

PET-Guided Physiologically-Based Pharmacokinetic Modeling of Tyrosine Kinase Inhibitors in NSCLC patients with brain metastases

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Introduction

- 70% of NSCLC patients develop **brain metastases** (BM).
- Osimertinib, a tyrosine kinase inhibitor (TKI), is a treatment option for NSCLC-BM with mutated epidermal growth factor receptor (mEGFR) but is a substrate for **efflux transport** at the blood-brain barrier (BBB).
- Target-site concentrations** at the BM are leading for response and dose determination.
- PBPK-modeling can be used to predict these target-site concentrations.

Methods

- Develop PBPK-model describing **passive and active transport** over BBB in healthy brain (HB), BM and cerebrospinal fluid (CSF) and changes in BBB microvasculature surrounding BM.
- Estimation of **correction factors** (CF) for *in vitro* determined passive permeability (P_{app}) and efflux ratio (ER) values based on quantitative ^{11}C -osimertinib PET data in brain and therapeutic CSF data derived from literature, where:

$$PS_{influx} = P_{app} * \text{Surface area}_{barrier} * CF_{in}$$

$$PS_{efflux} = P_{app} * \text{Surface area}_{barrier} * (2 * (ER - 1)) * CF_{out}$$

- Verify model predictions with available microdose ^{11}C -osimertinib PET and therapeutic plasma and CSF data.
- Simulation-based approach to determine required dose to reach IC50 values in NSCLC-BM.

Objective

Develop a semi-mechanistic PBPK-model to describe TKI BBB permeability and predict target-site concentrations

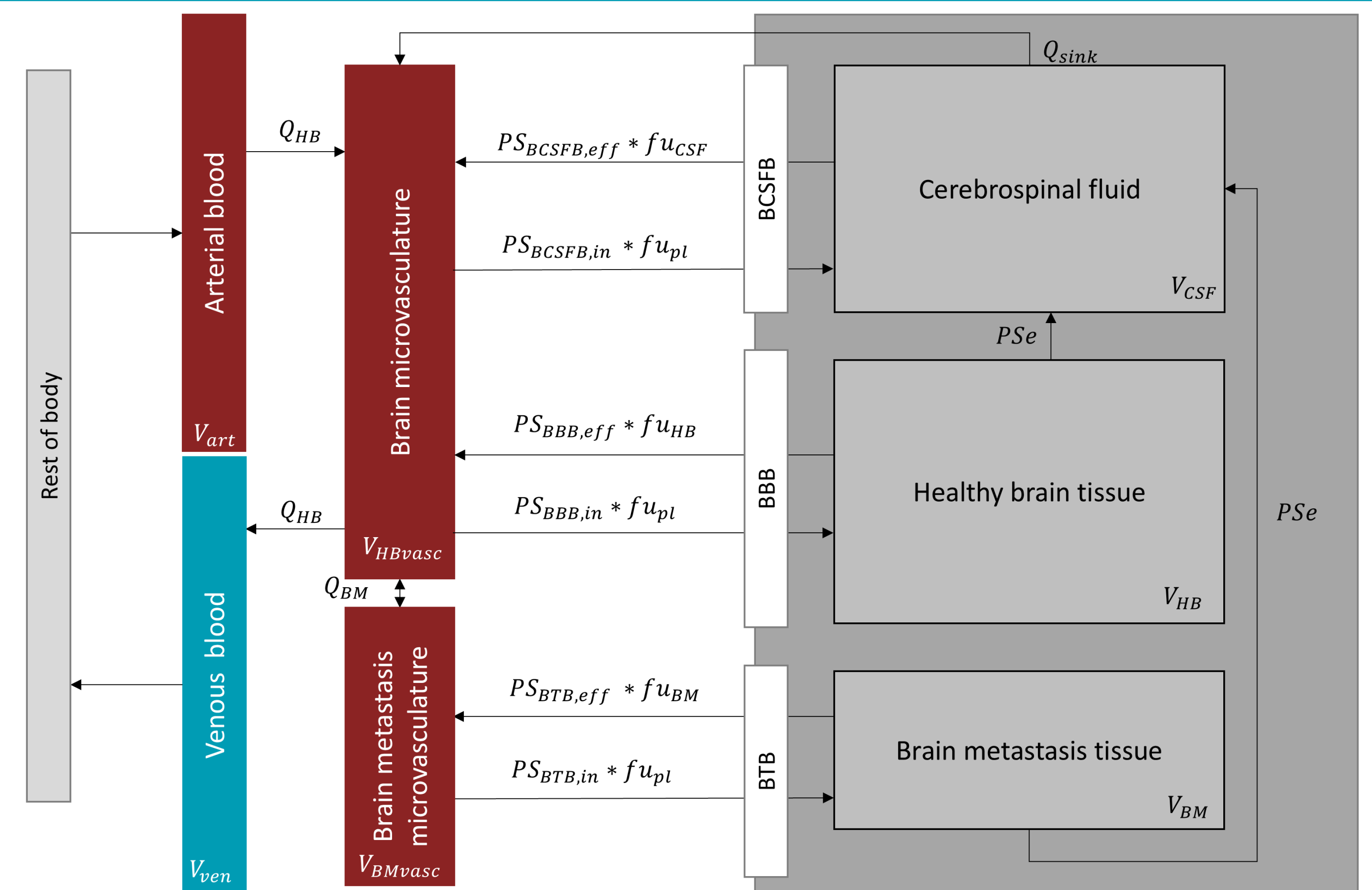


Figure 1. Blood-brain barrier PBPK-model schematic V = volume, Q = blood flow, PS = permeability surface area product, fu = fraction unbound, pl = plasma

