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Nilotinib versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia

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ABSTRACT

BACKGROUND

Nilotinib has been shown to be a more potent inhibitor of BCR-ABL than imatinib. We evaluated the efficacy and safety of nilotinib, as compared with imatinib, in patients with newly diagnosed Philadelphia chromosome–positive chronic myeloid leukemia (CML) in the chronic phase.

METHODS

In this phase 3, randomized, open-label, multicenter study, we assigned 846 patients with chronic-phase Philadelphia chromosome–positive CML in a 1:1:1 ratio to receive nilotinib (at a dose of either 300 mg or 400 mg twice daily) or imatinib (at a dose of 400 mg once daily). The primary end point was the rate of major molecular response at 12 months.

RESULTS

At 12 months, the rates of major molecular response for nilotinib (44% for the 300-mg dose and 43% for the 400-mg dose) were nearly twice that for imatinib (22%) ($P<0.001$ for both comparisons). The rates of complete cytogenetic response by 12 months were significantly higher for nilotinib (80% for the 300-mg dose and 78% for the 400-mg dose) than for imatinib (65%) ($P<0.001$ for both comparisons). Patients receiving either the 300-mg dose or the 400-mg dose of nilotinib twice daily had a significant improvement in the time to progression to the accelerated phase or blast crisis, as compared with those receiving imatinib ($P=0.01$ and $P=0.004$, respectively). No patient with progression to the accelerated phase or blast crisis had a major molecular response. Gastrointestinal and fluid-retention events were more frequent among patients receiving imatinib, whereas dermatologic events and headache were more frequent in those receiving nilotinib. Discontinuations due to aminotransferase and bilirubin elevations were low in all three study groups.

CONCLUSIONS

Nilotinib at a dose of either 300 mg or 400 mg twice daily was superior to imatinib in patients with newly diagnosed chronic-phase Philadelphia chromosome–positive CML. (ClinicalTrials.gov number, NCT00471497.)

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The use of the BCR-ABL tyrosine kinase inhibitor imatinib mesylate (Gleevec, Novartis Pharmaceuticals) improved outcomes for patients with Philadelphia chromosome–positive chronic myeloid leukemia (CML) and established BCR-ABL–targeted therapy as the standard of care for this disease. In the International Randomized Study of Interferon and STI571 (IRIS; ClinicalTrials.gov number, NCT00006343), imatinib was associated with a superior response rate and improved progression-free survival, as compared with the previous standard therapy, interferon alfa plus low-dose cytarabine.[1-3] Eight-year follow-up of IRIS revealed that responses to imatinib were durable and had an acceptable adverse-event profile, with an estimated rate of overall survival of 85%.[4]

Despite the positive effect of imatinib, nearly 20% of patients who take the drug do not have a complete cytogenetic response, and others may have intolerable side effects or drug resistance over time.[4] Loss of response and transformation to advanced disease occur mainly in the first 3 years of imatinib therapy, and the rate of overall survival is poor in these patients.[5] In addition, residual disease, detectable by real-time quantitative polymerase-chain-reaction (RQ-PCR) assay, is measurable in most patients treated with imatinib.[2,6,7] Thus, improved first-line therapy is needed.

Nilotinib (Tasigna, Novartis Pharmaceuticals) is an orally bioavailable drug with greater potency and selectivity for BCR-ABL than imatinib.[8] Nilotinib was first approved in the United States and elsewhere in 2007 for patients with CML in the chronic or accelerated phase who had resistance to or could not tolerate imatinib.[9,10]

In this phase 3, randomized, open-label, multicenter trial, called the Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENESTnd) study, we compared the efficacy and safety of nilotinib (at a dose of either 300 mg or 400 mg twice daily) with that of imatinib (at a dose of 400 mg once daily) in patients with newly diagnosed Philadelphia chromosome–positive CML in the chronic phase, with the rate of major molecular response at 12 months as the primary end point.

