Aspetti farmacologici

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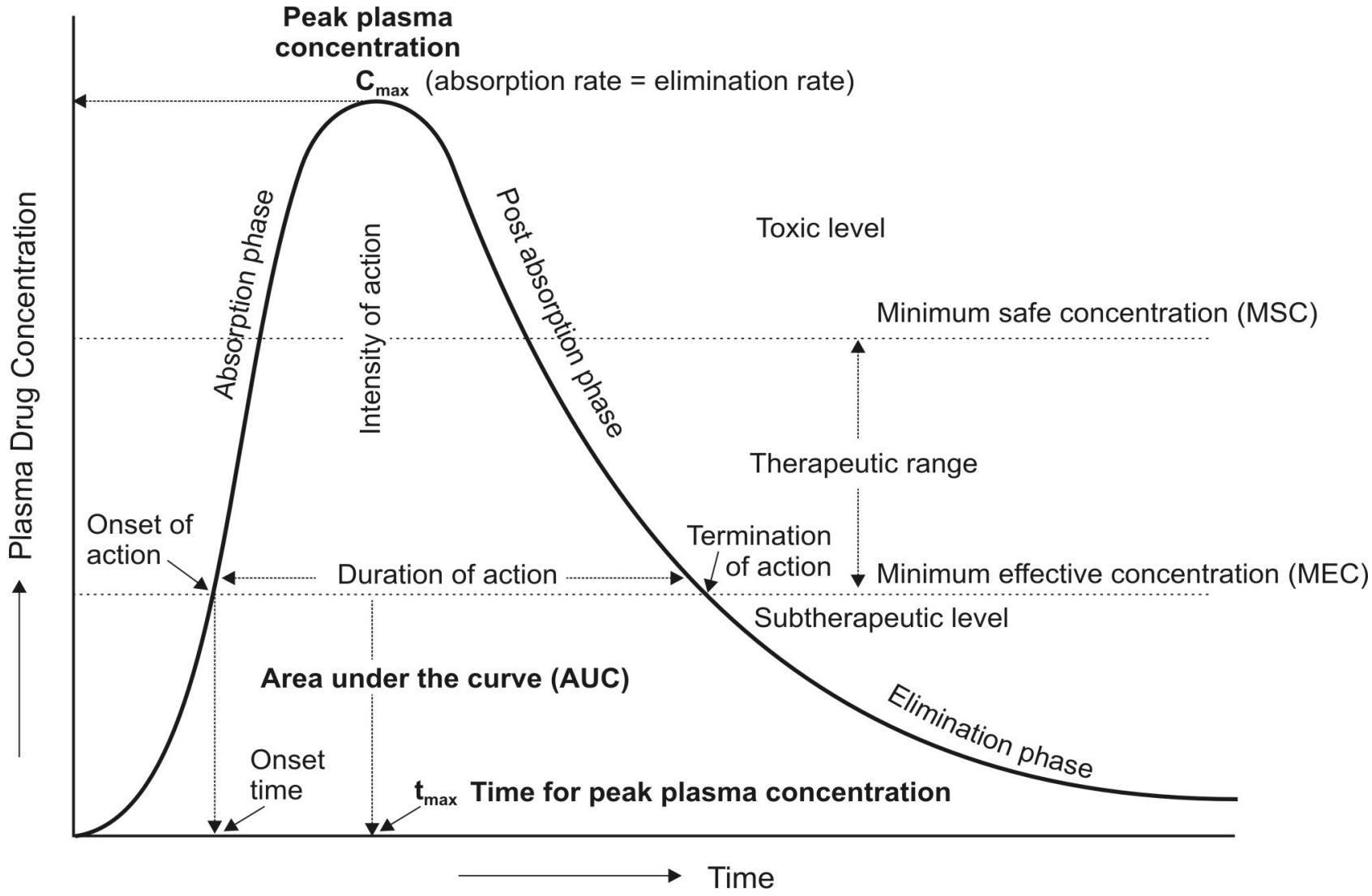
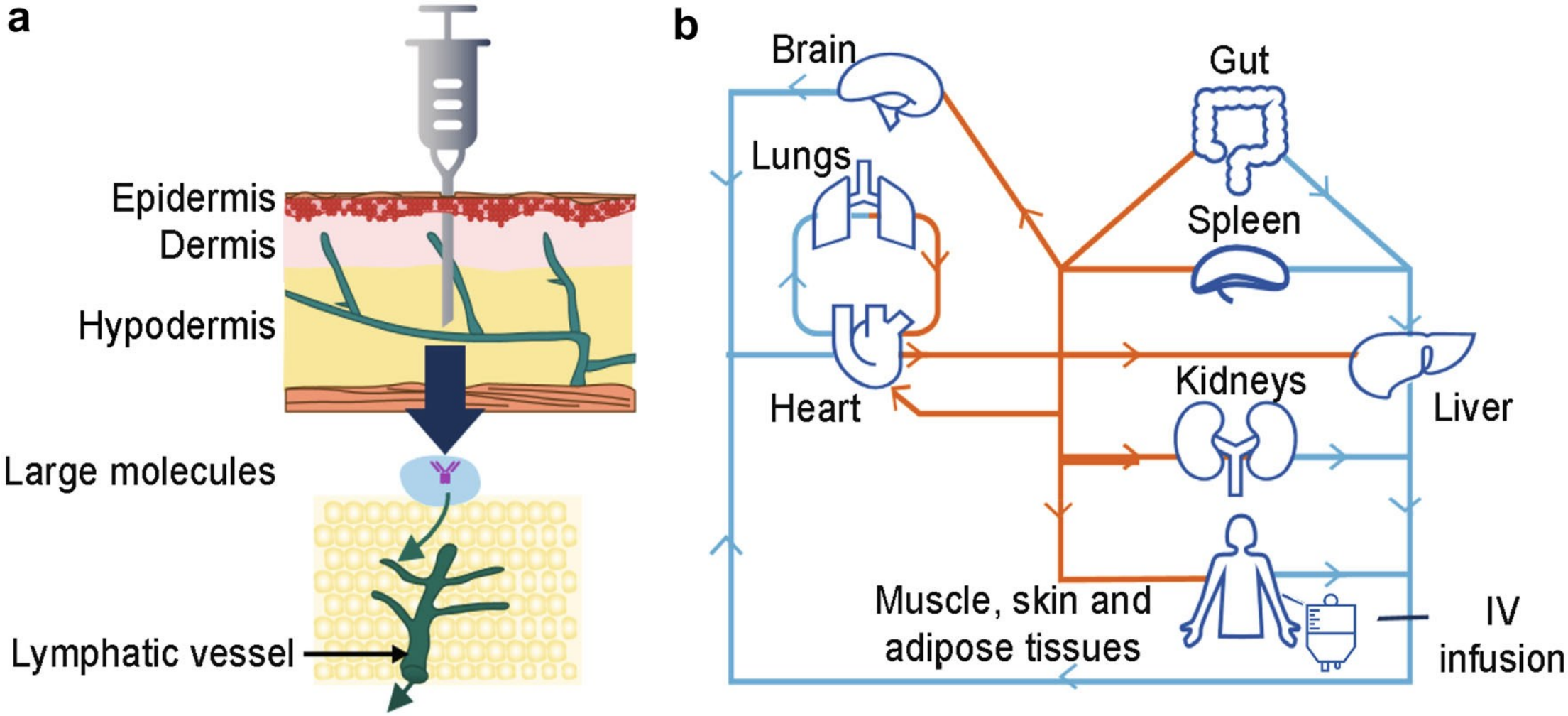
Main pharmacokinetic parameters



