

Transforming Oncology Clinical Development with Adaptive Studies

**Cyrus Mehta, PhD, Cytel Inc.
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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 \$1billion 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

Who is Affected?

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”?

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

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

Adaptive Strategies for Phase 3 Oncology Trials

**Promising Zone Designs
for Oncology Trials
April 7, 2011**

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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

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 Sta

Plan ID	Plan1	Plan2
Test Parameters		
1-Sided or 2-Sided Test	1-Sided	1-Sided
Significance Level (Alpha)	0.025	0.025
Power (1 - Beta)	0.9	0.9
Assigned Fraction (Treatment)	0.5	0.5
Boundary Parameters		
Planned Number of Looks	2	2
Spacing of Looks	Equal	Equal
Hypothesis to be Rejected	H0 or H1 (NB)	H0 or H1 (NB)
Boundary Family	SpF (Pub)	SpF (Pub)
Boundary to Reject H0	LD (OF)	LD (OF)
Boundary to Reject H1	Gm (-5)	Gm (-5)
Survival Parameters		
-Log-hazard Ratio	0.3567	0.2614
Number of Hazard Pieces	1	1
Number of Accrual Periods	1	1
Variance of -Log-hazard Ratio	Null	Null
Committed Accrual		
Committed Accrual (Duration)	24.0	24.0
Committed Accrual (Subjects)	417	763
Max. Duration and Events		
Maximum Study Duration	36.0	36.0
Maximum Number of Events	333	620
Expected Values under...		
Expected Accrual (Subjects)	H0: 377, H1: 400, H 1/2: 407	H0: 692, H1: 730, H 1/2: 743
Expected Study Duration	26.348, 31.852, 31.981	26.949, 31.821, 32.5
Expected Number of Events	258, 290, 311	480, 539, 578

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

True HR	Power of Optimistic Design	Power of Pessimistic Design
0.71	91%	99%
0.74	78%	97%
0.77	66%	90%

