

Evaluating phase I studies in small populations when incorporating pharmacokinetic information

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Context

Phase I dose-finding studies in oncology aim at determining the maximum tolerated dose (MTD) while limiting the number of patients exposed to high toxicity. In small populations, combining dose-finding and PK analysis to allow a better estimation of the dose-response curve should be considered. In this work we propose, study and compare methods involving PK measures in the dose allocation process during a phase I clinical trial, in order to understand if there is a benefit and, if so, when this might be beneficial. We have assumed toxicity to be related to PK measure of exposure.

Dose-finding Methods

In Bayesian methods, probability of toxicity $p_T(d)$ at dose d , $d \in \{d_1, \dots, d_K\}$, is estimated after each cohort and the dose assigned to the next cohort is computed using posterior distributions. We model this probability also as a function of exposure z . In the following, we use $z = \log(AUC)$. z is used in the dose-finding designs in different ways, that is as covariate [1] or dependent variable [2] or both ways [3].

Methods and dose allocation rules

CRM $P_T(d_k, \beta) = \frac{1}{1 + e^{-(\alpha + \beta \log d_k)}}$ $\logit(P_T(d_k, \beta)) = \alpha + \beta \log d_k$ Priors: $\beta \sim N(\mu_\beta, \sigma_\beta^2)$ $\alpha \sim N(\mu_\alpha, \sigma_\alpha^2)$ Dose allocation rule: $d_{i+1} = \arg \min_k P_T(d_k, \hat{\beta}) - \theta $	PKCOV $\logit[P_T(d_k, \Delta z d_k, \beta)] = -\beta_0 + \beta_1 \log d_k + \beta_2 \Delta z d_k$ Priors: $\beta_0 \sim U(\beta_0, \mu_{\beta_0})$ $\beta_1 \sim U(\beta_1, \mu_{\beta_1})$ $\beta_2 \sim U(\beta_2, \mu_{\beta_2})$ Dose allocation rule: $d_{i+1} = \arg \min_k P_T(d_k, \hat{\beta}) - \theta $
PKLIM $z_i \beta_i \sim N(\beta_i \log d_i, \sigma^2)$ Priors: $\beta \sigma \sim N(\mu_\beta, \sigma_\beta^2)$ $\sigma \sim \text{Beta}(\alpha, \beta)$ Dose allocation rule: $d_{i+1} = \arg \min_k P(z_{i+1} > L \hat{\beta}) - \theta $ L = fixed threshold parameter	PKLOG $\logit(P_T(z, \beta)) = -\beta_3 + \beta_4 z$ Priors: $\beta_3 \sim U(\beta_3, \mu_{\beta_3})$ $\beta_4 \sim U(\beta_4, \mu_{\beta_4})$ Dose allocation rule: $d_{i+1} = \arg \min_k P(z_{i+1} = z \hat{\beta}) - \theta $ $= \int \frac{1}{1 + \exp(\hat{\beta}_3 - \hat{\beta}_4 z)} g(z) dz$
PKTOX 1) PKLIM $z_i \beta_i \sim N(\beta_i \log d_i, \sigma^2)$ 2) $P_T(z, \beta) = \Phi(-\beta_3 + \beta_4 z)$ Priors: $\beta_3 \sim U(\beta_3, \mu_{\beta_3})$ $\beta_4 \sim U(\beta_4, \mu_{\beta_4})$ Dose allocation rule: $d_{i+1} = \arg \min_k P(z_{i+1} = z d_k) - \theta $ $= \int P_T(z, \hat{\beta}) g(z) dz$	DTOX $CDF \ N(0, 1)$ $P_T(d_k, \beta) = \Phi(-\beta_3 + \beta_4 \log d_k)$ Priors: $\beta_3 \sim U(\beta_3, \mu_{\beta_3})$ $\beta_4 \sim U(\beta_4, \mu_{\beta_4})$ Dose allocation rule: $d_{i+1} = \arg \min_k P_T(d_k, \hat{\beta}) - \theta $
PKPOP PKLOG with Dose allocation rule: $d_{i+1} = \arg \min_k P_T(d_k, \hat{\beta}_k) - \theta $ mean value predicted	PKCRM CRM + PKLIM Dose allocation rule: $d_{i+1} = \min(d_{CRM}, d_{PKLIM})$

