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A Critical Review of Trials of First-Line BCR-ABL Inhibitor Treatment in Patients With Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase

Elias Jabbour, MD[1] and **Jeffrey H. Lipton, PhD, MD**[2]

[1]The University of Texas, MD Anderson Cancer Center

[2]Princess Margaret Hospital, University of Toronto, Ontario, Canada

Abstract

The characteristic expression of the constitutively active oncoprotein, BCR-ABL tyrosine kinase, in chronic myeloid leukemia (CML) was the basis for the development of BCR-ABL tyrosine kinase inhibitors for treatment. Three BCR-ABL inhibitors, imatinib, nilotinib, and dasatinib, have been approved by the US Food and Drug Administration for first-line treatment of patients with newly diagnosed CML in chronic phase (CML-CP). This article reviews the key phase III clinical trials supporting the use of first-line imatinib, nilotinib, and dasatinib in patients with CML-CP as well as findings of supportive phase II studies. At the time of its approval in 2001, imatinib induced unprecedented response rates in patients with CML-CP; however, resistance and intolerance to imatinib prevent 20% to 30% of patients from deriving full therapeutic benefit. Nilotinib and dasatinib, both approved in 2010 for first-line CML-CP treatment, are more potent than imatinib and less susceptible to imatinib resistance mechanisms. Comparative clinical trials of each agent with imatinib have shown that they are associated with significantly deeper and more rapid responses than standard-dose imatinib, without compromising safety. Given that evidence suggests achievement of an early response is predictive of improved long-term outcomes, earlier use of these compounds may lead to more rapid, deeper responses corresponding with improvements in patient outcome. Although future studies will benefit from more uniform definitions of endpoints and methods of analysis, data from published studies of first-line BCR-ABL inhibitor treatment for patients with newly diagnosed CML-CP support the use of either dasatinib or nilotinib in place of imatinib.

Address for correspondence: Elias Jabbour, MD, The University of Texas, MD Anderson Cancer Center, Department of Leukemia, Unit 428, 1515 Holcombe Blvd, Houston, TX 77030, Phone: 713 792 4764, Fax: 713 794 4997, ejabbour@mdanderson.org.

Conflict of Interest

Dr Jabbour has received honoraria from Bristol-Myers Squibb, Novartis, Pfizer, and Ariad.

Dr Lipton has received research support from Bristol-Myers Squibb, Novartis, Roche, Pfizer (Wyeth), Merck (Schering), TEVA (ChemGenex), and Ariad; has been a consultant for Bristol-Myers Squibb, Novartis, Roche, Merck, TEVA (ChemGenex), and Pfizer; is a stockholder of Ariad; and has participated in Speakers Bureaus for Bristol-Myers Squibb, Novartis, Roche, and Pfizer and Scientific Advisory Boards for Bristol-Myers Squibb, Novartis, Roche, Pfizer, and TEVA (ChemGenex).

Keywords

Imatinib; Nilotinib; Dasatinib; Response; Outcomes

Introduction

Chronic myeloid leukemia (CML) is a hematopoietic malignancy caused by the protein product of the *BCR-ABL* fusion gene. In most cases, this fusion gene is generated by a balanced reciprocal translocation between band q34 of chromosome 9, which contains the Abelson (*ABL*) protooncogene, and band q11 of chromosome 22, which contains the breakpoint cluster region (*BCR*) gene.[1,2] The BCR-ABL oncoprotein has constitutively active ABL tyrosine kinase activity that leads to malignant cell transformation. Of its 3 phases (chronic, accelerated, and blast), CML usually presents in the chronic phase (CML-CP), characterized by leukocytosis and splenomegaly.[2] If left untreated, after 3 to 5 years CML-CP ultimately progresses through the accelerated phase (AP) to the blast phase (BP), which behaves much like acute disease.[3]

Treatments for CML are based predominantly on the use of tyrosine kinase inhibitors that target BCR-ABL. There are currently 3 orally administered BCR-ABL inhibitors approved by the US Food and Drug Administration for the treatment of newly diagnosed patients with CML—imatinib, nilotinib, and dasatinib. Imatinib (Gleevec®, Novartis Pharmaceuticals Corporation) was approved in 2002 for the first-line treatment of CML in any phase.[4] Recommended dosages of imatinib are 400 mg once daily (QD) for CML-CP and 600 mg QD for CML-AP/BP.[4] Although a phase III label-expansion study, Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS), was conducted to determine whether imatinib 800 mg (400 mg twice daily [BID]) would provide superior benefits to 400 mg QD in the first-line treatment of CML-CP, the higher dose provided no significant benefit over imatinib 400 mg QD in terms of the primary endpoint, major molecular response (MMR) at 12 months.[5]

Nilotinib (Tasigna®, Novartis Pharmaceuticals Corporation) was approved in 2010 for the first-line treatment of CML-CP based on findings from a phase III, randomized, open-label trial that compared the efficacy and safety of 2 doses of nilotinib with imatinib 400 mg QD.[6,7] The recommended dosage for first-line treatment is 300 mg BID.[6] Nilotinib 400 mg BID is approved for patients with CML-CP/AP resistant or intolerant to first-line treatment, including imatinib.[6]

Dasatinib (Sprycel®, Bristol-Myers Squibb) was approved in 2010 for the first-line treatment of CML-CP based on findings from a phase III, randomized, open-label trial that compared its efficacy and safety with imatinib 400 mg QD.[8,9] Dasatinib is also approved for the treatment of any-phase CML resistant or intolerant to previous treatment, including imatinib.[8] Approved dosages are 100 mg QD for CML-CP and 140 mg QD for CML-AP/BP.[8]

Key phase III imatinib studies

Imatinib, the first BCR-ABL inhibitor, was approved for the first-line treatment of CML based on data from the International Randomized Study of Interferon and STI571 (IRIS).[10] In IRIS, 1,106 patients with CML-CP were randomized to receive either imatinib 400 mg QD or the standard therapy at the time, interferon (IFN)-alpha plus low-dose cytarabine (n = 553 in each arm).[10] Patients were newly diagnosed within 6 months and untreated except for hydroxyurea and/or anagrelide.[10] Crossover to the other treatment arm was allowed in the following cases: failure to achieve a complete hematologic response (CHR) by 6 months, failure to achieve a major cytogenetic response (MCyR) by 12 months, loss of response, increased white blood cell (WBC) count, or intolerance at any time.[11] The primary endpoint was event-free survival (EFS; termed progression-free survival [PFS] in initial data presentations), defined as survival without transformation to AP/BP, loss of CHR, loss of MCyR, or increased WBC count (Table 1).[10–14]

