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ORIGINAL ARTICLE

Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up

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Evaluating Nilotinib Efficacy and Safety in Clinical Trials Newly Diagnosed Patients compares nilotinib and imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP). With a minimum follow-up of 3 years, major molecular response, molecular response of BCR-ABL $\leqslant$ 0.01% expressed on the international scale (BCR-ABL^{IS}; MR^{4}) and BCR-ABL^{IS} $\leqslant$ 0.0032% (MR$^{4.5}$) rates were significantly higher with nilotinib compared with imatinib, and differences in the depth of molecular response between nilotinib and imatinib have increased over time. No new progressions occurred on treatment since the 2-year analysis. Nilotinib was associated with a significantly lower probability of progression to accelerated phase/blast crisis vs imatinib (two (0.7%) progressions on nilotinib 300 mg twice daily, three (1.1%) on nilotinib 400 mg twice daily and 12 (4.2%) on imatinib). When considering progressions occurring after study treatment discontinuation, the advantage of nilotinib over imatinib in preventing progression remained significant (nine (3.2%) progressions on nilotinib 300 mg twice daily, six (2.1%) on nilotinib 400 mg twice daily and 19 (6.7%) on imatinib). Both nilotinib and imatinib were well tolerated, with minimal changes in safety over time. Nilotinib continues to demonstrate superior efficacy in all key response and outcome parameters compared with imatinib for the treatment of patients with newly diagnosed CML-CP.

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Keywords: chronic myeloid leukemia; ENESTnd; nilotinib; imatinib; progression; newly diagnosed

INTRODUCTION

Nilotinib (Tasigna; Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) is a selective inhibitor of BCR-ABL and a more potent inhibitor than imatinib *in vitro*.[1] Based on data from the Evaluating Nilotinib Efficacy and Safety in Clinical Trials Newly Diagnosed Patients (ENESTnd) phase 3 trial in which nilotinib demonstrated superiority over imatinib, nilotinib has been widely approved throughout the world for the treatment of patients with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP).[2]

ENESTnd is an international, open-label, randomized study comparing the efficacy and safety of nilotinib 300 and 400 mg twice daily and imatinib 400 mg once daily in patients with newly diagnosed Ph+ CML-CP.[3] In previous reports after 1 and 2 years of treatment, nilotinib demonstrated superior efficacy to imatinib with significantly faster and higher rates of complete cytogenetic response (CCyR), major molecular response (MMR), deeper molecular response of BCR-ABL $\leqslant$ 0.01% expressed on the international scale (BCR-ABL^{IS}; MR^{4}) and BCR-ABL^{IS} $\leqslant$ 0.0032% (MR$^{4.5}$).[3,4] Moreover, there were significantly lower rates of progression to accelerated phase/blast crisis (AP/BC) and fewer CML-related deaths in the nilotinib arms when compared with imatinib. The International Randomized Study of Interferon vs STI571 trial showed that most disease progression events on imatinib occurred within the first 3 years of treatment, indicating that this represents an important milestone.[5] This report presents the updated results of the ENESTnd trial for patients within this important 3-year time frame.

MATERIALS AND METHODS

Patients, study design and treatments

Study criteria for eligibility have been extensively described previously.[3,4] Written informed consent was obtained from each patient, and the study was conducted according to the ethical principles of the Declaration of Helsinki. As described previously, patients $\geqslant$18 years of age were eligible for this study if they had newly diagnosed Ph+ CML-CP within the previous 6 months. A total of 846 patients $\geqslant$18 years of age, with newly diagnosed Ph+ CML-CP within the previous 6 months, were randomized to nilotinib 300 mg twice daily ($n = 282$), nilotinib 400 mg twice daily ($n = 281$) or imatinib 400 mg once daily ($n = 283$).[3,4] Randomization was stratified according to Sokal risk score at the time of diagnosis.[3,4] The study was registered at ClinicalTrials.gov (NCT00471497).

As described previously,[3,4] patients in the imatinib arm could be dose-escalated to 400 mg twice daily if they had a suboptimal response per investigator assessment and could receive nilotinib as part of a separate extension study in the case of treatment failure.[6] In contrast, nilotinib-treated patients could not dose-escalate, although patients in the nilotinib 300 mg twice-daily arm could discontinue the study and also enter the extension study to receive nilotinib 400 mg twice daily for cases of

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suboptimal response or treatment failure, and patients in the nilotinib 400 mg twice-daily arm could only enter the extension study to receive imatinib 400 mg twice daily for treatment failure.

Using a central laboratory in Portland, OR, USA (MolecularMD), molecular response was assessed by real-time quantitative PCR at baseline, monthly (1 month = 28 days) for 3 months and every 3 months thereafter. At baseline and at 6, 12, 18 and 24 months, conventional bone marrow cytogenetic analyses were performed on core treatment. After 24 months on core treatment, only patients without MMR or with any clinical indication of progressive disease (that is, additional chromosomal abnormalities on previous bone marrow assessments, increase in BCR-ABL transcripts of at least fivefold) had a cytogenetic assessment. Progression to AP/BC while patients were on treatment was assessed based on hematological and cytogenetic data. Progression events were also reported solely based on the investigators' assessments every 3 months after discontinuation of treatment up to 10 years from randomization and were not censored at the time at which patients received subsequent therapy after discontinuation of treatment in the ENESTnd study. Also, overall survival (OS) information was collected every 3 months up to 10 years from randomization, including follow-up after treatment discontinuation. Only about 5% of patients in each arm were unavailable for these long-term assessments after discontinuation.

