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ORIGINAL ARTICLE

Phase 2 study of bosutinib in Japanese patients with newly diagnosed chronic phase chronic myeloid leukemia

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Abstract

This open-label, single-arm, phase 2 study (ClinicalTrials.gov, NCT03128411) evaluated the efficacy, safety, and pharmacokinetics of bosutinib at a starting dose of 400 mg once daily (QD) in Japanese patients with newly diagnosed chronic phase chronic myeloid leukemia (CP CML). The primary endpoint was major molecular response (MMR) at Month 12 in the modified as-treated population (Philadelphia chromosome–positive [Ph+] patients with e13a2/e14a2 transcripts). Sixty Japanese patients with CP CML were treated with bosutinib; median age was 55 years (range, 20–83), 60.0% were male, and all were Ph+ and had e13a2/e14a2 transcripts. After median follow-up of 16.6 months (range, 11.1–21.9), 41 (68.3%) patients remained on bosutinib. The MMR rate at Month 12 was 55.0% (2-sided 90% confidence interval: 44.4–65.6). There were no on-treatment transformations to accelerated/blast phase, and no patient died on treatment or within 28 days of the last bosutinib dose. The most common treatment-emergent adverse events were diarrhea (86.7%), increased alanine aminotransferase (55.0%), and increased aspartate aminotransferase (46.7%). The primary objective of this phase 2 study was met, and there were no new safety signals for bosutinib. These data suggest bosutinib is an effective first-line treatment option for Japanese patients with newly diagnosed CP CML.

Keywords Bosutinib · Tyrosine kinase inhibitor · Chronic myeloid leukemia · Japan

1. Introduction

Bosutinib, a second-generation Src/Abl tyrosine kinase inhibitor (TKI), is approved at a starting dose of 500 mg once daily (QD) in many countries, including Japan, for patients with Philadelphia chromosome–positive (Ph+) chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukemia (CML) after prior therapy [1-3]. The indication for bosutinib was expanded as first-line therapy for patients with newly diagnosed CP CML, at a starting dose of 400 mg QD, in 2017 by the US Food and Drug Administration [1] and in 2018 by the European Medicines Agency [2]. Approval of first-line bosutinib for CP CML was based on primary data from the global phase 3 BFORE trial, which compared bosutinib versus imatinib [4]. The primary endpoint of major molecular response (MMR) rate at Month 12 in patients with Ph+ CP CML and e13a2/e14a2 transcripts was significantly higher with bosutinib versus imatinib (47.2% vs 36.9%; 2-sided $P = 0.02$), and complete cytogenetic response rate (CCyR) by Month 12 was 77.2% versus 66.4% (2-sided $P = 0.0075$). The most common adverse events (AEs) in bosutinib-treated patients were diarrhea (70.1%), nausea (35.1%), thrombocytopenia (35.1%), and increased alanine aminotransferase (ALT; 30.6%), which were consistent with the known toxicity profile of bosutinib [5-7].

Although the efficacy and safety of first-line bosutinib have been established in a global population [4], regional populations have not been fully investigated. Therefore, we conducted a phase 2 study to evaluate the efficacy, safety, and pharmacokinetics of bosutinib at a starting dose of 400 mg QD in Japanese patients with newly diagnosed CP CML.

2. Methods

2.1. Study design

This is an ongoing open-label, single-arm, phase 2 study to evaluate the efficacy, safety, and pharmacokinetics of bosutinib in adult Japanese patients with newly diagnosed CP CML. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and local regulatory requirements. The study protocol, protocol amendments, and informed consent documents (provided by all patients) were approved by the Institutional Review Board/Ethics Committee at each study center in Japan. The trial is registered on ClinicalTrials.gov (NCT03128411).

2.2. Patients and treatment

Patients were ≥20 years of age with a molecular diagnosis of CP CML (detection of *BCR-ABL1* rearrangement) within 6 months, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, adequate renal and hepatic function, and had resolved acute effects of any prior therapy to baseline severity or grade ≤1. Female patients of childbearing potential were required to have a negative serum pregnancy test at screening. Patients were excluded if they had prior treatment for CML (except for hydroxyurea [hydroxycarbamide] within 6 months); central nervous system involvement; extramedullary disease only; major surgery or radiotherapy within 14 days of registration; history of clinically significant or uncontrolled cardiac disease; active, uncontrolled bacterial, fungal, or viral infection; clinically significant gastrointestinal disorder; history of another malignancy within 5 years prior to registration (except for basal cell carcinoma or cervical carcinoma in situ or stage 1/2 cancer in complete remission for ≥12 months); or uncontrolled hypomagnesemia or uncorrected hypokalemia.

Patients received bosutinib at a starting dose of 400 mg QD. The dose could be escalated in 100-mg increments to a maximum of 600 mg QD in patients with unsatisfactory response (e.g., *BCR-ABL1* transcripts >10% and/or Ph+ metaphases >35% at Month 3), no grade 3/4 AEs at the

time of dose escalation, and resolution of all prior grade 3/4 AEs to grade 1/2 and all grade 2 nonhematologic toxicities to grade ≤1. The bosutinib dose could be interrupted or reduced to 300 mg QD and further to a minimum of 200 mg QD (with approval by the study sponsor) to manage toxicities. Bosutinib treatment was to continue for approximately 3 years after registration of the last patient, representing the 12-month core treatment phase and the following ≥24-month extension phase, or until the end of the study, treatment failure, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first.

2.3. Assessments

Molecular response was assessed at a central laboratory by quantitative reverse transcriptase polymerase chain reaction (PCR) using peripheral blood collected at baseline, every 3 months for the first 24 months of treatment, and every 6 months thereafter, and was evaluated on the International Scale (IS) [8]. Cytogenetic response was locally assessed in Ph+ patients using bone marrow aspirate obtained at baseline, every 3 months for the first 24 months of treatment, and every 6 months thereafter until CCyR or MMR was attained, after which bone marrow aspirate was performed only if clinically indicated. Hematologic response was assessed using peripheral blood collected locally and by clinical evaluation of extramedullary disease. In patients with lack of response, suboptimal response, or loss of response, and in patients who completed treatment, mutation analysis was performed by sequencing at a central PCR laboratory using peripheral blood collected for molecular response assessment.

Progression to AP CML was defined as 15–29% blasts in blood or marrow, >30% blasts plus promyelocytes in blood or marrow with blasts <30%, or ≥20% basophils in blood; progression to BP CML was defined as ≥30% blasts in blood or bone marrow or extramedullary blast proliferation, other than in the spleen. Events included in the analysis of on-treatment

event-free survival (EFS) were death due to any cause, transformation to AP/BP, loss of a CCyR, loss of a complete hematologic response, and doubling of white blood cell count (≥1 month apart with a second value of $>20 \times 10^9$/L and maintained in subsequent assessments for ≥2 weeks) in patients not achieving complete hematologic response.

AEs were monitored throughout the study period and graded according to the National Cancer Institute Common Terminology Criteria, v4.03 [9]. A treatment-emergent AE (TEAE) was defined as any AE that first occurred or worsened in severity after the first administration of the study drug through 28 days after the last dose. The frequency and characteristics of TEAEs of special interest were analyzed by selecting Medical Dictionary for Regulatory Activities (MedDRA) system organ class higher-level group terms, higher-level terms, preferred terms, and standardized MedDRA queries to generate TEAE clusters (Online Resource 1).