Long-term follow-up of IRIS has shown that imatinib induced unprecedented response rates in patients with CML-CP. EFS was 92% at 18 months, 83% at 60 months, 83% at 6 years, and 81% at 8 years (Table 2).[10,11,14–19] After a minimum 6 years of follow-up, complete cytogenetic response (CCyR) had been achieved at any time in 82% of patients, and 63% of patients were in CCyR and remained on imatinib therapy.[19] After a minimum of 8 years of follow-up, 55% of patients remained on imatinib therapy, estimated freedom from progression to advanced CML was 92%, and estimated overall survival (OS) was 85%.[14] Among 98 patients enrolled in preplanned substudies of IRIS (total N = 553) who underwent molecular monitoring of BCR-ABL transcripts by real-time quantitative polymerase chain reaction analysis at regular intervals throughout imatinib therapy, 65% achieved MMR by 5 years.[20]

Resistance to and intolerance of the standard dose of imatinib 400 mg QD prevent many patients from deriving full therapeutic benefit. Approximately 25% to 30% of patients in imatinib clinical trials have exhibited primary resistance, defined as lack of CCyR by 18 months.[10,21] In addition, after 6 years of follow-up in IRIS, secondary resistance was observed as progression to advanced disease in approximately 7% of patients, loss of CHR occurred in 8% of patients, loss of MCyR was observed in 10% of patients, and loss of CCyR occurred in 16% of patients.[19] In an attempt to improve the outcomes observed with imatinib 400 mg QD, higher doses have been studied. In the TOPS trial, 476 patients who were newly diagnosed within 6 months and untreated except for hydroxyurea, anagrelide, or no more than 2 weeks of prior imatinib were randomized to receive imatinib 400 mg QD (n = 157) or 400 mg BID (n = 319).[5] The primary endpoint was the rate of MMR at 12 months.[5] After a median follow-up of 17 months, the rate of MMR at 12 months was 40% with imatinib 400 mg/day and 46% with imatinib 800 mg/day (P = .204). Cumulative rates of CCyR by 12 months were similar with imatinib 400 and 800 mg/day, 66% vs. 70%, respectively (P = .347) (Table 2).[5] The 24-month follow-up analysis showed no significant differences between imatinib 400 mg QD and 800 mg/day in the rates of cumulative CCyR (76% vs. 76%, respectively), MMR (54% vs. 51% respectively), EFS (95% vs. 95%, respectively), PFS (97% vs. 98%, respectively), or OS (97% vs. 98%, respectively).[22]

Because the regimens did not differ significantly in results obtained for the primary endpoint, imatinib 800 mg/day was not approved for the first-line treatment of CML-CP.

Two other randomized studies have compared the efficacy of high-dose and standard-dose imatinib. In the German CML Study IV, 1,012 newly diagnosed patients with CML-CP received high-dose imatinib (400 mg/day for 6 weeks, followed by imatinib 800 mg/day, adjusted for tolerability), imatinib 400 mg/day, or imatinib 400 mg/day + IFN-α.[23] Cumulative CCyR rates by 12 months were 63% in the high-dose imatinib group and approximately 50% in the 400-mg imatinib arms. Cumulative MMR rates by 12 months were 55% in the high-dose imatinib group, 31% in the standard-dose imatinib group, and 35% in the imatinib/IFN group.[23] Rates of grade 3/4 adverse events (AEs) were similar among treatment arms, reflecting tolerability adaptation of the 800-mg dose of imatinib.[23]

In the phase III STI571 Prospective Randomized Trial (SPIRIT), 636 patients with CML-CP received imatinib 400 mg/day, imatinib 600 mg/day, imatinib 400 mg/day + peg-IFN α-2a, or imatinib 400 mg plus cytarabine.[24] The 12-month CCyR rates did not differ among treatment groups; however, a significant difference was seen in MMR rates by 12 months and 24 months, indicating a better response in the imatinib/peg-IFN group.[24] The incidence of grade 3/4 neutropenia and thrombocytopenia was significantly higher in the combination treatment groups compared with monotherapy.[24] Incidence of nonhematologic AEs was generally lower in the imatinib 400 mg/day arm compared with the other treatment arms.[24]

Rationale for first-line trials of nilotinib and dasatinib

The newer BCR-ABL inhibitors nilotinib and dasatinib are effective and well tolerated in patients with CML who are resistant or intolerant to prior imatinib treatment.[25–29] Both compounds are thought to be less susceptible than imatinib to mechanisms that mediate imatinib resistance. Nilotinib and dasatinib are more potent than imatinib at inhibiting the proliferation of cells expressing wild-type BCR-ABL in vitro; nilotinib is 20- to 30-fold more potent, whereas dasatinib is 325-fold more potent.[30,31] Low activity levels of organic cation transporter-1 (OCT-1), a cell surface protein thought to mediate the uptake of imatinib into target cells, are associated with lower response rates to imatinib; however, unlike imatinib, OCT-1 does not mediate the intracellular transport of nilotinib and dasatinib.[32–34]

Evidence suggests that achievement of an early response is predictive of improved long-term patient outcome. In the IRIS trial, 97% of patients who had a CCyR after 12 months of imatinib treatment did not transform to CML-AP/BP after 5 years, compared with 93% who had achieved a partial cytogenetic response but not CCyR by 12 months and 81% of patients who had not achieved MCyR by 12 months ($P < .001$).[11] Furthermore, no patient who had achieved both a CCyR and MMR at 12 months had transformed to AP/BP by 5 years.[11] Several other analyses have reached similar conclusions regarding the predictive value of an early cytogenetic response to imatinib.[20,35–38] In addition, an early MMR on imatinib (by 12–18 months) has been associated with prolonged duration of CCyR.[20,37]

Similarly, for the newer BCR-ABL inhibitors, a retrospective pooled analysis of 3 studies of second-line dasatinib treatment in patients with CML-CP (N = 1,067) showed that 24-month

EFS rates (termed PFS in the publication) were higher in patients who had achieved CCyR or MMR at 12 months (96% to 97%) compared with patients who achieved no CCyR or MMR at 12 months (78%; $P < .0001$).[39] In a pooled analysis of patients with CML who received second-line dasatinib or nilotinib at a single institution (N = 113), those who had achieved MCyR by 12 months had significantly improved OS in the subsequent 12 months compared with patients with only CHR or minor CyR by 12 months (97% vs. 84%; $P = .02$).[40] Given that dasatinib and nilotinib are more potent than imatinib and less susceptible to imatinib resistance mechanisms, it was reasoned that earlier use of these compounds may result in more rapid, deeper responses, with corresponding improvements in patient outcome. Studies of these compounds in the first-line setting have recently been published.

