# An integrated pharmacokinetic-pharmacodynamic modeling analysis of T-DM1–induced thrombocytopenia and hepatotoxicity in patients with HER2-positive metastatic breast cancer

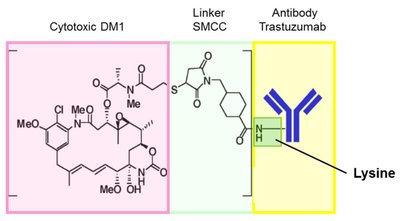
Bender BC (1, 2), Quartino A (2), Li C (2), Chen S-C (2), Smitt M (2), Strasak A (3), Chernyukhin N(2), Wang B (2), Girish S (2), Jin J (2), Friberg LE (1)
(1) Dept of Pharmaceutical Biosciences, Uppsala University, Sweden; (2) Genentech Inc, San Francisco, CA; (3) F. Hoffmann-La Roche Ltd.

## BACKGROUND

Trastuzumab emtansine (T-DM1; Kadcyla®) is an antibody-drug conjugate approved for HER2-positive metastatic breast cancer. T-DM1 is associated with Grade 3/4 adverse events (AE) of thrombocytopenia (TCP) and hepatotoxicity [1].

Objectives were to:

1) Develop a PKPD model simultaneously describing platelet, and transaminase (ALT and AST) response after T-DM1 administration
2) Incorporate parameter correlations and dose modification rules from the T-DM1 prescribing label for simulations
3) Compare simulated %'s of Grade ≥3 toxicities and dose intensities for different T-DM1 dose regimens




T-DM1 Structure

## DATA and METHODS

### Data

- 658 patients from five T-DM1 Phase I-III clinical trials
- T-DM1 doses from 0.3–4.8 mg/kg, under weekly (q1w) and every 3 week (q3w) regimen
- PD measurements = Platelet, ALT, and AST counts over time

### Population PKPD Modeling

- NONMEM version 7.3 with FOCE interaction
- The PKPD model was expanded from a previous analysis based only on platelet data [2]
- Post-hoc Bayesian estimates used to predict T-DM1 concentrations to drive PD responses [3]
- Correlations were assessed between Platelet, ALT, and AST parameters
- Covariate analyses included: ethnicity, liver metastases, ECOG status, age, and tumor burden

### Model Evaluation

- VPCs of 90$^{th}$ prediction interval, overlaid with platelet, ALT, and AST observations
- Posterior Predictive Checks (PPCs) for Grade ≥ 3 toxicities.
  - Phase III trial TDM4370 (N=338; 3.6 mg/kg q3w) used as an internal evaluation dataset [4]
  - 200 simulation replicates

### Model Simulations

- PKPD simulations of additional dose regimens matched T-DM1 steady state exposure ($AUC_{SS}$), *1.2 mg/kg q1w*, and steady state max concentrations ($Cmax_{SS}$), *2.4 mg/kg q1w*, to approved dose, *3.6 mg/kg q3w*
- 200 simulation replicates (N=338)
- Calculations of Grade 3/4 %s, dose intensity (DI), and relative dose intensity (RDI) were done
  - DI = the total dose given divided by the treatment course duration; "mg/kg/week"
  - RDI = ratio of the total dose received and the total intended dose; "%"

