Author/s:
Hughes, TP;Munhoz, E;Aurelio Salvino, M;Ong, TC;Elhaddad, A;Shortt, J;Quach, H;Pavlovsky, C;Louw, VJ;Shih, LY;Turkina, AG;Meillon, L;Jin, Y;Acharya, S;Dalal, D;Lipton, JH

Title:
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Date:
2017-10-01

Citation:
Hughes, T. P., Munhoz, E., Aurelio Salvino, M., Ong, T. C., Elhaddad, A., Shortt, J., Quach, H., Pavlovsky, C., Louw, V. J., Shih, L. Y., Turkina, A. G., Meillon, L., Jin, Y., Acharya, S., Dalal, D. & Lipton, J. H. (2017). Nilotinib dose-optimization in newly diagnosed chronic myeloid leukaemia in chronic phase: final results from ENESTxtnd. British Journal of Haematology, 179 (2), pp.219-228. https://doi.org/10.1111/bjh.14829.

Persistent Link:
https://hdl.handle.net/11343/254714

bjh research paper

Nilotinib dose-optimization in newly diagnosed chronic myeloid leukaemia in chronic phase: final results from ENESTxtnd

Timothy P. Hughes,[1] Eduardo Munhoz,[2] Marco Aurelio Salvino,[3] Tee Chuan Ong,[4] Alaa Elhaddad,[5] Jake Shortt,[6] Hang Quach,[7] Carolina Pavlovsky,[8] Vernon J. Louw,[9] Lee-Yung Shih,[10] Anna G. Turkina,[11] Luis Meillon,[12] Yu Jin,[13] Sandip Acharya,[14] Darshan Dalal[13] and Jeffrey H. Lipton[15]

[1]South Australian Health and Medical Research Institute (SAHMRI), University of Adelaide, SA Pathology, Adelaide, SA, Australia, [2]Hospital Erasto Gaertner – Liga Paranaense Combate ao Câncer, Curitiba, [3]Hospital São Rafael-Monte Tabor & Hospital Universitario Professor Edgard Santos-Universidade Federal da Bahia, Salvador, Brazil, [4]Hospital Ampang, Selangor, Malaysia, [5]National Cancer Institute, Cairo University, Cairo, Egypt, [6]School of Clinical Sciences at Monash Health, Monash University, Clayton, [7]St Vincent's Hospital, University of Melbourne, Melbourne, Vic., Australia, [8]FUNDALEU, Hospitalization and Clinical Research Centre, Buenos Aires, Argentina, [9]University of the Free State, Bloemfontein, South Africa, [10]Chang Gung Memorial Hospital-Linkou, Chang Gung University, Taoyuan City, Taiwan, [11]FGB Haematology Research Centre Health Ministry Research Facility, Moscow, Russia, [12]Hospital de Especialidades, CMN Siglo XXI, Mexico City, Mexico, [13]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [14]Novartis Healthcare Pvt. Ltd., Hyderabad, India and [15]Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Received 21 February 2017; accepted for publication 29 May 2017

Correspondence: Timothy P. Hughes, South Australian Health and Medical Research Institute, North Terrace, Adelaide, SA 5000, Australia.
E-mail: tim.hughes@sahmri.com

Summary

The Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Extending Molecular Responses (ENESTxtnd) study was conducted to evaluate the kinetics of molecular response to nilotinib in patients with newly diagnosed chronic myeloid leukaemia in chronic phase and the impact of novel dose-optimization strategies on patient outcomes. The ENESTxtnd protocol allowed nilotinib dose escalation (from 300 to 400 mg twice daily) in the case of suboptimal response or treatment failure as well as dose re-escalation for patients with nilotinib dose reductions due to adverse events. Among 421 patients enrolled in ENESTxtnd, 70·8% (95% confidence interval, 66·2–75·1%) achieved major molecular response (*BCR-ABL1* $\leq$ 0·1% on the International Scale) by 12 months (primary endpoint). By 24 months, 81·0% of patients achieved major molecular response, including 63·6% (56 of 88) of those with dose escalations for lack of efficacy and 74·3% (55 of 74) of those with dose reductions due to adverse events (including 43 of 54 patients with successful re-escalation). The safety profile of nilotinib was consistent with prior studies. The most common non-haematological adverse events were headache, rash, and nausea; cardiovascular events were reported in 4·5% of patients (grade 3/4, 3·1%). The study was registered at clinicaltrials.gov (NCT01254188).

Keywords: chronic myeloid leukaemia, tyrosine kinase inhibitor, nilotinib, molecular response, dose optimization.

First published online 12 July 2017
British Journal of Haematology, 2017, **179,** 219–228
doi: 10.1111/bjh.14829

Nilotinib (Tasigna, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) is a second-generation BCR-ABL1 tyrosine kinase inhibitor approved for the treatment of patients with newly diagnosed chronic myeloid leukaemia in chronic phase (CML-CP) and for those with resistance to or intolerance of imatinib (Gleevec, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) (Novartis Pharmaceuticals Corporation, 2016), the first approved BCR-ABL1 tyrosine kinase inhibitor (O'Brien *et al*, 2003). The recommended dose of nilotinib for patients with newly diagnosed CML-CP is 300 mg twice daily (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022068s024lbl.pdf).