Blood samples for pharmacokinetic analysis were collected within 3 hours before bosutinib administration on Days 1, 28, 56, and 84 of treatment. Bosutinib concentrations in plasma were assayed (Syneos Health; Princeton, NJ, USA) using a validated, sensitive, and specific high-performance tandem mass spectrometry method.

2.4. Statistical analysis

The as-treated population included all patients who received at least one dose of bosutinib. The modified as-treated population was the primary analysis population for efficacy evaluation and included patients who were Ph+, had e13a2/e14a2 transcripts, and received at least one dose of bosutinib. Safety was analyzed in the as-treated population. Continuous variables were summarized using descriptive statistics and categorical variables were summarized using frequencies and percentages.

The primary endpoint was MMR (≤0.1% *BCR-ABL1* on IS, corresponding to ≥3-log reduction from standardized baseline with ≥3000 *ABL* transcripts assessed) at Month 12 (Week 48) in the modified as-treated population. A total of 60 patients was required in the modified as-treated population for the study to have >82% power to reject the null hypothesis (MMR rate of 25% at Month 12, based on historical MMR rates with imatinib [7, 10]) and accept the alternative hypothesis (MMR rate of 40% at Month 12, derived from the null MMR rate and the higher MMR rate with bosutinib vs imatinib in the BFORE study [4]) with a 1-sided α-level of 5%. The 2-sided asymptotic 90% confidence interval (CI) of MMR rate at Month 12 was calculated.

Secondary endpoints included MMR and CCyR (0 Ph+ chromosomes of ≥20 metaphases or MMR; bone marrow aspirates not required once MMR was achieved) by Month 12 (patients are considered responders if MMR or CCyR occurs at or before Month 12), EFS, overall survival, safety, and pharmacokinetics. Exploratory endpoints included MMR at Months 3, 6, and 9; MR^4 (≤0.01% *BCR-ABL1* on IS, corresponding to ≥4-log reduction from the standardized baseline with ≥9800 *ABL* transcripts assessed) and $MR^{4.5}$ (≤0.0032% *BCR-ABL1* on IS, corresponding to ≥4.5-log reduction from the standardized baseline with ≥30,990 *ABL* transcripts assessed) at Months 3, 6, 9, and 12; MR^1 (≤10% *BCR-ABL1* on IS, corresponding to ≥1-log reduction from the standardized baseline) at Month 3; MR^2 (≤1% *BCR-ABL1* on IS, corresponding to ≥2-log reduction from the standardized baseline) at Month 6; and time to MMR, MR^4, $MR^{4.5}$, and CCyR.

The data for these analyses are from an unlocked trial database with a data cutoff date of March 12, 2019, after a minimum of 12 months (48 weeks) of follow-up of the last enrolled patient.

3. Results

3.1. Patients and treatment

In all, 60 Japanese patients with newly diagnosed CP CML were enrolled in the study and treated with bosutinib (i.e., the as-treated population). All patients were Ph+ and had e13a2/e14a2 transcripts and were included in the modified as-treated population analyzed for efficacy. Median age was 55 years (range, 20–83) and 41 (68.3%) patients were aged <65 years; 36 (60.0%) patients were male and median weight was 59.8 kg (range, 34.5–102.6; Table 1). A total of 27 (45.0%), 26 (43.3%), and 7 (11.7%) patients had low-, intermediate-, and high-risk Sokal scores, respectively; 58 (96.7%) patients had ECOG performance status 0.

Median duration of follow-up was 16.6 months (range, 11.1–21.9) and median duration of bosutinib treatment was 15.3 months (range, 0.3–21.9; Table 2). At the data cutoff date, 41 (68.3%) patients remained on bosutinib; 18 (30.0%) patients discontinued due to AEs and 1 (1.7%) due to physician decision. The most common TEAEs leading to discontinuation were increased ALT (*n* = 6) and increased aspartate aminotransferase (AST; *n* = 5). Other TEAEs that led to discontinuation were increased lipase, drug eruption, and erythema multiforme (*n* = 2 each) and thrombocytopenia, drug-induced liver injury, liver disorder, pneumonia, increased hepatic enzyme, increased pancreatic enzymes, decreased neutrophil count, and pleural effusion (*n* = 1 each). There were no bosutinib discontinuations due to lack of efficacy or suboptimal response.

To manage TEAEs, 33 (55.0%) patients had ≥1 bosutinib dose reduction and 46 (76.7%) had ≥1 dose interruption (Table 2). The bosutinib dose was escalated due to insufficient response in 6 (10.0%) patients. Median dose intensity was 354.7 mg/day (range, 95.3–494.1).

3.2. Efficacy

The MMR rate at Month 12 was 55.0% (2-sided 90% CI: 44.4–65.6); the test of the null hypothesis was rejected (1-sided $P < 0.0001$), and the primary endpoint was met (Table 3). In patients with low-, intermediate-, and high-risk Sokal scores, respectively, the MMR rate (90% CI) at Month 12 was 51.9% (36.0–67.7), 61.5% (45.8–77.2), and 42.9% (12.1–73.6). The MMR rate by Month 12, which included patients with a response at or before this time point, was 61.7% (90% CI: 51.3–72.0), and the CCyR rate by Month 12 was 80.0% (90% CI: 71.5–88.5). Deep molecular responses were attained starting at Month 6, with rates (90% CI) of 31.7% (21.8–41.5) for MR^4 and 21.7% (12.9–30.4) for $MR^{4.5}$ at Month 12 (Fig. 1). The MR^1 rate at Month 3 was 80.0% (90% CI: 71.5–88.5), and the MR^2 rate at Month 6 was 66.7% (90% CI: 56.7–76.7). Median (range) time to response in patients who achieved the respective response was 24.1 (12.0–60.1) weeks for MMR and 12.2 (11.9–36.1) weeks for CCyR (Online Resources 2 and 3).

The cumulative incidence (90% CI) of EFS events at Month 12 was 1.7% (0.2–6.4), although data for on-treatment EFS were not mature as of the data cutoff date; there were no on-treatment transformations to AP or BP CML. No patient died on treatment or within 28 days of the last dose of bosutinib. One patient (a 48-year-old male) died beyond 28 days of the last dose due to disease progression. This patient initially received bosutinib 400 mg QD but had the dose reduced to 300 mg QD due to grade 3 thrombocytopenia and subsequently discontinued treatment at Day 85 due to recurrence of grade 3 thrombocytopenia, with no molecular response recorded; death occurred on Day 403 of the long-term follow-up period.

Of the 18 patients who had mutation testing at treatment completion, 16 were evaluable; none had a newly detectable mutation.

3.3. Safety

All patients experienced ≥1 TEAE and 45 (75.0%) had ≥1 grade 3/4 TEAE; serious AEs occurred in 14 (23.3%) patients. TEAEs led to bosutinib dose reduction in 33 (55.0%) patients, to dose interruption in 42 (70.0%) patients, and to bosutinib discontinuation in 18 (30.0%) patients. The most common TEAEs were diarrhea (86.7%), increased ALT (55.0%), and increased AST (46.7%; Table 4). Grade 3/4 TEAEs reported in ≥10% of patients were increased ALT (33.3%), increased AST (18.3%), diarrhea (15.0%), increased lipase (15.0%), lymphopenia (13.3%), and neutropenia (11.7%). Grade 3/4 TEAEs were more common in patients aged ≥65 versus <65 years (89.5% vs 68.3%), as were TEAEs leading to bosutinib dose reduction (68.4% vs 48.8%), dose interruption (89.5% vs 61.0%), and discontinuation (47.4% vs 22.0%); the incidence of serious AEs was similar between age groups (26.3% vs 22.0%).

