The Effect of Body Weight on Necitumumab Pharmacokinetics and Pharmacodynamics in Patients with Squamous Non-Small Cell Lung Cancer: Dosing Implications

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Objectives: Necitumumab is a monoclonal antibody being investigated for the treatment of squamous non-small cell lung cancer. Having characterized the exposure-response relationship, we sought to determine patient factors that could potentially influence the pharmacokinetics and pharmacodynamics of necitumumab and investigate their impact on dosing recommendations.

Methods: A 2-compartment model with parallel first order and mixed order elimination was used to describe the pharmacokinetics of necitumumab in patients, when administered as 800 mg on day 1 and day 8 of a 21 day cycle. Body weight was positively correlated with both clearances and volumes of distribution. The pharmacodynamic model involved a simultaneous fit of tumor size and overall survival data. Tumor size dynamics were modeled as zero order growth with first order shrinkage due to drug effect. Dynamic tumor size was then applied as a predictor of hazard for overall survival in a time to event model. Monte-Carlo simulations were then carried out to compare flat dosing, weight-based, and BSA-based dosing in terms of variability in both exposure and efficacy in the study population.

Results: Allometric scaling with estimated exponents of 0.77 and 0.50 for clearances and volumes, respectively, adequately characterized the influence of body weight on necitumumab pharmacokinetics. The simulations revealed that no significant reduction in inter-patient variability of drug exposure would be obtained by weight-based (mg/kg) or BSA-based (mg/m²) dosing compared to a flat dose. Furthermore, the simulated median survival time stratified by drug exposure quartiles was similar across all 3 dosing regimens (flat dose, weight based and BSA-based).

Conclusion: A flat dose was effective and achieved adequate drug exposure in the vast majority of patients (99.6%). No improvement in efficacy can be expected with individualized dosing based on body size metrics.