
# Clinical Trial Designs for Incorporating Multiple Biomarkers in Combination Studies with Targeted Agents

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MD Anderson Cancer Center
Making Cancer History®

# 3 Primary Goals for Clinical Trials

- Test safety and efficacy of agents
- Identify prognostic and predictive markers
- Provide better treatments to patients enrolled in the trials

# How Do We Fare for Cancer Drugs?

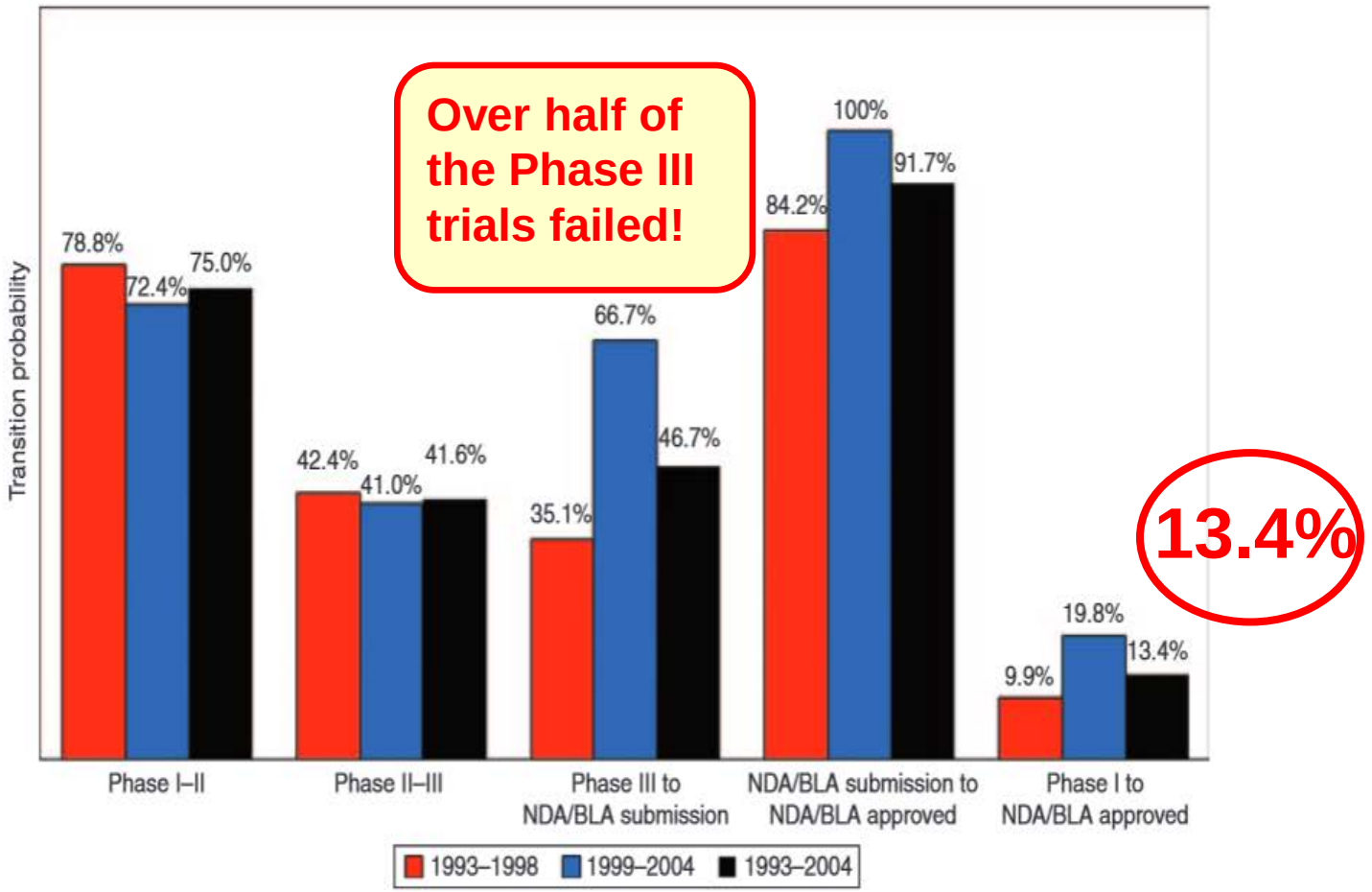
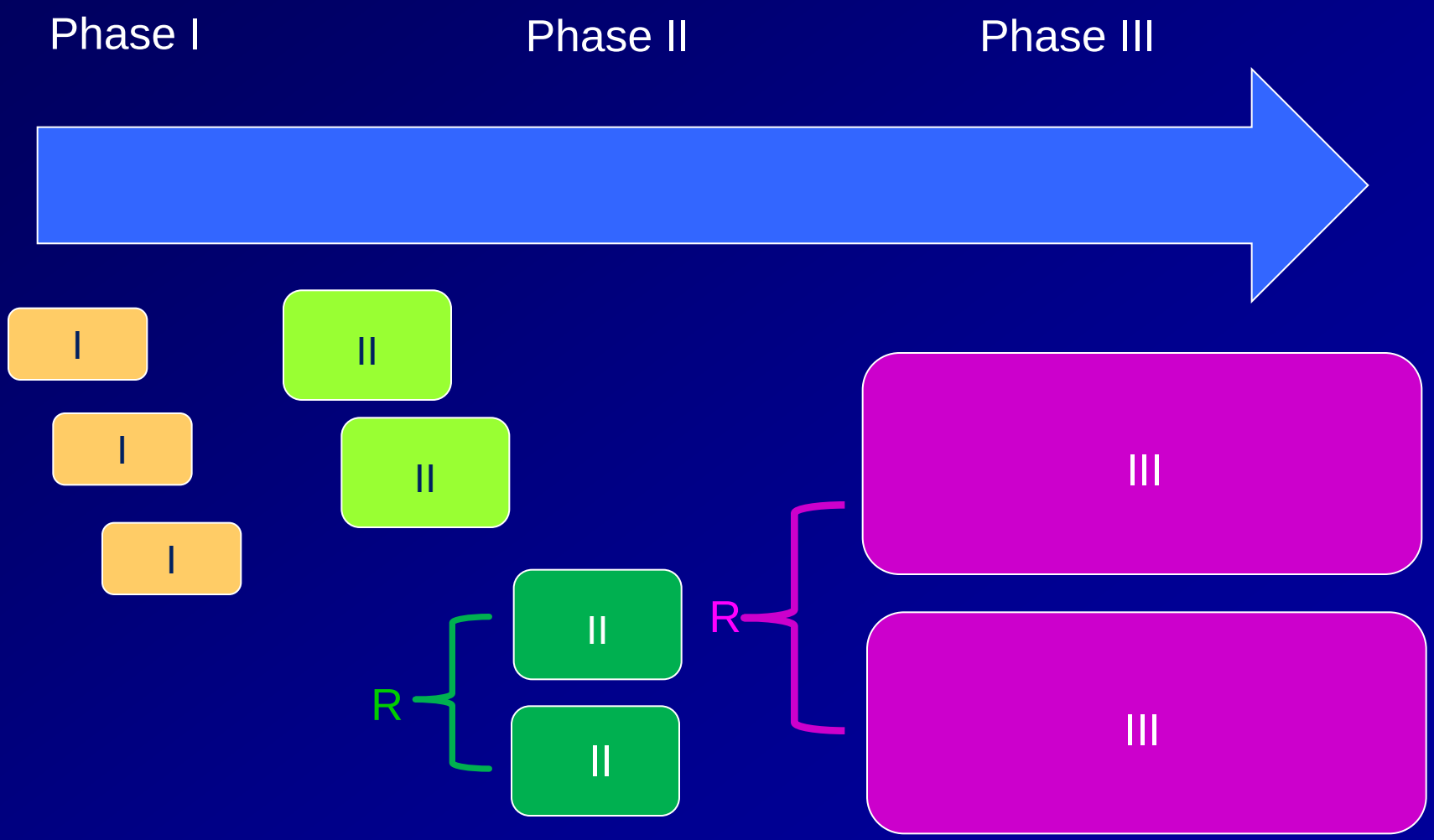


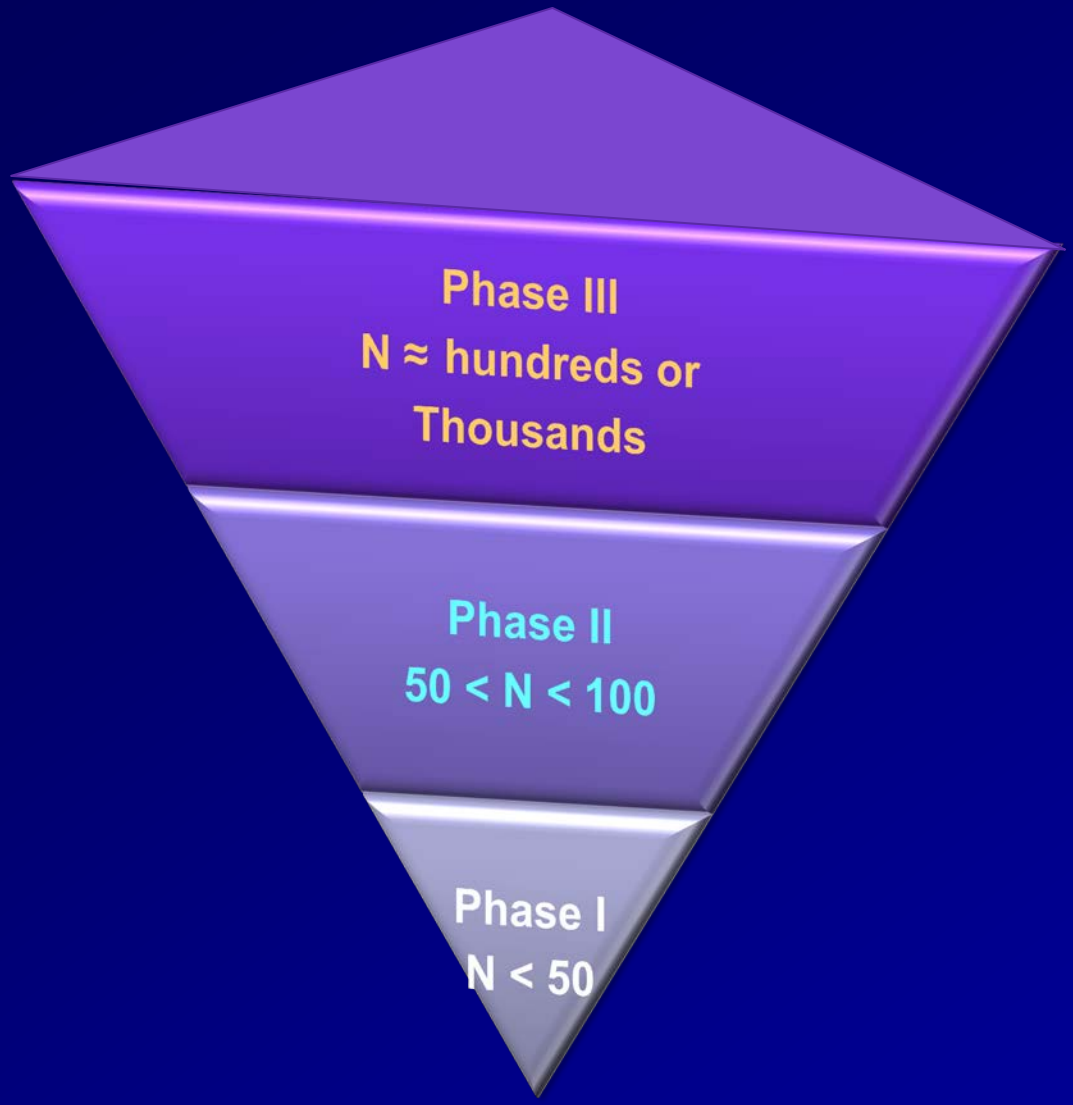

**Figure 1** Phase transition probabilities for cancer compounds by period of first clinical testing. NDA/BLA, New Drug Application/Biologic License Application.

