

II-51: Modeling of Tumor Dynamics and Overall Survival in Squamous Non-Small Cell Lung Cancer Patients When Treated With Necitumumab

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BACKGROUND

Necitumumab is a recombinant full human anti-Epidermal Growth Factor Receptor (EGFR) monoclonal antibody (mAb) that specifically binds to the immobilized EGFR with high affinity to inhibit epidermal growth factor-induced EGFR phosphorylation. Necitumumab pharmacokinetics have been investigated in cancer patients across various indications, and showed beneficial efficacy when investigated in squamous non-small cell lung cancer (sqNSCLC) when given in combination with gemcitabine (gem) and cisplatin (cis).

The SQUIRE study was a phase 3 study investigating the efficacy of necitumumab in 1093 stage IV sqNSCLC patients, when administered in combination with gem/cis, compared to gem/cis alone.

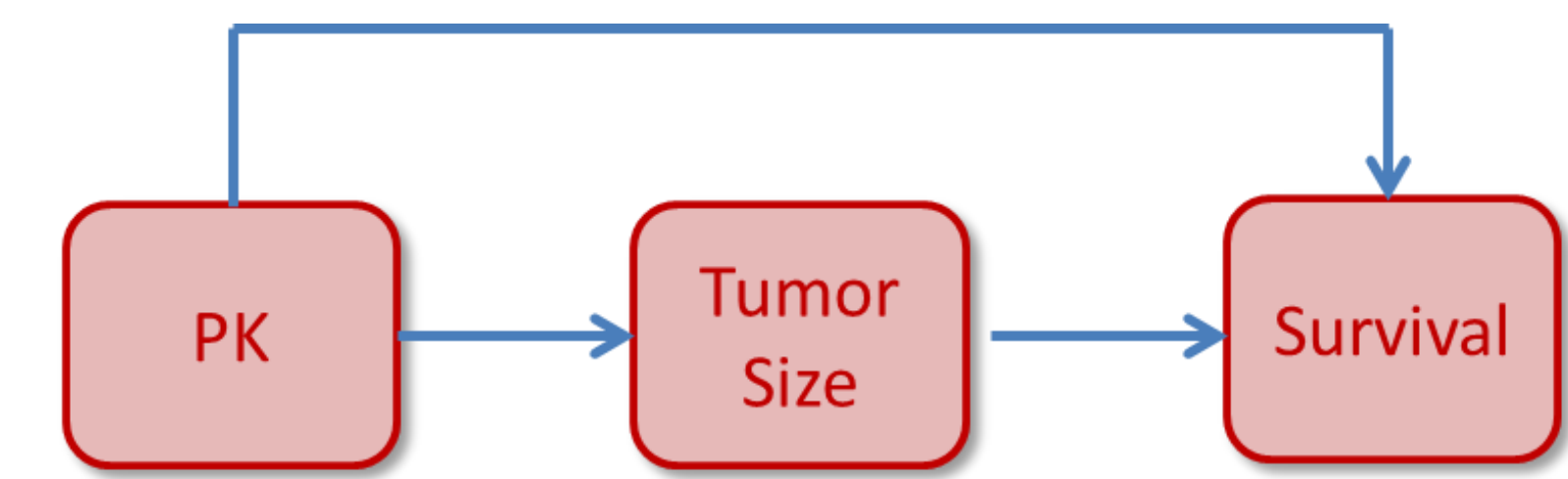


Figure 1. Schematic representation of efficacy model

OBJECTIVES

This work aimed at defining the exposure-response of necitumumab for the primary outcome overall survival (OS), as well as tumor dynamics.

METHODS

Data from both necitumumab and control patients were utilized to create the model. To increase predictability and facilitate extrapolation, an integrated model for tumor size dynamics and time to event/death where developed (**fig. 1**). Change in tumor size was determined from a summation of tumor growth and tumor shrinkage. Various growth models were tested including linear, exponential and Gompertz growth, whilst a first order process was used to describe tumor shrinkage. Development of resistance to necitumumab therapy was tested by means of a time-dependent reduction in the first order process of tumor shrinkage. Tumor size at any time during treatment was then tested as a predictor of the hazard of death at the corresponding time in a model simultaneously describing OS and CTS.

