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Research paper

Efficacy and safety of nilotinib 300 mg twice daily in patients with chronic myeloid leukemia in chronic phase who are intolerant to prior tyrosine kinase inhibitors: Results from the Phase IIIb ENESTswift study

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ABSTRACT

Background: Some patients receiving a tyrosine kinase inhibitor (TKI) for the first-line treatment of chronic phase chronic myeloid leukemia (CML-CP) experience intolerable adverse events. Management strategies include dose adjustments, interrupting or discontinuing therapy, or switching to an alternative TKI.

Methods: This multicenter, single-arm, Phase IIIb study included CML-CP patients intolerant of, but responsive to, first-line treatment with imatinib or dasatinib. All patients were switched to nilotinib 300 mg bid for up to 24 months. The primary endpoint was achievement of MR4.5 (BCR-ABL transcript level of ≤0.0032% on the International Scale) by 24 months.

Results: Twenty patients were enrolled in the study (16 imatinib-intolerant, 4 dasatinib-intolerant); which was halted early because of low recruitment. After the switch to nilotinib 300 mg bid, MR4.5 at any time point up to month 24 was achieved in 10 of 20 patients (50%) in the full analysis set. Of the non-hematological adverse events associated with intolerance to prior imatinib or dasatinib, 74% resolved within 12 weeks of switching to nilotinib 300 mg bid.

Conclusion: Nilotinib 300 mg bid shows minimal cross intolerance in patients with CML-CP who have prior toxicities to other TKIs and can lead to deep molecular responses.

1. Introduction

Guidelines recommend that the tyrosine kinase inhibitors (TKIs) imatinib, nilotinib, and dasatinib be used for first-line treatment of Philadelphia chromosome-positive (Ph+) chronic phase chronic myeloid leukemia (CML-CP) [1,2]. The goal of TKI therapy in CML-CP is to achieve a major molecular response (MMR; a ≥3 log reduction in BCR-ABL1 level corresponding to a BCR-ABL1 level of ≤0.1% on the International Scale [IS]) within 12 months of starting treatment and eventually a deep molecular response, as well as preventing progression to accelerated phase CML (CML-AP) or blast phase CML (CML-BP) [1–3]. The TKIs inhibit BCR-ABL1, a fusion protein that is a constitutively active, oncogenic tyrosine kinase that plays a critical role in CML pathogenesis. Measurement of BCR-ABL1 transcript levels using real-time quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) is the preferred method for monitoring the response to TKI

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therapy [1]. Regular monitoring of BCR-ABL1 levels should continue after a response has been achieved in order to detect emerging resistance or poor adherence [1,2].

Patients with newly diagnosed CML-CP who achieve a deep molecular response with TKI therapy have improved long-term outcomes [3–5], with MR4.5 (a ≥4.5 log reduction in BCR-ABL1 level corresponding to a BCR-ABL1 level of ≤0.0032% IS) being a better predictor of survival than complete cytogenetic response [5]. Achieving a deep molecular response appears more likely with the second-generation TKIs nilotinib or dasatinib than with the first-generation TKI imatinib [6–12]. Current guidelines recommend lifelong TKI therapy for most CML-CP patients [1,2]. However, recent data indicate that maintenance of treatment-free remission may be possible in patients who achieve a sustained deep molecular response [13]. Accordingly, discontinuation of TKI therapy may be feasible in carefully selected patients who achieve and maintain a deep molecular response [14,15].

The TKIs differ in terms of their adverse event (AE) profiles, possibly reflecting differences in their molecular mechanisms of action and target profiles [16]. For example, non-hematological AEs reported with imatinib include gastrointestinal AEs, edema, rash, and fatigue [1]; those reported with dasatinib include pleural effusion [11,17] and pulmonary arterial hypertension [18,19], ischemic heart disease (IHD) and ischemic cerebrovascular events (ICVE) [20]; and those reported with nilotinib include prolongation of the Fridericia-corrected QT (QTcF) interval [21] and an increased risk of cardiovascular events (including peripheral artery occlusive disease [PAOD], IHD and ICVE) [6]. AEs may negatively impact health-related quality of life (HRQoL), reduce treatment adherence, and lead to treatment interruption or discontinuation, ultimately resulting in suboptimal outcomes [22–25]. Switching to an alternative TKI is an option in patients who are intolerant of first-line TKI therapy. This strategy is supported by *post-hoc* data [26] from a Phase II trial [27,28] showing minimal cross intolerance with nilotinib 400 mg twice daily (bid) in CML patients who experienced imatinib-related AEs. In addition, the Phase II ENRICH study showed that switching to nilotinib 300 mg bid can mitigate chronic low-grade non-hematological AEs associated with imatinib in CML-CP patients [29].