DiMasi, Clinical pharmacology & Therapeutics, 2013

# Traditional Drug Development



# Traditional Drug Development

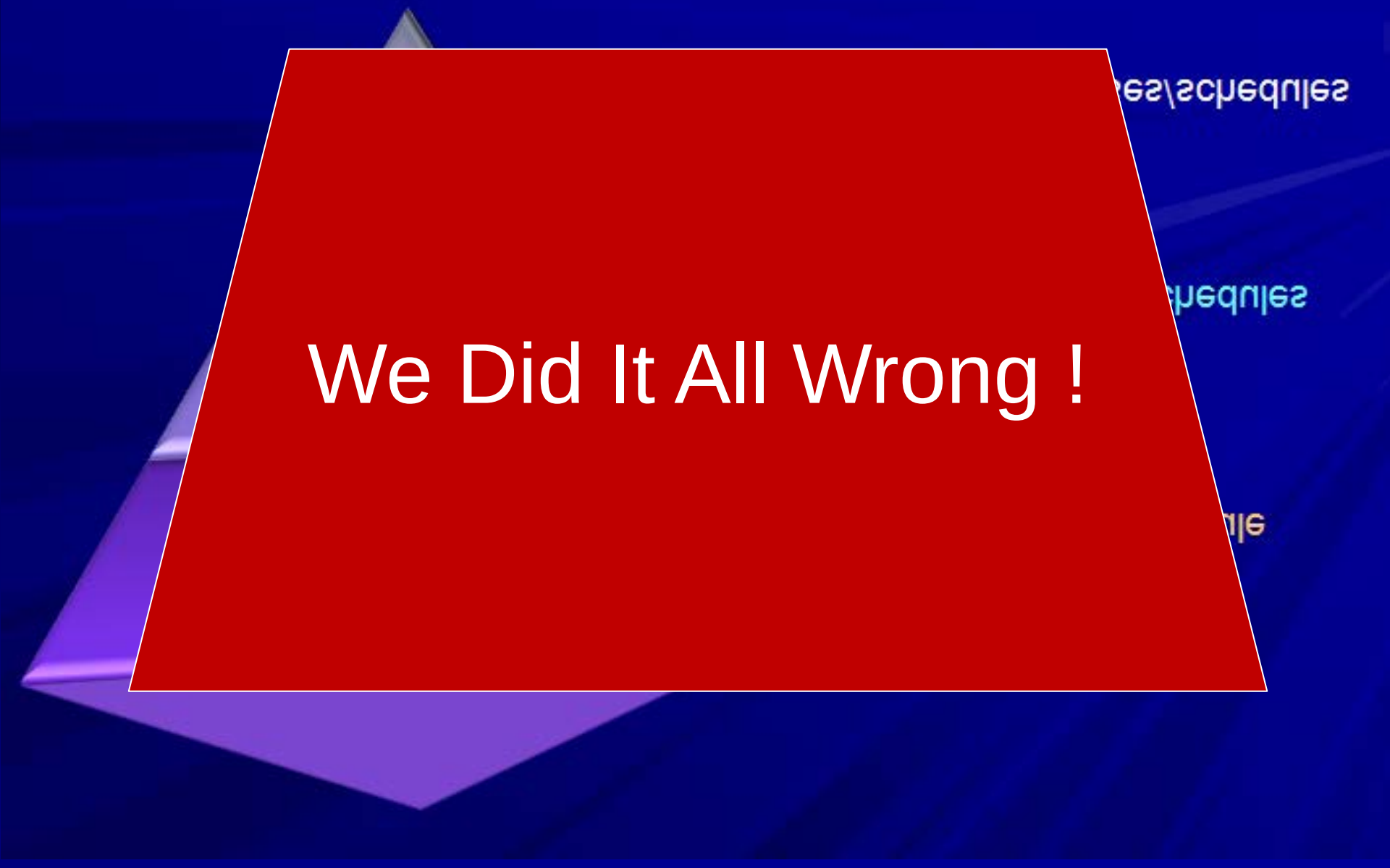



One dose/schedule

A few doses/schedules

Multiple doses/schedules

# Traditional Drug Development



# How to Fix the Problem?

- Do more Phase I trials to determine the best dose, schedule, and route of administration.
- Do more Phase II trials
  - Single-arm or randomized Phase IIA screening trials.
  - Randomized Phase IIB trials to confirm the efficacy.
- Do more combinations.
- Identify prognostic and predictive markers.
- Do smaller, more focused Phase III trials.
- Apply adaptive designs, e.g. adaptive enrichment, adaptive randomization & early stopping rules
- Continue to learn and to adapt.

# “ABC” on How to Fix the Problem?

- Adaptive Designs
- Biomarkers
- Combinations

# Biomarkers

# Selected List of Cancer Treatment-Related Companion Diagnostics

| CDx | | | Drug | Indication |
|---|---|---|---|---|
| Biomarker | Type | Year CDx approval | | |
| *KRAS* Mutation | LDT<br>PMA | 2006<br>2012 | Cetuximab, Panitumumab | Colorectal Cancer |
| *BRAF V600E* Mutation | PMA | 2011 | Vemurafenib | Melanoma |
| *ALK* Fusion | PMA | 2011 | Crizotinib | NSCLC |
| *EGFR* Mutation | LDT | 2003 | Gefitinib, Erlotinib | NSCLC |
| *HER2* Amplification | PMA<br>PMA | 1998<br>2008 | Trastuzumab | Breast Cancer |
| *BCR-ABL* Translocation | PMA | 2005 | Imatinib, Dasatinib, Nilotinib | CML |

CML: Chronic Myeloid Leukemia; LDT: Laboratory Developed Test in CLIA certified clinical laboratory; NSCLC: Non-Small Cell Lung Cancer; PMA: Pre-Market Approval by the FDA

*Source: Clin Chem 2013;59:198–201.*

What do all the biomarkers have in common?

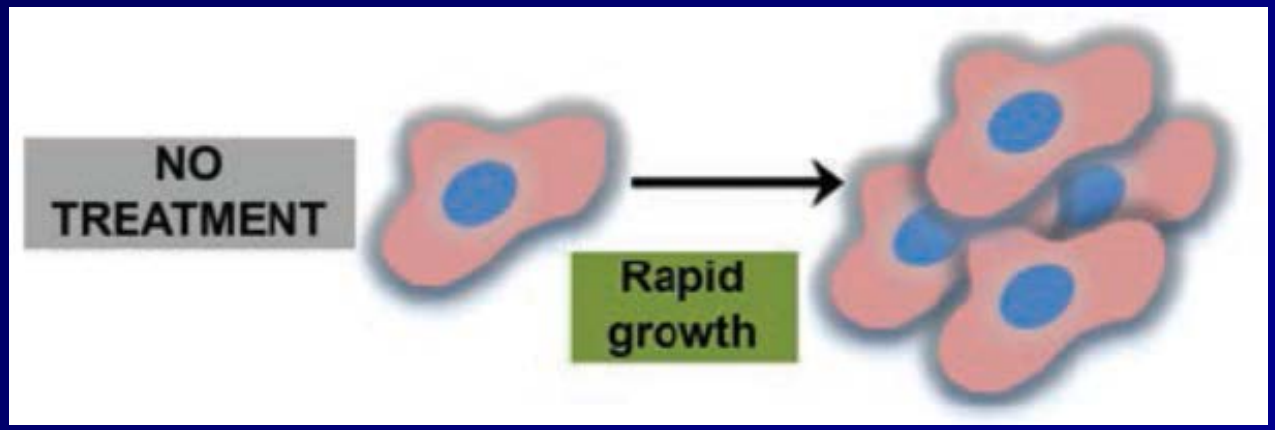
All are mechanism based!

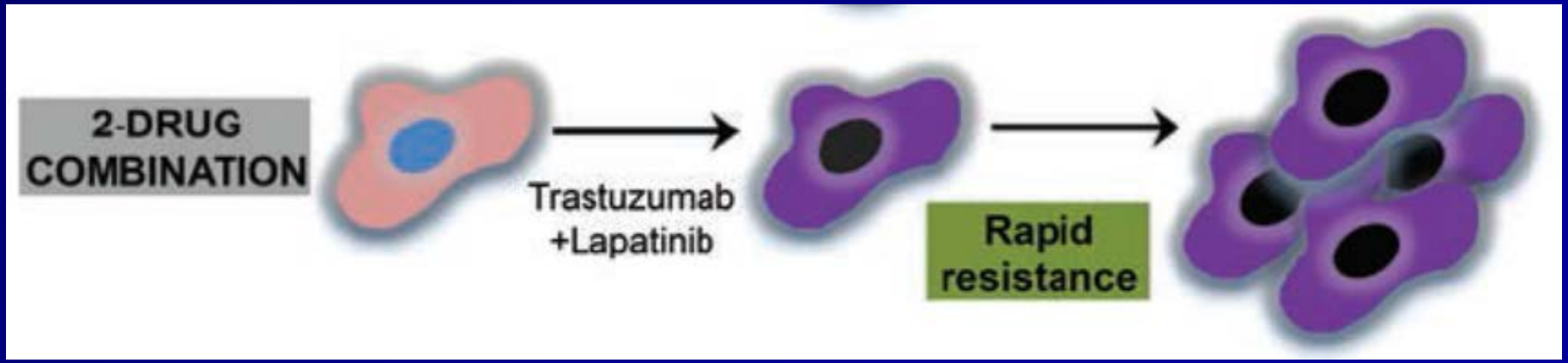
# Utility of Biomarkers

- Drug Delivery, Absorption, Metabolism
  - PK
- Surrogate Endpoint Biomarkers for measuring drug effect
  - PD
  - Toxicity
  - Efficacy
- Patient Selection
  - Enrichment Designs
- Treatment Selection
  - Outcome adaptive randomization

# Biomarker-guided sequential targeted therapies to overcome therapy resistance in rapidly evolving highly aggressive mammary tumors

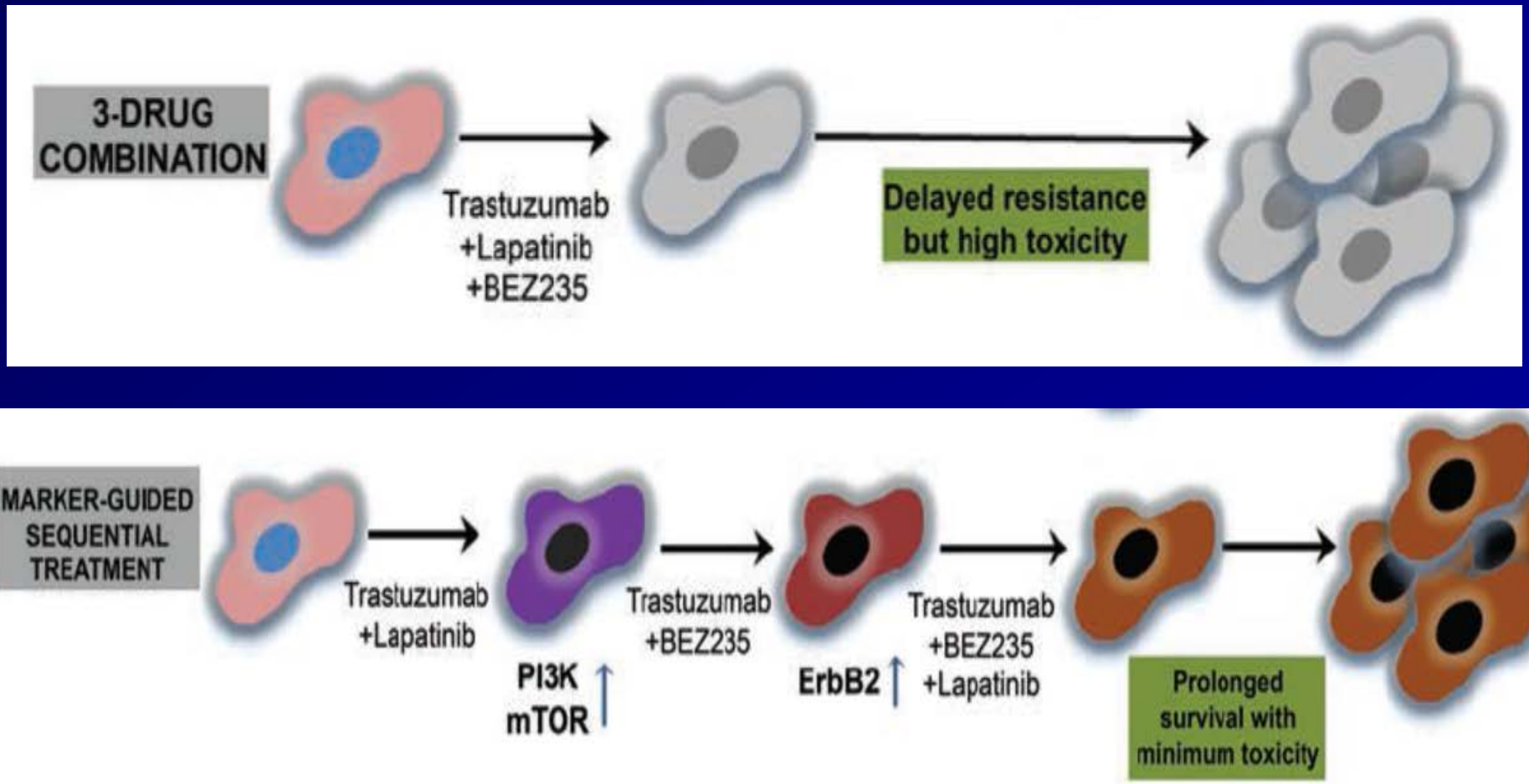
Model:ErbB2-overexpressed/PTEN-low, highly aggressive breast cancer



