SURROGATE ENDPOINTS IN ONCOLOGY: OBJECTIVES, METHODOLOGICAL OVERVIEW, AND CURRENT STATUS

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Acknowledgement to Marc Buyse

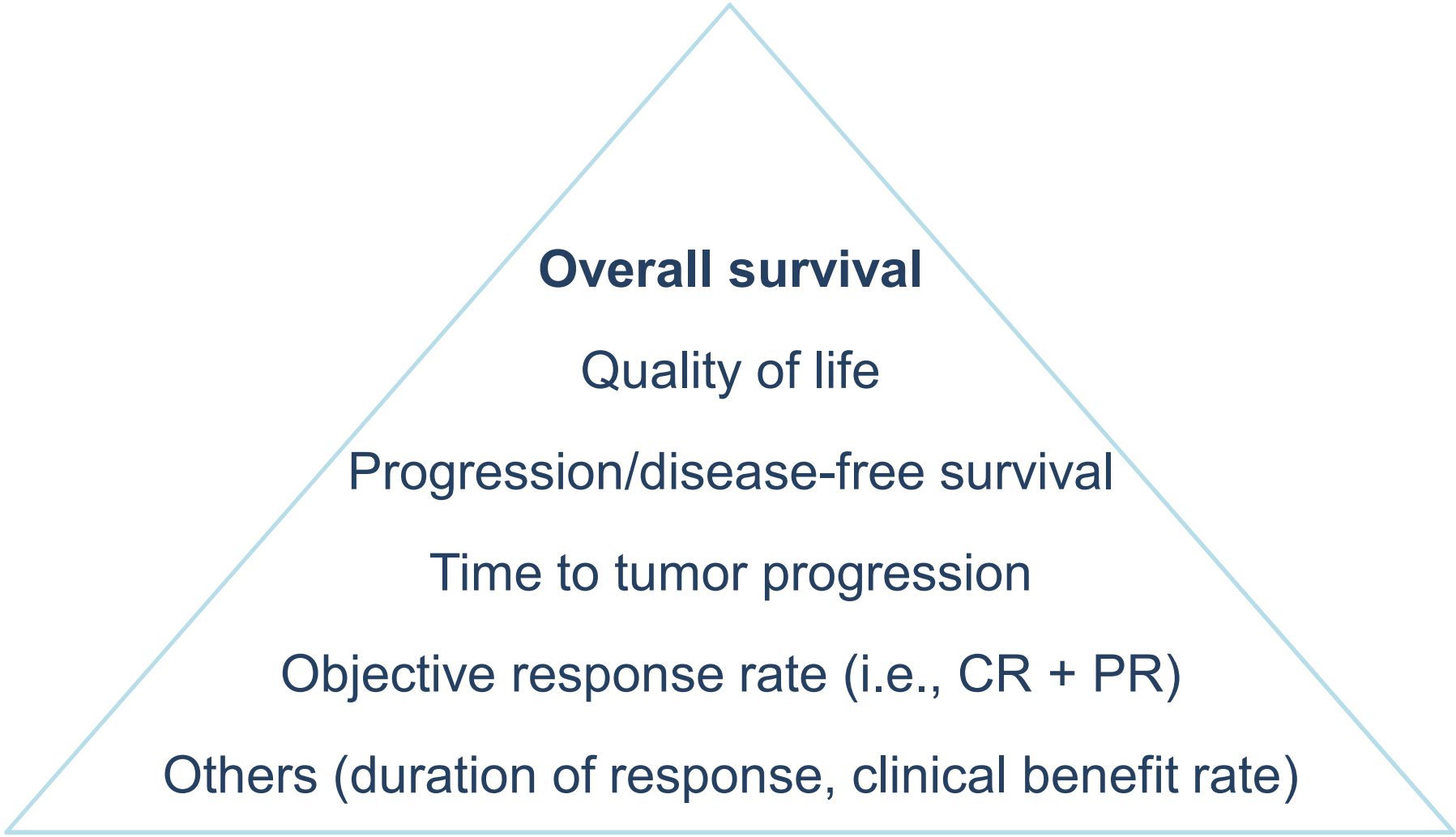
The ideal endpoint

- Capture all clinically relevant events
- Be easy to measure
- Provide little opportunity for ascertainment bias
- Be observed as early as possible
- Be observed in as many patients as possible
- Be statistically sensitive

Does the ideal endpoint exist?

	Ease of measurement	Time of measurement	Potential for bias	Statistical power	Clinical relevance
Overall survival	☺	☹	☺	☹	☺
Quality of life	☹	😐	☹	☹	☺
Time to progression	☹	😐	☹	☺	😐
Response rate	😐	☺	☹	☺	☹
Biomarker	☺	☺	☺	☺	☹

Overall survival (OS)



Surrogate endpoint

- A surrogate endpoint/biomarker is intended to substitute for a clinical endpoint.
- An endpoint that is merely correlated to a clinical endpoint may not be a good surrogate for it.
- A surrogate endpoint is expected to predict treatment effect (benefit, harm, or lack thereof) on the clinical endpoint.

Biomarkers Definition Working Group, Clin Pharmacol Ther 2001; 69:89.

Need for surrogate endpoints

Surrogate endpoints are needed (mostly) to

1. reduce development time (using surrogates that are observed earlier)

2. increase statistical power (using surrogates that are more commonly observed and/or more sensitive to treatment effects)

Burzykowski, Molenberghs & Buyse. The Evaluation of Surrogate Endpoints. Springer, 2005.

Surrogate validation

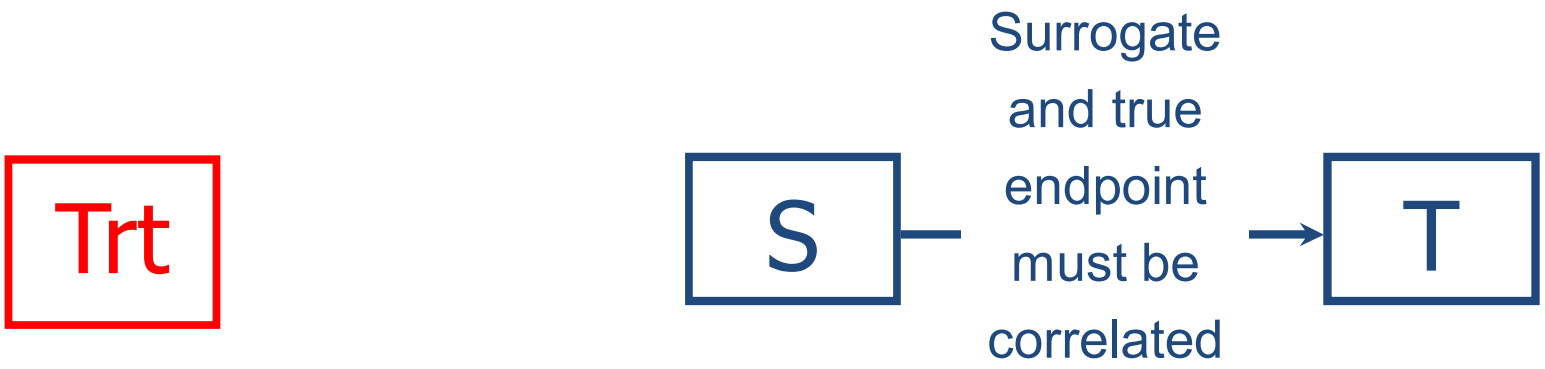
META-ANALYSIS OF SEVERAL TRIALS:

Buyse et al. criteria of surrogacy (2000):

1. Surrogate has an effect on true endpoint
   (individual-level surrogacy)
2. Treatment effect on true endpoint can be predicted from treatment effect on surrogate biomarker
   (trial-level surrogacy)

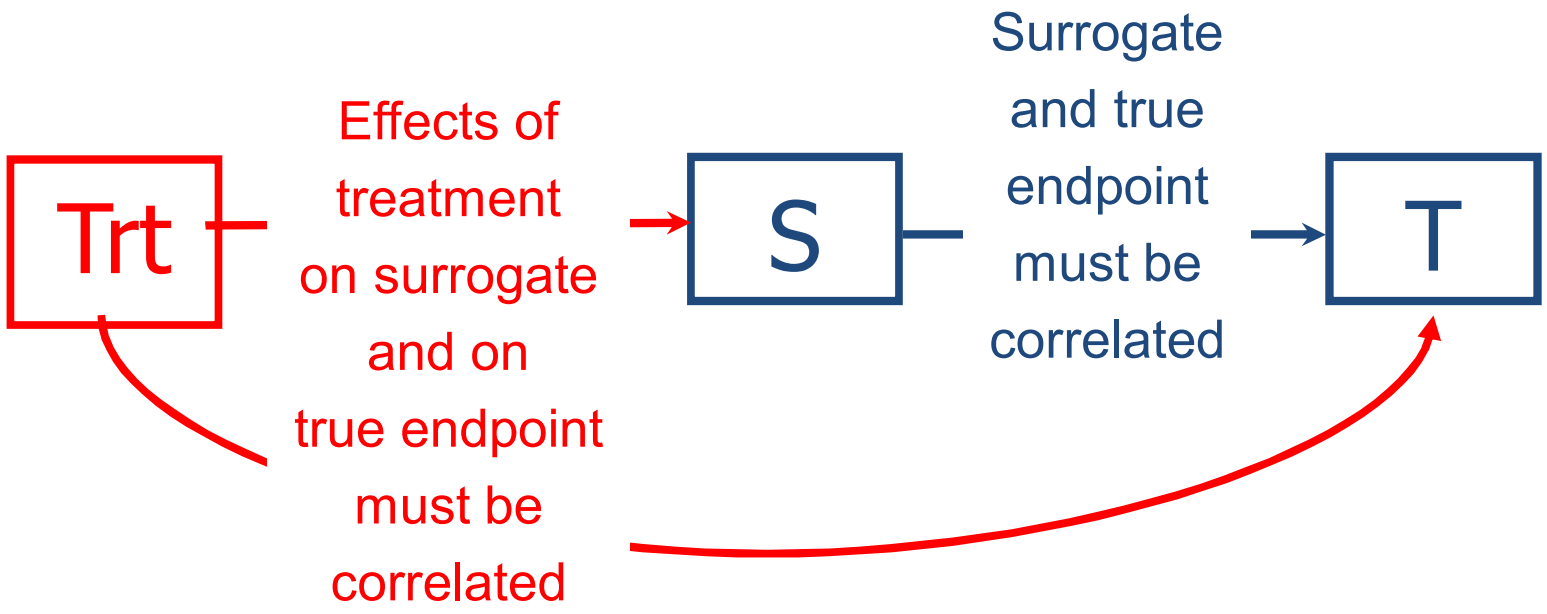
Buyse et al, Biostatistics 2000; 1:49.

