UniversitätsKlinikum Heidelberg

Optimal Subgroup Selection Rules in Adaptive Oncology Trials with Time-to-Event Outcome

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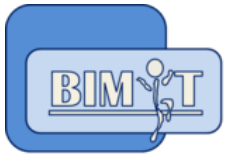

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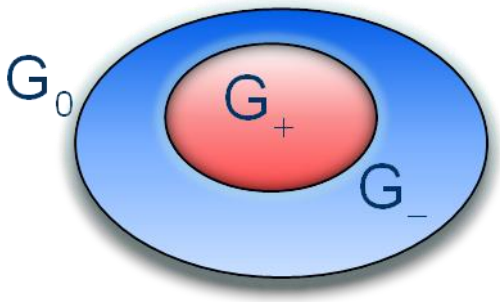
Outline

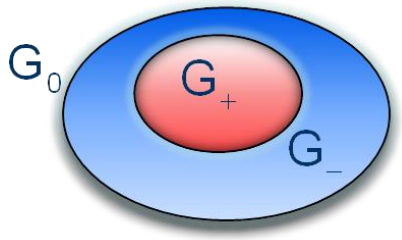
- Introducing background and basic notation and the statistical model
- Calculating optimal decision rules in case of uncertainty about trial design parameters for the situation of a time-to-event endpoint
- Deriving optimal decision rules based on data from a clinical trial example and comparing them to fixed *ad hoc* rules in terms of correct selection probability

Background

- Total patient population G_0
- Prospectively defined subgroup G_+
  - potentially increased benefit
  - identified by biomarker
- Complementary subgroup $G_- := G_0 \setminus G_+$
- Selection of the target population based on data
  - (pilot / phase II) study A $\rightarrow$ (pivotal / phase III) study B
  - first stage $\rightarrow$ second stage of adaptive seamless design (e.g. Jenkins et al., 2011; Brannath et al., 2011; Friede et al., 2012)

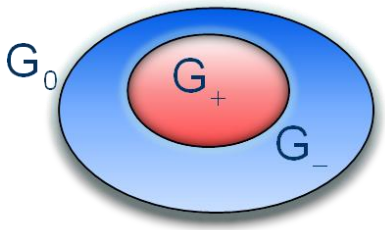


Assumptions and notations



- Assumptions:
  - time-to-event-outcome
  - two balanced groups T(=treatment), C(=control)
- Notations:
  - M_{iP} : median event times for patients from treatment group $i = T, C$ and subgroup G_P with $P = +, -$
  - Δ_P : logarithm of the hazard ratio in subgroup G_P with $P = 0, +, -$
  - π : prevalence of subgroup G_+
  - d : number of accumulated events per stage

Basics



- Let

$$\widehat{\Delta}_+ := U_+ \cdot 2/\sqrt{d_+}, \qquad \widehat{\Delta}_-: = U_- \cdot 2/\sqrt{d_-}, \qquad \widehat{\Delta}_0 := U_0 \cdot 2/\sqrt{d},$$

where U_P and are the „unsquared“ versions of the (stratified) log rank test statistics and, respectively, d_P the accumulated number of events in population $P = 0, +, -$.

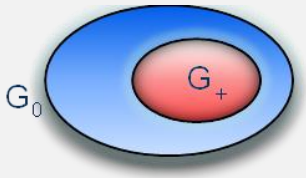
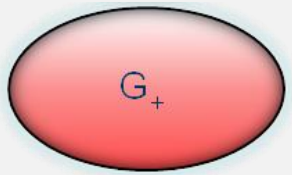
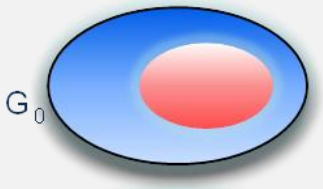
- If (Δ_+, Δ_0) are not „too far“ away from 0, $(\widehat{\Delta}_+, \widehat{\Delta}_0)$ are estimators for the log hazard ratios (Wassmer 2005), and (Brannath et al. 2009) can be assumed to be approximately normal with

$$(\widehat{\Delta}_+, \widehat{\Delta}_0)|\Delta_+, \Delta_0 \sim N\left[(\Delta_+, \pi\Delta_+ + (1-\pi)\Delta_-), \begin{pmatrix} 4/\pi d & 4/d \\ 4/d & 4/d \end{pmatrix}\right],$$

assuming πd events occurred in G_+ at interim.

Example for a decision rule

- Decision rule proposed by Jenkins et al. 2011:

Log hazard ratio estimates at interim	$\hat{\Delta}_0 > c_0$	$\hat{\Delta}_0 \leq c_0$
$\hat{\Delta}_+ > c_+$		
$\hat{\Delta}_+ \leq c_+$		

- **How to choose (c_0, c_+) in case of uncertain $\Delta_0, \Delta_+, \Delta_-$?**

Jenkins M, Stone A, Jennison C (2011). An adaptive seamless phase II/III design for oncology trials with subpopulation selection using correlated survival endpoints. *Pharmaceutical Statistics* **10**: 347-356.

