Institut für Biometrie und Klinische Forschung

AML-CG 2013: Planning a Clinical Trial with Population Enrichment and Consideration of Interim Patients

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40 Jahre Medizinische Informatik und Biometrie in Münster
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medizinische fakultät Westfälische Wilhelms-Universität Münster

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Primary Trial Objectives

I. All patients: $ORR_{FS\text{-}HAI} > ORR_{S\text{-}HAM}$

II. Subgroup (ELN intermediate/adverse):

$ORR_{FS\text{-}HAI} > ORR_{S\text{-}HAM}$

III. Safety: $ORR_{FS\text{-}HAI} < ORR_{S\text{-}HAM}$

- Design constraints
  - Overall significance level: 5%
  - Overall power: ~ 80% ($ORR_{S\text{-}HAM}/ORR_{FS\text{-}HAI}$ = 74%/83%)
  - Number of patients: 600 – 900 (~ 160 per year)
  - Trial Duration (years): 4-6 (Randomization) + 4 (Follow-Up)

Key Secondary Trial Objectives

- Feasibility and efficacy of MRD guided post remission therapy in ELN favorable patients
  - Comparison of RFS and OS to historic control (AML-CG 1999, AML-CG 2004, AML-CG 2008)
- Efficacy of 1 g/m^2 AraC in S-HAM induction treatment in patients < 60 years
  - Comparison of ORR, RFS, OS to historic control (AML-CG 2004, AML-CG 2008)

Key Secondary Trial Objectives

- Comparison of MRD status for treatment groups at different time points by χ^2-tests
- Investigation if early detection of molecular/hematological relapse is prognostic and predictive for RFS and OS in ELN favorable patients
  - Construction of time dependent Cox model

Further Secondary Trial Objectives

- Univariate and multivariate analyses of ORR, EFS, RFS, OS and RD according to treatment group, age, sex, CIRS score, karyotype, genotype, early response, extramedullary manifestations and molekular markers
- Investigation of treatment associated side effects
- Correlation analysis of PB-MRD and BM-MRD
- Investigation of quality of life
- …

Design for Primary Objectives I and II

- Problem: $ORR_{FS\text{-}HAI} > ORR_{S\text{-}HAM}$ true for all patients?
- Solution:
  - Two-stage adaptive design
  - Interim Analysis after 500 patients
  - Hierarchical testing:
    - 1st population: All patients
    - 2nd population: Subgroup (ELN intermediate/adverse)

Design for Primary Objectives I and II

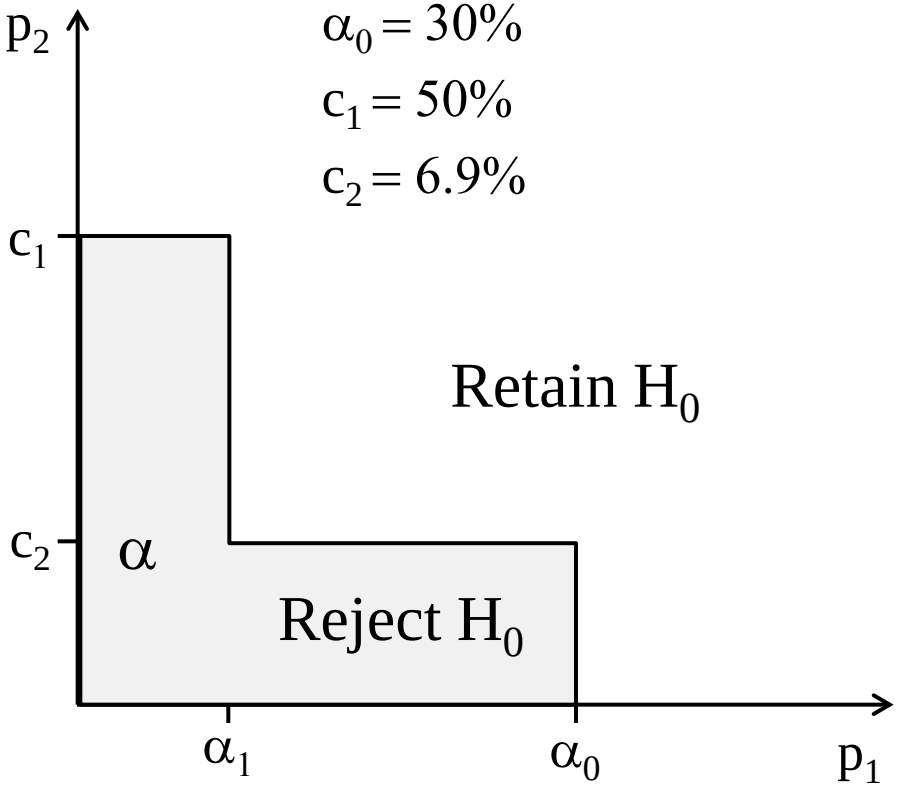
- Solution (continued):
  - If
    - All patients: $ORR_{FS\text{-}HAI} \sim ORR_{S\text{-}HAM}$
    - Subgroup: $ORR_{FS\text{-}HAI} >> ORR_{S\text{-}HAM}$
  - Then change hierarchical testing:
    - 1st population: Subgroup
    - 2nd population: All patients
  - End analysis according to original or revised hierarchical order