Surrogate validation



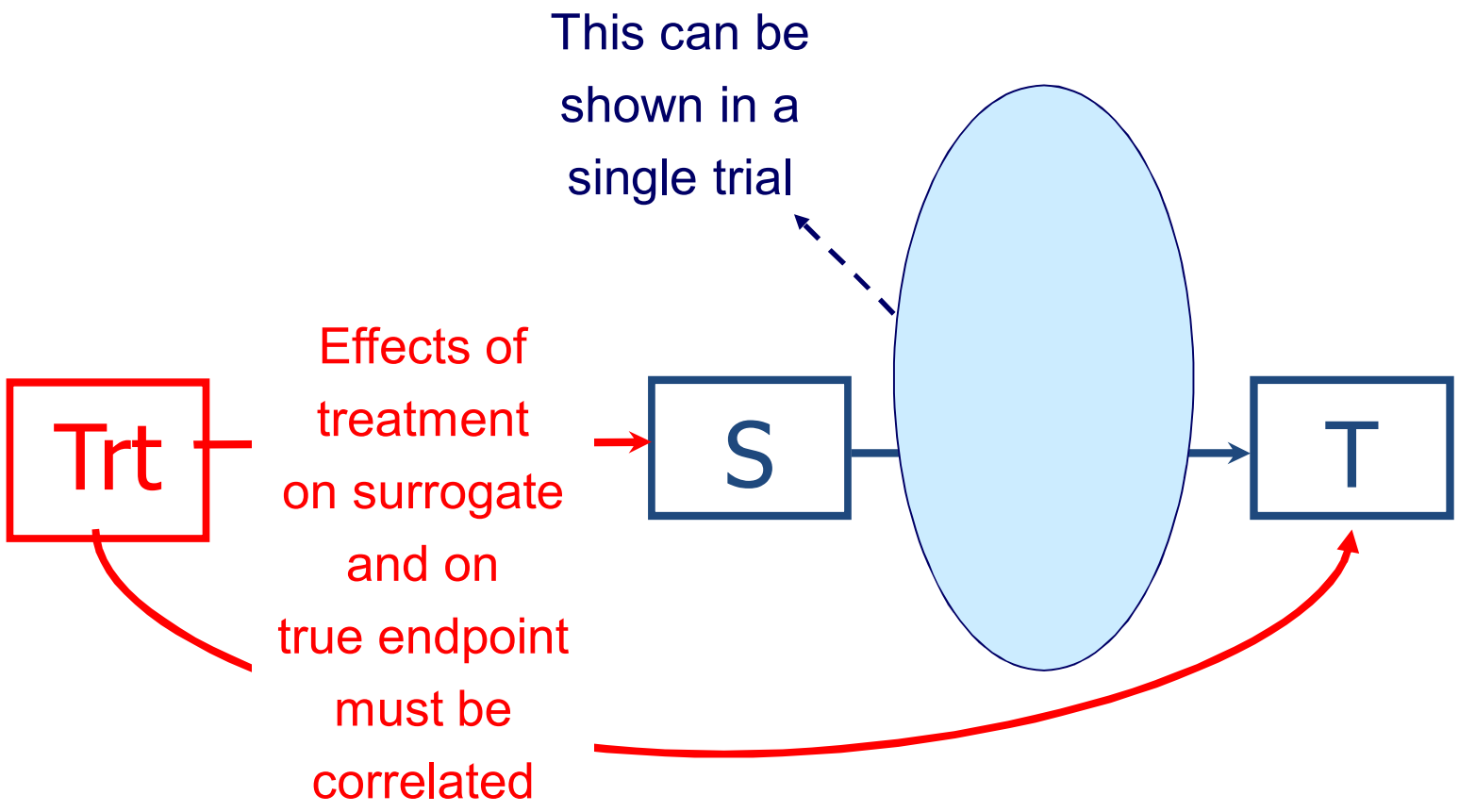
Buyse et al, Biostatistics 2000; 1:49.

Surrogate validation

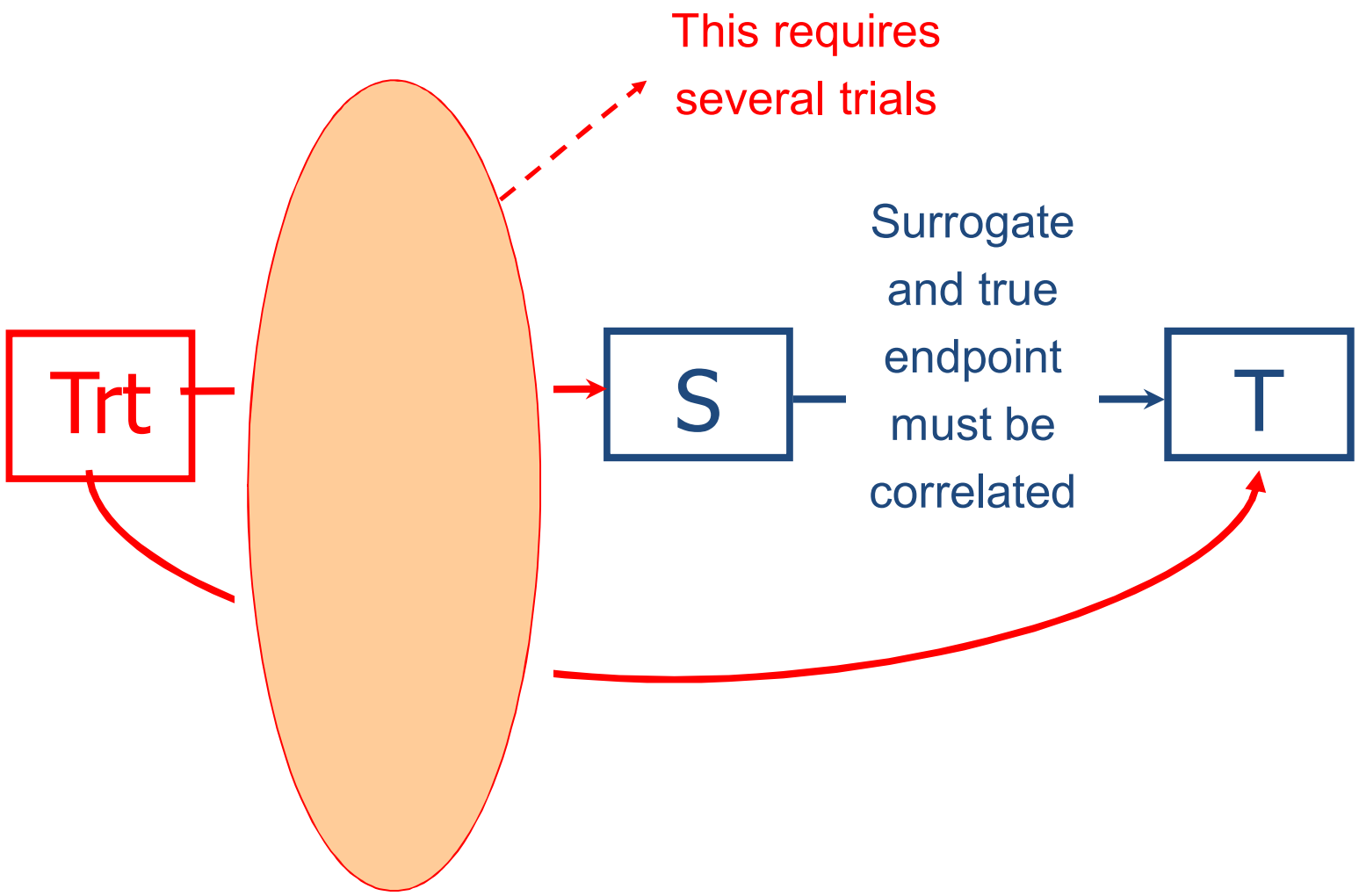


Buyse et al, Biostatistics 2000; 1:49.

