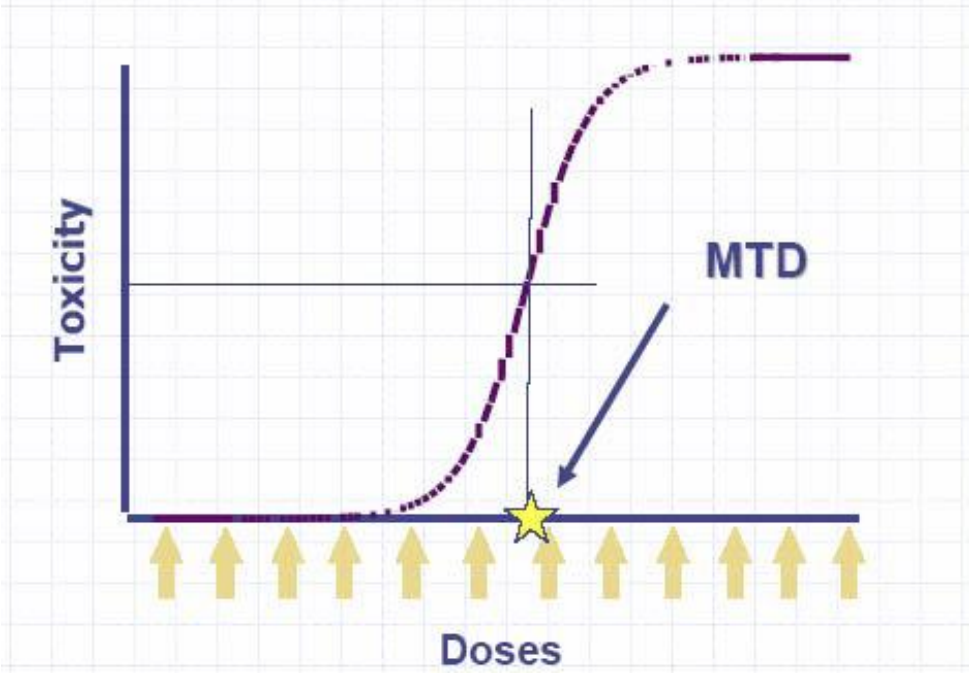
Dose-Finding Design Incorporating Intra-Patient Dose Escalation (IP-CRM)

Suyu Liu

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Department Name

Phase I Clinical Trials

- The primary objective of a Phase I clinical trial is to identify the maximum tolerated dose (MTD) of a new drug, typically defined as the dose with a toxicity probability closest to the target toxicity rate.



Phase I Trial Designs

- Algorithm-based: 3 + 3 design
  - simple to implement but has poor operating characteristics.

- Model-based: CRM (O'Quigley, Pepe and Fisher,1990)
  - produce good operating characteristics but are challenging to implement.

- Model-assisted: BOIN (Liu and Yuan, 2015)
  - combine the simplicity of algorithm-based designs with the superior performance of model-based designs.

Limitations of One-Patient-One-Dose Designs

- Each patient receives only one dose and therefore contributes a single data point.
- A minimum number of patients is required to adequately explore the dose space and reliably identify the MTD.
- Patients receiving subtherapeutic doses, particularly at the low dose levels, may experience reduced potential treatment benefits.

Intra-patient Dose Escalation

- ✅ **Improves patient benefit**
  - Patients can receive **higher, more effective doses** during the trial

- ✅ **Generates richer data**
  - Each patient contributes **multiple data points** at different dose levels
  - More information gained **with the same sample size**

- ✅ **Supports small sample size trials**
  - Particularly useful in **rare cancers** or **pediatric populations**
  - Accelerates dose-finding and drug development

Tial Example

- **FDA Accelerated Approval (June 15, 2023)**
  - **Agent:** Glofitamab-gxbm
  - **Indication:** Relapsed/refractory DLBCL or LBCL after ≥2 prior therapies
- **Step-Up Dosing Schedule**
  - Cycle 1 Day 8: **2.5 mg**
  - Cycle 1 Day 15: **10 mg**
  - Subsequent cycles (Day 1): **30 mg,** up to 12 cycles

