

Hematological toxicity of abexinostat (S-78454, PCI-24781), a new histone

deacetylase inhibitor, in patients with advanced solid tumors or lymphoma :

influence of the disease-progression on the drug-induced thrombocytopenia

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Introduction

In a recent work, Modelling and Simulations was a useful support in the clinical development of abexinostat by allowing the determination of its safest administration schedule in patients with advanced solid tumors (Article in press in *Pharm Res*). In the present work, we aim at developing a semi-mechanistic PKPD model of thrombocytopenia, dose-limiting toxicity of abexinostat, taking into account differences between patients treated for either solid tumors or various types of lymphoma, notably the effect of disease progression on circulating platelet levels in patients with liquid tumors.

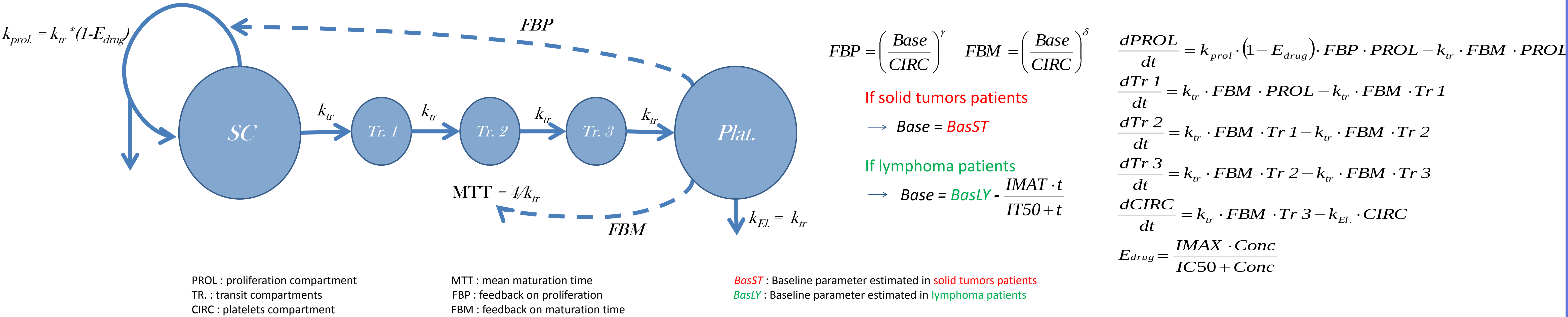
Materials & Methods

Data: Patients with either advanced **solid tumors** or **lymphoma** included in **4 Phase I clinical trials** were treated with **oral multiple dose of abexinostat**.

Clinical study	Clinical Phase	Indications	Patients (n=)		Platelet samples (n=)		Follow-up period med [min-max] (days)	
PCYC-402	Phase I	Solid tumors	23	11	158	83	42.95 [0-88.02]	42.17 [0-88.05]
CL1-78454-002	Phase I	Solid tumors	26	9	307	104	57.02 [0-92.04]	56.00 [0-70.13]
PCYC-403	Phase I	Lymphoma	22	3	138	23	55.89 [0-84.03]	57.90 [0-60.02]
CL1-78454-001	Phase I	Lymphoma	24	7	322	82	62.97 [0-70.17]	35.98 [0-63.36]

Information in bold/italic corresponded to the building/evaluation dataset

Model building: A sequential PKPD modelling approach, in compliance with the Individual PK Parameters (IPP) approach [1], was performed in **NONMEM 7.2** software, with **FOCEI**. Individual Empirical Bayesian Estimates of PK parameters (from a previous validated PK model) obtained using the POSTHOC method were input into a PKPD model of platelet dynamics, based on original Friberg *et al*'s one [2;3]. Improvements concerning disease progression were tested on baseline parameter. The Likelihood-Ratio-Test allowed the discrimination between hierarchical models. Model evaluation was based on standard goodness-of-fit plots, parameter precisions of estimation and Normalized Prediction Distribution Error (NPDE), based on 500 simulations [4].

