Statistical Designs for Combinations

Donald A. Berry
dberry@mdanderson.org

Financial Disclosure

Co-owner of Berry Consultants, LLC.

Designs adaptive clinical trials for

- Medical device companies
- Pharmaceutical companies
- NIH cooperative groups

Janet Woodcock, Dir CDER FDA at 2006 SPORE Meetings

“Improved utilization of adaptive and Bayesian methods” could help resolve low success rate of and expense of phase 3 clinical trials

Outline

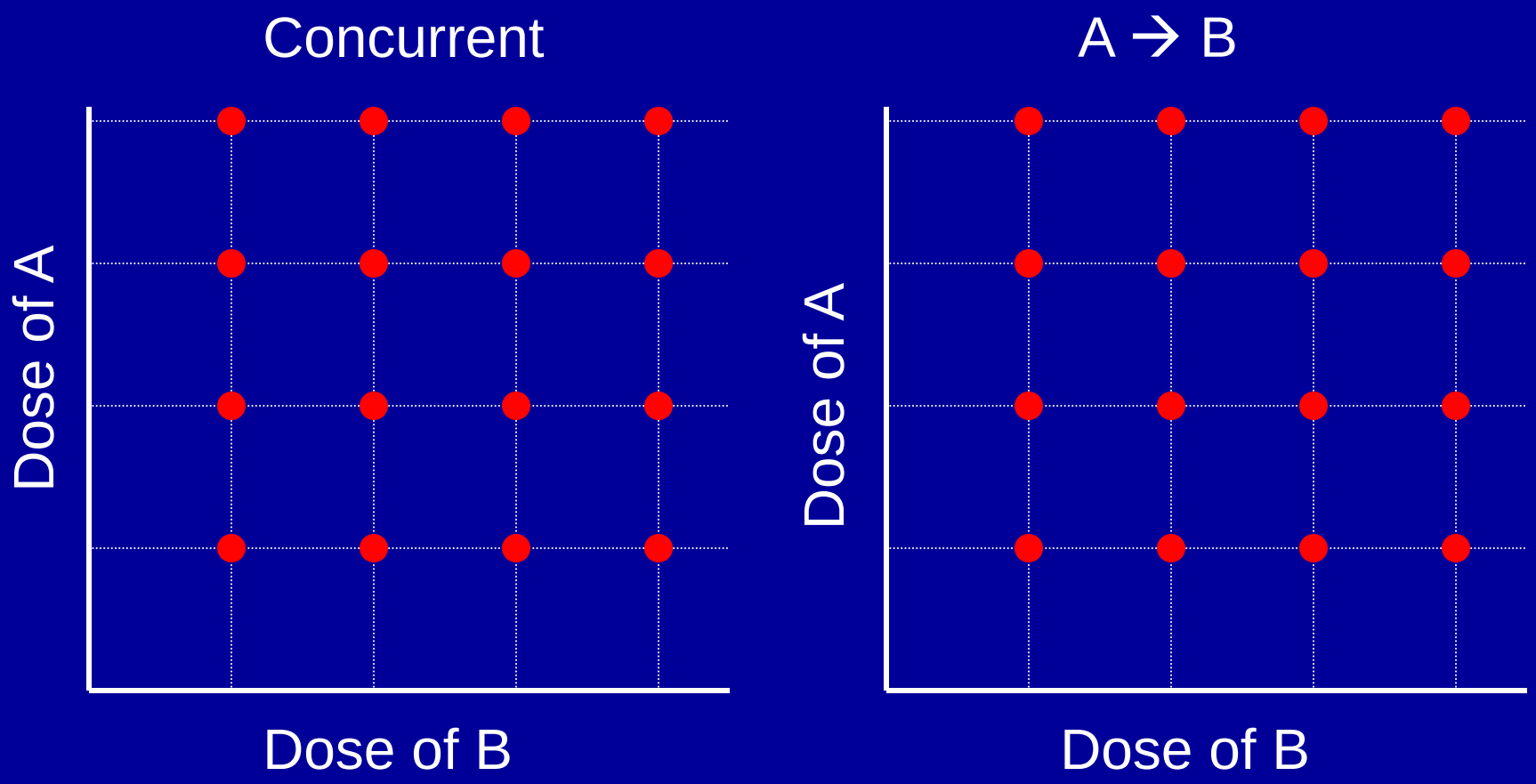
- Phase I/II combination trial
- Phase II/III combination trial
- I-SPY-like trial

A PHASE I/II TRIAL*

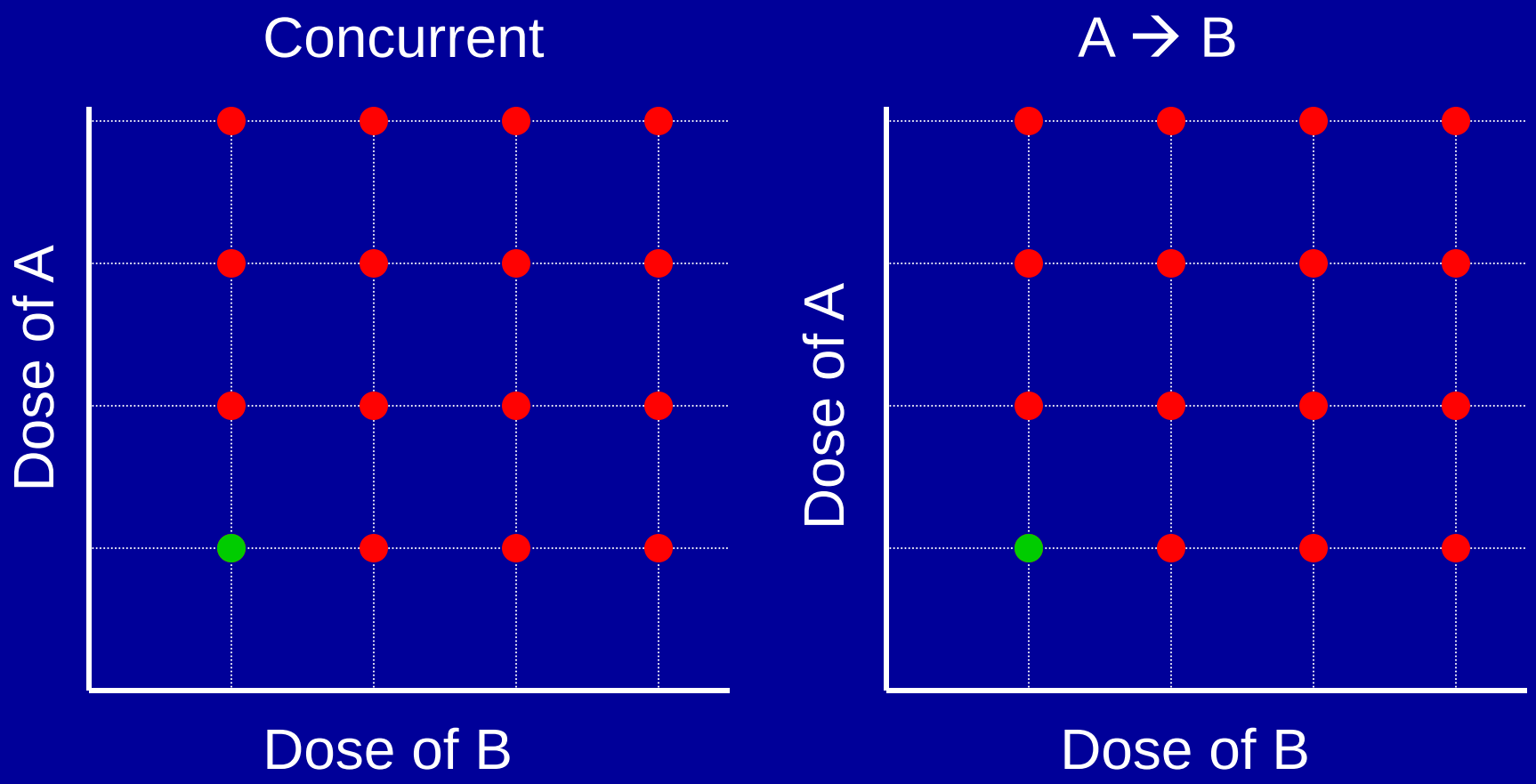
- Two drugs, A & B
  - Doses?
  - Concurrent or sequential?
  - Adaptively randomized factorial
  - Consider toxicity & efficacy

