Clinical Trials, Phase II

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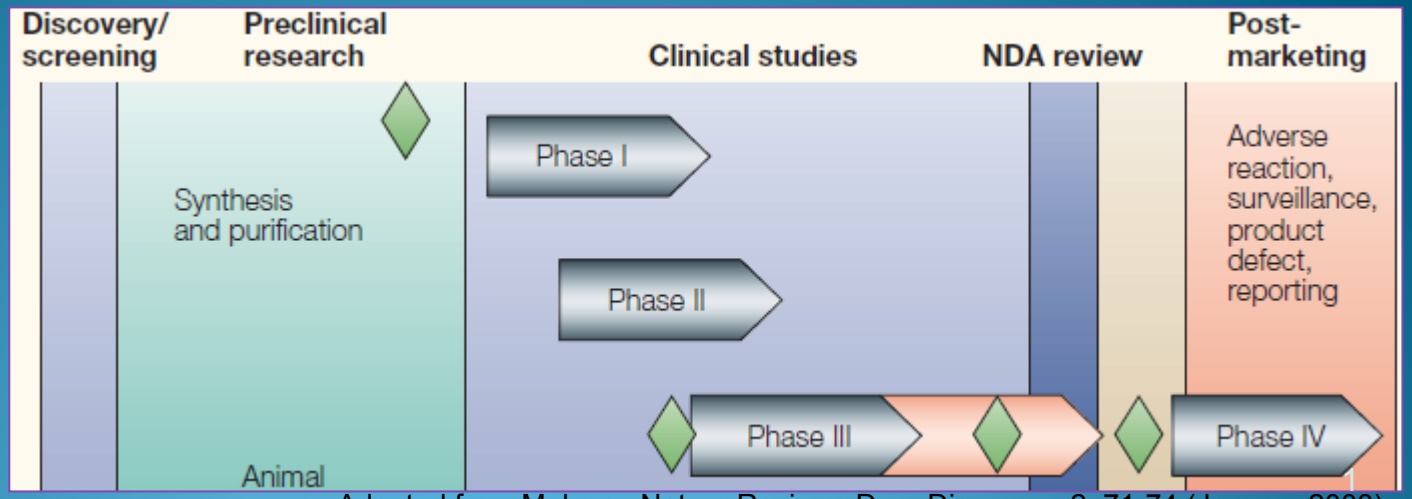
Clinical Pharmacology



Adapted from Molzon , Nature Reviews Drug Discovery, 2, 71-74 (January 2003)

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Clinical Trials

- A ***clinical trial*** is a prospectively planned experiment for the purpose of evaluating one or more potentially beneficial therapies or treatments
- In general these studies are conducted under as many controlled conditions as possible in order to provide definitive answers to well-defined questions

Phases of Drug Development

Phase I

@ To identify Maximum Tolerated Dose (MTD)

@ To characterize PK and if possible PD of compound

@ To characterize preliminary safety profile of compound after single and multiple dosing

Phase II

@ To establish Proof of Concept (POC)

@ To characterize the dose/exposure-response relationship of compound (in the target population)

@ To identify the dose(s) to be tested in Phase III

Phase III

@ To confirm safety and efficacy of the compound in larger studies in the target population

Phase IV

@ Post-approval commitment studies

@ Product Enhancement studies

@ Drug-Drug Interaction studies

Etc.

	# Subjects	Length	Purpose
Phase I	20 – 100	Several months	Mainly Safety
Phase II	Up to several 100	Several months-2 yrs.	Short term safety; mainly effectiveness
Phase III	100s – several 1000	1-4 yrs.	Safety, dosage & effectiveness

Why Do We Conduct Phase II Trials:

- Used for the purpose of determining if a particular agent (or combination) should be studied further

- They serve as a critical filtering mechanism such that a negative trial would lead to discontinuation of development of the novel agent
  - Too stringent of a filter may terminate promising agents improperly
  - Too porous of a filter may result in excessive number of costly negative Phase III trials

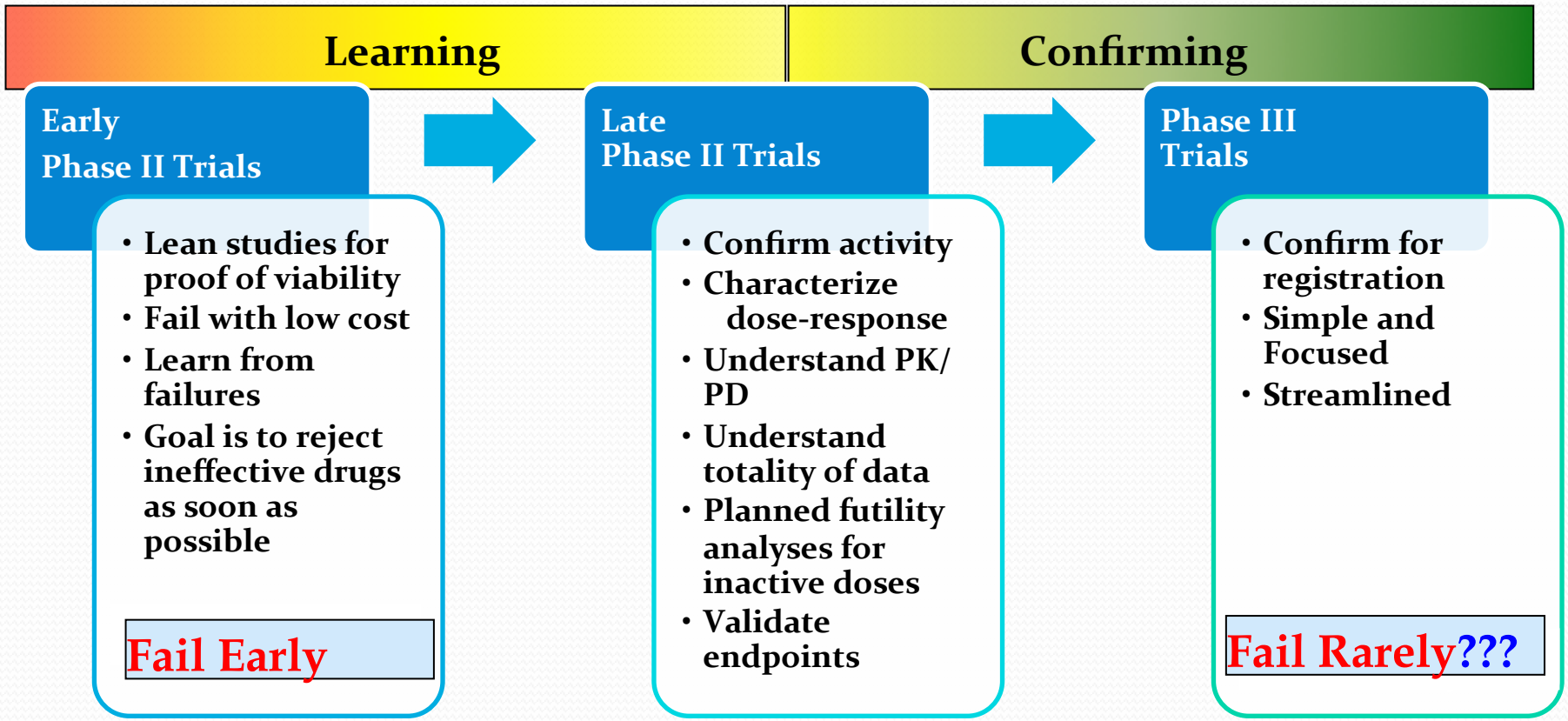
- In Phase 2 trials,
  - Efficacy: Outcome variable of interest
  - Safety: Embedded in the trial to serve as stopping rule