Endpoints

As reported, the MMR rate at 1 year was the primary efficacy endpoint.[3,4] MMR was defined as BCR-ABL$^{IS} \leqslant 0.1\%$ by real-time quantitative-PCR in peripheral blood. MMR was assessed conservatively based on evaluation of b3a2 and b2a2 BCR-ABL transcripts. Patients with atypical transcripts or unavailable or missing samples were considered as nonresponders. Other endpoints included the rate of MMR, MR^4 and MR$^{4.5}$ by 3 years; time to progression to AP/BC (defined as progression to AP/BC or death due to CML, whichever occurred first), including events on treatment and events after discontinuation of study treatment; progression-free survival (progression defined as progression to AP/BC or death due to any cause while on treatment); event-free survival (event defined as loss of response (any of complete hematological response, partial response or CCyR), progression to AP/BC or death due to any cause while on treatment); and OS (defined as freedom from death owing to any cause while on treatment or during follow-up after discontinuation of treatment).

Statistical analysis

All efficacy results are reported for the intention-to-treat population; patients were analyzed according to the treatment to which they were randomized. Response rates were provided by specific time points. Patients who had achieved a response at or before a specific time point were considered as responders by that time point. Therefore, this response rate represents the best response rate up to that specific time point. A two-sided stratified Cochran–Mantel–Haenszel test, based on the randomization strata, was used to test the statistical significance of differences in response rates. Time-to-response variables (MMR, MR^4 and MR$^{4.5}$) were also presented by cumulative incidence graphs, which were displayed by an increasing step function. This curve increased each time (after randomization) at which a new responder was recorded and thus increased up to the best recorded response rate. Long-term outcomes—including event-free survival, progression-free survival, time to progression to AP/BC and OS—were analyzed using the Kaplan–Meier method. All time-to-event variables were compared between groups with the stratified log-rank test on the basis of the randomization strata. Hazard ratios (HRs) and 95% confidence intervals were derived from a Cox model stratified by the randomization strata. For all secondary endpoints reported here, *P*-values are provided for descriptive purposes and are not adjusted for multiple comparisons. Safety analyses are reported for the safety population, which included all patients who received at least one dose of study treatment.

RESULTS

Patients and treatments

The data cutoff for this analysis was 27 July 2011, when all patients had either completed 36 months (1 month = 28 days) of treatment or discontinued early. At the time of data cutoff, the median time on treatment (from start of treatment to discontinuation of study treatment) was 36.4 (range, 0.1–46.7) months on nilotinib 300 mg twice daily, 36.6 (range, 0.2–46.0) months on nilotinib 400 mg twice daily and 35.5 (range, 0.0–46.5) months on imatinib. The median time on study (from randomization to last available date on study, including follow-up after discontinuation of treatment) was ~37.6 months across all three arms. The median (25th–75th percentile) dose intensity was 594 (548–600) mg/day in the nilotinib 300 mg twice-daily arm and 778 (594–799) mg/day in the nilotinib 400 mg twice-daily arm. In the imatinib arm, the median dose intensity was 400 (395–470) mg/day.

By the time of data cutoff, ~95% of patients in each treatment arm were still in active follow-up (that is, either remained on treatment or remained in follow-up after discontinuation of study treatment) or completed follow-up (that is, died on treatment or during follow-up after discontinuation of treatment). Overall, 29.1%, 26.3% and 38.2% of patients in the nilotinib 300 mg twice-daily, nilotinib 400 mg twice-daily and imatinib arms, respectively, discontinued core treatment by the time of data cutoff (Table 1). Discontinuations due to adverse events or laboratory abnormalities were observed in 9.9%, 14.2% and 11.0% of patients in the nilotinib 300 mg twice-daily, nilotinib 400 mg twice-daily and imatinib arms, respectively. More patients in the imatinib arm (20.1%) discontinued treatment due to disease progression, treatment failure or suboptimal response compared with the nilotinib 300 mg twice-daily arm (9.9%) or the nilotinib 400 mg twice-daily arm (5.3%).

Efficacy

Consistent with the results at 1 and 2 years of follow-up, the MMR rate by 3 years (Figure 1) was significantly higher for nilotinib 300 mg twice daily (73%, $P \leqslant 0.0001$) and nilotinib 400 mg twice daily (70%, $P \leqslant 0.0001$) compared with imatinib (53%). The rate of MMR at 3 years in patients with evaluable samples was also higher for nilotinib compared with imatinib, with 165 of 195 (85%) patients with evaluable samples achieving MMR in the nilotinib 300 mg twice-daily arm, 161 of 203 patients (79%) in the nilotinib 400 mg twice-daily arm and 109 of 171 (64%) patients in the

