LETTER TO THE EDITOR

Cross-intolerance with bosutinib after prior tyrosine kinase inhibitors for Philadelphia chromosome-positive leukemia: long-term analysis of a phase I/II study

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Supplementary Table S1. Overall safety of bosutinib in imatinib-intolerant and dasatinib-intolerant patients.*

	Imatinib-Intolerant (N=148)		Dasatinib-Intolerant (N=75)	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any TEAE†, N (%)	147 (99.3)	122 (82.4)	75 (100.0)	65 (86.7)
Diarrhea	118 (79.7)	16 (10.8)	62 (82.7)	5 (6.7)
Nausea	71 (48.0)	4 (2.7)	39 (52.0)	2 (2.7)
Rash	64 (43.2)	12 (8.1)	29 (38.7)	4 (5.3)
Vomiting	60 (40.5)	10 (6.8)	35 (46.7)	3 (4.0)
Thrombocytopenia	59 (39.9)	43 (29.1)	30 (40.0)	26 (34.7)
Abdominal pain	39 (26.4)	3 (2.0)	17 (22.7)	1 (1.3)
Anemia	37 (25.0)	23 (15.5)	17 (22.7)	9 (12.0)
Cough	36 (24.3)	0	19 (25.3)	0
Fatigue	34 (23.0)	4 (2.7)	24 (32.0)	4 (5.3)
Headache	34 (23.0)	3 (2.0)	19 (25.3)	5 (6.7)
Pleural effusion	18 (12.2)	5 (3.4)	17 (22.7)	7 (9.3)
Dyspnea	18 (12.2)	2 (1.4)	17 (22.7)	4 (5.3)
Pyrexia	27 (18.2)	2 (1.4)	16 (21.3)	1 (1.3)

AE: adverse event; TEAE: treatment-emergent adverse event.

*≥20% of patients experiencing the TEAE (any grade) in either the imatinib- or dasatinib-intolerant groups. Classifications of AEs are based on the Medical Dictionary for Regulatory Activities (MedDRA version 18.0) preferred terms. For each patient, AEs are reported for the highest toxicity observed.

†TEAE was defined as any AE that first occurred or worsened in severity after the first administration of bosutinib through 30 days after the last dose. AE severity was graded according to the NCI Common Terminology Criteria for Adverse Events version 3.0.

Supplementary Table S2. Adverse event recurrence, bosutinib dose modifications, and cross-intolerance in patients with prior nilotinib intolerance.*

Cause of nilotinib intolerance	No. of patients who discontinued nilotinib due to intolerance, n	Nilotinib-intolerant patients (N=7)				
		Same AE with bosutinib, n (%)	Same grade 3/4 AE with bosutinib n (%)	Bosutinib dose delay due to same AE, n (%)	Bosutinib dose reduction due to same AE, n (%)	Bosutinib discontinuation due to same AE, n (%)
Any adverse event	7	6 (85.7)	3 (42.9)	5 (71.4)	2 (28.6)	1 (14.3)
Hematologic AE						
Thrombocytopenia	2	2 (100.0)	2 (100.0)	2 (100.0)	1 (50.0)	0
Neutropenia	1	1 (100.0)	1 (100.0)	1 (100.0)	0	0
Non-hematologic AE						
Rash	3	2 (66.7)	0	1 (33.3)	0	0
Pleural effusion	1	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)
Headache	1	0	0	0	0	0

AE: adverse event.

*All patients who received at least one dose of bosutinib were included in the safety analysis.

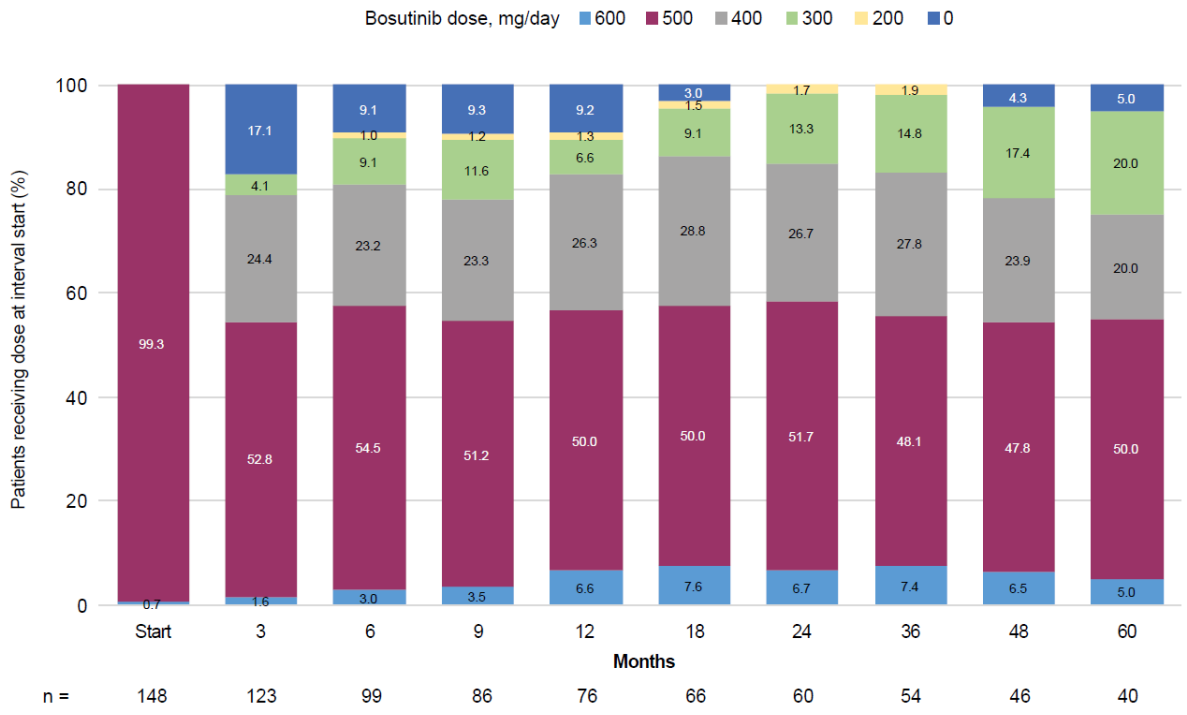
Supplementary Figure S1. Bosutinib treatment summary in (A) imatinib-intolerant and dasatinib-intolerant patients and bosutinib dose over time in (B) imatinib-intolerant and (C) dasatinib-intolerant patients.

