Long-term evaluation of cardiac and vascular toxicity in patients with Philadelphia chromosome-positive leukemias treated with bosutinib

Jorge E. Cortes1,*, H. Jean Khoury2, Hagop Kantarjian1, Tim H. Brümmendorf3,4, Michael J. Mauro5, Ewa Matczak6, Dmitri Pavlov6, Jean M. Aguiar7, Kolette D. Fly7, Svetoslav Dimitrov6, Eric Leip6, Mark Shapiro6, Jeff H. Lipton9, Jean-Bernard Durand1, and Carlo Gambacorti-Passerini10,*

1University of Texas MD Anderson Cancer Center, Houston, Texas
2Winship Cancer Institute of Emory University, Atlanta, Georgia
3Universitätsklinikum RWTH Aachen, Aachen, Germany
4Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
5Memorial Sloan Kettering Cancer Center, New York, New York
6Pfizer Inc, New York, New York
7Pfizer Inc, Groton, Connecticut
8Pfizer Inc, Cambridge, Massachusetts
9Princess Margaret Cancer Center, Toronto, Ontario, Canada
10University of Milano-Bicocca, Monza, Italy

Abstract

Vascular and cardiac safety during tyrosine kinase inhibitor (TKI) therapy is an emerging issue. We evaluated vascular/cardiac toxicities associated with long-term bosutinib treatment for Philadelphia chromosome-positive (Ph+) leukemia based on treatment-emergent adverse events (TEAEs) and changes in QTc intervals and ejection fraction in two studies: a phase 1/2 study of second-/third-/fourth-line bosutinib for Ph+ leukemia resistant/intolerant to prior TKIs (N = 570) and a phase 3 study of first-line bosutinib (n = 248) versus imatinib (n = 251) in chronic phase chronic myeloid leukemia. Follow-up time was ≥48 months (both studies). Incidences of vascular/cardiac TEAEs in bosutinib-treated patients were 7%/10% overall with similar incidences observed with first-line bosutinib (5%/8%) and imatinib (4%/6%). Few patients had grade ≥3 vascular/cardiac events (4%/4%) and no individual TEAE occurred in >2% of bosutinib patients. Exposure-adjusted vascular/cardiac TEAE rates (patients with events/patient-year) were low for second-line or later bosutinib (0.037/0.050) and not significantly different between first-line

*Correspondence to: Dr. Jorge Cortes; Department of Leukemia, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030. jcortes@mdanderson.org or Dr. Carlo Gambacorti-Passerini; Department of Health Sciences, University of Milano-Bicocca, Via Cadore, 48, 20900 Monza, Italy. carlo.gambacorti@unimib.it. Cortes and Gambacorti-Passerini contributed equally to this work.

Additional Supporting Information may be found in the online version of this article.
bosutinib (0.015/0.024) and imatinib (0.011/0.017; P ≥ 0.267). Vascular/cardiac events were managed mainly with concomitant medications (39%/44%), bosutinib treatment interruptions (18%/21%), or dose reductions (4%/8%); discontinuations due to these events were rare (0.7%/1.0%). Based on logistic regression modelling, performance status >0 and history of vascular or cardiac disorders were prognostic of vascular/cardiac events in relapsed/refractory patients; hyperlipidemia/hypercholesterolemia and older age were prognostic of cardiac events. In newly diagnosed patients, older age was prognostic of vascular/cardiac events; history of diabetes was prognostic of vascular events. Incidences of vascular and cardiac events were low with bosutinib in the first-line and relapsed/refractory settings following long-term treatment in patients with Ph+ leukemia.

Introduction

Tyrosine kinase inhibitors (TKIs) are standard treatment for Philadelphia chromosome-positive (Ph+) leukemias [1,2]. Although generally well tolerated, severe cardiac and vascular events have been linked to TKI therapy, particularly second- and third-generation TKIs [3,4]. There have been reports of serious arterial thrombotic events with long-term ponatinib, nilotinib, and dasatinib treatment [5–8], QT interval prolongation with nilotinib or dasatinib therapy [9–11], pulmonary hypertension with dasatinib [7], and peripheral arterial occlusive disease (PAOD) with nilotinib treatment [11–13]. Because TKI-treated patients can have a normal life expectancy, characterization of cardiac and vascular events associated with TKI therapy is important to prevent or minimize complications [14,15].

Bosutinib (SKI-606) is an oral, dual Src/Abl TKI active in patients with Ph1 chronic phase (CP) chronic myeloid leukemia (CML) resistant or intolerant to prior TKI therapy [16]. Bosutinib is a second-generation TKI with a distinct and manageable safety profile [17–22]; however, thorough characterization of the cardiac and vascular toxicity profile of bosutinib has not been widely published to date.

We conducted a retrospective analysis of two large clinical trials [17–24] to characterize cardiac and vascular treatment-emergent adverse events (TEAEs), the risk factors associated with these events, and their management in Ph1 leukemia patients receiving bosutinib as first-line therapy (vs. the first-generation TKI, imatinib) and as second-line therapy and beyond. Changes in QTc intervals and ejection fraction also were assessed. To our knowledge, this analysis represents one of the most comprehensive assessments to date of vascular and cardiac toxicities associated with TKIs.

Patients and Methods

Study design and patients

This retrospective assessment evaluated data from two ongoing, open-label, international studies [19,21]. The first is a two-part, phase 1/2 study of bosutinib (500 mg starting dose in phase 2; ClinicalTrials.gov: NCT00261846) [21] in Ph1 patients with CP CML (resistant/intolerant to imatinib [n = 284] or after failure of imatinib plus dasatinib and/or nilotinib [n = 119]) or advanced-phase leukemia (accelerated-phase [AP] CML, blast-phase [BP] CML,
or acute lymphoblastic leukemia [ALL] after prior TKI therapy with at least imatinib \( n = 167 \)). The second is a randomized, phase 3 study (BELA; ClinicalTrials.gov: NCT00574873) in which patients newly diagnosed with Ph1 CP CML were treated with bosutinib 500 mg/day \( n = 248 \) or imatinib 400 mg/day \( n = 251 \) \cite{19}. Patients in each study received treatment until disease progression, unacceptable toxicity, or consent withdrawal. Data for this interim publication are from unlocked trial databases with data cutoff dates of May 23, 2014, for the phase 1/2 study and November 21, 2013, (applied to the May 14, 2014, snapshot) for the phase 3 study.

Patients in both studies were excluded if they had a history of clinically significant or uncontrolled cardiac disease (including congestive heart failure, uncontrolled angina or hypertension within 3 months, myocardial infarction within 12 months, clinically significant ventricular arrhythmia, diagnosis/suspected congenital or acquired prolonged QT syndrome, history of prolonged QTc interval, or unexplained syncope), required medications known to prolong QT interval or had prolonged QTc (average >0.45 s at screening), or had uncorrected hypomagnesemia or hypokalemia. Full eligibility criteria have been published previously \cite{19,21}.

