A Review of the Therapeutic Role of Bosutinib in Chronic Myeloid Leukemia

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Abstract

The development of the BCR::ABL1 tyrosine kinase inhibitors (TKIs) has transformed Philadelphia chromosome (Ph)–positive chronic myeloid leukemia (CML) from a fatal disease to an often-indolent illness that, when managed effectively, can restore a life expectancy close to that of the normal population. Bosutinib is a second-generation TKI approved for adults with Ph-positive CML in chronic phase, accelerated phase, or blast phase that is resistant or intolerant to prior therapy, and for newly diagnosed Ph-positive chronic phase CML. This review details the efficacy of bosutinib for the treatment of CML in the first- and second-line settings, as well as in third- and later-line settings for high-risk patients resistant or intolerant to at least 2 TKIs. It also outlines bosutinib studies that provide evidence for dose-optimization strategies that can be used to improve efficacy and effectively manage adverse events. The studies that provide evidence for specific patient populations benefiting particularly from bosutinib dose-optimization strategies are also discussed. The well-established, long-term side-effect profile and the potential to make dose adjustments with bosutinib make it an appropriate treatment option for patients with CML. Bosutinib has demonstrated a positive impact on health-related quality of life and an important role in the long-term treatment of patients with CML.

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Introduction

Bosutinib is a second-generation BCR::ABL1 tyrosine kinase inhibitor (TKI) approved for the treatment of Philadelphia chromosome–positive (Ph-positive) chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukemia (CML) resistant or intolerant to prior therapy, as well as for newly diagnosed Ph-positive CP CML.[1,2] Several prospective trials have demonstrated the efficacy and acceptable safety profile of bosutinib as second-line therapy for patients with CP CML resistant or intolerant to imatinib and as a third- and fourth-line therapy after failure of imatinib, dasatinib, nilotinib, or any combination.[3-8] The 5-year final analyses from the BFORE trial demonstrated the superior efficacy of bosutinib versus imatinib for the treatment of patients with newly diagnosed CP CML[9] and supported the approval of bosutinib as a first-line treatment option for CML. A starting dose of 400 mg/d has been approved as frontline therapy and 500 mg/d in later-line therapy.[1,2] This review provides an overview of the efficacy of bosutinib for patients with CML. The importance of bosutinib dose optimization in improving efficacy outcomes, reducing treatment-related toxicity, and optimizing treatment exposure is discussed. The impact of bosutinib on improving quality of life is also detailed.

Abbreviations: AE, adverse event; AP, accelerated phase; BP, blast phase; cCHR, complete hematologic response; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CP, chronic phase; DMR, deep molecular response; IS, international scale; mCCI, modified Charlson Comorbidity Index; MCyR, major cytogenetic response; MMR, major molecular response; OS, overall survival; Ph-positive, Philadelphia chromosome–positive; TEAE, treatment-emergent AE; TKI, tyrosine kinase inhibitor.

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Bosutinib Efficacy in the Frontline Therapy of CML

Frontline TKI therapies recommended for patients with newly diagnosed CP CML are highly effective and result in long-term overall survival (OS) similar to the life expectancy of an age-matched normal population.[10-12] Compared with the first-generation TKI imatinib, second-generation TKIs such as dasatinib, nilotinib, and bosutinib produce higher and faster rates of cytogenetic and deep molecular responses.[13] However, they do not improve OS compared with imatinib therapy. Among the second-generation TKIs, bosutinib exhibits minimal inhibitory activity against 2 off-

target kinases (ie, c-KIT and platelet-derived growth factor receptor), which potentially contribute to TKI-related toxicities.[14-16] The efficacy and long-term safety of bosutinib as the frontline therapy of CML was evaluated in 2 pivotal trials: the BFORE trial comparing bosutinib 400 mg/d versus imatinib and the BELA trial investigating bosutinib 500 mg/d versus imatinib.

The phase 3 BFORE trial investigated bosutinib 400 mg/d versus imatinib for patients with newly diagnosed CP CML. In the modified intent-to-treat population, bosutinib therapy achieved significantly higher rates of major molecular response (MMR) by 12 months (primary endpoint) compared with imatinib (47.2% vs. 36.9%; Table 1).[17] In the final 5-year analysis,[9] the cumulative MMR rate in the intent-to-treat population remained higher with bosutinib versus imatinib (73.9% vs. 64.6%). Notably, these responses were achieved earlier with bosutinib than with imatinib. Moreover, the cumulative rates of MR^4 and $MR^{4.5}$ were higher with bosutinib than with imatinib, with the greatest benefit observed in patients with high-risk Sokal score. The proportion of patients achieving early response (*BCR::ABL1* transcripts on the International Scale [IS] ≤10% at 3 months) was higher with bosutinib compared with imatinib (80.6% vs. 60.5%). The cumulative incidence of on-treatment progression/death at 5 years was 6.7% for bosutinib and 9.3% for imatinib; 5-year OS rate was 94.5% with bosutinib and 94.6% with imatinib. Bosutinib demonstrated an acceptable toxicity profile; adverse events (AEs) were generally manageable and reversible. Although cardiovascular treatment-emergent AEs (TEAEs) remained low in both arms, the incidence was higher with bosutinib (4.9%) compared with imatinib (0.4%). Many patients were, in the end, treated successfully and durably with doses lower than the planned 400 mg daily dose (median dose 393.6 mg/d). These results from BFORE led to the approval of bosutinib as a frontline treatment option for Ph-positive CP CML.

In the phase 3 BELA trial (which proceeded the BFORE trial), a higher dose of bosutinib (500 mg/d, based on the initially established dose in the second- and later-line treatment setting) versus imatinib was investigated in patients with newly diagnosed CP CML. In the primary analysis at 12 months,[18] bosutinib did not demonstrate a superior rate of complete cytogenetic response (CCyR) compared with imatinib (70% vs. 68%, $P = .601$; Table 1). The higher starting dose of 500 mg/d and higher AE-related discontinuation rate with bosutinib versus imatinib (19% vs. 6%) potentially affected the observed efficacy outcomes: nearly one-third of patients in the bosutinib arm discontinued therapy before their first postbaseline assessment, which may have contributed to the lower rate of CCyR with bosutinib in the intent-to-treat population. In addition, bosutinib was associated with higher rates of diarrhea compared with imatinib (all-grade: 68% vs. 21%; grade 3/4: 11% vs. 1%). Nonetheless, a higher MMR rate (bosutinib 41%; imatinib 27%), faster time to CCyR and MMR, fewer on-treatment AP/BP transformations, and fewer CML-related deaths were observed with bosutinib compared with imatinib. The higher MMR rate with bosutinib versus imatinib observed at 12 months was maintained at 24 months (59% vs. 49%).[19] These responses were durable: most responders in both treatment arms were still on treatment and retained CCyR and MMR at the time of analysis. Importantly, an early response was associated with better CCyR and MMR rates with both bosutinib and imatinib.

