Three-year update from the OPTIC trial: A dose-optimization study of 3 starting doses of ponatinib

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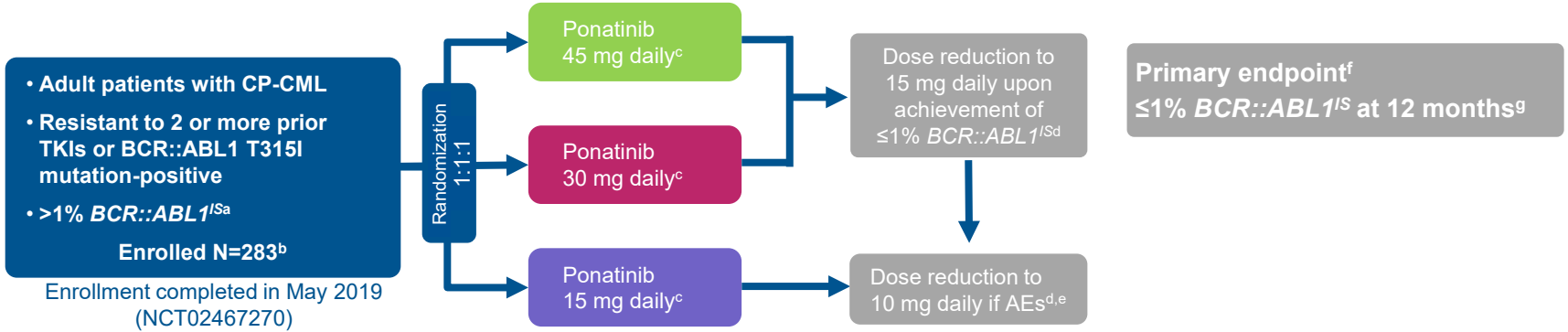
Introduction

- Ponatinib is the only pan-BCR::ABL1 third-generation tyrosine kinase inhibitor (TKI) designed to inhibit BCR::ABL1 with or without any single resistant mutation, including the T315I mutation[1–3]
- The Optimizing Ponatinib Treatment In CP-CML (OPTIC) trial is an ongoing Phase 2 trial that uses a novel response-based dose reduction strategy to assess the impact of ponatinib dose on efficacy and safety in patients with chronic-phase chronic myeloid leukemia (CP-CML) resistant to ≥2 prior TKIs or with a T315I mutation[3]
- The OPTIC primary analysis showed the optimal benefit:risk for ponatinib is achieved by starting at 45 mg daily, followed by dose reduction to 15 mg daily after a ≤1% *BCR::ABL1*^{IS} response[3]
- We present a 3-year update of efficacy and safety outcomes from the OPTIC trial

IS, International Standard ratio

1. O'Hare T, et al. Cancer Cell. 2009;16:401-12. 2. Cortes JE, et al. N Engl J Med. 2013;369:1783-96. 3. Cortes J, et al. Blood. 2021;138:2042–50.

OPTIC: Ongoing, Multicenter, Randomized Phase 2 Trial



- Median (range) duration of follow-up was 54 months (0–80)

[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::ABL1IS*
[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::ABL1IS* 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; IS, International Standard ratio; MCyR, major cytogenetic response; MMR, major molecular response

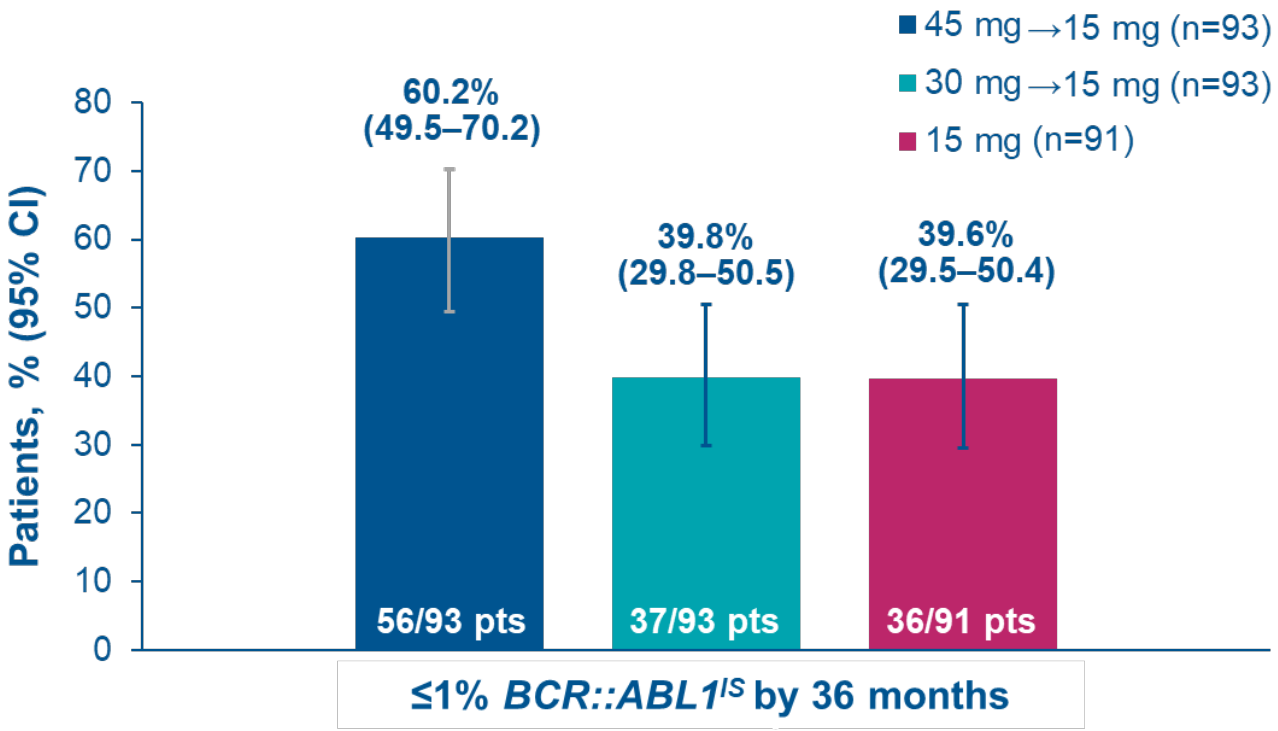
Demographics and baseline disease characteristics

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, median (range), years		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 (5.3)	4 (4.3)	3 (3.2)
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 (%)[a]	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)	54 (57)	57 (61)
	≤1% *BCR::ABL1*^{IS} or better	2 (2)	7 (7)	7 (7)

[a] Five patients (2 in 45 mg → 15 mg, 1 in 30 mg → 15 mg, and 2 in 15 mg cohorts) did not have any mutation testing performed at baseline

CHR, complete hematologic response; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status, IS, international standard ratio; TKI, tyrosine kinase inhibitor

≤1% *BCR::ABL1*^{IS} response rate by 36 months

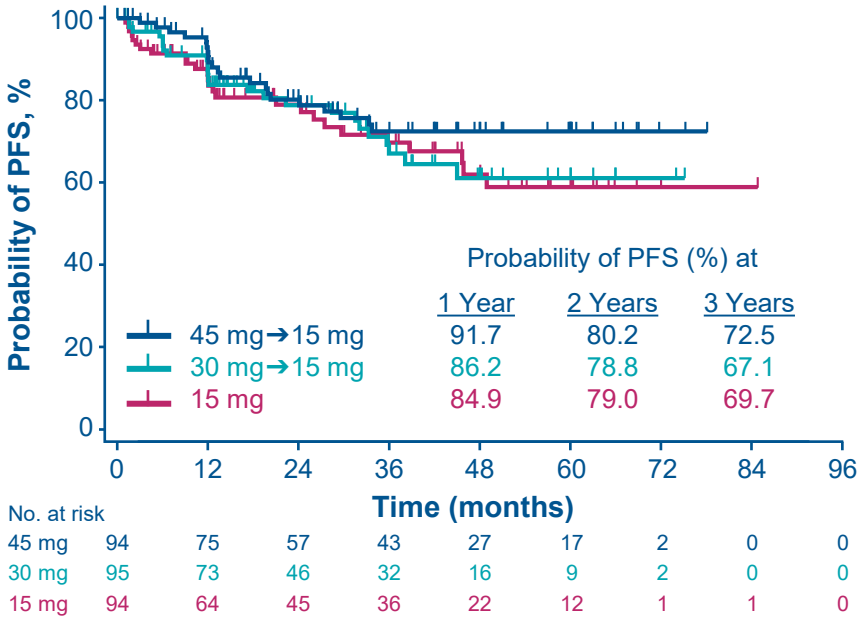


- At the first interim analysis of OPTIC, the primary endpoint of ≤1% *BCR::ABL1*^{IS} at 12 months was highest with the 45 mg➔15 mg regimen (44.1% [98.3% CI: 31.7–57.0]), which met the prespecified statistical endpoint (equivalent to *P*-value <0.017)
- As of May 9, 2022, median duration of response was not reached for patients in any treatment arm

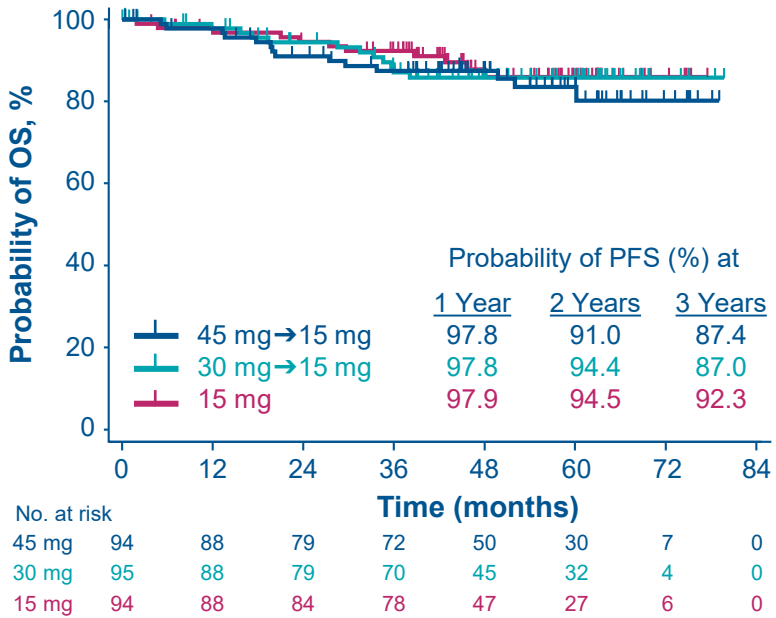
CI, confidence interval; IS, International Standard ratio; pts, patients

Kaplan-Meier–estimated probability of PFS and OS by ponatinib dosing regimen

PFS

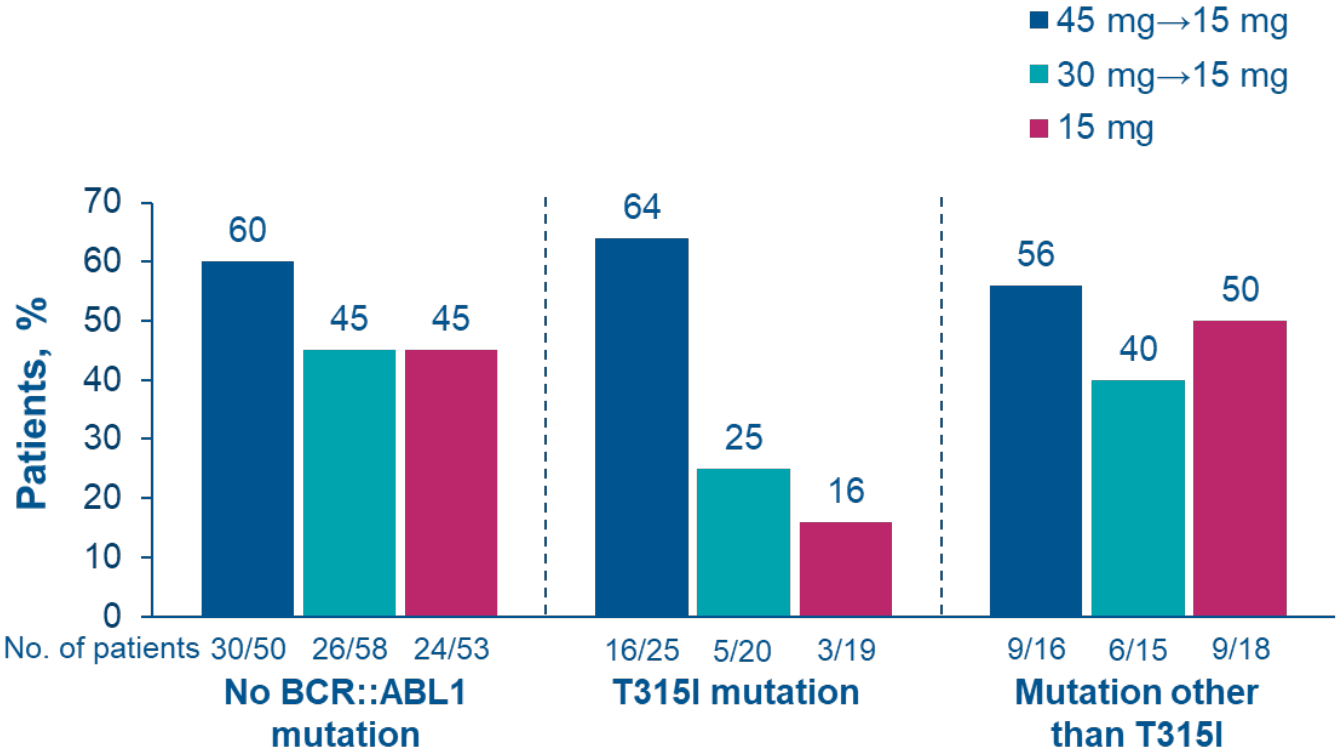


OS



OS, overall survival; PFS, progression-free survival

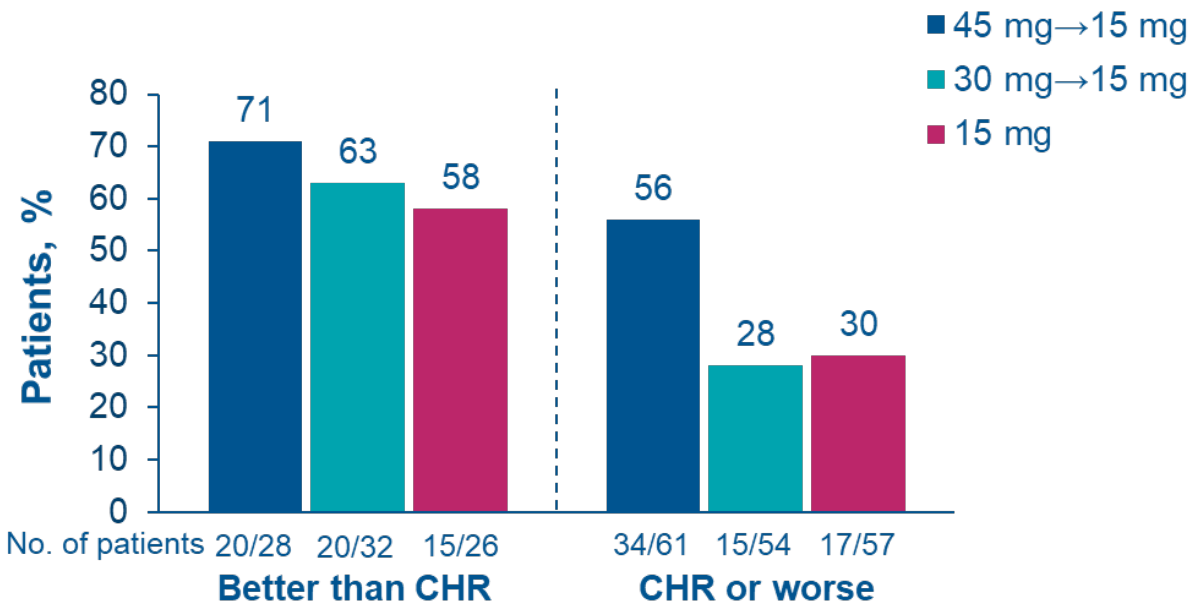
≤1% *BCR::ABL1*^{IS} response rate by 36 months by BCR::ABL1 mutation status at baseline



- Patients in the 30 mg➔15 mg and 15 mg cohorts without the T315I mutation had greater clinical benefit than patients with the T315I mutation
- Response rates in the 45 mg➔15 mg cohort were similar regardless of *BCR::ABL1* mutation status

IS, International Standard ratio

≤1% *BCR::ABL1*^{IS} response rate by 36 months by best response to last prior TKI



Among patients with CHR or worse as best response to last prior TKI, the 45 mg➔15 mg cohort had greater clinical benefit than the 30➔15 mg and 15 mg cohorts

CHR, complete hematological response; IS, International Standard ratio

Results (cont'd)

Dose re-escalation after loss of response[a] (ITT population)

Characteristic	45 mg→15 mg (n=93)	30 mg→15 mg (n=93)
Achieved ≤1% *BCR::ABL1*^{IS} at any time, n	56	38
Loss of ≤1% *BCR::ABL1*^{IS} at any time, n	15	9
Dose re-escalated after loss of response, n	12	3
Regained ≤1% *BCR::ABL1*^{IS}		
Yes, n	9	2
No, n	3	1
Median time to regain response after re-escalation, months[b]	4.1	N/A[c]

[a] Defined as loss of ≤1% *BCR::ABL1*^{IS} as assessed by quantitative real-time polymerase chain reaction
[b] For patients who did not regain response, the median duration of therapy was 26.1 months in the 45 mg cohort (n=3) and 10.2 months in the 30 mg cohort (n=1)
[c] Not applicable because there were only 2 responders
IS, International Scale ratio; ITT, intention-to-treat

Results (cont'd)

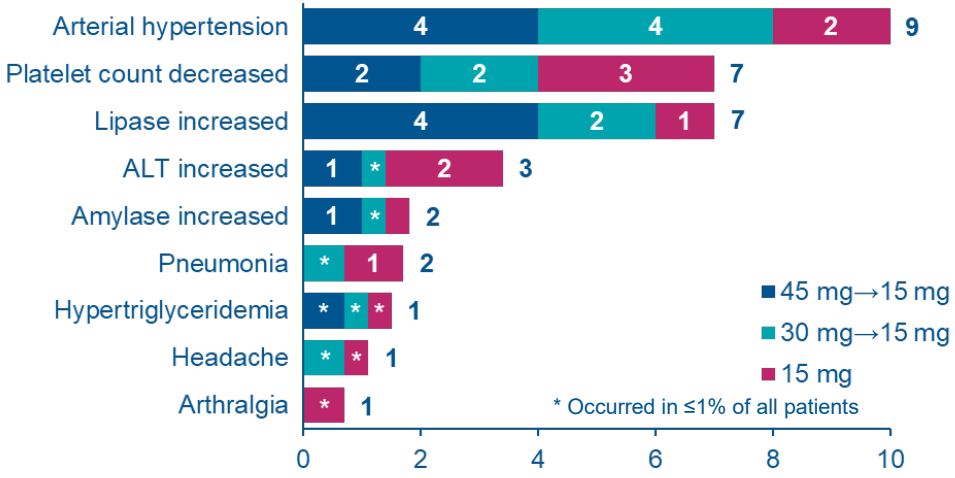
TEAE summary and related dose modifications and discontinuations

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,b]	3 (3)	1 (1)	3 (3)
Dose modification for TEAEs, n (%)			
Discontinuation	21 (22)	17 (18)	16 (17)
Reduction	46 (49)	34 (36)	30 (32)
Interruption	73 (78)	63 (67)	58 (62)

