First report of PhALLCON: a phase 3 study comparing ponatinib vs imatinib in newly diagnosed Ph+ ALL

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PhALLCON: Introduction

- Standard-of-care frontline therapy for Ph+ ALL is BCR::ABL1 TKIs + chemotherapy or steroids[1]
- Cross-trial comparison of low-dose chemotherapy and first- and second-generation BCR::ABL1 TKIs reported 12-week CMR rates of approximately 14%–39%.[2,3] Resistance was frequently driven by acquisition of T315I kinase domain mutation[4]
- Ponatinib is the only pan-inhibitory BCR::ABL1 TKI with activity against BCR::ABL1 WT and all single mutant variants, including T315I[5]
- Ponatinib in combination with chemotherapy or immunotherapy improved long-term outcomes[6,7]
- **Aim:** Compare the efficacy and safety of frontline ponatinib vs imatinib in combination with low-intensity chemotherapy in patients with newly-diagnosed Ph+ ALL[8]

1. Soverini S, et al. Cancer. 2014;120(7):1002–09. 2. Ottmann OG, et al. Blood. 2018;132(suppl 1):31. 3. Ribera J-M, et al. Br J Haematol. 2012;159(1):78–81.
4. Rousselot P, et al. Blood. 2016;128(6):774–82. 5. O'Hare T, et al. Cancer Cell. 2009;16(5):401–12. 6. Jabbour E, et al. Lancet Haematol. 2018;5(12):e618–27.
7. Martinelli G, et al. Blood Adv. 2022;6(6):1742–53. 8. Jabbour E, et al. J Clin Oncol. 2019;37(suppl 15):TPS761.

PhALLCON: Study design

- Adult patients with newly diagnosed Ph+ ALL or BCR::ABL1-positive ALL
- ECOG PS 0–2
- Absence of history or current diagnosis of CP-, AP-, or BP-CML
- Absence of clinically significant or uncontrolled CV disease
- Randomized, N=245

Randomization 2:1

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

Primary endpoint

Induction
Three 28-day cycles
TKI + vincristine + dexamethosone

Consolidation
Six 28-day cycles
TKI + methotrexate + cytarabine

Maintenance
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 once daily

- Primary endpoint: MRD-negative CR, defined as hematologic CR (for ≥4 weeks) in combination with MRD negativity (≤0.01% *BCR::ABL1/ABL1* transcripts [also referred to as MR4])
- Key secondary endpoint: event-free survival
- Other secondary endpoints: molecular response rates, duration of MRD-negative CR, OS, and incidence of TEAEs and AOEs

- Data cutoff date: 12 August 2022
- Median follow-up was 20.4 months (range: 18.4–23.9) in the ponatinib arm and 18.1 months (13.9–24.3) in the ponatinib arm

[a]Dose reductions to 15 mg once daily were implemented in patients who achieved MRD-negative CR after completion of the induction phase

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

PhALLCON: Patient disposition

No. of patients, n (%)	Ponatinib arm (n=164)	Imatinib arm (n=81)
ITT population	164 (100)	81 (100)
Efficacy evaluable population[a]	154 (94)	78 (96)
Safety evaluable population[b]	163 (99)	81 (100)
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)
Lack of efficacy	12 (7)	21 (26)
Adverse event	20 (12)	10 (12)
Progressive disease[c]	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)

- At the data cutoff (12 Aug 2022), more patients in the ponatinib arm continued to receive study treatment compared with the imatinib arm (41% vs 12%)
- Median (range) follow-up was 20 months (18–24) and 18 months (14–24) in the ponatinib and imatinib arms, respectively

[a] Patients in the ITT population with *BCR::ABL1* dominant variant of p190 or p210 confirmed by central lab

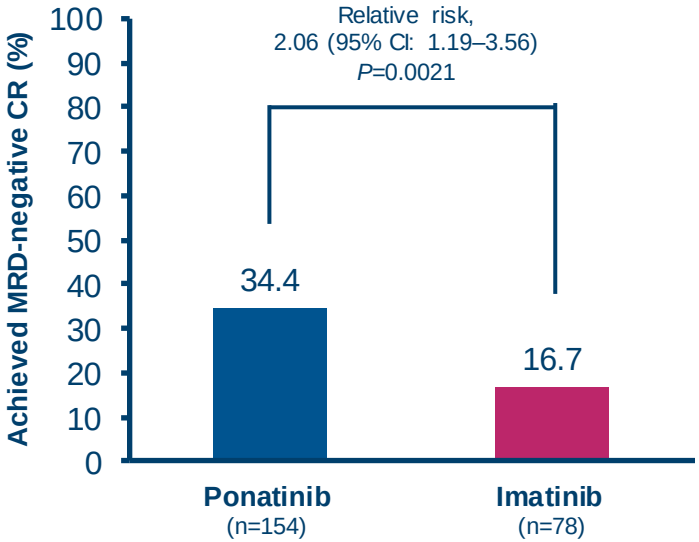
[b] One patient was randomized to the ponatinib arm and died prior to receiving treatment

