UNVEILING PHARMACOKINETIC VARIATIONS IN HER2- TARGETING ANTIBODIES: INSIGHT INTO BREAST CANCER

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BACKGROUND

Property	Herceptin (Trastuzumab)	Margenza (Margetuximab)	Perjeta (Pertuzumab)
Target	HER2	HER2	HER2
Approved Indication(s)	HER2-positive breast cancer, HER2-positive metastatic gastric or gastroesophageal junction adenocarcinoma	HER2-positive metastatic breast cancer	HER2-positive breast cancer
Adult Dosing Regimen	Initial dose of 4 mg/kg, followed by 2 mg/kg weekly or 6 mg/kg every 3 weeks	15 mg/kg every 3 weeks	Initial dose of 840 mg, followed by 420 mg every 3 weeks
Route of Administration	Intravenous infusion	Intravenous infusion	Intravenous infusion
Species	Humanized	Human	Humanized
Isotype	IgG1	IgG1	IgG1
Production Method	Mammalian cell culture	Mammalian cell culture	Mammalian cell culture
Format	Full-length antibody	Full-length antibody	Full-length antibody
Backbone	IgG1	IgG1	IgG1
Conjugation	Unconjugated	Unconjugated	Unconjugated

Table 1: Properties of FDA-approved Anti-HER2 mAbs

PURPOSE

- The purpose of this study was to:
  - Evaluate pharmacokinetic differences between HER2-targeting antibodies in **breast** cancer patients
  - Assess whether Perjeta and Margenza could utilize the same dosing regimen as "first in class" Herceptin

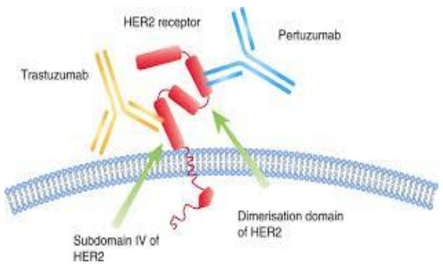


Figure 1. Mechanism of binding of Herceptin and Perjeta to HER2. Figure reproduced from: J Wang, B Xu. *Sig Transduct Target Ther*. 2019;4:34.

METHODOLOGY

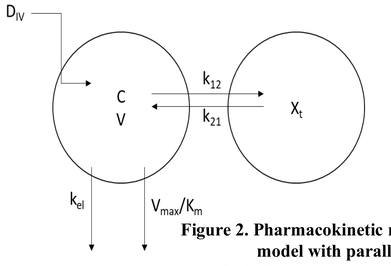
A literature search gathered pharmacokinetic data for the HER2-targeting antibodies trastuzumab (Herceptin), pertuzumab (Perjeta), and margetuximab (Margenza).

Concentration-time profiles were digitized from FDA reviews and publications using WebPlotDigitizer.

Non-compartmental analysis and compartmental modeling were utilized to characterize digitized data.

The compartmental model was utilized to predict anti-HER2 mAb concentrations following multiple dosing.

PHARMACOKINETIC MODELING



$$\frac{dC}{dt} = \frac{K_0}{V} - (k_{el} + k_{12}) \times C + \frac{k_{21}}{V} \times X_t - \frac{V_{max} \times C}{V \times (K_M + C)} \qquad C(0) = 0$$

$$\frac{dX_t}{dt} = k_{12} \times C \times V - k_{21} \times X_t \qquad X_t(0) = 0$$

Figure 2. Pharmacokinetic model structure for anti-HER2 mAbs. 2-compartment model with parallel linear and Michaelis-Menten elimination.

Symbols: C (Concentration in central compartment), V (volume of central compartment), D_{IV} (IV dose), k_{el} (1^{st} order elimination rate constant), V_{max} (maximum elimination rate of non-linear process), K_m (Michaelis-Menten constant), k_{12} (distribution rate from central to peripheral compartment), k_{21} (distribution rate from peripheral to central compartment), X_t (amount of drug in the peripheral compartment).

