

Recent Advances in the Design of Clinical Trials

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Acknowledgements/COI

- Examples contributed by
 - Cyrus Mehta, CYTEL
 - Lorenzo Trippa, Dana-Farber and Harvard
 - Mithat Gonen, MSKCC
- Conflicts
 - None to report

Outline

- Some general perspectives
- Bayesian adaptive randomization
- Basket trials
- Flexible/Adaptive Designs
- Reproducibility
- Data sharing

Scientific Issues driving new designs

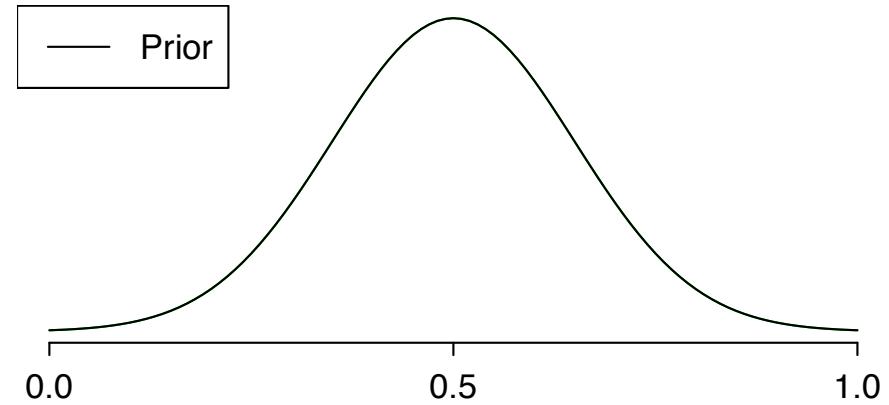
- A deeper understanding of biology for many diseases has led to an increase in the development of new drugs.
 - In many cases, these drugs may work better in patients with particular disease signatures.
 - Drugs may work across phenotypic subtypes of disease that have similar genetic or molecular signatures
- The design of phase III trials is as much art/intuition as science.
 - Too many phase III trials fail because of ‘poor’ design choices – wrong patients, in appropriate target treatment effects, insufficient sample size.

Ecological Issues

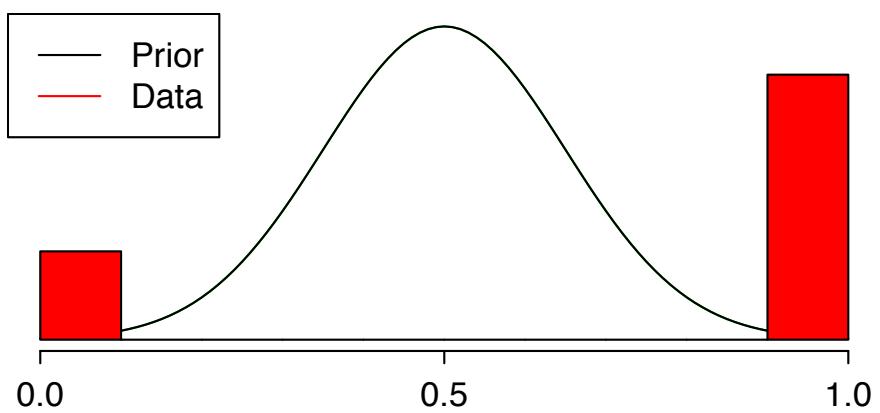
- Increased concern about reproducibility, especially in the results of post-hoc analyses
- Rapid development of new agents sometimes mean trial designers are working without sufficient information on
 - Subgroups
 - Likely treatment effects
 - Adherence

Bayesian Adaptive Randomization (BAR)

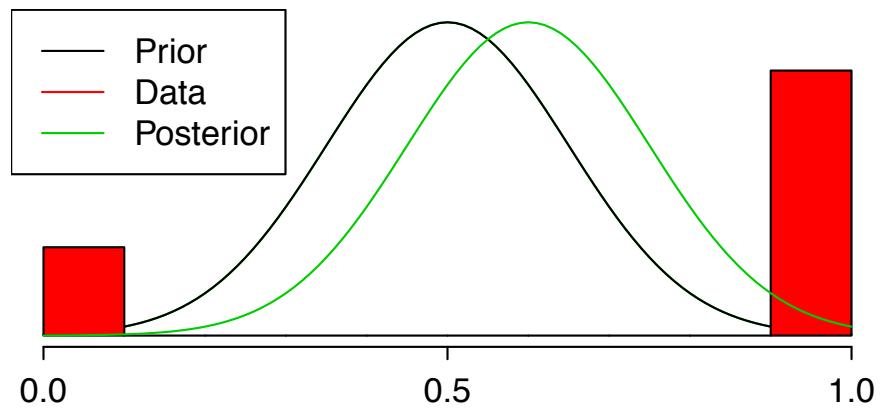
- Simple idea
 - Use accumulating information to adjust randomization fraction
- Complicated execution
 - Modeling assumptions
 - Analysis is complex
 - Logistic support is essential, since data are continually updated



