Friends Annual Meeting

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Global Harmonization of Drug Development

Richard Pazdur, MD; FDA OCE
Prudence Scott, MD; Medex Consulting
Francesco Pignatti, MD; EMA

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Panel Three: Optimization of Exploratory Randomized Trials

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Lisa LaVange, PhD
FDA

Panelists

- **Lisa LaVange, PhD**; FDA
- **Eric Kowack, MS, MBA**; Ignyta
- **Amy McKee, MD**; FDA
- **Cyrus Mehta, PhD**; Cytel
- **Richard Simon, D.Sc**; NCI
- **Rajeshwari Sridhara, PhD**; FDA
- **Yanping Wang, PhD**; Eli Lilly & Co.

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Optimization of Exploratory Randomized Trials

Lisa M. LaVange, PhD
Director, Office of Biostatistics
CDER, FDA

Friends of Cancer Research
Annual Meeting
November 16, 2016

Background

- Recent oncology research → new, highly effective therapies
  - May show large treatment effects early in development
  - Need to speed these new therapies to market while also ensuring sufficient rigor to allow regulatory scrutiny
- Specific challenges include:
  - Lack of planning in certain aspects of the trial can make results difficult to interpret, e.g., multiple looks at the data, multiple endpoints
  - Early evidence of effect may be seen in secondary endpoints, e.g., overall survival
  - Results can negatively impact ability of the next, larger pivotal trial to enroll

Session Objectives

- Better understand the problem through some recent examples
  - Focus is on early randomized trials designed to inform sponsors on a go/no-go decision
  - Options in reaction to exceptional results include trial expansion to determine if benefit is maintained or submission of data while possibly initiating pivotal trial
- Discuss options for FDA in interpreting early trial results
  - Are there statistical methods that can be applied post hoc to alleviate problems incurred with looser/unknown operating characteristics of early trials?
- Discuss options for sponsors to better plan for the possibility of exciting results in early trials
  - With care to not impede research by placing too many requirements on early trials

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Amy McKee, MD
FDA

Go/No-go Trials Supporting Approval: Case Studies

Amy McKee, M.D.
Deputy Office Director (acting)
Office of Hematology and Oncology Products
OND/CDER/FDA

Issue

- Small, activity-estimating, **randomized** trial reads out with unexpected results, perhaps in secondary endpoint
- Statistical plan written with less restrictive operating characteristics typical of phase 2 trial
- Regulatory conundrum: what to do with a marketing application based on this type of trial?

Case study #1: Olaratumab (Lartruvo™)

- Human Anti-PDGFRα Monoclonal Antibody
- Small, randomized phase 1b/2 trial (JGDG)
  - Phase 2 portion randomized as add-on versus standard therapy in first-line setting
  - 133 patients with advanced STS not amenable to curative surgery/radiation
  - Primary endpoint: PFS (2-sided alpha=0.2)
    - Secondary endpoint: OS

JGDG Trial Design

Stratification factors:
PDGFR-α expression
Prior lines of treatment
Histology
ECOG PS

130 Patients with Advanced STS

Randomize 1:1

1° endpoint:
PFS

Olaratumab 15 mg/kg day 1 & 8
Doxorubucin 75 mg/m^2 day 1

Treat x 8 21-day cycles

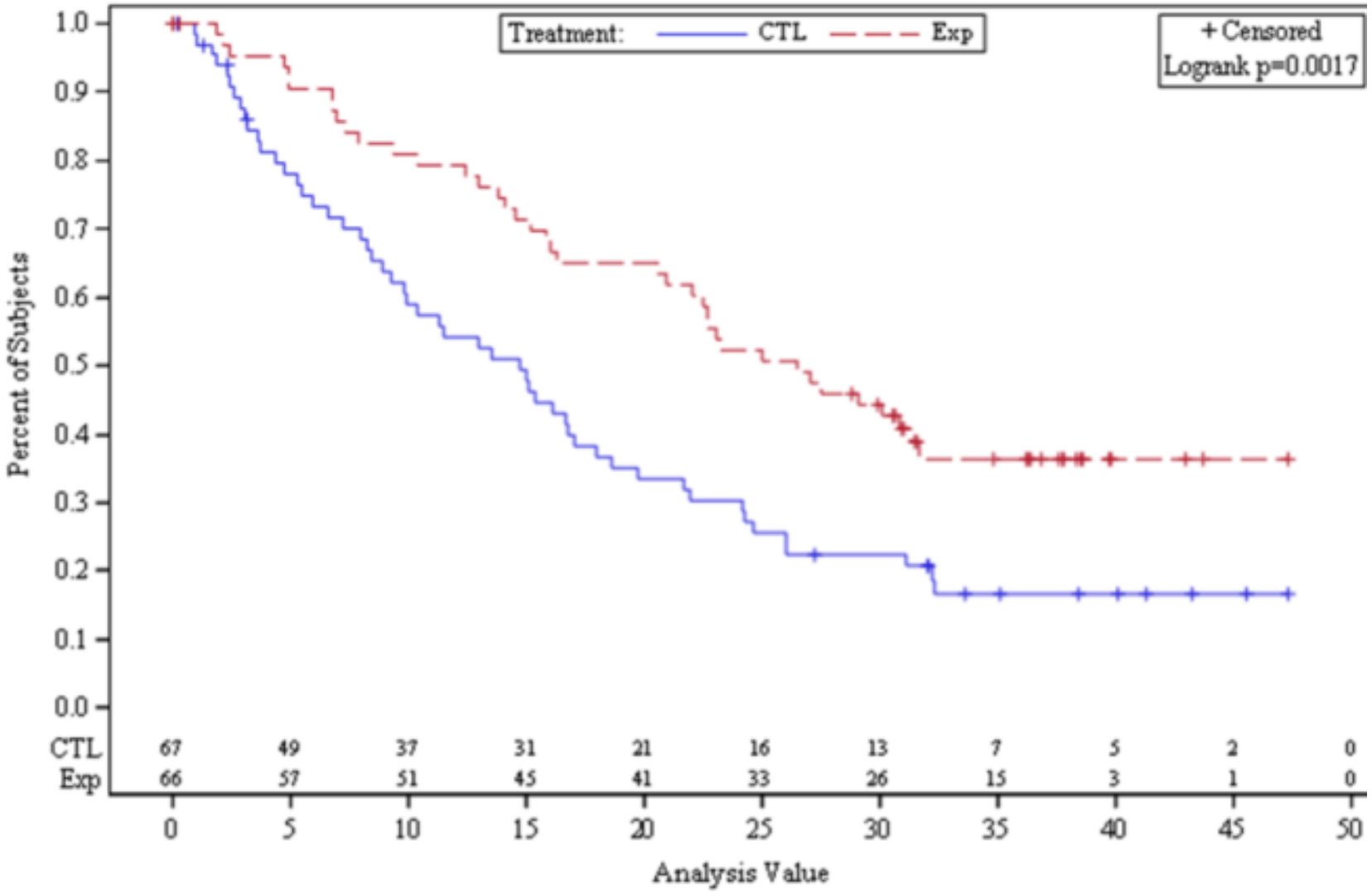
Olaratumab 15 mg/kg day 1 & 8

Doxorubucin 75 mg/m^2 day 1

Treat x 8 21-day cycles

Disease evaluations:
every 6 weeks x 4
then every 12 weeks

Case study #1: Olaratumab (Lartruvo™)



	No. of Subjects	Event		Censored		Median Survival (95% CL)	
CTL	67	78%	(52)	22%	(15)	14.719	(9.232 17.051)
Exp	66	59%	(39)	41%	(27)	26.513	(20.895 31.671)

Case study #1: Olaratumab (Lartruvo™)

	Olaratumab + Doxorubicin N=66	Doxorubicin N=67	p-value
PFS			
Median (months)	6.6 months [95% CI: 4.1, 8.3]	4.1 months [95% CI: 2.8, 5.4]	
Hazard Ratio	0.67		0.06*
OS			
Median (months)	26.5 months [95% CI: 20.9, 31.7]	14.7 months [95% CI: 9.2, 17.1]	
Hazard Ratio	0.46		0.0004

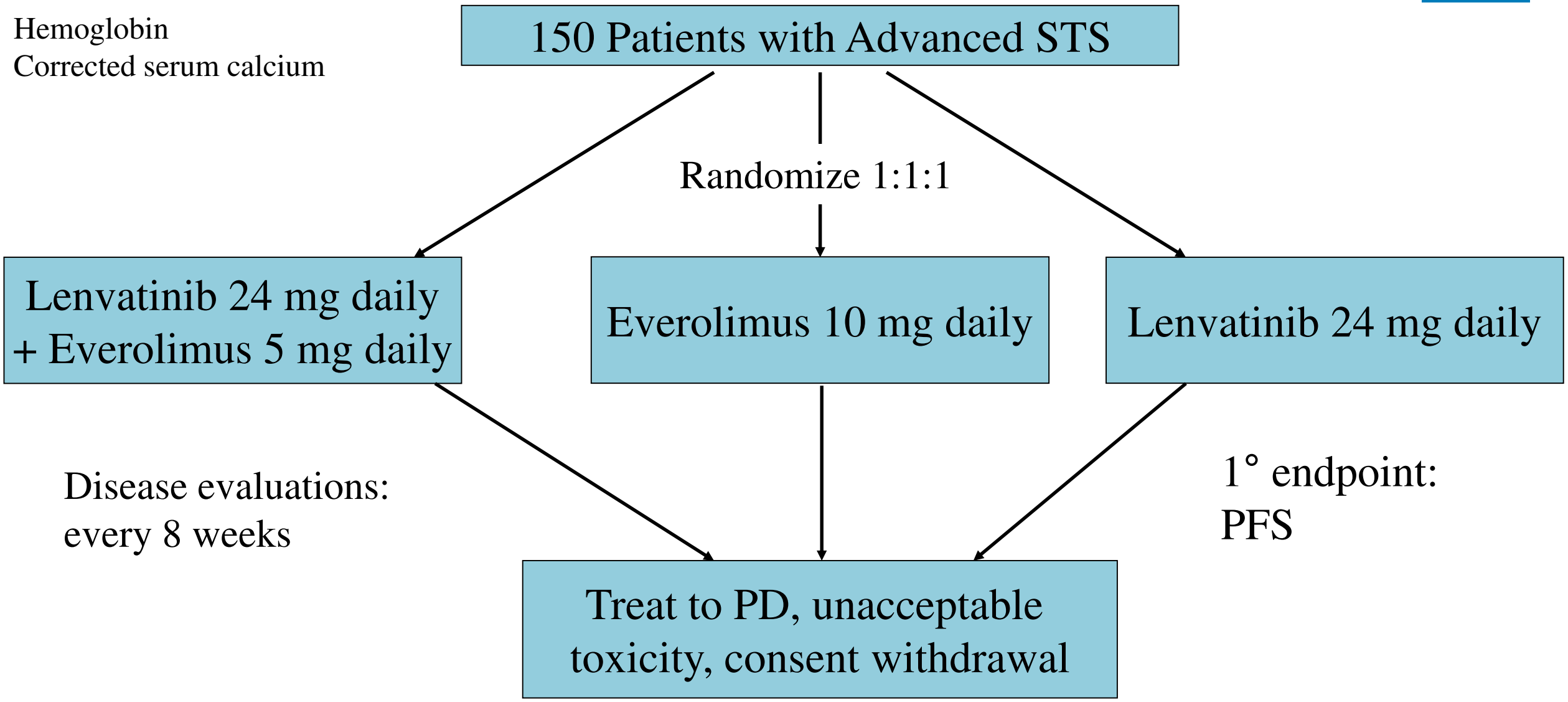
*2-sided alpha=0.1999

Case study #2: Lenvatinib (Lenvima®)

- Small molecule tyrosine kinase inhibitor against VEGFR1, VEGFR2 and VEGFR3
- Small, randomized phase 1b/2 trial
  - Phase 2 portion andomized 1:1:1 to lenvatinib + everolimus, everolimus alone, or lenvatinib alone
  - 153 patients with renal cell carcinoma in second-line setting
  - Primary endpoint: PFS
    - Secondary endpoint: OS