Overall survival was described using a time to event modeling approach implemented using NONMEM Version 7.3 with the Stochastic Approximation Expectation-Maximization (SAEM) estimation algorithm. Various hazard models were tested including exponential, Weibull, Gompertz, combined Weibull and Gompertz, and log-logistic distributions of event times. Necitumumab drug effect was evaluated both as a function increasing the rate of tumor shrinkage, as well as directly on overall survival [1].

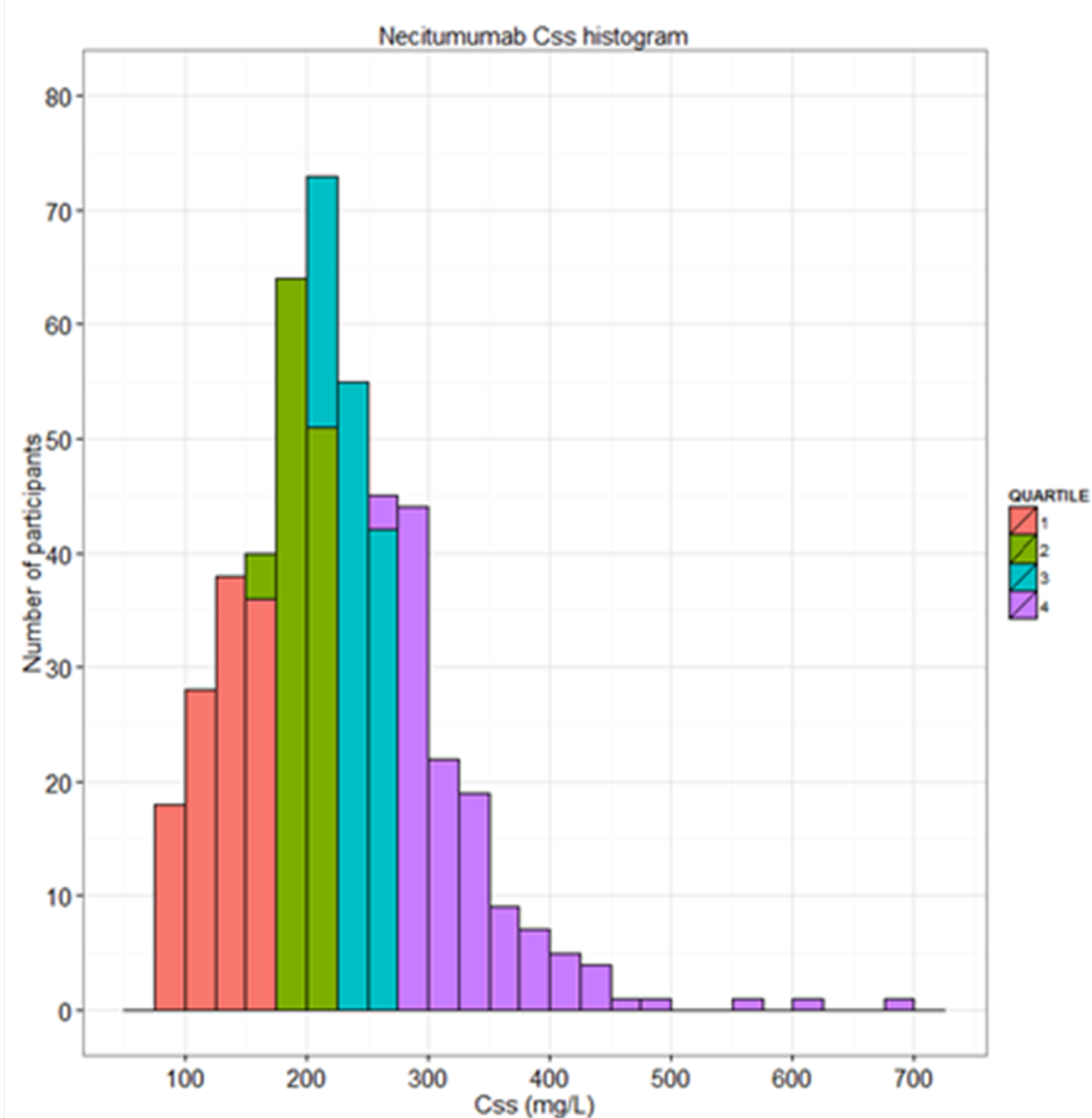


Figure 2. Histogram of necitumumab $C_{ss,ave}$ for Study SQUIRE

A previously developed PK model was used to obtain individual patient posthoc PK parameters. Using the mean dose a patient received in the study and the individual PK parameters, an average steady state concentration was obtained for each patient (Cave,ss) (**fig.2**).