Methods

Patients

Adult patients were eligible within 6 months after the diagnosis of Philadelphia chromosome–positive CML in the chronic phase. Diagnosis was determined by conventional cytogenetic analysis of bone marrow containing at least one Philadelphia chromosome–positive metaphase cell. Diagnosis by fluorescence in situ hybridization was not allowed. The definition of chronic-phase CML has been described previously.[3] Patients needed to have adequate organ function and an Eastern Cooperative Oncology Group (ECOG) performance status of at least 2, which indicates that the patient is capable of all self-care but is unable to carry out any work activities and is out of bed more than 50% of waking hours.[9] (The ECOG performance status is graded on a scale from 0 to 5, with a higher score indicating a greater severity of illness.)

Patients were excluded if they had received treatment with a tyrosine kinase inhibitor before study entry (except imatinib for ≤2 weeks) or any medical treatment for CML for more than 2 weeks (except hydroxyurea or anagrelide). Patients with impaired cardiac function were excluded. The use of therapeutic coumarin derivatives, drugs that block or stimulate the activity of the liver enzyme cytochrome P450-3A4 (CYP3A4 inhibitors or inducers), or any medication with the potential to prolong the QT interval was prohibited.

Randomization and Treatments

Patients with newly diagnosed Philadelphia chromosome–positive chronic-phase CML were randomly assigned in a 1:1:1 ratio to receive nilotinib (at a dose of either 300 mg or 400 mg twice daily) or imatinib (at a dose of 400 mg once daily). Randomization was stratified according to the Sokal risk score at the time of diagnosis. The Sokal score[10] is based on age, spleen size, and peripheral-blood platelet count and blast count. Patients are classified as being low-risk (Sokal score, <0.8), intermediate-risk (0.8 to 1.2), or high-risk (>1.2).

Patients could discontinue therapy because of treatment failure (including progression), intolerable side effects, or other reasons. An escalation in the imatinib dose to 400 mg twice daily was permitted in patients who had a suboptimal response or treatment failure, as defined by the European LeukemiaNet.[11] Dose escalation of nilotinib was not permitted. In contrast to the protocol of the IRIS study,[1] crossover was not permitted in our protocol. Instead, patients were eligible to participate in an extension study.

Molecular response was assessed for BCR-ABL

by means of RQ-PCR at baseline, monthly for 3 months, and every 3 months thereafter. Conventional bone marrow cytogenetic analyses were performed at baseline and at months 6, 12, 18, and 24. Complete blood counts were measured at baseline; at weeks 1, 2, and 4; monthly until month 6; and every 3 months thereafter until study completion.

END POINTS

The primary efficacy end point was the rate of major molecular response at 12 months, defined as a BCR-ABL transcript level of 0.1% or less in peripheral blood on RQ-PCR assay, as expressed on the International Scale.[12-16] This corresponds to a reduction of 3 $\log_{10}$ copies or more in BCR-ABL transcripts, as compared with the standardized baseline established in IRIS.[12] Patients who did not undergo RQ-PCR assessment at 12 months were considered to have had no response. RQ-PCR assays were performed in a central laboratory (MolecularMD). The assay was standardized through an exchange of samples from patients with the molecular laboratory in Adelaide, Australia. The International Scale conversion factor was 0.81.[12,13]

The key secondary end point was a durable major molecular response by 24 months. However, for this study, the rate of complete cytogenetic response by 12 months was the main secondary end point. Results on the secondary end point of progression to accelerated phase or blast crisis (defined as such progression or CML-related death) are also provided.

