Behavior Sciences Biostatics Workshop, October 13, 2014

Concept, Design, and Implementation of Novel Clinical Trials

J. Jack Lee, Ph.D.
Department of Biostatistics

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

How well did we do in developing cancer drugs?

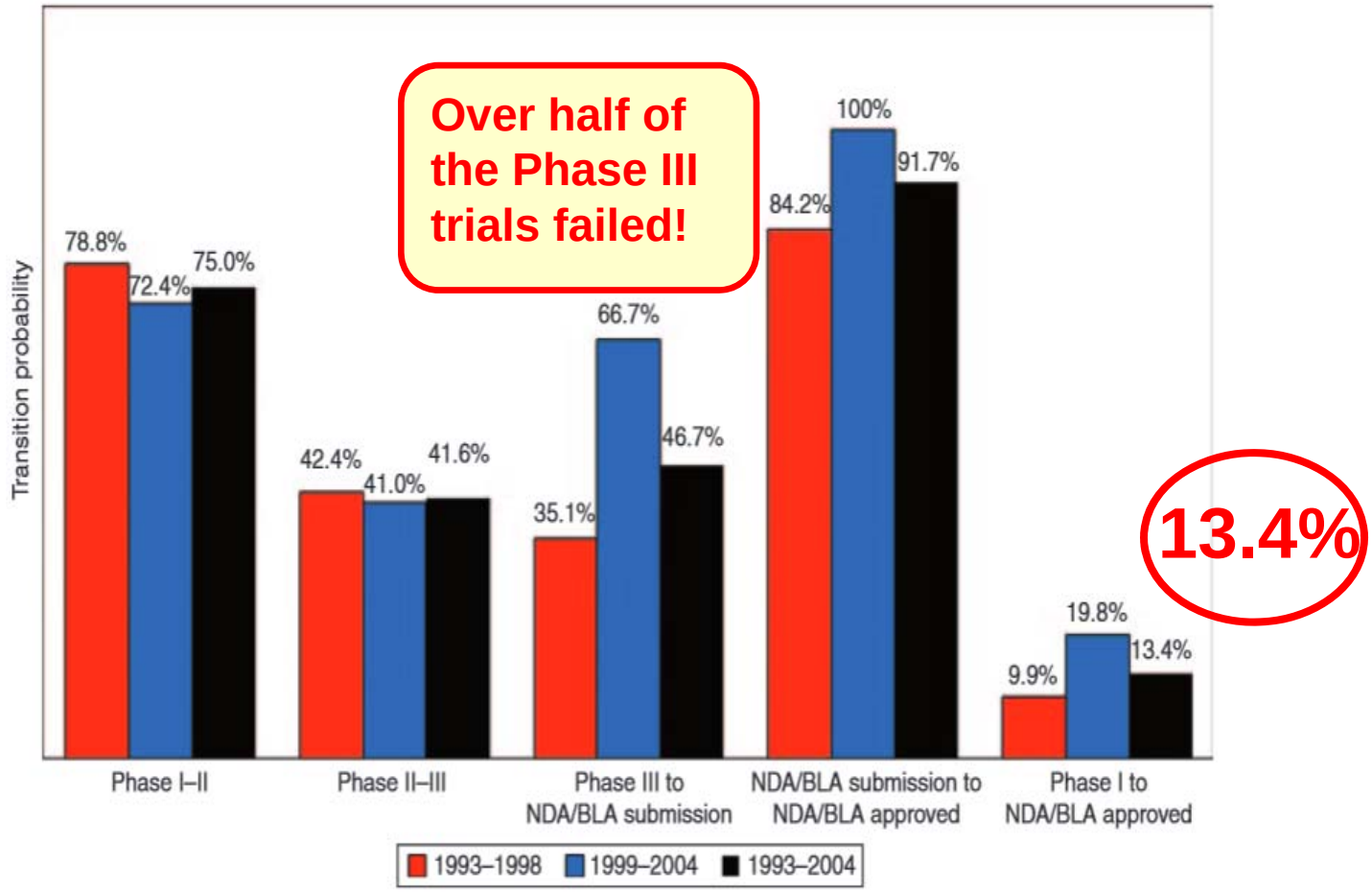


Figure 1 Phase transition probabilities for cancer compounds by period of first clinical testing. NDA/BLA, New Drug Application/Biologic License Application.

DiMasi, Clinical pharmacology & Therapeutics, 2013

Limitations of Traditional Clinical Trials

- Design depends on good estimation of unknown parameters and assumptions:
  - Treatment effect and its standard error (effect size)
  - Accrual rate
  - Patient heterogeneity
  - Known and unknown prognostic and predictive markers
- What if the design assumptions are wrong?
  - Mid-trial correction?
- Conduct is rigid
  - No interim analyses – bad !
  - Few, fixed interim analysis (number/time) helps but hard to accommodate unplanned interim analysis
  - Typically, patients are equally randomized.

How Can We Do Better?

- 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.
- Identify prognostic and predictive markers.
- Apply adaptive designs, e.g. adaptive enrichment, adaptive randomization, adaptive marker selection & validation, predictive probability for early stopping for futility and efficacy, etc.
- Do smaller, more focused Phase III trials.
- Continue to learn and to adapt.

3 Primary Goals for Clinical Trials

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

Traditional Designs

Adaptive Designs

What Are Adaptive Designs?

Trials that use interim data to guide the study conduct

- 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 randomization in Phase II or Phase III trials
- Seamless phase I/II, II/III designs; combination studies
- Adaptive marker identification and validation
- Adaptive learning
  - Build a comprehensive knowledge database
  - Assign best treatment for each patient
  - Continuous updating of information; testing and validation of hypotheses

Why Adaptive?

- Clinical trial is a learning process.
- It makes sense to adjust the study conduct based on real-time learning during the trial.
- Can identify predictive marker(s) adaptively to enrich the study population
- Use 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:

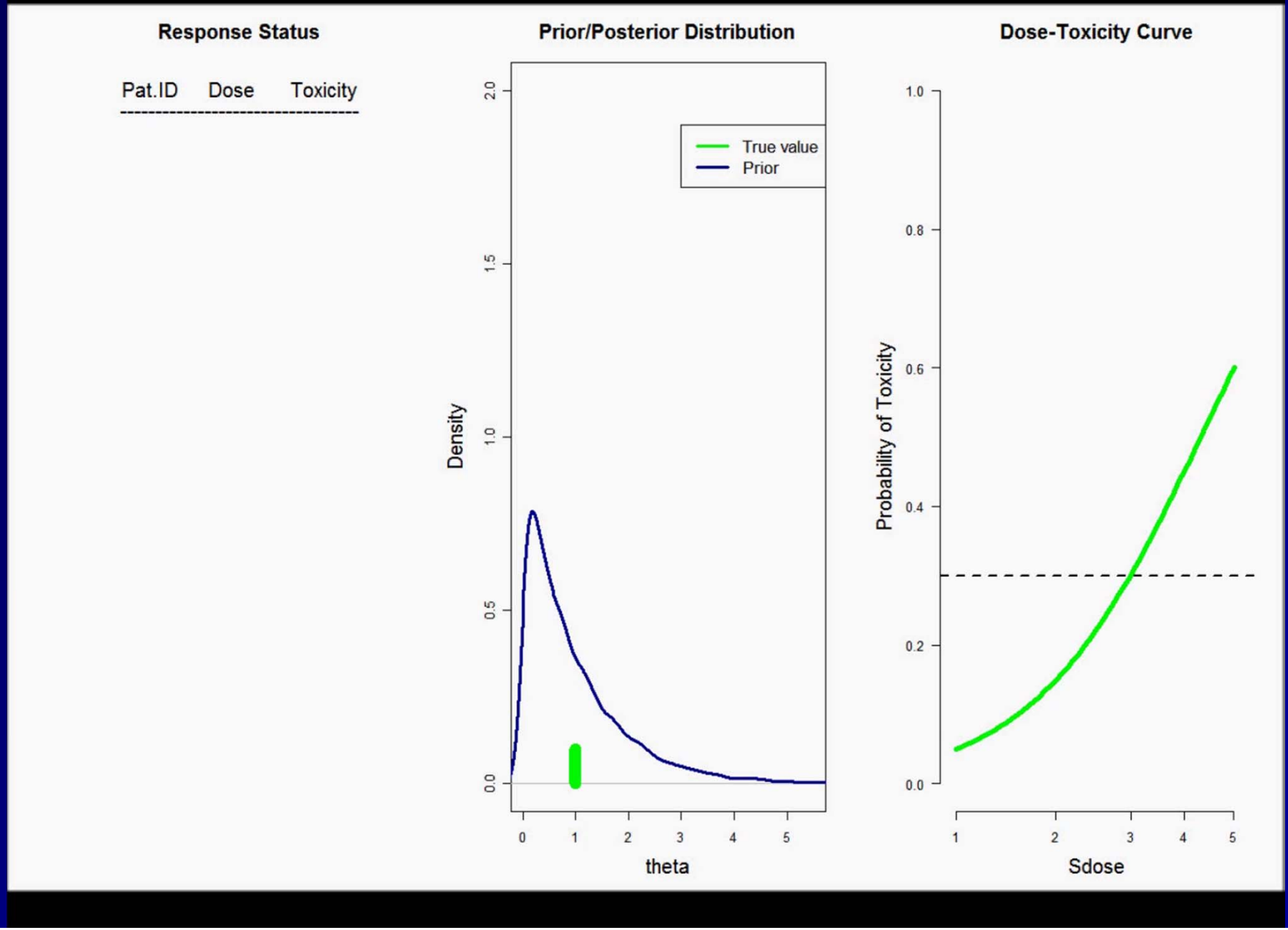
      "*Many are Called, But Few Are Chosen*"

Berry DA. Adaptive clinical trials in oncology. Nature Reviews Clinical Oncology, 2012.
Lee and Chu, Bayesian Clinical Trials in Action. Statistics in Medicine, 2012

Adaptive Dose Finding

- Continual reassessment method (CRM)
  - A model-based method for estimating the dose-toxicity curve
  - Estimate MTD based on the available data
  - Assign the next patient to the dose closest to the current estimate of the MTD
  - Rapid dose escalation
  - Simulations consistently show that the model-based method outperforms the 3+3 method in accurately identifying MTD
  - 3+3 design only use the information in the current dose to decide the next dose. It is a myopic and inefficient design
- Escalation with over-dose control (EWOC), Bayesian model averaging (BMA-CRM), TIme-To-Event (TITE-CRM)
- > 90 trials reported in the literature
- Translation of innovative designs such as Bayesian adaptive designs into trials is a long and slow process (Rogatko, JCO 2007; Chevret, SIM 2011)

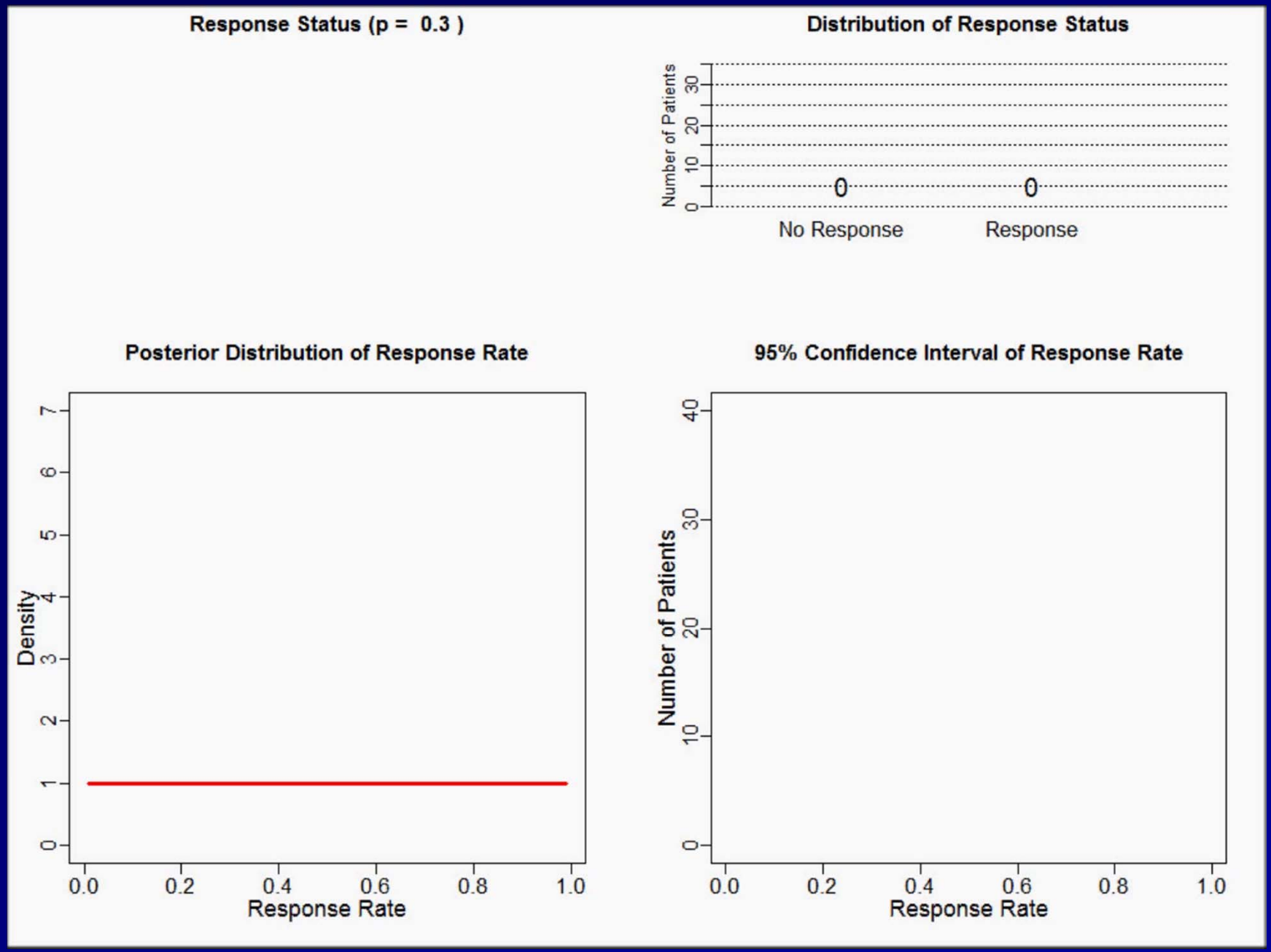
Video 1 – Continuous Reassessment Method



Adaptive Estimation of the Response Rate

- Suppose we developed a new targeted agent MDA01.
- What is the response rate in metastatic lung cancer patients?
- The response rate (θ) is an unknown parameter of interest.
- Conduct a clinical trial to collect ***data***.
- Estimate the unknown parameter θ from the ***data***
  - Point and Interval Estimation
  - Hypothesis testing
  - ***All inferences can be made from the posterior distribution of θ***

Video 2: Estimate the Response Rate



Phase IIA Design for A Single Treatment

- An efficacy screening trial
- Binary response endpoint with a response rate p.
- For testing H_0: $p \leq p_0$ vs. H_1: $p \geq p_1$
- Find the sample size to control
  - Type I (α) error
  - Type II (β) error
- Frequentist Designs
  - One-stage
  - Two-stage
    - Gehan's design
    - Simon's optimal and minimax designs
- Bayesian Design
  - Predictive probability design for continuous monitoring

Predictive Probability Design - Adaptive Stopping

- For testing H_0: $p \leq p_0$ vs. H_1: $p \geq p_1$
- Predictive Probability (PP):
  - The probability of a positive conclusion at the end of study should the current trend continue.
- At any given time of the trial, try to predict whether the drug is likely to work or not
  - If PP is very low, then, stop the trial for futility
  - Otherwise, continue to the end of study
  - No early stopping for efficacy

Lee JJ, Liu D. *Clin Trials* 2008; 5: 93–106.

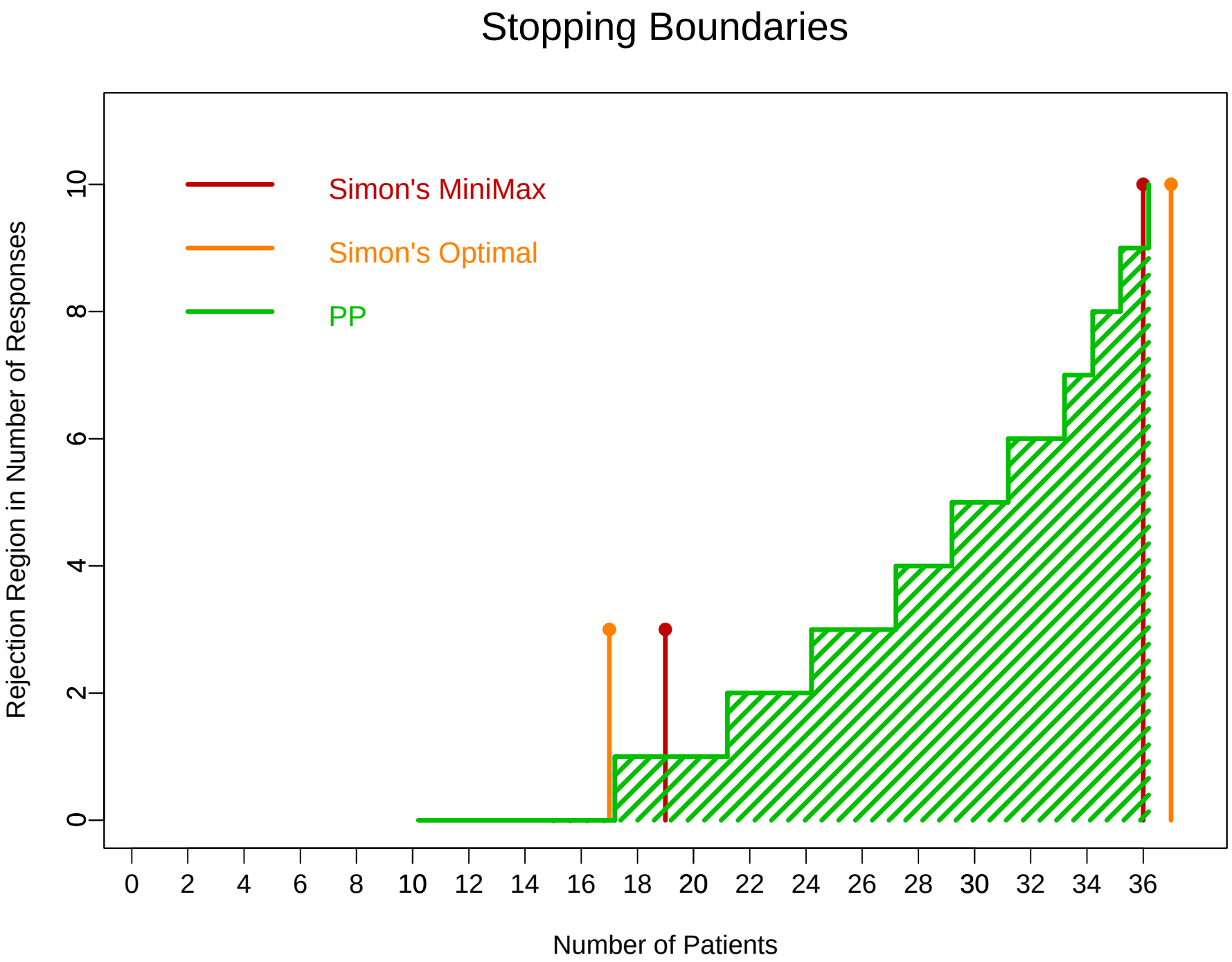
Stopping Boundaries for p_0=0.20, p_1=0.40, α= β= 0.10

