



Memorial Sloan Kettering  
Cancer Center

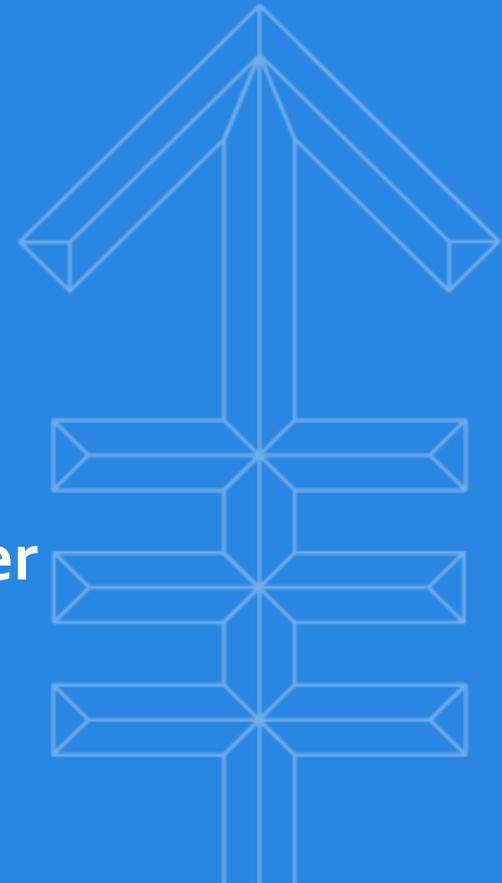
# Basket Trials in Oncology

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**Memorial Sloan Kettering Cancer Center**

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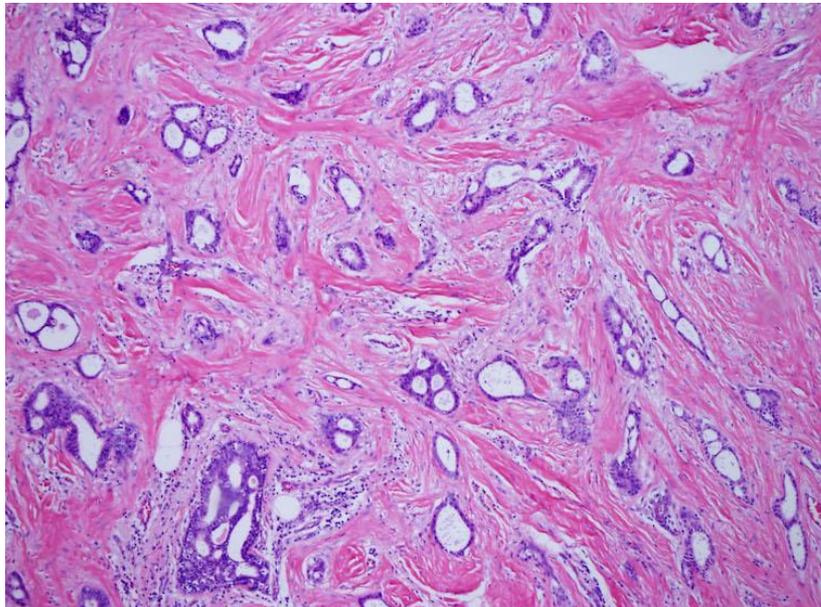
# A Brief History of Oncologic Taxonomy

- Cancer taxonomy was based on the location of primary tumor up until 2005-2010
  - Breast cancer, lung cancer, colon cancer ...
- “Location of tumor” is really a layman’s term
  - Fundamentally it was the theory that normal tissues turned malignant
  - Colon cancer cells were formed from normal colon cells etc
  - It is possible to tell lung cancer from breast under the microscope
- Some call this taxonomy “histopathologic” classification

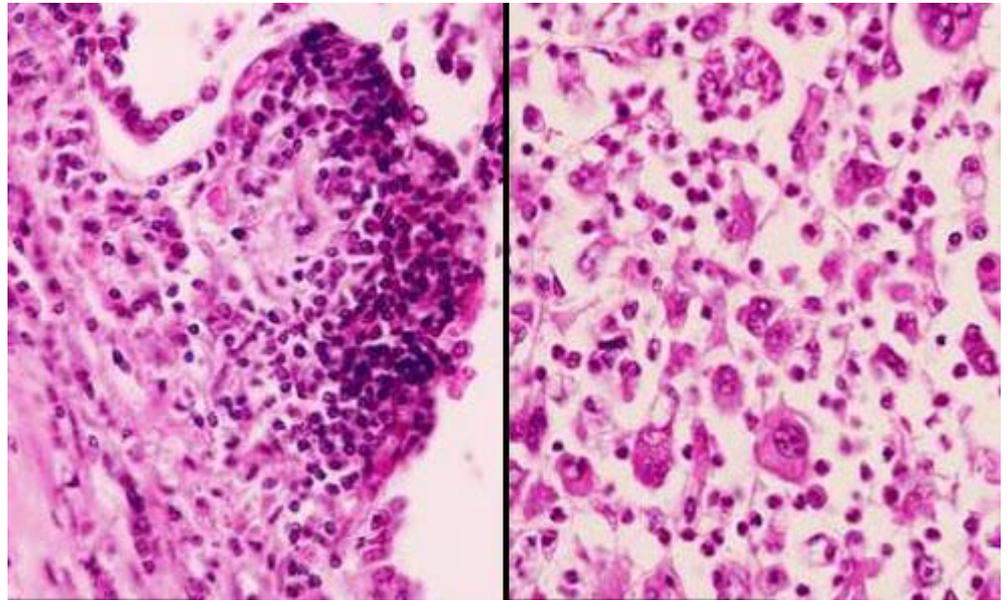


# Under the Microscope

Breast Cancer



Lung Cancer



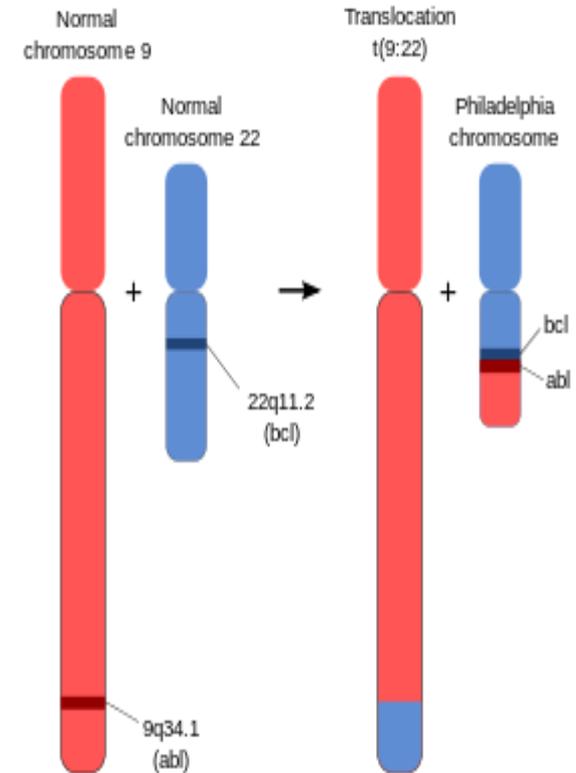
# Implications for Clinical Trial Design

- Phase I studies usually open for all solid tumor patients
- Phase Ib studies (or Phase I expansion cohorts) are stratified by or specific to histology
- Phase II / IIb studies are specific to histology
- Phase III studies are specific to histology (with labeling in mind)



# Molecular taxonomy

- Past decade has brought new knowledge of how cancers evolve
- Cancer is a genetic disease
  - Alterations in normal cells lead to oncotypic features: unchecked growth, mechanisms preventing cell death, loss of cell surface proteins that keep a cell in place
- 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)

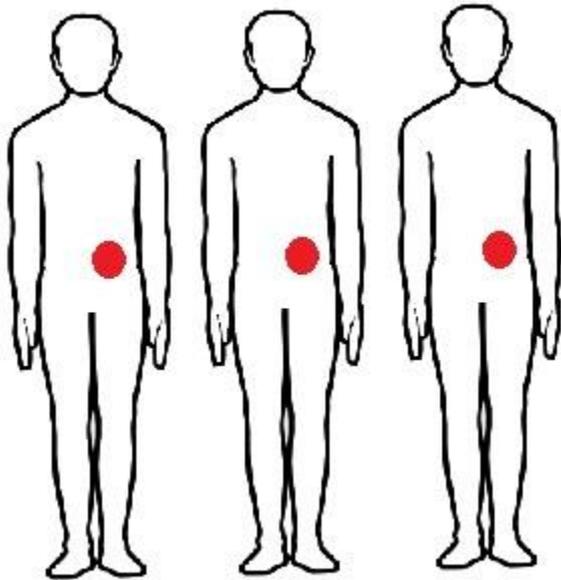


# BCR-ABL Cancers

- Chronic myeloid leukemia (CML)
- Gastrointestinal stromal tumor (GIST)
- Development of BCR-ABL in the past decade followed the histology-specific pattern
- Separate Phase II and III trials for CML and GIST
- With the new taxonomy, does it make more sense to have a trial for BCR-ABL cancers regardless of their histology?