Prior assumption
about distribution of
response
probabilities



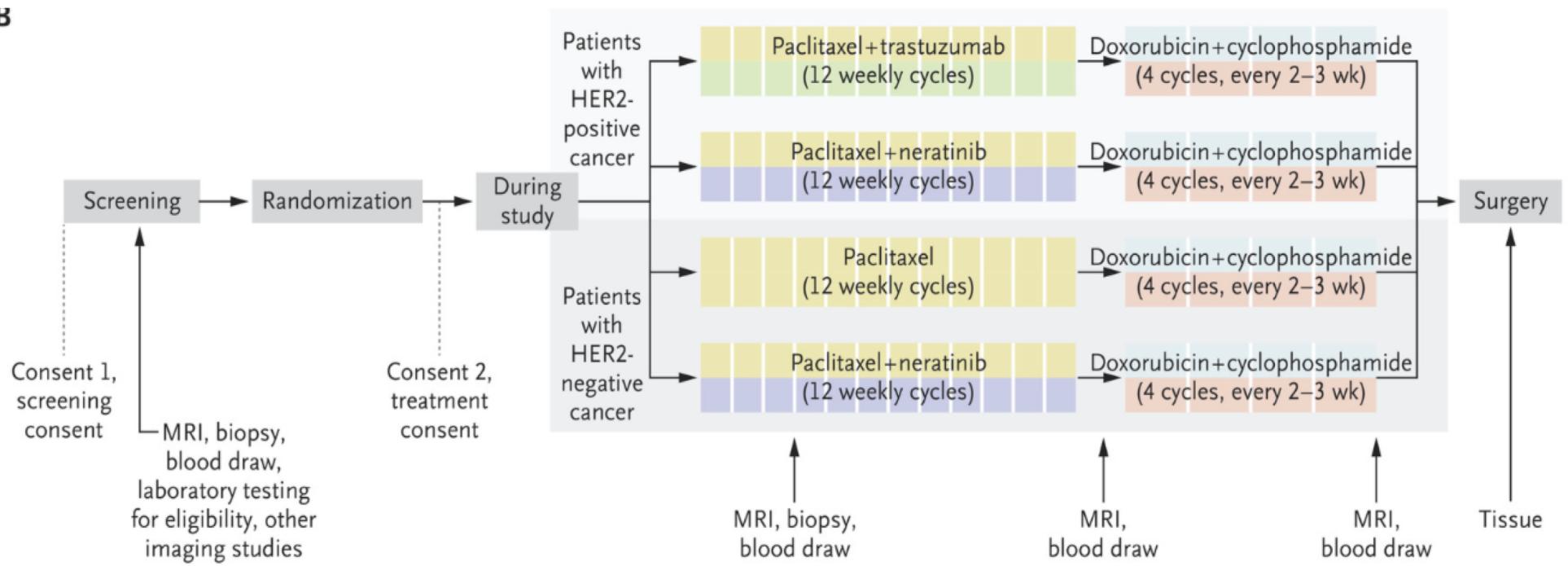
Data during trial on
response ($x = 1$) and non-
response ($x = 0$)



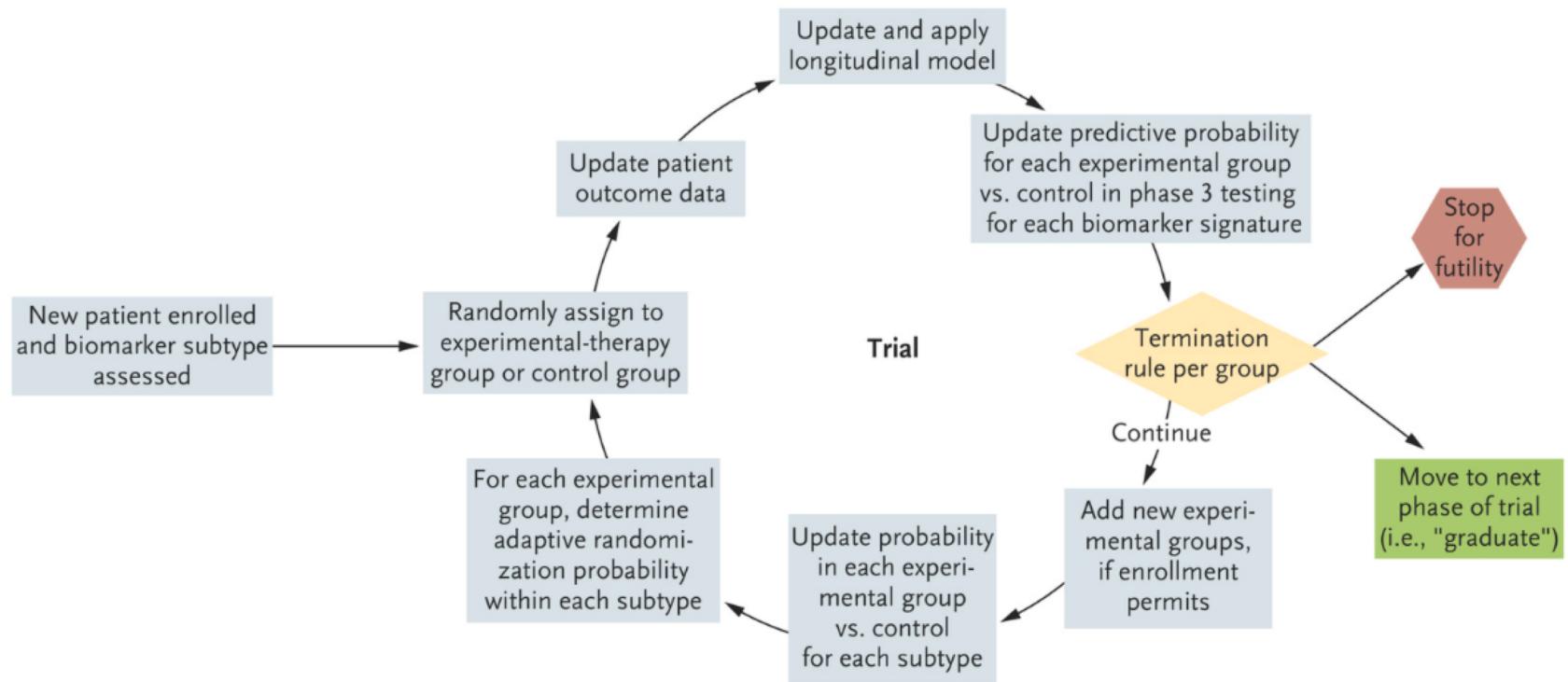
Update assumption
of response
probabilities
(posterior
distribution)

