Event-free survival and safety with ponatinib in patients with chronic-phase chronic myeloid leukemia: 5-year follow-up of OPTIC

CML-516

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Background

- Ponatinib, a BCR::ABL1 tyrosine kinase inhibitor (TKI), potently inhibits *BCR::ABL1* and clinically relevant single mutations, including T315I[1,2]
- In the primary analysis of the Phase 2 OPTIC trial (NCT02467270) evaluating 3 ponatinib dosing strategies in patients with chronic-phase chronic myeloid leukemia (CP-CML), optimal benefit:risk occurred with a ponatinib starting dose of 45 mg once daily with dose reduction to 15 mg once daily on achievement of ≤1% *BCR::ABL1*^{IS}; this regimen was subsequently approved in the United States for this CP-CML population[3,4]
- OPTIC 5-year follow-up data showed durable clinical benefit of ponatinib and outcomes consistent with earlier analyses[5]
- Although overall survival (OS) and progression-free survival (PFS) were similar across starting doses at 5-year follow-up,[5] additional exploratory analyses, such as event-free survival (EFS), may provide further insight into long-term outcomes across starting doses

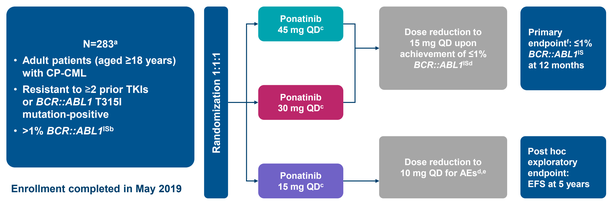
Objective

- To evaluate 5-year EFS (defined as time from first dose to disease progression, discontinuation due to adverse event [AE] or lack of efficacy, or death) with ponatinib treatment across 3 dosing cohorts in patients with CP-CML

Methods

- Patients were randomized to ponatinib 45 mg, 30 mg, or 15 mg once daily; patients in the 45-mg and 30-mg cohorts had dose reduction to 15 mg upon response (≤1% *BCR::ABL1*^{IS}) (**Figure 1**)
- EFS, defined as time from first dose to disease progression, discontinuation due to AE or lack of efficacy, or death, was estimated using the Kaplan-Meier method
  - EFS was evaluated by dosing cohort for all patients, those with T315I mutation at baseline, and by age group
- Exposure-adjusted rates were calculated per 100 patient-years (PY)

Figure 1: OPTIC study design (NCT02467270)



[a]99% of patients were TKI-resistant
[b]As shown by quantitative real-time polymerase chain reaction
[c]Dose reductions due to AEs were permitted
[d]Escalation to the starting dose was allowed for patients who lost their response following dose reduction; no dose escalation was allowed beyond starting dose
[e]Dose reduction below 10 mg was not permitted during the main treatment period, but reduced dosing frequency was permitted during the treatment continuation period
[f]Key secondary endpoints: MMR rate at 12 and 24 months and major cytogenic response rate by 12 months, duration of MMR, and safety across the 3 doses; others include PFS, OS, and duration of response in responders
MMR, major molecular response; QD, once daily

