

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

Jaeyeon Kim¹, Juan Gonzalez Maffe², Eugene Tan³, Janna Sand Dejmek², Claire Fabre², Christophe Meille²

¹Novartis Institutes for Biomedical Research, Cambridge, MA, USA, ²Novartis Pharma AG, Basel, Switzerland, ³Novartis Pharmaceuticals, East Hanover, NJ, USA

Background

- Bayesian Logistic Regression Model (BLRM) is a statistical method to analyze the relationship between dose and dose limiting toxicities (DLT) [1]
- Semi-physiological PKPD models can describe longitudinal PD safety markers such as platelet count [2].
- BLRM and PKPD models were combined, during the phase I dose escalation study, to identify the maximum tolerated dose of the PCA062 antibody drug conjugate targeting P-Cadherin.

Conclusion

- The BLRM incorporates all toxicities considered as DLTs as a binary outcome, while the PKPD model describes only the platelet count observations, but as a longitudinal continuous measurement.
- Before the end of the escalation process, the PKPD model projected a higher risk of thrombocytopenia DLT compared to the risk of overall DLT estimated by the BLRM.
- Longitudinal measurement of safety PD markers can be leveraged through PKPD models to supplement the BLRM analysis and have an impact on optimal dose selection.

Objective: To illustrate, for the PCA062 compound, how a safety PKPD model can be developed in parallel with the BLRM to help decision making during the phase I dose escalation

Methods

- PCA062 was administered by one hour infusion every two weeks (Q2W).
- Ten dose levels ranging from 0.4mg/kg to 5.0mg/kg were tested.

Bayesian Logistic regression model (BLRM)

The Dose Determining Set (DDS) used for BLRM included patients that took two doses in the first 28 days of treatment (DLT period) or experienced a DLT

Table 1 – Subjects treated, DDS and DLTs by dose level

Dose (mg/kg)	0.4	0.6	0.9	1.4	2.1	3.2	3.6	4.4	4.7	5.0
Number of patients	3	4	4	5	4	6	9	8	1	3
Number of patients DDS	3	3	4	5	4	5	9	6	0	2
DLTs	0	0	0	1	0	1	2	1	0	2

The dose-DLT relationship was described by the following model:

$$DLT(d) \sim \text{bernoulli}(\pi(d)) \quad \text{with } \text{logit}(\pi(d)) = \log(\alpha) + \beta \cdot \log\left(\frac{d}{d^*}\right)$$

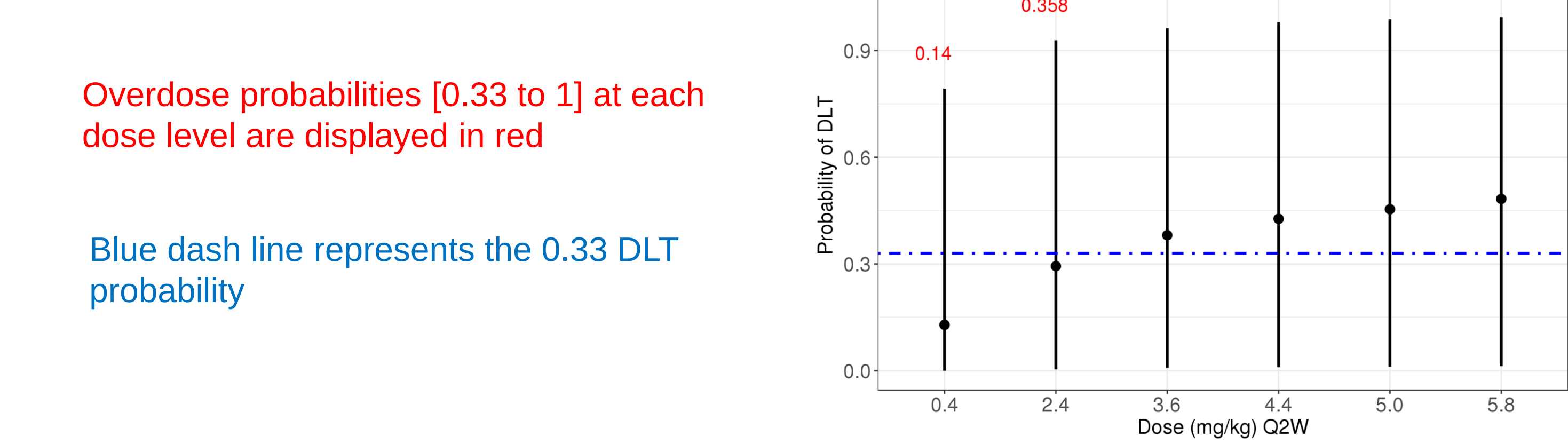
Doses re-scaled as d/d* with reference dose d* = 3mg/kg → α is equal to the odd of DLT at the reference dose d*.

