Méta-analyse sur données individuelles et biomarqueurs

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TYPES OF BIOMARKERS

"a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (FDA)

1. prognostic biomarkers, which affect the outcome of patients in terms of a clinical endpoint

2. predictive biomarkers, which affect the effect of a specific treatment on a clinical endpoint

3. surrogate biomarkers, which may replace a clinical endpoint in clinical trials carried out to evaluate the effect of a specific treatment

Buyse & Michiels, in Kelly & Halabi, Oncology Clinical Trials 2010

Prognostic and predictive biomarkers

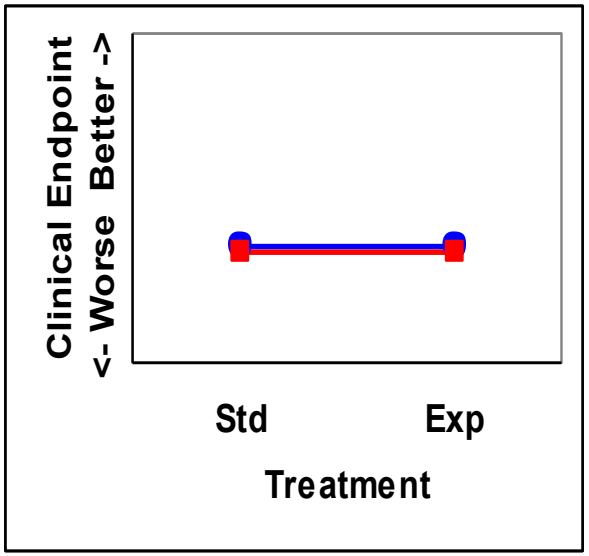
Biomarker present

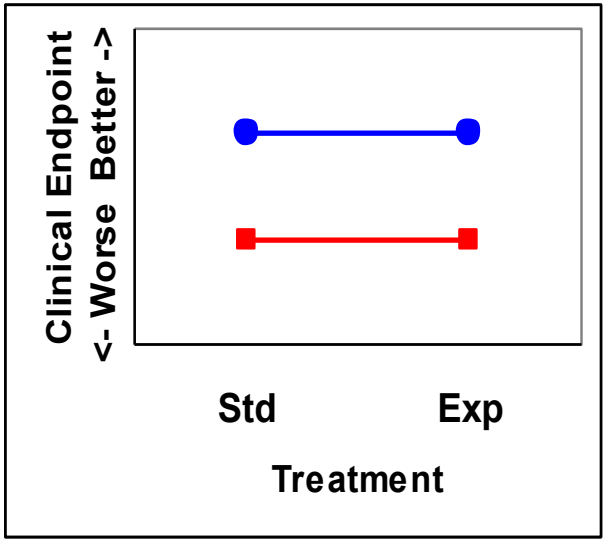
Biomarker absent

Std: standard arm; Exp: experimental arm

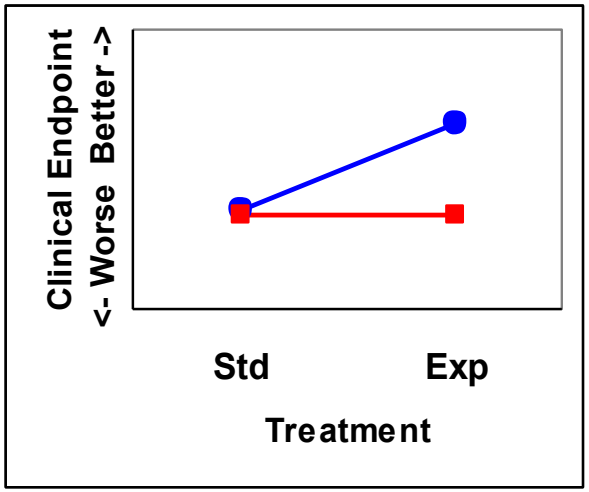
Buyse & Michiels, in Kelly & Halabi, Oncology Clinical Trials: Successful design, conduct and analysis 2010

Prognostic biomarker

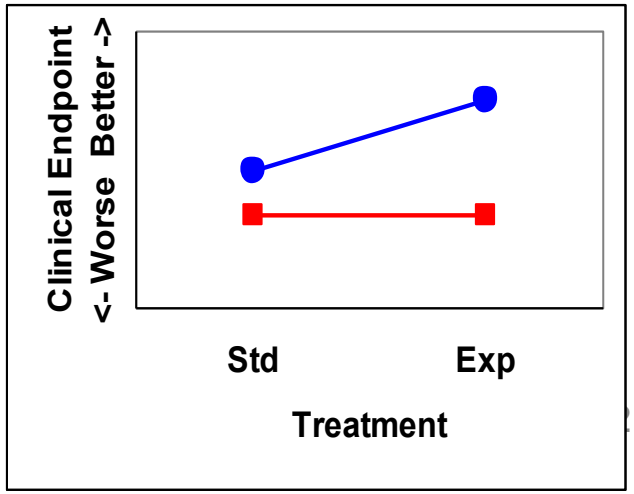




Predictive biomarker



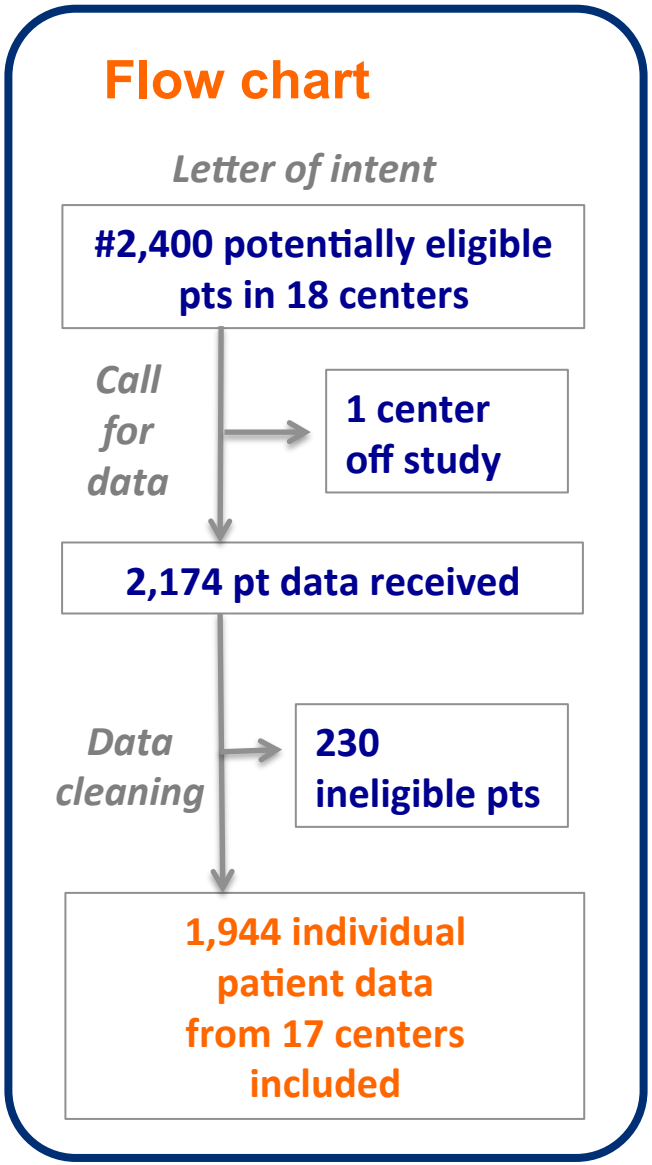
Prognostic and predictive



Outline

- 1) Meta-analyses of prognostic biomarkers
  - Circulating tumour cells (CTC) in metastatic breast cancer
  - Gene expression signatures
- 2) Meta-analysis of predictive biomarkers: ERCC1 in non-small cell lung cancer (NSCLC)
- 3) Surrogate biomarker evaluation in the meta-analytic setting

