Close window

PAGE. Abstracts of the Annual Meeting of the Population Approach Group in Europe.
ISSN 1871-6032

Reference:
PAGE 28 (2019) Abstr 9120 [www.page-meeting.org/?abstract=9120]

Prospective Evaluation of a Model-Based approach to select Phase 1 Dosing Regimen for MEN1309/OBT076, a novel antibody drug conjugate (ADC) targeting Ly75 antigen for the treatment of CD205-positive metastatic solid tumours and Non-Hodgkin lymphoma

E. Borella (1), P. Mazzei (1), C. Piana (1), A. Tagliavini (1), P. Magni (2), S. Buontempo (1), D. Tagliacozzi (1), V. Fedi (1), A. Capriati (1), A. Pellacani (1)

(1) Menarini Ricerche SpA (Italy), (2) Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia (Italy)

Paolo Mazzei

Poster: Drug/Disease modelling - Oncology

Objectives: The aim of this work is to prospectively evaluate the model-based approach used to select Phase 1 study dosing regimen for MEN1309/OBT076, a novel antibody drug conjugate (ADC) targeting Ly75 antigen, with the observed clinical PK and safety data emerging during the ongoing first-in-human (FIH) SHUTTLE-01 study in patients with CD205-positive metastatic solid tumours and Relapsed/Refractory (R/R) Non-Hodgkin Lymphoma (NHL).

Methods: First, a population PK model was developed based on preclinical PK data from 3 toxicological studies in cynomolgus monkeys. Monkey plasma concentration–time data were modelled, and PK parameters appropriately scaled to derive human PK parameters. Second, toxicokinetic (TK) data (i.e. absolute neutrophils counts, ANC) from these studies were used to describe MEN1309/OBT076 neutropenic effects in cynomolgus monkeys and, once appropriately scaled, to predict onset and recovery of hematologic toxicity in human. Third, a translational PK/PD model was established to quantitatively express the relationship between MEN1309/OBT076 plasma concentration and tumour volume in nude mice bearing orthotopic HPAF-II tumours. MATLAB, R and NONMEM VII were used to perform the analyses. Using the previously established translational strategy, an appropriate dosing schedule for the FIH study was proposed. Finally, model-projected PK and safety profile in human for MEN1309/OBT076 have been compared to PK and safety data from the ongoing FIH study in an interim PK/PD analysis to verify the goodness and adequacy of model predictions.

Results: A two compartment PK model with linear and saturable elimination best described preclinical PK data. An exponent of 1 was used to scale clearance and intercompartmental clearance. The neutropenia model structure developed by Friberg et al. [1] was applied for MEN1309/OBT076-associated neutropenia in cynomolgus monkeys. The estimated drug-related parameters in cynomolgus monkeys, together with the scaled PK model and the typical system-related parameters in human [1], were used to scale up to human the Friberg model and to predict the time course of myelosuppression in patients. The semi-mechanistic model developed by Simeoni et al. [2] was applied to model tumour growth inhibition data from xenograft experiments. The threshold concentration for tumour eradication was derived and used as a reference concentration for achieving a significant activity in human. According to the predictions of the developed translational exposure–efficacy and safety modelling framework, a starting dose in human of 0.05 mg/kg was considered to provide an adequate safety margin. Moreover, the PK/PD model predictions supported an accelerated titration design (ATD) from 0.05 mg/kg to 6.4 mg/kg. Finally, median and 90% prediction intervals (PI) of fully-scaled simulated MEN1309/OBT076 concentration-time profiles and ANC-time profiles in human were compared against observed data in patients from FIH study. In general, observed values were well distributed around median predictions and the extent of inter-individual variability was well represented by the 90% PI.

Conclusions: A translational strategy developed from preclinical data proved to be a valuable tool for the selection of the dose of a FIH study of a novel ADC. Good agreement between the model-based predictions and the clinical PK and safety data collected from the ongoing Phase 1 study shown in a subsequent model validation analysis confirmed the adequacy of the followed approach.