## RESULTS: Population PKPD Modeling

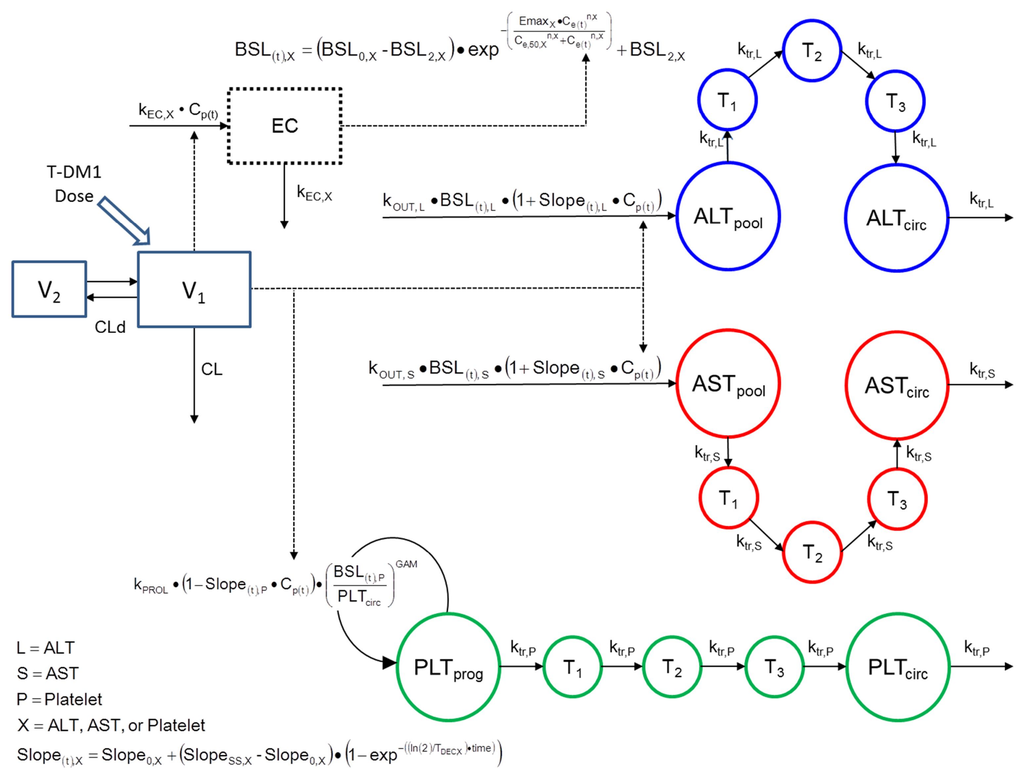



***Figure 1 Schematic of Final PKPD model for platelet, ALT, and AST response to T-DM1.*** ALT: alanine transaminase; $ALT_{circ\ (pool)}$: ALT circulating or pool compartment; AST: aspartate transaminase; $AST_{circ\ (pool)}$: AST circulating or pool compartment; $BSL_{(t)}$: baseline time–course; CL: clearance; CLd: distributional clearance; Cp(t): T-DM1 central compartment concentration time–course; Ce(t): T-DM1 EC concentration time–course; $k_{OUT}$: output rate; $k_{PROL}$: rate of $PLT_{prog}$ proliferation; $PLT_{circ}$: circulating platelet compartment; $PLT_{prog}$: proliferative progenitor platelet pool compartment; $Slope_{(t)}$: Slope time–course; $T_1$, $T_2$, and $T_3$: transit compartments; $V_1$: T-DM1 central volume of distribution; $V_2$: T-DM1 peripheral volume of distribution. Additional parameters are defined in Table 1.

Table 1. Final PKPD Model Estimates

| Parameter | Description | Unit | Platelet | | ALT | | AST | |
|---|---|---|---|---|---|---|---|---|
| | | | Value | IIV% | Value | IIV% | Value | IIV% |
| $Slope_0$ ($\bullet 10^{-3}$) | Initial Slope value | L/mg | 52.0 | 23.1 | 40.7 | 40.5 [b] | 42.6 | 40.5 [b] |
| $Slope_{SS}$ ($\bullet 10^{-3}$) [a] | Slope at steady state | L/mg | 2.08 | 47.9 | 4.28 | 83.0 [b] | 10.2 | 83.0 [b] |
| $T_{DEC}$ ($\bullet 10^{-2}$) | Half-life for $Slope_0 \rightarrow Slope_{SS}$ | week | 1.39 | 53.7 | 2.97 | 85.3 [b] | 3.17 | 85.3 [b] |
| $BSL_0$ | Baseline at time = 0 | count[c] | 264 | 28.2 | 24.0 | 46.4 | 27.2 | 37.7 |
| $BSL_2$ | Secondary baseline | count[c] | 1.41 | 52.9 | 43.7 | 67.9 | 56.6 | 42.4 |
| P(1) | Probability for $k_{EC,\ POP1}$ | — | 0.840 | — | 1.0 | — | 1.0 | — |
| $k_{EC,\ POP1}$ ($\bullet 10^{-5}$) | EC rate constant; POP1 | $hr^{-1}$ | 0.889 | 86.9 | 0.917 | 84.6 | 0.164 | 74.0 |
| $k_{EC,\ POP2}$ ($\bullet 10^{-5}$) | EC rate constant; POP2 | $hr^{-1}$ | 7.64 | 51.0 | — | — | — | — |
| $C_{eff,50}$ [d] | T-DM1 [EC] at 50% Emax | mg/L | 0.900 | 0 | 0.303 | 0 | 0.156 | 0 |
| Emax | Maximum drug effect from EC | L/mg | 0.635 | 54.2 | 1.20 | 111 | 3.70 | 67.2 |
| n | Hill factor | — | 2.67 | — | 2.67 | — | 1.66 | — |
| GAM | Platelet feedback parameter | — | 0.150 | — | — | — | — | — |
| $k_{tr}$ ($\bullet 10^{-2}$) [e] | Intercompartmental transit rate | $hr^{-1}$ | — | — | 2.35 | 31.6 | 3.29 | 28.5 |
| MTT | Mean transit time | hr | 59.5 | 23.8 | — | — | — | — |
| Res. Err. | Residual error | — | 19.2% | — | 15.1% | | 9.85% | |