In a number of countries, nilotinib 400 mg bid is the approved dosage in patients with CML-CP and resistance or intolerance to prior TKI therapy, whereas nilotinib 300 mg bid is the approved dosage in newly diagnosed CML-CP patients. Although some reimbursement agencies may allow patients intolerant to TKIs to switch to nilotinib 300 mg bid (instead of the recommended 400 mg bid dose in the second-line setting), limited data are available to support the use of nilotinib 300 mg bid in these patients [29].

The aim of the current study, ENESTswift, was to assess the efficacy and safety of switching to nilotinib 300 mg bid in CML-CP patients who were intolerant of first-line treatment with imatinib or dasatinib, without having demonstrated treatment resistance, and who were yet to achieve MR4.5.

2. Methods

2.1. Study design and population

ENESTswift was a multicenter, single-arm, Phase IIIb study evaluating the safety and efficacy of nilotinib in CML-CP patients intolerant of first-line treatment with imatinib or dasatinib and not in MR4.5 (NCT02108951). Eligibility criteria included age ≥18 years, an Eastern Cooperative Oncology Group performance status of 0–2, Ph+ CML-CP with BCR-ABL1 quantifiable by qRT-PCR, ≥3 months' therapy with imatinib or dasatinib or both, BCR-ABL1 level of < 1% IS during imatinib or dasatinib treatment, and experience of any non-hematological AEs (any grade) that persisted for ≥1 month or recurred despite supportive care. Patients requiring interruption of imatinib or dasatinib (dose interruption of ≤28 consecutive days) because of non-hematological AEs were also eligible. Key exclusion criteria were: prior nilotinib; prior CML-AP, CML-BP, or allogeneic stem cell transplantation; documented MR4.5 at the screening visit; presence of a nilotinib-resistant kinase mutation (mutation analysis not mandatory); known impaired cardiac function; cytokine therapy within 4 weeks of study entry. The study was conducted in accordance with the Declaration of Helsinki, the protocol was approved by an independent ethics committee, and written informed consent was provided by patients.

2.2. Treatments

Prior to starting nilotinib, patients had an imatinib or dasatinib washout period of ≥3 days. Patients then received oral nilotinib 300 mg bid for up to 24 months. The nilotinib dose could be reduced to 450 mg once daily in patients unable to tolerate the 300 mg bid dose. Treatment interruptions and dose reductions were allowed for management of AEs.

2.3. Study objectives

The primary endpoint was achievement of MR4.5 (BCR-ABL1 ≤0.0032% IS) within 24 months of switching to nilotinib. MMR (BCR-ABL1 ≤0.1% IS) and MR4.0 (a ≥4 log reduction in BCR-ABL1 level corresponding to a BCR-ABL1 level of ≤0.01% IS) were also assessed as supportive endpoints. Secondary endpoints included molecular response kinetics, improvement in AE grading from baseline to month 3 of nilotinib treatment, the safety profile of nilotinib 300 mg bid, and the change over time in HRQoL.

2.4. Efficacy assessments

BCR-ABL1 levels were determined using qRT-PCR testing of peripheral blood [30], with samples collected pre-dose at day 1 (baseline), at months 1, 2, and 3, and then every 3 months to month 24. The percent ratio of BCR-ABL1 transcripts versus control gene (BCR) transcripts converted to IS was calculated for each sample.

2.5. Safety assessments

Safety assessments included AEs (graded using Common Terminology Criteria for Adverse Events [CTCAE] version 4.03), laboratory parameters, vital signs, and physical examination. The QTcF interval was monitored using a standard 12-lead electrocardiogram. AEs of special interest, including IHD, ICVE, and PAOD, were also monitored.

Cardiovascular risk was assessed using Framingham Heart Study calculators (http://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/index.php), which provide an estimate of the 10-year general risk of cardiovascular disease (CVD) using baseline total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) values. Data concerning other risk factors (eg diabetes mellitus, dyslipidemia, hypertension) were also collected, and risk factors were managed as per local guidelines. The ankle-brachial index for each leg was assessed at day 1 (baseline) and at months 12 and 24, with the lowest value being automatically retained in the clinical database as part of the data entry process.

