Outcome by Mutation Status and Line of Treatment in OPTIC, a Dose-Ranging Study of 3 Starting Doses of Ponatinib in Patients With CP-CML

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Introduction

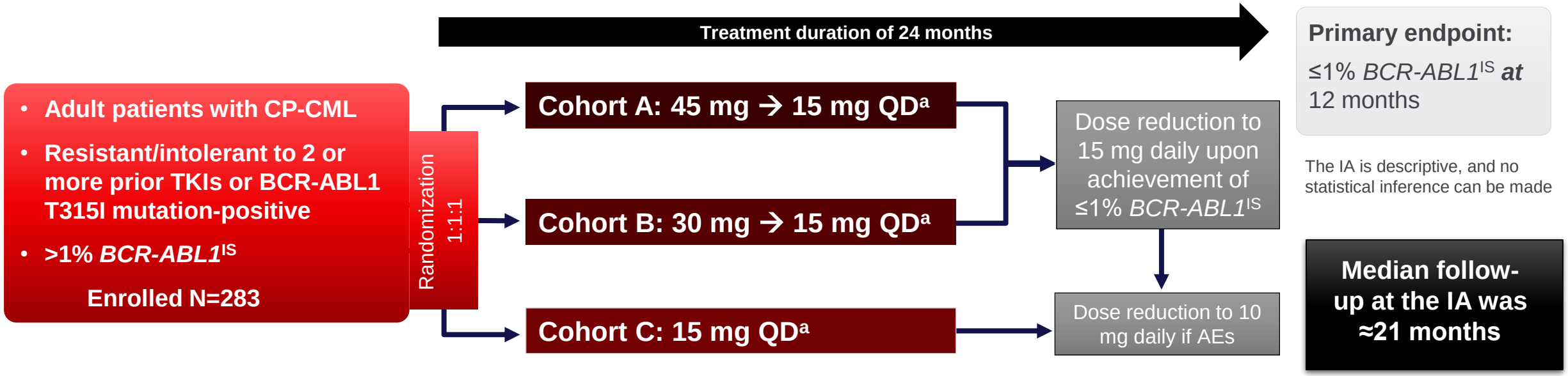
- **In PACE patients with highly resistant CP-CML with substantial prior second-generation TKI treatment demonstrated deep, lasting responses to ponatinib[1]**
- **OPTIC is a randomized Phase 2 trial evaluating response-based dosing regimens of ponatinib with 3 starting doses: 45 mg, 30 mg, and 15 mg daily in patients with CP-CML resistant/intolerant to ≥2 TKIs or with a *BCR-ABL1* T315I mutation[2]**
- **At the interim analysis with a median follow-up of ≈21 months, OPTIC showed benefit across 3 starting doses, with optimal benefit:risk profile seen with 45 mg/d starting dose**
- **Here, we present efficacy and safety outcomes by baseline mutation status and line of treatment for all 3 starting-dose groups**

AOE, arterial occlusive event; CP-CML, chronic phase chronic myeloid leukemia; OPTIC, Optimizing Ponatinib Treatment In CP-CML; PACE, Ponatinib Ph+ ALL and CML Evaluation; TKI, tyrosine kinase inhibitor

1. Cortes JE, et al. *Blood*. 2018;132(4):393-404. 2. Cortes JE, et al. *J Clin Oncol*. 2020;38(15 suppl):7502.

Phase 2 OPTIC Trial (NCT02467270) Subset Analyses

- Outcomes were analyzed by baseline mutation status (none, any, T315I, and mutation other than T315I) and number of prior TKIs (≤2 or ≥3) in the ITT population
  - Mutation status was determined by a central lab
- TEAEs, serious TEAEs, and AOEs by adjudication were summarized by number of prior TKIs (≤2 or ≥3)



[a] Dose reductions due to AEs were permitted

→15 mg, Cohort A is referred to as 45 mg → 15 mg and Cohort B as 30 mg → 15 mg because the study design has a dose reduction to 15 mg upon achievement of ≤1% BCR-ABL1IS. There also were patients in Cohorts A and B who dose-reduced to different dose levels (30, 15, and 10 mg) due to safety