Studies included in the CTC study



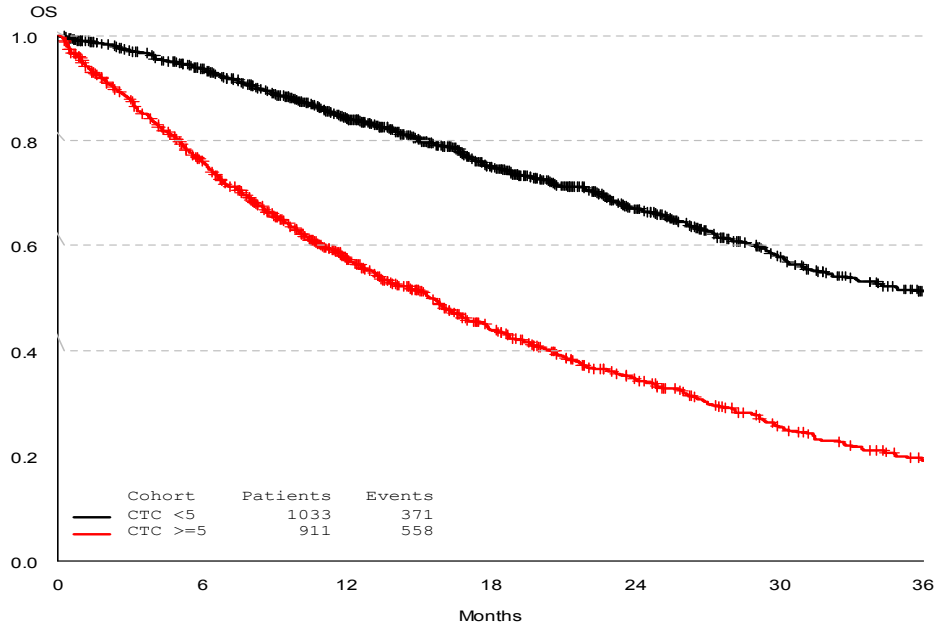
Goals:

- Analysis in homogeneous fashion (both endpoints and biomarker data)
- Resolve conflicting results between studies (heterogeneity)
- Increase statistical power (published and unpublished)
- Adjust for clinicopathological factors
- Added value to established clinicopathological factors
- Subgroups

Bidard et al Lancet Oncol 2014

CTC in metastatic breast cancer study

CTC < 5 /7.5 ml
CTC ≥ 5 /7.5 ml



Overall Survival

N= 1,944 patients
HR = 2.77
p<0.0001

Bidard et al Lancet Oncol 2014

Early breast cancer: prognostic signatures

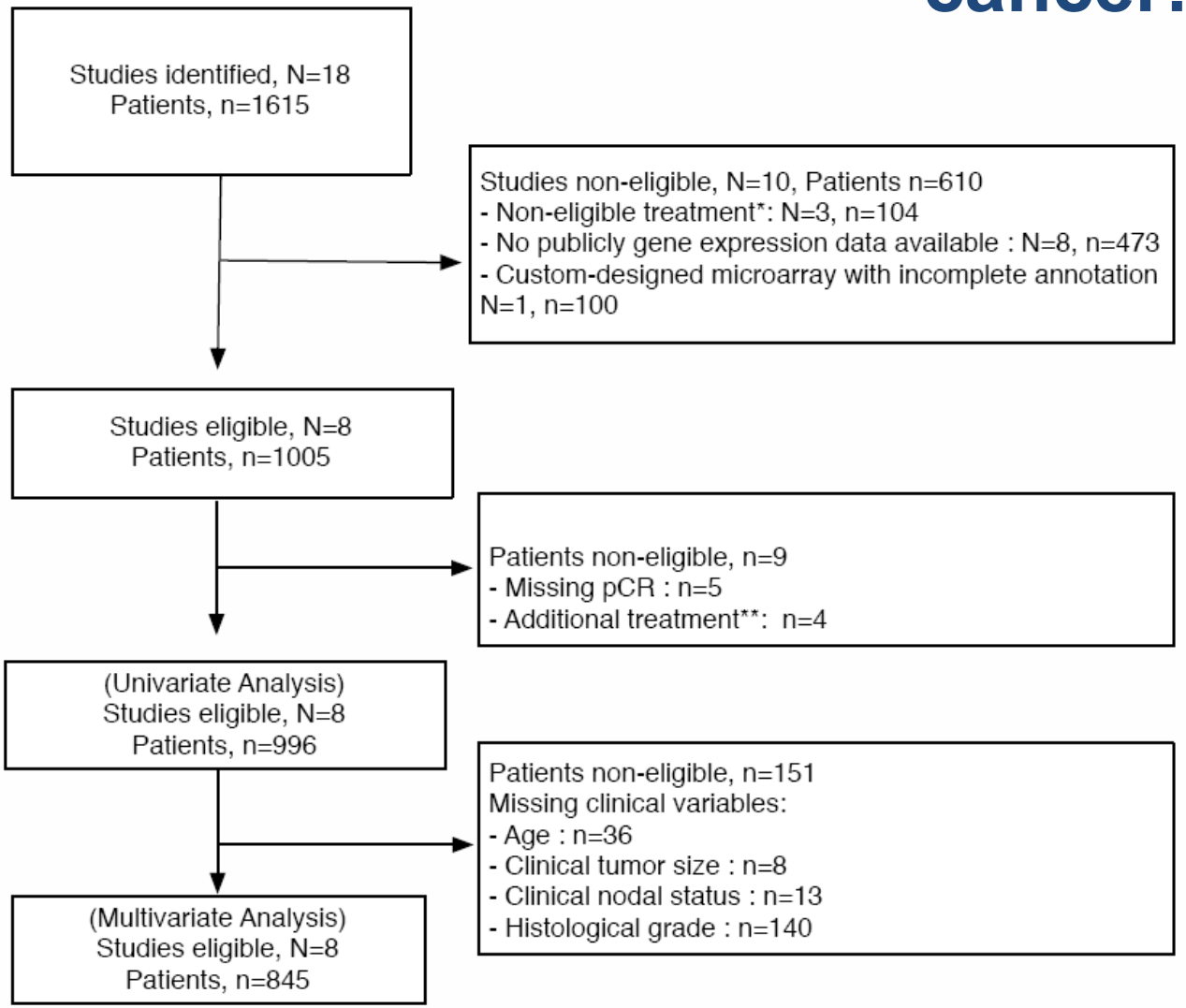
Clinicopathological model

- Adjuvant!: age, tumour size, nodal status, histological tumour grade, ER (hormone recepter), comorbidity

Available gene signatures for a price of 400-3000$…

- IHC4: 4 genes i.e. Ki67, ER, PR, HER2
- Oncotype Dx: 16 cancer genes including Ki67, ER, PR, HER2
- PAM50: 50 genes including Ki67, ER, PR, HER2
- Mammaprint Dx: 70 genes
- Endopredict: 8 cancer genes
- Mapquant Dx : 97 genes (GGI)
- …

Pooled gene expression analysis of neoadjuvant chemotherapy trials in breast cancer: flow chart



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PLoS MEDICINE

Guidelines and Guidance

Key Issues in Conducting a Meta-Analysis of Gene Expression Microarray Datasets

Adaikalavan Ramasamy*, Adrian Mondry, Chris C. Holmes, Douglas G. Altman

Microarray technology measures the mRNA levels of tens of thousands of genes in tissue samples simultaneously in a high-throughput and cost-effective manner. Since its introduction over a decade ago [1], it has found widespread use in the fields of molecular genetics and functional genomics. It has been applied in order to understand underlying biological mechanisms [2], to discover novel subgroups of diseases [3–5], to examine drug response [6,7], to classify patients into disease groups [3], and to predict disease outcomes [8–10]. Some molecular signatures discovered with microarray technology are now being evaluated in prospective randomized clinical trials [11,12].

Despite their great prom
report findings that are no
to the mildest of data pertu
include improper analysis
false positives, and inadequ
The situation is exacerbate
to large numbers of potent
thousands of probes are in
of biological samples.

Generalizability across st
assessed before considerin
For example, the findings
from a particular geograph

Summary Points

- Improvements in microarray technology and its increasing use have led to the generation of many highly complex datasets that often try to address similar biological questions.
- Meta-analysis, a statistical approach that combines results from independent but related studies, is a relatively inexpensive option that has the potential to increase both the statistical power and generalizability of single-study analysis.
- Meta-analysis of microarray datasets, and genomic data in general, is desirable, and is much enhanced when raw data are available.