Emerging evidence has shown that TKI therapy can be discontinued in patients with CP CML who achieve a stable durable deep molecular response (DMR). The current National Comprehensive Cancer Network criteria state that patients with CML can be considered as candidates for TKI discontinuation if they received BCR::ABL1 TKIs for ≥3 years and have achieved a stable and prolonged DMR for ≥2 years.[13] Indeed, a longer treatment and DMR duration significantly increase the probability of successful treatment-free remission outcomes. One study demonstrated optimal outcomes following TKI discontinuation in patients who achieved a DMR for ≥5 years.[20] Although there are no formal studies on treatment-free remission with bosutinib, appropriate guidelines for eligibility, monitoring, and therapy reinitiation with other second-generation TKIs may be used to consider bosutinib discontinuation. Moreover, anecdotal experience suggests the outcomes are similar as with other TKIs.

Bosutinib Efficacy in Second- and Later-Line CML Therapy

With long-term follow-up of patients with CML treated with frontline TKI, 25% to 40% will eventually require a switch of frontline TKI therapy due to the development of resistance (traditionally defined as *BCR::ABL1* transcripts International Scale >1% after ≥1 year of TKI therapy) or intolerance.[17,21,22] Although TKI resistance is not completely understood, several mechanisms, pathways, and drug-able targets have been proposed to contribute to the phenotype, including alterations in PI3K, Wnt, and JAK/STAT signaling; genomic instability, DNA damage, and repair mechanisms; interactions within the bone marrow microenvironment; and the development of TKI-resistant leukemic stem cell clones.[23] However, failure due to frontline TKI resistance is uncommon, occurring in 10% to 15% of patients receiving imatinib and <10% of patients receiving second-generation TKIs as frontline treatment.[24] More commonly, frontline failure of TKI therapy is due to the development of treatment-related AEs.[9,25,26]

Bosutinib has been extensively investigated in patients with prior TKI therapy. Although slight variabilities in the baseline patient characteristics exist between studies, much has been learned about the effectiveness and tolerability of second- and later-line bosutinib in CML (Table 2).

Study 200, a phase 1/2 trial, investigated bosutinib 500 mg/d as a second- and third-line treatment for CP CML.[3] As second-line treatment in patients with CP CML resistant or intolerant to imatinib and who had no prior TKI exposure other than imatinib, the major cytogenetic response (MCyR) rate with bosutinib at 24 weeks (primary endpoint) was 31% (Table 1).[3] In the final analysis, based on ≥10 years of follow-up, the cumulative CCyR rate was 50% and the MMR rate was 42%.[6] In addition, the probability of maintaining CCyR and MMR was over 58% and 56%, respectively, after ≥10 years.[6] These long-term results established the durable efficacy and acceptable safety profile of second-line bosutinib for CP CML.[6]

Treatment options are less effective for high-risk patients with CP CML resistant or intolerant to at least 2 TKIs.[24] Unlike the well-

Table 1 Clinical Efficacy of Bosutinib Across Lines of Therapy

Trial	Study Design	Primary Analysis	Long-term Follow-up
First-line setting			
BFORE	Phase 3 trial; $N = 536$; newly diagnosed CP CML randomized 1:1 to 400 mg/d bosutinib ($n = 268$) or imatinib ($n = 268$)	Primary efficacy endpoint • MMR rate at 12 mo, bosutinib versus imatinib: 47.2% versus 36.9% ($P = .02$) Key secondary and exploratory efficacy endpoints • MR^4 rate at 12 mo, bosutinib versus imatinib: 20.7% versus 12% • $MR^{4.5}$ at 12 mo, bosutinib versus imatinib: 8.1% versus 3.3% • CCyR rate at 12 mo, bosutinib versus imatinib: 77.2% versus 66.4% • AP/BP progression, bosutinib versus imatinib: 1.6% versus 2.5% Dose modification • Dose escalations due to suboptimal response, bosutinib versus imatinib: 17.2% versus 27.5%	Key efficacy data • Cumulative MMR rate at 60 mo, bosutinib versus imatinib: 73.9% versus 64.6% • Cumulative MR^4 rate at 60 mo, bosutinib versus imatinib, 58.2% versus 48.1% • Cumulative $MR^{4.5}$ rate at 60 mo, bosutinib versus imatinib, 47.4% versus 36.6% • Cumulative CCyR rate at 60 mo, bosutinib versus imatinib: 83.3% versus 76.8% Dose modification • Dose interruption, bosutinib versus imatinib: 68.7% versus 45.7% • Dose reductions, bosutinib versus imatinib: 45.5% versus 24.5% • Dose escalations to >400 mg/d, bosutinib versus imatinib: 21.6% versus 31.3%
BELA	Phase 3 trial; $N = 502$; newly diagnosed CP CML randomized 1:1 to 500 mg/d of bosutinib ($n = 250$) or 400 mg/d of imatinib ($n = 252$)	Primary efficacy endpoint • CCyR rate at 12 mo, bosutinib versus imatinib: 70% versus 68% ($P = .601$) Key secondary and exploratory efficacy endpoints • Median time to CCyR, bosutinib versus imatinib: 12.9 wk versus 24.6 wk • MMR rate at 12 mo, bosutinib versus imatinib: 41% versus 27% • Median time to MMR, bosutinib versus imatinib: 37.1 wk versus 72.3 wk • AP/BP progression, bosutinib versus imatinib: 2% versus 4% Dose modification • Dose escalation to 600 mg/d due to suboptimal response, bosutinib versus imatinib: 4% versus 12%	Key efficacy data • Cumulative CCyR rate by 24 mo, bosutinib versus imatinib: 79% versus 80% • Cumulative MMR rate at 24 mo, bosutinib versus imatinib: 59% versus 49% • Responders (n) remained on treatment and maintained CCyR, bosutinib versus imatinib: 151/197 versus 172/204 • Responders (n) remained on treatment and maintained MMR, bosutinib versus imatinib: 125/153 versus 117/131 • AP/BP progression since 12-mo analysis (n), bosutinib versus imatinib: 0 versus 4 Dose modification • Dose escalation to 600 mg/d due to suboptimal response, bosutinib versus imatinib: 6% versus 18%