*Huang et al. 2007 Biometrics

Dose/schedule possibilities



Admissible doses



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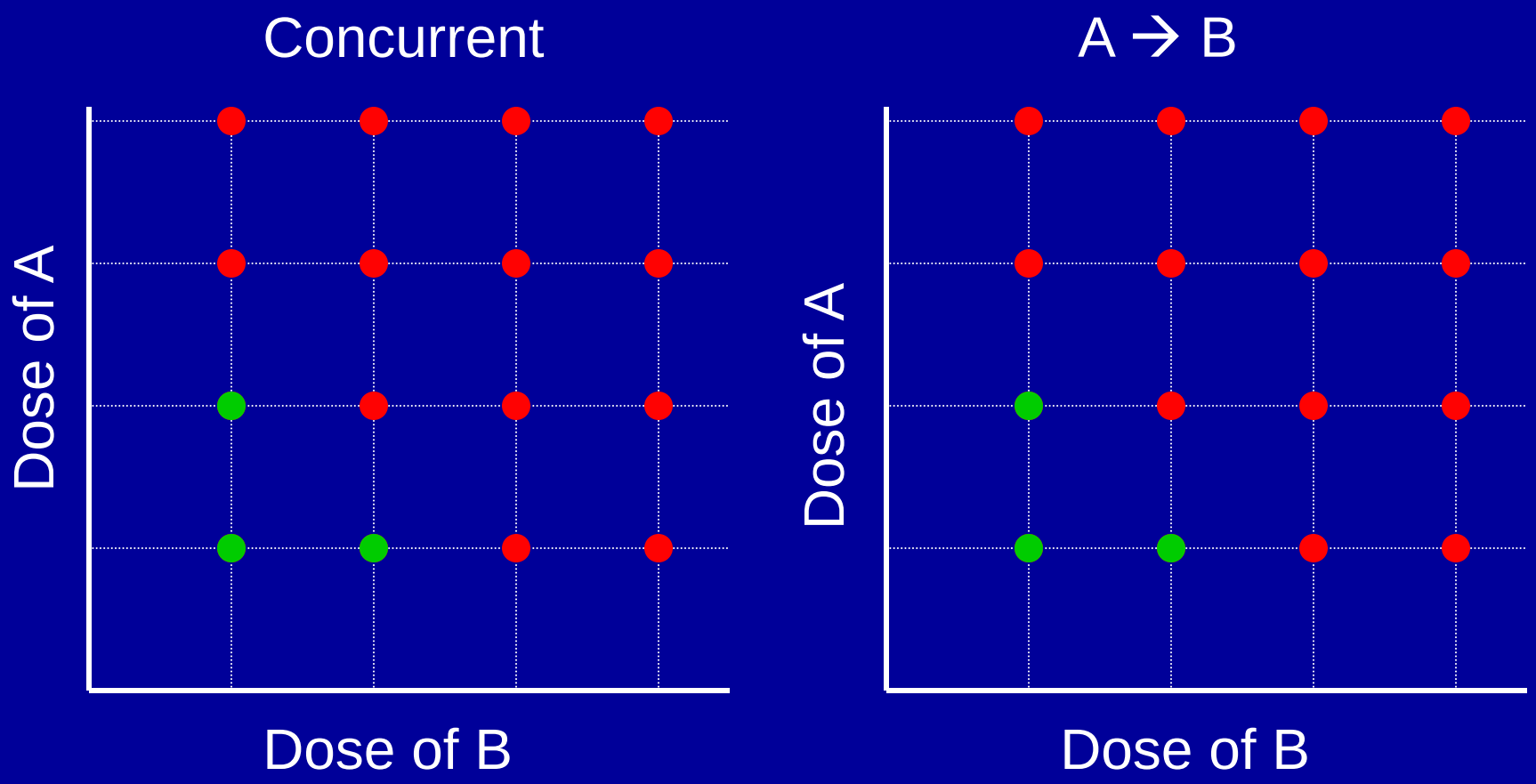

