Practical considerations for cancer trials of finding the right doses of multiple drugs

EFSPI - Oncology Webinar part 2
Development of Combination Treatments in Oncology

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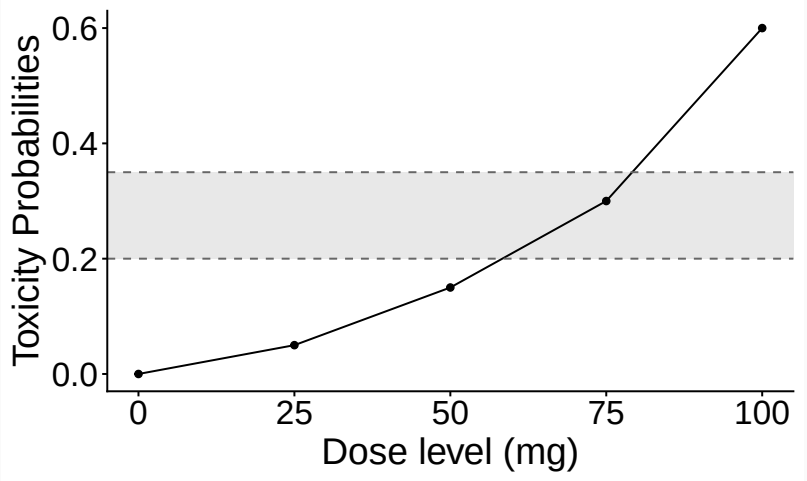
Phase I dose-escalation trials in oncology

- Aim: Inform dose-escalation decisions and find the maximum tolerated dose (MTD).
- Monotonicity assumption: Toxicity stays the same or increases with increasing dose levels.
- Continual Reassessment Method (CRM) (O'Quigley et al., 1990)

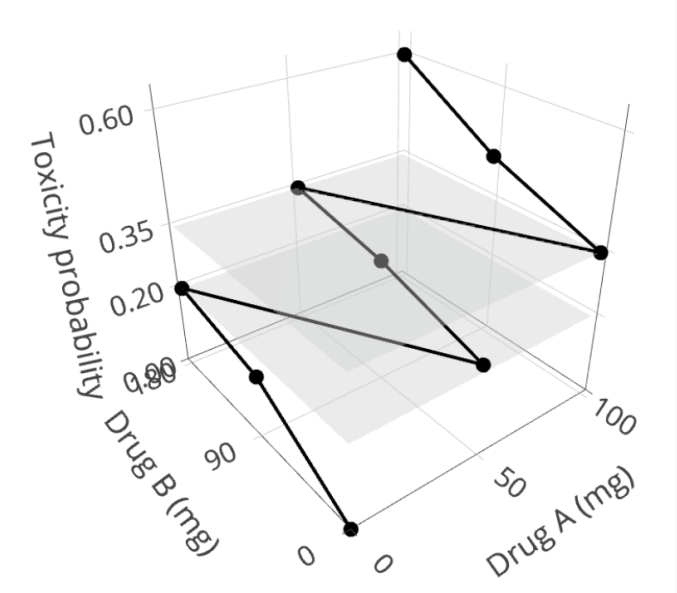


Bayesian Logistic Regression Model (Neuenschwander et al., 2015)

- For doses d
  - Number of DLTs: $r_d \sim \text{Bin}(\pi_d, n_d)$
  - DLT probabilities: $\text{logit}(\pi_d) = \log(\alpha) + \beta \log(d/d^*)$ where d^* is the reference dose.
- Interpretation of α is odds of a DLT probability at d^*
- Prior distribution
  - $(\log(\alpha), \log(\beta)) \sim \mathcal{N}(m, S)$ where $m = (m_1, m_2)$ and S composed of standard deviations s_1, s_2, and correlation ρ

Combination treatments in dose-escalation trials

- Varying only dose level of drug A
  - Drug B has associated DLT probability
  - Potential interaction between drugs
- Varying dose level of both drugs
  - A multiple-dimension optimization problem
  - Potential interaction between drugs
- Varying treatment schedule
  - Not only dose level