# Traditional Phase II Trial



- One primary question asked: ***Does the drug work in this particular cancer?***
- The design is built around this question:
  - Is the response rate with this drug greater than the response rate of standard therapy?

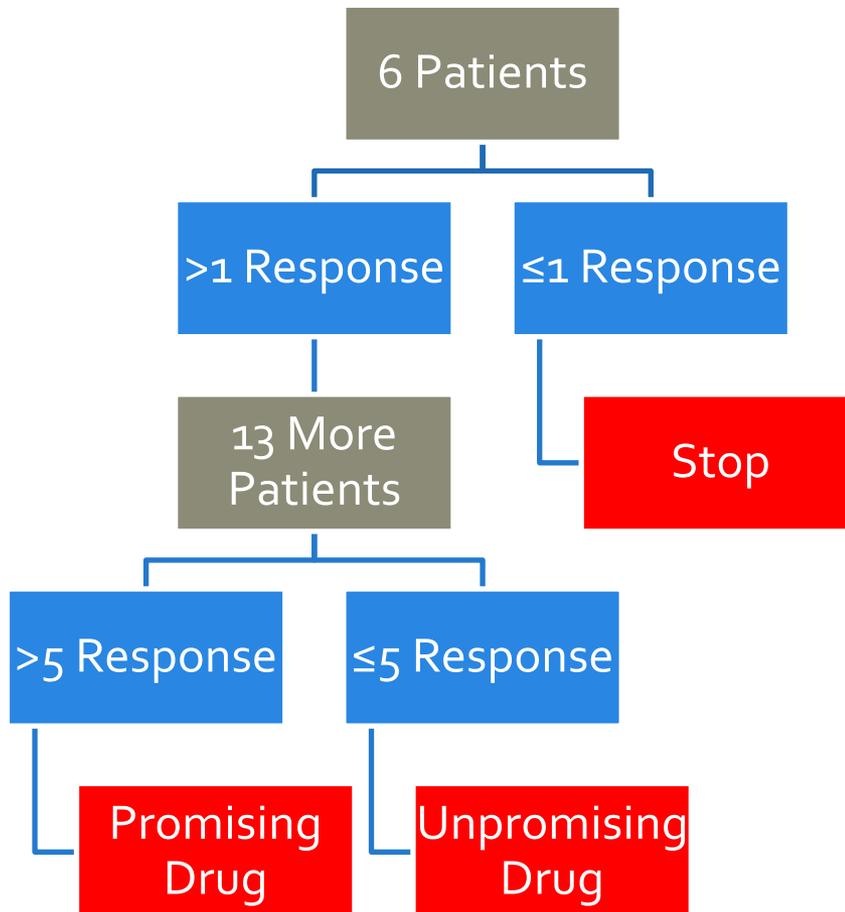


# Response Rate as Phase II Endpoint

- Phase III oncology trials use survival or progression-free survival as endpoints.
- These are usually not suitable for Phase II trials since it takes a while to observe the event
- Typical Phase II trials use response rate
- Response is binary and ascertained at ~6-8 weeks after treatment
- Usually means more than 50% reduction in tumor size and absence of new lesions
- Widely criticized but yet to be replaced



# Example Phase II Design



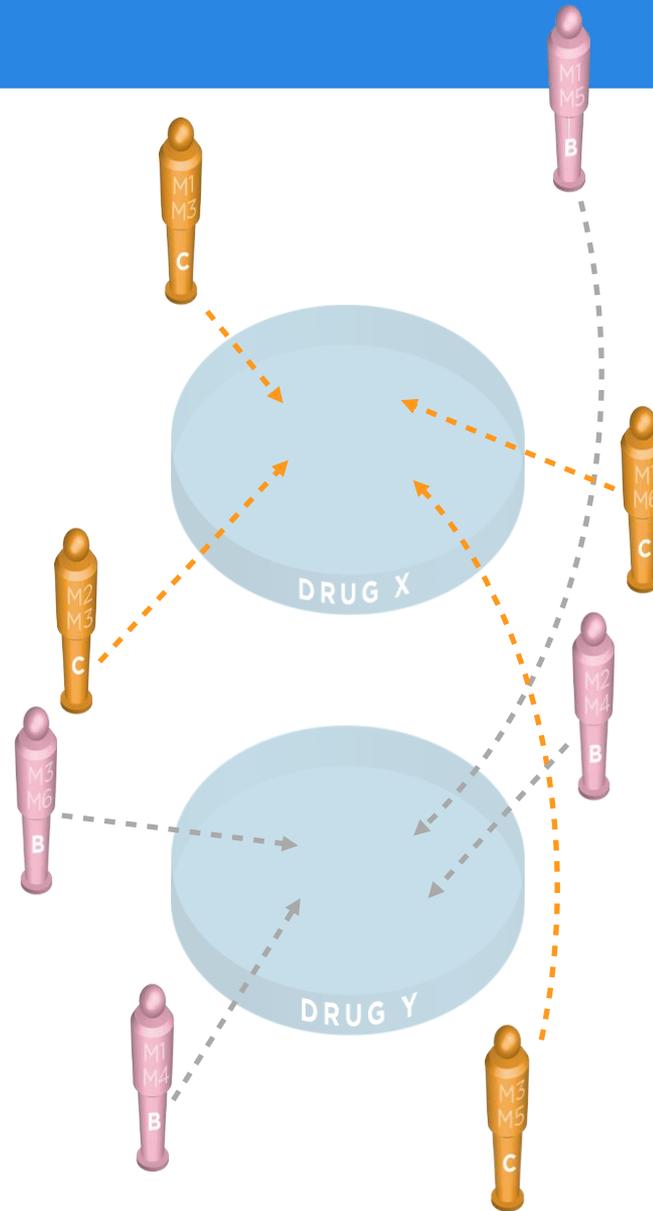
- **Two-Stage Design**
- **Allows for Early Stopping for Futility**
- **This Particular Design**
  - Distinguishes Between Response Rates of 15% and 45%
  - 5% type I error and 80% power



# Basket Trials

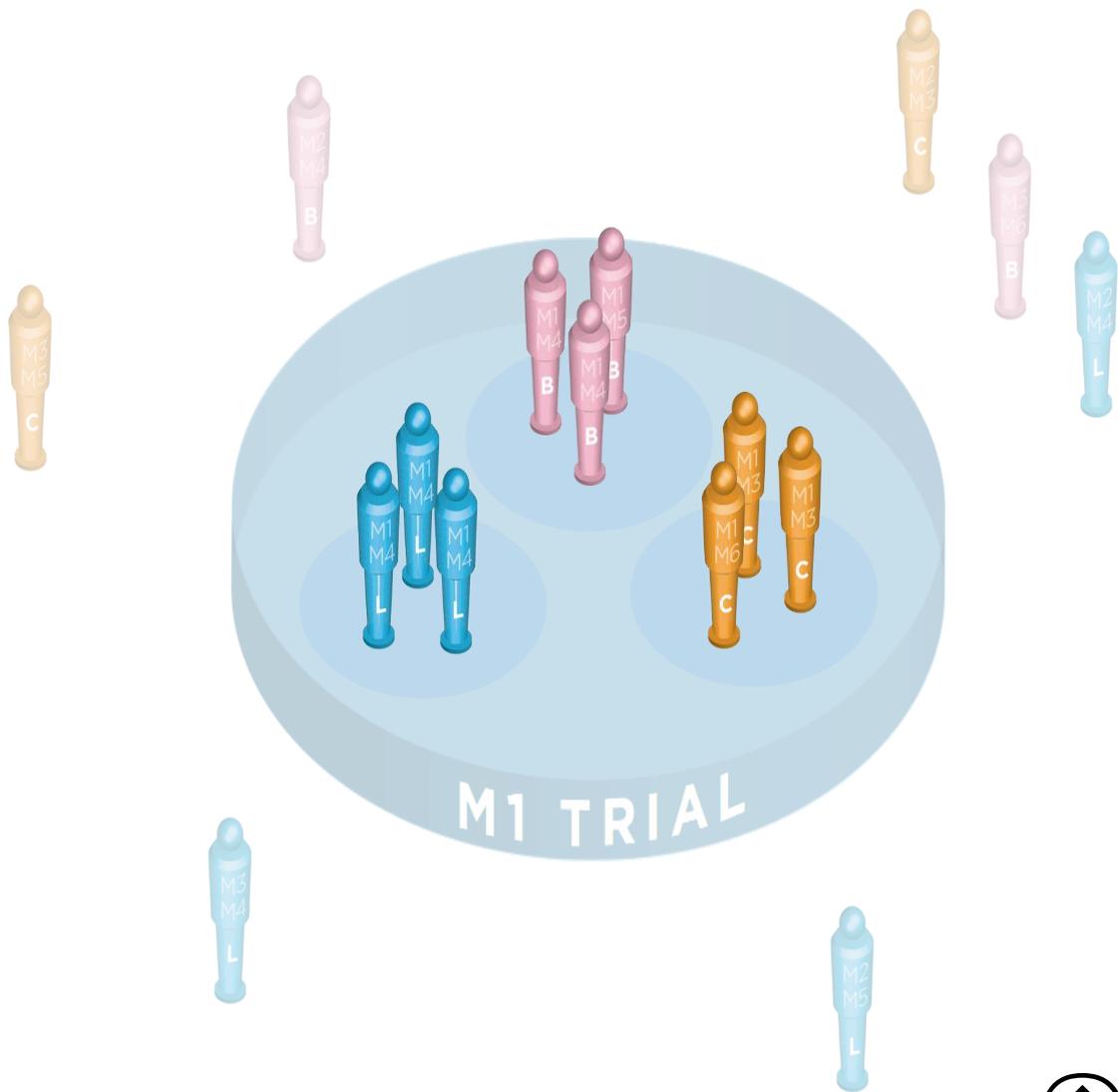
- Novel and non-specific (imprecise) terminology that generally means combining multiple histologies in a single trials
- In its most basic form a basket trial is specific to a molecular target and a targeted regimen, with histologies forming the baskets
  - BCR-ABL Imatinib trial with CLL and GIST as baskets
- But other “basket” trials (such as NCI-MATCH) also emerged with multiple targets and regimens forming baskets in addition to histologies



