Molecular response of ≤10% *BCR::ABL1*^{IS} is predictive of positive outcomes in treatment-resistant patients with chronic phase chronic myeloid leukemia (CP-CML) treated with ponatinib from the Phase 2 OPTIC trial

CML-319

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Background

- Ponatinib, the only approved all known BCR::ABL1 inhibitor, is a third-generation TKI designed to potently inhibit BCR::ABL1 with or without any single resistance mutation, including T315I[1,2]
- The Phase 2 Optimizing Ponatinib Treatment In CP-CML (OPTIC; NCT02467270) trial evaluated benefit:risk outcomes of ponatinib using a novel response-based dosing strategy in patients with heavily pretreated resistant CP-CML[3]
- All 3 dosing regimens in OPTIC demonstrated benefit in this highly resistant CP-CML patient population, with optimal benefit:risk outcomes observed in patients who received the response-based dosing of 45 mg/day → 15 mg/day[3]
- We present a post hoc analysis of long-term survival outcomes of patients in the OPTIC trial who reached landmark clinical responses

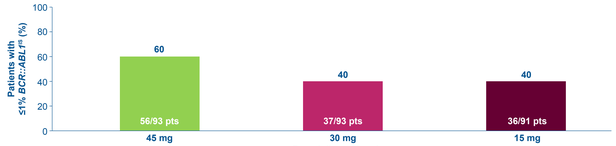
Methods

- The OPTIC trial enrolled adults with CP-CML (N=283) whose disease was resistant to at least 2 prior TKIs or who had a *BCR::ABL1* T315I mutation
- Patients in OPTIC received once daily starting doses of ponatinib 45 mg, 30 mg, or 15 mg; patients in the 45- and 30-mg cohorts had their dose reduced to 15 mg upon achievement of ≤1% *BCR::ABL1*^{IS}
- This landmark analysis evaluated PFS and OS in patients with ≤1%, >1%–≤10%, and >10% *BCR::ABL1*^{IS} by Months 3, 6, and 12
  - The proportion of patients attaining ≤1% *BCR::ABL1*^{IS} by 36 months was also assessed
- Disease progression was primarily defined as:
  - Progression to accelerated- or blast-phase CML, or
  - Loss of complete hematologic response (CHR; confirmed by loss of complete blood counts ≥4 weeks apart) or major cytogenetic response, death, or 2 instances of white blood cell count increases (>20,000 cells/µL, ≥4 weeks apart after the first 4 weeks of treatment) were also considered as disease progression
- The estimated probabilities of PFS and OS were calculated using the Kaplan-Meier method

Results

- At the May 9, 2022, cutoff date, high proportions of patients across the dose cohorts had achieved ≤1% *BCR::ABL1*^{IS} by 36 months (**Figure 1**)
- The landmark analysis population consisted of 270 patients and excluded patients who had ≤1% *BCR::ABL1*^{IS} at baseline (n=4) and patients for whom baseline *BCR::ABL1*^{IS} level was unknown (n=8)

Figure 1: Achievement of ≤1% *BCR::ABL1*^{IS} by 36 months



- Demographic and baseline characteristics of patients in the landmark analysis population who attained or did not attain ≤10% *BCR::ABL1*^{IS} by 12 months are shown in **Table 1**

Table 1: Demographic and baseline characteristics of the landmark analysis population

