Original Study

Effects of Bosutinib Treatment on Renal Function in Patients With Philadelphia Chromosome-Positive Leukemias

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Abstract

We evaluated the incidence of renal adverse events and estimated glomerular filtration rate in patients with Philadelphia chromosome-positive leukemias receiving first-line bosutinib (n = 248) or imatinib (n = 251), or second-line or later bosutinib (n = 570). Results show that long-term bosutinib treatment is associated with an apparently reversible decline in renal function with frequency and characteristics similar to those observed with long-term imatinib.

Background: The purpose of the study was to assess renal function in patients with Philadelphia chromosome-positive leukemias receiving bosutinib or imatinib. **Patients and Methods:** Patients received first-line bosutinib (n = 248) or imatinib (n = 251; phase III trial), or second-line or later bosutinib (phase I/II trial; n = 570). Adverse events (AEs) and changes from baseline in estimated glomerular filtration rate (eGFR) and serum creatinine were assessed. **Results:** Time from the last patient's first dose to data cutoff was ≥ 48 months. Renal AEs were reported in 73/570 patients (13%) receiving second-line or later bosutinib, and in 22/248 (9%) and 16/251 (6%) receiving first-line bosutinib and imatinib, respectively. eGFR in patients receiving bosutinib declined over time with more patients developing Grade ≥ 3b eGFR (< 45 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease method) with second-line or later bosutinib (139/570, 24%) compared with first-line bosutinib (26/248, 10%) and imatinib (25/251, 10%); time to Grade ≥ 3b eGFR was shortest with second-line or later bosutinib. Similar proportions of patients receiving second-line or later bosutinib (74/139, 53%), first-line bosutinib (15/26, 58%), and first-line imatinib (15/25, 60%) improved to ≥ 45 mL/min/1.73 m^2 eGFR as of the last follow-up. In a regression analysis, first-line treatment with bosutinib versus imatinib was not a significant predictor of Grade ≥ 3b eGFR. **Conclusion:** Long-term bosutinib treatment is associated with an apparently reversible decline in renal function with frequency and characteristics similar to renal decline observed with long-term imatinib treatment. Patients with risk factors for Grade ≥ 3b eGFR should be monitored closely.

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Introduction

Although generally well tolerated, tyrosine kinase inhibitors (TKIs) are associated with adverse events (AEs).[1-5] Renal toxicity has been reported during TKI treatment for Philadelphia chromosome-positive (Ph^+) leukemias[2,6-13]; however, information is mostly limited to case reports.[7-9,11-14] Because of the long-term

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nature of TKI therapy and the different kinetics observed, particularly with regard to nonhematologic toxicities, a better understanding of the renal safety profiles of TKIs is important for optimizing patient management.

Bosutinib (Bosulif; SKI-606) is an oral TKI approved in the United States for treatment of Ph^+ chronic phase (CP), accelerated phase (AP), and blast phase (BP) chronic myeloid leukemia (CML) resistant/intolerant to previous TKI therapy and in Europe for treatment of Ph^+ CML in patients previously treated with $\geq$ 1 TKI and for whom other TKIs are not considered appropriate.[2,15] Bosutinib has a manageable safety profile in patients with all phases of CML, with predominantly low-grade gastrointestinal toxicities most commonly reported.[16-21]

Only a small portion (< 4%) of bosutinib is recovered in the urine, and excretion of unchanged bosutinib is low at approximately 1%, indicating minimal renal clearance of the active drug.[22] However, bosutinib administration has been associated with a decline in estimated glomerular filtration rate (eGFR) and dose adjustments are recommended in patients with baseline and treatment-emergent renal impairment.[5] In this study, renal function was comprehensively analyzed in Ph^+ leukemia patients enrolled in 2 large clinical studies[16-18] receiving either bosutinib as first-line treatment (randomized vs. imatinib) or as second-line or later therapy after failure of $\geq$ 1 TKI. The objectives were to assess the extent and time course of renal dysfunction, to identify predictors of Grade $\geq$ 3b eGFR in bosutinib-treated patients, and to evaluate reversibility of treatment-emergent eGFR decline. Additionally, the effect of Grade $\geq$ 3b eGFR on the efficacy of bosutinib across treatment lines was evaluated.

Patients and Methods

Study Design and Patients

This retrospective analysis included data from 2 open-label, multinational studies. The first is a 2-part, phase I/II study of bosutinib (starting dose, 500 mg/d [part 2]) in patients with Ph^+ CP CML resistant/intolerant to $\geq$ 1 previous TKI (n = 403 [n = 284 second-line and n = 119 third- or fourth-line]), or AP CML (n = 79), BP CML (n = 64), or acute lymphoblastic leukemia (n = 24) after previous TKI therapy.[16] The second is a phase III study of patients with newly diagnosed Ph^+ CP CML treated with bosutinib 500 mg/d (n = 248) or imatinib 400 mg/d (n = 251).[17] Data are from unlocked trial databases with data cutoff dates of May 23, 2014 (phase I/II study) and November 21, 2013 (phase III; applied to the March 14, 2014 snapshot).

Patients were required to have adequate renal function (creatinine $\leq$ 1.5 times the upper limit of normal [ULN]); those with significant preexisting conditions were excluded.[16,17]

Renal Toxicity Assessments

Renal toxicity was assessed on the basis of treatment-emergent AEs (TEAEs) and laboratory parameters reported at each visit and for 28 days (phase III study) or 30 days (phase I/II study) after the last dose of study drug (for details, see the Supplemental Methods section of the Supplemental Material in the online version). Laboratory end points included serum creatinine and eGFR (calculated using the Modification of Diet in Renal Disease formula and graded on the basis of the Kidney Disease Improving Global Outcomes criteria).[23] Normal/high eGFR and mildly to moderately decreased eGFR encompassed Grades $\leq$ 3a ($\geq$ 45 mL/min/1.73 m^2); moderately to severely decreased eGFR included Grades $\geq$ 3b (< 45 mL/min/1.73 m^2).[24-26]

Renal Safety and Efficacy Analyses and Statistical Methods

Treatment-emergent AEs are reported descriptively according to disease stage (CP vs. advanced) for the phase I/II study and according to treatment (bosutinib vs. imatinib) for the phase III study; baseline characteristics are described in patients with and without Grade $\geq$ 3b eGFR. Changes from baseline in eGFR and serum creatinine levels are reported for the safety population (received $\geq$ 1 dose of study treatment) and for patients whose bosutinib dose was reduced (400 mg/d) or escalated (600 mg/d). The effect of dose reductions/escalations on changes from baseline in eGFR were compared with that in matched control participants who received 500 mg/d during their entire course of treatment. Matching was on the basis of age (within 10 years), baseline eGFR category (Grades 1-5), and treatment duration (within 6 months). On-treatment changes in creatinine levels were assessed in bosutinib-treated patients (combined studies) with baseline creatinine levels > ULN versus $\leq$ ULN (as specified by the local laboratory).

Baseline and on-treatment time-dependent predictors of time to Grade $\geq$ 3b eGFR were assessed using forward selection from Cox proportional hazard regression models. Forward entry criteria was $P = .20$. Two analyses were performed, one combining all bosutinib data from CP CML patients in both studies, and another from patients receiving only first-line bosutinib and imatinib. P values were not adjusted for multiple testing.

Response was assessed in patients before and after first Grade $\geq$ 3b eGFR and for patients who did not experience Grade $\geq$ 3b eGFR. Complete cytogenetic response (CCyR) and major cytogenetic response (MCyR) were determined using standard cytogenetics with $\geq$ 20 metaphases counted for postbaseline assessments. If < 20 metaphases were available postbaseline, fluorescence in situ hybridization analysis of bone marrow aspirate or peripheral blood with $\geq$ 200 cells for the presence of breakpoint cluster region-Abelson kinase 1 fusion gene was used.

Results

Patients

Demographic and baseline clinical characteristics are presented in Table 1. Of 56 bosutinib-treated patients with baseline creatinine levels > ULN, only 4 were newly diagnosed with CML. Median (range) treatment duration in the phase I/II trial was 18.1 (0.2-94.9) months for CP CML patients and 3.95 (0.03-89.2) months for advanced patients (AP CML: 10.2 [0.1-88.6], BP CML: 2.8 [0.03-55.9], acute lymphoblastic leukemia: 0.97 [0.3-89.2] months). Treatment duration was longer for second- versus third- and fourth-line CP CML patients (25.6 [0.16-94.9] months vs. 8.6 [0.23-87.7] months). In the phase III study, the median (range) duration of first-line bosutinib and imatinib treatment was 54.4 (0.03-69.1) and 49.5 (0.5-62.6) months, respectively. Time from the last patient's first dose to data cutoff was $\geq$ 48 months (both studies).