A mixture prior with 3 Bivariate Normal (BVN) components is used for the model parameters:

Table 2 – Prior distribution parameters

BVN components	log(α) Means (sd)	log(β) Means (sd)	Correlation	Weight
Based on pre-clinical data in monkeys	-1.099 (2)	0 (1)	0	0.80
More sensitive population	-0.405 (2)	0 (1)	0	0.10
Less sensitive population	-1.792 (2)	0 (1)	0	0.10

Figure 1 – Prior dose-DLT relationship



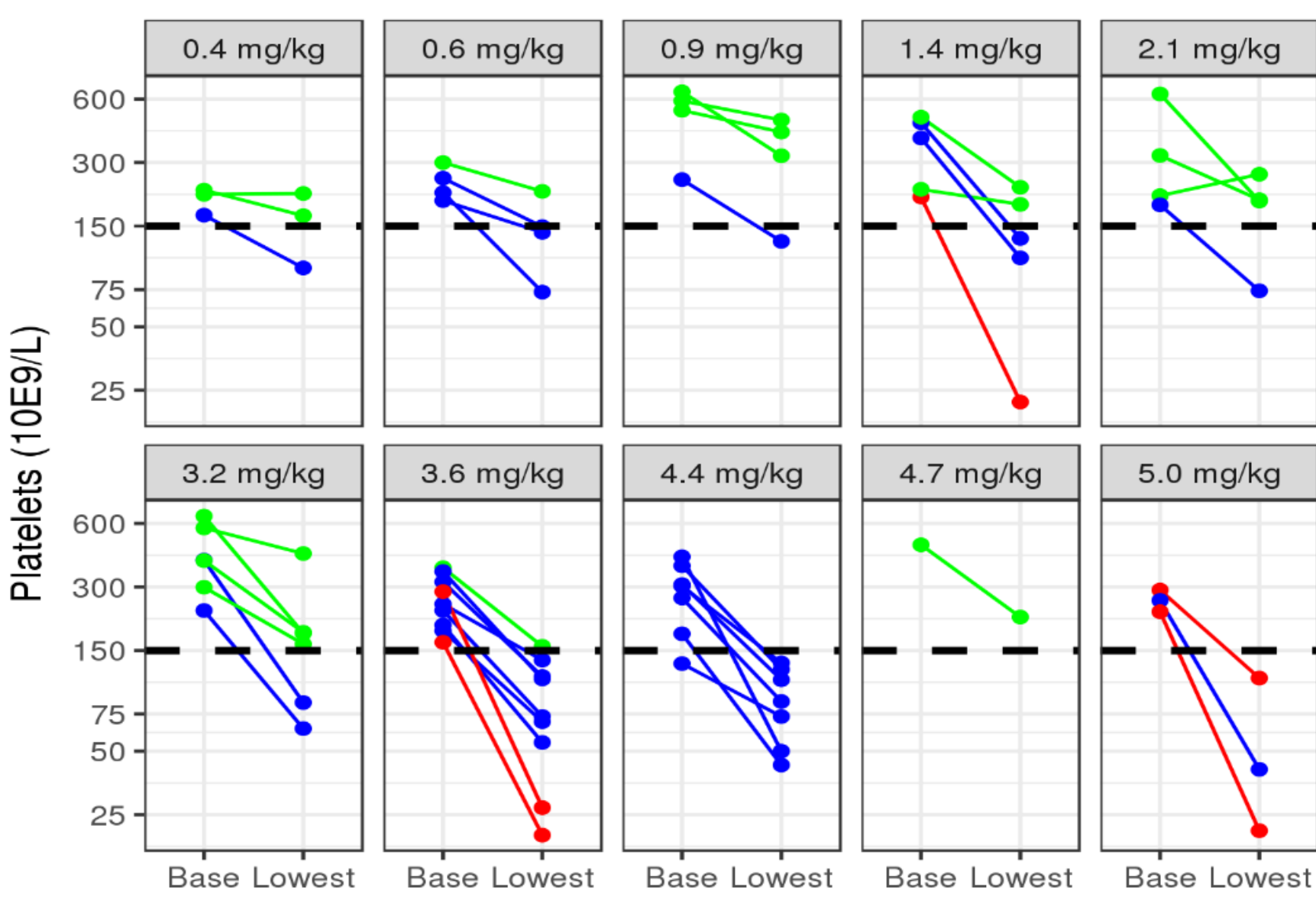
Results

Exploratory analysis for platelets

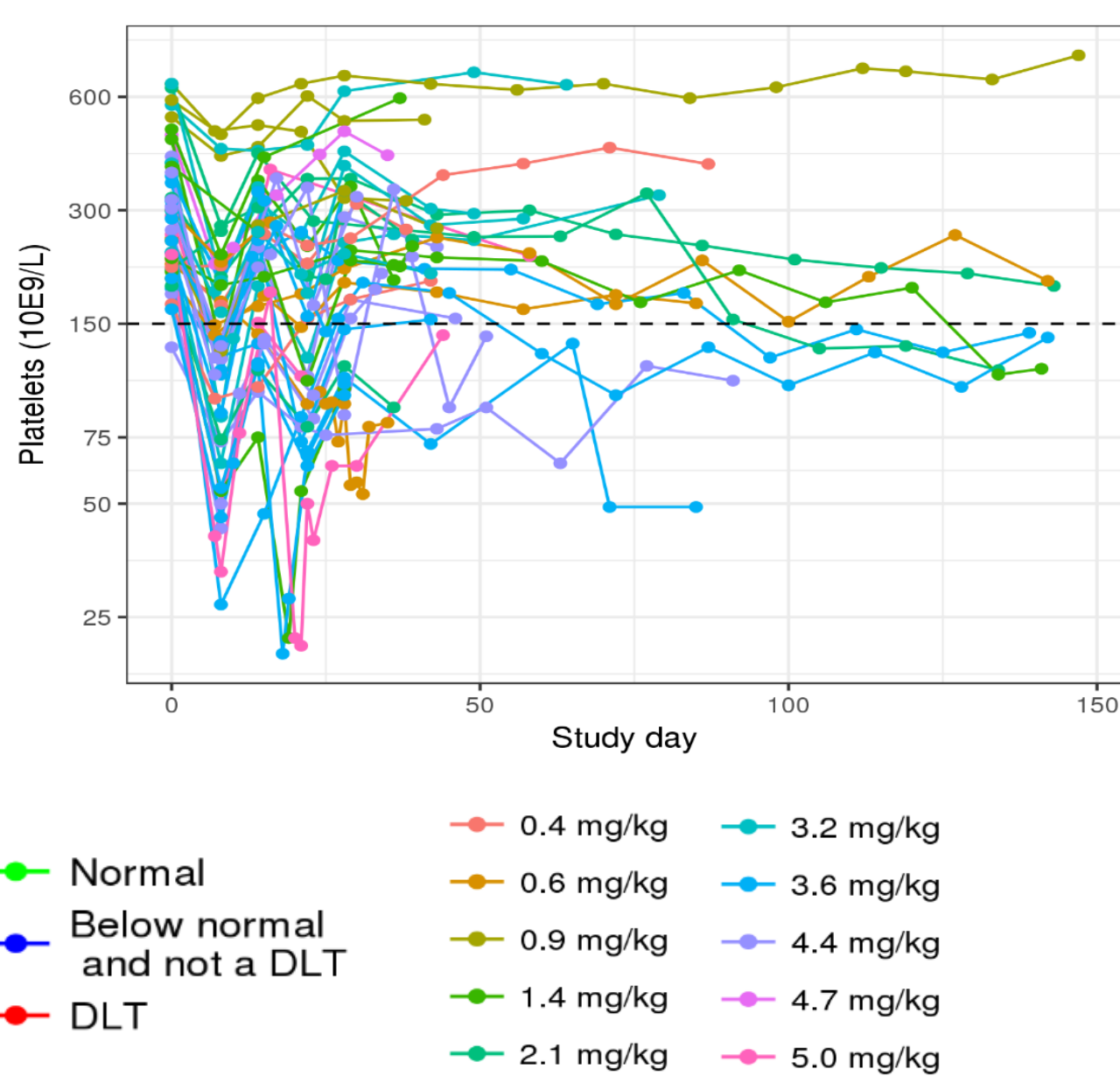
- 29 out of 47 patients showed an abnormal platelets level during the DLT period
- Only 5 patients reported a bone marrow toxicity DLT

