A multicompartmental population PK model elucidating the complex disposition of trastuzumab emtansine (T-DM1): an antibody-drug conjugate for the treatment of HER2-positive cancer

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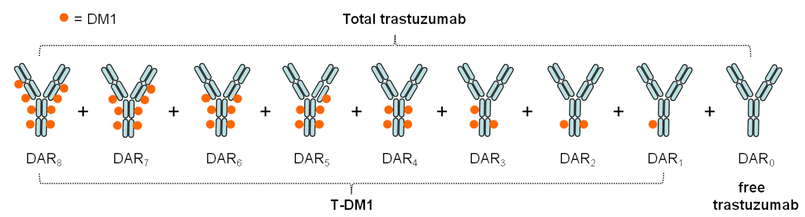
Background

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

T-DM1 drug product is a heterogeneous mix of drug:antibody ratio (DAR) moieties in which trastuzumab (Herceptin®) is conjugated with from 1–8 molecules of the potent microtubule inhibitor DM1 (DAR_1–DAR_8)

The pharmacokinetics of T-DM1, and the underlying DAR_0–DAR_8 moieties, has not been fully elucidated



Objectives

A population PK model was developed from preclinical data in order to:

- Conceptualize the PK system, linking concentrations of measurable DAR moieties
- Quantify PK parameters and rates of T-DM1 deconjugation (loss of DM1)
- Simulate concentrations of DAR moieties, free trastuzumab (DAR_0), total trastuzumab, T-DM1, and the average DAR (DAR_{AVG}) versus time to further elucidate its complex PK

Methods

Analytical Methods

- Relative DAR_0–DAR_8 concentrations were measured by affinity capture LC-MS [2]
- Total trastuzumab concentrations were measured by ELISA

T-DM1 Drug Products for *in vitro* and *in vivo* PK studies

	DAR_0	DAR_1	DAR_2	DAR_3	DAR_4	DAR_5	DAR_6	DAR_7	DAR_8
$T\text{-}DM1_{DAR1.5}$:	21%	35%	26%	13%	4%	1%	not detected (ND)		
$T\text{-}DM1_{DAR3.1}$:	2%	13%	23%	26%	19%	10%	5%	2%	ND

In vitro Plasma Stability Study

- Rat, monkey, and human plasma incubations with 100 µg/mL $T\text{-}DM1_{DAR3.1}$ at 37°C
- Total trastuzumab and DAR_0–DAR_7 measurements (mmts) from 0 to 4 days

In vivo PK Studies (n=34 rats; n=18 cynomolgus monkeys)

- Rat: $T\text{-}DM1_{DAR1.5}$ 10 mg/kg (n=5); $T\text{-}DM1_{DAR3.1}$ 0.3 (n=7), 3.0 (n=8), 10.0 (n=5), and 20.0 mg/kg (n=9); Total trastuzumab mmts from 0–42 days ; DAR_0–DAR_8 mmts from 0–21 days
- Monkey: $T\text{-}DM1_{DAR3.1}$ 30.0 (n=4) [3] and 10.0 mg/kg every 3 weeks (q3w) (n=14); Total trastuzumab mmts from 0–105 days; DAR_0–DAR_7 mmts from 0–28 days

Population PK Modeling

- PK model (Figure 1) was fit to rat (plus *in vitro*) or monkey (plus *in vitro*) data
- NONMEM version 7 with FOCE interaction.
- # of DAR_0–DAR_7 and total trastuzumab mmts = 673 (rat) and 762 (monkey)

Results

Figure 1: Final PK Model

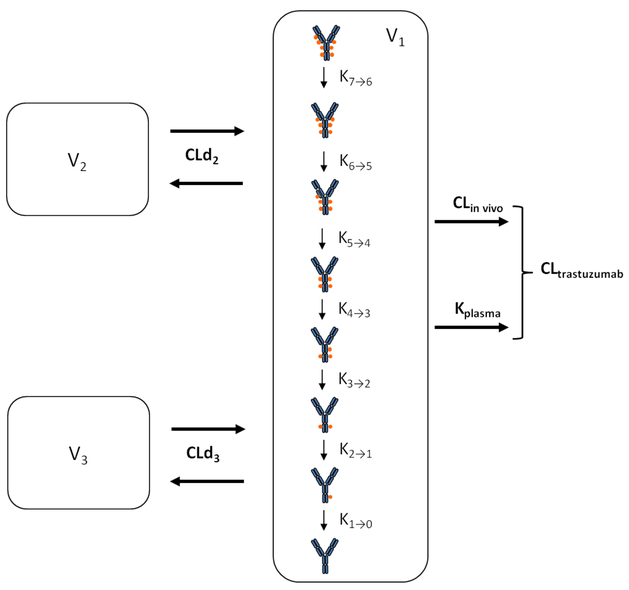
Each DAR_0–DAR_7* moiety:

1. Distributes (CLd_2, CLd_3) into a central (V_1) and two peripheral compartments (V_2,V_3)

2. Deconjugates (loses DM1) at variable rates ($K_{n\rightarrow n\text{-}1}$)

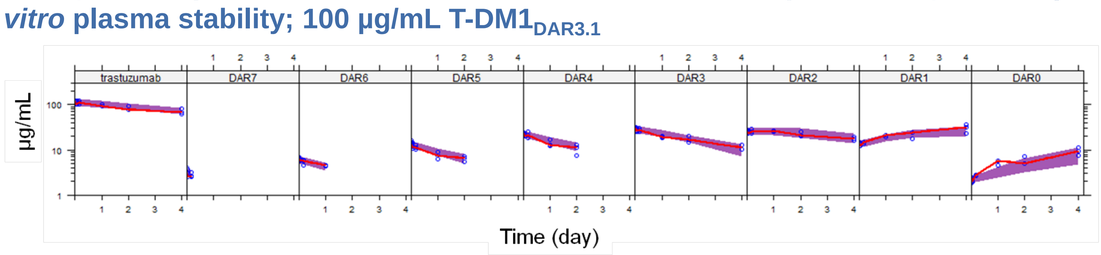
3. Undergoes plasma degradation (K_{plasma}) and other clearance ($CL_{in\ vivo}$) processes

**DAR*$_8$ not detected by LC-MS*
Parameter estimates are shown Table1

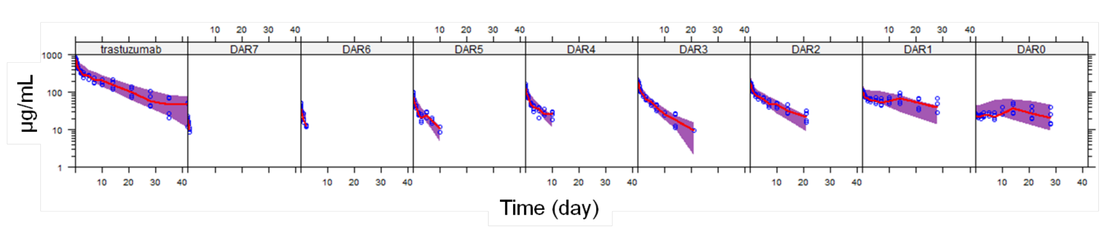


Figures 2a,2b: Representative Visual Predictive Checks (50th %-ile; 95% CI)

2a: *in vitro* plasma stability; 100 µg/mL $T\text{-}DM1_{DAR3.1}$

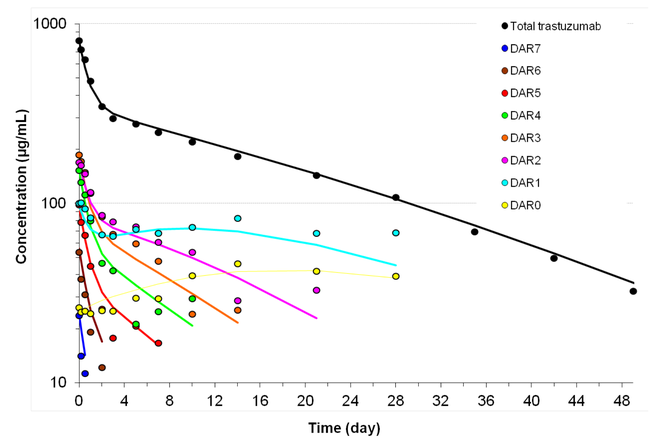


2b: *in vivo* Cynomolgus monkey PK; 30 mg/kg $T\text{-}DM1_{DAR3.1}$



Results (cont'd)

