

## Bosutinib Versus Imatinib in Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia: Results From the BELA Trial

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### A B S T R A C T

#### Purpose

Bosutinib is an oral Src/Abl tyrosine kinase inhibitor. The phase III Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia (BELA) trial compared bosutinib with imatinib in newly diagnosed, chronic-phase chronic myeloid leukemia (CML).

#### Patients and Methods

A total of 502 patients were randomly assigned 1:1 to bosutinib 500 mg per day or imatinib 400 mg per day.

#### Results

The complete cytogenetic response (CCyR) rate at 12 months was not different for bosutinib (70%; 95% CI, 64% to 76%) versus imatinib (68%; 95% CI, 62% to 74%; two-sided  $P = .601$ ); therefore, the study did not achieve its primary end point. The major molecular response (MMR) rate at 12 months was higher with bosutinib (41%; 95% CI, 35% to 47%) compared with imatinib (27%; 95% CI, 22% to 33%; two-sided  $P < .001$ ). Time to CCyR and MMR was faster with bosutinib compared with imatinib (two-sided  $P < .001$  for both). On-treatment transformation to accelerated/blast phase occurred in four patients (2%) on bosutinib compared with 10 patients (4%) on imatinib. A total of three CML-related deaths occurred on the bosutinib arm compared with eight on the imatinib arm. The safety profiles of bosutinib and imatinib were distinct; GI and liver-related events were more frequent with bosutinib, whereas neutropenia, musculoskeletal disorders, and edema were more frequent with imatinib.

#### Conclusion

This ongoing trial did not meet its primary end point of CCyR at 12 months, despite the observed higher MMR rate at 12 months, faster times to CCyR and MMR, fewer on-treatment transformations to accelerated/blast phase, and fewer CML-related deaths with bosutinib compared with imatinib. Each drug had a distinct safety profile.

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### INTRODUCTION

Chronic myeloid leukemia (CML) is characterized by a constitutively active Bcr-Abl fusion protein, which is produced by a chromosomal translocation that forms the Philadelphia chromosome (Ph).<sup>1</sup> Imatinib, a Bcr-Abl tyrosine kinase inhibitor (TKI), is currently indicated as first-line therapy of Ph-positive chronic-phase (CP) CML.<sup>2,3</sup> A recent study of imatinib in newly diagnosed CML showed a correlation with major molecular response (MMR) by 12 months, including better progression-free survival (99% v 94% with no MMR;  $P = .0023$ ) and improved overall survival (99% v 93% with no MMR;  $P = .0011$ ) at 3 years.<sup>4</sup>

In recent phase III studies, dasatinib and nilotinib have also demonstrated efficacy in newly diagnosed CP CML.<sup>5-9</sup>

Bosutinib (SKI-606) is an oral, dual Src/Abl TKI with more potent inhibitory activity against Bcr-Abl than imatinib in CML cell lines<sup>10,11</sup> and minimal inhibitory activity against c-KIT or platelet-derived growth factor receptor,<sup>10,12</sup> 2 non-specific targets potentially associated with toxicities reported for other second-generation TKIs.<sup>10,12-14</sup> Bosutinib demonstrated clinical activity in patients with CP CML who had resistance or intolerance to prior TKI therapy.<sup>15,16</sup> The current phase III trial (Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia [BELA]) compared the

efficacy and safety of bosutinib with imatinib in newly diagnosed CP CML.

## PATIENTS AND METHODS

### Patient Eligibility

Eligible patients were adults with new ( $\leq 6$  months) diagnosis of Ph-positive CP CML<sup>17-19</sup> who had received no prior antileukemia treatment (except  $\leq 6$  months of anagrelide or hydroxyurea). Full eligibility criteria are listed in Appendix Table A1 (online only).

The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent, and the protocol was approved by institutional review boards at each site. The trial was registered at ClinicalTrials.gov (identifier: NCT00574873).

### Study Design and Treatment

BELA is an open-label, randomized, multinational, phase III study. Patients were randomly assigned 1:1 to bosutinib 500 mg per day or imatinib 400 mg per day. Patients could continue study treatment until disease progression or early discontinuation. Patients were discontinued from treatment if they could not tolerate at least 300 mg per day of bosutinib or imatinib. Dose escalation to 600 mg per day of either bosutinib or imatinib was allowed for patients not achieving an optimal response per current European LeukemiaNet guidelines<sup>20</sup> if no grade 3 or 4 or persistent grade 2 drug-related toxicity had been observed.

### Efficacy and Safety Assessments

The primary efficacy end point was complete cytogenetic response (CCyR) at 12 months. Key secondary and exploratory efficacy end points included MMR, major cytogenetic response, and complete hematologic response (CHR) at 12 months; time to on-treatment transformation to accelerated phase (AP) or blast phase (BP) CML; time to first response; duration of response; response by Sokal risk group; on-treatment event-free survival (EFS); and overall survival (Appendix Table A2, online only).

