# Adaptive Population Enrichment for Oncology Trials with Time to Event Endpoints

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## References and Acknowledgements


- Statistical research with Sebastien Irle and Helmut Schäfer, Institute of Medical Biometry, University of Marburg, Germany
- Problem formulation based on collaborations with the Pfizer Inc., and M.D. Anderson Cancer Center
- Key Reference:
  - Irle and Schäfer. "Interim design modifications in time-to-event studies." JASA, 2012; 107:341-348
- We thank Pranab Ghosh for expert programming of the simulation tools

## Outline of Talk

- Motivation for enrichment trials in oncology
- Adaptive enrichment design for PFS endpoints
- Statistical methodology
  - Conditional error function in time-to-event trials
  - Performing a closed test
- Simulation guided design
- Future directions



## Current State of Oncology Trials

- Failure rate for late stage oncology trials is almost 60% (Kola and Landis, 2004)
- Two recent scientific developments can improve this track record
  - development of molecularly targeted agents
  - statistical methodology of adaptive trial design applied to time-to-event data
- Fact: Some subgroups benefit differentially from others when treated with the targeted agent

## Oncology Products Approved in the US for Selected Patient Populations

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| Compound/Target | Indication (prevalence target) |
|---|---|
| Crizotinib (Xalkori®)/ ALK-rearrangement | •Non-small cell lung cancer with ALK-rearrangements (5%) |
| Vemurafenib (Zelboraf®)/ BRAF mutation | •Advanced melanoma with mutant BRAF (30-40%) |
| Trametinib (Mekinist™)/ MEK | •Advanced melanoma with mutant BRAF (30-40%) |
| Trastuzumab (Herceptin®); Lapatinib (Tykerb®)/ Her2 | •Her2 expressing breast cancer (25%)<br>•Her2 expressing metastatic gastric cancer (20-30%) |
| Aromatase inhibitors (letrozole, exemestane) | •ER(+) breast cancer (60-70%) |
| Rituximab (Rituxan®)/ CD20 | •CD20(+) B-cell lymphomas (90%+) |
| Cetuximab (Erbitux®); Panitumumab (Vectibix®) / EGFR | •Advanced Head/neck cancer (~100%)<br>•EGFR(+) metastatic colorectal cancer (60-80%)<br>•$KRAS^{WT}$ metastatic colorectal cancer (60%) |



## Considerations for Evaluation of Biomarker Predictivity

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- Randomize patients in both biomarker subgroups
- Evaluate predictivity in a phase 2 setting
  - Phase 3 requires validated companion diagnostic
- Issues to consider for the phase 2 trial
  - Strength of preclinical evidence
  - Prevalence of the marker
  - Sample size limitations (160-200 patients)
  - Time-to-event endpoint (PFS or OS)
  - No more than 3-year study duration
  - Reproducibility and validity of assays

## Features of an Adaptive Enrichment Design

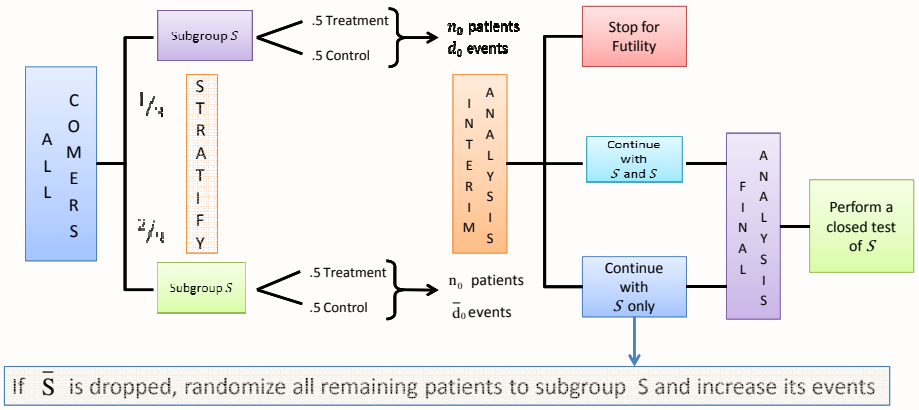
- Two-stage design: all comers at Stage 1
- Interim analysis at end of Stage 1, utilizing ALL available information (censored and complete)
- Adaptation decision implemented in Stage 2:
  - Proceed with no design change (except possible SSR)
  - Proceed with biomarker subgroup (and possible SSR)
  - Terminate for futility
- Perform a closed test for the final analysis