Trial Design

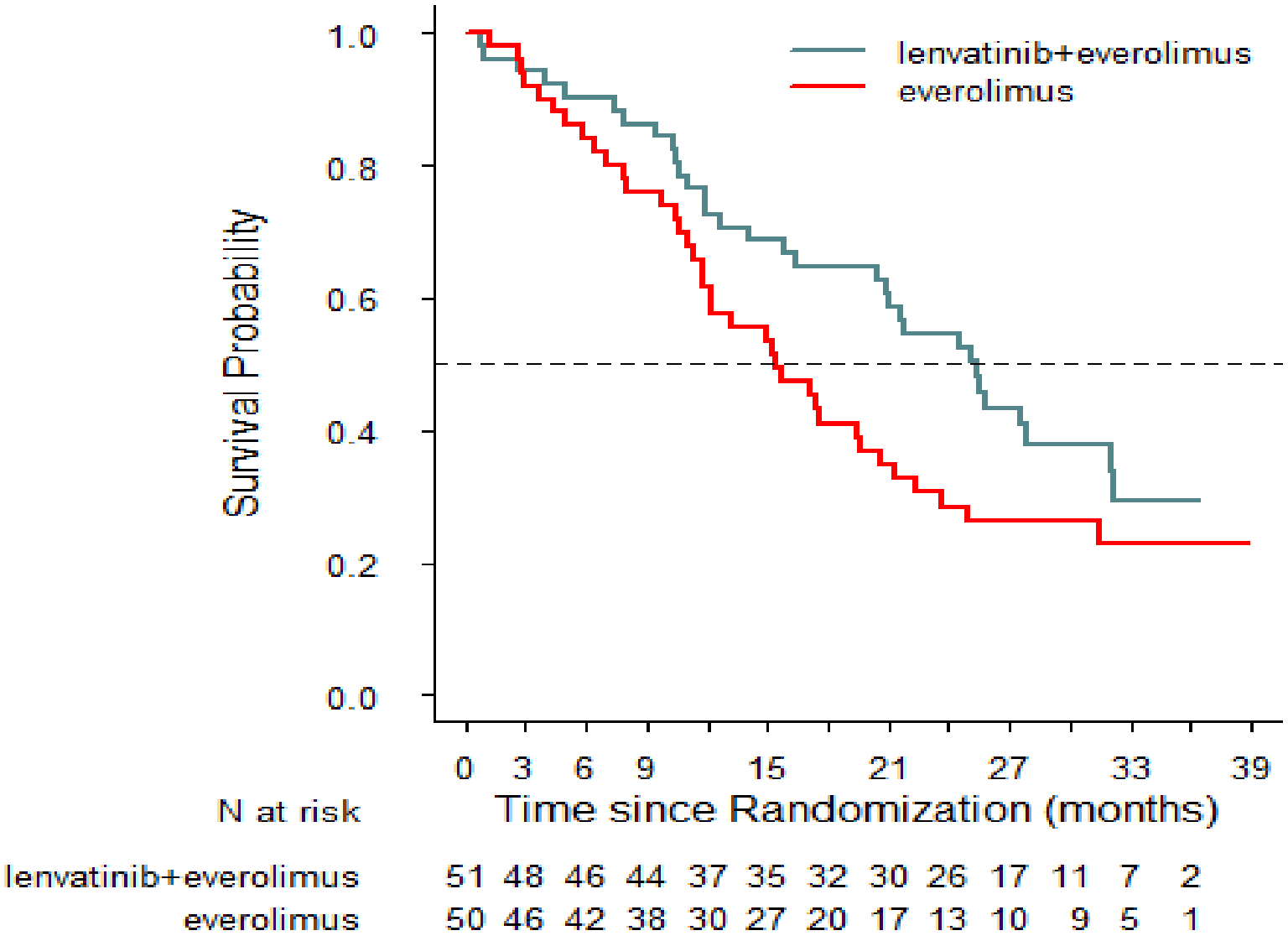
Stratification factors:
Hemoglobin
Corrected serum calcium



Disease evaluations:
every 8 weeks

1° endpoint:
PFS

Case study #2: Lenvatinib (Lenvima®)



Case study #2: Lenvatinib (Lenvima®)

	Lenvatinib + Everolimus N=51	**Everolimus alone N=50**	**Lenvatinib alone N-52**
PFS			
Median	14.6 months	5.5 months	7.4 months
Hazard Ratio vs evero alone	0.37* [95% CI: 0.22, 0.62]		0.57* [95% CI: 0.36, 0.91]
OS			
Median	25.5 months	15.4 months	19.1 months
Hazard Ratio vs evero alone	0.67* [95% CI: 0.42, 1.08]		0.80* [95% CI: 0.50, 1.27]

*p-values uninterpretable due to lack of pre-specified multiplicity adjustment

Conclusions

- Both olaratumab and lenvatinib received approval
- How can we prospectively design Phase 2 trials potentially to be both go/no-go and registration trials?

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Richard Simon, D.Sc
NCI

Bayesian analysis of unexpected survival “significance” in a randomized phase II trial

Richard Simon, D.Sc.

- Many phase II trials are randomized because:
  - New drug is combined with standard regimen
  - Evaluation of progression free survival requires control group
  - Toxicity better assessed with control group

Differences Between Phase III and Randomized Phase II

	Phase II	Phase III
Primary endpoint	Progression-free survival Response rate	Survival
Sample size	Small - moderate	Large
Significance threshold	0.10 1-sided	0.05 2-sided
Analysis	Not-blinded	Blinded
Analysis plan	Flexible	Pre-specified

Surprises in RCT Outcomes

- Treatment difference for secondary endpoint
  - When OS is the secondary endpoint
- Treatment difference for subset of patients when there is no overall difference
- Treatment difference for a subset of clinical centers
- Un-expected serious toxicity from a list of examined toxicities

Some Problems With p Values for Data-driven Hypotheses

- The interpretation of p value as false-positive error requires pre-specification of hypothesis
- Proper calculation of p value depends on sampling plan which may have been flexible or data driven; not fixed sample size as assumed
- Same p value calculation for primary as for 10 secondary hypotheses. Only way of penalizing is by multiplicity correction.

Some Problems With p Values for Data-driven Hypotheses

- Based on null hypothesis of no treatment effect; does not reflect clinical significance

Why a Bayesian Model?

