Title: Second-Generation Tyrosine Kinase Inhibitors: The Future of Frontline CML Therapy

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Statement of Translational Relevance

Recently, second-generation TKIs have been approved for the treatment of patients with newly diagnosed Philadelphia-positive chronic myeloid leukemia in chronic phase (CML-CP). This article provides a critical review of the ongoing frontline phase 2 nilotinib and dasatinib MDACC studies published in the *Journal of Clinical Oncology* earlier this year and the frontline phase 2 nilotinib GIMEMA study published in *Blood*. In addition, the pivotal phase 3 nilotinib ENESTnd and the phase 3 dasatinib DASISION studies, each published in *The New England Journal of Medicine* and serve as the foundation of these recent approvals, are described. This review article aims to summarize and provide the first comprehensive discussion of recent landmark data on the use of second-generation tyrosine kinase inhibitors for the treatment of patients with newly diagnosed CML-CP to assist physicians in evaluating these new treatment options.
ABSTRACT

All available data from ongoing studies of second-generation tyrosine kinase inhibitors (TKIs) for treatment of patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) were reviewed. In two nilotinib phase 2 trials, the speed and depth of molecular and cytogenetic responses were greater than responses to imatinib. Furthermore, only one patient in each study progressed to accelerated or blastic phase. In the phase 3 ENESTnd study, molecular and cytogenetic responses to nilotinib were superior to imatinib, and more patients achieved undetectable levels of disease with nilotinib. Nilotinib also demonstrated significantly lower progression than did imatinib. In the ongoing phase 2 study of dasatinib, the speed and depth of molecular and cytogenetic responses were higher compared with expected responses to imatinib; no patient to date has progressed. In the phase 3 DASISION study, molecular and cytogenetic responses to dasatinib were superior to those of imatinib and fewer patients progressed. The results suggest that second-generation TKIs have the potential to replace imatinib as the standard of care for patients with early CML-CP. Future CML therapy might include earlier use of these agents to help more patients achieve complete molecular remission and may be a path to a CML cure.
INTRODUCTION

Imatinib revolutionized the treatment of Philadelphia-positive (Ph+) chronic myeloid leukemia (CML) and established targeted BCR-ABL inhibitors as the standard of care. (1) Recent 8-year follow-up of patients with newly diagnosed chronic phase CML (CML-CP), in the phase 3 IRIS trial, reported a cumulative best complete cytogenetic response (CCyR) of 83% and an estimated overall survival of 93% (CML-related deaths). (2) However, 17% of imatinib-treated patients do not achieve a CCyR, and 10% who do will relapse. An additional 8% of patients are intolerant of imatinib. (3)

Second-generation tyrosine kinase inhibitors (TKIs) are more potent BCR-ABL inhibitors with demonstrated efficacy in patients resistant to or intolerant of imatinib. (4-8) Dasatinib and nilotinib are approved for in this setting and are active against all BCR-ABL mutations (except T315I), and have well-established safety profiles. (9, 10) The increased potency of these agents make them attractive candidates for use in the frontline setting.

Four phase 2 studies of the efficacy of second-generation TKIs in patients with newly diagnosed CML-CP are ongoing and reviewed here. The Gruppo Italiano Malattie Ematologiche dell’Adulto (GIMEMA) working party and investigators at the M.D. Anderson Cancer Center (MDACC) are conducting single-arm trials with nilotinib, and the MDACC is conducting a similarly designed phase 2 study of dasatinib in this setting. (11-13) The All Ireland Cooperative Oncology Research Group is also investigating nilotinib in patients with newly diagnosed CML-CP, although results thus
far are preliminary. Three randomized, multicenter, phase 3 studies are ongoing, including one for nilotinib (ENESTnd), one for dasatinib (DASISION), and one for bosutinib. To date, ENESTnd and DASISION have reported results. Nilotinib was recently approved for use in patients with newly diagnosed CML-CP in the US and Switzerland based on the results of ENESTnd. This review summarizes the promising results of the studies and offers a perspective on the future use of these agents in the frontline treatment of CML.

