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

The approval of tyrosine kinase inhibitors (TKI) has significantly improved patient outcomes *versus* previous standard of care for Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) and reduced the frequency of progression from chronic phase (CP) to accelerated phase (AP) and blast phase (BP). Although most patients have a favorable outcome with front-line TKI, approximately half may require switching to an alternative TKI due to resistance or intolerance to one or more prior TKI.[1] Long-term (≥4 years) follow-up data from a phase I/II study (*clinicaltrials.gov identifier: NCT00261846*) was analyzed to assess the safety profile of bosutinib, an orally active, dual Src/Abl TKI, in patients with prior TKI intolerance, and to identify cross-intolerance between bosutinib and prior TKI across patients with Ph+ CP CML and advanced (ADV) leukemias (AP or BP CML or Ph+ acute lymphoblastic leukemia [ALL]). The results confirm that cross-intolerance with bosutinib in patients with prior TKI intolerance was <20%.

Bosutinib was approved as a second-line (2L) or third-/fourth-line (3L/4L) therapy for Ph+ CP, AP, or BP CML following resistance or intolerance to prior TKI therapy based on data from a phase I/II study (*clinicaltrials gov identifier: NCT00261846*).[2-4] Bosutinib is also approved as front-line therapy based on results from the phase III BFORE trial.[5] Since TKI share a common mechanism of action, cross-intolerance, i.e., discontinuation of a TKI due to the same adverse event (AE) responsible for discontinuation of a prior TKI, is a frequent concern. Previous reports have suggested this to be modest to minimal for dasatinib or nilotinib after intolerance to prior imatinib therapy.[6,7]

Study details were published previously.[2,3] This analysis included all patients who had developed intolerance to prior imatinib, dasatinib, and/or nilotinib, defined as an inability to take the drug(s) due to treatment-related grade 4 hematologic toxicity lasting >7 days, treatment-related grade ≥3 non-hematologic toxicity, persistent grade 2 toxicity not responding to dose reductions and/or medical management, or loss of previously attained response on a lower TKI dose and an inability to receive a higher dose due to treatment-related toxicity. Patients should have recovered to grade ≤1 or to baseline from any toxicities of prior anti-cancer treatment prior to enrollment.

Patients received a starting dose of 500 mg bosutinib once daily. Dose increases were permitted for lack of efficacy (in the absence of treatment-related grade ≥3 AE) and dose decreases/interruptions for treatment-related toxicities. Patients continued treatment with bosutinib until disease progression, death, unacceptable toxicity, or withdrawal of consent.

Safety was assessed throughout the study and AE graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. A treatment-emergent AE (TEAE) was defined as any AE that first occurred or worsened in severity after the first dose of bosutinib through 30 days after the last dose. Here we assessed the incidence of AE recurrence, bosutinib dose delay (temporary halt due to an AE) or reduction (a decrease in dose from the initial dose or from an escalated dose, due to an AE), and cross-intolerance across AE and AE clusters (which included a set of Medical Dictionary for Regulatory Activities AE terms). Data from ≥4 years of follow-up from a locked database were used for this analysis.

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Practice Guidelines, and local regulatory requirements. The protocol was approved by the Institutional Review Board at each study center. All patients provided written informed consent.

This analysis included 148 imatinib-intolerant, 75 dasatinib-intolerant (Table 1) and seven nilotinib-intolerant patients. Given the small nilotinib-intolerant cohort, only AE recurrence, bosutinib dose modifications, and cross-intolerance data are presented. Twenty-seven imatinib-intolerant patients were also intolerant to dasatinib (21 in the CP CML 3L cohort and 6 in the ADV cohort) and were included in both imatinib-intolerant and dasatinib-intolerant groups. At study completion, 81.8% and 89.3% of patients had discontinued treatment in the imatinib-intolerant and dasatinib-intolerant cohort respectively, 37.8% and 36.0%, respectively, due to AE. Median duration of bosutinib treatment for imatinib-intolerant and dasatinib-intolerant patients was 11.1 and 8.6 months, respectively; median dose intensity was 417.5 and 428.6 mg/day, respectively (*Online Supplementary Figure S1A*). Sixty (40.5%) and 27 (36.0%) imatinib- and dasatinib-intolerant patients received bosutinib for >2 years, and 46 (31.1%) and 20 (26.7%) for >4 years, respectively. At all time points, 500 mg/day was the most commonly-utilized dosage and ≥68% of patients with prior imatinib and/or dasatinib intolerance were receiving ≥400 mg/day (*Online Supplementary Figure S1B, C*).

