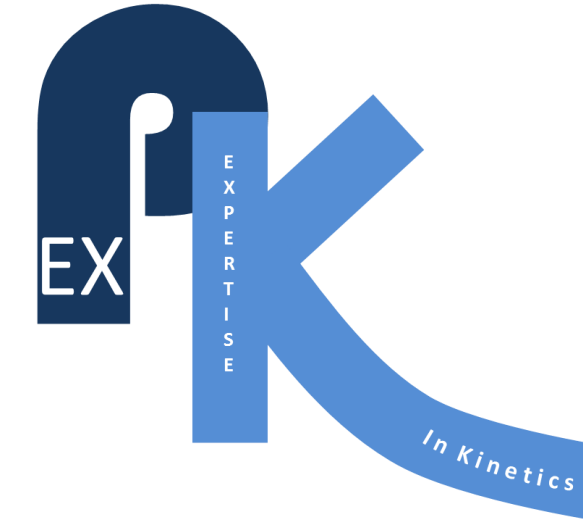


Population K-PD modelling of lymph node size in lymphoma patients treated with abexinostat, a histone deacetylase inhibitor (HDACi)



Katie Owens, Sylvain Fouliard, and Marylore Chenel
Department of Clinical Pharmacokinetics and Pharmacometrics
Institut de Recherches Internationales Servier
Suresnes, France



Introduction

The evaluation of the Objective Response Rate (ORR) in lymphoma patients is based on the assessment of various clinical measures [1-3]. One of the clinical measures assessed for response is lymph node size, recorded as the sum of the product of diameters (SPD). The analysis of multiple types of clinical measures in an integrated framework may improve the evaluation of the ORR in lymphoma patients. The objective was to develop a K-PD model to characterise the time course of SPD in lymphoma patients treated with abexinostat. The overall strategy is to integrate information on lymph node shrinkage data with other clinical measures of response to optimise the prediction of the ORR in lymphoma patients.

Methods

1. Study design and data

❖ SPD data were available for 121 patients from two phase I and II clinical studies indicated for:

- Chronic Lymphocytic Leukaemia (CLL)
- Hodgkin's Disease (HD)
- Non-Hodgkin lymphoma (NHL)

❖ Patients received either fixed or BSA-adjusted oral doses of abexinostat (BID) according to one of three 21-day dosing schedules:

- Schedule 1: Treatment on days 1-14
- Schedule 2: Treatment on days 1-5 and 8-12
- Schedule 3: Treatment on days 1-4, 8-11 and 15-18

Table 1. Study details

Clinical phase	Indication	n patients	n SPD observations	Follow up period median [range] (days)
I	HD	11	43	271 [50-734]
	NHL	20	87	201 [10-1178]
	CLL	4	22	199 [73-1250]
II	HD	-	-	-
	NHL	71	189	98 [6-602]
	CLL	15	48	78 [44-348]

HD=Hodgkin's Disease, NHL=non-Hodgkin lymphoma, CLL=Chronic Lymphocytic Leukaemia

2. SPD-time course modelling

❖ A mechanism-based population K-PD tumour growth inhibition (TGI) model was used to describe the SPD data^[4-5]

❖ Dose and AUC were evaluated as measures of exposure

$$\frac{dy}{dt} = K_G \cdot y(t) - K_{DRUG} \cdot Exposure \cdot R(t) \cdot y(t)$$
$$R(t) = e^{-\lambda t}$$

