Dose-optimization study of 3 starting doses of ponatinib: Long-term results from the OPTIC trial

CML-425

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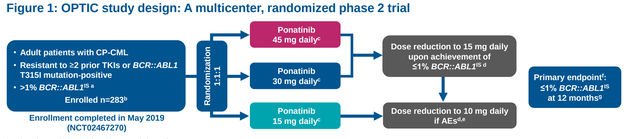
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Background

- Ponatinib is a BCR::ABL1 tyrosine kinase inhibitor (TKI) that potently inhibits native BCR::ABL1 and all reported single-resistance mutants, including T315I[1,2]
- Patients with chronic-phase chronic myeloid leukemia (CP-CML) who become resistant to a second-generation BCR::ABL1 TKI, with or without point mutations in *BCR::ABL1*, have poor long-term outcomes when treated with another second-generation BCR::ABL1 TKI[1,2]
- The phase 2 OPTIC trial (NCT02467270) is evaluating the efficacy and safety of ponatinib in patients with CP-CML whose disease is resistant to ≥2 TKIs or who harbor T315I[3]
  - OPTIC used a novel response-based dose-adjustment strategy in which patients were randomized to once-daily 45-, 30-, or 15-mg ponatinib starting doses, with dose reduction to 15 mg upon achievement of ≤1% *BCR::ABL1*^{IS} in the 45-mg and 30-mg cohorts
- Results from the OPTIC primary analysis demonstrated an improved risk:benefit ratio for the 45-mg/d starting dose cohort
- We present here the 4-year update with long-term efficacy and safety outcomes from OPTIC

Methods

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



[a]As shown by quantitative real-time polymerase chain reaction.
[b]99% of patients were TKI-resistant.
[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]Key secondary endpoints: MMR rate at 12 and 24 months and MCyR rate by 12 months, duration of MMR, and safety across the 3 doses; others include PFS, OS, and DOR in responders.
[g]Statistical analysis: n/d2 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; DOR, duration of response; MCyR, major cytogenetic response; MMR, major molecular response; PFS, progression-free survival; OS, overall survival.

Results

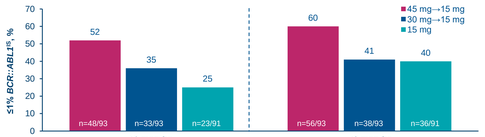
Table 1: Demographics and baseline disease characteristics

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**	**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, Eastern Cooperative Oncology Group; PS, performance status.

- At the 4-year analysis data cutoff date (May 8, 2023), median duration of follow-up was 63 months in the 45-mg cohort, 65 months in the 30-mg cohort, and 63 months in the 15-mg cohort
- ≤1% *BCR::ABL1*^{IS} response rate by 12 months (primary endpoint) and 48 months was highest in the 45-mg cohort **(Figure 2)**
  - Response rates improved from 12 months to 48 months

Figure 2: ≤1% *BCR::ABL1*^{IS} response rate by 12 and 48 months[a,b]



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

- ≤0.1% *BCR::ABL1*^{IS} response rate was highest in the 45-mg cohort by 48 months **(Figure 3)**
- Rates of ≤0.01% and ≤0.0032% *BCR::ABL1*^{IS} were similar between cohorts by 48 months **(Figure 3)**
- ≤1% *BCR::ABL1*^{IS} response rate was also highest in the 45-mg cohort regardless of mutation status **(Figure 4)**
- Median DOR was not reached in any dosing cohort

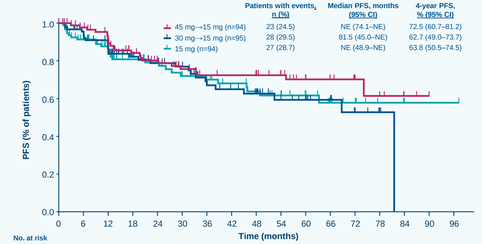
Question Did ponatinib provide long-term PFS benefit for patients in the OPTIC study?

