Post Hoc Analysis of Responses to Ponatinib in Patients With Chronic-Phase Chronic Myeloid Leukemia (CP-CML) by Baseline *BCR::ABL1* Level and Baseline Mutation Status in the OPTIC Trial

CML-047

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Introduction

- Ponatinib is the only approved pan-BCR::ABL1 inhibitor and the only third-generation TKI designed to potently inhibit BCR::ABL1 with or without any single resistance mutation, including T315I[1,2]
- Patients with resistant and intolerant CP-CML with substantial prior treatment demonstrated deep, lasting responses to ponatinib 45 mg once daily in the pivotal phase 2 PACE trial[2,3]
- The phase 2 OPTIC trial prospectively evaluated a response-based dose-reduction strategy to optimize the benefit: risk of ponatinib in patients with CP-CML resistant or intolerant to at least 2 prior second-generation BCR::ABL1 TKI therapies or with a T315I mutation[a]
  - All 3 dosing regimens showed benefit (≤1% *BCR::ABL1*^{IS}) in these largely resistant patients; however, the 45-mg → 15-mg cohort had the optimal benefit:risk

Results

Patient Demographics and Baseline Disease Characteristics

- At baseline, 80.9% of patients had a high (>10% *BCR::ABL1*^{IS}) disease burden; 23.8% had T315I mutation; 17.0% had a mutation other than T315I; and 57.8% had no mutation **(Table 1)**

Table 1. Patient Demographics and Baseline Disease Characteristics

Characteristic	45 mg → 15 mg (N=94)	30 mg → 15 mg (N=94)	15 mg (N=94)
Median (range) age, y	**46 (19–81)**	**51 (21–77)**	**49 (18–81)**
Gender, male, n (%)	**50 (53)**	**38 (40)**	**53 (56)**
ECOG PS score 0 or 1, n (%)	**93 (99)**	**93 (99)**	**94 (100)**
Median (range) time since diagnosis, y	**5.5 (1–21)**	**5.1 (1–29)**	**5.7 (1–22)**
Patients with at least 1 CV risk factor[a], n (%)	**32 (34)**	**30 (32)**	**32 (34)**
Stopped prior TKI for resistance, n (%)	**92 (98)**	**94 (100)**	**94 (100)**
Best response to last prior TKI, n (%)			
CHR or worse	**61 (65)**	**55 (59)**	**57 (61)**
***BCR::ABL1*^{IS} at baseline[b], n (%)**			
≤1% *BCR::ABL1*^{IS}	**3 (3)**	**1 (1)**	**4 (4)**
1–10% *BCR::ABL1*^{IS}	**16 (17)**	**11 (12)**	**15 (16)**
>10% *BCR::ABL1*^{IS}	**74 (79)**	**81 (86)**	**73 (78)**
***BCR::ABL1* mutation, n (%)[c,d]**			
No mutation	**51 (54)**	**58 (62)**	**54 (57)**
Any mutation	**41 (44)**	**35 (37)**	**39 (42)**
T315I	**25 (27)**	**21 (22)**	**21 (22)**
Mutations other than T315I[e]	**16 (17)**	**14 (15)**	**18 (19)**
G250E	**7 (7)**	**2 (2)**	**4 (4)**
F317L	**2 (2)**	**4 (4)**	**2 (2)**
F359V	**1 (1)**	**1 (1)**	**5 (5)**
E255K	**1 (1)**	**2 (2)**	**3 (3)**
V299L	**3 (3)**	**1 (1)**	**2 (2)**
M244V	**1 (1)**	**2 (2)**	**2 (2)**
≥2 mutations detected	**10 (11)**	**6 (6)**	**5 (5)**
≥2 mutations with T315I mutation and another mutation(s)	**3 (3)**	**2 (2)**	**3 (3)**

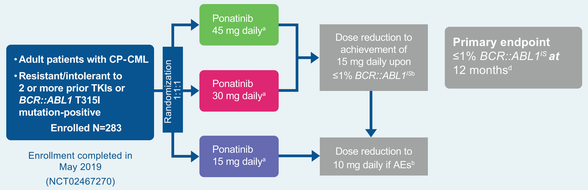
[a] CV risk factors included hypertension, diabetes, and hypercholesterolemia. [b] One patient in the 45-mg cohort, 1 in the 30-mg cohort, and 2 in the 15-mg cohort were missing *BCR::ABL1*^{IS} evaluation at baseline. [c] Sanger sequencing was used for mutation testing. [d] Four patients did not have a mutation test result at baseline. [e] Mutations identified in at least 5 patients (combined for the 3 cohorts) are being presented here.

