

Adaptive Designs for Survival Studies with Subgroup Selection based on Predictive Biomarkers

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Problem Definition

Targeted Therapies in Oncology

- Tumours are heterogeneous \Rightarrow Only some patients may benefit
- Recruit patients with a certain type of cancer
- Might draw wrong conclusion or even miss an effective agent!

Idea

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Illustration: KRAS Biomarker

Panitumumab

- Metastatic colorectal cancer
- Monoclonal antibody directed at EGFR
- Subgroups KRAS mutant & wild-type [Amado et al., 2008]

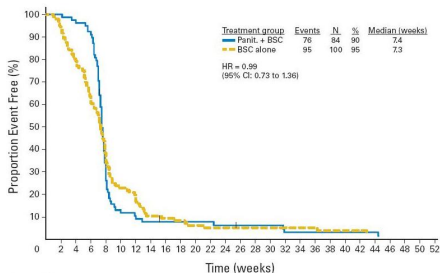


Figure: Outcome for KRAS mutant tumour patients - Amado et al (2008) JCO, 26

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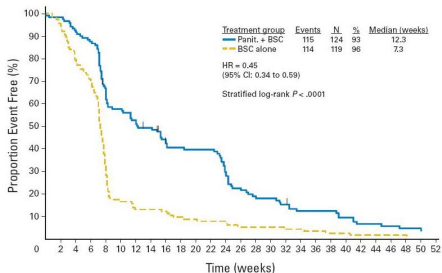


Figure: Outcome for KRAS wild-type tumour patients - Amado et al (2008) JCO, 26

General Design Framework

Test Statistics

Efficient score $Z = \frac{\partial \ell(0)}{\partial \theta}$: cumulative measure of advantage of experimental treatment E over control C

(Observed) Fisher's information $V = -\frac{\partial^2 \ell(0)}{\partial \theta^2}$: amount of information on treatment difference contained in Z

- θ - Measure of treatment difference
- Under H_0 : $\frac{Z}{\sqrt{V}} \sim N(0, 1)$ (Score test)
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 - Final analysis Z_S
 - V correspondingly

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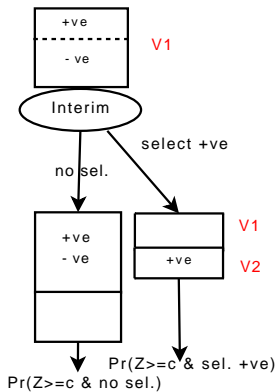
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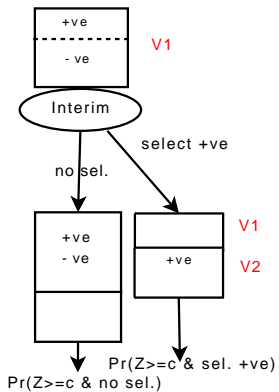
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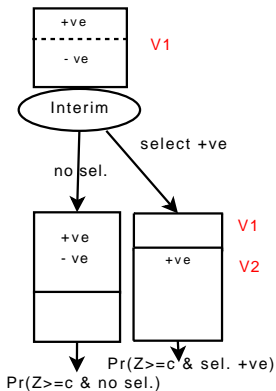
Design Illustration



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Cochran's Q test

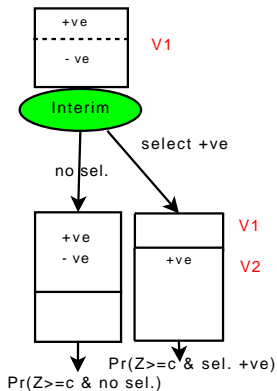
$$Q = \sum_{i=1}^m (\hat{\theta}_i - \hat{\theta})^2 \omega_i$$

In terms of Z and V:

$$Q = \frac{Z_{+,1}V_{-,1} - Z_{-,1}V_{+,1}}{\sqrt{(V_{+,1} + V_{-,1})V_{+,1}V_{-,1}}}$$

