

OPTIC Primary Analysis: A Dose-Optimization Study of 3 Starting Doses of Ponatinib

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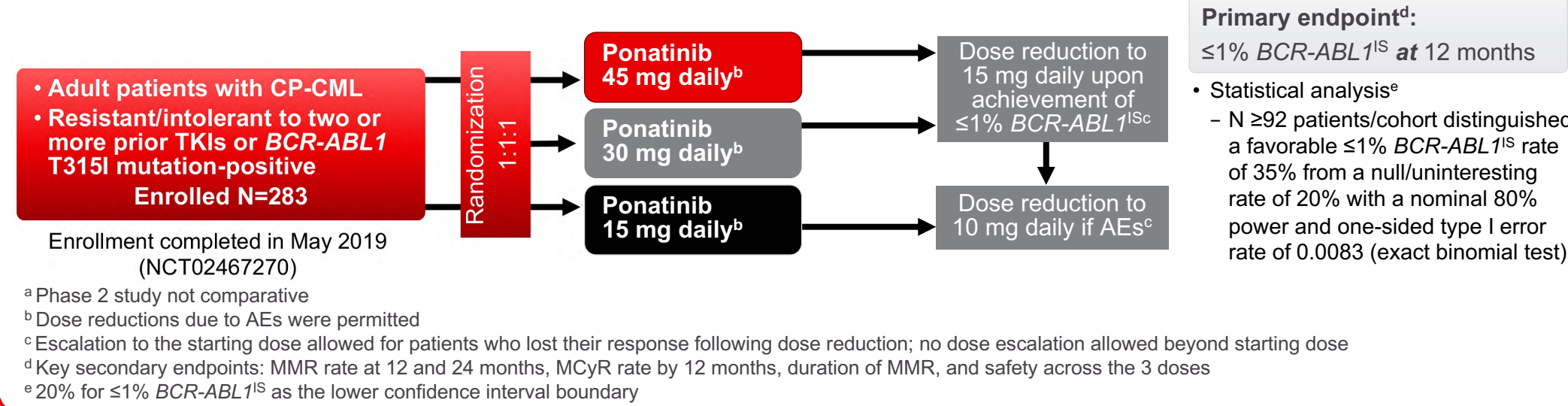
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Introduction

- Ponatinib, the only pan-BCR-ABL1 inhibitor, is a third-generation tyrosine kinase inhibitor (TKI) designed to potently inhibit BCR-ABL1 with or without any single resistance mutation, including T315I¹
- Patients with resistant and intolerant chronic-phase chronic myeloid leukemia (CP-CML) with substantial prior treatment demonstrated deep, lasting responses to ponatinib 45 mg once daily in the pivotal phase 2 PACE trial^{2,3}
- Arterial occlusive events (AOEs) emerged as notable adverse events in PACE; a post hoc multivariate regression analysis of pooled clinical trial data suggested that the occurrence of AOE with ponatinib was dose dependent^{3,4}
- The OPTIC trial prospectively evaluates a novel response-based dose-reduction strategy to further understand the impact of ponatinib dose on safety and efficacy in patients with CP-CML resistant to a prior second-generation BCR-ABL1 TKI therapy or with a T315I mutation
- Here, we present the primary analysis of the OPTIC trial with a median follow-up of 32 months

Methods

Figure 1. OPTIC (Optimizing Ponatinib Treatment In CP-CML): Ongoing, Multicenter, Randomized Phase 2 Trial^a



- Median (range) duration of follow-up: 32 months (1–57)
- Minimum follow-up (date last patient was randomized to data cutoff date [5/31/20]): 12.8 months

Results

Table 1. Patient Demographics and Baseline Disease Characteristics

Characteristic	Subcategory	45 mg → 15 mg (N=94)	30 mg → 15 mg (N=94)	15 mg (N=94)
Median age, y (range)		46 (19–81)	51 (21–77)	49 (18–81)
Gender, male, n (%)		50 (53)	38 (40)	53 (56)
ECOG PS score 0 or 1, n (%)		93 (99)	93 (99)	94 (100)
Median time since diagnosis, y (range)		5.5 (1–21)	5.1 (1–29)	5.7 (1–22)
Patients with CV risk factors, n (%)		26 (28)	25 (27)	22 (23)
	Arterial hypertension	5 (5)	3 (3)	7 (7)
	Diabetes mellitus	19 (20)	14 (15)	16 (17)
	Hyperlipidemia	27	26	26
Median body mass index — kg/m ²		1 (1)	1 (1)	4 (4)
Prior TKIs, n (%)		2	43 (46)	42 (45)
	1	50 (53)	56 (60)	48 (51)
	≥3	92 (98)	94 (100)	94 (100)
Stopped immediate prior TKI for resistance, n (%)		51 (54)	58 (62)	54 (57)
<i>BCR-ABL1</i> mutation, n (%) ^a		25 (27)	21 (22)	21 (22)
	T315I	16 (17)	14 (15)	18 (19)
	Mutation other than T315I	61 (65)	55 (59)	57 (61)
Best response to last prior TKI, n (%)		2 (2)	7 (7)	7 (7)
	≤1% <i>BCR-ABL1</i> ^{IS} or better			

