Bayesian Designs in Early Phase Clinical Trials

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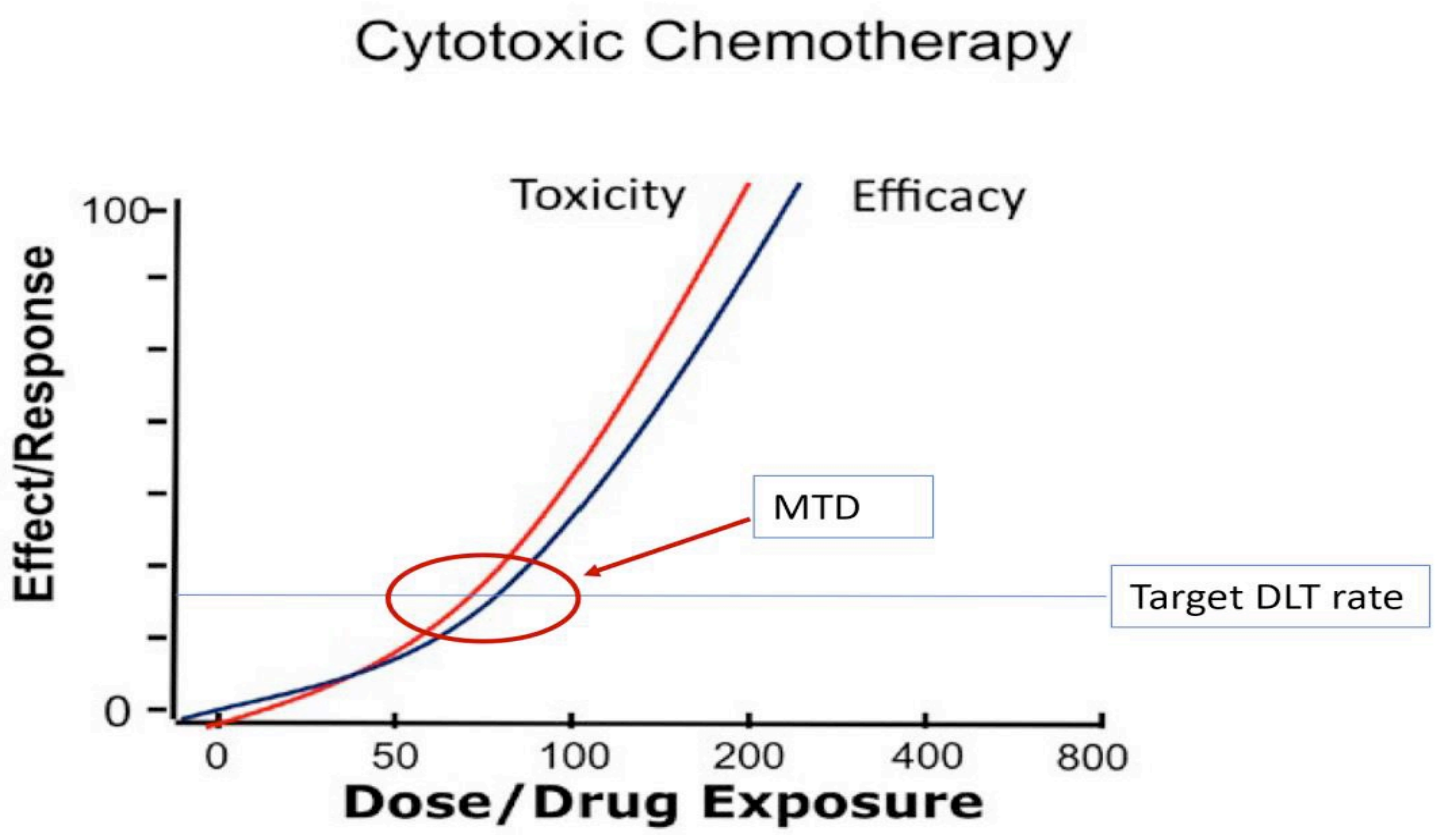
Traditional Assumptions