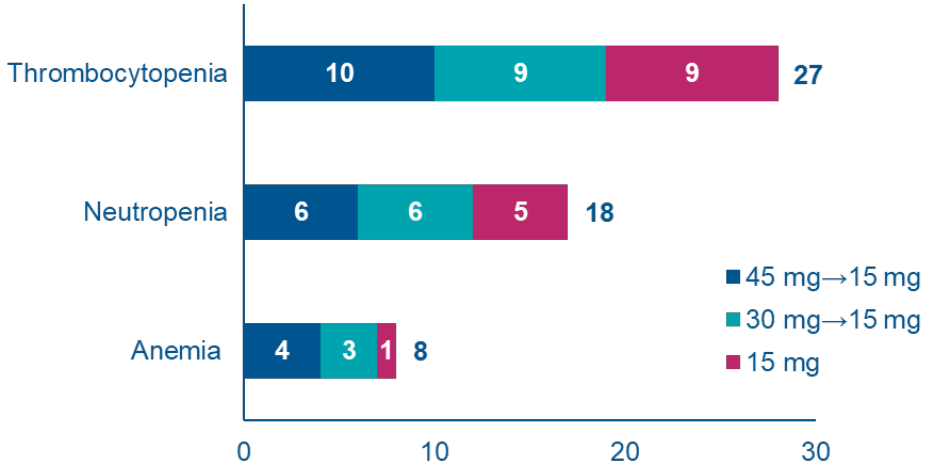
[a] Includes deaths that occurred up to 30 days after the last ponatinib dose
[b] Grade 5 TEAEs were sudden death (n=2) and loss of consciousness (n=1) in the 45 mg cohort and cardiac arrest (n=1) in the 30 mg cohort
TEAE, treatment-emergent adverse effect

Most common grade 3–5 TEAEs

Incidence of most common grade 3–5 nonhematologic TEAEs, %



Incidence of most common grade 3–5 hematologic TEAEs, %



- The most common grade 3–5 TEAEs (thrombocytopenia, neutropenia, arterial hypertension, and anemia) did not appear to be more common in the 45 mg→15 mg cohort

ALT, alanine aminotransferase; TEAE, treatment-emergent adverse effect

Adjudicated[a] 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)	6 (6)	4 (4)
Exposure-adjusted AOE rate[b] (95% CI)	4.5 (1.7–7.3)	3.0 (0.6–5.5)	1.9 (0.04–3.8)
Grade 3–4 TE-AOEs	6 (6)	6 (6)	4 (4)
Grade 5 TE-AOEs	0	0	0
Dose modifications for TE-AOE, n (%)			
Discontinuation	6 (6)	4 (4)	1 (1)
Reduction	0	2 (2)	0
Interruption	3 (3)	3 (3)	2 (2)

Rates of grade 3–5 TE-AOEs were consistent with the OPTIC primary analysis (45 mg: 5%; 30 mg: 5%; 1 mg: 3%)[1]

[a] All documentation related to an AOE (including, but not limited to, clinical features, changes in concomitant medications, urgent revascularization, ECG changes, presence of diagnostic criteria on imaging, and hospital discharge summaries) was reviewed by a cardiovascular endpoint adjudication committee composed of independent experts. If a serious vascular occlusive adverse drug reaction occurred, treatment was interrupted and not restarted unless the potential benefit outweighed the risk of recurrent arterial or venous occlusions.

[b] Exposure-adjusted AOE rate is based on the number of patients with events per 100 person-years

CI, confidence interval; ECG, electrocardiogram; TE-AOE, treatment-emergent arterial occlusive event

1. Cortes J, et al. Blood. 2021;138:2042–50.

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 the patient's T315I mutation status
- Patients without a T315I mutation at baseline had greater benefit than those with T315I in the 30 mg→15 mg and 15 mg cohorts
- At this updated 3-year analysis, response-based ponatinib dosing regimens demonstrated long-term manageable safety and AOE profiles, with optimal benefit:risk achieved with an initial 45 mg dose reduced to 15 mg upon attainment of a ≤1% *BCR::ABL1*^{IS} response[1]
- 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

1. Cortes J, et al. Blood. 2021;138:2042–50.

Acknowledgments

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