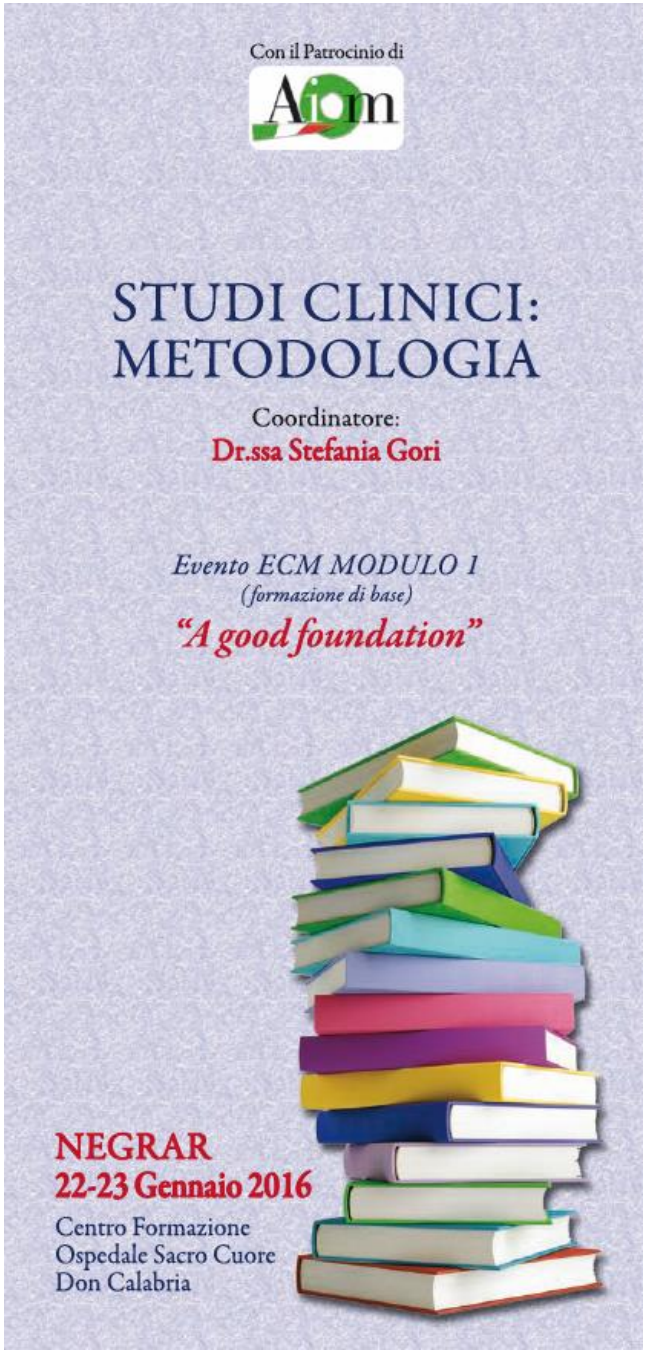
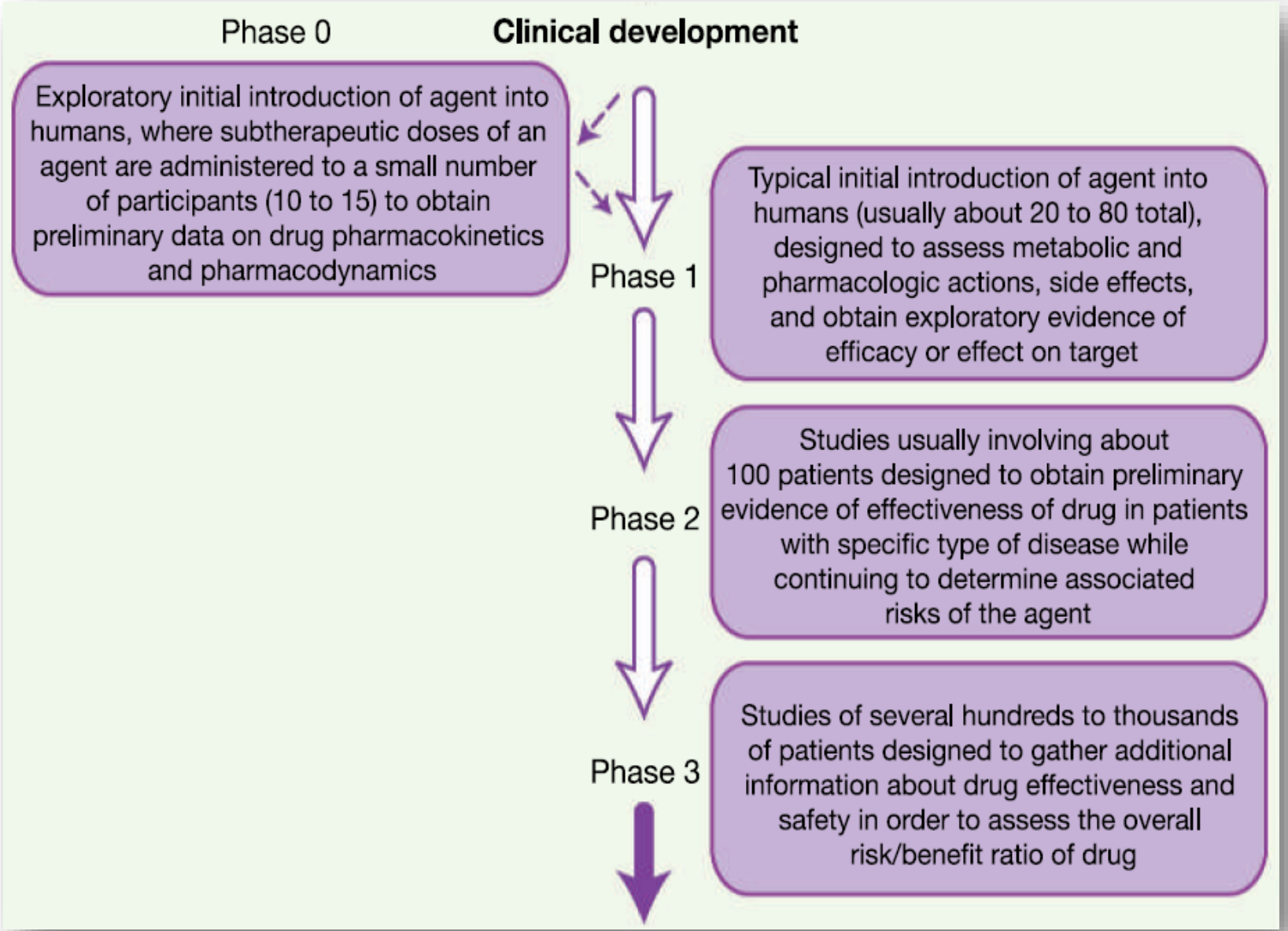


Venerdì 22 gennaio 2016

- Plausibilità e opportunità dello studio
  - ✓ criteri FINER
- Obiettivi (primario e secondari)
  - ✓ strutturazione sec. P.I.C.O.
- Disegno dello studio
  - ✓ tipologie di disegno di studio
  - ✓ procedure di randomizzazione
  - ✓ scelta del braccio di controllo
- Endpoints (primario e secondari)
  - ✓ endpoints surrogati
  - ✓ PROs
- Selezione dei pazienti
  - ✓ criteri restrittivi Vs inclusivi
  - ✓ conseguenze su trasferibilità e precisione delle evidenze



Clin Cancer Res; 16(6) March 15, 2010

Endpoints (ICH E9)

- The primary variable ('target' variable, primary endpoint)
- Capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial
- A reliable and validated variable measuring some clinically relevant and important treatment benefit in the patient population

International Conference for Harmonization (ICH). Efficacy Guidelines. ICH Topic E 9, Statistical Principles for Clinical Trials

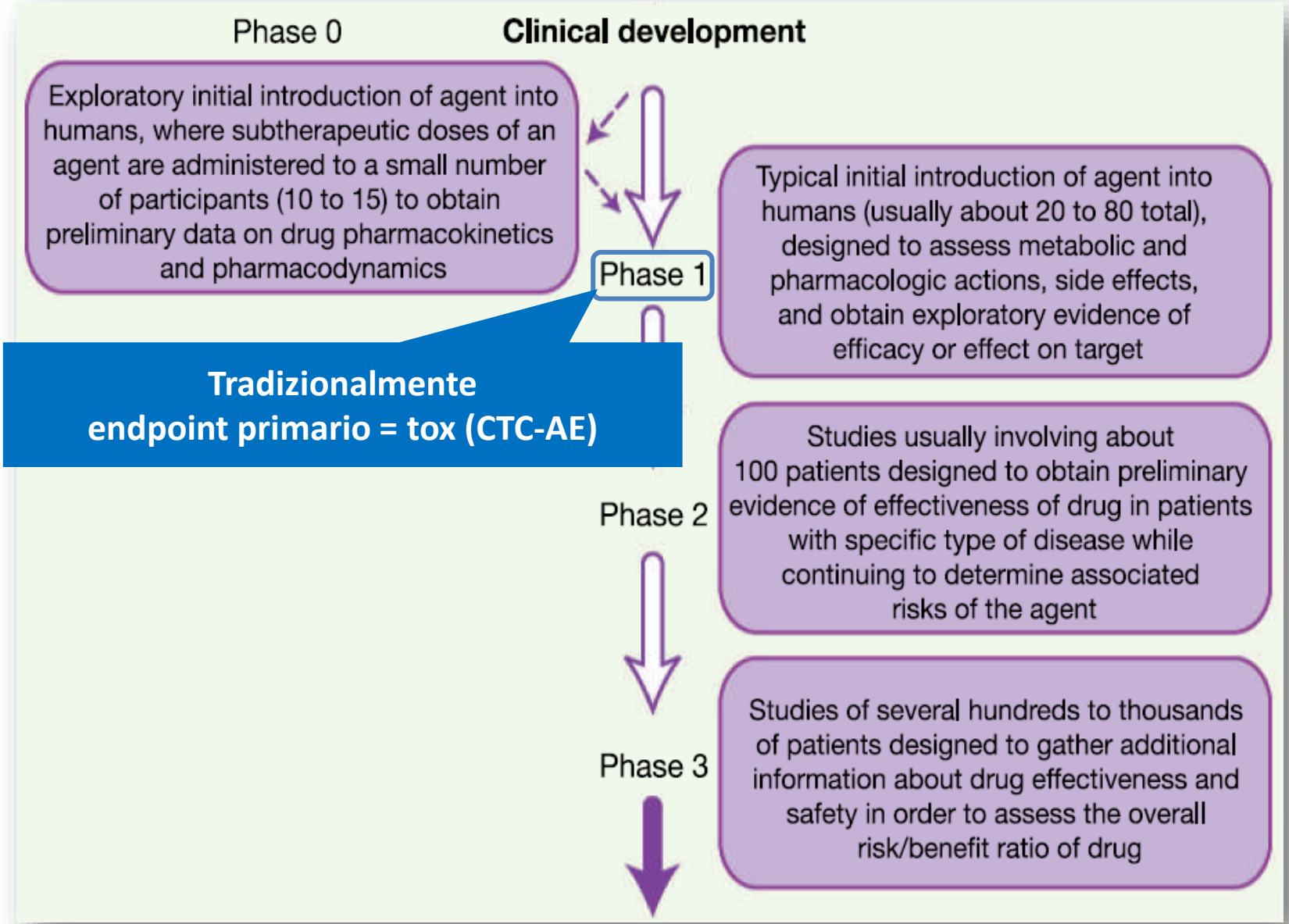
What makes a good endpoint?

Characteristic	Meaning
Relevant	Clinically important/useful
Quantifiable	Measured on an appropriate scale
Valid	Measures the intended effect
Objective	Interpreted the same by all observers
Reliable	Same effect yields consistent measurements
Sensitive	Responds to small changes in the effect
Specific	Unaffected by extraneous influences
Precise	Small variability
Other	Tradition, cost, time, missing data

S. Piantadosi (2005)

VARIABILE DI RISPOSTA

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



Clin Cancer Res; 16(6) March 15, 2010

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Publish Date: May 28, 2009

Quick Reference

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Issues with Novel Targeted Non-Cytotoxics

- Dose-Toxicity and Dose-Effect relationships: may not be parallel
- May not cause regression of established tumours
- Thus, for newer agents:
  - phase I trials: endpoint should be ????
  - phase II trials: endpoint should be ????

National Cancer Institute Of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe Des Essais Cliniques

E. Eisenhauer, ESMO 2002

EFFICACY AND SAFETY OF A SPECIFIC INHIBITOR OF THE BCR-ABL TYROSINE KINASE IN CHRONIC MYELOID LEUKEMIA

BRIAN J. DRUKER, M.D., MOSHE TALPAZ, M.D., DEBRA J. RESTA, R.N., BIN PENG, PH.D., ELISABETH BUCHDUNGER, PH.D., JOHN M. FORD, M.D., NICHOLAS B. LYDON, PH.D., HAGOP KANTARJIAN, M.D., RENAUD CAPDEVILLE, M.D., SAYURI OHNO-JONES, B.S., AND CHARLES L. SAWYERS, M.D.

N Engl J Med, Vol. 344, No. 14 · April 5, 2001

ADVERSE EVENT	25–140 mg (N=14)		200–300 mg (N=23)		350–500 mg (N=18)		600–1000 mg (N=28)		TOTAL (N=83)
	GRADE 1 OR 2	GRADE 3 OR 4	GRADE 1 OR 2	GRADE 3 OR 4	GRADE 1 OR 2	GRADE 3 OR 4	GRADE 1 OR 2	GRADE 3 OR 4	GRADES 1–4
	% of patients								no. (%)
Nausea	21	0	30	0	50	0	59	0	36 (43)
Myalgias	21	0	52	0	33	6	28	14	34 (41)
Edema	21	0	22	0	33	0	55	7	32 (39)
Diarrhea	14	0	4	0	33	0	38	3	21 (25)
Fatigue	14	0	22	0	11	0	24	3	17 (20)
Rash	7	0	17	0	11	0	28	3	16 (19)
Dyspepsia	14	0	13	0	28	0	17	0	15 (18)
Vomiting	0	0	13	0	11	0	34	0	15 (18)
Thrombocytopenia	0	0	4	0	11	6	7	24	13 (16)
Neutropenia	0	0	9	4	6	6	0	24	12 (14)
Arthralgias	0	0	4	0	6	0	28	3	11 (13)

STI571 was generally well tolerated, and a maximal tolerated dose was not identified.