- Depends on data at analysis, not on data at earlier analyses
- Provides direct method for taking account of the fact that the outcome was for a secondary endpoint
- Can take into account clinical significance

Model

- δ = log hazard ratio for survival of patient receiving test treatment T relative to survival of patient receiving control C
- Hazard (t) = risk of death in interval (t, t + ε) given that the patient is alive at time t
- Proportional hazard models assume that the hazard ratio is the same at all times t.
- $$hazard\ ratio = \frac{Rx\ T\ hazard(t)}{Rx\ C\ hazard(t)}$$

Model

- hazard ratio =1 means no treatment effect
- hazard ratio = 0.75 or 0.70 means there is a minimally clinically significant treatment effect
- hazard ratio $\leqq$0.75 or $\leqq$0.70 means that there is a treatment effect that is at least minimally clinically significant
- The true hazard ratio is unknown. The clinical trial provides us some information about it.

Model

- Using the data from the clinical trial, we would like to compute the probability that hazard ratio $\leqq 0.75$ or 0.70
- Since it uses the data from the clinical trial, it is called a posterior probability
- In order to compute the posterior probability, we have to specify our prior probability about the hazard ratio

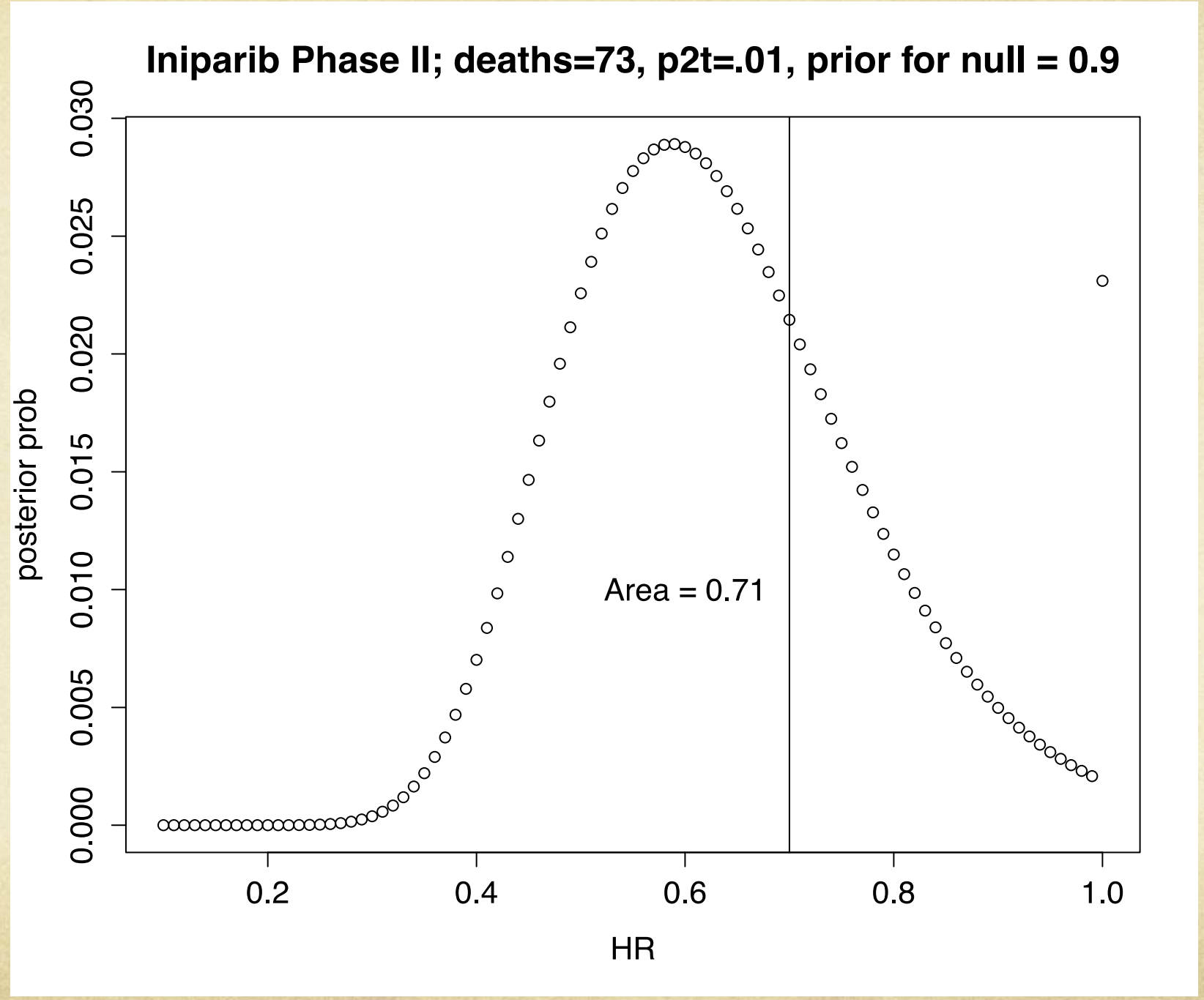
- Our prior belief about the hazard ratio is not a number; it is a specification of possible hazard ratio values and strengths of belief we hold for those numbers.
- People with very strong prior beliefs that hazard ratio=1 will need very strong evidence to change their beliefs

