

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

Program: Oral and Poster Abstracts

Type: Oral

Session: 632. Chronic Myeloid Leukemia: Therapy— Building The Future CML

Hematology Disease Topics & Pathways:

Biological, Adult, Diseases, CML, Therapies, Study Population, Myeloid Malignancies, TKI

Saturday, December 5, 2020: 8:15 AM

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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 \rightarrow 15 mg), 30 mg (B; 30 mg \rightarrow 15 mg), and 15 mg (C) once daily (qd). Doses were reduced to 15 mg on achievement of $\leq 1\%$ *BCR-ABL1*_{IS} in Cohorts A and B. Doses also could be reduced for safety. The primary endpoint is $\leq 1\%$ *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 AOE 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-T315I mutation. In all categories of mutation status, the rate of $\leq 1\%$ *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 $\leq 1\%$ *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 of prior TKIs. There was a trend toward higher event rates in Cohort A and for patients treated with ≥ 3 TKIs. Rates of adjudicated AOE were low ($\leq 6\%$) 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

Baseline Characteristic	Ponatinib Starting Dose Cohort			Total
	Cohort A 45 mg → 15 mg	Cohort B 30 mg → 15 mg	Cohort C 15 mg	
≤1% BCR-ABL^{1S} 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)
T315I mutation	15/25 (60)	5/20 (25)	1/16 (6)	21/61 (34)
Non-T315I 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-ABL^{1S}. 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

n (%)	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	
	≤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)
Grades 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-AOE ^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 AOE 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-ABL^{1S}. 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

Disclosures: **Cortes:** *Daiichi Sankyo:* Consultancy, Research Funding; *Pfizer:* Consultancy, Research Funding; *Novartis:* Consultancy, Research Funding; *Immunogen:* Research Funding; *Merus:* Research Funding; *Jazz Pharmaceuticals:* Consultancy, Research Funding; *Bristol-Myers Squibb:* Research Funding; *BiolineRx:* Consultancy, Research Funding; *Astellas:* Research Funding; *Amphivena Therapeutics:* Research Funding; *Arog:* Research Funding; *Takeda:* Consultancy, Research Funding; *BioPath Holdings:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Telios:* Research Funding; *Sun Pharma:* Research Funding. **Apperley:** *Pfizer:* Honoraria, Research Funding, Speakers Bureau; *Novartis:* Honoraria, Speakers Bureau; *Incyte:* Honoraria, Research Funding, Speakers Bureau; *Bristol Myers Squibb:* Honoraria, Speakers Bureau. **Hochhaus:** *Novartis:* Honoraria, Research Funding; *Incyte:* Honoraria, Research Funding; *Bristol-Myers Squibb:* Honoraria, Research Funding; *Pfizer:* Honoraria, Research Funding; *Takeda:* Honoraria; *MSD:* Research Funding. **Mauro:** *Novartis:* Consultancy, Honoraria, Other: Travel, Accommodation, Expenses, Research Funding; *Takeda:* Consultancy, Honoraria, Other: Travel, Accommodation, Expenses, Research Funding; *Bristol-Myers Squibb:* Consultancy, Honoraria, Other: Travel, Accommodation, Expenses, Research Funding; *Pfizer:* Consultancy, Honoraria, Other: Travel, Accommodation, Expenses, Research Funding; *Sun Pharma/SPARC:* Research Funding. **Rousselot:** *Bristol-Myers Squibb:* Consultancy; *Pfizer:* Consultancy, Research Funding; *Novartis:* Consultancy; *Takeda:* Consultancy; *Incyte:* Consultancy, Research Funding. **Sacha:** *Incyte:* Consultancy, Honoraria, Speakers Bureau; *Bristol-Myers Squibb Company:* Consultancy, Honoraria, Speakers Bureau; *Adamed:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Speakers Bureau; *Pfizer:* Consultancy, Honoraria, Speakers Bureau. **Talpaz:** *Novartis:* Research Funding; *IMAGO:* Consultancy; *Constellation Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees; *Takeda:* Research Funding. **Chuah:** *Korea Otsuka Pharmaceutical:* Honoraria; *Pfizer:* Other: Travel, Research Funding; *Novartis:* Honoraria; *Bristol-Myers Squibb:* Honoraria, Research Funding. **Lipton:** *Bristol-Myers Squibb:* Honoraria; *Pfizer:* Consultancy, Honoraria, Research Funding; *BMS:* Consultancy, Research Funding; *Novartis:* Consultancy, Research Funding; *Ariad:* Consultancy, Research Funding; *Takeda:* Consultancy, Honoraria, Research Funding. **Deinger:** *SPARC:* Research Funding; *Novartis:* Consultancy, Other, Research Funding; *Blueprint Medicines Corporation:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: part of a study management committee, Research Funding; *Incyte:* Consultancy, Honoraria, Other, Research Funding; *Sangamo:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Fusion Pharma:* Consultancy; *Takeda:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: part of a study management committee, Research Funding; *Medscape:* Consultancy, Honoraria; *Gilead Sciences:* Research

Funding; *Celgene*: Research Funding; *Galena*: Consultancy, Honoraria, Other; *Bristol-Myers Squibb*: Consultancy, Honoraria, Other, Research Funding; *Ariad*: Consultancy, Honoraria, Other; *DisperSol*: Consultancy; *Leukemia & Lymphoma Society*: Research Funding; *Pfizer*: Honoraria, Other, Research Funding. **Schiffer**: *BMS*: Consultancy; *Novartis*: Consultancy; *Takeda*: Research Funding. **García Gutiérrez**: *Novartis Pharma AG*: Consultancy, Honoraria, Other: travel/accommodations/expenses, Research Funding; *Pfizer*: Honoraria, Other: travel/accommodations/expenses, Research Funding; *Incyte*: Consultancy, Honoraria, Other: travel/accommodations/expenses, Research Funding. **de Lavallade**: *Novartis*: Honoraria; *Pfizer*: Honoraria; *BMS*: Honoraria, Research Funding; *Incyte*: Honoraria, Research Funding. **Etienne**: *Bristol-Myers Squibb*: Consultancy, Research Funding, Speakers Bureau; *Novartis*: Consultancy, Research Funding, Speakers Bureau; *Pfizer*: Consultancy, Speakers Bureau; *Incyte*: Consultancy, Speakers Bureau. **Lu**: *Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited*: Current Employment. **Srivastava**: *Takeda*: Current Employment. **Rosti**: *Novartis*: Speakers Bureau; *Incyte*: Speakers Bureau; *Bristol-Myers Squibb*: Speakers Bureau; *Pfizer*: Research Funding, Speakers Bureau.