Efficacy, safety, and end-of-treatment mutational results in patients with chronic-phase chronic myeloid leukemia: 5-year follow-up of the phase 2 OPTIC study

CML-641

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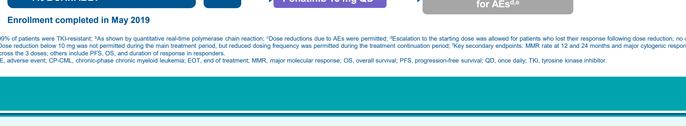
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Introduction

- Ponatinib, a BCR::ABL1 tyrosine kinase inhibitor (TKI), potently inhibits BCR::ABL1 and all clinically relevant single mutations, including T315I[1,2]
- The phase 2 OPTIC trial (NCT02467270) aimed to optimize efficacy and safety of ponatinib by evaluating 3 dosing strategies in patients with chronic-phase chronic myeloid leukemia (CP-CML) resistant to ≥2 TKIs or a T315I mutation[3]
  - Optimal benefit:risk outcomes were observed with a once-daily (QD) 45-mg ponatinib starting dose and dose reduction to 15 mg QD upon achievement of *BCR::ABL1*^{IS} ≤1% (MR2), which led to approval of this optimized dosing strategy by the US Food and Drug Administration for this CP-CML population[3,4]
- We report results from the 5-year update of efficacy and safety outcomes from the OPTIC trial and present the results from the end-of-treatment (EOT) mutation analyses

Methods

Figure 1: OPTIC Study Design (NCT02467270)



Enrollment completed in May 2019

- Blood samples were collected at screening and EOT for *BCR::ABL1* mutation analysis by a central laboratory using Sanger sequencing[3]

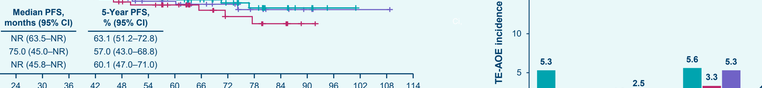
[a]93% of patients were TKI-resistant; [b]As shown by quantitative real-time polymerase chain reaction; [c]Dose reductions due to AEs were permitted; [d]Escalation to the starting dose was allowed for patients who lost their response following dose reduction; no dose escalation was allowed beyond starting dose; [e]Dose reduction below 10 mg was not permitted during the main treatment period, but reduced dosing was permitted during the treatment continuation period; [f]Key secondary endpoints: MMR rate at 12 and 24 months and major cytogenic response rate by 12 months, duration of MMR, and safety across the 3 doses; others include PFS, OS, and duration of response in responders.
AE, adverse event; CP-CML, chronic-phase chronic myeloid leukemia; EOT, end of treatment; MMR, major molecular response; OS, overall survival; PFS, progression-free survival; QD, once daily; TKI, tyrosine kinase inhibitor.

Results

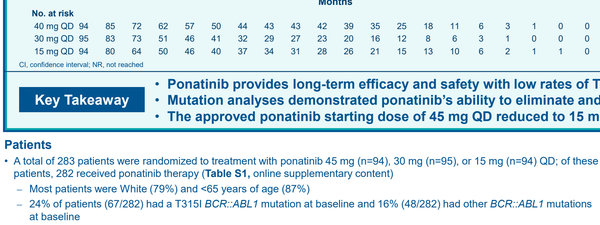
Objective

Evaluate the long-term efficacy, safety, and *BCR::ABL1* mutations from ponatinib treatment across 3 dosing cohorts in patients with CP-CML

Study design



PFS across starting-dose cohorts

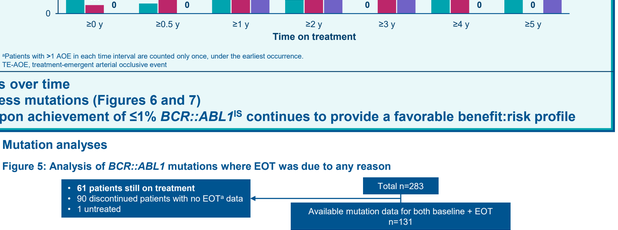


	Median PFS, months (95% CI)	5-Year PFS, % (95% CI)
45 mg→15 mg	NR (63.5–NR)	63.1 (51.2–72.8)
30 mg→15 mg	75.0 (45.0–NR)	57.0 (43.0–68.8)
15 mg	NR (45.8–NR)	60.1 (47.0–71.0)