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**

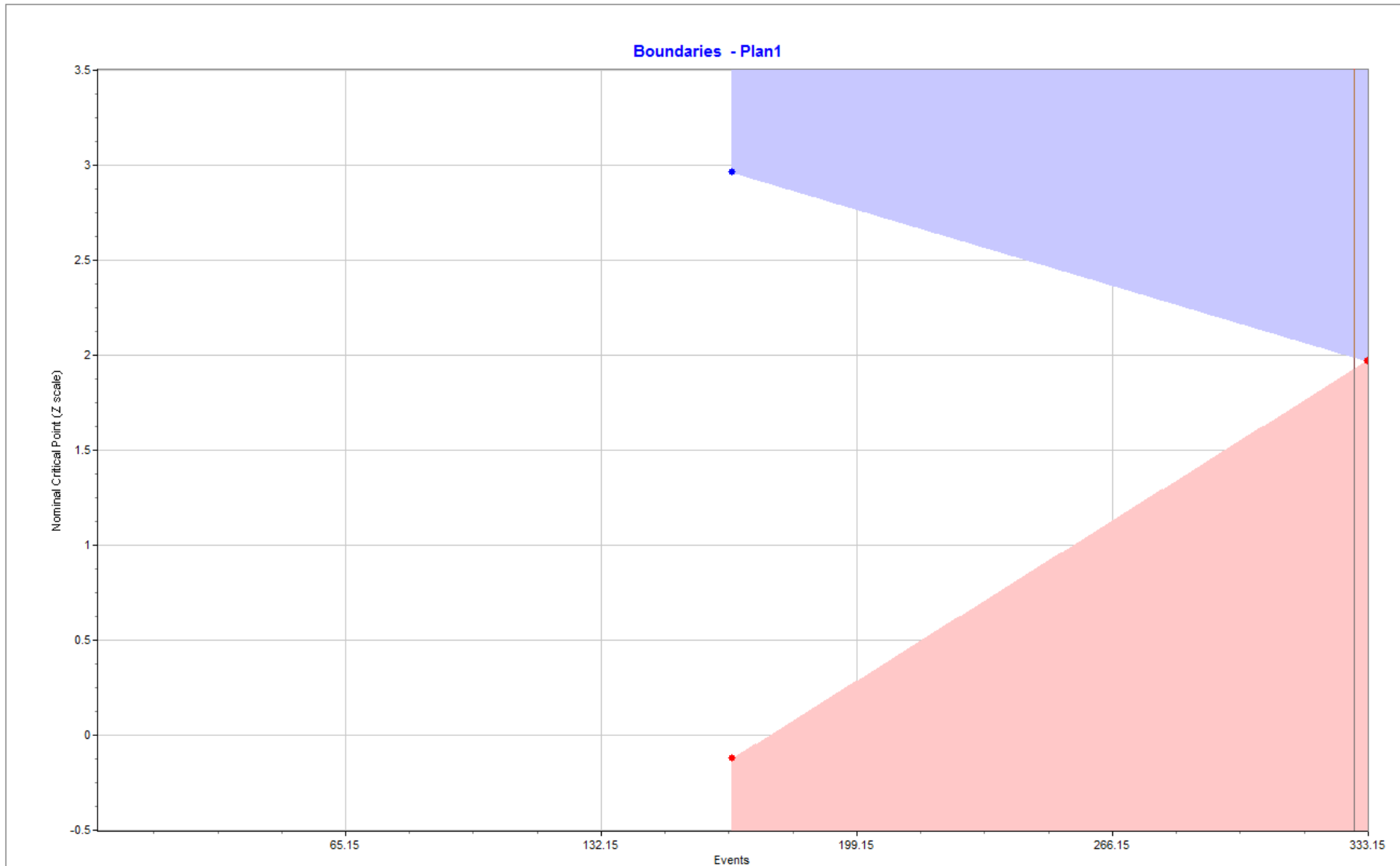
Specify the Promising Zone

- Specified in terms of Conditional Power (CP)

Conditional power is the probability that the study