I-SPY 2 (N Engl J Med 2016; 375:11-22)

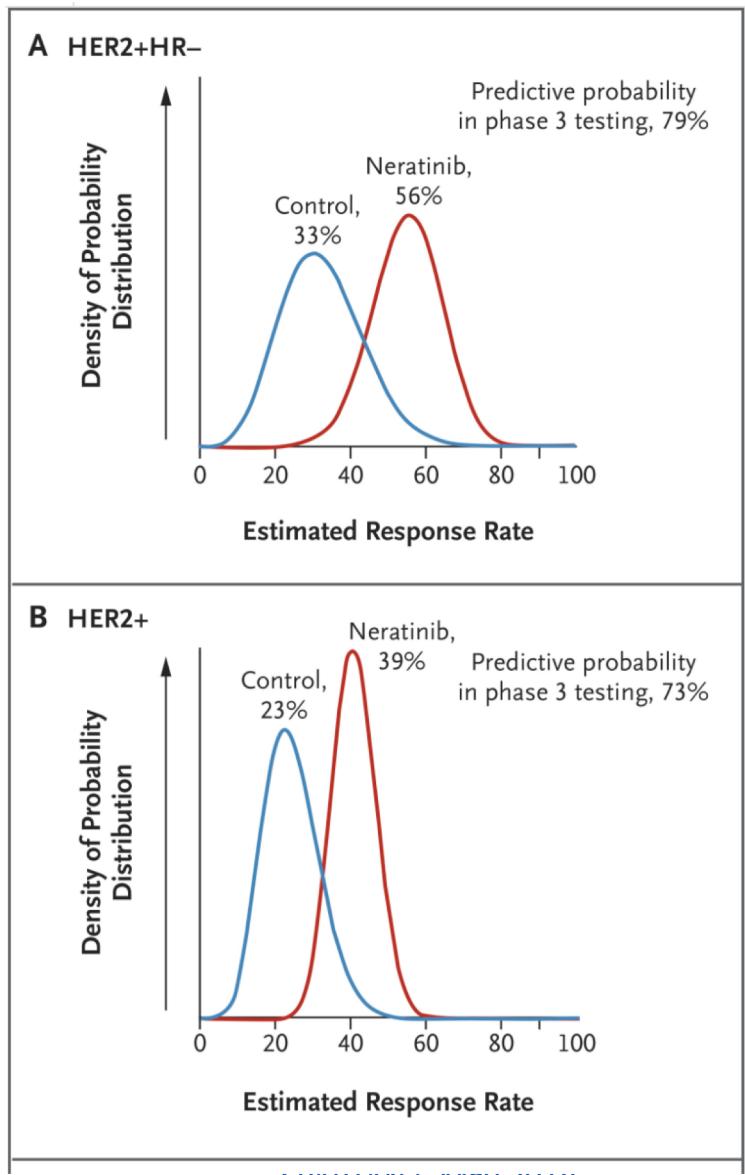
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I-SPY 2 (N Engl J Med 2016; 375:11-22)

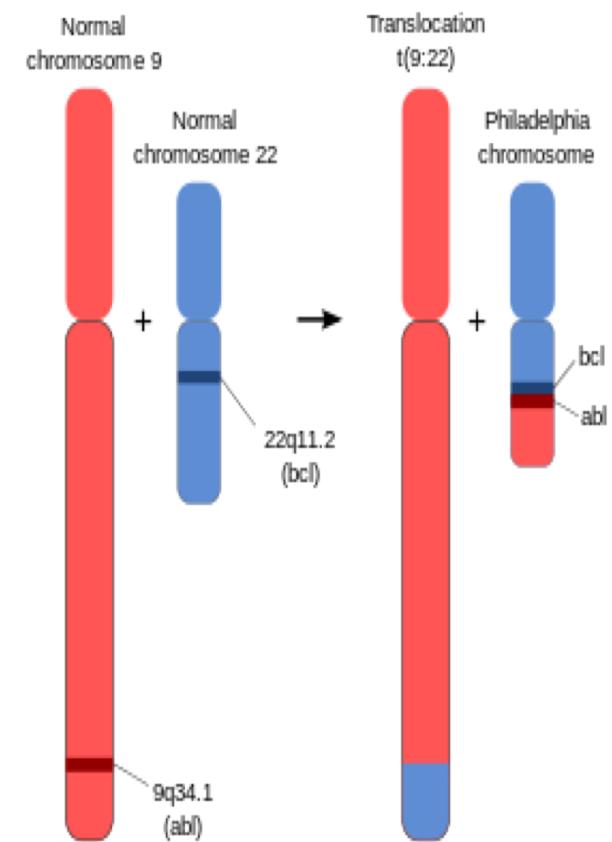


I-SPY 2 (N Engl J Med 2016; 375:11-22)

