Title

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Journal

Cancer, 126(7)

Authors

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Publication Date

2020-04-01

DOI

10.1002/cncr.32623

Peer reviewed

HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2024 September 10.

Published in final edited form as:

Cancer. 2020 April 01; 126(7): 1448–1459. doi:10.1002/cncr.32623.

Long-term results of a phase 2 trial of nilotinib 400 mg twice daily in newly diagnosed patients with chronic phase of chronic myeloid leukemia

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Abstract

Background ––Nilotinib is a potent, second generation inhibitor of *BCR-ABL1* tyrosine kinase, approved for frontline and salvage therapy of patients with chronic phase chronic myeloid leukemia (CP-CML).

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Author contributions:

JEC and HMK designed the study, and provided administrative support. JEC, FR, SV, AF, ZE, TMK, SOB, HMK treated patients, and provided study materials. LM, JEC, GMN, and SDS reviewed patient's charts, collected and analyzed the data. LM and JEC wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

Disclosure of Conflicts of Interest:

LM; AF; TMK; SD; GB; PKP; GMGN; MK: None.

SV: Research funding from Incyte. JEC: Research funding from Ambit BioSciences, ARIAD, Arog, Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Celator, Celgene, Novartis, Pfizer, Sanofi, Sun Pharma, Teva; consultant for Ambit BioSciences, ARIAD, Astellas Pharma, BiolineRx, Bristol-Myers Squibb, Novartis; Pfizer. **FR:** Research funding from Amgen, Bristol-Myers Squibb, Merck, Seattle Genetics, Sunesis Pharmaceuticals, Honoraria from Amgen, Pfizer, Seattle Genetics, Sunesis Pharmaceuticals; Consulting or advisory role for Amgen, Seattle Genetics, Sunesis Pharmaceuticals. **GGM**: Research funding and Advisory Role for Novartis. **EJJ:** Research funding from Amgen, Novartis, Pfizer. **SOB:** Consultant or Advisory Role: Amgen, Astellas, Celgene, GlaxoSmithKline, Janssen Oncology, Aptose Biosciences Inc., Vaniam Group LLC, AbbVie, Alexion, Gilead, Pharmacyclics, TG Therapeutics, Pfizer, Sunesis; Research funding: Kite, Regeneron, Acerta, Gilead, Pharmacyclics, TG Therapeutics, Pfizer, Sunesis. **HMK:** Research Funding from Amgen, ARIAD, Bristol-Myers Squibb, Delta-Fly Pharma, Novartis, Pfizer.

Trial Registration ID [Clinicaltrials.gov]: NCT00129740

Methods ——In this single institutional, phase 2 study, 122 patients with newly diagnosed CP-CML received nilotinib 400 mg twice daily. The median follow-up on study was 78.3 months (IQR, 58.4–96.5).

Results ——Fifty six percent of patients remained on therapy at last follow-up. The overall rate of both complete cytogenetic and major molecular response was 91%. Seventy five percent and 59% of patients achieved $MR^{4.5}$ and sustained $MR^{4.5}$ beyond 2 years, respectively. The estimated event free survival and overall survival at 5 years were 89% and 93%, respectively. Corresponding rates at 10 years were 85% and 88%, respectively. Treatment discontinuation due to toxicity occurred in 19% of patients, mostly due to cardiovascular events (10%), and biochemical abnormalities (6%). The top three non-hematologic toxicities were rash (55%), elevated bilirubin (57%) and elevated aminotransferases (48%). Hematologic toxicity was transient and mild. Ischemic cardiovascular adverse events occurred in 8% of patients. Four patients (3%) progressed to accelerated or blast phase while on therapy, and 7 patients (6%) died on study.

Conclusion ——Our data confirm the long-term efficacy of nilotinib 400 mg twice daily in patients with CP-CML. A majority of patients can achieve sustained $MR^{4.5}$. Clinical trial.gov : NCT00129740.

Precis / key points:

Nilotinib is effective frontline treatment for patients with early chronic phase CML resulting in a high rate of deep and sustained molecular responses. The long term safety profile remains favorable.

Keywords

CML; nilotinib; frontline; safety; efficacy

INTRODUCTION

Nilotinib (Tasigna, Novartis Pharmaceutical Corporation, NJ) is a second generation *BCR-ABL1* tyrosine kinase inhibitor which is 30-fold more potent than imatinib; it has activity against the majority of imatinib-resistant *BCR-ABL1* mutations, except, most notably, T315I, Y253H/F, F359V/C and E255V/K.[1,2] Nilotinib is approved for the frontline and salvage therapy of adults, and more recently children, with Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia in chronic phase (CP-CML). Approval in the frontline setting was based on the results from a phase 3 randomized study initiated in 2007 in 846 newly diagnosed patients with CP-CML comparing nilotinib 300 or 400 mg twice daily (BID) to imatinib 400 mg once daily (ENESTnd - Evaluating Nilotinib Efficacy and Safety in Clinical Trials Newly Diagnosed patients).[3–6] Both doses resulted in a significantly higher rate of major molecular response (MMR) at 12 months and less progression to accelerated phased (AP) or blast phase (BP) than with imatinib.[6] Given the similar efficacy and lower toxicity with nilotinib 300 mg BID, this dose became the frontline standard of care for patients with CP-CMP.

In 2005, prior to the start of the ENESTnd trial, we initiated a single institutional, phase 2, prospective study evaluating nilotinib 400 mg BID in the frontline setting in patients with

CP-CML. Preliminary results were reported after a median follow-up of 17 months.[7] Here we report the long-term efficacy and safety data from this trial after a median follow-up of 78.3 months (IQR, 58.4–96.5).

PATIENTS AND METHODS

Patients

From July 2005 to March 2014, patients with newly-diagnosed CP-CML were treated at MD Anderson Cancer Center. Eligibility and exclusion criteria were published.[7] Briefly, patients were age ≥18 years with previously untreated CP-CML (hydroxyurea or a maximum of 1 month of standard-dose imatinib allowed) with adequate performance status and organ function. Exclusion criteria included patients with pre-existing cardiac conditions, such as uncontrolled hypertension or angina, myocardial infarction within 12 months, pretreatment QTc prolongation >450 milliseconds, certain conduction disorders and history of clinically significant ventricular arrhythmias. The study was approved by the institutional review board. All patients signed an informed consent in accordance with Declaration of Helsinki. The current report is based on the data cutoff of December 31st, 2016 when the study was closed. Clinical trial.gov: NCT00129740.

Therapy and evaluation on study

Patients received nilotinib 400 mg BID orally, administered at least 2 hours after and 1 hour before meals. Treatment was continued until disease progression or unacceptable toxicity.

Patients with grade ≥3 non-hematologic adverse events (AE) had their treatment transiently interrupted until recovery to grade ≤1 with a reduction by one dose level (up to the lowest acceptable daily dose of 150 mg once daily). For hematologic AE, treatment was interrupted for grade 4 neutropenia (neutrophils $<0.5 \times 10^9$/L), or for platelets $<40 \times 10^9$/L. Treatment was restarted at the same dose if recovery (neutrophils $>1 \times 10^9$/L, and/or platelets $>60 \times 10^9$/L) occurred within 2 weeks, or at a reduced dose if recovery time was longer.

Evaluations included blood counts and chemistry every 1 to 2 weeks for the first 3 months and then every 6 weeks. Bone marrow aspiration, cytogenetic analysis (conventional cytogenetics using the G-banding technique in ≥ 20 metaphases), and peripheral-blood quantitative reverse transcription polymerase chain reaction for the *BCR-ABL1* transcripts were performed at baseline, every 3 months for 1 year, and every 6 months thereafter. Patients with stable deep molecular remissions did not have further bone marrow aspirations.

Adherence to therapy was measured through a patient diary, pill count of returned medication, and patient interview during follow-up visits.

Definition of response, survival endpoints and statistical analysis

Response criteria were as previously reported.[7] Cytogenetic response (CyR) was categorized as complete (0% Ph-positive metaphases), partial (1% to 35% Ph-positive metaphases), or minor (36% to 95% Ph-positive metaphases). Molecular response was expressed as a *BCR-ABL1/ABL1* transcript ratio (IS) as follows: major molecular response (MMR) ≤0.1%, $MR^4 \leq 0.01\%$, $MR^{4.5} \leq 0.0032\%$ and complete (CMR), with undetectable transcripts with at

least 100,000 *ABL1* copies detected. Sustained MR$^{4.5}$ was defined as persistent MR$^{4.5}$ ≥2 years in patients who completed ≥ 27 months of therapy considering the first assessment at 3 months. Patients without adequate response or clinical evidence of treatment failure (European LeukemiaNet criteria[8]), had performed mutational analysis of the *ABL1* codons 220 to 500 (ABL KD) by standard Sanger sequencing. Adverse events (AEs) were assessed by the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03.[9]

The primary endpoints of the study were the rate of MMR at 12 months and the toxicity rates. Stopping rules were set at the start of the study for unacceptable rates of MCyR and MR at 6 and 12 months, respectively, and for toxicity at any time.

