Long-term results from the OPTIC trial: A dose-optimization study of 3 starting doses of ponatinib

Jorge Cortes,[1] Michael Deininger,[2] Elza Lomaia,[3] Beatriz Moiraghi,[4] Maria Undurraga Sutton,[5] Carolina Pavlovsky,[6] Charles Chuah,[7] Tomasz Sacha,[8] Jeffrey H. Lipton,[9] James McCloskey,[10] Andreas Hochhaus,[11] Philippe Rousselot,[12] Gianantonio Rosti,[13] Hugues de Lavallade,[14] Anna Turkina,[15] Lori Maness,[16] Moshe Talpaz,[17] Michael Mauro,[18] Vickie Lu,[19] Alexander Vorog,[19] Jane Apperley[20]

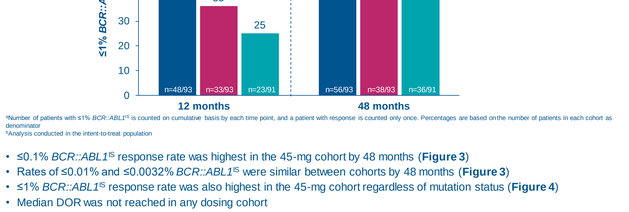
[1]Georgia Cancer Center, Augusta, GA, USA; [2]Versiti Blood Research Institute, Milwaukee, WI, USA; [3]Almazov National Medical Research Centre, St. Petersburg, Russia; [4]Hospital Jose Maria Ramos Mejia, Buenos Aires, Argentina; [5]Hospital del Salvador, Santiago, Chile; [6]Fundaleu, Buenos Aires, Argentina; [7]Singapore General Hospital, Duke-NUS Medical School, Singapore; [8]Jagiellonian University Hospital in Krakow, Krakow, Poland; [9]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [10]The John Theurer Cancer Center at Hackensack Meridian Health, Hackensack, NJ, USA; [11]Universitätsklinikum Jena, Jena, Germany; [12]Centre Hospitalier de Versailles, UMR1184, Université de Versailles Saint-Quentin-en-Yvelines, Paris, France; [13]IRST/IRCCS "Dino Amadori," Meldola (FC), Italy; [14]King's College Hospital NHS Foundation, London, UK; [15]National Medical Research Center for Hematology, Moscow, Russia; [16]University of Nebraska Medical Center, Omaha, NE, USA; [17]Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI, USA; [18]Memorial Sloan Kettering, New York, NY, USA; [19]Takeda Development Center Americas, Inc., Lexington, MA, USA; [20]Imperial College London, London, UK

Background

- Ponatinib is an approved BCR::ABL1 tyrosine kinase inhibitor (TKI) that potently inhibits native BCR::ABL1 and all reported single-resistance mutants, including T315I[1,2]
- Patients with chronic-phase chronic myeloid leukemia (CP-CML) who become resistant to a second-generation BCR::ABL1 TKI, with or without point mutations in *BCR::ABL1*, have poor long-term outcomes if treated with another second-generation BCR::ABL1 TKI[1,2]
- The phase 2 OPTIC (Optimizing Ponatinib Treatment in CP-CML, NCT02467270) trial is evaluating the efficacy and safety of ponatinib in patients with CP-CML whose disease is resistant to ≥2 TKIs or who harbor T315I[3]
  - OPTIC used a novel response-based dose-adjustment strategy in which patients were randomized to once-daily 45-, 30-, or 15-mg ponatinib starting doses, with dose reduction to 15 mg upon achievement of ≤1% *BCR::ABL1*^{IS} in the 45-mg and 30-mg cohorts
- Results from the OPTIC primary analysis demonstrated an improved risk:benefit ratio for the 45-mg/d starting dose cohort
- We present here the first analysis of the 4-year update with long-term efficacy and safety outcomes from the OPTIC trial

Methods

Figure 1: OPTIC study design: An ongoing multicenter randomized phase 2 trial



Enrollment completed in May 2019 (NCT02467270)

