Statistical Considerations in Preoperative Clinical Trials

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Dispense with sample size issue when pCR is primary endpoint:

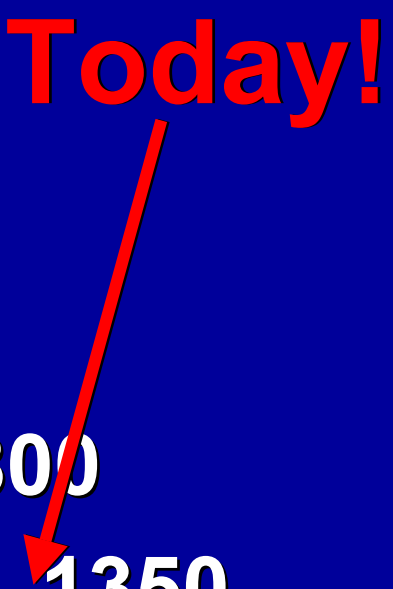
Essentially same as for metastatic BC with tumor response as primary endpoint, and “interest in” PFS and OS

OUTLINE

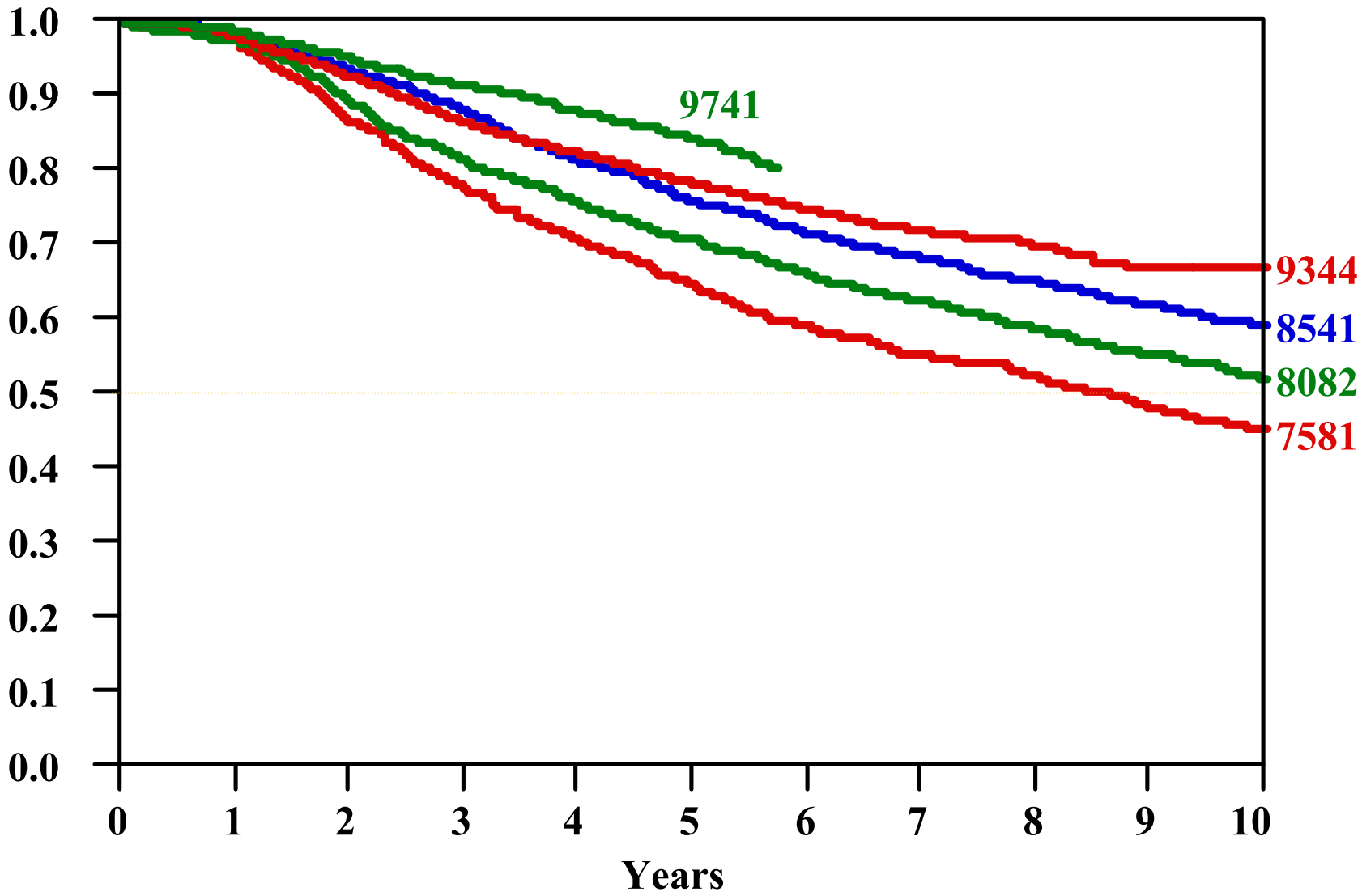
- Are adjuvant trials still viable?
- Efficiency of neoadjuvant trials
- pCR as correlate or surrogate?
- Modeling pCR:DFS:OS
- Fine tuning pCR

