Novartis: Challenging to Accelerate Oncology New Drug Development

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Bayesian Clinical Trials in Novartis Oncology

- **Phase 1 study**
  - To estimate the maximum tolerated dose (MTD)
  - Global (1998-): > 60 trials, Japan (2008-): 6 trials

- **Phase 2 study**
  - Early stopping by futility
  - >50 trials

- For Novartis oncology P1 studies, Bayesian trials are the global standard!
Outline

- Why do we conduct Bayesian Phase I Trials?
- How do we conduct Bayesian Phase I Trials?
- What benefits can Bayesian Design bring us to?
Challenges and Design Requirements in Oncology Phase I Trials

Phase I Trial Challenges

- High toxicity potential: **safety first**
  - Most responses occur **80%-120% of MTD**

Design Requirements

- **Avoid subtherapeutic doses** while **controlling overdosing**
- **Estimate MTD accurately**
- **Utilize available information efficiently**
- **Make adequate decisions in timely fashion**

Primary objective: **determine MTD**
Traditional 3+3 Design

To determine the next dose, only the number of DLT at the current cohort is used.
Bayesian Statistics

- Different sources of information are combined probabilistically
- Accurate prediction can be obtained by putting together our historical knowledge and ongoing trial data

**Advantages**

- **Contextual Evidence**
  - Expert Knowledge

- **Observed Data**
  - Updated Evidence

- **Predictions Decisions**

**derived quantity**

- **Pr(DLT)**
- **Pr(DLT)**
- **Pr(DLT)**
- **Pr(DLT)**
# 3+3 Design vs Bayesian Design

<table>
<thead>
<tr>
<th></th>
<th>3+3 Design</th>
<th>Bayesian Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usability</td>
<td>Easy - algorithm</td>
<td>More complex - model</td>
</tr>
<tr>
<td>Available information</td>
<td>• The number of DLT at current cohort</td>
<td>• Prior information</td>
</tr>
<tr>
<td></td>
<td>• Ongoing trial data</td>
<td>• Ongoing trial data</td>
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<tr>
<td>Flexibility</td>
<td>Not flexible</td>
<td>Flexible</td>
</tr>
<tr>
<td></td>
<td>• fixed cohort size at 3</td>
<td>• adjustable cohort size</td>
</tr>
<tr>
<td></td>
<td>• fixed doses</td>
<td>• unplanned doses</td>
</tr>
<tr>
<td>Accuracy of MTD</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>estimation</td>
<td>• Observed DLT rates</td>
<td>• Estimate DLT rates at each doses</td>
</tr>
<tr>
<td></td>
<td>• Inference for true DLT rates</td>
<td>• Risks of DLT occurrence at each doses</td>
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Bayesian Design can solve Challenges in Oncology Phase I Trials!
Challenge in Japan Development

<Delayed-Start Development>

<Simultaneous Development>

Accumulate clinical experience
Outline

- Why do we conduct Bayesian Phase I Trials?
- How do we conduct Bayesian Phase I Trials?
- What benefits can Bayesian Design bring us to?
Novartis Bayesian Approach to Oncology Phase I Trials

- Assume dose-toxicity model

- Update probability of DLT rate at each dose by incorporating prior information (pre-clinical, human) and observed data into model

- Assess the risk of that the true DLT rate at each dose exceeds 33%, given all of our prior information and observed data

\[
\Pr(DLT)\]

Mean DLT rate = 25%
Risk dose is too toxic = 30%
Clinically driven, statistically supported decisions

- Historical Data (prior info)
- Trial Data 0/3, 0/3, 1/3, ...
- Model based dose-DLT relationship

DLT rates $p_1, p_2, \ldots, p_{MTD}, \ldots$ (uncertainty!)

Dose recommendations

Decisions
Dose Escalation Decision

Clinical Expertise

Model

Inference

Decision/Policy

Responsible: Statistician
Informing: Clinician (Prior, DLT)

Responsible: Clinician
Informing: Statistician (risk)
Example of Dose Escalation/De-escalation in Bayesian Oncology Phase I Trials

Bayesian

Dose

Non-DLT DLT Dosage range recommended by Bayesian statistics

Cohort

1 2 3 4 5 6 7

10 20 30 40 50
Outline

- Why do we conduct Bayesian Phase I Trials?
- How do we conduct Bayesian Phase I Trials?
- What benefits can Bayesian Design bring us to?
Benefits of Bayesian Oncology Phase I Trials

- Accurately estimate MTD
  - Utilize all relevant information
  - Select next dose clinically
  - Little-affected by DLT occurred by chance

Cost

Quality

Speed
New Challenges

- **Combination phase I study**
  - Incorporate each historical SINGLE agent data into prior
  - Allow flexible dose escalation decisions clinically (dosage/agent)

- **Global/Asian phase I study**
  - Estimate Global/Asian MTD considering the ethnic sensitivity in one trial
Example of Novartis Bayesian Approach to Oncology phase II Trials

Endpoint: ORR
Objective: to observe an ORR $\geq 25\%$

- Prior Information
- Observed Data
- Updated Evidence
- Prediction

Predict the “probability of success” at the end of the study
$\Pr(\text{Final ORR} \geq 25\%|\text{data})$
Bayesian study design can maximize the quality of the new drug development!
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