CML-413

Efficacy and Safety of Bosutinib Versus Imatinib in US Patients With Newly Diagnosed Chronic Myeloid Leukemia After 5-Years' Follow-Up in the BFORE Trial

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Objective

- To characterize the efficacy and safety of bosutinib vs imatinib in US patients enrolled in BFORE.

Conclusions

- After 5 y of follow-up in US patients, bosutinib continued to show superior efficacy compared with imatinib, as demonstrated by deeper molecular responses.
  - In both treatment arms, cumulative MR and deep molecular responses were similar in US vs non-US patients.
- Long-term TEAEs in US patients were generally manageable and consistent with the known safety profiles of both drugs.[3,4]
  - Differences in certain TEAEs (eg, nausea and fatigue) were observed in US vs non-US patients in both treatment arms.
  - Dose interruptions were more frequent in US vs non-US patients in both treatment arms.
- At study completion, the majority of US patients in both arms were still receiving treatment.
  - The most common primary reasons for permanent treatment discontinuation were AEs with bosutinib, and AEs and lack of efficacy with imatinib.
  - Increases (≥10%) in the rate of US vs non-US patients permanently discontinuing bosutinib treatment due to AEs as the primary reason were observed.
- These results confirm the use of 400 mg QD bosutinib as a standard of care in US patients with newly diagnosed CP CML.

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References: 1. Bosulif® (bosutinib) prescribing information. Pfizer; revised May 2021. **2.** Bosulif® (bosutinib) summary of product characteristics. European Medicines Agency; revised Aug 2021. **3.** Cortes JE, et al. J Clin Oncol 2018;36:231-7. **4.** Brümmendorf TH, et al. Leukemia 2022;36:1825-33.

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Background

- Bosutinib is an oral *BCR::ABL1*-targeting tyrosine kinase inhibitor approved to treat adult patients with Philadelphia chromosome–positive chronic myeloid leukemia (CML) resistant or intolerant to prior therapy, and patients with newly diagnosed chronic phase (CP) CML.[1,2]
- Approval of first-line bosutinib was based on primary results from the phase 3 BFORE trial (ClinicalTrials.gov ID: NCT02130557).[3]
  - The major molecular response (MMR) rate at 12 mo was higher with bosutinib (47.2%) vs imatinib (36.9%).
  - The complete cytogenetic response rate by 12 mo was higher with bosutinib (77.2%) vs imatinib (66.4%).
- After 5 y of follow-up in the BFORE trial, bosutinib continued to show efficacy in patients with newly diagnosed CP CML. Treatment-emergent adverse events (TEAEs) were generally manageable, reversible, and consistent with the known safety profile of bosutinib.[4]

Methods

- BFORE was an open-label, randomized, multicenter, phase 3 study.[3]
- Patients aged ≥18 y with newly diagnosed CP CML received bosutinib or imatinib at a starting dose of 400 mg once daily (QD).[4]
- This sub-analysis includes patients treated with bosutinib or imatinib in the United States (US) and in other regions (non-US).
  - Efficacy was evaluated in all randomized patients.
  - Safety was assessed in patients who received ≥1 dose of study treatment.
- This analysis was based on the final 5-y analysis (database lock: June 12, 2020).

Results

PATIENTS AND TREATMENT

- The BFORE trial (N=536) enrolled and randomized patients in the US (bosutinib, n=39; imatinib, n=49) and non-US regions (bosutinib, n=229; imatinib, n=219 [3 untreated]). This analysis focuses on outcomes in US patients (**Table 1**).
- Median (range) duration of treatment with bosutinib and imatinib in US patients was 54.8 (0.9–58.9) mo and 54.8 (1.2–56.4) mo, respectively.
- Median (range) dose intensity with bosutinib and imatinib was 383.5 (162–562) mg/d and 400.0 (189–754) mg/d, respectively.
- At study completion, 53.8% vs 51.0% of bosutinib- vs imatinib-treated US patients were still receiving treatment.
  - Among Black or African American patients in the US receiving bosutinib (n=5) and imatinib (n=5), respectively, 20% and 40% were still receiving treatment at study completion.
- The most common primary reasons for permanent treatment discontinuation are shown in **Table 1**.