http://www.turkupetcentre.net/petanalysis/pk_1cm.html

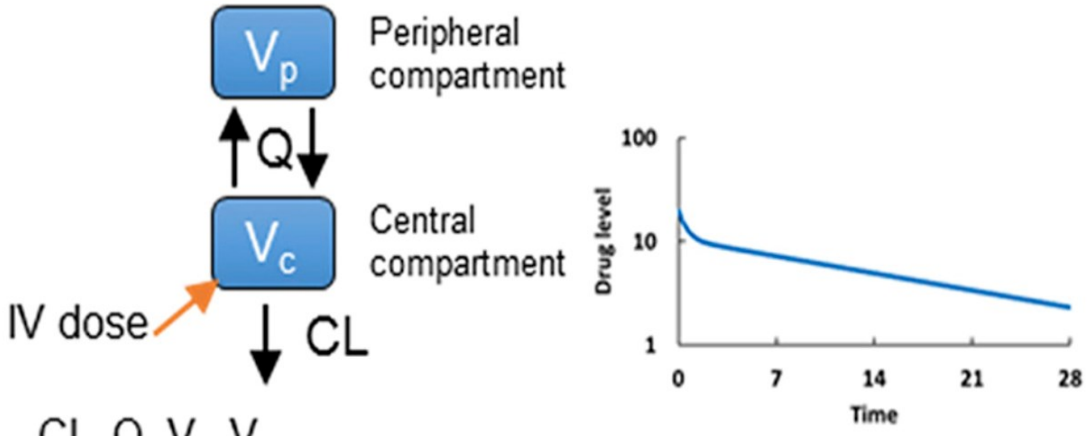
SC (a) vs IV (b) administration of moAb



Hauser SL et al. Neurol Ther (2023) 12:1491–1515

Pharmacokinetics of moAbs after IV or SC administration

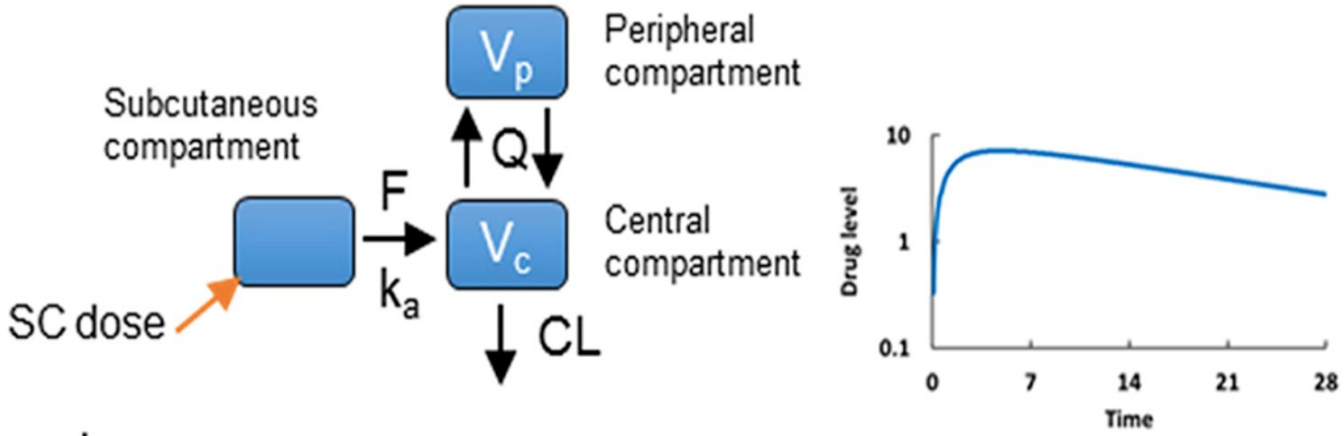
Prediction of PK after intravenous injection in human



CL, Q, V_c, V_p

Allometric scaling from parameters in cynomolgus monkey using exponents (0.8 for CL, 0.75 for Q, 1.0 for V_c, 0.95 for V_p)

