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Basket Trials in Oncology

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Disclosures

- DSMB
- Mylan
- BrightPath Biotherapeutics Co., Ltd.

Working group on targeted therapy / trial design

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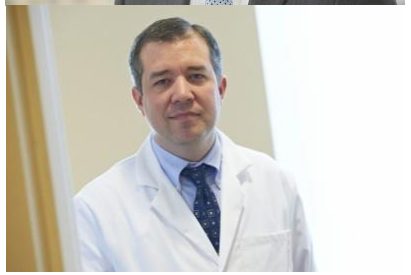

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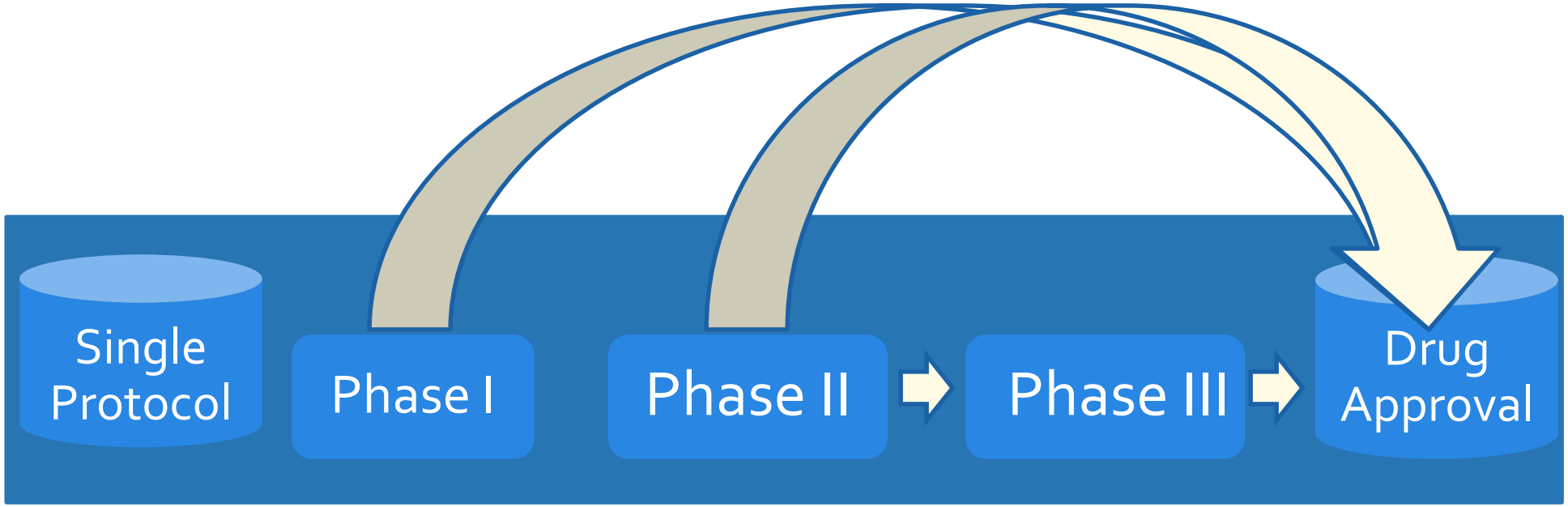
New landscape of drug development



Single Protocol	Objectives
•Early phase trials	Safety and efficacy Identify right population, dose, schedule, combination
•Adaptive protocol	Multiple and prespecified hypotheses
•Amended protocol	Evolve over time

Objective

Can we do many trials with the cost and sample size of a single trial?

Can we answer multiple questions in a single trial?

- It can be done in a rigorous and efficient way
- What is the price to pay?

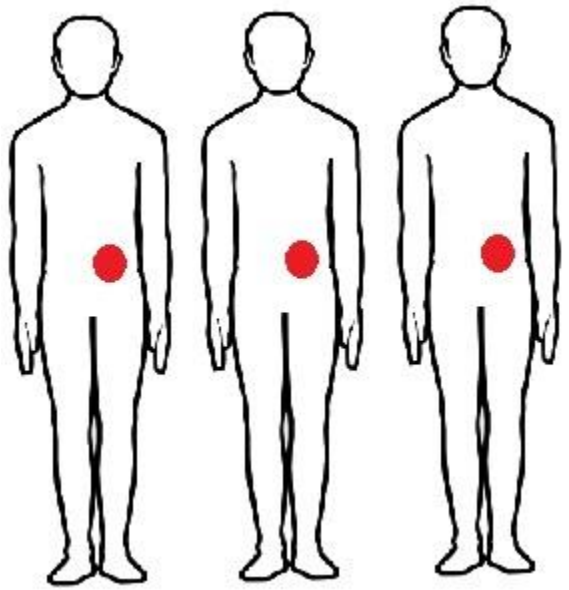
Innovative designs (adaptive, Bayesian)

- Premise: they are more efficient than traditional/ conventional designs in terms of sample size and trial duration

- Phase I – Model based dose escalation designs
  - Dose; Schedules; Groups (pediatrics vs adults)