Objective

Here, we present an in-depth analysis of patient responses from the OPTIC trial (primary analysis data cut-off May 31, 2020) based on baseline *BCR::ABL1* level and mutation status

Methods

Figure 1. OPTIC Trial Design



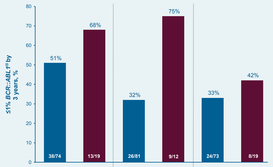
Enrollment completed in May 2019 (NCT02467270)

[a] Dose reductions due to AEs were permitted. [b] Escalation to the starting dose allowed for patients who lost their response following dose reduction; no dose escalation allowed beyond starting dose. [c] Key secondary endpoints: MMR rate at 12 and 24 months, MCyR rate by 12 months, duration of MMR, and safety across the 3 doses. [d] Statistical analysis: N ≥92 patients/cohort distinguished a favorable ≤1% *BCR::ABL1*^{IS} rate of 35% from a null/uninteresting rate of 20% with a nominal 80% power and one-sided type I error rate of 0.0083 (exact binomial test)

- OPTIC (Optimizing Ponatinib Treatment In CP-CML) is an ongoing, multicenter, randomized phase 2 trial
- Median (range) duration of follow-up: 32 months (1–57)

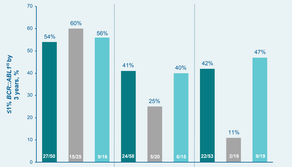
Results

Figure 2. ≤1% *BCR::ABL1*^{IS} Response Rate by Baseline *BCR::ABL1* Level



[a] There is 1 patient from 15-mg cohort without a baseline % *BCR::ABL1*^{IS} value; patient is not included in the graph shown here

Figure 3. ≤1% *BCR::ABL1*^{IS} Response Rate by Mutation Status[a]



[a] Based on ITT population. [b] Does not include patients with unknown baseline mutation status. [c] One patient with ≤1% *BCR::ABL1* by 3 years in 15-mg cohort was excluded from this analysis due to missing *BCR::ABL1* value at baseline

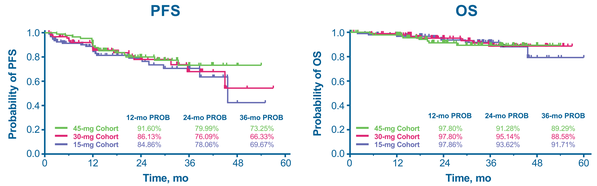
- Patients with higher baseline *BCR::ABL1* levels achieved the highest response rates with 45-mg → 15-mg dosing
- mDoR were all N/R except in T315I mut in the 45-mg cohort (26.9 months; n=15) and in T315I mut in the 30-mg cohort (12.0 months; n=5)

Key Takeaways

Regardless of baseline disease burden and mutation status, patients achieved clinically meaningful response rates with the most success demonstrated in the 45-mg → 15-mg cohort

- Survival outcomes were similar regardless of ponatinib starting dose **(Figure 4)**

Figure 4. Sustained PFS and OS Across All Dosing Cohorts[4]



- Regardless of mutation status, patients treated with ponatinib 45-mg starting dose demonstrated robust survival outcomes **(Figure 5** and **Figure 6)**

Figure 5. PFS for Patients With No Mutations, T315I Mutation, and Mutation Other Than T315I by Dose Cohort

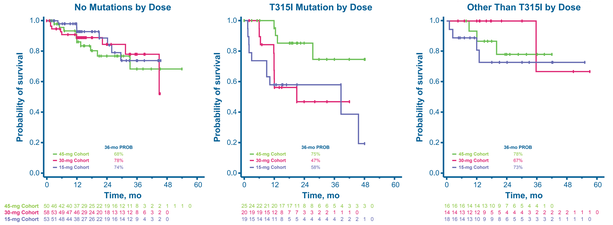
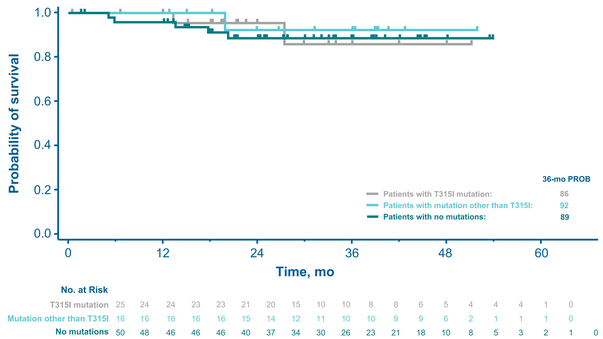


Figure 6. Sustained Overall Survival Regardless of Mutation Status (45-mg Cohort)



Safety

- The overall incidence of TEAEs was similar across dosing cohorts **(Table 2)**

Table 2. Safety Profile Across All Dosing Cohorts

TEAE/TE-AOE, n (%)	45 mg → 15 mg (N=94)	30 mg → 15 mg (N=94)	15 mg (N=94)
Any TEAE	**94 (100)**	**88 (94)**	**89 (95)**
Grade ≥3 TEAE	**64 (68)**	**58 (62)**	**60 (64)**
Serious TEAE	**32 (34)**	**24 (26)**	**31 (33)**
Grade 5 TEAE	**2 (2)**	**0**	**2 (2)**
Dose modifications[a] for TEAE	**69 (73)**	**61 (65)**	**57 (61)**
Discontinuation for TEAE	**18 (19)**	**15 (16)**	**13 (14)**
Any TE-AOE	**9 (10)**	**5 (5)**	**3 (3)**
Serious TE-AOE	**4 (4)**	**4 (4)**	**3 (3)**
Grade ≥3 TE-AOE	**5 (5)**	**5 (5)**	**3 (3)**
Dose modifications[a] for TE-AOE	**5 (5)**	**5 (5)**	**2 (2)**
Discontinuation for TE-AOE	**4 (4)**	**3 (3)**	**1 (1)**