Table 1 Baseline Demographic and Clinical Characteristics in Patients According to Maximum On-Treatment eGFR Grade ≤ 3a and Grade ≥ 3b

	Phase I/II (Second-Line or Later Bosutinib; CP and Advanced)								Phase III (First-Line; CP CML)			
	CP CML (n = 403)		AP CML (n = 79)		BP CML (n = 64)		Total Adv (n = 167)		Bosutinib (n = 248)		Imatinib (n = 251)	
	Gr ≤ 3a (n = 298)	Gr ≥ 3b (n = 104)	Gr ≤ 3a (n = 61)	Gr ≥ 3b (n = 17)	Gr ≤ 3a (n = 52)	Gr ≥ 3b (n = 11)	Gr ≤ 3a (n = 130)	Gr ≥ 3b (n = 35)	Gr ≤ 3a (n = 222)	Gr ≥ 3b (n = 26)	Gr ≤ 3a (n = 225)	Gr ≥ 3b (n = 25)
Median Age (Range), y	50 (18-86)	64 (37-91)	49 (18-83)	58 (40-73)	46 (19-82)	53 (22-80)	48 (18-83)	60 (22-84)	45 (19-76)	61 (48-91)	44 (18-89)	59 (36-79)
Men	157 (53)	45 (43)	35 (57)	8 (47)	37 (71)	5 (45)	81 (62)	16 (46)	131 (59)	17 (65)	125 (56)	9 (36)
Race												
White	191 (64)	81 (78)	33 (54)	13 (77)	29 (56)	8 (73)	76 (58)	26 (74)	140 (63)	18 (69)	144 (64)	19 (76)
Asian	64 (21)	13 (13)	18 (30)	3 (18)	13 (25)	2 (18)	31 (24)	5 (14)	58 (26)	7 (27)	53 (24)	4 (16)
Black	17 (6)	5 (5)	6 (10)	0	10 (19)	1 (9)	18 (14)	1 (3)	2 (1)	0	3 (1)	0
Other	26 (9)	5 (5)	4 (7)	1 (6)	0	0	5 (4)	3 (9)	22 (10)	1 (4)	25 (11)	2 (8)
ECOG Performance Status												
0	238 (80)	63 (61)	36 (59)	8 (47)	18 (35)	3 (27)	62 (48)	12 (34)	169 (76)	16 (62)	162 (72)	19 (76)
1	58 (19)	40 (38)	23 (38)	9 (53)	24 (46)	5 (45)	54 (42)	17 (49)	53 (24)	10 (39)	63 (28)	6 (24)
2	1 (<1)	0	2 (3)	0	10 (19)	3 (27)	14 (11)	6 (17)	0	0	0	0
Missing	1 (<1)	1 (<1)	0	0	0	0	0	0	0	0	0	0
Sokal Risk Score												
Low	NA	NA	NA	NA	NA	NA	NA	NA	83 (37)	5 (19)	83 (37)	6 (24)
Intermediate	NA	NA	NA	NA	NA	NA	NA	NA	101 (45)	15 (58)	103 (46)	14 (56)
High	NA	NA	NA	NA	NA	NA	NA	NA	38 (17)	6 (23)	39 (17)	5 (20)
Number of Previous CML Therapies[a]												
1	150 (50)	34 (33)	24 (39)	4 (24)	26 (50)	4 (36)	59 (45)	14 (40)	NA	NA	NA	NA
2	106 (36)	45 (43)	21 (34)	4 (24)	14 (27)	3 (27)	42 (32)	8 (23)	NA	NA	NA	NA
3	41 (14)	24 (23)	12 (20)	7 (41)	10 (19)	4 (36)	23 (18)	11 (31)	NA	NA	NA	NA
4	1 (<1)	1 (<1)	4 (7)	2 (12)	2 (4)	0	6 (5)	2 (6)	NA	NA	NA	NA
Previous CML Therapy												
Interferon	104 (35)	61 (59)	29 (48)	12 (71)	16 (31)	3 (27)	46 (35)	15 (43)	NA	NA	NA	NA
Imatinib	298 (100)	104 (100)	61 (100)	17 (100)	52 (100)	11 (100)	130 (100)	35 (100)	NA	NA	NA	NA
Dasatinib	60 (20)	31 (30)	17 (28)	8 (47)	18 (35)	3 (27)	43 (33)	11 (31)	NA	NA	NA	NA
Nilotinib	27 (9)	4 (4)	11 (18)	4 (24)	6 (12)	5 (45)	17 (13)	10 (29)	NA	NA	NA	NA
SCT	12 (4)	5 (5)	5 (8)	2 (12)	3 (6)	0	11 (8)	2 (6)	NA	NA	NA	NA
Medical History												
Diabetes[b]	18 (6)	6 (6)	5 (8)	1 (6)	2 (4)	2 (18)	10 (8)	6 (17)	10 (5)	2 (8)	9 (4)	6 (24)
Hypertension[c]	58 (19)	47 (45)	13 (21)	8 (47)	10 (19)	6 (55)	27 (21)	16 (46)	32 (14)	14 (54)	41 (18)	16 (64)
Renal failure/impairment[d]	4 (1)	11 (11)	2 (3)	2 (12)	3 (6)	0	6 (5)	4 (11)	0	0	0	0

Table 1 Continued

	Phase I/II (Second-Line or Later Bosutinib; CP and Advanced)								Phase III (First-Line; CP CML)			
	CP CML (n = 403)		AP CML (n = 79)		BP CML (n = 64)		Total Adv (n = 167)		Bosutinib (n = 248)		Imatinib (n = 251)	
	Gr ≤ 3a (n = 298)	Gr ≥ 3b (n = 104)	Gr ≤ 3a (n = 61)	Gr ≥ 3b (n = 17)	Gr ≤ 3a (n = 52)	Gr ≥ 3b (n = 11)	Gr ≤ 3a (n = 130)	Gr ≥ 3b (n = 35)	Gr ≤ 3a (n = 222)	Gr ≥ 3b (n = 26)	Gr ≤ 3a (n = 225)	Gr ≥ 3b (n = 25)
Baseline Medical Condition												
Gr ≥ 3b eGFR	1 (<1)	19 (18)	0	1 (6)	1 (2)	0	1 (<1)	4 (11)	0	0	0	2 (8)
Proteinuria	21 (7)	15 (14)	4 (7)	1 (6)	7 (13)	4 (36)	16 (12)	6 (17)	7 (3)	2 (8)	10 (4)	3 (12)
Hyperuricemia	45 (15)	16 (15)	10 (16)	2 (12)	8 (15)	2 (18)	23 (18)	8 (23)	33 (15)	5 (19)	42 (19)	5 (20)

Values are presented as n (%) unless noted otherwise. eGFR was calculated on the basis of the Modification in Diet in Renal Disease method. Grading is on the basis of the Kidney Disease Improving Global Outcomes criteria where Grade ≥ 3b is < 45 mL/min/1.73 m^2 and Grade ≤ 3a is ≥ 45 mL/min/1.73 m^2.

Abbreviations: Adv = advanced; AP = accelerated phase; BP = blast phase; CML = chronic myeloid leukemia; CP = chronic phase; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; Gr = Grade; HLT = high-level term; NA = not assessed; PT = preferred term; SCT = stem cell transplant.

[a]If a patient received > 1 treatment regimen with imatinib, dasatinib, nilotinib, or interferon, the patient was counted only once for that treatment.

[b]Terms used to identify events of diabetes included HLT diabetes mellitus and all subordinate terms.

[c]Terms used to identify events of hypertension were the high-level group terms vascular hypertensive disorders and cardiac and vascular investigations (excluding enzyme tests), the HLT vascular tests not elsewhere classified (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.

[d]Terms used to identify events of renal impairment/failure were the PTs acute prerenal failure, anuria, crush syndrome, diabetic end stage renal disease, neonatal anuria, oliguria, pancreatorenal syndrome, postrenal failure, prerenal failure, renal failure, acute renal failure, chronic renal failure, neonatal renal failure, renal impairment, neonatal renal impairment, scleroderma renal crisis, abnormal blood creatinine, increased blood creatinine, abnormal creatinine renal clearance, decreased creatinine renal clearance, abnormal glomerular filtration rate, and decreased glomerular filtration rate.

Assessment of Renal TEAEs

Thirteen percent (n = 73 of 570) of patients who received second-line or later bosutinib experienced renal TEAEs (any Grade, all causality); 5% (n = 29 of 570) of patients experienced renal events considered treatment-related by the investigator (Table 2). Similar frequencies of renal TEAEs were observed across disease stages; however, with a shorter duration of treatment, exposure-adjusted incidence rates (EAIRs) were higher in patients with advanced leukemias (see Supplemental Table 1 in the online version). Among the 73 relapsed/refractory patients who experienced renal TEAEs, 14 (19%) had a medical history of renal events. Grade ≥ 3 renal TEAEs were experienced by 10 of 403 (2%) CP CML and 7 of 167 (4%) advanced patients; 1 CP CML patient died because of acute renal failure unrelated to treatment (see the Supplemental Methods section of the Supplemental Materials in the online version). In the first-line setting, 9% (n = 22 of 248) of bosutinib-treated and 6% (n = 16 of 251) of imatinib-treated patients experienced renal TEAEs (any Grade, all causality); treatment-related renal events were equally uncommon in both arms (3% [n = 8] each). EAIRs were also similar with both treatments (Table 2 and see Supplemental Table 1 in the online version). None of the newly diagnosed patients who experienced renal TEAEs had a medical history of renal events. Five of 248 (2%) patients experienced Grade 3 renal TEAEs in the bosutinib arm versus no patients in the imatinib arm (no Grade ≥ 4 events were reported in either arm). Only 2 patients underwent on-treatment hemodialysis, both in the second-line setting (see the Supplemental Methods section of the Supplemental Materials in the online version).

Renal TEAEs (any Grade) with second-line or later bosutinib resolved in 46% (24 of 52) of patients with CP CML and 48% (10 of 21) with advanced disease (Table 2). In patients receiving first-line bosutinib or imatinib, renal events resolved in 55% (n = 12 of 22) and 63% (n = 10 of 16) of patients with events, respectively. Among patients with renal events, median (range) time to first renal AE and cumulative duration of events with second-line or later bosutinib was 29 (1-1176) days and 38 (5-1406) days, respectively, for patients with advanced leukemias versus 497 (1-2695) days and 128 (1-1167) days with CP CML. Corresponding median times to first event with first-line bosutinib and imatinib were 421 (7-1765) days and 419 (2-1513) days, respectively. The median cumulative duration of AEs was substantially shorter with first-line bosutinib versus imatinib (25 [range, 2-923] days vs. 167 [range, 12-512] days).