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Table 1 (*continued*)

Trial	Study Design	Primary Analysis	Long-term Follow-up
Second-line setting			
Study 200	Phase 1/2 study; $N=288$; imatinib-resistant ($n=200$) or imatinib-intolerant ($n=88$) CML and no prior TKI exposure received 500 mg/d bosutinib	Primary efficacy endpoint • MCyR rate at 24 wk: 31% in total population (imatinib-resistant 33%; imatinib-intolerant 27%) Key secondary and exploratory efficacy endpoints • CHR achieved during study: 86% • MCyR rate achieved during study: 53% • CCyR rate achieved during study: 41% • MMR rate achieved during study: 64%	Key efficacy data • Cumulative CCyR rates after ≥10 y: 50% • Cumulative MMR rates after ≥10 y: 42% • Probabilities of maintaining CCyR after ≥10 y: 58% • Probabilities of maintaining MMR after ≥10 y: 56%
BYOND	Single-arm, open-label, nonrandomized, phase 4 study; $N=46$; CP or AP CML resistant/intolerant to prior TKIs received bosutinib 500 mg/d (starting dose)	Key secondary and exploratory efficacy endpoints • Cumulative CCyR in patients with CP CML after 1 y of follow-up: 83.7% • Cumulative MCyR in patients with CP CML after 1 y of follow-up: 88.4%	Key efficacy data • MMR in patients with CP CML after 2 y of follow-up and 1 prior TKI: 82.6%
Third- and later-line setting			
Study 200	Phase 1/2 study; $N=118$; CP CML pretreated with imatinib followed by dasatinib, nilotinib, or both received 500 mg/d bosutinib • Dasatinib-resistant: $n=37$ • Dasatinib-intolerant: $n=50$ • Nilotinib-resistant: $n=27$ • Nilotinib-intolerant: $n=1$ • Dasatinib- and nilotinib-resistant: $n=2$ • Dasatinib- and nilotinib-intolerant: $n=1$	Key efficacy data • MCyR after 28.5 mo follow-up: 32% • CCyR after 28.5 mo follow-up: 24% • CHR after 28.5 mo follow-up: 73% • AP/BP transformation after 28.5 mo follow-up: $n=5$ Dose modification/interruption • Dose interruptions: 70% • Dose escalation to 600 mg/d bosutinib due to suboptimal response: 17%	Key efficacy data • Cumulative MCyR rate at 4 y: 40% • Cumulative CCyR rate at 4 y: 32% • Cumulative cCHR rate at 4 y: 74% • Kaplan–Meier probability of maintaining CHR at 4 y: 63% • Kaplan–Meier probability of maintaining MCyR at 4 y: 69% • Cumulative on-treatment disease progression (including AP/BP transformation)/death at 4 y: 24% Dose modification/interruption • Dose reduction due to AEs: 50% • Dose escalation to 600 mg/d bosutinib due to suboptimal response: 18%
BYOND	Single-arm, open-label, nonrandomized, phase 4 study; $N=110$; CP or AP CML resistant/intolerant to prior TKIs received bosutinib 500 mg/d (starting dose)	Primary endpoint • Cumulative confirmed MCyR rate by 1 y in patients with CP CML after 1 or 2 prior TKIs: 75.8% • Cumulative confirmed MCyR rate by 1 y in patients with CP CML after 3 prior TKIs: 62.2% • Cumulative cCHR rate by 1 y in patients with AP CML: 75%	

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Table 1 (*continued*)

Trial	Study Design	Primary Analysis	Long-term Follow-up
		Key secondary and exploratory efficacy endpoints • Cumulative MCyR rate by 1 y in patients with CP CML and 2 prior TKIs: 83.9% • Cumulative MCyR rate by 1 y in patients with CP CML and 3 prior TKIs: 77.8% • Cumulative CCyR rate by 1 y in patients with CP CML and 2 prior TKIs: 83.9% • Cumulative CCyR rate by 1 y in patients with CP CML and 3 prior TKIs: 73.3% • Cumulative MMR rate by 1 y in patients with CP CML and 2 prior TKIs: 74.5% • Cumulative MMR rate by 1 y in patients with CP CML and 3 prior TKIs: 56.3% • AP/BP transformation: 0 Dose modification • 500 mg/d was the most commonly utilized dosage and >50% of patients with Ph-positive CP CML receiving 400 or 500 mg/d bosutinib	Key efficacy data • CCyR in patients with CP CML after 3 y follow-up: 81.1% • MMR in patients with CP CML after 3 y follow-up: 71.8% • Kaplan–Meier probabilities of maintaining MMR at 3 y: 87.2% • AP/BP transformation: 0 Dose modification/interruption • Dose interruptions due to AEs: 76.3% • Dose reductions due to AEs: 79.5%

AE = adverse event; AP = accelerated phase; BP = blast phase; cCHR = confirmed complete hematologic response; CCyR = complete cytogenetic response; CHR = complete hematologic response; CML = chronic myeloid leukemia; CP = chronic phase; MCyR = major cytogenetic response; MMR = major molecular response; Ph-positive = Philadelphia chromosome–positive; TKI = tyrosine kinase inhibitor.

established frontline and second-line therapies, later-line treatment options are not well defined by available treatment guidelines.[13,24,25] Also, in the third- and later-line treatment setting, individualization of therapy becomes significant due to preexisting comorbidities and AEs that may develop in patients during long-term therapy. Bosutinib was evaluated in the third- and fourth-line setting in an exploratory analysis of Study 200,[3] as well as in BYOND and ASCEMBL trials.

