

A TUMOUR GROWTH INHIBITION MODEL BASED ON SERUM M-PROTEIN LEVELS IN PATIENTS WITH MULTIPLE MYELOMA TREATED BY LENALIDOMIDE.

Guglieri-López Beatriz (1,2), Pérez-Pitarch Alejandro (1,3), Climente-Martí Mónica (2), Merino-Sanjuán Matilde (1).

(1) Department of Pharmacy and Pharmaceutical technology, Faculty of Pharmacy, University of Valencia. Valencia. Spain.

(2) Pharmacy Department . Doctor Peset University Hospital of Valencia. Spain.

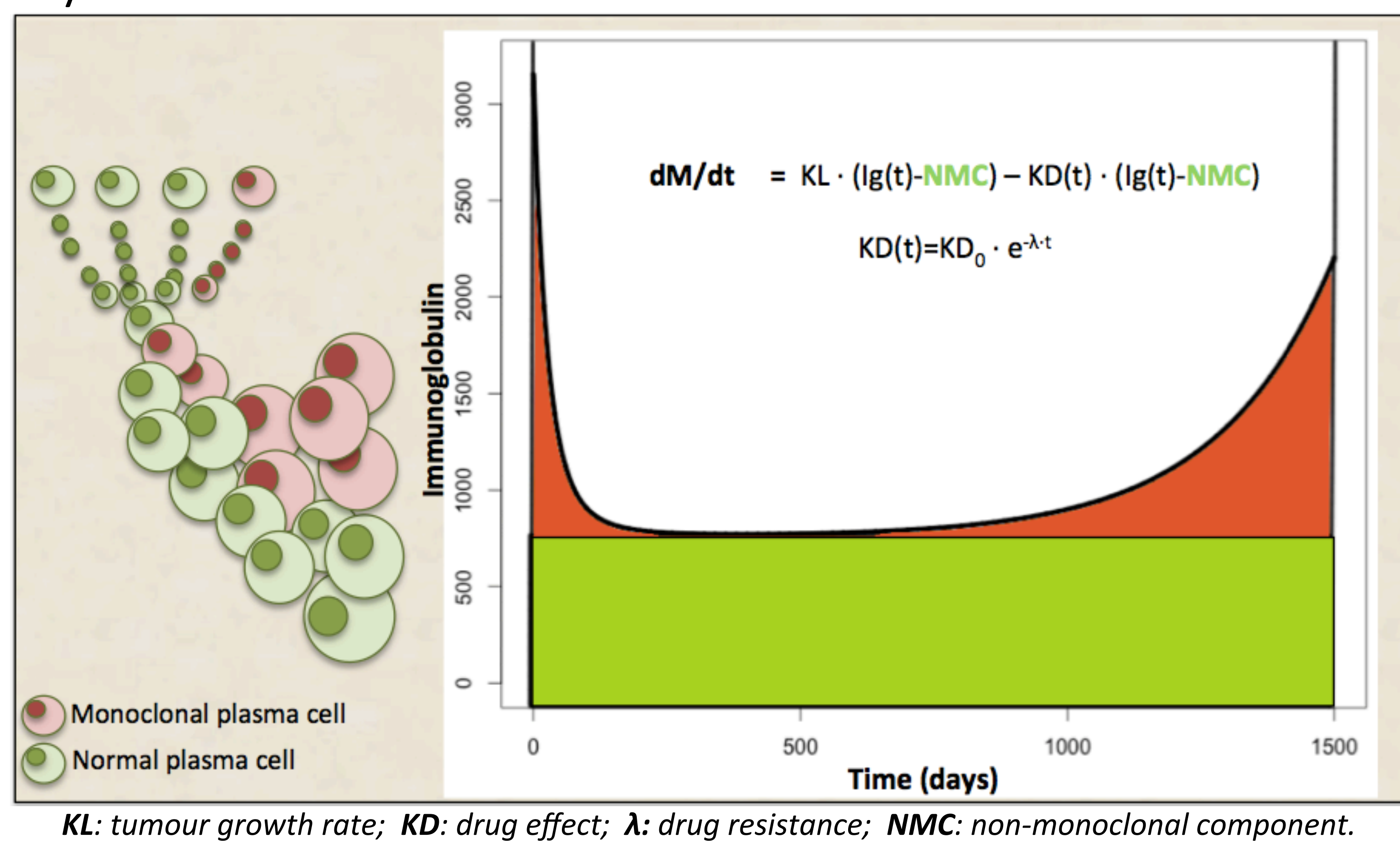
(3) Pharmacy Department . University Clinical Hospital of Valencia. Spain.