Characteristic	≤10% *BCR::ABL1*^{IS} (n=42)	>10% *BCR::ABL1*^{IS} (n=228)	Total (N=270)
Age, median, years (range)	45 (26–77)	49 (18–81)	48 (18–81)
Male, n (%)	22 (52)	114 (50)	136 (50)
Time from diagnosis to first dose, median, years (range)	5.7 (0.9–21.8)	5.4 (0.7–29.5)	5.4 (0.7–29.5)
Prior TKI therapy, n (%)			
1	1 (<1)	4 (<1)	5 (<1)
2	20 (48)	97 (43)	117 (43)
≥3	21 (50)	127 (56)	148 (55)
Resistant/intolerant to most recent TKI, n (%)			
Resistant	40 (95)	193 (85)	233 (86)
Intolerant	0	7 (3)	7 (3)
Other	2 (5)	27 (12)	29 (11)
Unknown	0	1 (<1)	1 (<1)
Best response to most recent TKI[a], n (%)			
≤1% *BCR::ABL1*^{IS}	7 (17)	8 (4)	14 (5)
>1% to ≤10% *BCR::ABL1*^{IS}	3 (7)	16 (7)	19 (7)
>10% *BCR::ABL1*^{IS}	21 (50)	124 (54)	145 (54)
Other[b]	8 (19)	66 (29)	74 (27)
Mutation status, n (%)			
No mutation	25 (60)	136 (60)	161 (60)
T315I	6 (14)	56 (25)	62 (23)
Other mutation	11 (26)	36 (16)	47 (17)

[a] Data were missing for 17 patients
[b] Includes no response, minor molecular response, progressive disease, or T315I mutation detected

Objective

To assess progression-free survival (PFS) and overall survival (OS) in OPTIC trial patients who reached ≤1%, >1%–≤10%, and >10% *BCR::ABL1*^{IS} by Months 3, 6, and 12

Results

- Patients with ≤10% *BCR::ABL1*^{IS} by 3, 6, and 12 months had significantly better PFS rates than those remaining at >10% *BCR::ABL1*^{IS} (**Figure 2**)
- Patients with ≤10% *BCR::ABL1*^{IS} by 3, 6, and 12 months had significantly better OS rates than those remaining at >10% *BCR::ABL1*^{IS} (**Figure 3**)

Figure 2: Estimated PFS by *BCR::ABL1*^{IS} level by 3, 6, and 12 months

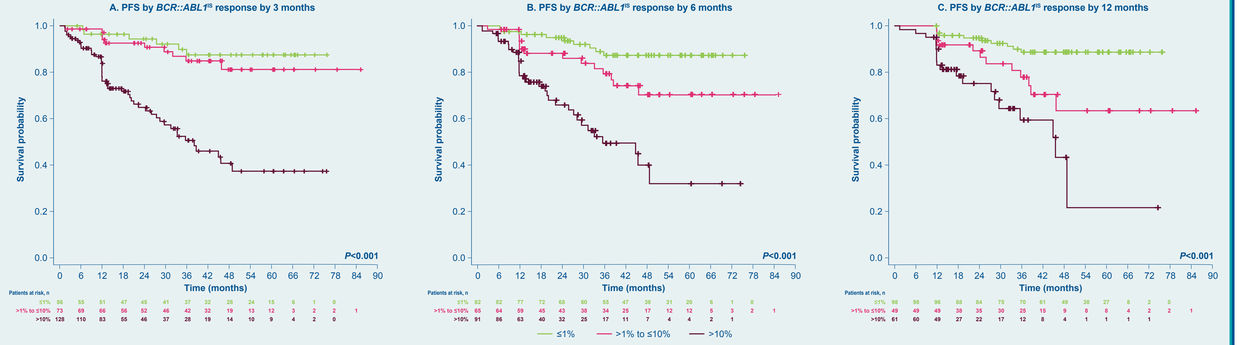
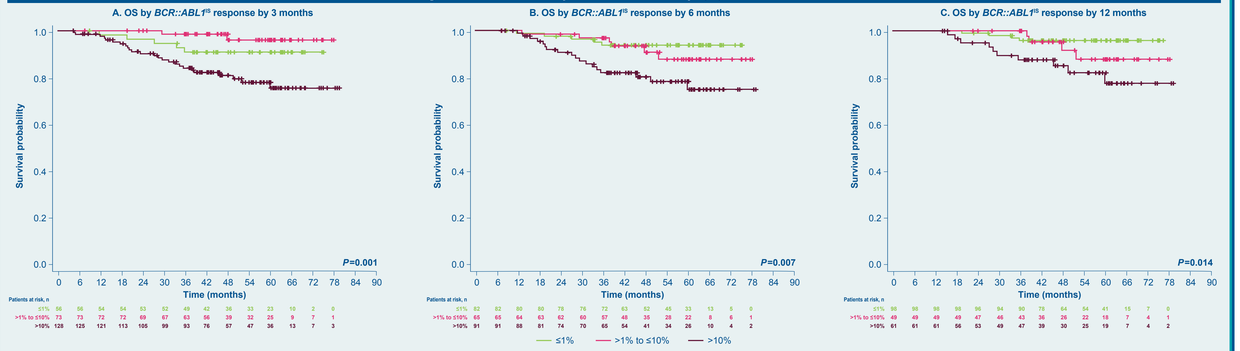