The distributions of time-to-event end points and survivals were estimated using the methods of cumulative incidence functions and the Kaplan-Meier method as appropriate, and were measured from the start of treatment to a specific event as previously reported (death as a competing risk for time-to event end points).[7,10] Overall survival (OS) was measured to the date of death from any cause or last follow-up; event free survival (EFS) to the date of death from any cause, loss of CHR, loss of MCyR, or progression to AP/BP[11]; transformation-free survival (TFS) to the date of AP/BP, death on study, or last follow-up; and failure free survival (FFS) to EFS-defined events, failure to achieve ELN response[12], loss of CCyR, or discontinuation of therapy for any reason. Treatment-free remission (TFR) was defined as time between elective discontinuation while in sustained MR$^{4.5}$ until resuming therapy. Categorical and continues variables were calculated using descriptive statistics as appropriate. Univariate Cox proportional hazards regression was used to identify variables associated with survival (OS, EFS, TFS, and FFS). Statistical analysis was performed using Stata / SE version 14.2 (College Station, TX), and GraphPad Prism / version 7.01 (San Diego, CA).

RESULTS

Patient characteristics and disposition, treatment details

A total of 122 patients were enrolled (Table 1). Eighteen patients (15%) had received imatinib before enrollment for a median of 21 days (IQR, 2.4–30.3 days). Eighty three patients had a low Sokal score (68%). Median follow-up was 78.3 months (IQR, 58.4–96.5) for all patients, and 80.9 months (IQR, 59–115.3) for living patients.

Table 2 and Supplemental Figure 1 summarize patient disposition. The median duration of nilotinib therapy was 69 months (IQR, 35.5–96.1). At the time of this analysis, 62 (51%) patients remained on therapy with nilotinib, and 60 (49%) patients had discontinued nilotinib after a median time of 66 months (IQR, 27.4–84.2). The most common reason for study treatment discontinuation was AE in 19% (n = 23), an elective treatment discontinuation in 11% (n = 9), and financial reasons in 7% (n = 9) of patients (Supplemental Figure 1). Among all enrolled patients, the median dose at the last time on the study was 200 mg BID.

Fifty one patients (42%) did not require any dose adjustments throughout the study conduct. Seventy one patients (58%) required 89 transient treatment interruptions, with 27 patients requiring more than one interruption. The most common reasons were AE in 56 patients (46%, total of 78 events; the remaining were unrelated to study therapy (surgeries, or other medical conditions; n = 15).

Efficacy

Overall response—Figure 1 outlines overall response. Complete hematologic response was achieved in 119 patients (98%). Three patients did not achieve CHR: two stopped therapy within the first 3 weeks due to toxicity (speech and memory impairment [1], and nausea with headache [1]); the third patient was taken off study after 3.5 months due to non-compliance.

The overall rate of CyR was 93% (all but 2 were CCyR, Figure 1). Two patients achieved only a PCyR: one progressed to AP after 2 months, and the other discontinued treatment after 4 months in PCyR due to AEs. CCyR was sustained in 94% of patients who achieved such a response (median duration was not reached). Seven patients (6%) lost their CCyR, 6 while on therapy and one 13 months after treatment discontinuation due to an AE (while in $MR^{4.5}$). Loss of CCyR was accompanied by rapid progression to AP/BP in 3 patients, two of them with *ABL1* KD mutations (E255K and F359C). Four patients lost CCyR without progression to AP/BP. Three of these patients were likely undertreated (dose of 150 mg daily with frequent treatment interruptions in 1, documented non-compliance in 1, and 13 months off therapy for cardiac AE in 1). Early molecular response (EMR, *BCR-ABL1/ABL1* transcript <10% IS at 3 months and / or <1% IS at 6 months) was achieved in 115 of 116 evaluable patients (94% total; 99% in evaluable patients).

Overall, 91%, 79% and 76% achieved MMR, MR^4 and $MR^{4.5}$, respectively, at any time during therapy (Figure 1). Sustained $MR^{4.5}$ ($susMR^{4.5}$) was achieved in 72 patients (60% of all enrolled patients). Molecular responses were durable, with MMR and $MR^{4.5}$ sustained in 95% and 78% of patients with these responses, respectively (median duration not reached for both, Figure 1). The cumulative incidence of CCyR, MMR, MR^4, and $MR^{4.5}$ at 4 years were 84%, 84%, 73%, and 70%, respectively (Figure 2a, b). Nine patients lost $MR^{4.5}$, five of them while still on therapy (200 mg daily in 3 patients, 300 mg and 400 mg daily in 1 patient each, respectively); three of them regained $MR^{4.5}$ with nilotinib dose re-escalation[to 400 mg daily] from 200 mg and 300 mg daily in 2 and 1 patients, respectively). Four additional patients lost $MR^{4.5}$ after elective discontinuation. Three patients resumed therapy (dasatinib in 1, bosutinib in 2), and one died without any therapy due to complications from coronary artery disease.

Both CCyR and MMR occurred rapidly with a median time to response of 3 months (95% CI 2.1–6.5) and 5.7 months (95% CI, 3.4–6.9), respectively (Supplemental Figure 2). By 6 months, 88% and 66% of all patients had achieved CCyR and MMR, respectively. Median time to MR^4 was 17.4 months (95% CI 10.3–18.5), to $MR^{4.5}$ 22.7 months (95% CI 16.2–21.1), to CMR 47.8 months (95% CI 41.9–59.5). Median time to attain $susMR^{4.5}$ measured in 72 evaluable patients (i.e., patients who completed ≥ 27 months of therapy) was 17.8 months (95% CI 11.6–24.2). At at the time of database-lock, these patients had maintained

susMR$^{4.5}$ for a median of 66.8 months (IQR, 48.0–85.6). Rates of MR^{4}, MR$^{4.5}$ and CMR by 24 months in patients already in MMR, and overall kinetics of the *BCR-ABL1* transcript over time are shown in Supplemental Figures 3.

Among patients with EMR, 110 patients (96%) achieved MMR. The only patient who was evaluated for and did not achieve EMR, attained MMR after 20 months of therapy.

Treatment emergent *ABL1* KD mutations occurred in 4 of 8 patients assessed at the time of treatment failure or suboptimal response (3 of them with transformation to AP/BP) (F359C, Y253H, E255K; Figure 3). The last patient who had detectable *ABL1* mutation without progression to AP/BP, developed K378R after 1 year on nilotinib. Since K378R was considered of uncertain clinical significance, this patient continued on nilotinib and achieved MMR after an additional 6 months of therapy and has maintained MMR for more than 10 years.

Among 71 patients who required nilotinib dose reductions, 64 (90%) patients had subsequent response assessment. Thirty four patients (53%) achieved deeper MR on a reduced dose and it was sustained throughout the entire follow-up, 17 patients (27%) maintained the same MR, 8 patients (13%) experienced decrease in the depth of MR without losing MMR and 5 patients (8%) lost their MMR while being on a lower dose than 400 mg BID of nilotinib (Supplemental Table 1).

Factors predictive of MMR, MR$^{4.5}$, and sustained MR$^{4.5}$

Univariate analysis for prediction of responses evaluated clinical parameters (shown in Table 1) at the start of therapy. Variables associated with achievement of MMR included WBC, absence of leukopenia, absence of palpable splenomegaly, and low Sokal score (Table 3). For achievement of MR$^{4.5}$ and sustained MR$^{4.5}$, predictive variables represented b2a2 transcript, and age (assessed as a continuous variable), respectively (Table 3). There were not enough statistically significant events to create a multivariate analysis for each of these responses.

Survival analysis

Figure 4 shows the 5-year probabilities of survivals with an estimated OS, EFS, FFS, and TFS of 93%, 89%, 72%, and 92%, respectively. Predictive factors for OS by univariate analysis were age<50 years, and b2a2 transcript (Table 3, Supplemental Figures 4a and 4b), and age as continues variable for EFS and PFS. Again, there were not enough statistically significant events to create multivariate analysis.