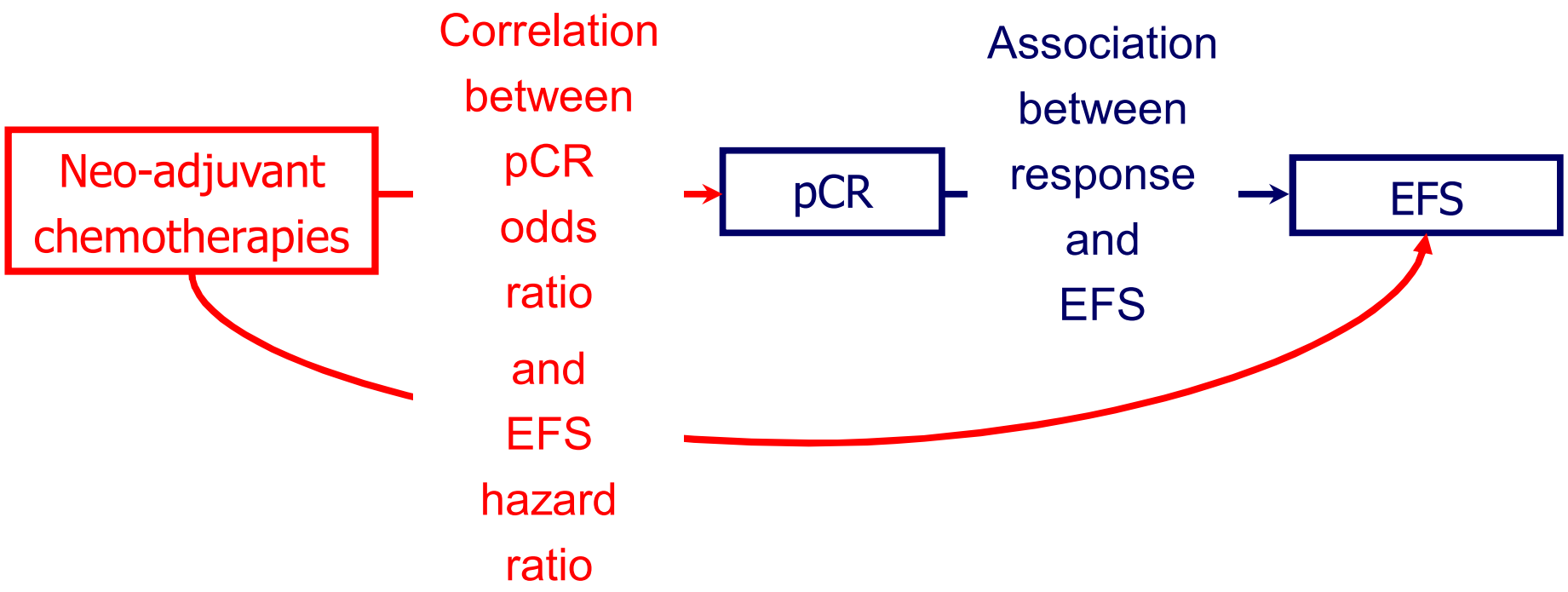
Surrogate validation



Surrogate validation

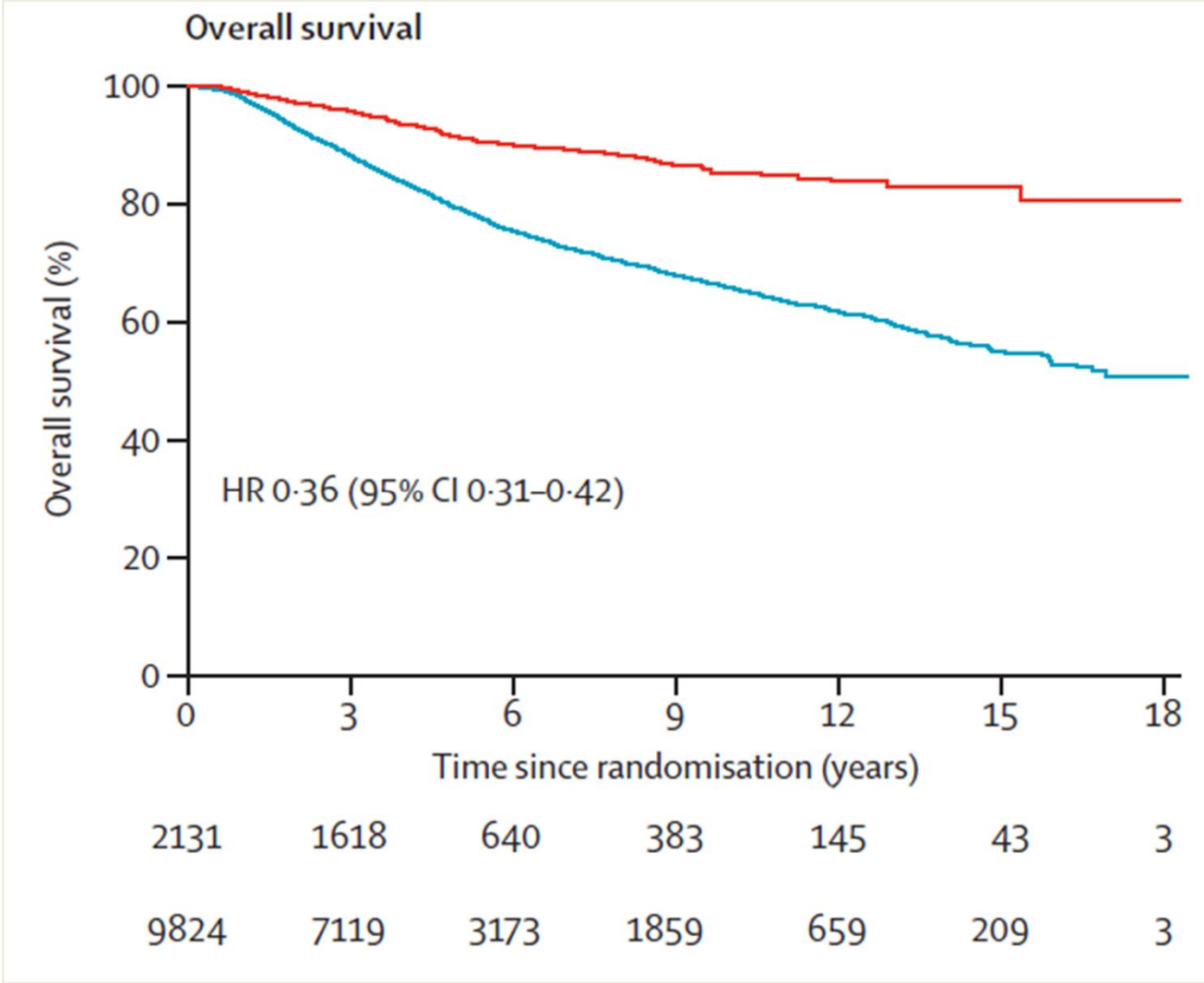


Surrogate validation: an example



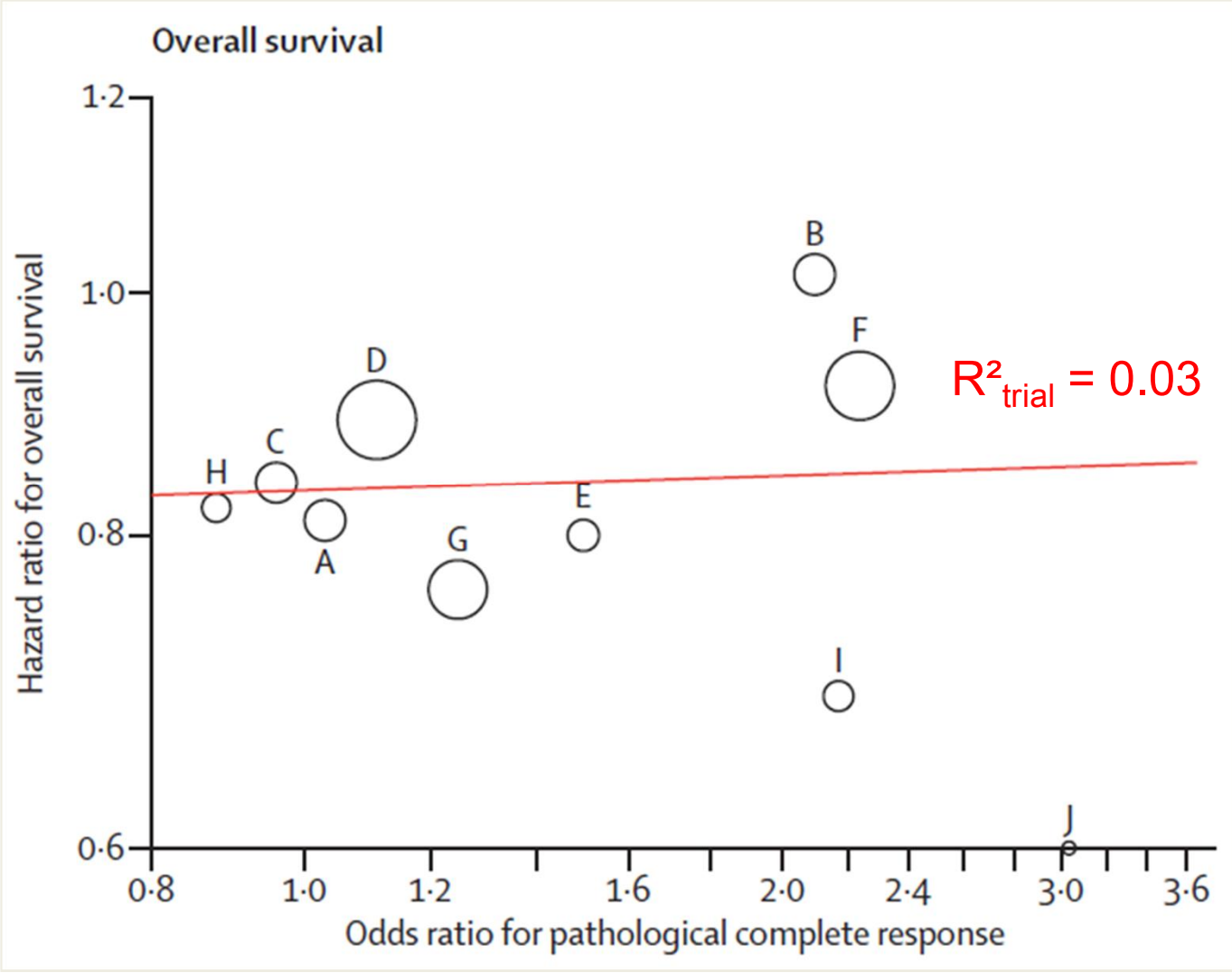
Cortazar et al., Lancet 2014; 356:373.

