# *Complex Adaptive Designs in Drug Development*

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# Adaptive Design: Definition

Adaptive Design is defined as a *multistage* study design that uses *accumulating data* to decide how to modify aspects of the study without undermining the *validity* and *integrity* of the trial

**Validity**

- providing correct statistical inference:
  - adjusted p-values, estimates, confidence intervals
- providing convincing results to a broader scientific community
- minimizing statistical bias

**Integrity**

- preplanning based on intended adaptations
- maintaining confidentiality of data
- 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
- Randomization Ratio
- Number of Interim Analyses
- Hypotheses

- Combining Conventional Phases in a Single Trial
  - Seamless Phase I/II
  - MAD and POC
  - POC and ADRS (Adaptive Dose Ranging Studies)
  - Seamless Phase II/III
  - Population finder
  - Indication Finder
  - Compound Finder

# Seamless Adaptive Designs

- **Seamless AD** - adaptive design, applied on the program level of a compound that achieves efficiency by combining in a single trial, objectives that are usually addressed in two separate conventional studies
- Such a strategy provides the obvious benefit of
  - reducing the timeline by running the two studies seamlessly
  - under a single protocol, with the same clinical team, the same centers and
  - achieves trial efficiency by combining the information from subjects in both studies in the final analysis

# Types of Seamless Adaptive Designs

| | |
|---|---|
| **Seamless Phase I/II Design** | • Phase I/II Oncology Trials with cytostatic and biological agents<br>• To identify the Optimal Safe Dose |
| **MAD and PoC** | • Two-stage adaptive approach in patients<br>• 1st stage – to identify MTD<br>• 2nd stage – to select dose and exposure levels (necessary cond.) |
| **PoC and ADRS** | • Start with the highest feasible tolerated dose and placebo<br>• If a pre-specified futility condition is satisfied => stop<br>• Otherwise, open enrollment to lower doses |
| **Adaptive Dose Ranging Design** | • Finding a target dose (MED, EDp, Optimal Safe Dose)<br>• Response Adaptive Allocation with 2 endpoints: efifcacy and safety<br>• Covariate Adjusted Response Adaptive Allocation |

# Types of More Complex Adaptive Designs

| | |
|---|---|
| Population Finder | • The fixed aspect of the trial is the indication (e.g., breast cancer) and the treatment (e.g., epidermal growth factor receptor inhibitor)<br>• The design aims to establish which subset of the population benefits most |
| Indication Finder | • The fixed aspect of the trial is the compound<br>• The competing options are different indications<br>• The design aims to establish which of the indications show therapeutic benefit |
| Compound Finder | • The competing options are several different compounds for the same indication.<br>• The design aims to identify the compound with the most impressive therapeutic index |
| Compound / Population Finder | • Multiple development candidates are assessed in parallel and matched with biomarker signatures of different subpopulations<br>• The design aims to dynamically change the allocation of new patients with a given signature to different compounds |

# SEAMLESS PHASE I/II DESIGNS

# Seamless Phase I/II Trials

- Dose escalation in Oncology Trials
  - With cytotoxic compounds
    - Higher the tolerated dose -- better potential for efficacy
    - Toxicity -- primary endpoint
    - Accurate determination of MTD -- optimal dose recommended for phase II
  - with cytostatic compounds
    - Probability of success is not monotonically increasing with dose
    - Both Toxicity and Efficacy -- primary endpoints
    - Accurate determination of best acceptable dose -- dose maximizing probability of positive efficacy response without toxicity

