Dosing Regimen selection supported by population PKPD model of thrombocytopenia

Christophe Meille[1], Nelson Guerreiro[1], Claire Fabre[1] and Astrid Jullion[1]

[1]Novartis, Basel, Switzerland

Objectives

- To develop a PK/PD model describing the longitudinal time-course of platelet (PLT) changes in patients treated with the p53-HDM2 protein-protein interaction inhibitor HDM201
- To apply a methodology to identify an optimized dosing regimen that could be tolerated for at least six treatment cycles

Background

- Phase I study in patients (n=101) with p53 wild-type solid tumors:
  - 1623 PK and 1385 PLT observations
  - platelet transfusions and HDM201 dosing events
- Oral regimens tested : Q3W, day 1 and day 8 in a 4W cycle, QD 2Won/2Woff, and QD 1Won/3Woff
- Delayed thrombocytopenia is the primary dose limiting toxicity resulting in dose reductions and/or interruptions.
- Efficacy is assumed to be regimen independent [1]

Methods

- PK and PLT models were established in a two-step approach using non-linear mixed-effects modeling implemented in Monolix 2016R1
- Original methodology [2] was extended to integrate impact of inter-individual variability (IIV)
- **Optimization criterion** was defined as the maximum total dose per cycle while having the proportion of Grade 4 thrombocytopenia during 6 cycles less than 25%
- The following steps were applied:
  1. Define a set of **140 dosing regimens** for a 28 day cycle (daily dose from 10 mg to 500 mg and number of daily administrations from 1 to 14)
  2. Simulate platelet profiles for 500 virtual patients over 6 cycles
  3. Derive for each dosing regimen the total dose per cycle and the compliance to the safety constraint

Results

PK model

- One-compartment with a delayed parallel zero- and first-order absorption process, and linear clearance (*Cl/F*).

Table 1 PK parameters

	r	*T1 (h)*	*T2 (h)*	*Tk0 (h)*	*ka (1/h)*	*V/F (L)*	*Cl/F (L/h)*	*Beta_V*
Estimate	0.753 (4)	0.688 (5)	0.410 (2)	1.105 (7)	1 (21)	120 (4)	6.936 (6)	0.855 (14)
IIV	-	-	-	-	1.346 (12)	0.333 (9)	0.482 (9)	-

Mean estimates with relative standard error (%)

PD model

- PK/PD model for thrombocytopenia was modified from Friberg et al. (2002) [3] to:
  - include a drug action decoupled from feedback
  - add an indirect drug effect on feedback through an effect compartment.
- PLT transfusion events were implemented as 0.5h infusions with estimation of amount and PLT half life

$$\frac{dE}{dt} = ke0 \cdot C - ke01 \cdot E \qquad E(0) = 0 \qquad EP1 = kr1D \cdot C$$

$$\frac{dP1}{dt} = ktrP \cdot (sfbkP - EP1) \cdot P1 - ktrP \cdot P1 \qquad P1(0) = \frac{PLTz}{ktrP} \cdot KTR12 \qquad KTR12 = \frac{\log(2)}{T12}$$

$$\frac{dP2}{dt} = ktrP \cdot P1 - ktrP \cdot P2 \qquad P2(0) = \frac{PLTz}{ktrP} \cdot KTR12 \qquad ktrP = \frac{4}{MMTP}$$

$$\frac{dP3}{dt} = ktrP \cdot P2 - ktrP \cdot P3 \qquad P3(0) = \frac{PLTz}{ktrP} \cdot KTR12$$

$$\frac{dP4}{dt} = ktrP \cdot P3 - ktrP \cdot P4 \qquad P4(0) = \frac{PLTz}{ktrP} \cdot KTR12$$

$$\frac{dP5}{dt} = ktrP \cdot P4 - KTR12 \cdot P5 + u(t) \qquad P5(0) = PLTz$$

$$sfbkP = \left(\frac{PLTz}{P5} \cdot \exp(cfrP \cdot E)\right)^{(SPm + SPa \cdot \exp(cfr \cdot E) \cdot (1 - t^z/(t^z + t50^z)))}$$

$$u(t) = \frac{alp}{0.5} \quad tinf_j < t < (tinf_j + 0.5h) \quad for\ each\ PLT\ transfusion\ event\ j$$