[a] Includes discontinuation, dose reduction, or dose interruption

Conclusions

- The OPTIC post hoc analysis showed clinical benefit across all 3 dosing regimens in these largely resistant patients
  - The 45-mg → 15-mg cohort showed the highest response rates regardless of baseline disease burden and showed the optimal benefit:risk
- Regardless of baseline *BCR::ABL1*^{IS} levels, most patients achieved response (≤1% *BCR::ABL1*^{IS}) by 3 years and the 45-mg → 15-mg cohort had the highest response rate
- Regardless of mutation status, patients treated with ponatinib demonstrated robust survival outcomes
  - For patients with T315I mutations, PFS was greater with 45-mg → 15-mg dosing compared with the other arms
  - Patients with mutations other than T315I also achieved long-term PFS and OS
- The data presented further support the benefit of using ponatinib post–second-generation TKI for patients with resistant disease regardless of baseline disease burden or T315I mutation status

References

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Acknowledgments

We thank all the patients and their families, and the investigators and staff at all clinical sites, for their participation in the study. This study is sponsored by Takeda Development Center Americas, Inc. The authors acknowledge Sarah Huh, PharmD, of Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, USA, for medical writing support for the development of this presentation under the direction of the authors, which was funded by Takeda Pharmaceuticals, USA, Inc., and complied with the Good Publication Practice 3 ethical guidelines (Battisti WP, et al. *Ann Intern Med*. 2015;163:461–4).

Abbreviations

AE, adverse event; CHR, complete hematologic response; CP-CML, chronic-phase chronic myeloid leukemia; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status; IS, International Scale; ITT, intention-to-treat; MCyR, major cytogenetic response; mDoR, median duration of response; MMR, major molecular response; mut, mutation; NR, not reached; OPTIC, Optimizing Ponatinib Treatment In CP-CML; OS, overall survival; PACE, Ponatinib Ph+ ALL and CML Evaluation; PFS, progression-free survival; PROB, probability; TEAE, treatment-emergent adverse event; TE-AOE, treatment-emergent arterial occlusive event; TKI, tyrosine kinase inhibitor; y, year

Disclosures

MD: Consultancy, membership on an entity's board of directors or advisory committees, part of a study management committee and research funding (Blueprint Medicines); consultancy (Fusion Pharma, Medscape, DiscperSol); 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, DiscperSol, Leukemia & Lymphoma Society); **JA:** Honoraria, research funding, and speakers bureau (Incyte, Pfizer); honoraria and speakers bureau (Bristol Myers Squibb, Novartis); **CKA:** Nothing to disclose; **CC:** Honoraria (Novartis, Korea Otsuka Pharmaceutical, Otsuka [Philippines] Pharmaceutical, Steward Cross: Korea Otsuka International Asia Arab, Novartis, Bristol Myers Squibb); travel and research funding (Pfizer); **AH:** Research funding (Bristol Myers Squibb, Novartis, Pfizer, Incyte); **HDL:** Honoraria and Research Funding (Bristol Myers Squibb, Incyte); honoraria (Pfizer, Novartis); **JL:** Consultancy and research funding (Bristol Myers Squibb, ARIAD, Pfizer, Novartis); **EL:** Speakers bureau (Novartis, Pfizer, Fusion Pharma); travel, accommodation, and expenses (Novartis, Pfizer); **JM:** Nothing to disclose; **LM:** Nothing to disclose; **MM:** Consultancy, honoraria, travel, accommodation, expenses, and research funding (Bristol Myers Squibb, Novartis, Takeda, Pfizer); research funding (Sun Pharma/SPARC); **BM:** Speakers bureau (Novartis, Pfizer, Takeda); **CP:** Speakers bureau (Novartis, Pfizer, Bristol Myers Squibb, Pint Pharma); advisory board (Novartis, Pfizer); **GR:** Steering Committee and advisory board (Novartis, Pfizer, Incyte); speakers bureau (Novartis, Incyte, BMD, and Pfizer); **PR:** Consultancy and research funding (Incyte, Pfizer); consultancy (Bristol Myers Squibb, Novartis, Takeda); **MUS:** Advisory Board (AbbVie, Janssen, Novartis, Pfizer, Roche); Speakers Bureau (Janssen, Novartis, Pfizer); **XR:** Employment (Takeda); **AV:** Employment (Takeda); **JC:** Consultancy and research funding (Bristol Myers Squibb, Daiichi Sankyo, Jazz Pharmaceuticals, Astellas, Novartis, Pfizer, Takeda, BioPath Holdings); research funding (Sun Pharma, Telios Pharma, Arog Pharmaceuticals, Merus, ImmunoGen); membership on an entity's board of directors or advisory committees (BioPath Holdings); consultancy (Amphivena Therapeutics, BioLineRx)

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