## Notation

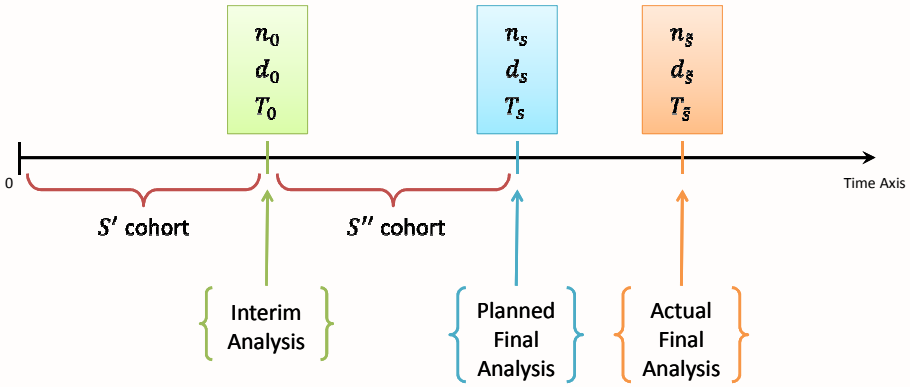
- 
- $S$ and $\bar{S}$ are biomarker subgroups
- n denotes sample size
- d denotes events
- T denotes the logrank statistic

## Schematic Representation of Protocol






## Time Line of S Subgroup



## Time Line of $\bar{S}$ Subgroup

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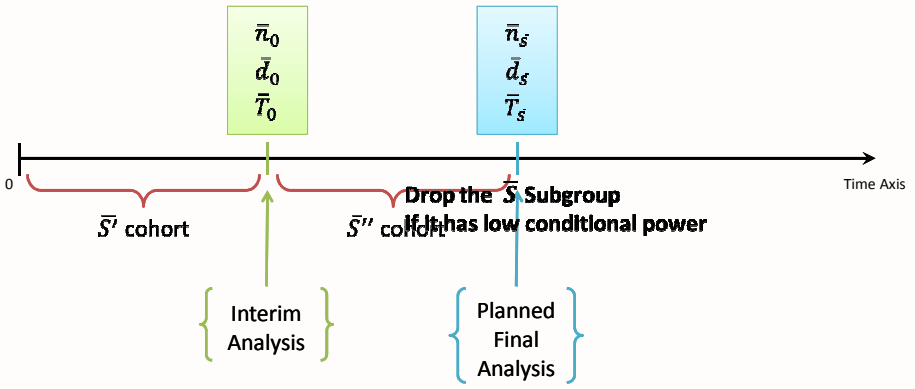




## Hypothesis Testing at Final Analysis (a) If you do not drop $\bar{S}$ at interim

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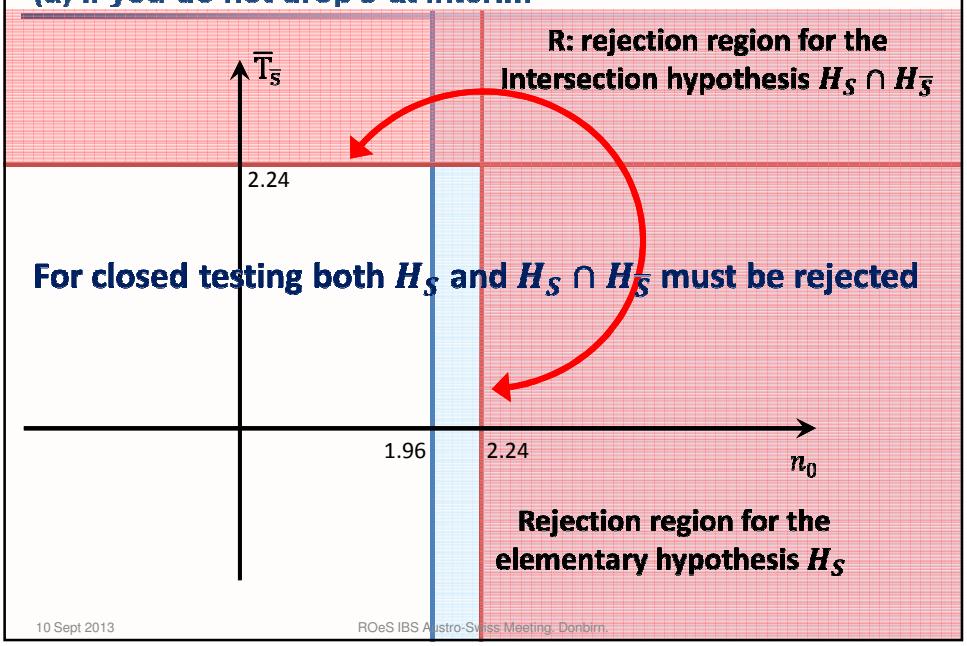