Types of Phase 1 Designs

Rule-based

- **3+3 algorithm**
- Rolling six design

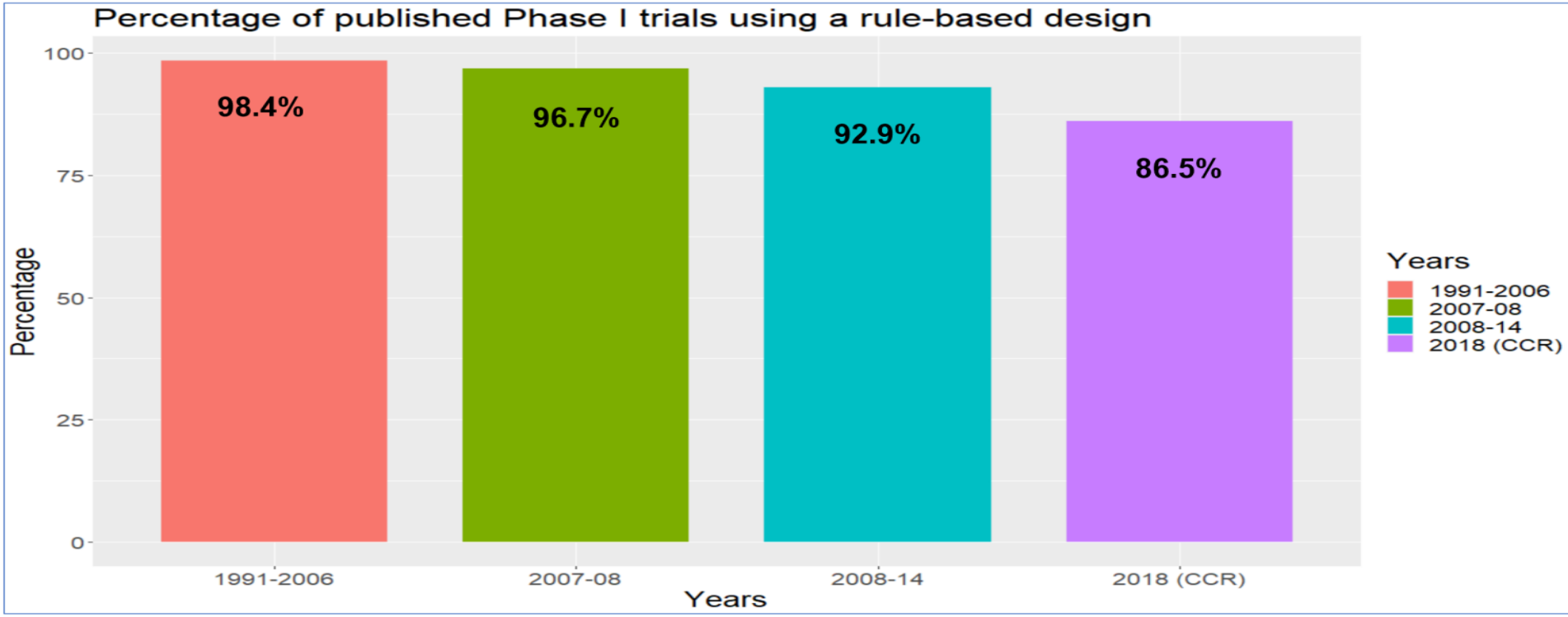
Model-assisted

- **Bayesian optimal interval (BOIN)**
- Modified toxicity probability interval (MTPI)