OBJECTIVE

Lenalidomide is an oral immunomodulatory drug with antineoplastic, antiangiogenic and anti-inflammatory properties. The aim of this project was to model the pharmacodynamic M-protein response induced by lenalidomide given in patients with double refractory multiple myeloma (MM).

METHODS

Data were available from 39 MM patients with measurable M-protein levels who started treatment with lenalidomide between March 2009 and October 2014 in two Spanish Hospitals. A simplified tumour growth inhibition (TGI) model based on a previous published model [1] was used to estimate response metrics based on time profiles of M-protein (taken as a marker of tumour size) after lenalidomide administration. A parameter representing non-monoclonal component (NMC) was added to the model in order to restrict the tumour growth and the effect of lenalidomide to myeloma cells.



Model parameters were estimated using non-linear mixed-effects modelling implemented in NONMEM V7.3.0 [2]. Relationship between these TGI metrics and covariates was assessed using Stepwise Covariate Model building tool of PsN v4.2.0. The performance of the model was evaluated using a visual predictive check (VPC) based on 1000 simulated replicates of the development dataset (30 patients) from week 8 onwards. The bootstrap resampling technique was also used for internal validation. External validation was conducted by assessing the ability of the population model to predict M-protein levels from week 8 onwards in a separate group of 9 patients using the normalized prediction discrepancy distribution error (NPDE) add-on package for R [3].

RESULTS

The model was composed of sub-models for tumour growth dynamics, drug effect and drug resistance. The decrease of M-protein levels to normal range at the end of cycle 2 (week 8) was linearly correlated to drug effect and drug resistance. The M-protein level at week 8 was correlated to NMC. The model indicated good prediction and a lack of bias in goodness-of-fit plots and VPC. The external validation showed that NPDE were not different from a normal distribution (global adjusted p-value=0.987).

Table 1. Summary of model parameter estimates and bootstrap results.

PARAMETERS	BASE MODEL		FINAL MODEL		200 BOOTSTRAP RUNS	
	Estimate	RSE(%)	Estimate	RSE(%)	Median	95% CI
KL (day ⁻¹)	0.0044	30%	-	-	-	-
KL IgA (day ⁻¹)	-	-	0.0101	27%	0.0089	0.0063-0.0131
KL IgG (day ⁻¹)	-	-	0.0043	31%	0.0041	0.0024-0.0082
KD (day ⁻¹)	0.0592	15%	0.0478	20%	0.0482	0.0333-0.0721
λ (day ⁻¹)	0.0132	19%	0.0127	36%	0.0131	0.0078-0.0253
NMC (mg/dL)	480	22%	-	-	-	-
NMC IgA (mg/dL)	-	-	101	12%	105	9-178
NMC IgG (mg/dL)	-	-	571	6%	586	433-758
ONMRZ on LND effect	-	-	0.839	55%	0.7761	0.1466-1.7104
ONMRZ on Decay	-	-	0.348	72%	0.3556	0.0316-0.6280
Olog-PROT8 on NMC IgA	-	-	0.751	20%	0.7909	0.1177-25.5
Olog-PROT8 on NMC IgG	-	-	0.864	10%	0.8769	0.2547-1.9953
Interindividual variability						
IIV Growth (CV%)	84.7	21%	47.9	20%	38.5	10.8-69.8
IIV LND effect (CV%)	54.9	23%	35.2	14%	36.7	7.96-63.5
IIV Decay (CV%)	66.9	42%	43.0	18%	45.7	21.4-98.7
IIV Basal (CV%)	83.0	16%	21.0	17%	18.1	7.8-45.8
Random residual variability						
σ^2 (proportional error)	2.16%	-	2.4%	-	2.53%	1.85-3.37

