

Hematology

ISSN: (Print) 1607-8454 (Online) Journal homepage: https://www.tandfonline.com/loi/yhem20

Frontline nilotinib treatment in Turkish patients with Philadelphia chromosome–positive chronic Myeloid Leukemia in chronic phase: updated results with 2 years of follow-up

Guray Saydam, Ibrahim Celalettin Haznedaroglu, Leylagul Kaynar, Akif S. Yavuz, Ridvan Ali, Birol Guvenc, Olga M. Akay, Zafer Baslar, Ugur Ozbek, Mehmet Sonmez, Demet Aydin, Mustafa Pehlivan, Bulent Undar, Simten Dagdas, Orhan Ayyildiz, Gülnur Akin, Ilkiz M. Dag & Osman Ilhan

To cite this article: Guray Saydam, Ibrahim Celalettin Haznedaroglu, Leylagul Kaynar, Akif S. Yavuz, Ridvan Ali, Birol Guvenc, Olga M. Akay, Zafer Baslar, Ugur Ozbek, Mehmet Sonmez, Demet Aydin, Mustafa Pehlivan, Bulent Undar, Simten Dagdas, Orhan Ayyildiz, Gülnur Akin, Ilkiz M. Dag & Osman Ilhan (2018) Frontline nilotinib treatment in Turkish patients with Philadelphia chromosome–positive chronic Myeloid Leukemia in chronic phase: updated results with 2 years of follow-up, Hematology, 23:10, 771-777, DOI: 10.1080/10245332.2018.1498167

To link to this article: https://doi.org/10.1080/10245332.2018.1498167

Published online: 11 Jul 2018.

Submit your article to this journal

Article views: 448

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=yhem20

HEMATOLOGY
2018, VOL. 23, NO. 10, 771–777
https://doi.org/10.1080/10245332.2018.1498167

Taylor & Francis
Taylor & Francis Group

Check for updates

Frontline nilotinib treatment in Turkish patients with Philadelphia chromosome–positive chronic Myeloid Leukemia in chronic phase: updated results with 2 years of follow-up

Guray Saydam[a], Ibrahim Celalettin Haznedaroglu[b], Leylagul Kaynar [c], Akif S. Yavuz[d], Ridvan Ali[e], Birol Guvenc[f], Olga M. Akay[g], Zafer Baslar[h], Ugur Ozbek[i], Mehmet Sonmez[j], Demet Aydin[k], Mustafa Pehlivan[l], Bulent Undar[m], Simten Dagdas[n], Orhan Ayyildiz[o], Gülnur Akin[p], Ilkiz M. Dag[p] and Osman Ilhan[q]

[a]Ege University Medical Faculty Hospital, Department of Internal Medicine, Izmir, Turkey; [b]HacettepeUniversity Medical Faculty Hospital, Department of Internal Medicine, Ankara, Turkey; [c]Erciyes University Medical Faculty Hospital, Hematology Division, Kayseri, Turkey; [d]Istanbul University, Istanbul Medical Faculty, Department of Internal Medicine, Istanbul, Turkey; [e]Uludag University Medical Faculty, Department of Internal Medicine, Bursa, Turkey; [f]Cukurova University Medical Faculty Hospital, Department of Internal Medicine, Adana, Turkey; [g]Eskisehir Osmangazi Unıversity Medical Faculty Hospital, Department of Internal Medicine, Eskisehir, Turkey; [h]Istanbul University Cerrahpasa Medical Faculty, Department of Internal Medicine, Istanbul, Turkey; [i]Acibadem University Faculty of Medicine, Department of Medical Genetics, Istanbul, Turkey; [j]Karadeniz Technical University Medical Faculty, Department of Internal Medicine, Trabzon, Turkey; [k]Okmeydani Training and Research Hospital, Department of Hematology, Istanbul, Turkey; [l]Gaziantep University Medical Faculty, Department of Internal Medicine, Gaziantep, Turkey; [m]Dokuz Eylul University Medical Faculty, Department of Internal Medicine, Izmir, Turkey; [n]Ankara Numune Training and Research Hospital, Department of Internal Medicine, Ankara, Turkey; [o]Dicle University Medical Faculty Hospital, Department of Internal Medicine, Diyarbakir, Turkey; [p]Novartis Pharmaceuticals Corporation, Istanbul, Turkey; [q]Ankara University School of Medicine, Department of Hematology, Ankara, Turkey

ABSTRACT

Objectives: This report presents final results (24 months of follow-up) from the first prospective, national study of frontline nilotinib in chronic myeloid leukemia (CML) patients in Turkey.

