In Vivo Mechanisms of Drug-load Release for Antibody Drug Conjugates and Their Relationships To Drug-Related Toxicity

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Objectives: To develop a unified model describing the pharmacokinetics (PK) of trastuzumab emtansine (TDM1) and brenduximab vedutin (SGN35), and their myelosuppressive effects in mice.

Methods: TDM1 and SGN35 PK and their effects on platelets (PLT) and neutrophils (ANC) counts were assessed in balbc normal or human xenografted mice after single or repeated doses and compared to control groups. Total trastuzumab concentrations were measured while total plasma concentrations for SGN35, the payloads (DM1 and MMAE for TDM1 and SGN35), and the antibodies (trastuzumab and anti-CD30 for TDM1 and SGN35) were extracted from the literature [1,2]. MONOLIX and Berkeley Madonna were used to model the data.

Results: Two-compartment models with linear elimination and de-conjugation from the ADCs (kdec) described the PK of the 2 ADCs, and their respective payloads and monoclonal antibodies. Myelosuppression from both ADCs was captured with a series of five transit compartments representing cell proliferation and maturation in the bone marrow, and PLT or ANC in blood. A negative feedback loop accounted for the observed tolerance. TDM1 and SGN35 half-lives were estimated at 4.8 and 4.6 days and kdec were 0.46 and 0.12 h-1. The lifespans for PLT under TDM1 and ANC under SGN35 were 3.73 and 4.72 days. Comparison of alternative model performance suggested that TDM1 and SGN35 myelosuppressions are caused by different mechanisms: ADC binding to FcgR for TDM1 and payload-driven toxicity for SGN35 due to high lipophilicity of MMAE. Model based-simulations suggested that a 6-fold increase and 70% decrease in kdec of TDM1 and SGN35 would improve myelosuppression.

Figure 1: Prediction-corrected visual predictive check plots

Conclusions: The proposed model successfully captured the PK and myelosuppressive effects of TDM1 and SGN35 and may serve as a general PK/PD platform for ADCs.

References: