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Analysis of 2013 European LeukaemiaNet (ELN) responses in chronic phase CML across four frontline TKI modalities and impact on clinical outcomes

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Summary

This study assessed the relevance of 2013 European LeukaemiaNet (ELN) response categories on patients treated with common frontline tyrosine kinase inhibitors (TKI) in chronic myeloid leukaemia in chronic phase (CML-CP) . Four hundred and eighty-seven patients treated with imatinib (400 mg; IM 400, n=70; 800 mg; IM800, n=201), dasatinib (n=107) or nilotinib (n=109) were analysed. Intention to treat (ITT) analysis indicated that the proportion of patients falling into optimal, warning and failure ELN categories were 89%, 6%, 6% at 3 months, 78%, 17% and 6% at 6 months, and 75%, 13% and 13% at 12 months, respectively. Rates of optimal response at 3 months were 75% for IM400, 90% for IM800, 89% for dasatinib and 97% for nilotinib; 41%, 80%, 86% and 89% at 6 months; and 47%, 77%, 76% and 87% at 12 months, respectively. Patients achieving optimal response had longer eventfree (EFS), failurefree (FFS), transformationfree (TFS) and overall survival (OS) compared to warning and failure responses at all-time points. Treatment with imatinib 800, dasatinib or nilotinib predicted for achieving an optimal response. Optimal response predicted for significantly longer EFS, FFS, TFS and OS at 3, 6 and 12 months, irrespective of the TKI modality used. ELN response categories reliably predicted outcomes in CML patients receiving commonly used TKIs.

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Authorship Contributions

P.J., H.K. and J.C. designed the study.
G.N.G., P.J, K.S. and J.C. analysed results.
P.J., G.N.G, J.D. and J.C. wrote the paper.
P.J., G.N.G., S.D., S.P. and J.C. did clinical correlation.
H.K., S.O.B., S.V., G.B., T.K., W.W., F.R., E.J. and J.C. contributed patient samples.
All authors reviewed and gave the final approval for the paper.

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Keywords

ELN; European LeukaemiaNet; Chronic myeloid leukaemia; Tyrosine kinase inhibitor (TKI); response in CML

Introduction

BCR-ABL1 tyrosine kinase inhibitors (TKI) have been used as frontline treatment for patients with chronic myeloid leukaemia in chronic phase (CML-CP) since the year 2000. Imatinib (Deininger, *et al* 2009, O'Brien, *et al* 2003) is the most widely used frontline TKI. More recently, second generation TKIs - dasatinib and nilotinib - were also approved for frontline treatment. (Cortes, *et al* 2010a, Cortes, *et al* 2010b) Single arm and randomized clinical trials have demonstrated that patients receiving second generation TKIs attain more, faster and deeper responses, have a lower risk of transformation to accelerated and blast phase, and experience fewer overall side effects as compared to imatinib, albeit with some troublesome exceptions (e.g., pleural effusions, arterio-thrombotic events). (Kantarjian, *et al* 2010, Kantarjian, *et al* 2012, Larson, *et al* 2012) Although the majority of patients respond well to TKIs, a proportion of them do not achieve deep cytogenetic and molecular response. (Alvarado, *et al* 2009, Jabbour, *et al* 2012, Marin, *et al* 2008) Various studies have also shown that achievement of different levels of cytogenetic and molecular response at specific time points after starting treatment with TKIs is significantly predictive of better outcomes. (Branford, *et al* 2003, Branford, *et al* 2013, Hanfstein, *et al* 2012, Hanfstein, *et al* 2014, Hehlmann, *et al* 2013, Hughes, *et al* 2013, Jabbour, *et al* 2011, Jabbour, *et al* 2014, Jain, *et al* 2013, Marin, *et al* 2012a, Milojkovic, *et al* 2010, Ohm, *et al* 2012, Wang, *et al* 2003)

Lack of universal recommendations to adequately monitor response to TKIs in patients with CML-CP, led to the development of European Leukaemia Net (ELN) recommendations for the management of CML. First proposed in 2006 and revised in 2009 (Baccarani, *et al* 2009, Baccarani, *et al* 2006, Marin, *et al* 2008) these recommendations were mostly applicable to patients treated with standard-dose imatinib as frontline therapy. Increasing use of second generation TKIs in the frontline therapy of CML-CP by clinicians has generated a need for the modification of the ELN guidelines. The revised ELN guidelines (Baccarani *et al* 2013) have proposed new definitions of ELN responses - optimal, warning and failure categories, accounting for the deeper and faster responses achieved with these agents. ELN response categories can be utilized to recognize those patients who may be candidates for dose escalation (Jabbour, *et al* 2009) or to switch therapy (Cortes *et al* 2013, Deangelo, *et al* 2014, Hughes, *et al* 2014, Yeung, *et al* 2011) to a different TKI and monitor these patients more rigorously.