CALGB node+ adjuvant trials

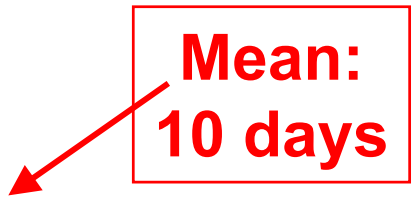
- CALGB 7581: N = 888
- CALGB 8082: N = 933
- CALGB 8541: N = 1550
- CALGB 9344: N = 3120
  - Targeted # DFS events: 1800
  - Interim analyses: 450, 900, 1350



Survival in Node+ Trials



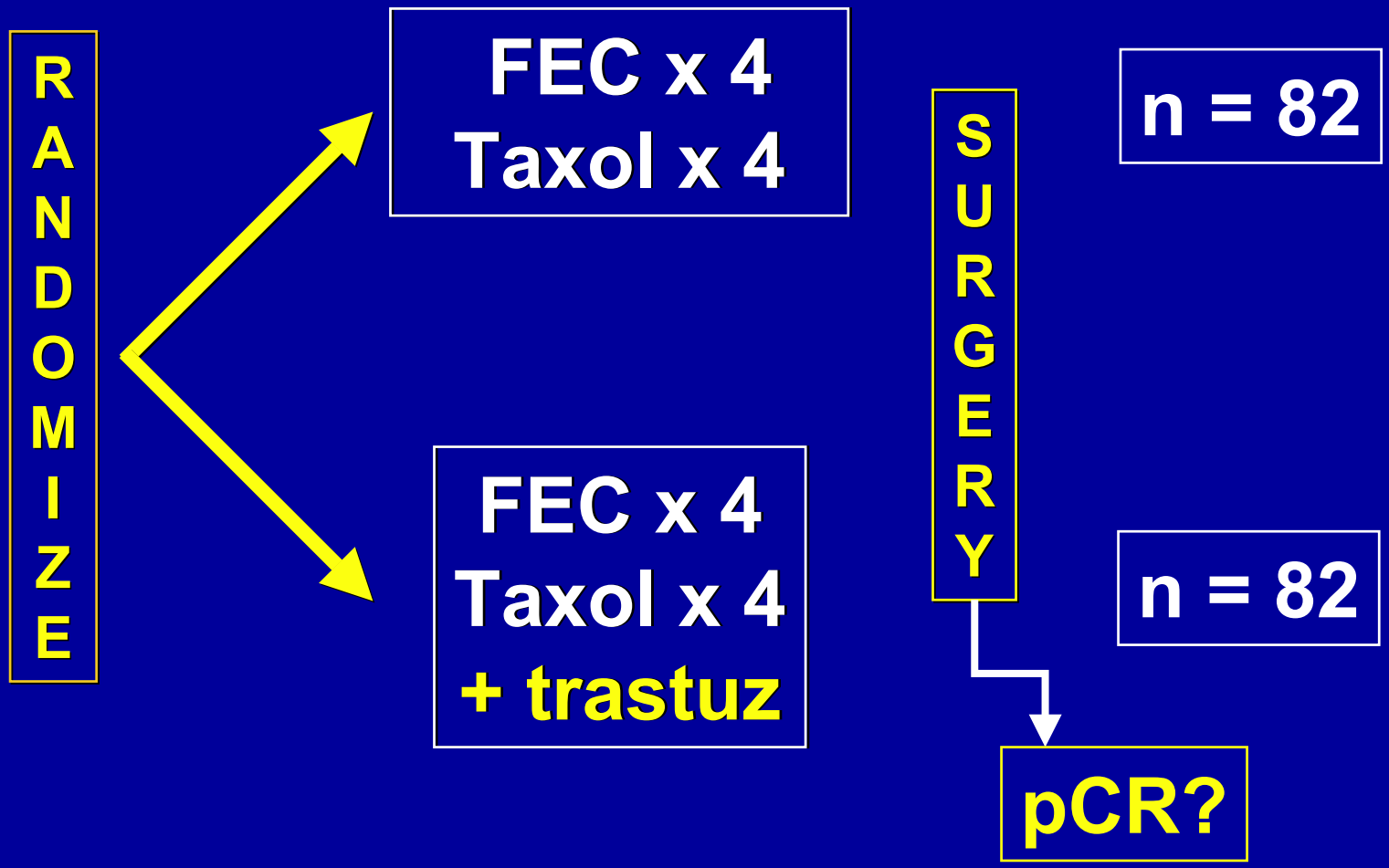
ATAC: N=9366



p=0.0013 for A vs T

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

Neoadjuvant Trastuzumab in HER2+ Breast Cancer*



*Buzdar et al, *JCO* (2005)