Assessment of eGFR and Serum Creatinine Levels

Twenty-four percent (n = 139 of 570) of patients who received second-line or later bosutinib and 10% each of bosutinib- (n = 26 of 248) and imatinib-treated (n = 25 of 251) patients in the first-line setting developed Grade ≥ 3b eGFR, with a median (range) time to first occurrence of 23 (2-1869), 265 (6-1764), and 589 (7-1763) days, respectively. Incidences over time are presented according to disease stage (phase I/II study) and treatment (phase III study) in Supplemental Figure 1 in the online version. Median (range) duration of treatment after the first occurrence of Grade ≥ 3b eGFR was 347 (0-2684) days in relapsed/refractory patients, 839 (22-1798) days in bosutinib-treated, and 513 (0-1479) days in newly diagnosed imatinib-treated patients.

Decreases from baseline in eGFR and increases in serum creatinine were observed over time in both studies. Median changes from baseline in eGFR at 48 months were −10.51 mL/min/1.73 m^2 with second-line or later bosutinib, −15.62 mL/min/1.73 m^2 with first-line bosutinib, and −17.69 mL/min/1.73 m^2 with first-line imatinib (Figure 1A); median increases in serum creatinine at 48 months were 11.49, 11.49, and 13.00 μmol/L, respectively (Figure 1B). In both studies, no consistent trend toward higher on-treatment creatinine levels was seen over time in patients with baseline levels > ULN versus ≤ ULN; however, patient numbers were small in the > ULN group (see Supplemental Figure 2 in the online version).

Most shifts from baseline in eGFR were of 1 Grade level from baseline (see Supplemental Table 2 in the online version). A considerably greater percentage of patients with eGFR Grade 3a at baseline progressed to Grade ≥ 3b during treatment (second-line and later; n = 43 of 69 [62%]; first-line: bosutinib, n = 4 of 10 [40%]; imatinib, n = 8 of 12 [67%]) relative to those with baseline eGFR Grades 1 (normal) or 2 (n = 73 of 475 [15%]; n = 22 of 237 [9%]; n = 15 of 236 [6%], respectively).

Reversibility of eGFR Decline

Of 139 patients who received second-line or later bosutinib who developed Grade ≥ 3b eGFR, 50 (36%) showed improvement to Grade ≤ 3a with no return to Grade ≥ 3b as of the most recent assessment recorded, 25 (50%) and 38 (76%) of whom, respectively, had dose reductions or delays because of AEs (mostly other, nonrenal AEs). Fifty-eight of the 139 patients (42%) improved to Grade ≤ 3a but subsequently returned to Grade ≥ 3b, whereas 31 (22%) patients did not improve from Grade ≥ 3b (Table 3). Ultimately, 74 of the 139 patients (53%) returned to Grade ≤ 3a as of their last follow-up assessment. Forty-three of the 139 patients (31%) discontinued because of AEs, of whom only 7 discontinued because of renal AEs (reported as increased blood creatinine [n = 3], renal failure [n = 3], and renal impairment [n = 1]).

Among patients who received first-line bosutinib versus imatinib who developed Grade ≥ 3b eGFR, similar proportions (35% [n = 9 of 26] vs. 36% [n = 9 of 25]) had improvement to Grade ≤ 3a with no return to Grade ≥ 3b. More patients who received bosutinib had dose reductions (n = 5 vs. n = 2) and/or dose delays (n = 6 vs. n = 3) because of TEAEs (renal as well as nonrenal). Improvement to Grade ≤ 3a with subsequent return to Grade ≥ 3b was observed in 15 of the 26 bosutinib-treated patients (58%) versus 10 of the 25 imatinib-treated patients (40%); 2 (8%) versus 6 (24%) patients, respectively, did not improve from Grade ≥ 3b. Ultimately, 58% and 60% of the 26 and 25 patients (n = 15 in each arm), respectively, returned to Grade ≤ 3a as of their last follow-up assessment. None of the patients who received first-line bosutinib or imatinib discontinued treatment because of renal AEs (Table 3).

Effects of Bosutinib Dose on Renal Function

Median changes from baseline in eGFR over time for patients with bosutinib dose reductions (to 400 mg/d) or escalations (to 600 mg/d) are presented in Supplemental Figure 3 in the online version. For interpretability, changes were compared with age, treatment duration, and baseline eGFR matched control patients who continued treatment at 500 mg/d. In the second-line or later setting, median changes from baseline in eGFR at 48 months were similar in patients who received a dose reduced to 400 mg/d (−11.11 mL/min/1.73 m^2) compared with matched control participants (−16.30 mL/min/1.73 m^2; see Supplemental Figure 3A in the online version). Findings were similar in the first-line setting (−20.19 vs. −15.34 mL/min/1.73 m^2 at month 48; see Supplemental Figure 3B in the online version). In both studies, median time to bosutinib dose reduction was < 60 days.

In the second-line or later setting, median changes from baseline in eGFR at 48 months appear lower in patients whose dose was escalated (−7.65 mL/min/1.73 m^2) to 600 mg/d compared with matched controls (−17.02 mL/min/1.73 m^2); however, creatinine data at month 48 were available for < 20 patients in each group (see Supplemental Figure 3A in the online version). In the first-line setting, a median change of −17.67 mL/min/1.73 m^2 was observed at month 48 in patients who received a dose escalation compared with −15.43 mL/min/1.73 m^2 for matched control participants; however, creatinine data at month 48 were available for only 11 patients in each group (see Supplemental Figure 3B in the online version). Median time to dose escalation was 128 days with second-line or later bosutinib and 696 days with first-line bosutinib.

Prognostic Factors for Time to Grade ≥ 3b eGFR Decline

In the pooled analysis of data from bosutinib-treated CP CML patients in both studies, baseline factors associated with development of Grade ≥ 3b eGFR (all $P < .05$) were older age, lower eGFR (both continuous), having proteinuria, previous hypertension, or previous interferon (all yes vs. no; Figure 2). On-treatment, time-dependent prognostic factors associated with Grade ≥ 3b eGFR included the use of antihypertensive agents or loop diuretics, Grade 3/4 vomiting, and congestive heart failure (vs. none for all). Treatment line (first- vs. third- and fourth-line and second- vs. third- and fourth-line) was not associated with development of Grade ≥ 3b eGFR.

In the analysis of CP CML patients receiving first-line bosutinib or imatinib in the phase III study, baseline prognostic factors associated with development of Grade ≥ 3b eGFR were older age, lower eGFR (both continuous), and previous hypertension (Figure 2). Associated on-treatment, time-dependent prognostic factors were use of loop diuretics, amino glycosides, antihypertensive agents, and Grade 3/4 diarrhea (vs. none).

Efficacy Assessments

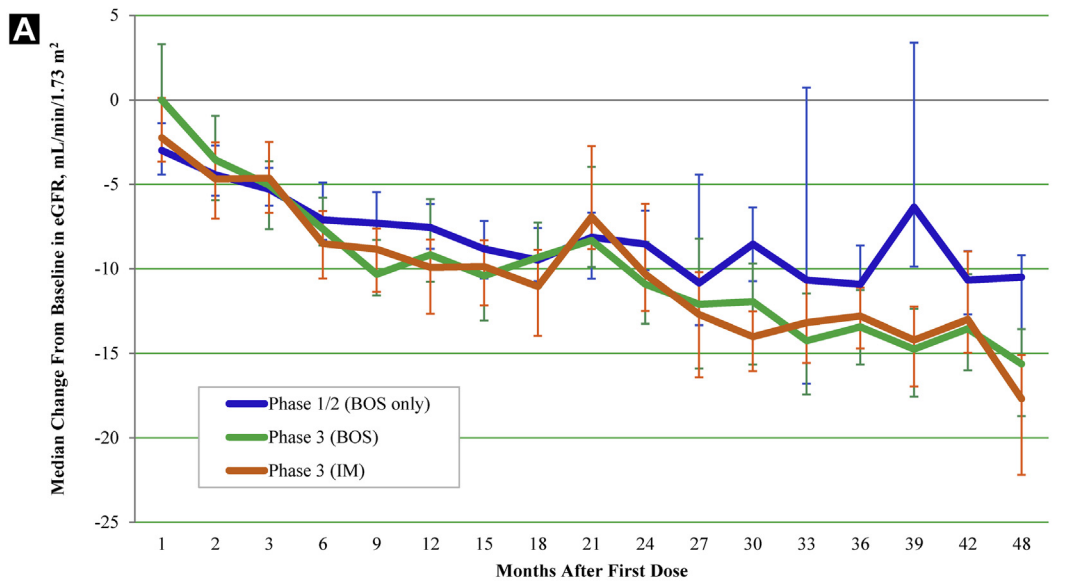
Of 139 patients who received second-line or later bosutinib who developed Grade ≥ 3b eGFR, 75 (54%) newly attained or maintained a baseline MCyR (CCyR in 62 [45%]) after Grade ≥ 3b eGFR. Thirty-six (26%) and 35 (25%) of these patients, respectively, had their initial MCyR or CCyR after the first occurrence of Grade ≥ 3b eGFR; 39 (28%) and 27 (19%) patients attained/maintained MCyR or CCyR before and after the first occurrence of Grade ≥ 3b eGFR. Only 5 of the 139 patients (4%) lost their previously attained MCyR; these patients continued treatment a median of 140 (range, 0-247) days after onset of Grade ≥ 3b eGFR. Of 428 patients who had not experienced Grade ≥ 3b eGFR, 192 (45%) attained or maintained MCyR (CCyR in 155 [36%]).

