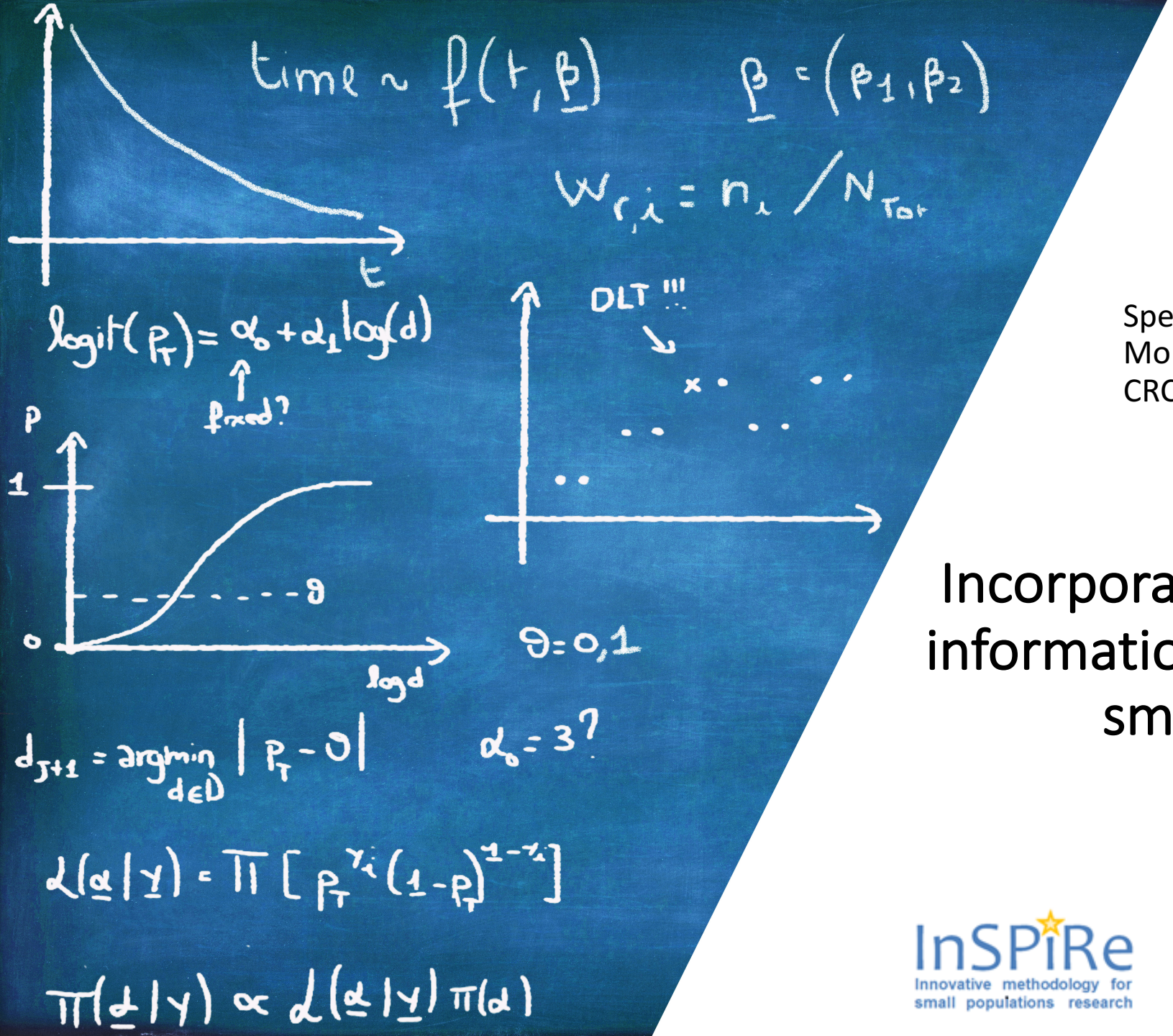


30/03/2017
London UK

Speaker:
Moreno Ursino, PhD
CRC, INSERM UMR 1138

Incorporating pharmacokinetic information in phase I studies in small populations

InSPiRe
Innovative methodology for small populations research

CRC
CENTRE DE RECHERCHE
DES CORDELIERS

Inserm
Institut national
de la santé et de la recherche médicale

Clinical context

First in human trials:

- phase I dose-finding clinical trials

Objective:

- estimation of the Maximum Tolerated Dose (MTD)