Model-based

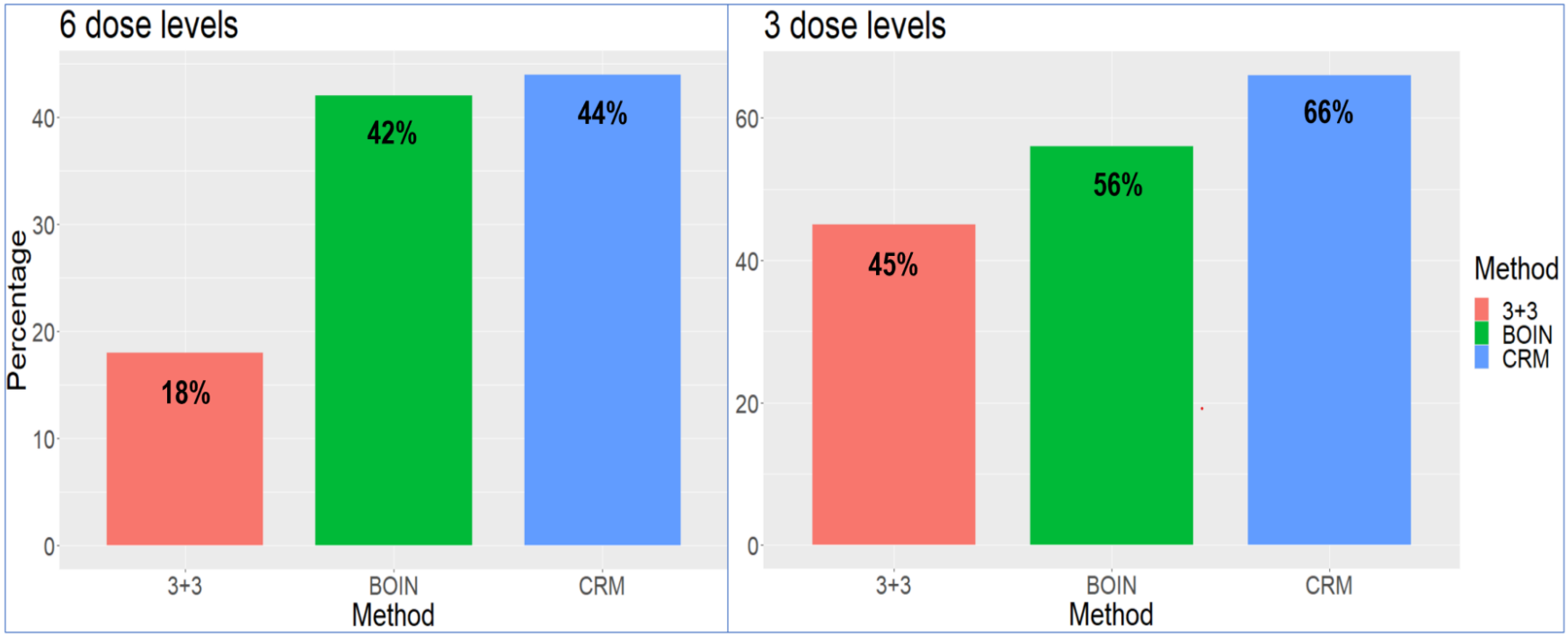
- **Continual Reassessment Method (CRM)**
- Escalation with overdose control (EWOC)

What Has Been Used



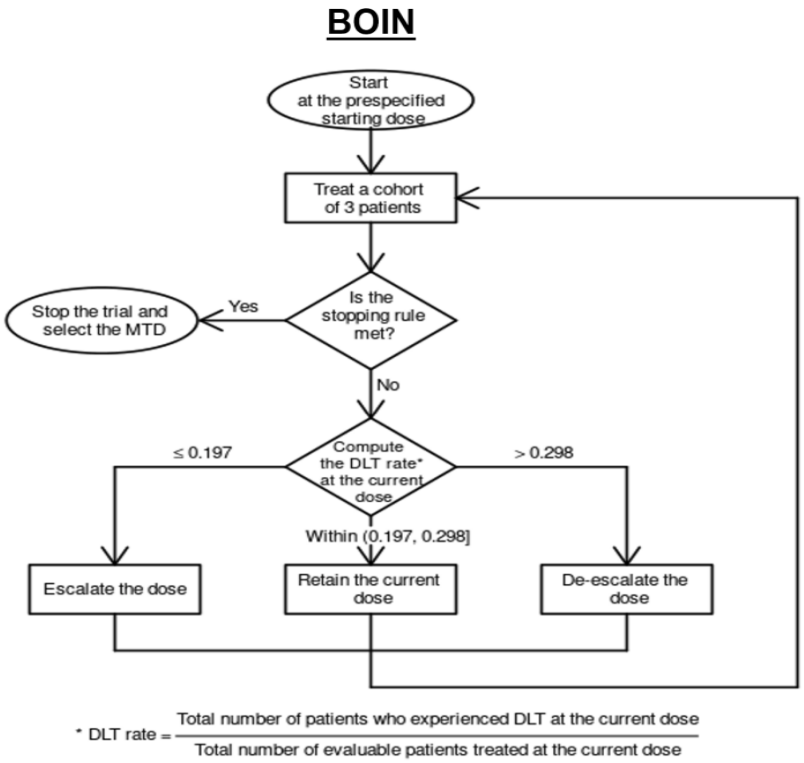
Rogatko et al, *J Clin Oncol*, 2007; Le Tourneau et al, *JNCI*, 2009; Chiuzan et al, *J Biopharm Stat*, 2017; Conaway, Petroni, *Clin Cancer Res*, 2019

