Post hoc analysis of patient responses by T315I mutation status from the 3-year update of the OPTIC trial: A dose-optimization study of 3 starting doses of ponatinib

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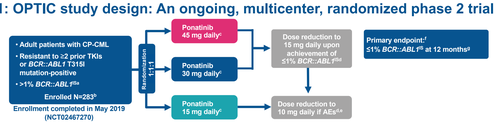
Background

- Patients with chronic-phase chronic myeloid leukemia (CP-CML) harboring the *BCR::ABL1* T315I mutation respond inadequately to first- and second-generation BCR::ABL1 tyrosine kinase inhibitors (TKIs), leading to poor survival outcomes[1,2]
- Ponatinib is the only *BCR::ABL1* inhibitory TKI currently approved to potently inhibit all known native and single resistance-mutation variants of *BCR::ABL1*, including T315I[2]
- OPTIC (Optimizing Ponatinib Treatment in CP-CML, NCT02467270) is a phase 2 trial evaluating the efficacy and safety of ponatinib using a novel, response-based dose-adjustment strategy in patients with CP-CML whose disease is resistant to ≥2 TKIs or who harbor T315I[3]
- Here we present a post hoc analysis of patient responses by T315I mutation status from the OPTIC trial 3-year data cut

Methods

Figure 1: OPTIC study design: An ongoing, multicenter, randomized phase 2 trial



[a] As shown by quantitative real-time polymerase chain reaction
[b] 99% of patients were TKI-resistant; 61% had a best response to their last prior therapy of complete hematologic response or worse; 84% had a best response to prior therapy of >10% *BCR::ABL1*[IS]
[c] Dose reductions due to AEs were permitted
[d] Escalation to the starting dose was allowed for patients who lost their response following dose reduction; no dose escalation was allowed beyond starting dose
[e] Dose reduction below 10 mg was not permitted during the main treatment period, but reduced dosing frequency was permitted during the treatment continuation period
[f] Secondary endpoints: MMR rate at 12 and 24 months and MCyR rate by 12 months, duration of MMR, and safety across the 3 doses
[g] Statistical analysis: n ≥92 patients/cohort distinguished a favorable ≤1% *BCR::ABL1*[IS] rate of 35% from a null or uninteresting rate of 20% with a nominal 80% power and 1-sided type I error rate of 0.0083 (exact binomial test)
AE, adverse event; MCyR, major cytogenetic response; MMR, major molecular response

- At the 3-year analysis data cutoff date (May 9, 2022), median duration of follow-up was 54 months in the 45-mg cohort, 51 months in the 30-mg cohort, and 55 months in the 15-mg cohort
- In the 45-mg, 30-mg, and 15-mg cohorts, 44%, 27%, and 29% of patients were still on treatment at the data cutoff date, respectively

Results

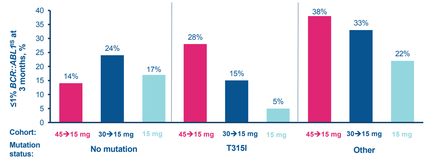
Table 1: Demographics and baseline disease characteristics

Characteristic	Subcategory	45 mg→15 mg (n=94)	30 mg→15 mg (n=94)	15 mg (n=94)
Age, years, median (range)		46 (19–81)	51 (21–77)	49 (18–81)
Male, n (%)		50 (53)	38 (40)	53 (56)
ECOG PS score 0 or 1, n (%)		93 (99)	93 (99)	94 (100)
Time since diagnosis, years, median (range)		5.5 (1–21)	5.1 (1–29)	5.7 (1–22)
Patients with CV risk factors, n (%)	Arterial hypertension	26 (28)	25 (27)	22 (23)
	Diabetes mellitus	5 (5)	3 (3)	7 (7)
	Hyperlipidemia	19 (20)	14 (15)	16 (17)
Patients with ≥2 CV risk factors, n (%)		5 (5)	4 (4)	3 (3)
Prior TKIs, n (%)	1	1 (1)	1 (1)	4 (4)
	2	43 (46)	37 (39)	42 (45)
	≥3	50 (53)	56 (60)	48 (51)
Stopped prior TKI for resistance, n (%)		92 (98)	94 (100)	94 (100)
BCR::ABL1 mutation, n (%)	No mutation	51 (54)	58 (62)	54 (57)
	T315I mutation	25 (27)	21 (22)	21 (22)
	Other mutations	16 (17)	14 (15)	18 (19)
Best response to last prior TKI, n (%)	CHR or worse	61 (65)	55 (59)	57 (61)
	≤1% *BCR::ABL1*[IS] or better	2 (2)	7 (7)	7 (7)

CHR, complete hematologic response; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status

- In the overall population, ≤1% *BCR::ABL1*[IS] response rate at 36 months was 60%, 40%, and 40% for the 45-mg, 30-mg, and 15-mg cohorts, respectively
- ≤1% *BCR::ABL1*[IS] response rate at 3 and 36 months was highest in the 45-mg cohort regardless of mutation status (**Figure 2, 3**)
- Median duration of exposure at 36 months was 84 days across all dosing cohorts
- In patients with no mutation or a mutation other than T315I, median duration of response (mDOR) was not reached in any dosing cohort
- In patients with the T315I mutation, mDOR was 16.7 months in the 45-mg cohort, 12.04 months in the 30-mg cohort, and was not reached in the 15-mg cohort

Figure 2: ≤1% *BCR::ABL1*[IS] response rate at mutation status at 3 months[a,b]



[a] Number of subjects with ≤1% *BCR::ABL1*[IS] are counted on cumulative basis by each time point, and a subject with response is counted only once. Percentages are based on a number of subjects in each cohort as denominator
[b] Analysis conducted in the ITT population

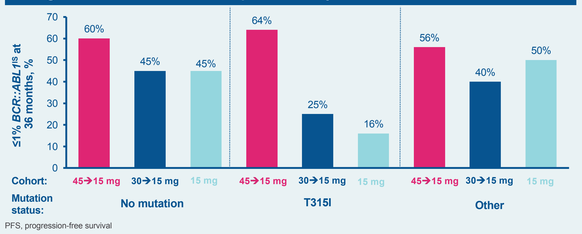
Objective

To assess the results from the OPTIC trial at the 3-year data cutoff date by mutation status

Results

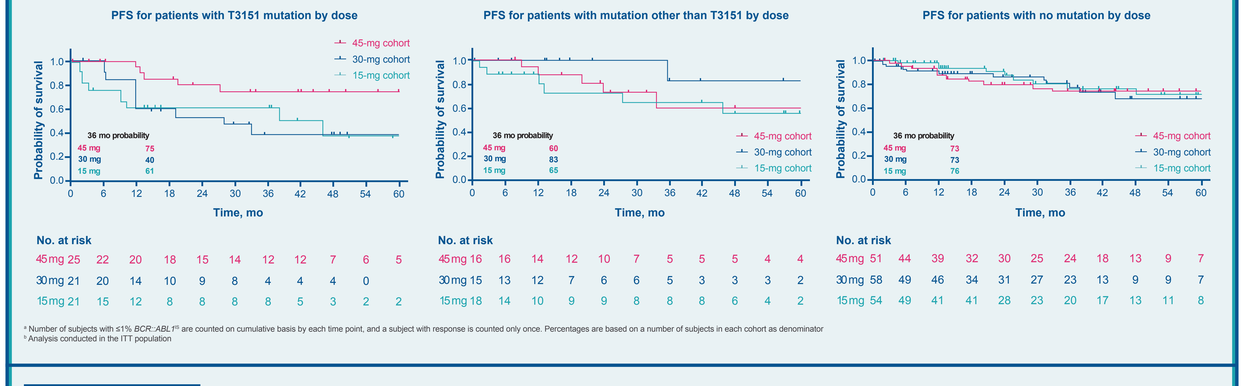
- By 36 months, median PFS in the overall population was 72.5, 67.1, and 69.7 months in the 45-mg, 30-mg, 15-mg cohorts, respectively
- Median PFS was not reached in any dosing cohort for patients with no *BCR::ABL1* mutation (**Figure 4**)
- In patients with the T315I mutation, median PFS was not reached in the 45-mg cohort and was 28.4 months and 45.6 months in the 30-mg and 15-mg cohorts, respectively
- Median PFS was not reached in any dosing cohort for patients with a mutation other than T315I

Figure 3: ≤1% *BCR::ABL1*[IS] response rate by mutation status at 36 months[a,b]



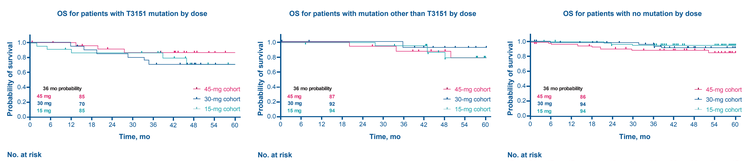
PFS, progression-free survival

Figure 4: PFS for patients with no mutations, T315I mutation, and mutation other than T315I by dose cohort



[a] Number of subjects with ≤1% *BCR::ABL1*[IS] are counted on cumulative basis by each time point, and a subject with response is counted only once. Percentages are based on a number of subjects in each cohort as denominator
[b] Analysis conducted in the ITT population

Figure 5: OS for patients with no mutations, T315I mutation, and mutation other than T315I by dose cohort



OS, overall survival

- Median OS was not reached in any dosing cohort for patients in all mutation subgroups (**Figure 5**)
- Few patients lost response, regardless of mutation status, in the 45-mg and 30-mg cohorts (**Table 2**)
  - Of the patients who lost response, most re-achieved ≤1% *BCR::ABL*[IS] after dose re-escalation

Table 2: Dose re-escalation after loss of response[a] (intent-to-treat population)

