

A Bayesian (P)K-TTE model to support early dose escalation decisions in phase 1 Oncology studies

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Background

- Oncology phase I trials follow mainly a dose-escalation (DE) design, monitoring dose limiting toxicity (DLT) in the 1st treatment cycle to decide on the dose for the next cohort during the trial.
- Pharmacokinetics (PK), pharmacodynamics (PD) and dose reductions/interruptions are considered less formally due to data sparsity/incompleteness at early stages.
- The focus on cycle 1 is becoming a limitation in modern multi-cycle therapies.
- A Bayesian (P)K-TTE (TTE = Time To Event) model that relies on readily available dose history and possibly PK summaries will be developed, the model is formulated as an extension to the Bayesian Logistic Regression Model (BLRM)
- A BLRM is often used as safety model to analyze the dose-toxicity relationship in order to limit the risk for safety events at each DE decision point of a trial.

Conclusions

- The use of Bayesian modeling allows to integrate prior knowledge (disease models, prior distributions on parameters) and trial data. This facilitates decision making at early stages of a trial.
- The simplified PK model in the context of the integrated popPD approach [1] allows for the construction of a longitudinal exposure measure
- An integrated popPD model handles incomplete PK data in DE trials by using model-based imputation of the exposure while considering dose interruptions/changes
- TTE models can incorporate events from multiple cycles allowing a more efficient use of the trial data
- Assess risk for future patients while accounting for planned dosing regimens, between-patient variability and baseline characteristics

Objectives: to build a (P)K-TTE safety model including data beyond cycle 1 that (1) uses the actual dose history to form a longitudinal exposure measure aligned with the known drug pharmacology, (2) uses partially observed patient data (e.g., for most recent cohort), (3) predict outcome for future patients to inform DE decisions during the trial

Methods

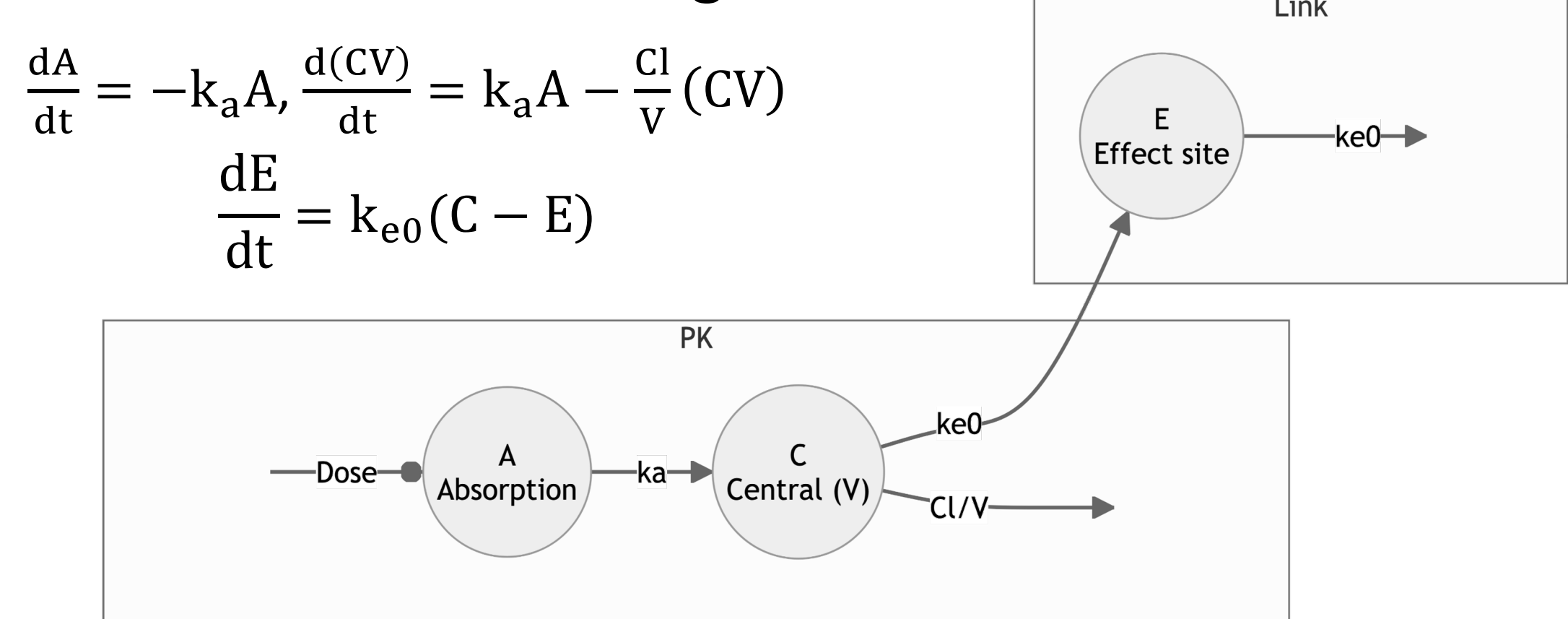
- Data from trial NCT02375958 studying PCA062 given as infusion (in mg/kg) every 2 weeks (q2w) to patients with pCAD+ tumors [2, 3].
- DE data was emulated with the cut-off date for each DE meeting, with the PK data of the last two patients enrolled in a cohort set to missing.

