46 Bosutinib (BOS) Versus Imatinib for Newly Diagnosed Chronic Phase (CP) Chronic Myeloid Leukemia (CML): Final 5-Year Results from the Bfore Trial.

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Tim H Brümmendorf, MD[1,2], Jorge E. Cortes, MD[3], Dragana Milojkovic[4], Carlo Gambacorti-Passerini, MD[5], Richard E. Clark, MA, MD, MRCP, FRCPath[6*], Philipp D le Coutre, MD[7], **Valentín Garcia-Gutiérrez, MD, PhD[8]**, Charles Chuah, MD[9], Vamsi Kota, MD[3], Jeffrey H. Lipton, MD, PhD[10], Philippe Rousselot, MD PhD[11*], Michael J. Mauro, MD[12], Andreas Hochhaus, MD[13], Rafael Hurtado Monroy, MD[14], Eric Leip[15*], Simon Purcell[16*], Anne Yver, PharmD[17*], Andrea Viqueira, MD[18*] and Michael W. Deininger, MD, PhD[19]*

*[1]Dept. of Hematology and Oncology, Center for Integrated Oncology (CIO), Uniklinik RWTH Aachen, Aachen, Germany [2]Department of Hematology and Oncology, Center for Integrated Oncology (CIO), Uniklinik RWTH Aachen, Aachen, Germany [3]Georgia Cancer Center Augusta University, Augusta, GA [4]Department of Haematology, Hammersmith Hospital, Imperial College NHS Trust, London, United Kingdom [5]Dept of Medicine and Surgery, University of Milano Bicocca, Monza, MB, Italy [6]Department of Haematology, Royal Liverpool University Hospital, Liverpool, United Kingdom [7]Charité – Universitätsmedizin Berlin, Berlin, Berlin, Germany [8]**Hematology, Hospital Universitario Ramón y Cajal, Madrid, Spain** [9]Department of Haematology, Singapore General Hospital, Singapore, Singapore [10]Hans Messner Allogeneic Transplant Program, Division of Medical Oncology and Haematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada [11]Centre Hospitalier de Versailles, Le Chesnay, France [12]Myeloproliferative Neoplasms Program, Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY [13]Klinik für Innere Medizin II, Jena, Germany [14]Head Hematology Department, Hospital Angeles del Pedregal, Mexico, Mexico [15]Pfizer Inc., Cambridge, MA [16]Pfizer Ltd, London, GBR [17]Pfizer Inc, Paris, France[18]Pfizer SLU, Madrid, Spain [19]Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Introduction: BOS is approved for patients (pts) with Philadelphia chromosome-positive (Ph+) CML resistant/intolerant to prior therapy and pts with newly diagnosed Ph+ CP CML. Approval of first-line BOS was based on the primary results from the phase 3 BFORE trial, which showed superior efficacy vs imatinib (IMA) in the modified intent-to-treat (ITT) population (pop; Ph+ with e13a2/e14a2 transcripts) after ≥12 mo of follow-up. We report the final efficacy and safety results from the BFORE trial after 5 y of follow-up.

Methods: In the open-label BFORE trial (NCT02130557), 536 pts with newly diagnosed CP CML were randomized 1:1 to receive BOS (n=268) or IMA (n=268; 3 untreated), both at 400 mg once daily. Efficacy was assessed in the ITT pop (all randomized pts). Long-term secondary endpoints included duration of response (DOR), on-treatment event-free survival (EFS) and overall survival (OS). Safety was assessed in the safety pop (all treated pts). This final analysis was based on an April 17, 2020 last pt last visit (June 12, 2020 database lock), 5 y (240 weeks) after the last enrolled pt.

