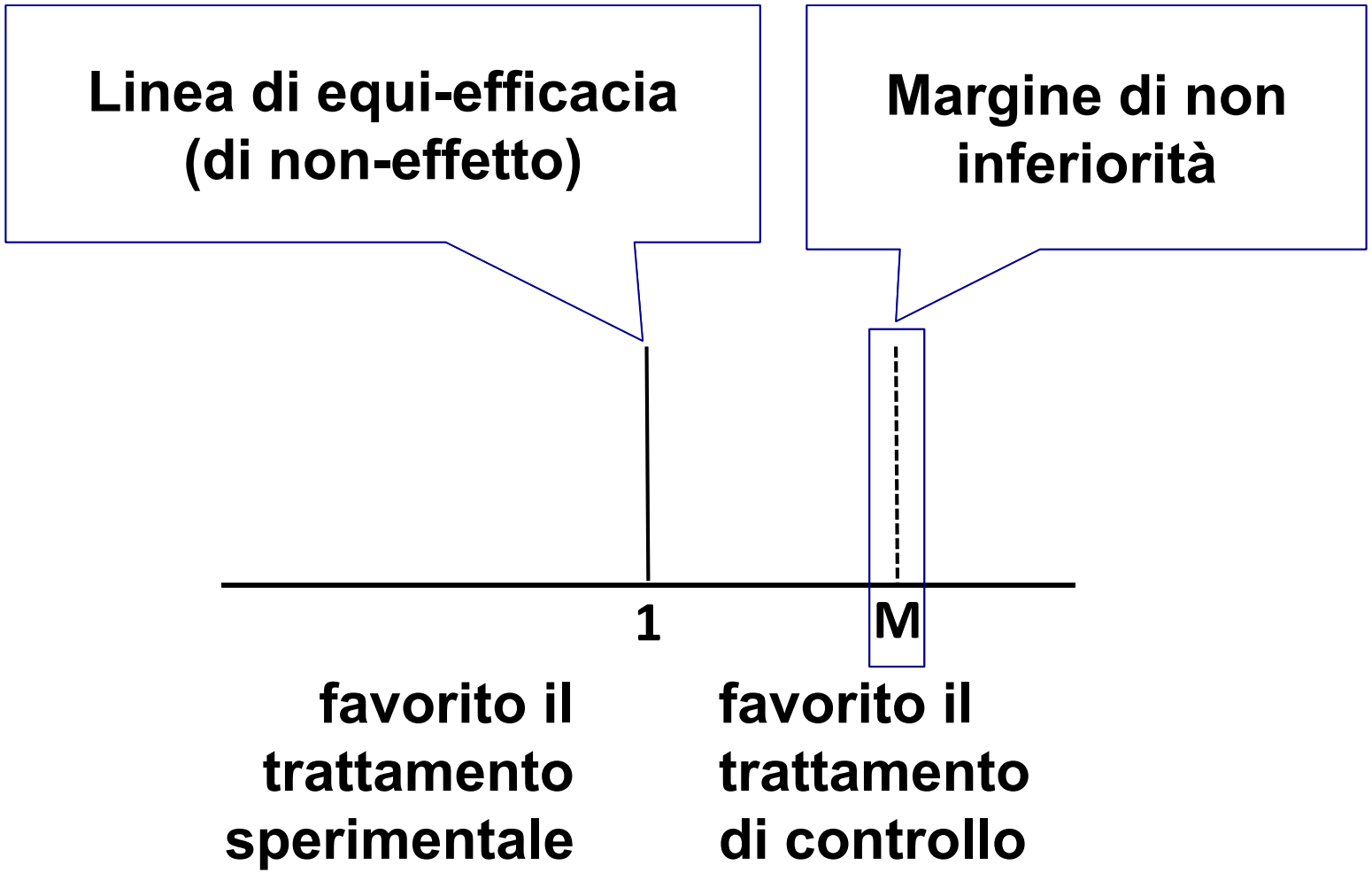
studio di superiorità

A > B di una quantità Δ di interesse clinico

studio di non inferiorità

A < B non oltre una quantità M di rilevanza clinica

Interpretazione degli studi clinici mediante Forest (Forrest?) Plot



Through the looking glass: understanding non-inferiority

Jennifer Schumi* and Janet T Wittes

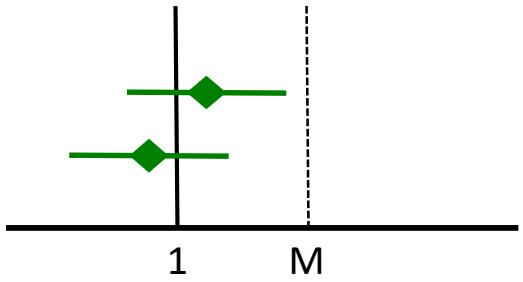
Trials 2011, **12**:106

One focuses on the upper bound for this non-inferiority comparison; what happens at the lower end of the CI is not the primary concern.