No. at risk																			
40 mg QD	94	85	72	62	57	50	44	43	43	42	39	35	25	18	11	6	3	1	0	0
30 mg QD	95	83	73	51	46	41	32	29	27	23	20	16	12	8	6	3	1	0	0	0
15 mg QD	94	80	64	50	46	40	37	34	31	28	26	21	15	13	10	6	2	1	1	0

CI, confidence interval; NR, not reached

Frequency of cumulative adjudicated TE-AOEs by duration of treatment exposure[a]



[a]Patients with >1 AOE in each time interval are counted only once, under the earliest occurrence.
TE-AOE, treatment-emergent arterial occlusive event

Key Takeaway

- Ponatinib provides long-term efficacy and safety with low rates of TE-AOEs over time
- Mutation analyses demonstrated ponatinib's ability to eliminate and suppress mutations (Figures 6 and 7)
- The approved ponatinib starting dose of 45 mg QD reduced to 15 mg QD upon achievement of ≤1% *BCR::ABL1*^{IS} continues to provide a favorable benefit:risk profile

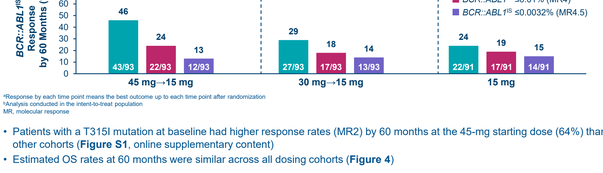
Patients

- A total of 283 patients were randomized to treatment with ponatinib 45 mg (n=94), 30 mg (n=95), or 15 mg (n=94) QD; of these patients, 282 received ponatinib therapy (**Table S1,** online supplementary content)
  - Most patients were White (79%) and <65 years of age (87%)
  - 24% of patients (67/282) had a T315I *BCR::ABL1* mutation at baseline and 16% (48/282) had other *BCR::ABL1* mutations at baseline
- At the data cutoff date (May 15, 2024), 61 patients remained on ponatinib treatment
  - Proportions of patients who remained on ponatinib by cohort: 45 mg, 29% (27/94); 30 mg, 19% (18/95); 15 mg, 17% (16/94)
  - Across cohorts, the most common reasons for treatment discontinuation were lack of efficacy (23%), adverse events (19%), and progressive disease (9%)
- Median durations of follow up were 78, 75, and 75 months in the 45-, 30-, and 15-mg cohorts, respectively
- Median dose intensities were 27.7, 23.5, and 14.7 mg/day in the 45-, 30-, and 15-mg cohorts, respectively

Efficacy

- By 60 months, 60%, 41%, and 40% of patients in the 45-mg, 30-mg, and 15-mg cohorts, respectively, achieved ≤1% *BCR::ABL*^{IS} (**Figure 2**)
- Median duration of ≤1% *BCR::ABL1*^{IS} was not reached in any cohort

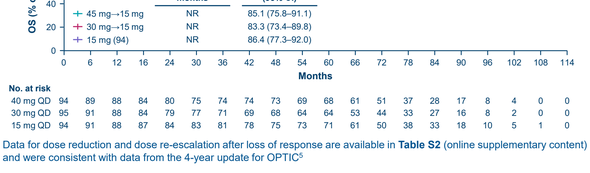
Figure 2: ≤1% *BCR::ABL1*^{IS} response rate[a,b]



[a]Numbers of patients with ≤1% *BCR::ABL*^{IS} are 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 by 60 months was highest in the 45-mg cohort (**Figure 3**)
- Rates of ≤0.01% and ≤0.0032% *BCR::ABL1*^{IS} were similar between cohorts

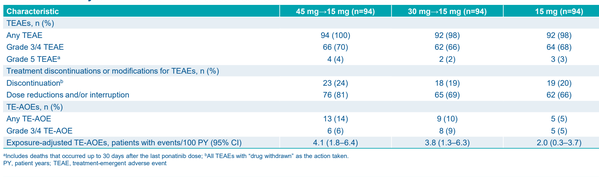
Figure 3: MMR, MR4, and MR4.5 by 60 months[a,b]



[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

- Patients with a T315I mutation at baseline had higher response rates (MR2) by 60 months at the 45-mg starting dose (64%) than other cohorts (**Figure S1**, online supplementary content)
- Estimated OS rates at 60 months were similar across all dosing cohorts (**Figure 4**)

Figure 4: Overall survival in the 45-, 30-, and 15-mg dosing cohorts



	Median OS, months	5-Year OS (95% CI)
45 mg→15 mg	NR	85.1 (75.8–91.1)
30 mg→15 mg	NR	83.3 (73.4–89.8)
15 mg (94)	NR	86.4 (77.3–92.0)