Vascular and cardiac toxicity assessments

Adverse events (AEs) were monitored throughout the study and for 28 days (phase 3 study) or 30 days (phase 1/2 study) after the last dose of study drug; treatment-related AEs were followed until resolution (grade \( \leq 1 \)) or return to baseline. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0. TEAEs (serious/non-serious, related/unrelated), as reported by investigators, were coded and classified using Medical Dictionary for Regulatory Activities version 17.0. A comprehensive list of preferred terms (PTs) likely indicating vascular or cardiac toxicities were selected by primary System Organ Class (SOC) designation, with further selection by High-Level Group Terms (HLGTs), High-Level Terms (HLT), and PTs (Supporting Information Table 1). The vascular analysis examined cerebrovascular TEAEs (related HLTS under the HLGT Central nervous system [CNS] vascular disorders, including CNS hemorrhages and cerebrovascular accidents, CNS vascular disorders not elsewhere classified [NEC], and Transient cerebrovascular events), cardiovascular TEAEs (all PTs under the HLTs Ischemic coronary artery disorders and Coronary artery disorders NEC), and peripheral vascular TEAEs (related terms under the HLGTs Arteriosclerosis, stenosis, vascular insufficiency and necrosis, Embolism and thrombosis, Vascular disorders NEC, Cardiac and vascular investigations excluding enzyme tests, and Vascular therapeutic procedures). The cardiac analysis included terms under the HLGTs Cardiac arrhythmias and Heart Failures (SOC Cardiac disorders), cardiac-related terms under the HLGTs Cardiac and vascular investigations excluding enzyme test and Fatal outcomes, and the PT congenital long QT syndrome under the HLGT Congenital cardiac and vascular disorders. In addition, incidence of hypertension-related TEAEs (related terms under the HLGT Vascular hypertensive disorders and blood pressure-related terms under the HLGT Cardiac and vascular investigations excluding enzyme tests) and pericardial disorders (all PTs under the HLGT Pericardial disorders) were analyzed separately. Treatment discontinuations due to vascular and cardiac TEAEs and clinical trial AE management strategies were evaluated.
Echocardiogram (ECHO) or multigated acquisition (MUGA) scan assessments were performed for all patients to assess left ventricular ejection fraction (LVEF) at screening, at week 24 (phase 1/2 study only), when clinically indicated, and at end of treatment. Triplicate electrocardiograms (ECGs) were performed and averaged for all patients to assess QTcF (Fridericia’s method) at screening, on treatment (predose and postdose on days 1 and 21 [phase 1/2] and days 1, 28, 56, and 84 [phase 3]), at ≥1 week after last dose, or if clinically indicated. Grading of LVEF and QTc intervals was based on the NCI CTCAE criteria; ECHO/MUGA and ECG data were analyzed for factors including decreased LVEF (decrease to <60%) and QTc interval prolongation (to >450 or ≥60 ms increase over baseline).

Analysis and statistical methods
Vascular and cardiac TEAEs are reported descriptively for each study; data for bosutinib were also pooled. In addition to descriptive data presentation, TEAE incidence for bosutinib versus imatinib in the phase 3 study was compared using Fisher’s exact test, and exposure-adjusted rate (patients with events/patient-year) estimates were compared using the exact log-rank test [25]. Incidence and exposure-adjusted rates of newly occurring TEAEs were evaluated in patients on treatment during that time interval. In cases for which a patient experienced recurrent episodes of a TEAE, the event was counted only once according to the first year of occurrence. Discontinuations due to vascular or cardiac TEAEs also were assessed by treatment year. Baseline characteristics were assessed in patients with or without cardiac or vascular TEAEs. Shifts from baseline for LVEF and QTcF were analyzed.

Multivariable logistic regression analyses using backward elimination were performed to identify significant baseline prognostic factors of vascular and cardiac TEAEs in each study; odds ratios with 95% confidence intervals (CIs) are presented. Backward elimination criterion for all models was 0.20; P values <0.05 were considered significant; however, no adjustments were made for multiple testing.

Results
Exposure and follow-up
Median (range) duration of exposure (time between treatment start and stop dates) was 11.1 (0.03–94.9) months overall (second-line: 25.6 [0.16–94.9] months; third-line: 8.6 [0.23–87.7] months; advanced-phase: 4.0 [0.03–89.2] months) in the phase 1/2 study of second-line or later bosutinib and 55.0 (0.03–69.4) and 49.5 (0.5–62.6) months for first-line bosutinib and imatinib, respectively, in the phase 3 study. The time from last patient’s first visit to data cutoff was ≥48 months for both studies.

Patients
Demographic and baseline characteristics for patients with on-treatment vascular TEAEs, cardiac TEAEs, either or both types of events, or neither type of event are shown in Supporting Information Table II. A medical history of cardiac or vascular disorders was more common among patients who experienced events while receiving bosutinib in the second-line or later setting. In both studies, patients who experienced events were older than those who experienced neither cardiac nor vascular TEAEs. In both studies, baseline use of
beta blockers was more common in bosutinib-treated patients who developed events versus those who did not; no imatinib-treated patients with vascular or cardiac TEAEs were receiving beta blockers at baseline. No substantial differences in baseline use of other medications were observed.

**Cerebrovascular, cardiovascular, and peripheral vascular events**

The overall incidence of vascular TEAEs was low with 6.8% and 3.7% of bosutinib-treated patients across both studies experiencing any grade and grade ≥3 events, respectively. The incidence was higher with second-line or later bosutinib versus first-line bosutinib (7.7% vs. 4.8%; Table I). In the first-line setting, there were no significant differences in incidence between the bosutinib and imatinib arms, either overall or for individual vascular TEAEs (any grade or grade ≥3; Supporting Information Table III), or for the exposure-adjusted analysis (any grade or grade ≥3; Table I). Among the 56 patients who experienced vascular AEs during bosutinib treatment, 17 (30.4%) had a medical history of vascular events, 16 of whom were in the second-line or later setting.