^aFive 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

Figure 2. Patient Disposition^a

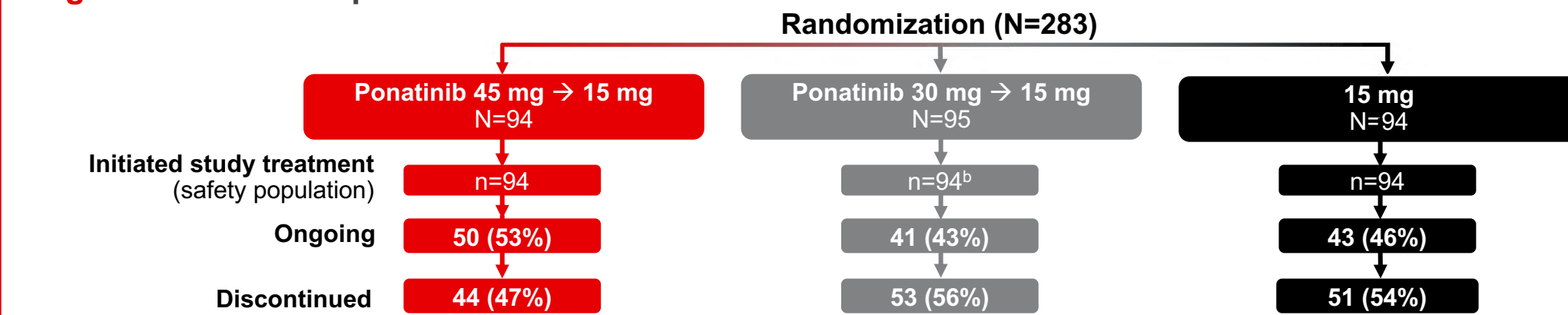
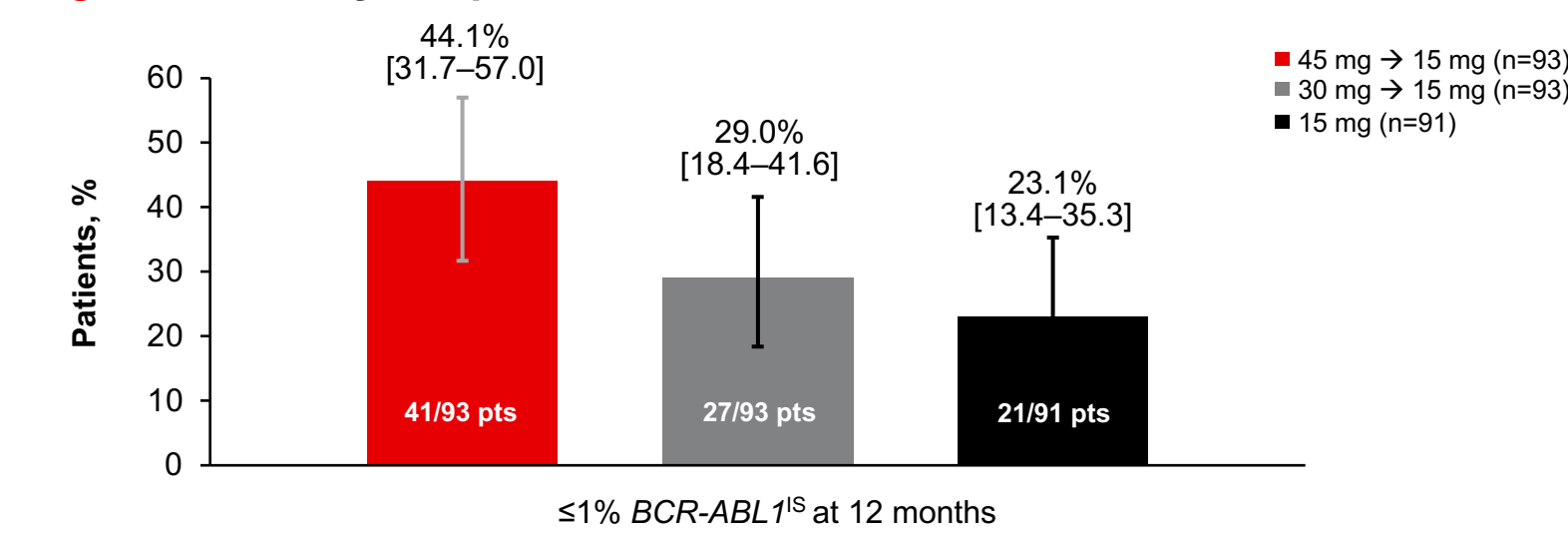


Figure 3. Primary Endpoint: ≤1% *BCR-ABL1*^{IS} at 12 Months



- The response rate was highest with the 45 mg → 15 mg regimen, 44.1% (31.7–57.0)
- The prespecified statistical endpoint was met with the 45 mg → 15 mg regimen ($P < 0.017$)

