Ponatinib versus imatinib in patients with newly diagnosed Ph+ acute lymphoblastic leukemia in the phase 3 PhALLCON trial: In-depth responder analysis

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Introduction

- Ponatinib, a third-generation BCR::ABL1 TKI, effectively inhibits BCR::ABL1 with or without any single resistance mutation, including T315I[1]
- In March 2024, the US FDA approved ponatinib + chemotherapy for the treatment of adults with newly diagnosed Ph+ ALL based on results of the phase 3 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, the MRD-negative CR rate at EOI, was clinically meaningfully and significantly higher with ponatinib vs imatinib + reduced-intensity chemotherapy (34.4% vs 16.7%; *P*=0.002)[3]
  - Safety data indicate that ponatinib has a comparable safety profile to imatinib
- Here, we investigate rates of MRD negativity at any time and PFS by age and *BCR::ABL1* variant subgroups and explore outcomes in patients who proceeded to HSCT

ALL, acute lymphoblastic leukemia; CR, complete remission; EOI, end of induction; FDA, Food and Drug Administration; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; Ph+, Philadelphia chromosome positive; PFS, progression-free survival; TKI, tyrosine kinase inhibitor

1. O'Hare T, et al. *Cancer Cell* 2009;16:401–12. 2. Iclusig [package insert]. Takeda Pharmaceutical Company Limited; 2024. 3. Jabbour E, et al. *JAMA*. 2024:e244783. Epub ahead of print.

Study design

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

Key inclusion criteria

- Adults with newly diagnosed Ph+ ALL or *BCR::ABL1*-positive ALL
- ECOG PS 0–2
- No clinically significant or uncontrolled CV disease

Randomization (N=245) 2:1[a]

Ponatinib + reduced-intensity chemotherapy (n=164)
Ponatinib starting dose 30 mg QD with dose reduction to 15 mg QD[b]

Primary endpoint

Induction
Three 28-day cycles
TKI + vincristine + dexamethasone

Consolidation
Six 28-day cycles
TKI + methotrexate + cytarabine

Post consolidation
Eleven 28-day cycles
TKI + vincristine + prednisone

Single-agent
TKI only until end of study

- Intrathecal therapy was performed twice per month for the first 6 cycles for CNS disease prophylaxis

Imatinib + reduced-intensity chemotherapy (n=81)
Imatinib starting dose 600 mg QD

- **Primary endpoint: MRD-negative CR[c] at EOI**
- **Key secondary endpoint: EFS[d]**
- **Other secondary endpoints: molecular response rates, duration of MRD-negative CR, OS, and incidence of TEAEs and AOEs**

[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

Endpoint definitions and statistical analyses

Endpoint definitions

- **MRD negativity:** *BCR::ABL1*^{IS} ≤0.01% (i.e., MR4) assessed by central laboratory
- **PFS[a] events:**
  - No MRD negativity by end of treatment
  - Loss of MRD negativity
  - Any EFS event:
    - Death due to any cause
    - No CR by EOI
    - Relapse from CR

Statistical analyses

- Post hoc subgroup analyses:
  - Age <65 vs ≥65 y
  - *BCR::ABL1* variant p190 vs p210)
- **Analysis population:** Randomized patients with p190/p210 confirmed by central laboratory
- **MRD negativity rate comparisons**: Unstratified CMH chi-square test; unadjusted RR (95% CI)
- **PFS comparisons:** Unstratified Cox regression; HR (95% CI)
- 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

[a]Analyses of PFS were post hoc
CI, confidence interval; CMH, Cochran-Mantel-Haenszel; HR, hazard ratio; RR, relative risk

Patients

- 245 patients were randomized (ponatinib, n=164; imatinib, n=81)
- 232 patients had p190/p210 confirmed by central laboratory (ponatinib, n=154; imatinib, n=78)
- At data cutoff (Aug 12, 2022), median follow-up was 19.4 months for patients with confirmed p190/210
- Demographics and baseline characteristics were balanced between treatment arms