Methods: Patients with newly diagnosed Philadelphia chromosome–positive CML in chronic phase (CML-CP; $N = 112$) received nilotinib 300 mg twice daily. The primary endpoint, which was the cumulative rate of major molecular response (MMR; *BCR-ABL1* $\leq 0.1\%$ on the International Scale [*BCR-ABL1*^{IS}]) by 12 months, was previously reported (66.1% [80% CI, 59.7%–72.0%]). ClinicalTrials.gov identifier NCT01274351

Results: By 24 months, 83.0% of patients achieved MMR, and 50.9% achieved MR$^{4.5}$ (*BCR-ABL1*^{IS} $\leq 0.0032\%$). Safety results at 24 months were consistent with those at 12 months. No additional deaths or disease progressions to accelerated phase/blast crisis were observed between 12 and 24 months.

Discussion: Treatment with nilotinib 300 mg twice daily for 2 years provided high MMR with a good safety/tolerability profile in newly diagnosed CML-CP patients in Turkey. Assessment of MMR across time points showed increasing rates through 18 months, after which as lower rate of increase was observed. The safety profile of nilotinib 300 mg twice daily with 24 months of follow-up was similar to that observed at 12 months, and no new safety concerns were identified. These efficacy and safety findings are consistent with the results from the 12-month analysis of this study and from previous nilotinib studies. These findings support nilotinib as an option for frontline treatment of CML-CP.

Conclusion: Frontline nilotinib treatment provided sustained efficacy, with good tolerability, over 24 months in newly diagnosed CML-CP patients.

KEYWORDS
BCR-ABL1; chronic myeloid leukemia; molecular response; nilotinib; tyrosine kinase inhibitor

Introduction

With the availability of BCR-ABL1 tyrosine kinase inhibitors (TKIs), many patients with Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP) now have near-normal life expectancies [1]. The first-generation TKI, imatinib, provided higher rates of responses and improved survival than did the previous standard of care [2–4]. However, some patients are resistant to or intolerant of imatinib treatment [5] and for such patients, other therapy options are needed.

The second-generation TKI nilotinib has been shown to provide improved efficacy compared with imatinib and to be associated with a good overall safety/tolerability profile in patients with CML-CP [6–11]. In the Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENESTnd) study of frontline nilotinib, higher rates of major molecular response (MMR; BCR-ABL1 $\leq 0.1\%$on the International Scale [BCR-ABL1IS]) were observed with nilotinib 300 mg twice daily than with imatinib 400 mg twice daily at 12 months (44% vs 22%; $P < 0.001$). Faster and higher rates of deep molecular responses such as MR$^{4.5}$ (BCR-ABL1IS $\leq 0.0032\%$) were also seen with nilotinib than with imatinib (55.7% vs 32.9% by 6 years;

CONTACT Guray Saydam guray.saydam@ege.edu.tr Ege University Medical Faculty Hospital, Department of Internal Medicine, Izmir 35100, Turkey
© 2018 Informa UK Limited, trading as Taylor & Francis Group

nominal $P < 0.0001$). The higher rate of $MR^{4.5}$ with nilotinib suggests that it may enable more patients to reach the molecular response levels required for participation in clinical trials of treatment-free remission (i.e. stopping TKI treatment without losing molecular response), which is an emerging treatment goal for patients with CML-CP [12,13].

The first prospective, national clinical study of frontline nilotinib in patients with CML in Turkey was conducted between 2011 and 2013. This study evaluated treatment with nilotinib 300 mg twice daily in newly diagnosed Turkish patients with Ph+ CML-CP ($N = 112$), and results from a 12-month analysis were previously reported [14]. The cumulative rate of MMR by 12 months, which was the primary efficacy endpoint, was 66.1% (80% CI, 59.7%–72.0%); 22.3% of patients also achieved $MR^{4.5}$ by 12 months. Nilotinib was generally well tolerated over 12 months of treatment and showed a safety/tolerability profile consistent with that seen in previous studies. Overall, findings from the 12-month analysis supported nilotinib 300 mg twice daily as frontline therapy for patients with CML-CP. Here, we report final 24-month results from this study of frontline nilotinib in Turkish patients with CML-CP.

Materials and methods

Study design and patients

This open-label, multicenter, single-arm, phase 2 study (ClinicalTrials.gov identifier NCT01274351) evaluated nilotinib frontline therapy in patients with newly diagnosed Ph+ CML-CP in Turkey. Patients were enrolled at 15 study centers between 25 January 2011 and 21 March 2013. The study design and patient inclusion/exclusion criteria have been reported previously in detail [14]. Briefly, eligible patients were adults (aged ≥18 years) diagnosed with Ph+ CML-CP within 6 months prior to study entry who had an Eastern Cooperative Oncology Group performance status of ≤2. Those who had previously been treated for CML with agents other than anagrelide and hydroxyurea were not eligible, with the exception of patients requiring treatment pending the start of the study, who could have received ≤31 days of imatinib therapy; no other prior TKI treatment was allowed. Patients who had serious, uncontrolled medical conditions or cardiac function impairment were also excluded.

Patients were treated with oral nilotinib at a dose of 300 mg twice daily for planned study duration of 24 months. Dose reductions or treatment interruptions were permitted in cases of intolerance or toxicity. However, a dose reduction below 400 mg/day was not allowed, and patients who were intolerant of this dose were to discontinue from the study. Patients could also discontinue from the study for other reasons, including disease progression to accelerated phase (AP) or blast crisis (BC) or treatment failure. AP was defined as ≥15% but <30% blasts in peripheral blood or bone marrow, ≥30% blasts and promyelocytes in peripheral blood and bone marrow, ≥20% basophils in peripheral blood, or thrombocytopenia (>100 × 109 platelets/L) not associated with treatment. BC was defined as ≥30% blasts in peripheral blood or extramedullary involvement (excluding hepatosplenomegaly). Treatment failure was defined as the absence of a complete hematologic response (CHR) or a cytogenetic response (i.e. >95% Ph+ metaphases) at 6 months; the absence of a partial cytogenetic response (PCyR; i.e. >35% Ph+ metaphases) at 12 months; the absence of a complete cytogenetic response (CCyR; i.e. >0% Ph+ metaphases) at 18 months; or loss of CHR, PCyR, or CCyR, progression to AP/BC, or an increase in white blood cell counts at any time.

Ethics

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and all local laws and regulations. All patients provided written informed consent prior to enrollment in the study. The study protocol and all amendments were approved by the institutional review board, independent ethics committee, or research ethics board at each study center.

Study endpoints and assessments

The primary efficacy endpoint was the cumulative rate of MMR by 12 months; cumulative rates of MMR across assessment time points, time to and duration of MMR, and the cumulative rate of $MR^{4.5}$ were also assessed. Cytogenetic and hematologic responses were evaluated based on rates of CCyR and CHR, and clinical outcomes were evaluated based on rates of progression-free survival (PFS; defined as the time from the first dose of study drug until progression to AP/BC or death from any cause) and event-free survival (EFS; defined as the time from the first dose of study drug until any of the following: loss of CHR, loss of PCyR/CCyR, progression to AP/BC, or death from any cause). Molecular and cytogenetic response rates were also assessed based on baseline Sokal risk and achievement of BCR-ABL1IS ≤10% at 3 months.

Details regarding study assessments have previously been reported [14]. Briefly, molecular responses were evaluated based on real-time quantitative polymerase chain reaction analysis of peripheral blood samples collected at months 3, 6, 9, 12, 15, 18, 21, and 24. Real-time quantitative polymerase chain reaction assays were performed at a single European Treatment and Outcome Study (EUTOS)–

standardized central laboratory [15]; results were reported as a ratio of BCR-ABL1 to ABL1 and were standardized to the IS. Cytogenetic responses were evaluated via bone marrow aspirations and/or biopsies at 6 and 12 months and at the final study visit or until CCyR or MMR was achieved. Hematologic assessments were performed every 15 days for the first 3 months, every month through 12 months, and every 3 months thereafter through 24 months. Safety was evaluated throughout the study based on physical examinations, adverse event (AE) reporting (using the Common Terminology Criteria for Adverse Events v3.0), and clinical laboratory assessments. For patients who discontinued early from the study, follow-up for survival was performed every 3 months through 24 months after study initiation.

Statistical analyses

Sample size calculation was previously described [14]. Efficacy analyses were performed in the intent-to-treat population, and safety analyses were performed in the safety population, which included all patients who received ≥1 dose of nilotinib and had ≥1 safety assessment post baseline. For analysis of the primary efficacy endpoint, patients who did not have evaluable data for the primary endpoint or who discontinued early from the study were considered non-responders. Descriptive summary statistics were provided for secondary efficacy endpoints, safety parameters, and patient baseline characteristics.

