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Interim Analysis From the OPTIC Trial: A Dose-Ranging Study of 3 Starting Doses of Ponatinib

Jorge Cortes,[1] Elza Lomaia,[2] Anna Turkina,[3] Beatriz Moiraghi,[4] Maria Undurraga Sutton,[5] Carolina Pavlovsky,[6] Christine Rojas,[7] Charles Chuah,[8] Christopher Kevin Arthur,[9] Jane Apperley,[10] Dong-Wook Kim,[11] Andreas Hochhaus,[12] Philippe Rousselot,[13] Gianantonio Rosti,[14] Michael Mauro,[15] Jeffrey Lipton,[16] Daniel Naranjo,[17] Guohui Liu,[17] Shouryadeep Srivastava,[17] Michael Deininger[18]

[1]Georgia Cancer Center, Augusta, GA, USA; [2]Almazov National Medical Research Centre, Moscow, Russia; [3]Russian Academy of Medical Sciences, Moscow, Russia; [4]Hospital Jose Maria Ramos Mejia, Buenos Aires, Argentina; [5]Hospital del Salvador, Santiago, Chile; [6]Fundaleu, Buenos Aires, Argentina; [7]Centro de Investigaciones Clinicas Vina del Mar, Valparaíso, Chile; [8]Singapore General Hospital, Duke-NUS Medical School, Singapore; [9]Royal North Shore Hospital, St. Leonards, Australia; [10]Imperial College Healthcare NHS Trust, London, United Kingdom; [11]Catholic University of Korea – Seoul, Seoul, South Korea; [12]Universitätsklinikum Jena, Jena, Germany; [13]Hospital Mignot University de Versailles Saint-Quentin-en-Yvelines, Paris, France; [14]University of Bologna, Bologna, Italy; [15]Memorial Sloan Kettering, New York, NY, USA; [16]University of Toronto, Toronto, Ontario, Canada; [17]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [18]University of Utah, Huntsman Cancer Hospital, Salt Lake City, UT, USA

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CML Clinical

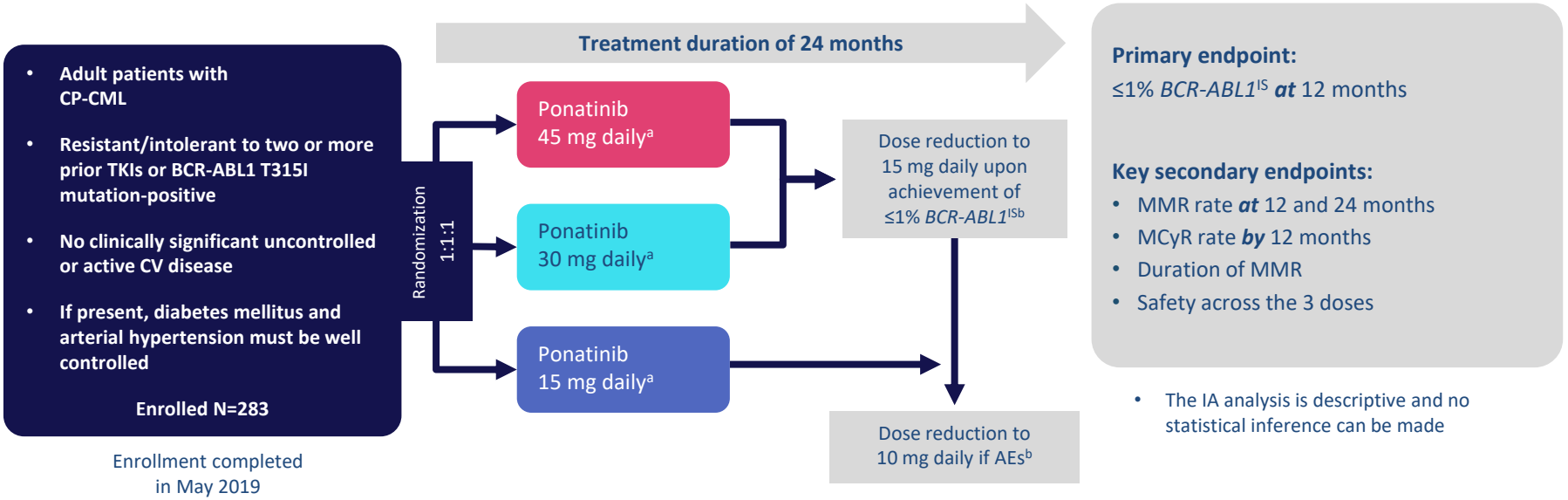
Introduction

- Ponatinib is an orally active third-generation TKI designed to optimally inhibit all BCR-ABL1 single mutants[1,2]
- Patients with resistant and intolerant CP-CML with substantial prior treatment demonstrated deep, lasting responses to ponatinib in the pivotal PACE trial[1]
- A post hoc analysis modeling the data from PACE suggested a relationship between dose and both adverse events (AEs) and response rates[3]
- Lower ponatinib doses may mitigate AOE risk while maintaining efficacy[3]
- At this interim analysis, we present 21-month results (data cutoff: 20 July 2019) from the OPTIC trial, which evaluates the safety and efficacy of ponatinib over a range of 3 starting doses (45, 30, or 15 mg/d)

