

A semi-mechanistic pharmacokinetic-pharmacodynamic model to characterize thrombocytopenia in patients with biliary tract cancer, and other advanced or metastatic solid tumors treated with a selective antagonist of MDM2-p53 interaction

Tassadit Belabbas,¹ Ida Neldemo,² Lukas Kovar,¹ Mehdi Lahmar,¹ Angela Märten,¹ Alejandro Pérez-Pitarch,^{1*} Celine Sarr,² Ulrike Schmid,¹ Reinhard Sailer,¹ David Busse.¹

1. Boehringer Ingelheim Pharma GmbH Co. KG., Ingelheim and Biberach, Germany; *at time of project involvement, now: Regeneron Pharmaceuticals, Inc., Tarrytown, NY ; 2. Pharmetheus AB, Uppsala, Sweden

Introduction

- Brigimadlin (BI 907828) is a murine double minute 2 (MDM2)-tumor suppressor protein p53 (TP53) (MDM2-p53) antagonist developed for the treatment of locally advanced and metastatic solid tumors.
- Nonclinical data suggests that inhibition of the MDM2-p53 protein interaction results in cell cycle arrest and/or apoptosis in tumors harbouring wild-type TP53 but not in mutant TP53. The main dose-limiting toxicities reported were myelosuppressive events, including thrombocytopenia.

Methods

- The population modeling analysis included data from a Phase I (NCT03449381) and a Phase II study (NCT05512377).
- Individual concentration-time profiles, reflecting the actual dose given and potential dose delay, were predicted from a population PK model, and a semi-physiological model for myelosuppression was used as base model. ¹
- Tested covariates: Age, sex, baseline body weight (WT), biliary tract cancer (BTC), Asian, baseline total bilirubin (TBIL), severity of previous myelosuppressive therapy, Eastern cooperative oncology group performance status (ECOG), baseline ALBI score grade, and baseline fibrosis index (Low vs intermediate or higher risk)

283 patients

● 4982 PK observations
● 5747 platelet count observations

Software

• NONMEM® 7.5.1
• Perl-speaks-NONMEM 5.3.1
• R version 4.3.1

Covariates

• Stepwise forward addition (p=0.01) and backward elimination (p=0.001) procedure (SCM)

Evaluation

• Goodness-of-fit plots
• Visual predictive checks (VPCs)

Model application

• Platelet time course over two cycles was simulated (n=1000) for two oral doses (30 mg vs 45 mg Q3W).
• The proportions of thrombocytopenia grade 4 and dose delay (platelet count <100 x 10⁹ cells/L) were compared between the two dosing regimens. ²

Conclusions

- ✓ An exposure-safety analysis was performed, assessing the relationship between brigimadlin PK and the occurrence of severe thrombocytopenia. The developed semi-mechanistic model was successfully applied to simulate the platelet time course and potential dose delay.
- 🔗 The target dose of 45 mg Q3W is expected to result in an increased risk of grade 4 thrombocytopenia compared to 30 mg. For the purpose of dose optimization, these results need to be interpreted in context of other relevant safety endpoints as well as anti-tumor activity for the two assessed dose levels.

Results – Final Model parameters

- After the SCM, significant covariates included; fibrosis index and age on baseline platelet count, ECOG on EC50, WT on mean maturation time, and TBIL on power of feedback regulation. However, no covariate was found to be clinically relevant based on the forest plot (Data not shown).

Table 1. Parameter estimates of the final platelet model for brigimadlin.

Parameter	Unit	Estimate (RSE%)
Baseline platelet count	(10 ⁹ cells/L)	204 (2.5)
Mean maturation time	(h)	173 (12.2)
Baseline power of feedback regulation		0.0128 (14.5)
E _{max,PLA}		1.0 (FIX)
EC _{50,PLA}	(nmol/L)	2670.0 (9.8)
Y _{Hill,PLA}		2.92 (12.7)
SLP _{PLA}	(10 ⁻³ L/nmol)	0.0184 (11.6)
SLP _{YFBK,PLA,t}	(10 ⁻⁴ h ⁻¹)	0.969 (13.9)
T _{50,FBK,PLA}	(h)	1020.0 (3.7)
Y _{Hill,FBK,PLA}		20.0 (FIX)
IIV PLA _{circ,0}	(ω ²)	0.0927 (10.9)
IIV MMT	(ω ²)	0.504 (16.1)
IIV Y _{FBK,PLA,0}	(ω ²)	0.845 (17.5)
IIV EC _{50,PLA}	(ω ²)	0.107 (17.1)
IIV SLP _{PLA}	(ω ²)	0.238 (55.0)
IIV T _{50,FBK,PLA}	(ω ²)	0.043 (19.7)
Proportional error		0.182 (5.8)
Additive error	(10 ⁹ cells/L)	19.500 (11.5)

