How To Design Clinical Trials To Demonstrate Value Of Oncology Drugs

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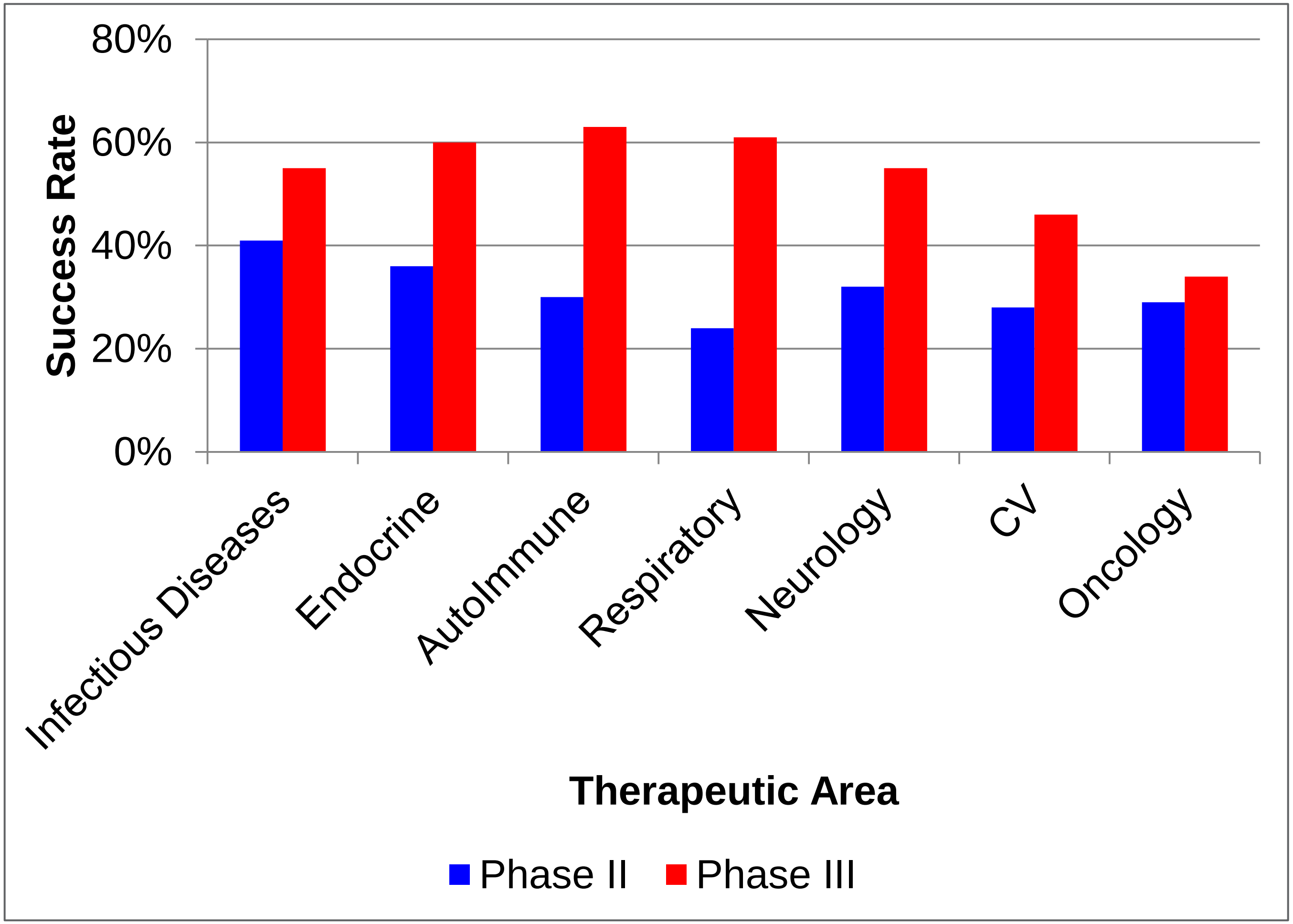
Outline