In the present analysis, we applied the 2013 ELN response categories at various time points on patient cohorts treated with different TKI modalities. We identified the factors predictive of achieving optimal ELN response and analysed whether the type of ELN response achieved by commonly used TKI modalities (imatinib 400 mg/day, imatinib 800 mg/day, dasatinib and nilotinib) has similar predictive value for different outcomes.

Methods

We reviewed all clinical information from all patients with CML-CP (n=487) treated in prospective consecutive or parallel clinical trials with one of four frontline TKI modalities (imatinib 400 mg/day, imatinib 800 mg/day, dasatinib or nilotinib) from May 2000 to September 2013. Patients with evaluable responses were included in the analyses. Patients were treated on protocols approved by the institutional review board and informed consent was obtained in accordance with the declaration of Helsinki. Entry criteria were similar for all trials, and TKI therapy was started within 6 months from initial diagnosis. Patients with clonal evolution at the time of diagnosis were not included in this analysis. Follow-up and response assessment schedules were similar among all the trials and included cytogenetic analysis every 3 months for the first year, then every 6 months for the next 2–3 years, then as clinically indicated. Molecular response was generally assessed every 3 months for the first year, then every 6 months. We used standard methods and definitions for cytogenetic and molecular response assessment. (Baccarani, *et al* 2009) All responses (cytogenetic and molecular) were categorized into optimal, warning and failure categories at 3-, 6- and 12-month assessment points according to 2013 ELN response criteria (*see* supplemental Table-1).(Baccarani, *et al* 2013)

Statistical analysis

Patients were categorized according to attainment of ELN response categories (optimal, warning and failure) at 3, 6 and 12 months. Landmark analyses for predicting outcomes were performed according to ELN responses achieved at these time-points. Event-free survival (EFS) was measured from the start of treatment to the date of event [as defined in the International Randomized Study of Interferon and STI571 (IRIS) study] (O'Brien, *et al* 2003) Because of the limitations of this definition of EFS, we also measured the failure-free survival (FFS), which accounted for other events, such as failure to achieve response at set times as defined by ELN, loss of complete cytogenetic response (CCyR), intolerance or treatment discontinuation for any reason. Overall survival (OS) was measured from the time treatment was started to the date of death from any cause at any time or date of last follow-up. Transformation-free survival (TFS) was measured from the start of therapy to the date of transformation to accelerated or blast phase or any deaths while on therapy or to the date of last follow-up.

Differences between various groups were evaluated by the X^2 test and Mann-Whitney U test for categorical and continuous variables, respectively. Survival probabilities were estimated by the Kaplan-Meier method and log rank test. Univariate and multivariate (MVA) analyses were performed to identify factors (including treatment modality) that may predict for achievement of optimal ELN response at 3, 6 and 12 months. MVA was also performed to determine whether the type of ELN response (optimal vs non-optimal) predicts long-term patient outcomes. Univariate analysis was performed using the Kaplan-Meier and differences evaluated by the log-rank test. Variables with p-value ≤ 0.10 in the univariate analysis were entered into a multivariate model and analysed using the Cox proportional hazard regression. A p-value of < 0.05 was considered significant. Statistical analyses were

carried out using STATA/SE version 13.1 statistical software (Stata Corp. LP, College Station, Texas).

Results

Patient characteristics

A total of 487 consecutive patients with newly diagnosed CML-CP treated with four TKI modalities were included in this analysis. Their median age was 49 years (range, 15–86 years), and the median follow-up was 99 months (range - 91–107 months). The majority of patients (70%) had a low Sokal score. Patients received imatinib 400 mg daily (imatinib 400, n=70), imatinib 800 mg daily (imatinib 800, n=201), dasatinib 100 mg daily (n=107) or nilotinib 400 mg twice daily (n=109). Patient characteristics were comparable among these four cohorts (*see* supplemental Table 2). Imatinib was introduced in 2000 and therefore the follow-up is much longer for patients treated with imatinib (imatinib 400: median 144 months, range 16–154 months; imatinib 800: median 120 months, range 4–145) than with second generation TKIs (dasatinib: median 54 months, range 12–89; nilotinib: median 49 months, range 3–93). Disease transformation occurred in 21 (4%) patients (blast phase, n=7; accelerated phase; n=14) and 14 (3%) patients died on study. An additional 39 patients died after coming off study drug for a total of 53 (11%) deaths (16 were CML-related and 37 non-CML related). Events occurred in 77 (16%) patients.