In the imatinib-intolerant group, 147 (99.3%) patients had at least one TEAE of any grade with bosutinib, and 122 (82.4%) had a grade ≥3 TEAE (*Online Supplementary Table*

S1). In the dasatinib-intolerant group, all patients experienced at least one TEAE while receiving bosutinib; 65 (86.7%) had a grade ≥3 TEAE (*Online Supplementary Table S1*). In both groups, the most frequent TEAE of any grade were diarrhea, nausea, vomiting, thrombocytopenia, and rash.

Overall, of the 142 patients in which the AE responsible for imatinib intolerance was reported, 23 (16.2%) patients were cross-intolerant to bosutinib. The incidence of grade 3/4 recurrence with bosutinib of hematologic AE leading to imatinib discontinuation was highest for thrombocytopenia (n=23 [67.6%]), followed by pancytopenia (n=7 [63.6%]) (Table 2). Thrombocytopenia was also the AE that most frequently led to bosutinib dose delay (n=22 [64.7%]) and dose reduction (n=15 [44.1%]), and led to cross-intolerance in 11 (32.4%) patients. Pancytopenia led to dose delay, dose reduction, or cross-intolerance in six (54.5%), four (36.4%), and four (36.4%) patients, respectively. In addition, three (12.5%) patients were cross-intolerant to bosutinib due to neutropenia. Non-hematologic AE that resulted in bosutinib cross-intolerance were rash (4.5%), diarrhea (7.7%), vomiting (14.3%), pleural effusion (33.3%), renal impairment (100%), pulmonary fibrosis (100%), and glomerular filtration rate decreased (100%) (n=1 each; Table 2).

Overall, of the 74 patients in which the AE responsible for dasatinib intolerance was reported, 13 (17.6%) patients were cross-intolerant to bosutinib. Thrombocytopenia and neutropenia recurred at grade 3/4 with bosutinib in all patients with prior dasatinib intolerance due to these AE; thrombocytopenia led to bosutinib dose delay or reduction in 11 (84.6%) and ten (76.9%) patients, respectively, and was the hematologic AE that most frequently led to bosutinib cross-intolerance (n=5 [38.5%]). One (25.0%) and two (16.7%) patients were cross-intolerant to bosutinib due to neutropenia and pancytopenia, respectively (Table 3). Pleural effusion was the most frequent reason for prior dasatinib intolerance (n=23) and recurred with bosutinib at any grade and grade 3/4 in 12 (52.2%) and five (21.7%) patients, respectively. Bosutinib cross-intolerance due to recurrence of pleural effusion occurred in two (8.7%) patients. Other non-hematologic AE resulting in bosutinib cross-intolerance were edema

Table 1. Demographics and disease characteristics of patients with prior imatinib and/or dasatinib intolerance.

	Imatinib-intolerant*				Dasatinib-intolerant		
	CP2L N=89	CP3L N=36	ADV N=23	Total N=148	CP3L N=52	ADV N=23	Total N=75
Patient demographics							
Median age in years (range)	55 (23-91)	59.5 (23-77)	52 (31-83)	55 (23-91)	57 (25-79)	54 (27-83)	57 (25-83)
Sex, N (%)							
Female	53 (59.6)	22 (61.1)	15 (65.2)	90 (60.8)	32 (61.5)	12 (52.2)	44 (58.7)
Male	36 (40.4)	14 (38.9)	8 (34.8)	58 (39.2)	20 (38.5)	11 (47.8)	31 (41.3)
Race, N (%)							
White	55 (61.8)	29 (80.6)	11 (47.8)	95 (64.2)	39 (75.0)	16 (69.6)	55 (73.3)
Asian	21 (23.6)	5 (13.9)	5 (21.7)	31 (20.9)	9 (17.3)	2 (8.7)	11 (14.7)
Black	5 (5.6)	1 (2.8)	5 (21.7)	11 (7.4)	2 (3.8)	4 (17.4)	6 (8.0)
Other	8 (9.0)	1 (2.8)	2 (8.7)	11 (7.4)	2 (3.8)	1 (4.3)	3 (4.0)
Duration of CML and baseline cytogenetic response							
Median time in years since first diagnosis of Ph+ leukemia (range)	2.7 (0.1-13.6)	4.7 (0.6-18.3)	2.8 (0.2-15.4)	3.2 (0.1-18.3)	6.1 (0.6-18.3)	6.6 (1.5-20.0)	6.4 (0.6-20.0)
Baseline MCyR rate# (%)	24 (30.0) N=80	10 (31.3) N=32	6 (30.0) N=20	40 (30.3) N=132	17 (36.2) N=47	7 (36.8) N=19	24 (36.4) N=66
Baseline CCyR rate# (%)	12 (15.0) N=80	3 (9.4) N=32	4 (20.0) N=20	19 (14.4) N=132	7 (14.9) N=47	4 (21.1) N=19	11 (16.7) N=66
Previous history of TKI therapy							
Median duration in months of prior imatinib (range)†	18.1 (<0.1-90.1)	19.7 (1.1-79.2)	13.0 (0.5-88.3)	18.1 (<0.1-90.1)	40.7 (1.1-79.4)	29.3 (4.1-63.0)	34.9 (1.1-79.4)
Median duration in months of prior dasatinib (range)	NA	11.7 (0.9-39.0)	6.2 (0.2-34.6)	8.3 (0.2-39.0)	14.4 (0.9-35.7)	8.8 (0.1-32.7)	11.9 (0.1-35.7)

