Converting a biomarker to a surrogate

What should it take?

AstraZeneca Priority List- case studies

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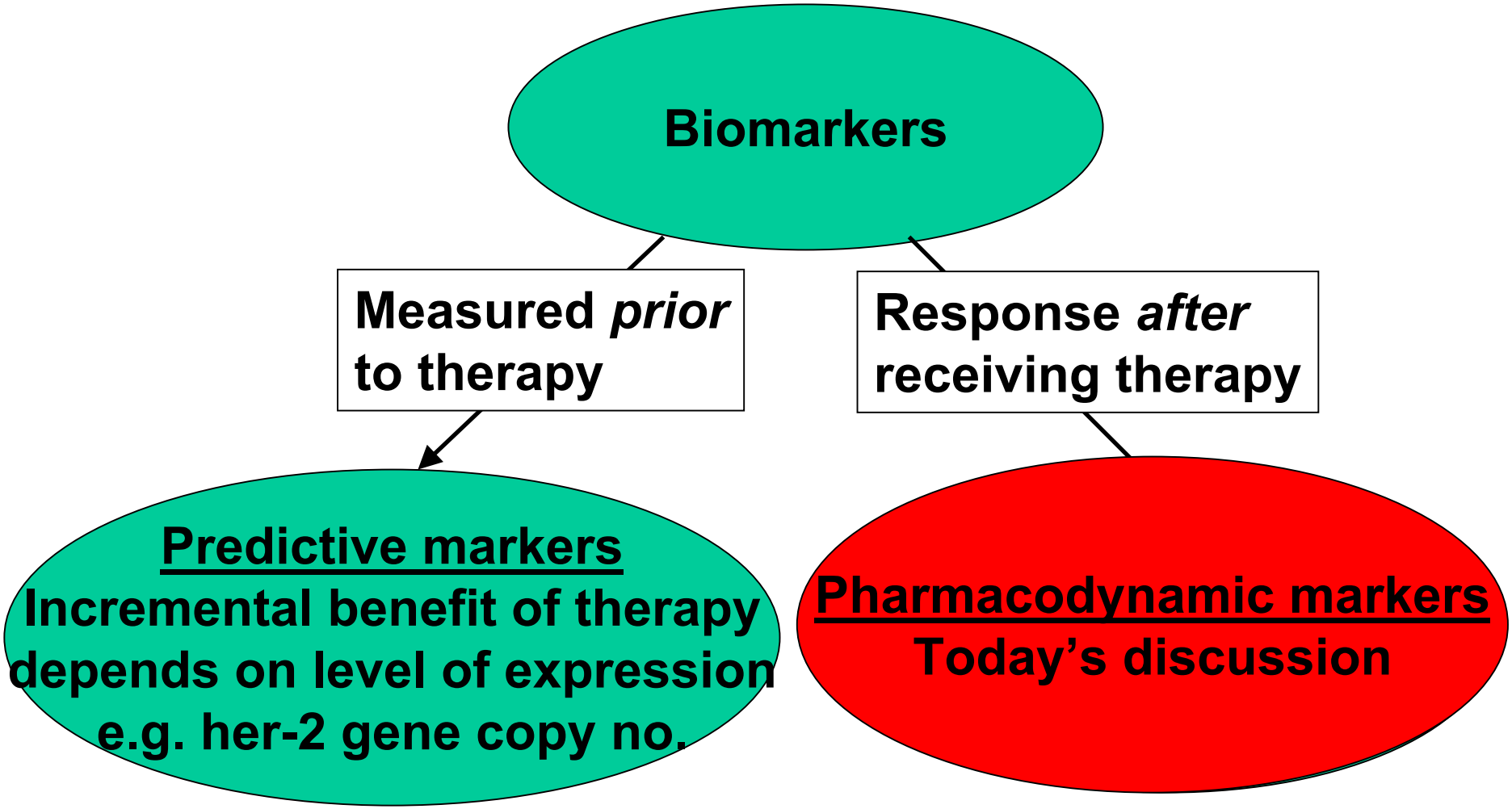
The need for surrogate endpoints

- In many settings, the primary clinical endpoint takes large, long term trials
  - e.g. early breast and prostate cancer
- In other settings the underlying effect of therapy is obscured by later line therapies
- To reduce time and to bring effective medicines to patients quickly, in an area of high unmet need, requires use of intermediate or surrogate endpoints

