Bosutinib in the management of chronic myelogenous leukemia

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Abstract: Bosutinib (SKI-606) is an orally available, once-daily dual Src and Abl kinase inhibitor, approved by the US Food and Drug Administration for the treatment of adults with chronic, accelerated, or blast-phase Philadelphia chromosome-positive chronic myelogenous leukemia who are intolerant of or resistant to first- or second-generation tyrosine kinase inhibitors. Bosutinib effectively overcomes the majority of imatinib-resistance-conferring BCR-ABL mutations except V299L and T315I. In the Bosutinib Efficacy and Safety in chronic myeloid LeukemiA (BELA) trial, bosutinib attained a faster and deeper molecular response than imatinib in newly diagnosed chronic-phase chronic myelogenous leukemia patients. Treatment-emergent adverse events are usually very manageable. Low grade, mostly self-limiting diarrhea represents the most frequently observed toxicity of bosutinib. Anti-diarrheal drugs, antiemetic agents, and/or fluid replacement should be used to treat these patients. The improved hematological toxicity of bosutinib compared with other tyrosine kinase inhibitors has been ascribed to its minimal activity against platelet-derived growth factor receptor and KIT. In this review, we give an overview on the profile of bosutinib, the clinical potential and treatment-emergent adverse events.

Keywords: CML, BCR-ABL, SRC/ABL kinase inhibitor, resistance-conferring mutation

Introduction

The treatment landscape for chronic myelogenous leukemia (CML) was dramatically changed after the US Food and Drug Administration (FDA) approval of the tyrosine kinase inhibitor (TKI) imatinib (IM; formerly STI571 or CGP57148). IM effectively targets bcr-abl – a fusion protein resulting from the reciprocal translocation of the proto-oncogene c-ABL localized on chromosome 9 to the breakpoint cluster region (BCR) on chromosome 22. In the International Randomized Interferon versus STI571 (IRIS) trial, the 8-year follow-up data revealed an estimated overall survival of 85% for IM, suggesting a high and persistent efficacy of this TKI in chronic-phase (CP) CML. However, due to intolerance and/or resistance, only 55% to 75% of the patients in the clinical trials are still on IM therapy after 5 to 8 years. The off-target effects of IM, with inhibition of platelet-derived growth factor receptor, kit, and abl kinases, mediate at least some of the toxicities and the BCR-ABL kinase-domain mutations that prevent IM binding are the main causes of IM resistance. Alternative treatment strategies are under investigation to address these important therapeutic issues.

The second-generation TKIs nilotinib (formerly AMN107) and dasatinib (formerly BMS354825) and third-generation TKI bosutinib (formerly SKI-606) have been found capable of overcoming the majority of IM-resistance-conferring BCR-ABL mutations. Convincing results of clinical trials led to the approval of nilotinib, dasatinib, and
bosutinib for the treatment of CML patients, resistant or intolerant to IM.

Due to the high efficacy of nilotinib, dasatinib, and bosutinib in preclinical and clinical studies, each compound was compared with IM in Phase III clinical trials for patients with newly diagnosed, untreated CP-CML. In all trials, nilotinib, dasatinib, and bosutinib were found to be superior to IM in terms of molecular response rate, time to the accomplishment of the remissions, and frequency of clonal evolution to accelerated phase (AP) and/or blast crisis (BC). However, direct comparisons between the trials are not admissible because of the distinct differences in trial design – in particular, regarding the primary study endpoints as well as different definitions for “freedom from progression,” “event-free survival,” and “progression-free survival.”

In this review, we give an overview of the clinical potential of bosutinib, with a special focus on treatment-emergent adverse events and the potential role of bosutinib in the future.

**Drug class**

Bosutinib is a third-generation TKI with the chemical name 3-quinolinecarboxonitrile, 4-[(2,4-dichloro-5-methoxyphenyl) amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-, hydrate (1:1). The chemical formula is C_{26}H_{29}Cl_{2}N_{5}⋅H_{2}O. Bosutinib can also be classified as a histone deacetylase inhibitor and induces differentiation and/or cell death of malignant cells.

**Dosage, administration, and pharmacokinetics**

The recommended dose of bosutinib for CML patients is 500 mg orally, taken once daily with food. Bosutinib is mainly metabolized by cytochrome P450 (CYP) 3A4 and is primarily excreted in the feces. Under feeding conditions, bosutinib exposure is linear and dose proportional over the entire evaluated dosage range, from 200 to 800 mg. In healthy adult subjects, median time to peak plasma concentration is approximately 6 hours and mean terminal elimination half-life is 32–39 hours.

**Target profile of bosutinib**

Bosutinib shows potent inhibitory activity against src and bcr-abl, while activity against other kinases is low. Thus, Bosutinib virtually abrogates tyrosine phosphorylation of bcr-abl at concentrations of 25 to 50 nM whereas 200 nM is needed to decrease Abelson murine leukemia viral oncogene homolog 1 (v-abl1) phosphorylation to a similar extent. In addition, bosutinib effectively targets SRC at nanomolar concentrations with an half maximal inhibitory concentration (IC50) of 1.2 nM in SRC enzymatic assay (bosutinib corresponds to compound 31a). This is of special interest because the SRC family kinases have been linked to disease progression and BCR-ABL-independent forms of IM resistance (reviewed in Li). Additionally, in chemical proteomics and in vitro kinase assays, more than 45 potential target tyrosine and serine/threonine kinases of bosutinib were discovered. Apoptosis-linked STE20 kinases and CAMK2G – both associated with myeloid leukemia cell proliferation – were among these kinases. Further, bosutinib decreases activity of cyclin-dependent kinase 2, which leads to a prominent G1 arrest of clonal hematopoietic progenitors expressing BCR-ABL.

**Clinical potential of bosutinib**

Bosutinib is effective in upfront treatment of CP-CML and after failure of first- and second-generation TKIs. It can overcome most IM-resistant BCR-ABL mutations.

**First-line therapy for CP-CML**

In the open-label, randomized, multinational, Phase III Bosutinib Efficacy and Safety in chronic myeloid LeukemiaLA (BELA) trial, bosutinib (500 mg/d) was compared with IM (400 mg/d) for first-line treatment of CP-CML. A total of 502 patients were randomly assigned (1:1) to the two treatment groups after stratification for Sokal risk score and geographic region of the centers the patients were enrolled in for the study.

Bosutinib did not meet the primary endpoint of the study because in the intention-to-treat population, complete cytogenetic response (CCyR) at 12 months was not significantly different for bosutinib (70%; 95% confidence interval [CI]: 64%–76%) when compared with IM (68%; 95% CI: 62%–74%; P = 0.601).

However, secondary endpoints as well as additional findings of the study suggest bosutinib is superior. Thus, the rate of major molecular remission (MMR) at 12 months was significantly higher in bosutinib-treated patients (41%; 95% CI: 35%–47%) than in IM-treated patients (27%; 95% CI: 22%–33%; P < 0.001). Additionally, complete molecular remission was reported for 12% of bosutinib-treated patients but for only 3% of IM-treated individuals (P < 0.001) and the median time to CCyR and MMR was significantly shorter for bosutinib – 12.9 weeks (95% CI: 12.6–13.4 weeks) and 37.1 weeks (95% CI: 36.1–48.6 weeks), respectively – than with IM (24.6 weeks [95% CI: 24.3–25.6 weeks, P < 0.001]) and 72.3 weeks [95% CI: 61.1 weeks-not reached, P < 0.001],
respectively). Most importantly, on-treatment transformation to AP or BC occurred in only four patients (2%) treated with bosutinib, whereas this occurred in ten patients on IM (4%). A total of three and eight CML-related deaths were reported for the bosutinib and the IM treatment arm, respectively.12

Second-line therapy after failure of imatinib

The efficacy of bosutinib secondary to treatment failure of IM in CP-CML was examined in a Phase I/II, nonrandomized clinical trial. The study population included imatinib-resistant (n = 200) and imatinib-intolerant (n = 88) patients. No other previous TKI exposure was allowed. “IM resistance” was defined as no hematological improvement within 4 weeks, no complete hematological response (CHR) by 3 months, no cytogenetic response by 6 months, or no major cytogenetic response (MCyR) by 12 months, with a daily IM dosage of at least 600 mg. “IM intolerance” was defined as grade IV hematological toxicity lasting for more than 7 days, appearance of grade 3 and 4 non-hematological toxicities, or grade 2 toxicities that did not improve despite adequate management or dose adjustments, or when a loss of previously attained response was observed after toxicity determined dose reduction of IM.11

Thirty-one percent of the patients achieved a MCyR at 24 weeks, thus met the primary endpoint of the study (33% of IM-resistant patients; 27% of IM-intolerant patients). MCyR and CCyR were observed in 53% and 41% of patients, respectively, after a median follow-up time of 24.2 months. Dose intensities exceeding 350 mg were associated with increased rates of MCyR. Within a median time of 2 weeks, 86% of the patients achieved a CHR, although 78% of study participants did not have a CHR at the time of study enrollment. Among patients with CCyR, MMR and complete molecular remission were reported for 64% and 49% of IM-resistant and 65% and 61% of IM-intolerant patients, respectively.11

Third- and fourth-line therapy after failure of IM and nilotinib and/or dasatinib

The clinical potential of bosutinib in third- or fourth-line therapy was examined in a subgroup of patients (n = 118) of the just-described multicenter clinical trial.26 All patients were previously treated with IM and had failed secondary therapy with nilotinib and/or dasatinib: 27 and 37 patients were resistant to nilotinib and dasatinib while intolerance was documented for one patient receiving nilotinib and 50 patients receiving dasatinib. Two patients were resistant to dasatinib and nilotinib, while one patient was intolerant to both second-generation TKIs.

The median duration of follow-up was 28.5 months (range: 0.3–56.2 months) at the data cutoff date of March 28, 2011. At this time, the median time of bosutinib treatment was 8.3 months (range: 0.2–51.8 months). Of the patients, 32% attained a MCyR and 24% attained CCyR, including one patient who achieved CCyR and had previously received all three TKIs.

A confirmed CHR was achieved or maintained by 73% of the patients including 65% of patients who did not have a CHR at baseline. Remarkably, two of three patients who were treated with all three TKIs had a confirmed CHR. Among 20 patients who showed inadequate treatment responses, dose escalation to 600 mg/d subsequently resulted in responses in 30% of the individuals, with three cases of CCyR. On-treatment transformation to AP was observed in five patients after 16 to 428 days on study, while no patient transformed to BC.26,27 To identify the group of patients that might respond best to bosutinib treatment, baseline characteristics of patients were analyzed. However, only minor cytogenetic response prior to dasatinib and/or nilotinib treatment and a lower percentage of Philadelphia chromosome-positive cells at baseline were found to be consistently predictive of better outcomes on bosutinib.28

Efficacy of bosutinib against IM-resistance-conferring BCR-ABL mutations

Structural and spectroscopic analyses have helped to understand the activity of bosutinib against IM-resistant BCR-ABL mutants.29 Preclinical activity of bosutinib has been reported against most IM-resistant mutants of BCR-ABL with the exception of T315I and V299L.20,30

In clinical studies, the impact of preexisting BCR-ABL mutations on bosutinib efficacy was evaluated in patients pretreated with IM only (n = 115) or with IM followed by nilotinib and/or dasatinib (n = 39). Similar rates of CHR and MCyR were observed in patients with and without mutations and broadly across all BCR-ABL mutations, including in individuals harboring the dasatinib-resistant F317L or the nilotinib-resistant Y253H and F359C/I/V mutations but not T315I (Table 1). When patients with T315I at baseline were excluded from the second-line setting, response rates for the remaining patients with ≥1 mutation were 93% for CHR and 62% for MCyR.31 During second-line therapy, 18 patients who discontinued treatment had one or more new BCR-ABL mutations (T315I, n = 8; V299L, n = 3; E255V, E450A, E450G, G250E, K378E, L273M, and M244V, n = 1 each) and, indeed, for 15 of these individuals,
Table I Efficacy of bosutinib against BCR-ABL mutations in clinical studies

| Location of mutation | Pretreatment | Imatinib | Imatinib + nilotinib and/or dasatinib |
|----------------------|-------------|----------|--------------------------------------|
|                      | CHR | MCR | CHR | MCR |
| | (n/n evaluable) | (n/n evaluable) | (n/n evaluable) | (n/n evaluable) |
| P-loop                |     |     |     |     |
| L248V                | 3/3 | 2/3 | 3/6 | 0/5 |
| G250E                | 1/1 | 2/2 | 0/1 |     |
| Y253F                | 1/1 | 1/1 | 1/1 | 1/1 |
| Y253H                | 1/1 | 1/1 | 5/6 | 4/6 |
| E255K                | 2/2 | 1/2 | 0/1 | 1/1 |
| E255V                | 1/1 | 1/1 | 1/1 | 1/1 |
| Non-p-loop           |     |     |     |     |
| M315T                | 3/3 | 6/6 | 1/1 | 0/1 |
| F359V                | 6/6 | 4/7 | 0/2 | 1/2 |
| F317L                | 0/0 | 3/3 | 4/8 | 1/7 |
| T315I                | 1/2 | 0/3 | 2/7 | 0/6 |
| M244V                | 2/2 | 2/3 | 3/3 | 2/3 |
| D276G                | 1/1 | 0/1 |     |     |
| L298V                | 1/1 | 0/1 |     |     |
| F311L                | 1/1 | 1/1 |     |     |
| N331S                | 0/0 | 1/1 |     |     |
| E355G                | 2/2 | 1/2 |     |     |
| F359I                | 1/1 | 1/1 |     |     |
| L364P                | 0/0 | 1/1 |     |     |
| L387F                | 0/0 | 0/1 |     |     |
| H396P                | 1/1 | 2/2 |     |     |
| H396R                | 1/1 | 0/0 | 0/1 | 0/1 |
| D421G                | 1/1 | 0/1 |     |     |
| H322T                | 0/0 | 0/1 |     |     |
| E450V                | 1/1 | 1/1 |     |     |
| E453K                | 0/0 | 1/1 |     |     |
| E453Q                | 1/1 | 1/1 |     |     |
| E453A                | 1/1 | 1/1 |     |     |
| E459K                | 0/0 | 0/1 |     |     |
| P480A                | 0/0 | 1/1 |     |     |
| V299L                | 1/2 | 0/2 |     |     |
| Q300R                | 1/1 | 1/1 |     |     |
| N336S                | 1/1 | 0/1 |     |     |
| F359C                | 2/2 | 1/2 |     |     |
| F359I                | 2/2 | 2/2 |     |     |
| L387F                | 1/1 | 0/1 |     |     |
| C475V                | 1/1 | 1/1 |     |     |
| F486S                | 0/0 | 0/1 |     |     |
| Unknown              | 3/3 | 9/11 |     |     |

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Efficacy of bosutinib in CML patients without resistance-conferring mutations at baseline

In the second-line setting, 42.5% of the patients with IM resistance did not harbor a mutation at baseline. In addition, in 53% of the patients who were classified as resistant to IM and nilotinib and/or dasatinib, no mutation was detected at initiation of the study medication. Similar rates of CHR and MCR were observed for both subgroups when compared with individuals of the respective trial who did have a resistance-conferring mutation at baseline.11,26

Safety and tolerability of bosutinib

Bosutinib shows an acceptable safety profile in the first-, second- and third-line therapy of CML patients.13 Following, a selection of the most frequent treatment-emergent adverse events is summarized.

Hematological toxicity

It should be noted that bosutinib has a favorable hematological toxicity profile compared with other TKIs. Thus, grade 3/4 neutropenia appeared significantly less frequently in patients treated with bosutinib when compared with IM in upfront therapy (11% vs 24%). This has been ascribed to the minimal inhibitory activity of bosutinib against c-kit. Anemia and thrombocytopenia occurred to similar extents in bosutinib- and IM-treated patients.12 In clinical trials, grade 3/4 hematological toxicities increased with the number of prior TKI therapies. Thus, grade 3/4 thrombocytopenia was reported for 14%, 25%, and 26% and neutropenia for 11%, 17%, and 20% of the patients receiving first-, second- or third-line bosutinib therapy, respectively. Worsening of grade 3/4 anemias was less pronounced and ranged between 6% and 12% for bosutinib-treated patients.11,12,26 These findings are in line with observations of clinical studies performed with other TKIs in second- and third-line CML treatment.15

Gastrointestinal toxicity

Low grade, mostly self-limiting diarrhea has been reported in up to 84% of patients treated with bosutinib11,12,26 and thus represents the most frequently observed toxicity of the drug.
The diarrhea usually occurs within the first 4 weeks after treatment initiation, is typically of low grade, and self-limits within the first 2 to 3 months of treatment. Anti-diarrheal drugs, antiemetic agents, and/or fluid replacement should be used to treat these patients. However, in the BELA trial, up to 11% of patients developed grade 3/4 diarrhea under bosutinib therapy. In the bosutinib treatment arm, the diarrhea required dose interruptions and reductions in 21% and 8% of patients, respectively. In contrast, dose reduction was not necessary in any of the IM-treated patients and in only 6% of IM-treated patients was the TKI temporarily discontinued. Other gastrointestinal toxicities of bosutinib include nausea (31%–46%, all grades), vomiting (32%–40%, all grades), and abdominal pain (11%–22%, all grades).