AE, adverse event; 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. O'Hare T, et al. *Cancer Cell*. 2009;16:401-412. 3. Pinilla-Ibarz J, et al. Poster presented at: 55th Annual Meeting of the American Society of Hematology; December 7–10, 2013; New Orleans, LA, USA. Abstract 5682/Poster 4007.

OPTIC (Optimizing Ponatinib Treatment In CP-CML): Ongoing, Multicenter, Randomized Phase 2 Trial



Enrollment completed in May 2019

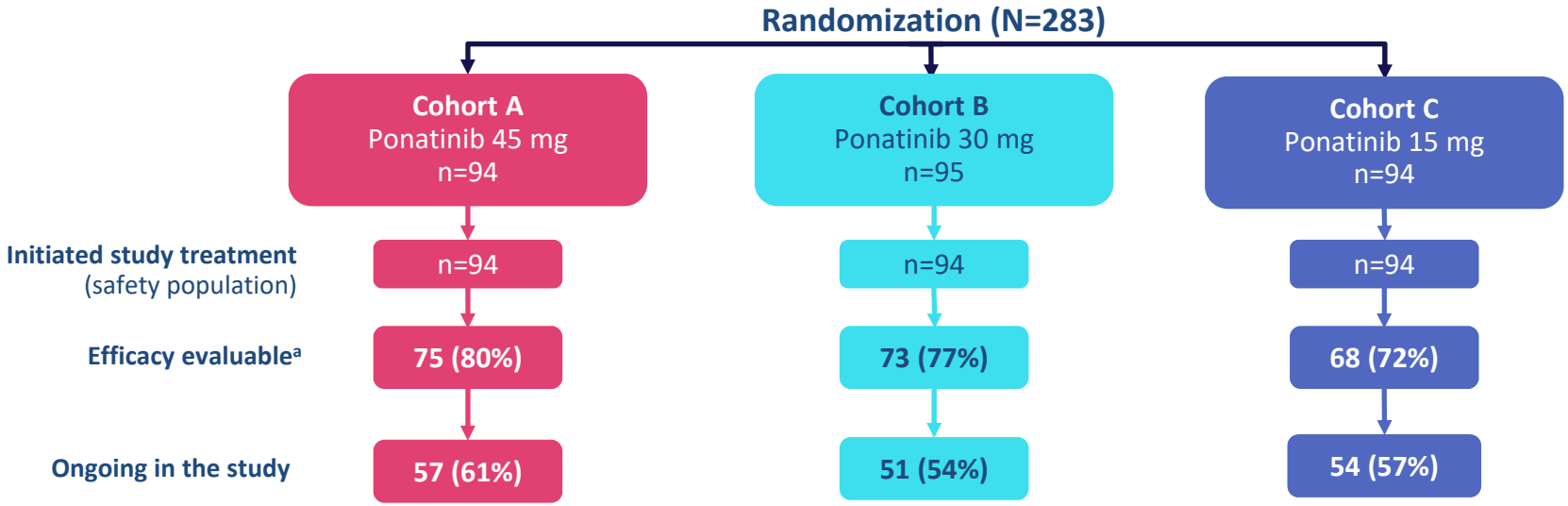
[a] Dose reductions due to AEs were permitted
[b] Escalation to the starting dose allowed for patients who lose their response following dose reduction; no dose escalation allowed beyond starting dose
AOE, arterial occlusive event; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CV, cardiovascular; IA, interim analysis; IS, International Scale; MCyR, major cytogenetic response; MMR, major molecular response; VTE, venous thromboembolism

Patient Demographics and Baseline Disease Characteristics

Demographic/Disease Characteristic		Cohort A 45 mg (n=94)	Cohort B 30 mg (n=94)	Cohort C 15 mg (n=94)
Age, y	Median (range)	46.0 (19–81)	50.5 (21–77)	49.0 (18–81)
Gender, n (%)	Male	50 (53.2)	38 (40.4)	53 (56.4)
ECOG PS score, n (%)	0 or 1	93 (98.9)	93 (98.9)	94 (100)
Time since diagnosis, y	Median (range)	5.5 (1–21)	4.9 (1–29)	5.7 (1–22)
Prior TKIs, n (%)	1	1 (1.1)	1 (1.1)	4 (4.3)
	2	43 (45.7)	37 (39.4)	42 (44.7)
	≥3	50 (53.2)	56 (59.6)	48 (51.0)
BCR-ABL1 mutation at baseline, n (%)	No mutation detected	51 (54.3)	58 (61.7)	54 (57.4)
	T315I	25 (26.6)	21 (22.3)	20 (21.3)
	1 mutation detected	31 (33.0)	29 (30.9)	33 (35.1)
	≥2 mutations detected	10 (10.6)	6 (6.4)	5 (5.4)
Reason prior therapy stopped, n (%)	Resistant	93 (98.9)	94 (100.0)	94 (100.0)
Best response to last prior TKI, n (%)	None/PD	29 (31)	27 (29)	18 (19)
	CHR	31 (33)	28 (30)	39 (41)
	MCyR	20 (21)	16 (17)	10 (11)
	CCyR	7 (7)	6 (6)	7 (7)
	MMR	2 (2)	6 (6)	7 (7)

CHR, complete hematologic response; PD, progressive disease; SD, standard deviation

Patient Disposition



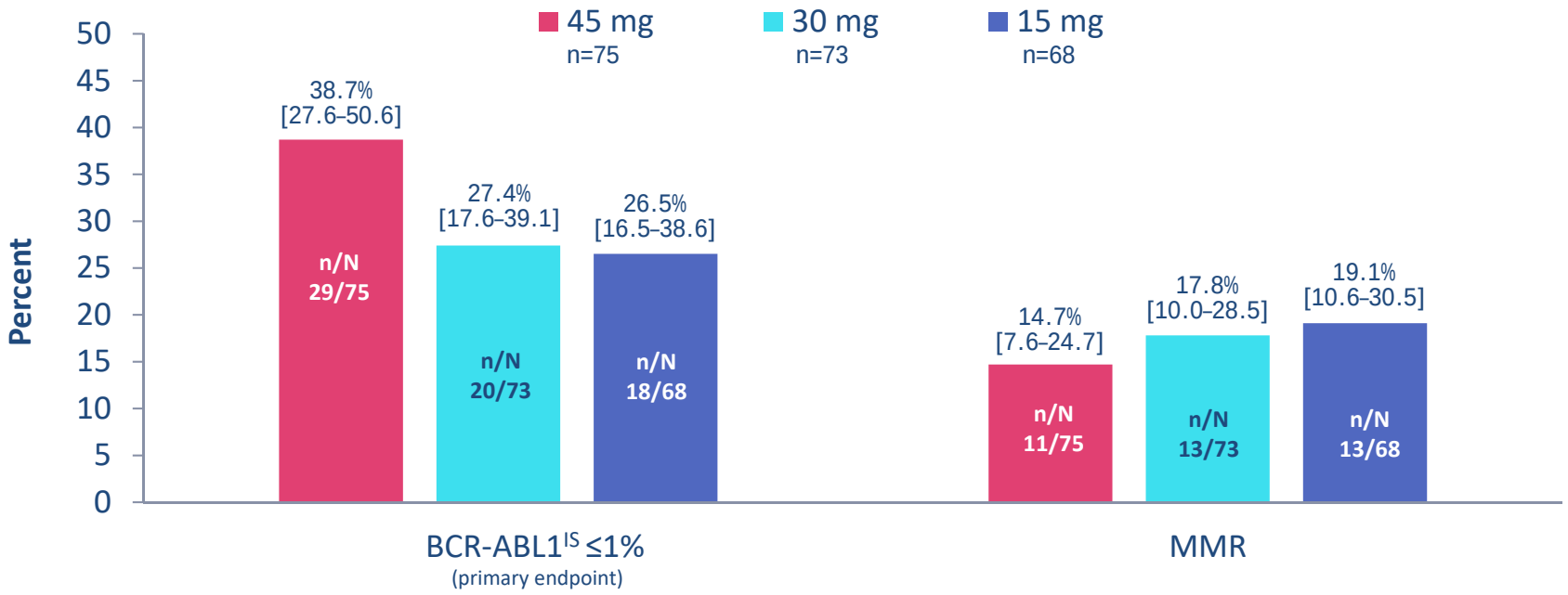
By the IA (cutoff date of July 20, 2019), 77% (n/N=216/282) of patients in the OPTIC trial were evaluable for the primary endpoint

[a] Includes patients who have reached 12 months' follow-up, those who had early termination (ie, not reached 12-month mark but discontinued treatment), and those who have the b2a2/b3a2 transcript type at baseline

Exposure and Follow-up by Ponatinib Starting Dose

Exposure		Cohort A 45 mg (n=94)	Cohort B 30 mg (n=94)	Cohort C 15 mg (n=94)
Duration of exposure, months	Median (range)	14 (0.1–43.6)	12 (0.1–46.2)	12 (0.3–51.6)
Duration of exposure, n (%)	<1 month	3 (3.2)	4 (4.3)	2 (2.1)
	1–<3 months	6 (6.4)	10 (10.6)	8 (8.5)
	3–<6 months	13 (13.8)	8 (8.5)	14 (14.9)
	6–<12 months	18 (19.1)	21 (22.3)	23 (24.5)
	≥12–<24 months	27 (28.7)	30 (31.9)	26 (27.7)
	≥24 months	27 (28.7)	21 (22.3)	21 (22.3)
Dose intensity, mg/d	Median (range)	30.0 (10.5–45.0)	24.3 (5.5–30.0)	15.0 (6.0–15.0)
Follow-up, months	Median (range)	21 (15.0–24.0)	20 (13.7–23.9)	21 (12.6–24.1)

BCR-ABL1^{IS} ≤1% and MMR at 12 Months



BCR-ABL1^{IS} ≤1% at Month 12, n (%) [95% CI]; BCR-ABL1^{IS} ≤0.1% (MMR) at Month 12, n (%). At this IA, the analysis for primary endpoint is descriptive and no statistical inference is to be made.
CI, confidence interval. Patients who have not reached 12-month primary endpoint evaluable criteria were not included in the IA (Cohort A, n=18; Cohort B, n=20; Cohort C, n=22).

Maintenance of Response Upon Dose Reduction

	Cohort A, 45 mg (n=93)		Cohort B, 30 mg (n=93)	
	Number of Patients Who Achieved BCR-ABL1^{IS} ≤1%, n	Percent of Responders Who Maintained BCR-ABL1^{IS} ≤1%, n/n (%)	Number of Patients Who Achieved BCR-ABL1^{IS} ≤1%, n	Percent of Responders Who Maintained BCR-ABL1^{IS} ≤1% n/n (%)
TOTAL	48		33	
No dose reduction to 15 mg[a]	6		2	
Dose reduction to 15 mg *BEFORE* achieving BCR-ABL1^{IS} ≤1%	6	6/6 (100)	5	3/5 (60)
Dose reduction to 15 mg *AFTER* achieving BCR-ABL1^{IS} ≤1%	36	27/36 (75)	24	21/24 (88)
<90 days after dose reduction	13	4/13 (31)	10	7/10 (70)
≥90 days after dose reduction	23	23/23 (100)	14	14/14 (100)
≥180 days after dose reduction	19	19/19 (100)	13	13/13 (100)
≥360 days after dose reduction	12	12/12 (100)	8	8/8 (100)

- Molecular responses were maintained in all patients who were on the reduced dose for at least 90 days
- Patients who could not maintain their response on a reduced dose of 15 mg/d, can be identified in less than 90 days after dose reduction

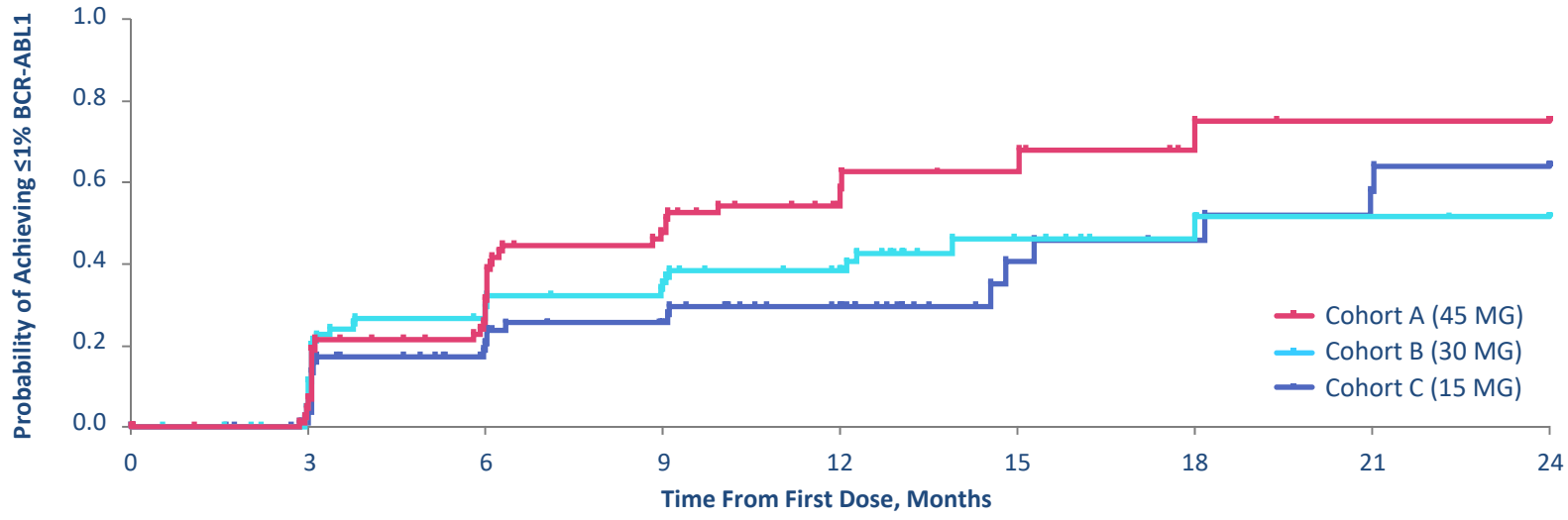
[a] Protocol deviation

Re-escalation[a] of Dose in Patients Who Lost Response

	Cohort A (45 mg) (n=93)	Cohort B (30 mg) (n=93)	Cohort C (15 mg) (n=90)
Achieved ≤1% BCR-ABL1^{IS} at any time, n	48	33	29
Loss of ≤1% BCR-ABL1^{IS} at any time, n	9	5	2
Dose re-escalated after loss of response, n	9	4	0
Regained ≤1% BCR-ABL1^{IS}			
Yes, n (%)	3 (33.3)	2 (50.0)	0
No, n (%)	6 (66.7)	2 (50.0)	0
Median (range) follow-up for patients with dose re-escalation after loss of response, days	134 (1–746)	392 (1–510)	–

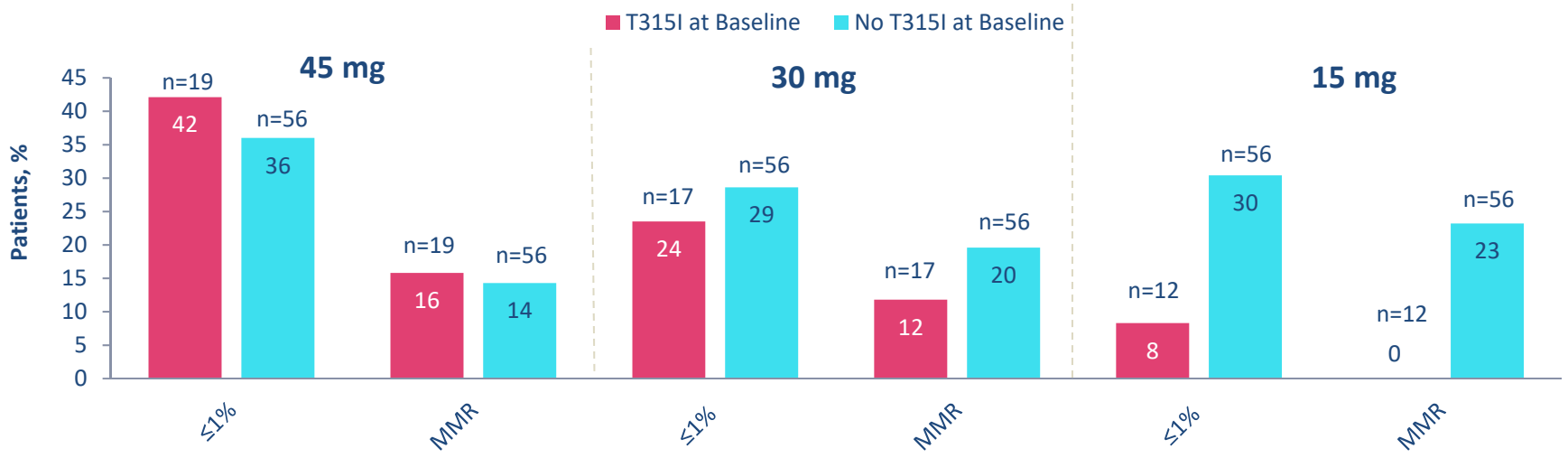
[a] Escalation was not allowed beyond the starting dose

Time to ≤1% BCR-ABL1^{IS} Response by Ponatinib Starting Dose



Number at risk									
Cohort A	93	78	47	33	20	14	7	6	0
Cohort B	93	70	50	43	31	14	9	7	0
Cohort C	90	78	49	37	25	11	9	7	0

BCR-ABL1^{IS} Response at 12 Months[a] by T315I Baseline Status



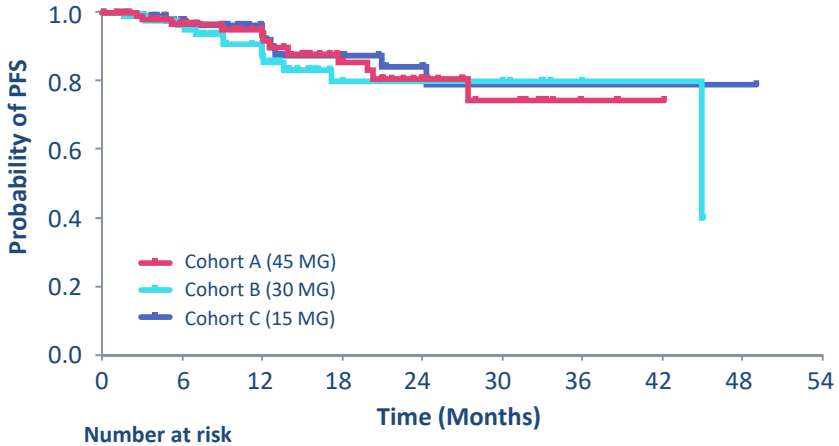
- In the 15-mg/d starting dose cohort, a lower proportion of patients with the T315I mutation at baseline achieved ≤1% BCR-ABL1^{IS} vs those without (8.3% vs 30.4%), suggesting that this starting dose is not as effective as the higher starting doses for patients with the T315I mutation

MMR is ≤0.1% BCR-ABL1^{IS}

[a] Not all patients reached 12 months' follow-up at the time of the analysis

Progression-Free[a] and Overall Survival[a]

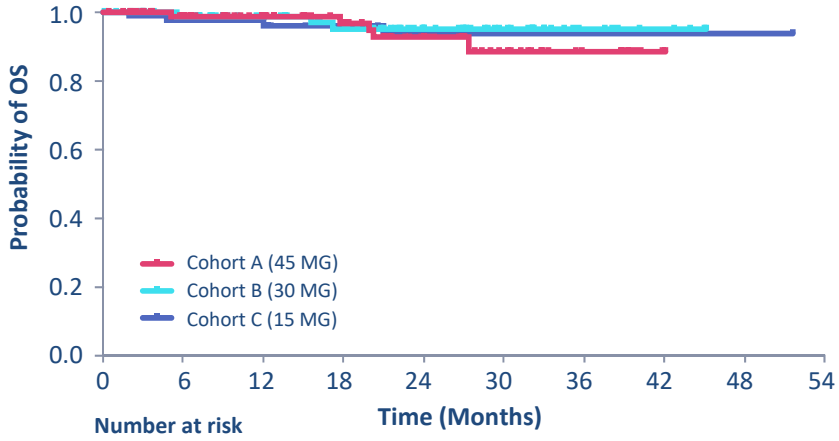
PFS



Number at risk

Cohort A	94	72	54	38	26	11	3	1	0	0
Cohort B	95	74	53	23	18	9	3	2	0	0
Cohort C	94	69	46	30	20	7	3	1	1	0

OS



Number at risk

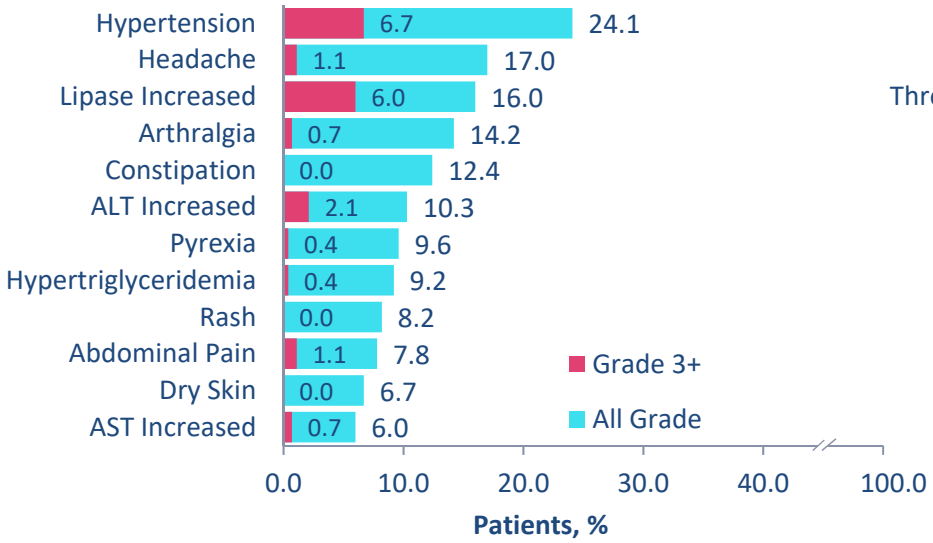
Cohort A	94	78	63	51	36	18	8	1	0	0
Cohort B	95	80	64	51	36	20	8	4	0	0
Cohort C	94	76	60	50	36	19	8	2	1	0