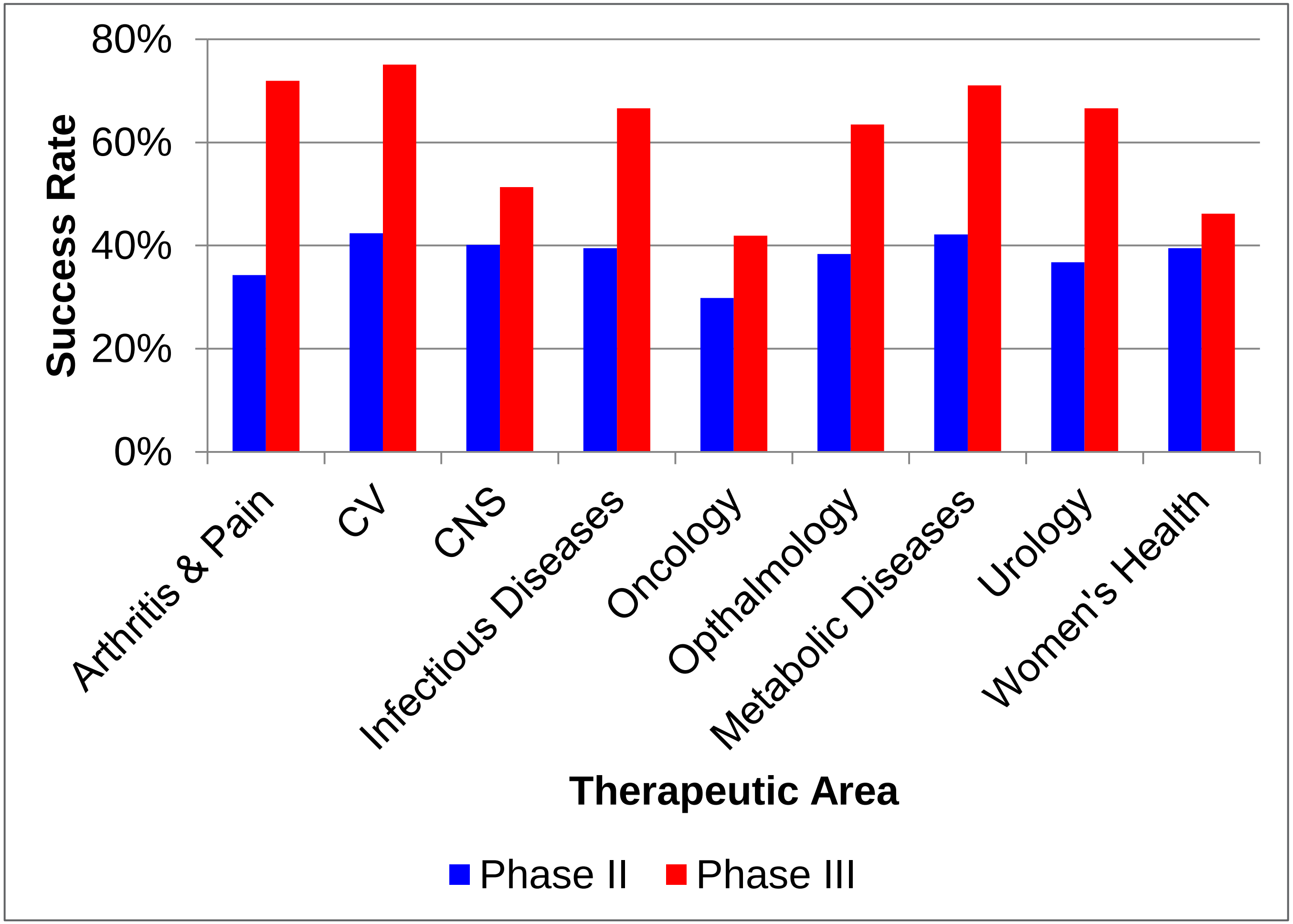
- Background
- Adaptive Designs
- Case Studies
  - Phase I – Determining the MTD
  - Phase II – Use of Early Outcomes
  - Population / Biomarker Selection
- Conclusion

Background

Kola and Landis (2004)
Nature Reviews Drug Discovery



Biomed Tracker February 2011



Adaptive Designs

What are Adaptive Clinical Trials?

