Translation of semi-mechanistic neutropenia model for vc-MMAE antibody-drug conjugate (ADC)

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Objectives: Preclinical and clinical semi-mechanistic neutropenia models were developed separately to characterize neutrophil count profile in cynomolgus monkey and cancer patients treated with vc-MMAE antibody-drug conjugate (ADCs). The potential to predict neutropenia risk in patients based on monkey data was also examined.

Methods: Time courses of neutrophil count were obtained from cynomolgus monkey and cancer patients treated with five different vc-MMAE ADCs (Drug S1-S5). Pharmacokinetic models of antibody-conjugated MMAE (acMMAE) were used to predict concentration-time profile of cynomolgus monkey and each patient, and a semi-mechanistic model was established to characterize neutrophil count profile using NONMEM\textsuperscript{®} software. Neutrophil count profile of monkey or patients were either fitted individually for each drug or with pooled data to evaluate the variability of system-related parameters for cynomolgus monkey and patients. The drug-related parameter Slope was allowed to differ among drugs. The differences in Slope estimates between cynomolgus monkey and patient for each drug were examined.

Results: The semi-mechanistic models to describe the neutrophil count profile following vc-MMAE ADC treatment has been developed for cynomolgus monkey and patients. The system-related parameter estimates were comparable between fitting individually for each drug and fitting with pooled data, except for mean transit time (MTT) of Drug S5 in monkey data. The deviation is likely due to limited data (i.e. n=10 and one dose level for Drug S5 vs. n=30 and three dose levels for other drugs). The nadir of neutrophil count profile was correlated well with the estimates of drug-related parameter Slope. Unlike translation of cytotoxic drugs, where correction of protein binding and bone marrow sensitivity are required, drug-related parameter Slope of vc-MMAE ADCs are approximately comparable between monkey and human (mostly within 2-fold, except for Drug S1).

Conclusions: The semi-mechanistic model of neutropenia well described the neutrophil count profiles of cynomolgus monkey and patients following administration of five different vc-MMAE ADCs. The drug-related parameter Slope are approximately comparable between monkey and patients, and the system-related parameters are independent of drugs, suggesting the potential to predict neutropenia risk in patients based on monkey data.