Figure 4. ≤1% *BCR-ABL1*^{IS} by 6, 12, and 24 Months and Median Dose Intensity

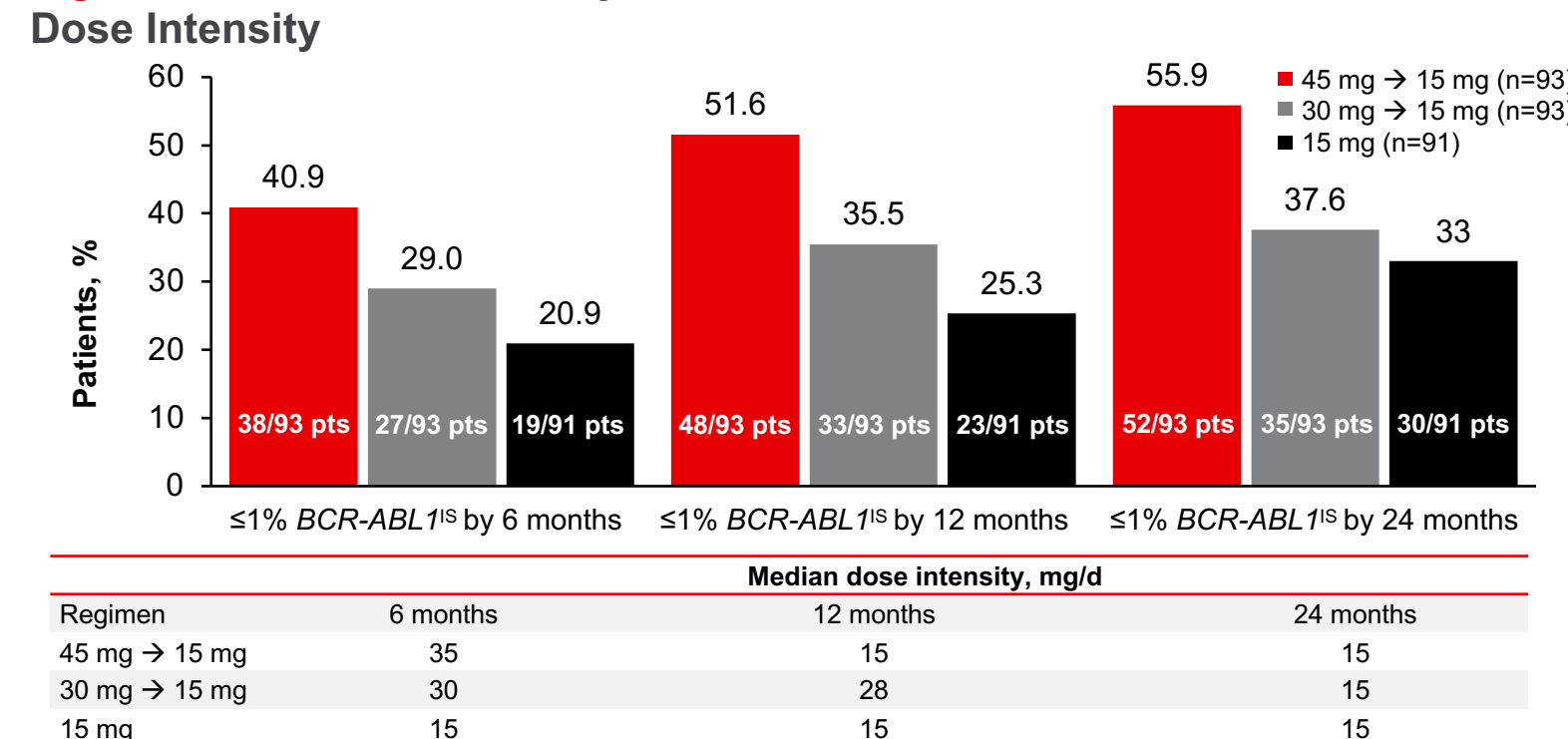


Figure 5. ≤1% *BCR-ABL1*^{IS} Response Rate by Best Response to Last Prior Therapy

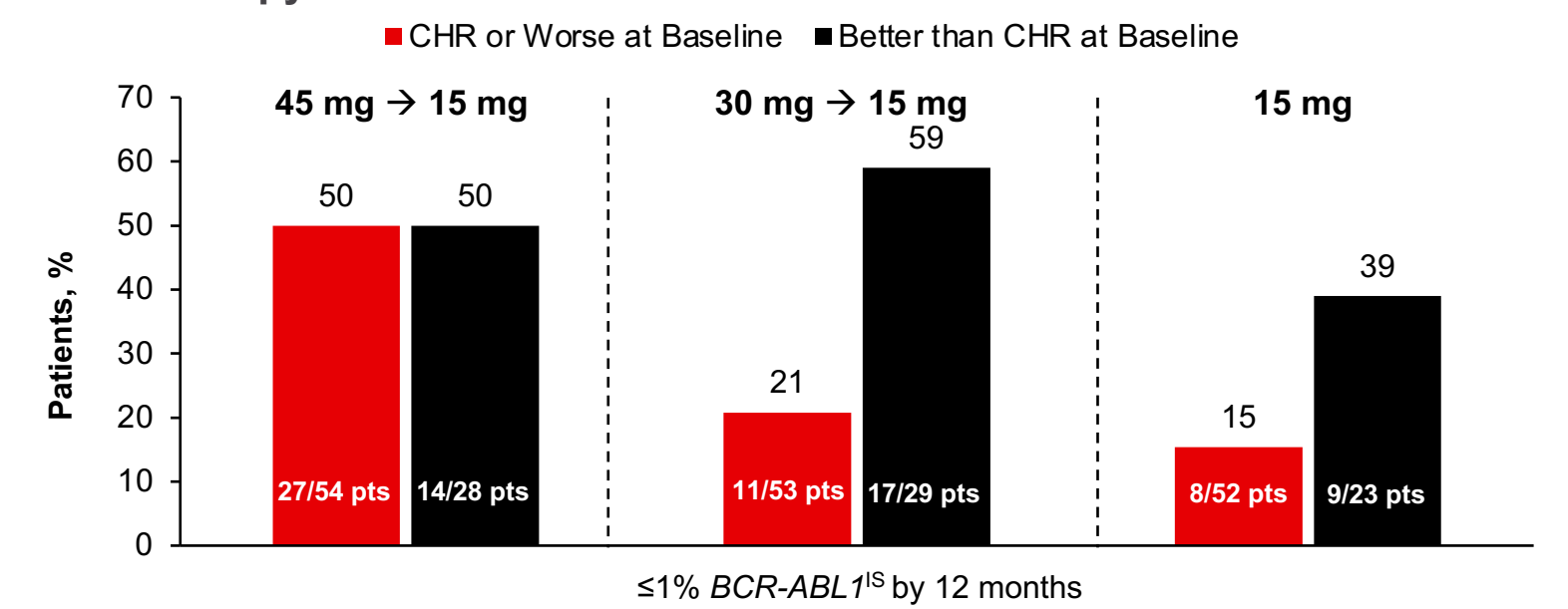


Figure 6. ≤1% *BCR-ABL1*^{IS} Response Rate by 12 Months^a by T315I Baseline Status