Figure 3 – Platelets count by PCA062 dose levels

Lowest value compared to baseline during DLT period



Time profile for the first 150 days

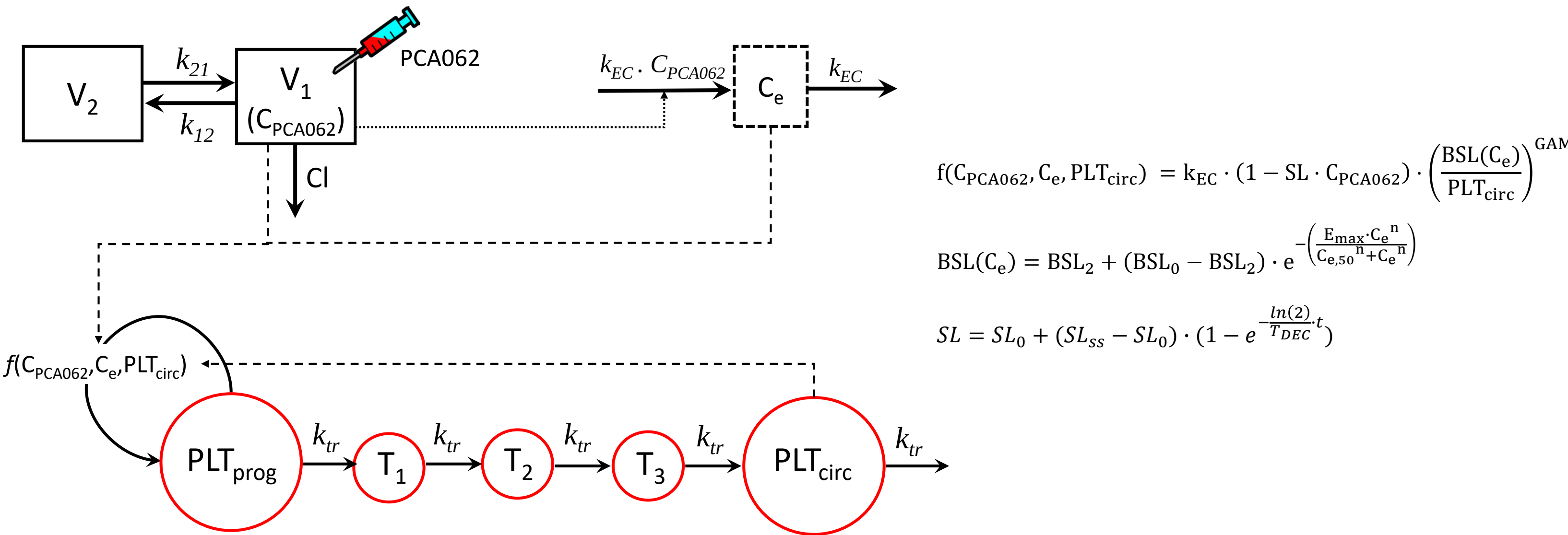


References

- Neuenschwander, Branson, Gsponer. Critical aspects of the Bayesian approach to phase I cancer trials. Statistics in Medicine 2008
- Bender BC, Quartino A, Li C, Chen S-C, Smitt M, Strasak A, Chernyukhin N, Wang B, Jin J, Girish S, Friberg LE. An integrated pharmacokinetic–pharmacodynamic (PKPD) modeling analysis of T-DM1–induced thrombocytopenia and hepatotoxicity in patients with HER2–positive metastatic breast cancer. PAGE Meeting 2016

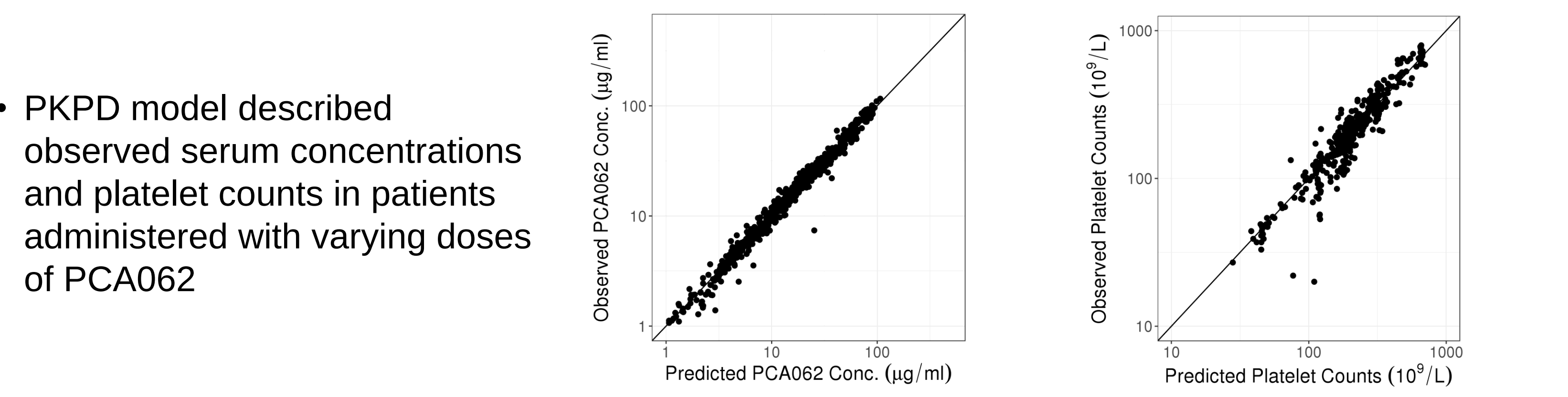
PK-PD model for platelets count profiles

Figure 2 – PCA062 PK-Platelets PD model diagram



- Two compartments model with linear clearance was used to describe serum PCA062 pharmacokinetics (Figure 2).
- The existing platelet PD model developed for T-DM1 [2] was combined with the PCA062 PK model to describe platelet count dynamics for PCA062 patients:
- Population PD parameters from T-DM1 model were fixed and individual PD parameters estimated based on the platelet count data from PCA062 patients.
- Platelet counts were simulated for 2.4, 3.6, 4.4, 5.0 and 5.8 mg/kg Q2W by using post-hoc individual PK/PD parameters for all PCA062 patients.
- The thrombocytopenia DLT (Grade 4 or Grade 3 > 7 days) probability was calculated based on the simulated platelet count dynamics.
- The probability confidence bounds were calculated using the Clopper-Pearson exact method

Figure 4 – PKPD model diagnostic plots (Left: PK model, Right: PD model)



BLRM and PKPD models predictions

- Only PKPD modeling accurately predicted thrombocytopenia toxicity rates for unexplored dose ranges (>4.4mg/kg Q2W) (Figure 5 left).