No. at risk																			
40 mg QD	94	89	88	84	80	75	74	74	73	69	68	61	51	37	28	17	8	4	0	0
30 mg QD	95	91	88	84	79	77	71	69	68	64	64	53	44	33	27	16	8	2	0	0
15 mg QD	94	91	88	87	84	83	81	78	75	73	71	61	50	38	33	18	10	5	1	0

- Data for dose reduction and dose re-escalation after loss of response are available in **Table S2** (online supplementary content) and were consistent with data from the 4-year update for OPTIC[5]

Safety

- Grade ≥3 TEAE and exposure-adjusted AOE rates were similar across dosing cohorts (**Table 1** and **Table S3**, online supplementary content)
- No grade 5 TE-AOEs occurred

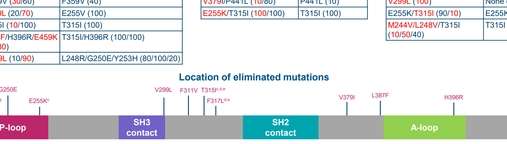
Table 1: Summary of TEAEs and related dose modifications and discontinuations

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 TEAE	66 (70)	62 (66)	64 (68)
Grade 5 TEAE[a]	4 (4)	2 (2)	3 (3)
Treatment discontinuations or modifications for TEAEs, n (%)			
Discontinuation[b]	23 (24)	18 (19)	19 (20)
Dose reductions and/or interruption	76 (81)	65 (69)	62 (66)
TE-AOEs, n (%)			
Any TE-AOE	13 (14)	9 (10)	5 (5)
Grade 3/4 TE-AOE	6 (6)	8 (9)	5 (5)
Exposure-adjusted TE-AOEs, patients with events/100 PY (95% CI)	4.1 (1.8–6.4)	3.8 (1.3–6.3)	2.0 (0.3–3.7)

[a]Includes deaths that occurred up to 30 days after the last ponatinib dose; [b]All TEAEs with "drug withdrawn" as the action taken.
PY, patient years; TEAE, treatment-emergent adverse event

Mutation analyses

Figure 5: Analysis of *BCR::ABL1* mutations where EOT was due to any reason



[a]No samples or unevaluable data (e.g. poor samples, insufficient amplification for sequencing, did not pass technical QC).
Mutation data cutoff date: August 22, 2024

- 131 patients had both baseline and EOT mutation data available (analysis in **Figure 6**)
- Of these patients, 74 patients had no detectable mutations at baseline (analysis in **Figure 7**)

Figure 6: Ponatinib eliminates multiple pre-existing *BCR::ABL1* mutations

A.

45 mg→15 mg

Mutations at enrollment[a] (Estimated %[b])	Mutations at EOT (Estimated %[b])
H396R (90)	None detected
E459K (90)	None detected
G250E/F359V (30/60)	F359V (40)
E255V/V299L (20/70)	E255V (100)
G250E/T315I (10/100)	T315I (100)
F311V/L387F/H396R/E459K (20/10/100/30)	T315I/H396R (100/100)
G250E/V299L (10/90)	L248R/G250E/Y253H (80/100/20)

30 mg→15 mg

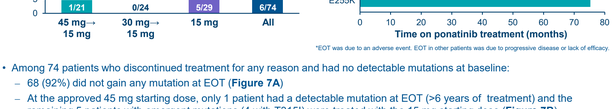
Mutations at enrollment[a] (Estimated %[b])	Mutations at EOT (Estimated %[b])
T315I/F317L (60/40)	T315I (100)
M244V/T315I (10/5)	T315I (60)
V379I/P441L (10/80)	P441L (10)
E255K/T315I (100/100)	T315I (100)

15 mg

Mutations at enrollment[a] (Estimated %[b])	Mutations at EOT (Estimated %[b])
T315I (50)	None detected
F317L (80)	None detected
V299L (100)	None detected
E255K/T315I (90/10)	E255K (90)
M244V/L248V/T315I (10/50/40)	T315I (100)

B.

Location of eliminated mutations



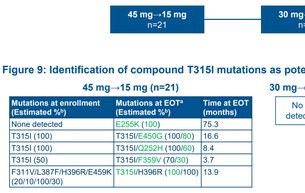
[a]Mutations in red were no longer detectable at EOT; [b]Percent mutation based on Sanger sequencing of amplified product; [c]Nilotinib contraindication; [d]Dasatinib contraindication; [e]Bosutinib contraindication.