We assessed the characteristics of the common TEAEs, diarrhea, increased ALT, and increased AST. Median time to first event of diarrhea was 1 day (range, 1–271). Diarrhea was frequently managed with concomitant medications, in 49 of 52 (94.2%) patients who experienced diarrhea; 6 (11.5%) patients had bosutinib dose interruptions and 2 (3.8%) had dose reductions due to diarrhea. All 6 patients who had dose interruptions due to diarrhea had successful bosutinib rechallenge, i.e., they did not have subsequent diarrhea or discontinue due to subsequent or persistent events. Median time to first event of increased ALT was 15 days (range, 1–169). Of 33 patients with increased ALT, 17 (51.5%) had bosutinib dose interruptions and 13 (39.4%) had dose reductions; 16 (48.5%) patients received concomitant medications. All 17 patients who had dose interruptions due to increased ALT had bosutinib rechallenge; 13 (76.5%) rechallenges were successful. Median time to first event of increased AST was 15 days (range, 1–57). In all, 14 of 28 (50.0%) of patients with increased AST were treated with concomitant

medications; 10 (35.7%) patients had bosutinib dose interruptions and 8 (28.6%) had dose reductions. Nine of 10 patients with dose interruptions for increased AST had bosutinib rechallenge; 6 (66.7%) rechallenges were successful.

When evaluated according to categories of special interest, the most frequently reported TEAEs of any grade were gastrointestinal (86.7%), liver function–related (80.0%), infection (65.0%), rash (55.0%), and myelosuppression (45.0%; Online Resource 4). The most common grade 3/4 TEAEs of special interest were liver function–related (48.3%) and myelosuppression (26.7%). Within the gastrointestinal cluster, all TEAEs were considered related to bosutinib treatment, and the maximum toxicity for most patients was grade 1 (30.0%) or grade 2 (41.7%) events; 9 (15.0%) patients had a maximum toxicity of grade 3 gastrointestinal TEAE. No patient discontinued bosutinib owing to a gastrointestinal TEAE. Of the 48 (80.0%) patients with liver function TEAEs, 47 had events considered bosutinib-related; the maximum toxicity was grade 1 in 16.7% of patients, grade 2 in 15.0%, grade 3 in 40.0%, and grade 4 in 8.3%. Ten (16.7%) patients permanently discontinued treatment due to liver function TEAEs, all of which were characterized by or associated with laboratory abnormalities of increased ALT, increased AST, or both; 8 of these 10 patients discontinued bosutinib within 6 months of initiating treatment. In addition, 28 patients temporarily stopped bosutinib because of this TEAE, with 19 rechallenged successfully. There were no cases of Hy's law or permanent liver injury. The incidence of cardiac, vascular, and hypertension TEAEs was low (5.0%, 1.7%, and 1.7%, respectively). Three patients had pericardial effusion; all events were grade 2 and considered related to bosutinib treatment. One patient had grade 1 peripheral coldness, which was not considered related to study drug. One patient had grade 3 treatment-related hypertension, but this patient had pre-existing hypertension at the time of starting bosutinib.

The most common laboratory abnormalities, based on laboratory test values, were increased creatinine (95.0%), decreased lymphocyte count (91.7%), increased ALT (85.0%), increased AST (81.7%), and decreased hemoglobin (81.7%; Table 5).

3.4. Pharmacokinetics

Bosutinib plasma trough concentrations were stable over time (Online Resources 5 and 6). The mean ± standard deviation of bosutinib concentration averaged over Days 28, 56, and 84 was 82.7 ± 48.0 ng/mL. In patients aged <65 versus ≥65 years, bosutinib plasma trough concentrations were similar (mean averaged over Days 28, 56, and 84 was 80.3 vs 89.3 ng/mL), except at Day 56, where lower mean concentrations were seen in the younger versus older group (79.3 vs 113.6 ng/mL; Online Resources 7 and 8). For other baseline covariates (e.g., sex and body weight), an analysis of covariance model found no differences between subgroups (data not shown).

4. Discussion

The primary objective of this phase 2 study of bosutinib in Japanese patients with newly diagnosed CP CML was met, and the safety profile of bosutinib was consistent with previous studies [4-7]. The data reported here suggest bosutinib is an effective first-line treatment option for Japanese patients with newly diagnosed CP CML, in addition to its established role in the second-line or later setting in this regional population.

Our findings extend those of the global phase 3 BFORE trial, which established improved efficacy of bosutinib versus imatinib in patients with newly diagnosed CP CML [4]. In addition to the proportion of Asian patients in the BFORE trial who received bosutinib (12.2%), differences between the Japanese population analyzed here and the global BFORE population

should be noted. The proportion of patients aged ≥65 years (31.7% vs 19.5%), with low-risk Sokal scores (45.0% vs 38.2%), and with ECOG performance status 0 (96.7% vs 70.7%) was higher in the present phase 2 Japan study versus the bosutinib arm of the BFORE trial [4]. Interestingly, this is in contrast with prior publications that reported a lower age for diagnosis of CML in Asian versus Western patients [11, 12], as well as higher Sokal risk score [13]. Treatment characteristics also differed in the present study versus BFORE. There was, in the present study versus BFORE, a lower median dose intensity (354.7 vs 391.8 mg/day), likely due to the higher rate of bosutinib dose reductions (55.0% vs 34.0%) and dose interruptions (70.0% vs 56.7%) due to AEs [4].

Notwithstanding the variability in patient and treatment characteristics in this Japanese population versus a global population with newly diagnosed CP CML, the MMR rate at Month 12 (55.0%) was consistent with that reported in the bosutinib arm of the multinational BFORE trial (47.2%). Other efficacy endpoints were also comparable or more favorable in this phase 2 study versus the bosutinib arm of BFORE, including CCyR rate by Month 12 (80.0% vs 77.2%), rates of MR^4 (31.7% vs 20.7%) and $MR^{4.5}$ (21.7% vs 8.1%) at Month 12, and time to MMR (24.1 vs 24.7 weeks) and CCyR (12.2 vs 23.9 weeks) [4].

No new safety signals were observed for first-line bosutinib in Japanese patients. The most common individual TEAEs with bosutinib were consistent between the current phase 2 Japan study and the global BFORE trial [4]. The rate of grade 3/4 TEAEs in bosutinib-treated patients was higher in the Japanese population than in the BFORE population (75.0% vs 56.0%), although rates of any grade TEAEs (100% vs 98.1%) and serious AEs (21.7% vs 20.1%) were similar. In addition, a greater proportion of patients in this study versus BFORE discontinued bosutinib due to AEs (30.0% vs 13.8%); the most common TEAEs leading to bosutinib

discontinuation in the respective studies were increased ALT (10.0% vs 4.9%) and increased AST (8.3% vs 2.2%). When evaluated according to categories of special interest, liver function (80.0% vs 39.9%), infection (65.0% vs 44.4%), and rash TEAEs (55.0% vs 33.6%) occurred at higher rates with bosutinib in Japanese patients compared with the global population of BFORE, as did the rate of grade 3/4 liver function TEAEs (48.3% vs 24.3%). Despite the higher frequency of any-grade and grade 3/4 liver function TEAEs in this study, there were no Hy's law cases, permanent drug-induced liver injuries, or hepatotoxicity-related fatalities. In a prior phase 1/2 study of bosutinib in Japanese patients with CP CML after prior therapy, the incidence of liver function TEAEs was 62% [14], which prompted a recommendation for more frequent monitoring of liver function, i.e., twice monthly during the first 2 months and once during the third month of bosutinib treatment, in the Japan versus US prescribing information [1, 3]; physicians may opt for additional monitoring beyond this guidance.