Key studies of first-line nilotinib: efficacy data

The activity of nilotinib in the first-line setting was initially established in two phase II studies.

The study performed at the MD Anderson Cancer Center of the University of Texas (MDACC) included 100 patients with CML-CP who were treated with first-line nilotinib 400 mg BID (Table 2).[41] Patients were newly diagnosed within 6 months and untreated except for hydroxyurea or no more than 1 month of standard-dose imatinib.[12] The primary objective was to improve the MMR rate at 12 months to more than the rate of ~40% historically achieved with standard-dose imatinib.[12,15] Rates were calculated based on the number of evaluable patients at each time point.[41] Response rates at 12, 24, and 48 months were 97%, 98%, and 100% for CCyR and 86%, 88%, and 95% for MMR.[41] CCyR rates at 3 and 6 months were 78% and 92%, respectively, suggesting a rapid response to nilotinib treatment.[41] At 48 months, the estimated rate of EFS (loss of CHR, loss of MCyR, AP/BP, or death) was 88%, 2 patients had transformed to AP/BP, and OS was 96%.[41]

The other phase II study was from the Gruppo Italiano Malattie e Matologiche dell'Adulto (GIMEMA) (Table 2).[42] In this study, 73 patients with CML-CP were treated with nilotinib 400 mg BID.[42] Patients were newly diagnosed within 6 months and untreated except for hydroxyurea or anagrelide. The primary endpoint was CCyR at 1 year and rates were calculated based on all 73 patients (intent-to-treat population).[42] The cumulative rates of CCyR and MMR at 12 months were 100% and 96%, respectively, and the proportions of patients in CCyR and MMR at the 12-month landmark were 96% and 85%, respectively. Responses occurred rapidly, as shown by a 3-month CCyR of 78% and MMR of 52%.[16]

The pivotal phase III study of nilotinib in the first-line treatment setting was the Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENESTnd) trial.[7] Eligible patients with CML-CP were entered into the study within 6 months of diagnosis and were untreated except for hydroxyurea, anagrelide, or no more than 2 weeks of prior imatinib.[7] Patients (N = 846) were randomized to receive nilotinib 300 mg BID (n = 282), nilotinib 400 mg BID (n = 281), or imatinib 400 mg QD (n = 283).[7] The primary endpoint was MMR rate at 12 months.[7]

The MMR and CCyR rates at 12 months were significantly higher ($P < .001$) in the nilotinib arms compared with those in the imatinib arm (Table 2).[7] In addition, MMRs were achieved

more rapidly in the nilotinib arms compared with the imatinib arm ($P < .001$ for both comparisons).[7] Six-month MMR rates were 33%, 30%, and 12% in the nilotinib 300 mg BID, nilotinib 400 mg BID, and imatinib arms, respectively.[7] Nilotinib 300 mg BID ($P = .01$) and 400 mg BID ($P = .004$) were reported to significantly extend the time to transformation to CML-AP/BP compared with imatinib.[7] Rates of EFS and OS are shown in Table 2. Data after a minimum follow-up of 24 months confirmed the superiority of nilotinib 300 mg BID and 400 mg BID over imatinib.

By 24 months, cumulative MMR rates were 71% and 67% vs. 44%, respectively ($P < .0001$); and CCyR rates were 87% and 85% vs. 77%, respectively ($P \leq .016$).[17] PFS, defined as progression to AP/BP or death due to any cause while on treatment, was 98% for nilotinib 300 mg BID, 97.7% for nilotinib 400 mg BID, and 95.2% for imatinib ($P < .09$).[17,43] After a median treatment duration of 25 months, transformation to AP/BP on study had occurred in 1% with nilotinib 300 and 400 mg BID and 4% with imatinib 400 mg QD.[17] Efficacy data after a follow-up of 36 months are consistent with those reported for 24 months.[44] Landmark analyses showed that early molecular response at 3 months correlated with PFS and OS at 36 months. More patients in the nilotinib arm vs. the imatinib arm achieved BCR-ABL transcript levels ≤1% (56% vs. 16%) and ≤10% (91% vs. 67%) at 3 months.[45]

In the ENESTnd study, assessment of progression to AP or BP on treatment was based on hematologic and cytogenetic analyses and transformations after discontinuation were only considered “on treatment” within 14 days after the last dose.[17] Both the 24-month and 36-month follow-up publications reported significantly lower probability of transformation to AP/BP on study in the nilotinib arms compared with the imatinib arm (rates in Table 3 apply to both time points, 36-month $P = .0059$ for nilotinib 300 mg BID and .0185 for nilotinib 400 mg BID).[17,44] This apparent advantage was maintained when including all transformations following discontinuation of treatment (Table 3 shows rates from the 24-month follow-up; by the 36-month follow-up one more patient progressed in the nilotinib 400 mg BID and imatinib arms, resulting in $P = .0496$ and .0076 for nilotinib 300 and 400 mg BID, respectively, compared with imatinib). It is important to mention that only patients receiving imatinib could undergo dose escalation on-study, whereas patients in the nilotinib arms switched to an extension study to be dose-escalated to nilotinib 400 mg BID or to receive imatinib 400 mg BID.[7] Furthermore, although patients receiving nilotinib 300 mg BID could enter the extension study in case of suboptimal response or treatment failure, patients receiving imatinib (n = 31) or nilotinib 400 mg BID (n = 18) entered upon treatment failure only.[7,46]

Key studies of first-line dasatinib: efficacy data

The activity of dasatinib in the first-line treatment setting was initially established in a phase II study performed at MDACC in parallel to the nilotinib phase II study described above. Patients with CML-CP (N = 62) were randomized to receive dasatinib 100 mg QD (n = 31) or 50 mg BID (n = 31).[13] Patients were newly diagnosed within 6 months and were untreated other than with hydroxyurea or no more than 1 month of standard-dose imatinib.[13] Consistent with the design of the nilotinib study, the primary objective was to improve the MMR rate at 12 months to more than the rate of ~40% historically achieved with standard-

dose imatinib.[13,15] After a median follow-up of 24 months, 82% of the 50 patients who had received treatment for at least 3 months had achieved MMR and 98% had achieved CCyR.[13] The MMR rate at 12 months was 71%.[13] Responses were rapid, as shown by the CCyR rate at 6 months of 94%.[13] The estimated 24-month EFS rate was 88%.[13] At last follow-up, no patient had transformed to CML-AP/BP and all patients were alive.[13]