Cerebrovascular TEAEs were experienced by 1.8% (grade ≥3, 1.2%) of bosutinib-treated patients, more commonly in the second-line or later versus first-line setting (2.3% vs. 0.8%). Across studies, no cerebrovascular events occurred in >1 bosutinib-treated patient except for cerebral hemorrhage (n = 3 [1 treatment-related]) and subarachnoid hemorrhage (n = 3 [none treatment-related]; see Supporting Information text for additional information). Cardiovascular TEAEs occurred in 3.7% (grade ≥3, 2.3%) of bosutinib-treated patients (second-line or later, 4.2%; first-line, 2.4%). Among cardiovascular events, only angina pectoris and coronary artery disease (CAD; n = 10 [1.2%] each) occurred in >1% of bosutinib-treated patients. Peripheral vascular TEAEs were also uncommon, occurring in 2.0% of bosutinib-treated patients overall, with higher incidence in the second-line or later versus first-line setting (2.1% vs. 1.6%); grade ≥3 events occurred in only 0.2%, all in the second-line or later setting. Individual peripheral vascular events occurring in >1 bosutinib-treated patient were aortic arteriosclerosis, peripheral coldness, venous insufficiency, and deep vein thrombosis (n = 2 [0.2%] each). One patient experienced Raynaud’s phenomenon (grade 1; considered probably not treatment related), occurring in year 1 in a BP CML patient with prior imatinib treatment. Another patient experienced PAOD (serious and grade 2; considered unrelated to treatment), occurring in year 1 in a CP CML patient with prior imatinib and nilotinib exposure. Incidences of newly occurring vascular TEAEs were low in each treatment year (Fig. 1).

Serious vascular TEAEs occurred in 4.2% (n = 34; grade ≥3, 3.1% [n = 25]) of bosutinib-treated patients overall, most commonly CAD (0.9% [n = 7]) and acute myocardial infarction (0.6% [n = 5]; Supporting Information Table IV). These events were more common in relapsed/refractory (any grade, 5.1% [n = 29]; grade ≥3, 3.9% [n = 22]) versus newly diagnosed (any grade, 2.0% [n = 5]; grade ≥3, 1.2% [n = 3]) patients. There were no statistically significant differences in the incidence or exposure-adjusted rate of serious vascular TEAEs between first-line bosutinib (2.0% and 0.006, respectively) and imatinib (1.6% and 0.005) in the phase 3 study.
Discontinuations due to vascular TEAEs were rare, with 5 (0.9%; CAD, n = 2; myocardial infarction, n = 2; and cerebral infarction, n = 1) relapsed/refractory patients and only 1 (0.4%; cerebral hemorrhage) newly diagnosed patient discontinuing bosutinib because of vascular events; no imatinib-treated patient discontinued treatment because of a vascular TEAE (Tables II and III). Except for discontinuations due to CAD (1 each in years 2 and 3), all occurred in year 1 (Supporting Information Table IV).

Nine deaths from vascular TEAEs were reported with bosutinib, all in second-line or later setting (Supporting Information Table VI). Five deaths were due to cerebrovascular events (cerebral hemorrhage, cerebral infarction, cerebrovascular accident, intraventricular hemorrhage, and subarachnoid hemorrhage; n = 1 each), all of which occurred in patients with advanced disease (Ph+ ALL, n = 2; AP CML, n = 1; BP CML, n = 1; myeloid BP CML, n = 1). Four patients died as a result of cardiovascular events (myocardial infarction, n = 2; acute myocardial infarction, n = 1; coronary artery disease, n = 1), two of whom had AP CML. The median (range) age was lower among patients who died as a result of cerebrovascular events versus cardiovascular events (42 [24–74] vs. 73 [62–77] years). Only 1 of these deaths (due to myocardial infarction in a patient aged 62 years with AP CML and no reported medical history of cardiac or vascular disease) was considered probably related to treatment. In the first-line setting, one death from a vascular TEAE was reported with imatinib (CNS hemorrhage; considered not treatment related); no deaths due to vascular TEAEs occurred with first-line bosutinib.

**Hypertension-related events**

Hypertension-related TEAEs occurred in 7.8% (grade 3, 2.2%; no grade 4/5) of bosutinib-treated patients overall with similar incidences across treatment lines (see Supporting Information Table III for incidences of individual events). In the first-line setting, there were no significant differences in the incidence of hypertension-related TEAEs with bosutinib (7.7%) and imatinib (5.6%).

Among 64 bosutinib-treated patients who experienced hypertension, 21 (32.8%) had a history of hypertension. Most (89.2%) of the 195 patients with a history of hypertension did not experience a new event of hypertension during bosutinib treatment and no patient discontinued because of hypertension. Of 90 bosutinib-treated patients receiving antihypertensive therapy at baseline, 77 continued the same antihypertensive therapy after starting study treatment and 46 required a new antihypertensive medication (Supporting Information Table VII).

**Non-cardiovascular cardiac events**

Across studies, 9.5% (any grade; grade ≥3, 3.9%) of all 818 bosutinib-treated patients reported cardiac TEAEs, most commonly arrhythmias (6.1%; grade ≥3, 1.6%) and heart failure (3.3%; grade ≥3, 2.2%). Overall incidence and exposure-adjusted event rates were higher in the second-line or later setting versus first-line setting (10.4% and 0.050 vs. 7.7% and 0.024; Table I and Supporting Information Table III). In the first-line setting, there were no significant differences in overall cardiac TEAE incidence (any grade or grade ≥3) between bosutinib and imatinib (7.7% vs. 5.6%; grade ≥3, 2.4% vs. 0.4%) or in exposure-
adjusted incidence rates (Table I). The only cardiac HLGT with a significantly higher 
incidence with bosutinib versus imatinib was Pericardial disorders (analyzed separately; \( n = 6 \) [2.4%] vs. \( n = 0 \), respectively, \( P = 0.015 \)). Five of these patients experienced pericardial 
effusion (2 were grade ≥3) with a median (range) time to onset of 900 (434–1,402) days. Of 
these five patients, one was also diagnosed with pericarditis, one also experienced 
pericardial disease, and four had a medical history of hypertension. A sixth patient 
experienced pericarditis without any other pericardial disorders (Supporting Information 
Table III). Eight (1.0%) bosutinib-treated patients discontinued treatment because of a 
pericardial disorder.

Individual cardiac TEAEs, whether assessed by HLGT or PT, were infrequent with 
bosutinib, overall and per treatment year (Fig. 1). The most common cardiac HLGT was 
Cardiac arrhythmias (any grade, 6.1%; grade ≥3, 1.6%; Table I); among these, only atrial 
fibrillation (2.0%; 0.7%) and tachycardia (1.3%; 0.1%) occurred in >1% of patients 
(Supporting Information Table III). Heart failure (HLGT) occurred with similar frequency 
with first-line bosutinib (0.8%; grade ≥3, 0.8%) and imatinib (0.8%; none grade ≥3) but 
more frequently with bosutinib in the salvage setting (any grade, 4.4%). Overall, incidence 
in bosutinib-treated patients was low (any grade, 3.3%; grade ≥3, 2.2%). The standardized 
Medical Dictionary for Regulatory Activities (MedDRA) query Torsade de pointes/QT 
prolongation (narrow cluster) was reported in 1.5% (\( n = 12 \) [3 grade 3; no grade 4/5]) of all 
bosutinib-treated patients and was less frequently reported in the phase 1/2 study compared 
with the phase 3 study (any grade, 0.9% vs. 2.8%). However, there was no difference 
between bosutinib (2.8% \([n = 7; 2 \text{ grade } 3; \text{ no grade } 4/5]) \) and imatinib (3.2% \([n = 8; \text{ none } \text{ grade } \geq 3]) \) in the phase 3 study. The AE Torsades de pointes was not reported in any patient.

