Statistical Considerations in Preoperative Clinical Trials

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Dispense with sample size issue when pCR is primary endpoint:

Essentially same as for metastatic BC with tumor response as primary endpoint, and "interest in" PFS and OS

OUTLINE

- **Are adjuvant trials still viable?**

- **Efficiency of neoadjuvant trials**

- **pCR as correlate or surrogate?**

- **Modeling pCR:DFS:OS**
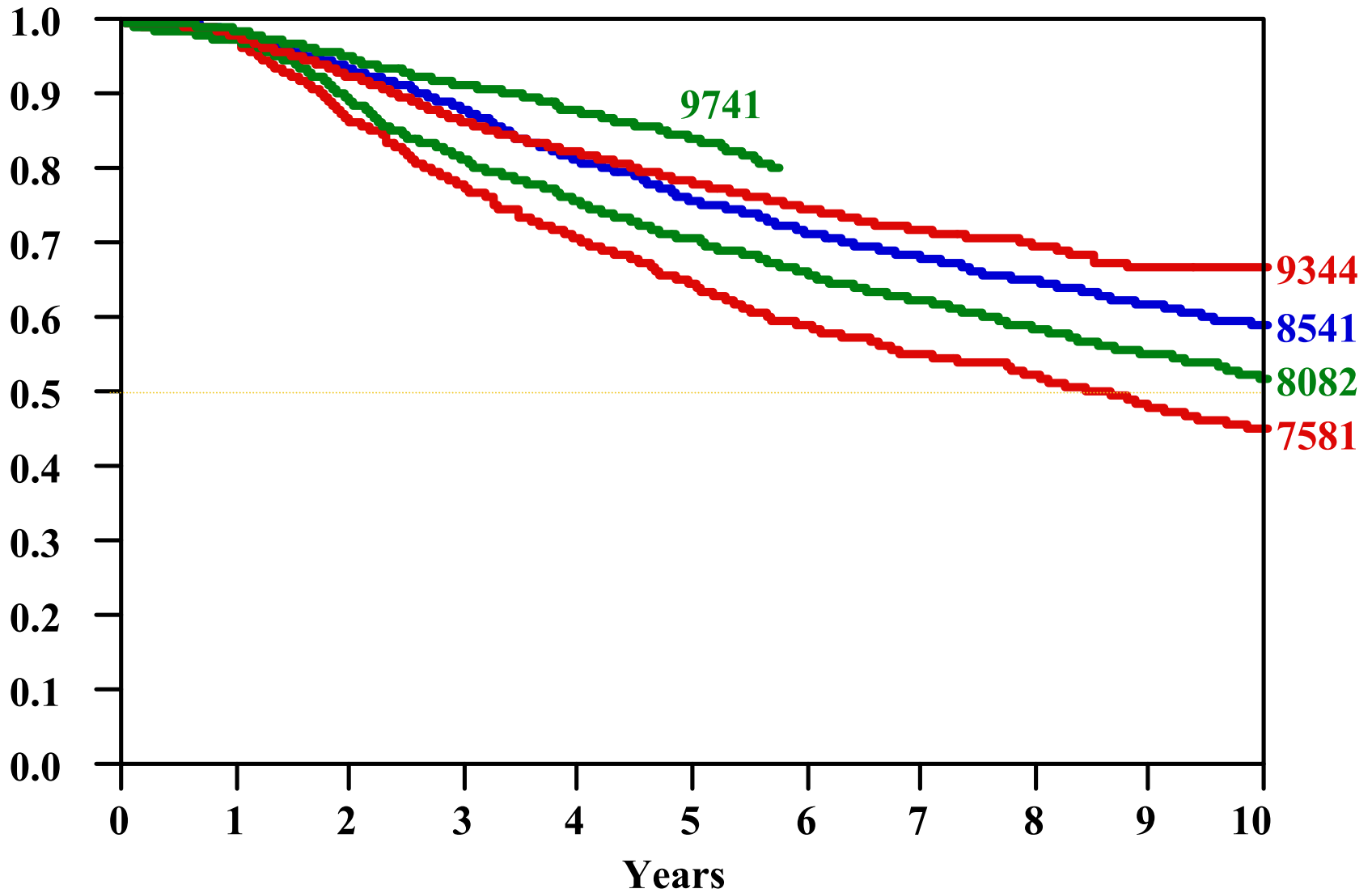
- **Fine tuning pCR**

CALGB node+ adjuvant trials

- **CALGB 7581: N = 888**
- **CALGB 8082: N = 933** **Today!**
- **CALGB 8541: N = 1550**
- **CALGB 9344: N = 3120**
  - **Targeted # DFS events: 1800**
  - **Interim analyses: 450, 900, 1350**