Bear in mind that the opposite of 'non-inferior' is not 'inferior'; it is 'not non-inferior'.

Interpretazione clinica di uno Studio di Non-Inferiorità

(dato uno specifico M di interesse)



Dimostrazione di Non-Inferiorità

Il limite superiore dell'intervallo di confidenza non interseca la linea di non-effetto …indipendentemente da dove si colloca la stima puntuale dell'effetto

Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial

Dipen J Parekh, Isildinha M Reis, Erik P Castle, Mark L Gonzalgo, Michael E Woods, Robert S Svatek, Alon Z Weizer, Badrinath R Konety, Mathew Tollefson, Tracey L Krupski, Norm D Smith, Ahmad Shabsigh, Daniel A Barocas, Marcus L Quek, Atreya Dash, Adam S Kibel, Lynn Shemanski, Raj S Pruthi, Jeffrey Scott Montgomery, Christopher J Weight, David S Sharp, Sam S Chang, Michael S Cookson, Gopal N Gupta, Alex Gorbonos, Edward M Uchio, Eila Skinner, Vivek Venkatramani, Nachiketh Soodana-Prakash, Kerri Kendrick, Joseph A Smith Jr, Ian M Thompson

Lancet **2018; 391: 2525–36**

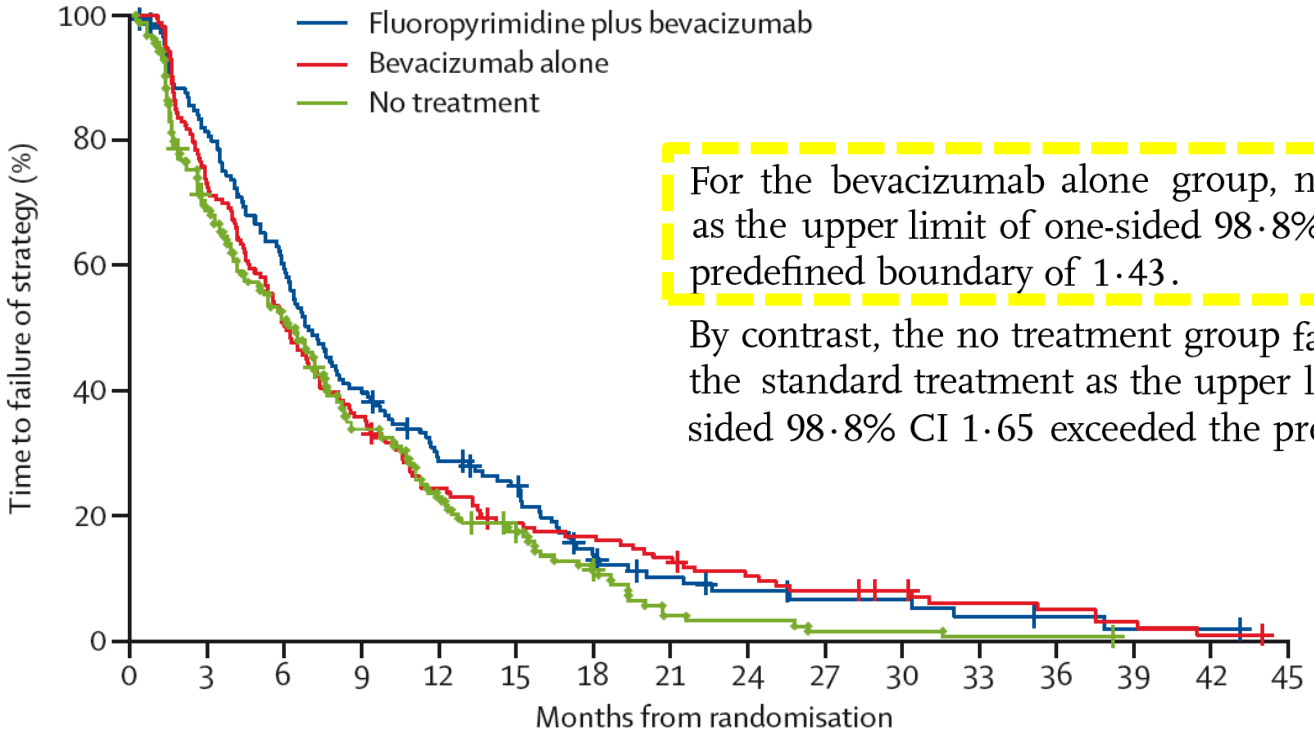
Non-inferiority would be established if the lower bound of the one-sided 95% CI for the treatment difference (robotic cystectomy minus open cystectomy) was greater than –15 percentage points.

