Clinical Trial Design to Expedite Drug Development

Mary W. Redman, Ph.D.
What do we mean by expediting drug development?

Phase I → Single Arm Phase II (expansion cohort) → Randomized Phase II → Phase III


Necessary?
Considerations for Choosing a Trial Design

• What is known about the disease?
  • How prevalent is the disease?
  • How is clinical efficacy typically measured?
  • What is current standard of care?

• What is known about the investigational therapy?
  • Mechanism of action
  • Safety/AE profile?
  • Studied in other populations?

• Is there a biomarker-defined population?
  • If yes, is it biomarker well defined?
  • Is there a candidate biomarker or a set of candidates?
  • Is the marker continuous or categorical – will a cut-point need to be investigated?
What is the underlying marker/outcome association?

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**Perfect Biomarker**

- Biomarker Threshold

**Perfect Biomarker?**

- Treatment effect

- What is clinically meaningful?
Designs to Evaluate Biomarkers/Subgroups

**Primary Analysis:**
Unselected or Minimally selected population

**Secondary Analyses:**
Biomarker evaluation

**Design:**
Single Arm Phase II
Randomized Phase III
Designs to Evaluate Biomarkers/Subgroups

Overall Population-focused
Majority $\alpha$ to entire study population

- Subgroup
  - Entire Study Population

Targeted or Master Protocol Design

```
“Positive” Subgroup 1
“Positive” Subgroup n
“Negative” Subgroup
```

Split type I error?

Subgroup-focused
Majority $\alpha$ to Subgroup

- Subgroup
  - Entire Study Population

Independent studies

“Positive” Subgroup
“Positive” Subgroup n
“Negative” Subgroup
Design and Definitive Evaluation

- Phase I -> Single Arm Phase II?
- Phase I -> Phase II followed by Phase III?
- Phase I -> Phase II/III?

Any of the biomarker designs can be used for either a single arm, randomized phase II, or randomized phase III

Approaches can use Outcome Adaptive versus Non-Adaptive Design Features
And/or
Frequentist versus Bayesian Inference
An adequate sample size is important for precision of parameter estimates.
Biomarker Discovery and a Single Arm Study

N = 100

<table>
<thead>
<tr>
<th>% w/ Marker</th>
<th>N Marker +</th>
<th>Power to Detect Difference Response Rate of:</th>
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<tr>
<td></td>
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<td>20%</td>
</tr>
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<td>10%</td>
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<tr>
<td>50%</td>
<td>50</td>
<td>73%</td>
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Based on example with response rate of 10% in “marker negative” group. 1-sided 0.05 level testing.
Biomarker Discovery/evaluation and a Phase III Study

N = 400

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<td>50%</td>
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<td>59%</td>
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<tr>
<td>60%</td>
<td>240</td>
<td>67%</td>
</tr>
<tr>
<td>70%</td>
<td>280</td>
<td>73%</td>
</tr>
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Based on example with median OS of 12 months, 24 months of accrual and 18 months of follow-up

NOTE: This is simply to detect an effect in the subgroup, not to detect an interaction!
Design for “Known” Biomarker as Primary Population

SWOG S0819

EGFR FISH +
PFS HR = 1.33
Power: 90%
\( \alpha = 0.02 \)
N=588

Entire Study Population
PFS HR = 1.2
Power: 84%
\( \alpha = 0.015 \)
N=1462

Other examples:
PD-L1 >50% vs. 1%

Activated: 07/09
Closed: 06/14

Redman, Crowley, Herbst et al CCR 2012
Proposed ECOG/SWOG Trial: INSIGNA

Study Chairs:
H. Borghaei
A. Chiang
TM: K Schalper
Stats: S. Dahlberg
M. Wu
M. Redman

Is PD-L1 expression enough or can we improve on it for patient selection?

N = 294/arm
Assume TM data: N = 235/arm
Discovery and Validation: Biomarker Adaptive Signature Design

**Stage I:**
- Initiate Accrual To Phase III Trial
  - Interim Analyses Per standard
    - Completion of Accrual

**Stage II:**
- **1. Biomarker Selection:** Select Biomarker Set for Testing Patient Specimens
- **2. Test Cohort:** Randomly select 50% of patients (with specimens) for biomarker discovery “signature” development
- **3. Validation Cohort:** Among remaining patients, classify as “signature” positive or negative. Test within the Positive subgroup

Freidlin and Simon CCR 2005
INSIGNA Study Design

Primary Population: PD-L1 > 1%

Co-primary: PD-L1 > 50%

Secondary: Biomarker “sensitive” Population determined During study conduct

Proposed Biomarker Analyses:
• PD-1 axis measures
• Tumor microenvironment
• mRNA immunoprofiling
• Whole exome DNA sequencing

