A semi-mechanistic population Pharmacokinetic-Pharmacodynamic (PKPD) model of thrombocytopenia characterizing the effect of trastuzumab-DM1 (T-DM1) on platelet counts in patients with HER2-positive metastatic breast cancer

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Background

Trastuzumab-DM1 (T-DM1) is an antibody-drug conjugate in development for the treatment of human epidermal growth factor receptor 2 (HER2)-positive cancers [1]

T-DM1 is composed of the potent cytotoxic agent DM1 (derivative of maytansine) conjugated to trastuzumab (Herceptin®) via a unique, stable linker

T-DM1 is designed to target HER2 receptors on tumor cells, and kill tumor cells by releasing DM1 intracellularly and via the anti-tumor activities of trastuzumab

Thrombocytopenia (TCP) is the dose-limiting toxicity in clinical studies. TCP was generally grade 1 or 2, reversible, and not associated with serious hemorrhage [2, 3]; the mechanism(s) of platelet response to T-DM1 is unclear

Objectives

A semi-mechanistic population PKPD model was developed in order to:

- describe the time course of patient platelet response to T-DM1
- support mechanistic hypotheses for platelet response(s)
- to evaluate patient baseline characteristics as covariates on model PD parameters
- predict patient platelet response and incidence of Grade ≥ 3 TCP in future clinical trials

Methods

Patients and Data

Women with previously treated MBC were treated with single agent T-DM1

Model building dataset (n=164 patients; 4340 platelet measurements)

- Phase I dose escalation study (TDM3569g, n=52); 0.3–4.8 mg/kg every 3 weeks (q3w); 1.2–2.9 mg/kg weekly
- Phase II proof of concept study (TDM4258g, n=112); 3.6 mg/kg q3w

Model evaluation dataset (n=110 patients; 1841 platelet measurements)

- Phase II pivotal study (TDM4374g); 3.6 mg/kg q3w

Population PKPD Modeling

Data analysis: NONMEM version 7 with FOCE interaction

The final PKPD model (Figure 1) was modified from Friberg et al [4]

- *Post-hoc* Bayesian estimates of patient PK parameters [5] drove platelet response
- Two primary drug effects ($C \bullet Slope_1$ for the first dose and $C \bullet Slope_2$ for subsequent doses) were used to describe the low Cycle 1 platelet nadir
- A mixture model quantified a subpopulation of patients with downward platelet drifts
  - The Platelet Proliferation (PP) compartment was divided into a non-depletable and depletable pool
  - A secondary T-DM1 drug effect ($C_{avg} \bullet K_{deplete}$) acted on the depletable pool

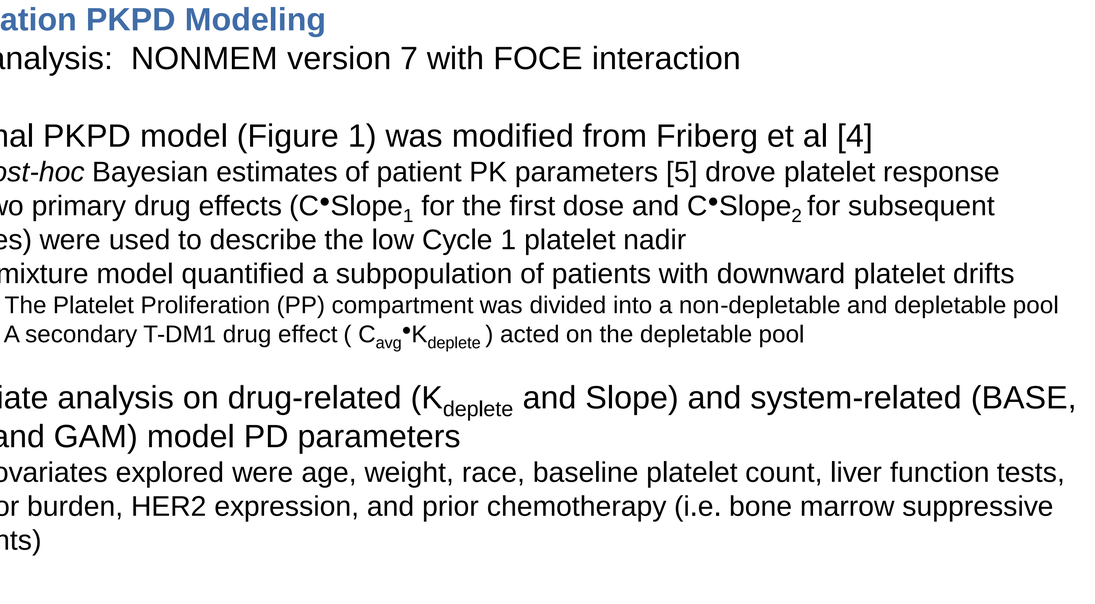
Covariate analysis on drug-related ($K_{deplete}$ and Slope) and system-related (BASE, MTT, and GAM) model PD parameters

- Covariates explored were age, weight, race, baseline platelet count, liver function tests, tumor burden, HER2 expression, and prior chemotherapy (i.e. bone marrow suppressive agents)