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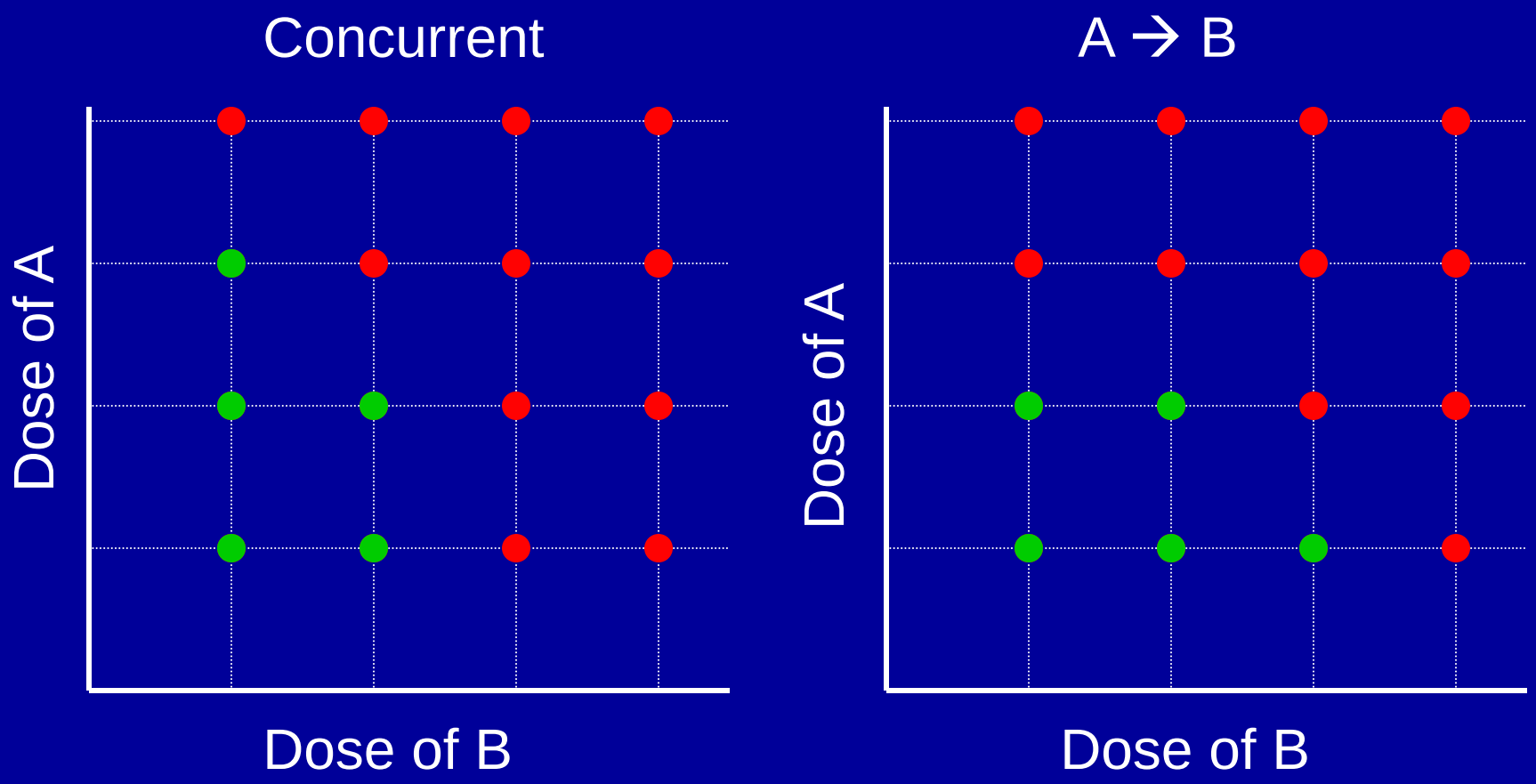

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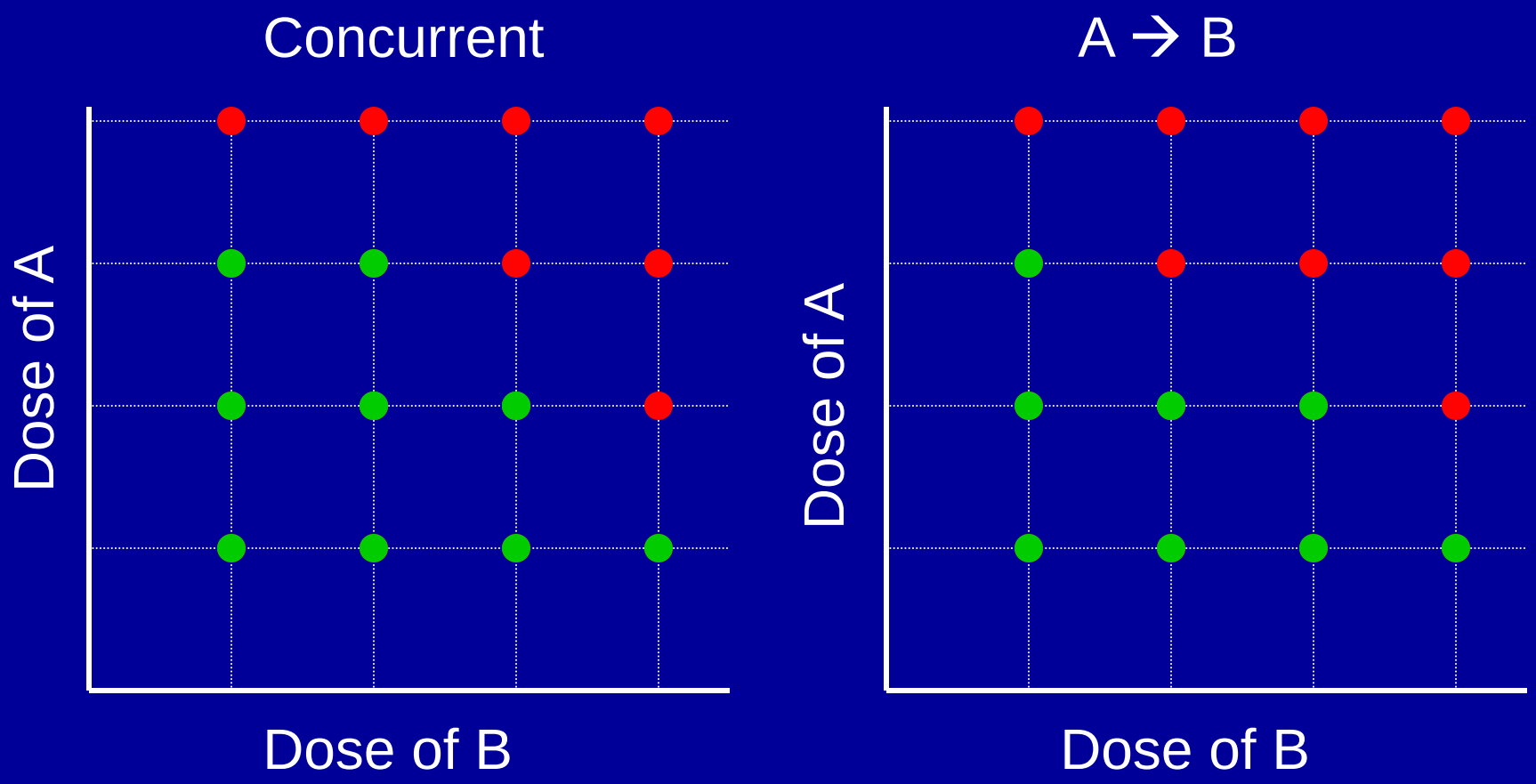