Table 1. Patient disposition

	Nilotinib 300 mg twice daily (n = 282) n (%)	*Nilotinib 400 mg twice daily* (n = 281) n (%)	*Imatinib 400 mg once daily* (n = 283) n (%)
Still on active follow-up[a] or died	268 (95.0)	268 (95.4)	267 (94.3)
Still on core treatment	200 (70.9)	207 (73.7)	175 (61.8)
Discontinued core treatment and entered extension study	21 (7.4)[b]	3 (1.1)[c]	35 (12.4)[b]
Discontinued core treatment without entering extension study	61 (21.6)	71 (25.3)	73 (25.8)
Disease progression	2 (0.7)	4 (1.4)	10 (3.5)
Suboptimal response or treatment failure	5 (1.8)	8 (2.8)	12 (4.2)
Adverse events/laboratory abnormalities	28 (9.9)	40 (14.2)	31 (11.0)
Death	4 (1.4)	1 (0.4)	1 (0.4)
Other reason[d]	22 (7.8)	18 (6.4)	19 (6.7)

[a]Patients were either on study drug or in follow-up after discontinuation of study treatment. [b]Patients with suboptimal response or treatment failure were allowed to discontinue core study and enter into extension study. [c]Patients were allowed to enter the extension study only in case of treatment failure, not if they had suboptimal response. [d]Includes abnormal test procedure result(s), condition no longer requires study drug, consent withdrawn, loss to follow-up, administrative problems and protocol deviation.

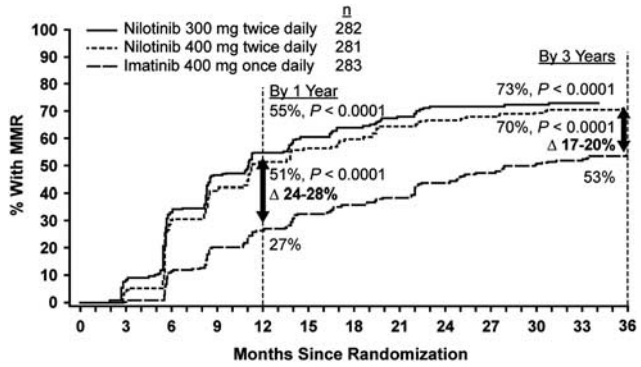

Figure 1. Cumulative incidence of MMR.

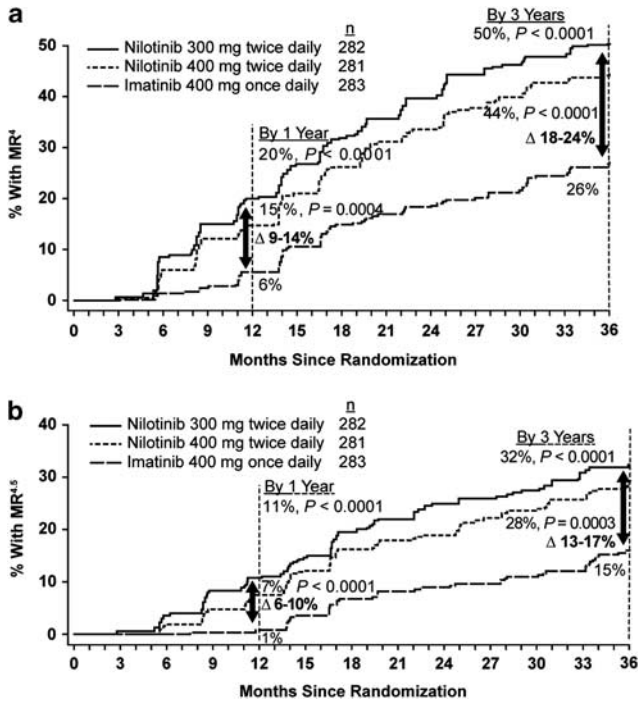

Figure 2. Cumulative incidence of MR^4 (**a**) and $MR^{4.5}$ (**b**). MR^4, molecular response of BCR-ABL $\leqslant$ 0.01% expressed on the international scale ($BCR\text{-}ABL^{IS}$) $\leqslant$ 0.01%; $MR^{4.5}$, molecular response of $BCR\text{-}ABL^{IS} \leqslant 0.0032\%$.

imatinib arm. Overall, 34 patients had a confirmed loss of MMR at any time (nine patients in the nilotinib 300 mg twice-daily arm, 11 patients in the nilotinib 400 mg twice-daily arm and 14 patients in the imatinib arm). Confirmed loss of MMR was transient in some patients: 6 of 9 patients in the nilotinib 300 mg twice-daily arm, 5 of 11 patients in the nilotinib 400 mg twice-daily arm and 6 of 14 patients in the imatinib arm regained MMR after losing it.

Similarly, the rate of MR^4 by 3 years was significantly higher for nilotinib 300 mg twice daily compared with imatinib (50% vs 26%, $P \leqslant 0.0001$) and nilotinib 400 mg twice daily compared with imatinib (44% vs 26%, $P \leqslant 0.0001$; Figure 2a). Also, the achievement of $MR^{4.5}$ by 3 years was significantly higher for nilotinib 300 mg twice daily compared with imatinib (32% vs 15%, $P \leqslant 0.0001$) and for nilotinib 400 mg twice daily compared with imatinib (28% vs 15%, $P = 0.0003$; Figure 2b). Furthermore, the difference in the rates of MR^4 and $MR^{4.5}$ increased over time between the nilotinib and imatinib arms (Figures 2a and b). The difference in the rate of MR^4 increased by approximately twofold between the nilotinib 300 mg twice-daily and imatinib arms, from 14% by 1 year to 24% by 3 years. Similarly, the difference in the rate of $MR^{4.5}$ increased by approximately twofold between the nilotinib 300 mg twice-daily and imatinib arms from 10% by 1 year to 17% by 3 years.