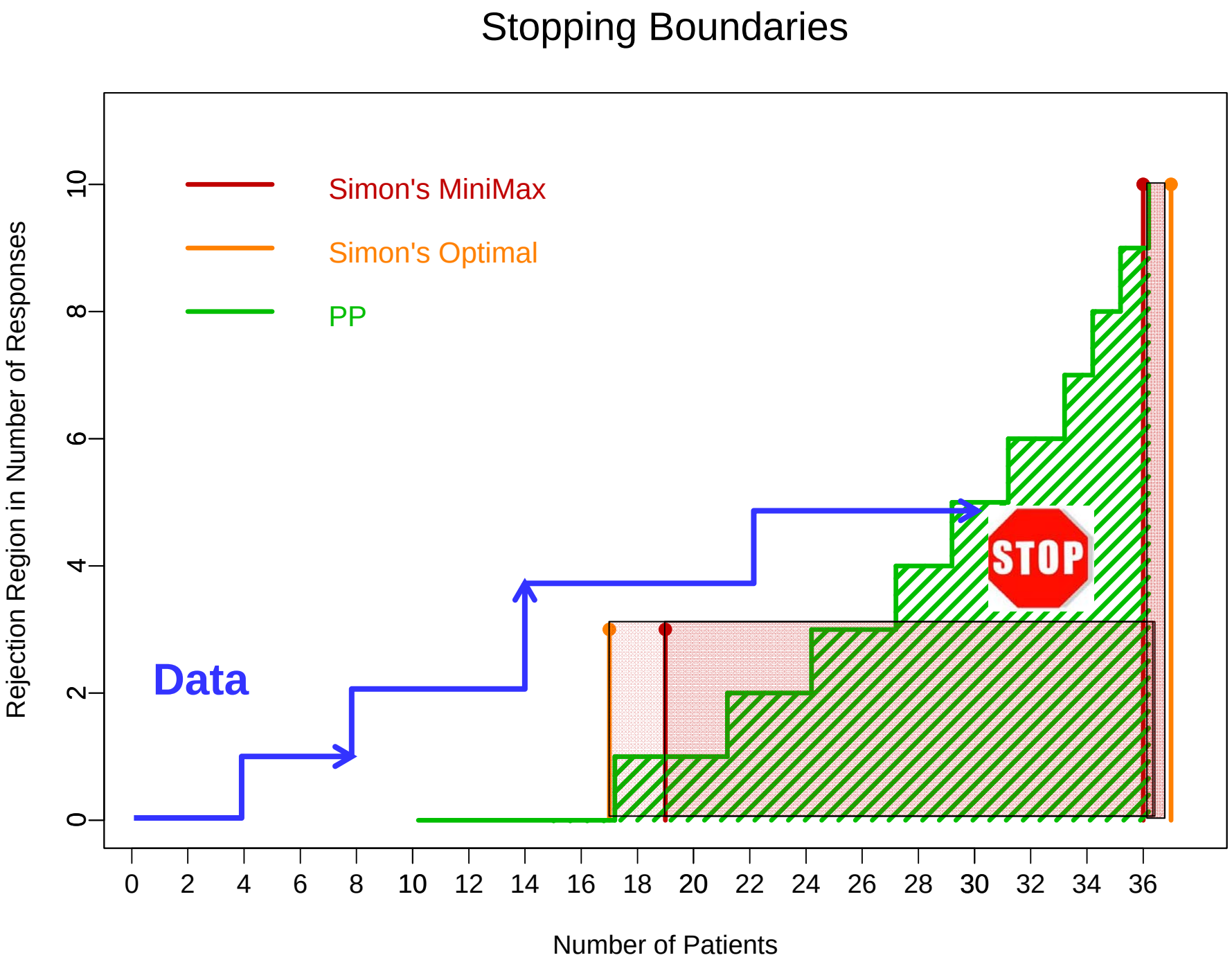
	Simon's Optimal		PP	
n	Rej Region	PET(p_0)	Rej Region	PET(p_0)
10			0	0.1074
17	3	0.55	1	0.0563
21			2	0.0663
24			3	0.0815
27			4	0.0843
29			5	0.1010
31			6	0.0996
33			7	0.0895
34			8	0.0946
35			9	0.0767
36	10	0.55	10	0.86

prior for
p = beta(0.2,0.8)
θ_L=0.001, θ_T =0.900
α = 0.088
β = 0.094
E(N | p_0) = 27.67
PET(p_0) = 0.86

Simon's MiniMax:
α = 0.086
β = 0.098
E(N | p_0) = 28.26
PET(p_0) = 0.46

Simon's Optimal:
α = 0.095
β = 0.097
E(N | p_0) = 26.02
PET(p_0) = 0.55


Stopping Boundaries
Simon's MiniMax
Simon's Optimal
PP
Rejection Region in Number of Responses
0
2
4
6
8
10
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
Number of Patients

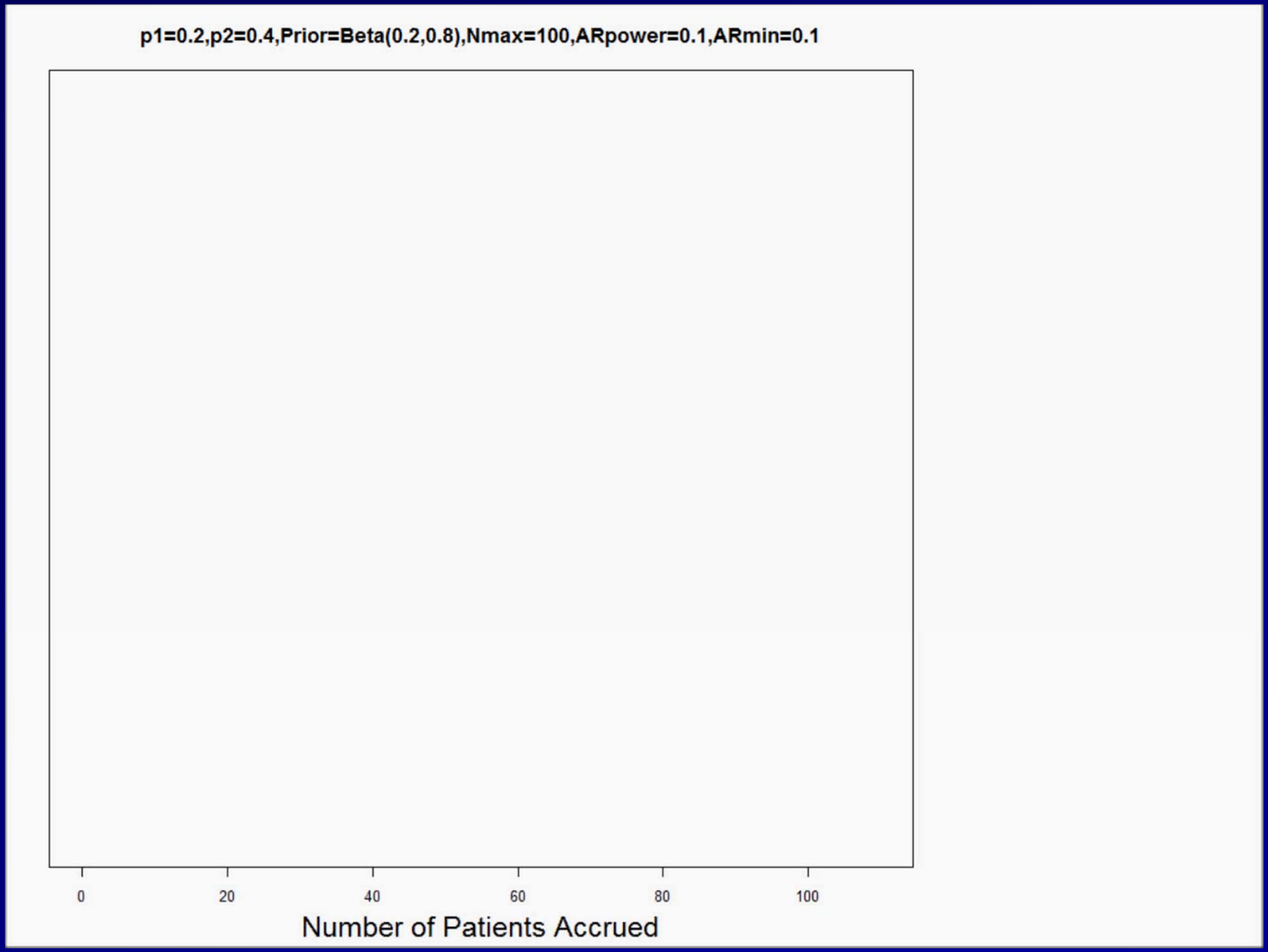

Stopping Boundaries
Simon's MiniMax
Simon's Optimal
PP
Data
STOP
Rejection Region in Number of Responses
Number of Patients
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36

Adaptive Randomization

- Traditional designs randomize patients equally to treatments via equal randomization (ER)
  - Simple: 1:1 for two-arm trials; 1:1:1 for three-arm trials
  - Consistent to the "clinically equipoise" principle.
  - Maximize statistical power (collective ethics)
- Outcome adaptive randomization (AR)
  - Assigning more patients to the better arm based on the observed data; Treat patients better in the trial (individual ethics)
  - Imbalance causes loss of statistical power
  - Study accrual may be faster
- AR has substantial benefit over ER when
  - the efficacy difference between treatments is large
  - Outside trial population is small, e.g., rare disease, and there is an effective treatment

Lee, Chen, and Yin, Worth adaptive? (CCR, 2012)

Video 3: Adaptive Randomization: P_1=0.2, P_2=0.4



Bayesian AR with Predictive Probability

- Start with ER for initial learning
- Switch to AR to assign more patients to the better treatment
- Test treatment efficacy by computing the predictive probability
  - If PP is very large, stop the trial for efficacy
  - If PP is very small, stop the trial for futility
- Continue until reaching early stopping criteria or N_{max}
- Make a final decision on treatment efficacy

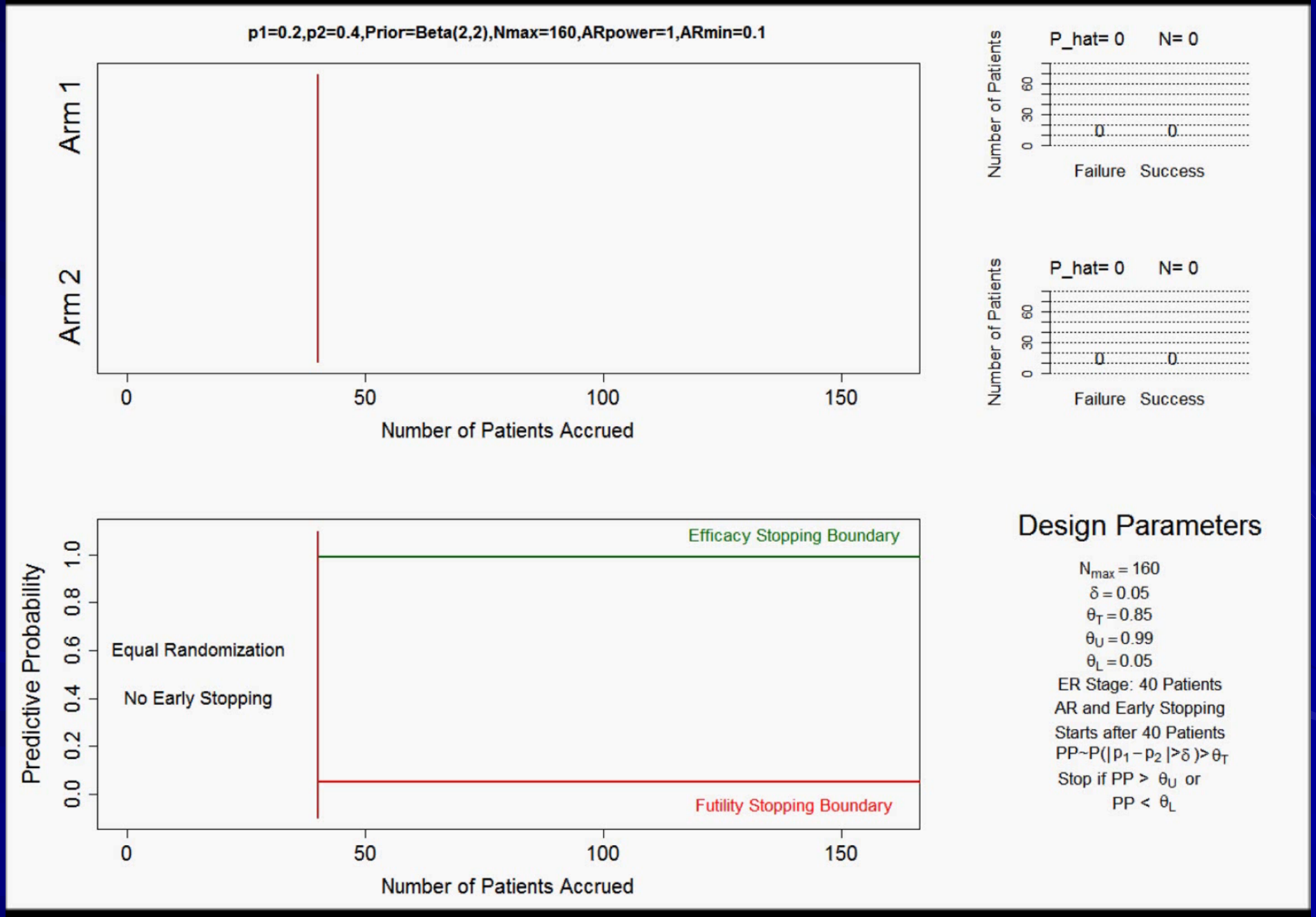
Korn and Freidlin. Outcome-Adaptive Randomization: Is It Useful? *JCO* 2011

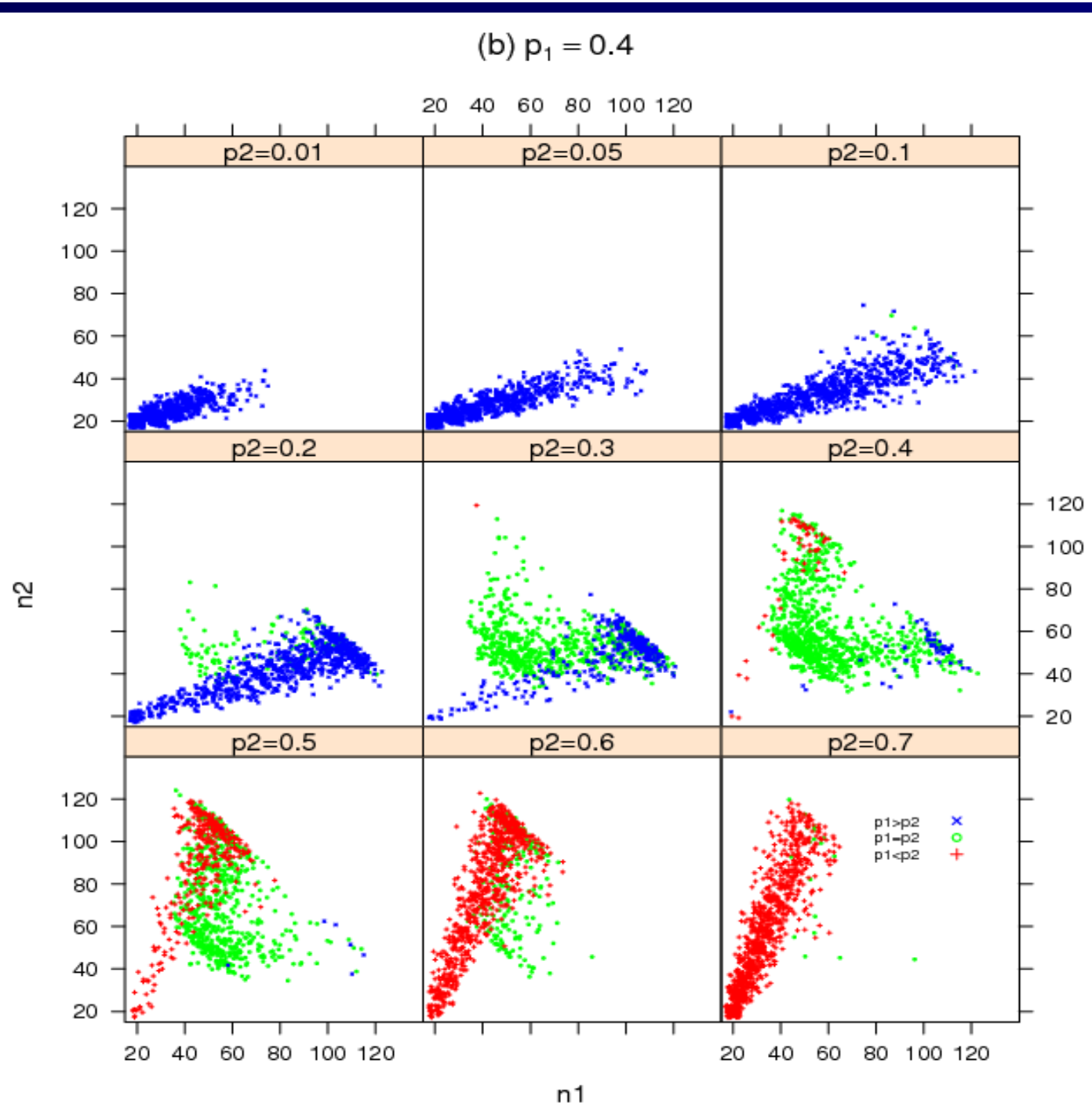
Berry DA. Adaptive Clinical Trials: The Promise and the Caution. *JCO* 2011

Lee, Chen, and Yin. Worth adapting? Revisiting the Usefulness of Outcome-Adaptive Randomization. *CCR*, 2012

Yin, Chen, and Lee. Phase II trial design with Bayesian adaptive randomization and predictive probability. *Applied Statistics (JRSS-C)*, 2012

Video 4: Adaptive Randomization /w Predictive Probability




(b) $p_1 = 0.4$
p2=0.01
p2=0.05
p2=0.1
p2=0.2
p2=0.3
p2=0.4
p2=0.5
p2=0.6
p2=0.7
n1
n2
p1>p2
p1=p2
p1<p2