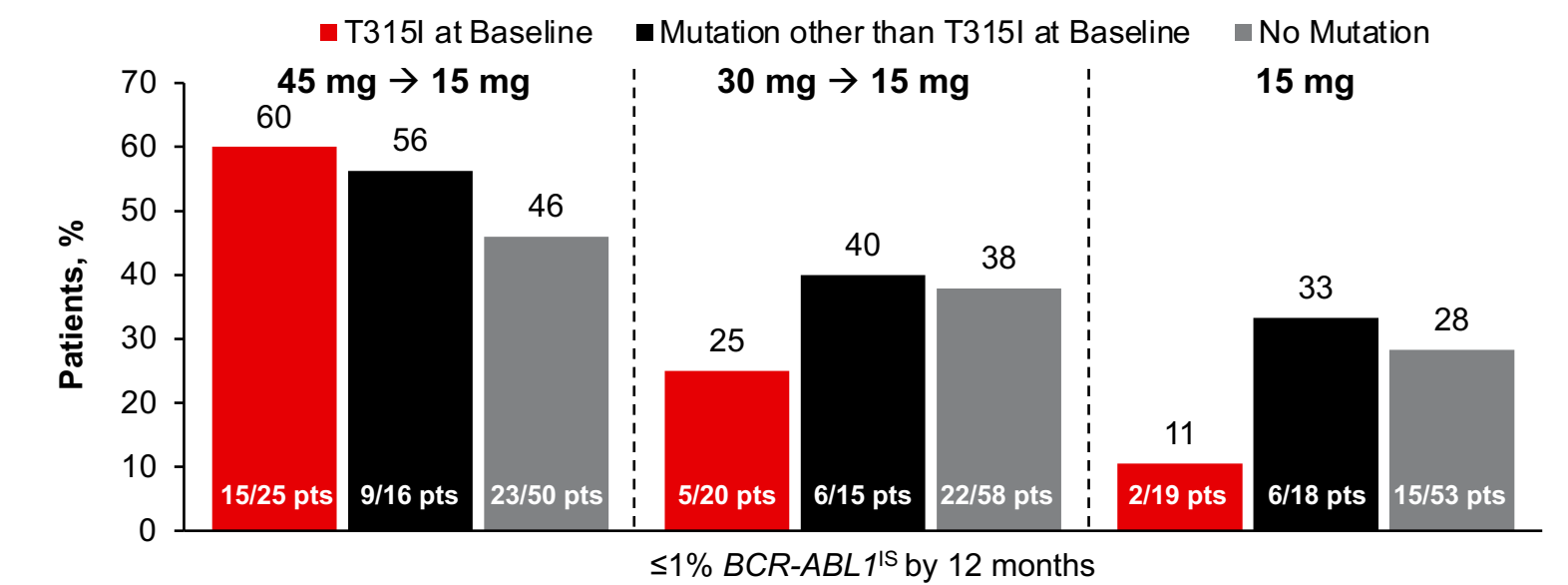
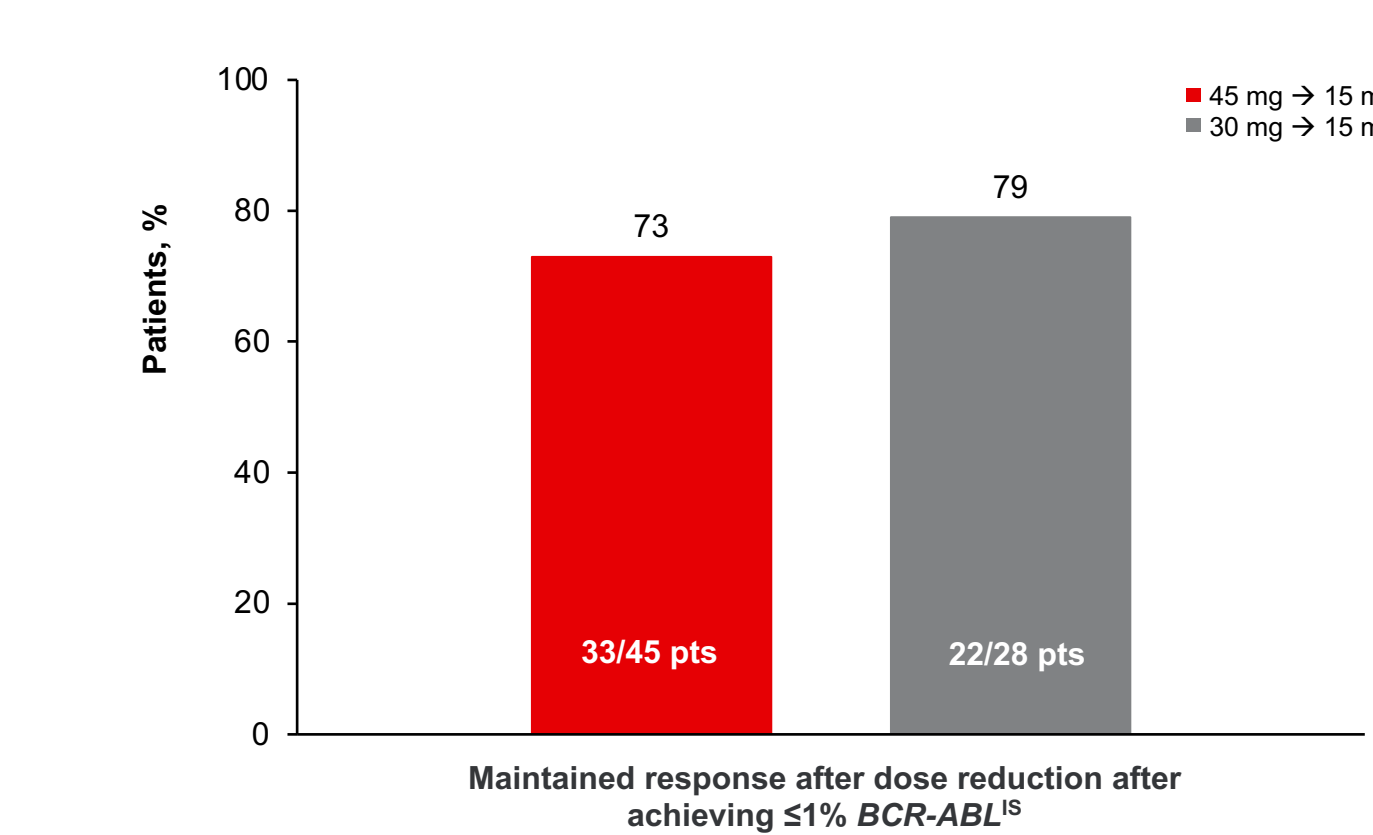


Figure 7. Maintenance of Response After Dose Reduction to 15 mg After Achieving ≤1% *BCR-ABL1*^{IS}



- In the 30 mg and 45 mg cohorts combined, 73 patients had a dose reduction to 15 mg after achieving ≤1% *BCR-ABL1*^{IS}
 - 75% (55/73) maintained response after dose reduction; 33/45 patients in the 45 mg cohort and 22/28 patients in the 30 mg cohort
 - 93% (51/55) of those patients continued to maintain response for 6 months or longer

Table 2. Dose Re-escalation^a After Loss of Response (ITT Population)

	45 mg → 15 mg (N=93)	30 mg → 15 mg (N=93)
Achieved ≤1% <i>BCR-ABL1</i> ^{IS} at any time, n	52	35
Loss of ≤1% <i>BCR-ABL1</i> ^{IS} at any time, n	13	9
Dose re-escalated after loss of response, n	13	5
Regained ≤1% <i>BCR-ABL1</i> ^{IS}		
Yes, n (%)	8 (61.5)	4 (80.0)
No, n (%)	5 (38.5)	1 (20.0)
Median time to regain response after re-escalation, mo	3.9	4.2
Median duration of therapy for those who did not regain response, mo	12.5 (n=5)	N/A (n=1)

^aEscalation was not allowed beyond the starting dose
^bOne patient did not regain response; this patient was on therapy for 28 months after dose re-escalation

- Most patients who dose re-escalated after loss of response regained ≤1% *BCR-ABL1*^{IS}