EC = effect compartment; [EC] = effect compartment concentration; POP = population
[a] Asian ethnicity was a significant covariate for Platelet Slopess
[b] Shared ETA implemented due to approximately 100% correlation; scaled values = 1.93, 1.58, and 1.24 for ALT $Slope_0$, ALT $Slope_{ss}$, and ALT $T_{DEC}$, respectively
[c] units = U/L for ALT and AST; units = count•1000/μL for platelets
[d] IIV% fixed to 0
[e] $k_{PROL}$ set equivalent to $k_{tr}$ for platelet submodel; $k_{OUT}$ set equivalent to $k_{tr}$ for ALT and AST submodels

## RESULTS: Model Evaluation, Parameter Correlations, and Covariate Effects

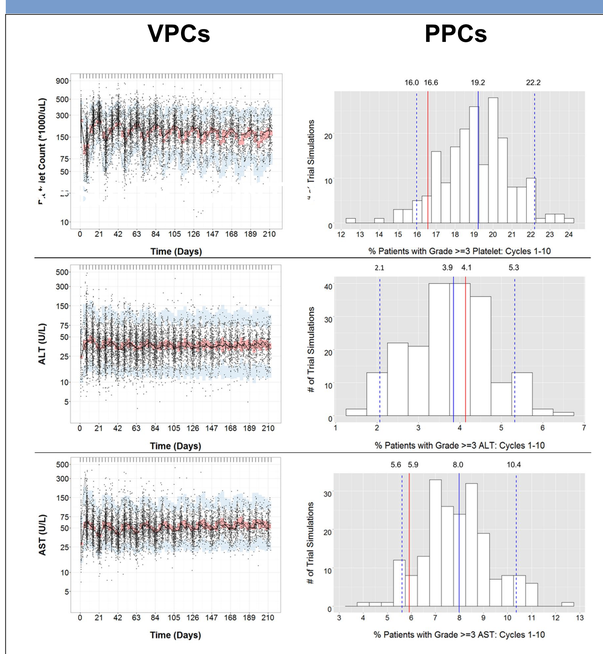



***Figure 2.*** For VPCs, solid black line is median of observations. Red shaded region is 95% CI of the 50$^{th}$ prediction. Blue shaded regions are 95% CIs of the 5$^{th}$ and 95$^{th}$ %-iles. Stippled black lines are 5$^{th}$ and 95$^{th}$ %-iles of observations. For PPCs, histograms show model predicted %s of patients with Grade ≥3. Solid blue line is the 50th %-ile of the model predicted %s. Stippled blue lines are 5th and 95th %-iles of the model predicted %s. Solid red line is the observed %-ile of the evaluation dataset.