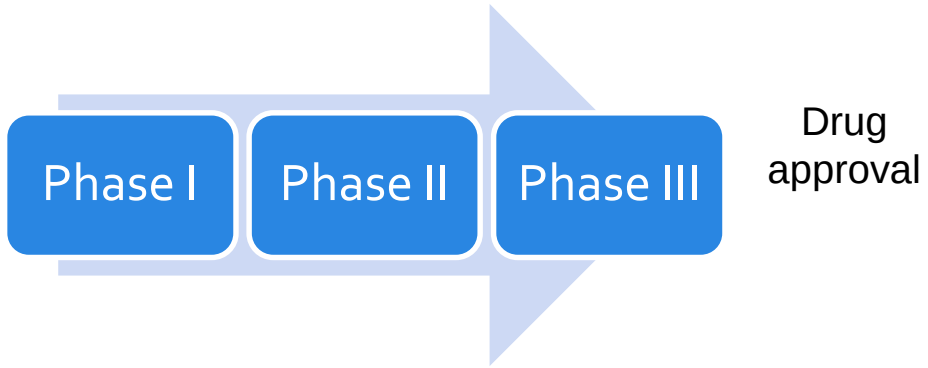
- Phase II (basket trials) - efficacy
  - Borrow information across baskets
  - Evaluate emerging evidence in a formal statistical model

Traditional Single arm Phase II Trial

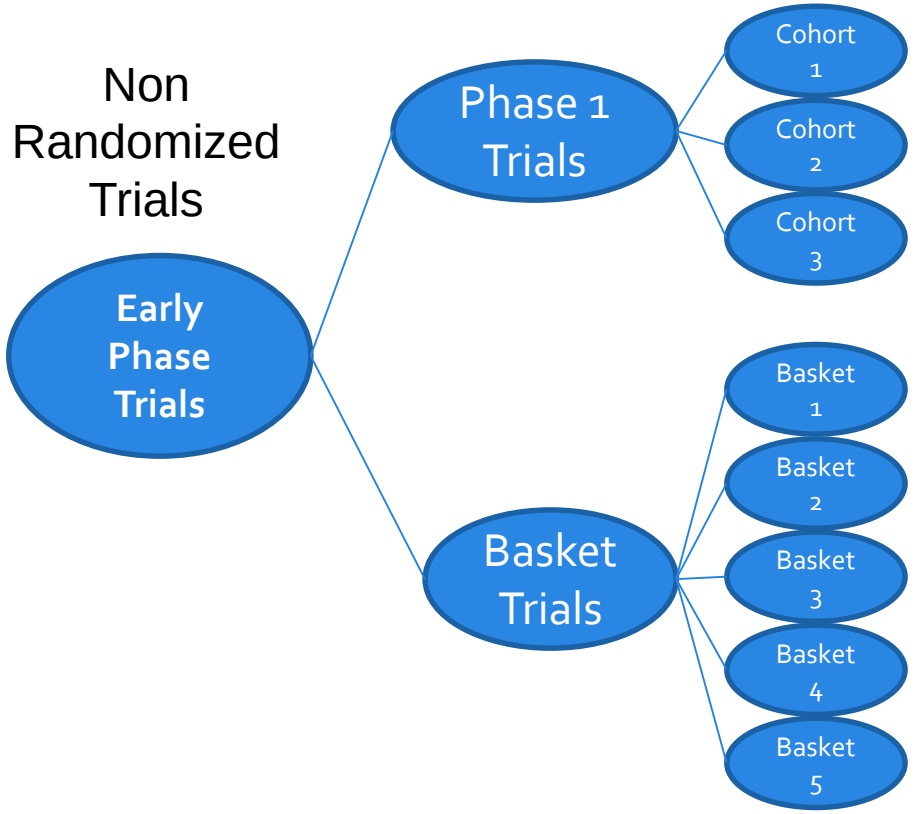


- ***Does the drug work in this particular cancer?***
  - Is the response rate with this drug greater than the response rate of standard therapy (historical estimate)?

Current landscape



Old paradigm: single disease



Multiple disease types

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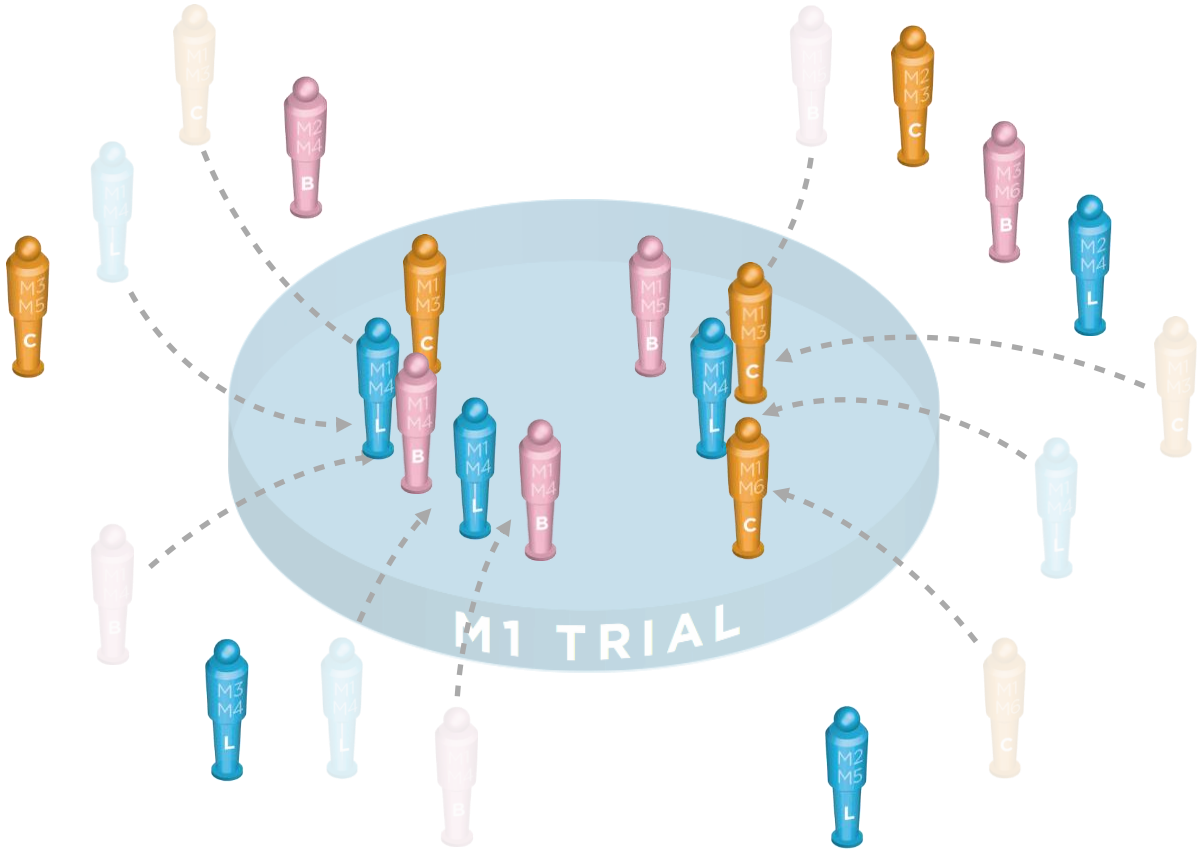
Basket Trials

