Surrogate Endpoints and Statistical Considerations

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Disclosure

Co-owner of Berry Consultants, LLC, a company that designs Bayesian adaptive clinical trials for pharmaceutical and medical device companies, NIH & NCI cooperative groups, patient advocacy groups, and international consortia.

Guidance for Industry

Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical/Medical

IV. A. Rationale for Use of Pathological Complete Response as a Surrogate Endpoint in Neoadjuvant Trials

CTNeoBC, Cortazar et al.

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,
[illegible]
Richard Pazdur, Nina Ditsch, Priya Rastogi, Wolfgang Eiermann, Gunter von Minckwitz

Findings We obtained data from 12 identified international trials and 11955 patients

Summary

Background Pathological complete response has been proposed as a surrogate endpoint for prediction of long-term clinical benefit, such as disease-free survival, event-free survival (EFS), and overall survival (OS). We had four key objectives: to establish the association between pathological complete response and EFS and OS, to establish the definition of pathological complete response that correlates best with long-term outcome, to identify the breast cancer subtypes in which pathological complete response is best correlated with long-term outcome, and to assess whether an increase in frequency of pathological complete response between treatment groups predicts improved EFS and OS.

Methods We searched PubMed, Embase, and Medline for clinical trials of neoadjuvant treatment of breast cancer. To be eligible, studies had to meet three inclusion criteria: include at least 200 patients with primary breast cancer treated with preoperative chemotherapy followed by surgery; have available data for pathological complete response, EFS, and OS; and have a median follow-up of at least 3 years. We compared the three most commonly used definitions of pathological complete response—ypT0 ypN0, ypT0/is ypN0, and ypT0/is—for their association with EFS and OS in a responder analysis. We assessed the association between pathological complete response and EFS and OS in various subgroups. Finally, we did a trial-level analysis to assess whether pathological complete response could be used as a surrogate endpoint for EFS or OS.

Findings We obtained data from 12 identified international trials and 11955 patients were included in our responder analysis. Eradication of tumour from both breast and lymph nodes (ypT0 ypN0 or ypT0/is ypN0) was better associated

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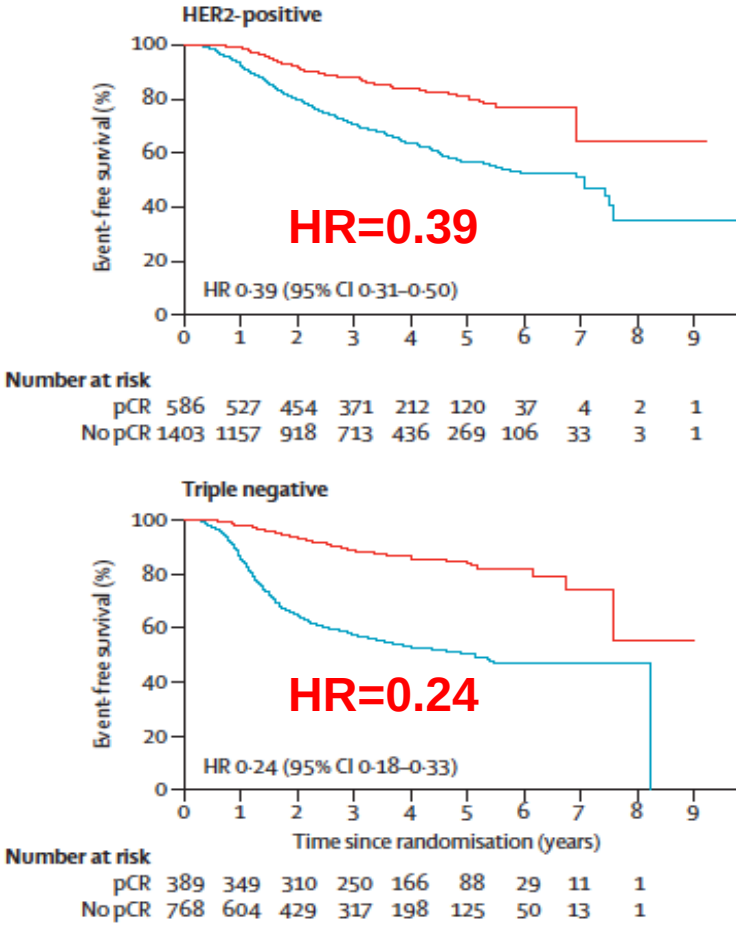
US Food and Drug Administration, Silver Spring, MD, USA (P Cortazar MD, L Zhang PhD, T Prowell MD, G Blumenthal MD, R Justice MD, R Sridhara PhD, S Tang PhD, R Pazdur MD); **HELIOS Klinikum, Berlin, Germany** (Prof M Untch MD); **German Breast Group, Neu-Isenburg, Germany** (K Mehta MBA, Prof S Liobl MD, Prof G von Minckwitz MD); **National Surgical Adjuvant Breast and Bowel Project**