# Binary Efficacy and Safety Endpoints

**Bivariate Models** — Gumbel Model, Cox Model, Probit Model

**Probability of Efficacy**

$$\Pr(Y = 1 \mid D = x) \geq q_E$$

**Probability of unacceptable Safety**

$$\Pr(Z = 1 \mid D = x) \leq q_T$$

**Probability of Success**

$$\Pr(Y = 1, Z = 0 \mid D = x).$$

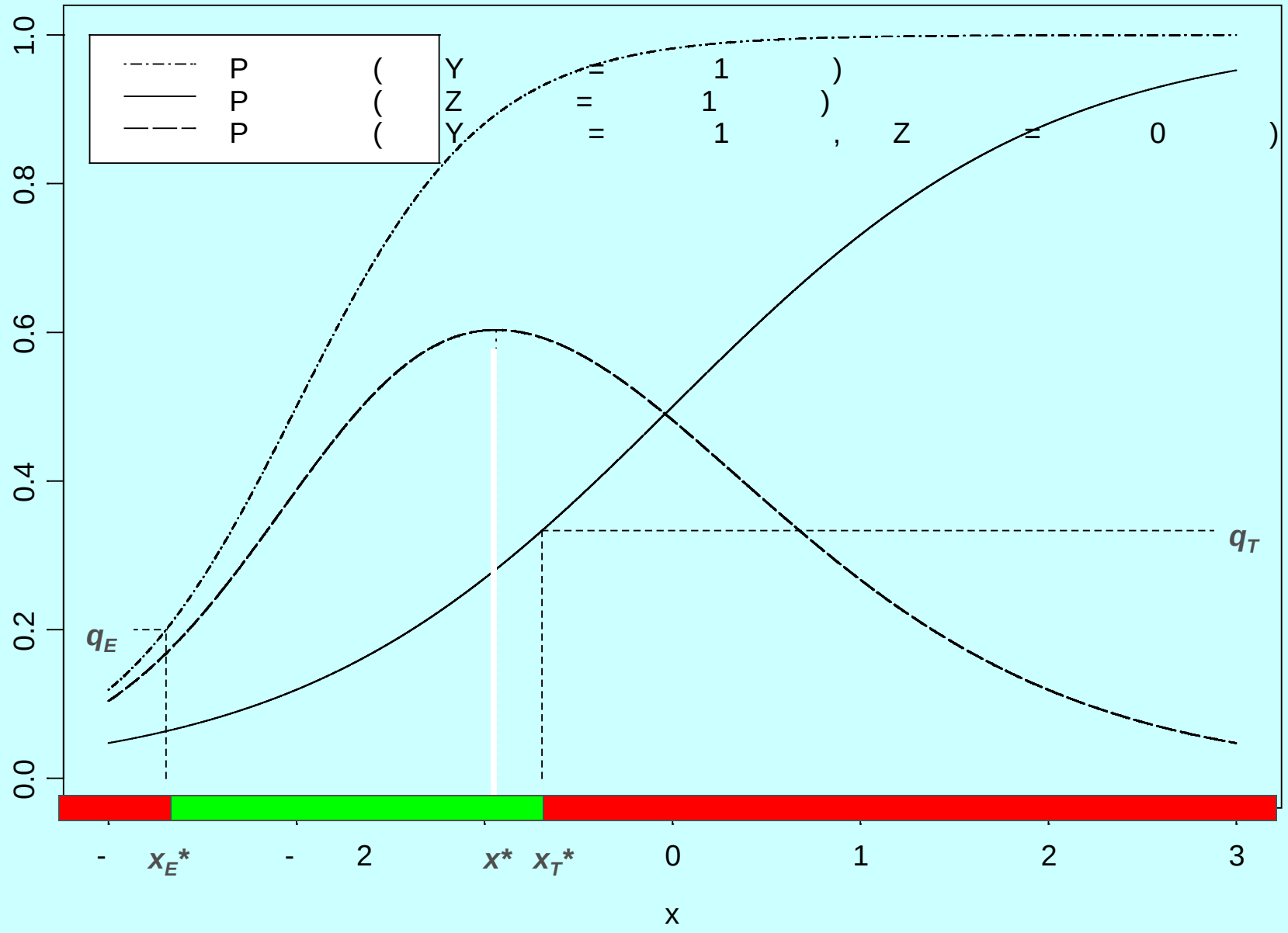
**Optimal Dose**

**OD = arg max** $\Pr(Y = 1, Z = 0 \mid D = x).$

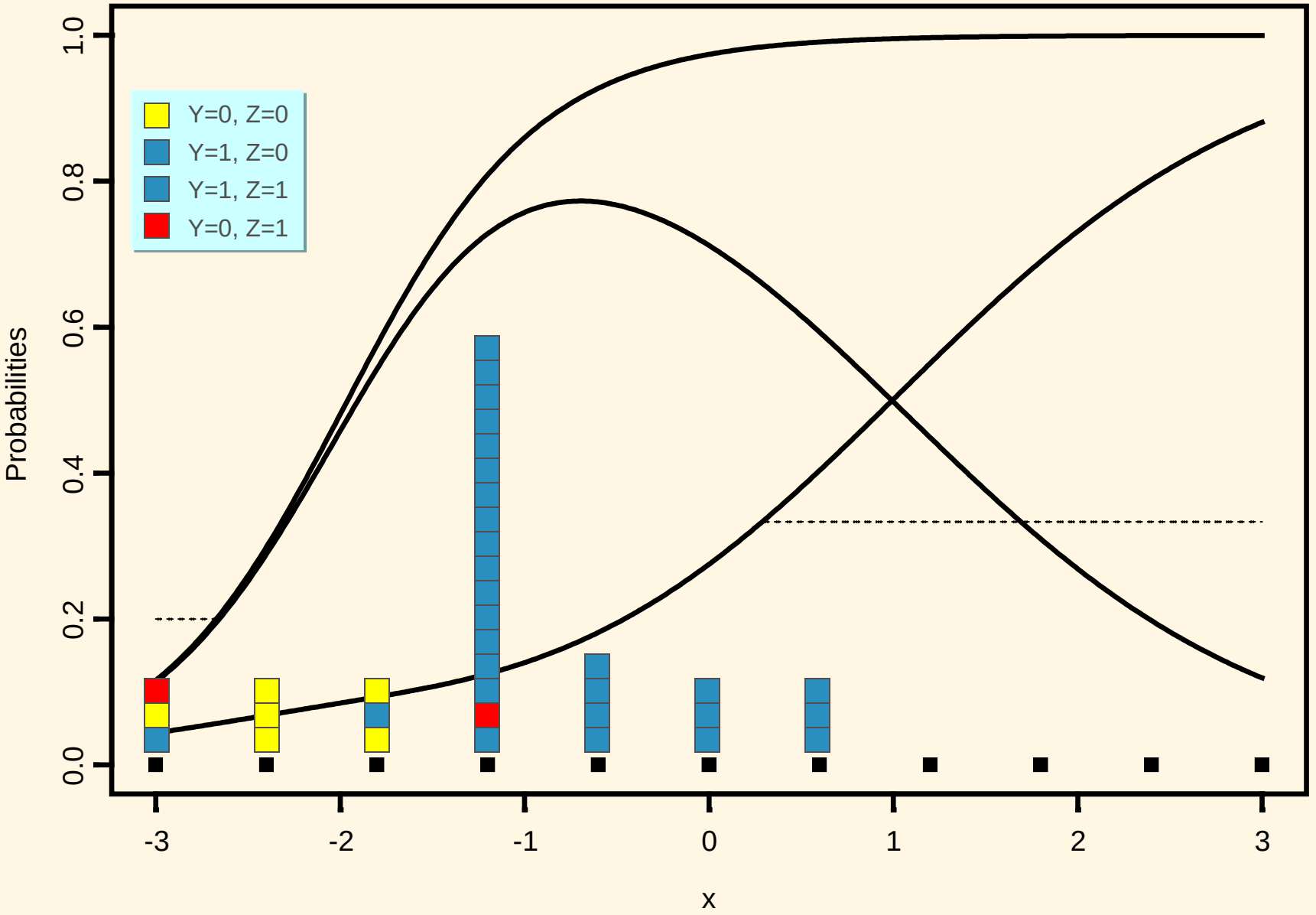

Dragalin, Fedorov. **Adaptive designs for dose-finding based on efficacy-toxicity response.** *JSPI.* 2006, 136: 1800-1823.

Dragalin, Fedorov, Wu. **Adaptive designs for selecting drug combinations based on efficacy-toxicity response.** *JSPI.* 2008, 138: 352-373.

# Dose Efficacy-Toxicity Response



# Simulation of the PADoD



# ADAPTIVE MAD and POC

# Adaptive MAD/POC Study in RA

- Seamless phase 1/2, randomized, double-blind, placebo-controlled, sequential/parallel design
- 6 cohorts (up to 33 subjects each)
  - 5 doses (10, 30, 50, 60, and 100 mg)
  - 1 pooled placebo cohort
- Treatment duration: 16 weeks, 4 subcutaneous injections
- Primary endpoint
  - ACR20 response at week 16
- Randomization
  - **Stage 1**: Initial dose escalation according to traditional MAD sequential format (3:1 active to placebo) using W4 DLT endpoint
  - **Stage 2**: After highest tolerated cohort is open, randomization will proceed in a parallel fashion for all “safe” treatment arms and placebo
  - Enrollment to futile doses can be stopped using W4 biomarker