A cohort of study 200 included patients with CP CML previously treated with imatinib followed by dasatinib, nilotinib, or both.[8] The MCyR rate was 32%, and the confirmed complete hematologic response (cCHR) was 73% after a median follow-up time of 28.5 months (Table 1).[8] After 4 years of follow-up in the cohort of patients receiving third-line bosutinib in Study 200, similar cumulative rates of MCyR (40%) and cCHR (74%) were observed, and responses were durable.[4] The probability of maintaining MCyR or cCHR at 4 years was 69% and 63%, respectively.[4] Interestingly, 76% of patients discontinued treatment by year 4, primarily due to AEs (24%), progressive disease (20%), and lack of efficacy (18%).[4] Bosutinib dose was escalated to 600 mg in 18% of patients to improve efficacy and reduced to 400 to 300 mg in 50% of patients to manage AEs.[4] The most common TEAE of diarrhea was managed by dose reduction, along with the use of concomitant medications.[4] Overall, bosutinib demonstrated durable efficacy and manageable toxicity in CP CML resistant or intolerant to multiple prior TKIs, making bosutinib a treatment option in the third- or later-line settings, particularly in patients with intolerance to multiple prior TKIs.[4,8]

The phase 4 BYOND trial confirmed and extended the value of bosutinib as a standard of care in patients with CP CML resistant or intolerant to multiple prior TKIs. The cumulative confirmed MCyR rate by 1 year (primary endpoint) was 75.8% in patients with CP CML previously treated with 1 or 2 TKIs and 62.2% in those previously treated with 3 TKIs (Table 1).[7] In the same patient population, the cumulative CCyR rate by 1 year was 83.7%, 83.9%, and 73.3% in patients previously treated with 1, 2, or 3 prior lines of therapy, respectively; cumulative CCyR rate by 1 year was 75.3% and 86.6% in patients who were TKI-resistant and -intolerant, respectively. Likewise, the cumulative MMR rates by 1 year were 80.4%, 74.5%, and 56.3% in patients previously treated with 1, 2, or 3 prior lines of therapy, respectively. The cumulative MMR rates by 1 year were 60.5% and 80.8% in patients who were TKI-resistant and -intolerant, respectively. In the overall treatment population, 25.8% of patients discontinued treatment due to AEs. In the final analysis after ≥3 years of follow-up, high rates of CCyR (81.1%) and MMR (71.8%) were attained or maintained.[5] Furthermore, most patients achieved a deeper molecular response relative to baseline while on bosutinib. No patients progressed to AP/BP CML.

Table 2 Baseline Characteristics of Patients With CP CML Across Second-Line Bosutinib Studies: BYOND and ASCEMBL

	BYOND				ASCEMBL	
	Second-Line Bosutinib (*n* = 46)	Third-Line Bosutinib[a] (*n* = 61)	Fourth-Line Bosutinib (*n* = 49)	Total (*N* = 156)	Bosutinib (*n* = 76)	Asciminib (*n* = 157)
Male, *n* (%)	23 (50)	37 (60.7)	21 (42.9)	81 (51.9)	31 (40.8)	82 (52.2)
Age, median (range), y	54 (19-88)	65 (27-85)	61 (21-85)	61 (19-88)	52 (19-77)	52 (24-83)
Race, *n* (%)						
White	NR	NR	NR	NR	56 (73.7)	118 (75.2)
Asian	NR	NR	NR	NR	11 (14.5)	22 (14)
Black or African American	NR	NR	NR	NR	2 (2.6)	8 (5.1)
Native American	NR	NR	NR	NR	0	1 (0.6)
Other	NR	NR	NR	NR	7 (9.2)	5 (3.2)
Unknown	NR	NR	NR	NR	0	3 (1.9)
ECOG PS, *n* (%)						
0	34 (73.9)	40 (65.6)	32 (65.3)	106 (67.9)	62 (81.6)	126 (80.3)
1	12 (26.1)	20 (32.8)	13 (26.5)	45 (28.8)	14 (18.4)	28 (17.8)
2	0	1 (1.6)	4 (8.2)	5 (3.2)	0	2 (1.3)
Missing	0	0	0	0	0	1 (0.6)
Median (range) Duration since CML Diagnosis, y	2.2 (0.2-11.4)	5 (0.3-18.6)	7.3 (0.7-27.7)	4.7 (0.2-27.7)	NR	NR
MCyR	NR	NR	NR	NR	22 (28.9)	46 (29.3)
Prior TKI, *n* (%)						
Imatinib	35 (76.1)	57 (93.4)	49 (100)	141 (90.4)	63 (82.9)	130 (82.8)
Dasatinib	5 (10.9)	41 (67.2)	49 (100)	95 (60.9)	65 (85.5)	131 (83.4)
Nilotinib	6 (13)	24 (39.3)	49 (100)	79 (50.6)	56 (73.7)	104 (66.2)
Ponatinib	NA	NA	NA	NA	18 (23.7)	23 (14.6)
Radotinib	NA	NA	NA	NA	2 (2.6)	4 (2.5)
Other	NA	NA	NA	NA	4 (5.3)	5 (3.2)
Number of lines of prior TKI therapy, *n* (%)[b]						
2	NR	NR	NR	NR	30 (39.5)	82 (52.2)
3	NR	NR	NR	NR	29 (38.2)	44 (28)
4	NR	NR	NR	NR	10 (13.2)	24 (15.3)
≥5	NR	NR	NR	NR	7 (9.2)	7 (4.5)
Prior interferon alpha, *n* (%)	2 (4.3)	3 (4.9)	6 (12.2)	11 (7.1)	NR	NR
Resistant: any prior TKI, *n* (%)	17 (37)	35 (57.4)	31 (63.3)	83 (53.2)	NR	NR
Intolerant: all prior TKIs, *n* (%)	29 (63)	26 (42.6)	18 (36.7)	73 (46.8)	NR	NR
Reason for discontinuation of last TKI, *n* (%)						
Lack of efficacy	NR	NR	NR	NR	54 (71.1)	95 (60.5)
Lack of tolerability	NR	NR	NR	NR	22 (28.9)	59 (37.6)
Other[c]	NR	NR	NR	NR	0	3 (1.9)
BCR::ABL1^{IS} at baseline, *n* (%)						
>0.1% to ≤1%[c]	NR	NR	NR	NR	4 (5.3)	15 (9.6)
>1% to ≤10%	NR	NR	NR	NR	23 (30.3)	45 (28.7)
>10%	NR	NR	NR	NR	49 (64.5)	97 (61.8)
Patients with any *BCR::ABL1* mutation, *n* (%)	NR	NR	NR	NR	10 (13.2)	20 (12.7)
Patients with multiple *BCR::ABL1* mutations, *n* (%)	NR	NR	NR	NR	0	3 (1.9)

All patients with *BCR::ABL1*^{IS} <1% at baseline were intolerant to the last TKI, except 1 in the asciminib arm (who deviated from the protocol).
BCR::ABL1^{IS} = *CML*, *BCR::ABL1* transcript levels on the International Scale. CML = chronic myeloid leukemia; CP = chronic phase; ECOG PS = Eastern Cooperative Oncology Group performance status; MCy= major cytogenetic response; NR = not reported, TKI = tyrosine kinase inhibitor.
[a] In the third-line cohort, 37 (60.7%) patients received prior imatinib and dasatinib, 20 (32.8%) received prior imatinib and nilotinib, and 4 (6.6%) received prior dasatinib and nilotinib.
[b] The number of lines of prior TKI therapy was based on sequence of treatments.
[c] Includes study medication wrongly assigned, lack of efficacy and tolerability, and optimal response not reached after 5 y of treatment.