Characteristic	No mutation		T315I		Other	
	45 mg→15 mg (N=50)	30 mg→15 mg (N=58)	45 mg→15 mg (N=25)	30 mg→15 mg (N=20)	45 mg→15 mg (N=16)	30 mg→15 mg (N=15)
Achieved ≤1% *BCR::ABL1*[IS] at any time, n	30	27	16	5	9	6
Loss of ≤1% *BCR::ABL1*[IS] at any time, n	4	6	9	3	2	0
Dose re-escalated after loss of response, n	3	3	8	2	2	0
Regained ≤1% *BCR::ABL1*[IS]						
Yes, n (%)	2 (67)	3 (100)	6 (75)	1 (50)	1 (50)	0
No, n (%)	1 (33)	0	2 (25)	1 (50)	1 (50)	0

[a] Includes all patients who had the first dose reduction to 15 mg occurred after MR2 achieved
[b] Numbers reported for the entire 45-mg and 30-mg cohorts

Key takeaways

At the 3-year data cutoff, ponatinib treatment resulted in long-term survival in patients with CP-CML resistant to second-generation *BCR::ABL1* TKI therapy, regardless of the presence of *BCR::ABL1* mutations

Safety

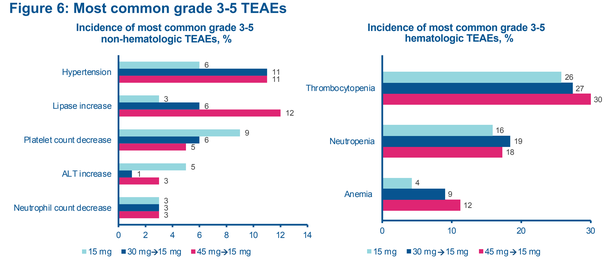
- Most common nonhematologic grade ≥3 TEAEs in the overall population were hypertension (9%), lipase increase (7%), and platelet count decrease (7%) (**Figure 6**)
- Most common hematological grade ≥3 TEAEs in the overall population were thrombocytopenia (27%) and neutropenia (18%)
- There were no grade 5 TE-AOEs in any dosing cohort (**Table 4**)
- Exposure-adjusted AOE rates were 4.48% (95% CI 1.69, 7.26), 3.01% (95% CI 0.56, 5.46), and 1.92% (95% CI 0.04, 3.81) in the 45-mg, 30-mg, and 15-mg cohorts, respectively

Table 3: TEAE summary and related dose modifications and discontinuations

Characteristic	45 mg→15 mg (n=94)	30 mg→15 mg (n=94)	15 mg (n=94)
TEAEs, n (%)			
Any TEAE	94 (100)	91 (97)	92 (98)
Grade 3–4 TEAEs	63 (67)	60 (64)	59 (63)
Serious TEAEs	35 (37)	31 (33)	37 (39)
Grade 5 TEAEs[a]	3 (3)	1 (1)	3 (3)
Dose modification for TEAEs, n (%)			
Discontinuation[b]	21 (22)	17 (18)	16 (17)
Reduction	46 (49)	34 (36)	30 (32)
Interruption	73 (78)	63 (67)	58 (62)

[a] Includes deaths that occurred up to 30 days after the last ponatinib dose
[b] All TEAEs with 'Drug Withdrawn' as the action taken

Figure 6: Most common grade 3-5 TEAEs



ALT, alanine transaminase

Table 4: TE-AOE summary and related dose modifications and discontinuations

Characteristic	No mutation			T315I			Other		
	45 mg→15 mg (N=51)	30 mg→15 mg (N=58)	15 (N=51)	45 mg→15 mg (N=25)	30 mg→15 mg (N=21)	15 (N=21)	45 mg→15 mg (N=16)	30 mg→15 mg (N=14)	15 (N=18)
TE-AOEs, n (%)									
Any TE-AOE	4 (8)	1 (2)	3 (6)	2 (8)	3 (14)	1 (5)	5 (31)	2 (14)	0
Grade 3–4 TE-AOEs	2 (4)	1 (2)	3 (6)	1 (4)	3 (14)	1 (5)	3 (19)	2 (14)	0
Grade 5 TE-AOEs	0	0	0	0	0	0	0	0	0
Dose modifications for TE-AOE, n (%)									
Discontinuation	2 (4)	1 (2)	1 (2)	0	1 (5)	0	3 (19)	2 (14)	0
Reduction	0	0	0	0	2 (10)	0	0	0	0
Interruption	0	0	1 (2)	1 (4)	2 (10)	1 (5)	2 (13)	1 (7)	0

TE, treatment-emergent

Conclusions

- This global, multicenter, prospective, phase 2 study is the first to evaluate a response-based dose-reduction strategy to optimize the benefit:risk ratio of TKI therapy in patients with CP-CML
- Clinical benefit was observed at all 3 ponatinib dosing regimens in this highly resistant patient population; however, patients in the 45-mg→15-mg treatment arm had the best response regardless of T315I mutation status
- Patients with a T315I mutation at baseline had the greatest benefit in the 45-mg→15-mg cohort
- At this 3-year analysis, response-based ponatinib dosing regimens demonstrated long-term manageable safety, including exposure-adjusted AOE rates (<5%)
- Observed responses were associated with robust long-term survival in patients with CP-CML resistant to second-generation BCR::ABL1 TKI therapy, regardless of the presence of *BCR::ABL1* mutations

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