Dasatinib was compared with imatinib in the first-line treatment setting in the pivotal phase III Dasatinib versus Imatinib Study in Treatment-Naïve CML Patients (DASISION).[9] Eligible patients with CML-CP were entered into the study within 3 months of diagnosis and were untreated except for hydroxyurea or anagrelide.[9] Patients (N = 519) were randomized to receive either dasatinib 100 mg QD (n = 259) or imatinib 400 mg QD (n = 260).[8] The primary endpoint was a confirmed CCyR by 12 months; a confirmed CCyR was defined as CCyR documented on 2 consecutive assessments performed at least 28 days apart.[9]

The confirmed CCyR rate by 12 months was significantly higher in the dasatinib arm compared with the imatinib arm (77% vs. 66%, respectively; $P = .007$).[9] Rates of CCyR assessed using the standard definition (ie, unconfirmed; $P = .001$) and MMR ($P < .0001$) by 12 months were also significantly higher in the dasatinib arm compared with those in the imatinib arm (Table 2).[9] In addition, the rate of MMR at any time was significantly higher among patients receiving dasatinib than among patients receiving imatinib (52% vs. 34%; $P < .0001$).[9] Responses were faster in the dasatinib arm than in the imatinib arm, as shown by analyses of time to CCyR and MMR (both $P < .0001$); 3-month CCyR rates were 54% and 31% in the dasatinib and imatinib arms, respectively.[9] After a median treatment duration of 14 months, transformation to AP/BP on study had occurred in 1.9% of patients who had received dasatinib and 3.5% of patients who had received imatinib.[9] Rates of EFS (termed PFS in DASISION; see Table 1) and OS are shown in Table 2. Data after a median follow-up of 26.5 and 26.7 months confirmed the superiority of dasatinib over imatinib, as shown by cumulative rates of MMR by 24 months (64% vs. 46%; $P < .0001$) and confirmed CCyR by 24 months (80% vs. 74%).[18] Landmark analyses showed that CCyR and MMR at 3 and 12 months, respectively, were predictive of PFS at 36 months. More patients in the dasatinib arm vs. the imatinib arm achieved CCyR at 3 months (54% vs. 31%) and MMR at 12 months (47% vs. 28%).[47] Further landmark analyses showed that early molecular response at 3 months correlated with PFS and OS at 36 months. More patients in the dasatinib arm vs. the imatinib arm achieved BCR-ABL transcript levels ≤1% (48% vs. 13%) and ≤10% (84% vs. 64%) at 3 months.[48]

During study treatment (median duration 24.9 months), progression to AP/BP on study occurred in 6 patients (2.3%) on dasatinib vs. 13 patients (5.0%) on imatinib.[18] Transformations were considered “on treatment” if they occurred within 60 days after discontinuation, or within 30 days for patients who received secondary treatment (Table 3). In addition, 3 patients treated with dasatinib and 2 treated with imatinib transformed after the 30-day or 60-day cutoff following discontinuation of treatment.[18] Clonal evolution was not included in the definition of progression to AP/BP in DASISION.

Recently, data from another study that compared dasatinib and imatinib in newly diagnosed, untreated CML-CP patients, the open-label phase II S0325 Intergroup Trial, have been

reported.[49] Patients (N = 253) were randomized to receive dasatinib 100 mg QD or imatinib 400 mg QD (Table 2). The primary endpoint was ≥4-log reduction in *BCR-ABL* transcript levels at 12 months. Cumulative rates of CCyR by 12 months in evaluable patients in the dasatinib and imatinib arms were 84% and 69%, respectively ($P = .04$); cytogenetic data were available for only 53% of patients.[49] No significant difference between treatment arms was seen in the rate of ≥4-log reduction in *BCR-ABL* transcript levels at 12 months (27% with dasatinib vs. 21% with imatinib; $P = .32$). However, the difference between the dasatinib and imatinib arms for rates of patients achieving ≥3-log reductions in BCR-ABL transcript levels (ie, MMR) were statistically significant (59% with dasatinib vs. 44% with imatinib; $P = .059$).[49] Rates of PFS at 3 years were 93% with dasatinib and 90% with imatinib.[49]

Implications of trial design and analysis

Cross-trial comparisons provide a broad indication of the relative efficacy of nilotinib and dasatinib, but values cannot be compared directly among studies. Consideration of study design and analysis is essential. Although response definitions are standardized and are generally uniform, the primary endpoint of the ENESTnd trial of nilotinib and the S0325 trial of dasatinib, MMR/molecular response at 12 months (which includes only patients who were assessed at the 12-month time point) is different from standard cumulative response rates (which may provide numerically higher rates due to the inclusion of responses achieved prior to 12 months but not reassessed at the 12-month landmark).[3,50] However, cumulative MMR rates from the ENESTnd trial have also been reported. Similarly, although achievement of a confirmed CCyR was the primary endpoint in the DASISION trial, rates of CCyR assessed using the standard definition (unconfirmed) were also reported.

Although the definition of OS is standard, the trials discussed varied in the terminology/definitions used for EFS/PFS (Table 1). In general, the greater the number of different events used to define this parameter, the lower the likelihood of survival free of events over a given period. For example, the TOPS trial of imatinib and the ENESTnd trial of nilotinib consistently defined “progression” as development of advanced CML or death (consistently described as transformation/transformation-free survival (TFS) in this review, irrespective of terminology used in the study). In contrast, the definition of “progression” in DASISION was broadly consistent with the definition of events/EFS in other trials and also included loss of response. The MDACC phase II studies of nilotinib and dasatinib avoided the term “progression,” using instead the terms “TFS” to denote survival without transformation to advanced disease and “EFS” to capture a broader range of events (death from any cause, loss of CHR, loss of CCyR, discontinuation of therapy for toxicity or lack of efficacy, progression to AP or BP).[12,13] The definition of EFS employed by the MDACC phase II studies is the broadest of the EFS definitions used in the studies discussed in this article.