Figure 5 – Predictions from BLRM and PKPD model

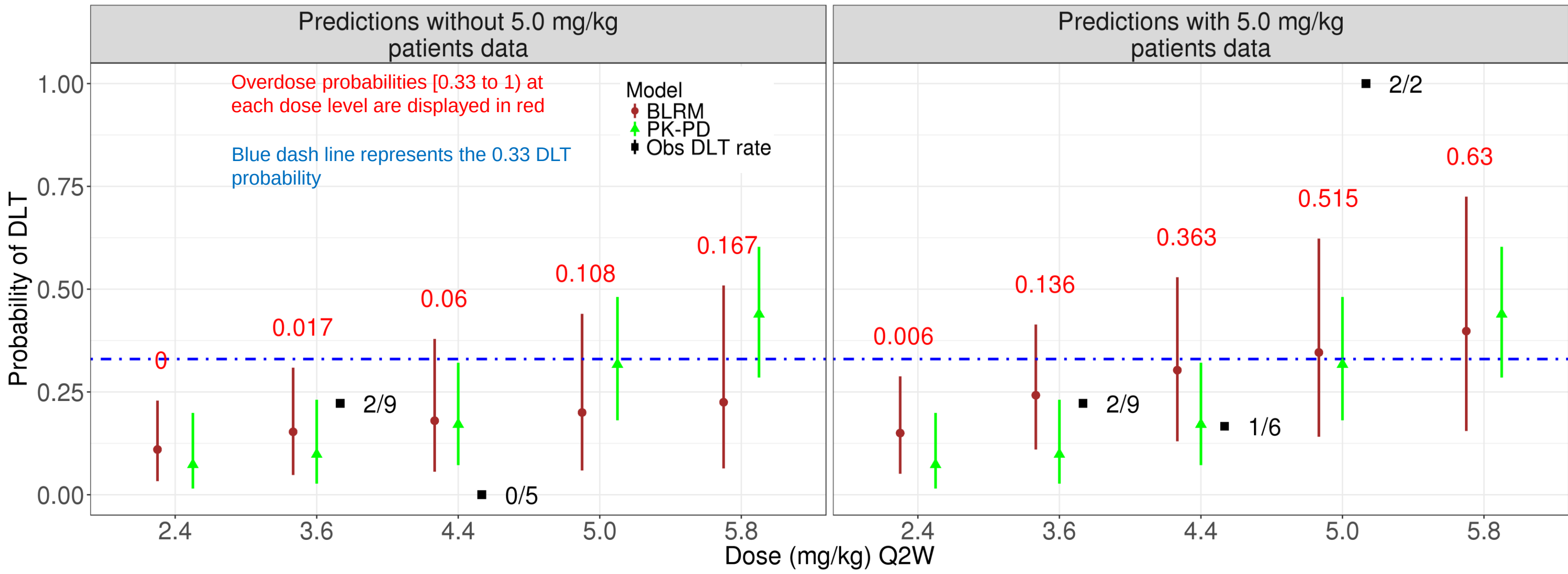


Table 3 – Projected toxicity rates at 5mg/kg from PKPD model and BLRM

	PKPD	BLRM	
	Without 5mg/kg pts data	Without 5mg/kg pts data	With 5mg/kg pts data
DLT rate at 5mg/kg	31.7% (95% CI 18.1 to 48.1)	20.1% (95% CI 5.8 to 43.7)	34.2% (95% CI 13.9 to 61.1)