RECENT ADVANCES IN DOSE-FINDING: AN INTRODUCTION

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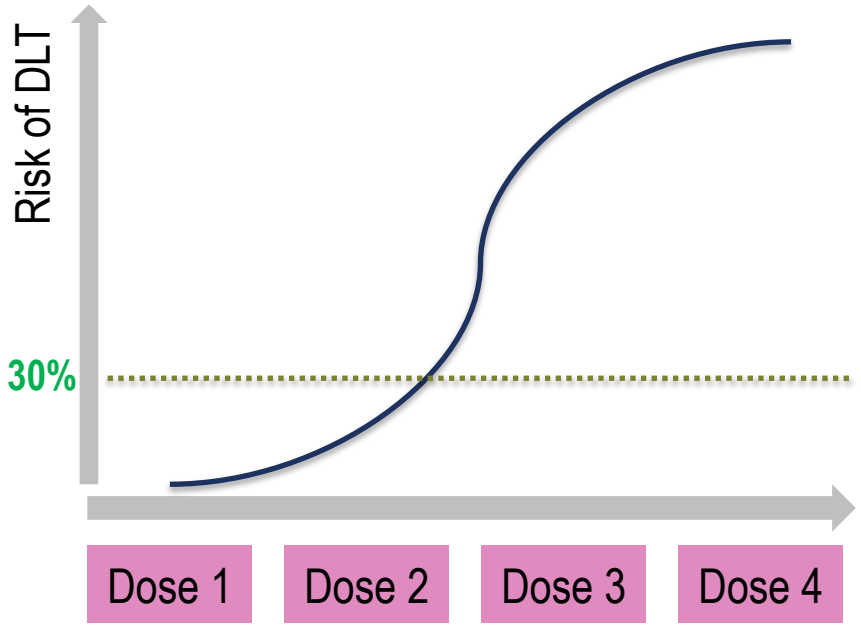
CONVENTIONAL DOSE-FINDING IN SINGLE-AGENT TRIALS

- Several doses of an experimental agent
- First-in-human trial
- The focus is on the **toxicity and tolerability**
- Patients are added **sequentially**
- The objective is to find the **target dose (TD)**
- Conventionally, TD corresponds to certain risk of Dose Limiting Toxicity (DLT), e.g. **20%-33%**



MODEL-BASED APPROACHES TO DOSE-FINDING

- Assume a **working model** for dose-toxicity

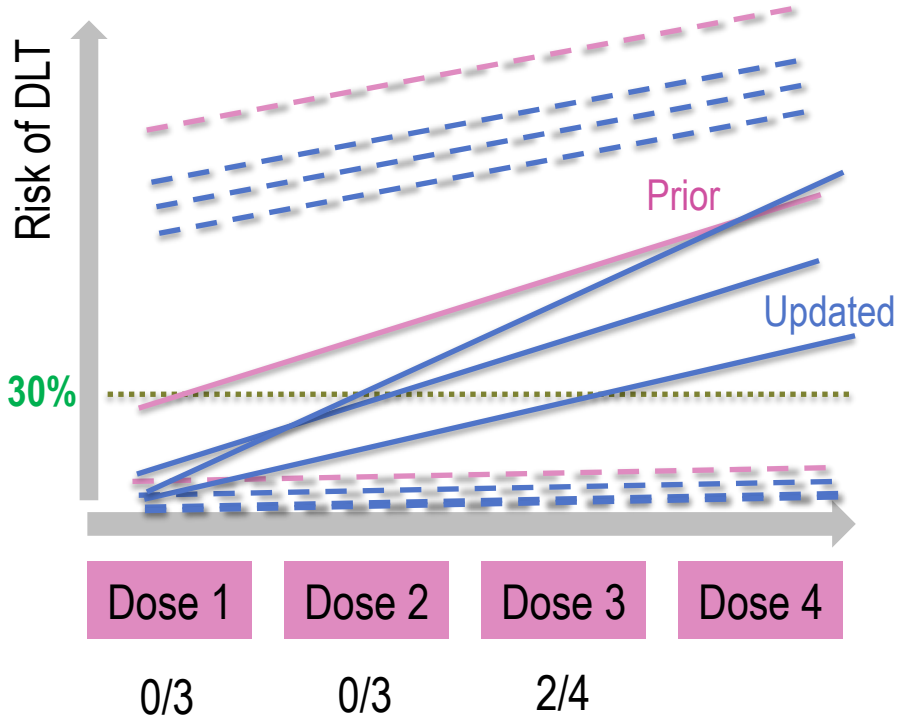
  Risk of DLT = function (dose, parameters)

- Estimate parameters **using all the data**

*Continual reassessment method (**CRM**), Bayesian Logistic Regression Model (**BLRM**), Escalation with Overdose Control **(EWOC)***

Design:

- Specify the target (e.g. 30%)
- Specify criteria (e.g. closest but below 30%)
- Specify "prior" dose-toxicity curve
- Update model and estimates **for all doses**



HOW TO SET UP THE MODEL

“Prior information” can be based on

- Clinical knowledge (including “we do not know much”, aka **operational prior**)
- Historical clinical data or pre-clinical data

10 mg	20 mg	30 mg	40 mg	50 mg
n=4	n=0	n=0	n=0	n=0
DLTs=2	DLTs=0	DLTs=0	DLTs=0	DLTs=0
Mean Tox=0.26	Mean Tox=0.38	Mean Tox=0.46	Mean Tox=0.53	Mean Tox=0.59
95%CI=(0.04,0.66)	95%CI=(0.07,0.79)	95%CI=(0.09,0.85)	95%CI=(0.12,0.9)	95%CI=(0.15,0.93)
Overdose=31%	Overdose=56%	Overdose=70%	Overdose=80%	Overdose=86%
Target=27%	Target=23%	Target=18%	Target=13%	Target=9%

Means of evaluation:

- **Example outputs**

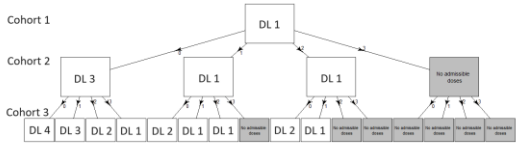
What will be toxicity estimates if 2/4 DLTs?

- **Decision-tree**

Ensures that escalation/de-escalation decisions are aligned

- **Simulations**

Ensures that the design, on average, results in accurate dose selection (over different dose-toxicity curves)

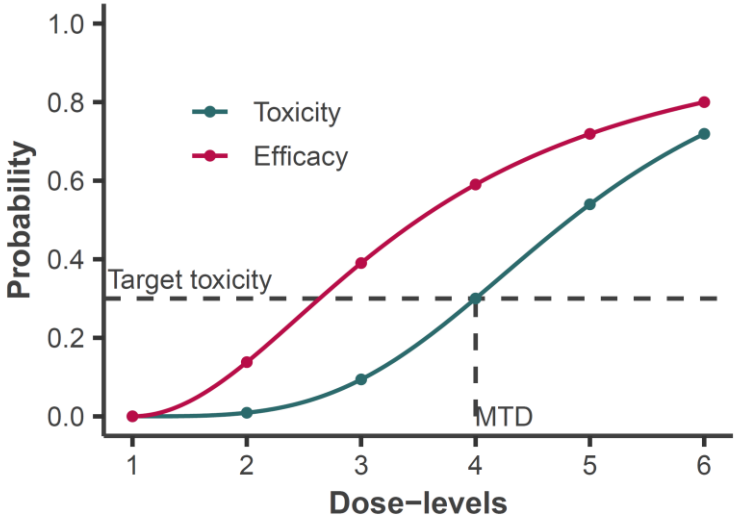


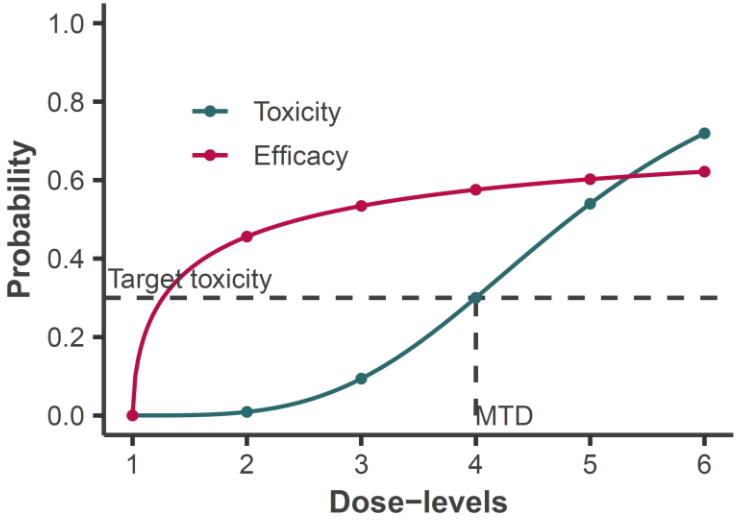
Characteristics	Option 1: Slow and semi-efficient	Option 2: Fast and efficient
Chance to select the right mono dose	64%	67%
Chance to select toxic mono dose	16%	8%
Chance to select the right combo dose	58%	58%
Chance to select the toxic combo dose	12%	5%