Differences in some safety outcomes in the present phase 2 study versus BFORE may, in part, reflect the higher proportion of patients aged ≥65 years in the phase 2 study. In the current study and in previous analyses of the phase 3 BFORE [15] and BELA [16] trials, the rate of grade 3/4 TEAEs was higher in bosutinib-treated patients aged ≥65 years compared with those aged <65 years. In addition, the average bosutinib plasma trough concentration in this Japanese population was ~1.12-fold higher than that observed in bosutinib-treated patients in the global BFORE trial (Pfizer Inc., data on file). A pharmacokinetic-pharmacodynamic analysis using data from the BELA and phase 1/2 studies of bosutinib at a starting dose of 500 mg QD in patients with newly diagnosed [7] and previously treated CP CML [5, 6], respectively, identified an exposure–response relationship for diarrhea and rash in patients with CML receiving bosutinib, but not for increased ALT or AST [17]. Another study of different bosutinib dosing regimens in

Japanese patients with CML found that liver dysfunction was more prevalent in patients with higher bosutinib trough concentrations [18]. Noting small patient numbers, relationships were not observed here for bosutinib trough concentrations and either increased ALT or AST (data not shown). It will be of interest to identify factors, including comorbidities and pharmacokinetic parameters, which might have influenced the occurrence of TEAEs in Japanese patients—particularly increased ALT and AST, which most frequently led to bosutinib discontinuation. An exposure–response analysis to evaluate the relationships between bosutinib concentration and TEAEs or efficacy endpoints using a population pharmacokinetic model based on a combined dataset including this study is now being conducted and will be reported separately.

The safety profile of bosutinib is distinct from other TKIs approved as first-line treatment for CP CML [4, 10, 19]; AE profiles should be considered by physicians and patients when selecting an appropriate treatment. Strategies to manage AEs and allow patients to remain on bosutinib treatment have been reported [20, 21] and can be applied to Japanese patients. These include dose reductions and interruptions, as well as initiating treatment at a lower dose and incrementally escalating the dose until the recommended dose is reached. Supportive care, including antidiarrheal or antiemetic medication and increased hydration, can help mitigate gastrointestinal AEs. As noted above, liver function abnormalities during bosutinib treatment are a particular concern for Japanese patients, necessitating more intensive monitoring in this population [3]. Bosutinib dose reductions and interruptions are recommended for patients with liver toxicities [20, 21], but concomitant medications, such as steroids or glycyrrhizic acid, have also been administered to manage increased ALT or AST in the multinational phase 1/2 study of bosutinib for previously treated patients with CML [22].

The occurrence of cardiovascular events with long-term TKI treatment, although infrequent, has become a concern [23, 24]. A retrospective analysis found that Japanese patients with CML treated with TKIs, in particular nilotinib, were at a higher risk for ischemic heart disease compared with the general Japanese population [25]. In the current study, rates of cardiac, vascular, and hypertension TEAEs were low, but longer follow-up is needed to characterize cardiovascular events in Japanese patients receiving first-line bosutinib. It is recommended that a patient's cardiovascular risk factors are assessed prior to initiating bosutinib therapy to determine if additional monitoring for cardiac, vascular, and hypertension TEAEs is warranted [20, 21].

To date, two second-generation TKIs, dasatinib and nilotinib, have been approved in Japan as first-line CP CML treatment, based on the global phase 3 DASISION [19] and ENESTnd [10] trials, respectively, both of which showed improved efficacy versus the first-generation TKI imatinib. Analyses of the Japanese subgroups in these trials were reported after 24 months [26] and 5 years of follow-up [27] for DASISION and after 12 months [28] and 5 years of follow-up [29] for ENESTnd. Another recent publication based on a 5-year observational study of first-line TKI treatment in Japan reported higher rates of early molecular response (MR^{1} at Month 3) and durable deep molecular response ($MR^{4.5}$ by Month 36) in patients who received dasatinib or nilotinib compared with those administered imatinib [30]. Although cross-trial comparisons are challenging due to differences such as study design and endpoints, the MMR rate at Month 12 was consistent between the current phase 2 Japan study population (55.0%) and the Japanese subgroups of ENESTnd who received 300 mg or 400 mg nilotinib twice daily (57% and 50%, respectively) [28], as was the MMR rate by Month 12 in the current phase 2 Japan study versus the Japanese population treated with dasatinib in DASISION (61.7% vs 69%) [26]. The $MR^{4.5}$

rate at 12 months appeared higher with bosutinib (21.7%) than with 300 mg nilotinib (6.7%) or 400 mg nilotinib (4.2%) in the Japanese subgroups of ENESTnd [28]. In line with the known profiles of second-generation TKIs [4, 10, 19], fluid retention and effusion TEAEs were more common in dasatinib-treated Japanese patients with CP CML [26] and increased glucose was more frequently reported in nilotinib-treated Japanese patients [28] compared with bosutinib-treated Japanese patients in the current study. Similar to our findings, there were differences in the rates of certain TEAEs with dasatinib and nilotinib in the Japanese subgroup compared with the global population of DASISION and ENESTnd, respectively [26, 28].

This study is limited by the single-arm design with no comparator, small number of patients, and short follow-up period. Nevertheless, an acceptable toxicity profile was observed for bosutinib in Japanese patients with CP CML, and a substantial proportion of patients had deep molecular responses. Since durable deep molecular responses allow some patients to discontinue TKI treatment and attain treatment-free remission [31], the results from this study are promising; longer follow-up is needed to assess if deep molecular responses with bosutinib are maintained in Japanese patients. It should be noted that the possibility for treatment-free remission after discontinuation of bosutinib has not been prospectively assessed in clinical trials, in contrast with other second-generation TKIs [32-36], but it is anticipated that feasibility is not dependent on the administered TKI.

In conclusion, our findings further substantiate the efficacy and safety of first-line bosutinib in a specific regional population, as was also reported in the overall population in the phase 3 BFORE trial [4], and provide support for bosutinib as an effective treatment option for Japanese patients with newly diagnosed CP CML.

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Research Data Policy/Data Availability

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Conflict of interest

Masayuki Hino reports research funding from Pfizer, Novartis, and Otsuka, and honoraria from Pfizer, Novartis, Otsuka, and Bristol-Myers Squibb. Itaru Matsumura reports research funding from Pfizer and Otsuka, speakers bureau with Novartis and Bristol-Myers Squibb, and consultancy with Otsuka. Shin Fujisawa reports honoraria and research funding from Novartis, Pfizer, Otsuka, and Bristol-Myers Squibb. Kenichi Ishizawa reports research funding from Pfizer

and Otsuka and speakers bureau with Novartis and Bristol-Myers Squibb. Takaaki Ono reports honoraria from Celgene, Merck Sharp & Dohme, Ono, Novartis, Bristol-Myers Squibb, Pfizer, Otsuka, and Takeda and research funding from, Celgene, Merck Sharp & Dohme, Ono, Kyowa Hakko Kirin, and Chugai. Emiko Sakaida reports research funding from Bristol-Myers Squibb, Chugai, Ono, and Kyowa Kirin. Naohiro Sekiguchi reports research funding from Ono, A2 Healthcare, Astellas, Janssen, Merck Sharp & Dohme, Otsuka, Pfizer, PPD-SNBL, Sumitomo Dainippon Pharma, Daiichi Sankyo Company, and Bristol-Myers Squibb. Yusuke Tanetsugu, Kei Fukuhara, Masayuki Ohkura, and Yuichiro Koide report employment by Pfizer R&D Japan G.K. Naoto Takahashi reports research funding and honoraria from Pfizer, Otsuka, and Novartis, and research funding from Chugai, Eizai, Asahikasei, Ono, Kyowahakko-Kirin, and Toyamakagaku, outside the submitted work.

