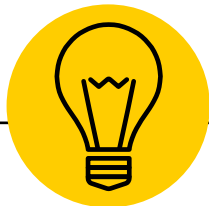


Bayesian Seamless Strategy for Early-Phase Drug Development



Yuan Ji, PhD



Outlines

- ❖ Introduction to the Bayesian Seamless Strategy
- ❖ The Bayesian Early-Phase Seamless Transformation (**BEST**) Platform
 - ❖ Platform overview
 - ❖ Bayesian Hierarchical Model (BHM) --- Key feature in BEST
 - ❖ Pilot simulation results for BHM
 - ❖ Bayesian multiplicity control



Bayesian adaptive design boost drug development

2006: “Improved utilization of adaptive and Bayesian methods” in clinical trials

2013: FDA will need to "turn the clinical trial paradigm on its head" to allow personalized drug therapies to get on the market faster

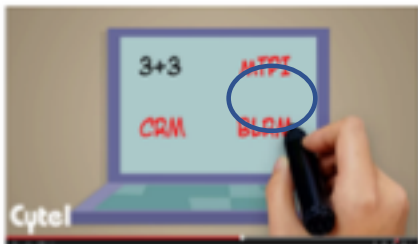
2015, Press launch of GBM AGILE: “This is the future.”

Janet Woodcock, Director CDER FDA

- ❑ The use of adaptive trial designs are well accepted in late-phase oncology drug development in US
- ❑ Early-phase drug development is even **MORE FLEXIBLE** and important: incorrect dose selection leads to disastrous late phase trials.
- ❑ Now is the time to deploy Bayesian adaptive designs in early-phase trials globally

The mTPI design (Ji et al., 2010, 2013) is a success story in dose finding

East ESCALATE



EAST includes the mTPI design



- N = 21 (Part A); N = 30 (Part B) (Total N = 51)
- Pretreated metastatic castration-resistant prostate cancer (mCRPC)
- More than 3 prior systemic treatment regimens with chemotherapy, hormonal, or immunotherapy or more than 1 prior chemotherapeutic regimen in the metastatic setting

PART A

ADXS-PSA Monotherapy

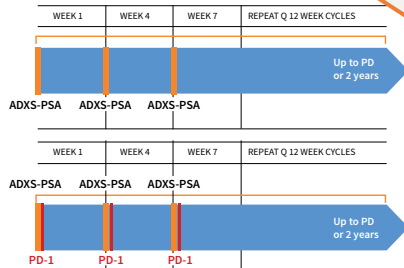
Dose escalation (3 dose levels)
Goal: To determine safety and RP2D
N = 21

PART B

ADXS-PSA + Pembrolizumab (PD-1)

Dose determination and confirmation
Goal: To determine safety and RP2D of the combination
N = 30

- mTPI design (Part A) to determine recommended Phase 2 dose (RP2D)
- Following the completion of enrollment and the RP2D, ADXS-PSA in Part A, Part B combination arm with pembrolizumab
- Part B ADXS-PSA dose = Part A RP2D + pembrolizumab



The mTPI design for ADXS-PSA + PD-1

In collaboration with MERCK
<https://clinicaltrials.gov/ct2/show/NCT02325557>

For more information, contact Janet Flisak, Senior Director, Clinical Operations:
Advaxis, Inc. Copyright Advaxis, Inc. 2016 305 College Road East Princeton, NJ 08540

flisak@advaxis.com
Phone: 609-452-9813

Phone: 609-250-7505
Fax: 609-452-9818

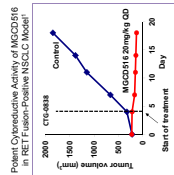
A First-in-Human Phase 1/1b Study of Receptor Tyrosine Kinase (RTK) Inhibitor MGC0516 in Patients with Advanced Solid Tumors

TP52621
Gary K. Schwartz¹, Douglas Adkins², Rebecca Suk-Hoist³, Theresa L. Werner⁴, Maura Abbott⁵, Stephanie Barber⁶, Richard C. Chao⁷, Sanku T.C. Neuteboom⁸, Isan Chen⁹, James G. Christensen⁹, Todd M. Bauer⁹

¹Columbia University Medical Center, New York, NY; ²Washington University School of Medicine, St. Louis, MO; ³Massachusetts General Hospital Cancer Center, Boston, MA; ⁴The Houstonian Cancer Institute, Salt Lake City, UT; ⁵Immun Therapeutics, San Diego, CA; ⁶Samuel Cannon Research Institute/Female Oncology, LLC, Waterville, NY

Background

- MGC0516 is an oral drug that inhibits a related spectrum of RTKs including:
 - RET, TRK and DDR family members
 - Split RTK families including VEGFR, PDGFR and KIT
 - MET and TAM family
- RTKs inhibited by MGC0516 are genetically altered in a variety of cancers
- MGC0516 has demonstrated preclinical anti-tumor activity and tumor regression in preclinical tumor models (8 playing)
- RET Rearrangement
 - TRK Rearrangement
 - Chromosome 4q12 amplification (PDGFRA, KIT, KDR gene loci)