A Practical Approach: Phase I Design Non-Cytotoxics

- Continue to limit dose using toxicity.
- Explore alternative endpoints as part of trial including:
  - Target inhibition
  - Blood levels
- Final dose decision may be based on a composite of these.
- Further exploration of dose effects may need (randomized) phase II designs.

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E. Eisenhauer, ESMO 2002

Table 1. Overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions*

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

*CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease. *See* text for more details.

cal initial introduction of agent into
ans (usually about 20 to 80 total),
signed to assess metabolic and
rmacologic actions, side effects,
d obtain exploratory evidence of
efficacy or effect on target

Studies usually involving about
100 patients designed to obtain preliminary
evidence of effectiveness of drug in patients
with specific type of disease while
continuing to determine associated
risks of the agent

Phase 2

Tradizionalmente
endpoint primario = risposta (RECIST)

Phase 3

Studies of several hundreds to thousands
of patients designed to gather additional
information about drug effectiveness and
safety in order to assess the overall
risk/benefit ratio of drug

Clin Cancer Res; 16(6) March 15, 2010

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E. Eisenhauer, ESMO 2002

ICH E8 and E9

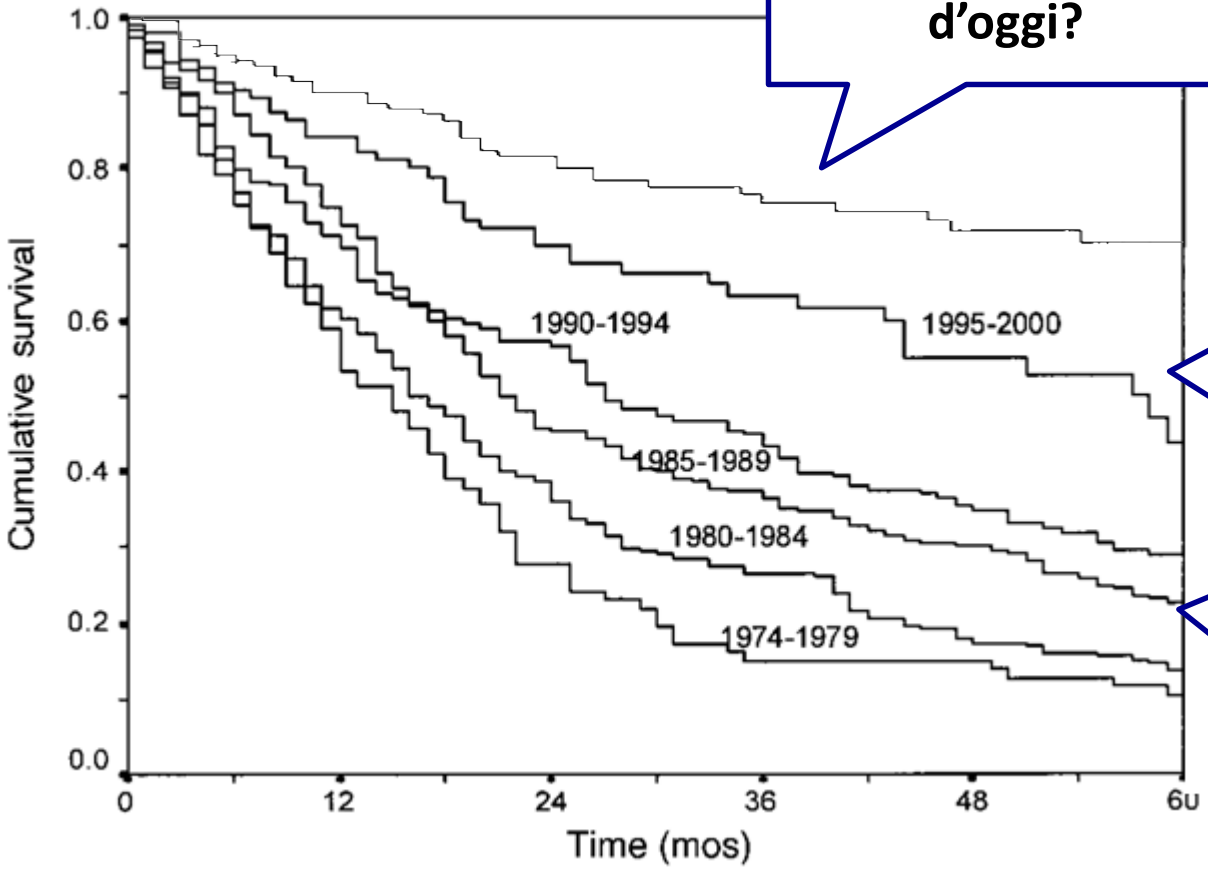
- Confirmatory trials should demonstrate clinical benefit
- The primary endpoint
  - Should provide the most clinically relevant and convincing evidence
  - Valid and reliable measure of some clinically relevant and important treatment benefit

Regular Approval Basis – "Clinical Benefit"

- Longer life
- Better life
- Established Surrogate for one of above

Trends in Breast Cancer Survival/Giordano et al.
CANCER January 1, 2004 / Volume 100 / Number 1

Overall survival from time of recurrence

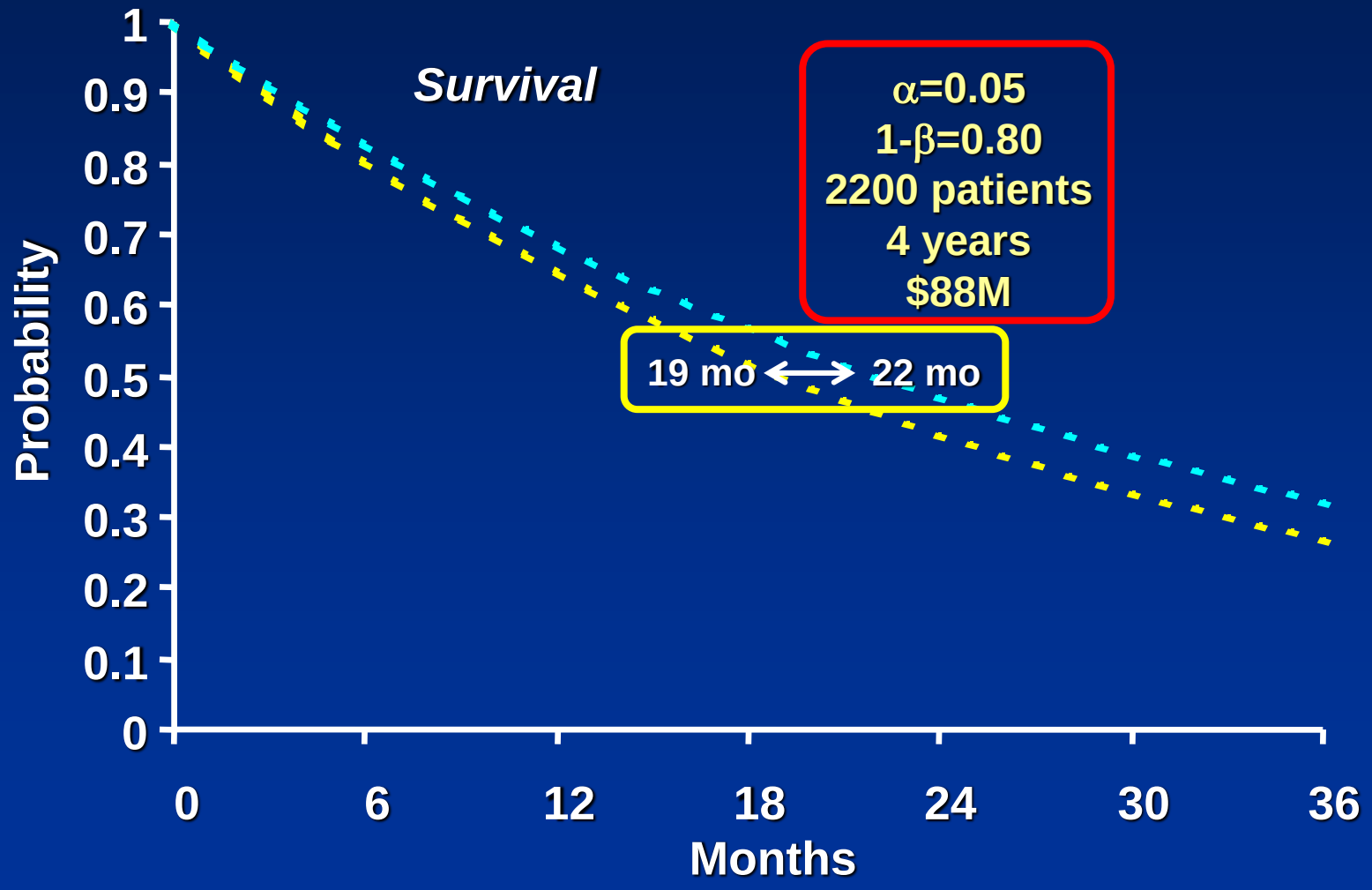


… e al giorno d'oggi?

Più difficile ottenere un beneficio relativo di Sopravvivenza

(abbastanza) facile ottenere un beneficio relativo di Sopravvivenza

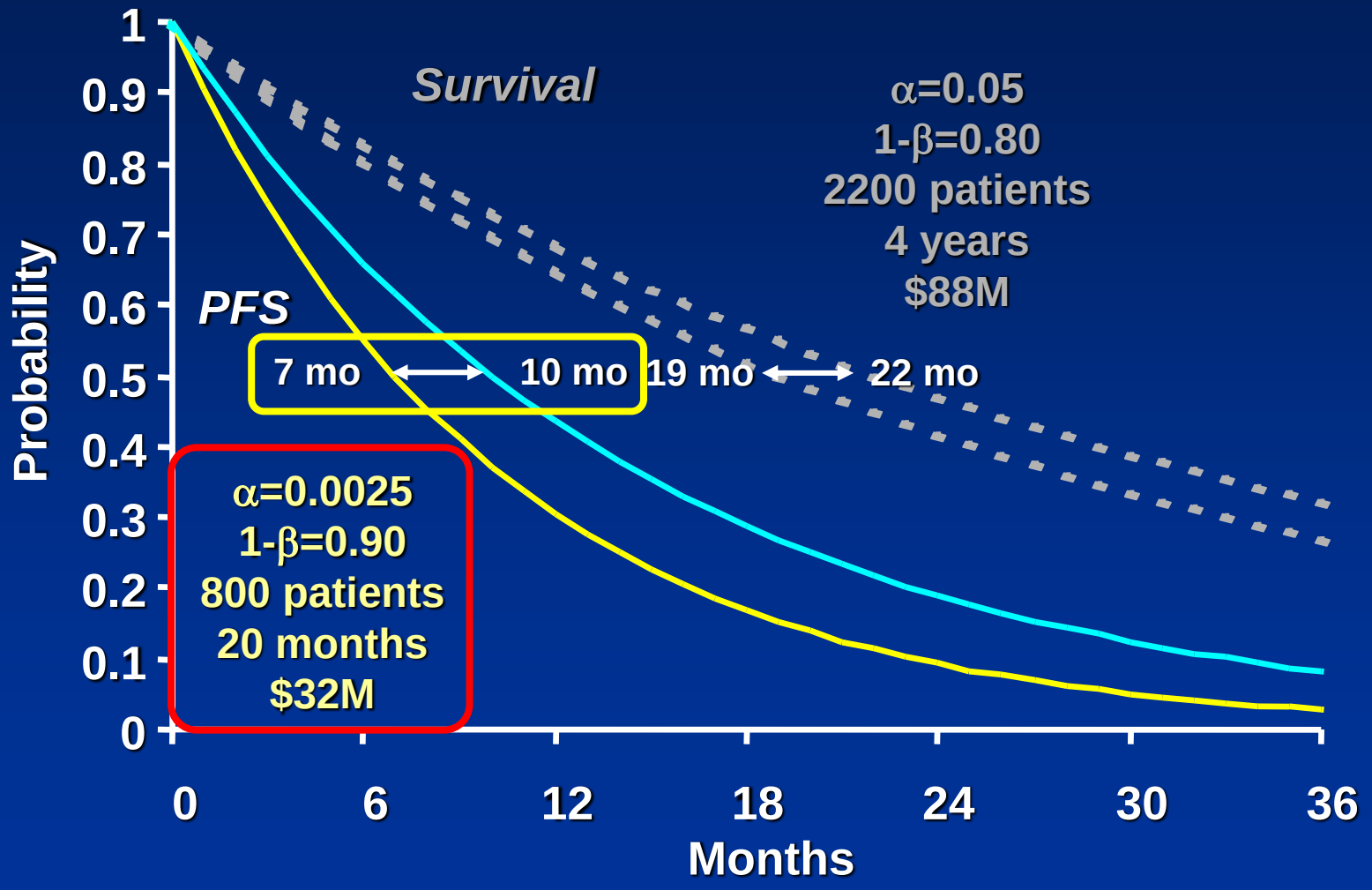
Survival Superiority Study Offers Too Little, Too Late, For Too Much



Assumes accrual = 100 patients/mo; follow-up = largest median + 2 mo (TTP) or 4 mo (survival)

L.L. Miller, 2003

Single Superiority Study Can Offer Highly Robust PFS Assessment (α=0.0025)



Assumes accrual = 100 patients/mo; follow-up = largest median + 2 mo (TTP) or 4 mo (survival)

L.L. Miller, 2003

“Surrogate” endpoints

- **Issue:**
  - **Quicker, less expensive, less clinically relevant endpoint or**
  - **More expensive, clinically definitive endpoint?**
- **Hesitate to use the term "surrogate"**
- **Has a specific technical definition**

