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Population Pharmacokinetics Characteristics of *nab*-Sirolimus (ABI-009) in Pediatric Patients with Recurrent Solid or CNS Tumors

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Introduction: Recurrent pediatric solid and CNS tumors pose significant challenges in pediatric oncology, resulting in considerable morbidity and mortality due to a lack of effective treatments. Dysregulation of the PI3K-Akt-mTOR pathway complex can lead to tumorigenesis and may be implicated in CNS tumors. *nab*-Sirolimus, also recognized as ABI-009, is a nanoparticle albumin-bound injectable form of sirolimus, a potent mTOR inhibitor. The pharmacokinetic behavior of *nab*-sirolimus is currently not completely elucidated in the pediatric population. Consistent with the *nab*-sirolimus US prescribing information and mTOR inhibitor class effects, toxicities commonly observed in the phase 1 trial of *nab*-sirolimus in adults (NCT00635284) included thrombocytopenia, mucositis, fatigue, rash, diarrhea, and hypertriglyceridemia. The aims of the present study were to characterize the population pharmacokinetics of *nab*-sirolimus in pediatric patients with relapsed/refractory solid tumors, including CNS tumors and to identify factors significantly affecting pharmacokinetic parameters.

Methods: *nab*-Sirolimus was administered intravenously as a weekly dose on days 1 and 8 of a 21-day cycle at doses of 15, 20, and 35 mg/m^2. Patients were assessed on days 1,2,4 and 8 of cycle 1 of single agent *nab*-sirolimus. Blood samples were collected at the following time points: at Day 1 (pre-dose, and 1, 2, 4, 8 hrs. after beginning the infusion), Day 2 (24 hrs. after beginning the Day 1 infusion), Day 4 (72 hrs. after beginning the Day 1 infusion), and Day 8 (pre-infusion) . A total of 29 pediatric patients (258 concentrations) were included in a population pharmacokinetic analysis. Non-linear mixed effect models were developed using the whole blood concentrations attained from the phase 1 clinical trial by implementing the Phoenix NLME program. Covariates that may be related to pharmacokinetics were screened using stepwise methods. The final model was validated by goodness-of-fit plots, visual predictive check, and non-parametric bootstrap.

Results: A three-compartment model was selected as the best structural base model to adequately characterize *nab*-sirolimus pharmacokinetics. Body surface area (BSA) was the most influential factor on clearance of the central compartment, while BSA, age, sex and dose level affected the overall volume of distribution. The population estimates of clearance, and volume of distribution of the central compartment in the final model were 3.0 L/h, and 14.7 L respectively.

Conclusion: The first robust population pharmacokinetic model of *nab*-sirolimus was successfully developed following the intravenous infusion of *nab*-sirolimus in pediatric patients with relapsed/refractory solid tumors, including CNS tumors. Notably, BSA emerged as a significant covariate influencing the pharmacokinetics of *nab*-sirolimus. This model serves as a valuable reference for guiding dose regimens in future pediatric studies involving *nab*-sirolimus.

Keywords: *nab*- Sirolimus; Population Pharmacokinetics; Pediatric Oncology.

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