Since the time of the original report[7], only 3 additional transformations to AP/BP have occurred for a total of 6 cases (5%), Figure 3). Of the 3 previously reported patients (#1, 4 and 6 in Figure 4), 2 are alive following allogeneic stem cell transplantation (SCT) with an OS from diagnosis of 68 and 117 months, respectively. Among the 3 newly transformed patients, 2 developed AP/BP while being on nilotinib for 5 and 60 months, respectively, whilst the last patient had therapy on hold for 11 months because of neutropenia (after previous treatment for 6 months). The first patient was in PCyR, and the two remaining

patients were in MMR at the time of transformation. All 3 patients are alive after SCT with an OS from diagnosis of 64, 74, and 104 months, respectively.

Over the study period, 12 patients (10%) died after a median follow-up of 53.9 months (IQR, 37.1–78.6; Figure 3). Seven deaths (6%) occurred while on study (6 on active therapy). Two patients died of vascular events (#8, and #14 in Figure 3). Failure defining events occurring by year on therapy are summarized in Supplemental Table 2.

Elective treatment discontinuation

Eleven patients (9%) discontinued therapy while in sustained $MR^{4.5}$ for at least 2 years, and median treatment duration prior to discontinuation was 113.4 months (IQR, 92.9–130.1). Six patients were experiencing concurrent events, mostly cardiovascular disease, which in some instances contributed to their decision of discontinuing therapy (Supplemental Table 3). One patient was lost to follow-up immediately after discontinuation. Among the remaining 10 patients, 4 lost their MR (1 lost $MR^{4.5}$, 3 MMR) after a median time of 5.6 months (IQR, 2.1–10.7) from discontinuation. One patient died shortly after loss of MMR due to pneumonia and chronic heart failure; two started on bosutinib and one on dasatinib (ongoing cardiovascular disease). All 3 patients regained response: two patients achieved $MR^{4.5}$ within 3 months of dasatinib and 9 months of bosutinib, respectively, and one regained MMR within 12 months of bosutinib. All MRs are ongoing for the past 1.5, 2 and 3 years. Six patients are in $susMR^{4.5}$ after elective discontinuation with a median follow-up of 9.5 months (IQR, 3.1–18.5). Projected TFR for all 11 patients who discontinued therapy was 54% at 3 years (Supplemental Figure 5).

Safety

The most frequent treatment-emergent AE observed while on study are depicted in Table 4. The most common non-hematologic AE were elevation in bilirubin (57%), skin rash (52%), fatigue (44%), and elevated aminotransferases (48%). Grade ≥3 non-hematologic AE were uncommon, the most frequent being hypertension (16%), and elevation of bilirubin (13%). Six patients developed clinical pancreatitis, 3 of them of ≥ grade 3. Overall, 45 patients (39%) experienced at least one cardiovascular event (CV AE, total number of 70), with 21 of them being ≥ grade 3 (Table 4). The most frequent CV AE were hypertension (total of 30 events in 26 patients, 25%) and arrhythmia (12%). Thirty one percent of patients with hypertension (n=8) were overweight, including 8% who were obese with BMI >30. Ischemic CV AE (cardiovascular [CAD], peripheral arterial [PAOD] and cerebrovascular [CVS]) occurred in 10 (8%) patients (total of 12 events; 8 patients with single ischemic CV AE [CAD in 4, CVS in 3 and PAOD in 1] and 2 patients with ischemic CAD and CVS). Patients had received therapy for a median of 44 months (IQR, 6.0–89.1) when the first ischemic CV AE occurred. Ischemic CV AE occurred more frequently in patients with a history of hypertension vs those without such history (6/26 vs 4/96, $p = 0.005$, OR 7.2), and in older patients (median age of patients with and without CV AE; 59.5 [IQR, 57.2–67.6] vs 48.9 [IQR, 37.5–58.4] years, respectively; $p = 0.001$). Sixteen patients (13%) had more than one CV AE, 10 of them had also an ischemic CV AE (Supplemental Table 4). Fever occurred in 47 patients (38%), and was identified as infectious in 41 patients. Most of these were mild

upper respiratory infections; only 5 instances of grade 3 infections occurred (pneumonia [3], skin cellulitis [1], and cholecystitis [1]).

The most common hematologic AE were anemia and neutropenia. Grade ≥3 neutropenia, thrombocytopenia, and anemia occurred in 6 (5%), 5 (4%), and 1 (1%) patient, respectively. Hematologic AE occurred early; all grade ≥3 (except for one episode of thrombocytopenia) occurred within the first 3 months.

Median time to first AE was 3 months (95% CI, 2.7–75.9), with 103 (84%) patients having AE within the 1st year and 112 (92%) experiencing at least one AE during the entire study duration. In general, the frequency of AE decreased over time, except for elevation of bilirubin and hypertension which were commonly observed later during therapy (Supplemental Table 5).

Treatment interruption related to AE occurred in 56 patients (46%; total 78 events), with the most common reasons being rash (n = 17), increased bilirubin or aminotransferases (n = 11 each), fatigue (n = 10), muscle cramps / pain / nausea (n = 9 each), and headache (n = 7). Twenty three patients (19%) required more than one interruption due to AE. Annual permanent discontinuation rate due to AE was 11% during the 1st year and 4% or less during the 6th year and beyond.

DISCUSSION

This manuscript provides the long-term follow-up of the first study of frontline nilotinib for patients with CML-CP. We report on 122 patients treated with nilotinib 400 mg BID with a median follow-up of 78 months. The encouraging early results of this study reported after a median follow-up of 17 months in the first 51 patients[7] supported initiation of the randomized, phase 3, ENESTnd trial that led to the approval of frontline nilotinib as therapy for CML-CP at the current standard dose of 300 mg BID.[3] At around the same time our study was started, GIMEMA initiated a similar study (also using 400 mg BID).[13]

The long-term results of our initial observation from this trial[7], confirms the efficacy of nilotinib as frontline therapy. The primary endpoint of MMR at 12 months seen in 71% of our patients compares to the 69% observed in the GIMEMA trial, and is somewhat higher to the 55% in the ENESTnd trial.[6,13,3] Considering the differences between studies and patients populations, such as the lower proportion of high risk Sokal score patients in our study (6.6% vs 28% in ENESTnd), the results appear consistent and reproducible for nilotinib as frontline therapy.

As regards to DMR, we observed a higher cumulative rate of $MR^{4.5}$ at 2 and 4 years of 52% and 70%, respectively, than reported in the ENESTnd trial (19% and 37% with 400 mg BID nilotinib, respectively).[6] Some studies have suggested that DMR may provide additional benefit in overall survival compared to achievement of only CCyR.[14] In addition, this endpoint has become an increasingly relevant for possible treatment discontinuation. In our study, we report a cumulative incidence of sustained $MR^{4.5}$ (>2 years) at 6 years of 52%, which compares favorably to that observed recently in the ENESTnd trial (41–44%).[6] However, it will be important to continue following these studies as additional patients

may still reach this goal. Similarly encouraging was the rate of treatment free remission in patients who discontinued therapy while in sustained MR[4.5]; which was observed in 55% (6 out of 11) of our patients. Despite the small number of patients, and a median follow-up of only 40 weeks, these results appear similar to that reported in other series, including the STOP2GTKI[15] and ENESTfreedom[16] trials. Our study also confirmed similarly high rates of estimated OS, EFS, FFS and TFS (5 years: 93%, 89%, 71%, and 92%, respectively), and low rates of AP / BP (5%) or death (6%), as those reported in the ENESTnd[6] and the GIMEMA.[13]

Regarding safety, our long-term follow-up shows what appears to be a higher incidence of some AE than what has been reported in ENESTnd with 400 mg BID.[6] For example, we observed a higher incidence of hypertension (25% all, 16% ≥ grade 3) then noted in the ENESTnd (8% all, 1% ≥ grade 3). This may be influenced in part by a more relaxed eligibility criteria, and inclusion of a population with more co-morbidities, such as obesity. However, the rate of ischemic cardiovascular AE, which are reportedly higher in those with a history of hypertension[6,13], was similar in our study (8%) to that seen in the GIMEMA (7%) and in the ENESTnd (8.7%).

A major limitation of our study is its single arm design and relatively small sample size. Still, the results are consistent with other reports using nilotinib as frontline therapy but provide longer follow up with 14% of patients followed now for more than 10 years. Another limitation also includes an evaluation of a dose that is not approved for standard clinical practice (400 mg BID versus approved 300 mg BID). At the time the study was initiated, this was the standard dose for the only approved indication. Importantly, a majority of patients were receiving a lower dose than the starting dose at the time of last follow-up and attained their best achieved MR. It has been reported that efficacy with TKIs can be maintained after dose reduction both in the salvage and the frontline setting.[17,18] These dose reductions may have contributed to maintain the incidence of adverse events, particularly arterio-occlusive events, similar to what has been reported in other series using the standard 300 mg BID. Also, in assessing the predictive factors for molecular responses, no adjustment was made for type I error and no correction was made for multiplicity. These results should be thus considered descriptive only.

