RESEARCH ARTICLE

Safety of bosutinib versus imatinib in the phase 3 BELA trial in newly diagnosed chronic phase chronic myeloid leukemia

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Bosutinib, an orally active, Src/Abl tyrosine kinase inhibitor, has demonstrated clinical activity and acceptable tolerability in chronic phase chronic myeloid leukemia (CP CML). This updated analysis of the BELA trial assessed the safety profile and management of toxicities of bosutinib versus imatinib in adults with newly diagnosed (≤6 months) CP CML after >30 months from accrual completion. Among patients randomized to bosutinib 500 mg/d ($n = 250$) or imatinib 400 mg/d ($n = 252$), 248 and 251, respectively, received ≥1 dose of study treatment. Adverse events (AEs; any grade) with bosutinib versus imatinib were significantly more common for certain gastrointestinal events (diarrhea, 70% vs. 26%; $P < 0.001$; vomiting, 33% vs. 16%; $P < 0.001$), alanine aminotransferase (33% vs. 9%; $P < 0.001$) and aspartate aminotransferase (28% vs. 10%; $P < 0.001$) elevations, and pyrexia (19% vs. 12%; $P = 0.046$). AEs significantly less common with bosutinib included edema (periorbital, 2% vs. 14%; $P < 0.001$; peripheral, 5% vs. 12%; $P = 0.006$), musculoskeletal (myalgia, 5% vs. 12%; $P = 0.010$; muscle cramps, 5% vs. 22%; $P < 0.001$; bone pain, 4% vs. 11%; $P = 0.003$), increased creatine phosphokinase (8% vs. 20%; $P < 0.001$), neutropenia (13% vs. 30%; $P < 0.001$), and leukopenia (9% vs. 22%; $P < 0.001$). Between-group differences in the incidence of cardiac and vascular AEs were not significant. Diarrhea was typically transient, mostly Grade 1/2, occurring early during treatment, and was manageable with antidiarrheal medication. Despite higher rates of aminotransferase elevation with bosutinib, events were managed in most patients with dose modification and/or concomitant medication. Bosutinib had a manageable safety profile distinct from that of imatinib in patients with newly diagnosed CP CML.

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Introduction

Chronic myeloid leukemia (CML) is typically characterized by the constitutively active Bcr-Abl tyrosine kinase, which is a fusion product of genetic translocation between chromosomes 9 and 22 that produces the Philadelphia chromosome (Ph) [1–3]. Targeted inhibition of the Bcr-Abl oncoprotein by the tyrosine kinase inhibitors (TKIs) imatinib, dasatinib, and nilotinib has become a standard treatment for all phases of Ph+ CML [4–8]. However, each TKI is associated with a distinct selectivity profile [9–11]. Differences in the selectivity for additional targets (e.g., c-KIT and platelet-derived growth factor receptor [PDGFR]) may contribute to the distinct toxicity profiles of these TKIs [9–11]. Overall, imatinib,

Additional Supporting Information may be found in the online version of this article.

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dasatinib, and nilotinib are associated with manageable side effect profiles in most patients with CML; however, some patients have been found to develop intolerance to each of these TKIs [12–14].

Bosutinib (SKI-606) is an orally active dual Src and Abl TKI with minimal activity against PDGFR or c-KIT [9,10]. It is approved in the United States and Europe for the treatment of patients with Ph+ CML following resistance or intolerance to prior TKIs or for whom other TKIs are not appropriate choices [15,16]. Bosutinib has demonstrated clinical activity in all phases of CML previously treated with imatinib only or imatinib plus dasatinib and/or nilotinib in a previous phase 1/2 study [17,18]. In the same study, bosutinib was associated with a manageable toxicity profile across cohorts, primarily characterized by mild or moderate gastrointestinal events and rash [17,18].

The Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia (BELA) trial is an open-label, multinational, randomized phase 3 trial investigating the efficacy and safety of bosutinib as compared with imatinib in newly diagnosed chronic phase CML (CP CML) [19]. Results from the primary analysis of the BELA trial (after a minimum follow-up of 12 months) also demonstrated clinical activity and manageable toxicity for bosutinib. On the basis of all randomized patients, the rate of complete cytogenetic response (CCyR) at 12 months was similar between the bosutinib (70%) and imatinib (68%) treatment arms, although the rate of major molecular response (MMR) at 12 months was significantly higher with bosutinib (41% vs. 27%; $P < 0.001$) [19]. Additionally, time to CCyR and MMR were significantly shorter with bosutinib versus imatinib ($P < 0.001$). Data from the 12-month analysis of this study also suggested distinct safety and tolerability profiles for bosutinib as compared with imatinib [19].

The current analysis of the BELA trial describes the safety profiles of bosutinib and imatinib in patients with newly diagnosed CP CML after a minimum of 30 months from the last patient's first visit and addresses the management of toxicities observed with each agent.