- ***An Adaptive Design*** is one that uses accumulating data from the ongoing trial to modify aspects of the study without undermining the validity and integrity of the trial - *PhRMA ADWG, Gallo et al (2006)*

Validity

- providing correct statistical inference
- providing convincing results to a broader scientific community
- minimizing statistical bias

Integrity

- maintaining data confidentiality
- assuring consistency between different stages of the study
- minimizing operational bias

Dragalin. **Adaptive Designs: Terminology and Classification.** *DIJ* 2006, 40: 425-435

Aspects of the Study to be Modified

- Number of Subjects
- Study Duration
- Endpoint Selection
- Treatment Duration
- Patient Population
- Number of Treatments
- Number of Interim Analyses
- Hypotheses

General Structure

- An adaptive design requires the trial to be conducted in several stages with access to the accumulated data
- An adaptive design may have one or more rules:

  - **Allocation Rule**: how subjects will be allocated to available arms
  - **Sampling Rule**: how many subjects will be sampled at next stage
  - **Stopping Rule**: when to stop the trial (for efficacy, harm, futility)
  - **Decision Rule**: the terminal decision rule and interim decisions pertaining to design change not covered by the previous three rules

- At any stage, the data may be analyzed and next stages redesigned taking into account all available data

Determining the MTD

The Background (Oncology)

- Given several doses of a new compound, determine an acceptable dose for treating patients in future trials
- Assumptions
  - Definition of **D**ose **L**imiting **T**oxicity (DLT)
  - Definition of **M**aximum **T**olerated **D**ose (MTD)
    - Prob (DLT | MTD) = π^*
  - Prob (Response) ↑ with dose A)
  - Prob (Toxicity) ↑ with dose B)
    - These conflict : A) is good; B) is bad

Determining the Maximum Tolerated Dose (MTD) Standard 3+3 Method (Storer, 1989)

- Dose levels (Fibonacci), DLT escalation scheme specified

# Patients with DLT	Next Dose Level
0/3	↑ To next level
1/3	3 more patients at this level
1/3 + 0/3	↑ To next level
1/3 + (1/3, 2/3 or 3/3)	Stop: choose previous level
2/3	Stop: choose previous level
3/3	Stop: choose previous level

Problems with 3+3 design

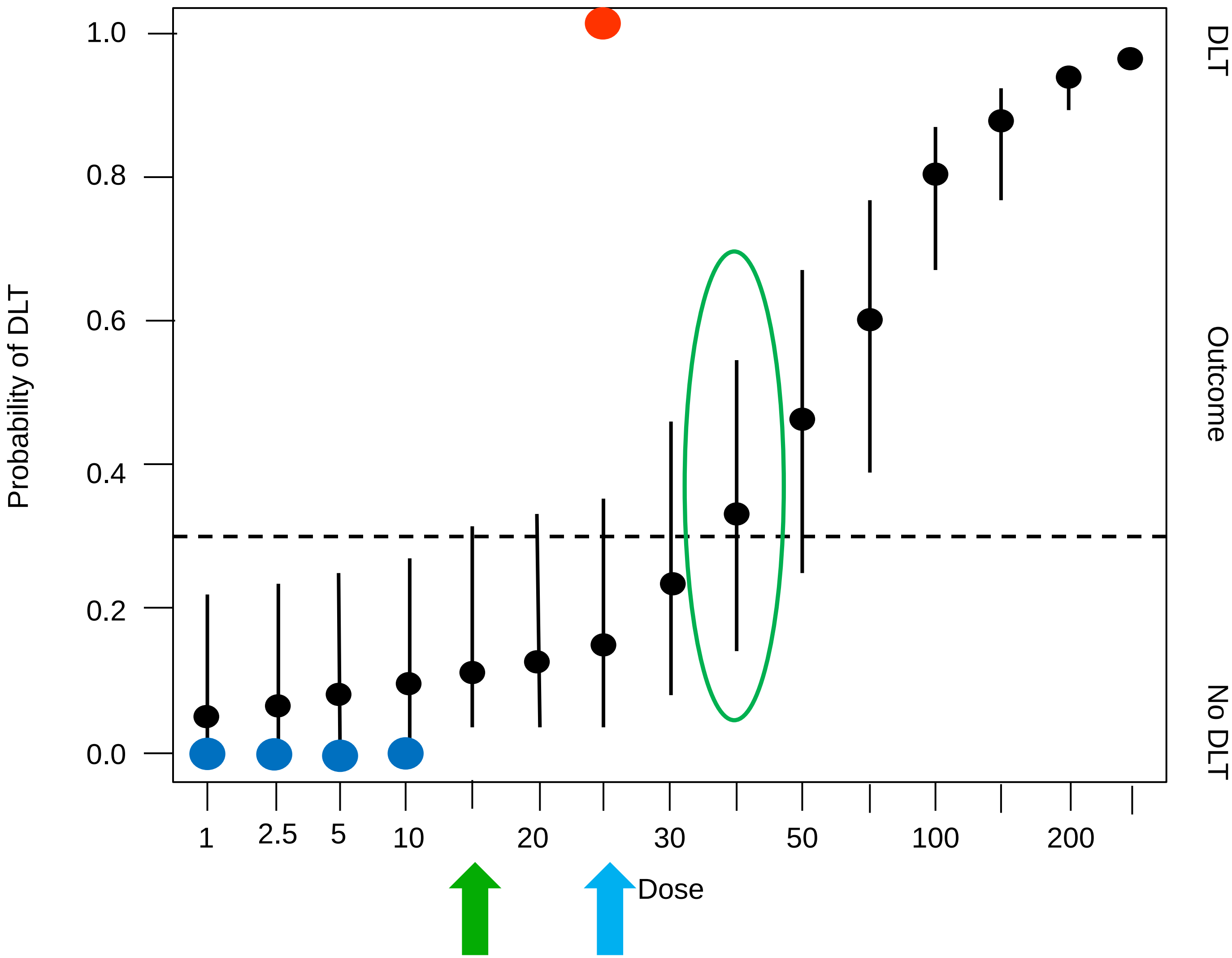
- MTD is not defined – Prob (DLT | MTD) = π^* ?
- It has a high chance of picking an ineffective dose – ($\pi_{MTD} < \pi$)
- It doesn't utilise all of the toxicity data – only the information from the last 3 or 6 patients
- It has poor operating characteristics

