Ponatinib monotherapy following combination with chemotherapy in patients with newly diagnosed Ph+ ALL: Phase 3 PhALLCON post hoc subgroup analysis

ALL-636

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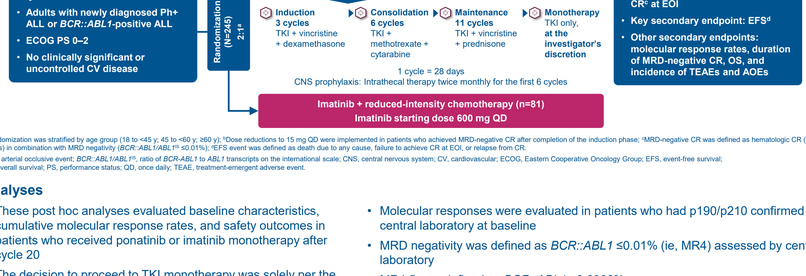
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Introduction

- BCR::ABL1 tyrosine kinase inhibitors (TKIs) in combination with chemotherapy and/or steroids are standard of care for patients with newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL)
- Ponatinib is a potent third-generation BCR::ABL1 TKI approved by the US Food and Drug Administration (FDA) for the treatment of adults with newly diagnosed Ph+ ALL in combination with chemotherapy based on results from the PhALLCON trial[1,2]
  - Ponatinib is the first and only BCR::ABL1 TKI approved by the FDA for frontline treatment of Ph+ ALL in combination with chemotherapy
- PhALLCON is the first global, phase 3 trial to compare 2 TKIs in combination with reduced-intensity chemotherapy in adults with newly diagnosed Ph+ ALL[2]
  - PhALLCON met its primary endpoint, showing a clinically meaningful and significantly higher rate of minimal residual disease (MRD)–negative complete remission (CR) at the end of induction (EOI) with ponatinib versus imatinib (34.4% vs 16.7%; *P*=0.002)[2]
  - Ponatinib and imatinib demonstrated comparable safety profiles
- The PhALLCON study protocol allowed patients who did not proceed to hematopoietic stem cell transplant (HSCT) or other alternative therapy to receive monotherapy with ponatinib or imatinib after 20 cycles of the TKI-chemotherapy combination
- We report post hoc analyses of the subset of patients who received maintenance monotherapy post cycle 20

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%); [d]EFS event was defined as death due to any cause, failure to achieve CR at EOI, or relapse from CR.
AOE, arterial occlusive event; *BCR::ABL1*/*ABL1*[IS], ratio of *BCR-ABL1* to *ABL1* transcripts on the international scale; CNS, central nervous system; CV, cardiovascular; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; OS, overall survival; PS, performance status; QD, once daily; TEAE, treatment-emergent adverse event.

Analyses

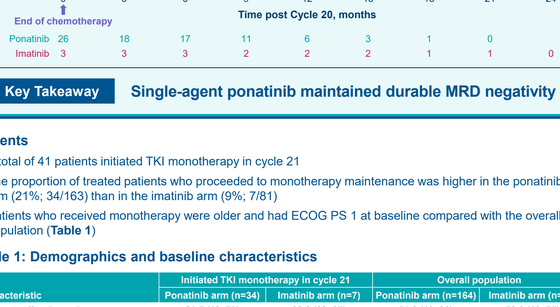
- These post hoc analyses evaluated baseline characteristics, cumulative molecular response rates, and safety outcomes in patients who received ponatinib or imatinib monotherapy after cycle 20
- The decision to proceed to TKI monotherapy was solely per the investigator's discretion
- Patients could continue monotherapy with ponatinib or imatinib until disease progression or unacceptable toxicity
- Molecular responses were evaluated in patients who had p190/p210 confirmed by central laboratory at baseline
- MRD negativity was defined as *BCR::ABL1* ≤0.01% (ie, MR4) assessed by central laboratory
- MR4.5 was defined as *BCR::ABL1* ≤0.0032%
- TEAEs occurring post cycle 20 and at any time during the study were evaluated
- The data cutoff date was August 12, 2022

Results

Maintenance of MRD negativity (MR4) with ponatinib monotherapy after combination therapy



Results: Duration of MR4 Post Cycle 20



Outcome	Patients who initiated monotherapy and had MR4 at start of Cycle 21	
	Ponatinib (n=26)	Imatinib (n=3)
Loss of MR4 post cycle 20, n (%)	1 (4)	1 (33)
Median duration of MR4 post cycle 20, months (95% CI)	NE (NE–NE)	NE (6.0–NE)
Maintained response at 12 months post cycle 20 [KM estimate], % (95% CI)	95 (70–99)	67 (5–95)
Median follow up post cycle 20, months (95% CI)	6.1 (3.0–11.6)	18.4 (15.7–NE)