STUDY DESIGN

The study was designed by representatives of the sponsor, Novartis Pharmaceuticals, with input from the investigators on the study-management committee. The data were collected with the use of the sponsor's data-management systems and were analyzed and interpreted by the sponsor's statistical team in close collaboration with the other investigators. An independent data and safety monitoring board reviewed the trial data and made recommendations regarding the continuation of the study. All authors contributed to the writing, reviewing, and amending of an outline of the manuscript. The first draft of the manuscript was written by a medical writer employed by an independent company with funding provided by Novartis. All authors and representatives of the sponsor reviewed and amended the manuscript and vouch for the completeness and integrity of the reported data. The authors also certify that the study as reported conforms with the protocol (as amended) and statistical analysis plan. (For details, see the protocol, available with the full text of this article at NEJM.org.)

For details regarding other secondary end points, the statistical analysis, and ethics and study management, see the Methods section in the Supplementary Appendix, available at NEJM.org.

RESULTS

PATIENTS AND TREATMENTS

From September 6, 2007, to September 30, 2008, we randomly assigned 846 patients with newly diagnosed, Philadelphia chromosome–positive, chronic-phase CML to receive nilotinib twice daily (with 282 patients assigned to receive 300 mg and 281 patients assigned to receive 400 mg) or imatinib once daily (with 283 patients assigned to receive 400 mg). The cutoff date for this study was September 2, 2009, on the basis of the 12-month visit for the last patient who underwent randomization.

Baseline characteristics and distributions of the Sokal risk score were well-balanced in the three study groups (Table 1). The median dose intensities of nilotinib were high (and close to the planned regimens) at 592 mg per day (interquartile range, 543 to 600) in the group receiving the 300-mg dose and 779 mg per day (interquartile range, 581 to 800) in the group receiving the 400-mg dose. The median dose intensity of imatinib was 400 mg per day (interquartile range, 389 to 400). At the time of data cutoff, the median duration of treatment was approximately 14 months in all study groups; the proportions of patients receiving a study drug were 84% in the group receiving 300 mg of nilotinib, 82% in the group receiving 400 mg of nilotinib, and 79% in the group receiving imatinib (Table 1 in the Supplementary Appendix). In the imatinib group, 45 patients had a dose escalation to 800 mg per day. By the time of data cutoff, 13 patients had discontinued treatment (7 patients because of treatment failure, 3 patients because of disease progression, and 1 patient each because of a suboptimal response, adverse events, and a protocol violation).

EFFICACY

At 12 months, rates of major molecular response (the primary end point) were significantly higher

Table 1. Baseline Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Nilotinib, 300 mg (N=282)†	Nilotinib, 400 mg (N=281)†	Imatinib (N=283)†
Median age (range) — yr	47 (18–85)	47 (18–81)	46 (18–80)
Male sex — no. (%)	158 (56)	175 (62)	158 (56)
Race or ethnic group — no. (%)‡			
Asian	76 (27)	66 (23)	71 (25)
Black	12 (4)	11 (4)	7 (2)
White	170 (60)	185 (66)	187 (66)
Other	24 (9)	19 (7)	18 (6)
Median time since diagnosis (range) — days	31 (0–182)	31 (3–189)	28 (1–183)
Sokal risk group — no. (%)			
Low	103 (37)	103 (37)	104 (37)
Intermediate	101 (36)	100 (36)	101 (36)
High	78 (28)	78 (28)	78 (28)
Chromosomal abnormalities in addition to the Philadelphia chromosome — no. (%)	34 (12)	44 (16)	31 (11)
Atypical BCR-ABL transcripts — no. (%)	5 (2)	1 (<1)	2 (1)
Spleen size ≥10 cm below costal margin — no. (%)	31 (11)	34 (12)	40 (14)
Median hemoglobin (range) — g/dl	12.0 (5.5–17.6)	12.0 (6.2–17.6)	12.2 (6.4–17.1)
Median platelet count (range) — $\times 10^{-3}/mm^3$	424 (90–3880)	374 (103–1819)	375 (66–2232)
Median white-cell count (range) — $\times 10^{-3}/mm^3$	23 (2–247)	23 (2–435)	26 (3–482)
Previous treatment for CML — no. (%)§	2 (1)	1 (<1)	4 (1)