**SUMMARY OF FRONTLINE TRIAL RESULTS FOR SECOND-GENERATION TKIs**

**GIMEMA Nilotinib Study**

The GIMEMA study of nilotinib in the first-line setting included 73 patients with Ph+ CML-CP diagnosed within 6 months of enrollment, who were either untreated or treated only with hydroxyurea or anagrelide prior to study entry. Patients were treated with nilotinib 400 mg twice daily. Responses were defined on the basis of the 2006 European LeukemiaNet (ELN) criteria. The primary trial endpoint was a CCyR at 12 months measured by either conventional bone marrow cytogenetics or fluorescence in situ hybridization (FISH) (Table 1). The secondary endpoint, major molecular response (MMR)—defined as a BCR-ABL percentage ratio (International Scale) ≤ 0.1%—was determined by real-time polymerase chain reaction (RT-PCR) and expressed as a percentage according to the International Scale (conversion factor: 0.6).

The percentages of patients with low, intermediate, and high Sokal risk scores were 45%, 41%, and 14%, respectively (Table 2). At a median follow-up of 15 months, rates
of CCyR and MMR by 12 months were 96% and 85%, respectively, in all patients (Table 3). Responses were achieved rapidly, with 78% and 96% of patients achieving a CCyR and 52% and 66% of patients achieving an MMR by 3 and 6 months, respectively. Only one patient (1.3%) progressed to AP in the first 12 months of therapy.

The frequencies of nonhematologic adverse events (AEs) and laboratory abnormalities were similar to those observed in phase II studies of nilotinib. Grade 3 AEs included skin rash (5%), bone/muscle/joint pain (4%), and pruritus (4%). Peripheral edema was rare (4% overall), and no grade 3/4 abnormalities were reported. Laboratory abnormalities included elevated lipase (29%) and amylase (18%). No instances of pancreatitis were observed, and hyperglycemia (12% overall, 3% grade 3) was transient and not clinically relevant. Rates of hematologic AEs were low, with rates of grade 3/4 anemia, neutropenia, and thrombocytopenia of 0%, 4%, and 3%, respectively (Table 4). Dose intensity of nilotinib was achieved, with a mean daily nilotinib dose of 600 to 800 mg achieved by most patients (74%). Thirty-eight patients (52%) experienced a total of 86 dose interruptions, with a median cumulative duration of 19 days (range, 3-169) or about 4% of the total duration of treatment.

With a median follow-up of 36 months, results from this study remain positive, with 97% of patients achieving MMR and all responses being durable. Responses deepened over time, as CMR4 was obtained in 70% of patients (25% confirmed). Still, only the 1 patient with T315I mutation progressed to AP/BP within the first 6 months of the study. Three patients discontinued with on study due to persistent lipase or amylase increases
however, none of these patients had pancreatitis and all were in CCyR and MMR at the
time of discontinuation.

MDACC Nilotinib Study

The MDACC study of nilotinib in the frontline setting included 67 patients with Ph+ CML-
CP (and seven patients with CML-AP), diagnosed within 6 months of enrollment, who
were either untreated or treated with hydroxyurea or anagrelide only or imatinib 400 mg
once daily for a maximum of 1 month prior to study entry.(20) Patients were treated with
nilotinib 400 mg twice daily. The primary trial endpoint in the MDACC trial was an MMR
at 12 months defined as a BCR-ABL percentage ratio (International Scale) ≤ 0.1%. The
secondary endpoint was a CCyR at 12 months based on G-banding with at least 20
metaphases (Table 1). The distributions of patients with low, intermediate, and high
Sokal risk scores (including the seven patients with CML-AP) were 70%, 23%, and 7%,
respectively, which was consistent with the distribution of patients in the GIMEMA study
(Table 2).

At a median follow-up of 17.3 months, 93% and 81% of evaluable CML-CP patients had
achieved a CCyR and an MMR, respectively, at 12 months (Table 3). Responses were
rapid and durable, with 78% and 96% of CML-CP patients achieving a CCyR and 42%
and 75% of patients achieving an MMR by 3 and 6 months, respectively, and 93% and
79% of patients maintaining a CCyR and an MMR, respectively, at 24 months. Rates of
complete molecular response (CMR) increased from 11% at 12 months to 20% at 24
months. One patient, who discontinued nilotinib because of intolerance after having achieved a CCyR, progressed to BP after an allogeneic stem cell transplant.