Serious cardiac TEAEs occurred in 3.3% (\( n = 27 \)) of bosutinib-treated patients (grade ≥3, 
2.6% \([n = 21]\) each) (Supporting Information Table IV). The incidence of serious cardiac TEAEs was 
higher with second-line or later versus first-line bosutinib (any grade, 4.0% vs. 1.6%; grade 
≥3, 3.0% vs. 1.6%). There were no significant differences between first-line bosutinib and 
imatinib, overall or for individual PTs. The exposure-adjusted serious cardiac TEAE rate 
(any grade) was 0.019 patients with events/patient-year with second-line or later bosutinib. 
There was no significant difference with first-line bosutinib versus imatinib (0.005 vs. 0.002 
patients with events/patient-year).

Eight patients (1.0%) discontinued bosutinib because of cardiac TEAEs, 5 (0.9%) in the 
phase 1/2 study and 3 (1.2%) in phase 3 study (Table II and Supporting Information Table 
V); no imatinib-treated patient discontinued because of cardiac TEAEs. In the phase 1/2 
study, three deaths were reported with cardiac TEAEs as the reason (cardiac failure \([n = 1]\) 
and congestive cardiac failure \([n = 2]\), none of which were considered treatment related) 
(Supporting Information Table VI). In the phase 3 study, two patients died as a result of 
cardiac TEAEs (congestive cardiac failure considered unrelated to treatment and sudden 
death of unknown cause), both in the bosutinib arm.

A total of 681 patients (phase 1/2: \( n = 326 \); phase 3: bosutinib, \( n = 187 \) and imatinib, \( n = 168 \) ) had baseline and postbaseline ECHO/MUGA assessments or were still on treatment.
and did not have a clinically indicated on-treatment LVEF assessment; baseline assessments were not available for 14 additional patients with grade ≥1 LVEF (13 bosutinib-treated and 1 imatinib-treated). Of the 326 bosutinib-treated patients in the second-line or later setting, 43 (13.2%) had decreased LVEF from baseline and 46 (14.1%) had improved LVEF on treatment; four patients had worsening to grade ≥2 LVEF (Supporting Information Table VIII; see Supporting Information Fig. 1A for maximum changes from baseline). In the first-line setting, decreases from baseline LVEF were less common with bosutinib versus imatinib (n = 5 [2.7%] vs. n = 25 [14.9%]) and a similar proportion of patients had improved LVEF (n = 14 [7.5%] vs. n = 12 [7.1%]); none of the 187 bosutinib-treated patients and 1 of 168 imatinib-treated patients had a shift to grade ≥2. Twelve of 121 bosutinib-treated patients with on-treatment grade ≥1 LVEF experienced heart failure (congestive cardiac failure, cardiac failure, chronic cardiac failure, or cardiorenal syndrome), all in the phase 1/2 study. No newly diagnosed bosutinib-treated patients and 1 imatinib-treated patient with grade ≥1 LVEF (bosutinib, n = 8; imatinib, n = 38) had heart failure.

All but 10 patients had baseline and postbaseline QTcF assessments (assessed via the central laboratory; phase 1/2: n = 564; phase 3: bosutinib, n = 247 and imatinib, n = 248). The proportion of patients with increases from baseline in QTcF interval was similar for relapsed/refractory patients (n = 46 [8.2%]) and newly diagnosed patients receiving either bosutinib (n = 15 [6.1%]) or imatinib (n = 19 [7.7%]); few patients in either study had shifts to grade ≥2 (phase 1/2: n = 11; phase 3: bosutinib, n = 3 and imatinib, n = 4) (Supporting Information Table IX; see Supporting Information Fig. 1B for maximum changes from baseline). Although some patients experienced grade ≥1 QTc interval prolongation (QTcF >450 ms or ≥60 ms increase over baseline; phase 1/2: n = 59; phase 3: bosutinib, n = 16 and imatinib, n = 19), incidence of arrhythmia-related TEAEs (any grade) in these patients was low. Atrial fibrillation (n = 4 [3 treatment related]) and bradycardia (n = 4 [1 treatment related]) occurred in more than 1 of these patients, all in the second-line or later setting; no arrhythmia-related TEAEs were reported in more than 1 patient with QTc prolongation in either arm of the phase 3 study, and no cases of Torsades de pointes were reported (see Supporting Information text for details).

TEAE characteristics and management

Among bosutinib-treated patients with vascular (n = 56) or cardiac (n = 78) TEAEs (pooled data), 46.4% and 59.0%, respectively, experienced grade ≥2 events. The median (range) time to first event (any grade) was 318 (1–2,452, vascular) and 89 (1–2,229, cardiac) days; the cumulative median (range) duration of events was 10 (1–359, vascular) and 11 (1–1,848, cardiac) days. These events resolved in 42.9% and 61.5% of patients, respectively (Table II). In the phase 3 study, vascular and cardiac TEAEs were experienced by 12 and 19 bosutinib-treated patients, respectively; these events resolved in 50.0% and 57.9% of patients. Among imatinib-treated patients with vascular (n = 9) or cardiac (n = 14) TEAEs in the phase 3 study, these events resolved in 77.8% and 64.3% of patients (Table II).

In bosutinib-treated patients with events, vascular and cardiac TEAEs were mostly managed with concomitant medication(s) (n = 22 [39.3%] and n = 34 [43.6%], respectively); dose interruptions or reductions for vascular (n = 10 [17.9%] and n = 2 [3.6%], respectively) or
cardiac ($n = 16$ [20.5%], $n = 6$ [7.7%]) TEAEs were less common. In the first-line setting, dose interruptions or reductions for vascular or cardiac TEAEs were generally similar with bosutinib and imatinib. All ($n = 9/9$) patients with bosutinib dose interruptions due to vascular TEAEs and most ($n = 12/14$) patients with bosutinib dose interruptions due to cardiac TEAEs who were then readministered the study drug responded successfully (Table II).

**Prognostic factors for vascular or cardiac events**

Prognostic risk factors for vascular TEAEs (all $P \leq 0.046$) were age $\geq 65$ years and a history of diabetes with first-line bosutinib; Eastern Cooperative Oncology Group performance status (ECOG PS) $>0$ and a history of vascular disorders in the second-line or later setting (Table III). The only prognostic risk factor for cardiac TEAEs with first-line bosutinib was age $\geq 65$ years ($P < 0.001$) whereas age $\geq 65$ years, ECOG PS $>0$, history of cardiac disorders, and history of hyperlipidemia/increased cholesterol (all $P \leq 0.028$) were prognostic in the second-line or later setting (Table III). Notably, treatment (bosutinib vs. imatinib) was not a prognostic risk factor for either vascular or cardiac TEAEs in the first-line setting.