Subgroup selection if: $Q \sim N(0, 1) \geq k$

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Interim Analysis in Detail

Futility Stopping Criterion

- Cond. power (CP) approach
- CP stopping unlikely if early in study
 \Rightarrow stop if:

$$\text{CP}_{\theta_R}(V) \leq 1 - \beta_{CP}$$

or $Z_{i,1} \leq 0, \quad i \in \{+, B\}$

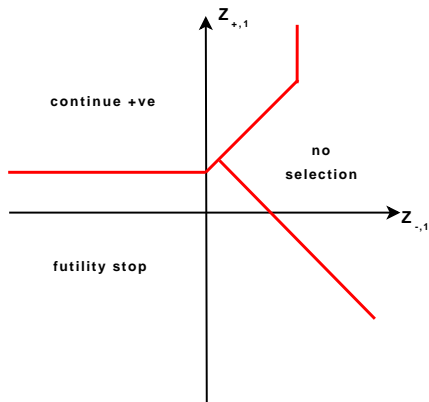
for respective interim decision

Upper Selection Limit Criterion

- Undesireable to select if drug has certain effect in -ve patients
- Do not select +ve patients if:

$$\hat{\theta}_{-,1} \geq \tau\theta_R, \quad 0 < \tau \leq \lambda$$

Natural choice $\tau = 1$



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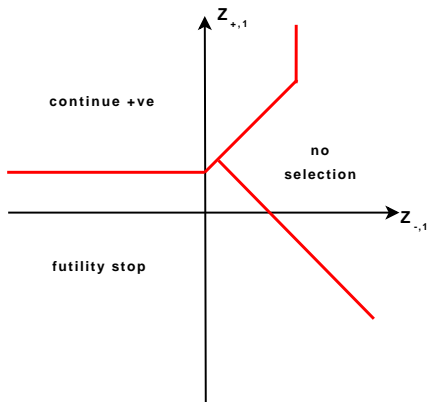
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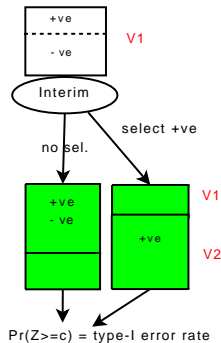
Power Requirements

Power Requirement I

- Study-wise type-I error rate
- $\Pr(Z_S \geq c \mid \theta_+ = \theta_- = 0) = \alpha$

Power Requirement II

- $\Pr(Z_S \geq c \cap \text{no sel.} \mid \theta_+ = \theta_- = \theta_R) = 1 - \beta_B = \text{Power}_B$
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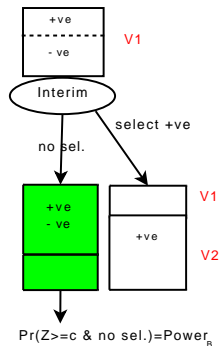
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Power Requirement III

- $\Pr(Z_S \geq c \cap \text{sel +ve} \mid \theta_+ = \lambda\theta_R, \theta_- = 0) = 1 - \beta_+ = \text{Power}_+$
- $\lambda \geq 1 \Rightarrow$ demand larger effect for selection



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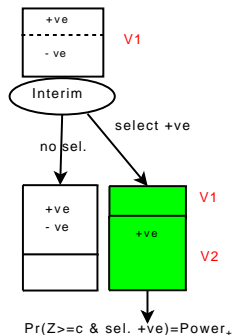
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Calculation of Design Variables

Score function properties:

- ① Approximately $Z \sim N(\theta V, V)$
- ② Independent increment structure

Numerical root finding procedure

For each Power Requirement:

$$\Pr(Z_S \geq c) = \sum_i \int_{l_i^-}^{u_i^-} \int_{l_i^+}^{u_i^+} \left\{ 1 - \Phi\left(\frac{c - (z \cdot) - \theta_j(V_S - V_{\cdot,1})}{\sqrt{V_S - V_{\cdot,1}}}\right) \right\} f(z_+) f(z_-) dz_+ dz_-,$$

where $f(z) = \frac{1}{\sqrt{V}} \phi\left(\frac{z - \theta V}{\sqrt{V}}\right)$

Design Framework for Survival Outcome

Superiority Trial

- Outcome: time to unfavourable event
- $S_E(t), S_C(t)$ survival probabilities
- $H_0 : \theta = 0$ vs $H_1 : \theta > 0$