Trials Settings

We simulated 1000 clinical trials for each of the 7 scenarios. 30 patients per trial, 6 dose levels and cohort of 1 were set for simulations. A no skipping rule was added in each method and all methods were run after the first toxicity or, at least, at the end of the trial. We used the package rjags in R to implement the dose-finding methods and estimates of the AUC were obtained by individual non-linear regression with the nls function in R. 10 sampling time points were used, 6 around the peak and 4 in the tail, in order to have a quite precise estimation.

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Example

We implemented and evaluated the performance of these methods using a simulation study. We chose a real clinical trial describing a PK/PD model for toxicity and efficacy of the TGF- β inhibitor LY2157299 in patients with glioma [4]. In the present work, we considered only the toxicity model, and we simplified the model as in [5], who used a similar setting to investigate adaptive sampling designs. We also introduced patient variability in the PK-toxicity relationship

by defining toxicity for the i th patient if $\alpha_i AUC_i \geq \tau_T L^{-1} h$, where α_i was assumed to come from a lognormal distribution with zero mean and standard deviation ω_α and τ_T is a given threshold. k_a was assumed to be fixed and equals to 2 h^{-1} , while $CL_{pop} = 10 \text{ L/h}$ and $V_{pop} = 100 \text{ L}$ with IIV of 70% or 30% (lognormal distribution), depending on the scenario. The probability of toxicity, p_T , is then given by

$$p_T(d) = \Phi \left(\frac{\log(d) - \log(\tau_T) - \log(CL_{pop})}{\sqrt{\omega_{CL}^2 + \omega_\alpha^2}} \right)$$