Association between pCR and OS



Cortazar et al., Lancet 2014; 356:373.

Lack of association between treatment effects on pCR and OS



Cortazar et al., Lancet 2014; 356:373.

Potential explanations…

…for lack of association between treatment effects on pCR and OS:

- Patient heterogeneity
- Treatment heterogeneity
- Other sources of heterogeneity
- Small absolute treatment effects (except in NOAH)

Cortazar et al., Lancet 2014; 356:373.

A biological explanation?

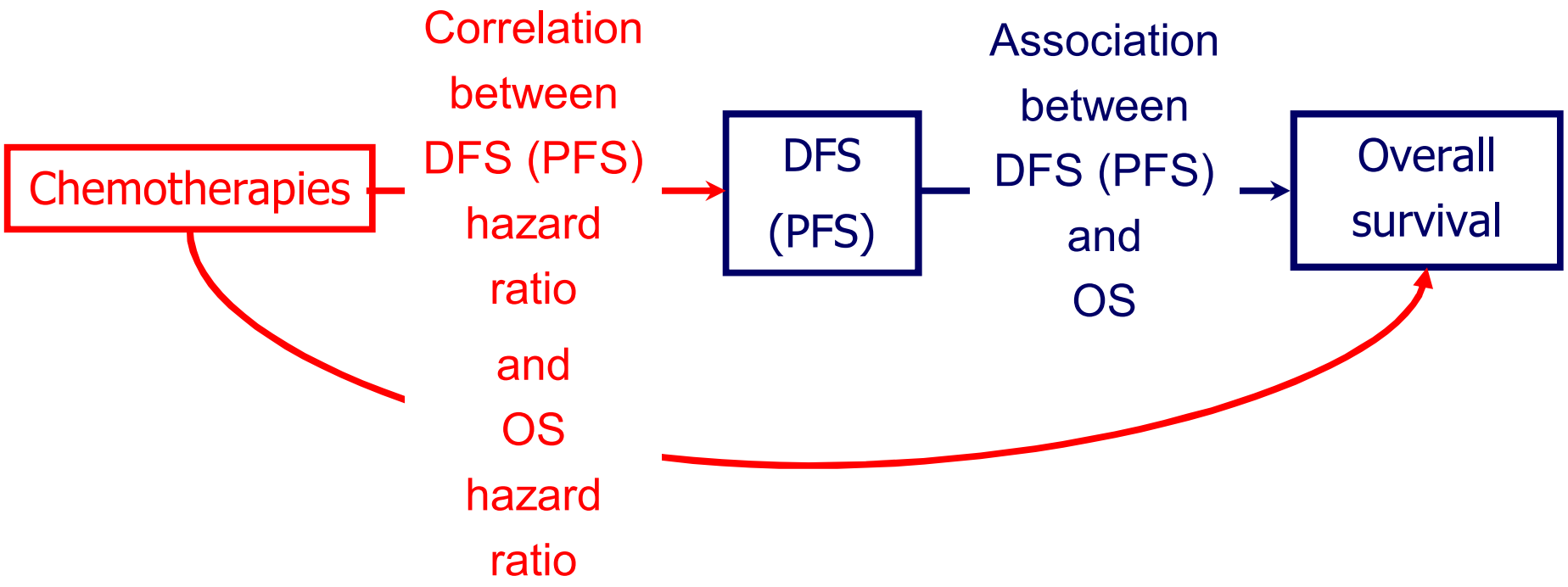
EDITORIAL

Lisa A. Carey, M.D., and Eric P. Winer, M.D.

The reasons for this are myriad, including the molecular heterogeneity of breast cancer and the possible effect of post-surgical interventions. Most importantly, pathological complete response rate will correlate with survival outcomes only if the neoadjuvant agents leading to the improvement in pathological complete response also eradicate resistant tumor clones.

Carey and Winer, N Engl J Med 2016;375:83.

Gastric cancer
DFS (PFS) and OS



Oba et al, JNCI 2013; 5:1600
Paoletti et al, JNCI 2013; 5:1608.

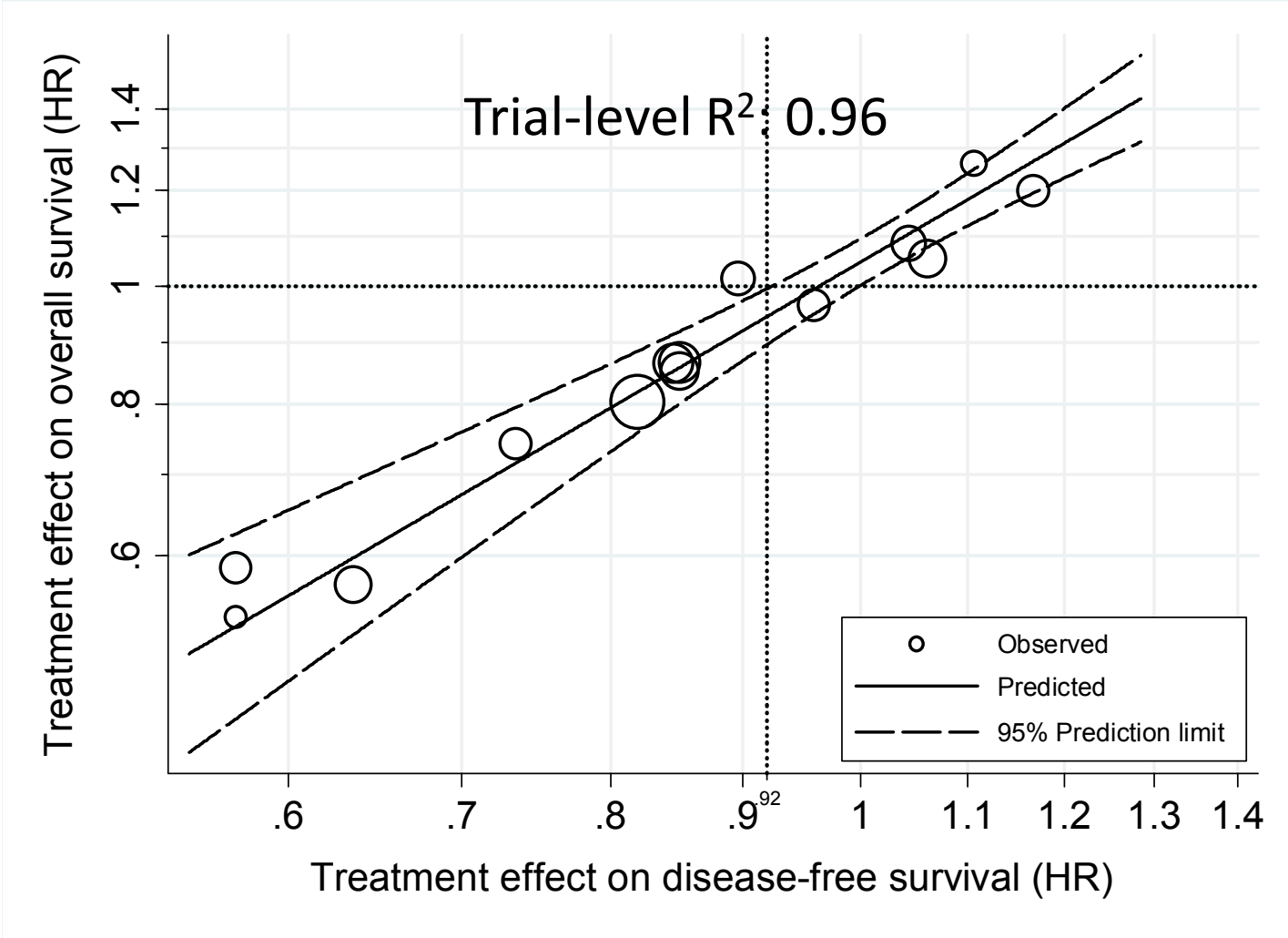
Gastric cancer
DFS (PFS) and OS

- Localized gastric cancer:
  - 14 randomized trials
  - Patient-level data (treatment/DFS/OS) on 3,288 pts
  - 5 validation trials (2 with patient-level data)

