First report of PhALLCON: a phase 3 study comparing ponatinib vs imatinib in newly diagnosed Ph+ ALL

ALL-300

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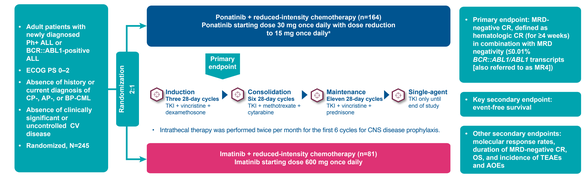
Introduction

- Standard-of-care frontline therapy for Philadelphia chromosome-positive (Ph+) acute lymphocytic leukemia (ALL) is BCR::ABL1 tyrosine kinase inhibitors (TKIs) + chemotherapy or steroids[1]
- Cross-trial comparison of low-dose chemotherapy and first- and second-generation BCR::ABL1 TKIs reported 12-week complete molecular response (CMR) rates of approximately 14%–39%.[2,3] Resistance was frequently driven by acquisition of T315I kinase domain mutation[4]
- Ponatinib, the only approved pan-BCR::ABL1 inhibitor, is a third-generation TKI designed to potently inhibit BCR::ABL1 with or without any single resistance mutation, including T315I[5]
- Ponatinib in combination with chemotherapy or immunotherapy improved long-term outcomes[6,7]

Methods

- Phase 3 open-label randomized study in adult patients with newly diagnosed Ph+ ALL (**Figure 1**)
  - Patients were randomized 2:1 to ponatinib (30mg once daily) or imatinib (600mg once daily) with reduced-intensity chemotherapy through the end of induction (EOI), consolidation, and post-consolidation
  - After post-consolidation, patients received single-agent ponatinib or imatinib until disease progression or unacceptable toxicity
- **Composite primary endpoint:** minimal residual disease (MRD)-negative (*BCR::ABL1* ≤0.01%) complete remission (CR) for ≥4 weeks at EOI
- **Key secondary endpoint:** event-free survival (EFS) defined as any-cause death, failure to achieve CR by EOI, relapse from CR

Figure 1: Study design



*Dose reductions to 15 mg once daily were implemented in patients who achieved MRD-negative CR after completion of the induction phase
ALL, acute lymphocytic leukemia; AOE, arterial occlusive event; AP, accelerated phase; BP, blastic phase; CML, chronic myeloid leukemia; CNS, central nervous system; CP, chronic phase; CR, complete response; CV, cardiovascular; ECOG, Eastern Cooperative Oncology Group; EOI, end of induction; MRD, minimal residual disease; OS, overall survival; Ph+, Philadelphia chromosome-positive; PS, performance status; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

Results

- At the data cutoff (12 August 2022), the median (range) follow-up was 20 months (range: 18–24) in the ponatinib arm and 18 months (14–24) in the imatinib arm
- More patients in the ponatinib arm continued to receive study treatment vs the imatinib arm (41% vs 12%) (**Table 1**)
- Demographics and baseline characteristics were generally balanced between treatment arms (**Table 2**)
  - P190 was the dominant *BCR::ABL1* variant in both arms, occurring in 68% of patients overall
  - 59% of patients had 1 or more cardiovascular (CV) comorbidities and ~30% of patients had 2 or more comorbidities at baseline
- Ponatinib was associated with better disease control (**Figure 3**), provided more durable responses, and showed a trend toward remaining on therapy longer without treatment failure (**Figure 4**) than imatinib
- 37% of the 81 patients in the imatinib arm later received a second- or third-generation TKI and/or immunotherapy; 16% of 81 received ponatinib (**Table 3**)
- Although not mature at the data cutoff date, EFS and progression-free survival (PFS) showed positive trends
  - EFS showed a favorable trend toward improvement; the median was already reached with imatinib arm but not ponatinib (**Figure 5**)
  - PFS showed a favorable trend toward improvement, with median PFS of 20 months for ponatinib versus 8 months for imatinib (**Figure 6**)
- OS was not mature at the data cutoff date; the median was not reached in either arm (**Figure 7**)

Table 1: Patient disposition

No. of patients, n (%)	Ponatinib arm (n=164)	Imatinib arm (n=81)
ITT population	164 (100)	81 (100)
Efficacy evaluable population[a]	154 (94)	78 (96)
Safety evaluable population[b]	163 (99)	81 (100)
Patients randomized and treated	163 (99)	81 (100)
Ongoing on study treatment	68 (41)	10 (12)
Discontinued study treatment	95 (58)	70 (86)
HSCT	50 (30)	30 (37)
Lack of efficacy	12 (7)	21 (26)
Adverse event	20 (12)	10 (12)
Progressive disease[c]	7 (4)	5 (6)
Other	6 (4)	4 (5)
Discontinued study	29 (18)	18 (22)
Death	21 (13)	13 (16)
Patient withdrawal	6 (4)	4 (5)
Lost to follow-up	0	1 (1)
Other	2 (1)	0
Received HSCT at any time	56 (34)	39 (48)

[a] Patients in the ITT population with *BCR::ABL1* dominant variant of p190 or p210 confirmed by central lab.
[b] One patient was randomized to the ponatinib arm and died prior to receiving treatment. [c] Defined as an increase of at least 25% in the absolute number of circulating or BM blasts or development of extramedullary disease.
HSCT, hematopoietic stem cell transfer; ITT, intent-to-treat.