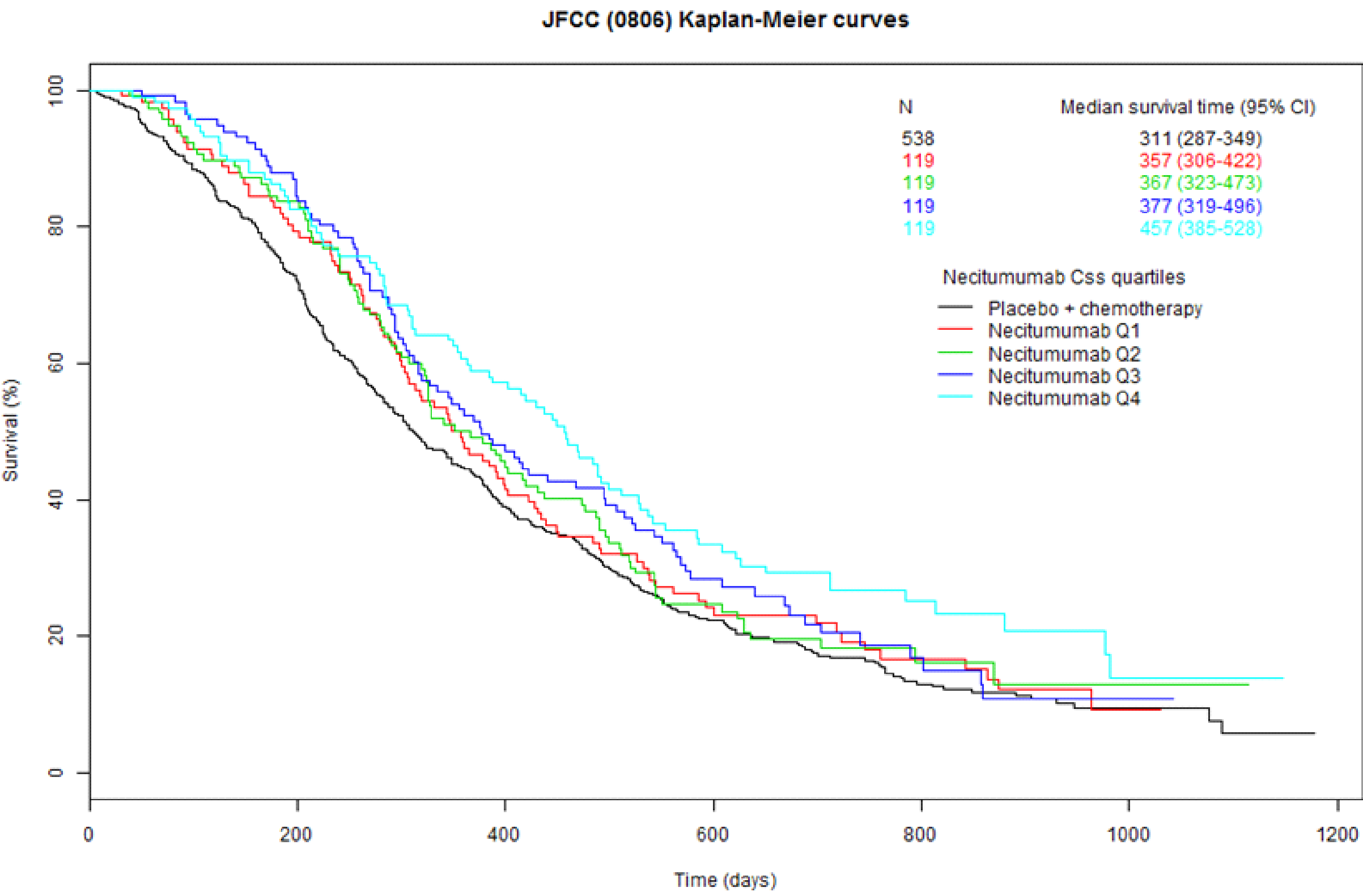


Figure 3. Kaplan-Meier curve of the observed survival in SQUIRE stratified by necitumumab exposure

RESULTS

The model that best described change in tumor size was comprised of linear growth and first order shrinkage (**fig.4**) (*eq.1*) [2].

$$(1) \frac{dSize}{dt} = Size_0 \cdot e^{-shrink \cdot t} \cdot (-shrink) + growth$$

The development of resistance was incorporated into the model using a first order decline in the shrink rate of the tumor (*eq.2*).