Figure 8. Progression-Free Survival (PFS)^a

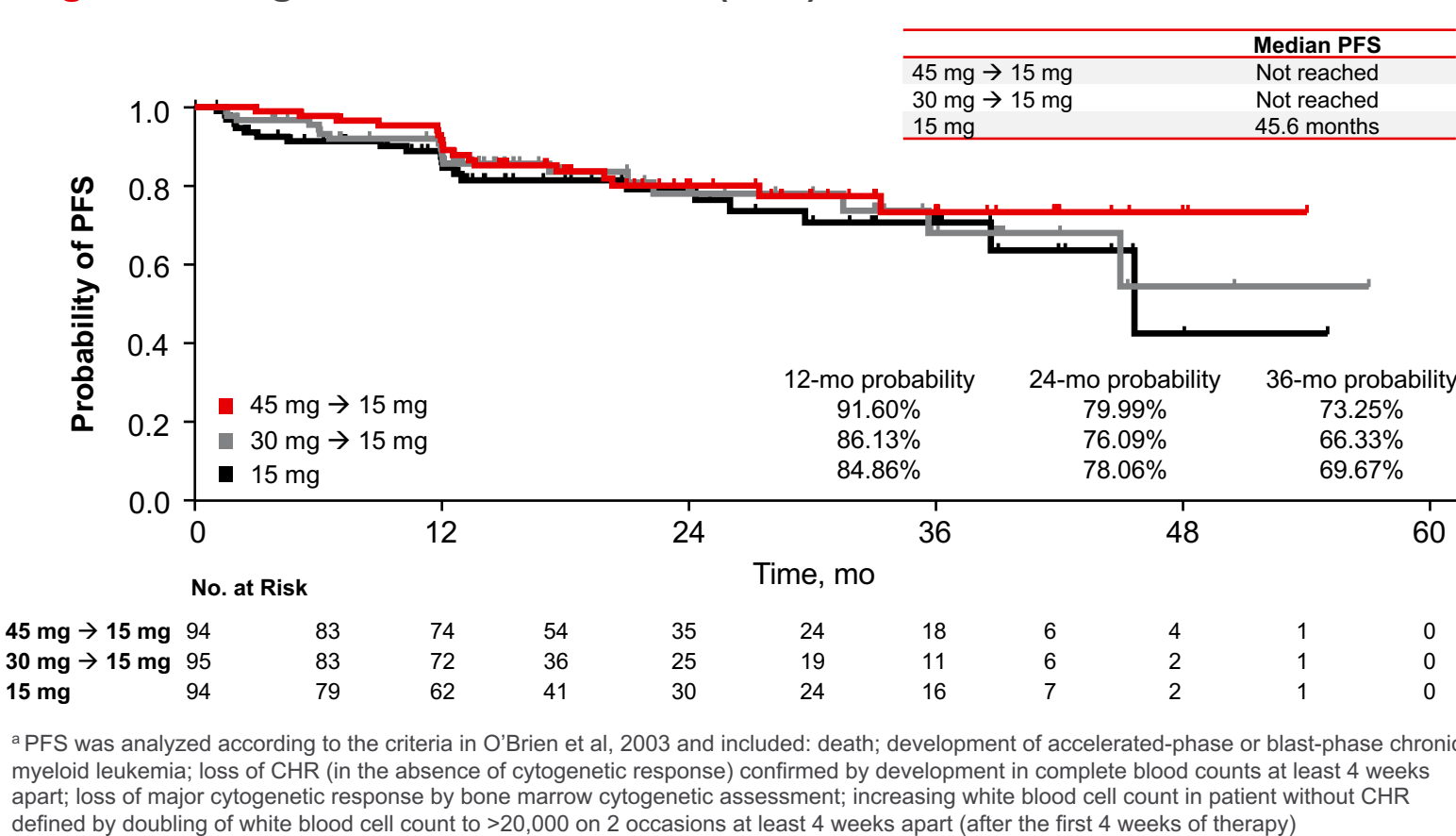