Table 2: Demographics and baseline disease characteristics

Characteristic	Ponatinib arm (n=164)	Imatinib arm (n=81)
Age, years, median (range)	54 (19–82)	52 (19–75)
≥60 years, n (%)	61 (37)	30 (37)
Male, n (%)	74 (45)	38 (47)
ECOG PS score 0 or 1, n (%)	157 (96)	76 (94)
Leukocyte count, x 10^9/L, median (range)	4.4 (0.4–198)	3.2 (0.2–81)
Leukemic blasts, %, median (range)	80 (0–100)	75 (0–100)
Patients with ≥1 CV comorbidity	92 (56)	52 (64)
Patients with ≥2 CV comorbidities	45 (28)	27 (33)
BCR::ABL1 dominant variant, n (%)		
p190	114 (70)	53 (65)
p210	40 (24)	25 (31)

CV, cardiovascular; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

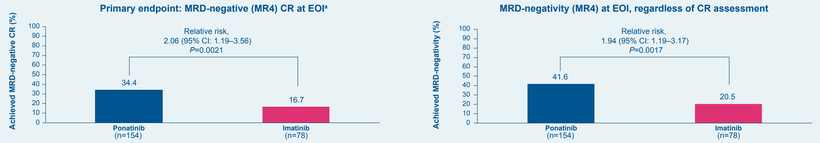
Objective

Compare the efficacy and safety of frontline ponatinib vs imatinib in combination with low-intensity chemotherapy in patients with newly-diagnosed Ph+ ALL[8]

Results

- PhALLCON met its primary endpoint, with a 2-fold higher MRD-negative CR rate at the EOI with ponatinib vs imatinib (*P*=0.0021) (**Figure 2**)

Figure 2: MRD-negative CR and MRD-negativity

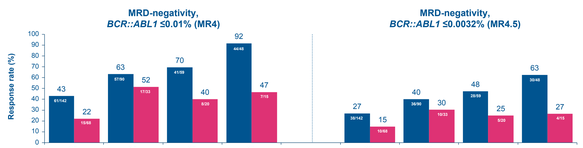


[a] Primary endpoint of MRD-negative CR at the EOI was defined as hematologic CR (for ≥4 weeks) + MRD negativity (≤0.01% *BCR::ABL1*).
CR, complete remission; EOI, end of induction; MRD, minimal residual disease.

Key takeaways

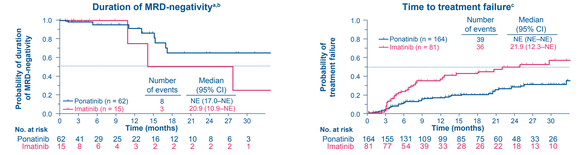
- Ponatinib + reduced-intensity chemotherapy was superior to imatinib in the first-line setting
- The safety profile of ponatinib was comparable with imatinib

Figure 3: Molecular response rates at corresponding treatment cycles for available patients continuing study treatment



MRD, minimal residual disease.

Figure 4: Duration of MRD-negativity and time to treatment failure



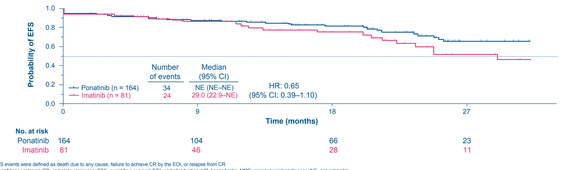
[a] Duration of MRD-negativity is defined as the time from the date of first documentation of MRD-negativity to the date of first documentation of loss of MRD-negativity for patients who achieved MRD-negativity. [b] MRD status was not reported after patients discontinued study treatment, including for HSCT. [c] Time to treatment failure was defined as time to cessation of study treatment (except for HSCT without loss of MRD-negative CR) due to safety and/or loss of efficacy reasons.
CI, confidence interval; MRD, minimal residual disease; NE, not estimable.