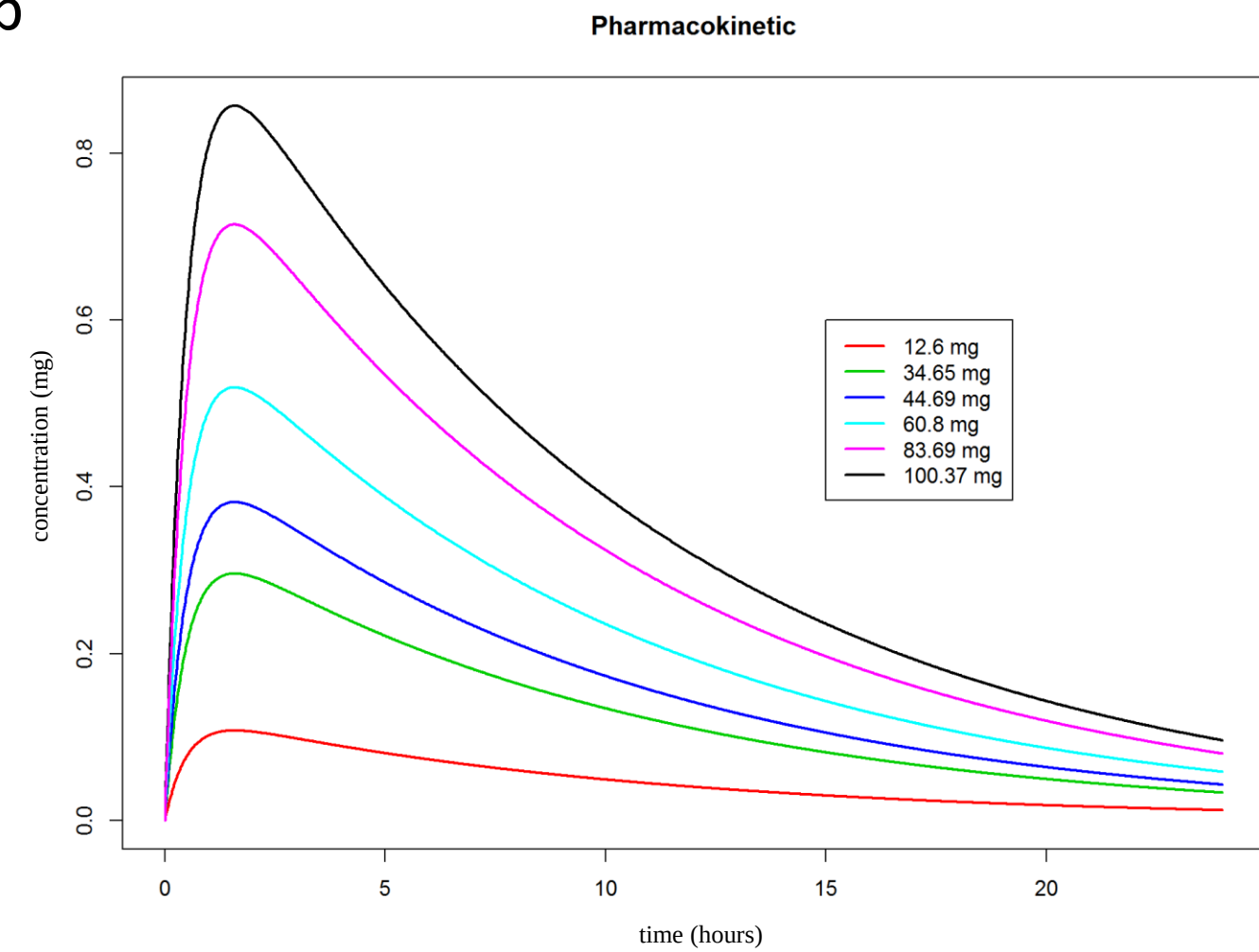


Figure 1. Plot of the concentration versus time for the six dose levels with population parameters.