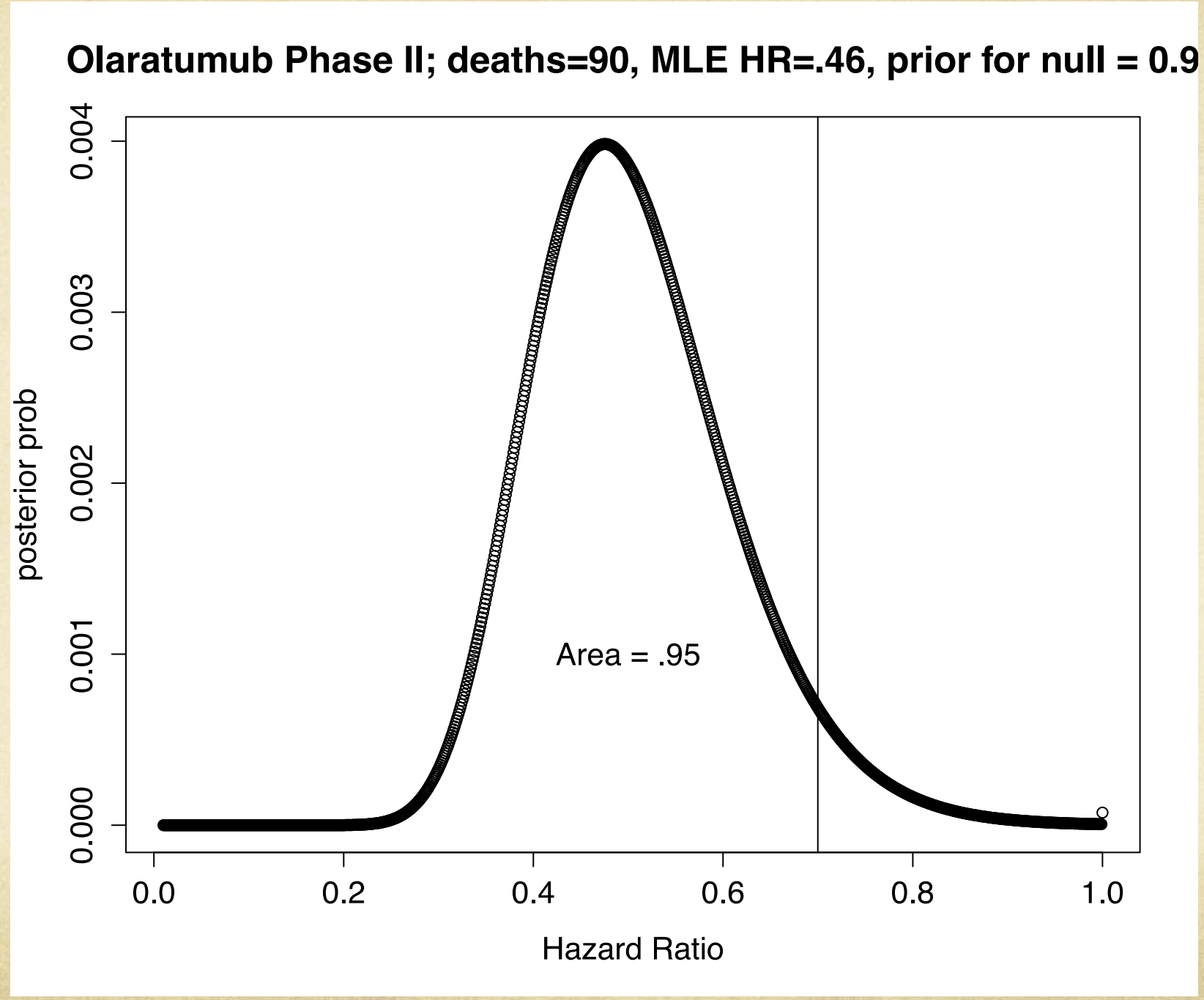
- If the clinical trial were a phase III trial being conducted because previous phase II trials indicated that the test treatment was effective, our prior belief that the hazard ratio =1 might be about 50% or less.
- For a phase II trial being planned to evaluate whether the treatment has an effect on PFS, a “surprising result” on OS means we have a greater prior belief that the hazard ratio for OS =1.
- For our calculations, we take the prior probability that the hazard ratio = 1 as 0.90

- With this Bayesian model, we have placed the rest of the prior probability about the hazard ratio over the entire region < 1 using the negative part of a Gaussian distribution $N(0,\tau)$ for log(hazard ratio).
  - We have found that the results are robust with regard to the specification of the standard deviation τ.

To Compute the Posterior Probability Distribution of the hazard ratio

- Specify the estimated hazard ratio based on the clinical trial data
- Specify the number of total deaths observed in the final analysis of the clinical trial
  - The sample variance of the observed log hazard ratio equals 4/total deaths
- Specify your prior beliefs about the OS hazard ratio
  - Prior probability hazard ratio = 1 (0.90)
  - Standard deviation τ of distribution of log hazard ratio (1)


Iniparib Phase II; deaths=73, p2t=.01, prior for null = 0.9
posterior prob
0.000
0.005
0.010
0.015
0.020
0.025
0.030
Area = 0.71
0.2
0.4
0.6
0.8
1.0
HR


Olaratumub Phase II; deaths=90, MLE HR=.46, prior for null = 0.9
posterior prob
0.000
0.001
0.002
0.003
0.004
Area = .95
0.0
0.2
0.4
0.6
0.8
1.0
Hazard Ratio

Relationship of Nominal p value for OS to Posterior Probability of Clinical Significance

# events	p_{2t}	Posterior Probability	
		Hr ≤ .70	Hr ≤.75
25	.05	.75	.81
	.01	.88	.91
	.001	.96	.97
	.0001	.99	.99
50	.05	.66	.75
	.01	.83	.89
	.001	.95	.97
	.0001	.98	.99
100	.01	.71	.82
	.001	.89	.95
	.0001	.96	.98

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Yanping Wang, PhD
Eli Lilly & Co.

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Cyrus Mehta, PhD
Cytel Inc

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Panel 3: Optimization of Exploratory Randomized Trials

Cyrus Mehta, Ph.D.