[a]As shown by quantitative real-time polymerase chain reaction
[b]99% of patients were TKI-resistant
[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]Key secondary endpoints: MMR rate at 12 and 24 months and MCyR rate by 12 months, duration of MMR, and safety across the 3 doses; others include PFS, OS, and DOR in responders
[g]Statistical analysis: n/92 patients/cohort distinguished a favorable ≤1% *BCR::ABL1*^{IS} 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; DOR, duration of response; MCyR, major cytogenetic response; MMR, major molecular response; PFS, progression-free survival; OS, overall survival

Results

Table 1: Demographics and baseline disease characteristics

Characteristic	Subcategory	45 mg→15 mg (n=94)	30 mg→15 mg (n=95)	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 0 or 1, n (%)		93 (99)	93 (99)	94 (100)
Time since diagnosis, years, median (range)		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)	4 (4)	3 (3)
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 (%)	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)	55 (59)	57 (61)
	≤1% *BCR::ABL1*^{IS} or better	2 (2)	7 (7)	7 (7)

CV, cardiovascular; ECOG, Eastern Cooperative Oncology Group; PS, performance status

- At the 4-year analysis data cutoff date (May 8, 2023), median duration of follow-up was 63 months in the 45-mg cohort, 65 months in the 30-mg cohort, and 63 months in the 15-mg cohort
- ≤1% *BCR::ABL1*^{IS} response rate by 12 months (primary endpoint) and 48 months was highest in the 45-mg cohort (**Figure 2**)
  - Response rates improved from 12 months to 48 months

Figure 2: ≤1% *BCR::ABL1*^{IS} response rate by 12 and 48 months[a,b]

[a]Number of patients with ≤1% *BCR::ABL1*^{IS} is 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 was highest in the 45-mg cohort by 48 months (**Figure 3**)
- Rates of ≤0.01% and ≤0.0032% *BCR::ABL1*^{IS} were similar between cohorts by 48 months (**Figure 3**)
- ≤1% *BCR::ABL1*^{IS} response rate was also highest in the 45-mg cohort regardless of mutation status (**Figure 4**)
- Median DOR was not reached in any dosing cohort

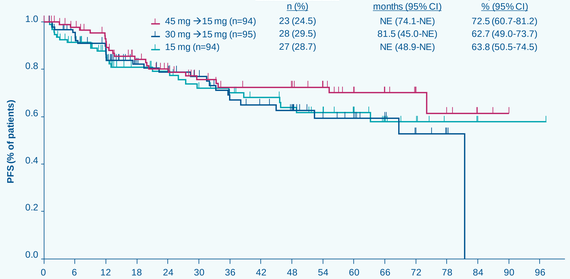
Objective To assess the results from the OPTIC trial at the 4-year data cutoff date

Results

- By 48 months, the progression-free survival (PFS) rate was highest in the 45-mg cohort

PFS in the 45-mg, 30-mg, and 15-mg starting dose cohorts

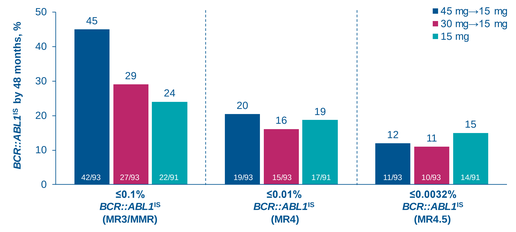
	Patients with events, n (%)	Median PFS, months (95% CI)	4-year PFS, % (95% CI)
45 mg →15 mg (n=94)	23 (24.5)	NE (74.1-NE)	72.5 (60.7-81.2)
30 mg →15 mg (n=95)	28 (29.5)	81.5 (45.0-NE)	62.7 (49.0-73.7)
15 mg (n=94)	27 (28.7)	NE (48.9-NE)	63.8 (50.5-74.5)



No. at risk																	
45 mg →15 mg	94	84	75	64	57	48	43	42	40	36	25	19	12	7	3	1	0
30 mg →15 mg	95	83	73	51	46	41	32	29	26	18	15	11	7	4	0		
15 mg	94	80	65	49	46	40	37	33	30	26	19	13	8	3	2	1	1