Model Based Alternatives

- Instead of using an algorithm – specify a model
- O'Quigley et al (1990) introduced a one-parameter model
- Outcome is binary : DLT / No DLT
- Assumption : There exists a monotone dose-response function $\psi(d;\theta) = Prob(DLT|d,\theta)$ depending on a single parameter θ
- The number of patients N is fixed in advance

Neuenschwander, Branson & Gsponer SIM, 2008

Power Model, target=0.3, EXACT



Way Forward

- Better models
  - A 1-parameter model doesn't have the flexibility to model dose-response data very well
  - Why not a 2-parameter model
- This is necessary but it is not sufficient
- Choosing the dose
  - Basing dose choice on point estimates is inefficient
  - Basing dose choice on point estimates ignores the safety issues: Babb et al (1998), Neuenschwander et al (2008)

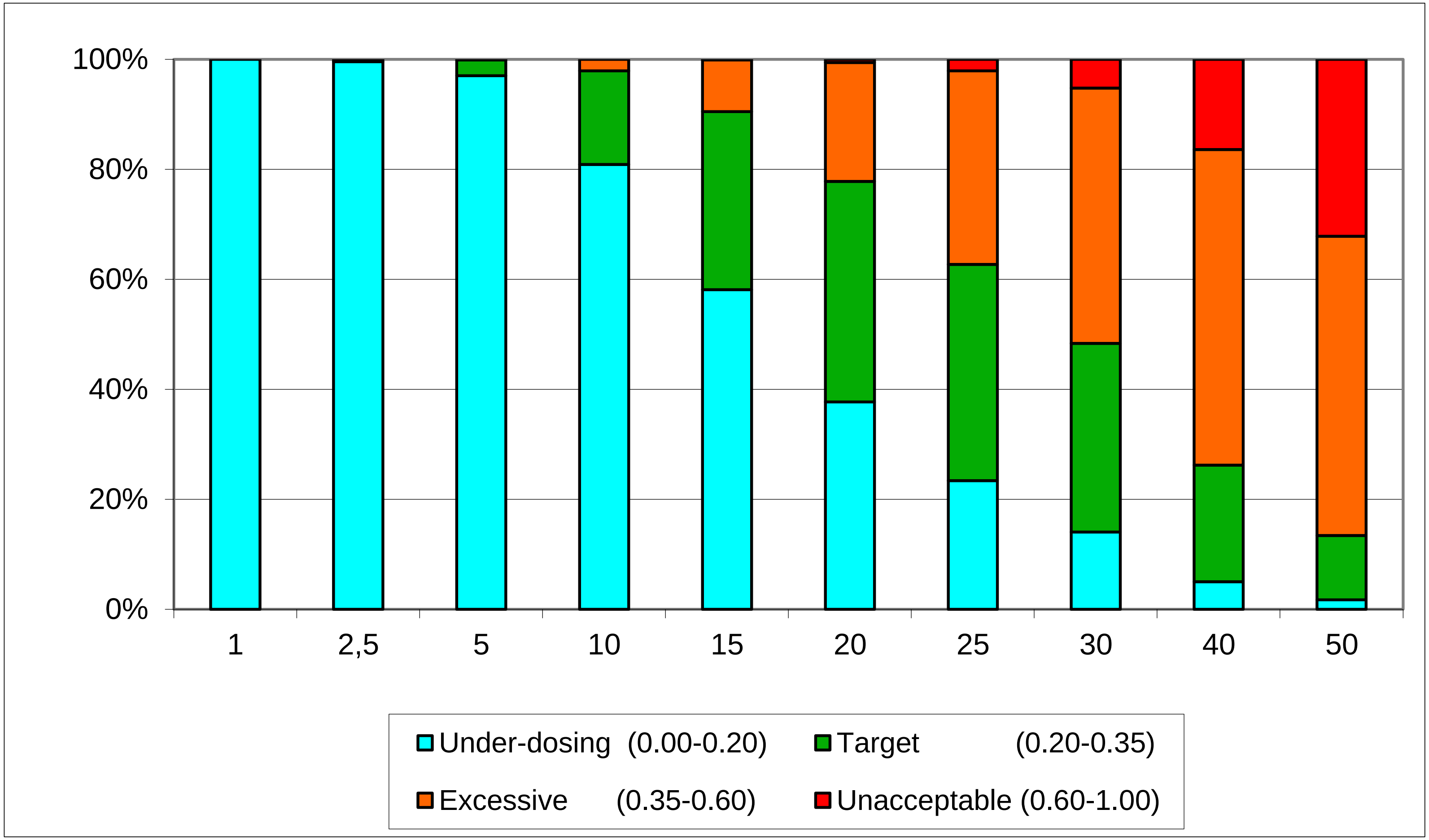
Neuenschwander, Branson & Gsponer SIM, 2008

- Determine the posterior probability that the DLT probability at each dose is in the range:

Underdosing	: 0.00-0.20
Target	: 0.20-0.35
Excessive	: 0.35-0.60
Unacceptable	: 0.60-1.00

- Choose the dose with the largest posterior probability

Neuenschwander, Branson & Gsponer SIM, 2008



Adaptation Based on Short-term Endpoints

Issues in Adaptation for Survival

- The long lag time of months/years to observe a survival endpoint makes it difficulty to design an RCT if using outcome-adaptive randomization.
- In leukemia, the most commonly used response criterion in phase II trials is complete remission(CR)
- It is relatively easy to implement adaptive randomization if the endpoint is readily available soon after treatment – CR

Adaptation for Survival

- Huang et al (2008) use survival as the primary endpoint, but incorporate information about early response to allow a more effective adaptive randomization
- Short-term response
  - (1) resistance to treatment or death, (2) stable disease, (3) partial remission (PR), (4) CR.
- Treatment effect:
  - short-term response – changes to proportions
  - survival – conditional on short term outcome (k), PFS has an exponential distribution with the parameter depending on k – link between short and long-term outcomes

Adaptation for Survival

- The model comprises a mixture of exponential models
- If the mean survival times for treatments A and B are μ_A and μ_B then $\pi=\Pr(\mu_A > \mu_B \mid \text{data})$ is used to assign patients to treatment A with probability π and to treatment B with probability $1-\pi$.
- The approach utilises historical information to start the process with the information being updated as information on the relationship in the trial accrues