[a] Not all patients reached 12 months' follow-up at the time of the analysis. PFS was analyzed according to the criteria in O'Brien et al, 2003 and included: death; development of accelerated-phase or blast-phase chronic myeloid leukemia; loss of CHR (in the absence of cytogenetic response) confirmed by development in complete blood counts at least 4 weeks apart; Loss of major cytogenetic response by bone marrow cytogenetic assessment; increasing white blood cell count in patient without CHR defined by doubling of white blood cell count to >20,000 on 2 occasions at least 4 weeks apart (after the first 4 weeks of therapy)

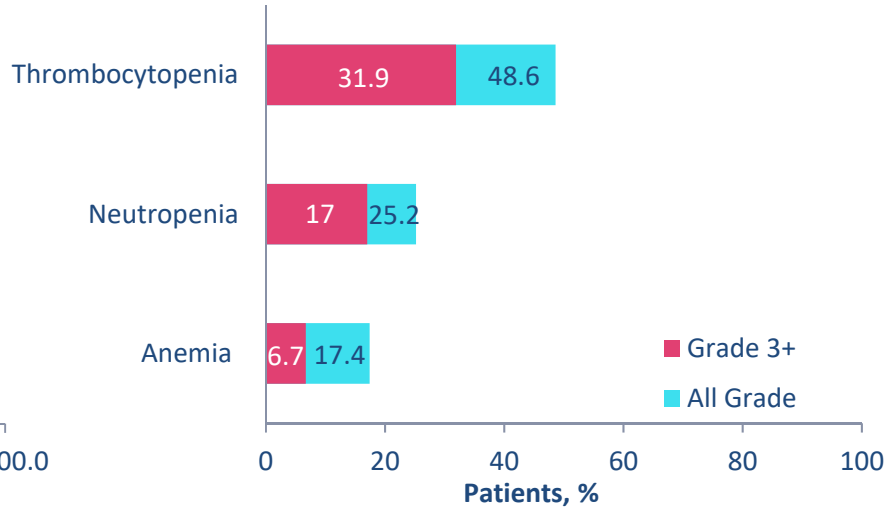
OS, overall survival; PFS, progression-free survival

Most Common Treatment-Emergent Adverse Events

Incidence of Most Common Non-Hematologic TEAEs, %[a,b]



Incidence of Most Common Hematologic TEAEs, %[a,c]



[a] All patients (safety population); [b] AST, dry skin, abdominal pain, rash, hypertriglyceridemia, and pyrexia occurred in ≥10% of the population within Cohort A or B, but not in the total population;
[c] Thrombocytopenia includes platelet count decreased
ALT, alanine aminotransferase increased; AST, aspartate aminotransferase increased; TEAEs, treatment-emergent adverse events

TEAE Summary and Related Dose Modifications/ Discontinuations

TEAE Summary and Dose Modifications, n (%)	Cohort A 45 mg (n=94)	Cohort B 30 mg (n=94)	Cohort C 15 mg (n=94)
Any TEAE	97.9%	92.6%	91.5%
Grade ≥3 TEAEs	66.0%	56.4%	57.4%
SAEs	30.9%	23.4%	27.7%
Deaths on-study, n	2[a]	--	2[b]
TEAEs leading to treatment discontinuation, dose reduction, or dose interruption, n (%)	65 (69.1)	54 (57.4)	52 (55.3)
TEAE leading to dose reduction, n (%)	41 (43.6)	29 (30.9)	26 (27.7)
TEAE leading to dose interruption, n (%)	64 (68.1)	48 (51.1)	50 (53.2)
TEAE leading to treatment discontinuation, n (%)	17 (18.1)	14 (14.9)	13 (13.8)

[a] Sudden death was the cause of death for both patients
[b] Pneumonia was the cause of death for both patients
SAEs, serious adverse events