In all patients (including seven patients with CML-AP), grade 3/4 nonhematologic AEs were uncommon, with elevations of bilirubin, lipase, and amylase occurring at rates of 8%, 6%, and 3%, respectively. Grade 3/4 hematologic AEs included neutropenia (12%), thrombocytopenia (11%), and anemia (5%) (Table 4). Overall, 24 patients (37%) required 45 transient treatment interruptions, 11 patients required dose reductions, and 10 patients discontinued therapy (four because of AEs; two for progression to BP, one of whom was already in AP; two for financial reasons; one for personal reasons; and one for noncompliance).

**MDACC Dasatinib Study**

The design of the MDACC study of dasatinib in the frontline setting was similar to that of the MDACC study of nilotinib. The dasatinib study included 62 patients with Ph+ CML-CP diagnosed within 6 months of enrollment, who were either untreated or treated with only hydroxyurea or anagrelide or imatinib 400 mg/day for a maximum of 1 month prior to study entry.(21) The dasatinib trial included a 100 mg/day arm (n = 31) and a 50 mg twice-daily arm (n = 31). Dose escalation of dasatinib was permitted. Similar to the MDACC nilotinib trial, the primary and secondary endpoints of the dasatinib trial were MMR and CCyR rates at 12 months, and the response definitions were identical to those in the nilotinib trial (Table 1). The overall distributions of patients with low,
intermediate, and high Sokal risk scores were 81%, 13%, and 6%, respectively (Table 2), which were correspondingly distributed across the two trial arms.

At a median follow-up of 24 months, 98% and 71% of patients evaluable at 12 months had achieved a CCyR and an MMR, respectively (Table 3). Responses were also rapid, with 81% and 94% of evaluable patients achieving a CCyR and 24% and 63% of evaluable patients achieving an MMR by 3 and 6 months, respectively. CCyR and MMR rates were 84% and 87% at 24 months, and rates of CMR were 7% at 12 months and 6% at 24 months in evaluable patients. No patients have yet progressed to AP/BP.

Grade 3/4 nonhematologic AEs were uncommon and included fatigue (6%), joint and muscle pain (6%), and dyspnea (5%). Pleural effusions were observed in 13% of patients, with only one instance of a grade 3 pleural effusion in a patient randomly assigned to the 100 mg once-daily dosing schedule. Overall, the rate of pleural effusions was 3% in the 100 mg once-daily arm and 10% in the 50 mg twice-daily arm (P = .26). Grade 3/4 hematologic AEs included neutropenia (21%), thrombocytopenia (10%), and anemia (6%) (Table 4). Overall, 84 treatment interruptions have been reported in 30 of 62 study patients (48%). The most common reasons for treatment interruption were pleural effusion (20 interruptions), dyspnea (16 interruptions), and headache (12 interruptions). Treatment interruptions were more frequent in the once-daily dosing arm (n = 18, 58%) than in the twice-daily arm (n = 12, 39%). Dose reductions were required in 25% of patients, and five patients have discontinued
dasatinib therapy (two because of pleural effusions, one because of prolonged myelosuppression, one because of patient choice, and one because of noncompliance).

**Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients (ENESTnd)**

ENESTnd is a phase 3, randomized, open-label, multicenter study comparing the efficacy and safety of nilotinib with imatinib in patients with newly diagnosed CML.\(^{(15)}\)

The trial included 846 patients randomly assigned 1:1:1 to nilotinib 300 mg twice daily (\(n = 282\)), nilotinib 400 mg twice daily (\(n = 281\)), or imatinib 400 mg/day (\(n = 283\)). MMR at 12 months was the primary endpoint (Table 1). Response assessments in ENESTnd were measured conservatively; patients with atypical transcripts, missing samples, or invaluable cytogenetic samples were considered to be nonresponders. Imatinib dose escalation to 400 mg twice daily was permitted in the imatinib arm to ensure that therapy was optimized for patients with suboptimal responses to standard-dose imatinib.

Patients were also stratified by Sokal risk score, which resulted in equal distributions of low, intermediate, and high Sokal risk scores in each arm of the trial (Table 2).