- Advanced gastric cancer:
  - 20 randomized trials
  - Patient-level data (treatment/PFS/OS) on 4,069 pts
  - 12 validation trials with summary data

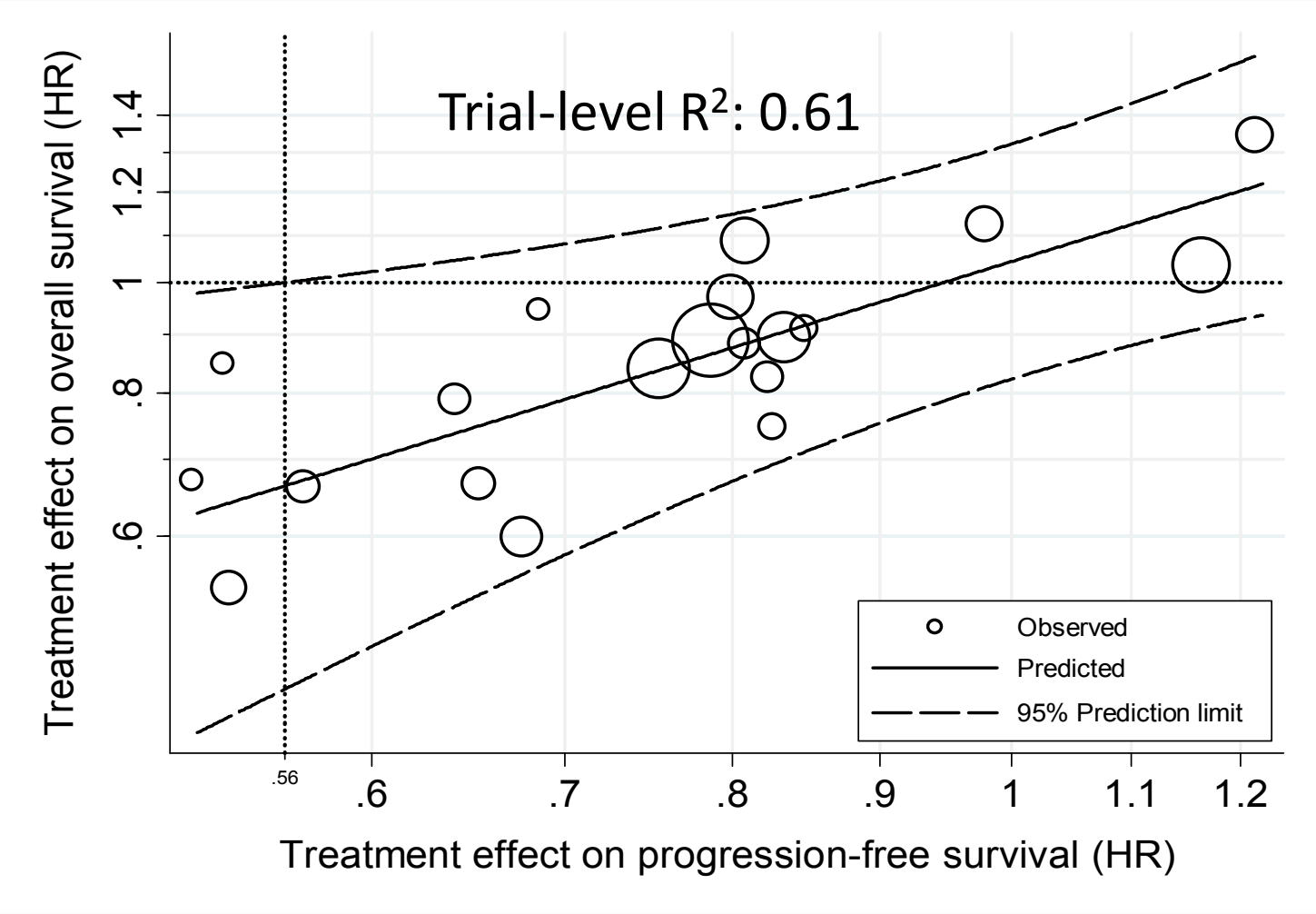
Oba et al, JNCI 2013; 5:1600
Paoletti et al, JNCI 2013; 5:1608.

Localized gastric cancer
DFS and OS



Oba et al, JNCI 2013; 5:1600

Advanced gastric cancer
PFS and OS



Paoletti et al, JNCI 2013; 5:1608.

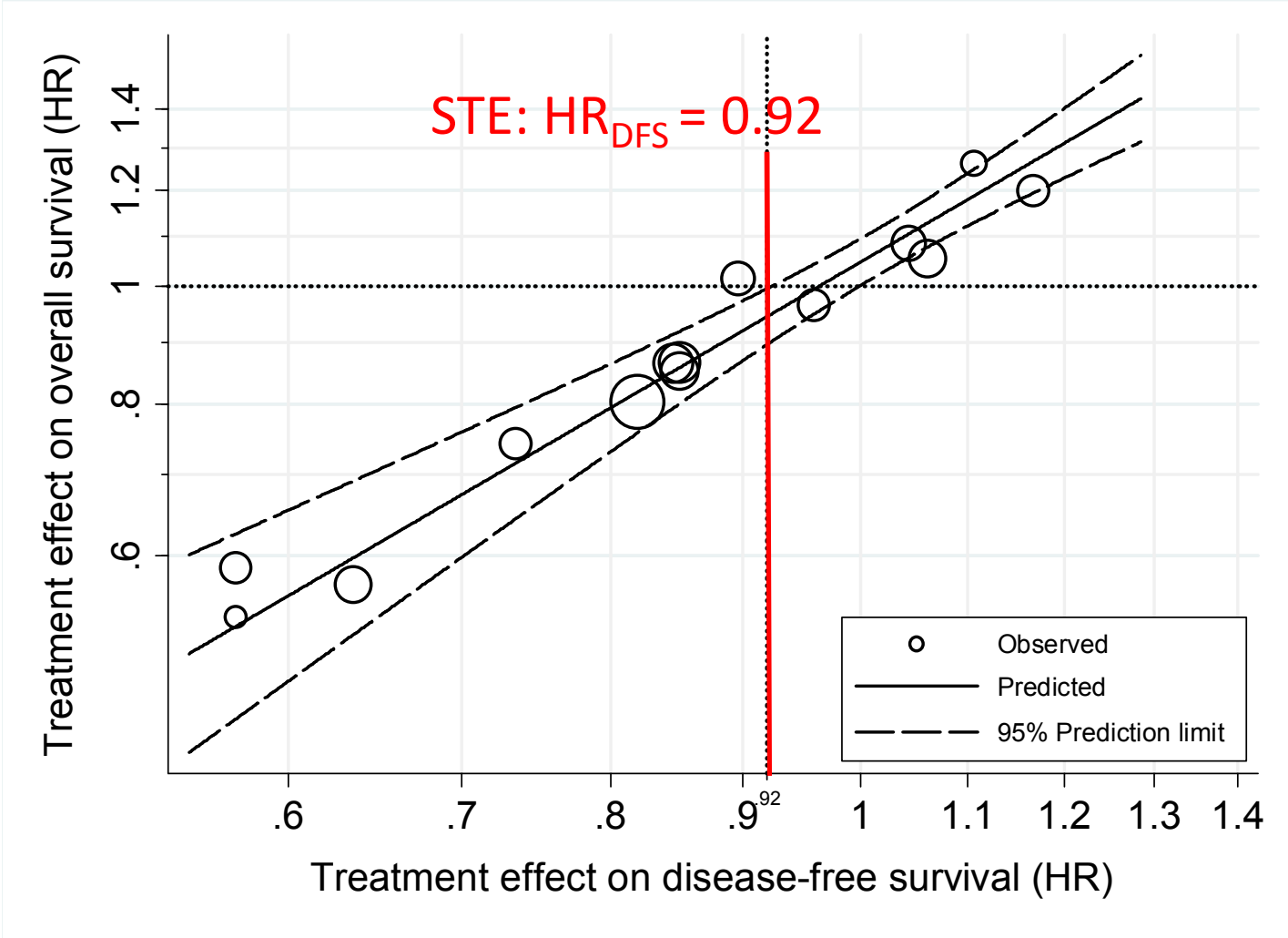
Surrogate threshold effect (STE)

The “Surrogate Threshold Effect” is the treatment effect on the surrogate that would predict a statistically significant treatment effect on the true endpoint.

Instead of testing a treatment effect on the true endpoint, a trial could test if the treatment effect on the surrogate exceeds STE.

Burzykowski and Buyse, Pharmaceutical Stat 2015; 5:173.

