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ORIGINAL REPORT

Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: Results From the Randomized BFORE Trial

Jorge E. Cortes, Carlo Gambacorti-Passerini, Michael W. Deininger, Michael J. Mauro, Charles Chuah, Dong-Wook Kim, Irina Dyagil, Nataliia Glushko, Dragana Milojkovic, Philipp le Coutre, Valentin Garcia-Gutierrez, Laurence Reilly, Allison Jeynes-Ellis, Eric Leip, Nathalie Bardy-Bouxin, Andreas Hochhaus, and Tim H. Brümmendorf

Author affiliations and support information (if applicable) appear at the end of this article.

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Corresponding author: Jorge E. Cortes, MD, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030; e-mail: jcortes@mdanderson.org.

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A B S T R A C T

Purpose

Bosutinib is a potent dual SRC/ABL kinase inhibitor approved for adults with Philadelphia chromosome–positive chronic myeloid leukemia (CML) resistant and /or intolerant to prior therapy. We assessed the efficacy and safety of bosutinib versus imatinib for first-line treatment of chronic-phase CML.

Methods

In this ongoing, multinational, phase III study, 536 patients with newly diagnosed chronic-phase CML were randomly assigned 1:1 to receive 400 mg of bosutinib once daily (n = 268) or imatinib (n = 268). Per protocol, efficacy was assessed in patients who were Philadelphia chromosome–positive with typical (e13a2/e14a2) transcripts (bosutinib, n = 246; imatinib, n = 241). Patients with Philadelphia chromosome–negative–/*BCR-ABL1*–positive status and those with unknown Philadelphia chromosome status and/or atypical *BCR-ABL1* transcript type were excluded from this population.

Results

The major molecular response (MMR) rate at 12 months (primary end point) was significantly higher with bosutinib versus imatinib (47.2% *v* 36.9%, respectively; $P = .02$), as was complete cytogenetic response (CCyR) rate by 12 months (77.2% *v* 66.4%, respectively; $P = .0075$). Cumulative incidence was favorable with bosutinib (MMR: hazard ratio, 1.34; $P = .0173$; CCyR: hazard ratio, 1.38; $P < .001$), with earlier response times. Four patients (1.6%) receiving bosutinib and six patients (2.5%) receiving imatinib experienced disease progression to accelerated/blast phase. Among treated patients, 22.0% of patients receiving bosutinib and 26.8% of patients receiving imatinib discontinued treatment, most commonly for drug-related toxicity (12.7% and 8.7%, respectively). Grade ≥ 3 diarrhea (7.8% *v* 0.8%) and increased ALT (19.0% *v* 1.5%) and AST (9.7% *v* 1.9%) levels were more common with bosutinib. Cardiac and vascular toxicities were uncommon.

Conclusion

Patients who received bosutinib had significantly higher rates of MMR and CCyR and achieved responses faster than those who received imatinib. Consistent with the known safety profile, GI events and transaminase elevations were more common with bosutinib. Results indicate bosutinib may be an effective first-line treatment for chronic-phase CML.

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INTRODUCTION

Management of chronic myeloid leukemia (CML) has changed significantly since the development of tyrosine kinase inhibitors (TKIs), with greatly improved response rates and lower risk of transformation[1-3] translating into a relative survival similar to that of the general population.[4-6] This evolution has been paralleled by the establishment of increasingly stringent criteria for clinical response. In the era of TKIs,[7] complete cytogenetic response (CCyR) became the minimum acceptable response, with greater emphasis placed on achieving major molecular response (MMR) and deeper molecular responses.

Bosutinib is a second-generation TKI with considerable activity against the BCR-ABL1 kinase

ASSOCIATED CONTENT

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Data Supplements

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and most imatinib-resistant BCR-ABL1 mutants except T315I and V299L.[8] Bosutinib 500 mg daily is approved for use in CML as second- or subsequent-line therapy. In a phase I/II study, significant clinical activity was reported with bosutinib in patients with CML resistant and/or intolerant to prior TKIs and in patients with advanced disease.[9-12] This led to a randomized trial of bosutinib versus imatinib as initial therapy for patients with Philadelphia chromosome (Ph)–positive chronic phase (CP) CML (Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia [BELA]).[13,14] Despite an improvement in MMR rate at 12 months, shorter time to response, and a lower rate of transformation to accelerated phase (AP) or blast phase (BP) with bosutinib, the study's primary objective (superior rate of CCyR at 12 months) was not met.[14]

Considering the clinical efficacy of bosutinib in these trials, and recognizing the shortcomings of the BELA study, we designed another randomized trial of bosutinib versus imatinib as front-line therapy for CP CML—the BFORE (Bosutinib Trial in First-Line Chronic Myelogenous Leukemia Treatment) study—in which a lower starting dose of bosutinib (400 mg daily) was administered. Herein we present the primary results of this study.

METHODS

Patients

Eligible patients were adults diagnosed with CP CML (confirmed by the presence of *BCR-ABL1* transcripts) within 6 months before random assignment, Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hepatic and renal function. Additional eligibility criteria are available in the Data Supplement. Patients who were Ph-positive or Ph-negative/*BCR-ABL1*–positive were eligible, but primary end point analysis was restricted to a modified intent-to-treat (mITT) population comprising Ph-positive patients with typical *BCR-ABL1* transcript types (e13a2 and/or e14a2); Ph-negative patients (ie, 0 out of ≥ 10 to 99 metaphases at baseline) and those with unknown Ph status and/or atypical transcript type were excluded from this population but included in the safety analyses and analyses of the ITT population of all patients randomly assigned. The study was approved by institutional review boards and independent ethics committees. All patients provided written informed consent before random assignment in accordance with the Declaration of Helsinki.