Figure 9. Overall Survival (OS)

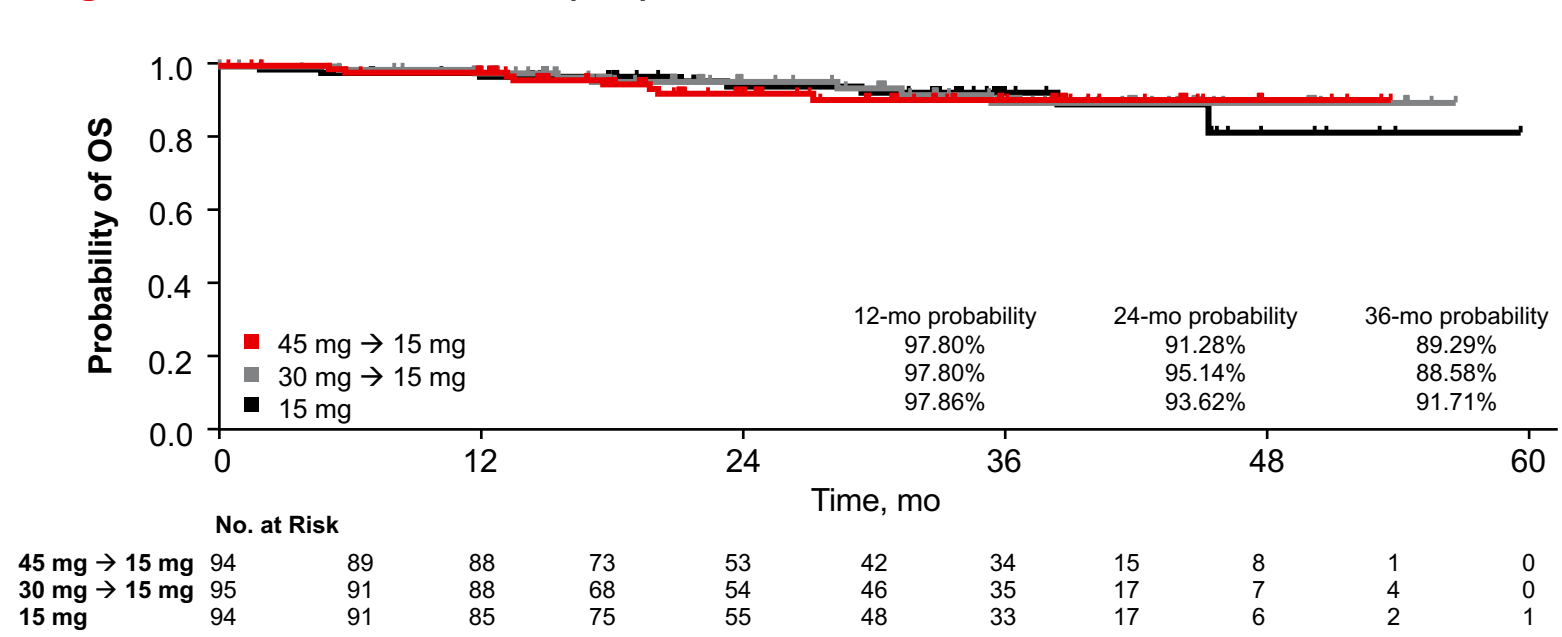
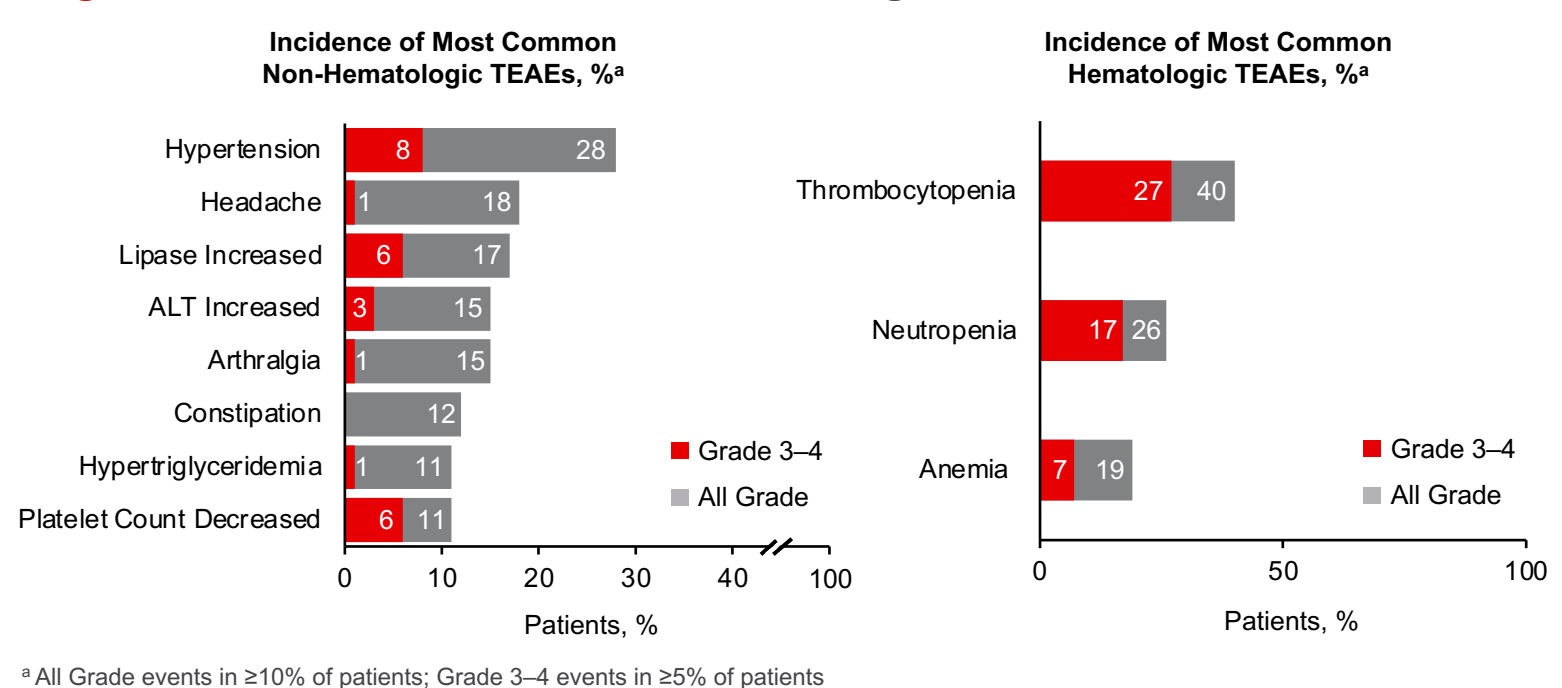


