Integrated Three-Analyte Population Pharmacokinetic (PPK) Model for Antibody-Drug-Conjugates (ADC) in Patients with Non-Hodgkin Lymphoma

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Objectives: To develop a three-analyte PPK model that describes PK of total antibody (Tab), conjugate (evaluated as antibody-conjugated toxin [acMMAE]), and unconjugated toxin (MMAE) following polatuzumab vedotin (pola) 0.1 - 2.4 mg/kg Q3W administration to patients as monotherapy and in combination regimens.

Methods: A total of 3517 Tab, 3552 acMMAE, and 3599 MMAE measurements from 386 patients from four clinical studies were used. A previously developed Tab-acMMAE model [1] with parallel linear and Michaelis-Menten elimination and time-dependent linear clearance was extended to include unconjugated MMAE data. The impact of major covariates on model parameters was investigated.

Results: PPK model (Figure 1) demonstrated a good fit of all observed Tab, acMMAE and MMAE PK data. Among covariates, body weight had the strongest effect on acMMAE and MMAE PPK parameters. Specifically, CL_{inf} increased with weight (power 0.787); both V_{1} and V_{2} increased with weight (power 0.496). CL_{MMAE} (MMAE apparent clearance, which equals MMAE clearance divided by fraction of formation) increased with weight (power 0.651). In addition, male sex, higher baseline tumour burden, B-cell count and lower albumin concentrations were correlated with higher CL_{inf}; combination with rituximab (R) or obinutuzumab (G) decreased CL_{inf}; males and previously-untreated patients had higher V_{1}; CL_{MMAE} increased with albumin concentration (power 1.12), combination with R or G (by 62% and 44%); CL_{MMAE} was higher in previously-untreated patients (by 36%) and lower (by 18%) in patients with mild hepatic impairment (defined by NCI criteria).

Conclusions: The integrated PPK model provided good description of all observed data and justified weight-based dosing. The PPK model can be applied for drug interaction assessment, to understand impacts of covariates especially PK in patients with organ impairment, and to predict exposure for efficacy and safety exposure-response analyses, and to explore various dosing regimens via simulations.


Figure 1. Model Structure for Integrated Population PK Model
A\textsubscript{1}, A\textsubscript{2}: molar amounts of Tab; A\textsubscript{3}, A\textsubscript{4}: molar amounts of acMMAE; A\textsubscript{5}, A\textsubscript{6}, A\textsubscript{7}: molar amounts of MMAE; CL = CL\textsubscript{inf} + CL\textsubscript{T} \cdot \exp(-k_{\text{des}} t): time-dependent clearance; D, D\textsubscript{ac}: molar dose of Tab and acMMAE; mDAR, average drug to antibody ratio in the dosing solution; k\textsubscript{dec}: deconjugation rate; k\textsubscript{50}, k\textsubscript{56}, k\textsubscript{65}: MMAE inter-compartment rate constants; Q: inter-compartment rate; V\textsubscript{1}, V\textsubscript{2}: central and peripheral volume; V\textsubscript{max}\textsubscript{Tab}, K\textsubscript{SS}: maximum elimination rate and Michaelis-Menten constant of Tab; V\textsubscript{max}, K\textsubscript{M}, \gamma: maximum elimination rate, Michaelis-Menten constant, and power of the Hill model for MMAE elimination from the delay compartment; CL\textsubscript{MMAE}: MMAE apparent clearance (MMAE clearance divided by fraction of formation).

$$\text{Tab} = \frac{A\textsubscript{1}}{V\textsubscript{1}} \cdot 0.146455, \text{acMMAE} = \text{CORR} \cdot \frac{A\textsubscript{3}}{V\textsubscript{1}} \cdot 0.718, \text{MMAE} = k\textsubscript{50} \cdot \frac{A\textsubscript{5}}{\text{CL}_{\text{MMAE}}} \cdot 0.718.$$ Red compartments: where PK data are observed.