

# Pharmacokinetic/Pharmacodynamic modeling of abexinostat-induced thrombocytopenia across different patient populations: application for the determination of the maximum tolerated doses in both lymphoma and solid tumour patients

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**Summary** *Background* In the clinical development of oncology drugs, the recommended dose is usually determined using a 3+3 dose-escalation study design. However, this phase I design does not always adequately describe dose-toxicity relationships. *Methods* 125 patients, with either solid tumours or lymphoma, were included in the study and 1217 platelet counts were available over three treatment cycles. The data was used to build a population pharmacokinetic/pharmacodynamic (PKPD) model using a sequential modeling approach. Model-derived Recommended Doses (MDRD) of abexinostat (a Histone Deacetylase Inhibitor) were determined from simulations of different administration schedules, and the higher bound for the probability of reaching these MDRD with a 3+3 design were obtained. *Results* The PKPD model developed adequately described platelet kinetics in both patient populations with the inclusion of two platelet baseline counts and a disease progression component for patients with lymphoma. Simulation results demonstrated that abexinostat administration during the first 4 days of each week in a 3-week cycle led to a higher MDRD compared to the

other administration schedules tested, with a maximum probability of 40 % of reaching these MDRDs using a 3+3 design. *Conclusions* The PKPD model was able to predict thrombocytopenia following abexinostat administration in both patient populations. A model-based approach to determine the recommended dose in phase I trials is preferable due to the imprecision of the 3+3 design.

**Keywords** Abexinostat · Thrombocytopenia · PKPD model · Recommended Dose · Simulation · Disease progression

## Introduction

The principal aim of a phase I clinical trial in oncology is to determine the recommended dose (RD) and/or the administration schedule of the investigated drug in order to continue drug development in phase II [1]. Therefore, phase I clinical trial protocols must be planned rigorously as this initial stage will have considerable influence throughout drug development [2, 3]. Phase I trial designs in current use can be divided into three types: rule-based designs (e.g. the classical 3+3 design), model-based designs (e.g. continuous reassessment method) and designs for trials of combined agents [1, 4–8]. Of these, the classical 3+3 design is the most widely used [1, 4–6, 8, 9].

For cytotoxic agents, dose escalation is driven by toxicity, as the highest safe dose is assumed to be the most efficacious. This assumption is supported by pre-clinical models and clinical experiments [10] that have demonstrated that toxicity is a surrogate endpoint for efficacy [1]. Chemotherapy-induced myelosuppression, and subsequent thrombocytopenia (TCP), has become

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an increasingly major dose-limiting toxicity (DLT) [11]. TCP may lead to dose reduction or dose delay and can also cause major complications (including bleeding and death) [12]. The relationship between haemorrhage and the extent and/or duration of TCP is well known [13], but its significance can differ between solid tumour patients and patients with acute leukemia or lymphoma [14–16]. TCP is a frequent DLT of Histone Deacetylase Inhibitors (HDACi) [17–20], such as abexinostat (S-78454), a new HDACi currently at the phase II stage for the treatment of lymphoma [21]. Our previous research demonstrated that TCP was frequently observed and limited dose-escalation in two different phase I clinical studies including solid tumour patients treated by abexinostat [22]. In this previous study a semi-mechanistic pharmacokinetic/pharmacodynamic (PKPD) model of TCP [22] was built and simulations were performed using this model to define the optimal administration schedule for solid tumour patients. The amended protocol favoured a new administration schedule (4 days ON, 3 days OFF every week of a three week-cycle [4ON3OFF]), which was predicted to decrease the depth of TCP. As a result, the dose-escalation process led to the definition of a higher MTD for this new administration schedule [22]. A clinical study including lymphoma patients was also amended, but the change in administration schedule (in favour of 4ON3OFF) did not lead to a higher MTD in this population. This showed that the previous PKPD model predictions were not reliable in lymphoma patients. One explanation for this difference in the PKPD relationship could be due to pathophysiological differences in lymphoma patients compared to solid tumour patients and/or differences in sensitivity to the design or administration schedules (disease-related explanation). Another explanation could be due to the weakness of the 3+3 design to determine the real MTD [23–25], leading to an erroneous observed MTD in the amended study. Investigation into the platelet time-course in patients in both clinical trials (including solid tumour and lymphoma patients) showed differences between the two groups. These included smaller platelet counts at inclusion for lymphoma patients and/or a decrease in the platelet count over time compared to solid tumour patients. The first aim of our study was to refine the previously developed PKPD model describing abexinostat-induced TCP in patients with solid tumours by including lymphoma patients in the analysis, in order to accurately predict their platelet kinetics and determine the safest dosing regimen. The second aim was to simulate from the PKPD model to determine the model-derived recommended doses (MDRD) for both populations under different administration schedules.

The third aim was to assess the ability of a 3+3 design to accurately determine the MDRD.

## Materials and methods

### Clinical studies

The results presented here include data from four studies (Table 1) performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Seoul, 2008. Protocols were approved by independent ethic committees. All patients provided written informed consent before inclusion in the study.

Patients with solid tumours were included in the PCYC-402 and CL1-78454-002 phase I clinical studies [26]. Patients with lymphoma were included in the PCYC-403 and CL1-78454-001 phase I/II clinical studies.

