Dose Modification Dynamics of Ponatinib in Patients With Chronic-Phase Chronic Myeloid Leukemia (CP-CML) From the PACE and OPTIC Trials

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Introduction

- Ponatinib is a potent, oral, third-generation tyrosine kinase inhibitor (TKI) that is US Food and Drug Administration (FDA) approved for the treatment of patients with relapsed CML[1,2]
- In the Ponatinib Ph+ ALL and CML Evaluation (PACE) trial, patients with highly resistant CP-CML with substantial prior second-generation (2G) TKI treatment demonstrated deep, lasting responses to 45 mg once daily ponatinib[2]
  - PACE did not have a response-based dose-reduction strategy
- The phase 2 Optimizing Ponatinib Treatment In CP-CML (OPTIC) trial prospectively evaluated a response-based dose-reduction strategy in an attempt to optimize the dose schedule of ponatinib in patients with CP-CML whose disease was resistant to 2G *BCR::ABL1* TKI therapy or with a T315I mutation[3]
  - OPTIC was designed with required dose reductions upon achievement of ≤1% *BCR::ABL1*^{IS}

Methods

Table 1. PACE and OPTIC Trial Key CV Inclusion and Exclusion Criteria

Trial	PACE	OPTIC
Inclusion Criteria	• ≥18 years of age • ECOG ≤2 • Normal QT interval corrected by Fridericia calculation (QTcF) on screening ECG evaluation[a]	• ≥18 years of age • ECOG ≤2 • Normal QT interval corrected by Fridericia calculation (QTcF) on screening ECG evaluation[a]
Exclusion Criteria	• Significant or active CV • Uncontrolled hypertriglyceridemia[b]	• Clinically significant, uncontrolled, or active CV disease • Uncontrolled hypertension[c] • Poorly controlled diabetes[d]

[a] Defined as QTcF of ≤450 ms in males or ≤470 ms in females. [b] Triglycerides >450 mg/dL. [c] Defined as >150 mm Hg and >90 mm Hg for systolic and diastolic blood pressure, respectively. [d] Hemoglobin A1c values of >7.5%

- The propensity score analysis was conducted to reduce potential bias from differences in baseline characteristics when comparing the TE-AOE incidence rates in PACE and OPTIC
- The propensity score calculation was adjusted for 14 parameters including baseline characteristics, disease parameters, and exposure

Results

Table 2. Demographics and Baseline Disease Characteristics

Characteristic	PACE CP-CML (N=270)[a]	OPTIC 45 mg → 15 mg (N=94)
Median age, y	60	46
Male gender, n (%)	144 (53)	50 (53)
Median time since diagnosis, y	7.03	5.5
Patients with CV risk factors, n (%)		
Hypercholesterolemia	65 (24)	3 (3.2)
Baseline BMI ≥30 kg/m^2	73 (27)	26 (28)
Diabetes mellitus	32 (12)	5 (5.3)
Vascular disorders	119 (44)	30 (32)
Arterial hypertension	102 (38)	29 (31)
Deep vein thrombosis	4 (1.5)	0
Concomitant medications, n (%)		
Statins	64 (24)	24 (26)
Acetylsalicylic acid	87 (32)	18 (19)
Best response to last prior TKI[b], n (%)		
CHR or worse	171 (63)	66 (70)
Better than CHR	99 (37)	28 (30)
***BCR::ABL1* mutation at baseline[c-e], n (%)**		
≤1% *BCR::ABL1*^{IS}	6 (2.2)	3 (3.2)
>1 to 10% *BCR::ABL1*^{IS}	54 (20)	26 (28)
>10% *BCR::ABL1*^{IS}	200 (74)	74 (79)
Mutations[f], n (%)		
No mutation	138 (51)	51 (54)
T315I	64 (24)	25 (27)
Mutation other than T315I	68 (25)	26 (28)
≥2 mutations detected	29 (11)	10 (11)
Stopped prior therapy due to resistance, n (%)	260 (96)	92 (98)
Prior TKIs, n (%)		
1	18 (6.7)	1 (1.1)
≥2	252 (93)	93 (99)
≥3	162 (60)	50 (53)

[a] PACE: Includes 3 patients with CP-CML who were not T315I+ at study entry and not resistant to dasatinib or nilotinib. [b] OPTIC: Baseline response to last prior TKI is missing for 4 patients. [c] Sanger sequencing was used for mutation testing. [d] PACE: Four patients had an e1a2 variant, 4 had atypical transcripts, and 2 had missing data. [e] OPTIC: One patient in the 45-mg cohort does not have *BCR::ABL1*. [f] OPTIC: Two patients in the 45-mg cohort did not have any mutation testing performed at baseline