* CML denotes chronic myeloid leukemia. Percentages may not total 100 because of rounding.
† Nilotinib was administered at a dose of either 300 mg or 400 mg twice daily, and imatinib at a dose of 400 mg once daily.
‡ Race or ethnic group was self-reported.
§ This category does not include treatment with hydroxyurea or anagrelide or with imatinib for 2 weeks or less.

in patients receiving 300 mg of nilotinib (44%) or 400 mg of nilotinib (43%) twice daily than in those receiving imatinib (22%) (P<0.001 for both comparisons) (Fig. 1). Among patients who underwent a 12-month assessment on RQ-PCR assay, a major molecular response at 12 months occurred in 51% of patients receiving 300 mg of nilotinib, in 50% of those receiving 400 mg of nilotinib, and in 27% of those receiving imatinib (Table 2 in the Supplementary Appendix). The rates of major molecular response up to the data cutoff were 57% for patients receiving 300 mg of nilotinib, 54% for those receiving 400 mg of nilotinib, and 30% for those receiving imatinib. Table 3 in the Supplementary Appendix shows molecular responses in patients who underwent molecular analysis at 15 months and 18 months of therapy.

Among patients with a high Sokal risk, rates of major molecular response at 12 months were 41% for patients receiving 300 mg of nilotinib, 32% for those receiving 400 mg of nilotinib, and 17% for those receiving imatinib. Rates of major molecular response were also higher for nilotinib at either dose, as compared with imatinib, at 3, 6, and 9 months. The Kaplan–Meier estimate of the median time to major molecular response among all patients was shorter for patients receiving 300 mg of nilotinib (8.6 months) and 400 mg of nilotinib (11.0 months) than for those receiving imatinib (median not yet achieved) (Fig. 2). The probability of the occurrence of a major molecular response at different time points was higher in both nilotinib groups than in the imatinib group (P<0.001 for both comparisons). The Kaplan–Meier analysis represents an estimate of response if all patients had continued to receive therapy and therefore may be higher than

the observed rate. Overall, by data cutoff, the BCR-ABL transcript level was 0.0032% or less on the International Scale (the most sensitive measure of disease burden available) in 13% of patients receiving 300 mg of nilotinib, 12% of those receiving 400 mg of nilotinib, and 4% of those receiving imatinib.

By 12 months, rates of complete cytogenetic response (the key secondary end point) were significantly higher among patients receiving 300 mg of nilotinib (80%) and those receiving 400 mg of nilotinib (78%), as compared with those receiving imatinib (65%) (P<0.001 for both comparisons) (Fig. 3). By 6 and 12 months, 25 to 26% and 12 to 14% of patients, respectively, in all three study groups had missing cytogenetic data either because the sample was inadequate (<20 metaphases) or no test was performed, and these patients were considered to have had no response. Among patients who underwent a 12-month cytogenetic assessment, a complete cytogenetic response occurred in 93% of patients receiving 300 mg of nilotinib, 93% of those receiving 400 mg of nilotinib, and 76% of those receiving imatinib (Table 4 in the Supplementary Appendix). Among patients with a high Sokal risk, rates of a complete cytogenetic response by 12 months were 74% among patients receiving 300 mg of nilotinib, 63% among those receiving 400 mg of nilotinib, and 49% among those receiving imatinib. By 6 months, rates of complete cytogenetic response were higher in both nilotinib groups than in the imatinib group.

By the cutoff date, progression to the accelerated phase or blast crisis had occurred in 14 patients: 11 patients (4%) receiving imatinib, 2 patients (<1%) receiving 300 mg of nilotinib, and 1 patient (<1%) receiving 400 mg of nilotinib. No patient who had a major molecular response had progression to the accelerated phase or blast crisis. However, three patients receiving imatinib who had a complete cytogenetic response had such progression. Both doses of nilotinib were also significantly better than imatinib with respect to the time to progression to the accelerated phase or blast crisis (P=0.01 for the 300-mg group and P=0.004 for the 400-mg group) (Fig. 1 in the Supplementary Appendix). Of the 45 patients who received an escalation in the dose of imatinib, 1 patient had both a major molecular response and a complete cytogenetic response, and 13 patients had a complete cytogenetic response.