Results

Patients

A total of 112 patients with Ph+ CML-CP were enrolled, all of whom received treatment with nilotinib 300 mg twice daily. Baseline characteristics of the patient population have previously been reported [14]. Briefly, the median age was 47 years (range, 19–78 years), and 56.3% of patients were male. A higher proportion of patients had low Sokal risk scores (54.5%) than intermediate or high Sokal risk scores (39.3% and 6.3%, respectively). Among enrolled patients, 92 (82.1%) completed 24 months of treatment (Table 1); of the 20 patients (17.9%) who discontinued before month 24, 15 did so before month 12. AEs ($n = 9$ [8.0%]) and withdrawal of consent ($n = 4$ [3.6%]) were the most common reasons for discontinuation; 2 patients discontinued due to both AEs and withdrawal of consent. Overall, patients received nilotinib treatment for a median duration of 713 days (range, 3–728 days); the median duration of follow-up was 719 days (range, 3–732 days).

Table 1. Patient disposition.

Patients, *n* (%)	Nilotinib 300 mg twice daily (*N* = 112)
Completed 24 months	92 (82.1)
Discontinued before month 24	20 (17.9)
Reasons for discontinuation	
Adverse events[a]	9 (8.0)[b]
Withdrawal of consent	4 (3.6)[b]
Disease progression	3 (2.7)
Death	2 (1.8)
Pregnancy	1 (0.9)
Loss to follow-up	1 (0.9)
Other[c]	2 (1.8)

[a]Adverse events leading to discontinuation included grade 4 hematologic toxicity ($n = 1$), grade 4 thrombocytopenia and grade 4 neutropenia ($n = 1$), acute pancreatitis ($n = 1$), chest pain ($n = 1$; patient had unstable angina and was included among the 4 patients with ischemic heart disease), brain tumor ($n = 1$), and adverse events of unknown cause ($n = 4$).

[b]Two patients discontinued treatment due to both adverse events and withdrawal of consent.

[c]Other reasons for discontinuation included noncompliance with study protocol ($n = 1$) and study drug withheld due to hospitalization ($n = 1$).

Efficacy

The primary efficacy endpoint was the cumulative rate of MMR by 12 months, which was previously reported (66.1% [80% CI, 59.7%–72.0%]) [14]. By 24 months, the cumulative rate of MMR was 83.0% (93 patients; Table 2). Cumulative rates of MMR across time points through month 24 are shown in Figure 1. In addition to the 74 patients who had achieved MMR by 12 months, 10 achieved MMR between 12 and 15 months, and another 8 achieved MMR between 15 and 18 months; only 1 additional patient achieved MMR between 18 and 24 months. Among the 93 patients who achieved MMR by 24 months, the median time to MMR was 194 days (range, 90–637 days). Twelve of these 93 patients had a subsequent loss of MMR (defined as BCR-ABL1IS >0.1%, disease progression, or death); among these 12 patients, the median duration of MMR was 91 days (range, 85–102 days). Excluding the patients with a loss of MMR, the noncumulative rate of MMR at 24 months was 72.3% (81 patients). The proportion of patients who achieved a deep molecular response of $MR^{4.5}$ by 24 months was 50.9% (57 patients) compared with 21.4% (24 patients) by 12 months.

Table 2. Molecular, cytogenetic, and hematologic responses

Patients, *n* (%)	Nilotinib 300 mg twice daily (*N* = 112)
Molecular response	
Cumulative rate of MMR by 24 months	93 (83.0)
Cytogenetic response	
Cumulative rate of CCyR by 24 months	100 (89.3)
Noncumulative rate of CCyR	
At 3 months	86 (76.8)
At 6 months	89 (79.5)
At 12 months	84 (75.0)
At 24 months	90 (80.4)
Hematologic response	
Cumulative rate of CHR by 24 months	109 (97.3)

Note: CCyR: complete cytogenetic response; CHR: complete hematologic response; IS: International Scale; MMR: major molecular response (*BCR-ABL1*^{IS} ≤0.1%); $MR^{4.5}$:*BCR-ABL1*^{IS} ≤0.0032%.

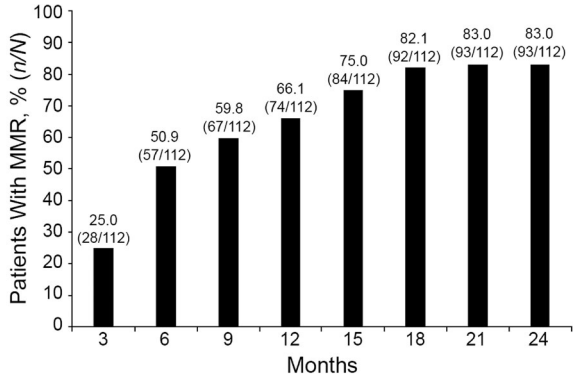


Figure 1. Cumulative rates of major molecular response across time points through month 24. IS: International Scale; MMR: major molecular response (BCR-ABL1IS ≤0.1%).