Cytogenetic assessments were based on at least 20 metaphases or fluorescence in situ hybridization with at least 200 cells on peripheral blood or bone marrow (if cytogenetics were not available). Molecular assessments were based on quantitative reverse transcriptase polymerase chain reaction for Bcr-Abl in peripheral blood, all performed at one central laboratory (Molecular MD, Portland, OR). Molecular response was categorized as major (Bcr-Abl/Abl ratio of  $\leq 0.1\%$  on the International Scale) or complete (Bcr-Abl/Abl ratio of  $\leq 0.01\%$  on the International Scale with a sensitivity of 4.0 logs). The definition of CHR was standard<sup>15</sup> and required confirmation after at least 4 weeks (Appendix Table A2). Assessments were performed every 3 months in the first year during study treatment.

Safety was assessed on an ongoing basis by physical examination (including vital signs), laboratory testing, and adverse event (AE) reporting. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

### Statistical Analyses

Response rates were calculated along with associated 95% CIs for each treatment arm (Appendix Table A3, online only). These analyses were stratified by Sokal risk group (low, score  $< 0.8$ ; intermediate, score of 0.8 to 1.2; high, score  $> 1.2$ ) and geographic region based on a Cochran-Mantel-Haenszel test (two-sided  $P$  value) unless an unstratified test based on the Fisher's exact test (two-sided  $P$  value) was deemed more appropriate.

For key secondary and exploratory time-to-event end points, distributions and medians were estimated using the Kaplan-Meier method, and associated 95% CIs for the medians were obtained using Brookmeyer-Crowley methodology. A Cox proportional hazards model stratified by Sokal risk group and geographic region was used to provide an estimate of the hazard ratio. All time-to-event end points are not yet mature, except time to response; duration of response is not reported, and no formal testing is available for other long-term end points at this time.

Efficacy analyses were performed on the intent-to-treat (ITT) population, which included all randomly assigned patients. Safety analyses were performed on the safety population, which included all patients who received at least one dose of study drug.

## RESULTS

### Patients and Treatment

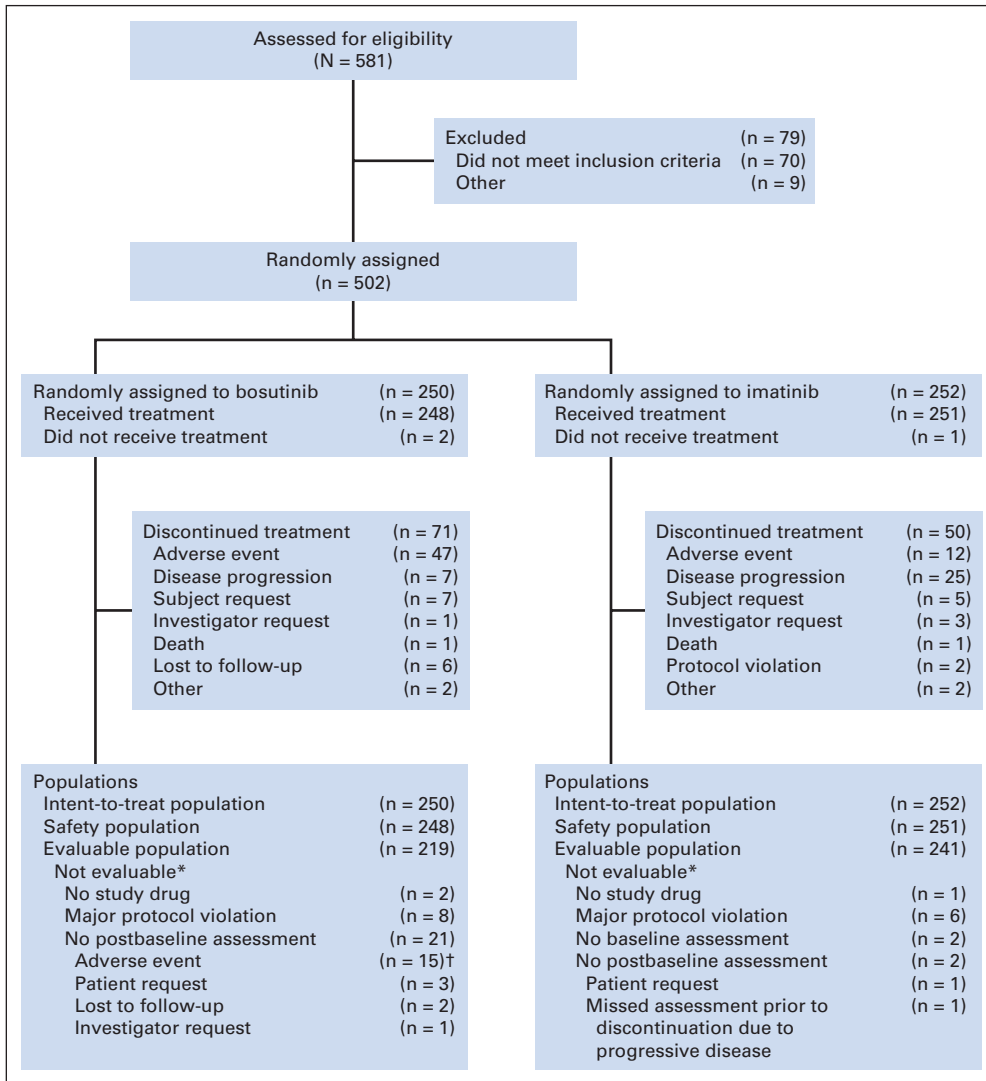
A total of 502 patients with newly diagnosed CP CML were enrolled between February 2008 and July 2009, in 139 centers in 31 countries; 250 patients were randomly assigned to bosutinib, and 252 patients were randomly assigned to imatinib (Fig 1). Demographics and baseline disease characteristics are listed in Table 1. The current analysis was based on at least 12 months after the last patient's first visit. Median duration of treatment for both study arms was 13.8 months (bosutinib range, 0.03 to 30.3 months; imatinib range, 0.5 to 25.1 months). Median dose-intensities were 489 mg per day for bosutinib (range, 115 to 575 mg per day) and 400 mg per day for imatinib (range, 201 to 542 mg per day). During the study, nine patients (4%) receiving bosutinib and 30 patients (12%) receiving imatinib had their dose escalated to 600 mg per day because of lack of efficacy. As of the data cutoff date, 71% of patients in the bosutinib arm and 80% in the imatinib arm were still receiving study treatment.