Results: At study completion in BOS and IMA arms, respectively, 59.7% and 57.4% were still on treatment, 86.6% and 86.2% completed 5 y on study. Median duration of treatment and time on study was 55.2 mo for pts receiving BOS or IMA; respective median (range) dose intensity was 394 (39–583) vs 400 (189–765) mg/d. Cumulative major molecular response (MMR) rate by 60 mo was higher with BOS vs IMA (73.9% vs 64.6%), as was cumulative molecular response (MR^4) (58.2% vs 48.1%) and $MR^{4.5}$ rate (47.4% vs 36.6%; Table). Among evaluable pts, more pts in the BOS arm achieved *BCR-ABL1* ≤10% at 3 months (Table); cumulative MMR by 60 mo was higher in pts with transcripts ≤10% vs >10% in both treatment arms (BOS, HR 2.67 [95% CI, 1.90–3.75]; IMA, HR 3.12 [2.19–4.45]). Pts in the BOS arm achieved responses earlier than pts in the IMA arm; cumulative incidence function for MMR, MR^4 and $MR^{4.5}$ was higher with BOS vs IMA (HR [95% CI]: MMR 1.34 [1.10–1.64], MR^4 1.34 [1.07–1.69], $MR^{4.5}$ 1.41 [1.09–1.83]). Among responders, duration of MMR was similar for BOS and IMA (Table). Superior MRs with BOS vs IMA were consistent across Sokal risk groups, with the greatest difference seen in pts with high Sokal risk (Table). On-treatment transformations to accelerated/blast phase (AP/BP) occurred in 6 (AP 3; BP 3) BOS- and 7 (AP 6; BP 1) IMA-treated pts. No transformation occurred after the 24-mo follow-up. In all, 18 BOS- vs 25 IMA-treated pts had EFS events. There were no differences in EFS between treatment arms; cumulative incidence of on treatment progression/death at 60 mo was 6.7% for BOS vs 9.3% for IMA (Table). The 60-mo OS rates were similar (94.5% and 94.6%; Table); 14 BOS- and 14 IMA-treated pts died during the study period: 3 and 4 were CML-related, 0 and 1 were due to adverse events (AEs) related to study treatment.

The most common reasons for permanent discontinuation were AEs (25.0% vs 12.5%) and lack of efficacy (4.9% vs 16.2%). Treatment-emergent AEs (TEAEs) occurred in 98.9% of pts in each arm; most common (>30%) were diarrhea (75.0%), nausea (37.3%), thrombocytopenia (35.8%) and increased alanine aminotransferase (ALT; 33.6%) with BOS, and diarrhea (40.4%), nausea (42.3%) and muscle spasms (30.6%) with IMA. Most TEAEs occurred during the first year of treatment. Grade 3/4 TEAEs occurred in 73.5% of BOS- vs 57.0% of IMA-treated pts; most common (>5%) were increased ALT (20.9%) and lipase (13.4%), thrombocytopenia (14.2%), increased aspartate aminotransferase (10.4%), diarrhea (9.0%) and neutropenia (7.5%) with BOS, and neutropenia (13.6%), thrombocytopenia (6.0%), anemia (5.7%) and increased lipase (5.7%) with IMA. No individual AE led to discontinuation

in >5% of pts. The most frequent AEs leading to permanent treatment discontinuation were increased ALT (4.9%) with BOS vs thrombocytopenia (1.5%) with IMA; 1.5% vs 1.1% of pts discontinued due to diarrhea.

Conclusions: At 5 y, first-line BOS continued to show superior efficacy vs IMA; BOS-treated pts achieved earlier and deeper molecular response. An improvement in MR with BOS was demonstrated across Sokal risk groups, with the greatest benefit vs IMA observed in Sokal high-risk pts. Long-term AEs were generally manageable, and consistent with previous reports and the known safety profiles of both drugs. These results confirm the use of BOS as a standard of care in pts with newly diagnosed CP CML.

