Safety and efficacy of second-line bosutinib for chronic phase chronic myeloid leukemia over a five-year period: final results of a phase I/II study

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Supplementary Materials

Methods

Eligibility criteria

Eligible patients were aged ≥18 years with a confirmed diagnosis of Philadelphia chromosome–positive (Ph+) chronic phase (CP) chronic myeloid leukemia that was either resistant to full-dose imatinib or intolerant to any dose of imatinib. Primary imatinib resistance was defined as failure to achieve or maintain either hematologic improvement within 4 weeks, a complete hematologic response after 12 weeks, any cytogenetic response by 24 weeks, or a major cytogenetic response (MCyR) by 12 months with imatinib ≥600 mg/day. Acquired resistance was defined as loss of MCyR or hematologic response. Imatinib intolerance was defined as an inability to receive imatinib because of imatinib-related grade 4 hematologic adverse events (AEs) lasting >7 days, imatinib-related grade ≥3 nonhematologic AEs, grade 2 AEs that persist despite dose reductions and concomitant medications, or loss of response on lower-dose imatinib among patients with previous toxicity.

In addition to prior imatinib therapy, patients were required to have an Eastern Cooperative Oncology Group Performance Status of 0 or 1, no antiproliferative or antileukemia treatment (with the exception of hydroxyurea or anagrelide) within 7 days of initiating bosutinib therapy, and adequate bone marrow function (imatinib-resistant patients), hepatic function, and renal function. Patients were excluded if they had a history of clinically significant or uncontrolled cardiac disease, had prolonged QTc

(average of >0.45 sec at screening), or had uncorrected hypomagnesemia or hypokalemia. Full eligibility criteria have been previously described.[1]

Patients with documented history of T315I mutation could enroll in the study until a protocol amendment (May 28, 2008) made these patients ineligible. Patients already being treated could remain on study if enrollment had occurred before the amendment or if a baseline sample had subsequently tested positive for the T315I mutation.

Statistical methods

Time-to-event distributions and probabilities were estimated using the Kaplan-Meier method or cumulative incidence adjusting for the competing risk of treatment discontinuation without an event of PD/death or transformation. Two-sided 95% confidence intervals (CIs) for response rates and Kaplan-Meier quartiles were determined using the exact binomial and Brookmeyer-Crowley linear transformation methods, respectively. For Kaplan-Meier and cumulative incidence yearly probability estimates, two-sided 95% CIs were based on Greenwood's formula and Gray's method, respectively.

Baseline and on-treatment (time-dependent) patient characteristics were evaluated as potential prognostic factors using backward-elimination, multivariate, cause-specific Cox regression models for duration of response and progression-free survival and a multivariate Cox regression model for overall survival. *P* values <0.05 were statistically significant and no adjustments for multiple comparisons were made.

Backward elimination criteria was 0.20 for all models. Results are presented as hazard ratios (95% confidence intervals).

Covariates for multivariate Cox regression analysis

Prior response to imatinib was defined as achievement of at least a minimal cytogenetic response (standard cytogenetic criteria: 66%–95% Ph+ cells from bone marrow or *BCR-ABL1* from fluorescence in situ hybridization [FISH]). Determination of Ph+ ratio occurred during the screening visit within 14 days before registration of the patient in the study and required ≥20 metaphases for standard cytogenetics or ≥200 cells for FISH. Disease duration is defined as the time between the primary diagnosis and date of administration of first dose of study drug. Patients initiating imatinib treatment ≥6 months after diagnosis or after prior interferon therapy were considered to be in late CP. Bosutinib-sensitive mutations are those resulting in half maximal inhibitory concentration (IC_{50}) ≤3-fold higher than wild type (M244V, Q252H, Y253H, Y253F, D276G, E279K, E292L, F317L, M343T, M351T, F359I, F359V, L384M, H396P, H396R, G398R, F486S); moderately bosutinib-resistant mutations are those with IC_{50} values ≥3 to ≤10-fold higher than wild type (L248V, G250E, E255V, and T315A); highly bosutinib-resistant mutations are those with IC_{50} values >10-fold higher than wild type (L248R, L248R+F359I, E255K, V299L, T315I, T315V, F317R, F317V); the sensitivity of all other mutations is unknown.[2,3] Patients with multiple mutations of different sensitivities were categorized based on the following hierarchy: highly bosutinib-insensitive, bosutinib-insensitive, unknown sensitivity, and bosutinib-sensitive.