Methods

Study design. The BELA trial is an ongoing, open-label, randomized, multinational phase 3 study (ClinicalTrials.gov Identifier: NCT00574873). The design of the trial has been described previously [19]. Patients were randomized 1:1 to bosutinib 500 mg/d or imatinib 400 mg/d and stratified by Sokal risk group and geographic region. Dose escalation to bosutinib 600 mg/d or imatinib 600 mg/d was permitted for lack of efficacy (defined according to European LeukemiaNet recommendations [20]) if no Grade 3/4 or persistent Grade 2 drug-related adverse event (AE) had occurred. Patients discontinued treatment upon treatment failure or if they could not tolerate at least 300 mg/d bosutinib or imatinib. Patients could participate in the BELA trial for up to 5 years; however, bosutinib-treated patients are permitted to enroll in an extension protocol until they have received bosutinib or undergone follow-up for 10 years from the time of initial enrollment in the BELA trial.

The study was conducted in accordance with ethical principles consistent with the Declaration of Helsinki. The protocol was approved by an institutional review board at each study site before enrolling any patients. All patients provided written informed consent before any procedures that were part of the protocol were performed.

Patients. Inclusion and exclusion criteria for the BELA trial have been previously described [19]. Briefly, eligible patients were aged ≥18 years with a new cytogenetic diagnosis of Ph+ CP CML ≤6 months of enrollment. Additional key criteria included no prior antileukemia treatment (except ≤6 months of anagrelide or hydroxyurea), an Eastern Cooperative Oncology Group Performance Status score of 0 or 1, and adequate hepatic and renal function.

Safety analyses. The safety population included all randomized patients who received ≥1 dose of study drug. Safety assessments were performed on an ongoing basis from the time of consent throughout the study, with patients followed for AEs for 28 days after the last dose of study drug and, in the case of treatment-related AEs, until return to baseline, Grade 0 or 1, or until the condition stabilized for those with impairment. Assessments included physical examination (including vital signs), laboratory testing, and AE reporting based on the National Cancer Institute Common Terminology Criteria for AEs, version 3.0. Grade 3/4 laboratory abnormalities were assessed based on objective reports taken directly from the laboratory case report form. Fisher exact test was used to assess treatment differences in treatment-emergent AE rates (all grades).

Results

Patients

A total of 502 patients with newly diagnosed CP CML were enrolled and randomized between February 2008 and July 2009 at 139 centers in 31 countries, among whom, 499 (bosutinib, $n = 248$; imatinib, $n = 251$) received treatment and were included in the safety population [19]. Patient demographic and baseline disease characteristics, described previously [19], were well balanced between treatment arms (Appendix Table AI [Supporting Information]), with median patient ages of 48 and 47 years, respectively, median times since diagnosis of 23 and 22 days, respectively, and 18% of patients in each arm categorized as high Sokal risk.

Treatment summary

Among randomized patients, 248 and 251 patients received ≥1 dose of bosutinib or imatinib, respectively. As of February 15, 2012, all patients in both treatment arms who did not discontinue follow-up for survival had a minimum follow-up of 30 months (with a median time on study for all patients of 35.2 months). The median (range) treatment duration was 30.4 (<0.1–46.8) months for the 248 patients receiving bosutinib and 30.6 (0.5–43.9) months for the 251 patients receiving imatinib. Median (range) dose intensities in bosutinib and imatinib arms were 492 (115−589) and 400 (201−575) mg/d, respectively. Sixteen (7%) and 50 (20%) patients in the bosutinib and imatinib arms, respectively, had their dose escalated to 600 mg/d.

At the time of the data snapshot, 63% and 70% of patients in the bosutinib and imatinib arms, respectively, were still receiving treatment. The primary reason for discontinuation was AEs for bosutinib (25%, vs. 8% with imatinib) and disease progression for imatinib (14%, vs. 4% with bosutinib).

Overall safety profile

Among nonhematologic AEs (any grade), bosutinib was primarily associated with significantly higher incidences of gastrointestinal AEs (any grade) versus imatinib, including diarrhea (70% vs. 26%; $P < 0.001$) and vomiting (33% vs. 16%; $P < 0.001$). Grade 3/4 diarrhea AEs occurred at a higher rate in bosutinib versus the imatinib arm (12% [no Grade 4 events] vs. 1%; Table I). Other nonhematologic AEs that occurred at a significantly higher rate in the bosutinib versus imatinib arm included upper abdominal pain (15% vs. 8%; $P = 0.015$), abdominal pain (14% vs. 8%; $P = 0.029$; although upper abdominal pain and the more general abdominal pain terms represent separate categories, patients may have been counted under both categories), and pyrexia (19% vs. 12%; $P = 0.046$; Table I). Pleural effusions also occurred at a significantly higher rate in the bosutinib versus imatinib arms, although these rates were low in both arms (4% vs. <1%; $P = 0.006$). In contrast, bosutinib was associated with significantly lower incidences of certain events versus imatinib, such as edema (periorbital edema [2% vs. 14%; $P < 0.001$] and peripheral edema [5% vs. 12%; $P = 0.006$]), musculoskeletal events (myalgia [5% vs. 12%; $P = 0.010$], muscle cramps [5% vs. 22%; $P < 0.001$], and bone pain [4% vs. 11%; $P = 0.003$]). The incidence of cardiac AEs (System Organ Class [SOC]: cardiac disorders) of any grade was low in both the bosutinib and imatinib arms (8% vs. 6%). The most commonly reported cardiac AEs were palpitations (2% vs. 2%) and pericardial effusion (2% vs. 0%); no cases of myocardial infarction were reported in either treatment group. The incidence of vascular AEs (SOC: vascular disorders) was also low in both the bosutinib (10%) and imatinib (8%) arms. The most frequent vascular AEs in the bosutinib and imatinib arms were hypertension (6% vs. 4%) and hematoma (2% vs. 1%); no cases of peripheral arterial occlusive disease, deep venous thrombosis, or pulmonary embolism were reported