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Table 1 Patient demographics and clinical characteristics

	Bosutinib (*N* = 60)
Age, median (range), years	55 (20–83)
Age group, *n* (%)	
<65 years	41 (68.3)
≥65 years	19 (31.7)
Sex, *n* (%)	
Male	36 (60.0)
Female	24 (40.0)
Weight, median (range), kg	59.8 (34.5–102.6)
Body mass index, median (range), kg/m^2	23.0 (15.6–36.3)
Time from CML diagnosis, median (range), days	15 (1–153)
Prior CML therapy,[a] *n* (%)	28 (46.7)
Sokal risk group, *n* (%)	
Low	27 (45.0)
Intermediate	26 (43.3)
High	7 (11.7)
ECOG performance status, *n* (%)	
0	58 (96.7)
1	2 (3.3)

[a]Hydroxyurea (hydroxycarbamide) within 6 months

CML chronic myeloid leukemia, *ECOG* Eastern Cooperative Oncology Group

Table 2 Treatment summary

	Bosutinib (*N* = 60)
Duration of follow-up, median (range), months	16.6 (11.1–21.9)
Duration of treatment, median (range), months	15.3 (0.3–21.9)
Completed 12 months of treatment,[a] *n* (%)	42 (70.0)
Discontinued treatment within 12 months,[a] *n* (%)	18 (30.0)
Discontinued treatment, *n* (%)	19 (31.7)
Due to adverse events	18 (30.0)
Physician's decision	1 (1.7)
Dose reduction due to adverse events, *n* (%)	
400 to 300 mg QD	33 (55.0)
300 to 200 mg QD	8 (13.3)
Dose interruption due to adverse events, *n* (%)	46 (76.7)
Dose escalation due to insufficient response, *n* (%)	
400 to 500 mg QD	6 (10.0)
500 to 600 mg QD	1 (1.7)
Dose intensity, median (range), mg/day	354.7 (95–494)

[a]Core treatment phase

Table 3 Efficacy summary

% (90% CI)	Bosutinib (*N* = 60)
Primary endpoint	
MMR at Month 12	55.0 (44.4–65.6)
Secondary endpoints	
MMR by Month 12	61.7 (51.3–72.0)
CCyR by Month 12	80.0 (71.5–88.5)
Exploratory endpoints	
MMR at Month 3	10.0 (3.6–16.4)
MMR at Month 6	50.0 (39.4–60.6)
MMR at Month 9	53.3 (42.7–63.9)

CCyR complete cytogenetic response, *IS* International Scale, *MMR* major molecular response (≤0.1% *BCR-ABL1* on IS)

Table 4 Treatment-emergent adverse events[a]

	Bosutinib (*N* = 60)	
n (%)	Any grade	Grade 3/4
Any treatment-emergent adverse event	60 (100)	45 (75.0)
Gastrointestinal	52 (86.7)	9 (15.0)
Diarrhea	52 (86.7)	9 (15.0)
Nausea	17 (28.3)	0
Vomiting	15 (25.0)	1 (1.7)
Constipation	7 (11.7)	0
Upper abdominal pain	6 (10.0)	0
Liver function	48 (80.0)	29 (48.3)
Increased ALT	33 (55.0)	20 (33.3)
Increased AST	28 (46.7)	11 (18.3)
Increase blood alkaline phosphatase	16 (26.7)	0
Liver disorder	7 (11.7)	5 (8.3)
Hematologic	27 (45.0)	16 (26.7)
Thrombocytopenia[b]	18 (30.0)	5 (8.3)
Lymphopenia[c]	11 (18.3)	8 (13.3)
Neutropenia[d]	10 (16.7)	7 (11.7)
Anemia[e]	10 (16.7)	0
Leukopenia[f]	6 (10.0)	2 (3.3)
Infection	39 (65.0)	4 (6.7)
Nasopharyngitis	17 (28.3)	0
Upper respiratory tract infection	6 (10.0)	0
Rash	33 (55.0)	3 (5.0)
Rash	16 (26.7)	1 (1.7)
Maculopapular rash	8 (13.3)	1 (1.7)
Other		
Increased lipase	16 (26.7)	9 (15.0)
Pyrexia	14 (23.3)	1 (1.7)
Increased GGT	11 (18.3)	3 (5.0)
Increased amylase	9 (15.0)	1 (1.7)
Back pain	7 (11.7)	0
Headache	7 (11.7)	0

[a]Any-grade adverse events reported in ≥10% of patients; coded using Medical Dictionary for Regulatory Activities v21.1 terms and graded according to Common Terminology Criteria for Adverse Events v4.03

[b]Clustered terms were thrombocytopenia and platelet count decreased

[c]Clustered terms were lymphopenia and lymphocyte count decreased

[d]Clustered terms were neutropenia and neutrophil count decreased

[e]Clustered terms were anemia and hemoglobin decreased

[f]Clustered terms were leukopenia and white blood cell count decreased

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma-glutamyltransferase

Table 5 Laboratory abnormalities[a]

	Bosutinib (*N* = 60)	
n (%)	Any grade	Grade 3/4
Any laboratory abnormality	60 (100)	43 (71.7)
Increased creatinine	57 (95.0)	0
Decreased lymphocyte count	55 (91.7)	13 (21.7)
Increased ALT	51 (85.0)	29 (48.3)
Increased AST	49 (81.7)	16 (26.7)
Decreased hemoglobin	49 (81.7)	3 (5.0)
Decreased platelet count	38 (63.3)	6 (10.0)
Decreased calcium[b]	37 (62.7)	0
Increased alkaline phosphatase	31 (51.7)	0
Increased lipase	28 (46.7)	13 (1.7)
Decreased neutrophil count	26 (43.3)	9 (15.0)
Decreased albumin	25 (41.7)	0
Decreased white blood cell count	23 (38.3)	2 (3.3)
Decreased phosphate	23 (38.3)	1 (1.7)
Increased serum amylase	21 (35.0)	1 (1.7)
Increased creatine phosphokinase	20 (33.3)	2 (3.3)
Decreased potassium	14 (23.3)	2 (3.3)
Increased glucose	13 (21.7)	2 (3.3)

[a]Any-grade laboratory abnormality reported in ≥20% of patients; graded according to Common Terminology Criteria for Adverse Events v4.03