### Platelets samples and modeling datasets

Blood samples were obtained to assess haematological toxicity and in particular platelet profiles over time (Table 1). Three different datasets were selected from the present study using only data from the first three cycles of treatment (approximately 60 days), as the samples from later cycles were few and provided limited additional information. Of the 125 patients available from the four clinical studies, 95 and 30 patients were randomly selected for inclusion in the “*Building dataset*” and “*Advanced internal evaluation dataset*”, respectively; data from all patients constituted the “*Final dataset*” (Table 1).

### Modeling strategy

Platelet-time profiles were analyzed using nonlinear mixed effect modeling (population approach) [27], with a sequential PKPD approach [28], in NONMEM 7.2 (GNU fortran 95 compiler). Empirical Bayesian Estimates (EBE) of individual PK parameters (obtained from the POSTHOC analysis in NONMEM) derived from the previously evaluated PK model [22] of abexinostat were used as the fixed PK parameters during subsequent PD modeling. PD parameters were estimated in NONMEM 7.2 using the ADVAN 6 subroutine and the FOCE-I estimation method.

Several drug effects were tested in this model (Fig. 1) such as a linear ( $E_{Drug1} = Slope \cdot Conc$ ), Imax ( $E_{Drug2} = \frac{IMAX \cdot Conc}{IC_{50} + Conc}$ ) or full sigmoid Imax model ( $E_{Drug3} = \frac{IMAX \cdot Conc^{Hill}}{IC_{50}^{Hill} + Conc^{Hill}}$ ), where *Slope* is the patients’ sensitivity to abexinostat hematotoxicity ( $\mu\text{g/mL}^{-1}$ ), *IMAX* the intrinsic activity, *IC<sub>50</sub>* the potency, *Hill* the sigmoidicity coefficient, and *Conc* the concentration in abexinostat ( $\mu\text{g/mL}$ ). Improvements on the previous PKPD structural model (Fig. 1) were investigated using the *Building*

**Table 1** Summary of the four clinical trials in solid tumour and lymphoma patients; description of the data included in the *Building dataset* and *Advanced internal evaluation dataset*. The *Final dataset* includes both the Building and Advanced Internal evaluation datasets

Clinical Study	PCYC-402	PCYC-403	CL1-78454-001	CL1-78454-002
Phase	I	I/II	I/II	I
Indication	Solid tumours	Lymphoma	Lymphoma	Solid tumours
Administration schedules	• Days 1–7, 15–21 • Days 1–5, 15–19 • Days 1–5, 8–12, 15–19	• Days 1–7, 15–21 • Days 1–5, 15–19 • Days 1–5, 8–12, 15–19	• Days 1–14 • Days 1–5, 8–12 • Days 1–4, 8–11, 15–18	• Days 1–14 • Days 1–4, 8–11, 15–18
Dose escalation	30–75 mg/m <sup>2</sup> BID or TID 4–6 h apart	30–60 mg/m <sup>2</sup> BID 4–6 h apart	30–60 mg/m <sup>2</sup> BID 4–6 h apart	30–105 mg/m <sup>2</sup> BID 4–6 h apart
Cycle	4 weeks	4 weeks	3 weeks	3 weeks
Sampling times	• Pre-dose, days 1, 8, 15, 22 during cycle 1 • Days 1, 15 for cycle 2 • Day 1 for later cycles	• Pre-dose, days 1, 8, 15, 22 during cycle 1 • Days 1, 15 for cycle 2 • Day 1 for later cycles	• Pre-dose, days 1, 4, 5, 8, 12, 15, 18 for cycle 1 • Days 1, 8, 15 for later cycles	• Pre-dose, days 1, 4, 8, 12, 15, 18 for cycle 1 • Days 1, 8, 15 for later cycles
Building dataset				
• Patients (n=)	• 23	• 22	• 24	• 26
• Platelets samples (n=)	• 158	• 138	• 322	• 307
• Follow-up period (med [min-max]) in days	• 42.95 [0–88.02]	55.89 [0–84.03]	62.97 [0–70.17]	57.02 [0–92.04]
Advanced internal evaluation dataset				
• Patients (n=)	• 11	• 3	• 7	• 9
• Platelets samples (n=)	• 83	• 23	• 82	• 104
• Follow-up period (med [min-max]) in days	42.17 [0–88.05]	57.90 [0–60.02]	35.98 [0–63.36]	56 [0–70.13]

*dataset* [22]. A second feedback mechanism affecting the mean transit time (MTT) parameter was also tested in order to quicken/slow down the bone marrow in case of thrombocytopenia/thrombocytosis: the delta feedback parameter ( $\delta$ ):  $MTT = \frac{(n+1)}{k_{tr}} \cdot \left(\frac{BASE}{CIRC}\right)^\delta$  [29, 30]. To account for the observed differences in platelet count at inclusion (BASE) between both populations, two different baseline parameters ( $BASE_{0\ ST}$  for solid tumour patients, and  $BASE_{0\ LY}$  for lymphoma patients) were tested. Furthermore, the slight decrease in platelets over treatment cycles observed in some patients was taken into account by the addition of disease progression (impaired bone marrow) on the baseline parameter. Several disease progression models leading to a decrease of the baseline parameter with time were tested: either a linear  $BASE = BASE_0 - Slope_{DP} \cdot t$  or an Imax disease progression model  $BASE = BASE_0 \frac{IMAT \cdot t}{IT_{50} + t}$ , where  $BASE_0$  is the baseline value at inclusion (i.e.  $BASE_{0\ LY}$  or  $BASE_{0\ ST}$ ) and  $t$  the time (in days) since the first abexinostat administration.