Supplementary Table S1. Demographics and Baseline Disease Characteristics

	IM-R (n=195)	IM-I (n=89)	Total (n=284)
Median (range) age, y	51 (18–86)	55 (23–91)	53 (18–91)
<65 y, n (%)	159 (82)	62 (70)	221 (78)
≥65 y, n (%)	36 (18)	27 (30)	63 (22)
Men, n (%)	113 (58)	36 (40)	149 (52)
Race, n (%)			
White	131 (67)	55 (62)	186 (65)
Asian	41 (21)	21 (24)	62 (22)
Black	11 (6)	5 (6)	16 (6)
Other	12 (6)	8 (9)	20 (7)
ECOG Performance Status, n (%)			
0	151 (77)	66 (74)	217 (76)
1	44 (23)	21 (24)	65 (23)
2	0	1 (1)	1 (<1)
Median time since CML diagnosis (range), y	4.1 (0.6–15.1)	2.7 (0.1–13.6)	3.7 (0.1–15.1)
Number of prior therapies, n (%)			
1	118 (61)	66 (74)	184 (65)
2	77 (39)	23 (26)	100 (35)
Prior non-TKI therapies, n (%)			
Interferon	77 (39)	23 (26)	100 (35)
Stem cell transplant	6 (3)	2 (2)	8 (3)

CML=chronic myeloid leukemia; ECOG=Eastern Cooperative Oncology Group; IM-I=imatinib intolerant; IM-R=imatinib-resistant; TKI=tyrosine kinase inhibitor.

Supplementary Table S2. Treatment Discontinuations by Year of Treatment*

Reasons for Discontinuation	Year 1 (n=284)	Year 2 (n=197)	Year 3 (n=153)	Year 4 (n=136)	Year 5 (n=123)	Total† (n=284)
Discontinued treatment,‡ n (%)	87 (31)	44 (22)	17 (11)	13 (10)	8 (7)	284 (100)
AE	47 (17)	10 (5)	2 (1)	4 (3)	1 (1)	67 (24)
PD	21 (7)	15 (8)	7 (5)	3 (2)	1 (1)	51 (18)
Patient request	9 (3)	5 (3)	2 (1)	2 (1)	1 (1)	24 (8)
Unsatisfactory response (efficacy)	5 (2)	9 (5)	4 (3)	1 (1)	2 (2)	23 (8)
Death	0	2 (1)	1 (1)	0	2 (2)	8 (3)
Investigator request	1 (<1)	0	1 (1)	1 (1)	0	8 (3)
Lost to follow-up	1 (<1)	1 (<1)	0	2 (1)	0	4 (1)
Symptomatic deterioration	1 (<1)	1 (<1)	0	0	0	2 (1)
Other	2 (1)	1 (<1)	0	0	1 (1)	96# (34)
Discontinuation due to any AE,§,‖ n						
Thrombocytopenia	14	2	0	0	1	17
Neutropenia	6	0	0	0	0	6
ALT increased	6	0	0	0	0	6
Diarrhea	3	1	0	0	0	4
Rash	3	0	0	0	0	3
AST increased	3	0	0	0	0	3
Anemia	3	0	0	0	0	3
Pneumonia	0	1	0	0	0	1
Intestinal obstruction	0	1	0	0	0	1
Abdominal adhesions	0	1	0	0	0	1
Cardiac failure	0	1	0	0	0	1
Lipase increased	0	1	0	0	0	1
White blood cell count increased	0	1	0	0	0	1
CAD	0	0	1	0	0	1
Scleroderma	0	0	1	0	0	1
Renal failure	0	0	1	0	0	1

Ascites[¶]	0	0	0	1	0	1
Serositis[¶]	0	0	0	1	0	1
Increased blood creatinine	0	0	0	1	0	1
Pulmonary hypertension	0	0	0	1	0	1

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CAD=coronary artery disease; PD=progressive disease.

*In both Parts 1 and 2, patients received treatment until PD, death, unacceptable toxicity, or withdrawal of consent; denominators for years 1–5 are the number of patients on treatment during those time periods.

[†]Includes data after year 5 until the cutoff date.

[‡]One year=48 weeks.

[§]AEs presented include those resulting in treatment discontinuation in years 2−5 or in ≥1% of patients overall.

[‖]Totals are not necessarily the sum of those for individual AEs as patients may report multiple AEs leading to discontinuation.

[¶]The same patient discontinued due to ascites and serositis.

[#]Includes patients who enrolled in an extension study and those for whom discontinuation of study by the sponsor was the primary reason for treatment discontinuation.