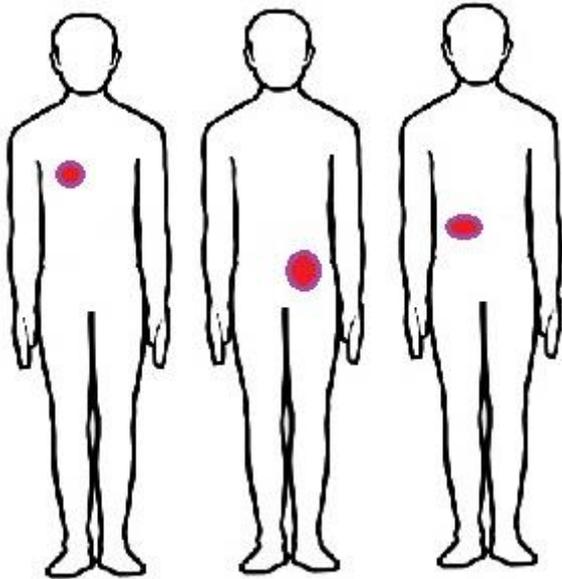








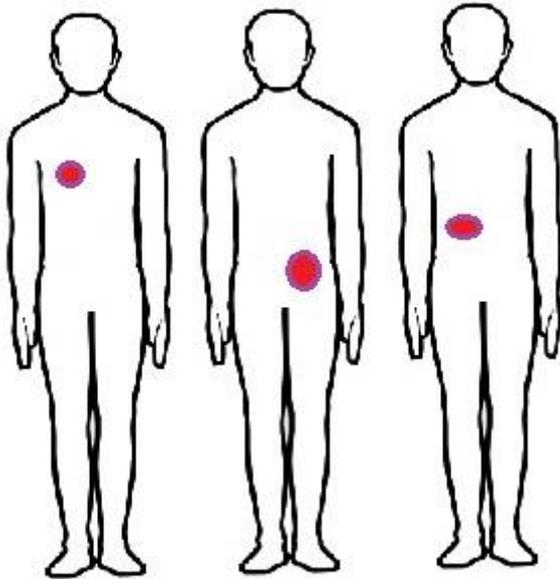
# Phase II Basket Trial



- Single Target (a particular genomic alteration)
- Multiple Histologies (Anatomic Sites)
- What questions are of interest?



# Basket Trial: What Questions?



- Does the treatment work at all?
- If yes, which sites?



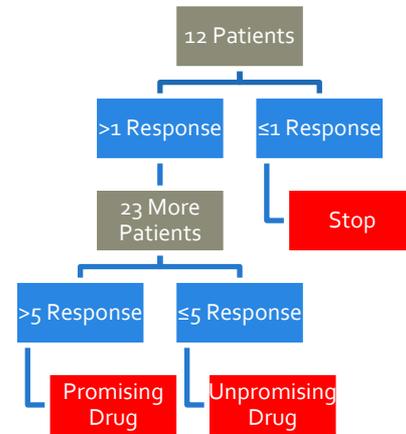
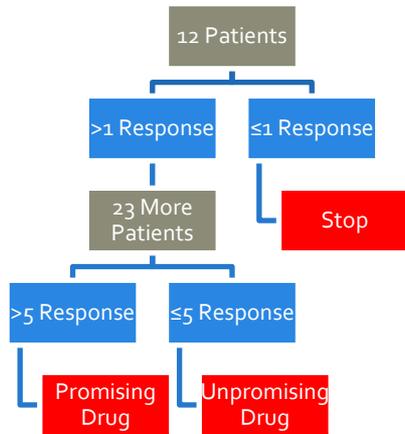
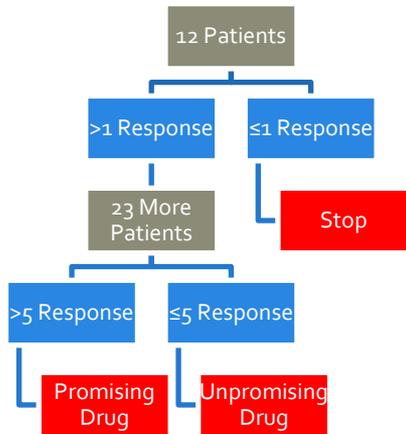
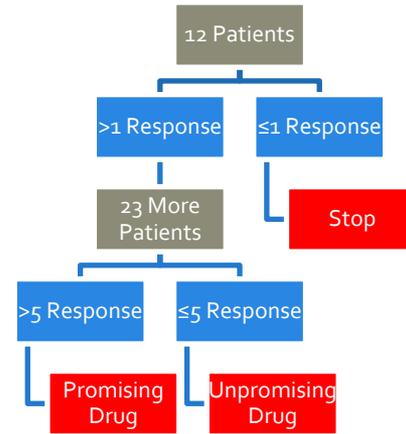
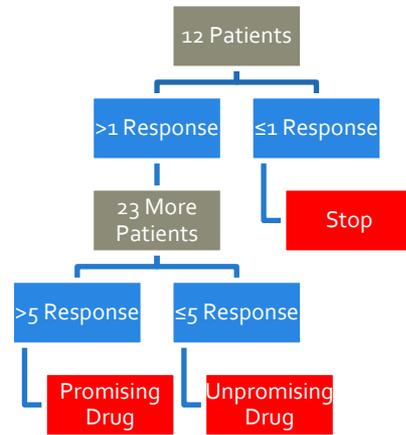
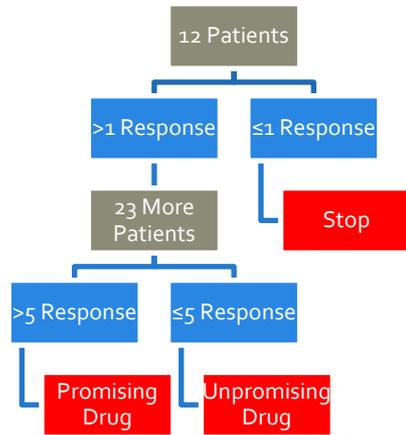
# Why these questions?

- The drug may not be hitting the target sufficiently
  - Tumor Heterogeneity
  - Non-specific binding
  - Incorrect dosing
  - ....
- → Hence the first question: Does the drug work?

- If the drug works, it may not work in all tumor sites
  - Secondary mutations interfering with sensitivity to treatment
  - ...
- → Hence the second question: Where does it work?