IP-CRM: Intra-patient Dose Escalation with the Continual Reassessment Method

- Dose-toxicity modeled with logistic regression
- MTD estimated at each interim decision
- Initial titration dose for each new cohort adaptively updated using accumulated patient data
- Intra-patient escalation by cycles:
    - Toxicity → halt titration
    - No toxicity → escalate dose (unless above current MTD estimate)

IP-CRM: Toxicity Model

- J doses with corresponding toxicity probabilities $\pi_1 < \pi_2 < \cdots < \pi_J$

$$\text{logit}(\pi_j) = \beta_0 + \beta_1 \tilde{d}_j$$

- the effective dose $$\tilde{d}_j = \left\{ \log\left(\frac{p_j}{1-p_j} \right) - \tilde{\beta}_0 \right\} / \tilde{\beta}_1$$

- p_j is the prior estimate or “skeleton" of the toxicity probability at dose level j
- Prior: $\beta_1 \sim exp.(1)$, $\beta_0 \sim N(3, 0.5^2)$
- Given interim data $\mathcal{D}_n = \{(n_j, y_j), j = 1, \cdots, J\}$, possible $\sum_{j=1}^{J} n_j > n$

$$L(\beta_0, \beta_1; \mathcal{D}_n) = \prod_{j=1}^{J} \left\{ \frac{\exp\left(\beta_0 + \beta_1 \tilde{d}_j\right)}{1+\exp\left(\beta_0 + \beta_1 \tilde{d}_j\right)} \right\}^{y_j} \left\{ \frac{1}{1+\exp\left(\beta_0 + \beta_1 \tilde{d}_j\right)} \right\}^{n_j - y_j}$$

IP-CRM: Notations

- Target toxicity rate: ∅
- Each patient is allowed up to K − 1 intra-patient dose escalations.
- Based on the interim data,
  - Estimate toxicity probability at dose level j: the posterior mean, $\tilde{\pi}_j$
  - Estimated MTD is the dose level j, denoted as j^{MTD} :

$$j^{\text{MTD}} = \underset{j \in (1, \cdots, J)}{\arg \min} \mid \hat{\pi}_j - \phi \mid$$

  - Let the currently highest tried dose level to be j^{H} , and the current starting dose level to be j^{S}

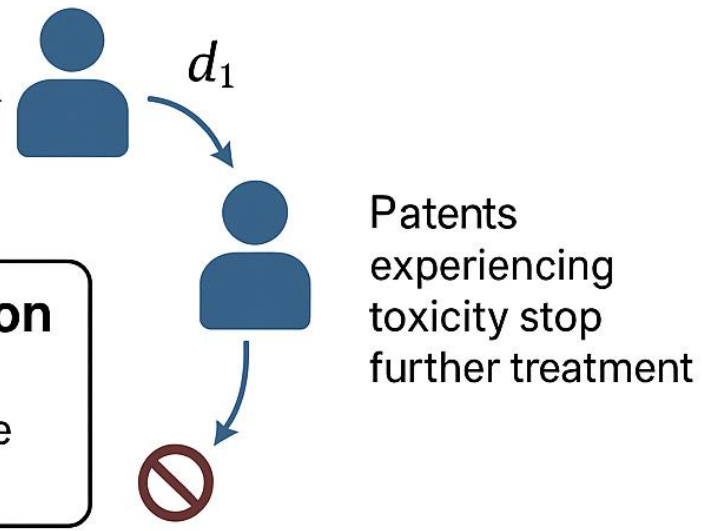
IP-CRM Dose-Finding Algorithm

1. First Cohort

Treat the first cohort at the lowest dose in cycle1

2. Intra-Patient Dose Escalation

If a patient completes a cycle without toxicity, escalate to the next higher dose in the next cycle



3. Updating Starting Dose for New Cohorts

Estimate MTD j^{MTD} using all current data

- Escalate starting dose if $j^{MTD} > j^{H}$ (highest tried dose), new cohort starts at $j^{H}+1$
- De-escalate if $j^{MTD} < j^{S}$ (previous starting dose), new cohort starts at $j^{S}-1$
- Otherwise, start at j^{MTD}