Study Design and Treatments

Patients were randomly assigned 1:1 to receive 400 mg of bosutinib or imatinib once daily. Randomly assigned patients who discontinued treatment or withdrew from the study before treatment began could not be re-enrolled and randomly assigned again. Stratification by Sokal risk group and geographic region was done to ensure balance between treatments.

Up to two sequential dose escalations for suboptimal response were permitted unless prohibitive toxicity was present (Data Supplement). Dose interruptions and reductions were permitted to manage toxicity. Patients continued treatment until unacceptable toxicity or treatment failure (defined as disease progression to AP or BP; confirmed loss of previously achieved cytogenetic response or complete hematologic response [CHR]; failure to achieve a CHR after 24 weeks or an adequate cytogenetic response after 24, 48, and 72 weeks; or doubling of WBC count for patients without CHR after dose escalation [unless prohibited]).

Molecular response was centrally assessed (MolecularMD, Portland, OR) on peripheral blood by real-time quantitative polymerase chain reaction and reported at baseline and on the international scale every 3 months thereafter during the core treatment phase. Cytogenetic assessment was performed locally at baseline and every 3 months thereafter until achievement of MMR, after which it was performed only if clinically indicated, disease progression was suspected, or MMR was lost and a five-fold increase in *BCR-ABL1* transcripts was demonstrated.

End Points

Per protocol, efficacy was assessed in the mITT population, with the prespecified primary efficacy end point being MMR rate at 12 months (48 weeks). Key secondary efficacy end points include CCyR (0% Ph-positive from ≥ 20 metaphases or MMR because, per protocol, bone marrow aspirates were not required once MMR was achieved) by month 12; MMR by month 18; duration of CCyR and MMR; event-free survival (EFS); and overall survival (OS). Exploratory end points include MMR at 12 months in the ITT population; MMR at 3, 6, and 9 months; MR^4 (defined as ≤ 0.01% *BCR-ABL1* transcripts on the international scale with ≥ 9,800 *ABL1* assessed) and $MR^{4.5}$ (defined as ≤ 0.0032% *BCR-ABL1* transcripts on the international scale with ≥ 30,990 *ABL1* assessed) at 3, 6, 9, and 12 months; time to MMR; time to CCyR; and time to on-treatment transformation to AP or BP CML; additional information about end points is in the Data Supplement.

Adverse events (AEs), serious AEs, suspected or unexpected serious adverse reactions, and laboratory evaluations were assessed throughout the treatment phase up to 28 days after last dose in all patients who received one or more doses of study drug (safety population). Events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

The primary end point (MMR at 12 months in the mITT population) was tested at a two-sided significance level of .05. CCyR by month 12 was tested at a level of .025.

All efficacy end points included data up to 28 days after last dose except OS, which included deaths occurring after this time point. Treatment-emergent AEs (TEAEs) were defined as AEs that first occurred or worsened in severity after the first administration of study drug up to 28 days after the last dose. Additional details can be found in the Data Supplement.

Data up to and including the last 12-month visit are presented. As of the data snapshot (November 2, 2016), < 0.5% of data remained to be captured, principally relating to visits after 12 months. All data were analyzed and cleaned through central data review. The study is ongoing and is expected to last approximately 5 years per patient.

RESULTS

Patients and Treatments

A total of 590 patients with newly diagnosed CP CML were screened for eligibility between July 2014 and August 2015 at 151 centers in 26 countries. Among them, 536 patients were randomly assigned to receive bosutinib (n = 268) or imatinib (n = 268); 54 patients (9.2%) failed screening (Data Supplement). All patients randomly assigned to bosutinib received study therapy; three patients randomly assigned to imatinib were not treated. At the time of data cutoff (August 11, 2016), all patients had a minimum follow-up of 12 months (48 weeks). The treatment groups were well balanced with regard to baseline demographics and disease characteristics, including the primary mITT population (bosutinib, n = 246; imatinib, n = 241; Table 1). Excluded from this population were 12 patients who were Ph-negative (six in each arm), eight patients with atypical transcripts (bosutinib, n = 3; imatinib, n = 5), and 31 patients with unknown Ph status (bosutinib, n = 13; imatinib,

Table 1. Patient Demographics and Clinical Characteristics, Modified Intent-to-Treat Population

Characteristic	Bosutinib (n = 246)	Imatinib (n = 241)	Total (N = 487)
Age			
Median (range), years	52 (18-84)	53 (19-84)	53 (18-84)
Age ≤ 64 years	198 (80.5)	199 (82.6)	397 (81.5)
Age ≥ 65 years	48 (19.5)	42 (17.4)	90 (18.5)
Male sex	142 (57.7)	135 (56.0)	277 (56.9)
Race*			
White	191 (77.6)	186 (77.2)	377 (77.4)
Asian	30 (12.2)	30 (12.4)	60 (12.3)
Black	10 (4.1)	10 (4.1)	20 (4.1)
Other	14 (5.7)	14 (5.8)	28 (5.7)
Median time from diagnosis to random assignment, days (range)†	23 (4-183)	26 (1-183)	24 (1-183)
Prior CML therapy‡	130 (52.8)	133 (55.2)	263 (54.0)
Sokal risk group			
Low	94 (38.2)	95 (39.4)	189 (38.8)
Intermediate	101 (41.1)	95 (39.4)	196 (40.2)
High	51 (20.7)	51 (21.2)	102 (20.9)
ECOG performance status§			
0	174 (70.7)	170 (70.5)	344 (70.6)
1	72 (29.3)	70 (29.0)	142 (29.2)
Extramedullary disease	14 (5.7)	8 (3.3)	22 (4.5)
History of cardiac disease‖	28 (11.4)	29 (12.0)	57 (11.7)
History of cardiac procedures	15 (6.1)	16 (6.6)	31 (6.4)