IA, interim analysis; ITT, intent to treat; QD, daily; TEAE, treatment-emergent adverse event

Demographics and Baseline Disease Characteristics
(Slide 1 of 3)

Characteristic	15 mg (n=94)	30 mg→15 mg (n=94)	45 mg→15 mg (n=94)
Median age, y	49	51	46
Male gender, n (%)	53 (56)	38 (40)	50 (53)
Median time since diagnosis, y	5.7	4.9	5.5
Patients with CV risk factors			
Arterial hypertension, n (%)	22 (23)	25 (27)	26 (28)
Diabetes mellitus, n (%)	7 (7)	3 (3)	5 (5)
Hypercholesterolemia, n (%)	15 (16)	14 (15)	19 (20)
Median body mass index, kg/m^2	26	26	27
Best response to last prior TKI, n (%)[a]			
CHR or worse	57 (61)	55 (59)	61 (65)
Better than CHR	28 (30)	32 (34)	28 (30)

[a] Baseline response to last prior TKI is missing for 20 patients.

CV, cardiovascular; y, year

Demographics and Baseline Disease Characteristics
(Slide 2 of 3)

Characteristic	15 mg (n=94)	30 mg→15 mg (n=94)	45 mg→15 mg (n=94)
***BCR-ABL1* mutation at baseline[a,b], n (%)**			
No mutation	54 (57)	58 (62)	51 (54)
Any mutation	38 (40)	35 (37)	41 (44)
T315I	20 (21)	21 (22)	25 (27)
Mutation other than T315I[c]	18 (19)	14 (15)	16 (17)
G250E	4 (4)	2 (2)	7 (7)
F317L	2 (2)	4 (4)	2 (2)
F359V	5 (5)	1 (1)	1 (1)
E255K	3 (3)	2 (2)	1 (1)
M244V	2 (2)	1 (1)	3 (3)
V299L	2 (2)	2 (2)	1 (1)
≥2 mutations detected	5 (5)	6 (6)	10 (11)

[a]Sanger sequencing was used for mutation testing

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

[c]Mutations identified in at least 5 patients (combined for the 3 cohorts) are being presented here

Demographics and Baseline Disease Characteristics
(Slide 3 of 3)

Characteristic	15 mg (n=94)	30 mg→15 mg (n=94)	45 mg→15 mg (n=94)
Reason for prior therapy stopped, resistance, n (%)	94 (100)	94 (100)	92 (98)
Prior TKIs, n (%)			
1	4 (4)	1 (1)	1 (1)
2	42 (45)	37 (39)	43 (46)
≥3	48 (51)	56 (60)	50 (53)
Prior 2G-TKIs, n (%)			
≥1	90 (96)	93 (99)	93 (99)
≥2	56 (60)	64 (68)	56 (60)

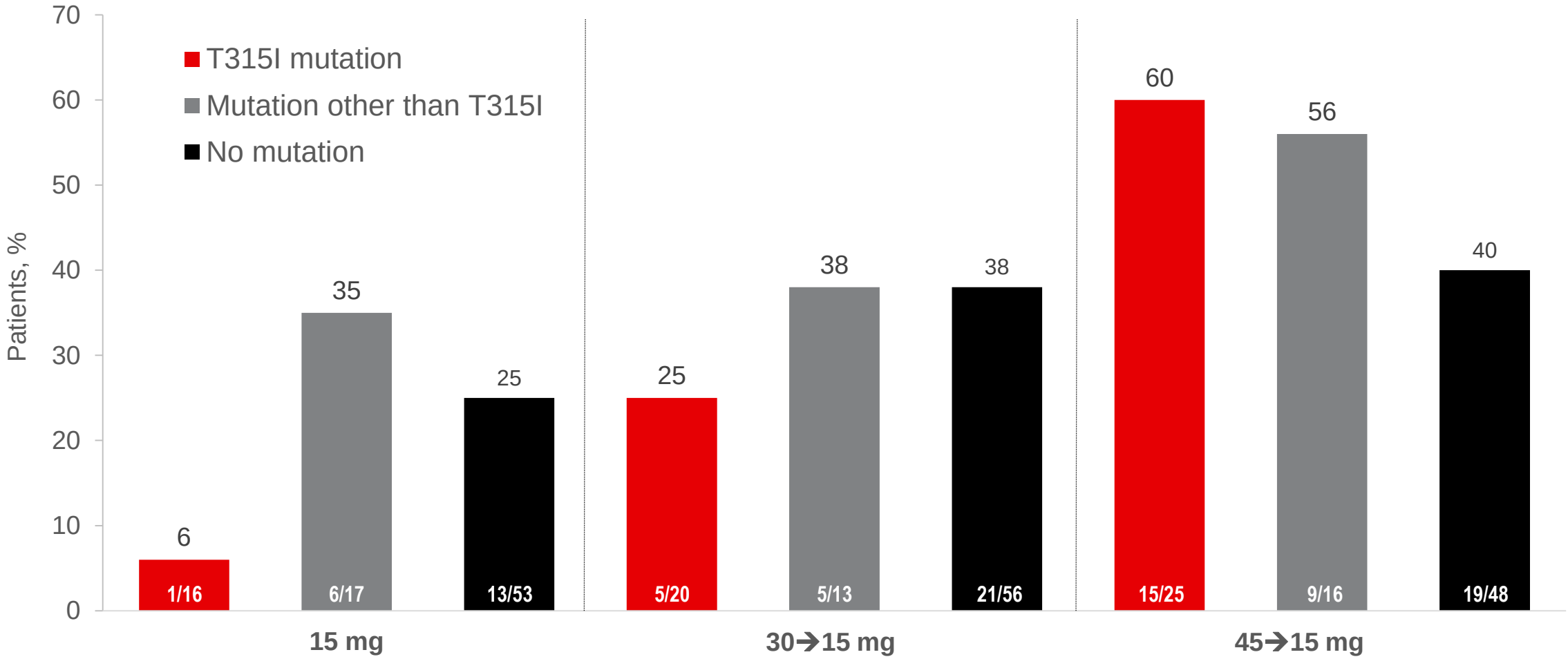
CHR, complete hematologic response.