In the pivotal trial of frontline nilotinib *versus* imatinib in patients with CML-CP (Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Newly Diagnosed Patients [ENESTnd]), the efficacy and safety of nilotinib 300 mg twice daily and nilotinib 400 mg twice daily were compared with that of imatinib 400 mg once daily (Saglio *et al*, 2010). Throughout 6 years of follow-up in ENESTnd, both nilotinib doses resulted in improved efficacy *versus* imatinib, including faster and higher rates of molecular responses and lower rates of disease progression and death due to advanced CML (Saglio *et al*, 2010; Kantarjian *et al*, 2011; Larson *et al*, 2012; Hughes *et al*, 2014a, 2015; Hochhaus *et al*, 2016a). By 6 years, 77·3% (nominal $P < 0{\cdot}0001$ *versus* imatinib), 79·0% (nominal $P < 0{\cdot}0001$ *versus* imatinib) and 61·1% of patients in the nilotinib 300-mg twice-daily, nilotinib 400-mg twice-daily and imatinib arms, respectively, achieved a major molecular response [MMR; defined as *BCR-ABL1* $\leq 0{\cdot}1\%$ on the International Scale (*BCR-ABL1*^{IS})]; among all randomized patients in each arm, 11 of 282 (nilotinib 300 mg twice daily; nominal $P = 0{\cdot}0661$ *versus* imatinib), 6 of 281 (nilotinib 400 mg twice daily; nominal $P = 0{\cdot}0030$ *versus* imatinib), and 21 of 283 patients (imatinib) progressed to accelerated phase/blast crisis (AP/BC) by 6 years (including after discontinuation of study treatment) (Hughes *et al*, 2015). Estimated rates of overall survival at 6 years were 91·6% in the nilotinib 300-mg twice-daily arm (nominal $P = 0{\cdot}7085$ *versus* imatinib), 95·8% in the nilotinib 400-mg twice-daily arm (nominal $P = 0{\cdot}0314$ *versus* imatinib) and 91·4% in the imatinib arm (Hughes *et al*, 2015). The safety profile of nilotinib is well established and distinct from that of imatinib (Saglio *et al*, 2010; Kantarjian *et al*, 2011; Larson *et al*, 2012; Hughes *et al*, 2015; Hochhaus *et al*, 2016a).

There are data to suggest that nilotinib dose escalations or reductions, as necessary, can be beneficial for some patients, maximizing both efficacy and tolerability (Rosti *et al*, 2009; Hughes *et al*, 2014b; Gugliotta *et al*, 2015). An ENESTnd extension study evaluated the impact of nilotinib dose escalation in a small cohort of patients ($n = 19$) with suboptimal response or treatment failure on nilotinib 300 mg twice daily; among patients who had not achieved a complete cytogenetic response (CCyR) or MMR at the time of dose escalation, approximately one-third [33% (2 of 6) and 39% (7 of 18), respectively] achieved CCyR and MMR, respectively, on nilotinib 400 mg twice daily by the data cut-off (median follow-up after dose escalation, 19 months) (Hughes *et al*, 2014b). Additionally, an independent study of frontline nilotinib 400 mg twice daily in patients with newly diagnosed CML-CP demonstrated the feasibility of managing adverse events (AEs) and laboratory abnormalities with nilotinib dose reductions (Rosti *et al*, 2009; Gugliotta *et al*, 2015).

The ENEST–Extending Molecular Responses (ENESTxtnd) study was conducted to explore the kinetics of molecular response in patients treated with frontline nilotinib, investigate novel nilotinib dose-optimization strategies, and further evaluate the efficacy and safety of nilotinib 300 mg twice daily in patients with newly diagnosed CML-CP. Here we present an analysis of the ENESTxtnd primary endpoint (rate of MMR by 12 months), as well as final efficacy and safety results from the study, based on 2 years of follow-up.

Methods

Patients and study design

ENESTxtnd was a 2-year, open-label, prospective, multicentre, phase 3b study of nilotinib 300 mg twice daily in adult patients (aged ≥18 years) who had received a diagnosis of CML-CP within the prior 6 months. Patients' baseline Sokal risk scores were not collected. Molecular responses were monitored by real-time quantitative polymerase chain reaction at local laboratories standardized to the IS (using peripheral blood samples) at baseline; at the end of months 1, 2 and 3, and every third month thereafter; and at the end of the study or upon early discontinuation (Hughes & Branford, 2006). Bone marrow cytogenetic analyses were performed locally at screening, month 6 and at the end of the study or upon early discontinuation; between month 6 and the end of the of study, cytogenetic assessments were required only in patients without CCyR or MMR and patients with progression to AP/BC, loss of MMR, or treatment failure [defined as complete haematological response (CHR) after 3 months, >95% Philadelphia chromosome–positive (Ph+) metaphases after 6 months, >35% Ph+ metaphases after 12 months, >0% Ph+ metaphases after 18 months, loss of CHR, partial cytogenetic response, or CCyR at any time, or increasing white blood cell count at any time]. Mutational analysis was performed at discontinuation or end of study and in patients with suboptimal response, treatment failure, or progression to AP/BC. Eligibility criteria and study endpoints are detailed in the Supplemental methods.

ENESTxtnd was conducted according to the Declaration of Helsinki. The study protocol was reviewed by an independent ethics committee or institutional review board for each centre. Written informed consent was obtained from each patient. ENESTxtnd was registered at clinicaltrials.gov (NCT01254188). All authors had access to the study data.

The authors, in collaboration with the study sponsor, analysed and interpreted the data.

Treatments and dose adjustments

All patients received an initial dose of nilotinib 300 mg twice daily. Dose escalation to nilotinib 400 mg twice daily was permitted for suboptimal response or treatment failure (Table SI) (Baccarani *et al*, 2009). Dose escalation above nilotinib 400 mg twice daily was not permitted. Patients who progressed to AP/BC were not eligible for dose escalation. Protocol-defined criteria for dose reduction and re-escalation are shown in Table SII. Briefly, in patients with drug-related grade 3/4 haematological AEs concerning leucocytes or platelets or grade 2/3 non-haematological AEs on nilotinib 300 mg twice daily, nilotinib treatment was interrupted; upon improvement, treatment was resumed at 300 mg twice daily (following the first and second occurrence) or 450 mg once daily (following the third and fourth occurrence), with re-escalation to 300 mg twice daily after 1 week (third occurrence) or 1 month [fourth occurrence (haematological events only)]. Successful re-escalation was defined as ≥4 weeks of nilotinib 300 mg twice daily with no dose adjustments for any AE. Patients who were unable to tolerate nilotinib 450 mg once daily were discontinued from the study. While on study, individual patients could have their dose both escalated and reduced.

Statistical analysis

Efficacy analyses included all enrolled patients or all patients in the relevant subset. Progression-free and overall survival were analysed using the Kaplan–Meier method. Safety analyses included all patients who received ≥1 dose of study treatment and who had ≥1 post-baseline safety assessment. Nominal *P* values for secondary and exploratory endpoints, when provided, are for descriptive purposes only without multiplicity adjustments; therefore, no formal statistical claim can be made and statistical interpretations should be made with caution.