Table. Long-term outcomes in pts with newly diagnosed CP CML (ITT population)

	BOS n=268	IMA n=268	
Early molecular response, n (%)	n=248	n=253	**OR (95% CI)**
BCR-ABL1 transcripts ≤10% at 3 mo[¶]	200 (80.6)	153 (60.5)	2.72 (1.82–4.08)
Cumulative molecular response rates by 60 mo, n (%)[±]			**OR (95% CI)***
MMR	198 (73.9)	173 (64.6)	1.57 (1.08–2.28)
MR^4	156 (58.2)	129 (48.1)	1.50 (1.07–2.12)
$MR^{4.5}$	127 (47.4)	98 (36.6)	1.57 (1.11–2.22)
Cumulative molecular response rates by Sokal risk group, n (%)[±]			**OR (95% CI)**
MMR by 60 mo			
Low risk[a]	72 (75.8)	77 (72.6)	1.18 (0.63–2.22)
Intermediate risk[b]	87 (74.4)	67 (63.8)	1.65 (0.93–2.92)
High risk[c]	39 (69.6)	29 (50.9)	2.22 (1.03–4.79)
MR^4 by 60 mo			
Low risk[a]	57 (60.0)	59 (55.7)	1.20 (0.68–2.10)
Intermediate risk[b]	66 (56.4)	49 (46.7)	1.48 (0.87–2.51)
High risk[c]	33 (58.9)	21 (36.8)	2.46 (1.15–5.24)
$MR^{4.5}$ by 60 mo			
Low risk[a]	51 (53.7)	45 (42.5)	1.57 (0.90–2.74)
Intermediate risk[b]	50 (42.7)	39 (37.1)	1.26 (0.74–2.17)
High risk[c]	26 (46.4)	14 (24.6)	2.66 (1.20–5.92)
DOR for responders only[±§]			**HR (95% CI)[†]**
Maintaining MMR at 48 mo, % (95% CI)	92.6 (87.6–95.7)	91.8 (85.9–95.3)	1.01 (0.46–2.23)
Cumulative incidence of on-treatment progression/death at 60 mo[‖]			**HR (95% CI)[‡]**
% (95% CI)	6.7 (4.1–10.1)	9.3 (6.2–13.2)	0.70 (0.38–1.27)
OS at 60 mo**			**HR (95% CI)[†]**
% (95% CI)	94.5 (90.8–96.7)	94.6 (91.0–96.8)	0.95 (0.45–1.99)

Note: all ratios are BOS vs IMA. Ratios <1 for DOR, EFS and OS (and ratios >1 for other response endpoints) favor BOS. CIs excluding 1 were considered predictive of outcome.

[¶]Pts with ≥3000 ABL transcripts assessed at month 3.

[a]MMR: *BCR-ABL1* IS ≤0.1%. MR^4: *BCR-ABL1* IS ≤0.01%. $MR^{4.5}$: *BCR-ABL1* IS ≤0.0032%.

* Adjusted for Sokal risk group and region as determined at the time of randomization.

[a] BOS, n=95, IMA, n=106; [b] BOS, n=117, IMA, n=105; [c] BOS, n=56, IMA, n=57.

† Based on a stratified (by Sokal risk group at randomization and region) Cox proportion hazards model.

‡ Based on a stratified (by Sokal risk group at randomization and region) proportional subdistribution hazards model. Competing risk was treatment discontinuation without an event.

§ Kaplan–Meier yearly rate at 48 mo (pts have not been followed for 60 mo after initial response). Events were defined as confirmed loss of response (both at least 5 times greater than lowest observed value), treatment discontinuation due to transformation to AP or BP CML or on-treatment death due to CML.

‖ EFS events were defined as confirmed loss of CCyR (Ph+ pts only), confirmed loss of ≤1% transcripts (Ph– or unknown Ph status only), confirmed loss of complete hematologic response, doubling of white blood cells in pts without CHR, on-treatment transformation to AP or BP CML or on-treatment death.

** Estimated by Kaplan–Meier analysis.

CCyR=complete cytogenetic response; HR=hazard ratio IS=international scale; OR=odds ratio

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