Localized gastric cancer
DFS and OS



Oba et al, JNCI 2013; 5:1600

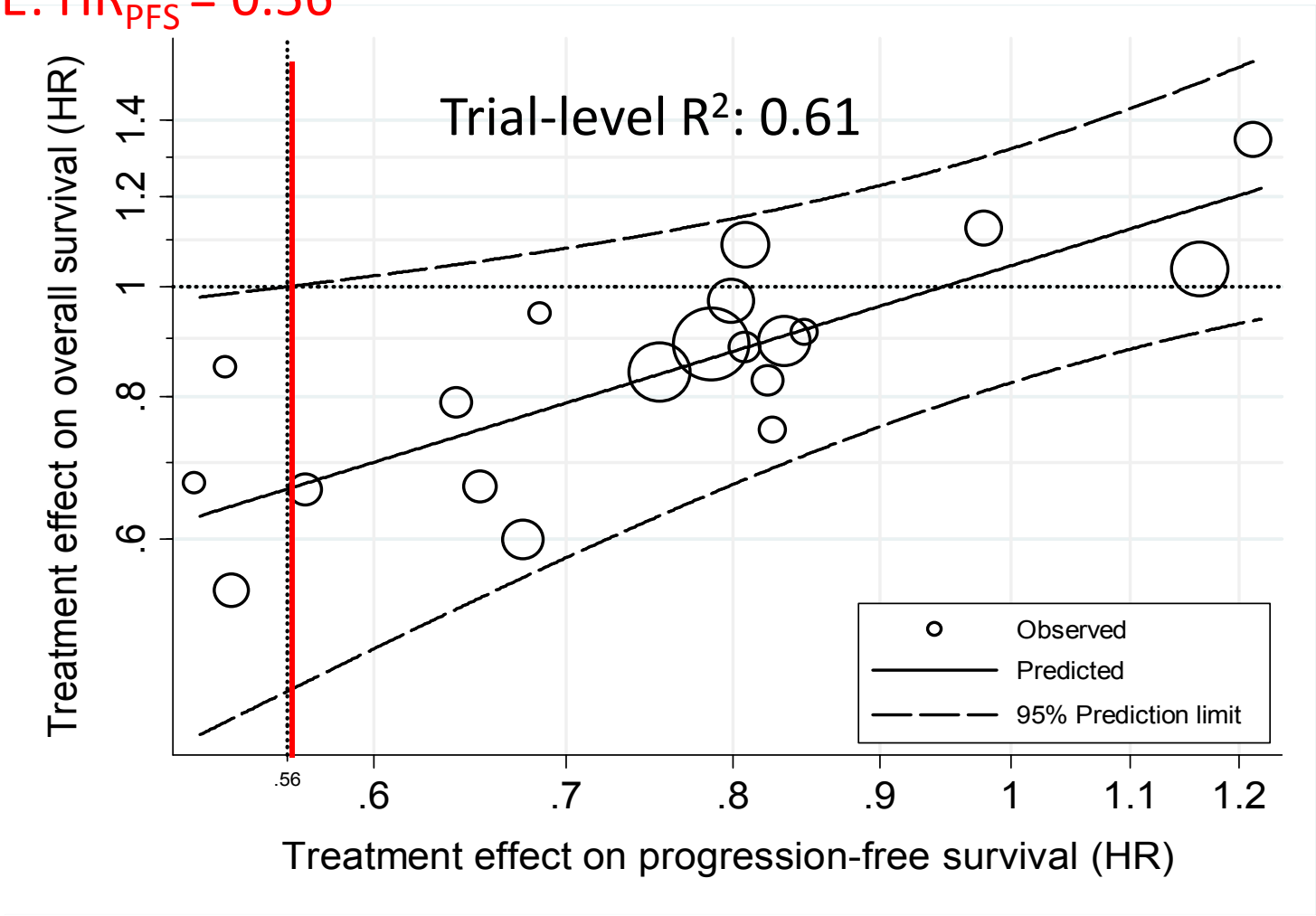
Localized gastric cancer
DFS and OS

Trial	Type of data	Observed HR_{DFS} (95%CI)	Observed HR_{OS} (95%CI)	Predicted HR_{OS} (95% limits)
Cirera et al.	Published	0.55 (0.36,0.85)	0.60 (0.39,0.93)	0.50 (0.28, 0.87)
Sakuramoto et al.	IPD	0.65 (0.54,0.79)	0.67 (0.54,0.83)	0.61 (0.47, 0.81)
MacDonald et al.	IPD	0.66 (0.53,0.82)	0.75 (0.61,0.92)	0.63 (0.46, 0.84)
DeVita et al.	Published	0.88 (0.66,1.17)	0.91 (0.69,1.21)	0.89 (0.62, 1.28)
Di Constanzo et al.	Published	0.92 (0.66,1.27)	0.90 (0.64,1.26)	0.94 (0.63, 1.42)

Buyse et al, Biometrical J 2016; 58:104.

Advanced gastric cancer
PFS and OS

STE: $HR_{PFS} = 0.56$



Paoletti et al, JNCI 2013; 5:1608.

Advanced gastric cancer
PFS and OS

Trial	Observed HR_{PFS} (95% CI)	Observed HR_{OS} (95% CI)	Predicted HR_{OS} (95% limits)
Jeung et al.	0.63 (0.38, 1.05)	0.56 (0.35, 0.88)	0.73 (0.46, 1.04)
Albatran et al	0.67 (0.43, 1.04)	0.82 (0.47 ,1.45)	0.76 (0.53, 1.07)
Bang et al (TOGA)	0.71 (0.59, 0.85)	0.74 (0.60, 0.91)	0.80 (0.58, 1.09)
Ohtsu et al. (avastin)	0.80 (0.68, 0.93)	0.87 (0.73, 1.03)	0.88 (0.76, 1.14)
Kang et al.	0.80 (0.63, 1.03)	0.85 (0.64, 1.13)	0.88 (0.76, 1.14)
Park et al.	0.86 (0.54, 1.37)	0.96 (0.60, 1.52)	0.93 (0.71, 1.18)
Cunningham et al (a)	0.92 (0.81, 1.05)	0.86 (0.80, 0.99)	0.98 (0.77, 1.22)
Cunningham et al. (b)*	0.92 (0.80, 1.04)	0.92 (0.80, 1.10)	0.98 (0.77, 1.22)
Ross et al.	0.95 (0.80, 1.08)	0.91 (0.76, 1.04)	1.00 (0.79, 1.29)
Ajani et al (FLAG)	0.99 (0.86, 1.14)	0.92 (0.80, 1.05)	1.03 (0.81, 1.31)
Rao et al.	1.13 (0.63, 2.01)	1.02 (0.61, 1.70)	1.14 (0.89, 1.46)
Moehler et al.	1.14 (0.59, 2.21)	0.77 (0.51, 1.17)	1.15 (0.90, 1.48)

Buyse et al, Biometrical J 2016; 58:104.

Surrogacy at two “levels”

- Individual-level surrogacy establishes that the surrogate and the clinical endpoints are correlated
  - *useful for patient management*

- Trial-level surrogacy establishes that the treatment effects on the surrogate and the clinical endpoints are correlated
  - *useful to assess new treatments*

- For normally distributed data, these two levels are mathematically independent of each other
  - *evidence on both levels is required*

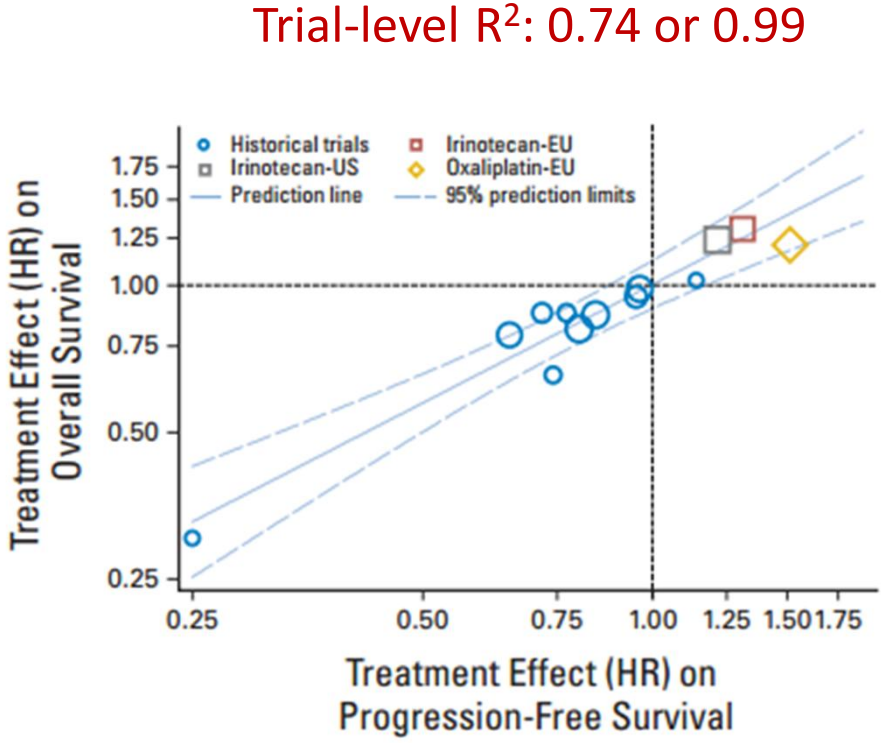
Evolution of surrogacy within a given setting

- Treatment changes over time may affect the associations between endpoints
- In advanced colorectal cancer (CRC), 5-FU was the only sufficiently active agent until the early 90s
- Irinotecan and oxaliplatin were introduced and improved outcomes when combined with 5-FU
- Since 2004, monoclonal antibodies (*e.g.*, bevacizumab and cetuximab) further improved outcomes

Surrogacy of PFS for OS in CRC

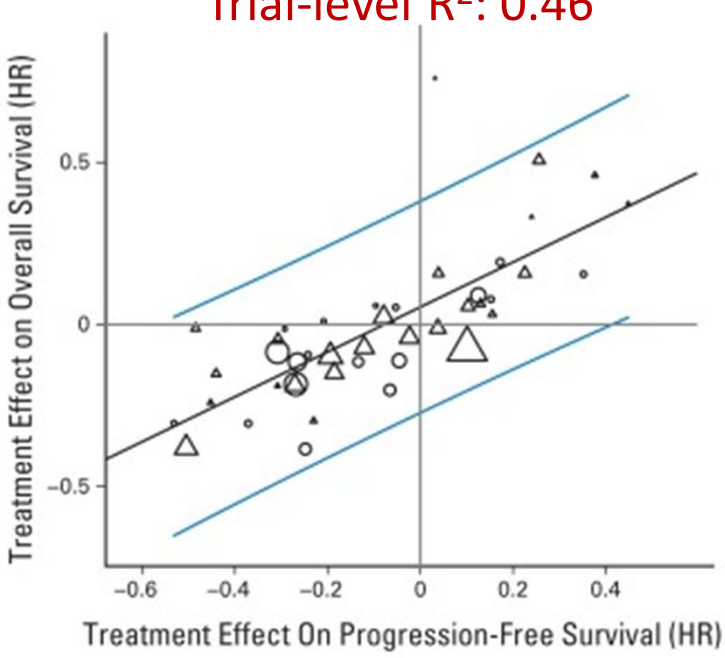
5-FU era

Trial-level R^2: 0.74 or 0.99



5-FU plus newer agents

Trial-level R^2: 0.46



Buyse et al, J Clin Oncol 2007;25:5218.
Shi et al, J Clin Oncol 2015;33:22.