Clarity on terminology

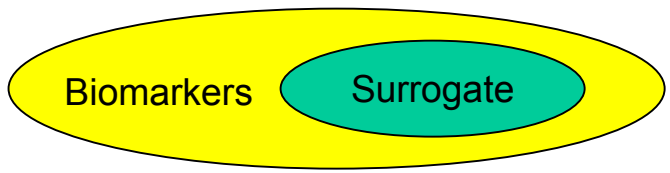


Considerations in the Evaluation of Surrogate Endpoints in Clinical Trials: Summary of a National Institutes of Health Workshop*

Biological Marker (Biomarker): A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Clinical Endpoint: A characteristic or variable that reflects how a patient feels or functions, or how long a patient survives.

Surrogate Endpoint: A biomarker intended to substitute for a clinical endpoint. A clinical investigator uses epidemiologic, therapeutic, pathophysiologic, or other scientific evidence to select a surrogate endpoint that is expected to predict clinical benefit, harm, or lack of benefit or harm.



*Controlled Clinical Trials 22:485–502 (2001)

How do we establish surrogacy

Goal of analysis is to be confident that if we observe a treatment effect on the surrogate it will translate into a clinical benefit

- Acts a substitute

- A strong correlation within an individual is necessary but not sufficient
- Longer survival in responders vs non-responders would not necessarily deem response a surrogate endpoint