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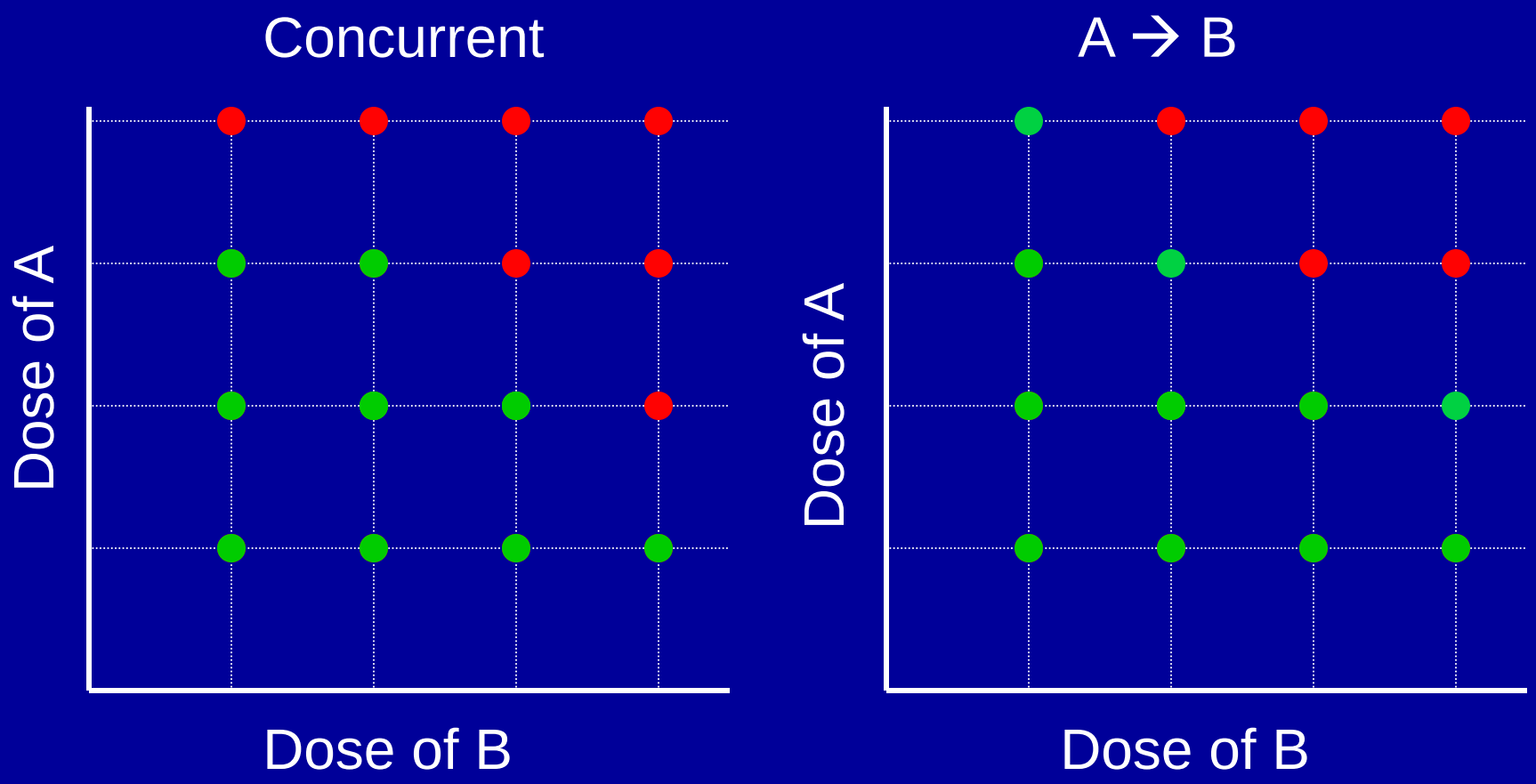