[b]59 patients evaluated for decreased calcium

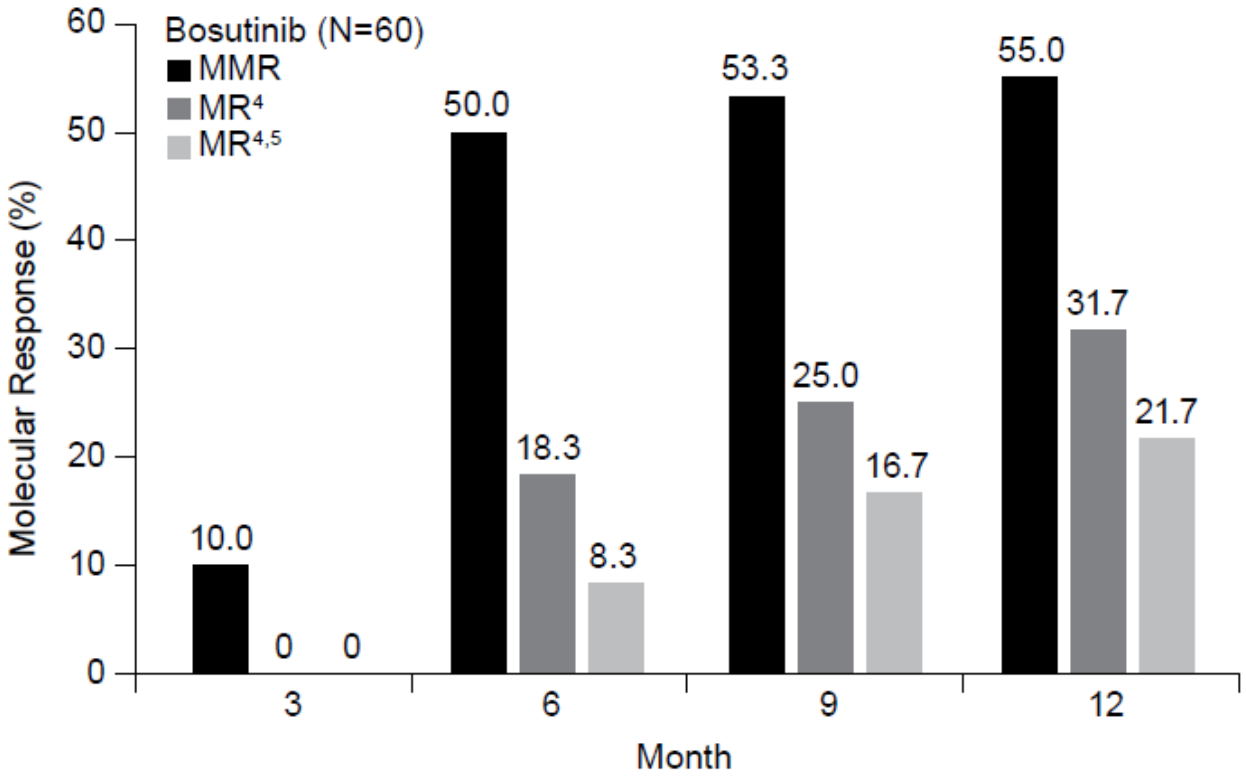
ALT alanine aminotransferase, *AST* aspartate aminotransferase

FIGURE LEGEND

Fig. 1 Molecular response rates at Months 3, 6, 9, and 12

IS, International Scale; *MMR*, major molecular response (≤0.1% *BCR-ABL1* on IS); MR^4, ≤0.01% *BCR-ABL1* on IS; $MR^{4.5}$, ≤0.0032% *BCR-ABL1* on IS

Fig. 1 Molecular response rates at Months 3, 6, 9, and 12



IS, International Scale; *MMR*, major molecular response (≤0.1% *BCR-ABL1* on IS); MR^4, ≤0.01% *BCR-ABL1* on IS; $MR^{4.5}$, ≤0.0032% *BCR-ABL1* on IS

SUPPLEMENTAL MATERIALS

- **Online Resource 1** Adverse events of special interest categories
- **Online Resource 2** Time to molecular response, adjusting for competing risk of discontinuation without response
- **Online Resource 3** Time to complete cytogenetic response, adjusting for competing risk of discontinuation without response
- **Online Resource 4** Treatment-emergent adverse events of special interest
- **Online Resource 5** Bosutinib trough concentrations
- **Online Resource 6** Box plot of trough bosutinib plasma concentrations
- **Online Resource 7** Bosutinib trough concentrations according to age group
- **Online Resource 8** Box plot of trough bosutinib plasma concentrations according to age group

SUPPLEMENTAL MATERIALS

International Journal of Hematology

Phase 2 study of bosutinib in Japanese patients with newly diagnosed chronic phase chronic myeloid leukemia

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Contents

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Online Resource 1 Adverse events of special interest categories