With a minimum follow-up of 12 months, more patients remained on study in both nilotinib arms (84% for nilotinib 300 mg twice daily, 82% for nilotinib 400 mg twice daily) than in the imatinib arm (79%). Efficacy results were presented in the intent-to-treat (ITT) population. The MMR rate at 12 months (ITT) was significantly higher for nilotinib 300 mg twice daily (44%, \(P < .0001\)) and nilotinib 400 mg twice daily (43%, \(P < .0001\)) than for imatinib (22%) (Table 5). The best cumulative MMR rates by 12 months were
also significantly higher for nilotinib 300 mg twice daily (55%, \( P < .0001 \)) and nilotinib 400 mg twice daily (51%, \( P < .0001 \)) than for imatinib (27%).(15) Likewise, cumulative rates of CCyR by 12 months (ITT) were also significantly higher for nilotinib 300 mg twice daily (80%, \( P < .0001 \)) and 400 mg twice daily (78%, \( P < .0005 \)) than for imatinib (65%). Responses were rapidly achieved with nilotinib, with 6-month MMR rates (ITT) of 33%, 30%, and 12% and 9-month MMR rates of 43%, 38%, and 18% for nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, and imatinib, respectively. Also, more patients achieved undetectable levels of disease (defined as a complete molecular response of \( \leq 0.0032\% \) BCR-ABL IS, CMR\(^{4,5}\)) with nilotinib 300 mg twice daily (13%) and nilotinib 400 mg twice daily (12%) than with imatinib (4%). These higher responses were also associated with significantly fewer progressions with nilotinib than with imatinib (Table 5).

Discontinuations due to AEs occurred in 5%, 9%, and 7% of patients on nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, and imatinib, respectively. The median dose intensities of nilotinib delivered were close to planned dosing at 592 mg/day on the 300 mg twice-daily arm and 779 mg/day on the nilotinib 400 mg twice-daily arm. The median dose intensity of imatinib was 400 mg/day. Grade 3/4 nonhematologic AEs were uncommon across all three arms of ENESTnd, and all occurred at rates of \( \leq 1\% \), except for rash, which occurred at a rate of 3% in the nilotinib 400 mg twice-daily arm. No instances of QTcF prolongation > 500 msec were observed in any of the treatment arms. Grade 3/4 laboratory abnormalities were uncommon in the nilotinib arms and included elevated levels of lipase, alanine aminotransferase, aspartate aminotransferase, total
bilirubin, and glucose. Rates of grade 3/4 anemia and neutropenia were higher in the imatinib arm of the trial, whereas grade 3/4 thrombocytopenia was more frequently observed in the nilotinib arms (Table 4).

All efficacy endpoints assessed continued to be superior for nilotinib with a minimum of 24 months of follow-up. (22) Achievement of MMR by 24 months was significantly higher for nilotinib 300 mg twice daily (71%, \( P < .0001 \)) and nilotinib 400 mg twice daily (67%, \( P < .0001 \)) compared with imatinib (44%). Achievement of CMR\(^{4,5}\), continued to be significantly higher for nilotinib 300 mg twice daily (26%, \( P < .0001 \)) and nilotinib 400 mg twice daily (21%, \( P = .0004 \)) compared with imatinib (10%). There were no new progression events in the nilotinib 300 mg twice daily arm and there was 1 in the imatinib arm. There was also a numerically higher rate of overall survival in the nilotinib 300 mg twice daily (97.4%) and 400 mg twice daily (97.8%) arms vs imatinib (96.3%). The safety and tolerability profiles of nilotinib and imatinib were unchanged with longer follow-up.

**Dasatinib versus Imatinib Study In Treatment-Naïve CML (DASISION)**

DASISION is a phase 3, randomized, open-label, multicenter study comparing the efficacy and safety of dasatinib 100 mg once daily with that of imatinib. (16) 519 patients with newly diagnosed CML-CP were randomly assigned 1:1 to dasatinib 100 mg once daily (\( n = 259 \)), or imatinib 400 mg/day (\( n = 260 \)). Patients were also stratified by Hasford risk score, which resulted in equal distributions of low, intermediate, and high
Hasford risk scores in each arm of the trial (Table 2). Confirmed CCyR by 12 months was the primary endpoint of the study. Dose escalation to imatinib 400 mg twice daily and to dasatinib 140 mg once daily was permitted for patients with suboptimal responses. Efficacy results are summarized in Table 5. The best cumulative MMR rate by 12 months was significantly higher for dasatinib (46%, \( P < .0001 \)) than for imatinib (28%). Best cumulative rates of CCyR by 12 months were also significantly higher for dasatinib (83%, \( P < .001 \)) than for imatinib (72%). Along with these higher response rates, there were numerically fewer progressions to AP/BP (not significant) with dasatinib (1.9%) than with imatinib (3.5%). There was no OS advantage for dasatinib (97%) compared with imatinib (99%).