- Combining multiple histologies in a single trial

- In its most basic form a basket trial is specific to a molecular target and a targeted regimen, with histologies forming the baskets
  - Single drug/target, multiple disease sites
  - Example: Vemurafenib Hyman et al. NEJM 2015

- Implications for Clinical Trial Design: non randomized setting

Patient Selection: molecularly defined subgroups



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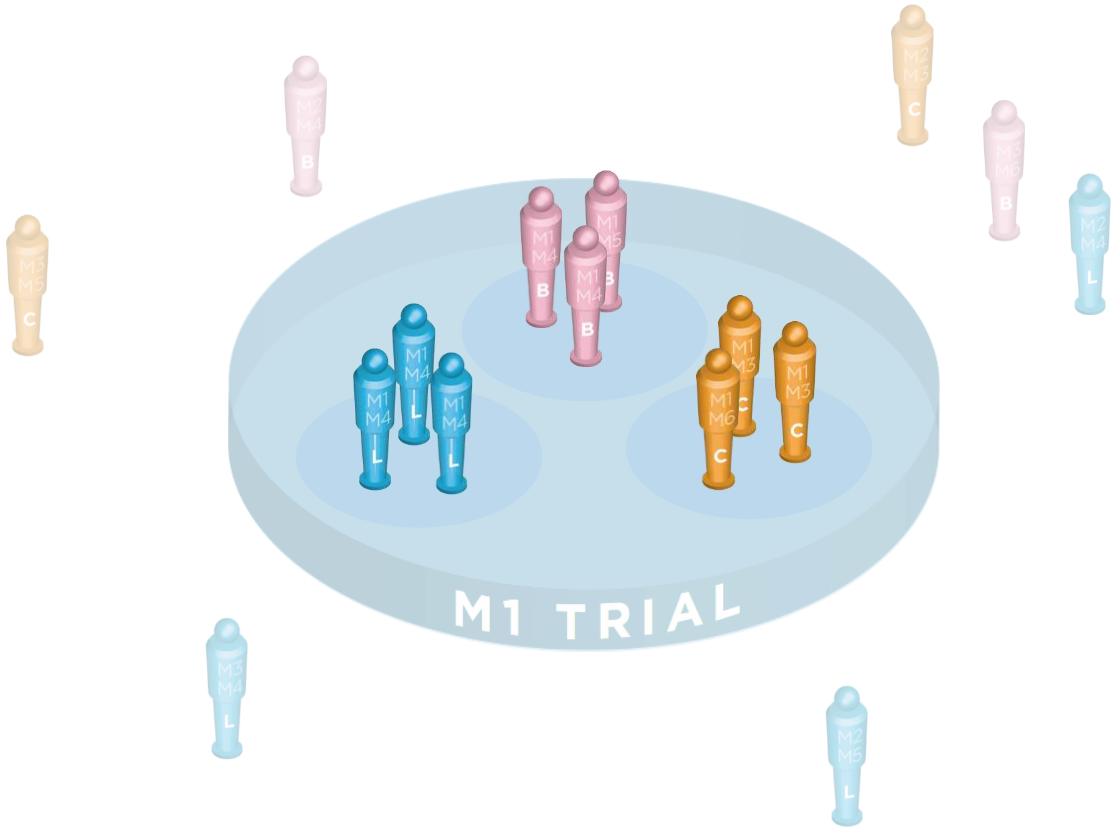
Basket trials: definition of basket



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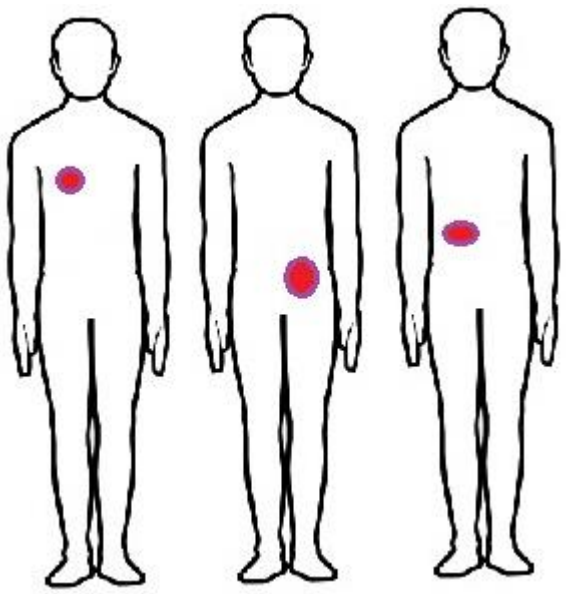
Phase II Basket Trial: current field



- Single Target (a particular genomic alteration)
- Multiple Histologies (Anatomic Sites)

