Determination of the recommended phase 2 dose: choice of design in an oncology trial

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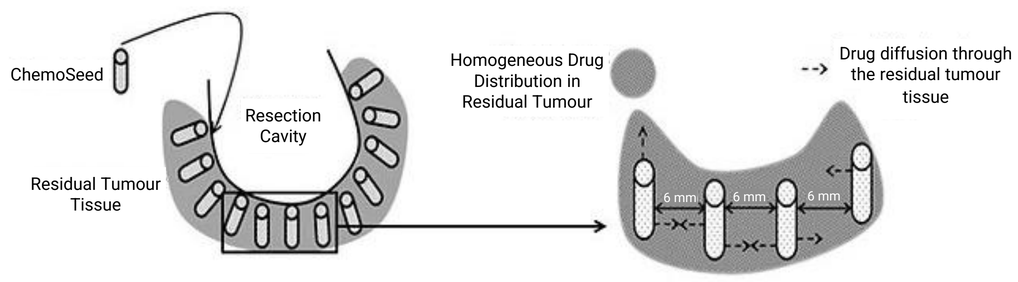
Background

Glioblastoma: fast-growing brain tumour, poor long-term prognosis. Treatment options: surgery to remove the tumour, radiation and chemotherapy.
Unique challenges:

- Infiltrative & highly invasive tumour → complete surgical resection is not possible,
- Blood-brain barrier → chemoresistance increased & higher doses of systemic therapies required → higher toxicity.

ChemoSeed®: drug delivery system that releases chemotherapy directly into cancer tissues, allowing to reduce the systemic dose while still achieving higher local drug concentration levels.



A phase 2 trial is planned to assess safety and efficacy of irinotecan ChemoSeed® in patients with surgically resectable glioblastoma. The first part of the trial will select the dose.

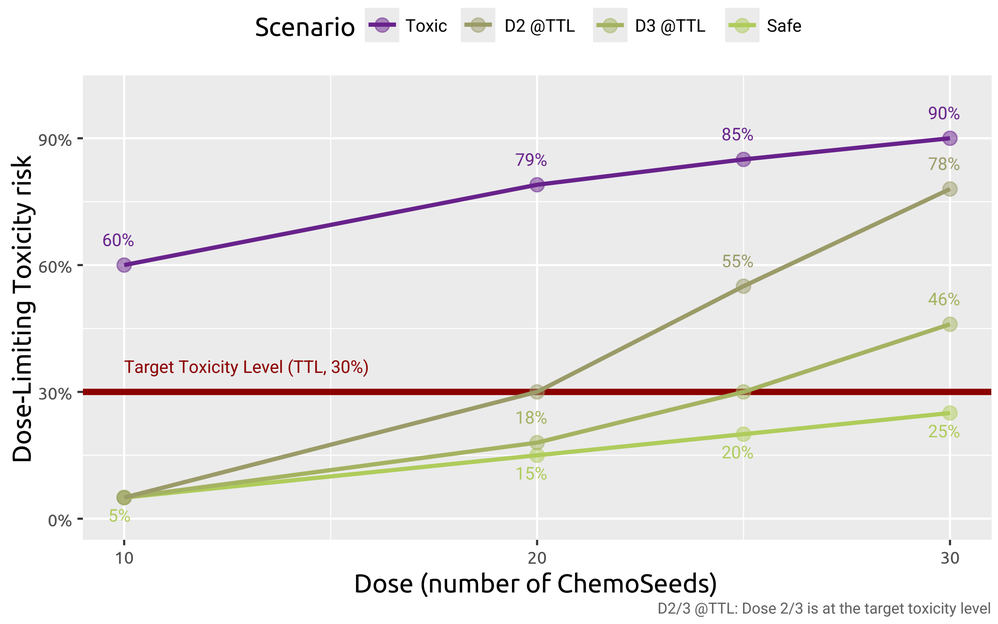
Conclusions from comparisons of statistical performance of dose escalation designs [1] depend on assumptions made on dose-toxicity. Decisions depend on setting and context. We report on the design choice for dose selection.

