Ponatinib versus imatinib in patients with newly diagnosed Ph+ ALL: Subgroup analysis of the phase 3 PhALLCON study

Ibrahim Aldoss, MD,[1] Jose-Maria Ribera, MD, PhD,[2] Hagop Kantarjian, MD,[3] Pau Montesinos, MD, PhD,[4] Jessica T. Leonard, MD,[5] David Gomez-Almaguer, MD,[6] Maria R. Baer, MD,[7] Carlo Gambacorti-Passerini, MD,[8] James McCloskey, MD,[9] Yosuke Minami, MD, PhD,[10] Cristina Papayannidis, MD, PhD,[11] Vanderson Rocha, MD, PhD, MS,[12] Philippe Rousselot, MD, PhD,[13] Pankit Vachhani, MD,[14] Eunice S. Wang, MD,[15] Meliessa Hennessy, MPH,[16] Niti Patel, PhD,[16] Alexander Vorog, MD,[16] Bingxia Wang, PhD,[16] Elias Jabbour, MD[3]

[1]City of Hope National Medical Center, Duarte, CA, USA; [2]ICO Badalona-Hospital Universitari Germans Trias i Pujol, Josep Carreras Leukaemia Research Institute, Badalona, Spain; [3]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Hospital Universitari i Politecnic La Fe de Valencia, Valencia, Spain; [5]Oregon Health and Science University, Portland, OR, USA; [6]Hospital Universitario Dr. José Eleuterio Gonzalez, UANL, Monterrey, Mexico; [7]University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA; [8]University of Milano-Bicocca, Monza, Italy; [9]Hackensack University Medical Center, Hackensack, NJ, USA; [10]National Cancer Center Hospital East, Kashiwa, Japan; [11]IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli", Bologna, Italy; [12]Instituto do Câncer do Estado de São Paulo, University of São Paulo, São Paulo, Brazil; [13]Centre Hospitalier de Versailles, UMR1184, Université Versailles Paris-Saclay, Versailles, France; [14]University of Alabama at Birmingham, Birmingham, AL, USA; [15]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [16]Takeda Development Center Americas, Inc., Lexington, MA, USA

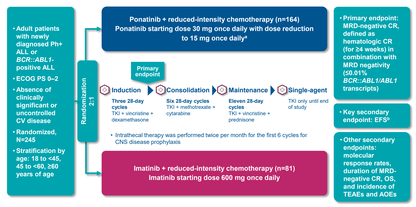
Introduction

- BCR::ABL1 tyrosine kinase inhibitors (TKIs) in combination with chemotherapy or steroids remain the standard of care in patients with newly diagnosed Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL)[1,2]
  - However, the incidence of the Philadelphia chromosome in ALL increases with age (~53% of patients over age 55), and older patients with Ph+ ALL have traditionally had poor outcomes with chemotherapy[3,4]
  - Patients harboring the *BCR::ABL1* p210 transcript variant may have slower molecular response and poorer survival outcomes versus patients with the *BCR::ABL1* p190 variant[5]
- Most treatment failure is due to recurrence of disease resulting from resistance to first- or second-generation TKIs[2,6,7]
- Ponatinib is the only FDA-approved TKI that suppresses all clinically relevant BCR::ABL1 single mutations, including T315I,[8] in patients whose disease is resistant or intolerant to prior kinase inhibitors
- In adult patients with Ph+ ALL, multiple studies have shown promising minimal residual disease (MRD)–negative BCR::ABL1 molecular response rates and survival outcomes with ponatinib in combination with chemotherapy or chemotherapy-free regimens[9-11]
- However, no BCR::ABL1 TKIs have been FDA-approved for frontline treatment in Ph+ ALL, leading to a lack of universal consensus on the optimal BCR::ABL1 TKI treatment regimen in this setting
- The phase 3 PhALLCON trial (NCT03589326) is the first head-to-head randomized study comparing frontline TKIs in adults with Ph+ ALL
- PhALLCON met its primary endpoint, with a clinically significantly higher MRD-negative complete remission (CR) rate at end of induction (EOI) with ponatinib versus imatinib
- Here we report subgroup efficacy analyses from PhALLCON

