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PB1762 PONATINIB VERSUS IMATINIB WITH REDUCED-INTENSITY CHEMOTHERAPY IN PATIENTS WITH NEWLY DIAGNOSED PHILADELPHIA CHROMOSOME–POSITIVE (PH+) ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): PHALLCON STUDY

Topic: 02. Acute lymphoblastic leukemia - Clinical

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Background: Ponatinib (PON) is active against native *BCR::ABL1* and all identified single-resistance mutations, including T315I. In newly diagnosed patients with Ph+ ALL treated with first- or second-generation tyrosine kinase inhibitors (TKIs), development of secondary resistance mutations in BCR::ABL1 is strongly associated with disease progression. Use of first-line PON in Ph+ ALL may decrease likelihood of these mutations and provide deeper, more durable responses. A Phase 2 study of PON in combination with chemotherapy in patients with newly diagnosed Ph+ ALL reported improved long-term outcomes with a 5-year event free survival and overall survival of 67% and 71%, respectively.

Aims: This study aims to compare efficacy and safety of first-line PON versus imatinib with reduced-intensity chemotherapy in patients with newly diagnosed Ph+ or *BCR::ABL1*–positive ALL (p190/p210 transcript type).

Methods: PhALLCON (NCT03589326) is a Phase 3, open-label, parallel-assignment, randomized study. Patients remain on treatment until relapse from complete remission (CR), have progressive disease, have unacceptable toxicity, withdraw consent, proceed to hematopoietic stem cell transplant (HSCT), complete study (20 cycles), are deceased, or sponsor terminates study. The trial will enroll ≈230 evaluable patients (aged ≥18 years) with ECOG performance status ≤2, randomized 2:1 to PON 30 mg/d or imatinib 600 mg/d orally, with reduced-intensity chemotherapy in induction (Cycles 1–3), consolidation (Cycles 4–9), and maintenance (Cycles 10–20). Enrollment is defined as randomized to study drug. Primary endpoint is minimal residual disease (MRD)-negative (*BCR::ABL1/ABL1* ≤0.01%) CR at end of induction (≈3 months). Key secondary endpoint is EFS, defined as dates of randomization until death (any cause), failure to achieve MRD-negative CR by end of induction, or relapse from CR. Other secondary endpoints include CR/incomplete blood count recovery rates, molecular response rates, MRD-negative CR duration, primary induction failure, overall response rate, CR duration, time to treatment failure, overall survival, and safety, including arterial occlusive/venous thromboembolic events. After induction, durations will be measured from first report. Other analyses include a subgroup analysis of patients with/without HSCT and an exploratory analysis by mutation status.

Results: First patient was randomized into the study in January 2019 with enrollment ongoing in 18 countries at 117 initiated sites; ≈226 patients were randomized as of February 2022.

Summary/Conclusion: This is the only registrational RCT Phase 3 study in Ph+ ALL, and it compares efficacy and safety of the only third-generation pan-inhibitor BCR::ABL1 TKI PON with first-generation imatinib in combination with chemotherapy in the first-line setting for adult patients with Ph+ ALL.

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