ELN responses at 3, 6 and 12 months - overall and according to TKI modality (Intent to treat)

Figure 1A shows ELN responses achieved by patients at the 3-, 6- and 12-month time points. At all-time points the majority of patients treated with any TKI achieved optimal response as compared to warning and failure categories. Patients falling into optimal, warning and failure ELN categories were 89%, 6%, 6% at 3 months, 78%, 17% and 6% at 6 months, and 75%, 13% and 13% at 12 months respectively.

Figures 1B–C depict the proportions of patients falling into optimal, warning and failure ELN categories at 3, 6 and 12 months according to the TKI modality used. There was a general trend for higher rates of optimal response at all times with imatinib 800, dasatinib and nilotinib compared to imatinib 400. Rates of optimal response at 3 months according to TKI modality were 75% for imatinib 400, 90% for imatinib 800, 89% for dasatinib and 97% for nilotinib. Corresponding rates for optimal response at 6 months were 41%, 80%, 86% and 89%, and 47%, 77%, 76% and 87% at 12 months respectively. The proportion of patients achieving optimal ELN response was similar in the imatinib 800, dasatinib and nilotinib cohorts. Higher proportions of patients who received imatinib 400 met the criteria of warning and failure categories at all time points as compared to other 3 TKI modalities.

Type of TKI modality is predictive of optimal ELN response – Multivariate analysis

Because patients treated with imatinib 400 had a numerically lower rate of optimal ELN response at all time points (Figure 1B–C), we performed MVA to assess whether the type of TKI therapy could independently predict for achievement of optimal ELN response with imatinib 400 as reference. Treatment with any of the other three TKI modalities, imatinib

800, dasatinib and nilotinib, was associated with a significantly higher probability of achieving an optimal ELN response at 3, 6 and 12 months (Table I). Other factors that significantly predicted for optimal ELN response at 3 months were high haemoglobin concentration and lack of splenomegaly. In addition to the type of TKI modality, high platelet count was a significant predictor for optimal response at 6 and 12 months (not shown).

Clinical outcomes according to ELN response categories at 3, 6 and 12 months

Outcomes were determined according to ELN responses achieved at different time points. Patients who achieved an optimal response at any time point had significantly longer EFS at 3, 6 and 12 months as compared to patients with warning or failure ELN categories (Figure 2A, 3A, 4A; all P≤0.001). Patients meeting criteria for failure had the worst EFS among the three ELN categories. Patients who attained optimal ELN response also had significantly longer FFS (Figure 2B, 3B, 4B; all P≤0.001). Of note, patients meeting the warning criteria at 3 months i.e. *BCR-ABL1* >10% and/or Ph+ >35% appear to have inferior EFS and FFS as compared to those patients in the warning category at 6 and 12 months. Warning appears to be a heterogeneous category as patients who belong to warning category at 3 months have outcome more similar to failure, while at 6 and 12 months the outcomes are more similar to those of patients with optimal response.

Similar to EFS and FFS, patients who attained optimal response at various time points had significantly better TFS (Figure 2C, 3C, 4C; P≤0.001, P≤0.001 and P=0.009) compared to those who did not achieve the optimal ELN response (warning and failure).

Finally, we analysed OS based on ELN responses at different time points. Similar to other outcomes, five-year OS probabilities were significantly better in patients who attained optimal responses at 3, 6 and 12 months (Figure 2D, 3D, 4D; P≤0.001, P≤0.001 and P=0.007). Of note, OS did not differ between patients with optimal response vs warning categories at 3, 6 or 12 months. Table II summarizes the cumulative probability of time to event outcomes according to ELN response categories and the type of TKI modality at specific time points.

Clinical outcomes according to TKI modality in each ELN category at 3, 6 and 12 months

We then explored whether the long-term outcome for each ELN response category varied depending on which TKI was used. Within each ELN response category at all time points, long-term outcomes (EFS, FFS, TFS and OS) had a similar distribution regardless of the TKI used (data not shown).