## Hypothesis Testing at Final Analysis (b) If you do drop $\bar{S}$ at interim

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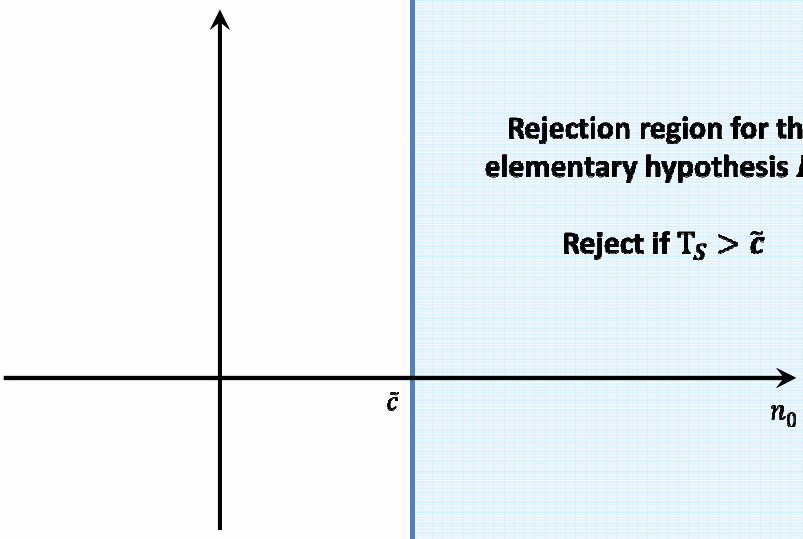




## Preserving Type-1 Error: CER Method 1 ( Mullër and Schafër, 2001)

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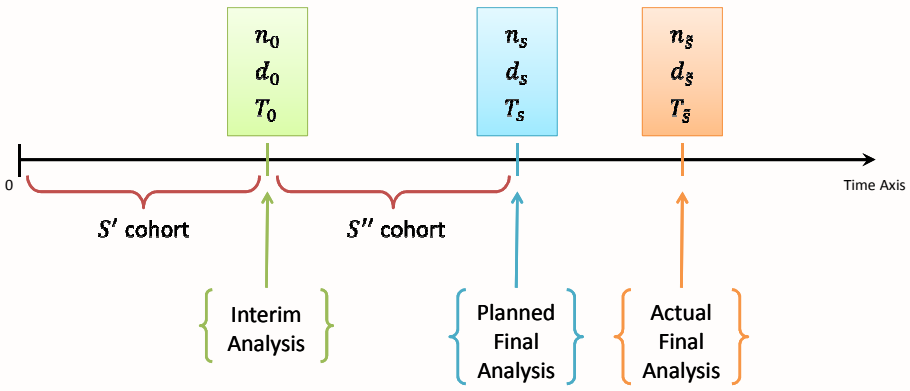


Reject $H_S$ if $T_{\bar{S}} \geq \tilde{c}$. To preserve type-1 error $\tilde{c}$ must satisfy:

$$P\{T_{\bar{S}} \geq \tilde{c} | T_0\} \leq P\{T_S \geq 1.96 | T_0\}$$
$$P\{T_{\bar{S}} \geq \tilde{c} | T_0\} \leq P\{(T_S, \overline{T}_{\overline{S}}) \in R | T_0, \overline{T}_0\}$$

## Comments on CER Method 1

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- Decision to drop $\bar{S}$ must only utilize the interim data from the patients for whom the event has occurred (Brannath et. al.,2009)
- Cannot utilize extra information in the censored observations such as tumor response
- This limitation is specific to survival data