Model Evaluation (using Phase II dose of 3.6 mg/kg q3w)

- Diagnostic Plots and Visual Predictive Check
- External dataset evaluation
  - 100 simulations; 110 patients/simulation; nominal dosing times and platelet sampling times
  - Comparison with platelet data from Phase II pivotal study (TDM4374g)
- Probability of grade ≥ 3 TCP
  - Patient dosing and sampling history from model building dataset used for simulations
  - Patient platelet baseline, T-DM1 C_{max}, and AUC were assessed for grade ≥3 TCP propensity

Figure 1. Final PKPD Model



K_{PROL}= Rate of platelet pool proliferation; K_{tr} =rate of transit between compartments; K_{el} = rate of physiological elimination of circulating platelets; CL = clearance; V1 = central compartment volume; V2 = peripheral compartment volume; CLd = inter-compartmental clearance; C = T-DM1 concentration–time profile; C_{avg} = average T-DM1 concentration over dosing intervals. (See Table 1 for description of other parameters)

Results

Table 1. Final Parameter Estimates

Parameter	Parameter Description	Unit	Value	SEE (%)	IIV	SEE (%)
$Slope_1$	T-DM1 drug effect for first dose	L/mg	0.00297	4.01	36.1%	16.1
$Slope_2$	T-DM1 drug effect for subsequent doses	L/mg	0.00182	5.19	56.3%	19.9
MTT	Mean transit time	hr	37.4	0.0204	24.5%	8.36
GAM	Feedback term	–	0.135	0.0439	–	–
BASE	Baseline platelet count	(•1000/μL)	255	2.64	32.2%	13.8
$BASE_1$	Baseline platelet count not depleted	(•1000/μL)	118	7.59	37.4%	46.8
$BASE_2$	Baseline platelet count depleted by ($C_{avg} \bullet K_{deplete}$) rate	(•1000/μL)	137	–	–	–
$K_{deplete, POP1}$ [a]	Depletion rate of $BASE_2$ platelet pool for population 1 patients	L/mg • wk^{-1}	0.000625	24.8	88.1% [b]	27.4
$K_{deplete, POP2}$ [a]	Depletion rate of $BASE_2$ platelet pool for population 2 patients	L/mg • wk^{-1}	0.00842	19.4	88.1% [b]	27.4
Res Err	Residual Error	–	18.4%	3.10	–	–

[a] 55.4% and 44.6% of patients were assigned to $K_{deplete, POP1}$ and $K_{deplete, POP2}$ populations, respectively
[b] The OMEGA SAME option was used for IIV on $K_{deplete}$

Fig 2. Visual Predictive Check

(3.6 mg/kg q3w; 90% prediction interval)

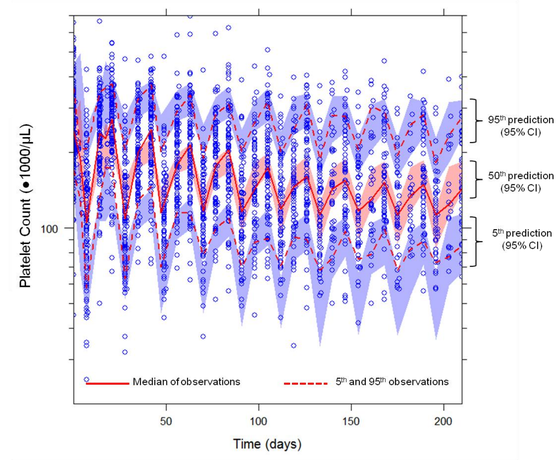


Fig 3. Representative fits for weekly (q1w) and every 3 week (q3w) dosing

| = *dosing; DV=platelet observations; IPRED=individual prediction; PRED=population prediction*

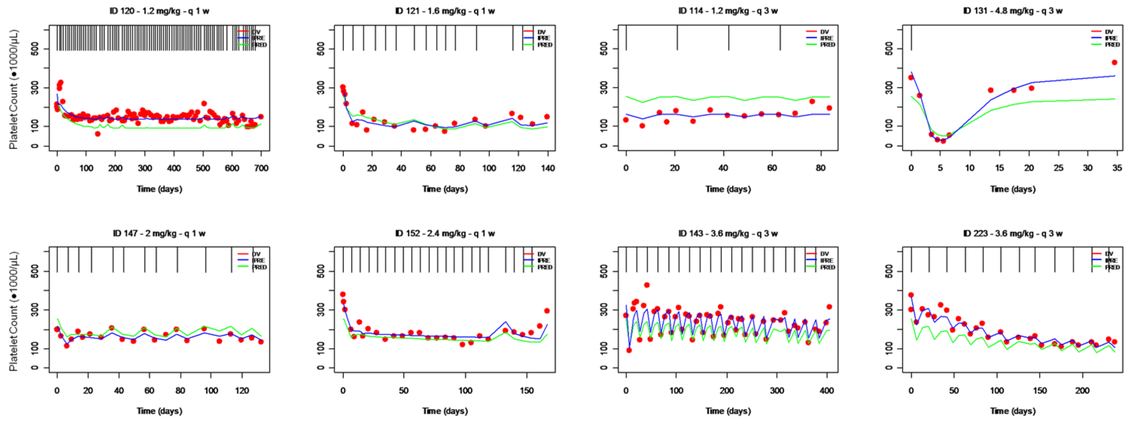


Fig 4. PKPD model simulations; 2 populations of platelet response

Pop 1: Stable Platelet Profiles (75% of patients) *Pop 2: Declining Platelet Profiles (25%)*

