418TiP Phase 1/2 study of the selective TRK inhibitor larotrectinib, in pediatric patients with cancer

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Background: Neurotrophin ligands and their receptors TRKA, TRKB, and TRKC (encoded by *NTRK1, NTRK2, and NTRK3)* are important for growth regulation, differentiation and survival of neurons. Translocations involving the *NTRK1/2/3* kinase domain have been described in a broad range of adult and pediatric tumors, including infantile fibrosarcoma (IFS), spindle-cell sarcoma, congenital mesoblastic nephroma, pediatric papillary thyroid cancer, high- and low-grade gliomas and Ph-like acute lymphoblastic leukemia. Larotrectinib is the first small-molecule selective inhibitor of TRKA, -B, and -C in clinical development and has demonstrated tumor growth inhibition in preclinical models and clinically meaningful and durable responses in patients with *NTRK*-translocated cancers in an adult phase 1 trial.

Trial design: We have initiated an open-label, multi-center, international Phase 1/2 study with larotrectinib in pediatric patients with solid tumors and primary CNS tumors. A pediatric recommended phase 2 dose of 100mg/m^2 (caped at 100mg BID) has been established. Enrollment to phase 2 began in April 2017 and is ongoing. For the phase 2 component, patients from 1-month of age with IFS or an *NTRK*-fusion positive tumor, including those who have not undergone definitive surgery are eligible. Patients who have not undergone definitive surgery are eligible as well. Larotrectinib is administered as an oral liquid formulation or capsules twice daily on a continuous 28-day schedule. Dosing is based on body surface area. The phase 2 portion enrolls patients with *NTRK*-translocated tumors and measurable disease into three cohorts: 1) infantile fibrosarcoma; 2) other extracranial solid tumors; and 3) primary CNS tumors. The primary endpoint is objective response rate, with duration of response and progression free survival as secondary efficacy endpoints. Quality of life measures and ctDNA are exploratory endpoints. Each phase 2 cohort will enroll in a single stage of up to 10 patients. Molecular abnormalities will be characterized through the analysis of archival tissue.

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