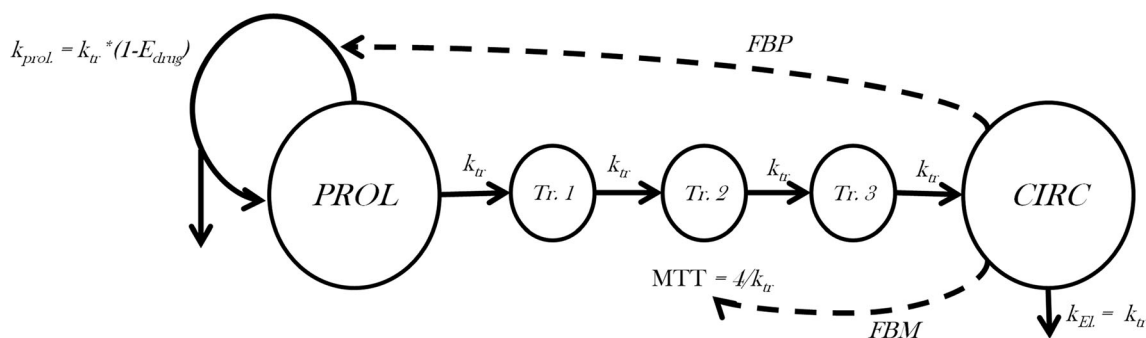
Inter-individual variability (IIV) was considered to have a log-normal distribution for all parameters except the *IMAT* parameter, for which a normal distribution was assumed. Finally, as patients were treated over several treatment cycles, inter-occasion variability (IOV) was tested on each of the PD parameters to improve the quality of the statistical model. The residual variability was modelled using a combined additive and proportional model, as this was the best description of the residual error in the original PKPD model [22].

## Model selection

Discrimination between hierarchical models was based on the objective function value (OFV) of NONMEM using the Likelihood-Ratio-Test (LRT). An OFV difference greater than 3.84 corresponding to a significance level of 5 % was used to discriminate between two nested models with one parameter difference. Model development was guided by precision in parameter estimates, visual inspection of the classic goodness-of-fit plots (GOFs), and normalized prediction discrepancy errors (NPDE) [31, 32]. Five hundred simulations of the *Building dataset*, based on the dose regimen and sampling time points of each patient were performed using the PD parameter estimates in order to compute NPDE. These were plotted *versus* time and *versus* population prediction (PRED) in order to identify a possible bias in the model. The best model according to the LRT, acceptable parameter precision supported by the GOFs and NPDE was finally selected and named “*Intermediate PKPD model*” in the present work.

## Advanced internal model evaluation

Individual Visual Predictive Checks (VPC) [33, 34] and NPDE [31, 32] were used to evaluate the ability of the *Intermediate PKPD model* to describe and predict external data. Five hundred simulations, based on the dosing regimen and sampling time points of the 30 patients included in the *Advanced internal*



$$\frac{dPROL}{dt} = k_{prol} \cdot (1 - E_{drug}) \cdot FBP \cdot PROL - k_{tr} \cdot FBM \cdot PROL$$

$$\frac{dTr\ 1}{dt} = k_{tr} \cdot FBM \cdot PROL - k_{tr} \cdot FBM \cdot Tr\ 1$$

$$\frac{dTr\ 2}{dt} = k_{tr} \cdot FBM \cdot Tr\ 1 - k_{tr} \cdot FBM \cdot Tr\ 2$$

$$\frac{dTr\ 3}{dt} = k_{tr} \cdot FBM \cdot Tr\ 2 - k_{tr} \cdot FBM \cdot Tr\ 3$$

$$\frac{dCIRC}{dt} = k_{tr} \cdot FBM \cdot Tr\ 3 - k_{El.} \cdot CIRC$$

$$E_{drug} = \frac{IMAX \cdot Conc}{IC_{50} + Conc}$$

$$FBP = \left(\frac{BASE}{CIRC}\right)^\gamma \quad FBM = \left(\frac{BASE}{CIRC}\right)^\delta$$

If solid tumour patients :  $BASE = BASE_{0,ST}$

If lymphoma patients :  $BASE = BASE_{0,LY} - \frac{IMAT \cdot t}{IT_{50} + t}$

**Fig. 1** Semi-mechanistic PKPD model of thrombocytopenia, based on Friberg *et al.* [40]. PROL, Tr and CIRC represent the proliferation, transit and circulation compartment. BASE is the platelet value at inclusion. FBP and FBM represent the feedback on proliferation and maturation

respectively. MTT is the mean transit time. the drug effect ( $E_{drug}$ ) affects the constant rate on proliferation ( $k_{prol}$ ).  $k_{tr}$  and  $k_{El.}$  are the rate constants of transit and elimination respectively. to avoid identifiability issues,  $k_{prol}$  was set to be equal to  $k_{tr}$  and  $k_{El.}$ .  $t$  denotes the time, in days

*evaluation dataset*, were performed using both the PK and PD parameter estimates of the *Intermediate PKPD model*. By definition, NPDEs follow a standard normal distribution, consequently a Kolmogorov-Smirnov test was performed [31, 32].