Molecular responses were also deeper in patients who achieved MMR on nilotinib compared with patients who achieved MMR on imatinib. Of the 207 patients who achieved MMR at any time on nilotinib 300 mg twice daily, 70% achieved a response of MR^4 or $MR^{4.5}$ (46% achieved $MR^{4.5}$). Similarly, of the 199 patients who achieved MMR at any time on nilotinib 400 mg twice daily, 65% achieved a response of MR^4 or $MR^{4.5}$ (43% achieved $MR^{4.5}$). In contrast, of the 153 patients who achieved MMR at any time on imatinib, 52% achieved a response of MR^4 or $MR^{4.5}$ (33% achieved $MR^{4.5}$). Rates of MMR, MR^4 and $MR^{4.5}$ by 3 years were significantly higher for both nilotinib arms across low, intermediate and high Sokal risk groups compared with imatinib (Table 2). Note that after the 2-year visit, cytogenetic assessments were not required for all patients; hence, no update on CCyR rates is provided.

There were no new cases of progression to AP/BC on core treatment with or without clonal evolution since the 2-year analysis. Overall, by the 3-year data cutoff, 17 patients had progressed to AP/BC on core treatment (excluding clonal evolution): 2 (0.7%) in the nilotinib 300 mg twice-daily arm, 3 (1.1%) in the nilotinib 400 mg twice-daily arm and 12 (4.2%) in the imatinib arm. Patients receiving either dose of nilotinib had a significantly lower probability of progression to AP/BC on treatment than patients receiving imatinib (HR = 0.16 and $P = 0.0059$ between nilotinib 300 mg twice daily and imatinib, HR = 0.25 and $P = 0.0185$ between nilotinib 400 mg twice daily and imatinib (Table 3)).

Table 2. Best cumulative response according to Sokal risk by 3 years

Sokal risk	*Low*			*Intermediate*			*High*		
	Nilotinib 300 mg twice daily (n = 103) n (%)	*Nilotinib 400 mg twice daily* (n = 103) n (%)	*Imatinib 400 mg once daily* (n = 104) n (%)	*Nilotinib 300 mg twice daily* (n = 101) n (%)	*Nilotinib 400 mg twice daily* (n = 100) n (%)	*Imatinib 400 mg once daily* (n = 101) n (%)	*Nilotinib 300 mg twice daily* (n = 78) n (%)	*Nilotinib 400 mg twice daily* (n = 78) n (%)	*Imatinib 400 mg once daily* (n = 78) n (%)
MMR	79 (76.7)	79 (76.7)	65 (62.5)	76 (75.2)	69 (69.0)	55 (54.5)	52 (66.7)	50 (64.1)	30 (38.5)
MR^4	52 (50.5)	53 (51.5)	35 (33.7)	56 (55.4)	40 (40.0)	25 (24.8)	33 (42.3)	30 (38.5)	14 (17.9)
$MR^{4.5}$	31 (30.1)	35 (34.0)	19 (18.3)	40 (39.6)	22 (22.0)	17 (16.8)	19 (24.4)	21 (26.9)	7 (9.0)

Abbreviations: MMR, major molecular response, molecular response of BCR-ABL $\leqslant$ 0.1% expressed on the international scale ($BCR\text{-}ABL^{IS}$); MR^4, molecular response of $BCR\text{-}ABL^{IS} \leqslant 0.01\%$; $MR^{4.5}$, molecular response of $BCR\text{-}ABL^{IS} \leqslant 0.0032\%$.

Table 3. Long-term endpoints

	Nilotinib 300 mg twice daily (n = 282)	*Nilotinib 400 mg twice daily (n = 281)*	*Imatinib 400 mg once daily (n = 283)*
Progression to AP/BC on core treatment			
Number of events, *n*	2	3	12
Estimated 3-year rate of patients free from progression[a], %	99.3	98.7	95.2
HR (95% CI)	0.16 (0.04–0.71)	0.25 (0.07–0.87)	—
P-value	0.0059	0.0185	—
Progression to AP/BC including clonal evolution on core treatment			
Number of events, *n*	2	5	17
Estimated 3-year rate of patients free from progression[a], %	99.3	97.9	93.2
HR (95% CI)	0.11 (0.03–0.48)	0.28 (0.11–0.77)	—
P-value	0.0003	0.0085	—
Progression to AP/BC on study (ITT analysis)[b]			
Number of events, *n*	9	6	19
Estimated 3-year rate of patients free from progression[a], %	96.7	98.1	93.5
HR (95% CI)	0.46 (0.21–1.02)	0.31 (0.12–0.77)	—
P-value	0.0496	0.0076	—
EFS on core treatment			
Number of events, *n*	10	6	17
Estimated 3-year rate of EFS[a], %	95.3	97.4	93.1
HR (95% CI)	0.55 (0.25–1.21)	0.34 (0.13–0.86)	—
P-value	0.1317	0.0170	—
PFS on core treatment			
Number of events, *n*	6	4	13
Estimated 3-year rate of PFS[a], %	96.9	98.3	94.7
HR (95% CI)	0.44 (0.17–1.15)	0.30 (0.10–0.92)	—
P-value	0.0842	0.0260	—
OS on study (ITT analysis)[b]			
Total number of deaths, *n*	13	8	17
Estimated 3-year rate of OS[a], %	95.1	97.0	94.0
HR (95% CI)	0.75 (0.37–1.55)	0.46 (0.20–1.07)	—
P-value	0.4413	0.0639	—
CML-related deaths, *n*	5	4	14
Estimated 3-year OS considering only CML-related deaths on study[a,b], %	98.1	98.5	95.2
HR (95% CI)	0.35 (0.13–0.97)	0.28 (0.09–0.85)	—
P-value (considering only CML-related deaths)	0.0356	0.0159	—