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TABLE I. Treatment-Emergent AEs and On-Treatment Laboratory Abnormalities

	Bosutinib (n=248)		Imatinib (n=251)	
Toxicity, n (%)	All Grades	Grade 3/4	All Grades	Grade 3/4
Treatment-emergent AEs reported for ≥10% (all grades) of patients				
Hematologic				
Thrombocytopenia	69 (28)	31 (13)	70 (28)	34 (14)
Neutropenia	33 (13)	20 (8)	75 (30)	41 (16)
Anemia	61 (25)	21 (9)	58 (23)	14 (6)
Leukopenia	23 (9)	6 (2)	54 (22)	14 (6)
Nonhematologic				
Diarrhea	173 (70)	29 (12)	65 (26)	2 (1)
Vomiting	82 (33)	8 (3)	41 (16)	1 (<1)
Increased ALT	81 (33)	46 (19)	23 (9)	8 (3)
Nausea	80 (32)	2 (1)	91 (36)	1 (<1)
Increased AST	69 (28)	20 (8)	24 (10)	8 (3)
Rash	61 (25)	4 (2)	49 (20)	2 (1)
Pyrexia	46 (19)	3 (1)	30 (12)	3 (1)
Increased lipase	36 (15)	21 (9)	28 (11)	15 (6)
Upper abdominal pain	36 (15)	0	19 (8)	0
Abdominal pain	34 (14)	3 (1)	19 (8)	1 (<1)
Fatigue	32 (13)	3 (1)	34 (14)	2 (1)
Headache	32 (13)	1 (<1)	30 (12)	0
Upper respiratory tract infection	30 (12)	0	21 (8)	0
Cough	23 (9)	0	27 (11)	0
Hypophosphatemia	20 (8)	3 (1)	49 (20)	25 (10)
Increased creatine phosphokinase	20 (8)	2 (1)	51 (20)	12 (5)
Arthralgia	19 (8)	0	32 (13)	1 (<1)
Myalgia	13 (5)	0	30 (12)	2 (1)
Muscle cramps	12 (5)	0	56 (22)	0
Peripheral edema	12 (5)	0	30 (12)	0
Bone pain	9 (4)	0	27 (11)	2 (1)
Periorbital edema	4 (2)	0	36 (14)	0
Laboratory abnormalities reported for ≥30% (all grades) of patients				
Hematologic				
Anemia	207 (84)	20 (8)	223 (89)	19 (8)
Thrombocytopenia	165 (67)	34 (14)	160 (64)	37 (15)
Leukopenia	115 (46)	10 (4)	179 (71)	24 (10)
Neutropenia	103 (42)	25 (10)	156 (62)	54 (22)
Lymphopenia	90 (36)	0	103 (41)	0
Nonhematologic				
Increased ALT	173 (70)	57 (23)	94 (38)	11 (4)
Increased AST	148 (60)	29 (12)	94 (38)	11 (4)
Hypophosphatemia	124 (50)	17 (7)	172 (69)	55 (22)
Hypocalcemia	119 (48)	11 (4)	138 (55)	6 (2)
Increased lipase	113 (46)	29 (12)	97 (39)	16 (6)
Increased alkaline phosphatase	112 (45)	1 (<1)	98 (39)	1 (<1)
Hyperglycemia	93 (38)	6 (2)	99 (39)	4 (2)
Decreased bicarbonate	88 (36)	1 (<1)	82 (33)	1 (<1)
Increased creatine kinase	83 (34)	1 (<1)	186 (74)	17 (7)
Hypokalemia	45 (18)	4 (2)	92 (37)	15 (6)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

in either treatment group. Between-group differences in the incidence of cardiac or vascular AEs were not significant. The cumulative incidences of selected treatment-emergent toxicities by maximum severity grade are shown in Appendix Figure A1 (Supporting Information).