Table 3 Efficacy and Safety Outcomes of ASCEMBL and Post hoc Analysis of BYOND

	ASCEMBL[27]		Post hoc Analysis of BYOND		
	Bosutinib ($n=76$)	Asciminib ($n=157$)	TKI-Resistant Bosutinib ($n=18$)	TKI-Intolerant Bosutinib ($n=30$)	Total ($N=48$)
Efficacy					
Duration of treatment, median (range), mo	7.3 (0.3-29.3)	10.9 (0.03-32.5)	10.6 (1.6-48.5)	28.3 (0.2-48.6)	27 (0.2-48.6)
Dose intensity, median (range), mg/d	478.6 (181-566)	79.8 (33-80)	447.1 (131.3-520.4)	288.8 (79.7-500)	301.8 (79.7-520.4)
MMR, % (95% CI)					
6 mo	13.2	25.5[a]	18.8 (4-45.6)	56.7 (37.4-74.5)	43.5 (28.9-58.9)
4 y	NR	NR	31.3 (11-58.7)	66.7 (47.2-82.7)	54.3 (39-69.1)
CCyR, % (95% CI)					
6 mo	24.2	40.8	33.3 (13.3-59)	56.5 (34.5-76.8)	46.3 (30.7-62.6)
4 y	NR	NR	44.4 (21.5-69.2)	69.6 (47.1-86.8)	58.5 (42.1-73.7)
Safety					
Any grade AE, %	96.1	89.7	100	96.7	97.9
Grade ≥3 AE, %	60.5	50.6	72.2	83.3	79.2
AE-related treatment discontinuation, %	21.1	5.8	27.8	16.7	20.8
Insufficient clinical response–related treatment discontinuation, %	NR	NR	16.7	6.7	10.4
≥1 AE-related dose reduction, %	42.1	21.2	55.6	80	70.8
≥1 AE-related dose interruption, %	56.6	38.5	66.7	80	75

AE = adverse event; CCyR = complete cytogenetic response; MMR = major molecular response; NR = not reported; TKI = tyrosine kinase inhibitor.
[a] $P < .05$.

Long-term AEs were generally manageable with dose interruptions and reductions (>70% patients).

Comparative Efficacy of Bosutinib and Asciminib as Third- and Later-Line Treatment Options for CML

The phase 3 ASCEMBL trial compared asciminib (BCR::ABL1 inhibitor that specifically targets the ABL myristoyl pocket) 40 mg twice daily versus bosutinib 500 mg/d for patients with CP CML after treatment with at least 2 prior TKIs.[27] It is important to note that dose escalation ("ramping up" strategies) to improve tolerability and therefore efficacy (see next section on dose optimization) and dose reductions below 300 mg/d in the bosutinib arm were not allowed in ASCEMBL[27]; however, in the BYOND trial, dose escalations of ≤600 mg/d were permitted for unsatisfactory response or signs of disease progression, and dose reductions down to 200 mg/d were allowed for managing toxicity and tolerability.[7] Patients in the bosutinib treatment arm of ASCEMBL who experienced lack of efficacy could switch to asciminib rather than receive an increased dose of bosutinib; overall, 22 of 24 patients switched to asciminib due to reported lack of efficacy with bosutinib.

The MMR rate at 6 months (primary endpoint) was 13.2% for patients receiving bosutinib (Table 3). Treatment discontinuation, dose reduction, and dose interruption due to AEs occurred in 21.1%, 42.1%, and 56.6% of patients receiving bosutinib, respectively. With a longer follow-up time of 2.3 years, the MMR rate continued to be low (15.8%), and 80.3% of patients had discontinued bosutinib. The most common reason for discontinuation was lack of efficacy (35.5%) followed by AEs (25%).

The outcomes with bosutinib therapy in ASCEMBL were not consistent with previously reported clinical trials; notably, the MMR rates with bosutinib were much lower than that reported previously.[3,5-8] This raises concerns about how patients on the standard therapy arm (bosutinib) were managed in this study. The findings also suggest that the primary endpoint of MMR at 6 months in the ASCEMBL trial[27] might not be a good surrogate endpoint for survival in the salvage setting (or even in frontline therapy), since the improvement in the 6-month MMR rate did not translate into a survival benefit (2-year OS rate of 97% and 99% for asciminib and bosutinib, respectively). The treatment discontinuation rate of 21.1% due to AEs in patients receiving bosutinib is 50% greater than in the BEST dose-optimization study (14%), even when the latter study had longer follow-up and included only older patients, highlighting the importance of flexible dosing.[26,27] Also, despite the randomization, there were more TKI-resistant patients on bosutinib versus asciminib in ASCEMBL at baseline (71.1% vs. 60.5%; Table 2), and more patients received bosutinib than asciminib as fourth- and later-line therapy (60.5% vs. 47.8%),[27] which has been associated with reduced efficacy.

A recent post hoc analysis of BYOND that applied study criteria evaluating third- and later-line therapies only was comparable to

the 6-month evaluation used in ASCEMBL. This revised analysis of third- and later-lines of therapy in BYOND demonstrated an MMR and AE-related treatment discontinuation rate with bosutinib that was more consistent with the outcomes expected for a second-generation TKI in this setting (Table 3).[28] The post hoc analysis showed a 6-month MMR rate of 43.5% with bosutinib, which is a sharp contrast to the low 6-month MMR rate with bosutinib (13.2%) observed in ASCEMBL.[27,28] Moreover, the post hoc analysis showed that discontinuation due to AEs after >3 years of follow-up was higher in patients resistant to TKI versus patients intolerant to TKI (27.8% vs. 16.7%), even with a shorter follow-up time.[28]

Although BYOND is a nonrandomized study, the post hoc analysis offers insights into the importance of bosutinib dose modifications.[28] Although both BYOND and ASCEMBL used a starting bosutinib dose of 500 mg/d, greater flexibility in dosing may have contributed to higher response rates and lower discontinuation rates in BYOND than in ASCEMBL.[27,28]

In summary, the findings from ASCEMBL and the post hoc analysis of BYOND suggest an impact of differences in baseline characteristics between treatment arms on the study results. These findings also highlight the importance of bosutinib dose optimization.