2.6. Quality of life assessments

HRQoL and symptom burden were assessed using the MD Anderson Symptom Inventory – Chronic Myeloid Leukemia (MDASI-CML) questionnaire [31].

2.7. Statistical analyses

The primary efficacy analysis was conducted in all enrolled patients.

Safety was assessed in all enrolled patients who received at least one dose of study drug and had at least one post-baseline safety assessment. The planned enrollment target of 130 patients was expected to comprise 100 imatinib-intolerant patients and 30 dasatinib-intolerant patients.

The primary efficacy endpoint was considered as a binary response, with the MR4.5 rate calculated as the ratio of the number of responders (ie patients achieving MR4.5) to the sum of the number of responders and non-responders. An overall 95% confidence interval (CI) was determined using the Clopper-Pearson method.

Additional analyses were conducted for MMR and MR4.0, with the MMR analysis conducted in the subgroup of patients not in MMR at baseline (patients who were MMR, MR4.0, or MR4.5 were excluded) and the MR4.0 analysis conducted in the subgroup of patients not in MR4.0 at baseline (patients who were MR4.0 or MR4.5 were excluded).

The kinetics of the molecular response were assessed descriptively by summarizing the BCR-ABL1 ratio each month for the first 3 months of the study and then at 3-monthly intervals until 24 months.

MDASI-CML scores were summarized descriptively at baseline and at 3-monthly intervals until 24 months.

Improvement in the severity of non-hematological AEs was analyzed in the safety set, with improvement defined as a reduction in the CTCAE grading 3 months after switching to nilotinib or the resolution of the AE in the 3 months after the switch.

3. Results

3.1. Study population

Twenty patients were screened and enrolled in the study, which was halted early because of low recruitment. Four patients (20.0%) completed the study (completers were defined as patients who had a study completion evaluation performed 30 days after the end of therapy), 14 patients (70.0%) were withdrawn because of early study termination (ie study closure), one patient (5.0%) was lost to follow-up, and one patient (5.0%) withdrew their consent and discontinued the trial due to planned pregnancy. Overall, no patient had 2 years of follow up, with a maximum follow up duration of approximately 94 weeks seen in two patients.

Baseline demographics are shown in Table 1. Sixteen patients had received imatinib and four patients had received dasatinib as their most recent TKI.

Table 1
Summary of patient demographics and baseline characteristics.

	N = 20
Age, years	
Mean (SD)	53.9 (15.1)
Median (range)	55.0 (31–77)
Sex, n (%)	
Male	6 (30.0%)
Female	14 (70.0%)
Duration of prior TKI therapy, months	
Mean (SD)	51.0 (44.14)
Median (range)	42.5 (2–154)
Most recent TKI, n (%)	
Imatinib	16 (80.0)
Dasatinib	4 (20.0)
BCR-ABL1 response at baseline, n (%)	
No MMR	8 (40.0)
MMR	9 (45.0)
MR4.0	1 (5.0)
MR4.5	2 (10.0)

MMR, major molecular response; SD, standard deviation; TKI, tyrosine kinase inhibitor.

At baseline, eight patients (40.0%) were not in MMR, nine patients (45.0%) were in MMR and one patient (5.0%) was in MR4.0. Two patients (10.0%) who were not in MR4.5 at screening, but were in MR4.5 at baseline, were therefore eligible for study entry (Table 1).

The median duration of nilotinib treatment was 415 days (range 128–658 days) and the median daily nilotinib dose (excluding zero dose periods) was 600 mg (range 279–600 mg). Nilotinib dose reduction and interruption occurred in one (5.0%) and two (10.0%) patients, respectively. One patient (5.0%) discontinued nilotinib therapy because of planned pregnancy, with no patients permanently discontinuing nilotinib because of AEs.

3.2. Efficacy

MR4.5 between baseline and month 3 of nilotinib treatment was seen in 7 of 20 patients (35.0%; 95% CI 15.4, 59.2); at baseline, one of these patients was not in MMR, three were in MMR, one was in MR4.0, and two were in MR4.5. MR4.5 at any time point up to month 24 (primary endpoint) was seen in 10 of 20 patients (50.0%; 95% CI 27.2, 72.8). All 10 patients had achieved MR4.5 by month 12 of the study; the duration of prior TKI exposure in these patients versus those not achieving MR4.5 is presented in the Supplementary material. Molecular response rates over time are shown in Fig. 1.