In summary, our study of nilotinib 400 mg BID as a frontline therapy of patients with early CP-CML highlights its robust and rapid anti-leukemic activity. The most noticeable immediate benefit is the achievement of early molecular response. With continued therapy, most patients achieve a deep and durable molecular response. This provides the possibility for patients to attempt treatment free remission in the future. Although the overall incidence of AE was higher than reported on the approved dose of 300 mg BID, the rate of major ischemic cardiovascular AEs was acceptable with a prolonged use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We thank the participating patients and their families; the nurses, and members of the study management team. This study was supported in part by BMS, and by the MD Anderson Cancer Center Support Grant CA016672 (PI: Dr. Ronald DePinho) and Award Number P01 CA049639 (PI: Dr. Richard Champlin) from the National Cancer Institute.

Funding: Leukemia Support Grant CA016672, Leukemia SPORE the MD Anderson Cancer Center CA100632, the Charif Souki Cancer Research Fund

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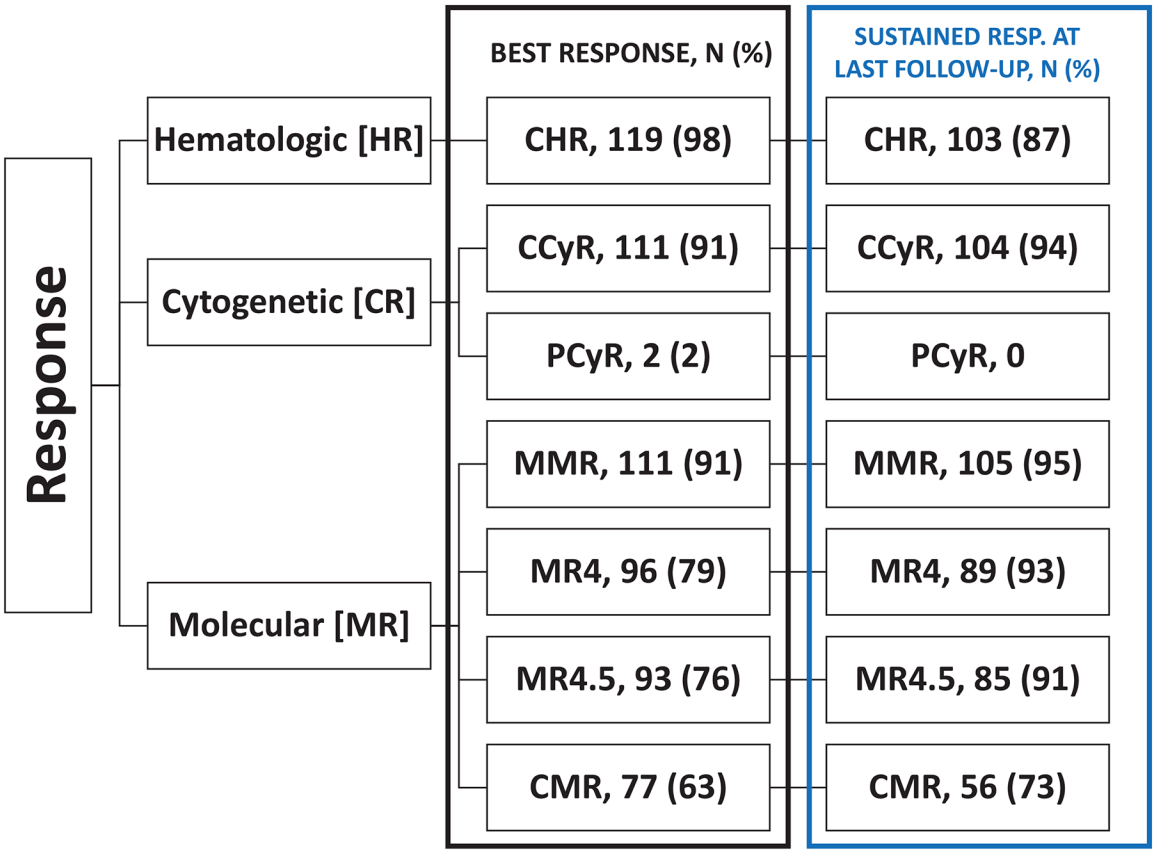
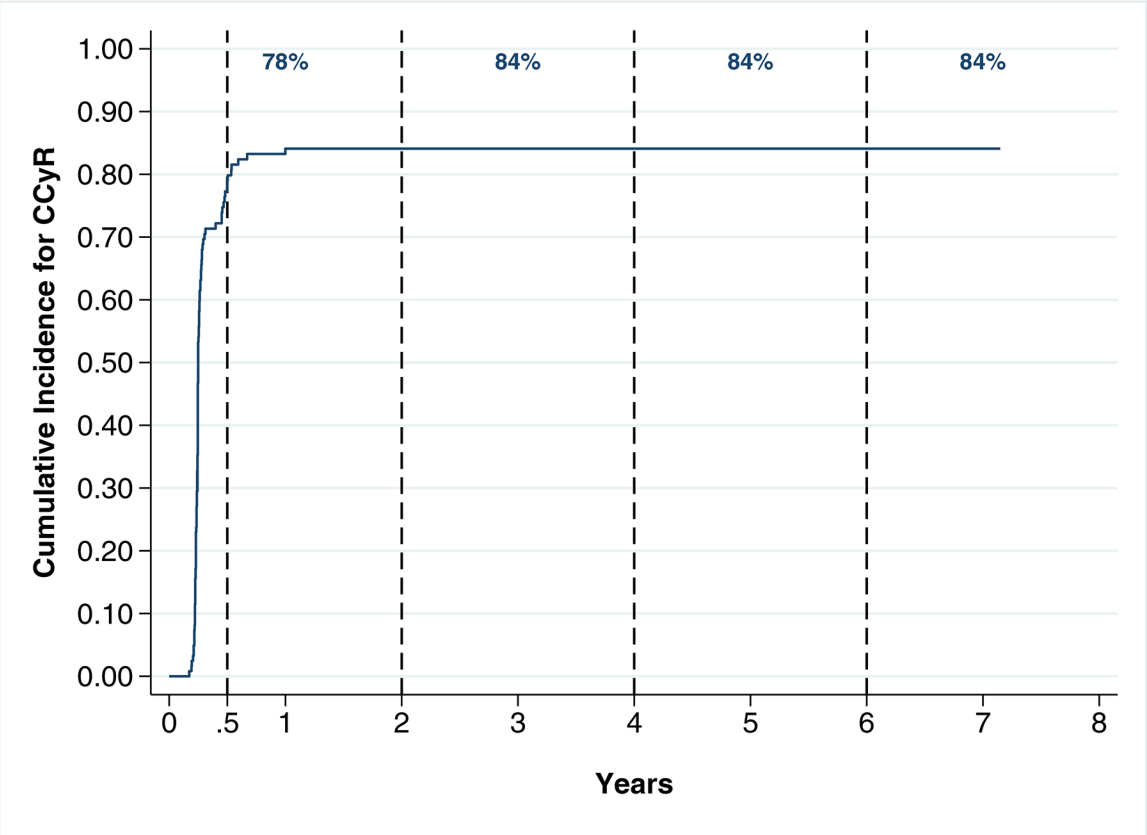


Figure 1.

Diagram showing overall responses on therapy. Sustained CMR excludes patients with CMR on at least 2 occasions with subsequent detectable BCR-ABL at any level (inc. $MR^{4.5}$).