Results

Patients and treatment

A total of 421 patients from 18 participating countries (Algeria, Argentina, Australia, Brazil, Canada, Egypt, India, Israel, Lebanon, Malaysia, Mexico, Oman, Russia, Saudi Arabia, South Africa, Taiwan, Thailand and Tunisia) were enrolled in the study between 28 April 2011 and 21 September 2012. Median age was 48 years, and 53·7% of patients were male (Table I). As of the data cut-off date for this analysis (11 March 2015), 328 patients (77·9%) had completed 24 months of treatment (the full, per-protocol study duration) and 93 patients (22·1%) had discontinued early (Fig 1).

Table I. Patient characteristics.

	Nilotinib *N* = 421
Median age (range), years	48 (18–87)
≥65 years, *n* (%)	53 (12·6)
Sex, *n* (%)	
Male	226 (53·7)
Female	195 (46·3)
Race, *n* (%)	
White	284 (67·5)
Black	16 (3·8)
Asian	75 (17·8)
Other	46 (10·9)
ECOG performance status, *n* (%)	
0	316 (75·1)
1	93 (22·1)
2	12 (2·9)
Median time since initial diagnosis (range), days	25 (0–170)
Prior therapy, *n* (%)	
Hydroxycarbamide	297 (70·5)
Imatinib*	19 (4·5)
Anagrelide	5 (1·2)
Interferon	1 (0·2)
Other	8 (1·9)

ECOG, Eastern Cooperative Oncology Group.
*≤2 weeks' duration.

The most common reason for early discontinuation was AEs (10·2% of all patients). The median time on treatment was 23·7 months (range, 0·03–26·05 months). The median actual nilotinib dose intensity (including periods of zero dose) was 599 mg/day (25th–75th percentile, 582–600 mg/day), and the median average daily dose (excluding periods of zero dose) was 600 mg (25th–75th percentile, 599–600 mg).

Overall, 144 patients (34·2%) received a reduced dose of nilotinib at any time during the study [due to AEs ($n = 74$), dosing errors ($n = 36$), scheduling conflicts ($n = 27$), dose reductions as per protocol ($n = 11$), dispensing errors ($n = 3$) and re-escalations to a dose lower than that prescribed ($n = 84$)]. Among these 144 patients, 106 (73·6%) attempted to re-escalate to nilotinib 300 mg twice daily, 92 of whom successfully re-escalated; 76 of 92 patients with successful dose re-escalation went on to complete the study treatment duration per protocol. In the subset of patients with dose reductions due to AEs, 63 of 74 (85·1%) attempted dose re-escalation to nilotinib 300 mg twice daily, 54 of whom successfully re-escalated.

A total of 88 patients (20·9%) had their nilotinib dose escalated to 400 mg twice daily due to lack of efficacy (suboptimal response: $n = 83$, 19·7%; treatment failure: $n = 5$, 1·2%). Four additional patients (1·0%) received nilotinib 400 mg twice daily due to dosing error. Of the 88 patients whose nilotinib dose was escalated to 400 mg twice daily at any time due to lack of efficacy, 5 and 9 patients subsequently discontinued due to suboptimal response and

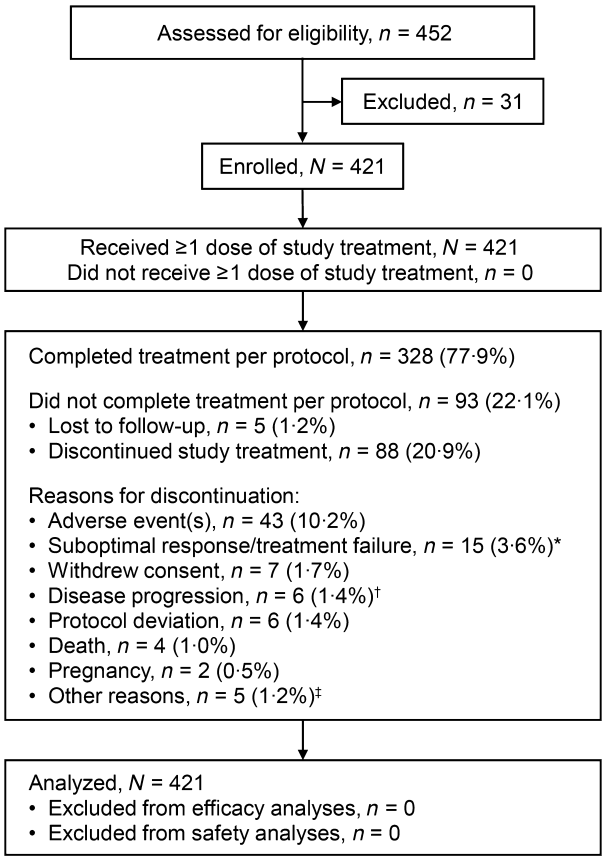

Fig 1. Patient disposition and analysis populations. *Nine additional patients with suboptimal response/treatment failure discontinued due to disease progression ($n = 6$), adverse event(s) ($n = 2$) or protocol deviation ($n = 1$). †Disease progression was defined as progression to accelerated phase/blast crisis, per investigator's judgment. ‡Patients discontinued due to intolerance, noncompliance with the protocol, F359V mutation, switching medication, or an adverse event that had previously resolved ($n = 1$ each).

treatment failure, respectively; 83 of these 88 patients remained on nilotinib 400 mg twice daily at the end of treatment.