**Discussion**

The results of this analysis suggest that the vascular and cardiac toxicity profile of bosutinib is distinct relative to other TKIs. The incidence of vascular (including cerebrovascular, cardiovascular, and peripheral vascular) and cardiac TEAEs during long-term bosutinib therapy is relatively low in the first-line (phase 3 study) and second-/third-/fourth-line (phase 1/2 study) settings. In addition, no significant differences in overall incidence were observed between bosutinib and imatinib in the first-line setting. Though infrequent, pericardial effusion was the only individual cardiac TEAE to occur at a nominally significantly higher incidence with bosutinib versus imatinib ($P = 0.030$). Importantly, peripheral vascular events were uncommon, with venous thromboembolic events occurring in six bosutinib-treated patients (five in the second-line or later setting) and only 1 case of PAOD reported among 818 bosutinib-treated patients. Other events, such as heart failure, prolonged QTc interval, and arrhythmias were also infrequent.

Most patients who experienced vascular and cardiac events initially did so during the first year of bosutinib treatment; however, very few patients discontinued treatment because of these events. Over the 4-year follow-up period, overall incidences of newly occurring events did not increase in either study and substantially decreased in the first-line setting. Importantly, patients with clinically significant or uncontrolled cardiac disease, prolonged QTc, or uncorrected hypomagnesemia or hypokalemia present at baseline were excluded from the studies; these results then cannot be extrapolated to patients with such conditions for whom no adequate information exists. Furthermore, patients with a high risk of vascular or cardiac events at baseline experience events earlier compared with patients at a lower risk. Therefore, the population at risk for experiencing a first event shifts over time to lower risk patients. Because vascular and cardiac events may still accumulate over time, and since follow-up for events after treatment discontinuation is limited, additional investigation
longer than the current ≥48 months will be necessary to fully understand the risks associated with longer-term bosutinib treatment.

It should be noted that the median age of the overall patient population in both studies (53 years in the phase 1/2 study; 48 and 47 years for first-line bosutinib and imatinib, respectively, in the phase 3 study) was lower than the average CML patient at diagnosis [17,21]. Although the incidences of vascular and cardiac events were higher with second-line or later bosutinib compared with first-line treatment, this may be partly due to the higher median age of the phase 1/2 study population. However, a recent meta-analysis of major arterial events observed with TKIs across 29 studies demonstrated a lower pooled rate of arterial events with first-line TKIs versus first-, second, and third-line TKI therapy (2% vs. 5%) [26]. This suggests factors other than older age may contribute to the higher incidence of TEAEs observed in relapsed/refractory patients.

The incidence of vascular and cardiac events with bosutinib has been reported in part in the context of the overall results for the second-line or later setting [17,18,23] and for first-line bosutinib and imatinib [19,20,24]. However, those previous reports included a shorter duration of follow-up, were not specifically focused on vascular and cardiac events, and included a considerably smaller number of specific terms being investigated compared with the present analysis [17–20,23,24]. In some instances, previous reports presented only treatment-related vascular or cardiac events [18,19]. Results of the present analysis represent a comprehensive assessment of vascular and cardiac events with bosutinib.

Comparisons with results of analyses of other TKIs are also complicated by the above mentioned methodology differences. However, a 6-year follow-up of a study of newly diagnosed patients (ENESTnd trial) demonstrated a dose-dependent increased risk of vascular events with nilotinib versus imatinib, with 28/279 (10%) patients treated with nilotinib 300 mg twice per day, 44/277 (16%) patients treated with nilotinib 400 mg twice per day, and 7/280 (3%) patients treated with imatinib 400 mg once per day experiencing vascular AEs [27,28]. In a comprehensive assessment of ponatinib after a median follow-up of 15 months, a 12% rate of serious arterial thrombotic events, including cardiovascular, cerebrovascular, and peripheral vascular events, was noted in heavily pretreated (≥2 TKIs) patients [5]. In our analysis, 5.1% (grade ≥3, 3.9%) of pretreated bosutinib patients had serious vascular events; the incidence of serious vascular events in the first-line setting was lower (2.0%; grade ≥3, 1.2%) and similar to imatinib (1.6%; grade ≥3, 1.2%).

Patients with known risk factors for cardiac and vascular events tend to have the highest incidence of cardiac and vascular complications [3]. For example, in a phase 2 ponatinib study, 55% of patients with arterial thrombotic events had a documented ischemic condition, and 95% had ≥1 risk factor at baseline [5]. It is crucial to identify such risk factors, particularly those established through long-term follow-up. We therefore examined various patient characteristics and identified several factors associated with a risk of cardiac and vascular events. However, no adjustments were made for multiple testing, which increases the likelihood of false-positive results. Therefore, caution is advised when interpreting results.
In the present analysis, ECOG PS >0 and history of vascular disorders were significant risk factors for vascular TEAEs in the second-line or later setting, whereas age ≥65 years and a history of diabetes were significant risk factors in the first-line setting. Significant risk factors for cardiac TEAEs in the second-line or later setting included ECOG PS >0 and a history of increased lipids/hypercholesterolemia or cardiac disorders; age ≥65 years was a significant risk factor for these events in both the first- and second-line or later settings.

While epidemiological studies have demonstrated the association between diabetes and vascular dysfunction, controlling hyperglycemia alone has not been entirely successful at reducing the incidence of vascular events in patients [29]. In contrast, management of hyperlipidemia/ hypercholesterolemia has been shown to substantially decrease mortality and the frequency of cardiac events in high-risk patients [30,31]. Patients with risk factors should be monitored carefully during therapy. Although the correct intervention(s) to minimize risk in such patients remains to be prospectively investigated, aggressive management of modifiable risk factors, including hypertension, diabetes, and hyperlipidemia, should be standard of care prior to initiation of TKIs. Conditions that can be corrected, such as hypomagnesemia and hypokalemia, should be addressed prior to starting bosutinib therapy.