ON THE IMPORTANCE OF FINDING THE OPTIMAL BIOLOGIC DOSE (OBD)

Dosage considerations for the full development:

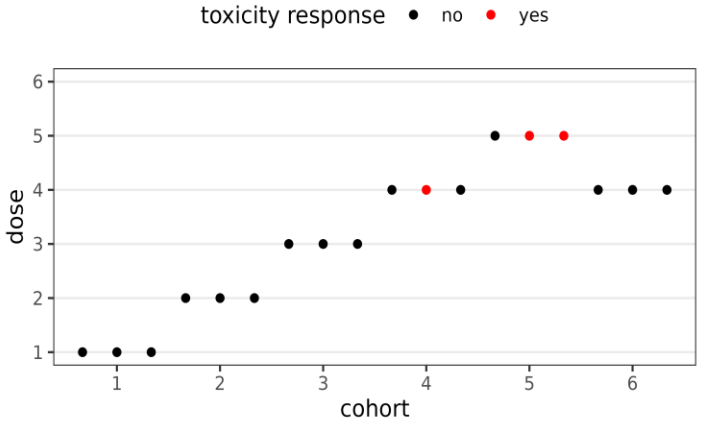
- Too high dosage may bring safety concerns, potentially leading to an efficacious compound not entering into market
- Wrong dosing regimen may decrease the efficacy
- Postmarketing trials to evaluate lower doses





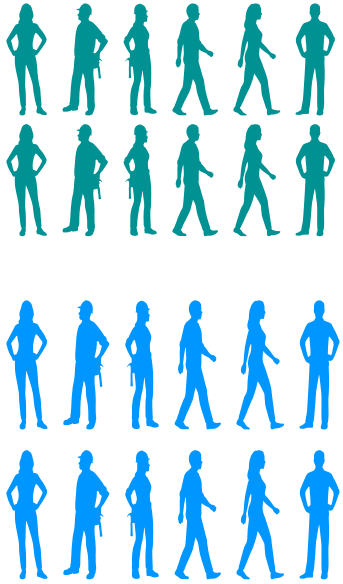
FURTHER STRATEGIES FOR DOSE OPTIMISATION: DOSE EXPANSION

- **Dose expansion** at the end of the dose-escalation
  - Dose escalation may **not yield enough data** to reliably identify a safe and efficacious dose
  - Collect more information on efficacy and toxicity before recommending a dose for study in Phase II



d_a

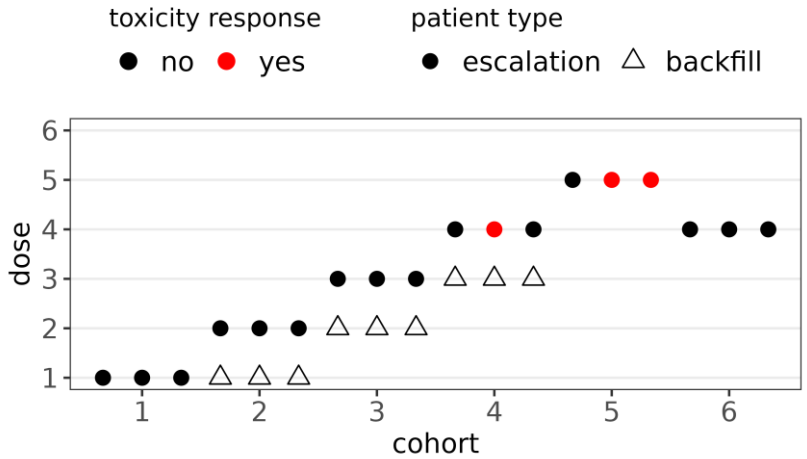
d_b



At how many doses expand? How many patients?