Abbreviations: AP/BC, accelerated phase/blast crisis; CI, confidence interval; CML, chronic myeloid leukemia; EFS, event-free survival; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival. [a]Estimated by Kaplan–Meier analysis. [b]On study includes an event occurring in core or extension treatment or during the follow-up period after discontinuation of core or extension treatment.

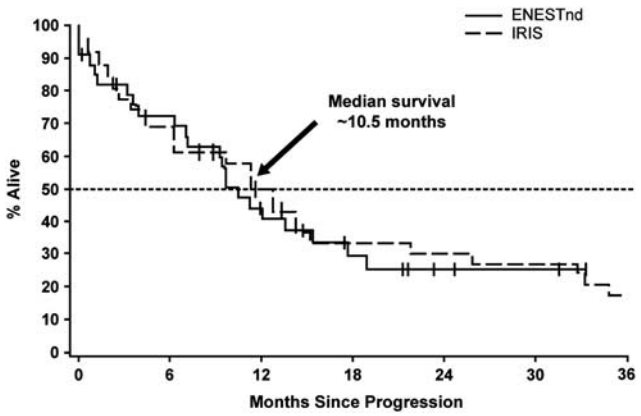

Figure 3. OS after progression to AP/BC in the ENESTnd and International Randomized Study of Interferon vs STI571 trials.

When clonal evolution was considered as a criterion for progression to AP, two additional patients in the nilotinib 400 mg twice-daily arm and five additional patients in the imatinib arm had progression events. Overall, by the 3-year data cutoff, 24 patients progressed to AP/BC on treatment (including clonal evolution): 2 (0.7%) in the nilotinib 300 mg twice-daily arm, 5 (1.8%) in the nilotinib 400 mg twice-daily arm and 17 (6.0%) in the imatinib arm. Patients receiving either dose of nilotinib had a significantly lower probability of progression to AP/BC on treatment than patients receiving imatinib, when clonal evolution was considered as a criterion for progression (HR = 0.11 and $P = 0.0003$ between nilotinib 300 mg twice daily and imatinib, HR = 0.28 and $P = 0.0085$ between nilotinib 400 mg twice daily and imatinib (Table 3)).

Since the 2-year analysis,[4] two new cases of progression to AP/BC (one in the nilotinib 400 mg twice-daily arm and one in the imatinib arm) were observed after discontinuation of study treatment. Overall, by the 3-year data cutoff, 34 patients progressed to AP/BC on treatment or during follow-up after discontinuation of treatment: 9 (3.2%) in the nilotinib 300 mg twice-daily arm, 6 (2.1%) in the nilotinib 400 mg twice-daily arm and 19 (6.7%) in the imatinib arm. When considering progression events occurring on treatment or during follow-up after discontinuation of treatment, the advantage on both nilotinib arms over imatinib in preventing progression remained significant (HR = 0.46 and $P = 0.0496$ between nilotinib 300 mg twice daily and imatinib, HR = 0.31 and $P = 0.0076$ between nilotinib 400 mg twice daily and imatinib).

The long-term outcome of patients who progressed to AP/BC was poor. The median OS of patients after progression to AP/BC in any treatment arm of ENESTnd was only 10.5 months (Figure 3).

Estimated 3-year rates of event-free survival, progression-free survival and OS were all higher for both nilotinib arms compared with the imatinib arm (Table 3). Since the 2-year analysis, three new event-free survival events were observed on treatment, one in each treatment arm (one patient died in the nilotinib 300 mg twice-daily arm, one patient died in the imatinib arm and one patient had a loss of CCyR in the nilotinib 400 mg twice-daily arm). There were two new progression-free survival events observed on treatment: the death events described for the nilotinib 300 mg twice-daily and imatinib arms.

The estimated rates of OS at 3 years were 95.1% for nilotinib 300 mg twice daily, 97.0% for nilotinib 400 mg twice daily and 94.0% for imatinib. In all, 12 new deaths were reported since the 2-year analysis: 4 in the nilotinib 300 mg twice-daily arm (1 on treatment (cardiogenic shock) and 3 after treatment discontinuation (multi-organ failure, ovarian epithelial cancer