Supplementary Table S3. Treatment Outcomes for Patients Aged <65 and ≥65 Years

Parameter	<65 y (n=221)	≥65 y (n=63)	Total (n=284)
Response,* n/N evaluable[†] (%) [95% CI]			
Attained/maintained MCyR	123/201 (61) [54.1–68.0]	33/61 (54) [40.9–66.9]	156/262 (60) [53.3–65.5]
Attained MCyR	115/192 (60) [52.6–66.9]	26/54 (48) [34.3–62.2]	141/246 (57) [50.9–63.6]
Attained/maintained CCyR	101/201 (50) [43.1–57.4]	29/61 (48) [34.6–60.7]	130/262 (50) [43.4–55.8]
Attained CCyR	93/192 (48) [41.2–55.7]	23/54 (43) [29.2–56.8]	116/246 (47) [40.8–53.6]
Probability of maintaining MCyR at 5 y, % [95% CI][‡]	73 [64–81]	63 [42−78]	71 [63−78]
Probability of maintaining CCyR at 5 y, % [95% CI] [‡]	73 [62–81]	58 [35−75]	69 [60−77]
≥1 dose interruption due to AEs, n (%)	159 (72)	50 (79)	209 (74)
≥1 dose reduction due to AEs, n (%)	105 (48)	36 (57)	141 (50)
On-treatment death due to an AE,[§] n (%)	3 (1)	2 (3)	5 (2)
Discontinued treatment, n (%)	221 (100)	63 (100)	284 (100)
Enrolled in extension study	71 (32)	12 (19)	83 (29)
AE	47 (21)	20 (32)	67 (24)
PD	41 (19)	10 (16)	51 (18)
Patient request	15 (7)	9 (14)	24 (8)
Efficacy	18 (8)	5 (8)	23 (8)
Other	12 (5)	1 (2)	13 (5)
Death	3 (1)	5 (8)	8 (3)
Investigator request	7 (3)	1 (2)	8 (3)
Lost to follow-up	4 (2)	0	4 (1)
Symptomatic deterioration	2 (1)	0	2 (1)

Study discontinued by sponsor	1 (<1)	0	1 (<1)
Transformation to AP/BP CML at 5 y, ‖ % [95% CI]	5 [3–9]	3 [1–12]	5 [3–8]
PD/death at 5 y,¶ % [95% CI]	19 [15–25]	19 [11–32]	19 [15–24]
OS at 5 y,‡,** % [95% CI]	85 [79–90]	77 [61–86]	84 [78–88]

AE=adverse event; AP=accelerated phase; BP=blast phase; CCyR=complete cytogenetic response; CI=confidence interval; CML=chronic myeloid leukemia; MCyR=major cytogenetic response; OS=overall survival; PD=progressive disease.

*Response among evaluable patients. Response could be newly achieved during the study or maintained from baseline for ≥4 weeks and was determined using standard cytogenetics with ≥20 metaphases counted for postbaseline assessments (fluorescence in situ hybridization analysis of bone marrow aspirate or peripheral blood with ≥200 cells to detect *BCR-ABL1* was used if <20 metaphases were available postbaseline).[4]

†Evaluable patients received ≥1 bosutinib dose and had a valid baseline assessment of cytogenetic response with ≥20 metaphases or ≥1 Ph+ metaphase from bone marrow cytogenetics. Patients with a CCyR at baseline were excluded from the attained-only analyses.

‡Based on Kaplan-Meier estimates.

§AEs resulting in death were acute cardiac decompensation, heart failure and chronic obstructive pulmonary disease (same patient), congestive heart failure, suicide, and pneumonia.

‖Based on cumulative incidence adjusting for competing risk of treatment discontinuation without transformation.

¶Based on cumulative incidence adjusting for competing risk of treatment discontinuation without PD or death; PD defined as transformation to AP or BP CML, increasing white blood cell count (doubling over ≥1 mo with second count >20×10^9/L and confirmed ≥1 week later), or loss of confirmed complete hematologic response or unconfirmed MCyR).

