Transforming Oncology Clinical Development with Adaptive Studies

Cyrus Mehta, PhD, Cytel Inc.
Dr. John Grous, MD, Medelis
Introductions : Today’s Speakers

Cyrus Mehta, PhD., President and a Co-Founder of Cytel Inc.
Cyrus is among the pioneers of the biostatistical methodologies for adaptive trials. Cytel provides trial design software and consultancy services.

www.cytel.com

Dr. John Grous, MD, Vice President Medical Affairs, Medelis, Inc.
Medelis is an oncology-focused global CRO providing full service clinical studies.

www.medelis.com
Why “Transform” - What’s Wrong?

Trial innovations are in response to current discouraging state of drug development

- Staggering costs – up to $1 billion to develop an approved medicine
- Inordinate time – takes years, conventional studies stop & start gaps further impede
- High failure rate – over 50% in phase 3

and even higher in oncology studies
A New Era of Clinical Study

Adaptive approaches are profoundly changing the very nature of clinical trials

Industry, academia and regulators all progressing together

Worth the increased complexity, planning time, infrastructure because of the resulting increases in

- successful study outcomes
- development process improvements
- ultimately, approvals of more safe & effective treatments
Adaptive trial designs now impacting:

- Sponsor companies & research centers all sizes, at every stage: clinical strategy, study planning, implementation & execution
- Investors, development stakeholders
- Medical community - especially severe disease areas, oncology
- Patients in the study

These new approaches are radically changing clinical research - but, what exactly is an “adaptive trial design”? 

Who is Affected?

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What is an Adaptive Study?

2010 FDA Guidance Document Definition

“An adaptive design clinical study is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study.

Analyses of the accumulating study data are performed at prospectively planned timepoints within the study, can be performed in a fully blinded manner or in an unblinded manner, and can occur with or without formal statistical hypothesis testing.”

U.S. Dept. of Health & Human Services Food & Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
February 2010 Clinical/Medical
# Main Types of Adaptive Trials

<table>
<thead>
<tr>
<th>Adaptive types</th>
<th>Adaptations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 Dose Escalation CRM (CRM)</td>
<td>Choice of Next Dose</td>
</tr>
<tr>
<td>(Continual Reassessment Method)</td>
<td></td>
</tr>
<tr>
<td>Phase 2 Adaptive Dose Finding</td>
<td>Change of Randomization Fraction</td>
</tr>
<tr>
<td>Group Sequential</td>
<td>Early Stopping</td>
</tr>
<tr>
<td>SSR Blinded : Sample Size Re-Estimation - Based on Variance, Standard of Care...</td>
<td>Increase Sample Size</td>
</tr>
<tr>
<td>SSR Unblinded : Sample Size Re-Estimation - Based on Efficacy</td>
<td>Increase Sample Size</td>
</tr>
<tr>
<td>Population Enrichment</td>
<td>Modification of Inclusion Criteria → Sub-Population</td>
</tr>
<tr>
<td>Combined Phases 2 and 3 (was “Seamless”)</td>
<td>Dose Selection</td>
</tr>
</tbody>
</table>
Adaptive Strategies for Phase 3 Oncology Trials

Promising Zone Designs for Oncology Trials
April 7, 2011

Cyrus R. Mehta
President, Cytel Inc.

email: mehta@cytel.com – web: www.cytel.com – tel: 617-661-2011
Topics Covered

• Motivation for Sample Size Re-estimation
• Applicable to trials with short survival duration (e.g., metastatic lung or colorectal cancer, AML, etc.)
• Case Study: Metastatic Non-small Cell Lung Cancer
• Simulation Based Design
• Results
• Regulatory Issues
Sample Size Re-estimation

Motivation

• Primary endpoint is usually overall survival (OS)
• Small gains in OS (e.g. hazard ratios between 0.7 and 0.8) can nevertheless be clinically meaningful
• Sample size requirements for such small gains are large, and pose a major design challenge

Promising Zone designs resolve this difficulty by requiring a smaller up-front sample size commitment, to be followed up by a larger commitment only if interim results are promising

