Effective Implementation of Bayesian Adaptive Randomization in Early Phase Clinical Development

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Acknowledgement

Joint work with

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- Virginie Jego, Cytel Inc
Overview

• Oncology Proof Of Concept Trials: Some Considerations

• Bayesian Adaptive Randomization methodology

• Case Study

• Summary of Simulation Results

• Discussion and Conclusions
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Oncology Proof Of Concept Studies

OBJECTIVES:

- **Activity:** determine whether the treatment is sufficiently promising to proceed in further development

- **Safety:** better characterize the safety profile of the compound

- **Doses:** determine the best dose (efficacy / safety)

- **Biomarkers:** for stratification or prediction of response

- **Strategy:** Add-on strategy or replacement strategy

Challenging design and studies given their limited size and duration!
SINGLE ARM STUDIES

• Endpoint: Response Rate or rates of PFS/OS at predefined timepoint

• Early stopping rules for futility (Simon two-stage design)

• Designed for cytotoxic compounds, not fitting with compounds with different Mode Of Action

• Designs characteristics not consistent with phase III program
  • Not comparative with efficacy hypothesis testing based on historical control
  • Endpoints not used in phase III programs
  • Selection bias

• Difficult assessment of add-on therapies
Oncology Proof Of Concept Studies

SCREENING DESIGNS

• Design characteristics similar to phase III studies
  • Time To Event Endpoints used (PFS more frequently than OS)
  • Comparative ➔ Treatment effect (HR)
    Hypothesis testing procedure (Log-rank)
  • Randomized ➔ Selection bias better controlled

• Sample Size smaller than phase III trials but wider than single arm studies (150 / 300 subjects)
  ➔ Inflation of type I and II error rates ➔ alpha 10% - 30%; power ~ 80%
  ➔ Not optimal decision making process
  ➔ Limited to address dose-response or biomarker questions

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MAIN CHALLENGES

• Learning phase of development ➔ still limited knowledge on compound characteristics during study planning

• Classical study designs
  • Fixed treatment allocation
  • No changes allowed during the trial
  • Design independent of data generated during the study

• In studies of limited size, many subjects exposed to control may not be informative (e.g. for safety or for predictive biomarkers)
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  • Concept & Rationale
  • Workflow
  • Statistical model

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Bayesian Adaptive Randomization

• CONCEPT

• Trial design: randomized & comparative

• Adapt the randomization ratio during the study favoring treatment arm(s) showing best performance

• Intermediate data of activity available during the study will be used to perform the adaptation

• Implement efficient stopping rule for futility as soon as the drug shows no activity
Bayesian Adaptive Randomization

- Fewer subjects assigned to less effective treatment arms
- Keep flexible design during a learning / exploratory phase of development
- Use prior information on the compound and specific indication setting (Bayesian)
- More information on experimental treatment arm (if active)
  - increased precision in the point estimates of activity within arm
  - more safety information
  - improve dose selection
- Improve decision making process
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Bayesian Adaptive Randomization: workflow

Step 0: Preliminary activity before start of the study

- Feasibility of the design
- Definition of prior information to be included in the model
- Fine tuning of model parameters
- Evaluation of operating characteristics versus standard designs

TOOL: SIMULATIONS
Bayesian Adaptive Randomization: workflow

**MODEL SET-UP**

**BURN-IN PERIOD**

**STUDY START:**

**Step 1: BURN-IN PERIOD**

- First group of subjects is assigned to treatment arms according to standard procedures (block randomization with equal allocation ratio)

- Allows model to incorporate enough information to adapt the randomization in a robust way
Bayesian Adaptive Randomization: workflow

- **MODEL SET-UP**
- **BURN-IN PERIOD**
- **Analyze Data Collected***
- **New subject in**

**Step 2a: ADAPTIVE RANDOMIZATION**

At the completion of the burn-in period before new subject is randomized

Data are transferred from the clinical database to IVRS supplier
Bayesian Adaptive Randomization: workflow

**Step 2b: ADAPTIVE RANDOMIZATION**

Data unblinding and analysis within an independent process

Trial Team and sponsor blinding should be adequately insured
Bayesian Adaptive Randomization: workflow

MODEL SET-UP

BURN-IN PERIOD

Analyze Data Collected*

New subject in

Allocate new subject to treatment

Update the model

Update assignment probabilities

Study STOP For futility
Bayesian Adaptive Randomization: workflow

MODEL SET-UP

BURN-IN PERIOD

Analyze Data Collected*

Update assignment probabilities

For n ≤ N Randomized subjects

New subject in

Allocate new subject to treatment

For futility

Update the model

Study STOP

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A Bayesian model

• Assignment probabilities are derived by combining prior information with observed data
  • Guarantees that observed likelihood does not exclusively drive the adaptive randomization.