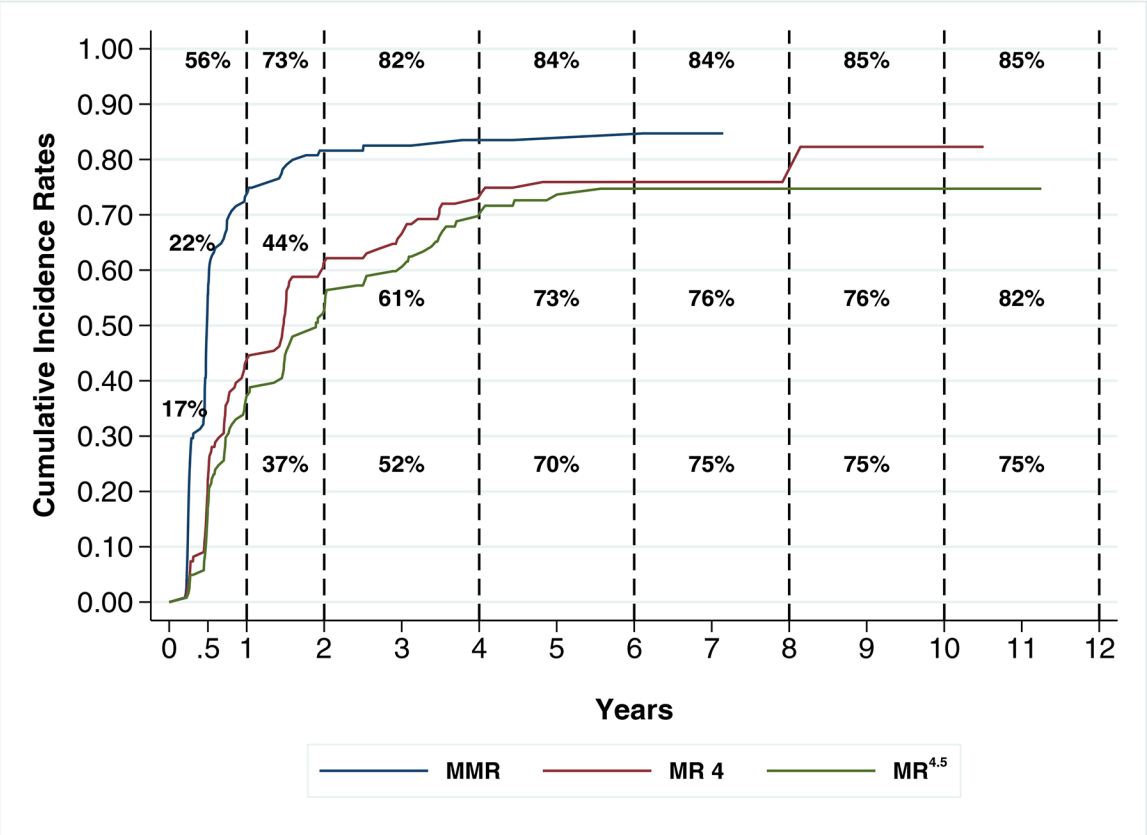


Figure 2.
Kaplan-Meier curves showing cumulative incidence of CCyR, MMR, MR^4, $MR^{4.5}$.