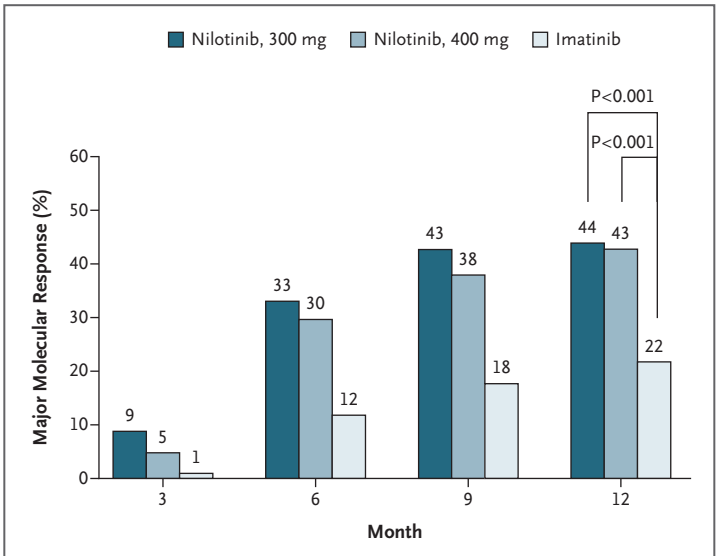

Figure 1. Rates of Major Molecular Response at 3, 6, 9, and 12 Months.
The results in the intention-to-treat population were calculated by means of the Cochran–Mantel–Haenszel test, stratified according to the Sokal risk group, after the last patient had completed 12 cycles of therapy (with a 28-day duration for each cycle). Nilotinib was administered at a dose of either 300 mg or 400 mg twice daily, and imatinib at a dose of 400 mg once daily.

ADVERSE EVENTS

The safety population consisted of all 836 patients who received at least one dose of a study drug. Nilotinib and imatinib both had good safety and adverse-event profiles, although specific differences were noted. The most frequently reported study-related adverse events of any grade are reported in Table 2. Overall, grade 3 or 4 nonhematologic adverse events were uncommon in all patients. Rates of nausea, diarrhea, vomiting, muscle spasm, and edema of any grade were higher for patients in the imatinib group than for those in either nilotinib group. Conversely, rates of rash, headache, pruritus, and alopecia were higher in both nilotinib groups than in the imatinib group.

Grade 3 or 4 neutropenia and anemia were more frequent in the imatinib group, whereas thrombocytopenia was more frequent in both nilotinib groups. All newly occurring grade 3 or 4 hematologic laboratory abnormalities occurred within the first 2 months of therapy in the three study groups. The most frequently reported biochemical laboratory abnormalities are reported in Table 2. Grade 3 or 4 laboratory abnormalities were uncommon in any group. Elevations of any