**Final PKPD model**

The *Final dataset*, including all patients, was analysed to re-estimate the PD parameters without modifying the structural or statistical models. NPDE *versus* time and *versus* PRED plots for each patient population and a Kolmogorov-Smirnov test were performed to evaluate the *Final PKPD model*.

**Model-derived recommended doses (MDRD) determination for lymphoma and solid tumour patients**

In a standard 3+3 design, if two or more patients in a cohort of maximum six patients exhibit a DLT at the dose level studied, the dose-escalation is stopped. This dose level corresponds to the maximum tolerated dose (MTD) and the dose just below is defined as being the RD for subsequent phases [1, 5, 7]. Consequently, this threshold of 33.33 % (2/6 patients) of

DLT was used to determine the MDRD for different administration schedules and for each type of patient (lymphoma and solid tumours) during the simulations.

Simulations were performed using the *Final PKPD model*. The platelet-time course from 3000 patients with solid tumours and 3000 patients with lymphoma, treated with abexinostat over three cycles, were simulated (*i.e.* 500 cohorts of six patients for each population) every 20 mg starting from 20 mg up to 500 mg per day (once daily). The following administration schedules were tested:

- 14 days ON (treatment), 7 days OFF in a three-week cycle (14ON7OFF),
- 4 days ON, 3 days OFF every week of a three-week cycle (4ON3OFF),
- 5 days ON, 2 days OFF the first 2 weeks of a three-week cycle (5ON2OFF).

The sampling schedule for the platelet count was identical to that of the CL1-78454-001 clinical study (Table 1).

From the simulations the percentage of grade 4 of TCP (*i.e.* platelet count less than  $25 \times 10^9$  platelets per litre) was

computed. The MDRD was defined as the dose just below the one exceeding the 33.33 % threshold of toxicity.

DLT percentages at the MDRD in a 3+3 dose escalation design

Asymptotically (*i.e.* with an infinite number of patients) at the RD dose level, the probability of escalating to a higher dose (PRD) level is 100 %. For each administration schedule tested (*i.e.* 14ON7OFF, 4ON3OFF and 5ON2OFF), 500 cohorts of 6 patients with either solid tumours or lymphoma were simulated at the MDRD using the *Final PKPD model*. The PRD was calculated as the percentage of the 6-patient cohorts in which only zero or one patient underwent a DLT (*i.e.* thus leading to dose escalation).

Again, the sampling schedule for the platelet count was identical to that of the CL1-78454-001 clinical study (Table 1).