Potent Cytoreductive Activity of MGC0516 in RET Fusion Positive NSCLC Model¹

¹RET fusion positive NSCLC Model¹

²RET fusion positive NSCLC Model¹

³RET fusion positive NSCLC Model¹

⁴RET fusion positive NSCLC Model¹

⁵RET fusion positive NSCLC Model¹

⁶RET fusion positive NSCLC Model¹

⁷RET fusion positive NSCLC Model¹

⁸RET fusion positive NSCLC Model¹

⁹RET fusion positive NSCLC Model¹

¹⁰RET fusion positive NSCLC Model¹

¹¹RET fusion positive NSCLC Model¹

¹²RET fusion positive NSCLC Model¹

¹³RET fusion positive NSCLC Model¹

¹⁴RET fusion positive NSCLC Model¹

¹⁵RET fusion positive NSCLC Model¹

¹⁶RET fusion positive NSCLC Model¹

¹⁷RET fusion positive NSCLC Model¹

¹⁸RET fusion positive NSCLC Model¹

¹⁹RET fusion positive NSCLC Model¹

²⁰RET fusion positive NSCLC Model¹

Methods

Study Design: open label phase 1/1b study evaluating Safety, PK, Metabolism, PD and Clinical activity of MGC0516 in patients with advanced solid tumor malignancies.

Phase 1a Dose Finding: dose-toxicity, dose-limiting toxicity (DLT), and maximum tolerated dose (MTD) in 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1b Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1c Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1d Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1e Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1f Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1g Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1h Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1i Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1j Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1k Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1l Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1m Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1n Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1o Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1p Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1q Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1r Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1s Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1t Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1u Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1v Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1w Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1x Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

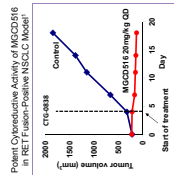
Phase 1y Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1z Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

ASCO 2016 Protocol for FIH phase 1/1b study using the mTPI design

Background

- MGC0516 is an oral drug that inhibits a related spectrum of RTKs including:
 - RET, TRK and DDR family members
 - Split RTK families including VEGFR, PDGFR and KIT
 - MET and TAM family
- RTKs inhibited by MGC0516 are genetically altered in a variety of cancers
- MGC0516 has demonstrated preclinical anti-tumor activity and tumor regression in preclinical tumor models (8 playing)
- RET Rearrangement
 - TRK Rearrangement
 - Chromosome 4q12 amplification (PDGFRA, KIT, KDR gene loci)



Potent Cytoreductive Activity of MGC0516 in RET Fusion Positive NSCLC Model¹

¹RET fusion positive NSCLC Model¹

²RET fusion positive NSCLC Model¹

³RET fusion positive NSCLC Model¹

⁴RET fusion positive NSCLC Model¹

⁵RET fusion positive NSCLC Model¹

⁶RET fusion positive NSCLC Model¹

⁷RET fusion positive NSCLC Model¹

⁸RET fusion positive NSCLC Model¹

⁹RET fusion positive NSCLC Model¹

¹⁰RET fusion positive NSCLC Model¹

¹¹RET fusion positive NSCLC Model¹

¹²RET fusion positive NSCLC Model¹

¹³RET fusion positive NSCLC Model¹

¹⁴RET fusion positive NSCLC Model¹

¹⁵RET fusion positive NSCLC Model¹

¹⁶RET fusion positive NSCLC Model¹

¹⁷RET fusion positive NSCLC Model¹

¹⁸RET fusion positive NSCLC Model¹

¹⁹RET fusion positive NSCLC Model¹

²⁰RET fusion positive NSCLC Model¹

Methods

Study Design: open label phase 1/1b study evaluating Safety, PK, Metabolism, PD and Clinical activity of MGC0516 in patients with advanced solid tumor malignancies.

Phase 1a Dose Finding: dose-toxicity, dose-limiting toxicity (DLT), and maximum tolerated dose (MTD) in 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1b Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1c Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1d Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1e Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1f Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1g Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1h Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1i Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1j Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1k Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1l Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1m Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1n Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1o Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1p Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1q Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1r Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1s Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1t Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1u Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1v Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1w Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1x Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Phase 1y Dose Finding: 3 to 5 unselected patients are enrolled per dose level cohort.

Summary

Dose Escalation Phase 1:

Started in September 2014.

Cohort 1, 40mg; Cohort 2, 20mg; Cohort 3, 10mg; Cohort 4, 5mg.

Cohort 5, 10mg; Cohort 6, 5mg; Cohort 7, 2.5mg; Cohort 8, 1.25mg.

Cohort 9, 10mg; Cohort 10, 5mg; Cohort 11, 2.5mg; Cohort 12, 1.25mg.

Cohort 13, 10mg; Cohort 14, 5mg; Cohort 15, 2.5mg; Cohort 16, 1.25mg.

Cohort 17, 10mg; Cohort 18, 5mg; Cohort 19, 2.5mg; Cohort 20, 1.25mg.

Cohort 21, 10mg; Cohort 22, 5mg; Cohort 23, 2.5mg; Cohort 24, 1.25mg.

Cohort 25, 10mg; Cohort 26, 5mg; Cohort 27, 2.5mg; Cohort 28, 1.25mg.

References

1. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
2. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
3. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
4. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
5. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
6. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
7. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
8. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
9. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
10. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
11. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
12. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
13. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
14. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
15. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
16. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
17. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
18. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
19. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
20. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
21. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
22. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
23. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
24. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
25. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
26. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
27. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
28. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
29. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.
30. "Phase 1 Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases (RET, TRK, and DDR) in Patients with Advanced Solid Tumor Malignancies." *Journal of Clinical Oncology* 31:1765-1771.