Dosing Optimization Strategies for Bosutinib

The determination of optimal dosing for chemotherapeutic drugs is traditionally based on identifying the maximum tolerated dose in a phase 1 study and the recommended phase 2/3 dose. However, this strategy may not be suitable for newer targeted agents where a direct dose–efficacy relationship may be lacking, and the highest tolerable doses are not necessarily the most effective. Furthermore, because of the significantly longer survival and the potential need for years-long targeted therapy in CML, existing or newer toxicities may eventually affect quality of life, making treatment with the targeted agent unacceptable. This led to the concept of using an optimal biologic dose for targeted therapies, which involves identification of the minimal dose associated with an optimal predefined biologic effect that would maintain efficacy and significantly reduce toxicities.[29,30] Using an optimal biologic dose of a TKI may require a combination of lowering the starting dose, using a reduced or escalated dose, or interrupting treatment based on the AE severity and clinical setting.[31] Several clinical trials have elucidated the various dose-optimization strategies for TKIs—including bosutinib—in CML and their critical role in improving patient management (Table 4).[32]

The BODO trial is one of the largest studies published on the efficacy and safety of bosutinib after failure due to resistance or intolerance (or both) to frontline second-generation TKIs. The study used a bosutinib step-in dosing regimen to evaluate whether the gastrointestinal toxicity could be reduced while maintaining an optimal efficacy in patients ($N=57$) with CML.[33] The starting dose was 300 mg/d, which was increased by 100 mg/d (in the absence of grade >1 toxicity) every 2 weeks to a maximum dose of 500 mg/d. Overall, 35% of patients entered the study in molecular response (at least MMR at screening). After 24 months of treatment, the probability of MMR increased to 79%. Of the 30 patients that were refractory to previous treatment and not in MMR at baseline, 64% achieved an MMR during treatment. Unfortunately, the BODO study was stopped prematurely due to slow recruitment, and the reported rate of grade 2-4 gastrointestinal toxicity within the first 6 months of treatment was 60%, which is comparable with Study 200 and BYOND, for which the most common TEAE was diarrhea, occurring in >80% of patients.[3-8] Only 1 patient discontinued bosutinib in the BODO trial because of gastrointestinal toxicity. A possible explanation for the lack of an advantage with step-in dosing in the study is that the 300 mg starting dose might have been too high. Perhaps a starting dose of 100 to 200 mg/d for 2 to 4 weeks might have been a better approach to achieving optimal efficacy and safety.[34] Thus, the step-in dosing regimen with bosutinib induced optimal responses in nearly two-thirds of patients previously resistant or intolerant (or both) to second-generation TKIs, and gastrointestinal toxicity rarely led to treatment discontinuation.

In a study from Japan, a 180-day trial of bosutinib used a dose-escalation or "ramping up" regimen in patients with CML and resistance or intolerance to imatinib.[34] Patients either received a standard 500 mg/d dose of bosutinib ($n=10$) or a bosutinib dose escalation that started at 100 mg/d and increased by 100 mg every 2 weeks ($n=15$). Although 90% of patients in the standard-dose group were unable to continue bosutinib without interruption due to AEs, this was noted in only 13.3% in the dose-escalation group. Of note, the mean final dose in both treatment groups was the same (343 mg/d and 346 mg/d in the standard-dose and dose-escalation groups, respectively). These findings demonstrate that to avoid AE-related treatment interruptions, the bosutinib dose-escalation regimen was better suited than the standard 500 mg/d fixed dose.

The prospective phase 2 study BEST in 63 older adults (aged ≥60 years) with CML evaluated whether second-line bosutinib was effective and better tolerated at doses lower than 500 mg/d.[35] Dosing began at 200 mg/d and was increased to 300 mg/d or 400 mg/d, according to molecular response, to find the minimum effective dose. The gradual dose increase allowed ~70% of patients to remain on treatment with bosutinib dosed at ≤300 mg, achieving an MMR in 60% of cases (Table 4).

A real-world retrospective study of 101 patients with CP CML aged >65 years from 23 Italian centers evaluated the usefulness of bosutinib in older patients with comorbidities (present in 93%) who had resistance or intolerance to prior TKI therapy.[36] The starting doses of bosutinib were 500 mg/d ($n=25$), 400 mg/d ($n=7$), 300 mg/d ($n=33$), 200 mg/d ($n=34$), and 100 mg/d ($n=2$). Among patients evaluable for response, 77% achieved a CCyR, and 66.6% achieved a molecular response. Thus, a bosutinib dose lower than the standard dose of 500 mg/d might be effective and better tolerated in older patients.

An interim analysis of the DESTINY trial examined the effects of TKI de-escalation for patients with CP CML who had received TKIs for ≥3 years and were either in stable MR[4] or stable MMR for ≥12 months.[37] Treatment de-escalation was initiated as a prelude to complete cessation of treatment and was undertaken by administering half the standard dose of imatinib, dasatinib, or nilotinib for 12 months. Upon de-escalation, only 7% of patients lost MMR, all of whom regained MMR within 4 months of treatment