## Results

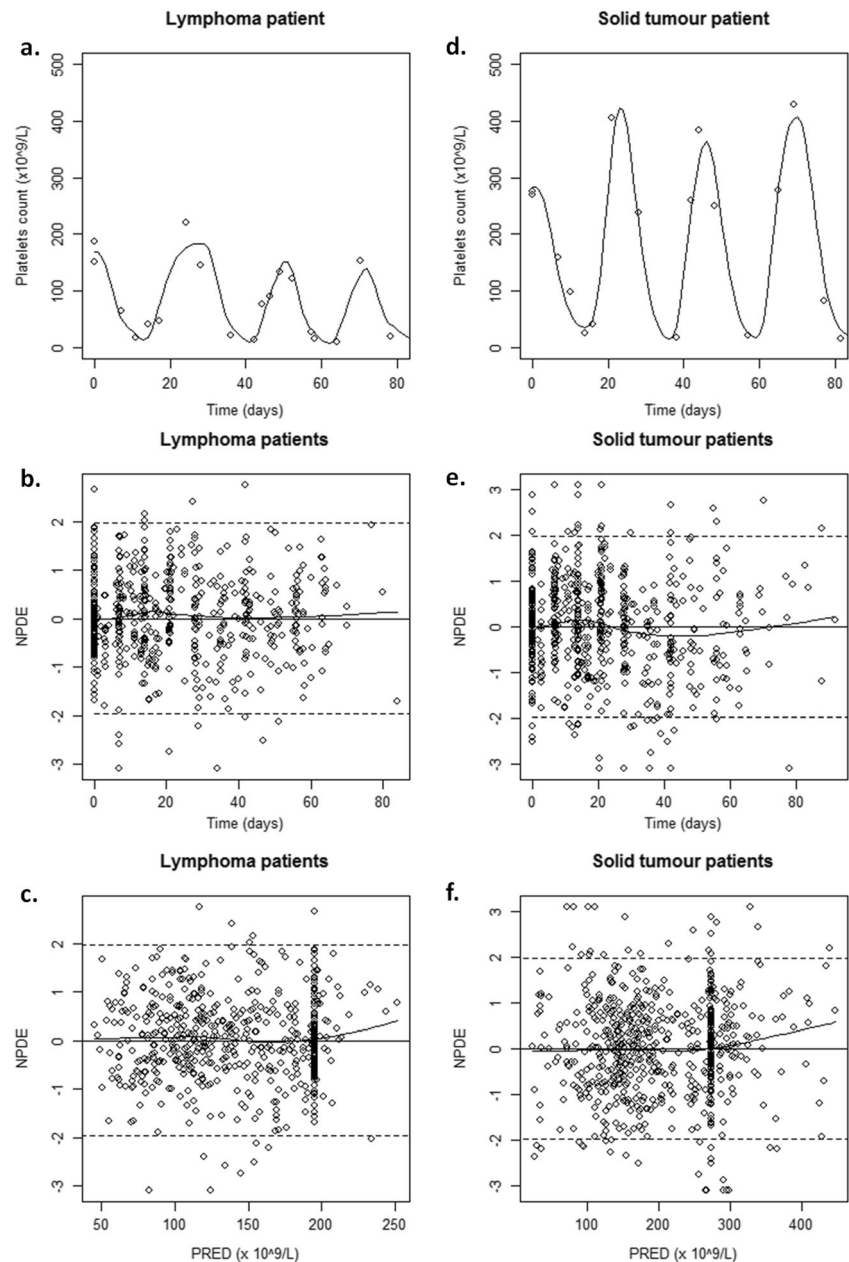
### Intermediate PKPD model

The *Building dataset* contained 925 platelet counts over the first 3 cycles of treatment in 95 patients (49 and 46 solid tumour and lymphoma patients, respectively) (Table 1). Several improvements were made to the previous PKPD model [22]. First, a feedback mechanism affecting the MTT was added to quicken/slow down the bone marrow maturation in case of thrombocytopenia/thrombocytosis (Fig. 1) [29, 30, 35, 36]. Secondly, the drug effect on the proliferation rate was best described using an Imax model, as previously described by Quartino *et al.* [29]. Two different baseline parameters of  $203 \times 10^9$  and  $274 \times 10^9$  platelets per litre for lymphoma ( $BASE_{0_{LY}}$ ) and solid tumour ( $BASE_{0_{ST}}$ ) patients were estimated, respectively. Finally, the addition of a disease progression model on the baseline parameter improved the description of

**Table 2** PKPD parameter estimates of the *Intermediate* and *Final PKPD models*, with Inter-Individual (IIV) and Inter-Occasion (IOV) Variabilities. Combined residual error model was comprised of an additive (a) and a proportional residual error model (b)

Models	Parameters	Population mean estimates (RSE)	IIV (RSE)	IOV (RSE)
Intermediate PKPD model ( $n=95$ )	IC <sub>50</sub> (( $\mu\text{g}/\text{mL}$ ) <sup>-1</sup> )	0.0787 (42.7 %)	67.5 % (15.8 %)	17.5 % (19.8 %)
	Imax	0.92 (21.1 %)	-	-
	MTT (h)	95.3 (2.1 %)	9.1 % (14.8 %)	-
	$\gamma$ (-)	0.515 (7.1 %)	8.4 % (57.2 %)	-
	$\delta$ (-)	0.188 (16.2 %)	27.4 % (30.9 %)	19.9 % (45.8 %)
	BASE <sub>0<sub>LY</sub></sub> ( $\times 10^9/\text{L}$ )	203 (6.2 %)	37.9 % (10.1 %)-	-
	BASE <sub>0<sub>ST</sub></sub> ( $\times 10^9/\text{L}$ )	274 (6.5 %)	-	-
	IT <sub>50</sub> (days)	64.2 (63.4 %)	-	-
	IMAT	108 (38.8 %)	71.4 % (37 %)	-
	a ( $\times 10^9/\text{L}$ )	14.3 (9.7 %)	-	-
	b (%)	19.2 (3 %)	-	-
	$\varepsilon$ -shrinkage (%)	17.6 %	-	-
Final PKPD model ( $n=125$ )	IC <sub>50</sub> (( $\mu\text{g}/\text{mL}$ ) <sup>-1</sup> )	0.0743 (30.4 %)	66.3 % (13.7 %)	30.4 % (18.5 %)
	Imax	0.881 (15.1 %)	-	-
	MTT (h)	95 (1.7 %)	8.7 % (13.6 %)	-
	$\gamma$ (-)	0.498 (5.4 %)	9.7 % (39.4 %)	-
	$\delta$ (-)	0.177 (12.1 %)	22.8 % (33.4 %)	22.4 % (16.1 %)
	BASE <sub>0<sub>LY</sub></sub> ( $\times 10^9/\text{L}$ )	195 (5.8 %)	39 % (8.5 %)	-
	BASE <sub>0<sub>ST</sub></sub> ( $\times 10^9/\text{L}$ )	273 (5.4 %)	-	-
	IT <sub>50</sub> (days)	68.2 (43.5 %)	-	-
	IMAT	101 (34.7 %)	84.2 % (35 %)	-
	a ( $\times 10^9/\text{L}$ )	13.5 (8.1 %)	-	-
	b (%)	19 (2.7 %)	-	-
	$\varepsilon$ -shrinkage (%)	18.5 %	-	-
RSE (%)	Relative Standard Error, calculated as $RSE=(\text{Standard Error}/\text{Final parameter estimate}) \times 100$			
IIV (%)	Inter-individual Variability, calculated as $IIV=(\omega_{IIV}) \times 100$			
IOV (%)	Inter-occasion variability, calculated as $IOV=(\omega_{IOV}) \times 100$			
n	Number of patients included in the dataset			