Mark Conaway, June 2006

Validation of Surrogate Endpoints

Property of a Valid Surrogate

Effect of the Intervention
on the Clinical Endpoint

is reliably predicted by the

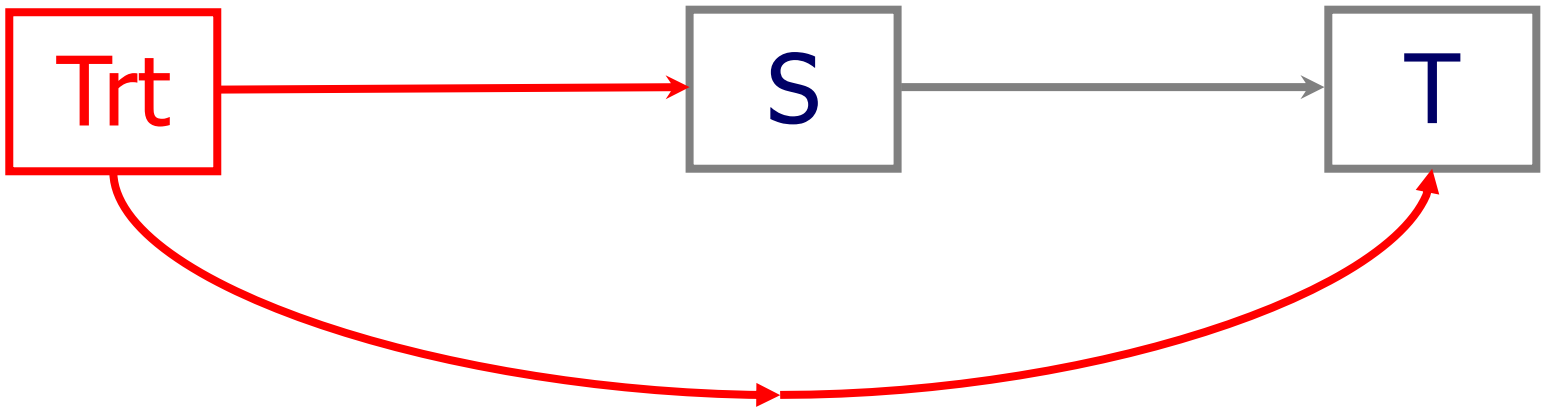
Effect of the Intervention
on the Surrogate Endpoint

D. Sargent, ASCO 2011

VALIDATION OF SURROGATE ENDPOINTS: "FULL CAPTURE OF EFFECT"

Effect of treatment on surrogate

Effect of surrogate on true endpoint



Effect of treatment on true endpoint must be fully captured by surrogate

*Prentice, Statist Med 1989;**8**:431.*

SURROGATE ENDPOINTS IN CLINICAL TRIALS: DEFINITION AND OPERATIONAL CRITERIA

ROSS L. PRENTICE

Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104, U.S.A.

SUMMARY

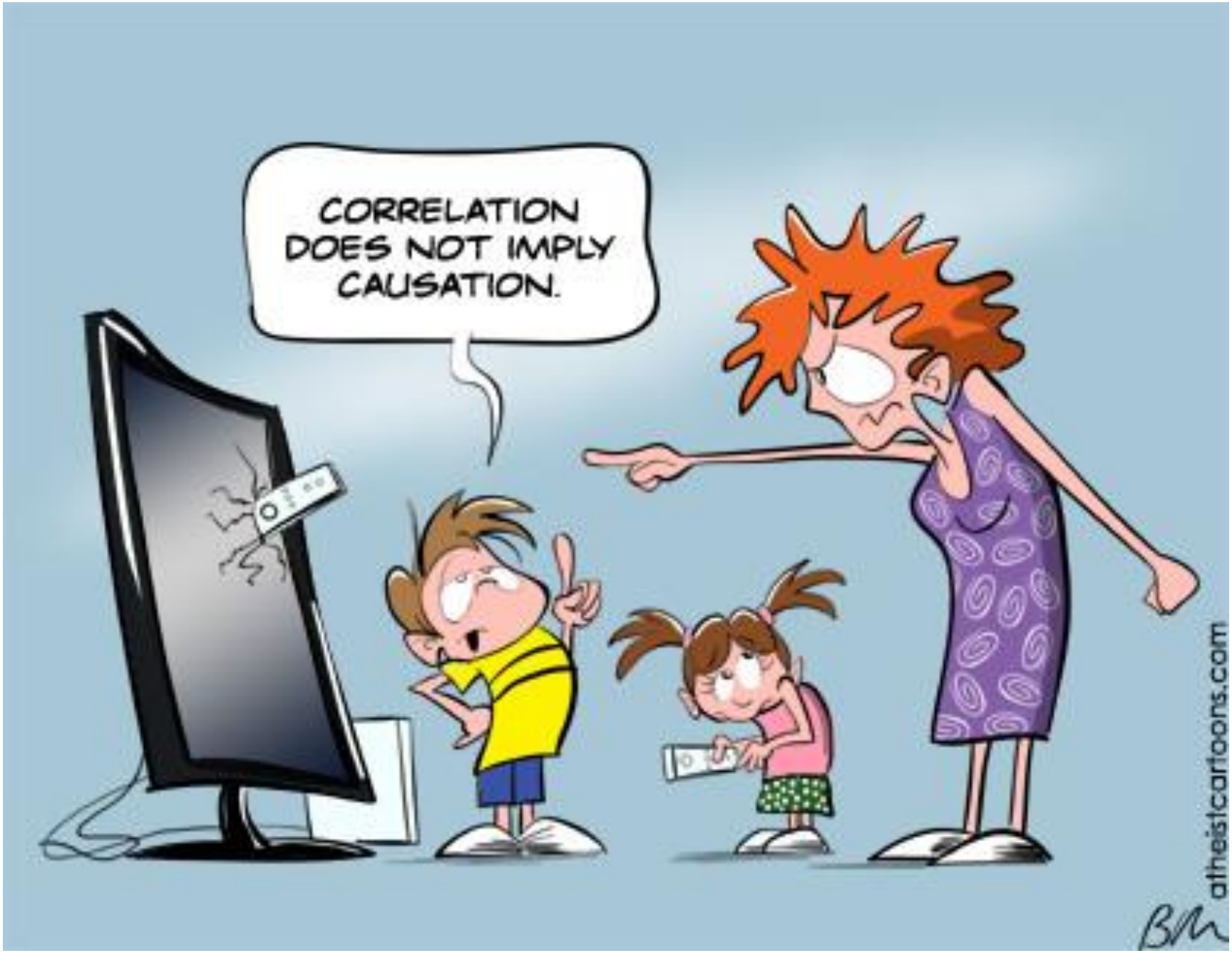
I discuss the idea of using surrogate endpoints in the context of clinical trials to compare two or more treatments or interventions in respect to some 'true' endpoint, typically a disease occurrence. In order that treatment comparison based on a surrogate response variable have a meaningful implication for the corresponding true endpoint treatment comparison, a rather restrictive criterion is proposed for use of the adjective 'surrogate'. Specifically, I propose that a surrogate for a true endpoint yield a valid test of the null hypothesis of no association between treatment and the true response. This criterion essentially requires the surrogate variable to 'capture' any relationship between the treatment and the true endpoint, a notion that can be operationalized by requiring the true endpoint rate at any follow-up time to be independent of treatment, given the preceding history of the surrogate variable. I then discuss this operational criterion in the examples of the accompanying papers[1-3] and in the setting of trials aimed at the primary and secondary prevention of cancer.

KEY WORDS Clinical trials Disease prevention trials Hazard rates Surrogate endpoints Therapeutic trials

I Criteri di Prentice prevedono…

La dimostrazione di **correlazione**:

- tra trattamento e outcome clinico
- tra endpoint surrogato e outcome clinico
- tra trattamento ed endpoint surrogato

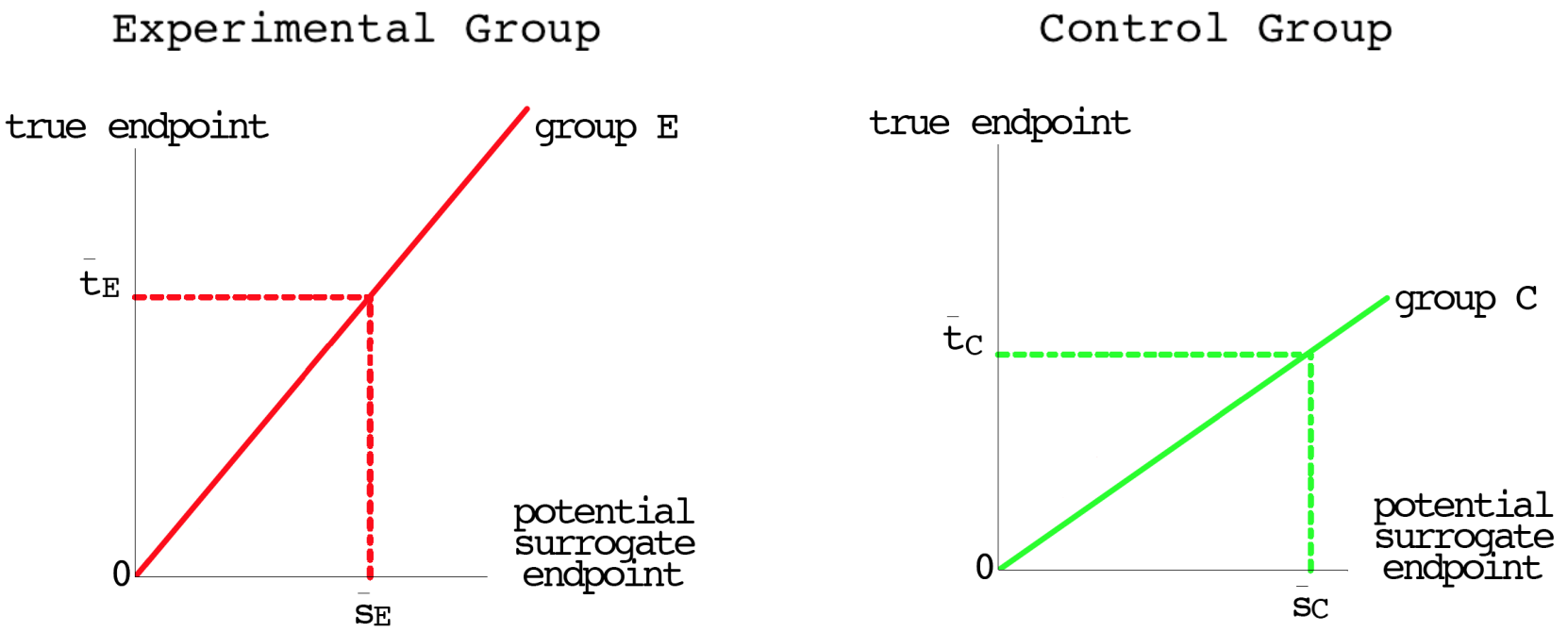

CORRELATION DOES NOT IMPLY CAUSATION.
atheistcartoons.com

A perfect correlate does not a surrogate make

Stuart G Baker*[1] and Barnett S Kramer[2]

BMC Medical Research Methodology 2003, **3**:16

Background: There is common belief among some medical researchers that if a potential surrogate endpoint is highly correlated with a true endpoint, then a positive (or negative) difference in potential surrogate endpoints between randomization groups would imply a positive (or negative) difference in unobserved true endpoints between randomization groups.



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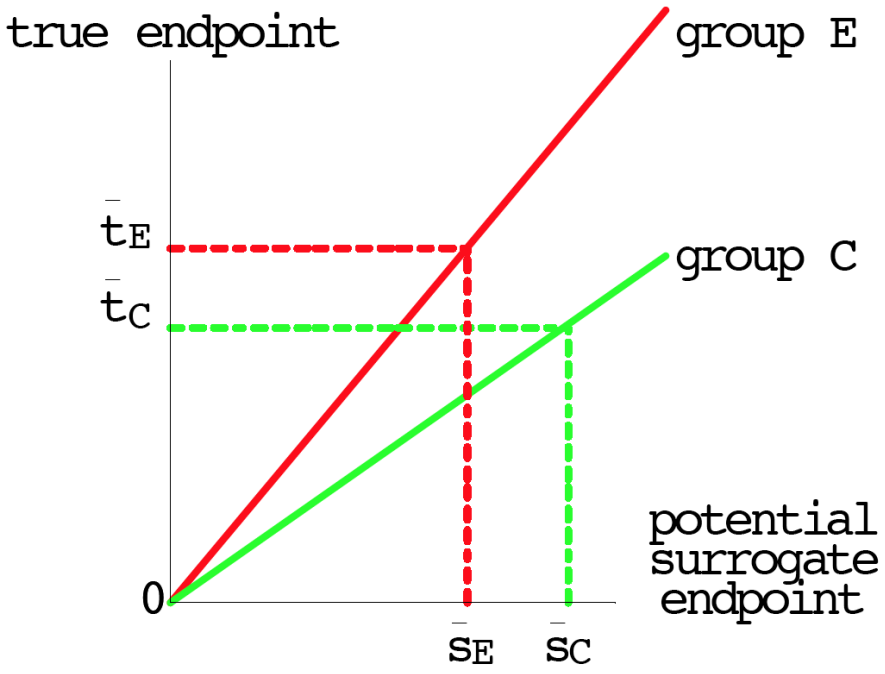

The mean surrogate outcome in the E group $\bar{s}_E$ is smaller than the mean surrogate outcome in the C group $\bar{s}_C$. However the mean true outcome in the E group $\bar{t}_E$ is larger than the mean true outcome in the C group $\bar{t}_C$, yielding the opposite conclusion for the effect of experimental intervention.

Conclusion: Perfect correlation between potential surrogate and unobserved true outcomes within randomized groups does not guarantee correct inference based on a potential surrogate endpoint.

