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POSTER ABSTRACTS

632.CHRONIC MYELOID LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Long-Term Results from the Optic Trial: A Dose-Optimization Study of 3 Starting Doses of Ponatinib

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Background: Ponatinib is a BCR::ABL1 TKI currently approved to potently inhibit all known native and single resistance mutation variants of BCR::ABL1, including T315I. The phase 2 OPTIC (Optimizing Ponatinib Treatment in CP-CML, NCT02467270; ongoing) trial is evaluating the efficacy and safety of ponatinib using a novel, response-based, dose-reduction strategy in patients with CP-CML whose disease is resistant to ≥2 TKIs or who harbor T315I. The response-based dosing strategy aims to optimize efficacy and improve the safety of ponatinib. Results from the OPTIC primary analysis and the 3-year update demonstrated an improved risk:benefit ratio for ponatinib starting with 45 mg/d, followed by dose reduction to 15 mg/d upon attaining ≤1% *BCR::ABL1* ^{IS}. We present for the first time the long-term 4-year update of efficacy and safety outcomes from the OPTIC trial.
Methods: Patients with CP-CML resistant to ≥2 TKIs or with the *BCR::ABL1*T315I mutation were randomized to starting doses of ponatinib 45 mg, 30 mg, and 15 mg once daily. Upon achievement of ≤1% *BCR::ABL1* ^{IS}, doses were reduced to 15 mg in the 45-mg and 30-mg cohorts. The primary endpoint was ≤1% *BCR::ABL1* ^{IS} at 12 months; secondary endpoints included molecular response rates and safety outcomes, including arterial occlusive event (AOE) rates that were adjudicated prospectively by an independent review committee. Probabilities of progression-free survival (PFS) and overall survival (OS) by 48 months were estimated using the Kaplan-Meier method.
Results: A total of 283 patients were randomized (45 mg/30 mg/15 mg: n=94/95/94). The median age was 48 years (range: 18–81 years). As of May 8, 2023, 60.2% (56/93), 40.9% (38/93), and 39.6% (36/91) of patients in the 45-mg, 30-mg, and 15-mg cohorts, respectively, achieved ≤1% *BCR::ABL1* ^{IS} by 48 months (**Table**). Median duration of response was not reached in any cohort. Of the patients with T315I mutations, 64.0% (16/25), 25.0% (5/20), and 15.8% (3/19) achieved ≤1% *BCR::ABL1* ^{IS}

by 48 months versus 60.0% (30/50), 46.6% (27/58), and 45.3% (24/53) of patients without mutations and 56.3% (9/16), 40.0% (6/15), and 50.0% (9/18) of patients with other mutations in the 45-mg, 30-mg, and 15-mg cohorts, respectively. Of the patients who achieved ≤1% *BCR::ABL1* ^{IS}, 80.4% (45/56) and 71.1% (27/38) in the 45-mg and 30-mg cohorts, respectively, had dose reductions to 15 mg upon achieving ≤1% *BCR::ABL1* ^{IS};11 patients did not reduce dose upon achieving ≤1% *BCR::ABL1* ^{IS}, including 6 dose reductions for adverse events (AEs; 3 maintained response), 2 discontinuations for AEs, and 3 lost to follow-up/other. Of the 86.7% (13/15) and 55.6% (5/9) of patients in the 45-mg and 30-mg cohorts who had dose re-escalations after loss of ≤1% *BCR::ABL1* ^{IS}response, 69.2% (9/13) and 80.0% (4/5) regained a ≤1% *BCR::ABL1* ^{IS}response, respectively. The median time to regain response after dose re-escalation among patients who achieved ≤1% *BCR::ABL1* ^{IS}response was 126 days (95% CI, 39-167) in the 45-mg cohort and was not applicable in the 30-mg cohort. Of the patients who did not regain response, 3 discontinued due to AE or progressive disease and 1 remains on treatment. Median PFS (72.5 months) was highest in the 45-mg cohort. Most common grade ≥3 treatment-emergent AEs were thrombocytopenia (27.3%), neutropenia (17.7%), and hypertension (9.9%). Exposure-adjusted AOE rates (95% CI) were 3.87 (1.45, 6.30) in the 45-mg cohort, 3.66 (1.11, 6.20) in the 30-mg cohort, and 1.73 (0.02, 3.44) 15-mg cohort.

Conclusions: Results from the first long-term analysis of the OPTIC study support ponatinib's robust long-term efficacy and manageable safety profile in patients with highly resistant CP-CML. These results are also consistent with previous analyses of the OPTIC trial and demonstrate that a ponatinib starting dose of 45 mg/d with reduction to 15 mg/d upon attainment of ≤1% *BCR::ABL1* ^{IS} continued to provide the optimal benefit:risk ratio.

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Table

Response of ≤1% *BCR::ABL1*^{IS}, n (%)[a]	45-mg Cohort N=93	30-mg Cohort N=93	15-mg Cohort N=91
By 12 mo	48 (51.6)	33 (35.5)	23 (25.3)
By 24 mo	56 (60.2)	37 (39.8)	32 (35.2)
By 48 mo	56 (60.2)	38 (40.9)	36 (39.6)
Survival probability, % (95% CI)	**45-mg Cohort (N=94)**	**30-mg Cohort (N=95)**	**15-mg Cohort (N=95)**
At 12 mo			
PFS	93.3 (84.4, 97.2)	87.3 (76.9, 93.3)	94.1 (84.5, 97.8)
OS	98.8 (91.6, 99.8)	98.8 (91.6, 99.8)	97.7 (91.1, 99.4)
At 24 mo			
PFS	80.6 (67.0, 89.1)	79.8 (65.8, 88.5)	84.0 (69.3, 92.1)
OS	92.7 (81.5, 97.3)	95.1 (85.3, 98.4)	94.0 (84.2, 97.8)
At 48 mo			
PFS	72.5 (60.7, 81.2)	62.8 (49.0, 73.7)	63.8 (50.5, 74.5)
OS	87.6 (78.6, 92.9)	85.9 (76.4, 91.7)	87.6 (78.7, 92.9)

[a]Includes all patients who were randomized and had measurable *BCR::ABL1*^{IS} at baseline.
Abbreviations: CI, confidence interval; mo, months; OS, overall survival, PFS, progression-free survival

Figure 1

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