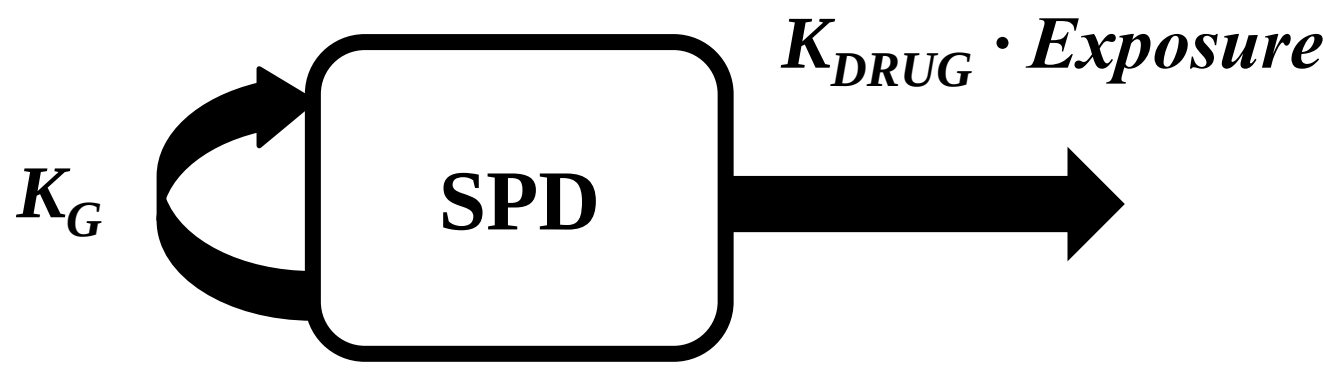


Figure 1. Schematic of structural SPD model

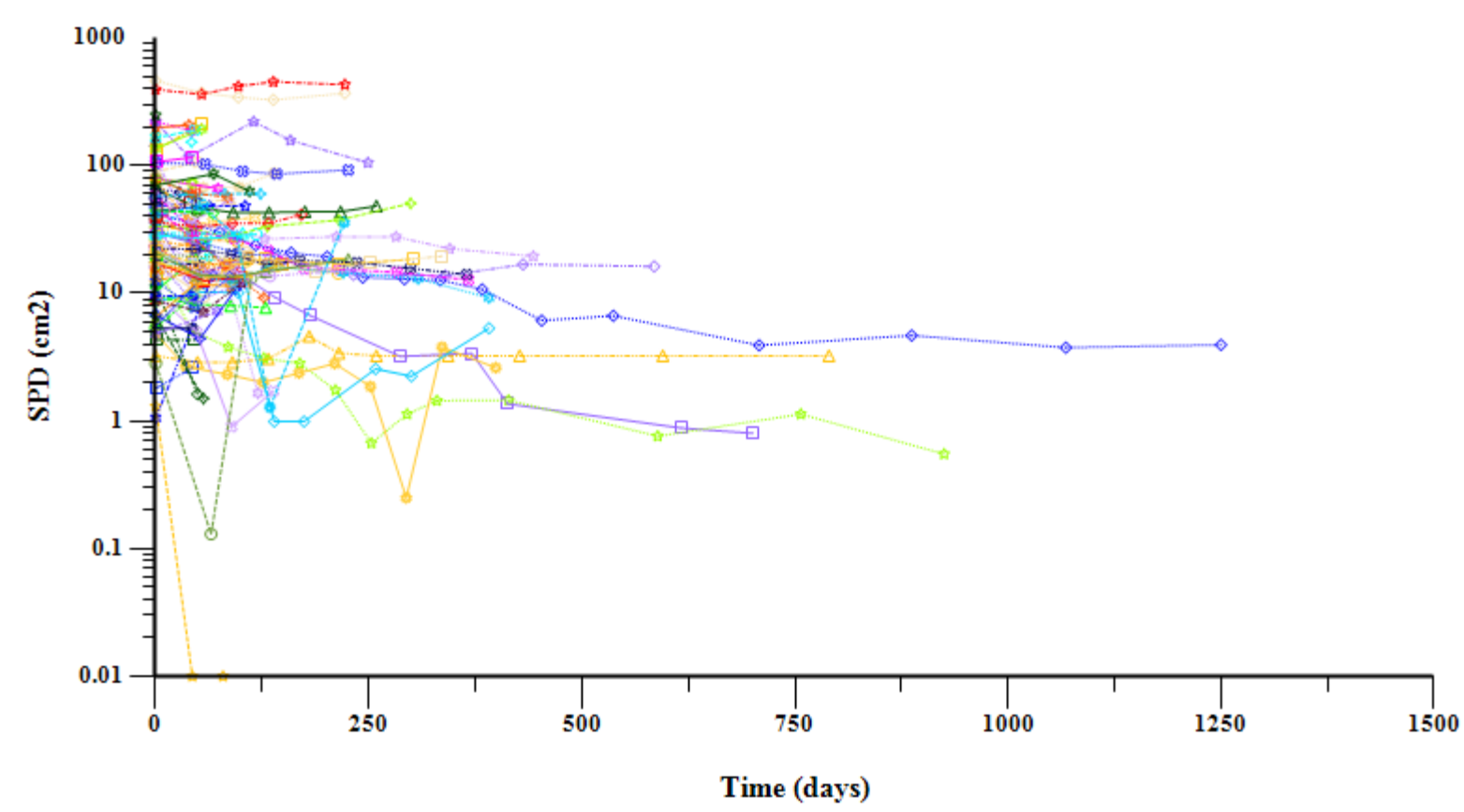
$y(t)$ SPD at time t
 K_G tumour growth rate (days⁻¹)
 K_{DRUG} drug-constant cell kill rate (days⁻¹·mg⁻¹)
 R resistance function (-)
 λ resistance appearance rate function (days⁻¹)
Exposure:
Dose dose administered at study inclusion (mg)
AUC area under the concentration-time curve (h·mg/L)