The cumulative rates of CCyR and CHR by 24 months were the same as the rates by 12 months [14]: 100 patients (89.3%) achieved CCyR and 109 (97.3%) achieved CHR by 24 months. As previously reported, the median time to CCyR among the 100 patients who achieved CCyR was 90 days (range, 78–362 days). Noncumulative rates of CCyR at 3, 6, 12, and 24 months are presented in Table 2 and were generally similar across time points. Among the 109 patients who achieved CHR by 24 months, the median time to CHR was 29 days (range, 22–33 days).

Rates of molecular and cytogenetic responses were evaluated in subgroups of patients based on Sokal risk category at baseline (Table 3). Although the number of patients with high Sokal risk was small, a general trend toward higher MMR rates with lower Sokal risk was seen across time points. As previously reported [14], 80.4% of patients achieved BCR-ABL1IS ≤10% at 3 months. Evaluation of molecular and cytogenetic responses based on achievement of this milestone showed higher response rates among patients who had BCR-ABL1IS ≤10% at 3 months than among those who did not (Table 4), although these data should be interpreted with caution due to the small number of patients without BCR-ABL1IS ≤10% at 3 months.

Table 3. Molecular and cytogenetic response rates by baseline Sokal risk category

	Sokal risk category at baseline		
Patients, *n/N* (%)	Low	Intermediate	High
MMR			
3 months			
Cumulative	18/61 (29.5)	9/44 (20.5)	1/7 (14.3)
Noncumulative	18/57 (31.6)	9/41 (22.0)	1/7 (14.3)
12 months			
Cumulative	43/61 (70.5)	27/44 (61.4)	4/7 (57.1)
Noncumulative	37/50 (74.0)	22/34 (64.7)	3/5 (60.0)
24 months			
Cumulative	53/61 (86.9)	34/44 (77.3)	6/7 (85.7)
Noncumulative	45/47 (95.7)	31/35 (88.6)	6/6 (100.0)
CCyR			
3 months			
Cumulative	44/61 (72.1)	36/44 (81.8)	6/7 (85.7)
Noncumulative	44/54 (81.5)	36/41 (87.8)	6/7 (85.7)
12 months			
Cumulative	55/61 (90.2)	39/44 (88.6)	6/7 (85.7)
Noncumulative	47/49 (95.9)	32/36 (88.9)	5/6 (83.3)
24 months			
Cumulative	55/61 (90.2)	39/44 (88.6)	6/7 (85.7)
Noncumulative	50/50 (100.0)	34/36 (94.4)	6/6 (100.0)
$MR^{4.5}$			
12 months (noncumulative)	14/61 (23.0)	8/44 (18.2)	2/7 (28.6)
24 months (noncumulative)	32/61 (52.5)	23/44 (52.3)	2/7 (28.6)

Note: CCyR: complete cytogenetic response; IS: International Scale; MMR: major molecular response (*BCR-ABL1*^{IS} ≤0.1%); $MR^{4.5}$: *BCR-ABL1*^{IS} ≤0.0032%.

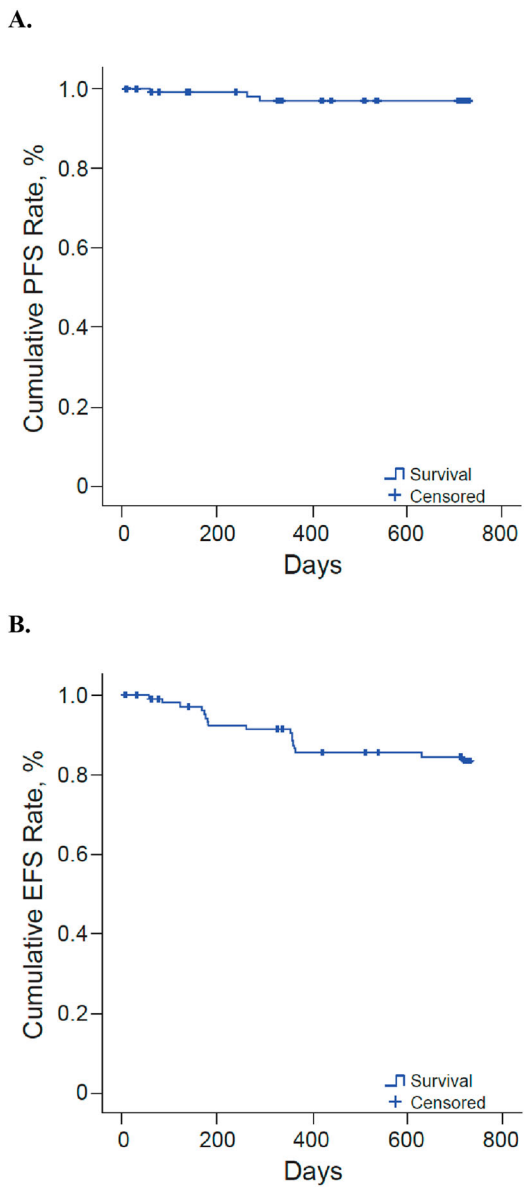
Table 4. Molecular and cytogenetic response rates by achievement of *BCR-ABL1*^{IS} ≤10% at 3 months.

