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Abstract 2842

A Phase 1/2 Study to Evaluate the Safety and Efficacy of Ponatinib with Chemotherapy in Pediatric Patients with Philadelphia Chromosome–Positive (Ph+) Acute Lymphoblastic Leukemia (ALL)

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Introduction: Ph+ ALL accounts for 3–5% of pediatric ALL and is associated with improved outcomes when tyrosine kinase inhibitors (TKIs) are added to chemotherapy, with 5-year event-free survival (EFS) and overall survival (OS) of 58–60% and 70–86%, respectively. Ponatinib is a potent third-generation TKI pan-BCR-ABL1 inhibitor that is active against *BCR-ABL1* and all identified single resistance mutations, including the gatekeeper alteration, T315I, which confers resistance to other TKIs. Ponatinib has marketing approval in more than 50 countries, which includes the United States and European Union, for adults with chronic-/accelerated-/blast-phase chronic myeloid leukemia or Ph+ ALL that are resistant/intolerant to other TKIs or are T315I+. Ponatinib may also overcome drug resistance in pediatric patients with relapsed or resistant Ph+ ALL. This study will assess the pharmacokinetics, safety, and efficacy of ponatinib in pediatric patients.

Methods: This Phase 1/2, single-arm, open-label, multicenter study (NCT04501614) will enroll approximately 18 patients in Phase 1 and 68 patients in Phase 2, including those enrolled in Phase 1 at the recommended Phase 2 dose (RP2D). Patients (aged ≥1 year to ≤21 years) with Ph+ ALL, Ph+ mixed phenotype acute leukemia, or Ph-like ALL (US only) with ABL class lesions will be enrolled. Enrolled patients must have either relapsed or are resistant or intolerant to ≥1 prior therapy with a BCR-ABL1-targeted TKI or have a *BCR-ABL1* T315I mutation. Patients >16 years must have a Karnofsky performance status ≥50%; patients ≤16 years must have a Lansky Play Scale ≥50%. During Phase 1, prior to availability of an age-appropriate formulation (AAF), patients must weigh ≥30 kg and be able to swallow tablets.

The Phase 1 study will establish the RP2D of ponatinib in combination with the chemotherapy backbone using the adult tablet formulation in patients able to swallow tablets. Patients will receive fixed doses of ponatinib based on body weight ranges. The initially selected doses are expected to achieve systemic exposures that approximately match adult exposures after a 30-mg dose. Dose selection for the AAF will be in a separate cohort and informed by the results of a relative bioavailability study in healthy adult volunteers. A rolling 6 design will be used for both cohorts; additional cohorts may be enrolled at lower or higher doses based on the emerging data.

In both Phase 1 and Phase 2, patients will receive two 35-day blocks of therapy (reinduction and consolidation). Each block includes 29 days of study treatment consisting of daily ponatinib and a modified United Kingdom ALL R3 chemotherapy backbone regimen, followed by a rest period of at least 6 days with daily ponatinib only. Disease assessment will occur at the end of each block. Patients will undergo an end-of-treatment visit 25 to 30 days after the last dose of study treatment in the consolidation block, or earlier if the patient is proceeding to alternate therapy or optional ponatinib continuation therapy.

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For the Phase 1 study, the primary endpoint is the RP2D of ponatinib (tablet and AAF) in combination with chemotherapy. Secondary endpoints are complete response (CR) rate at the end of the reinduction block and characterization of *BCR-ABL1* domain mutations prior to and following ponatinib treatment. For the Phase 2 study, the primary endpoint is the CR rate at the end of the reinduction block. Secondary endpoints will be summarized descriptively, and include the proportion of patients in continued CR or who achieve CR at the end of consolidation, the proportion with minimal residual disease–negative status <0.01% at the end of each block, and the proportion who relapsed or progressed, and time-to-event estimates including EFS, progression-free survival, and OS. The study will include approximately 70 study sites in approximately 16 countries.

Disclosures: Matloub: *Takeda:* Current Employment. **Gore:** *Amgen, Novartis, Roche:* Membership on an entity's Board of Directors or advisory committees. **Loh:** *Medisix Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Other: Institutional Research Funding. **Pui:** *Adaptive Biotechnologies:* Membership on an entity's Board of Directors or advisory committees. **Hanley:** *Takeda:* Current Employment. **Lu:** *Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited:* Current Employment. **Leonard:** *Takeda:* Current Employment. **Granier:** *Incyte:* Current Employment. **Silverman:** *Servier:* Other: advisory board; *Syndax:* Other: advisory board; *Takeda:* Other: advisory board.

OffLabel Disclosure: Ponatinib has marketing approval in the United States and European Union for adult patients with chronic-/accelerated-/blast-phase chronic myeloid leukemia or Ph+ ALL that are resistant/intolerant to other TKIs or are T315I+. This trials-in-progress abstract describes a study in pediatric patients.

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