Table 1. Risk set and number of G3+ AEs for cycle 1 by DE meeting

DE meeting	Dose (mg/kg)	DEM4					DEM7					Tot.		
		0.4	0.6	0.9	1.4	Tot.	0.4	0.6	0.9	1.4	2.1		3.2	3.6
Risk set	TTE	3	4	4	5	16	3	4	4	5	4	5	4	29
	BLRM	3	3	4	5	15	3	3	4	5	4	4	4	27
G3+ AEs in cycle 1		0	0	0	1	1	0	0	0	1	0	1	1	3

For the integrated popPD model, a simplified PK model which focuses on steady state kinetics is set up. This includes reaching, maintaining, and leaving steady state.

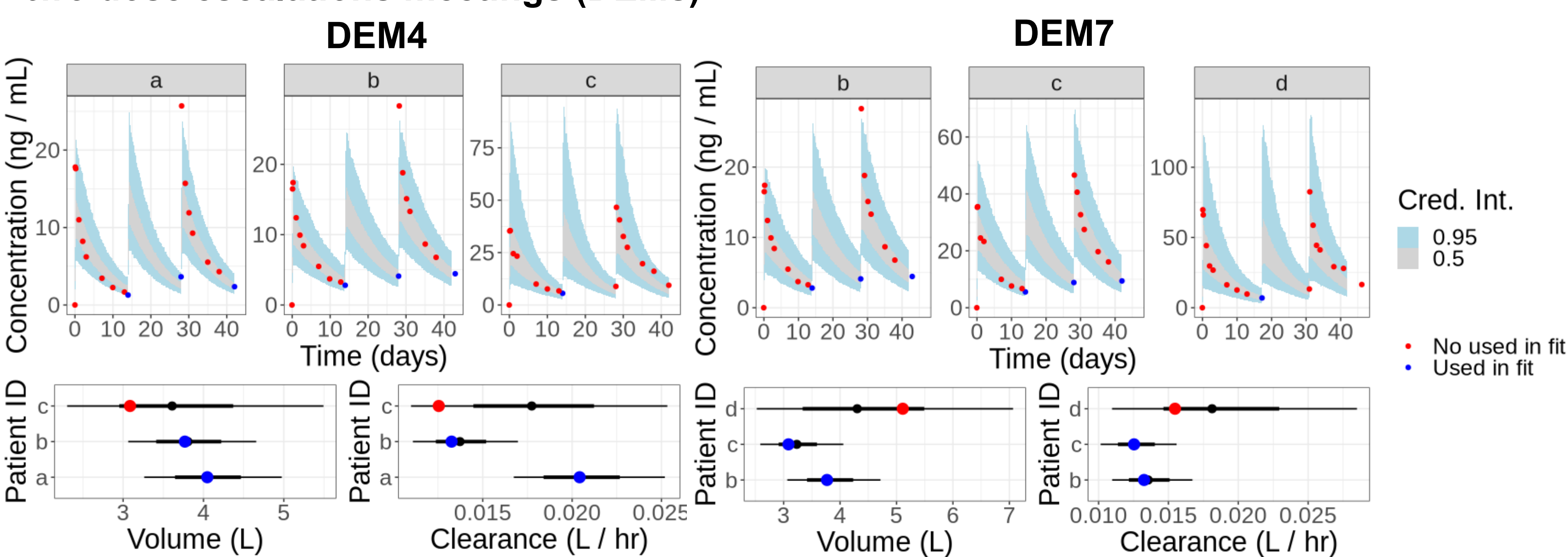
Figure 1. PCA062 PK-TTE model diagram



A: drug amount in absorption compartment (mg); where dosing happens, C: drug concentration in central compartment (ng/mL); what is measured, with elimination rate define as $k = Cl/V$, E: drug in the effect compartment. Other parameters are defined in table 2.