Case study 1: a phase I dose-escalation trial (NCT06421935)

- M9466 (a PARP1 inhibitor) and tuvusertib (ATR inhibitor) are both investigational drugs.[1]
- Doses of both drugs and the matching schedule can be varied.[2]

Matching schedule	M9466 dose	Cohorts		
2w/1w	100 mg	A7	A8	A9
1w/1w		B7	B8	B9
2w/1w	70 mg	A4	A5	A6
1w/1w		B4	B5	B6
2w/1w	50 mg	A1 (Start)	A2	A3
1w/1w		B1	B2	B3
Tuvusertib dose		90 mg	130 mg	180 mg

[1] Merck obtained exclusive rights from Jiangsu Hengrui Pharmaceuticals Co., Ltd. to research, develop, manufacture, use and commercialize the PARP1 inhibitor M9466 (also known as HRS-1167) outside China

[2] Currently being evaluated in patients with advanced solid tumours. Yap TA, et al. 2024 Clin Cancer Res 30 (10), 2057-2067. Zimmermann A, et al. AACR 2025 abstract and poster 1171

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Monotonicity assumption for multiple schedules/drugs

- For given dose, more intense schedule $\Rightarrow$ higher (or equal) toxicity.
- How to order the toxicity of different schedules (different drugs)?
    - More intense schedule vs higher dose level?
- Partial-ordered Continual Reassessment Method (PO-CRM) (Mozgunov et al., 2022)

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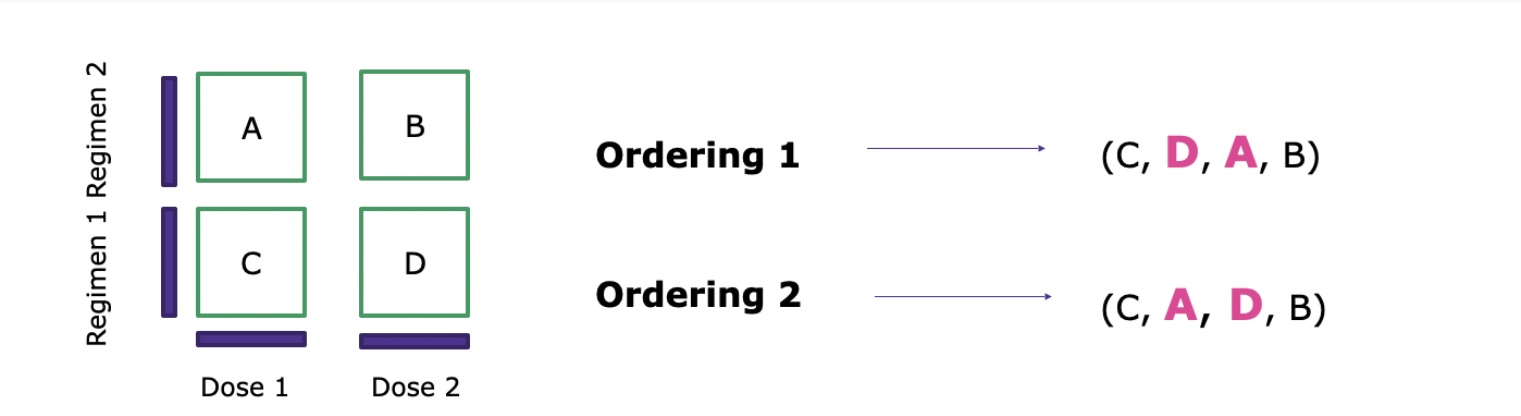