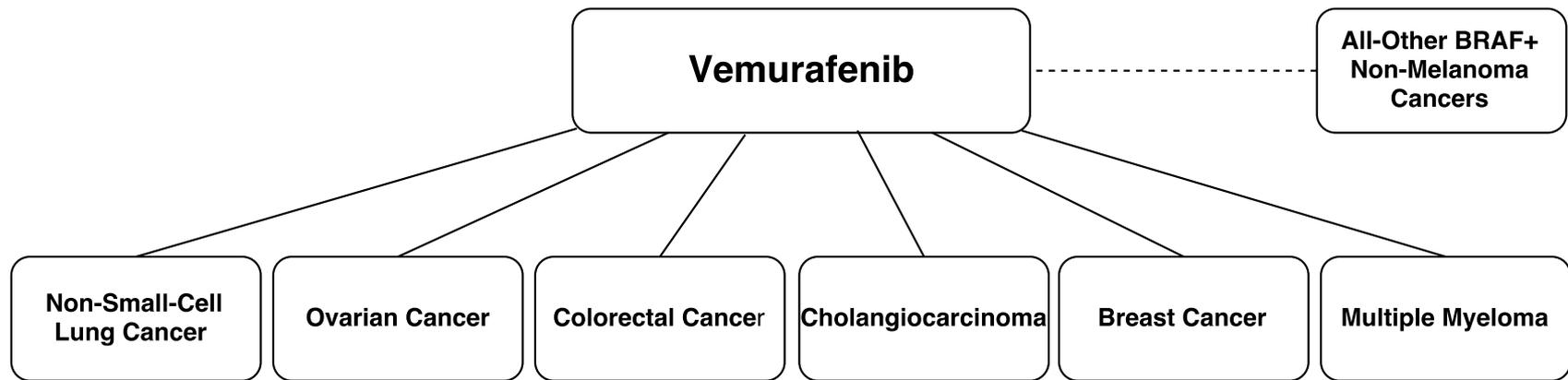
# Parallel Design



# “Parallel Design”

- Each basket has its own design
- There is no information sharing between baskets
- Two implications
  - Does not address the first question (does the drug work?)
  - Ignores the commonality among the baskets (same mutation)
- Advantages
  - Simple
  - Familiar
  - Easy to implement
- Can we do better?
  - Allowing some information sharing between baskets may help us
    - Address the first question
    - More efficient design (fewer patients)





ORIGINAL ARTICLE

## Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

David M. Hyman, M.D., Igor Puzanov, M.D., Vivek Subbiah, M.D., Jason E. Faris, M.D., Ian Chau, M.D., Jean-Yves Blay, M.D., Ph.D., Jürgen Wolf, M.D., Ph.D., Noopur S. Raje, M.D., Eli L. Diamond, M.D., Antoine Hollebecque, M.D., Radj Gervais, M.D., Maria Elena Elez-Fernandez, M.D., Antoine Italiano, M.D., Ph.D., Ralf-Dieter Hofheinz, M.D., Manuel Hidalgo, M.D., Ph.D., Emily Chan, M.D., Ph.D., Martin Schuler, M.D., Susan Frances Lasserre, M.Sc., Martina Makrutzki, M.D., Florin Sirzen, M.D., Ph.D., Maria Luisa Veronese, M.D., Josep Tabernero, M.D., Ph.D., and José Baselga, M.D., Ph.D.



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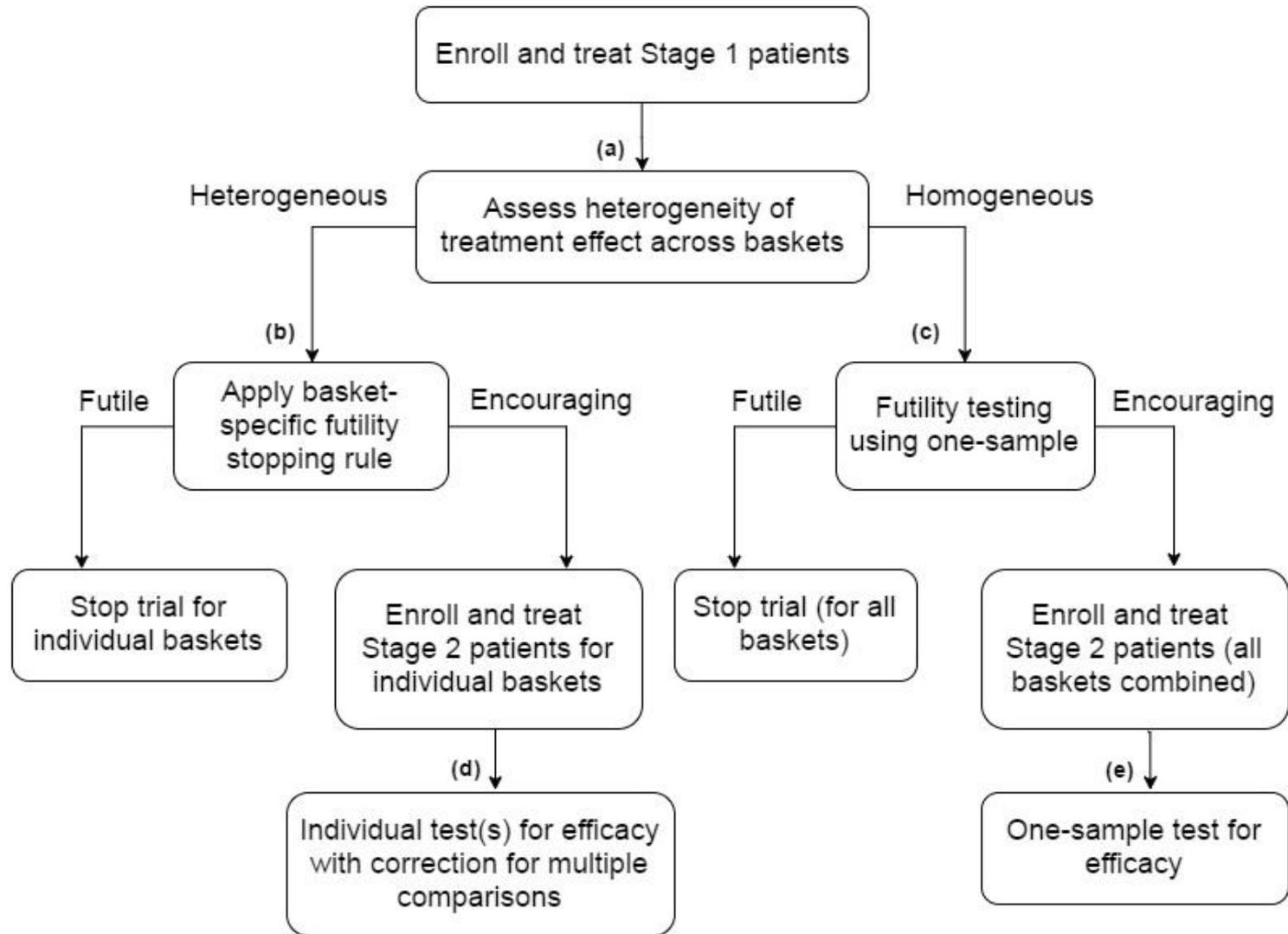
# An efficient basket trial design

**Kristen M. Cunanan,<sup>\*†</sup> Alexia Iasonos, Ronglai Shen,  
Colin B. Begg and Mithat Gönen**

The landscape for early phase cancer clinical trials is changing dramatically because of the advent of targeted therapy. Increasingly, new drugs are designed to work against a target such as the presence of a specific tumor mutation. Because typically only a small proportion of cancer patients will possess the mutational target, but the mutation is present in many different cancers, a new class of basket trials is emerging, whereby the drug is tested simultaneously in different baskets, that is, subgroups of different tumor types. Investigators desire not only to test whether the drug works but also to determine which types of tumors are sensitive to the drug. A natural strategy is to conduct parallel trials, with the drug's effectiveness being tested separately, using for example, the popular Simon two-stage design independently in each basket. The work presented is motivated by the premise that the efficiency of this strategy can be improved by assessing the homogeneity of the baskets' response rates at an interim analysis and aggregating the baskets in the second stage if the results suggest the drug might be effective in all or most baskets. Via simulations, we assess the relative efficiencies of the two strategies. Because the operating characteristics depend on how many tumor types are sensitive to the drug, there is no uniformly efficient strategy. However, our investigation demonstrates that substantial efficiencies are possible if the drug works in most or all baskets, at the cost of modest losses of power if the drug works in only a single basket. Copyright © 2017 John Wiley & Sons, Ltd.



# Diagram of Aggregation Design



# Operating Characteristics

- **Familywise Error Rate (FWER):** Under the compete null (if the drug is inactive in all baskets), what is the probability of rejecting at least one test (concluding that the drug is active in at least one basket)?
- **Power:** Parameter space under the alternative hypothesis is multi-dimensional so the definition of power requires some thought
  - **1 Active** The drug is active in one of the  $K$  baskets
  - **2 Active** The drug is active in one of the  $K$  baskets
  - ...
  - **$K$  Active** The drug is active in one of the  $K$  baskets
- Unrealistic to expect a trial design to be uniformly (under all scenarios) more powerful than the reference design



# Calibration and Metrics for Comparison

- Calibration
  - To compare reference design with aggregation design we need to make sure they have the same FWER
  - In addition we need to choose one of the points in the parameter space under the alternative ( $K$  scenarios) and ensure the two designs have the same power under that particular alternative
- Metrics
  - Power under the un-calibrated scenarios
  - Total sample size
  - Time to completion of trial
    - Poisson accrual process, same for each basket



# What about FWER?

- Is it needed?
- If each basket is its own protocol we would not control Type I error across protocols, so why do it here?
- Counter-arguments
  - The biological premise of the basket trial invites Type I error control
  - Number of baskets will grow and size of baskets will diminish → Phase II trials may serve as the basis for decision making
  - Need to force thoughtful selection of baskets → Prevent kitchen sink trials

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JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