Early termination: Stop trial if $\Pr(\pi_1 > \varphi | \text{data}) > c$ (lowest dose too toxic)

Once the maximum sample size is reached, we choose the MTD as the dose among all tried doses with $\tilde{\pi}_j$ closest to $\emptyset$.

$$j^{\text{MTD}} = \underset{j \in (1, \cdots, J)}{\arg\min} \mid \hat{\pi}_j - \phi \mid$$

Simulations

- N=9, $\emptyset = 0.3$, 5 dose levels
- skeleton toxicity: (0.02, 0.12, 0.3, 0.5, 0.65)
- cohort size: 3 patients
- 2000 simulation trials per scenario
- compare to:
  - CRM cohort size 1 and 3
  - BOIN cohort size 1 and 3
  - 3+3 design

Simulation Results

	dose level				
	1	2	3	4	5
			Scenario 1		
π	**0.3**	0.5	0.7	0.8	0.9
IP-CRM	**0.726 (7.3)**	0.159 (6.2)	0.004 (1.5)	0.000 (0.0)	0.000 (0.0)
CRM-cohsize 3	**0.642 (7.1)**	0.232 (1.8)	0.025 (0.1)	0.000 (0.0)	0.000 (0.0)
CRM-cohsize 1	**0.674 (6.1)**	0.200 (2.1)	0.023 (0.6)	0.002 (0.1)	0.000 (0.0)
BOIN-cohsize 3	**0.641 (6.6)**	0.226 (1.9)	0.010 (0.1)	0.000 (0.0)	0.000 (0.0)
BOIN-cohsize 1	**0.567 (5.0)**	0.259 (2.4)	0.051 (0.9)	0.007 (0.2)	0.000 (0.0)
3+3	**0.406 (4.3)**	0.080 (2.0)	0.004 (0.3)	0.000 (0.0)	0.000 (0.0)
			Scenario 2		
π	0.05	0.15	**0.3**	0.5	0.8
IP-CRM	0.010 (3.4)	0.270 (4.9)	**0.602 (7.0)**	0.114 (3.6)	0.004 (0.8)
CRM-cohsize 3	0.066 (3.8)	0.440 (3.7)	**0.495 (1.5)**	0.000 (0.0)	0.000 (0.0)
CRM-cohsize 1	0.072 (2.0)	0.304 (2.6)	**0.416 (2.6)**	0.202 (1.4)	0.007 (0.4)
BOIN-cohsize 3	0.082 (3.7)	0.490 (3.7)	**0.429 (1.6)**	0.000 (0.0)	0.000 (0.0)
BOIN-cohsize 1	0.035 (1.8)	0.219 (2.5)	**0.500 (2.6)**	0.228 (1.6)	0.018 (0.6)
3+3	0.173 (3.4)	0.408 (3.8)	**0.330 (3.4)**	0.062 (1.6)	0.000 (0.2)
			Scenario 3		
π	0.02	0.05	0.1	**0.3**	0.5
IP-CRM	0.000 (3.0)	0.011 (3.3)	0.232 (4.8)	**0.526 (4.9)**	0.232 (3.7)
CRM-cohsize 3	0.013 (3.3)	0.183 (3.3)	0.805 (2.4)	**0.000 (0.0)**	0.000 (0.0)
CRM-cohsize 1	0.009 (1.3)	0.053 (1.6)	0.286 (2.3)	**0.508 (2.3)**	0.146 (1.6)
BOIN-cohsize 3	0.012 (3.2)	0.208 (3.4)	0.781 (2.4)	**0.000 (0.0)**	0.000 (0.0)
BOIN-cohsize 1	0.004 (1.2)	0.023 (1.5)	0.317 (2.1)	**0.428 (2.3)**	0.229 (1.8)
3+3	0.021 (3.2)	0.088 (3.4)	0.451 (3.6)	**0.360 (3.9)**	0.076 (1.8)

Sensitivity Analysis

- Maximum sample size: N=6, 9, 12, and 24
- When carryover effects and intra-patient correlations existed: $\gamma = 0.2, 0.4$

$$\pi_{j+1}^{c} = \min(\pi_{j+1} + \gamma\pi_{j}^{c}, 1)$$

For example, if a patient escalates from dose level 1 to 2 to 3.