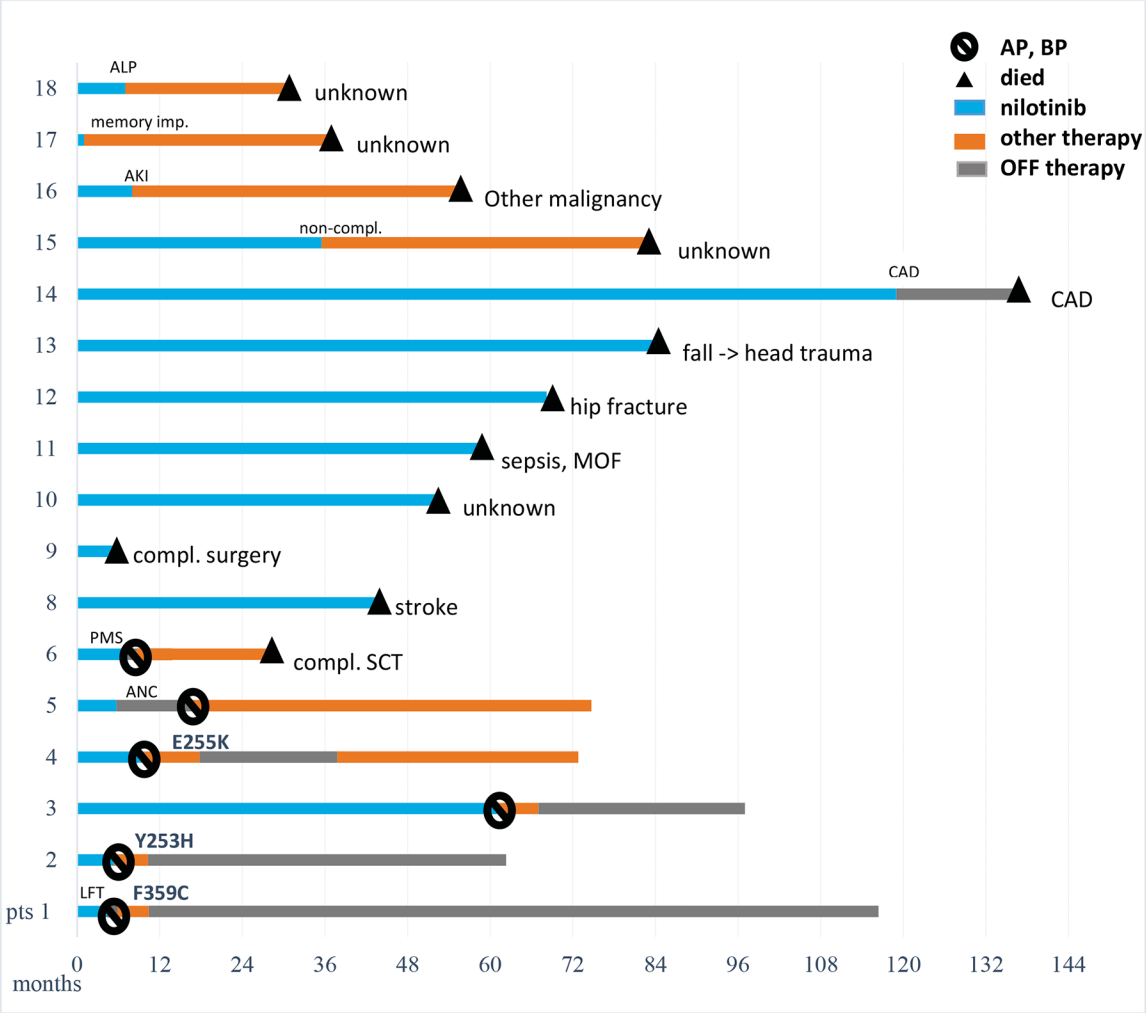
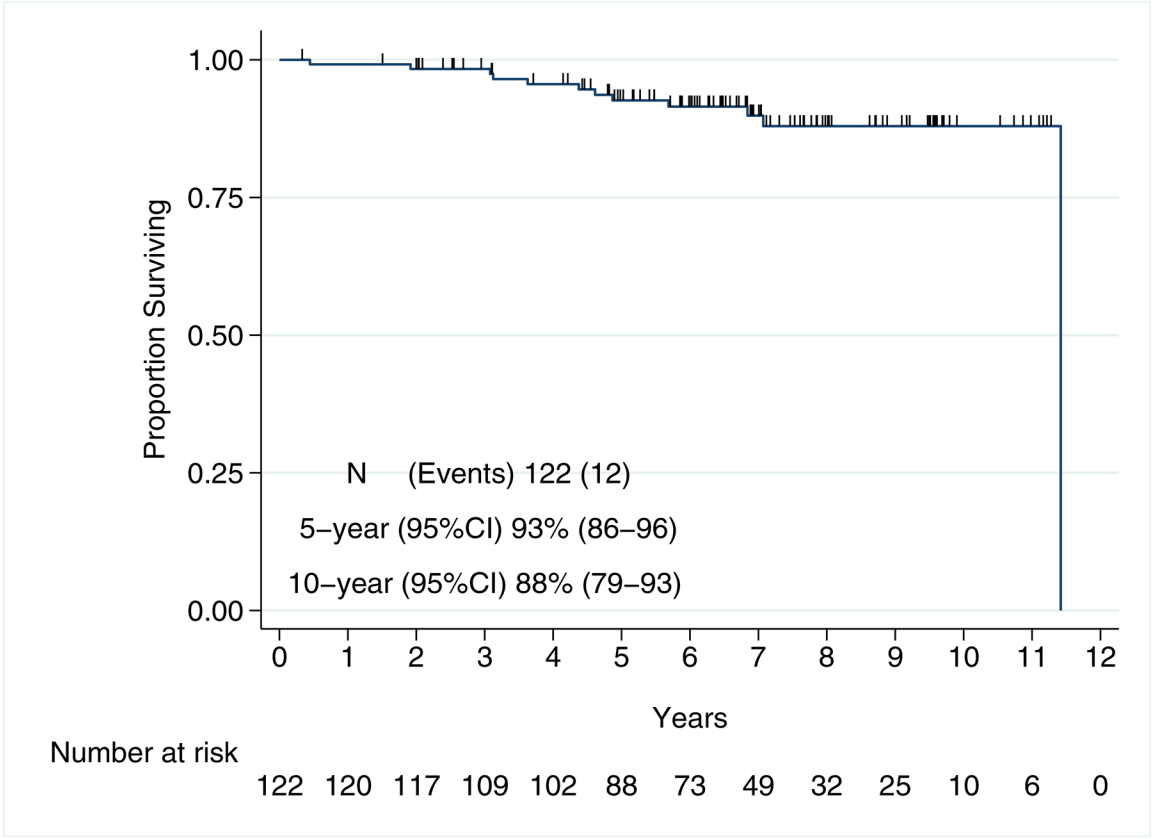
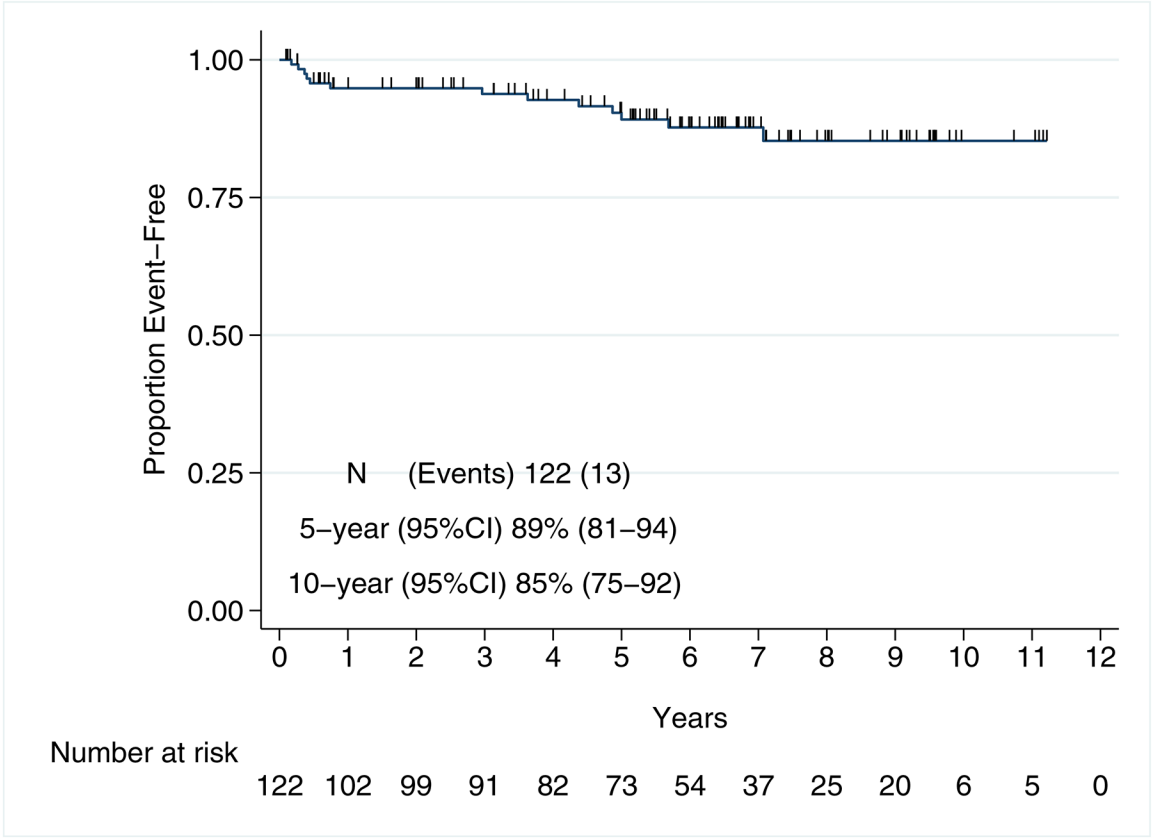
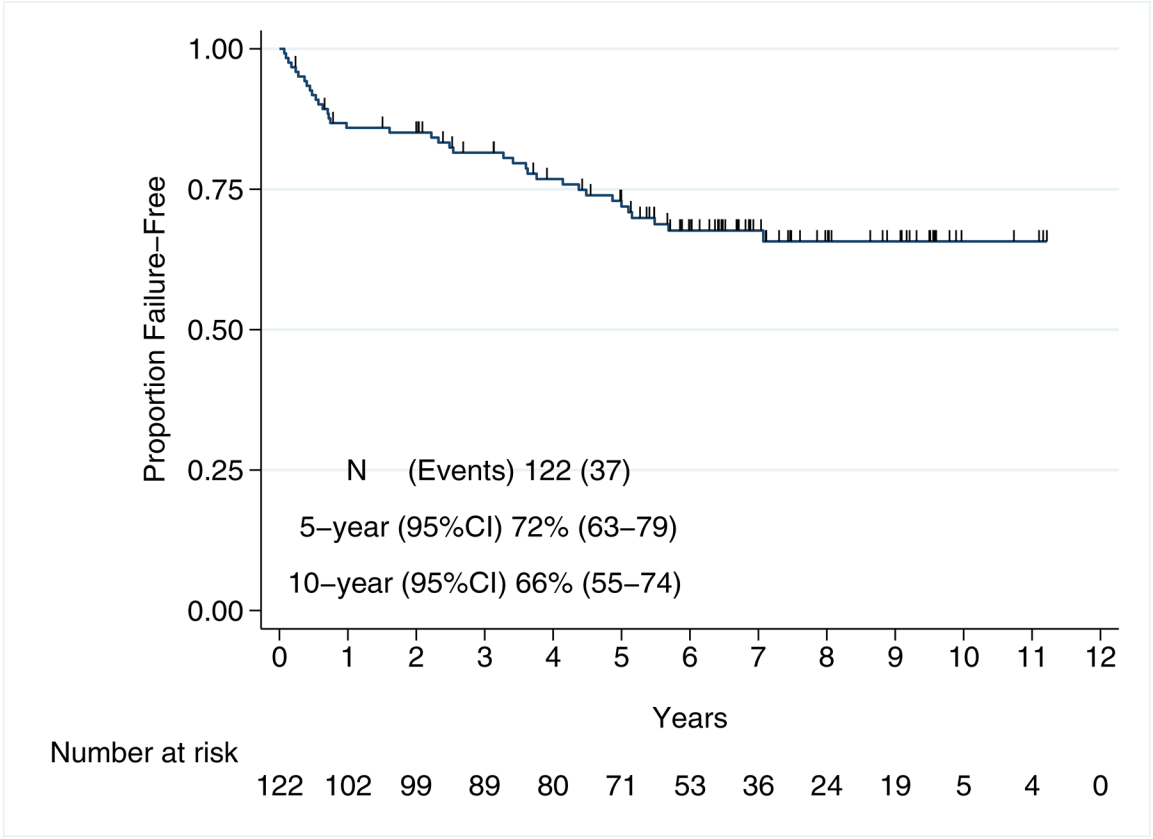


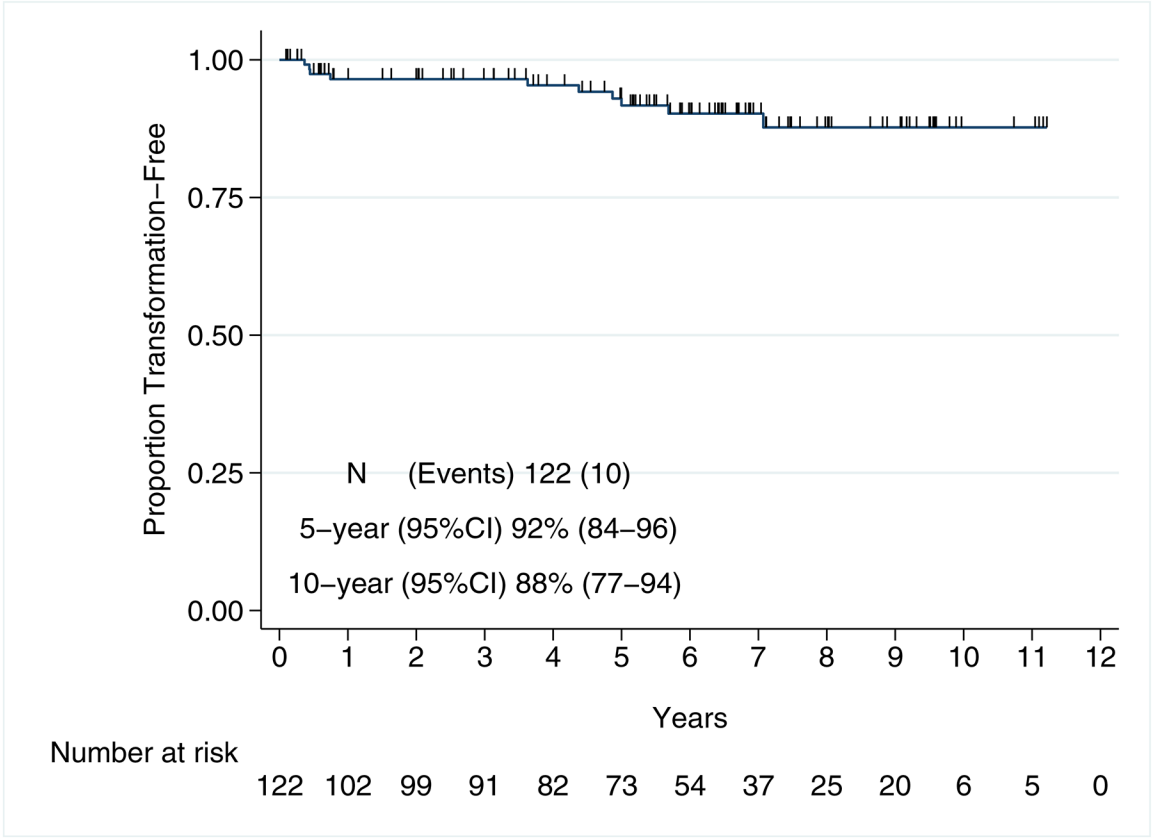
Figure 3.