Prediction of PK after subcutaneous injection in human



k_a

Geometric mean of reported values in human

F

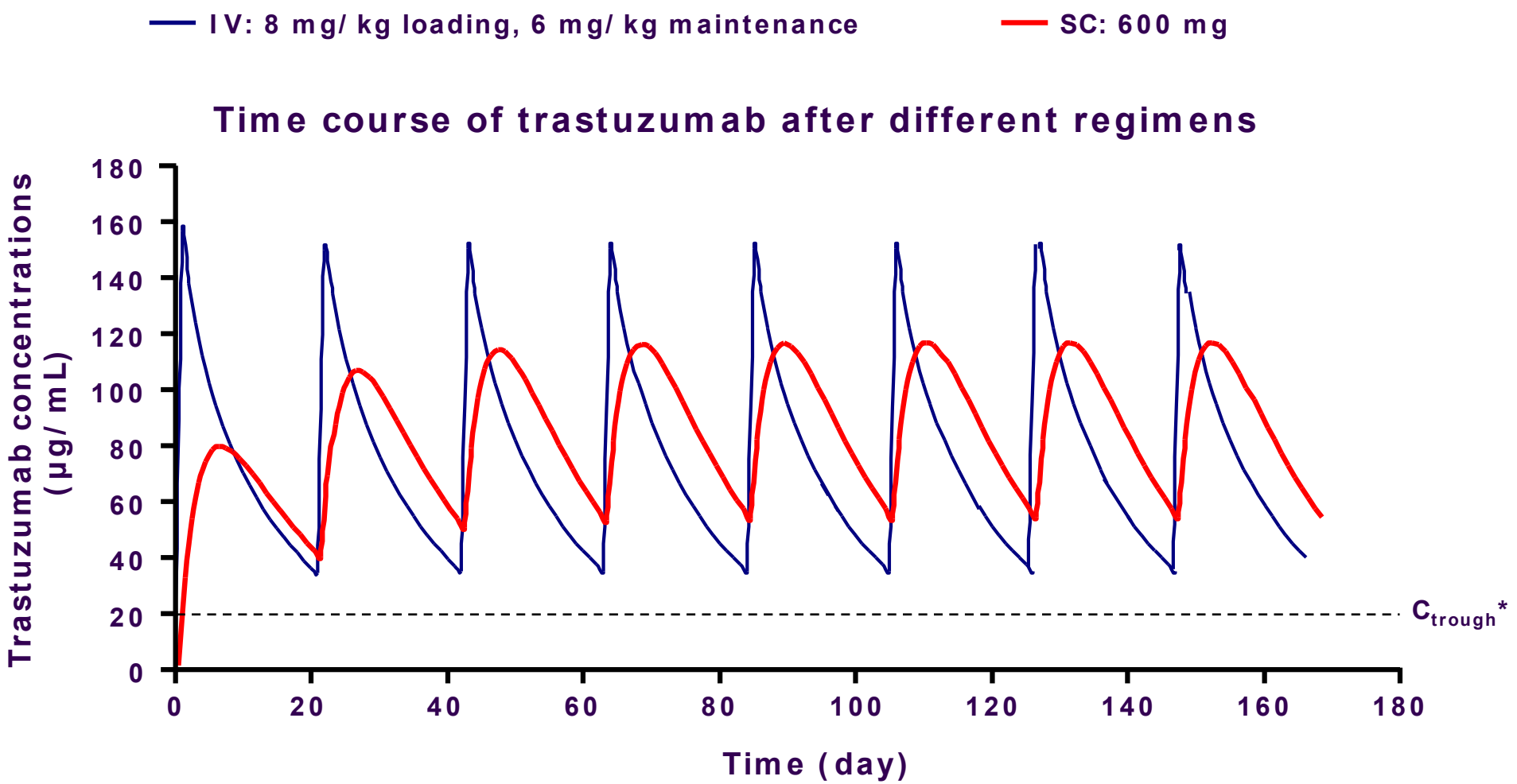
Prediction from CL (−6.72 * predicted CL + 89.4)

Haraya K et al. Drug Metabolism and Pharmacokinetics 32 (2017) 208e217

SC (a) vs IV (b) administration of moAb

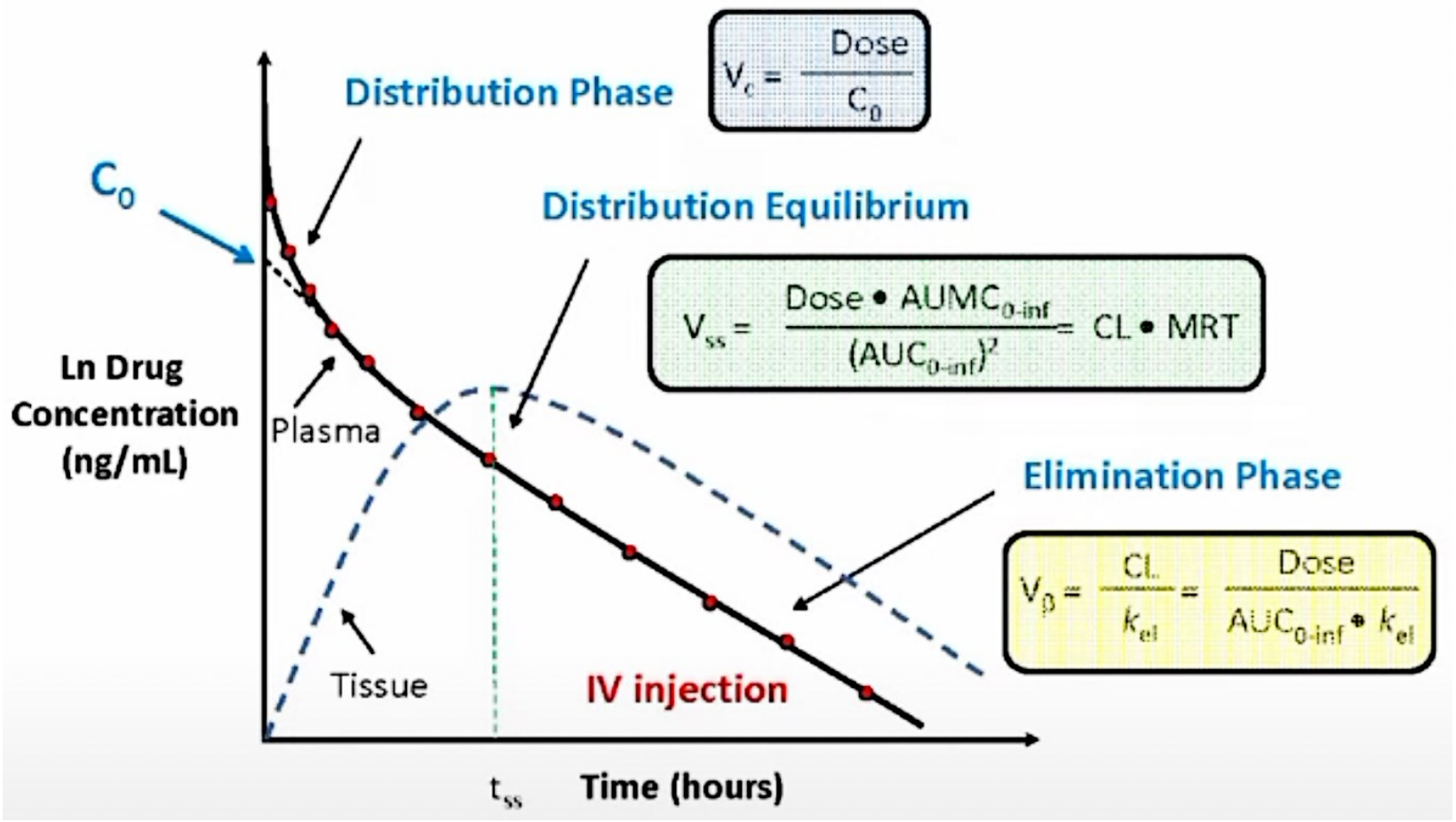
1) moAbs have high affinity for the target → fast reach of the target compartment and target saturation
2) No need of high concentration (IV) because of 1) (high concentration useful for small molecules as tissue gradient)
3) No plasmatic peak → no toxicities