At dose level 1: $\pi_1^c = \pi_1$

At dose level 2: $\pi_2^c = \min(\pi_2 + \gamma\pi_1^c, 1)$

At dose level 3: $\pi_3^c = \min(\pi_3 + \gamma\pi_2^c, 1)$

- Alternative initial toxicity skeleton: (0.05, 0.08, 0.35, 0.55, 0.7)

Sample size (ss) = 6, 9, 12, 24

	dose level				
	1	2	3	4	5
			Scenario 1		
π	**0.3**	0.5	0.7	0.8	0.9
ss=6	**0.701 (5.1)**	0.188 (4.1)	0.004 (1.1)	0.000 (0.0)	0.000 (0.0)
ss=9	**0.726 (7.3)**	0.159 (6.2)	0.004 (1.5)	0.000 (0.0)	0.000 (0.0)
ss=12	**0.718 (9.3)**	0.145 (8.2)	0.001 (1.8)	0.000 (0.0)	0.000 (0.0)
ss=24	**0.792 (19.1)**	0.098 (16.4)	0.000 (2.8)	0.000 (0.0)	0.000 (0.0)
			Scenario 2		
π	0.05	0.15	**0.3**	0.5	0.8
ss=6	0.031 (3.3)	0.342 (3.9)	**0.455 (4.5)**	0.159 (1.7)	0.013 (0.5)
ss=9	0.010 (3.4)	0.270 (4.9)	**0.602 (7.0)**	0.114 (3.6)	0.004 (0.8)
ss=12	0.006 (3.4)	0.244 (5.8)	**0.657 (9.4)**	0.095 (5.3)	0.000 (1.1)
ss=24	0.000 (3.5)	0.151 (8.2)	**0.811 (20.1)**	0.038 (12.7)	0.000 (1.7)
			Scenario 3		
π	0.02	0.05	0.1	**0.3**	0.5
ss=6	0.002 (3.0)	0.037 (3.2)	0.273 (4.0)	**0.433 (2.8)**	0.256 (1.7)
ss=9	0.000 (3.0)	0.011 (3.3)	0.232 (4.8)	**0.526 (4.9)**	0.232 (3.7)
ss=12	0.000 (3.0)	0.001 (3.3)	0.195 (5.7)	**0.613 (7.2)**	0.193 (5.8)
ss=24	0.000 (3.0)	0.000 (3.4)	0.092 (7.5)	**0.786 (17.0)**	0.122 (13.9)

