Abstract: S110

Title: PHALLCON: A PHASE 3 STUDY COMPARING PONATINIB VERSUS IMATINIB IN NEWLY DIAGNOSED PH+ ALL

Abstract Type: Oral Presentation

Session Title: Immune therapeutic treatment in ALL

Background:

The standard of care in patients with newly diagnosed Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) is BCR::ABL1 tyrosine kinase inhibitors (TKIs) in combination with chemotherapy or steroids. Treated with first- or second-generation TKIs, patients eventually progress due to emergence of resistance. Multiple studies have reported promising minimal residual disease (MRD) negativity (neg) rates and survival outcomes with ponatinib in combination with chemotherapy or chemotherapy-free regimens.

Aims:

PhALLCON (NCT03589326), the first randomized study comparing TKIs in patients with Ph+ ALL, evaluates ponatinib versus imatinib in combination with reduced-intensity chemotherapy.

Methods:

This phase 3 open-label study randomized newly diagnosed Ph+ ALL adult patients 2:1 to receive ponatinib (30 mg once daily [QD]) or imatinib (600 mg QD) with reduced-intensity chemotherapy through end of induction (EOI), consolidation, and post-consolidation. After post-consolidation, patients received single-agent ponatinib or imatinib until disease progression or unacceptable toxicity. The composite primary endpoint was MRD-neg (*BCR*::*ABL1* ≤0.01%*)* complete remission (CR) for 4 weeks at EOI. Event-free survival (EFS: any-cause death, failure to achieve CR by EOI, relapse from CR) was a key secondary endpoint.

Results:

A total of 245 pts were randomized to ponatinib (n=164) or imatinib (n=81); median age was 54 years (37% ≥60 years). At data cutoff (Aug 2022), 78 patients (ponatinib vs imatinib: 42% vs 12%) were on study treatment; the top 3 reasons for discontinuation were hematopoietic stem cell transplantation (30% vs 37%), adverse events (12% vs 12%), and lack of efficacy (7% vs 26%). Median follow-up was 20 months vs 18 months (ponatinib vs imatinib). The primary endpoint was met (**Table**), with a significantly higher MRD-neg CR rate at EOI for ponatinib vs imatinib (34% vs 17%; *P*=0.0021). Additionally, MRD-neg rate regardless of CR at EOI was significantly higher for ponatinib vs imatinib (43% vs 21%; *P*=0.0017). Median duration of MRD-neg and time to treatment failure were not reached for ponatinib and were 20.9 months and 21.9 months, respectively, for imatinib. EFS data were not mature; however, the median EFS was reached in imatinib and not in ponatinib, with a trend toward improvement (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.39–1.10). The treatment-emergent adverse event (TEAE) rates (any-grade and Grade 3/4/5) were comparable between treatment arms. Most common any-grade hematologic TEAEs were anemia (ponatinib 72%, imatinib 67%) and platelet count decrease (ponatinib 68%, imatinib 69%). The most common Grade 3/4 nonhematologic TEAEs were headache (ponatinib and imatinib 43%) and nausea (ponatinib 35%, imatinib 50%). Incidence of arterial occlusive events (AOEs) were infrequent and similar between the arms (**Table**).

Summary/Conclusion:

Ponatinib was superior to imatinib in combination with reduced-intensity chemotherapy in the front-line setting for patients with Ph+ ALL, with a significantly higher MRD-neg CR rate at EOI. Ponatinib was associated with deeper and more durable responses, with a trend toward improved EFS and comparable safety vs imatinib.

Table

	Ponatinib	Imatinib
Responses at EOI, n (%)*	**(N=154)**	**(N=78)**
MRD-neg (*BCR*::*ABL1* ≤0.01%) CR	53 (34)	13 (17)
P value	0.0021	
MR 4 (*BCR*::*ABL1* ≤0.01%)	64 (42)	16 (21)
MR 4.5 (*BCR*::*ABL1* ≤0.0032%)	39 (25)	10 (13)
AEs, n (%)	**(N=163)**	**(N=81)**
Grade 5 TEAEs/TRAEs	8 (5)/0	4 (5)/1 (1)
Grade 3–4 TEAEs	139 (85)	71 (88)
TE AOE (any grade)	4 (2)	1 (1)

*Efficacy evaluable.
AE, adverse event; AOE, arterial occlusive event; CR, complete remission; EOI, end of induction; MR, molecular response; MRD-neg, minimal residual disease negativity; TE, treatment-emergent; TR, treatment-related.

Keywords: Ph+ ALL