FURTHER STRATEGIES FOR DOSE OPTIMISATION: BACKFILLING

- **Backfilling cohorts** during the escalation
  - Dose escalation schemes target the MTD, so the majority of the data will be near the estimated MTD
  - OBD and MTD might not be the same for the new targeted therapies
  - Collect more efficacy and toxicity information on the lower dose

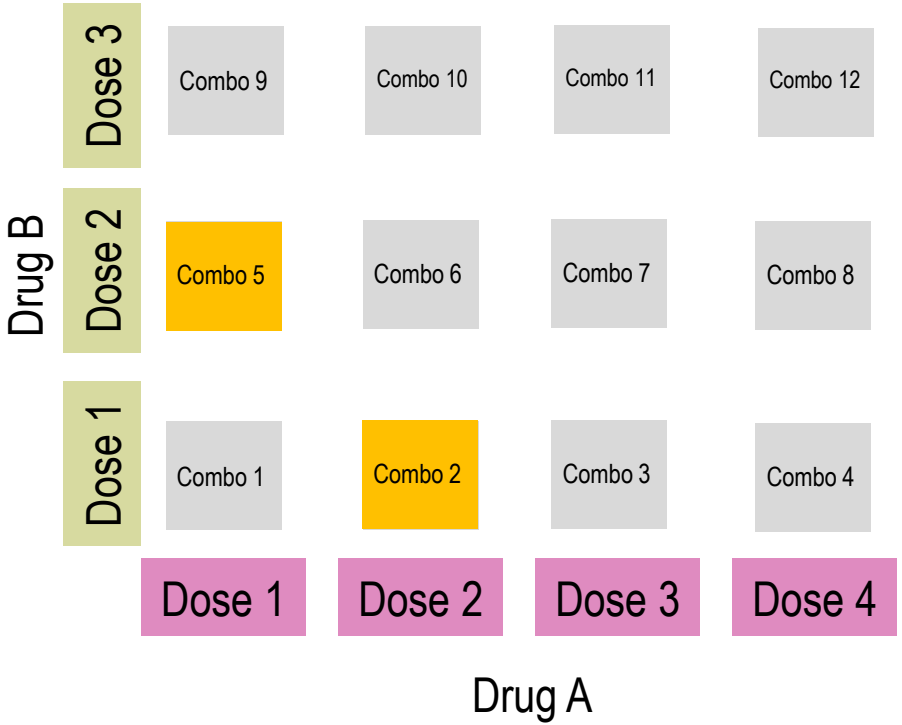


At how many doses expand? How many patients? When to start? When to finish?

DOSE-FINDING IN DRUG COMBINATIONS

- Dual-agent combination
- 4 doses of Drug A; 3 doses of Drug B
- The objective is to find the **target combo (TC)**
- Commonly, defined in terms of **target DLT rate**

- **Challenge:** unknown toxicity ordering between some of the combination, e.g. Combo 2 and Combo 5



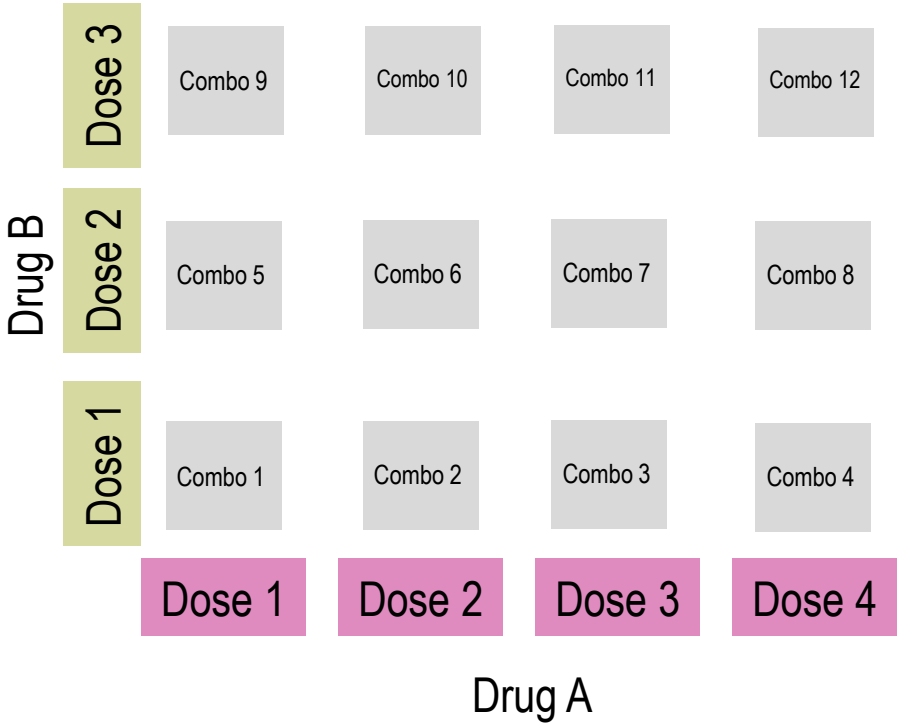
DOSE-FINDING IN DRUG COMBINATIONS: APPROACHES

- **Fixing a dose?**

Combining with novel agent? Existing/approved agent? What was the toxicity rate for the backbone?

