Objective: The aim of this study was to characterize the PK of auristatin-based ADCs and their analytes using the platform PBPK model developed for ADCs.

Methods: A platform PBPK model was developed, by integrating previously developed PBPK model for antibodies (1) and classical PBPK model for small molecule drugs. The model is capable of characterizing the PK of ADC and its unconjugated drug (i.e. MMAF), which is assumed to generate upon ADC degradation and non-specific deconjugation. Each tissue compartment was further divided into vascular, endosomal, interstitial, and cellular sub-compartments (fig. 1), to incorporate complex ADME processes such as FcRn recycling of antibodies. In addition, a mechanistic tumor model was integrated to account for tumor disposition of ADCs and target mediated ADC disposition (2). Whole body disposition data of following two MMAF-based ADCs were digitized and characterized: anti-CD70 antibody-mc-MMAF ADC administered in renal cell carcinoma-bearing mice (3) and anti-5T4 antibody-mc-MMAF ADC in mice bearing lung cancer (4). PBPK model was translated to humans and a priori predicted plasma concentrations of ADC and its analyte were compared with clinical observations.

Results: The concentration-time profiles of ADCs and MMAF analyte were characterized well using the integrated PBPK model. In addition, the model reasonably estimated the clearance and distribution parameters of MMAF in various mouse tissues. Model was extrapolated to humans by scaling up unconjugated drug clearance and distribution parameters by allometric method.

Conclusions: Present study shows the successful application of platform PBPK model developed for ADCs to characterize the disposition of two auristatin-based ADCs. The model was also extrapolated to human to a priori predict plasma PK of ADCs and related analytes.

References

Figure 1: Structure of the tissue level PBPK model developed for ADCs