Table 2 Characteristics and Management of Renal Adverse Events[a]

	Phase I/II (Second-Line or Later Bosutinib; CP and Advanced)				Phase III (First-Line; CP CML)	
	CP CML (n = 403)	AP CML (n = 79)	BP CML (n = 64)	Total Adv (n = 167)	Bosutinib (n = 248)	Imatinib (n = 251)
Patients With Events, n (%)	52 (13)	11 (14)	7 (11)	21 (13)	22 (9)	16 (6)
Serious AE	7 (2)	2 (3)	3 (5)	6 (4)	6 (2)	0
Leading to withdrawal from treatment	6 (1)	1 (1)	0	1 (<1)	0	0
Treatment-related[b]	22 (5)	5 (6)	2 (3)	7 (4)	8 (3)	8 (3)
Number of Events Per Patient, n (%)						
1	29 (7)	8 (10)	5 (8)	16 (10)	14 (6)	10 (4)
2	12 (3)	2 (3)	0	2 (1)	3 (1)	3 (1)
3-5	9 (2)	1 (1)	2 (3)	3 (2)	3 (1)	3 (1)
6-9	2 (<1)	0	0	0	2 (<1)	0
Maximum Toxicity Grade, n (%)						
1	19 (5)	6 (7)	1 (2)	9 (5)	11 (4)	12 (5)
2	23 (6)	3 (4)	2 (3)	5 (3)	6 (2)	4 (2)
3	8 (2)	2 (3)	2 (3)	5 (3)	5 (2)	0
4	1 (<1)	0	2 (3)	2 (1)	0	0
5	1 (<1)	0	0	0	0	0
Outcome in Patients With Events, n (%)[c]						
Death	1 (2)	0	0	0	0	0
Persisted[d]	27 (52)	4 (36)	5 (71)	11 (52)	10 (45)	6 (38)
Resolved[d]	24 (46)	7 (64)	2 (29)	10 (48)	12 (55)	10 (63)
Treatment Change in Patients With Events, n (%)[c]						
Temporarily stopped	7 (13)	1 (9)	3 (43)	4 (19)	5 (23)	0
No rechallenge/discontinued study drug	1/7 (14)	0	1/3 (33)	1/4 (25)	0	NA
Rechallenged	6/7 (86)	1/1 (100)	2/3 (67)	3/4 (75)	5/5 (100)	NA
Successful[e]	4/6 (67)	0	2/2 (100)	2/3 (67)	5/5 (100)	NA
Subsequent/persistent AE, no permanent discontinuation	4/4 (100)	NA	2/2 (100)	2/2 (100)	3/5 (60)	NA
No subsequent AE	0	NA	0	NA	2/5 (40)	NA
Dose reduced[c]	2 (4)	1 (9)	0	1 (5)	2 (9)	0
Patients With Events Treated With Concomitant Medications, n (%)[c]	5 (10)	4 (36)	3 (43)	7 (33)	6 (27)	0
Patients With Medical History of Renal Events, n (%)[c]	9 (17)	3 (27)	1 (14)	5 (24)	0	0
Median Time to and Duration of Events in Patients With Events (Range), d						
Time to first event	497 (1-2695)	33 (1-1176)	22 (6-811)	29 (1-1176)	421 (7-1765)	419 (2-1513)
Time to first Grade 3/4 event	955 (92-1827)	466 (33-898)	301 (22-811)	276 (22-898)	355 (11-970)	NA
Cumulative duration of events[f]	128 (1-1167)	62 (5-1406)	33 (28-38)	38 (5-1406)	25 (2-923)	167 (12-512)
Cumulative duration of Grade 3/4 events[f]	21 (1-74)	14 (8-20)	13 (13-13)	13 (8-20)	10 (1-19)	NA

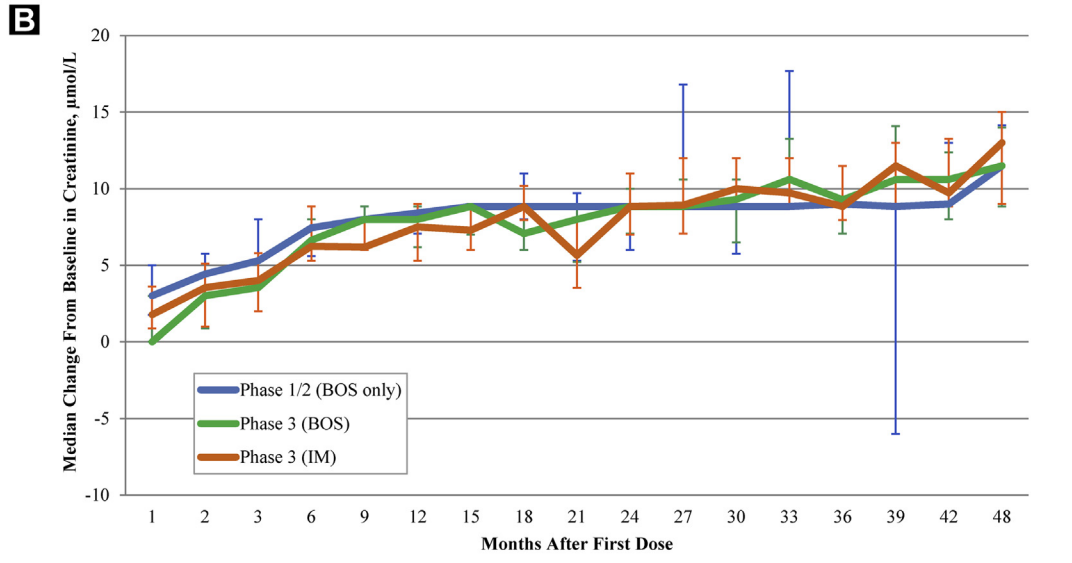
Abbreviations: Adv = advanced; AE = adverse event; AP = accelerated phase; BP = blast phase; CML = chronic myeloid leukemia; CP = chronic phase.
[a]Includes the following preferred terms from the Medical Dictionary for Regulatory Activities (version 17.0): acute prerenal failure, anuria, crush syndrome, diabetic end stage renal disease, neonatal anuria, oliguria, pancreatorenal syndrome, postrenal failure, prerenal failure, renal failure, renal failure acute, renal failure chronic, renal failure neonatal, renal impairment, renal impairment neonatal, scleroderma renal crisis, blood creatinine abnormal, blood creatinine increased, creatinine renal clearance abnormal, creatinine renal clearance decreased, glomerular filtration rate abnormal, glomerular filtration rate decreased.
[b]Treatment-related AEs were followed until resolution (Grade $\leq$ 1) or return to baseline.
[c]Denominator is the number of patients with an event.
[d]Outcome categories are mutually exclusive; patients were classified on the basis of the worst event outcome.
[e]Successful rechallenge includes patients who did not subsequently experience an AE of the same type or did not permanently discontinue treatment because of an AE of the same type.
[f]Cumulative duration of AE was calculated as the sum of (stop date − start date) + 1 for nonmissing/nonpartial dates, adjusting for overlapping dates of different AEs. Every change in toxicity Grade is counted as a different AE.

Figure 1 Median Change From Baseline in eGFR (A) and Serum Creatinine (B) Over Time in Both Studies. Baseline Was Defined as the Last Nonmissing Value Before the First Dose of Test Drug. Analyses for Each Time Interval Were Done Using Data With Nonmissing Baseline and Postbaseline Values. Per Protocol, Assessments at Months 27, 33, and 39 Were Not Done in the Phase I/II Study. 1 Month = 4 Weeks. Nonparametric 95% Confidence Intervals Provided for the Median



Number of patients with nonmissing baseline values

Phase 1/2	509	469	429	372	322	290	255	231	221	210	27	191	12	185	3	177	167
Phase 3 (BOS)	239	233	214	203	191	187	181	175	172	169	164	164	162	156	153	151	152
Phase 3 (IM)	243	245	243	234	219	212	204	202	186	187	180	179	177	173	173	172	169



Number of patients with nonmissing baseline values

Phase 1/2	569	469	429	372	322	290	255	231	221	210	27	191	12	185	3	177	167
Phase 3 (BOS)	239	233	214	203	191	187	181	175	172	169	164	164	162	156	153	151	152
Phase 3 (IM)	243	245	243	234	219	212	204	202	186	187	180	179	177	173	173	172	169

Abbreviations: BOS = bosutinib; eGFR = estimated glomerular filtration rate; IM = imatinib.

Eighty-five percent (n = 22 of 26) and 84% (n = 21 of 25) of patients who received first-line bosutinib or imatinib, respectively, newly attained or maintained a CCyR after developing on-treatment Grade ≥ 3b eGFR. Nine (35%) and 4 (16%) of these patients, respectively, had their initial CCyR after the first Grade ≥ 3b eGFR event; 13 (50%) and 17 (68%) maintained a CCyR achieved before the first Grade ≥ 3b eGFR event. Among 26 bosutinib-treated and 25 imatinib-treated patients, 3 (12%) and 2 (8%), respectively, lost a previously attained CCyR and continued treatment a median of 102 (range, 30-168) and 13 (range, 1-25) days after onset of

Grade ≥ 3b eGFR; among 222 bosutinib-treated and 225 imatinib-treated patients who had not experienced Grade ≥ 3b eGFR, 173 (78%) and 181 (80%), respectively, attained CCyR.

Discussion

In this long-term analysis, patients in the first-line and relapsed/refractory settings who received bosutinib for the treatment of Ph^+ leukemias experienced a decline in renal function, as evidenced by increases from baseline in serum creatinine and decreases in eGFR. Neither the overall degree nor the cumulative rate of eGFR decline appeared to be bosutinib dose-dependent. The pattern of results suggests that the observed changes in eGFR associated with bosutinib might not be because of a direct nephrotoxic effect. However, it should be noted that in a dedicated renal impairment study in volunteers with preexisting renal impairment, 35% and 60% increases in bosutinib exposure were observed in patients with moderate (creatinine clearance 30-50 mL/min) or severe (creatinine clearance < 30 mL/min) renal impairment relative to those with normal renal function.[4] Therefore, careful monitoring remains important. Dose adjustments are recommended in patients with moderate to severe renal impairment,[4] accompanied by close response monitoring at the reduced dose.

In the first-line setting, the magnitude as well as pattern of eGFR decline with bosutinib were similar to those observed with imatinib. Importantly, for most patients who developed Grade ≥ 3b eGFR during bosutinib and imatinib treatment, there was an improvement in eGFR over time. A substantial proportion of patients who developed eGFR Grade ≥ 3b returned to, and remained at, Grade ≤ 3a during therapy regardless of treatment line, suggesting a reversible effect in at least some patients. In addition, development of Grade ≥ 3b eGFR does not appear to negatively affect cytogenetic response to bosutinib or imatinib.

The current analyses of baseline characteristics and treatment-related factors in CP CML patients might allow identification of patient populations at greatest risk for Grade ≥ 3b eGFR. Consistent with the age-related decline in renal function observed in the general population,[27] this risk appeared higher in older patients. Other patients potentially at risk include those with early signs of kidney dysfunction (ie, proteinuria, lower baseline eGFR) at the start of treatment and those with a history of hypertension or who required concomitant antihypertensive agents or loop diuretics.

The association of on-treatment AEs with eGFR decline was also examined; in particular, Grade 3/4 diarrhea, Grade 3/4 vomiting, any Grade infection/sepsis, and any Grade congestive heart failure were evaluated on the basis of their potential to result in hemodynamic changes that could lead to renal dysfunction. In the model pooling bosutinib data from CP CML patients in both studies, congestive heart failure, although infrequent, was associated with Grade ≥ 3b eGFR, which is in keeping with the reported relationship between hypertension, heart failure, and kidney disease.[28-30] Grade 3/4 vomiting (pooling both studies) and diarrhea (first-line bosutinib vs. imatinib) were also significant risk factors. As in patients taking diuretic medications, this could involve dehydration as a contributing factor. Taken together, these results suggest that patients who experience Grade 3/4 diarrhea or vomiting should be kept well hydrated. Patients who experience these events or congestive heart failure should be monitored closely for renal dysfunction.

In both studies, onset of Grade ≥ 3b eGFR occurred early, after which renal function decreased at a rate consistent with the physiologic decline associated with aging (Figure 1A).[31] This is in contrast to established models of drug-induced nephrotoxicity, where loss of renal function begins gradually then becomes more significant over time with continued treatment.[32,33] The time to first Grade ≥ 3b eGFR was shorter in the study of second-line or later bosutinib, suggesting that previous TKI exposure and other factors associated with advanced disease might predispose patients to renal dysfunction. Among patients who developed Grade ≥ 3b eGFR, median time to onset with first-line bosutinib was less than half that of imatinib, although the overall incidence of Grade ≥ 3b eGFR was the same in both arms. Despite the earlier onset of eGFR decline with first-line bosutinib, median duration of bosutinib treatment after first occurrence of Grade ≥ 3b eGFR was comparable with that observed with first-line imatinib and with CP CML patients who received second-line or later bosutinib. Few patients with normal eGFR at baseline developed Grade ≥ 3b eGFR; among those who did, most subsequently improved during continued therapy. These findings suggest that factors other than bosutinib likely played a role in the decline of eGFR.

It should be noted that development of Grade ≥ 3b eGFR did not result in a loss of cytogenetic response. In fact, most patients (54%) who developed Grade ≥ 3b eGFR during bosutinib treatment in the phase I/II study either maintained an ongoing MCyR or first attained an MCyR after documentation of Grade ≥ 3b eGFR.

Renal dysfunction has been reported with other TKIs, including imatinib,[6-10,14,34-36] nilotinib,[37-39] and dasatinib,[6,9,11-14,40-43] suggesting a possible drug class effect. This is supported by the similar frequency and characteristics of renal decline observed with imatinib and bosutinib treatment in our analyses. Tumor lysis and toxic tubular damage have been proposed as possible mechanisms for renal failure with TKI therapy.[7,13] Imatinib-induced tubular damage might be related to the off-target inhibition of platelet-derived growth factor receptor (PDGF-R), which regulates the proliferation and regeneration of proximal tubular cells in the kidney and is notably not targeted by bosutinib.[44,45] However, findings from a recent study suggested that long-term treatment with imatinib, but not dasatinib or nilotinib, might cause a significant decline in eGFR.[42] Because these TKIs also inhibit PDGF-R, there is likely a more complex explanation.[45] Vidal-Petiot et al recently discovered that tubular secretion of creatinine is greatly diminished in imatinib-treated CML patients resulting in a reversible increase in serum creatinine levels.[46] Although further research is needed to understand the mechanism of this decreased tubular secretion, because the observed increase in serum creatinine was independent of any loss of glomerular function, renal function might be underestimated when using creatinine-derived formulas to calculate eGFR. Therefore, it is possible that the increased creatinine values observed with bosutinib could be due to decreased tubular secretion of creatinine, thus not reflecting a true decrease in glomerular filtration. More work is needed to determine the mechanism of renal toxicity associated with TKIs and if this toxicity is associated with inhibition in critical kidney tissues.

Table 3 Potential Reversibility for Patients With Grade ≥ 3b eGFR[a]

	Phase I/II (Second-Line or Later Bosutinib; CP and Adv)				Phase III (First-Line; CP CML)	
	CP CML (n = 104)	AP CML (n = 17)	BP CML (n = 11)	Total Adv (n = 35)	Bosutinib (n = 26)	Imatinib (n = 25)
Improved to Grade ≤3a, No Return to Grade ≥3b	37 (36)	8 (47)	3 (27)	13 (37)	9 (35)	9 (36)
Received dose reduction because of AE	20/37 (54)	5/8 (63)	0	5/13 (38)	5/9 (56)	2/9 (22)
Received dose delay because of AE	30/37 (81)	6/8 (75)	0	8/13 (62)	6/9 (67)	3/9 (33)
Discontinued because of AE[b]	14/37 (38)	2/8 (25)	0	3/13 (23)	1/9 (11)	1/9 (11)
Improved to Grade ≤3a, Subsequent Return to Grade ≥3b	47 (45)	5 (29)	6 (55)	11 (31)	15 (58)	10 (40)
Received dose reduction because of AE	37/47 (79)	4/5 (80)	3/6 (50)	7/11 (64)	8/15 (53)	4/10 (40)
Received dose delay because of AE	44/47 (94)	5/5 (100)	5/6 (83)	10/11 (91)	13/15 (87)	7/10 (70)
Discontinued because of AE[b]	12/47 (26)	3/5 (60)	1/6 (17)	4/11 (36)	4/15 (27)	0
No Improvement to Grade ≤3a	20 (19)	4 (24)	2 (18)	11 (31)	2 (8)	6 (24)
Received dose reduction because of AE	12/20 (60)	2/4 (50)	0	2/11 (18)	1/2 (50)	1/6 (17)
Received dose delay because of AE	17/20 (85)	3/4 (75)	2/2 (100)	6/11 (55)	2/2 (100)	3/6 (50)
Discontinued because of AE[b]	7/20 (35)	3/4 (75)	0	3/11 (27)	0	0
Improved to Grade ≤3a as of the Last Follow-up Assessment	58 (56)	10 (59)	4 (36)	16 (46)	15 (58)	15 (60)
Discontinued, n (%)[b,c]	93 (89)	17 (100)	11 (100)	35 (100)	7 (27)	8 (32)
AE[d]	32 (31)	8 (47)	1 (9)	11 (31)	5 (19)	1 (4)
Renal AE[e]	6 (6)	1 (6)	0	1 (3)	0	0
Death	8 (8)	0	0	0	2 (8)	0
Disease progression	11 (11)	3 (18)	6 (55)	11 (31)	0	2 (8)
Symptomatic deterioration	0	0	0	2 (6)	0	0
Unsatisfactory efficacy	12 (12)	2 (12)	1 (9)	4 (11)	0	0
Discontinuation of study by sponsor	3 (3)	0	1 (9)	1 (3)	0	1 (4)
Investigator request	0	0	1 (9)	1 (3)	0	0
Subject request	8 (8)	0	0	0	0	3 (12)
Protocol violation	0	0	0	0	0	1 (4)
Lost to follow-up	1 (1)	0	0	0	0	0
Other	18 (17)	4 (24)	1 (9)	5 (14)	0	0
Median Time to Treatment Discontinuation After First Grade ≥3b eGFR (Range), d	383 (1-2458)	260 (1-2685)	224 (1-823)	118 (1-2685)	246 (33-839)	133 (34-869)

Values are presented as n (%) unless noted otherwise. eGFR was calculated on the basis of the Modification in Diet in Renal Disease method. Grading is on the basis of the Kidney Disease Improving Global Outcomes criteria where Grade ≥ 3b is < 45 mL/min/1.73 m^2 and Grade ≤ 3a is ≥ 45 mL/min/1.73 m^2.

Abbreviations: Adv = advanced; AE = adverse event; ALL = acute lymphoblastic leukemia; AP = accelerated phase; BP = blast phase; CML = chronic myeloid leukemia; CP = chronic phase; eGFR = estimated glomerular filtration rate.

[a]Denominators are the number of patients with an event; events occurring on-treatment or during follow-up are included.

[b]Includes discontinuations with AE listed as a secondary reason.