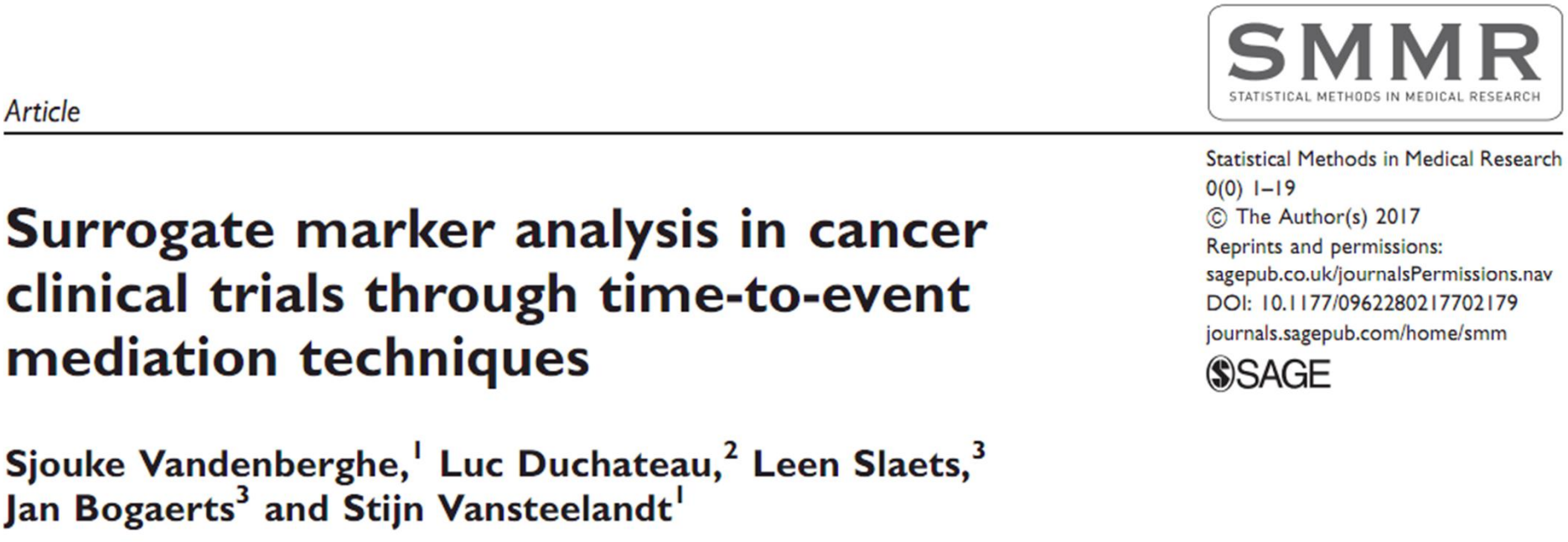
Current status

VALIDATION OF SURROGATE ENDPOINTS IN ADVANCED SOLID TUMORS: SYSTEMATIC REVIEW OF STATISTICAL METHODS, RESULTS, AND IMPLICATIONS FOR POLICY MAKERS

Conclusions: Not in all solid tumors the treatment-level association between PFS/TTP and OS has been investigated. According to IQWiG's framework, only PFS achieved acceptable evidence of surrogacy in metastatic colorectal and ovarian cancer treated with cytotoxic agents.

Ciani et al, Int J Technol Assess Health Care 2014; 30:312.

Recent developments



Article

SMMR
STATISTICAL METHODS IN MEDICAL RESEARCH

Statistical Methods in Medical Research
0(0) 1–19

DOI: 10.1177/0962280217702179
journals.sagepub.com/home/smm
SAGE

Surrogate marker analysis in cancer clinical trials through time-to-event mediation techniques

Sjouke Vandenberghe,[1] Luc Duchateau,[2] Leen Slaets,[3] Jan Bogaerts[3] and Stijn Vansteelandt[1]

Vandenberghe et al, Stat Methods Med Res 2017; Jan 1:962280217702179.

Therapeutic objectives

- What do patients expect from treatment?
- What do physicians want to accomplish with treatment?

1. Cure
2. Extension of survival
3. Maintenance or improvement of quality of life

Current evidence

- Patients' perspectives are different from those of the well person, and often those of the health-care professional
- When asked, patients tend to accept toxicity in exchange for relatively small health benefits
- In most surveys, patients have given more importance to survival than well people and health-care professionals

Matsuyama R, et al. JCO 2006;24:3490-6

What is ‘survival’?

JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

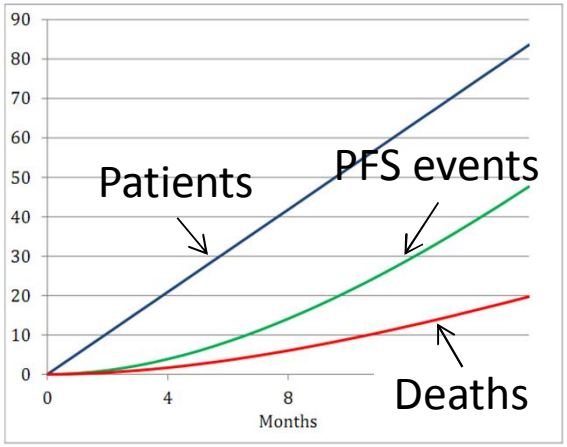
Overall Survival: Patient Outcome, Therapeutic Objective, Clinical Trial End Point, or Public Health Measure?

Patient outcome	Is individual patient likely to be cured (ie, can this individual survive as long as matched healthy individual)?
	Is individual patient’s survival likely to be prolonged, and if so, by how much?
Therapeutic objective	Can survival of group of individuals be prolonged, and if so, by how much?
	Does treatment effect vary across patients with different characteristics?
Clinical trial end point	Can impact of treatment on survival be demonstrated statistically with affordable sample sizes and trial durations?
Public health measure	Is gain in survival justified by treatment cost and complexity?