**Bleeding disorders**

Bosutinib has a minor influence on platelet function, resulting in a distinctly lower number of bleeding complications compared with other TKIs. Thus, hemorrhagic events appeared in only 5% of bosutinib-treated patients (all grades) with only one grade 3 bleeding event. In contrast, for dasatinib, bleeding disorders (all grades) were reported for 40% of the patients, with 10% classified as grade 3/4.

**Non-hematological laboratory abnormalities**

The most frequent non-hematological laboratory abnormalities include hyperglycemia, hypermagnesemia; elevation of alanine aminotransferase and aspartate aminotransferase, uric acid, creatinine, lipase, and alkaline phosphatase; hypocalcaemia; and hypophosphatemia. An increase in liver enzymes was associated with a significantly increased rate of treatment discontinuations under bosutinib treatment compared with IM in first-line treatment. However, despite the occurrence of liver function abnormalities, no permanent liver injury was observed in patients treated with bosutinib. Other non-hematological treatment-emergent adverse events in first-, second- and third-line therapy include rashes (20%–34%, all grades), fatigue (11%–22%, all grades), headache (11%–25%, all grades), upper respiratory infections and cough (12%–16%, all grades).

**Bosutinib application in patients with chronic hepatic impairment**

Bosutinib is mainly metabolized by CYP3A4 and, indeed, in a drug interaction study, ketoconazole, a potent CYP3A4 inhibitor, increased the maximal plasma concentration and concentration–time curve of 100 mg oral bosutinib by 5.2- and 8.6-fold, respectively. Therefore, the pharmacokinetics of bosutinib were evaluated in patients with impaired liver function (Child–Pugh A n = 6; Child–Pugh B n = 6; Child–Pugh C n = 6) and compared to healthy matched controls (n = 9). Elimination half-life was increased from 55 hours in healthy subjects to 86 hours in Child–Pugh A-, 113 hours in Child–Pugh B-, and 111 hours in Child–Pugh C-class patients. In addition, an increase of peak plasma concentration of 1.52- to 2.42-fold was observed in patients with impaired liver function when compared with healthy controls. Thus, dose adjustment needs to be taken into account when administering bosutinib to patients with impaired liver function or – if it cannot be avoided – to patients receiving CYP3A4 inhibitors at the same time.

**Expert commentary**

Bosutinib is approved by the FDA for the treatment of CML secondary to failure of IM, dasatinib, and/or nilotinib. Although bosutinib did not meet the primary endpoint of the BELA trial, it demonstrated high efficacy in the first-line treatment of CP-CML. Thus, deeper molecular response rates were reported for bosutinib than for IM. In addition, times to CCyR and MMR were significantly shorter for bosutinib than for IM, indicating a more rapid debulking of tumor burden with bosutinib. It has been speculated that one reason for the equal CCyR rates of both TKIs at 12 months was the unexpectedly high number of bosutinib discontinuations and interruptions in the intention-to-treat population due to adverse events. In fact, according to the study protocol, patients who discontinued the study counted as non-responders in the final analyses. However, remarkably, an exposure–response relationship for bosutinib has been observed for patients with newly diagnosed CP-CML with regard to CCyR, MMR, and cumulative CHR at 1 year.

Bosutinib effectively targets most IM-resistance-conferring BCR-ABL mutations, with the exception of the highly resistant T315I (resistant to IM, dasatinib, nilotinib, and bosutinib) and V299L mutations (resistant to dasatinib and bosutinib). For patients who do not respond to first- or second-generation TKIs, allogeneic stem cell transplantation and interferon therapy are currently the only approved treatment modalities with the potential for life prolongation. It has been speculated that a growing selection pressure in TKI treatment will promote the appearance of the T315I mutation. Novel compounds such as the aurora kinase inhibitors – including danusertib (formerly PHA-739358), homoharringtonine, and ponatinib – successfully target the T315I mutation. In fact, clinical trials are currently underway and have attained promising results (see O’Hare et al for a
review of these). Most convincingly, ponatinib demonstrated high efficacy independently of mutational status (including the highly resistant T315I mutation) in a Phase II clinical trial with heavily pretreated CP-, AP-, and BC-CML patients as well as patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Consequently, ponatinib was approved by the FDA in December 2012 for the treatment of adult patients with CP-, AP-, or BC-CML resistant or intolerant to prior TKI therapy.

