Population Pharmacokinetics and Exposure-Response Analyses to Support Dose Selection of Daratumumab in Multiple Myeloma Patients

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OBJECTIVE

Daratumumab is an IgG1 human CD38 monoclonal antibody with broad-spectrum antitumor activity. The aim of this project was to explore the pharmacokinetics (PK), pharmacodynamic (PD) response and the exposure-response relationship of daratumumab from a Phase I study in patients with advanced multiple myeloma (MM).
This information was an integral aspect of dose selection.
The exposure-response cascade might be displayed as follow:

METHODS

Data were available from 25 MM patients with measurable PK who received daratumumab 0.1 to 16 mg/kg weekly by intravenous infusion (data cut 31 July 2012). A population PK model was developed to derive systemic exposure to daratumumab in patients using non linear mixed effect model and NONMEM 7.

A simplified tumor growth inhibition (TGI) model [1] was used to estimate response metrics based on time profiles of M-protein and involved free light chain (Involved FLC) after daratumumab administration. Model parameters are estimated in NONMEM 7. Relationship between these TGI metrics and drug exposure, and progression free survival (PFS) were assessed.

Tumor size data can be described by a simplified TGI (sTGI) model as follows:

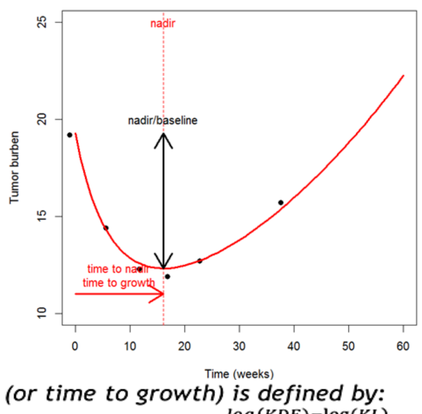
$$KDE_i = KD_{i,0} \cdot Exposure_i$$

$$TS(t_{ij}) = TS_{i,0} \cdot \exp\left[KL_i \cdot t_{ij} - \frac{KDE_i}{\lambda_i} \cdot \left(1 - e^{-\lambda_i \cdot t_{ij}}\right)\right] + \varepsilon_{ij}$$

$$\theta_i = \theta \cdot e^{\eta_i}, \eta_i \rightarrow N(0, \omega^2),\ \varepsilon_{ij} \rightarrow N(0, \sigma^2),\ \theta = \{TS_0, KDE, KL, \lambda\}$$

$$i = 1,\ldots,n \text{ individuals}, j = 1,\ldots,m \text{ observations}$$

TS: tumor size, t: time,
KD: cell kill rate (onset of effect)
KL: tumor growth rate (disease progression)
λ: drug efficacy decay rate (offset of effect)



Time to NADIR (or time to growth) is defined by:

$$tnadir = \frac{\log(KDE) - \log(KL)}{\lambda_{nadir}}$$

$$\text{nadir} = TS(tnadir) \text{ and ratio} = \frac{\lambda_{nadir}}{baseline}$$

RESULTS

A 2-compartment population PK model with parallel linear and Michaelis-Menten eliminations best described daratumumab pharmacokinetics, as often described for monoclonal antibodies targeting receptors [2].

Table 1 - Final PK parameters estimates

Parameter	Unit	Estimate	SEE	RSE (%)	95% CI	Variability	Shrinkage
Fixed Effects							
CL	L/h	0.0033	0.00119	36.1	[0.0010 - 0.0056]		
V1	L	5.12	0.318	6.2	[4.50 - 5.74]		
V2	L	4.47	0.925	20.7	[2.66 - 6.28]		
Q	L/h	0.0459	0.00717	15.6	[0.0318 - 0.0600]		
V_M	mg/h	1.18	0.262	22.2	[0.6665 - 1.6935]		
K_M	µg/mL	1.49	0.774	51.9	[-0.027 - 3.01]		
Random Effects (variance)							
CL	1	0.196	0.19	96.9	[-0.176 - 0.57]	44%	67.5%
V1	1	0.145	0.0555	38.3	[0.036 - 0.25]	38%	12.0%
V_M	1	0.748	0.185	24.7	[0.385 - 1.11]	86%	5.4%
K_M	1	0.797	0.46	57.7	[-0.105 - 1.70]	89%	32.7%
Residual variability (variance)							
Proportional	1	0.0896	0.0185	20.6	[0.053 - 0.126]	30%	

CL: Linear clearance; V1: central volume of distribution; V2: peripheral volume of distribution; Q: inter-compartmental clearance; V_M: Maximum rate; K_M: Michaelis constant ; SEE: standard error of estimate; RSE : relative standard error; CI: confidence interval

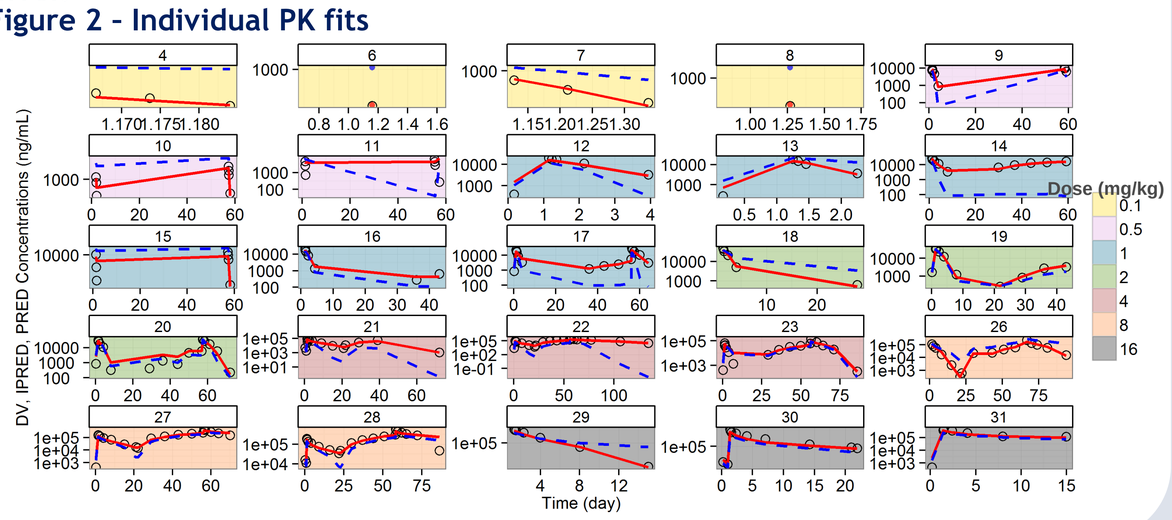
Linear clearance (CL) was estimated to 0.08 L/day, volume of central compartment (V1) to 5L and of peripheral compartment (V2) to 4.5L. Inter-compartmental clearance was estimated to 1L/day.

Parameters of the concentration-dependent elimination (Michaelis-Menten), were estimated to 28 mg/day and 1.5 µg/mL respectively for V_M and K_M.

IIV was estimated on CL, V1, V_M and K_M, with the values 44, 38, 86, and 89%, respectively.

Proportional residual error was estimated to 30%, that include model analytical error.

Figure 2 - Individual PK fits



RESULTS

Figure 3 - Relationship between exposure and predicted M-protein (panel A) or Involved FLC (panel B) time to nadir : there are correlations with log(CMIN)