Table 4. Important safety findings

Safety parameter	*Cutoff date: 20 August 2010*			*Cutoff date: 27 July 2011*		
	Nilotinib 300 mg twice daily (n = 279) n *(%)*	*Nilotinib 400 mg twice daily (n = 277)* n *(%)*	*Imatinib 400 mg once daily (n = 280)* n *(%)*	*Nilotinib 300 mg twice daily (n = 279)* n *(%)*	*Nilotinib 400 mg twice daily (n = 277)* n *(%)*	*Imatinib 400 mg once daily (n = 280)* n *(%)*
Study drug-related AEs	254 (91.0)	267 (96.4)	259 (92.5)	254 (91.0)	267 (96.4)	262 (93.6)
AEs leading to discontinuation	25 (9.0)	35 (12.6)	30 (10.7)	28 (10.0)	39 (14.1)	32 (11.4)
Study drug-related AEs leading to discontinuation	23 (8.2)	32 (11.6)	28 (10.0)	26 (9.3)	35 (12.6)	29 (10.4)
AEs leading to dose reduction/interruption	154 (55.2)	175 (63.2)	129 (46.1)	160 (57.3)	184 (66.4)	140 (50.0)
Important AEs (any grade, regardless of study drug relationship)						
Symptomatic QT prolongation	4 (1.4)	3 (1.1)	5 (1.8)	5 (1.8)	4 (1.4)	7 (2.5)
Pancreatitis	5 (1.8)	6 (2.2)	2 (0.7)	5 (1.8)	6 (2.2)	2 (0.7)
Hepatotoxicity	4 (1.4)	11 (4.0)	7 (2.5)	4 (1.4)	11 (4.0)	7 (2.5)
Fluid retention	46 (16.5)	63 (22.7)	155 (55.4)	52 (18.6)	65 (23.5)	158 (56.4)
Effusions	3 (1.1)	2 (0.7)	3 (1.1)	5 (1.8)	2 (0.7)	5 (1.8)
Rash	113 (40.5)	130 (46.9)	61 (21.8)	115 (41.2)	130 (46.9)	62 (22.1)
Significant bleeding	8 (2.9)	11 (4.0)	3 (1.1)	8 (2.9)	12 (4.3)	4 (1.4)
CNS hemorrhage	1 (0.4)	1 (0.4)	0	1 (0.4)	2 (0.7)	1 (0.4)
GI hemorrhage	7 (2.5)	10 (3.6)	3 (1.1)	7 (2.5)	11 (4.0)	3 (1.1)
IHD[a]	5 (1.8)	6 (2.2)	1 (0.4)	9 (3.2)	11 (4.0)	3 (1.1)
PAOD[b]	5 (1.8)	3 (1.1)	0	4 (1.4)	3 (1.1)	0
Grade 3/4 laboratory abnormalities						
AST increased	4 (1.4)	8 (2.9)	3 (1.1)	4 (1.4)	8 (2.9)	4 (1.4)
ALT increased	12 (4.3)	26 (9.4)	7 (2.5)	12 (4.3)	26 (9.4)	7 (2.5)
Bilirubin (total) increased	10 (3.6)	22 (7.9)	1 (0.4)	11 (3.9)	22 (7.9)	1 (0.4)
Lipase (blood) increased	20 (7.2)	21 (7.6)	9 (3.2)	21 (7.5)	22 (7.9)	11 (3.9)
Glucose increased	17 (6.1)	13 (4.7)	0	17 (6.1)	15 (5.4)	0
Hemoglobin	10 (3.6)	11 (4.0)	14 (5.0)	11 (3.9)	13 (4.7)	16 (5.7)
Absolute neutrophils (seg. + bands)	33 (11.8)	30 (10.8)	59 (21.1)	33 (11.8)	30 (10.8)	60 (21.4)
Platelet count (direct)	29 (10.4)	34 (12.3)	24 (8.6)	29 (10.4)	34 (12.3)	25 (8.9)
QTc prolongation						
Absolute QTcF ⩾ 480 ms	0	1 (0.4)	1 (0.4)	0	1 (0.4)	2 (0.7)
Absolute QTcF ⩾ 500 ms	0	0	1 (0.4)	0	0	1 (0.4)
QTcF ⩾ 60 ms change from baseline	1 (0.4)	2 (0.7)	0	1 (0.4)	3 (1.1)	1 (0.4)

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; CNS, central nervous system; GI, gastrointestinal; IHD, ischemic heart disease; ms, millisecond; PAOD, peripheral arterial occlusive disease; seg., segmented. AEs were assessed according to the Common Terminology Criteria for Adverse Events (Version 3). [a]In all, 3 of the 11 patients with newly appearing IHD had an event onset date before the 2-year analysis cutoff. Two of these events appeared newly with this data cutoff as a result of a MedDRA version change, and the third event was reported late by the investigator and therefore was not included at the 2-year cutoff. [b]One patient in the nilotinib 300 mg twice-daily arm and two patients in the nilotinib 400 mg twice-daily arm who were reported with PAOD during the 2-year analysis were not included in the 3-year analysis because of changes in the grouped AE search algorithm (the terms 'arteriosclerosis' and 'poor peripheral circulation' were removed from the PAOD search terms used for the 3-year analysis).

and 1 unknown cause)), 2 in the nilotinib 400 mg twice-daily arm (both after treatment discontinuation (1 CML-related and 1 metastatic neoplasm)) and 6 in the imatinib arm (1 on treatment (bronchopneumonia) and 5 after treatment discontinuation (4 CML-related and one pneumonia)). Of the 38 total deaths on study, 23 were considered CML-related. In all, 20 of these 23 deaths were considered CML-related as they were attributed to progressive disease by the investigator. In addition, three patients in the imatinib arm progressed to AP/BC and then died (one patient each due to sepsis, pneumonia and septic shock). These three deaths were also considered CML-related.