Objective

Here, we descriptively compared the potential impact of dosing differences between the 2 trials on efficacy and safety, as well as explored the impact of dosing differences on AOEs

Figure 1. PACE and OPTIC Trial Designs[a]

PACE
- PACE (NCT01207440): A phase 2, single-arm study, of ponatinib in patients with CML or Ph+ ALL

OPTIC
- OPTIC (NCT02467270): A multicenter, randomized phase 2 trial characterizing the safety and efficacy of ponatinib

- Adults with CML or ALL
- Resistant/intolerant to dasatinib or nilotinib or *BCR::ABL1* T315I+
- Enrolled N=449

→ Ponatinib 45 mg/day[b,c]

- Adults with CP-CML
- Resistant/intolerant to ≥2 TKIs or *BCR::ABL1* T315I+
- Enrolled N=283

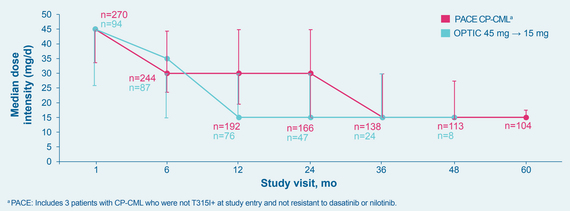
→ Ponatinib 45 mg/day[b] / Ponatinib 30 mg/day / Ponatinib 15 mg/day → Dose reduced to 15 mg/day upon achieving ≤1% *BCR::ABL1*^{IS}

- This dosing dynamics analysis was conducted on the CP-CML cohort (N=270) of PACE and 45-mg cohort (N=94) of OPTIC

[a] In the PACE trial, AOEs were retrospectively adjudicated and in OPTIC AOEs were prospectively adjudicated. [b] In the PACE trial, proactive dose reductions were mandated in 2013, ≈2 years after initiation of the first patient. Patients who achieved MCyR had doses reduced to 15 mg once daily and those without MCyR had doses reduced to 30 mg once daily, unless benefit-risk analysis justified treatment with a higher dose. Dose reductions for adverse events also were permitted in PACE (to 15 mg). [c] The OPTIC trial was designed to incorporate a mandatory response-based dose-reduction strategy as described above; dose reductions for adverse events also were permitted (to 10-15 mg)

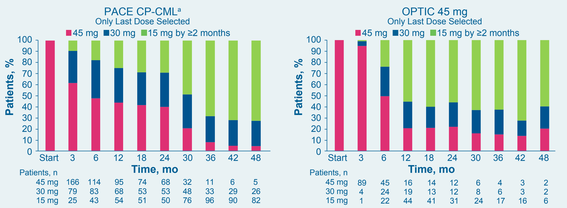
Results

Figure 2. Median Dose Intensity Over Time



[a] PACE: Includes 3 patients with CP-CML who were not T315I+ at study entry and not resistant to dasatinib or nilotinib.

Figure 3. Change in Dose Over Time



[a] PACE: Includes 3 patients with CP-CML who were not T315I+ at study entry and not resistant to dasatinib or nilotinib.

Key Takeaways

The response-based dose-reduction strategy in the OPTIC trial resulted in more rapid dose reductions, fewer dose reductions related to AEs, and longer median time on therapy in OPTIC compared with PACE, further demonstrating the benefit of the response-based dosing regimen used in OPTIC

Table 3. Dose Reductions and Dose Intensity in PACE and OPTIC

	PACE CP-CML (N=270)	OPTIC 45 mg → 15 mg (N=94)
Dose reduction		
Dose reduction due to AEs, n (%)	175 (65)	42 (45)
Dose reductions per FDA mandate or per protocol upon response[a], n (%)	46 (17)	33 (35)
No dose reductions, n (%)	49 (18)	19 (20)
Median time to dose reduction, mo	2.9	3.6
For safety	2.1	6.3
For efficacy	23.8	2.6

[a] Dose reductions in PACE were FDA mandated after 2013 for safety concerns; for OPTIC, dose reductions were due to efficacy according to study design

- Efficacy outcomes were generally comparable or better in OPTIC when compared with PACE (**Figures 4–6, Table 4**)

Figure 4. Efficacy Outcomes in PACE and OPTIC by 12, 24, and 60 Months

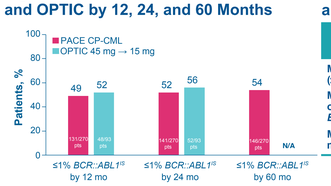
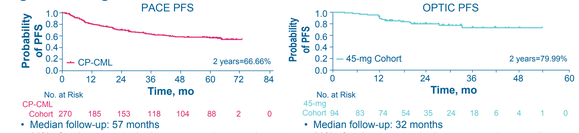