[c] Defined as an increase of at least 25% in the absolute number of circulating or BM blasts or development of extramedullary disease

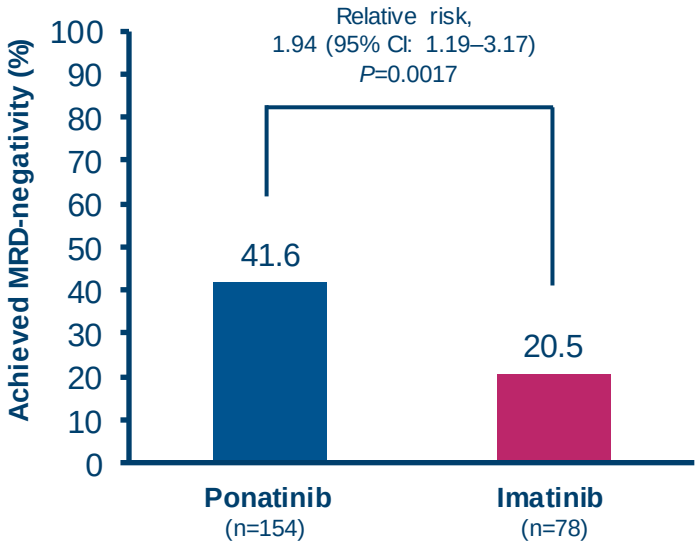
PhALLCON: MRD-negative CR and MRD-negativity

- **Primary endpoint: MRD-negative CR at the end of induction:**
  hematologic CR (for ≥4 weeks) + MRD negativity (≤0.01% *BCR::ABL1*)

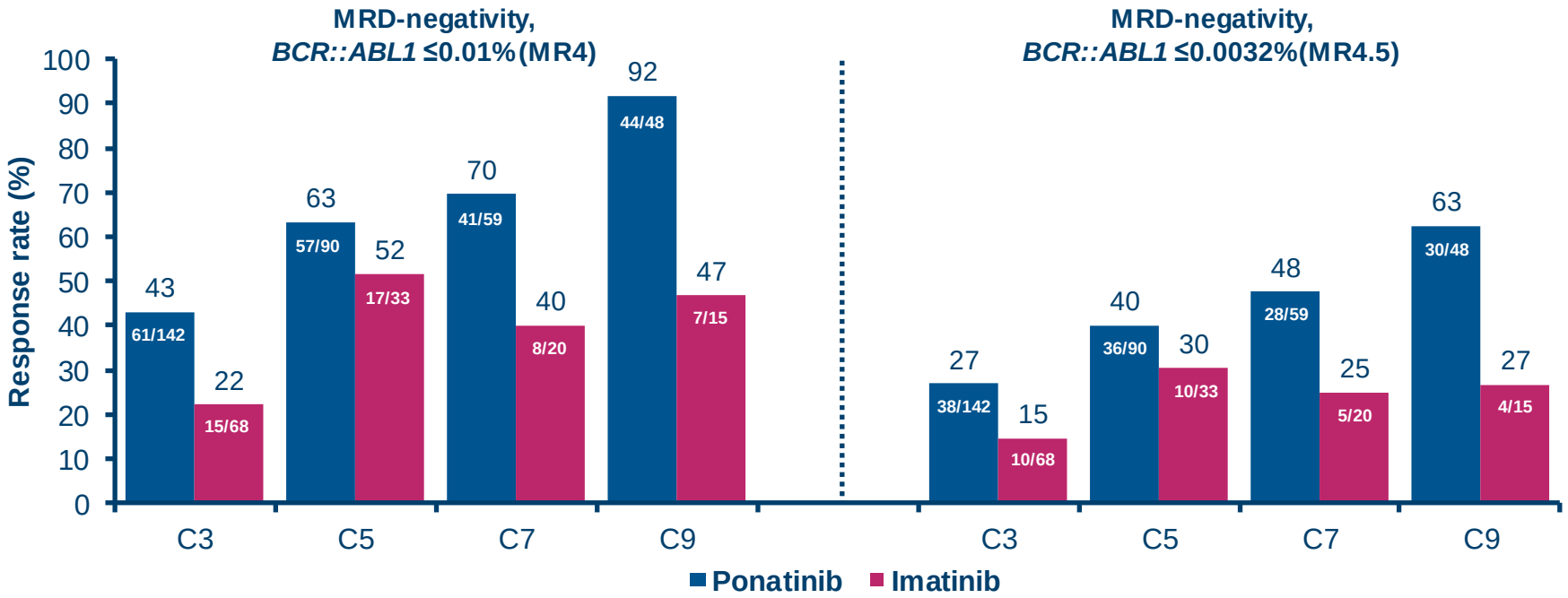
Primary endpoint: MRD-negative (MR4) CR at end of induction