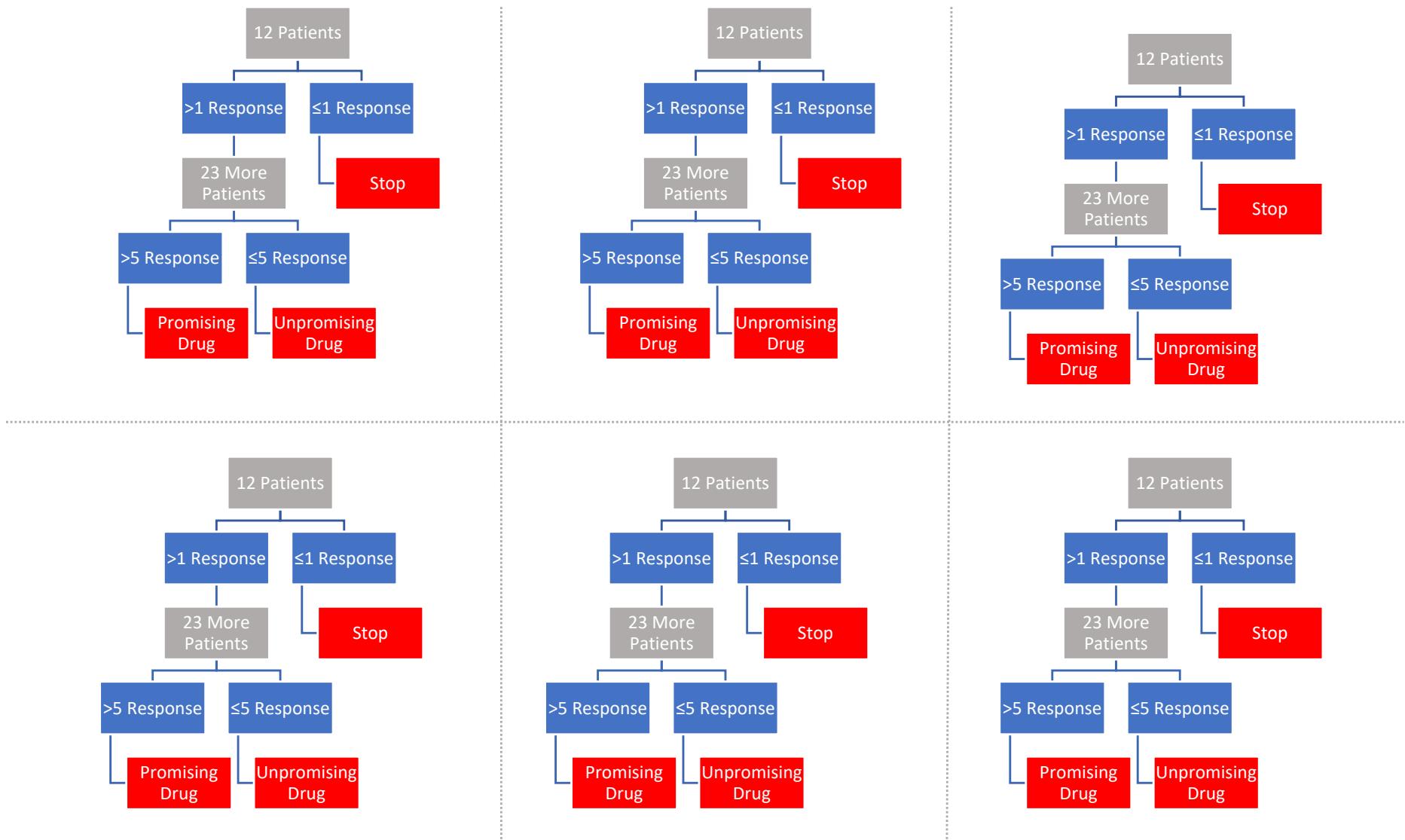


Basket trials

- Basket trials test therapies in diseases that are
 - Phenotypically different
 - Similar in molecular or genetic signatures
- Most often used in Phase 2 trials in cancer
- Example: BCR-ABL Translocation
 - Parts of two chromosomes (9 and 22) switch places
 - Results in a “fusion gene”: juxtaposition of ABL1 gene (9q34) to the BCR gene (22q11)