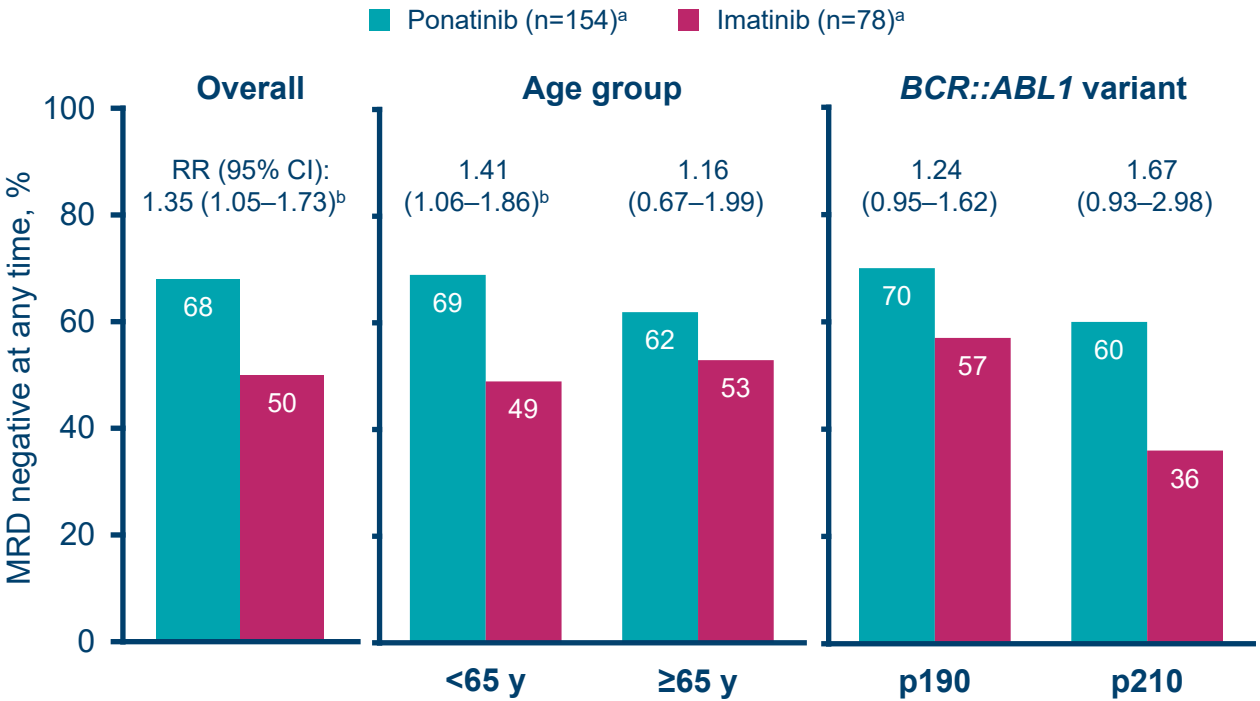
Key demographics and baseline characteristics[a]

Characteristic		Ponatinib arm (n=154)	Imatinib arm (n=78)
Age, y, median (range)		54.5 (19–82)	52.5 (19–75)
≥65 y, %		22	19
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

