Population Pharmacokinetics of Mirvetuximab Soravtansine in Patients with Folate Receptor-α Positive Ovarian Cancer: the Antibody-Drug Conjugate, Payload and Metabolite

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Abstract

Aims: Mirvetuximab soravtansine is the first-in-class antibody-drug conjugate approved in November 2022 for the treatment of folate receptor-α positive ovarian cancer. The aim of this study was to develop a population pharmacokinetic (PK) model to describe the concentration-time profiles of mirvetuximab soravtansine, the payload (DM4) and a metabolite (S-methyl-DM4). Methods: Mirvetuximab soravtansine was administered intravenously from 0.15 to 7 mg/kg to 543 patients with predominantly platinum-resistant ovarian cancer in three clinical studies, and the plasma drug concentrations were analyzed using a nonlinear mixed-effects modelling approach to estimate the PK parameters, inter-individual variabilities, and residual errors. Stepwise covariate modelling was performed to identify covariates. Results: We developed a semi-mechanistic population PK model that included linear and nonlinear routes for the elimination of mirvetuximab soravtansine and a target compartment for the formation and disposition of the payload and metabolite in tumor cells. The model adequately described the concentration-time profiles for the three analytes. Patient body weight, serum albumin, and age were identified as the major covariates. Exposures in patients with renal or hepatic impairment were estimated. The effect of inhibition of cytochrome P450 (CYP) 3A4 on drug exposures was also evaluated. Conclusions: There is no need for dose adjustment due to covariate effects for mirvetuximab soravtansine administered at the recommended dose of 6 mg/kg based on adjusted ideal body weight. The model also showed that dose adjustment is not required for patients with mild or moderate renal impairment, mild hepatic impairment, or when concomitant weak and moderate CYP3A4 inhibitors are used.

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