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Abstract 1026

Ponatinib Versus Imatinib with Reduced-Intensity Chemotherapy in Patients with Newly Diagnosed Philadelphia Chromosome–Positive (Ph+) Acute Lymphoblastic Leukemia (ALL): Phallcon Study

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Introduction: Therapies for adults with newly diagnosed Ph+ ALL are limited and associated with poor outcomes. Ponatinib is active against native *BCR-ABL1* and all identified single resistance mutations, including T315I. In the PACE study, ponatinib had a 41% major hematologic response rate in heavily pretreated Ph+ ALL, but responses were not durable due to emergence of new compound mutations (Cortes 2013, 2018). Ponatinib resistance in Ph+ ALL is acquired through these mutations. Sequential use of TKIs can select for T315I and compound *BCR-ABL1* mutants. The use of first-line ponatinib in Ph+ ALL may decrease the likelihood of these mutations, which will lead to more durable responses. A Phase 2 study of ponatinib with chemotherapy in newly diagnosed Ph+ ALL reported improved long-term outcomes versus a second-generation tyrosine kinase inhibitor (TKI) (Sasaki 2016).

Objective: The PhALLCON trial (NCT03589326) is a randomized study that compares efficacy and safety of first-line ponatinib versus imatinib with reduced-intensity chemotherapy.

Design: Phase 3, global, open-label, parallel-assignment trial. Patients randomized 2:1 to ponatinib or imatinib with reduced-intensity chemotherapy. Patients remain on study treatment until they complete study, relapse from complete remission (CR), have progressive disease, have unacceptable toxicity, withdraw consent, proceed to hematopoietic stem cell transplant (HSCT), or sponsor terminates study. The study was initiated August 2018.

Setting: The trial will be conducted in up to 35 countries. Currently, there are 110 active sites (Argentina, Australia, Austria, Belarus, Brazil, Bulgaria, Canada, China, Finland, France, Greece, Italy, Mexico, Poland, Romania, Russia, South Korea, Spain, Taiwan, Turkey, and the United States). Accrual is ongoing with 87 patients currently enrolled.

Patients: The trial will enroll ~230–320 patients (≥18 years) with newly diagnosed Ph+ or BCR-ABL1–positive ALL (p190/p210 transcript type) and Eastern Cooperative Oncology Group status ≤2.

Interventions: Patients will be randomized 2:1 to ponatinib 30 mg/d or imatinib 600 mg/d PO with reduced-intensity chemotherapy in induction (Cycles 1–3), consolidation (Cycles 4–9), and maintenance (Cycles 10–20). The reduced-intensity chemotherapy backbone consists of three 28-day cycles of vincristine and dexamethasone for the induction phase, six 28-day cycles of alternating cytarabine (even-numbered cycles) and methotrexate (odd-numbered cycles), and eleven 28-day cycles of vincristine and prednisone for the maintenance phase. Ponatinib dose will be reduced to 15 mg once minimal residual disease (MRD)–negative CR is achieved. After 20 cycles, patients stay on single-agent ponatinib/imatinib. Central nervous system prophylaxis will be administered 2×/month in Cycles 1–6.

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Main outcome measures: The primary endpoint is MRD-negative (*BCR-ABL1/ABL1* ≤0.01%) CR at the end of induction (~3 months). The key secondary endpoint is event-free survival, which is defined as the dates of randomization until death due to any cause, failure to achieve MRD-negative CR by the end of induction, or relapse from CR. Other secondary endpoints include CR/incomplete blood count recovery rates, molecular response rates (MR3, MR4, MR4.5), MRD-negative CR duration; primary induction failure; overall response rate, CR duration, time to treatment failure, MR4.5 duration after induction, overall survival, and safety, including arterial occlusive/venous thromboembolic events. Other analyses include a subgroup analysis of patients with/without HSCT and an exploratory by mutation status.

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