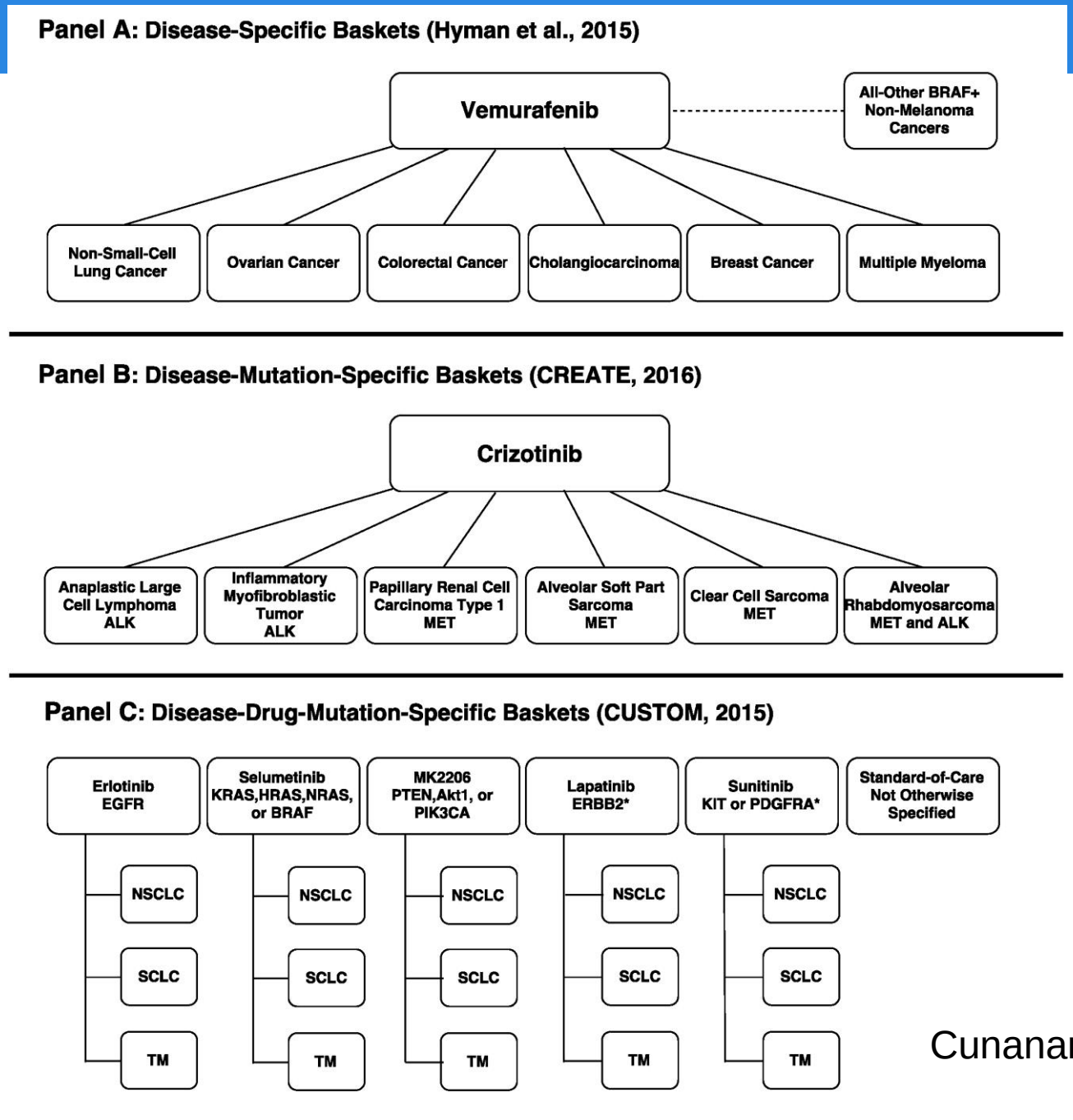
- Questions:
  - Does the treatment work at all?
  - If it works, does efficacy differ by histology?

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
  - Hypothesized mechanism of action
  - …
- → Hence the second question: Where does it work?



Cunanan et al JCO 2017

VOLUME 35 · NUMBER 3 · JANUARY 20, 2017

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.*

Basket, umbrella, platform trials

Woodcock J, and LaVange L 2017 NEJM

Eliminate the confusion and provide a more precise terminology

Table 1. Types of Master Protocols.

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Scientific and ethical design and review of innovative protocols

- Can the study answer the scientific question?
  - Safe
  - Ethical
  - Scientifically valid (addressing objectives)
  - Accurate (precision - error)
    - » Iasonos, Gonen, Bosl, JCO 2015