3. Random effects

❖ Inter-individual variability was investigated on the following parameters (using a log-normal distribution):

- Baseline SPD
- K_{DRUG}
- Resistance appearance rate function (λ)

❖ A combined additive + proportional model described the residual error



4. Time-to-event (TTE) dropout modelling

❖ Median time in the study = 2 cycles (66 days); 44% of dropout was due to disease progression

❖ Dropout was either due to:

- Right-censoring of data
- Patient withdrawal following clinical evaluation (informative dropout)

❖ Study dropout was described by a hazard model

5. Parameter estimation

❖ A joint model simultaneously estimated parameters from the longitudinal SPD and TTE dropout models^[6-10]

❖ Parameter estimation was carried out in NONMEM 7.2 using the Laplacian estimation method

❖ Precision of estimation was evaluated by bootstrap (PsN)

6. Model evaluation

❖ Longitudinal model: parameter estimation precision, goodness-of-fit (GOF) plots, visual predictive checks (VPC)

❖ TTE dropout model: parameter estimation precision, Kaplan-Meier VPC of study dropout

Results

Table 2. Parameter estimates of the joint NLMEM (SPD + TTE data)

Fixed effects				
Parameter	Original estimate	Bootstrap estimate	Bootstrap RSE%	Bootstrap 95%CI
K_{GROW} (day ⁻¹)	1.20 (fixed)	—	—	—
K_{DRUG} (day ⁻¹ ·mg ⁻¹)	0.0265	0.209	36.8	(0.00283–0.0330)
Baseline (cm ²)	30.6	28.0	40.1	(5.10–49.0)
λ (day ⁻¹)	0.152	0.157	5.22	(0.140–0.173)
β_0 (events·day ⁻¹)	0.0587	0.0587	2.35	(0.0564–0.0618)
β_{last}	0.0163	0.0156	15.9	(0.0125–0.0222)
Residual error				
Additive (cm ²)	0.001 (fixed)	—	—	—
Proportional (%)	0.423	0.388	40.0	(0.0757–0.684)

Inter-individual variability (IIV)				
Parameter	Original estimate	Bootstrap estimate	Bootstrap RSE%	Bootstrap CV%
ω^2_{KDRUG}	0.458	2.01	112	142
$\omega^2_{Baseline}$	0.683	2.24	144	143
ω^2_{λ}	0.840	3.56	303	143

❖ Dose was found to be the best predictor of change in SPD (lower BIC)

Table 3. Summary of clinical measures

Clinical measures	n patients	n observations
Sum of product of diameters	121	389
PET scan (Standardised Uptake Value)	75	214
Liver enlargement	114	657
Spleen enlargement	113	656
Leukocytes	121	2679
Platelets	121	2660
Haemoglobin	121	2672
Circulating B-lymphocytes	15	67
Serum monoclonal IgM	5	40