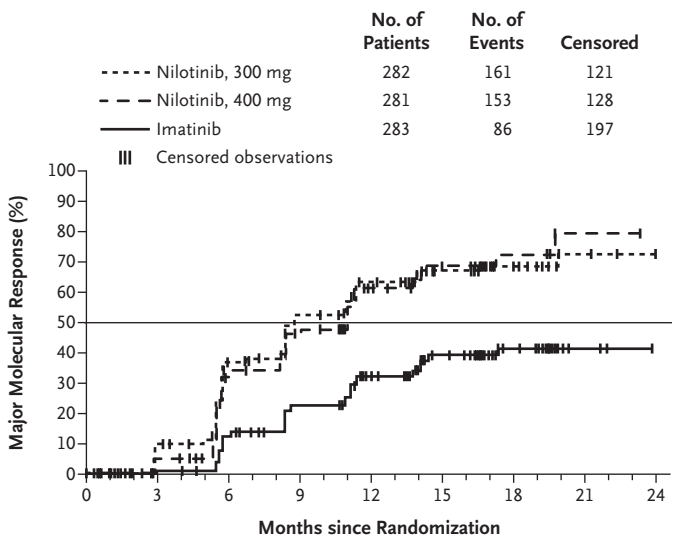

Figure 2. Kaplan–Meier Estimates of the Time to the First Major Molecular Response.

All time-to-event comparisons in the intention-to-treat population were performed with the use of the log-rank test, stratified according to Sokal risk group. Nilotinib was administered at a dose of either 300 mg or 400 mg twice daily, and imatinib at a dose of 400 mg once daily.

grade in levels of alanine aminotransferase, aspartate aminotransferase, and bilirubin were more frequently observed in both nilotinib groups than in the imatinib group, although rates of discontinuation were low and consistent across the study groups. As observed in previous nilotinib trials, these specific laboratory abnormalities are typically manageable and not clinically important. Additional data regarding serious adverse events are available in Table 5 in the Supplementary Appendix.

Dose reductions or interruptions occurred in 59% of patients receiving 300 mg of nilotinib, in 66% receiving 400 mg of nilotinib, and in 52% receiving imatinib. Median cumulative durations of dose interruptions because of adverse events or laboratory abnormalities were 19 days among patients receiving 300 mg of nilotinib, 22 days among patients receiving 400 mg of nilotinib, and 15 days among patients receiving imatinib. Discontinuations because of adverse events occurred in 5% of patients receiving 300 mg of nilotinib, 9% of those receiving 400 mg of nilotinib, and 7% of those receiving imatinib.

Up to the data cutoff, nine patients died during the study. Among patients receiving imatinib, four discontinued treatment because of disease progression and died during follow-up from CML-related reasons; among patients receiving 300 mg of nilotinib, two died (one from a small-intestine obstruction and one from suicide) during the study, and one died during follow-up after bone marrow transplantation; and among patients receiving 400 mg of nilotinib, one discontinued treatment because of progression and died during follow-up and one discontinued treatment and died 6 weeks later from gastric cancer.

Patients were closely monitored for QT prolongation and changes in the left ventricular ejection fraction. No patient in any of the study groups had a QT interval corrected for heart rate (QTcF) of more than 500 msec. No decrease from baseline in the mean left ventricular ejection fraction was observed at any time during the study. A total of 11 patients in all three study groups combined had an ischemic heart disease event, with only one event resulting in treatment discontinuation.

DISCUSSION

In this trial, nilotinib was superior to imatinib in both the primary end point (major molecular response) and the key secondary end point (complete cytogenetic response). The number of patients who had disease progression or transformation to the accelerated phase or blast crisis was significantly lower in both nilotinib groups than in the imatinib group, showing that nilotinib improved disease control in patients with newly diagnosed CML. Our findings establish both the twice-daily 300-mg and 400-mg doses of nilotinib as highly effective, as compared with imatinib.

This study is being reported with a minimal follow-up of 12 months and is ongoing. In two recent phase 3 trials comparing two daily doses of imatinib (800 mg and 400 mg) — the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study and the German CML Study IV — the rate of response with the 400-mg dose was lower than that with the 800-mg dose early in the studies; however, later in the studies, the responses were equivalent to or even better than those for the 800-mg dose.[17-19] However, in our study, it is not expected that even a higher dose of imatinib would have reduced the number of progressions to the extent that was seen with

nilotinib. The 800-mg dose of imatinib has not been shown to have a progression advantage over the 400-mg dose in any study, despite improved early responses. Indeed, both the TOPS and German CML IV studies show similar rates of progression-free survival and event-free survival with the 400-mg and 800-mg doses of imatinib.

