Post hoc analysis of MRD negativity after end of induction in the phase 3 PhALLCON trial

ALL-589

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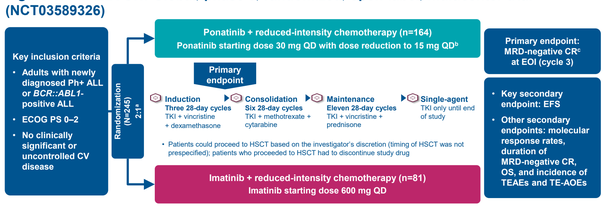
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Introduction

- Ponatinib is a potent third-generation BCR::ABL1 tyrosine kinase inhibitor (TKI) approved by the FDA for the treatment of adults with newly diagnosed Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL) in combination with chemotherapy based on the results of the phase 3 PhALLCON trial[1-3]
  - PhALLCON met its primary endpoint, demonstrating a clinically meaningful and significantly higher rate of minimal residual disease (MRD)-negative complete remission (CR) at the end of induction (EOI) with ponatinib + chemotherapy compared with imatinib + chemotherapy (34.4% vs 16.7%; *P*=0.002)
  - The safety profiles of ponatinib + chemotherapy and imatinib + chemotherapy were comparable
- We report post hoc analyses of molecular response rates, event-free survival (EFS), overall survival (OS), progression-free survival (PFS), and safety in patients who did not achieve MRD negativity by EOI in the PhALLCON trial

Methods

Figure 1: PhALLCON: Global, phase 3, randomized, open-label, multicenter trial (NCT03589326)



[a]Randomization was stratified by age group (18 to <45 y; 45 to <60 y; ≥60 y); [b]Dose reductions to 15 mg QD were implemented in patients who achieved MRD-negative CR after completion of the induction phase; [c]MRD-negative CR was defined as hematologic CR (≥4 weeks) in combination with MRD negativity (*BCR::ABL1*/*ABL1*^{IS} ≤0.01%).

CV, cardiovascular; ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplantation; PS, performance status; QD, once daily; TEAE, treatment-emergent adverse event; TE-AOE, treatment-emergent arterial occlusive event.

Analyses

- These post hoc analyses (data cutoff: August 12, 2022) evaluated baseline characteristics, molecular response rates, EFS, OS, PFS, and safety in patients who were not MRD-negative by EOI and in those who subsequently achieved MRD negativity post-EOI (ie, after Cycle 4 Day 1)
- Patients included in these analyses had *BCR::ABL1* variant p190 or p210 confirmed by central laboratory at baseline

Endpoints

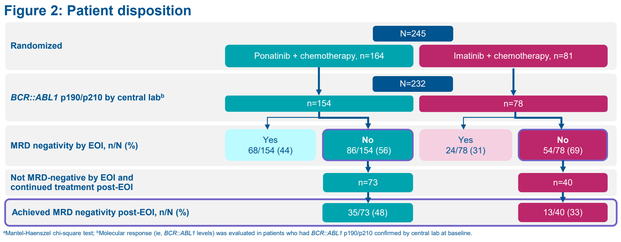
- A molecular response of MRD negativity was defined as *BCR::ABL1*^{IS} ≤0.01% (ie, MR4) assessed by central laboratory; deeper molecular response was defined as *BCR::ABL1*^{IS} ≤0.0032% (ie, MR4.5)
- EFS was defined as the time from the date of randomization until death due to any cause, failure to achieve CR by EOI, or relapse from CR
- OS was defined as the time from the date of randomization until death due to any cause
- PFS was defined as the time from the date of randomization until EFS events, failure to achieve MRD negativity by end of treatment, or loss of MRD negativity
- Patients could proceed to HSCT based on the investigator's discretion (timing of HSCT was not prespecified); patients who proceeded to HSCT had to discontinue study drug

Results

Patients

- Among 232 patients with *BCR::ABL1* p190/p210 confirmed by central laboratory at baseline, 140 patients did not achieve MRD negativity (MR4 or better) by EOI (**Figure 2**)
  - Of these, 113 patients continued treatment after EOI
  - A higher proportion of patients in the imatinib arm vs ponatinib arm did not achieve MRD negativity by EOI (69% vs 56%; *P*=0.0494[a])