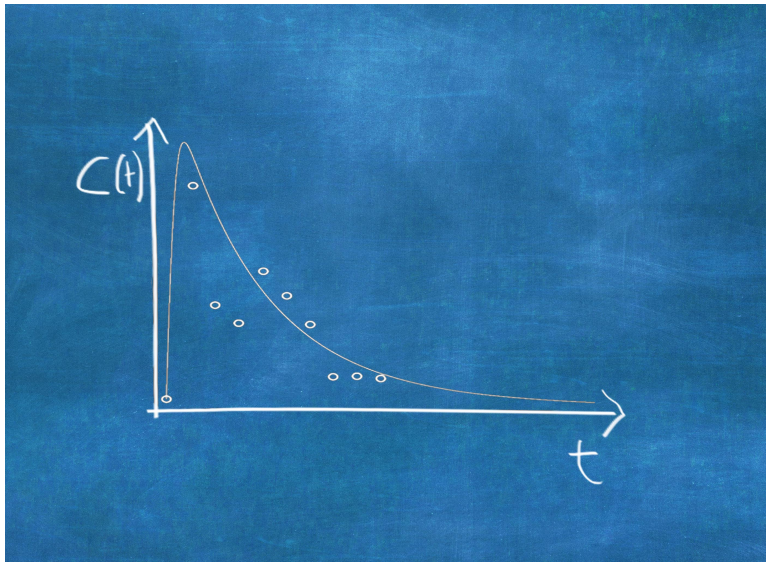
Context:

- discrete and fixed dose levels
- binary criteria
- very small sample size
- toxicity target (θ)
- adaptive design

Motivation

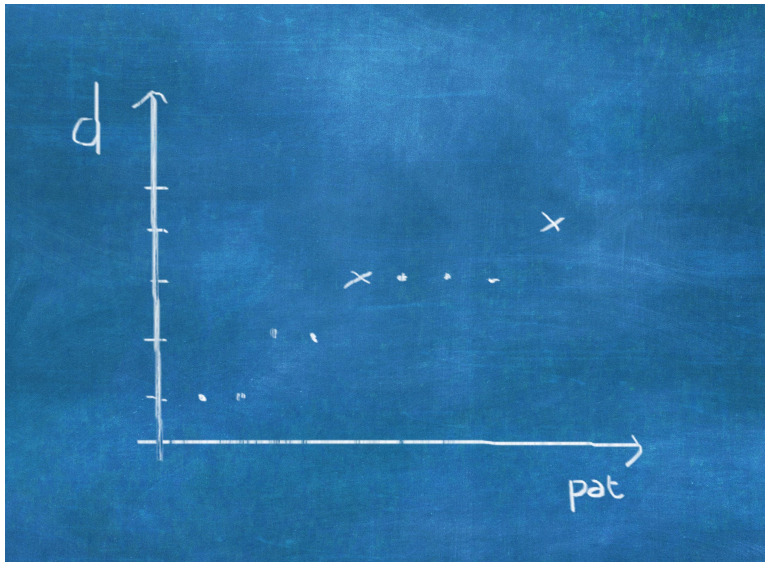
In phase I studies, even if dose-finding and PK/PD analysis are carried out in the same trial, they are often conducted and reported independently in different sections in publications reporting trial results.

PK



*

Dose-finding



In cases such as rare diseases and paediatrics, the available population size will limit the number of possible clinical trials that can be conducted.

Combining dose-finding and PK analyses to allow better estimation of the dose-toxicity curve should then be considered.

* Comets, E. and Zohar, S. (2009) A survey of the way pharmacokinetics are reported in published phase I clinical trials, with an emphasis on oncology. Clinical Pharmacokinetics, 48 (6), 387–395

Incorporating PK in dose-finding (1)

Concentration
(AUC, C_{max})

Dose

Toxicity

Incorporating PK in dose-finding (1)

Concentration
(AUC, C_{max})