ELN response categories (optimal vs non-optimal) predict clinical outcomes

In order to assess whether the type of ELN response can independently predict for clinical outcomes, we conducted univariate and multivariate analyses where the type of TKI and response categories (optimal vs non-optimal) were included in the multivariate model. Due to the lower number of cases in the warning and failure categories, we combined warning and failure categories as non-optimal response although we recognize that warning and failure categories appear to have different impact on EFS at different time points (Figure

2A). Table III shows the factors predictive of EFS when analysed at 3 months. Covariates with a p value <0.10 were included in the final multivariate model. ELN response is treated as an effect modifier of the association between type of treatment and EFS. Patients who met the criteria for non-optimal category predicted for inferior EFS compared to optimal category when assessed at 3, 6 or at 12 months. Non-optimal response at 3 months had a hazard ratio (HR) of 4.84, 95% confidence interval (95%CI) 2.86–8.19 (p<0.001), at 6 months – HR=4.60, 95%CI 2.72–7.77 (p<0.001) and at 12 months - HR=3.86, 95%CI 2.26–6.59 (p<0.001). Furthermore, using imatinib 400 and non-optimal response as the reference, patients achieving optimal response at 3 months predicted for a significantly better probability of EFS irrespective of TKI modality, HR 95%CI with imatinib 400 – 0.27 (0.11–0.65) (p=0.003), with 3TKI (imatinib 800, dasatinib and nilotinib) was 0.15 (0.08–0.31) (p<0.001) (Table III). Similar results were obtained in MVA at 6 and 12 months for EFS. Corresponding values for imatinib 400 with optimal response and optimal response with 3TKI at 6 months were - HR=0.20, 95%CI 0.06–0.70 (p=0.01) and HR=0.19, 95%CI 0.11–0.35 (p<0.001) respectively and at 12 months were HR=0.19, 95%CI 0.05–0.67 (p=0.01) and HR=0.16, 95%CI 0.08–0.32 (p<0.001), respectively.

Similarly, achievement of optimal response significantly predicted for longer FFS at 3, 6 and 12 months, irrespective of TKI modality (not shown). Achievement of optimal response at 3, 6 or 12 months also predicted for a longer TFS, however, optimal response achieved by the non-imatinib 400 TKI modalities predicted for improved TFS probability at 3, 6 and 12 months while optimal response achieved by imatinib 400 predicted for improved TFS only at 3 months (data not shown).

We then analysed the factors predicting for longer OS. Compared to the non-optimal category, achievement of optimal response at 3, 6 or at 12 months was associated with a significantly improved probability of long-term OS (Table IV and Supplemental Tables 3–4). The HR (95%CI) for non-optimal category at 3 months was 3.53 (1.86–6.68) (p<0.001), at 6 months it was 2.32, (1.21–4.44) (p=0.012) and at 12 months it was 2.63, (1.31–5.27) (p=0.006). Furthermore, optimal response achieved by any TKI modality at 3 months was associated with a significantly better probability of OS compared to non-optimal response by imatinib 400. Furthermore, optimal response with 3TKI was also associated with a significantly longer OS compared to non-optimal response achieved by 3TKI at 3, 6 and 12 months (p values 0.006, 0.01 and 0.05, respectively). Corresponding HR values for optimal response with imatinib 400 and with 3TKI at 3 months were - HR=0.25, 95%CI 0.08–0.74 (p=0.01) and HR=0.27, 95%CI 0.12–0.62 (p=0.002) respectively (Table IV). At 6 and 12 months, optimal response by 3TKI showed a trend for better OS (p=0.07 and 0.08 respectively) and optimal response by imatinib 400 showed a trend for better OS at 12 months (p=0.07) (Supplemental Tables 3–4)

Discussion

In 2013, the European LeukaemiaNet (ELN) (Baccarani, *et al* 2013) updated its previous recommendations for CML.(Baccarani, *et al* 2009) As the previous ELN response categories were based on data obtained from clinical trials of imatinib(Kim, *et al* 2012, Marin, *et al* 2008), the new ELN response categories were modified for wider applicability across the

commonly used TKIs, taking into consideration the results expected with these agents. (Kantarjian, *et al* 2010, Kantarjian, *et al* 2012, Larson, *et al* 2012) With the newer TKIs a higher rate of responses was achieved and these responses were generally deeper and achieved faster compared to what was observed with imatinib 400. Several studies have documented the positive impact on patient outcomes by attaining cytogenetic and molecular responses at earlier time-points.(Branford, *et al* 2003, Hanfstein, *et al* 2012, Hughes, *et al* 2010, Jabbour, *et al* 2011, Marin, *et al* 2012a, Marin, *et al* 2012b, Merx, *et al* 2002, Ohm, *et al* 2012, Quintas-Cardama, *et al* 2009, Wang, *et al* 2003) A few reports confirmed the clinical relevance of the ELN 2009 recommendations for patients treated with imatinib 400. (Etienne, *et al* 2014, Iriyama, *et al* 2014) Such an analysis has not been reported for the ELN 2013 recommendations when using the newer TKI options. Therefore, this study was envisaged to fill that void across a large cohort of patients treated with one of four TKI modalities.