When only CML-related deaths were considered, OS was significantly higher in the nilotinib 300 mg twice-daily and nilotinib 400 mg twice-daily arms vs imatinib. The estimated rates of OS for CML-related deaths at 3 years were 98.1%, 98.5% and 95.2% in the nilotinib 300 mg twice-daily, nilotinib 400 mg twice-daily and imatinib arms, respectively (HR = 0.35 and $P = 0.0356$ between nilotinib 300 mg twice daily and imatinib, HR = 0.28 and $P = 0.0159$ between nilotinib 400 mg twice daily and imatinib).

Safety

The safety data are consistent with the previous report at 2 years, and a minimal change in the safety profile was observed since the 2-year analysis. Table 4 summarizes the newly occurring or worsening hematological and biochemical abnormalities, together with clinically important adverse events at 2 and 3 years. One patient experienced newly occurring grade 3/4 neutropenia and another patient experienced thrombocytopenia (both on imatinib), and five additional patients experienced grade 3/4 anemia (one on nilotinib 300 mg twice daily, two on nilotinib 400 mg twice daily and two on imatinib) since the 2-year analysis. Four additional patients experienced newly occurring grade 3/4 lipase increase (one each on both nilotinib arms and two on imatinib), two new cases of grade 3/4 hyperglycemia on nilotinib 400 mg twice daily, one new case of grade 3/4 bilirubin increase on nilotinib 300 mg twice daily and one new case of grade 3/4 aspartate transaminase increase on imatinib since the 2-year analysis.

During their time on treatment, seven patients on nilotinib (four on nilotinib 300 mg twice daily and three on nilotinib 400 mg twice daily) had a peripheral arterial occlusive disease (PAOD)

event; there were no PAOD events on the imatinib arm. Two of these seven patients had PAOD events that occurred between 2 and 3 years, and both occurred in the nilotinib 400 mg twice-daily arm. No patient discontinued the study as a result of PAOD, and pre-existing risk factors for PAOD were identified at study entry in six of these seven patients (85.7%). Adverse events related to ischemic heart disease (IHD) were more frequent with nilotinib than with imatinib: 9 patients (3.2%) in the nilotinib 300 mg twice-daily arm, 11 patients (4.0%) in the nilotinib 400 mg twice-daily arm and 3 patients (1.1%) in the imatinib arm. In all, 11 of these 23 patients had IHD events that occurred between 2 and 3 years on study (4 in the nilotinib 300 mg twice-daily arm, 5 in the nilotinib 400 mg twice-daily arm and 2 in the imatinib arm). Three patients in the nilotinib 400 mg twice-daily arm discontinued study drug as a result of an IHD event. No patient in either nilotinib arm had a QTcF $\geqslant$ 500 ms or LVEF $\leqslant$ 45% during treatment at any time.

DISCUSSION

These results from the ENESTnd study following a minimum follow-up period of 3 years confirm the superiority of nilotinib compared with imatinib for the treatment of patients with newly diagnosed Ph+ CML-CP. Nilotinib induces superior rates of MMR, MR^4 and $MR^{4.5}$ compared with imatinib. Rates of progression to AP or BC are significantly lower among patients treated with nilotinib compared with those treated with imatinib. Also, the risk of CML-related death was lower for patients treated with nilotinib compared with patients treated with imatinib. The incidence of IHD was higher on nilotinib than on imatinib, and several new cases of IHD were observed between 2 and 3 years. PAOD was infrequent on nilotinib and occurred primarily in patients with pre-existing risk factors. The estimated rate of OS at 3 years was numerically higher for nilotinib compared with imatinib, but the differences were not statistically significant. All patients, including those who were discontinued from the study, will continue to be followed up for survival every 3 months for 10 years.

This 3-year follow-up is especially important to the CML community, because the previous landmark International Randomized Study of Interferon vs STI571 study with imatinib indicated that most disease progression events occurred within the first 3 years of treatment.[5] Results from ENESTnd demonstrate that, compared with imatinib, patients treated with nilotinib had lower rates of progression throughout this entire 3-year period. Importantly, the OS of patients who progressed to AP or BC was poor, with a median OS time after progression of only 10.5 months. Interestingly, the median OS of patients following progression in ENESTnd is very similar to that from the International Randomized Study of Interferon vs STI571 trial (Figure 3), showing that current therapies are relatively ineffective at extending life once CML progresses beyond the chronic phase. These data suggest that treatment with first-line nilotinib is a better clinical strategy than starting with imatinib followed by switching to nilotinib for inadequate responses. Results of randomized clinical studies switching patients from imatinib to nilotinib would be required before this could be validated in the community setting.

