Design Making in an Early Oncology Event Study

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Innovative Design and Optimal Decision-making in Clinical Trials

5 November 2015
Outline

- Introduction
- Decision Making
- Study Design
- Delivery
Goals:

- Clear decision to proceed into confirmatory phase
- Trials are smaller earlier in development
  - Early safety
  - Initial investment in unproven compounds
Decision Making

• Defining success
  – Stop ineffective compounds early
  – Accelerate development for effective compounds

• Consider scientific evidence for endpoints
  – external and internal data
  – Justification for targets

• Understand risk
  – What actions will be taken given the decision
  – What is the probability of making each decision

Decision making drives the clinical development of compounds
What is done at AZ

- Prospective decision making criteria in place before the study begins
  - Promotes forward thinking
  - Provides context for future results
  - Speeds up decision making at the end of the study
    - Both within the study team and at governance

- 3 outcome framework – Red Amber Green
  - Partitions the sample space
  - Quantifies the risks attached to decision making
The framework

Based on published method (Lalonde et al, 2007)

- **Target value**
  - TV - desired/meaningful performance, product profile

- **Lower reference value**
  - LRV - Minimally clinical acceptable performance

Justified by TPP / meta analysis or profile figure (see slide 4)

- **False Stop risk**
  - Risk of stopping the study when the truth is better than the Target value

- **False Go risk**
  - Risk of continuing the study when the truth is less than the Lower reference value
  - Desired confidence (1 – False Go)

Function of company’s risk tolerance
Example – Decision Criteria (builds)

GNG Criteria for Progression Free Survival

<table>
<thead>
<tr>
<th>Value/Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Value</td>
<td>A Hazard Ratio of 0.47</td>
</tr>
<tr>
<td>Lower Reference Value</td>
<td>A Hazard Ratio of 0.67</td>
</tr>
<tr>
<td>Go</td>
<td>If there is ≥80% chance that the Hazard Ratio is ≤0.67*</td>
</tr>
<tr>
<td></td>
<td>eg observed Hazard Ratio** ≥ 0.64</td>
</tr>
<tr>
<td>Stop</td>
<td>If there is &lt;10% chance that the Hazard Ratio is ≤0.47*</td>
</tr>
<tr>
<td></td>
<td>eg observed Hazard Ratio** ≥ 0.64</td>
</tr>
</tbody>
</table>

** Assuming 100 patients, 50 per arm, 70 events
* Stop and Go correspond to lower-limit of 1-sided 90% CI and upper-limit of 1-sided 80% CI
The actual criteria will be driven by the stated probabilities so that if the observed data do not follow the assumptions, the GNG values will change

At study end the observed HR is compared to the decision criteria. The previously agreed action is taken.
Example – Operating Characteristics and decision

<table>
<thead>
<tr>
<th>True HR</th>
<th>Probability of being in Green Amber or Red given different truths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good</strong></td>
<td></td>
</tr>
<tr>
<td>TV HR = 0.47</td>
<td>Green 73%  Amber 17%  Red 10%</td>
</tr>
<tr>
<td><strong>Reasonable</strong></td>
<td></td>
</tr>
<tr>
<td>LRV HR = 0.67</td>
<td>Green 20%  Amber 23%  Red 57%</td>
</tr>
<tr>
<td><strong>No effect</strong></td>
<td></td>
</tr>
<tr>
<td>HR=1</td>
<td>Green 1%  Amber 3%  Red 96%</td>
</tr>
</tbody>
</table>

Managing the change of indecisiveness (Amber) in the primary variable is key.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Action at Final Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red</td>
<td>Stop development</td>
</tr>
<tr>
<td>Amber</td>
<td>Consider other data</td>
</tr>
<tr>
<td>Green</td>
<td>Continue development planning</td>
</tr>
</tbody>
</table>

Actions are agreed at time of trial design.
## Breaking the tie (example)

When analysis of the primary variable yields a result in the ‘consider’ zone other variables in the trial should be considered in order to arrive at a clear decision.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) DoR (difference in mean, wks)</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>2) DCR (difference in %)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>3) OS (HR)</td>
<td>&gt; 0.8</td>
</tr>
<tr>
<td>4) Gr 3 Hepatotox (difference in %)</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>5) Gr 3 Nausea (difference in %)</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>6) QoL (difference in mean score)</td>
<td>&lt; 10</td>
</tr>
</tbody>
</table>

When analysis of the primary variable yields a result in the ‘consider’ zone other variables in the trial should be considered in order to arrive at a clear decision.

- Secondary variables are considered in order.
- Once a red or green is reached, stop and take the corresponding action.
- Criteria can be set using similar methodology as for the primary.
- The sample space for the last variable should be partitioned by stop and go only.
Principles

- Targets (TV/LRV) are well supported by data (Internal/External)
- Decision risks reflect the company’s tolerance for error
- All aspects of setting the decision criteria are agreed at the time of trial design
  - Includes the framework for breaking ties
- Control the chance for an indecisive result at a reasonable level
  - Can drive sample size
- Have agreed actions based on trial results
- Have a plan to decide when the primary variable is not decisive
Wider applications within AZ

- Applied in all phases of development
- Can be applied in most variables and variable types
  - Usually to primary and key secondary variables
- Can be applied in various designs
  - Comparative and non-comparative
- Interim analyses
A note on sample size

Randomized Patients, Events in Each Treatment and Overall Events as a Function of
18 Month Recruitment time (RMSP = -0.11) and 70% Data Maturity Two sided Type I
Events Needed: 112, Hypothesized HR: 0.67, Reference Median OS: 9.4 Months, Nu

- Similar Phase II event study sized with 80% power and one sided 0.1 type 1 error requires
  112 events and 161 patients assuming an alternative hypothesis of HR = 0.67 (LRV)
- Using the decision procedure discussed, and controlling the chance to observe a HR in the
  ‘consider zone’ at no more than 30%, no more than 100 patients and 70 events are
  required
References


• Julious SA. Sample Sizes for Clinical Trials. Chapman & Hall/CRC Press 2010

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