NOTE. Data are No. (%) unless noted otherwise. Modified intent-to-treat population includes Philadelphia chromosome–positive patients with typical (e13a2 and/or e14a2) *BCR-ABL1* transcript types.
Abbreviations: CML, chronic myeloid leukemia; ECOG, Eastern Cooperative Oncology Group.
*Self-reported. Data missing for one patient in each arm.
†Defined as time from primary diagnosis to random assignment. Initial date of diagnosis missing for 23 patients.
‡Prior therapy for CML included hydroxyurea and/or anagrelide treatment only as permitted by eligibility criteria; no prior treatment with a tyrosine kinase inhibitor was allowed.
§Data missing for one patient in the imatinib arm.
‖Per case report form collected at screening if the patient had history of coronary disease.

Table 2. Treatment Status of Study Patients, Safety Population

Treatment Status	Bosutinib (n = 268)	Imatinib (n = 265)
Completed 12 months of treatment	219 (81.7)	218 (82.3)
Discontinued treatment within 12 months	49 (18.3)	47 (17.7)
Discontinued treatment	59 (22.0)	71 (26.8)
Adverse event	37 (13.8)	24 (9.1)
Related to study treatment	34 (12.7)	23 (8.7)
Not related to study treatment	3 (1.1)	1 (0.4)
Suboptimal response/treatment failure	5 (1.9)	16 (6.0)
Investigator request	5 (1.9)	12 (4.5)
Patient request	6 (2.2)	2 (0.8)
Disease progression to AP/BP	1 (0.4)	4 (1.5)
Protocol deviation	3 (1.1)	2 (0.8)
Death	0	4 (1.5)
Failed to return	0	1 (0.4)
Lost to follow-up	1 (0.4)	0
Other	1 (0.4)	6 (2.3)

NOTE. Data are No. (%). Safety population includes all patients who received one or more doses of study treatment; three patients randomly assigned to imatinib were not treated.
Abbreviations: AP, accelerated phase; BP, blast phase.

n = 18; which included two patients receiving imatinib also listed as having atypical transcripts). The safety population includes all patients randomly assigned who received one or more doses of study drug.

Median dose intensity was 392 mg once daily (range, 39 to 557 mg/d) for bosutinib and 400 mg once daily (range, 189 to 679 mg/d) for imatinib. Median duration of study treatment in the safety population was 14.1 months for bosutinib and 13.8 months for imatinib; median on-study duration in the mITT population was 15.6 and 15.3 months, respectively, including post-treatment survival follow-up. A total of 22.0% of patients receiving bosutinib and 26.8% of patients receiving imatinib discontinued treatment; reasons for discontinuation are listed in Table 2. Discontinuation owing to treatment-related AEs as the primary reason occurred in 12.7% of patients in the bosutinib group and 8.7% in the imatinib group. More patients in the imatinib group (7.5%) discontinued treatment because of disease progression to AP/BP and suboptimal response/treatment failure as assessed by the investigator compared with patients in the bosutinib group (2.2%).

Efficacy

The MMR rate at 12 months (primary end point) was significantly higher among patients receiving bosutinib versus imatinib (47.2% *v* 36.9%; $P = .0200$; Table 3). MMR rates were also higher in the bosutinib group at 3, 6, and 9 months (Fig 1), and the cumulative incidence function of MMR was more favorable with bosutinib (hazard ratio, 1.34 [95% CI, 1.06 to 1.69]; Gray's test $P = .0173$; Data Supplement), indicating a shorter time to response. MMR rates at 12 months were higher with bosutinib versus imatinib in patients with high (34.0% *v* 16.7%), intermediate (44.9% *v* 39.1%), and low (58.1% *v* 46.3%) Sokal risk scores. MMR rates at 12 months in the ITT population were similar to the mITT population: 46.6% (95% CI, 40.7% to 52.6%) with bosutinib and 36.2% (95% CI, 30.4% to 41.9%) with imatinib (odds ratio, 1.57 [95% CI, 1.10 to 2.22]; $P = .0126$).

A greater proportion of patients in the bosutinib versus imatinib group had *BCR-ABL1* transcripts ≤ 10% at 3 months (75.2% *v* 57.3%) and had achieved deeper molecular responses at months 3, 6, 9, and 12 (Fig 1). Rate of CCyR by 12 months was significantly higher for patients receiving bosutinib versus imatinib (77.2% *v* 66.4%; $P = .0075$). The cumulative incidence function of CCyR was also more favorable in the bosutinib group (hazard ratio, 1.38 [95% CI, 1.13 to 1.69]; Gray's test $P < .001$; Data Supplement).