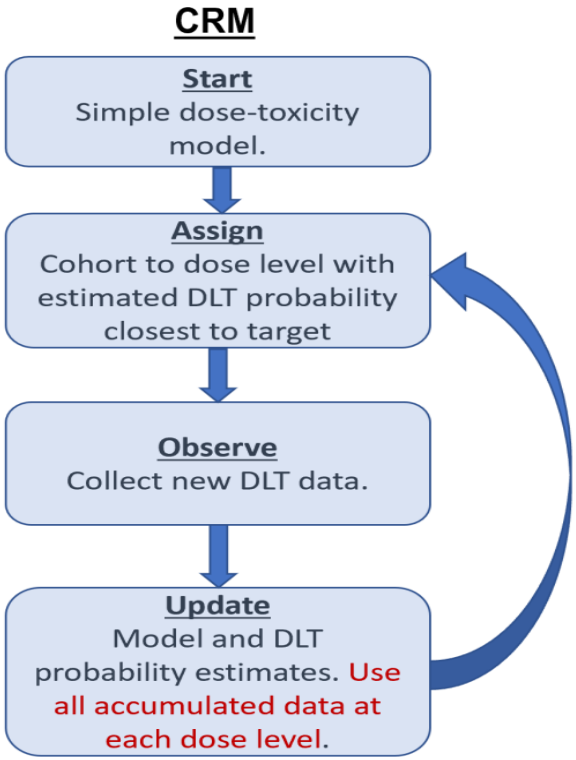
Targeting 25 % DLT Rate



Algorithmic designs more often obtain doses with lower DLT probabilities. More dose levels increases 'conservativeness'.