[c]Discontinuations within 4 years are reported for the phase III study because sponsor-initiated discontinuation of the study resulted in early discontinuation of some imatinib-treated patients before year 5. Discontinuations at any time are reported for the phase I/II study.

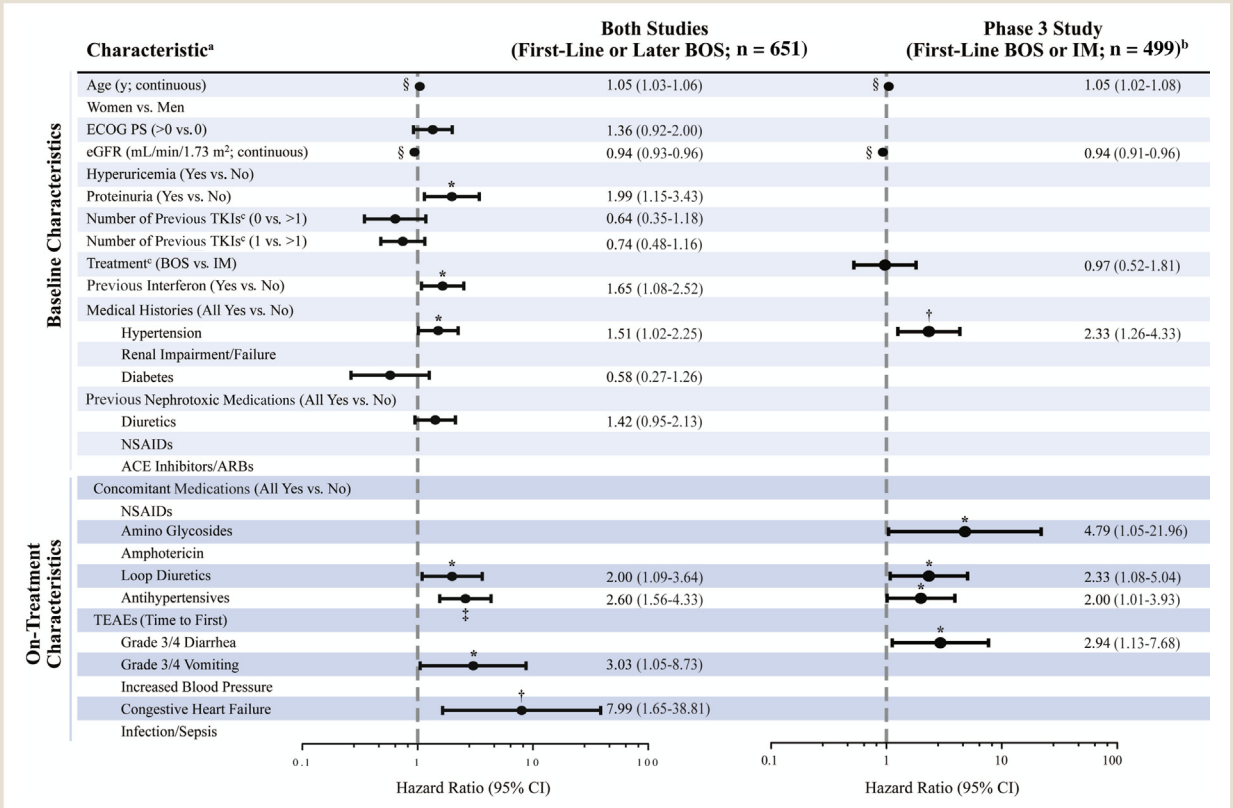
[d]Discontinuations with AEs listed as the primary reason. Events leading to discontinuation were abdominal adhesions, abdominal pain, anemia, ascites, atrial fibrillation, back pain, coronary artery disease, cough, diarrhea, fluid retention, hemoglobin decreased, hypersensitivity vasculitis, intestinal ischemia, intestinal obstruction, liver function test abnormal, myocardial infarction, renal impairment, pancytopenia, pericardial effusion, pericarditis, pneumonia, and pulmonary hypertension (all n = 1), as well as blood creatinine increased and serositis (n = 2), cardiac failure, renal failure, and vomiting (all n = 3), thrombocytopenia, dyspnea, and pleural effusion (all n = 4) in patients with CP CML; alanine aminotransferase increased, amylase increased, blood alkaline phosphatase increased, blood creatinine increased, chest pain, coronary artery disease, disease progression, dyspnea, lipase increased, pleural effusion, and serositis (all n = 1), as well as pericardial effusion (n = 2) in patients with AP CML; cardiac failure congestive (n = 1) in the BP CML cohort; and cerebral infarction (n = 1) in patients with ALL in the phase I/II study; atypical pneumonia, exfoliative rash, fluid retention, platelet count decreased, and pleural effusion (all n = 1) in the bosutinib arm, and exfoliative rash (n = 1) in the imatinib arm of the phase III study.

[e]Includes the following preferred terms from the Medical Dictionary for Regulatory Activities (version 17.0): acute prerenal failure, anuria, crush syndrome, diabetic end stage renal disease, neonatal anuria, oliguria, pancreatorenal syndrome, postrenal failure, prerenal failure, renal failure, renal failure acute, renal failure chronic, renal failure neonatal, renal impairment, renal impairment neonatal, scleroderma renal crisis, blood creatinine abnormal, blood creatinine increased, creatinine renal clearance abnormal, creatinine renal clearance decreased, glomerular filtration rate abnormal, glomerular filtration rate decreased.

Conclusions

These long-term safety analyses suggest that the benefit-risk profile remains favorable for bosutinib in patients with Ph+ CML. Although the follow-up duration for safety data collection upon treatment discontinuation was ≤ 30 days for both studies, the treatment benefit of bosutinib likely outweighs the risk of developing renal dysfunction in most Ph+ leukemia patients. However, patients treated with TKIs should be monitored for renal function at baseline and during therapy, with particular attention paid to those who have preexisting renal impairment or associated risk

Figure 2 Baseline and On-Treatment Time-Dependent Predictors of Time to First Grade ≥ 3b eGFR in CP CML Patients. Hazard Ratios < 1 Indicate Better Outcome for Group 1 Versus Group 2 (ie, Reference) or for a 1-Unit Increase for the Continuous Variables; 95% Confidence Intervals From the Cox Model Provided. Terms Used to Define Medical Histories Are Included in the Footnotes of Table 1. *P* Values Were Not Adjusted for Multiple Comparisons (**P* < .05; †*P* ≤ .01; ‡*P* ≤ .001; §*P* ≤ .0001). eGFR Was Calculated on the Basis of the Modification in Diet in Renal Disease Method. Grading Is on the Basis of Kidney Disease Improving Global Outcomes Criteria Where Grade ≥ 3b is < 45 mL/min/1.73 m^2 and Grade ≤ 3a Is ≥ 45 mL/min/1.73 m^2. Patients Without Grade ≥ 3b Were Censored at the Last on-Treatment Laboratory Assessment. [a]Forward Selection Was Used to Select Covariates for Inclusion in the Final Model (*P* = .20; Treatment Forced Into the Model for the Phase III Study); Maximum Likelihood Estimates, *P* Values, and Hazard Ratios Are Shown for Covariates Included in the Final Model. [b]Data From the BOS and IM Treatment Arms Were Combined in the Model for the Phase III Study. [c]Number of Previous TKIs (0 vs. > 1 and 1 vs. > 1) Was Included Only in the Model for the Phase I/II Study; Treatment (BOS vs. IM) Was Included Only in the Model for the Phase III Study. These Covariates Were Included in the Respective Models Regardless of Their Statistical significance



Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BOS = bosutinib; CP CML = chronic phase chronic myeloid leukemia; ECOG PS = Eastern Cooperative Oncology Group performance status; eGFR = estimated glomerular filtration rate; IM = imatinib; NSAID = nonsteroidal anti-inflammatory drug; TEAE = treatment-emergent adverse event; TKI = tyrosine kinase inhibitor.

factors. Because of the increase in bosutinib exposure in patients with renal impairment,[4] the product label recommends dose adjustments in patients with moderate or severe baseline or treatment-emergent renal impairment.

Clinical Practice Points

- Renal toxicity has been reported during TKI treatment for Ph^+ leukemias.
- Information on TKI-associated renal toxicity is mostly limited to case reports.
- A better understanding of the renal safety profiles of TKIs is important for optimizing outcomes.
- Long-term bosutinib treatment appears to be associated with a reversible decline in renal function in patients with CP CML or advanced disease that is resistant or intolerant to previous TKI therapy.
- The frequency and characteristics of this decline are similar to the renal decline observed with long-term imatinib treatment and suggest that the changes might not be due to direct nephrotoxic effects.
- Declines in eGFR did not affect cytogenetic response.
- The benefit of bosutinib likely outweighs the risk of developing renal dysfunction in most Ph^+ leukemia patients, although patients should be monitored for renal function at baseline and during therapy.

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Supplemental Data

Supplemental text, tables, and figures accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clml.2017.06.001.

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Supplemental Methods

Renal Toxicity Assessments

Renal toxicity was assessed on the basis of AE reports and laboratory parameters. AEs as reported by investigators were graded according to version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events and were coded and classified according to the Medical Dictionary for Regulatory Activities, version 17.0. The following preferred terms were considered indicative of renal toxicity: acute prerenal failure, anuria, blood creatinine abnormal, blood creatinine increased, creatinine renal clearance abnormal, creatinine renal clearance decreased, crush syndrome, diabetic end stage renal disease, glomerular filtration rate abnormal, glomerular filtration rate decreased, neonatal anuria, oliguria, pancreatorenal syndrome, postrenal failure, prerenal failure, renal failure acute, renal failure chronic, renal failure neonatal, renal failure, renal impairment neonatal, renal impairment, and scleroderma renal crisis.