## Basket Trials in Oncology: A Trade-Off Between Complexity and Efficiency

Kristen M. Cunanan, Mithat Gonen, Ronglai Shen, David M. Hyman, Gregory J. Riely, Colin B. Begg, and Alexia Iasonos, *Memorial Sloan Kettering Cancer Center, New York, NY.*

# How Can We Improve Over the Aggregation Design?

- Flexibility more complex settings
  - Multiple drugs, multiple targets, multiple histologies
- Increased efficiency
- General framework

CLINICAL  
TRIALS *ARTICLE*

*Clinical Trials* 2013; 10: 720–734

## Bayesian hierarchical modeling of patient subpopulations: Efficient designs of Phase II oncology clinical trials

*Scott M Berry<sup>a</sup>, Kristine R Broglio<sup>a</sup>, Susan Groshen<sup>b</sup> and Donald A Berry<sup>a,c</sup>*



# Modified Bayesian Design

1. Treat 10K patients. Stop an individual basket with at least  $n_{min} = 10$  patients, if:

$$Pr(RR_k > 0.3|data) < 0.05,$$

$$Pr(RR_k > 0.3|data) > 0.90$$

2. After every 5K\* patients, perform interim analyses
3. Perform final analysis after max sample size enrolled and apply final decision rule:

$$Pr(RR_k > 0.15|data) > \gamma$$



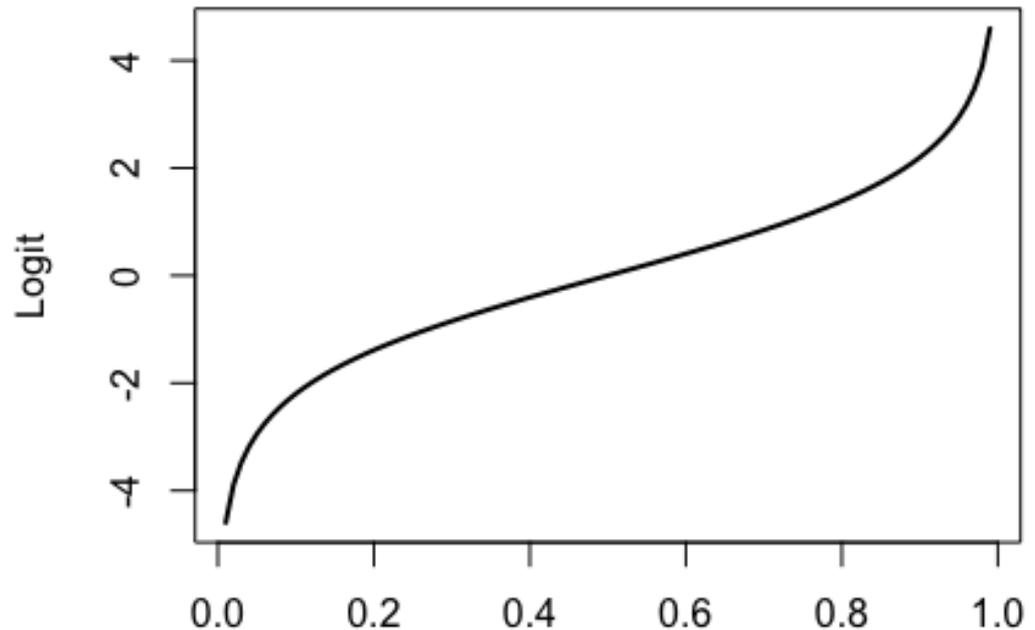
# How Can We Improve Over the Aggregation Design?

$$\theta_k = \text{logit}(RR_k) - \text{logit}(0.15),$$

$$\theta_k \sim \text{Normal}(\mu, \sigma^2)$$

$$\mu \sim \text{Normal}(0, 10^2)$$

$$\sigma^2 \sim g(\cdot)$$



# How Can We Improve Over the Aggregation Design?

$$\theta_k = \text{logit}(RR_k) - \text{logit}(0.15),$$

$$\theta_k \sim \text{Normal}(\mu, \sigma^2)$$

$$\mu \sim \text{Normal}(0, 10^2)$$

$$\sigma^2 \sim g(\cdot)$$

This could also be a parameter but affords little gain

Choice of  $g(\cdot)$  is the single most important statistical decision

Sharing is controlled by this variance parameter

- Large  $\rightarrow$  More variability in response rates across baskets  $\rightarrow$  Less sharing
- Small  $\rightarrow$  Less variability in response rates across baskets  $\rightarrow$  More sharing



# Choice of $g(\cdot)$

- Inverse-gamma is an automatic prior for this purpose
  - Used by Berry et al (2013)
- Works well when there are “many” groups as it might be the case in the analysis of clustered data
- There is some evidence that when the number of groups are small a prior which puts too much weight near zero never updates itself away from zero  
→ oversharing
- Gelman and others advocated using a uniform prior

Bayesian Analysis (2006)

1, Number 3, pp. 515–533

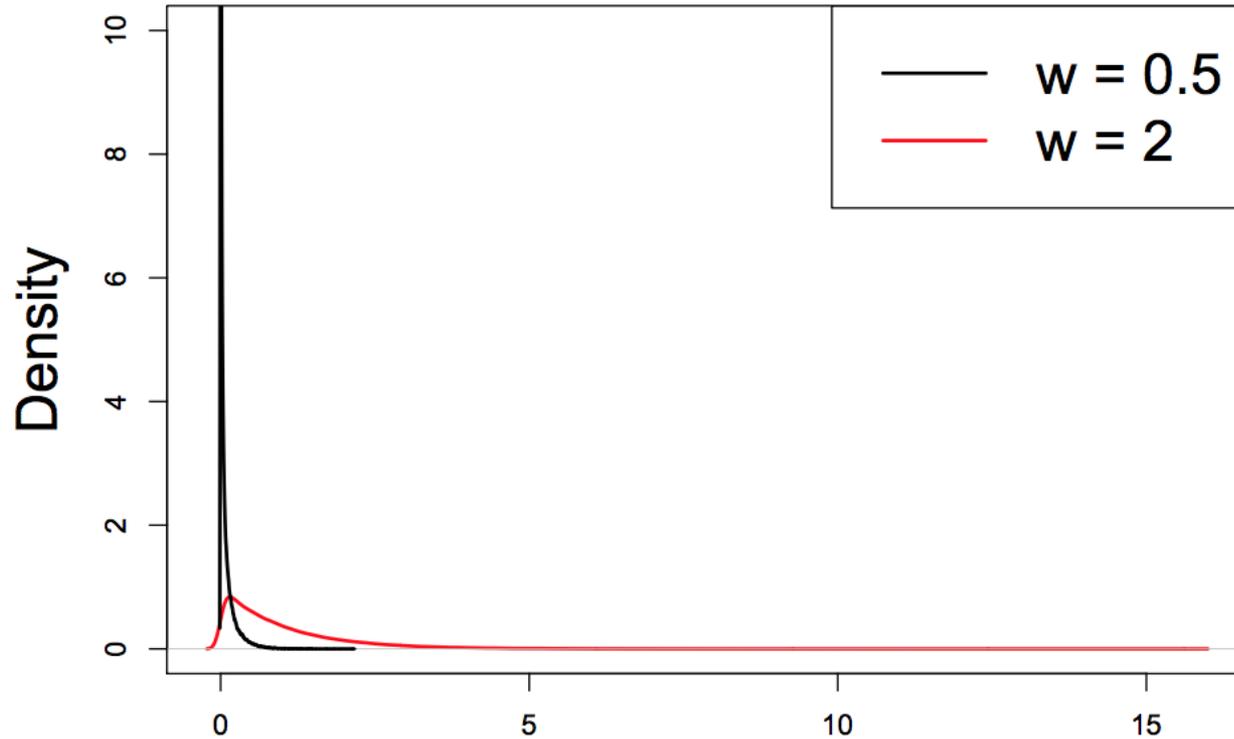
## **Prior distributions for variance parameters in hierarchical models**

Andrew Gelman

Department of Statistics and Department of Political Science  
Columbia University