	BCR-ABL1^{IS} at 3 months[a]	
Patients, *n* (%)	≤10% (*n* = 90)	>10% (*n* = 15)
MMR		
12 months (cumulative)	70 (77.8)	4 (26.7)
24 months (cumulative)	84 (93.3)	9 (60.0)
CCyR		
12 months (cumulative)	89 (98.9)	11 (73.3)
24 months (cumulative)	89 (98.9)	11 (73.3)
$MR^{4.5}$		
12 months (noncumulative)	24 (26.7)	0
24 months (noncumulative)	52 (57.8)	5 (33.3)

CCyR: complete cytogenetic response; IS: International Scale; MMR: major molecular response (*BCR-ABL1*^{IS} ≤0.1%); $MR^{4.5}$:*BCR-ABL1*^{IS} ≤0.0032%.
[a]*BCR-ABL1*^{IS} levels at 3 months were unknown for 7 patients, as they discontinued from the study before 3 months.

One patient (0.9%) progressed to BC, and 2 patients (1.8%) died (both due to myocardial infarction) by 12 months; no additional disease progressions to AP/BC or deaths were reported between 12 and 24 months. The estimated 2-year rate of PFS (proportion of patients with no progression to AP/BC or death from any cause) was 97.1%, and the median duration of PFS was not reached by 2 years (Figure 2(A)). The 2 patients who died due to myocardial infarction have been described previously in detail [14]. Briefly, 1 patient (male, aged 75 years) did not have any known cardiovascular risk factors at baseline and died after 57 days on study treatment. The other patient (male, aged 72 years) had a prior myocardial infarction not reported during screening. The patient had a prolonged QT interval on study that led to treatment interruption for 15 days, declined to undergo the recommended angiography and bypass surgery, and died 119 days following resumption of treatment (total of 263 days on study before death).

Analysis of EFS showed that 17 patients experienced an EFS event (loss of CHR, loss of PCyR/CCyR, progression to AP/BC, or death from any cause) by 24 months, resulting in an estimated 2-year EFS rate of 83.3%; the median duration of EFS was not reached by 2 years (Figure 2(B)). Fourteen of the 17 patients with EFS events experienced the event(s) by 12 months; these included 9 patients with loss of CCyR, 2 with loss of CHR, 2 who died, and 1 with loss of PCyR and progression to BC. Of the remaining 3



EFS: event-free survival; PFS: progression-free survival.

Figure 2. Cumulative rates of (A) progression-free survival and (B) event-free survival by 24 months.

patients, who experienced an EFS event between 12 and 24 months, 2 had loss of CCyR and 1 had loss of CHR.

Safety

The safety profile of nilotinib 300 mg twice daily with 24 months of follow-up was similar to that observed at 12 months [14], and no new safety concerns were identified. The most commonly reported non-hematologic AEs (any grade) were hyperbilirubinemia (15.2%), pruritus (15.2%), rash (12.5%), alanine aminotransferase increased (11.6%), and influenza (11.6%; Table 5). Hematologic AEs (any grade) that occurred in >1 patient were thrombocytopenia (20.5%), decreased hemoglobin (6.3%), neutropenia (6.3%), and anemia (4.5). Overall, rates of non-hematologic and