Phase II Stages

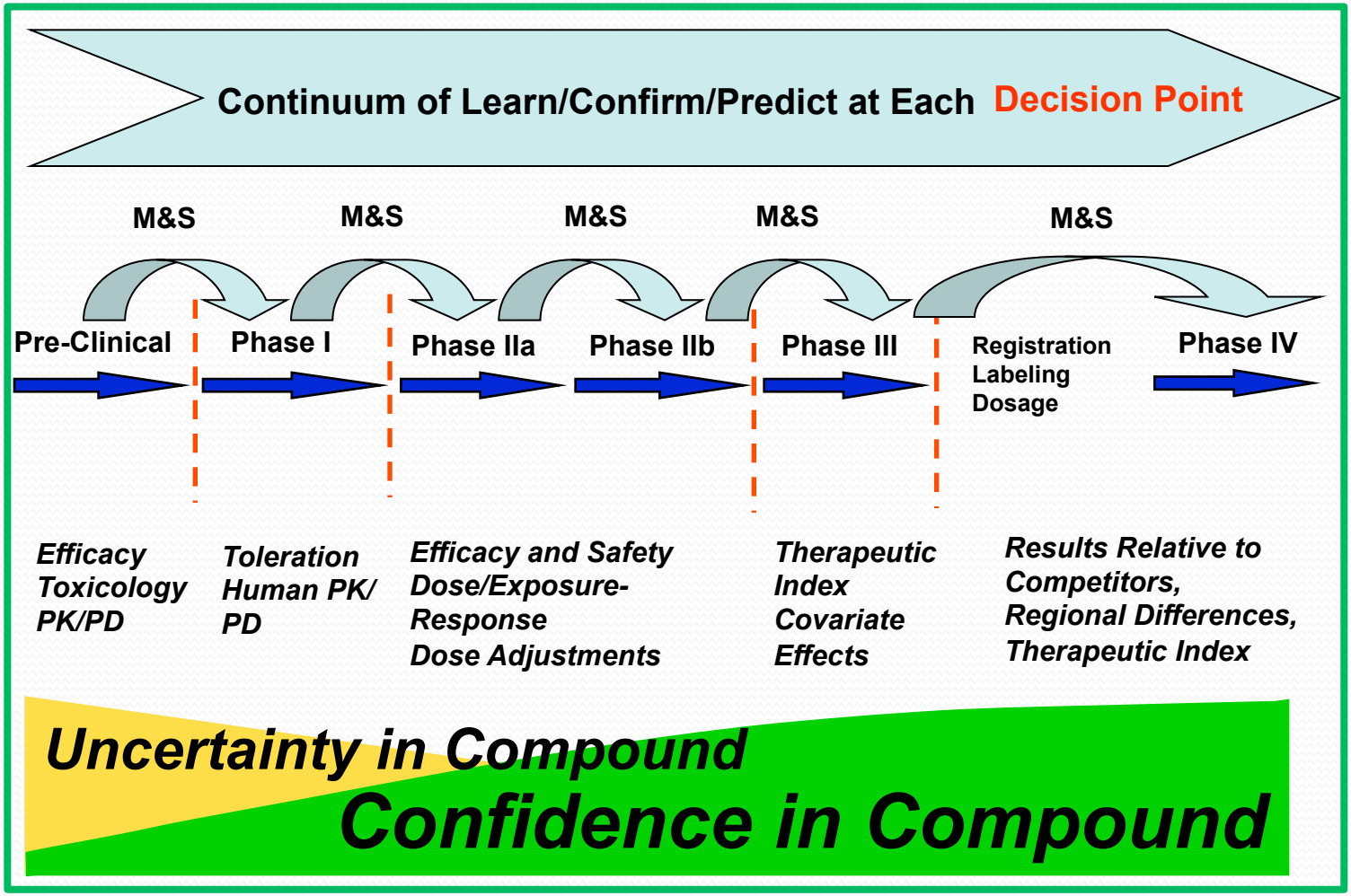
- Phase IIa
  - Proof of Concept (POC)
  - Usually a 2-arm study with test drug given at MTD versus Standard of Care (SOC) as control arm

- Phase IIb
  - Dose finding study
  - Multiple arm study where different doses of the test compound are given versus the standard dose of SOC

Need to Understand Totality of Data: Learn while Doing



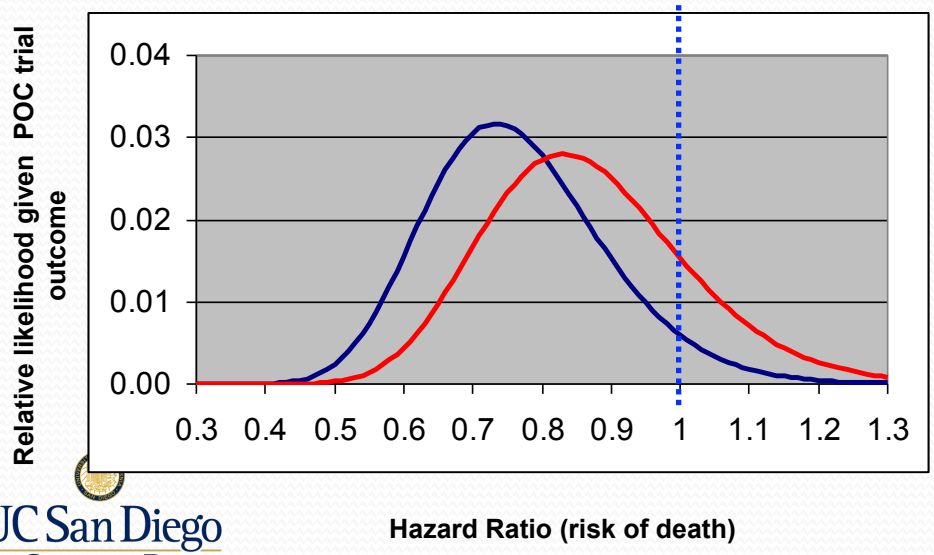
Drug development process and Modeling & Simulation (M&S)



POC Trial Design Issues: Uncertainty in the Level of Efficacy

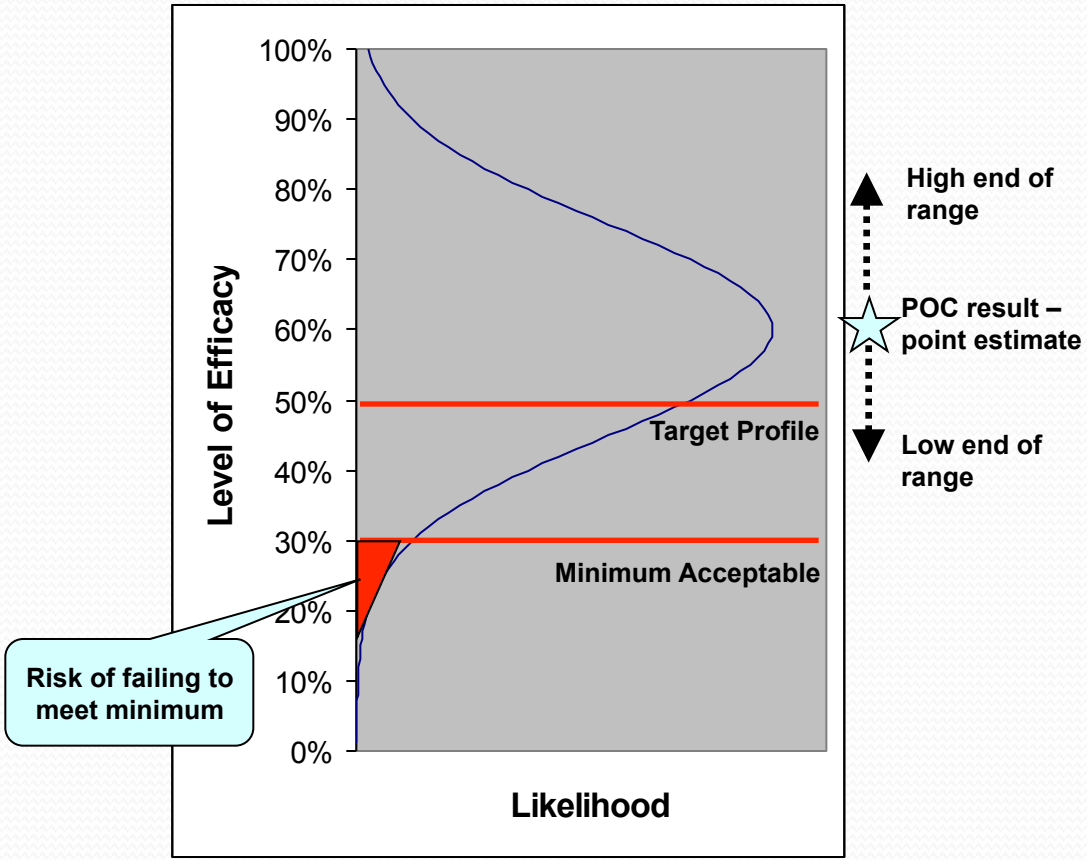
A Phase 2 trial is designed so that an assumed "effect size", seen in a certain number of patients, would be convincing evidence that the drug provides a real benefit. For example, a trial with an assumed efficacy (hazard ratio) of 0.75 might be described by the blue curve. With a readout of 0.75, there is a small chance, about 5% in this illustration, that the drug is completely ineffective.* (This chance is equivalent to the area under the blue curve to the right of HR=1.0, about 5% of the total area under the curve.)

However, we don't know in advance how effective the drug will be. The *real* effect we see in the POC study might be smaller, such as a risk reduction to 85% (red curve) instead of 75%. Even though the point estimate of 0.85 is still well under 1.0, this result would make us much less certain that the drug is effective: 15% of the area under the red curve is to the right of HR=1.0, implying a 15% chance of a drug with no benefit at all. This hazard of a smaller-than-anticipated effect size is an important consideration for designing POC trials. It should also be considered that effect sizes in Phase 3 tend to be smaller than in Phase 2, so this view may still be too optimistic.