- **Fixing a "path"?**

How is this path selected before the trial has started?



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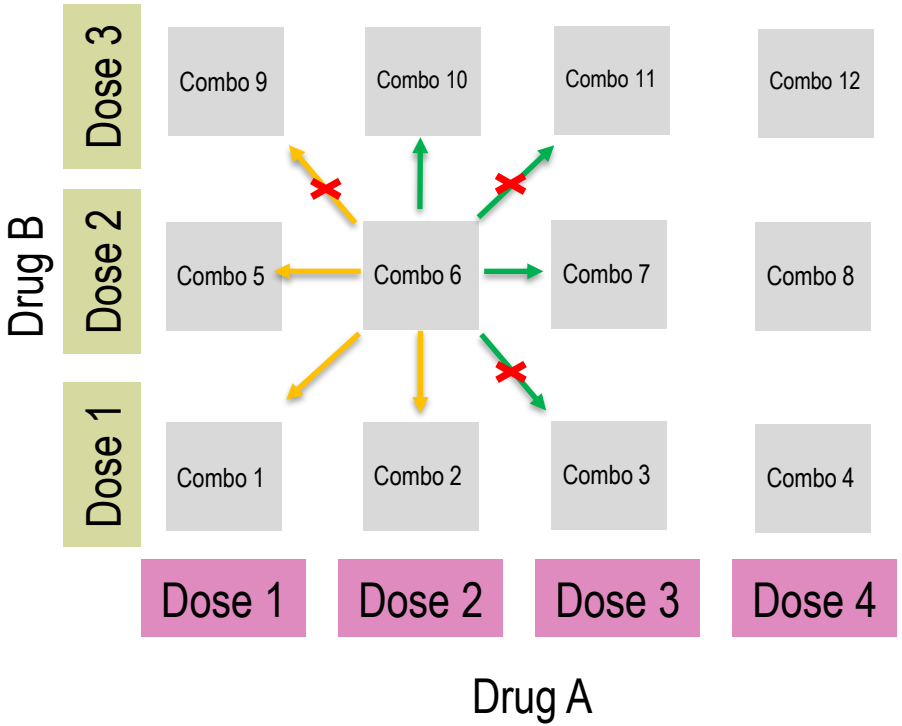
- **Considering the whole combination grid**

Define "admissible" set. No diagonal escalation? Parallel cohorts?

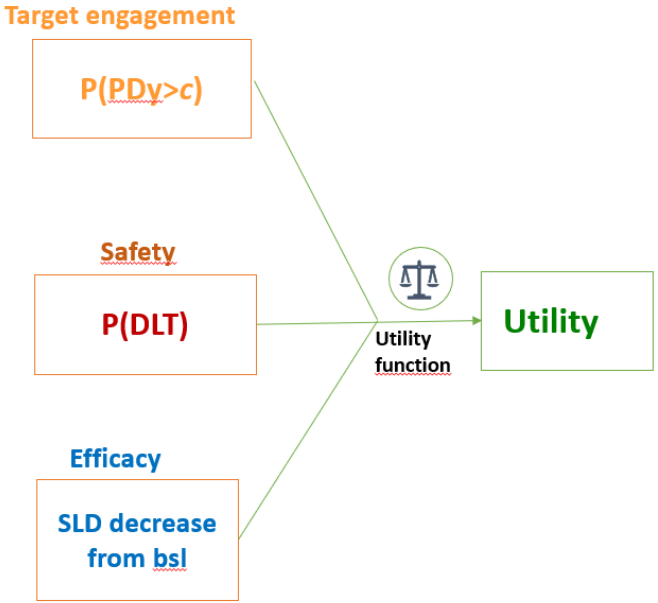


What if the optimal combination is not included in the grid?

MODEL-BASED APPROACHES TO OBD SELECTION

The fundamentals of model-based approaches remain

- Choose the **working model for each endpoint**
- Choose the **utility function**
- **Update the model** with information
- Recommend the dose for the next cohort



Means of evaluation:

- Decision-trees, examples, simulations are used to fine-tune the design

THANK YOU!