Figure 3: Representative Model Fit



- Cynomolgus monkey; 30 mg/kg $T\text{-}DM1_{DAR3.1}$
- Lines = model predicted
- O = observations

Table 1: Parameter Estimates

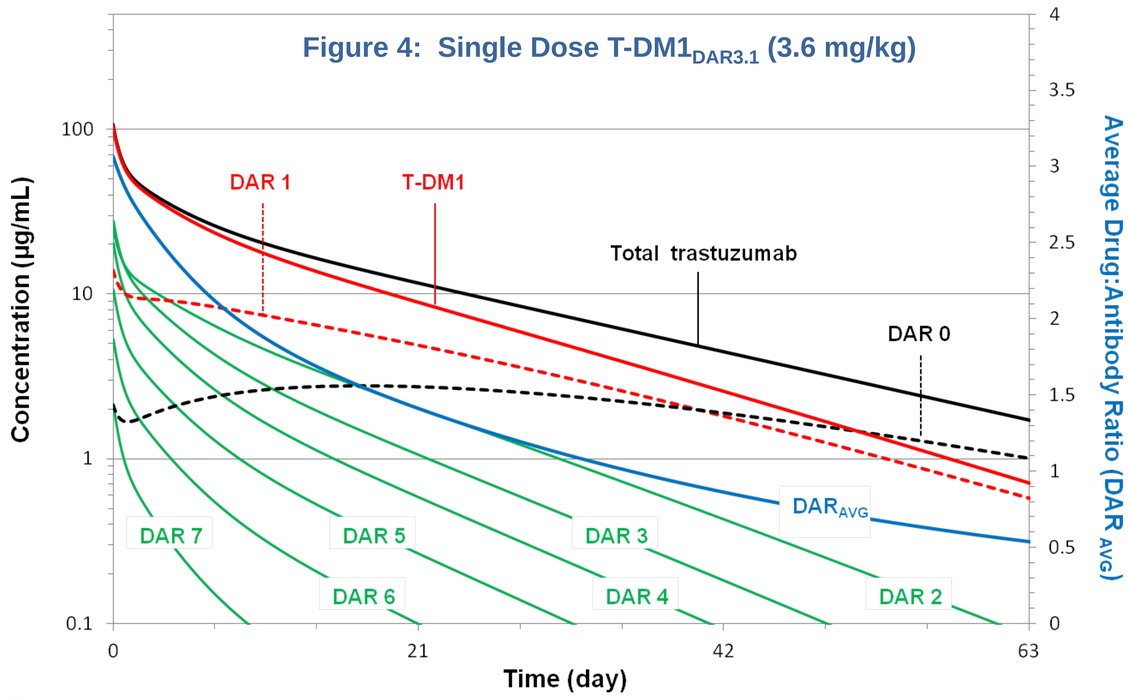
			Rat		Cynomolgus Monkey	
Parameter	Description	Unit	Value *RSE%*	IIV % *RSE%*	Value *RSE%*	IIV % *RSE%*
$CL_{trastuzumab}$	Total trastuzumab Clearance	mL/day	2.32 *4.4*	24.8 *15*	16.0 *6.5*	24.9 *15*
$CL_{in\ vivo}$	*in vivo* antibody clearance	mL/day	1.02 [a]	–	3.61 [a]	–
K_{plasma}	Plasma degradation	day^{-1}	0.113 *14*	–	0.105 *12*	–
V_1	Central volume	mL	11.5 *4.1*	20.6 *14*	118 *4.7*	19.8 *12*
CLd_2	Distribuitional Clearance 2	mL/day	22.1 *21*	–	99.0 *8.0*	–
V_2	Peripheral volume 2	mL	6.41 *25*	58.5 *30*	69.2 *23*	58.7 *16*
CLd_3	Distribuitional Clearance 3	mL/day	6.60 *23*	–	18.8 *24*	–
V_3	Peripheral volume 3	mL	14.7 *11*	19.2 *23*	117 *50*	116 *14*
$K_{7\rightarrow6}$ $K_{6\rightarrow5}$ $K_{5\rightarrow4}$ $K_{4\rightarrow3}$ $K_{3\rightarrow2}$	DAR_7–DAR_3 deconjugation rate [b]	day^{-1}	0.455 *10*	23.9 *39*	0.341 *9.7*	–
$K_{2\rightarrow1}$	DAR_2 deconjugation rate	day^{-1}	0.326 *7.0*	13.5 *59*	0.265 *9.3*	17.5 *15*
$K_{1\rightarrow0}$	DAR_1 deconjugation rate	day^{-1}	0.081 *14*	44.0 *26*	0.0759 *38*	40.1 *14*
Tot trast. $t_{1/2,v}$	Total trastuzumab terminal $t_{1/2}$	day	10.5	–	15.3	–
T-DM1 $t_{1/2,v}$	T-DM1 terminal $t_{1/2}$	day	8.33	–	11.6	–
Res. Err.	Residual error	–	0.125 *6.7*	–	0.139 *3.1*	–