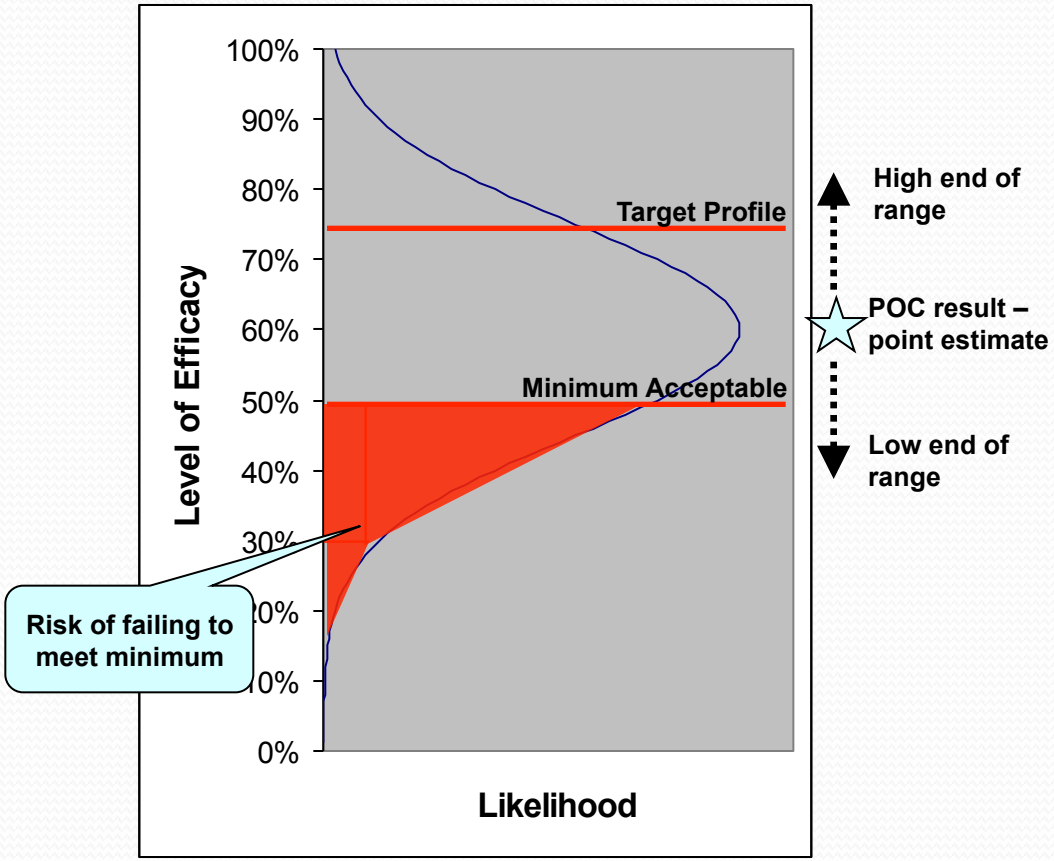
- **Blue Curve:**
  Observed HR of 0.75
  ~5% chance of HR >= 1.0
- **Red Curve:**
  Observed HR of 0.85
  ~15% chance of HR >= 1.0

Likelihood of success for the POC decision depends on the "hurdle" that must be cleared



- The POC decision needs to incorporate a Commercial/ Medical perspective on what level of effectiveness is necessary for success
- The observed effect size, and the degree of uncertainty in the measured effect, are both taken into consideration when comparing with the minimum and target levels needed

A higher hurdle can mean a much lower likelihood of success



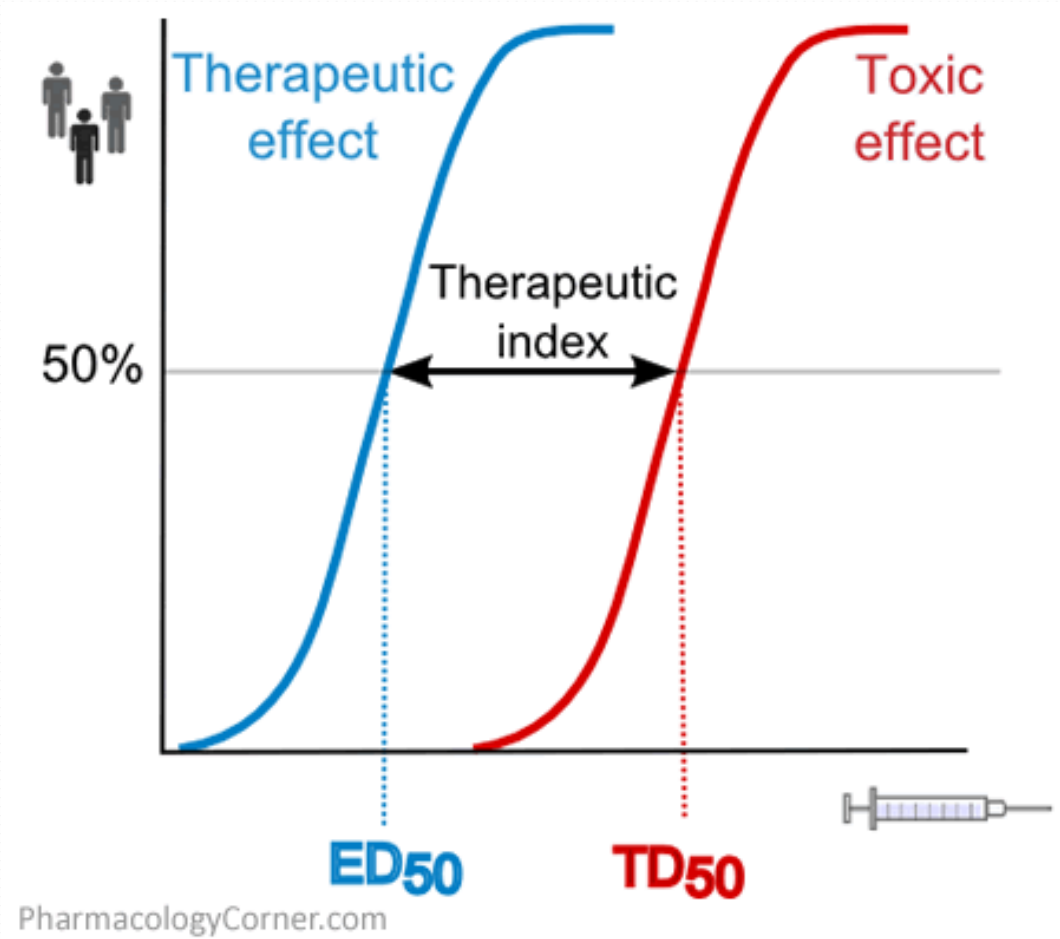
- A point estimate that meets the minimum requirement, but not by very much, implies a sizeable risk due to the uncertainty of the measurement
- This kind of analysis provides an upper limit to our level of certainty. There are other risks as well, such as emergent safety problems or the effects of a broader Phase 3 population
- Similar analysis can be applied to safety metrics or other important factors that can be measured in Phase 2

Therapeutic Index

- In order to ensure that Phase III trials attain success on their specified end-point, the explicit modeling of the relationship of dose to both efficacy and toxicity is critical.

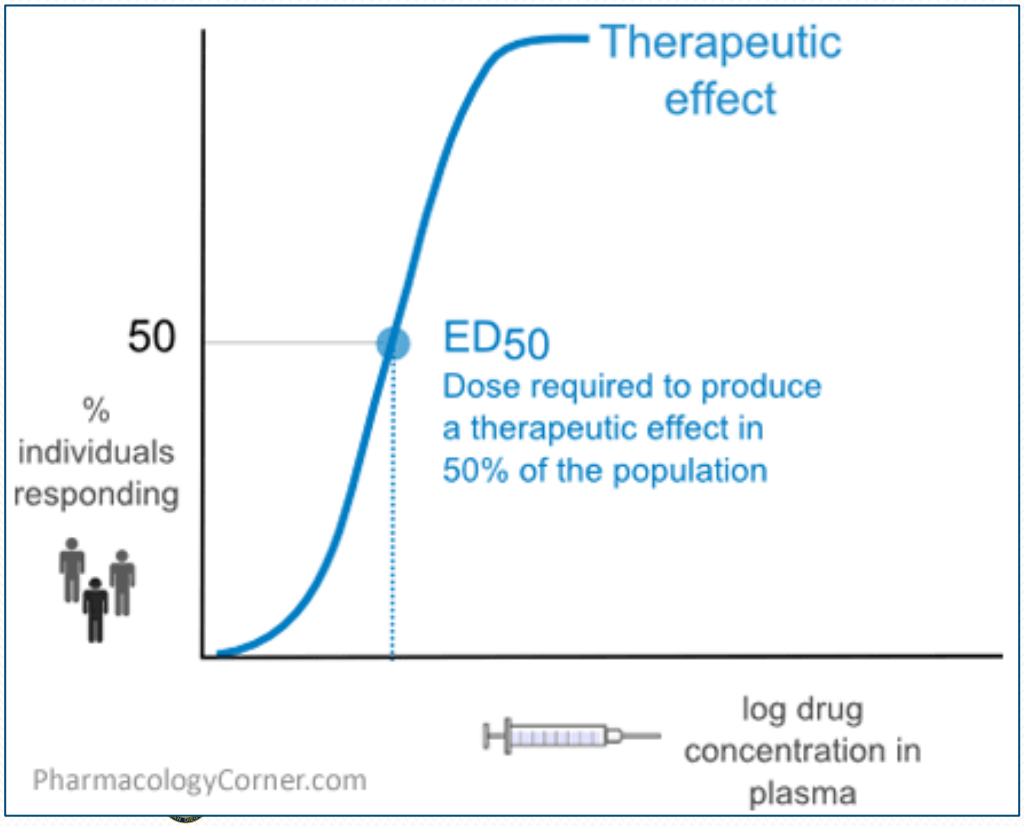
- If an **identifiable and reliable relationship** between dose and chosen efficacy end-point can be established, considerable evidence is provided in support of success of an eventual Phase III trial, particularly if that efficacy is apparent at doses with acceptable toxicity.