**Analysis includes data from the long-term extension study.

Supplementary Table S4. Cytogenetic Response Before and After Bosutinib Dose Reduction

	IM-R (n=195)	IM-I (n=89)	Total (n=284)
Patients reducing dose to 400 mg, n	81	51	132
Attained/maintained MCyR,* n (%)	51 (63)	30 (59)	81 (61)
MCyR after reduction	39 (48)	18 (35)	57 (43)
Median (range) duration of MCyR (non-K-M), wk	134 (0–338)	185 (0–290)	167 (0–338)
MCyR before and after reduction	9 (11)	10 (20)	19 (14)
Median (range) duration of MCyR (non-K-M), wk	299 (11–324)	281 (44–342)	283 (11–342)
MCyR before but not after reduction	3 (4)	2 (4)	5 (4)
Newly-attained MCyR,* n (%)	44 (63)	23 (58)	67 (61)
Attained MCyR after reduction	32 (46)	16 (40)	48 (44)
Median (range) duration of MCyR (non-K-M), wk	122 (0–338)	185 (0–290)	150 (0–338)
Attained MCyR before and after reduction	9 (13)	6 (15)	15 (14)
Median (range) duration of MCyR (non-K-M), wk	299 (11–324)	281 (44–342)	283 (11–342)
Attained MCyR before but not after reduction	3 (4)	1 (3)	4 (4)
Patients reducing dose to 300 mg, n	32	18	50
Attained/maintained MCyR,† n (%)	22 (69)	7 (39)	29 (58)
MCyR after reduction	6 (19)	2 (11)	8 (16)
Median (range) duration of MCyR (non-K-M), wk	17 (0–251)	116 (0–233)	17 (0–251)
MCyR before and after reduction	15 (47)	5 (28)	20 (40)
Median (range) duration of MCyR (non-K-M), wk	252 (11–323)	276 (97–331)	260 (11–331)
MCyR before but not after reduction	1 (3)	0	1 (2)
Newly-attained MCyR,† n (%)	20 (69)	5 (36)	25 (58)

Attained MCyR after reduction	7 (24)	2 (14)	9 (21)
Median (range) duration of MCyR (non-K-M), wk	22 (0–251)	116 (0–233)	22 (0–251)
Attained MCyR before and after reduction	12 (41)	3 (21)	15 (35)
Median (range) duration of MCyR (non-K-M), wk	254 (11–323)	276 (97–283)	267 (11–323)
Attained MCyR before but not after reduction	1 (3)	0	1 (2)

IM-I=imatinib intolerant; IM-R=imatinib-resistant; K-M=Kaplan-Meier; MCyR=major cytogenetic response.
*Denominators are the number of patients who dose reduced to bosutinib 400 mg daily for the respective cohort. Denominators for newly-attained response rates also exclude patients with CCyR at baseline.
†Denominators are the number of patients who dose reduced to bosutinib 300 mg daily for the respective cohort. Denominators for newly-attained response rates also exclude patients with CCyR at baseline.

Supplementary Table S5. Incidence of and Response by Mutation Status

	Incidence*			Response to BOS, n/n Evaluable	
	IM-R	**IM-I**	**Total**	**CHR**	**MCyR**
Baseline					
Patients assessed for mutations at baseline, n	156	68	224	194/223	121/208
No mutation at baseline	83 (53)	62 (91)	145 (65)	128/145	75/130
1 mutation	60 (38)	6 (9)	66 (29)	56/65	40/66
≥1 mutations	73 (47)	6 (9)	79 (35)	66/78	46/78
≥2 mutations	13 (8)	0	13 (6)	10/13	6/12
Individual mutations					
L248V	5 (3)	0	5 (2)	5/5	3/5
G250E	6 (4)	0	6 (3)	5/6	3/5
Y253F	1 (1)	0	1 (<1)	1/1	0
Y253H	4 (3)	0	4 (2)	4/4	4/4
E255K	3 (2)	0	3 (1)	0	2/3
E255V	2 (1)	0	2 (1)	2/2	1/2
M244V	6 (4)	0	6 (3)	6/6	4/6
D276G	1 (1)	0	1 (<1)	1/1	0
E286G	1 (1)	0	1 (<1)	1/1	1/1
L298V	1 (1)	0	1 (<1)	0	0
F311I	2 (1)	0	2 (1)	2/2	1/2
F311L	2 (1)	0	2 (1)	2/2	2/2
T315I	9 (6)	0	9 (4)	2/9	2/9
F317L	4 (3)	0	4 (2)	4/4	3/4
N331S	1 (1)	0	1 (<1)	1/1	1/1
V338A	1 (1)	0	1 (<1)	1/1	1/1
M351T	8 (5)	0	8 (4)	8/8	7/8
E355A	1 (1)	0	1 (<1)	1/1	1/1