Optimal decision rules

- Assumptions:
  - selection of G_0 desired if $\Delta_0 > \tau_0$
  - selection of G_+ desired if $\Delta_+ > \tau_+$
  - Normal prior distribution assumed for either

    a) (Δ_0, Δ_+) with

    $$(\Delta_0, \Delta_+) \sim N\left[(m_0, m_+), \begin{pmatrix} w_0 & \rho_a\sqrt{w_0 w_+} \\ \rho_a\sqrt{w_0 w_+} & w_+ \end{pmatrix}\right] \text{ or}$$

    b) (Δ_+, Δ_-) with

    $$(\Delta_+, \Delta_-) \sim N\left[(m_+, m_-), \begin{pmatrix} w_+ & \rho_b\sqrt{w_+ w_-} \\ \rho_b\sqrt{w_+ w_-} & w_- \end{pmatrix}\right]$$

  - quadratic loss function for wrong decision

  → **optimal decision rule minimizes expected loss (“risk”)**

Optimal decision rules (2)

- Under the previous assumptions, an optimal decision threshold pair (c_0^*, c_+^*) can be explicitly determined:

a) assuming a normal prior for (Δ_0, Δ_+), the threshold pair is

$$(c_0^*, c_+^*) = \left(-\frac{4(m_0 - \tau_0)}{dw_0} + \tau_0, -\frac{4(m_+ - \tau_+)}{\pi dw_+} + \tau_+ \right),$$

Optimal decision rules (2)

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b) assuming a normal prior for (Δ_+, Δ_-), the threshold pair is

$$(c_0^*, c_+^*) = \left(-\frac{4(\pi m_+ + (1-\pi)m_- - \tau_0)}{d(\pi^2 w_+ + 2\pi(1-\pi)\rho_b\sqrt{w_+ w_-} + (1-\pi)^2 w_-)} + \tau_0, -\frac{4(m_+ - \tau_+)}{\pi dw_+} + \tau_+ \right).$$

General remarks on optimal decision rules

a) Assuming a normal prior for (Δ_0, Δ_+), the threshold pair is

$$(c_0^*, c_+^*) = \left(-\frac{4(m_0 - \tau_0)}{\boldsymbol{d} w_0} + \tau_0, -\frac{4(m_+ - \tau_+)}{\pi \boldsymbol{d} w_+} + \tau_+ \right),$$

b) assuming a normal prior for (Δ_+, Δ_-), the threshold pair is

$$(c_0^*, c_+^*) = \left(-\frac{4(\pi m_+ + (1-\pi) m_- - \tau_0)}{\boldsymbol{d}(\pi^2 w_+ + 2\pi(1-\pi)\rho_b \sqrt{w_+ w_-} + (1-\pi)^2 w_-)} + \tau_0, -\frac{4(m_+ - \tau_+)}{\pi \boldsymbol{d} w_+} + \tau_+ \right).$$

- For an increasing number of events d, (c_0^*, c_+^*) converge towards (τ_0, τ_+).

General remarks on optimal decision rules (2)

a) Assuming a normal prior for (Δ_0, Δ_+), the threshold pair is

$$(c_0^*, c_+^*) = \left(-\frac{4(\boldsymbol{m_0 - \tau_0})}{dw_0} + \tau_0, -\frac{4(\boldsymbol{m_+ - \tau_+})}{\pi dw_+} + \tau_+ \right),$$

b) assuming a normal prior for (Δ_+, Δ_-), the threshold pair is

$$(c_0^*, c_+^*) = \left(-\frac{4(\boldsymbol{\pi m_+ + (1-\pi) m_- - \tau_0})}{d(\pi^2 w_+ + 2\pi(1-\pi)\rho_b\sqrt{w_+ w_-} + (1-\pi)^2 w_-)} + \tau_0, -\frac{4(\boldsymbol{m_+ - \tau_+})}{\pi dw_+} + \tau_+ \right).$$

- Whether c_0^*/c_+^* lies above or below τ_0/τ_+ is determined via the sign of $(\pi m_+ + (1-\pi)m_-) - \tau_0/m_0 - \tau_0/m_+ - \tau_+$, and the smaller the respective difference, the closer c_i^* will be to τ_i, $i = 0, +$.