Cytel
Metastatic Non-small Cell Lung Cancer

- Primary endpoint is overall survival
- Design for 90% power; 5% significance level
- Plan for 24 month enrollment; 36 month trial
- Optimistic Scenario
  - Assume 8/11.4 month median on Ctrl/Trtm ($HR=0.7$)
  - Require 333 events and 400 subjects @ 17/month
- Pessimistic (but clinically meaningful) Scenario
  - Assume 8/10.4 month median on Ctrl/Trtm ($HR=0.77$)
  - Require 539 events and 763 subjects @ 32/month
  - Not a feasible option for sponsor
# Group Sequential Design

**Survival Superiority Trials: Two Sample Test - Logrank Test. Given Accrual Duration and Status**

<table>
<thead>
<tr>
<th></th>
<th>Plan ID</th>
<th>Plan 1</th>
<th>Plan 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Sided or 2-Sided Test</td>
<td>1-Sided</td>
<td>1-Sided</td>
<td></td>
</tr>
<tr>
<td>Significance Level (Alpha)</td>
<td>0.025</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>Power (1 - Beta)</td>
<td>0.9</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Assigned Fraction (Treatment)</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td><strong>Boundary Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned Number of Looks</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Spacing of Looks</td>
<td>Equal</td>
<td>Equal</td>
<td></td>
</tr>
<tr>
<td>Hypothesis to be Rejected</td>
<td>H0 or H1 (NB)</td>
<td>H0 or H1 (NB)</td>
<td></td>
</tr>
<tr>
<td>Boundary Family</td>
<td>SpF (Pub)</td>
<td>SpF (Pub)</td>
<td></td>
</tr>
<tr>
<td>Boundary to Reject H0</td>
<td>LD (OF)</td>
<td>LD (OF)</td>
<td></td>
</tr>
<tr>
<td>Boundary to Reject H1</td>
<td>Gm (-5)</td>
<td>Gm (-5)</td>
<td></td>
</tr>
<tr>
<td><strong>Survival Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Log-hazard Ratio</td>
<td>0.3567</td>
<td>0.2614</td>
<td></td>
</tr>
<tr>
<td>Number of Hazard Pieces</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Number of Accrual Periods</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Variance of -Log-hazard Ratio</td>
<td>Null</td>
<td>Null</td>
<td></td>
</tr>
<tr>
<td><strong>Committed Accrual</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Committed Accrual (Duration)</td>
<td>24.0</td>
<td>24.0</td>
<td></td>
</tr>
<tr>
<td>Committed Accrual (Subjects)</td>
<td>417</td>
<td>763</td>
<td></td>
</tr>
<tr>
<td><strong>Max. Duration and Events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum Study Duration</td>
<td>36.0</td>
<td>36.0</td>
<td></td>
</tr>
<tr>
<td>Maximum Number of Events</td>
<td>333</td>
<td>620</td>
<td></td>
</tr>
<tr>
<td><strong>Expected Values under...</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expected Accrual (Subjects)</td>
<td>377</td>
<td>692</td>
<td></td>
</tr>
<tr>
<td>Expected Study Duration</td>
<td>26.348</td>
<td>26.949</td>
<td></td>
</tr>
<tr>
<td>Expected Number of Events</td>
<td>258</td>
<td>480</td>
<td></td>
</tr>
</tbody>
</table>
Sponsor is Resource and Time Constrained

- Unable to invest up-front to protect power in case of pessimistic scenario
- But willing to invest additional resources if interim results are promising

<table>
<thead>
<tr>
<th>True HR</th>
<th>Power of Optimistic Design</th>
<th>Power of Pessimistic Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.71</td>
<td>91%</td>
<td>99%</td>
</tr>
<tr>
<td>0.74</td>
<td>78%</td>
<td>97%</td>
</tr>
<tr>
<td>0.77</td>
<td>66%</td>
<td>90%</td>
</tr>
</tbody>
</table>
Sponsor Adopts an Adaptive Strategy