A comparative analysis of outcomes in 435 newly diagnosed patients treated with imatinib, nilotinib, or dasatinib was performed by applying the different EFS/PFS definitions from the ENESTnd, DASISION, IRIS, and MDACC studies.[51] After a median follow-up of 67 months, the results of the analysis indicated that the MDACC definition of EFS detected the most events (82), followed by DASISION (43), IRIS (40), and ENESTnd (15).[51]

Corresponding 5-year PFS/EFS rates (based on the differing definitions) within this study population were 82%, 89%, 90%, and 96%, respectively.[51] Thus, different definitions of PFS/EFS applied to the same population of patients resulted in estimated 5-year outcome rates that ranged from 82% to 96%.

Discontinuation criteria also have an effect on outcomes, as differences among trials in discontinuation criteria are likely to affect the numbers of patients stopping study treatment. The IRIS trial was designed before contemporary recommendations for imatinib were published and before the availability of effective second-line treatments; thus, its discontinuation criteria were not as strict as those in subsequent BCR-ABL inhibitor studies. In addition, dose escalation in the imatinib arm (to 400 mg BID) was permitted for patients without CHR at 3 months or minor cytogenetic response at 12 months.[10] Currently, these outcomes are considered parameters of treatment failure, necessitating discontinuation of imatinib.[3,50] Dose escalation was also permitted in TOPS (standard-dose imatinib arm only) and DASISION.[5,9] As mentioned above, in the ENESTnd trial, dose escalation was permitted in the imatinib arm but not in the nilotinib arms (Table 3).[7] Patients who had a suboptimal response or treatment failure on nilotinib in ENESTnd were discontinued from the study and were permitted to enroll in an extension study (Table 3). Therefore, one could speculate that the longer a patient is kept on trial, the greater their likelihood of experiencing an event such as transformation, which highlights once more the importance of including progression events after treatment discontinuation.

The capture of progression events after treatment discontinuation may be affected by the length of time patients are followed after discontinuation and is an important consideration in the interpretation of clinical study results. A letter to the editor published in the *New England Journal of Medicine* demonstrated the need for standardizing duration of follow-up after discontinuation and reporting of study results.[52] The authors reported that one patient who had received nilotinib in the ENESTnd study discontinued treatment because of thrombocytopenia and shortly thereafter developed BP, but was not reported as a progression. As cytopenias may be an early sign of progression to AP/BP, short follow-up after discontinuation for cytopenias may result in their inaccurate attribution as a drug-related AE rather than as a progression event. With the low number of progression events seen with newer BCR-ABL inhibitors, even a few additional cases of disease progression could alter study conclusions. Close scrutiny of differences in treatment protocols is, therefore, warranted when evaluating transformation rates from different studies.

Table 3 shows the transformation data in the ENESTnd and DASISION reports based on 24 months of follow-up, and highlights differences in study protocols that could impact the transformation rates reported. Differing criteria for discontinuation and differing definitions of “on treatment” make it difficult to compare on-treatment transformation rates at the 24-month follow-up for ENESTnd and DASISION. Moreover, definitions of suboptimal response and treatment failure differed slightly between the trials. Only the imatinib arm in the ENESTnd trial had similar criteria for discontinuation compared with DASISION. The recent ENESTnd 3-year report included transformations occurring on treatment or during follow-up after discontinuation, which included transformations on the extension study: 9

(3%) with nilotinib 300 mg BID, 6 (2%) with nilotinib 400 mg BID, and 19 (7%) with imatinib 400 mg QD.[44]

As an illustrative example of the impact of these protocol differences on rates of transformation, an ad hoc analysis was conducted to investigate the effect of "event" definition, discontinuation criteria, and length of follow up after treatment discontinuation on progression events in ENESTnd and DASISION. The 24-month DASISION transformation data were reanalyzed by applying the ENESTnd study criteria used to measure progression (discontinuation from study due to suboptimal response/treatment failure required for nilotinib but not imatinib, 14 day follow-up after last study dose) (Table 3). This example of the impact of differing protocols on the comparison of results highlights the need for standardized definitions of progression, standard length of follow-up after treatment discontinuation (≥30 days), and uniform discontinuation criteria across treatment arms.

Cross-trial comparisons are inappropriate and do not have statistical validation because of differences in patient populations, study designs, and overall management. Although some attempts have been made to compare outcomes between trials, such as the recently published matching-adjusted indirect comparison of nilotinib and dasatinib data from the ENESTnd and DASISION trials, such comparisons are inappropriate.[53]

Comparison of safety data

Table 4 presents total and toxicity-related discontinuation data for studies of BCR-ABL inhibitors in the first-line treatment of CML-CP. Data sources were selected to maximize similarity of follow-up times among studies (median 12–27 months) and completeness of data. Of the studies listed in Table 4, the IRIS trial had the lowest toxicity-related discontinuation rate (3%), which may reflect the lack of available, effective second-line treatments at the time and the greater reluctance of physicians to discontinue imatinib compared with more recent trials.

Toxicity-related dose interruption/reduction data were not published for IRIS.[10] In the TOPS trial, dose reductions were required by 18% and 61% of patients in the imatinib 400 mg QD and BID arms, respectively, and dose interruptions lasting >5 days were required in 38% and 67% of patients, respectively.[5] In the ENESTnd study, at 24 months the incidence of AEs leading to dose interruption/reduction was 55%, 63%, and 46% in the nilotinib 300 mg BID, nilotinib 400 mg BID, and imatinib arms, respectively.[17] In the GIMEMA study, nilotinib dose interruptions were required in 52% of patients, and at 12 months, permanent reductions to nilotinib 400 mg had occurred in 25% of patients.[42] In the MDACC nilotinib study, 37% of patients required a dose interruption and 17% required a dose reduction.[12] In the MDACC dasatinib study, 48% of patients required a dose interruption and 35% required a dose reduction.[13] During treatment with dasatinib or imatinib (median duration 24.9 mo) in the DASISION trial, dose interruption was required in 59% vs. 43% of patients, respectively, and dose reduction was required in 28% vs. 15% of patients, respectively.[18]

Across all studies, hematologic AEs were the most frequent type of AE with each agent and grade 3/4 incidence data for median follow-up durations of 12 to 27 months are shown in

Table 5. In the TOPS trial, AE rates for imatinib 400 mg BID were higher than those for imatinib 400 mg QD.[5] In ENESTnd, AE rates for nilotinib 300 mg BID appeared similar to those for nilotinib 400 mg BID.[17] Higher rates of thrombocytopenia were seen with dasatinib vs. imatinib in DASISION and the S0325 study.[18,49] The lowest rates of hematologic AEs were reported in the GIMEMA study.[42]