Advantages of the Design

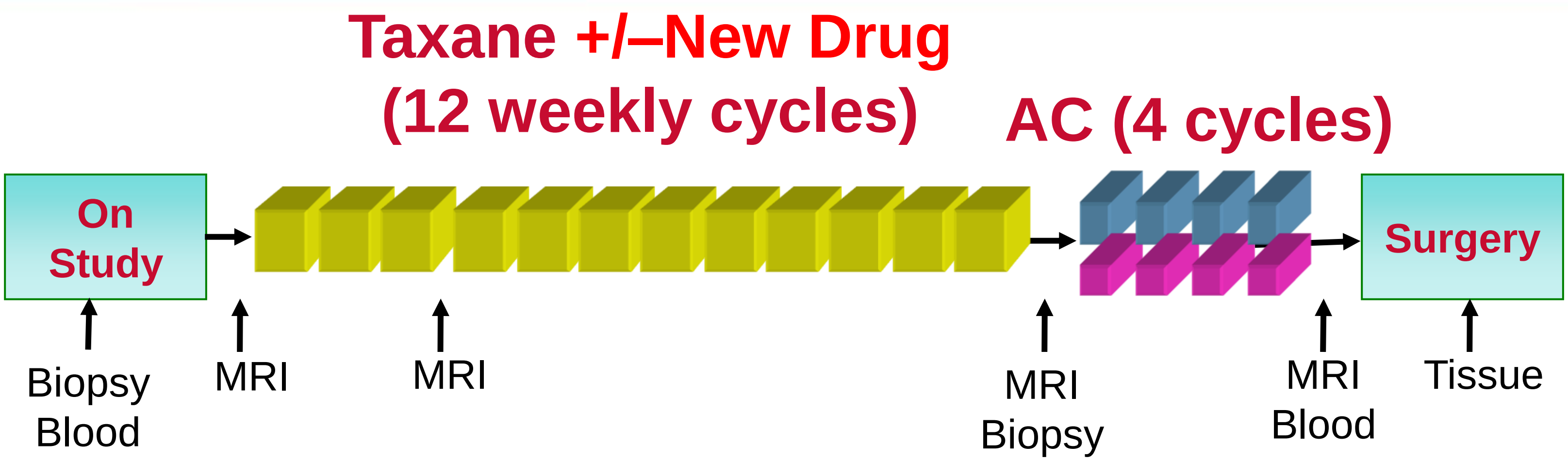
- Simulations have shown:
  - Substantial reductions in the total number of patients required under this design can result in saving time. substantial save
  - The reduction in the number of patients assigned to the inferior treatment arm is ethically appealing.
  - The design addresses the ultimate treatment goal of prolonging patient survival
  - The use of early response information to increase the efficiency of adaptive randomization.

Biomarker / Population Selection

I-SPY2: Adaptive Phase II Neoadjuvant Breast Cancer

- Moderate to high-risk primary breast cancer
- Baseline biopsy: assess biomarkers
  - hormone receptor (HR) status (+/−),
  - human epidermal growth factor receptor 2 (HER2)status (+/−),
  - MammaPrint status (highest MP2, other MP1).
- Primary endpoint: pathCR (pathological complete response)
- Many drugs, each added to standard (control)

I-SPY2: Adaptive Phase II Neoadjuvant Breast Cancer



- Identify biomarker signatures that predict path CR to drugs or combinations of drugs
- Confirm observations within trial—at least partially
- Graduate drug/biomarker pairs to smaller, more focused Phase III

Biomarker Signatures

- Graduate drugs/signatures from trial:
  - Based on effectiveness
  - Based on prevalence
- Biomarker signatures (2^8 combinations of subtypes): B_1, B_2, …, B_{256}

Biomarker Signatures

- But restrict to (10) marketable signatures

Subtype Prevalences

	MP-		MP+	
	HR+	HR-	HR+	HR-
HER2+	16%	7%	4%	10%
HER2-	23%	6%	6%	28%

Signature	All Patients	HR +	HR -	HER2 +	HER2 -	MP +	MP -	HR + HER2 +	HR + HER2 -	HR – HER2 +
Expected Prevalence	100	49	51	37	63	48	52	20	29	17

Dropping, Graduating Drugs

- For each possible biomarker signature B, calculate probability drug >> control in B
- If Bayesian predictive probability of a 300 pt Phase III being successful < 10% for all B, drop drug
- If > 85% for some B then drug graduates
- At graduation predictive probability Phase III success for each B is provided

Conclusions

- Adaptive designs are increasingly accepted by pharmaceutical companies, researchers and regulators
- Allocation adaptive designs are still controversial
- Allocation adaptive designs are particularly suited for:
  - Selection: dose, schedule, population etc
  - Complex, biomarker driven trials