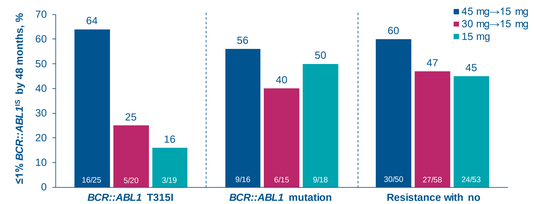
Key takeaways At the 4-year data cutoff, ponatinib treatment resulted in robust long-term PFS in patients with CP-CML resistant to second-generation BCR::ABL1 TKI therapy

Figure 3: ≤0.1%, ≤0.01%, and ≤0.0032% *BCR::ABL1*^{IS} response rate by 48 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

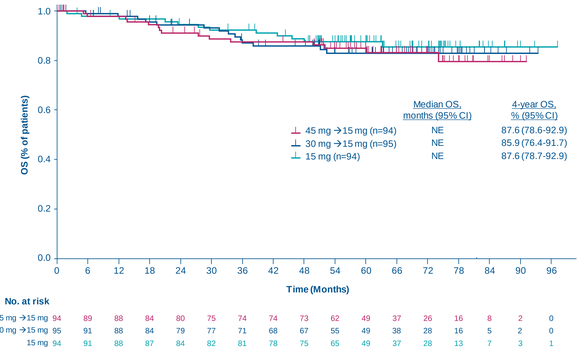
Figure 4: ≤1% *BCR::ABL1*^{IS} response rate by 48 months by mutation status at baseline[a,b]



[a]Number of patients with ≤1% *BCR::ABL1*^{IS} is 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

- OS was similar between all dosing cohorts (**Figure 5**)

Figure 5: OS in the 45-mg, 30-mg, and 15-mg starting dose cohorts



No. at risk																	
45 mg →15 mg	94	89	88	84	80	75	74	74	73	62	49	37	26	16	8	2	0
30 mg →15 mg	95	91	88	84	79	77	71	68	67	55	49	38	28	16	5	2	0
15 mg	94	91	88	87	84	82	81	78	75	65	49	37	28	13	7	3	1

- Of the patients who achieved ≤1% *BCR::ABL1*^{IS}, 80.4% (45/56) and 71.1% (27/38) in the 45-mg and 30-mg cohorts, respectively, had dose reductions to 15 mg upon achieving ≤1% *BCR::ABL1*^{IS}
  - 11 patients did not have dose reductions upon achieving ≤1% *BCR::ABL1*^{IS}, including 6 dose reductions for AEs (3 maintained response), 2 discontinuations for AEs, and 3 lost to follow-up/other
- Few patients lost response in the 45-mg and 30-mg cohorts (**Table 2**)
  - Of the patients who lost response, most regained ≤1% *BCR::ABL*^{IS} after dose re-escalation
  - Of the patients who did not regain response, 3 discontinued due to AE or progressive disease, and 1 remains on treatment
- The median time to regain response after dose re-escalation among patients who achieved ≤1% *BCR::ABL1*^{IS} response was 126 days (95% CI, 39–167) in the 45-mg cohort and was not estimable in the 30-mg cohort due to low patient numbers

Table 2: Dose re-escalation after loss of response[a] (intent-to-treat population)

Characteristic	45 mg→15 mg (n=93)	30 mg→15 mg (n=93)
Achieved ≤1% *BCR::ABL1*^{IS} at any time, n (%)	56 (60)	38 (41)
Loss of ≤1% *BCR::ABL1*^{IS} at any time, n (%)	15 (27)	9 (24)
Dose re-escalated after loss of response, n (%)	13 (87)	5 (56)
Regained ≤1% *BCR::ABL1*^{IS} after re-escalation		
Yes	9 (69)	4 (80)
No	4 (31)	1 (20)

[a]Includes all patients who had the first dose reduction to 15 mg after ≤1% *BCR::ABL1*^{IS} achieved

Safety

- The incidence of grade 3–4 treatment-emergent AEs (TEAEs) and serious TEAEs was similar across dosing cohorts (**Table 3**)
- In Figure 6, the bar graphs indicate the number of patients by year who experienced particular TEAEs
  - The most common nonhematologic grade ≥3 TEAEs in the overall population were hypertension (10%) and lipase increase (7%)
  - The most common hematologic grade ≥3 TEAEs in the overall population were thrombocytopenia (27%) and neutropenia (18%)
  - Across the most common TEAEs, the number of TEAEs decreased from year 1 through subsequent years
- No grade 5 treatment-emergent arterial occlusive events (TE-AOEs) occurred in any dosing cohort (**Table 4**)