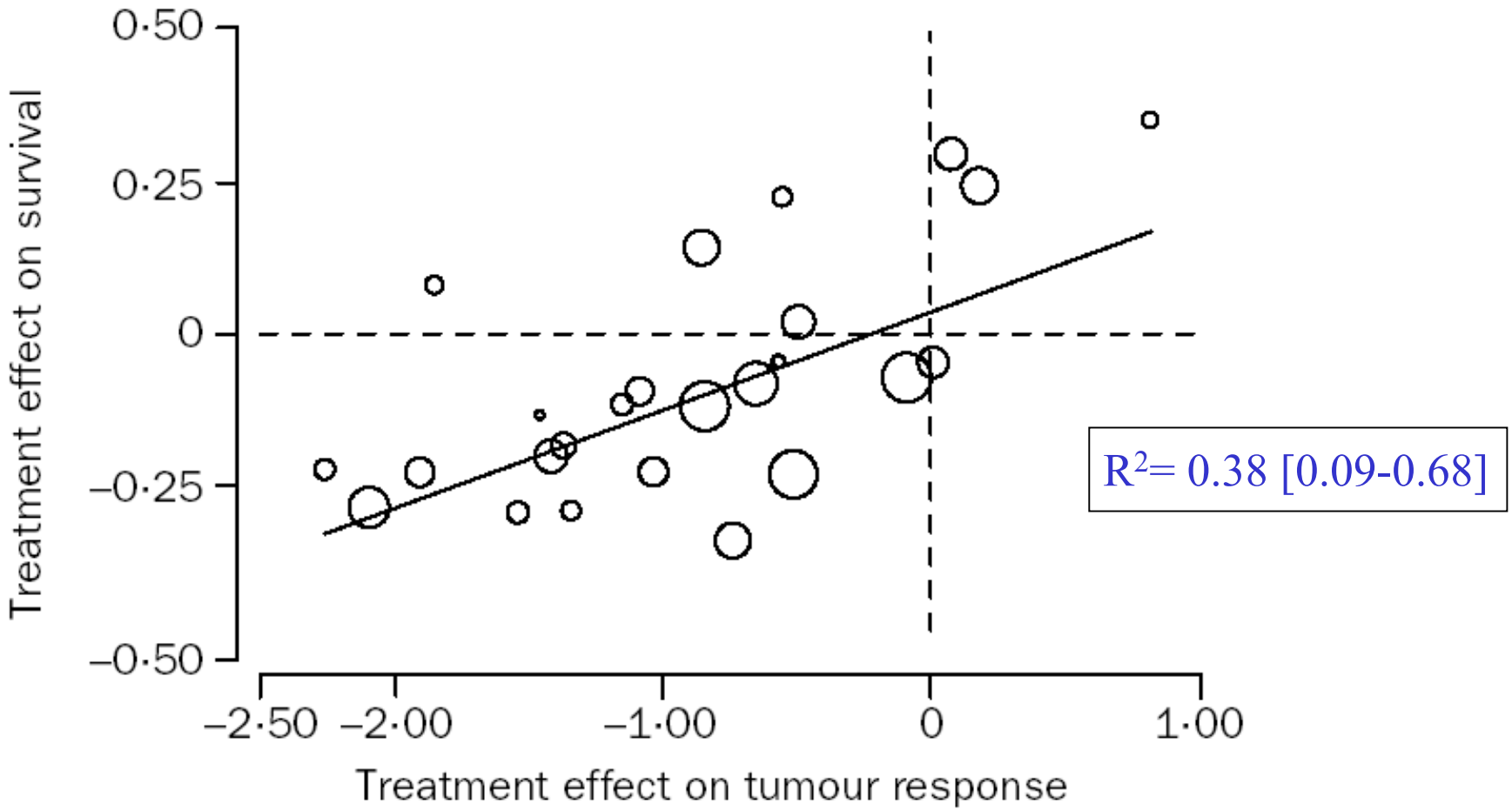
Newer Approaches to Surrogacy

- Prentice criteria are restrictive
- Newer approaches[1] directly address the question of surrogacy
  - Can an intermediate endpoint act as a substitute
- Assess how robustly between group changes on one endpoint predict for later changes on another

[1]The evaluation of surrogate endpoints:

Burzykowski T, Molenburghs G, Buyse M (eds). Springer. New York, 2005

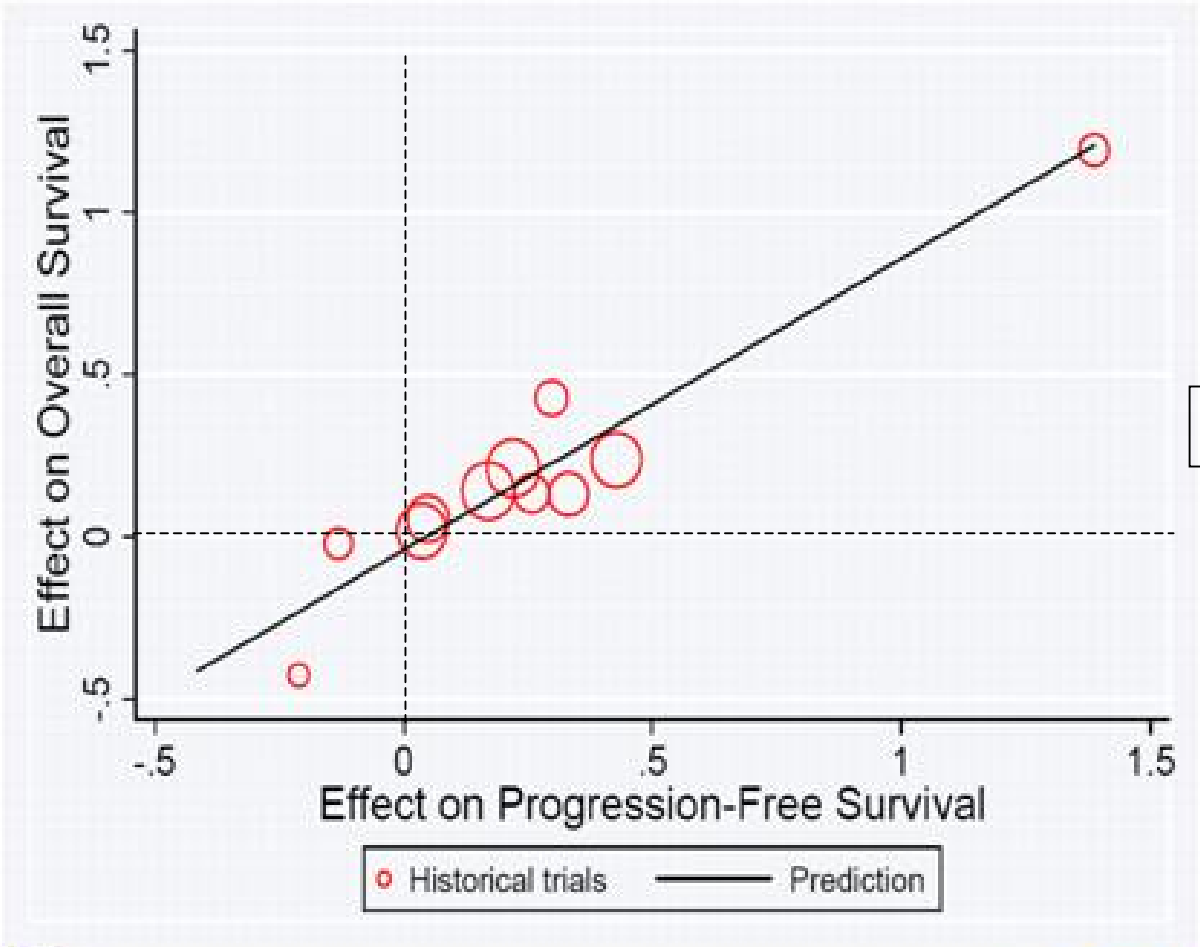
Relation between tumour response to first-line chemeotherapy and survival in advanced colorectal cancer: a meta-analysis



Marc Buyse, Pierre Thirion, Robert W Carlson, Tomasz Burzykowski, Geert Molenberghs, Pascal Piedbois, *Lancet* 2000: **356:** 373–78

Much stronger evidence for surrogacy in same setting, in absence of active 2nd line therapy.

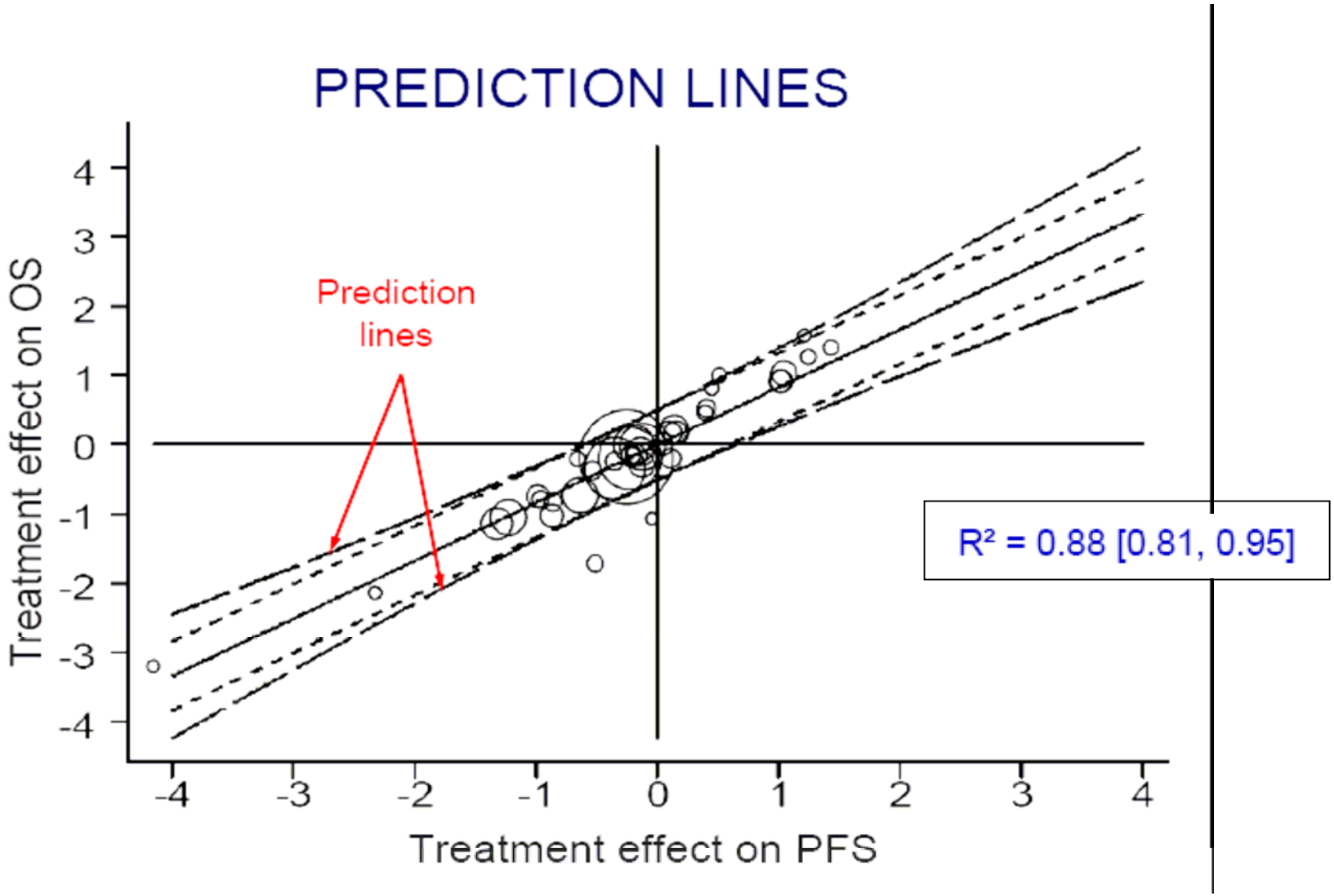
OBSERVED EFFECTS IN HISTORICAL TRIALS



R^2=0.97

Buyse et al: Progression-free survival as a surrogate for Overall Survival (OS) in patients with advanced colorectal cancer. An analysis of 3159 patients randomized in 11 trials. ASCO 2005

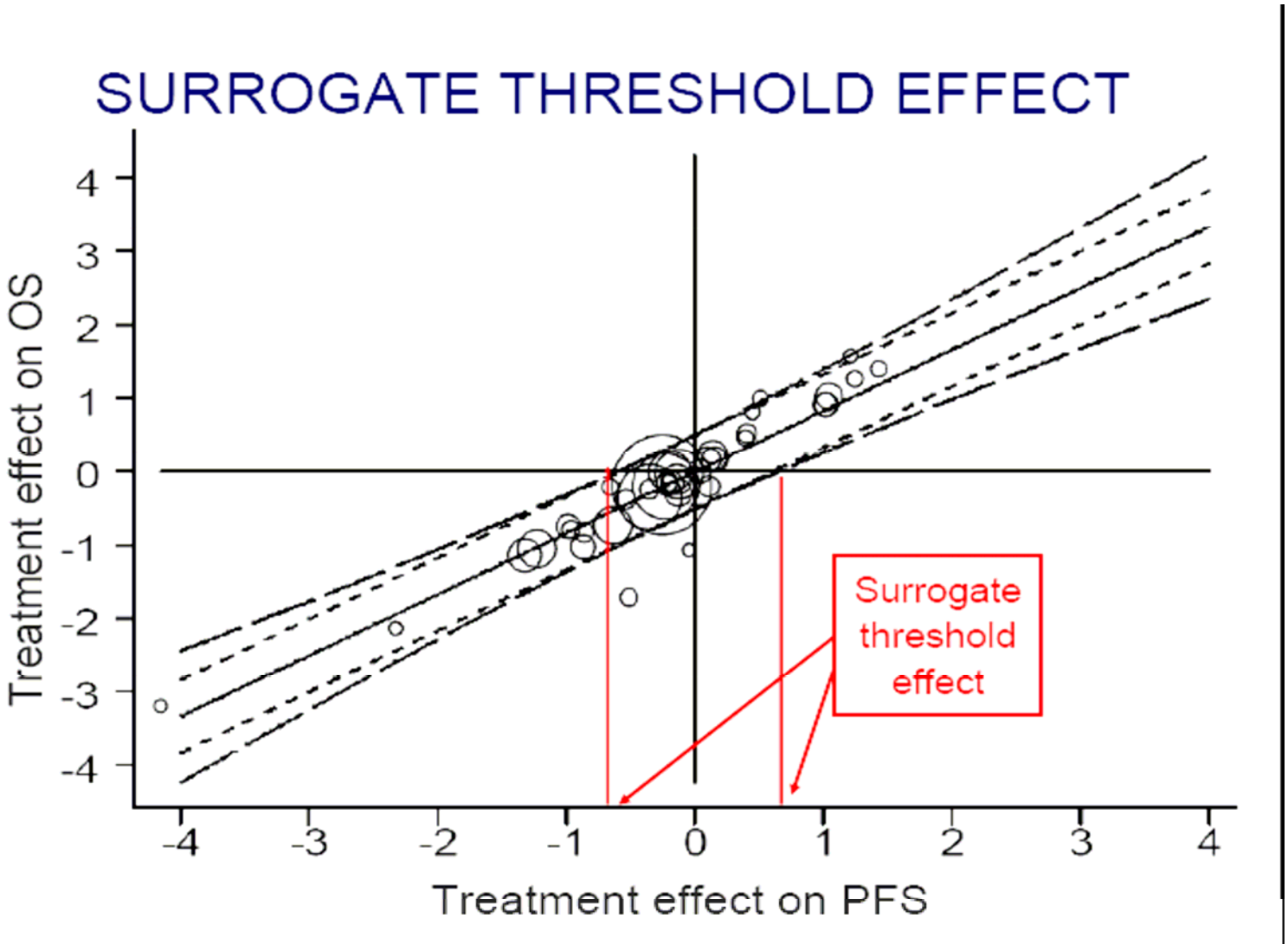
Using methodology to quantitate uncertainty in prediction – Ovarian cancer



http://www.fda.gov/cder/drug/cancer_endpoints/ovarian/buyse.pdf: Burzykowski T & Buyse M - Pharmaceut. Statist. 2006;5:173-186

Estimation of a “Surrogate Threshold Effect”

HR of 0.55 on PFS provides high confidence of eventual OS effect



Pause for thought

- To **prove** surrogacy we need data from large trials
  - Exactly the trials we are hoping to avoid
- Will therefore conversion of biomarkers to surrogates take much longer than we hoped?
- Many surrogates used routinely today (e.g. BP and cholesterol) were not subject to the rigorous assessment described

Conditional approval

- Requires endpoints that are reasonably likely to predict clinical benefit; but not proof. Does this require 97.5% certainty?

- Proposal: Using Surrogate Threshold Effect (STE) methodology; use a change in biomarker which enables conclusion that there is a 70%/80% probability that it will translate into clinical benefit?

- Issue: Rare diseases, with high unmet need, where meta-analyses of by necessity large trials will not be possible?

Pharmacodynamic Biomarkers considered promising to characterise the STE

-performance characteristics commensurate with clinical use
-dynamic effect across drugs demonstrated

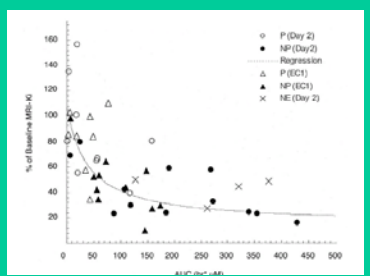
Imaging	Histopathology	Blood borne
FDG-PET*	Ki67	Disease specific markers e.g. PSA
DCE-MRI	Cell Turnover index (proliferation-Ki67:Apoptosis-caspase 3)	Circulating Tumour cells
		Circulating free DNA

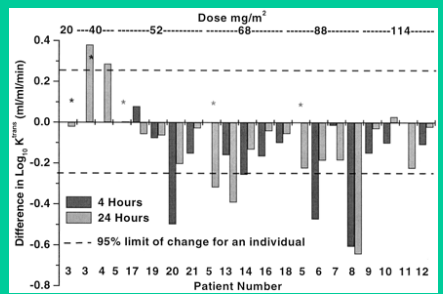
*already being tested for surrogacy by FDA-NIH-PhRMA consortium

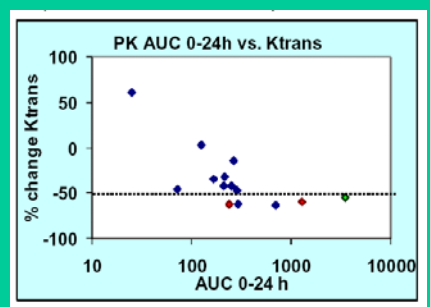
DCE-MRI: Literature review

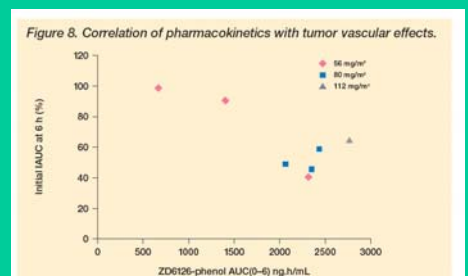
- Intrasubject CV% ~25%
- Gd uptake (K^{trans} or IAUC) decreases in a dose-dependent way in rodent and human

	RODENT	PHASE 1 HUMAN
Vatalanib	Drevs 2002	Morgan 2003
Combretastatin A4P	Galbraith 2003	Galbraith 2003
AG-013736	Wilmes 2003	McShane 2004
ZD6126	Robinson 2003	Evelhoch 2004