Table 4. Efficacy Outcomes in PACE and OPTIC

	PACE CP-CML (N=270)	OPTIC 45 mg → 15 mg (N=94)
Median time to response (≤1% *BCR::ABL1*^{IS}), mo	5.6	6
Median duration of response (≤1% *BCR::ABL1*^{IS}), mo	NR	NR
Median time on therapy, mo	12.6	19.5

- The preemptive dose adjustment in OPTIC led to longer time on therapy (19.5 mo vs 12.6 mo median time on therapy)

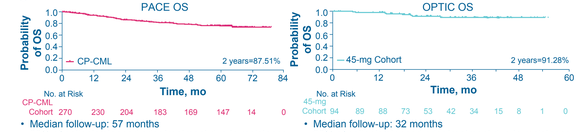
Figure 5. Progression-Free Survival[a,b]



- Median follow-up: 57 months
- 96% of patients stopped prior treatment due to resistance
- Median follow-up: 32 months
- 98% of patients stopped prior treatment due to resistance

[a] Dose reductions in PACE were FDA mandated after 2013 for safety concerns; for OPTIC, dose reductions were due to efficacy according to study design. [b] Progression defined as progression of disease to accelerated phase or blastic phase CML.

Figure 6. Overall Survival



- Median follow-up: 57 months
- 96% of patients stopped prior treatment due to resistance
- Median follow-up: 32 months
- 98% of patients stopped prior treatment due to resistance

Safety

- The overall incidence of TEAEs was similar between the 2 trials, AOEs were substantially lower in OPTIC when compared with PACE (**Table 5, Figure 7**)
- Propensity score analyses comparing AOE incidence showed a reduction in relative risk for AOEs in OPTIC versus PACE (**Table 6**)

Table 5. Safety Summary for PACE and OPTIC

Safety Parameter	PACE CP-CML (N=270)	OPTIC 45 mg → 15 mg (N=94)
Any TEAE, n (%)	269 (100)	94 (100)
Grade 3/4	227 (84)	64 (68)

Figure 7. Exposure-Adjusted AOEs in PACE and OPTIC

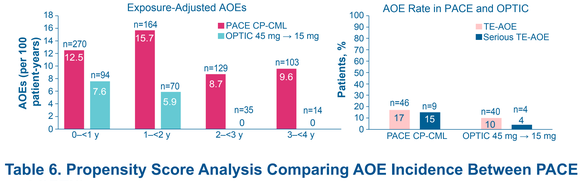


Table 6. Propensity Score Analysis Comparing AOE Incidence Between PACE and OPTIC

Safety Parameter	PACE CP-CML (N=270)	OPTIC 45 mg → 15 mg (N=94)
Patients with AOE	61	9
Unadjusted AOE rate (95% CI)	0.2230 (0.1733, 0.2728)	0.0879 (0.0297, 0.1461)
Adjusted AOE rate		
Odds ratio (95% CI)		0.3288 (0.1499, 0.7212)
Relative risk (95% CI)		0.4066 (0.2060, 0.8027)

- The propensity score analysis, which accounted for a variety of factors including baseline risk factors, showed an overall risk reduction of 60% in OPTIC compared with PACE

Conclusions

- The response-based dose-reduction strategy in the OPTIC trial resulted in more rapid dose reductions, fewer dose reductions related to AEs, and longer median time on therapy in OPTIC compared with PACE, further demonstrating the benefit of the response-based dosing regimen used in OPTIC
- These data from the PACE and OPTIC trials suggest that treatment with a response-based dose-reduction strategy may provide comparable or better efficacy while mitigating risk of AEs/AOEs with ponatinib
  - After adjusting for differences in baseline characteristics, OPTIC had lower AOE rates than PACE
- Furthermore, this analysis supports the rationale to explore response-based dose-modification strategies for other *BCR::ABL1* TKIs

References

1. Cortes JE, et al. *N Engl J Med*. 2013;369:1783-96. **2.** Cortes JE, et al. *Blood*. 2018;132(4):393-404. **3.** Cortes JE, et al. *Blood*. 2021; blood.2021012082 [online ahead of print].