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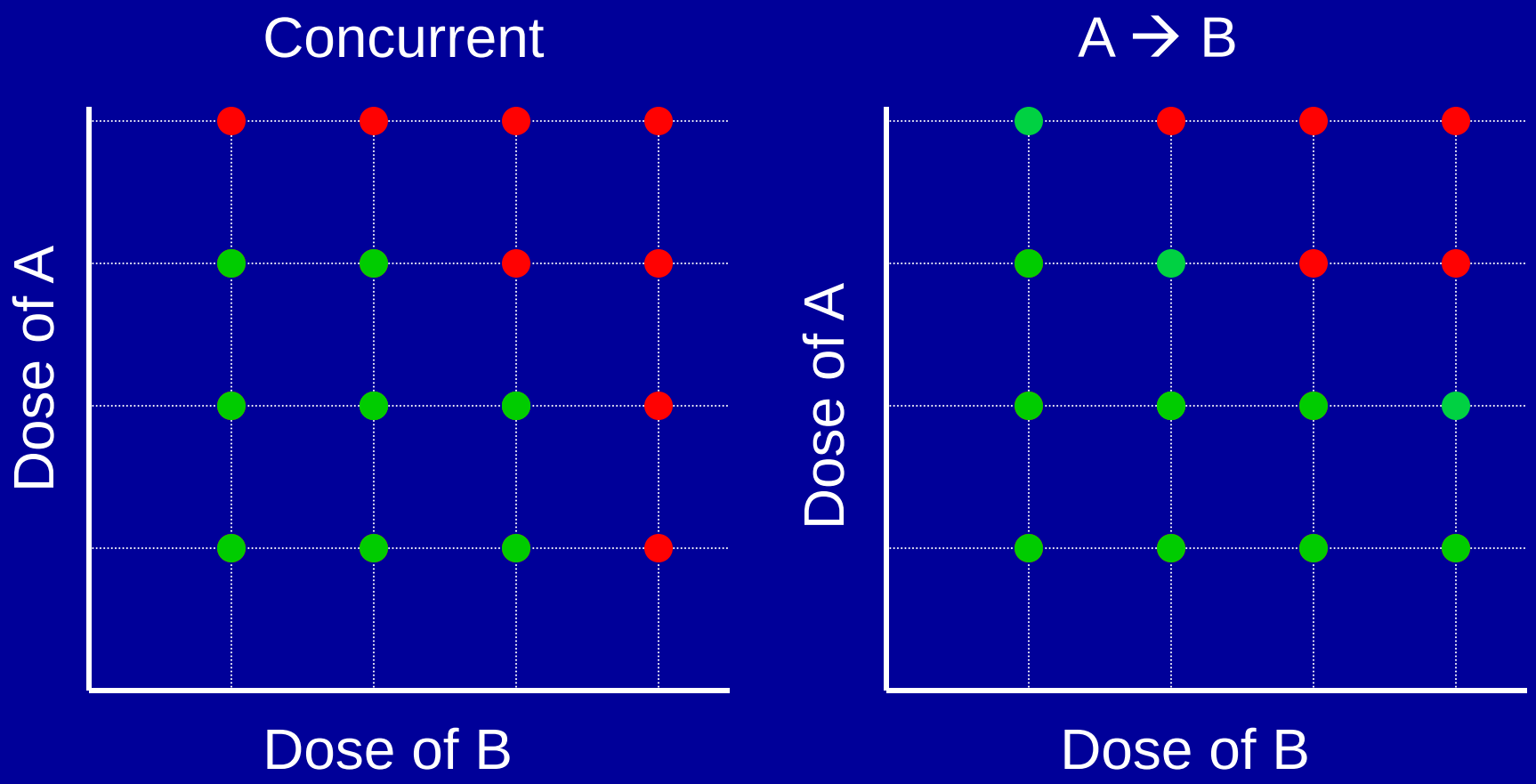
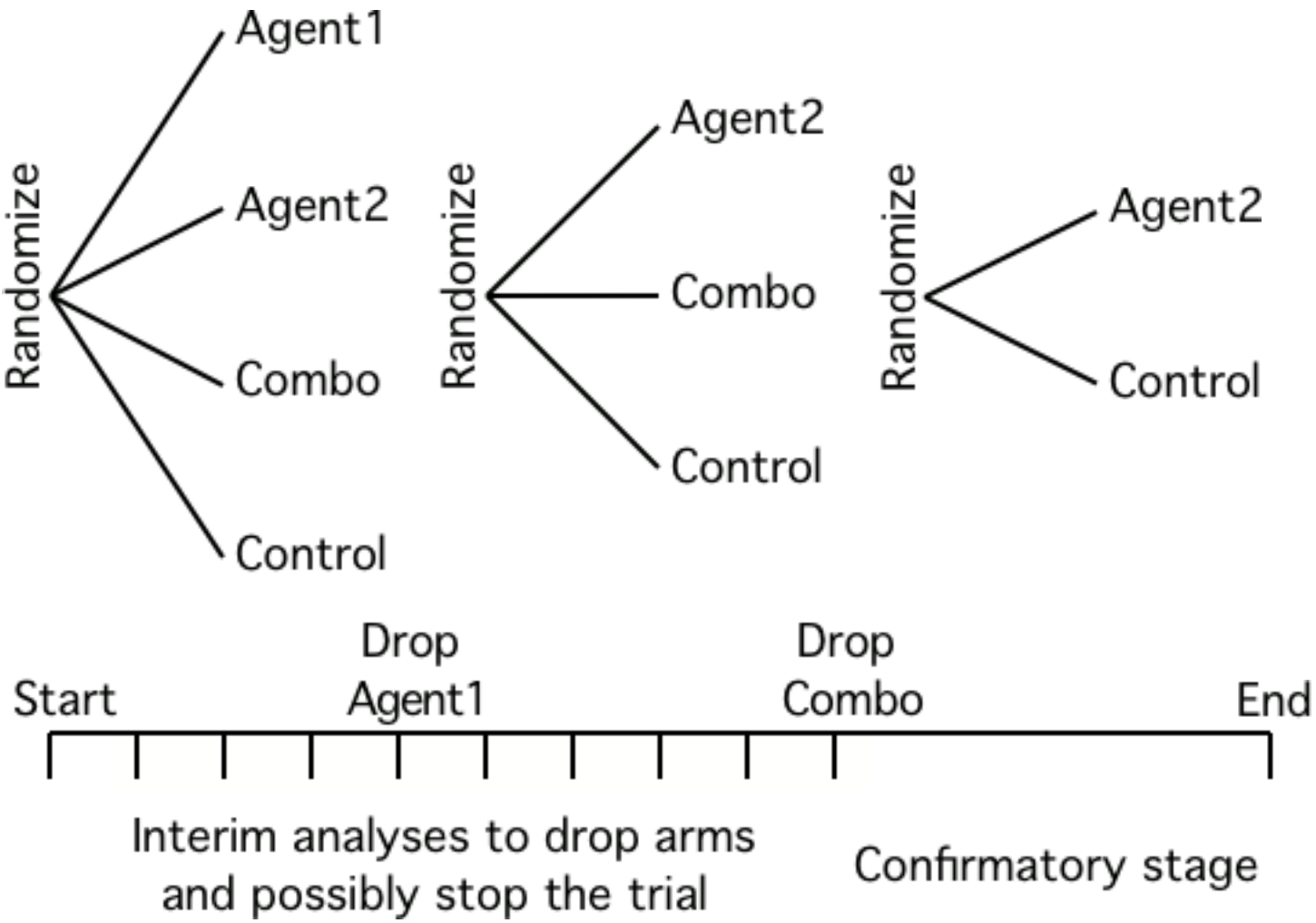


At any given time

- Expand or contract admissible doses depending on toxicity
- Randomize to admissible doses, adapting to efficacy outcomes
- (So might expand dose-range but still focus on lower doses)

Better Phase II trial designs are needed to more accurately assess which patients benefit from a particular therapy, and thus guide the **decisions about whether to move into Phase III** trials.

Improved designs for Phase III trials … could lead to faster more accurate conclusions about new therapeutics and in the process reduce costs and conserve resources.