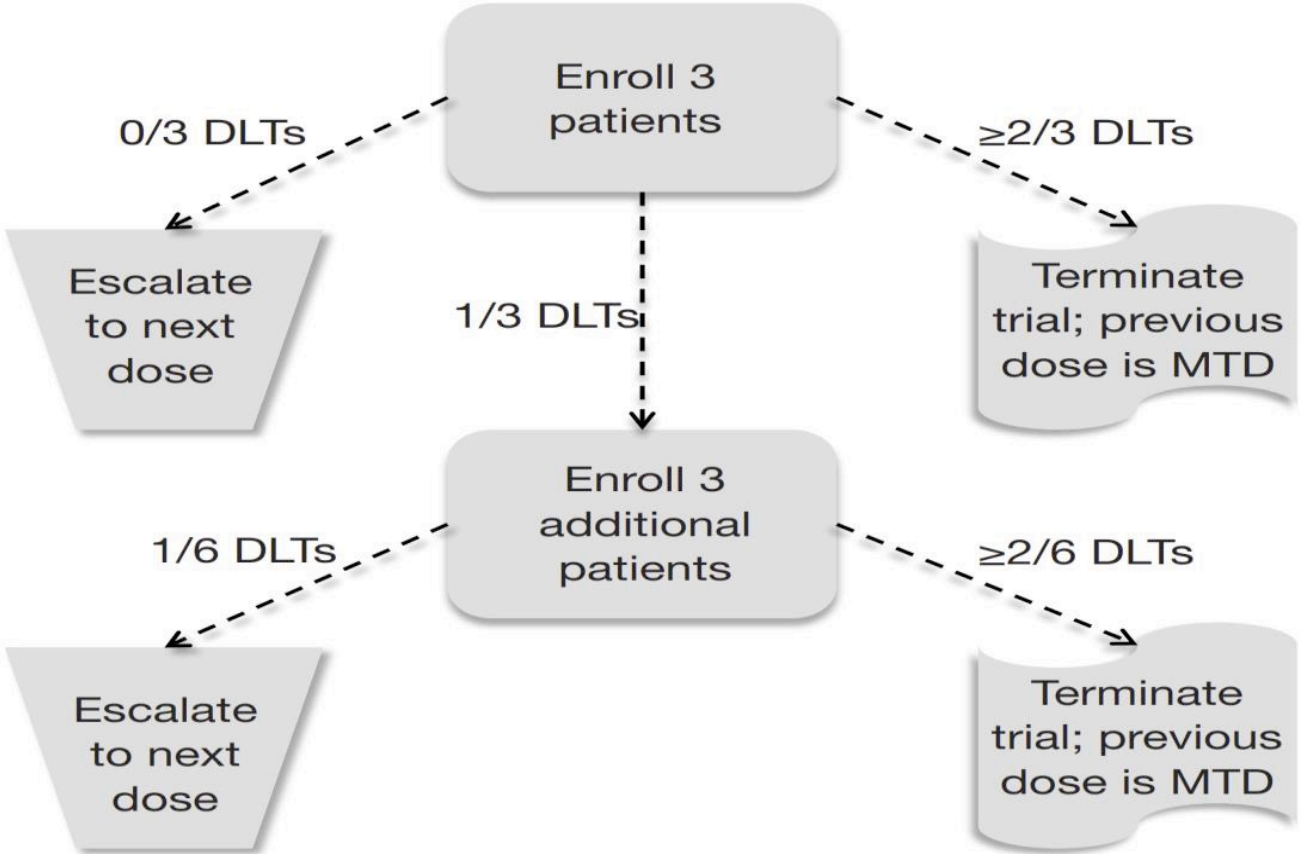
Model Assisted/Model Based Designs





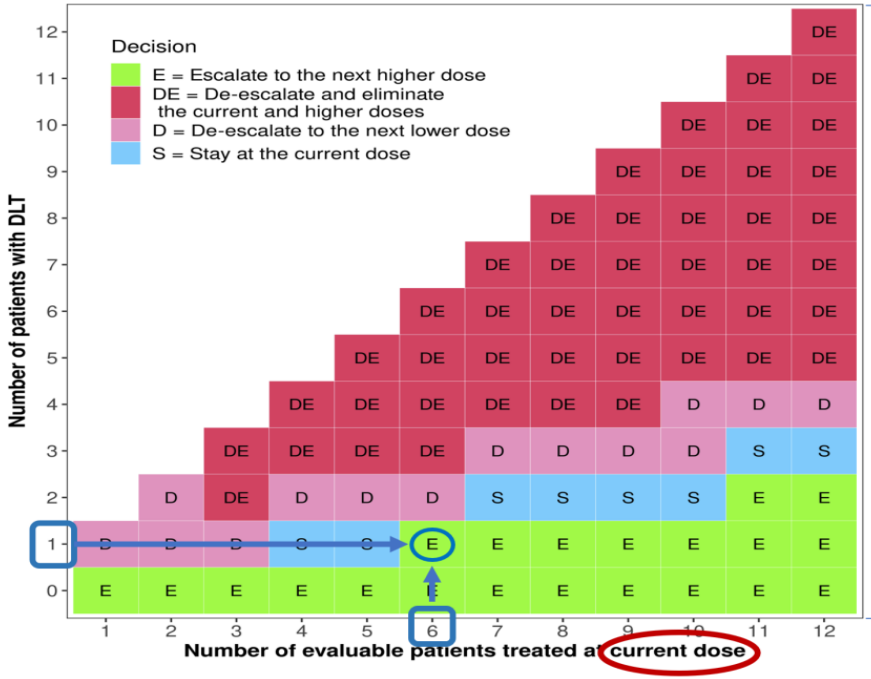
BOIN relies primarily on the toxicity experience at the particular dose level
CRM (EWOC) rely on the toxicity experience across dose levels