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PLoS MEDICINE

Guidelines and Guidance

Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK): Explanation and Elaboration

Douglas G. Altman[1]*, Lisa M. McShane[2], Willi Sauerbrei[3], Sheila E. Taube[4]

1 Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom, **2** US National Cancer Institute, Bethesda, Maryland, United States of America, **3** Institut fuer Medizinische Biometrie und Medizinische Informatik, Universitaetsklinikum Freiburg, Freiburg, Germany, **4** ST-Consulting, Bethesda, Maryland, United States of America

Selected gene modules

Prognostic Signatures
- GGI
- Gene70

Chromosomal Instability
- CIN70

Microenvironment
- Stroma1
- Stroma2
- Immune1
- Immune2

Oncogenic Pathways
- RAS
- MAPK
- PTEN
- AKTmTOR
- PIK3CA
- IGF1
- SRC
- MYC
- E2F3
- Betacatenin

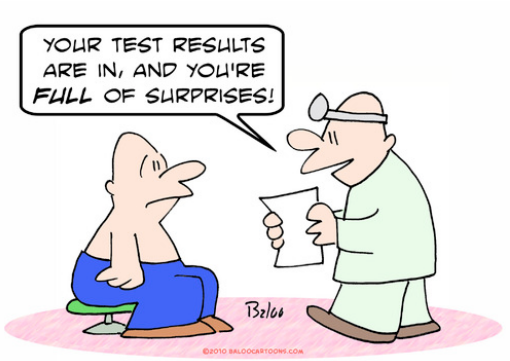
$$module\ score(s) = \frac{\sum_{i=1,\ldots,n} w_i\, x_i}{\sum_{i=1,\ldots,n} |w_i|}$$

x_i= expression of gene i
w_i= ± 1 depending on sign of assocation with phenotype in oringinal publication
$i=1,..,n$ (number of genes in module)

2.5% and 97.5% quantiles of gene modules scaled to [-1,1] within a study

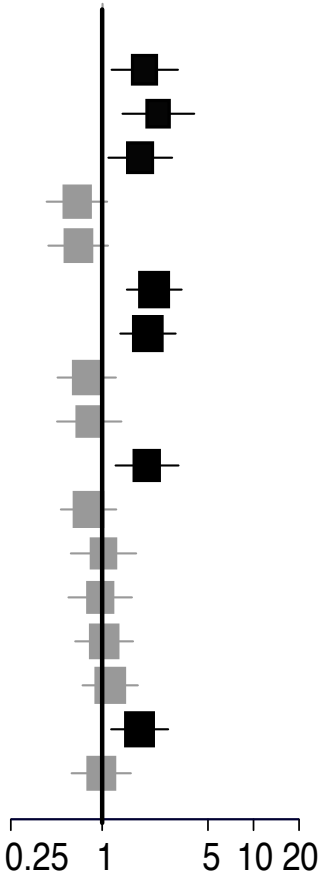
Wirapati et al BCR 2008

Multivariate logistic regression model for pathological complete response (pCR): clinical model + a gene module



ALL
(845 pts, 189 pCR)

	OR	95% CI	P	FDR
GGI	1.7	(1.12,2.6)	1.3E−02	3.7E−02
Gene70	2.02	(1.29,3.2)	2.4E−03	1.3E−02
CIN70	1.61	(1.08,2.42)	2.1E−02	5.1E−02
Stroma1	0.73	(0.49,1.06)	1.0E−01	2.1E−01
Stroma2	0.74	(0.5,1.07)	1.1E−01	2.1E−01
Immune1	1.92	(1.36,2.73)	2.2E−04	3.7E−03
Immune2	1.78	(1.25,2.53)	1.3E−03	1.1E−02
RAS	0.82	(0.57,1.18)	3.0E−01	4.9E−01
MAPK	0.85	(0.56,1.27)	4.2E−01	6.0E−01
PTEN	1.75	(1.18,2.62)	5.8E−03	2.5E−02
AKTmTOR	0.84	(0.59,1.19)	3.2E−01	4.9E−01
PIK3CA	1.01	(0.67,1.53)	9.5E−01	9.5E−01
IGF1	0.97	(0.65,1.45)	8.9E−01	9.5E−01
SRC	1.02	(0.71,1.47)	9.1E−01	9.5E−01
MYC	1.1	(0.78,1.56)	5.8E−01	7.6E−01
E2F3	1.6	(1.12,2.3)	1.1E−02	3.7E−02
BetaCatenin	0.98	(0.68,1.43)	9.4E−01	9.5E−01



OR: odds ratio for a 1-unit change in gene module, adjusted for clinicopathological factors

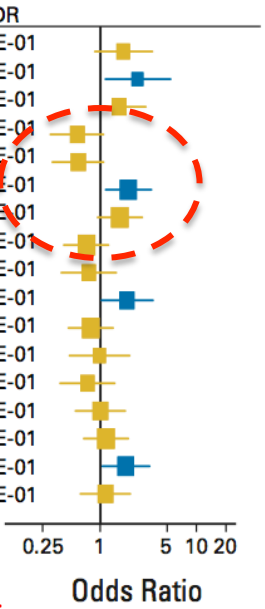
FDR: false discovery rate

Ignatiadis et al JCO 2012

Pathways associated with pCR in different breast cancer subtypes?

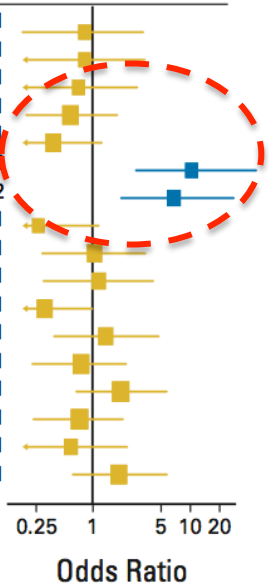
ER-/HER2-

	OR	95% CI	P	FDR
GGI	1.59	0.91 to 2.81	1.0E-01	2.2E-01
Gene70	2.11	1.12 to 4.03	2.2E-02	1.6E-01
CIN70	1.47	0.88 to 2.47	1.4E-01	2.7E-01
Stroma1	0.65	0.38 to 1.08	9.7E-02	2.2E-01
Stroma2	0.66	0.4 to 1.08	9.9E-02	2.2E-01
Immune1	1.76	1.13 to 2.76	1.3E-02	1.6E-01
Immune2	1.49	0.96 to 2.31	7.4E-02	2.2E-01
RAS	0.77	0.5 to 1.19	2.4E-01	4.1E-01
MAPK	0.81	0.47 to 1.38	4.3E-01	5.7E-01
PTEN	1.71	1.04 to 2.85	3.7E-02	1.6E-01
AKTmTOR	0.84	0.54 to 1.3	4.3E-01	5.7E-01
PIK3CA	1.00	0.55 to 1.8	9.9E-01	9.9E-01
IGF1	0.79	0.46 to 1.34	3.8E-01	5.7E-01
SRC	1.02	0.62 to 1.65	9.5E-01	9.9E-01
MYC	1.13	0.73 to 1.75	5.7E-01	6.9E-01
E2F3	1.67	1.06 to 2.67	2.9E-02	1.6E-01
BetaCatenin	1.12	0.69 to 1.82	6.4E-01	7.3E-01



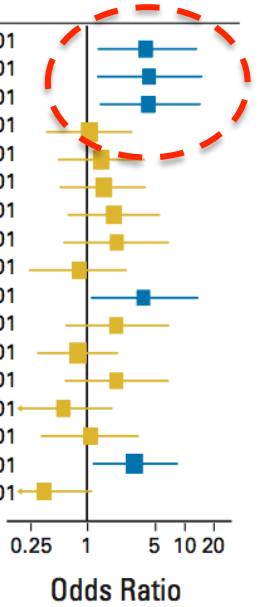
HER2+

	OR	95% CI	P	FDR
GGI	0.86	0.25 to 2.72	8.0E-01	8.7E-01
Gene70	0.85	0.24 to 2.8	8.0E-01	8.7E-01
CIN70	0.76	0.22 to 2.41	6.4E-01	8.4E-01
Stroma1	0.65	0.25 to 1.62	3.5E-01	7.5E-01
Stroma2	0.46	0.17 to 1.19	1.2E-01	4.0E-01
Immune1	7.13	2.38 to 25.51	1.0E-03	1.8E-02
Immune2	5.01	1.77 to 16.35	4.1E-03	3.5E-02
RAS	0.34	0.09 to 1.12	8.7E-02	3.7E-01
MAPK	1.04	0.37 to 2.84	9.4E-01	9.4E-01
PTEN	1.13	0.38 to 3.31	8.2E-01	8.7E-01
AKTmTOR	0.39	0.14 to 0.99	5.4E-02	3.1E-01
PIK3CA	1.30	0.47 to 3.69	6.2E-01	8.4E-01
IGF1	0.79	0.3 to 1.94	6.2E-01	8.4E-01
SRC	1.74	0.73 to 4.33	2.2E-01	6.1E-01
MYC	0.77	0.31 to 1.82	5.6E-01	8.4E-01
E2F3	0.65	0.21 to 1.97	4.5E-01	8.4E-01
BetaCatenin	1.68	0.68 to 4.35	2.7E-01	6.5E-01