**Fig. 2** Internal evaluation of the *Final PKPD model*. individual platelet count predictions are shown over time for two representative lymphoma **a** and solid tumour **d** patients. *open circles* represent the observations and the *solid lines* the individual predictions. NPDE *versus* time and *versus* PRED are shown for lymphoma **b, c** and solid tumour **e, f** patients respectively. the *dashed lines* represent the 95 % prediction interval. the *solid curve* shows the trend curve



the platelet-time profiles in lymphoma patients. Disease progression was best described by an *Imax* model; characterised by  $IT_{50}$ , the time necessary to obtain half the maximum decrease (*IMAT*). *IIV* was estimated on all parameters except on *Imax* and  $IT_{50}$ .  $BASE_{0\ ST}$  and  $BASE_{0\ LY}$  shared the same *IIV*. *IOV* significantly improved the model only when estimated on  $\delta$  and  $IC_{50}$ . The *Intermediate PKPD model* parameter estimates are presented in Table 2. *GOFs* and *NPDE* were satisfactory (figures not shown). The *p*-value of the Kolmogorov-Smirnov test was approximately 0.13 indicating that the null hypothesis of a standard normal distribution for *NPDE* could not be rejected.

The *Intermediate PKPD model* was evaluated using data from 30 additional patients (Table 1). Individual *VPC* were satisfactory and *NPDE* showed the absence of any bias in the structural model (results not shown) indicating the ability of the *Intermediate PKPD model* to predict the individual platelet time-course of patients treated by abexinostat. However, the *p*-value of the Kolmogorov-Smirnov test was  $3.8 \times 10^{-5}$ , rejecting the null-hypothesis of normality.

#### Final PKPD model

Finally, the *PD* parameter estimates were re-estimated with the *Final dataset* (Table 1) containing 1217 platelet samples from

125 patients (56 and 69 lymphoma and solid tumour patients respectively) over three treatment cycles (Table 2). The *Final PKPD model* described the data well as shown in Fig. 2a and d NPDE versus TIME or versus PRED showed that the *Final PKPD model* had a good ability to describe and predict platelet time-course of both lymphoma (Fig. 2b and c) and solid tumour (Fig. 2e and f) patients treated with abexinostat. The *p*-value of the Kolmogorov-Smirnov test was 0.12, indicating that the null hypothesis of a standard normal distribution for the NPDE could not be rejected.

Model-derived recommended doses (MDRD) determination for both lymphoma and solid tumour patients

For the lymphoma patients, the MDRD were 80, 200 and 140 mg/day for the 14ON7OFF, 4ON3OFF and 5ON2OFF administration schedules, respectively (Fig. 3a). These MDRDs led to a cumulated dose of 1,120, 2,400 and 1,400 mg per cycle for the 14ON7OFF, 4ON3OFF and 5ON2OFF administration schedules, respectively. For the solid tumour patients the MDRD were 180, 440 and 280 mg/day for the 14ON7OFF, 4ON3OFF and 5ON2OFF administration schedules respectively (Fig. 3b). These MDRDs led to a cumulated dose of 2,520, 5,280 and 2,800 mg per cycle for the 14ON7OFF, 4ON3OFF and 5ON2OFF administration schedules, respectively.

DLT percentages at the MDRD in a 3+3 dose escalation design

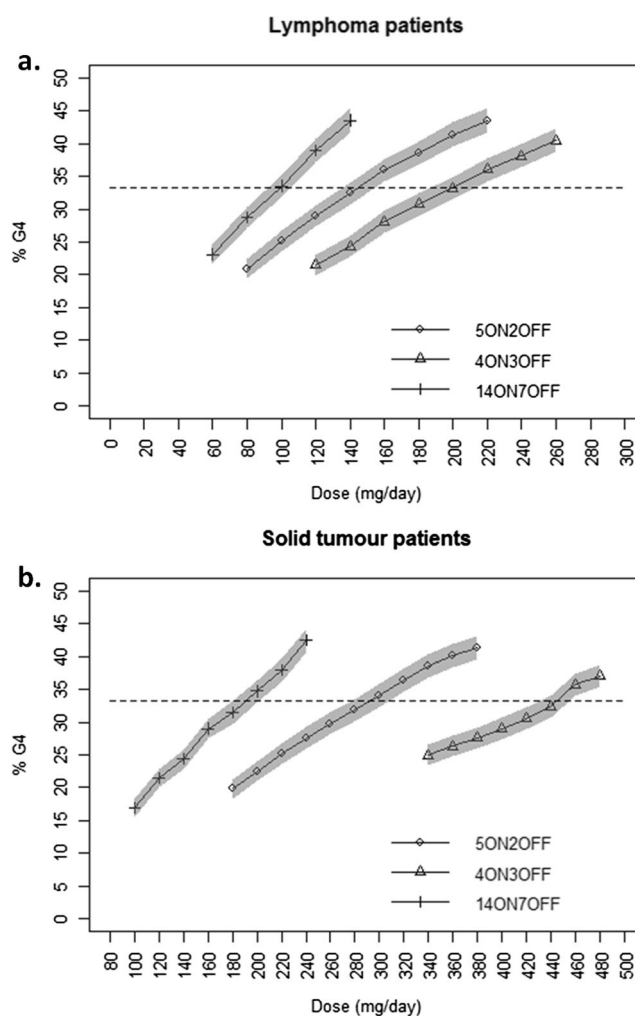
Asymptotically (*i.e.* with an infinite number of patients) at the RD dose level, the probability of escalating to a higher dose level is 100 %. However, simulations of a 3+3 design in lymphoma patients (*i.e.* 500 cohorts of six patients) showed that these probabilities were only 45.6, 36.6 and 36.2 % for the 14ON7OFF, 4ON3OFF and 5ON2OFF administration schedules, respectively (Fig. 4a–c). For solid tumour patients these probabilities were only 40, 39.8 and 39.6 % for the 14ON7OFF, 4ON3OFF and 5ON2OFF administration schedules, respectively (Fig. 4d–f).