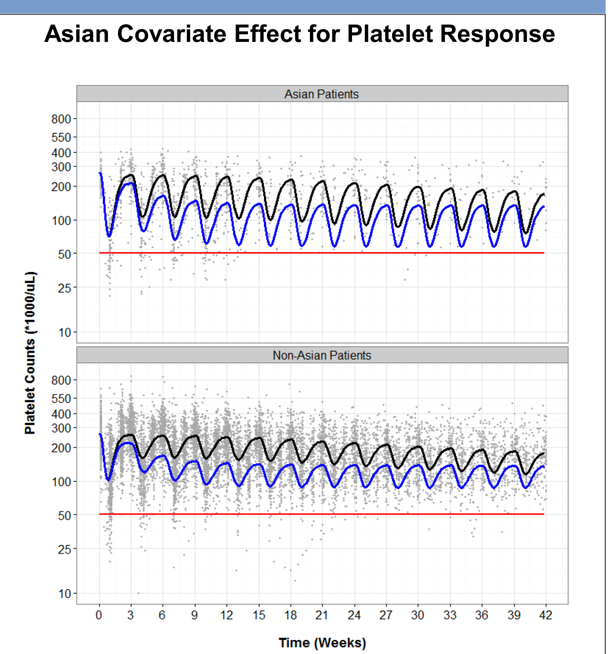



***Figure 3.*** Typical platelet–time profiles following T-DM1 administration (3.6 mg/kg q3w). Asian ethnicity is predictive of higher incidence of Grade 3/4 incidence. Black and blue lines are patients stratified to $k_{EC,POP1}$ and $k_{EC,POP2}$ groups, respectively. Patients in the $k_{EC,POP2}$ show a decline in platelet counts over time from repeated T-DM1 doses. Grey points are individual patient platelet data from the model building dataset. The solid red line is Grade 3 threshold for platelets.

- VPCs and PPC show the PKPD model simultaneously well–predicted the longitudinal platelet, ALT, and AST data and incidences of Grade ≥3 events for platelet (~17%), ALT (~4%), and AST (~6%), respectively
- PD parameters $Slope_0$, $Slope_{SS}$, $T_{DEC}$, and $k_{EC,POP1}$ were highly correlated (>88%) between ALT and AST. No platelet PD parameters were correlated between ALT and AST.
- From covariate analysis, Asian ethnicity is predictive of greater sensitivity to the T-DM1 drug effect that inhibits platelet production, leading to higher incidences of Grade ≥3 thrombocytopenia (i.e. platelet count decrease)
- A subset of patient platelet profiles ($k_{EC,POP2}$) decline slowly over time upon repeated T-DM1 doses

## RESULTS: Model Simulations

1. The following T-DM1 dose modification rules were incorporated into the model for dose simulations:

| ALT or AST | | Platelet | |
|---|---|---|---|
| Grade 3 | Grade 4 | Grade 3 | Grade 4 |
| Delay the next dose until concentrations recover to Grade ≤ 2 | Discontinue T-DM1 Dosing | Delay the next dose until concentrations recover to Grade ≤ 1 | Delay the next dose until concentrations recover to Grade ≤1 |
| Dose reduce by 0.6 mg/kg for q3w regimens, and by 0.4 mg/kg for q1w regimens | | Do not dose reduce | Dose reduce by 0.6 mg/kg for q3w regimens, and by 0.4 mg/kg for q1w regimens |
| Discontinue T-DM1 treatment if more than 2 dose reductions are necessary | | | |

2. Representative simulations for 2 patients

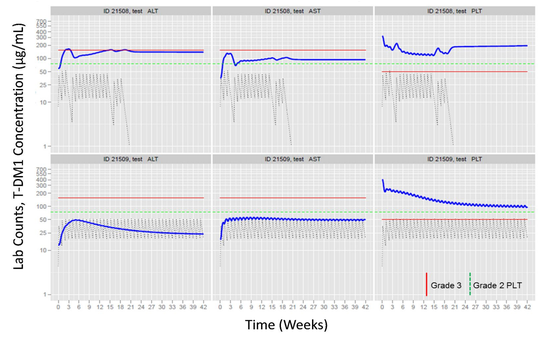



***Figure 4.*** *Representative model-predicted ALT, AST, platelet (PLT) time–courses (solid curves) and TDM1 concentration time–courses (stippled lines) for 2 patients receiving T-DM1 2.4 mg/kg q1w.* ALT levels for Patient ID# 21508 reach Grade 3 (horizontal solid line) multiple times. The model initiates a dose delay each time, reducing the dose to 2.0 mg/kg, and then to 1.6 m/kg upon returning to Grade 2 levels (stippled horizontal line). As only two dose reductions are allowed per the dosing rules, this patient is discontinued after the 3rd Grade 3 ALT event. Patient ID 21509 remains below Grade 3 levels and no dose modifications are necessary.