E355G	1 (1)	0	1 (<1)	1/1	1/1
F359I	1 (1)	0	1 (<1)	1/1	1/1
F359S	0	1 (1)	1 (<1)	1/1	1/1
F359V	8 (5)	1 (1)	9 (4)	8/9	4/9
L364P	1 (1)	0	1 (<1)	1/1	1/1
N368S	1 (1)	0	1 (<1)	1/1	0
L387F	0	1 (1)	1 (<1)	1/1	0
L387M	1 (1)	0	1 (<1)	1/1	1/1
M388L	1 (1)	0	1 (<1)	1/1	1/1
H396P	1 (1)	1 (1)	2 (1)	2/2	2/2
H396R	2 (1)	0	2 (1)	1/2	0
T406A	1 (1)	0	1 (<1)	1/1	0
S417F	1 (1)	0	1 (<1)	1/1	1/1
D421G	1 (1)	0	1 (<1)	1/1	0
I432T	1 (1)	0	1 (<1)	1/1	0
E450G	1 (1)	0	1 (<1)	1/1	0
E450V	1 (1)	0	1 (<1)	1/1	1/1
E453G	1 (1)	0	1 (<1)	0	0
E453K	0	1 (1)	1 (<1)	1/1	1/1
E453Q	1 (1)	0	1 (<1)	1/1	1/1
E453R	1 (1)	0	1 (<1)	0	0
E459K	0	1 (1)	1 (<1)	1/1	0
K459G	1 (1)	0	1 (<1)	1/1	0
K459R	1 (1)	0	1 (<1)	1/1	0
P480A	1 (1)	0	1 (<1)	1/1	1/1
				Best Response to BOS, n/n With Mutation	
				CHR	**PCyR**	**CCyR**
***Newly-emerging*[†]**					

Patients assessed for new mutations, n	73	31	104	–	–	–
Patients with new mutations	20 (27)	6 (19)	26 (25)	–	–	–
Individual mutations						
T315I[‡,§,¶]	7 (35)	2 (33)	9 (35)	5/9	2/9	1/9
V299L[‡]	3 (15)	2 (33)	5 (19)	3/5	1/5	1/5
M244V[¶]	1 (5)	1 (17)	2 (8)	0	0	1/2
E255V	1 (5)	0	1 (4)	1/1	0	0
E450A	1 (5)	0	1 (4)	1/1	0	0
E450G	0	1 (17)	1 (4)	1/1	0	0
F359V[§]	1 (5)	0	1 (4)	0	0	1/1
G250E[‡,§]	1 (5)	0	1 (4)	1/1	0	0
H295L	1 (5)	0	1 (4)	0	0	1/1
K378E	1 (5)	0	1 (4)	0	1/1	0
L273M	1 (5)	0	1 (4)	0	0	1/1
S348L	1 (5)	0	1 (4)	0	0	1/1
S410G	1 (5)	0	1 (4)	0	0	1/1

BOS=bosutinib; CHR=complete hematologic response; CCyR=complete cytogenetic response; IM-I=imatinib-intolerant; IM-R=imatinib-resistant; MCyR=major cytogenetic response; PCyR=partial cytogenetic response.

Values are expressed as n (%) unless otherwise noted. Shaded rows indicate mutations that are resistant (light gray) or highly resistant (dark gray) to BOS.[2]

*Denominators are number of patients assessed for mutations at baseline or newly-emerging during the study.

[†]Newly-emerging mutations are those not present at baseline.

[‡]Mutations that are resistant or highly resistant to dasatinib.

[§]Mutations that are resistant or highly resistant to nilotinib.

[¶]One patient had no detectable response.

Supplementary Table S6. TEAEs Occurring in ≥10% of Patients and Laboratory Abnormalities Occurring in 30% of Patients Overall