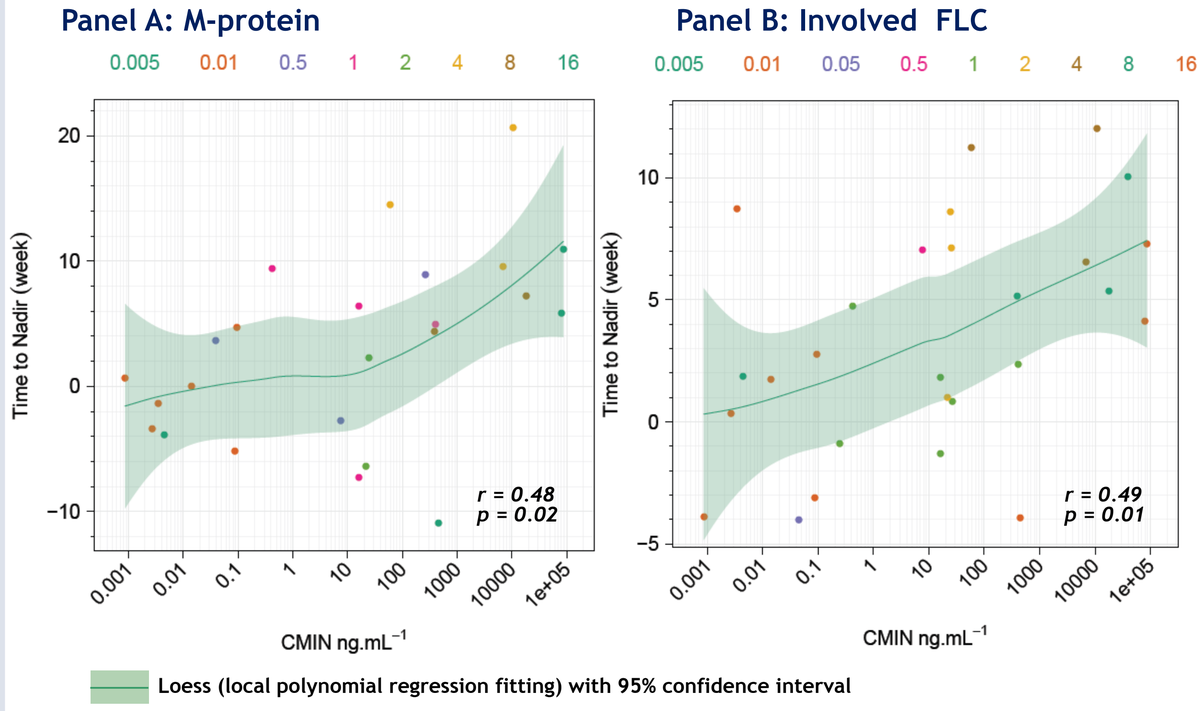


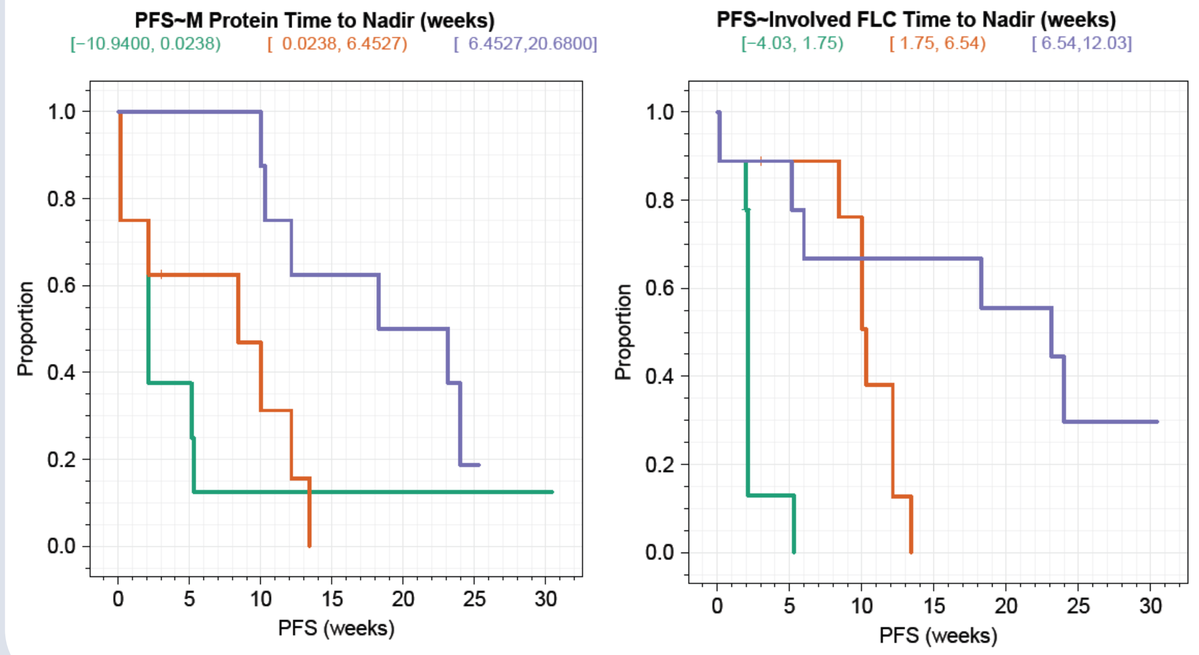
Table 2 - Variables are analyzed one by one with a Cox model, p value of likelihood ratio test (LRT) is reported with the sign of the coefficient (sign on risk)

Variable	Score	p.LRT	N	Sign on risk*
Involved FLC Time to Nadir	7.6	0.0001	27	-
M-protein Time to Nadir	3.4	0.009	24	-
Involved FLC Nadir/baseline	3.3	0.0098	27	+
CMIN	1.7	0.0618	29	-
AUC	1.4	0.0992	29	-
Dose	0.9	0.1973	29	-
M-protein Nadir/baseline	0.5	0.342	24	+

* "+" sign indicates covariate increase the risk of event (progression or death)

Univariate Cox analysis: Only marker response metrics are significant, Involved FLC and M-protein time to nadir are the best

Figure 5 - Relationship (Cox-regression) between M-protein time to nadir and Involved FLC time to Nadir with PFS



CONCLUSIONS

The simplified TGI model is used to analyze time profiles of M-protein, and involved FLC after daratumumab administration.

Daratumumab was shown to inhibit tumor growth and to prolong PFS in an exposure-dependent manner. M-protein and involved FLC TGI responses metrics (time to nadir) would appear to be biomarkers of response to daratumumab. The PK/PD model together with drug independent clinical endpoint models [3] may be used to optimize dose and schedule for daratumumab single agent and support further clinical development.

REFERENCES

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