### Efficacy

In the ITT population, the CCyR rate at 12 months was similar between patients receiving bosutinib (70%; 95% CI, 64% to 76%) and imatinib (68%; 95% CI, 62% to 74%;  $P = .601$ ; Fig 2A), with 21 patients (4%; 10 patients on bosutinib; 11 on imatinib) included as having a CCyR at 12 months based on fluorescence in situ hybridization data only. Therefore, a superior CCyR rate at 12 months was not demonstrated for bosutinib versus imatinib, and the primary study end point was not met. However, median time to first CCyR was faster with bosutinib (12.9 weeks; 95% CI, 12.6 to 13.4 weeks) compared with imatinib (24.6 weeks; 95% CI, 24.3 to 25.6 weeks;  $P < .001$ ), with higher rates of CCyR at months 3, 6, and 9 for bosutinib (Fig 2A). The cumulative rate of CCyR by 12 months was also similar between bosutinib and imatinib (79%; 95% CI, 74% to 84% v 75%; 95% CI, 69% to 80%, respectively). The major cytogenetic response rate at 12 months was 73% for bosutinib and 78% for imatinib.

The MMR rate at 12 months was higher with bosutinib (41%; 95% CI, 35% to 47%) than imatinib (27%; 95% CI, 22% to 33%;  $P < .001$ ; Fig 2B), with the complete molecular response rate at 12 months being 12% compared with 3%, respectively ( $P < .001$ ). Median time to first MMR was faster with bosutinib (37.1 weeks; 95% CI, 36.1 to 48.6 weeks) compared with imatinib (72.3 weeks; 95% CI, 61.1 weeks to not reached;  $P < .001$ ). The cumulative rate of MMR by 12 months was also higher with bosutinib (47%; 95% CI, 41% to 53%) versus imatinib (32%; 95% CI, 26% to 38%;  $P < .001$ ).

The influence of Sokal risk group on treatment effect for CCyR and MMR at 12 months was further explored. The test for interaction showed that the association of either CCyR or MMR at 12 months with treatment did not demonstrate differences across Sokal risk groups ( $P = .951$  and  $P = .159$ , respectively). CCyR rates at 12 months for bosutinib and imatinib were 78% and 75%, respectively, in the low-risk group ( $P = .623$ ), 69% and 67%, respectively, in the intermediate-risk group ( $P = .708$ ), and 56% for both treatment arms



**Fig 1.** Disposition of patients. (\*) Categories were calculated in sequential order to make the groups mutually exclusive. (†) Fifteen patients in the bosutinib arm had no postbaseline assessment because of adverse events, including elevated liver function tests (n = 5); vomiting (n = 3); anaphylactic shock (n = 2); and dissociative disorder, dyspepsia, elevated lipase, decreased platelet count, and rash (n = 1 each).

in the high-risk group ( $P > .999$ ). MMR rates at 12 months were higher for bosutinib versus imatinib in the low-risk group (53% v 28%, respectively;  $P < .001$ ), intermediate-risk group (31% v 24%, respectively;  $P = .226$ ), and high-risk group (33% v 28%, respectively;  $P = .651$ ).

The rate of confirmed CHR at 12 months was 71% for bosutinib versus 85% for imatinib ( $P > .999$ ). Median times to first CHR were 4.4 weeks (95% CI, 4.3 to 4.7 weeks) for bosutinib and 4.6 weeks (95% CI, 4.4 to 5.0 weeks) for imatinib ( $P = .5790$ ).