Results

Table 1. *In vitro* derived transport values underestimate *in vivo* transport into healthy brain and brain metastases, but overestimate transport into cerebrospinal fluid. Estimation performed in NONMEM based on literature data^[1-4].

Transport rate	Estimated CF (RSE%)
Influx healthy brain	19.5 (9.9%)
Efflux healthy brain	102 (6.3%)
Influx brain metastasis	2.61 (1.4%)
Efflux brain metastasis	99.4 (1.6%)
Influx cerebrospinal fluid	0.787 (224.9%)
Efflux cerebrospinal fluid	0.459 (230.9%)

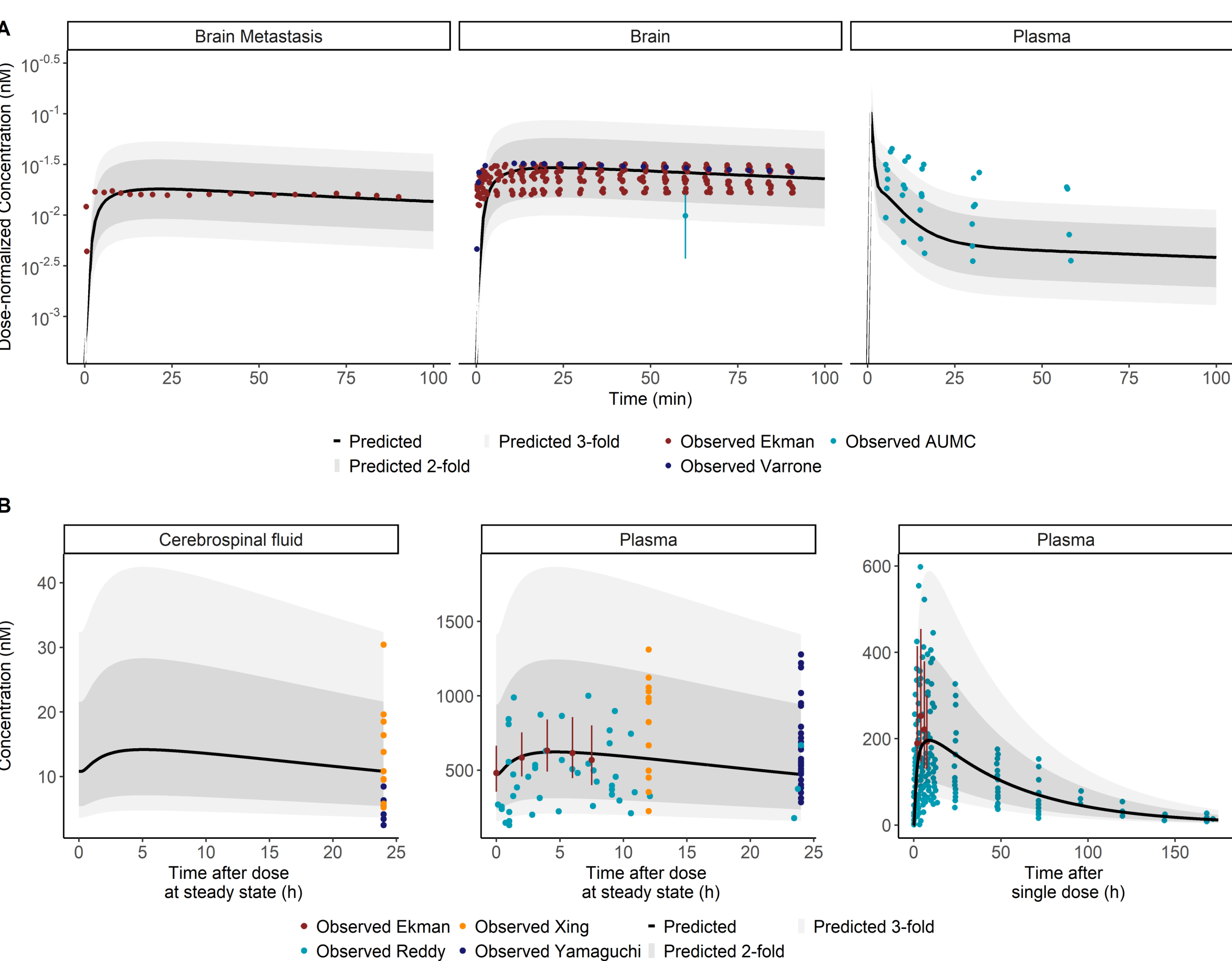


Figure 2. Predicted concentrations fall within accurate ranges of observations. A) Dose-normalized concentrations in brain (metastasis) tissue and plasma after an IV-bolus microdose (0.55-2.7 μg) B) Therapeutic concentrations in cerebrospinal fluid and plasma after 80mg oral dosing. Data from AmsterdamUMC and derived from literature^[1-5].