	IM-R (n=195)		IM-I (n=89)		Total (n=284)	
TEAE, n (%)	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Any TEAE	194 (99.5)	145 (74.4)	89 (100)	75 (84.3)	283 (99.6)	220 (77.5)
*Hematologic**						
Thrombocytopenia	77 (39.5)	45 (23.1)	41 (46.1)	27 (30.3)	118 (41.5)	72 (25.4)
Anemia	51 (26.2)	23 (11.8)	32 (36.0)	15 (16.9)	83 (29.2)	38 (13.4)
Neutropenia	29 (14.9)	16 (8.2)	17 (19.1)	12 (13.5)	46 (16.2)	28 (9.9)
Leukopenia	22 (11.3)	8 (4.1)	15 (16.9)	7 (7.9)	37 (13.0)	15 (5.3)
Gastrointestinal						
Diarrhea	167 (85.6)	18 (9.2)	76 (85.4)	9 (10.1)	243 (85.6)	27 (9.5)
Nausea	85 (43.6)	1 (0.5)	46 (51.7)	4 (4.5)	131 (46.1)	5 (1.8)
Vomiting	73 (37.4)	3 (1.5)	33 (37.1)	8 (9.0)	106 (37.3)	11 (3.9)
Abdominal pain	52 (26.7)	4 (2.1)	25 (28.1)	2 (2.2)	77 (27.1)	6 (2.1)
Upper abdominal pain	42 (21.5)	1 (0.5)	17 (19.1)	0	59 (20.8)	1 (0.4)
Constipation	22 (11.3)	0	17 (19.1)	1 (1.1)	39 (13.7)	1 (0.4)
Infections and infestations						
Nasopharyngitis	25 (12.8)	0	13 (14.6)	0	38 (13.4)	0
Urinary tract infection	22 (11.3)	2 (1.0)	8 (9.0)	0	30 (10.6)	2 (0.7)
Influenza	22 (11.3)	0	7 (7.9)	2 (2.2)	29 (10.2)	2 (0.7)
Upper respiratory tract infection	19 (9.7)	0	10 (11.2)	1 (1.1)	29 (10.2)	1 (0.4)
Investigations						
ALT increased	42 (21.5)	15 (7.7)	21 (23.6)	9 (10.1)	63 (22.2)	24 (8.5)
AST increased	38 (19.5)	7 (3.6)	18 (20.2)	4 (4.5)	56 (19.7)	11 (3.9)
Weight decreased	28 (14.4)	1 (0.5)	8 (9.0)	2 (2.2)	36 (12.7)	3 (1.1)
Other						
Rash	64 (32.8)	15 (7.7)	39 (43.8)	11 (12.4)	103 (36.3)	26 (9.2)
Pyrexia	58 (29.7)	1 (0.5)	18 (20.2)	2 (2.2)	76 (26.8)	3 (1.1)

Fatigue	49 (25.1)	1 (0.5)	24 (27.0)	2 (2.2)	73 (25.7)	3 (1.1)
Cough	46 (23.6)	0	19 (21.3)	0	65 (22.9)	0
Headache	35 (17.9)	0	18 (20.2)	0	53 (18.7)	0
Arthralgia	31 (15.9)	2 (1.0)	17 (19.1)	1 (1.1)	48 (16.9)	3 (1.1)
Decreased appetite	30 (15.4)	2 (1.)	12 (13.5)	0	42 (14.8)	2 (0.7)
Asthenia	26 (13.3)	7 (3.6)	16 (18.0)	0	42 (14.8)	7 (2.5)
Back pain	22 (11.3)	1 (0.5)	16 (18.0)	0	38 (13.4)	1 (0.4)
Oropharyngeal pain	25 (12.8)	0	10 (11.2)	0	35 (12.3)	0
Dyspnea	24 (12.3)	5 (2.6)	10 (11.2)	0	34 (12.0)	5 (1.8)
Pain in extremity	28 (14.4)	2 (1.0)	4 (4.5)	0	32 (11.3)	2 (0.7)
Pleural effusion	21 (10.8)	5 (2.6)	9 (10.1)	4 (4.5)	30 (10.6)	9 (3.2)
Cardiac AEs†	25 (12.8)‡	11 (5.6)	12 (13.5)	5 (5.6)	37 (13.0)‡	16 (5.6)
Vascular AEs§	13 (6.7)	9 (4.6)	9 (10.1)	2 (2.2)	22 (7.7)	11 (3.9)
Hypertension-related AEs‖	19 (9.7)	7 (3.6)	7 (7.9)	1 (1.1)	26 (9.2)	8 (2.8)
Renal AEs¶	27 (13.8)#	5 (2.6)	10 (11.2)	1 (1.1)	37 (13.0)#	6 (2.1)
Laboratory Abnormalities, n (%)	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Any laboratory abnormality	194 (99.5)	136 (69.7)	89 (100)	68 (76.4)	283 (99.6)	204 (71.8)
Hematologic						
Low hemoglobin	180 (92.3)	24 (12.3)	76 (85.4)	17 (19.1)	256 (90.1)	41 (14.4)
Low lymphocytes	149 (76.4)	25 (12.8)	71 (79.8)	16 (18.0)	220 (77.5)	41 (14.4)
Low platelet count	131 (67.2)	47 (24.1)	64 (71.9)	27 (30.3)	195 (68.7)	74 (26.1)
Low WBC count	102 (52.3)	13 (6.7)	47 (52.8)	10 (11.2)	149 (52.5)	23 (8.1)
Low ANC	98 (50.3)	25 (12.8)	47 (52.8)	19 (21.3)	145 (51.1)	44 (15.5)
Nonhematologic						
High ALT	109 (55.9)	20 (10.3)	61 (68.5)	13 (14.6)	170 (59.9)	33 (11.6)
High AST	97 (49.7)	8 (4.1)	50 (56.2)	7 (7.9)	147 (51.8)	15 (5.3)
Low phosphorous	91 (46.7)	20 (10.3)	35 (39.3)	6 (6.7)	126 (44.4)	26 (9.2)
Low calcium	85 (43.6)	6 (3.1)	40 (44.9)	4 (4.5)	125 (44.0)	10 (3.5)

