Cytel

Adaptive Design in Early Phase Clinical Trials

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Console Overview

***Configurable windows – expand or contract as needed**

Media Player

Speaker Bio

Resources

Questions

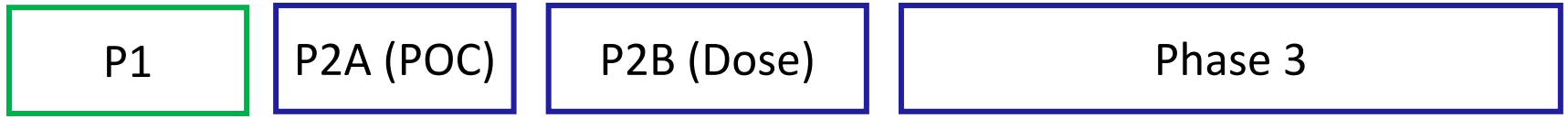
Survey

Agenda

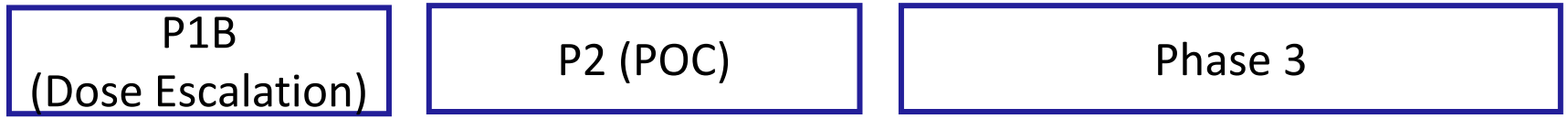
- Background
- Dose Escalation
- Decision Making
- Combination Studies
- Dose Finding
- Enrichment
- Q&A

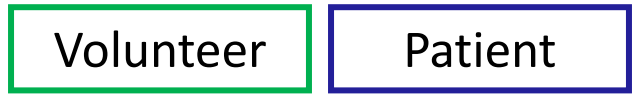
Clinical Development Plans

Non-Oncology

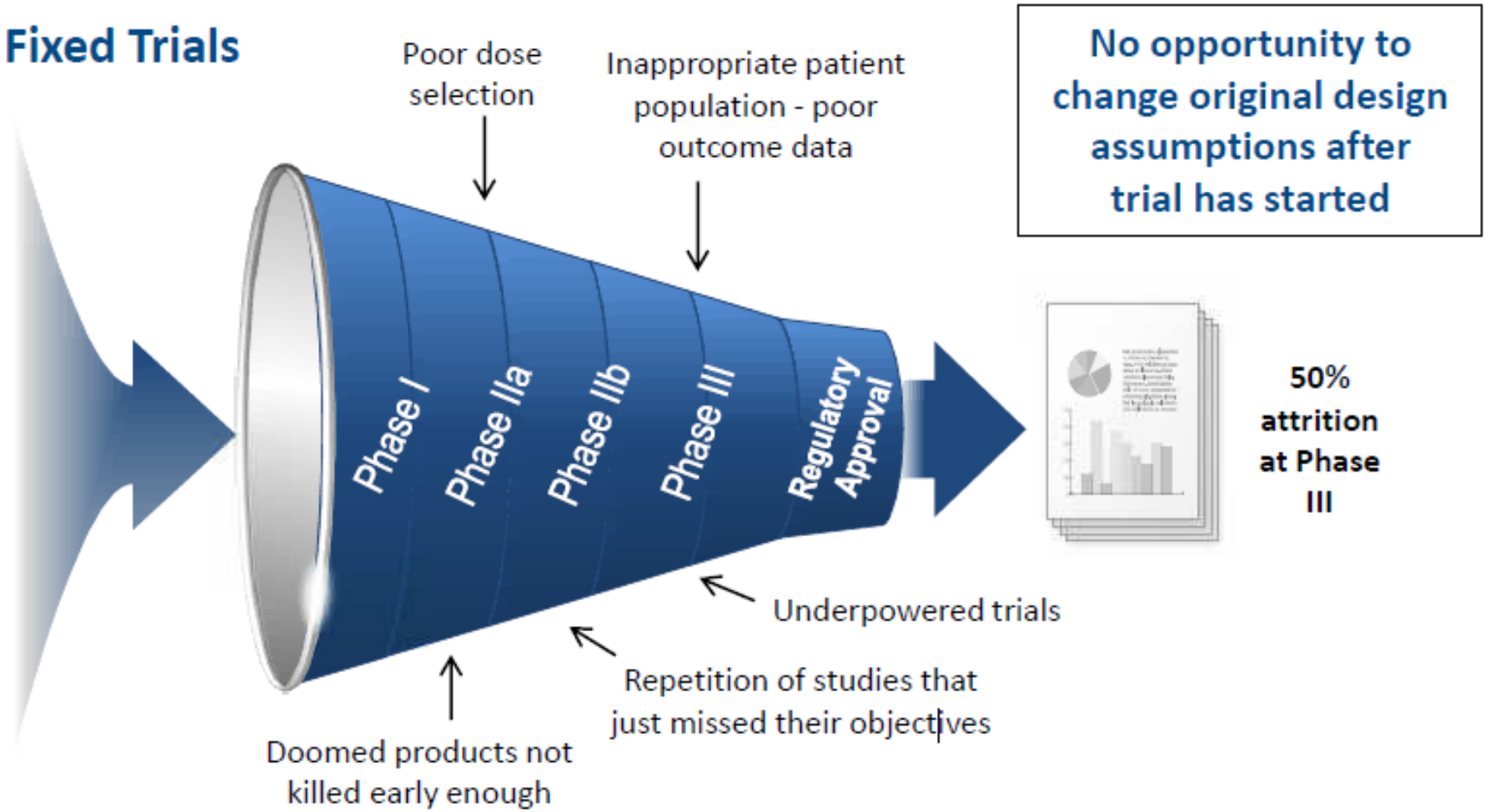


Oncology

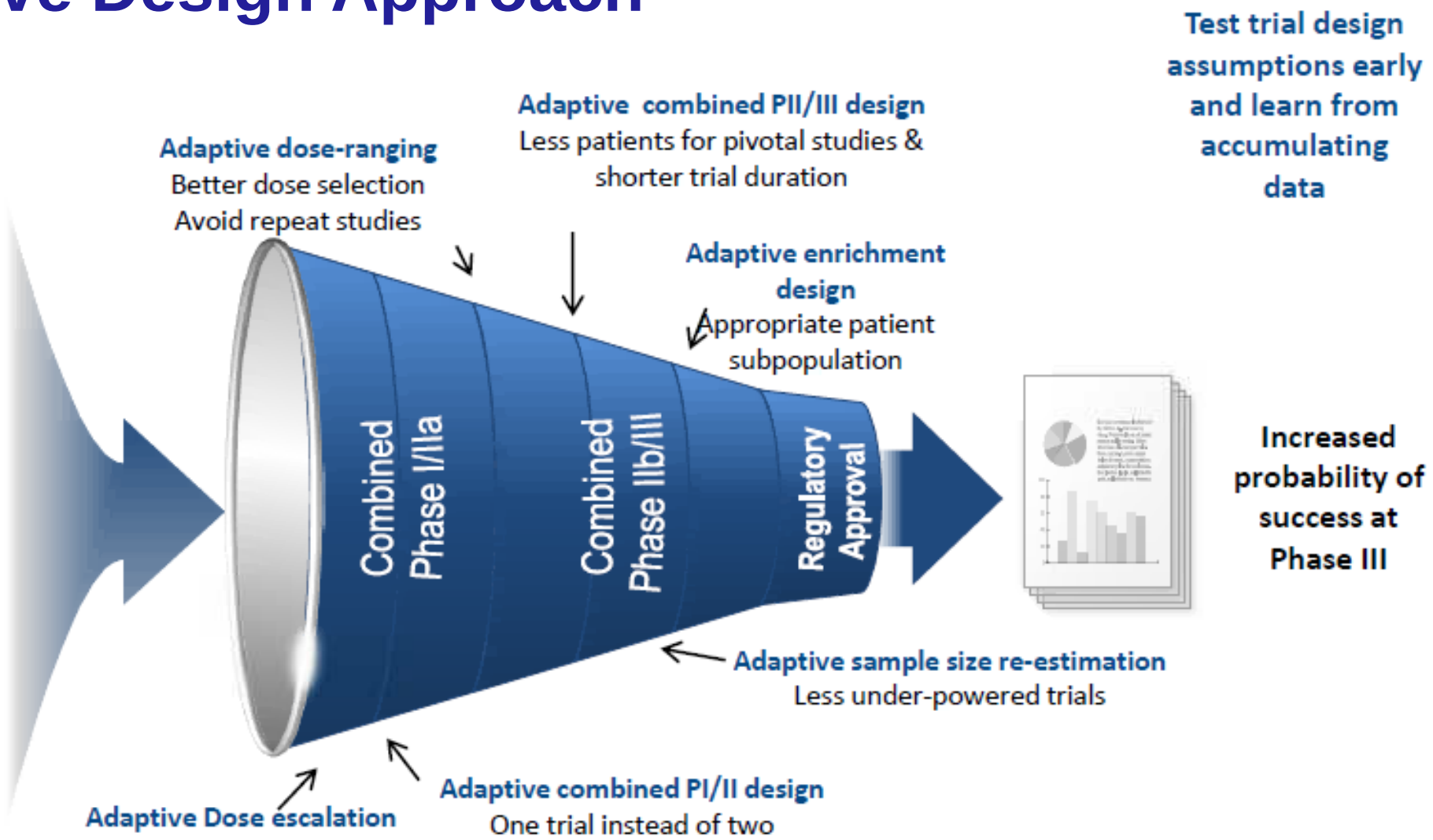




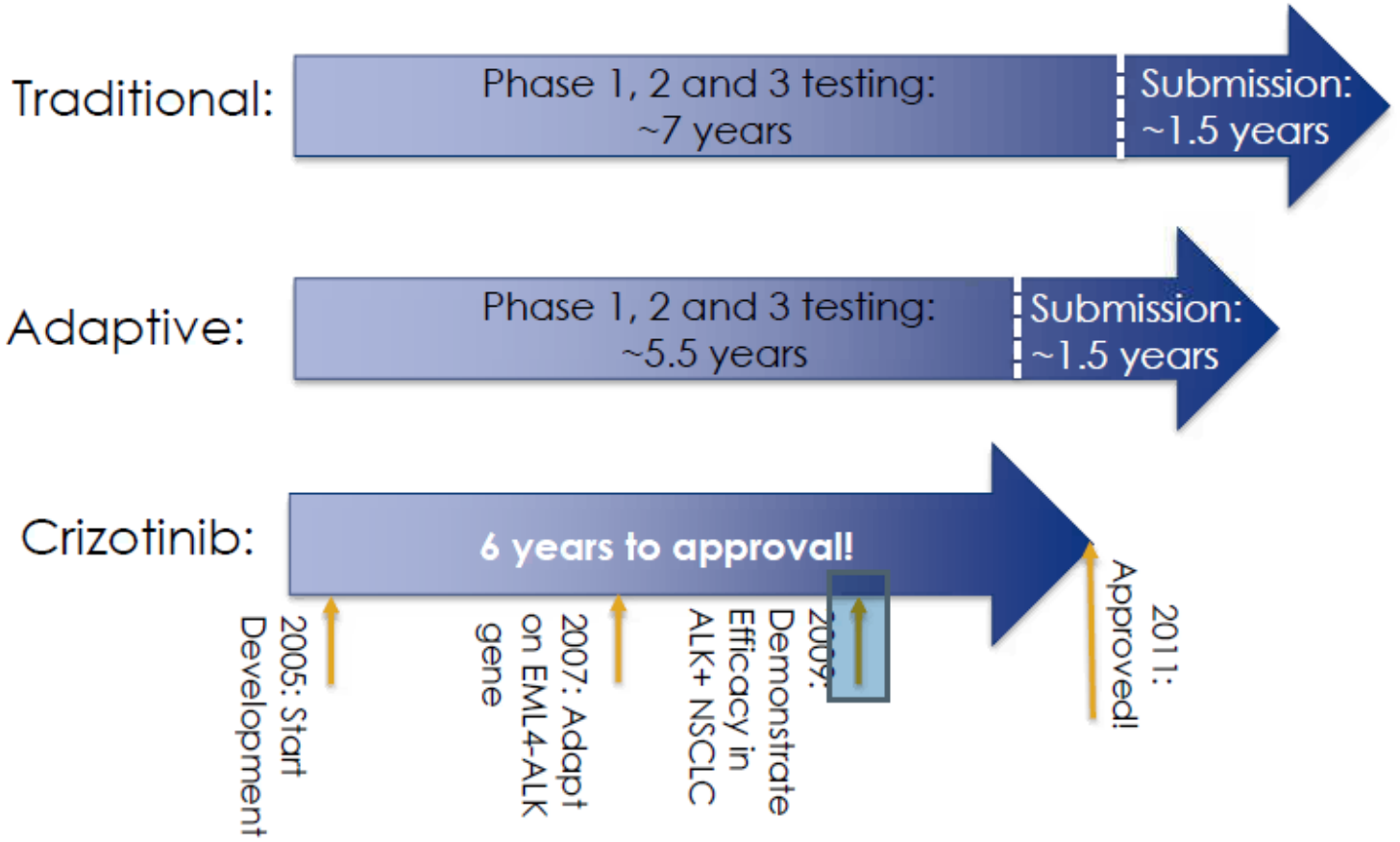
Traditional Approach



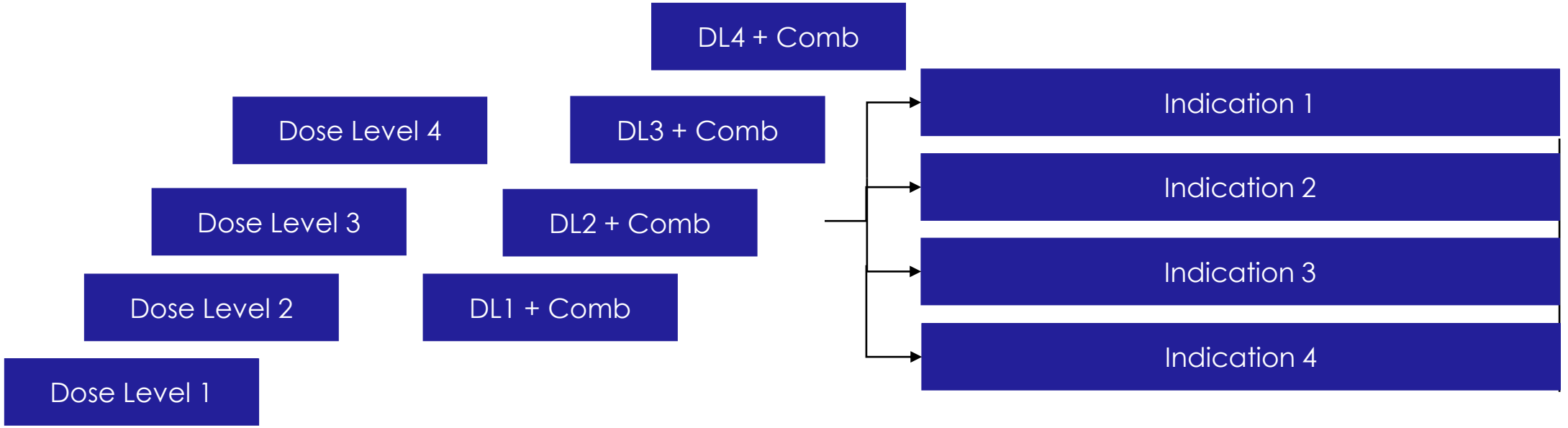
Adaptive Design Approach



Benefit of Adaptive Designs



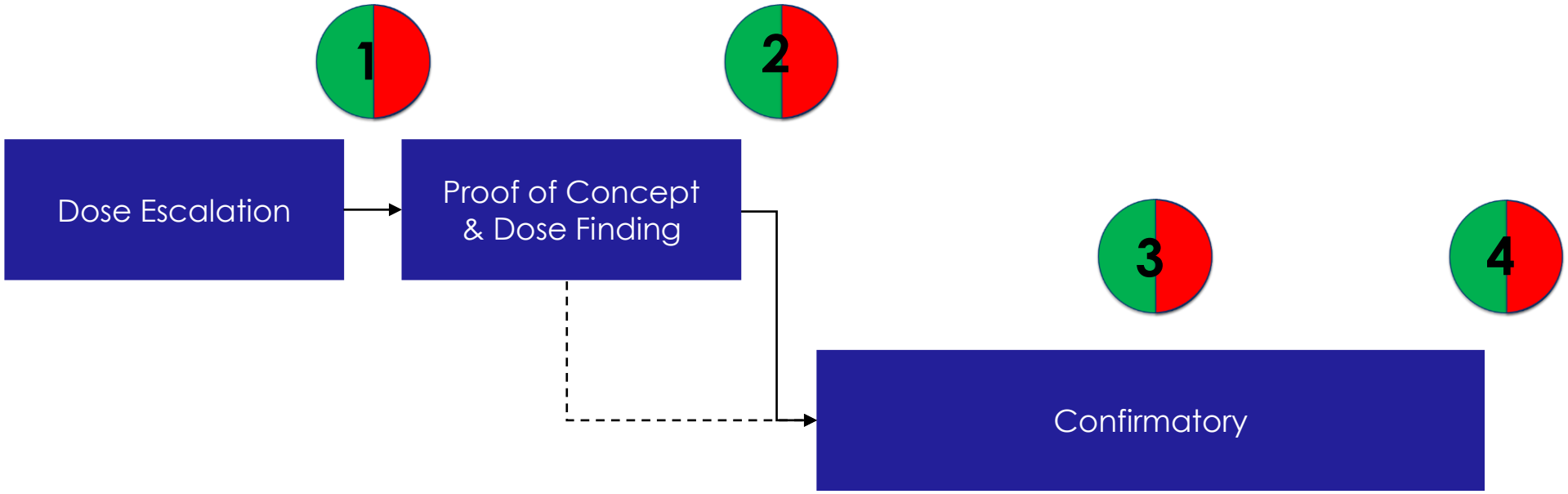
Example Adaptive Phase 1/2 Design



Objectives
Dose Limiting Toxicity
PK
Efficacy Biomarker

Objectives
Comparison to Target Responses
Interim for Accelerate/Futility decision