Both retrospective [5,12,32–35] and prospective [13] studies have noted a relationship between other TKIs and arterial events. In an analysis of three separate trials (IRIS, TOPS, and ENESTnd), nilotinib was associated with an increased risk of PAOD compared with imatinib [12]. In a phase III trial (EPIC) of first-line ponatinib versus imatinib in CP CML patients, 7% of ponatinib-treated patients experienced serious arterial events compared with 1% for imatinib [36]. In our analysis, PAOD was reported in only one patient who had received prior imatinib and nilotinib; the overall incidence of serious vascular events was low and similar with first-line bosutinib and imatinib. In a recent meta-analysis of arterial thrombotic events in CML patients treated with TKIs, bosutinib demonstrated a rate of PAOD of just 0.1 per 100 patient-years (the same as imatinib) compared with 1.3 and 3.9 per 100 patient-years for nilotinib and ponatinib, respectively [26]. An analysis of data from a large, population-based Swedish cohort registry (N = 896) found that, relative to imatinib, treatment of CML patients with nilotinib or dasatinib was associated with an increased risk of arterial thromboembolic events (incident rate ratios [95% CIs]: 1.92 [0.71–5.18] and 2.40 [1.12–5.12], respectively) and myocardial infarction (incident rate ratios [95% CIs]: 2.98 [1.05–8.49] and 2.89 [1.20–7.00], respectively) [37].

Certain cardiac toxicities have been reported previously in patients treated with TKIs [38]. In particular, nilotinib and dasatinib have been associated with QT interval prolongation and sudden death [11,39–41]. In our analysis, based on the standardized MedDRA query Torsade de pointes/QT prolongation, such events occurred in only 1.5% of all bosutinib-treated patients (there were no cases of Torsades de pointes in this analysis). These rates may be an underestimation, however, because ECG analyses were not prospectively planned to assess all potential cardiac events.

A possible association between TKIs and heart failure was identified during early studies of imatinib [42]. Further investigation showed a similar incidence of heart failure for imatinib-treated patients (1.7%) and the general population [43]. In the current analysis, heart failure
incidence was similar for first-line bosutinib and imatinib (0.8% vs. 0.8%) and low with bosutinib overall (3.3%).

One reason for the distinct cardiac and vascular toxicity profile of bosutinib versus other TKIs may relate to divergent specificities for BCR-ABL1 versus other important kinases. Bosutinib is more selective than other TKIs associated with off-target effects \[44,45\]. In contrast to all other TKIs, bosutinib exhibits minimal inhibitory activity against c-Kit and platelet-derived growth factor receptor [44–47]. Vascular dysfunction associated with multikinase TKIs, such as ponatinib, is thought to relate to strong inhibition of vascular endothelial growth factor receptor (VEGFR) signaling, a pathway affected less by bosutinib than other TKIs [3,44,48]. Notably, hypertension, commonly observed with small-molecule TKIs that inhibit VEGFR signaling pathways [49], was observed in 300/449 (67%) ponatinib-treated patients [50]. In the present analysis, hypertension incidence was relatively low (7.8% overall). Notwithstanding these associations, the precise mechanisms of cardiovascular toxicity of TKIs remain to be fully elucidated [51,52].

This comprehensive analysis suggests that, relative to other new-generation TKIs, vascular, and cardiac TEAE incidences in leukemia patients receiving bosutinib are generally low, even after long-term treatment, and not significantly different from those observed in imatinib-treated patients. Likewise, dose adjustments and discontinuations due to these events were rare; therefore, bosutinib could be considered among the treatment options for patients with cardiac or vascular comorbidities. However, direct comparisons with results from other studies are limited by differing definitions used to quantitate incidence of cardiac and vascular events [27]. Regardless of TKI choice, all patients should be evaluated for cardiac and vascular risk factors, with those considered to be at increased risk possibly benefiting from the involvement of cardiologists. Close monitoring, particularly in high-risk patients, and proactive management should be standard of care before starting therapy.

Acknowledgments

The authors would like to thank all of the patients who participated in this study and their families, as well as the global network of investigators, research nurses, study coordinators, and operations staff. Medical writing support was provided by Tiffany Brake, PhD, Johna Van Stelten, PhD, and Cynthia Gobbel, PhD, of Complete Healthcare Communications, LLC, and was funded by Pfizer Inc.

Disclosure: This study was sponsored by Pfizer Inc. JC has received research support from Ariad, Bristol-Myers Squibb, Novartis, Pfizer, and Teva and has been a consultant for Ariad, Bristol-Myers Squibb, Novartis, and Pfizer. JC’s participation in these trials was supported in part by the MD Anderson Cancer Center Support Grants CA016672 and CML P01 CA049639 from the National Cancer Institute. HJK has received honoraria for participation in advisory boards from Pfizer and has received research support through his institution from Pfizer. HK has received research support through his institution from Pfizer, Novartis, Bristol-Myers Squibb, Amgen, and Ariad. THB has received research support through his institution from Novartis, Pfizer, and Bristol-Myers Squibb; has been a consultant for and received honoraria and reimbursement for travel, accommodations, or expenses from Ariad, Bristol-Myers Squibb, Novartis, and Pfizer; and holds a patent on the role of hypusination inhibitors in combination with imatinib. MM has received research funding from Novartis, has been a consultant/advisor to and received honoraria and reimbursement for travel, accommodations, or expenses from Bristol-Myers Squibb, Novartis, Pfizer, and Ariad. JHL has received research funding from, has been a consultant/advisor to, and has received honoraria and reimbursement for travel, accommodations, or expenses from Bristol-Myers Squibb, Novartis, Pfizer, and Ariad. JBD has received payment for a consulting or advisory role from Celgene and Roche. CGP has been a consultant/advisor to Bristol-Myers Squibb and Pfizer and has received research funding, honoraria, and reimbursement for travel, accommodations, or expenses from Pfizer. DF, KDF, JMA, and MS are employees of and own stock in Pfizer. EM was an employee of Pfizer when the manuscript was written.