Cortazar patient-level analyses in Figure 5



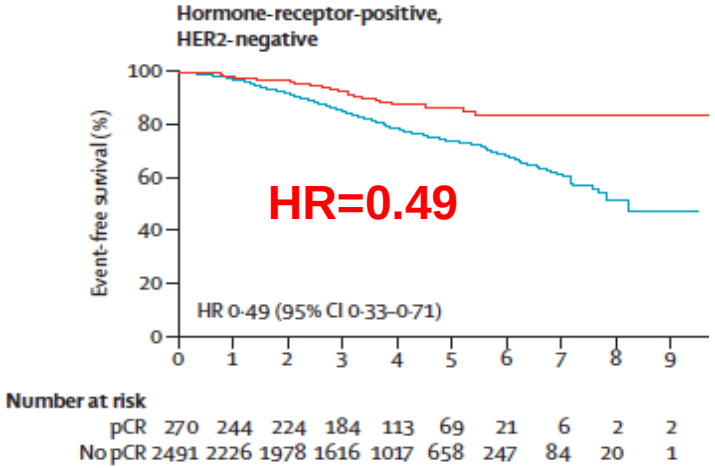
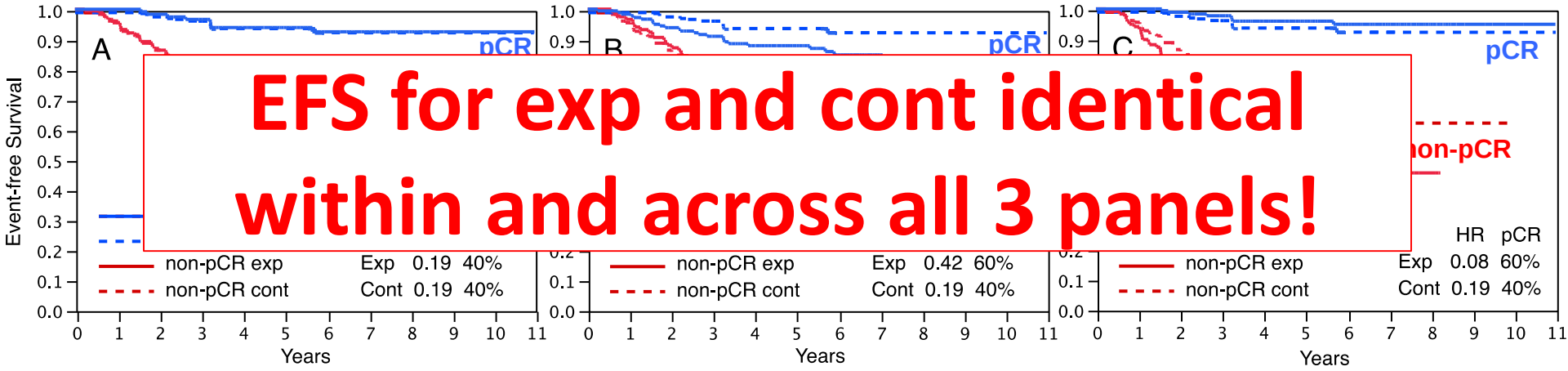


Figure 5: **Association between pCR and event-free survival,**

Impressive! Why isn’t patient-level analyses enough for pCR to be a “validated” surrogate endpoint?