3a. PK Simulations of T-DM1 weekly dose regimens matched 3.6 mg/kg q3w by $AUC_{SS}$ and $Cmax_{SS}$

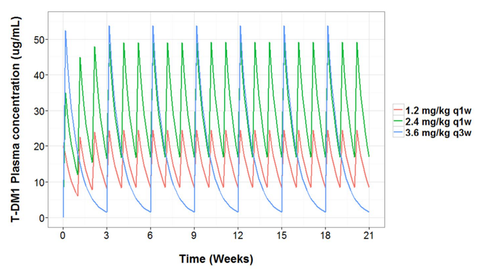



***Figure 5.*** *Model–predicted T-DM1 concentration time–courses for the typical patient receiving 1.2 mg/kg q1w, 2.4 mg/kg q1w, and 3.6 mg/kg q3w T-DM1.* q1w: weekly; q3w: every 3 weeks
- 1.2 mg/kg q1w is equivalent to 3.6 mg/kg q3w by $AUC_{SS}$
- 2.4 mg/kg q1w approximates 3.6 mg/kg q3w by $Cmax_{SS}$

3b. PKPD Simulations of T-DM1 weekly dose regimens matched 3.6 mg/kg q3w by $AUC_{SS}$ and $Cmax_{SS}$

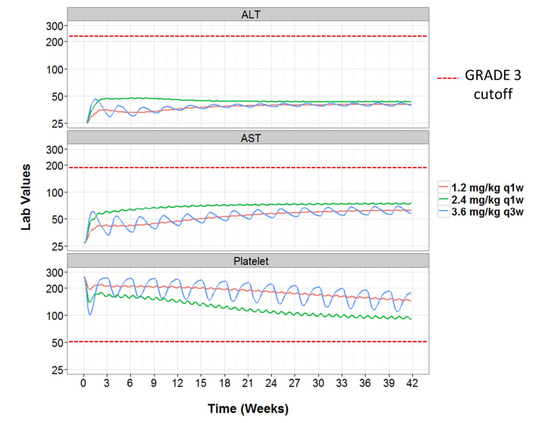



***Figure 6.*** *Model–predicted ALT, AST, and platelet time–courses for the typical patient receiving 1.2 mg/kg q1w, 2.4 mg/kg q1w, and 3.6 mg/kg q3w T-DM1.* q1w: weekly; q3w: every 3 weeks

4. PKPD Model Simulation Results (200 replicates)

Table 2. PKPD Model Simulations of Grade 3/4 Adverse Events and Dose Modifications [a]