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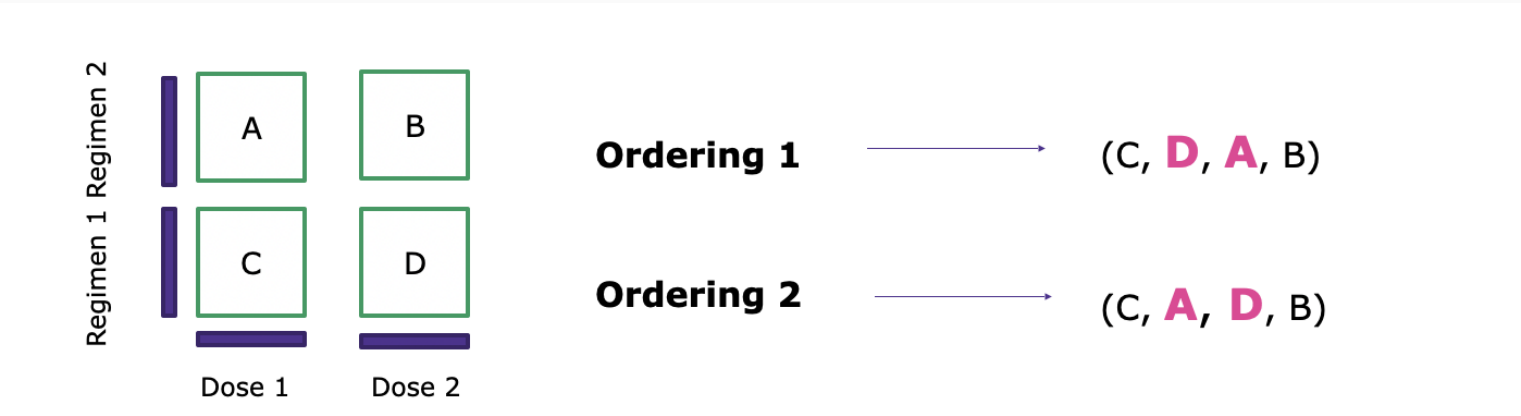


- Partial-ordered Continual Reassessment Method (PO-CRM) (Mozgunov et al., 2022)