Comparing experimental and control arms for pCR vs non-pCR



EFS for exp and cont identical within and across all 3 panels!

Panel A: Exp same as control

Panel B: For exp, randomly selected non-pCR controls (20% of total) relabeled pCR

Panel C: For exp, non-pCR controls with non-events (20% of total) relabeled pCR

Improve pCR means improve EFS? Cortazar trial-level analyses in Figure 6

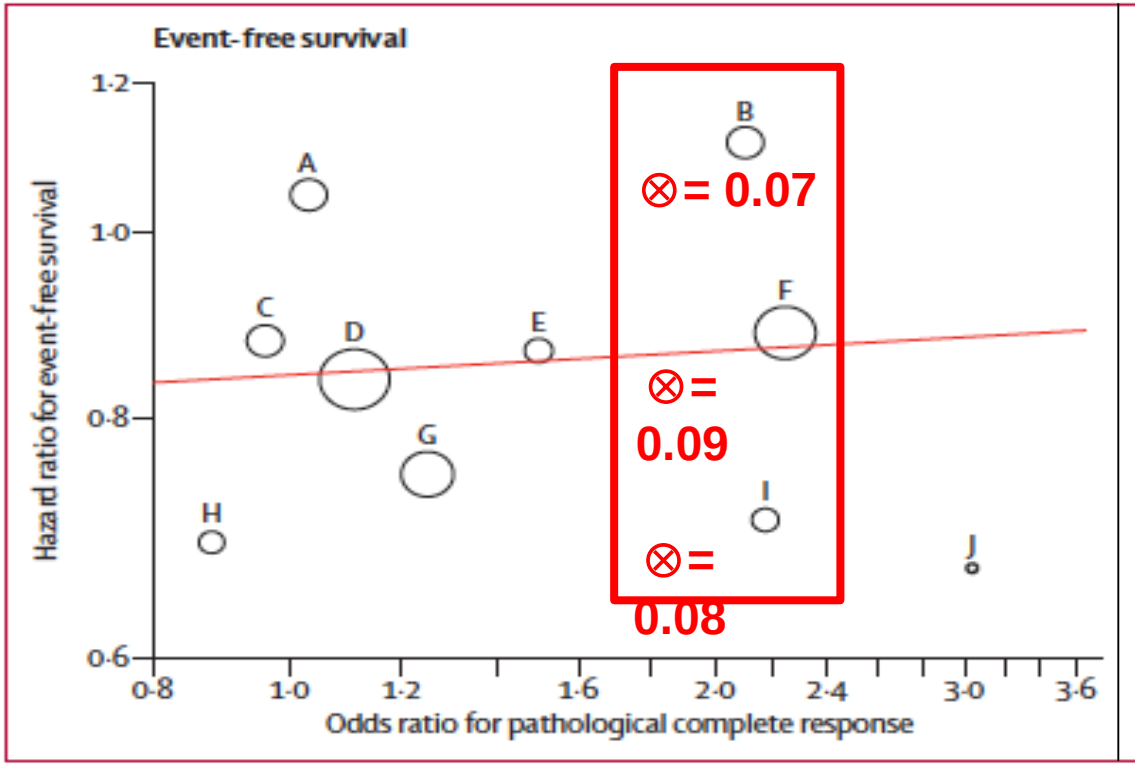
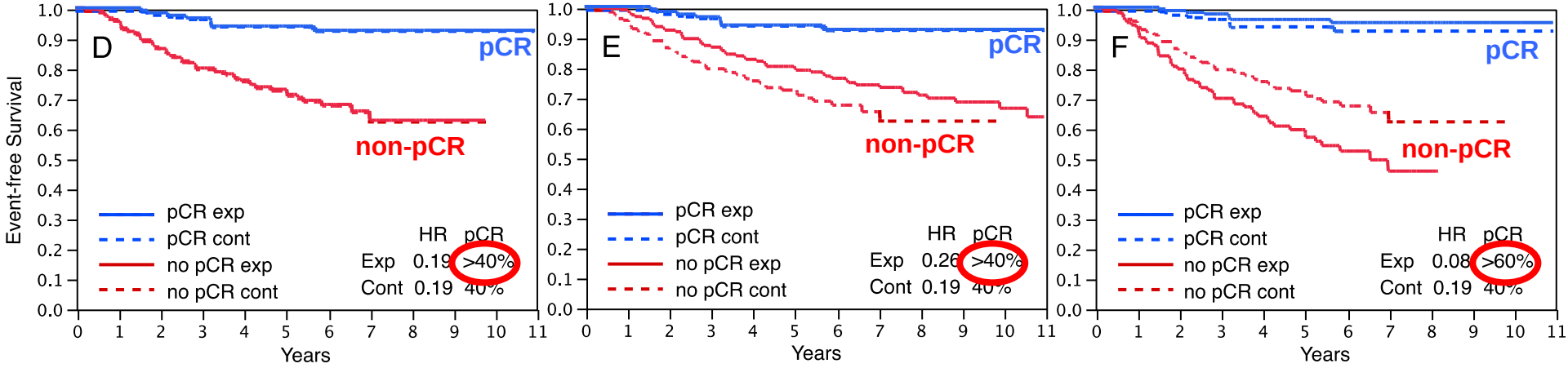


