Prediction of occurrence of thrombocytopenia to select Phase 1b dose and dosing regimen for a selective inhibitor of p53-MDM2 in patients with solid tumors

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Introduction

- RG7112 is a selective inhibitor of p53-MDM2 binding that frees p53 from negative control, activating the p53 pathway in cancer cells leading to cell cycle arrest and apoptosis. Data collected in a Phase Ia program reported some occurrence of delayed thrombocytopenia (TCP). Those safety issues occur - (i) for patients receiving doses of RG7112 for 10 days quo die every 28 days, that dosing regimen generating exposures at or near the anticipated expected therapeutic range - (ii) late in the first cycle (nadir around 28 days) which limits a retreatment on a 28 day cycle.

Objectives

- To develop a population pharmacokinetics (PK) /pharmacodynamics (PD) model describing the time course of platelets after repeated RG7112 administrations and to identify doses and dosing regimens that would maintain the exposure into the therapeutic range while limiting the occurrence of TCP in Phase Ib.

Materials & Methods

Dataset of platelet measurements

- Platelets data were collected on 102 patients receiving RG7112 doses in three multiple ascending dose studies. The administrations were performed on a 28 days cycle basis, with drug given either every days during 10 days (N=70, 30 mg to 3900 mg), every days during 5 days (N=22, 2500 mg), or twice a day during 10 days (N=10, 30 mg to 1700 mg). A total of 21 platelet measurements were planned per patient from the screening period to the end of Cycle 6. Additional unscheduled platelet data were also collected if required by the patient state.

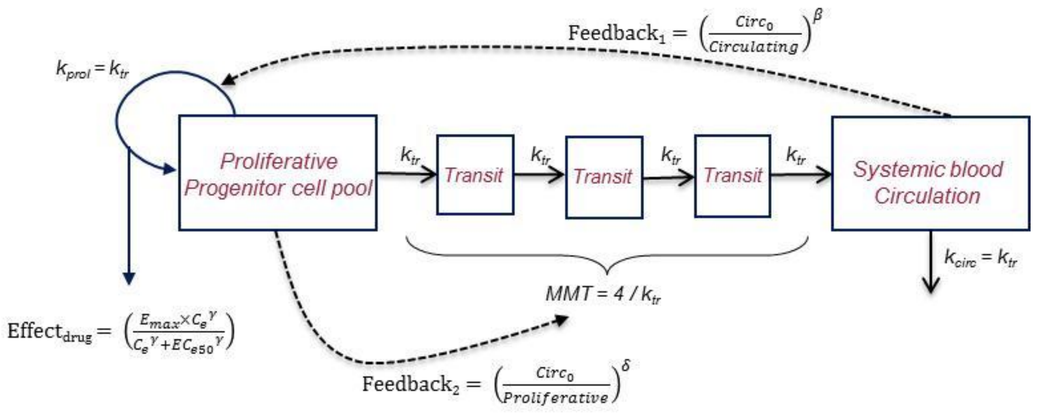
Population PK model

- A population PK model was previously built on concentration data collected on the same patients. Data were best described by a two-compartment model with a zero order followed by a first order absorption rate. A very large between-patient variability was detected on the apparent clearance (78%) and within occasion variability on the absorption parameters (~50%) were also estimated. The estimated effective half-life is around 1.4 days.

Population PKPD modeling

- A semi-mechanistic model was used to describe the platelet time course. This model has originally been proposed by Friberg et al [1] to model chemotherapy-induced myelosuppression and has been extended in-house by the pre-clinical M&S group to analyze platelet changes in different species receiving RG7112 and other drugs [2]. It involves 5 compartments to link the progenitors in bone marrow to platelets in circulation via a maturation process and two feedback mechanisms: one from the circulating platelets to proliferative compartment and one from the proliferative compartment to the maturation compartments (see Figure 1). That model integrates also the whole concentration time profile via an effect compartment to account for a potential accumulation of the drug at the site of action, as suggested by the sustained TCP observed in some patients. Lastly, it is assumed that the drug inhibits the rate of platelet synthesis.
- A non-linear mixed effect approach, using NONMEM 7.1 (FOCE INTER method) was used to characterize the PK / platelet time course relationship of RG7112. A sequential PK/PD approach was used, dealing with the individual PK parameter estimates as covariates in the platelets modeling process. Model performance was then assessed using both goodness of fit plots and posterior predictive check.