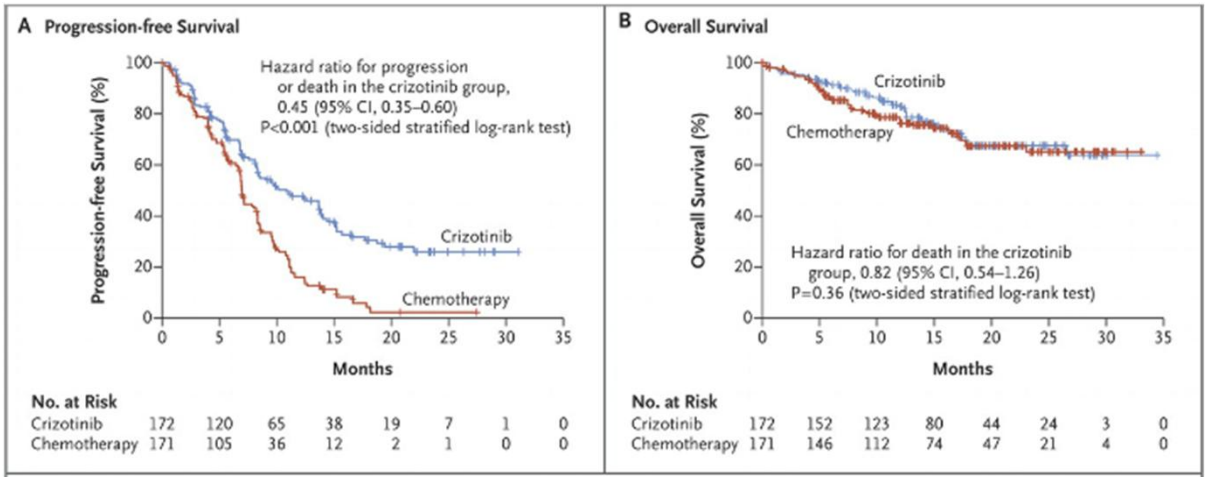
Saad and Buyse, JCO 2012;30:1750

Problems with OS

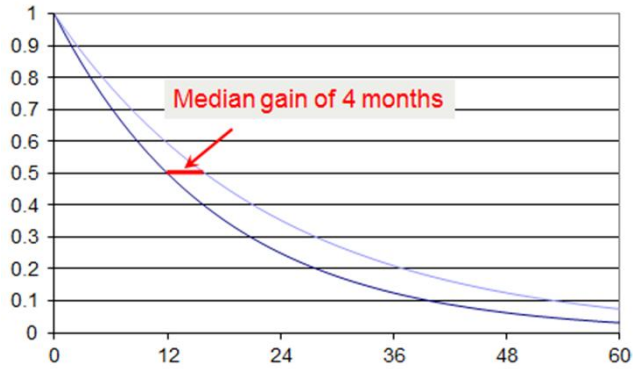
smaller number of events



competing risks and cross-overs



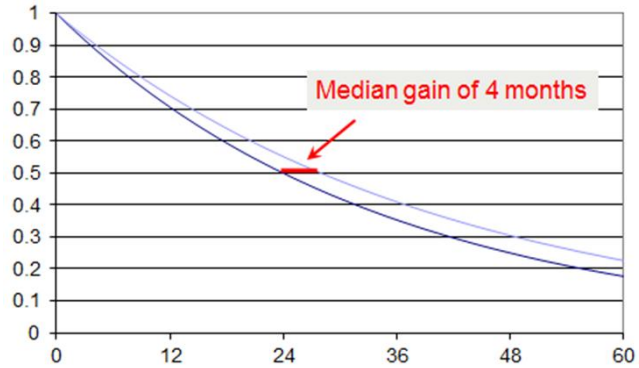
longer median time to event



PFS
HR=0.75
380 events

smaller relative effect

OS
HR=0.86
1,380 events



Saad and Buyse, Ann Oncol 2016;27:373
Solomon, et al, N Engl J Med 2014;371:2167

OS with immunotherapy

Selected phase III trials of CPIs as single agents

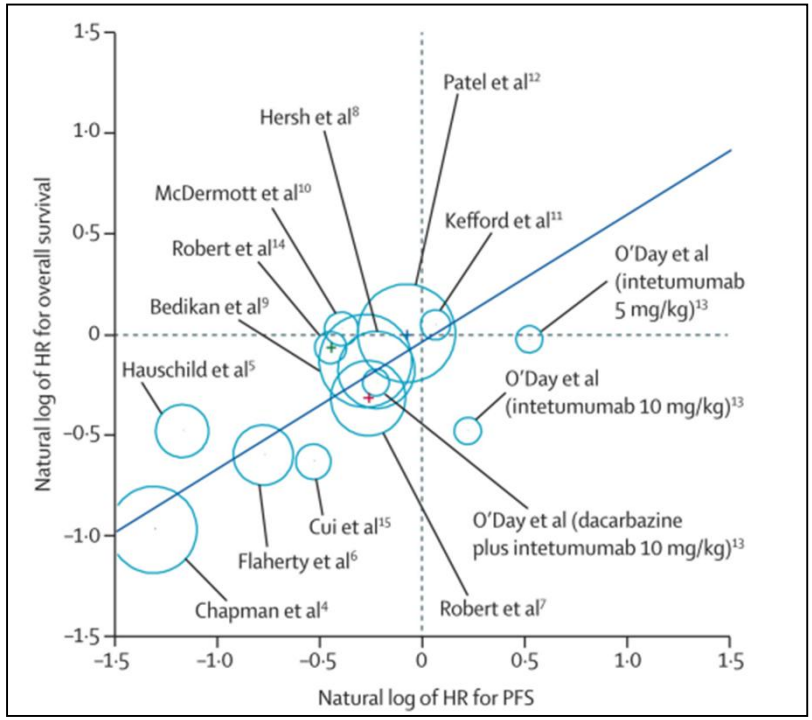
Agent	Indication	Gain in OS	Gain in PS
Ipilimumab	Melanoma, 2L	**Yes**	**Yes**
	Melanoma, 1L	**Yes**	**Yes**
Nivolumab	Renal cell, 2L	**Yes**	**No**
	Melanoma, 2L	**Yes**	**Yes**
	NSCLC, 2L	**Yes**	**No**
	H&N, 2L	**Yes**	**No**
	Gastric/GEJ, 3L	**Yes**	**Yes**
Pembrolizumab	NSCLC, 2L	**Yes**	**No**
	NSCLC, 1L	**Yes**	**Yes**
	Urothelial, 2L	**Yes**	**No**

Ongoing Attempts in I-O

Only melanoma

Various treatments, including I-O

CPIs



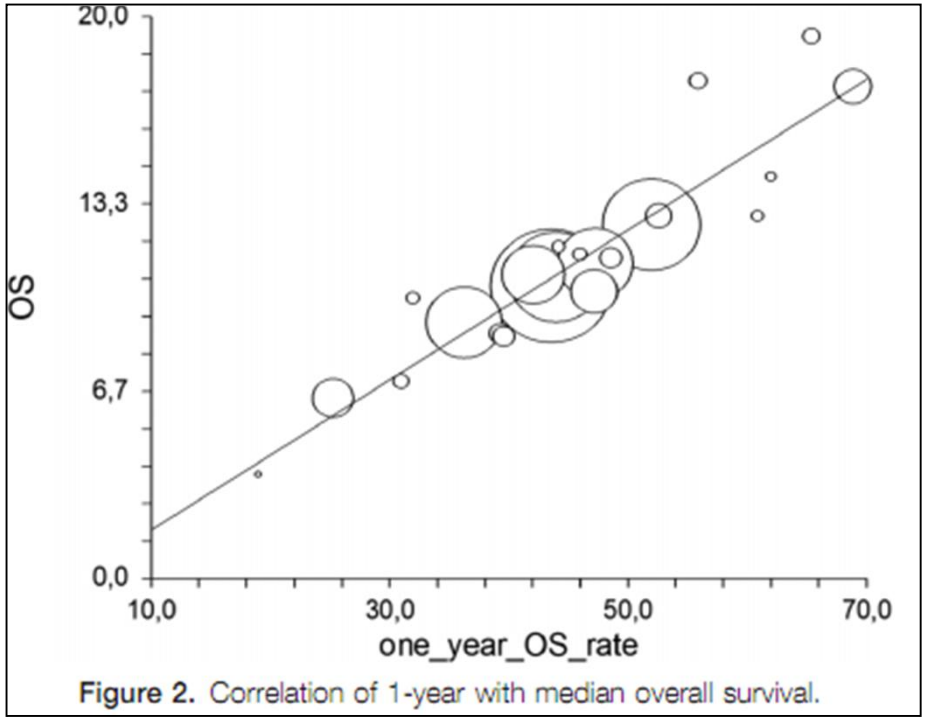


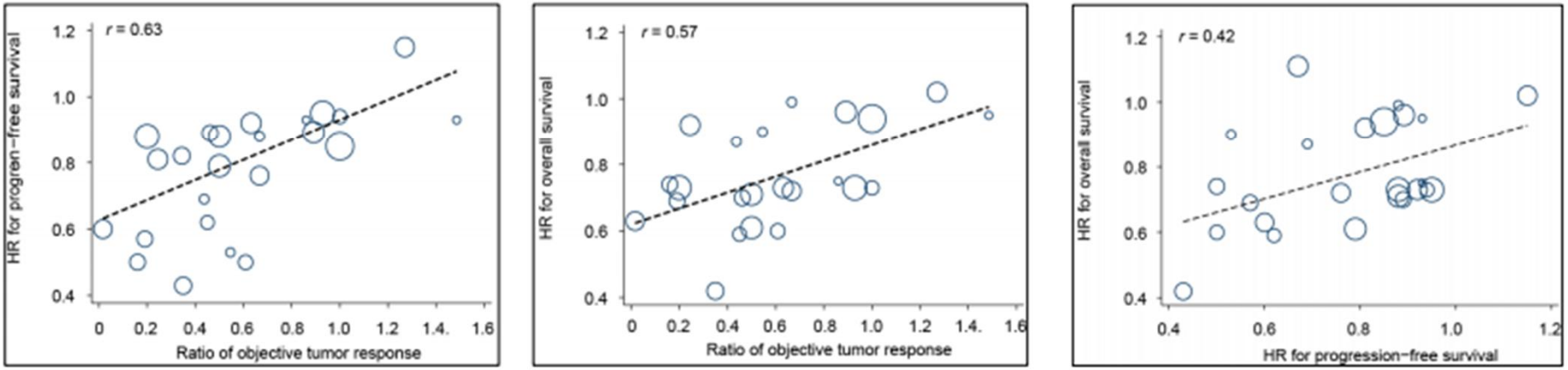
Figure 2. Correlation of 1-year with median overall survival.

Flaherty et al, Lancet Oncol 2014; 15: 297–304
Petrelli et al, Medicine (2016) 95:26(e3997)

Ongoing Attempts in I-O

Various indications

Fig 2: Correlations in relative treatment effect between: (A) ratio of ORR and HR for PFS, (B) ratio of ORR and HR for OS, and (C) HR for PFS and HR for OS



Ritchie et al, ESMO 2017, #1158

Conclusions

- Considering OS as the ‘true’ endpoint…
- A limited number of studies have been conducted thus far
- In general, DFS performs better than PFS as a surrogate for OS
- Surrogacy is context-dependent, and may change as treatments evolve
- Validation is best done using individual patient data
- The added contribution of causal methods to association methods is being assessed