Table 5. All-grade and grade ¾ adverse events

	Nilotinib 300 mg twice daily ($N = 112$)	
Patients, *n* (%)	All-grade AEs	Grade 3/4 AEs
Non-hematologic AEs in >5% of patients		
Hyperbilirubinemia	17 (15.2)	1 (0.9)
Pruritus	17 (15.2)	2 (1.8)
Rash	14 (12.5)	0
Alanine aminotransferase increased	13 (11.6)	0
Influenza	13 (11.6)	0
Blood triglycerides increased	11 (9.8)	0
Hypercholesterolemia	11 (9.8)	0
Lipase increased	11 (9.8)	7 (6.3)
Blood alkaline phosphatase increased	10 (8.9)	0
Leukopenia	10 (8.9)	0
Pain in extremity	8 (7.1)	1 (0.9)
Upper respiratory tract infection	8 (7.1)	0
Abdominal pain	7 (6.3)	0
Alopecia	7 (6.3)	0
Amylase increased	7 (6.3)	2 (1.8)
Blood phosphorus decreased	7 (6.3)	6 (5.4)
Constipation	7 (6.3)	0
Myalgia	7 (6.3)	0
Abdominal pain upper	6 (5.4)	0
Chest pain	6 (5.4)	0
Hematologic AEs in >1 patient		
Thrombocytopenia	23 (20.5)	8 (7.1)
Hemoglobin decreased	7 (6.3)	0
Neutropenia	7 (6.3)	3 (2.7)
Anemia	5 (4.5)	0
Selected AEs of interest[a] *in >1 patient*		
Hypophosphatemia	2 (1.8)	0
Ischemic heart disease[b]	4 (3.6)	3 (2.7)
Hyperglycemia	3 (2.7)	0
Hypertension	2 (1.8)	0

Note: AE: adverse event.
[a]Selected AEs that have been reported with nilotinib [16,17].
[b]Includes acute myocardial infarction ($n = 2$, both grade 4), myocardial ischemia ($n = 1$, grade 2), and angina unstable ($n = 1$, grade 4).

hematologic AEs at 24 months were not substantially higher than those reported at 12 months [14]. Incidences of hyperglycemia and hypertension, which have been reported previously with nilotinib [16,17], were low and unchanged from the 12-month analysis (2.7% and 1.8%, respectively). However, most AEs were grade 1/2 in severity, with grade 3/4 AEs reported in 104 patients (92.9%). The most commonly reported grade 3/4 AEs were thrombocytopenia (7.1%), lipase increased (6.3%), and blood phosphorus decreased (5.4%). Reported influenza rate (11.6%) was high but not led to discontinuation.

The proportion of patients who temporarily or permanently discontinued nilotinib treatment due to an AE (49 [43.8%]) was the same as that previously observed at 12 months [14]. The most common AEs leading to treatment interruption or discontinuation were thrombocytopenia (10 [8.9%]), increased lipase (10 [8.9%]), hyperbilirubinemia (9 [8.0%]), and neutropenia (5 [4.5%]). As was reported in the 12-month analysis [14], 4 patients (3.6%) had ischemic heart disease, including the 2 patients described earlier who died of myocardial infarction and 2 patients who completed the study with no interruption of nilotinib treatment. No additional patients experienced ischemic heart disease between 12 and 24 months, and no patients had ischemic cerebrovascular events

or peripheral artery disease at any time on study. The incidence of QTc prolongation was also unchanged from the 12-month analysis (4 patients [3.6%]) [14].

Discussion

Final results, based on 24 months of follow-up, from the first prospective, national study of frontline nilotinib in patients with CML in Turkey are reported herein. Among 112 patients with newly diagnosed CML-CP, nilotinib 300 mg twice daily provided high rates of molecular response, with a cumulative rate of MMR of 83.0% by 24 months compared with 66.1% by 12 months (primary endpoint). In addition, 50.9% of patients achieved a deep molecular response of $MR^{4.5}$ by 24 months compared with 21.4% by 12 months. Cumulative rates of CCyR and CHR remained stable between 12 and 24 months (89.3% and 97.3%, respectively). Thus, nilotinib demonstrated sustained efficacy through 24 months in newly diagnosed patients with CML-CP.

Assessment of MMR across time points showed increasing rates through 18 months, after which as lower rate of increase was observed. This finding is similar to that seen in the ENESTnd study, in which MMR rates with nilotinib 300 mg twice daily showed substantial increases through 24 months, after which smaller increases through 6 years were observed (55% by 1 year, 71% by 2 years, and 77% by 6 years) [10,11]. Notably, rates of $MR^{4.5}$ with nilotinib 300 mg twice daily in ENESTnd increased from 11% by 1 year to 25% by 2 years and continued to increase over time to 32%, 40%, 54%, and 56% by 3, 4, 5, and 6 years, respectively. Similarly, the rate of $MR^{4.5}$ in our study increased from 21.4% by 1 year to 50.9% by 2 years. As previously discussed [14], the relatively higher response rates seen in our study compared with the ENESTnd study may be related to differences between the 2 patient populations.