High glucose	87 (44.6)	4 (2.1)	29 (32.6)	5 (5.6)	116 (40.8)	9 (3.2)
High creatinine	78 (40.0)	5 (2.6)	38 (42.7)	2 (2.2)	116 (40.8)	7 (2.5)
High alkaline phosphatase	73 (37.4)	0	34 (38.2)	0	107 (37.7)	0
Low bicarbonate	62 (31.8)	0	28 (31.5)	1 (1.1)	90 (31.7)	1 (0.4)
High lipase	57 (29.2)	24 (12.3)	32 (36.0)	9 (10.1)	89 (31.3)	33 (11.6)

AE=adverse event; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; IM-I=imatinib-intolerant; IM-R=imatinib-resistant; TEAE=treatment-emergent adverse event; WBC=white blood cell.

*Hematologic TEAEs (thrombocytopenia, anemia, neutropenia, leukopenia) were clustered separately with the corresponding terms from the Medical Dictionary for Regulatory Activities system order class (SOC) Investigations (Platelet count decreased, Hemoglobin decreased, Neutrophil count decreased, WBC count decreased).

[†]Includes the high-level group terms (HLGTs) Cardiac arrhythmias, Pericardial disorders, and Heart failures under the Cardiac disorders SOC; the preferred terms (PTs) Cardiac death, Sudden cardiac death, and Sudden death under the General disorders and administration site conditions SOC; the PTs Decreased ejection fraction, Abnormal electrocardiogram QT interval, Prolonged electrocardiogram QT, Torsade de pointes, Ventricular tachycardia, Congenital long QT syndrome under the Investigations SOC.

[‡]Includes 2 patients who had grade 5 events.

[§]Includes the HLGTs Coronary artery disorders, Arteriosclerosis, stenosis, vascular insufficiency and necrosis, and Embolism and thrombosis; the high-level terms (HLTs) Arterial therapeutic procedures (excluding aortic), Central nervous system hemorrhages and cerebrovascular accidents, and Central nervous system vascular disorders not elsewhere classified (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.

[‖]Includes 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.

[¶]Includes the HLT Renal failure and impairment; the PTs Blood creatinine abnormal, Blood creatinine increased, Creatinine renal clearance abnormal, Creatinine renal clearance decreased, Glomerular filtration rate abnormal, and Glomerular filtration rate decreased.

[#]Includes 1 patient who had a grade 5 event.

Supplementary Table S7. Cross-Intolerance* in Patients Intolerant to Imatinib

Reason for Prior Intolerance†	Intolerant to Prior IM, n	Same AE on BOS, n (%)	Outcome with BOS Due to Same AE		
			Dose Delay, n (%)	Dose Reduction, n (%)	Discontinued, n (%)
Any AE	85‡	52 (61)	25 (29)	14 (16)	14 (16)
Hematologic disorders					
Anemia	11	5 (45)	1 (9)	0	0
Leukopenia	4	1 (25)	1 (25)	0	0
Neutropenia	13	5 (38)	3 (23)	2 (15)	2 (15)
Thrombocytopenia	16	12 (75)	8 (50)	6 (38)	4 (25)
Gastrointestinal disorders					
Diarrhea	7	6 (86)	2 (29)	2 (29)	1 (14)
Nausea	5	4 (80)	1 (20)	0	0
Vomiting	4	2 (50)	2 (50)	0	1 (25)
Other					
Fatigue	6	2 (33)	1 (17)	1 (17)	1 (17)
Edema	10	4 (40)	0	0	0
Liver disorder	3	1 (33)	0	0	0
Fluid retention	3	0	0	0	0
Myalgia	4	1 (25)	0	1 (25)	0
Rash	12	8 (67)	4 (33)	0	1 (8)