IIV, interindividual variability; RSE, relative standard error; [a] Derived by: $CL_{in\ vivo} = CL_{trastuzumab} - K_{plasma} \cdot V_1$; [b] Rates were determined to be equal from model building

Final Model Simulations

T-DM1 single and multiple dose simulations were done using the final model (Figure 1) and monkey parameter estimates (Table 1) to further elucidate T-DM1 PK

Figure 4: Single Dose $T\text{-}DM1_{DAR3.1}$ (3.6 mg/kg)



From Figure 4:

- T-DM1 clearance is composed of antibody clearance ($CL_{trastuzumab}$) and DM1 deconjugation ($K_{n\rightarrow n\text{-}1}$)
- Total trastuzumab terminal $t_{1/2}$ (15.3 days) can be derived from 3-compartment model PK parameters; T-DM1 terminal $t_{1/2}$ is shorter (11.6 days) due to the additional $K_{1\rightarrow0}$ elimination rate (rate limiting step)
- The DAR_{AVG} curve is multiphasic, and depends on the T-DM1 drug product, deconjugation rates, and PK
  - The drop in DAR_{AVG} in the first week, starting at DAR_{AVG} = 3.1, is due to the more rapid loss of DAR ≥ 3
  - After the first week, the DAR_{AVG} profile results primarily from the slower elimination of DAR_0–DAR_2

Figure 5: Multiple Dose $T\text{-}DM1_{DAR3.1}$ (3.6 mg/kg q3w)

From Figure 5:

- Under a q3w dose regimen, the steady state maximum DAR_{AVG} goes down from 3.1 to 2.8, due to accumulation of DAR_1 and DAR_0

- T-DM1 $C_{max,ss}$ is < total trastuzumab $C_{max,ss}$ due to 1) the greater T-DM1 clearance from DM1 deconjugation and 2) DAR_0 accumulation

- Concentrations of total trastuzumab, T-DM1, DAR_0–DAR_7, and DAR_{AVG} can be evaluated as PK drivers for the PKPD modeling of efficacy and toxicity with T-DM1 treatment

Conclusions

- T-DM1 disposition, and underlying DAR moieties, was well described by a multicompartmental PK model based on preclinical *in vivo* and *in vitro* data
- In both rats and monkeys, the higher conjugated DAR moieties (≥ 3 DM1/trastuzumab) deconjugated faster than lower conjugated DAR moieties
- This model can be used to simulate concentrations of DAR moieties, free trastuzumab, total trastuzumab, T-DM1, as well as DAR_{AVG} versus time; these analytes can be evaluated as PK drivers of efficacy and toxicity
- PK concepts elucidated here may aid the design and analyses of similar ADCs

References

[1] Lewis-Phillips GD, Li G, Dugger DL, et al. *Cancer Res.* 2008;22:9280-9290.
[2] Xu, K. et al. *Anal Biochem* **412**, 56-66 (2011).
[3] Leipold D, Bender B, Xu K, Theil F-P, and Tibbitts J. Understanding the de-conjugation of Trastuzumab-MCC-DM1 through application of a multi-compartmental model of individual drug:antibody species in cynomolgus monkey. Presented at the 2009 American Association for Cancer Research (AACR) Meeting, Denver, Colorado. April 18th, 2009.