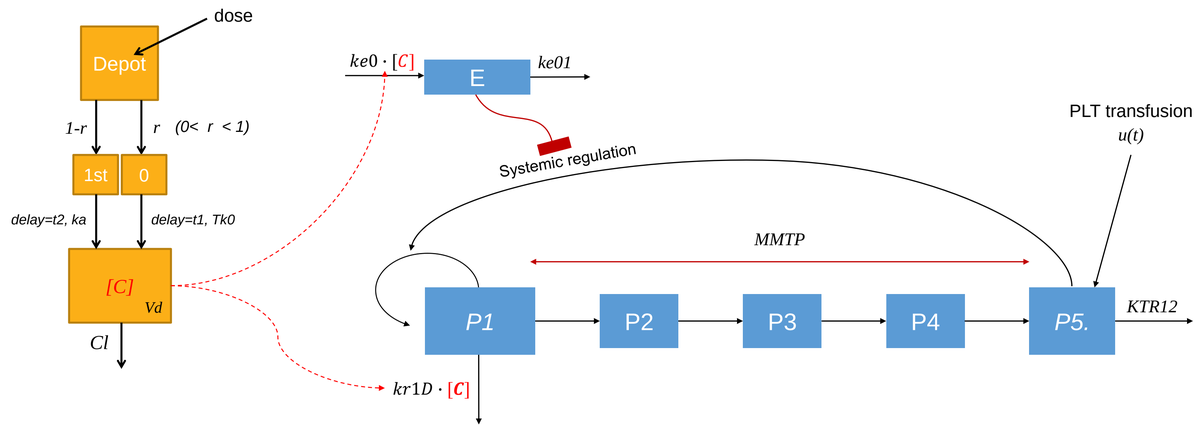
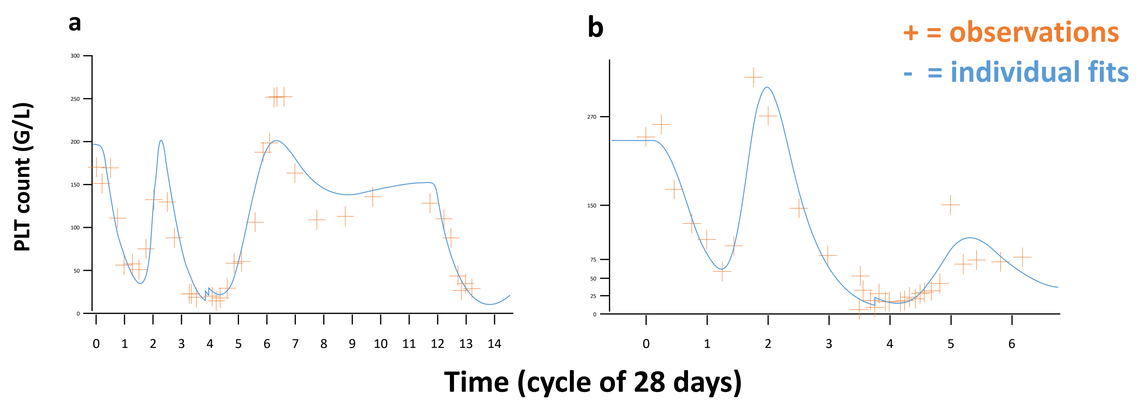


Table 2 PD parameters

	PLT (G/L)	*MMTP (h)*	*T12 (h)*	*sPa -*	*sPm -*	*alp (G/L)*	*cfrP (mL/ng)*	*ke0 (1/h)*	*cfr (mL/ng)*	*ilag (h)*	*t50 (h)*	*z -*	*H -*	*G -*	*kr1D (mL/ng)*	*ke01 (mL/ng)*
Estimate	241 (4)	294 (8)	126 (14)	0.76 (15)	0.08 (27)	10.2 (26)	-6.15 (21)	$1.19\ 10^{-6}$ (24)	5.44 (46)	5 (-)	719 (8)	7.46 (22)	1 (-)	0.93 (18)	$4.3\ 10^{-5}$ (94)	0.0003 (49)
IIV	0.62 (8)	0.27 (17)	0.25 (-)	0.24 (48)	1.06 (20)	0.25 (-)	0.2 (-)	0.84 (10)	0.39 (105)	0.1 (-)	0.38	0.1 (-)	0.26 (39)	0.1 (-)	0.2 (-)	1.19 (20)