Figure 10. Most Common Treatment-Emergent Adverse Events



- The most common TEAEs (thrombocytopenia, hypertension, headache, lipase increased) did not appear to be more common in the 45 mg → 15 mg cohort

Table 3. TEAE Summary and Related Dose Modifications/Discontinuations

	45 mg → 15 mg (N=94)	30 mg → 15 mg (N=94)	15 mg (N=94)
TEAEs, n (%)			
Any TEAE	94 (100)	88 (93.6)	89 (94.7)
Grade 3–4 TEAEs	62 (66.0)	58 (61.7)	58 (61.7)
Grade 5 TEAEs ^a	2 (2.1)	0	2 (2.1)
Serious TEAEs	32 (34.0)	24 (25.5)	31 (33.0)
Dose modifications for TEAEs, n (%)			
Discontinuation	18 (19.1)	15 (16.0)	13 (13.8)
Reduction	43 (45.7)	33 (35.1)	30 (31.9)
Interruption	67 (71.3)	58 (61.7)	55 (58.5)

^aGrade 5 TEAEs were 2 sudden deaths in the 45 mg → 15 mg cohort and 2 deaths from pneumonia in the 15 mg cohort

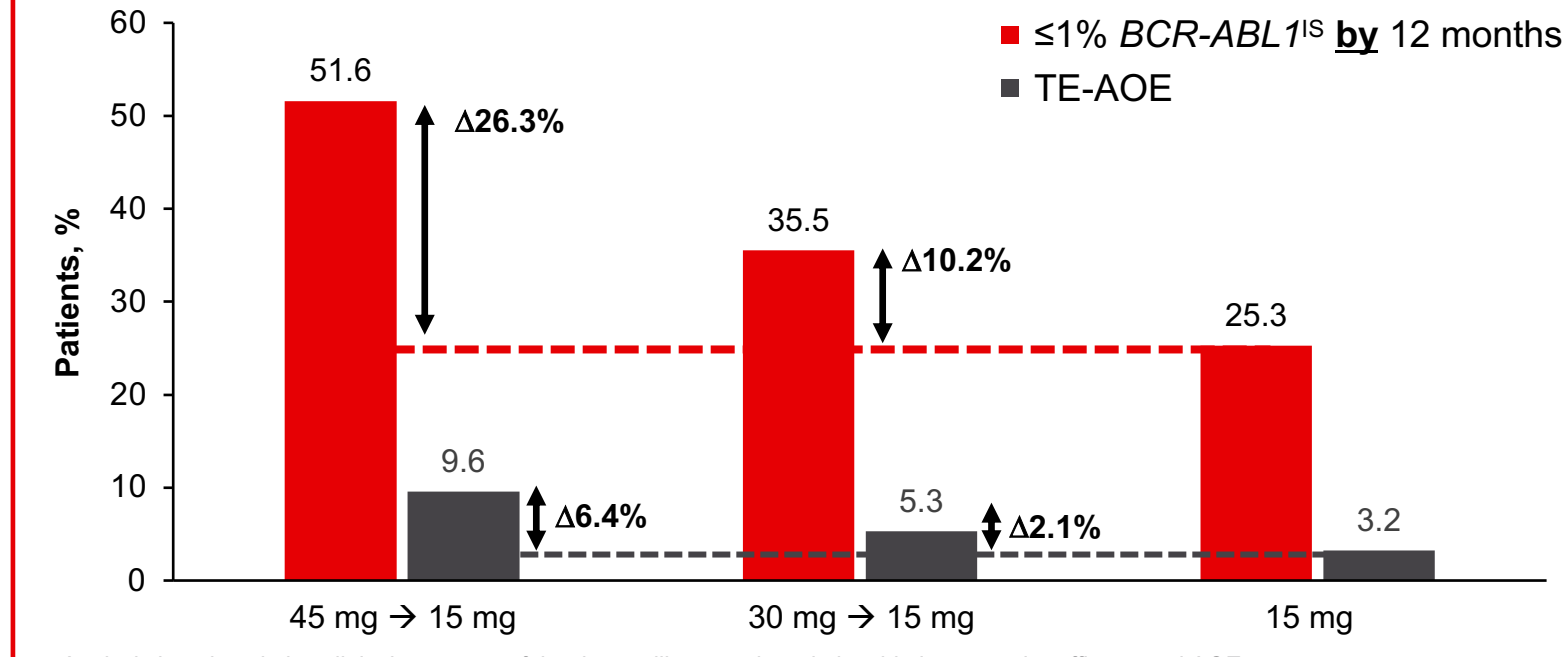
Table 4. Adjudicated^a TE-AOE Summary and Related Dose Modifications/Discontinuations

	45 mg → 15 mg (N=94)	30 mg → 15 mg (N=94)	15 mg (N=94)
TE-AOEs, n (%)			
Any AOE	9 (9.6)	5 (5.3)	3 (3.2)
Grade ≥3 TE-AOEs	5 (5.3)	5 (5.3)	3 (3.2)
Dose modifications for AOE, n (%)			
Discontinuation	4 (4.3)	3 (3.2)	1 (1.1)
Reduction	0	1 (1.1)	0
Interruption	2 (2.1)	3 (3.2)	1 (1.1)

^aAn independent cardiovascular endpoint adjudication committee composed of independent experts reviewed 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, or hospitalization. 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

- 6% of patients overall experienced a TE-AOE

Figure 11. Overall Safety and Efficacy by Starting Dose^a



- The percentage of patients with ≤1% *BCR-ABL1*^{IS} decreased with decreasing doses
- The incidence of TE-AOEs decreased with decreasing doses

Conclusions

- This global, multicenter, **phase 2 study is the first to prospectively evaluate a response-based dose-reduction strategy** to optimize the benefit:risk of a TKI in patients with CP-CML
- All **3 dosing regimens showed benefit** in these largely resistant patients; however, the **45 mg → 15 mg cohort had the best response**
- In the **30 mg → 15 mg and 15 mg cohorts**, patients with **less-resistant disease and without a T315I mutation** at baseline had **greater benefit** than those with T315I in these 2 cohorts
- At this primary analysis, novel response-based ponatinib dosing regimens had clinically **manageable safety and AOE profiles**, with an **optimal benefit:risk profile** achieved with a **45 mg starting dose** reduced to 15 mg upon response (≤1% *BCR-ABL1*^{IS})
- Observed responses were associated with **robust survival outcomes** in patients with CP-CML resistant to second-generation BCR-ABL1 TKI therapy, both with and without *BCR-ABL1* mutations

References

- O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. *Cancer Cell*. 2009;16:401-412.
- Cortes JE, Kim D-W, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2013;369:1783-1796.
- Cortes JE, Kim D-W, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood*. 2018;132:393-404.
- Dorer DJ, Knickerbocker RK, Baccarani M, et al. Impact of dose intensity of ponatinib on selected adverse events: multivariate analyses from a pooled population of clinical trial patients. *Leuk Res*. 2016;48:84-91.

Abbreviations

AE, adverse event; ALT, alanine aminotransferase; AOE, arterial occlusive event; CHR, complete hematologic response; CML, chronic myeloid leukemia; CP, chronic phase; CP-CML, chronic-phase chronic myeloid leukemia; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status; IS, International Scale; ITT, intent to treat; MCoR, major cytogenetic response; MMR, major molecular response; N/A, not applicable; OPTIC, Optimizing Ponatinib Treatment In CP-CML; OS, overall survival; PACE, Ponatinib Ph+ ALL and CML Evaluation; PFS, progression-free survival; TEAE, treatment-emergent adverse event; TE-AOE, treatment-emergent arterial occlusive event; TKI, tyrosine kinase inhibitor.

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