General remarks on optimal decision rules (3)

a) Assuming a normal prior for (Δ_0, Δ_+), the threshold pair is

$$(c_0^*, c_+^*) = \left(-\frac{4(m_0 - \tau_0)}{d\boldsymbol{w_0}} + \tau_0, -\frac{4(m_+ - \tau_+)}{\pi d\boldsymbol{w_+}} + \tau_+ \right),$$

b) assuming a normal prior for (Δ_+, Δ_-), the threshold pair is

$$(c_0^*, c_+^*) = \left(-\frac{4(\pi m_+ + (1-\pi)m_- - \tau_0)}{d(\pi^2 \boldsymbol{w_+} + 2\pi(1-\pi)\rho_b\sqrt{\boldsymbol{w_+ w_-}} + (1-\pi)^2 \boldsymbol{w_-})} + \tau_0, -\frac{4(m_+ - \tau_+)}{\pi d\boldsymbol{w_+}} + \tau_+ \right).$$

- The larger the prior variances $w_i,\ i = 0, +, -,$ the closer the optimal decision thresholds c_i^* are to $\tau_i,\ i = 0, +.$

General remarks on optimal decision rules (4)

a) Assuming a normal prior for (Δ_0, Δ_+), the threshold pair is

$$(c_0^*, c_+^*) = \left(-\frac{4(m_0 - \tau_0)}{dw_0} + \tau_0, -\frac{4(m_+ - \tau_+)}{\pi d w_+} + \tau_+ \right),$$

b) assuming a normal prior for (Δ_+, Δ_-), the threshold pair is

$$(c_0^*, c_+^*) = \left(-\frac{4(\pi m_+ + (1-\pi)m_- - \tau_0)}{d(\pi^2 w_+ + 2\pi(1-\pi)\boldsymbol{\rho_b}\sqrt{w_+ w_-} + (1-\pi)^2 w_-)} + \tau_0, -\frac{4(m_+ - \tau_+)}{\pi d w_+} + \tau_+ \right).$$

- Only in case the optimal decision thresholds are modelled via (Δ_+, Δ_-), they are affected by the prior correlation ρ_b, and for a higher correlation, c_+^* is closer to τ_+.

General remarks on optimal decision rules (5)

a) Assuming a normal prior for (Δ_0, Δ_+), the threshold pair is

$$(c_0^*, c_+^*) = \left(-\frac{4(m_0 - \tau_0)}{dw_0} + \tau_0, -\frac{4(m_+ - \tau_+)}{\boldsymbol{\pi} dw_+} + \tau_+ \right),$$

b) assuming a normal prior for (Δ_+, Δ_-), the threshold pair is

$$(c_0^*, c_+^*) = \left(-\frac{4(\pi m_+ + (1-\pi) m_- - \tau_0)}{d(\pi^2 w_+ + 2\pi(1-\pi)\rho_b \sqrt{w_+ w_-} + (1-\pi)^2 w_-)} + \tau_0, -\frac{4(m_+ - \tau_+)}{\boldsymbol{\pi} dw_+} + \tau_+ \right).$$

- The larger the subgroup prevalence π, the closer c_+^* is to τ_+.

Clinical trial example

- Histone deacetylase inhibitors (HDACis) have been shown to overcome resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) linked to epigenetic changes.

- In a randomized phase II trial (n=132) study, the overall survival of erlotinib with and without the isoform selective HDACi, **entinostat**, was evaluated for NSCLC-patients who progressed on a prior chemotherapy. (Witta et al., 2012)

Witta SE et al. (2012). Randomized phase II trial of erlotinib with and without entinostat in patients with advanced non–small-cell lung cancer who progressed on prior chemotherapy. *Journal of Clinical Oncology*, **30**(18), 2248-2255.

Clinical trial example (2)

- Entinostat showed promising results in both the total patient population as well as in several subgroups (Witta et al. 2012):

	Erlotinb + Placebo Median	Erlotinib + Entinostat Median	Hazard Ratio	95% CI
All subjects (n = 132)	6.7	8.9	0.85	0.59 to 1.23
Ecad 0, +1, +2 (n = 40)	7.0	4.4	0.94	0.47 to 1.89
Ecad +3 (n = 26)	5.4	9.4	0.35	0.13 to 0.92
Ecad H score ≤ 150 (n = 33)	8.2	6.1	0.96	0.44 to 2.10
Ecad H score >150 (n = 30)	4.6	8.0	0.45	0.19 to 1.04
EGFR-FISH positive (n = 29)	10.3	7.7	1.14	0.49 to 2.65
EGFR-FISH negative (n = 30)	4.8	7.1	0.57	0.25 to 1.33
KRAS mutant = yes (n = 11)	8.2	NR	0.24	0.03 to 2.12
KRAS mutant = no (n = 72)	5.9	8.4	0.71	0.43 to 1.18