Table 3: Subsequent anticancer therapy

Treatment, n (%)	Ponatinib arm (n=163)	Imatinib arm (n=81)
Any subsequent anticancer therapy	57 (35)	46 (57)
Any BCR::ABL1 TKI or immunotherapy	48 (29)	37 (46)
First-generation BCR::ABL1 TKI	17 (10)	7 (9)
Second-/third-generation BCR::ABL1 TKI and/or immunotherapy	31 (19)	30 (37)
Ponatinib-based	13 (8)	13 (16)

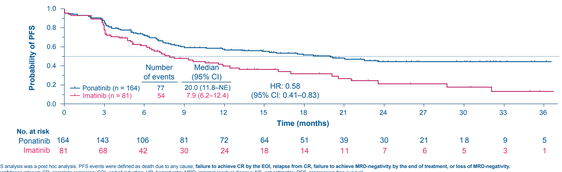
TKI, tyrosine kinase inhibitor.

Figure 5: Secondary endpoint: event-free survival[a]



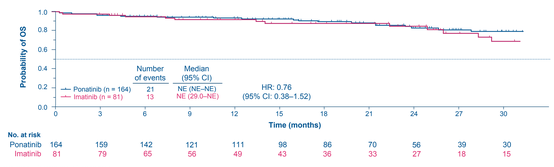
[a] EFS events were defined as death due to any cause, failure to achieve CR by the EOI, or relapse from CR.
CI, confidence interval; CR, complete remission; EFS, event-free survival; EOI, end of induction; HR, hazard ratio; MRD, minimal residual disease; NE, not estimable.

Figure 6: Progression-free survival[a]



[a] PFS analysis was a post hoc analysis. PFS events were defined as death due to any cause, **failure to achieve CR by the EOI, relapse from CR, failure to achieve MRD-negativity by the end of treatment, or loss of MRD-negativity.**
CI, confidence interval; CR, complete remission; EOI, end of induction; HR, hazard ratio; MRD, minimal residual disease; NE, not estimable; PFS, progression-free survival.

Figure 7: Overall survival

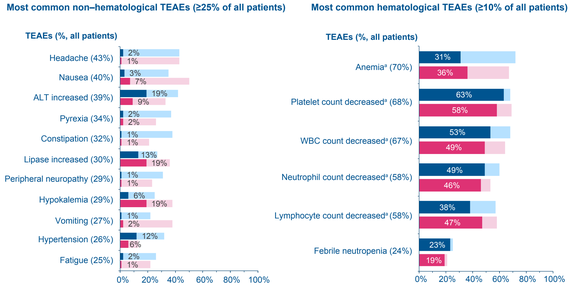


CI, confidence interval; HR, hazard ratio; NE, not estimable.

Safety Results

- In the safety-evaluable population, the most common hematological treatment-emergent adverse events (TEAEs) were anemia, thrombocytopenia, and neutropenia (**Figure 8**)
- The rate and severity of TEAEs was comparable between arms, including grades 3 and 4 adverse events (**Table 4**)

Figure 8: Most common TEAEs



[a] Based on laboratory values
TEAE, treatment-emergent adverse event.

Table 4: TEAE summary and dose modifications

Characteristic	Ponatinib arm (n=163)	Imatinib arm (n=81)
TEAEs, n (%)		
Any TEAE	162 (99)	80 (99)
Serious TEAEs	97 (60)	45 (56)
Grade 3–4 TEAEs	147 (90)	75 (93)
Grade 5 TEAEs[a,b,c]	8 (5)	4 (5)
TE-AOEs, n (%)	4 (2)	1 (1)
TE-VTEs[d], n (%)	19 (12)	10 (12)
Dose modification for TEAEs, n (%)		
Discontinuation	17 (10)	7 (9)
Reduction	33 (20)	18 (22)
Interruption	111 (68)	32 (40)

[a] Includes deaths that occurred up to 30 days after the last ponatinib dose. [b] Grade 5 TEAEs were: ponatinib arm: septic shock (n=4), abdominal sepsis, sepsis, pneumonitis, and respiratory failure (n=1 each); imatinib arm: septic shock, pseudomembranous colitis, pulmonary sepsis, and depressed level of consciousness (n=1 each). [c] There was one treatment-related death reported in the imatinib arm and none in the ponatinib arm. [d] PICC-line or CVC-related VTEs were reported in 8 (5%) patients in the ponatinib arm and 6 (7%) patients in the imatinib arm.
CVC, central venous catheter; TEAE, treatment-emergent adverse event; PICC, peripherally inserted central catheter; TE-AOE, treatment-emergent arterial occlusive event; TE-VTE, treatment-emergent venous thromboembolic event; VTE, venous thromboembolic event.

Conclusions

- Ponatinib + reduced-intensity chemotherapy was superior to imatinib in the first-line setting:
  - Primary endpoint: MRD-negative CR rate at the EOI: 34% vs 17% (*P*=0.0021)
  - MRD-negativity rate: 42% vs 21%
- The safety profile of ponatinib was comparable with imatinib
- Adverse events of special interest were similar with ponatinib and imatinib:
  - TE-AOEs: 2% vs 1%
  - TE-venous thromboembolic events: 12% in both
- Ponatinib + reduced-intensity chemotherapy has the potential to be standard of care in patients with newly diagnosed Ph+ ALL

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