Table 4 Bosutinib Dose-Optimization Trials and AEs

Trial	Study Design	Median Treatment Duration	Final Dose	AEs/Safety
BODO[33]	Phase 2 trial; $N=57$; CP CML resistant or intolerant to second-generation TKIs started with bosutinib 300 mg/d, which increased by 100 mg/d every 2 wk (in the absence of grade >1 toxicity) to a maximum dose of 500 mg/d	NR	NR	Any grade TEAE: 100% Grade 3-4 TEAE: 72% Most frequently reported: • GI disorders: ○ Diarrhea: 74% ○ Nausea: 53% ○ Abdominal pain: 30% • Investigations: ○ ALT increase: 42% ○ AST increase 30%
Japanese dose-escalation study[34]	Observational; $N=25$; CP CML bosutinib 500 mg/d ($n=10$) or bosutinib dose escalation started at 100 mg/d and increased by 100 mg every 2 wk ($n=15$). Patients were imatinib-resistant or -intolerant, except for 1 patient with newly diagnosed CML	6 mo	Standard-dose group: Final dose 100/200/300/400/500 mg/d: 0/0/5/1/1 (mean 343 mg/d) Dose-escalation group: Final dose 100/200/300/400/500 mg/d: 1/2/4/4/3 (mean 346 mg/d)	Standard-dose group: • Duration of treatment interruption: 35 d • Median time to liver dysfunction: 28 d • Maximum grade (grade 2/3/4) liver dysfunction: 4/1/0 • Median time to diarrhea: 1 d • All-grade diarrhea: 100% • Maximum grade (grade 0/1/2/3/4) diarrhea: 0/4/3/3/0 • Median cumulative days of diarrhea: 20.5 Dose-escalation group: • Duration of treatment interruption: 14 d • Median time to liver dysfunction: 53.5 d • Maximum grade (grade 2/3/4) liver dysfunction: 1/2/1 • Median time to diarrhea: 19 d • All-grade diarrhea: 73.3% • Maximum grade (grade 0/1/2/3/4) diarrhea: 4/6/2/3/0 • Median cumulative days of diarrhea: 6
BEST[35]	Phase 2: $N=63$, aged ≥60 y; CP CML resistant or intolerant to first-line TKI, administered bosutinib 200 mg/d for 2 wk with increases to 300 or 400 mg/d, according to molecular response, to find minimum effective dose	9 mo	15.9% ($n=10$) had dose increase to 400 mg/d; 77.8% ($n=49$) to 300 mg/d; and 6.3% ($n=4$) continued 200 mg/d without any dose increase	Cardiac ischemia: 3.2% ($n=2$) Pericardial effusion: 3.2% ($n=2$) Events leading to treatment discontinuation: • Unrelated deaths: $n=2$ • AEs: $n=7$ ○ Hypertransaminasemia: $n=3$ ○ Nephrotoxicity: $n=1$ ○ Diarrhea: $n=1$ ○ Skin rash: $n=1$ ○ Myalgia/fatigue $n=1$

(*continued on next page*)

Table 4 (*continued*)

Trial	Study Design	Median Treatment Duration	Final Dose	AEs/Safety
Italian real-world study[36]	Real-world study; $N=101$; aged >65 y; CP CML resistant or intolerant to prior TKI therapy received different bosutinib doses: 500 mg/d ($n=25$), 400 mg/d ($n=7$); 300 mg/d ($n=33$); 200 mg/d ($n=34$); and 100 mg/d ($n=2$)	19.9 mo	NR	Hematologic toxicity (all-grade/grade 3-4): 13.8% (14/101)/6.9% (7/101) Extra-hematologic toxicity (all-grade/grade 3-4): 52.4% (53/101)/18.8% (19/101) Toxicity-related temporary bosutinib discontinuation, <6 wk />6 wk: 21.8% ($n=22$) / 1.9% ($n=2$) Toxicity-related permanent bosutinib discontinuation: 11.9% ($n=12$) All-grade/grade 3-4 AEs (incidence >5%): • Diarrhea: 15.8% ($n=16$)/ 3.9% ($n=4$) • Skin toxicity: 9.9% ($n=10$)/ 0.9% ($n=1$) • Abdominal pain: 7.9% ($n=8$)/0 • Liver toxicity: 7.9% ($n=8$)/ 2.9% ($n=3$)

AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BODO = Bosutinib Dose-Optimization Study, CML = chronic myeloid leukemia, CP = chronic phase, NR = not reported, TEAE = treatment-emergent adverse event, TKI = tyrosine kinase inhibitor.

with full-dose TKI. Importantly, AEs such as lethargy, diarrhea, rash, and nausea also improved during the first 3 months of de-escalation but not thereafter. New AEs arising during the TKI de-escalation showed only mild and transient evidence of musculoskeletal symptoms that have previously been described with complete TKI withdrawal. These findings suggest that when patients are in a stable MMR, a TKI dose de-escalation is a reasonable option and is associated with an improvement in the TKI-related side effects.

These studies highlight that justified dose reductions due to toxicity do not seem to jeopardize efficacy of TKI treatment in CML, even in later-line treatment; however, careful monitoring is still recommended.

Bosutinib Treatment in the Context of Common Comorbidities and AEs

Comorbidities are prevalent among patients with CML, and the use of concomitant medications may increase the risk of AEs associated with standard TKI dosing,[38-42] which could trigger new or aggravate previous comorbidities.[43] The well-established, long-term side-effect profile and the potential for dose adjustments makes bosutinib a good treatment option for patients with CML who may be at a higher-than-normal risk of toxicity and treatment discontinuation. In particular, bosutinib may be a preferable treatment option in older patients and those with certain conditions, such as cardiac, vascular, pulmonary, and diabetic comorbidities.[13,24,40,44,45] In older patients, including those with comorbidities, lower starting doses of bosutinib have demonstrated better tolerability and maintained favorable efficacy.[33,35,36,46] Bosutinib may be the preferred frontline treatment for patients with cardiovascular comorbidities due to the low risk of arterio-occlusive events.[42] Emerging evidence indicates that older patients and patients with comorbidities may benefit from bosutinib dose modifications to manage AEs and that efficacy is not compromised by dose reductions to 400, 300, or 200 mg daily or dose interruptions.[47] In the BYOND study, a post hoc analysis evaluated the impact of age and comorbidities on the tolerability and efficacy of bosutinib in patients with previously treated CP CML.[47] The cumulative MMR rates in patients <65, 65 to 74, and ≥75 years of age were 73.6%, 64.5%, and 74.1%, respectively. Among patients with Charlson Comorbidity Index scores without the age component (mCCI) of 2, 3, and ≥4, the cumulative MMR rates were 77.9%, 63.0%, and 59.3%, respectively.[47] Older patients (≥75 years of age) and those with high comorbidity burden (mCCI ≥4) may require more frequent monitoring due to a trend towards higher rates of TEAEs and treatment discontinuation.[47]

Patients With Cardiac and Vascular Comorbidities and AEs

Most cardiovascular ischemic events that occur during TKI treatment manifest among patients with preexisting cardiovascular disease or risk factors.[21,48] A retrospective analysis identified the following prognostic risk factors of cardiac AEs among patients with CP CML treated with bosutinib after resistance or intolerance to imatinib, or imatinib plus dasatinib with or without nilotinib.[44] Patients were ≥65 years of age, an Eastern Cooperative Oncology Group performance status >0, a history of hyperlipidemia, and a

history of cardiac events.[44] Despite an increased risk of cardiovascular events with newer-generation TKIs, the relatively low incidence of cardiac and vascular toxicities observed in the clinical trials of bosutinib may make it a valuable treatment option for patients with cardiovascular comorbidities.[49] Patients in the BFORE trial had a higher cardiovascular comorbidity burden at baseline than observed in other trials of bosutinib, and although cardiovascular TEAEs remained low overall (≤5% in each treatment arm), the rates were higher in the bosutinib arm (4.9%) compared with imatinib (0.4%) after 5 years of follow-up.[9] The incidence of cerebrovascular TEAEs (0.7% and 1.1%) and peripheral vascular TEAEs (2.2% and 2.3%) were similar between bosutinib and imatinib.[9] Hypertension TEAEs were lower with bosutinib (9.7%) than with imatinib (10.9%).[9] Cardiac AEs were higher with bosutinib versus imatinib (9.7% vs. 8.7%), and the most common cardiac AEs were sinus bradycardia (2.2% vs. 0%) and QT prolongation (1.5% vs 3.8%)[9]. The most common strategies for managing cardiac AEs during bosutinib treatment are concomitant medication and bosutinib dose interruption/reduction.[50] Using such approaches enables most patients who experience cardiovascular AEs to continue bosutinib treatment.