Laboratory end points included serum creatinine (assessed at screening, and at months 1, 2, 3, and then every 3 months in both studies [also at weeks 1, 2, and 3 in the phase I/II study]) and eGFR. Calculation of eGFR was done using the Modification of Diet in Renal Disease formula (eGFR = 175 × serum creatinine value$^{1.154}$ [in mg/dL] × age$^{0.203}$ × 0.742 [if female] × 1.212 [if black]); grading of eGFR was on the basis of Kidney Disease Improving Global Outcomes criteria.[23]

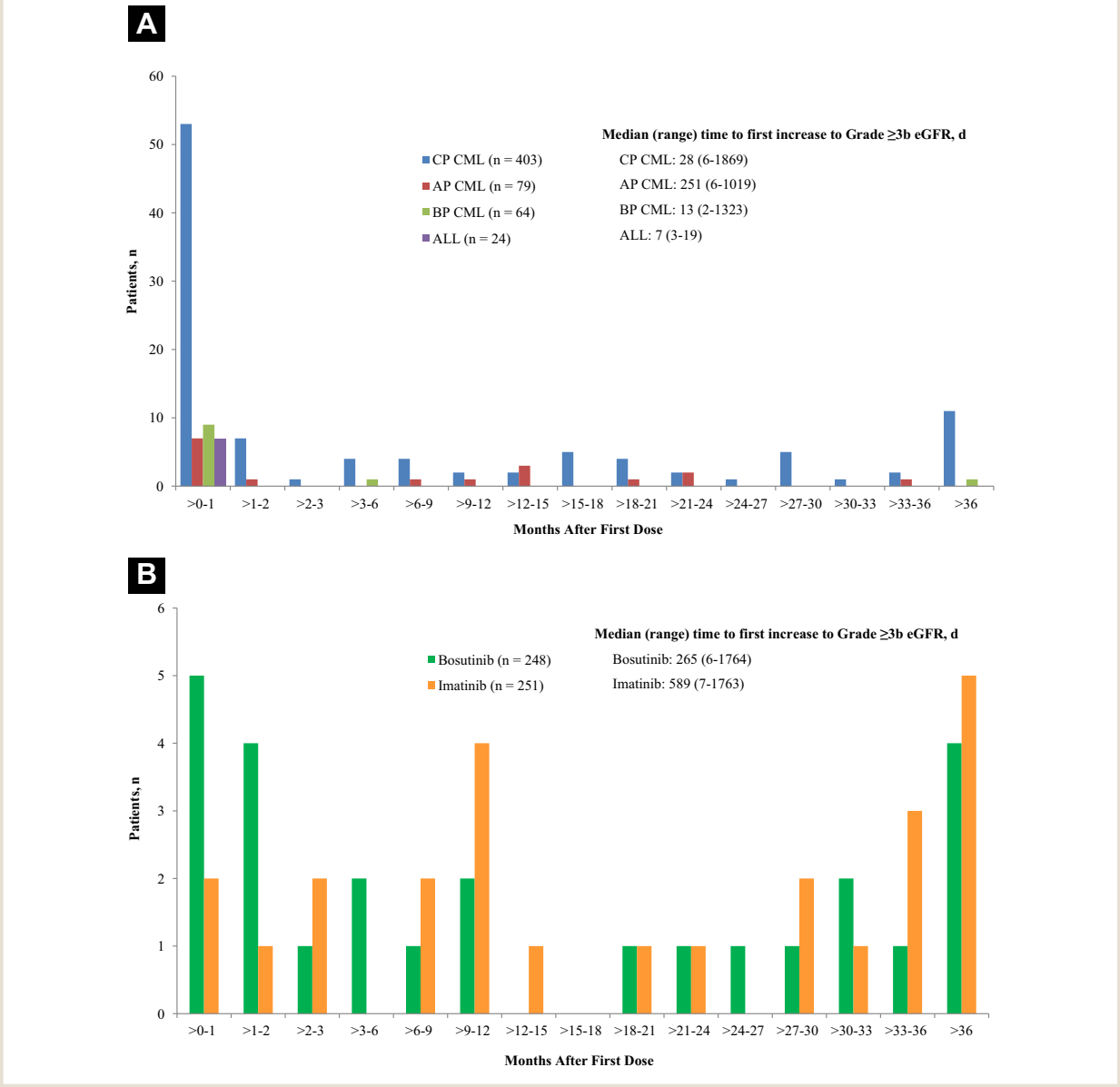
Patient Narratives From the Phase I/II Study

1. Patients who underwent on-treatment hemodialysis. (A) A 61-year-old man with advanced phase CML at study entry and medical history significant for urolithiasis, atherosclerosis, ischemic heart disease, reflux esophagitis/gastritis, and osteoarthritis. Previous medications included imatinib, hydroxyurea, cytarabine, 6-mercaptopurine, doxorubicin, epirubicin, mitoxantrone, and interferon. The patient was briefly treated with furosemide during the study for edema (9 months before onset of acute renal failure). The patient developed acute renal failure on August 5, 2010, and then developed blast crisis CML and died on August 29, 2010.

(B) A 40-year-old woman with chronic phase CML at study entry. Her medical history was significant for leukopenia, anemia, edema, mild atrial fibrillation, pericardial effusion, and aortic stenosis. Previous medications included imatinib, interferon, and hydroxyurea. The patient developed pneumonia (July 15-20, 2009) during the course of the study, which was treated with ceftriaxone, clarithromycin, and oseltamivir, and which preceded the onset of acute renal failure (July 17, 2009). The patient died on July 21, 2009, as a result of the pneumonia.

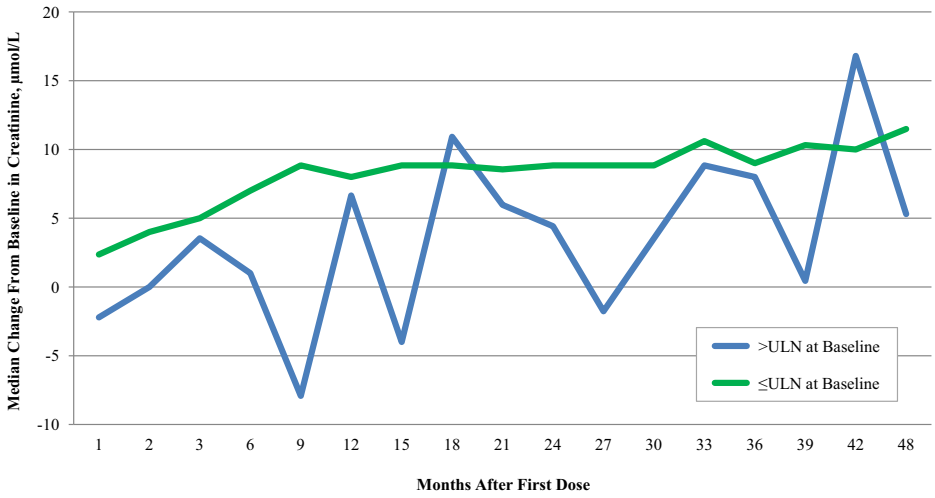
2. Patient who died due to acute renal failure (considered by the investigator as definitely not treatment-related). A 43-year-old man with chronic phase CML at study entry and no significant medical history. Previous medications included imatinib only. The patient developed chronic intermittent diarrhea during the course of the study; no other AEs of significance were noted. Acute renal failure occurred on October 21, 2008, in the setting of disease progression (October 6, 2008), and the death was attributed to renal failure as well as disease progression.

Supplemental Figure 1 Time to (A) First Grade ≥ 3b eGFR in the Phase I/II Study (Second-Line or Later; BOS Only) and (B) Phase III Study (First-Line; BOS vs. IM)



Abbreviations: ALL = acute lymphocytic leukemia; AP = accelerated phase; BOS = bosutinib; BP = blast phase; CML = chronic myeloid leukemia; CP = chronic phase; eGFR = estimated glomerular filtration rate; IM = imatinib.

Supplemental Figure 2 **Median Change From Baseline in Serum Creatinine Over Time in Patients With Increased or Normal Baseline Serum Creatinine Levels (Both Studies Combined). Baseline Was Defined as the Last Nonmissing Value Before the Day of the First Dose of Test Drug. Analyses for Each Time Interval Were Performed Using Data With Nonmissing Baseline Values**

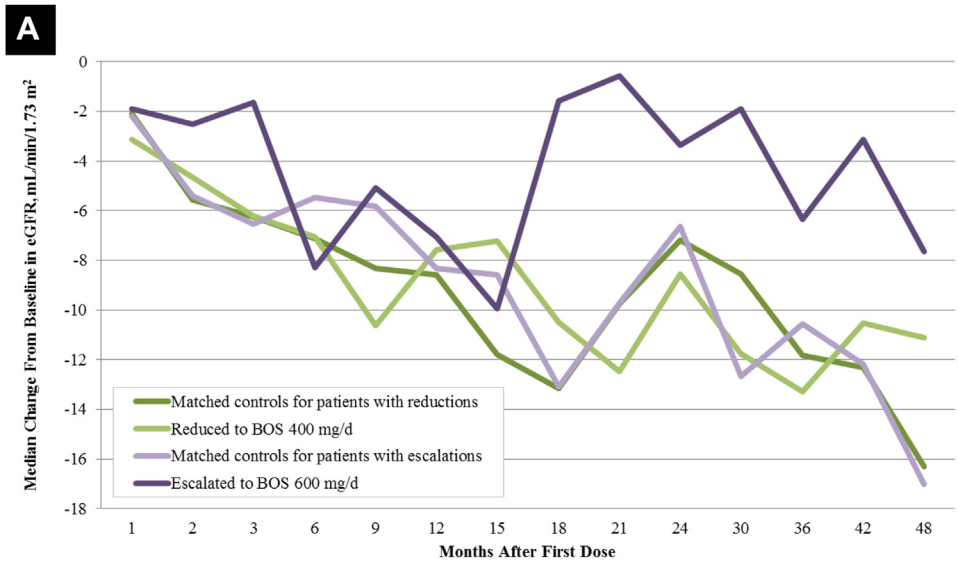


Number of patients with matching baseline values

>ULN	48	47	43	29	26	24	21	18	16	15	5	15	2	15	2	15	13
≤ULN	700	655	600	546	487	453	415	388	377	364	186	340	172	326	154	313	306