At 12 calendar months (365 days) from treatment start, 306, 33 and 23 patients were receiving treatment with nilotinib 300 mg twice daily, 400 mg twice daily and ≤450 mg once daily, respectively; 59 patients had discontinued (Table SIII). Among the 306 patients receiving nilotinib 300 mg twice daily at 12 months, 170 had ≥1 dose modification or interruption prior to 12 months, including 88 patients who had temporarily received a reduced nilotinib dose for any reason. Among the 23 patients on a reduced dose of nilotinib at 12 months, 6 later attempted re-escalation of nilotinib to 300 mg twice daily. At 24 months, 249, 66, and 13 patients were receiving treatment with nilotinib 300 mg twice daily, 400 mg twice daily, and ≤450 mg once daily, respectively. Among the 249 patients receiving nilotinib 300 mg twice daily at 24 months, 153 had ≥1 dose modification or interruption prior to 24 months, including 71 who had temporarily received a reduced nilotinib dose.

Efficacy

Median *BCR-ABL1*^{IS} levels decreased over time, with a rapid decrease during the first 12 months followed by a comparatively slower decrease over the next 12 months (Fig 2). The cumulative rate of MMR by 12 months (primary endpoint) was 70·8% [95% confidence interval (CI), 66·2–75·1%], and by 24 months it was 81·0% (95% CI, 76·9–84·6%; Fig 3). Among the 341 patients who achieved MMR by 24 months, the median time to MMR was 5·8 months and the Kaplan–Meier estimated rate of maintaining MMR at 24 months was 85·2% (95% CI, 75·8–94·5%).

Fifty-six of 88 patients (63·6%) with dose escalations due to lack of efficacy and 55 of 74 patients (74·3%) with dose reductions due to AEs achieved MMR by 24 months (Fig 4). Overall among the 144 patients who received a reduced dose of nilotinib for any reason, 109 (75·7%) achieved MMR by 24 months, including 78 of 92 (84·8%) with successful re-escalation, 9 of 14 (64·3%) with unsuccessful re-escalation and 22 of 38 (57·9%) who did not attempt re-escalation.

Few patients ($n = 36$; 8·6%) had *BCR-ABL1*^{IS} >10% at 3 months. Among these, 10 patients had their dose escalated due to *BCR-ABL1*^{IS} >10% at 3 months, and 11 had their dose escalated at other time points (6, 3 and 2 of these escalations were due to *BCR-ABL1*^{IS} > 1% at 6 months, lack of MMR at 12 months and treatment failure, respectively). Overall, 19 of these 36 patients (52·8%) completed study treatment, and 13 of 36 (36·1%) achieved MMR by 24 months.

Most patients ($n = 247$; 58·7%) achieved CCyR by 6 months. The rate of CCyR was 61·5% (95% CI, 56·7–66·2%) by 12 months and 74·1% (95% CI, 69·6–78·2%) by 24 months. Among the 312 patients who achieved CCyR, 3 lost CCyR during the study and 28 had ≥1 assessment showing *BCR-ABL1*^{IS} > 1% after achieving CCyR.

BCR-ABL1 mutations were detected in 23 patients on study: T315I mutations in 4 patients, E255 mutations in 7 patients, F359 mutations in 7 patients (2 of these 7 patients also had E255 mutations), Y253 mutations in 3 patients, and other mutations in 9 patients (5 of these 9 patients also had T315I, E255 and/or F359 mutations).

Ten patients (2·4%) had progression-free survival events on treatment (progression to AP/BC, $n = 6$; death, $n = 4$). Of the 6 patients with progression to AP/BC on treatment, 4 had mutations that were detected at the end of treatment (Y253, $n = 2$; F359, $n = 1$; T315I, $n = 1$). The Kaplan–Meier estimated rate of progression-free survival on treatment at 24 months was 97·0% (95% CI, 95·1–98·8%). One additional patient progressed to BC during the follow-up phase after discontinuing study treatment due to treatment failure (lack of partial cytogenetic response at 12 months). Nine patients (2·1%) died during the study, including 5 who died during study treatment or within 28 days of discontinuation (1 each due to intestinal infection, increased intracranial pressure, road traffic accident, sudden death and cardiorespiratory

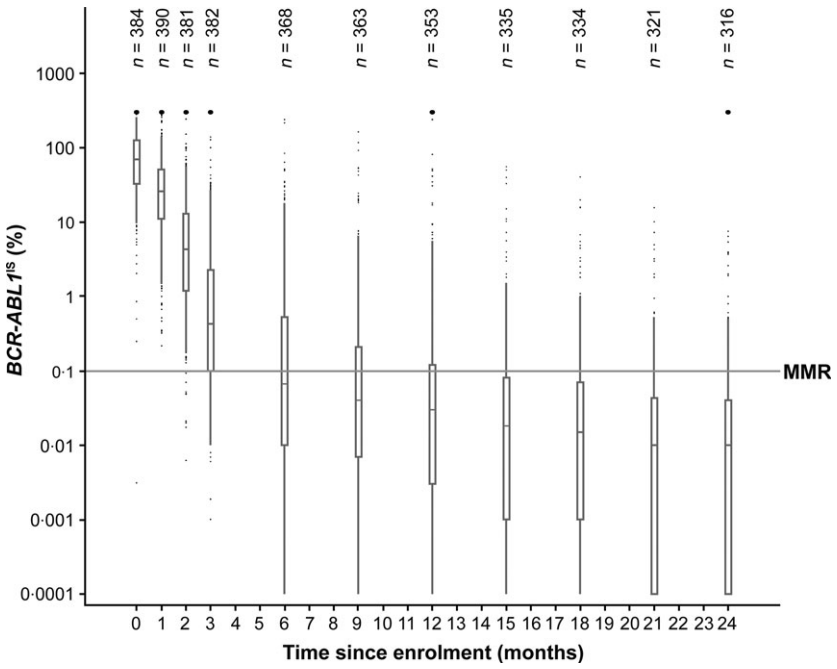

Fig 2. Median *BCR-ABL1*^{IS} levels over time. Among evaluable patients, the median (25th–75th percentile) *BCR-ABL1*^{IS} level was 69·45% (32·39–127·1%) at baseline, 26·11% (11·00–51·00%) at 1 month, 0·43% (0·10–2·26%) at 3 months, 0·07% (0·01–0·53%) at 6 months, 0·03% (0·00–0·12%) at 12 months and 0·01% (0·00–0·04%) at 24 months. One patient with *BCR-ABL1*^{IS} <0·01% at baseline did not have a confirmed CML diagnosis; the patient discontinued from the study after <1 month due to this protocol deviation but was included in the intent-to-treat population. The patient with *BCR-ABL1*^{IS} >100% at 24 months had previously achieved a best molecular response of *BCR-ABL1*^{IS} = 20% at month 21.

