Population pharmacokinetic/pharmacodynamic models to support dose selection of daratumumab in multiple myeloma patients

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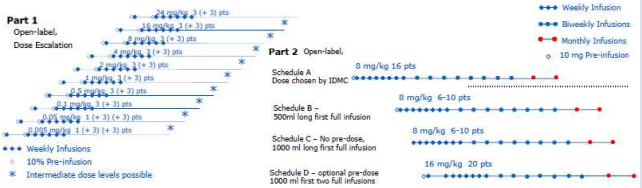
OBJECTIVE

Daratumumab is a human CD38 monoclonal antibody with broad-spectrum antitumor activity. The aim of this project was to model the pharmacokinetics (PK), pharmacodynamic (PD) M-protein response induced by daratumumab given in patients with double refractory multiple myeloma (MM) from a Phase I/II study. Those patients do not have further established treatment options so far. PK/PD modelling and simulation are used to guide dose selection of daratumumab in MM patients. The exposure-response cascade might be displayed as follows, the work presented will focus on the blue elements.

METHODS

Data were available from 72 MM patients with measurable PK who received daratumumab 0.005 to 16 mg/kg weekly by intravenous infusion. The study (GEN501) was composed of two parts: Part 1 was an open-label, dose-escalation design while Part 2 was an open-label, single-arm design as described below.

Figure 1 - Study design



A population PK model was developed to derive systemic exposure to daratumumab in patients using non linear mixed effect model and NONMEM 7.

A concentration-driven tumor growth inhibition (TGI) model [1] was used to assess the exposure-response of daratumumab based on time profiles of M-protein. Model parameters are estimated in NONMEM 7.
M-protein data can be described by an exposure-driven TGI model as follows:

$$\frac{dMprot}{dt} = \underbrace{KL}_{\text{Growth rate}} \cdot Mprot(t) - \underbrace{KD(t)}_{\text{Kill rate}} \cdot Conc_{dara}(t) \cdot Mprot(t)$$

$$KD(t) = KD_0 \cdot e^{-\lambda t}$$ Resistance: exponential decrease of kill rate
λ: rate constant for resistance appearance, KD(0)=KD_0

$$Mprot(0) = BASE$$ Baseline M-Protein

KD_0, λ: drug specific parameters
BASE, KL: disease/patient specific parameters
Concentration, $Conc_{dara}(t)$, was predicted using individual empirical Bayes estimates (EBEs) of the population PK model

Model-based simulations were performed to guide dose-selection. 2000 subjects per dosing regimen were simulated across inter-individual variability (random effects) and residual error, uncertainty in parameter estimates was not accounted for.

RESULTS

Study GEN501 is still ongoing and further refinement of models may be needed.

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 -PK parameters estimates

Parameter	Unit	Estimate	SE	RSE (%)	Variability (%)	Shrinkage (%)
Fixed Effects						
CL	L/h	0.00795	0.0011	14		
V1	L	4.73	0.216	5		
V2	L	5.47	0.675	12		
Q	L/h	0.043	0.0123	29		
V_M	mg/h	0.782	0.109	14		
K_M	µg/mL	0.71	0.115	16		
Random Effects (variance)						
CL		0.377	0.174	46	61	38
V1		0.0875	0.022	25	30	10
V2		0.238	0.106	45	49	10
V_M		0.681	0.144	21	83	22
covariance V1 - V2 *		0.144	0.0433	30		
Residual variability (variance)						
Proportional error		0.0492	0.00738	15	22	

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 ; SE: standard error of estimate; RSE : relative standard error; * correlation V1-V2 = 0.998

Results are overall consistent with a preliminary analysis performed on 25 patients of Part 1 but with a higher linear clearance: 0.19 L/day versus 0.08 L/day in the former analysis and lower V_M and K_M values: 19 mg/day and 0.7 µg/mL versus 28 mg/day and 1.5 µg/mL respectively [3]. Inter-individual variability was estimated on CL, V1, V2 and V_M , to 61, 30, 49, and 83% respectively. The residual error was estimated to 22%, including analytical error.