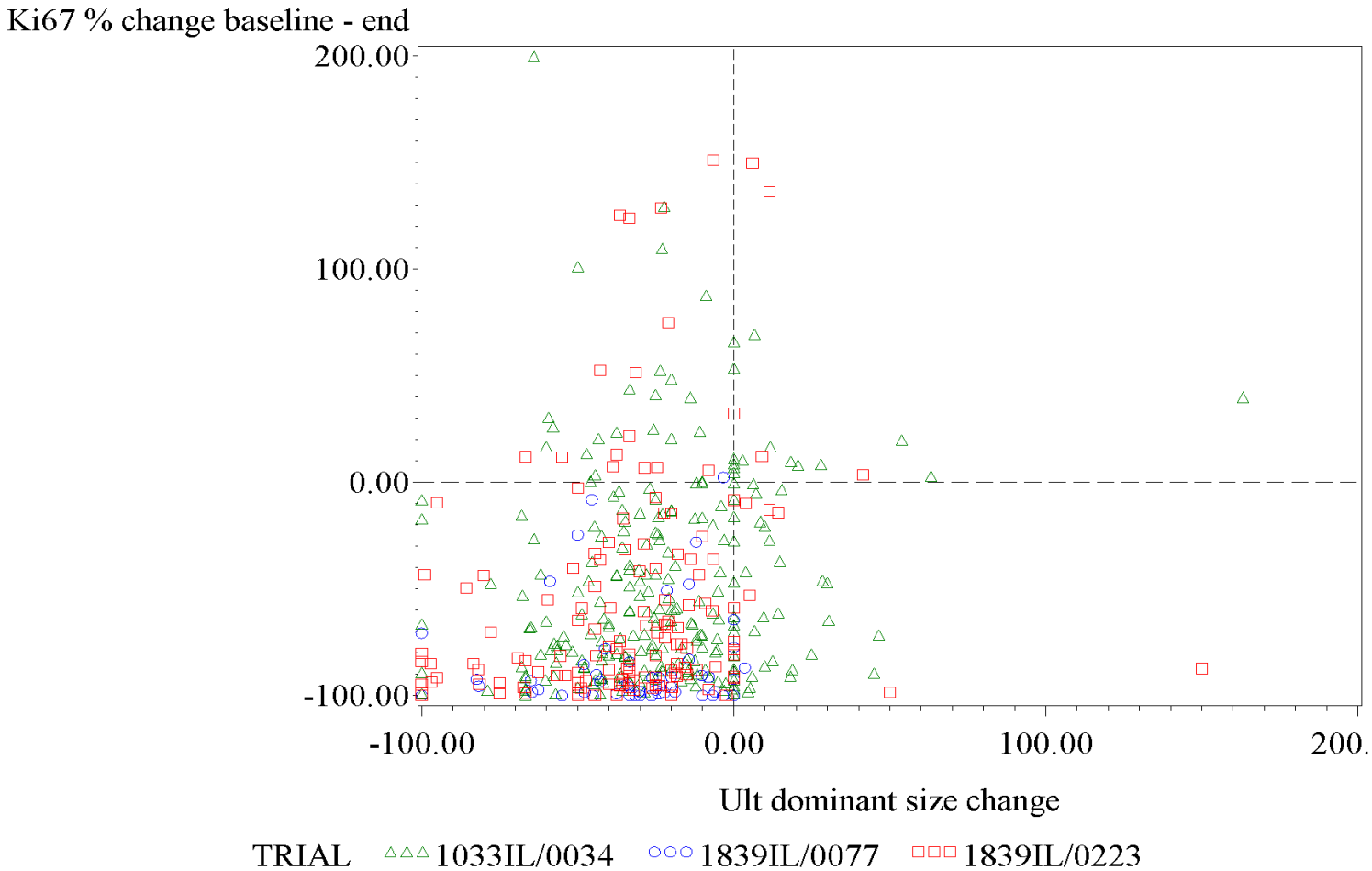






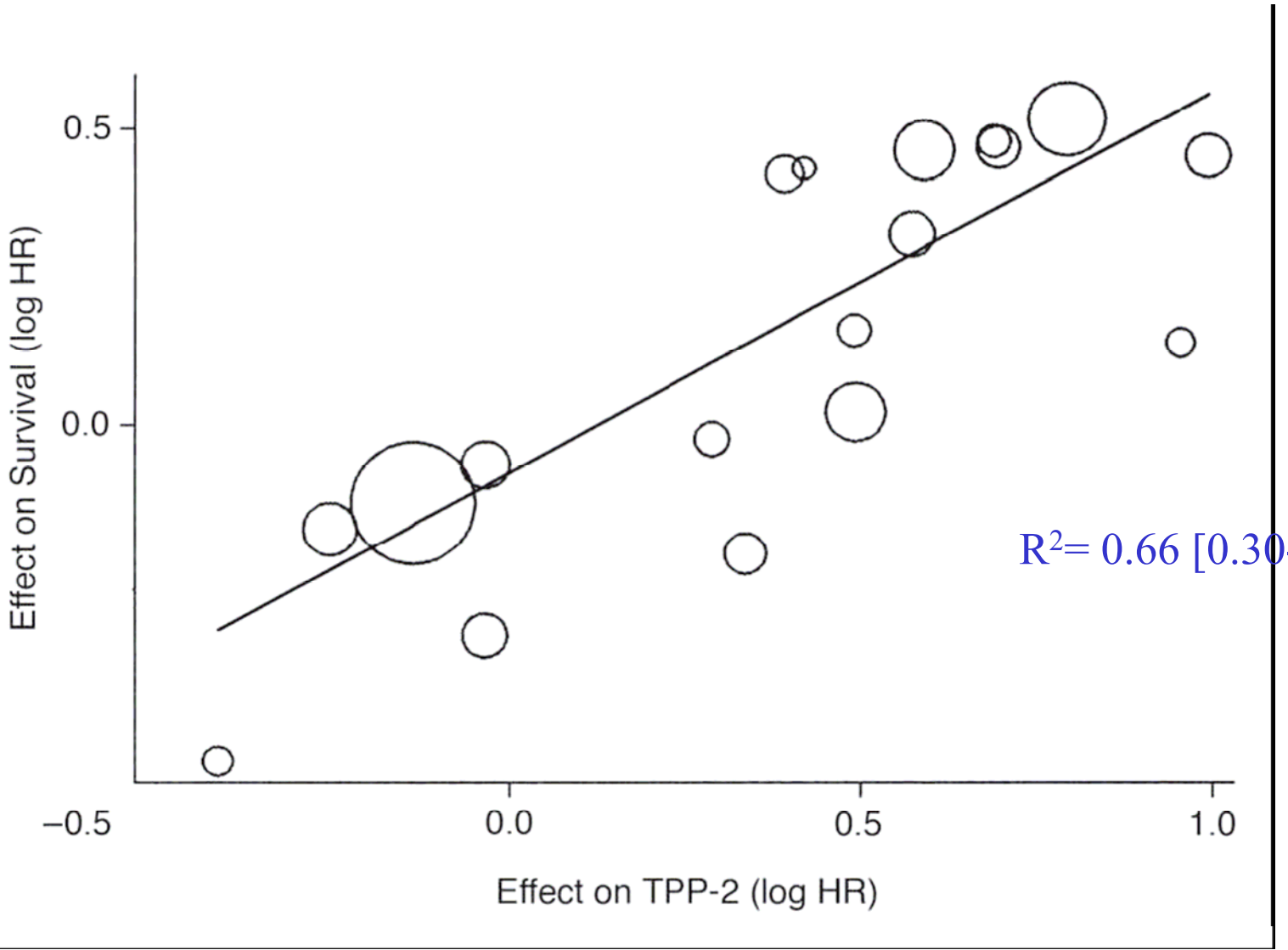
Ki67: Unpublished review (AstraZeneca)

- Intrasubject CV% =11%
- Using ANOVA find significant relationship between Ki-67 and tumour response by diameter ($p<0.0001$) and RECIST ($p=0.0004$)



n=>300

PSA: Published review



R^2= 0.66 [0.30-0.85]

n=>2000

Collette L et al.; (2005) JCO, 23; 6139-6148 2005

Pharmacodynamic Biomarkers:
Moving Forward

(1) Request Regulatory Guidance for

- Criteria to establish level of proof
  - depending on biological plausibility and extent of unmet need
  - Incorporate Surrogate Threshold Effect
  - employing conditional approval process with further trials to establish this benefit
- Recommended nomenclature

(2) Above would pave the way for pre-competitive collaboration between interested parties to collate requisite weight of evidence data to assess surrogacy of those pharmacodynamic biomarkers considered most promising