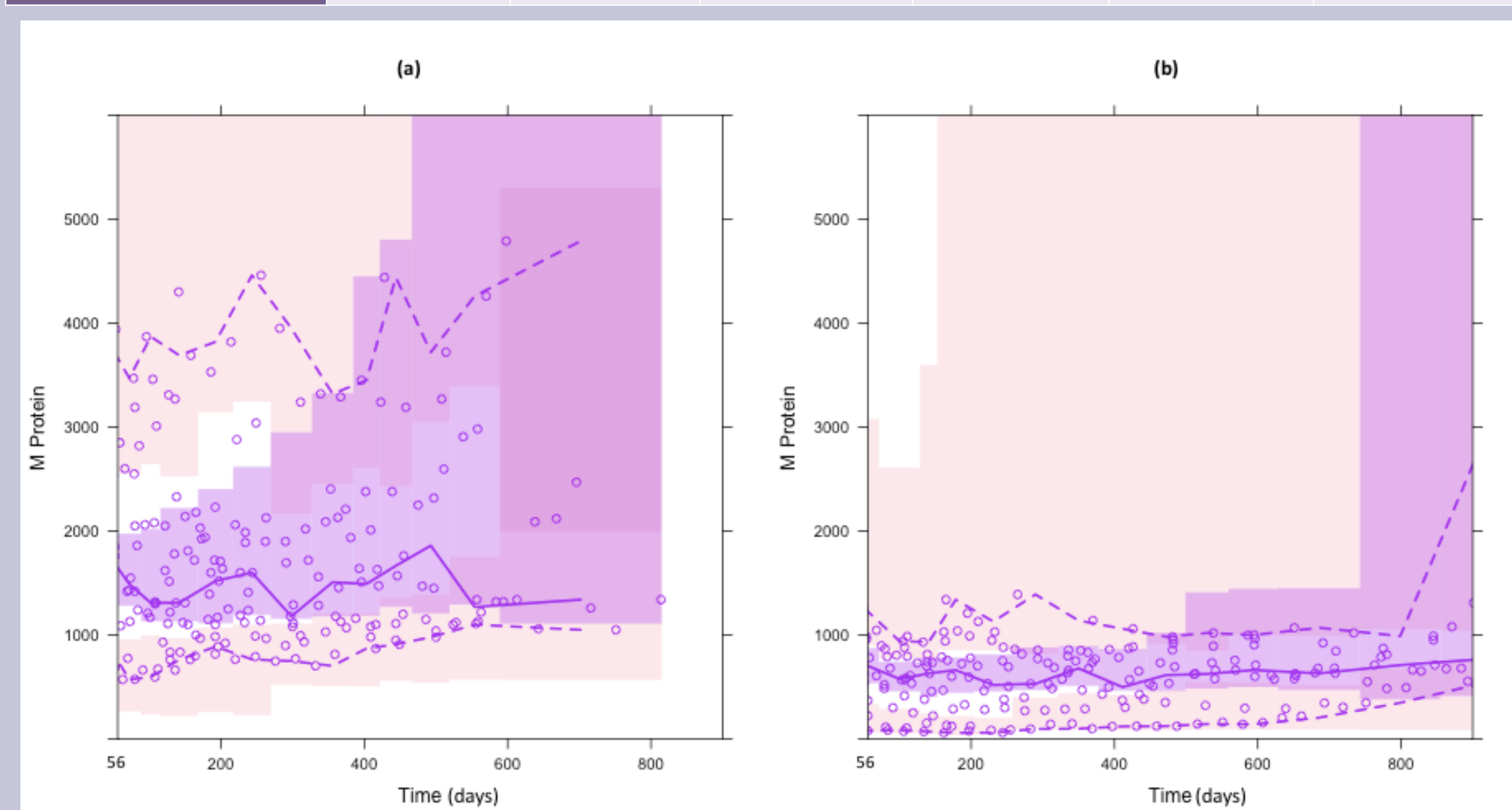


Figure 1. Visual predictive check plots in patients who reached normal range immunoglobulin levels at week 8 of treatment (b) and in patients who did not (a).

CONCLUSIONS

Internal and external validation techniques demonstrate that this model can be used to predict M-protein profile from week 8 onwards in multiple myeloma patients treated by lenalidomide. The described model could be part of a PK/PD model framework to simulate expected survival taking into account drug exposure.

REFERENCES

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