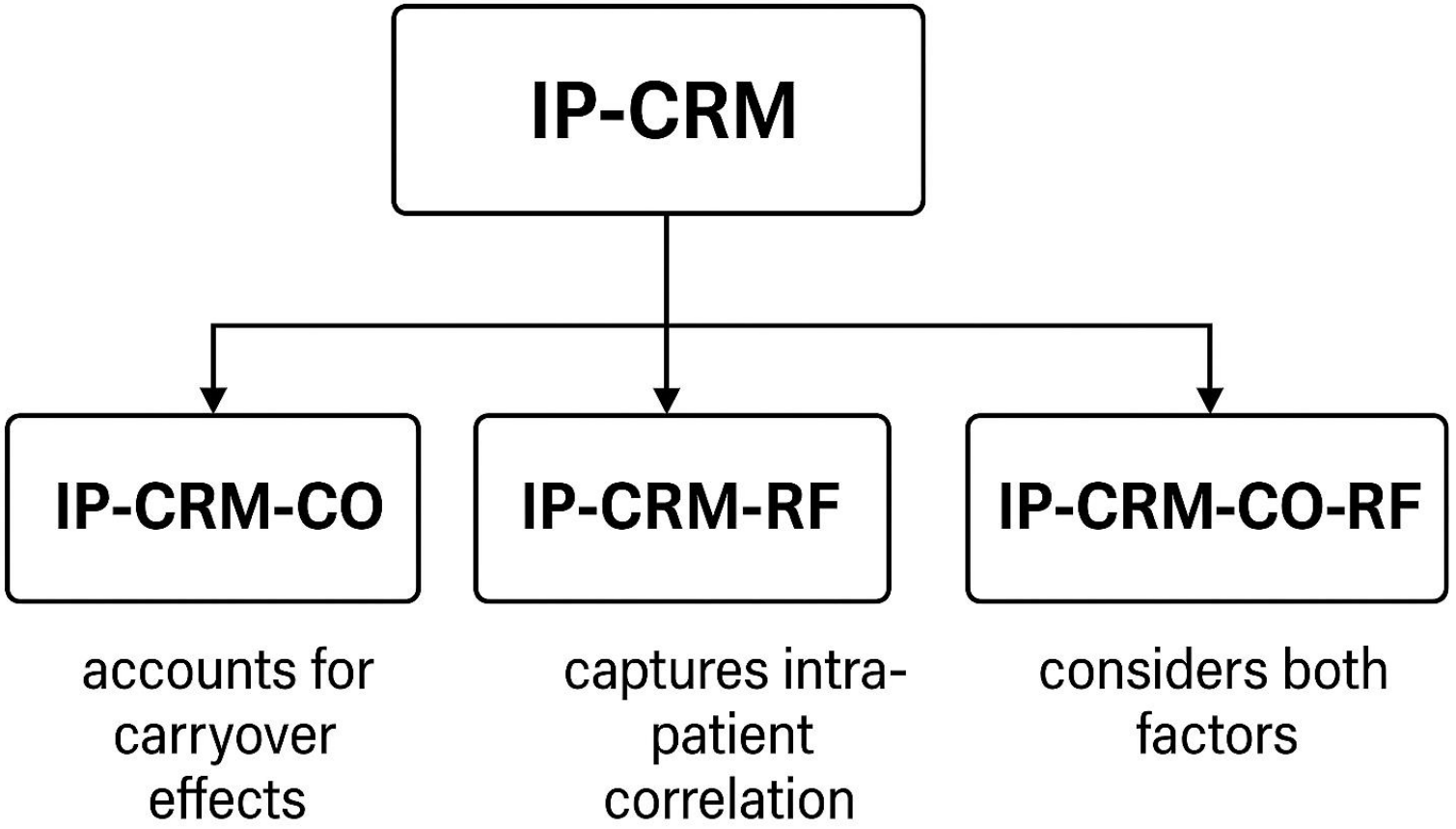
$\gamma = 0.2, 0.4$

	dose level				
	1	2	3	4	5
			Scenario 1		
π	**0.3**	0.5	0.7	0.8	0.9
$\gamma = 0.2$	**0.714 (7.2)**	0.164 (6.2)	0.002 (1.5)	0.000 (0.0)	0.000 (0.0)
$\gamma = 0.4$	**0.779 (7.6)**	0.089 (6.1)	0.000 (1.1)	0.000 (0.0)	0.000 (0.0)
			Scenario 2		
π	0.05	0.15	**0.3**	0.5	0.8
$\gamma = 0.2$	0.011 (3.4)	0.250 (4.9)	**0.623 (6.8)**	0.113 (3.6)	0.003 (0.9)
$\gamma = 0.4$	0.012 (3.4)	0.309 (5.0)	**0.633 (7.1)**	0.047 (3.4)	0.000 (0.7)
			Scenario 3		
π	0.02	0.05	0.1	**0.3**	0.5
$\gamma = 0.2$	0.000 (3.0)	0.009 (3.3)	0.228 (4.8)	**0.540 (4.9)**	0.224 (3.7)
$\gamma = 0.4$	0.001 (3.0)	0.007 (3.3)	0.261 (4.9)	**0.537 (5.0)**	0.196 (3.7)