An important objective of defining response endpoints is to help guide practice, such as when treatment change might be indicated. Achievement of a major cytogenetic response and/or *BCR-ABL1* ≤10% at 3 months is now considered an optimal ELN response. (Baccarani, *et al* 2013) In contrast, the ELN 2009 recommendations (Baccarani, et al 2009) considered this level optimal only after 6 months of therapy. A large majority of patients achieved optimal responses at 3 months with all 4 TKI modalities, although the proportion was higher with imatinib 800, dasatinib or nilotinib. According to the ELN recommendations, for patients who fall into the category of warning a change in therapy is not necessarily indicated, mainly due to the lack of prospective data demonstrating the data of this approach. One deficiency of recognizing intermediate categories (e.g., suboptimal response or warning) is that management strategies are not well defined. One randomized trial – the LASOR trial (Cortes *et al* 2013) compared changing from imatinib 600 to nilotinib in patients with suboptimal response at 6 or 12 months by ELN 2009 criteria (Baccarani, *et al* 2009). Preliminary results from this study suggest higher rates of responses after switching to nilotinib as compared to imatinib dose escalation (Cortes *et al* 2013). However, any possible long-term term benefit of the change remains to be identified. Importantly, the group of patients included in the LASOR trial would now be considered to have failure. However, although several studies have shown the merits of treatment change for patients with failure criteria (Casado, *et al* 2015, Yeung, *et al* 2015), this particular subset of patients was not included in such studies. One approach for patients who met warning criteria was tested in TIDEL-II (Therapeutic intensification in de novo leukaemia) trial (Yeung, *et al* 2015). In this study, patients with CML-CP (n=210) were started on frontline imatinib 600 mg. Two sequential cohorts of 105 patients each were enrolled. If the patients failed to achieve imatinib plasma trough level at day-22 of >1000 ng/ml then they were dose escalated to imatinib 800. Subsequently, if the patients failed to achieve *BCR-ABL1* levels ≤10%, ≤1%, and ≤0.1% at 3, 6, and 12 months (akin to the warning criteria by ELN) they were offered dose escalation to imatinib 800 mg in the first part of the study or directly switched to nilotinib in the second part (Cohort 1) and patients failing any molecular response targets were switched to nilotinib directly (Cohort 2). Of the 25 patients (12%) meeting the warning criteria at 3 months, 16 (64%) achieved *BCR-ABL1* levels ≤10% at 6 months and 5 achieved major molecular response at 12 months. However, similar results

have been reported for patients not offered any change in strategy.(Branford, *et al* 2014, Nazha, *et al* 2013) Patients who switched to nilotinib due to imatinib intolerance had better outcomes then those who failed to achieve optimal response at 3 months, suggesting that there may be an intrinsic TKI resistance in these patients, the mechanism of which is not understood well at this time point. In a separate retrospective study from Spain, Casado, *et al* (2015) reported that switching to 2nd generation TKI after failing to achieve optimal response at 3 months can improve the responses but does not improve the OS of the patients who were categorized as warning or failure. Patients with failure at 3 months i.e. lack of complete haematological response or Ph+ >95% could be considered as primary refractory patients; only some of them could be salvaged by changing therapy.(Casado, *et al* 2015) However, it is still unclear whether a patient who attains failure while taking any of the 2nd generation TKIs can improve the response if the therapy is changed to any of the modalities currently available as there is no prospective data to confirm this.