Methods

- Global, phase 3, open-label, randomized study in adult patients with newly diagnosed Ph+ ALL (**Figure 1**)
- **Composite primary endpoint:** MRD-negative (*BCR::ABL1* ≤0.01%) 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
- **Post hoc analyses:**
  - Progression-free survival (PFS), defined as failure to achieve MRD negativity or loss of MRD negativity in addition to EFS-defined events
  - MRD-negative CR and PFS by patient age (<60 vs ≥60 years) and *BCR::ABL1* variant status (p190 vs p210)
  - Safety outcomes by patient age (<60 vs ≥60 years) and *BCR::ABL1* variant status (p190 vs p210)

Figure 1: PhALLCON study design



*Dose reductions to 15 mg once daily were implemented in patients who achieved MRD-negative CR after completion of the induction phase
†EFS events defined as death due to any cause, failure to achieve CR at EOI, relapse from CR
AOE, arterial occlusive event; CNS, central nervous system; CV, cardiovascular; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PS, performance status; TEAE, treatment-emergent adverse event

Results

- At the August 12, 2022, data cutoff, the median follow-up was 20 months (range: 17.8–23.1)
- More patients in the ponatinib arm continued to receive study treatment vs the imatinib arm (41% vs 12%) (**Table 1**)
- Demographics and baseline disease characteristics were generally balanced between treatment arms (**Table 2**)

Table 1: Patient disposition

Patients, n (%)	Ponatinib arm (n=164)	Imatinib arm (n=81)
ITT population	164 (100)	81 (100)
ITT with p190/p210 for MR assessment[a]	154 (94)	78 (96)
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)
Adverse event	20 (12)	10 (12)
Lack of efficacy	12 (7)	21 (26)
Progressive disease[b]	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)

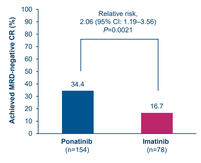
[a]Patients evaluable for MRD assessment included the ITT population with *BCR::ABL1* dominant variant of p190 or p210 confirmed by central lab
[b]Defined as an increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease
HSCT, hematopoietic stem cell transplant; ITT, intention-to-treat; MR, molecular response

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 in bone marrow, %, median (range)	80 (0–100)	75 (0–100)
Patients with ≥1 CV comorbidity, n (%)	92 (56)	52 (64)
Patients with ≥2 CV comorbidities, n (%)	45 (28)	27 (33)
***BCR::ABL1* dominant variant, n (%)**		
p190	114 (70)	53 (65)
p210	40 (24)	25 (31)

- Ponatinib in combination with chemotherapy demonstrated a statistically significant and clinically meaningful higher MRD-negative CR rate at EOI, demonstrating superiority over imatinib (**Figure 2**)
- In the overall population, ponatinib had a significantly higher rate of MRD negativity regardless of CR outcome (MR4) and a higher proportion of patients with deeper molecular response (MR4.5) at EOI compared with imatinib
  - MR4: 41.6% ponatinib vs 20.5% imatinib; *P*=0.0017
  - MR4.5: 26.8% ponatinib vs 14.7% imatinib

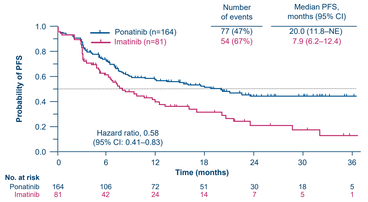
Figure 2: PhALLCON overall MRD-negative CR at EOI



CI, confidence interval

- In a post hoc analysis, median PFS was 12 months longer for patients in the ponatinib arm than for patients in the imatinib arm (**Figure 3**)

Figure 3: PhALLCON overall Kaplan-Meier–estimated PFS



NE, not estimable

Objective

To perform post hoc subgroup analyses of efficacy and safety from the phase 3 PhALLCON trial comparing frontline ponatinib versus imatinib in combination with low-intensity chemotherapy

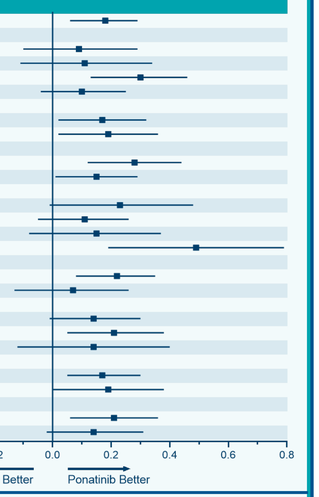
Results

- Benefit for ponatinib was observed across all subgroups analyzed (**Figure**)
  - All age subgroups had higher rates of MRD-negative CR with ponatinib vs imatinib, with the greatest benefit observed in patients ≥60 years of age (40.0% vs 10.3%; *P*=0.0005)
  - The MRD-negative CR rate was significantly higher for ponatinib vs imatinib among patients with the *BCR::ABL1* p190 variant