Per-protocol analysis set			
Patients with disease progression within 2 years of surgery	41/150 (27%)	42/152 (28%)	
			(–9·6 to 10·9)
Patients with disease progression (total events)†	49/150 (33%)	50/152 (33%)	..

Maintenance strategies after first-line oxaliplatin plus fluoropyrimidine plus bevacizumab for patients with metastatic colorectal cancer (AIO 0207): a randomised, non-inferiority, open-label, phase 3 trial

Susanna Hegewisch-Becker, Ullrich Graeven*, Christian A Lerchenmüller, Birgitta Killing, Reinhard Depenbusch, Claus-Christoph Steffens, Salah-Eddin Al-Batran, Thoralf Lange, Georg Dietrich, Jan Stoehlmacher, Andrea Tannapfel, Anke Reinacher-Schick, Julia Quidde, Tanja Trarbach, Axel Hinke, Hans-Joachim Schmoll, Dirk Arnold*

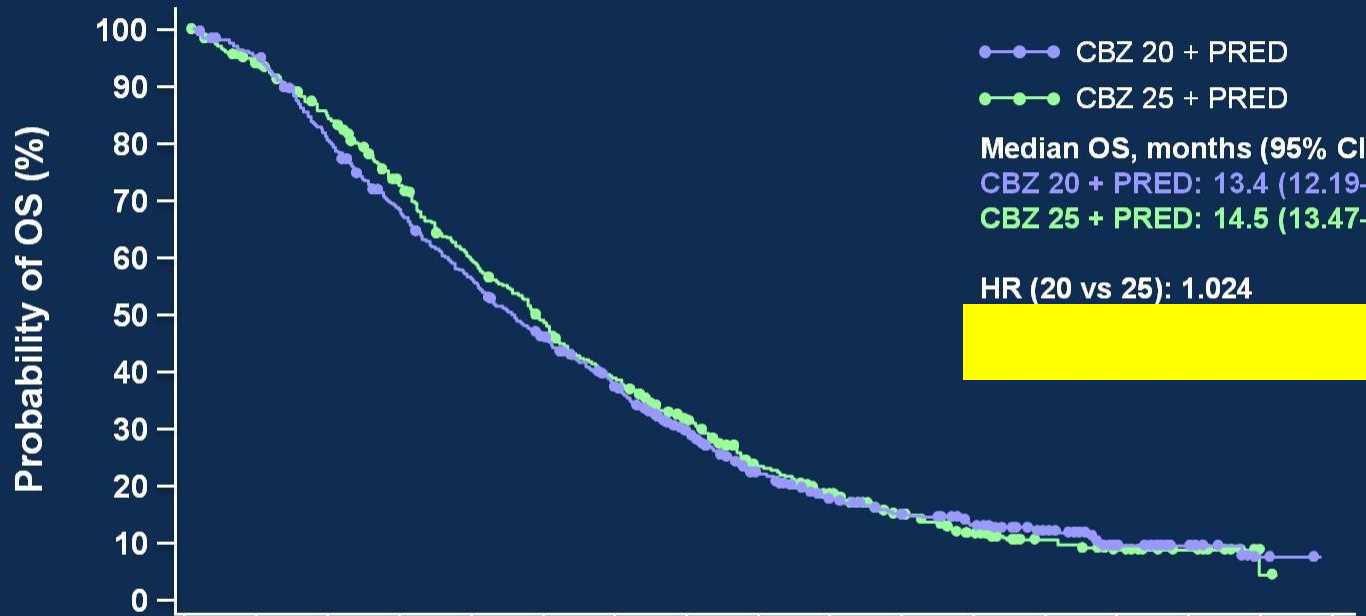
Lancet Oncol **2015; 16: 1355–69**



For the bevacizumab alone group, non-inferiority can be claimed as the upper limit of one-sided 98·8% CI of 1·42 did not exceed the predefined boundary of 1·43.

By contrast, the no treatment group failed to show non-inferiority to the standard treatment as the upper level of non-inferiority of one-sided 98·8% CI 1·65 exceeded the predefined boundary.