**References:** Bauer and Posch (2004, *Stat. in Med*); Jenkins et. al. (2010, *Pharmaceut. Statist.*)



## Preserving Type-1 Error: Method 2 (Irle, Schafër,Mehta, 2012, methodology)

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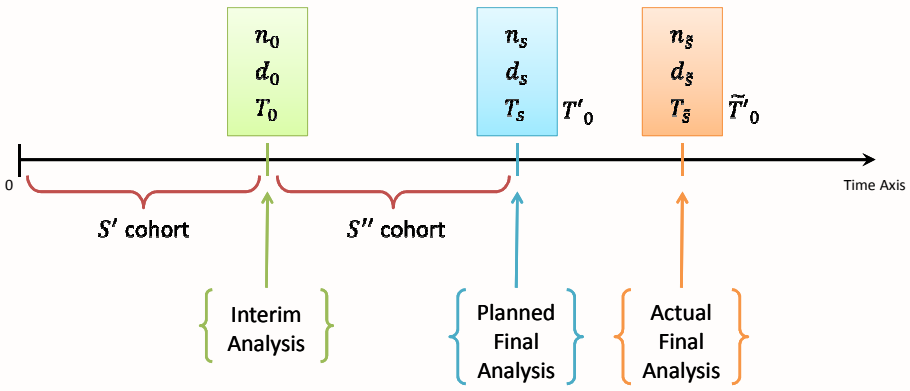


Reject $H_S$ if $T_{\bar{S}} \geq \tilde{c}$. To preserve type-1 error $\tilde{c}$ must satisfy:

$$P\{T_{\bar{S}} \geq \tilde{c} | \tilde{T}'_0\} \leq P\{T_S \geq 1.96 | T'_0\}$$
$$P\{T_{\bar{S}} \geq \tilde{c} | \tilde{T}'_0\} \leq P\{(T_S, \overline{T}_{\bar{S}}) \in R | T'_0, \overline{T}'_0\}$$

## Comments on CER Method 2

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- Conditions on future value of logrank statistic rather than value obtained at interim.
- Permits examination of all the interim data, not just the uncensored observations
- In particular, can combine short and long term data for interim decision making
- Related work of Jenkins, Stone, Jennison (2011):
  - Error control based on combination functions
  - Closed test of ($H_S$ and $H_{Full}$) not ($H_S$ and $H_{\bar{S}}$)

**Ref:** Irle and Schäfer. "Interim design modifications in time-to-event studies." JASA, 2012; 107:341-348



## The setting for a simulation guided design

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- Phase 2 trial of metastatic non-small cell lung cancer
- Sample size limit of N = 160 patients with 80 for each subgroup
- Primary endpoint is progression free survival (PFS)
- Median PFS for control arm is 5 months
- Prior evidence that subgroup S (EGFR mutation) is predictive of PFS:
  - HR(S) = 0.5, 06 is plausible
  - HR($\bar{S}$) < 0.7 is unlikely

## Decision Rule for Dropping $\bar{S}$ at Interim

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- Based on conditional power (CP)
- Drop $\bar{S}$ if CP($\bar{S}$) < A and CP(S) > B
- Desirable properties of a good decision rule:
  - If HR(S) is small and HR($\bar{S}$) is large, decision rule should **reject** $H_S$ and **accept** $H_{\bar{S}}$
  - If HR(S) and HR($\bar{S}$) are both small, decision rule should **reject** $H_S$ and **reject** $H_{\bar{S}}$
- Phase 2 results should guide Phase 3 design



## Use Phase 2 Simulations to Guide Phase 3 Go/No-Go/Enrich Decisions

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Decision rules for initiating a Phase 3 trial based on the results of the Phase 2 adaptive enrichment trial

| Phase 2 Outcome: | Decision Rule for Phase 3 |
|---|---|
| Win on S; Lose on $\bar{S}$ | Initiate Phase 3 in S only |
| Win on S; Win on $\bar{S}$ | Initiate Phase 3 in S and $\bar{S}$ |
| Lose on S; Win on $\bar{S}$ | No Go/investigate |
| Lose on S; Lose on $\bar{S}$ | No Go |