Table 3: 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)	92 (98)	92 (98)
Grade 3–4 TEAEs	66 (70)	62 (66)	61 (65)
Serious TEAEs	37 (39)	32 (34)	37 (39)
Grade 5 TEAEs[a]	4 (4)	2 (2)	3 (3)
Dose modification for TEAEs, n (%)			
Discontinuation[b]	21 (22)	18 (19)	16 (17)
Reduction	47 (50)	35 (37)	31 (33)
Interruption	76 (81)	64 (68)	60 (64)

[a]Includes deaths that occurred up to 30 days after the last ponatinib dose
[b]All TEAEs with "Drug Withdrawn" as the action taken

Figure 6: Most common grade ≥3 TEAEs by year of treatment

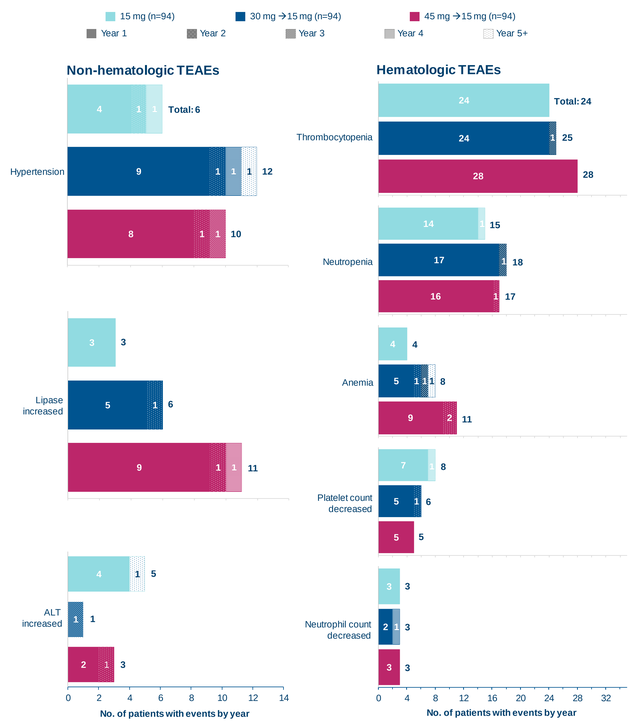


Table 4: TE-AOE summary and related dose modifications and discontinuations

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)	8 (9)	4 (4)
Grade 3–4 TE-AOEs	6 (6)	7 (7)	4 (4)
Grade 5 TE-AOEs	0	0	0
Dose modifications for TE-AOEs, n (%)			
Discontinuation	5 (5)	4 (4)	1 (1)
Reduction	0	2 (2)	0
Interruption	3 (3)	5 (5)	2 (2)
Exposure-adjusted AOEs, patients with events/100 person-years (95% CI)	3.87 (1.45–6.30)	3.66 (1.11–6.20)	1.73 (0.02–3.44)

Conclusions

- Results from the 4-year follow-up of the OPTIC study support ponatinib's long-term efficacy and manageable safety profile in patients with highly resistant CP-CML
- These results are consistent with previous analyses of the OPTIC trial and demonstrate that a ponatinib starting dose of 45 mg/d with reduction to 15 mg/d upon attainment of ≤1% *BCR::ABL1*^{IS} continued to provide the optimal risk:benefit ratio
  - High response rates were observed in the 45-mg cohort, regardless of mutation status, along with improved PFS over the 30-mg and 15-mg cohorts
- The maintenance benefit with ponatinib was also demonstrated, with ≤1% *BCR::ABL1*^{IS} response rates maintained or improved from 12 months to 48 months
- At this 4-year analysis, response-based ponatinib dosing regimens demonstrated long-term manageable safety, including a low rate of exposure-adjusted AOEs
- Observed responses were associated with robust long-term survival in patients with CP-CML resistant to second-generation BCR::ABL1 TKI therapy

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Email for questions or comments: Jorge.cortes@augusta.edu

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