For Comparison: 3+3

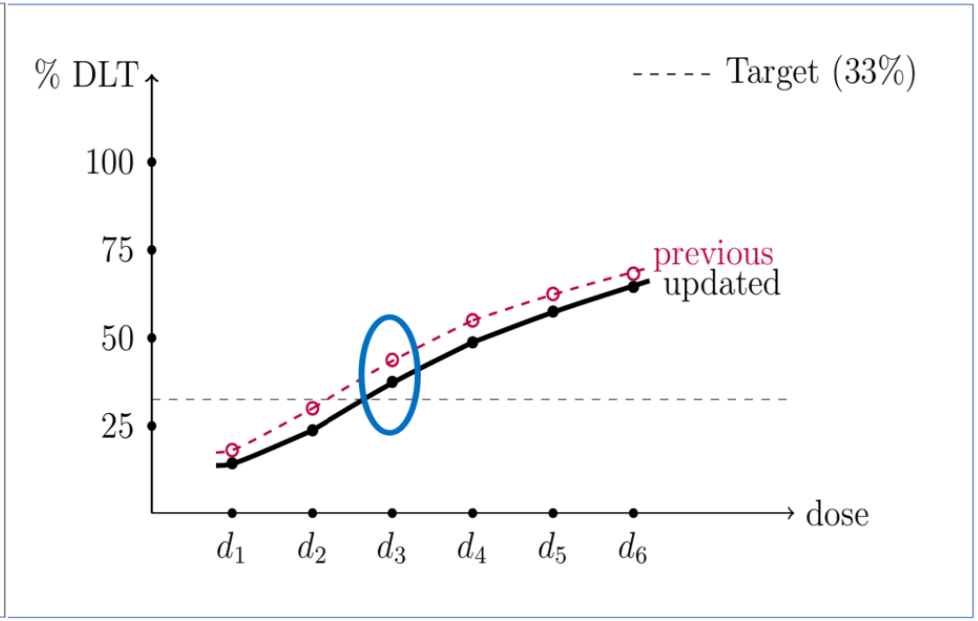


Examples of Escalation Rules

BOIN



CRM



BOIN targets 25% DLT probability with an "indifference region" of 5% around 25%; There is an algorithm at each dose.

CRM targets 33%. Mathematical recalibration is required as patient data accumulate

Re-escalation for Model Designs

- BOIN
  - 6 patients enrolled at level A with 2 DLTs
  - Action – Reduce 1 dose level for next cohort
  - 3 enrolled with 0 DLT at reduced level
    - Re-escalation to level A
- 3+3
  - 6 patients enrolled at level A with 2 DLTs
  - Action – Reduce 1 dose level and do not consider level A again

Current Issues

Traditional		Contemporary
• Dose levels are ordered with respect to probability of DLT (and efficacy)	→	• Ordering of probabilities between some dose levels may be unknown (drug combinations)
• Single binary DLT endpoint drives dose allocation and MTD recommendation	→	• Primary objective may require accounting for both toxicity and efficacy (multiple endpoints)
• DLT observed in *early cycles* drives dose allocation and MTD recommendation.	→	• Relevant toxicity events may occur in later cycles (late-onset toxicities).

Late Onset Toxicities (LOT)

- Dosing decisions based on toxicity in early cycles of treatment
- Patients are on targeted and immune therapies longer
  - More late cycle DLTs
- Toxicities associated with radiation therapy

Late Onset Toxicities

- Review of 2084 patients on 54 phase I trials of targeted therapy
  - 48% of observed DLTs occurred after cycle 1
- Pooled analysis of 576 patients who received Nivolumab
  - Median time to DLT onset was 15 weeks for some toxicity types

LOT Challenges

- Could lengthen evaluation window
  - 8 weeks of follow-up to be considered not dose-limited
  - If average enrollment is 1 patient/week could pass over 5 patients
- Methods to use “partial information” on pending patients