In our analysis, we have shown that a growing percentage of the patients who received imatinib 400 fell into the warning and failure categories from 3 to 6 and 12 months as compared to those treated with imatinib 800, dasatinib and nilotinib. This data is consistent with the data from randomized studies comparing dasatinib or nilotinib with imatinib, such as the ENESTnd (Hughes, *et al* 2013, Larson, *et al* 2012) and DASISION (Jabbour, *et al* 2014, Kantarjian, *et al* 2012) trials, although the actual rates of warning and failure were not reported. Importantly, the proportion of patients who achieved optimal response at 3, 6 or at 12 months was similar for patients taking imatinib 800 or 2nd generation TKIs. Initial reports of using imatinib at a starting dose of 800 mg suggested deeper responses were achieved earlier compared to what could be expected with standard-dose imatinib both in the post-interferon failure and frontline settings.(Cortes, *et al* 2003, Jain, *et al* 2015, Kantarjian, *et al* 2004) A randomized trial of imatinib standard versus high dose confirmed this earlier rate of cytogenetic and molecular responses.(Cortes, *et al* 2009) More recently, the randomized German CML Study IV showed that deep molecular responses are achieved in a majority of patients treated with Imatinib 800 compared to imatinib 400.(Hehlmann, *et al* 2013) Unfortunately, all studies comparing imatinib to 2nd generation TKI have been done using imatinib at the standard dose of 400 mg daily. The present analysis suggests that the results using imatinib 800 mg daily may be similar to those achieved with 2nd generation TKIs dasatinib and nilotinib used as frontline therapy. Considering the growing concern of cost of medicines and in the context of the growing availability and use of generic imatinib, exploring the merits of imatinib 800 compared to 2nd generation TKI in a prospective randomized trial is an important need.

Patients who achieved optimal ELN responses had significantly better long-term outcomes at 3, 6 or at 12 months compared to non-optimal (warning and failure categories). One caveat of this analysis is the low numbers of patients in the failure category (and to some extent, the warning category), particularly with imatinib 800 mg and 2nd generation TKI, and at later time-points. Patients in the failure category had poor outcomes whether assessed at 3, 6 or at 12 months, whereas the outcomes for those meeting the warning category criteria at 6 or 12 months appear better than those with in this category at 3 months. These results are consistent with previous analyses evaluating ELN 2009 categories in a cohort of

patients treated with imatinib (Marin, *et al* 2008) (Alvarado, *et al* 2009), which are similar to the current study including other TKI modalities, in that patients in the warning category under ELN-2013 have an outcome (at least as measured by EFS) more similar to that of patients with failure, while those meeting warning criteria at 6 or 12 months have an outcome more similar to that of patients with optimal response. We acknowledge that our clustering of patients with non-optimal response into one category fails to recognize this variability. However, because of the small number of patients in each group we could only test the value of optimal response compared to other outcomes. Patients in the warning category appear to represent a heterogeneous population depending on the time when this outcome is assessed. Our analysis shows that the patients in the warning category have a disease course that is similar to patients in the failure category when analysed at the 3-month time point while at 6 and 12 months the outcomes of these patients are more similar to those of patients with optimal response. On-going studies are exploring the possible benefit of treatment change (e.g., to a different TKI, dose increase, etc) for these patients as soon as a warning is identified, with particular emphasis on the 3-month assessment.

Finally, we have shown by MVA that achievement of optimal response predicted for significantly better outcomes (EFS, FFS, TFS and OS) at all-time points (3, 6 and 12 months). These results suggested the strong prognostic impact on patients of achieving optimal response. Moreover, we demonstrate that optimal response predicted for longer outcomes as compared to non-optimal response, irrespective of the TKI modality. Our results confirm that achieving optimal ELN response is important in predicting the long-term outcome of chronic phase CML patients and we have verified that the 2013 ELN responses have significant prognostic value across 4 commonly used TKI modalities. However, recognition of the prognostic implication of responses that are not optimal cannot be equated to a recommendation for change in therapy until studies with such approaches demonstrate that a given intervention changes outcome. This also has to be decided in the context of the options available to a given patient.

