PK/PD modeling predicts robust target engagement and low probability of grade 4 hematological toxicity at recommended phase 2 starting dose of VX-970 in combination with carboplatin (AUC=5)

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Objectives: Perform model-based analyses of 1) preclinical pharmacokinetics (PK) and target engagement (TE) biomarker data and 2) PK and safety data from a phase 1 dose escalation trial of VX-970 in combination with carboplatin.

Methods: The exposure-response relationship between plasma PK and phosphorylated Chk1 (a TE biomarker for VX-970) in tumors was modeled using data from experiments in tumor-bearing mice dosed with VX-970 in combination with a DNA-damaging agent. The human phosphorylated Chk1 response was predicted using plasma PK of VX-970 in humans. PK/PD models for neutropenia and thrombocytopenia were developed using data from the phase 1 trial and a published model structure¹.

Results: Estimated plasma IC50 for VX-970 inhibition of Chk1 phosphorylation from preclinical experiments is 76 ng/ml (95% CI 42–108). Human VX-970 doses ≥90 mg/m² are predicted to achieve >75% inhibition of Chk1 phosphorylation. At 90 mg/m², preliminary clinical evidence of target modulation was reported². Furthermore, exposures equivalent to the human dose of 90 mg/m² led to tumor regression in preclinical models. Models of hematological toxicity identified exposure response relationships and predicted a risk for grade 4 toxicity of <5% and <1% for neutropenia and thrombocytopenia, respectively, at 90 mg/m² VX-970 in combination with carboplatin (AUC=5). These rates of hematological toxicity are similar to predictions for carboplatin alone².

Conclusions: Modeling predicts robust target engagement and low probability of grade 4 hematological toxicity at the recommended starting phase 2 dose of 90 mg/m² VX-970 in combination with carboplatin (AUC=5).