- Design optimistically (HR=0.7; 333 events; 400 subjects)
- One interim analysis after 50% information
  - Stop early if overwhelming evidence of efficacy
  - Stop early for futility if low conditional power
  - Increase number of events, sample size and (if possible) rate of recruitment at the interim if results are promising
Specify the Promising Zone

• Specified in terms of Conditional Power (CP)
  
  Conditional power is the probability that the study will be positive, given the current outcome trend

• We define the promising zone as \( 30\% \leq CP < 90\% \)

• This is equivalent to observing a hazard ratio between 0.74 and 0.83
Early Stopping Boundaries
The Adaptive Decision Rules

- Conditional Power = Prob of success at end of trial given interim results
- Increase the number of events if conditional power is in the Promising Zone

(The % increase in number of events is typically between 50% and 100%)

% increase in number of events

- Futility (0.2%)
- Unfavorable Zone
- Promising Zone
- Favorable Zone
- Efficacy (99%)

Conditional Power

0% 30% (HR=0.83) 90% (HR = 0.74) 100%
Schema of Adaptive Design

Flow chart for the Adaptive Decision Rules

1. Interim Analysis
   Calculate one-sided p-value: $p_1$
   - $p_1 < 0.0015$: STOP for efficacy
   - $p_1 \geq 0.0015$: CONTINUE Analysis

2. Compute Conditional Power (CP)
   - HR $\geq 1.02$: STOP for futility
   - HR $< 1.02$: CONTINUE Analysis
   - CP "high" or "low": CONTINUE as originally planned (333 events)
   - CP in "Promising Zone": Increase to a maximum of 500 events

Group-sequential portion acc. to Lan DeMets / O’Brien Fleming
Adaptation Principles

- Primary driver of power is number of events
- FDA Guidance recommends increase only, not decrease
- Increase events by amount needed to achieve some target conditional power, subject to a cap
- Increase sample size only to avoid undue prolongation of trial
- Complex relationship between power, events, sample size and study duration is best evaluated by simulation
Simulate the Design

### Survival Superiority Trials: Two Sample Test - Logrank Test: Given Accrual Duration and Study Duration

<table>
<thead>
<tr>
<th>Input Parameters</th>
<th>Output for all Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use NMax Till 'L' Looks, L = 1</td>
<td>Show Summary for</td>
</tr>
<tr>
<td>Maximum Increase in Events</td>
<td>All Trials</td>
</tr>
<tr>
<td>50.00%</td>
<td>557</td>
</tr>
<tr>
<td>Fixed increase in Subjects</td>
<td>671</td>
</tr>
<tr>
<td>Expected Study Duration</td>
<td></td>
</tr>
<tr>
<td>Upper Limit on Study Duration</td>
<td>90.00</td>
</tr>
<tr>
<td>Shape Parameter for Reestimating # Events</td>
<td>0.99</td>
</tr>
<tr>
<td>Promising Zone: Min CP:</td>
<td>0.30</td>
</tr>
<tr>
<td>Max CP:</td>
<td>0.90</td>
</tr>
<tr>
<td>Type of Adaptation</td>
<td>Increase Sample Size</td>
</tr>
<tr>
<td>Accrual Rate After Adaptation</td>
<td>No Change</td>
</tr>
</tbody>
</table>