I Criteri di Prentice prevedono…

La dimostrazione di **correlazione**:

- tra trattamento e outcome clinico
- tra endpoint surrogato e outcome clinico
- tra trattamento ed endpoint surrogato

La "**cattura***" dell'effetto del trattamento da parte dell'endpoint (candidato) surrogato

* L'effetto del trattamento sull'outcome clinico, misurato in assenza dell'endpoint surrogato, "scompare" quando nel modello di regressione viene aggiunto l'endpoint surrogato

Objective Response to Chemotherapy As a Potential Surrogate End Point of Survival in Metastatic Breast Cancer Patients

Paolo Bruzzi, Lucia Del Mastro, Maria P. Sormani, Lars Bastholt, Marco Danova, Christian Focan, George Fountzilas, James Paul, Riccardo Rosso, and Marco Venturini

J Clin Oncol 23:5117-5125. © 2005 by American Society of Clinical Oncology

Validation of Tumor Response As a Surrogate of Survival

To validate objective response as a surrogate end point of survival in advanced breast cancer, it was necessary to demonstrate:

(1) that the experimental treatment prolongs survival

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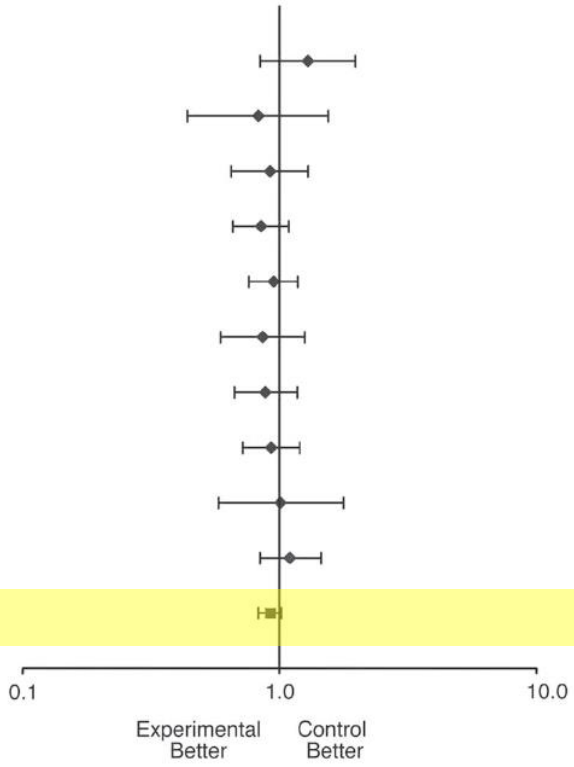
Study	Experimental O/N	Control O/N	E	O – E	VAR	HR	95% CI
DelMastro[16]	60/77	55/74	56.3	3.7	28.7	1.14	0.79 to 1.64
Ardizzoni[17]	19/32	20/30	20.7	–1.7	9.3	0.83	0.44 to 1.55
Focan[18]	66/85	67/80	68.9	–2.9	33.1	0.92	0.65 to 1.29
French study[19]	126/141	124/132	136.0	–10.0	61.1	0.85	0.66 to 1.09
Brufman[20]	154/214	169/241	158.4	–4.4	80.1	0.95	0.76 to 1.18
Fountzilas[21]	53/86	52/81	56.8	–3.8	25.6	0.86	0.59 to 1.26
Marschner[22]	92/121	115/148	98.2	–6.2	50.9	0.88	0.67 to 1.17
Bastholt[23]	113/123	134/142	117.4	–4.4	61.4	0.94	0.73 to 1.21
Riccardi[24]	24/33	29/37	23.9	0.1	12.2	1.01	0.58 to 1.78
Habeshaw[25]	103/106	102/105	98.1	4.9	50.0	1.1	0.84 to 1.45
Total	810/1,018	867/1,070	834.7	–24.7	412.4	0.944	0.857 to 1.041



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To validate objective response as a surrogate end point of survival in advanced breast cancer, it was necessary to demonstrate:

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(2) that the experimental treatment is associated with an increase in response rates

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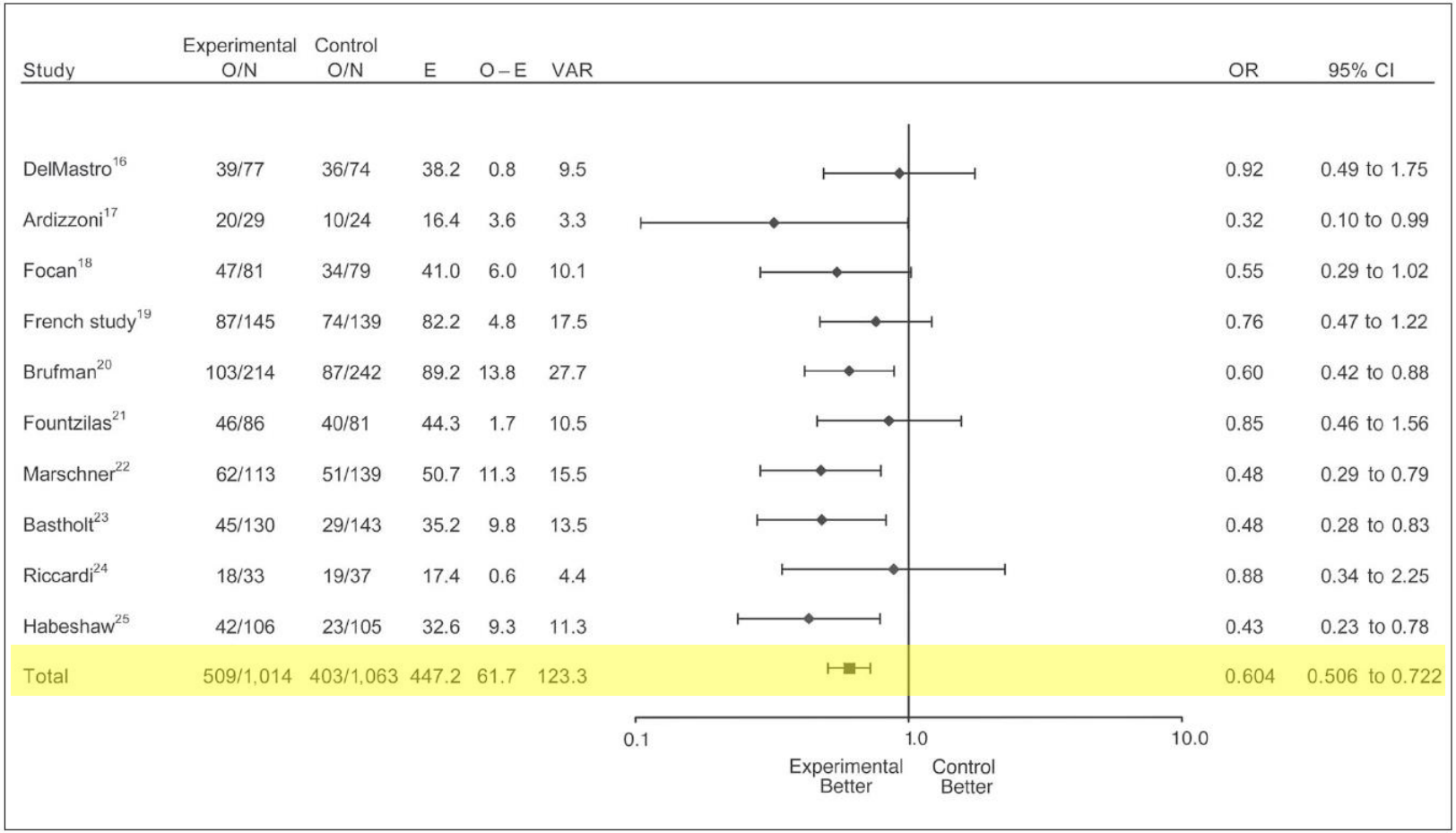

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(3) that responders live longer than nonresponders

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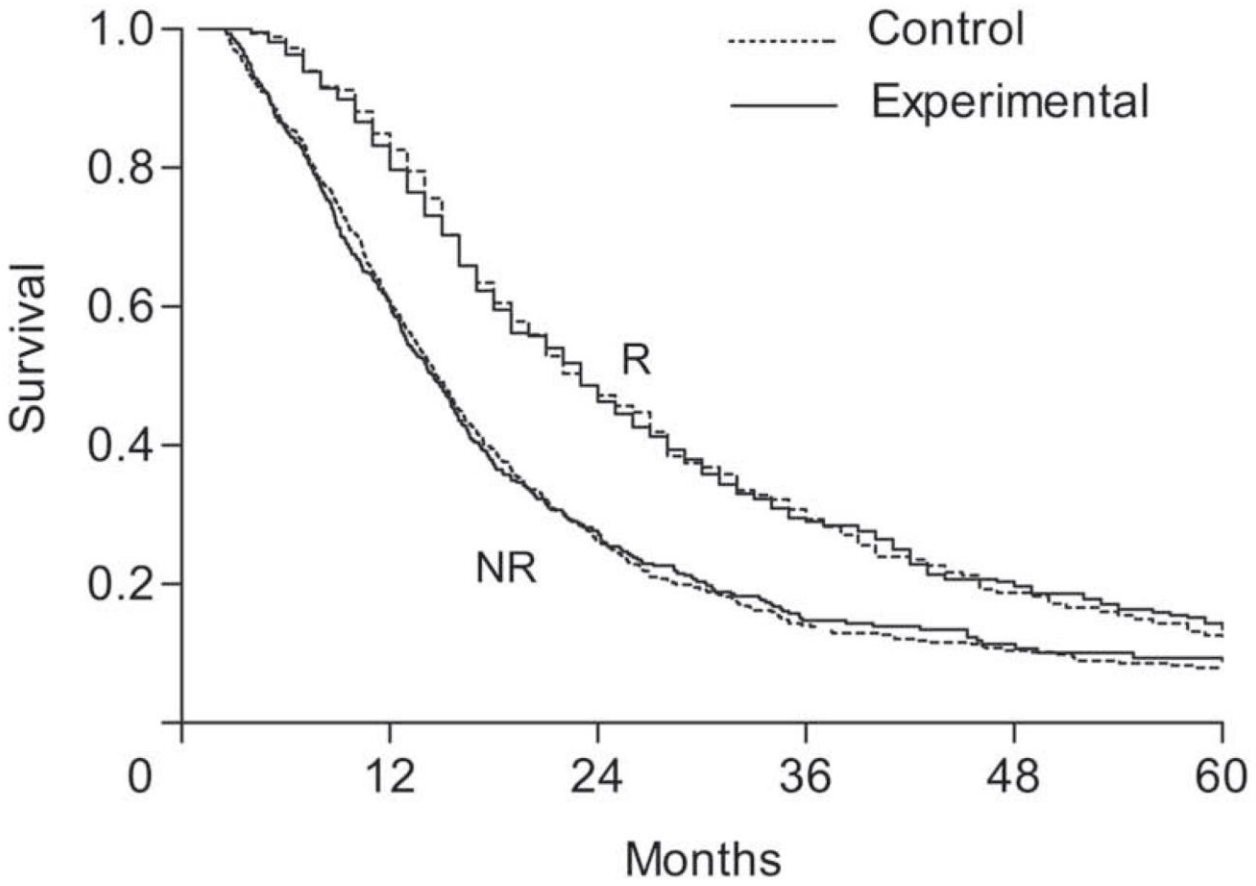

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(2) that the experimental treatment is associated with an increase in response rates

(3) that responders live longer than nonresponders

(4) that the effect of treatment on survival disappears when response status is adjusted for.

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Table 3. Treatment Effect on Survival Adjusted for Tumor Response

Treatment Effect	β	SE	HR	95% CI	*P*
Unadjusted	−0.06	0.05	0.94	0.86 to 1.04	.24
Adjusted for tumor response, yes/no	0.005	0.05	1.005	0.91 to 1.11	.92
Adjusted for tumor response category, NR, PR, CR	0.01	0.05	1.01	0.92 to 1.12	.83

Abbreviations: HR, hazard ratio; β, log (hazard ratio); NR, no response; PR, partial response; CR, complete response.

When tumor response was introduced in the model, the hazard ratio in favor of the experimental regimen became 1.005 (95% CI, 0.91 to 1.11; $P = .92$), indicating that no residual effect of the experimental treatment on survival, either positive or negative, was present once tumor response was adjusted for.

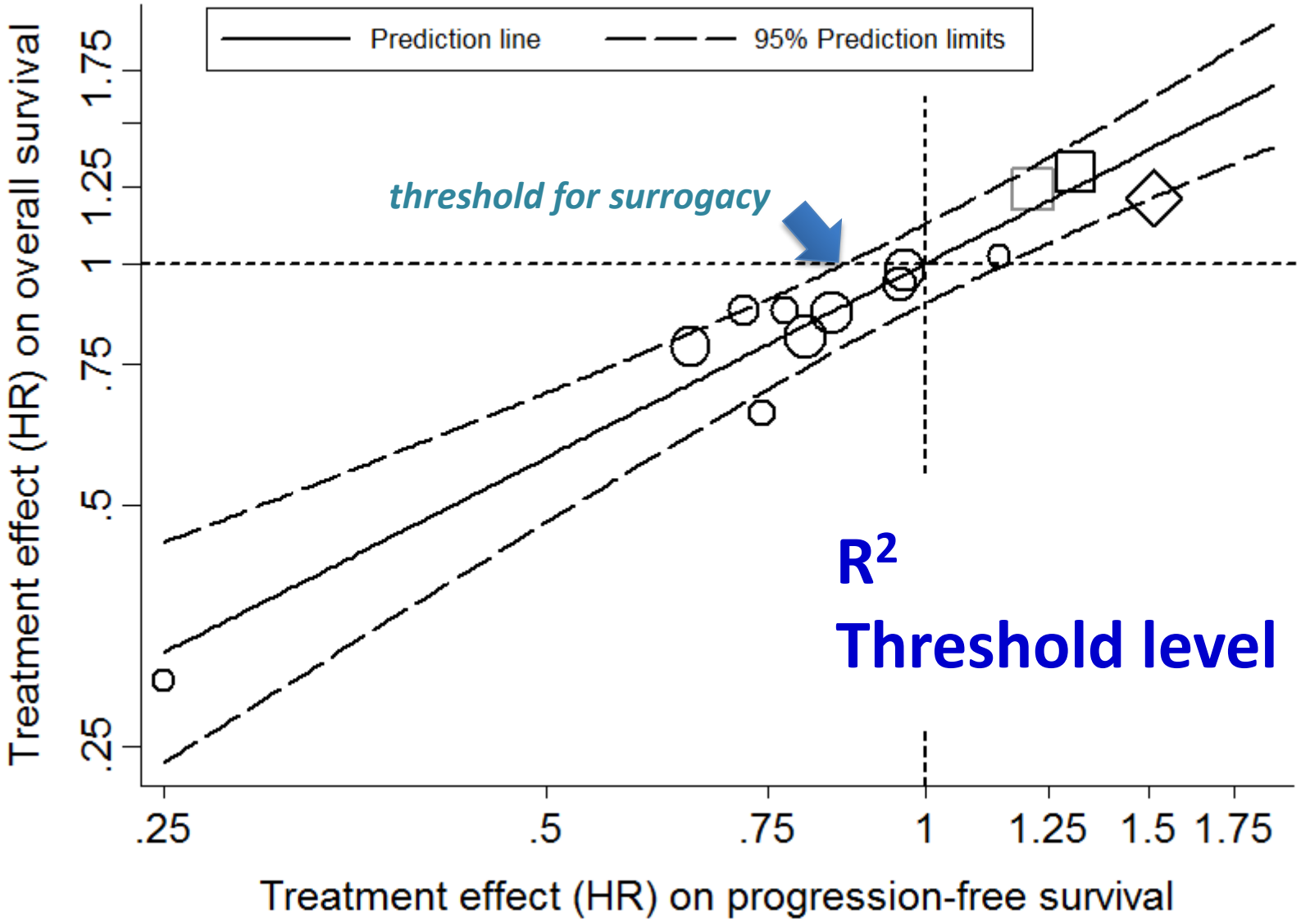
Quando si hanno dati di molti RCT…

… si deriva un **modello di regressione**:

- che possa predire la magnitudine
- dell'effetto del trattamento sull'endpoint "vero"
- in base all'effetto del trattamento sull'endpoint (candidato) surrogato

Il surrogato è tale se la predizione è sufficientemente **precisa**

TRIAL LEVEL CORRELATION BETWEEN EFFECTS



Burzykowski and Buyse, Pharmaceutical Statist 2006;5:173

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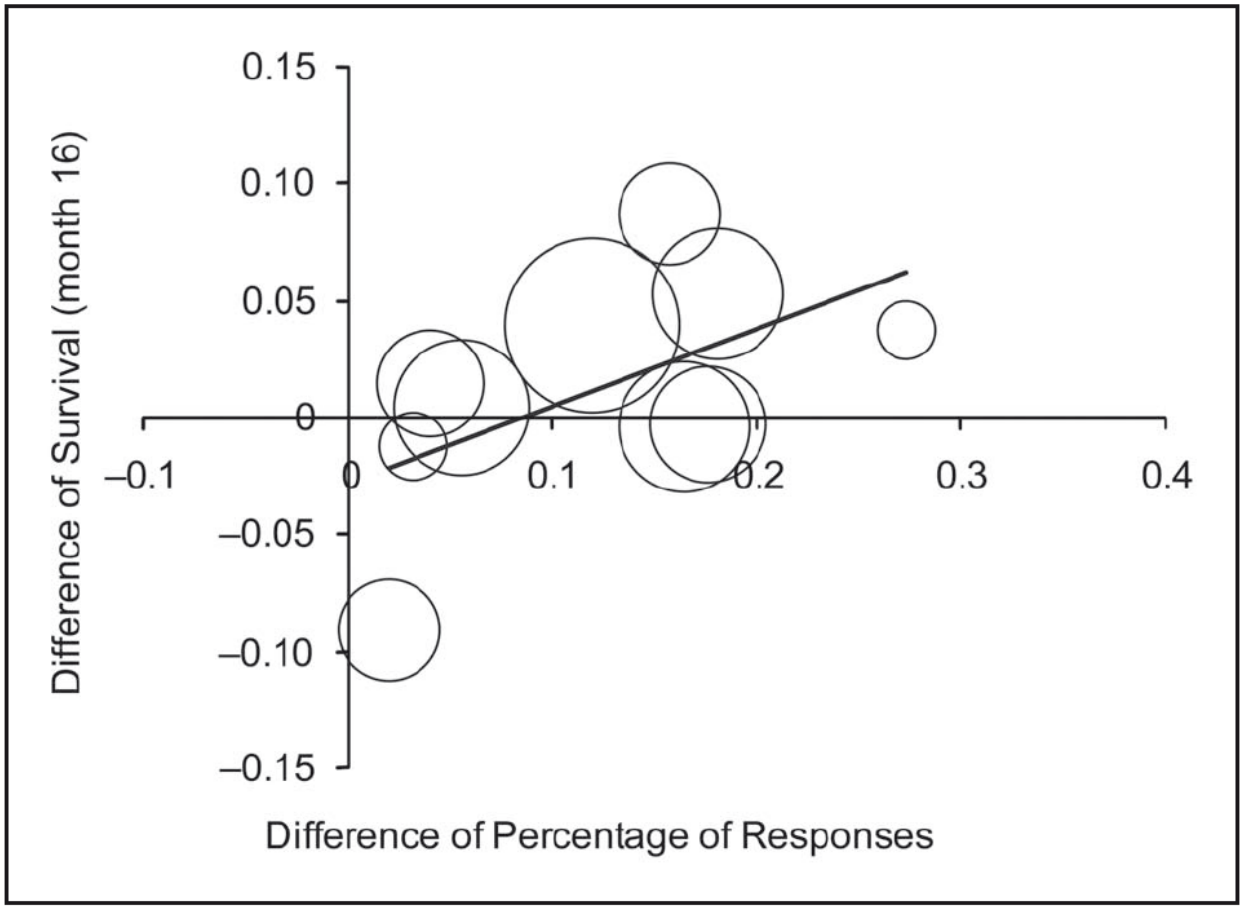
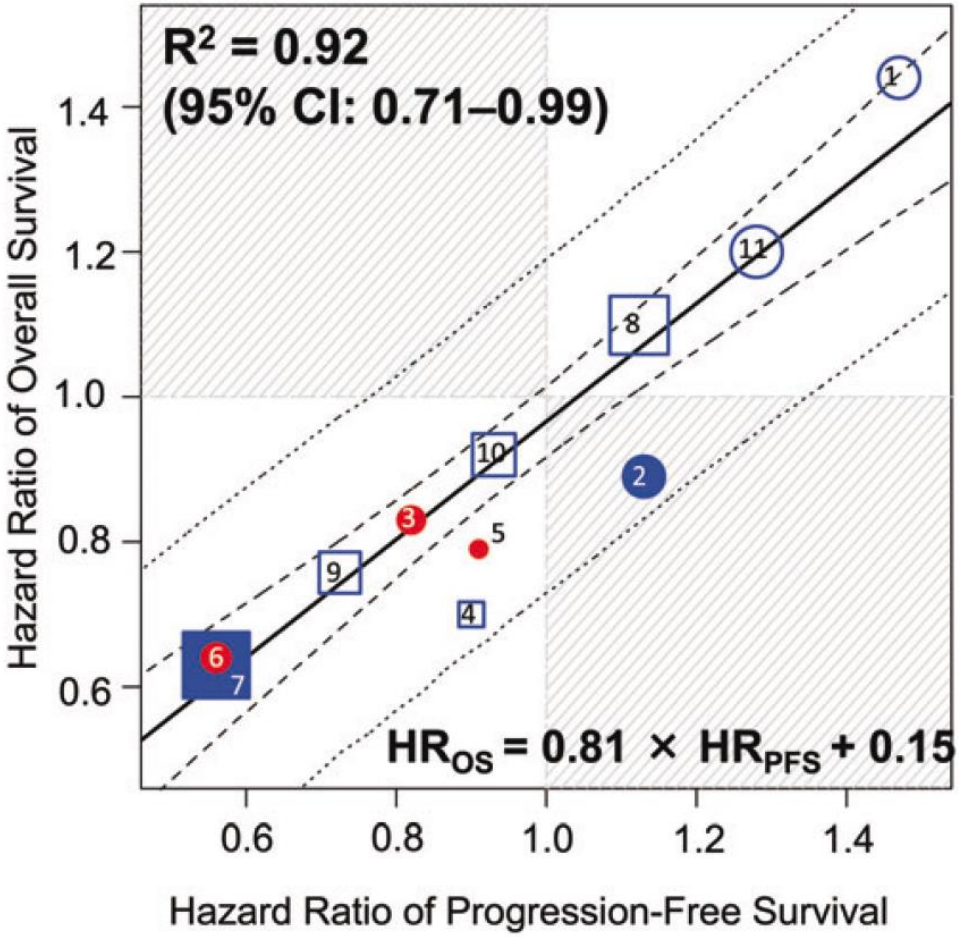


($R^2 = 0.20$; 95% CI, 0 to 0.65)

Progression-free survival as a surrogate endpoint for overall survival in glioblastoma: a literature-based meta-analysis from 91 trials

Kelong Han, Melanie Ren, Wolfgang Wick, Lauren Abrey, Asha Das, Jin Jin, and David A. Reardon

Neuro-Oncology 16(5), 696–706, 2014



Round symbols:	Glioblastoma
Square symbols:	Mixed high-grade glioma
Solid symbols:	Newly diagnosed
Hollow symbols:	Recurrent
———	Weighted linear fit
- - - - -	95% confidence interval
----------	95% prediction interval
Blue symbols:	Head-to-head comparison
Red symbols:	Single-arm trials using historical data as control

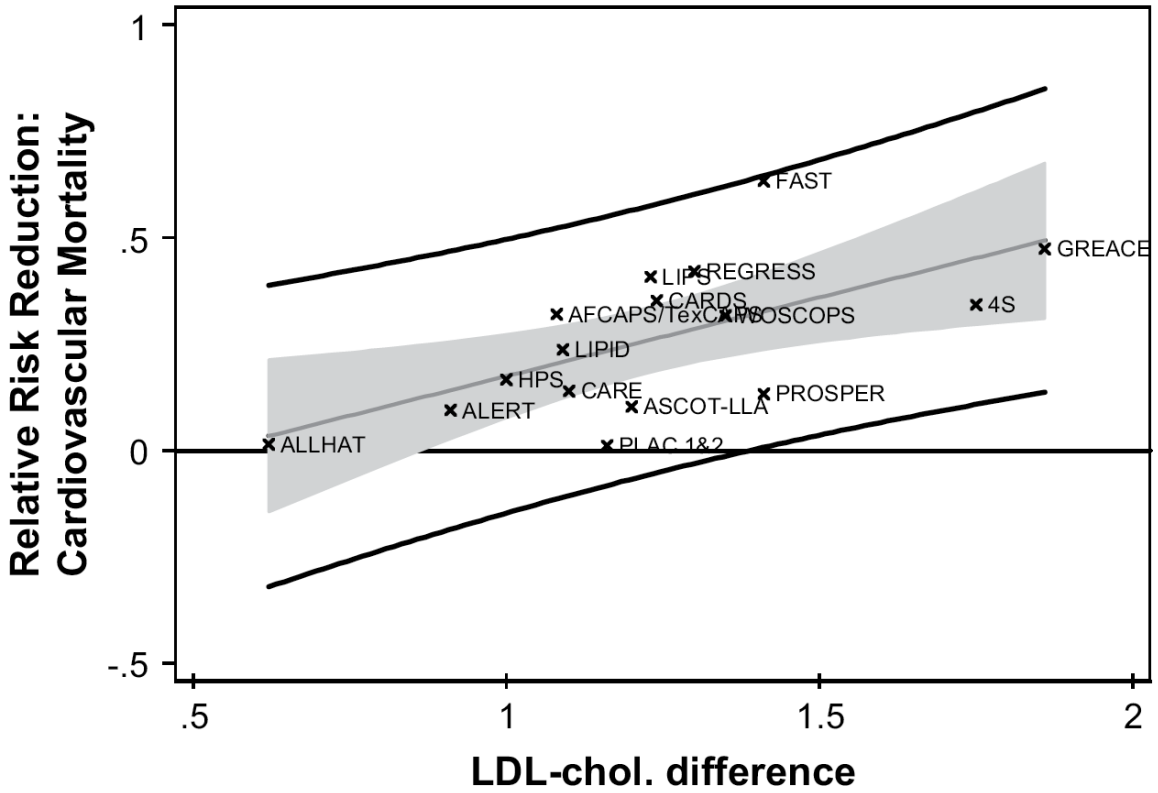
Linear regression determined that a 10% PFS risk reduction would yield an 8.1% ± 0.8% OS risk reduction.

LDL-cholesterol differences predicted survival benefit in statin trials by the surrogate threshold effect (STE)

Kent R. Johnson[a,*], Nick Freemantle[b], Danielle M. Anthony[a], Marissa N.D. Lassere[c]

[a]*Department of Clinical Pharmacology, University of Newcastle, Mater Hospital, Waratah NSW 2298, Australia*
[b]*Department of Primary Care and General Practice, University of Birmingham, Birmingham B15 2TT, UK*
[c]*Department of Rheumatology, University of New South Wales, St. George Hospital, Kogarah NSW 2217, Australia*

Journal of Clinical Epidemiology 62 (2009) 328−336



In 16 qualifying trials, regression analysis yielded a cardiovascular mortality model whose prediction bands demonstrated no cardiovascular survival benefit with LDL-cholesterol difference values below 1.4 mmol/L.

Prostate-Specific Antigen (PSA) as a Surrogate End Point for Survival in Prostate Cancer Clinical Trials

Laurence Collette

EUROPEAN UROLOGY 53 (2008) 6–9

Prognostic versus surrogate

A *prognostic factor* is a set of physical signs or laboratory measurements that occur in association with a pathologic process and are significantly associated with the disease evolution and survival of a patient. For example, biochemical relapse after radical prostatectomy is prognostic for clinical relapse.

A *surrogate* is a "(set of) biochemical measurements or clinical signs used as substitute for a clinical endpoint in the assessment of a therapeutic benefit."

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A *prognostic factor* is a set of physical signs or laboratory measurements that occur in association with a pathologic process and are significantly associated with progression and survival of a patient with clinical relapse after radical prostatectomy is prognostic for clinical relapse.