Data Monitoring Committee

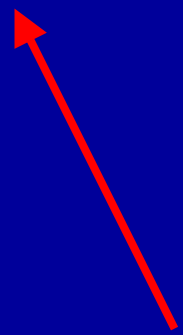
- Annual monitoring by DMC
- Interim results after 34 patients:

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)

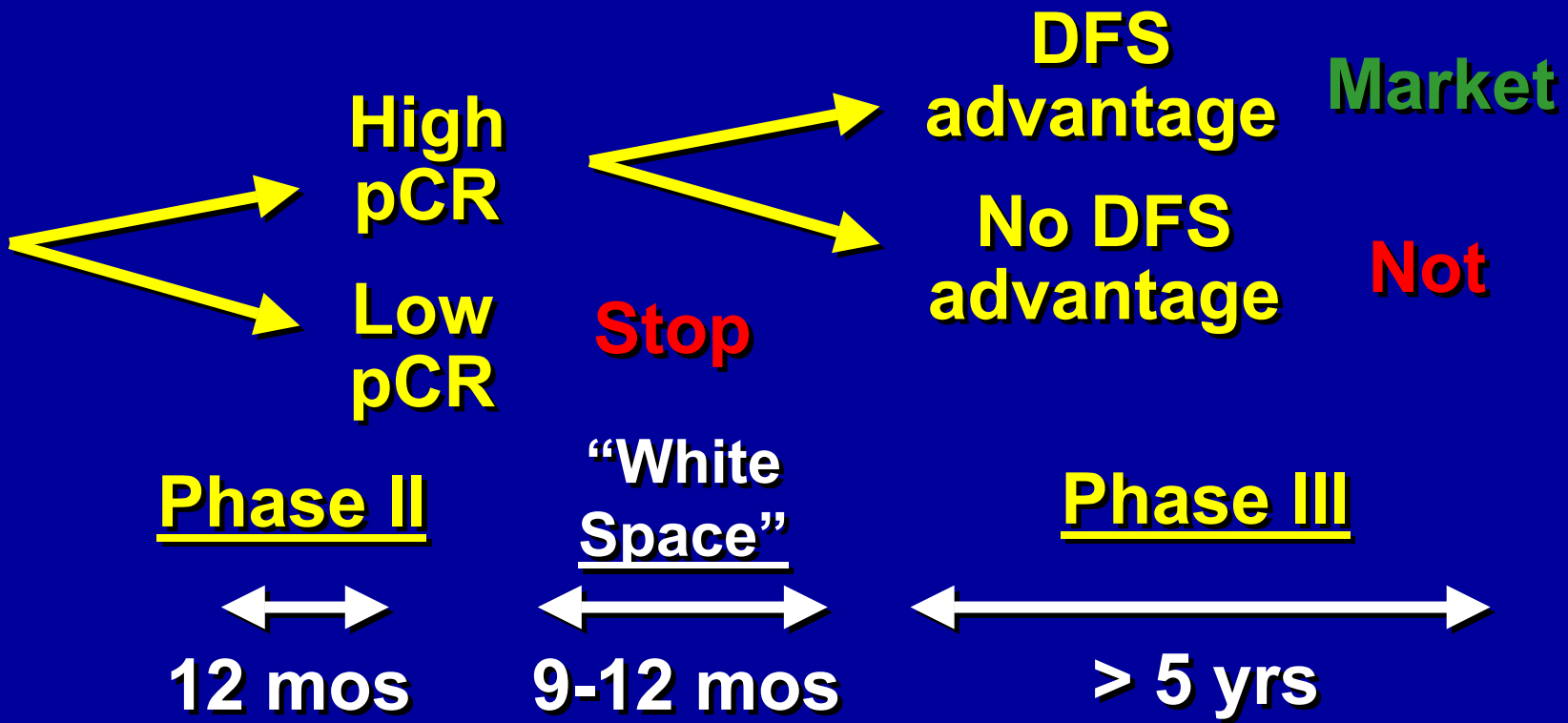
- "a response variable for which a test of the null hypothesis of no relation to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true endpoint."
- High hurdle: pCR doesn't qualify
- But pCR is useful nonetheless!