Efficacy Results by Baseline Mutation Status

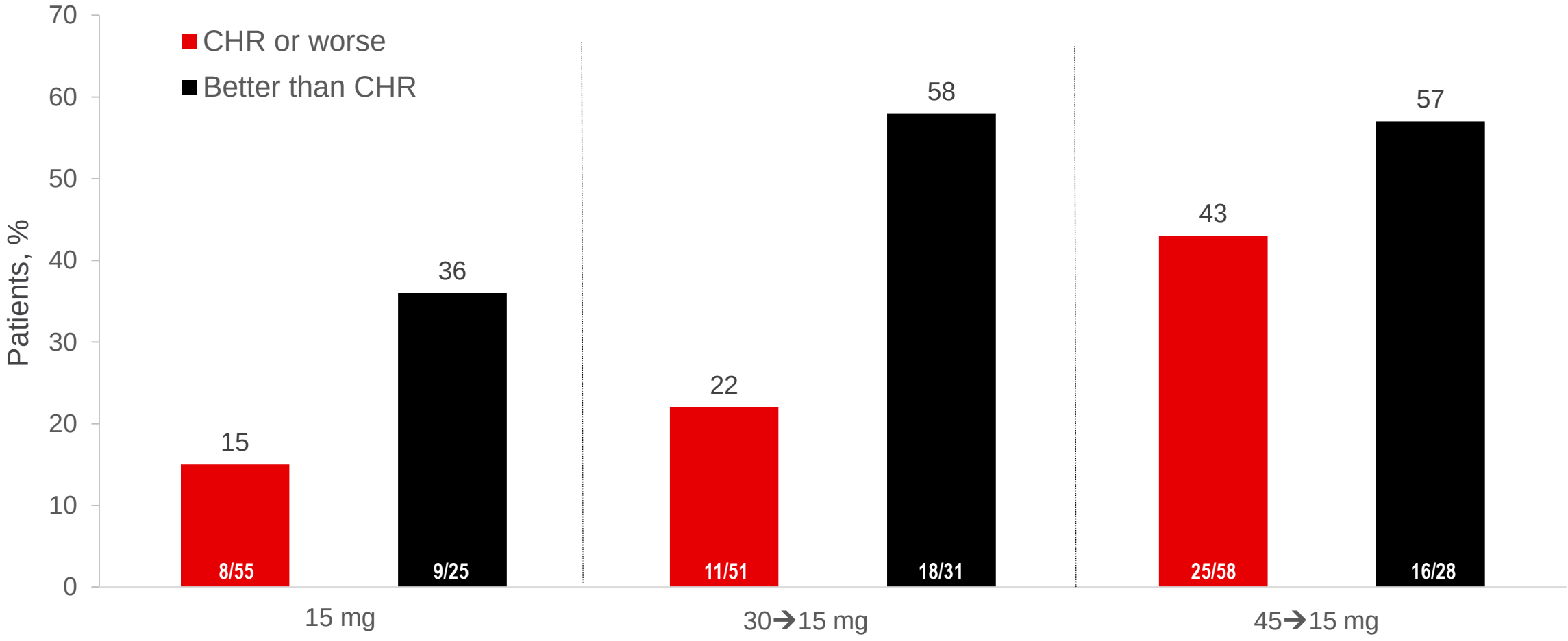
	Ponatinib Starting Dose Cohort		
Baseline Characteristic	**15 mg**	**30 mg → 15 mg**	**45 mg → 15 mg**
≤1% *BCR-ABL1^{IS}* rate by 12 months, n/N (%)			
Total patients[a]	20/86 (23)	31/89 (35)	43/89 (48)
No mutation	13/53 (25)	21/56 (38)	19/48 (40)
Any mutation	7/33 (21)	10/33 (30)	24/41 (59)
T315I mutation	1/16 (6)	5/20 (25)	15/25 (60)
Mutation other than T315I	6/17 (35)	5/13 (38)	9/16 (56)

[a] Analysis based on the ITT population and includes patients who had at least 1 postbaseline molecular assessment; patients on study for less than 12 months were excluded from the denominator

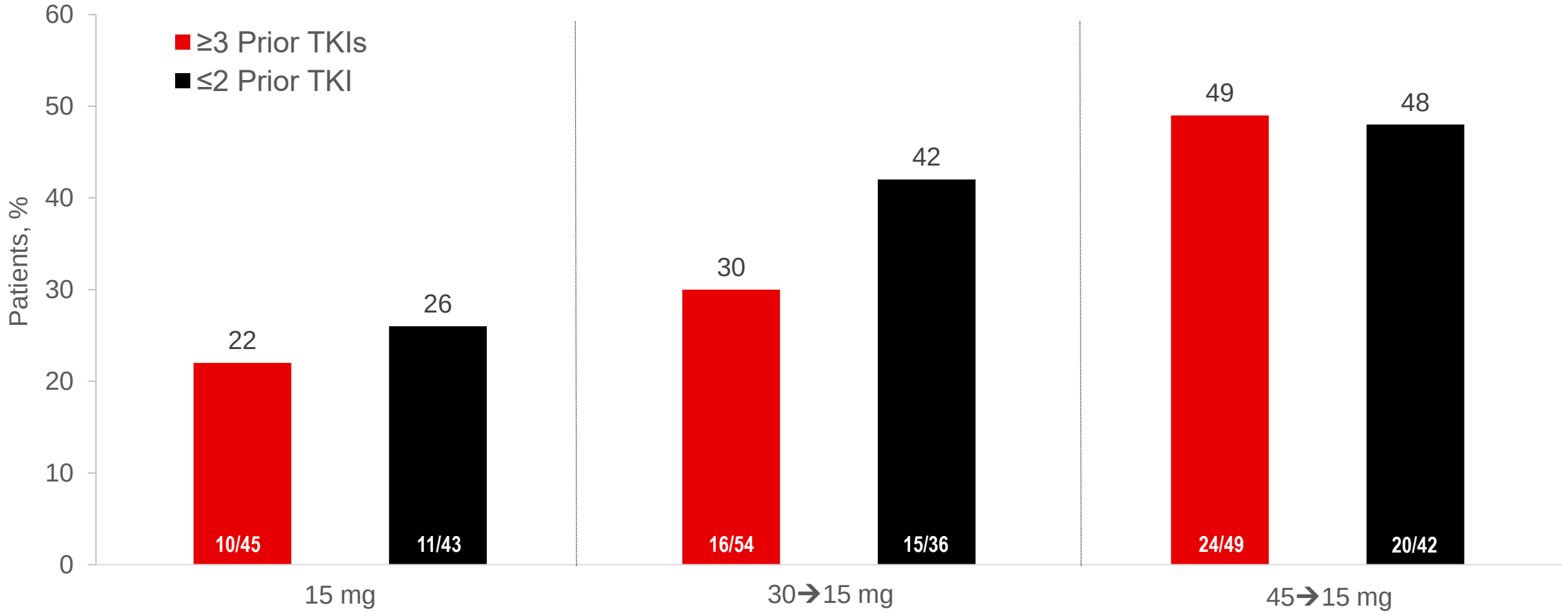
≤1% *BCR-ABL1*^{IS} Rate by 12 Months by T315I Mutation Status