Ref: IOM Report on cooperative groups

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

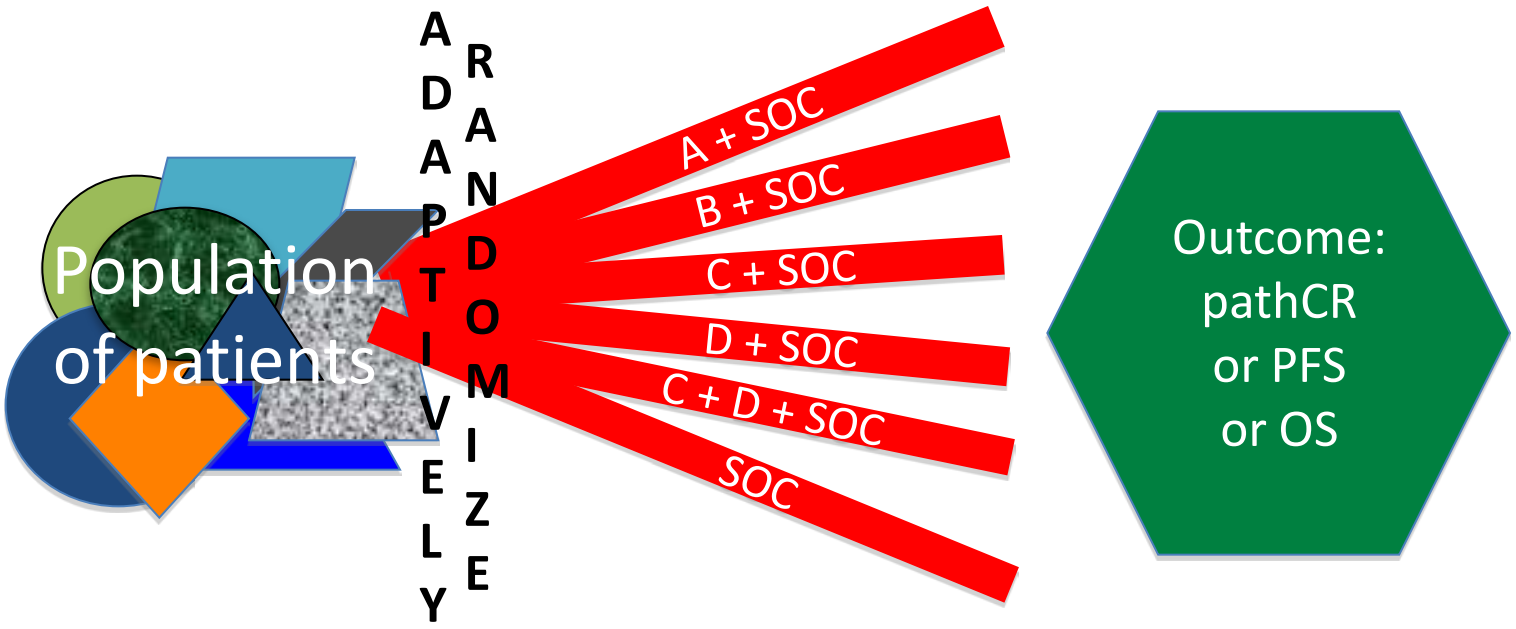
Development of Novel Combination Therapies

Janet Woodcock, M.D., Joseph P. Griffin, J.D., and Rachel E. Behrman, M.D., M.P.H.

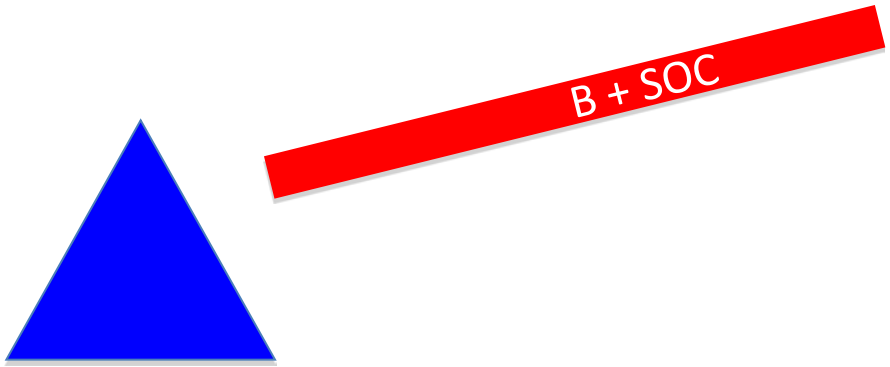
For example, in 2010, the Biomarkers Consortium–a public-private partnership that includes the NIH, the FDA, patient groups, and pharmaceutical and biotech–initiated a groundbreaking trial in breast cancer to predict drug responsiveness based on the presence or absence of genetic and biological markers, … I-SPY 2 (ClinicalTrials.gov NCT01042379).

This article (10.1056/NEJMp1101548) was published on February 16, 2011, at NEJM.org.