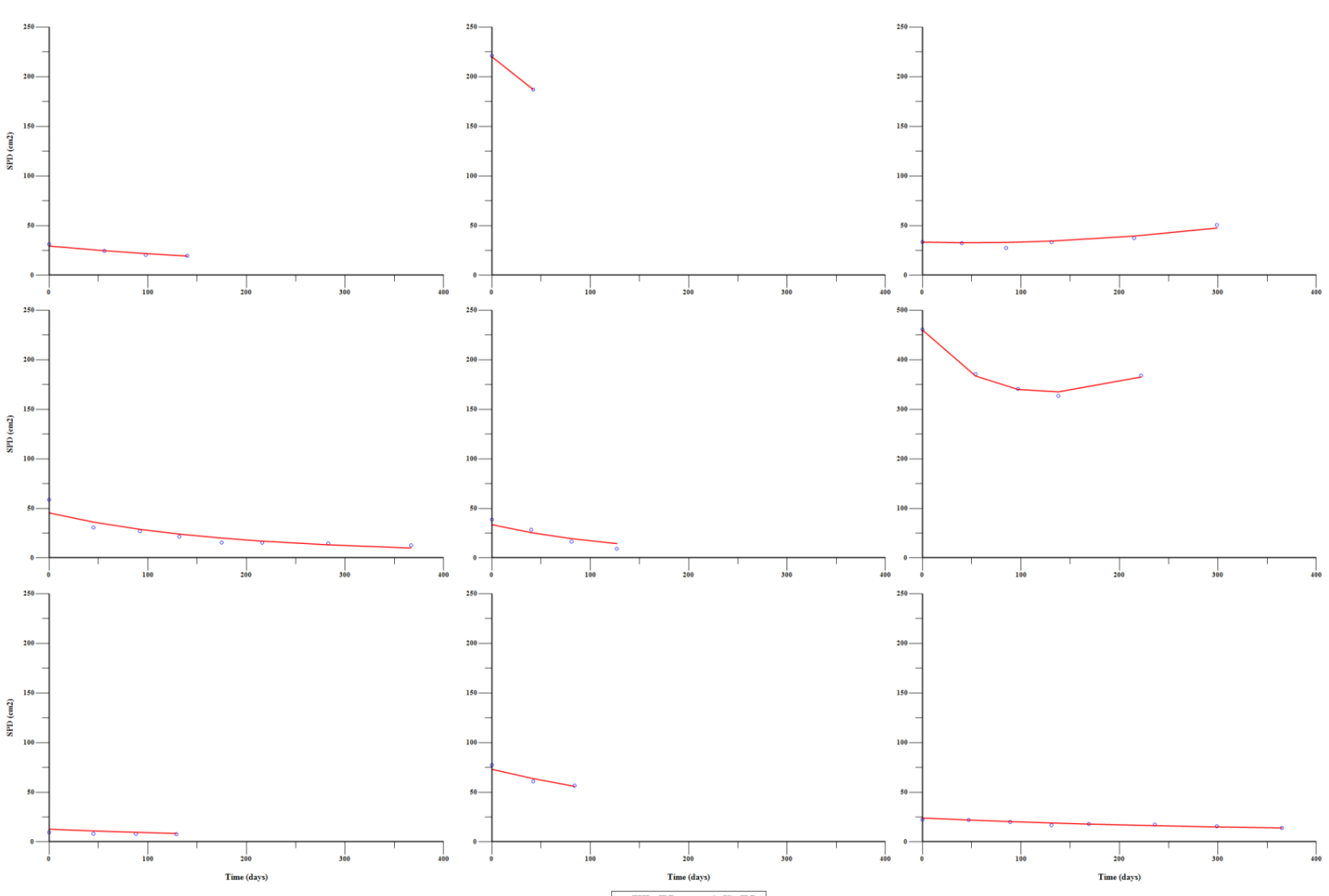


Figure 3. Individual fits of SPD versus time for nine representative patients.