≤1% *BCR-ABL1*^{IS} Rate by 12 Months by Best Response to Last Prior TKI



≤1% BCR-ABL1^{IS} Rate by 12 Months by Number of Prior TKIs[a]



[a] At baseline 45% of patients had ≤2 prior TKIs; 2% with 1 prior TKI and 43% with 2 prior TKIs.

TEAEs by Number of Prior TKIs (Safety Population)[a]

	Ponatinib Starting Dose Cohort					
	15 mg (n=94)		30 mg →15 mg (n=94)		45 mg →15 mg (n=94)	
	≤2 prior TKIs (n=46)	≥3 prior TKIs (n=48)	≤2 prior TKIs (n=38)	≥3 prior TKIs (n=56)	≤2 prior TKIs (n=44)	≥3 prior TKIs (n=50)
Serious TEAE, n (%)	8 (17)	18 (38)	8 (21)	14 (25)	12 (27)	17 (34)
Grades 3–4 TEAE, n (%)	25 (54)	27 (56)	23 (61)	30 (54)	28 (64)	32 (64)
Grade 5 TEAE, n (%)	1 (2)	1 (2)	0	0	1 (2)	1 (2)
TE-AOE (pre-adjudication), n (%)	1 (2)	1 (2)	1 (3)	3 (5)	2 (5)	6 (12)
TE-AOE (adjudicated), n (%)	0	1 (2)	1 (3)	3 (5)	2 (5)	3 (6)
Serious TE-AOE (pre-adjudication), n (%)	0	0	1 (3)	2 (4)	0	4 (8)
Serious TE-AOE (adjudicated), n (%)	0	0	1 (3)	2 (4)	0	2 (4)