MRD-negativity (MR4) at end of induction, regardless of CR assessment



PhALLCON: Molecular response rates at corresponding treatment cycles



PhALLCON: Subsequent anticancer therapy

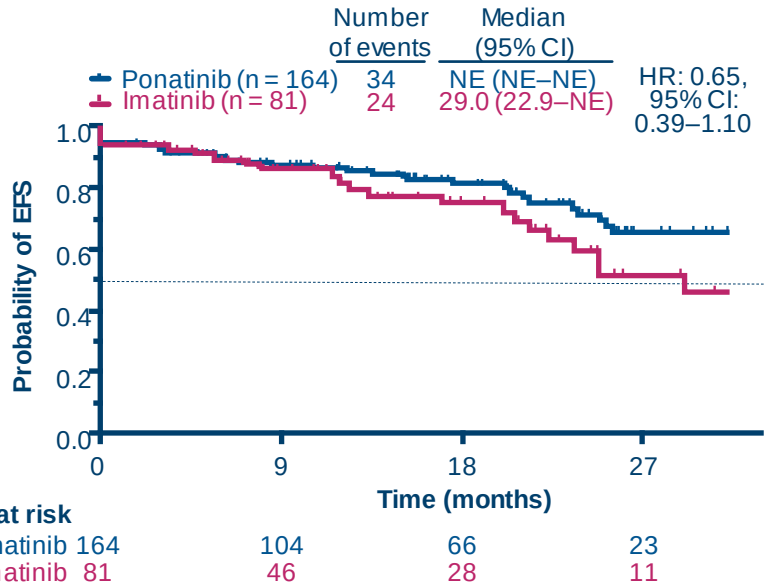
- 37% of the 81 patients in the imatinib arm later received a second- or third-generation TKI and/or immunotherapy
  - 16% of 81 received ponatinib

Treatment, n (%)	Ponatinib arm (n=163)	Imatinib arm (n=81)
Any subsequent anticancer therapy	57 (35)	46 (57)
Any BCR::ABL1 TKI or immunotherapy	48 (29)	37 (46)
First-generation BCR::ABL1 TKI	17 (10)	7 (9)
Second-/third-generation BCR::ABL1 TKI and/or immunotherapy	31 (19)	30 (37)
Ponatinib-based	13 (8)	13 (16)

PhALLCON: Event-free survival versus progression-free survival

- **EFS event definition:** death due to any cause, failure to achieve CR by the end of induction, or relapse from CR
- **PFS event definition:** death due to any cause, failure to achieve CR by the end of induction, relapse from CR, failure to achieve MRD-negativity by the end of treatment, or loss of MRD-negativity[a]