Results

(P)K-TTE model for PCA062 was implemented from DE meeting 4 (n=15, 4 cohorts) onwards. Weakly informative priors were used for all model parameters (see table 2). **Figure 2. Simplified PK model posterior predictive distribution vs observed data for two dose escalations meetings (DEMs)**



The top plot show the posterior predictive distribution for the PK profiles: gray area show the 50% CrI, light blue area show the 95% CrI. The bottom plots show the posterior predictive distribution for volume and clearance. **The red dots represent the data that was not used in the fitted model and the blue is the data that was used in the fitted model.**

References

- [1] S Weber, J Gonzalez Maffe, G Baneyx, L Widmer, L Markovtsova. Novel integrated population PD modeling framework to inform decision making during Oncology phase I dose-escalation. PAGE 32 (2024) Poster IV-081
- [2] Duca M, et al. A First-in-Human, Phase I, Multicenter, Open-Label, Dose-Escalation Study of PCA062: An Antibody-Drug Conjugate Targeting P-Cadherin, in Patients With Solid Tumors. Mol Cancer Ther. 2022 Apr 1;21(4):625-634. doi: 10.1158/1535-7163.MCT-21-0652. PMID: 35131875.
- [3] J Kim, et al. Combining BLRM and safety PKPD models to improve decision making in a phase I dose escalation study: case study of PCA062, an antibody drug conjugate targeting P-Cadherin. PAGE 28 (2019) Abstr 9108 [www.page-meeting.org/?abstract=9108]
- [4] Stan Development Team. 2023. Stan Modeling Language Users Guide and Reference Manual, 2.32.2. <https://mc-stan.org>
- [5] Bürkner P. C. (2017). brms: An R Package for Bayesian Multilevel Models using Stan. Journal of Statistical Software. 80(1), 1-28. doi.org/10.18637/jss.v080.i01.

This simplified PK model is informed using the actual dose history and non-compartmental analysis (NCA) estimates of clearance and volume as well as observed C_{min}, and linked to the time to first adverse event (AE) process by modeling the log of the hazard as:

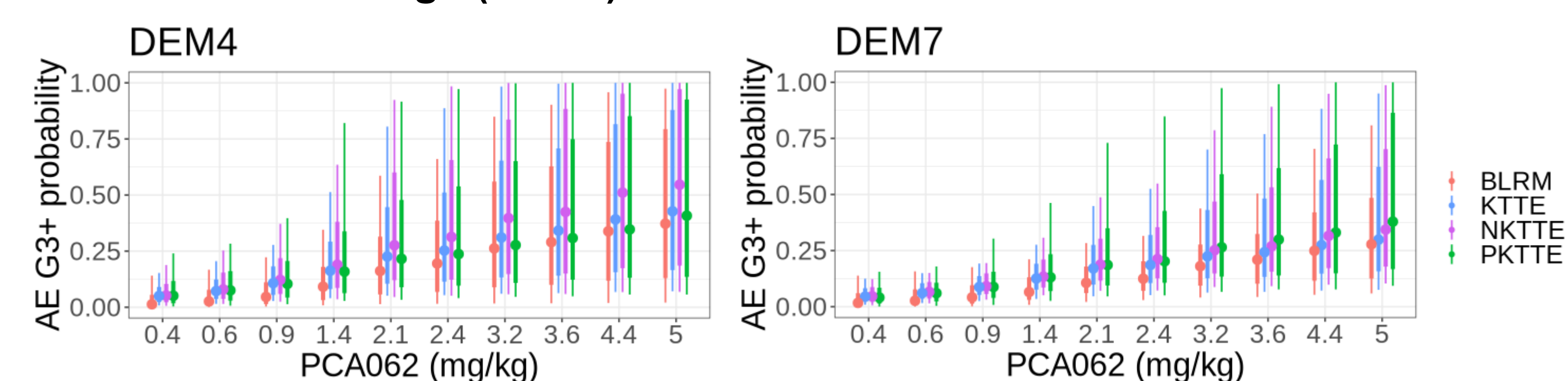
$$\log(h(t)) = \alpha + \beta \log\left(\frac{E(t)}{E_{ref}(t_{ref})}\right)$$

E(t): exposure measure at time t. E_{ref}(t_{ref}): reference exposure defined based on a reference time point t_{ref} and reference dosing regimen. The value of α can then be interpreted as the cloglog of the toxicity rate up to t_{ref} when patients are given the reference dosing regime. All models are fitted in Stan [4] using the brms R package [5].