Initial toxicity skeleton: (0.05, 0.08, 0.35, 0.55, 0.7)

	dose level				
	1	2	3	4	5
			Scenario 1		
π	**0.3**	0.5	0.7	0.8	0.9
IP-CRM	**0.637 (6.9)**	0.154 (5.8)	0.009 (1.6)	0.000 (0.1)	0.000 (0.0)
			Scenario 2		
π	0.05	0.15	**0.3**	0.5	0.8
IP-CRM	0.019 (3.4)	0.208 (4.6)	**0.668 (7.1)**	0.101 (3.6)	0.005 (0.7)
			Scenario 3		
π	0.02	0.05	0.1	**0.3**	0.5
IP-CRM	0.000 (3.0)	0.005 (3.1)	0.271 (5.0)	**0.509 (5.0)**	0.216 (3.6)

Extensions to Address Carryover & Correlation



- same the dose-finding algorithm as for the IP-CRM design
- but different toxicity models

IP-CRM-RF Design

- Capture intra-patient correlation using random effects
- **Model:**

$$\text{logit}(\pi_{ij}|\tilde{d}_j, u_i) = \beta_0 + \beta_1 \tilde{d}_j + u_i$$

  - $u_i \sim N(0, \sigma^2)$
  - π_{ij}: probability of toxicity for patient i at effective dose $\tilde{d}_j$
- **Priors:**
  - β_0, β_1 same as IP-CRM
  - $\sigma \sim \text{half-Cauchy}(1.25)$ → u_i mostly between -5 and 5
- **Likelihood (patient i):**

$$L_i = \int \prod_{j=1}^{k_i} \frac{\exp\left(y_{ij}(\beta_0 + \beta_1 \tilde{d}_j + u_i)\right)}{1 + \exp(\beta_0 + \beta_1 \tilde{d}_j + u_i)} f(u_i) du_i$$

IP-CRM-CO Design

- Account for potential carryover effects
- **Model:**

$$\text{logit}(\pi_{ij}|d_j, T_{ij}) = \beta_0 + \beta_1 d_j + \beta_2 T_{ij}$$

  - T_{ij}: cumulative dose received prior to d_j
  - Dose standardization: $d_j/(2\text{SD})$ → SD = 0.5
- **Priors:**
  - $\beta_0 \sim \text{Cauchy}(-4, 0.5)$ → baseline toxicity ~0.018
  - $\beta_1 \sim \text{Gamma}$ → ensures logit difference < 5
  - $\beta_2 \sim \text{Exponential}(1)$ → weak/moderate carryover effect
- **Likelihood (patient i):**

$$L_i = \prod_{j=1}^{k_i} \frac{\exp\left(y_{ij}(\beta_0 + \beta_1 d_j + \beta_2 T_{ij})\right)}{1 + \exp(\beta_0 + \beta_1 d_j + \beta_2 T_{ij})}$$

IP-CRM-CO-RF Design

- Incorporates both **cumulative dose** T_{ij} and **random patient effects** u_i in the logistic model:

$$\text{logit}(\pi_{ij} \mid d_j, T_{ij}, u_i) = \beta_0 + \beta_1 d_j + \beta_2 T_{ij} + u_i$$

- Random effects: $u_i \sim N(0, \sigma^2)$
- **Parameter priors**:
  - $\beta_0 \sim \text{Cauchy}(-4, 0.5)$
  - $\beta_1 \sim \text{Gamma}(\text{as in IP-CRM-CO})$
  - $\beta_2 \sim \text{Exponential}(1)$
  - $\sigma \sim \text{Half-Cauchy}(1.25)$