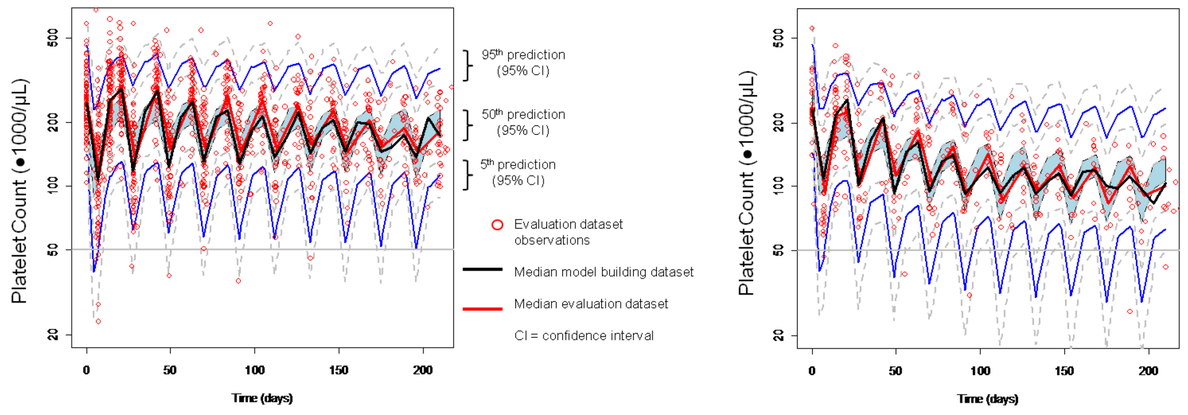
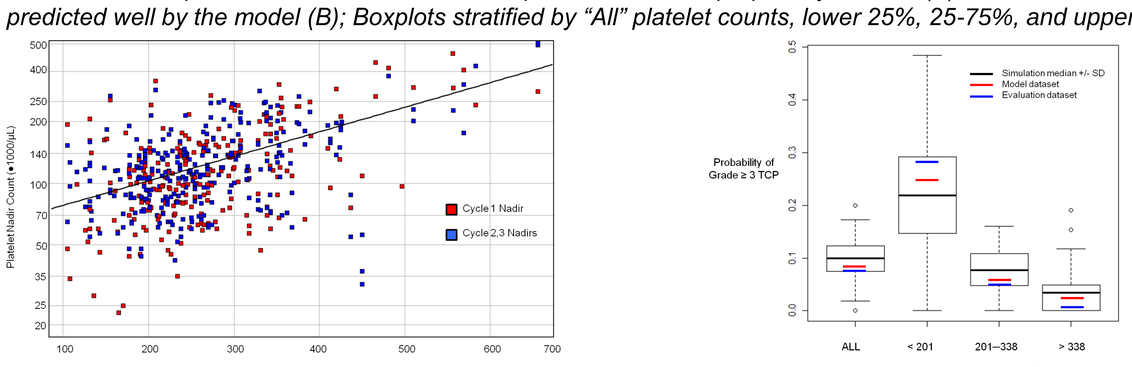


Fig 5. PKPD model simulations; Grade ≥3 TCP Probability

Patient baseline platelet count is correlated with platelet nadir and propensity for TCP (A); Grade ≥ 3 TCP is predicted well by the model (B); Boxplots stratified by "All" platelet counts, lower 25%, 25-75%, and upper 75%



Conclusions

The PK/PD model accurately predicts clinical observations of platelet counts and incidences of Grade ≥ 3 TCP with T-DM1 treatment of 3.6 mg/kg q3w

Platelet profiles from 25% of patients decline more rapidly than the rest of patients and stabilize within 8 treatment cycles to typically 50% of the original baseline platelet count

85% of patients demonstrate a pattern of lowest platelet nadir in the first cycle

Patients with low baseline platelet counts ≤ 200(•1000/μL) have an increased propensity for grade ≥ 3 TCP with T-DM1 3.6mg/kg q3w

Baseline covariates were not statistically significant for any PD parameter; platelet response to T-DM1 cannot be predicted *a priori*

References

[1] Lewis-Phillips GD, Li G, Dugger DL, et al. *Cancer Res.* 2008;22:9280-9290.
[2] Krop IE, Beeram M, Modi S, et al. *J Clin Oncol*. 2010;28:2698-2704.
[3] Burris H, Rugo H, Vukelka S, et al. *J Clin Oncol.* 2011;29:398-405.
[4] Friberg LE, Henningsson A, Maas H, et al. *J Clin Oncol.* 2002;20:4713-4721.
[5] Gupta M, LoRusso PM, Wang B, et al. *J Clin Pharmacol.* In press.