Study Objectives

- Primary Objectives:**
 - To characterize safety and tolerability profile of MGC0516
 - To characterize the PK of MGC0516
- Secondary Objectives:**
 - To explore potential PD markers in blood plasma
 - To explore use of tumor molecular markers for selection of patients with increased potential for response to MGC0516

FDA's Woodcock: The Clinical Trials System is 'Broken'

Posted 20 September 2017

The clinical trials system is "broken" and there needs to be new ways to collect and utilize patient data, Janet Woodcock, director of FDA's Center for Drug Evaluation and Research, told a workshop on real world evidence (RWE) at the National Academies of Sciences, Engineering, and Medicine on Wednesday.

The comment came at the end of Woodcock's talk in which she also noted that **use of master protocols (ie. protocols for trials that look at multiple therapies in a single disease or a single treatment in multiple diseases) and the development of new clinical trial networks** "need to be the future."



FDA proposed “Seamless design and cohort expansion efficiently expedite the clinical development”

- ❖ “Approaches like basket trials, master protocols, and **seamless trial designs** allow us to learn more about new drugs, and even evaluate different drugs in the conduct of the same clinical trial. ... **Multiple, concurrently accruing and individual cohorts** can allow us to better assess a lot of information in one large trial, ... **With more efficient development using a seamless design, the whole trial can be completed with a few hundred patients.** ”

----- by Dr. Scott Gottlieb, M.D. Commissioner, Food and Drug Administration, Department of Health and Human Services on July 25, 2018

- ❖ FDA released a drafted guidance on multiple expansion cohorts in FIH trials on August 2018.

Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lee Pai-Scherf at 301-796-3490 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

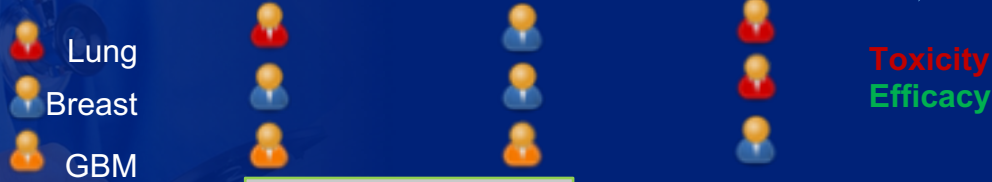
August 2018
Procedural



The BEST Platform for Early-Phase Drug Development

Bayesian Early-Phase Seamless Transformation

Doses: d=1 d=2 d=3



phase I dose-finding
mTPI-2 or R-TPI

Phase I



1b Cohort Expansion



Phase IIa

Seamless Graduation

Real-time monitoring prob. of success
Real-time monitoring toxicity events
Early exclusion of the inefficacious or overly-toxic doses
Acceleration in enrollment of highly-efficient doses

- Phase II randomized controlled design
- Subgroup analysis
- Go/No-Go

Seamless Graduation

- Bayesian hierarchical model;
- Select disease type and doses;
- Umbrella/Basket design;
- Adaptive randomization;

dose 2 & randomization & control arm

Master Protocol

Implementation Detail

Data set

Patient	Tox	Eff	Disease Type	Dose	...
1	0/1	0/1	Lung	d=1	...
2	0/1	0/1	Breast	d=2	...
3	0/1	0/1	GBM	d=2	...
...

	Lung	Breast	GBM
Resp.	10	3	2
No Resp.	3	5	7

$d = MTD$
 $\hat{p} = 0.28$

	Lung	Breast	GBM
Resp.
No Resp.

$d = MTD-1$
 $\hat{p} = 0.2$

	Lung	Breast	GBM
Resp.
No Resp.

$d = MTD+1$
 $\hat{p} = 0.35$

How to decide **indication** $T^* \in \{L, B, G\}$,
DOSE $D^* \in \{1, \dots, MTD + 1\}$?