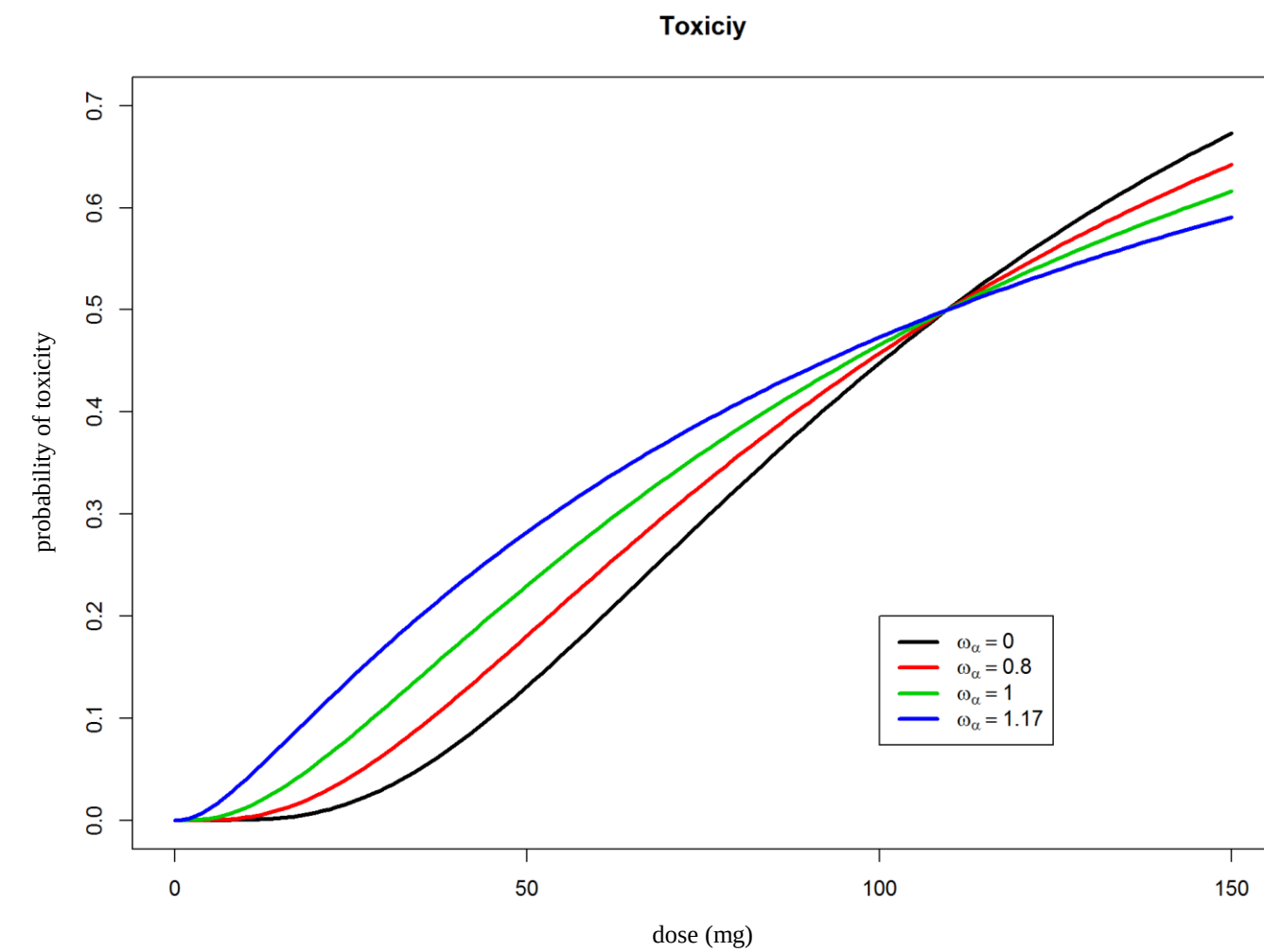