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Abbreviations

2G, second-generation; AE, adverse event; ALL, acute lymphoblastic leukemia; AOE, arterial occlusive event; BMI, body mass index; CHR, complete hematologic response; CI, confidence interval; CML, chronic myeloid leukemia; CP-CML, chronic-phase chronic myeloid leukemia; CV, cardiovascular; d, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; FDA, US Food and Drug Administration; MCyR, major cytogenetic response; mo; month; N/A, not available; NR, not reached; OPTIC, Optimizing Ponatinib Treatment In CP-CML; OS, overall survival; PACE, Ponatinib Ph+ ALL and CML Evaluation; PFS, progression-free survival; Ph+, Philadelphia chromosome–positive; pts, patients; TEAE, treatment-emergent adverse event; TE-AOE, treatment-emergent AOE; TKI, tyrosine kinase inhibitor; y, year

Disclosures

Elias Jabbour: Research grants and advisory roles (AbbVie, Adaptive Biotechnologies, Amgen, BMS, Genentech, Pfizer, Takeda) **Michael Deininger:** Consultancy, membership on an entity's board of directors or advisory committees, part of a study management committee and research funding (Blueprint Medicines Corporation); consultancy (Fusion Pharma, Medscape, DisperSol); consultancy, membership on an entity's board of directors or advisory committees, and research funding (Takeda); consultancy and membership on an entity's board of directors or advisory committees (Sangamo); consultancy and research funding (Novartis); consultancy, honoraria, and research funding (Incyte); research funding (SPARC, DisperSol, Leukemia & Lymphoma Society) **Elisabetta Abruzzese:** Advisory board/consultancy (Incyte, Novartis, Pfizer); honoraria (Bristol Myers Squibb) **Jane Apperley:** Honoraria, research funding and speakers bureau (Incyte, Pfizer); honoraria and speakers bureau (Bristol Myers Squibb, Novartis) **Jorge Cortes:** Consultancy and research funding (Bristol Myers Squibb, Daiichi Sankyo, Jazz Pharmaceuticals, Astellas, Novartis, Pfizer, Takeda, BioPath Holdings); research funding (Sun Pharma, Telios, Arog, Merus, Immunogen); membership on an entity's board of directors or advisory committees (BioPath Holdings); consultancy (Amphivena Therapeutics, BioLineRx) **Charles Chuah:** Honoraria (Novartis, Korea Otsuka Pharmaceutical); honoraria and research funding (Bristol Myers Squibb); travel and research funding (Pfizer) **Daniel J DeAngelo:** Consulting/advisory role (Incyte, Pfizer, BMS, Amgen, Novartis, Celgene, Immunogen, Takeda, Blueprint Medicines), research funding (all to institution: Novartis, AbbVie, GlycoMimetics, Blueprint Medicines) **John DiPersio:** Equity ownership (Magenta Therapeutics, WUGEN); board/advisory membership (RiverVest Venture Partners); research funding (Amphivena Therapeutics, NeoImmune Tech, Macrogenics, Incyte, Bioline Rx, WUGEN); speaking fees (Incyte), patents/pending patents (CART with WashU and WUGEN, VLA-4 Inhibitors with WashU and Magenta) **Andreas Hochhaus:** Honoraria and research funding (Bristol Myers Squibb, Novartis, Pfizer); research funding (Incyte, Merck Sharp & Dohme); honoraria (Takeda) **Jeffrey H Lipton:** Consultancy and research funding (Bristol Myers Squibb, ARIAD, Pfizer, Novartis) **Franck Nicolini:** Honoraria, speakers bureau, travel/accommodations/expenses (Novartis, Incyte Biosciences, Pfizer); consulting/advisory role (Sun Pharma, Novartis, Analysis group); research fundings (Incyte Biosciences, Novartis); board entity (Novartis, Pfizer; Incyte Biosciences) **Javier Pinilla-Ibarz:** Consulting/advisory role (AbbVie, Janssen, AstraZeneca, Novartis, TG Therapeutics, Takeda); speakers bureau (AbbVie, Janssen, AstraZeneca, Takeda); research funding (MEI, Sunesis); patents/royalties/other intellectual property (Sellas) **Delphine Rea:** Steering committee (Novartis); advisory board (Incyte, Pfizer, Novartis) **Gianantonio Rosti:** Research funding and speakers bureau (Pfizer); speakers bureau (Bristol Myers Squibb, Incyte, Novartis) **Philippe Rousselot:** Consultancy and research funding (Incyte, Pfizer); consultancy (Bristol Myers Squibb, Novartis, Takeda) **Michael Mauro:** Consultancy, honoraria, travel, accommodation, expenses and research funding (Bristol Myers Squibb, Novartis, Takeda, Pfizer); research funding (Sun Pharma/SPARC) **Neil Shah:** Research funding (Bristol Myers Squibb) **Moshe Talpaz:** Grant/research support (Takeda, Novartis) **Alexander Vorog:** Employment (Takeda) **Vickie Lu:** Employment (Takeda) **Hagop Kantarjian:** Honoraria (AbbVie, Amgen, ARIAD, BMS, Immunogen, Orsenix, Pfizer, Agios, Takeda, Actinium Pharmaceuticals); research funding (all to institution: Pfizer, Amgen, BMS, Novartis, ARIAD, Astex Pharmaceuticals, AbbVie, Agios, Cyclacel, Immunogen, Jazz Pharmaceuticals)

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