#### Simulation Results by Zone

<table>
<thead>
<tr>
<th>Zone</th>
<th>Simulations Rejecting H0</th>
<th>Simulations not Rejecting H0</th>
<th>Total Simulations</th>
<th>Avg. Study Duration</th>
<th>Avg. Number of Events</th>
<th>Avg. Accrual Duration</th>
<th>Avg. Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>Row %</td>
<td>Count</td>
<td>Row %</td>
<td>Count</td>
<td>Column %</td>
<td></td>
</tr>
<tr>
<td>Futility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfavorable: CP &lt; 0.300</td>
<td>896</td>
<td>27.8%</td>
<td>2324</td>
<td>72.2%</td>
<td>3220</td>
<td>32.2%</td>
<td>29.1</td>
</tr>
<tr>
<td>Promising: 0.300 ≤ CP &lt; 0.900</td>
<td>2925</td>
<td>84.7%</td>
<td>530</td>
<td>15.3%</td>
<td>3455</td>
<td>34.6%</td>
<td>38.2</td>
</tr>
<tr>
<td>Favorable: CP ≥ 0.900</td>
<td>3031</td>
<td>91.2%</td>
<td>294</td>
<td>8.8%</td>
<td>3325</td>
<td>33.3%</td>
<td>29.2</td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Trials</td>
<td>6852</td>
<td>68.5%</td>
<td>3148</td>
<td>31.5%</td>
<td>10000</td>
<td>100.0%</td>
<td>32.3</td>
</tr>
</tbody>
</table>
### Operating Characteristics of Optimistic Design (Powered to Detect HR=0.7)

1. **Simulations Under Pessimistic Scenario, HR = 0.77 (10,000 simulations)**

<table>
<thead>
<tr>
<th>Zone</th>
<th>P(Zone)</th>
<th>Power</th>
<th>Duration (months)</th>
<th>SampSize</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NonAdpt</td>
<td>Adapt</td>
<td>NonAdpt</td>
</tr>
<tr>
<td>Unf</td>
<td>32%</td>
<td>31%</td>
<td>31%</td>
<td>33</td>
</tr>
<tr>
<td>Prom</td>
<td>32%</td>
<td>69%</td>
<td>88%</td>
<td>35</td>
</tr>
<tr>
<td>Fav</td>
<td>36%</td>
<td>93%</td>
<td>93%</td>
<td>31</td>
</tr>
</tbody>
</table>

2. **Simulations Under Optimistic Scenario, HR = 0.7 (10,000 simulations)**

<table>
<thead>
<tr>
<th>Zone</th>
<th>P(Zone)</th>
<th>Power</th>
<th>Duration</th>
<th>SampSize</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NonAdpt</td>
<td>Adapt</td>
<td>NonAdpt</td>
</tr>
<tr>
<td>Unf</td>
<td>14%</td>
<td>57%</td>
<td>57%</td>
<td>35</td>
</tr>
<tr>
<td>Prom</td>
<td>26%</td>
<td>88%</td>
<td>98%</td>
<td>36</td>
</tr>
<tr>
<td>Fav</td>
<td>60%</td>
<td>98%</td>
<td>98%</td>
<td>29</td>
</tr>
</tbody>
</table>
Attractiveness of Approach

• Up-front sample size investment can be modest
• Additional investment of sample size is only made if interim results are promising
• If that happens, chances of success are dramatically increased, thereby justifying the additional investment
• A practical approach for reducing the risk of designing an underpowered study
Regulatory Considerations

• Statistical methods for preventing error inflation are well established and published

• Nevertheless, FDA Guidance classifies this method as less well understood

• Regulators are more concerned about Logistical and Operational biases that about statistical validity of unblinded sample size re-estimation
Logistical and Operational Biases

- Are interim decision rules pre-specified?
- Are they carried out as pre-specified?
- Who has access to them?
- Who prepares the interim report?
- Who has access to the interim report and how is confidentiality maintained?
- Can interim results be reverse engineered from actions taken?
Concluding Comments

Considerable planning and documentation is required in order to obtain regulatory approval for a pivotal adaptive design.

- Explain why the adaptation is necessary? Can the study not meet its objectives by other means?
- Including all technical details of the statistical methodology, supported by simulation results, in the charter
- Create processes for preventing operational and logistical biases by premature disclosure of interim results
Population Enrichment

Motivation: Proliferation of Targeted Therapies

- Non-Small Cell Lung Cancer: 65% response rate with EGFR mutations vs 5% without, if treated with erlotnib (Jackman, ASCO, 2009)
- Colorectal Cancer: 23% response rate with KRAS wild-type vs 0% with KRAS mutations, if treated with cetuximab (Souglakos, Br. J. Cancer, 2009)
- Breast Cancer: 0.53 HR with high Ki-67 labelling index, versus 0.81 HR with low Ki-67, if treated with letrozole (Viale, JCO, 2009)