- How do we get to the answer **faster?**

- Minimize sample size; Trial duration

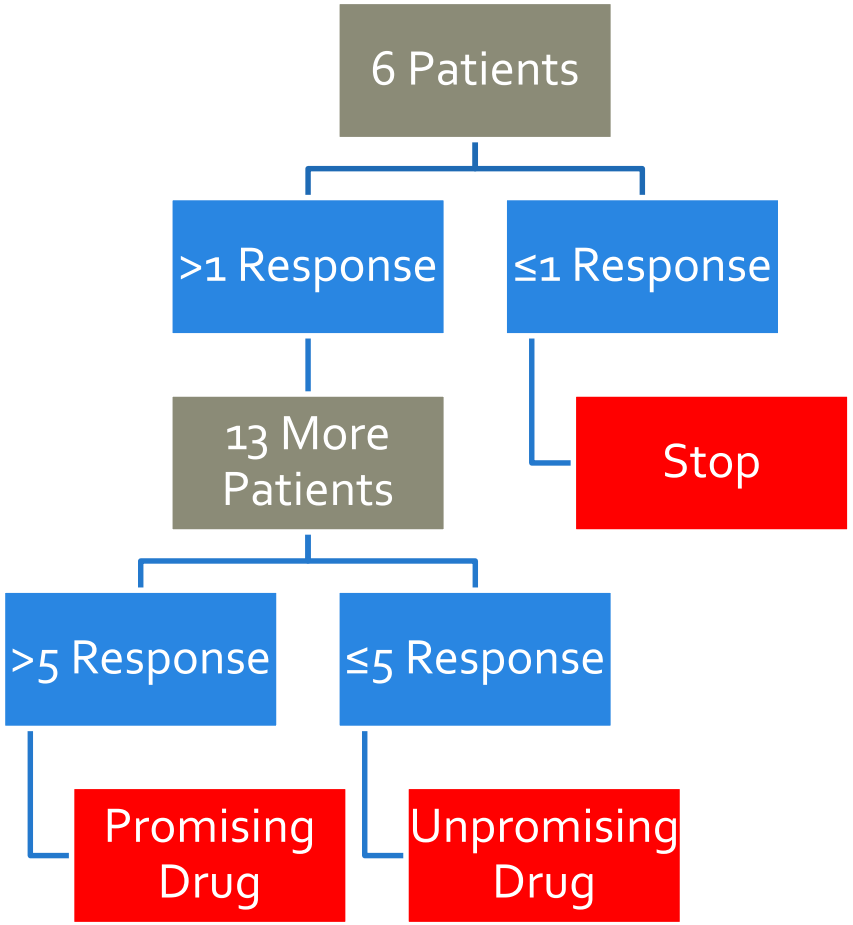
- Patient allocation/treatment: receiving inefficient treatment

- Are these designs optimal /efficient?

Protocols with multiple questions

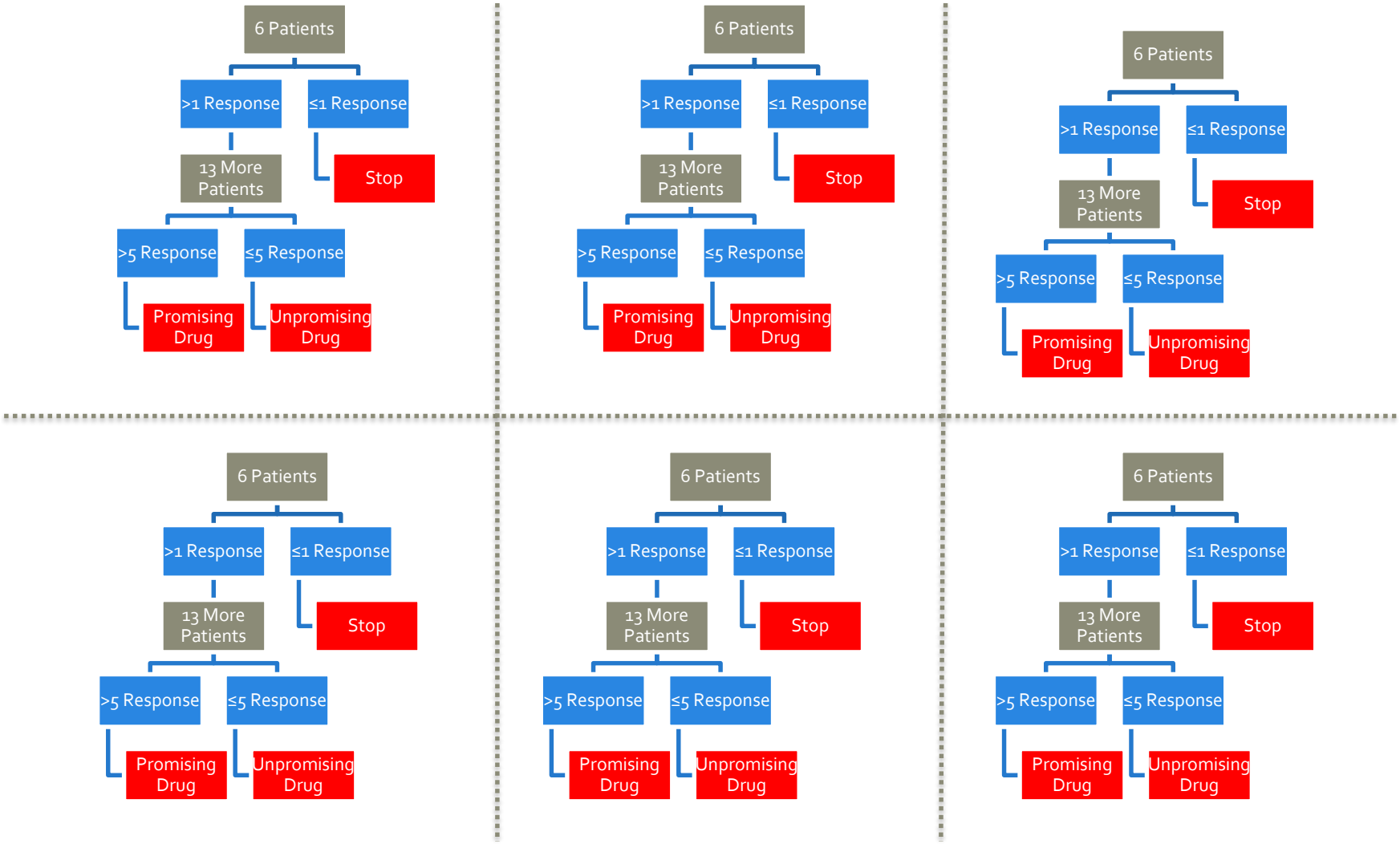
- Primary vs secondary vs exploratory
- Ideal design options must be aligned with the numerous questions being asked
- Basket trial setting:
  - Does the drug work at all?
  - Does efficacy differ by disease site?