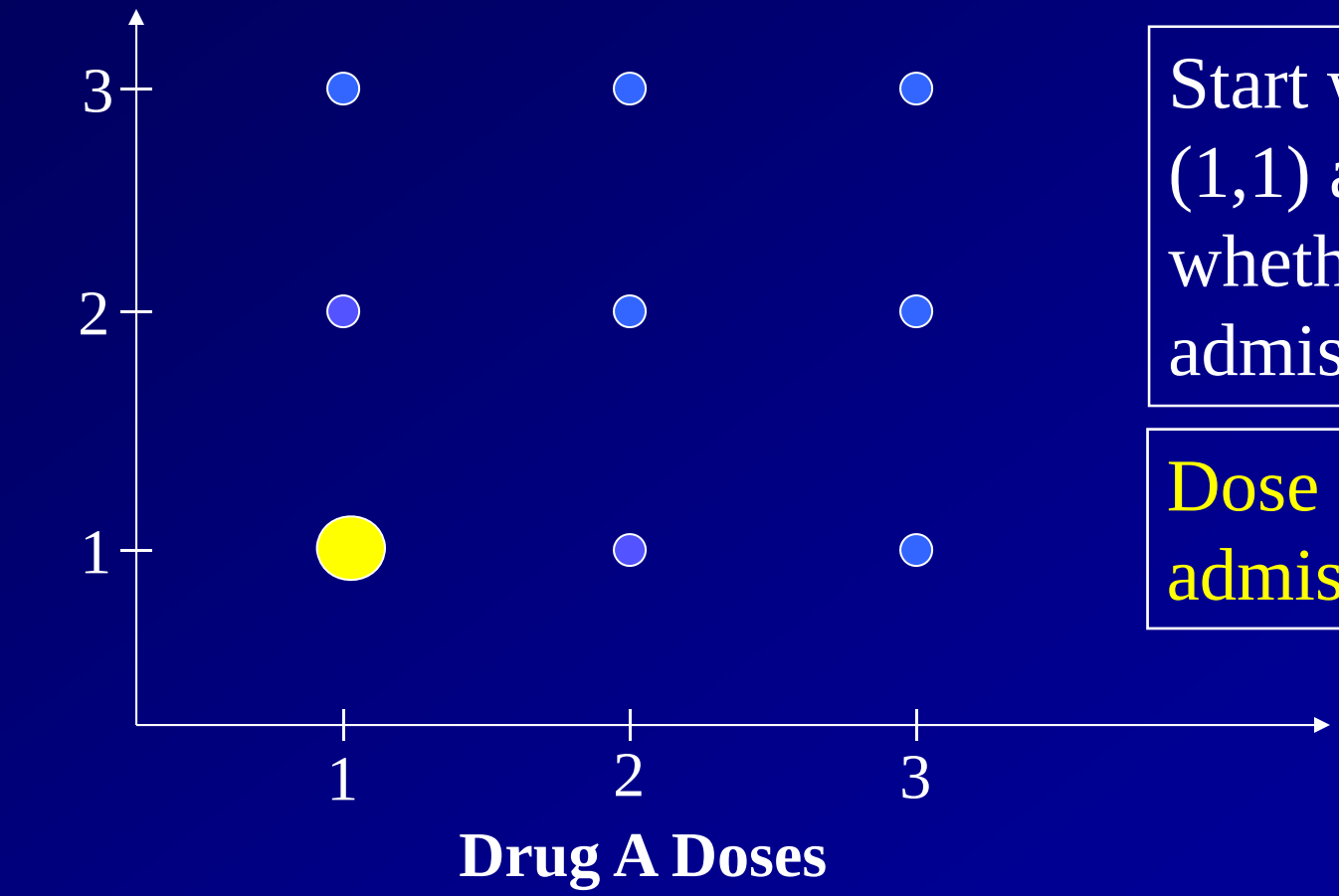
Promise & Challenge of Combination Therapy

- Promise
  - Overcome drug resistance induced by single agents.
  - Block the potential by-pass mechanisms in signaling pathways and induce synthetic lethality
  - Increase efficacy without increasing toxicity
- Challenge
  - 2 drugs, 3 drugs, 4 drugs, …?
  - Select dose of each drugs
  - 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

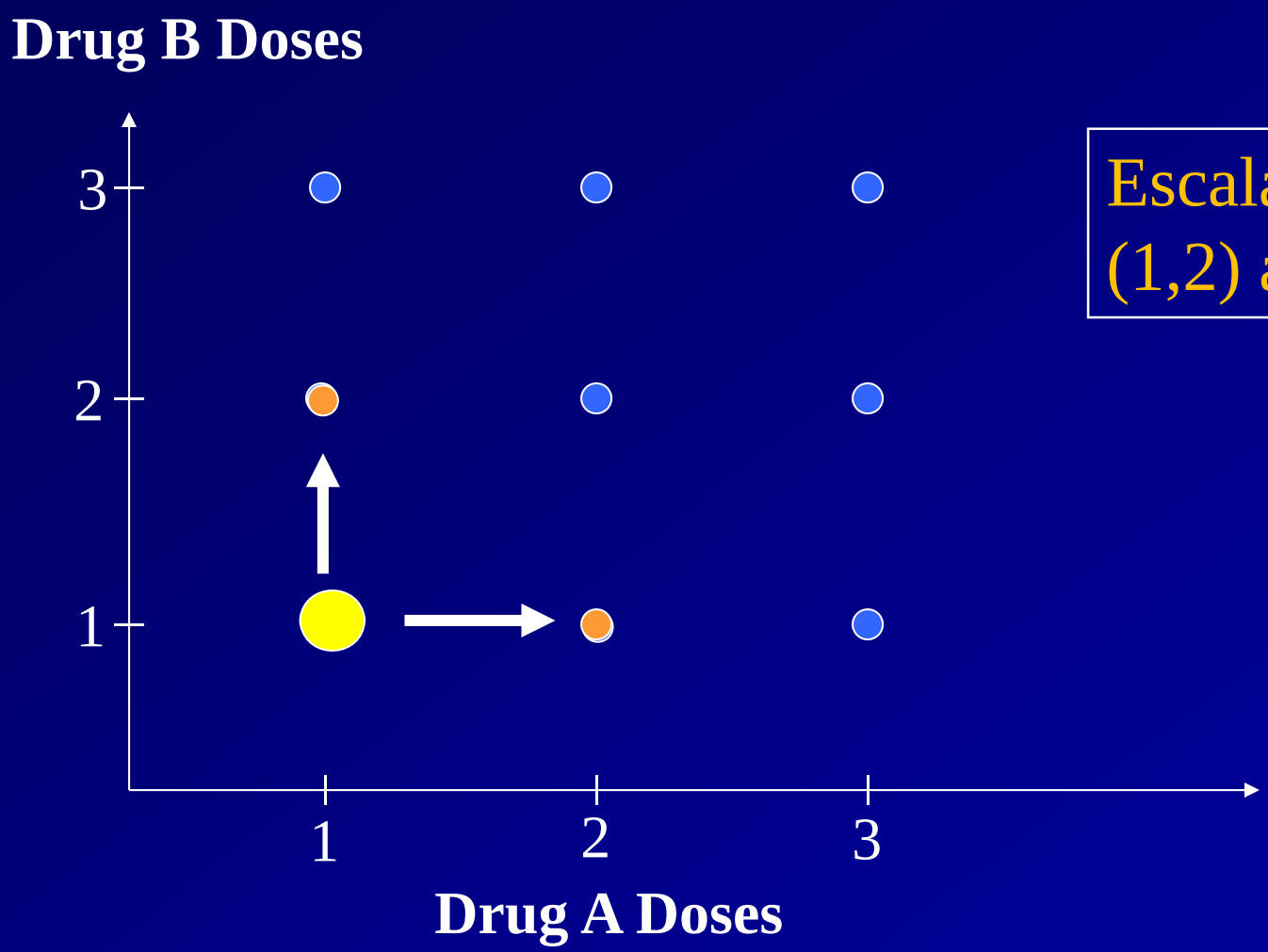
- Choose dose grid for single/combination treatments.
- Simultaneously evaluate toxicity and efficacy. Define doses with acceptable toxicity as "admissible doses."
- Start at the lowest dose. Then, move up the grid if the current doses are admissible.
- Adaptively randomize patients into all admissible 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.

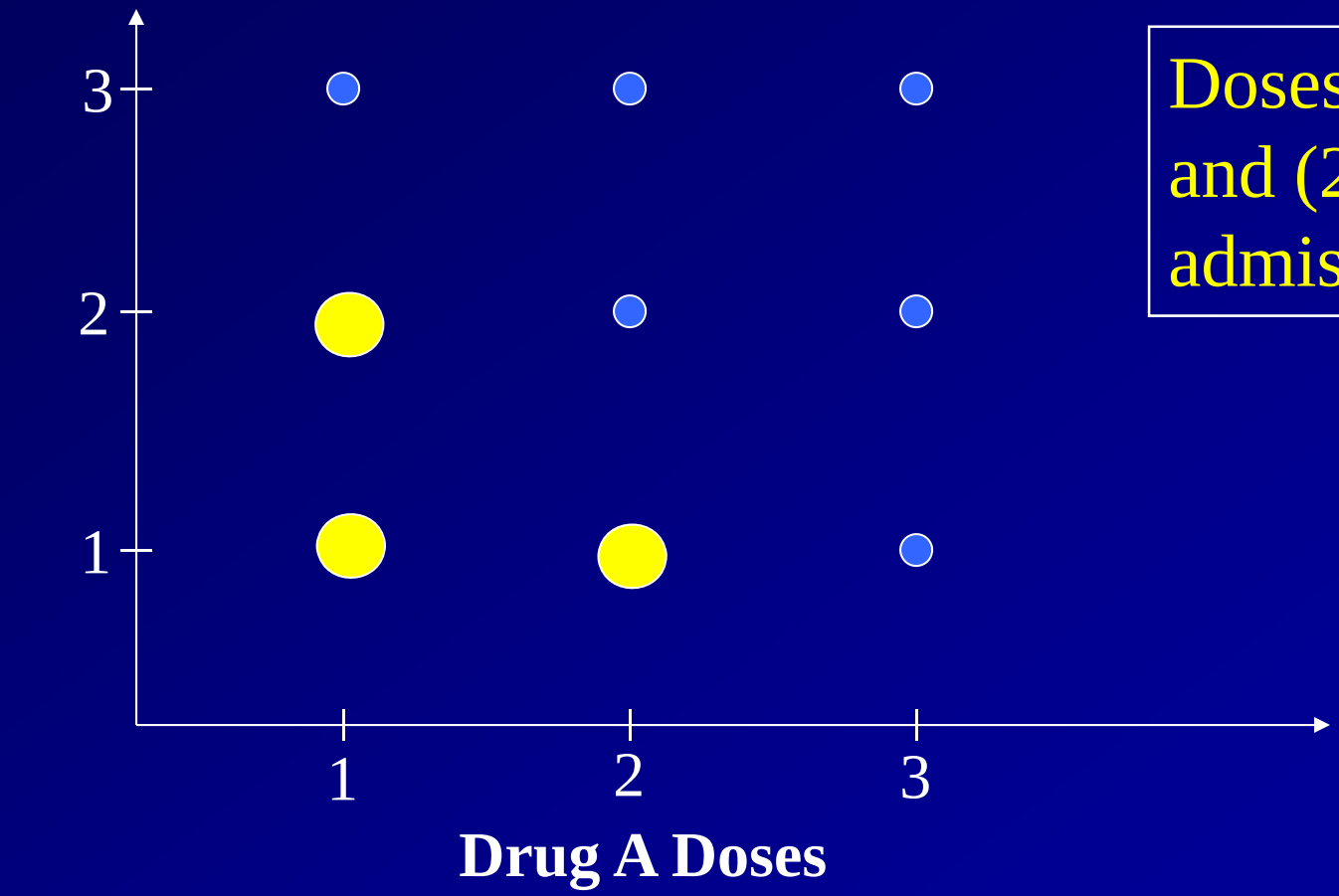


Start with dose (1,1) and check whether it is admissible or not

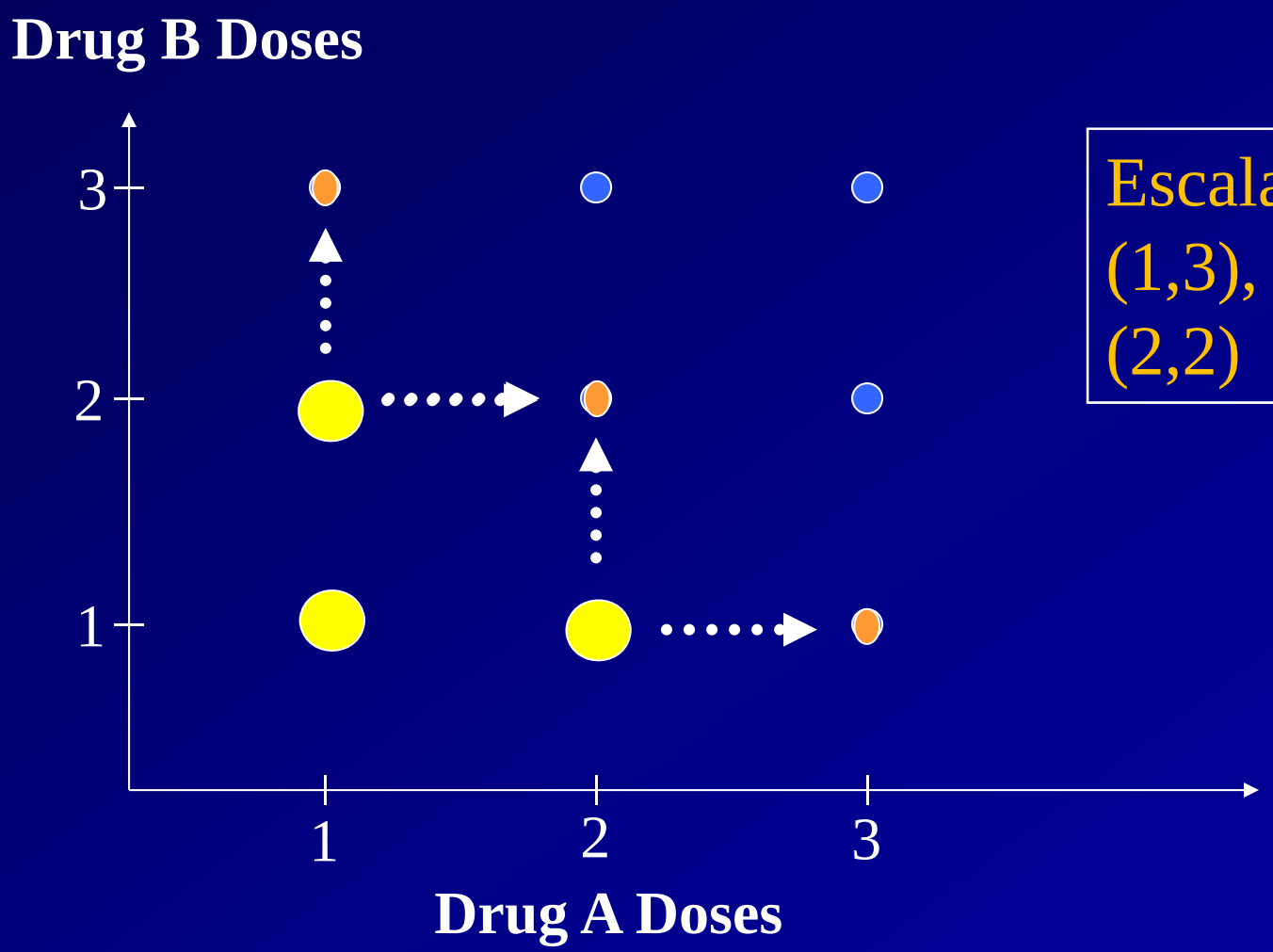
Dose (1,1) is admissible



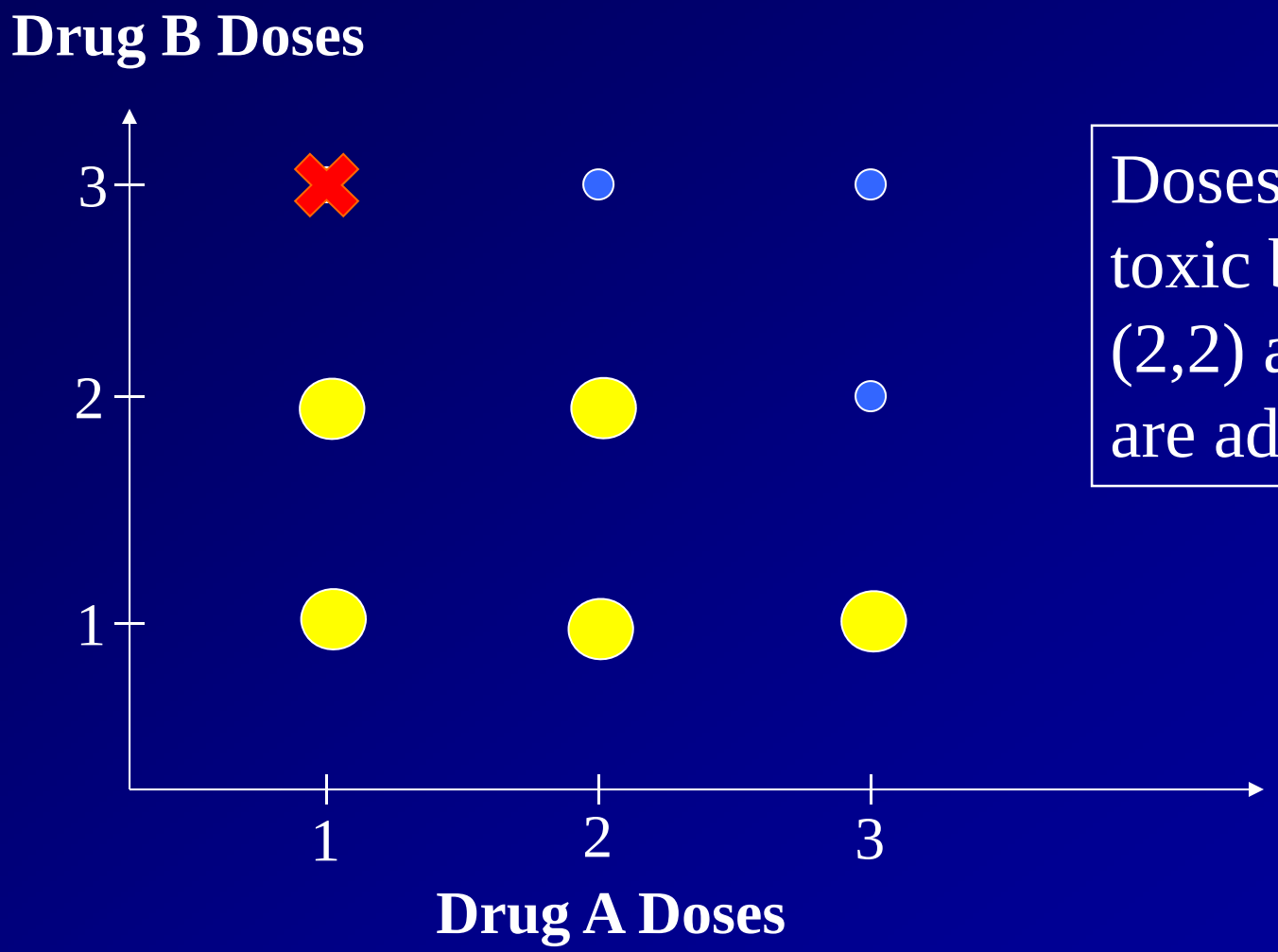
Escalate to doses (1,2) and (2,1)



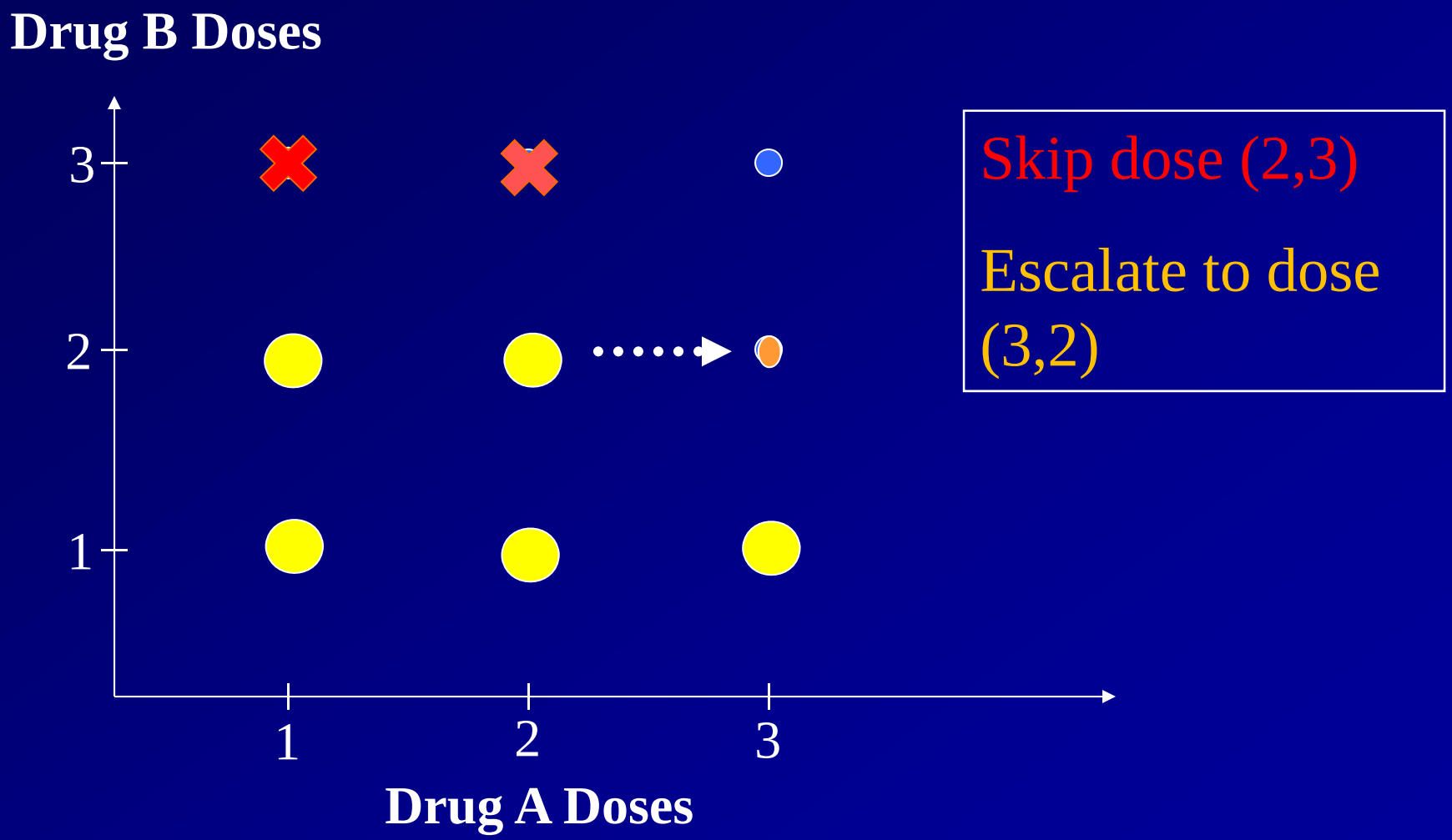
Doses (1,1), (1,2) and (2,1) are all admissible