PO-CRM implementation

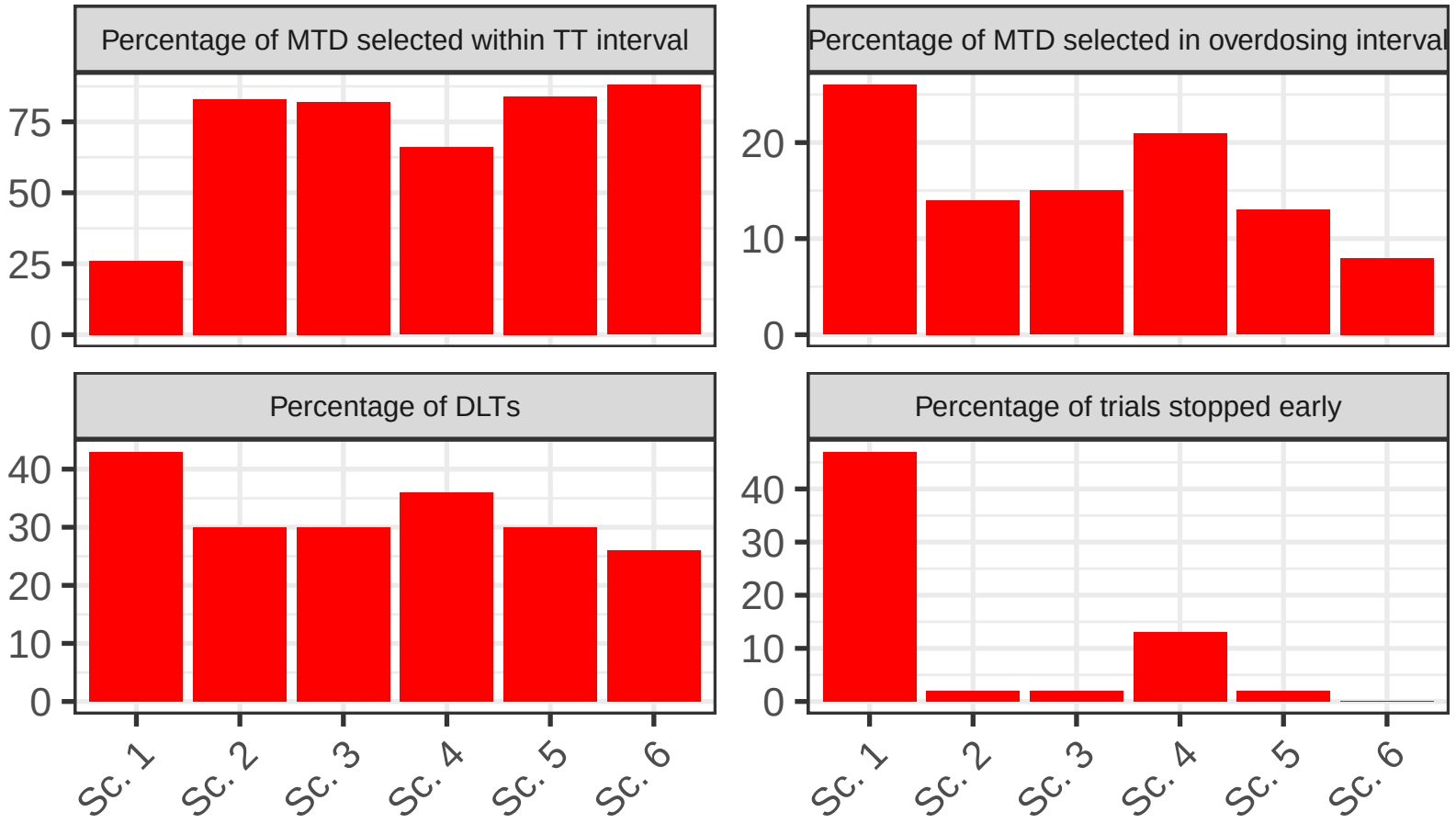
- Starting dose–schedule combination.
- Observe dose-limiting toxicities (DLTs)
- Fit the PO-CRM model under each of the selected toxicity orderings.
- Compute posterior probabilities for each ordering.
- Make inferences about the combination–toxicity relationship using model-averaged estimates (Kovačević et al., 2025).

Simulations: Toxicity scenarios

		Scenario 1			Scenario 2			Scenario 3		
		90	130	180	90	130	180	90	130	180
2w/1w	100 mg	0.60	0.70	0.80	0.45	0.60	0.70	0.50	0.60	0.70
1w/1w		0.50	0.60	0.70	**0.30**	0.50	0.60	0.45	0.50	0.60
2w/1w	70 mg	0.50	0.60	0.70	**0.30**	0.50	0.60	**0.30**	0.50	0.60
1w/1w		0.45	0.50	0.60	**0.20**	0.45	0.50	**0.20**	0.45	0.50
2w/1w	50 mg	0.45	0.50	0.60	**0.20**	**0.30**	0.50	**0.20**	**0.30**	0.45
1w/1w		**0.30**	0.45	0.50	0.10	**0.20**	0.45	0.10	**0.20**	**0.30**

		Scenario 4			Scenario 5			Scenario 6		
		90	130	180	90	130	180	90	130	180
2w/1w	100 mg	0.50	0.70	0.80	0.50	0.60	0.70	**0.30**	0.50	0.60
1w/1w		0.45	0.60	0.70	0.45	0.50	0.60	**0.20**	0.45	0.50
2w/1w	70 mg	0.45	0.60	0.70	**0.30**	0.45	0.60	**0.20**	**0.30**	0.45
1w/1w		**0.30**	0.50	0.60	**0.20**	**0.30**	0.50	0.10	**0.20**	**0.30**
2w/1w	50 mg	**0.30**	0.50	0.60	**0.20**	**0.30**	0.50	0.10	**0.20**	**0.30**
1w/1w		**0.20**	0.45	0.50	0.10	**0.20**	0.45	0.00	0.10	**0.20**

Simulations: Results of different metrics



Case study 2: a phase I dose-escalation trial (NCT06509906)

- FOLFIRI (folinic acid + fluorouracil + irinotecan) is standard of care for first- and second-line metastatic CRC.