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



Seamless phase II/III

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

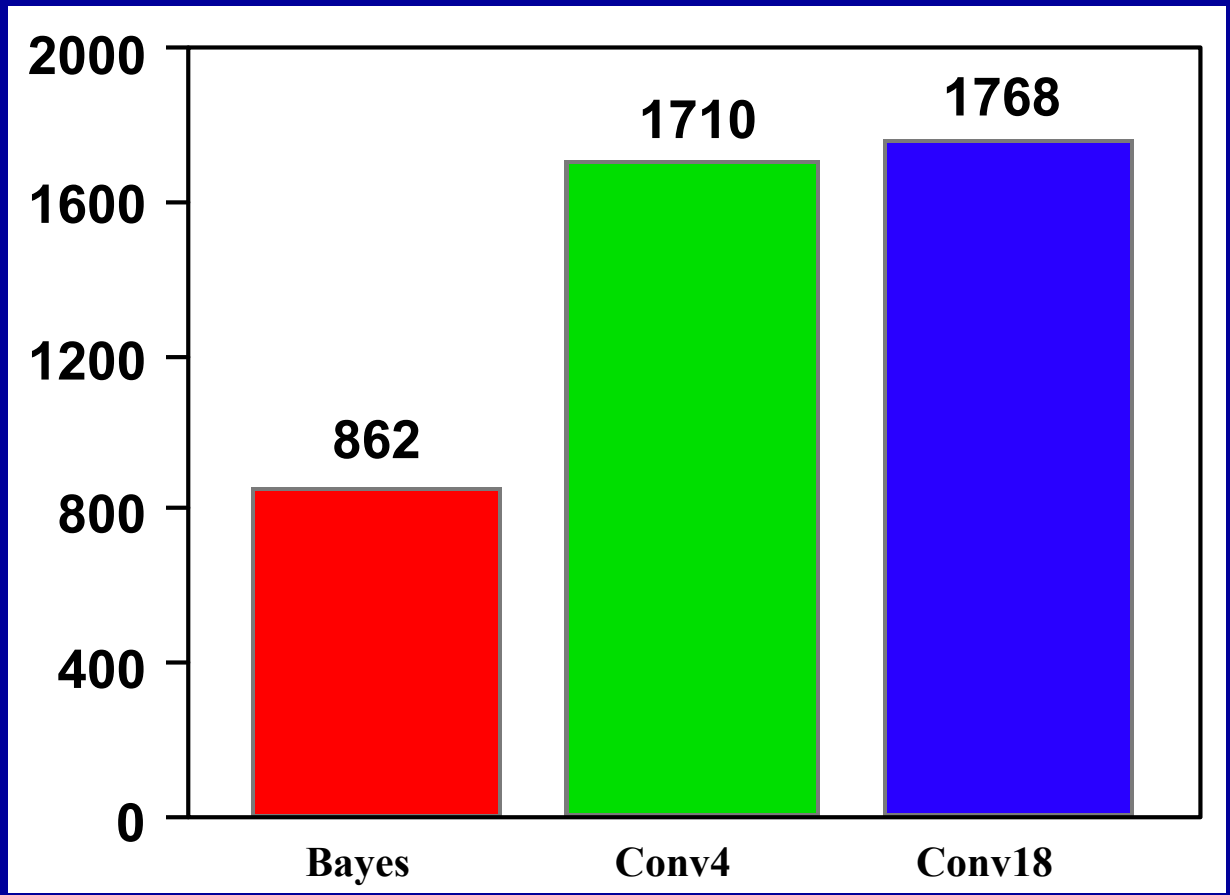
- Use pred probs of stat signif
- Frequent analyses (total of 18) using predictive probs to:
  - Switch to Phase III
  - Stop accrual for
    - Futility
    - Superiority