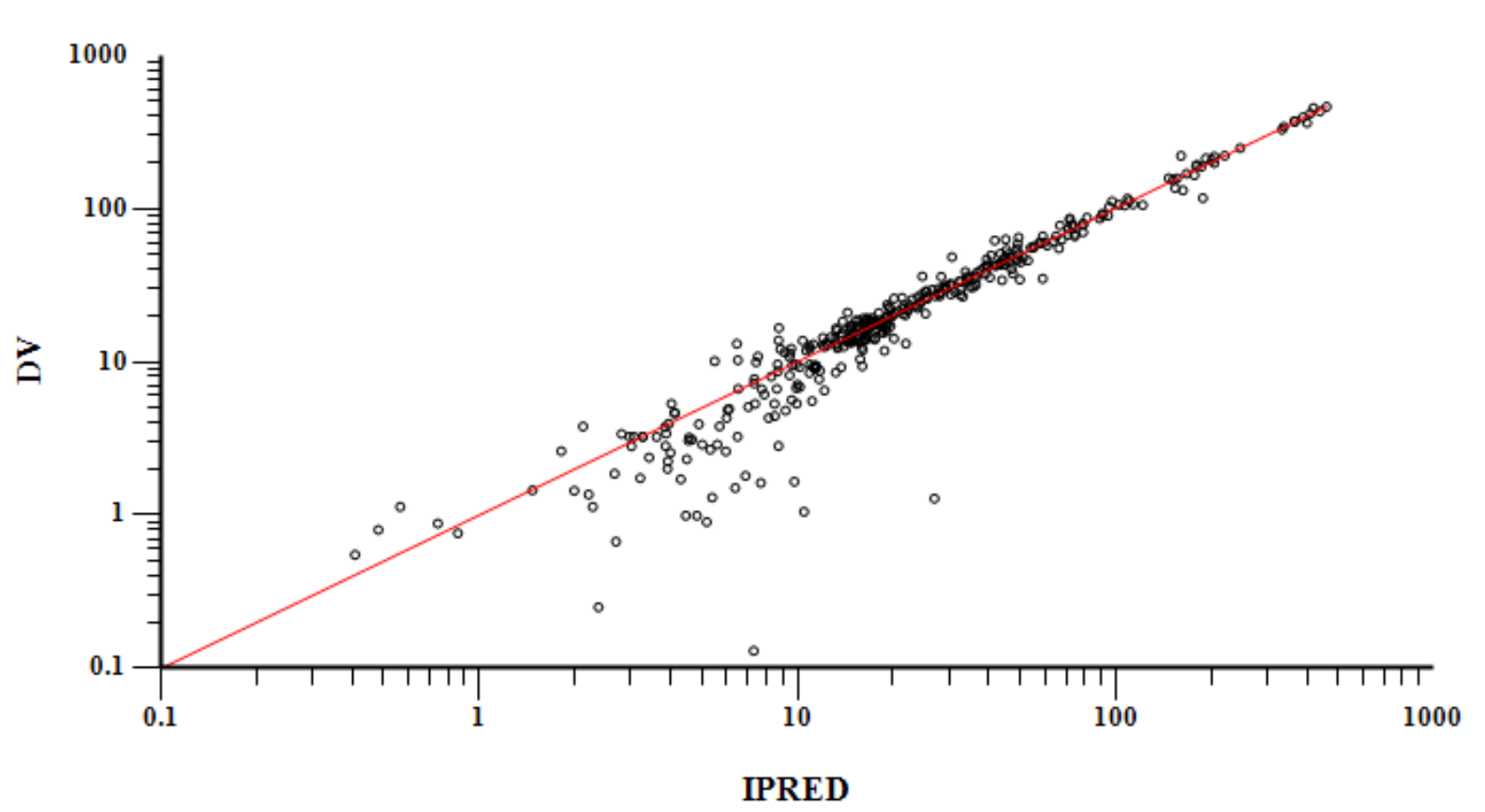


Figure 4. DV versus IPRED.