The median dose intensity of dasatinib was 99 mg/day and the median dose intensity of imatinib was 400 mg/day. Five percent of patients received dasatinib dose escalation while 14% received imatinib dose escalation for suboptimal response or treatment failure. Grade 3/4 nonhematologic AEs were uncommon across both treatment arms. Pleural effusions were mostly grade 1-2 and occurred in 10% of patients treated with dasatinib. One patient (0.4%) in each treatment arm experienced QTcF increases > 500 msec and 5% in each arm experienced QTcF > 60 msec from baseline. Rates of grade 3/4 anemia and thrombocytopenia were higher on dasatinib than imatinib (Table 4). Overall, discontinuations due to drug-related AEs occurred in 5% of patients in the dasatinib arm and 4% of patients in the imatinib arm.
The DASISION trial demonstrated similar results with a minimum of 18 months of follow-up. (23) Overall cumulative achievement of CCyR was higher on dasatinib (85%) compared with imatinib (80%). Overall cumulative achievement of MMR was significantly higher on dasatinib (57%, P = 0.0002) compared with imatinib (41%). Rates of CMR\textsuperscript{4.5} were numerically higher on dasatinib (13%) compared with imatinib (7%) at any time (not significant). There was 1 new progression event in the dasatinib arm and none in the imatinib arm with longer follow-up (difference in progression to AP/BP not significant). There was no overall survival advantage for dasatinib (96%) compared with imatinib (97.9%). The safety and tolerability profiles of dasatinib and imatinib were similar with longer follow-up, with the exception of 1 grade 3 pleural effusion on dasatinib.

**Bosutinib Efficacy and safety in newly diagnosed chronic myeloid Leukemia (BELA)**

BELA is a phase 3, randomized, open-label, multicenter study comparing the efficacy and safety of bosutinib 500 mg daily with that of imatinib. (24) 502 patients with newly diagnosed CML-CP were randomly assigned 1:1 to bosutinib 500 mg daily (n = 250) or imatinib 400 mg/day (n = 252). CCyR by 12 months was the primary endpoint of the study. Best cumulative rates of CCyR by 12 months were not significantly higher for bosutinib (70%, \( P = .601 \)) compared with imatinib (68%) although MMR rates by 12 months were higher for bosutinib (39%, \( P = .002 \)) compared with imatinib (26%). There were numerically fewer progressions to AP/BP (not significant) with bosutinib (2%) than with imatinib (4%). Overall, discontinuation due to drug-related AEs occurred in 19% of
patients in the bosutinib arm and 5% of patients in the imatinib arm. The authors suggested that these discontinuations were mostly attributable to the non-hematologic AE profile of bosutinib that some centers/investigators had not had prior experience with, potentially including the higher rates of diarrhea on bosutinib (68%) compared with imatinib (21%) that have historically been categorized as transient and occurring early. Unfortunately, these issues may have confounded the primary endpoint of the study.

**DISCUSSION**

Taken together, the results from all trials of nilotinib and dasatinib in the frontline setting have demonstrated that second-generation TKIs provide faster response rates and deeper responses compared with imatinib, coupled with a lower rate of progression to AP/BP.

Differences in study design must be considered when comparing results from these trials (Table 2). For example, the simple difference between reporting responses in patients “at” a specific time point vs “by” a specific time point can influence results and the ability to compare efficacy rates across studies. For example, the ENESTnd study reported MMR rates “at” 12 months of 44% for nilotinib 300 mg twice daily, while the DASISION trial reported best cumulative MMR rates “by” 12 months for dasatinib 100 mg once daily of 46% (Table 5). In this instance, patients who may have either lost the response or discontinued treatment prior to 12 months would not be considered responders in the “at” analysis, but would be considered as responders in the “by” analysis. In ENESTnd, the MMR rate for nilotinib 300 mg twice daily was 55% “by” 12
months, an increase of 11% in the MMR rate by reporting response rates in the cumulative fashion. Concerning efficacy, analysis of the primary endpoints in the phase 3 studies and in the GIMEMA study was conducted in the ITT population, and patients with missing or nonevaluable samples were treated as nonresponders; however, efficacy in the other phase 2 trials was reported in evaluable patients at each time point. This is appropriate given the nature of the differences between phase 2 and phase 3 studies and the differences in patient population size between trials.