Figure 2: Patient disposition



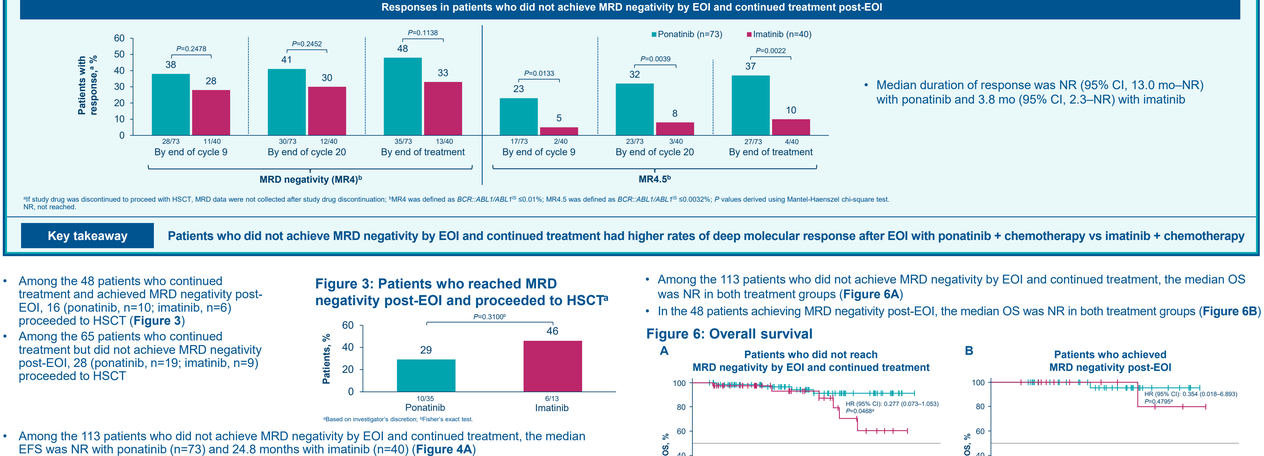
[a]Mantel-Haenszel chi-square test; [b]Molecular response (ie, *BCR::ABL1* levels) was evaluated in patients who had *BCR::ABL1* p190/p210 confirmed by central lab at baseline.

- Baseline characteristics of patients who did not achieve MRD negativity by EOI and those who achieved MRD negativity post-EOI were comparable with those of the overall population (**Table 1**)
  - Patients who did not achieve MRD negativity by EOI and did not continue treatment post-EOI had higher rates of ECOG PS of 2 compared with the overall population, but other baseline characteristics were similar

Table 1: Key demographics and baseline characteristics

	Not MRD-negative by EOI		MRD-negative post-EOI		Overall population (randomized)	
Characteristic	Ponatinib (n=86)	Imatinib (n=54)	Ponatinib (n=35)	Imatinib (n=13)	Ponatinib (n=164)	Imatinib (n=81)
Age, y, median (range)	53.5 (19–82)	54.0 (19–75)	53.0 (19–79)	60.0 (19–71)	54.0 (19–82)	52.0 (19–75)
≥60 y, n (%)	31 (36)	21 (39)	9 (26)	7 (54)	61 (37)	30 (37)
Female, n (%)	48 (56)	29 (54)	21 (60)	8 (62)	90 (55)	43 (53)
ECOG PS, %						
0	42 (49)	20 (37)	19 (54)	3 (23)	72 (44)	33 (41)
1	39 (45)	30 (56)	16 (46)	10 (77)	85 (52)	43 (53)
2	5 (6)	4 (7)	0	0	7 (4)	5 (6)
Leukocyte count, x 10^9/L, median (range)	5.9 (0.4–197.3)	3.3 (0.2–81.2)	4.1 (0.8–197.3)	2.4 (0.2–47.5)	4.4 (0.4–197.3)	3.2 (0.2–81.2)
Leukemic blasts, %, median (range)	82.0 (0.0–100.0)	75.0 (0.0–100.0)	80.0 (9.0–99.0)	85.0 (2.0–95.0)	80.0 (0.0–100.0)	75.0 (0.0–100.0)
***BCR::ABL1* dominant variant, n (%)**						
p190	57 (66)	35 (65)	23 (66)	11 (85)	114 (70)	53 (65)
p210	29 (34)	19 (35)	12 (34)	2 (15)	40 (24)	25 (31)
Received prephase therapy, n (%)	38 (44)	31 (57)	16 (46)	8 (62)	74 (45)	41 (51)
Extramedullary disease present, n (%)	5 (6)	2 (4)	3 (9)	0	10 (6)	3 (4)

Achievement of MRD negativity after EOI



[a]If study drug was discontinued to proceed with HSCT, MRD data were not collected after study drug discontinuation; [b]MR4 was defined as *BCR::ABL1*/*ABL1*^{IS} ≤0.01%; MR4.5 was defined as *BCR::ABL1*/*ABL1*^{IS} ≤0.0032%; *P* values derived using Mantel-Haenszel chi-square test.
NR, not reached.