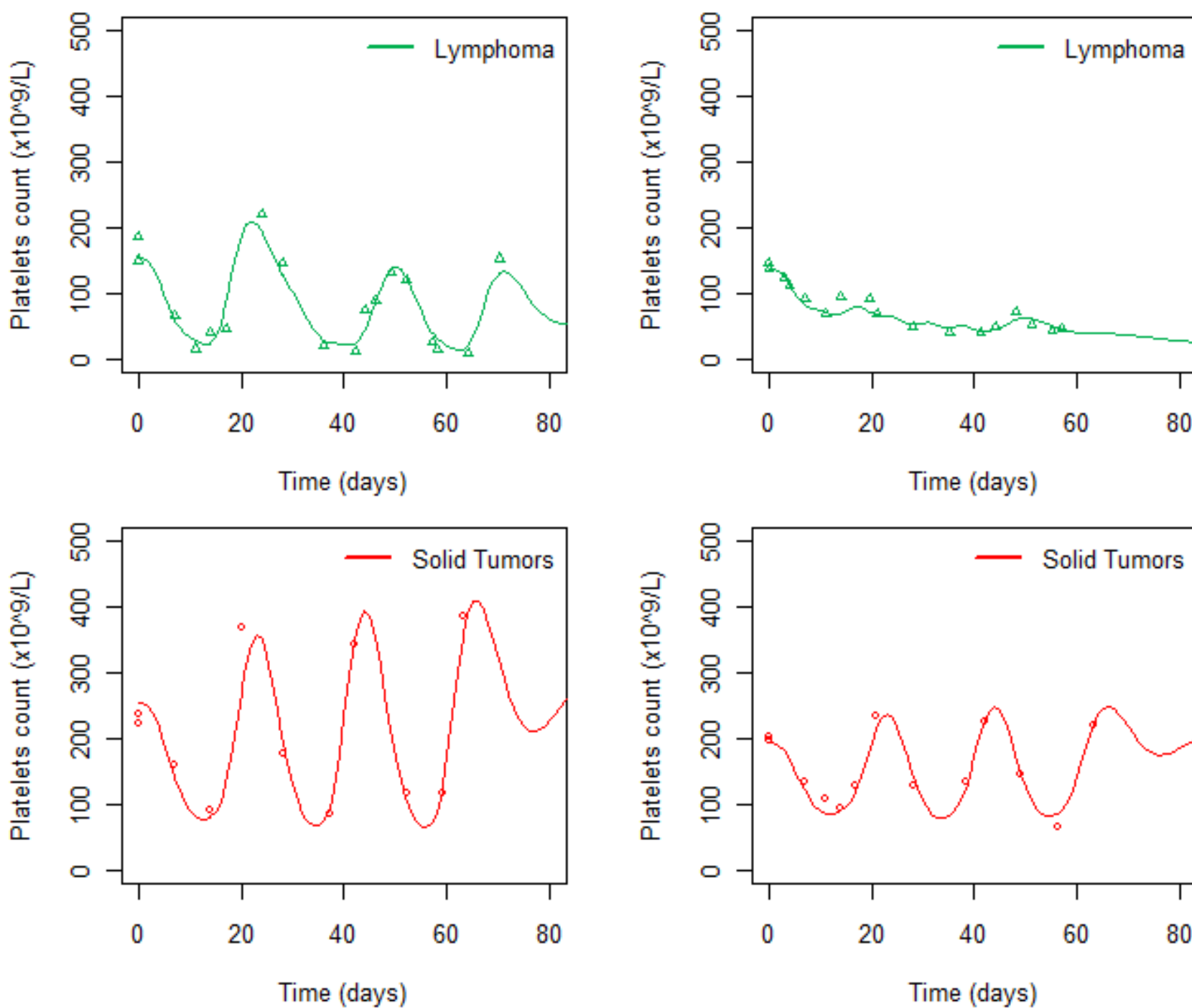


Results

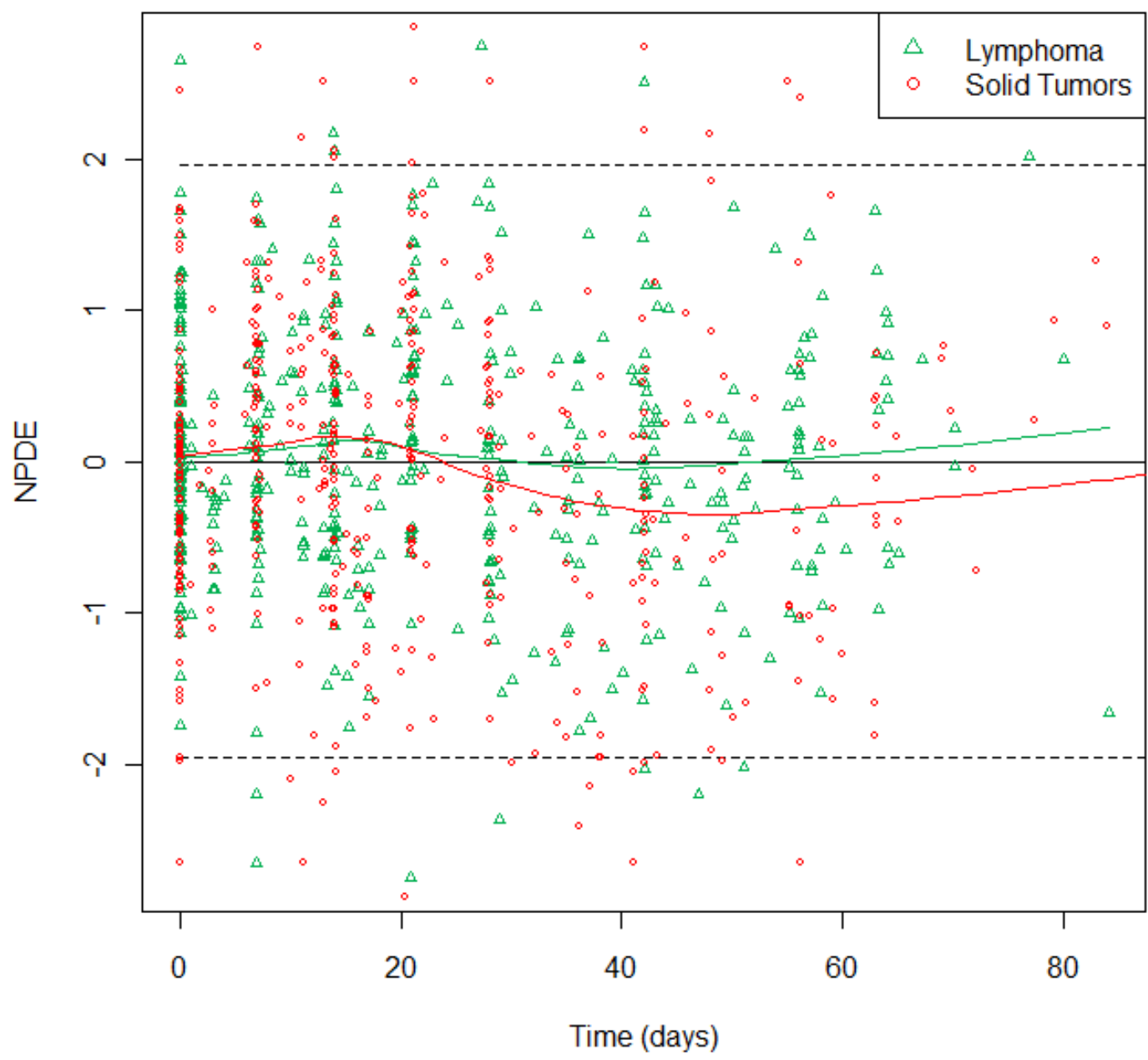
Final parameter estimates

Parameters	Estimates	RSE (%)	BSV (%)	RSE (%)	Sh. Std. (%)
IC ₅₀ (μg/mL) ⁻¹	0.1	45.7	65.1	15.1	17.4
I _{MAX}	1.04	24.5	/	/	/
MTT (hours)	95.23	2.2	9.4	15.8	35.6
γ	0.51	8	7.6	71.9	62.7
δ	0.19	18.6	28.3	26.3	41.4
BasST (x10⁹/L)	271.74	6.2	37.9	10.2	4
BasLY (x10⁹/L)	201.54	6.6	/	/	/
IT ₅₀ (days)	69.30	75.9	/	/	/
I _{MAT}	109.24	47.1	71	38	55.8
Add (μg/mL) ⁻¹	14.30	10.3	/	/	/
Prop (%)	21.14	2.6	/	/	/
Eps. Shrinkage (%)	14				