Plasma profiles of trastuzumab after SC vs. IV 3-weekly administration
-Cmax is higher after IV and AUC is higher after SC dose-



Baselga J, *et al. J Clin Oncol* 2005; 23 (10)

The Volume of distribution



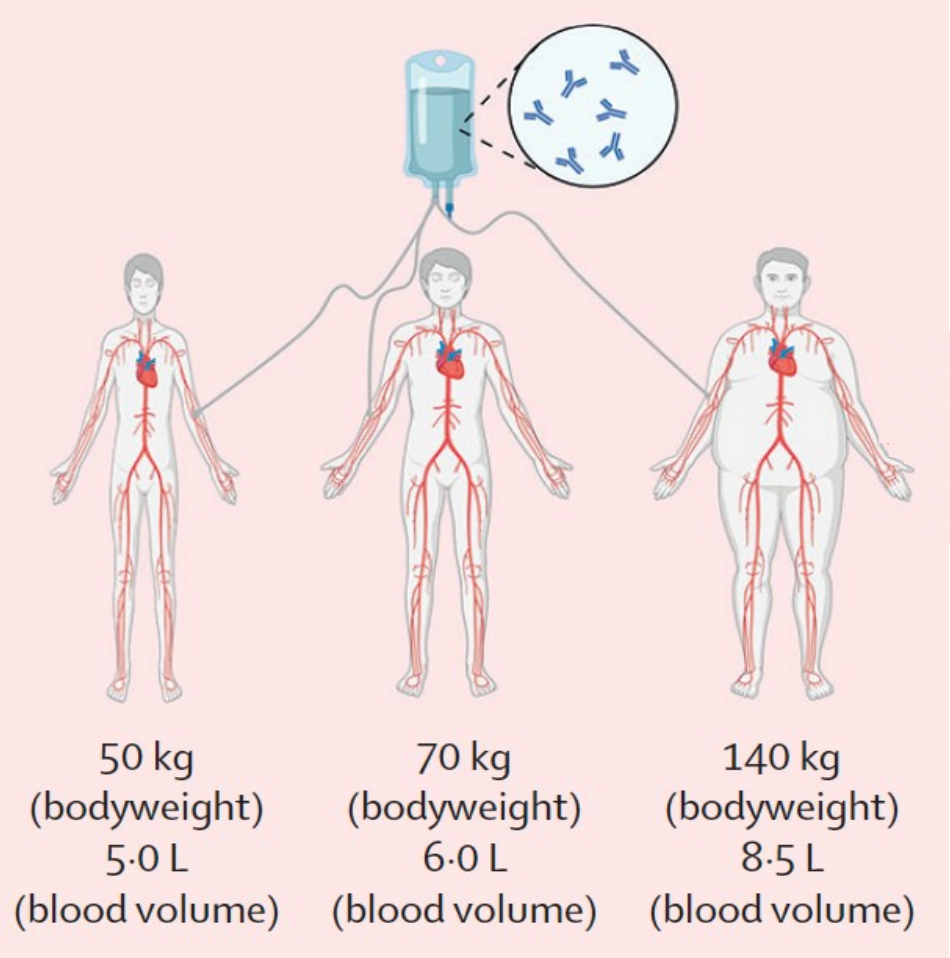
Vd <5 L
Plasma

Vd <15 L
Interstitial liquids

Vd >15 <42 L
Total water

Vd > 42 L
Target tissue

Volume of distribution of moAbs

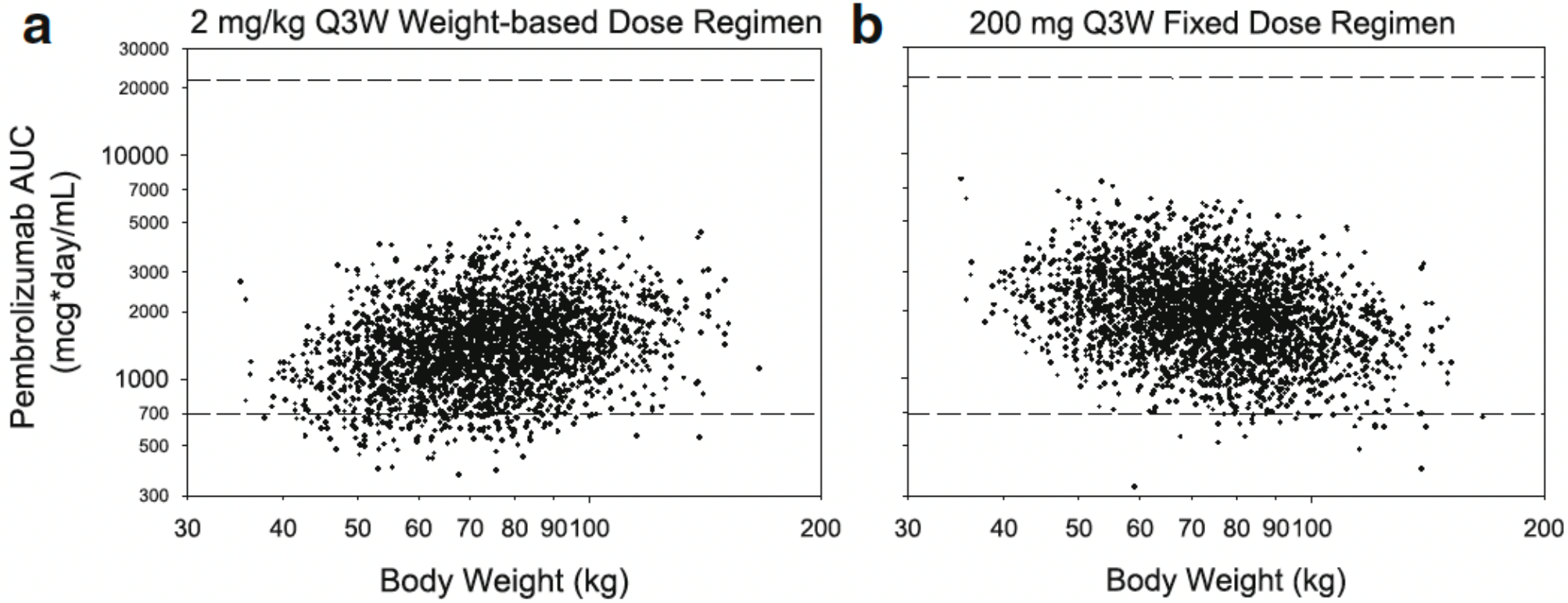


- Due to their large molecular size, the **volume of distribution (VD)** of moAbs is limited to blood, which has a non-linear correlation with bodyweight.

- Small molecule anti-cancer drugs are often dosed on the basis of body weight or body surface area to correct for interpatient variability in distribution and clearance, which correlate to body size.