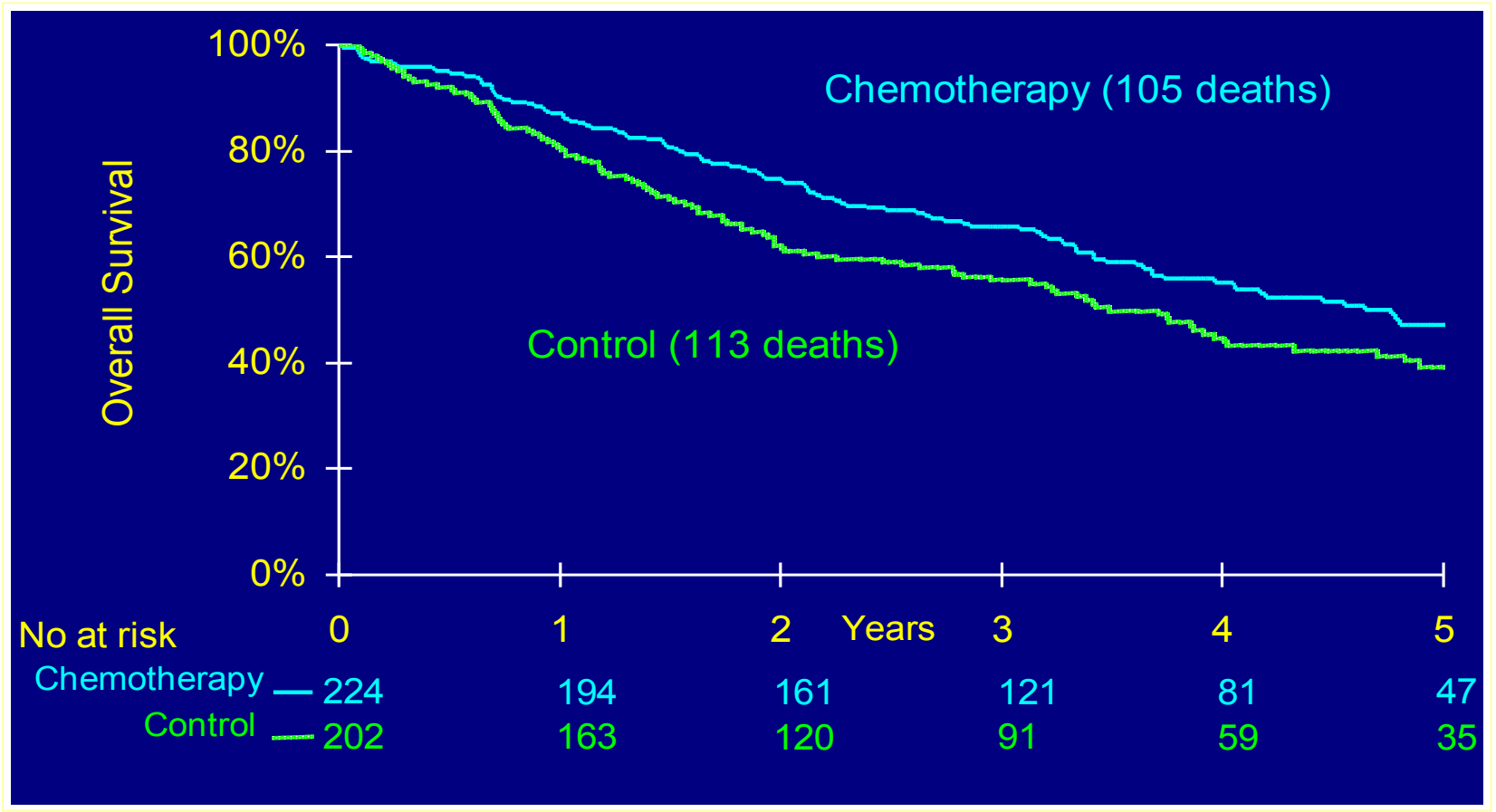


ER+/HER2-

	OR	95% CI	P	FDR
GGI	3.19	1.26 to 8.72	1.8E-02	1.0E-01
Gene70	3.43	1.25 to 9.66	1.8E-02	1.0E-01
CIN70	3.38	1.31 to 9.35	1.4E-02	1.0E-01
Stroma1	1.05	0.45 to 2.42	9.1E-01	9.1E-01
Stroma2	1.33	0.57 to 3.1	5.1E-01	6.7E-01
Immune1	1.40	0.59 to 3.15	4.3E-01	6.1E-01
Immune2	1.71	0.7 to 4.17	2.4E-01	4.4E-01
RAS	1.81	0.64 to 5	2.6E-01	4.4E-01
MAPK	0.86	0.32 to 2.16	7.5E-01	8.5E-01
PTEN	3.06	1.1 to 8.94	3.5E-02	1.2E-01
AKTmTOR	1.78	0.66 to 5.02	2.6E-01	4.4E-01
PIK3CA	0.84	0.38 to 1.83	6.6E-01	8.0E-01
IGF1	1.78	0.65 to 4.96	2.6E-01	4.4E-01
SRC	0.63	0.23 to 1.63	3.5E-01	5.4E-01
MYC	1.07	0.41 to 2.73	8.9E-01	9.1E-01
E2F3	2.56	1.14 to 5.97	2.5E-02	1.1E-01
BetaCatenin	0.43	0.17 to 1.09	7.5E-02	2.1E-01



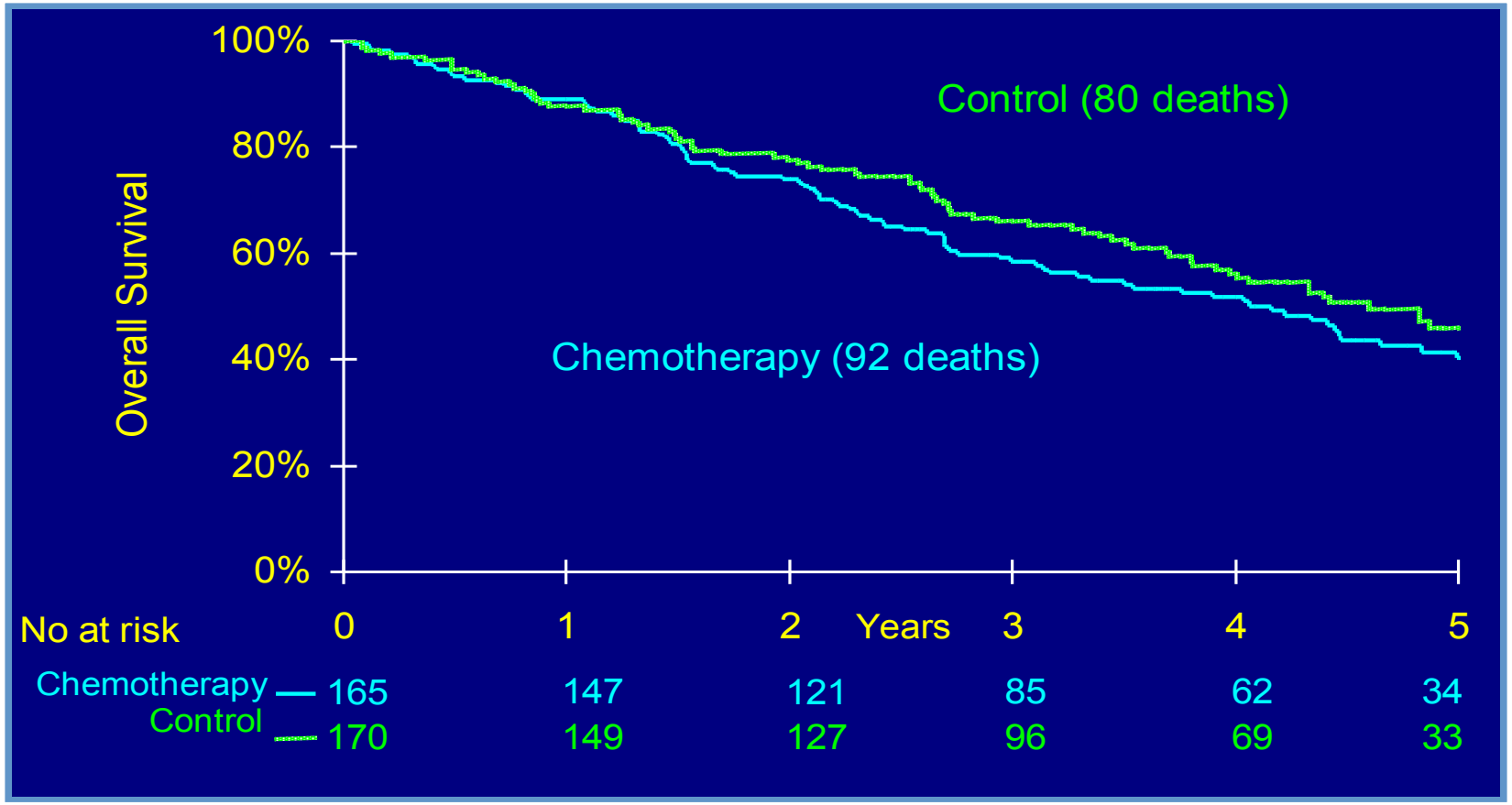
Effet bénéfique de la chimiothérapie adjuvante chez pts avec tumeur ERCC1 négative