Clinical Development Decision Points



Agenda

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- **Dose Escalation**
- Decision Making
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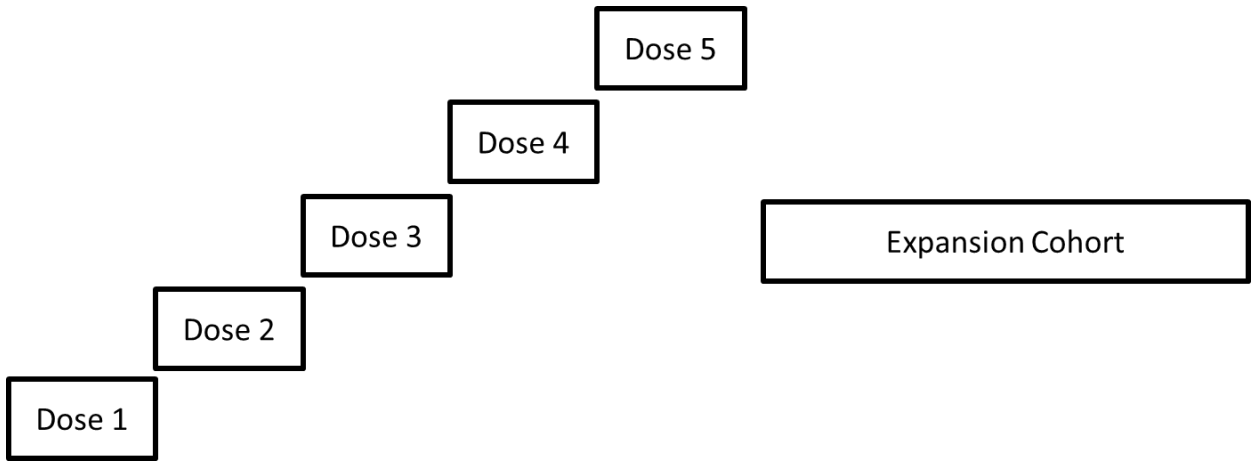
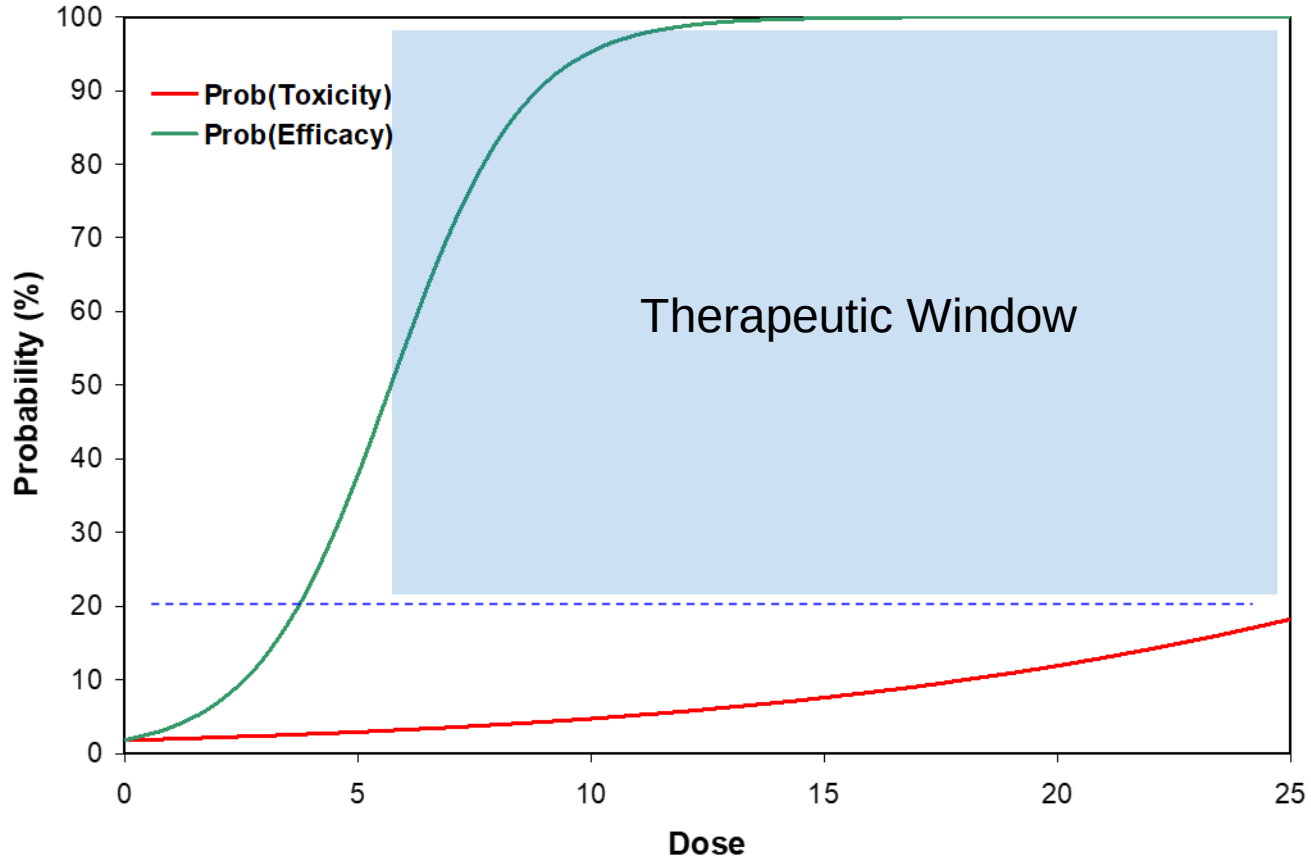
- Q&A

SAD/MAD/Dose Escalation



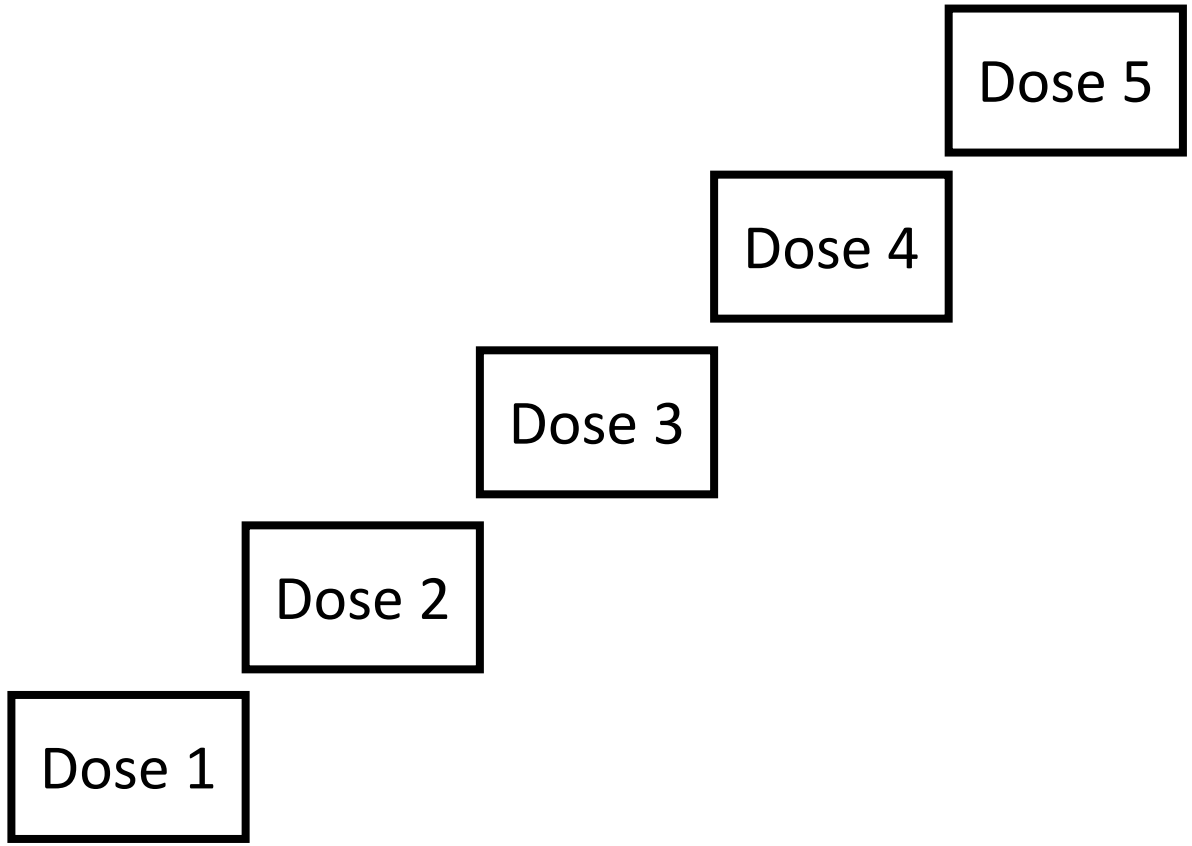
- Sequential cohorts, can repeat doses in Single Ascending Dose (SAD) and Multiple Ascending Dosing (MAD)
- Escalation is based on observing Dose Limiting Toxicities (DLT)
- Dose Escalation Committee (DEC) govern escalation decisions
- PK data collected for further dose/schedule decisions
- Response Biomarkers are valuable to determine correct activity thresholds

Dose Ranging



Questions: Is there a range of safe doses where we can explore efficacy?
Is there a Maximum Tolerated Dose?

Dose Escalation



- Small cohorts with randomization to placebo
- Doses are logarithmically spaced – usually doubled
- Starting dose < 1/100 predicted human dose
- At the end of each dose cohort a Data Review Committee assesses safety data and decides on dose increases
- Escalation is based on observing Dose Limiting Toxicities
- Traditional 3+3 rule common
- No statistician involved

Escalation Rules

Algorithm-Based

- 3+3
- mTPI
- i3+3
- Adaptive Dose Insertion
- Dual Agent PIPE

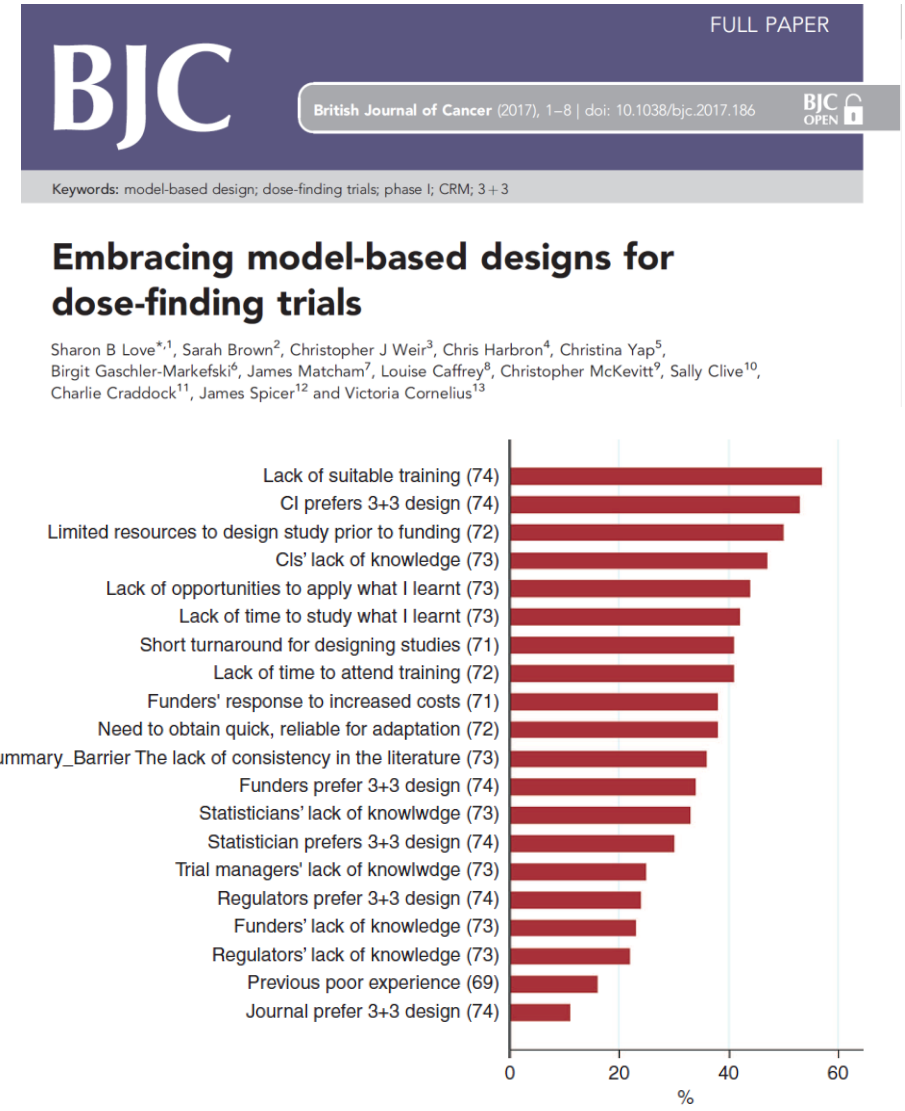
Model-based

- CRM
- TITE-CRM
- BOIN
- BLRM
- Dual Agent BLRM

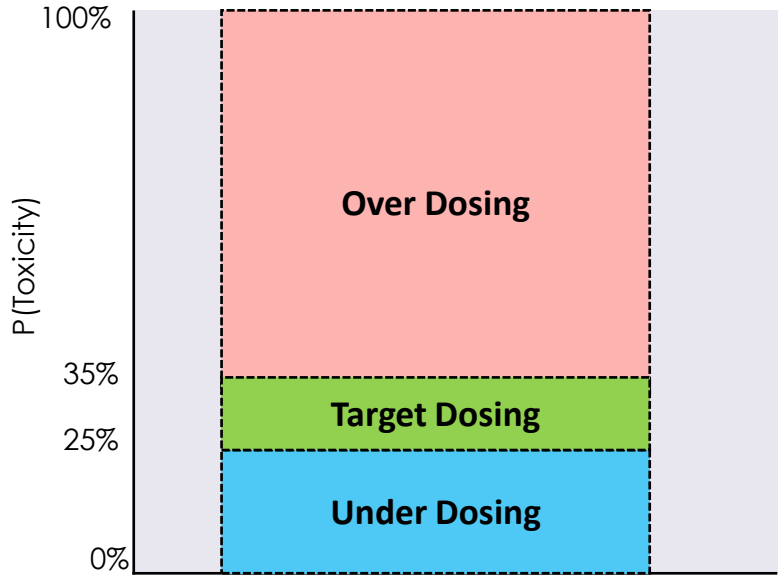
All approaches are methods to estimate the Maximum Tolerated Dose