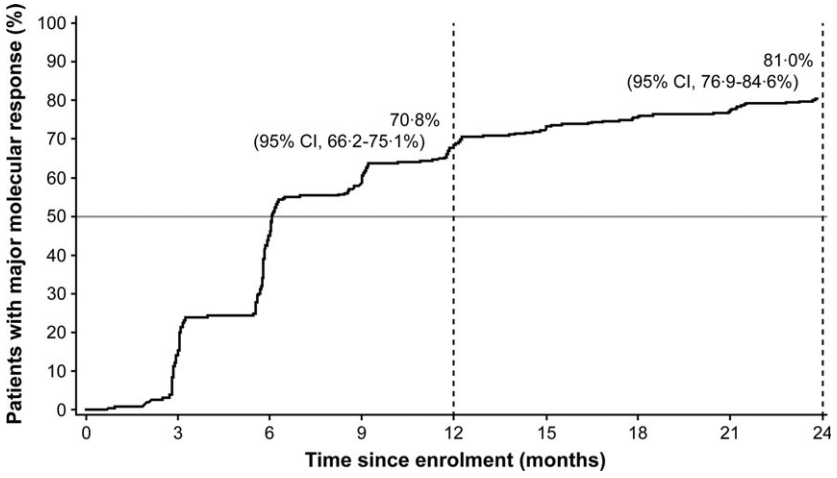

Fig 3. Cumulative incidence of major molecular response (*BCR-ABL1* ≤0·1% on the International Scale). 95% CI, 95% confidence interval.

arrest) and 4 who died >28 days after discontinuation of study treatment (the investigators attributed 3 deaths to CML/acute leukaemia; the remaining death was a suicide). The Kaplan–Meier estimated rate of overall survival at 24 months was 97·6% (95% CI, 96·1–99·2%).

Safety

A total of 205 patients (48·7%) had AEs leading to dose adjustments or interruptions, most commonly increased lipase (n = 37; 8·8%), thrombocytopenia (n = 35; 8·3%), and neutropenia (n = 32; 7·6%). Forty-one patients (9·7%) had AEs that led to study treatment discontinuation, most frequently increased alanine aminotransferase (n = 4; 1·0%). Five patients (1·2%) discontinued due to cardiovascular events (coronary artery disease, n = 2; peripheral artery disease, n = 2; myocardial ischaemia, n = 1).

The most common non-haematological AEs, regardless of relationship with the study drug, were headache (18·5%), rash (18·3%) and nausea (14·5%; Table II). Most AEs were grade 1/2. Cardiovascular events were reported in 19 patients (4·5%), including events related to ischaemic heart disease in 14 patients (3·3%), events related to peripheral artery disease in 5 patients (1·2%), cerebrovascular accident in 1 patient (0·2%) and arterial stenosis in 1 patient (0·2%). Among 19 patients with cardiovascular events on study, 18 had ≥1 prior cardiovascular event and/or known pre-existing cardiovascular risk factor at baseline, including 9 patients with prior cardiovascular events (5 with prior myocardial infarction), as well as pre-existing dyslipidaemia [n = 9 (treated in 6)],