Example Design: Two-Stage Simon Design



- **Allows for Early Stopping for Futility**
  - **RR 15% and 45%**
  - **5% type I error; 80% power**

Using the Traditional Design in Basket Trial



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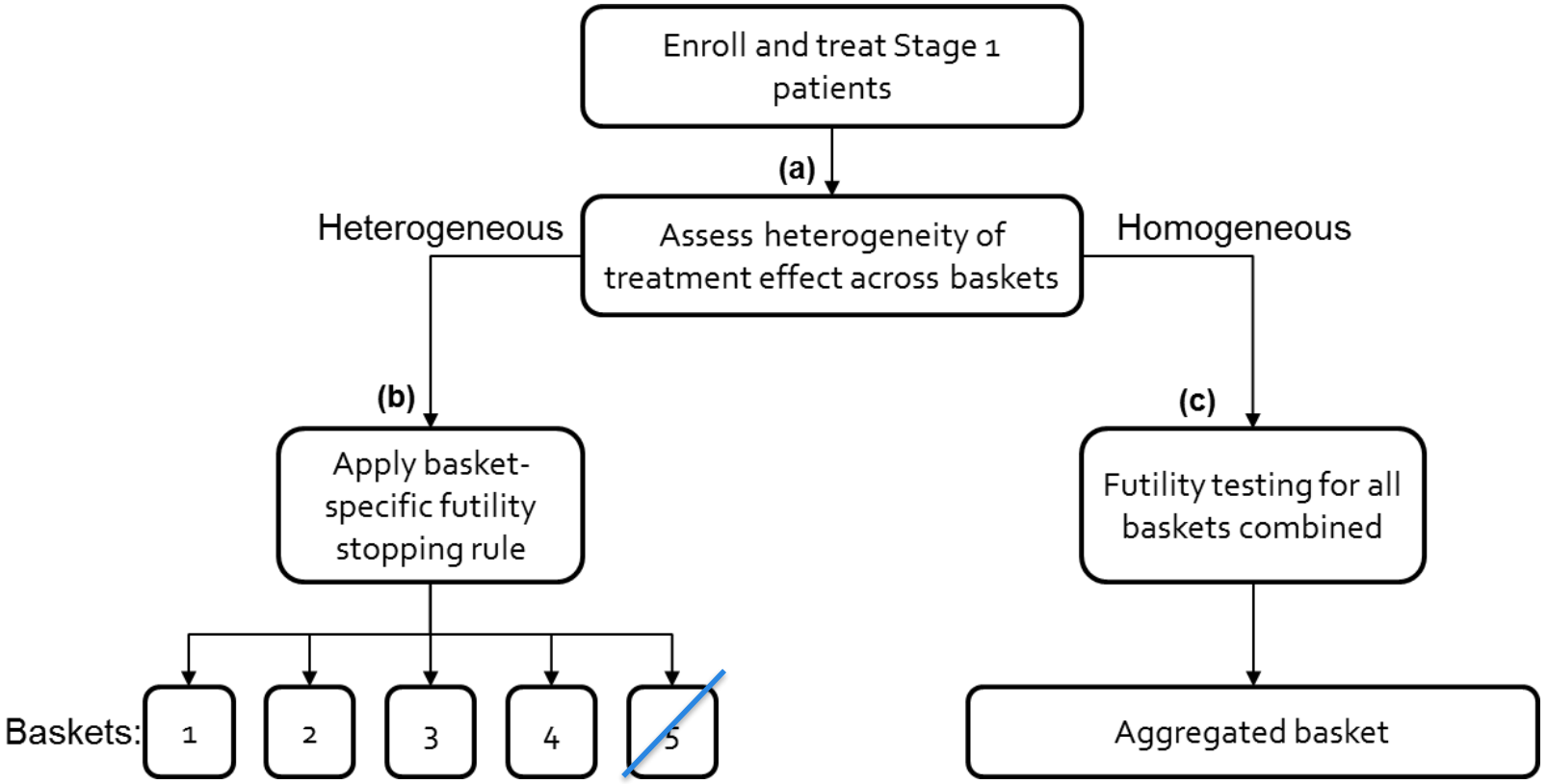
Parallel or Independent Design

Implications

- There is no information sharing between baskets
- Ignores the commonality among the baskets (same mutation)
- Does it address the first question (does the drug work overall?)

- Higher chance it will declare the drug effective in at least one basket when the drug is truly ineffective; 40% when k=10, 5%)