Design for Primary Objectives I and II

- Test Procedure: One-sided χ^2-test
- Overall significance level: One-sided 2.5%
- Study Design: Two-stage adaptive (modified Simes)
  - In interim analsis additionally possibility of
    - Stopping for futility
    - Stopping for promising efficacy
    - Recalculation of sample size for 2nd stage
  - Accounting for interim patients

Design for Primary Objectives I and II

$\alpha_1 = 1\%$
$\alpha_0 = 30\%$
$c_1 = 50\%$
$c_2 = 6.9\%$



1st stage (500 patients)

a) Stop recruitment if $p_1 \leq \alpha_1$
b) Go on if $\alpha_1 < p_1 \leq \alpha_0$
c) Stop for futility if $\alpha_0 < p_1$

2nd stage

a) Reject H_0 if $p_2 \leq c_1$ (120 interim patients)
b) Reject H_0 if $p_2 \leq c_2$ (374 further patients)
c) Retain H_0

Power for Primary Objective I

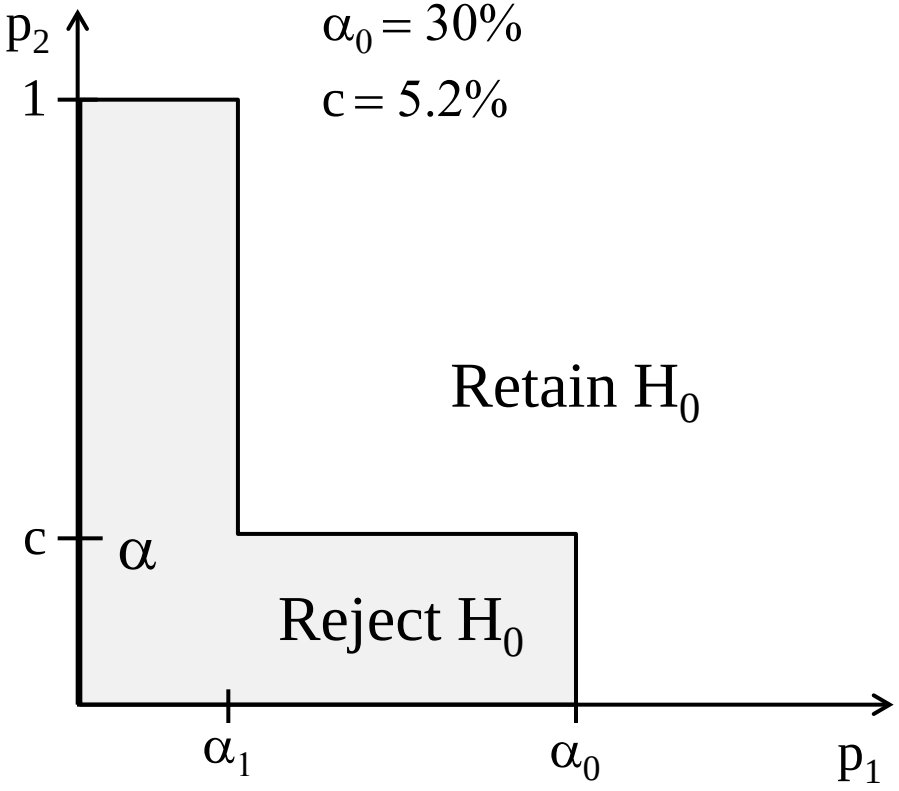
$ORR_{S\text{-}HAM} = 0.74$	$ORR_{FS\text{-}HAI} = 0.83$
Power for $p_1 \leq \alpha_1$ $(n_1 = 500)$	54.9%
Power for $p_1 \leq \alpha_0$ $(n_1 = 500)$	97.4%
Power for $p_2 \leq c_1$ $(n_2 = 120)$	88.6%
Power for $p_2 \leq c_2$ $(n_2 = 374)$	73.8%
Overall Power (n = 620-874)	80%