…in the individual patient
(patient level)

A *surrogate* is a "(set of) biochemical measurements or clinical signs used as substitute for a clinical endpoint in the assessment

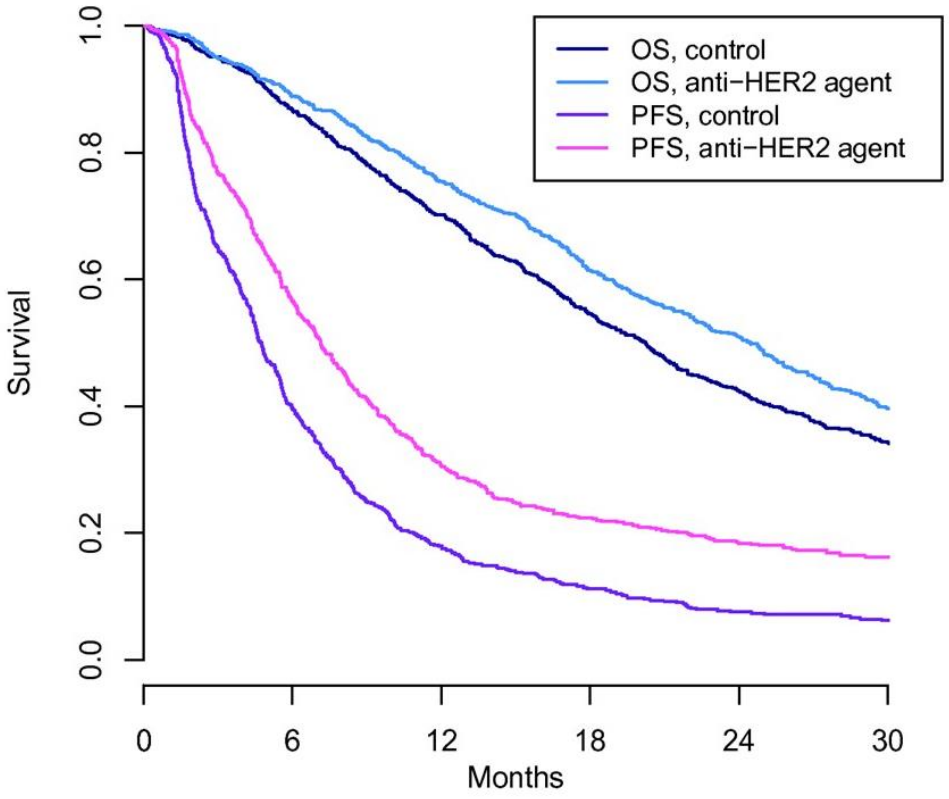
…across groups of patients
(trial level)

Progression-free survival (PFS) as surrogate endpoint for overall survival (OS) in clinical trials of HER2-targeted agents in HER2-positive metastatic breast cancer (MBC): An individual patient data (IPD) analysis.

S. Michiels[1,2], L. Pugliano[1,3], D. Grun[1], S. Marguet[2], J. Barinoff[4], D. Cameron[5], M. Cobleigh[6], A. Di Leo[7], S. Johnston[8], G. Gasparini[9], B.Kaufman[10], M. Marty[11], V. Nekjudova[12], S. Paluch-Shimon[13], F.Penault-Llorca[14], D. Slamon[15], C. Vogel[16], G. von Minckwitz[12], M. Buyse[17], M. Piccart[1,3]

ASCO 2013
CHICAGO
30 MAY - 04 JUN

Individual level ρ=0.66 (95% CI 0.65-0.66)



- For HER2-targeted therapies in HER2+ MBC, PFS is moderately correlated with OS at the individual level (ρ=0.66)

Progression-free survival (PFS) as surrogate endpoint for overall survival (OS) in clinical trials of HER2-targeted agents in HER2-positive metastatic breast cancer (MBC): An individual patient data (IPD) analysis.

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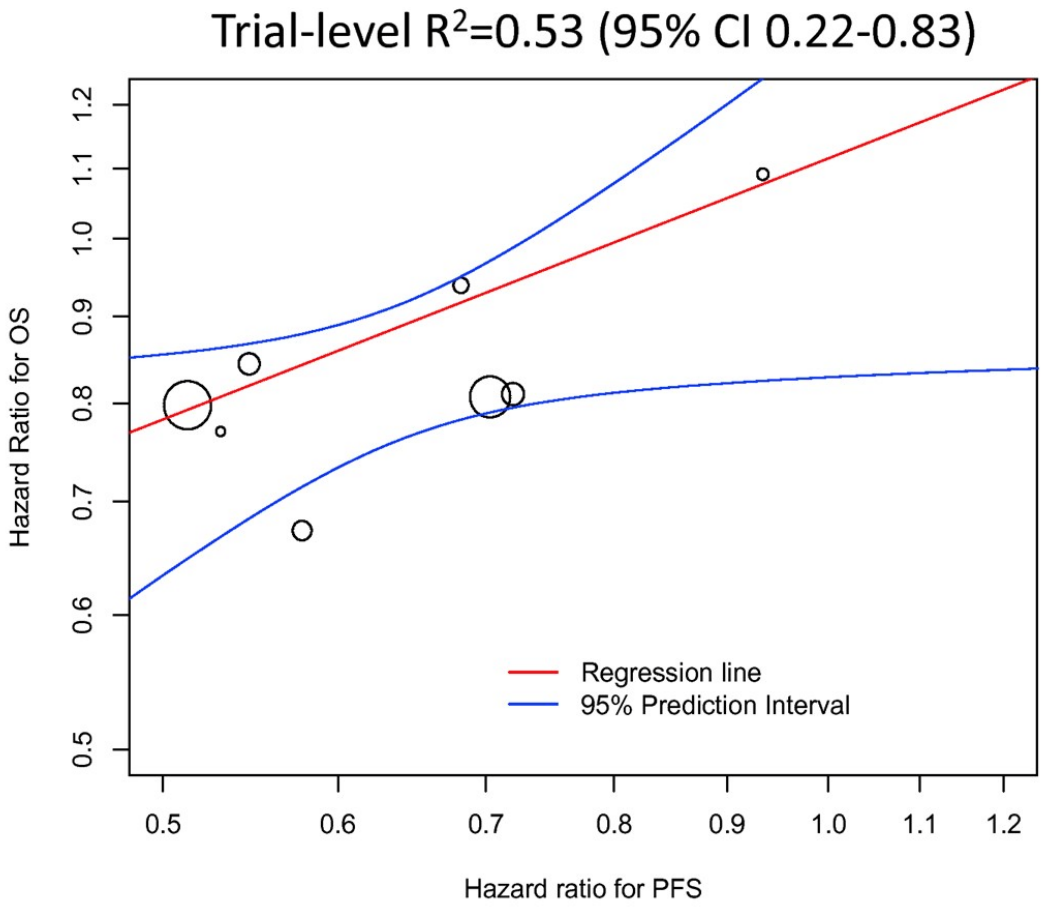
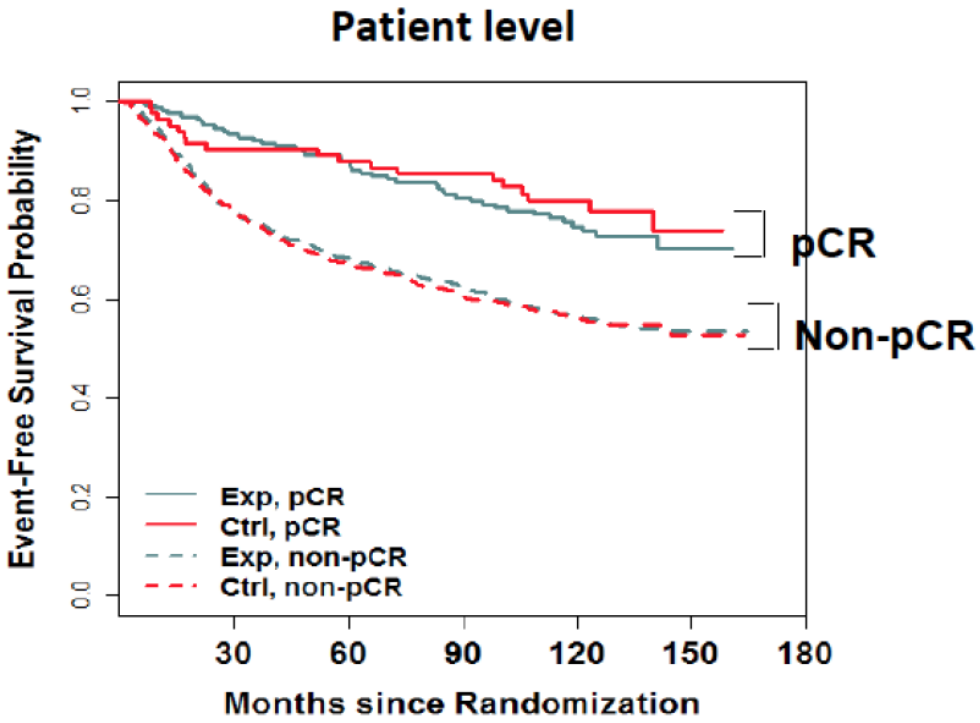
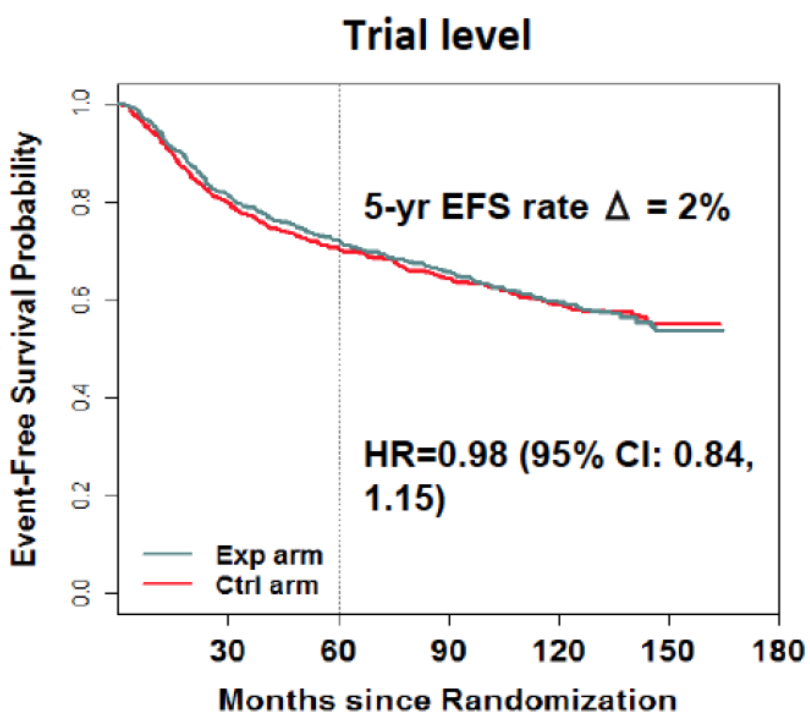


- At the trial level, only 53% of the variation in treatment effects on OS can be explained by effects on PFS (trial-level R^2=0.53).

Responder Analysis vs Trial Level Analysis





	Exp	Ctrl
pCR	21%	10%
No pCR	79%	90%

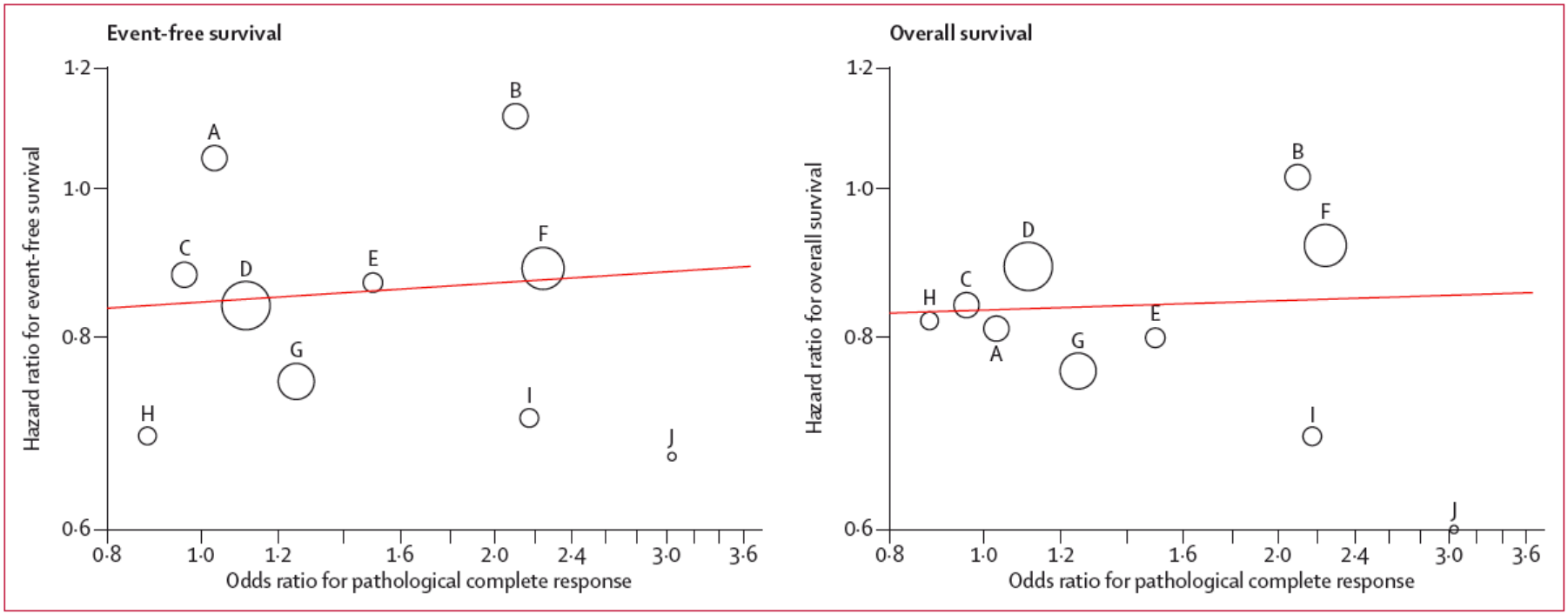
Although patients with pCR have better EFS irrespective of treatment. There is no difference on EFS between the two randomized treatment arms.

Cortazar P & Zhang L Neoadjuvant Breast Cancer Workshop FDA 2013

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**



Interpretation Patients who attain pathological complete response defined as ypT0 ypN0 or ypT0/is ypN0 have improved survival. The prognostic value is greatest in aggressive tumour subtypes. Our pooled analysis could not validate pathological complete response as a surrogate endpoint for improved EFS and OS.

Gli Endpoint surrogati

- Rivestono un ruolo molto importante
  - nella pratica
  - nella ricerca clinica
- la sola dimostrazione di associazione tra un biomarker e l'endpoint clinico
  - non fornisce una evidenza sufficiente di surrogacy
- data l'alta variabilità e la scarsa conoscenza sui meccanismi biologici che collagano il trattamento con l'outcome clinico,
  - il ruolo dei SE deve essere dimostrato e validato per ogni specifica malattia e per ogni singola classe di farmaco

Take home messages

V. Torri, AIOM 2014

Co-primary endpoints can be different medical assessments angled at different aspects of a disease, therefore, are used collectively to strengthen evidence for the treatment effect.