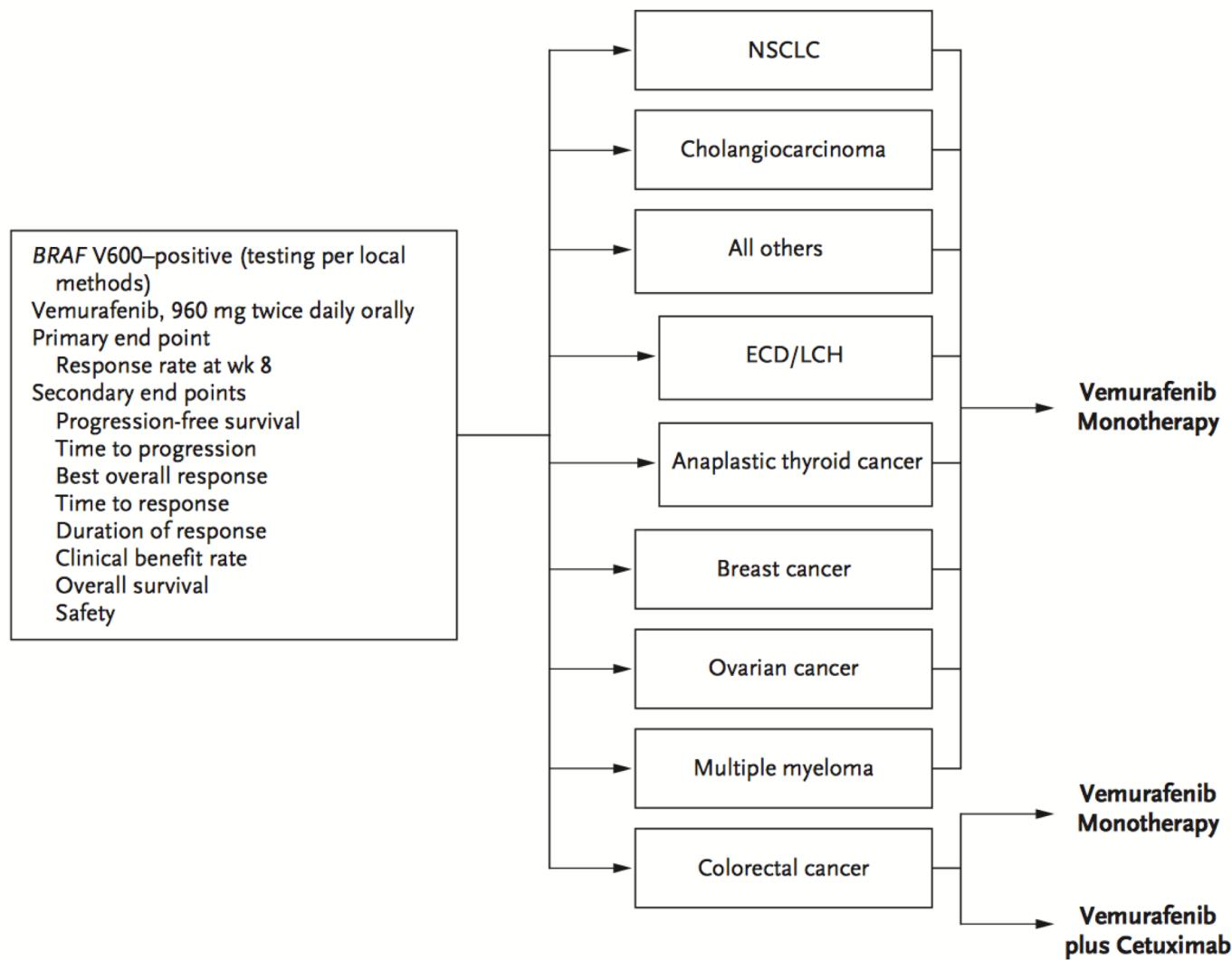


Using the Traditional Design in Basket Trial



Source: M. Gonen, MSKCC

Hyman, et al. (NEJM 373:8, Aug 20, 2015)



Hyman, et al. (NEJM 373:8, Aug 20, 2015)

- “*BRAF* V600 appears to be a targetable oncogene in some, but not all, nonmelanoma cancers.
- Preliminary vemurafenib activity was observed in non–small-cell lung cancer and in Erdheim–Chester disease and Langerhans’-cell histiocytosis.
- The histologic context is an important determinant of response in *BRAF* V600–mutated cancers.”

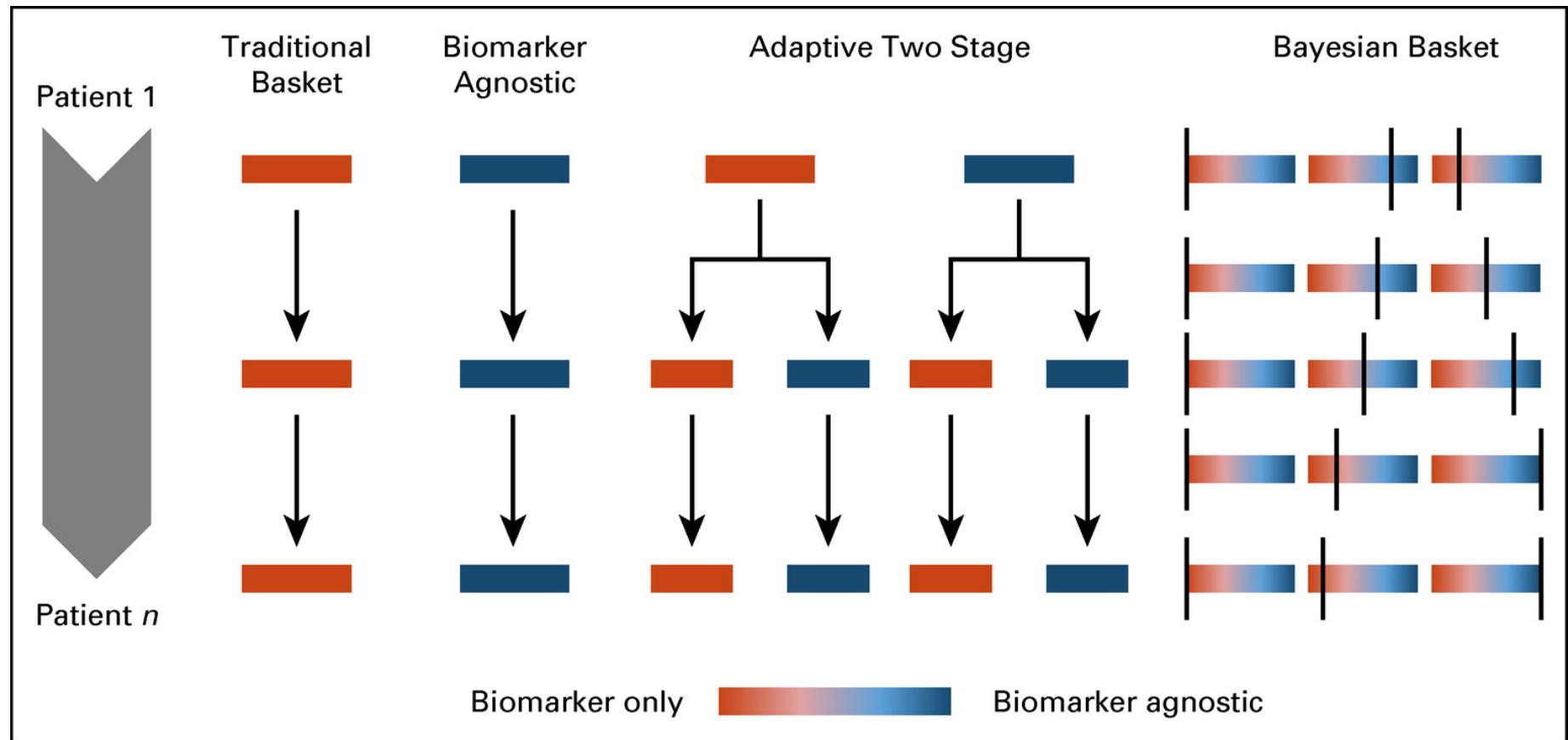
Aggregation Design (M. Gonen, et al., MSKCC working paper)

- Stage 1
 - Allocate a (modest) number of patients in each basket
 - Evaluate if response rates are heterogeneous across baskets to determine if baskets should be treated as independent or aggregated
 - Apply a futility rule to individual baskets or the aggregated basket, depending on assessment of heterogeneity
- Stage 2
 - Continue allocating patients to the aggregated basket and use a one-sample test for efficacy
 - OR
 - Continue allocating patients only to selected baskets and test for efficacy using many one-sample tests, adjusting for multiple testing