Dose → Toxicity

p_T: probability of toxicity versus dose

CRM

$$p_T(d_k, \beta) = \tilde{d}_k^{\gamma}$$

$$\gamma = \exp(\beta)$$

$\{\tilde{d}_k\}$ = skeleton

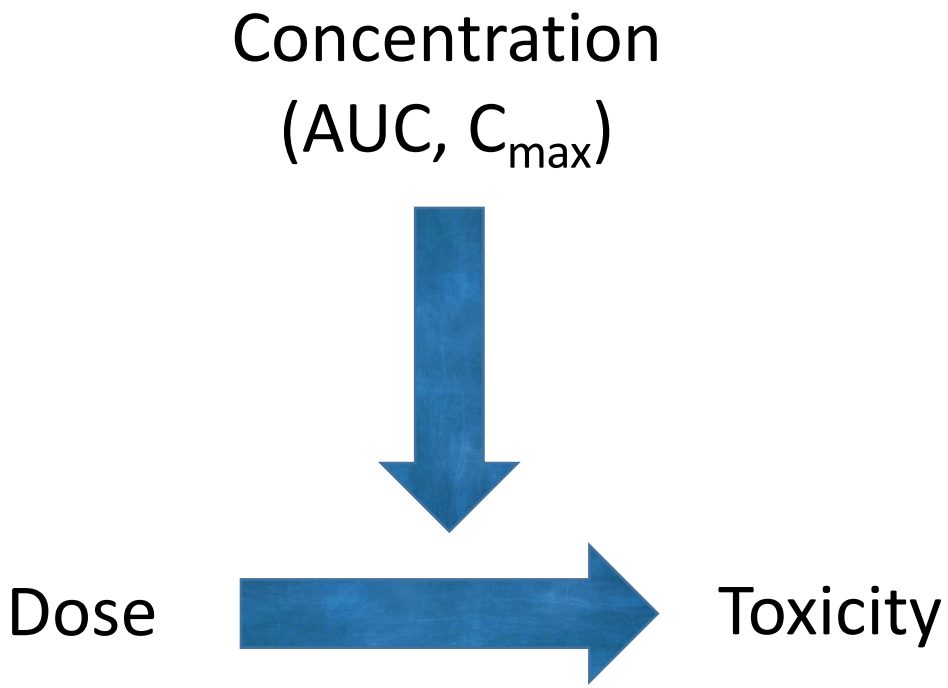
$$\beta \sim \mathcal{N}(0, 1.34)$$

Dose allocation rule:

$$d_{i+1} = \underset{d_k}{\operatorname{argmin}} \left| p_T(d_k, \hat{\beta}) - \theta \right|$$

J. O'Quigley, M. Pepe, and L. Fisher. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. Biometrics, 46 (1), 33–48, 1990.

Incorporating PK in dose-finding (1)



p_T: probability of toxicity versus dose and AUC

Δz: difference between log(AUC) of patient and log(AUC of population)

PKCOV

$$\text{logit}[p_T(d_k, \Delta z_{d_k}, \beta)] = \beta_0 + \beta_1 \log d_k + \beta_2 \Delta z_{d_k}$$

Priors: $\beta_1 \sim U(l_1, u_1)$

$\beta_2 \sim U(l_2, u_2)$

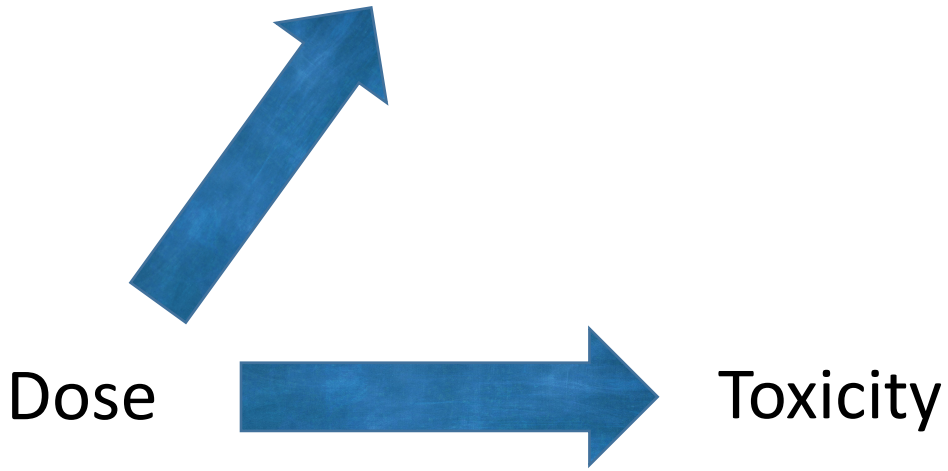
β_0 fixed

Dose allocation rule:

$$d_{i+1} = \underset{d_k}{\text{argmin}} \left| p_T(d_k, 0, \hat{\beta}) - \theta \right|$$

S. Piantadosi and G. Liu. Improved designs for dose escalation studies using pharmacokinetic measurements. Statistics in Medicine, 15(15): 1605 - 1618, 1996.

Incorporating PK in dose-finding (2)



z: log(AUC)

PKLIM

$$z_i \mid \underline{\beta}, \upsilon \sim \mathcal{N}(\beta_0 + \beta_1 \log d, \upsilon^2)$$

Priors: $\underline{\beta} \mid \upsilon \sim \mathcal{N}(m, \upsilon^2 \underline{\underline{G}})$

$\upsilon \sim \text{Beta}(a, b)$

Dose allocation rule:

$$d_{i+1} = \underset{d_k}{\text{argmin}} \left| P(z_{i+1} > L \mid \hat{\beta}) - \vartheta \right|$$