LOT Approaches

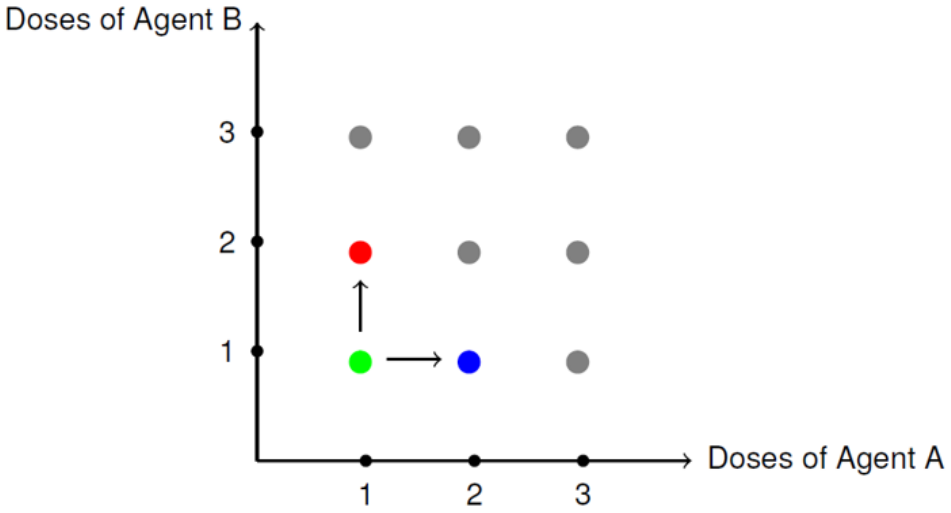
- For single agent studies
  - Time-to-Event CRM (TITE-CRM)
  - Time-to-Event BOIN (TITE-BOIN)
- Use data on patients who complete evaluation and those who are not dose-limited but under observation
  - Pending patient contributions weighted by proportion of evaluation window has been completed

TITE-Methods

- TITE-CRM requires model for dose-toxicity relationship
  - Allows user to value follow-up time differently across the evaluation window
- TITE-BOIN
  - Escalation decision based on all patients *at that dose level*
  - Current implementation weights a pending non-DLT patients according to proportion of expected follow-up time has been completed

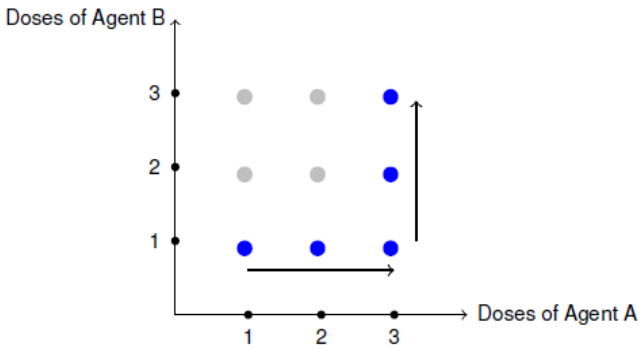
Studies of Combinations

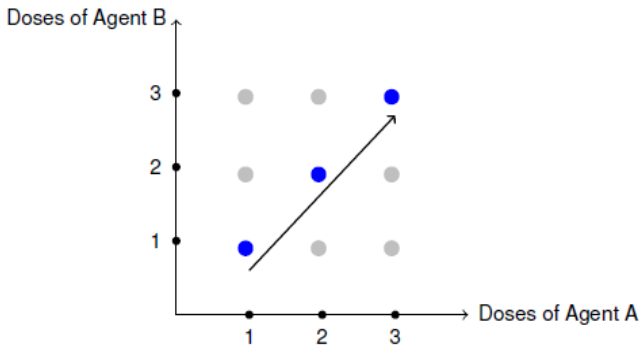
- Escalate more than 1 agent
- If Green is safe, do we go Blue or Red