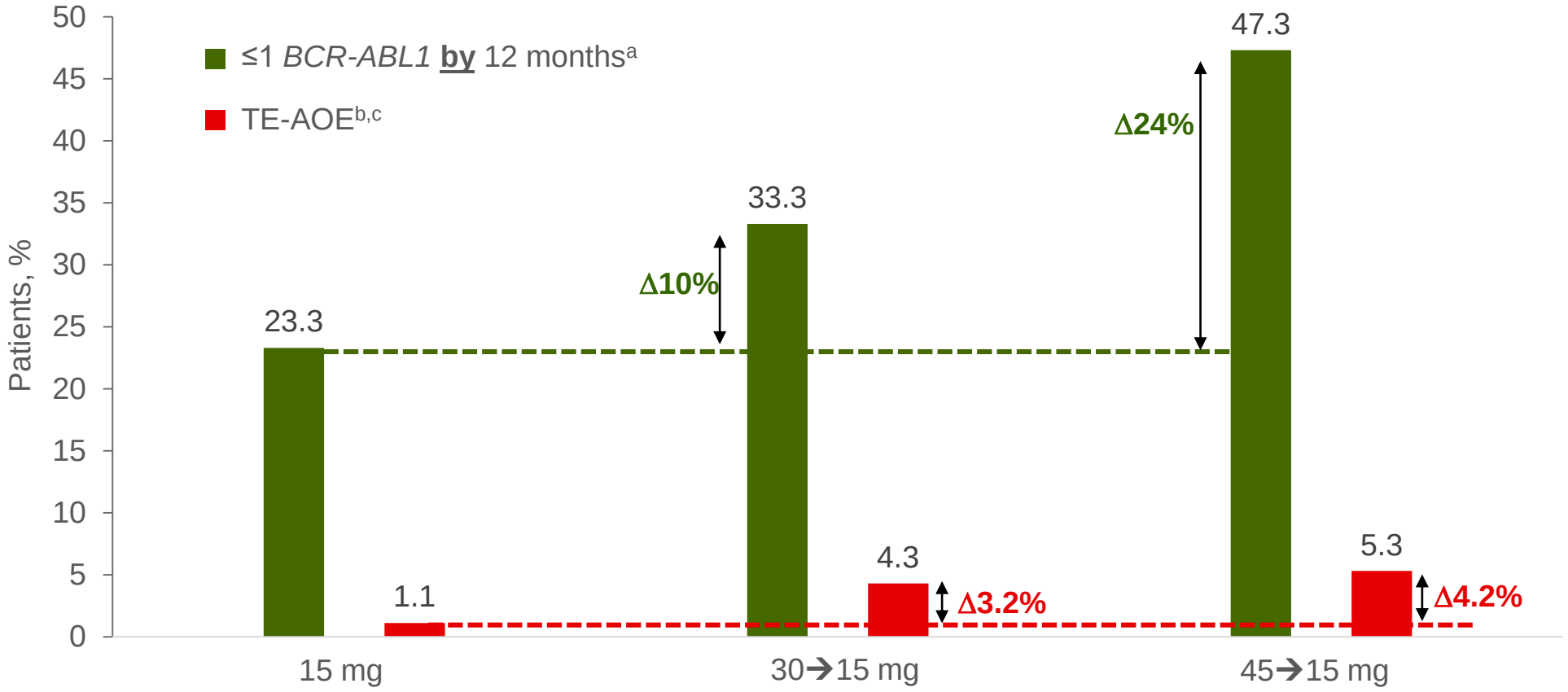
- **There was a trend toward higher serious TEAE rates for patients treated with ≥3 TKIs**
- **Rates of adjudicated AOEs were low (0%–6%) in all 3 cohorts irrespective of the number of prior TKIs**
- **There were no AOEs related to death**

[a] The safety population included all randomized patients who received at least 1 dose of study drug (N=282)

→ 15 mg , Cohort A is referred to as 45 mg → 15 mg and Cohort B as 30 mg → 15 mg because the study design has a dose reduction to 15 mg upon achievement of ≤1% *BCR-ABL1*^{IS}. There also were patients in Cohorts A and B who dose-reduced to different dose levels (30, 15, and 10 mg) due to safety