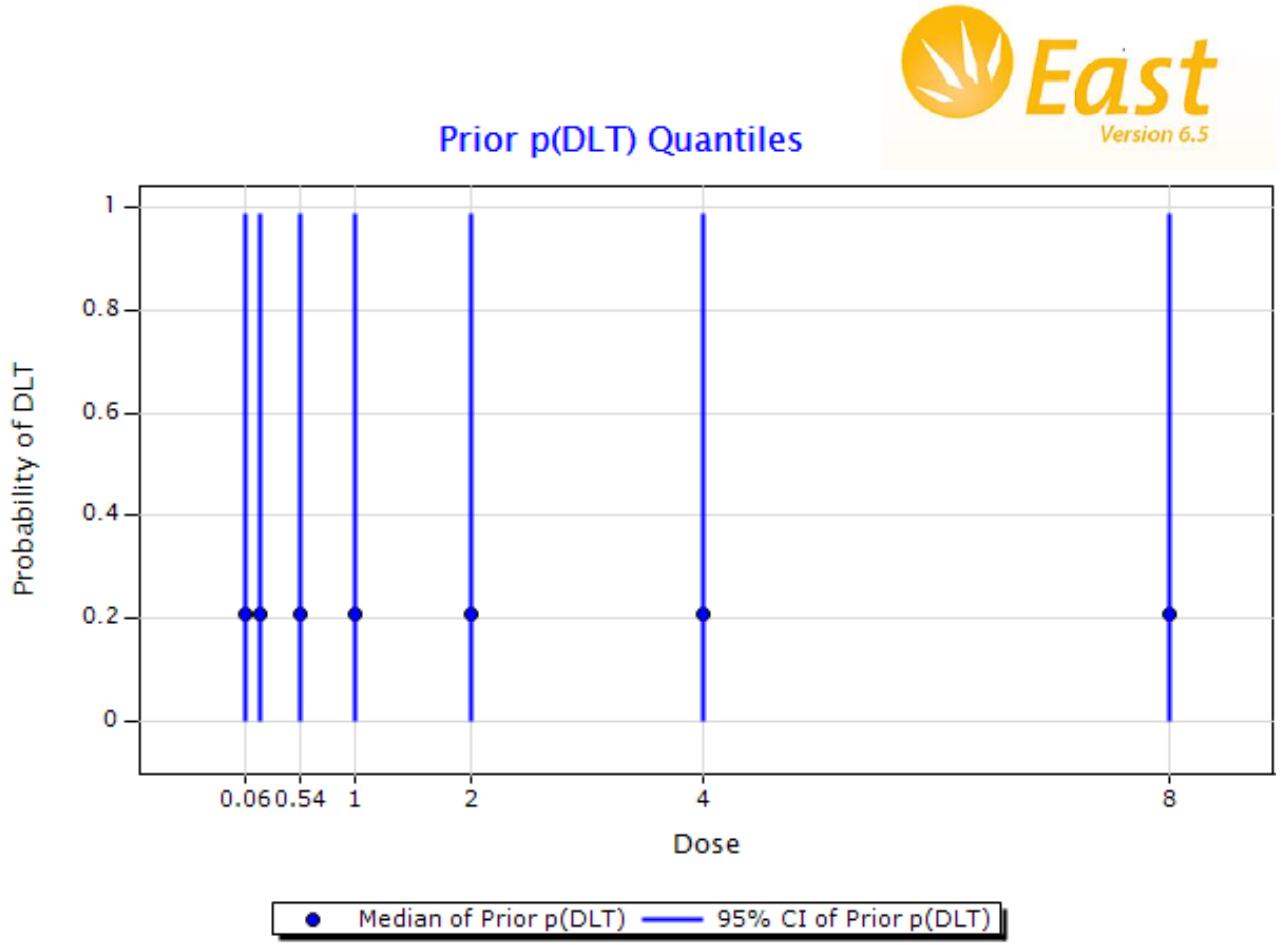
Documented Issues with 3+3 Design

- Chance of recommending wrong Phase 2 Dose is high, so future trials will need to dose adjust
- What happens with N=2, 4, 5 in a cohort?
- Considerable inertia amongst trialists to adopt better methods
- Cannot include intermediate doses
- No information to guide stepping from monotherapy to combination
- Need to repeat recommended dose with additional cohort to confirm safety outcome

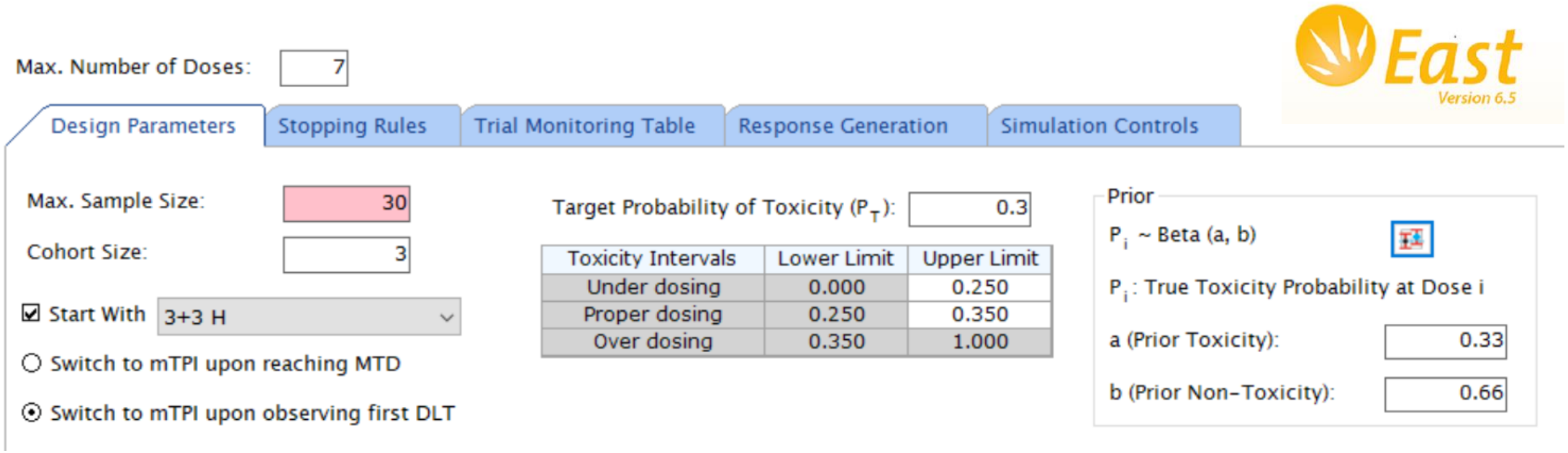


Modified Target Probability Interval (mTPI)





mTPI in EAST


Max. Number of Doses: 7
East
Version 6.5
Design Parameters
Stopping Rules
Trial Monitoring Table
Response Generation
Simulation Controls
Max. Sample Size: 30
Cohort Size: 3
Start With 3+3 H
Switch to mTPI upon reaching MTD
Switch to mTPI upon observing first DLT
Target Probability of Toxicity (P_T): 0.3
Toxicity Intervals | Lower Limit | Upper Limit
Under dosing | 0.000 | 0.250
Proper dosing | 0.250 | 0.350
Over dosing | 0.350 | 1.000
Prior
P_i ~ Beta (a, b)
P_i: True Toxicity Probability at Dose i
a (Prior Toxicity): 0.33
b (Prior Non-Toxicity): 0.66

mTPI Trial Monitoring Table

East Version 6.5

Edit Trial Monitoring Table: Click any cell to edit ◉ mTPI ○ mTPI-2

Number of patients treated at current dose

Number of Toxicities

r\n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	DU	DU	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		DU	DU	DU	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E
3			DU	DU	DU	DU	DU	S	S	S	S	S	S	E	E	E	E	E	E	E
4				DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S	S	S	E	E
5					DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S	S
6						DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S
7							DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
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13													DU	DU	DU	DU	DU	DU	DU	DU
14														DU	DU	DU	DU	DU	DU	DU
15															DU	DU	DU	DU	DU	DU
16																DU	DU	DU	DU	DU
17																	DU	DU	DU	DU
18																		DU	DU	DU
19																			DU	DU

E = Escalate to the next higher dose

S = Stay at the current dose

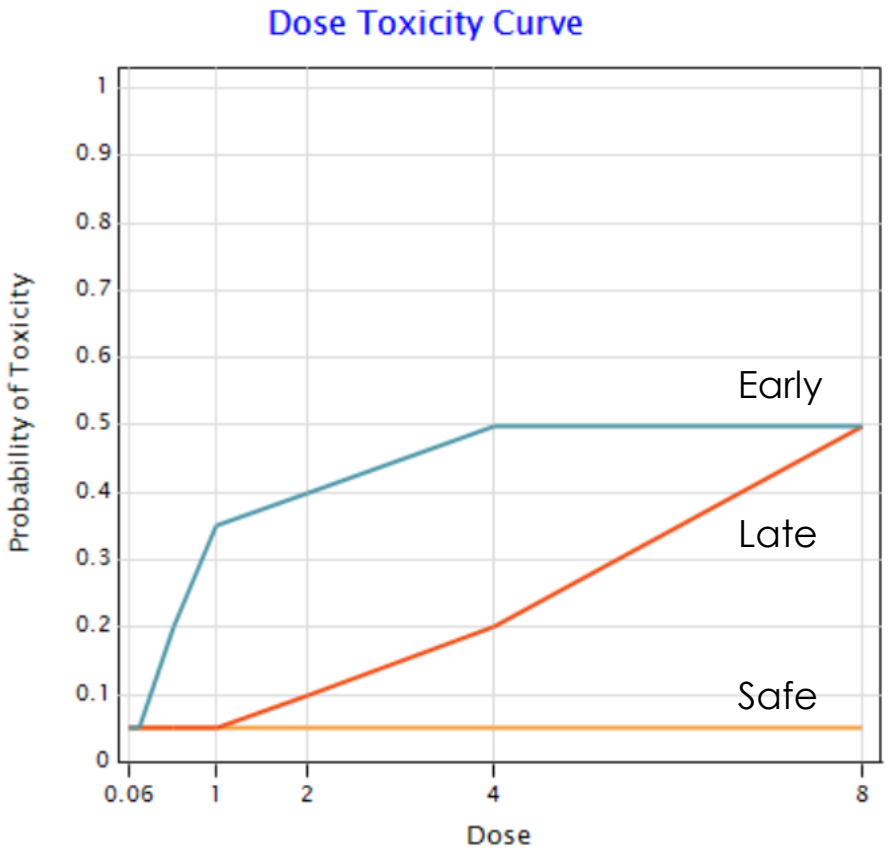
D = De-escalate to the next lower dose

DU = The current dose is unacceptably toxic

Target Toxicity (%) = 30%

Sample Size = 30

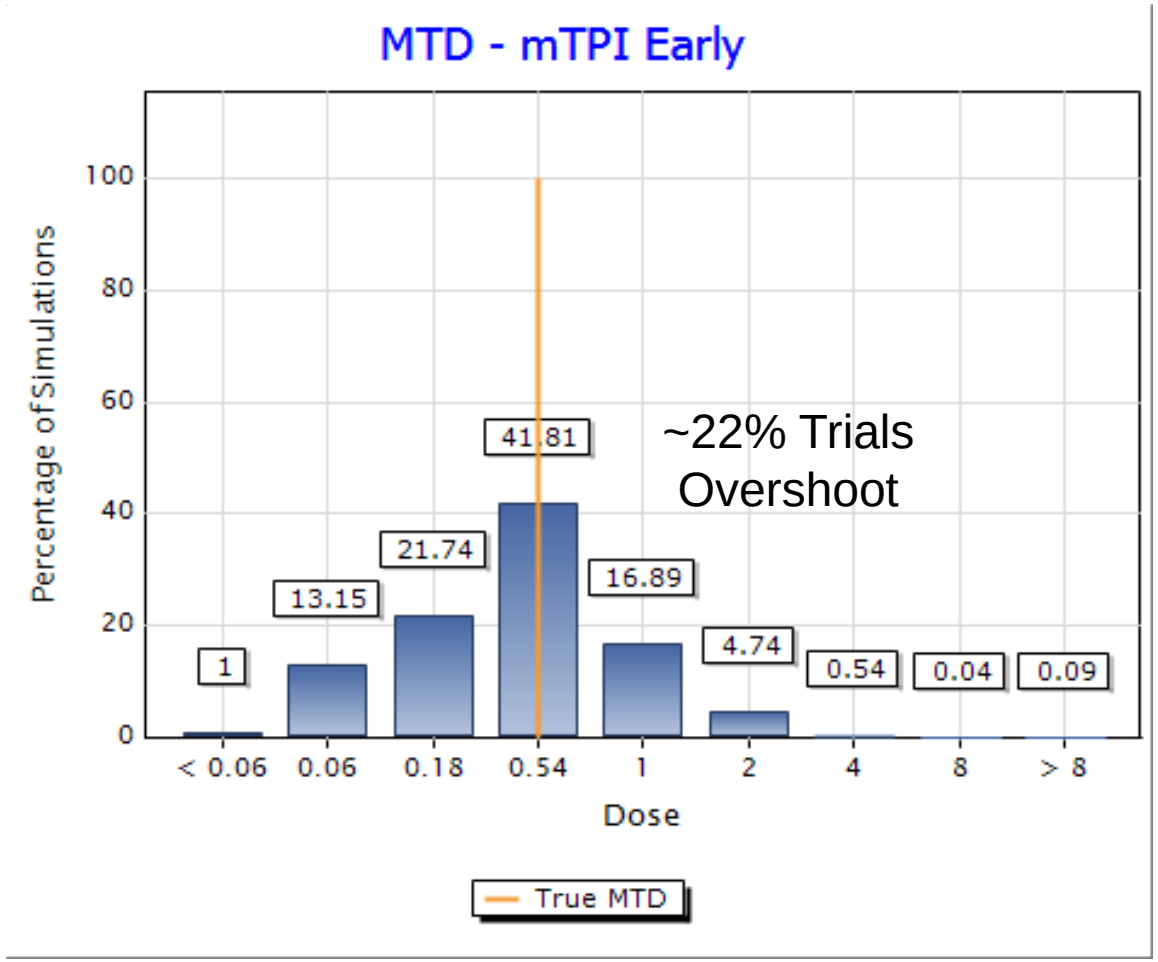
Example: Toxicity Profile Scenarios

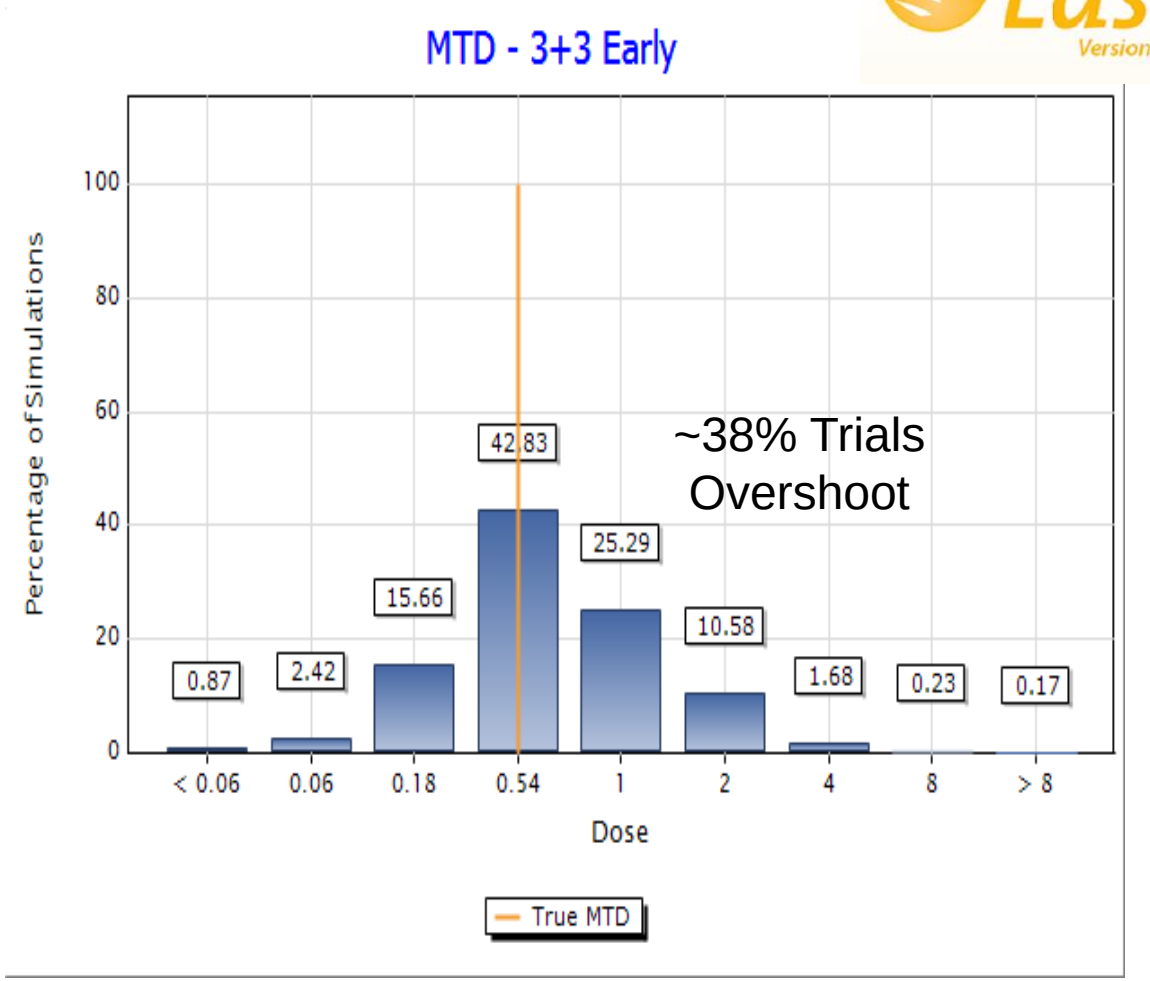


Probability of Toxicity

Toxicity Profile	Dose Level						
	0.06	0.18	0.54	1	2	4	8
Safe	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Late	0.05	0.05	0.05	0.05	0.1	0.2	0.5
Early	0.05	0.05	0.2	0.35	0.4	0.5	0.5

mTPI vs 3+3: Early Scenario





mTPI Comments

- mTPI provides a ‘statistician-free’ DRC meeting
- Allows possibility of any number of patients at each dose
- Does not use any information from adjoining doses
- Each dose is treated separately
- Does not inform intermediate doses

Bayesian Logistic Regression Model

We can model the toxicity response curve using a logistic model relating the P(toxicity) to the dose

$$\text{logit}(p_i) = \ln(\alpha) + \beta \ln(x_i/x_{ref})$$

where p_i is the P(toxicity) at dose x_i and x_{ref} is a reference dose.