PROSELICA: Overall Survival



Number at risk										
CBZ 20 + PRED	598	469	393	324	210	109	55	30	9	0
CBZ 25 + PRED	602	494	416	338	219	120	58	25	11	0

Presented By Johann De Bono at 2016 ASCO Annual Meeting

Interpretazione clinica di uno Studio di Non-Inferiorità

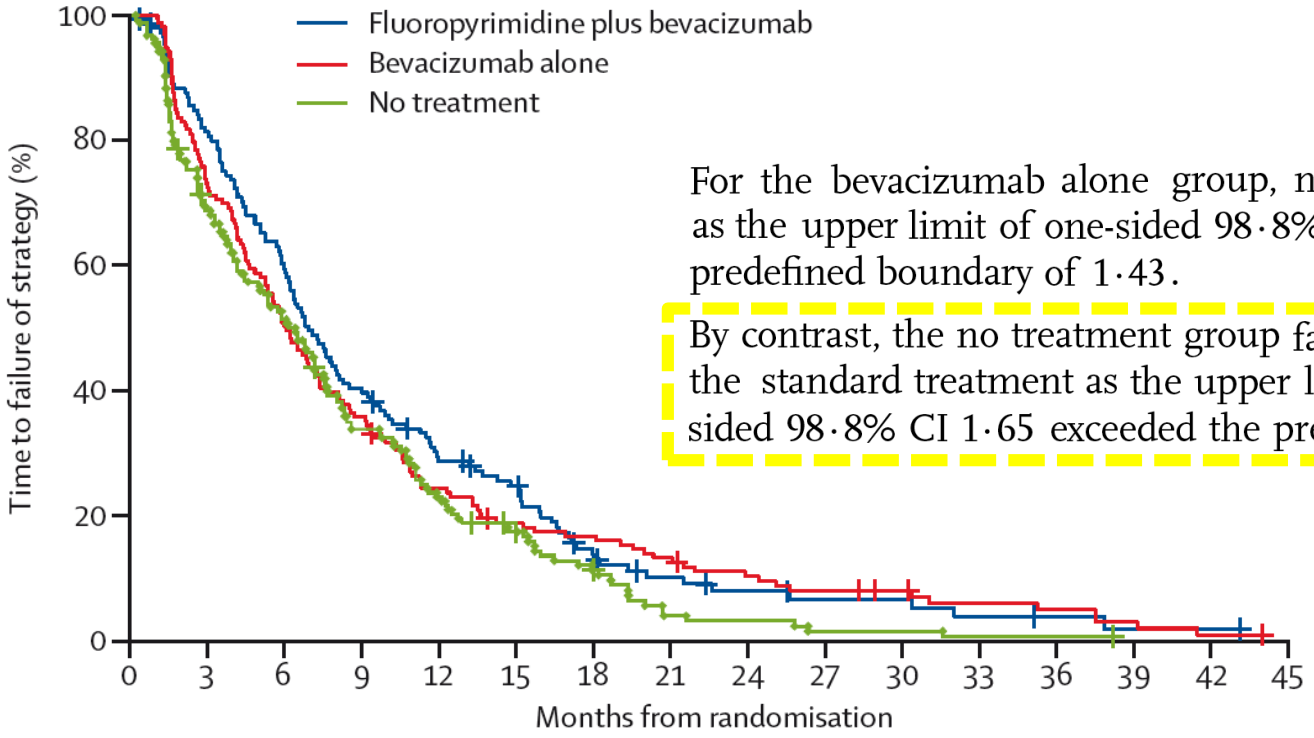
(dato uno specifico M di interesse)

NON Dimostrazione di Non-Inferiorità

Maintenance strategies after first-line oxaliplatin plus fluoropyrimidine plus bevacizumab for patients with metastatic colorectal cancer (AIO 0207): a randomised, non-inferiority, open-label, phase 3 trial

Susanna Hegewisch-Becker, Ullrich Graeven*, Christian A Lerchenmüller, Birgitta Killing, Reinhard Depenbusch, Claus-Christoph Steffens, Salah-Eddin Al-Batran, Thoralf Lange, Georg Dietrich, Jan Stoehlmacher, Andrea Tannapfel, Anke Reinacher-Schick, Julia Quidde, Tanja Trarbach, Axel Hinke, Hans-Joachim Schmoll, Dirk Arnold*