RESULTS

The TGI model for M-protein confirmed a concentration dependent drug efficacy that was suggested in a previous exploratory data analysis [3].

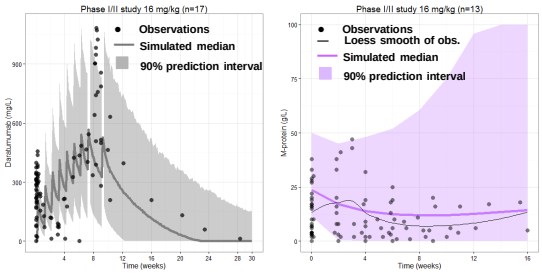
Table 2 - Parameters estimates of the TGI model

Parameter	Unit	Estimate	SE	RSE (%)	Variability (%)	Shrinkage (%)
Fixed Effects						
KL	day^{-1}	0.00515	0.00136	26		
KD_0	$L.mg^{-1}.day^{-1}$	0.000229	7.56E-05	33		
λ	day^{-1}	0.0467	0.00805	17		
$BASE_1$	$g.L^{-1}$	3.61	0.781	22		
$BASE_2$	$g.L^{-1}$	23.7	1.77	7		
FRACTION $BASE_1$		0.201	0.0562	28		
Random Effects (variance)						
KL		1.01	0.367	36	100	11 and 11*
KD_0		2.05	0.688	34	143	36 and 27*
λ		0.171	0.0816	48	41	90 and 45*
BASE		0.187	0.0438	23	43	9 and 3*
Residual variability (variance)						
Additive error		1.58	1.20	76	1.26 g/L	
Proportional error		0.00405	0.00192	47	6.36%	

Model parameters of the exposure driven TGI model and their associated inter-individual variability were well estimated. Baseline M-Protein was found to follow a bimodal distribution with respective values of 4 g/L (20% of subjects) and 24 g/L (remaining 80%). M-protein growth rate estimate (KL) was consistent to previous analysis for daratumumab (0.00694 /day using a non-exposure driven simplified TGI model) [3] and similar analyses on dexamethasone [1], tabalumab [4] and carfilzomib [5] (0.004 /day).

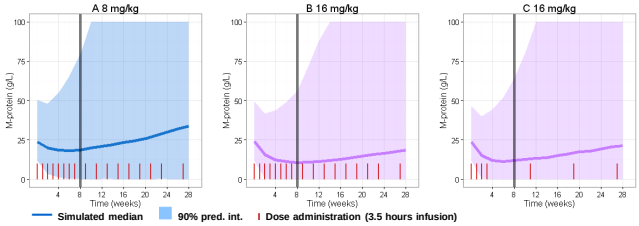
Both models are able to reproduce the observed data as illustrated by Figure 2.

Figure 2 - Qualifications of PK and TGI models at 16mg /kg



There is clearly a better efficacy at 16 mg/kg (panels B and C) than at 8 mg/kg (A), despite a lower overall dose intensity (Panel C versus A).

Figure 3 - Exploratory simulations of daratumumab dosing regimens



Change from baseline at 8 weeks expressed as a ratio is a predictor of survival [6] and confirmed the superiority of 16 mg/kg versus 8 mg/kg:

Median [90% prediction interval]

Panel A 8mg/kg: -0.146 [-0.998;1.606]
Observed value in Phase I/II was -0.056 (n=17)

Panel B 16mg/kg: -0.531 [-1.000;0.944]

Panel C 16mg/kg: -0.391 [-1.000;1.189]

CONCLUSIONS

Daratumumab was shown to inhibit tumor growth in a concentration-dependent manner in MM patients. PK/PD models are used to optimize dosing regimen and support Phase III design. A dose of 16 mg/kg using an intensive dosing schedule of weekly for 8 doses followed by every 2 weeks for 8 doses then every 4 weeks was found most appropriate in terms of continuous M-protein suppression.

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