- **Dosing of moAbs based on bodyweight** typically results in lower exposures in patients with low bodyweight and higher exposures in patients with high bodyweight.
- On the contrary, **fixed dosing** results in higher exposures in patients with lower bodyweight and lower exposures in patients with higher bodyweight.

Malmberg R, et al. Lancet Oncol 2022; 23: e552–61

Variation in pembrolizumab AUC after weight-based or fixed-dose administrations

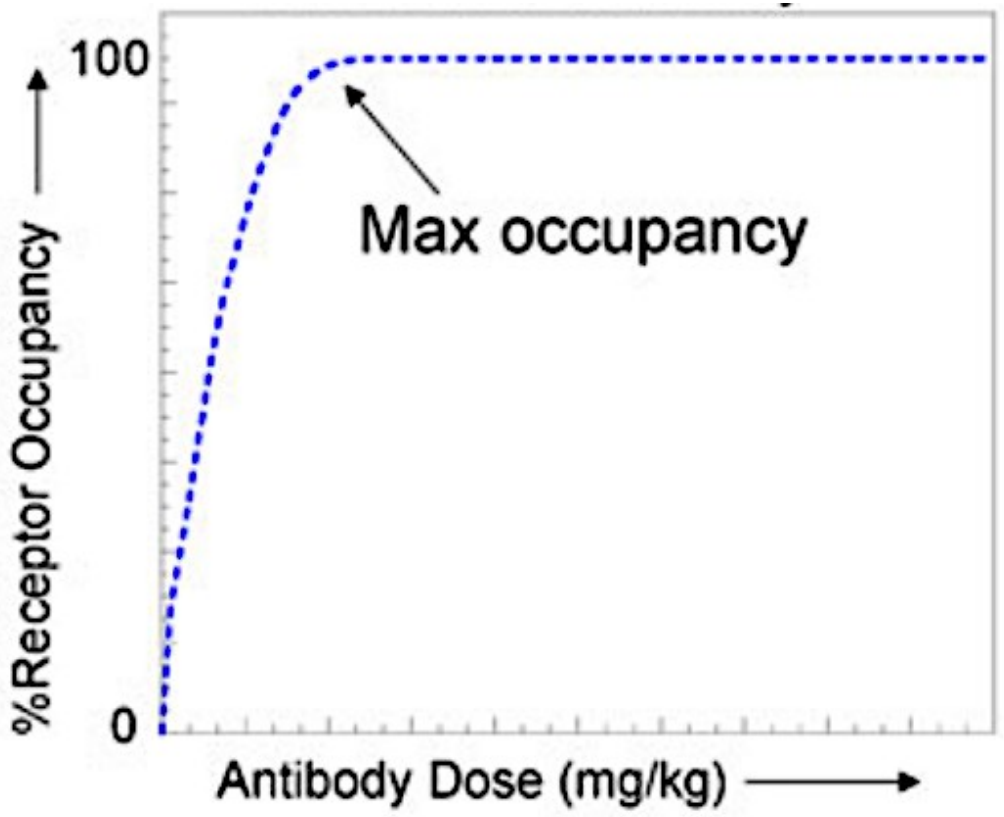


With the weight-dose regimen lower-weight patients tend to have lower exposures compared to higher-weight patients, while the opposite trend is seen with fixed dosing.