Therapeutic Index (TI) = TD_{50}/ED_{50}



Hill Equation

$$E_{drug} = \frac{C^{\gamma} \cdot E_{max}}{C^{\gamma} + EC^{\gamma}_{50}}$$



- E=Intensity of Effect
- C=Concentration of drug
- E_{max}=Maximum effect observed
- EC_{50}=Concentration leading to 50% of maximum effect
- γ= shape factor

Design Options for Phase II Studies:

Phase II strategy	Result	Strength of inference
Single-arm trial with no control	Positive signal	Unknown if due to true efficacy or bias
Single-arm trial with no control	Negative signal	Unknown if due to lack of efficacy, bias or wrong end-point
Two-arm randomized trial with no control	Positive signal	Some sign that one agent more promising than another, but overall efficacy unclear
Two-arm randomized trial with no control	Negative signal	Unknown if due to lack of efficacy, bias or wrong end-point
Two-arm randomized trial with control	Positive signal	Strong efficacy signal, but dosing may not be optimized
Two-arm randomized trial with control	Negative signal	Dose ineffective
Multiple-arm randomized trial with control	Positive signal	Strong efficacy signal, dosing able to be optimized
Multiple-arm randomized trial with control	Negative signal	Drug ineffective

Fixed vs. Adaptive Designs

- **Fixed Design:** A number of pre-identified doses around the expected therapeutic concentration, as identified in animal models, are given to the target population
  - Pros: Logistically simple
  - Cons: The pre-identified doses may miss the actual shape of dose-response curve due to differences in efficacy between humans and animals leading to lack of dose-response (either too high or too low in the dose range)
- **Adaptive Design:** A trial design that allows modifications to some aspects of the trial after its initiation without undermining the validity and integrity of the trial. This design would allow to drop the ineffective doses and add new doses in the expected effective range.
  - Pros: Lowers the development costs and time to market
  - Cons: More complex statistical models needed, need for more precise dose increments, logistically much more complex

Illustration: Uncertainty About ED50 from Fixed Design (Not enough dose levels)

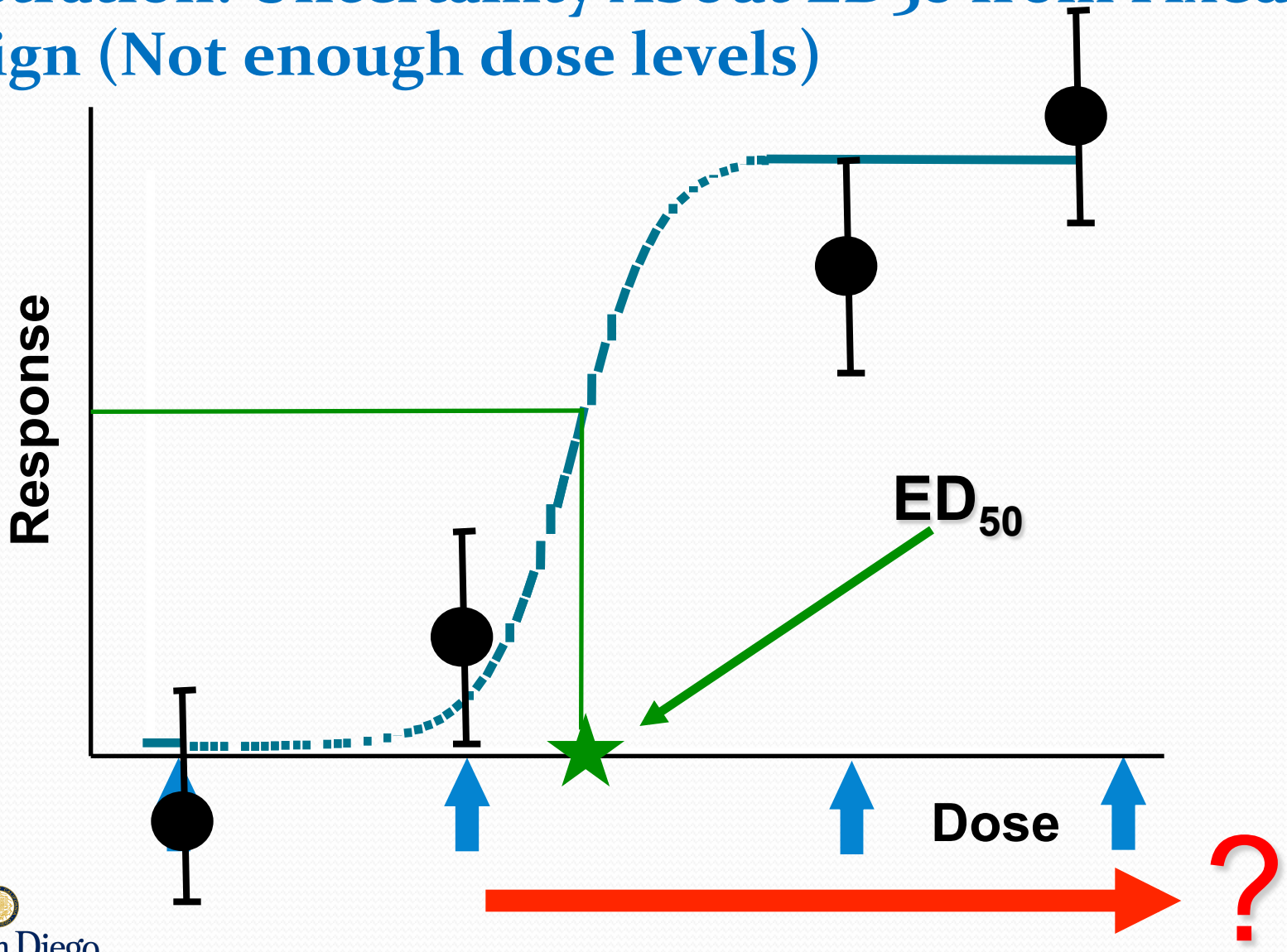


Illustration: Many Doses to Estimate Dose-Response in Fixed Design (Cost/Time!)

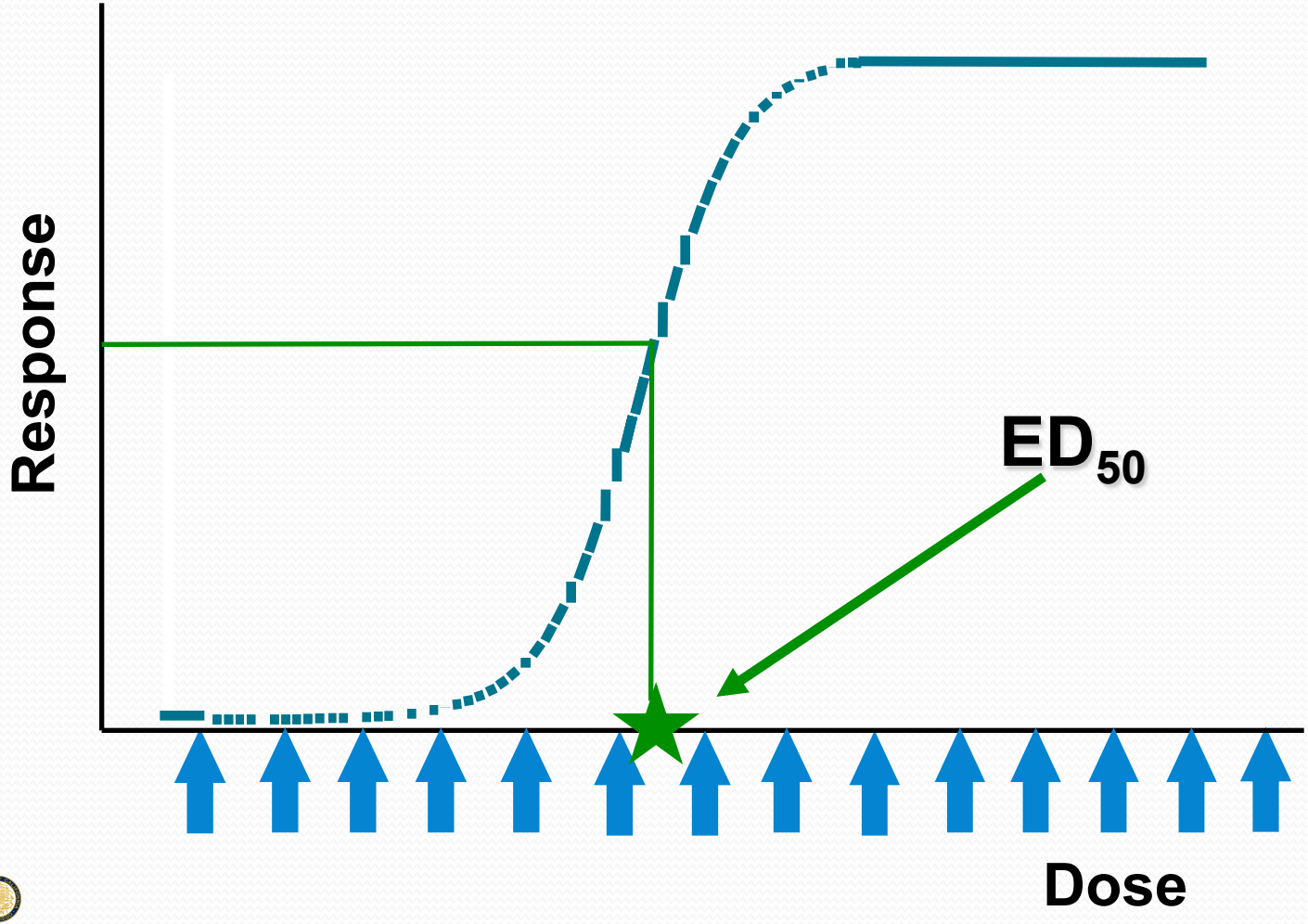
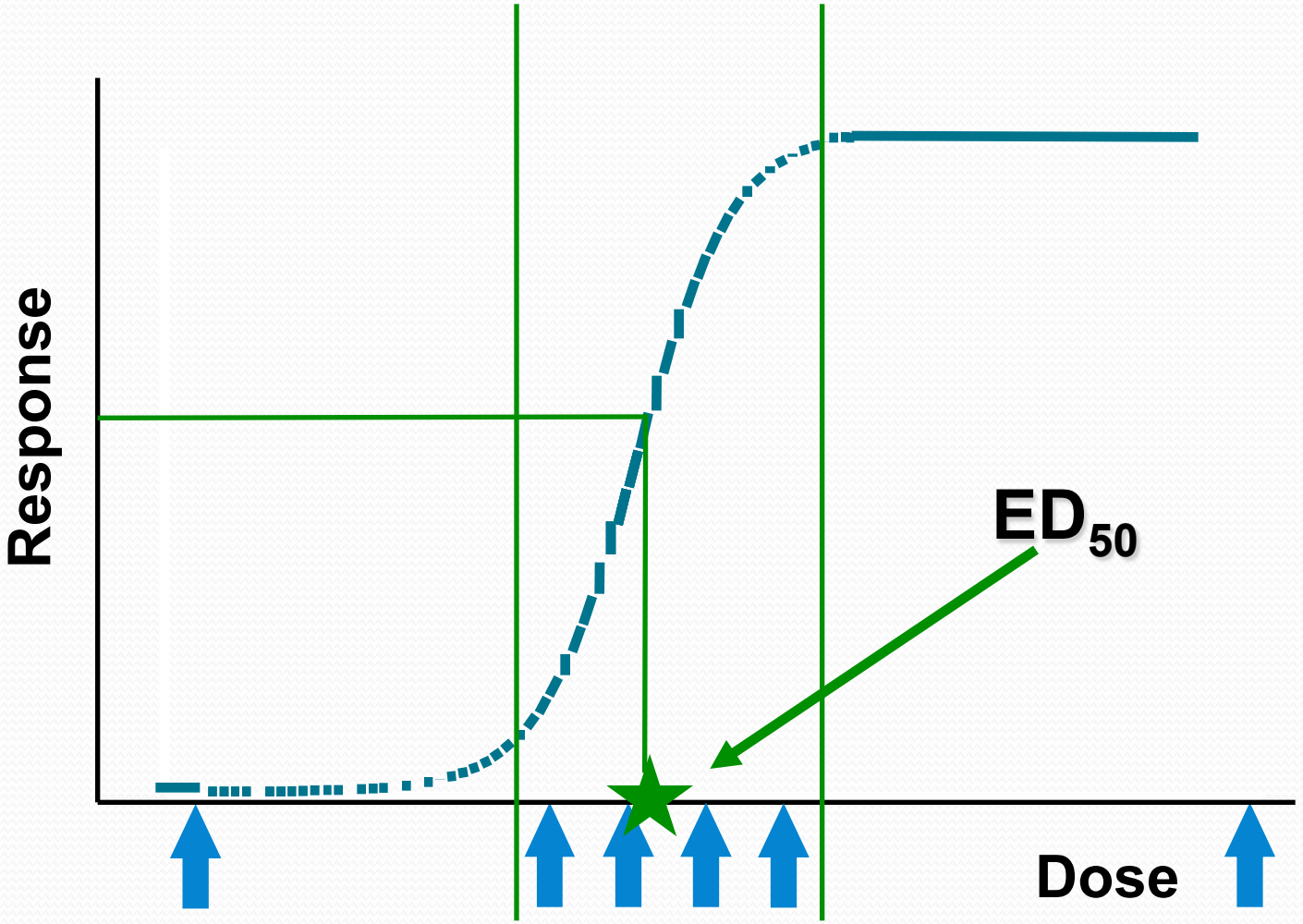