Adjusted HR=0.65, 95%CI [0.50-0.86], p = 0.002

Olaussen et al NEJM 2007

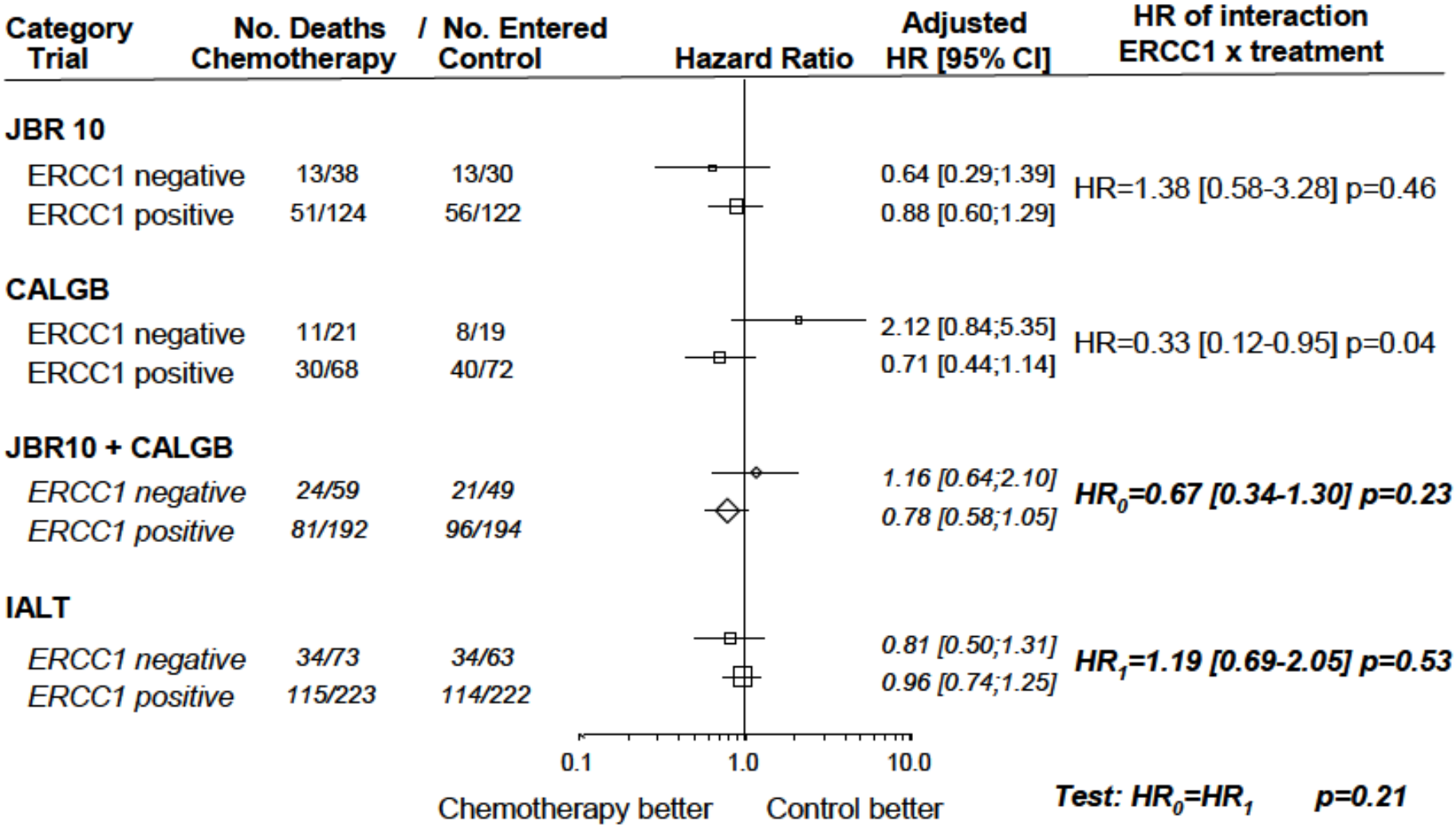
.. et aucun effet de la chimiothérapie adjuvante sur la survie globale chez pts avec tumeur ERCC1 positive



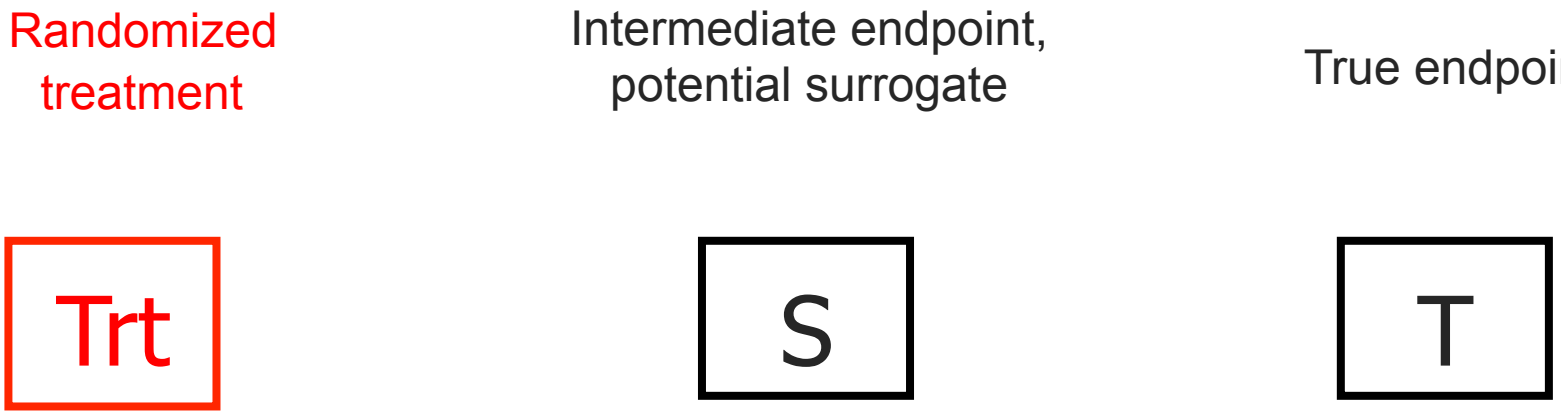
Adjusted HR=1.14, 95%CI [0.84-1.55], P = 0.40

Test d'interaction ERCC1 vs. traitement: p = 0.009

Meta-analysis (LACE-BIO): Trial effect with the same antibody for the 3 trials (Ab3)