CI, confidence interval; KM, Kaplan–Meier; NE, not estimable

- For patients with MR4 at start of Cycle 21, 1 patient (4%) in the ponatinib arm and 1 (33%) in the imatinib arm lost MR4 response after starting monotherapy
- By Kaplan-Meier estimates, MR4 was maintained at 12 months post Cycle 20 in 95% of patients with ponatinib monotherapy versus 67% with imatinib
- Median duration of MR4 post Cycle 20 was not reached in either arm

Key Takeaway Single-agent ponatinib maintained durable MRD negativity post Cycle 20

Patients

- A total of 41 patients initiated TKI monotherapy in cycle 21
- The proportion of treated patients who proceeded to monotherapy maintenance was higher in the ponatinib arm (21%; 34/163) than in the imatinib arm (9%; 7/81)
- Patients who received monotherapy were older and had ECOG PS 1 at baseline compared with the overall population (**Table 1**)

Table 1: Demographics and baseline characteristics

Characteristic	Initiated TKI monotherapy in cycle 21		Overall population	
	Ponatinib arm (n=34)	Imatinib arm (n=7)	Ponatinib arm (n=164)	Imatinib arm (n=81)
Age, y, median (range)	61.5 (19–79)	63.0 (29–67)	54.0 (18–82)	52.0 (19–75)
≥60 y, n (%)	18 (53)	5 (71)	61 (37)	30 (37)
Female, n (%)	20 (59)	6 (86)	90 (55)	43 (53)
ECOG PS, %				
0	11 (32)	1 (14)	72 (44)	33 (41)
1	22 (65)	6 (86)	85 (52)	43 (53)
2	1 (3)	0	7 (4)	5 (6)
Region, n (%)				
Europe	12 (35)	3 (43)	71 (43)	33 (41)
North America	12 (35)	2 (29)	50 (30)	26 (32)
South America	7 (21)	1 (14)	21 (13)	10 (12)
APAC	3 (9)	1 (14)	22 (13)	12 (15)
Leukocyte count, x 10^9/L, median (range)	3.2 (1.0–31.1)	3.6 (1.4–18.3)	4.4 (0.4–197.3)	3.2 (0.2–81.2)
Leukemic blasts, %, median (range)	71.0 (18.0–99.0)	68.5 (2.0–90.0)	80.0 (0.0–100.0)	75.0 (0.0–100.0)
BCR::ABL1 dominant variant, n %				
p190	24 (71)	5 (71)	114 (70)	53 (65)
p210	6 (18)	2 (29)	40 (24)	25 (31)

APAC, Asia-Pacific (includes Australia and Oceania).

Molecular response status prior to TKI monotherapy treatment

- For patients who initiated TKI monotherapy at cycle 21, the MRD-negativity (MR4) rate was 97% with ponatinib and 71% with imatinib by the ends of cycles 20 and 32 (**Figure 2A**)
- The rate of deeper molecular response (MR4.5) was 93% with ponatinib and 43% with imatinib by the ends of cycles 20 and 32 (**Figure 2B**)

Figure 2: Molecular response rates in patients who initiated TKI monotherapy at cycle 21[a]



[a]Molecular responses were evaluated in the subpopulation of patients who had p190/p210 confirmed by central laboratory at baseline.
[b]MR4 was defined as *BCR::ABL1*/*ABL1*[IS] ≤0.01%.
[c]MR4.5 was defined as *BCR::ABL1*/*ABL1*[IS] ≤0.0032%.

Safety

- In patients who initiated TKI monotherapy post cycle 20, TEAEs occurred at substantially lower rates after cycle 20 than at any time during the study (**Table 2**), as most TEAEs occurred earlier during the combination with chemotherapy
- The rates and grades of TEAEs after cycle 20 were similar with ponatinib and imatinib (**Table 2**)
- Grade ≥3 TEAEs that occurred after cycle 20 were
  - Ponatinib: hypertension (n=1), peripheral arterial occlusive disease (n=1), recurrent leukemia (n=1), and neutropenia (n=1)
  - Imatinib: depression (n=1)

Table 2: TEAEs in >25% (≥15%) of patients who initiated TKI monotherapy in cycle 21