Problem: All discoveries based on retrospective analysis
Prospective Design

• Start out by opening enrollment to the broader population with and without the biomarker

• At interim look, restrict enrollment to the subgroup that appears to benefit

• Methodology Papers:
  – Brannath et. al. (Statist. Med., 2009)
  – Mehta et. al. (Circulation, 2009)
Who Benefits - Why this Matters

Sponsors and stakeholders: Improved outcomes

Driven by high attrition rates and high cost of traditional methods:
- All the major biopharmas,
- increasingly at small-to-mid size pharmas & biotechs,
- CROs, hospitals, research centers – all are staging adaptive studies.

Medical community: Better treatments, sooner

Adaptive approaches are playing a growing role toward making more safe & effective medicines available sooner.

Study patients: Ethical advantages

The patient in an adaptive study is more likely to receive an effective treatment to beneficially shift research focus to best responding dose levels and/or sub-populations.
Adaptive Impact on Clinical Operations

- **Randomization changes** resulting from design modification(s)
- **Drug supply management** realities of multiple doses at multiple sites, then carrying out the adaptive change
- “**Reverse-engineering**” the treatment plan by stakeholders, or by investigators, perhaps by patients
- **Potential increased resources/costs (tradeoffs):**
  - Additional patient recruitment from sample-size increase, or from population enrichment
  - Additional sites, requisite staffing and support
Key Guidance Points

Regulatory outlook, the 2010 adaptive guidance draft

• Only pre-defined changes allowed, as specified in the study protocol
• The adaptive design must rigorously control type one error, assure validity
• Use of trial simulations encouraged, employ and share “predictive tools”
• Larger, later stage studies more complex, consult regulators early and allow adequate review
• Design modifications usually interim analyses-based (IA)
• Often at confirmatory stage, an independent Data Monitoring Committee (DMC) makes the adaptive decisions – not the sponsor

FDA, EMA, MHRA, etc. all essentially consistent in policy
Learn More - Meet Us

Check [www.cytel.com](http://www.cytel.com) and [www.medelis.com](http://www.medelis.com) often

ASCO/Chicago June 3 – 7

Cyrus hosts viewing of poster accepted at ASCO

*Adaptive design of VALOR, a phase 3 trial of vosaroxin or placebo in combination with cytarabine for patients with first relapsed or refractory acute myeloid leukemia.* Abstract ID: TPS201

Exact time & place TBA (watch cytel.com and/or medelis.com)

DIA/Chicago June 19 – 22

Cytel and colleague speakers, adaptive talks to include oncology applications.

Additional 2011 oncology development conferences

The Oncology Leaders Forum, Boston in November
Please complete the short survey that appears immediately upon webinar end.

Your opinions and interests will help guide our thinking toward shaping an agenda for a potential operations-focused webinar.

Thank you.
Learn More - References

More on www.cytel.com and www.medelis.com

General audience, overviews


• *Innovation in Drug Development: Adaptive Designs for Clinical Trials*
  ©Bay Clinical R&D Services San Ramon, CA aretzios@adrclinresearch.com

Selected Publications, technical

• FDA Adaptive Trial Guidance [www.fda.gov](http://www.fda.gov) search: “download adaptive guidance”

• *Adaptive increase in sample size when interim results are promising* by Cyrus Mehta, Stuart Pocock, *Statistics in Medicine* 2010 ©A John Wiley Publication

• *Confirmatory adaptive designs with Bayesian decision tools for a targeted oncology therapy* by Werner Brannath, et al, *Statistics in Medicine* 2010 ©A John Wiley Publication (Novartis adaptive population enrichment trial)

• *Optimizing trial design: sequential, adaptive, and enrichment strategies.*
Thank you for your attention and Good Day.

Cyrus Mehta, PhD, Cytel Inc.
John Grous, MD, Medelis
Promising Zone