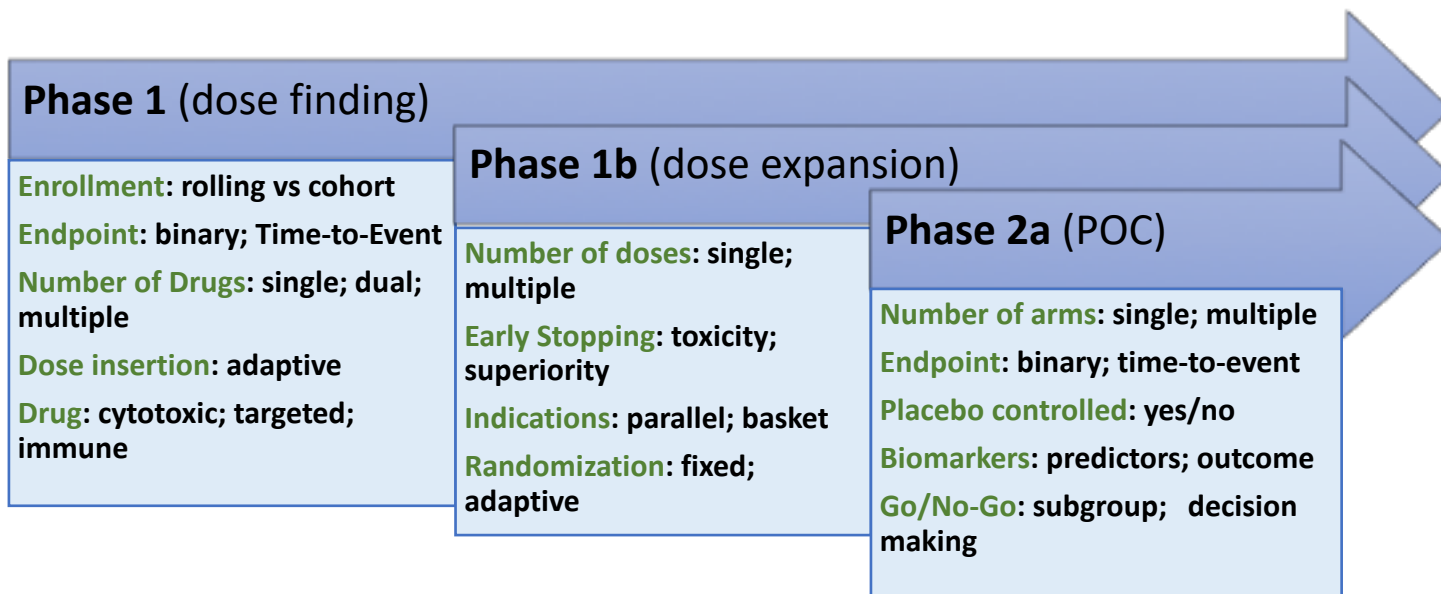
Basket Design
Bayesian Hierarchical Model

dose expansion

- ❖ Sample size of each D^*/T^* ?
- ❖ Randomization? Equal OR Adaptive?
- ❖ Control arm?
- ❖ Platform trial design, selection/exclusion of doses



The BEST Platform is a Flexible Module Design



Solution Suites

mTPI-2	single agent	Binomial/stopping boundary	single dose
AAA	dual agents	Parallel group/stopping boundary	multi doses
Laiya001	multi agents	Basket/Umbrella	biomarkers
R-TPI	fast enrollment	SEARS	seamless
TEAMS	dose insertion	Bayesian hierarchical model	AR, Go/No-Go
TEPI	Immune oncology	SCUBA	Subgroup analysis



BEST Scheme Advantages

1. **Multi doses versus single control**
2. **Borrow information across doses and indications**
3. Save sample size
4. Early stop inefficacious arms
5. Reduce time: seamlessly graduate efficacious arms
6. Higher probability of success

The advantages come from three key features

- **Bayesian hierarchical model**
- Seamless strategy
- mTPI-2 in dose finding
- A pilot simulation study: to demonstrate the superiority of the proposed Bayesian hierarchical model
- The advantages of the latter two have been shown in literatures (mTPI-2, Guo et al 2017; SEARS, Pan et al 2014)



Bayesian Hierarchical Model

- The objective of the trial is to test whether the any dose i is efficacious in any indication j

$$H_0: q_{ij} \leq q_0 \text{ v.s. } H_1: q_{ij} > q_0,$$

where q_0 is the response rate that is considered as futile.

- Suppose n_{ij} patients from indication j have been enrolled and treated at dose i , among which y_{ij} patients responded to the treatment. We assume y_{ij} follows a hierarchical model

$$\begin{aligned} y_{ij} | n_{ij}, q_{ij} &\sim \text{Bin}(n_{ij}, q_{ij}) \\ q_{ij} &= \text{logit}(\theta_{ij}) \\ \theta_{ij} | \lambda_{ij} &\sim f_1(\theta_{ij})^{I(\lambda_{ij}=1)} f_2(\theta_{ij})^{I(\lambda_{ij}=2)}; \\ \lambda_{ij} &= \begin{cases} 1; & \text{if } Z_{ij} \leq 0 \\ 2; & \text{if } Z_{ij} > 0 \end{cases} \\ Z_{ij} &\sim N(\xi_i + \eta_j, 1) \end{aligned}$$

Inference based on λ_{ij} instead of θ_{ij} \rightarrow automatically handle **multiplicity control**.

Introduce ξ_i and η_j \rightarrow **borrow information** across doses and indications; the degree of information borrowed from doses and indications could be different.



Simulation Study Overview

- Cohort Expansion of four arms: **Two doses** and **two indications**
 - Each cohort arm n=20
 - Aim to identify efficacious arm for phase II and III trials

 - ❖ Three methods are compared regarding the **power** and **sample size**:
 - ❖ Bayesian hierarchical model in BEST (BEST BHM)
 - ❖ Bayesian inference based on independent beta binomial distribution for each dose-indication arm (BayInd)
 - ❖ Frequentist method for each dose-indication arm (Freq)

 - ❖ **BEST BHM uses a smaller sample size to achieve equal or higher power**
 - ❖ **BEST BHM shows higher power than BayInd and Freq at the same Type I error rate**
- ❑ **Power**: select true efficacious arms
 - ❑ **Type I error**: select true inefficacious arms



BEST reduces sample size without losing power

- Sample size reduction of BEST BHM – save 20 subjects; match the same power!