# Inverse Gamma (m, w)

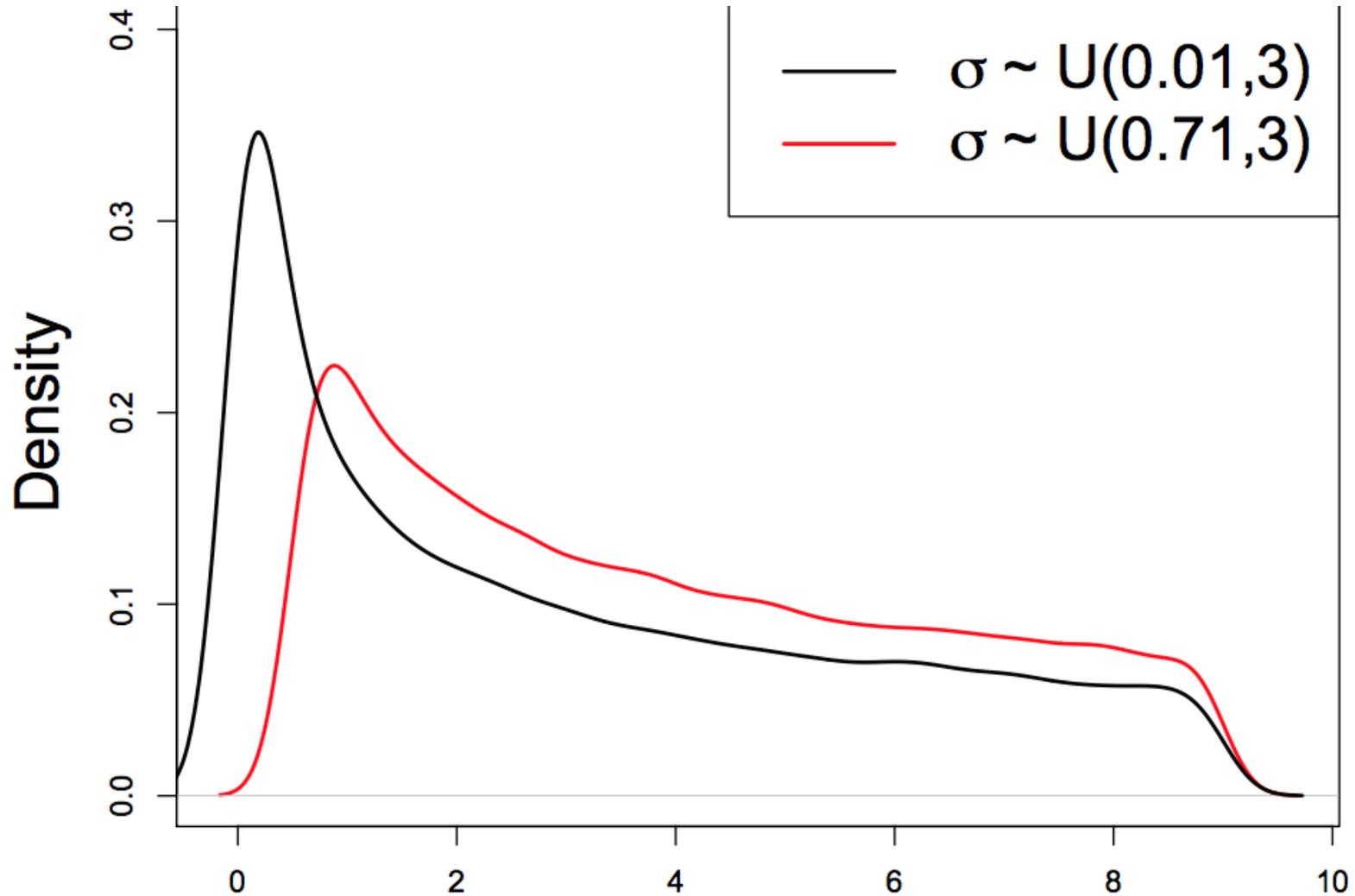
mean = 1



$$\alpha = w_{\sigma^2}/2 \text{ and } \beta = m^2_{\sigma^2} w_{\sigma^2}/2$$



# Uniform for $\sigma$



# Simulation Study

- Null RR: 15%; Target RR 45%
- Max sample size per basket: 20 patients
- 35 IG prior specifications:

$$m_{\sigma^2} = \{0.1, 0.5, 1, 2, 10\}$$

$$w_{\sigma^2} = \{0.01, 0.1, 0.5, 1, 2, 5, 10\}$$

- 36 Unif prior specifications:

$$a = \{0, 0.01, 0.05, 0.3, 0.5, 0.71\}$$

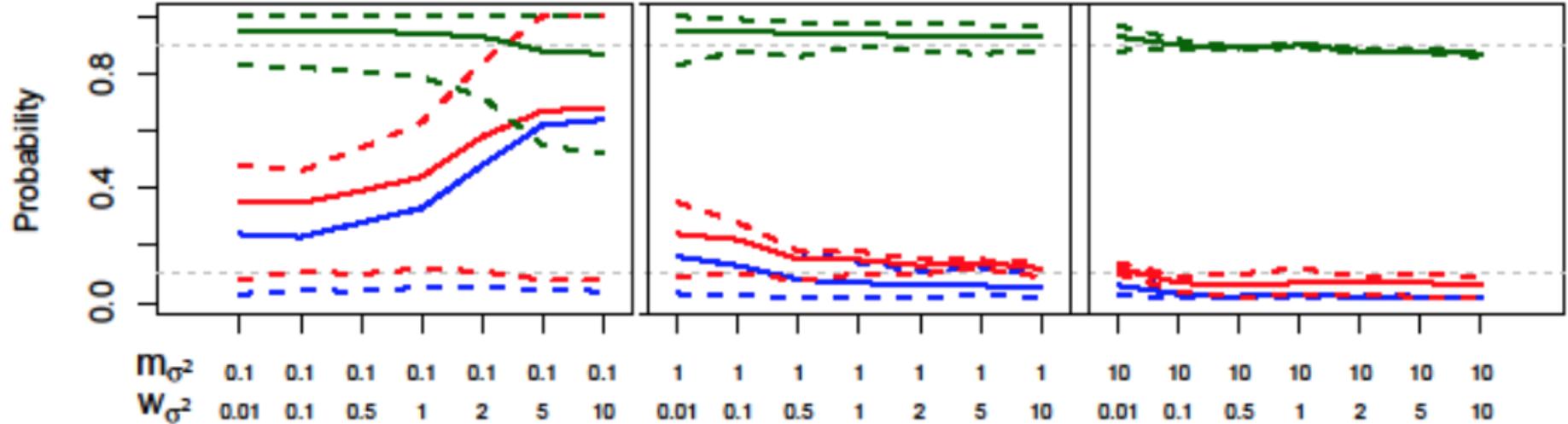
$$b = \{1, 2, 3, 10, 100, 10000\}$$

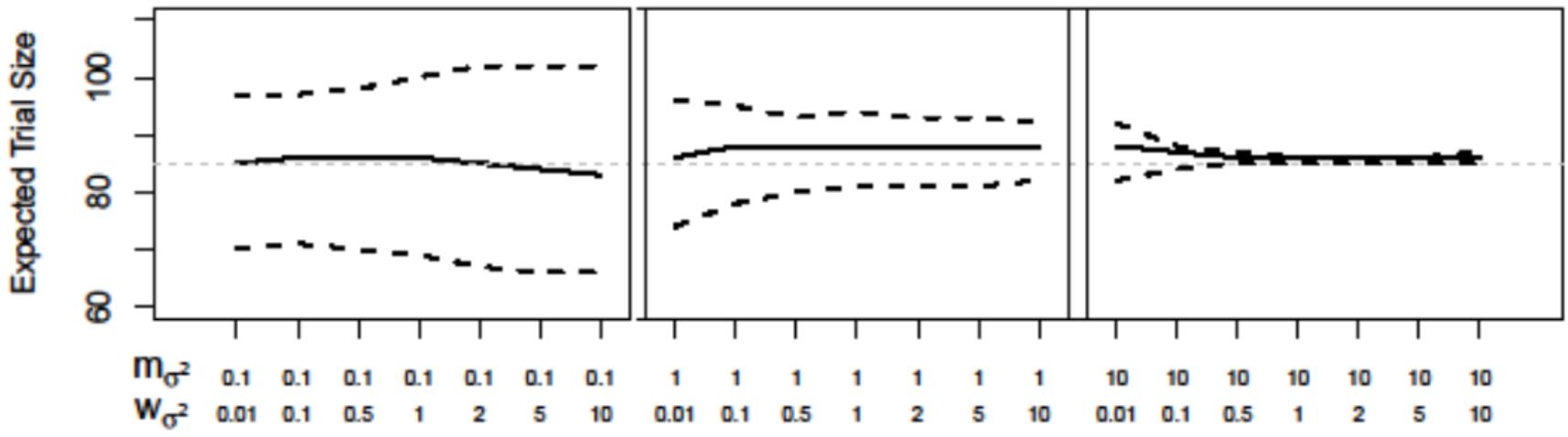


# Results for Inverse Gamma

Green: Power; Red: FWER; Blue: type 1 error

Solid: Average over 0:5 Active; Dash: Range over 0:5 Active



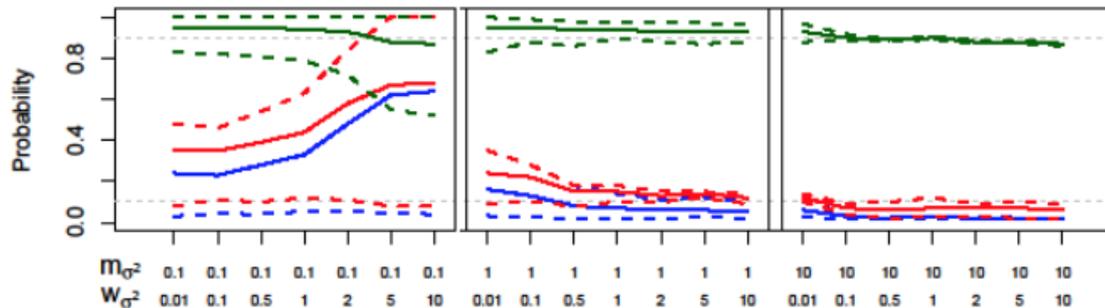


$(m_\sigma, w_\sigma)$	A	FWER	% Declare Drug Works					N	$\hat{\sigma}$
			B1	B2	B3	B4	B5		
(0.1,1)	0	12	6	6	6	6	6	70	0.23
	1	38	79	19	19	19	19	87	0.62
	2	52	95	95	34	34	34	100	0.77
	3	57	99	99	99	45	45	99	0.70
	4	63	100	100	100	100	63	88	0.45
	5	-	100	100	100	100	100	69	0.2
(1,2)	0	10	2	2	2	2	2	81	1.00
	1	13	88	3	3	3	3	89	1.19
	2	14	90	90	5	5	5	92	1.24
	3	15	95	95	95	8	8	93	1.18
	4	11	96	96	96	96	11	90	1.04
	5	-	97	97	97	97	97	83	0.85
(10,10)	0	9	2	2	2	2	2	85	9.05
	1	8	86	2	2	2	2	85	8.99
	2	6	87	87	2	2	2	85	8.94
	3	4	87	87	87	2	2	87	8.87
	4	2	87	87	87	87	2	86	8.81
	5	-	86	86	86	86	86	86	8.74



# Summary: Inverse-Gamma

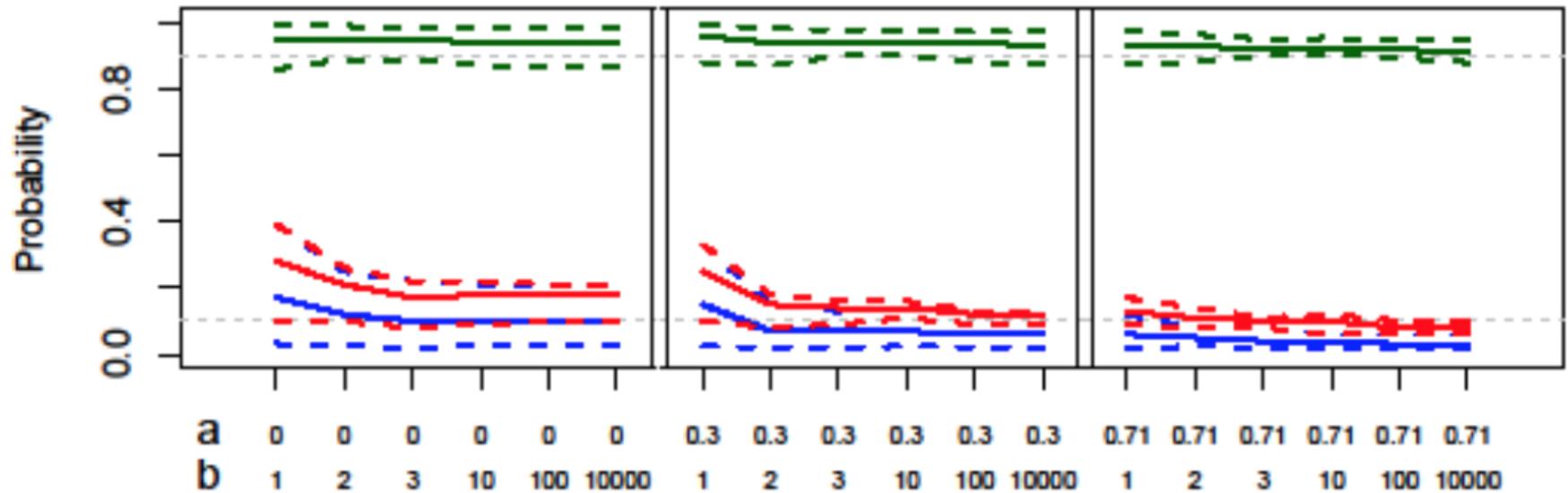
- Highly sensitive to input values
- Small prior mean value (near zero), results in:
  - large range in OCs
  - over-powered when drug works in all baskets
  - high false positive rates when drugs works in only some baskets
- Increasing prior mean value, results in:
  - narrow range in OCs
  - loss in efficiency (ind designs)
  - loss of power

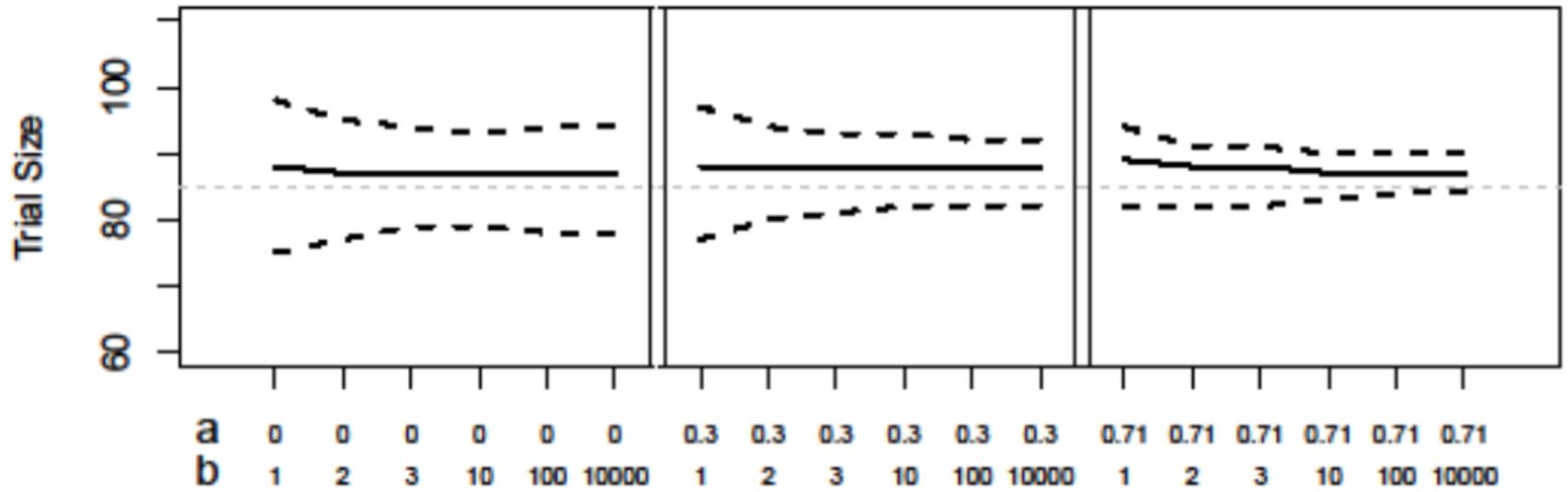


# Uniform

Green: Power; Red: FWER; Blue: type 1 error

Solid: Average over 0:5 Active; Dash: Range over 0:5 Active



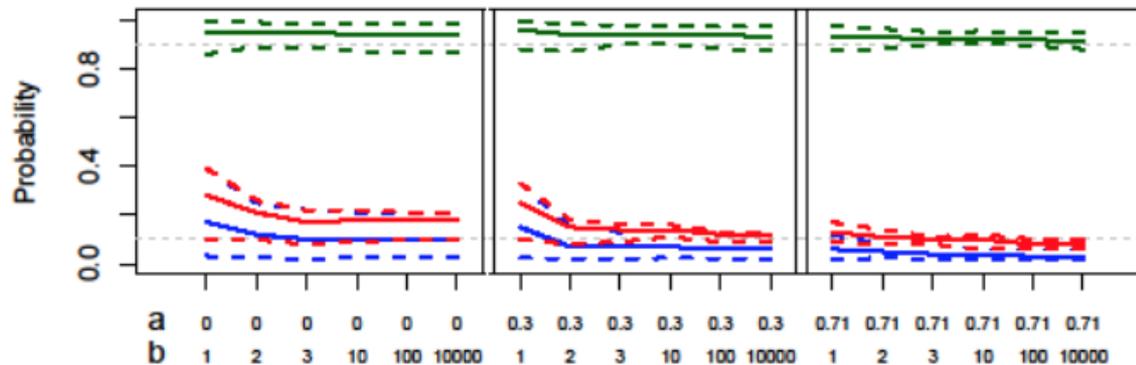


$(a, b)$	A	FWER	% Declare Drug Works					N	$\hat{\sigma}$
			B1	B2	B3	B4	B5		
(0,1)	0	10	3	3	3	3	3	75	0.44
	1	22	86	8	8	8	8	90	0.63
	2	32	94	94	14	14	14	98	0.68
	3	36	98	98	98	23	23	98	0.67
	4	39	99	99	99	99	39	91	0.58
	5	-	100	100	100	100	100	76	0.39
(0,3)	0	8	2	2	2	2	2	79	0.82
	1	18	89	6	6	6	6	88	1.29
	2	20	93	93	9	9	9	93	1.39
	3	18	95	95	95	11	11	94	1.29
	4	22	98	98	98	98	22	90	1.00
	5	-	99	99	99	99	99	79	0.55
(0.71,3)	0	10	2	2	2	2	2	82	1.37
	1	11	90	3	3	3	3	88	1.53
	2	11	91	91	4	4	4	90	1.57
	3	10	93	93	93	6	6	91	1.50
	4	8	94	94	94	94	8	89	1.38
	5	-	95	95	95	95	95	85	1.18