Fewer patients had an on-treatment EFS event with bosutinib (n = 11) than imatinib (n = 18). Kaplan-Meier estimates of on-treatment EFS at 12 months were 94% for bosutinib compared with 93% for imatinib. Fewer patients in the bosutinib arm (n = 4, 2%) experienced on-treatment transformation to AP/BP CML compared with the imatinib arm (n = 10, 4%). In an additional analysis of EFS that included death at any time or on-treatment transformation to AP/BP CML, six patients had an event in the bosutinib arm compared with 15 patients in the imatinib arm; these events consisted of seven patients reporting death (two patients v five patients, respectively), seven patients reporting transformation to AP/BP (two patients v five patients, respectively), and seven patients reporting both events (two

patients v five patients, respectively). There were fewer deaths in the bosutinib arm (n = 4; causes were CML related [n = 3] and mesenteric embolism/intestinal necrosis [n = 1]) compared with the imatinib arm (n = 10; causes were CML related [n = 8], cardiovascular disease [n = 1], and lung embolism [n = 1]; Fig 3). None of the deaths were considered related to study treatment. Kaplan-Meier estimates of overall survival at 12 months were greater than 99% in the bosutinib arm and 97% in the imatinib arm.

### Safety and Tolerability

Treatment interruptions caused by AEs were required for 152 patients (61%) receiving bosutinib and 105 patients (42%) receiving imatinib; dose reductions as a result of AEs occurred for 97 patients (39%) and 45 patients (18%), respectively. Discontinuations as a result of AEs occurred in 48 patients (19%) receiving bosutinib and 14 patients (6%) receiving imatinib. Fifteen patients in the bosutinib arm discontinued treatment as a result of an AE (elevated aminotransferase [n = 5], vomiting [n = 3], anaphylactic shock [n = 2], and dissociative disorder, dyspepsia, elevated lipase, decreased platelet count, and rash [n = 1 each]) before their first postbaseline assessment at month 3.

**Table 1.** Patient Demographics and Baseline Disease Characteristics

| Demographic or Characteristic                | Bosutinib<br>(n = 250) |    | Imatinib<br>(n = 252) |    |
|--|------------------------|----|-----------------------|----|
|  | No. of Patients        | %  | No. of Patients       | %  |
| <b>Age, years</b>                            |                        |    |                       |    |
| Median                                       | 48                     |    | 47                    |    |
| Range  | 19-91                  |    | 18-89                 |    |
| Sex, male                                    | 149                    | 60 | 135                   | 54 |
| <b>Race</b>                                  |                        |    |                       |    |
| White  | 160                    | 64 | 164                   | 65 |
| Asian  | 64                     | 26 | 57                    | 23 |
| Other  | 26                     | 10 | 31                    | 12 |
| <b>Hematologic analysis</b>                  |                        |    |                       |    |
| WBC count, 10 <sup>9</sup> /L                |                        |    |                       |    |
| Median                                       | 21.7                   |    | 23.5                  |    |
| 25th percentile                              | 10.6                   |    | 11.3                  |    |
| 75th percentile                              | 56.3                   |    | 58.0                  |    |
| Platelet count, 10 <sup>9</sup> /L           |                        |    |                       |    |
| Median                                       | 386                    |    | 451                   |    |
| 25th percentile                              | 262                    |    | 291                   |    |
| 75th percentile                              | 680                    |    | 629                   |    |
| <b>Time since diagnosis, days</b>            |                        |    |                       |    |
| Median                                       | 23                     |    | 22                    |    |
| Range*                                       | 0-183                  |    | 0-241                 |    |
| Interquartile range                          | 9-45                   |    | 11-57                 |    |
| <b>ECOG performance status</b>               |                        |    |                       |    |
| 0  | 185                    | 74 | 181                   | 72 |
| 1  | 65                     | 26 | 71                    | 28 |
| <b>Sokal risk†</b>                           |                        |    |                       |    |
| Low  | 88                     | 35 | 89                    | 35 |
| Intermediate                                 | 117                    | 47 | 118                   | 47 |
| High   | 45                     | 18 | 45                    | 18 |
| <b>Geographic region</b>                     |                        |    |                       |    |
| United States, Canada, western EU, Australia |                        |    |                       |    |
|  | 65                     | 26 | 66                    | 26 |
| Eastern EU, Latin America, South America     |                        |    |                       |    |
|  | 77                     | 31 | 79                    | 31 |
| Other (eg, India, Japan, Singapore)          |                        |    |                       |    |
|  | 108                    | 43 | 107                   | 42 |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EU, European Union.  
 \*Range minimum is zero because of chronic myeloid leukemia diagnosis during the study screening period; range maximum is > 6 months because of one patient who was considered a major protocol violator.  
 †Low corresponds to Sokal score of < 0.8; intermediate corresponds to Sokal score of 0.8 to 1.2; and high corresponds to Sokal score of > 1.2.