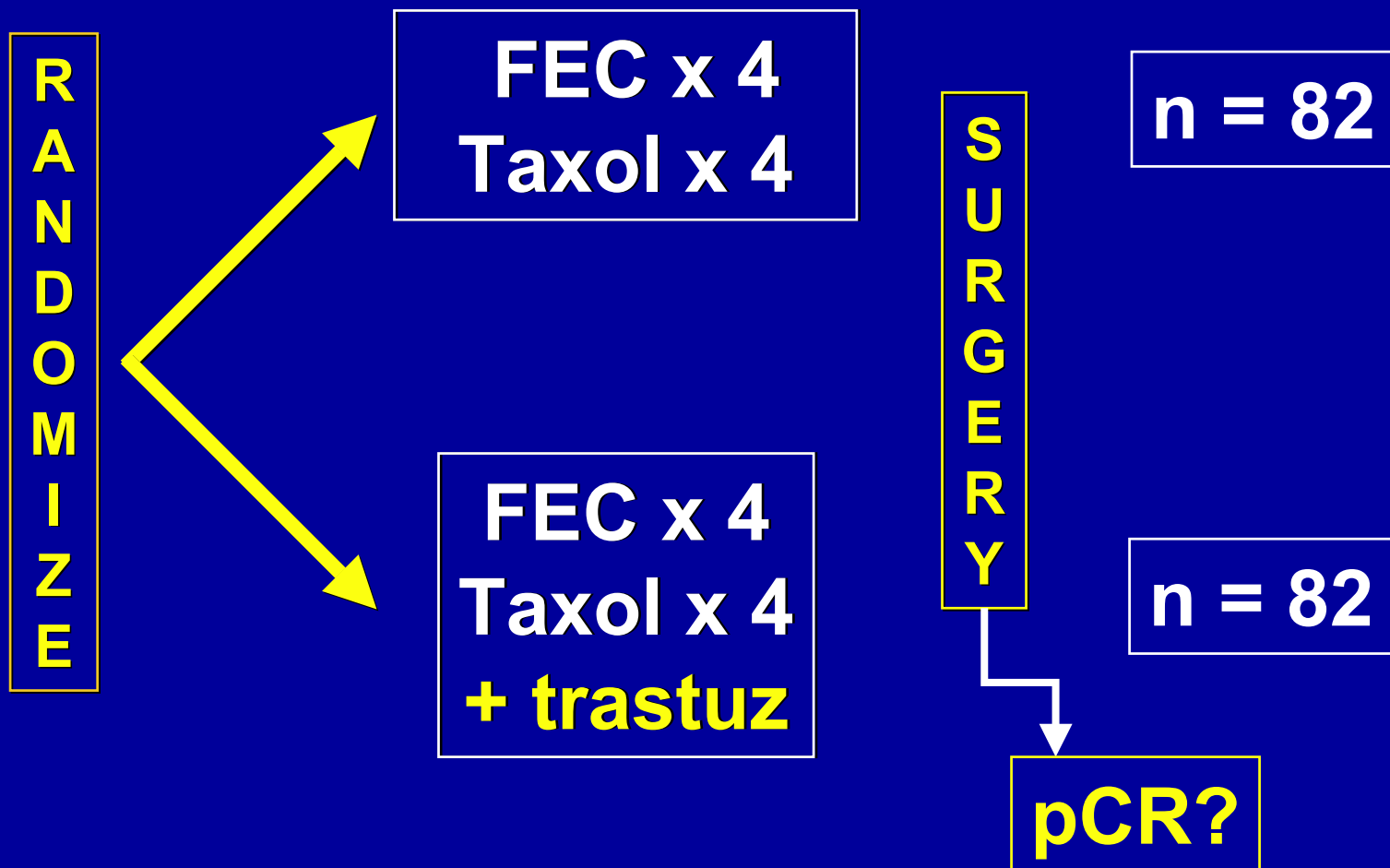# Survival in Node+ Trials

ATAC: N=9366

p=0.0013 for A vs T

6

Potential for more sensitive —and earlier!— comparisons in neoadjuvant trials: An example

Neoadjuvant Trastuzumab in HER2+ Breast Cancer*

RANDOMIZE

FEC x 4
Taxol x 4

FEC x 4
Taxol x 4
+ trastuz

SURGERY

n = 82

n = 82

pCR?

