

Development of an integrated, multiple analytes mechanistic model of SAR408701, an anti-CEACAM5 antibody-drug conjugate indicated in solid tumors.

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Poster: Drug/Disease Modelling - Oncology

Introduction:

Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) is a cell-surface glycoprotein highly expressed in several tumor types [1]. SAR408701 is an antibody-drug conjugate (ADC), combining a humanized monoclonal antibody (IgG1) targeting CEACAM5. DM4, a potent cytotoxic maytansinoid derivative that inhibits microtubule assembly, is covalently bound to the antibody through a thiobutylamide linker (SPDB), stable in plasma and cleavable inside cells.

SAR408701 is currently tested in clinical trials for the treatment of advanced solid tumors expressing CEACAM5. It is administered intravenously as a mixture of conjugated antibodies (species with different payload densities). The drug to antibody ratios (DAR) distribution is heterogeneous and ranges from 0 to 8, with an average DAR in the administered drug of 3.1 mol/mol. During SAR408701 clinical development, four entities were measured in plasma: ADC, naked antibody (NAB), DM4 and its methylated metabolite (MeDM4) (both moieties being active [2,3]). DAR was assessed in a sample of patients only.

Objectives:

Developing a multiscale modeling framework that investigates SAR408701 disposition mechanisms and supports its ongoing clinical development.

Methods:

For ADC, DM4, MeDM4 and NAB, data from 6 cohorts of phase I study, enrolling 154 patients, were included in the analysis. LC-HRMS allowed quantification of relative expression of each ADC_{DARi} entities, to assess DAR decrease over time in 13 patients out of the 154 enrolled in the current analysis. An integrated model that describes the kinetics of all entities in plasma has been developed [4,5]. To assure model stability and parameters identifiability the model was restricted to five DAR entities, each corresponding to the ADC with a given DAR ratio (ADC_{DAR0} , ADC_{DAR1} , ADC_{DAR2} , ADC_{DAR4} and ADC_{DAR6}). NAB was represented as the ADC_{DAR0} species.

Each ADC_{DARi} entity was described by a two-compartment PK model. The ADC_{DARi} were assumed to share the same distribution (same value of central volume, peripheral volume and intercompartmental clearance), but not the same clearance which could differ depending on DAR. The SAR408701 administered dose was fractioned between each of the ADC_{DARi} compartments as the proportion of ADC_{DARi} was measured in the administered dose. The conversion of higher DAR to lower DAR species resulted in a DAR-dependent ADC deconjugation in central compartment and was represented as an irreversible first-order process.

DM4 disposition was described by a one compartment PK model, with a first order elimination. Each $ADC_{DAR\geq 1}$ deconjugation process was assumed to contribute to DM4 formation. MeDM4 was modelled sequentially with a one compartment model, a first order formation process directly from DM4 elimination and a first order elimination process. Derived DAR, as a function of time, was defined as the ratio between DM4 over total ADC concentrations.

All entities data were fitted simultaneously and inter-individual variability was estimated. The estimation of the nonlinear mixed effect model parameters was performed using SAEM algorithm of MONOLIX software (version 2019R1, Lixoft).

Results:

All model parameters were estimated with good precision. Model diagnostic plots confirmed good agreement between the predicted and the observed data for all entities.

For $ADC_{DAR\geq 1}$ the clearance was linear and comparable over DAR range ($CL_{ADC} = 0.47$ L/day). $ADC_{DAR\geq 1}$ exhibited a faster elimination compared to NAB ($CL_{NAB} = 0.27$ L/day, value consistent with IgG1 typical clearance of 0.21 L/day [6]). The high DM4 apparent clearance ($CL_{DM4} = 127$ L/day), compared to MeDM4 apparent clearance ($CL_{MeDM4} = 0.283$ L/day) was in line with DM4 poor stability (a rapid methylation allows conversion of the thiol bearing DM4 metabolite to the stable methyl-DM4 derivative [2,3]). Deconjugation process was shown to increase with DAR (L6 estimated to 12.1, L4 to 4.1 and L2 to 3.8) and rate of deconjugation was estimated to 0.040 day^{-1} .

Conclusions:

The integrated model described appropriately the plasma PK profiles of ADC, unconjugated DM4 and its active metabolite MeDM4, NAB and DAR entities. Such a structural model could be translated to other ADCs and provides a mechanistic understanding of the formation and disposition of all ADC entities. For SAR408701, this model will be expanded to evaluate and interpret potential covariates effects on the disposition of each species.

References:

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