L = fixed threshold parameter

PKCRM

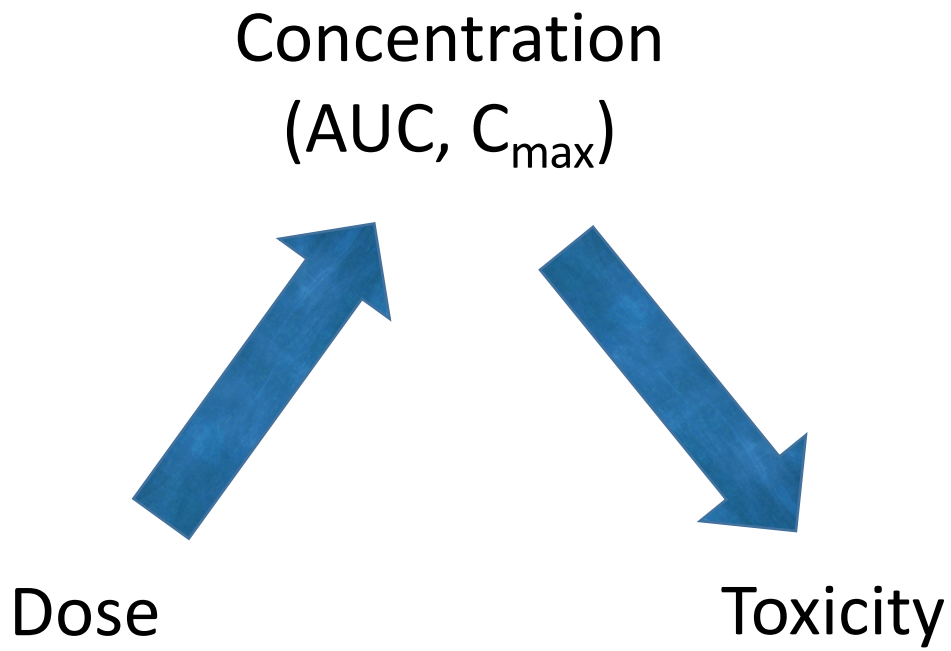
PKCRM = CRM + PKLIM

Dose allocation rule:

$$d_{i+1} = \min(d_{CRM}, d_{PKLIM})$$

S. Patterson et al.. A novel Bayesian decision procedure for early-phase dose-finding studies. Journal of Biopharmaceutical Statistics, 9(4): 583 - 597, 1999.

Incorporating PK in dose-finding (3)



p_T: probability of toxicity versus AUC

z: log(AUC)

PKLOGIT

PKLIM model

$$\text{logit}(p_T(z,\beta)) = -\beta_3 + \beta_4 z$$

Priors: $\beta_3 \sim U(l_3, \mu_3)$

$\beta_4 \sim U(l_4, \mu_4)$

Dose allocation rule:

$$d_{i+1} = \underset{d_k}{\text{argmin}} \left| P(Y_{i+1} = 1 \mid \hat{\beta}) - \theta \right|$$

$$= \int \frac{1}{1 + \exp(\hat{\beta}_3 - \hat{\beta}_4 z)} g(z)\,dz$$

J. Whitehead et al.. A Bayesian approach for dose-escalation in a phase I clinical trial incorporating pharmacodynamic endpoints. Journal of Biopharmaceutical Statistics, 17(6): 1117 - 1129, 2007.

Simulating scenarios (1)

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12256

Defining a therapeutic window for the novel TGF-β inhibitor LY2157299 monohydrate based on a pharmacokinetic/ pharmacodynamic model

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PK/PD model, TGF-β inhibitor, therapeutic window

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RESEARCH PAPER

Influence of the Size of Cohorts in Adaptive Design for Nonlinear Mixed Effects Models: An Evaluation by Simulation for a Pharmacokinetic and Pharmacodynamic Model for a Biomarker in Oncology

Giulia Lestini[1] • Cyrielle Dumont[1] • France Mentré[1]

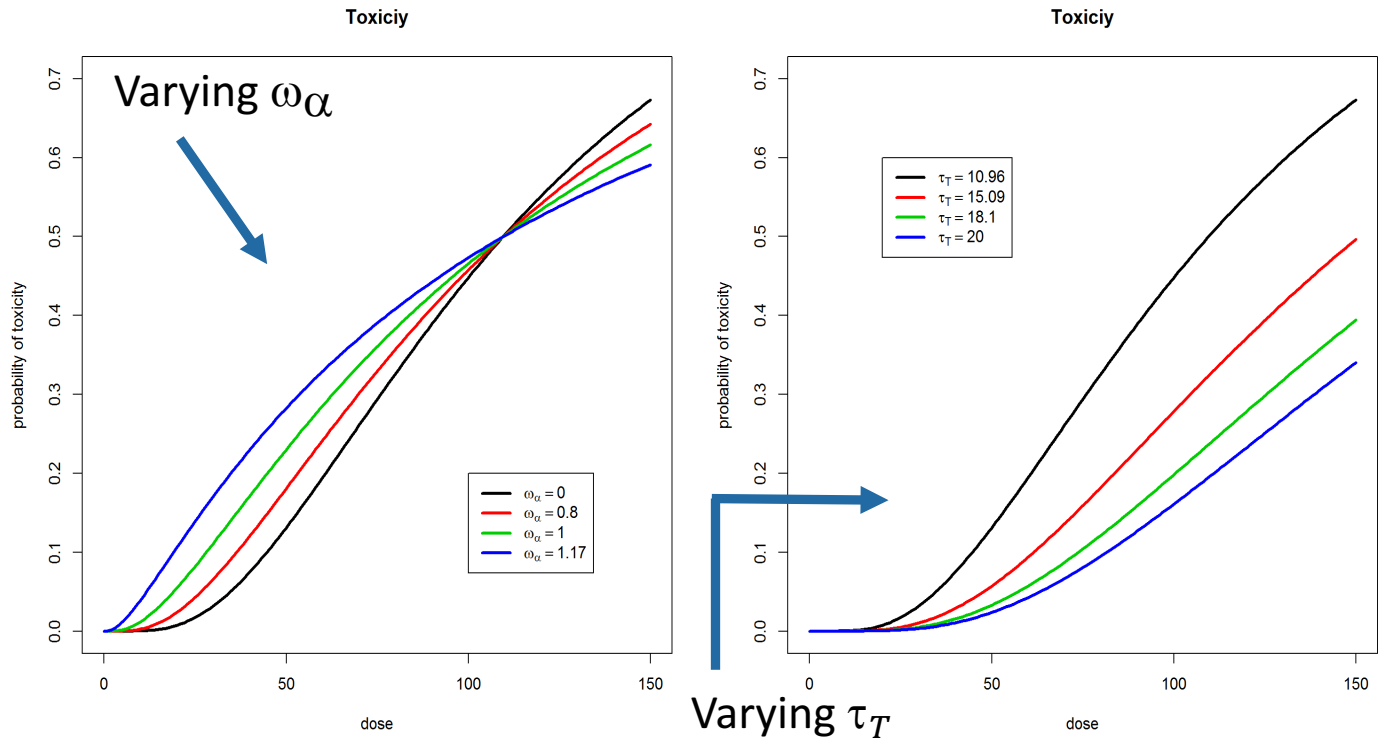
Simulating scenarios (2)