	M9466 dose		
M9466 duration	**50 mg**	**70 mg**	**100 mg**
Dose-finding cohorts (FOLFIRI)			
D1→9 (9 days)	A7	A8	A9
D1→7 (7 days)	A4	A5	A6
D1→5 (5 days)	A1 (Start)	A2	A3
Run-in cohort (Irinotecan)			
D1→5 (5 days)	A0		

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Run-in cohort (Irinotecan)			
D1→5 (5 days)	A0		

A modified dual-agent BLRM (Neuenschwander et al., 2015)

- M9466 component (dose and duration is varied)

$$\text{logit}(\pi_A(d, \text{dur})) = \log(\alpha) + \beta \log\left(\frac{d}{d^*}\right) + \gamma \log\left(\frac{\text{dur}}{\text{dur}^*}\right)$$

- FOLFIRI component

  π_B: DLT probabilities are available from historical data

- Joint model without interaction:

$$\pi^0_{A,B} = \pi_A + \pi_B - \pi_A \pi_B$$

- Final model: Joint model with positive interaction

$$\text{odds}(\pi_{A,B}) = \text{odds}(\pi^0_{A,B}) \exp(\eta)$$

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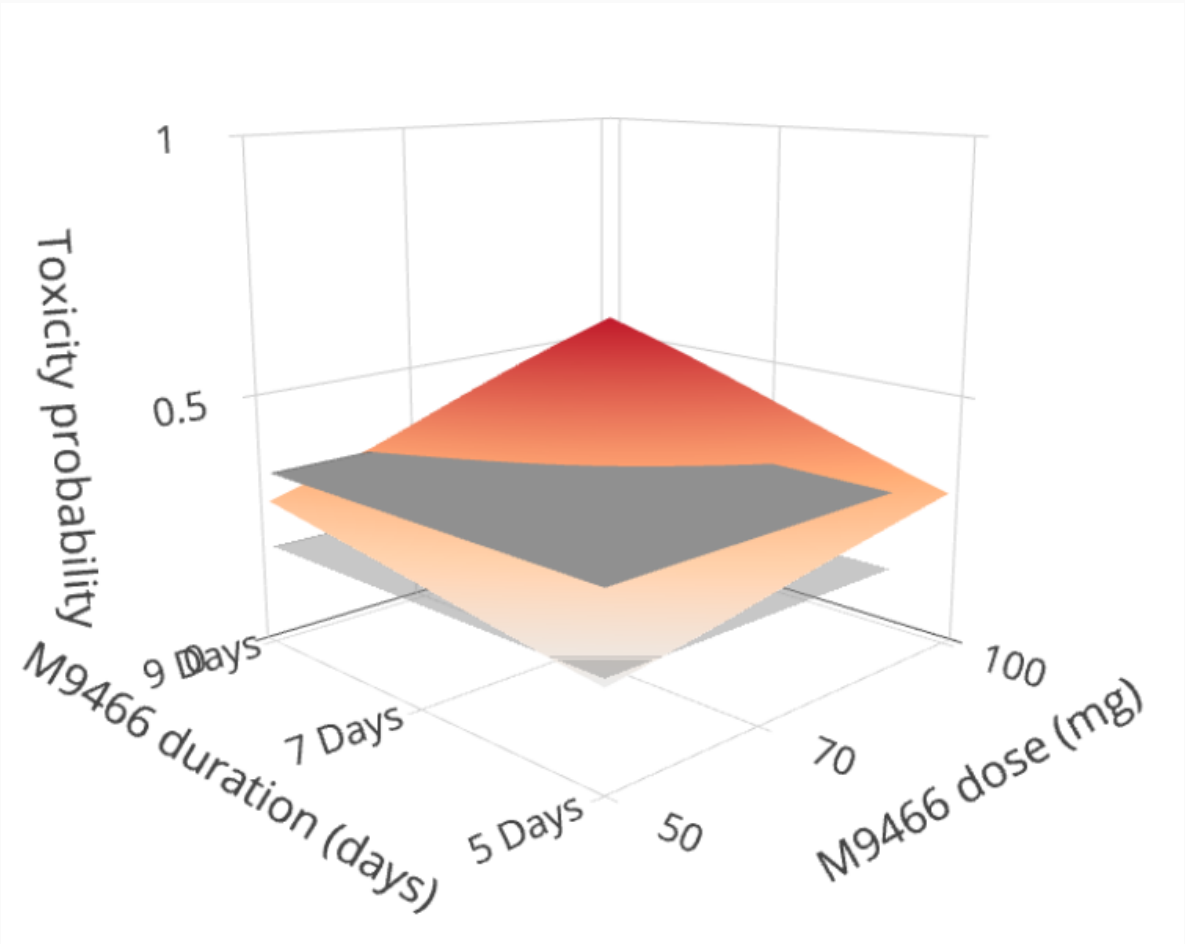
Illustrative dataset for case study 2