Figure 1: Semi-mechanistic platelet model



Dose and Dosing regimen selection

- For different daily doses (1500 mg to 5000 mg) and regimens (28 day cycles with daily doses during 3, 5, or 10 days), we investigated by simulation the tradeoff between the percentage of patients with TCP in the first cycle and the percentage of patients above a given threshold of exposure for anti-tumor activity. For each of the doses and dosing regimens, both percentages were computed based on a simulated database composed of 10000 patients.

Conclusion

- A robust model of the relationship between the PK of RG7112 and its effect on platelet time course has been developed.
- This model shows good predictive performance. It provides a robust quantitative tool to support the dose and dosing regimen selection for future studies.

References

- 1. Friberg L. et al. J Clin Oncol. 2002 Dec 15;20(24):4713-21.
- 2. Meille C. et al. PAGE 21 (2012) Abstr 2446.

Results

PKPD model

The parameter estimates for the PKPD model are presented in Table 1. The minimization was successful but no variance covariance matrix was obtainable. Some basic goodness of fit plots are given on Figure 2, as well as some individual fits on Figure 3, showing the good performance of the model to describe the data, especially around the nadir of the platelet concentrations.

Table 1. Parameter estimates

	Value	Inter subject variability (%)
Emax (-)	0.79	-
EC_{50} (mg/L)	5.72	59%
MMT (days)	11.20	42%
β (-)	0.20	50%
K_{e0} (day^{-1})	0.0326	80%
δ (-)	0.13	47%
γ (-)	1.13	67%
Prop_error (%)	27%	-

Figure 2. Diagnostic Plots

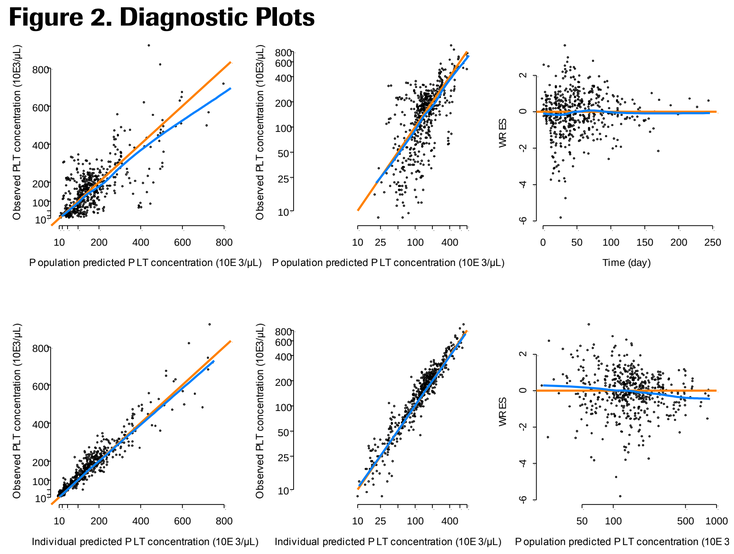
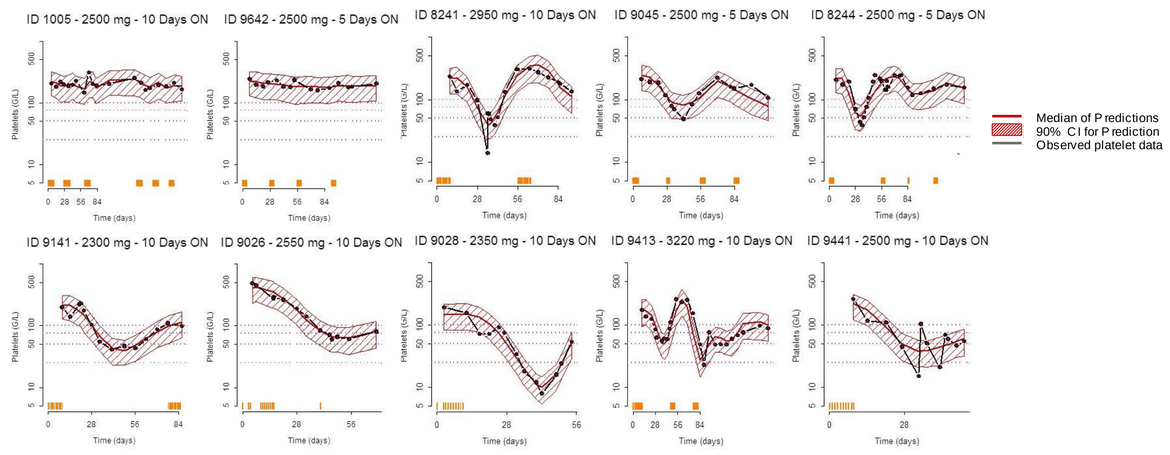