The most frequent biochemical nonhematologic laboratory AEs (any grade) associated with bosutinib were elevations in alanine aminotransferase (ALT; 33% vs. 9%; $P < 0.001$) and aspartate aminotransferase (AST; 28% vs. 10%; $P < 0.001$) as compared with imatinib. In contrast, bosutinib was associated with lower rates of hypophosphatemia (8% vs. 20%; $P < 0.001$) and increased blood creatine phosphokinase (8% vs. 20%; $P < 0.001$; Table I). Grade 3/4 biochemical laboratory abnormalities observed more frequently with bosutinib (i.e., by ≥5%) included increased ALT (23% vs. 4%), increased AST (12% vs. 4%), and increased lipase (12% vs. 6%); those observed less frequently with bosutinib included hypophosphatemia (7% vs. 22%) and increased creatine kinase (<1% vs. 7%; Table I). Incidences of Grade 3/4 nonhematologic laboratory abnormalities, which were based on objective reports taken directly from the laboratory case report form, were generally similar to those for Grade 3/4 nonhematologic laboratory AEs, which were based on investigator report (Table I).

Hematologic AEs (any grade) were generally similar between treatments, except that neutropenia (13% with bosutinib vs. 30% with imatinib; $P < 0.001$) and leukopenia (9% vs. 22%; $P < 0.001$) were significantly less frequent with bosutinib (Table I). The incidence of Grade 3/4 hematologic laboratory abnormalities was similar between treatments for thrombocytopenia (14% vs. 15%) and anemia (8% vs. 8%) and lower with bosutinib for neutropenia (10% vs. 22%) and leukopenia (4% vs. 10%; Table I). Incidences of Grade 3/4 hematologic laboratory abnormalities were generally similar to those for Grade 3/4 hematologic laboratory AEs (Table I).

Serious AEs were experienced by 81 (33%) patients in the bosutinib arm versus 51 (20%) in the imatinib arm ($P = 0.002$). Serious AEs occurring in >5 patients included diarrhea ($n = 9$ [4%]), increased ALT ($n = 7$ [3%]), pneumonia ($n = 7$ [3%]), and pyrexia ($n = 6$ [2%])

in the bosutinib arm and anemia ($n = 8$ [3%]), thrombocytopenia ($n = 8$ [3%]), and neutropenia ($n = 6$ [2%]) in the imatinib arm.

Treatment modifications due to AEs were more common with bosutinib (reductions, 42%; interruptions, 67%) versus imatinib (reductions, 21%; interruptions, 46%). Permanent treatment discontinuation due to AEs also occurred more frequently with bosutinib (25%) versus imatinib (8%); AEs most commonly associated with permanent treatment discontinuation are shown in Appendix Table AII (Supporting Information). Among patients who discontinued permanently because of AEs, a greater proportion receiving imatinib discontinued without attempts to manage AEs with concomitant pharmacotherapy or dose adjustment compared with bosutinib (14/21 [67%] vs. 26/62 [42%]). Notably, the majority of bosutinib discontinuations due to AEs occurred during the first 9 months on study (months 1−3 [$n = 15$], months 3−6 [$n = 18$], months 6−9 [$n = 7$]) and tapered thereafter ($\leq$4 patients discontinued treatment because of an AE during any subsequent 3-month period).

There were 4 deaths in the bosutinib arm and 3 in the imatinib arm due to non–CML-related causes. In the bosutinib arm, all 4 deaths were due to AEs considered by the investigator to be unrelated to treatment (mesenteric embolism and intestinal necrosis during treatment, congestive heart failure 3 days after treatment discontinuation, gastric carcinoma with lung metastases 175 days after treatment discontinuation, and respiratory failure 1021 days after treatment discontinuation). In the imatinib arm, all 3 deaths were due to AEs considered unrelated to treatment (cardiovascular disease 53 days after treatment discontinuation, pneumonia 190 days after treatment discontinuation, and suspicion of lung embolism 209 days after treatment discontinuation).

Characteristics and management of individual toxicities

Gastrointestinal events (diarrhea, nausea, and vomiting) were among the most frequently reported nonhematologic treatment-emergent AEs of any grade with both bosutinib (76%) and imatinib (47%); however, few patients discontinued treatment because of gastrointestinal events (bosutinib, $n = 4$; imatinib, $n = 1$). Most events were transient, of maximum Grade 1 or 2 severity, and manageable. Specifically, in the bosutinib arm, diarrhea most frequently occurred early during treatment (median time to first event, 3 days), and the incidence tapered after the first month on treatment. In the imatinib arm, the median time to first event of diarrhea was 53 days (Table II and Appendix Fig. A2 [Supporting Information]). Among 62 patients receiving bosutinib who discontinued treatment because of any AE (Appendix Table AII [Supporting Information]), 27 had diarrhea at the time of discontinuation. No patients in the bosutinib arm and 1 patient in the imatinib arm discontinued treatment because of diarrhea. Diarrhea was primarily managed with antidiarrheal medication in both bosutinib (46%) and imatinib (31%) arms; among these patients, the median (range) duration of concomitant medication for diarrhea was 2 (1−741) and 4 (1−281) days, respectively. Additional management included dose modification of study drugs. In both treatment arms, all patients who temporarily discontinued treatment to manage diarrhea were successfully rechallenged (bosutinib, $n = 35$; imatinib, $n = 7$) and either did not experience subsequent diarrhea or experienced diarrhea that did not lead to treatment discontinuation (Table II).