will be positive, given the current outcome trend

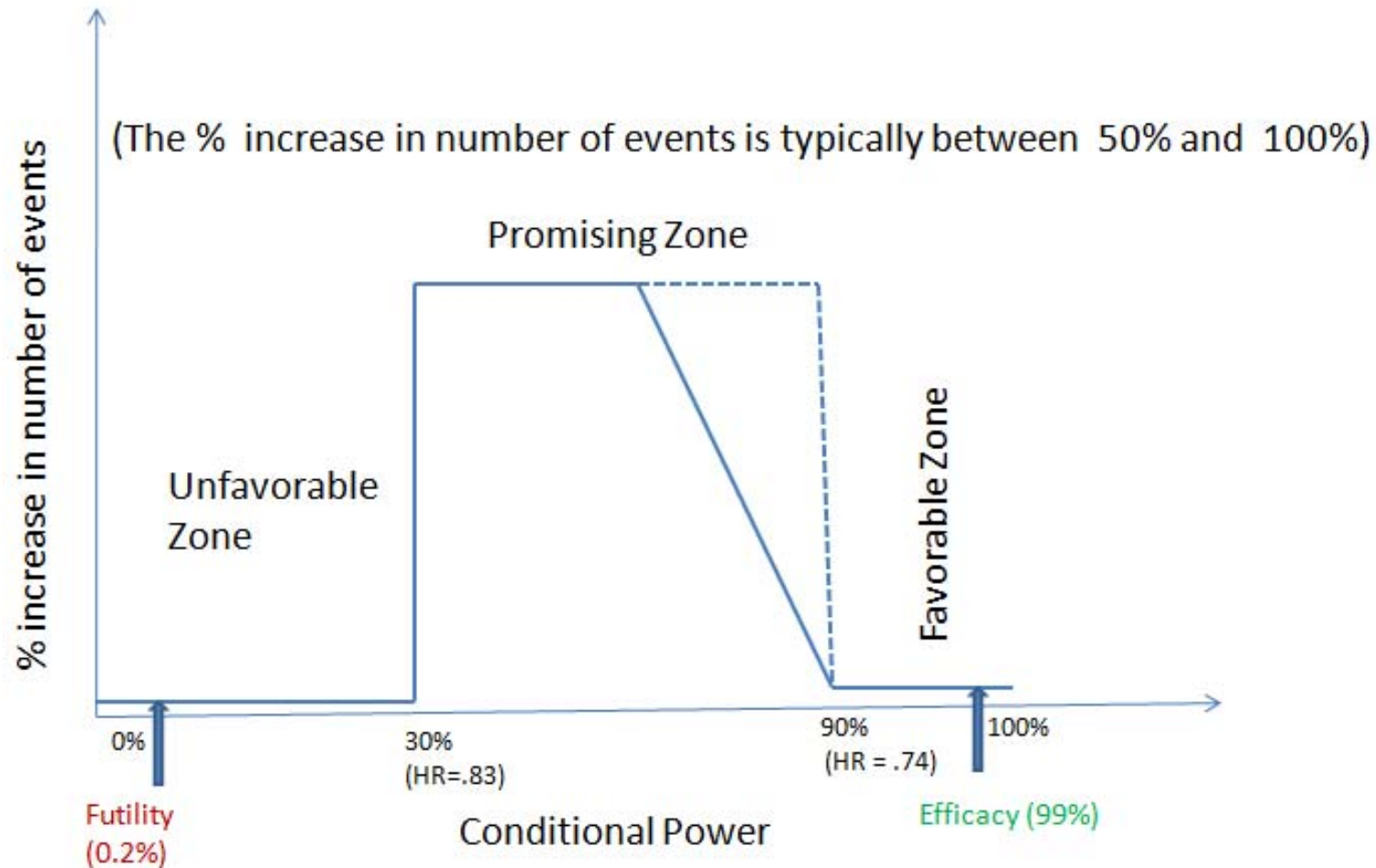
- We define the promising zone as $30\% \leq \text{CP} < 90\%$
- This is equivalent to observing a hazard ratio between 0.74 and 0.83