Results

Figure: MRD-negative CR at EOI by patient subgroup

Subgroup	Ponatinib	Imatinib	Risk difference (95% CI)
	No. of patients		Ponatinib vs Imatinib
Overall	154	78	0.18 (0.06, 0.29)
Age — yr			
18 to <45	50	27	0.09 (−0.10, 0.29)
45 to <60	44	22	0.11 (−0.11, 0.34)
≥60	60	29	0.30 (0.13, 0.46)
<60	94	49	0.10 (−0.04, 0.25)
Sex			
Female	85	40	0.17 (0.02, 0.32)
Male	69	38	0.19 (0.02, 0.36)
Race			
Non-White	57	18	0.28 (0.12, 0.44)
White	97	60	0.15 (0.01, 0.29)
Region			
Asia-Pacific	22	12	0.23 (−0.01, 0.48)
Europe	68	31	0.11 (−0.05, 0.26)
North America	47	25	0.15 (−0.08, 0.37)
South America	17	10	0.49 (0.19, 0.79)
BCR::ABL1 variant			
p190	114	53	0.22 (0.08, 0.35)
p210	40	25	0.07 (−0.13, 0.26)
ECOG performance status			
0	67	32	0.14 (−0.01, 0.30)
1	80	42	0.21 (0.05, 0.38)
2	7	4	0.14 (−0.12, 0.40)
White blood cell count			
<30 x 10^9/L	131	70	0.17 (0.05, 0.30)
≥30 x 10^9/L	16	4	0.19 (0.00, 0.38)
Prephase therapy			
Yes	69	40	0.21 (0.06, 0.36)
No	85	38	0.14 (−0.02, 0.31)

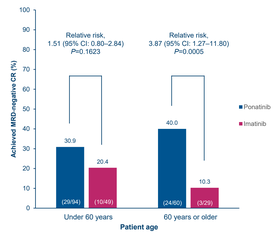


Key Takeaways

Ponatinib was superior to imatinib in combination with reduced-intensity chemotherapy across all patient subgroups analyzed, including patients ≥60 years of age

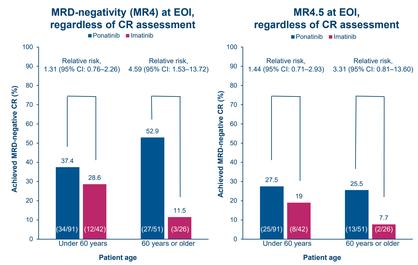
- Ponatinib demonstrated higher MRD-negative CR rates compared with imatinib in patients <60 years and ≥60 years of age, with significantly greater benefit observed in patients ≥60 years (**Figure 4**)

Figure 4: MRD-negative CR by treatment arm and patient age (<60 vs ≥60 years)



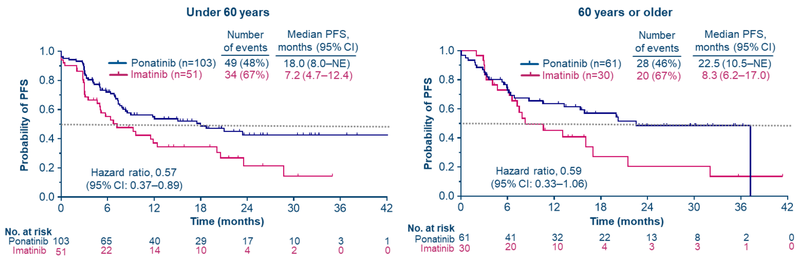
- Patients in the ponatinib arm demonstrated deeper molecular responses compared with imatinib regardless of age (<60 vs ≥60 years; **Figure 5**)

Figure 5: Depth of molecular response by treatment arm and patient age (<60 vs ≥60 years)