A bar time graphs showing progression to accelerated or blast phase, and deaths observed on study. Abbreviations: X axis = months of observation, Y axis = patient 1–18; pts #1–5 are alive after ASCT, all except #1 and # 5 off TKI in CR, pts #1 and #5 are on dasatinib post ASCT for molecular relapse, pts #15–18 were treated with imatinib standard dose after nilotinib, *BCR-ABL1* domain mutation is unknown in pts #3, 5, 6; AP/BP occurred on nilotinib in pts #2, 3, 4, and while nilotinib was on hold in pts # 1, 5, 6; best response at the time of AP/BP: MMR in pts #3, 5, MCyR in pt #2, and CCyR in pts #1, 4, 6. ALP – alkaline phosphatase, imp. = impairment, AKI = acute kidney injury, N-C = non – compliant, PMS = polymyositis and endocarditis, ANC = absolute neutrophil counts aka neutropenia, LFT = elevated liver function tests, compl. = complication, MOF = multi-organ









Figures 4.

Kaplan -Meier curves showing overall outcomes; overall survival [4a], event free survival [4b], failure free survival [4c], transformation free survival [4d] observed on a study.

Table 1.

Clinical characteristics of all patients, N = 122

Characteristics	Median [IQR], or N (%)
Age at enrollment, years	50.7 (37.7–59.1)
Males	73 (59.8)
White blood cells ×10^9/L	39.6 (15.1–70.4)
WBC ≤ 4.5 ×10^9/L	11 (9)
WBC≥ ×10^9/L	99 (81.1)
Hemoglobin g/dL	12.3 (10.8–13.1)
Hemoglobin <10 g/dL	18 (14.8)
Platelets ×10^9/L	311.5 (221.0–474.0)
Platelets > 450 ×10^9/L	32 (26.2)
Peripheral blood blasts	0 (0–7)
Bone marrow blasts	2 (0–8)
Peripheral blood basophils	2 (0–19)
Bone marrow basophils	2 (0–13)
Splenomegaly > 5 cm BCM	17 (13.9)
ECOG performance status ≥ 1	70 (57.4)
Transcript type: b2a2	51 (41.8)
b3a2	49 (40.2)
b2a2 & b3a2	21 (17.2)
e1a2	1 (0.8)
Sokal risk score – low	83 (68)
high	8 (6.6)
intermediate	31 (25.4)

Table 2.

Patient disposition and treatment characteristics

Patients	Median [IQR], or N (%)
Reasons for study discontinuation	
Study closure	62 (51)
Adverse events (AE) - overall	23 (19)
AE - abnormal laboratory value[¶]	7 (6)
AE - cardiovascular[§]	10 (8)
AE - other clinical[¥]	6 (5)
Elective discontinuation	11 (9)
Death[≠]	6 (5)
Loss of CyR response / progression to AP, BP	1 (1) / 4 (3)
Non-compliance	6 (5)
Financial difficulties	9 (7)
Treatment duration	68.8 (35.5–96.1)
Median Nilotinib dose while on study	
800 mg daily	71 (58)
600–800 mg daily	13 (11)
400–600 mg daily	26 (21)
< 400 mg daily	14 (11)
Nilotinib dose on last follow-up on study in all 122 patients	
800 mg daily	51 (42)
400 mg daily	42 (34)
200 mg daily	25 (20)
300 mg daily	2 (2)
150 mg daily	2 (2)
Dose reductions while on study	71 (58)
Dose reduction to the lowest dose	
400 mg and 300 mg daily	53 (43) and 2 (2)
200 mg and 150 mg daily	17 (14) and 3 (2)
Repeated dose reduction	27 (22)

All patients will discontinue therapy by the end of 2017;

[¶]abnormal lab value contains: increased creatinine [2], liver enzymes (AST, ALT) [1], alkaline phosphatase (ALP) [1], lipase [1], bilirubin [1], and neutropenia [1],

[§]CV AE: coronary artery disease [5], acute myocardial infarction [2], arrhythmia [1], ischemic stroke [2],

[¥]other clinical: pancreatitis [2], polymyositis [1], headache [2], speech and memory impairment [1],

[≠]only 6 deaths occurred while on active therapy leading to treatment discontinuation (one additional patient discontinued therapy due to cardiovascular toxicity, and died during the subsequent follow-up)

Table 3.