ADV: advanced Ph+ leukemia cohort; CML: chronic myeloid leukemia; CP2L: chronic phase chronic myeloid leukemia second-line cohort; CP3L: chronic phase chronic myeloid leukemia third-/fourth-line cohort; NA: not applicable; Ph+: Philadelphia chromosome-positive; TKI: tyrosine kinase inhibitor. *All patients in this study were treated with imatinib first; 38 (28 CP3L and 10 ADV) were subsequently treated with dasatinib. †Imatinib-intolerant: data missing for 1 patient in the CP2L cohort; dasatinib-intolerant: data missing for 1 patient in the CP3L cohort. #Analysis included patients who had a valid baseline molecular or cytogenetic assessment.

Table 2. Adverse event recurrence, bosutinib dose modifications, and cross-intolerance in patients with prior imatinib intolerance.*

Cause of imatinib intolerance‡	Patients who discontinued imatinib due to intolerance, N	Imatinib-intolerant patients, N=148†				
		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 AE	142	88 (62.0)	47 (33.1)	48 (33.8)	32 (22.5)	23 (16.2)
Hematologic AE						
Thrombocytopenia	34	27 (79.4)	23 (67.6)	22 (64.7)	15 (44.1)	11 (32.4)
Neutropenia	24	11 (45.8)	9 (37.5)	7 (29.2)	3 (12.5)	3 (12.5)
Anemia	17	9 (52.9)	8 (47.1)	3 (17.6)	1 (5.9)	0
Pancytopenia	11	10 (90.9)	7 (63.6)	6 (54.5)	4 (36.4)	4 (36.4)
Leukopenia	6	4 (66.7)	1 (16.7)	2 (33.3)	2 (33.3)	0
Non-hematologic AE						
Rash	22	11 (50.0)	2 (9.1)	5 (22.7)	0	1 (4.5)
Edema	16	4 (25.0)	0	0	0	0
Diarrhea	13	11 (84.6)	5 (38.5)	4 (30.8)	4 (30.8)	1 (7.7)
Asthenia	8	2 (25.0)	0	0	1 (12.5)	0
Hepatotoxicity	8	2 (25.0)	0	0	0	0
Vomiting	7	4 (57.1)	1 (14.3)	3 (42.9)	0	1 (14.3)
Nausea	6	4 (66.7)	0	1 (16.7)	0	0
Myalgia	4	3 (75.0)	1 (25.0)	0	1 (25.0)	0
Pleural effusion	3	1 (33.3)	0	0	1 (33.3)	1 (33.3)
Abdominal pain	2	1 (50.0)	0	1 (50.0)	0	0
Pyrexia	2	1 (50.0)	0	1 (50.0)	0	0
Bone pain	2	1 (50.0)	1 (50.0)	0	0	0
Renal impairment	1	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)
Angioedema	1	1 (100.0)	1 (100.0)	0	0	0
Pulmonary fibrosis	1	1 (100.0)	0	0	0	1 (100.0)
Weight decreased	1	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0
Arthralgia	1	1 (100.0)	1 (100.0)	0	0	0
Glomerular filtration rate decreased	1	1 (100.0)	0	1 (100.0)	0	1 (100.0)