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

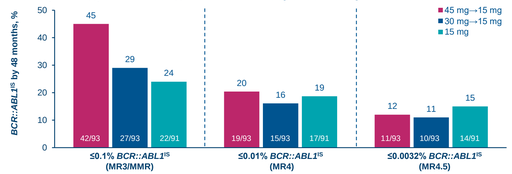
- By 48 months, the progression-free survival (PFS) rate was highest in the 45-mg cohort

PFS in the 45-mg, 30-mg, and 15-mg starting dose cohorts



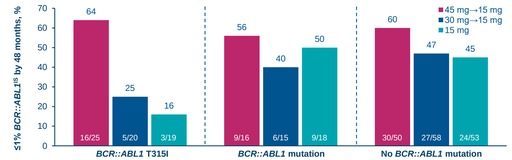
Key takeaway At the 4-year data cutoff, ponatinib treatment resulted in robust long-term PFS in patients with CP-CML resistant to second-generation BCR::ABL1 TKI therapy

Figure 3: ≤0.1%, ≤0.01%, and ≤0.0032% *BCR::ABL1*^{IS} response rate by 48 months[a,b]



[a]Response by each time point means the best outcome up to each time point after randomization.
[b]Analysis conducted in the intent-to-treat population.
MR, molecular response.

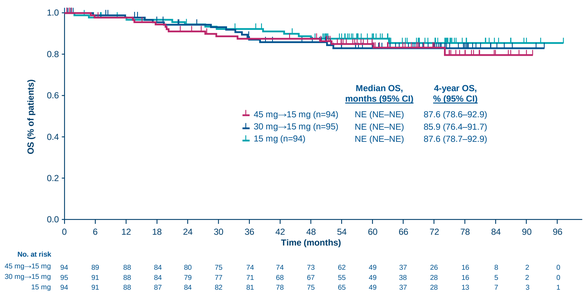
Figure 4: ≤1% *BCR::ABL1*^{IS} response rate by 48 months by mutation status at baseline[a,b]



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

- OS was similar between all dosing cohorts **(Figure 5)**

Figure 5: OS in the 45-mg, 30-mg, and 15-mg starting dose cohorts



- Of the patients who achieved ≤1% *BCR::ABL1*^{IS}, 80.4% (45/56) and 71.1% (27/38) in the 45-mg and 30-mg cohorts, respectively, had dose reductions to 15 mg upon achieving ≤1% *BCR::ABL1*^{IS}
  - 11 patients did not have dose reductions upon achieving ≤1% *BCR::ABL1*^{IS}, including 6 dose reductions for AEs (3 maintained response), 2 discontinuations for AEs, and 3 lost to follow-up/other
- Few patients lost response in the 45-mg and 30-mg cohorts **(Table 2)**
  - Of the patients who lost response, most regained ≤1% *BCR::ABL1*^{IS} after dose re-escalation
  - Of the patients who did not regain response, 3 discontinued due to AE or progressive disease, and 1 remains on treatment
- The median time to regain response after dose re-escalation among patients who achieved ≤1% *BCR::ABL1*^{IS} response was 126 days (95% CI, 39–167) in the 45-mg cohort and was not estimable in the 30-mg cohort due to low patient numbers

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

Characteristic	45 mg →15 mg (n=93)	30 mg →15 mg (n=93)
Achieved ≤1% *BCR::ABL1*^{IS} at any time, n (%)	**56 (60)**	**38 (41)**
Loss of ≤1% *BCR::ABL1*^{IS} at any time, n (%)	**15 (27)**	**9 (24)**
Dose re-escalated after loss of response, n (%)	**13 (87)**	**5 (56)**
Regained ≤1% *BCR::ABL1*^{IS} after re-escalation		
Yes	**9 (69)**	**4 (80)**
No	**4 (31)**	**1 (20)**

[a]Includes all patients who had the first dose reduction to 15 mg after ≤1% *BCR::ABL1*^{IS} achieved.

