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Abstract 48

Outcome By Mutation Status and Line of Treatment in Optic, a Dose-Ranging Study of 3 Starting Doses of Ponatinib in Patients with CP-CML

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Introduction: In PACE (NCT01207440), patients with refractory chronic-phase chronic myeloid leukemia (CP-CML) with substantial prior second-generation tyrosine kinase inhibitor (TKI) treatment demonstrated deep, lasting responses to ponatinib. However, long-term follow-up identified rates of arterial occlusive events (AOEs) as a risk. OPTIC (NCT02467270) is a randomized Phase 2 trial evaluating ponatinib at 3 starting doses: 45 mg, 30 mg, and 15 mg daily in patients with CP-CML resistant/intolerant to ≥2 TKIs or with a T315I mutation. The interim analysis showed that the 45-mg (vs 30 mg or 15 mg) starting dose (with reduction to 15 mg upon response) provided the best clinical outcomes and responses were maintained in >75% of patients who dose reduced. Here, we present efficacy and safety outcomes by baseline mutation status and line of treatment for the 3 dose cohorts.

Methods: Patients with CP-CML resistant/intolerant to ≥2 TKIs or with T315I mutation were randomized to ponatinib starting doses of 45 mg (Cohort A; 45 mg → 15 mg), 30 mg (B; 30 mg → 15 mg), and 15 mg (C) once daily (qd). Doses were reduced to 15 mg on achievement of ≤1% *BCR-ABL1*^{IS} in Cohorts A and B. Doses also could be reduced for safety. The primary endpoint is ≤1% *BCR-ABL1*^{IS} at 12 months. In this analysis, the outcome was analyzed by baseline mutation status (none, any, T315I, and non-T315I) and number of prior TKIs (≤2 or ≥3) in the intent-to-treat (ITT) population. Treatment-emergent adverse events (TEAEs), serious TEAEs, and AOEs by adjudication were summarized by number of prior TKIs (≤2 or ≥3). Interim analysis results are descriptive.

Results: Patients (N=283) were randomized: A/B/C n=94/95/94; median age was 48 y (18–81 y). Seven patients were excluded from the intent-to-treat population (N=276) because they had atypical transcripts. Mutation status was well balanced between cohorts; 59% had no mutation, 41% had ≥1 baseline mutation, 24% had T315I, and 17% had a non-

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T315I mutation. In all categories of mutation status, the rate of ≤1% *BCR-ABL1*^{IS} by 12 months was highest in Cohort A, with the most notable differences seen in patients with T315I (A: 60%, B: 25%, C: 6%) (**Table 1**). Patients with no mutations or other mutations had smaller differences but the outcomes all still favored 45 mg. Patients in all cohorts were treated with multiple TKIs, with 54% (A), 60% (B), and 53% (C) having 3 or more prior TKIs. The rate of ≤1% *BCR-ABL1*^{IS} by 12 months was highest in Cohort A, both in patients treated with ≤2 or ≥3 prior TKIs (43% and 49%, respectively) (**Table 1**). **Table 2** shows rates of TEAEs and TE-AOEs by cohort and number or prior TKIs. There was a trend toward higher event rates in Cohort A and for patients treated with ≥3 TKIs. Rates of adjudicated AOEs were low (≤6%) in all 3 cohorts irrespective of the number of prior TKIs.

Conclusions: At this interim analysis with a median follow-up of ~21 months, the maximum benefit:risk, regardless of mutation status or number of prior TKIs, was observed in patients treated with a 45-mg starting dose, with a reduction to 15 mg upon achievement of response. Patients with the T315I mutation who initiated ponatinib at 45 mg experienced better response rates than those who initiated ponatinib at 30-mg or 15-mg starting doses. Primary analysis will provide a refined understanding of the benefit:risk profile of 3 different starting doses of ponatinib.

Table 1. Efficacy Results by Baseline Mutation Status and Number of Prior TKIs

	Ponatinib Starting Dose Cohort			
Baseline Characteristics	**Cohort A 45 mg → 15 mg**	**Cohort B 30 mg → 15 mg**	**Cohort C 15 mg**	**Total**
≤1% *BCR-ABL1*^{IS} rate by 12 months, n/n (%)				
Total patients[a]	44/91 (48)	31/90 (34)	21/88 (24)	96/269 (36)
No mutation	20/49 (41)	20/56 (36)	14/54 (26)	54/159 (34)
Any mutation	24/42 (57)	11/34 (32)	7/34 (21)	42/110 (38)
T315l mutation	15/25 (60)	5/20 (25)	1/16 (6)	21/61 (34)
Non-T315l mutation	9/17 (53)	6/14 (43)	6/18 (33)	21/49 (43)
Patients with ≤2 prior TKIs	20/42 (48)	15/36 (42)	11/43 (26)	46/121 (38)
Patients with ≥3 prior TKIs	24/49 (49)	16/54 (30)	10/45 (22)	50/148 (34)

[a] Analysis based on the ITT population and includes patients who had at least one postbaseline molecular assessment

→ 15 mg, Cohort A is referred to as 45 mg → 15 mg and Cohort B as 30 mg → 15 mg because the study design has a dose reduction to 15 mg upon achievement of ≤1% *BCR-ABL1*^{IS}. There also were patients in Cohorts A and B who dose-reduced to different dose levels (30, 15, and 10 mg) due to safety
ITT, intent-to-treat population; TKIs, tyrosine kinase inhibitors

Table 2. TEAEs by Number of Prior TKIs (Safety Population)[a]

Ponatinib Starting Dose Cohort								
	Cohort A 45 mg → 15 mg (n=94)		Cohort B 30 mg → 15 mg (n=94)		Cohort C 15 mg (n=94)		Total N=282	
n (%)	≤2 prior TKIs (n=44)	≥3 prior TKIs (n=50)	≤2 prior TKIs (n=38)	≥3 prior TKIs (n=56)	≤2 prior TKIs (n=46)	≥3 prior TKIs (n=48)	≤2 prior TKIs (n=128)	≥3 prior TKIs (n=154)
Serious TEAE	12 (27)	17 (34)	8 (21)	14 (25)	8 (17)	18 (38)	28 (22)	49 (32)
Grade 3–5 TEAE	29 (66)	33 (66)	23 (61)	30 (54)	26 (57)	28 (58)	78 (61)	91 (59)
TE-AOE[b]	2 (5)	3 (6)	1 (3)	3 (5)	0	1 (2)	3 (2)	7 (5)
Serious TE-AEO[b]	0	2 (4)	1 (3)	2 (4)	0	0	1 (1)	4 (3)

[a] The safety population included all randomized patients who received at least 1 dose of study drug (N=282)
[b] AOEs are based on adjudication

→ 15 mg, Cohort A is referred to as 45 mg → 15 mg and Cohort B as 30 mg → 15 mg because the study design has a dose reduction to 15 mg upon achievement of ≤1% *BCR-ABL1*^{IS}. There also were patients in Cohorts A and B who dose-reduced to different dose levels (30, 15, and 10 mg) due to safety
AOE, arterial occlusive event; TEAEs, treatment-emergent adverse events; TE-AOE, treatment-emergent arterial occlusive event; TKIs, tyrosine kinase inhibitors

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