In first-line therapy, a progression to AP or BC was observed less frequently in bosutinib-, dasatinib- and nilotinib-treated patients than in IM-treated individuals. An improved bcr-abl binding – resulting in early and deep molecular responses and therefore a more pronounced reduction of tumor cell burden – seems to be of high impact. In addition, src inhibition may further contribute to improved disease control in bosutinib- and dasatinib-treated patients. Indeed, src family tyrosine kinases have been associated with disease progression in CML, for example, increased expression and/or activation of Hck and Lyn were reported for patients progressing to AP or BC.

The minimal activity of bosutinib against platelet-derived growth factor receptor and c-kit and a different inhibition profile against other target kinases are probably the cause of bosutinib’s different toxicity profile compared with IM, nilotinib, and dasatinib. Thus, grade 3/4 neutropenia was observed significantly less frequently with bosutinib than with IM in the BELA trial. One reason for this seems to be that bosutinib has lower toxicity toward normal progenitor cells than IM. Other advantages of bosutinib over other TKIs include a reduced number of bleeding disorders and fluid retention issues. As previously outlined, the most dominant adverse events resulting from bosutinib treatment are gastrointestinal toxicities (mainly grade 1/2 diarrhea and nausea), which are mostly easily managed and self-limiting.

**Future perspectives**

The choice of the best treatment strategy for CML has become increasingly difficult due to the growing armada of approved TKIs supplemented by several pipeline medications. In addition, in a growing number of countries, the standardization of molecular monitoring according to the international scale and the continuous improvement of techniques for molecular monitoring has resulted in increasingly precise BCR-ABL values. However, this raises the question of the optimal time for a therapeutic intervention – for example when suboptimal responses according to the definition of the European LeukemiaNET are observed.

Different clinical observations suggest that MMR is associated with increased individual life expectancy. Thus, Marin et al found a significantly higher 8-year probability of survival for patients with BCR-ABL transcript levels < 9.84% when compared with individuals with BCR-ABL transcript levels above this value at 3 months. In addition, Hanfstein et al reported lower 5-year survival rates for IM-treated patients with BCR-ABL levels > 10% according to the international scale at 3 months.

In the BELA trial, BCR-ABL/ABL ratios < 10% at 3, 6, and 9 months were associated with higher rates of MMR and CCyR at later time points of the study in bosutinib- and IM-treated patients. Remarkably, more patients treated with bosutinib than with IM fell below the 10% BCR-ABL/ABL ratio. Similarly, in first-line trials with dasatinib (Dasatinib versus Imatinib Study in Treatment-Naive CML Patients [DASISION]) and nilotinib (Evaluating Nilotinib Efficacy and Safety in Clinical Trials Newly Diagnosed Patients [ENESTnd]), more patients treated with the second-generation TKIs achieved BCR-ABL/ABL ratios < 10% at 3 months than with IM. Independent of the TKI treatment, better molecular responses were associated with improved long-term outcome and a lower risk of transformation to AP/BC.

**Conclusion**

Highly potent second- and third-generation TKIs may be the better choice for first-line therapy of patients with long life expectancy. In addition, in our opinion, a TKI switch should be considered if the BCR-ABL/ABL ratio exceeds 10% 3 months after treatment initiation to avoid an unfavorable course of disease with an increased risk of disease progression. For the choice of the second- or third-line TKI, mutational analyses, the patient’s coexisting medical conditions, and possible treatment-emergent adverse events are of high importance. Because of its distinctly different toxicity profile, bosutinib is a genuine alternative to IM, nilotinib, and dasatinib.

**Disclosure**

Philippe Schafhausen is a consultant/advisor for Novartis and Pfizer and both authors have received travel support and lecture honoraria from Bristol-Myers Squibb and Novartis. The authors declare no other conflicts of interest in this work.

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