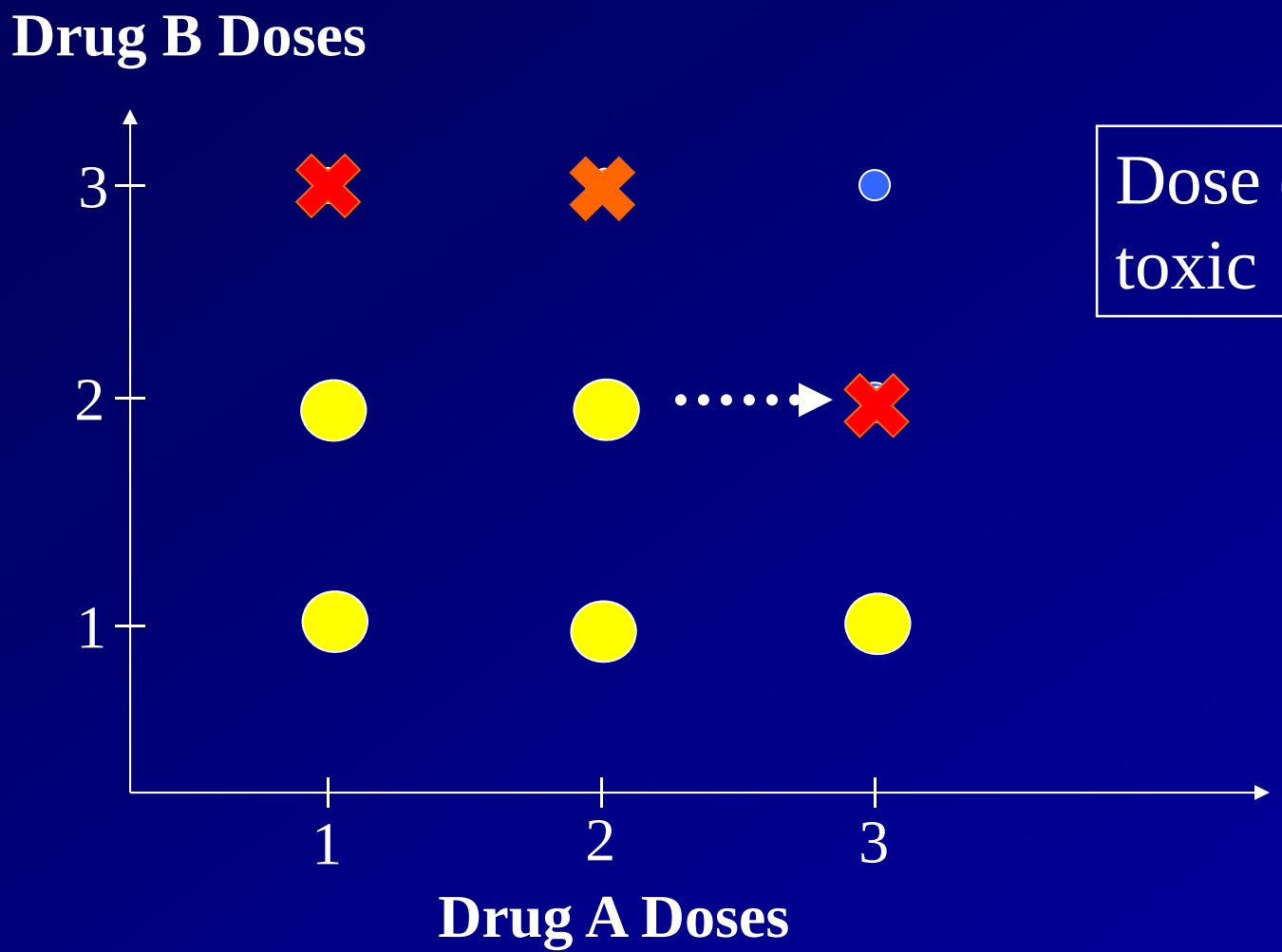


Escalate to doses (1,3), (3,1), and (2,2)

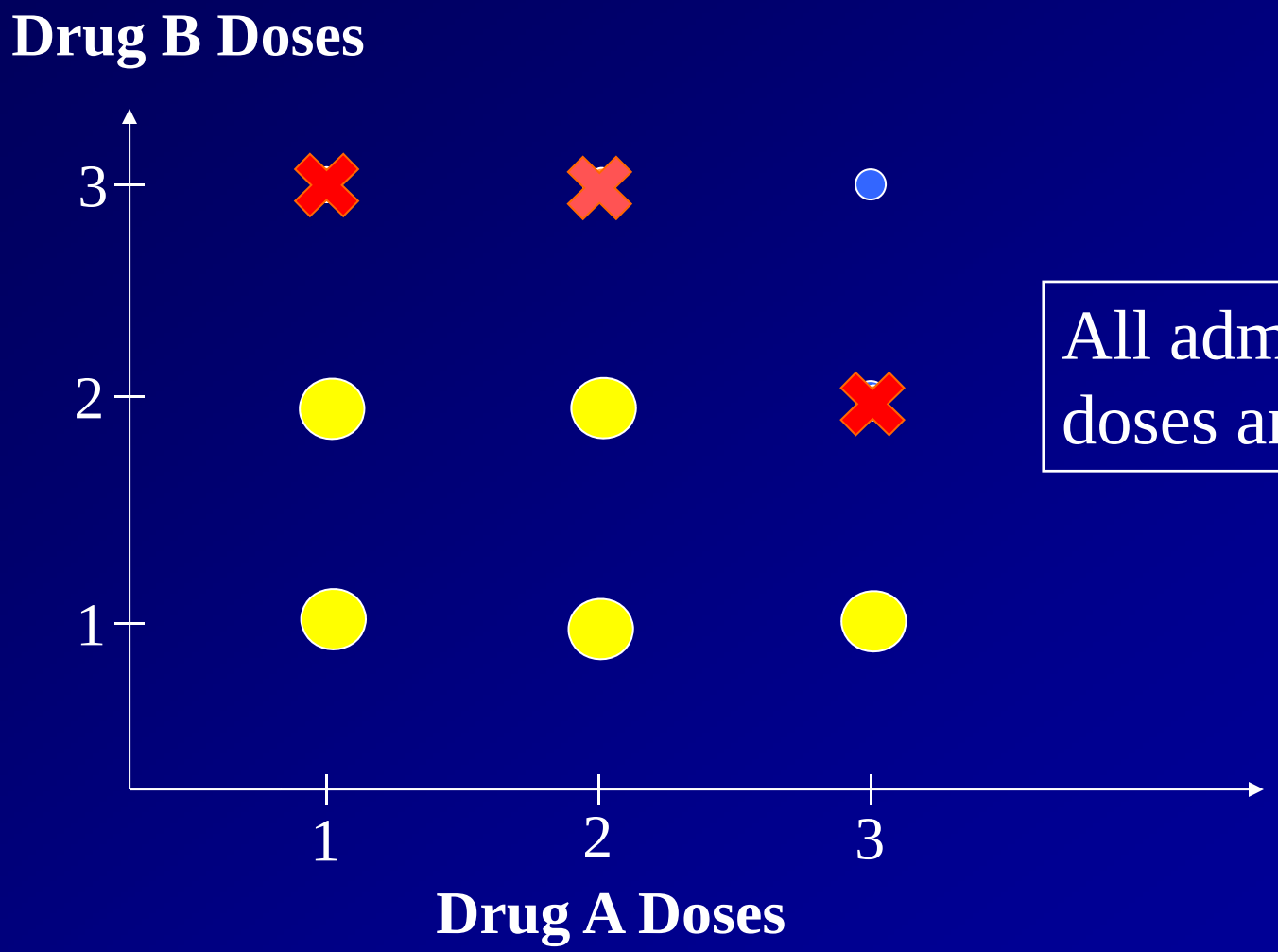


Doses (1,3) is too toxic but doses (2,2) and (3,1) are admissible

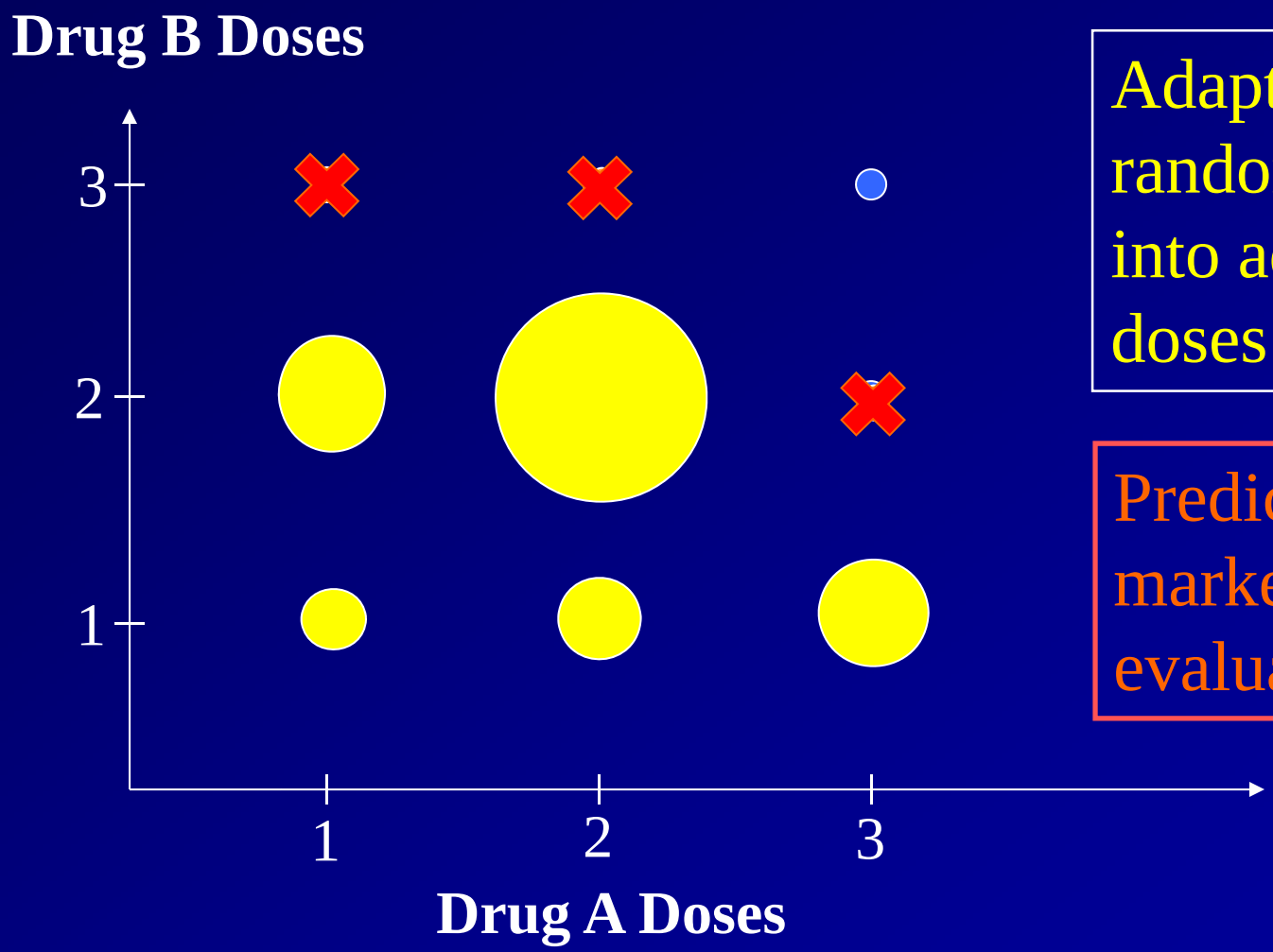

Drug B Doses
3
2
1
1
2
3
Drug A Doses
Skip dose (2,3)
Escalate to dose (3,2)



Dose (3,2) is too toxic



All admissible doses are identified



Adaptive randomizing pts into admissible doses

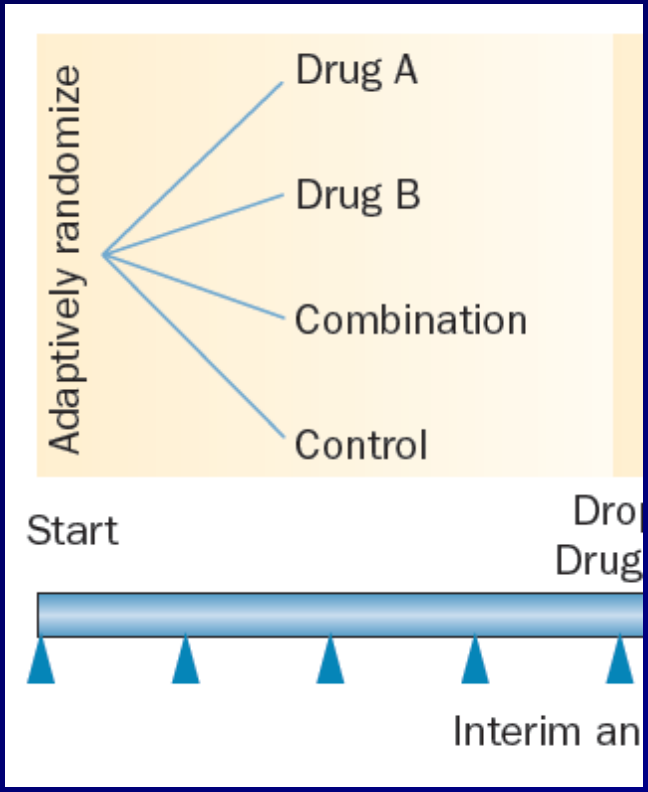
Predictive markers are evaluated

Seamless Phase II/III Design

- Start with a randomized Phase II trial with an active control (standard treatment) and several experimental arms with different treatments and/or doses
- Use a short-term endpoint in the Phase II part, e.g., ORR to inform the long-term endpoint, e.g. OS.
- Drop inefficacious arms
- Suspend accrual in the marker subgroups with inferior outcomes
- If at least one experimental arm is promising, roll into Phase III with one standard treatment and one or more selected experimental treatments. Use longer-term endpoint, e.g. OS.
- Information collected in the Phase II part is used in Phase III. No “white space” in trial conduct.

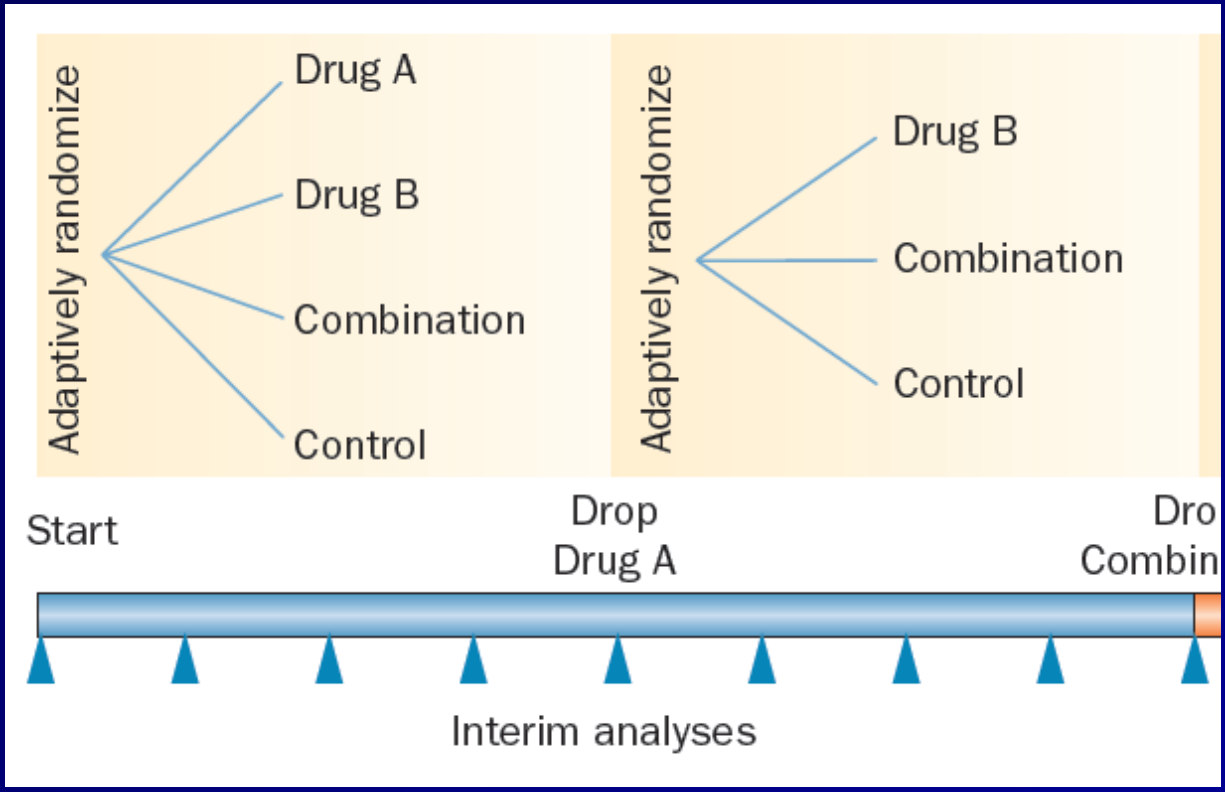
Inoue et al, Biometrics 2002; Bretz et al, Biometrical J 2006; Stallard, SIM 2010

