4-year results with ponatinib by mutation status in patients with chronic-phase chronic myeloid leukemia (CP-CML): OPTIC study

CLL-431

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Background

- Patients with CP-CML and the *BCR::ABL1* T315I mutation often develop resistance to first- and second-generation BCR::ABL1 tyrosine kinase inhibitors (TKIs), leading to poor survival[1–3]
- Ponatinib is the only approved BCR::ABL1 TKI that potently inhibits native BCR::ABL1 and all known single-mutation variants associated with resistance, including T315I[2,3]
- The phase 2 OPTIC study is assessing the efficacy and safety of response-based ponatinib dosing in patients with CP-CML whose disease is resistant to ≥2 TKIs or who harbor T315I[1]
- Results from the OPTIC primary analysis demonstrated robust efficacy of ponatinib in the overall CP-CML population and in patients with CP-CML and the T315I mutation[1]
- This post hoc analysis evaluated 4-year results from OPTIC by T315I mutation status

Methods

- This subanalysis of 4-year data from the OPTIC study **(Figure 1)** assessed *BCR::ABL1*^{IS} response rates, progression-free survival (PFS), overall survival (OS), and safety in patients with and without the T315I mutation

Figure 1: Study design



[a]Dose reductions due to AEs were permitted. [b]Escalation to the starting dose was allowed for patients who lost their response following dose reduction; no dose escalation was allowed beyond the starting dose. [c]Dose reduction below ponatinib 10 mg was not permitted during the main treatment period, but reduced dosing frequency was permitted during the treatment continuation period. [d]Secondary endpoints included MR4 and MR4.5 by and at 3-month intervals, PFS, OS, and safety. AE, adverse event.

Results

Patients

- At the data cutoff for the 4-year analysis (May 8, 2023), median follow-up in patients with the T315I mutation was 60.6, 63.5, and 60.7 months in the 45-mg, 30-mg, and 15-mg cohorts, respectively
- Demographics and baseline disease characteristics were similar across the 3 dose cohorts **(Table 1)**

Table 1: Demographics and baseline disease characteristics (safety population)

Characteristic	Subcategory	45 mg →15 mg (n=94)	30 mg →15 mg (n=95)	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 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[a] or 2	44 (47)	38 (40)	46 (49)
	≥3	50 (53)	56 (60)	48 (51)
Stopped prior TKI for resistance, n (%)		92 (98)	94 (100)	94 (100)
***BCR::ABL1* mutation,[b] 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)

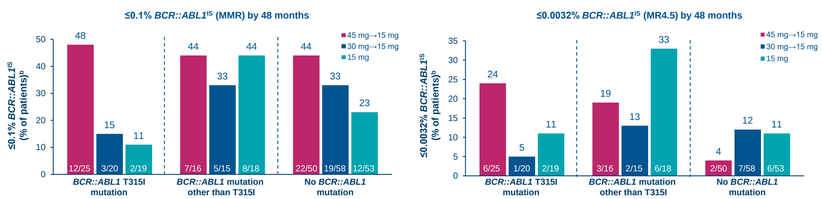
[a]Patients with 1 prior TKI: 45-mg cohort: n=1; 30-mg cohort: n=1; 15 mg cohort: n=4. [b]Five patients (45 mg, n=2; 30 mg, n=1; 15 mg, n=2) did not have mutation testing performed at baseline.
CHR, complete hematologic response; CV, cardiovascular; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

- At 48 months, 22, 18, and 65 patients remained on treatment in the T315I, other mutation, and no mutation cohorts, respectively

Efficacy

- Response rates for ≤0.1% *BCR::ABL1*^{IS} (major molecular response [MMR]) and ≤0.0032% *BCR::ABL1*^{IS} (MR4.5) by 48 months for the 45-mg cohort were highest in patients with the T315I mutation **(Figure 2)**
- Despite low patient numbers in each group, trends supported efficacy of the ponatinib 45-mg dosing regimen across all subgroups

Figure 2: Rates of ≤0.1% *BCR::ABL1*^{IS} (MMR) and ≤0.0032% *BCR::ABL1*^{IS} (MR4.5) by 48 months[a]



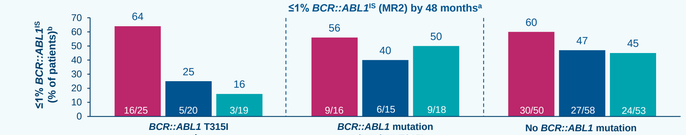
[a]Analysis conducted in the ITT population. [b]Number of patients with each type of *BCR::ABL1*^{IS} response is counted on cumulative basis by each time point, and a patient with response is counted only once.