Predictive factors for responses and outcomes by univariate analysis

Variable	HR (95% CI), p - value			
	OS	**EFS**	**FFS**	**PFS**
Age ¶	**1.08 (1.03–1.13), 0.001**	**1.04 (1.00–1.08), 0.05**	1.01 (0.99–1.03), 0.32	**1.05 (1.01–1.10), 0.02**
Male	1.05 (0.31–3.59), 0.94	1.06 (0.36–3.17), 0.91	0.91 (0.49–1.67), 0.75	0.59 (0.17–2.03), 0.40
WBC ¶	1.0 (0.99–1.01), 0.82	1.0 (0.99–1.01), 0.74	0.99 (0.99–1.00), 0.18	1.0 (0.99–1.01), 0.87
WBC ≥ 11 ×10^9/L	2.43 (0.31–19.0), 0.38	0.87 (0.24–3.11), 0.83	0.72 (0.36–1.47), 0.37	2.08 (0.26–16.4), 0.49
WBC ≤ 4.5 ×10^9/L	NE, 0.23	0.64 (0.08–4.9), 0.67	1.45 (0.61–3.46), 0.40	0.94 (0.12–7.44), 0.95
Hgb ¶	1.08 (1.03–1.13), 0.31	1.12 (0.83–1.51), 0.46	1.12 (0.94–1.33), 0.21	1.0 (0.70–1.41), 0.98
Hgb < 10 d/dL	0.50 (0.06–3.90), 0.51	0.82 (0.18–3.67), 0.79	0.88 (0.37–2.09), 0.77	1.22 (0.26–5.78), 0.70
Plt ¶	1.0 (1.0–1.0), 0.42	1.0 (1.00–1.00), 0.89	1.0 (1.00–1.00), 0.87	1.0 (0.9–1.00), 0.33
Plt > 450 ×10^9/L	0.67 (0.14–3.10), 0.61	0.54 (0.12–2.42), 0.42	0.92 (0.45–1.88), 0.83	0.36 (0.05–2.83), 0.33
Blast % PB	0.79 (0.38–1.63), 0.53	0.66 (0.29–1.53), 0.34	0.79 (0.56–1.12), 0.19	0.5 (0.13–1.84), 0.29
Blast % BM	0.92 (0.57–1.47), 0.73	1.29 (0.93–1.79), 0.13	1.13 (0.91–1.40), 0.28	1.47 (0.9–2.07**), 0.06**
Palpable spleen	1.29 (0.28–6.0), 0.75	0.92 (0.2–4.11), 0.91	0.79 (0.31–2.00), 0.62	1.4 (0.30–6.61), 0.67
ECOG PS ≥ 1	2.18 (0.58–8.25), 0.25	1.36 (0.45–4.06), 0.59	1.38 (0.73–2.59), 0.32	3.11 (0.66–14.7), 0.15
Sokal Int vs low	2.23 (0.26–19.2), 0.46	1.78 (0.22–14.5), 0.59	1.22 (0.37–4.02), 0.74	--
Sokal high vs low	3.17 (0.92–11.0), 0.07	2.39 (0.80–7.12), 0.12	1.03 (0.51–2.06), 0.93	2.83 (0.82–9.8), 0.10
Comb. transcript vs b2a2	**0.53 (1.12–2.35), 0.04**	0.85 (0.21–3.39), 0.81	1.23 (0.49–3.13), 0.66	0.88 (0.16–4.8), 0.88
Comb. transcript vs b3a2	0.44 (0.09–2.20), 0.32	0.66 (0.15–2.96), 0.59	1.62 (0.64–4.08), 0.31	0.76 (0.13–4.6), 0.77
Comb. transcript vs others	7.3 (0.74–71.4), 0.09	6.69 (0.69–65.1), 0.10	3.4 (0.41–28.40), 0.26	9.39 (0.8–105), 0.07
	MMR	***MR*** [4]	***MR*** [4.5]	***Sust MR*** [4.5]
Age ¶	0.99 (0.98–1.0), 0.16	0.99 (0.98–1.01), 0.25	**0.99 (0.98–1.0), 0.04**	**0.98 (0.96–1.0), 0.02**
Male	0.86 (0.57–1.3), 0.46	0.93 (0.61–1.42), 0.73	0.85 (0.55–1.31), 0.47	0.92 (0.56–1.52), 0.75
WBC ¶	**1.0 (0.99–1.0), 0.02**	1.0 (0.99–1.0), 0.07	1.0 (0.99–1.0), 0.11	1.0 (1.0–1.0), 0.96
WBC ≥ 11 ×10^9/L	0.64 (0.39–1.03), 0.07	0.64 (0.38–1.1), 0.11	0.76 (0.42–1.35), 0.35	1.34 (0.82–1.29), 0.24
WBC ≤ 4.5 ×10^9/L	**2.74 (1.22–6.12), 0.01**	1.95 (0.89–4.3), 0.09	1.36 (0.53–3.46), 0.52	0.6 (0.35–1.03), 0.07
Hgb ¶	1.1 (0.96–1.2), 0.22	1.07 (0.95–1.21), 0.26	1.09 (0.96–1.23), 0.17	0.7 (0.86–1.1), 0.68
Hgb < 10 g/dL	0.73 (0.46–1.15), 0.17	0.82 (0.47–1.43), 0.49	0.76 (0.42–1.37), 0.36	1.17 (0.62–2.2), 0.63
Plt ¶	1.0 (0.96–1.0), 0.98	1.0 (0.99–1.1), 0.99	1.0 (1.0–1.1), 0.86	1.0 (1.0–1.0), 0.80
Plt > 450 ×10^9/L	1.03 (0.64–1.67), 0.90	1.95 (0.89–4.3), 0.09	1.1 (0.67–1.85), 0.69	--
Blast % PB	0.94 (0.85–1.05), 0.22	0.95 (0.84–1.07), 0.39	0.87 (0.75–1.01), 0.45	1.02 (0.9–1.15), 0.71
Blast % BM	0.92 (0.80–1.05), 0.21	0.88 (0.76–1.01), 0.08	0.87 (0.75–1.01), 0.07	1.1 (0.87–1.38), 0.44
Palpable spleen	**0.64 (0.41–0.99), 0.04**	0.67 (0.41–1.1), 0.11	0.66 (0.38–1.14), 0.14	1.19 (0.66–2.13), 0.56
ECOG PS ≥ 1	1.1 (0.74–1.63), 0.64	1.15 (0.76–1.75), 0.51	0.66 (0.38–1.14), 0.14	0.76 (0.45–1.28), 0.30
Sokal Int vs low	**0.41 (0.17–0.98), 0.05**	0.41 (0.15–1.07), 0.07	0.43 (0.16–1.14), 0.09	1.20 (0.67–2.16), 0.53
Sokal high vs low	**0.63 (0.41, 0.98), 0.04**	0.77 (0.48–1.23), 0.28	0.73 (0.45–1.18), 0.19	0.59 (0.31–1.12), 0.11
Comb. transcript vs b2a2	0.79 (0.46–1.37), 0.40	**0.49 (0.27–0.89), 0.02**	**0.44 (0.25–0.8), 0.001**	1.1 (0.61–1.97), 0.76
Comb. transcript vs b3a2	1.06 (0.59–1.9), 0.84	0.84 (0.46–1.52), 0.56	0.79 (0.44–1.44), 0.44	1.42 (0.76–2.65), 0.26

Variable	HR (95% CI), p - value			
Comb. transcript vs others	--	--	--	--

¶continuous variables; remaining variables are categorical with binominal comparison unless further specified, univariate analysis for MMR, MR^4, $MR^{4.5}$, sustained $MR^{4.5}$ performed with competing risks for death; BOLD represent statistically significant results; NE = not evaluable; palpable spleen equals spleen palpable > 5 cm below left costal margin, Int = international, Comb. = combination, PS = performance status, PB = peripheral blood, BM = bone marrow, Plt = platelets, WBC = white blood cells, Hgb = hemoglobin.

Table 4.

Adverse events observed regardless of causality

AE in ≥ 10% of patients	AE	All grades, (%)	Grade ≥ 3, (%)
	NON-HEMATOLOGIC AE		
GENERAL	Fatigue	54 (44)	3 (2)
SKIN / ADNEXA	Rash	63 (52)	2 (2)
	Pruritus	32 (26)	0
	Hair loss / thickening	12 (10)	0
MUSCULOSKELETAL	Muscle pain / cramps	16 (13)	1 (1)
	Arthralgia	18 (15)	1 (1)
CARDIOVASCULAR / PULMONARY	Hypertension	30 (25)	20 (16)
	Arrhythmia / conduction D	15 (12)	0
GASTROINTESTINAL	Nausea / vomiting	27 (22)	1 (1)
	Diarrhea	12 (10)	1 (1)
NEUROLOGIC / PSYCHIATRIC	Headache	32 (26)	2 (2)
	Sensoric neuropathy	13 (11)	0
INFECTIONS	Nasopharyngitis / sinusitis	27 (22)	0
ABNORMAL LAB. PARAMETERS	Bilirubin	69 (57)	16 (13)
	Increased liver enzymes	59 (48)	7 (6)
	Increased lipids¶¶	29 (24)	2 (2)
	Electrolytes	16 (13)	1 (1)
	OTHER NON-HEMATOLOGIC AE OF INTEREST OR GRAGE ≥ 3		
CARDIOVASCULAR / PULMONARY	Ischemic cardiac (MI, angina)¥	6 (5)	1 (1)
	Ischemic cerebrovascular (TIA, stroke)¥	5 (4)	0
	Ischemic peripheral arterial occlusive disease	1 (1)	1 (1)
	Deep venous thrombosis	1 (1)	0
	QT prolongation	4 (3)	0
	Dyspnea	8 (7)	1 (1)
	Fluid retention	7 (6)	0
	Pericarditis	2 (2)	2 (2)
GASTROINTESTINAL	Abdominal pain	7 (6)	1 (1)
	Pancreatitis	6 (5)	3 (2)
	Dyspepsia / GERD	9 (7)	0
	Anorexia / weight loss	7 (6)	0
	Constipation	7 (6)	0
	Weight gain	4 (3)	3 (2)
NEUROLOGIC / PSYCHIATRIC	Insomnia	11 (9)	0
	Anxiety	8 (7)	0
	Memory impairment	7 (6)	0
INFECTIONS / FEVER	Fever without signs of infection	6 (5)	1 (1)
	Pneumonia	3 (2)	3 (2)

AE in ≥ 10% of patients	AE	All grades, (%)	Grade ≥ 3, (%)
	Other infections[§]	11 (9)	2 (2)
ABNORMAL LAB. PARAMETERS	Increased amylase / lipase[≠]	9 (7)	4 (3)
	Increased ALP	3 (3)	2 (2)
	Increased creatinine	6 (5)	1 (1)
	Increased glucose	9 (7)	0
OTHER	Other malignancy[¶]	3 (2)	0
	HEMATOLOGIC AE		
	Anemia	16 (13)	1 (1)
	Thrombocytopenia	9 (7)	5 (4)
	Neutropenia	13 (11)	6 (5)

[§]Skin cellulitis in 5 (one grade 3), cholecystitis in 3 (one grade 3), prostatitis & epididymidis & cystitis in one each,

[≠]asymptomatic elevation in amylase and lipase without clinical signs of pancreatitis,

[¶]adenocarcinoma of prostate [3],

[¥]includes 2 patients with both cardiac and cerebrovascular ischemic events.

[¶¶]Elevated cholesterol in 20 (one grade 3), elevated triglycerides in 1, and elevation of cholesterol and triglycerides in 8 (one grade 3).