Seamless Phase II-III Design



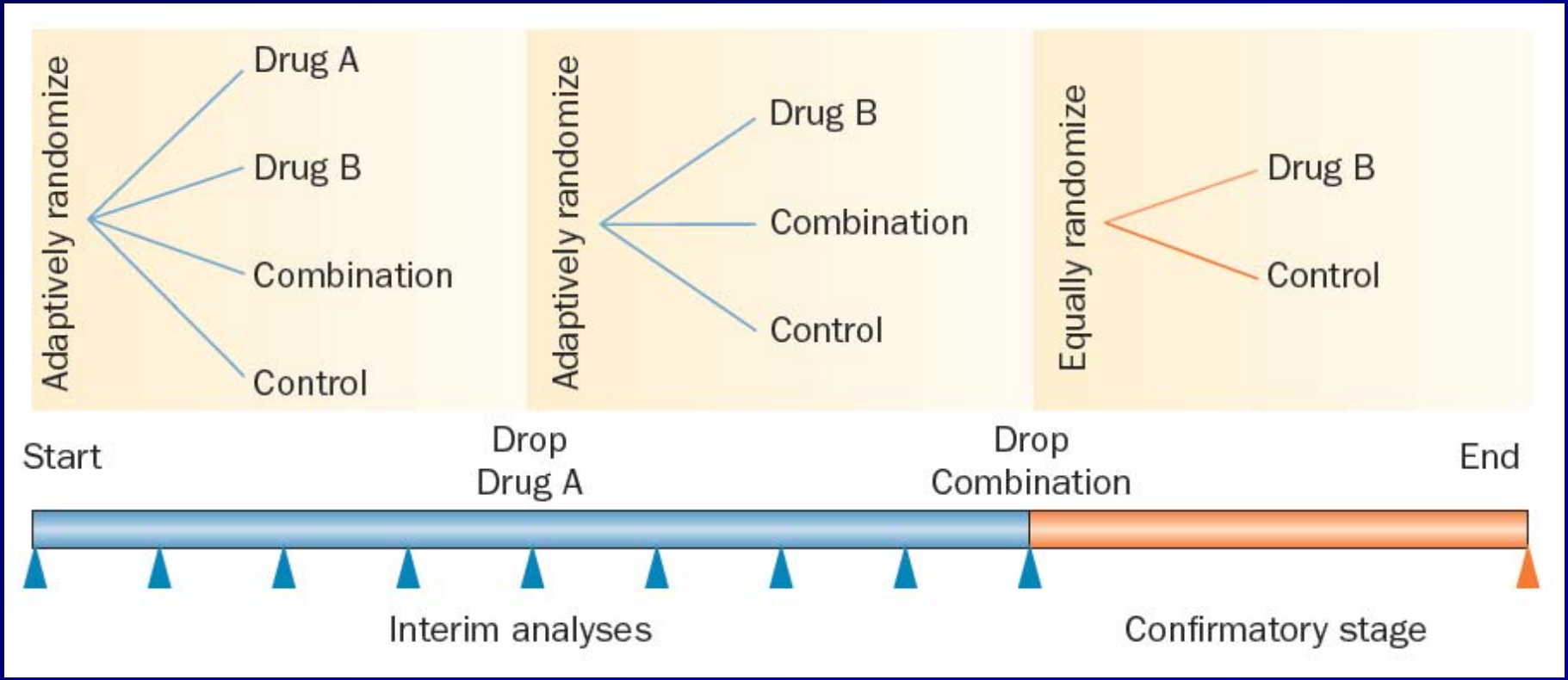
Berry, Nature Review Clinical Oncology, 2012

Seamless Phase II-III Design



Berry, Nature Review Clinical Oncology, 2012

Seamless Phase II-III Design

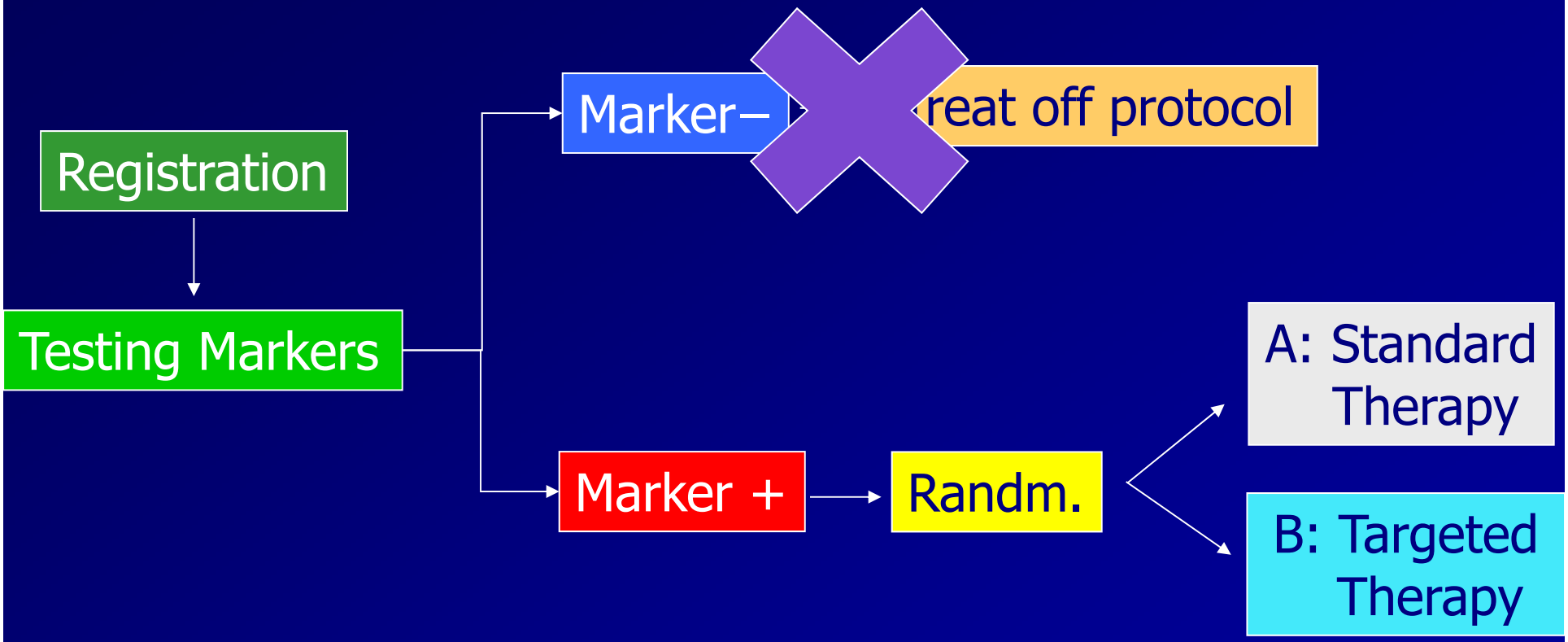


Berry, Nature Review Clinical Oncology, 2012

Biomarker Based Designs

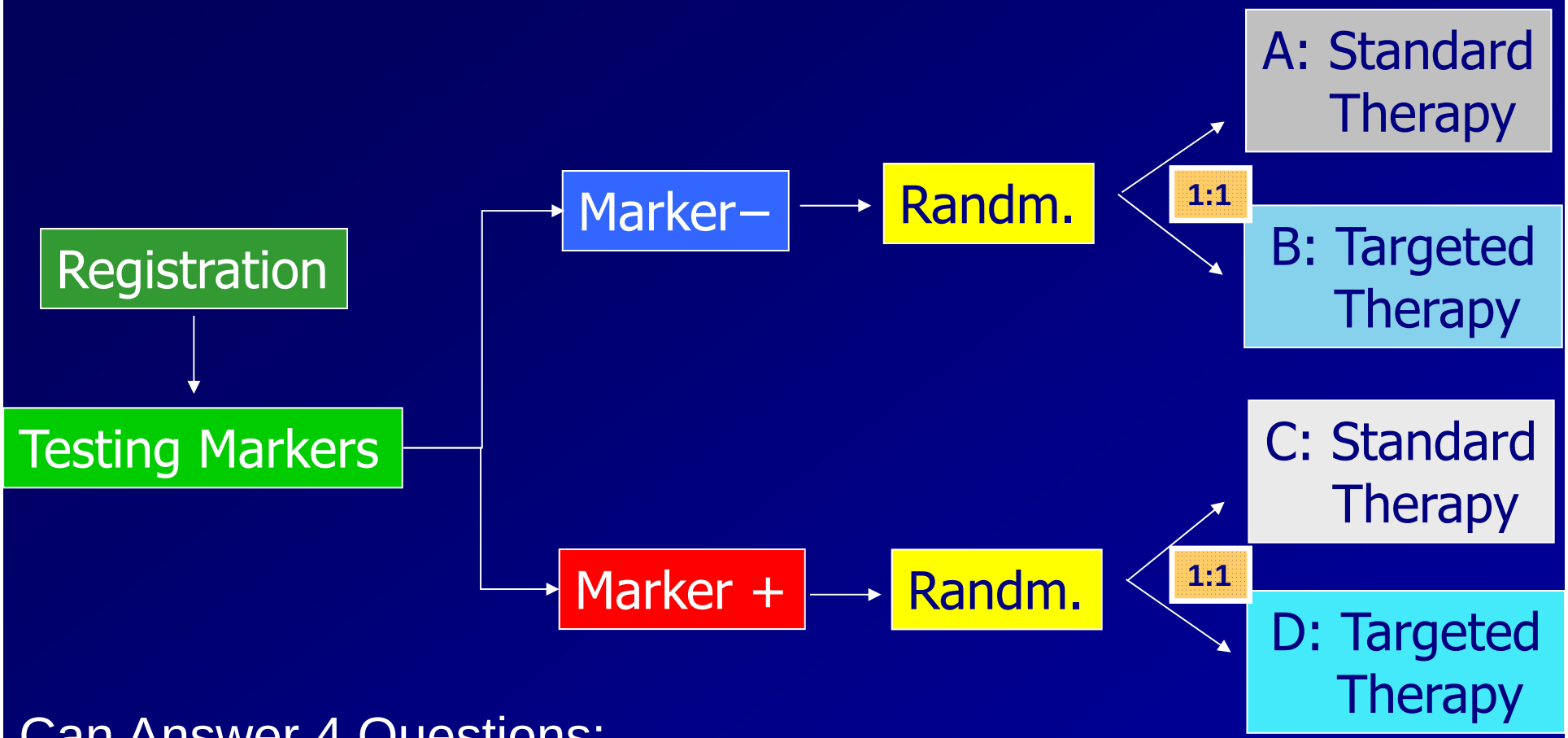
- Efficient target design
- Marker stratified design
- Adaptive enrichment design
- Bayesian adaptive randomized design
  - Outcome adaptive randomization
  - Early stopping for futility and/or efficacy
- BATTLE-1 and BATTLE-2 trials
  - Biomarker training (discovery), testing, and validation
- Multiple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

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

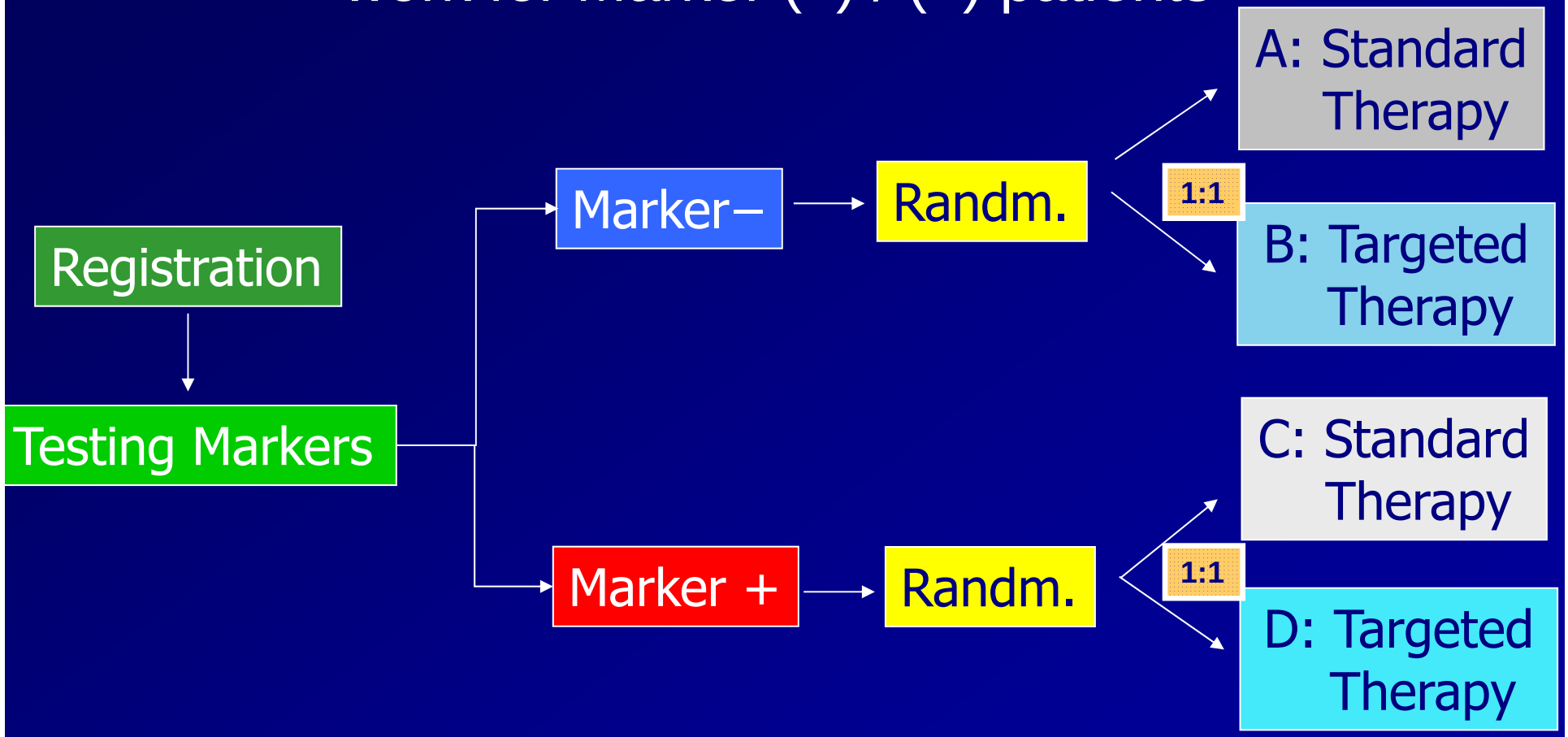


Can Answer 4 Questions:

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

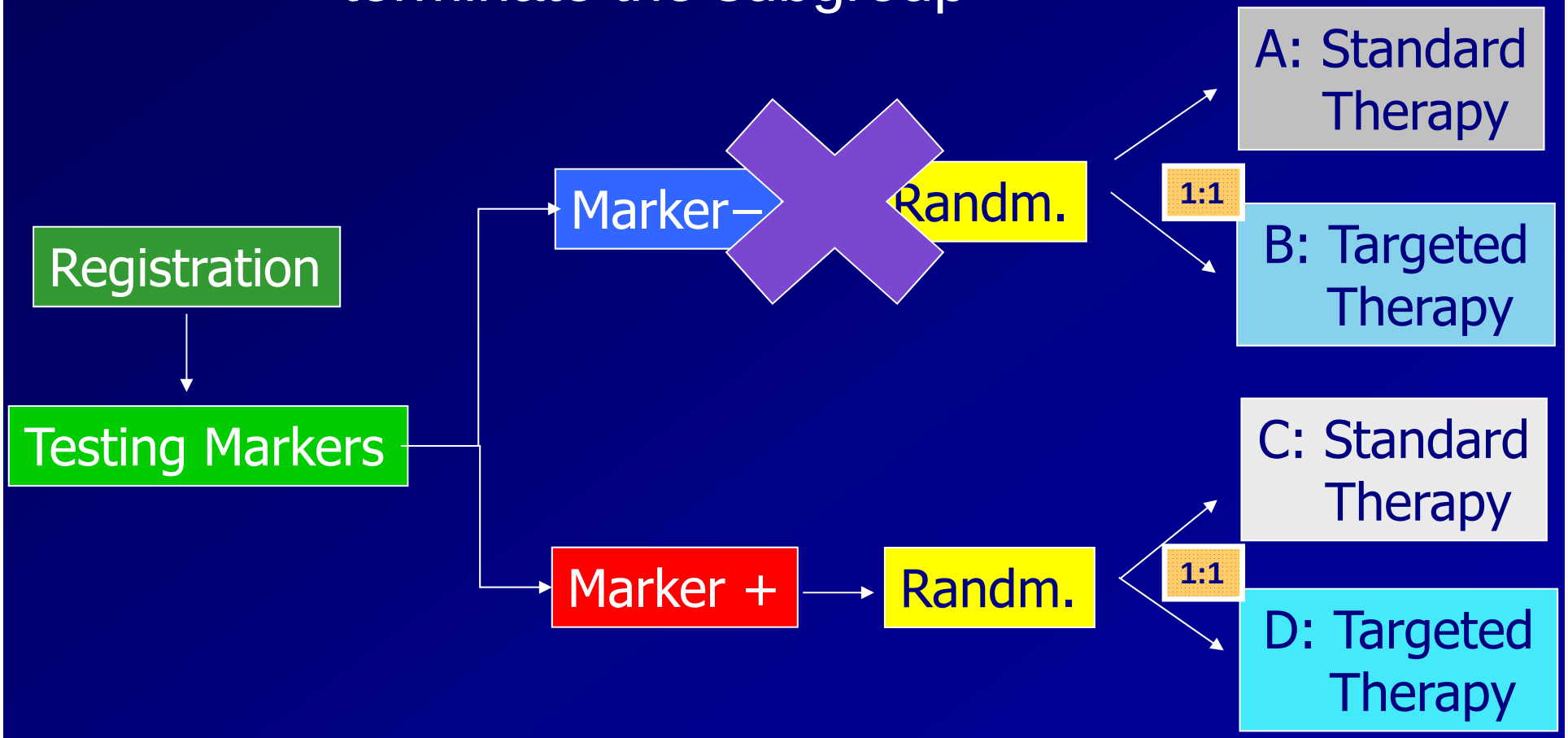
Stage 1 : Test whether targeted therapy work for Marker (–) / (+) patients



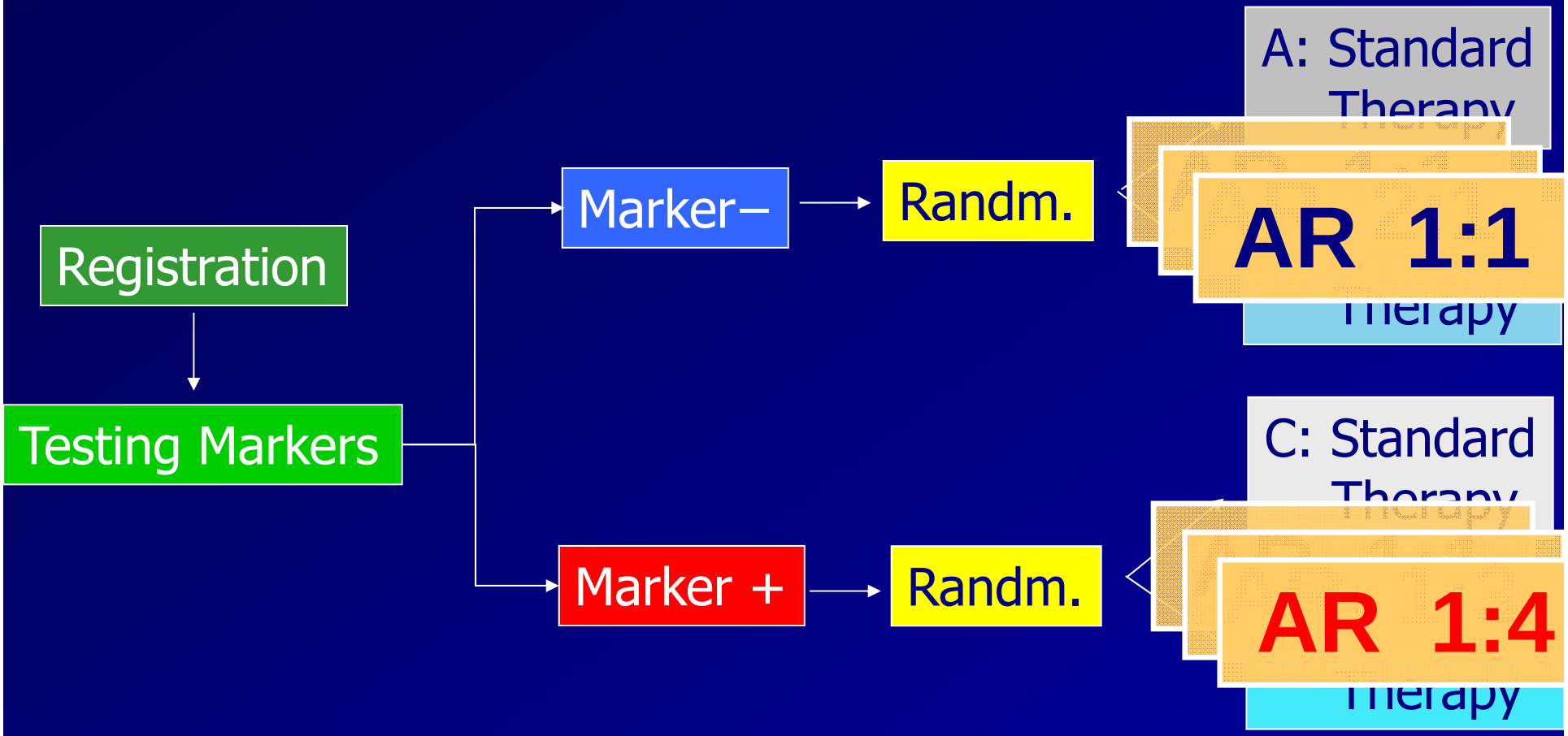
Wang and Hung, Contemporary Clinical Trials, 2013
Simon and Simon: Biostatistics, 2013