Using a Bayesian approach we can

- use informative priors for α and β
- predict the P(toxicity) after each cohort
- use this to choose the next dose

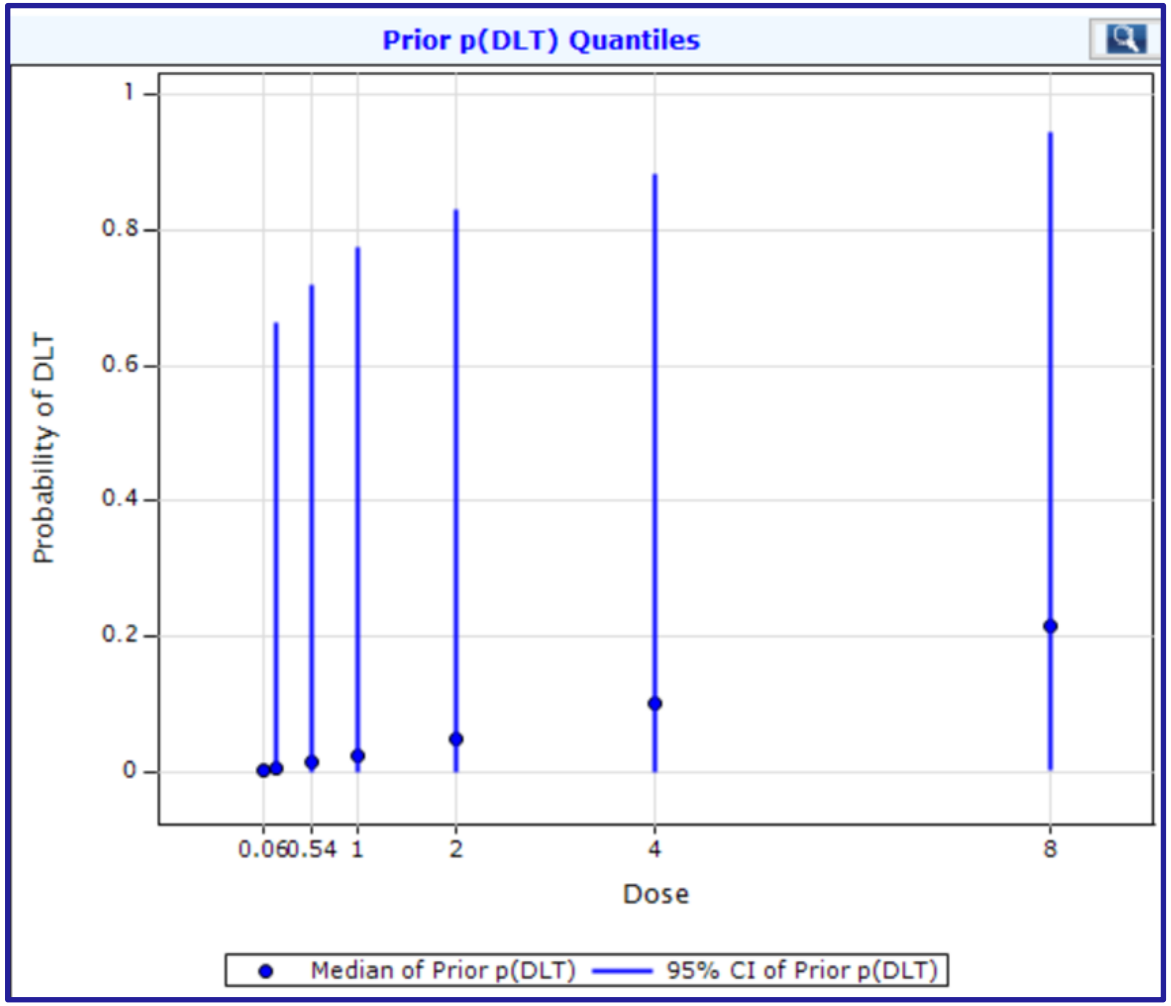
Priors for α and β

Ln(α) ~ N(-0.847, 2)

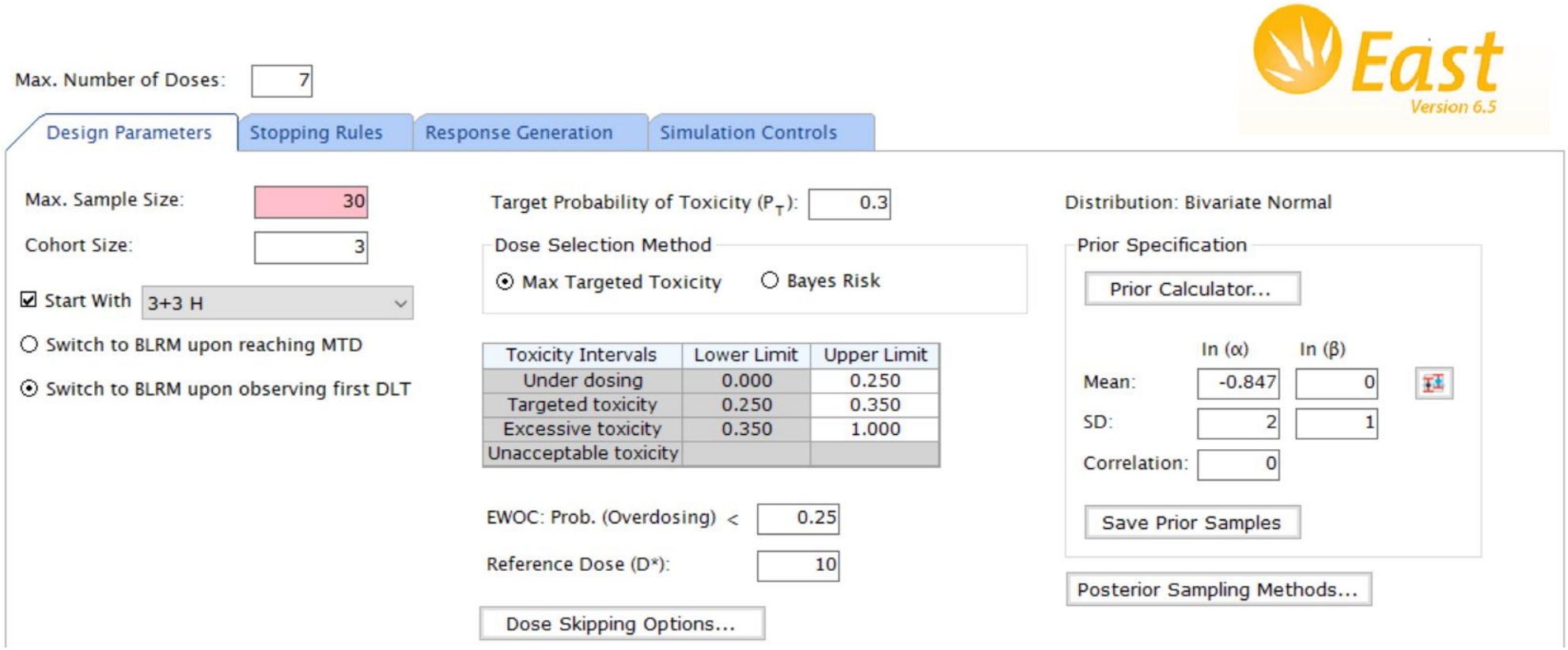
P(tox)=42% at dose=10

Ln(β) ~ N(0,1)

Assumes monotonic increasing

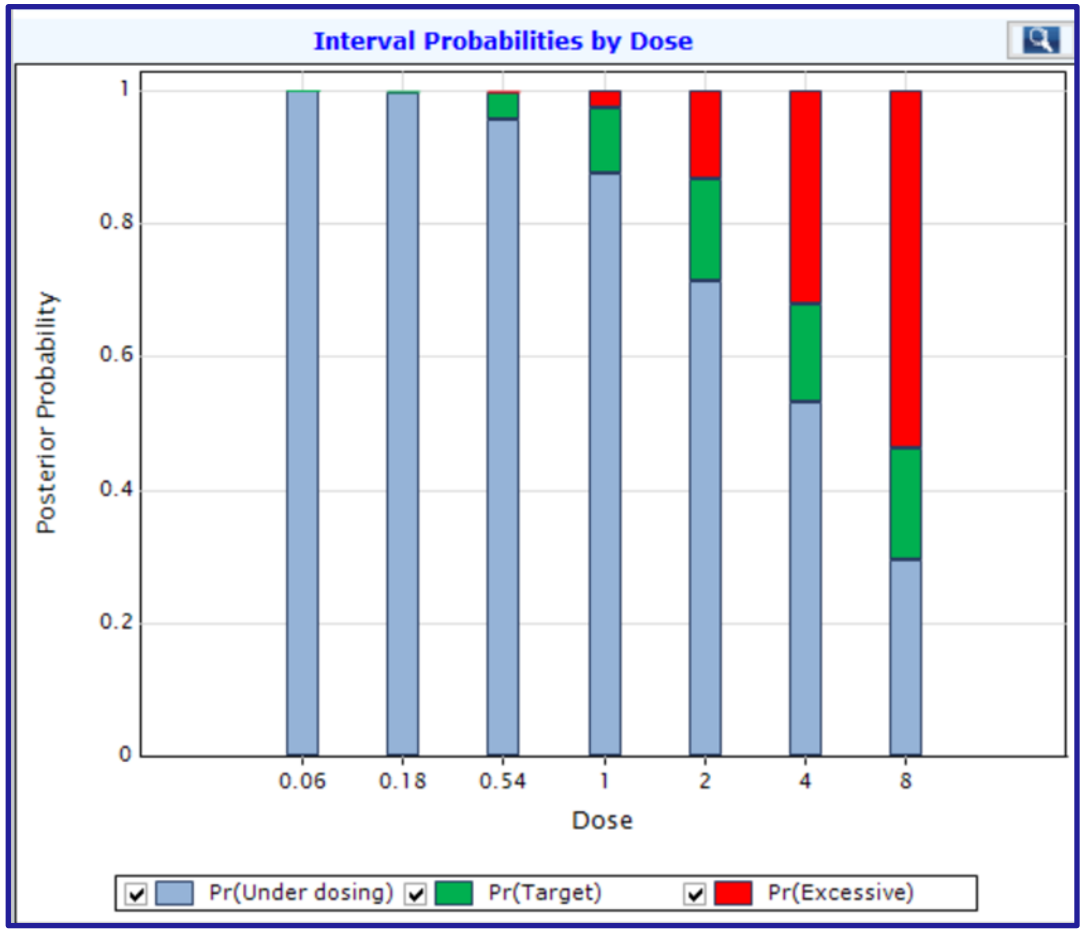


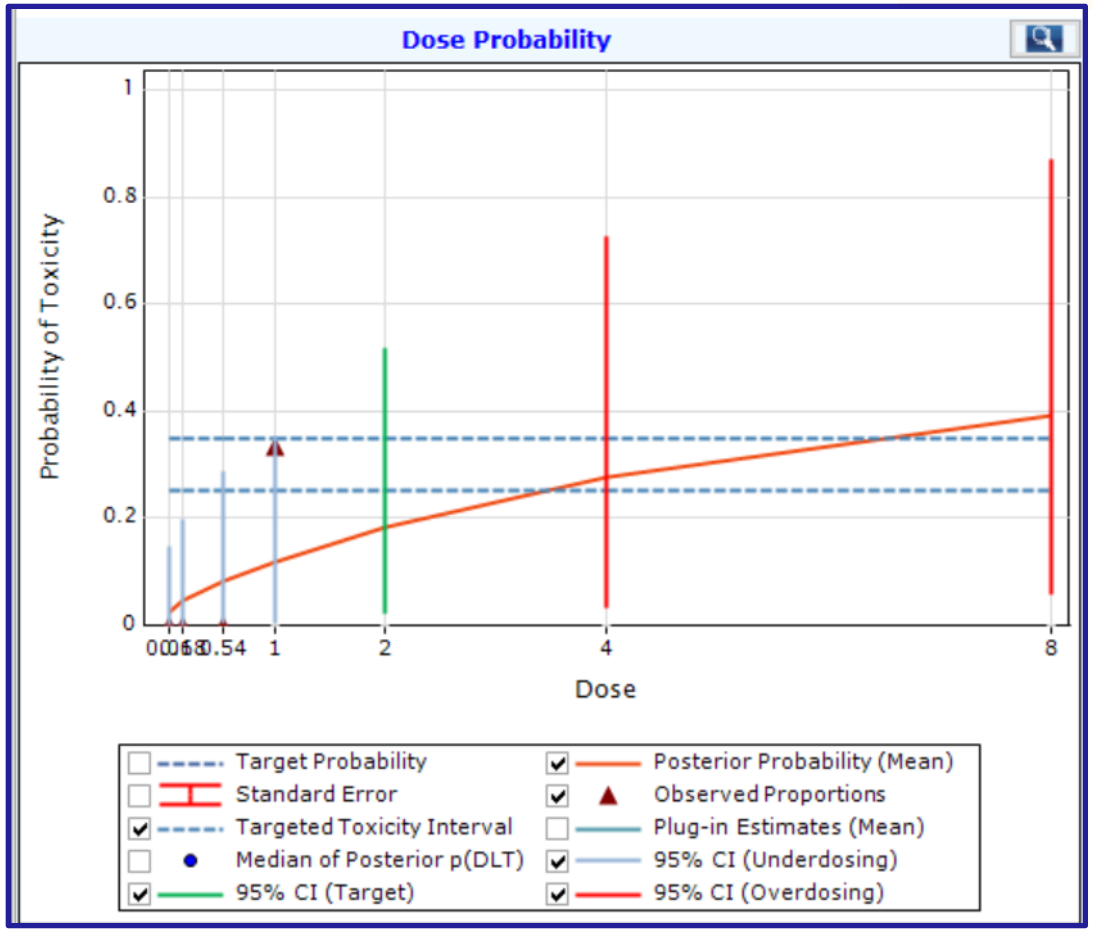
BLRM Specification in EAST



Output

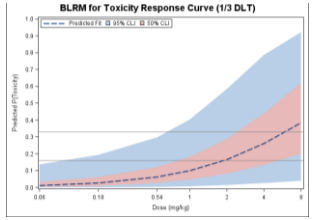
East Version 6.5





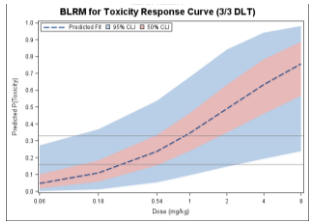
Playbook Support

DLT=1/3



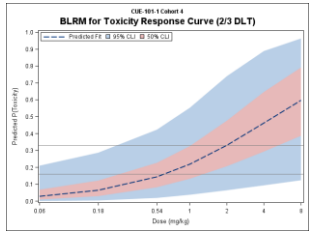
Dose (mg/kg)	0.06	0.18	0.54	1.0	2.0	4.0	8.0
Excess: P(Tox) ≥33%	0.1	0.2	1.5	5.7	19.2	38.8	56.6
Target: P(Tox) ≥16%, <33%	1.5	4.2	13.8	24.4	32.1	30.5	24.3
Under: P(Tox) <16%	98.5	95.6	84.7	69.9	48.7	30.6	19.1

DLT=2/3



Dose (mg/kg)	0.06	0.18	0.54	1.0	2.0	4.0	8.0
Excess: P(Tox) ≥33%	0.3	1.2	8.5	24.3	50.2	69.7	81.1
Target: P(Tox) ≥16%, <33%	5.3	14.1	36.0	42.6	33.8	22.2	14.3
Under: P(Tox) <16%	94.3	84.7	55.5	33.1	15.9	8.1	4.6

DLT=3/3



Dose (mg/kg)	0.06	0.18	0.54	1.0	2.0	4.0	8.0
Excess: P(Tox) ≥33%	1.0	4.3	25.9	53.9	78.0	89.0	93.8
Target: P(Tox) ≥16%, <33%	10.7	27.3	47.5	36.1	18.6	9.6	5.4
Under: P(Tox) <16%	88.3	68.4	26.5	9.9	3.3	1.4	0.7