MRD negativity at any time

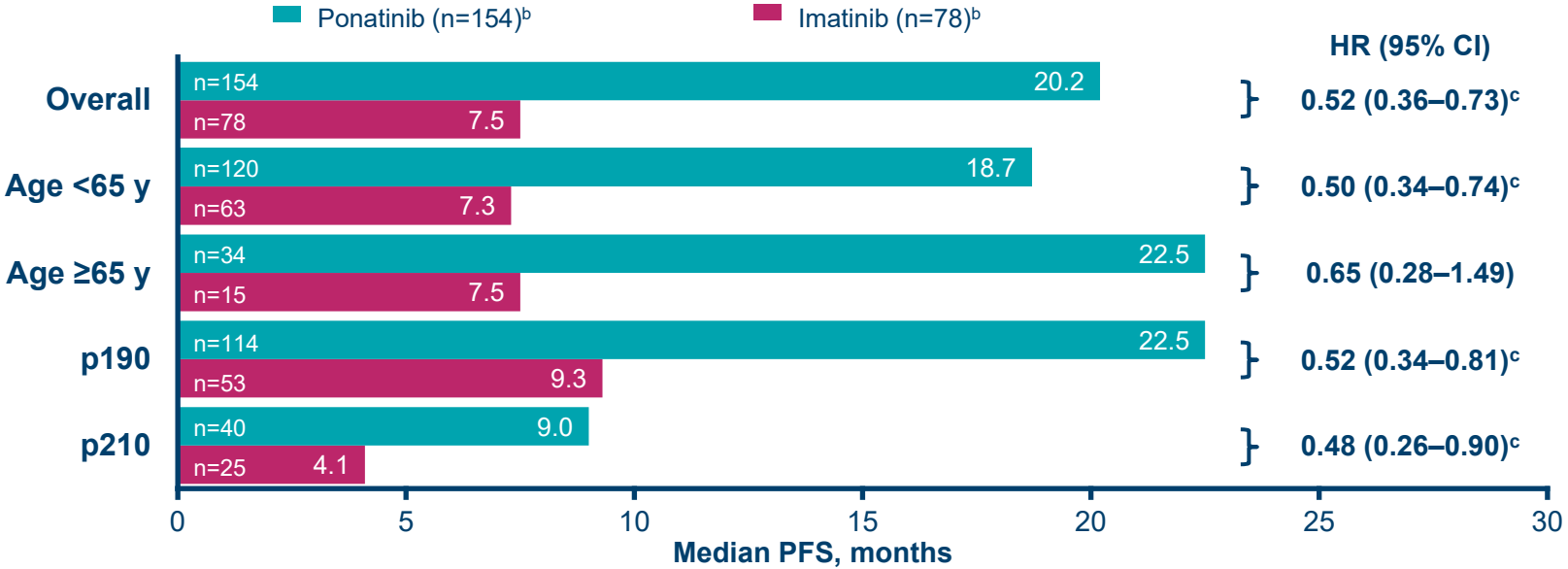
- Rates of MRD negativity at any time were higher with ponatinib than imatinib
- Although not statistically significant in all subgroups, the trend for the benefit of ponatinib was similar across age and variant subgroups



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

PFS[a]

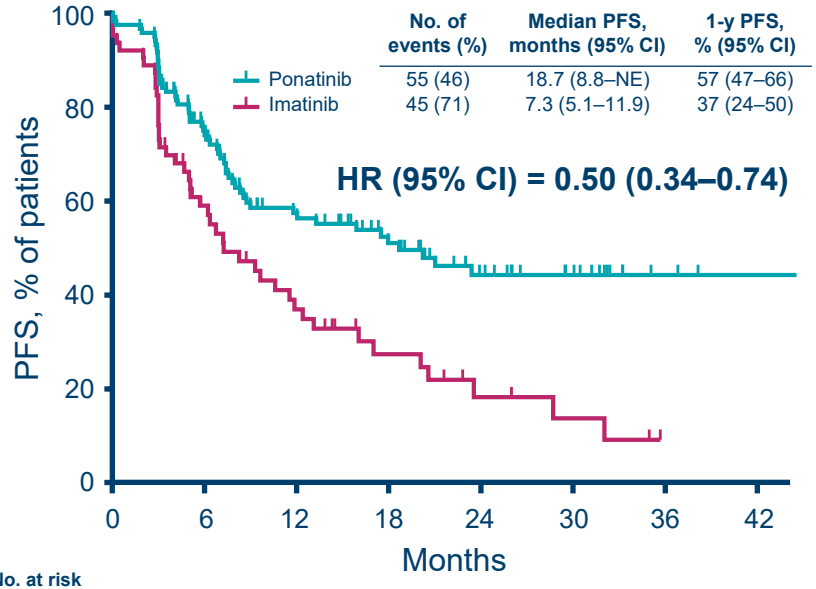
- Median PFS was longer with ponatinib vs imatinib, with similar benefit of ponatinib across age and variant subgroups