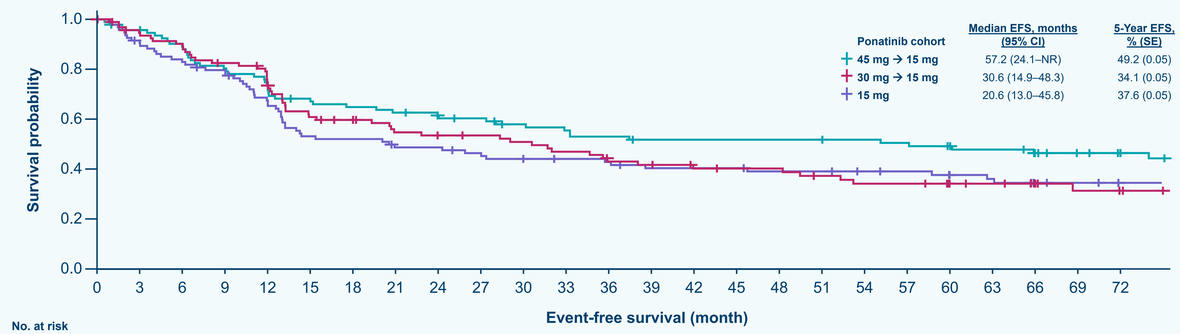
Results

Patients

- In total, 283 patients were randomized to receive ponatinib 45 mg (n=94), 30 mg (n=95), or 15 mg (n=94) once daily (**Table 1**)
  - 1 patient in the 30-mg cohort did not receive treatment and was not included in the safety population
- At the end of study (May 15, 2024), 61 patients remained on ponatinib treatment
  - 27/94 patients (29%) in the 45-mg cohort, 18/95 patients (19%) in the 30-mg cohort, and 16/94 patients (17%) in the 15-mg cohort
  - The most common reasons for treatment discontinuation in the overall population were lack of efficacy (66/283, 23%), AEs (55/283, 19%), and progressive disease (26/283, 9%)
- Median durations of follow-up in the 45-, 30-, and 15-mg cohorts were 78, 75, and 75 months, respectively

Key results

EFS by dosing cohort



Based on the intent-to-treat population, defined as all randomized patients. 45 mg → 15 mg is a 45-mg starting dose with dose reduction to 15 mg upon response (≤1% *BCR::ABL1*^{IS}); 30 mg → 15 mg is a 30-mg starting dose with dose reduction to 15 mg upon response (≤1% *BCR::ABL1*^{IS}).
NR, not reached

Key Takeaways

- **Ponatinib 45 mg → 15 mg provided greater long-term event-free survival than lower starting doses**
- **Long-term exposure-adjusted arterial occlusive event rates were low, regardless of dosing cohort**

Table 1: Demographics and baseline disease characteristics[a]

Characteristic	45 mg → 15 mg (n=94)	30 mg → 15 mg (n=94)	15 mg (n=94)	Total (n=282)
Age, y, median (range)	46 (19–81)	51 (21–77)	49 (18–81)	48 (18–81)
Age group, y, n (%)				
18–49	52 (55)	46 (49)	51 (54)	149 (53)
50–64	26 (28)	37 (39)	34 (36)	97 (34)
65–74	14 (15)	10 (11)	7 (7)	31 (11)
≥75	2 (2)	1 (1)	2 (2)	5 (2)
Male, n (%)	50 (53)	38 (40)	53 (56)	141 (50)
ECOG PS 0 or 1, n (%)	93 (99)	93 (99)	94 (100)	280 (99)
Time since diagnosis, y, median (range)	5.5 (1–21)	4.9 (1–29)	5.7 (1–22)	5.4 (1–29)
Medical history				
Any hypertension	29 (31)	27 (29)	24 (26)	80 (28)
Diabetes mellitus	5 (5)	3 (3)	7 (7)	15 (5)
Hyperlipidemia	19 (20)	14 (15)	15 (16)	48 (17)
Prior TKIs, n (%)				
1	1 (1)	1 (1)	4 (4)	6 (2)
2	43 (46)	37 (39)	42 (45)	122 (43)
≥3	50 (53)	56 (60)	48 (51)	154 (55)
***BCR::ABL1* mutation, n (%)[b]**				
No mutation	51 (54)	58 (62)	54 (57)	163 (58)
T315I mutation	25 (27)	21 (22)	20 (22)	66 (23)
Other mutations	16 (17)	14 (15)	18 (19)	48 (17)

[a]Based on the safety population, defined as all patients who received at least 1 dose of the study drug
[b]Sanger sequencing was used for mutation testing. Five patients (45 mg, n=2; 30 mg, n=1; 15 mg, n=2) did not have mutation testing performed at baseline.
ECOG, Eastern Cooperative Oncology Group; PS, performance status

Safety

- Median dose intensity was 16.6 mg/day overall and was 27.7, 23.5, and 14.7 mg/day in the 45-mg, 30-mg, and 15-mg cohorts, respectively
- Grade 3/4 treatment-emergent AEs (TEAEs; in 68% of patients overall) and treatment discontinuation due to AEs (in 21% of patients overall) were similar across cohorts (**Table 2**)
- Exposure-adjusted Grade 3/4 TEAE rates per 100 PY were comparable across cohorts (**Table 2**)
- Exposure-adjusted arterial occlusive event (AOE) rates per 100 PY were also comparable across cohorts (**Table 2**)