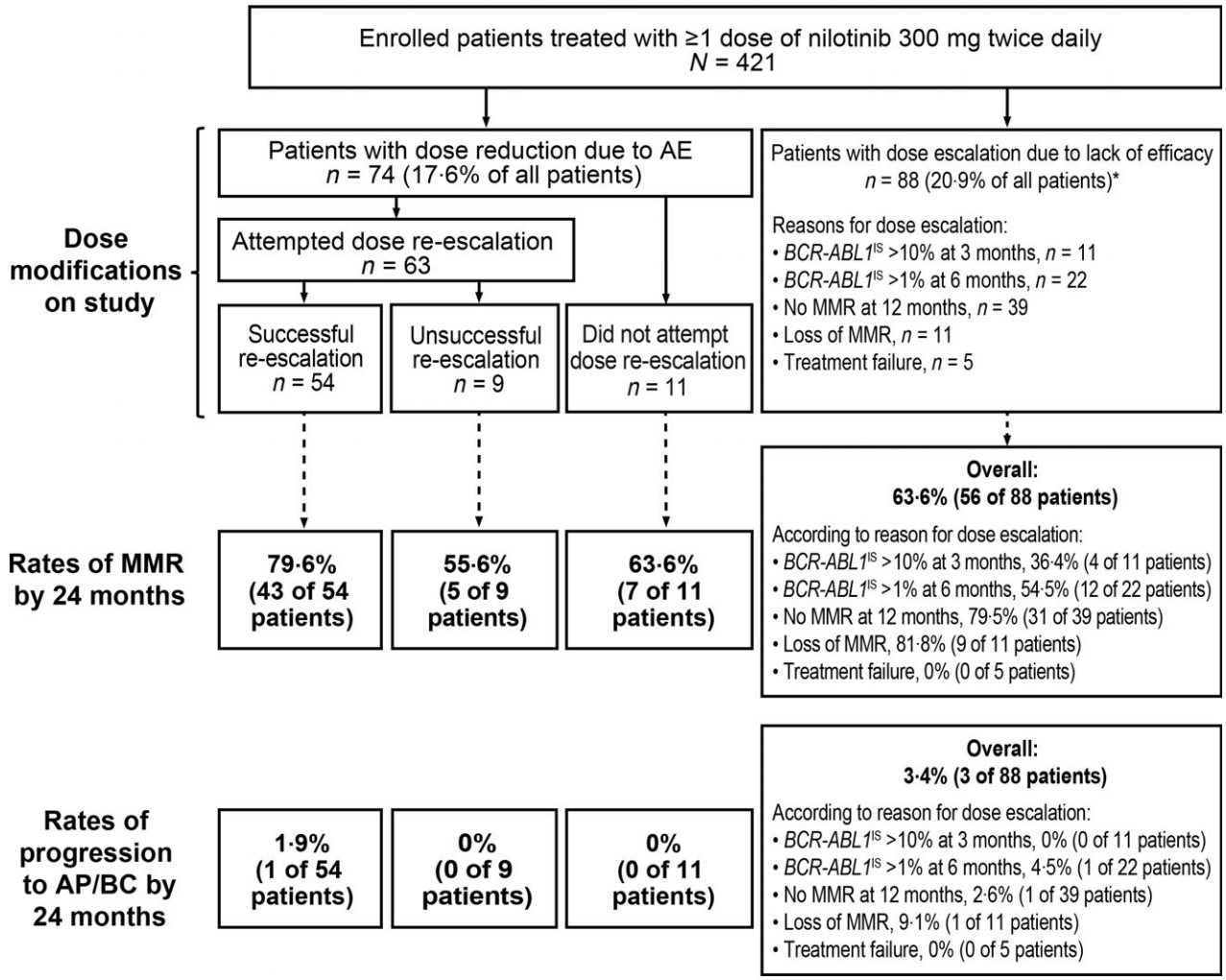

Fig 4. Outcomes of patients with dose modifications. Dose escalation and dose reduction were not mutually exclusive categories. Patients could be included in both groups. For MMR rates in patients with dose reduction, patients with MMR detected at any time before or after dose reduction were considered responders. For MMR rates in patients with dose escalation, only patients with MMR detected after dose escalation were considered responders. *Includes 4 patients with dose escalation due to lack of efficacy per investigator assessment despite not meeting the indicated criteria for dose escalation (*BCR-ABL1*^{IS} > 10% at 3 months, n = 1; *BCR-ABL1*^{IS} > 1% at 6 months, n = 1; no MMR at 12 months, n = 1; loss of MMR, n = 1). AE, adverse event; AP, accelerated phase; BC, blast crisis; MMR, major molecular response.

hypertension [n = 9 (treated in 8)], diabetes [n = 3 (all treated)], smoking/tobacco use (n = 6) and age ≥65 years (n = 7, including 2 patients with no other known pre-existing risk factors). Pancreatitis was reported in 2·1% of patients. Few patients experienced hepatotoxicity (1·2%) or significant bleeding (1·2%). The most frequently reported newly occurring or worsening grade 3/4 haematological abnormalities were neutropenia (11·9%) and thrombocytopenia (10·5%; Table III), and the most frequently reported grade 3/4 biochemical abnormalities were abnormal levels of lipase (14·5%), glucose (5·2%) and phosphate (4·5%).

Discussion

Results from ENESTxtnd confirm the efficacy and safety of frontline treatment with nilotinib 300 mg twice daily in patients with CML-CP and demonstrate the feasibility and potential benefits of nilotinib dose optimization; in many of the participating countries, this was the first prospective, local study to demonstrate the efficacy and safety of frontline nilotinib. Most patients (77·9%) completed the full 24-month duration of study treatment, and 70·8% achieved the primary endpoint of MMR by 12 months.

Compared with historical data from the nilotinib 300-mg twice-daily arm of ENESTnd, MMR rates were consistently higher in ENESTxtnd (by 12 months, 55% of patients in the nilotinib 300-mg twice-daily arm of ENESTnd achieved MMR *versus* 70·8% in ENESTxtnd; by 24 months, 71% vs. 81·0%, respectively) (Kantarjian *et al*, 2011). Notably, the median age and median time since diagnosis were generally comparable among patients in ENESTnd and ENESTxtnd (Saglio *et al*, 2010); however, the Sokal risk score distribution

Table II. Most frequently reported non-haematological adverse events (at least 10%) and other adverse events of interest, regardless of relationship to study drug.

	Nilotinib $N = 421$	
Patients, *n* (%)	All grades	Grade 3/4
Most frequent non-haematological AEs		
Headache	78 (18·5)	3 (0·7)
Rash	77 (18·3)	3 (0·7)
Nausea	61 (14·5)	1 (0·2)
Constipation	52 (12·4)	3 (0·7)
Alopecia	50 (11·9)	0
Pruritus	50 (11·9)	1 (0·2)
Fatigue	48 (11·4)	2 (0·5)
Upper respiratory tract infection	44 (10·5)	1 (0·2)
Other AEs of interest*		
Fluid retention	43 (10·2)	4 (1·0)
Peripheral oedema	11 (2·6)	0
Pleural effusion	4 (1·0)	1 (0·2)
Pulmonary oedema	3 (0·7)	1 (0·2)
Hepatotoxicity	5 (1·2)	2 (0·5)
Pancreatitis	9 (2·1)	5 (1·2)
Significant bleeding	5 (1·2)	3 (0·7)
CNS haemorrhage	2 (0·5)	2 (0·5)
GI haemorrhage	3 (0·7)	1 (0·2)
Symptomatic QT prolongation	5 (1·2)†	2 (0·5)
Retinal vein occlusion	1 (0·2)	1 (0·2)
Thrombophlebitis	2 (0·5)	0
Deep vein thrombosis	1 (0·2)	0
Cardiovascular event	19 (4·5)	13 (3·1)
Ischaemic heart disease	14 (3·3)	11 (2·6)
Ischaemic cerebrovascular event	1 (0·2)	0
Peripheral artery disease	5 (1·2)	3 (0·7)
Other	1 (0·2)‡	0

CNS, central nervous system; GI, gastrointestinal.

*Listed frequencies of fluid retention, hepatotoxicity, pancreatitis, significant bleeding, CNS haemorrhage, GI haemorrhage, symptomatic QT prolongation, cardiovascular events, ischaemic heart disease, ischaemic cerebrovascular events, peripheral artery disease, and other cardiovascular events reflect the total frequencies of patients with ≥1 adverse event in the predefined group of preferred terms. Preferred terms included in the definition of each group are listed in 'Supplemental Methods'.

†Preferred terms for these events were convulsion ($n = 2$), syncope ($n = 2$), and sudden death ($n = 1$). A QT interval of >450 ms was detected in 1 of these 5 patients (a Fridericia-corrected QT interval of 453 ms was detected on study day 8 in the patient who later died suddenly on study day 384).