Figure 3. Individual observed and predicted platelet time course. The horizontal dotted lines at 100, 75, 50 and 25 G/L correspond to the level of platelet concentrations for Grade 1, 2, 3 and 4 respectively. The orange vertical lines represent drug administrations.



Posterior Predictive Check

- The model was used to predict, for 3 different doses and dosing regimens, the percentage of patients having their platelet concentrations lower than 100 G/L (Grade 1 TCP) at the end of Cycle 1. Those percentages are very close to the ones observed in our current database, as shown in Table 2, demonstrating (i) the ability of the model to reproduce the current observations in terms of occurrence of TCP and (ii) the possibility to use it to simulate the occurence of TCP with respect to different dosing scenarios.

Table 2. Comparison of the predicted and observed percentages of patients with Grade 1 at the end of Cycle 1.

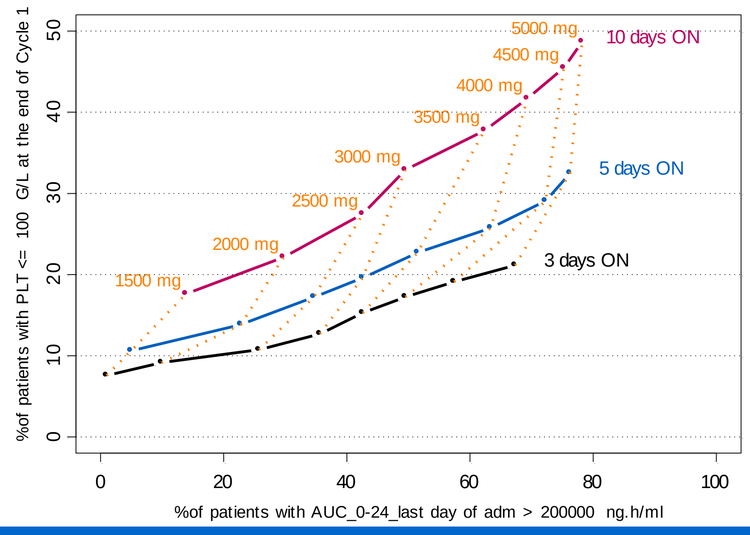
	5 Days on 2500 mg	10 Days on 1500 mg	10 Days on 2500 mg
Number of patients in the database	21	12*	26**
Observed %PT with PLT ≤ 100 G/L (Cycle 1) 90% CI	19 % [9% - 36%]	17%* [6% - 40%]	23%** [12% - 39%]
Predicted %PT with PLT ≤ 100 G/L (Cycle 1) 90% PI	17 % [5% - 29%]	17% [4% - 33%]	27 % [15% - 40%]

* Extension to range [1000 – 2000 mg] in the current database to increase the number of patients
** Extension to range [2000 – 3000 mg] in the current database to increase the number of patients

Dose and Dosing regimen selection

- Figure 4 summarizes the simulated tradeoffs between the percentage of patients with TCP at the end of Cycle 1 and the percentage of patients having their exposure at the last day of treatment higher than 200000 ng.h/ml, this threshold being determined by the clinical team as a level of exposure needed for anti-tumor activity.

Figure 4. Tradeoff between safety and efficacy criteria with respect to different dosing scenarios



- This graph allows to select, for a given acceptable percentage of patients with Grade 1 TCP, the best dose and dosing regimen maximising the efficacy criterion.
- For example, for less than 20% of patients with TCP, 4500 mg daily of RG7112 during 3 days would provide the best benefit/risk ratio.

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