Compared with hematologic AEs, nonhematologic AEs were less frequent and grade 3/4 events were uncommon. For this reason, our discussion focuses on the most common toxicities observed in phase III studies for which all-grade event data are available. Fluid-related events were among the most common nonhematologic AEs. In IRIS, after a median follow-up of 19 months, superficial edema had occurred in 56% of imatinib-treated patients.[10] In DASISION, after a median treatment duration of 24.9 months, fluid-related AEs had occurred in fewer patients receiving dasatinib (25%) than imatinib (43%), including superficial edema in 11% vs. 36%, respectively. Grade 3/4 fluid retention occurred in 2% and 1% of patients, respectively.[18] Pleural effusion occurred with dasatinib but not with imatinib. After 14 months of follow-up, 10% of dasatinib-treated patients had experienced pleural effusion (grade 1 or 2 in all cases).[9] After a median follow-up of 27 months, pleural effusion of any grade had occurred in 14%, including grade 3 in <1%, but no grade 4 pleural effusions were recorded.[18]

For other nonhematologic AEs (all grades) in DASISION, after a median follow-up of 14 months, those reported less frequently in the dasatinib arm compared with the imatinib arm included nausea (8% vs. 20%), vomiting (5% vs. 10%), myalgia (6% vs. 9%), muscle inflammation (4% vs. 17%), musculoskeletal pain (11% vs. 14%), fatigue (8% vs. 10%) and rash (11% vs. 17%).[9] Only headache was reported more frequently in the dasatinib arm compared with the imatinib arm (12% vs. 10%). In ENESTnd, after a median treatment duration of 14 months, edema was less frequent in both the nilotinib 300 mg BID and 400 mg BID arms compared with the imatinib arm, including peripheral edema (5%, 5%, and 14%), eyelid edema (1%, 2%, and 13%), and periorbital edema (<1%, 1%, and 12%). Other AEs reported less frequently in the nilotinib arms included nausea (11%–19% vs. 31%), vomiting (5%–9% vs. 14%), diarrhea (6%–8% vs. 21%), and muscle spasm (6%–7% vs. 24%). In contrast, rash (31%–36% vs. 11%), alopecia (8%–13% vs. 4%), pruritus (13%–15% vs. 5%), and headache (14%–21% vs. 8%) were reported in more patients in the nilotinib arms than in the imatinib arm.[7]

Although rare, cardiovascular AEs have been observed in CML patients receiving nilotinib or dasatinib. The risk of drug-related pulmonary arterial hypertension (PAH) with dasatinib is a topic of ongoing research as post-marketing surveillance revealed a number of confirmed cases in patients receiving second-line dasatinib.[54–60] No cases of drug-related PAH have been confirmed in DASISION, although 3 patients were diagnosed with pulmonary hypertension, indicated by elevated pulmonary artery systolic pressure measured with Doppler echocardiography (1%; grade 1 in 2 patients, grade 2 in 1 patient).[18] None of the 3 discontinued due to pulmonary hypertension and right heart catheterization was performed in 1 patient but found no evidence of PAH; no further investigations were performed in the other 2 cases.

Cardiovascular AEs of concern with nilotinib include those related to peripheral arterial occlusive disease (PAOD) and ischemic heart disease (IHD).[61] In the 24-month report of ENESTnd, PAOD was reported in 6 patients receiving nilotinib (3 [1%] in each arm) and in no patients receiving imatinib.[17] Similarly, the 36-month analysis reported PAOD in 7 patients receiving nilotinib (4 on 300 mg BID and 3 on 400 mg BID) and in no patients receiving imatinib.[44] AEs related to IHD were also more frequent with nilotinib than with imatinib, occurring in 5 patients (2%) in the nilotinib 300 mg BID arm, 6 patients (2%) in the nilotinib 400 mg BID arm, and 1 patient (<1%) in the imatinib arm within 24 months.[17] These rates were 3%, 4%, and 1%, respectively, within 36 months.[44] No patients discontinued because of PAOD, but 3 patients in the nilotinib 400 mg BID arm discontinued because of an IHD-related event.[44] In an independent study, newly diagnosed PAOD was observed more frequently in patients on first-line nilotinib (3 of 31 patients, 10%) or second-line nilotinib (5 of 32 patients, 16%) and in patients previously exposed to nilotinib (4 of 23 patients, 17%) compared with patients on first-line imatinib (1 of 53, 2%).[62] Further analyses are needed to understand these observations.

In the ENESTnd trial, 1 patient in the imatinib arm and no patients in either nilotinib arm had QTc prolongation >500 ms (grade ≥3).[17] After a median follow-up of 24 months, the incidence of QTc prolongation >60 ms in the nilotinib 300 mg BID and 400 mg BID arms was 0.4% and 0.7%, respectively; no patient in the imatinib arm experienced such an event.[17] There has been no decrease of <45% in mean left ventricular ejection fraction.[17] In the MDACC nilotinib study, the incidence of grade ≤2 QTc prolongation was 3%.[12] In the GIMEMA nilotinib study, 3% of patients had grade 1–2 QTc prolongation after median follow-up of 30 months.[16] In DASISION, after a median treatment duration of 14 months, 1 patient in each arm (<1%) had QTc prolongation >500 ms. QTc intervals of 450 to 500 ms (grade 2) had an incidence of 2% in the dasatinib arm and 4% in the imatinib arm.[9]

With regard to laboratory abnormalities, in DASISION, the rate of grade 3/4 hypophosphatemia after a median treatment duration of 14 months was higher in imatinib-treated patients (21%) than in dasatinib-treated patients (4%).[9] In ENESTnd, after the same median treatment duration, grade 3/4 hypophosphatemia was observed in 8% of imatinib-treated patients and 5% of nilotinib-treated patients (both arms).[7] In the DASISION study, rates of grade 3/4 laboratory abnormalities associated with pancreatic or hepatic toxicity occurred in 0% to 1% of patients in the dasatinib and imatinib arm.[9] In the ENESTnd study, pancreatic and hepatic abnormalities appeared to be more common in nilotinib-treated patients than in imatinib-treated patients. For both nilotinib arms vs. imatinib, after a median treatment duration of 24 months, grade 3/4 incidences were total bilirubin (4%–8% vs. <1%), increased glucose (5%–6% vs. 0%), increased lipase (7%–8% vs. 3%), increased alanine aminotransferase (4%–9% vs. 3%), and increased aspartate aminotransferase (1%–3% vs. 1%).[17] These events were considered not clinically important and were typically manageable.[7]

Conclusions

A review of studies of first-line BCR-ABL inhibitor treatment for patients with newly diagnosed CML-CP supports the use of either dasatinib or nilotinib in place of imatinib.