*Buzdar et al, *JCO* (2005)

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Data Monitoring Committee

- **Annual monitoring by DMC**
- **Interim results after 34 patients:**

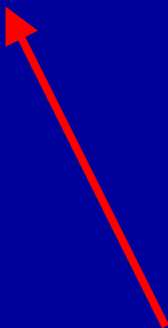| Trastuzumab	12/18 = 67%
Control	4/16 = 25%

- **Bayesian probability that outcome will still be significant after 164 patients: 95%**
- **ASCO —> JCO**

Trastuzumab chronology

Metastatic   **Buzdar**   **Adjuvant**

1000s of pts   **34 pts**   **1000s of pts**

**Neat link,
though small**

What about pCR?

- **Great statistically because:**
  - **Fixed time of assessment**
  - **Early**
  - **Enables adaptive designs**
- **Should be fine tuned**
- **But is it a surrogate for anything of clinical relevance?**
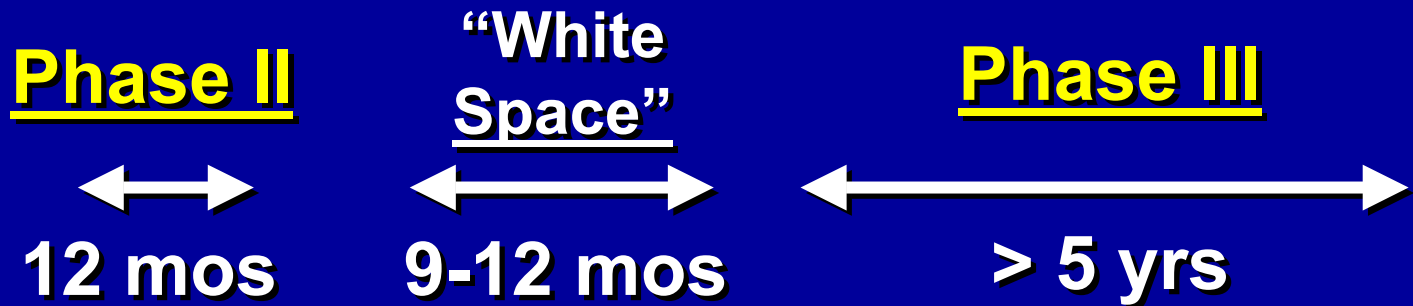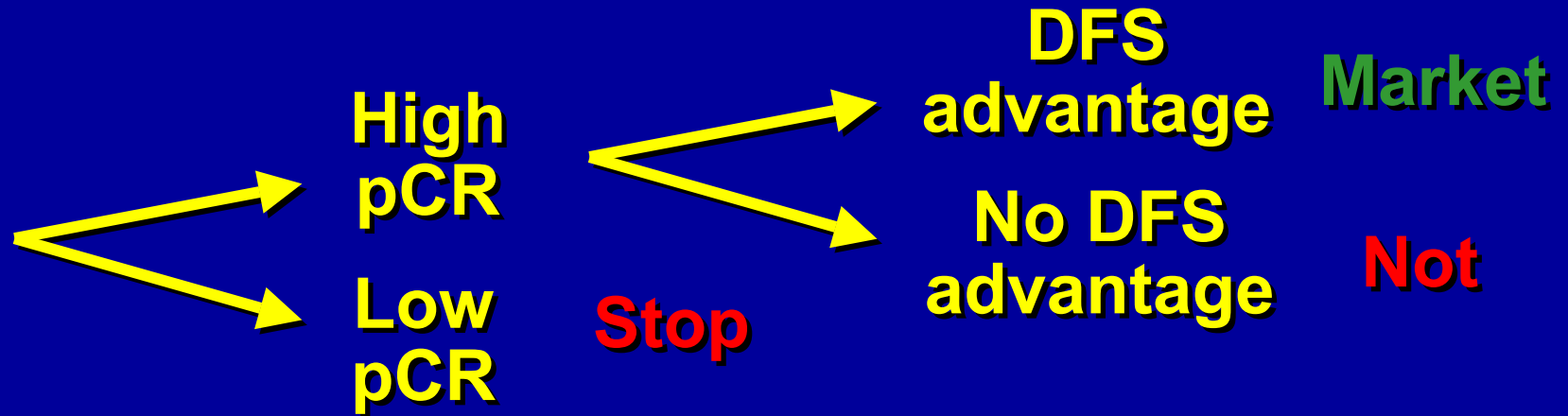
"Surrogate endpoint" (Prentice 1989)

- "a response variable for which a test of the null hypothesis of no relation to **the treatment groups** under comparison is also a valid test of the corresponding null hypothesis based on the true endpoint."