Question Is ponatinib effective in patients with CP-CML harboring the T315I mutation?

Study design Adults with CP-CML with resistance to ≥2 prior TKIs or the T315I mutation → Ponatinib dose cohorts: • 45 mg →15 mg • 30 mg →15 mg • 15 mg → *BCR::ABL1*^{IS} transcript levels

Results

- The percentage of patients with ≤1% *BCR::ABL1*^{IS} (MR2) by 48 months was highest in the 45-mg cohort
- The difference in response between dosing cohorts was highest for patients with T315I

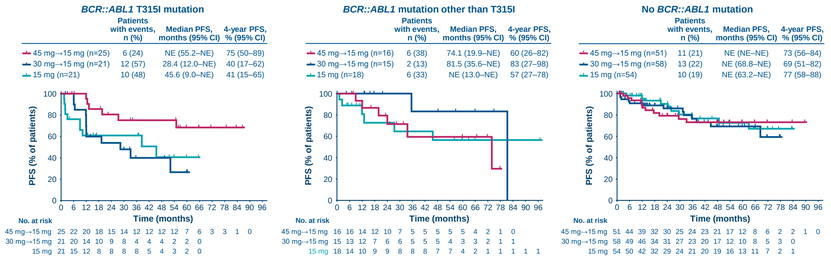


[a]Analysis conducted in the ITT population. [b]Number of patients with ≤1% *BCR::ABL1*^{IS} is counted on cumulative basis by each time point, and a patient with response is counted once.
ITT, intent-to-treat.

Key takeaway Results from these post hoc analyses of the 4-year follow-up of the OPTIC study support ponatinib's long-term efficacy in patients with the T315I mutation

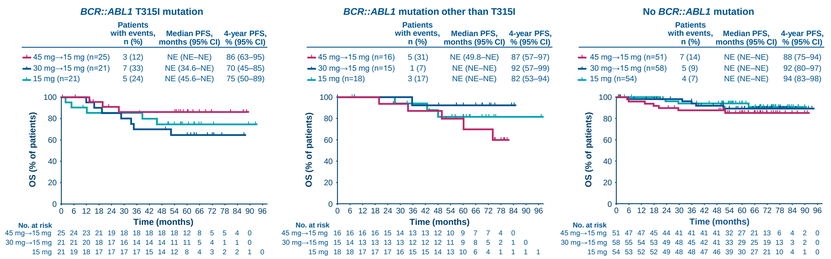
- In the 45-mg cohort, median PFS was not reached in patients with the T315I mutation or those with no *BCR::ABL1* mutation **(Figure 3)**

Figure 3: PFS by mutation status and dosing cohort



- Median OS was not reached at the 4-year analysis regardless of mutation status across all dosing cohorts **(Figure 4)**

Figure 4: OS by mutation status and dosing cohort



Dose modifications

- Dose reductions for efficacy and re-escalations after loss of response were successful in maintaining ≤1% *BCR::ABL1*^{IS} **(Table 2)**
- Of the patients who achieved response at any time but subsequently lost response, most regained ≤1% *BCR::ABL1*^{IS} after dose re-escalation

Table 2: Dose reductions for efficacy and re-escalations after loss of response[a,b]

Characteristic	T315I mutation: 45 mg →15 mg (n=25)	T315I mutation: 30 mg →15 mg (n=20)
Achieved ≤1% *BCR::ABL1*^{IS} at any time, n (%)	16 (64)	5 (25)
Dose reduced for efficacy, n (%)	15 (94)	5 (100)
Maintained response, n (%)	7 (47)	2 (40)
Loss of ≤1% *BCR::ABL1*^{IS} at any time, n (%)	9[c] (60)	3 (60)
Dose re-escalated after loss of response, n (%)	8 (89)	2 (67)
Regained ≤1% *BCR::ABL1*^{IS} after re-escalation		
Yes	6 (75)	1 (50)
No	2 (25)	1 (50)

[a]Includes all patients who had first dose reduction to 15 mg after achieving ≤1% *BCR::ABL1*^{IS}. [b]ITT population. [c]One patient did not have dose a reduction to 15 mg upon achieving ≤1% *BCR::ABL1*^{IS}; this patient lost response after achieving ≤1% *BCR::ABL1*^{IS}.