Although the use of nilotinib and dasatinib in frontline CML therapy leads to faster and deeper responses, the long-term implications of these benefits remain under investigation. For example, in a subanalysis of the IRIS trial data, patients who achieved a CCyR at 12 months had better long-term outcomes. However, in another analysis, it was suggested that the outcomes of patients who achieved a CCyR were similar regardless of when the response was achieved. Furthermore, in an analysis conducted at the MDACC, achievement of a molecular response (MMR and less than an MMR) was not associated with improved overall survival in patients who achieved a CCyR. However, these examples included preselected groups of responding patients (those with a CCyR), which resulted in a selection bias for patients already known to have favorable outcomes. Findings from the ENESTnd trial have demonstrated that the faster and deeper rates of response in nilotinib-treated patients resulted in better rates of freedom from progression in this group than in imatinib-treated patients at 12 and 24 months. A similar trend was observed with dasatinib in the DASISION trial. Unlike the Tyrosine Kinase Inhibitor Optimization and Selectivity
(TOPS) Study and German CML Study IV trials,(27-29) in which an early response advantage of imatinib 800 mg/day over imatinib 400 mg/day became equivocal by 12 months, progression was never in favor of high-dose imatinib, whereas response rates and freedom from progression were superior for nilotinib than for imatinib in ENESTnd.

**The Potential for a Cure**

The impact of using more potent agents in the frontline setting on the potential to discontinue TKI therapy at a later time remains to be determined. The future of CML therapy may include early use of these potent agents to help more patients achieve CMR, perhaps in combination with interferon-alpha, vaccines, or other new molecules that could lead to therapy discontinuation and cure.

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### Table 1. Study Design and Endpoints Across Frontline Studies of Second-Generation Tyrosine Kinase Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Nilotinib 400 mg twice daily (GIMEMA) (n = 73)</th>
<th>Nilotinib 400 mg twice daily (MDACC) (n = 74)</th>
<th>Dasatinib 100 mg once daily or 50 mg twice daily (MDACC) (n = 62)</th>
<th>ENESTnd (n = 846)</th>
<th>DASISION (n = 519)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>CCyR (0% Ph+)</td>
<td>MMR (&lt; 0.1% BCR-ABL, IS)*</td>
<td>MMR (&lt; 0.1% BCR-ABL, IS)*</td>
<td></td>
<td>Confirmed CCyR (0% Ph+)</td>
</tr>
<tr>
<td><strong>Secondary endpoint</strong></td>
<td>MMR (&lt; 0.1% BCR-ABL, IS)*</td>
<td>CCyR (0% Ph+)</td>
<td>CCyR (0% Ph+)</td>
<td></td>
<td>MMR (&lt; 0.1% BCR-ABL, IS)*</td>
</tr>
<tr>
<td><strong>MMR by:</strong></td>
<td>RT-PCR in central lab (Bologna, Italy)</td>
<td>RT-PCR in central lab (Houston, Texas)</td>
<td>RT-PCR by MolecularMD (Portland, OR)</td>
<td></td>
<td>RT-PCR by MolecularMD (Portland, OR)</td>
</tr>
<tr>
<td><strong>CCyR by:</strong></td>
<td>Bone marrow cytogenetics or FISH</td>
<td>Bone marrow cytogenetics only</td>
<td>Bone marrow cytogenetics only</td>
<td></td>
<td>Bone marrow cytogenetics only</td>
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*IS = International Scale*
<table>
<thead>
<tr>
<th>Efficacy presented in:</th>
<th>ITT population</th>
<th>Evaluable patients</th>
<th>Evaluable patients</th>
<th>ITT population</th>
<th>ITT population</th>
</tr>
</thead>
</table>

Abbreviations: **CCyR**, complete cytogenetic response; **ENESTnd**, Evaluating Nilotinib Efficacy and Safety in Clinical Trials - Newly Diagnosed Patients; **FISH**, fluorescence in situ hybridization; **GIMEMA**, Gruppo Italiano Malattie Ematologiche dell'Adulto; **IS**, International Scale; **ITT**, intent-to-treat; **MDACC**, M.D. Anderson Cancer Center; **MMR**, major molecular response; **Ph+**, Philadelphia chromosome positive; **RT-PCR**, real-time polymerase chain reaction.