A

	Imatinib-Intolerant (N=148)				**Dasatinib-Intolerant (N=75)**		
	CP2L (N=89)	**CP3L (N=36)**	**ADV (N=23)**	**Total (N=148)**	**CP3L (N=52)**	**ADV (N=23)**	**Total (N=75)**
Median duration of bosutinib therapy (range), months	24.2 (0.3–84.3)	8.0 (0.2–71.5)	5.6 (<0.1–88.6)	11.1 (<0.1–88.6)	9.9 (0.2–93.2)	7.6 (0.3–85.6)	8.6 (0.2–93.2)
Median bosutinib dose intensity (range), mg/day	421.1 (127.8–596.2)	391.9 (184.8–584.9)	488.1 (171.0–571.7)	417.5 (127.8–596.2)	407.1 (184.8–563.2)	442.9 (171.0–539.2)	428.6 (171.0–563.2)
≥1 bosutinib dose reduction due to AE, n (%)	52 (58.4)	25 (69.4)	9 (39.1)	86 (58.1)	33 (63.5)	12 (52.2)	45 (60.0)
≥1 bosutinib dose interruption due to AE, n (%)	76 (85.4)	29 (80.6)	15 (65.2)	120 (81.1)	42 (80.8)	17 (73.9)	59 (78.7)
Bosutinib dose escalation to 600 mg, n (%)	3 (3.4)	6 (16.7)	3 (13.0)	12 (8.1)	10 (19.2)	3 (13.0)	13 (17.3)

ADV: advanced Ph+ leukemia cohort; AE: adverse event; CP2L: chronic phase chronic myeloid leukemia second-line cohort; CP3L: chronic phase chronic myeloid leukemia third-/fourth-line cohort.

B



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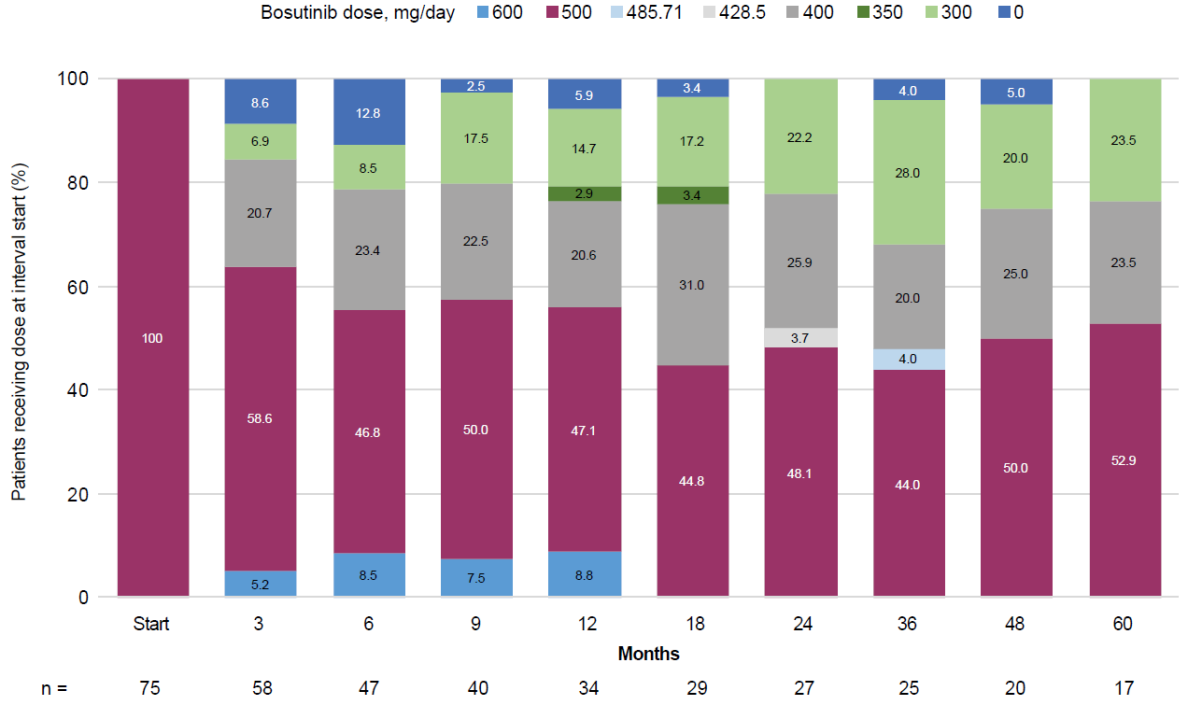

n = patients who remain on treatment at each time point