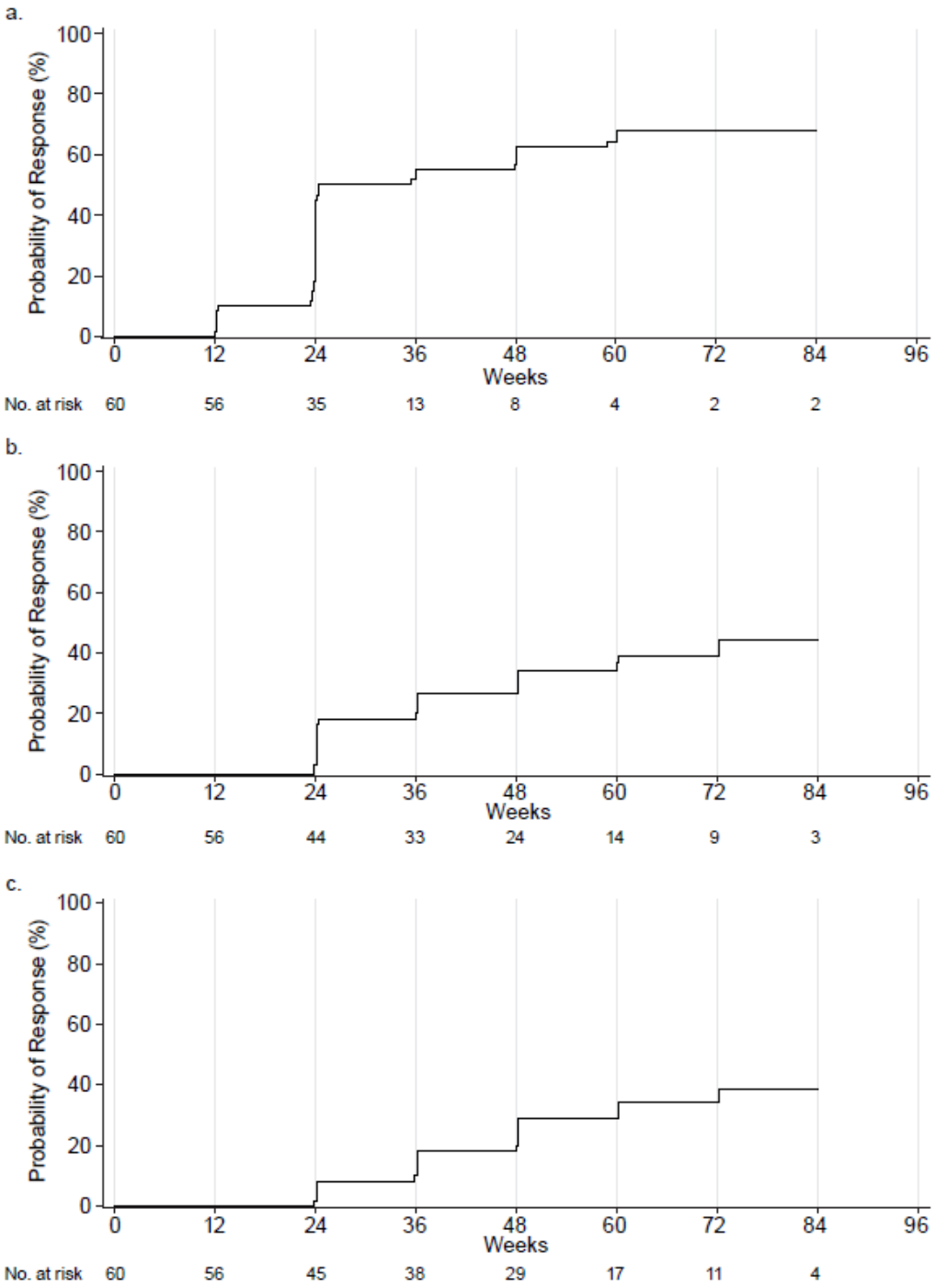
Category	Adverse event criteria
Cardiac	• HLGTs in cardiac arrhythmias, heart failure, pericardial disorders • PTs in cardiac death, sudden cardiac death, sudden death, ejection fraction decreased • MedDRA SMQ (narrow): Torsade de pointes/QT prolongation
Edema	• PTs contain edema, weight increased
Effusion	• PTs in pleural effusion, pericardial effusion
Gastrointestinal	• PTs in nausea, regurgitation, retching, vomiting, vomiting projectile, diarrhea, defecation urgency, frequent bowel movements, gastrointestinal hypermotility
Hemorrhage	• PTs in gastric occult blood positive, occult blood positive • MedDRA SMQ (narrow): hemorrhage terms (excluding laboratory terms)
Hypertension	• HLGT in vascular hypertensive disorders • PTs in BP abnormal, BP ambulatory abnormal, BP ambulatory increased, BP diastolic abnormal, BP diastolic increased, BP increased, BP systolic abnormal, BP systolic increased
Infection	• SOC in infections and infestations
Liver function	• MedDRA (SMQ) hepatic disorders: sub-SMQs (narrow) in cholestasis and jaundice of hepatic origin; hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions; hepatitis, noninfectious; liver-related investigations, signs and symptoms (selected relevant) • PTs: ALT abnormal, AST increased, AST abnormal, AST increased, bilirubin conjugated abnormal, bilirubin conjugated increased, blood bilirubin abnormal, blood bilirubin increased, blood bilirubin unconjugated increased, hepatic enzyme abnormal, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinemia, hypertransaminasemia, liver function test abnormal, transaminases abnormal, transaminases increased, blood ALP abnormal, blood ALP increased, liver function test increased
Myelosuppression	• MedDRA SMQs (narrow): hematopoietic cytopenias affecting >1 type of blood cell,[a] hematopoietic erythropenia, hematopoietic leukopenia, hematopoietic thrombocytopenia • PTs in bone marrow toxicity, hematocrit decreased, hemoglobin decreased, hematotoxicity, anemia
Rash	• HLTs in rashes, eruptions, and exanthem NEC; erythema; acne; dermatitis and eczema
Renal	• HLT in renal failure and impairment • PTs in blood creatinine abnormal, blood creatinine increased, creatinine renal clearance abnormal, creatinine renal clearance decreased, glomerular filtration rate abnormal, glomerular filtration rate decreased
Vascular	• HLGTs in coronary artery disorders; arteriosclerosis, stenosis, vascular insufficiency and necrosis; embolism and thrombosis • HLTs in arterial therapeutic procedures (excluding aortic), CNS hemorrhages and cerebrovascular accidents, CNS vascular disorders NEC, non-site specific vascular disorders NEC, peripheral vascular disorders NEC (excluding the 2 PTs flushing and hot flush), transient cerebrovascular events, vascular imaging procedures NEC, vascular therapeutic procedures NEC

[a]The following MedDRA PTs were used for cytopenias: anemia, thrombocytopenia (thrombocytopenia, acquired amegakaryocytic thrombocytopenia), neutropenia (cyclic neutropenia, febrile neutropenia, idiopathic neutropenia, neutropenia)

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* alanine aminotransferase, *BP* blood pressure, *CNS* central nervous system, *HLGT* higher-level group term, *HLT* higher-level term, *MedDRA* Medical Dictionary for Regulatory Activities, *NEC* not elsewhere classified, *PT* preferred term, *SMQ* standardized MedDRA query, *SOC* system organ class

Online Resource 2 Time to first molecular response[a]~~, adjusting for competing risk of discontinuation without response~~

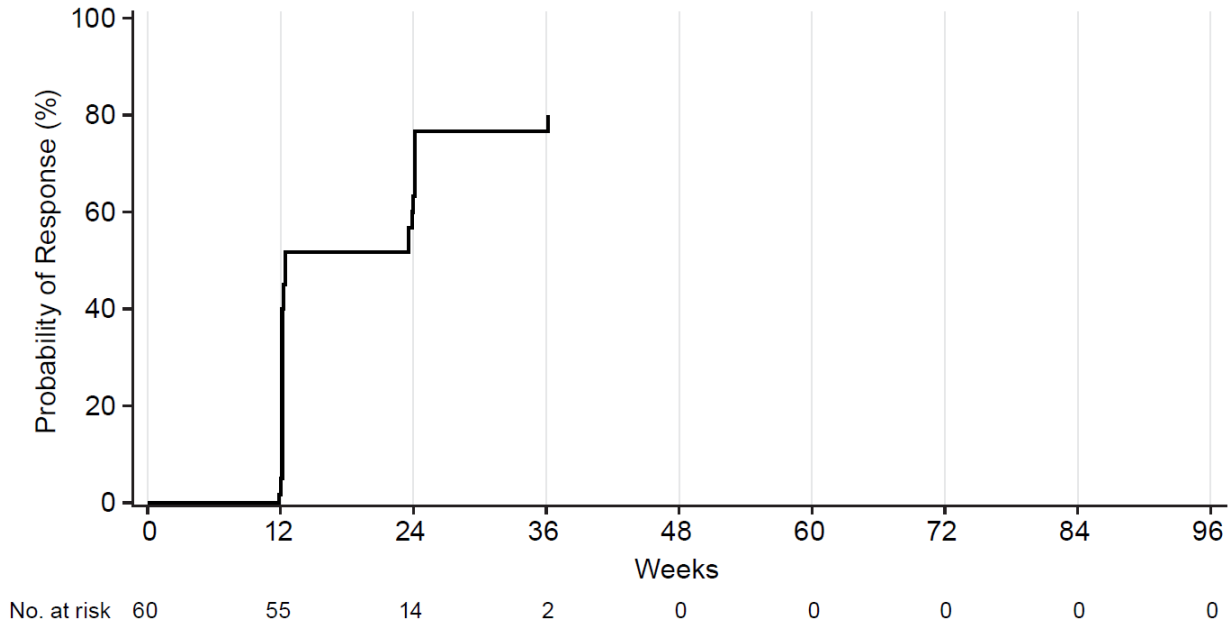
(a) MMR, (b) MR^4, and (c) $MR^{4.5}$



[a]Molecular response was analyzed using cumulative incidence, adjusting for the competing risk without response.

IS International Scale, *MMR* major molecular response (≤0.1% *BCR-ABL1* on IS), MR^4 ≤0.01% *BCR-ABL1* on IS, $MR^{4.5}$ ≤0.0032% *BCR-ABL1* on IS

Online Resource 3 Time to first complete cytogenetic response[a]~~, adjusting for competing risk of discontinuation without response~~



[a]Cytogenetic response was analyzed using cumulative incidence, adjusting for the competing risk without response.