$$(2) Shrink_t = Shrink_0 \cdot e^{-resist \times (t - delay)}$$

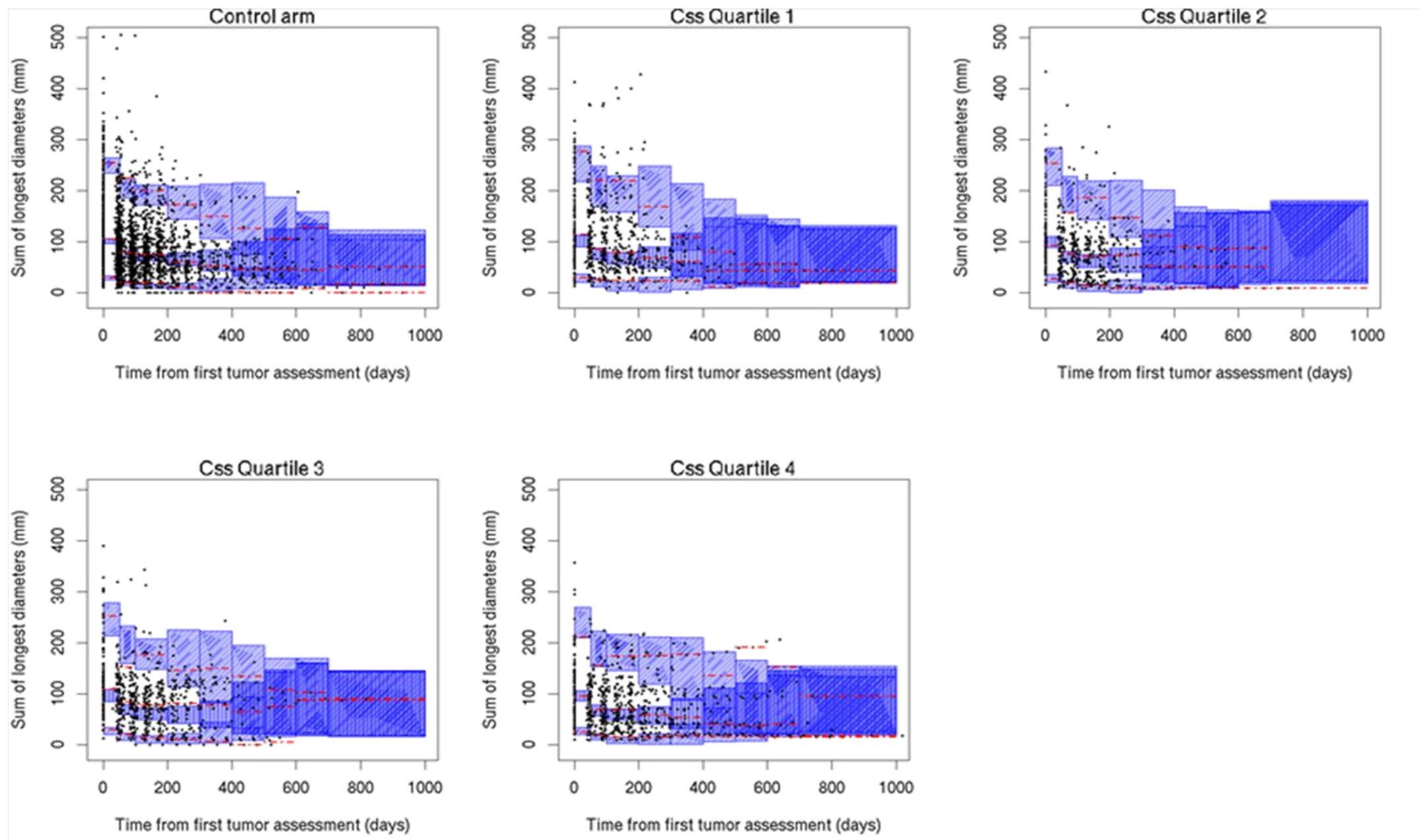


Figure 4. Visual predictive check for tumor growth inhibition model.

The time to event model that best described the overall survival was a combination of a Weibull function and Gompertz function for the hazard at time t (**fig.5**).

$$(3) \frac{dHaz}{dt} = Basehaz \times e^{[Gomp \times t + Weib \times LOG(t)]} \times e^{DPHAZ \times Size}$$