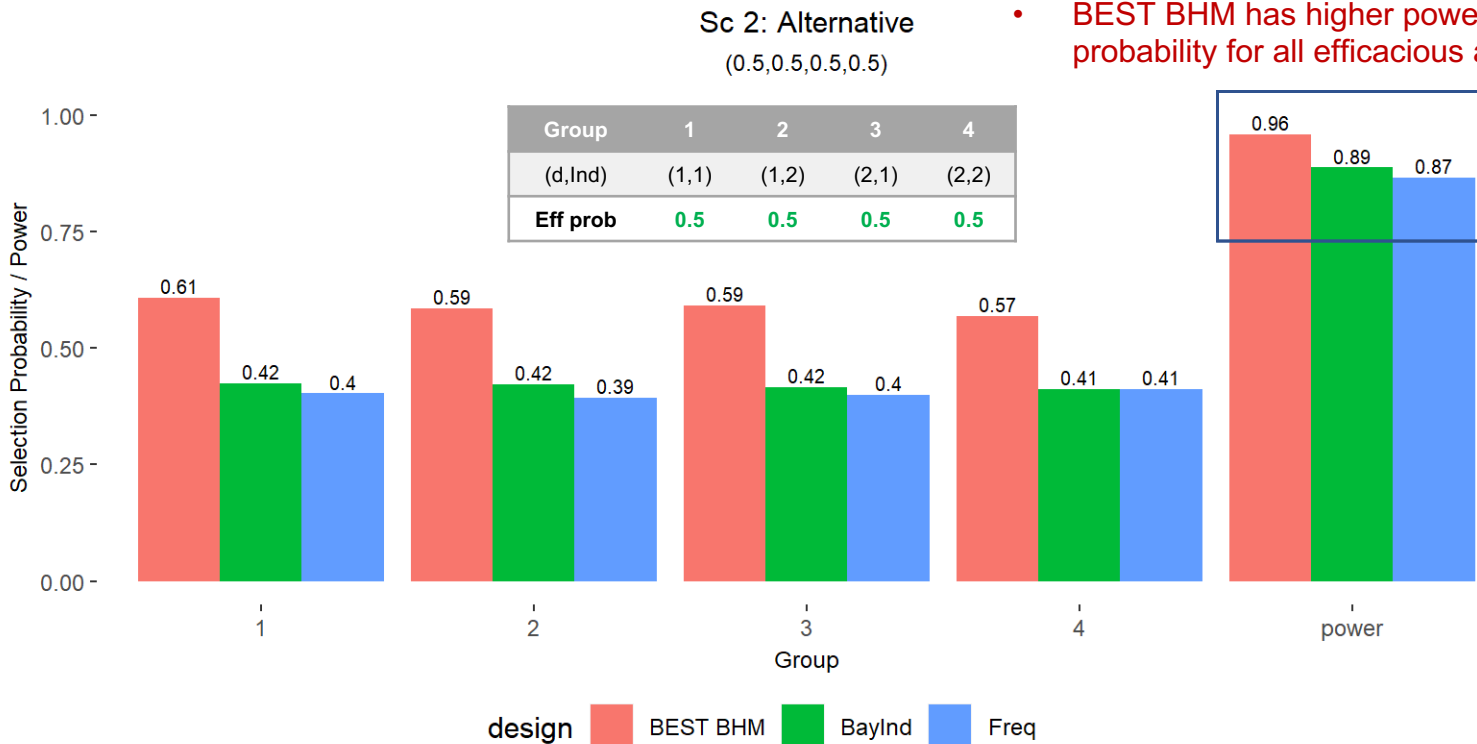
	Method	BEST BHM	BayInd	Freq
All four arms are better than control	Power	0.703	0.709	0.716
	Sample size	80	100	100
	Power	0.771	0.820	0.783
	Sample size	100	120	120

While maintaining similar power, BEST BHM saves about 20% sample size.



Compare power with 20 subjects per arm

- All four arms are efficacious.
- **BEST BHM has higher power and selection probability for all efficacious arms.**