I-SPY-like TRIAL

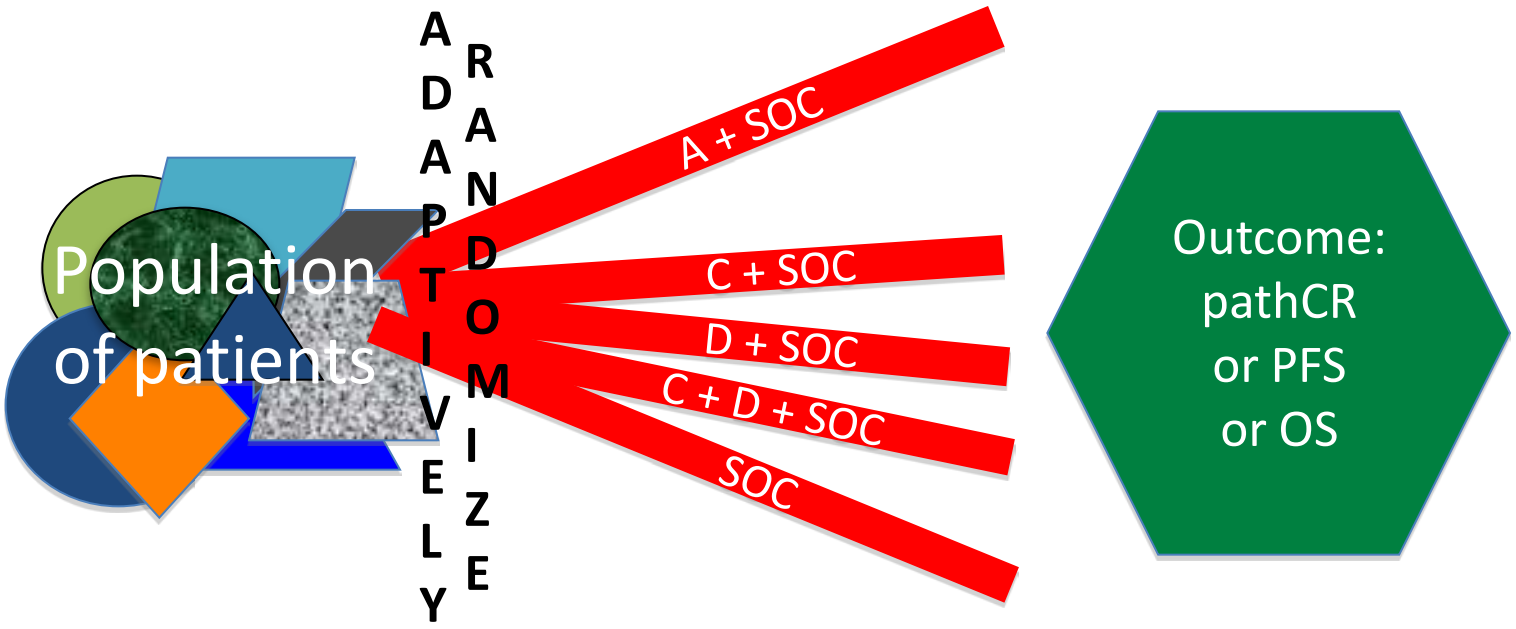


I-SPY-like TRIAL

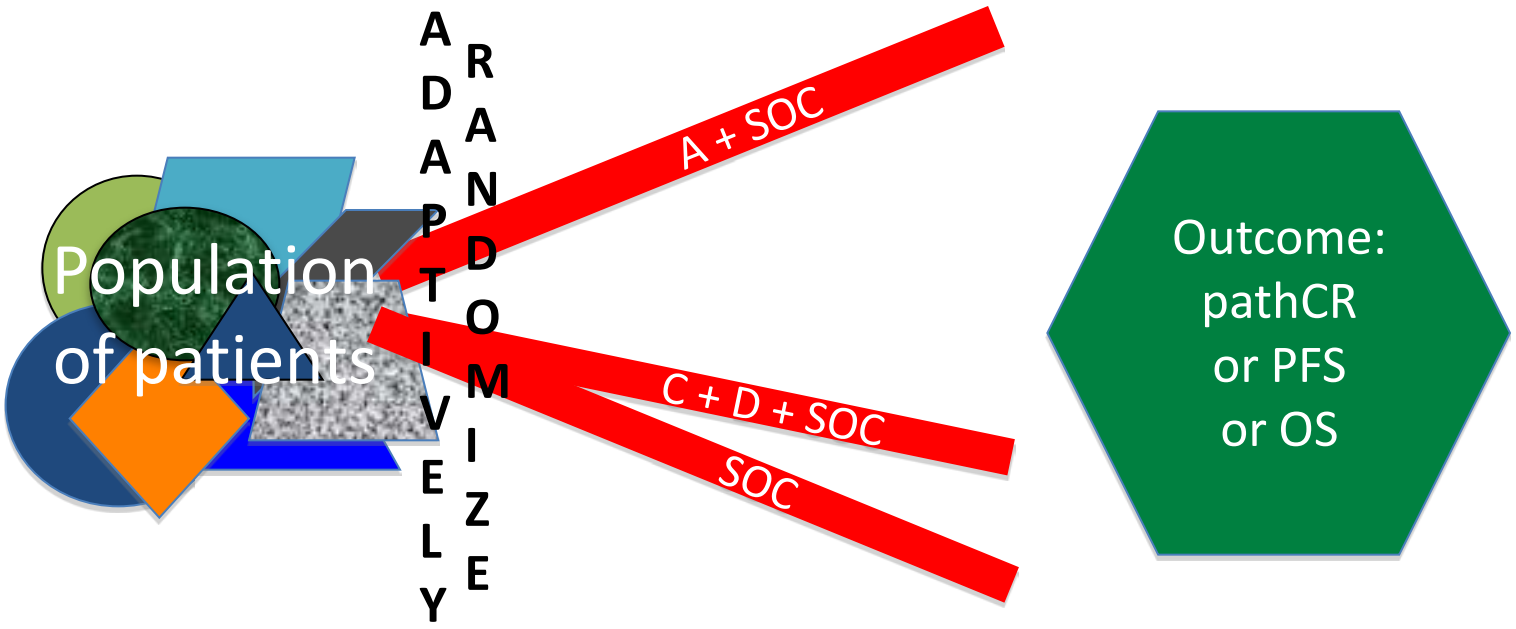


Arm B graduates
to small focused
Phase 3 trial—perhaps
seamlessly within same trial!

