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

CML-425

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]

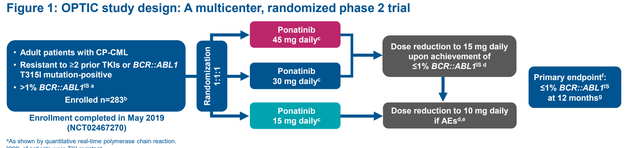
[1]Georgia Cancer Center, Augusta, USA; [2]Versiti Blood Research Institute, Milwaukee, USA; [3]Almazov National Medical Research Centre, St. Petersburg, Russia; [4]Hospital Jose Maria Ramos Mejia, Buenos Aires, Argentina; [5]Hospital del Salvador, Santiago, Chile; [6]Fundaleu, Buenos Aires, Argentina; [7]Singapore General Hospital, Duke-NUS Medical School, Singapore; [8]Jagiellonian University Hospital in Krakow, Krakow, Poland; [9]Princess Margaret Cancer Centre, Toronto, Canada; [10]The John Theurer Cancer Center at Hackensack Meridian Health, Hackensack, USA; [11]Universitätsklinikum Jena, Jena, Germany; [12]Centre Hospitalier de Versailles, UMR1184, University 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, USA; [17]Comprehensive Cancer Center, University of Michigan, Ann Arbor, USA; [18]Memorial Sloan Kettering, New York, USA; [19]Takeda Development Center Americas, Inc., Cambridge, USA; [20]Imperial College London, London, UK

Background

- Ponatinib is a 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 when treated with another second-generation BCR::ABL1 TKI[1,2]
- The phase 2 OPTIC trial (NCT02467270) 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 4-year update with long-term efficacy and safety outcomes from OPTIC

Methods

Figure 1: OPTIC study design: A multicenter, randomized phase 2 trial



[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/d2 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

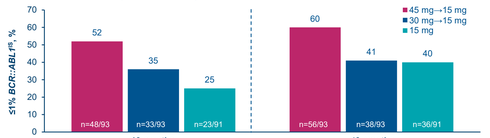
Table 1: Demographics and baseline disease characteristics

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)**

CHR, complete hematologic response; 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

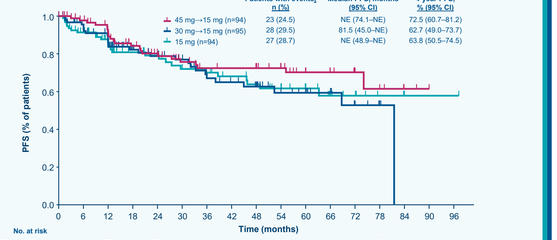
Question Did ponatinib provide long-term PFS benefit for patients in the OPTIC study?

Study design

Results

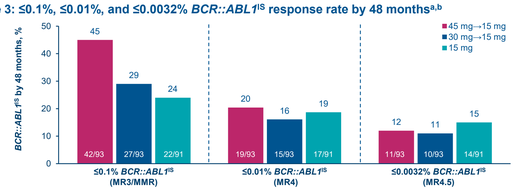
- By 48 months, the progression-free survival (PFS) rate was highest in the 45-mg cohort

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



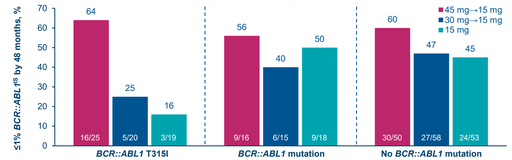
Key takeaway At the 4-year data cutoff, ponatinib treatment resulted in robust long-term PFS in patients with CP-CML resistant to second-generation BCR::ABL1 TKI therapy

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.

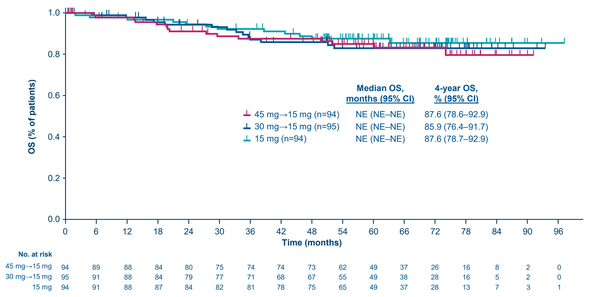
Figure 4: ≤1% *BCR::ABL1*^{IS} response rate by 48 months by mutation status at baseline[a,b]