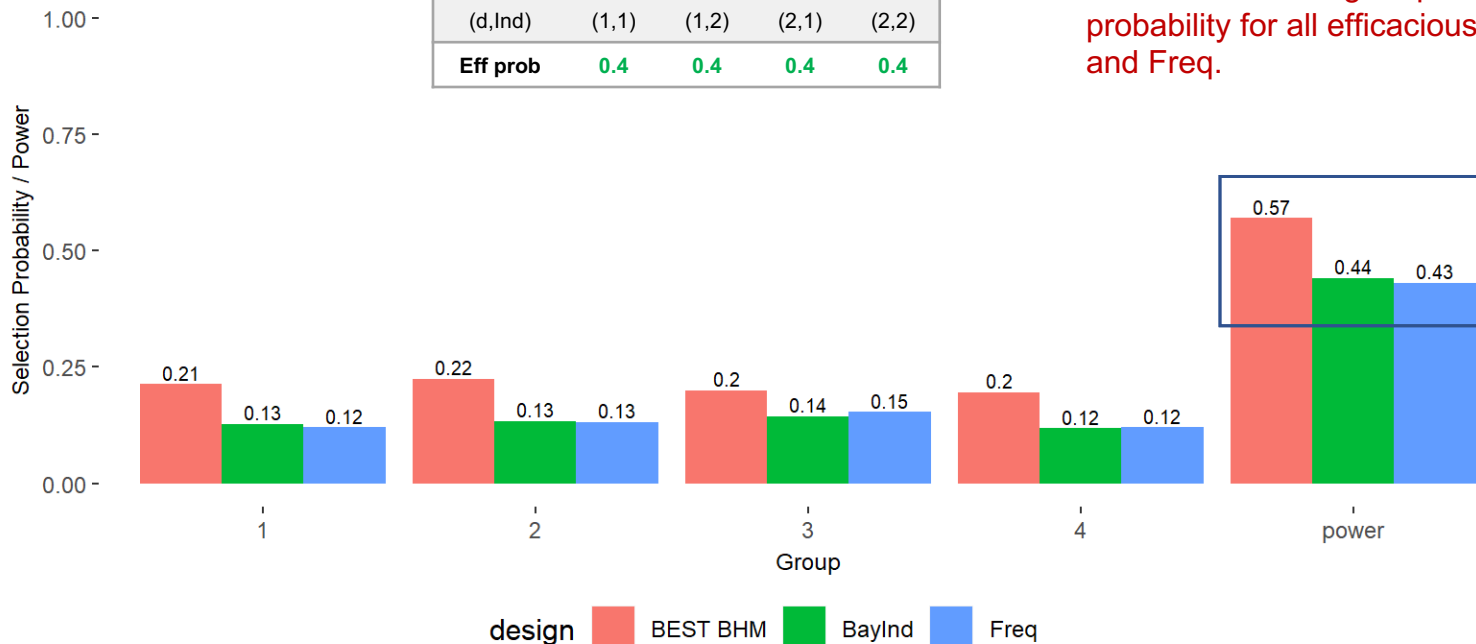




Compare power with 20 subjects per arm

Sc 3: All in middle

Group	1	2	3	4
(d,Ind)	(1,1)	(1,2)	(2,1)	(2,2)
Eff prob	0.4	0.4	0.4	0.4



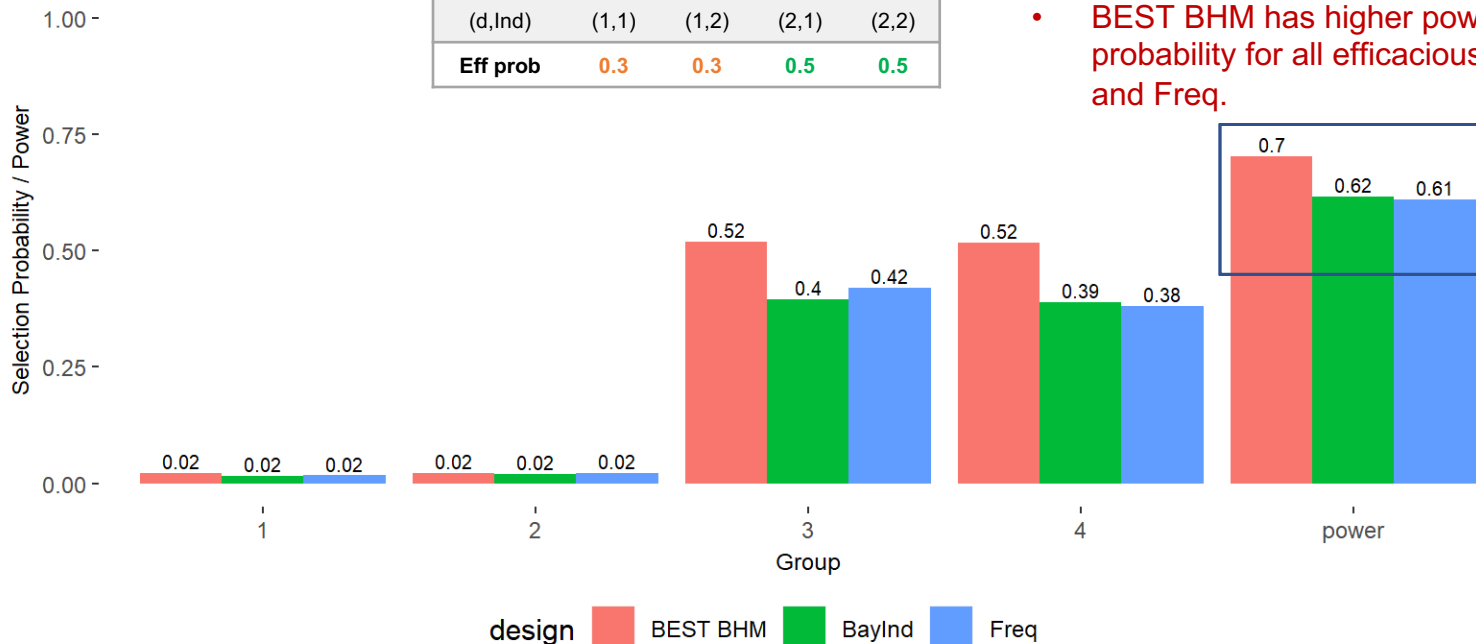
- All arms are efficacious. The effect size is smaller than Sc 2.
- BEST BHM has higher power and selection probability for all efficacious arms than BayInd and Freq.