# Seamless MAD/POC Design

**1st Stage**: Begin randomization in ascending MAD format until all doses are open

**Randomization**: 3:1 (TRT:Plbo) in each cohort

**Safety Decision**: Subjects will receive a 2nd dose only after a safety review of the 2nd dose in the preceding cohort

**Internal DMC** established for safety & futility decisions

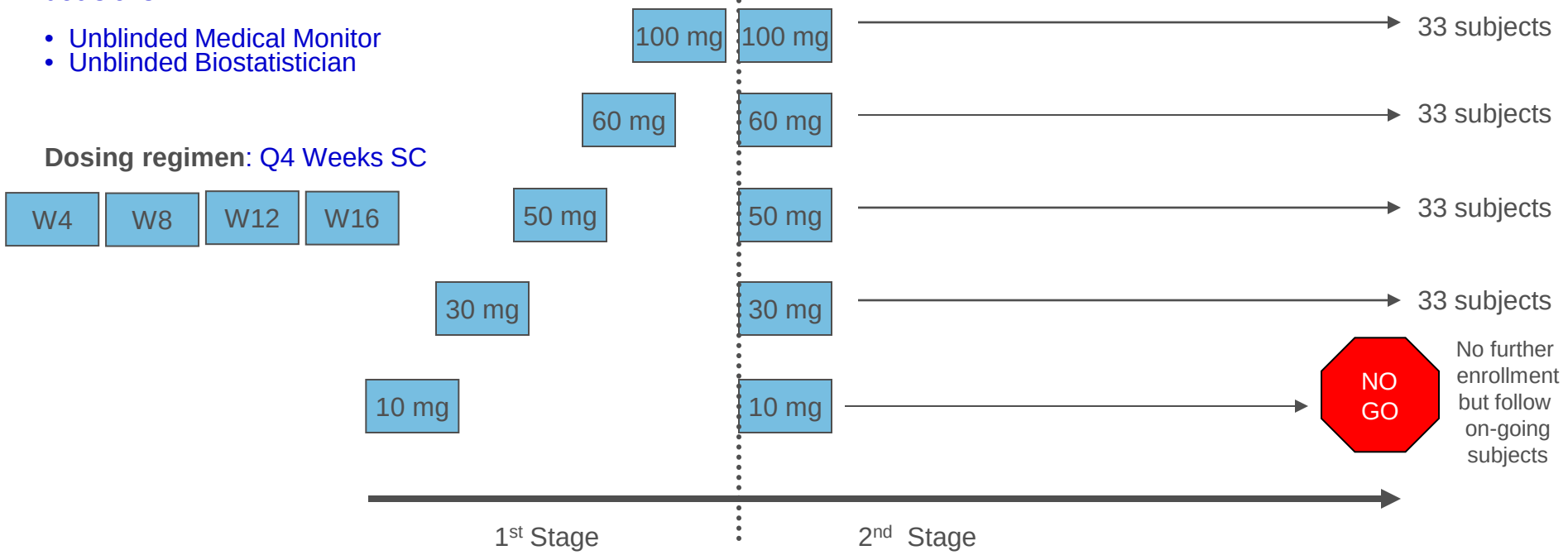
- Unblinded Medical Monitor
- Unblinded Biostatistician

**Dosing regimen**: Q4 Weeks SC

**2nd Stage**: After escalating to the maximum tolerated dose, new subjects will be randomized in equal allocation ratios to all tolerated TRT arms and placebo until futility is concluded or 33 subjects have been enrolled in a given treatment arm.

**Futility Decision**: Based on ACR20 and 25% reduction in CRP at 4 weeks

To avoid incongruent data, enrollment will not be stopped for futility in a higher dose if a lower dose is still ongoing



# POC and ADRS

# POC and Dose Ranging Study in Dental Pain

## Stage I

DR 900mg
DR 750mg
DR 600mg
DR 450mg
DR 300mg
DR 150mg
Plbo
Ctrl

Stop Futility

IA I

Stop NAS

Total Ssize ~30:

10 pats/arm

## Stage II

DR 900mg
DR 750mg
DR 600mg
DR 450mg
DR 300mg
DR 150mg
Plbo
Ctrl

Stop Futility

IA II

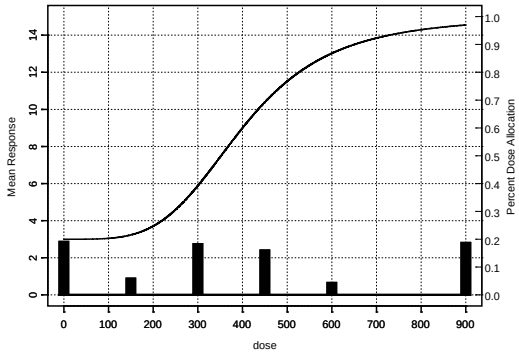
Stop NAS

Total Ssize ~ 65:

5:10 pats/arm

## Stage III

- Fit the Sig Emax Model
- Find the D-Optimal Design
- Allocate new patients




Total Ssize ~ 210

# ADAPTIVE DOSE RANGING STUDIES

# ADRS: Continuous Both Efficacy and Safety Endpoints

**Bivariate Normal**

$$(Y, Z) \sim \mathcal{N}_2\left((\mu_y, \mu_z), \begin{pmatrix} \sigma_y^2 & \rho\sigma_y\sigma_z \\ \rho\sigma_y\sigma_z & \sigma_z^2 \end{pmatrix}\right)$$

**Mean Efficacy**

$$\mu_y(x, \theta) = \theta_1 + (\theta_2 - \theta_1)\frac{x^{\theta_4}}{x^{\theta_4} + \theta_3^{\theta_4}}$$

**Mean Safety**

$$\mu_z(x, \theta) = \theta_5 \exp(\theta_6 x)$$

**Conditional Mean Efficacy given acceptable Safety**

$$E(Y|Z < z^*) = \mu_y - \rho\sigma_y\lambda(-\alpha_Z),$$

where

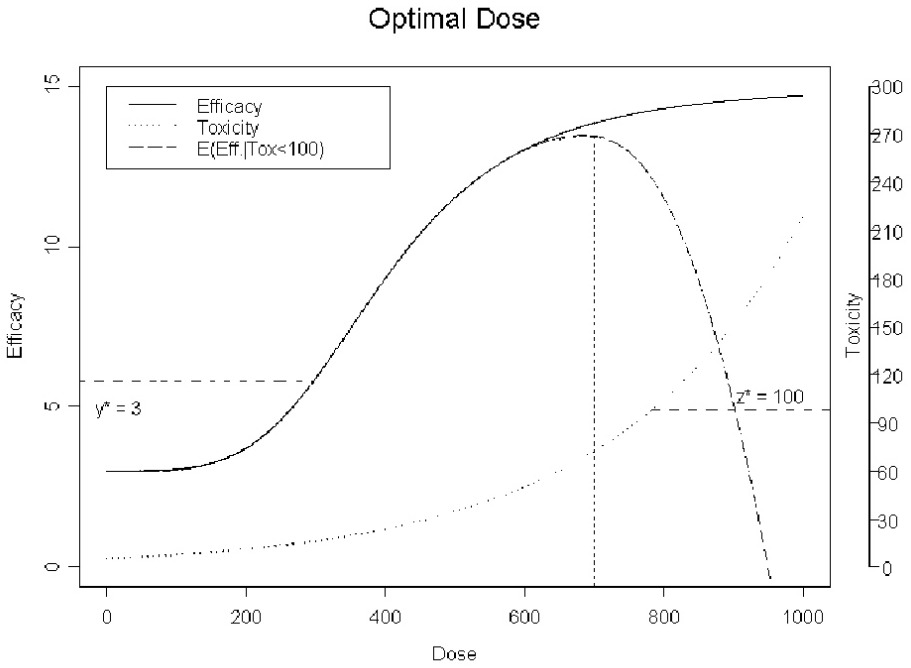
$$\alpha_Z = \frac{z^* - \mu_z}{\sigma_z} \quad \text{and} \quad \lambda(\alpha_Z) = \frac{\phi(\alpha_Z)}{1 - \Phi(\alpha_Z)}.$$