| Event | Description | T-DM1 Dose Regimen | | | | | |
|---|---|---|---|---|---|---|---|
| | | 3.6 mg/kg q3w | | 1.2 mg/kg q1w | | 2.4 mg/kg q1w | |
| | | Median % | Range % (5$^{th}$–95$^{th}$) | Median % | Range % (5$^{th}$–95$^{th}$) | Median % | Range % (5$^{th}$–95$^{th}$) |
| Grade ≥ 3 Events | Platelet, ALT, or AST [b] | 33.0 | (28.6–37.2) | 14.5 | (11.8–18.3) | 44.5 | (40.4–49.0) |
| | Platelet | 23.6 | (19.7–27.7) | 7.67 | (5.60–10.3) | 27.1 | (22.4–31.3) |
| | ALT | 4.42 | (2.64–6.19) | 2.06 | (1.18–3.26) | 6.49 | (4.42–8.26) |
| | AST | 10.9 | (8.26–13.6) | 5.60 | (3.54–7.67) | 17.7 | (15.3–21.2) |
| | ALT or AST | 12.4 | (9.72–15.1) | 7.08 | (5.00–9.44) | 20.4 | (17.7–24.2) |
| Grade 4 Events | Platelet, ALT, or AST | 5.31 | (3.24–7.09) | 0 | (0–0.590) | 2.07 | (0.885–3.25) |
| | Platelet | 5.01 | (3.24–7.08) | 0 | (0–0.590) | 1.77 | (0.885–3.25) |
| | ALT | 0 | (0–0.295) | 0 | (0–0) | 0 | (0–0) |
| | AST | 0 | (0–0.295) | 0 | (0–0) | 0 | (0–0.295) |
| | ALT or AST | 0 | (0–0.590) | 0 | (0–0) | 0 | (0–0.295) |
| Dose Modifications | ≥ 1 Dose Reduction | 2.07 | (0.885–3.25) | 7.08 | (5.01–9.14) | 21.8 | (19.2–25.7) |
| | ≥ 1 Dose Delay | 4.87 | (3.24–6.80) | 14.5 | (11.8–18.3) | 44.5 | (40.4–49.0) |
| | Dose discontinuations | 0.295 | (0–0.885) | 1.18 | (0.295–2.36) | 6.78 | (4.72–9.14) |
| Dose Intensity | (mg/kg/wk) [c] | 1.18 | (1.17–1.19) | 1.15 | (1.13–1.16) | 2.07 | (2.02–2.11) |
| | Relative (%) [d] | 98.3 | (97.5–99.0) | 95.7 | (94.3–96.9) | 86.2 | (84.3–88.1) |

[a] The incidences of Grade 3/4 events are based on weekly assessments. Dose modification and dose intensity calculations derive from predose assessments per clinical guidelines.
[b] Platelet, ALT, or AST Grade 3/4 events may be less than the sum of the individual incidences (i.e. ALT+AST+Platelet), as Grade 3 events may occur simultaneously
[c] Dose intensity is calculated by the total dose given divided by the treatment duration
[d] Relative dose intensity is calculated by the ratio of the total dose received and the total dose intended during the treatment duration

- From simulations, the 2.4 mg/kg q1w regimen has:
  - the highest dose intensity (2.07 mg/kg/wk),
  - the most dose modifications
  - the lowest RDI (86.2 %)
- Simulated T-DM1 dose modifications are triggered mostly by Grade ≥3 platelet levels

## CONCLUSIONS

- The integrated PKPD model simultaneously well–described ALT, AST, and platelet response
  - ALT and AST response were correlated between each other; Platelet response was independent
  - Dose modification rules for T-DM1 provided more relevant simulation results, reproducing clinical practice
- The matching of T-DM1 $AUC_{SS}$ (1.2 mg/kg q1w) and $Cmax_{SS}$ (2.4 mg/kg q1w) to the approved dose (3.6 mg/kg q3w) is a clinical simulation strategy that may be useful when a target exposure or concentration is used to guide dose optimizations, respectively.
- The simulated 2.4 mg/kg q1w dose provided the highest T-DM1 dose intensity
- Asian patients are predicted to have higher incidences of Grade 3/4 TCP than Non-Asian patients

### References

[1] Dieras, V., et al., *Trastuzumab emtansine in human epidermal growth factor receptor 2-positive metastatic breast cancer: an integrated safety analysis.* J Clin Oncol, 2014. 32(25): p. 2750-7.
[2] Bender, B.C., et al., *A population pharmacokinetic/pharmacodynamic model of thrombocytopenia characterizing the effect of trastuzumab emtansine (T-DM1) on platelet counts in patients with HER2-positive metastatic breast cancer.* Cancer Chemother Pharmacol, 2012. 70(4): p. 591-601.
[3] Lu, D., et al., *Population pharmacokinetics of trastuzumab emtansine (T-DM1), a HER2-targeted antibody-drug conjugate, in patients with HER2-positive metastatic breast cancer: clinical implications of the effect of covariates.* Cancer Chemother Pharmacol, 2014. 74(2): p. 399-410.
[4] Verma, S., et al., *Trastuzumab emtansine for HER2-positive advanced breast cancer.* N Engl J Med, 2012. 367(19): p. 1783-91.