*Consistent with definition of MMR as defined by Hughes and colleagues(30)*
Table 2. Patient Demographics and Disposition Across Frontline Studies of Second-Generation Tyrosine Kinase Inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Details</th>
<th>Median Duration of Treatment, Months</th>
<th>Age, Years</th>
<th>Risk, %</th>
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<tbody>
<tr>
<td></td>
<td>Nilotinib 400 mg twice daily (GIMEMA) (n = 73)</td>
<td>18</td>
<td>47</td>
<td>Sokal Low</td>
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<tr>
<td></td>
<td>Nilotinib 400 mg twice daily (MDACC) (n = 74)*</td>
<td>21</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Dasatinib 100 mg once daily or 50 mg twice daily (MDACC) (n = 62)</td>
<td>24</td>
<td>47</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>ENESTnd Nilotinib 300 mg twice daily (n = 282)</td>
<td>13.8</td>
<td>18-85</td>
<td>81</td>
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<td></td>
<td>ENESTnd Nilotinib 400 mg twice daily (n = 281)</td>
<td>13.8</td>
<td>18-81</td>
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<tr>
<td></td>
<td>ENESTnd Imatinib 400 mg once daily (n = 283)</td>
<td>13.8</td>
<td>18-80</td>
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<td></td>
<td>DASISION Dasatinib 100 mg once daily (n = 259)</td>
<td>14.0</td>
<td>18-84</td>
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<td></td>
<td>DASISION Imatinib 400 mg once daily (n = 260)</td>
<td>14.3</td>
<td>18-78</td>
<td>48</td>
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* Indicates the number of patients in parentheses.
<table>
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<tr>
<th>High</th>
<th>14</th>
<th>7</th>
<th>6</th>
<th>28</th>
<th>28</th>
<th>28</th>
<th>19</th>
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<tbody>
<tr>
<td>Clonal evolution, %</td>
<td>4</td>
<td>7</td>
<td>7</td>
<td>NR</td>
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<td>NR</td>
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<td>NR</td>
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<tr>
<td>Prior imatinib, %</td>
<td>NA</td>
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<td>31</td>
<td>13</td>
<td>9</td>
<td>11</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Median dose intensity, mg/day†</td>
<td>784</td>
<td>800</td>
<td>100</td>
<td>592</td>
<td>779</td>
<td>400</td>
<td>99</td>
<td>400</td>
</tr>
</tbody>
</table>

Abbreviations: **ENESTnd**, Evaluating Nilotinib Efficacy and Safety in Clinical Trials - Newly Diagnosed Patients; **GIMEMA**, Gruppo Italiano Malattie Ematologiche dell’Adulto; **MDACC**, M.D. Anderson Cancer Center; **NA**, not allowed; **NR**, not reported.

*Includes seven patients with chronic myeloid leukemia in accelerated phase.

†Dose escalation of nilotinib not permitted in any studies.


Table 3. Efficacy of Second-Generation Tyrosine Kinase Inhibitors in Phase 2 Frontline Studies

<table>
<thead>
<tr>
<th></th>
<th>Nilotinib 400 mg twice daily (GIMEMA) (n = 73)</th>
<th>Nilotinib 400 mg twice daily (MDACC) (n = 67)†,*</th>
<th>Dasatinib 100 mg once daily or 50 mg twice daily (MDACC) (n = 62)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>52</td>
<td>42</td>
<td>24</td>
</tr>
<tr>
<td>6 months</td>
<td>66</td>
<td>75</td>
<td>63</td>
</tr>
<tr>
<td>12 months</td>
<td>85</td>
<td>81</td>
<td>71</td>
</tr>
<tr>
<td>CCyR, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>78</td>
<td>90</td>
<td>82</td>
</tr>
<tr>
<td>6 months</td>
<td>96</td>
<td>96</td>
<td>94</td>
</tr>
<tr>
<td>12 months</td>
<td>96</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>CMR, %</td>
<td>24 months</td>
<td>36 months</td>
<td>Progression, n</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: **CCyR**, complete cytogenetic response; **GIMEMA**, Gruppo Italiano Malattie Ematologiche dell’Adulta; **MDACC**, M.D. Anderson Cancer Center; **MMR**, major molecular response; **CMR**, complete molecular response

†Includes only patients with chronic myeloid leukemia in chronic phase; **NA**, not available.