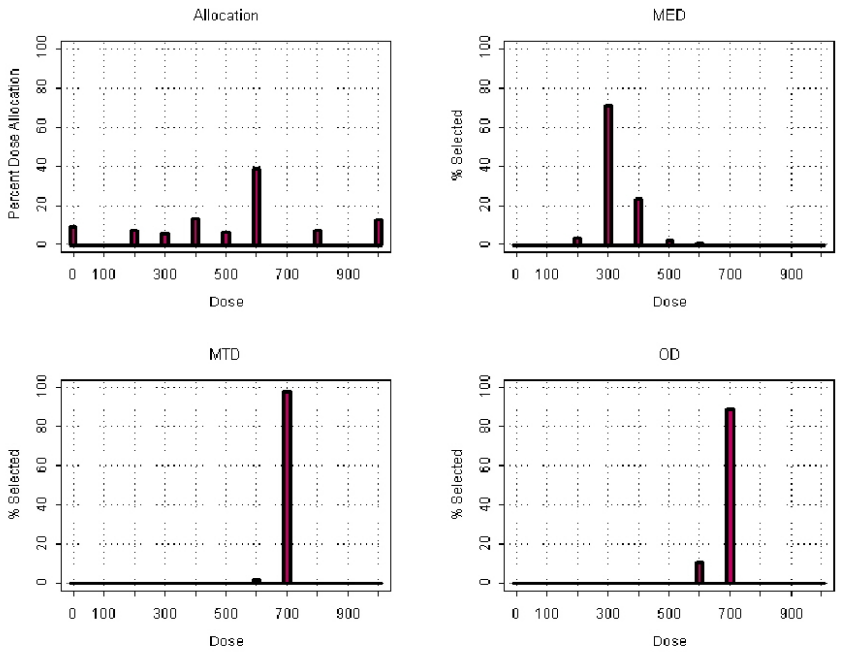
**Optimal Dose**

$$\begin{aligned} \text{OD} &= \arg\max_{\mathcal{X}} E(Y|Z < z^*) \\ &= \arg\max_{\mathcal{X}} \{\mu_y - \rho\sigma_y\lambda(\alpha_Z)\}. \end{aligned}$$

Padmanabhan, Hsuan, Dragalin.
**Adaptive Penalized *D*-Optimal Designs for Dose Finding Based on Continuous Efficacy and Toxicity**.
*Statistics in Biopharmaceutical Research.* 2010, 2(2): 182-198

# Adaptive D-optimal Design



# Continuous Efficacy-Binary Safety Endpoints

**Mean Efficacy**

$$\mu_y(x,\theta) = \theta_1 + (\theta_2 - \theta_1)\frac{x^{\theta_4}}{x^{\theta_4} + \theta_3^{\theta_4}}$$

**Probability of unacceptable Safety**

$$P(Z = 1|x) = \int \pi f(y|x)dy = p,$$

**Conditional Probability of unacceptable Safety given Efficacy**

$$\begin{aligned} \pi &= P(Z = 1|Y, D = x) \\ &= logit\ (\lambda_0 + \lambda_x x + \lambda_y Y) \end{aligned}$$