Hypothetical Design for Primary Objectives I and II with no Consideration of Interim Patients

$\alpha_1 = 1\%$

$\alpha_0 = 30\%$

$c = 5.2\%$



1st stage (500 patients)

a) Stop recruitment if $p_1 \leq \alpha_1$

b) Go on if $\alpha_1 < p_1 \leq \alpha_0$

c) Stop for futility if $\alpha_0 < p_1$

2nd stage

a) Reject H_0

b) Reject H_0 if $p_2 \leq c_2$
(288 further patients)

c) Retain H_0

Hypothetical Design for Primary Objectives I and II with no Consideration of Interim Patients

$\alpha_1 = 1\%$

$\alpha_0 = 30\%$

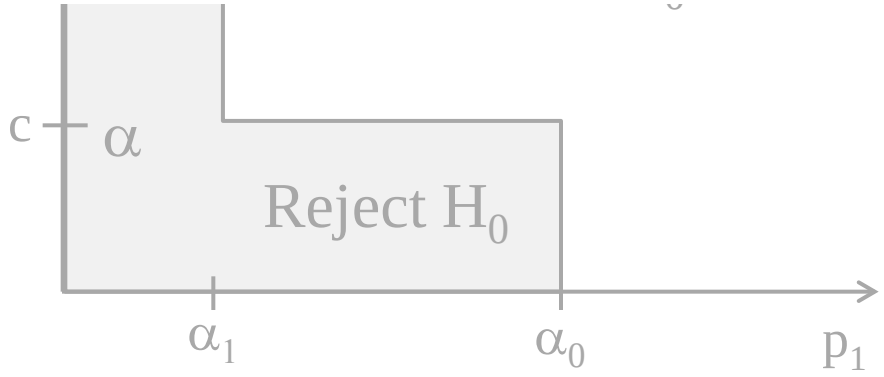
$c = 5.2\%$

1st stage (500 patients)

a) Stop recruitment if $p_1 \leq \alpha_1$

b) Go on if $\alpha_1 < p_1 \leq \alpha_0$

Stop recruitment if $p_1 \leq \alpha_1$ and reject H_0 if $p_2 \leq 0.5$ (120 interim patients)
$\Rightarrow$ Power 73.8%, α = 2% (n_2 = 428 patients necessary for power 80%)