Am J Hematol. Author manuscript; available in PMC 2017 August 08.
References


### B) Phase 1/2 (second line or later; BOS only)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral hemorrhage</td>
<td>0.4</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>0.5</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>0.7</td>
</tr>
<tr>
<td>Angina unstable</td>
<td>0.7</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.4</td>
</tr>
<tr>
<td>Coronary artery stenosis</td>
<td>0.2</td>
</tr>
<tr>
<td>Coronary artery arteriosclerosis</td>
<td>0.2</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0.7</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.5</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>0.2</td>
</tr>
<tr>
<td>Aortic arteriosclerosis</td>
<td>0.2</td>
</tr>
<tr>
<td>Peripheral coldness</td>
<td>0</td>
</tr>
<tr>
<td>Venous insufficiency</td>
<td>0.2</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0.2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.9</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1.6</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0.7</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>0.4</td>
</tr>
<tr>
<td>Right bundle branch block</td>
<td>0.6</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0.4</td>
</tr>
<tr>
<td>Complete atrioventricular block</td>
<td>0.2</td>
</tr>
<tr>
<td>Supraventricular extrasystoles</td>
<td>0.2</td>
</tr>
<tr>
<td>Ventricular extrasystoles</td>
<td>0.4</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>0.7</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>0.7</td>
</tr>
<tr>
<td>Chronic cardiac failure</td>
<td>0.7</td>
</tr>
<tr>
<td>ECG QT prolonged</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Year 1 (n=570)  Year 2 (n=273)  Year 3 (n=208)  Year 4 (n=179)*
Figure 1.
Incidence of treatment-emergent adverse events occurring in year 1 and newly occurring in years 2, 3, and 4 in both studies overall (A), in the phase 1/2 study (B) and the phase 3 study (C). BOS, bosutinib; EAIR, exposure-adjusted incidence rate; ECG, electrocardiogram; IM, imatinib; TEAE, treatment-emergent adverse event. Newly occurring TEAEs were defined as those Medical Dictionary for Regulatory Activities preferred terms not experienced by the same patient previously for patients on treatment during a given year. Denominators are the number of patients on treatment at the start of the specific years (1 year = 365.25 days). TEAEs occurring in ≥2 bosutinib-treated patients overall (pooled data from both studies) or
with a between-arm difference of ≥2 patients in the phase 3 study are presented. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
<table>
<thead>
<tr>
<th></th>
<th>Phase 1/2 (second line or later)</th>
<th>Phase 3 (first line)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bosutinib (n = 570)</td>
<td>Bosutinib (n = 248)</td>
</tr>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td><strong>Exposure-adjusted rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular TEAEs</td>
<td>0.037</td>
<td>0.022</td>
</tr>
<tr>
<td>Cardiac TEAEs</td>
<td>0.080</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Incidence of TEAEs, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any vascular TEAE</td>
<td>44 (7.7)</td>
<td>27 (4.7)</td>
</tr>
<tr>
<td>Any cardiac TEAE</td>
<td>59 (10.4)</td>
<td>26 (4.6)</td>
</tr>
<tr>
<td><strong>Cerebrovascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS vascular disorders</td>
<td>13 (2.3)</td>
<td>9 (1.6)</td>
</tr>
<tr>
<td><strong>Cardiovascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disorders</td>
<td>24 (4.2)</td>
<td>17 (3.0)</td>
</tr>
<tr>
<td><strong>Peripheral vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>12 (2.1)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Arteriosclerosis, stenosis, vascular insufficiency, and necrosis</td>
<td>8 (1.4)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Embolism and thrombosis</td>
<td>5 (0.9)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Vascular disorders NEC</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hypertension-related events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac and vascular investigations (excluding enzyme tests)</td>
<td>4 (0.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular hypertensive disorders</td>
<td>42 (7.4)</td>
<td>14 (2.5)</td>
</tr>
<tr>
<td><strong>Cardiac assessment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>56 (9.8)</td>
<td>26 (4.6)</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>39 (6.8)</td>
<td>12 (2.1)</td>
</tr>
</tbody>
</table>

*TABLE I*

Exposure-Adjusted Incidence Rates and Treatment-Emergent Vascular and Cardiac Adverse Events

Am J Hematol. Author manuscript; available in PMC 2017 August 08.
<table>
<thead>
<tr>
<th>Event</th>
<th>Phase 1/2 (second line or later)</th>
<th>Phase 3 (first line)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bosutinib (n = 570)</td>
<td>Bosutinib (n = 248)</td>
</tr>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Heart failure</td>
<td>25 (4.4)</td>
<td>16 (2.8)</td>
</tr>
<tr>
<td>General disorders and administration site conditions [^d^]</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatal outcomes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Investigations [^d^]</td>
<td>4 (0.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pericardial disorders [^c^]</td>
<td>24 (4.2)</td>
<td>10 (1.8)</td>
</tr>
</tbody>
</table>

CNS, central nervous system; NEC, not elsewhere classified; TEAE, treatment-emergent adverse event.

\[^a^\] System Organ Class (SOC) and high-level group terms (HLGTs) from the Medical Dictionary for Regulatory Activities are presented. See Supporting Information Table I for a list of MedDRA terms included in each analysis and Supporting Information Table III for incidences of preferred terms.

\[^b^\] Computed as the number of patients with cardiac or vascular TEAEs/total patient-year (total patient-year = sum of total time to first TEAE for all patients with TEAEs plus total time on treatment for patients without TEAEs).

\[^c^\] Totals for the number of patients at a higher level are not necessarily the sum of those at the lower levels because a patient may report ≥2 adverse events within the higher level category.

\[^d^\] Incidences at the SOC level are not reported if only 1 HLGT is included.

\[^e^\] Electrocardiogram QT interval prolonged was the only preferred term experienced with the exception of 1 bosutinib-treated patient in the phase 3 study who experienced decreased ejection fraction.

\[^f^\] \(P = 0.015\) vs. imatinib (any grade) for this high-level group term.
## TABLE II