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

PFS by age <65 y and ≥65 y

Age <65 y

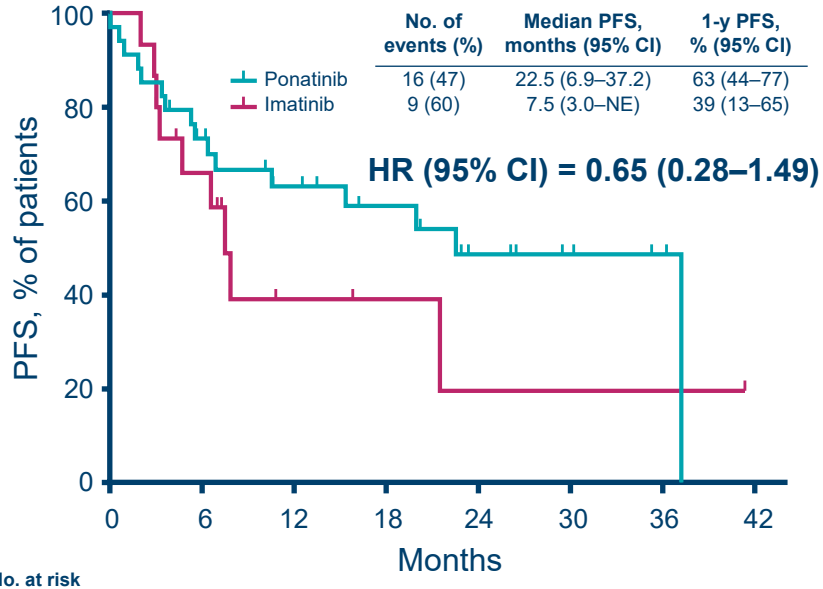


	No. of events (%)	Median PFS, months (95% CI)	1-y PFS, % (95% CI)
Ponatinib	55 (46)	18.7 (8.8–NE)	57 (47–66)
Imatinib	45 (71)	7.3 (5.1–11.9)	37 (24–50)

No. at risk

Ponatinib	120	78	50	36	22	13	3	1
Imatinib	63	30	18	10	5	3	0	

Age ≥65 y



	No. of events (%)	Median PFS, months (95% CI)	1-y PFS, % (95% CI)
Ponatinib	16 (47)	22.5 (6.9–37.2)	63 (44–77)
Imatinib	9 (60)	7.5 (3.0–NE)	39 (13–65)

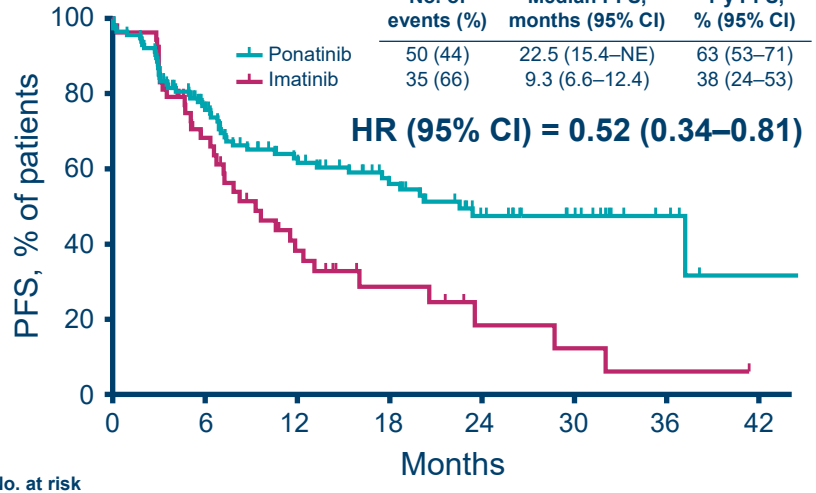
No. at risk

Ponatinib	34	23	17	12	7	4	2	0
Imatinib	15	9	3	2	1	1	1	0

NE, not estimable

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

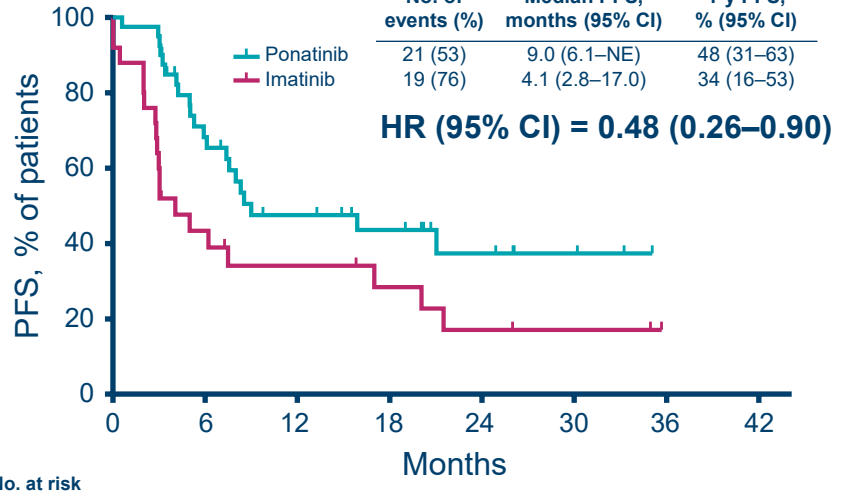
p190



	No. of events (%)	Median PFS, months (95% CI)	1-y PFS, % (95% CI)
Ponatinib	50 (44)	22.5 (15.4–NE)	63 (53–71)
Imatinib	35 (66)	9.3 (6.6–12.4)	38 (24–53)