Treatment-emergent AEs of increased ALT and AST were more frequent with bosutinib (33% and 28%, respectively) versus imatinib (9% and 10%). The incidences of laboratory abnormalities of increased ALT and AST were also higher with bosutinib (70% and 60%) versus imatinib (38% and 38%), with incidences decreasing over time (Supplemental Fig. A3 [Supporting Information]). Although Grade 3/4 ALT and AST AEs were relatively common in the bosutinib arm (19% and 8%, respectively), events typically resolved (median durations from Grade 3/4 to Grade 0/1, 21.5, and 21 days). Additionally, ALT and AST AEs infrequently led to treatment discontinuation ($n = 11$ and $n = 0$; Table III) and were primarily managed with dose interruptions (57% and 41% of patients with an event, respectively), and less frequently with dose reductions (31% and 13%) or concomitant medication (30% and 22%). Common concomitant medications used for ALT and AST AE management (both treatment arms) included prednisone/prednisolone ($n = 5$), ornithine aspartate ($n = 5$), essential phospholipids (e.g., Essentiale/Essentiale Forte; $n = 5$), herbal preparations (e.g., silymarin [$n = 3$] and cynara scolymus [$n = 3$]), and hepabene ($n = 3$). Among patients who were rechallenged with bosutinib after a temporary dose interruption for increased ALT or AST, 32/41 (78%) and 26/26 (100%) patients, respectively, were rechallenged successfully without recurrence of the events and/or permanent discontinuation of bosutinib because of increased ALT or AST.

Treatment-emergent rash/skin toxicity AEs occurred in 35% and 25% of patients in the bosutinib and imatinib arms, respectively, although most patients experienced a maximum severity of Grade 1 or 2. Rash/skin toxicity AEs typically occurred earlier with bosutinib versus imatinib (median time to first event, 57.5 vs. 125 days; Table IV). The majority of patients in the bosutinib ($n = 17/19$ [89%]) and imatinib ($n = 6/8$ [75%]) arms who were rechallenged after dose interruption because of rash/skin toxicity were rechallenged successfully without recurrence of rash or permanent treatment discontinuation. Few patients in either treatment arm discontinued treatment because of rash/skin toxicity (bosutinib, $n = 2$; imatinib, $n = 3$).

Overall, treatment-emergent edema AEs were less common with bosutinib (13%) versus imatinib (41%). Compared with imatinib, bosutinib was associated with a longer median time to first event (174 vs. 43 days) and a shorter median (any grade) event duration (22.5 vs. 85 days). However, few patients with an edema AE required management with dose modification (temporary dose interruption, 4 patients on bosutinib, and 1 patient on imatinib), and no patient in either arm required dose reduction or permanent discontinuation of treatment because of edema.

TABLE II. Management of Diarrhea Treatment-Emergent AEs (in Patients With ≥1 AE of Diarrhea)

Parameter	Bosutinib ($n = 173$)	Imatinib ($n = 65$)
Median (range) time to first event, d	3 (1–591)	53 (1–1089)
Median (range) duration of an event[a] d		
Any grade	3 (1–836)	6 (1–854)
From grade 3/4 to grade 0/1	8 (2–103)	9 (5–13)
Cumulative median (range) duration of an episode[b] d	37.0 (1–844)	16.5 (1–878)
Diarrhea management, *n* (%)		
Received concurrent medication only	80 (46)	20 (31)
Median (range) duration, d	2 (1–741)	4 (1–281)
Received dose reduction	13 (8)	0
Received dose interruption	37 (21)	7 (11)
No rechallenge	2 (5)	0
Rechallenge	35 (95)	7 (100)
Successful rechallenge[c]	35 (100)	7 (100)
Unsuccessful rechallenge	0	0
Discontinued treatment because of diarrhea	0	1/251 (<1)

AE, adverse event.
[a] Event defined based on start to stop of diarrhea with no grade change; any change in grade represents a new event.
[b] Episode defined based on start to stop of diarrhea with resolution across grades.
[c] Successful rechallenge includes patients who did not experience subsequent diarrhea (bosutinib, $n = 9$; imatinib, $n = 3$) or experienced subsequent diarrhea that did not lead to treatment discontinuation (bosutinib, $n = 26$; imatinib, $n = 4$).

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TABLE III. Management of ALT and AST Treatment-Emergent AEs (in Patients With ≥1 AE of Increased ALT or AST)