Memorial Sloan Kettering
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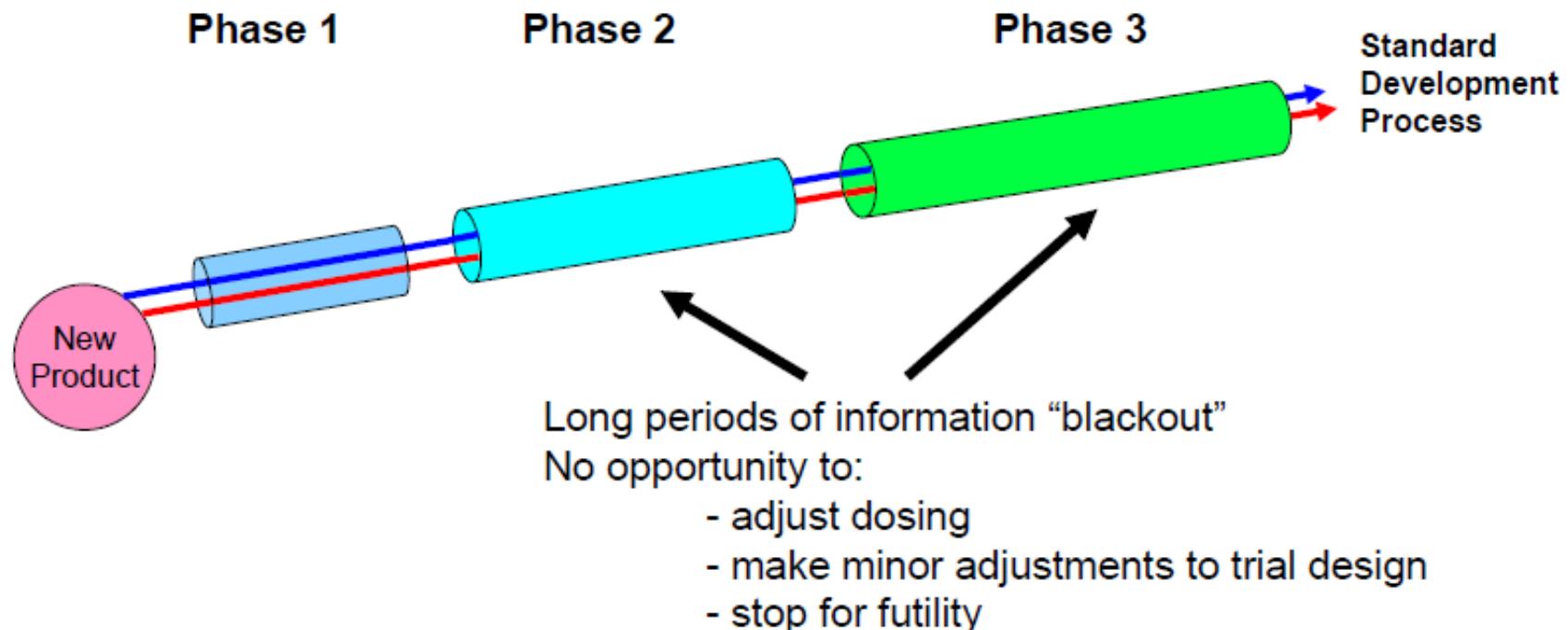
Bayesian Basket Designs, Trippa & Alexander, JCO 2017.



Adaptive, flexible designs

- **Traditional Design:** fix the sample size in advance and only perform one efficacy analysis after all subjects have been enrolled and evaluated.
- **Flexible Design:** monitor the accruing efficacy data at administratively convenient intervals and make important decisions concerning the future course of the study along the way.
- Flexible designs more appealing to pharma than academic trials, but can be useful in both settings.