Figure 6: Trial-level correlation between treatment effect on pathological comp

Deficiencies and inefficiencies in Figure 6

- **Ignores whether patients with longer EFS are those with pCRs**
- **Reduces information in 10,000 patients to 10 datapoints; loses 99.9% of information about correlation between EFS and pCR—even the sign of the correlation is difficult to estimate**
- **There is little treatment effect in the 10 RCTs; difficult to show correlation based on treatment effect when there is no treatment effect**
- **Requires RCTs**

How else but Fig 6 for showing validated surrogacy? Trade-off between pCR improvement and EFS by pCR effect

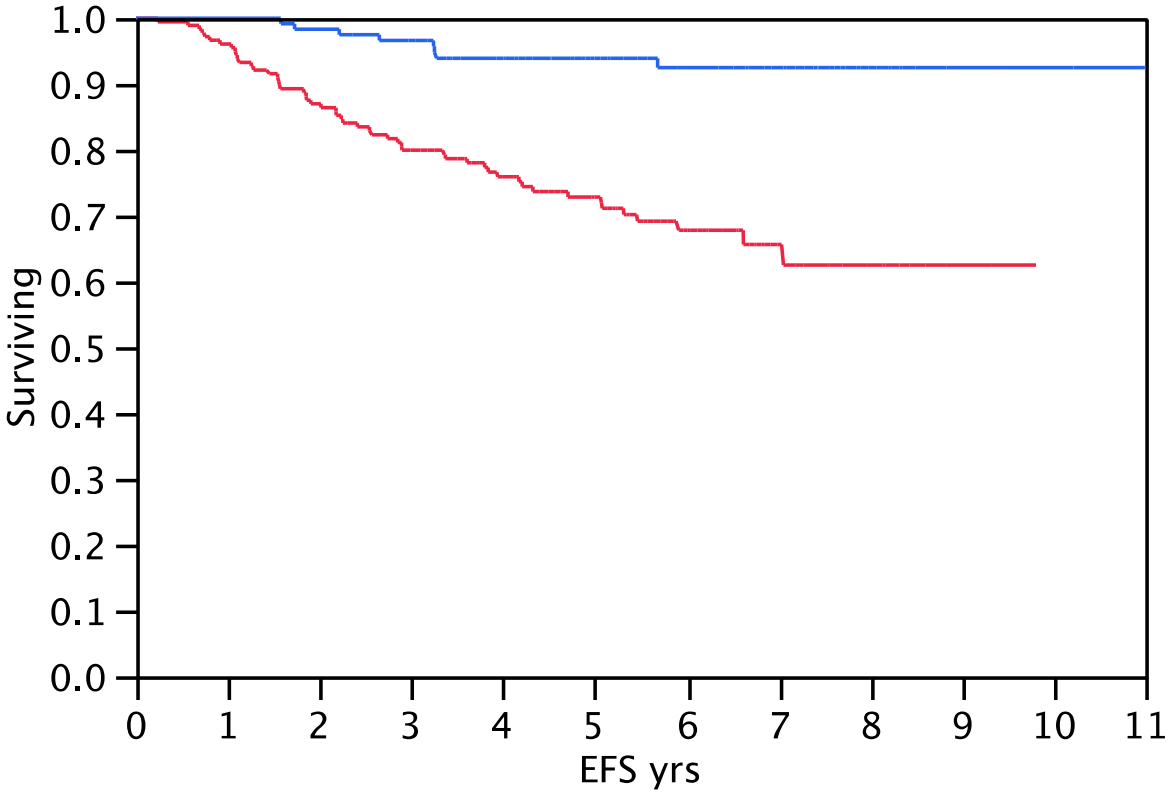


Panel D: Same as Panel A but pCR rate greater than control

Panel E: Experimental arm EFS increased by 50% for all non-pCR; pCR rate > 40%

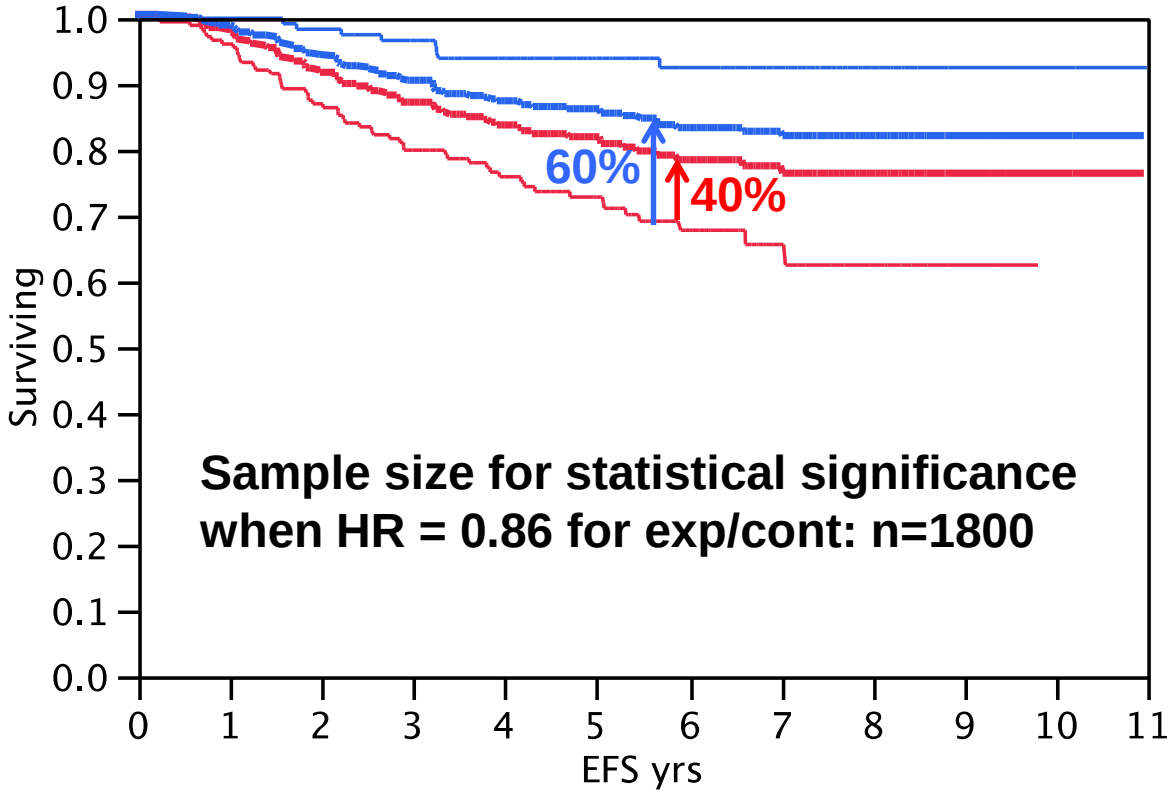
Panel F: Same as Panel C [non-pCR controls with non-events (20% of total) relabeled pCR] but pCR rate > 60%

Predicting pCR rate, assuming panel A
Cont pCR rate 40% but with exp arm rate 60%



HR= 0.19

Predicting pCR rate, assuming panel A
Cont pCR rate 40% but with exp arm rate 60%



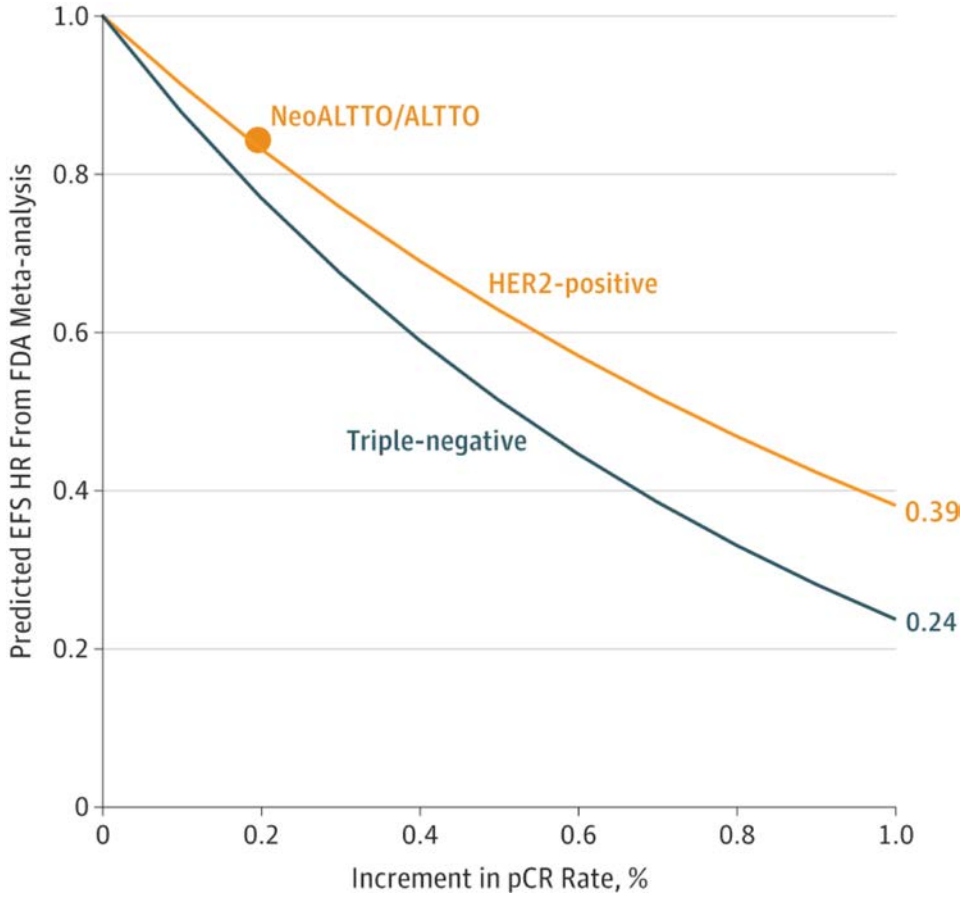
HR= 0.19

The historical relationship between EFS and pCR may be different in a future trial