## Discussion

TCP is the major DLT of HDACi such as abexinostat [17, 19, 22]. To determine the dose/toxicity relationship it is vital to both describe and predict the time-course of platelet counts in the entire study population. This study has refined the previously developed PKPD model [22] to adequately describe platelet profiles after administration of abexinostat in both patients with solid tumours and lymphoma (Fig. 1). The extended semi-mechanistic PKPD model was used to

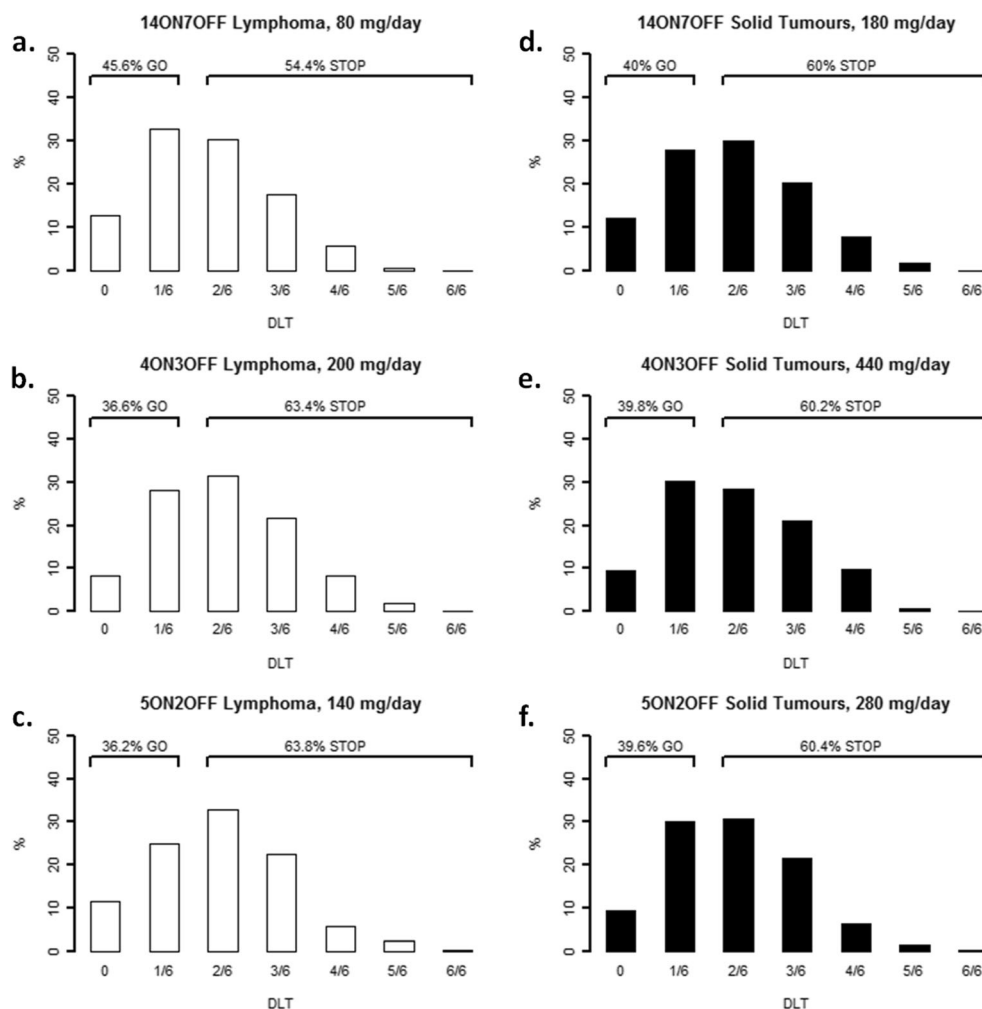
determine the MDRD for different administration schedules and patient populations using a simulation study. Finally, the ability of the 3+3 escalation design to properly determine the MDRD was evaluated using a simulation study.

Although the Kolmogorov-Smirnov test rejected the null-hypothesis of NPDE normality (*p*-value of  $3.8 \times 10^{-5}$ ) in the advanced internal evaluation step, the *Intermediate PKPD model* showed good predictability features after examining NPDE versus Time, PRED and QQ plots. As suggested by Comets *et al.* [37], the normality assumption test of the NPDE distribution is very powerful in case of a rich dataset and may be considered conservative. Indeed, the visual inspection of the NPDE graphs showed the descriptive and predictive ability of the model. In this study the *Advanced internal evaluation dataset* was probably too small (292 platelet counts from 30 patients) to enable a powerful Kolmogorov-Smirnov test.