Illustration: Adapted Doses (More Efficient)



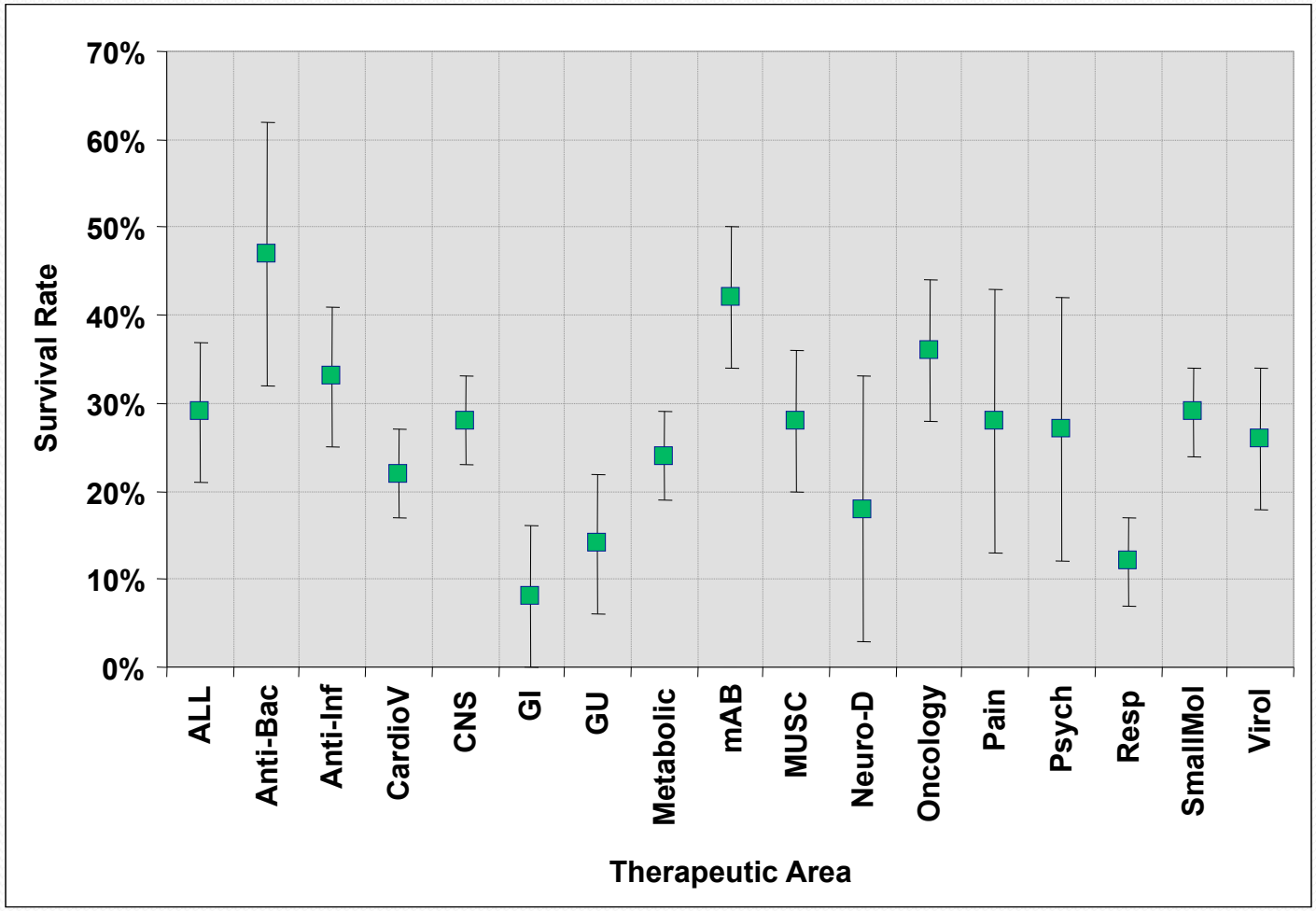
Statistical Comparison in Phase II (oncology)

- Phase II trials do not need to provide reliable comparisons at a traditional two-sided type I error of 0.05.
- The objective is to show superiority of one or more experimental arms to control arm
- Given the need for Phase II trials to be as small as possible and that a Phase III trial will be required to confirm the efficacy, the standard type I error of 0.05 level is too high of a hurdle.
- A one-sided test of null hypothesis that the true primary outcome is no different between treatment and control with a false-positive rate of 0.20 (type I error) is appropriate.