Figure 3: Estimated OS by *BCR::ABL1*^{IS} level by 3, 6, and 12 months

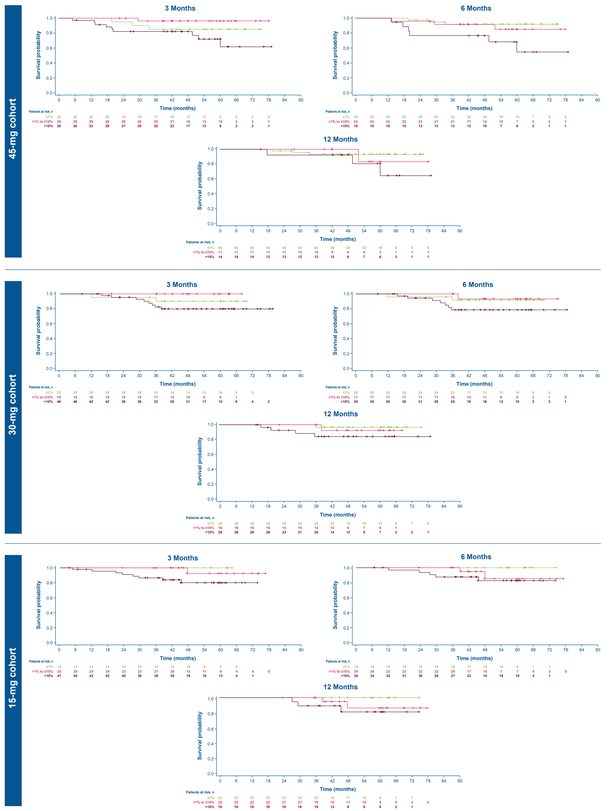


Key Takeaway

Achievement of ≤10% *BCR::ABL1*^{IS} with ponatinib within 12 months is associated with improved long-term survival compared with remaining at a level of >10% *BCR::ABL1*^{IS} in this highly resistant patient population

- In the 45- or 30-mg dose cohorts, patients who reached ≤10% *BCR::ABL1*^{IS} by 3 and 6 months had better OS than those who did not (**Figure 4**); a similar trend was seen for PFS (data not shown)

Figure 4: Estimated OS by *BCR::ABL1*^{IS} level by 3, 6, and 12 months based on ponatinib dose



Conclusions

- This post hoc analysis of the OPTIC trial demonstrated the importance of achieving landmark responses with ponatinib on survival outcomes in patients with heavily pretreated, highly TKI-resistant CP-CML
  - Regardless of ponatinib starting dose, achievement of ≤10% *BCR::ABL1*^{IS} by 3, 6, and 12 months was associated with improved long-term PFS
  - Achievement of ≤10% *BCR::ABL1*^{IS} within 3–6 months in patients who received 45- or 30-mg ponatinib was associated with improved OS
- These results highlight the clinical benefit of achieving molecular responses of ≤10% *BCR::ABL1*^{IS} with ponatinib, especially within 12 months of therapy

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