A sensitivity analysis excluding the two patients in MR4.5 at baseline found that MR4.5 between baseline and month 3 of nilotinib treatment was achieved in 5 of 18 patients (27.8%; 95% CI 9.7, 53.5) and MR4.5 at any time point up to month 24 was achieved in 8 of 18 patients (44.4%; 95% CI 21.5, 69.2).

At any time point up to month 12, MMR was achieved in 6 of 8 patients not in MMR at baseline (75.0%; 95% CI 34.9, 96.8) and MR4.0 was achieved in 11 of 17 patients not in MR4.0 at baseline (64.7%; 95% CI 38.3, 85.8). At any time point up to month 24, MMR was achieved in 6 of 8 patients (75.0%; 95% CI 34.9, 96.8) and MR4.0 was achieved in 12 of 17 patients (70.6%; 95% CI 44.0, 89.7). The lowest BCR-ABL levels seen in the two patients not achieving MMR at any time during the study were 2.200% at week 24 and 0.180% at week 48, respectively.

Median BCR-ABL1 values were 0.068% IS at baseline and 0.006% IS at week 96/end of study (EOS) (Fig. 2).

The proportion of patients achieving a 1-log reduction in BCR-ABL1 levels over time is shown in Fig. 3. Among the subgroup of patients not in MR4.0 or MR4.5 at baseline, a 1-log reduction in BCR-ABL1 levels occurred as early as week 8 in three patients, with an additional five patients achieving a 1-log reduction in BCR-ABL1 levels by week 12.

There were no reports of death during the study, or withdrawal because of progression to CML-AP or CML-BP, or treatment failure.

3.3. Overall safety profile

In total, 61 non-hematological AEs were reported at baseline across the 20 patients in the safety set who had been receiving prior TKI therapy (AEs had persisted for ≥1 month or recurred despite supportive care). The vast majority of these AEs were Grade 1 or 2, and there were no Grade 4 AEs (Table 2 and Supplementary Table 1). The most commonly reported AEs were nausea and fatigue (Table 2). The change over time in pre-existing AEs is shown in Supplementary Table 2 and Fig. 4. Twelve weeks following the switch from imatinib or dasatinib to nilotinib, 73.8% of the AEs had resolved (Table 2).

Subgroup analysis revealed that after 12 weeks of nilotinib therapy, 35 of the 50 (70%) AEs reported during prior imatinib therapy and 10 of the 11 (91%) AEs reported during prior dasatinib therapy had resolved.

All 20 patients experienced at least one treatment-emergent AE (TEAE) during nilotinib therapy (Table 3). The majority of non-serious TEAEs were of grade 1 (113 of 148; 76.4%) or grade 2 (32 of 148; 21.6%) intensity. Of the remaining non-serious TEAEs, two were of

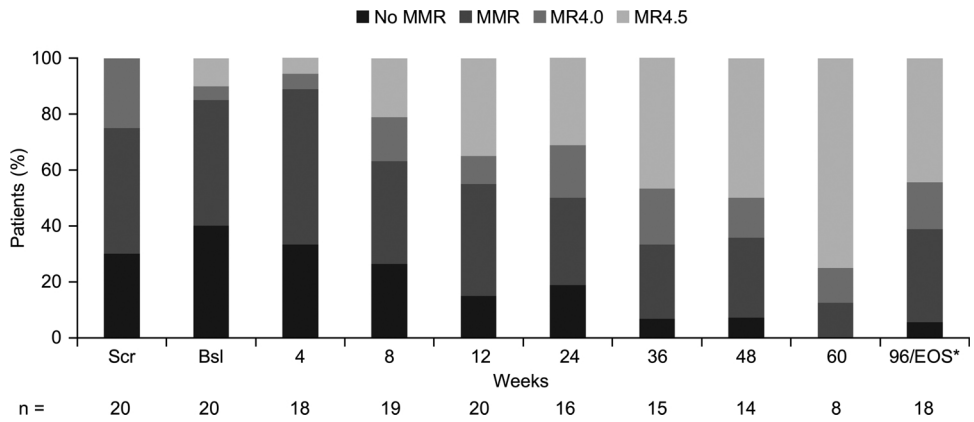

Fig. 1. Proportion of patients achieving a molecular response over time.
*Two patients did not have BCR-ABL results at week 96/EOS (EOS was defined as the early termination visit).
Bsl, baseline; EOS, end of study; MMR, major molecular response; Scr, screening.