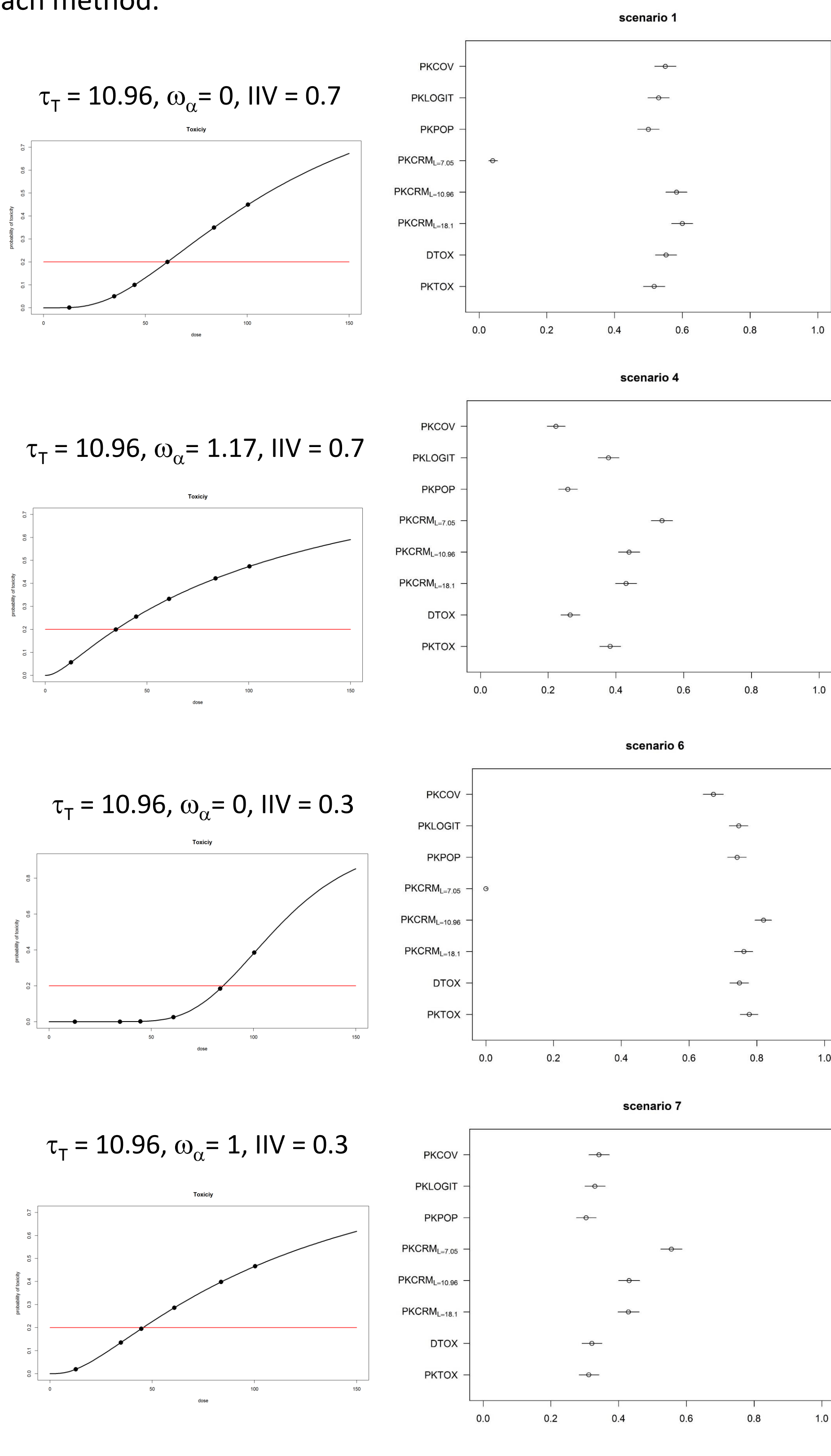