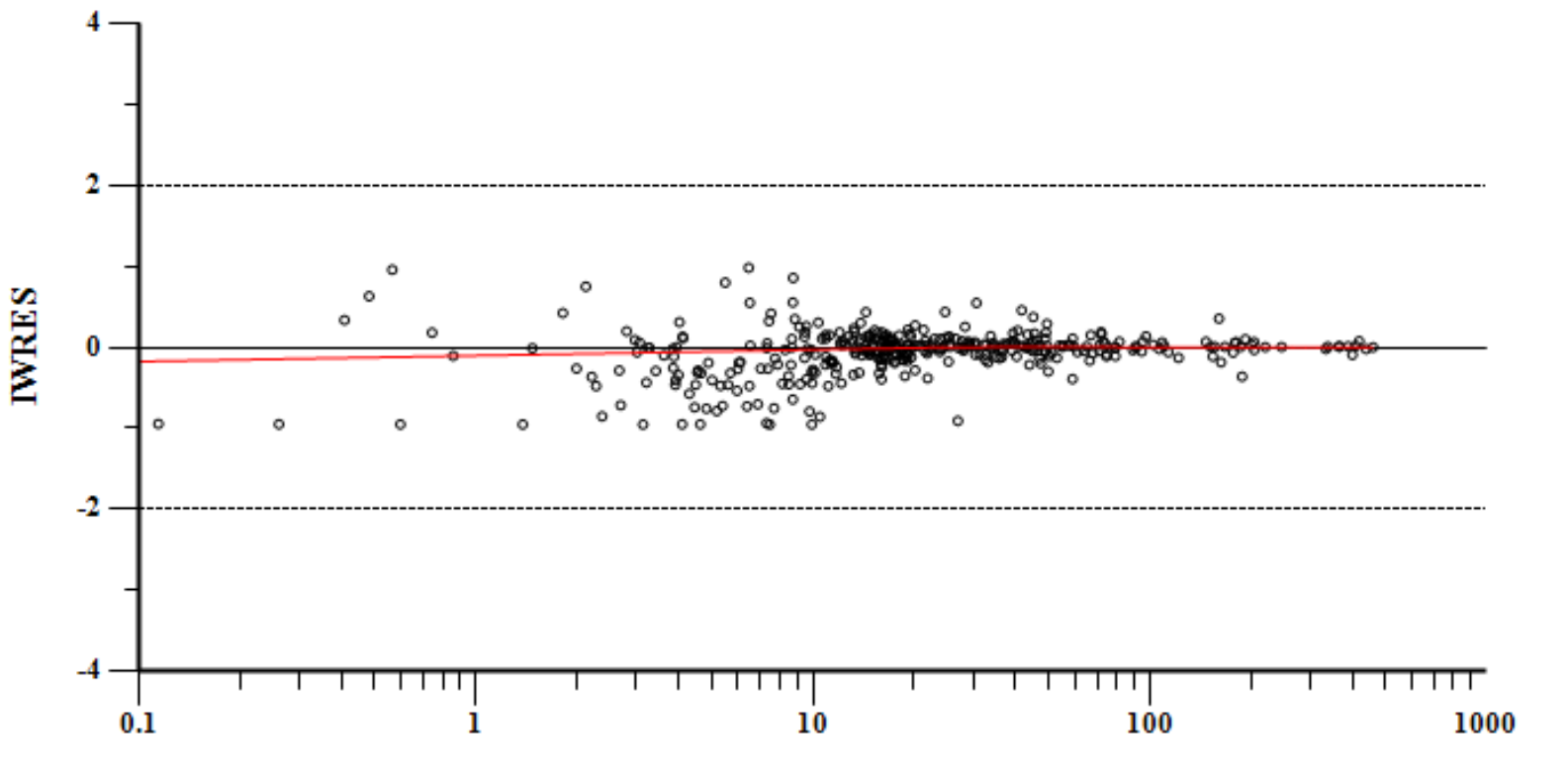


Figure 5. IWRES versus IPRED.