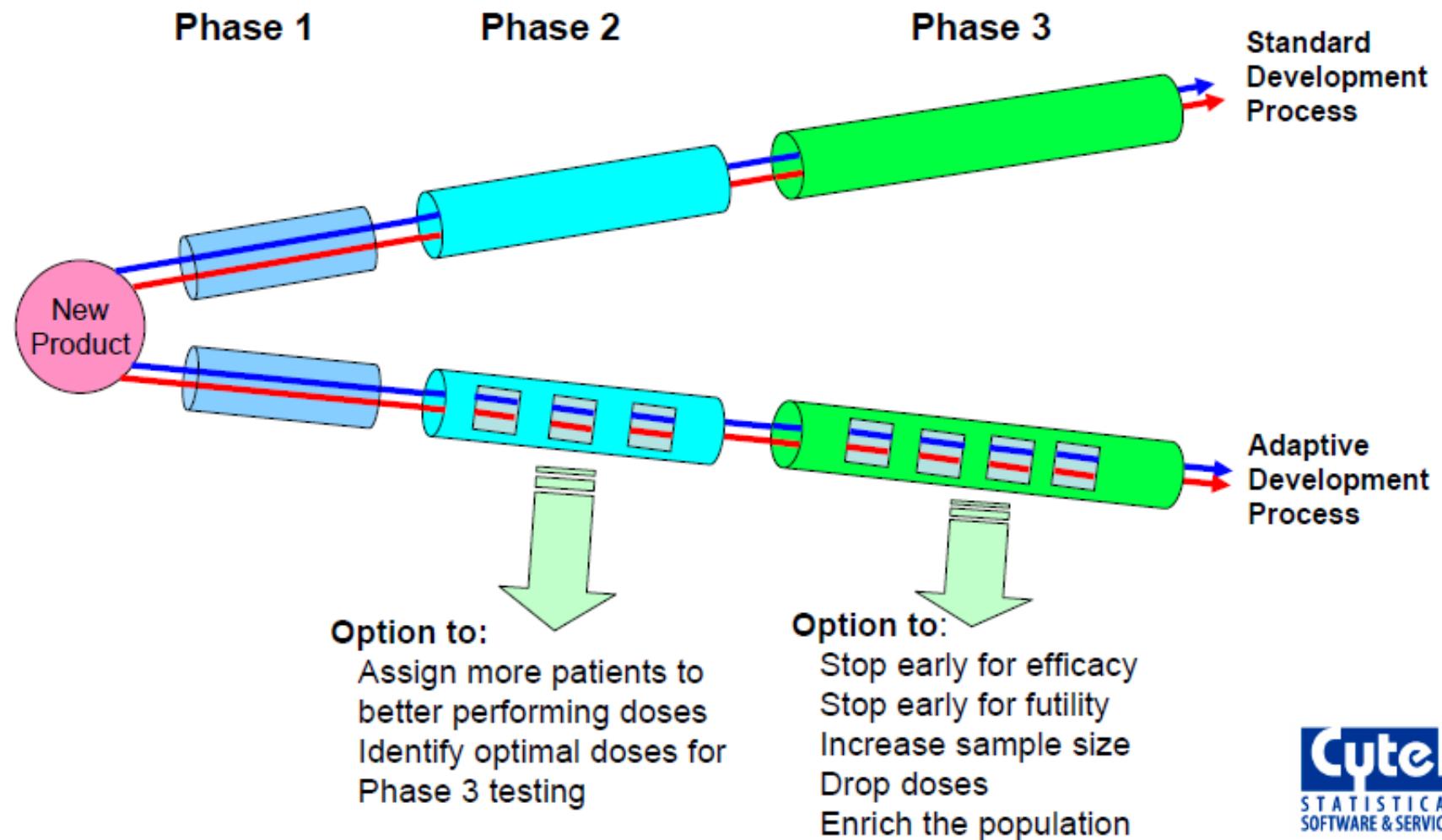
Traditional Clinical Development Process



**What if we had a “window” into the process
to check to see if we are on track?**



Adaptive Clinical Development Process

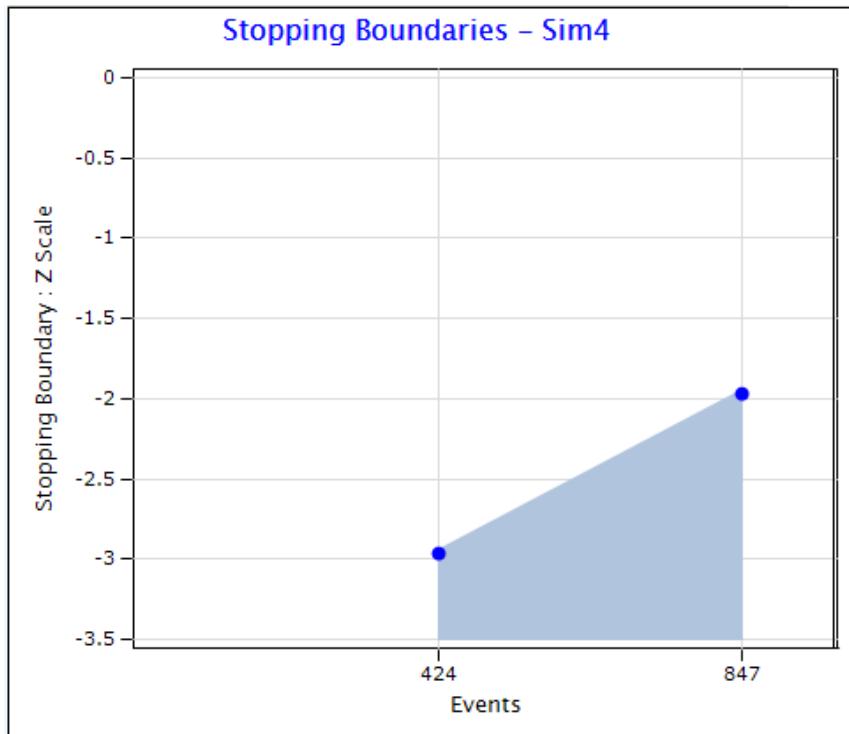


Event Driven Trial to Detect HR=0.75

- Enroll 7000 patients over 4 years; and follow for 1 more year until 530 CV events obtained
- Given 3.25% events/year on placebo, trial has:
 - 91% power to detect $HR=0.75$ (25% risk reduction)
 - 73% power to detect $HR=0.8$ (20% risk reduction)
- Possible to recover lost power if $HR=0.8$?