grade 3 intensity (type 2 diabetes and osteoarthritis) and one (hyperuricemia) was of grade 4 intensity, although this event was not considered to be related to nilotinib and was not classified as serious. One serious TEAE (pneumonia) was reported during the study, but was not considered to be related to nilotinib.

The most commonly reported treatment-related AEs included fatigue and constipation (Table 3).

Five patients (25%) had grade 1 or 2 elevations in liver enzymes, creatinine phosphokinase, lipase, or amylase. No patient experienced hematological AEs during the study.

A change from baseline in the QTcF interval of > 60 ms was reported in one patient; it was considered treatment related and nilotinib was temporarily interrupted.

3.4. Cardiovascular risk assessment and monitoring

Regarding baseline Framingham index estimates, three patients were not evaluated because of missing lipid values. Of the remaining patients, 13, 1, and 3 patients were at low (Framingham estimate < 10%), moderate (10–15%), and high (> 15%) risk of CVD, respectively (see the Supplementary material).

According to the American Heart Association, the goal is to keep the TC:HDL-C ratio (an indicator of cardiovascular risk [32]) < 5:1, with a ratio of < 3.5:1 considered an ideal target [33]. Among patients with baseline data for TC and HDL-C (n = 16), 81% of patients had a TC:HDL-C ratio of < 5:1 and 56% of patients had a TC:HDL-C ratio of < 3.5:1 before starting nilotinib. At EOS, TC:HDL-C ratios remained within the target ranges in the majority of patients (87% of patients had a TC:HDL-C ratio of < 5:1 and 53% had a TC:HDL-C ratio of < 3.5:1).

None of the seven patients who had low-density lipoprotein cholesterol (LDL-C) to target at baseline were at target at EOS, and of six patients with LDL-C not to target at baseline, five were still not to target at EOS, with data from the sixth patient missing.

At baseline before starting nilotinib, all 17 evaluable patients had glycated hemoglobin (HbA_{1c}) levels within the target range (100%), and 89% of patients also had fasting plasma glucose (FPG) levels within the target range. At EOS, the majority of patients remained within the target ranges for HbA_{1c} and FPG (92% and 80%, respectively).

There were no reports of IHD, ICVE, or PAOD.

3.5. Quality of life

Changes from baseline to week 96/EOS in mean total scores for symptom severity (part 1 core and CML questions) and interference of symptoms on daily life (part 2 core questions) are shown in Table 4.

4. Discussion

Inadequate management of AEs in patients receiving TKI therapy may lead to reduced treatment adherence and poor outcomes, including

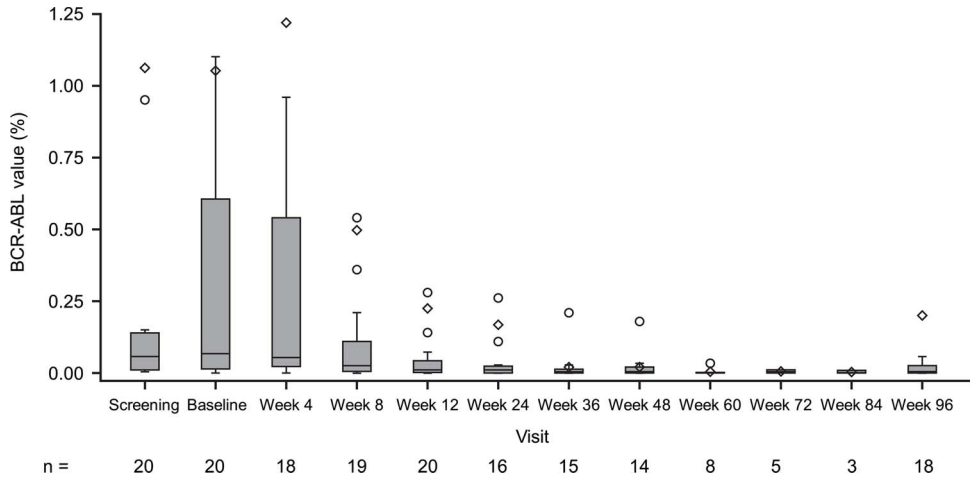

Fig. 2. BCR-ABL1 levels over time.
Boxes represent the inter-quartile range (IQR, 25th and 75th percentiles), horizontal bars represent median values, whiskers represent 1.5 × IQR, diamonds represent mean values, and circles represent individual values outside of 1.5 × IQR. Values > 2 are not shown.

