PREDICTION OF FIRST-IN-HUMAN DOSE FOR HPN536, A T-CELL ENGAGER TARGETING MESOTHELIN: MABEL VS MECHANISTIC TRANSLATIONAL PK/RO/PA MODELING

Oleg Demin*, Dmitry Shchelokov. ISyBio CY, Paphos, Cyprus

Background The minimal anticipated biological effect level (MABEL) approach is recommended for the selection of safe clinical starting dose for T-cell engagers (TCE). The approach allows to estimate the minimal recommended starting dose (MRSD) by setting predicted drug exposure in humans less than concentration of the drug resulting in desirable percentage of maximal pharmacological activity (PA) observed in vitro (in the range of 10%-50%, e.g. EC20). However, this method may lead to low MRSD and multiple dose escalations, resulting in sub-therapeutic doses for patients.1 The aim of our work was to predict MRSD for HPN536, a TCE targeting mesothelin, using mechanistic translational pharmacokinetic (PK), receptor occupancy (RO), PA modeling and compare it with MRSD calculated using MABEL.

Methods Two mechanistic models were developed: translational PK/RO/PA model and in vitro model of HPN536. In vitro model describes data on T-cell dependent cytotoxicity, cytokine secretion (IFNg, TNFa), and T-cell activation (% of CD25+ cells) in presence of various HPN536 concentrations.2 PK/RO/PA model describes PK in cynomolgus monkey and its translation to human, distribution of TCE into the tumor (ovarian cancer was considered), and PA (cytotoxicity, T-cells activation and cytokine secretion) based on EC50 values identified in the in vitro model. PA in both models depends on a number of timers of HPN536 bound with CD3 and mesothelin in immunological synapse between T-cell and cancer cell rather than on HPN536 concentration as in MABEL approach.

Results Data on HPN536 PK in cynomolgus monkey was fitted two-compartmental PK model.2 PK data in cancer patients were described with adequate precision using standard allometric scaling exponents without fitting.3 Predictions of the starting dose by MABEL approach based on EC50 (nM) identified by in vitro experiments and mechanistic modeling based on EC50 (number of trimers) fitted by in vitro model are presented in table 1. Mechanistic modeling predicted higher dose than MABEL: ranges based on all assays are 170–3150 ng/kg vs 0.9–22.6 ng/kg, respectively.

Conclusions The starting dose chosen for HPN536 first-in-human trial was 6 ng/kg which is in the range predicted by MABEL approach.4 However, doses recommended by mechanistic modeling are higher, e.g., 50% PA is observed in the model at doses around 1000 ng/kg or greater. This prediction is validated by the fact that maximal tolerated dose in HPN536 first-in-human trial was not reached even at dose 3600 ng/kg.

REFERENCE