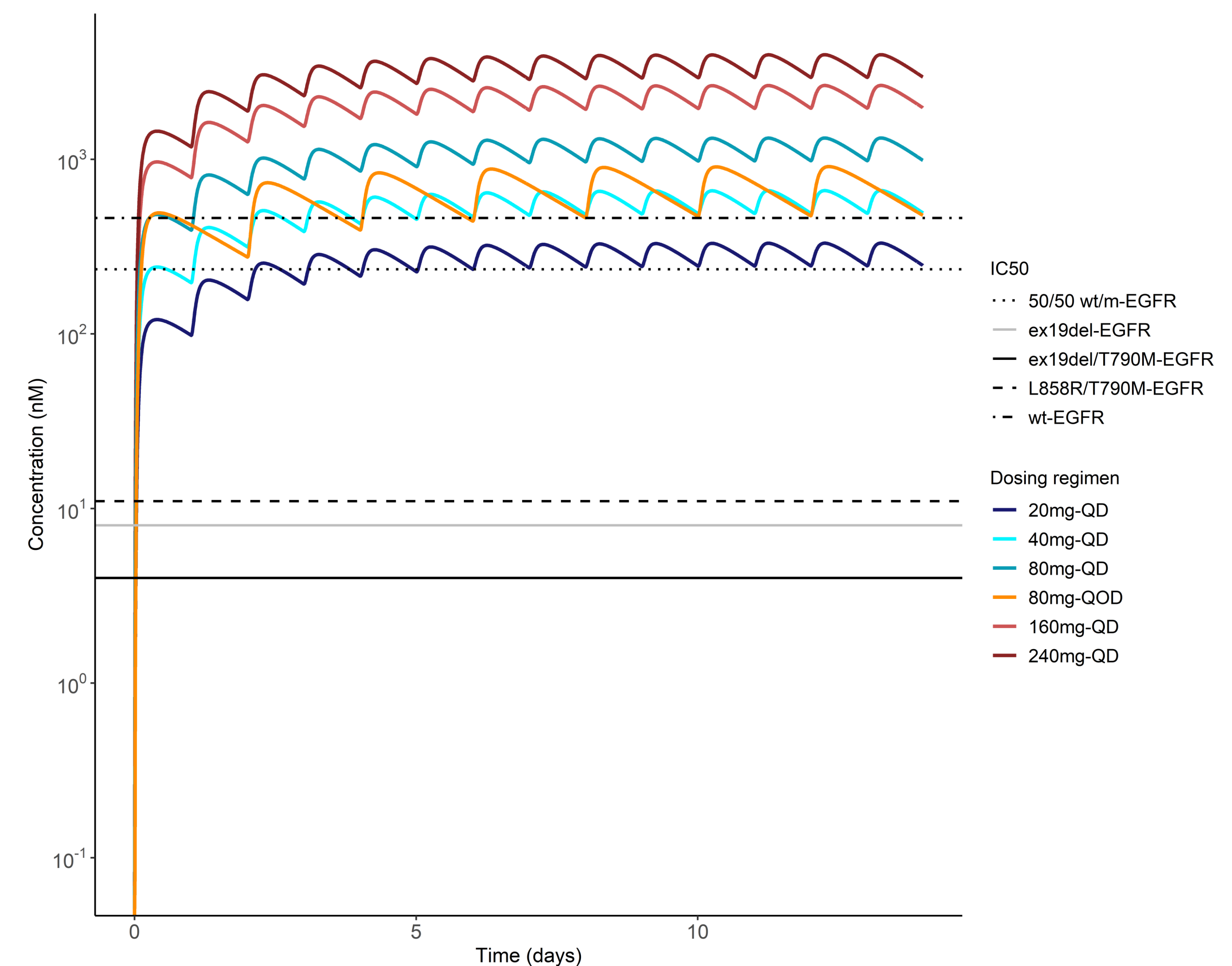


Figure 3. With standard 80mgQD dosing concentrations in brain metastasis are reached that succeed clinically relevant IC50 values to inhibit cell viability. Predicted brain metastasis concentrations over time after various dosing regimens versus reported IC50^[6] values for different EGFR mutations statuses regarding cell viability inhibition.

IC50 = half maximal inhibitory concentration, QD = daily dosing, QOD = every-other day dosing, wt = wild-type, 50/50 wt/m-EGFR = equal ratio of wild-type and mutated EGFR

Conclusion

Quantitative PET data can guide and verify PBPK-model building processes.

The developed PBPK-model can be used to predict BM target-site concentrations and is hence a first step towards personalized dosing.

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