	Increased ALT		Increased AST	
Parameter	Bosutinib ($n = 81$)	Imatinib ($n = 23$)	Bosutinib ($n = 69$)	Imatinib ($n = 24$)
Median (range) time to first event, d	28 (7–1091)	168 (6–924)	29 (7–1091)	155 (3–928)
Median (range) duration of an event,[a] d				
Any grade	17 (1–421)	29 (5–184)	14 (1–496)	28 (5–173)
From grade 3/4 to grade 0/1	21.5 (5–207)	45 (14–92)	21 (3–56)	27 (14–92)
Cumulative median (range) duration of an episode,[b] d				
Any grade	71 (7–780)	83.5 (14–311)	29 (4–699)	58 (8–331)
Grade 3/4	17.5 (4–166)	29.0 (13–97)	14 (3–73)	16.5 (6–91)
ALT/AST management, *n* (%)				
Received concurrent medication	24 (30)	6 (26)	15 (22)	5 (21)
Received dose reduction	25 (31)	3 (13)	9 (13)	2 (8)
Received dose interruption	46 (57)	5 (22)	28 (41)	5 (21)
No rechallenge	5 (11)	0	2 (7)	1 (20)
Rechallenge	41 (89)	5 (100)	26 (93)	4 (80)
Successful rechallenge[c]	32 (78)	4 (80)	26 (100)	4 (100)
Unsuccessful rechallenge	9 (22)	1 (20)	0	0
Discontinued treatment because of event	11/248 (4)	1/251 (<1)	0	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] Event defined based on start to stop of increased ALT or increased AST with no grade change; any change in grade represents a new event.
[b] Episode defined based on start to stop of increased ALT or increased AST with resolution across grades.
[c] Successful rechallenge includes patients who did not experience subsequent ALT and AST AEs (bosutinib, $n = 9$ and $n = 10$; imatinib, $n = 1$ and $n = 0$) or experienced subsequent ALT and AST AEs that did not lead to treatment discontinuation (bosutinib, $n = 23$ and $n = 16$; imatinib, $n = 3$ and $n = 4$).

TABLE IV. Management of Rash/Skin Toxicity Treatment-Emergent AEs[a] (in Patients With ≥1 AE of Rash/Skin Toxicity)

Parameter	Bosutinib ($n = 86$)	Imatinib ($n = 63$)
Median (range) time to first event, d	57.5 (1–931)	125 (2–1118)
Median (range) duration of an event,[b] d	22 (1–552)	26 (2–601)
Cumulative median (range) duration of an episode,[c] d	64 (2–731)	43 (2–601)
Rash management, *n* (%)		
Received dose reduction	11 (13)	6 (10)
Received dose interruption	19 (22)	8 (13)
No rechallenge	0	0
Rechallenge	19 (100)	8 (100)
Successful rechallenge[d]	17 (89)	6 (75)
Unsuccessful rechallenge	2 (11)	2 (25)
Discontinued treatment because of rash	2/248 (1)	3/251 (1)

AE, adverse event.
[a] Rash/skin toxicity AEs included Medical Dictionary for Regulatory Activities preferred terms containing rash, acne, erythema, or dermatitis.
[b] Event defined based on start to stop of rash/skin toxicity with no grade change; any change in grade represents a new event.
[c] Episode defined based on start to stop of rash/skin toxicity with resolution across grades.
[d] Successful rechallenge includes patients who did not experience subsequent rash (bosutinib, $n = 1$; imatinib, $n = 0$) or experienced subsequent rash that did not lead to treatment discontinuation (bosutinib, $n = 16$; imatinib, $n = 6$).

TABLE V. Management of Myelosuppression Treatment-Emergent AEs[a] (in Patients With ≥1 AE of Myelosuppression)

Parameter	Bosutinib ($n = 118$)	Imatinib ($n = 136$)
Median (range) time to first event, d	29 (8–924)	32 (1–1009)
Median (range) duration of an event,[b] d		
Any grade	26 (1–1212)	27 (1–532)
From Grade 3/4 to Grade 0/1	22 (2–914)	16 (2–311)
Cumulative median (range) duration of an episode,[c] d		
Any grade	56.5 (1–1246)	85.5 (2–817)
Grade 3/4	22 (1–913)	25 (5–199)
Myelosuppression management, *n* (%)		
Received dose reduction	17 (14)	24 (18)
Received dose interruption	42 (36)	64 (47)
Discontinued treatment because of myelosuppression	9/248 (4)	10/251 (4)

AE, adverse event.
[a] Myelosuppression AEs included Medical Dictionary for Regulatory Activities preferred terms of anemia, hemoglobin decreased, thrombocytopenia, platelets decreased, neutropenia, and neutrophil count decreased.
[b] Event defined based on start to stop of myelosuppression with no grade change; any change in grade represents a new event.
[c] Episode defined based on start to stop of myelosuppression with resolution across grades.

Treatment-emergent myelosuppression AEs (anemia, neutropenia, and thrombocytopenia) occurred in 48% and 54% of patients in the bosutinib and imatinib arms, respectively. The median time to the first myelosuppression event and duration were similar between treatment arms (Table V). Myelosuppression AEs were commonly managed with dose interruption (bosutinib: 36%; imatinib: 47%) and/or dose reduction (bosutinib: 14%; imatinib: 18%), with events leading to treatment discontinuation in 9 and 10 patients receiving bosutinib and imatinib, respectively. The incidence and characteristics of thrombocytopenia, the most common myelosuppression AE in both arms, were generally similar between the bosutinib and imatinib arms (median time to first event, 29 vs. 31 days; median event duration, 24 vs. 23 days; management with dose interruption, 42% vs. 48% of patients with thrombocytopenia). Although neutropenia AEs occurred significantly less frequently with bosutinib versus imatinib, the median time to first event (70 vs. 71 days) and median event duration (17 vs. 24 days) were similar between treatment arms. Neutropenia AEs were managed with dose interruption (bosutinib, 36%; imatinib, 47%) and/or dose reduction (bosutinib, 24%; imatinib, 16%).