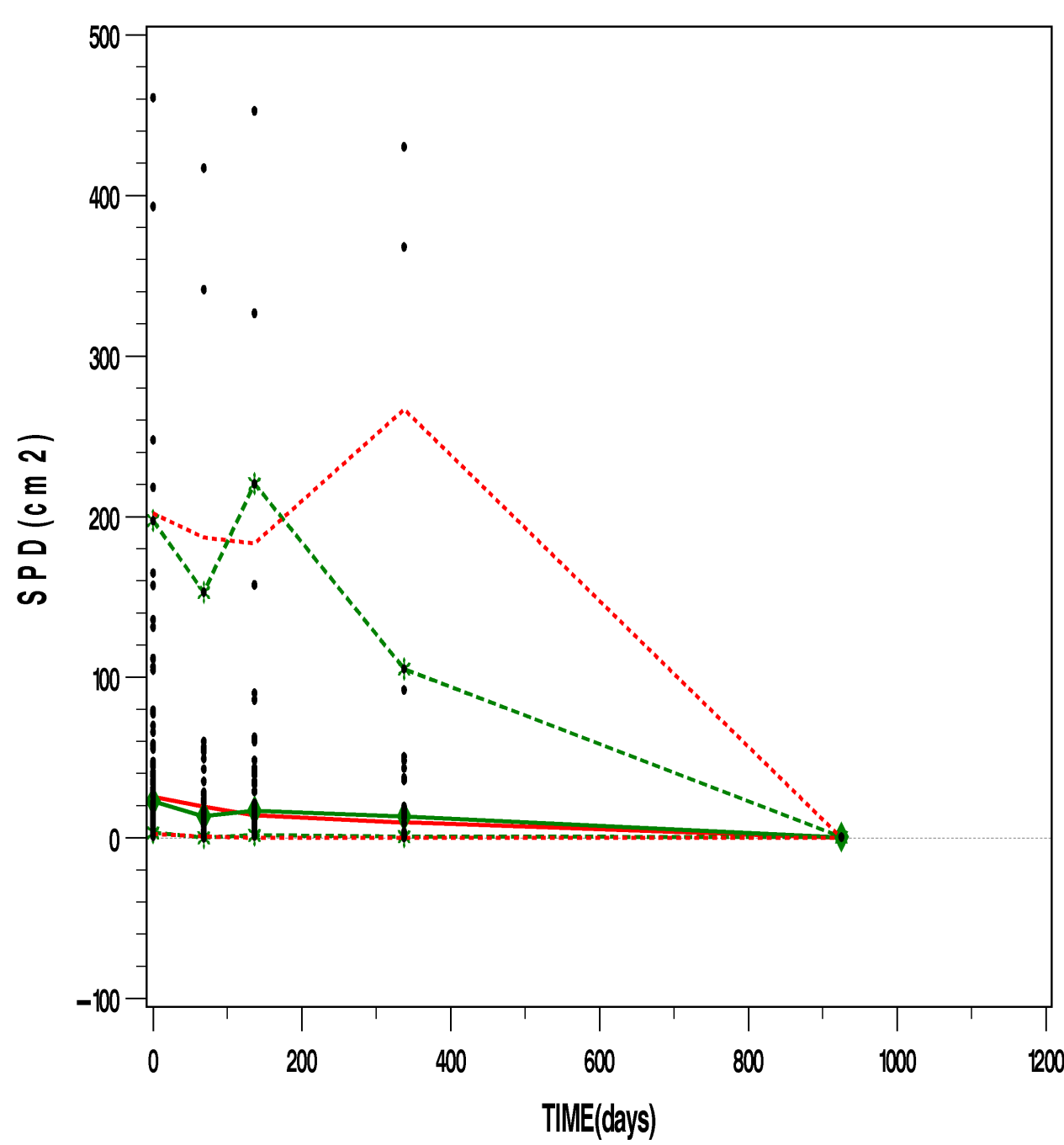


Figure 6. Visual predictive check for the SPD longitudinal model + dropout model; 80 mg dose.