IP-CRM-RF

	dose level				
	1	2	3	4	5
			Scenario 1		
π	**0.3**	0.5	0.7	0.8	0.9
$\gamma = 0.2$	**0.766 (7.7)**	0.117 (6.2)	0.001 (1.0)	0.000 (0.0)	0.000 (0.0)
$\gamma = 0.4$	**0.780 (7.8)**	0.069 (6.0)	0.001 (0.8)	0.000 (0.0)	0.000 (0.0)
			Scenario 2		
π	0.05	0.15	**0.3**	0.5	0.8
$\gamma = 0.2$	0.049 (3.7)	0.327 (5.4)	**0.530 (6.6)**	0.093 (3.1)	0.001 (0.6)
$\gamma = 0.4$	0.055 (3.9)	0.366 (5.6)	**0.525 (6.5)**	0.054 (3.0)	0.000 (0.5)
			Scenario 3		
π	0.02	0.05	0.1	**0.3**	0.5
$\gamma = 0.2$	0.005 (3.2)	0.035 (3.6)	0.295 (4.9)	**0.462 (4.7)**	0.204 (3.3)
$\gamma = 0.4$	0.010 (3.3)	0.032 (3.7)	0.300 (5.1)	**0.488 (4.8)**	0.171 (3.2)

IP-CRM-CO

	dose level				
	1	2	3	4	5
			Scenario 1		
π	**0.3**	0.5	0.7	0.8	0.9
$\gamma = 0.2$	**0.353 (5.0)**	0.524 (6.7)	0.026 (3.1)	0.000 (0.2)	0.000 (0.0)
$\gamma = 0.4$	**0.432 (5.3)**	0.449 (6.9)	0.002 (2.6)	0.000 (0.0)	0.000 (0.0)
			Scenario 2		
π	0.05	0.15	**0.3**	0.5	0.8
$\gamma = 0.2$	0.000 (3.1)	0.095 (4.1)	**0.642 (6.9)**	0.254 (4.2)	0.009 (1.2)
$\gamma = 0.4$	0.001 (3.0)	0.111 (4.2)	**0.702 (7.1)**	0.185 (4.1)	0.001 (0.9)
			Scenario 3		
π	0.02	0.05	0.1	**0.3**	0.5
$\gamma = 0.2$	0.000 (3.0)	0.000 (3.1)	0.129 (4.7)	**0.527 (4.7)**	0.345 (4.0)
$\gamma = 0.4$	0.000 (3.0)	0.000 (3.1)	0.150 (4.9)	**0.560 (4.9)**	0.291 (3.9)

IP-CRM-CO-RF

	dose level				
	1	2	3	4	5
			Scenario 1		
π	**0.3**	0.5	0.7	0.8	0.9
$\gamma = 0.2$	**0.492 (5.8)**	0.376 (6.8)	0.006 (2.4)	0.000 (0.0)	0.000 (0.0)
$\gamma = 0.4$	**0.561 (6.2)**	0.310 (6.7)	0.001 (2.0)	0.000 (0.0)	0.000 (0.0)
			Scenario 2		
π	0.05	0.15	**0.3**	0.5	0.8
$\gamma = 0.2$	0.015 (3.2)	0.254 (5.0)	**0.575 (6.9)**	0.146 (3.5)	0.004 (0.7)
$\gamma = 0.4$	0.016 (3.2)	0.279 (5.1)	**0.594 (7.1)**	0.104 (3.3)	0.001 (0.5)
			Scenario 3		
π	0.02	0.05	0.1	**0.3**	0.5
$\gamma = 0.2$	0.007 (3.1)	0.027 (3.4)	0.267 (5.2)	**0.507 (5.0)**	0.189 (3.2)
$\gamma = 0.4$	0.006 (3.1)	0.024 (3.4)	0.265 (5.3)	**0.523 (5.0)**	0.174 (3.2)

Conclusions

- This initiative is motivated by the practical need for trial designs that can reliably determine the MTD with very small sample sizes while improving patients' chances of treatment success.
- Throughout the trial, the starting dose for each incoming cohort is adaptively updated based on accumulated data. Decisions on intra-patient dose escalation are informed by both the patient's current outcome and prior trial data.
- Simulation study shows that the IP-CRM design works reasonably well and is generally robust.

Guo B, Liu S. A Phase I Dose-Finding Design Incorporating Intra-Patient Dose Escalation. Pharm Stat. 2025 Mar-Apr;24(2):e2461. doi: 10.1002/pst.2461. Epub 2024 Dec 25. PMID: 39722206.

Thank You !