AE: adverse event. *All patients who received at least 1 dose of bosutinib were included in the safety analysis. †The AE responsible for imatinib intolerance was not reported for 6 patients. ‡In at least 5 patients in the total population of imatinib-intolerant and/or those resulting in recurrent grade 3/4 AE on bosutinib, or bosutinib dose delay, reduction, or discontinuation. Treatment-emergent AE clusters based on Medical Dictionary for Regulatory Activities (MedDRA; v18) preferred terms (PT): clusters for AE leading to discontinuation of previous tyrosine kinase inhibitor (TKI): Abdominal pain: PT abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, gastrointestinal (GI) pain, abdominal distention, abdominal symptom. Anemia: PT anemia, hemoglobin decreased. Asthenia: PT asthenia, fatigue. Cardiac failure: PT cardiac failure, cardiac failure congestive, cardiac failure acute, cardiac failure chronic, left ventricular (LV) failure, acute LV failure, chronic LV failure, ventricular failure, ventricular dysfunction, ejection fraction decreased, cardiogenic shock, LV dysfunction, systolic dysfunction. Edema: PT generalized edema, edema, edema peripheral, fluid retention, peripheral swelling, fluid overload. GI toxicity: PT GI toxicity, GI disorder. Glomerular filtration rate (GFR) decreased: PT GFR decreased, creatinine clearance decreased, blood creatinine increased. Hepatotoxicity: PT hepatotoxicity, liver disorder, drug-induced liver injury, cholestatic liver injury, hepatitis cholestatic, hepatitis toxic, hepatocellular injury, liver injury. Leukopenia: PT leukopenia, white blood cell count decreased. Neutropenia: PT neutropenia, neutrophil count decreased. Pancytopenia: PT pancytopenia, bone marrow failure, cytopenia, myelosuppression, hematotoxicity. Rash: PT rash, rash generalized, rash macular, rash maculo-papular, rash popular, eczema, erythema, rash erythematous, exfoliative rash, drug eruption, urticaria. Renal impairment: PT renal impairment, acute kidney injury, renal failure. Thrombocytopenia: PT thrombocytopenia, platelet count decreased. Clusters for AE occurring under bosutinib treatment: Abdominal pain: PT abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, GI pain, abdominal distention. Anemia: PT anemia, hemoglobin decreased. Asthenia: PT asthenia, fatigue. Cardiac failure: PT cardiac failure, cardiac failure congestive, cardiac failure acute, cardiac failure chronic, LV failure, acute LV failure, chronic LV failure, ventricular failure, ventricular dysfunction, ejection fraction decreased, cardiogenic shock, LV dysfunction, systolic dysfunction. Edema, periorbital edema: PT generalized edema, edema, edema peripheral, fluid retention, peripheral swelling, fluid overload, eyelid edema, periorbital edema, swelling of eyelid. GI toxicity: PT GI toxicity, GI disorder. Hepatotoxicity, hyperbilirubinemia, hypertransaminasemia: PT liver function test increased, transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, hepatic enzyme increased, hypertransaminasemia, hyperbilirubinemia, liver function test abnormal, alkaline phosphatase increased, blood bilirubin increased, liver disorder, gamma-glutamyltransferase increased, hepatic function abnormal, hepatotoxicity, drug-induced liver injury, cholestatic liver injury, hepatitis cholestatic, hepatitis toxic, hepatocellular injury, liver injury. Leukopenia: PT leukopenia, white blood cell count decreased.

Continued on following page.

Neutropenia: PT neutropenia, neutrophil count decreased. Pancytopenia: PT pancytopenia, bone marrow failure, cytopenia, myelosuppression, hematotoxicity OR all 3 any time on-treatment anemia/hemoglobin decreased AND thrombocytopenia/platelet count decreased AND any of neutropenia/neutrophil count decreased OR lymphopenia/lymphocyte count decreased OR leukopenia/white blood cell count decreased. Pericardial effusion: PT pericardial effusion, cardiac tamponade. Pleuropericarditis: PT pleuropericarditis, pleurisy, pericarditis. Rash: PT rash, rash generalized, rash macular, rash maculo-papular, rash popular, eczema, erythema, rash erythematous, exfoliative rash, drug eruption, urticaria. Renal impairment, GFR decrease: PT acute kidney injury, renal failure, blood creatinine increased, GFR decreased, creatinine renal clearance decreased, renal impairment. Thrombocytopenia: PT thrombocytopenia, platelet count decreased.