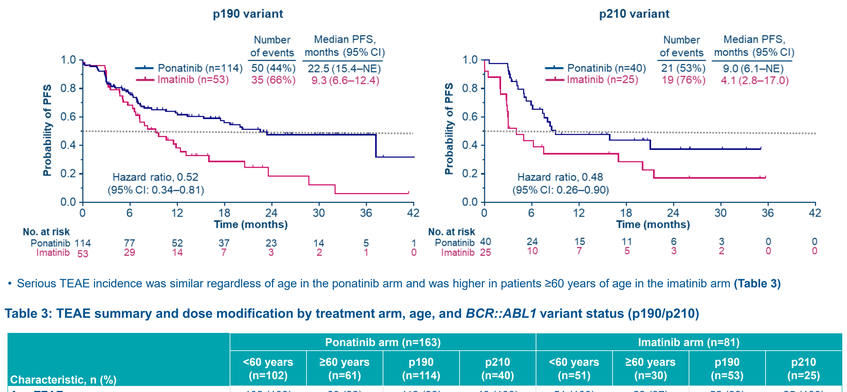
- In the ponatinib arm, median PFS was longer in both age groups compared with the imatinib arm (**Figure 6**)

Figure 6: PFS by treatment arm and patient age (<60 vs ≥60 years)



- Median PFS was longer with ponatinib vs imatinib regardless of p190/p210 variant present (**Figure 7**)
  - Median PFS was longer in both arms in patients with the p190 variant vs the p210 variant

Figure 7: PFS by treatment arm and *BCR::ABL1* variant status



- Serious TEAE incidence was similar regardless of age in the ponatinib arm and was higher in patients ≥60 years of age in the imatinib arm (**Table 3**)

Table 3: TEAE summary and dose modification by treatment arm, age, and *BCR::ABL1* variant status (p190/p210)

Characteristic, n (%)	Ponatinib arm (n=163)				Imatinib arm (n=81)			
	<60 years (n=102)	≥60 years (n=61)	p190 (n=114)	p210 (n=40)	<60 years (n=51)	≥60 years (n=30)	p190 (n=53)	p210 (n=25)
Any TEAE	102 (100)	60 (98)	113 (99)	40 (100)	51 (100)	29 (97)	52 (98)	25 (100)
Serious TEAEs	61 (60)	36 (59)	71 (62)	18 (45)	25 (49)	20 (67)	30 (57)	14 (56)
Grade 3–4 TEAEs	89 (87)	50 (82)	96 (84)	35 (88)	45 (88)	26 (87)	47 (89)	22 (88)
Grade 5 TEAEs[a,b,c]	3 (3)	5 (8)	6 (5)	1 (3)	2 (4)	2 (7)	2 (4)	2 (8)
TE-AOEs	0	4 (7)	4 (4)	0	0	1 (3)	1 (2)	0
TE-VTEs[d]	10 (10)	9 (15)	16 (14)	2 (5)	4 (8)	6 (20)	9 (17)	1 (4)
Dose modification for TEAEs	68 (67)	49 (80)	83 (73)	28 (70)	22 (43)	18 (60)	27 (51)	12 (48)
Discontinuation	9 (9)	8 (13)	14 (12)	3 (8)	3 (6)	4 (13)	3 (6)	4 (16)
Reduction	16 (16)	17 (28)	22 (19)	8 (20)	15 (29)	3 (10)	15 (28)	2 (8)
Interruption	66 (65)	45 (74)	78 (68)	28 (70)	15 (29)	17 (57)	19 (36)	12 (48)

[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; PICC, peripherally inserted central catheter; TE-AOE, treatment-emergent arterial occlusive event; TE-VTE, treatment-emergent venous thromboembolic event; VTE, venous thromboembolic event

- TE-AOE incidence was higher in patients ≥60 years of age and in patients with the p190 variant in both arms
- Dose modifications for TEAEs were higher in patients ≥60 years of age and in patients with the p190 variant in both arms

Conclusions

- Overall, ponatinib was superior to imatinib in combination with reduced-intensity chemotherapy in the front-line setting for patients with Ph+ ALL, with a clinically significantly higher MRD-negative CR rate at EOI
- All subgroups had higher rates of MRD-negative CR with ponatinib vs imatinib
- Median PFS was longer with ponatinib vs imatinib regardless of patient age (<60 years vs ≥60 years) or p190/p210 status
- Benefit was observed across all subgroups analyzed, particularly for patients ≥60 years of age and for those with the *BCR::ABL1* p190 variant

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Email for questions or comments: ialdoss@coh.org

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