	M9466 dose		
M9466 duration	**50 mg**	**70 mg**	**100**
Dose-finding cohorts (FOLFIRI)			
D1→9 (9 days)			
D1→7 (7 days)	1 DLT / 5 pts		
D1→5 (5 days)	0 DLT / 4 pts		

Median DLT probabilities in a 3-D plot

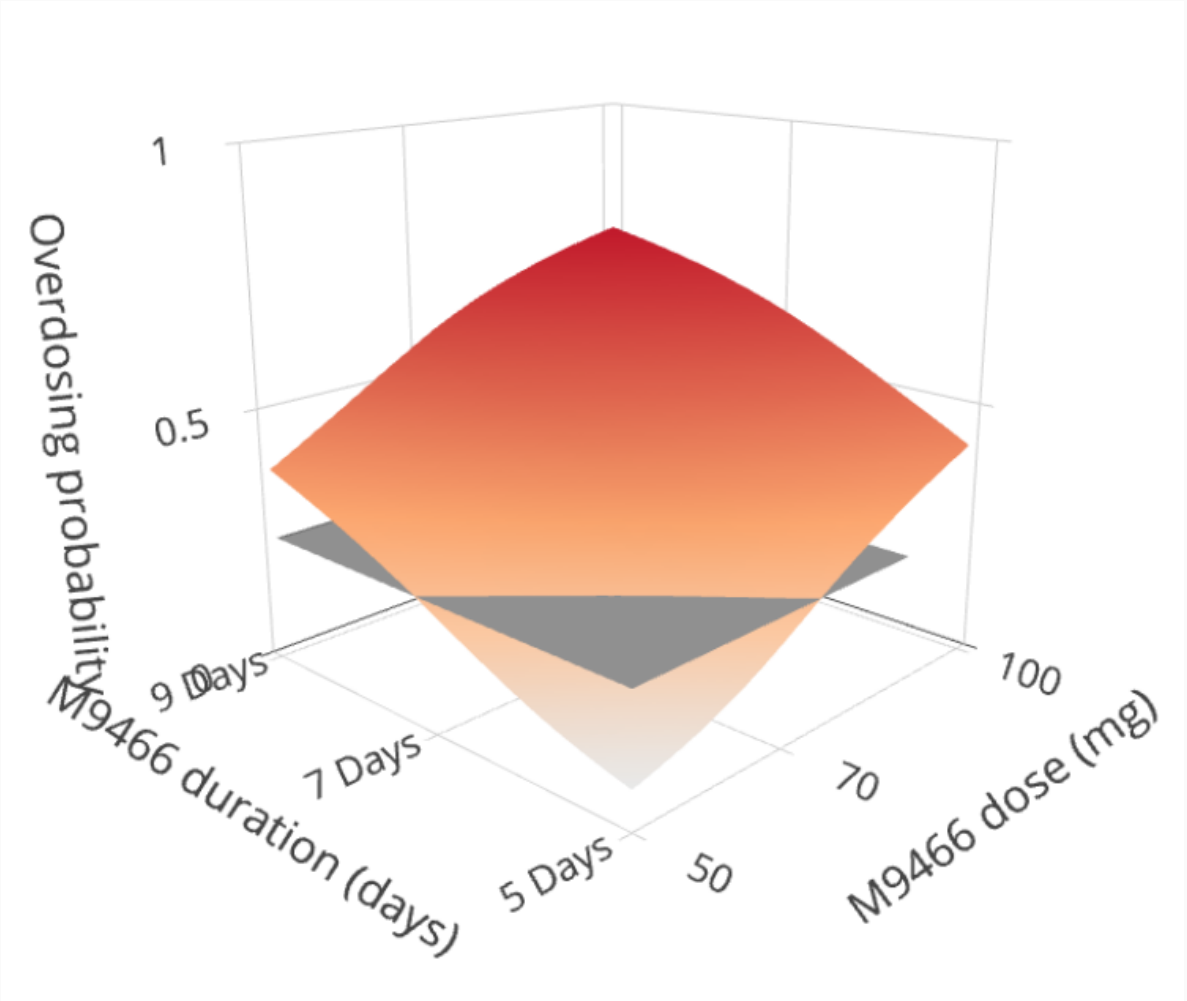
Targeted toxicity region



Starting combination

Overdose probabilities in a 3-D plot

Threshold for overdosing prob. - - - - - - - ›



Notes from regulatory guidances

- The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) published a guidance document on phase I clinical trials in oncology.[3]
  "... consider relevant scenarios based on the order of the combinations and explain the impact on operating characteristics based on simulations."

- The FDA published a draft guidance on the use of Bayesian methodology; "Dose-finding trials in oncology" are included as a situation where Bayesian methods have been used.[4]

[3] *Statistical Considerations When Planning Phase I Clinical Trials in Oncology – From the Safety Perspective*, December 2024. PMDA. `https://www.pmda.go.jp/files/000272426.pdf`

[4] *Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products: Draft Guidance for Industry*, January 2026. FDA. `https://www.fda.gov/media/190505/download`

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[4] *Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products: Draft Guidance for Industry*, January 2026. FDA. `https://www.fda.gov/media/190505/download`

Conclusions and discussion