Treatment-emergent AEs were reported by 96% of patients treated with bosutinib versus 95% treated with imatinib (Table 2). Bosutinib, compared with imatinib, was associated with higher incidences of diarrhea (68% v 21%, respectively), vomiting (32% v 13%, respectively), and abdominal pain (11% v 5%, respectively). Conversely, bosutinib, compared with imatinib, was associated with lower incidences of edema (11% v 38%, respectively), bone pain (4% v 10%, respectively), and muscle spasms (2% v 20%, respectively). The aggregate incidence of grade 3 or 4 AEs was 64% in the bosutinib arm and 48% in the imatinib arm (*P* < .001), with median durations of 13 and 15 days, respectively. Specific grade 3 or 4 nonhematologic AEs observed for more than 2% of patients included diarrhea (bosutinib, 11%; imatinib, 1%) and vomiting (bosutinib, 3%; imatinib, 0%; Table 2); all were grade 3 events in both treatment arms. Although diarrhea occurred in both treatment arms, most instances of diarrhea resolved

(bosutinib, 85%; imatinib, 77%) by the time of this analysis. Per the protocol, it was recommended that at the first sign of diarrhea, medications such as diphenoxylate/atropine or loperamide should be used as needed, which effectively controlled diarrhea in most instances. Of those who experienced diarrhea with bosutinib, 67% received concomitant medication for the management of diarrhea. The diarrhea events were frequently reported in the first 2 to 4 weeks from starting treatment but decreased over time among patients treated with bosutinib. Median time to onset was 3 days (range, 1 to 589 days) for bosutinib compared with 22.5 days (range, 1 to 476 days) for imatinib, and the median durations of a diarrhea event were 3 and 5 days, respectively. Of those who experienced diarrhea, dose interruptions and reductions for diarrhea were required by 21% and 8% of patients on bosutinib, respectively, versus 6% and 0% of patients on imatinib, respectively. Diarrhea was not the primary AE leading to treatment discontinuation for any patient on bosutinib, although one patient had concurrent diarrhea associated with GI toxicity (ie, vomiting) at the time of discontinuation.

Edema was less common (11%) and occurred later (median, 113 days) with bosutinib compared with imatinib (38%; median, 30 days). Seventy-eight percent of patients receiving bosutinib compared with 42% receiving imatinib had their edema resolve by the time of this analysis. No patient in either study arm discontinued treatment as a result of edema; three patients required dose interruption because of edema, with no recurrence on rechallenge.

Drug-related cardiac AEs were experienced by 10 patients (4%) receiving bosutinib and eight patients (3%) receiving imatinib. The most common drug-related cardiac AE was prolonged QT interval (bosutinib, n = 5 [one patient with grade 3]; imatinib, n = 6). The number of QT prolongations greater than 500 milliseconds with bosutinib versus imatinib was two (1%) versus none for QTcF and two (1%) versus one (< 1%) for QTcB, respectively.

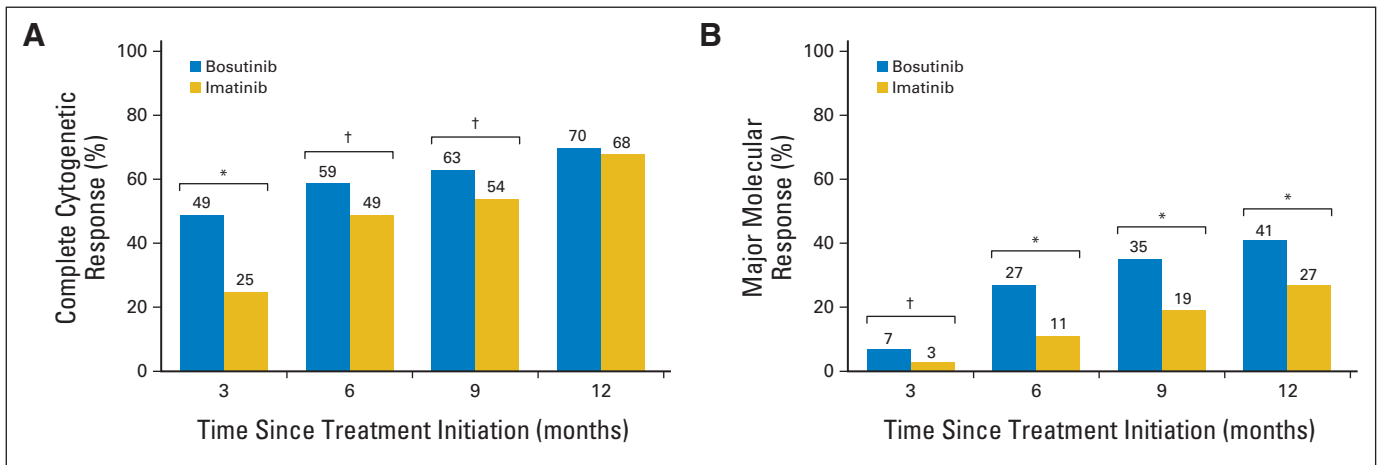
Transient liver aminotransferase elevations (grade 3 or 4) were more common on treatment among patients treated with bosutinib versus imatinib (ALT, 22% v 3%, respectively; and AST, 11% v 3%, respectively; Table 2). The median time to onset for ALT and AST elevations was 28 days (for both) for bosutinib compared with 91 and 97 days, respectively, for imatinib. Dose interruptions and/or reductions were common among patients with aminotransferase elevations (bosutinib, 57% and 36%; imatinib, 24% and 6%, respectively), and many patients in both arms experienced multiple ALT/AST events (bosutinib, 71%; imatinib, 53%).