Compare power with 20 subjects per arm

Sc 4: 2 null, 2 alternative

Group	1	2	3	4
(d,Ind)	(1,1)	(1,2)	(2,1)	(2,2)
Eff prob	0.3	0.3	0.5	0.5



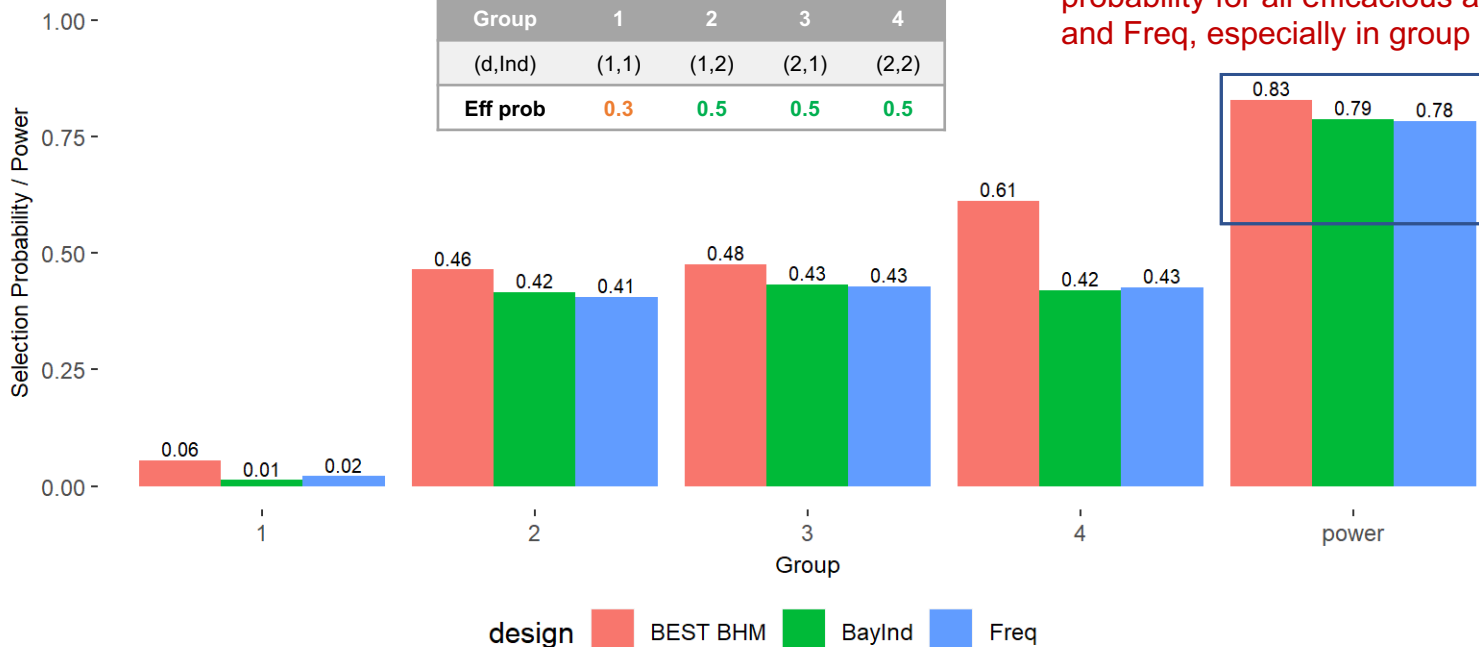
- One dose is efficacious for both indications, and the other is ineffective for either indication.
- **BEST BHM has higher power and selection probability for all efficacious arms than BayInd and Freq.**



Compare power with 20 subjects per arm

Sc 5: 1 null, 3 alternative
(0.3,0.5,0.5,0.5)

Group	1	2	3	4
(d,Ind)	(1,1)	(1,2)	(2,1)	(2,2)
Eff prob	0.3	0.5	0.5	0.5



- Other than one dose in one indication, all efficacious.
- BEST BHM has higher power and selection probability for all efficacious arms than BayInd and Freq, especially in group 4 (d2, Ind2)