Online Resource 4 Treatment-emergent adverse events of special interest

	Bosutinib (N = 60)	
n (%)	Any grade	Grade 3/4
Gastrointestinal	52 (86.7)	9 (15.0)
Liver function	48 (80.0)	29 (48.3)
Infection	39 (65.0)	4 (6.7)
Rash	33 (55.0)	3 (5.0)
Myelosuppression	27 (45.0)	16 (26.7)
Effusion	5 (8.3)	1 (1.7)
Hemorrhage	5 (8.3)	0
Renal	4 (6.7)	0
Cardiac	3 (5.0)	0
Edema	3 (5.0)	0
Hypertension	1 (1.7)	1 (1.7)
Vascular	1 (1.7)	0

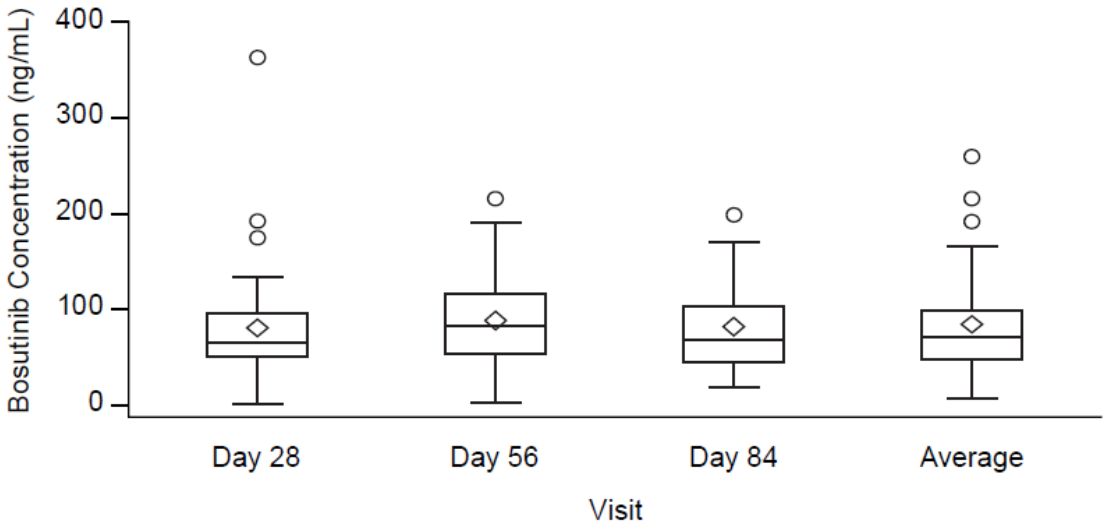
Online Resource 5 Bosutinib trough concentrations

Plasma levels, ng/mL	Bosutinib (*N* = 60)
Day 28	
n	34
Mean (SD)	83.6 (64.1)
95% CI	61.2–105.9
Median (range)	66.5 (1.38–363)
Day 56	
n	41
Mean (SD)	86.0 (46.4)
95% CI	71.3–100.6
Median (range)	82.6 (3.28–216)
Day 84	
n	44
Mean (SD)	79.7 (41.5)
95% CI	67.0–92.3
Median (range)	69.1 (19.10–199)
Average concentration[a]	
n	51
Mean (SD)	82.7 (48.0)
95% CI	69.3–96.2
Median (range)	71.2 (7.59–260)

[a]Mean of Day 28, 56, and 84 trough concentrations

CI confidence interval, *SD* standard deviation

Online Resource 6 Box plot of trough bosutinib plasma concentrations



Box plot bounds represent 25% and 75% quartiles; inside the box, solid line represents median, and diamond represents mean; circles represent outliers and whiskers to the last points within 1.5 times the interquartile range.

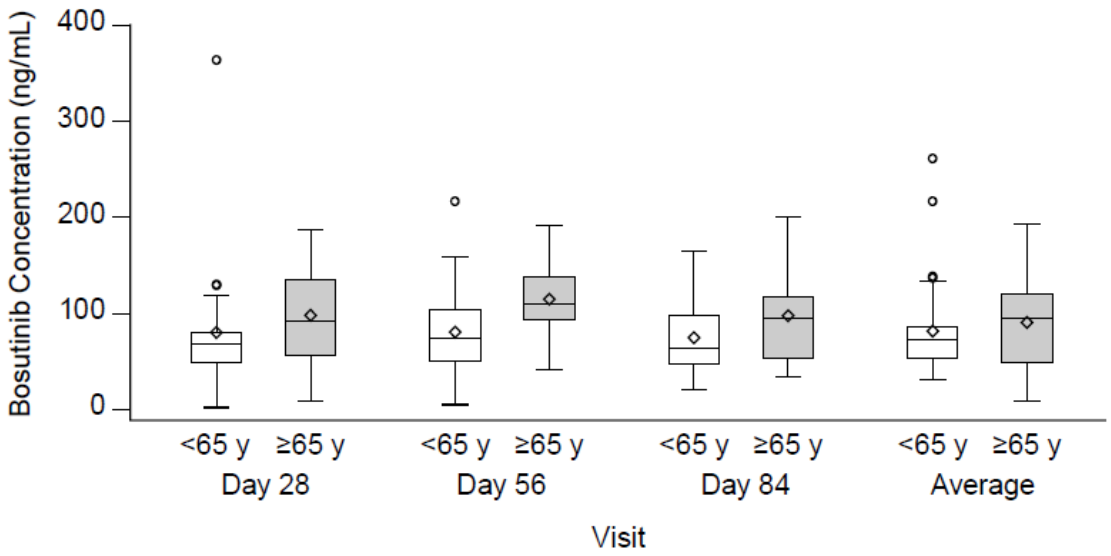
Online Resource 7 Bosutinib trough concentrations according to age group

	Age group	
Plasma levels, ng/mL	<65 years (*n* = 41)	≥65 years (*n* = 19)
Day 28		
n	25	9
Mean (SD)	78.8 (66.3)	96.7 (58.9)
95% CI	51.4–106.2	51.5–142.0
Median (range)	66.3 (1.4–363.0)	91.4 (7.6–186.0)
Day 56		
n	33	8
Mean (SD)	79.3 (44.9)	113.6 (45.0)
95% CI	63.4–95.2	76.0–151.1
Median (range)	72.5 (3.3–216.0)	108.5 (40.7–191.0)
Day 84		
n	32	12
Mean (SD)	73.4 (36.4)	96.3 (51.0)
95% CI	60.3–86.5	63.9–128.7
Median (range)	62.1 (19.1–163.0)	94.1 (32.2–199.0)
Average concentration[a]		
n	37	14
Mean (SD)	80.3 (47.5)	89.3 (50.4)
95% CI	64.4–96.1	60.2–118.4
Median (range)	70.8 (29.8–260.0)	93.2 (7.6–192.0)

[a]Mean of Day 28, 56 and 84 trough concentrations

CI confidence interval, *SD* standard deviation

Online Resource 8 Box plot of trough bosutinib plasma concentrations according to age group



Box plot bounds represent 25% and 75% quartiles; inside the box, solid line represents median, and diamond represents mean; circles represent outliers and whiskers to the last points within 1.5 times the interquartile range.