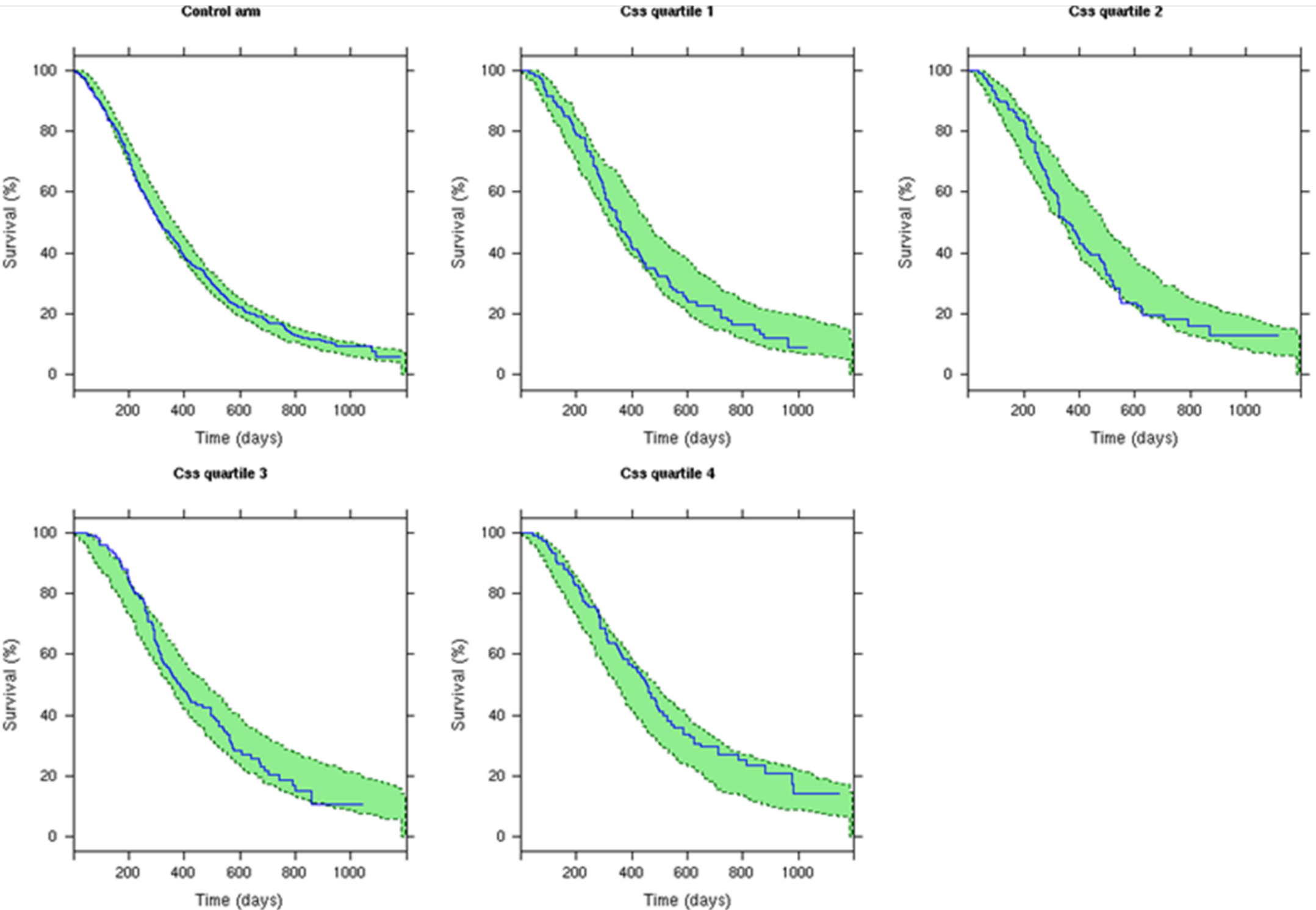


Figure 5. Visual Predictive Check for overall survival model stratified by exposure.

A significant predictor of the hazard at time t during the course of the study was the tumor size at that time, as was the Eastern Cooperative Oncology Group (ECOG) status status at baseline. Race, gender, smoking history or histological subtype was not influential. Due to numerical difficulties with the Laplacian estimation algorithm, the SAEM method was used for the integrated OS-CTS model.

The Monte Carlo noise in the IMP MOF was also kept to a minimum by increasing the number of random samples per subject (ISAMPLE) to 12000 such that MOF would oscillate by an average of about 1-3 points between iterations in the IMP evaluation step. Fifteen iterations of the evaluation step were carried out for each model, and the MOF for a model would be calculated as the average MOF from iteration 10 to 15, whereupon it would have stabilized

The drug effect was estimated as a fractional decrease (-) in the baseline hazard for the OS and as a fractional increase (+) in the first order shrink rate of the tumor, with separate E_{max} and EC_{50} estimated. Exposure-response analysis suggested that individuals with higher concentrations of necitumumab had improved efficacy, however 99.6% of patients had exposures above the EC_{50} with the population median exposure close to E_{max} . The relationship between exposure and efficacy remained statistically significant after adjusting for the baseline factors that were significantly associated with CTS and OS.

Simulations were performed to calculate the integrated exposure-response curve, when accounting for both tumor size mediated and independent drug effects, resulting in an efficacy EC_{50} which is a composite of the individual EC_{50} 's for CTS and OS (**fig.6**).