Link between PK and toxicity:

$$Y_i = \begin{cases} 0 & if \ \alpha_i AUC_i < \tau_T \ L^{-1}h \\ 1 & if \ \alpha_i AUC_i \geq \tau_T \ L^{-1}h \end{cases}$$

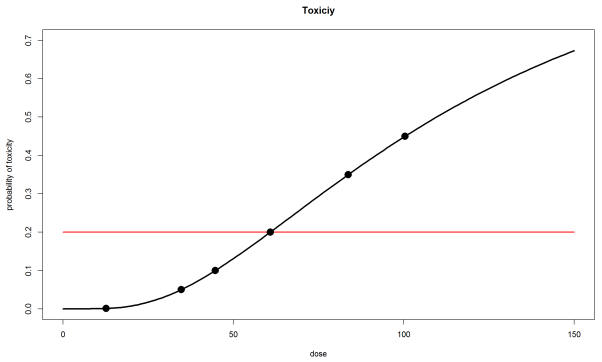
patient's sensitivity

toxicity threshold

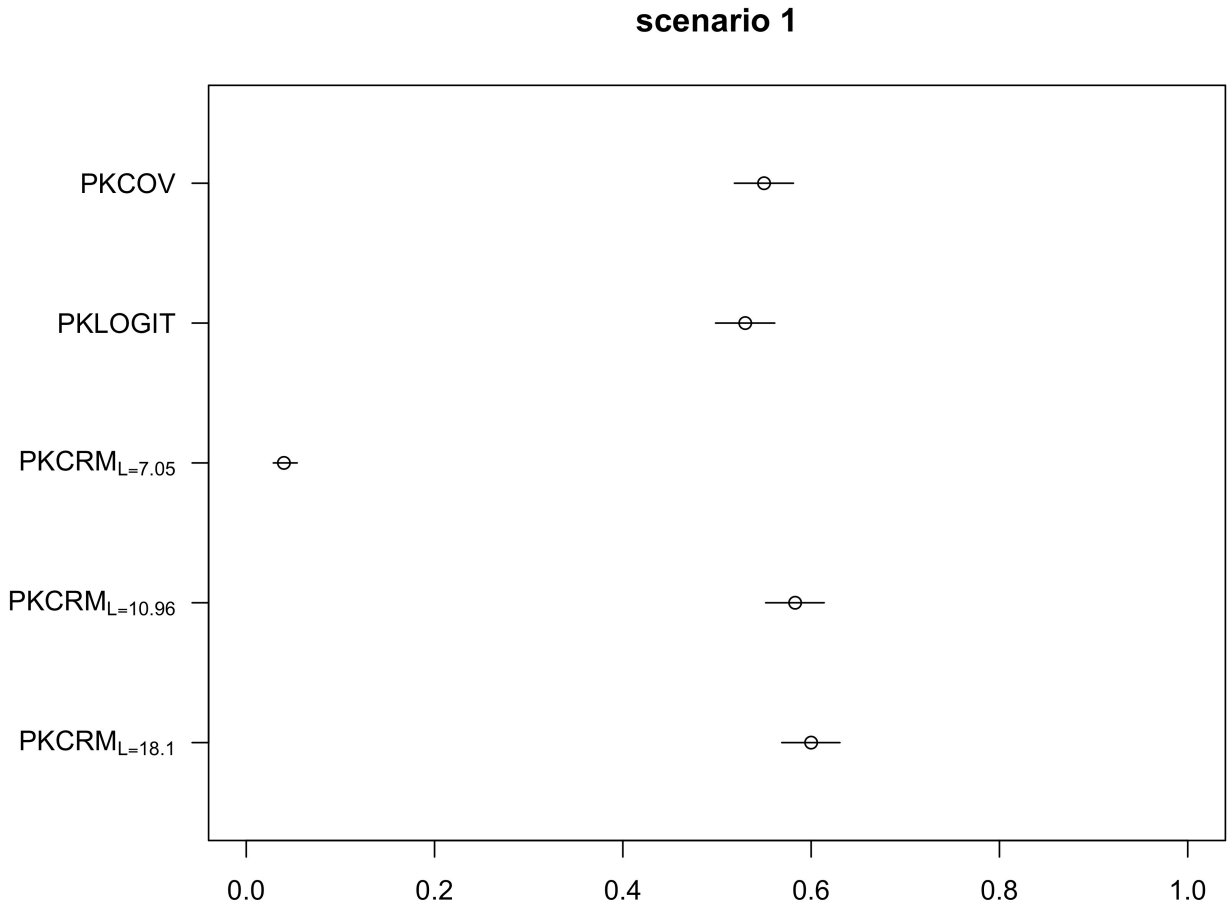


Results (1)

τ_T = 10.96
ω_α= 0
IIV = 0.7

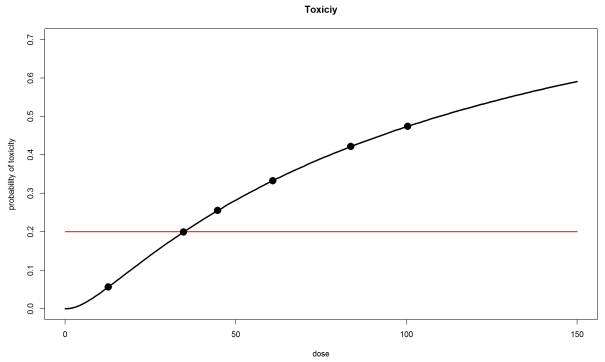


MTD:
dose level
4

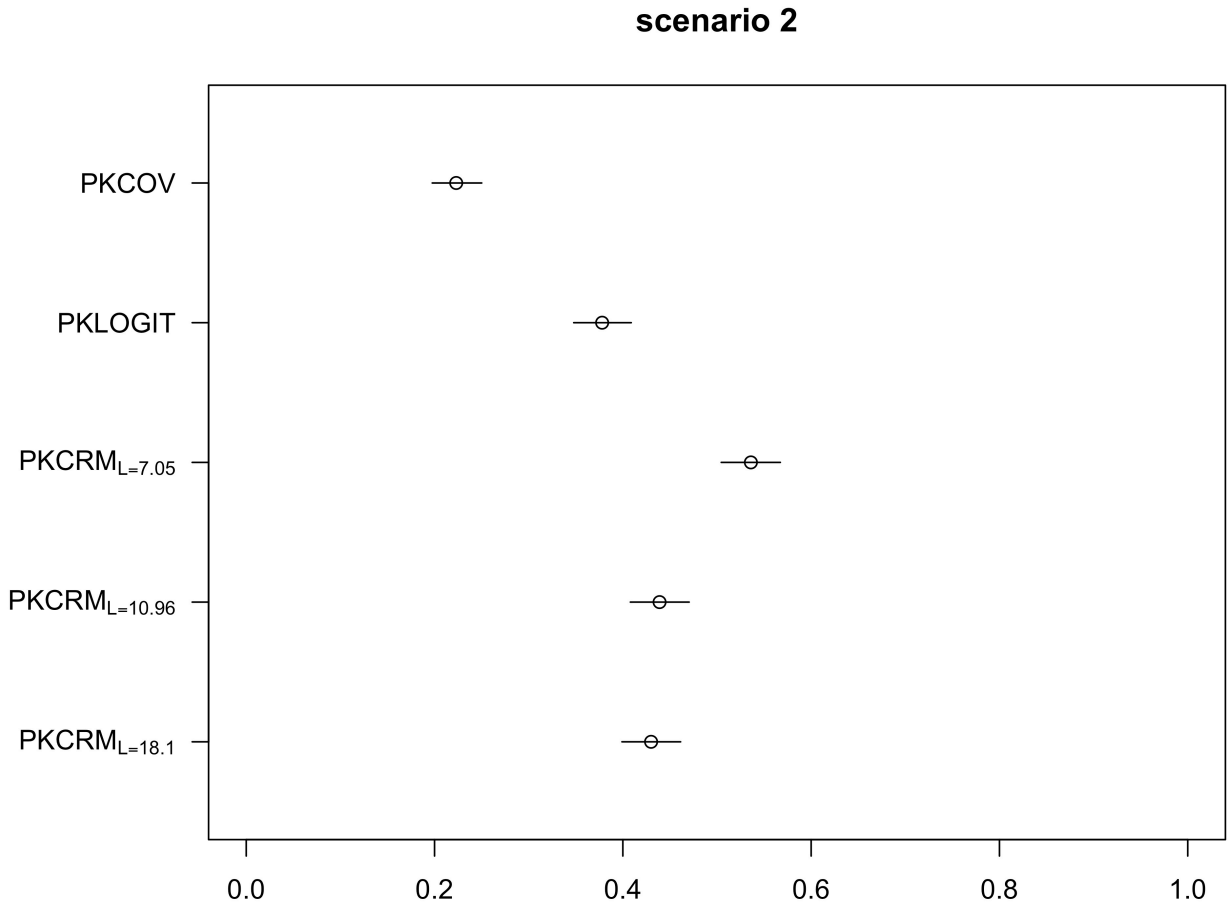


Results (2)