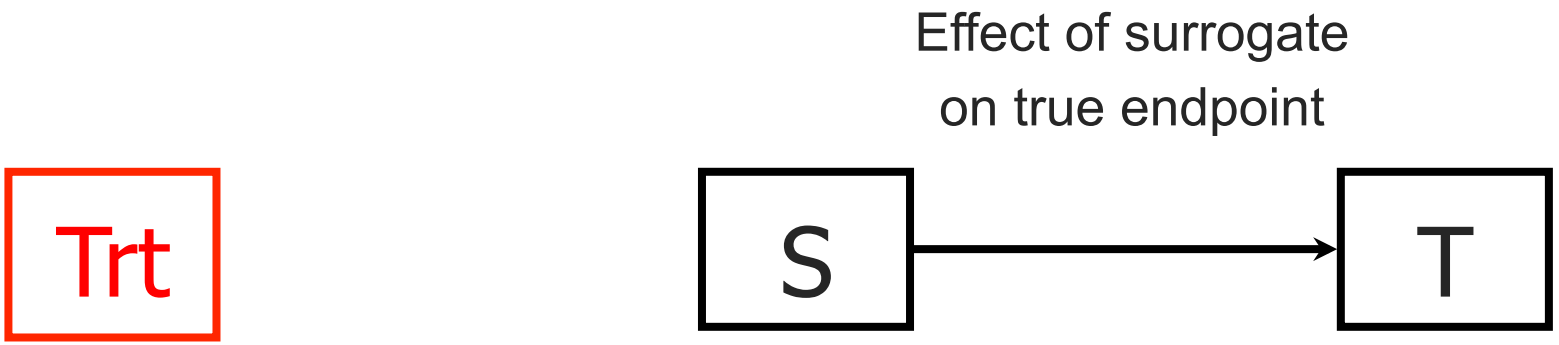


VALIDATION OF SURROGATE ENDPOINTS

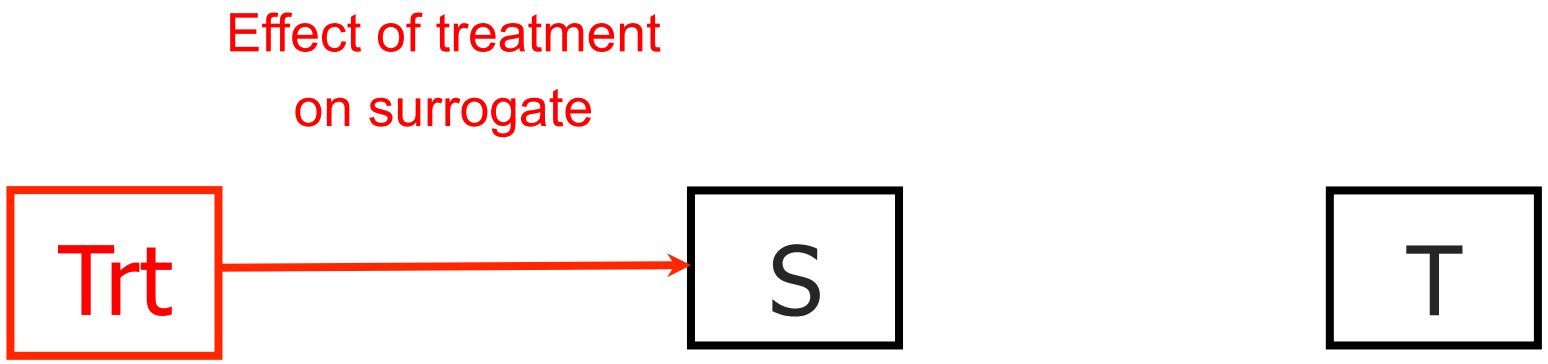


Buyse and Molenberghs, Biometrics 1998,54:1014

VALIDATION OF SURROGATE ENDPOINTS



VALIDATION OF SURROGATE ENDPOINTS

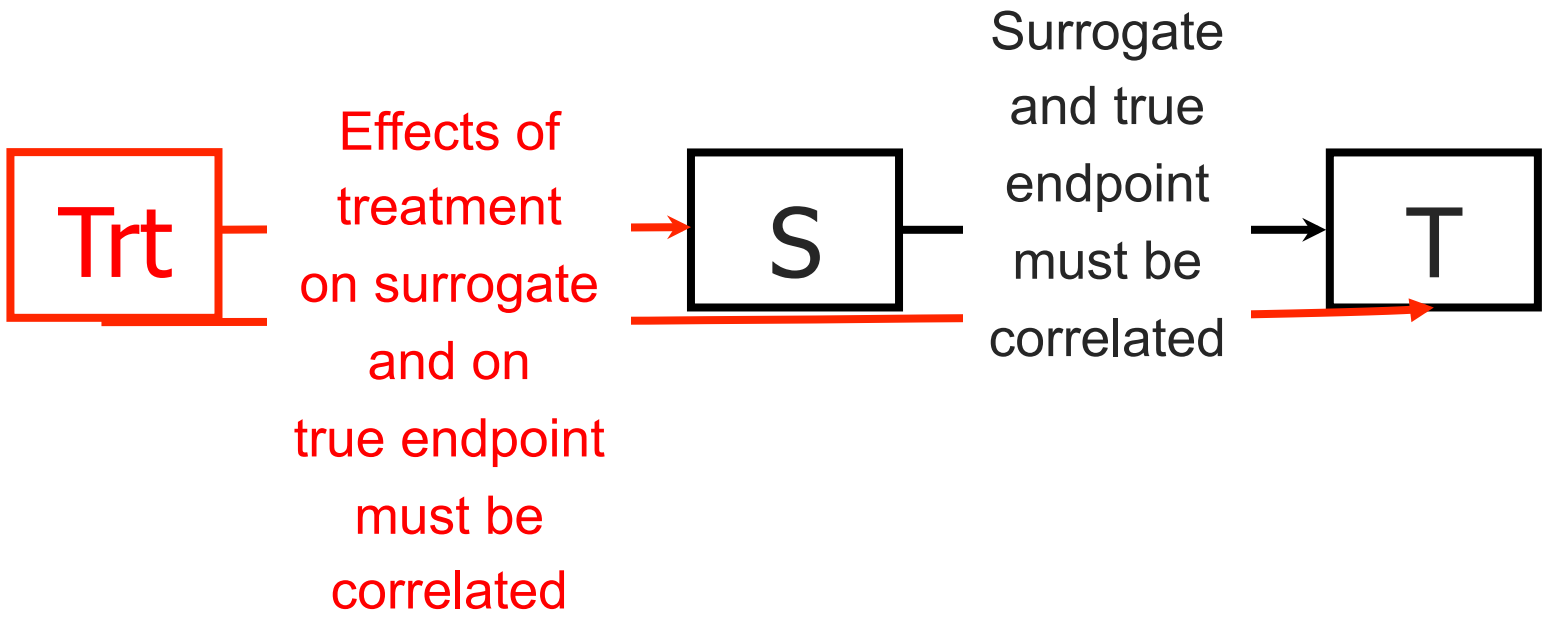