Table 1: Patient demographics and disposition

Characteristic	Bosutinib US patients	Bosutinib Non-US patients	Imatinib US patients	Imatinib Non-US patients
	n=39	n=229	n=49	n=219
Age, median (range), y	53 (20–80)	53 (18–84)	53 (19–80)	53 (19–84)
Sex, n (%)				
Female	21 (53.8)	91 (39.7)	20 (40.8)	93 (42.5)
Male	18 (46.2)	138 (60.3)	29 (59.2)	126 (57.5)
Race, n (%)				
White	33 (84.6)	178 (77.7)	36 (73.5)	170 (77.6)
Asian	0	33 (14.4)	2 (4.1)	32 (14.6)
Black or African American	5 (12.8)	5 (2.2)	5 (10.2)	5 (2.3)
Other/missing	1 (2.6)	13 (5.7)	6 (12.2)	12 (5.5)
	n=39	n=229	n=49	n=216
Completed 5 y of treatment, n (%)	21 (53.8)	139 (60.7)	25 (51.0)	129 (59.7)
Permanent treatment discontinuation, n (%)	18 (46.2)	90 (39.3)	24 (49.0)	87 (40.3)
AEs	13 (33.3)	54 (23.6)	6 (12.2)	27 (12.5)
Related to study drug[a]	8 (20.5)	45 (19.7)	6 (12.2)	23 (10.6)
Not related to study drug	5 (12.8)	9 (3.9)	0	4 (1.9)
Other[b]	2 (5.1)	5 (2.2)	5 (10.2)	2 (0.9)
Lack of efficacy[c]	2 (5.1)	13 (5.7)	6 (12.2)	41 (19.0)
Patient or investigator request	1 (2.6)	13 (5.7)	5 (10.2)	13 (6.0)
Death	0	3 (1.3)	0	4 (1.9)
Patient failed to return or lost to follow-up	0	2 (0.9)	2 (4.1)	0

[a] Relatedness as determined by the Investigator. [b] Includes protocol violation and other reasons. [c] Includes suboptimal response, treatment failure, or disease progression.
AE=adverse event; US=United States

EFFICACY

- The MMR rate (95% CI) at 12 mo for US patients was 41.0% (25.6%, 56.5%) vs 32.7% (19.5%, 45.8%) with bosutinib vs imatinib.
  - The rate difference (95% CI) was 8.4% (–11.9%, 28.6%).
- The MMR rate (95% CI) by 5 y for US patients was 74.4% (60.7%, 88.1%) vs 63.3% (49.8%, 76.8%) with bosutinib vs imatinib (**Table 2**).
  - The rate difference (95% CI) was 11.1% (–8.1%, 30.3%).
- Among Black or African American patients from the US (n=5 in each treatment arm), the MMR rate (95% CI) by 5 y was 60.0% (17.1%, 100%) vs 40.0% (–2.9%, 82.9%) with bosutinib vs imatinib.
- The MR[4] rate (95% CI) by 5 y for US patients was 51.3% (35.6%, 67.0%) vs 46.9% (33.0%, 60.9%) with bosutinib vs imatinib.
  - The rate difference (95% CI) was 4.3% (–16.7%, 25.4%).
- The MR[4.5] rates (95% CI) by 5 y for US patients was 35.9% (20.8%, 51.0%) vs 28.6% (15.9%, 41.2%) with bosutinib vs imatinib.
  - The rate difference (95% CI) was 7.3% (–12.3%, 27.0%).
- Cumulative MMR and deep molecular response rates by 5 y were similar for US vs non-US patients in both treatment arms (**Table 2**).

Table 2: MMR, MR[4], and MR[4.5] by 5 y in US and non-US patients

Cumulative response rates[a], % (95% CI)	Bosutinib US patients (n=39)	Bosutinib Non-US patients (n=229)	Bosutinib OR[b,c] (95% CI)	Imatinib US patients (n=49)	Imatinib Non-US patients (n=219)	Imatinib OR[b,c] (95% CI)
MMR[d]	74.4 (60.7, 88.1)	73.8 (68.1, 79.5)	1.03 (0.47, 2.24)	63.3 (49.8, 76.8)	64.8 (58.5, 71.2)	0.93 (0.49, 1.78)
MR[4]	51.3 (35.6, 67.0)	59.4 (53.0, 65.7)	0.72 (0.36, 1.42)	46.9 (33.0, 60.9)	48.4 (41.8, 55.0)	0.94 (0.51, 1.75)
MR[4.5]	35.9 (20.8, 51.0)	49.3 (42.9, 55.8)	0.58 (0.28, 1.16)	28.6 (15.9, 41.2)	38.4 (31.9, 44.8)	0.64 (0.33, 1.27)

[a] 95% confidence interval for response rates is based on asymptotic confidence limits. [b] Overall adjusted for Sokal risk group as determined at the time of randomization. [c] 95% confidence interval for adjusted OR is based on the Mantel–Haenszel confidence limits. [d] MMR defined as ≤0.1% *BCR::ABL1* transcripts on the IS.
IS=international scale; ITT=intent-to-treat; MMR=major molecular response; OR=odds ratio; US=United States