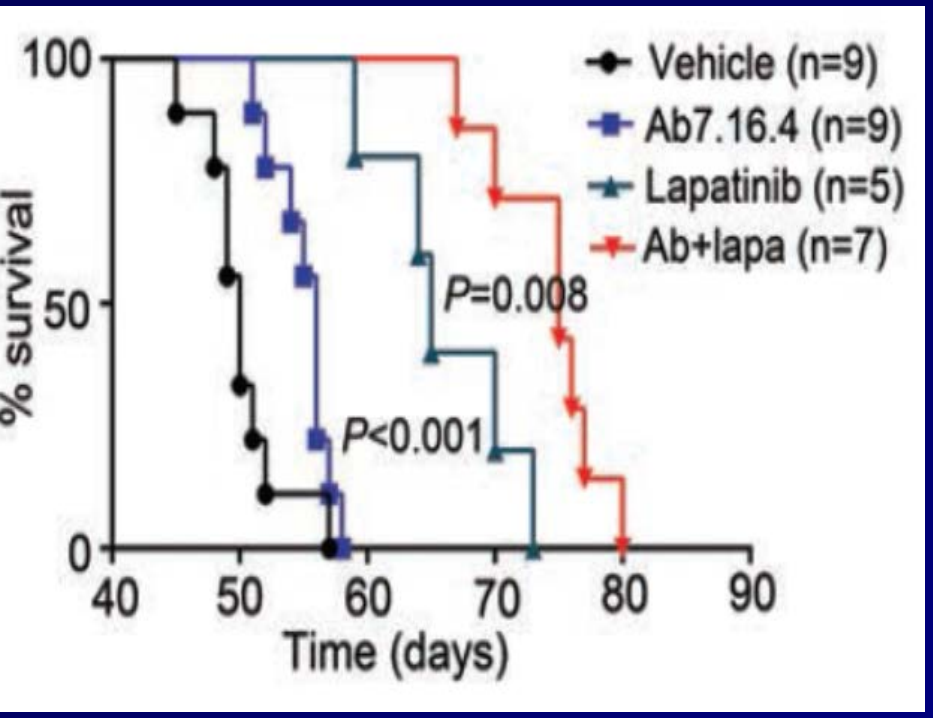



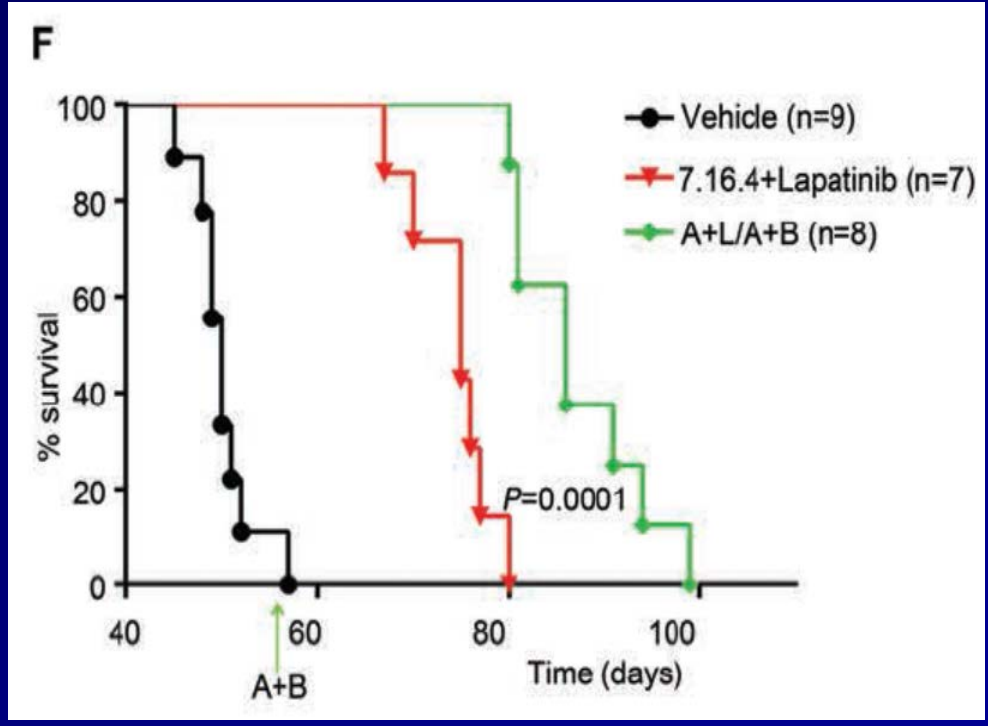

Ozgur Sahin, …, Dihua Yu, Cell Research 2014

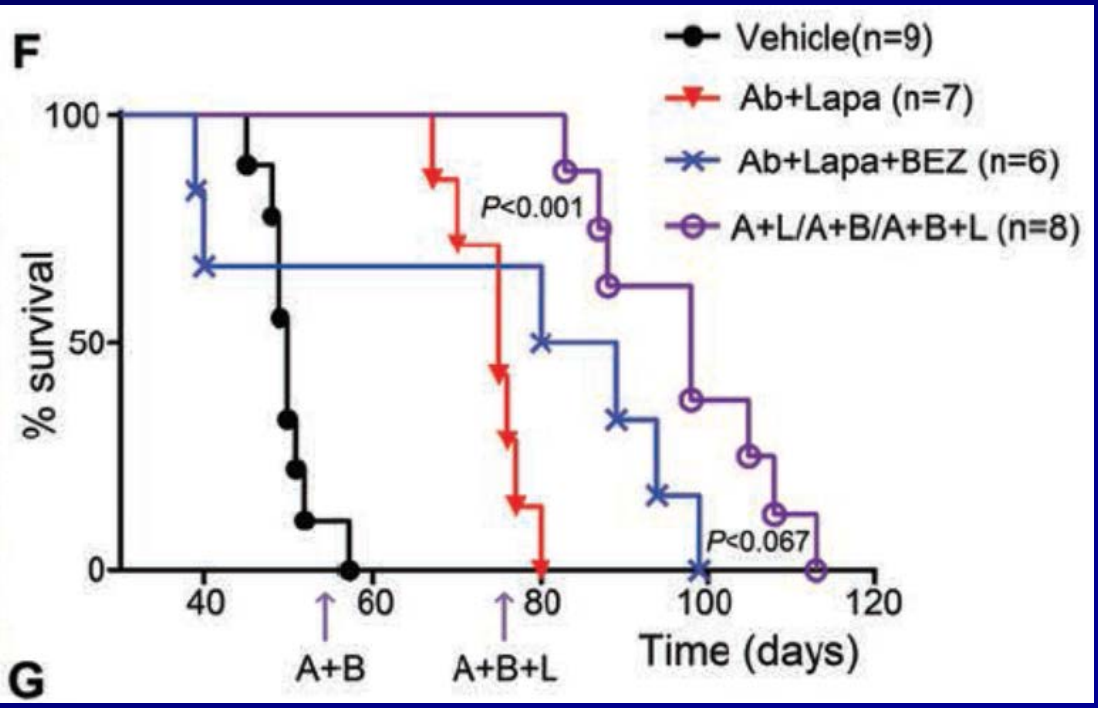
# Biomarker-guided sequential targeted therapies




Ozgur Sahin, …, Dihua Yu, Cell Research 2014




**Sequential application of targeted therapies guided by biomarker changes in the tumors rapidly evolving resistance doubled the life-span of mice bearing exceedingly aggressive tumors.**

# Biomarkers Summary

- Mechanism-based biomarkers, e.g., driver mutations are very useful for target selection and drug development.
- Preclinical testing for biomarker data
  - Cell lines
  - Animal models
    - PDX
- No shortage of methods for biomarker discovery
  - Variable selection
  - Control type I error and/or false discovery rate
- Validation is the key
  - Many are called; few are chosen.

# Combination Studies

# Promise of Combination Therapy

- Overcome drug resistance induced by single agents.
- Block the potential by-pass mechanisms in signaling pathways
- Induce synthetic lethality
- Increase efficacy without increasing toxicity

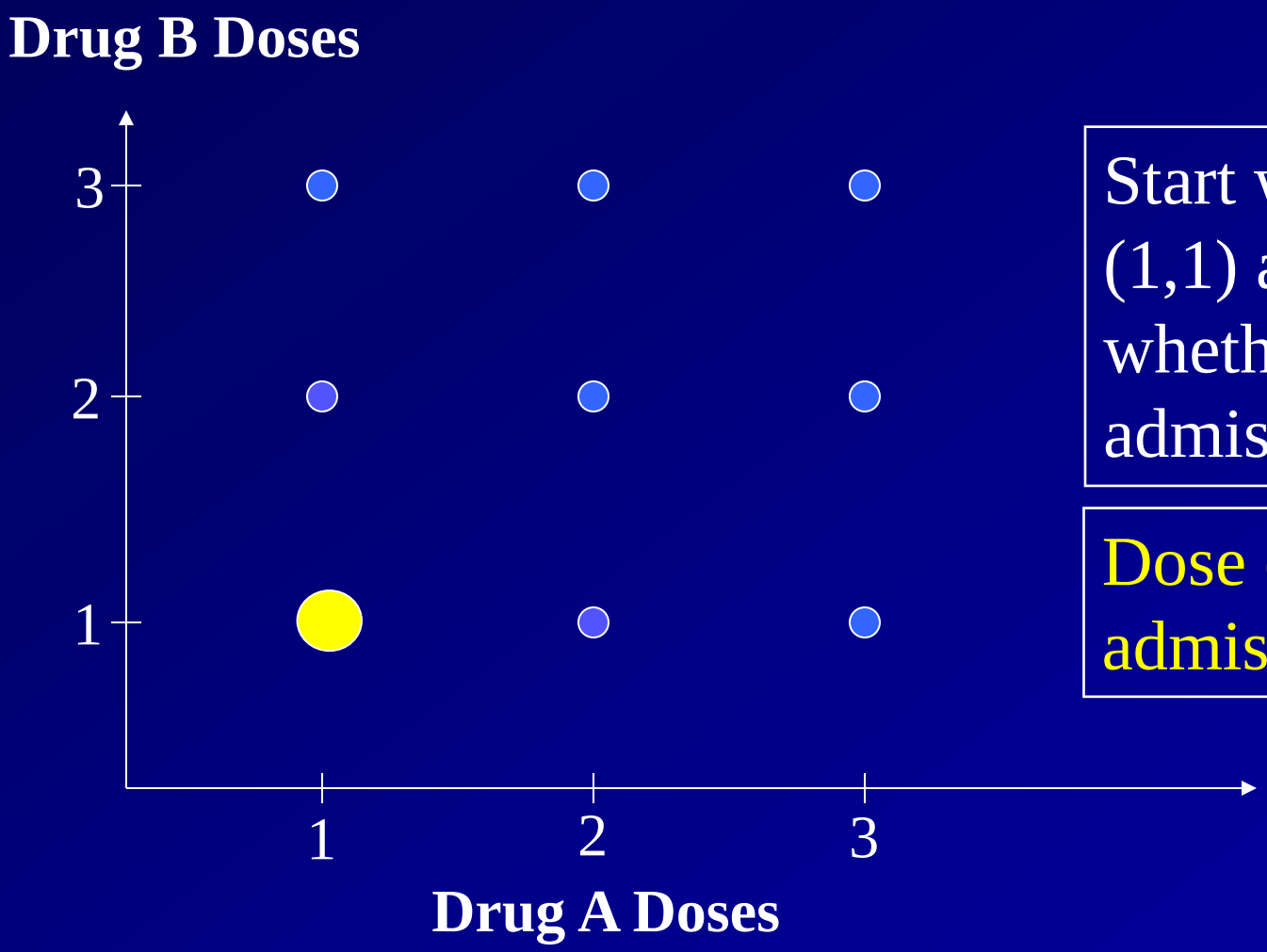
# Challenges of Combination Studies

- 2 drugs, 3 drugs, 4 drugs, …?
- Select dose of each drugs
- Added toxicity?
- Schedule
  - Simultaneous
  - Sequential (which sequence?)
  - Intermittent (how?)
- Biomarkers
  - Selection: discovery and validation
  - Main effect: additive?  Non-linear?
  - Interaction effect: treatment x marker; marker x marker
- Complexity exponentiates for combination studies!

# Phase I/II Parallel Design for Combinations

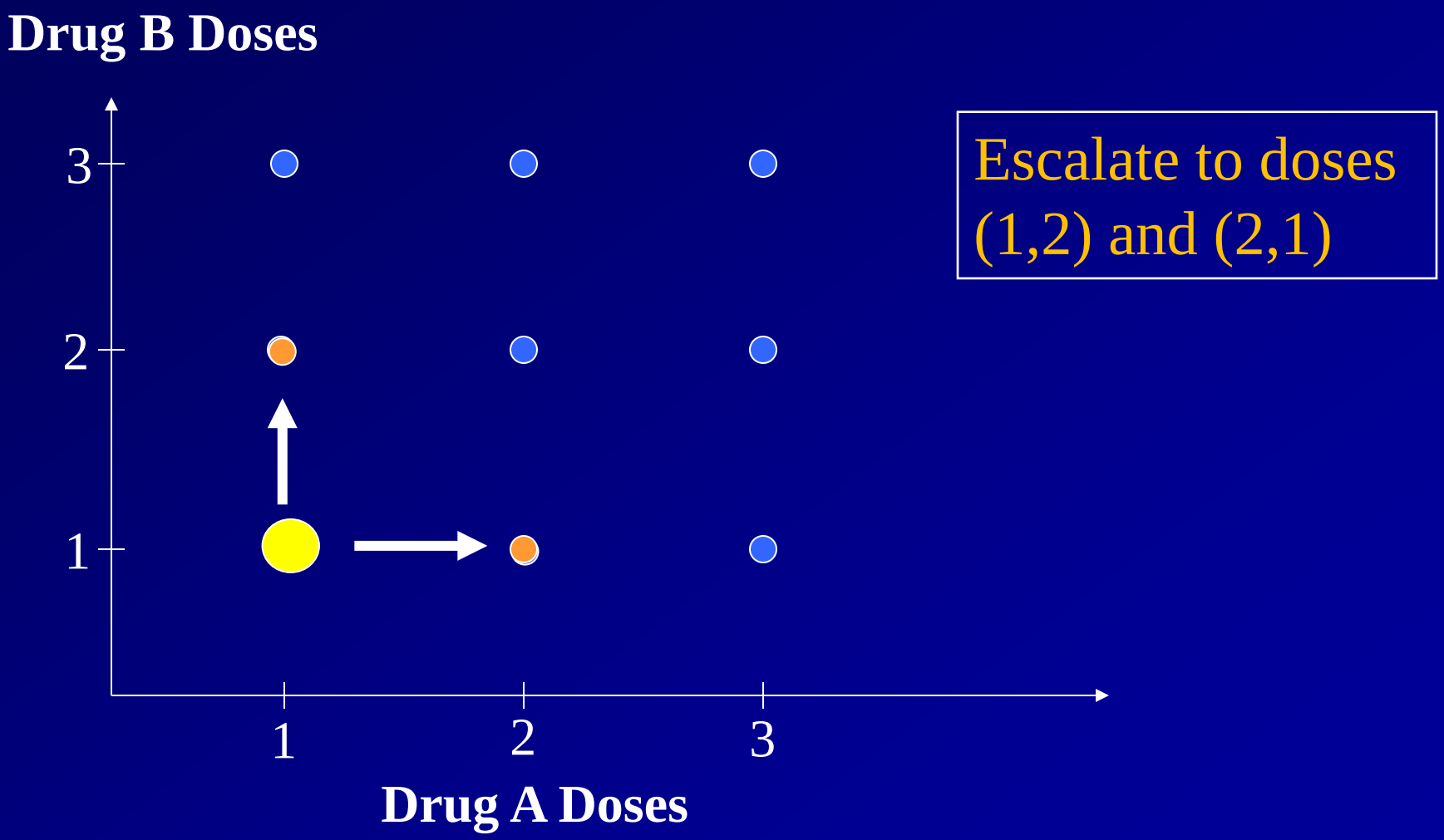
- Choose dose grid for single/combination treatments.
- Simultaneously evaluate toxicity and efficacy. Define doses with acceptable toxicity as "admissible doses."
- Start at the lowest dose. Then, move up the grid if the current doses are admissible.
- Adaptively randomize patients into all admissible doses in proportion to the efficacy at each dose. Hence, more patients can be treated at more effective doses.
- Allow early stopping when the trial results cross the pre-determined safety, efficacy, or futility boundaries.
- Identify predictive biomarkers