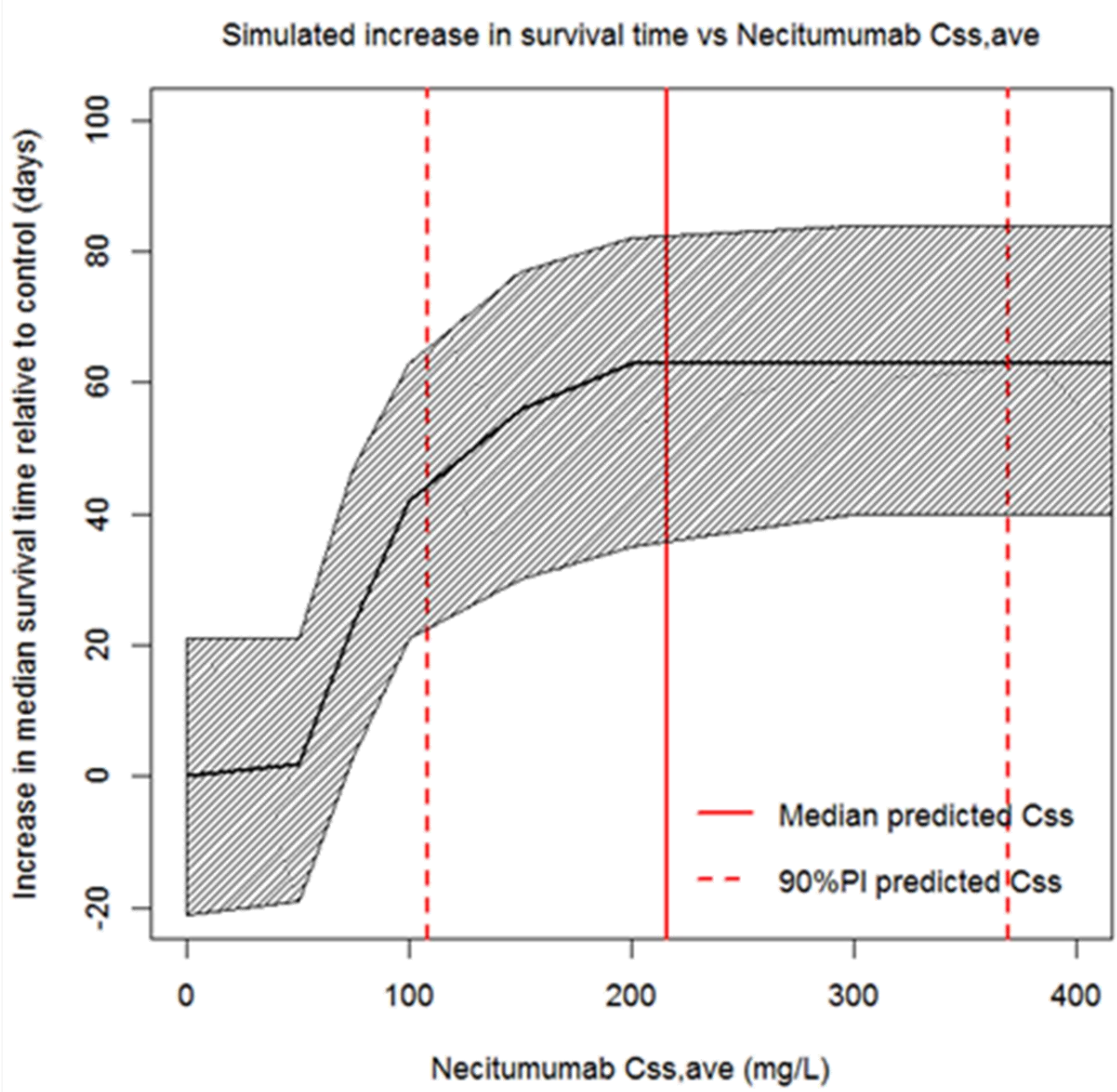


Figure 6. Necitumumab exposure-response curve for overall survival.

CONCLUSIONS

The model developed sufficiently describes the tumor growth dynamics and time of death in squamous non-small cell lung cancer patients. Model estimates indicate that patients treated with recommended dose of 800 mg on day 1 and day 8 of a three week schedule obtain survival benefit, with 99.6% of patients achieving exposure above the EC_{50} .

References:

[1] Hansson E, Amantea M, Westwood P, Milligan P, Houk B, French J, Karlsson M and Friberg L. PKPD Modeling of VEGF, sVEGFR-2, sVEGFR-3, and sKIT as Predictors of Tumor Dynamics and Overall Survival Following Sunitinib Treatment in GIST. *CPT: Pharmacometrics & Systems Pharmacology* (2013) 2, e84.
[2] Wang Y, Sung C, Dartois C, Ramchandani R, Booth BP, Rock E, Gobburu J. Elucidation of Relationship Between Tumor Size and Survival in Non-Small-Cell Lung Cancer Patients Can Aid Early Decision Making in Clinical Drug Development. *Clin Pharm Ther.* 2009. 86 (2):167-174.