‡The preferred term for this event was arterial stenosis.

among patients in each study cannot be compared because Sokal risk scores were not collected in ENESTxtnd, and it is possible that the patient population in ENESTxtnd was healthier overall.

The higher rates of MMR in ENESTxtnd *versus* ENESTnd may be due in part to the higher overall dose intensity [the 25th percentile for dose intensity was 582 mg/day in ENESTxtnd *versus* 553 mg/day in the nilotinib 300-mg twice-daily arm of ENESTnd (Kantarjian *et al*, 2011)], which in turn may have been due to the opportunity for dose optimization in ENESTxtnd. Whereas the protocol for ENESTxtnd allowed patients with insufficient response and those with drug-related AEs to have their nilotinib dose actively escalated or reduced and re-escalated, and then continue therapy, the ENESTnd protocol did not allow for nilotinib dose escalation and included more stringent guidelines for nilotinib dose reduction and re-escalation than those in ENESTxtnd (Saglio *et al*, 2010). For example, following the second occurrence of a drug-related, non-haematological grade 2 AE (or first occurrence if grade 3/4) in the nilotinib 300-mg twice-daily arm of ENESTnd, the study protocol called for dose reduction to 400 mg once daily, and subsequent re-escalation was allowed only if the AE resolved to grade ≤1 for 1 month (Saglio *et al*, 2010). The favourable outcomes (e.g., >50% MMR rate by 24 months) in patients with dose modifications in ENESTxtnd suggest that nilotinib dose optimization may be an appropriate strategy for the management of many nilotinib-treated patients. The benefit of nilotinib dose optimization is further supported by results from another study of frontline nilotinib in patients with CML-CP, ENEST1st (Hochhaus *et al*, 2016b). Although the ENEST1st protocol did not allow for nilotinib dose escalation, it called for a similar (although not identical) dose reduction schedule to that used in ENESTxtnd for patients with recurrent AEs (Hochhaus *et al*, 2016b). In ENEST1st, MMR rates by 12 and 24 months (68·9% and 80·4%, respectively) were very similar to those in ENESTxtnd and higher than those in ENESTnd (Hochhaus *et al*, 2016b).

Table III. Newly occurring or worsening grade 3/4 haematological and biochemical abnormalities reported in at least 2% of patients.

Patients, *n* (%)	Nilotinib $N = 421$
Haematological	
Neutropenia	50 (11·9)
Thrombocytopenia	44 (10·5)
Anaemia	22 (5·2)
Leucopenia	22 (5·2)
Lymphopenia	14 (3·3)
Biochemical	
Lipase	61 (14·5)
Glucose	22 (5·2)
Phosphate	19 (4·5)
Magnesium	16 (3·8)
Total bilirubin	15 (3·6)
Sodium	9 (2·1)

Approximately one-fifth of patients in ENESTxtnd (20·9%) had their nilotinib dose escalated to 400 mg twice daily after meeting the protocol-designated criteria for insufficient response to nilotinib 300 mg twice daily. Notably, although high-dose imatinib has been associated with poor

tolerability (Cortes *et al*, 2010; Hehlmann *et al*, 2011), most patients who had nilotinib dose escalation in this study were able to maintain the higher dose, with 83 of 88 remaining on nilotinib 400 mg twice daily at the end of treatment. Although some of these patients (14 of 88; 15·9%) later discontinued treatment due to suboptimal response or treatment failure, the majority (63·6%) achieved MMR by 24 months. This suggests that it may be possible to rescue the outcomes of many patients with poor early responses on nilotinib through dose escalation. However, 24-month MMR rates varied depending on the specific trigger for dose escalation. Whereas approximately one-third of patients with dose escalation due to *BCR-ABL1*^{IS} > 10% at 3 months achieved MMR, ≈80% of those with dose escalation due to lack of MMR at 12 months or loss of MMR went on to achieve MMR after their dose was escalated. The importance of achieving *BCR-ABL1*^{IS} ≤ 10% at 3 months is well established (Hanfstein *et al*, 2012; Marin *et al*, 2012; Hughes *et al*, 2014a; Hochhaus *et al*, 2016b), and this response milestone has been incorporated into CML management guidelines from the European LeukemiaNet and the National Comprehensive Cancer Network (Baccarani *et al*, 2013; National Comprehensive Cancer Network, 2017); however, optimal management strategies for patients who do not meet this milestone remain unclear. Overall among patients with *BCR-ABL1*^{IS} > 10% at 3 months (regardless of dose escalation), the rate of MMR by 24 months (36·1%) was comparable to that in the nilotinib 300-mg twice-daily arm of ENESTnd (29%) (Hughes *et al*, 2014a).

The potential for nilotinib dose optimization was further supported by results from an independent study conducted by the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) simultaneously with ENESTxtnd that, similar to ENESTxtnd, allowed for nilotinib dose escalation (from 300 mg twice daily to 400 mg twice daily) in patients with suboptimal response or treatment failure. High rates of deep molecular response were observed among patients in that study: with a median follow-up of 29 months, 58% of patients had achieved a molecular response of 4-log reduction (MR^4; *BCR-ABL1*^{IS} ≤ 0·01%) at least once (Castagnetti *et al*, 2016). By comparison, 39% of patients in the nilotinib 300-mg twice-daily arm of ENESTnd achieved MR^4 by 24 months (Kantarjian *et al*, 2011). Although results from ENESTxtnd, ENEST1st, and the GIMEMA study support the use of dose-optimized nilotinib, other factors may have also contributed to the higher response rates observed in these studies *versus* ENESTnd, including the accumulation of clinical experience with nilotinib in the years since ENESTnd was initiated and the use of different laboratories to monitor molecular responses.