Safety findings with nilotinib 300 mg twice daily at 24 months were similar to those observed at 12 months and were generally consistent with those reported in previous studies of nilotinib [6–8,10,11,14,18,19]. The majority of AEs were grade 1/2 in severity and incidences of most AEs, including hematologic AEs, were similar between the present analysis and the 12-month analysis, indicating that few new cases occurred between 12 and 24 months. By 24 months, only 9 patients (8.0%) had discontinued from the study due to AEs, similar to the 9% rate of AE-related discontinuations observed with nilotinib 300 mg twice daily with 24 months of follow-up in ENESTnd [7]. The incidence of cardiovascular events (ischemic heart disease [3.6%], ischemic cerebrovascular events [0%], and peripheral artery disease [0%]) was unchanged at 24 months compared with 12 months. Other than the 1 patient who progressed to BC and 2 patients who died of myocardial infarction by 12 months, which was previously reported [14], no additional patients had disease progression or died between 12 and 24 months. Overall, nilotinib was well tolerated over 24 months of treatment, with no new safety concerns identified.

In summary, treatment with nilotinib 300 mg twice daily for 2 years provided high molecular response rates with a good safety/tolerability profile in Turkish patients with newly diagnosed CML-CP. These efficacy and safety findings are consistent with the results from the 12-month analysis of this study and with results from previous studies of nilotinib. These findings support nilotinib as an option for frontline treatment of CML-CP.

Geolocation information

BCR-ABL1; chronic myeloid leukemia; molecular response; nilotinib; tyrosine kinase inhibitor

Acknowledgements

Medical editorial assistance was provided by Joy Loh, PhD, of Articulate Science LLC, and was funded by Novartis Pharmaceuticals Corporation.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Novartis Pharmaceuticals Corporation.

Data availability statement

The data that support the findings of this study are available from the corresponding author, [GS], upon reasonable request.

ORCID

Leylagul Kaynar http://orcid.org/0000-0002-2035-9462

References

[1] Bower H, Björkholm M, Dickman PW, et al. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol. 2016;34:2851–2857.

[2] Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. 2006;355:2408–2417.

[3] Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med. 2003;349:1423–1432.

[4] O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003;348:994–1004.
[5] Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia. Blood. 2013;122:872–884.
[6] Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362:2251–2259.
[7] Kantarjian HM, Hochhaus A, Saglio G, 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.
[8] Larson RA, Hochhaus A, Hughes TP, et al. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. Leukemia. 2012;26:2197–2203.
[9] Hughes TP, Saglio G, Kantarjian HM, et al. Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. Blood. 2014;123:1353–1360.
[10] Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 2016;30:1044–1054.
[11] Hughes TP, Larson RA, Kim DW, et al. Efficacy and safety of nilotinib vs imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase: 6-year follow-up of ENESTnd [abstract]. Haematologica. 2015;100:(Supplement).Abstract P228.
[12] Hughes TP, Ross DM. Moving treatment-free remission into mainstream clinical practice in CML. Blood. 2016;128:17–23.
[13] Saußele S, Richter J, Hochhaus A, et al. The concept of treatment-free remission in chronic myeloid leukemia. Leukemia. 2016;30:1638–1647.
[14] Saydam G, Haznedaroglu IC, Kaynar L, et al. Outcomes with frontline nilotinib treatment in Turkish patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase. Expert Opin Pharmacother. 2016;17:1851–1858.
[15] Cross NC, White HE, Müller MC, et al. Standardized definitions of molecular response in chronic myeloid leukemia. Leukemia. 2012;26:2172–2175.
[16] Tasigna (nilotinib) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation;2015.
[17] Tasigna (nilotinib) [summary of product characteristics]. Nuremberg, Germany: Novartis Pharma GmbH;2015.
[18] Wang J, Shen ZX, Saglio G, et al. Phase 3 study of nilotinib vs imatinib in Chinese patients with newly diagnosed chronic myeloid leukemia in chronic phase: ENESTchina. Blood. 2015;125:2771–2778.
[19] Hochhaus A, Rosti G, Cross NC, et al. Frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the European ENEST1st study. Leukemia. 2016;30:57–64.