Grade 3 or 4 lipase elevation was observed in 7% of patients receiving bosutinib and 5% receiving imatinib and was associated with pancreatitis in one patient on imatinib. The incidence of grade 3 or 4 laboratory abnormalities of anemia and thrombocytopenia was similar between treatment arms (anemia, 6% for bosutinib and 7% for imatinib; thrombocytopenia, 14% each); however, grade 3 or 4 neutropenia was lower in the bosutinib arm (11% v 24% for imatinib; Table 2).

## DISCUSSION

Bosutinib did not demonstrate a superior rate of CCyR at 12 months versus imatinib based on the ITT population, which was the primary end point of the study. However, bosutinib treatment did demonstrate superiority in some secondary and exploratory efficacy end points. Bosutinib resulted in a superior rate of MMR at 12 months,

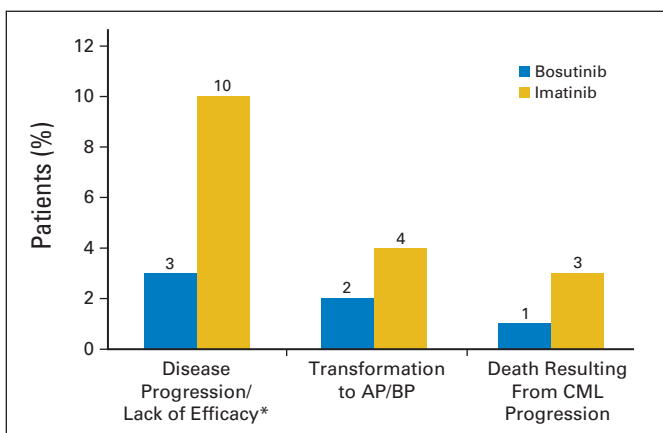




**Fig 2.** Rates of (A) complete cytogenetic response and (B) major molecular response in the intent-to-treat population. Cytogenetic analysis determined the presence of Philadelphia chromosome in bone marrow aspirate and included fluorescence in situ hybridization imputation; at least 20 metaphases were required. Molecular analysis determined the number of Bcr-Abl transcripts in peripheral blood. Patients who were not evaluable were counted as nonresponders. (\*) Indicates a 2-sided  $P < .001$ . (†) Indicates a 2-sided  $P < .05$ .  $P$  values were based on the Cochran-Mantel-Haenszel test and stratified by site-entered Sokal score and geographic region;  $P$  values at all time points were considered exploratory, with the exception of month 12.

which was the key secondary end point of the study. MMR is considered to represent approximately a 1-log deeper response than CCyR with respect to Bcr-Abl transcript levels and has been shown to predict longer duration of CCyR.<sup>21,22</sup> The times to CCyR and MMR were shorter with bosutinib, which supports a more rapid debulking of tumor burden with bosutinib compared with standard-dose imatinib. Additionally, patients receiving bosutinib had a lower rate of disease progression/lack of efficacy (3%) compared with patients receiving imatinib (10%), including a trend toward fewer transformations to AP/BP CML (2% *v* 4%, respectively). Together, these results indicate that bosutinib may be effective in some patients with newly diagnosed CP CML, even though the primary efficacy end point was not met. Continued follow-up will allow for long-term evaluation of bosutinib efficacy in this population.

There have also been two recent studies with the second-generation TKIs dasatinib and nilotinib versus imatinib in patients with CP CML in the first-line setting.<sup>5,6</sup> Allowing for differences in study design, patient population, and the inherent difficulties of com-



**Fig 3.** Rates of disease progression while on study treatment in the intent-to-treat population. (\*) Includes transformation to accelerated phase (AP)/blast phase (BP) chronic myeloid leukemia (CML).

paring data across multiple studies, rates of CCyR by 12 months were similar among all three studies (bosutinib, 79%; dasatinib, 83%; nilotinib, 78% to 80%), although the rate achieved with imatinib was slightly higher in the current study (75%) than in the dasatinib and nilotinib studies (72% and 65%, respectively),<sup>5,6</sup> possibly because of differences in ITT population definitions and Sokal and Hasford risk groups across studies. The MMR rate at 12 months was higher in both the bosutinib versus imatinib and nilotinib versus imatinib studies (bosutinib, 41%; nilotinib, 43% to 44%; imatinib, 27% and 22%, respectively),<sup>6</sup> and the rate of MMR by 12 months was also higher with bosutinib and dasatinib across studies (bosutinib, 47%; dasatinib, 46%; imatinib, 32% and 28%, respectively).<sup>5</sup> In addition, all three second-generation TKIs were associated with faster achievement of CCyR and MMR compared with imatinib.<sup>5,6</sup> Similar rates of transformation to AP/BP CML were observed in all three studies (bosutinib, 2%; dasatinib, 2%; nilotinib, 1%; imatinib, 4%, 3%, and 4%).<sup>5,6</sup>

Overall, bosutinib was associated with a toxicity profile distinct from that of imatinib. However, an unexpectedly high number of patients ( $n = 48$ , 19%) were discontinued from bosutinib treatment as a result of an AE, including 15 (31%) of 48 patients who discontinued before their first postbaseline assessment. These data require confirmation in future studies. Thus, early discontinuations as a result of toxicity may have contributed to the lower rate of CCyR associated with bosutinib in the ITT population, which included these patients as nonresponders.