Treatment-emergent cardiovascular AEs occurred in 10% and 8% of bosutinib- and imatinib-treated patients, respectively (Table VI). The median time to first cardiovascular event was longer (166 vs. 85 days) and the median duration of a cardiovascular event (any grade) was shorter (14 vs. 29 days) in the bosutinib arm as compared with the imatinib arm. Among patients with ≥1 cardiovascular AE, these

TABLE VI. Management of Cardiovascular Treatment-Emergent AEs[a]

Parameter	Bosutinib ($n = 26$)	Imatinib ($n = 21$)
Median (range) time to first event, d	166 (1–1023)	85 (10–1097)
Median (range) duration of an event,[b] d	14 (1–750)	29 (1–474)
Cumulative median (range) duration of an episode,[c] d	15.5 (1–750)	29 (1–656)
Outcome among patients with cardiovascular TEAEs, *n* (%)		
Death	1 (4)[d]	0
Persisted	10 (39)	6 (29)
Resolved	15 (58)	15 (71)
Cardiovascular TEAE management, *n* (%)		
Dose reduction	4 (15)	0
Dose interruption	8 (31)	4 (19)
No rechallenge	1 (13)	0
Rechallenged	7 (88)	4 (100)
Successful rechallenge[e]	5 (71)	4 (100)
Discontinued treatment because of cardiovascular TEAE	4/248 (2)	0

TEAE, treatment-emergent adverse event.
[a] Cardiovascular TEAEs included Medical Dictionary for Regulatory Activities System Organ Class terms of cardiac disorders or High-Level Group Term (HLGT), which included cardiac and vascular investigations (excluding enzyme tests).
[b] Event defined based on start to stop of cardiovascular TEAE with no grade change; any change in grade represents a new event.
[c] Episode defined based on start to stop of cardiovascular TEAE with resolution across grades.
[d] This patient was a 93-year-old woman who died from congestive heart failure 957 days after treatment initiation. The event was considered unrelated to bosutinib treatment or to a clinical trial procedure by the investigator. The patient had a history of pulmonary edema and hypothyroidism, which in combination with the patient's advanced age, may have contributed to the congestive heart failure event.
[e] Successful rechallenge includes patients who did not experience cardiovascular AEs (bosutinib, $n = 1$; imatinib, $n = 2$) or experienced subsequent cardiovascular AEs that did not lead to treatment discontinuation (bosutinib, $n = 4$; imatinib, $n = 2$).

AEs were more commonly managed by dose modification in the bosutinib versus imatinib arm (dose interruption: 31% vs. 19%; dose reduction: 15% vs. 0%). Most patients in the bosutinib ($n = 5/7$ [71%]) and imatinib ($n = 4/4$ [100%]) arms who were rechallenged after dose interruption because of cardiovascular AEs were rechallenged successfully without recurrence of cardiovascular AEs or permanent treatment discontinuation. Four patients in the bosutinib arm and no patients in the imatinib arm discontinued treatment because of cardiovascular AEs. One death due to a cardiac event occurred in the bosutinib arm. The patient was a 93-year-old woman who died from congestive heart failure 957 days after treatment initiation. The event was considered unrelated to bosutinib treatment or to a clinical trial procedure by the investigator. The patient had a history of pulmonary edema and hypothyroidism, which in combination with the patient's advanced age, may have contributed to the congestive heart failure event.

Discussion

Bosutinib and imatinib each demonstrated manageable toxicity in newly diagnosed CP CML in the BELA trial after >30 months from accrual completion. However, consistent with results from the primary analysis of the BELA trial after ≥12 months of follow-up [19], each TKI had a distinct toxicity profile in this patient population. The toxicity profile of bosutinib was notable for significantly higher incidences versus imatinib of several gastrointestinal AEs, increased aminotransferase levels, and pyrexia; whereas that of imatinib was notable for significantly higher incidences of certain edema and musculoskeletal AEs, hypophosphatemia, increased creatine phosphokinase, neutropenia, and leukopenia. Rash/skin toxicity AEs occurred at similar rates in the bosutinib and imatinib arms, although bosutinib was associated with a folliculitis-like rash, whereas rash associated with imatinib had a patchy appearance (data not shown). Rash AEs were managed with concomitant medications including topical and systemic steroid treatments (data not shown); few patients in either arm discontinued treatment because of this AE. The incidence of cardiac and vascular toxicities was low in both the bosutinib and imatinib arms, and differences between arms were not significantly different. Notably, the time to the first cardiovascular AE was longer and the duration of cardiovascular AEs was shorter in the bosutinib versus imatinib arm.