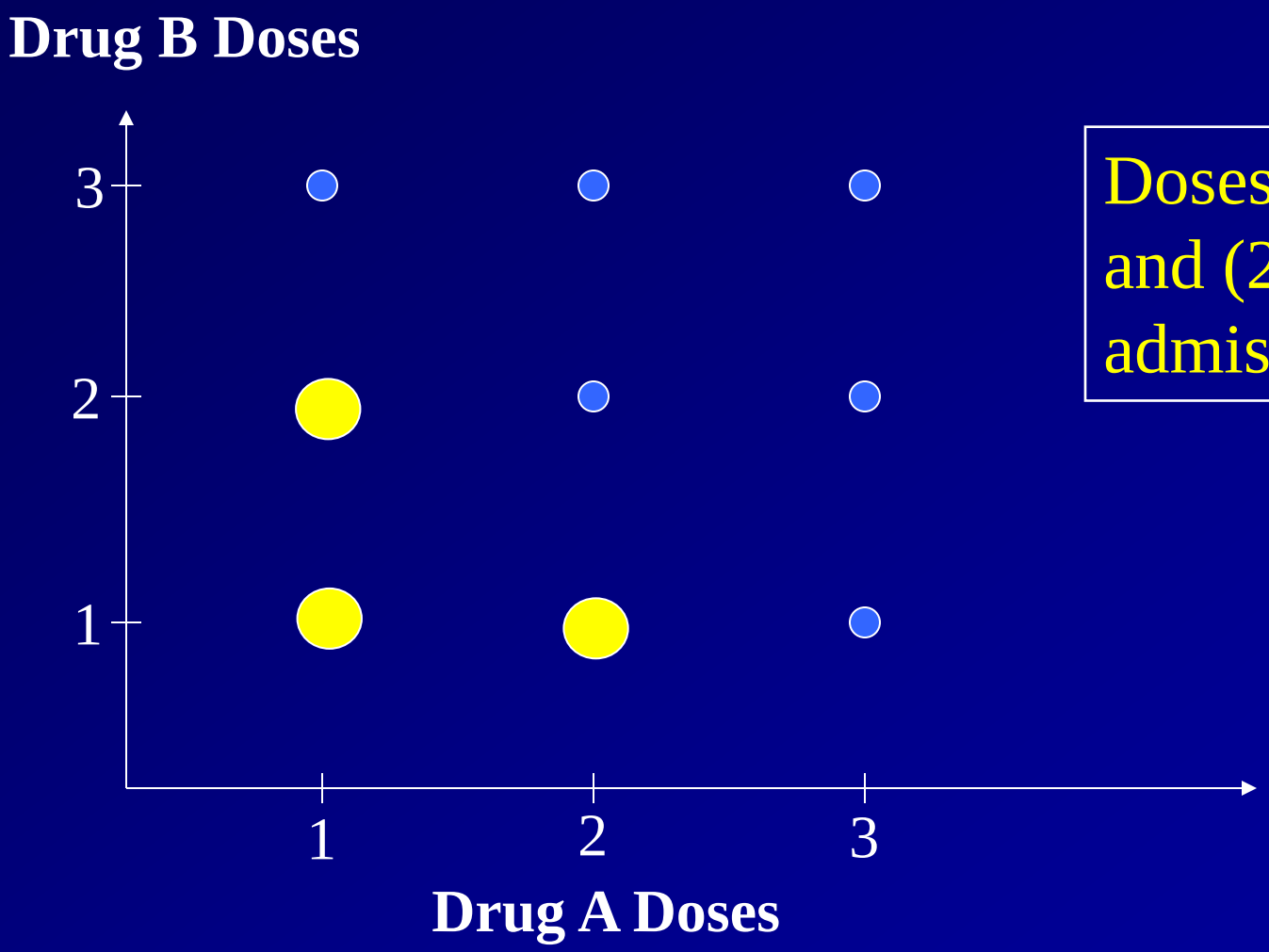
Adapted from Huang, Biswas, Oki, Issa, Berry. *Biometrics* 2007;63(2):429-36.



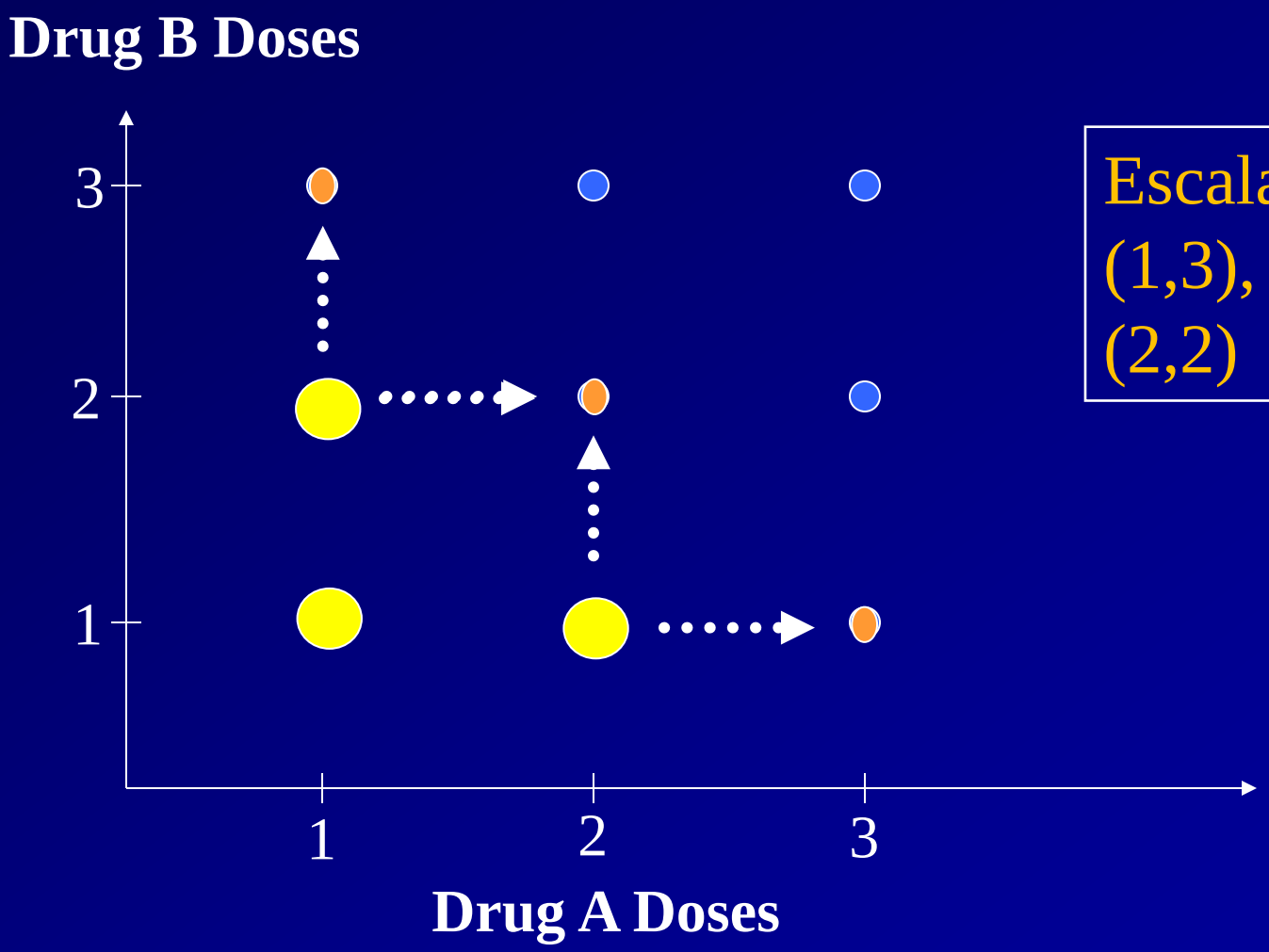

Start with dose (1,1) and check whether it is admissible or not

Dose (1,1) is admissible

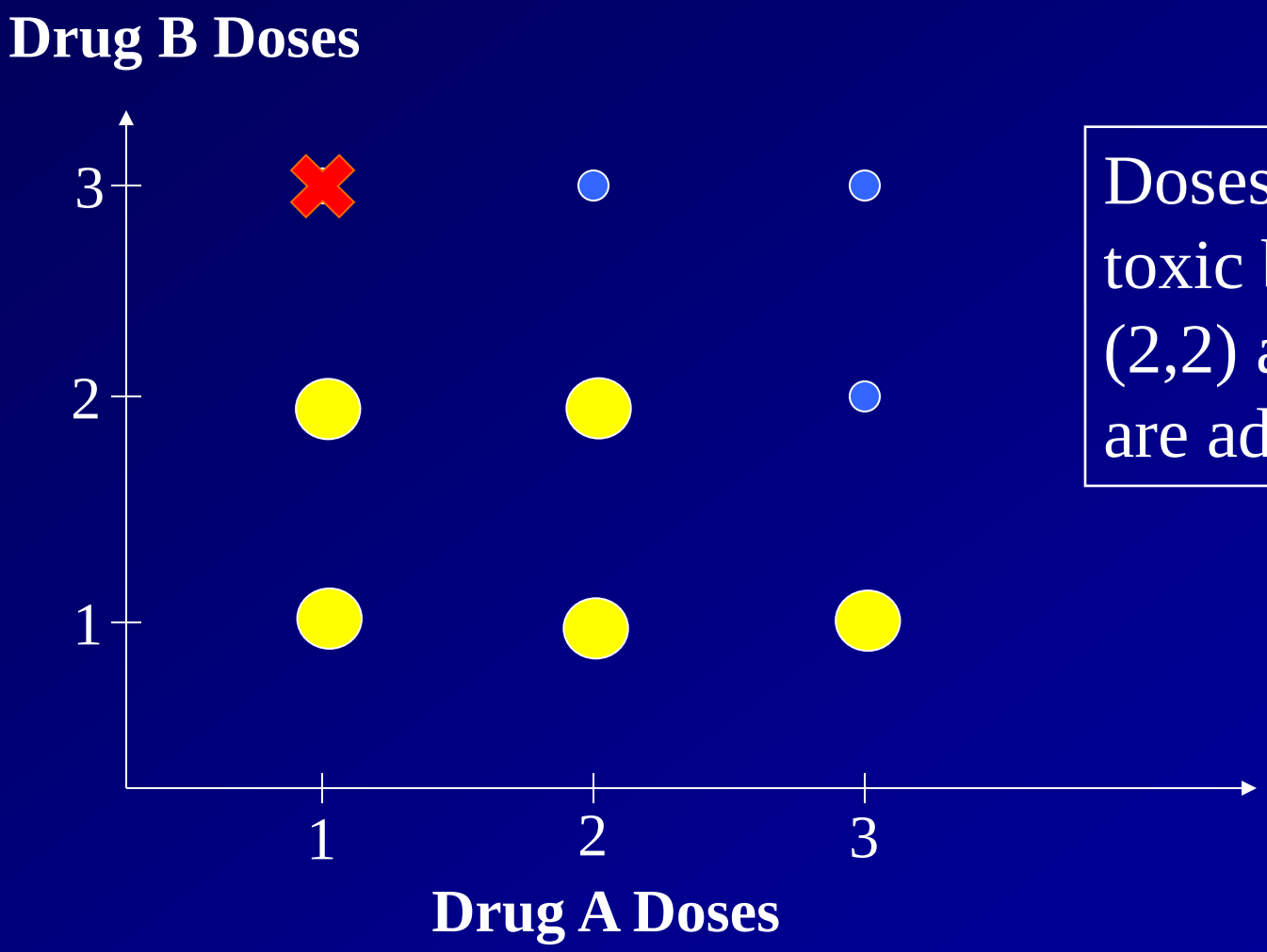

Drug B Doses
3
2
1
1
2
3
Drug A Doses
Escalate to doses
(1,2) and (2,1)