SAFETY

- All-causality, any grade TEAEs were reported by 100% of US patients in both treatment arms (**Table 3**).
  - The most common any grade TEAEs with bosutinib were diarrhea (84.6%), nausea (61.5%), and fatigue (53.8%).
  - The most common TEAEs with imatinib were nausea (63.3%), diarrhea (55.1%), and fatigue (36.7%).
- Among US vs non-US patients, increases (≥20%) in the incidence of any grade nausea, fatigue, and constipation were reported with bosutinib, and nausea, fatigue, and periorbital edema with imatinib (**Table 3**).
- All-causality Grade 3–4 TEAEs were reported by 79.5% and 69.4% of US patients treated with bosutinib and imatinib, respectively (**Table 3**).
  - The most common Grade 3–4 TEAEs with bosutinib were increased alanine aminotransferase (23.1%) and increased lipase (15.4%).
  - The most common Grade 3–4 TEAEs with imatinib were anemia, increased lipase, and hypertension (each 12.2%).
- More US patients receiving bosutinib vs imatinib had ≥1 dose interruption (74.4% vs 51.0%) or ≥1 dose reduction (59.0% vs 34.7%) due to TEAEs (**Table 4**).
  - Dose interruptions were more frequent in US vs non-US patients in both treatment arms.
- In the bosutinib vs imatinib treatment arm, 33.3% vs 14.3% of patients had adverse events (AEs) leading to permanent treatment discontinuation.
- The most frequent AEs leading to permanent treatment discontinuation were:
  - increased alanine aminotransferase (7.7%) with bosutinib, and
  - increased lipase (4.1%) with imatinib.

Table 3. Most common TEAEs

MedDRA PT, n (%)	Bosutinib US patients (n=39)	Bosutinib Non-US patients (n=229)	Imatinib US patients (n=49)	Imatinib Non-US patients (n=216)
Any grade TEAEs occurring in ≥30% of patients in any subgroup				
Any TEAE	39 (100)	226 (98.7)	49 (100)	213 (98.6)
Diarrhea	33 (84.6)	168 (73.4)	27 (55.1)	80 (37.0)
Nausea	24 (61.5)	76 (33.2)	31 (63.3)	81 (37.5)
Fatigue	21 (53.8)	36 (15.7)	18 (36.7)	36 (16.7)
Thrombocytopenia[a]	16 (41.0)	80 (34.9)	9 (18.4)	44 (20.4)
Headache	14 (35.9)	45 (19.7)	12 (24.5)	29 (13.4)
Rash	13 (33.3)	49 (21.4)	9 (18.4)	30 (13.9)
Constipation	12 (30.8)	24 (10.5)	4 (8.2)	13 (6.0)
ALT increased	12 (30.8)	78 (34.1)	3 (6.1)	13 (6.0)
Anemia[b]	11 (28.2)	48 (21.0)	14 (28.6)	46 (21.3)
Muscle spasms	3 (7.7)	7 (3.1)	15 (30.6)	66 (30.6)
Periorbital edema	0	4 (1.7)	17 (34.7)	27 (12.5)
Grade 3–4 TEAEs occurring in ≥10% of patients in any subgroup				
Any TEAE	31 (79.5)	166 (72.5)	34 (69.4)	117 (54.2)
ALT increased	9 (23.1)	47 (20.5)	0	4 (1.9)
Lipase increased	6 (15.4)	30 (13.1)	6 (12.2)	9 (4.2)
Hypertension	5 (12.8)	7 (3.1)	6 (12.2)	6 (2.8)
Thrombocytopenia[a]	5 (12.8)	33 (14.4)	4 (8.2)	12 (5.6)
Diarrhea	4 (10.3)	20 (8.7)	0	3 (1.4)
AST increased	4 (10.3)	24 (10.5)	0	5 (2.3)
Anemia[b]	3 (7.7)	9 (3.9)	6 (12.2)	9 (4.2)
Neutropenia[c]	2 (5.1)	18 (7.9)	5 (10.2)	31 (14.4)

TEAEs coded using MedDRA v23.0. [a] Clustered terms included thrombocytopenia and platelet count decreased. [b] Clustered terms included anemia and hemoglobin decreased. [c] Clustered terms included were neutropenia and neutrophil count decreased.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; TEAE=treatment-emergent adverse event; US=United States

Table 4. Management of TEAEs

	Bosutinib US patients (n=39)	Bosutinib Non-US patients (n=229)	Imatinib US patients (n=49)	Imatinib Non-US patients (n=219)
Patients with ≥1 dose reduction due to TEAEs, n (%)	23 (59.0)	99 (43.2)	17 (34.7)	48 (22.2)
Median time to first dose reduction, median (range), d	93.0 (18–1241)	92.0 (17–1631)	62.0 (27–848)	190.5 (15–1513)
Patients with ≥1 dose interruption due to TEAEs, n (%)	29 (74.4)	155 (67.7)	25 (51.0)	96 (44.4)
Median time to first dose interruption, median (range), d	43.0 (7–1569)	56.0 (6–1671)	46.0 (9–1436)	97.0 (5–1577)

TEAEs=treatment-emergent adverse events; US=United States