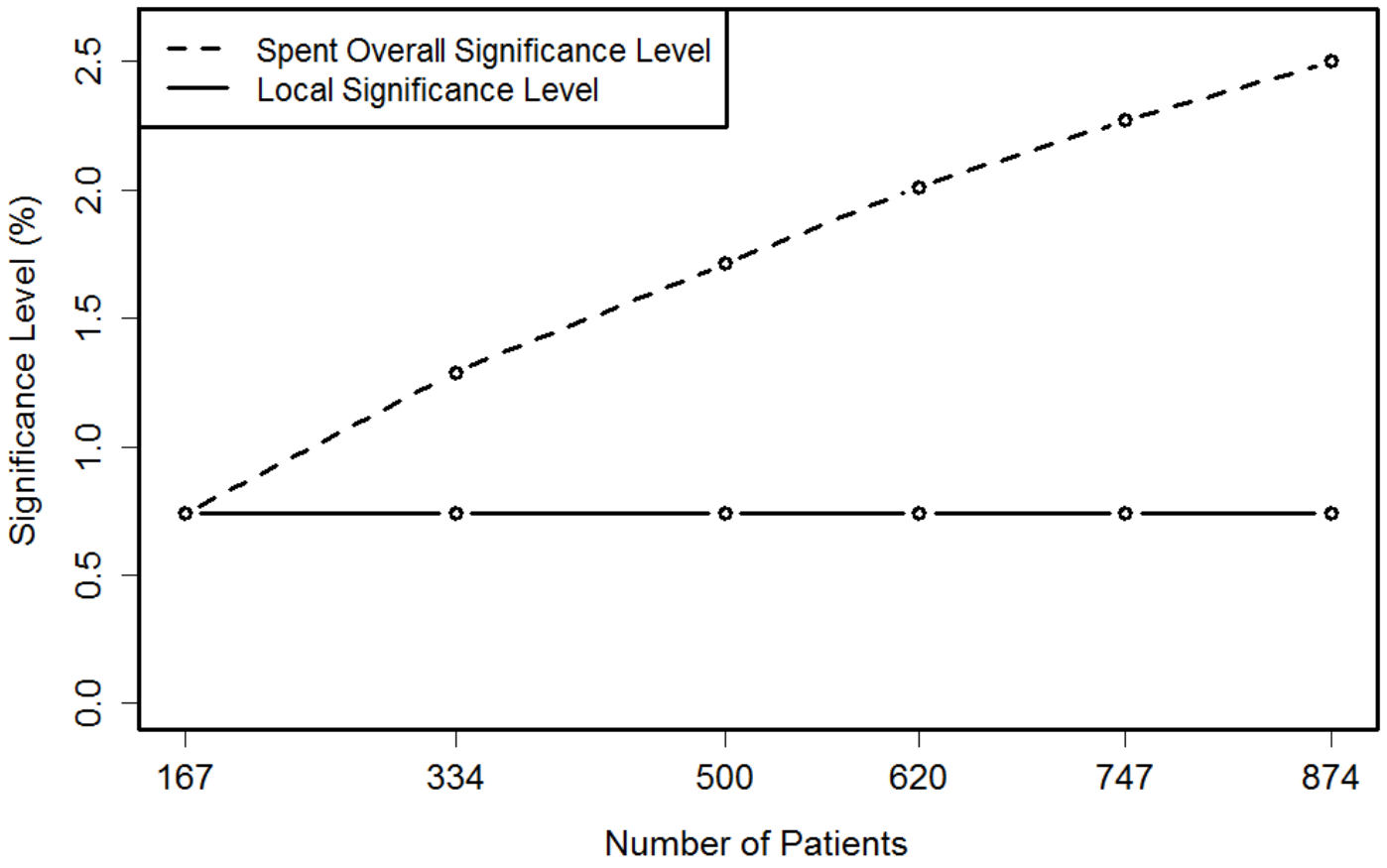
b) Reject H_0 if $p_2 \leq c_2$
(288 further patients)

c) Retain H_0

Design for Primary Objective III

- Problem:
  - Does FS-HAI harm: $ORR_{FS\text{-}HAI} < ORR_{S\text{-}HAM}$?
- Strategy:
  - Group Sequential Design with
    - 6 stages (frequent checks)
    - Unbalanced information rates $\Rightarrow$ merging of analyses
    - Pocock boundaries

Design for Primary Objective III



Power for Primary Objective III

$ORR_{S\text{-}HAM} = 0.74$	$ORR_{FS\text{-}HAI} = 0.56$	$ORR_{FS\text{-}HAI} = 0.64$	$ORR_{FS\text{-}HAI} = 0.72$
Stage 1 (n = 167):	51.2%	15.0%	1.6%
Stage 2 (n = 334):	86.5%	35.4%	3.2%
Stage 3 (n = 500):	97.2%	54.1%	4.6%
Stage 4 (n = 620):	99.2%	65.8%	5.7%
Stage 5 (n = 747):	99.8%	75.2%	6.8%
Stage 6 (n = 874):	>99.9%	82.4%	7.9%

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Thank you very much for your attention!

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