## Drop $\bar{S}$ if CP($\bar{S}$) < 0.5 and CP(S) > 0

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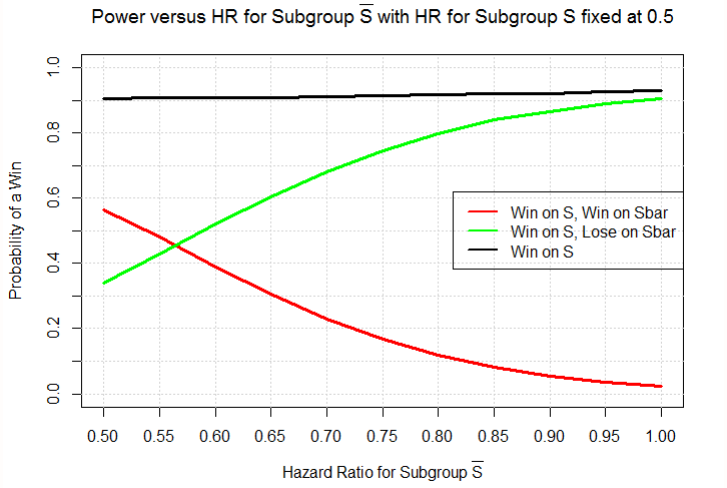


Assume HR(S) = 0.5



## Drop $\bar{S}$ if CP($\bar{S}$) < 0.5 and CP(S) > 0.5

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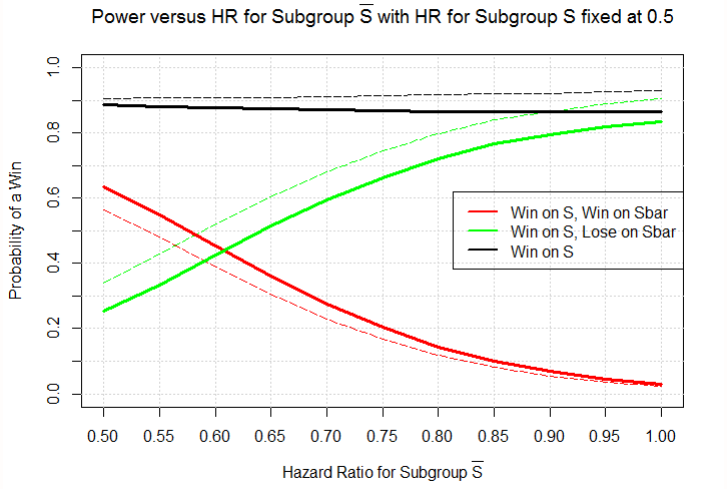


Assume HR(S) = 0.5

## Never Drop $\bar{S}$ (apply closed test only)

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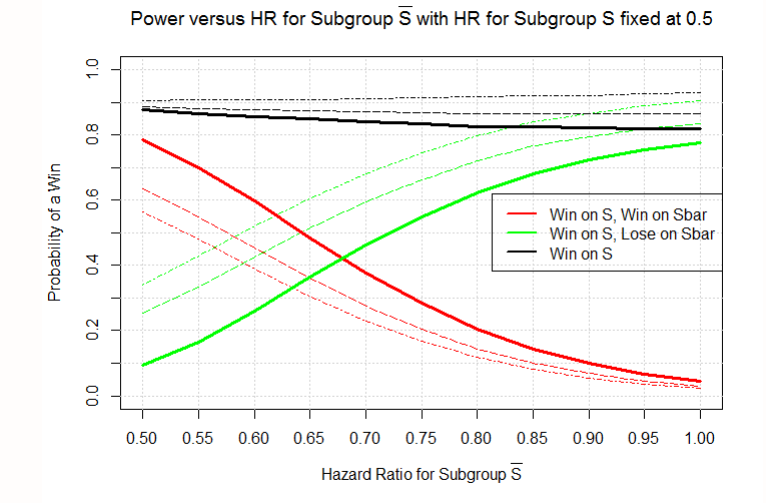


Assume HR(S) = 0.5



## Concluding Remarks and Future Work

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- Phase 2 trial produces go/no-go/enrich Phase 3 decision
- Simulate Phase 2 trial under scenarios where biomarker is predicitve and where it is prognostic
- Use simulation results to caliberate the performance of the go/no-go/enrich decision rules
- Improve the criteria for dropping $\bar{S}$ or for futility termination at interim analysis:
  - Utilize the information in the censored observations
  - Use Bayesian model incorporating tumor response and PFS for sharper criteria
- Consider modeling both Phase 2 and Phase 3