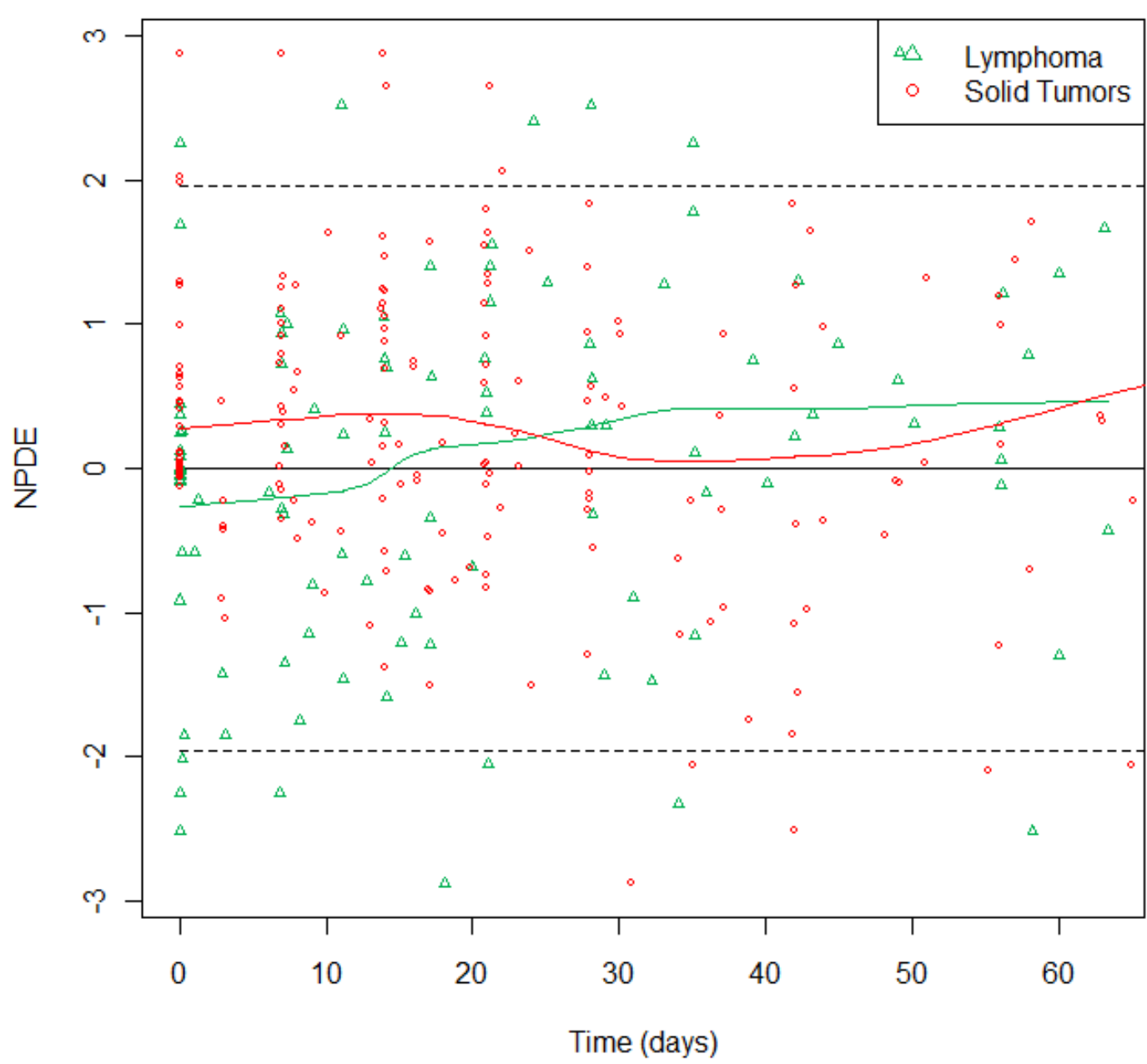
Individual predictions versus TIME of 4 representative patients