Lancet Oncol **2015; 16: 1355–69**



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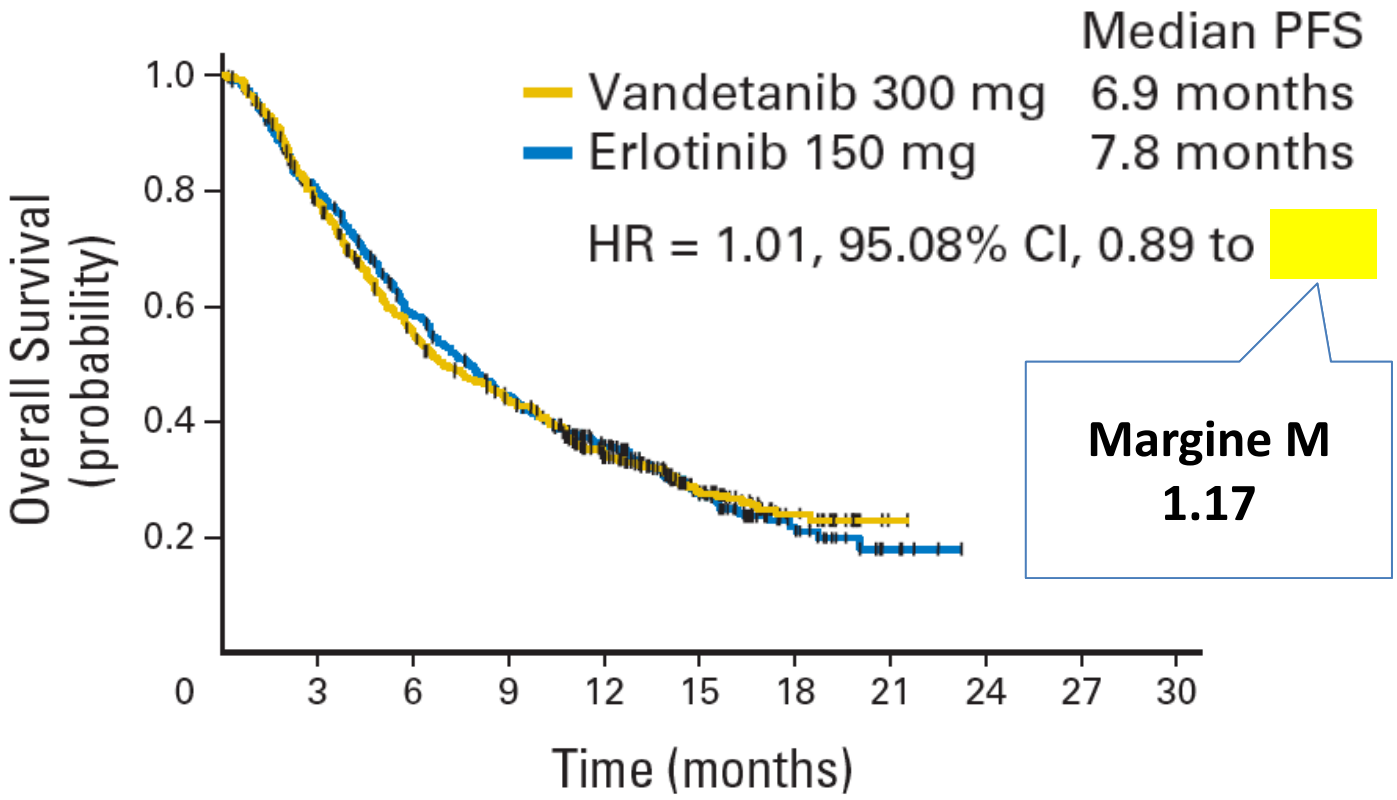
Phase III Trial of Vandetanib Compared With Erlotinib in Patients With Previously Treated Advanced Non–Small-Cell Lung Cancer

Ronald B. Natale, Sumitra Thongprasert, F. Anthony Greco, Michael Thomas, Chun-Ming Tsai, Patrapim Sunpaweravong, David Ferry, Clive Mulatero, Robert Whorf, Joyce Thompson, Fabrice Barlesi, Peter Langmuir, Sven Gogov, Jacqui A. Rowbottom, and Glenwood D. Goss

J Clin Oncol 29:1059-1066. © 2011 by American Society of Clinical Oncology



Margine M 1.17

The overall incidence of grade ≥ 3 AEs was higher with vandetanib than erlotinib (50% *v* 40%, respectively)

Non-inferiority trials are unethical because they disregard patients' interests

Silvio Garattini, Vittorio Bertele'

Lancet 2007; 370: 1875–77