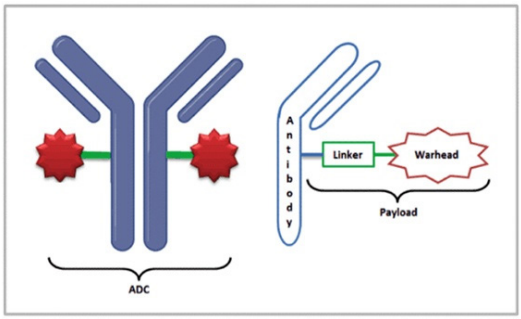
CERTARA®
Accelerating Medicines, Together

CASE STUDY

PBPK MODEL INFORMS ANTIBODY-DRUG CONJUGATE LABEL FOR DDIS WITHOUT CLINICAL TRIALS

Genentech was developing polatuzumab vedotin (Polivy), an anti-CD79b-vc-monomethyl auristatin E (MMAE) antibody-drug conjugate (ADC) to treat patients with transplantation-ineligible relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). MMAE is a potent anti-cancer drug that is a CYP3A substrate and a weak competitive CYP3A inhibitor.

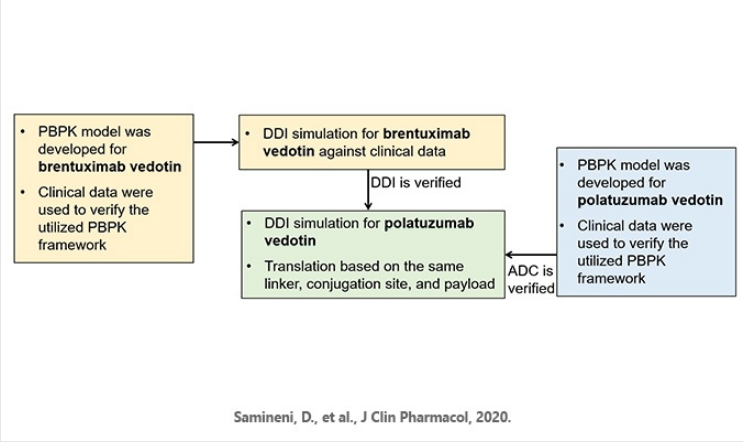
The cytotoxic payload of an ADC is a small molecule that could be metabolized and cleared via metabolic enzymes (cytochrome P450 enzymes (CYPs), UGTs, drug transporters, etc). Concomitant medications that alter inhibit or induce CYP3A could alter the pharmacokinetics (PK) of unconjugated MMAE and thereby affect clinical outcomes. Thus, the Genentech team needed to assess the risk of CYP3A-mediated DDIs for polatuzumab vedotin.



Sikorski, S.R.I.Q.R. The Clinical Landscape of Antibody-drug Conjugates. 2014 [cited 2021 30 September]; Available from: https://www.adcreview.com/articles/the-clinical-landscape-of-antibody-drug-conjugates/.

The results of simulations performed using the model were used to inform the drug label without the need for dedicated clinical trials.

Genentech scientists used the Simcyp Simulator to develop a physiologically-based pharmacokinetic (PBPK) model to perform an in silico DDI study. The model was first developed and verified using data from an existing clinical DDI study for brentuximab vedotin, an ADC using the same linker-drug combination as polatuzumab vedotin. Simulations performed using this model predicted that polatuzumab vedotin would not significantly inhibit or induce CYP3A. The PBPK simulations also demonstrate limited impact of strong CYP3A inhibitors/ inducers on the exposure of MMAE.



Samineni, D., et al., J Clin Pharmacol, 2020.

The results of simulations performed using the model were used to inform the drug label without the need for dedicated clinical trials. This is a novel, high impact application of PBPK modeling for ADCs.

The key findings from the PBPK report were also used to guide the regulatory strategy for the Biologics License Application/Marketing Authorization Application and support responses to questions from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Antibodies typically have low potency and high specificity, and cytotoxic drugs generally have high potency and low specificity. ADCs combine the targeting capability of monoclonal antibodies with the cancer-killing capability of the payload (linker + cytotoxic drug).