- High hurdle: pCR doesn't qualify

- But pCR is useful nonetheless!

Using neoadjuvant therapy in drug development: An adaptive example

Seamless phases II/III

- **Primary breast cancer**
- **pCR *may* predict DFS, depending on treatment (not a "surrogate")**
- **Primary endpoint: DFS**
- **Model pCR/DFS relationships**
- **Observe relationships—and "validate" within treatment group**

"Standard" approach

High pCR → DFS advantage → **Market**

Low pCR

Stop

High pCR → No DFS advantage → **Not**

Phase II

↔ 12 mos

"White Space"

↔ 9-12 mos

Phase III

↔ > 5 yrs

Seamless phase II/III

↔ < 4 yrs (usually)

Seamless phases

- Phase II: A few centers; 15 pts/mo, randomize equally to E vs C
- If predictive probs "look good," expand (Phase III): Many centers; 60 pts/mo; initial centers continue accruing
- Max N = 1800

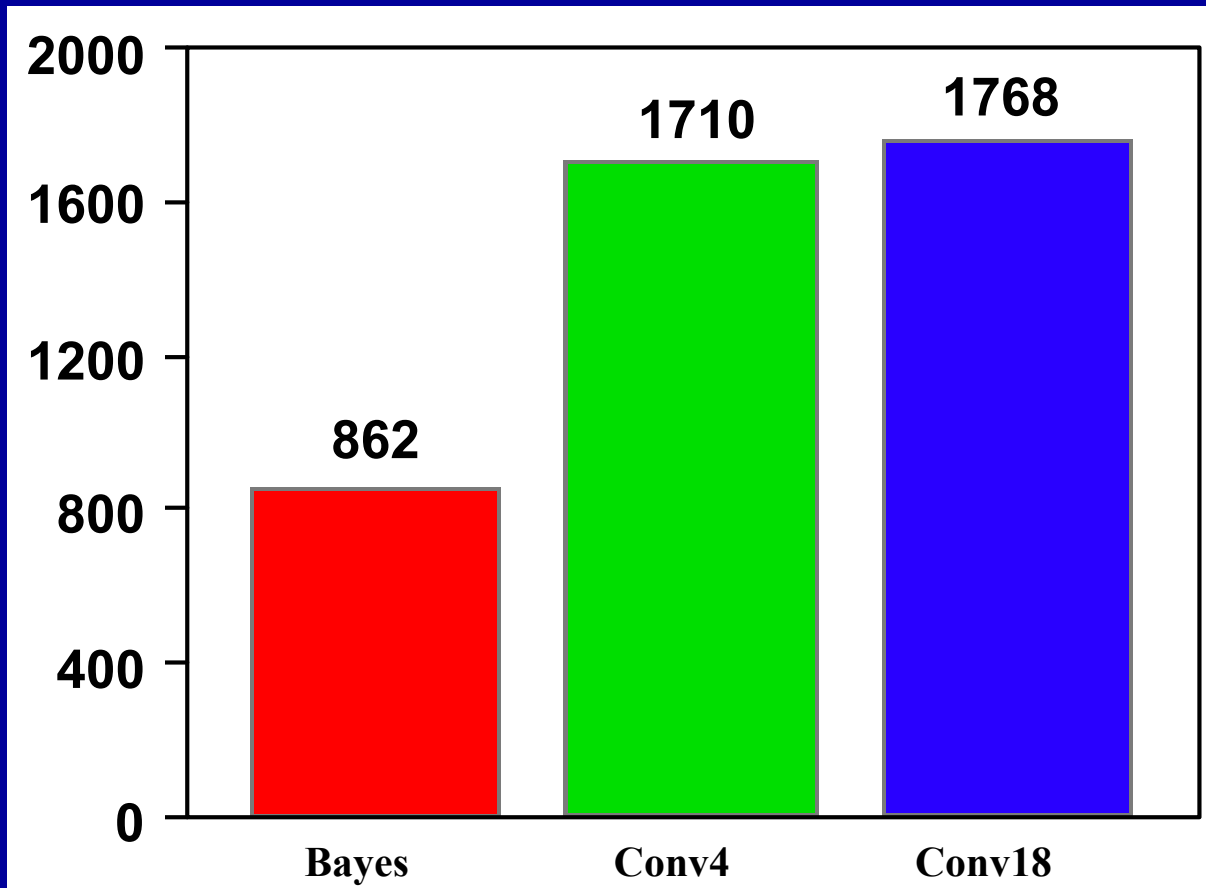[Single trial: All data used in final analysis]