Table 3. Adverse event recurrence, bosutinib dose modifications, and cross-intolerance in patients with prior dasatinib intolerance.*

Cause of dasatinib intolerance‡	Patients discontinued dasatinib due to intolerance, N	Dasatinib-intolerant patients, N=75†				
		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 AE	74	48 (64.9)	30 (40.5)	32 (43.2)	21 (28.4)	13 (17.6)
Hematologic AE						
Thrombocytopenia	13	13 (100.0)	13 (100.0)	11 (84.6)	10 (76.9)	5 (38.5)
Pancytopenia	12	7 (58.3)	5 (41.7)	5 (41.7)	4 (33.3)	2 (16.7)
Neutropenia	4	4 (100.0)	4 (100.0)	4 (100.0)	0	1 (25.0)
Leukopenia	2	1 (50.0)	1 (50.0)	0	0	0
Non-hematologic AE						
Pleural effusion	23	12 (52.2)	5 (21.7)	7 (30.4)	3 (13.0)	2 (8.7)
Gastrointestinal toxicity	3	2 (66.7)	0	1 (33.3)	0	0
Headache	3	2 (66.7)	1 (33.3)	1 (33.3)	0	0
Rash	3	1 (33.3)	0	1 (33.3)	0	0
Edema	2	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)
Cardiac failure	2	1 (50.0)	0	0	1 (50.0)	1 (50.0)
Pericardial effusion	2	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)
Gastritis	1	1 (100.0)	1 (100.0)	1 (100.0)	0	0
Pleuropericarditis	1	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0
Pyrexia	1	1 (100.0)	0	1 (100.0)	0	0

AE: adverse event. *All patients who received at least 1 dose of bosutinib were included in the safety analysis. †The AE responsible for dasatinib intolerance was not reported or classified for 1 patient. ‡In at least 5 patients in the total population of dasatinib-intolerant patients and/or those resulting in recurrent grade 3/4 AE on bosutinib, or bosutinib dose delay, reduction, or discontinuation. Treatment-emergent AE clusters based on Medical Dictionary for Regulatory Activities (MedDRA; v18) preferred terms (PT): see definition of clusters in Table 2 footnotes.

(50%), cardiac failure (50%), and pericardial effusion (50%) (n=1 each; Table 3).

Seven patients were nilotinib-intolerant. One (14.3%) patient with nilotinib intolerance due to pleural effusion was cross-intolerant to bosutinib. Three patients who discontinued nilotinib due to a hematologic AE experienced grade 3/4 AE recurrence (thrombocytopenia: n=2; neutropenia: n=1); none led to bosutinib cross-intolerance (*Online Supplementary Table S2*).

No deaths due to bosutinib cross-intolerance occurred in prior imatinib-, dasatinib-, or nilotinib-intolerant patients.

Cross-intolerance with bosutinib was low in prior imatinib-, dasatinib-, and nilotinib-intolerant patients, consistent with a previous study in patients with CP CML receiving bosutinib as a 4L treatment.[8] Most incidences of cross-intolerance occurred in those who discontinued prior TKI treatment due to a hematologic AE, a finding consistent with previous cross-intolerance analyses of dasatinib and nilotinib.[6,7] AE that recurred during treatment with bosutinib were manageable through bosutinib dose modifications and, in the majority of cases, did not lead to bosutinib discontinuation.

The incidence of cross-intolerance due to hematologic AE was similar in imatinib- and/or dasatinib-intolerant patients. Overall, thrombocytopenia was a common recurring hematologic AE leading to bosutinib discontinuation in prior imatinib- and dasatinib-intolerant patients. This finding supports previous studies that suggest thrombocytopenia to be the most likely cause of cross-intolerance among TKI.[6,7]

The most common non-hematologic AE leading to discontinuation of prior TKI were rash, edema, and diarrhea in imatinib-intolerant patients and pleural effusion in dasatinib-intolerant patients. For these AE that recurred with bosutinib, discontinuations were rare. Indeed, despite the high incidence of recurrence of diarrhea (84.6%) in patients with prior imatinib intolerance due to this AE, previous diarrhea is not a contraindication for bosutinib,

as <40% of patients experienced recurrence at grade 3/4, and <10% (1 patient) discontinued bosutinib due to this AE. Similarly, despite recurrence of pleural effusion in 52.2% of patients with previous dasatinib intolerance due to this AE, only 8.7% (2 patients) discontinued bosutinib due to pleural effusion.