Adaptive Enrichment Design

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



Bayesian Adaptive Randomization Design



Similar to Marker Stratify 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)

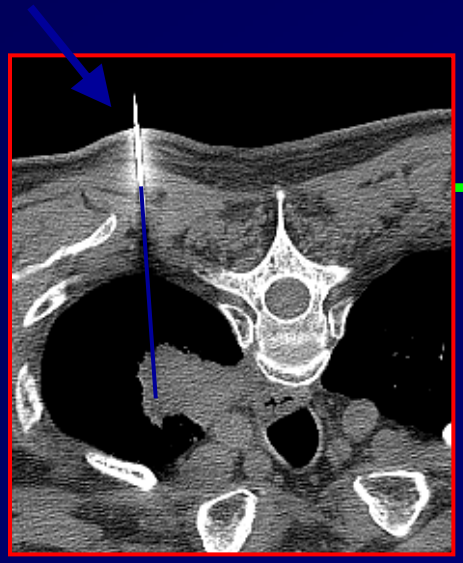
- Patient Population: Stage IV recurrent non-small cell lung cancer (NSCLC)
- Primary Endpoint: 8-week disease control rate (DCR)
- 4 Targeted treatments, 11 Biomarkers
- 200 evaluable patients
- Goal:
  - Test treatment efficacy
  - Test biomarker effect and their predictive roles to treatment
  - Treat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

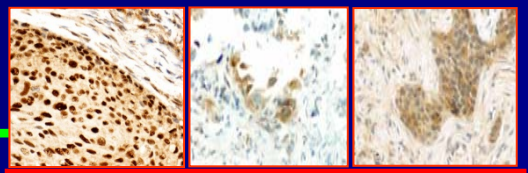
2. Kim ES, Herbst RS, Wistuba II, Lee JJ, et al, Hong WK. The BATTLE Trial: Personalizing Therapy for Lung Cancer. (*Cancer Discovery*, 2011)

BATTLE Schema

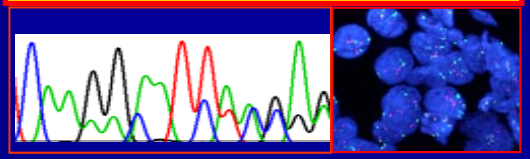
Umbrella Protocol



Core Biopsy



Biomarker Profile



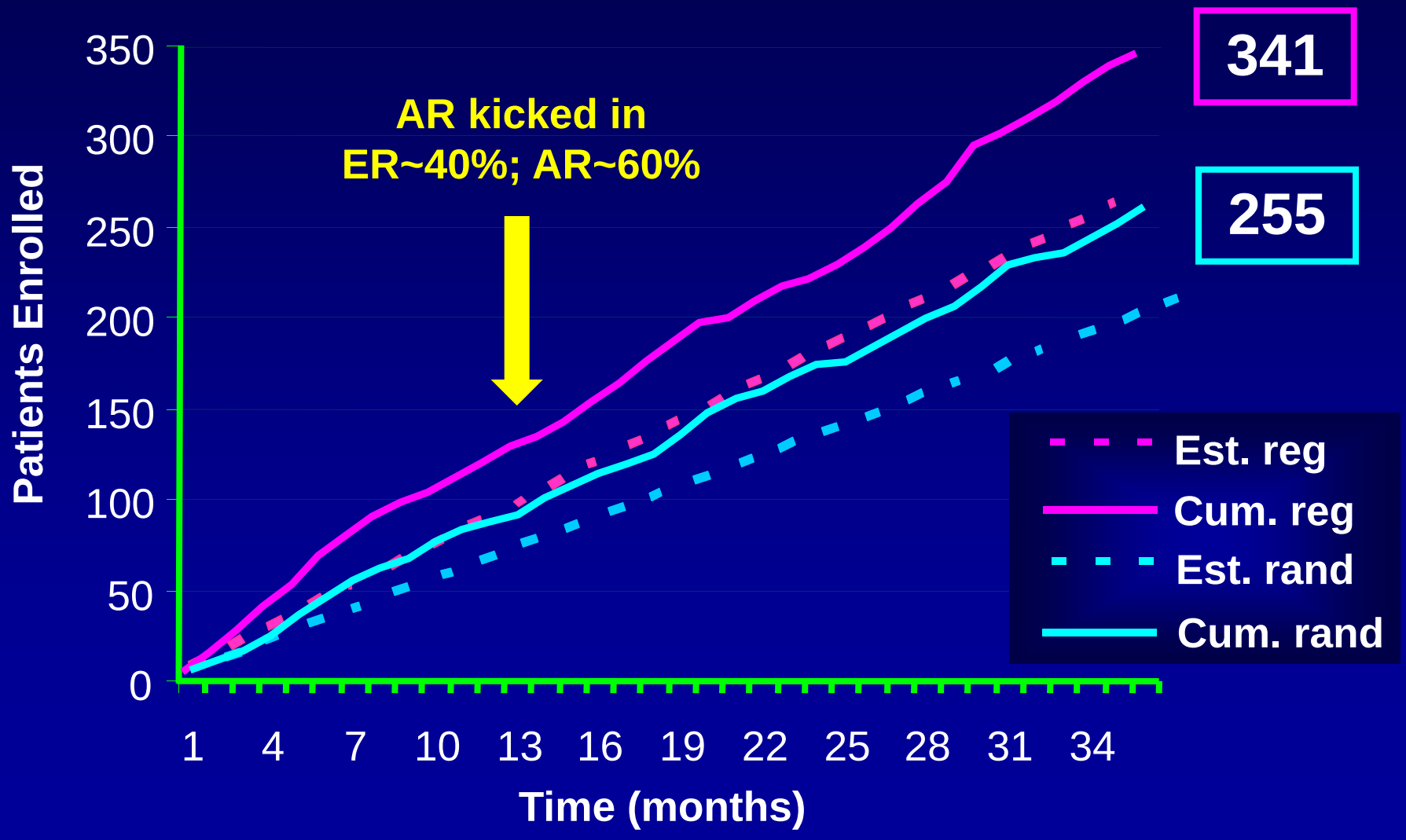
EGFR KRAS/BRAF
VEGF RXR/CyclinD1

Randomization:
Equal → Adaptive

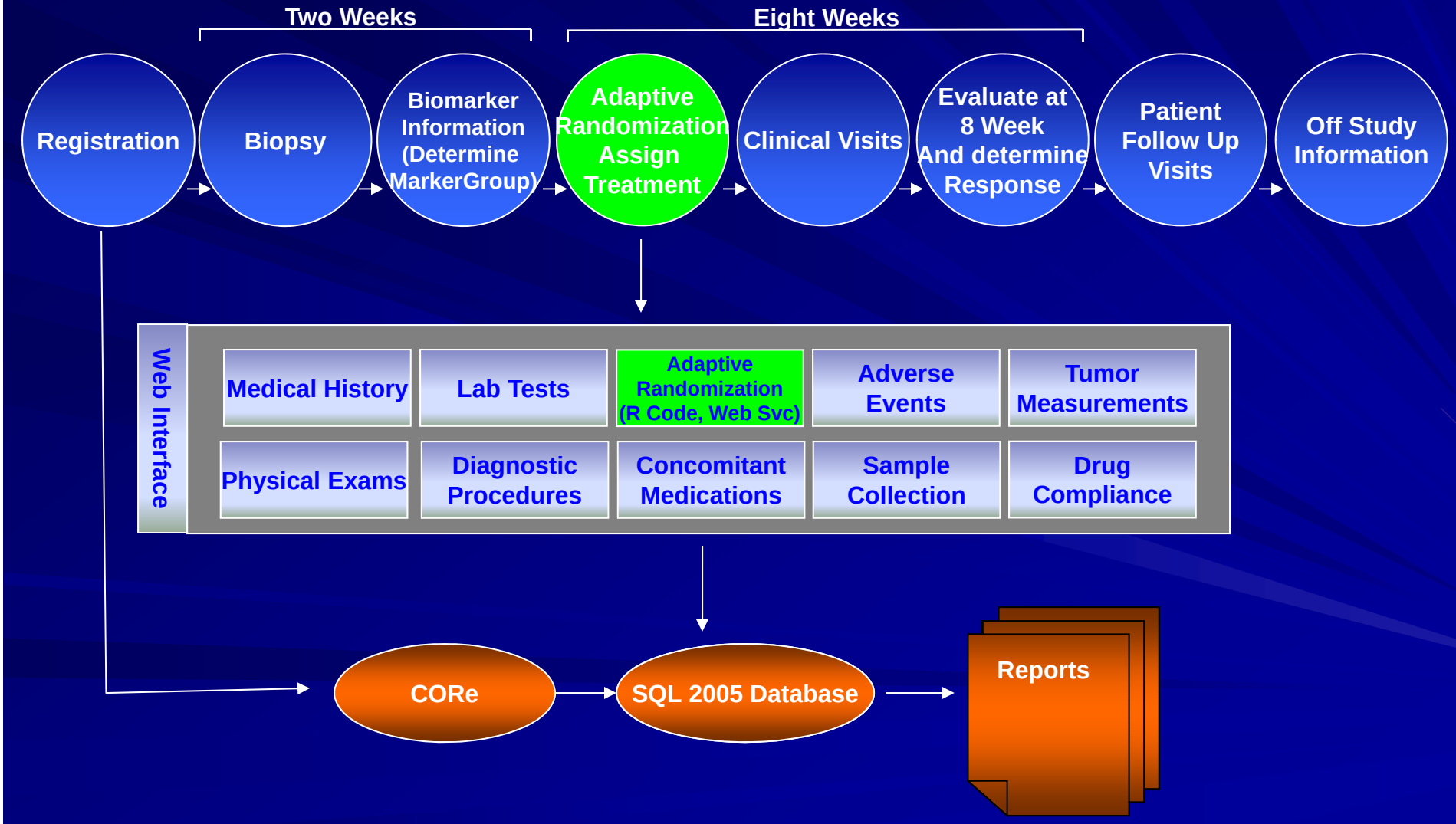
- Erlotinib
- Vandetanib
- Erlotinib + Bexarotene
- Sorafenib

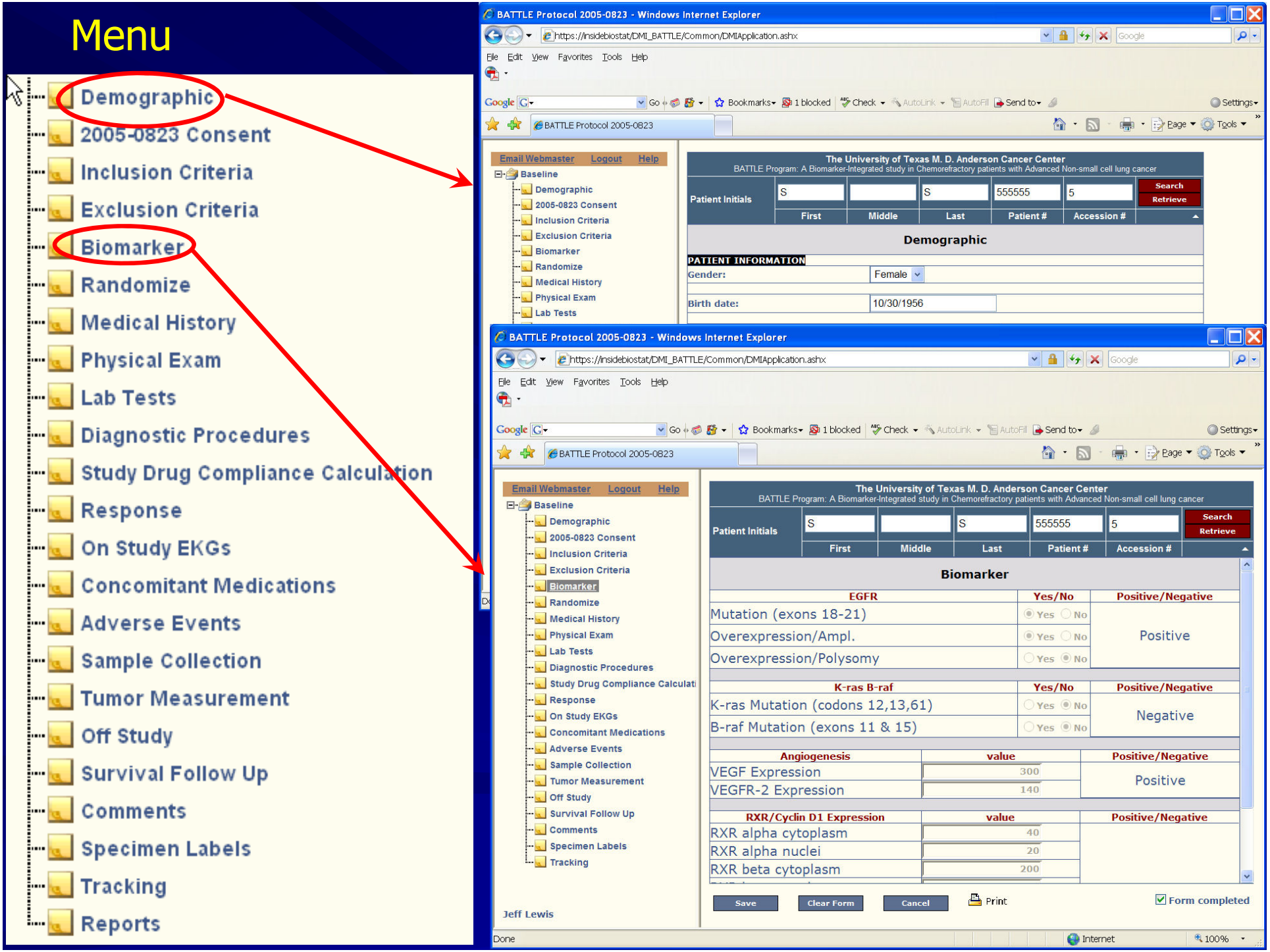
Primary end point: 8 week Disease Control (DC)

Study Accrual and Randomization



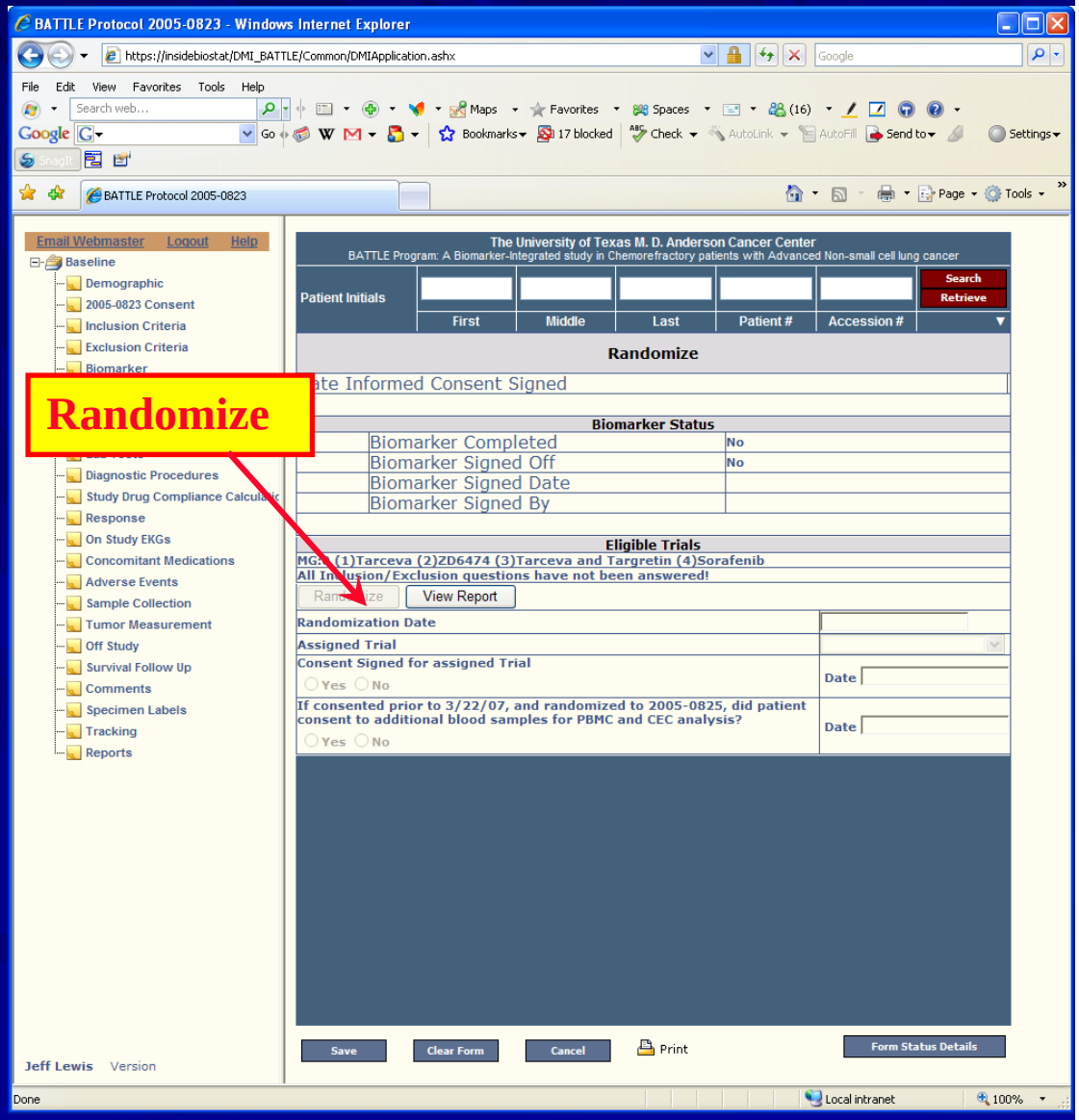
Schematic Diagram to run the web based "BATTLE" application