*Only includes evaluable patients
Table 4. Grade 3/4 Hematologic Laboratory Abnormalities Across Frontline Studies of Second-Generation Tyrosine Kinase Inhibitors

<table>
<thead>
<tr>
<th>Kinase Inhibitors</th>
<th>Nilotinib 400 mg twice daily (GIMEMA) (n = 73)</th>
<th>Nilotinib 400 mg twice daily (MDACC) (n = 74)*</th>
<th>Dasatinib 100 mg once daily or 50 mg twice daily (MDACC) (n = 62)</th>
<th>ENEStnd Nilotinib 300 mg twice daily (n = 282)</th>
<th>ENEStnd Nilotinib 400 mg twice daily (n = 281)</th>
<th>ENEStnd Imatinib 400 mg once daily (n = 283)</th>
<th>DASISION Dasatinib 100 mg once daily (n = 259)</th>
<th>DASISION Imatinib 400 mg once daily (n = 260)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic events, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4</td>
<td>12</td>
<td>21</td>
<td>12</td>
<td>10</td>
<td>20</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>9</td>
<td>19</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviations: ENEStnd, Evaluating Nilotinib Efficacy and Safety in Clinical Trials - Newly Diagnosed Patients; GIMEMA, Gruppo Italiano Malattie Ematologiche dell’Adulto; MDACC, M.D. Anderson Cancer Center.

*Includes seven patients with chronic myeloid leukemia in accelerated phase.
Table 5. Efficacy of Nilotinib in the Phase 3 ENESTnd Trial and Dasatinib in the Phase 3 DASISION Trial (Based on minimum 12 month follow-up data)

<table>
<thead>
<tr>
<th></th>
<th>ENESTnd Nilotinib</th>
<th>ENESTnd Nilotinib</th>
<th>ENESTnd Imatinib</th>
<th>DASISION Dasatinib</th>
<th>DASISION Imatinib</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300 mg twice daily</td>
<td>400 mg twice daily</td>
<td>400 mg once daily</td>
<td>100 mg once daily</td>
<td>400 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 282)</td>
<td>(n = 281)</td>
<td>(n = 283)</td>
<td>(n = 259)</td>
<td>(n = 260)</td>
<td></td>
</tr>
<tr>
<td>MMR, %</td>
<td>44</td>
<td>43</td>
<td>22</td>
<td>NR</td>
<td>NR</td>
<td>(&lt; .0001, &lt; .0001)</td>
</tr>
<tr>
<td>at 12 months (ITT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR, %</td>
<td>55</td>
<td>51</td>
<td>27</td>
<td>46</td>
<td>28</td>
<td>(&lt; .0001)</td>
</tr>
<tr>
<td>by 12 months (ITT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCyR, %</td>
<td>67</td>
<td>63</td>
<td>45</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>by 6 months (ITT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCyR, %</td>
<td>80</td>
<td>78</td>
<td>65</td>
<td>83</td>
<td>72</td>
<td>(&lt; .001)</td>
</tr>
<tr>
<td>by 12 months (ITT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMR, %</td>
<td>13</td>
<td>12</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Overall (ITT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P Value* indicates statistical significance compared to Imatinib.
<table>
<thead>
<tr>
<th>Progression (ITT), n</th>
<th>2</th>
<th>1</th>
<th>11</th>
<th>(.0095, .0037)</th>
<th>5</th>
<th>9</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (ITT), %</td>
<td>98.5</td>
<td>99.3</td>
<td>96.9</td>
<td>(.28, .03)</td>
<td>97</td>
<td>99</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: **CCyR**, complete cytogenetic response; **ENESTnd**, Evaluating Nilotinib Efficacy and Safety in Clinical Trials - Newly Diagnosed Patients; **ITT**, intent-to-treat; **MMR**, major molecular response; **NR**, not reported; **NS**, not significant.

*Difference between nilotinib 300 mg twice daily vs imatinib and nilotinib 400 mg twice daily vs imatinib.
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Hagop M. Kantarjian, Michele Baccarani, Elias Jabbour, et al.

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