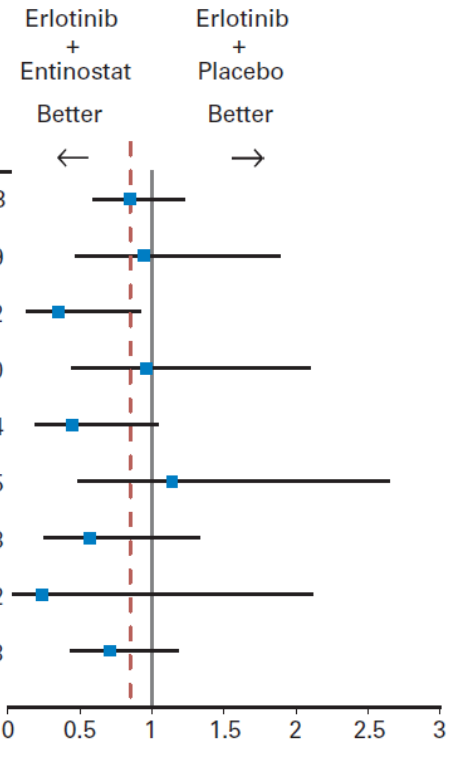

Fig 3. Forest plot of median overall survival and associated hazard ratios by biomarker status. Ecad, E-cadherin; EGFR, epidermal growth factor receptor; FISH, fluorescent in situ hybridization; KRAS, Kirsten rat sarcoma viral oncogene homolog.

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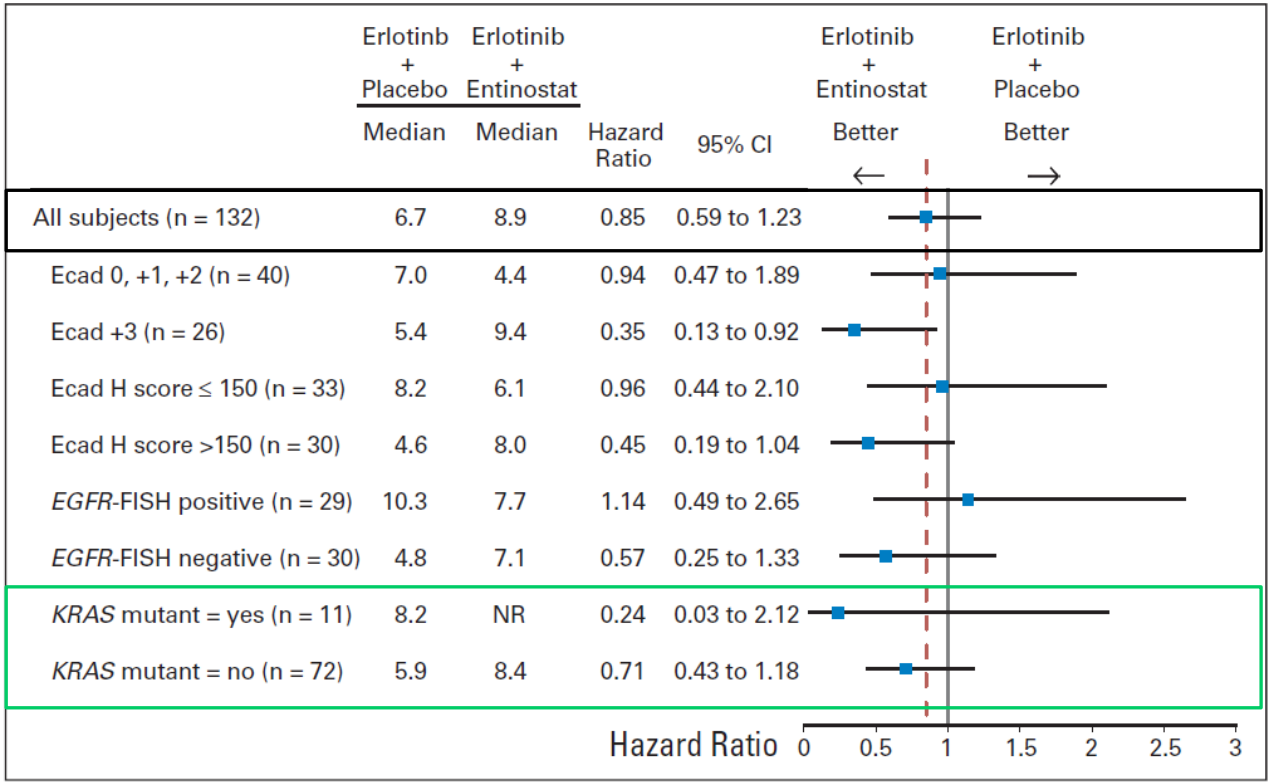

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Clinical trial example: Determination of prior distributions

- Considering the fact that Entinostat showed both a highly increased benefit in the subgroup of KRAS mutant as compared to KRAS wildtype, the proof of efficacy of entinostat within an **adaptive enrichment design** with G_+ being KRAS mutant might be pursued.
- Prior distributions can be obtained from the study by Witta et al. 2012 via choosing
  - m_i as the negative logarithm of the reported hazard ratios.
  - w_i as the squared standard error of the estimated log hazard ratios (can be computed from the reported confidence intervals).
- Since the correlation ρ_b can only be meaningfully estimated by several studies at hand, it is set here to 0.