Dose escalations due to suboptimal response were less common with bosutinib versus imatinib (17.2% *v* 27.5%; Data Supplement). After initial dose escalation, 7.1% of patients treated with bosutinib and 15.8% of patients treated with imatinib achieved CCyR; 3.4% and 10.6% achieved MMR, respectively. After a second dose escalation, 1.9% and 1.5% achieved CCyR, respectively; 0.7% and 0.8% achieved MMR, respectively.

Four patients (1.6%) receiving bosutinib and six patients (2.5%) receiving imatinib experienced disease progression to AP or BP during treatment. Five of these patients (bosutinib, n = 3; imatinib, n = 2) met AP criteria solely on the basis of basophil count within 2 weeks after random assignment. All five of these patients continued to receive the study drug; four achieved MMR. Ten (4.1%) patients receiving bosutinib and 15 (6.2%) patients receiving imatinib had EFS events. Cumulative incidence of EFS events at 12 months was

Table 3. Response Rates, Modified Intent-to-Treat Population

Response	% (95% CI)*			
	Bosutinib, (n = 246)	Imatinib (n = 241)	Odds Ratio (95% CI)†	*P*‡
Major molecular response at 12 months	47.2 (40.9 to 53.4)	36.9 (30.8 to 43.0)	1.55 (1.07 to 2.23)	.0200
Complete cytogenetic response by 12 months	77.2 (72.0 to 82.5)	66.4 (60.4 to 72.4)	1.74 (1.16 to 2.61)	.0075

NOTE. Modified intent-to-treat population includes patients with Philadelphia chromosome–positive status with typical (e13a2 and/or e14a2) *BCR-ABL1* transcript types.
*Asymptotic 95% CIs are presented for response rates.
†Adjusted for Sokal risk group (low, intermediate, high) and geographic region at time of random assignment. 95% CIs for odds ratios based on asymptotic Wald confidence limits.
‡*P* value was based on a Cochran-Mantel-Haenszel test for general association between treatment and response with stratification by Sokal risk group (low, intermediate, high) and region as determined at time of random assignment.

3.7% (95% CI, 1.8 to 6.7) for bosutinib and 6.4% (95% CI, 3.7 to 10.0) for imatinib.

Seven patients died while enrolled in the study (one patient who received bosutinib and six patients who received imatinib). Four of these deaths (all in the imatinib group) occurred within 28 days of last dose (disease progression, cardiovascular failure/cerebrovascular accident, pneumonia, and septicemia). One additional patient who received bosutinib died as a result of spindle cell lung carcinoma 257 days after last dose, and two other patients who received imatinib died as a result of disease progression 231 and 43 days after last dose. The 12-month Kaplan-Meier estimated survival rate was 99.6% (95% CI, 97.0 to 99.9) with bosutinib and 97.9% (95% CI, 95.0 to 99.1) with imatinib.

Safety

Adverse events were consistent with the known safety profiles of both drugs. The percentage of patients reporting one or more TEAEs was similar with bosutinib and imatinib (98.1% and 97.0%, respectively; Tables 4 and 5). The most common TEAEs of any grade (incidence ≥ 20%) in the bosutinib group were diarrhea (70.1%), nausea (35.1%), thrombocytopenia (35.1%), increased ALT (30.6%), and increased AST (22.8%). The most common