Patients With Pulmonary AEs

All TKIs have a risk of pulmonary AEs, especially pleural effusion, which can first occur years after starting treatment.[40] Generally, among all TKIs used in CML, the risk of pleural effusion is assumed to be highest with dasatinib.[42,51] However, although the risk of pleural effusion is probably lower with bosutinib than dasatinib, rates were higher in direct comparison with imatinib in the BELA and BFORE trials. In an updated safety analysis of BELA, which assessed bosutinib versus imatinib treatment for patients with newly diagnosed CP CML after >30 months, the incidence of pleural effusion was low in both treatment arms (4% vs. 1%).[52] In the final 5-year analysis of the BFORE trial, pleural effusion occurred in 5% of patients treated with bosutinib versus 2% with imatinib, increasing from 2% to 1.5% in the first year, respectively.[9] Cross-intolerance due to pleural effusion has been reported among TKIs, including in patients treated with bosutinib after dasatinib, which should be taken into consideration when choosing treatment.[53,54]

Patients With Diabetes and Other Metabolic Abnormalities

Managing any underlying metabolic abnormalities, such as diabetes or hyperlipidemia, is important prior to initiating TKI therapy, along with constant monitoring to mitigate the risk or exacerbation of metabolic AEs during TKI therapy.[55,56] Although diabetes is a common comorbidity in patients with CML, data evaluating the efficacy and safety of bosutinib in this patient population are limited. Bosutinib is associated with a lower risk of hyperglycemia compared with other TKIs, nilotinib in particular, and is a good treatment option for patients with diabetes.[43,57] As with all TKIs, other biochemical abnormalities to consider with bosutinib treatment are hyperlipidemia, which has primarily been associated with nilotinib, and increased lipase, which was the most common newly occurring AE with bosutinib after 12 months in the BFORE trial.[9,32,40]

Bosutinib-Related AEs

Bosutinib is associated with gastrointestinal, hepatic, and renal AEs and should therefore be used with caution in patients with these preexisting risk factors. If used, lower bosutinib doses should be considered.[32]

Gastrointestinal AEs are the most common AEs associated with bosutinib treatment, which should therefore be used with caution among patients with gastrointestinal comorbidities such as diarrhea, inflammatory bowel disease, or gastric ulcer.[40] In clinical trials,[3-9,17] diarrhea was usually mild and transient and managed with supportive care (eg, antiemetics and antidiarrheals) and dose interruption or reduction. Treatment discontinuation due to diarrhea was low (0.4%-3%).[3,4,7,9,18]

Bosutinib treatment has been associated with elevated serum transaminase levels, warranting regular monitoring of liver function and dose adjustments for patients with hepatic impairment.[57] A lower bosutinib dose of 200 mg/d was found to have acceptable tolerability in patients with mild, moderate, or severe chronic hepatic impairment and is therefore the recommended dose in this patient population.[58]

In patients with mild renal dysfunction (creatinine clearance 30-50 mL/min), patients with newly diagnosed CML should receive a lower bosutinib dose of 300 mg/d, and those resistant or intolerant to previous TKI therapy should receive 400 mg/d.[59] For creatinine clearance <30 mL/min, patients with newly diagnosed CML should receive 200 mg/d, and those resistant or intolerant to prior TKIs should receive 300 mg/d.[59]

Health-Related Quality of Life

Several studies of bosutinib have evaluated health-related quality of life (HRQoL) in patients with CML.[60] Using a variety of validated QoL measures, different studies demonstrated that bosutinib treatment in patients with CML improved or stabilized the HRQoL across domains such as physical and emotional well-being.[61-64] Not surprisingly, improvements of certain subdomains of HRQoL with bosutinib and imatinib (eg, emotional well-being) are particularly associated with improvements in response to therapy.[65]

Summary

The range of experience with bosutinib for patients with CML has shown it has a favorable efficacy profile in frontline treatment and later lines of therapy and a positive impact on HRQoL. The optimization of bosutinib dosing through dose reductions and dose escalations to manage AEs resulted in fewer treatment discontinuations due to manageable and reversible side effects. Pre-emptive assessment, early toxicity recognition, and prompt management of toxicities can minimize the treatment-limiting complications and improve the outcomes of patients with CML. Dose optimization of bosutinib is a primary approach to enable toxicity management, allowing continuation of therapy and improving efficacy across different CML patient populations.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

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.

Disclosure

HMK served as a consultant for AbbVie, Amgen, Amphista, Ascentage, Astellas, Biologix, Curis, Ipsen Biopharmaceuticals, KAHR Medical, Labcorp, Novartis, Pfizer, Shenzhen Target Rx, Stemline, Takeda, and has received research funding from AbbVie, Amgen, Ascentage, BMS, Daiichi-Sankyo, Immunogen, Jazz, Novartis. EJJ has received research grants and consultancy fees from Bristol Myers Squibb, Incyte, Novartis, Pfizer, and Takeda. JHL has served as a consultant for and has received research funding from Bristol Myers Squibb, Novartis, Pfizer, and Takeda, and has received honoraria from Bristol Myers Squibb, Incyte, Novartis, Pfizer, and Takeda. FC has received honoraria from Bristol Myers Squibb, Incyte, Novartis, and Pfizer. THB has been a consultant for Gilead, Janssen, Merck, Novartis, and Pfizer, and has received research support from Novartis and Pfizer.

CRediT authorship contribution statement

Hagop M. Kantarjian: Writing – review & editing. **Elias J. Jabbour:** Writing – review & editing. **Jeffrey H. Lipton:** Writing – review & editing. **Fausto Castagnetti:** Writing – review & editing. **Tim H. Brümmendorf:** Writing – review & editing.

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