Witta SE et al. (2012). Randomized phase II trial of erlotinib with and without entinostat in patients with advanced non–small-cell lung cancer who progressed on prior chemotherapy. *Journal of Clinical Oncology*, **30**(18), 2248-2255.

Clinical trial example: Determination of prior distributions (2)

- This yields the following parameters for the respective priors

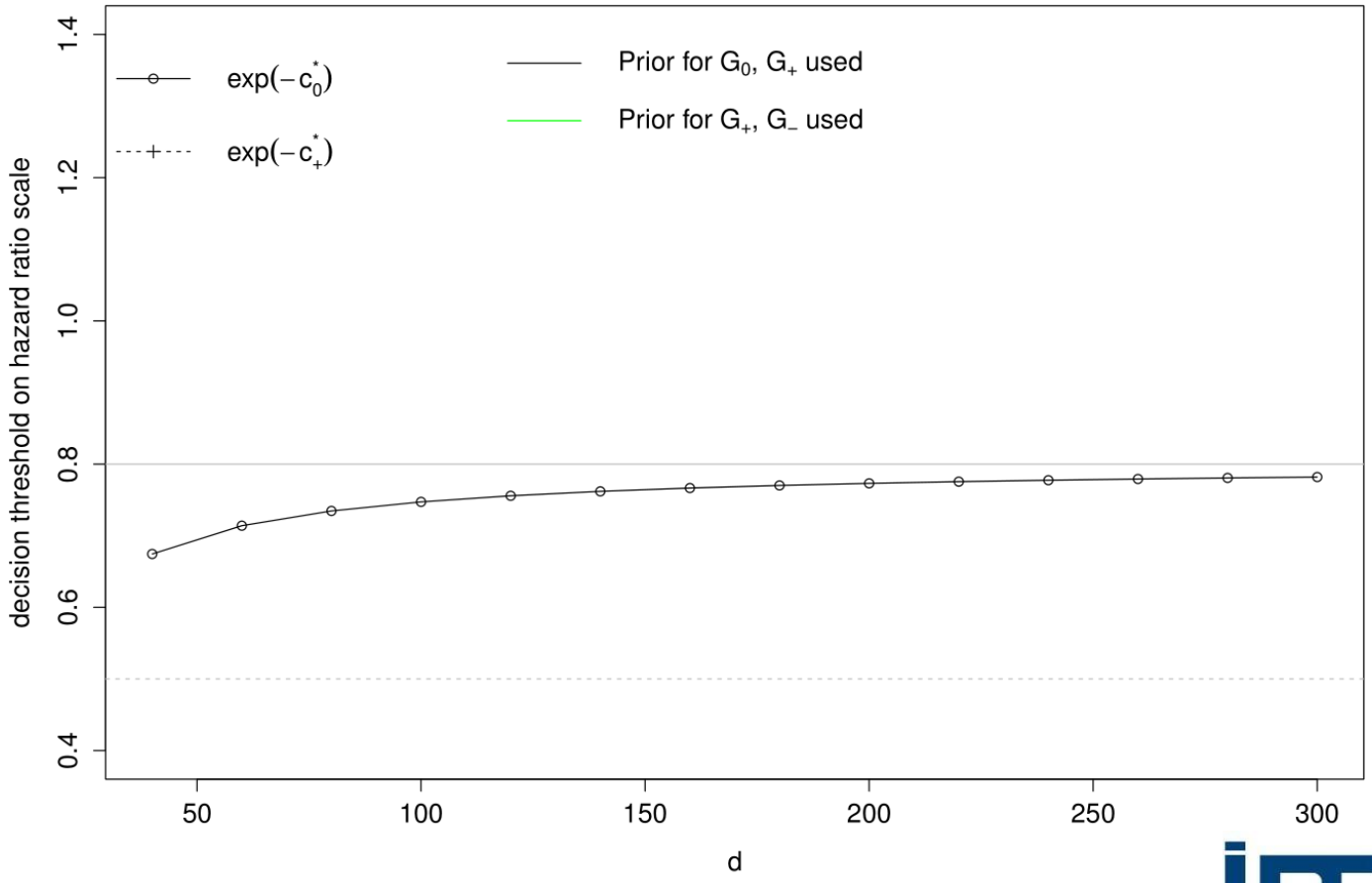
  - $m_+ = -log(0.24) = 1.43,\ \ w_+ = 1.24$
  - $m_- = -log(0.71) = 0.34,\ \ w_- = 0.067$
  - $\pi = 0.157$ according to a meta-analysis (Mao et al. 2010, n=1470)

- In case one chooses a prior for G_0 instead of G_- , $m_0 = -\log(0.85) = 0.16,\ w_0 = 0.04$.