- Extensions of CRM models (PO-CRM, dual-agent BLRM) provide flexible tools for combination dose-escalation trials.
- Early and constant collaboration with the clinical team is critical:
  - plausible set of toxicity orderings,
  - specifying interpretable priors.
- Design evaluation and implementation can be done using Bayesian MCMC software (e.g., `Stan`, `JAGS`) and simulation studies.

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  MRC Biostatistics Unit, Cambridge, UK
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References

Kovačević, L., Chen, W., Barnett, H., Jaki, T., & Mozgunov, P. (2025). Bayesian model averaging for partial ordering continual reassessment methods. *Biostatistics*. https://doi.org/10.1093/biostatistics/kxaf035.

Mozgunov, P., Jaki, T., Gounaris, I., Goddemeier, T., Victor, A., & Grinberg, M. (2022). Practical implementation of the partial ordering continual reassessment method in a phase i combination-schedule dose-finding trial. *Statistics in Medicine*. https://doi.org/10.1002/sim.9594.

Neuenschwander, B., Matano, A., Tang, Z., Roychoudhury, S., Wandel, S., & Bailey, S. (2015). A Bayesian industry approach to phase I combination trials in oncology. In *Statistical methods in drug combination studies*. Chapman and Hall/CRC. https://doi.org/10.1201/b17965.

O'Quigley, J., Pepe, M., & Fisher, L. (1990). Continual reassessment method: A practical design for phase 1 clinical trials in cancer. *Biometrics*. https://doi.org/10.2307/2531628.

Thanks!

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