- Median duration of response was NR (95% CI, 13.0 mo–NR) with ponatinib and 3.8 mo (95% CI, 2.3–NR) with imatinib

Key takeaway — Patients who did not achieve MRD negativity by EOI and continued treatment had higher rates of deep molecular response after EOI with ponatinib + chemotherapy vs imatinib + chemotherapy

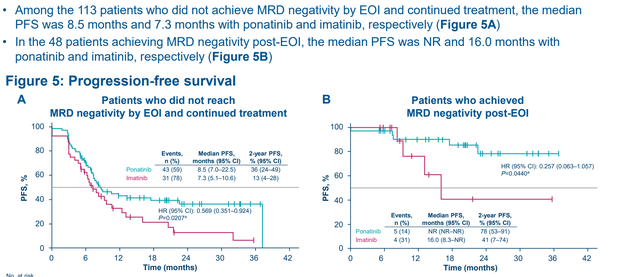
- Among the 48 patients who continued treatment and achieved MRD negativity post-EOI, 16 (ponatinib, n=10; imatinib, n=6) proceeded to HSCT (**Figure 3**)
- Among the 65 patients who continued treatment but did not achieve MRD negativity post-EOI, 28 (ponatinib, n=19; imatinib, n=9) proceeded to HSCT

Figure 3: Patients who reached MRD negativity post-EOI and proceeded to HSCT[a]

[a]Based on investigator's discretion; [b]Fisher's exact test.

- Among the 113 patients who did not achieve MRD negativity by EOI and continued treatment, the median EFS was NR with ponatinib (n=73) and 24.8 months with imatinib (n=40) (**Figure 4A**)
- In the 48 patients achieving MRD negativity post-EOI, median EFS was NR in both treatment groups (**Figure 4B**)

Figure 4: Event-free survival



[a]*P* values based on stratified log-rank test using stratification according to randomization strata (age): 18 through <45 years, ≥45 through <60 years, and ≥60 years.

- Among the 113 patients who did not achieve MRD negativity by EOI and continued treatment, the median PFS was 8.5 months and 7.3 months with ponatinib and imatinib, respectively (**Figure 5A**)
- In the 48 patients achieving MRD negativity post-EOI, the median PFS was NR and 16.0 months with ponatinib and imatinib, respectively (**Figure 5B**)

Figure 5: Progression-free survival



[a]*P* values based on stratified log-rank test using stratification according to randomization strata (age): 18 through <45 years, ≥45 through <60 years, and ≥60 years.

- Among the 113 patients who did not achieve MRD negativity by EOI and continued treatment, the median OS was NR in both treatment groups (**Figure 6A**)
- In the 48 patients achieving MRD negativity post-EOI, the median OS was NR in both treatment groups (**Figure 6B**)

Figure 6: Overall survival

[a]*P* values based on stratified log-rank test using stratification according to randomization strata (age): 18 through <45 years, ≥45 through <60 years, and ≥60 years.

- Rates of TEAEs and TE-AOEs were similar across groups (**Table 2**)

Table 2: TEAEs and TE-AOEs

	Not MRD-negative by EOI		MRD-negative post-EOI	
Event, n (%)	Ponatinib (n=86)	Imatinib (n=54)	Ponatinib (n=35)	Imatinib (n=13)
Any TEAE	86 (100)	53 (98)	35 (100)	13 (100)
Grade ≥3 TEAE	78 (91)	51 (94)	32 (91)	13 (100)
TEAE leading to dose modification[a]	61 (71)	29 (54)	24 (69)	8 (62)
Dose interruption	57 (66)	22 (41)	24 (69)	5 (38)
Dose reduction	14 (16)	15 (28)	4 (11)	6 (46)
Treatment discontinuation	13 (15)	5 (9)	2 (6)	0
Any TE-AOE	3 (3)	1 (2)	0	0
Grade ≥3 TE-AOE	2 (2)	0	0	0
TE-AOE leading to dose modification[a]	2 (2)	0	0	0
Dose interruption	0	0	0	0
Dose reduction	0	0	0	0
Treatment discontinuation	2 (2)	0	0	0

[a]Adverse events leading to treatment discontinuation, dose reduction, or dose interruption; an adverse event may be associated with >1 type of dose adjustment.

Conclusions

- In patients who did not achieve MRD negativity by EOI and continued treatment beyond Cycle 3, rates of deep molecular response after EOI were higher with ponatinib + chemotherapy compared with imatinib + chemotherapy
- Rates of TEAEs and TE-AOEs were similar with ponatinib and imatinib
- These post hoc analyses should be interpreted with caution due to small numbers of patients and the potential for selection bias
- These findings appear to support the clinical benefit and tolerability of continuing ponatinib beyond Cycle 3 in patients with newly diagnosed Ph+ ALL who do not achieve MRD negativity by EOI

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Disclosures

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