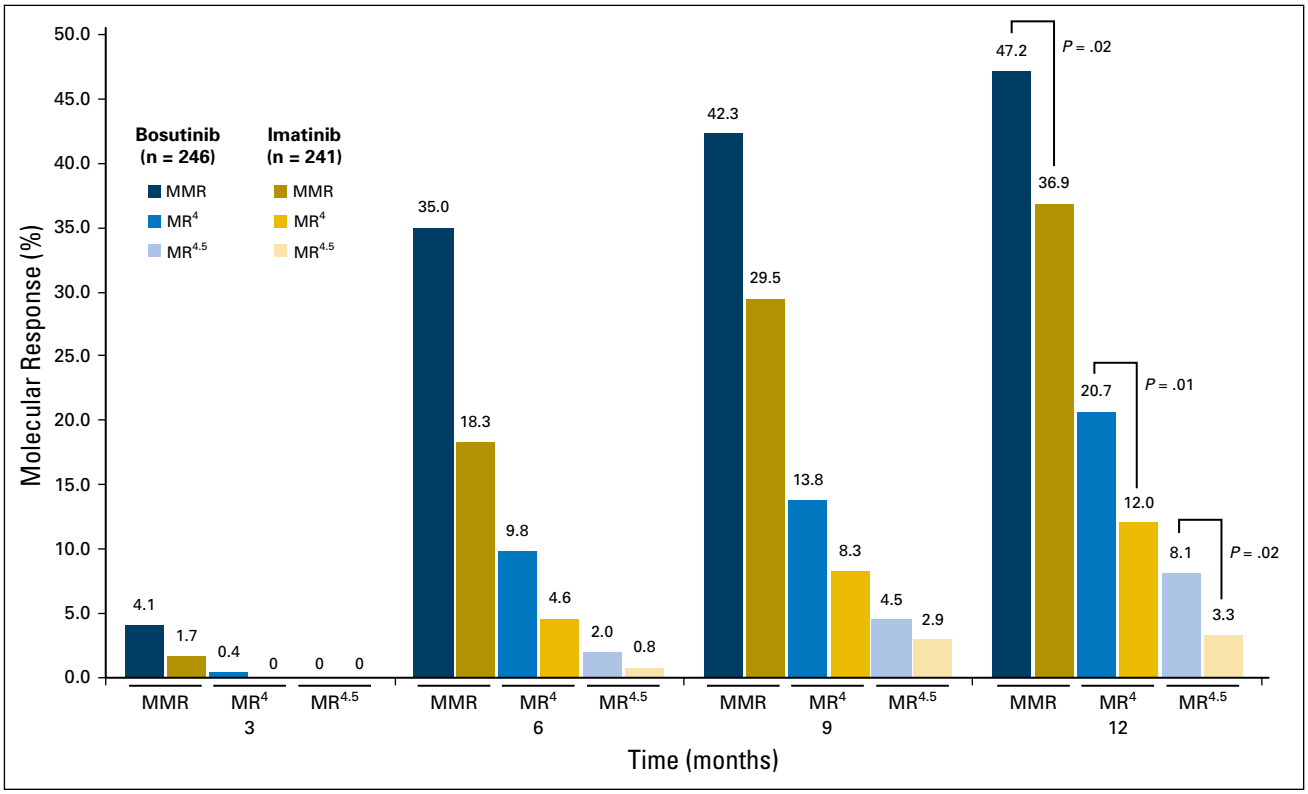

Fig 1. Molecular response rates at 3, 6, 9, and 12 months (modified intent-to-treat population). Major molecular response (MMR; defined as ≤ 0.1% *BCR-ABL1* transcripts on the international scale with ≥ 3,000 *ABL1* assessed), MR^4 (defined as ≤ 0.01% *BCR-ABL1* transcripts on the international scale with ≥ 9,800 *ABL1* assessed), and $MR^{4.5}$ (defined as ≤ 0.0032% *BCR-ABL1* transcripts on the international scale with ≥ 30,990 *ABL1* assessed) were compared using the Cochran-Mantel-Haenszel test, stratified by Sokal risk group and geographic region. Two-sided *P* values from analyses other than the primary end point and 12-month secondary end points are for descriptive purposes only, without adjustment for multiple comparisons. Percentages are based on number of Philadelphia chromosome–positive patients with typical (e13a2 and/or e14a2) *BCR-ABL1* transcript types (ie, modified intent-to-treat population) in each arm.

Table 4. Adverse Events, Safety Population

Adverse Event	Bosutinib (n = 268)		Imatinib (n = 265)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any adverse event	263 (98.1)	151 (56.3)	257 (97.0)	113 (42.6)
GI	218 (81.3)	29 (10.8)	163 (61.5)	9 (3.4)
Diarrhea	188 (70.1)	21 (7.8)	89 (33.6)	2 (0.8)
Nausea	94 (35.1)	0	103 (38.5)	0
Vomiting	48 (17.9)	3 (1.1)	43 (16.2)	0
Abdominal pain	48 (17.9)	5 (1.9)	19 (7.2)	1 (0.4)
Hematologic*	122 (45.5)	44 (16.4)	115 (43.4)	52 (19.6)
Thrombocytopenia*	94 (35.1)	37 (13.8)	52 (19.6)	15 (5.7)
Anemia*	50 (18.7)	9 (3.4)	50 (18.9)	12 (4.5)
Neutropenia*	30 (11.2)	18 (6.7)	55 (20.8)	32 (12.1)
Leukopenia*	15 (5.6)	3 (1.1)	29 (10.9)	8 (3.0)
Musculoskeletal	79 (29.5)	5 (1.9)	155 (58.5)	6 (2.3)
Muscle spasms	6 (2.2)	0	70 (26.4)	1 (0.4)
Arthralgia	30 (11.2)	2 (0.7)	35 (13.2)	0
Myalgia	8 (3.0)	1 (0.4)	41 (15.5)	2 (0.8)
Pain in extremity	12 (4.5)	1 (0.4)	33 (12.5)	0
Infections	119 (44.4)	9 (3.4)	125 (47.2)	13 (4.9)
Upper respiratory tract infection	23 (8.6)	1 (0.4)	27 (10.2)	0
Liver function†	107 (39.9)	65 (24.3)	36 (13.6)	11 (4.2)
ALT increased	82 (30.6)	51 (19.0)	15 (5.7)	4 (1.5)
AST increased	61 (22.8)	26 (9.7)	17 (6.4)	5 (1.9)
Other				
Fatigue	52 (19.4)	1 (0.4)	47 (17.7)	0
Rash	53 (19.8)	1 (0.4)	35 (13.2)	3 (1.1)
Headache	50 (18.7)	3 (1.1)	34 (12.8)	3 (1.1)
Lipase increased	36 (13.4)	26 (9.7)	22 (8.3)	14 (5.3)
Pyrexia	35 (13.1)	2 (0.7)	22 (8.3)	0
Peripheral edema	11 (4.1)	0	36 (13.6)	1 (0.4)
Asthenia	30 (11.2)	0	17 (6.4)	0
Periorbital edema	4 (1.5)	0	37 (14.0)	0
Decreased appetite	27 (10.1)	1 (0.4)	16 (6.0)	0

NOTE. Data presented as No. (%). Adverse events that occurred in ≥ 10% of patients in either arm are shown.
*Included Medical Dictionary for Regulatory Activities terms are listed in the Data Supplement.

TEAEs with imatinib were nausea (38.5%), diarrhea (33.6%), muscle spasms (26.4%), and neutropenia (20.8%). Grade 3 or higher TEAEs occurred in 56.3% of patients receiving bosutinib, most commonly (incidence ≥ 10%) ALT increase (19.0%) and thrombocytopenia (13.8%). Grade 3 or higher TEAEs occurred in 42.6% of patients receiving imatinib, most commonly neutropenia (12.1%).