Our findings regarding nilotinib differ from results of these studies of imatinib in several important respects. First, nilotinib is a more potent and selective BCR-ABL inhibitor than imatinib. Second, within the first year of therapy, the number of progression events was significantly lower in both nilotinib groups than in the imatinib group, a phenomenon that has not been observed for the 800-mg dose of imatinib. Finally, the overall rates of major molecular response in our study suggest that no plateau of response exists for patients receiving nilotinib. The difference in response between nilotinib and imatinib has increased over time, as compared with 12-month data.

These data are further supported by reports from two ongoing trials of nilotinib in patients with newly diagnosed, chronic-phase CML: the phase 2 trial (NCT00481052) conducted by the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) with 15 months of follow-up and the M.D. Anderson Cancer Center (MDACC) trial (NCT00129740) with 21 months of follow-up. In both of these trials, patients receiving nilotinib had high and rapidly achieved rates of cytogenetic and molecular responses, and only one patient in each study had disease progression while receiving nilotinib (both within the first year of therapy).[20-23] Possible explanations for the differences in progression that were observed between nilotinib and imatinib are nilotinib's increased potency for unmutated BCR-ABL and activity against imatinib-resistant BCR-ABL mutations. Also, nilotinib does not require transport into cells by human organic cation transporter 1 (hOCT1), unlike imatinib.[24] Therefore, the action of nilotinib is not impaired in patients with intrinsically low hOCT1 activity. Thus, nilotinib may inhibit leukemia that would progress with imatinib because of the emergence of clones bearing mutations associated with imatinib resistance.

The IRIS trial established that a complete cytogenetic response and a major molecular response are critical therapeutic milestones associated with good long-term outcomes.[2,5,7] The strong clinical data supporting this notion are embodied by the adoption of these milestones in the definitions of optimal response to imatinib recently put forth by the European LeukemiaNet.[25] In our study, nilotinib led to significantly higher rates of both major molecular response and complete cytogenetic response than did imatinib. These responses were associated with a significantly lower rate of disease progression. Nilotinib at both doses was also associated with fewer suboptimal responses or treatment failures than imatinib. The 300-mg dose of nilotinib had the lowest rates of discontinuation because of adverse events or laboratory abnormalities among the three study groups. Furthermore, no patient had a QTcF interval of more than 500 msec while receiving either dose of nilotinib, and cardiac events were consistent across all study groups. Taken together, these data suggest that second-generation agents that target BCR-ABL, like nilotinib, may become a new standard of care for patients with newly diagnosed, chronic-phase CML.

Additional follow-up will provide information about the potential long-term benefits or disad-

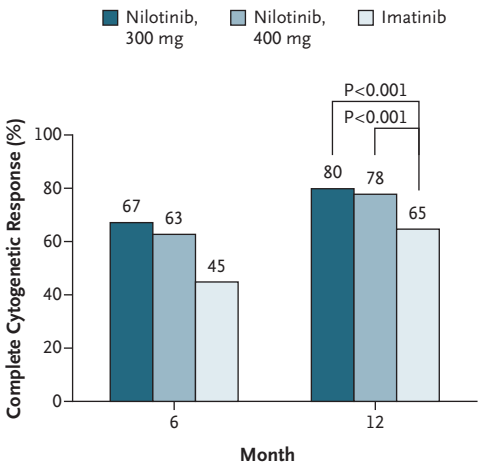

Figure 3. Rates of Complete Cytogenetic Response by 6 and 12 Months.

The results in the intention-to-treat population were calculated by means of the Cochran–Mantel–Haenszel test, stratified according to the Sokal risk group, after the last patient had completed 12 cycles of therapy (with a 28-day duration for each cycle). Nilotinib was administered at a dose of either 300 mg or 400 mg twice daily, and imatinib at a dose of 400 mg once daily.