VALIDATION OF SURROGATE ENDPOINTS

Effect of treatment on true endpoint

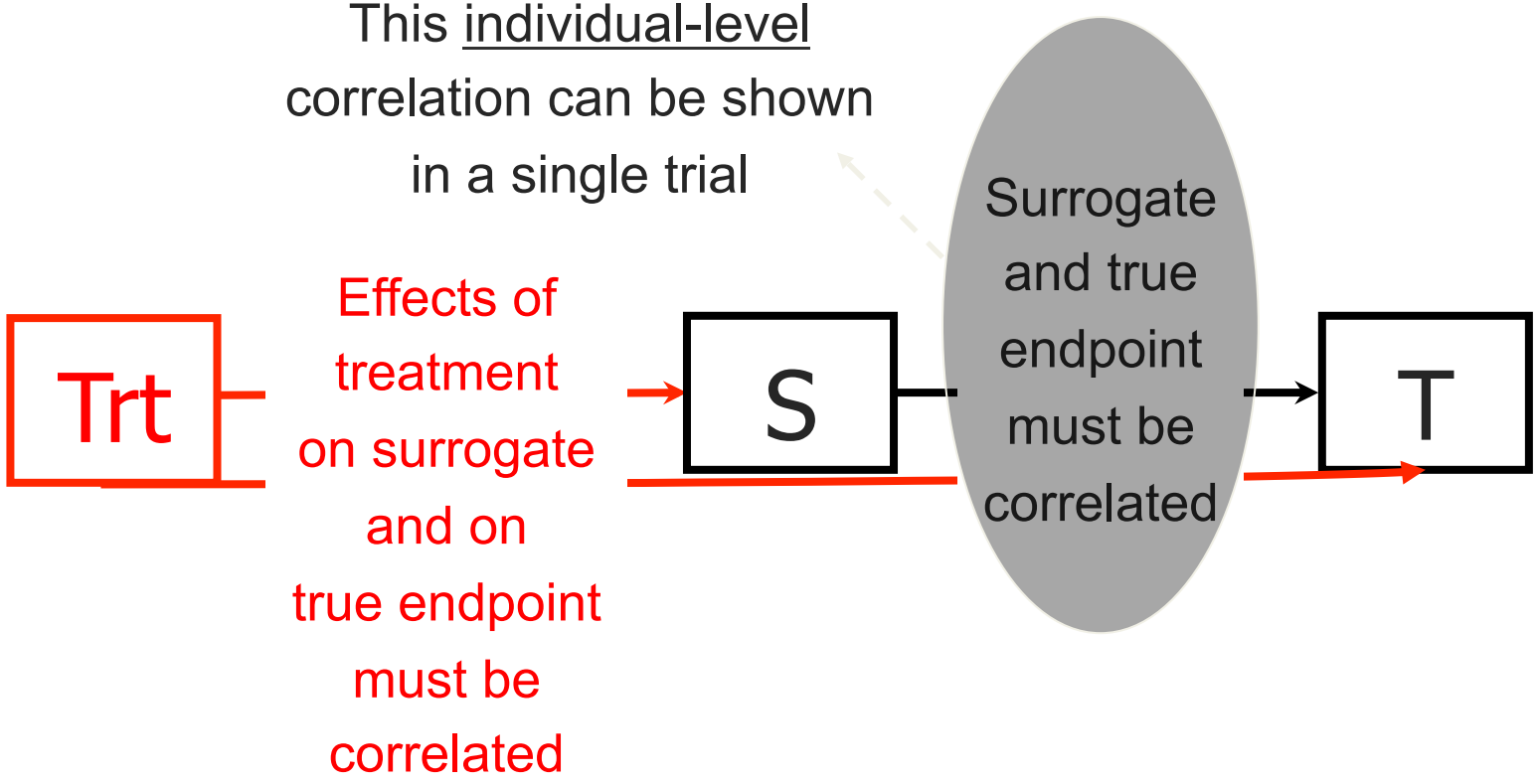
VALIDATION OF SURROGATE ENDPOINTS:

MULTI-LEVEL APPROACH

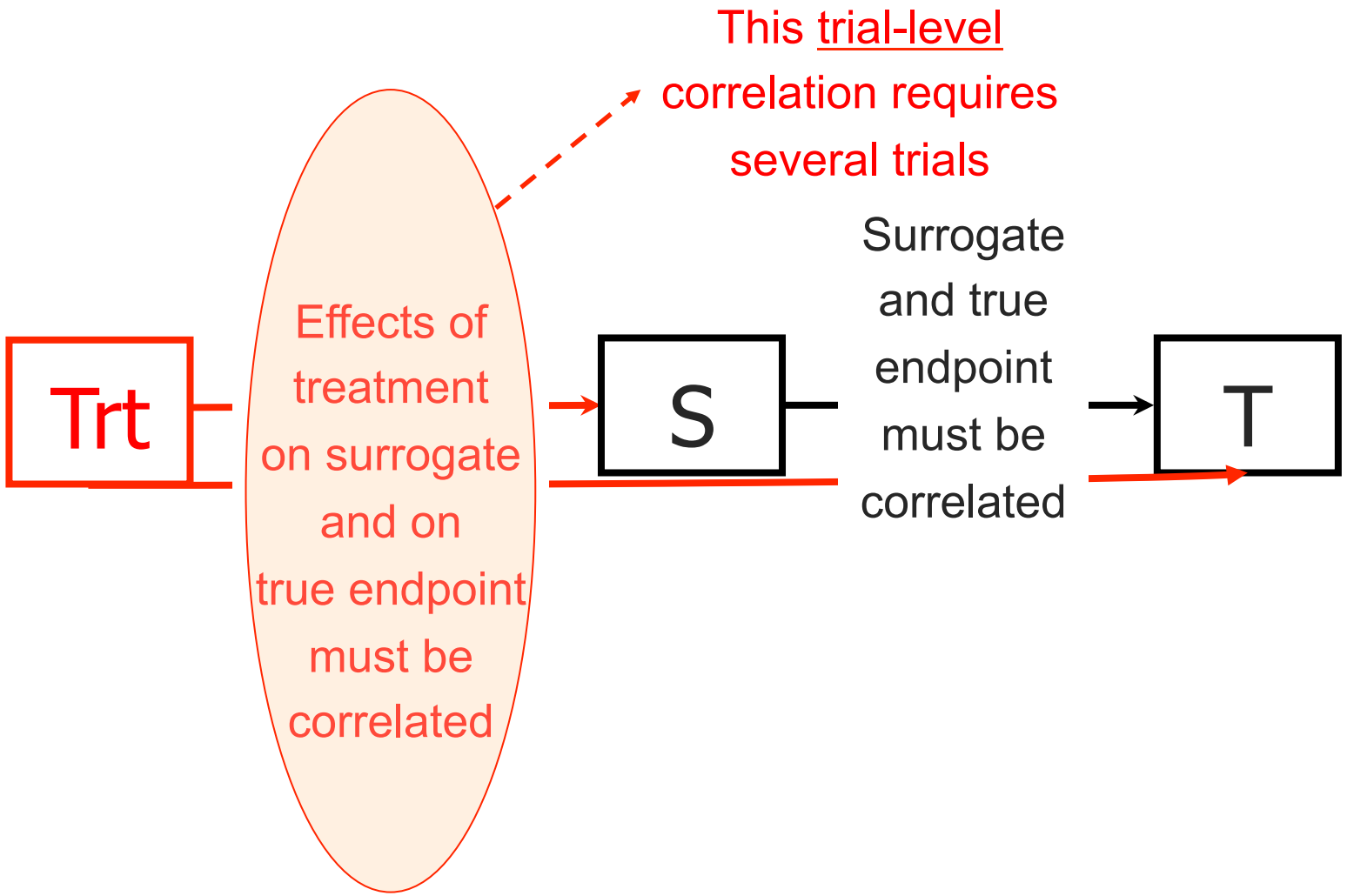


Buyse et al, Biostatistics 2000;1:49;
Gail, Pfeiffer and van Houwelingen, Biostatistics 2000;1:231.