• Prior information
  • Summarizes previous knowledge on the control arm (literature data) and on the experimental treatment arm (previous trials / preclinical / expectations)
  • Priors should not favor the experimental arm ➔ bias the randomization process.
Evolution of the randomized “play the winner” design

Model links the chance of assigning a subject to one treatment arm [$\gamma$] to the probability that that treatment has the best performance over the other(s) [$\pi$]

$$\gamma_j(i) = \text{Probability} \ [\text{subject } i \text{ is randomized to treatment } j]$$

$$\pi_j = \text{Prob} \ (\eta_j > \max(\eta_k) \mid \text{data, prior}) \quad \text{for } k \neq j$$

Posterior Prob [primary endpoint in treatment $j >$ all other arms]

$$\gamma_j(i) = \pi_j(i)^{\lambda} / \sum_j \pi_j(i)^{\lambda}$$
Model specification: the statistical engine

\[ \gamma_j(i) = \pi_j(i)^\lambda / \sum \pi(i)^\lambda \]

\( \lambda \) = tuning parameter controlling the degrees of freedom of the process

- \( \lambda = 0 \) \( \Rightarrow \) balanced randomization
- \( \lambda = 1 \) \( \Rightarrow \) \( \gamma_j(i) = \pi_j(i) \)

The value of lambda based on simulation results before study start
Decision making tool

\[ \pi_{SoC} = \text{Probability (Standard Of Care} > \text{Experimental Treatment Arm(s))} \]

*Direct measure of drug activity to be used for decision making*

- **During the study** High \( \pi_{SoC} \geq c_1 \)
  
  Stop for futility for weak drug activity

- **Final analysis** Low \( \pi_{SoC} \leq c_2 \)
  
  Claim drug activity within a hypothesis testing framework

- **Simulation results** will pre-define proper values for \( c_1 \) and \( c_2 \) leading to adequate control of type I and II error

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Trial Insights

- Cytostatic compound (monoclonal antibody) with not established dose-response curve (monotonic or bell-shaped)
- Phase II randomized
  - Standard Of Care (SoC)
  - SoC + “LOW” dose
  - SoC + “HIGH” dose
- Primary endpoint: Progression Free Survival
- Study Objective
  - **Primary:** Evaluate Drug activity
  - **Secondary:** Choose the best dose
Standard solution not completely satisfactory as

- Two parallel looks to data lead to multiplicity issues inflating alpha and increasing the power
  - the overall false positive rate (alpha) equal to 23%
  - power > 90% in case both arms are equally active
- Not feasible to have clearer and more robust decision rule for selection of the best dose
- Performance of Bayesian Adaptive Randomization evaluated through simulations
Trial Insights: Simulation plan

- Simulations were run to
  - Evaluate model operating characteristics versus standard design
  - Define the model parameters (burn-in period, tuning parameter, priors, futility stopping rule, rejection region definition)

- Scenarios of activity:
  - Negative
  - No drug activity
  - One arm active (mild / strong activity)
  - Dose response (mild / strong activity)
  - Both arms equally active (mild / strong activity)
## Simulation scenarios

### Scenario 1
**Negative Hypothesis**

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>( \lambda_p &gt; \lambda_L = \lambda_H )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median(months)</td>
<td>2.76</td>
</tr>
<tr>
<td>HR</td>
<td>120%</td>
</tr>
<tr>
<td>( \lambda )</td>
<td>3.98</td>
</tr>
</tbody>
</table>

### Scenario 2
**Null hypothesis**

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>( \lambda_p = \lambda_L = \lambda_H )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median(months)</td>
<td>2.76</td>
</tr>
<tr>
<td>HR</td>
<td>100%</td>
</tr>
<tr>
<td>( \lambda )</td>
<td>3.98</td>
</tr>
</tbody>
</table>

### Scenario 3.1
**Only one arm moderately active**

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>( \lambda_p = \lambda_L &lt; \lambda_H )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median(months)</td>
<td>2.76</td>
</tr>
<tr>
<td>HR</td>
<td>100%</td>
</tr>
<tr>
<td>( \lambda )</td>
<td>3.98</td>
</tr>
</tbody>
</table>

### Scenario 3.2
**Only one arm highly active**

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>( \lambda_p = \lambda_L &lt; \lambda_H )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median(months)</td>
<td>2.76</td>
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Summary of results: Model parameter

- **Burn-in period**: 81 subjects randomized (37% of sample size)

- Dynamic tuning parameter = \((2/3) \times \text{(number of subjects randomized / max sample size)}\)

- **Futility rule**: study stopped anytime for futility when
  
  - \(\pi_{\text{SoC}} = P[\text{SoC} > \text{experimental arms}] > 0.6\) and
  
  - \(\geq 150\) subjects randomized (2/3 of sample size)

- **Null Hypothesis of “No drug effect” rejected** if \(\pi_{\text{SoC}} < 0.095\)
Choice of the Priors

- **Standard Of Care**
  - Point estimate and 95% confidence interval of most recent and relevant pivotal studies in the same setting.