In conclusion, our study confirms that 2013 ELN categories can reliably predict patient long-term outcomes and are universally applicable across all commonly used TKI modalities. Patients with optimal ELN response have the best long-term outcomes and patients who receive imatinib 800, dasatinib or nilotinib have a higher probability of achieving optimal response at the different time points.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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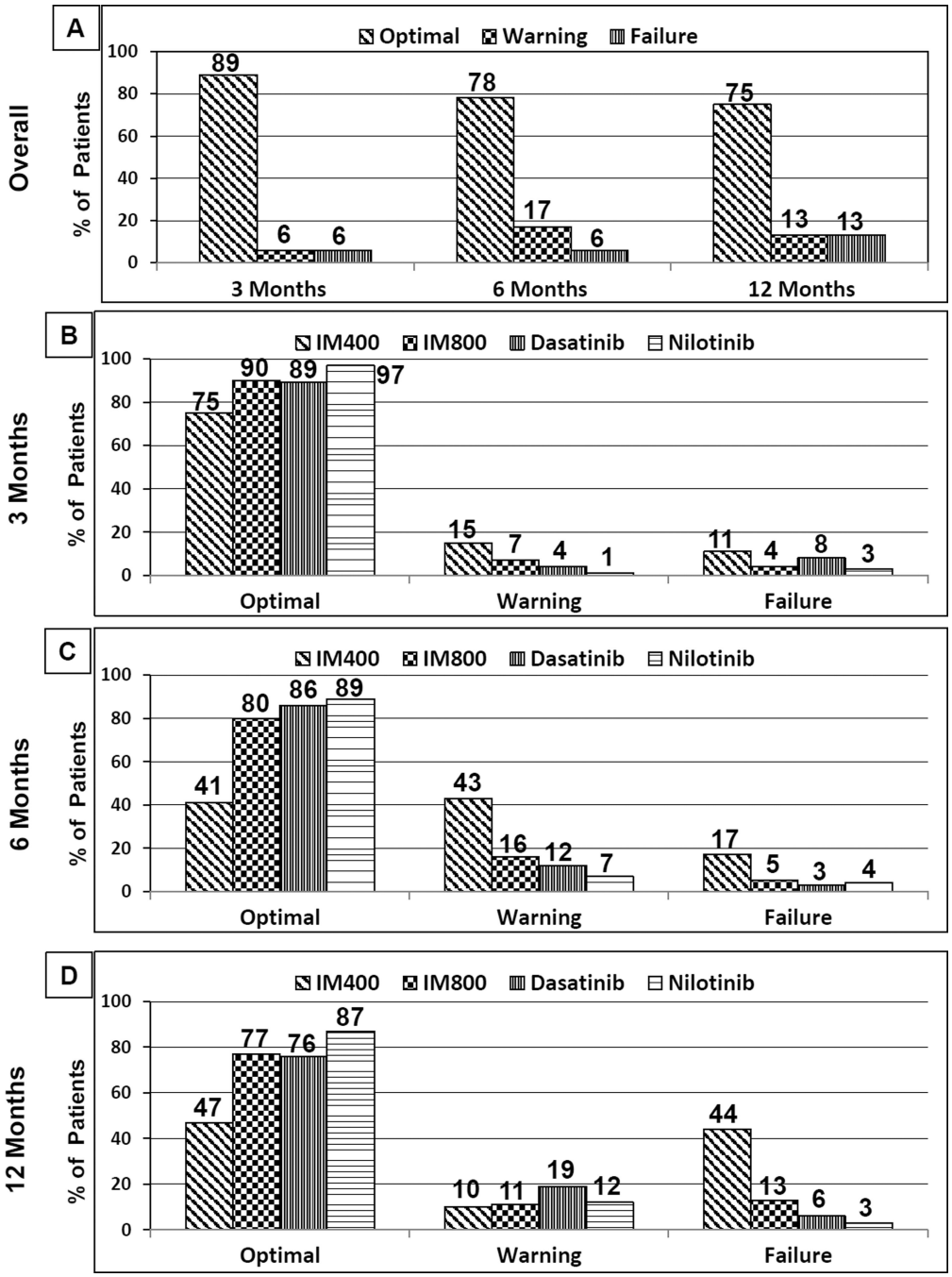

Figure 1. Proportion of patients across the four TKI modalities according to the ELN response categories determined at specific time points, intention to treat analysis

overall and by TKI modality **A)** Overall **B)** 3 months **C)** 6 months and **D)** 12 months