Dose interruptions and reductions due to AEs were more common for bosutinib versus imatinib, with 56.3% of patients receiving bosutinib and 35.8% of patients receiving imatinib having one or more dose interruptions. Median time to first dose interruption was shorter with bosutinib than imatinib (36 *v* 57 days) and median duration of dose delay was longer (23 *v* 15 days, respectively). Similarly, 34.7% of patients receiving bosutinib had one or more dose reductions (median time to first reduction, 65 days) versus 17.4% of patients receiving imatinib (median time to first dose reduction, 84 days).

In the bosutinib group, 14.2% of patients treated discontinued therapy because of AEs compared with 10.6% in the imatinib group. The most common AEs leading to discontinuation of bosutinib were ALT increase (4.9%) and AST increase (2.2%). The most common AEs leading to discontinuation of imatinib were thrombocytopenia (1.5%) and myalgia (1.1%).

Diarrhea was common with bosutinib (70.1%) but was typically of low severity. Twenty-one patients (7.8%) receiving bosutinib had grade 3 events (there were no grade 4 events), and only two patients (0.7%) receiving bosutinib and two patients (0.8%) receiving imatinib discontinued because of diarrhea. Liver function AEs occurred in 39.9% of patients receiving bosutinib and in 13.6% of patients receiving imatinib; grade 3 or higher events occurred in 24.3% and 4.2% of patients, respectively. There were no cases of hepatotoxicity-related fatalities during the study, and no patients were ever considered at high risk of fatal drug-induced liver injury. See the Data Supplement for additional safety data.

Cardiac events occurred in 5.2% of patients receiving bosutinib and 5.3% of patients receiving imatinib (Data Supplement), most commonly QT prolongation (1.5% and 3.0%, respectively). Cardiac events of grade 3 or higher considered by the investigator to be drug related occurred in 0.7% of patients receiving bosutinib (one event each of pericardial effusion and supraventricular tachycardia) and one (0.4%) patient receiving imatinib (ECG QT prolongation). Pleural effusion events were reported in 1.9% of patients treated with bosutinib and 1.5% treated with imatinib, none of which were grade 3 or higher.

Peripheral vascular events occurred in 1.5% of patients receiving bosutinib and 1.1% of patients receiving imatinib (Data Supplement). One patient who received imatinib experienced a cerebrovascular event (cerebrovascular accident resulting in death). Cardiovascular events occurred in 3.0% of patients receiving bosutinib and 0.4% of patients receiving imatinib, 2.2%

Table 5. Laboratory Abnormalities, Safety Population

	Bosutinib (n = 268)		Imatinib (n = 265)	
Laboratory Abnormality	All Grades	Grade 3/4	All Grades	Grade 3/4
Any abnormality	267 (99.6)	157 (58.6)	265 (100)	145 (54.7)
ALT increased	170 (63.4)	62 (23.1)	55 (20.8)	7 (2.6)
AST increased	132 (49.3)	32 (11.9)	53 (20.0)	8 (3.0)
Increased amylase	67 (25.0)	6 (2.2)	37 (14.0)	4 (1.5)
Decreased calcium	69 (25.7)	4 (1.5)	102 (38.5)	2 (0.8)
Increased creatine kinase	76 (28.4)	4 (1.5)	144 (54.3)	9 (3.4)
Increased creatinine*	248 (92.5)	0	252 (95.1)	2 (0.8)
Increased glucose	124 (46.3)	6 (2.2)	152 (57.4)	6 (2.3)
Decreased potassium	19 (7.1)	4 (1.5)	66 (24.9)	4 (1.5)
Increased lipase	106 (39.6)	35 (13.1)	77 (29.1)	16 (6.0)
Decreased phosphate	117 (43.7)	12 (4.5)	160 (60.4)	45 (17.0)
Decreased hemoglobin†	234 (87.3)	19 (7.1)	235 (88.7)	15 (5.7)
Decreased ANC	106 (39.6)	24 (9.0)	163 (61.5)	49 (18.5)
Decreased platelets	179 (66.8)	38 (14.2)	156 (58.9)	17 (6.4)
Decreased leukocytes	132 (49.3)	15 (5.6)	180 (67.9)	20 (7.5)

NOTE. Data are No. (%). Laboratory abnormalities that occurred in ≥ 20% of patients in either arm are shown.
Abbreviation: ANC, absolute neutrophil count.
*Incidence includes any increase from baseline per Common Terminology Criteria for Adverse Events, version 4.0.
†Incidence at baseline was 55.2% in the bosutinib arm and 60.4% in the imatinib arm.

and 0.4%, respectively, during the first year of therapy. There were no deaths due to cardiovascular toxicity.

DISCUSSION

Results of this trial indicate improved outcomes with bosutinib versus imatinib as initial therapy for patients with CP CML, as demonstrated by a higher rate of MMR at 12 months in the mITT population (47.2% *v* 36.9%; $P = .0200$; primary end point) and other efficacy measures. This improved response was accompanied by a favorable toxicity profile. In addition, although the magnitude of MMR rate improvement is numerically larger among patients with high-risk Sokal, there was a nonstatistically significant trend for benefit in all Sokal risk groups.