Safety

- Treatment-emergent adverse events (TEAEs) and dose modifications were comparable across dosing cohorts in patients with the T315I mutation **(Table 3)**
- The incidence of TEAEs was comparable across mutation status and dosing cohorts

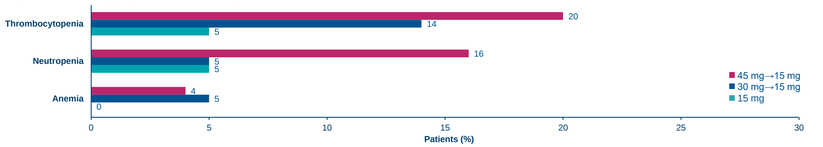
Table 3: TEAEs and dose modifications in patients with the T315I mutation

TEAEs	T315I mutation: 45 mg →15 mg (n=25)	T315I mutation: 30 mg →15 mg (n=21)	T315I mutation: 15 mg (n=21)
TEAEs, n (%)			
Any TEAE	25 (100)	20 (95)	20 (95)
Grade 3–4	13 (52)	7 (33)	6 (29)
Serious	9 (36)	7 (33)	6 (29)
Grade 5[a]	2 (8)	1 (5)	2 (10)
Dose modification for TEAEs, n (%)			
Discontinuation[b]	2 (8)	3 (14)	1 (5)
Reduction	12 (48)	5 (24)	1 (5)
Interruption	16 (64)	10 (48)	8 (38)

[a]Includes deaths that occurred up to 30 days after the last ponatinib dose. [b]All TEAEs with "drug withdrawn" as the action taken.

- The most common hematologic grade ≥3 TEAEs were thrombocytopenia, neutropenia, and anemia **(Figure 5)**

Figure 5: Hematologic grade ≥3 TEAEs in patients with the T315I mutation



- Rates of treatment-emergent arterial occlusive events (TE-AOEs) were low across dosing cohorts in patients with the T315I mutation **(Table 4)**

Table 4: TE-AOEs and dose modifications in patients with the T315I mutation

TE-AOEs	T315I mutation: 45 mg →15 mg (n=25)	T315I mutation: 30 mg →15 mg (n=21)	T315I mutation: 15 mg (n=21)
TE-AOEs, n (%)			
Any TE-AOE	2 (8)	3 (14)	1 (5)
Grade 3–4	1 (4)	3 (14)	1 (5)
Grade 5	0	0	0
Dose modifications for TE-AOEs, n (%)			
Discontinuation	0	1 (5)	0
Reduction	0	2 (10)	0
Interruption	1 (4)	2 (10)	1 (5)
Exposure-adjusted AOEs, patients with events/100 PY, % (95% CI)	2.37 (0.00–5.74)	7.32 (0.00–15.64)	2.83 (0.00–7.99)

PY, patient years.

- Rates of TE-AOEs were generally low across dosing cohorts regardless of mutation status, and there were no deaths due to TE-AOEs

Conclusions

- Results of these post hoc analyses of the 4-year follow-up of the OPTIC study support ponatinib's long-term efficacy and manageable safety profile in patients with the T315I mutation
  - In the 45-mg cohort, 64% of patients with the T315I mutation achieved ≤1% *BCR::ABL1*^{IS} (MR2) response with a low rate of discontinuations (8%) due to TEAEs
- Although some of the mutation and dose subgroups had small numbers of patients, the observed trends support ponatinib efficacy in patients with CP-CML with and without a T315I mutation and results are consistent with previous analyses of the OPTIC study[1]
- Response-based dosing of ponatinib demonstrated long-term manageable safety, including a low rate of exposure-adjusted AOEs of approximately 2% in the 45-mg cohort
- Observed responses were associated with robust long-term survival in patients with CP-CML resistant to second-generation BCR::ABL1 TKIs with or without the T315I mutation; neither PFS nor OS were mature in the 45-mg cohort in patients with the T315I mutation

References

1. Cortes J, et al. Blood 2021;138:2042–50.
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3. O'Hare T, et al. Cancer Cell 2009;16:401–12.

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