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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Primary Trial Objectives

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

II. Subgroup (ELN intermediate/adverse):

   $\text{ORR}_{\text{FS-HAI}} > \text{ORR}_{\text{S-HAM}}$

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

• Design constraints
  – Overall significance level: 5%
  – Overall power: $\sim 80\%$ ($\text{ORR}_{\text{S-HAM}} / \text{ORR}_{\text{FS-HAI}} = 74\% / 83\%$)
  – Number of patients: 600 – 900 ($\sim 160$ 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
• Efficacy of 1 g/m² 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 $\chi^2$-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 molecular 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:** $\text{ORR}_{\text{FS-HAI}} > \text{ORR}_{\text{S-HAM}}$ 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: $\text{ORR}_{\text{FS-HAI}} \sim \text{ORR}_{\text{S-HAM}}$
    - **Subgroup**: $\text{ORR}_{\text{FS-HAI}} >> \text{ORR}_{\text{S-HAM}}$
  - 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 $\chi^2$-test
- Overall significance level: One-sided 2.5%
- Study Design: Two-stage adaptive (modified Simes)
  - In interim analyses 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

\[ p_2 \]
\[ c_1 \]
\[ c_2 \]

Retain H_0

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

<table>
<thead>
<tr>
<th>ORR_{S-HAM} = 0.74</th>
<th>ORR_{FS-HAI} = 0.83</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power for $p_1 \leq \alpha_1$ ($n_1 = 500$)</td>
<td>54.9%</td>
</tr>
<tr>
<td>Power for $p_1 \leq \alpha_0$ ($n_1 = 500$)</td>
<td>97.4%</td>
</tr>
<tr>
<td>Power for $p_2 \leq c_1$ ($n_2 = 120$)</td>
<td>88.6%</td>
</tr>
<tr>
<td>Power for $p_2 \leq c_2$ ($n_2 = 374$)</td>
<td>73.8%</td>
</tr>
<tr>
<td><strong>Overall Power (n = 620-874)</strong></td>
<td><strong>80%</strong></td>
</tr>
</tbody>
</table>
Hypothetical Design for Primary Objectives I and II with no Consideration of Interim Patients Patients

1\textsuperscript{st} 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 \( \alpha_0 < p_1 \)

2\textsuperscript{nd} 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

$p_1$ $\alpha_1 = 1\%$

$p_2$ $\alpha_0 = 30\%$

c $= 5.2\%$

1\text{st 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 $p_2 \leq c$

c) Retain $H_0$

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%, $\alpha = 2\%$ ($n_2 = 428$ patients necessary for power 80%)
Design for Primary Objective III

• Problem:
  – Does \( \text{FS-HAI harm: } \text{ORR}_{\text{FS-HAI}} < \text{ORR}_{\text{S-HAM}} \)?

• Strategy:
  – Group Sequential Design with
    • 6 stages (frequent checks)
    • Unbalanced information rates \( \Rightarrow \) merging of analyses
    • Pocock boundaries
Design for Primary Objective III

- Spent Overall Significance Level
- Local Significance Level

Significance Level (%)

Number of Patients

167, 334, 500, 620, 747, 874
## Power for Primary Objective III

<table>
<thead>
<tr>
<th></th>
<th>$\text{ORR}_{\text{S-HAM}} = 0.74$</th>
<th>$\text{ORR}_{\text{FS-HAI}} = 0.56$</th>
<th>$\text{ORR}_{\text{FS-HAI}} = 0.64$</th>
<th>$\text{ORR}_{\text{FS-HAI}} = 0.72$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 (n = 167):</td>
<td>51.2%</td>
<td>15.0%</td>
<td>1.6%</td>
<td></td>
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<tr>
<td>Stage 2 (n = 334):</td>
<td>86.5%</td>
<td>35.4%</td>
<td>3.2%</td>
<td></td>
</tr>
<tr>
<td>Stage 3 (n = 500):</td>
<td>97.2%</td>
<td>54.1%</td>
<td>4.6%</td>
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<tr>
<td>Stage 4 (n = 620):</td>
<td>99.2%</td>
<td>65.8%</td>
<td>5.7%</td>
<td></td>
</tr>
<tr>
<td>Stage 5 (n = 747):</td>
<td>99.8%</td>
<td>75.2%</td>
<td>6.8%</td>
<td></td>
</tr>
<tr>
<td>Stage 6 (n = 874):</td>
<td>$&gt;99.9%$</td>
<td>82.4%</td>
<td>7.9%</td>
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</tbody>
</table>
References


Thank you very much for your attention!
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