Aggregation Design



Cunanan, Iasonos, Shen, Gonen, Begg;
Stats Med 2017

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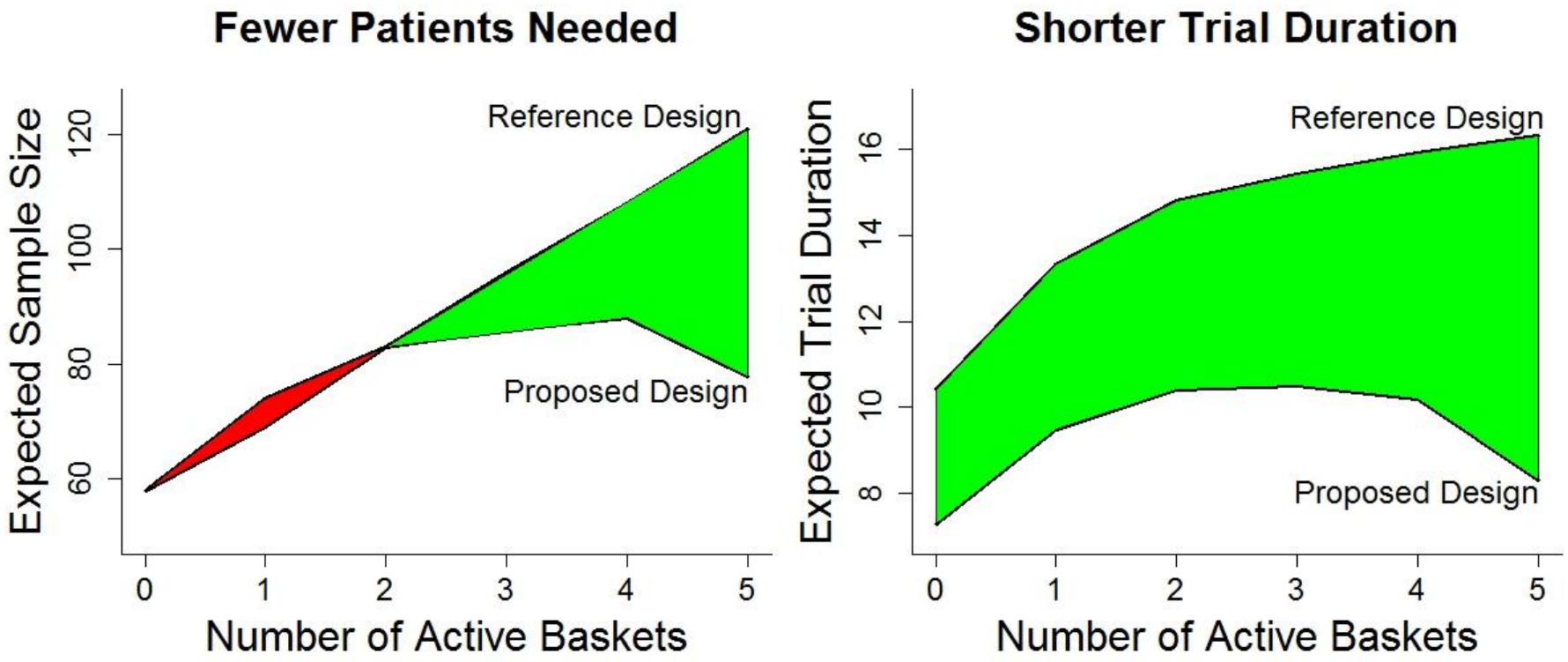
How does the aggregation design work?

- **Specifications:** Investigators choose interesting and uninteresting response rates (15% and 45% in the previous example) as well as Type I error (5%) and power (80%)
  - Similar to the parallel design
- There are **8 tuning parameters** for the information sharing design
  - 5 decision nodes
  - 3 sample size
  - → **Many possible designs** meeting specifications
- We choose these parameters in such a way that the resulting design optimizes a utility function

Cunanan et al, 2017; 2018 (available code)

Efficiencies, Cunanan et al JCO 2017



In Conclusion what are the benefits?

- It is possible to **reduce the number of patients** needed for basket trials by sharing information across baskets
- **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**

Discussion: are the error rates important?

commentary

Specifying the True- and False-Positive Rates in Basket Trials

Kristen M. Cunanan
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JCO Precision Oncology 2017

- Is 40% False positive rate acceptable?
  - The extent to which information is borrowed is determined by the variability among response rates across baskets

- Which error rate is more important to minimize?
  - Taking an inactive drug forward or
  - Stopping an active drug ?

Metrics for Evaluating Designs

- **Familywise Error Rate (FWER)**: If the drug is inactive in all baskets (null case), what is the probability of incorrectly declaring activity in one or more of the inactive basket?
  - **0 Active** The drug is active in none of the *K* baskets

- **Marginal power**: probability of correctly identifying an *individual* basket as active, when a true treatment effect exists.

- **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

- Operating Characteristics

World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research

Involving Human Subjects (JAMA 2013)

22. The design and **performance** of each research study involving human subjects must be **clearly described and justified** in a research protocol.

Table: [1]Marginal power (*FWER); [2]expected trial size, N; [3]expected trial duration, T (months)