Early Stopping Boundaries



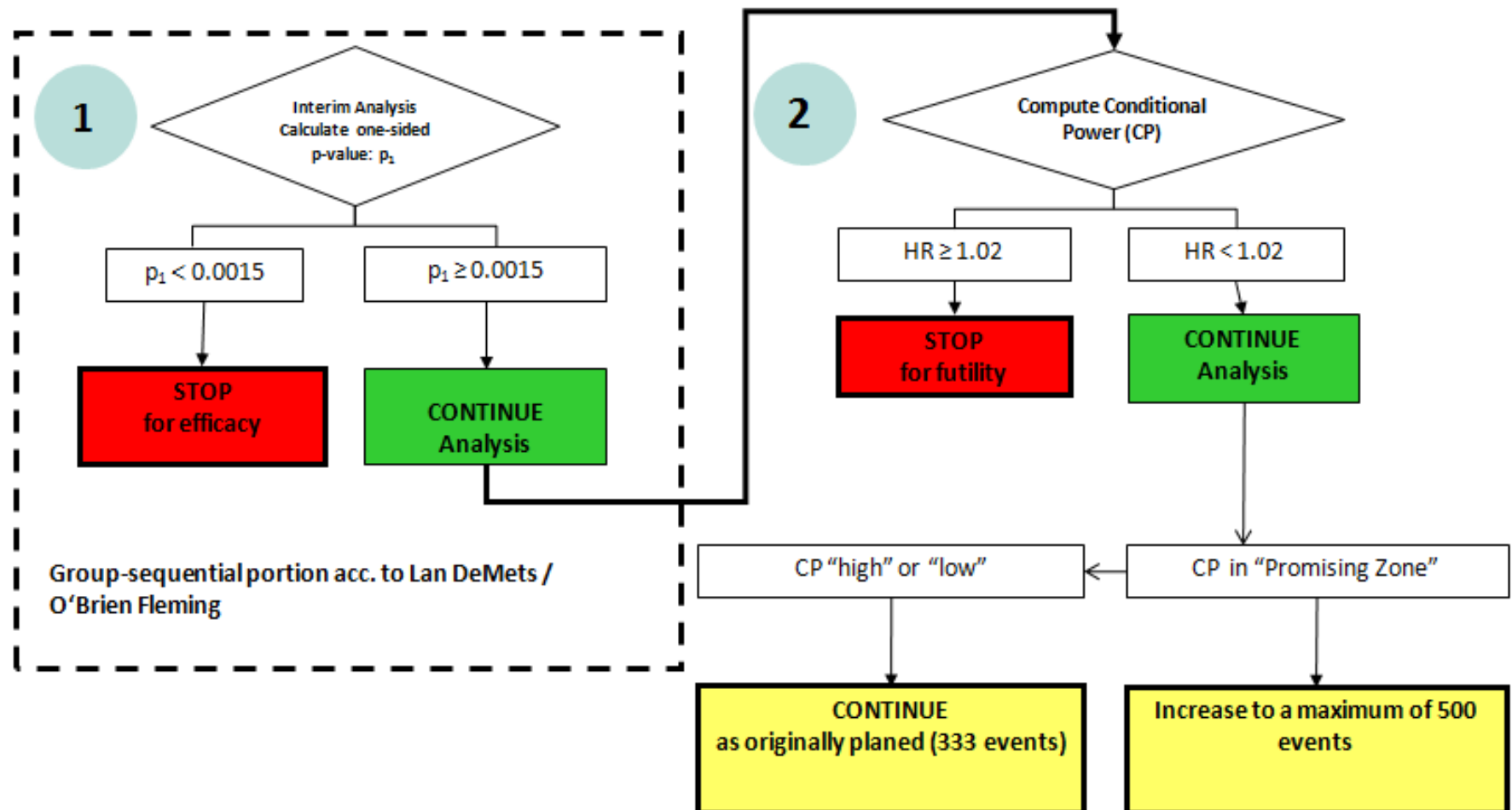
The Adaptive Decision Rules

- 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



Schema of Adaptive Design

Flow chart for the Adaptive Decision Rules



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

Perform Adaptation if Necessary

Input Parameters	
Use NMax Till 'L' Looks, L =	1
Maximum Increase in Events	50.00% 557
Fixed increase in Subjects	50.00% 671
Expected Study Duration	
Upper Limit on Study Duration	90.00
Shape Parameter for Reestimating # Events	0.99
Promising Zone :	Min CP: 0.30
	Max CP: 0.90
Type of Adaptation	Increase Sample Size
Accrual Rate After Adaptation	No Change

Output for all Trials				
Show Summary for		All Trials		
Percentile	Study Duration	Number of Events	Accrual Duration	Number of Subjects
5%	28.0	371	23.9	447
25%	28.9	371	23.9	447
50%	29.8	371	24.0	447
75%	37.8	557	35.6	671
95%	39.1	557	36.5	671
Average	32.3	435	28.1	524

Run Single Step Reset Stop

Simulation Results by Zone

Zone	Simulations Rejecting H0		Simulations not Rejecting H0		Total Simulations		Avg. Study Duration	Avg. Number of Events	Avg. Accrual Duration	Avg. Number of Subjects
	Count	Row %	Count	Row %	Count	Column %				
- Futility										
Unfavorable: CP < 0.300	896	27.8%	2324	72.2%	3220	32.2%	29.1	371	23.9	447
Promising: 0.300 ≤ CP < 0.900	2925	84.7%	530	15.3%	3455	34.6%	38.2	557	35.9	671
- Favorable: CP ≥ 0.900	3031	91.2%	294	8.8%	3325	33.3%	29.2	371	23.9	447
Efficacy										
All Trials	6852	68.5%	3148	31.5%	10000	100.0%	32.3	435	28.1	524

Operating Characteristics of Optimistic Design (Powered to Detect HR=0.7)

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

Zone	P(Zone)	Power		Duration (months)		SampSize	
		NonAdpt	Adapt	NonAdpt	Adapt	NonAdpt	Adapt
Unf	32%	31%	31%	33	33	409	409
Prom	32%	69%	88%	35	43	418	627
Fav	36%	93%	93%	31	31	398	398

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

Zone	P(Zone)	Power		Duration		SampSize	
		NonAdpt	Adapt	NonAdpt	Adapt	NonAdpt	Adapt
Unf	14%	57%	57%	35	35	414	414
Prom	26%	88%	98%	36	44	418	627
Fav	60%	98%	98%	29	29	390	390

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 than 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 erlotinib (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:
 - Wang, O'Neill, Hung (Pharm. Stat., 2007)
 - Friedlin & Simon (Clin. Cancer Res., 2005)
 - 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 and 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 Take the 5 minute Survey

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

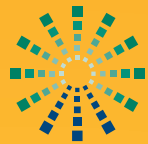
More on www.cytel.com and www.medelis.com

General audience, overviews

- **Nature Reviews Drug Discovery The Future of Drug Development: Advancing Clinical Trial Design “Perspectives”** article Oct 2009. doi:10.1039/rd3025
- **Innovation in Drug Development: Adaptive Designs for Clinical Trials**
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Selected Publications, technical

- FDA Adaptive Trial Guidance 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.**
Circulation 119, 597-605. Mehta C, Gao P, Bhatt DL, Harrington RA, Skerjanec S, Ware JH (2009)



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**Thank you for your attention
and Good Day.**

**Cyrus Mehta, PhD, Cytel Inc.
John Grous, MD, Medelis**

Promising Zone