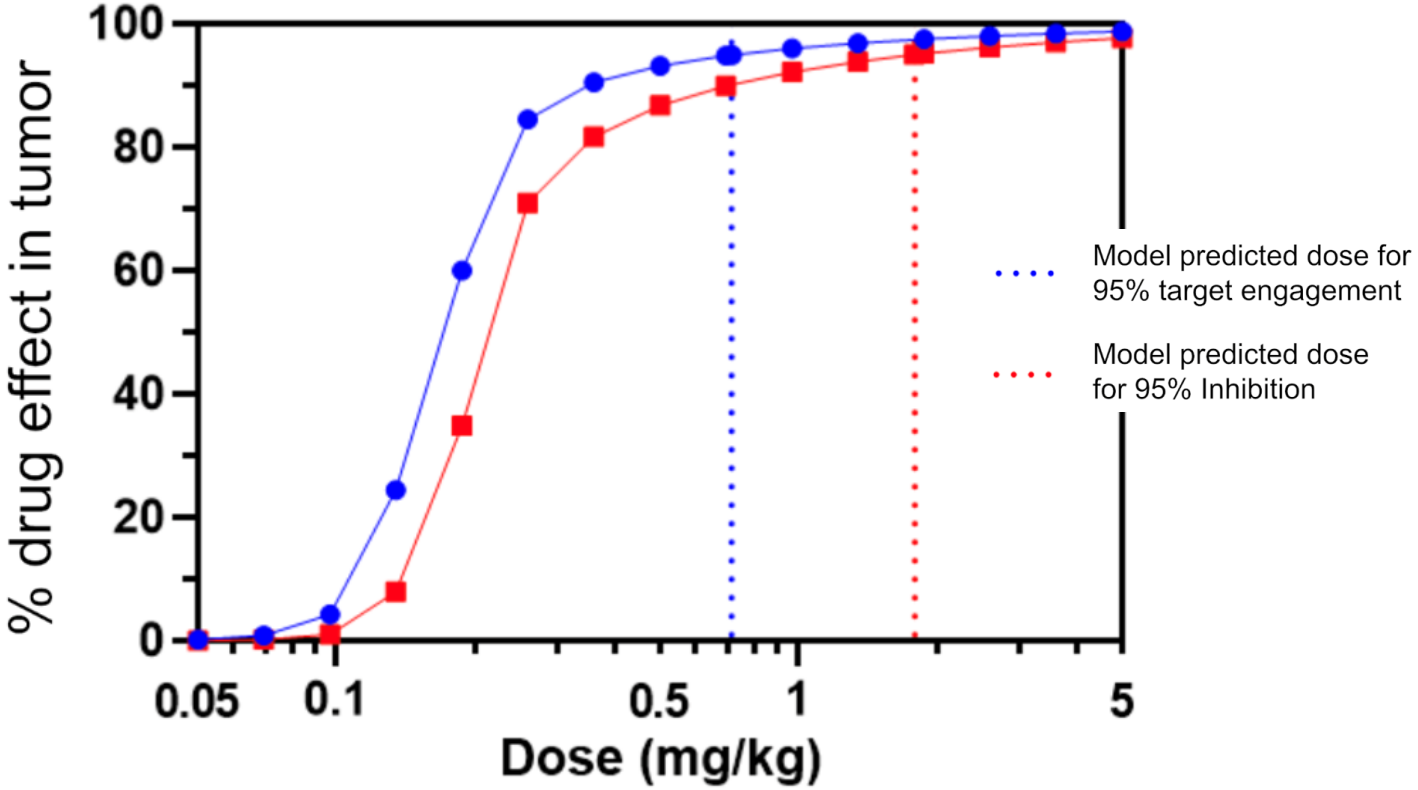
Freshwater T, et al. Journal for ImmunoTherapy of Cancer (2017) 5:43

The concept of “Receptor Occupancy” (RO)

In principle, the pharmacological effect is proportional to the number of targets occupied by the drug and maximal effect occurs when most of them (80-95%) are occupied



Atezolizumab RO



DOI:10.1208/s12248-012-9374-1

https://doi.org/10.1002/psp4.13152

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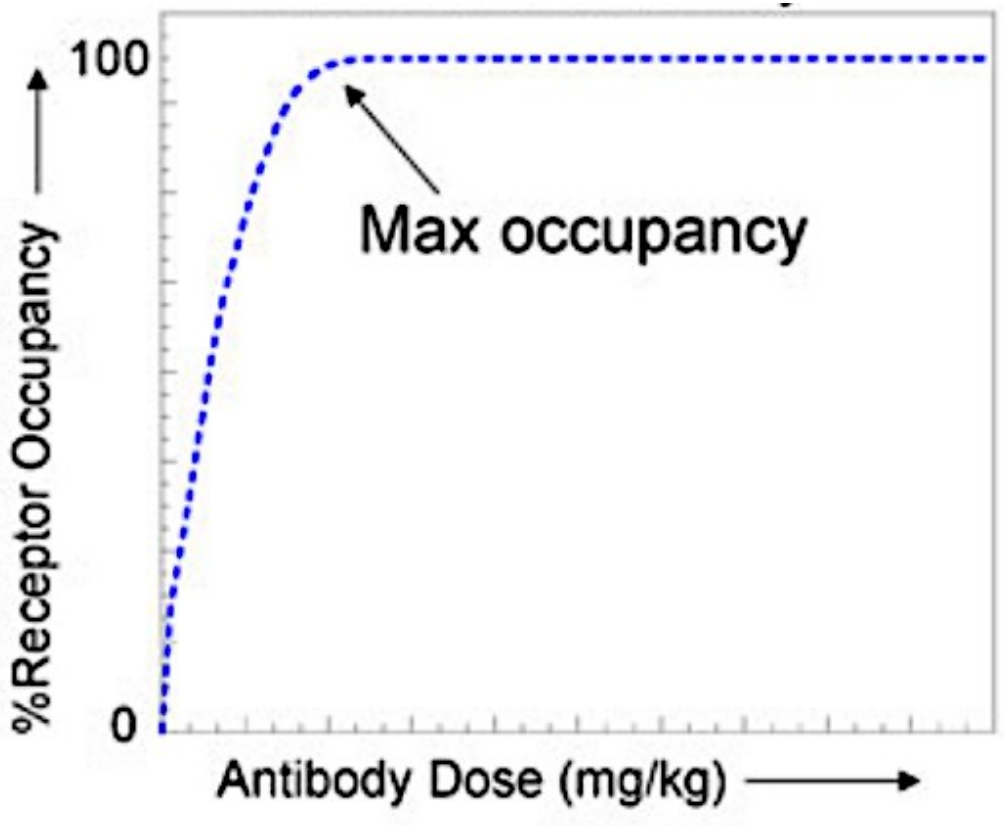
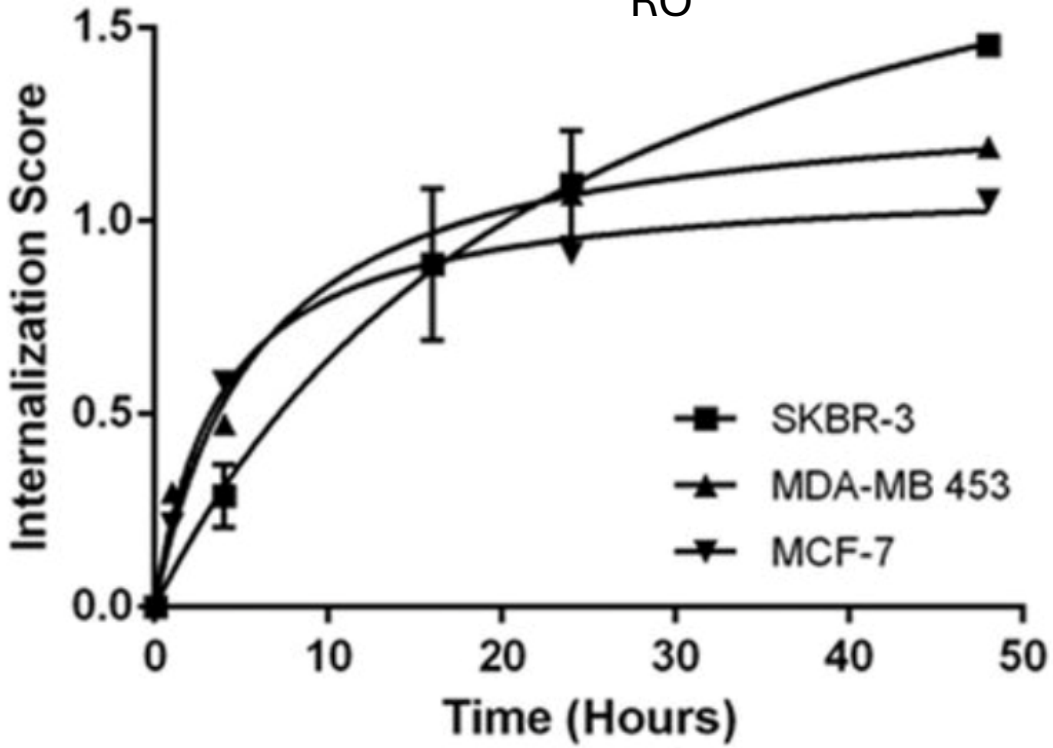