Table 2. Prior distribution for model parameters

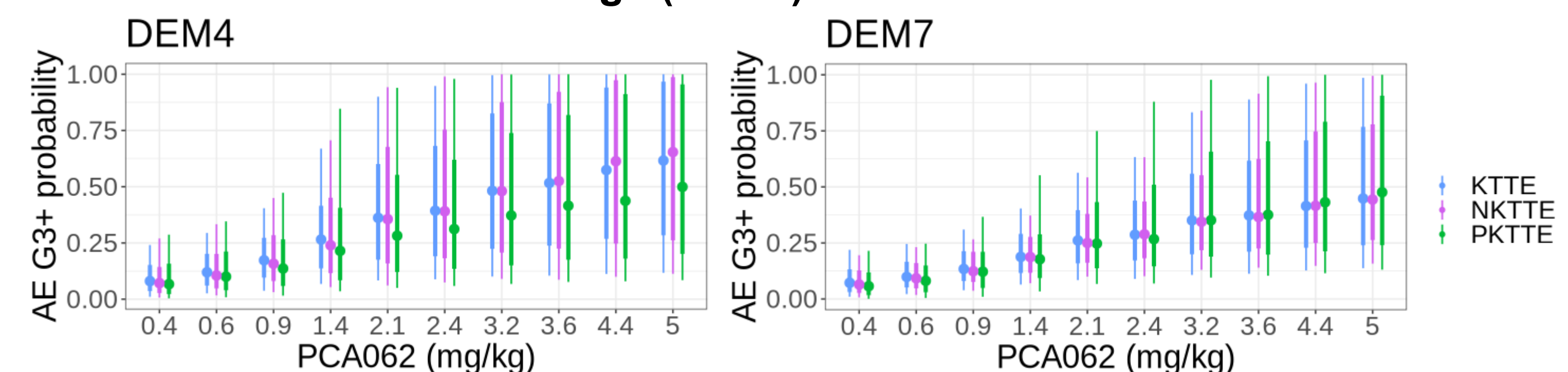
Parameter	Units	Definition		Distribution	Prior 95% CrI	Note
Cl	L/hr	Clearance from central compartment	μ_{CL}	Log-normal	0.0006, 0.16	
			ω_{CL}	Log-normal	0.04, 1.05	0 for KTTE
V	L	Volume of central compartment	μ_V	Log-normal	0.64, 156.71	5L for KTTE
			ω_V	Log-normal	0.12, 0.32	0 for KTTE
K _a	1/hr	Absorption rate	Const.	Log-normal	1.43	
F _r	None	overall scaling factor (applied to dose)	μ_{F_r}	Log-normal	0.62, 1.62	1 for KTTE & NKTE
			ω_{F_r}	Log-normal	0.04, 1.05	0 for KTTE & NKTE
κ	None	Transfer rate to effect compartment relative to Cl/V	NA	Log-normal	0.14, 7.10	
α	None	Intercept for TTE model.	NA	Normal	-11.68, -3.84	
$\log(\beta)$	None	Effect of the exposure in the TTE endpoint	NA	Normal	-1.66, 1.66	

Figure 3. BLRM and (P)K-TTE/NK-TTE model predictions at day 28 for two dose escalations meetings (DEMs).



The plots show the posterior distribution for the probability of observing G3+ AEs by day 28. **KTTE uses actual dosing history and average PK parameters for all patients. NKTE: adds NCA estimates of CL & V per patient. PKTTE: adds C_{min} measurements.** The models with time varying exposure leads to more conservative recommendations in relation to the classic BLRM.

Figure 4. (P)K-TTE/NK-TTE model predictions for long term toxicities at day 56 in two dose escalations meetings (DEMs).



With the (P)K-TTE/NK-TTE models, we could estimate the probability of G3+ AEs at later cycles. The plot show the posterior distribution for the probability of observing G3+ AEs by day 56. On average PK-TTE propagate more uncertainty in relation to the K-TTE and NK-TTE models.