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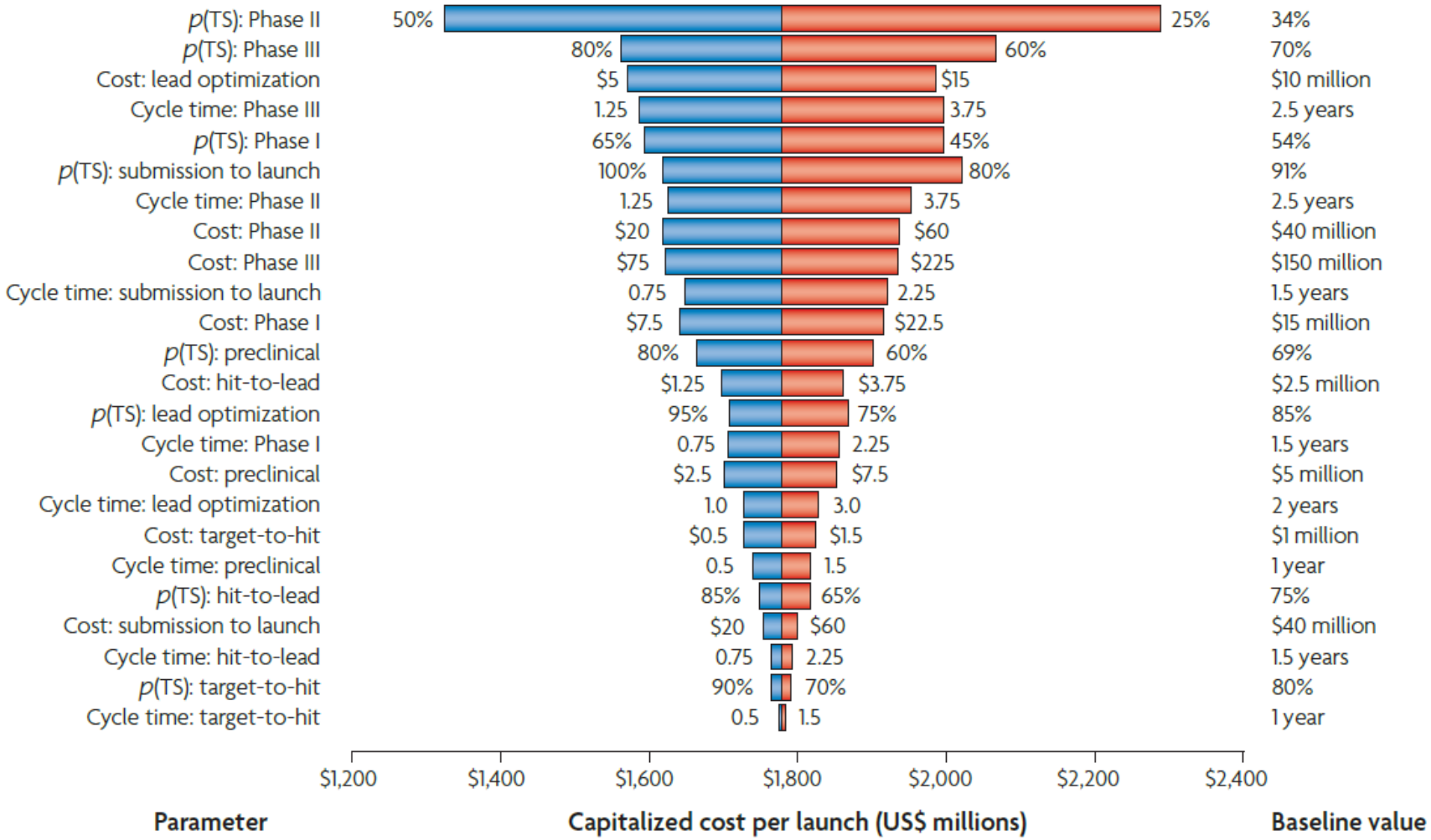
- Q&A

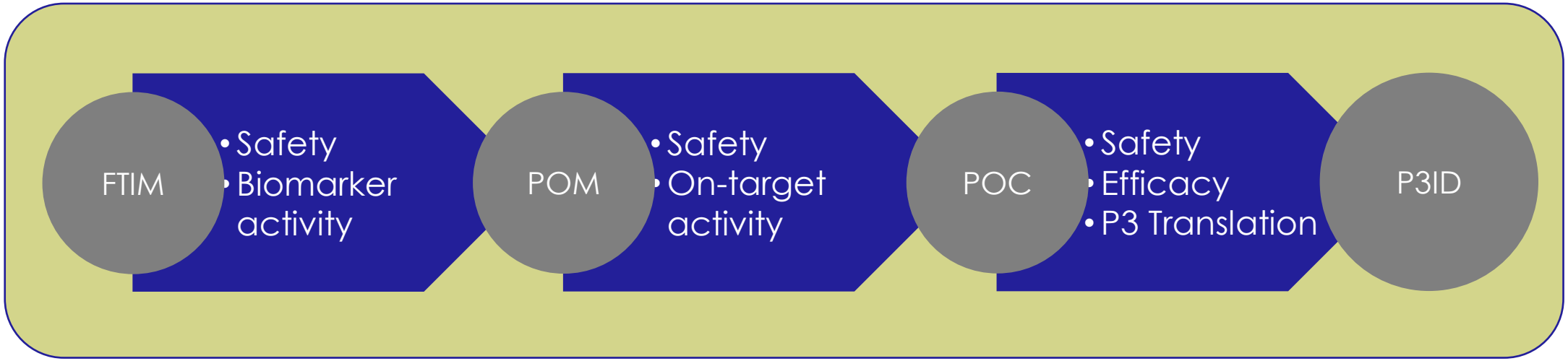
Decision Making Today



Paul et al (2010)

Early Phase Decision-Making

In a candidate-rich early phase portfolio, there is a focus on good decision-making at the point of investment decisions



Decision Making Approaches

- Decisions at interims are common
- Single indication
- Biomarker Endpoint
- Sized to exceed a minimum Target Response
- Simon's 2 Stage Design only gives futility decision
- Bayesian interim decisions are now more common

  GO = P(Response > p_o) > 80% , STOP if P(Response > p_o) < 10%
- Early phase studies can be expanded to pivotal for accelerated approval
- Determine baseline biomarker cut-off values
- Bayesian learning about biomarker cut-off points

  SCUBA, SBATT methods

Decision Outcomes

Two Outcome Decisions

Three Outcome Decisions

Example Decision Framework

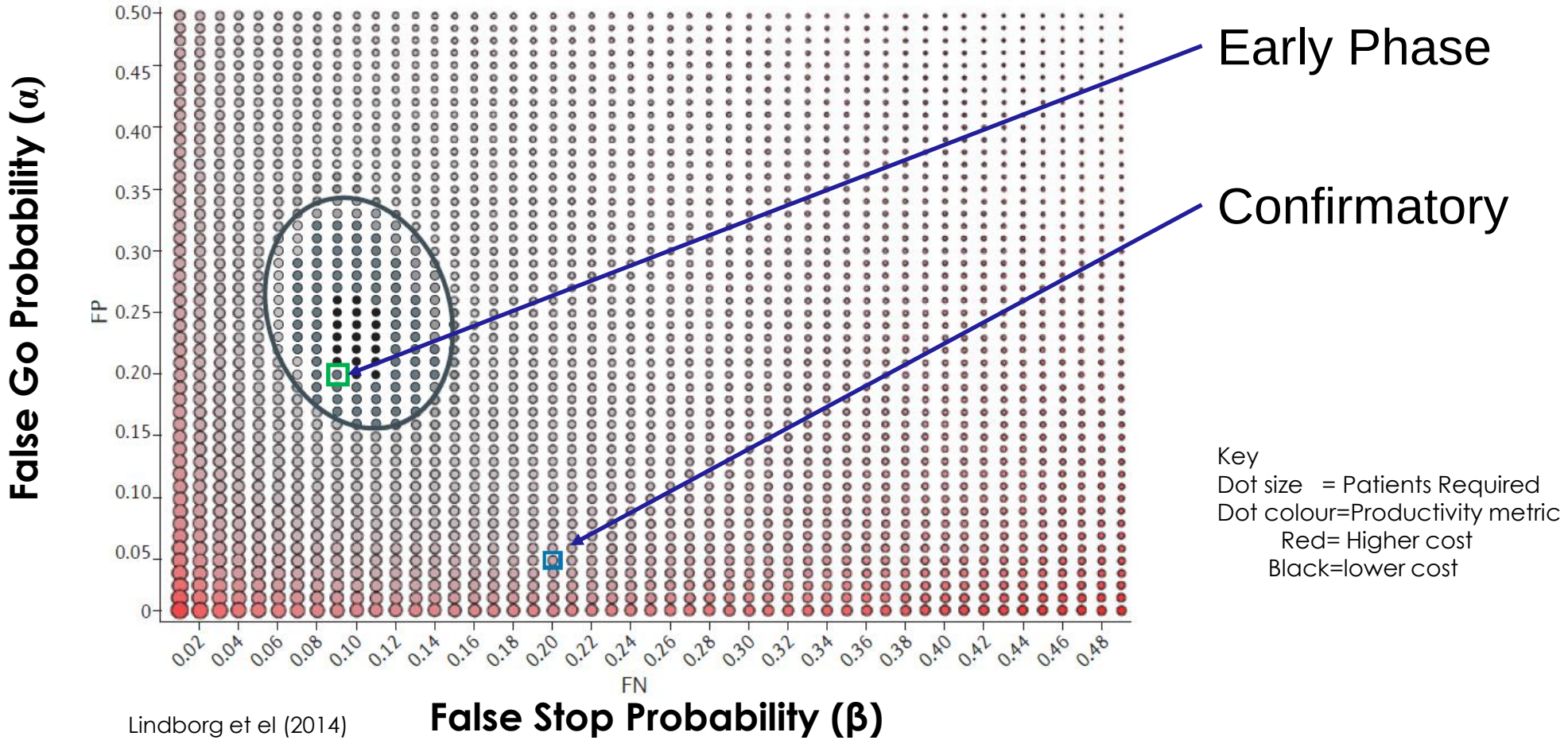
Three outcome decision

Decision parameters

Target Value (TV)	Desired level of performance
Lower Reference Value (LRV)	Minimal level of performance
False Stop Risk	Risk of a “Stop” decision if the truth is better than the TV
False Go Risk	Risk of “Go” decision if the truth is at worse than the LRV

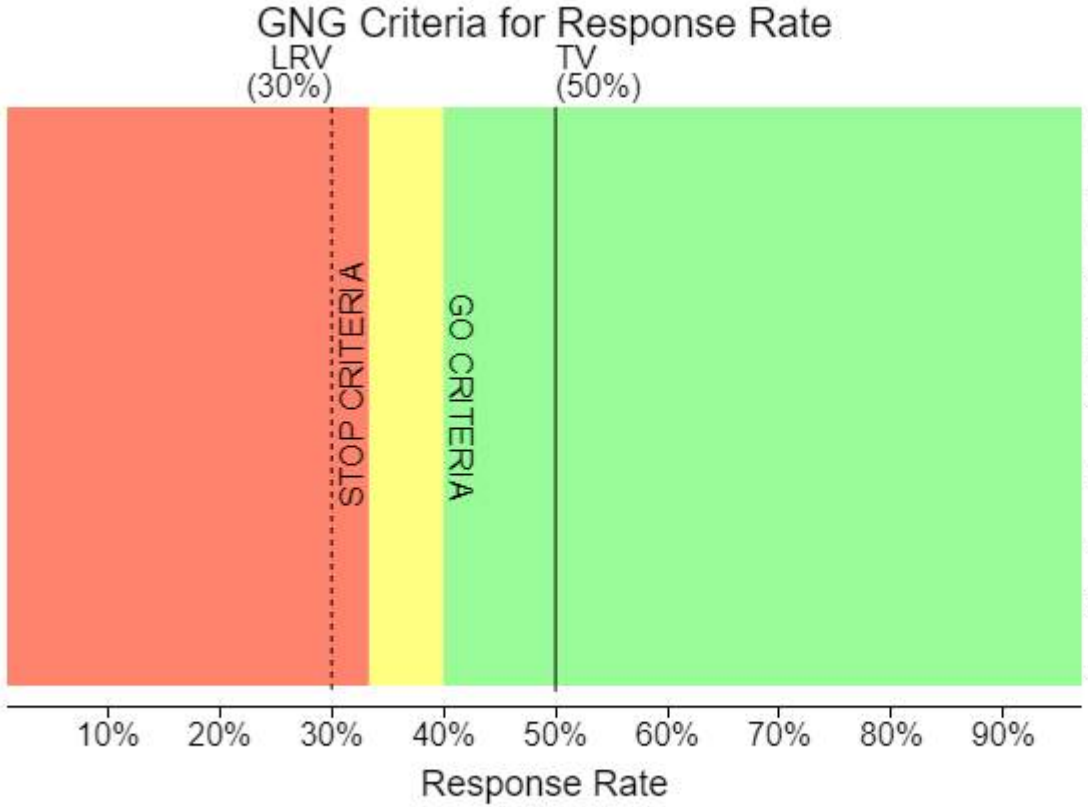
Frewer et al (2016)

Decision Error Probabilities



Lindborg et el (2014)

Decision Making



Value/Criteria	Description
Target Value	A proportion of 50%
Lower Reference Value	A proportion of 30%
Go	If there is ≥ 80% chance that the proportion is ≥ 30%* e.g. observed proportion** ≥ 40%
Stop	If there is <10% chance that the proportion is ≥ 50%* e.g. observed proportion** ≤ 33%

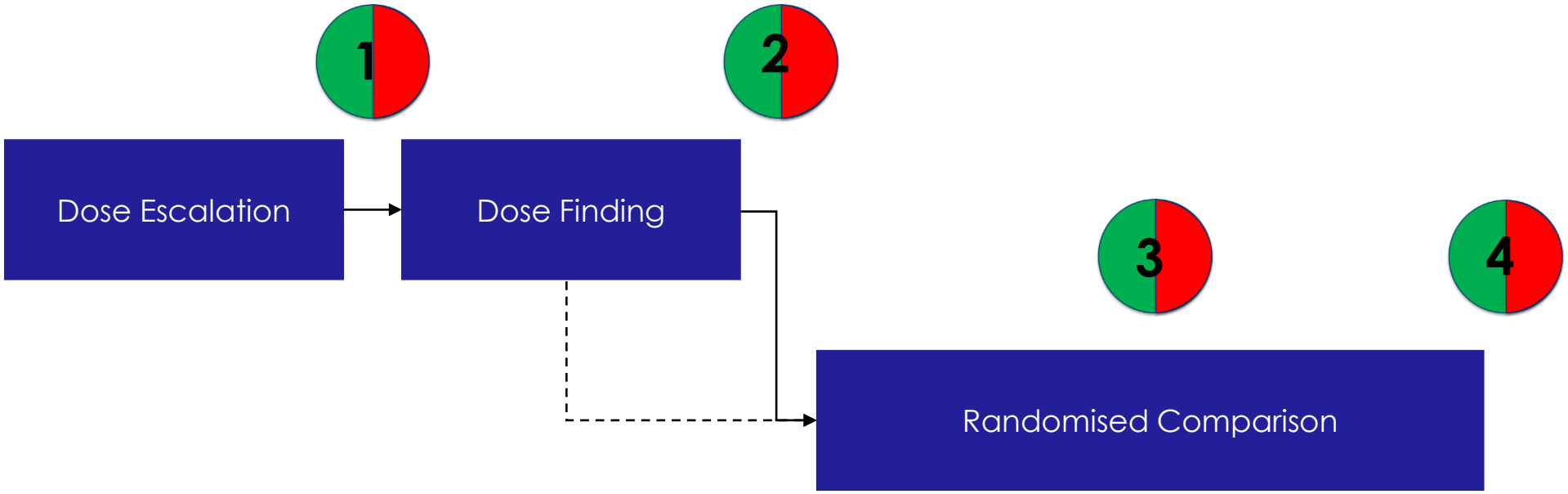
** Assuming 30 patients
* Stop and Go correspond to upper-limit of 1-sided 90% CI and lower-limit of 1-sided 80% CI

Probability of Success

At the end of Phase 2, the following probabilities can be calculated to help in the decision to proceed to the Phase 3 stage

Probability	Definition
Technical Success	Probability of Phase3 study with a significant p-value
Technical and Regulatory Success	... and a clinically relevant treatment effect
Market Success	… that is better than the competitor product

Clinical Development Decision Points



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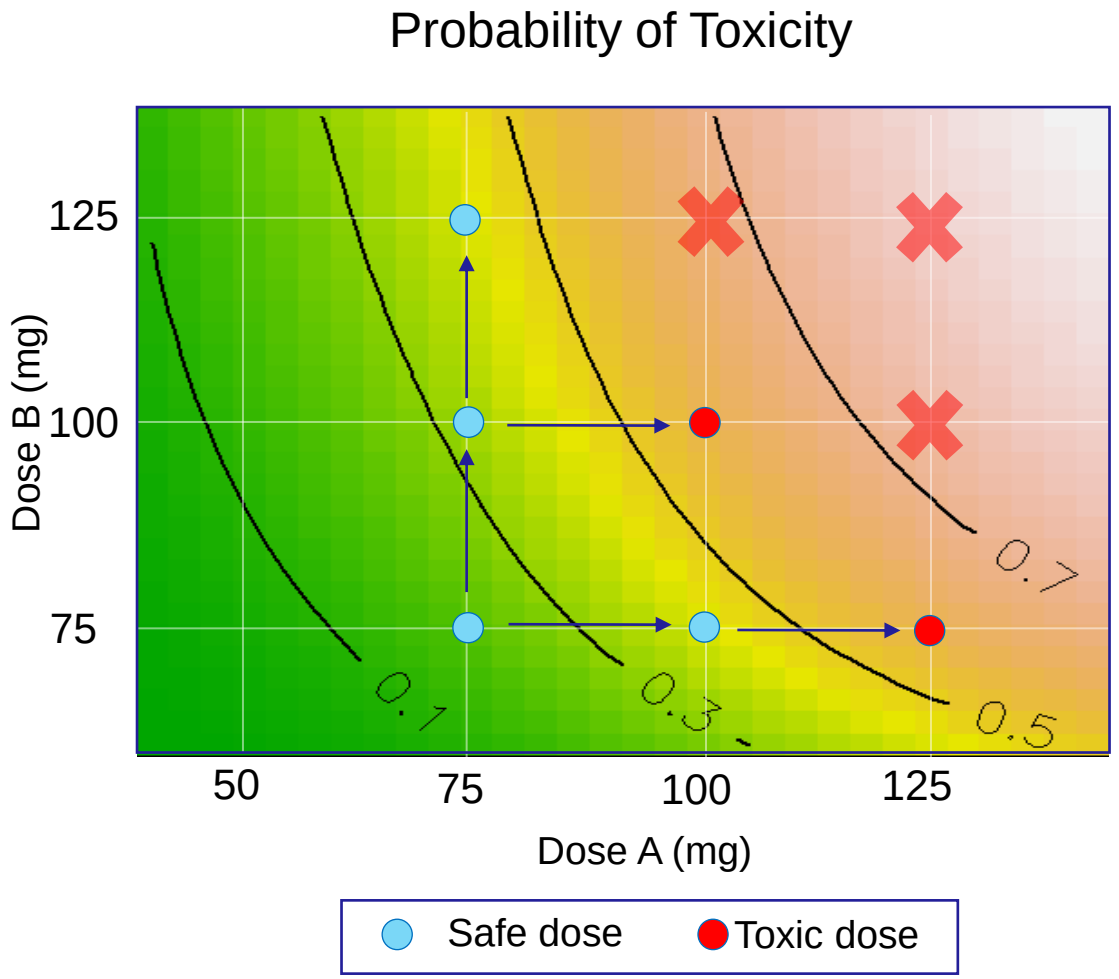
Combination Therapies