Characteristics and Management of Cardiac and Vascular Adverse Events

<table>
<thead>
<tr>
<th>Phase 1/2</th>
<th></th>
<th>Phase 3</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(second line or later)</td>
<td>(first line)</td>
<td></td>
<td>(N = 818)</td>
<td></td>
</tr>
<tr>
<td>Bosutinib (n = 570)</td>
<td>Bosutinib (n = 248)</td>
<td>Imatinib (n = 251)</td>
<td>Pooled Bosutinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac</td>
<td>Vascular</td>
<td>Cardiac</td>
<td>Vascular</td>
</tr>
<tr>
<td></td>
<td>59 (10.4)</td>
<td>44 (7.7)</td>
<td>19 (7.7)</td>
<td>12 (4.8)</td>
</tr>
<tr>
<td>Patients with events, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious AE</td>
<td>23 (4.0)</td>
<td>29 (5.1)</td>
<td>4 (1.6)</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Events leading to withdrawal</td>
<td>5 (0.9)</td>
<td>5 (0.9)</td>
<td>3 (1.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>16 (2.8)</td>
<td>5 (0.9)</td>
<td>13 (5.2)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Median (range) events per patient, n</td>
<td>1 (1–12)</td>
<td>1 (1–12)</td>
<td>1 (1–4)</td>
<td>1 (1–4)</td>
</tr>
<tr>
<td>Maximum toxicity grade, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15 (2.6)</td>
<td>7 (1.2)</td>
<td>12 (4.8)</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>2</td>
<td>18 (3.2)</td>
<td>10 (1.8)</td>
<td>1 (0.4)</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>3</td>
<td>17 (3.0)</td>
<td>11 (1.9)</td>
<td>4 (1.6)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>4</td>
<td>6 (1.1)</td>
<td>7 (1.2)</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>5</td>
<td>3 (0.5)</td>
<td>9 (1.6)</td>
<td>2 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Outcome, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3 (5.1)</td>
<td>9 (20.5)</td>
<td>2 (10.5)</td>
<td>0</td>
</tr>
<tr>
<td>Persisted</td>
<td>19 (32.2)</td>
<td>17 (38.6)</td>
<td>6 (31.6)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Resolved</td>
<td>37 (62.7)</td>
<td>18 (40.9)</td>
<td>11 (57.9)</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td>Treatment change, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporarily stopped</td>
<td>12 (20.3)</td>
<td>6 (13.6)</td>
<td>4 (21.1)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>No rechallenge/discontinued study drug</td>
<td>2/12 (16.7)</td>
<td>0</td>
<td>0</td>
<td>1/4 (25.0)</td>
</tr>
<tr>
<td>Rechallenged</td>
<td>10/12 (83.3)</td>
<td>66 (100)</td>
<td>4/4 (100)</td>
<td>3/4 (75.0)</td>
</tr>
<tr>
<td>Successful</td>
<td>9/10 (90.0)</td>
<td>66 (100)</td>
<td>3/4 (75)</td>
<td>3/3 (100)</td>
</tr>
<tr>
<td>Subsequent/persistent AE</td>
<td>5/9 (55.6)</td>
<td>2/6 (33.3)</td>
<td>3/3 (100)</td>
<td>1/3 (33.3)</td>
</tr>
<tr>
<td>No subsequent AE</td>
<td>4/9 (44.4)</td>
<td>4/6 (66.7)</td>
<td>0</td>
<td>2/3 (66.7)</td>
</tr>
<tr>
<td>Dose reduced</td>
<td>3 (5.1)</td>
<td>1 (2.3)</td>
<td>3 (15.8)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Patients with events treated by concomitant medications, n (%)</td>
<td>28 (47.5)</td>
<td>15 (34.1)</td>
<td>6 (31.6)</td>
<td>7 (38.3)</td>
</tr>
<tr>
<td></td>
<td>Phase 1/2 (second line or later)</td>
<td>Phase 3 (first line)</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bosutinib (n = 570)</td>
<td>Bosutinib (n = 248)</td>
<td>Pooled Bosutinib (N = 818)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac</td>
<td>Vascular</td>
<td>Cardiac</td>
<td>Vascular</td>
</tr>
<tr>
<td>Median (range) time to first event</td>
<td>91 (1–2,229)</td>
<td>327 (8–2,452)</td>
<td>85 (1–1,630)</td>
<td>245 (1–1,814)</td>
</tr>
<tr>
<td>Median (range) cumulative duration of events$^a$</td>
<td>8 (1–706)</td>
<td>9 (1–318)</td>
<td>23 (1–1,848)</td>
<td>106 (1–359)</td>
</tr>
</tbody>
</table>

$^a$AE, adverse event.

$^a$Treatment-related AEs were followed until resolution (grade ≤1) or return to baseline.

$^b$Denominator is the number of patients with an event (cardiac or vascular).

$^c$Outcome categories are mutually exclusive; patients were classified based on the worst event outcome.

$^d$Successful rechallenge includes patients who did not experience a subsequent AE of the same type or who experienced an AE of the same type that did not lead to treatment discontinuation.

$^e$Cumulative duration of AE was calculated as the sum of (stop date-start date) +1 for non-missing/non-partial dates, adjusting for overlapping dates of different AEs. Every change in toxicity grade is counted as a different AE.
### TABLE III
Logistic Regression Analysis of Risk Factors for Cardiac and Vascular Adverse Events

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Phase 1/2 (second line or later)</th>
<th>Phase 3 (first line)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac</td>
<td>Vascular</td>
</tr>
<tr>
<td></td>
<td>Estimate</td>
<td>P value</td>
</tr>
<tr>
<td>Age (≥65 y vs. &lt;65)</td>
<td>0.904</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>(1.33–4.59)</td>
<td></td>
</tr>
<tr>
<td>Sex (male vs. female)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ECOG PS (&gt;0 vs. 0)</td>
<td>1.171</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(1.76–5.90)</td>
<td></td>
</tr>
<tr>
<td>History of diabetes (no vs. yes)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of hypertension (no vs. yes)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of cardiac disorders (no vs. yes)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-1.166</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>(0.16–0.62)</td>
<td></td>
</tr>
<tr>
<td>History of vascular disorders (no vs. yes)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of increased lipids/cholesterol (no vs. yes)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>-0.863</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>(0.20–0.91)</td>
<td></td>
</tr>
<tr>
<td>Prior dasatinib (no vs. yes)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior nilotinib (no vs. yes)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IM-intolerant vs. IM-resistant</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Treatment (IM vs. BOS)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BOS, bosutinib; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HLGT, high-level group term; HLT, high-level term; IM, imatinib; N/A, not applicable; NEC, not elsewhere classified; OR, odds ratio; PT, preferred term. Dashes indicate factors that did not meet the criteria for inclusion in the final model.

<sup>a</sup> All parameters were included as covariates in the initial model, and backward selection was used to select covariates for inclusion in the final model (cutoff P value = 0.2, treatment forced into the model for the phase 3 study); maximum likelihood estimates, P values, and ORs are shown for covariates included in the final model. Positive estimates indicate better outcome for group 2 versus group 1.

<sup>b</sup> Terms used to identify events of diabetes included the HLGT Diabetes mellitus and all subordinate terms.
Terms used to identify events of hypertension were the HLGTs Vascular hypertensive disorders and Cardiac and vascular investigations (excluding enzyme tests), the HLT Vascular tests NEC (including blood pressure) and the PTs Abnormal blood pressure, Abnormal ambulatory blood pressure, Increased ambulatory blood pressure, Abnormal diastolic blood pressure, Increased diastolic blood pressure, Increased blood pressure, Abnormal systolic blood pressure, and Increased systolic blood pressure.

Terms used to identify cardiac events included the HLGTs Cardiac arrhythmias and Heart failures and all subordinate terms; the PTs Cardiac death, Sudden cardiac death, and Sudden death under the SOC General disorders and administration site conditions; and the PTs Ejection fraction decreased, Electrocardiogram QT interval abnormal, and Electrocardiogram QT prolonged, and Long QT syndrome congenital under the SOC in Investigations.

Terms used to identify vascular events were the HLGTs Coronary artery disorders, Arteriosclerosis, stenosis, vascular insufficiency and necrosis, Embolism and thrombosis, Arterial therapeutic procedures (excluding aortic); the HLTs Central nervous system hemorrhages and cerebrovascular accidents, Central nervous system vascular disorders NEC, Non-site specific vascular disorders NEC, Peripheral vascular disorders NEC (excluding the PTs Flushing and Hot flash), Transient cerebrovascular events, Vascular imaging procedures NEC, and Vascular therapeutic procedures NEC and all subordinate terms.

The term used to identify hyperlipidemia/increased cholesterol was the PT Increased blood cholesterol under the HLGT Lipid metabolism disorders.