- Relevance thresholds are set to $\tau_0 = -\log(0.8), \tau_+ = -\log(0.5)$.

Clinical trial example: optimal decision rules

- optimal decision thresholds on the hazard ratio scale in dependence of number of events d



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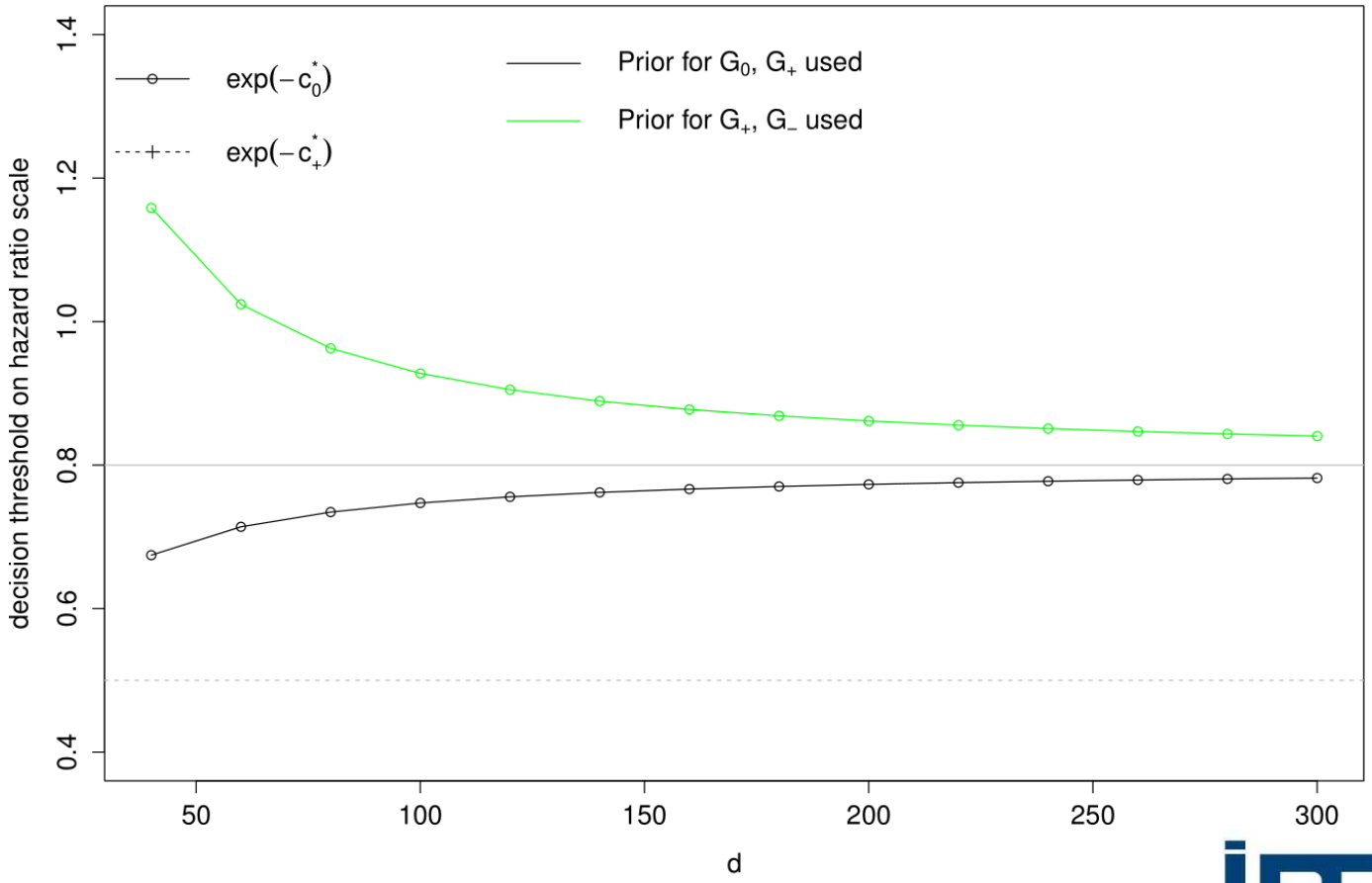