Early stopping

- **Use pred probs of stat signif**
- **Frequent analyses (total of 18) using predictive probs to:**
  - **Switch to Phase III**
  - **Stop accrual for**
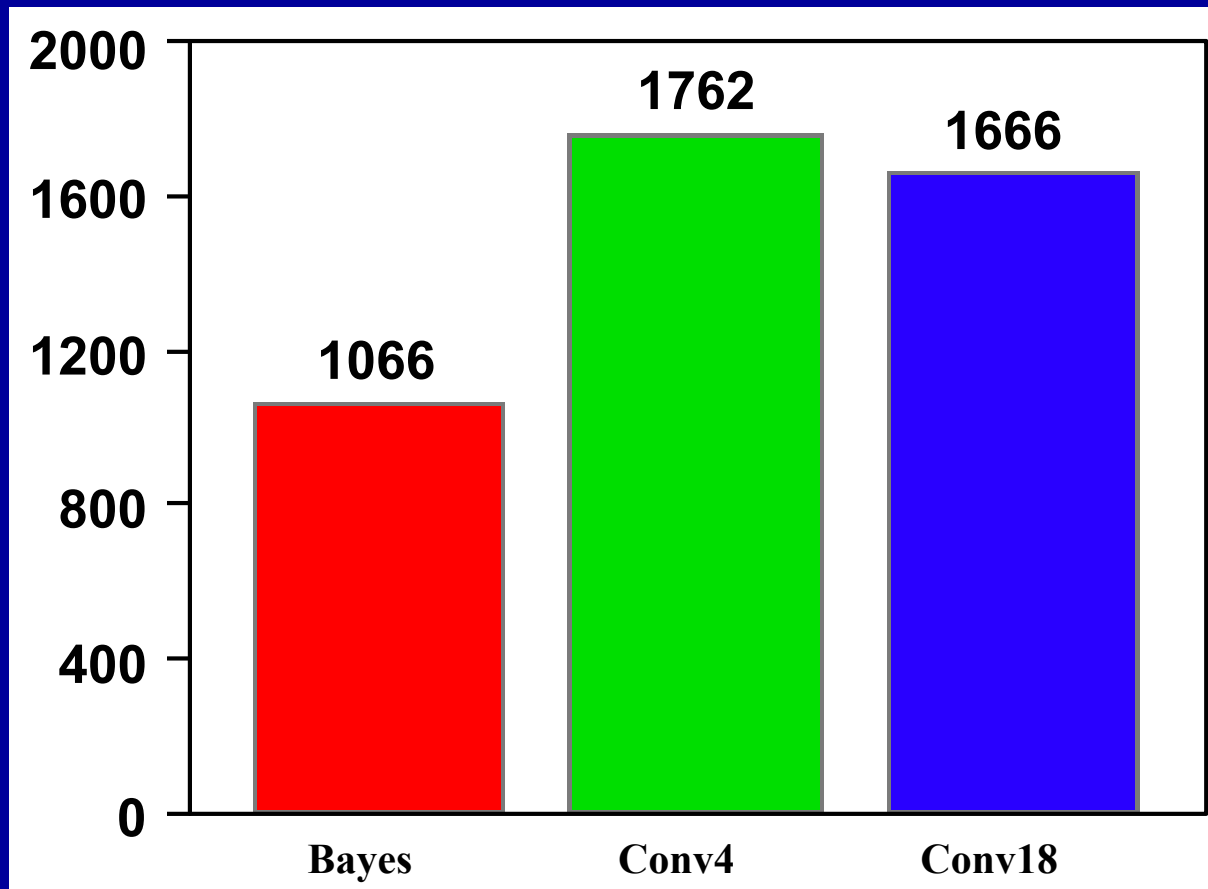   - **Futility**
    - **Superiority**

Comparisons

Conventional Phase III designs: Conv4 & Conv18, max N = 1800

(same significance level & power as adaptive Bayesian design)

Average N under H_0

Average N under H_1

Advantages

- **Duration of drug development shortened:**
  - **Fewer patients in trial**
  - **No hiatus for setting up phase III**
  - **All patients used for**
    - **Phase III endpoint**
    - **Relation between pCR & DFS**

- **N is seldom near 1800; when it is, it's necessary!**

Two reasons for advantages

- **Exploiting pCR and its potential predictability**

- **Bayesian approach and frequent assessments of predictive probabilities**

Further improvements possible in neoadjuvant settings (e.g., I-SPY2)

- Biomarkers

- Imaging

- Several drugs & combinations

- Adaptive randomization

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