Li QH. Evaluating co-primary endpoints collectively in clinical trials. Biom J. 2009 Feb;51(1):137-45.

Guidance for Industry

E9 Statistical Principles for Clinical Trials

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
September 1998
ICH

5. *Multiple Primary Variables (2.2.5)*

It may sometimes be desirable to use more than one primary variable, each of which (or a subset of which) could be sufficient to cover the range of effects of the therapies.

Applied Clinical Trials Online

Composite Endpoints: Proceed with Caution

By Peter Kleist May 1, 2006

Multiple single endpoints are combined in order to confront an investigational drug with a higher number of events expected during the trial.

Statistical precision and efficiency will be increased, trials become smaller, less costly, and the results of promising new treatments will be available earlier.

The selected individual components of a composite endpoint, as reported in the biomedical literature, are not always clinically meaningful.

Apixaban for Extended Treatment of Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*

N Engl J Med 2013;368:699-708.

OUTCOME MEASURES

The primary efficacy outcome was the composite of symptomatic recurrent venous thromboembolism or death from any cause — an outcome consistent with that recommended in regulatory guidelines for trials of extended treatment for venous thromboembolic diseases.[16] Recurrent venous thromboembolism included fatal and nonfatal pulmonary embolism and deep-vein thrombosis. Death was classified as related to venous thromboembolism, related to cardiovascular disease, due to bleeding, or due to other causes.

Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial

The TIME Investigators

Lancet 2001; **358:** 951–957

The frequency of the composite endpoint (death, nonfatal myocardial infarction, and hospital admission for ACS) was much lower with revascularization; however, this was due to a marked difference in hospital admissions, which accounted for 75% of the events in the medical treatment group. In contrast, there were twice as many deaths in the invasive treatment group.

The question remains how to interpret the results and inform a patient who has to decide between conservative or surgical therapy.

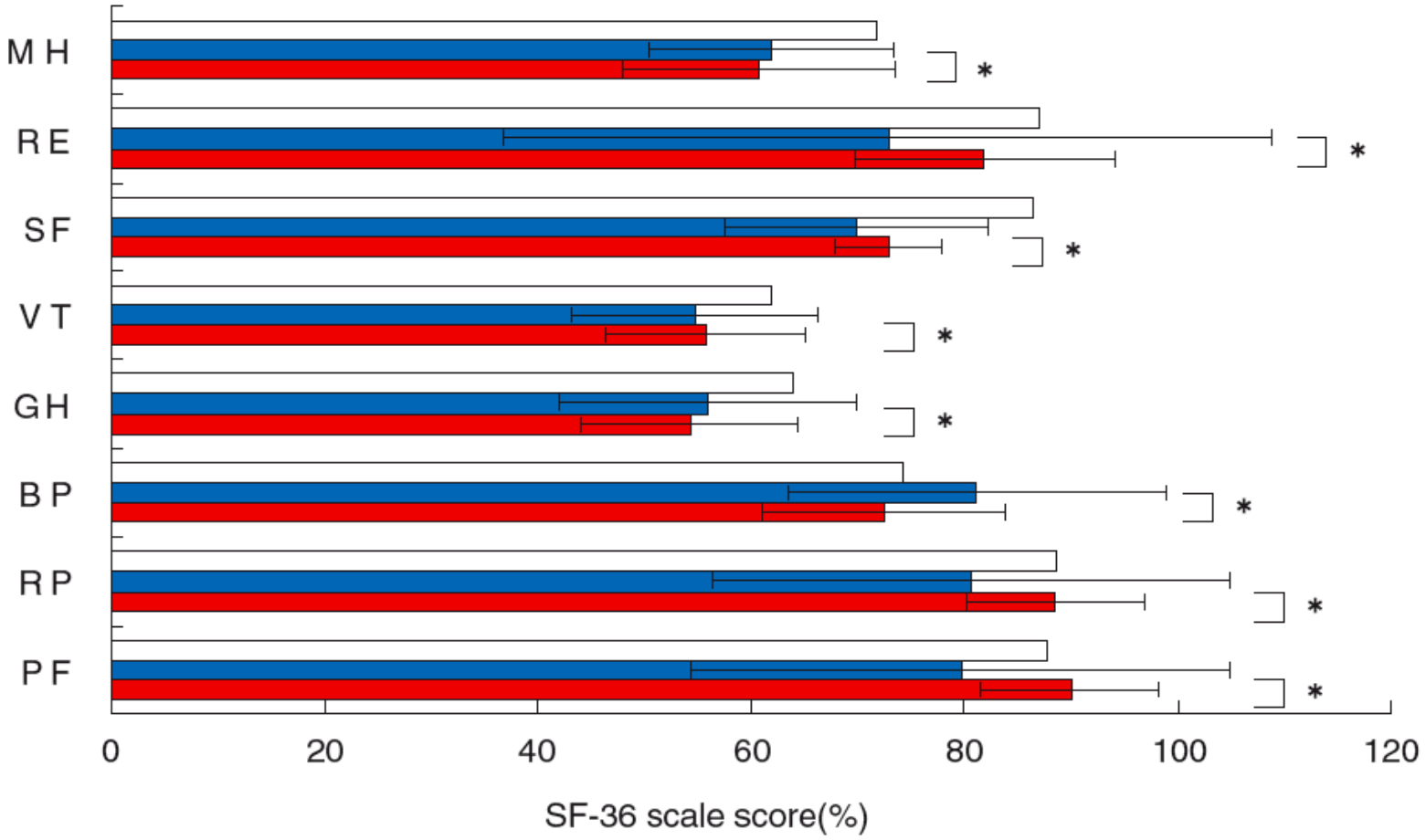
Regular Approval Basis – "Clinical Benefit"

- Longer life
- Better life
- Established Surrogate for one of above

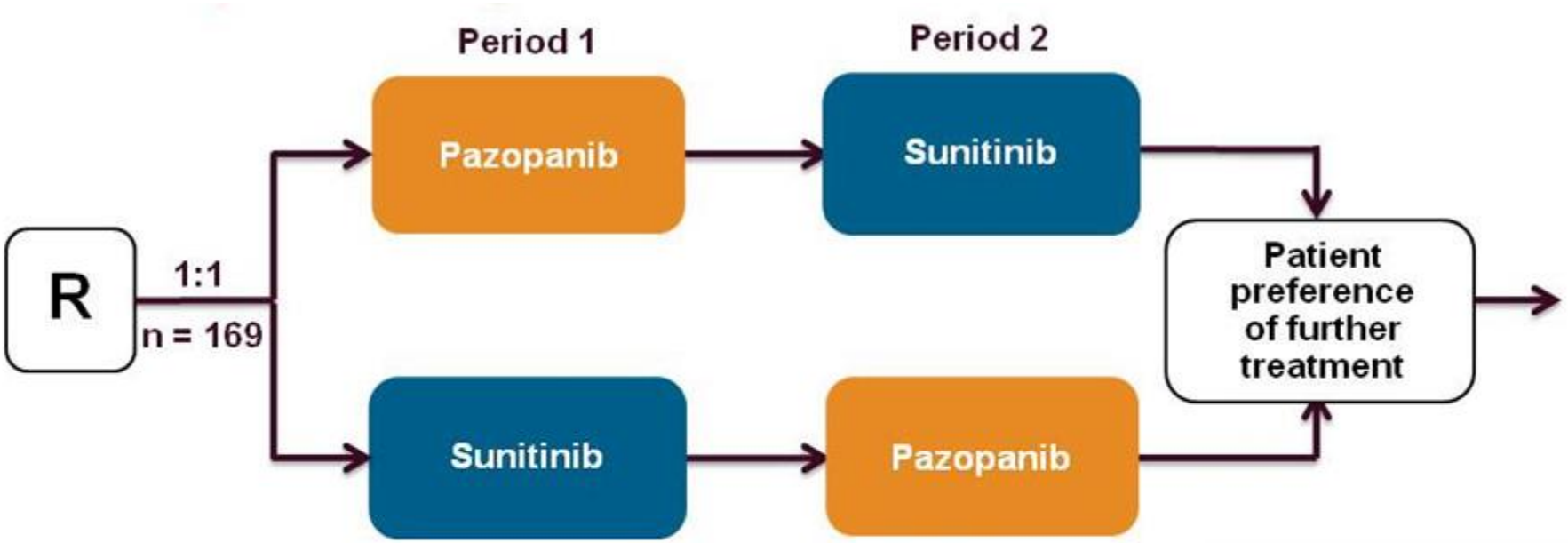
A pilot study of the assessment of the quality of life, functional results, and complications in patients with an ileal neobladder for invasive bladder cancer

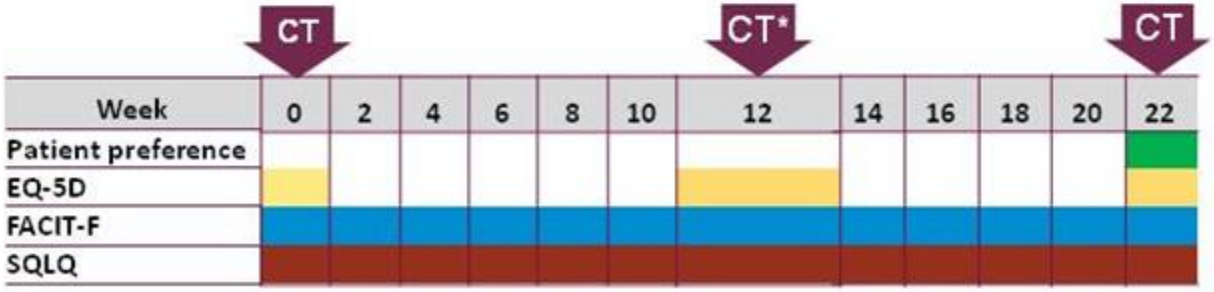
Masahiko Harano,[1] Masatoshi Eto,[1] Motonobu Nakamura,[2] Yoshihiro Hasegawa,[2] Motonori Kano,[3] Akito Yamaguchi[4] and Seiji Naito[1]

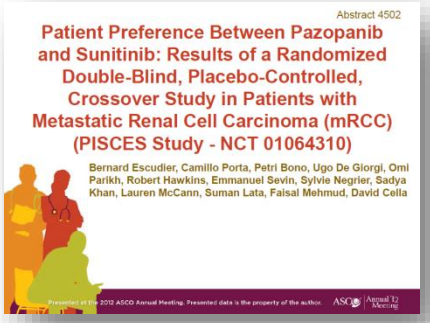
International Journal of Urology (2007) **14**, 112–117



Benefit to harm ratio







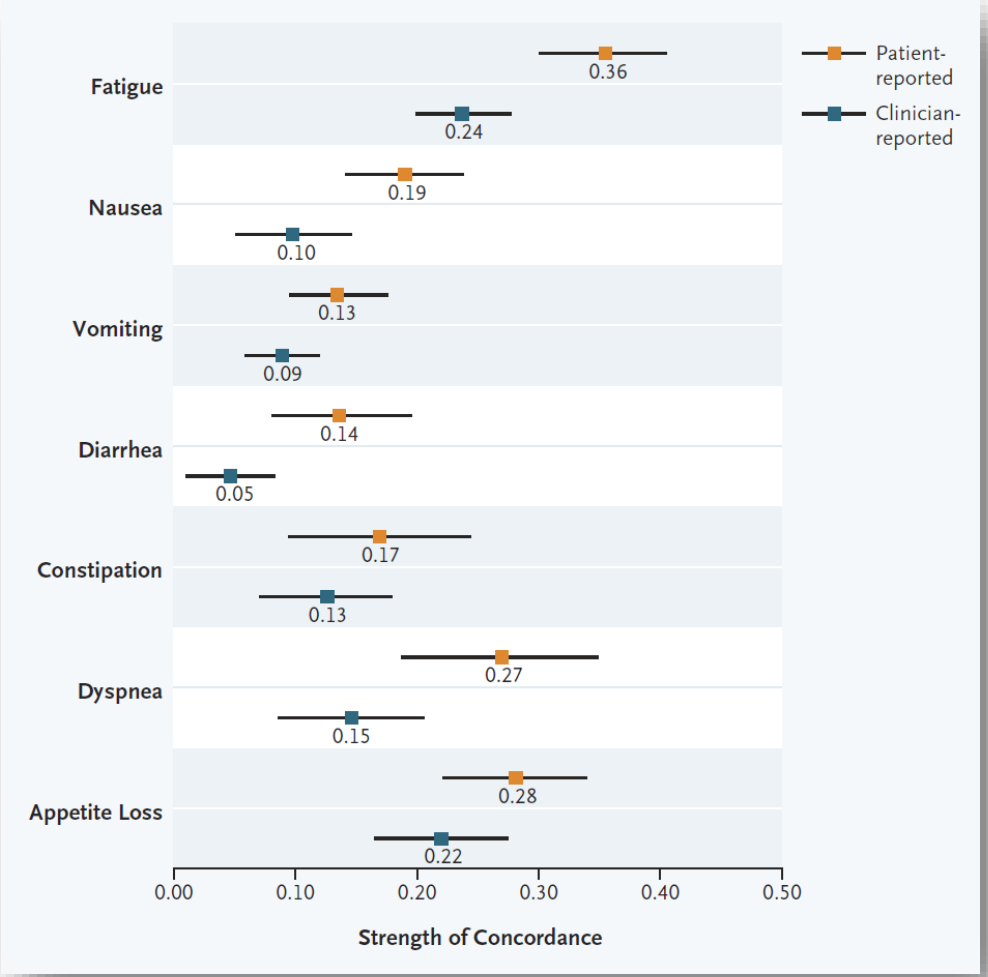
J Clin Oncol. 2014 May 10;32(14):1412-8

The Missing Voice of Patients in Drug-Safety Reporting

Ethan Basch, M.D.