**Fig. 3** Determination of the model-derived recommended doses (MRD) for both lymphoma **a** and solid tumour **b** patients. the *dashed lines* represent the threshold of 33.33 % (2/6 patients) of dose-limiting toxicity (DLT), which is a grade 4 thrombocytopenia. *open circle, triangle and dash* stand for the 5ON2OFF, 4ON3OFF and 14ON7OFF administration schedules respectively. *shaded areas* represent the 95 % prediction intervals

**Fig. 4** DLT percentages at the MDRD for both population (lymphoma and solid tumour patients in the white and black panels respectively), for each administration schedule (14ON7OFF a. and d./4ON3OFF b. and e./5ON2OFF c. and f.) in a 3+3 dose-escalation. GO is for the probability to escalate the dose and STOP is the probability to stop the dose escalation



Finally, the PD parameters were re-estimated using the whole dataset (1217 platelet counts from 125 patients treated according to six different administration schedules), leading to the *Final PKPD model*. GOFs, individual plots and NPDE versus Time or PRED (Fig. 2) showed that the model described the data well. Consequently, this *Final PKPD model* was able to describe and predict a larger and more heterogeneous population of patients, taking into account meaningful differences between solid tumours and lymphoma patients. Lymphoma patients had a lower baseline platelet count than solid tumour patients ( $195$  versus  $273 \times 10^9/L$ ), possibly due to a weakening of their bone marrow. The slight decrease in platelet counts over time observed in some patients was also accounted for by adding the effect of disease progression on this baseline parameter ( $BASE_{0LY}$ ). Disease progression was only observed and statistically significant in lymphoma patients. IOV from one treatment cycle to the other was added on  $IC_{50}$  and  $\delta$ , with population estimates of approximately 10 and 5 % respectively (Table 2).

Simulations were performed using the *Final PKPD model*. The MDRD were determined using a simulation approach for

each population and considered different administration schedules (Fig. 3). In comparison with the other administration schedules tested, the 4ON3OFF schedule was considered safer, as a higher dose could be administered to both populations of patients with an acceptable toxicity level. The duration (in days) of the first sequence of dose administration could partly explain these differences, as longer initial exposure to the treatment may lead to a stronger platelet decrease. The MDRD was approximately twice as high for the solid tumour patients compared to the lymphoma patients, despite administration schedule, reflecting the impact of the pathophysiology of lymphoma patients (lower platelet count at inclusion and decrease of platelet count over time).

The Observed Recommended Dose (ORD) associated with the 14ON7OFF administration schedule in CL1-78454-002 for patients with solid tumours was lower than the ORD associated with 4ON3OFF [22], which is consistent with Modeling & Simulations (M & S) predictions regarding their respective MDRDs (Fig. 3). In CL1-78454-001, involving lymphoma patients, the ORD were the same despite administration schedule, whereas M & S demonstrated that the



MDRD associated with the 14ON7OFF administration schedule was lower than that of the 4ON3OFF (Fig. 3). The fact that this difference was not observed in a clinical setting could partly be explained by the weakness and lack of sensitivity of the 3+3 design to discriminate across administration schedules. Changing dose schedule from 14ON7OFF to 4ON3OFF led to an increase of the MDRD of 260 mg/day in solid tumours *versus* 120 mg/day lymphoma, making it easier to detect.

Although the 3+3 design is predominantly used in phase I clinical trials, the determination of the MTD and also the RD tends to be erroneous as a result of using this design [23–25]. Our simulation study showed that for each administration schedule and for each population (Fig. 4), the maximum probability of reaching the MDRD, assuming that the actual RD was known, was approximately 40 % (only a single step of the 3+3 dose-escalation design was simulated). This leads to a 60 % minimum risk of stopping the dose-escalation process just before the actual RD is reached. Consequently, with the 3+3 design the probability of stopping the dose-escalation at each step is high, and therefore the probability of reaching the real RD is poor. Conversely, the small number of patients included at each step can lead to an erroneously high RD if these patients happen to have a high tolerance profile. In a 3+3 rule-based design, the decision to go up or to stop the dose escalation is only based on the information extracted from 3 to 6 patients at a particular dose level [1, 5, 38, 39]. Therefore, M & S is a useful tool to support the classical 3+3 design to determine the dose-toxicity relationship and guide the clinical development of a drug by taking into account all the information obtained throughout the dose-escalation process. The determination of the MDRD through simulations can be performed only after having built a PKPD model, and thus relies on the availability of PK and PD data. Nevertheless, such a model-based approach could be used at the end of a classical 3+3 dose escalation in order to determine the MDRD.

## Conclusion

TCP is the major dose-limiting toxicity of abexinostat in phase I clinical trials. The previous semi-mechanistic PKPD model of TCP in solid tumour patients treated by abexinostat [22] has been refined to predict the dose-toxicity relationship in a larger and more heterogeneous population including lymphoma patients. This PKPD model resulted in the development of an optimal administration schedule (4 days ON, 3 days OFF every week of a three week-cycle) associated with a model-based recommended dose of abexinostat of 200 and 440 mg per day for lymphoma and solid tumour patients, respectively. The weakness of the 3+3 design to properly determine the MTD, and therefore the RD, was demonstrated. The results

from this study have demonstrated the value of a model-based approach in the dose-escalation process to investigate the RD for future phase II trials.

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