Cytel Inc

and

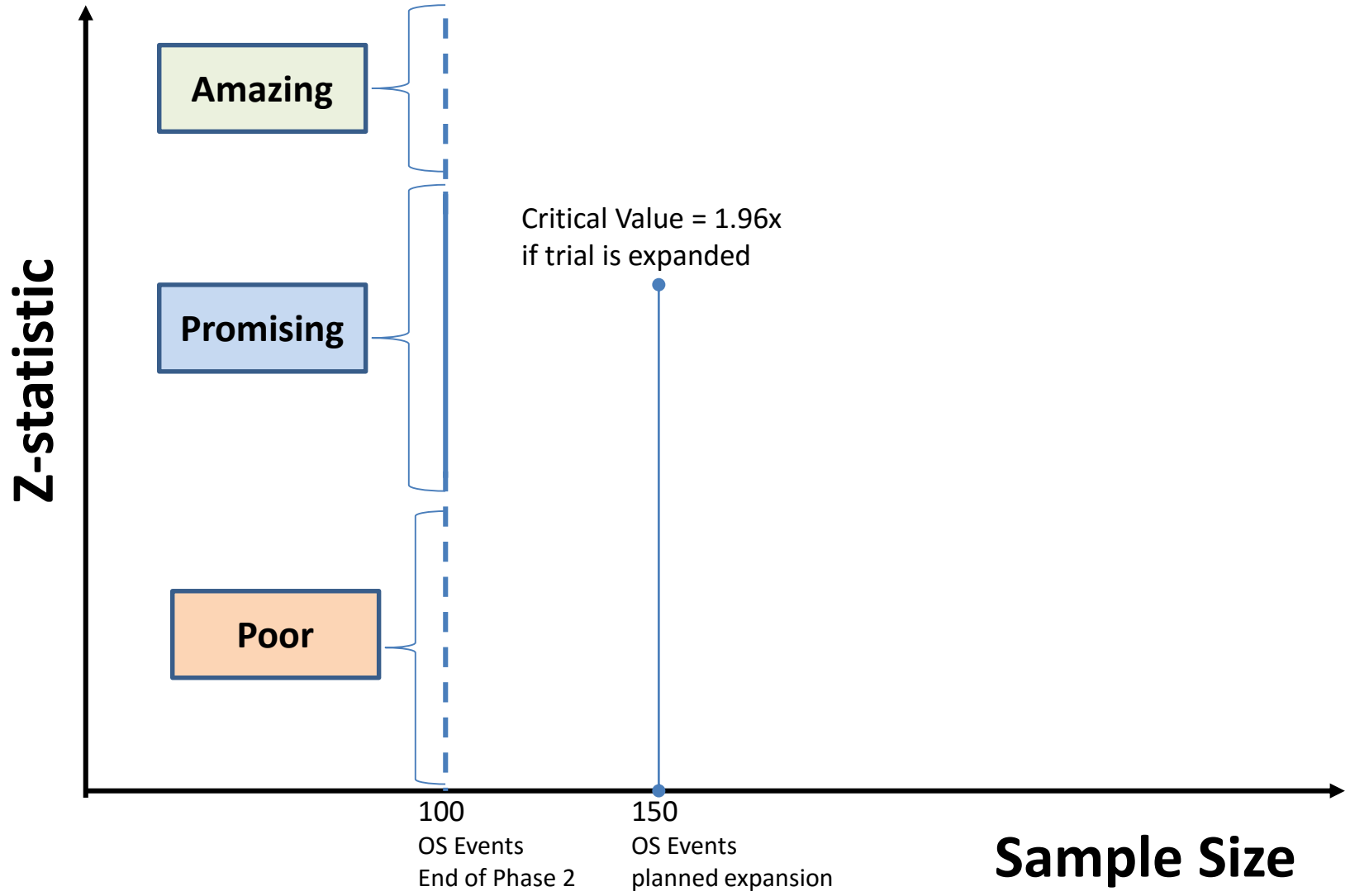
Harvard TH Chan School of Public Health

November 16, 2016, Washington DC

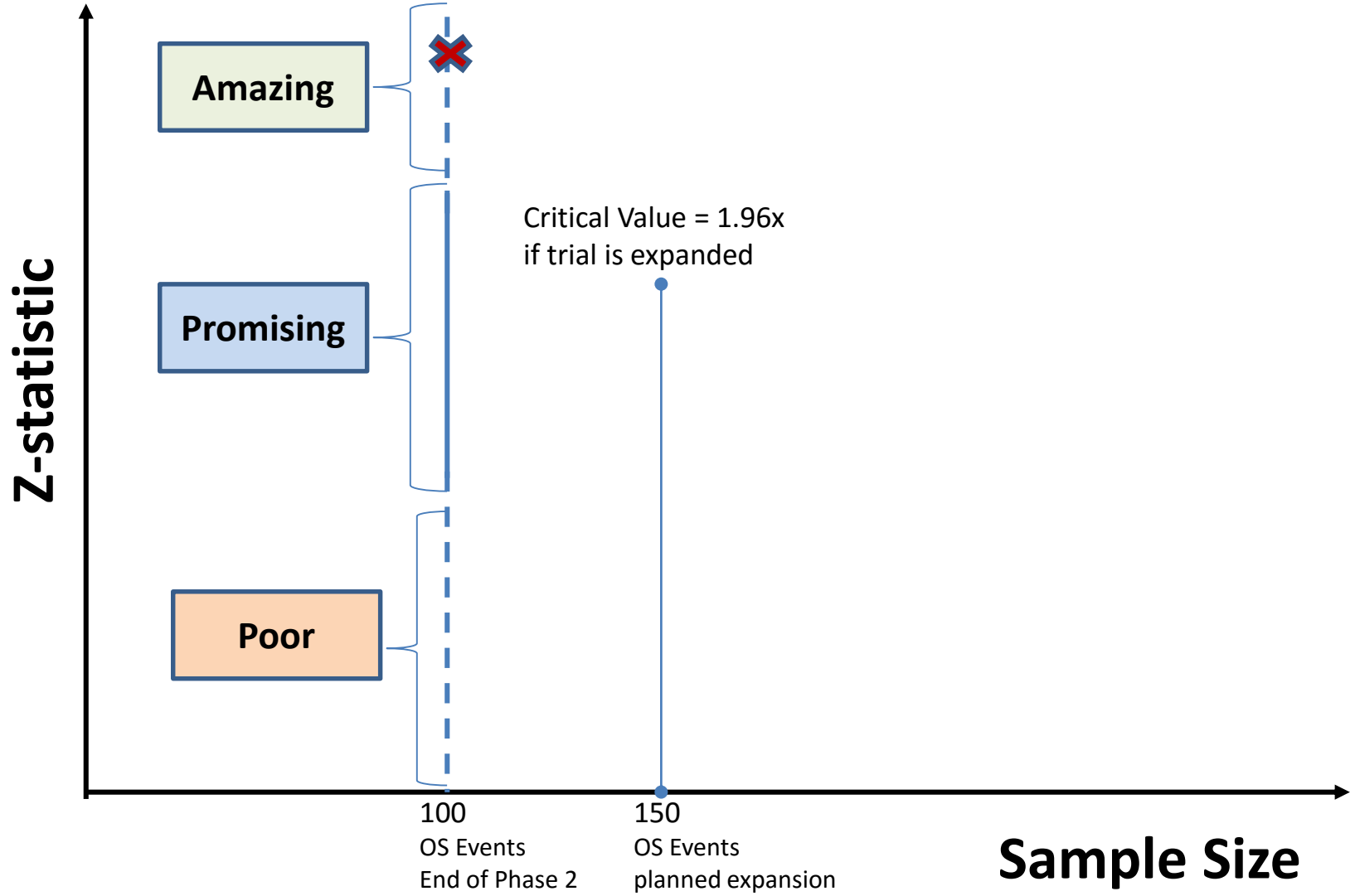
Making provision for unexpected results in Phase 2 trials

- Suppose a phase 2 oncology trials shows unexpectedly strong results in OS
- Depending on the strength of evidence and quality of the data it may be possible to:
  - File a regulatory submission (exceptional case)
  - Expand the trial with additional patients and follow-up (very promising case)
- What minimum design-time pre-specification will permit trial expansion without undermining statistical integrity?

