Bayesian Interim Monitoring for Faster Decision-Making in Early Oncology Trials

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Disclosure

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• Chang-Heok Soh and Victoria Chang are employees of AbbVie Inc.
Interim analysis (IA) in Phase 1-2 oncology studies

Decision-making at IA based on predictive probability of success
  – Is there sufficient confidence at IA in the outcome at final analysis to make decision early (though may still continue trial)?
  – Focus today: Phase 1 expansion cohorts or Phase 2 single-arm trials with binary efficacy endpoint (eg ORR, CBR)
  – Method extends to other endpoints and randomized trials

Operating characteristics via simulations
Interim Analysis of Efficacy in Clinical Trials

• Efficacy IA is any analysis intended to evaluate efficacy prior to formal completion of a trial

• Some motivations for IA:
  – Ethical imperative to avoid treating patients with ineffective or inferior therapies
  – Efficient allocation of resources
  – Faster decision-making for drug development
Interim Analysis of Efficacy in Phase 1-2 Oncology Studies

- May want to continue study in case of initial weak efficacy signals (unless unethical to continue)
  - Fuller understanding of drug’s effect may require info on patient population, PK/PD, biomarkers, safety, etc, especially in signal-seeking Ph 1
  - Initial weak efficacy signals may lead to potentially enriched populations or other protocol changes
Interim Analysis of Efficacy in Phase 1-2 Oncology Studies

• Typically want to continue the trial even if early data drives early GO decision:
  – Collect more info on safety data, dosing schedules, biomarkers and efficacy
  – Identify appropriate populations
  – Data to inform possibility for treatment combination

• But early evidence of efficacy could accelerate development, e.g.
  – Start additional expansion arms, extend current study into Phase 1/2, or initiate planning of additional trial at-risk
  – Trigger decision to increase manufacturing spending
Interim Analyses: Is the trial very likely to show evidence supporting entering NO-GO, grey or GO zone at the end of the trial?
Bayesian Interim Analyses (IA) for Faster Decision-Making

- Decision-making at IA based on predictive probability of success
  - Is there sufficient confidence at IA in the outcome at final analysis to make decision early (though may still continue trial)?

- Bayesian approach:
  - Allows flexibility in IA timing and uses data to-date for decision-making
  - Allows continuous monitoring of efficacy signals
  - Enables faster decision-making for drug development
Definition: The probability of achieving a successful result at a future analysis, given current interim data

Based on Bayesian framework and can incorporate prior belief or historical information

Prior Belief/Data about Distribution of True ORR

Observed Data at IA

Updated Belief about Distribution of True ORR

Predict future responders in rest of trial

Update Belief about Distribution of True ORR Again

(Predicted) Posterior distribution of true ORR for End of Trial

Compare to threshold for GO, NO-GO criteria

Predictive Probability of Success (PPOS)
Hypothetical Example:

- 13 more patients for rest of Ph 1, need 2 more responders to enter grey zone, 9 more responders for GO-zone

- Based on current data and predicted future data
  - Predictive prob that final decision is GO=Pr(≥9 responses in 13 more pts) = 0.1%
  - Predictive prob that final decision is NO-GO=Pr (0-1 response in 13 more pts) = 63%
  - Predictive prob that final decision is GREY = 37%

- Should we make early GO or early NO-GO decision?
Hypothetical Example:

- If team specifies confidence thresholds for early No-GO and early GO, e.g.
  - Early NO-GO if predictive prob/confidence that final outcome is NO-GO ≥ 80% (the higher the bar, the harder to trigger early NO-GO)
  - Early GO if predictive prob/confidence that final outcome is GO ≥ 80% (the higher the bar, the harder to trigger early GO)

<table>
<thead>
<tr>
<th>Observed ORR</th>
<th>Predictive prob for NO-GO (%)</th>
<th>Predictive prob for GO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/10</td>
<td>98</td>
<td>0.001</td>
</tr>
<tr>
<td>1/10</td>
<td>63</td>
<td>0.1</td>
</tr>
<tr>
<td>2/10</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>3/10</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>4/10</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>5/10</td>
<td>0</td>
<td>73</td>
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<tr>
<td>6/10</td>
<td>0</td>
<td>93</td>
</tr>
<tr>
<td>≥7/10</td>
<td>0</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>
Operating Characteristics
Hypothetical Phase 1

Design assumptions for simulations:

• Planned sample size of 23
• Min / Base TPP = 15% / 30%
• IA at n=10, 15 or continue to 23
• At end of Ph 1
  – NO-GO if Pr (true ORR < min TPP given final data) > 80%
  – GO if Pr (true ORR ≥ base TPP given final data) ≥ 80%
• At any IA,
  – Early NO-GO if predictive prob/confidence in final outcome being NO-GO given IA data > 80%
  – Early GO if predictive prob/confidence in final outcome being GO given IA data > 80%
Operating Characteristics
*Hypothetical Phase 1*

<table>
<thead>
<tr>
<th>True ORR</th>
<th>% Final decision is NO-GO</th>
<th>% Final decision is GREY</th>
<th>% Final decision is GO</th>
<th>Avg N</th>
<th>% Early Decision</th>
<th>% Early decision is early NO-GO</th>
<th>% Early decision is early GO</th>
<th>% Concordance between IA and final analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>59.2</td>
<td>40.8</td>
<td>&lt;0.01</td>
<td>16.6</td>
<td>57.9</td>
<td>57.8</td>
<td>&lt;0.01</td>
<td>80.6</td>
</tr>
<tr>
<td>15%</td>
<td>30.9</td>
<td>69.0</td>
<td>0.1</td>
<td>19.2</td>
<td>35.5</td>
<td>35.3</td>
<td>0.2</td>
<td>81.4</td>
</tr>
<tr>
<td>20%</td>
<td>13.3</td>
<td>85.9</td>
<td>0.8</td>
<td>20.8</td>
<td>20.6</td>
<td>19.7</td>
<td>0.9</td>
<td>85.7</td>
</tr>
<tr>
<td>30%</td>
<td>1.5</td>
<td>86.3</td>
<td>12.2</td>
<td>21.7</td>
<td>11.9</td>
<td>4.8</td>
<td>7.1</td>
<td>86.4</td>
</tr>
</tbody>
</table>
Considerations for Implementation

- Real-time monitoring requires good real-time data cleaning and efficient operational coordination with sites to get the data in-house.
- Operating characteristics should be assessed under different assumptions as part of design evaluation.
THANK YOU