A biomarker-based adaptive two-stage randomized phase II study design

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Trial Design Setting

- Phase II
- Putative targeted therapy
- Limited historical data
  - No well-defined sensitive subgroup
  - Outcome within biomarker-defined subgroups
- Potential biomarker to identify sensitive pop
  - Sufficient frequency of biomarker +
- Randomization
  - Reference arm
  - Intermediate endpoint
- Include all patients, allows preliminary assessment of biomarker-treatment interaction on short-term outcome
- interim analysis
Phase II Trials-Targeted Therapy

Q: How well do we know drug and target?

Q: Is the drug active AND do we have the correct biomarker to identify a sensitive population?

Goal of trial:
1. Assess Intervention’s activity AND
2. Assess Biomarker’s predictive ability AND
3. Inform Phase III trial design, eligibility
Phase II Evaluation of Biomarker & Agent

- Mechanistic diagram

Agent

Effect on target

Biomarker +

Effect through other pathways

Clinical Response

Correlation of biomarker with response through non-target pathways

Biomarker +

Effect through target pathway
Trial Designs Using Biomarkers

1. Single Arm Phase II
   a. with selection, stratification or parallel studies
   b. multi-stage
   c. adaptive

2. Randomized Phase III
   a. Target marker positive
   b. Randomized Treatment Strategy
   c. “Randomize-All”
   d. Adaptive (Interim analysis: futility, negative interaction, efficacy)

3. Phase II/III
Trial Design & Outcomes Stage I

Trial design

First stage accrual

Assume marker + subgroup most likely to respond

Interim Analysis

Futile in M+ (biomarker [+])

Yes

A: Stop trial early; no further drug evaluation

No

Futile in M- (biomarker [-])

Yes

Discontinue trial accrual in M- pts

No

Complete trial accrual in M+ and M- pts

Complete trial accrual in M+ pts

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Trial Design & Outcomes Stage II

**Trial design**

<table>
<thead>
<tr>
<th>Complete trial accrual in M+ &amp; M- pts</th>
<th>Complete trial accrual in M+ pts</th>
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<tbody>
<tr>
<td>Final Analysis</td>
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<tr>
<td>Significant treatment effect in M+ pts</td>
<td>Significant treatment effect in M+ pts</td>
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<td>Yes</td>
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**Trial outcome**

- **B:** Stop drug evaluation in M- pts; Consider further drug evaluation in M+ pts
- **C:** Stop drug evaluation in all pts
- **D:** Stop drug evaluation in M- pts; Consider further drug evaluation in M+ pts
- **E:** Consider further drug evaluation in all pts

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Simple Example

Marker +
- 65% of population
- 30% response
- Assumed most likely to be sensitive

Marker –
- 35% of population
- 10% response

Power to detect a 20% increase in response

Maximum Type I Error: 10%
Maximum Type II error: 20%
Marker + subgroup drives the trial outcome
Two stage design

Interim analysis based on futility: response rate in reference arm is greater than that in experimental arm

Final analysis utilizes Fisher’s Exact Test
Trial Design Characteristics

Power and Type I Error by Marker subgroup

- Power, Marker + (65%)
- Type I error, Marker + (65%)
- Power, Marker - (35%)
- Type I error, Marker - (35%)

Total Sample Size

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Summary

• Trial design is not general phase II design
• Requires consideration of the following:
  – Appropriate reference arm
  – Ratio of marker + (likely sensitive) to marker –
  – Sensitive population not well-defined
  – Lack of robust historical data
  – Can tolerate less precision for marker –
  – Aggressiveness of interim monitoring
  – Tolerable error rates for each subgroup
  – Can be generalized to other endpoints
Summary

- Enrolling all patients allows investigation of other biomarkers if biospecimens are collected.
- Can generalize to likelihood approach.
- In this setting a single arm trial can likely fail due to the failure of the biomarker.
- Weigh the amount of time to screen for a single arm trial in selected population against the time to accrue the first stage of the randomized trial in unselected patients.
Acknowledgements

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Thank you for your attention!