Although National Comprehensive Cancer Network guidelines indicate that CCyR by 12 months is the goal of TKI therapy along with prevention of disease progression,[15] the significance of achieving MMR within 12 months has been established in various studies to correlate with EFS. This hallmark is recognized by the European LeukemiaNet as an optimal response,[16] and the National Comprehensive Cancer Network considers *BCR-ABL1* transcript levels ≥ 0.1% as a consideration for possible changes in therapy.[15] Consistent with the current study, a previous trial of bosutinib versus imatinib in the front-line setting (BELA) demonstrated improvement in MMR rate at 12 months with bosutinib (41% *v* 27%, $P < .001$).[13,14] However, BELA did not meet its primary end point of CCyR at 12 months. In a subsequent analysis of BELA data, the rate of CCyR by 12 months was higher with bosutinib versus imatinib (75.6% *v* 67.1%; $P = .032$).[17] These results are similar to those of BFORE, which demonstrated a significantly higher CCyR rate by 12 months with bosutinib (77.2% *v* 66.4%; $P = .0075$). An important difference between the studies was the lower starting dose of bosutinib in BFORE versus BELA (400 *v* 500 mg/d). This was based on discontinuation rates from BELA (29% of patients receiving bosutinib *v* 20% of patients receiving imatinib) and increased experience with bosutinib gained over time. With a similar follow-up duration, 22.0% of patients discontinued bosutinib in BFORE despite more patients being ≥ 65 years of age (19.5% receiving bosutinib in BFORE *v* 12.0% in BELA)[13] and having medical histories that potentially predisposed them to AEs, suggesting the lower dose was associated with better tolerability and hence better responses. Differences in baseline characteristics may also account for the higher rate of imatinib discontinuation observed in this study (26.8%) compared with BELA and other studies of front-line imatinib.[1,2]

Similar studies that compared nilotinib (Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients [ENESTnd])[2] and dasatinib (Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients [DASISION])[1] with imatinib as front-line treatment of CML demonstrated higher response rates and deeper and earlier responses with the second-generation TKI therapies. However, there has been no clear benefit in EFS or OS with newer agents. Results in BELA and BFORE are consistent with these results.[1,2] With the short follow-up, there is currently no difference in EFS or OS between cohorts, although it is possible that differences will emerge with longer observation time. In addition, the higher rate of deep molecular responses may present an opportunity for more patients to become eligible for a trial of treatment discontinuation, an end point of increasing relevance.[18,19]

The toxicity profile of bosutinib observed in this study was similar to those previously reported,[13,14,20] with the most common AEs being diarrhea and liver function abnormalities. Diarrhea events occurred early and were transient, with frequency and severity typically improving over time. Diarrhea was primarily grade 1 or 2, was manageable, and did not lead to a higher discontinuation rate compared with the imatinib arm. Liver function abnormalities were the most common AEs leading to discontinuation of bosutinib.

In this study, 3.0% of patients receiving bosutinib and 0.4% of patients receiving imatinib had cardiovascular events; 2.2% and 0.4%, respectively, occurred during the first year of therapy. In BELA, incidence of cardiovascular events at 12 months was 0.8% in both arms; however, more patients enrolled in the current study had a history of cardiac disorders (BFORE: 14.2% of patients receiving bosutinib and 13.8% of patients receiving imatinib; BELA: 9.6% and 13.5%, respectively) and vascular disorders (BFORE: 36.9% and 33.6%, respectively; BELA: 24.4% and 27.4%, respectively; Medical Dictionary for Regulatory Activities System Organ Class) at baseline relative to those in BELA.[17] An analysis of 4-year data from BELA suggested no increased risk of cardiovascular events with long-term bosutinib versus imatinib treatment.[21] Longer follow-up is needed to better assess and understand any possible difference between the two studies in the incidence of these events.

We conclude that bosutinib 400 mg once daily provides benefit over imatinib, with higher rates of cytogenetic and molecular responses, and that these responses occur earlier. Bosutinib is associated with a favorable toxicity profile, with most AEs being low-grade, manageable, and improving over time. These results suggest that bosutinib can be an important alternative for patients with previously untreated CP CML.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Jorge E. Cortes, Carlo Gambacorti-Passerini, Michael J. Mauro, Laurence Reilly, Allison Jeynes-Ellis, Nathalie Bardy-Bouxin, Andreas Hochhaus, Tim H. Brümmendorf

Provision of study materials or patients: Jorge E. Cortes, Carlo Gambacorti-Passerini, Michael W. Deininger, Michael J. Mauro, Charles Chuah, Dong-Wook Kim, Irina Dyagil, Nataliia Glushko, Dragana Milojkovic, Philipp le Coutre, Valentin Garcia-Gutierrez, Andreas Hochhaus, Tim H. Brümmendorf

Collection and assembly of data: Jorge E. Cortes, Carlo Gambacorti-Passerini, Michael W. Deininger, Charles Chuah, Dong-Wook Kim, Irina Dyagil, Nataliia Glushko, Dragana Milojkovic, Philipp le Coutre, Valentin Garcia-Gutierrez, Eric Leip, Andreas Hochhaus, Tim H. Brümmendorf

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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Affiliations