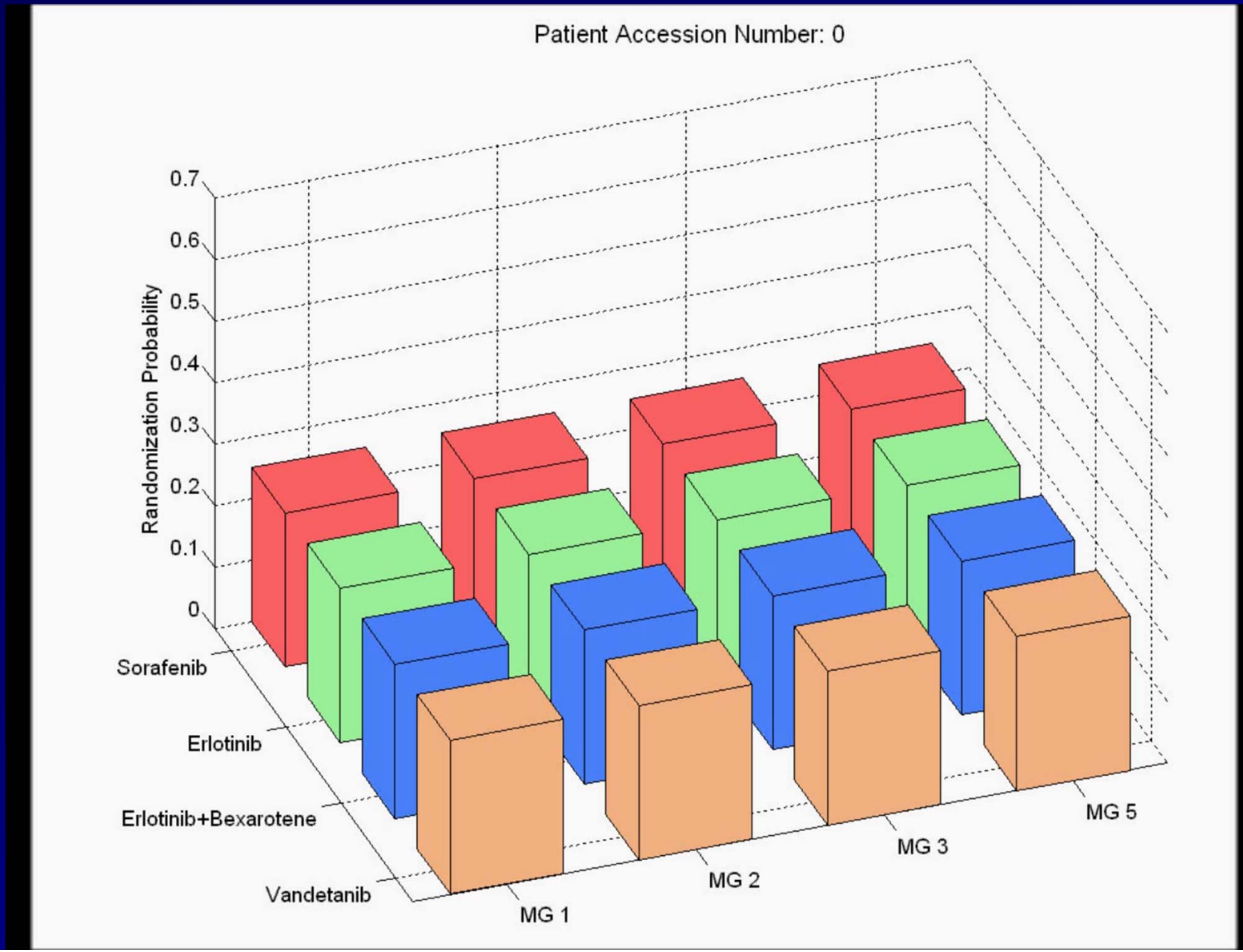

Menu
Demographic
2005-0823 Consent
Inclusion Criteria
Exclusion Criteria
Biomarker
Randomize
Medical History
Physical Exam
Lab Tests
Diagnostic Procedures
Study Drug Compliance Calculation
Response
On Study EKGs
Concomitant Medications
Adverse Events
Sample Collection
Tumor Measurement
Off Study
Survival Follow Up
Comments
Specimen Labels
Tracking
Reports
BATTLE Protocol 2005-0823 - Windows Internet Explorer
https://insidebiostat/DMI_BATTLE/Common/DMIApplication.ashx
Email Webmaster
Logout
Help
Baseline
The University of Texas M. D. Anderson Cancer Center
BATTLE Program: A Biomarker-Integrated study in Chemorefractory patients with Advanced Non-small cell lung cancer
Patient Initials
First
Middle
Last
Patient #
Accession #
Search
Retrieve
Demographic
PATIENT INFORMATION
Gender:
Female
Birth date:
10/30/1956
Biomarker
EGFR
Yes/No
Positive/Negative
Mutation (exons 18-21)
Overexpression/Ampl.
Overexpression/Polysomy
Positive
K-ras B-raf
Yes/No
Positive/Negative
K-ras Mutation (codons 12,13,61)
B-raf Mutation (exons 11 & 15)
Negative
Angiogenesis
value
Positive/Negative
VEGF Expression
VEGFR-2 Expression
300
140
Positive
RXR/Cyclin D1 Expression
value
Positive/Negative
RXR alpha cytoplasm
RXR alpha nuclei
RXR beta cytoplasm
40
20
200
Save
Clear Form
Cancel
Print
Form completed
Jeff Lewis
Done
Internet
100%

Randomization Process

- Patient Consented and Registered in Database
- Information sent to Surgical Team for biopsy
- Biopsy sent to Thoracic Molecular Path Lab
- Biomarker results entered into database
- Randomization of Patient to Trial
- Research Nurse Notified Automatically
- Patient Consented to Appropriate Trial



Video 5: Adaptive Randomization in BATTLE Trial



BATTLE Results: Disease Control in % (n)

Treatments	Marker Groups					Total
	EGFR	*KRAS*	VEGF	RXR/ CycD1	None	
Erlotinib	35% (17)	14% (7)	40% (25)	0% (1)	38% (8)	34% (58)
Vandetanib	41% (27)	0% (3)	38% (16)	NA (0)	0% (6)	33% (52)
Erlotinib + Bexarotene	55% (20)	33% (3)	0% (3)	100% (1)	56% (9)	50% (36)
Sorafenib	39% (23)	79% (14)	64% (39)	25% (4)	61% (18)	58% (98)
Total	43% (87)	48% (27)	49% (83)	33% (6)	46% (41)	46% (244)

AACR Presentation: http://app2.capitalreach.com/esp1204/servlet/tc?cn=aacr&c=10165&s=20435&e=12587&&m=1&br=80&audio=fals

Individual Biomarkers for Response and Resistance to Targeted Treatment: Exploratory Analysis

Drug Treatment	Biomarker	P–value	DC
Erlotinib	*EGFR* mutation	0.04	Improved
Vandetanib	High VEGFR-2 expression	0.05	Improved
Erlotinib + Bexarotene	High Cyclin D1 expression	0.001	Improved
	EGFR FISH Amp	0.006	Improved
Sorafenib	*EGFR* mutation	0.012	Worse
	EGFR high polysomy	0.048	Worse

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.

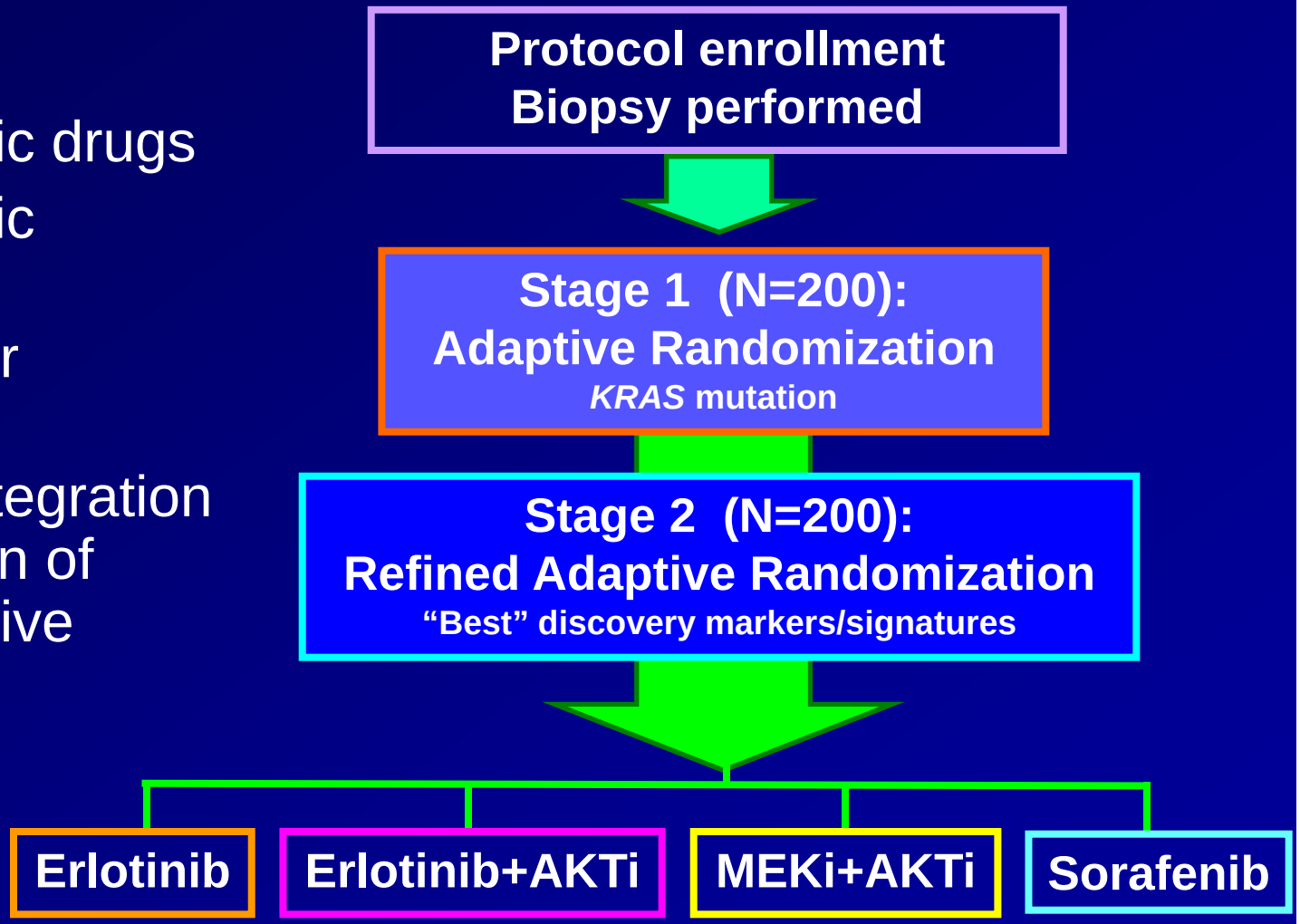
- AR works well only when we have good drugs and good predictive markers.

Marchenko, Fedorov, Lee, Nolan, and Pinheiro: Adaptive Clinical Trials: Overview of Early-Phase Designs and Challenges. Therapeutic Innovation & Regulatory Science, 2014,

BATTLE-2 Schema

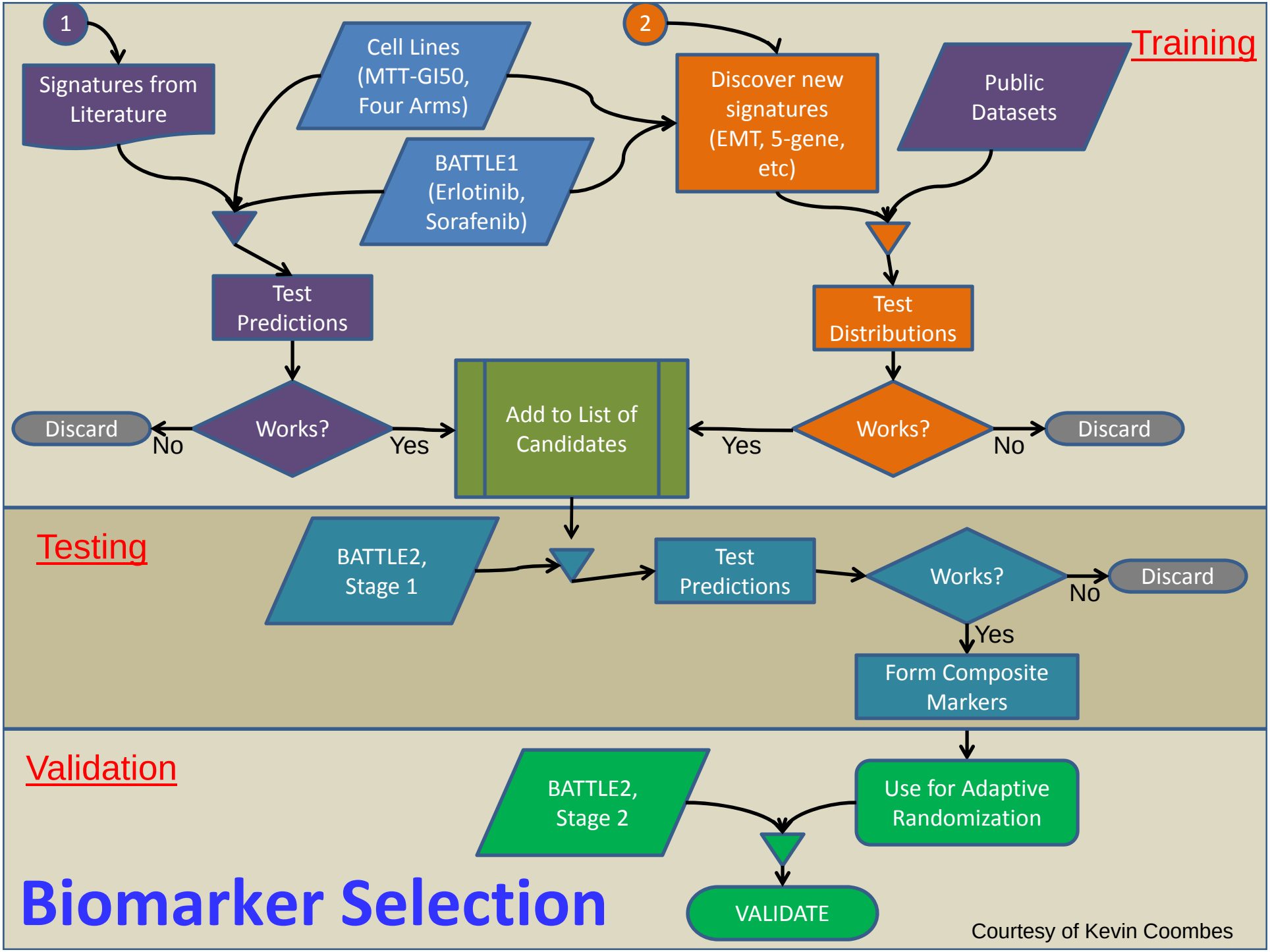
Principles

- 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


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

Statistical Design

- Main goals
  - Test treatment efficacy
  - Identify prognostic and predictive markers
  - Provide better treatment for patients enrolled in the trial based on their marker status
- Bayesian logistic regression model for 8-week DCR

$$\text{logit}(p_j) = \mu_0 + \alpha_j T_j + \sum_{k=1}^{K} \beta_k M_k + \sum_{k=1}^{K} \gamma_{jk} T_j M_k + \left(\alpha'_j T_j Z + \sum_{k=1}^{K} \gamma'_{jk} T_j M_k Z \right)$$

- Adaptive randomization
  - The prob. of a patient being randomized to Arm j is

$$\Pr(p_j > p_{j'}, j' \in \{1,2,3,4 \mid j' \neq j\})$$

Statistical Design (cont.)

- Early futility stopping rule
  - Evaluated starts from 71th patient to the end of trial
  - Stop the trial only if all three experimental arms are not better than the control arm with a high probability
- Markers Selection
  - A panel of putative prognostic and predictive markers will be analyzed in Stage 1
  - Extensive model apply the two-step LASSO
    - 1st step: Group selection of either prognostic or predictive markers to any treatments
    - 2nd step: Step-down test with adaptive LASSO to refine the selection
- Define "success" for treatment *j* in marker *k* if
  - For erlotinib-naïve patients: $\Pr(\alpha_j + \gamma_{jk} > 0) > \theta$
  - For erlotinib-resistant patients: $\Pr(\alpha_j + \alpha_j^{'} + \gamma_{jk} + \gamma_{jk}^{'} > 0) > \theta$
  - θ is chosen to control type I error to 10%

Step 1: Group LASSO

- For each marker k, let $\boldsymbol{\eta}_k = (\beta_k, \gamma_{2k}, \gamma_{3k}, \gamma_{4k}, \gamma'_{2k}, \gamma'_{3k}, \gamma'_{4k})$
- Priors $\begin{cases} \boldsymbol{\eta}_k \sim \boldsymbol{N}_{\boldsymbol{m_k}}(\mathbf{0}, \tau_k^2 \boldsymbol{I}_k) \\ \tau_k^2 \sim \text{InvGamma}\left(\frac{m_k+1}{2}, \frac{\lambda_k^2}{2}\right) \\ \lambda \sim \text{Gamma}(a, b) \end{cases}$
- Letting $\tilde{\boldsymbol{\eta}}_k$ be a posterior random sample of $\boldsymbol{\eta}_k$, and $\bar{\boldsymbol{\eta}}_k = (\bar{\beta}_k, \bar{\gamma}_{2k}, \bar{\gamma}_{3k}, \bar{\gamma}_{4k}, \bar{\gamma}'_{2k}, \bar{\gamma}'_{3k}, \bar{\gamma}'_{4k})$ be its posterior mean, compute the distance between the posterior sample and the zero vector: $T_k = (\tilde{\boldsymbol{\eta}}_k - \mathbf{0})^T \boldsymbol{W}_k^{-1} (\tilde{\boldsymbol{\eta}}_k - \mathbf{0})$, where $\boldsymbol{W}_k^{-1}$ is the sample variance–covariance matrix. Let $\tilde{T}_q$ be the q^{th} empirical quantile of T_k. For a given q, select the k^{th} marker if $\bar{\boldsymbol{\eta}}^T{}_k \boldsymbol{W}_k^{-1} \bar{\boldsymbol{\eta}}_k > \tilde{T}_q$.
- Choose $(a = 1, b = 10, q = 30\%)$ for selecting T_k

Park, T., Casella, G. The Bayesian Lasso. JASA 103, 681--686 (2008)
Kyung, M., Gill, J., and Ghosh, M.: Penalized Regression, Standard Errors, and Bayesian Lassos. Bayesian Analysis, 5, 369--412 (2010)
Meier, van de Geer, Buhlmann:The Group Lasso for Logistic Regression. JRSS B, 70, 53-71 (2008)

Step 2: Adaptive LASSO

- Let Ω be the set of markers selected in the first step, the prior distribution for $\{\theta_k : k \in \Omega\}$ in the adaptive lasso is
- $\pi(\theta_k|\lambda) \propto \exp\left(-\lambda \frac{|\theta_k|}{|\tilde{\theta}_k^{LS}|}\right)$, where θ_k is a generic representation of either the marker main effect or the marker–treatment interaction and $\tilde{\theta}_k^{LS}$ is the least squares estimation of the parameter
- A variable will be selected if the 80% empirical posterior credible interval does not cover zero. The selections of the credible interval in this second step and the $\tilde{T}_q$ in the first step can be adjusted to achieve a desirable false-positive rate and true-positive rate of the variable selection in the null case and alternative case separately.

Zou, H. The Adaptive Lasso and Its Oracle Properties, JASA 101, 1418--1429 (2006)
Chipman, H.: Bayesian variable selection with related predictors. Canadian Journal of Statistics, 24, 17--36 (1996)

N-of-ALL Design (Adaptive Learning)

- 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.