Methods

Trial setting

Toxicity & efficacy assumed to increase with dose → the recommended part 2 dose (RP2D) is the highest dose with a risk of dose-limiting toxicity (DLT) events below a 30% target toxicity level (TTL).
We consider 4 dose levels and about 12 patients (rare cancer).
Tolerance is expected to be high based on preliminary data [2].
→ base-case scenario: RP2D is the highest dose level. The design should allow for a quick escalation but control the risk of exposing patients to toxic doses.

Dose-toxicity scenarios to assess candidate designs



D2/3 @TTL: Dose 2/3 is at the target toxicity level

Candidate designs

◆ 3+3 design, algorithm-based, for benchmarking.
■ CRM design (continual reassessment method), model-based.
● BOIN design (Bayesian optimal interval), model-assisted.

All 3 designs start at the lower dose. To ensure fair comparisons, the same 5 000 virtual patient sets are used to assess the designs under each scenario.
Each patient is simulated with a latent DLT susceptibility (generated from a uniform distribution in the [0,1] range). If the patient's susceptibility is below the DLT risk for a given dose & scenario, they present the event. The performance of the 3+3 design presented is from the simulations, although it can be derived analytically [3].

Packages "dfcrm" and "BOIN" from R were used for the simulations.

Design performance outcomes

Design performance is illustrated based on number of patients required to reach the higher dose if no DLT occurs or if only the 1st patient presents a DLT, number of patients required to stop the trial for toxicity if all patients present DLTs, average sample size, probability to identify the correct RP2D and expected number of patients with DLTs observed in the trial.

Parametrization of the assessed designs

◆ 3+3: cohorts of 3 patients are assigned to each dose. Escalation occurs if no patient presents DLTs. If 1 patient presents a DLT, the next 3 remain on the same dose. If ≥ 2 present a DLT, the dose is terminated and the RP2D is set at the lower dose level, if it exists. Dose de-escalation is not allowed.
■ CRM: A one-stage Bayesian CRM was used, with a one-parameter logistic model at the dose level for the dose-toxicity curve. Model estimation occurs at each patient, the next receives the dose estimated as most likely to be the RP2D. Plugin estimates were used to derive the estimates. No dose skipping was allowed for dose escalation. The trial is stopped at 12 patients or with > 90% posterior probability that the DLT risk at the lowest dose exceeds the TTL. The priors for the model were derived as per [4], with calibration on 2 000 simulations in 4 dose-toxicity scenarios, assessing 24 candidate priors. Prior DLT probabilities are about 4.6%, 30.0%, 63.4% and 80.8% respectively. The prior standard deviation for the slope is set at about 0.63.
● BOIN: derives escalation and de-escalation decisions by comparing the current proportion of DLT at the considered dose to prespecified boundaries (about 23.6% and 35.9% respectively). Current and higher doses are eliminated from the trial if there is > 95% chance that the DLT risk is above the TTL and ≥ 3 patients have been treated. Otherwise, the trial stops at 12 patients. The RP2D is derived using isotonic regression, pooling information across all doses.