Jorge E. Cortes, University of Texas MD Anderson Cancer Center, Houston, TX; **Carlo Gambacorti-Passerini**, University of Milano-Bicocca, Monza, Italy; **Michael W. Deininger**, University of Utah, Salt Lake City, UT; **Michael J. Mauro**, Memorial Sloan Kettering Cancer Center, New York, NY; **Charles Chuah**, Singapore General Hospital, Duke-National University of Singapore Medical School, Singapore, Singapore; **Dong-Wook Kim**, Seoul St Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; **Irina Dyagil**, National Research Center for Radiation Medicine, Kiev; **Nataliia Glushko**, Ivano-Frankivsk Regional Clinical Hospital, Ivano-Frankivsk, Ukraine; **Dragana Milojkovic**, Imperial College London at Hammersmith Hospital London; **Laurence Reilly** and **Allison Jeynes-Ellis**, Avillion, London, United Kingdom; **Philipp le Coutre**, Charité-Universitätsmedizin Berlin, Berlin; **Andreas Hochhaus**, Klinik für Innere Medizin II, Universitätsklinikum Jena, Jena; **Tim H. Brümmendorf**, Universitätsklinikum RWTH Aachen, Aachen, Germany; **Valentin Garcia-Gutierrez**, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain; **Eric Leip**, Pfizer, Cambridge, MA; **Nathalie Bardy-Bouxin**, Pfizer International Operation, Paris, France.

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Jorge E. Cortes
Consulting or Advisory Role: ARIAD Pharmaceuticals, Bristol-Myers Squibb, BioLineRx, Novartis, Pfizer, Amphivena Therapeutics, Daiichi Sankyo, Bio-Path Holdings, Astellas Pharma
Research Funding: ARIAD Pharmaceuticals (Inst), Bristol-Myers Squibb (Inst), Novartis (Inst), Pfizer (Inst), Teva (Inst), Celgene (Inst), Arog Pharmaceuticals (Inst), Astellas Pharma (Inst), Ambit BioSciences (Inst), Celator Pharmaceuticals (Inst), ImmunoGen (Inst), Incyte (Inst)

Carlo Gambacorti-Passerini
Honoraria: Pfizer
Consulting or Advisory Role: Pfizer
Research Funding: Pfizer
Travel, Accommodations, Expenses: Pfizer, Bristol-Myers Squibb Italy

Michael W. Deininger
Honoraria: Novartis, Bristol-Myers Squibb, Incyte, ARIAD Pharmaceuticals, Pfizer, Galena Biopharma, CTI BioPharma, Blueprint Medicines, Gilead Sciences
Consulting or Advisory Role: Novartis, Incyte, ARIAD Pharmaceuticals, Pfizer, CTI BioPharma, Bristol-Myers Squibb, Galena Biopharma, Blueprint Medicines, Gilead Sciences
Research Funding: Novartis (Inst), Bristol-Myers Squibb (Inst), Celgene (Inst), Gilead Sciences (Inst), Pfizer (Inst), ARIAD Pharmaceuticals, Blueprint Medicines, Galena Biopharma, Incyte
Expert Testimony: Bristol-Myers Squibb
Travel, Accommodations, Expenses: ARIAD Pharmaceuticals, Novartis, Pfizer, CTI BioPharma, Galena Biopharma, Blueprint Medicines, Gilead Sciences, Incyte

Michael J. Mauro
Consulting or Advisory Role: Bristol-Myers Squibb, Pfizer, Novartis, ARIAD Pharmaceuticals, Takeda
Research Funding: Novartis (Inst)

Charles Chuah
Honoraria: Bristol-Myers Squibb, Chiltern, Novartis

Dong-Wook Kim
Honoraria: Novartis, Bristol-Myers Squibb, Pfizer, IL-Yang Pharm
Consulting or Advisory Role: Novartis, Bristol-Myers Squibb, IL-Yang Pharm
Research Funding: Novartis, Bristol-Myers Squibb, Pfizer, ARIAD Pharmaceuticals, Il-Yang Pharm
Travel, Accommodations, Expenses: Novartis, ARIAD Pharmaceuticals

Irina Dyagil
No relationship to disclose

Nataliia Glushko
Honoraria: Novartis, Roche, Takeda
Speakers' Bureau: Novartis, Pfizer
Travel, Accommodations, Expenses: Novartis, Pfizer, Takeda, Quintiles

Dragana Milojkovic
No relationship to disclose

Philipp le Coutre
No relationship to disclose

Valentin Garcia-Gutierrez
Honoraria: ARIAD Pharmaceuticals, Bristol-Myers Squibb, Novartis, Pfizer
Consulting or Advisory Role: ARIAD Pharmaceuticals, Bristol-Myers Squibb, Novartis, Pfizer
Research Funding: ARIAD Pharmaceuticals, Bristol-Myers Squibb, Novartis, Pfizer (Inst)

Laurence Reilly
Employment: Avillion
Leadership: Avillion
Stock or Other Ownership: Avillion

Allison Jeynes-Ellis
Employment: Avillion
Leadership: Avillion
Stock or Other Ownership: Avillion

Eric Leip
Employment: Pfizer
Stock or Other Ownership: Pfizer

Nathalie Bardy-Bouxin
Employment: Pfizer
Stock or Other Ownership: Pfizer
Travel, Accommodations, Expenses: Pfizer

Andreas Hochhaus
Honoraria: Novartis
Consulting or Advisory Role: Novartis
Research Funding: Novartis
Travel, Accommodations, Expenses: Novartis, Pfizer
Other Relationship: Bristol-Myers Squibb, Incyte, Pfizer

Tim H. Brümmendorf
Consulting or Advisory Role: Pfizer, Novartis, ARIAD Pharmaceuticals
Research Funding: Novartis (Inst), Pfizer (Inst)

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