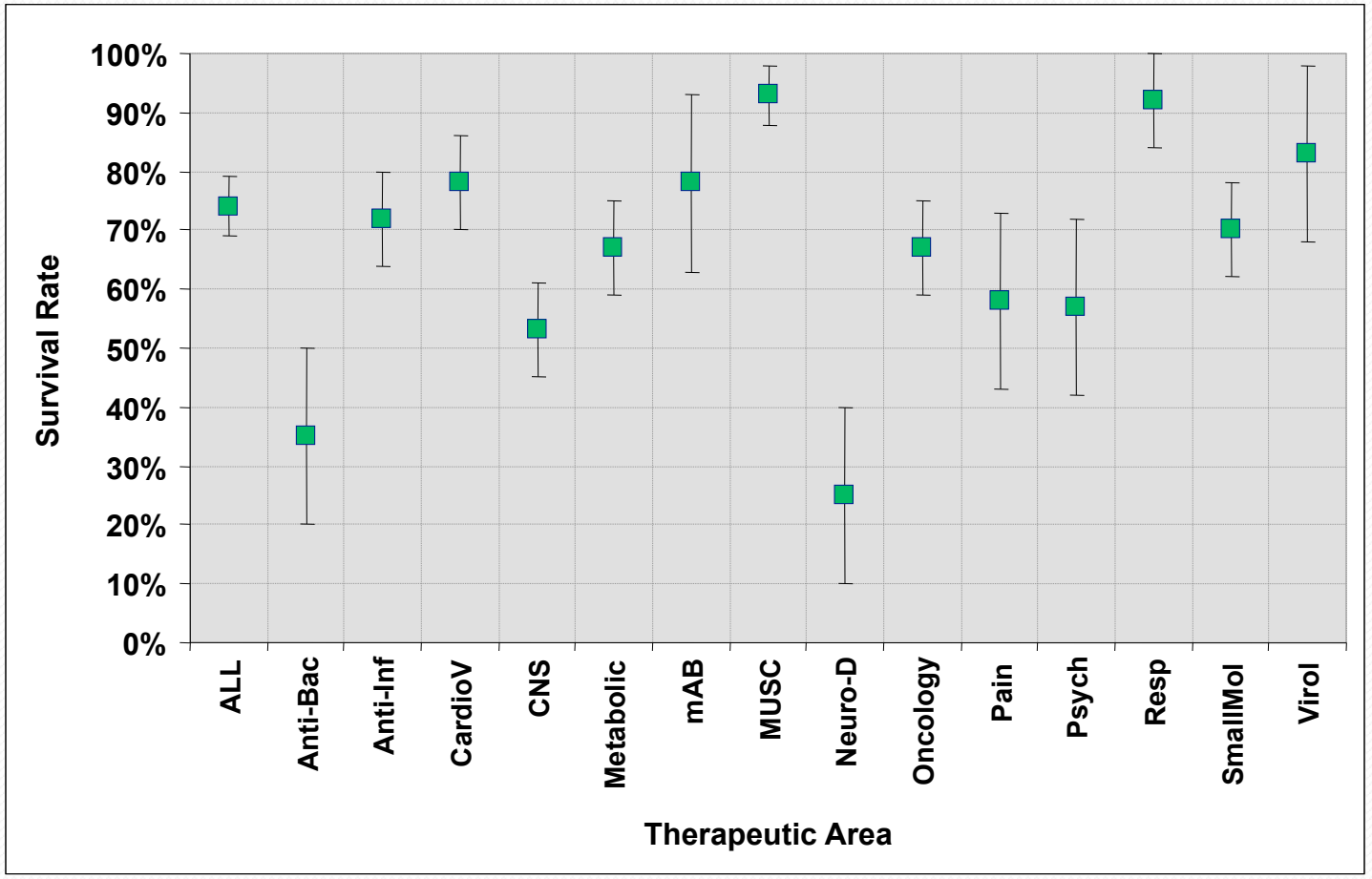
Differences Between Therapeutic Areas

- Many TAs use biomarkers in Phase II design and dose-selection
  - e.g. FBG in Diabetes Type II or Viral Load for HIV
- If reliable biomarkers are not available the final clinical end-point needs to be used which could significantly slow down Phase II
  - e.g. Overall Survival (OS) for most oncology indications
- A surrogate marker is a biomarker which in large clinical studies has shown to be a strong predictor of the final clinical end-point
  - e.g. Blood Pressure (BP) predicts the mortality in cardiovascular disease

Phase II Outcomes by Therapeutic Area



Phase III Outcome per Therapeutic Area



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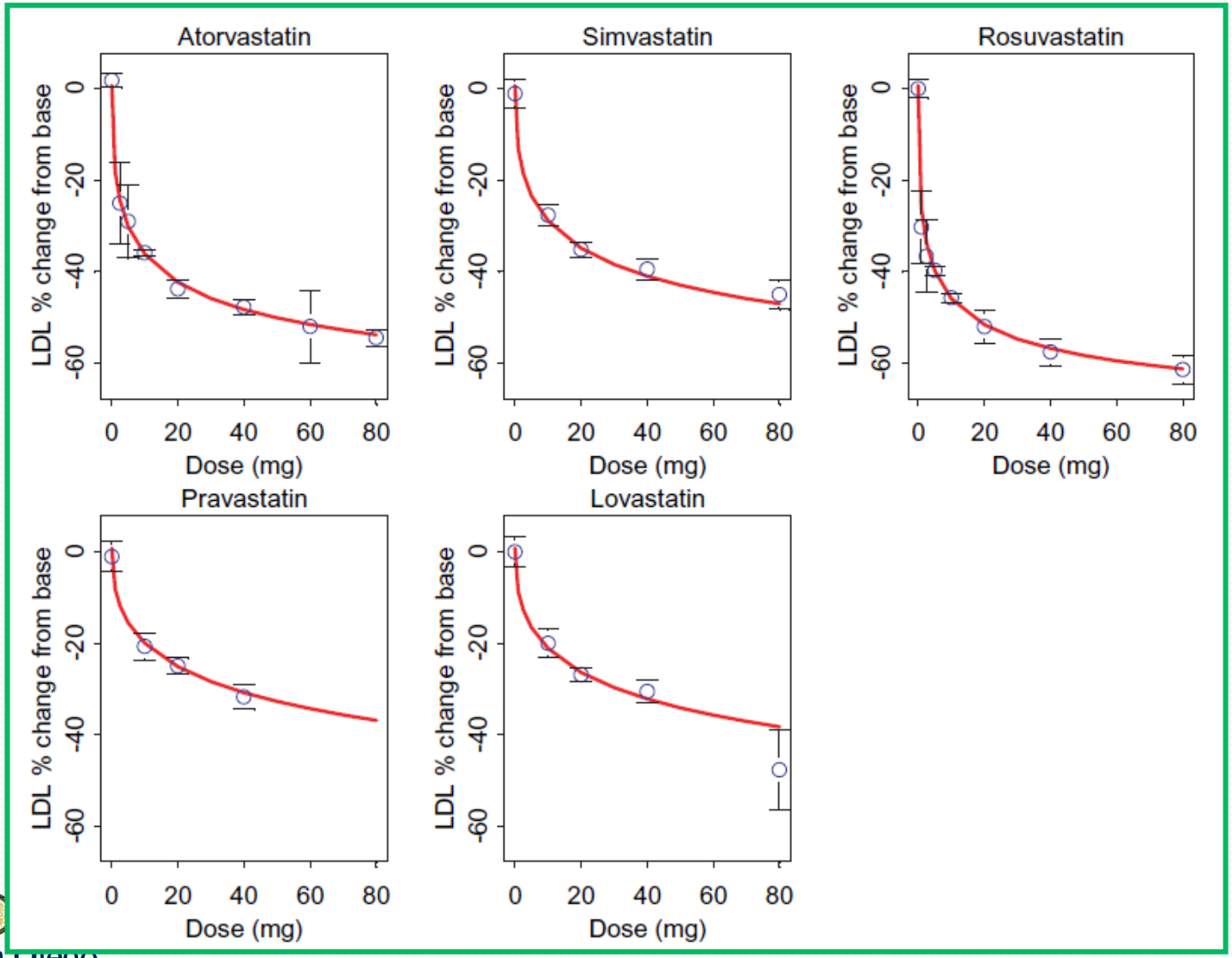
Example 1: Statins

- Objective: Evaluate impact of treatment of gemcabene vs. ezetimibe on coronary artery disease when used in combination with statins

- Dose-effect relationship of LDL-C predicted using nonlinear mixed-effects model
  - Considered trial location, treatment duration, baseline LDL-C, drug class and drug

The AAPS Journal 2005; 7 (3)

Dose-response relationship of statins alone



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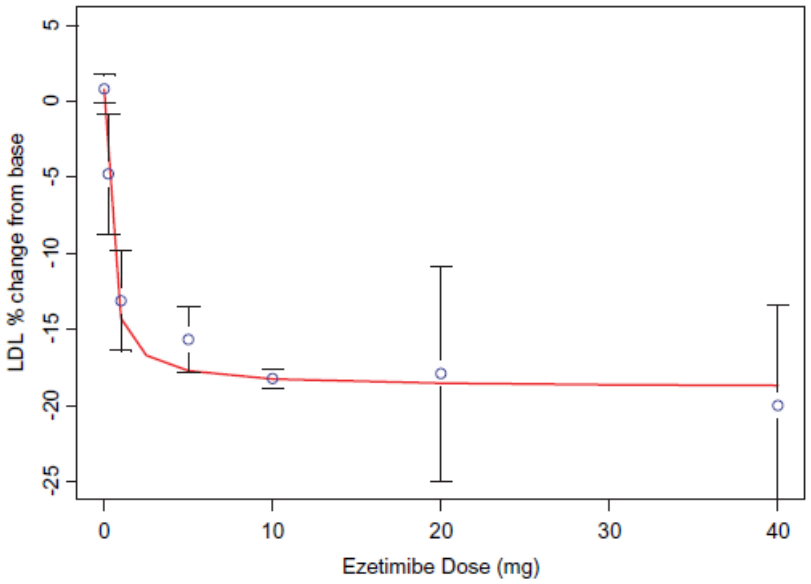
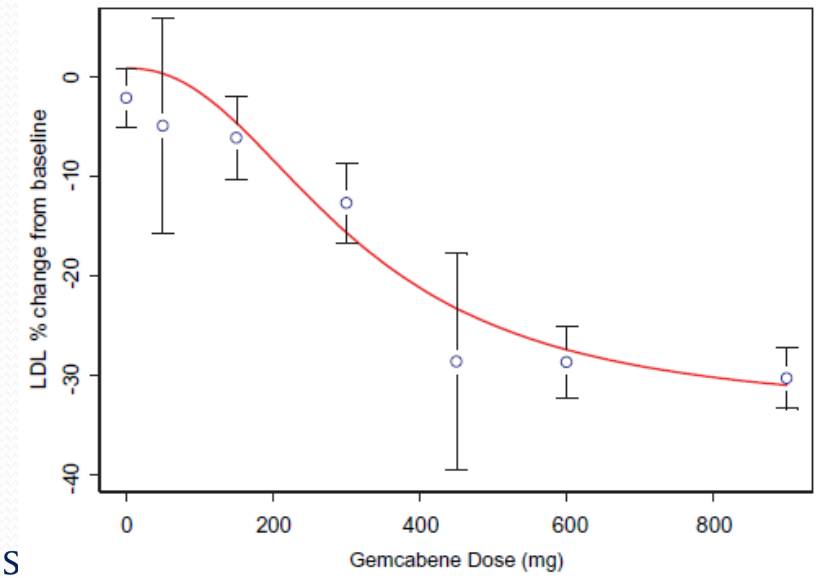
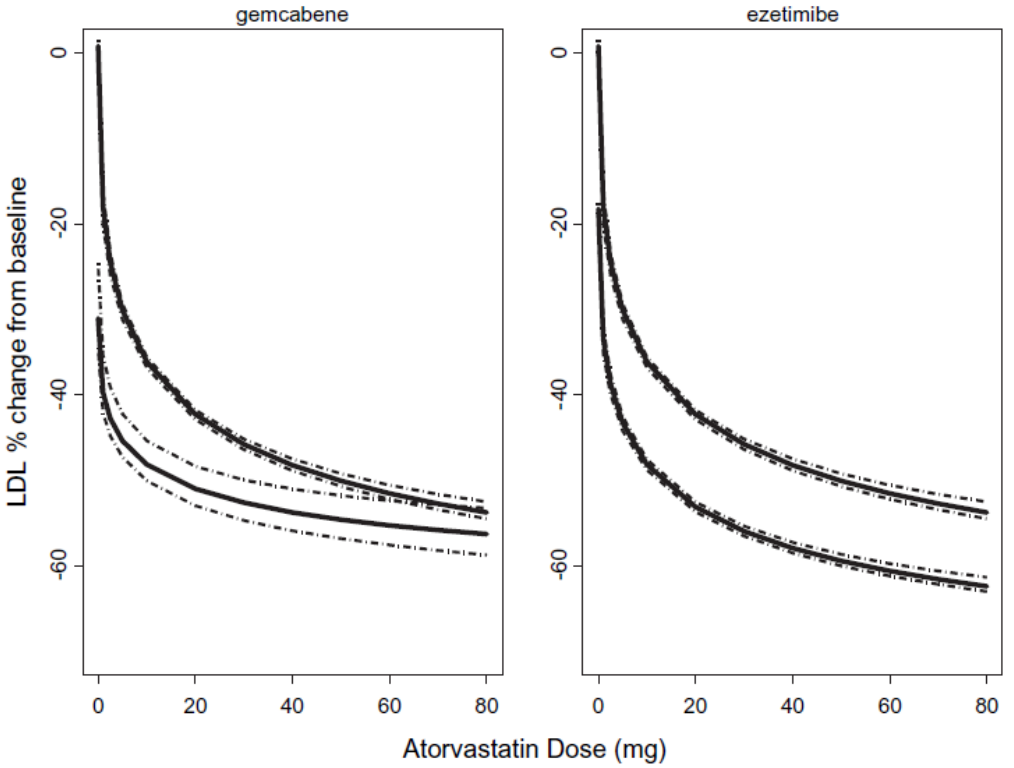
Statins Example