Example: IBM Watson

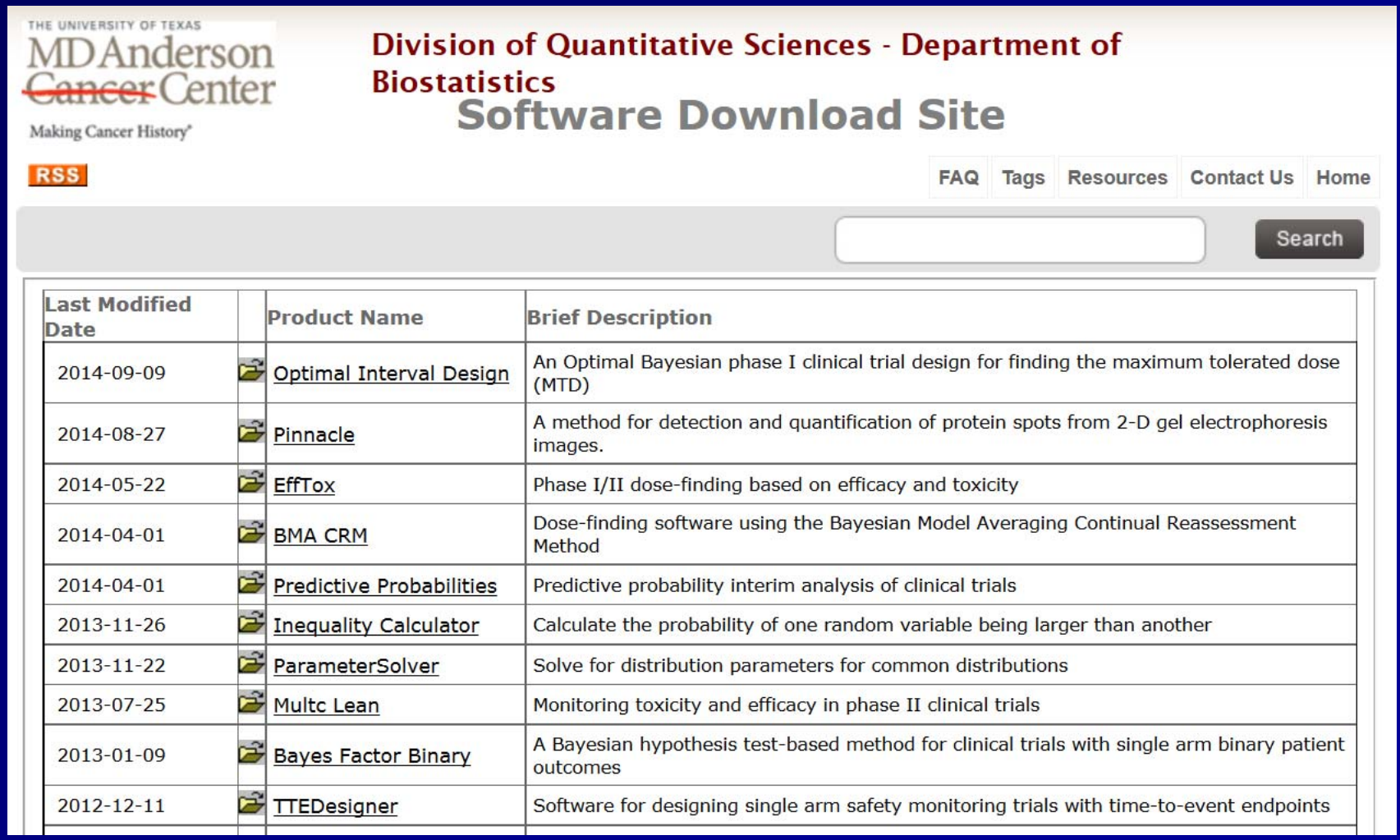
- Name after IBM's Thomas J. Watson
- Watson is a question answering (QA) computing system applying advanced natural language processing, information retrieval, knowledge representation, automated reasoning, and machine learning technologies to the field of open domain question answering.
  - It is optimized, integrating massively parallel POWER7 processors and IBM's DeepQA technology, which generates hypotheses, gather massive evidence, and analyze data.
  - Composed of a cluster of 90 IBM Power 750 servers, each of which uses a 3.5 GHz POWER7 eight core processor, with four threads per core. In total, the system has 2,880 POWER7 processor cores and has 16 terabytes of RAM.
- In 2011, Watson competed on Jeopardy! against former winners Brad Rutter and Ken Jennings. Watson received the first prize of $1 million.

Oncology Expert Advisor (OEA)

- MD Anderson's APOLLO/IBM-Watson project
  - A cognitive computing system piloted in leukemia
  - By pulling together, analyzing, and synthesizing vast amounts of information from patient and research databases, the goal of OEA is to help care teams identify and fine-tune the best possible cancer treatments
- Watson technology drives "adaptive learning environment" as part of its Moon Shots program.
  - Enable iterative and continued learning between clinical care and research
  - Streamline and standardize the longitudinal collection, ingestion and integration of patient's medical and clinical history, laboratory data as well as research data.
  - The complex data is linked and made available for deep analyses by advanced analytics to extract novel insights to improve effectiveness of care and better patient outcomes.

Software Tools

- https://biostatistics.mdanderson.org/SoftwareDownload/
- Over 80 programs freely available



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RSS

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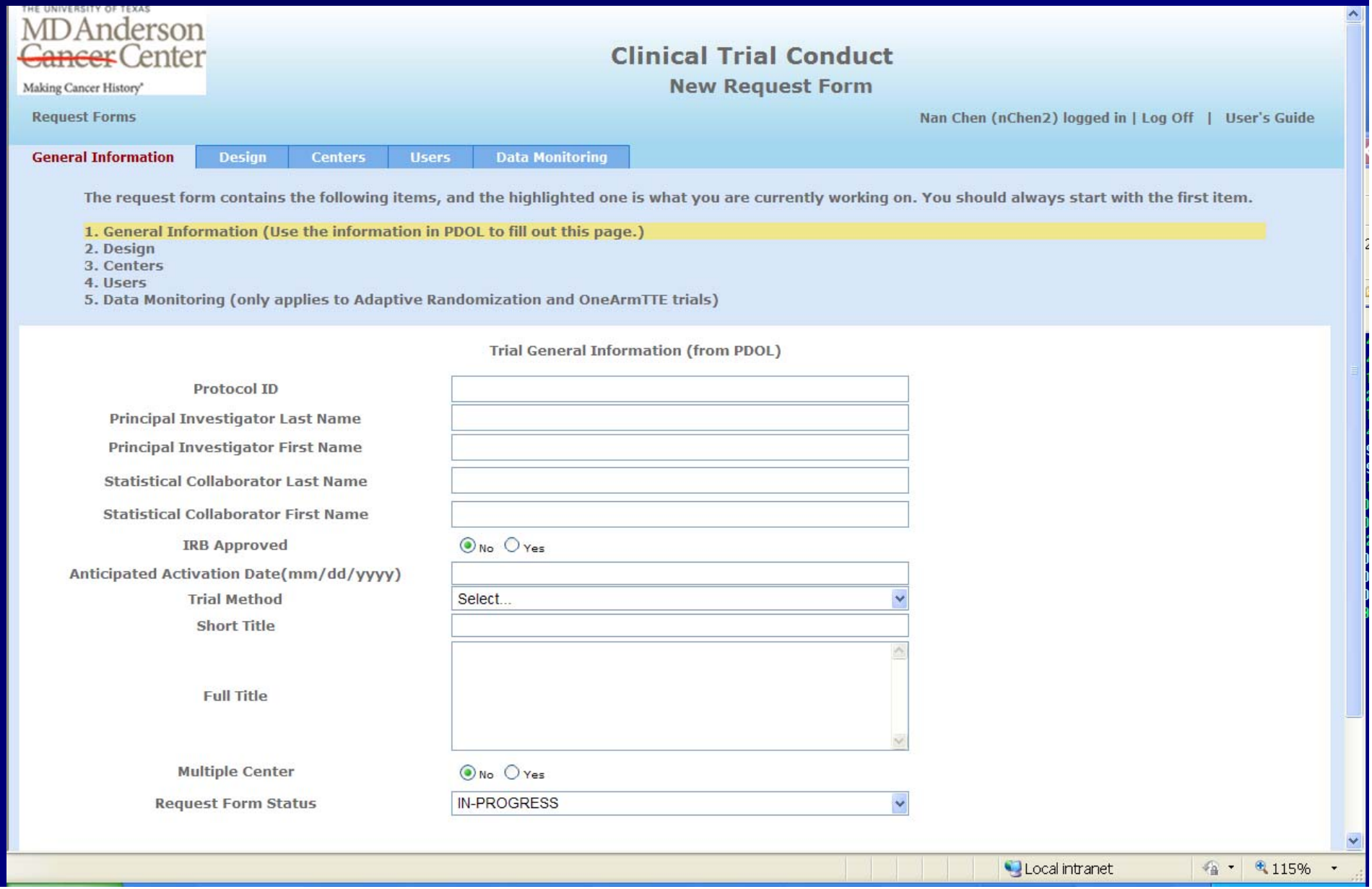
Last Modified Date		Product Name	Brief Description
2014-09-09		Optimal Interval Design	An Optimal Bayesian phase I clinical trial design for finding the maximum tolerated dose (MTD)
2014-08-27		Pinnacle	A method for detection and quantification of protein spots from 2-D gel electrophoresis images.
2014-05-22		EffTox	Phase I/II dose-finding based on efficacy and toxicity
2014-04-01		BMA CRM	Dose-finding software using the Bayesian Model Averaging Continual Reassessment Method
2014-04-01		Predictive Probabilities	Predictive probability interim analysis of clinical trials
2013-11-26		Inequality Calculator	Calculate the probability of one random variable being larger than another
2013-11-22		ParameterSolver	Solve for distribution parameters for common distributions
2013-07-25		Multc Lean	Monitoring toxicity and efficacy in phase II clinical trials
2013-01-09		Bayes Factor Binary	A Bayesian hypothesis test-based method for clinical trials with single arm binary patient outcomes
2012-12-11		TTEDesigner	Software for designing single arm safety monitoring trials with time-to-event endpoints

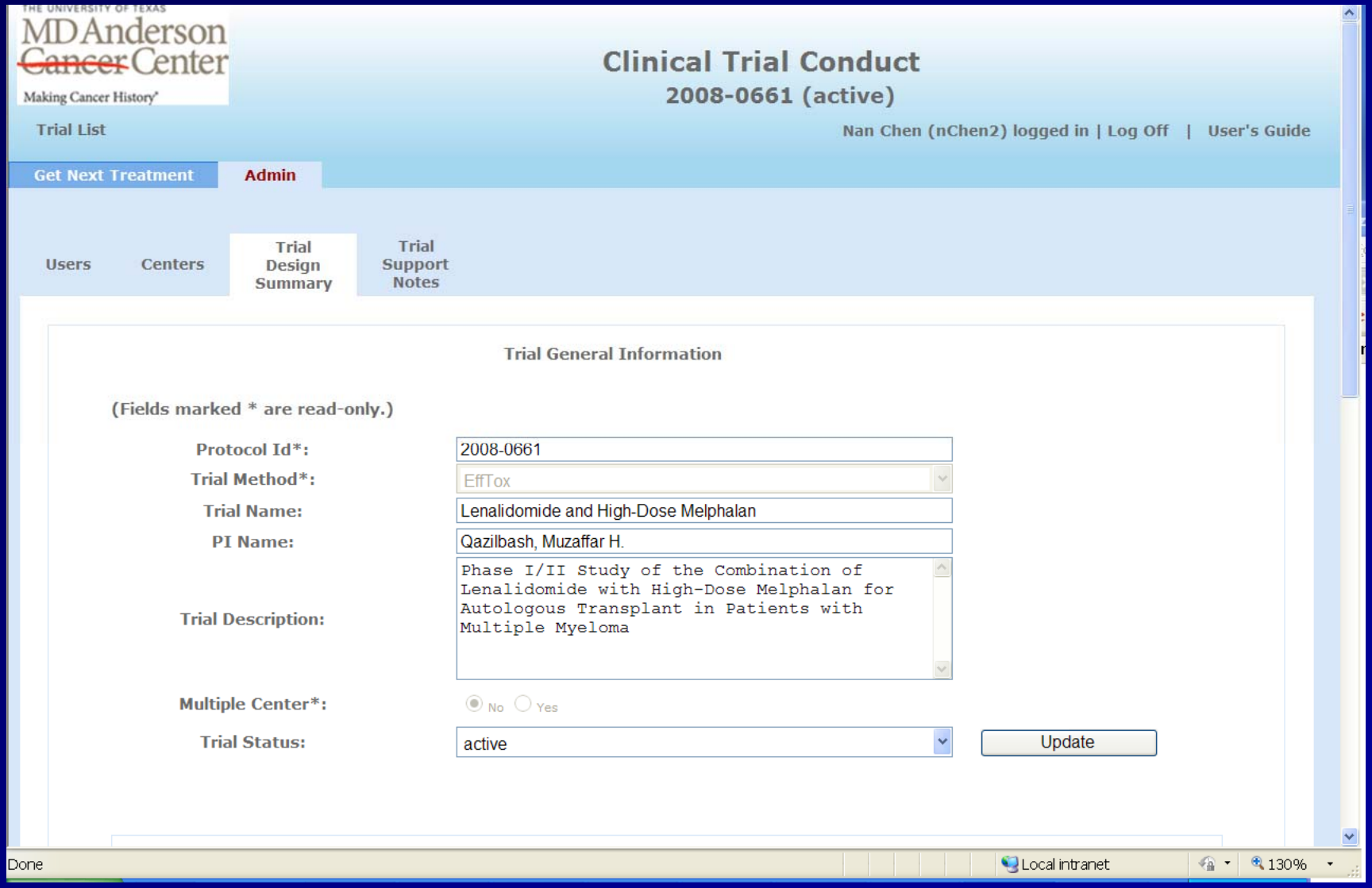
Tools for Conducting Bayesian / Adaptive Trials at MDA

- Clinical Trial Conduct (CTC) Website
- Secured web application for conducting Bayesian clinical trials
- Can be used to
  - Register patients
  - Log in key information for randomization
    - Baseline characteristics
    - Outcome (toxicity, efficacy)
  - Randomize patients
    - Connect to statistical software via web services
  - Capture endpoints for interim analysis

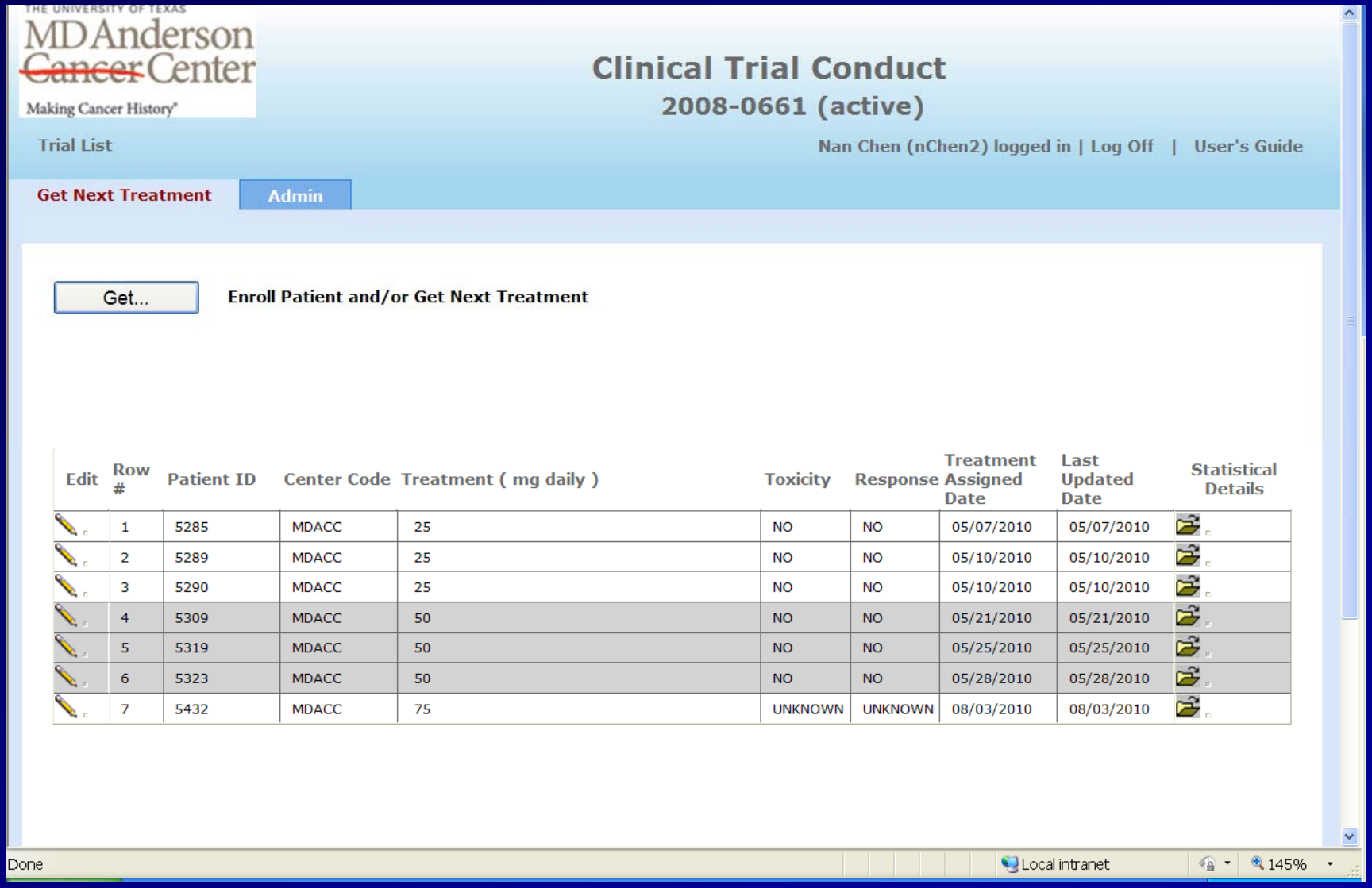
New Trial Request Form



Trial Information and Administration



Monitoring Efficacy and Toxicity



Edit	Row #	Patient ID	Center Code	Treatment (mg daily)	Toxicity	Response	Treatment Assigned Date	Last Updated Date	Statistical Details
	1	5285	MDACC	25	NO	NO	05/07/2010	05/07/2010	
	2	5289	MDACC	25	NO	NO	05/10/2010	05/10/2010	
	3	5290	MDACC	25	NO	NO	05/10/2010	05/10/2010	
	4	5309	MDACC	50	NO	NO	05/21/2010	05/21/2010	
	5	5319	MDACC	50	NO	NO	05/25/2010	05/25/2010	
	6	5323	MDACC	50	NO	NO	05/28/2010	05/28/2010	
	7	5432	MDACC	75	UNKNOWN	UNKNOWN	08/03/2010	08/03/2010	

Clinical Trial Conduct (CTC) Website
(from Jan 2012 to Dec 2013)

- Adaptive Randomization 21
- Bayes Factor One Arm Time to Event 2
- Bayesian Model Averaging CRM 6
- CRM 1
- CRM With Escalation Option 3
- Efftox 2
- Equal Randomization 8
- One Arm Time-To-Event Monitoring 19
- Pocock-Simon Design 25

- Total active trials during 2012-2013 87
- Total patients enrolled in 2012-2013 ~3,000

Summary

- Adaptive design continues to ***learn*** about the new agents' activities and provide best treatments to patients in real time.
  - Adaptive dose finding, estimation, treatment assignment, biomarker identification and validation, stopping for futility and/or efficacy, combination studies, seamless designs
- Adaptive learning is an ambitious and appealing concept. Need data to train and refine the algorithm and demonstrate how well it works.
- Adaptive designs can assist biomarker discovery and validation to match patients with treatments.
- Need more tools for study design, conduct & analysis.
- Biomarker-based adaptive designs can increase the study efficiency, allow flexibility in study conduct, and provide better treatment to study patients to
  - **Speed up drug development**
  - **Step towards personalized medicine**