τ_T = 10.96
ω_α= 1.17
IIV = 0.7

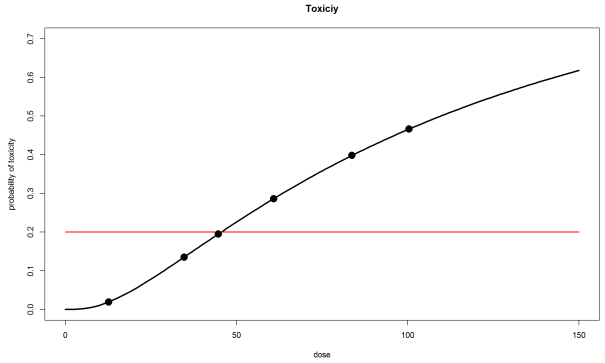


MTD:
dose level
2

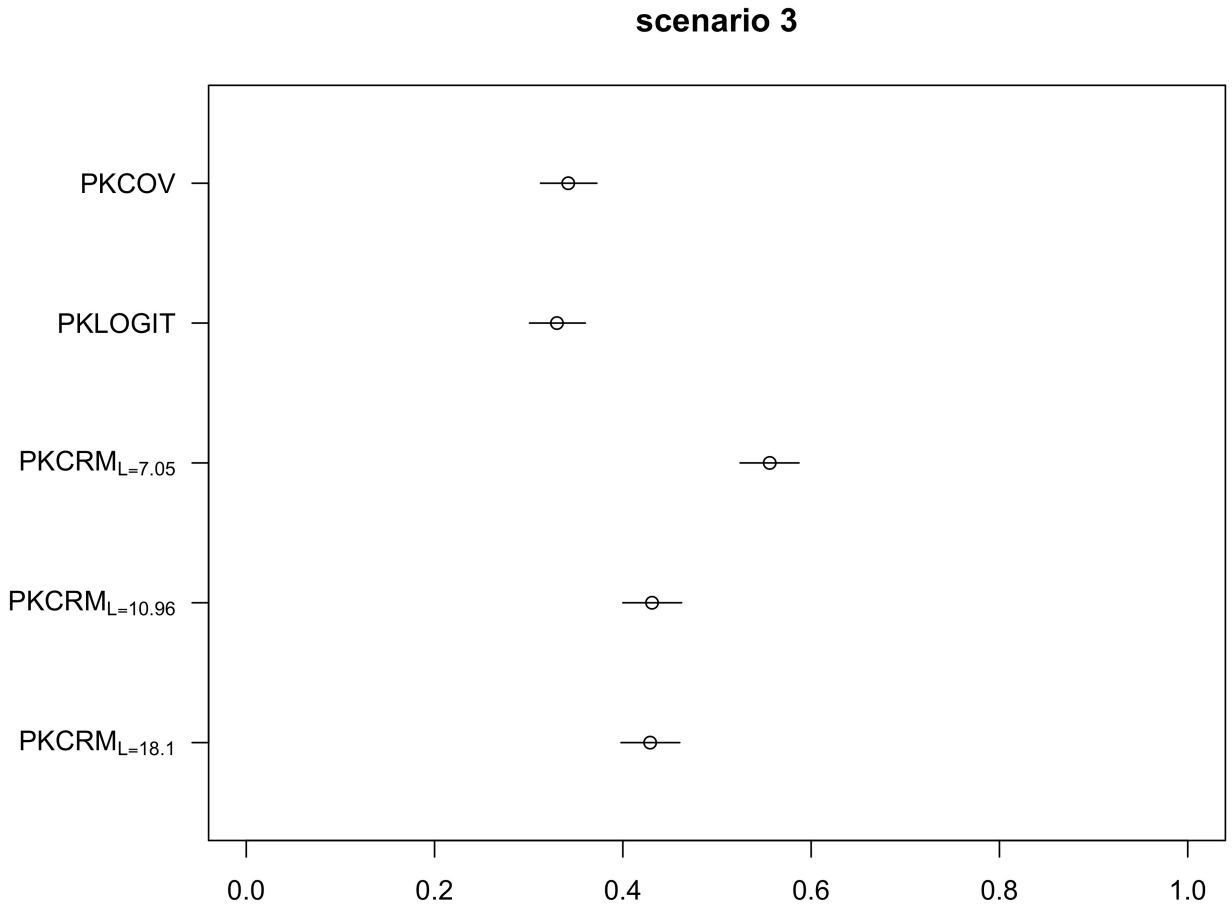


Results (3)