Importantly, nilotinib demonstrated significantly higher rates of MMR, MR^4 and $MR^{4.5}$ across all Sokal risk groups. In a subanalysis of older patients ($\geqslant$65 years) in ENESTnd with 2 years of follow-up, nilotinib demonstrated high rates of CCyR and MMR similar to those in younger patients and was superior to imatinib.[7] Thus, it is expected that more patients will achieve the deepest levels of response, perhaps including sustained undetectable levels of disease, on nilotinib than on imatinib.[8]

This is significant because an important goal of CML therapy has recently shifted to treatment cessation studies for patients in long-term complete molecular remission. These carefully monitored studies typically require deep molecular responses (that is, a minimum of $MR^{4.5}$ sustained for $\geqslant$2 years) as a prerequisite for discontinuation of tyrosine kinase inhibitor therapy.[9–13] Therefore, there is a need to increase the number of patients with the deepest levels of response, and results from ENESTnd suggest that first-line nilotinib therapy may increase the number of patients eligible for treatment cessation. Taken together, these data suggest that nilotinib is superior to imatinib for the treatment of patients with newly diagnosed Ph+ CML-CP and should be preferred as the first-line therapeutic option for this population.

CONFLICT OF INTEREST

RAL was a consultant for Novartis, BMS, Pfizer and Ariad, received research funding from Novartis, BMS and Ariad, and received honoraria from Novartis. AH received research funding and honoraria from BMS, Novartis, Pfizer, MSD and Ariad. TPH was a consultant for and received honoraria from Novartis, BMS and Ariad and research funding from Novartis, BMS and CSL. REC received research funding from Novartis and BMS, honoraria from Novartis, BMS and Pfizer, and was on the speakers' bureau for Novartis. GE has no relationships to disclose. D-WK was an advisor for and received research funding from Novartis, BMS and Pfizer, received honoraria from Novartis and BMS, was a consultant for Novartis and BMS, and was on the speaker's bureau for Novartis. IWF received research funding from Novartis. MK was on the speakers' bureau, an advisor, and received research funding from Novartis. BM was on the speakers' bureau for BMS and Novartis. RY and NJG are Novartis employees and stock holders. REB is a Novartis employee. GS is a consultant for Novartis, BMS and Pfizer and on the speakers' bureau for Novartis and BMS. HMK received research funding from Novartis, BMS and Pfizer and is a consultant for Novartis.

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AUTHOR CONTRIBUTIONS

AH and HMK designed research; RAL, AH, TPH, REC, D-WK, IWF, GS and HMK performed research; HMK contributed vital new reagents or analytical tool; AH, REC, GE, DW-K, MK, RY and HMK collected data; RAL, AH, TPH, GE, IWF, D-WK, RY, REB, NJG, GS and HMK analyzed and interpreted data; REB and HMK performed statistical analysis; and all authors drafted and approved the manuscript.

REFERENCES

1 Weisberg E, Manley PW, Breitenstein W, Bruggen J, Cowan-Jacob SW, Ray A *et al.* Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. *Cancer Cell* 2005; **7**: 129–141.
2 Tasigna (package insert). Novartis Pharmaceuticals Corporation: East Hanover, NJ, 2010.
3 Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C *et al.* Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2010; **362**: 2251–2259.
4 Kantarjian HM, Hochhaus A, Saglio G, De Souza C, Flinn IW, Stenke L *et al.* Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. *Lancet Oncol* 2011; **12**: 841–851.
5 Hochhaus A, O'Brien SG, Guilhot F, Druker BJ, Branford S, Foroni L *et al.* Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. *Leukemia* 2009; **23**: 1054–1061.
6 Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J *et al.* Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol* 2009; **27**: 6041–6051.
7 Larson R, Bunworasate U, Turkina A, Goldberg A, Dorlhiac-Llacer P, Lopez J *et al.* Nilotinib shows safety and efficacy in older patients ($\geqslant$65 years) with newly diagnosed chronic myeloid leukemia in chronic phase comparable with that in younger patients with chronic myeloid leukemia in chronic phase: results from ENESTnd. *Blood* 2011; **118**: 1608–1609.

8 Cross NCP, White H, Müller MC, Saglio G, Hochhaus A. Standardized definitions of molecular response in chronic myeloid leukemia. *Leukemia* 2012; e-pub ahead of print 16 April 2012; doi:10.1038/leu.2012.104.
9 Mahon FX, Rea D, Guilhot J, Guilhot F, Huguet F, Nicolini F *et al.* Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol* 2010; **11**: 1029–1035.
10 Goh HG, Kim YJ, Kim DW, Kim HJ, Kim SH, Jang SE *et al.* Previous best responses can be re-achieved by resumption after imatinib discontinuation in patients with chronic myeloid leukemia: implication for intermittent imatinib therapy. *Leuk Lymphoma* 2009; **50**: 944–951.
11 Matsuki E, Ono Y, Sakurai M, Kunimoto H, Ishizawa J, Shimizu T *et al.* Discontinuation of imatinib in patients with CML and sustained complete molecular response (CMR) for over 2 years in the Japanese population—an interim analysis of KEIO STIM study. *Blood* 2011; **118**: 1608 [abstract 3765].
12 Rea D, Rousselot P, Nicolini FE, Legros L, Tulliez M, Giraudier S *et al.* Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia (CML) patients (pts) with stable undetectable Bcr-Abl transcripts: results from the French CML Group (FILMC). *Blood* 2011; **118**: 277.
13 Ross DM, Branford S, Seymour JF, Schwarer AP, Arthur C, Bartley PA *et al.* Patients with chronic myeloid leukemia who maintain a complete molecular response after stopping imatinib treatment have evidence of persistent leukemia by DNA PCR. *Leukemia* 2010; **10**: 1719–1724.

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