Comparisons

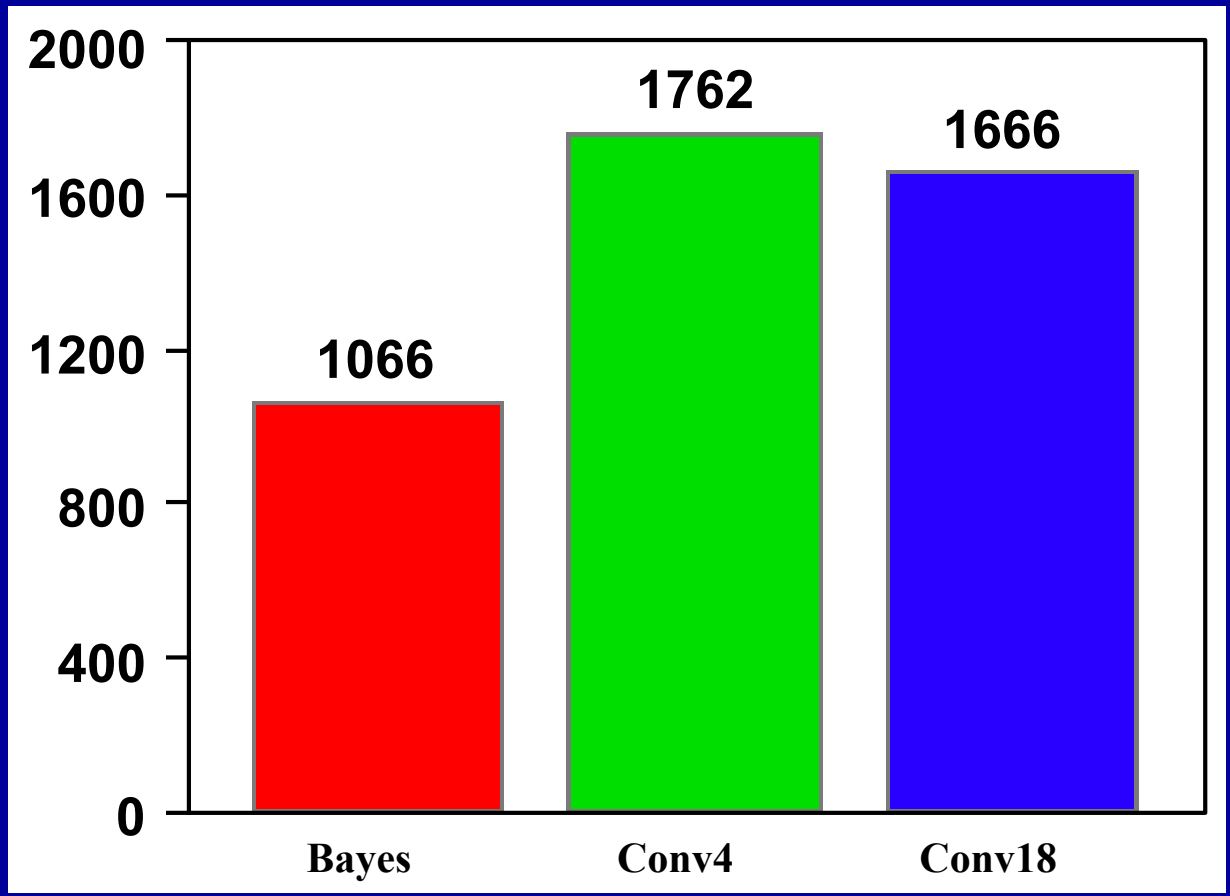
Conventional Phase III designs: Conv4 & Conv18, max N = 1800

(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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