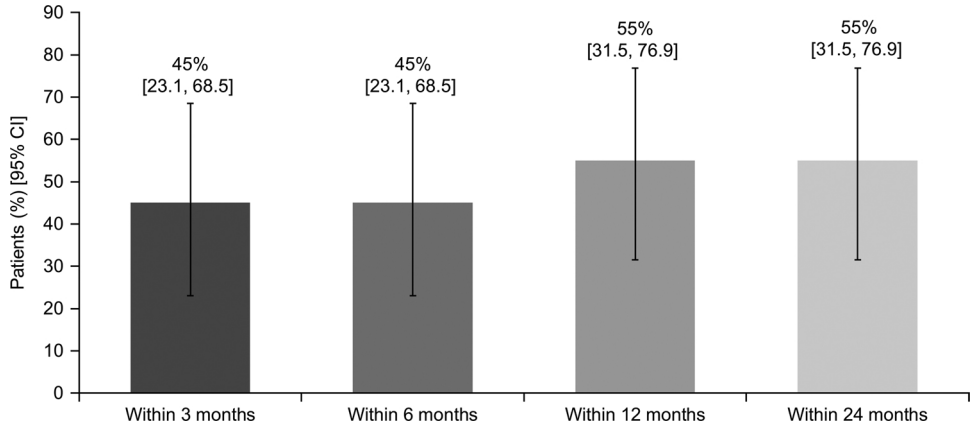

Fig. 3. Proportion of patients achieving a 1-log reduction in BCR-ABL1 levels over time *.
*Cumulative response rates are shown; there were 20 evaluable patients at each time point.

Table 2
Reasons for intolerance in patients receiving prior imatinib or dasatinib therapy and outcomes of these non-hematological adverse events following the switch to nilotinib.

	Events in safety set (n = 61)
Adverse events, n (%)	
Other*	26 (42.6)
Nausea	10 (16.4)
Fatigue	7 (11.5)
Rash	4 (6.6)
Superficial edema	4 (6.6)
Diarrhea	3 (4.9)
Myalgia	3 (4.9)
Headache	2 (3.3)
Pleural effusion	1 (1.6)
Vomiting	1 (1.6)
Maximum severity at baseline,† n (%)	
Grade 1	42 (68.9)
Grade 2	15 (24.6)
Grade 3	4 (6.6)
Grade 4	0
Changes in adverse events across 12 weeks, n (%)	
Resolved	45 (73.8)
No change	12 (19.7)
Improved	4 (6.6)
Worsened	0

* Other adverse events included leg/muscle cramps (n = 3), periorbital edema (n = 2), alopecia (n = 2), dry mouth (n = 1), mood swings (n = 1), intermittent subconjunctival hemorrhage (n = 1), anemia (n = 1), hypopigmentation (n = 1), hyperpigmentation of soft palate (n = 1), gynecomastia (n = 1), easy bruising (n = 1), thrombocytopenia (n = 1), non-specific florid follicular and paracortical hyperplasia (n = 1), dry/cracked skin (n = 1), hot flashes (n = 1), light-headedness (n = 1), reflux esophagitis (n = 1), lethargy (n = 1), gastritis (n = 1), indigestion (n = 1), anorexia (n = 1), and gastrointestinal toxicity (n = 1).
† Common Terminology Criteria for Adverse Events version 4.03.

suboptimal molecular responses [23,34,35]. Most AEs associated with TKI therapy can be managed using symptomatic treatment or dose reduction [22]. However, some patients experience AEs that do not respond to these measures and these patients are regarded as TKI-intolerant [22]. Managing TKI intolerance by discontinuing or interrupting treatment may lead to unfavorable outcomes, and a more appropriate strategy may be to switch to an alternative TKI.