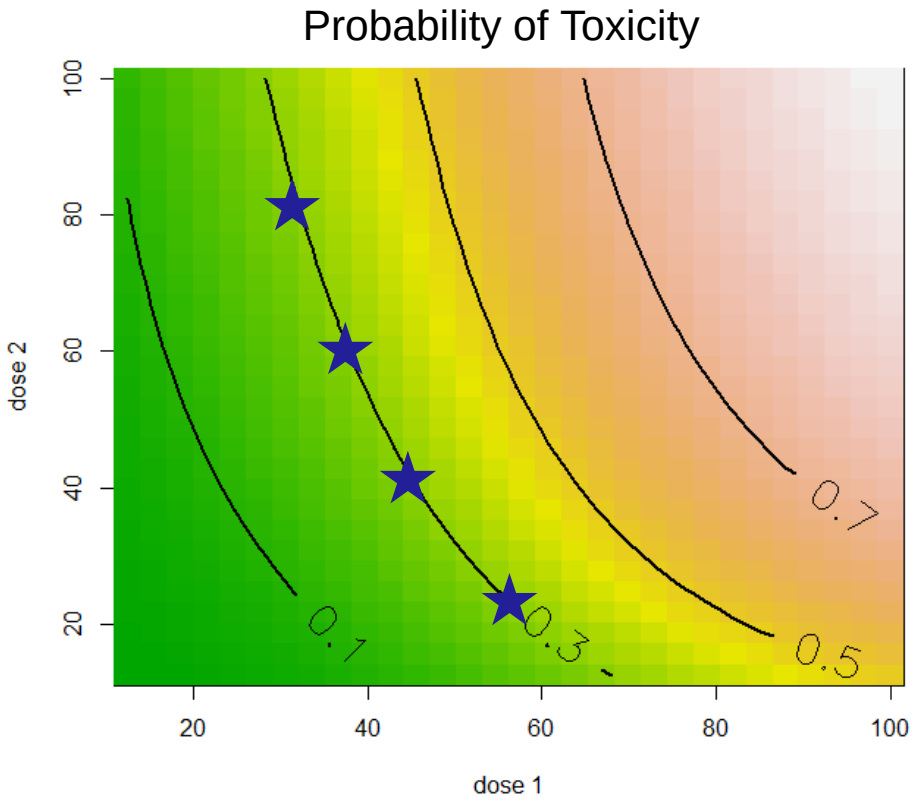
- Combination of two (or more) treatments to provide enhanced efficacy
  - Enhanced efficacy can also result in enhanced toxicity
  - Investigate overlapping toxicities
- One treatment is often new, and the other existing
  - Dose escalation with new treatment with fixed dose of standard
  - Dose escalation of both treatments
- Demonstration of correct doses and schedules are needed
- One treatment can influence the PKPD of the other treatment

Escalation with Dual Agents



Dose Escalation with Dual Agents

- Discover multiple dose combinations with similar safety for further exploration
- Then compare to get the best efficacy
- Use of historical data on the standard and all other data on new drug to improve escalation decisions



Dose Escalation with Dual Agents

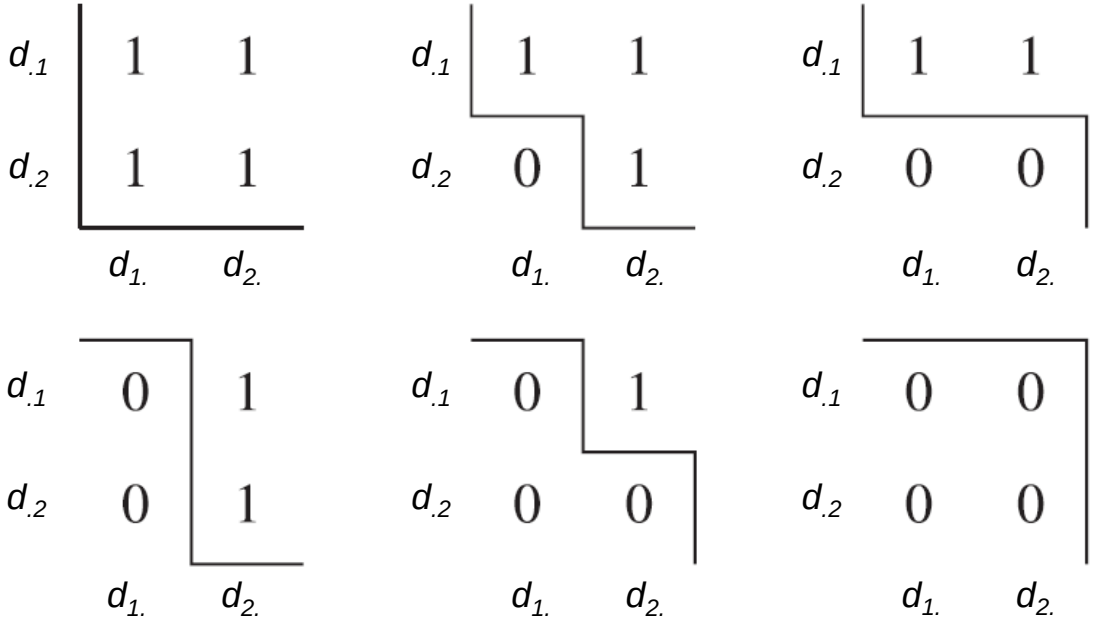
- One dimensional dose escalation
  - 3 parameter BLRM model: $\text{logit}(p_i) = \ln(\alpha_i) + \beta \ln(x_j / x_{ref})$
- Fix each dose of A then escalate up doses of B (Yuan and Yin, 2008)
- Assume prior ordering, then do single dimension CRM (Kramar et al (1999)
- Logistic model with 6 parameters (Thall et al, 2003)
- Contour finding methods (Mander and Sweeting, 2015)
- Assumption of monotonicity is not unreasonable

Product of Independent Probabilities (PIPE)

For dose combinations *i,j* assume

$$\pi_{ij}|a_{ij}, b_{ij} \sim Beta(a_{ij}, b_{ij}) \quad \forall i, j$$

Assume monotonicity and then evaluate all possible contours (Mander and Sweeting 2015)



Which Dual Agent Design?

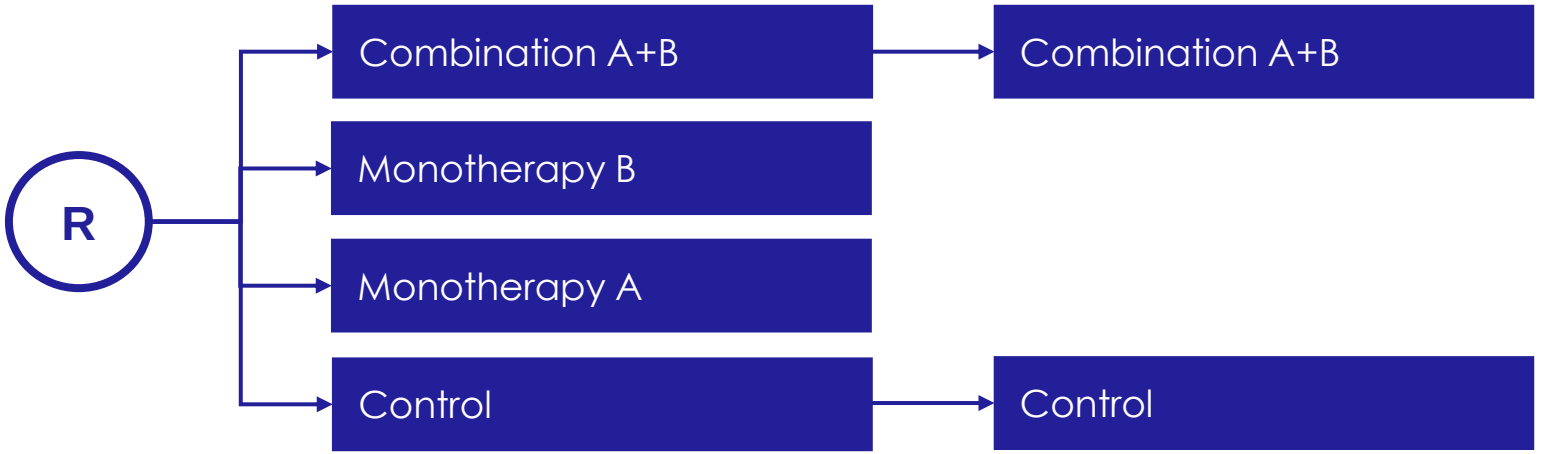
Table 1 | Summary of features for various dual-agent dose escalation study designs

Study	Number of model parameters	Stages	Outcomes	Response values	Number of RP2D combinations
Rule-based designs					
Hamberg and Verweij (2009)[57]	–	1	Toxicity	Binary	1 or 2
Lee and Fan (2012)[58]	–	1	Toxicity	Binary	1 or 2
Huang *et al.* (2007)[71]	–	2	Toxicity and efficacy	Binary	0 or 1
Lee *et al.* (2008)[59]	–	2	Toxicity	Binary	1
Model-based designs					
Wang and Ivanova (2005)[60]	3	2	Toxicity	Binary	Minimum number of doses of drug A or drug B
Yin and Yuan (2009)[62]	3	2	Toxicity	Binary	1
Yin and Yuan (2009)[63]	3	2	Toxicity	Binary	1
Kramar *et al.* (1999)[61]	2	2	Toxicity	Binary	1
Su (2010)[64]	1	3	Toxicity	Binary	1
Thall *et al.* (2003)[31]	6	2	Toxicity	Binary	3
Mandrekar *et al.* (2007)[73]	6	1	Toxicity and efficacy	Binary (toxicity and efficacy)	1
Houede *et al.* (2010)[77]	21	1	Toxicity and efficacy	Ordinal (toxicity and efficacy)	1
Dragalin *et al.* (2008)[79]	8	2	Toxicity and efficacy	Binary, ordinal or continuous (toxicity and efficacy)	1
Whitehead *et al.* (2011)[75]	Between K and $3K$*	1	Toxicity and efficacy	Binary (toxicity and efficacy)	Trial dependent (0–9)
Conaway *et al.* (2004)[68]	K	2	Toxicity	Binary	1
Wages *et al.* (2011)[70]	M‡	2	Toxicity	Binary	1
Wages *et al.* (2011)[69]	M‡	1	Toxicity	Binary	1
Braun and Wang (2010)[80]	6	1	Toxicity	Binary	1
Bailey *et al.* (2009)[67]	≥3§	1	Toxicity	Binary	1

*Number of parameters depends on the choice of discrete … one parameter for the dose-escalation model. §Two parameters required f… Abbreviations: K, number of combinations; M, number of simple orders; R…

Harrington et al (2013)

Seamless Phase 2a/b Combination Design

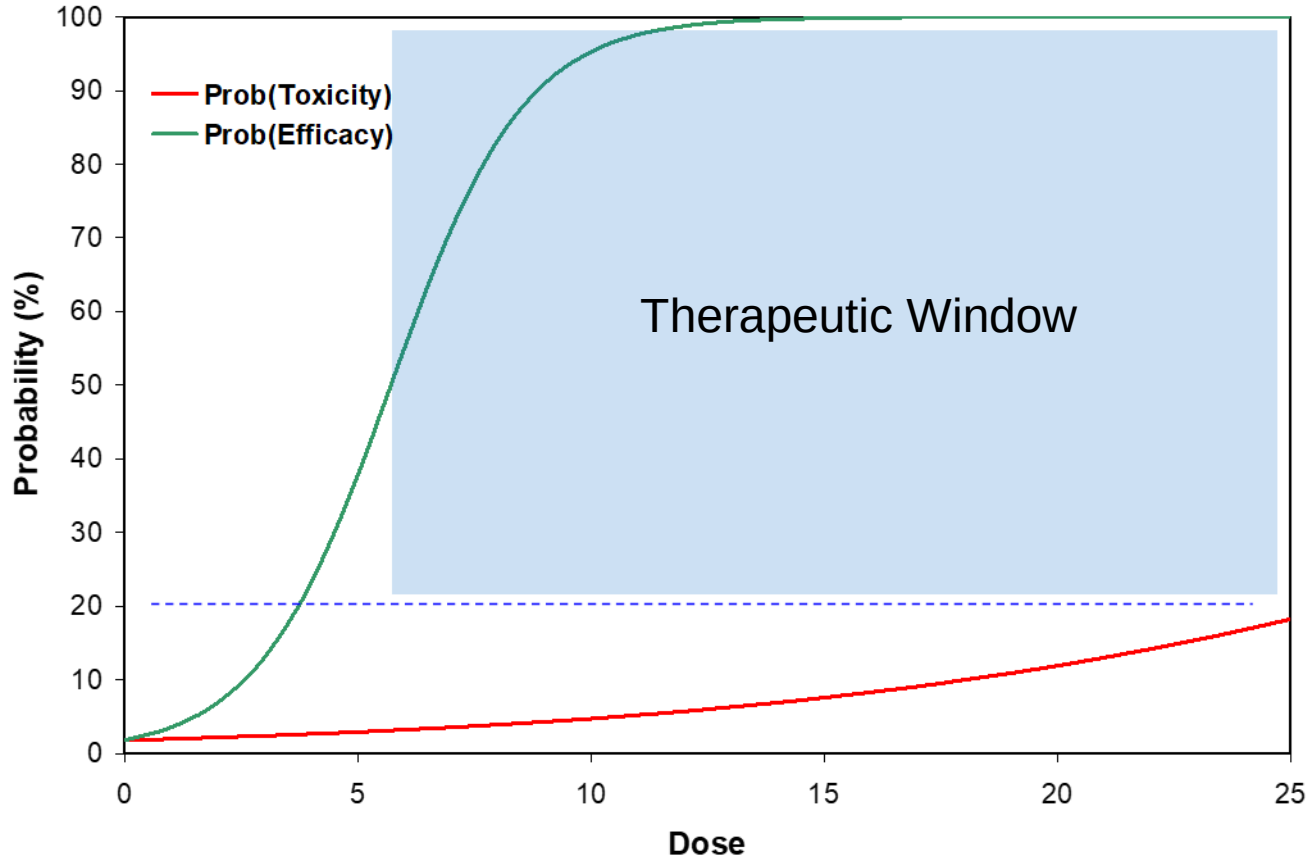


- Regulators require demonstration of contribution of components
- Minimise number of patients exposed to monotherapies
- Can use Historical Data for the established monotherapy
- Use unequal randomization ratios
- Adaptive dose dropping based on futility at interim

Agenda

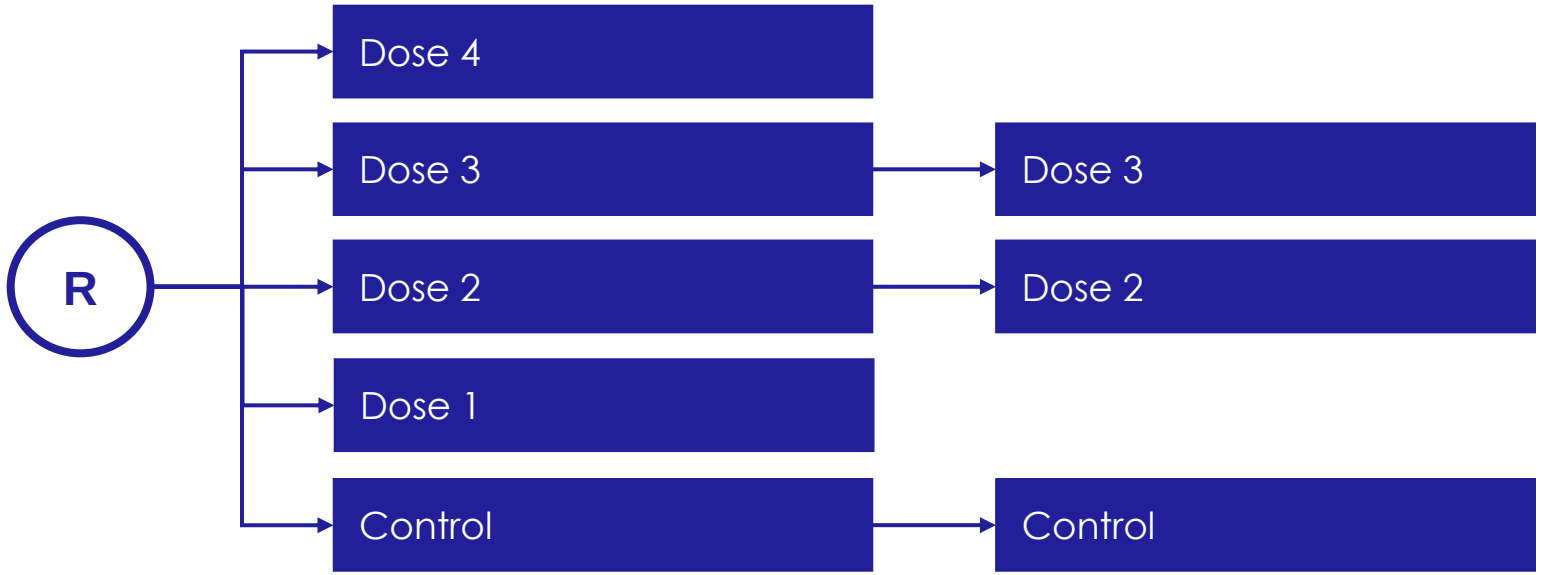
- Background
- Dose Escalation
- Decision Making
- Combination Studies
- **Dose Finding**
- Enrichment
- Q&A

Dose Finding



Questions: What is the minimum effective dose?
What is the dose that gives the desired efficacy?