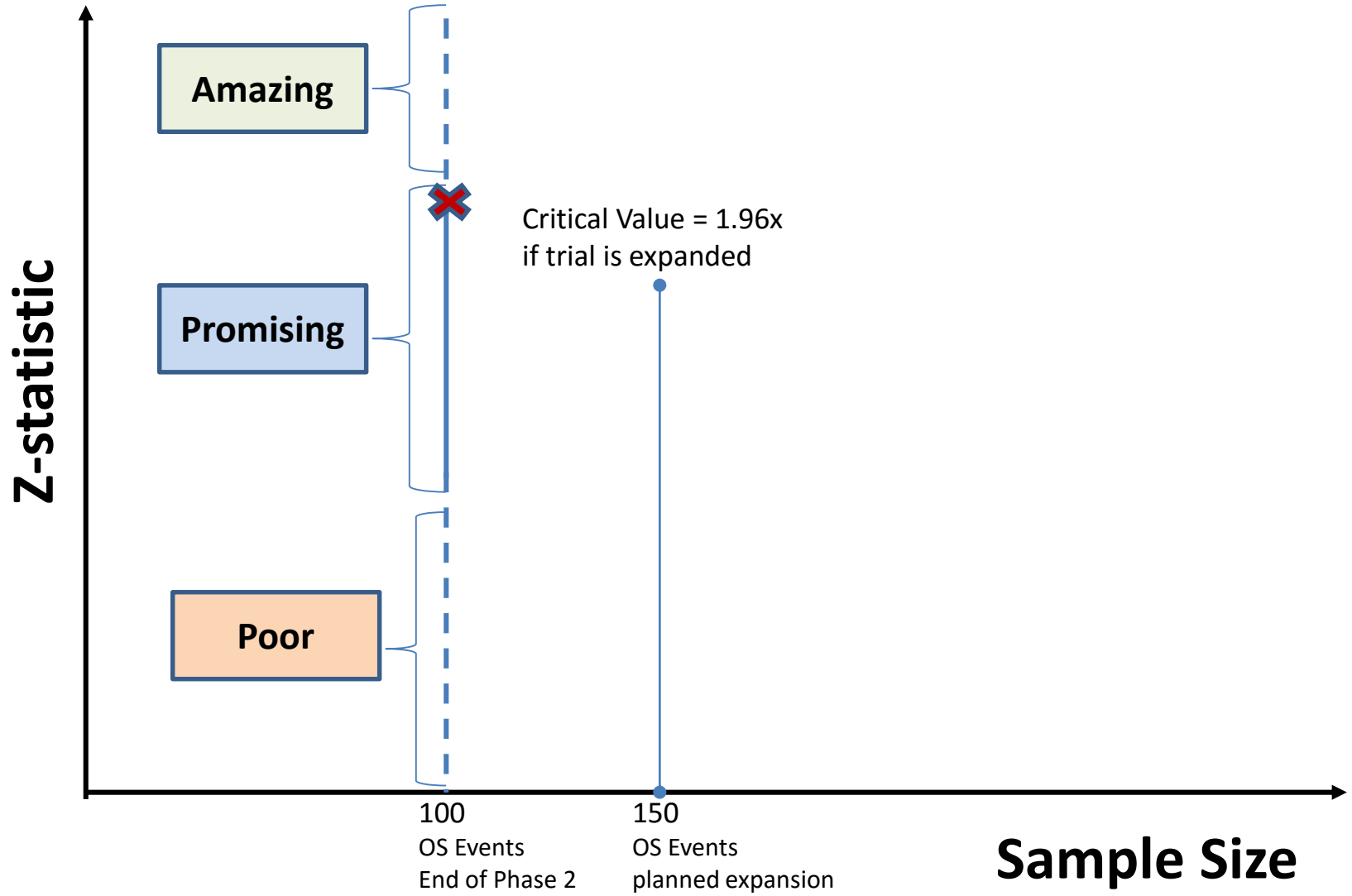
Basic Phase 2 Design with Provision for Expansion if Results are Promising