Although bosutinib therapy was associated with greater rates of diarrhea, vomiting, and aminotransferase elevations compared with imatinib, most instances were transient and, in the case of diarrhea, frequently self-limiting after the first 2 to 3 months of therapy. Fluid retention, which has commonly been observed with dasatinib<sup>5,17,23-28</sup> and imatinib,<sup>5,6,27,29</sup> occurred infrequently with bosutinib. Despite the occurrence of liver function test abnormalities with bosutinib treatment, no cases were associated with permanent liver injury. Low rates of grade 3 or 4 (all causality) anemia (6%), neutropenia (11%), and thrombocytopenia (14%) were reported with bosutinib. The minimal inhibition of c-KIT by bosutinib may have contributed to the low incidence of myelosuppressive events, particularly grade 3 or 4

**Table 2.** Treatment-Emergent Adverse Events and Laboratory Abnormalities

| Event  | Bosutinib (n = 248) |    |                 |     | Imatinib (n = 251) |    |                 |    |
|--|---------------------|----|-----------------|-----|--------------------|----|-----------------|----|
|  | All Grades          |    | Grade 3 or 4    |     | All Grades         |    | Grade 3 or 4    |    |
|  | No. of Patients     | %  | No. of Patients | %   | No. of Patients    | %  | No. of Patients | %  |
| Adverse events reported for ≥ 10% of patients with any grade             |                     |    |                 |     |                    |    |                 |    |
| Diarrhea   | 168                 | 68 | 26              | 11  | 52                 | 21 | 2               | 1  |
| Vomiting   | 78                  | 32 | 8               | 3   | 33                 | 13 | 0               | 0  |
| Nausea   | 76                  | 31 | 2               | 1   | 87                 | 35 | 0               | 0  |
| Rash   | 50                  | 20 | 3               | 1   | 38                 | 15 | 2               | 1  |
| Pyrexia  | 40                  | 16 | 2               | 1   | 23                 | 9  | 3               | 1  |
| Upper abdominal pain   | 30                  | 12 | 0               | 0   | 13                 | 5  | 0               | 0  |
| Abdominal pain   | 29                  | 11 | 3               | 1   | 12                 | 5  | 0               | 0  |
| Edema*   | 27                  | 11 | 1               | < 1 | 95                 | 38 | 2               | 1  |
| Fatigue  | 27                  | 11 | 3               | 1   | 29                 | 12 | 2               | 1  |
| Headache   | 25                  | 10 | 2               | 1   | 21                 | 8  | 0               | 0  |
| Upper respiratory infection  | 25                  | 10 | 0               | 0   | 16                 | 6  | 0               | 0  |
| Bone pain  | 9                   | 4  | 0               | 0   | 26                 | 10 | 2               | 1  |
| Muscle cramps  | 6                   | 2  | 0               | 0   | 50                 | 20 | 0               | 0  |
| Laboratory abnormalities reported for ≥ 5% of patients with grade 3 or 4 |                     |    |                 |     |                    |    |                 |    |
| Anemia   | 200                 | 81 | 16              | 6   | 211                | 84 | 17              | 7  |
| Thrombocytopenia   | 163                 | 66 | 35              | 14  | 157                | 63 | 36              | 14 |
| Hypophosphatemia   | 116                 | 47 | 10              | 4   | 159                | 63 | 38              | 15 |
| Elevated ALT   | 170                 | 69 | 55              | 22  | 74                 | 29 | 8               | 3  |
| Elevated AST   | 140                 | 56 | 26              | 11  | 68                 | 27 | 8               | 3  |
| Neutropenia  | 70                  | 28 | 27              | 11  | 135                | 54 | 60              | 24 |
| Elevated lipase  | 94                  | 38 | 22              | 9   | 85                 | 34 | 12              | 5  |

\*Edema includes edema, eye edema, orbital and periorbital edema, face edema, localized edema, edema peripheral, allergic edema, weight increased, pharyngeal edema, and pulmonary edema.

neutropenia.<sup>14</sup> Overall, there were fewer deaths in the bosutinib arm, with no treatment-related deaths and few CML-related deaths in both treatment arms. The trends in toxicity profile observed for bosutinib in the current study are similar to those previously observed for bosutinib in CP CML after failure of imatinib treatment.<sup>15</sup>

In conclusion, bosutinib did not achieve the primary efficacy end point of a superior rate of CCyR at 12 months versus imatinib; however, bosutinib did demonstrate other potential benefits in patients with newly diagnosed CP CML. In addition, the safety profile of bosutinib was distinct from that of imatinib. Further follow-up is needed to provide long-term data on duration of response, transformation to AP/BP CML, and overall survival, as well as the tolerability profile of bosutinib in newly diagnosed CP CML.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## REFERENCES