Table 2. Adverse Events and Newly Occurring or Worsening Hematologic or Biochemical Laboratory Abnormalities in the Safety Population.*

Adverse Event	All Grades†			Grade 3 or 4†		
	Nilotinib, 300 mg (N=279)	Nilotinib, 400 mg (N=277)	Imatinib (N=280)	Nilotinib, 300 mg (N=279)	Nilotinib, 400 mg (N=277)	Imatinib (N=280)
	number of patients (percent)					
Nonhematologic adverse event‡						
Rash	86 (31)	100 (36)	32 (11)	1 (<1)	7 (3)	4 (1)
Headache	39 (14)	58 (21)	23 (8)	3 (1)	3 (1)	0
Nausea	32 (11)	54 (19)	86 (31)	1 (<1)	3 (1)	0
Alopecia	22 (8)	36 (13)	11 (4)	0	0	0
Pruritus	41 (15)	36 (13)	15 (5)	1 (<1)	1 (<1)	0
Myalgia	27 (10)	28 (10)	28 (10)	1 (<1)	0	0
Fatigue	30 (11)	25 (9)	22 (8)	0	2 (1)	1 (<1)
Vomiting	13 (5)	24 (9)	40 (14)	0	3 (1)	0
Diarrhea	22 (8)	18 (6)	60 (21)	2 (1)	0	3 (1)
Muscle spasm	20 (7)	17 (6)	67 (24)	0	2 (1)	2 (1)
Peripheral edema	14 (5)	15 (5)	38 (14)	0	0	0
Eyelid edema	2 (1)	5 (2)	37 (13)	0	1 (<1)	1 (<1)
Periorbital edema	1 (<1)	2 (1)	34 (12)	0	0	0
Hematologic abnormality						
Neutropenia	120 (43)	106 (38)	189 (68)	33 (12)	27 (10)	56 (20)
Thrombocytopenia	133 (48)	136 (49)	156 (56)	28 (10)	33 (12)	24 (9)
Anemia	105 (38)	105 (38)	132 (47)	9 (3)	9 (3)	14 (5)
Biochemical abnormality						
Increased total bilirubin	149 (53)	171 (62)	27 (10)	10 (4)	21 (8)	1 (<1)
Increased alkaline phosphatase	59 (21)	76 (27)	92 (33)	0	0	1 (<1)
Decreased phosphate	88 (32)	94 (34)	126 (45)	13 (5)	13 (5)	21 (8)
Increased glucose	100 (36)	113 (41)	57 (20)	17 (6)	10 (4)	0
Increased lipase	67 (24)	80 (29)	30 (11)	16 (6)	16 (6)	9 (3)
Increased amylase	42 (15)	51 (18)	35 (12)	1 (<1)	3 (1)	4 (1)
Increased creatinine	13 (5)	15 (5)	36 (13)	0	0	1 (<1)
Increased ALT	184 (66)	203 (73)	57 (20)	11 (4)	25 (9)	7 (2)
Increased AST	112 (40)	134 (48)	65 (23)	4 (1)	8 (3)	3 (1)

* ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† Nilotinib was administered at a dose of either 300 mg or 400 mg twice daily, and imatinib at a dose of 400 mg once daily.
‡ Listed are all nonhematologic adverse events that occurred in at least 10% of patients in any group.

vantages of nilotinib therapy. The CML treatment landscape is evolving rapidly. Two ongoing phase 3 studies of two multitargeted, dual BCR-ABL and Src-family kinase inhibitors, dasatinib (NCT00481247) and bosutinib (NCT00574873), may provide further treatment options. It is clear that nilotinib is more effective than imatinib. Further follow-up will provide information on the durability of responses, the development of treatment resistance, and the side-effect profile of nilotinib in the front-line setting. Further studies will be necessary to evaluate cross-resistance mechanisms, sequencing of treatment options, and combinations of agents.

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