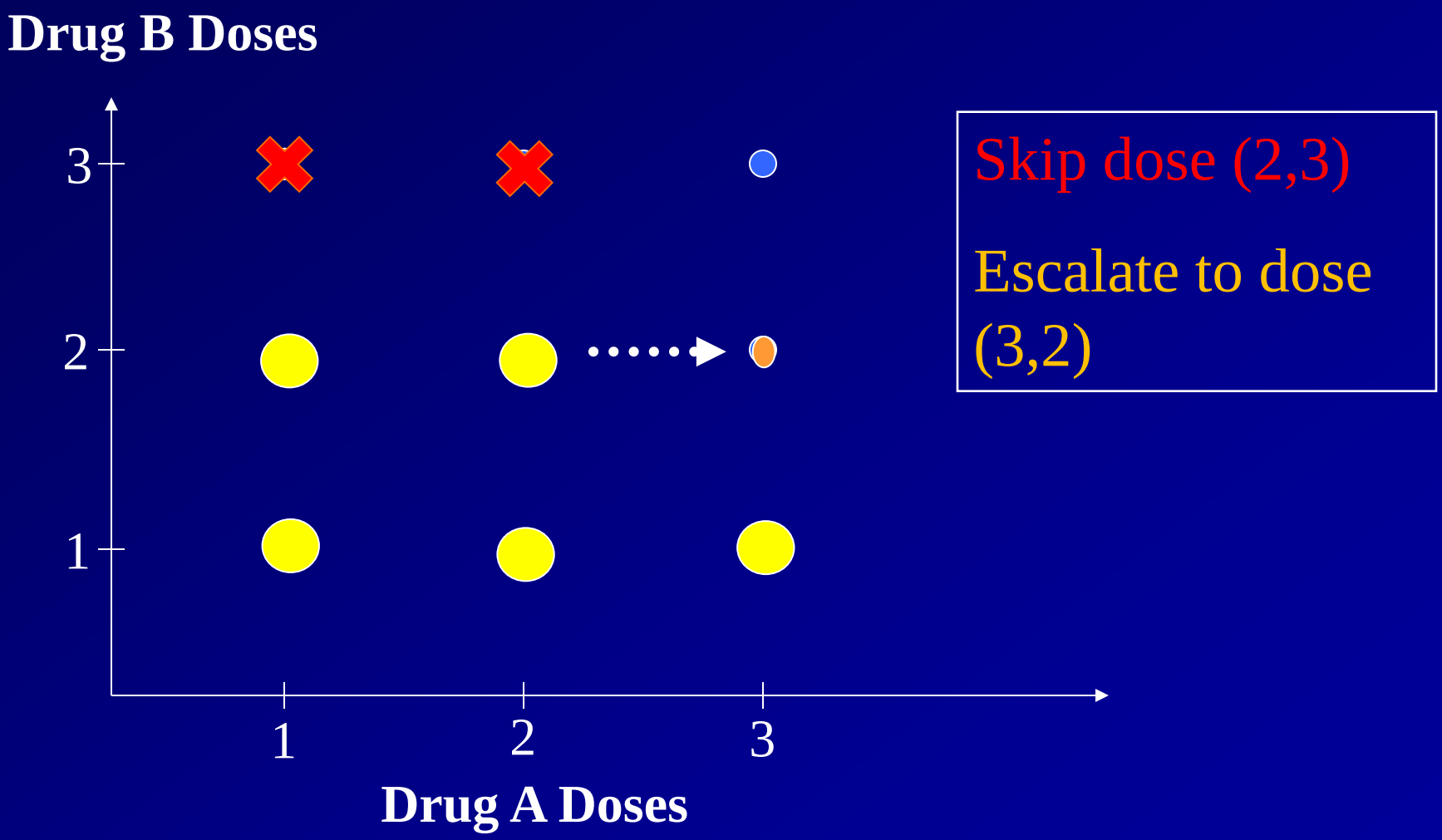

Doses (1,1), (1,2) and (2,1) are all admissible

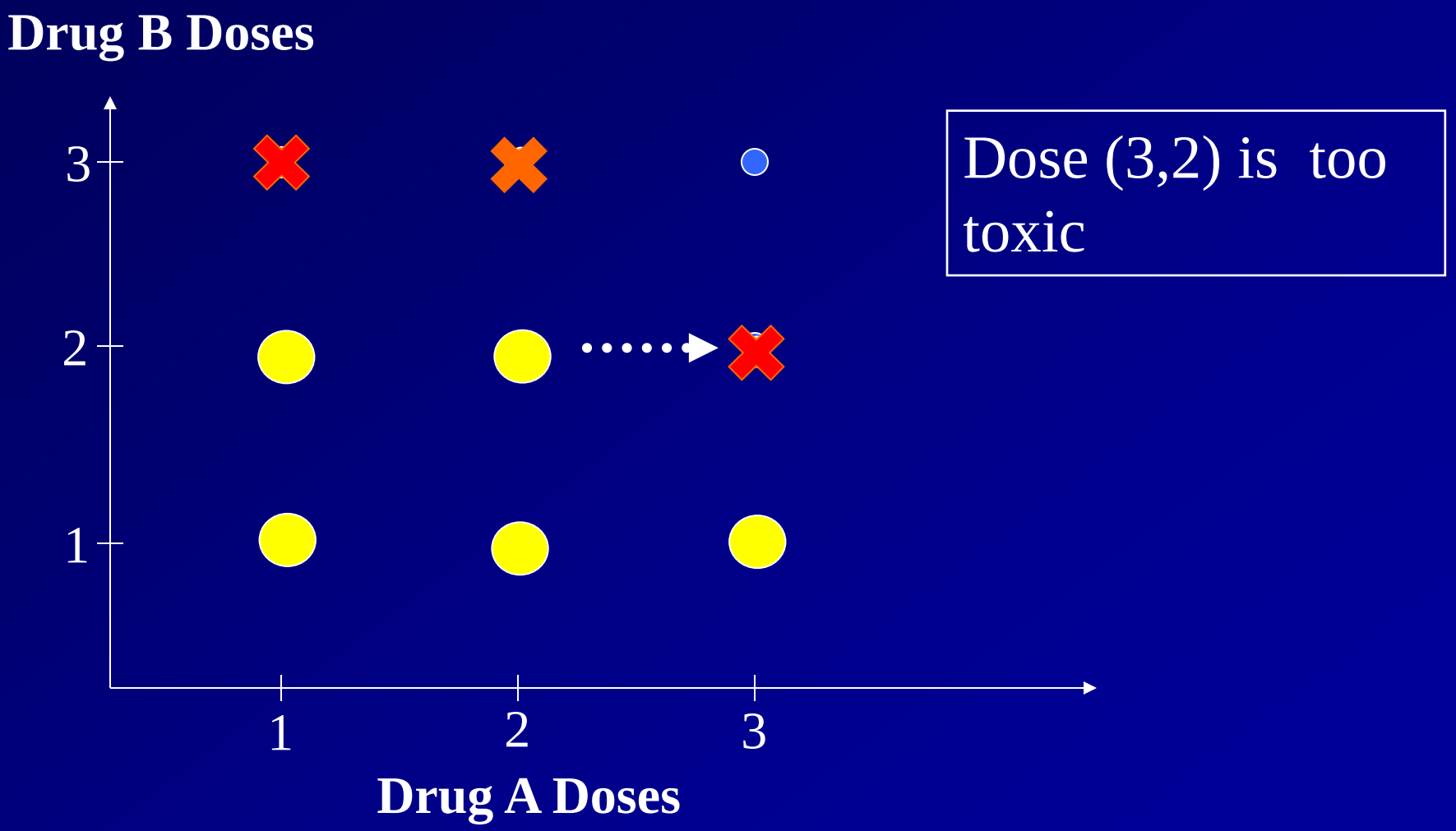


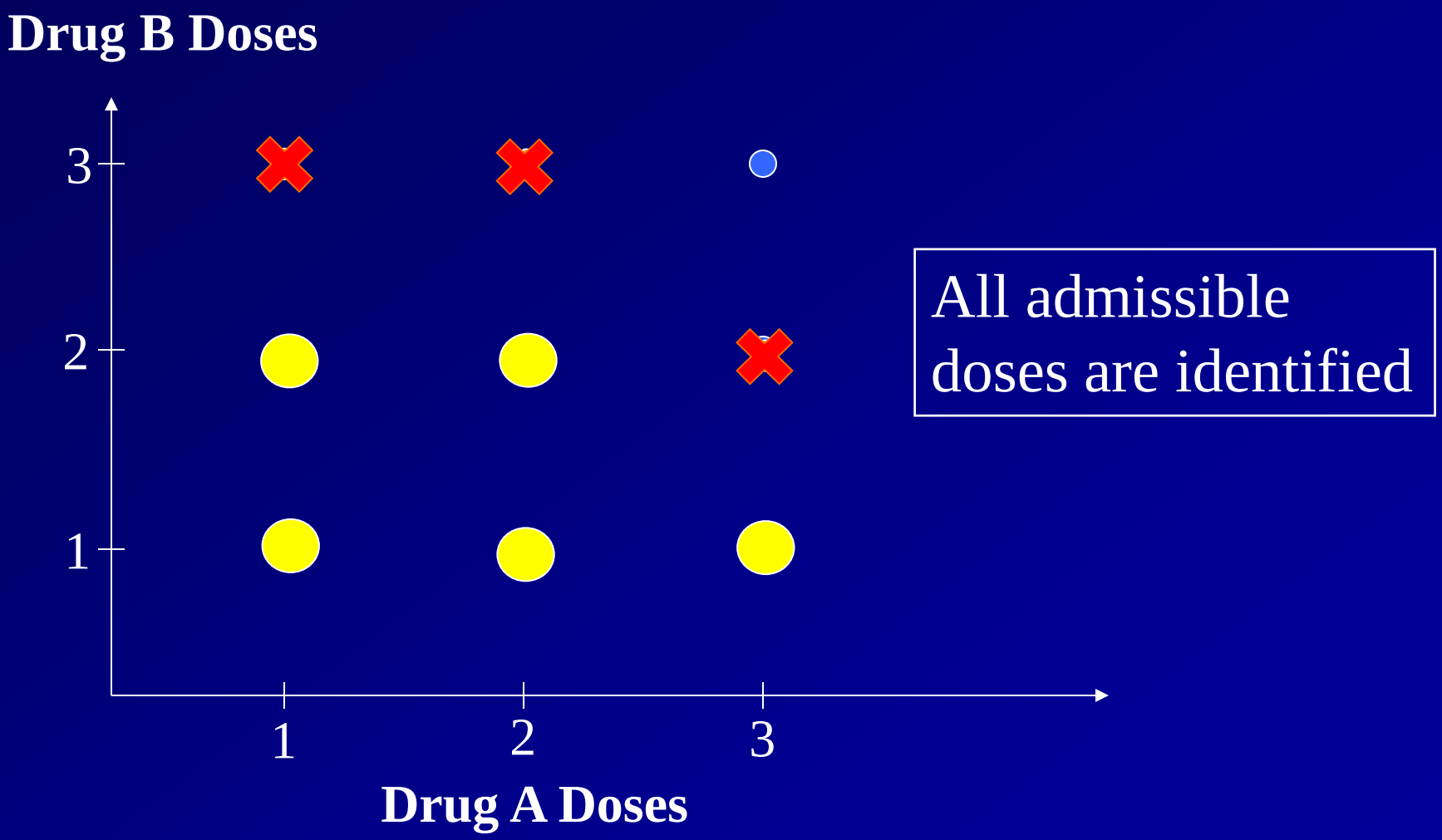

Escalate to doses (1,3), (3,1), and (2,2)

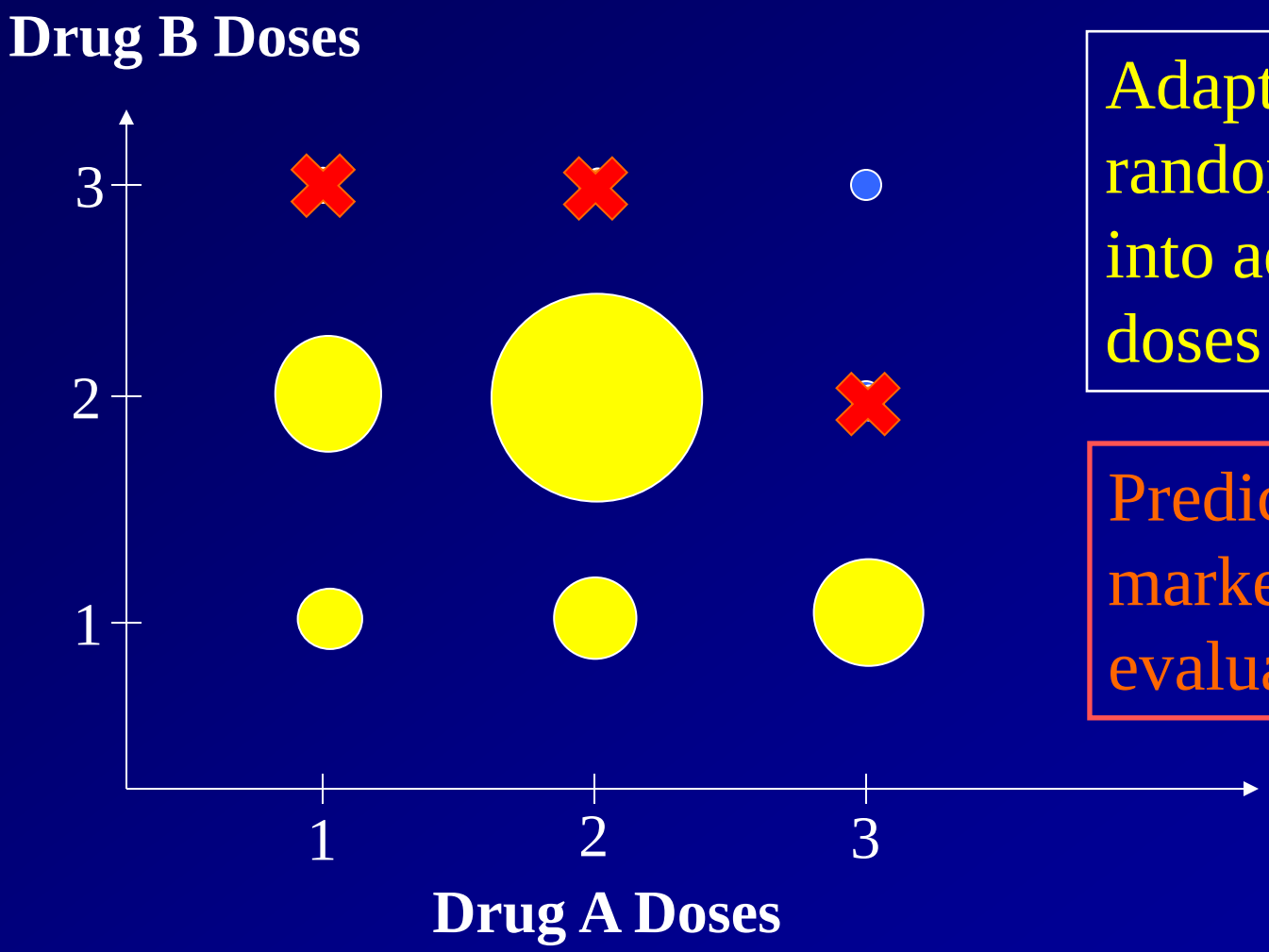



Doses (1,3) is too toxic but doses (2,2) and (3,1) are admissible


Drug B Doses
3
2
1
1
2
3
Drug A Doses
Skip dose (2,3)
Escalate to dose (3,2)