Seamless P2a/b Dose Response Design



- Model-based dose response is now preferred and should now be our standard approach to proposing doses for phase 3
- Uses fewer resources to get to dose decisions
- In most cases the form of the dose response model is known
- Current thinking is that Phase 2A should begin with 4-8 doses groups, covering an 80-fold range of doses. In phase 2b the number of dose groups should reduce to 2-4.

Dose-Response Studies

Establish Proof-of-Concept (PoC)

- Change in dose → desirable change in endpoint of interest

Dose finding step

- Select one (or more) “good” dose levels for confirmatory Phase III once PoC has been established

Traditional Approach

Proof-of-Concept: Conducted using (multiple) active arms and control

Selection of Target Dose:

1. statistically significant at the proof-of-concept stage
2. smallest of statistically significant doses but also clinically relevant

Dose-Response Modeling:

1. use data from PoC and earlier trials
2. find a statistical model capturing the effects of target dose on dose-response

Modern Approaches to Dose Finding

Traditional ANOVA

Design Focused

- Adaptive Bayesian Modelling
- D-Optimality

Analysis Focussed

- Multiple Testing Procedures
- MCP-Mod
- Bayesian Model Averaging

Multiple Testing Approaches

- Pairwise comparison of each dose to control
- Aim to control Type 1 Error

Parametric	P-Value
Dunnett's single step	Bonferroni
Dunnett's step-down	Sidak
Dunnett's step-up	Holm step down
	Weighted Bonferroni
	Hochberg's step up
	Hommel's step up

Bayesian Adaptive Model

Phase 2A: Doses = 0, 1, 3, 10, 30, 100, 300, 600

5 pts/dose group

Sigmoidal Emax Model

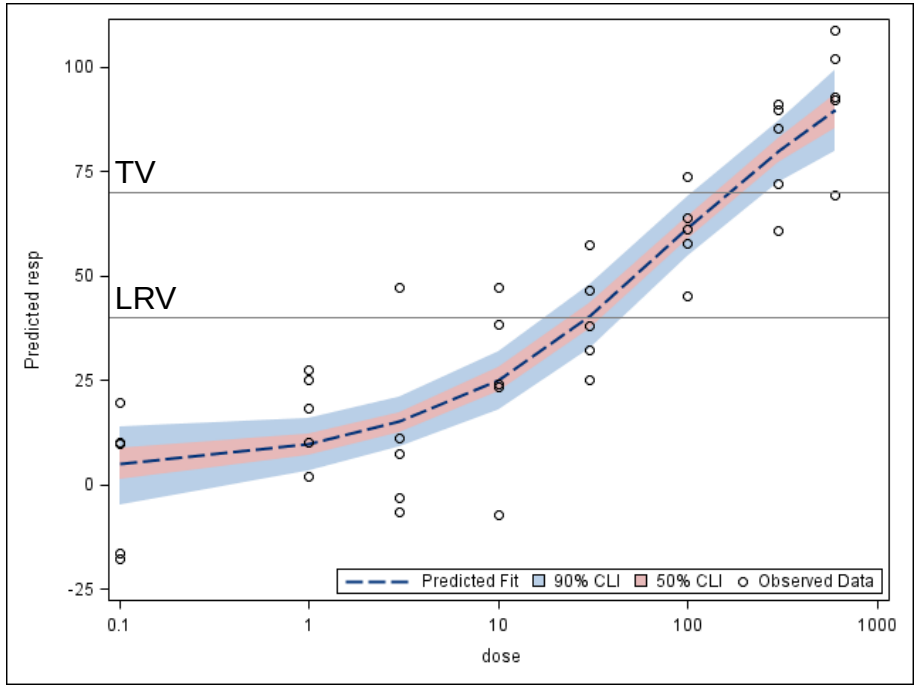
$$y = e_0 + e_{\max} \frac{dose^h}{dose^h + ED50^h}$$

Prior information available

Parameter	Prior	
hill	$Ln(h) \sim N(0,0.53^2)$	Median=1.0 90%CL(0.1,10)
ED50	$Ln(ED50) \sim N(1.3,0.53^2)$	Median=50 90%CL(1,500)
Placebo	$e_0 \sim N(0,100^2)$	Uninformative
Max Effect	$e_{max} \sim N(0,100^2)$	Uninformative

Bayesian Adaptive Model: Example

Interim



Optimisation

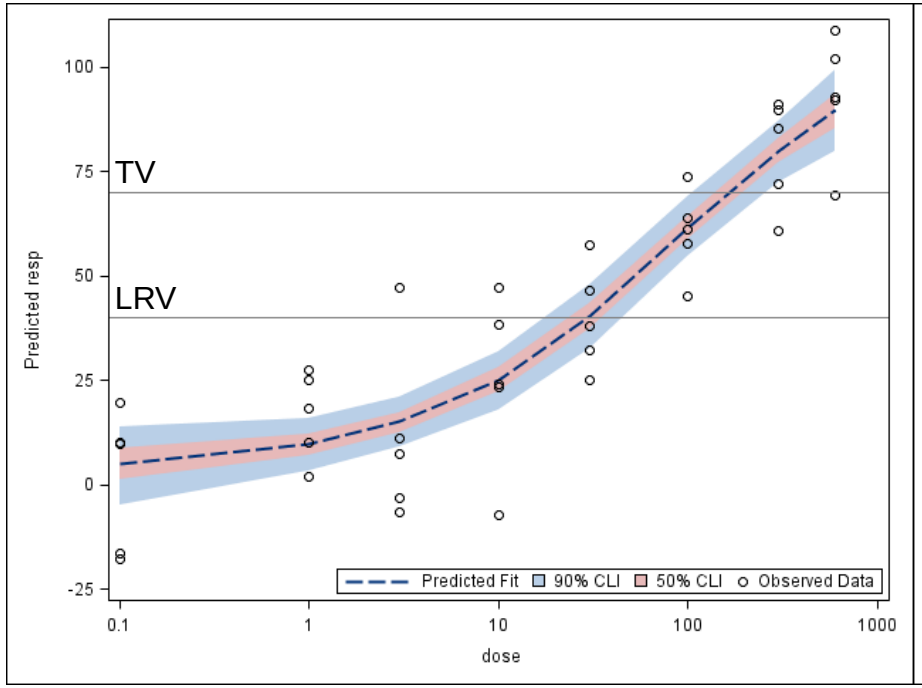
D-Optimality

C-Optimality

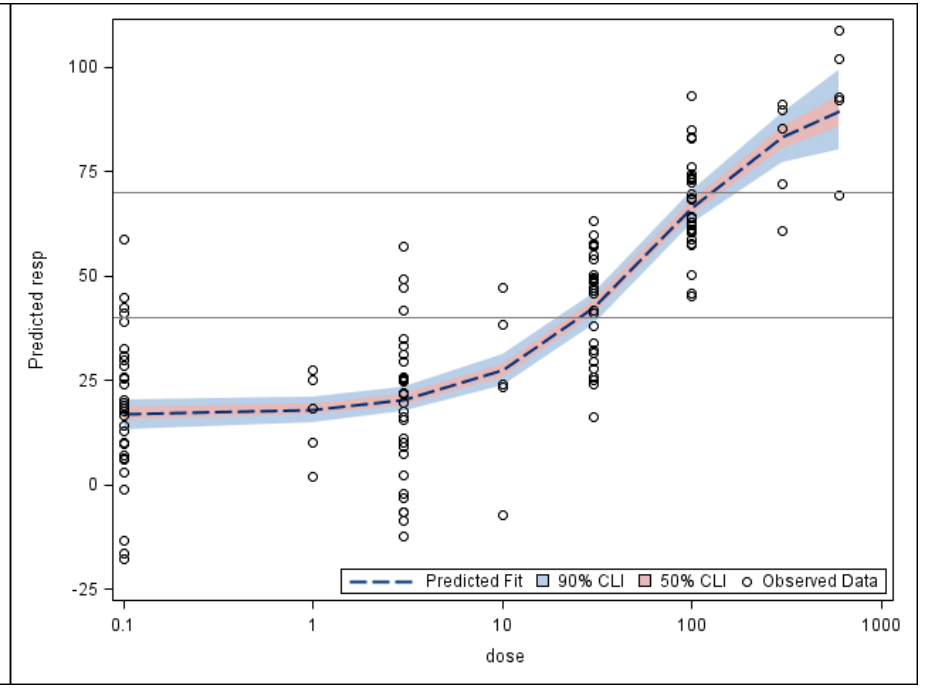
- ED50
- MED
- Target Response

Bayesian Adaptive Model: Example

Interim



Final



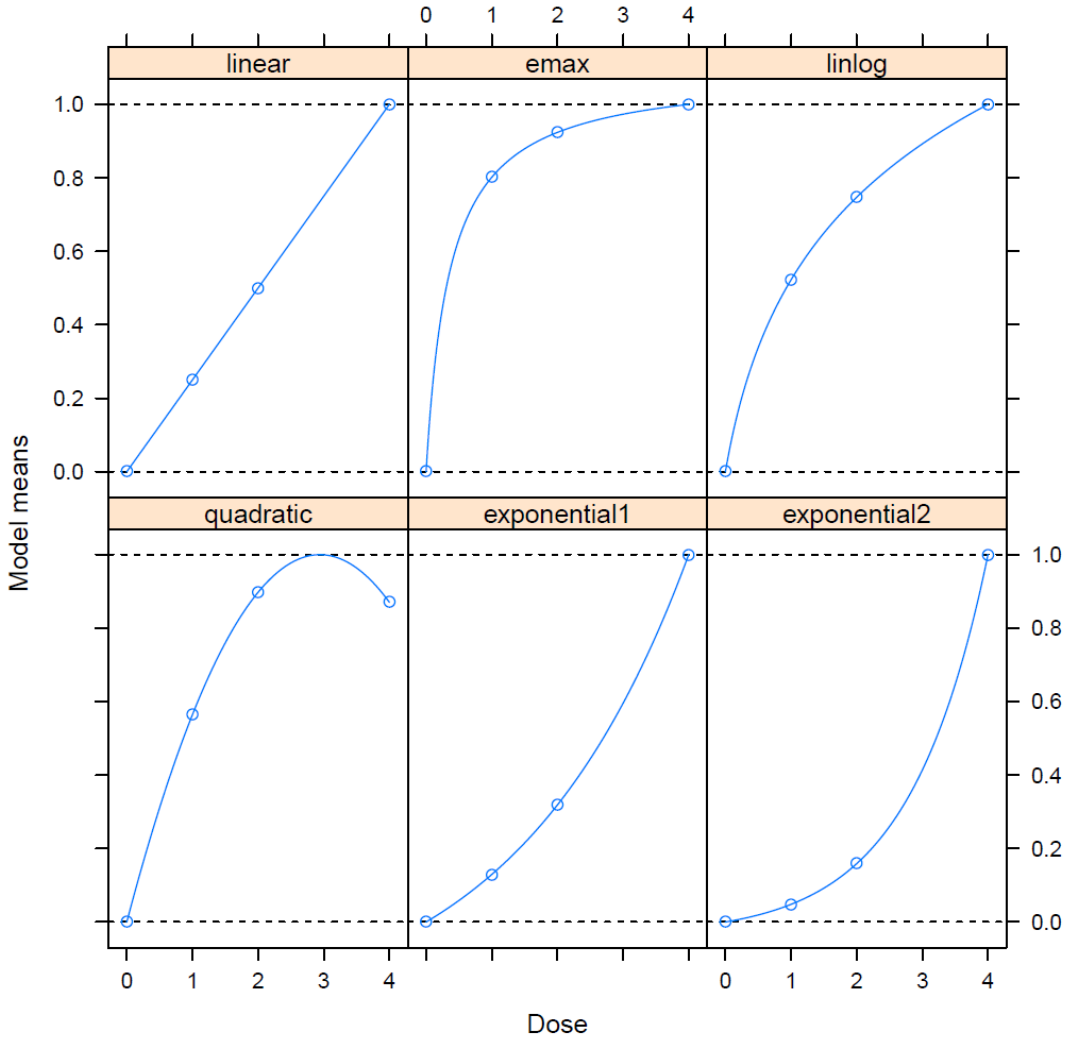
Optimisation

D-Optimality

C-Optimality

- ED50
- MED
- Target Response

Candidate Dose Response Models



MCP + Mod = MCPMod

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Design Stage

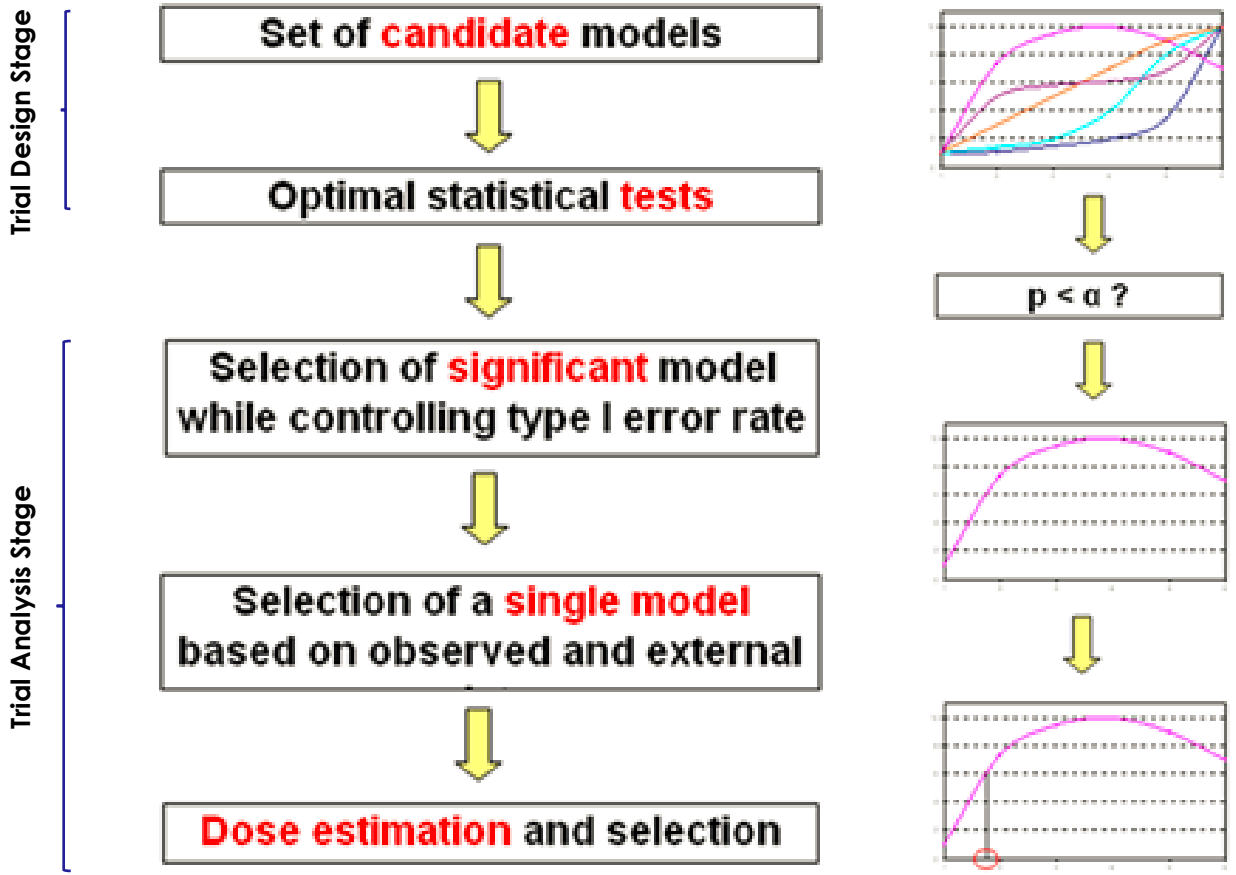
- Pre-specification of candidate dose-response models

Analysis Stage (MCP-step)

- Statistical test for dose-response signal. Model selection based on significant dose response models

Analysis Stage (Mod-step)

- Dose response and target dose estimation based on dose-response modeling



MCP-Mod Regulatory Opinion

CHMP: First opinion issued in 2010, since then 12 qualification opinions (biomarkers, technologies/devices, simulation models)

MCP-Mod first statistical methodology qualified

FDA: Issued its Fit-for-Purpose (FFP) designation for guiding dose selection for Phase III testing.