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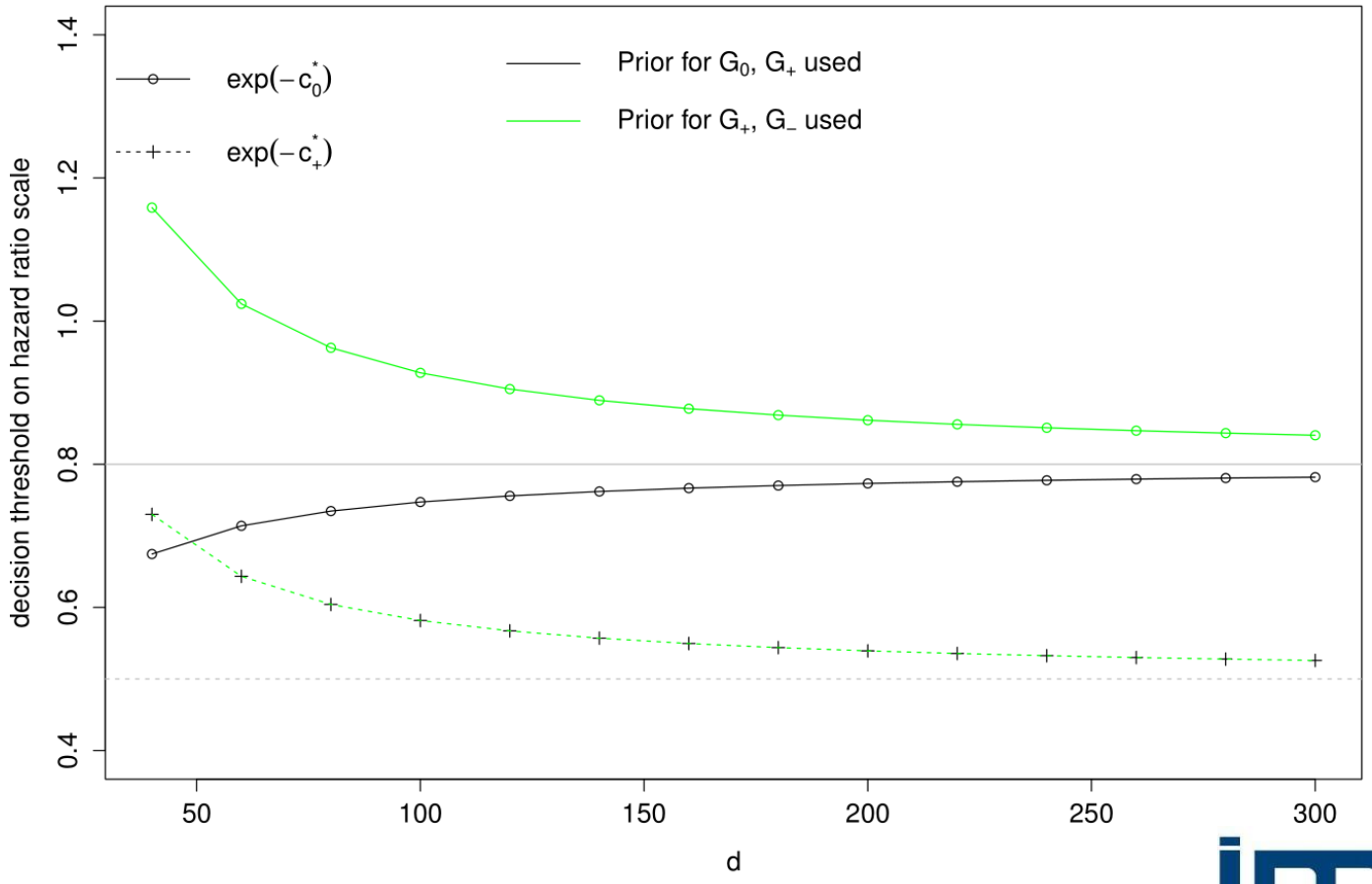
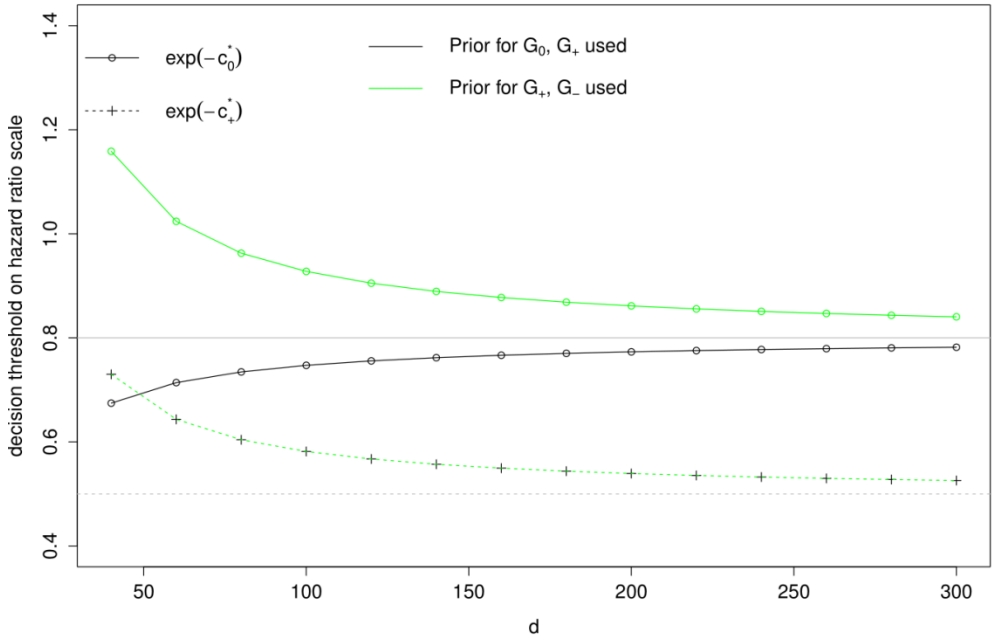