Option 1: Large Group Sequential Trial

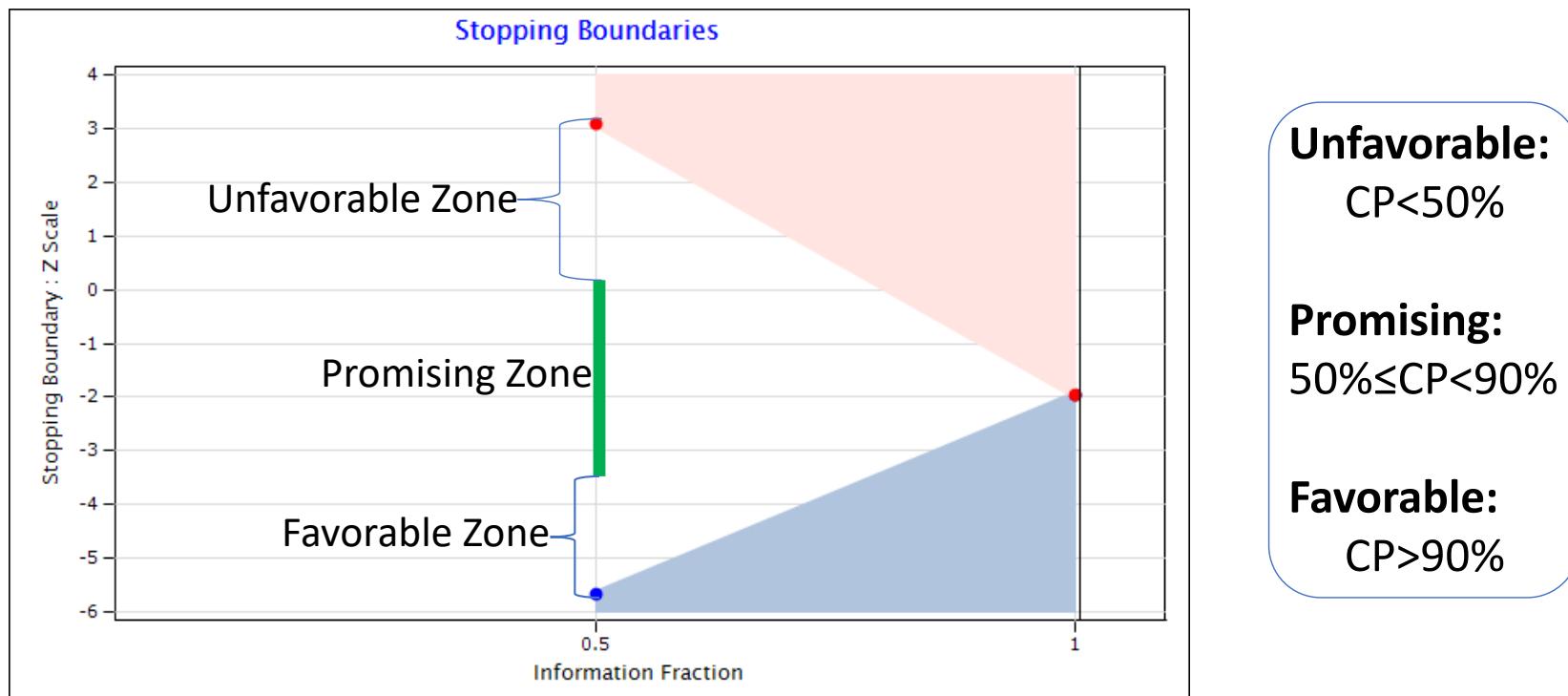
- 11,000 patients and 847 events over 5 years provides 91% power to detect $HR=0.8$
- Group sequential boundary for early stopping



- Early stopping probability:
 - 27% if $HR=0.8$
 - 50% if $HR=0.75$
- **Problem:** Only 1.5 years of average follow-up if early stop

Option 2: Promising Zone Design

- **Start small:** 7000 patients and 530 events
- Increase by 50% if interim results are promising
- Promising zone is defined by **conditional power**



Design Optimistically: Assume HR=0.75

Operating Characteristics if in Truth Risk Reduction is 20% (HR=0.8)

Zone	P(Zone)	Power		Sample Size		Study Duration	
		NonAdapt	Adaptive	NonAdapt	Adaptive	NonAdapt	Adaptive
Unfav	24%	38%	38%	7000	7000	4.9	4.9
Prom	36%	74%	90%	7000	10500	4.9	5.7
Fav	40%	95%	95%	7000	7000	4.9	4.9

Operating Characteristics if in Truth Risk Reduction is 25% (HR=0.75)

Zone	P(Zone)	Power		Sample Size		Study Duration	
		NonAdapt	Adaptive	NonAdapt	Adaptive	NonAdapt	Adaptive
Unfav	12%	57%	57%	7000	7000	5	5
Prom	28%	87%	98%	7000	10500	5	5.8
Fav	60%	99%	99%	7000	7000	5	5

Statistical Issues with Adaptive Designs

- For a regulatory filing, must maintain strong control of type-1 error
- Two sources of error inflation in these examples
 - due to unblinded sample size re-estimation
 - due to enrichment by subgroup selection
- Although the trial is expanded only if the IA shows promise of superiority:
 - Actual interim decision should only be conveyed on need to know basis (to drug supply and IVRS teams)
 - Investigators may be told only that this adaptive design has a maximum sample size of xxx patients and possibility of re-powering at IA
- Use a double blind design if possible to avoid operational bias

Operational and Bias Issues

- All design details are included in DMC charter
- DMC buys into design at the kick-off meeting, but reserves right to exercise clinical judgment
- Although the trial is expanded only if the IA shows promise of superiority:
 - Actual interim decision should only be conveyed on need to know basis (to drug supply and IVRS teams)
 - Investigators may be told only that this adaptive design has a maximum sample size of xxx patients and possibility of re-powering at IA
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Data sharing for complex designs

- As a trial designer, I would like to know what happened in previous trials.
- Information richer than overall summary statistics would be most helpful
 - Patient mix, including correlation among baseline characteristics
 - Time-dependent behavior of the trial
- Help may be on the way

EDITORIALS



Data Sharing Statements for Clinical Trials — A Requirement of the International Committee of Medical Journal Editors

The International Committee of Medical Journal Editors (ICMJE) believes there is an ethical obligation to responsibly share data generated by interventional clinical trials because trial participants have put themselves at risk. In January 2016 we published a proposal aimed at helping to create an environment in which the sharing of

explained at www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. If the data sharing plan changes after registration this should be reflected in the statement submitted and published with the manuscript, and updated in the registry record.

June 8, 2017

ICMJE Policy (NEJM June 8, 2017)

- “1. As of July 1, 2018, manuscripts submitted to ICMJE journals that report the results of clinical trials must contain a data sharing statement as described below.
- 2. Clinical trials that begin enrolling participants on or after January 1, 2019, must include a data sharing plan in the trial’s registration. The ICMJE’s policy regarding trial registration is explained at www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. “