- **Experimental treatment**
  - Same expected point estimate ➔ no drug activity assumed in order not to bias the randomization
  - Higher variability reflecting the uncertainty of performance
### Probability of stopping for futility

<table>
<thead>
<tr>
<th>SCENARIO</th>
<th>P(Futility)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>69.0%</td>
</tr>
<tr>
<td>No drug activity</td>
<td>27.9%</td>
</tr>
<tr>
<td>One arm mildly active</td>
<td>5.3%</td>
</tr>
<tr>
<td>One arm highly active</td>
<td>2.4%</td>
</tr>
<tr>
<td>Mild dose response</td>
<td>3.9%</td>
</tr>
<tr>
<td>High dose response</td>
<td>0.6%</td>
</tr>
<tr>
<td>Both arms mildly active</td>
<td>1.4%</td>
</tr>
<tr>
<td>Both arms highly active</td>
<td>0.3%</td>
</tr>
</tbody>
</table>
% Number of Subjects Randomized without Burn-In Period

- Negative
- No activity
- One arm mildly active
- One arm highly active
- Mild dose response
- High dose response
- Both arms mildly active
- Both arms highly active

Legend:
- SoC
- Dose A
- Dose B

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### Final $\pi_{SoC}$ (mean)

<table>
<thead>
<tr>
<th>SCENARIO</th>
<th>$\pi_{SoC}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>57.1%</td>
</tr>
<tr>
<td>No drug activity</td>
<td>33.0%</td>
</tr>
<tr>
<td>One arm mildly active</td>
<td>10.3%</td>
</tr>
<tr>
<td>One arm highly active</td>
<td>4.8%</td>
</tr>
<tr>
<td>Mild dose response</td>
<td>8.8%</td>
</tr>
<tr>
<td>High dose response</td>
<td>2.6%</td>
</tr>
<tr>
<td>Both arms mildly active</td>
<td>4.7%</td>
</tr>
<tr>
<td>Both arms highly active</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

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Discussion and Conclusions

• Bayesian Adaptive Randomization could be alternative design for Proof-Of-Concept studies in oncology

• Key points to consider when planning such designs:
  • Median Time to event / Recruitment rate
  • Schedule of assessment (PFS)
  • Control of covariates / Presence of treatment predictive factors
  • Model does not take into account safety
  • Operational burden (eCRF, blinding, etc)

• Simulations are of key importance to evaluate the applicability and the expected benefit of this design.
References

THANK YOU!
BACKUP SLIDES
The model: Likelihood

- Primary outcome is Progression Free Survival (PFS) time (measured in months)

- \( X_{ij} \) the theoretical PFS time for patient \( i \) on therapy \( j \), where \( j = 1,2,3 \) and \( i = 1,2,... \)

- We assume that \( X_{ij} \) has an exponential distribution with median \( \eta_j \) and corresponding mean \( \lambda_j \)

\[
f(x_{ij}) = \frac{1}{\lambda_j} e^{-x_{ij}/\lambda_j} \equiv \frac{\ln 2}{\eta_j} e^{-x_{ij} \ln 2 / \eta_j}.
\]
The model: Prior distributions

- The median parameters, $\eta_1$, $\eta_2$ and $\eta_3$ follow independent inverse gamma distributions with shape parameters $\alpha_j$ and scale parameters $\beta_j$.

- The data for each patient consist of a pair of the form $(Z_{ij}, \delta_{ij})$ where $Z_{ij}$ is the observed PFS time for patient $i$ under treatment $j$, and $\delta_{ij}$ is the indicator variable taking the value 1 if the event is observed and 0 if the patient is censored. The likelihood then becomes:

$$L(Z; \eta_j) = \left(\frac{\ln 2}{\eta_j}\right)^{E_j^+} \exp\left(-\frac{\ln(2) T_j^+}{\eta_j}\right)$$

- where $T_j^+ = \sum_{i=1}^{n_j} Z_{ij}$ and $E_j^+ = \sum_{i=1}^{n_j} \delta_{ij}$.
The model: Posterior distributions

• The combination of the exponential likelihood along with the Inverse Gamma priors result in the posterior distribution of the $\eta_j$ parameters,

  • i.e., $\pi(\eta_j | Z)$ being independent Inverse Gamma distributions as well with

  • shape parameters $\alpha_j + E_j^+$ and scale parameters $\beta_j + \ln(2) T_j^+$
Choice of Priors

- The prior distribution of median PFS time ($\eta_p$) for the placebo arm chosen based on results of publications (see Small 2006) in the same setting, where the median PFS time for active treatment was 11.7 weeks (95% CI, 9.1 to 16.6) and 10.0 weeks (95% CI, 8.7 to 13.1) for placebo-treated patients.

- Hence, assumed a prior distribution of the median PFS time for placebo with an expected median PFS of 2.76 months (12 weeks) and a 95% confidence interval of 1.86 to 4.09 months (8.06 to 17.7 weeks). This corresponds to:

  $$\eta_p \sim IG(25.0836; 66.4708)$$

- For the active treatments we assumed the same expected value but a higher variance in order to reflect the uncertainty over the drug.

  $$\eta_{exp} \sim IG(17.2352; 44.809152)$$