Mean estimates with relative standard error (%)

Figure 1 Example of individual observed and predicted PLT time course



Optimization

Figure 2 Simulation matrix results

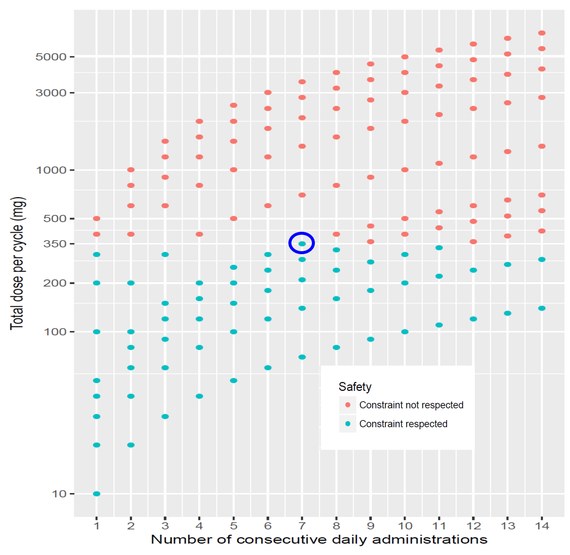
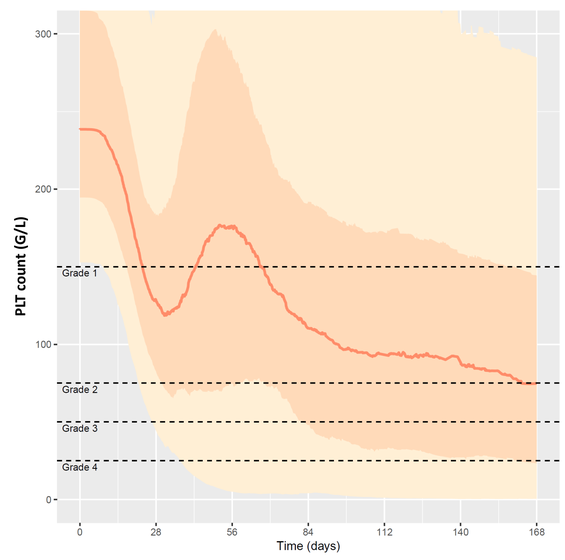


Figure 3 PLT profile with optimized dosing regimen



The optimized dosing regimen for consecutive daily administrations corresponds to a total dose per cycle of 350mg across 7 days with a daily dose of 50mg

Conclusions

- The methodology allows to suggest an optimal dosing regimen maximizing the total dose while mitigating the safety risk of severe thrombocytopenia
- A population PKPD approach with a safety endpoint (PLT) was used to optimize dosing regimen of HDM201 by simulating a set of 140 dosing regimens and taking into account impact of IIV on the safety constraint
- The metrics of “maximization of the total dose” could be replaced by “maximization of proportion of responders” using a PKPD model of efficacy endpoint

References

[1] PAGE 27 (2018) Abstr 8633 [www.page-meeting.org/?abstract=8633]
[2] Meille et al, 2016. “Revisiting Dosing Regimen Using Pharmacokinetic/ Pharmacodynamic Mathematical Modeling: Densification and Intensification of Combination Cancer Therapy.
[3] Friberg et al, 2002. “Model of chemotherapy-induced myelosuppression with parameter consistency across drugs.” J. Clin. Oncol. 20:4713–4721.

Poster presented at Population Approach Group Europe (PAGE) 29 May – 1 June, 2018, Montreux, Switzerland