PLA_{circ,0} Baseline platelet count; MMT, Mean maturation time; Y_{FBK,PLA,0} Baseline power of feedback regulation; E_{max,PLA} Maximum drug effect; EC_{50,PLA} Half maximal effective concentration; Y_{Hill,PLA} Emax shape parameter; SLP_{PLA} Slope of transit effect; SLP_{YFBK,PLA,t} Slope of time effect; T_{50,FBK,PLA} Time when power of feedback regulation is reduced by 50%; Y_{Hill,FBK,PLA} T_{max} shape parameter; IIV, Inter-individual variability error showed as variance (ω²); RSE, Residual standard error. The RSE for IIV and residual variability parameters are reported on the approximate SD scale.

References

1. Friberg LE, Henningsson A, Maas H, Nguyen L, Karlsson MO. Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. J Clin Oncol. 2002;20: 4713–4721. doi:10.1200/JCO.2002.02.140; 2. Common Terminology Criteria for Adverse Events (CTCAE) Version 5. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. 2017

This study was funded by Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version.



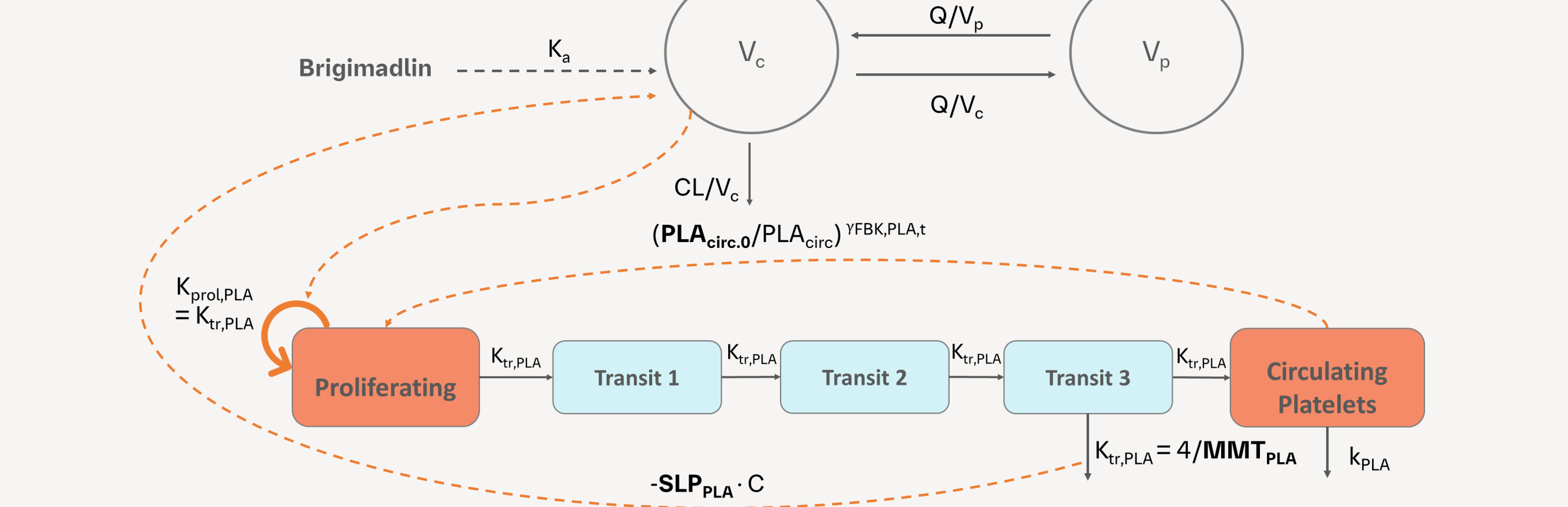
Objectives

- The aim of this analysis was to characterize the relationship between brigimadlin pharmacokinetics (PK), and platelet count via modelling and simulation by integrating relevant data across the program, with the objective of supporting the dose optimization of brigimadlin for future patient populations.

Results – Final Model structure

- The final model consisted of a proliferating compartment linking the PK model to a safety model, three transit compartments, and a compartment for the circulating platelets.
- The model is characterized by two drug effects: The first is a sigmoidal maximum effect model with maximum effect on the proliferating platelets, fixed to 1. The second is a linear drug effect describing a removal from the third transit compartment. Furthermore, addition of a time effect related to the platelet feedback parameter allowed a better prediction of the platelet time course including the nadir.