Table 2: Summary of TEAEs, dose modifications, and TE-AOEs

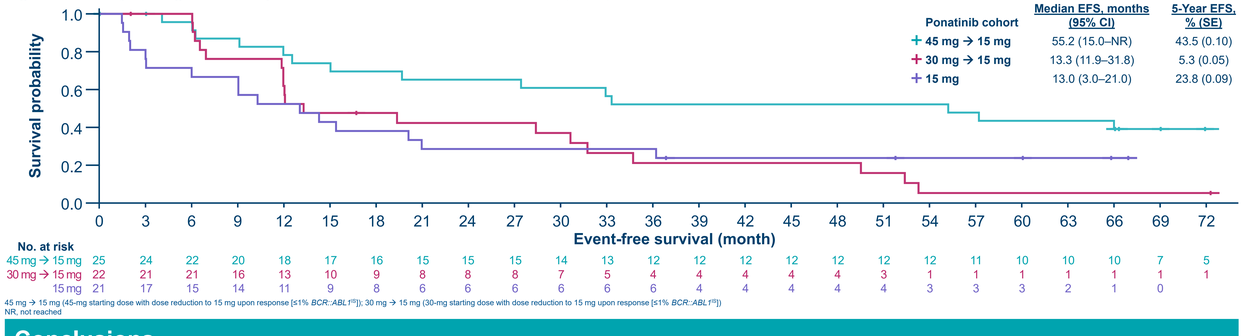
Characteristic	45 mg → 15 mg (n=94)	30 mg → 15 mg (n=94)	15 mg (n=94)	Total (n=282)
TEAEs, n (%)				
Any	94 (100)	92 (98)	92 (98)	278 (99)
Grade 3/4	66 (70)	62 (66)	64 (68)	192 (68)
Grade 5[a]	4 (4)	2 (2)	3 (3)	9 (3)
Exposure-adjusted Grade 3/4 TEAEs, patients with events per 100 PY (95% CI)	47.9 (27.0–68.8)	54.1 (33.0–75.2)	49.2 (29.8–68.6)	50.2 (38.3–62.1)
Treatment discontinuations or modifications,[b] n (%)				
Discontinuation	23 (24)	18 (19)	19 (20)	60 (21)
Dose reduction	48 (51)	37 (39)	32 (34)	117 (42)
Dose interruption	76 (81)	64 (68)	62 (66)	202 (72)
TE-AOEs, n (%)				
Any TE-AOE	13 (14)	9 (10)	5 (5)	27 (10)
Grade 3/4 TE-AOE	6 (6)	8 (9)	5 (5)	19 (7)
Exposure-adjusted TE-AOEs, patients with events per 100 PY (95% CI)	4.1 (1.8–6.4)	3.8 (1.3–6.3)	2.0 (0.3–3.7)	3.3 (2.1–4.6)

Based on the safety population, defined as all patients who received at least 1 dose of the study drug
[a]Number of deaths up to 30 days after the last dose date
[b]A TEAE may be associated with more than one type of dose adjustment
CI, confidence interval; TE-AOE, treatment-emergent arterial occlusive event

Efficacy

- Among patients with baseline T315I mutations (n=68), 5-year probability of EFS was highest and median EFS was longest in the 45-mg cohort (**Figure 2**)
- Across age groups, median EFS was 7.1 months to not reached in the 45-mg cohort, 19.4–36.0 months in the 30-mg cohort, and 12.1–36.2 months in the 15-mg cohort

Figure 2: EFS by dosing cohort for patients with T315I mutation at baseline (n=68)



45 mg → 15 mg (45-mg starting dose with dose reduction to 15 mg upon response [≤1% *BCR::ABL1*^{IS}]); 30 mg → 15 mg (30-mg starting dose with dose reduction to 15 mg upon response [≤1% *BCR::ABL1*^{IS}])
NR, not reached

Conclusions

- At 5 years of follow-up in the OPTIC trial, response-based ponatinib dosing of a 45-mg starting dose reduced to 15 mg was associated with longer EFS compared with lower starting doses
- This finding is consistent with findings for ≤0.1% *BCR::ABL1*^{IS} at 5 years, which was achieved by a greater proportion of patients (46%) in the 45-mg cohort than in the 30-mg (29%) and 15-mg (24%) cohorts[5]
- Overall, the safety profile was comparable across cohorts, including a low incidence of exposure-adjusted AOEs
- These findings provide additional understanding of the long-term outcomes of ponatinib and further support the clinical rationale for optimized response-based dosing with a 45-mg starting dose in patients with CP-CML

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