Drug B Doses
3
2
1
1
2
3
Drug A Doses
Dose (3,2) is too toxic


Drug B Doses
3
2
1
1
2
3
Drug A Doses
All admissible doses are identified




Adaptive randomizing pts into admissible doses

Predictive markers are evaluated

# Adaptive Designs

Trials that use interim data to guide the study conduct

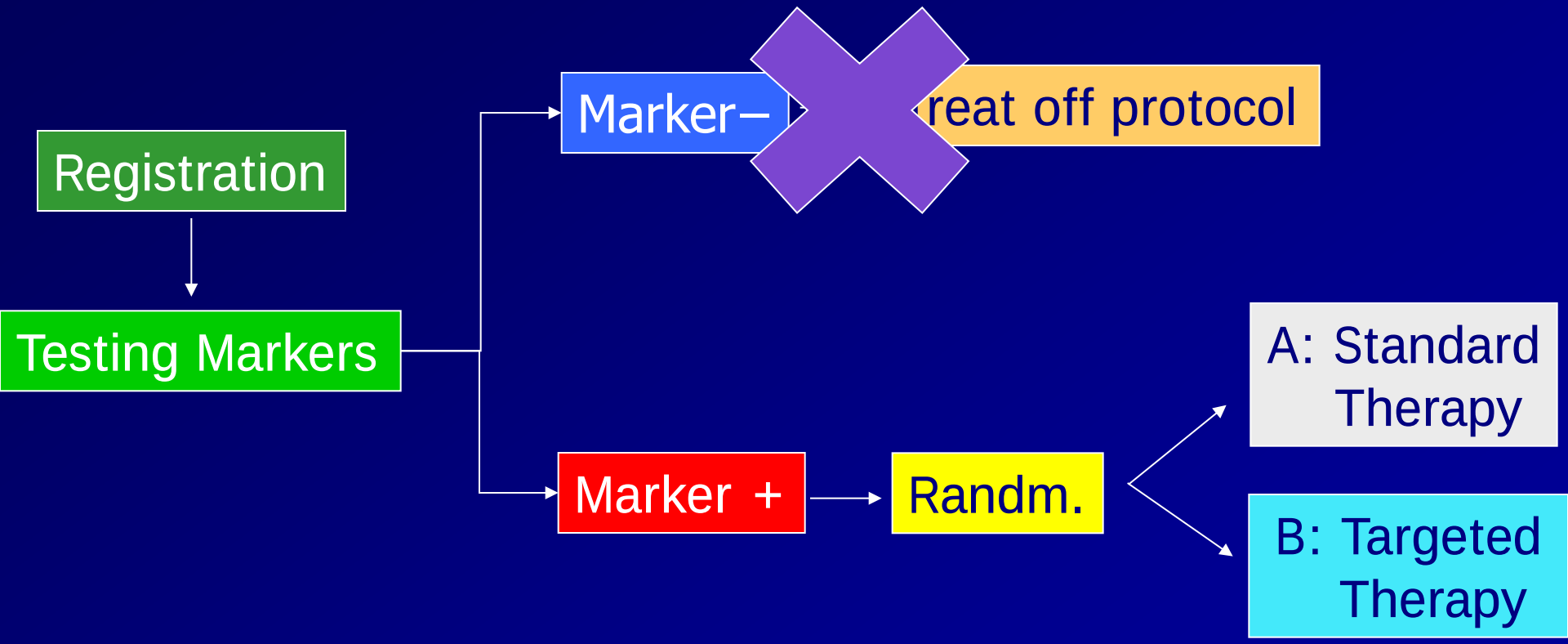
# What Are Adaptive Designs?

- Adaptive dose finding and estimation
  - Continual reassessment method (CRM) in Phase I trials
- Adaptive decision making
  - Predictive probability in Phase II trials
  - Dropping bad treatments; add new treatments
- Adaptive patient assignment to treatment
  - Adaptive enrichment
  - Adaptive randomization in Phase II or Phase III trials
- Seamless phase I/II, II/III designs
- Adaptive marker identification and validation
- Adaptive learning
  - Build a comprehensive knowledge database, continuous updating of information
  - Assign best treatment for each patient

# Biomarker Based Designs

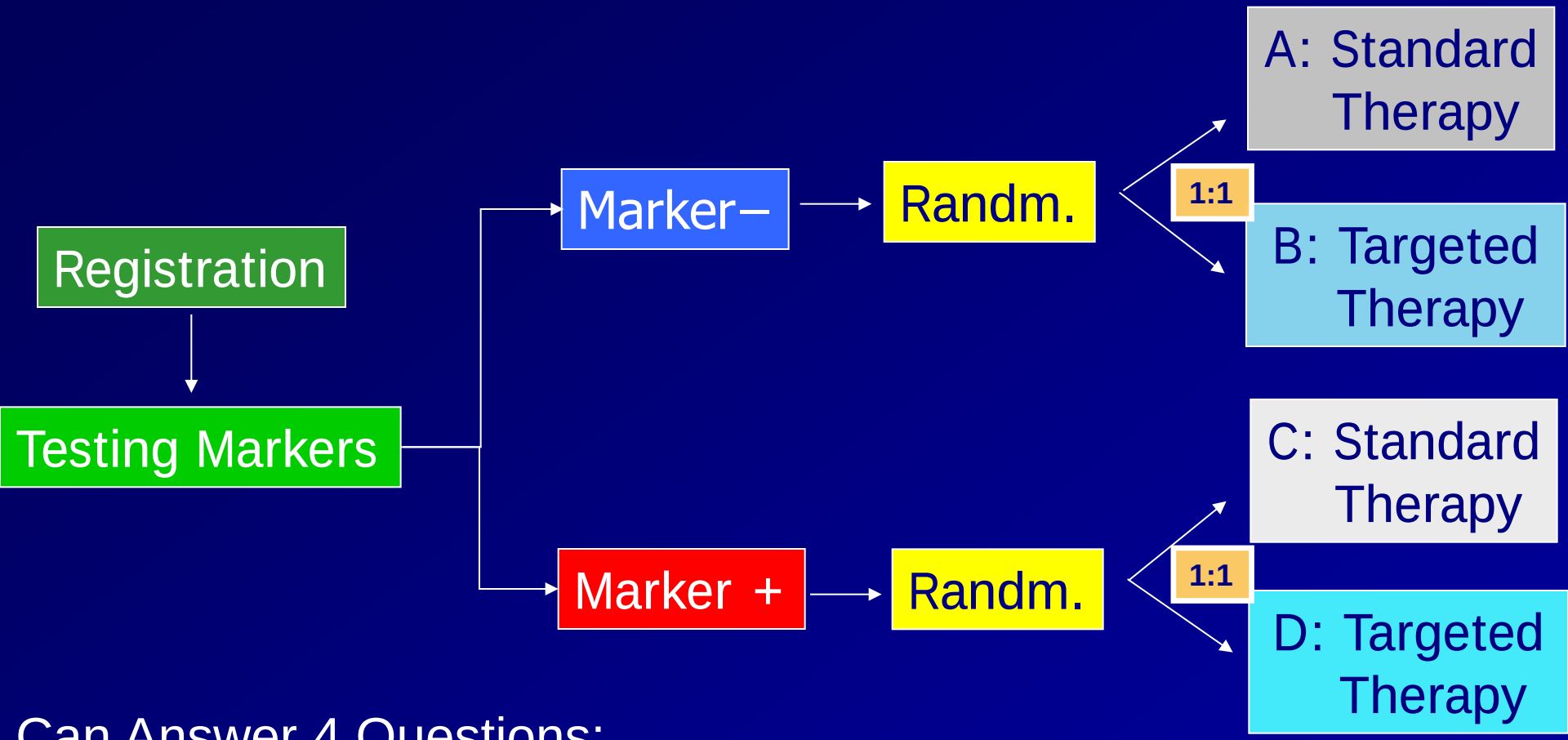
- Efficient target design
- Adaptive enrichment design
- Marker stratified design
- Bayesian adaptive randomized design
  - Outcome adaptive randomization
  - Early stopping for futility and/or efficacy
- BATTLE-1 and BATTLE-2 trials
  - Biomarker training (discovery), testing, and validation
- Adaptive learning (N-of-ALL Design)
- Multiple randomized phase II studies → a small, more focus randomized phase III study

# Efficient Target Design




1. Screen out Marker (–) patients and only focus on Marker + patients
2. Can answer the question: Does targeted therapy work in Marker (+)? (A vs. B)

# Marker Stratified Design

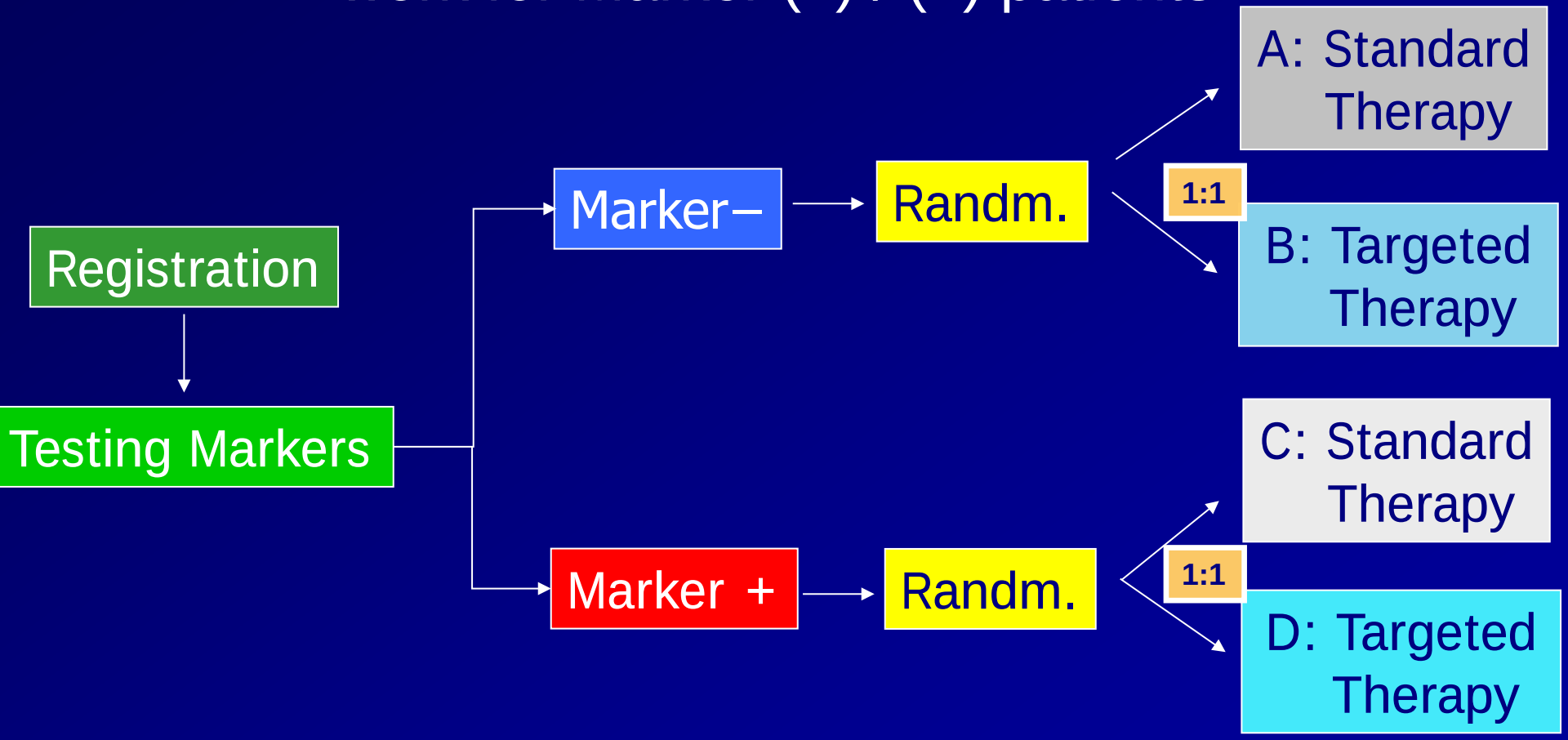



Can Answer 4 Questions:

1. Does targeted therapy work in Marker (–)? (A vs. B)
2. Does targeted therapy work in Marker (+)? (C vs. D)
3. Is marker prognostic? (A vs. C)
4. Is marker predictive (MK x TX Interaction)? (A/B vs. C/D)

# Adaptive Enrichment Design

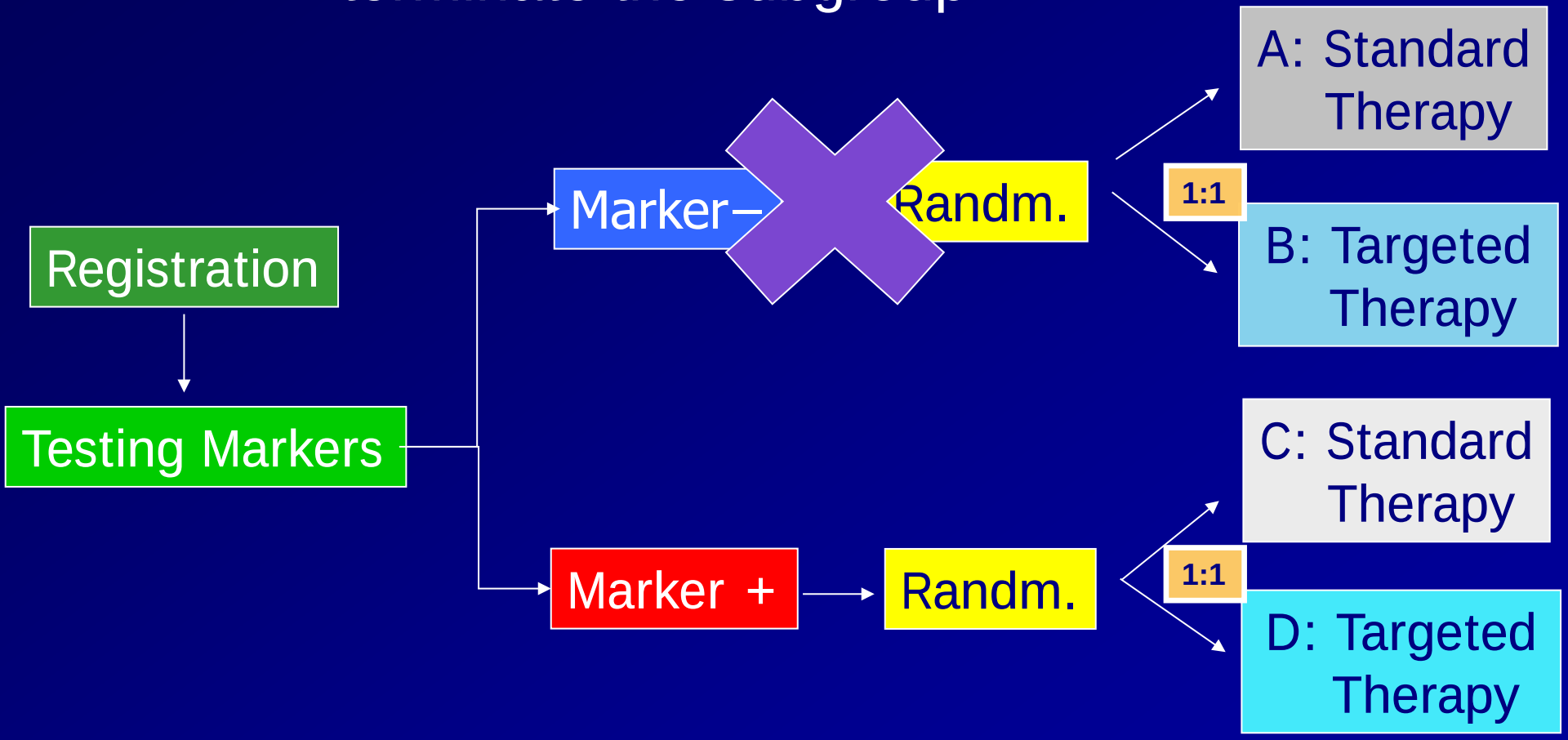
Stage 1 : Test whether targeted therapy work for Marker (–) / (+) patients



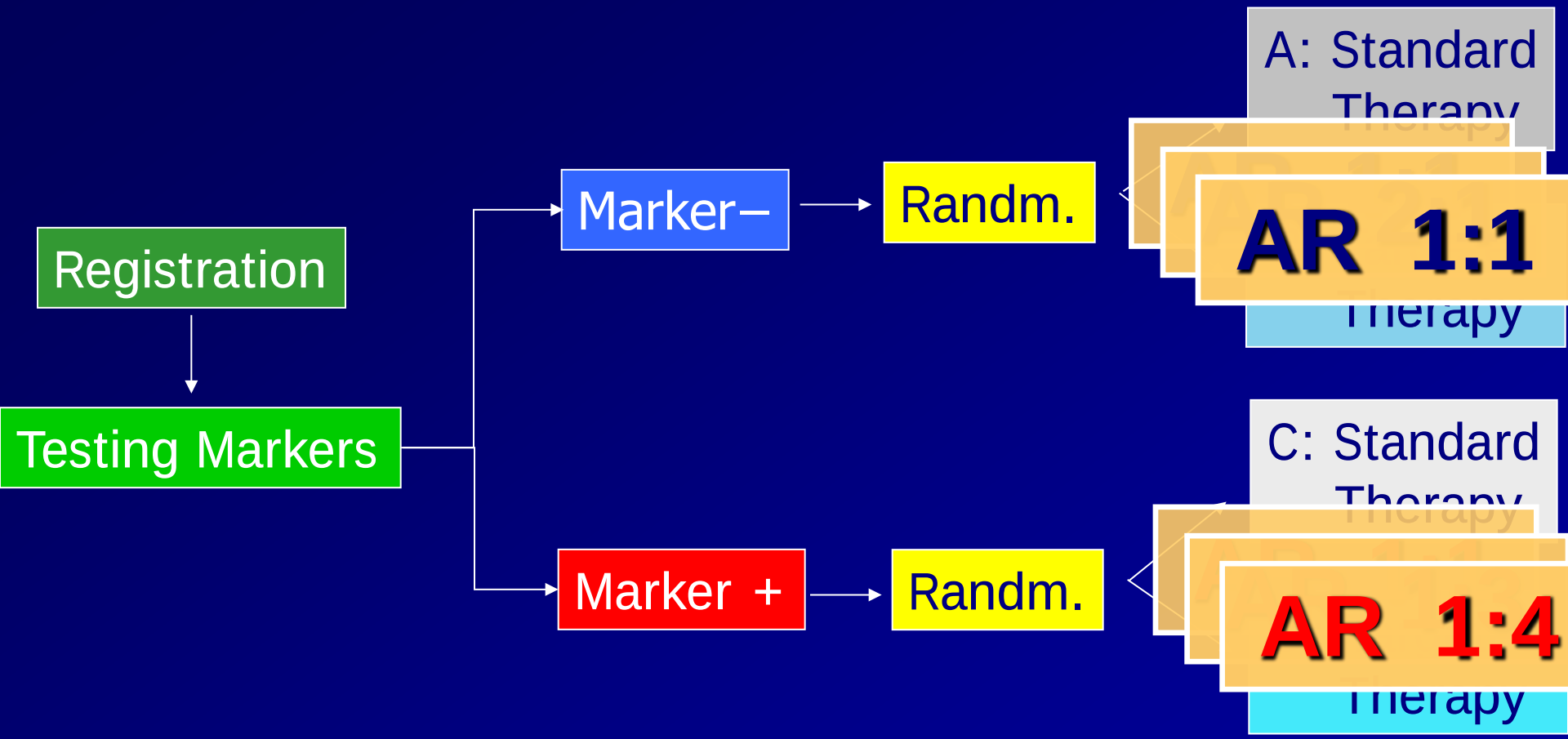

Wang and Hung, Contemporary Clinical Trials, 2013
Simon and Simon: Biostatistics, 2013

# Adaptive Enrichment Design

Stage 2 : If not working in Marker (–) patients, terminate the subgroup



# Bayesian Adaptive Randomization Design




Similar to Marker Stratified Design but instead of using ER, apply AR to assign more patients with more effective treatments.

Lee JJ, Gu X, Liu S. Bayesian adaptive randomization designs for targeted agent development. Clinical Trials, 2010;7:584-596

# BATTLE (Biomarker-based Approaches of Targeted Therapy for Lung Cancer Elimination)

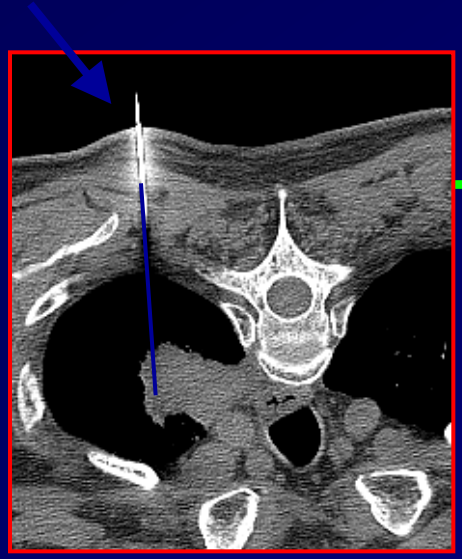
- Patient Population: Stage IV recurrent non-small cell lung cancer (NSCLC)
- Primary Endpoint: 8-week disease control rate (DCR)
- 4 Targeted treatments, 11 Biomarkers
- 200 evaluable patients
- Goal:
  - Test treatment efficacy
  - Test biomarker effect and their predictive roles to treatment
  - Treat patients better in the trial based on their biomarkers

1. Zhou X, Liu S, Kim ES, Lee JJ. Bayesian adaptive design for targeted therapy development in lung cancer - A step toward personalized medicine (*Clin Trials*, 2008).

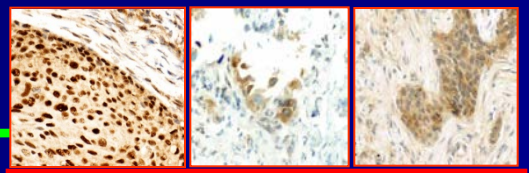
2. Kim ES, Herbst RS, Wistuba II, Lee JJ, et al, Hong WK. The BATTLE Trial: Personalizing Therapy for Lung Cancer. (*Cancer Discovery*, 2011)

# BATTLE Schema

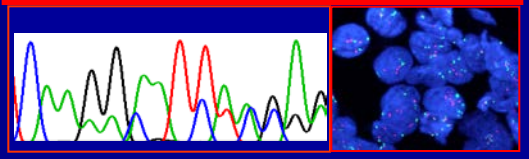
**Umbrella Protocol**



**Core Biopsy**



**Biomarker Profile**



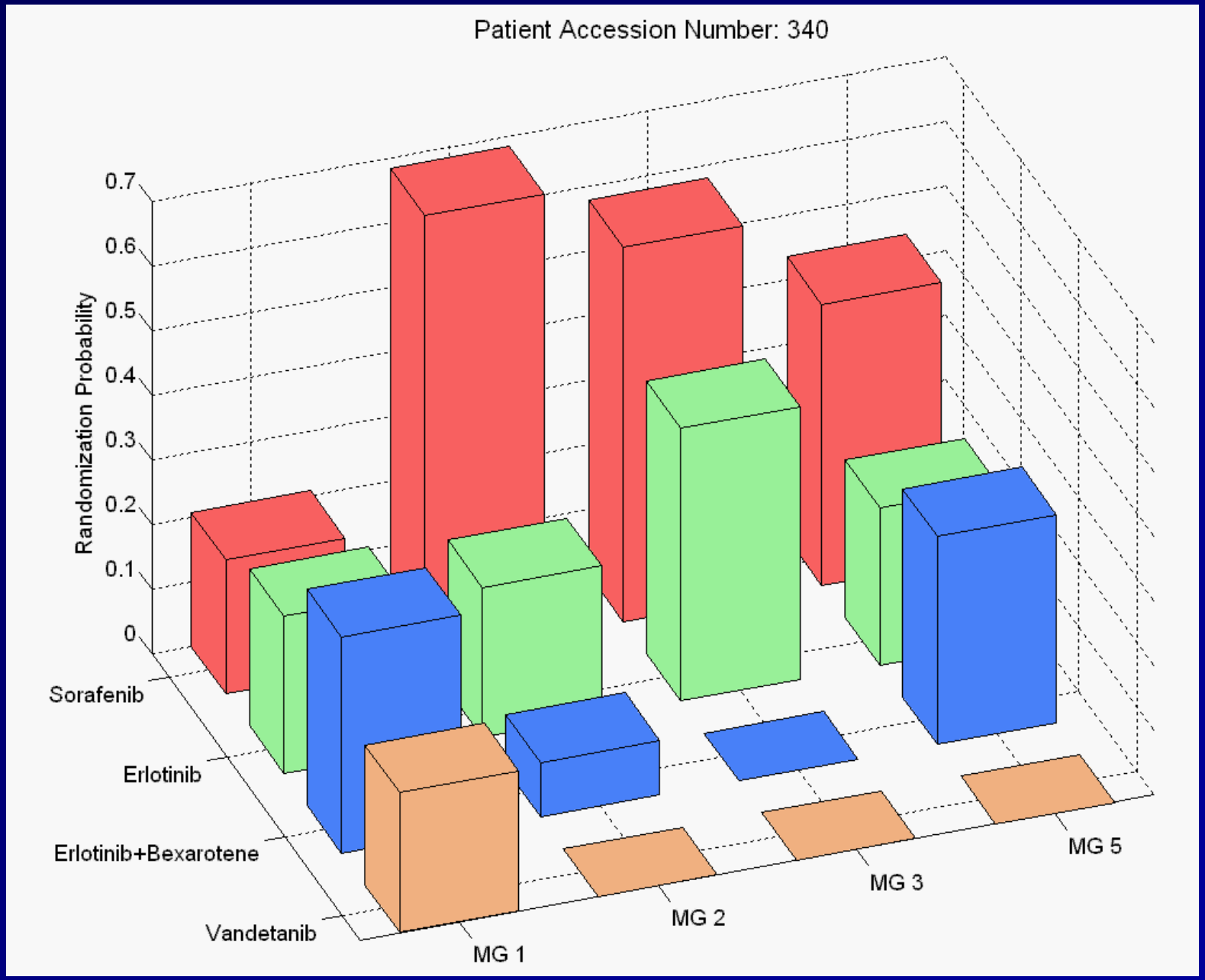
**EGFR KRAS/BRAF**
**VEGF RXR/CyclinD1**