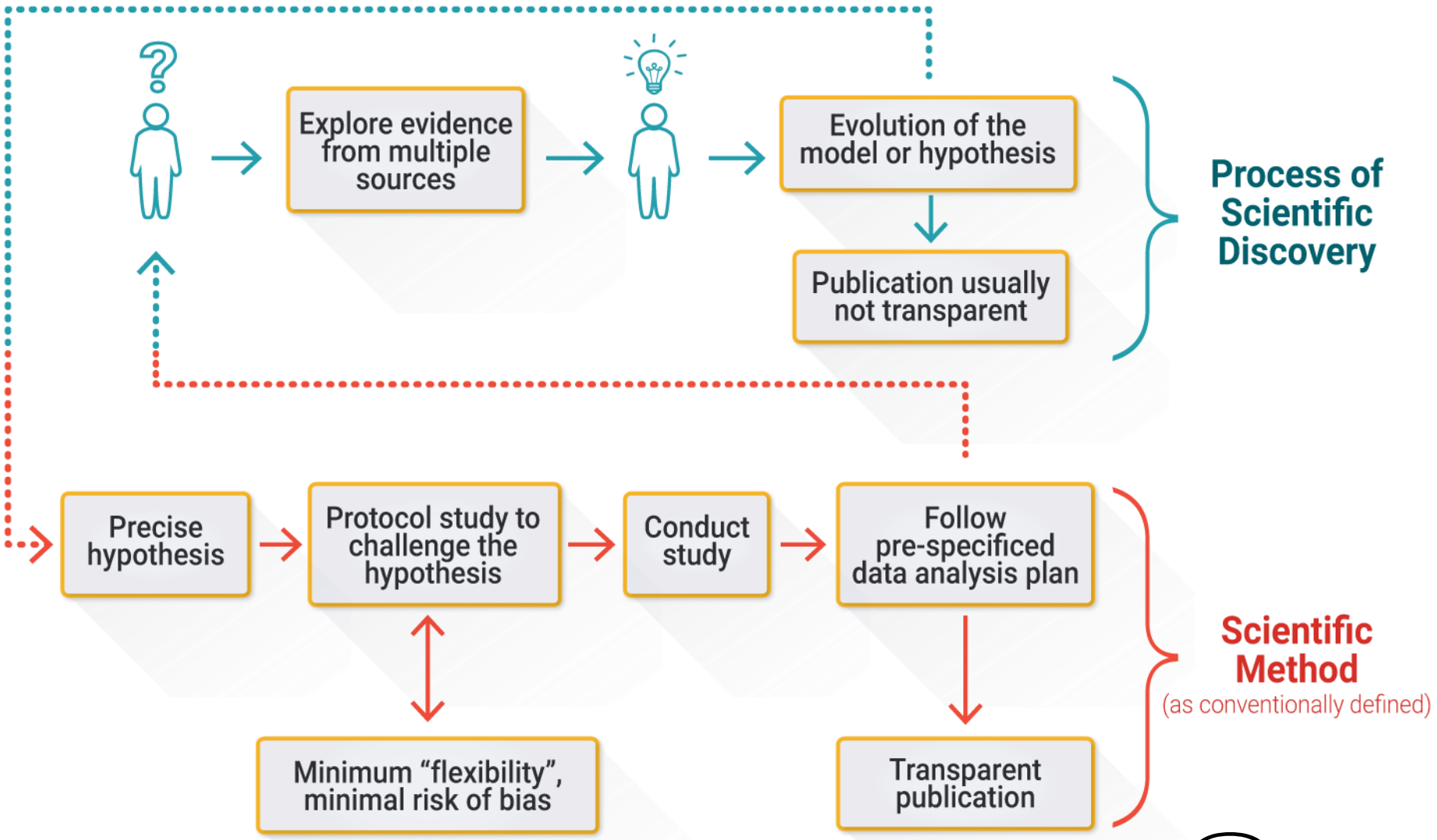
Scenario (Truth)	Proposed Power[1]	Proposed N[2]	Proposed T[3]	Reference Power[1]	Reference N[2]	Reference T[3]	Sample Size Reduction
0 Active	*5.2%	56	7	*5.3%	58	10	-
1 Active	70%	75	10	79%	69	13	-
2 Active	81%	84	11	81%	83	15	-
3 Active	85%	89	11	80%	96	15	7%
4 Active	88%	86	10	82%	108	16	20%
5 Active	89%	76	8	82%	121	16	37%

Not all drugs are a success story

- What can we learn from a negative trial to inform future trials /hypotheses?
  - Phase I and Phase II, Cannistra JCO 2009, 2010

- Do we have enough and reliable data (rigorous) to answer the questions:
  - Why did the drug/combination fail?
    - Wrong schedule /dose?
    - Did we choose the wrong patient population?
    - Is there efficacy in some subpopulation?
    - Was our historical control or estimate off?

The conventional scientific method



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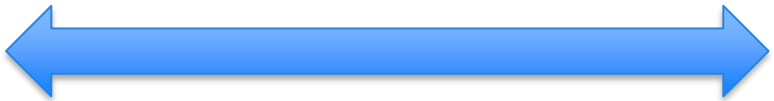
Tradeoff between drug access and rigor

Patients – drug access

Participate in early phase trials



Rigor - Scientific integrity

If the drug works
If the drug does not work

- Scientifically valid regardless of the level of activity
  Not all drugs are a success story

- There is no uniformly efficient strategy
  - Performance depends on how many tumor types are sensitive to the drug
  - False positive and false negative rates need to be studied / reported

Amendments: scientific review - rigor

- Eligibility
- Scope of the study
- Design
- Adding/dropping arms (cohorts)
- Expanding cohorts (increase or modify sample size)
- Safety of efficacy or futility stopping rules
- Multiple looks (descriptive/hypotheses generating/ no testing)

Questions

- iasonosa@mskcc.org

- Software
  - https://www.mskcc.org/departments/epidemiology-biostatistics/biostatistics/basket-trials

1: Cunanan KM, Iasonos A, Shen R, Gönen M. Variance prior specification for a basket trial design using Bayesian hierarchical modeling. Clin Trials. 2019 Apr;16(2):142-153. doi: 10.1177/1740774518812779. Epub 2018 Dec 7. PubMed PMID: 30526008.

2: Cunanan KM, Iasonos A, Shen R, Begg CB, Gönen M. An efficient basket trial design. Stat Med. 2017 May 10;36(10):1568-1579. doi: 10.1002/sim.7227. Epub 2017 Jan 18. PubMed PMID: 28098411; PubMed Central PMCID: PMC5380524.

3: Cunanan KM, Gonen M, Shen R, Hyman DM, Riely GJ, Begg CB, Iasonos A. Basket Trials in Oncology: A Trade-Off Between Complexity and Efficiency. J Clin Oncol. 2017 Jan 20;35(3):271-273. doi: 10.1200/JCO.2016.69.9751. Epub 2016 Nov 28. Review. PubMed PMID: 27893325; PubMed Central PMCID: PMC5559900.

4. Kristen M. Cunanan, Alexia Iasonos, Ronglai Shen, David M. Hyman, Gregory J. Riely, Mithat Gönen, and Colin B. Begg Specifying the True- and False-Positive Rates in Basket Trials. JCO Precision Oncology 2017 :1, 1-5

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