NONCOMPARTMENTAL ANALYSIS

PERJETA.	0.5 mg/kg	2 mg/kg	5 mg/kg	10mg/kg	15 mg/kg
AUC_{last} (µg/mL*day)	46.0	347	841	1802	2907
Terminal Slope (1/day)	0.166	0.0512	0.0570	0.0396	0.0496
AUC_{inf} (µg/mL*day)	47.2	507	1176	3030	4314
Half-Life (day)	4.17	13.5	12.2	17.5	14.0
C_{max} (ng/mL)	12.5	51.7	112	262	382
CL (mL/day/kg)	10.6	3.95	4.25	3.30	3.48
V_{ss} (ml/kg)	47.2	45.9	63.5	77.6	64.9

Table 2: Noncompartmental analysis of Perjeta pharmacokinetics in breast cancer patients.

HERCEPTIN	2 mg/kg	4 mg/kg	6 mg/kg	8 mg/kg
AUC_{last} (µg/mL*day)	163	592	1028	1674
Terminal Slope (1/day)	0.273	0.126	0.0670	0.0684
AUC_{inf} (µg/mL*day)	172	597	1092	1808
Half-Life (day)	2.54	5.50	10.3	10.1
C_{max} (ng/mL)	36.4	69.0	102	149
CL (mL/day/kg)	11.6	6.70	5.49	4.42
V_{ss} (ml/kg)	70.8	59.9	69.9	68.9

Table 3: Noncompartmental analysis of Herceptin pharmacokinetics in breast cancer patients.

RESULTS

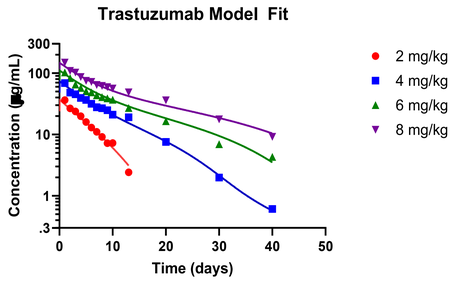


Figure 3. Pharmacokinetics of Herceptin in breast cancer patients. Symbols represent digitized data. Lines represent model fit.

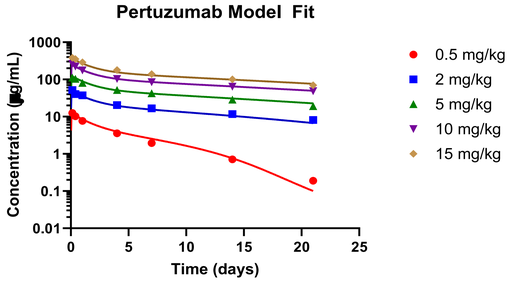


Figure 4. Pharmacokinetics of Perjeta in breast cancer patients. Symbols represent digitized data. Lines represent model fit.

- Margenza pharmacokinetic data has not been published in a format suitable for digitization
- We utilized PK model parameters reported in the FDA Clinical Pharmacology & Biopharmaceutics Review for this product
- Units were converted to match those used for Herceptin and Perjeta for ease of comparison

Parameter (Units)	Estimate (%CV)
k_{el} (day^{-1})	0.0295 (17.2%)
k_{12} (day^{-1})	0.101 (10.8%)
k_{21} (day^{-1})	0.0849 (15.6%)
V_1 (mL/kg)	54.1 (4.47%)
V_{max} (µg/day)	92.8 (10.1%)
K_m (µg/mL)	1.64 (36.1%)

Table 4. Parameter estimates for Herceptin

Parameter (Units)	Estimate (%CV)
k_{el} (day^{-1})	0.0730 (10.4%)
k_{12} (day^{-1})	0.326 (23.2%)
k_{21} (day^{-1})	0.311 (24.2%)
V_1 (mL/kg)	39.7 (4.15%)
V_{max} (µg/day)	22.6 (19.0%)
K_m (µg/mL)	0.403 (93.5%)

Table 4. Parameter estimates for Perjeta

Parameter (Units)	Published Value
k_{el} (day^{-1})	0.0843
k_{12} (day^{-1})	0.194
k_{21} (day^{-1})	0.209
V_1 (mL/kg)	40.9
V_{max} (µg/day)	3.83
K_m (µg/mL)	0.700