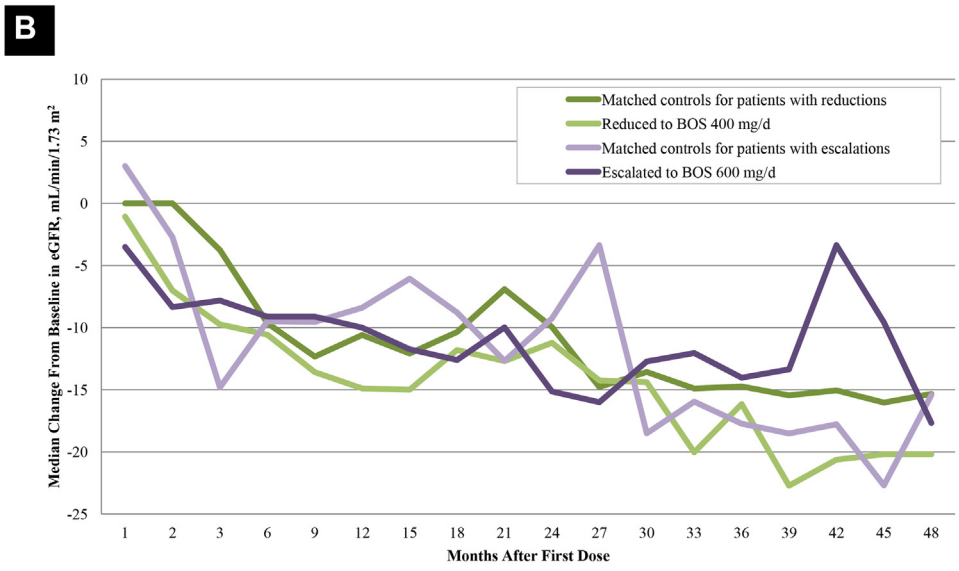
Abbreviations: BOS = bosutinib; Ctrl = matched controls; ULN = upper limit of normal.

Supplemental Figure 3 Effect of Bosutinib Dose on Median Changes From Baseline in eGFR Over Time in the (A) Phase I/II Study (Second-Line or Later) and (B) Phase III Study (First-Line). Patients Who Dose Reduced/Escalated Were Compared With and Matched 1:1 With a Control Group of Patients Who Received 500 mg/d During Their Entire Course of Treatment. Matching Was on the Basis of Baseline Age (Within 10 Years), Baseline eGFR Category (Grades 1-5), and Treatment Duration (Within 6 Months). Patients Without a Matched Control Were Excluded. Baseline Was Defined as the Last Nonmissing Value Before the Day of the First Dose of Test Drug. Analyses for Each Time Interval Were Done Using Data With Nonmissing Baseline Values. 1 Month = 4 Weeks



Number of patients with matching baseline eGFR, age, and treatment duration

Ctrl, reductions	108	94	87	72	59	48	46	42	41	42	37	37	35	33
400 mg/d	127	117	100	74	61	55	49	43	43	38	38	37	36	33
Ctrl, escalations	64	59	58	52	43	33	28	22	20	21	18	17	16	15
600 mg/d	63	61	57	51	44	39	30	24	22	21	18	17	16	16



Number of patients with matching baseline eGFR, age, and treatment duration

Ctrl, reduction	62	61	55	51	47	45	42	42	41	42	42	40	40	39	39	38	39	39
BOS 400 mg/d	64	62	54	51	44	43	42	42	42	41	40	39	39	39	39	38	39	39
Ctrl, escalation	15	15	15	15	14	13	12	12	11	12	11	11	10	11	10	11	10	11
BOS 600 mg/d	14	15	15	15	15	14	13	12	12	12	11	12	12	11	11	11	11	11

Abbreviations: BOS =bosutinib; Ctrl = matched controls; eGFR = estimated glomerular filtration rate.

Supplemental Table 1 Exposure-Adjusted Event Rates and Percentage of Patients With TEAEs[a]

	Phase I/II (Second-Line or Later Bosutinib; CP and Adv)								Phase 3 (First-Line; CP CML)			
	CP CML (n = 403)		AP CML (n = 79)		BP CML (n = 64)		Total Adv (n = 167)		Bosutinib (n = 248)		Imatinib (n = 251)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Exposure-Adjusted Rate[b]	5.31	0.93	9.16	1.55	21.39	12.17	12.84	4.05	2.86	0.63	1.96	0
Patients With Renal TEAEs, n (%)[c]												
Any TEAE	52 (13)	9 (2)[d]	11 (14)	2 (3)	7 (11)	4 (6)	21 (13)	7 (4)	22 (9)	5 (2)	16 (6)	0
Increased blood creatinine	40 (10)	2 (<1)	6 (8)	1 (1)	3 (5)	0	9 (5)	1 (1)	15 (6)	1 (<1)	16 (6)	0
Abnormal blood creatinine	1 (<1)	0	0	0	0	0	0	0	0	0	0	0
Decreased GFR	0	0	0	0	0	0	0	0	0	0	2 (1)	0
Renal impairment	4 (1)	1 (<1)	1 (1)	0	0	0	2 (1)	0	1 (<1)	0	0	0
Renal failure	10 (2)	4 (1)	5 (6)	0	1 (2)	1 (2)	8 (5)	2 (1)	2 (1)	1 (<1)	1 (<1)	0
Acute renal failure	5 (1)	3 (1)	1 (1)	1 (1)	3 (5)	2 (3)	4 (2)	3 (2)	5 (2)	2 (1)	0	0
Chronic renal failure	2 (<1)	0	0	0	1 (2)	1 (2)	1 (1)	1 (1)	2 (1)	1 (<1)	0	0
Acute prerenal failure	1 (<1)	1 (<1)	1 (1)	1 (1)	0	0	1 (1)	1 (1)	0	0	0	0
Anuria	1 (<1)	0	0	0	0	0	0	0	0	0	0	0
Oliguria	1 (<1)	0	0	0	0	0	0	0	2 (1)	0	0	0

Abbreviations: Adv = advanced; AP = accelerated phase; BP = blast phase; CML = chronic myeloid leukemia; CP = chronic phase; GFR = glomerular filtration rate; TEAE = treatment-emergent adverse event.

[a]Includes the following preferred terms from the Medical Dictionary for Regulatory Activities (version 17.0): acute prerenal failure, anuria, crush syndrome, diabetic end stage renal disease, neonatal anuria, oliguria, pancreatorenal syndrome, postrenal failure, prerenal failure, renal failure, renal failure acute, renal failure chronic, renal failure neonatal, renal impairment, renal impairment neonatal, scleroderma renal crisis, blood creatinine abnormal, blood creatinine increased, creatinine renal clearance abnormal, creatinine renal clearance decreased, glomerular filtration rate abnormal, glomerular filtration rate decreased.

[b]Computed as 100 × the number of patients with TEAEs/total patient-year (total patient-year = sum of time to first TEAE for all patients with TEAEs + total time of 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 might report ≥ 2 adverse events within the higher level category.

[d]One patient with a Grade 5 event did not experience a Grade 3/4 event and so is not included here.

Supplemental Table 2 Shifts From Baseline in Estimated Glomerular Filtration Rate

Baseline		Maximum Grade on-Treatment						
Grade	**Total**	**1**	**2**	**3a**	**3b**	**4**	**5**	**Missing**
Phase I/II Study (Bosutinib)								
Grade 1	156	35	95	13	10	1	1	1
Grade 2	319	8	124	124	50	9	2	2
Grade 3a	69	0	3	23	34	9	0	0
Grade 3b	24	0	1	1	6	15	1	0
Grade 4	1	0	0	0	0	0	1	0
Grade 5	0	0	0	0	0	0	0	0
Missing	1	0	1	0	0	0	0	0
Total	570	43	224	161	100	34	5	3
Phase III (Bosutinib)								
Grade 1	118	18	79	17	4	0	0	0
Grade 2	119	2	44	55	13	5	0	0
Grade 3a	10	0	1	5	3	1	0	0
Grade 3b	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0	0
Missing	1	0	1	0	0	0	0	0
Total	248	20	125	77	20	6	0	0
Phase III (Imatinib)								
Grade 1	112	17	80	12	0	2	0	1
Grade 2	124	2	61	48	11	2	0	0
Grade 3a	12	0	1	3	7	1	0	0
Grade 3b	2	0	0	0	1	1	0	0
Grade 4	0	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0	0
Missing	1	0	1	0	0	0	0	0
Total	251	19	143	63	19	6	0	1

Baseline is defined as the last nonmissing laboratory value before first dose. Estimated glomerular filtration rate was calculated on the basis of the Modification in Diet in Renal Disease method and graded on the basis of the Kidney Disease Improving Global Outcomes criteria defined as follows: Grade 1 = values $\geq$ 90, Grade 2 = values 60 to $<$ 90, Grade 3a = values 45 to $<$ 60, Grade 3b = values 30 to $<$ 45, Grade 4 = values 15 to $<$ 30, Grade 5 = values $<$ 15 mL/min/1.73 m^2.