Lack of substantial improvement over ezetimibe provided basis to terminate gemcabene development prior to Ph3

The AAPS Journal 2005; 7 (3)

Example 2: A Phase 2 study of Drug X, a potent inhibitor of VEGFRs, in patients with advanced thyroid cancer

Primary Objective:

- Determine the activity of Drug X in advanced thyroid cancer as measured by the overall response rate (CR/PR rate by RECIST)

Secondary Objectives:

- Safety profile of Drug X
- Progression-free survival (PFS)
- Duration of response (DR)
- Overall survival (OS)
- Population pharmacokinetic analyses
- Explore relationships between clinical response and plasma soluble proteins

Example 2: Trial Design

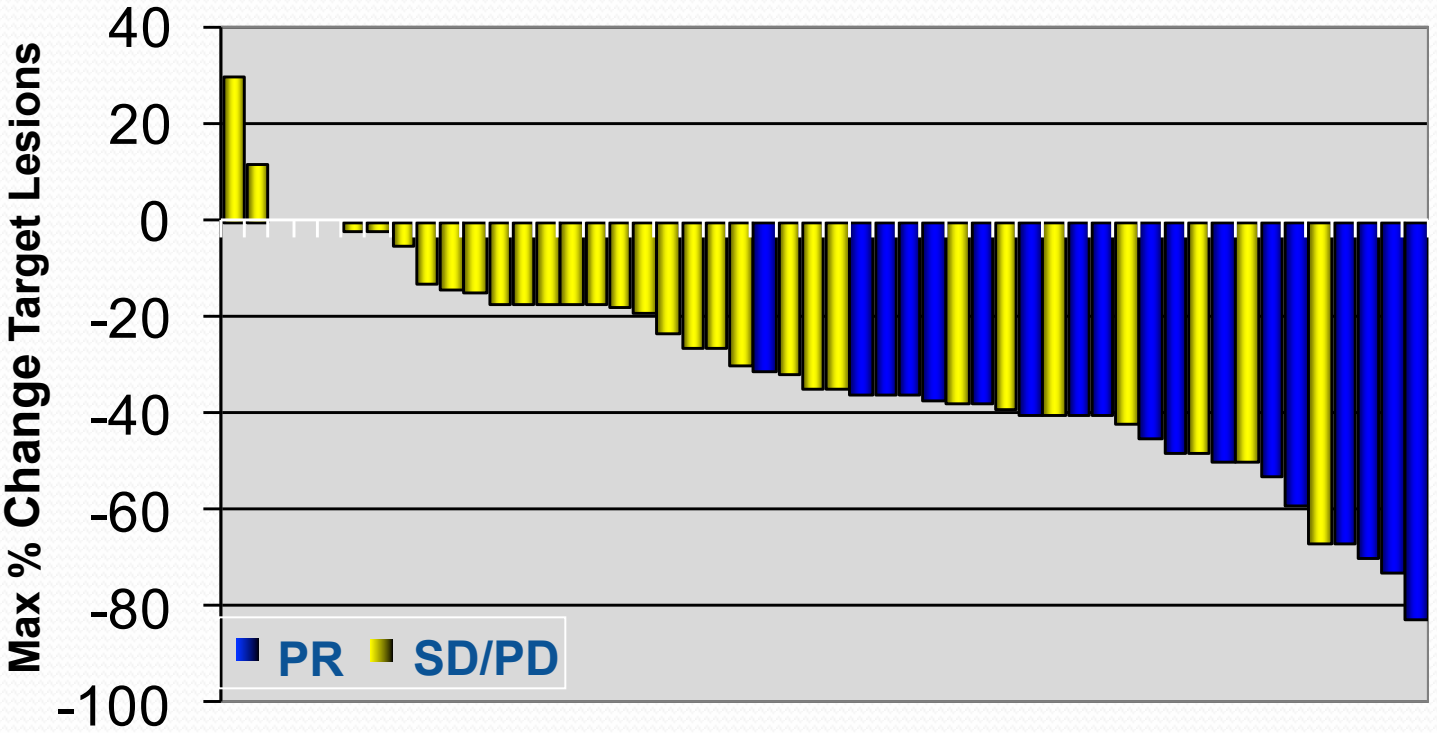
Design

- Phase 2, single-arm, multi-center trial
- Primary endpoint of overall response rate (H_0 = 5%, H_a = 20%)
- 2-stage design, target accrual of 32 patients
- Total N=60 if 4/32 responses observed