Table 5. Published model parameters for Margenza

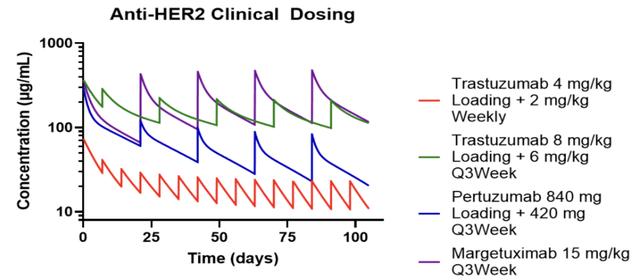


Figure 5. Model-predicted pharmacokinetics of Herceptin, Perjeta, and Margenza at their FDA-approved dosing regimens in breast cancer patients.

ALTERNATIVE DOSING REGIMEN

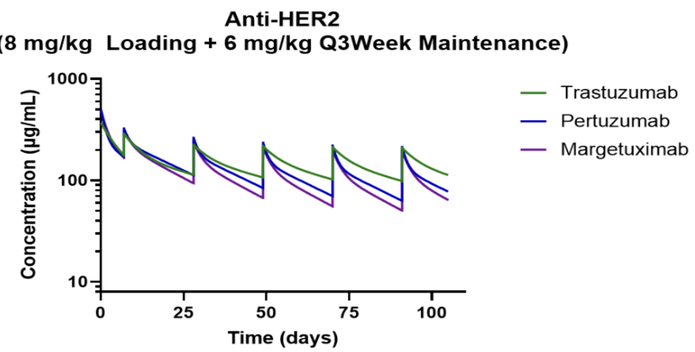


Figure 6. Model prediction of the pharmacokinetics of Herceptin, Perjeta, and Margenza when administered at the approved dosing regimen for Herceptin (8 mg/kg loading + 6 mg/kg Q3Week Maintenance).

Exposure	Herceptin	Perjeta	Margenza
Approved	$AUC_{ss} = 2.84x10^3$ µg*day/mL	$C_{min,C2} = 50.0$ µg/mL	$C_{av,ss} = 204$ µg/mL
Test		$C_{min,C2} = 112$ µg/mL	$C_{av,ss} = 87.6$ µg/mL

Table 6. Comparison of mAb exposure at FDA-approved dosing regimens and the test dosing regimen (8 mg/kg loading + 6 mg/kg Q3week). Outputs were based on published exposure-response analyses for each mAb. Herceptin: AUC_{ss}, Perjeta: $C_{min, Cycle\ 2}$, Margenza: $C_{av,ss}$

CONCLUSIONS

Non-compartmental analysis revealed that both Herceptin and Perjeta have non-linear PK.
- o Herceptin: Dose-dependent decreases in CL and increases in half-life.
- o Perjeta: Dose-dependent decreases in CL and increases in V_{ss} and half-life.

A 2-compartment model with parallel linear and Michaelis-Menten elimination was developed to characterize the PK of Herceptin and Perjeta.
Exposures of Herceptin, Perjeta, and Margenza were predicted to be distinct at FDA-approved dosing regimens.

Simulations were performed to evaluate whether the high dose Herceptin regimen could be utilized for Perjeta and Margenza.
- o Perjeta exposure was predicted to be sufficient at the test dosing regimen based on $C_{min, Cycle\ 2}$.
- o Model predicted concentrations were ~2.2-fold higher than the approved regimen.
- o In the absence of safety concerns, Perjeta could be dosed at this regimen.

Margenza exposure was predicted to be insufficient at the test dosing regimen based on $C_{av,ss}$
- o Model-predicted concentrations were ~2.4-fold lower than the approved regimen.
- o It is unlikely that Margenza could be dosed at the same regimen as Herceptin.

REFERENCES

Databases: FDA Label, PubMed
Software: ADAPT5, WebPlotDigitizer
Literature

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