Event, n (%)	Any time during the study				After cycle 20			
	Ponatinib arm (n=34)		Imatinib arm (n=7)		Ponatinib arm (n=34)		Imatinib arm (n=7)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	34 (100)	33 (97)	7 (100)	7 (100)	20 (59)	4 (12)	4 (57)	1 (14)
Nonhematologic TEAEs								
Headache	17 (50)	0	5 (71)	0	1 (3)	0	1 (14)	0
Peripheral neuropathy	17 (50)	0	1 (14)	1 (14)	0	0	0	0
Constipation	16 (47)	0	1 (14)	0	0	0	0	0
Hypertension	15 (44)	10 (29)	0	0	1 (3)	1 (3)	0	0
Nausea	15 (44)	0	4 (57)	1 (14)	0	0	0	0
ALT increased	14 (41)	8 (24)	3 (43)	1 (14)	1 (3)	0	0	0
Pyrexia	13 (38)	0	2 (29)	0	1 (3)	0	0	0
Fatigue	12 (35)	1 (3)	2 (29)	0	0	0	0	0
Lipase increased	12 (35)	6 (18)	3 (43)	2 (29)	2 (6)	0	0	0
Pain in extremity	11 (32)	0	1 (14)	0	1 (3)	0	0	0
Vomiting	11 (32)	0	3 (43)	0	1 (3)	0	1 (14)	0
Rash	10 (29)	0	1 (14)	0	0	0	0	0
Stomatitis	10 (29)	3 (9)	4 (57)	2 (29)	0	0	0	0
Arthralgia	9 (26)	1 (3)	1 (14)	0	2 (6)	0	1 (14)	0
AST increased	9 (26)	5 (15)	2 (29)	0	0	0	0	0
Back pain	9 (26)	0	1 (14)	0	1 (3)	0	0	0
Hypokalemia	9 (26)	3 (9)	3 (43)	1 (14)	0	0	0	0
Hematologic TEAEs								
Thrombocytopenia	24 (71)	23 (68)	5 (71)	5 (71)	0	0	0	0
Neutropenia	21 (62)	21 (62)	2 (29)	2 (29)	1 (3)	1 (3)	0	0
Anemia	20 (59)	16 (47)	3 (43)	3 (43)	1 (3)	0	0	0
Platelet count decreased	10 (29)	9 (26)	5 (71)	4 (57)	1 (3)	0	1 (14)	0
Febrile neutropenia	9 (26)	7 (21)	2 (29)	2 (29)	0	0	0	0
Neutrophil count decreased	8 (24)	8 (24)	4 (57)	4 (57)	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

- Two (6%) of the 34 patients receiving ponatinib monotherapy had vascular occlusive events (grade 2 peripheral arterial occlusive disease [n=1] and grade 2 venous thrombosis [n=1]) after cycle 20; both events resolved following dose reduction or interruption
- Although dose interruptions were more common with ponatinib than imatinib, there were few treatment discontinuations in both cohorts (**Table 3**)

Table 3: Dose modifications due to TEAEs in patients who initiated TKI monotherapy in cycle 21

Event	Any time during the study		Post cycle 20	
	Ponatinib arm (n=34)	Imatinib arm (n=7)	Ponatinib arm (n=34)	Imatinib arm (n=7)
TEAE leading to dose modification[a]	28 (82)	3 (43)	4 (12)	1 (14)
Dose interruption	26 (76)	3 (43)	3 (9)	0
Dose reduction	9 (26)	3 (43)	1 (3)	0
Treatment discontinuation	1 (3)	1 (14)	1 (3)	1 (14)

[a]TEAEs leading to treatment discontinuation, dose reduction, or dose interruption. A TEAE may be associated with >1 type of dose adjustment.

Conclusions

- A greater proportion of patients initiated ponatinib (21%) vs imatinib (9%) monotherapy maintenance post cycle 20 at the investigator's discretion
- Durable MRD negativity was maintained with ponatinib monotherapy after cycle 20
  - Among 26 patients with MR4 at the start of Cycle 21, only 1 patient (4%) who received ponatinib lost MR4 response after starting monotherapy (median follow-up: 6.1 months)
- Rates of TEAEs were similar with ponatinib and imatinib after cycle 20
- These post hoc analyses should be interpreted with caution due to small numbers of patients who entered the monotherapy phase, especially in the imatinib arm, and the potential for selection bias
- Importantly, available data further support the continued clinical benefit and tolerability of ponatinib monotherapy after combination with chemotherapy in patients with newly diagnosed Ph+ ALL

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2. Jabbour E, et al. *JAMA*. 2024;331(21):1814-1823.

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