[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



- 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

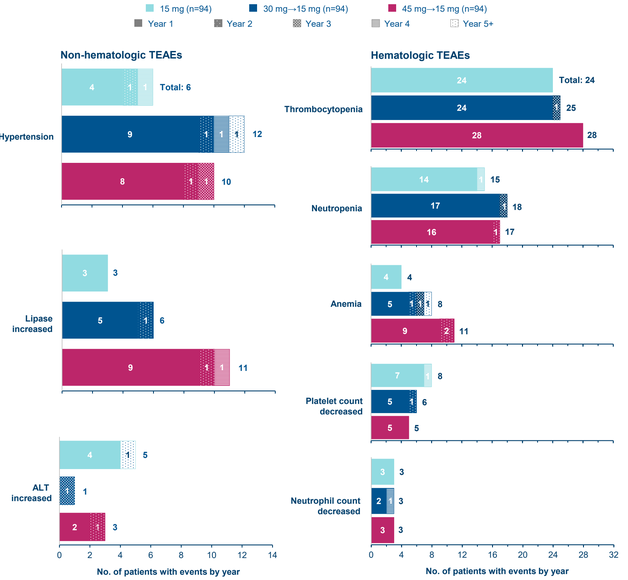


Table 4: TE-AOE summary and related dose modifications and discontinuations

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

References

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, Lang F. J Hematol Oncol 2021;14:44.

Acknowledgments

We thank all the patients and their families, and the investigators and staff at all clinical sites, for their participation in the study. This study is sponsored by Takeda Development Center Americas, Inc. Medical writing support for the development of this poster, under the direction of the authors, was provided by Lauren Gallagher, RPh, PhD, of Peloton Advantage, LLC, an OPEN Health company, and funded by Takeda Development Center Americas, Inc., Cambridge, MA, and complied with the Good Publication Practice (GPP) guidelines (DeTora LM, et al. Ann Intern Med 2022;175:1298–1304).

Disclosures

JC: Consultancy and research funding from Bristol Myers Squibb, Jazz Pharmaceuticals, Sun Pharma, Novartis, Pfizer, Takeda, and BioPath Holdings; research funding from Ascentage; membership on an entity's board of directors or advisory committees with BioPath Holdings; consultancy with Amphivena Therapeutics, and Daiichi Sankyo. **MD:** Consultancy, membership on an entity's board of directors or advisory committees, part of a study management committee and research funding from Blueprint Medicines and Cogent Therapeutics; consultancy with Fusion Pharma, Medscape, and DisperSol; consultancy, membership on an entity's board of directors or advisory committees, and research Funding from Takeda; consultancy and membership on an entity's board of directors or advisory committees with Sangamo and CTI BioPharma; consultancy and research funding from Novartis; consultancy, honoraria, and research funding from Incyte; research funding from SPARC, DisperSol, and Leukemia & Lymphoma Society). **EL:** Speakers bureau for Novartis, Pfizer, and Fusion Pharma; travel, accommodation, and expenses from Novartis and Pfizer). **BM:** Speakers bureau for Novartis, Pfizer, and Takeda. **MUS:** Advisory board for AbbVie, Janssen, Novartis, Pfizer, and Roche; speakers bureau for Janssen, Novartis, and Pfizer. **CP:** Speakers bureau for Novartis, Pfizer, Bristol Myers Squibb, and Pint Pharma; advisory board for Novartis and Pfizer. **CC:** Honoraria from Korea Otsuka Pharmaceutical; honoraria and research funding from Bristol Myers Squibb and Novartis; travel and research funding from Pfizer. **TS:** Consultancy, honoraria, and speakers bureau from Bristol Myers Squibb, Novartis, Pfizer, and Incyte; consultancy and honoraria from Adamed. **JHL:** Consultancy and research funding from Bristol Myers Squibb, ARIAD, Pfizer, and Novartis. **JM:** Nothing to disclose. **AH:** Research funding from Bristol Myers Squibb, Novartis, Pfizer, and Incyte. **PR:** Consultancy and research funding from Incyte and Pfizer; consultancy with Bristol Myers Squibb, Novartis, and Takeda. **GR:** Research funding and speakers bureau with Pfizer; speakers bureau for Bristol Myers Squibb, Incyte, and Novartis. **HL:** Honoraria and research funding from Bristol Myers Squibb and Incyte; honoraria from Pfizer and Novartis. **AT:** Speakers bureau from Novartis, Pfizer, and Fusion Pharma; travel and accommodation expenses from Novartis and Pfizer. **LM:** Nothing to disclose. **MT:** Grant/research support from Takeda and Novartis. **MM:** Consultancy, honoraria, travel, accommodation, expenses, and research funding from Bristol Myers Squibb, Novartis, Takeda, and Pfizer; research funding from Sun Pharma/SPARC. **VL:** Employment with Takeda. **AV:** Employment with Takeda. **JA:** Honoraria, research funding, and speakers bureau from Incyte and Pfizer; honoraria and speakers bureau from Bristol Myers Squibb and Novartis.

A plain language summary can be viewed through the QR (Quick Response) and is for personal use only and may not be reproduced without written permission of the authors.

Presented at the Society of Hematologic Oncology (SOHO) Annual Meeting, September 4–7, 2024, Houston, Texas

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