1. Background
Combination therapy in oncology
- Combination therapies have potential to improve efficacy and minimize resistance
- Co-development of multiple combinations is often necessary to find the optimal therapy
- Single agent dose-toxicity data is often available

Key development challenges
- Limited sample size
- Multidimensional escalation, drug-drug interaction, possibility of multiple MTDs
- Difficult to prespecify escalation/de-escalation rule

Objective
- Efficient design to identify RP2D for dual and triple combination therapies in a seamless fashion
- Allows on-trial adaptation based on evolving data
- Leverage all information for better precision

We propose an efficient model based approach to facilitate dose finding while co-developing dual and triple combinations

2. Study Design

Compounds of interest
- Drug A: fixed dose 20 mg
- Drug B: 35, 50, 70, 90 mg
- Drug C: 5, 7.5, 10 mg

Endpoint
- Dose limiting toxicity (DLT) in cycle 1

Framework: sequential dose finding
- Stage 1: Dual combo (A+B)
- Stage 2: Triple combo (A+B+C)
- Dose-DLT data available for single agent trial of drugs A, B, and C

No significant DDI expected but with considerable uncertainty

Starting dose of triple combo depends on dual data

3. Dosing Criteria

- Escalation with overdose control (EWOC): dose combinations with P(true DLT rate ≥ 0.33|data) ≥ 25% is not recommended for next cohort
- Escalation to any dose levels ≤100% from current dose is allowed; including skipping
- Flexible cohort size: 3-6
- Final decision based on additional data: PK, other safety than DLT, efficacy.

4. Methodology

- **Dose-DLT data for combination**
  No. DLT r at dose level d1, d2, d3 out of n patients:
  \[ r \sim \text{Binomial} \left( \pi_{123}(d_1,d_2,d_3), n \right) \]

- **Proportional odds model for DLT probabilities**

  - **Triplet model**: Odds \( \pi_{123}(d_1,d_2,d_3) \) = odds \( \pi_{123}^{(2)}(d_1,d_2,d_3) \times g(\eta_1,d_1,d_2,d_3) \)
  - Odds under no interaction
  - dose dependent interaction
  - Moreover, \( \pi_{123}^{(2)} = 1 - (1 - \pi_{d1})(1 - \pi_{d2})(1 - \pi_{d3}) \) and \( \eta \) (4 parameters) captures 2-way and 3-way interactions
  \[ \log(\pi_{d1}) = \log(\alpha_1) + \beta_1 \log(d_1); i=1,2,3 \]

- **Dual combo model**: Setting \( d_3 = 0 \)
- **Prior distribution**

  Meta-Analytic Predictive (MAP) approach to derive the prior distribution for (\( \alpha_i, \beta_i \)) historical single agent DLT-dose data and weakly informative prior for \( \eta \) (Neuenschwande et al. 2014).

5. Design Characteristics

5.1 Starting Dose for the Dual Combo

- Feasible to start dual combo at (Drugs A, B) = (20, 70)

5.2 Data Scenarios and Starting Dose for the Triple Combo

- **Data scenarios help to understand the on-trial dose recommendations of the proposed design**
- **Dose finding for dual combo can skip dose**
- **Triple combo starting dose adaptively use historical data and on-study dual combo data.**

6. Conclusions/Discussions

- Proposed approach allows seamless transition from dual to triple combinations
- Leverage all available data to elicit the starting dose for the triple combination
- Dosing decision guided by sound statistical inference and clinical relevance
- Flexible for incorporating intermediate doses
- Communication with non-statistician is the key for successful practical implementation
- Software available

7. References