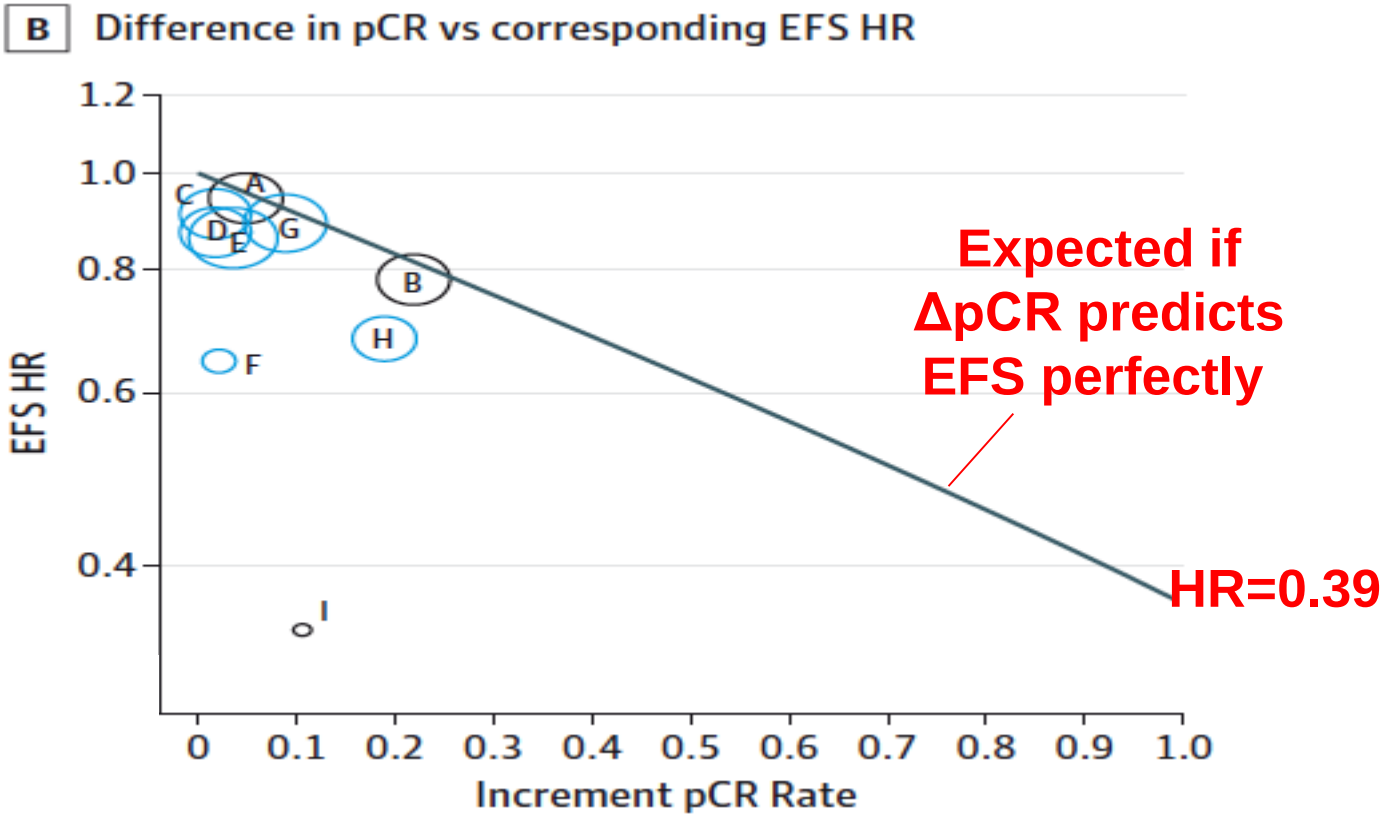
So re-estimate the trial's sample size adapting to the actual pCR rates by treatment, and the EFS by pCR relationships by treatment

Does it work in practice?

Berry-Hudis JAMA Oncol 2015



HER2+ metaanalysis: Broglio et al. *JAMA Oncology* 2016



Summary

- Reasonably likely vs. validated surrogates
- Patient-level vs trial-level analyses
- Demonstrating surrogacy from RCTs
- Demonstrating surrogacy from single-arm trials
- Designing trials, learning about pCR/EFS