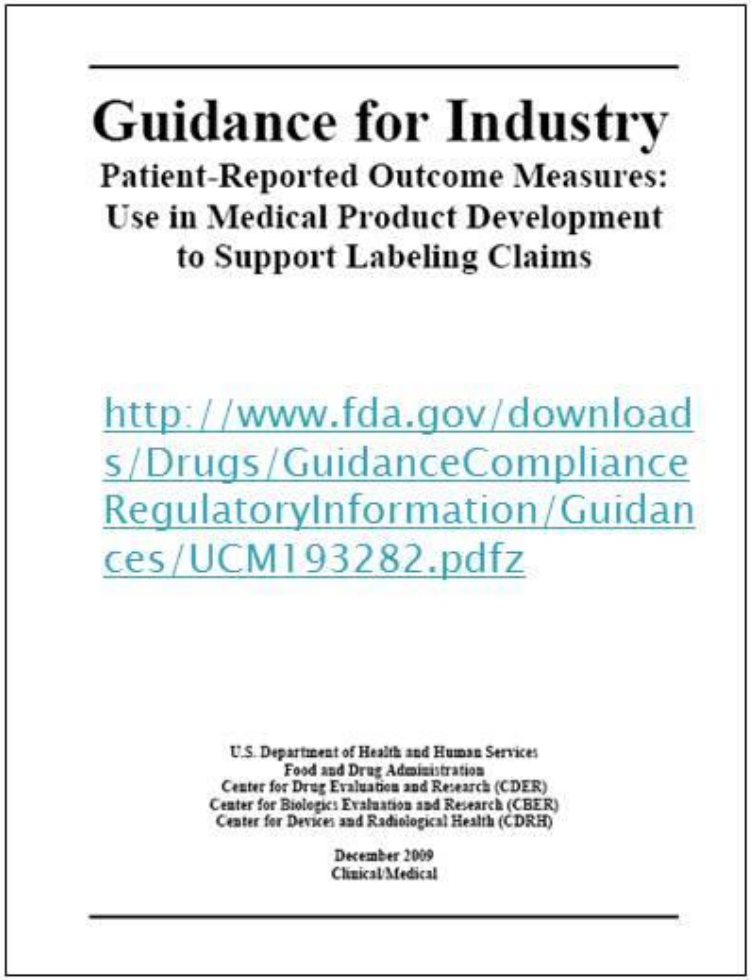
N ENGL J MED 362;10 NEJM.ORG MARCH 11, 2010

Current methods for detecting adverse events in clinical trials are acknowledged to lack sensitivity,[4] and worrisome symptoms might well come to light earlier in the drug-development cycle if reporting by patients were standard practice.



Definition of PROs

- "Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else"



Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdfz

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

Standards for PRO *Development*

- Reliability
  - Test-retest
  - Internal consistency
- Validity
  - Content validity (qualitative)
  - Construct validity (discriminant)
- Ability to detect change

Ethan Basch, 2010

Standards for PRO *Development*

- Reliability
  - Te[illegible]etest
- [illegible]
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  - Construct validity (discriminant)
- Ability to detect change

Reliability means the consistency or repeatability of the measure.

Ethan Basch, 2010

Standards for PRO *Development*

- Reliability
  - Test-retest
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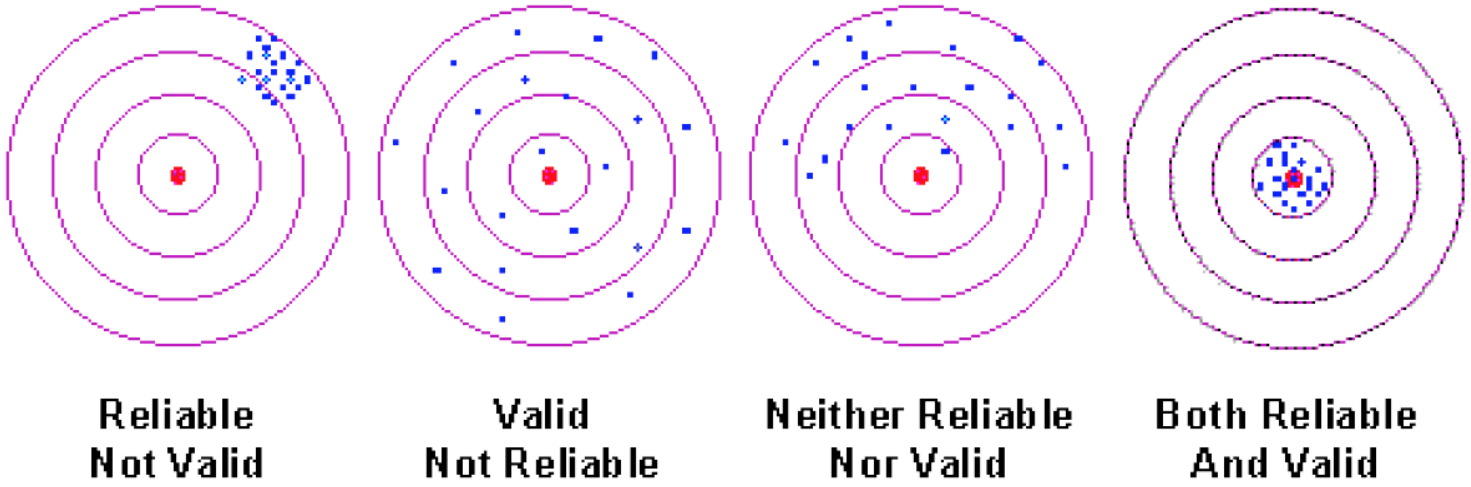
  - C[illegible]tent validity (qualitative)
  - [illegible]iminant)

Validity means measuring what you claim to be measuring.

Ethan Basch, 2010



- In the first situation, you are consistently and systematically measuring the wrong value for all respondents. This measure is reliable, but no valid.
- In the second situation, you get a valid group estimate, but you are inconsistent. Here, you can clearly see that reliability is directly related to the variability of your measure.
- The third scenario shows a case where your hits are spread across the target and you are consistently missing the center. Your measure in this case is neither reliable nor valid.
- Finally, we see the "Robin Hood" scenario – you consistently hit the center of the target. Your measure is both reliable and valid.

Standards for PRO *Development*

- Reliability
  - Test-retest
  - Internal consistency
- Valid
  - Co
  - Constr validity (discriminant)
- Ability to detect change

The PRO instrument can identify differences in scores over time

Ethan Basch, 2010

Symptom Endpoints (Patient-Reported Outcomes)

- Blinding is often difficult
- Data are often missing or incomplete
- Clinical significance of small changes unknown
- Few validated instruments

National Cancer Institute
U.S. National Institutes of Health | www.cancer.gov

PRO-CTCAE
PATIENT SYMPTOM REPORTER

A system for patient self-reporting of adverse symptoms in cancer trials

- providing a more full picture of patient experience;
- compatible with existing adverse event reporting systems
- widely accepted and used;
- generating useful data for investigators, regulators, clinicians and patients

CTCAE vs. PRO-CTCAE Item Structures

CTCAE					
Adverse Event	Grade				
	1	2	3	4	5
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest; limiting self care ADL	-	-

PRO-CTCAE
Please think back over the past 7 days:
What was the severity of your WEAKNESS OR TIREDNESS at their WORST? None / Mild / Moderate / Severe / Very severe
How much the WEAKNESS OR TIREDNESS interfere with your usual daily activities? Not at all / A little bit / Somewhat / Quite a bit / Very much

Presented By Lori M. Minasian, MD at 2013 ASCO Annual Meeting (*modified)*

Con il Patrocinio di

Aiom

STUDI CLINICI: METODOLOGIA

Coordinatore:
Dr.ssa Stefania Gori

Evento ECM MODULO 1
(formazione di base)
"A good foundation"

NEGRAR
22-23 Gennaio 2016
Centro Formazione
Ospedale Sacro Cuore
Don Calabria

Riflessioni e Sintesi

WHAT?

Cosa è emerso di particolarmente saliente e rilevante?

(indicare almeno 2 risposte condivise)

SO WHAT?

Perché le cose emerse sono così rilevanti?

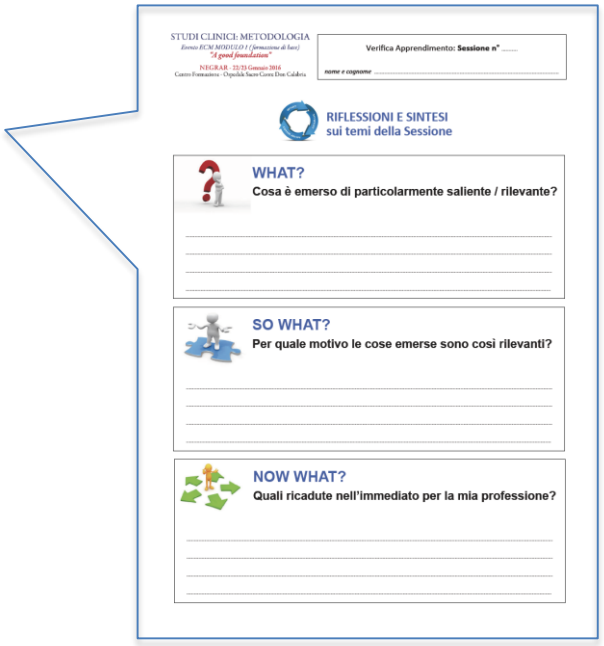
(indicare almeno 2 risposte condivise)

NOW WHAT?

Quali ricadute nell'immediato per la mia professione?

(indicare almeno 2 risposte condivise)

1. Riflettete da soli per 10 min.



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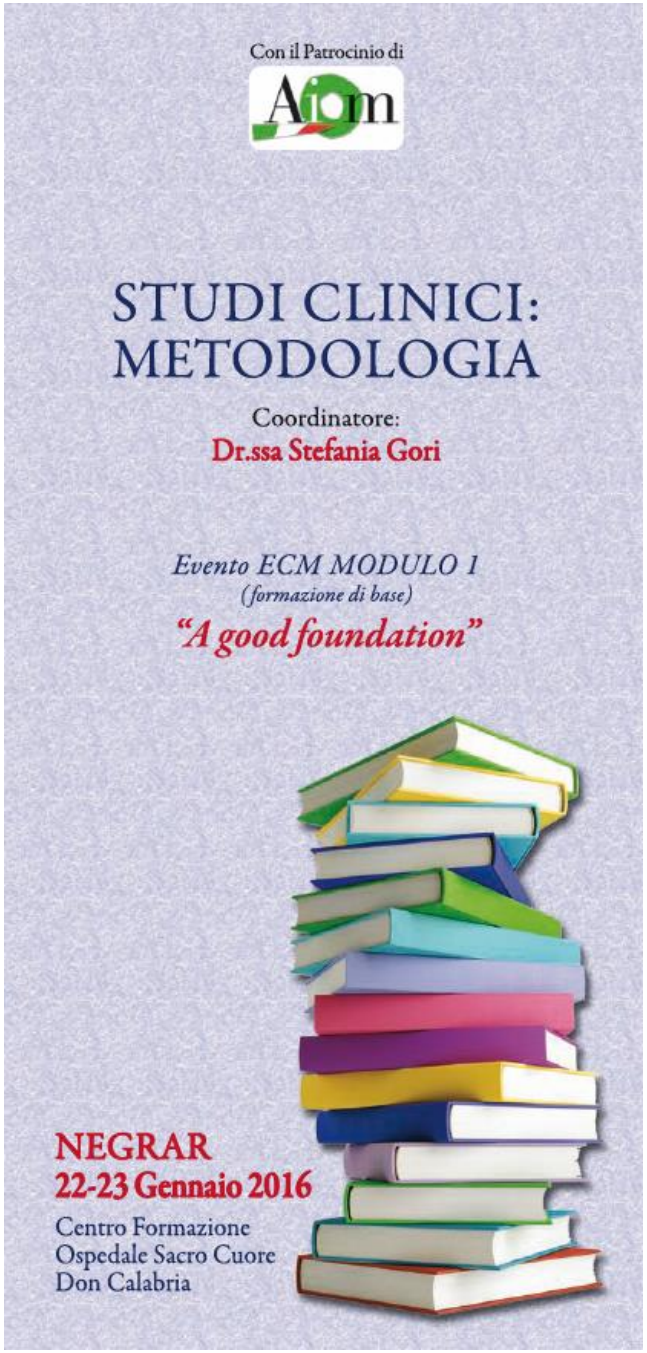
3. Riportate sulla lavagna il Vostro W^3 condiviso su almeno due aspetti ritenuti rilevanti e impattanti sulla professione (in 5 min.)
4. Presentate ai Colleghi degli altri tavoli il Vostro W^3 condiviso



Venerdì 22 gennaio 2016

- Plausibilità e opportunità dello studio
  - ✓ criteri FINER
- Obiettivi (primario e secondari)
  - ✓ strutturazione sec. P.I.C.O.
- Disegno dello studio
  - ✓ tipologie di disegno di studio
  - ✓ procedure di randomizzazione
  - ✓ scelta del braccio di controllo
- Endpoints (primario e secondari)
  - ✓ endpoints surrogati
  - ✓ PROs
- Selezione dei pazienti
  - ✓ criteri restrittivi Vs inclusivi
  - ✓ conseguenze su trasferibilità e precisione delle evidenze

Bria

Con il Patrocinio di

Aiom

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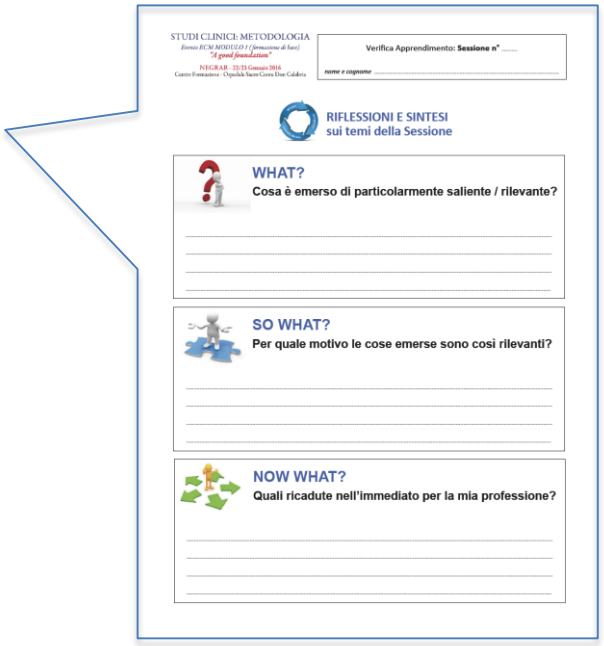

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