τ_T = 10.96
ω_α= 1
IIV = 0.3



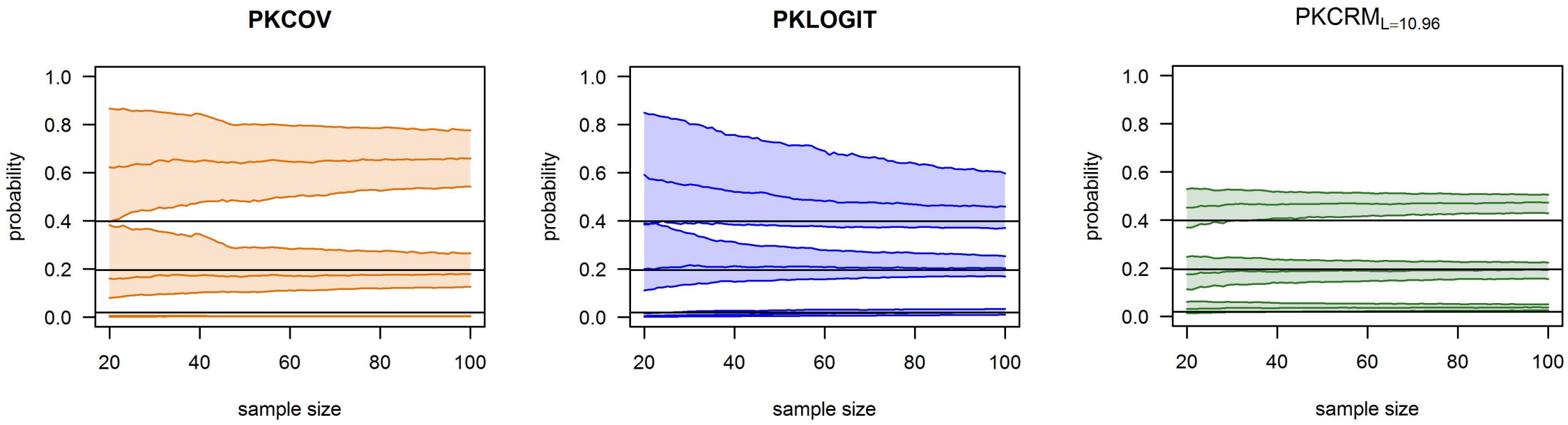
MTD:
dose level
3



Results (4)

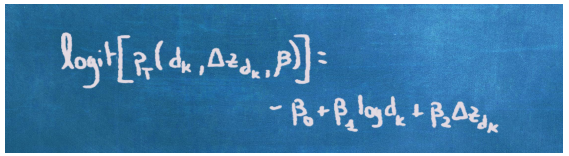
Estimated probability of toxicity at each dose level in case of scenario 3.

1000 trials; first, second and third quartile of p_1, p_3 (MTD), and p_5 for sample size from 20 to 100.



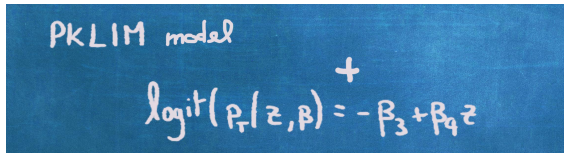
Discussion

PKCOV



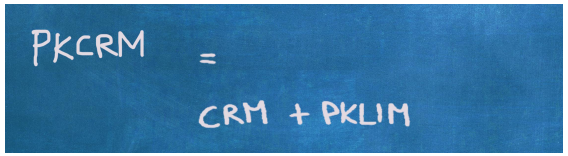
- It depends also on the right β_0
- It is similar to logit(p) vs log(dose)

PKLOGIT



- Issue in the estimation when the relationship between tox and AUC is an Heaviside function

PKCRM



- Dependence on the threshold *L*
- It tends to CRM alone while L increases

Conclusion

Including only PK measure of exposure, as the AUC, in dose-finding does not increase the percentage of right MTD selection …

usual dose-finding methods, such as CRM, are designed to focus on the MTD specifically

… but enriches the knowledge on the dose-toxicity relationship, facilitating a better dose recommendation for subsequent trials.

with a limited impact on observed toxicities (i.e. no overdosing)

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Giulia Lestini
France Mentré

Integrated DEsign and AnaLysis of small population group trials

Ivelina Gueorguieva

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R package `dfpk` available on CRAN repository https://cran.r-project.org/web/packages/dfpk/index.html