1. National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology: Chronic myelogenous leukemia—Version 2.2011. [http://www.nccn.org/professionals/physician\\_gls/PDF/cml.pdf](http://www.nccn.org/professionals/physician_gls/PDF/cml.pdf)
2. Druker BJ, Guilhot F, O'Brien SG, et al: Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 355:2408-2417, 2006
3. O'Brien SG, Guilhot F, Larson RA, et al: Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 348:994-1004, 2003
4. Hehlmann R, Lauseker M, Jung-Munkwitz S, et al: Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon-alpha in newly diagnosed chronic myeloid leukemia. *J Clin Oncol* 29:1634-1642, 2011
5. Kantarjian H, Shah NP, Hochhaus A, et al: Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 362:2260-2270, 2010
6. Saglio G, Kim DW, Issaragrisil S, et al: Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med* 362:2251-2259, 2010
7. Cortes JE, Jones D, O'Brien S, et al: Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. *J Clin Oncol* 28:392-397, 2010
8. Cortes JE, Jones D, O'Brien S, et al: Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. *J Clin Oncol* 28:398-404, 2010
9. Rosti G, Palandri F, Castagnetti F, et al: Nilotinib for the frontline treatment of Ph(+) chronic myeloid leukemia. *Blood* 114:4933-4938, 2009
10. Puttini M, Coluccia AM, Boschelli F, et al: In vitro and in vivo activity of SKI-606, a novel Src-Abl inhibitor, against imatinib-resistant Bcr-Abl+ neoplastic cells. *Cancer Res* 66:11314-11322, 2006
11. Golas JM, Arndt K, Etienne C, et al: SKI-606, a 4-anilino-3-quinolinecarbonitrile dual inhibitor of Src and Abl kinases, is a potent antiproliferative agent against chronic myelogenous leukemia cells in culture and causes regression of K562 xenografts in nude mice. *Cancer Res* 63:375-381, 2003
12. Remsing Rix LL, Rix U, Colinge J, et al: Global target profile of the kinase inhibitor bosutinib in primary chronic myeloid leukemia cells. *Leukemia* 23:477-485, 2009
13. Konig H, Holyoake TL, Bhatia R: Effective and selective inhibition of chronic myeloid leukemia primitive hematopoietic progenitors by the dual Src/Abl kinase inhibitor SKI-606. *Blood* 111:2329-2338, 2008
14. Bartolovic K, Balabanov S, Hartmann U, et al: Inhibitory effect of imatinib on normal progenitor cells in vitro. *Blood* 103:523-529, 2004
15. Cortes JE, Kantarjian HM, Brummendorf TH, et al: Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. *Blood* 118:4567-4576, 2011
16. Khoury HJ, Cortes JE, Kantarjian HM, et al: Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. *Blood* 119:3403-3412, 2012
17. Talpaz M, Shah NP, Kantarjian H, et al: Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med* 354:2531-2541, 2006
18. Kantarjian HM, Giles F, Gattermann N, et al: Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood* 110:3540-3546, 2007
19. Hochhaus A, Baccarani M, Deininger M, et al: Dasatinib induces durable cytogenetic responses in patients with chronic myelogenous leukemia in chronic phase with resistance or intolerance to imatinib. *Leukemia* 22:1200-1206, 2008
20. Baccarani M, Cortes J, Pane F, et al: Chronic myeloid leukemia: An update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol* 27:6041-6051, 2009
21. Cortes J, Talpaz M, O'Brien S, et al: Molecular responses in patients with chronic myelogenous leukemia in chronic phase treated with imatinib mesylate. *Clin Cancer Res* 11:3425-3432, 2005
22. Iacobucci I, Saglio G, Rosti G, et al: Achieving a major molecular response at the time of a complete cytogenetic response (CCgR) predicts a better duration of CCgR in imatinib-treated chronic myeloid leukemia patients. *Clin Cancer Res* 12:3037-3042, 2006
23. Hochhaus A, Kantarjian HM, Baccarani M, et al: Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 109:2303-2309, 2007
24. Kantarjian H, Pasquini R, Hamerschlag N, et al: Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia after failure of first-line imatinib: A randomized phase 2 trial. *Blood* 109:5143-5150, 2007
25. Shah NP, Kantarjian HM, Kim DW, et al: Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. *J Clin Oncol* 26:3204-3212, 2008
26. Quintás-Cardama A, Kantarjian H, O'Brien S, et al: Pleural effusion in patients with chronic myelogenous leukemia treated with dasatinib after imatinib failure. *J Clin Oncol* 25:3908-3914, 2007
27. Gora-Tybor J, Robak T: Targeted drugs in chronic myeloid leukemia. *Curr Med Chem* 15:3036-3051, 2008
28. Bristol-Myers Squibb: Sprycel (Dasatinib) tablet for oral use [package insert]. Princeton, NJ, Bristol-Myers Squibb, 2009
29. Novartis: Gleevec (Imatinib Mesylate) tablets for oral use [package insert]. East Hanover, NJ, Novartis, 2009