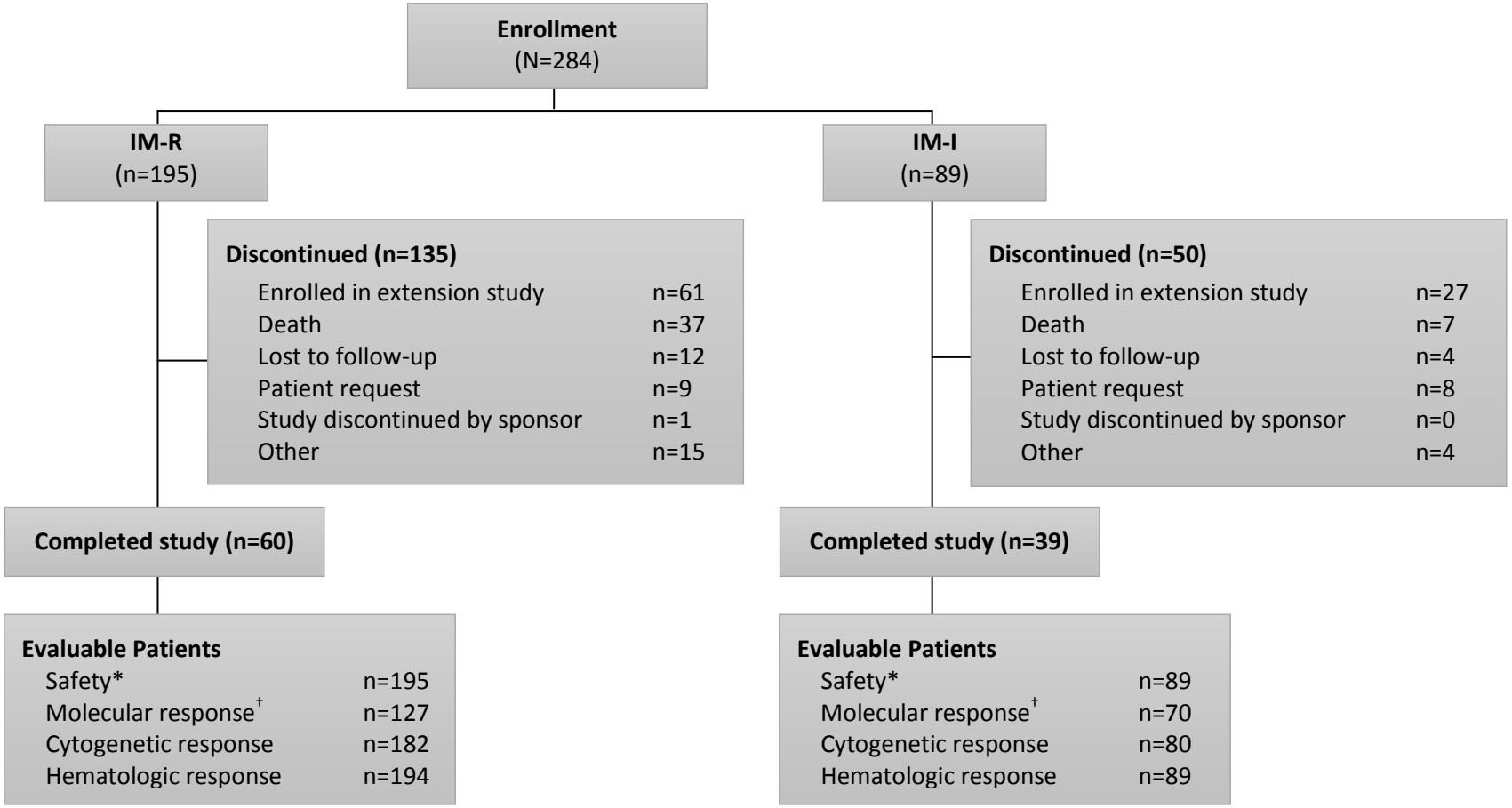
AE=adverse event; BOS=bosutinib; IM=imatinib.

*Defined as discontinuing bosutinib and a prior tyrosine kinase inhibitor due to the same AE.

†Defined as permanent discontinuation due to this treatment-emergent AE; AEs leading to discontinuation in ≥3 prior imatinib-treated patients are presented.

‡The specific AE reported as the reason for discontinuation of prior imatinib was unknown for 4 patients.

Figure S1. Patient Disposition.



IM-I=imatinib-intolerant; IM-R=imatinib-resistant.

*Includes all patients who received ≥1 dose.

†Not assessed using the international scale; data from patients at sites in China, India, Russia, and South Africa are not available.

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