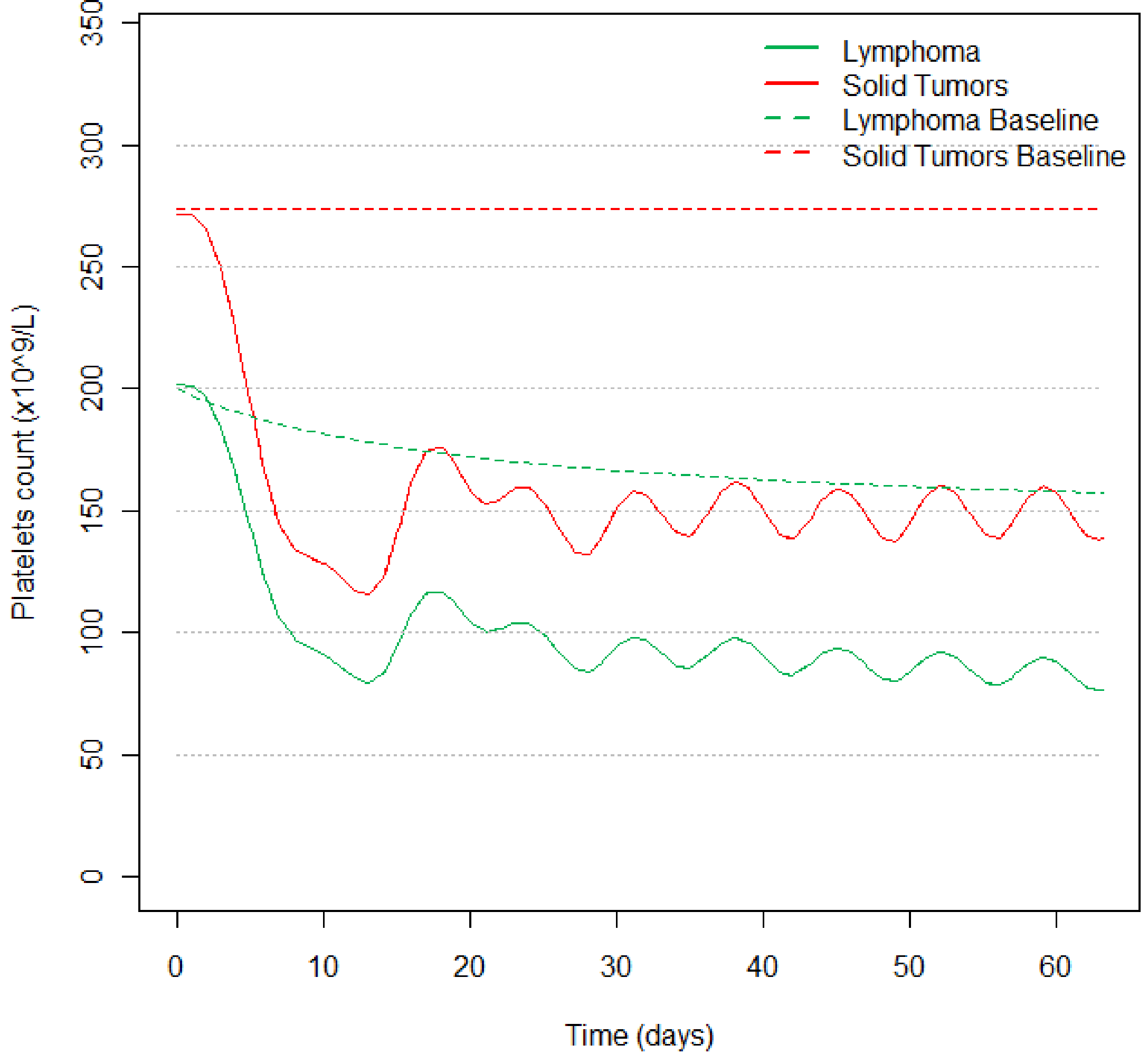
Internal evaluation by NPDE versus TIME



External evaluation by NPDE versus TIME



Population prediction (based on simulation) versus TIME for **lymphoma** or **solid tumors** patients, treated by abexinostat over 3 treatment cycles. Abexinostat was administered at the 90 mg/m² dose *bid*, the first 4 days of each week in a 3-week treatment cycle



Conclusion

A semi-mechanistic PKPD model able to predict toxicity in patients treated by abexinostat, particularly over the time by taking into account physiological or pathological characteristics of the bone marrow according to the patients' disease, was built. First, a feedback mechanism on MTT was added to quicken/slow down the maturation time of circulating platelets in cases of thrombocytopenia/thrombocytosis. Furthermore, the slight decrease observed in the platelet count over the time in lymphoma patients was modelled by adding an I_{max} disease progression effect on their *Base* parameter, mimicking a pathological effect.

In a recent work (article in press in *Pharm Res*), the 4-days ON/3-days OFF of each week of a 3-week treatment cycle was determined to be the safest administration schedule for patients with advanced solid tumors with a recommended dose of 90 mg/m² *bid*. However, noting the pathological evolution of platelets count over the time in lymphoma patients, a different optimal design could be envisaged in such patients' population and tested by simulations in a future work.

References

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- [4]. Brendel K, Comets E, Laffont C, et al: Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharm Res* 23:2036-49, 2006