It is difficult to compare the rates of CCyR in this study with those in ENESTnd because cytogenetic assessments were not required between 6 months and the end of study treatment for most patients in ENESTxtnd, whereas cytogenetic testing was required every 6 months for the first 2 years of therapy in ENESTnd (Saglio *et al*, 2010). Although the CCyR rates in ENESTxtnd were numerically lower than in ENESTnd (80% and 87% of patients in the nilotinib 300-mg twice-daily arm of ENESTnd achieved CCyR by 12 and 24 months, respectively), these differences are probably a result of differences in the cytogenetic assessment schedule rather than the efficacy of nilotinib. This observation is supported by the higher rates of MMR by 12 and 24 months in ENESTxtnd *versus* ENESTnd (Kantarjian *et al*, 2011).

Other efficacy and safety results were generally similar to those from ENESTnd and other studies of frontline nilotinib in patients with CML-CP (Rosti *et al*, 2009; Saglio *et al*, 2010; Kantarjian *et al*, 2011; Wang *et al*, 2015; Hochhaus *et al*, 2016b). Very few progressions to AP/BC were reported during or after discontinuation of study treatment, and very few patients died due to CML. Notably, despite the opportunity for dose optimization in ENESTxtnd, the rates of discontinuation of study treatment and discontinuation due to AEs were similar to those in the nilotinib 300-mg twice-daily arm of ENESTnd (by the 2-year data cut-off, 26% and 9%, respectively) (Kantarjian *et al*, 2011), as well as those in ENEST1st (by the end of the 2-year study, 19·1% and 10·7%, respectively) (Hochhaus *et al*, 2016b). As in prior studies, most non-haematological AEs were grade 1/2 (Rosti *et al*, 2009; Saglio *et al*, 2010; Kantarjian *et al*, 2011; Wang *et al*, 2015; Hochhaus *et al*, 2016b). Approximately half of patients had dose interruptions or adjustments due to AEs and overall, among patients with dose reductions, most of those who attempted to re-escalate were successful.

The incidence of cardiovascular events was 4·5%. This incidence may have been driven by a relatively short follow-up in the study but is consistent with the 2-year data from ENESTnd (Hughes *et al*, 2015). In ENESTnd, cardiovascular events were reported in 2·9% and 5·8% of patients in the nilotinib 300-mg twice-daily and nilotinib 400-mg twice-daily arms, respectively, during the first 2 years of treatment (Hughes *et al*, 2015); however, rates of these events cannot be compared directly across trials due to differences in study eligibility criteria. For example, patients with myocardial infarction within the past 12 months were excluded from ENESTxtnd, whereas patients with any history of clinically documented myocardial infarction were excluded from ENESTnd (Saglio *et al*, 2010); indeed, 5 of the 19 patients with cardiovascular events on study in ENESTxtnd were known to have had a myocardial infarction prior to enrolment.

The frequency of treatment-emergent *BCR-ABL1* mutations detected in ENESTxtnd was comparable to that in nilotinib-treated patients in ENESTnd (Kantarjian *et al*, 2011; Hochhaus *et al*, 2013). By the 2-year data cut-off in ENESTnd, treatment-emergent mutations were detected in 10 patients (3·5%) in the nilotinib 300-mg twice-daily arm and 8 patients (2·8%) in the nilotinib 400-mg twice-daily arm [*versus* 20 patients (7·1%) in the imatinib arm]. Similar

to ENESTnd, the majority of patients with treatment-emergent mutations in ENESTxtnd developed nilotinib-resistant mutations (i.e., T315I) or mutations less sensitive to nilotinib (i.e., E255, F359, and Y253) (Kantarjian *et al*, 2011; Hochhaus *et al*, 2013).

Although many patients in ENESTxtnd had dose modifications at some point during the study, the median average daily nilotinib dose and median actual nilotinib dose intensity were equivalent to the planned dose of 300 mg twice daily, with narrow interquartile ranges, suggesting that nilotinib 300 mg twice daily was an effective and well tolerated dose for the majority of patients in ENESTxtnd. Nonetheless, for those patients who required dose escalations or reductions, the protocol-defined nilotinib dose-optimization schedule used in this study provided an opportunity to continue nilotinib therapy and, in many cases, achieve MMR. Overall, these results support the use of nilotinib 300 mg twice daily as a standard-of-care treatment option for patients with newly diagnosed CML-CP, with individualized dose optimization as necessary.

Acknowledgements

We thank Kudrat Abdulkadyrov for his contributions to the ENESTxtnd study and the development of this manuscript. Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals. The authors thank Karen Kaluza, PhD, of ArticulateScience LLC for medical editorial assistance with this manuscript.

Funding sources

The ENESTxtnd study and work presented here were sponsored and funded by Novartis Pharmaceuticals Corporation.

Author contributions

TPH, CP, VJL, L-YS, AGT, LM, JHL and DD contributed to the study design; TPH, EM, MAS, OTC, AE, JS, HQ, CP, VJL, L-YS, AGT, LM and JHL collected data; all authors analysed and interpreted the data. All authors drafted and approved the manuscript for submission.

Conflicts of interest

TPH reports advisory board participation and grant and personal fees from Novartis, BMS and Ariad. MAS reports research funding from Novartis. JS reports personal fees for advisory boards, speakers bureau, and educational event sponsorship from Novartis and personal fees for speakers bureau and educational event sponsorship as well as a grant for CML nurse support from BMS. CP reports research funding and personal fees from Novartis. VJL reports research funding paid to the institution, unrestricted educational grant, speaker fees, and travel support to a congress and advisory board participation for Novartis; speaker fees and research funding paid to the institution and advisory board participation for BMS; speaker fees and advisory board participation for Amgen; speaker fees and research funding paid to the institution and advisory board participation for Key Oncologics; and speaker fees and research funding paid to institution from Janssen-Cilag. L-YS reports advisory board participation and grant from Novartis. YJ is employed by, and owns stock in, Novartis Pharmaceuticals Corporation. SA is employed by Novartis Healthcare Pvt. Ltd. DD is employed by, and owns stock in, Novartis Pharmaceuticals Corporation. Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals. All other authors declare no competing financial interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Supplemental methods.

Table SI. Nilotinib dose-escalation criteria.

Table SII. Study dose reduction and re-escalation criteria for patients receiving nilotinib 300 mg twice daily.

Table SIII. Proportion of patients receiving each nilotinib dose level at 12 and 24 months.

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