Available data suggest that dasatinib and nilotinib have broadly similar efficacy. They have not been compared directly in a phase III trial, and there are issues surrounding cross-trial comparisons; differences in trial design, trial conduct, and analysis each introduce variables that may influence the data and must be carefully considered when assessing outcomes. Most importantly, differences in study population (including geographical differences) inevitably introduce variability in patient response and outcome, making direct comparison of existing data for dasatinib and nilotinib inappropriate.

While results from the first-line studies with nilotinib and dasatinib may be too early to detect statistically significant differences in EFS and OS compared with imatinib, various landmark analyses have shown that early molecular responses (such as those recorded as BCR-ABL ≤ 10% vs. >10% at 3 months) correlate with improved long-term outcomes. The benefit of the earlier and deeper responses offered by nilotinib and dasatinib should be considered alongside their respective safety profiles to select a personalized treatment. Nilotinib and dasatinib both appear to be well tolerated, although each agent has a distinct AE profile. For example, nilotinib is associated with more dermatologic, pancreatic, and hepatic toxicity compared with imatinib, but it is also associated with less gastrointestinal toxicity, edema, muscle spasm, and grade 3/4 neutropenia. Dasatinib is associated with more pleural effusion and grade 3/4 thrombocytopenia compared with imatinib, but is also associated with less gastrointestinal toxicity, edema, muscle spasm, and rash. Regardless of the treatment chosen, all patients should be monitored closely for frequently observed side effects.

Both dasatinib and nilotinib are more potent than imatinib. It can be reasoned that the earlier use of these compounds in the treatment sequencing algorithm may result in faster, deeper responses, with corresponding improvements in long-term patient outcome. Although we can always benefit from additional clinical trials, the current data suggest that, in the absence of individual considerations which would preclude the use of a particular treatment in a given patient, dasatinib or nilotinib should be considered first-line agents for the treatment of patients with newly diagnosed CML-CP.

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Table 1

Varying Definitions of Progression or Events Used to Report PFS or EFS in First-Line Studies of BCR-ABL Inhibitors in CML-CP

		Criterion						
Study	***Terminology used for data presentation***	**Transformation to AP/BP**	**Loss of CHR**	**Loss of MCyR/ increased Ph +metaphases**	**Loss of CCyR**	**Increased WBC count**	**Death**	**Discontinuation for toxicity/lack of efficacy**
IRIS[10,11]	progression/event[a]	X	X	X[b]		X[c]	X[e]	
	progression[a]	X						
TOPS[5]	event	X	X	X			X[e]	
	progression	X					X[e]	
MDACC[12,13]	event	X	X		X		X[e]	X
	transformation	X					X[e]	
DASISION[9]	progression	X	X	X[d]		X[c]	X[e]	
ENESTnd[7]	event	X	X	X	X		X[e]	
	progression	X					X[f]	

Abbreviations: AP/BP = accelerated phase/blast phase; CCyR = complete cytogenetic response; CHR = complete hematologic response; EFS = event-free survival; MCyR = major cytogenetic response; PFS = progression-free survival; WBC = white blood cell.

[a] The parameter originally defined as PFS in the primary publication was redefined as EFS in subsequent publications.[11]

[b] Loss of MCyR defined as increase in Ph+ metaphases by >30%.

[c] Doubling of WBC count to >20 000/mm^3, in absence of CHR.

[d] Increase in Ph+ metaphases to >35%.

[e] Death from any cause.

[f] CML-related death.

Table 2

Efficacy Data for Studies of BCR-ABL Inhibitors in the First-Line Treatment of CML-CP

Study	*Regimen*	*CCyR by 12 mo*	*MMR by 12 mo*	*EFS*	*OS*
IRIS[10,11,15]	imatinib 400 mg QD	69%[a]	39%[a]	92% at 18 mo	97% at 18 mo
TOPS[5]	imatinib 400 mg/day	66%	40%[b]	95% at 24 mo	97% at 24 mo
	imatinib 800 mg/day	70%	46%[b]	95% at 24 mo	98% at 24 mo
GIMEMA[16]	nilotinib 400 mg BID	100%	96%	92% at 30 mo	99% at 30 mo
MDACC[12]	nilotinib 400 mg BID	97%[b]	81%[b]	90% at 24 mo	100% at 24 mo
MDACC[13]	dasatinib 50 mg BID or 100 mg QD	98%[b]	71%[b]	88% at 24 mo	100% at 24 mo
ENESTnd[7,17,44]	nilotinib 300 mg BID	80%	44%[b]	96% at 24 mo	97% at 24 mo
				95% at 36 mo	95% at 36 mo
	nilotinib 400 mg BID	78%	43%[b]	98% at 24 mo	98% at 24 mo
				97% at 36 mo	97% at 36 mo
	imatinib 400 mg QD	65%	22%[b]	94% at 24 mo	96% at 24 mo
				93% at 36 mo	94% at 36 mo
DASISION[9,18]	dasatinib 100 mg QD	83%	46%	94% at 24 mo	95% at 24 mo
	imatinib 400 mg QD	72%	28%	92% at 24 mo	95% at 24 mo

Abbreviations: BID = twice daily; CCyR = complete cytogenetic response; EFS = event-free survival; MMR = major molecular response; mo = months; OS = overall survival; QD = once daily.

[a] Estimated rate.

[b] Rate at 12 months (ie, not cumulative).