In conclusion, results showed that cross-intolerance with bosutinib in patients with prior TKI intolerance was <20%. Results also confirmed that cross-intolerance was limited for the most common AE associated with other TKI. Patients were pooled across cohorts (CP and ADV) to have a larger patient number for the purposes of these analyses. The authors recognize the limitation of including patients with advanced leukemias, as these patients may experience a higher incidence of specific types of AE, e.g., hematologic AE, compared with CP CML cohorts. Additionally, another limitation of this analysis is the small number of patients in some subgroups; therefore, an analysis of AE recurrence and cross-intolerance due to infrequent but important AE, such as pericardial effusion or renal impairment, is limited. In line with recommendations for management of AE,[9] recurrent AE with bosutinib were generally manageable with dose modifications and/or standard medical therapy. Although 500 mg is the recommended starting dose for patients previously treated with ≥1 TKI, other reports have shown that patients with prior TKI intolerance receive a lower dose intensity compared with patients resistant to previous TKI.[10] This suggests a higher dose intensity may be necessary for patients resistant to previous TKI, while a lower dose intensity might be sufficient to maintain response and improve tolerability in patients intolerant to prior TKI.[11] Some studies have evaluated and/or are currently evaluating run-in dosing regimens or alternative schedules starting at lower bosutinib doses and escalating based on tolerability and response.[12-15] This dosing strategy has also been suggested for the management of AE during bosutinib treatment.[9] Bosutinib has demonstrated durable efficacy at 2- and 5-year follow-ups in patients receiving the drug as a 2L therapy[16,17] and at ≥4-year follow-up when used as a 3L/4L therapy[18] in patients with prior TKI intolerance. Taken together, efficacy and safety data support use of bosutinib as an effective treatment option for Ph+ CML patients with prior TKI intolerance.

Authors

Jorge E. Cortes,[1] Jeff H. Lipton,[2] Vamsi Kota,[1] Fausto Castagnetti,[3] Sarit Assouline,[4] Tim H. Brümmendorf,[5,6] Eric Leip,[7] Andrea Viqueira[8] and Carlo Gambacorti-Passerini[9]

[1]Georgia Cancer Center, Augusta, GA, USA; [2]Princess Margaret Cancer Center, Toronto, Ontario, Canada; [3]Istituto di Ematologia "Seràgnoli", IRCCS Azienda Ospedaliero-Universitaria di Bologna, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy; [4]McGill University, Montreal, Quebec, Canada; [5]Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation, Faculty of Medicine, RWTH Aachen University Hospital, Aachen, Germany; [6]Center for Integrated Oncology Aachen Bonn Cologne Düsseldorf (CIO ABCD), Aachen Bonn Cologne Düsseldorf, Germany; [7]Pfizer Inc, Cambridge, MA, USA; [8]Pfizer SLU, Madrid, Spain and [9]University of Milano-Bicocca, Monza, Italy

Correspondence:
J.E. CORTES - jorge.cortes@augusta.edu

https://doi.org/10.3324/haematol.2022.281944

Received: August 15, 2022.
Accepted: June 30, 2023.
Early view: July 13, 2023.

Disclosures

JEC received research support to his institution from Bristol Myers Squibb, Novartis, Pfizer, Sun Pharmaceutical Industries, and Takeda; served as a consultant for Bristol Myers Squibb, Novartis, Pfizer, Takeda, and Fusion Pharmaceuticals. JHL received lecture fees and research support to his institution from Pfizer. VK received honorarium for advisory board participation from Ariad Pharmaceuticals, Incyte, Novartis, Pfizer, and Xcenda, and received research support to his institution from Pfizer. FC received research support to his institution from Pfizer and has served as a speaker or consultant for Bristol Myers Squibb, Incyte, Novartis, and Pfizer. SA received research support to his institution from Roche/Genentech and Pfizer and has served as a speaker or consultant for Roche Canada, Pfizer, Bristol Myers Squibb, Palladin, and Lundbeck. THB served as a consultant for Novartis, Pfizer, Janssen, Merck, Takeda, and received research funding from Novartis and Pfizer. AV and EL are employees of Pfizer. CG-P provides consultancy to Bristol Myers Squibb and received honoraria and research support from Pfizer.

Contributions

JEC, THB, and CG-P were involved in the study conception/design. All authors were involved in the acquisition, analysis, or interpretation of data. All authors contributed to the drafting of the manuscript and approved the final version.