Pre-adjudication and Adjudicated AOE Rates and Dose Modifications

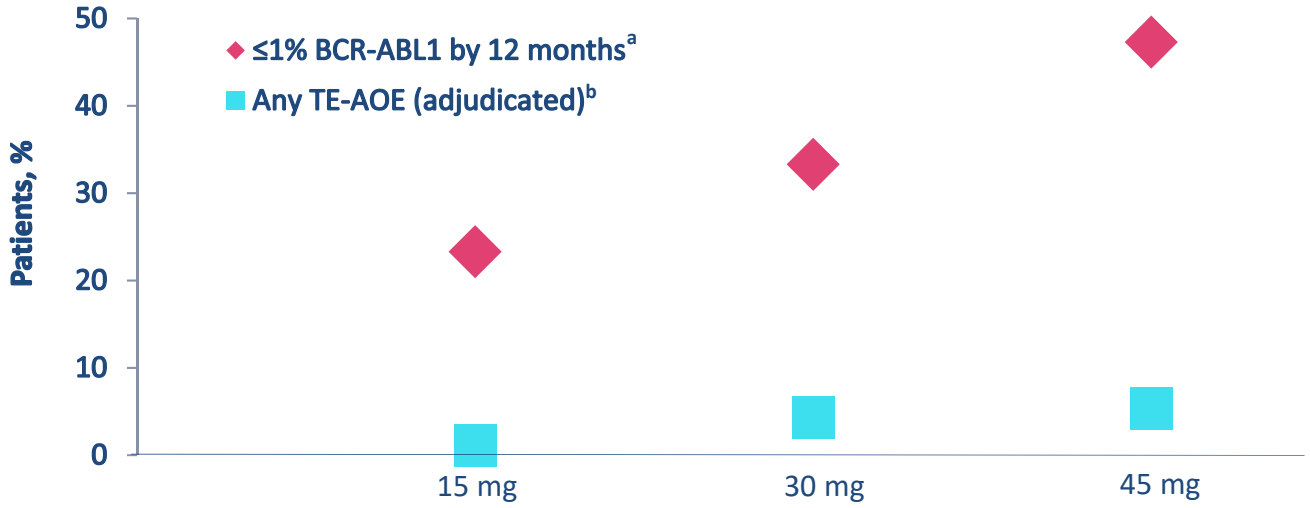
Treatment Emergent AOEs, n (%)	Cohort A Ponatinib 45 mg		Cohort B Ponatinib 30 mg		Cohort C Ponatinib 15 mg	
	Pre-adjudication	Adjudicated	Pre-adjudication	Adjudicated	Pre-adjudication	Adjudicated
AOEs	8 (8.5)	5 (5.3)	4 (4.3)	4 (4.3)	2 (2.1)	1 (1.1)
Serious AOEs	4 (4.3)	2 (2.1)	3 (3.2)	3 (3.2)	0	0
Grade ≥3 AOEs	4 (4.3)	3 (3.2)	4 (4.3)	4 (4.3)	0	0
Dose modifications for AOE, n (%)	**Pre-adjudication**	**Adjudicated**	**Pre-adjudication**	**Adjudicated**	**Pre-adjudication**	**Adjudicated**
Discontinuation	4 (4.3)	2 (2.1)	3 (3.2)	3 (3.2)	0	0
Reduction	1 (1.1)	0	1 (1.1)	1 (1.1)	0	0
Interruption	1 (1.1)	0	1 (1.1)	1 (1.1)	0	0

- Independent adjudication committee reviewed AOEs using the ACC/AHA, FDA, and STCI definitions[1]
- Blinded to dose, dose modification, and investigator causality opinion
- No AOE-related deaths reported
- Only 7 AOEs (4 in A and 3 in B) led to treatment discontinuation
- Overall adjudication AOE rate of 3.5%

ACC/AHA, American College of Cardiology/American Heart Association; FDA, US Food and Drug Administration; STCI, Standardized Data Collection for Cardiovascular Trials Initiative

1. Hicks KA, et al. *J Am Coll Cardiol*. 2015;66(4):403-469.

Observed Ponatinib Dose Relationship With Response Rate and TE-AOE Incidence Rate



- The percentage of patients with ≤1% BCR-ABL1^{IS} and TE-AOE rates increased with increasing ponatinib 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; TE-AOE, treatment-emergent arterial occlusive event

Conclusions

- OPTIC IA demonstrates benefit with ponatinib in all 3 dosing regimens in this resistant CP-CML population
- Maximum rates of ≤1% BCR-ABL1^{IS} at 12 months were achieved in the 45-mg/d starting dose cohort, and responses were maintained with the dose reduction to 15 mg/d
- At this IA, response-based ponatinib dosing regimens resulted in a clinically manageable safety and AOE profile
- With a median follow-up of ≈21 months, IA from OPTIC demonstrates that optimal benefit:risk profile for ponatinib was achieved with a response-adjusted dosing regimen starting with 45-mg/d dose, followed by dose reduction to 15 mg/d upon achieving ≤1% BCR-ABL1^{IS}
- Primary analysis will provide a refined understanding of the benefit:risk profile of 3 different starting doses of ponatinib

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