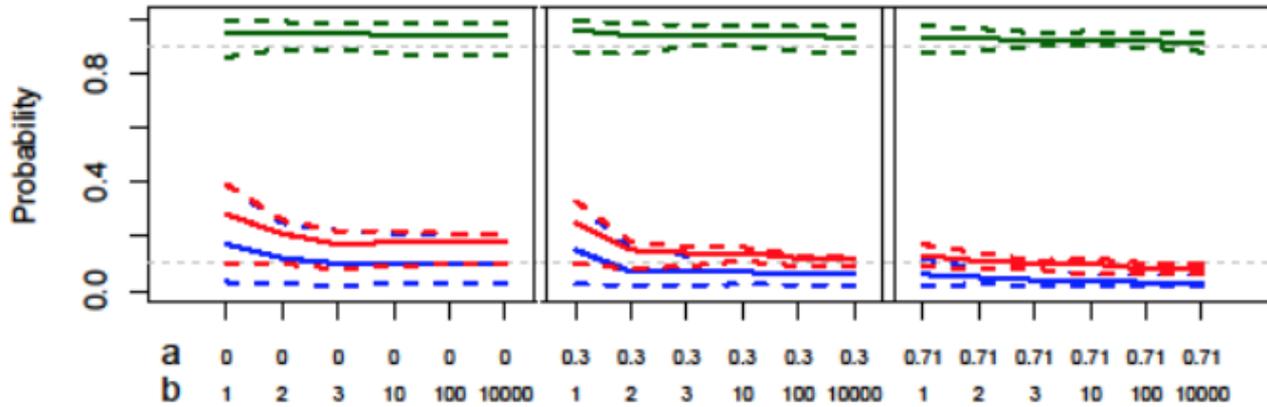
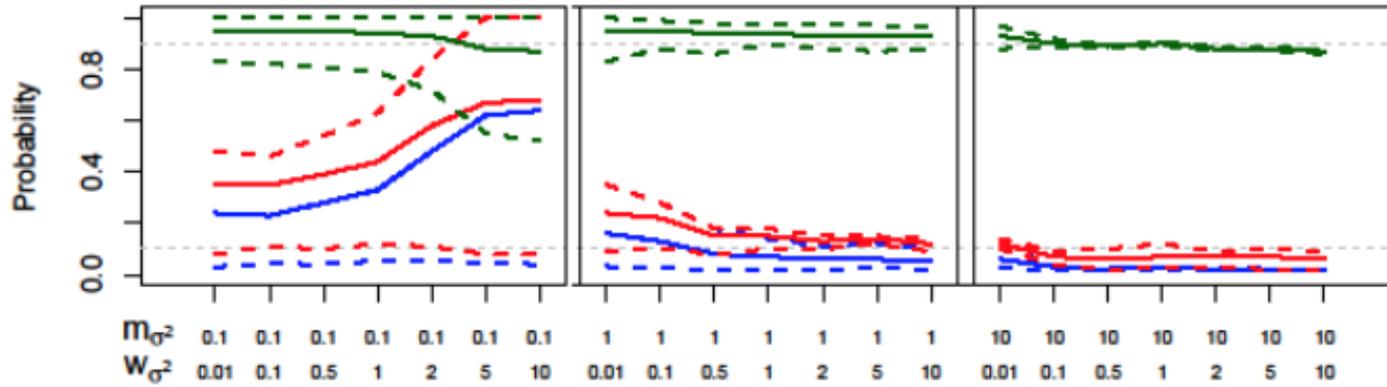


# Summary: Uniform

- OCs fairly robust for upper bound  $b > 1$
- Decreasing lower bound, results in:
  - more efficient trial sizes and higher power in homogeneous cases
  - higher error rates in heterogeneous cases
- Increasing lower bound  $\Rightarrow$  similar performance to independent designs
- Increasing upper bound  $\Rightarrow$  narrows OCs



# IG vs Uniform at a Glance



# More complicated designs

<b>Basket</b>	<b>Biomarker</b>	<b>Disease</b>
Cohort 1	M1 & M2	D1
Cohort 2	M1	All diseases/D1
Cohort 3	M3	D2
Cohort 4	M4	D3
Cohort 5	M4	D4
Cohort 6	M4	D5
Cohort 7	M5	All diseases



## A Nonparametric Bayesian Basket Trial Design

Yanxun Xu<sup>\*1</sup>, Peter Müller<sup>2</sup>, Apostolia M Tsimberidou<sup>3</sup>, and Donald Berry<sup>4</sup>

<sup>1</sup> Department of Applied Mathematics and Statistics, Johns Hopkins University, Baltimore, MD, USA

<sup>2</sup> Department of Mathematics, University of Texas at Austin, Austin, TX, 78705, USA

<sup>3</sup> Department of Investigational Cancer Therapeutics, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 77005, USA

<sup>4</sup> Department of Biostatistics, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Article

## A Bayesian basket trial design using a calibrated Bayesian hierarchical model

Yiyi Chu<sup>1</sup>  and Ying Yuan<sup>2</sup>

**CLINICAL  
TRIALS**

*Clinical Trials*  
2018, Vol. 15(2) 149–158  
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DOI: 10.1177/1740774518755122  
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Received: 11 August 2017 | Revised: 17 March 2018 | Accepted: 8 June 2018

DOI: 10.1002/sim.7893

**RESEARCH ARTICLE**

WILEY **Statistics**  
in **Medicine**

## Bayesian basket trial design with exchangeability monitoring

Brian P. Hobbs<sup>1</sup>  | Rick Landin<sup>2</sup>



Memorial Sloan Kettering  
Cancer Center



Appl. Statist. (2018)  
67, Part 3, pp. 723–740

## BLAST: Bayesian latent subgroup design for basket trials accounting for patient heterogeneity

Yiyi Chu

University of Texas School of Public Health, Houston, USA

and Ying Yuan

University of Texas MD Anderson Cancer Center Houston, USA

Journal  
**Journal of Biopharmaceutical Statistics** >  
Volume 28, 2018 - Issue 2: Special Issue: Precision Medicine in Cancer  
Research

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454

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### New designs for basket clinical trials in oncology

Richard Simon

Pages 245-255 | Received 01 Nov 2017, Accepted 08 Jul 2017, Accepted author version posted online: 06 Sep 2017, Published online: 30 Oct 2017

Download citation

<https://doi.org/10.1080/10543406.2017.1372779>

Check for updates

DOI: 10.1111/biom.12668

## Bayesian Response-Adaptive Designs for Basket Trials

Steffen Ventz,<sup>1,2,\*</sup> William T. Barry,<sup>2,3</sup> Giovanni Parmigiani,<sup>2,4</sup> and Lorenzo Trippa<sup>2,4</sup>

<sup>1</sup>University of Rhode Island, Kingston, Rhode Island

<sup>2</sup>Dana-Farber Cancer Institute, Boston, Massachusetts

<sup>3</sup>Harvard Medical School, Boston, Massachusetts

<sup>4</sup>Harvard School of Public Health, Boston, Massachusetts

\**email:* [steffen\\_ventz@uri.edu](mailto:steffen_ventz@uri.edu)

tering

# Practicalities

- Software software software!
- Freely available at GitHub
  - <https://github.com/kristenmay206/Btcode/>
- No need to know JAGS or any other Bayesian programming language
- Knowledge of R is required to organize the output and tailor calibration/simulation efforts

**Kristen Cunanan**



# In Conclusion

- It is possible to **reduce the number of patients** needed for basket trials by sharing information across baskets
- **Model-based designs** offer more **flexibility** and can achieve similar efficiencies with **careful prior modeling**
- **Sample size reductions of ~10% - 30%** depending on the homogeneity of the treatment effect
- **Price to pay: if the treatment works in only one basket** information sharing requires ~5 %- 10% more patients
- Considering the general premise of targeted treatment **this is a modest price to pay for the potential gains**



# Thanks!



**Kristen Cunanan**



**David Hyman**



**Alexia Iasonos**



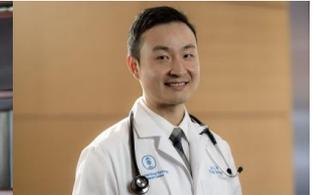
**Ronglai Shen**



**Greg Riely**



**Mark Kris**



**Bob Li**



**Colin Begg**



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