In ENESTswift, switching to nilotinib 300 mg bid because of intolerance to prior imatinib or dasatinib appeared to be an effective and well-tolerated strategy in most patients with CML-CP. It should be noted that early termination of the study has not allowed for a robust analysis. One possible reason for the slow accrual is that because the Australian Pharmaceutical Benefits Scheme permits patients to switch from imatinib to a second-generation TKI, switching may be occurring without patients being entered into a clinical study.

Despite low patient recruitment, the findings of ENESTswift are important considering that data concerning the efficacy and tolerability of nilotinib 300 mg bid in TKI-intolerant patients with CML-CP are limited [29]. The results of ENESTswift are particularly relevant for countries where reimbursement or access for TKI switching because of intolerance during first-line therapy is based on a nilotinib dosage of 300 mg bid.

In terms of the molecular response at baseline, the majority of patients were in MMR, with only one patient in MR4.0 and two patients in MR4.5. Within 24 months of switching to nilotinib 300 mg bid, MR4.5 was achieved in 10 of 20 patients overall and in 8 of 18 patients when the two patients in MR4.5 at baseline were excluded.

Following the switch to nilotinib, a rapid decrease in BCR-ABL1 levels was apparent in the subgroup of patients with higher BCR-ABL1 levels at baseline (ie those who were not in MR4.0 or MR4.5). Overall, a 1-log reduction in BCR-ABL1 levels was seen in 45.0% of patients by month 3 of nilotinib treatment.

Approximately three-quarters of non-hematological AEs associated with intolerance to prior imatinib or dasatinib therapy resolved within 12 weeks of switching to nilotinib 300 mg bid. These results support the findings of earlier studies indicating that cross intolerance between nilotinib and imatinib is infrequent [27,29].

The safety profile of nilotinib in ENESTswift was generally consistent with that seen in previous studies [6–9]. The vast majority of TEAEs were of mild-to-moderate severity, with the most commonly reported treatment-related AEs being fatigue and constipation. No cardiovascular safety concerns emerged during the study. Guidelines recommend that patients should be evaluated for pre-existing PAOD and vascular risk factors before they start, and during, nilotinib therapy [1].

4.1. Conclusions

This study supports a strategy of switching to nilotinib 300 mg bid in CML-CP patients who do not tolerate imatinib or dasatinib in the first-line setting. Given the small patient numbers, further study in a larger population is indicated.

Author disclosures

DH has received research funding from Novartis. JD has received consultancy fees and honoraria from Bristol Myers Squibb, Celgene, and Roche. SB has received research funding and honoraria from Novartis and Bristol Myers Squibb, consultancy fees and honoraria from Qiagen, consultancy fees from Cepheid and research funding from Ariad. DY has received research funding and honoraria and served on advisory

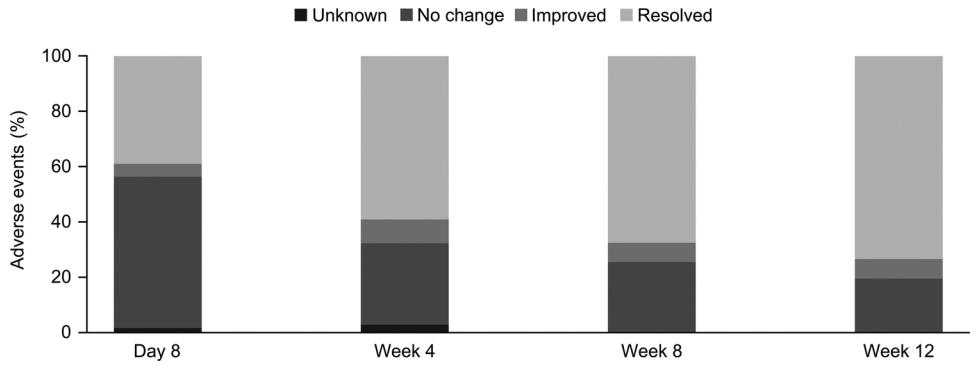

Fig. 4. Change over time in all non-hematological adverse events reported with prior TKI therapy after the switch to nilotinib.
TKI, tyrosine kinase inhibitor.

Table 3
Most commonly occurring adverse events during nilotinib treatment.