**Randomization:**
***Equal → Adaptive***

- Erlotinib
- Vandetanib
- Erlotinib + Bexarotene
- Sorafenib

**Primary end point: 8 week Disease Control (DC)**

# Video: Adaptive Randomization in BATTLE Trial



# Lessons Learned from BATTLE-1?

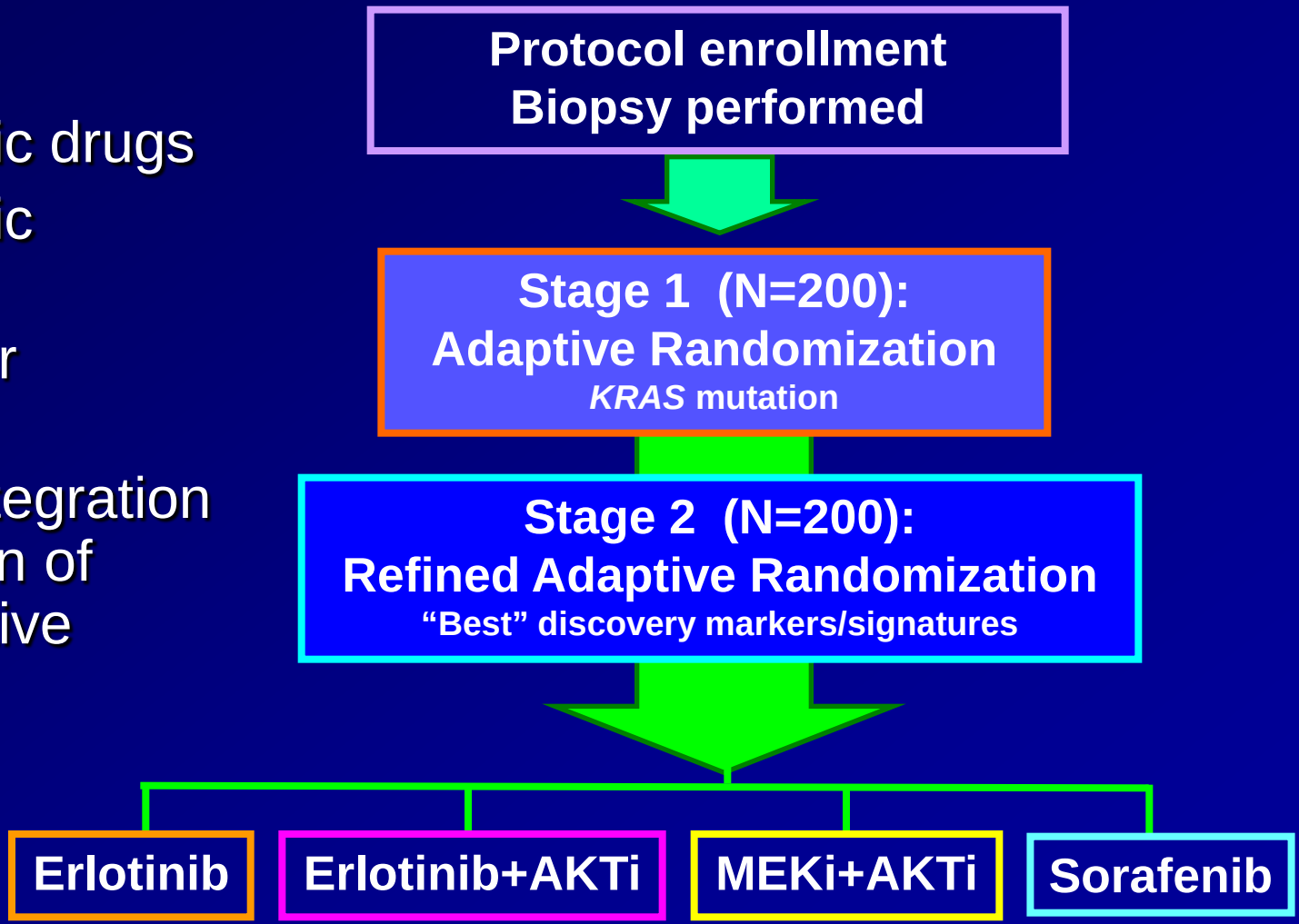
- Biomarker-based adaptive design is doable! It is well received by clinicians and patients.
- Prospective tissues collection & biomarkers analysis provide a wealth of information
- Treatment effect & predictive markers are efficiently assessed.
- Pre-selecting and grouping markers are not good ideas. We don't know what are the best predictive markers at get-go.
- AR should kick in earlier & be closely monitored.

- AR works well only when we have good drugs and good predictive markers.

# BATTLE-2 Schema

## Principles

- Better specific drugs
- Better specific targets
- No biomarker grouping
- Selection, integration and validation of novel predictive biomarkers




**Open:**
**MDA - June 2011**
**Yale - August 2012**
**200 Randomized, 12/2013**

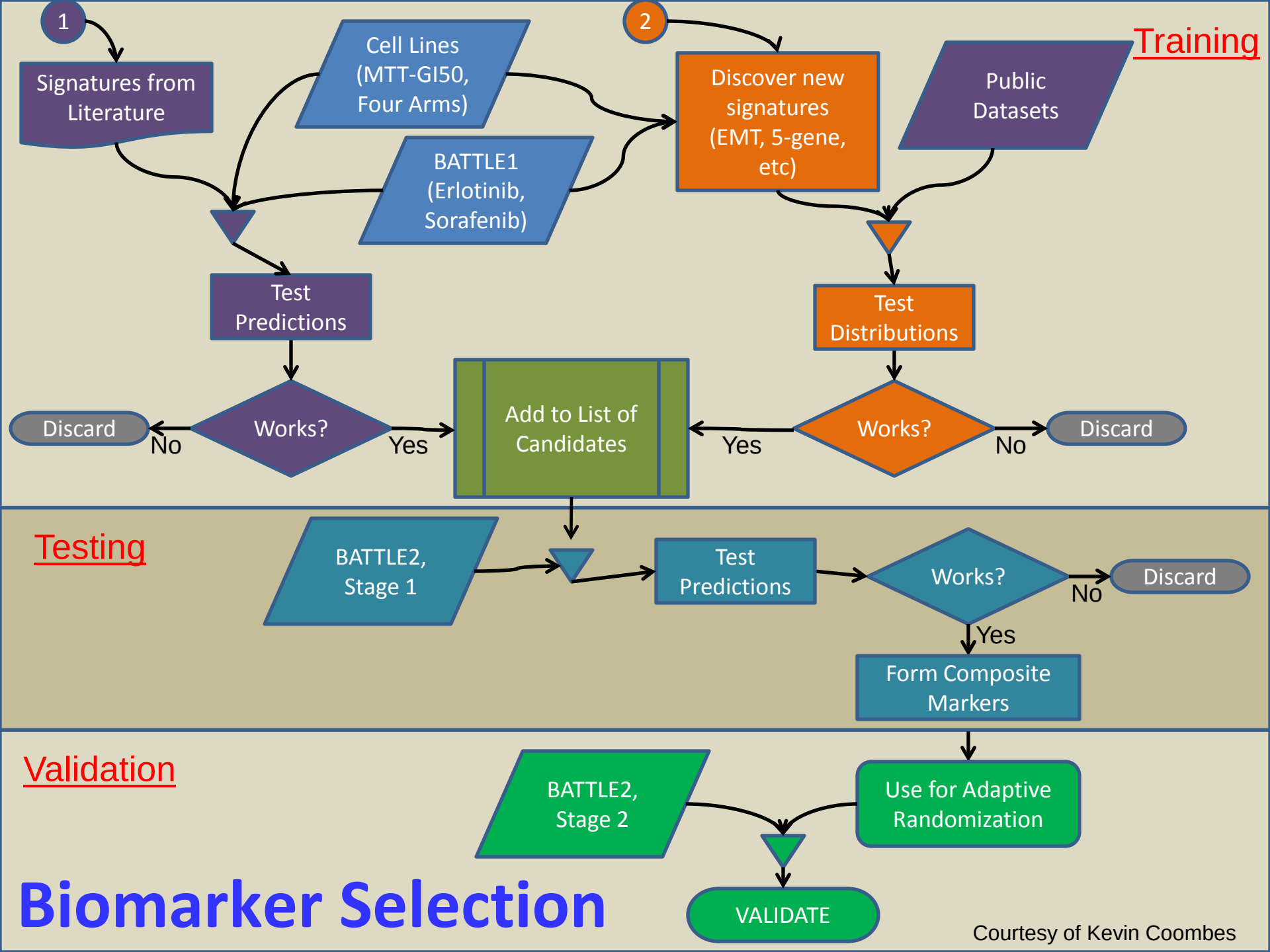
Primary endpoint: 8-week disease control
N = 400

# Methodology for Biomarker selection

***Training (Pre-BATTLE-2):*** From cell line, BATTLE-1 and other available data, derive predictive markers for the 8-week disease control for the 4 arms in BATTLE-2. Select 10-15 leading candidate markers.

***Testing (Stage 1 of BATTLE-2):*** Assess predictive strength for these markers using the Stage 1 of the BATTLE-2 data. Perform further variable selection and verification. Expect 5 markers will remain (1 prognostic and 4 predictive markers) after variable selection. Build the predictive model.

***Validation (Stage 2 of BATTLE-2):*** Applied adaptive randomization using the predictive model. Test treatment efficacy and validate the predictive markers at the end the study.


1
Signatures from Literature
Cell Lines (MTT-GI50, Four Arms)
BATTLE1 (Erlotinib, Sorafenib)
2
Discover new signatures (EMT, 5-gene, etc)
Public Datasets
Training
Test Predictions
Test Distributions
Discard
No
Works?
Yes
Add to List of Candidates
Yes
Works?
No
Discard
Testing
BATTLE2, Stage 1
Test Predictions
Works?
No
Discard
Yes
Form Composite Markers
Validation
BATTLE2, Stage 2
Use for Adaptive Randomization
VALIDATE
Biomarker Selection
Courtesy of Kevin Coombes

# Adaptive Learning (N-of-ALL Design)

- Build a comprehensive knowledge database with
  - Consistent and accurate curating of patient demographics, clinical characteristics, treatments, and outcomes
  - Frequent and timely updates
- Apply statistical analysis to identify the effective marker-treatment pairs
  - Classification, machine learning
  - Prediction, validation
- Refine the model based on the updated outcome
  - Real time learning; Continuous learning
- E.g.: MD Anderson's APOLLO/IBM-Watson project
  - A cognitive computing system piloted in leukemia
  - An "adaptive learning environment" as part of its Moon Shots program.

# Discovery Platform versus Confirmatory Platform

- Early phase of drug developing is about *discovery* and *learning*.
- Due to the large number of tests, the overall false positive rate may be large.
- Results found in the discovery platform need to be validated in the confirmatory platform
  - Validation of treatment efficacy
  - Validation of predictive markers
- After narrowing down the biomarkers and treatments combination(s), confirmatory trials can be more focused with smaller sample size.
- ***Prospective and independent validation is the key***

# What Are the 3 Key Attributes for the Successful Development of Useful Biomarkers

- Validation
  - Validation
    - Validation

# Recent Advancements in Adaptive Trials

- Identify predictive marker(s) adaptively to enrich the study population
- Apply adaptive designs in
  - Adaptive randomization
  - Early stopping
  - Add/drop arms
- Using Bayesian paradigm for flexible and efficient designs and adaptive learning
  - Adaptive design provides an ideal platform for learning – "We learn as we go."
  - Validation is the key!
    - For both drugs and markers:

      "*Many are Called, But Few Are Chosen*"

# Cancer Trials: Past, Present, and Future

- Past: large Phase III trials, long duration, expensive, high failure rate
  - All comers, non-targeted agents
  - Rush into Phase III too early
  - No or infrequent interim analyses
- Present: biomarker integrated
  - Biopsy required, biomarker-based patient selection and drug matching
  - Transit to more mechanism-based trials
- Future: ABC of smart trials
  - More adaptive designs in Phase I, II and Phase III trials
  - More biomarkers for study enrichment and guiding treatment selection
  - More combination trials