Table 3

Transformation Rates in First-Line CML-CP Studies: Measurement of Progression to AP/BP in ENESTnd and DASISION

Transformations to AP/BP, n (%)[a]					
	DASISION[9,18]		***ENESTnd***[7,17]		
	Dasatinib 100 mg QD (N = 259)	**Imatinib 400 mg QD (N = 260)**	**Nilotinib 300 mg BID (N = 282)**	**Nilotinib 400 mg BID (N = 281)**	**Imatinib 400 mg QD (N = 283)**
On treatment[b]	6 (2%)	13 (5%)	2 (1%)	3 (1%)	12 (4%)
On treatment or any time after discontinuation	9 (3%)	15 (6%)	9 (3%)	5 (2%)	18 (6%)

Key protocol differences affecting the measurement of progression to AP/BP				
	DASISION[9,18]	***ENESTnd***[7,17]		
		Nilotinib 300 mg BID	**Nilotinib 400 mg BID**	**Imatinib 400 mg QD**
Dose escalation criteria	Suboptimal response	Not allowed	Not allowed	Suboptimal response
Reasons for treatment discontinuation	Disease progression or treatment failure despite dose escalation	Suboptimal response (or worse)	Treatment failure (or worse)	No response or treatment failure despite escalation to imatinib 400 mg BID
Options after treatment discontinuation	Second-line therapy (not part of study)	Extension study, nilotinib 400 mg BID	Extension study, imatinib 400 mg BID	Extension study, nilotinib 400 mg BID
Suboptimal response criteria[c]		Loss of MMR unless associated with loss of CHR or loss of CCyR		
Treatment failure criteria[d]	No HR by 3 months	•Loss of CHR, PCyR, or CCyR •Increasing WBC in the absence of CHR even at maximum tolerated dose		
Disease progression criteria[e]	•Loss of CHR or MCyR •Increasing WBC in the absence of CHR			
Follow-up for transformation to AP/BP after discontinuation	All patients discontinuing were followed	Only patients not in extension study were followed for transformation to AP/BP[f]		
The number of days after discontinuation considered “on treatment” for calculating transformation rate	•30 days for patients receiving second-line treatment •60 days for patients not receiving second-line treatment	14 days (for patients not on extension study)		

Estimation of transformations in DASISION based on ENESTnd criteria		
	Dasatinib	***Imatinib***
Total transformations (on and off study)	9 (4%)	15 (6%)
Transformations after suboptimal response[g]	1 (<1%)[h]	3 (1%)[i]
Transformations >14 days after discontinuation[j]	5 (2%)	4 (2%)

Estimation of transformations in DASISION based on ENESTnd criteria

	Dasatinib	*Imatinib*
Transformations “on treatment” per ENESTnd criteria	3 (1%)	11 (4%)

Abbreviations: AP/BP = accelerated phase/blast phase; BID = twice daily; CCyR = complete cytogenetic response; CHR = complete hematologic response; HR = hematologic response; MCyR = major cytogenetic response; mo = months; PCyR = partial cytogenetic response; PFS = progression-free survival; QD = once daily; WBC = white blood cell.

[a] All rates exclude clonal evolution.

[b] The number of days after discontinuation considered to be “on treatment” differed between studies.

[c] Suboptimal response criteria in both studies included failure to achieve: CHR by 3 mo, PCyR by 6 mo, CCyR by 12 mo, MMR by 18 mo.

[d] Treatment failure criteria in both studies included failure to achieve: CHR by 6 mo, any cytogenetic response by 6 mo, PCyR by 12 mo, CCyR by 18 mo.

[e] Disease progression criteria in both studies included transformation to AP/BP or death.

[f] Transformations on the extension study were reported in the 3-year follow-up.[44]

[g] Based on DASISION suboptimal response criteria.

[h] Patients on nilotinib with suboptimal response in ENESTnd had the option to discontinue and change to an extension study; transformations on the extension study were not included in Kantarjian et al 2011.[17]

[i] Suboptimal response was not a cause for discontinuation for imatinib-treated patients in ENESTnd.

[j] No patients on dasatinib transformed after both suboptimal response and >14 days after discontinuation; 1 patient on imatinib did, but suboptimal response did not require discontinuation for imatinib-treated patients in the ENESTnd study.

Table 4

Discontinuation Data for Studies of BCR-ABL Inhibitors in the First-Line Treatment of CML-CP

Study	*Median follow-up (mo)*	*Regimen*	*Patients discontinued (%)*			
			Total	**AEs, or abnormal laboratory events**	**Treatment failure (including progression), suboptimal response, or death**	**Other**
IRIS[10]	19	imatinib 400 mg QD (n = 553)	14[a]	3	6	6
TOPS[5]	17	imatinib 400 mg QD (n = 157)	16	5	6	5
		imatinib 400 mg BID (n = 319)	20	10	7	3
GIMEMA[42]	15	nilotinib 400 mg BID (n = 73)	3	1	1	0
MDACC[12]	17	nilotinib 400 mg BID (n = 61)	16	7	3	7
MDACC[13]	24	dasatinib 50 mg BID or 100 mg QD (n = 62)	8	5	0	3
ENESTnd[17]	24[b]	nilotinib 300 mg BID (n = 282)	26	9	10	6
		nilotinib 400 mg BID (n = 281)	22	13	4	5
		imatinib 400 mg QD (n = 283)	32	10	17	5
DASISION[18]	27	dasatinib 100 mg QD (n = 258)	23	9	10	4
		imatinib 400 mg QD (n = 258)	25	5	11	9
S0325[49]	moMin. 12	dasatinib 100 mg QD (n = 123)	20	13	2	6
		imatinib 400 mg QD (n = 123)	28	10	7	11

Abbreviations: AE = adverse event; BID = twice daily; mo = months; QD = once daily.

[a] Includes patients who crossed over to alternative treatment arm.

[b] Median duration of treatment.

Table 5

Incidence of Grade 3/4 Hematologic AEs Studies of BCR-ABL Inhibitors in the First-Line Treatment of CML

Study	*Median follow-up (mo)*	*Regimen*	*Incidence (%)*		
			Thrombocytopenia	**Neutropenia**	**Anemia**
IRIS[10]	19	imatinib 400 mg QD	8	14	3
TOPS[5]	17	imatinib 400 mg QD	10	19	4
		imatinib 400 mg BID	18	29	7
GIMEMA[42]	15	nilotinib 400 mg BID	2	4	0
MDACC[12]	17	nilotinib 400 mg BID	11	12	5
MDACC[13]	24	dasatinib 50 mg BID or 100 mg QD	10	21	6
ENESTnd[17]	24[a]	nilotinib 300 mg BID	10	12	4
		nilotinib 400 mg BID	12	11	4
		imatinib 400 mg QD	9	21	5
DASISION[18]	27[a]	dasatinib 100 mg QD	19	24	11
		imatinib 400 mg QD	11	21	8
S0325[49]	Min. 12 mo	dasatinib 100 mg QD	18	15	10
		imatinib 400 mg QD	8	12	4

Abbreviations: AE = adverse event; BID = twice daily; mo = months; QD = once daily.

[a]Median duration of treatment.