- Among patients who discontinued treatment for any reason, 16 patients had baseline mutations that were no longer detectable at EOT (**Figure 6A**)
- Eliminated mutations were distributed across the BCR-ABL1 protein (**Figure 6B**) and were consistent with ponatinib's activity *in vitro*[6]

Figure 7: Ponatinib may suppress emergence of new *BCR::ABL1* mutations in the 45 and 30 mg starting-dose cohorts

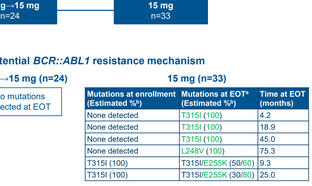
A.

Emergence of mutation at EOT



B.

Mutation type and time to EOT



[a]EOT was due to an adverse event. EOT in other patients was due to progressive disease or lack of efficacy.

- Among 74 patients who discontinued treatment for any reason and had no detectable mutations at baseline:
  - 68 (92%) did not gain any mutation at EOT (**Figure 7A**)
  - At the approved 45 mg starting dose, only 1 patient had a detectable mutation at EOT (>6 years of treatment) and the remaining 5 patients with emergent mutations (4 with T315I) were treated with the 15 mg starting dose (**Figure 7B**)

Figure 8: Analysis of *BCR::ABL1* mutations where EOT was due to progressive disease or lack of efficacy

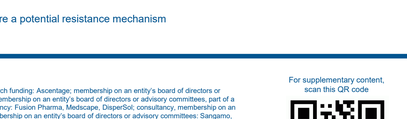


Figure 9: Identification of compound T315I mutations as potential *BCR::ABL1* resistance mechanism

45 mg→15 mg (n=21)

Mutations at enrollment (Estimated %[b])	Mutations at EOT[a] (Estimated %[b])	Time at EOT (months)
None detected	E255K (100)	75.3
T315I (100)	T315I/E450G (100/80)	16.6
T315I (100)	T315I/Q252H (100/60)	8.4
T315I (50)	T315I/F359V (70/30)	3.7
F311V/L387F/H396R/E459K (20/10/100/30)	T315I/H396R (100/100)	13.9

30 mg→15 mg (n=24)

No mutations detected at EOT

15 mg (n=33)

Mutations at enrollment (Estimated %[b])	Mutations at EOT[a] (Estimated %[b])	Time at EOT (months)
None detected	T315I (100)	4.2
None detected	T315I (100)	18.9
None detected	T315I (100)	45.0
None detected	L248V (100)	75.3
T315I (100)	T315I/E255K (60/60)	9.3
T315I (100)	T315I/E255K (30/80)	25.0

[a]New mutations at EOT are in green text; [b]Percent mutation based on Sanger sequencing of amplified product.

- Among patients who discontinued treatment for progressive disease or lack of efficacy (**Figure 8**), the majority (86%; 67/78) did not acquire new mutations
- Compound T315I mutations were observed in >50% of patients with any acquired mutations (6 of 11 patients across treatment groups; **Figure 9**)
- These observations are consistent with ponatinib's *in vitro* activity,[6] which is more robust against single mutations compared with compound mutations

Conclusions

- Long-term results from the OPTIC trial highlight the durable clinical benefit of ponatinib, including long-term PFS and OS, in patients with CP-CML that was resistant to ≥2 TKIs or harbor a T315I mutation
- These findings are consistent with those of previous analyses of OPTIC, demonstrating that the approved ponatinib starting dose of 45 mg QD with reduction to 15 mg QD upon achievement of ≤1% *BCR::ABL1*^{IS} continues to provide a favorable benefit:risk profile for patients with treatment-resistant CP-CML
- This EOT mutation analysis supports suppression and elimination of many *BCR::ABL1* mutations by ponatinib, and indicates that T315I compound mutations are a potential resistance mechanism
- Taken together, these data support the use of ponatinib after 2 prior TKIs in patients with CP-CML

References

1. O'Hare T, et al. *Cancer Cell*. 2009;16(5):401–12.
2. Cortes JE, et al. *N Engl J Med*. 2013;369:1783–96.
3. Cortes J, et al. *Blood*. 2021;138(21):2042–50.
4. Pulte ED, et al. *Oncologist*. 2022;27:149–57.
5. Cortes J, et al. Poster presented at the American Society of Hematology 2023 Annual Meeting; December 9–12, 2023; San Diego, CA, USA.
6. Gozgit JM, et al. Poster presented at the 55th Annual Meeting of the American Society of Hematology, December 7-10, 2013, New Orleans, LA. Abstr 3992

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