In-depth analysis of responders in the phase 3 PhALLCON trial of ponatinib vs imatinib in newly diagnosed Ph+ ALL

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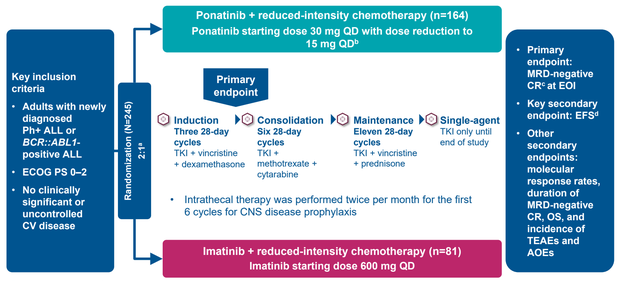
Introduction

- Ponatinib, a third-generation BCR::ABL1 tyrosine kinase inhibitor (TKI), effectively inhibits BCR::ABL1 with or without any single resistance mutation, including T315I[1]
- On March 19, 2024, ponatinib was approved by the US Food and Drug Administration (FDA) for the treatment of adults with newly diagnosed Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) in combination with chemotherapy based on minimal residual disease (MRD)–negative complete remission (CR) at the end of induction (EOI) in the PhALLCON (ponatinib-3001) trial[2,3]
- PhALLCON is the first global, phase 3 trial to compare 2 TKIs in adults with newly diagnosed Ph+ ALL[3]
  - The primary endpoint demonstrated a clinically meaningful and significantly higher rate of MRD-negative CR at EOI with ponatinib versus imatinib in combination with reduced-intensity chemotherapy (34.4% vs 16.7%; *P*=0.002)[3]
  - Safety data from this study indicate that ponatinib has a comparable safety profile to imatinib
- Here, we investigate rates of MRD negativity at any time and progression-free survival (PFS) in PhALLCON by age and *BCR::ABL1* variant subgroups and explore outcomes in patients who proceeded to hematopoietic stem cell transplantation (HSCT)

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* 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

Endpoint definitions

- MRD negativity was defined as *BCR::ABL1*^{IS} ≤0.01% (i.e., MR4) assessed by central laboratory
- PFS events included failure to achieve MRD negativity by end of treatment, loss of MRD negativity, and EFS events (death due to any cause, failure to achieve CR by EOI, or relapse from CR)

Statistical analyses

- Post hoc subgroup analyses evaluated MRD negativity at any time and PFS by age (<65 vs ≥65 years) and *BCR::ABL1* variant (p190 vs p210) in the population of randomized patients who had p190/p210 confirmed by central laboratory
  - Unadjusted relative risk (RR) and 95% confidence intervals (CIs) were calculated using an unstratified Cochran-Mantel-Haenszel chi-square test to compare rates of MRD negativity at any time between the ponatinib and imatinib arms
  - Hazard ratios (HRs) and 95% CIs were calculated using an unstratified Cox regression model to compare PFS between treatment arms
- MRD negativity was evaluated in patients who proceeded to HSCT at any time
  - The decision to proceed to HSCT was at the investigator's discretion
- TEAEs were evaluated in all patients and in those without HSCT

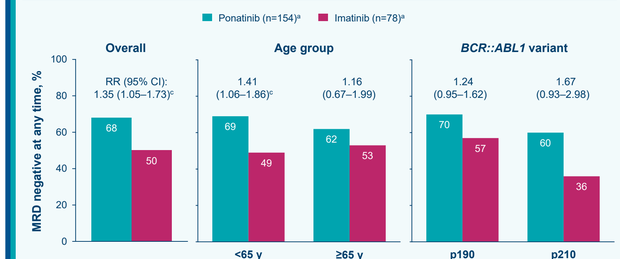
Question

Are rates of MRD negativity at any time and PFS (in post hoc analyses) improved with ponatinib versus imatinib in combination with reduced-intensity chemotherapy in patients with newly diagnosed Ph+ ALL?

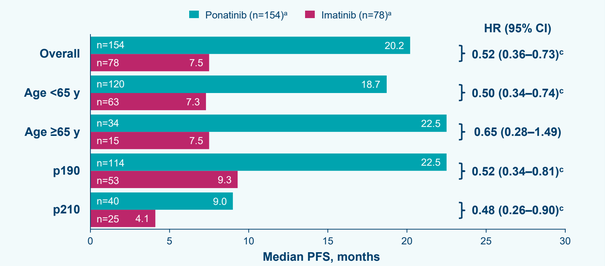
Study design

Results

MRD negativity at any time



PFS[b]



[a]Outcomes were evaluated in the population of randomized patients with p190/p210 confirmed by central laboratory (n=232). [b]Analyses of PFS were post hoc. [c]Rate is significantly different between treatment arms based on the 95% CI of the RR or HR not including 1.00

Key takeaway

Ponatinib demonstrated higher rates of MRD negativity at any time and longer PFS compared with imatinib in combination with chemotherapy, with similar benefit of ponatinib across age and variant subgroups

Results

- Of the 245 patients randomized (2:1) to the ponatinib arm (n=164) or the imatinib arm (n=81), 232 had p190/p210 confirmed by central laboratory (ponatinib, n=154; imatinib, n=78)
- As of the data cutoff date (Aug 12, 2022), median follow-up was 20.1 months (range, 17.8–23.1)
- Demographics and baseline characteristics were balanced between the 2 arms **(Table 1)**