VALIDATION OF SURROGATE ENDPOINTS



VALIDATION OF SURROGATE ENDPOINTS



Validation criteria using several trials

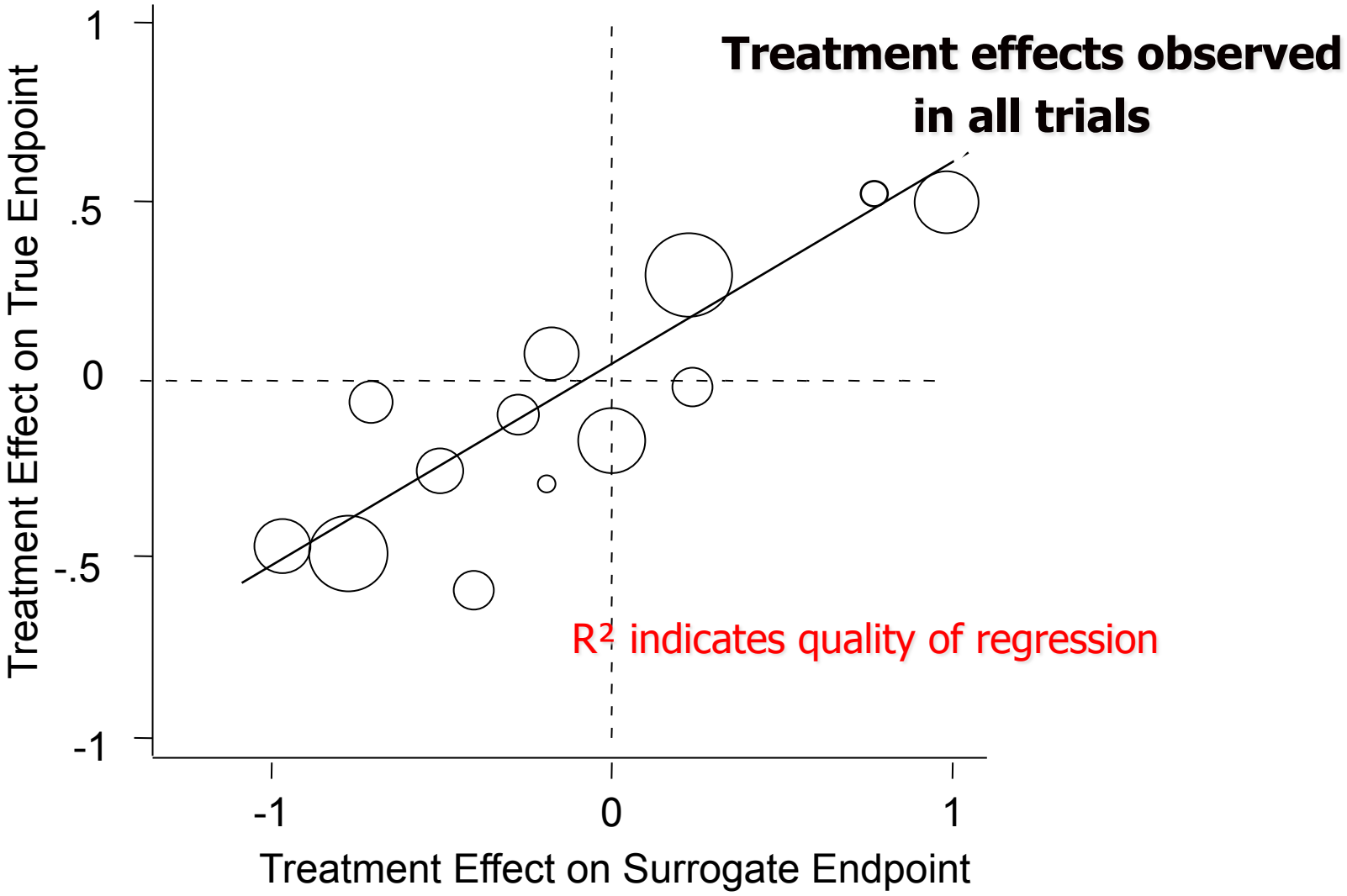
Parameters of interest

- effect of treatment on surrogate endpoint
- effect of treatment on true endpoint
- effect of surrogate on true endpoint

- measure of association between surrogate endpoint and true endpoint ($R^2_{individual}$)
- measure of association between effects of treatment on surrogate endpoint and on true endpoint (R^2_{trial})

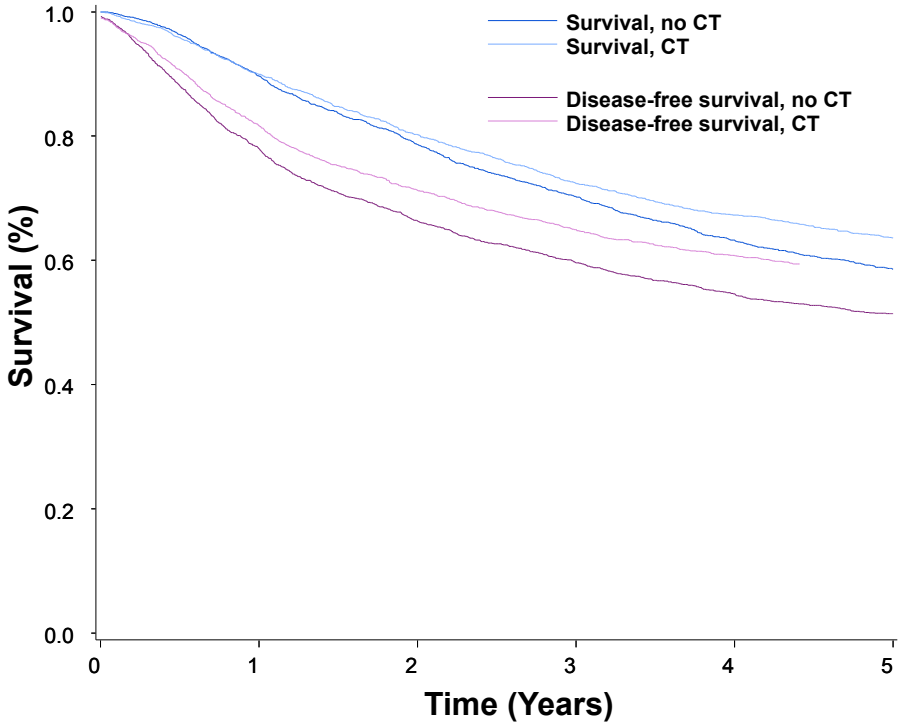
Buyse et al, Biostatistics 2000;1:49; Gail et al, Biostatistics 2000;1:231.

Prediction of treatment effect: several trials

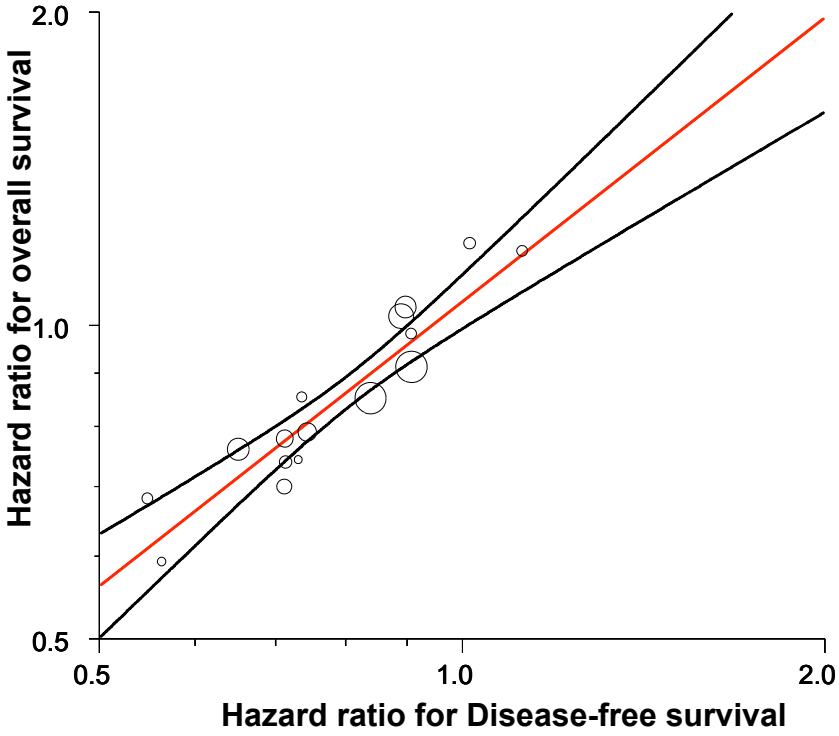


CT vs no CT

Individual level:
ρ=0.91



Trial level:
R=0.96



Mauguen et al, Lancet Oncol 2013

WHERE ARE WE IN ONCOLOGY WITH DISEASE-FREE/PROGRESION-FREE SURVIVAL?

- Adjuvant setting: DFS can be used as a surrogate for OS
  - CT in colorectal cancer (Sargent et al, JCO 2005)
  - CT in gastric cancer (GASTRIC group, JNCI 2013)
  - CT in lung cancer (Mauguen et al Lancet Oncol 2013)
  - CT in head and neck cancer (Michiels et al, Lancet Oncol 2009)

- Locally advanced setting: validated surrogates for OS
  - EFS for CT/RT in head-neck cancer (Michiels et al Lancet Oncol 2009)
  - PFS for CT/RT in lung cancer (Mauguen et al Lancet Oncol 2013)

- Advanced setting: can PFS be used as a surrogate for OS ?
  - Strong correlation for CT in colorectal cancer (Buyse et al 2007)
  - Moderate correlation for CT in lung (Laporte et al, BMJ Open 2013)
  - Moderate correlation for CT in gastric cancer (GASTRIC, JNCI 2013)
  - Low correlation for CT in breast (Burzykowski et al JCO 2007; Michiels et al ASCO 2013)

Needs to be repeated using data from trials investigating new agents such as targeted therapy!