Trastuzumab internalization rate as surrogate for RO

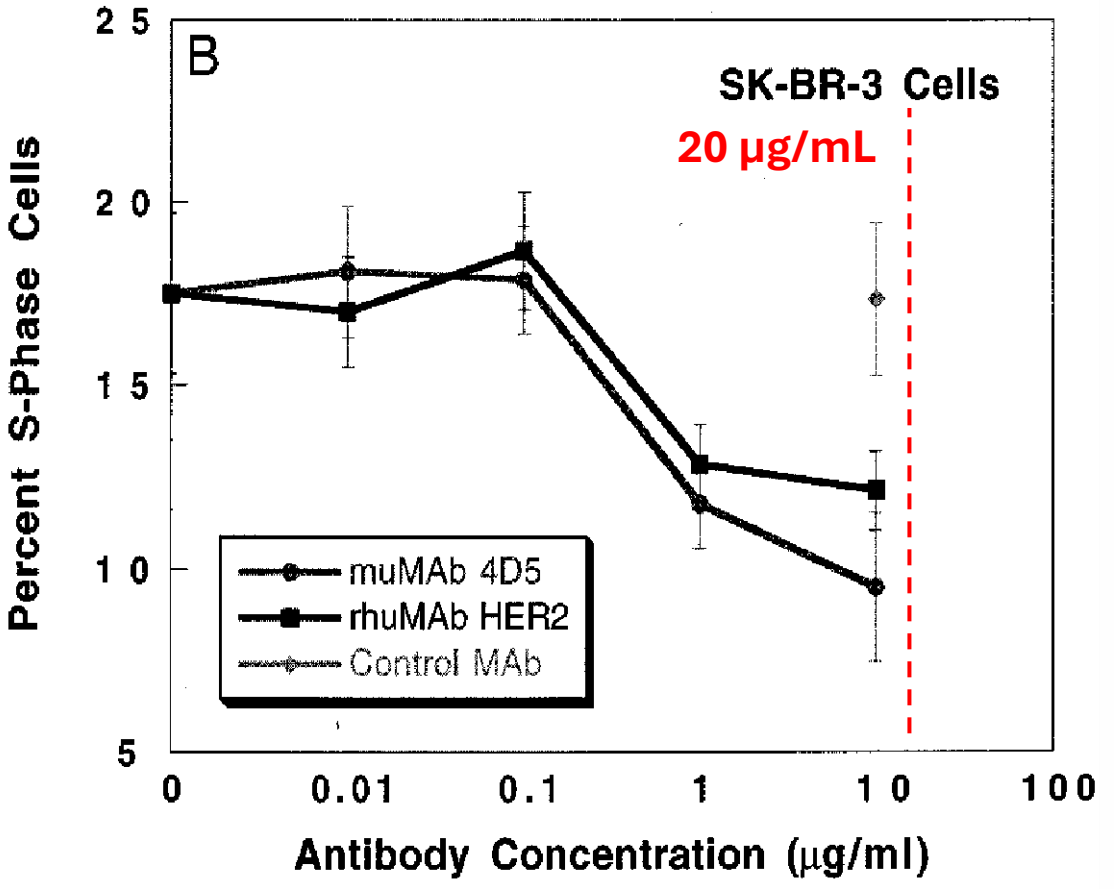


DOI:10.1208/s12248-012-9374-1

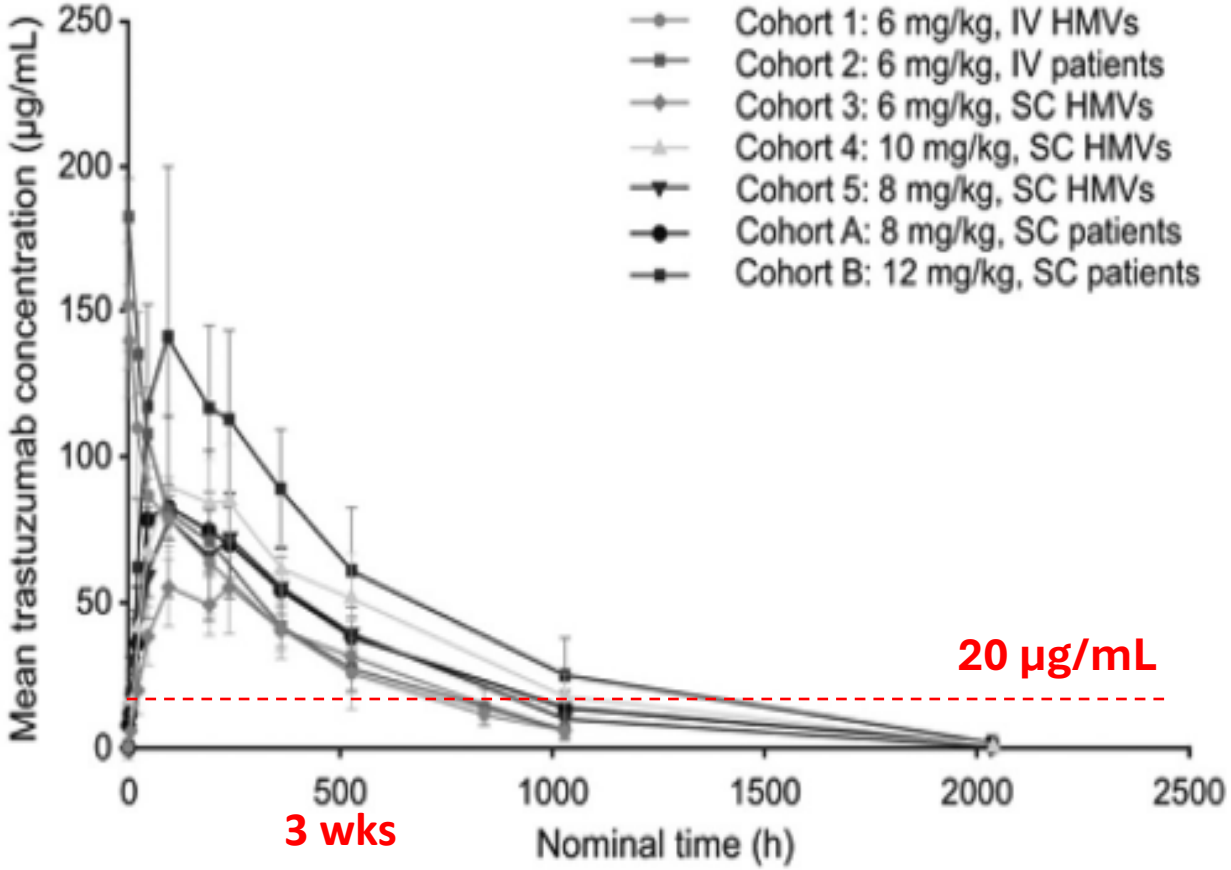
DOI:10.1124/dmd.119.089276

Effect of anti-HER2 moAb concentration on the proportion of HER2+ breast cancer cells in S-phase

Maximum effect is likely to be obtained at 20 µg/mL



PK profile of trastuzumab IV vs SC



Pegram M, *et al*. *Oncogene* 1999; **18**:2241–2251

Wynne C, *et al. J Clin Pharmacol* 2012 Feb 22

Feature	Trastuzumab	Pertuzumab	Atezolizumab
Target / class	**HER-2** inhibitor (monoclonal antibody)	**HER-2** dimerization inhibitor (monoclonal antibody)	**PD-L1** inhibitor (monoclonal antibody)
Antibody type / Fc	**Humanized IgG1** κ (ADCC/CDC-competent)	**Humanized IgG1** κ (ADCC/CDC-competent)	**Humanized IgG1** κ with engineered **effector-silent Fc** (minimizes ADCC/CDC)
Primary epitope / MOA	Binds HER-2 ECD IV → blocks ligand-independent signaling; mediates ADCC	Binds HER-2 ECD II → blocks HER2 dimerization (esp. HER2–HER3); mediates ADCC	Binds PD-L1 → blocks PD-1 and B7.1 interactions; restores T-cell activity
Half-life	≈26–30 days	≈17–19 days	≈26–28 days
Distribution/clearance (qualitative)	**Small Vd** (plasma volume – 3L); proteolytic catabolism; near-linear PK at therapeutic range	**Small Vd** (plasma volume – 3L); proteolytic catabolism; near-linear PK	**Small Vd** (plasma volume - 7L); proteolytic catabolism; near-linear PK
Immunogenicity (ADA)	**Low**; neutralizing antibodies uncommon	**Low**; neutralizing antibodies uncommon	**13% to 36%** (assay-dependent); **neutralizing antibodies (NAb): 4.3% - 27.5%** ~19% higher clearance; clinical efficacy to be confirmed
Biomarker requirement	HER2-positive disease by validated assay	HER2-positive; often used with trastuzumab	PD-L1 expression required for select indications (assay/threshold per label)