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM508700.pdf

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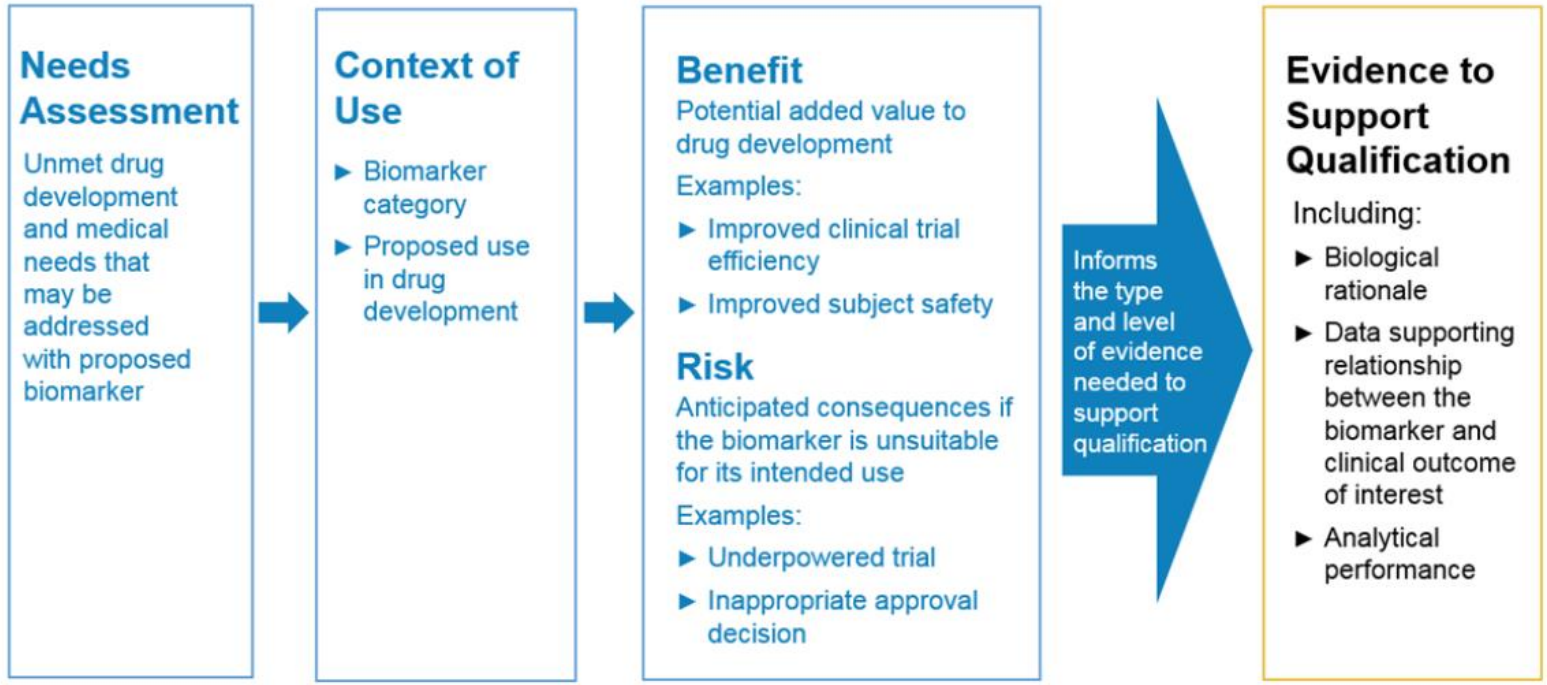
Biomarker Development

Category
Diagnostic
Monitoring
PD/Response
Predictive
Prognostic
Safety
Risk



Biomarker Development

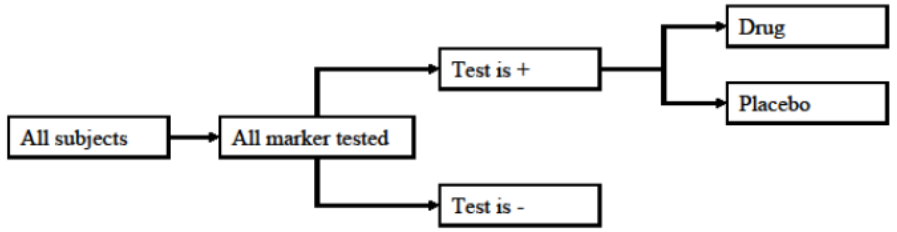
Regulatory guidance exists on the validation of biomarkers

Diagnostic Biomarker

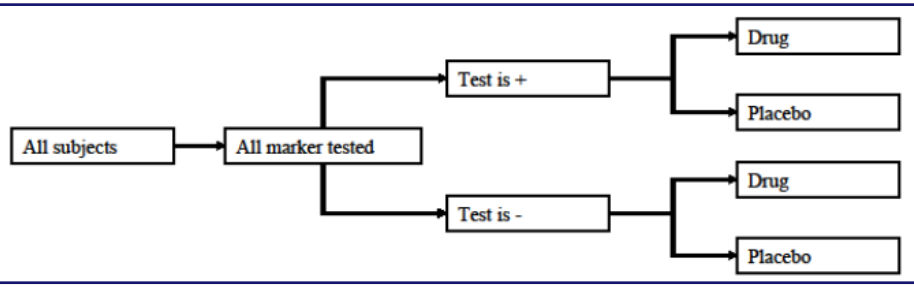
- Adaptive biomarker threshold setting

Population enrichment assessed using Adaptive Enrichment Design

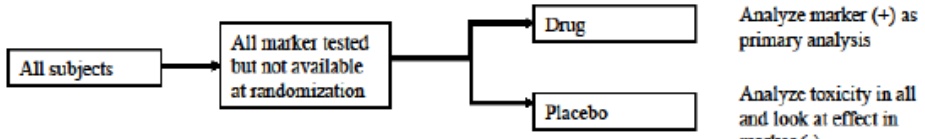
Diagnostic Biomarker Designs



No possible effect in marker-negative patients



A reduced effect in marker-negative patients



Marker cannot be assessed before randomisation of marker-negative patients

Studying Marker-Negative Patients

When the treatment represents an important advance for the marker-positive group, delaying approval because of limited data in the marker-negative group would generally be unreasonable

Determining the need for marker-negative data will be based on:

- the nature of the efficacy shown in the marker-positive population
- the risks of the drug
- whether the effect of treatment would be apparent to an individual patient
- the relative sizes of the marker-positive and -negative populations
- the desire to use the drug in the marker-negative

Population Enrichment

Prospective use of any patient characteristic to obtain a study population in which detection of effect is more likely than in unselected population

Types of PE

- Prognostic: identify high risk patients based on biomarkers
- Predictive: identify patients more likely to respond

Importance

- Help identify highly responsive group, detect treatment effect with smaller sample size
- Failed molecules from one study, may succeed in a different group

Example

- BMS immunotherapy Opdivo failed in lung cancer study whereas Merck competitor Keytruda succeeded: In later case study population was enriched by including only subjects with high level of PD-L1

Method and Assumptions

Study population: divided in two groups based on a predefined biomarker

Study will materialize into two independent cohorts

- First cohort recruits from full population
- Second cohort recruitment depends on an interim analysis based on the first cohort data only

At interim:

- Continue with full population
- Continue with sub-population
- Stop the trial for futility

Subpopulation prevalence will be user-specified

Case study: The TAPPAS trial

Angiosarcoma is an orphan disease

Poorly addressed by current treatments

- Pazopanib a VEGF inhibitor shows modest benefit
- TRC105 can compliment Pazopanib by inhibiting endoglin, a different angiogenic target

Adaptive trial considered optimal due to:

- Small population (1800 cases/year in US)
- Limited prior data
- Greater benefit possible with TRC105 for cutaneous vs visceral tumors

The TAPPAS trial

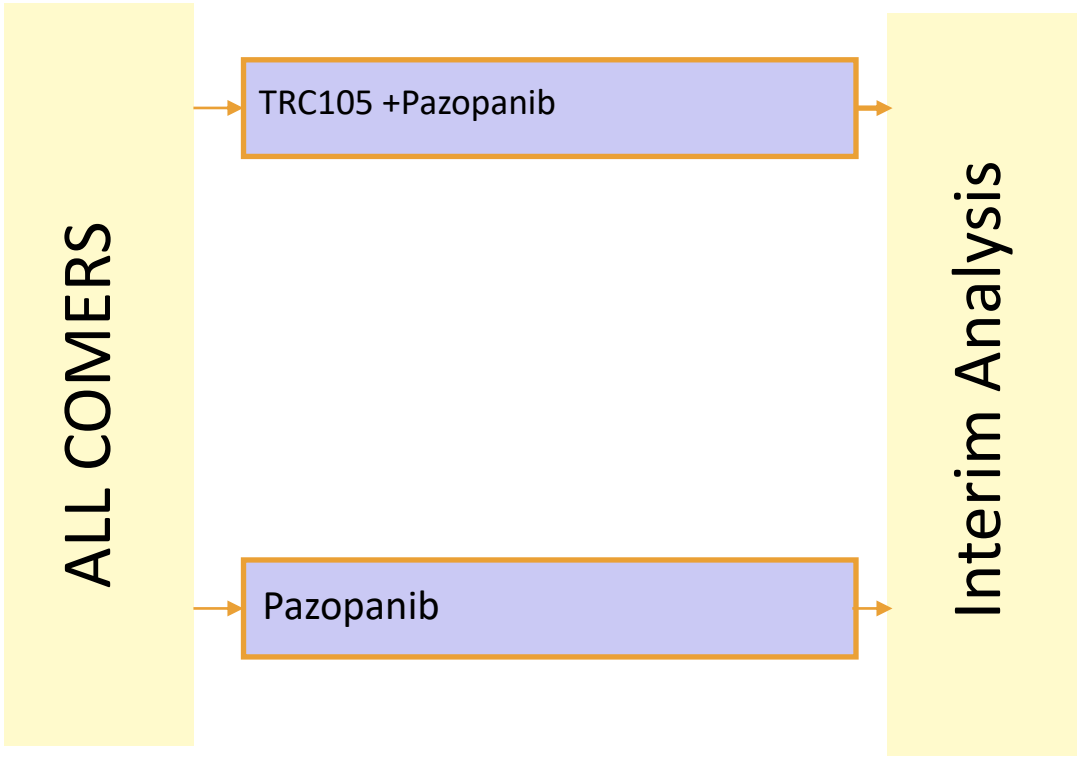
Objective

Demonstrate superior PFS of TRC105 + pazopanib vs pazopanib alone

Population

Overall, or in the cutaneous subgroup

Two-Stage Design with SSR and Enrichment



Favorable: Continue as planned

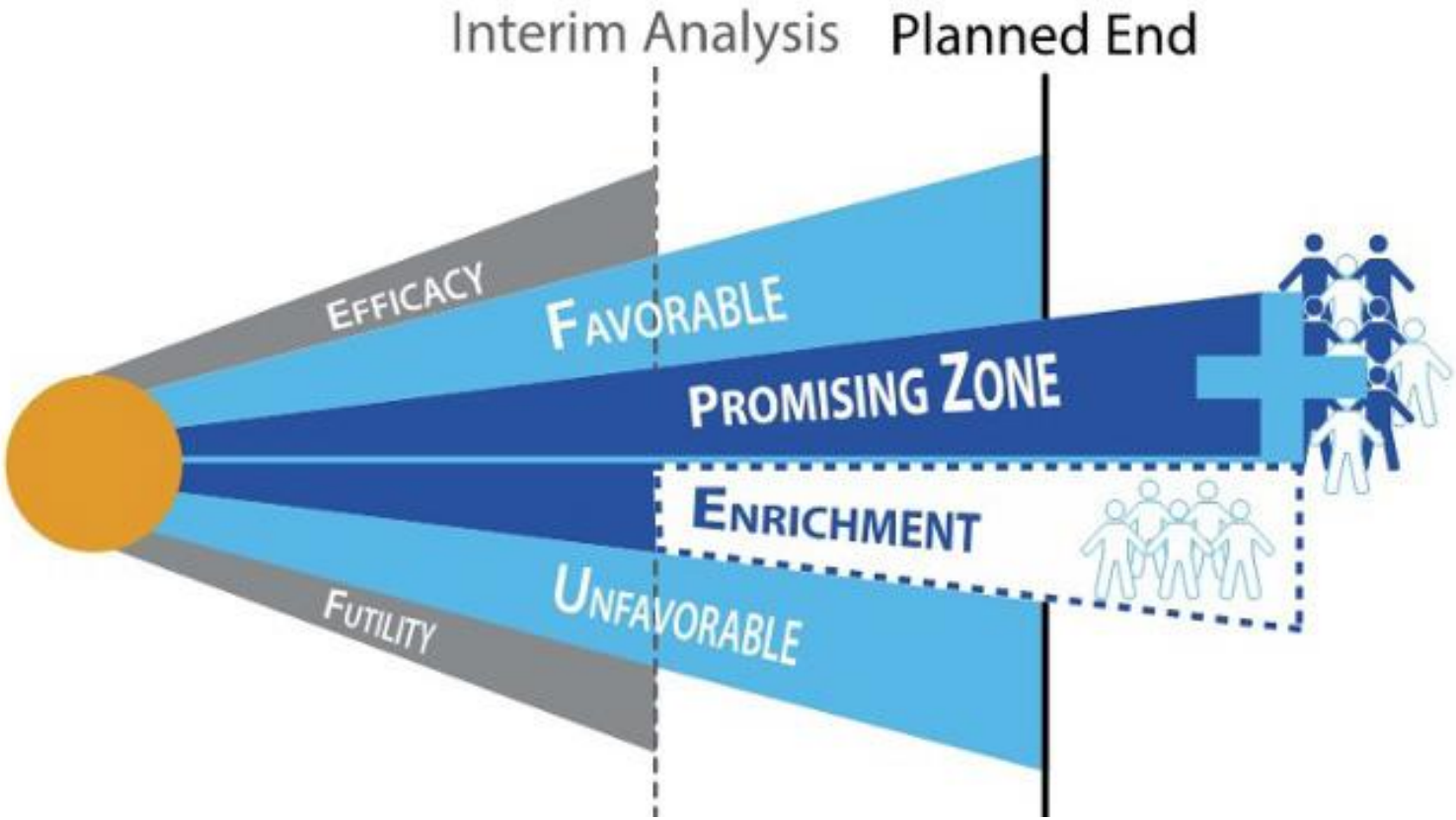
Promising: Increase sample size

Unfavorable

- Enrich with cutaneous subgroup
- Continue as planned
- Stop for futility

p_1: p-value for data from cohort 1
p_2: p-value for data from cohort 2

Adaptive Population Enrichment



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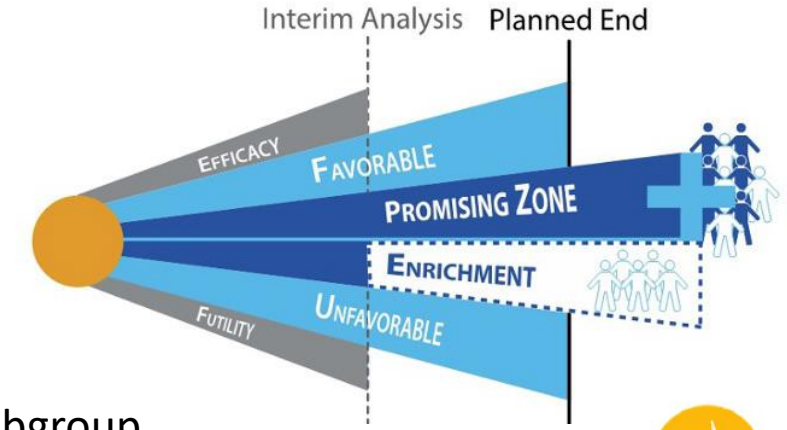
Analytical Approach



Interim Analysis

p_{int} < p-stop	**Efficacy Zone**. Recommend stopping for efficacy
Cp < Cp(fut)	**Futility Zone**. Recommend stopping for futility
Cp < Cp(min)	**Unfavourable Zone**. If Cp^s > Cp(enrich) Enrich for subgroup
Cp(min) ≤Cp<Cp(max)	**Promising Zone**. The results are currently in the 'promising zone'. Increase sample size to achieve a conditional power of Cp(max).
Cp ≥ Cp(Max)	**Favourable Zone**. Continue to the planned sample size as the results are currently 'favourable'

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Final Analysis

Based on combination of p-values

p^F_1: p-value for full data from cohort 1

p^F_2: p-value for full data from cohort 2

p^S_1: p-value for full data from cohort 1

p^S_2: p-value for full data from cohort 2

Preserving Type I Error

Let H_0^F and H_0^S denote the null hypotheses for the full population and the subgroup respectively

Let $H_0^{FS} = H_0^F \bigcap H_0^S$ denote the global null hypothesis

Closed testing principle states that type I error is strongly controlled as long as

- Each of the hypotheses in the closed family is tested at local level-α
- H_0^F significant only if both tests for H_0^F and H_0^{FS} are significant at local level-α
- H_0^S significant only if both tests for H_0^S and H_0^{FS} are significant at local level-α

TAPPAS Design

Adaptive design was smaller than the fixed design option (N=125 vs 200)

Adaptive design provides

- Greater power
- Smaller sample size
- Shorter duration

Enrichment Summary

- Population Enrichment should be considered if there is a strong chance of an enhanced treatment effect in an easy to define subgroup at baseline
- It potentially enriches for the subgroup after the interim analysis
- The adaptation needs to be pre-defined in the protocol
- The timing of the interim analysis requires careful planning
- Thorough simulation of the design is necessary to understand the operating characteristics

Conclusions

Adaptive design in early phases

- accelerates clinical development
- reduces costs
- reduces sample size
- reduces time
- better dose selection
- enhances subgroup detection
- introduces decision points
- involves evidence-based decision making
- need careful planning

Questions?

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