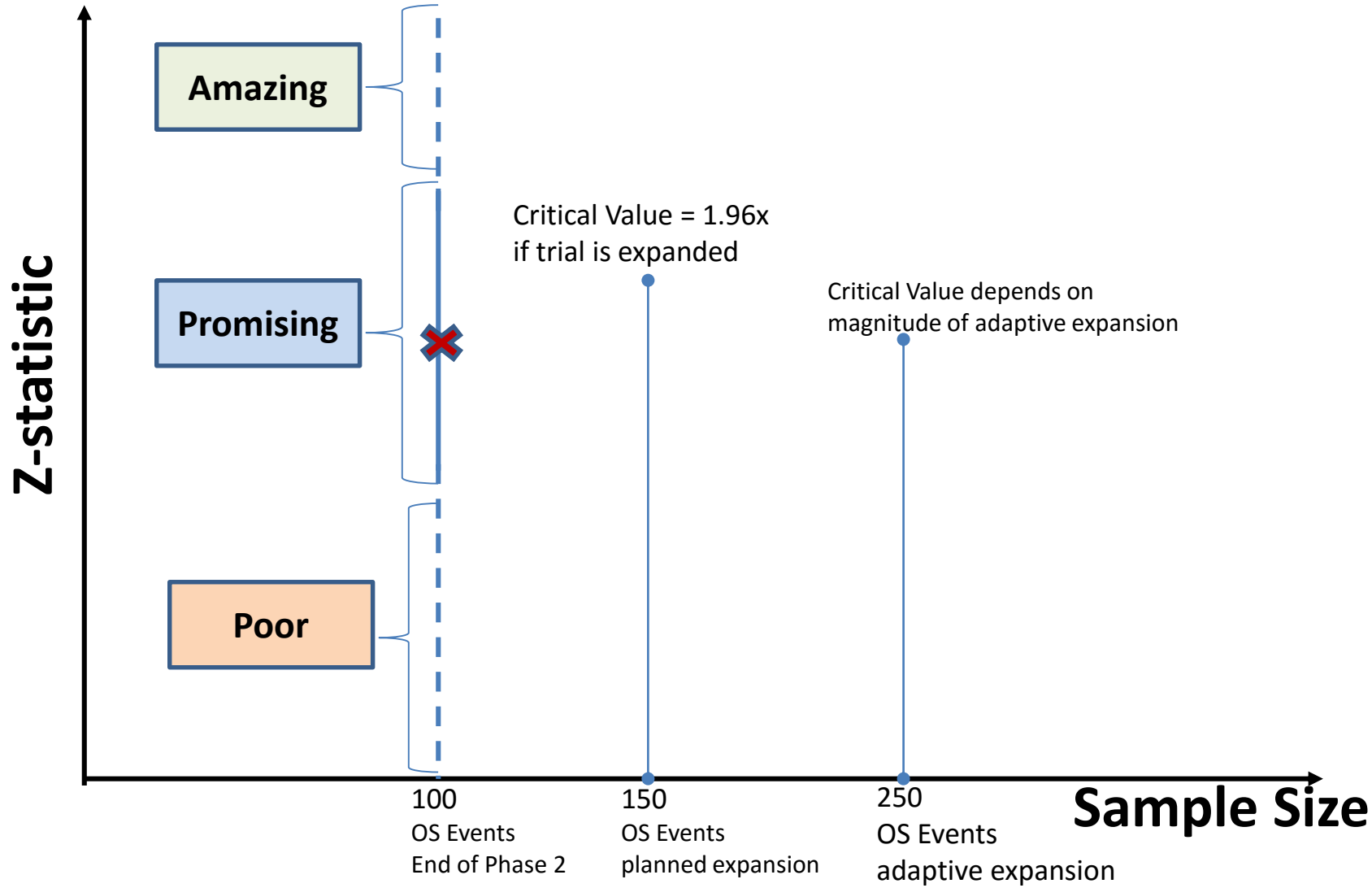
Case 1: Amazing result obtained. Stop trial and submit



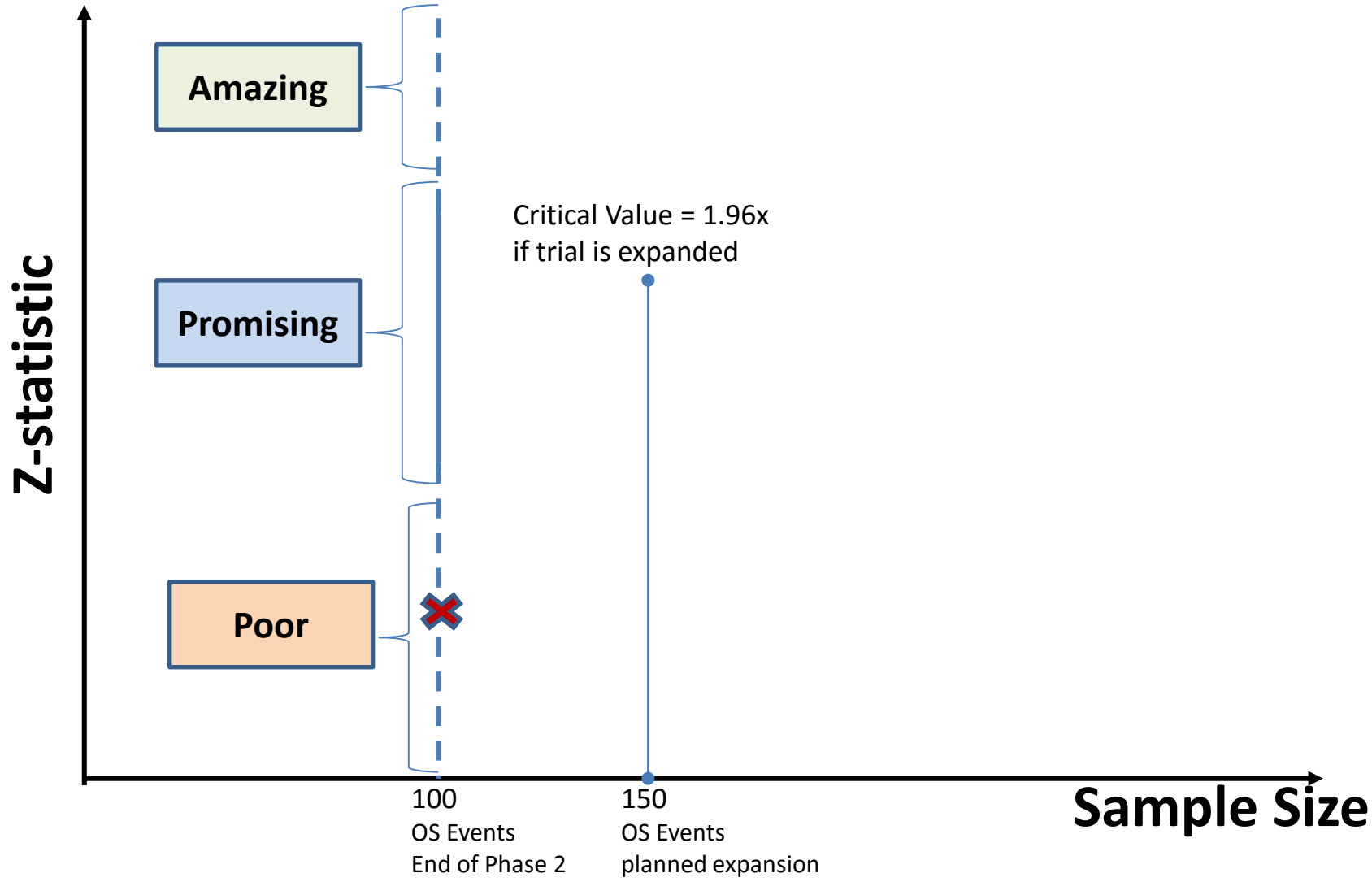
Case 2: Very promising result obtained. Continue to planned expansion



Case 3: Promising result obtained. Adapt sample size beyond planned expansion



Case 4: Poor result obtained. Stop trial without going to planned expansion



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