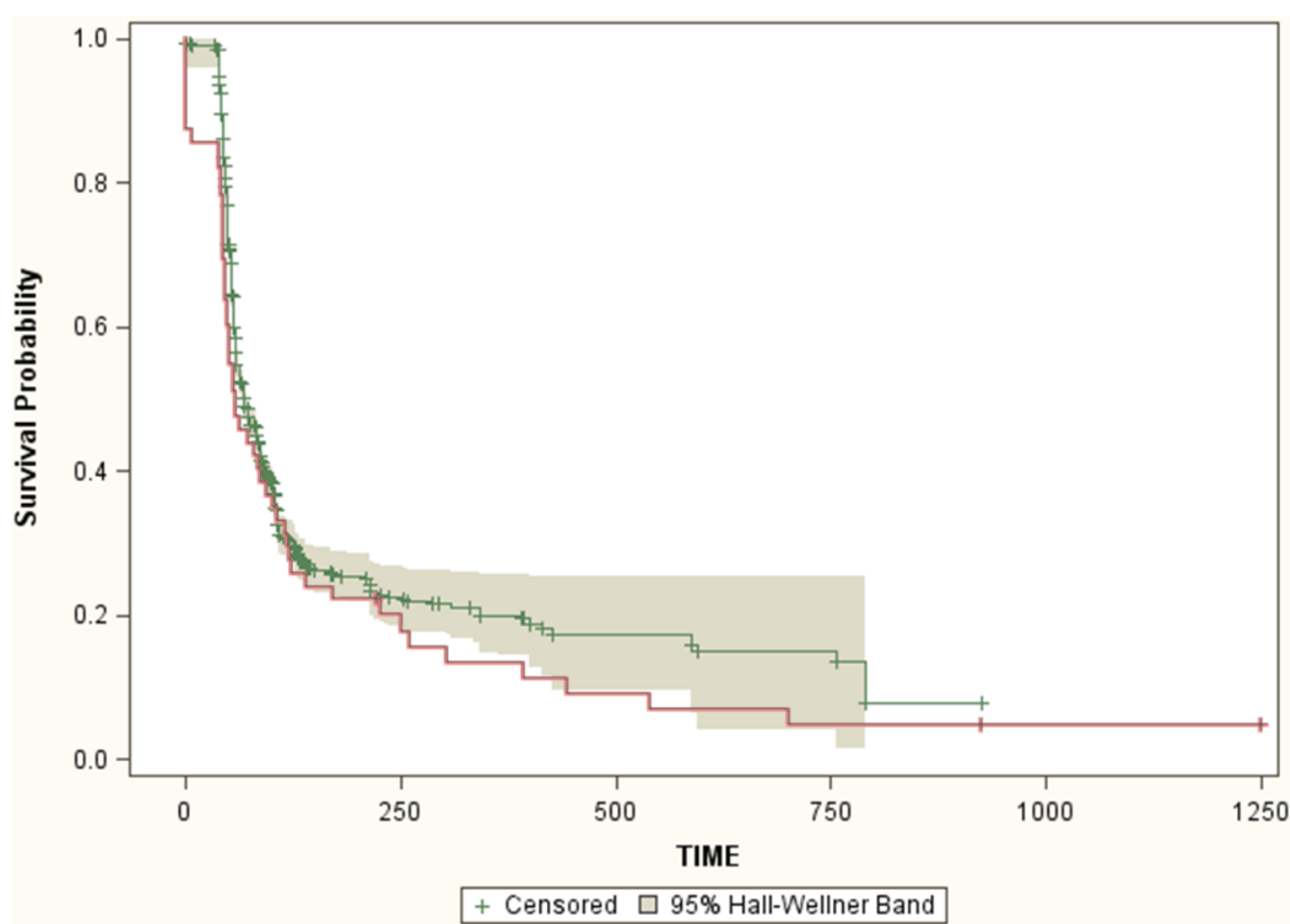


Figure 7. Kaplan-Meier plots of observed (red) and simulated study dropout, time in days

Discussion & Conclusions

The population K-PD TGI model was able to describe the time course of SPD in lymphoma patients and will be combined with other clinical measures in an integrated framework to optimise evaluation of the ORR.

Poster II-42 – Drug/Disease Modeling – Oncology
23rd PAGE Meeting – Alicante, Spain 10-13th June 2014

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