Proportional Hazard Model

- Assumption: $h_E(t) = \psi h_C(t), t > 0$
- Parameterisation: $\theta = -\log(h_E(t)/h_C(t))$

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Exponential assumption

- Survival times $EXP(\gamma_i)$ distributed
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Design Framework for Survival Outcome II

Design specification

- Specify trial in terms of time units (weeks) and no. patients
- Conduct trial in terms of V
- Recruit +ve and -ve patients according to population proportion

At the design stage calculate:

- Expected no. of events e
- $V \approx e/4$ (1:1 allocation ratio)

Example KRAS study

Pre-specified values:

- Power req.: $\alpha = 0.025$, $1 - \beta_B = 0.9$, $1 - \beta_+ = 0.9$
- Study duration: recruit 75 weeks, follow up 50 weeks, interim at week 50
- Treat. effect: $S_C(t_0) = 0.10$, $S_E(t_0) = 0.20$, $t_0 = 20$, $\lambda = 2.6$

Search procedure results:

| $S_E^+(t_0)$ | a | n | n^+ | k | c | $V_{1,+}$ | $V_{1,-}$ | V_S |
|--------------|-----|-----|-------|-------|-------|-----------|-----------|--------|
| 0.407 | 4.9 | 368 | 243 | 1.988 | 2.233 | 20.05 | 18.73 | 58.250 |

Table: Calculation of design variables for KRAS biomarker study

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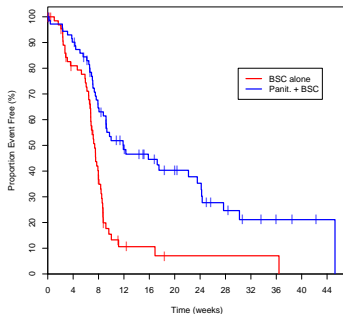
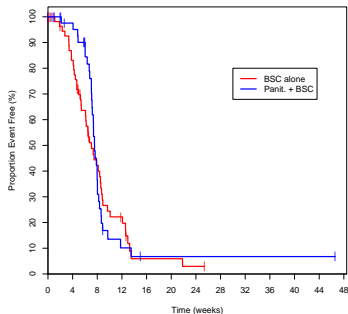


Figure: Interim outcome for mutant type

Figure: Interim outcome for wild type

- 252 patients recruited at interim: $Q = 2.958 \Rightarrow$ select wild-type
- Recruit remaining patients:
 $Z_S = Z_{+,1} + Z_2 = 38.9$, $V_S = V_{1,+} + V_2 = 47.947$
- p-value 0.000237 \Rightarrow Panitumumab significantly better for wild-type patients

Simulation study

| $S_E^+(t_0)$ | $S_E^-(t_0)$ | $S_C(t_0)$ | n | +ve | adaptive design | | |
|--------------|--------------|------------|-----|-----------|-----------------|--------|--------|
| | | | | selection | EP_O | EP_B | EP_+ |
| 0.25 | 0.25 | 0.25 | 358 | 3.13% | 0.049 | 0.043 | 0.006 |
| 0.40 | 0.40 | 0.25 | 358 | 3.5% | 0.9329 | 0.8989 | 0.034 |
| 0.671 | 0.25 | 0.25 | 358 | 87.68% | 0.9886 | 0.1119 | 0.8767 |

Table: Simulation results for the adaptive method. EP denotes the estimated power based on 20,000 simulated trials.

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Summary

- ① Developed a method that allows to draw inference for all patients in the trial or a subgroup
- ② Flexible approach that is useful if uncertainty exists about target population in late stage trial
- ③ Greater power than fixed sample trial designs in appropriate scenario and allows to draw more accurate conclusion
- ④ Problems:
 - Inefficient for survival endpoint setting where median survival rate is large
 - Point estimates (biased) and CIs

Other Survival designs

Weibull distribution

Modelling:

Survival $Weib(\gamma, \tau)$, Loss to follow-up $Weib(\nu, \tau)$

Discrete approximation

Anticipate $S_C(t_i), i = 1, \dots, G + F$

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References



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