No. at risk								
Ponatinib	114	77	52	37	23	14	5	1
Imatinib	53	29	14	7	3	2	1	0

p210



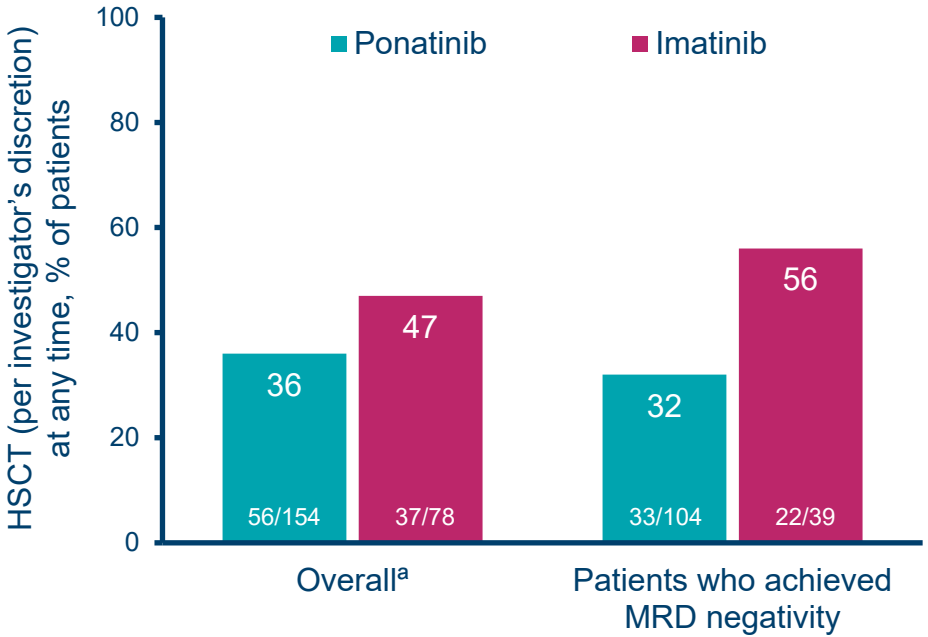
	No. of events (%)	Median PFS, months (95% CI)	1-y PFS, % (95% CI)
Ponatinib	21 (53)	9.0 (6.1–NE)	48 (31–63)
Imatinib	19 (76)	4.1 (2.8–17.0)	34 (16–53)

No. at risk								
Ponatinib	40	24	15	11	6	3	0	
Imatinib	25	10	7	5	3	2	0	

- 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 than in the imatinib arm (36% vs 47%)
- Among patients who achieved MRD negativity, the proportion who received HSCT was lower in the ponatinib arm than in the imatinib arm (32% vs 56%)



[a]Population of patients with p190/p210 confirmed by central lab.

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)

- In patients who did not have HSCT:
  - Median exposure was >2-fold longer in the ponatinib arm than in the imatinib arm
    - 12.8 months (range: 0.1–39.1) vs 5.1 months (0.2–41.3)
  - TEAE rates were comparable with ponatinib vs imatinib, including AOEs and VTEs
  - Dose interruptions due to TEAEs were more frequent with ponatinib vs imatinib (73% vs 41%)
  - Rates of dose reduction and treatment discontinuation due to TEAEs were similar across arms

[a]All deaths reported as an AE occurring within 30 days of last dose [b]TEAEs leading to dose interruption, dose reduction, or treatment discontinuation; a TEAE may be associated with >1 type of dose modification
AE, adverse event; VTE, venous thromboembolic event

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
  - Although not statistically significant in all subgroups, the trend for the benefit of ponatinib was similar 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 vs imatinib overall (20.2 vs 7.5 months) and across age and *BCR::ABL1* variant subgroups
- Among patients achieving MRD negativity at any time, the proportion receiving HSCT (at investigator's discretion) was lower in the ponatinib arm than in the imatinib arm (32% vs 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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- Thank you for your time and attention!

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