Figure 2. Probability of toxicity versus dose for several values of ω_α .

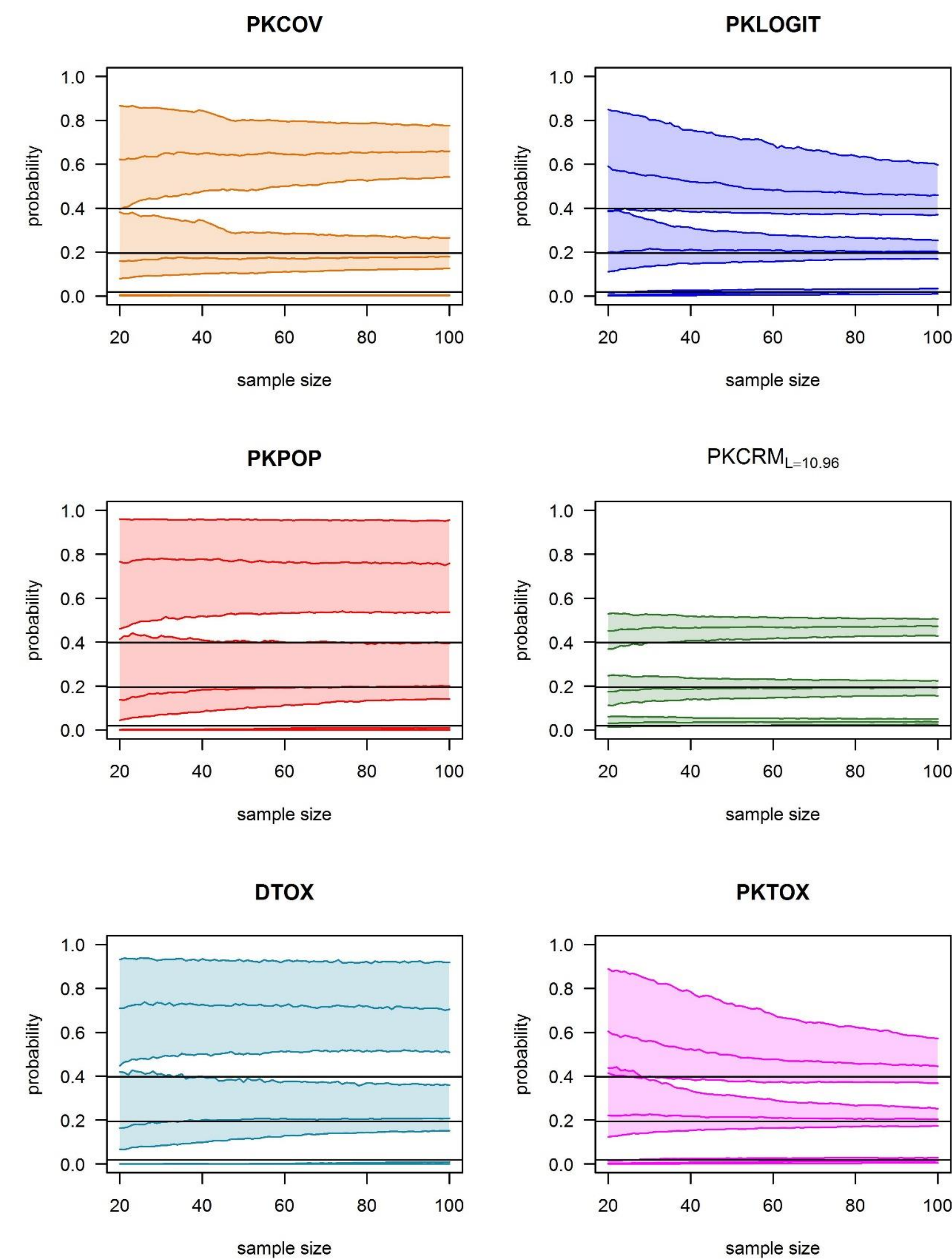
Results

Here we summarise the results on MTD selection. The plot on the left represents the specific scenario dose-toxicity relationship, while on the right we plotted the estimated percentage of choosing the true MTD with Clopper-Pearson 95% credible intervals after 1000 simulations for each method.



Similar results were achieved in scenario 2, 3 and 5. Scenario 2 and 3 share the same setting of scenario 1 with τ_T increased in order to move the MTD to dose level 5 and 6, respectively. Instead, scenario 5 was derived from scenario 4 by decreasing ω_α . DTOX, PKPOP and PKCOV tend to have the same performance. The same for PKLOGIT and PKTOX. PKCRM family has the best results when L is higher than τ_T .

We have also investigated the ability of each method to estimate the dose-toxicity relationship by considering the estimate of the probability of toxicity for each tested dose. This was evaluated for sample sizes increasing from 20 to 100 in order to evaluate the convergence of each method. The following Figure shows the results on scenario 7. Each quadrant shows three estimated probabilities (from below the p_T of dose level 1, dose level 3 and dose level 5 respectively) using a method. Median, first and third quartile over 1000 simulations of the corresponding estimated probabilities are plotted. The black horizontal lines represent the true probability used in the simulation. We plotted only one member of PKCRM family since they have similar results.



The same behaviour was also observed for all other scenarios. PKTOX and PKLOGIT are able to give good estimates in each scenario, while other methods tend to estimate correctly the probabilities of toxicity only for the MTD and adjacent doses. The PKCRM family is able to estimate all the probabilities of toxicity when the skeleton is identical to the true probability of toxicity.

Discussion

- Adding PK measurements as a covariate only does not improve the efficiency of dose-finding trials in terms correct percentage of dose selection.
- PKCRM with a proper L can achieve very good percentage of MTD selection. With high L , it behaves as CRM alone.
- Incorporating PK measures in a double regression, such as in PKLOGIT and PKTOX, allows a better estimation of the dose-toxicity curve while maintaining the performance of MTD selection compared to dose-finding designs that do not incorporate PK information.
- PKLOGIT and PKTOX are exposure target methods more than dose target methods and this suggests that they could be useful also for a personalised medicine approach.
- The dose-exposure-toxicity methods require additional PK information, but the models involved are simpler than in full-model based approaches and can easily be implemented in practice.
- There is a trade-off between immediate gain, which is the determination of the MTD for the next study, and long-term goals, that is, accruing information about the entire dose-toxicity relationship.