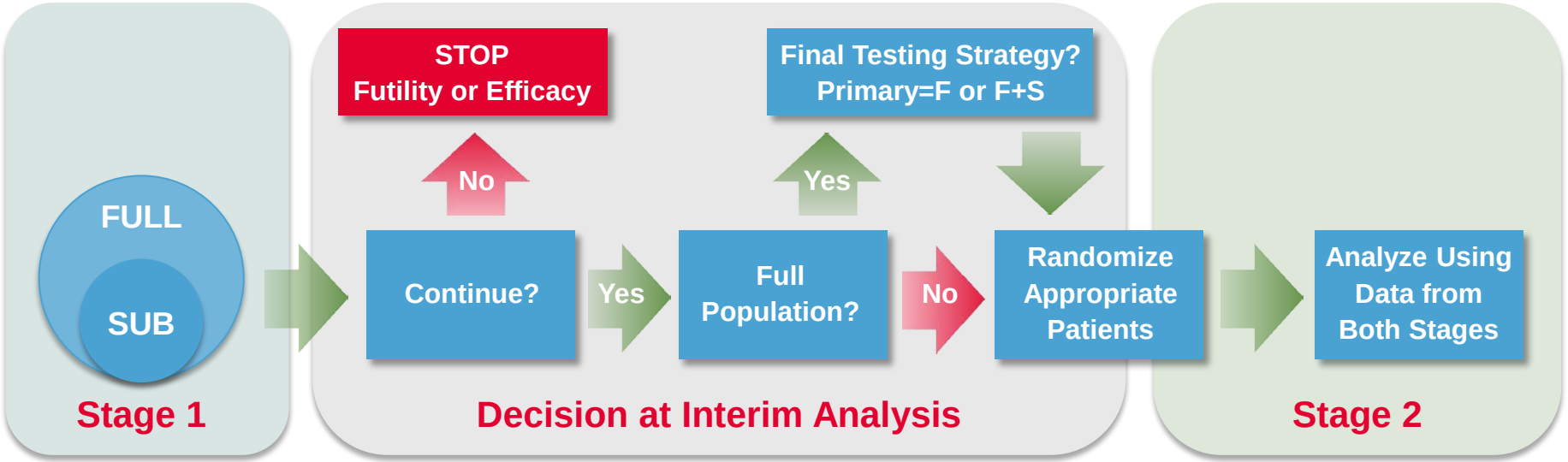
**Optimal Dose**

$$\mathrm{OD} = \arg\max_{\mathcal{X}} E(Y\ I_{\{Z=0\}}|x)$$

$$E(Y\ I_{Z=0}|x) = \mu_y(x,\theta) - \int y\pi f(y|x)dy$$

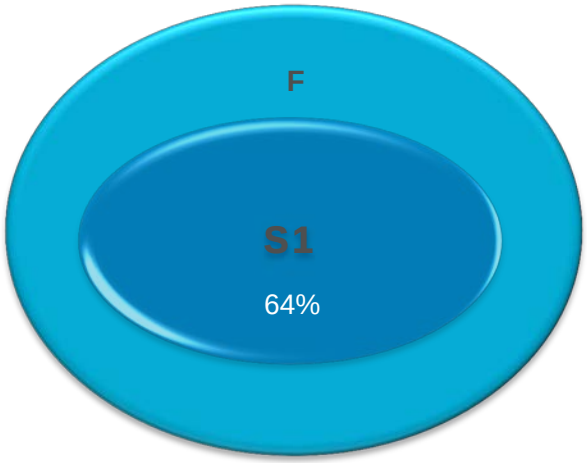
# ADAPTIVE POPULATION ENRICHMENT

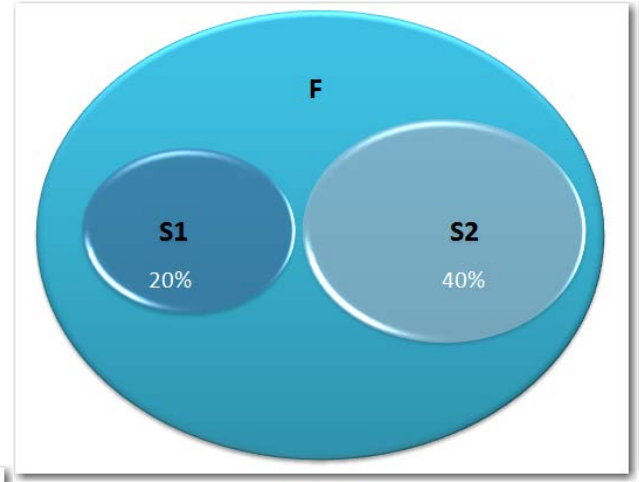
# Phase 2/3 Study in HER2- Early Stage BC Patients



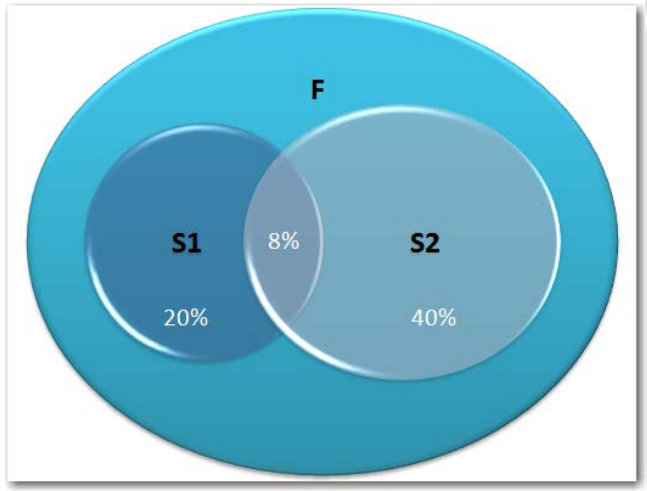

- Stage 1 objective
  - Stop for futility/efficacy
  - To continue with HER2- (Full) population – (F) or (F+S)
  - To confirm greater benefit in TNBC Subpopulation – (S)
  - To adjust the sample size
- Stage 2 data and the relevant groups from Stage 1 data combined