	Number (%) of patients experiencing AEs	Number (%) of AEs
Treatment-emergent AEs, n (%)	N = 20	N = 148
Fatigue	11 (55.0)	11 (7.4)
Bone pain	4 (20.0)	4 (2.7)
Muscle spasms	4 (20.0)	5 (3.4)
Upper respiratory tract infection	4 (20.0)	4 (2.7)
Gamma-glutamyltransferase increased	4 (20.0)	6 (4.1)
Constipation	4 (20.0)	4 (2.7)
Gastro-esophageal reflux disease	4 (20.0)	4 (2.7)
Back pain	3 (15.0)	4 (2.7)
Urinary tract infection	3 (15.0)	5 (3.4)
Rash	3 (15.0)	3 (2.0)
Influenza-like illness	2 (10.0)	2 (1.4)
Arthralgia	2 (10.0)	2 (1.4)
Myalgia	2 (10.0)	2 (1.4)
Lower respiratory tract infection	2 (10.0)	2 (1.4)
Nasopharyngitis	2 (10.0)	2 (1.4)
Eczema	2 (10.0)	2 (1.4)
Pruritus	2 (10.0)	2 (1.4)
Alanine aminotransferase increased	2 (10.0)	2 (1.4)
Blood alkaline phosphatase increased	2 (10.0)	2 (1.4)
Blood bilirubin increased	2 (10.0)	3 (2.0)
Weight decreased	2 (10.0)	2 (1.4)
Hypercholesterolemia	2 (10.0)	3 (2.0)
Cough	2 (10.0)	2 (1.4)
Skin papilloma	2 (10.0)	2 (1.4)
Treatment-related AEs,* n (%)	N = 20	N = 64
Fatigue	8 (40.0)	8 (12.5)
Constipation	4 (20.0)	4 (6.3)
Arthralgia	2 (10.0)	2 (3.1)
Bone pain	2 (10.0)	2 (3.1)
Muscle spasms	2 (10.0)	2 (3.1)
Pruritus	2 (10.0)	2 (3.1)
Rash	2 (10.0)	2 (3.1)
Gastro-esophageal reflux disease	2 (10.0)	2 (3.1)

Only AEs occurring in ≥10% of patients are shown. AEs were coded according to MedDRA-preferred terms.

* Related to the use of nilotinib in the opinion of the investigator. AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

committees for Novartis and Bristol Myers Squibb and has received research funding from Ariad. TH has received research funding and honoraria and served on advisory committees for Novartis, Bristol Myers Squibb and Ariad. PT, JT, AP, II, and MW have no disclosures to declare. LA, OG, CL, and WR are employees of Novartis. AS and RT are employed by a third-party contractor to Novartis.

Table 4
Change over time in MDASI-CML scores assessing symptom severity and interference of symptoms on daily life in patients receiving nilotinib.

Time point	Number of patients*	Mean (SD) total score for part 1 core questions	Mean (SD) total score for part 1 CML questions	Mean (SD) total score for part 2 core questions
Baseline	20/20/20	26.6 (23.88)	14.3 (11.71)	12.4 (14.17)
Week 12	19/18/18	22.7 (20.31)	7.4 (9.34)	7.8 (11.92)
Week 24	16/16/16	20.7 (18.08)	10.1 (11.19)	8.2 (12.20)
Week 36	15/14/14	19.1 (15.78)	8.9 (8.57)	6.1 (6.27)
Week 48	12/12/12	20.4 (16.57)	7.8 (9.00)	7.6 (10.53)
Week 60	7/7/7	24.0 (34.09)	7.7 (11.69)	2.9 (7.56)
Week 72	5/5/5	19.6 (29.52)	4.2 (6.72)	9.6 (21.47)
Week 84	3/3/3	32.7 (41.24)	12.3 (16.29)	13.3 (23.09)
Week 96/EOS†	19/19/18	17.5 (20.44)	7.8 (11.49)	9.9 (15.59)

EOS, end of study; MDASI-CML, MD Anderson Symptom Inventory – Chronic Myeloid Leukemia; SD standard deviation.
MDASI-CML assesses symptom severity (13 core items [part 1 core questions] and seven CML-specific items [part 1 CML questions] scored from 0 [not present] to 10 [as bad as imagined]) and interference of symptoms on daily life (six core items [part 2 core questions] scored from 0 [did not interfere] to 10 [interfered completely]).

* Number of evaluable patients for part 1 core questions/part 1 CML questions/part 2 core questions.

† Week 96 includes EOS results for patients who did not complete the study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.leukres.2018.02.013.

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