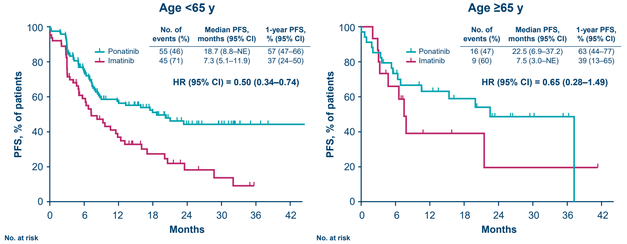
Table 1: Key demographics and baseline characteristics[a]

Characteristic		Ponatinib arm (n=154)	Imatinib arm (n=78)
Age, years, median (range)		54.5 (19–82)	52.5 (19–75)
≥60 y, %		39	37
Female, %		55	51
ECOG PS 0 or 1, %		95	95
Leukocyte count, x 10^9/L, median (range)		4.4 (0.4–197.3)	3.0 (0.2–81.2)
Leukemic blasts, %, median (range)		80 (0–100)	73 (0–100)
BCR::ABL1 dominant variant, %	p190	74	68
	p210	26	32

[a]Data are shown for the population of randomized patients with p190/p210 confirmed by central laboratory

- PFS is shown by age subgroup in **Figure 2**

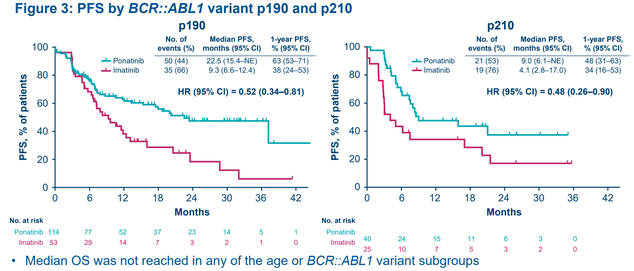
Figure 2: PFS by age <65 y and ≥65 y



NE, not estimable

- PFS is shown by *BCR::ABL1* variant in **Figure 3**

Figure 3: PFS by *BCR::ABL1* variant p190 and p210



- Median OS was not reached in any of the age or *BCR::ABL1* variant subgroups

Outcomes by HSCT status

- The proportion of patients proceeding to HSCT (per investigator's discretion) at any time was lower in the ponatinib arm (36%; 56/154) than in the imatinib arm (47%; 37/78)
- Among patients who achieved MRD negativity, the proportion who received HSCT was lower in the ponatinib arm (32%; 33/104) than in the imatinib arm (56%; 22/39)
- In patients who did not have HSCT, the median exposure was >2-fold longer in the ponatinib arm (12.8 months; range: 0.1–39.1) than in the imatinib arm (5.1 months; range: 0.2–41.3) with comparable rates of TEAEs, including AOEs and venous thromboembolic event (VTEs) **(Table 2)**
- For patients without HSCT, dose interruptions due to TEAEs were more frequent with ponatinib than imatinib (73% and 41%, respectively), but rates of dose reduction (43% and 31%) and treatment discontinuation (13% and 14%) due to TEAEs were similar across arms

Table 2: TEAEs overall and in patients who did not have HSCT

TEAE, n (%)	Safety population overall		Safety population without HSCT	
	Ponatinib arm (n=163)	Imatinib arm (n=81)	Ponatinib arm (n=107)	Imatinib arm (n=42)
Any TEAE	162 (99)	80 (99)	107 (100)	41 (98)
Serious	97 (60)	45 (56)	70 (65)	25 (60)
Grade 3–4	139 (85)	71 (88)	93 (87)	36 (86)
Grade 5[a]	8 (5)	4 (5)	8 (7)	4 (10)
TEAEs of interest				
Myelosuppression	135 (83)	71 (88)	93 (87)	37 (88)
Hepatoxicity	105 (64)	46 (57)	67 (63)	24 (57)
Hypertension	52 (32)	11 (14)	38 (36)	4 (10)
Pancreatitis	48 (29)	30 (37)	32 (30)	15 (36)
Arrhythmias	29 (18)	13 (16)	18 (17)	5 (12)
Adjudicated VTEs	19 (12)	10 (12)	12 (11)	5 (12)
Adjudicated AOEs	4 (2)	1 (1)	3 (3)	1 (2)
Cardiac failure	4 (2)	4 (5)	3 (3)	4 (10)
TEAE leading to dose modification[b]	117 (72)	40 (49)	80 (75)	23 (55)
Dose interruption	111 (68)	32 (40)	74 (69)	20 (48)
Dose reduction	33 (20)	18 (22)	25 (23)	10 (24)
Treatment discontinuation	17 (10)	7 (9)	14 (13)	6 (14)

[a]All deaths reported as an adverse event that occurred within 30 days of the last dose
[b]TEAEs leading to dose interruption, dose reduction, or treatment discontinuation; a TEAE may be associated with more than 1 type of dose modification

Conclusions

- In the phase 3 PhALLCON trial, patients with newly diagnosed Ph+ ALL experienced clinically meaningful and significantly higher rates of MRD negativity at any time with ponatinib (68%) than imatinib (50%) in combination with reduced-intensity chemotherapy, with similar benefit of ponatinib in younger (<65 y) and older patients (≥65 y) and in patients with p190 and p210
- In post hoc analyses, median PFS was more than twice as long with ponatinib versus imatinib in the overall population (20.2 vs 7.5 months) and across age and *BCR::ABL1* variant subgroups
- Among patients achieving MRD negative status at any time, the proportion receiving HSCT (at the investigator's discretion) was lower in the ponatinib arm (32%) than in the imatinib arm (56%)
- Among patients who did not have HSCT, exposure was >2-fold longer in the ponatinib arm than in the imatinib arm with comparable rates of AOEs, VTEs, and discontinuations due to TEAEs

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Disclosures

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