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

CML-313

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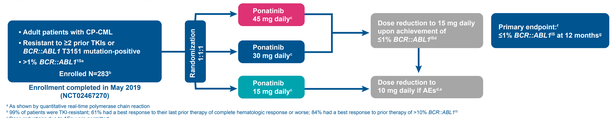
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Background

- 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, the only approved all known BCR::ABL1 inhibitor, is a third-generation TKI designed to potently inhibit BCR::ABL1 with or without any single resistance mutation, 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 41% *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

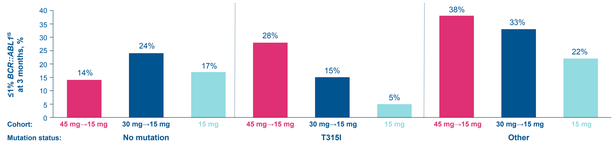
Table 1: Demographics and baseline disease characteristics

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 3 months by mutation status[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

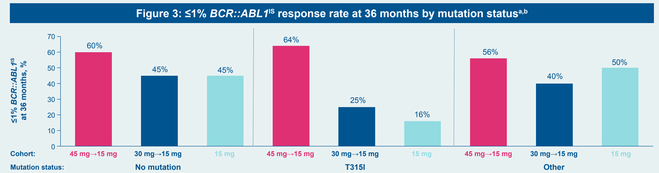
Objective

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

Results

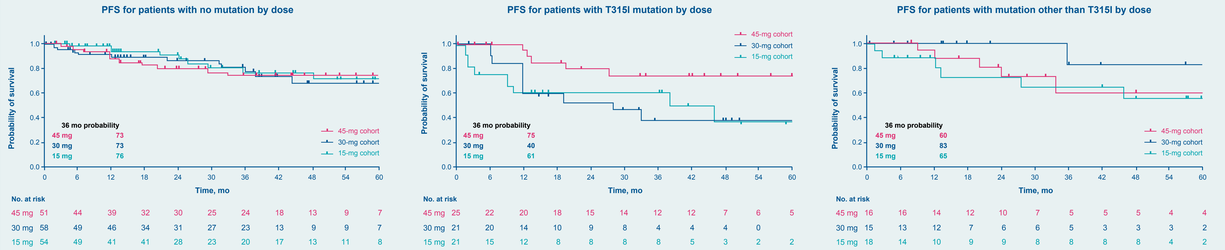
- By 36 months, median PFS in the overall population was 72.5, 67.1, and 69.7 months in the 45-mg, 30-mg, 15-mg cohorts, respectively
- Median PFS was not reached in any dosing cohort for patients with no *BCR::ABL1* mutation (**Figure 4**)
- In patients with the T315I mutation, median PFS was not reached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



PFS, progression-free survival

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

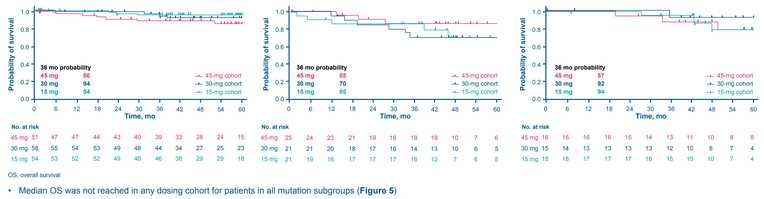


[a] Number of subjects with ≤1% *BCR::ABL1*[IS] are counted on cumulative basis by each time point, and a subject with response is counted only once. Percentages are based on a number of subjects in each cohort as denominator
[b] Analysis conducted in the ITT population

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

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::ABL1*[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

Safety

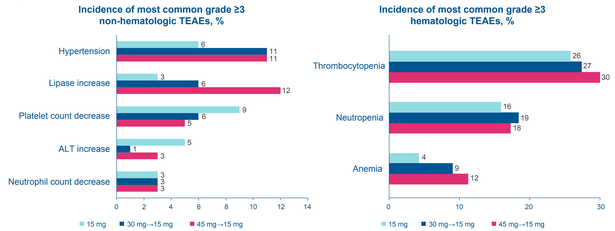
- Most common nonhematologic grade ≥3 TEAEs in the overall population were hypertension (9%), lipase increase (7%), and platelet count decrease (7%) (**Figure 6**)
- Most common hematological grade ≥3 TEAEs in the overall population were thrombocytopenia (27%) and neutropenia (18%)
- There were no grade 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 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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