Studies of Combinations

- Chose a path of known increasing risk of DLT and use single agent methods





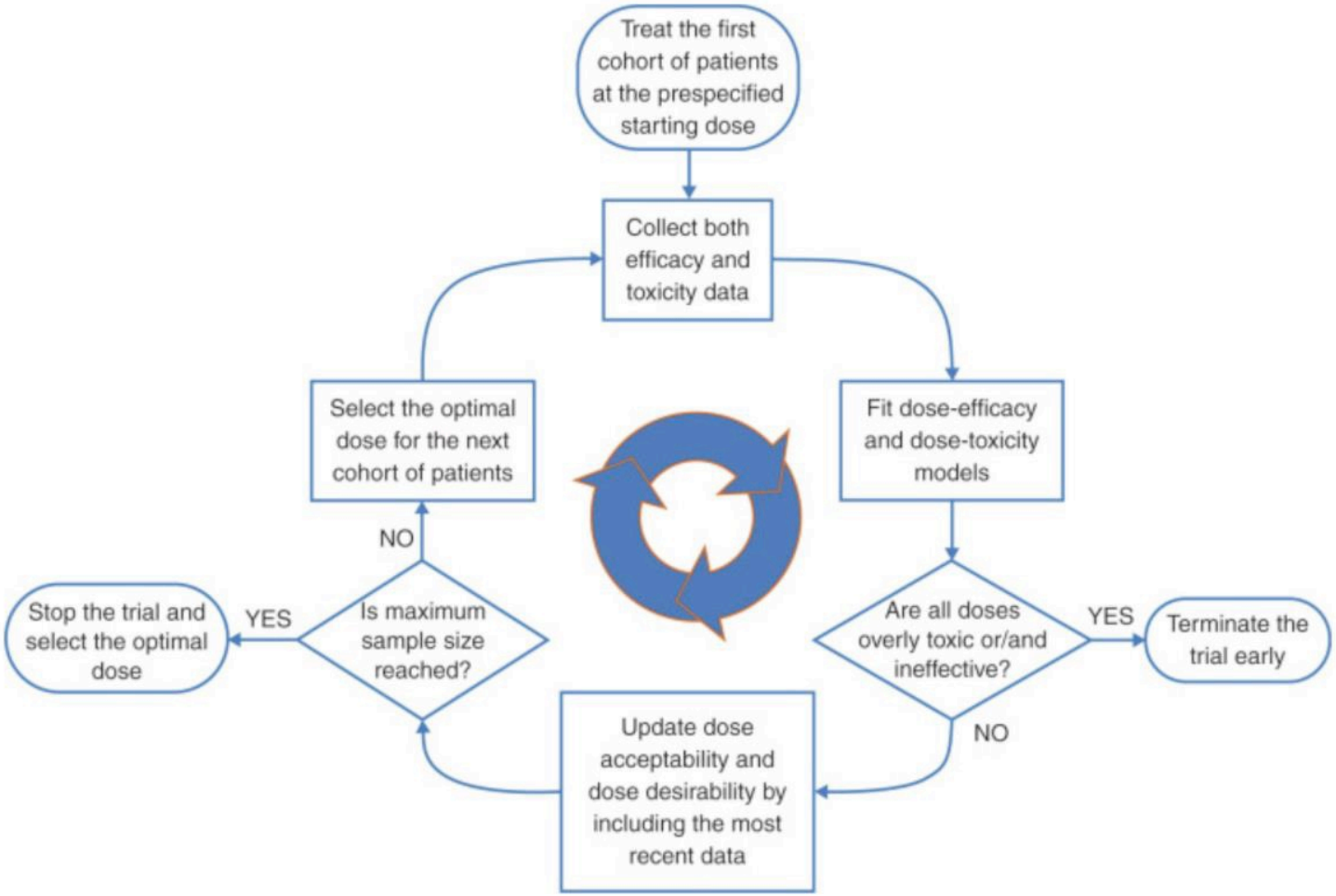
Studies of Combinations

- Accommodate non-monotone relationships
  - BOIN COMB Zhou *et al* JCO Clin Cancer Inform 2021
  - Partial order CRM Wages *et al* Clin Trials 2011

Multiple Endpoints

- Identify a toxicity endpoint
- Identify an “efficacy” endpoint
  - Efficacy can be defined as:
    - Clinical response
    - Achievement of PK/PD endpoint
    - Inhibition or expression of a biological target

Design Strategy



Methods

- Frequentist
  - Bryant and Day, Biometrics, 1995
- Bayesian
  - BOIN12: Bayesian optimal interval phase I/II trial design for utility-based dose finding. Zhou JCO Clin Cancer Info,2021
  - Early phase based on toxicity and efficacy. Wages and Tait J Biopharm Stat, 2015

Other Topics

- Backfilling lower levels in phase 1 studies
  - Dehbi *et al* Contemporary Clin Trials 2021
- Randomized phase 1 trials
  - Iasonos and O'Quigley Br J Cancer 2021

Summary

- Model-assisted and model-based designs can be implemented readily
- Designs to use multiple endpoints are well characterized
- Early phase designs don’t have to target just the MTD
  - Decision based on multiple endpoints
  - Algorithmic designs (3+3) are ill suited

Thanks

- Nolan Wages
- AACR/ASCO Vail course faculty