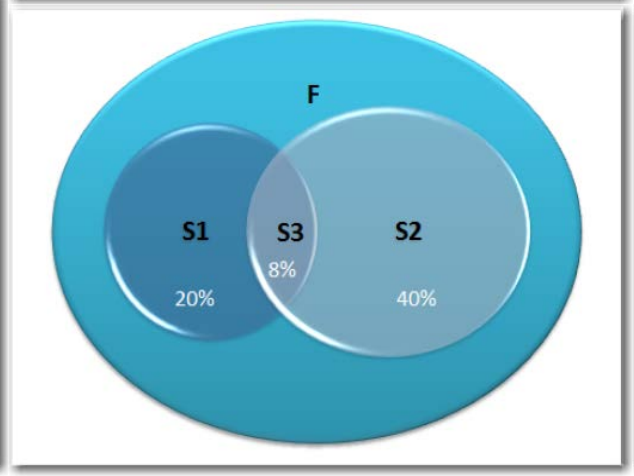
# Different Other Configurations

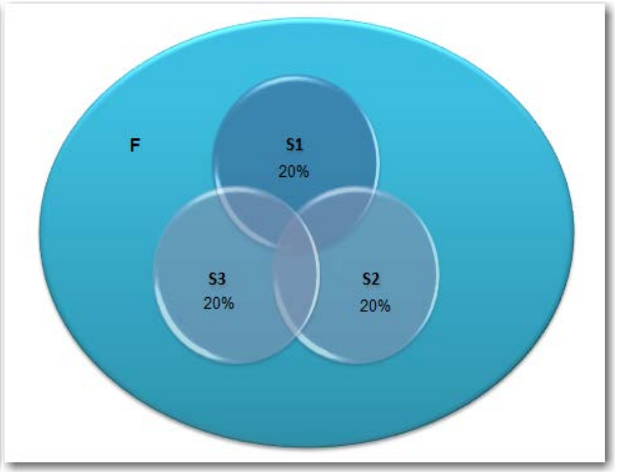






# Indication Finder in Erbb2+ Cancers

# Standard Proposed Phase II Design Setting

- Objective: evaluate Xnib activity in erbB2+ cancers
- Design : Five arm, open-label phase 2 study (group sequential)
  - Population : Patients with erbB2+ tumors (FISH+ or IHC3+)
  - Tumor types:
    - gastric, ovarian, pancreas, bladder, other erbB2+ cancers
  - Primary Objective: CBR (Responses + SD>=16Weeks)
  - Efficacy target: CBR>=30% (uninteresting rate=10%)
- Two-stage design: 2/18 first-stage, 6/36 second-stage (0.05/0.9)
- Sample size: up to 200 (~40 patients per arm)

# General design assumptions

- Overall max sample size=250
- 1st IA after 75 patients overall
  - Results in ~5-25 patients accrued in each histology
- 2nd and subsequent IAs – every 16 weeks
  - If look after each 8 wks, results in ~20+ IAs with only +2-3 information points added at later stages=> change to 16wks, anticipate ~10 IAs given enrollment numbers
- Max number of cycles to determine outcome: 3 (24wk endpoint)

# General design assumptions

- Hierarchical Model

$$\pi_h = \Pr\left(\text{Response} \mid \text{histology } h\right)$$

- $R_h$- historical (log-odds) rate of success in histology $h$

$$\theta_h = \log\left(\frac{\pi_h}{1-\pi_h}\right)$$

$$\theta_h \sim N\left(R_h + \mu, \sigma^2\right)$$

- Hyper-prior for each of the parameters

$$\mu \sim N\left(\mu_0, \tau_0^2\right)$$

$$\sigma^2 \sim IG\left(\alpha_0, \beta_0\right)$$

# Prior assumptions

- Dirichlet Prior for longitudinal modeling:
  - Transition probabilities: during cycles 1 and 2 (8 & 16 wks)
    - Pr (progress | stable)=0.5
    - Pr (stable | stable)=0.3
    - Pr (response | stable)=0.2
  - Transition probabilities: during cycle 3
    - Pr (progress | stable)=0.5
    - Pr (stable | stable)=0.001
    - Pr (response | stable)=0.499
  - Prior probability of response 0.3

# Summary

- Adaptive designs offer much more than just sample size re-estimation and early stopping, especially in exploratory phase
- Adaptive designs assist and enhance the decision on which product to develop
- Adaptive designs enable more effective decision-making throughout the whole development process
- The adoption of an adaptive design strategy across the drug development process brings a number of important benefits:
  - increased R&D efficiency,
  - increased R&D productivity,
  - increased probability of success at phase III