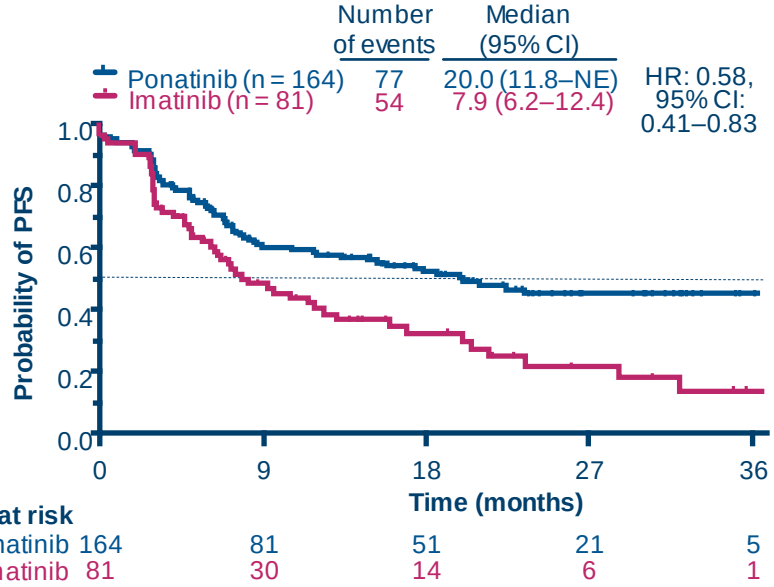
Event-free survival



No. at risk

Ponatinib	164	104	66	23
Imatinib	81	46	28	11

Progression-free survival

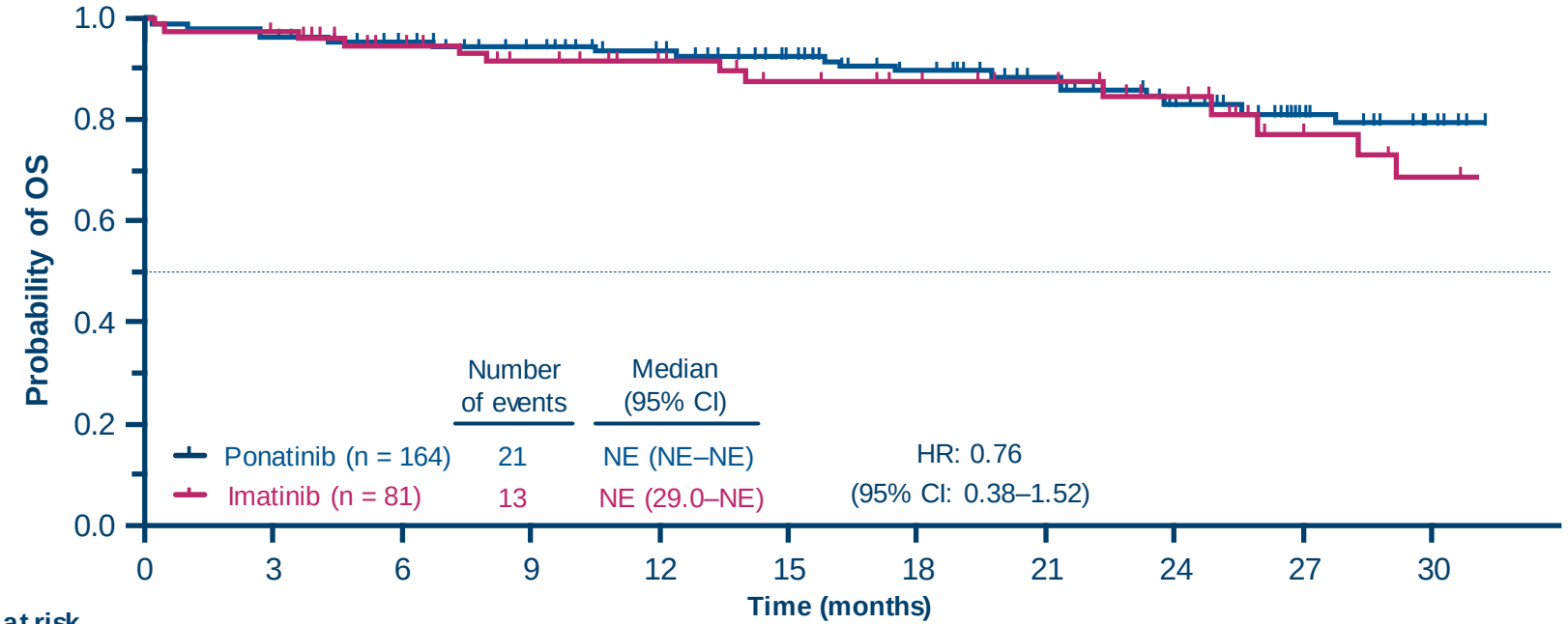


No. at risk

Ponatinib	164	81	51	21	5
Imatinib	81	30	14	6	1

[a] Post hoc analysis

PhALLCON: Overall survival



PhALLCON: TEAE summary and dose modifications

Characteristic	Ponatinib arm (n=163)	Imatinib arm (n=81)
TEAEs, n (%)		
Any TEAE	162 (99)	80 (99)
Serious TEAEs	97 (60)	45 (56)
Grade 3–4 TEAEs	147 (90)	75 (93)
Grade 5 TEAEs[a,b,c]	8 (5)	4 (5)
TE-AOEs, n (%)	4 (2)	1 (1)
TE-VTEs[d], n (%)	19 (12)	10 (12)
Dose modification for TEAEs, n (%)		
Discontinuation	17 (10)	7 (9)
Reduction	33 (20)	18 (22)
Interruption	111 (68)	32 (40)

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

PhALLCON: Conclusions

- Ponatinib + reduced-intensity chemotherapy was superior to imatinib in the first-line setting:
  - Primary endpoint: MRD-negative CR rate at the end of induction: 34% vs 17% (*P*=0.0021)
  - MRD-negativity rate: 42% vs 21%
- The safety profile of ponatinib was comparable with imatinib
- Adverse events of special interest were similar with ponatinib and imatinib:
  - TE-AOEs: 2% vs 1%
  - TE-VTEs: 12% in both
- Ponatinib + reduced-intensity chemotherapy has the potential to be standard of care in patients with newly diagnosed Ph+ ALL

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