Results

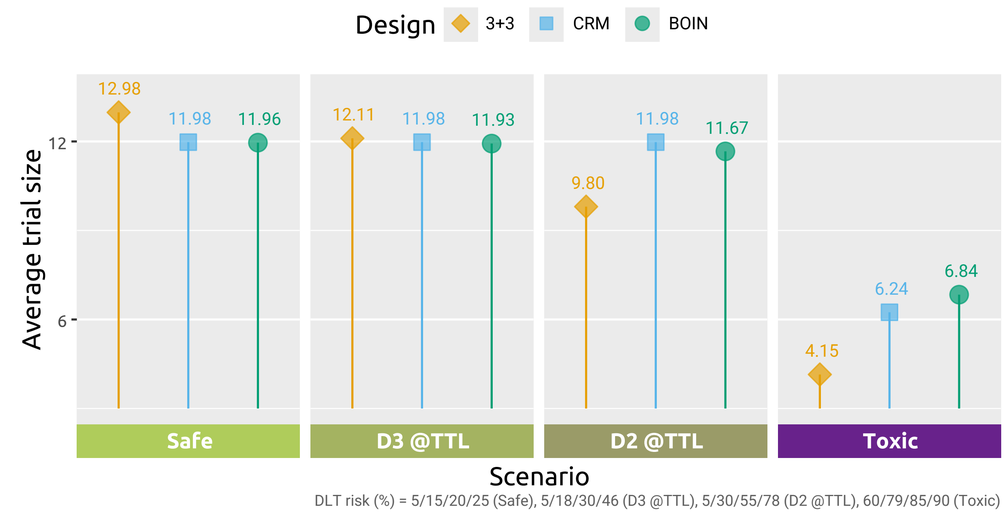
Dose allocation pathways

Numbers of required patients under 3 specific scenarios:

	3+3	CRM	BOIN
First patient to reach higher dose:			
▹ No DLTs	10	6	4
▹ Only 1st patient has a DLT	13	40*	8
Trial size when stopping for toxicity:			
▹ All patients have DLTs	3	2	3

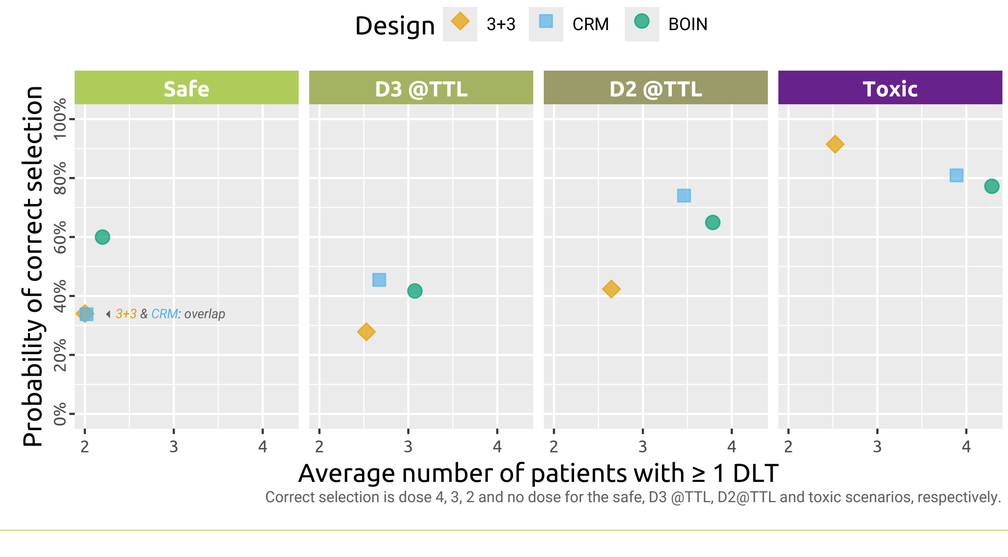
** In practice, the trial stops at 12 patients and selects the 2nd lowest dose as the RP2D*

Expected sample size according to design & scenario



DLT risk (%) = 5/15/20/25 (Safe), 5/18/30/46 (D3 @TTL), 5/30/55/78 (D2 @TTL), 60/79/85/90 (Toxic)

Probability of correct selection and average DLTs according to design & scenario



Correct selection is dose 4, 3, 2 and no dose for the safe, D3 @TTL, D2@TTL and toxic scenarios, respectively.

Discussion

The CRM design was sensitive to early DLT occurrence, as reported elsewhere [5]. Changes in priors explored resulted in poorer safety performance.

The BOIN design resulted in faster escalation and good performance in a safe setting, with, however, reduced performance in higher toxicity scenarios. This design was selected for this trial, based on expected performance in the base case safe scenario, ease of calibration and trial conduct (no need for continual reassessment), and expected regulatory acceptance (FDA's fit-for-purpose designation [6]).

References

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