Treatment discontinuations due to AEs increased in both treatment arms from the primary analysis with ≥12 months of follow-up [19] to the current analysis with ≥30 months of follow-up (bosutinib, 48 [19%] to 62 [25%]; imatinib, 14 [6%] to 21 [8%]). For comparison, rates of discontinuation due to AEs were 11% (imatinib), 10% (nilotinib 300 mg), and 14% (nilotinib 400 mg) in the ENESTnd trial with 36 months of follow-up [14], and 5% (imatinib), and 9% (dasatinib) in the DASISION trial with 24 months of follow-up [13]. In the present study, AEs commonly associated with bosutinib treatment, including diarrhea, liver enzyme elevations, rash, and myelosuppression, infrequently led to treatment discontinuation. Moreover, among the 93 (38%) patients who discontinued bosutinib treatment, a substantial number (20 [8%]) discontinued for reasons other than AEs, disease progression, or death. Treatment discontinuations due to AEs were most common during the first year of treatment, including 15 patients who discontinued bosutinib during the first 3 months of the study (i.e., before the first postbaseline assessment). The early rate of bosutinib discontinuation due to AEs suggests that some patients may have been discontinued without first thoroughly attempting toxicity management with concomitant medication and/or dose modification. In this regard, it should also be noted that because these treatment discontinuations occurred early in the clinical development of bosutinib, it may be conjectured that they may, at least in part, have reflected the relative unfamiliarity of clinicians with strategies for managing AEs associated with bosutinib during that time period.

The frequent occurrence of gastrointestinal events, particularly diarrhea, during bosutinib treatment has also been reported previously in clinical trials of patients with CML [17,21], breast cancer [22], and solid tumors [23]. Although common, diarrhea events associated with bosutinib in this and other studies [17,21–23] typically were of maximum Grade 1/2 severity, occurred early during treatment, and were transient. In the present study, diarrhea events were well managed with concomitant medications and/or dose modification. Notably, none of the 27 patients in the bosutinib arm who had diarrhea at the time of discontinuation discontinued treatment solely because of this AE.

Elevations of ALT and AST, including Grade 3/4 events, have also been consistently reported as treatment-emergent AEs and/or on-treatment laboratory abnormalities in clinical studies of bosutinib [17,21–23]. The characteristics of ALT and AST elevation reported in the current study are consistent with previous reports, with a median time to onset of 20–30 days and events that typically resolved without requiring treatment discontinuation.

The common occurrence of certain edema and musculoskeletal AEs in the imatinib arm of this study is also consistent with prior clinical reports of this TKI in patients with CML [6,12–14,24,25]. In contrast, bosutinib was associated with relatively low incidences of these events in the current study and in prior clinical studies in CML [17,21].

Myelosuppression AEs (e.g., thrombocytopenia, anemia, neutropenia, and leukopenia) occurred frequently with bosutinib and imatinib, although the incidence of certain events varied between treatment arms (i.e., neutropenia and leukopenia were more frequently observed with imatinib than bosutinib). The occurrence of myelosuppression in

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both arms is not unexpected because it appears to be common to all Bcr-Abl TKIs approved for treatment of CML [12–14,24,25], which has been hypothesized to be related to underlying features of Ph+ CML disease [12,24]. The modestly more favorable hematologic toxicity profile of bosutinib as compared with imatinib could be related to the reduced specificity for Bcr/Abl of imatinib and its potent inhibition of c-KIT and PDGFR [9,26].

The toxicity profile of bosutinib also appears to be distinct from those previously reported for the second-generation TKIs dasatinib in the DASISION trial [13] and nilotinib in the ENESTnd trial [14], each of which enrolled similar populations of patients with newly diagnosed CP CML. In DASISION, the toxicity profile of dasatinib differed from that of imatinib with respect to higher rates of pleural and pericardial effusion and Grade 3/4 thrombocytopenia and a lower rate of rash after ≥24 months of follow-up [6,13]. In ENESTnd, the toxicity profile of nilotinib differed from that of imatinib with respect to a higher rate of rash after ≥36 months of follow-up [14]. In the current study, pleural and pericardial effusions were reported infrequently with bosutinib and imatinib, and the incidences of rash and Grade 3/4 thrombocytopenia were similar between treatment arms. Taken together, these observations suggest that not only are the toxicity profiles between dasatinib/nilotinib and imatinib different, they are also different between dasatinib/nilotinib and bosutinib.

Overall, bosutinib demonstrated manageable toxicity in most patients with newly diagnosed CP CML in the BELA trial after >30 months from accrual completion, with a safety profile distinct from imatinib and likely also distinct from the second-generation TKIs dasatinib and nilotinib [13,14]. The incidences of some toxicities frequently observed with bosutinib (e.g., diarrhea and aminotransferase elevations) were found to taper over time. Toxicities observed with bosutinib were generally well managed with treatment modification and/or concomitant medication, with fewer treatment discontinuations due to AEs observed over time. Additional experience in managing toxicities associated with bosutinib treatment may reduce the overall number of patients discontinuing bosutinib because of toxicity.

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