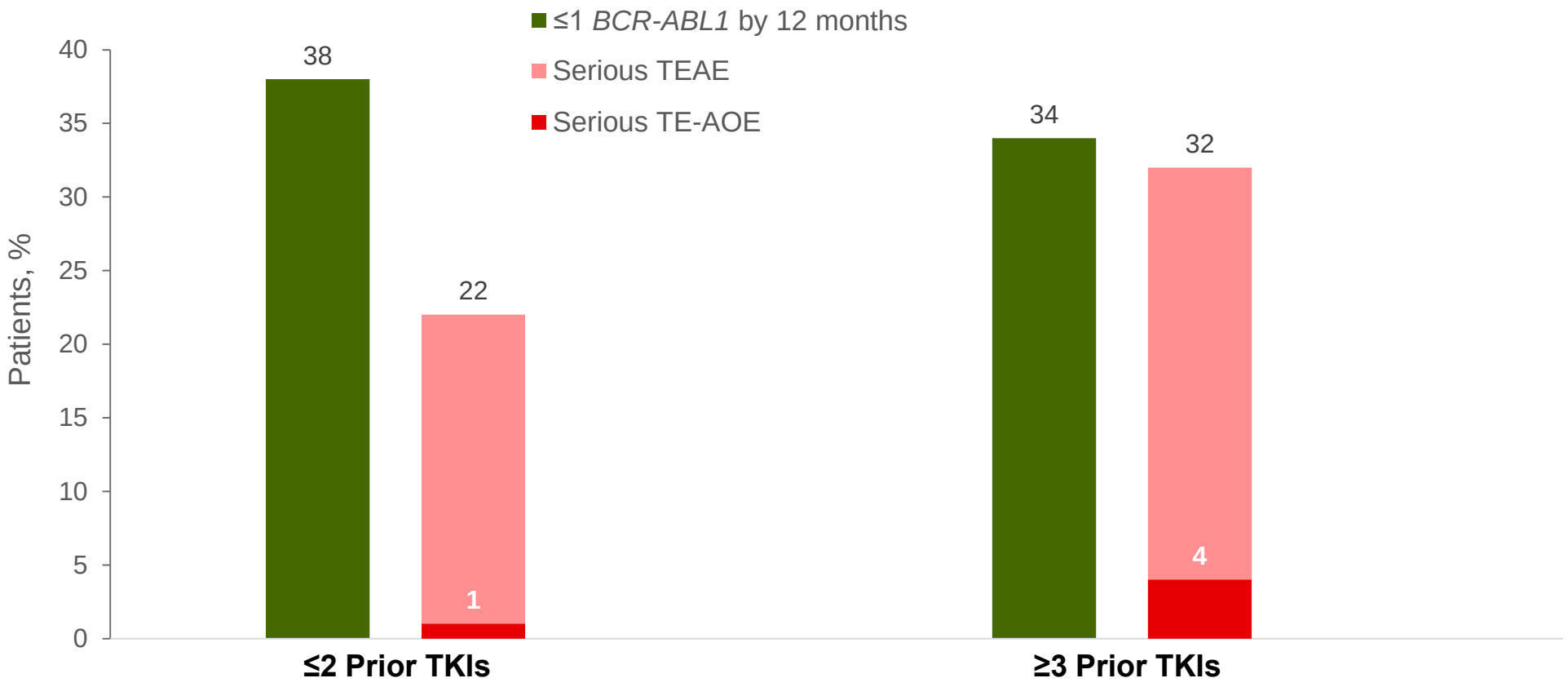
TE-AOE, treatment-emergent arterial occlusive event

Overall Safety and Efficacy by Starting Dose



[a] Efficacy n's by cohort: 15 mg, n=90; 30 mg and 45 mg, n=93. [b] TE-AOE n's by cohort: all cohorts, n=94. [c] AOEs are based on adjudication

Overall Safety and Efficacy by Number of Prior TKIs[a,b]



[a] The safety population included all randomized patients who received at least 1 dose of study drug (N=282)

[b] AOEs are based on adjudication

Conclusions

- At this interim analysis in patients with highly resistant CP-CML with a median follow-up of ≈21 months, the maximum benefit:risk, regardless of mutation status or number of prior TKIs, was observed with a 45-mg starting dose with a reduction to 15 mg upon achievement of response
- In resistant patients with or without mutations, the rate of ≤1% *BCR-ABL1*^{IS} by 12 months was highest in Cohort A (45-mg starting dose), with the most notable differences seen in patients with T315I mutation
- OPTIC IA shows the benefit of ponatinib in all 3 dosing regimens in a largely resistant population where the majority of patients (>60%) failed to achieve a response greater than CHR on immediate prior therapy
- Use of ponatinib in earlier lines of therapy provides an optimal benefit:risk profile with a potential trend toward better outcomes for patients previously treated with ≤2 TKIs
- Primary analysis will provide a refined understanding of the benefit:risk profile of 3 different starting doses of ponatinib

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