Dosing (adult)	**8 mg/kg** loading → **6 mg/kg q3w** (or 4→2 mg/kg weekly). **SC** single-agent: **600 mg q3w**	**840 mg** loading → **420 mg q3w**(often combined with trastuzumab). **SC fixed-dose combo (pertuzumab+trastuzumab)**	Fixed dose **1200 mg q3w**, or **840 mg q2w**, or **1680 mg q4w** (tumor-/label-specific)
IV vs SC pharmacology	**SC trastuzumab (with hyaluronidase) achieves non-inferior exposure vs IV** with lower Cmax and gradual absorption (Tmax ~days). Bioavailability ~75–80%; half-life similar. Safety comparable, with more injection-site reactions and slightly higher ADA (low overall).	Pertuzumab SC is available only as a fixed-dose combo with trastuzumab (co-formulated with hyaluronidase). PK bridging shows **non-inferior trough exposure vs IV;** lower Cmax, similar half-life. Safety broadly similar; injection-site reactions more frequent; immunogenicity slightly higher but generally low.	SC atezolizumab (co-formulated with hyaluronidase) PK shows **non-inferior exposure (Ctrough/AUC) vs IV** with lower Cmax and similar half-life; injection-site reactions more common; ADA rates may be slightly higher.

Take home messages

- PK SC is non inferior to IV administration
- The volume of distribution of moAbs should be considered for dose optimisation
- ICIs half-life may help in drug schedule.
- Target occupancy – approximately >90% - seems to be the best parameter to define the optimal dose of moABs
- moAbs clearance may be a surrogate marker to evaluate target occupancy: a reduced clearance is linked to target saturation (moAb is not internalised anymore).
- Target dynamic heterogeneity and tumor immunogenicity are additional variants to include in an effective predictive model.