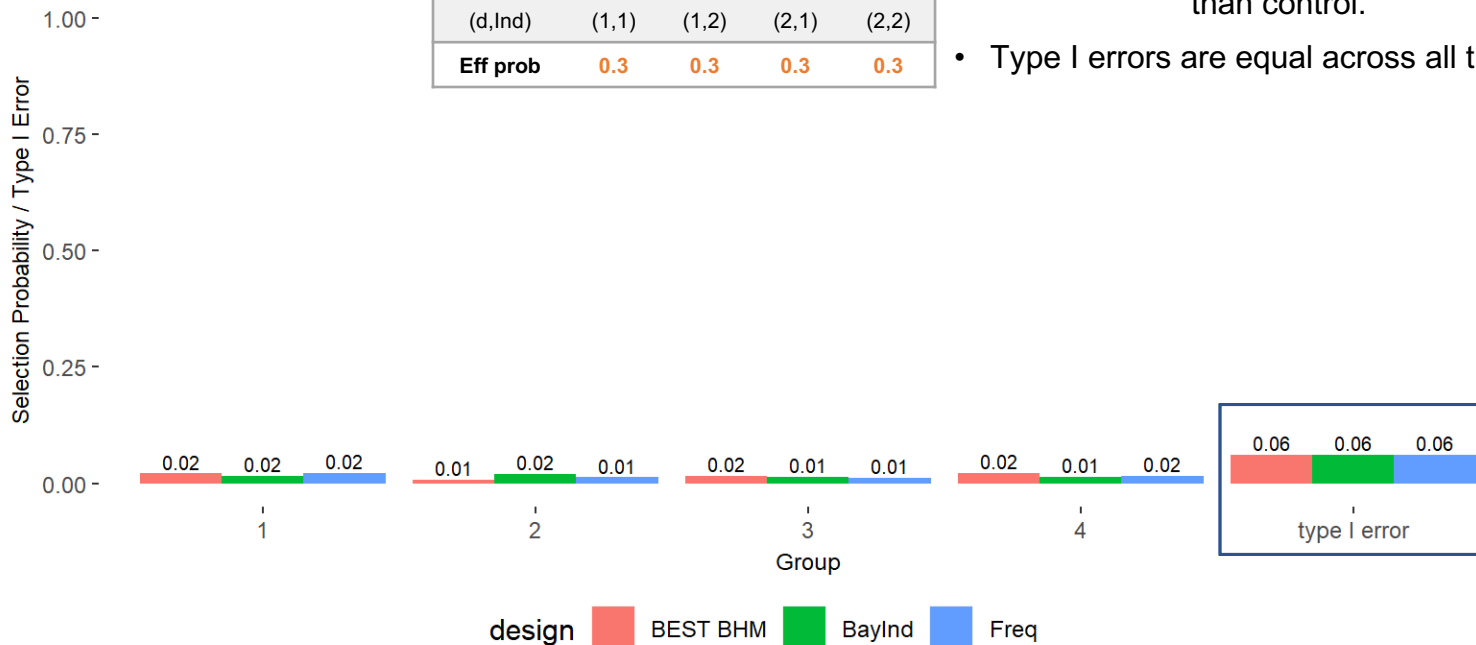


Null Results (n=20; control arm response rate = 0.3)

Sc 1: Null

Group	1	2	3	4
(d,Ind)	(1,1)	(1,2)	(2,1)	(2,2)
Eff prob	0.3	0.3	0.3	0.3

- Null scenario: No arms are more efficacious than control.
- Type I errors are equal across all three designs.





Pilot Simulation Study Summary

- ❖ BEST BHM shows **higher power** than BayInd and Freq when type 1 error is fairly controlled across all three methods
- ❖ BEST BHM shows **higher probability of selecting efficacious arms** than BayInd and Freq
- ❖ To achieve similar power, BEST BHM needs **smaller sample size** than BayInd and Freq.



Bayesian approach **automatically** handles multiplicity control

- ❖ James G. Scott and James O. Berger (2006) proposed that Bayesian approach could automatically handle multiple testing **by introducing a prior distribution for hypotheses** without introducing any penalty term. Because Bayesian testing has a built-in penalty or “Ockham’s razor effect” (cf. Jefferys and Berger, 1992).
- ❖ They also developed a decision-theoretical approach to control false positive and false negative (i.e. missing the true promising arm) by using a loss function.
- ❖ **Eg. Gene expression.**
 - ❖ The hypotheses are $H_1: \mu_i \neq 0$. Define model index parameter $\lambda_i = 1$, if $\mu_i \neq 0$; otherwise, $\lambda_i = 0$.
 - ❖ Give prior for p that each $\mu_i = 0$, then make inference based on the posterior probability $1 - p_i = 1 - P(\lambda_i = 0 | \mathbf{x})$.

The posterior probabilities of the 10 signal means being non-zero as n , the number of noise observations, increases, for two different priors on p

<i>10 Signal observations</i>										
n	-5.65	-5.56	-2.62	-1.20	-1.01	-0.90	-0.15	1.65	1.94	3.57
<i>Uniform prior on p</i> "Objective" prior										
25	.97	.97	.71	.31	.28	.26	.20	.43	.51	.88
100	.99	.99	.47	.21	.20	.19	.16	.26	.31	.75
500	1	1	.34	.07	.06	.06	.04	.11	.15	.79
5000	1	1	.11	.02	.02	.02	.01	.03	.04	.42
<i>Prior $\pi(p) = 11p^{10}$</i> "Subjective" prior										
25	.91	.90	.37	.10	.08	.08	.06	.15	.20	.65
100	.98	.98	.23	.06	.05	.05	.04	.08	.11	.58
500	1	1	.26	.04	.04	.03	.02	.07	.10	.74
5000	1	1	.08	.01	.01	.01	.01	.02	.03	.36

- the posterior inclusion probabilities, $1 - p_i$, decrease as the number of "noise" observations, n , grows, so that [the same observation implies less evidence of a non-zero mean when more tests are simultaneously considered](#).
- the prior on p does have a strong effect on the p_i 's. While this effect tends to fade as n increases, it becomes negligible only for extremely large n . So they recommend to use the subjective prior information, if available.

Thank you!!