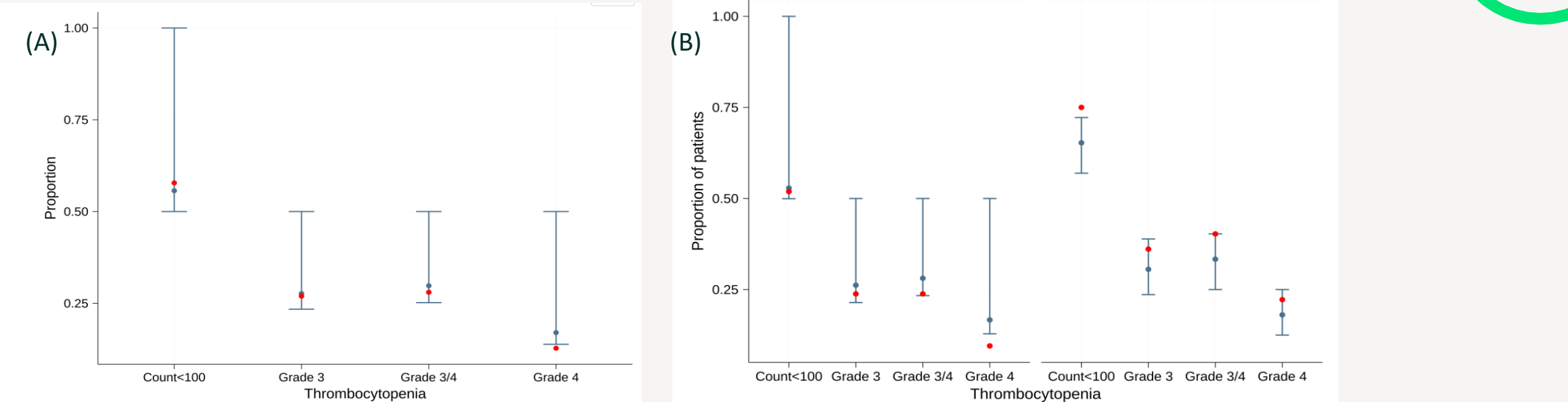
Figure 1 Schematic representation of the starting platelet count model. Parameters in bold are estimated



PLA_{circ,0} Baseline platelet count; MMT, Mean maturation time; Y_{FBK,PLA,t} Power of feedback regulation; SLP_{PLA} Slope of transit effect; k_{tr,PLA} Transit rate constant; K_{tr,PLA} Proliferation rate constant; k_{PLA} Elimination rate constant; C, Plasma concentration predicted by the PK model; K_a Absorption rate constant; CL, Clearance; V_c Central volume of distribution; V_p Peripheral volume of distribution; Q, Inter-compartmental clearance

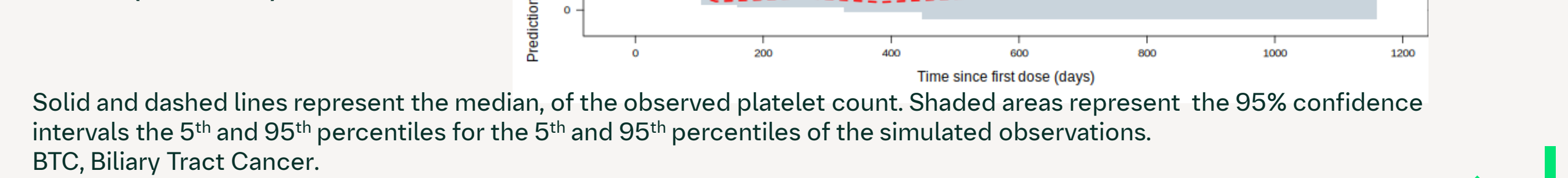
Results – Model evaluation

Figure 2. VPC of the proportion of patients that experience a platelet count below 100x10⁹/L, grade 3, grade 3 or 4 and grade 4 thrombocytopenia, overall (A) and stratified by BTC (B).



Closed red circle represent the median of the observed proportion in the dataset. Error bars represent the median, 5th and 95th percentiles of the simulated proportions. BTC, Biliary Tract Cancer.

Figure 3. pvcVPC platelet count versus time since first dose using the final PK-platelet model for all subjects and stratified by BTC (n=1000).



Results – Simulations

Table 2. Simulated proportion of thrombocytopenia events for 30 mg and 45 mg Q3W, for the first two cycles.

Dose	Risk of grade 3/4 (%)	Risk of grade 4 (%)	Dose delay (%)
30 mg	13.3	7.3	21.4
45 mg	21.7	13.8	31.4

13.8% of the patients were predicted to develop thrombocytopenia grade 4 following 45 mg Q3W compared to **7.3%** for the 30 mg Q3W dosing regimen.