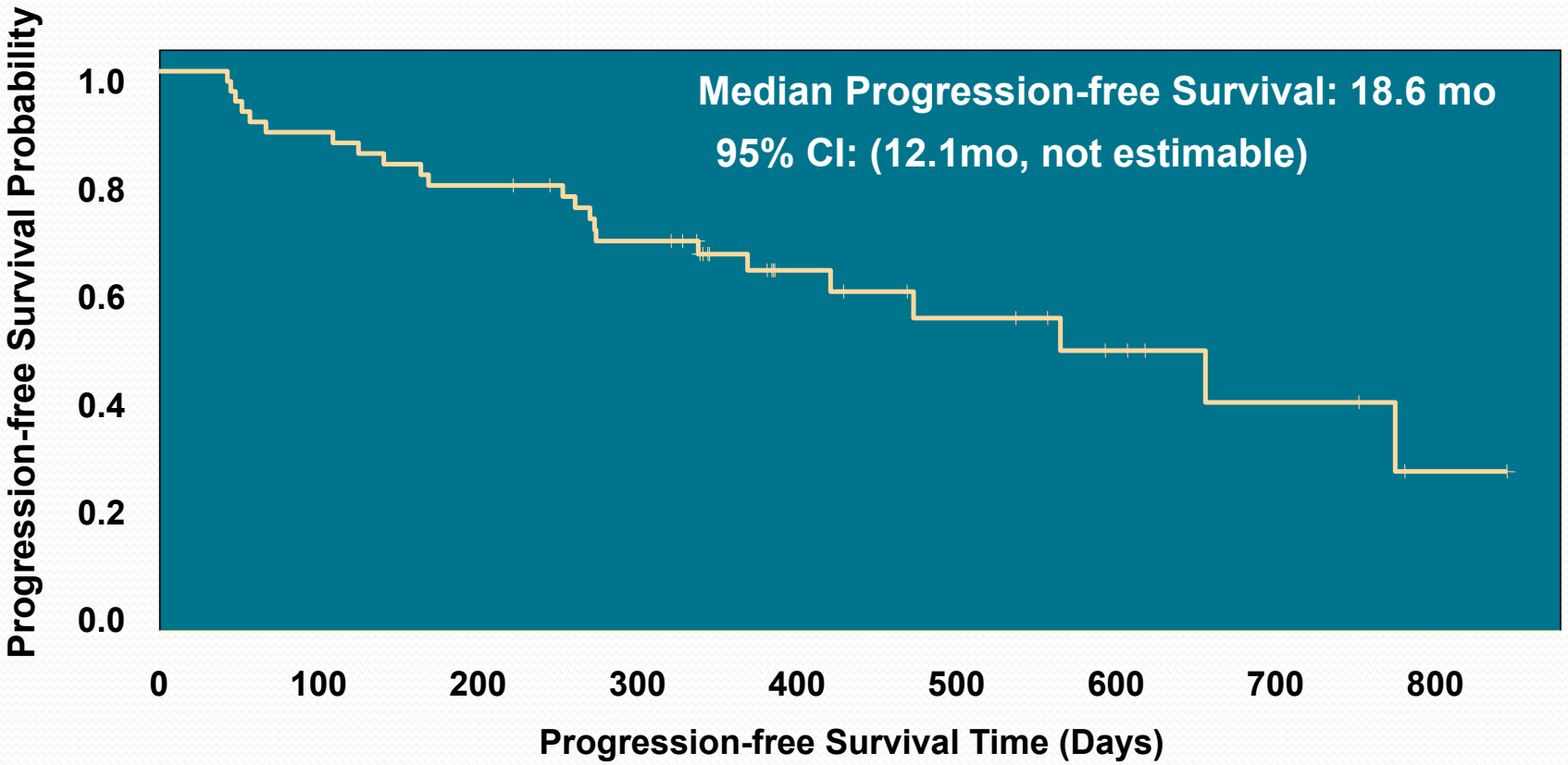
Treatment

- Drug X (starting dose): 5 mg orally twice daily
- Radiographic assessment at baseline and every 8 weeks

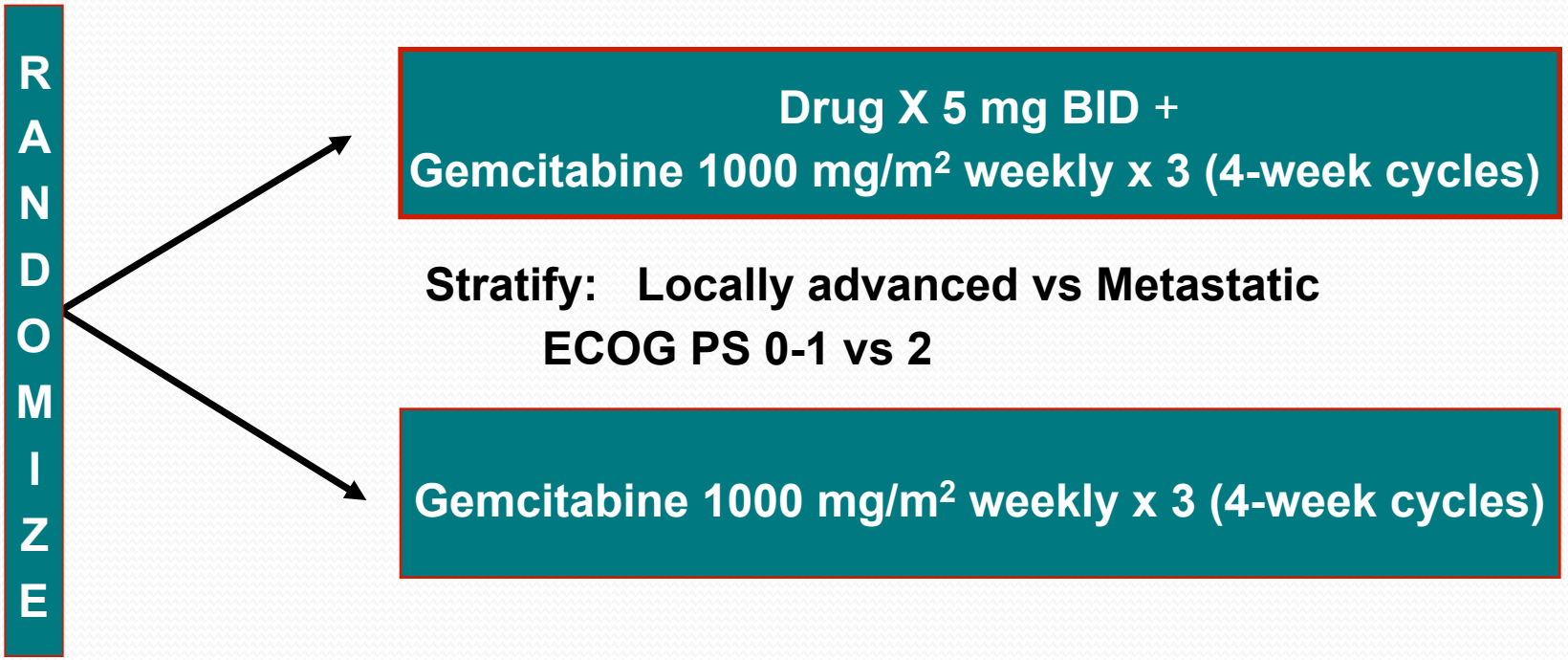
Example 2: Maximum % Reduction in Target Lesions (N=60)



Example 2: Progression-free Survival (N=60)

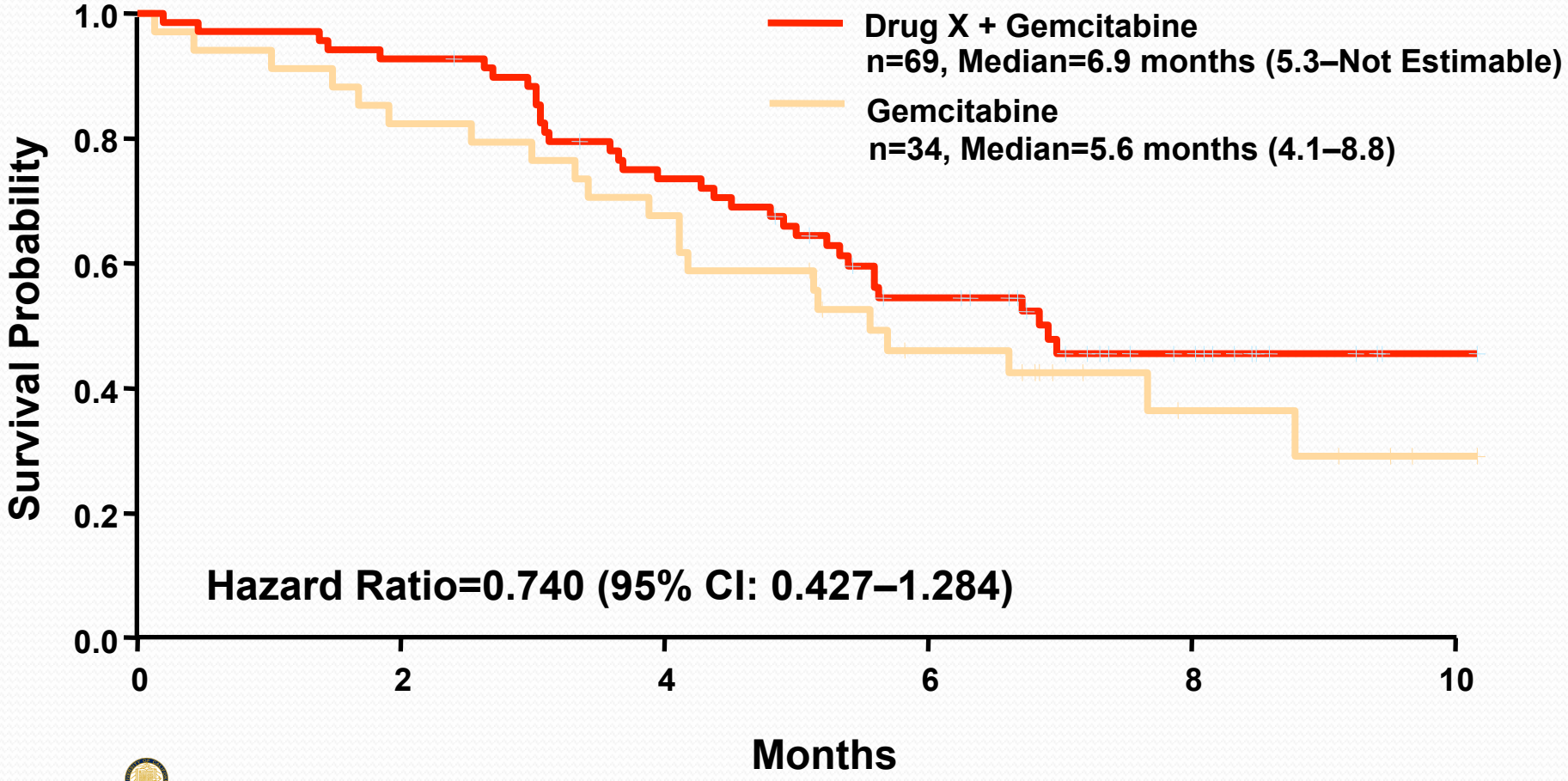


Example 3: A randomized phase 2 study of Drug X + gemcitabine vs. gemcitabine alone in advanced pancreatic cancer



N = 103	2:1 randomization	Primary Endpoint: OS

Example 3: Overall Survival, All Randomized Patients



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Summary:

- Phase II trials:
  - Test whether the therapeutic intervention benefits the patient (Efficacy)
  - Are designed to test response activity in a given type of cancer or disease.
  - Extend our understanding of toxicology and pharmacology of treatment (safety and tolerability)

- Phase II trials decide whether the new treatment is promising and warrants further investigation in a large-scale randomized Phase III clinical trial