Funding

This study (*clinicaltrials gov. identifier: NCT00261846*) was sponsored by Pfizer. Medical writing support was provided by Katy Beck, PhD, of Engage Scientific Solutions (Horsham, UK) and funded by Pfizer.

Acknowledgments

The authors thank Dr Simon Durrant for his contributions to the study.

Data-sharing statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

References

1. Garcia-Gutierrez V, Hernandez-Boluda JC. Tyrosine kinase inhibitors available for chronic myeloid leukemia: efficacy and safety. Front Oncol. 2019;9:603.
2. Cortes JE, Kantarjian HM, Brummendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood. 2011;118(17):4567-4576.
3. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood. 2012;119(15):3403-3412.
4. Gambacorti-Passerini C, Kantarjian HM, Kim DW, et al. Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors. Am J Hematol. 2015;90(9):755-768.
5. Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE trial. J Clin Oncol. 2018;36(3):231-237.
6. Cortes JE, Hochhaus A, le Coutre PD, et al. Minimal cross-intolerance with nilotinib in patients with chronic myeloid leukemia in chronic or accelerated phase who are intolerant to imatinib. Blood. 2011;117(21):5600-5606.
7. Khoury HJ, Goldberg SL, Mauro MJ, et al. Cross-intolerance with dasatinib among imatinib-intolerant patients with chronic phase chronic myeloid leukemia. Clin Lymphoma Myeloma Leuk. 2016;16(6):341-349.
8. Garcia-Gutierrez V, Martinez-Trillos A, Lopez Lorenzo JL, et al. Bosutinib shows low cross intolerance, in chronic myeloid leukemia patients treated in fourth line. Results of the Spanish compassionate use program. Am J Hematol. 2015;90(5):429-433.
9. Cortes JE, Apperley JF, DeAngelo DJ, et al. Management of adverse events associated with bosutinib treatment of chronic-phase chronic myeloid leukemia: Expert Panel review. J Hematol Oncol. 2018;11(1):143.
10. Hochhaus A, Gambacorti-Passerini C, Abboud C, et al. Bosutinib for pretreated patients with chronic phase chronic myeloid leukemia: primary results of the phase 4 BYOND study. Leukemia. 2020;34(8):2125-2137.
11. Gambacorti-Passerini C, Brümmendorf TH, Abruzzese E, et al. Efficacy and safety of bosutinib in previously treated patients with chronic myeloid leukemia: final results from the Byond Trial. Blood. 2021;138(Suppl 1):S1475.
12. Mita A, Abumiya M, Miura M, et al. Correlation of plasma concentration and adverse effects of bosutinib: standard dose or dose-escalation regimens of bosutinib treatment for patients with chronic myeloid leukemia. Exp Hematol Oncol. 2018;7:9.
13. Isfort S, Wolf D, Teichmann LL, et al. Step-in dosing in the Bosutinib Dose Optimization Study (BODO) failed to reduce gastrointestinal (GI) toxicity in patients failing second generation TKI (2G-TKI) in chronic phase chronic myeloid leukemia (CML) but suggests promising molecular response. Blood. 2021;138(Suppl 1):S3608.
14. Castagnetti F, Gugliotta G, Bocchia M, et al. Dose optimization in elderly CML patients treated with bosutinib after intolerance or failure of first-line tyrosine kinase inhibitors. Blood. 2019;134(Suppl 1):S496.
15. Latagliata R, Attolico I, Trawinska MM, et al. Bosutinib in the real-life treatment of chronic myeloid leukemia patients aged >65 years resistant/intolerant to previous tyrosine-kinase inhibitors. Hematol Oncol. 2021;39(3):401-408.
16. Gambacorti-Passerini C, BrÜmmendorf TH, Kim DW, et al. Bosutinib efficacy and safety in chronic phase chronic myeloid leukemia after imatinib resistance or intolerance: minimum 24-month follow-up. Am J Hematol. 2014;89(7):732-742.
17. Gambacorti-Passerini C, Cortes JE, Lipton JH, et al. 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. Haematologica. 2018;103(8):1298-1307.
18. Cortes JE, Khoury HJ, Kantarjian HM, et al. Long-term bosutinib for chronic phase chronic myeloid leukemia after failure of imatinib plus dasatinib and/or nilotinib. Am J Hematol. 2016;91(12):1206-1214.