Key secondary objective to discover and evaluate an immunosignature
Design: Seamless Phase II/III
Primary Endpoint: Phase II: PFS
Phase III: OS
Sample Size:
Phase II: 80-150
Phase III: 200-400#
# Includes phase II patients
Revised Lung-MAP Design (12/2015)

Previously-treated Stage IV or Recurrent Squamous Non-Small Cell Lung Cancer

Centralized NGS* Biomarker Profiling

NGS*-Biomarker Sub-studies

1. Biomarker 1 Positive
   - Sub-study 1
     - Biomarker-driven Targeted Therapy
       - Investigational therapy 1

2. ...Biomarker n Positive
   - ...Sub-study n
     - Biomarker-driven Targeted Therapy
       - Investigational therapy n

Non-NGS-Matched Sub-studies

1. Not Biomarker 1-n
   - Non-Match
     - Sub-study
       - Investigational therapy
       - Non-match Investigational therapy

   - Standard of Care

Stage 1:

Stage 2:

**Design:**
- Phase II -> III

**Primary Endpoint:**
- Phase II: Response
- Phase III: OS

**Sample Size:**
- Phase II: 40
- Phase III: 150-200

**Non-match**

**Unchanged**
Phase II/III Design

**Randomization**
- **Phase II Analysis:** 55 PFS events

**Phase III Interim Analyses**
- 50% and 75% OS
- PFS/OS Futility
- OS Efficacy

**Complete Accrual**

**Final Analysis:**
- 256 OS events
- ~290 PFS events

**Futility established**

**Stop**

12 months follow-up
Seamless transition between Single Arm Phase II and Phase III if study meets endpoint

Continuation to second stage will depend on accrual feasibility which will be assessed during Stage 1

If the ORR is very high, study may stop at Phase II for submission for FDA approval. To do so, would require discussions with FDA regarding sufficient data. Likely will need to accrue more patients (up to 100 total) and a small concurrent control population.
# Design Comparison

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<thead>
<tr>
<th></th>
<th>Phase II -&gt; Phase III</th>
<th>Phase II/III</th>
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<tbody>
<tr>
<td><strong>Endpoints Phase II</strong></td>
<td>Response or other robust single arm endpoint</td>
<td>Response, PFS, OS, other endpoints</td>
</tr>
<tr>
<td><strong>Efficiency gains?</strong></td>
<td>Yes, if investigational therapy is not effective or highly effective (and response is a good endpoint)</td>
<td>Yes, time-to-event endpoint is better reflective of drug activity, a phase III is needed</td>
</tr>
<tr>
<td><strong>Biomarker discovery/validation</strong></td>
<td>No/limited</td>
<td>Yes</td>
</tr>
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Proposed Lung-MAP New Design

Previously-treated Stage IV or Recurrent Non-Small Cell Lung Cancer (all histology) → Centralized NGS* Biomarker Profiling

NGS*-Biomarker Sub-studies

Biomarker 1 Positive
- Sub-study 1: Biomarker-driven Targeted Therapy
  - Investigational therapy 1

...Biomarker n Positive
- ...Sub-study n: Biomarker-driven Targeted Therapy
  - Investigational therapy n

Non-NGS-Matched Sub-studies

IO Naïve (squamous only)
- IO Sub-study 1
  - IO combo 1
  - Randomization
- IO combo m

IO Relapsed/Refractory
- Collect tissue for Immuno Biomarker Profiling

Stage 2:

Investigational therapy 1
- Standard of Care

Investigational therapy n
- Standard of Care

IO-relapsed/refractory study goals:
- Evaluate IO combinations
- Biomarker discovery (Immunoprofile) for evaluation in future studies
- Follow-on studies within Immuno-biomarker defined subsets may be done within this framework

Common Control
- Dealer’s choice based on histology

Old design

New design idea
Summary of Design Choices

All-comers Design
When you don’t know enough to include a biomarker-defined population as primary objective

Overall-population-focused Design
When there may be an overall effect but also have a candidate or set of candidate biomarkers (consider the discover/validate design)

Subgroup-focused Design
When you have good data on the biomarker, but all may benefit

Targeted/Master Protocol Design
When you think you know the biomarker and only the subgroup is going to benefit
Recommendations

General philosophy: Expediting drug development is not necessarily done by completing studies faster. It is done by designing trials that consider possible outcomes of a trial and the value of information provided by that trial.

• Biomarkers
  • Incorporate and explicit plan biomarker analysis in the design of clinical trials
  • Use a trial design that best incorporates what is known and objectives
  • Develop approaches to lessen reliance on tissue-based analyses and volumetric requirements

• Endpoints:
  • Design studies with an endpoint that can both reflect efficacy and futility
  • Develop intermediate (surrogate) endpoints that can be measured earlier.

• Trial design:
  • Randomize when it is the best way to answer a question and adds to broader knowledge
  • Spend more time in the discovery phase of drug and biomarker development