Safety

- The incidence of grade 3–4 treatment-emergent AEs (TEAEs) and serious TEAEs was similar across dosing cohorts **(Table 3)**
- In **Figure 6**, the bar graphs indicate the number of patients by year who experienced particular TEAEs
  - The most common nonhematologic grade ≥3 TEAEs in the overall population were hypertension (10%) and lipase increase (7%)
  - The most common hematologic grade ≥3 TEAEs in the overall population were thrombocytopenia (27%) and neutropenia (18%)
  - Across the most common TEAEs, the number of TEAEs decreased from year 1 through subsequent years
- No grade 5 treatment-emergent arterial occlusive events (TE-AOEs) occurred in any dosing cohort **(Table 4)**

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)**	**92 (98)**	**92 (98)**
Grade 3–4 TEAEs	**66 (70)**	**62 (66)**	**61 (65)**
Serious TEAEs	**37 (39)**	**32 (34)**	**37 (39)**
Grade 5 TEAEs[a]	**4 (4)**	**2 (2)**	**3 (3)**
Dose modification for TEAEs, n (%)			
Discontinuation[b]	**21 (22)**	**18 (19)**	**16 (17)**
Reduction	**47 (50)**	**35 (37)**	**31 (33)**
Interruption	**76 (81)**	**64 (68)**	**60 (64)**

[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 by year of treatment

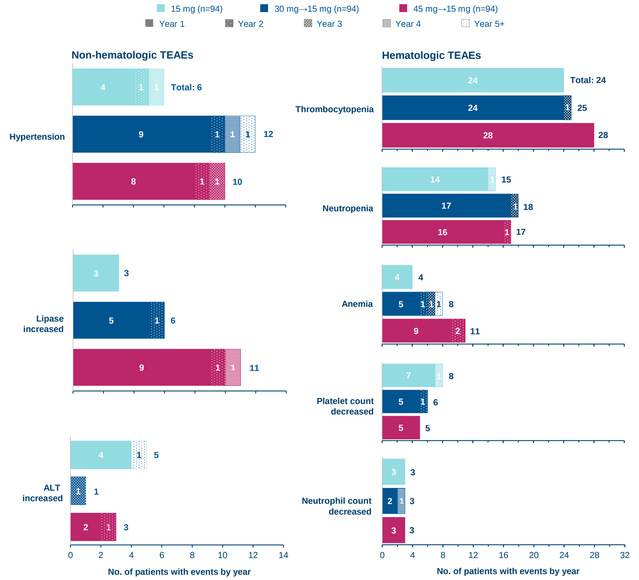


Table 4: TE-AOE summary and related dose modifications and discontinuations

Characteristic	45 mg →15 mg (n=94)	30 mg →15 mg (n=94)	15 mg (n=94)
TE-AOEs, n (%)			
Any TE-AOE	**11 (12)**	**8 (9)**	**4 (4)**
Grade 3–4 TE-AOEs	**6 (6)**	**7 (7)**	**4 (4)**
Grade 5 TE-AOEs	**0**	**0**	**0**
Dose modifications for TE-AOEs, n (%)			
Discontinuation	**5 (5)**	**4 (4)**	**1 (1)**
Reduction	**0**	**2 (2)**	**0**
Interruption	**3 (3)**	**5 (5)**	**2 (2)**
Exposure-adjusted AOEs, patients with events/100 person-years (95% CI)	**3.87 (1.45–6.30)**	**3.66 (1.11–6.20)**	**1.73 (0.02–3.44)**

Conclusions

- Results from the 4-year follow-up of the OPTIC study support ponatinib's long-term efficacy and manageable safety profile in patients with highly resistant CP-CML
- These results are consistent with previous analyses of the OPTIC trial and demonstrate that a ponatinib starting dose of 45 mg/d with reduction to 15 mg/d upon attainment of ≤1% *BCR::ABL1*^{IS} continued to provide the optimal risk:benefit ratio
  - High response rates were observed in the 45-mg cohort, regardless of mutation status, along with improved PFS over the 30-mg and 15-mg cohorts
- The maintenance benefit with ponatinib was also demonstrated, with ≤1% *BCR::ABL1*^{IS} response rates maintained or improved from 12 months to 48 months
- At this 4-year analysis, response-based ponatinib dosing regimens demonstrated long-term manageable safety, including a low rate of exposure-adjusted AOEs
- Observed responses were associated with robust long-term survival in patients with CP-CML resistant to second-generation BCR::ABL1 TKI therapy

References

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2. Cortes JE, et al. N Engl J Med 2013;369:1783–96.
3. Cortes J, Lang F. J Hematol Oncol 2021;14:44.

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