I-SPY-like TRIAL

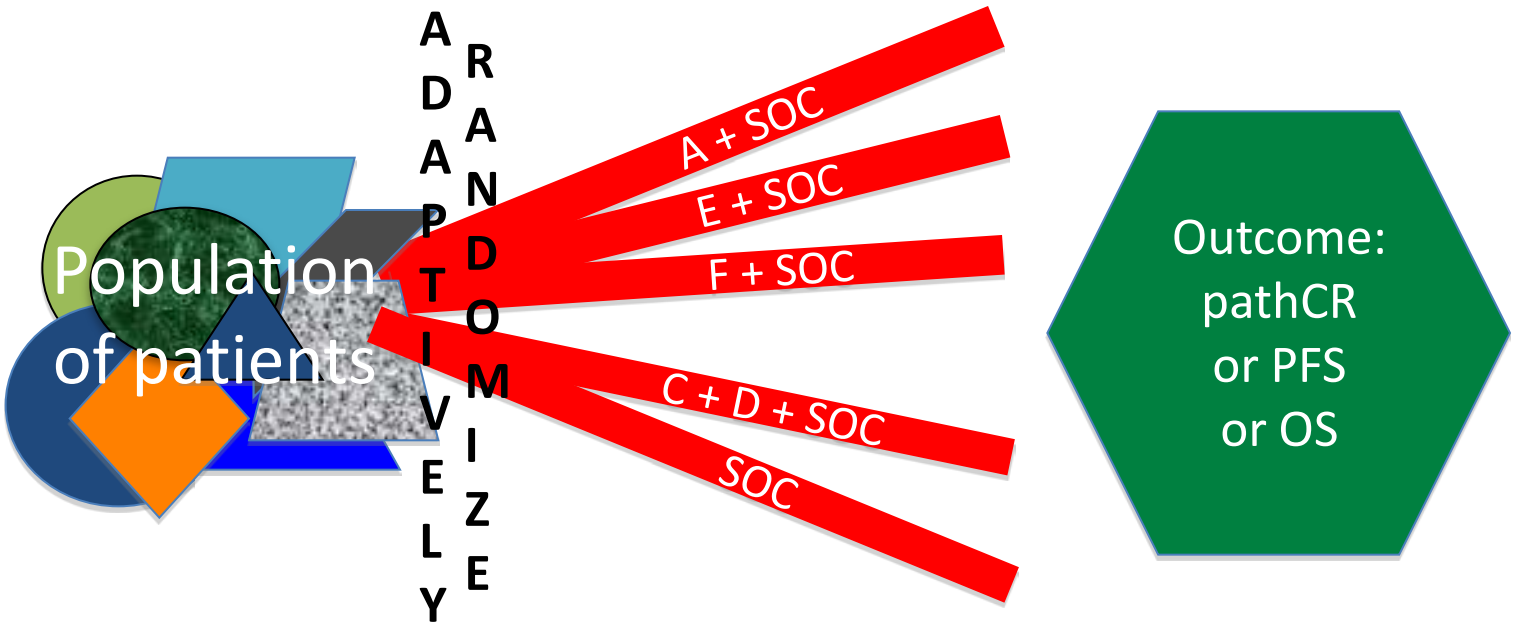


I-SPY-like TRIAL



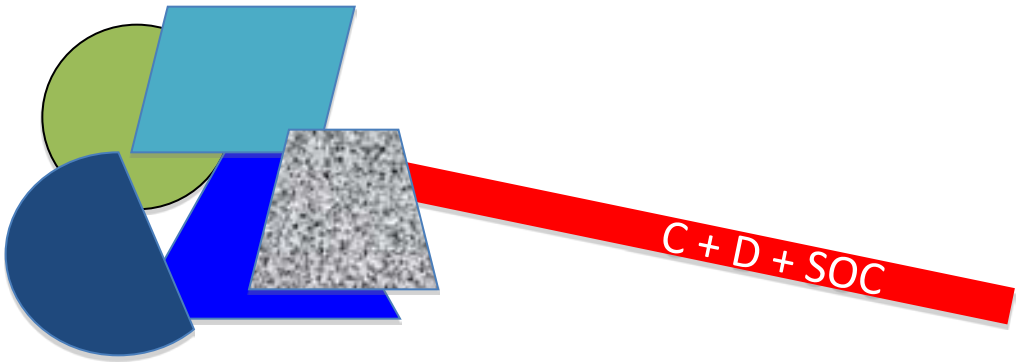
Arms C & D drop because C+D > C and C+D > D

I-SPY-like TRIAL

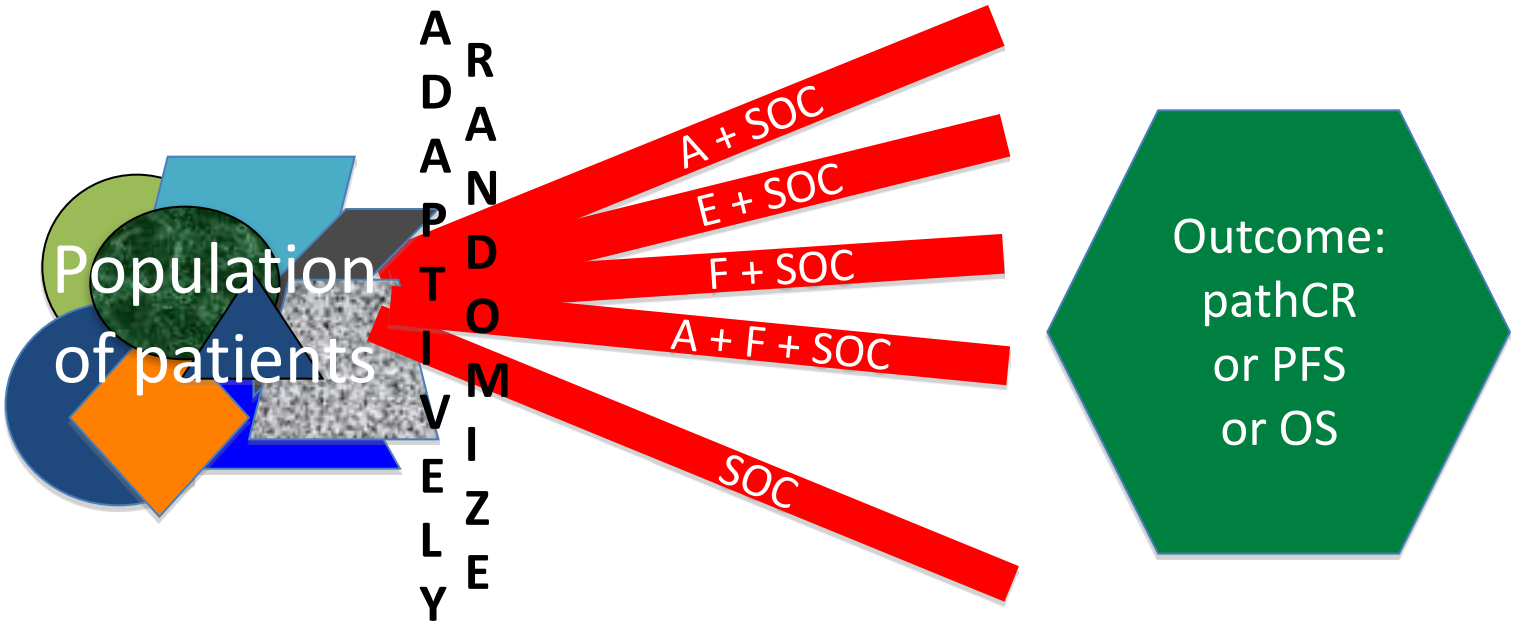


Arms E & F added

I-SPY-like TRIAL



Arm C + D
graduates to small
focused Phase 3 trial



Arm A + F is added

Important points:

- Adaptive randomization within biomarker subsets
- Biomarker x drug interactions include a priori information
- Experimental drugs from different companies: I-SPY2-like
- NCI cooperative groups and CER

Oh, and in every case …

Longitudinal modeling of endpoints!

E.g., change in tumor

- → **change in biomarkers**
- → **PFS**
- → **OS**