Clinical trial example: remarks on optimal decision rules

- Relatively generous decision thresholds c_+^*
- If prior for G_0 is used, $\exp(-c_0^*)$ is smaller than 0.8, in contrast to the scenarios where a prior for G_- is applied
- The larger the number of events, the closer the optimal decision thresholds c_0^*, c_+^* are to the relevance thresholds τ_0, τ_+



Assumptions for simulation study

- Assume that it is planned to investigate the efficacy of entinostat within an adaptive enrichment design with
  - ➢ subgroup selection at interim based on $d = 200$ observed events
  - ➢ subgroup prevalence from the meta-analysis holds true
- This would result in the following optimal decision thresholds:
  a) Based on a prior for G_+, G_-: $\exp(-c_0^*) = 0.862, \exp(-c_+^*) = 0.539$
  b) Based on a prior for G_+, G_0: $\exp(-c_0^*) = 0.773, \exp(-c_+^*) = 0.539$

Assumptions for simulation study (2)

- Furthermore assume exponentially distributed survival times and the following median survival times in months:

$$M_{T+} = 12, M_{C+} = 8, M_{T-} = 8, M_{C-} = 6$$

$$\Rightarrow \Delta_0 \approx -\log(0.74), \Delta_+ \approx -\log(0.67),$$

- Now, 3 different types of decision thresholds can be considered for each scenario:

  (a) *ad hoc* decision thresholds $(\tau_0, \tau_+) = (-\log(0.8), -\log(0.5))$

  (b) optimal decision thresholds with c_0^* based on a prior for G_+, G_-

  (c) optimal decision thresholds with c_0^* based on a prior for G_0

- Selection probabilities were evaluated using 1,000,000 simulated studies per scenario

Selection probabilities

probability \ decision thresholds on HR scale	**(a)** $(\mathbf{0.8, 0.5})$	(b) $(0.862, 0.539)$	**(c)** $(\mathbf{0.773, 0.539})$
select G_0 and G_+	0.1969		
select G_0 only	0.5169		
select G_+ only	0.0311		
stop for futility	0.2551		

Selection probabilities

decision thresholds on HR scale / probability	**(a)** $(\mathbf{0.8, 0.5})$	(b) $(0.862, 0.539)$	**(c)** $(\mathbf{0.773, 0.539})$
select G_0 and G_+	0.1969	0.2743	
select G_0 only	0.5169	0.5876	
select G_+ only	0.0311	0.0164	
stop for futility	0.2551	0.1217	

Selection probabilities

decision thresholds on HR scale / probability	**(a)** $(0.8, 0.5)$	**(b)** $(0.862, 0.539)$	**(c)** $(0.773, 0.539)$
select G_0 and G_+	0.1969	0.2743	0.2282
select G_0 only	0.5169	0.5876	0.3982
select G_+ only	0.0311	0.0164	0.0624
stop for futility	0.2551	0.1217	0.3112

- Rule **(b)** shows the overall best performance as compared to rules **(a)** and **(c)**
- Relatively high probability for a futility stop for both rules **(a)** and **(c)**
- Due to the relatively strict threshold for G_0, rule **(c)** performs worst.

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Conclusion

- Optimal decision rules incorporate various aspects of the design of a clinical trial with subgroup selection.
- These rules can either be modelled via prior knowledge in the two subgroups, or in the total population and subgroup of interest
- If there is prior knowledge on treatment effects, optimal decision rules may lead to an increased probability for a correct selection of the target population, which in turn positively influences the power of the trial (Krisam & Kieser 2015)

Krisam J, Kieser M (2015). Optimal decision rules for biomarker-based subgroup selection for a targeted therapy in oncology. *International Journal of Molecular Sciences* **16**(5), 10354-10375.

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