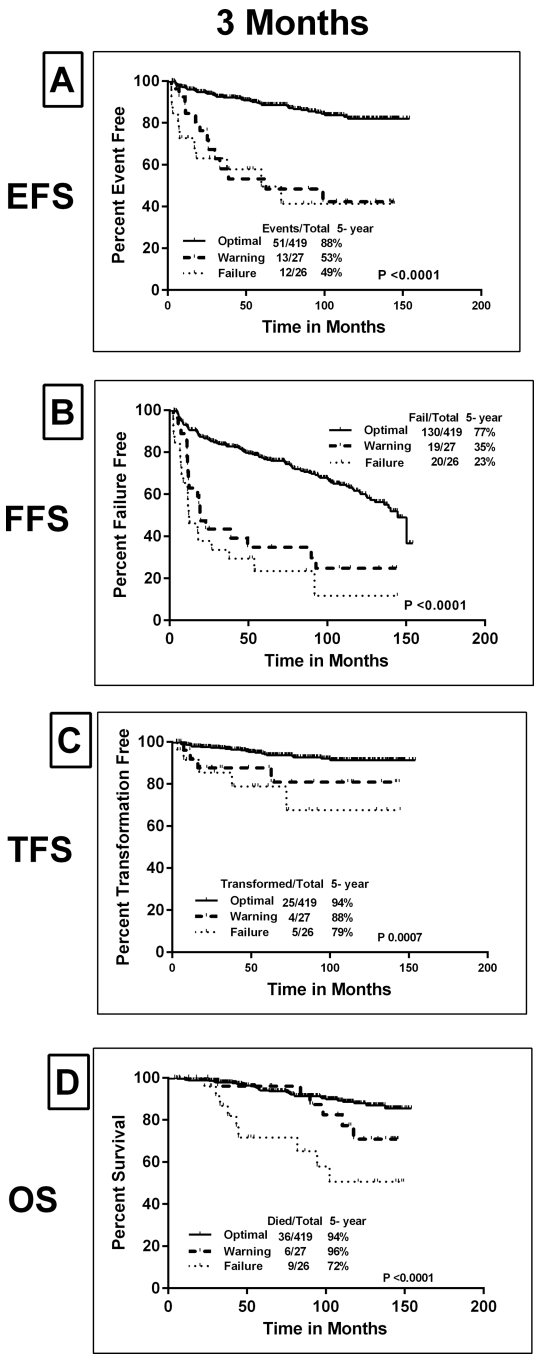

Figure 2. Clinical outcomes according to the response categories - optimal, warning and failure at 3 months

A) Event-free survival (EFS), **B)** Failure-free survival (FFS), **C)** Transformation-free survival (TFS) and **D)** Overall survival (OS)

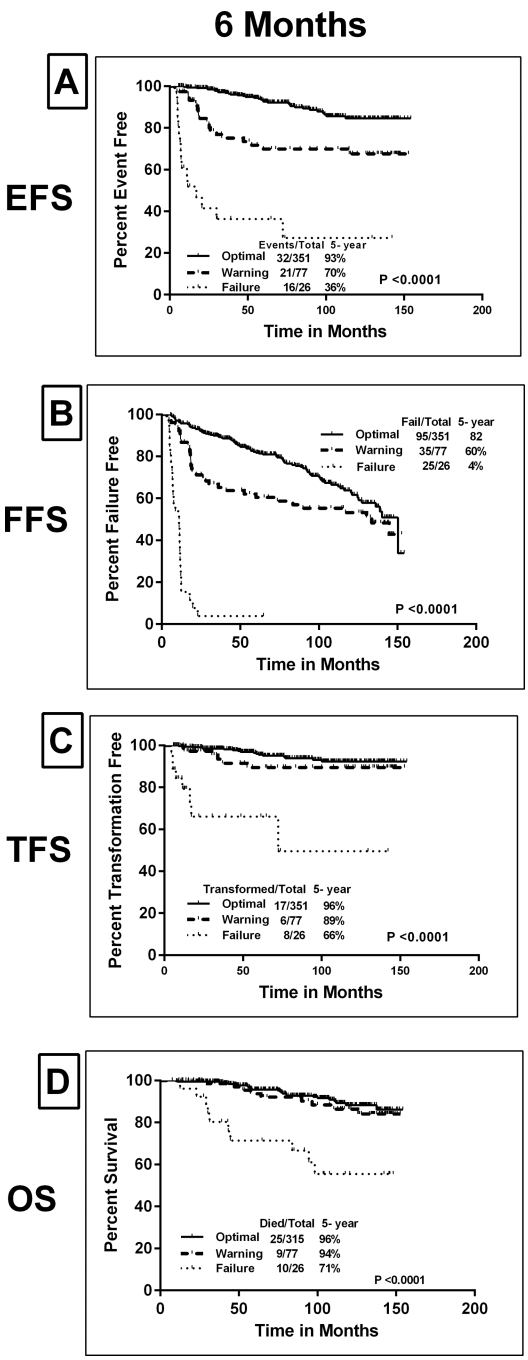

Figure 3. Clinical outcomes according to the response categories - optimal, warning and failure at 6 months

A) Event-free survival (EFS), **B)** Failure-free survival (FFS), **C)** Transformation-free survival (TFS) and **D)** Overall survival (OS)

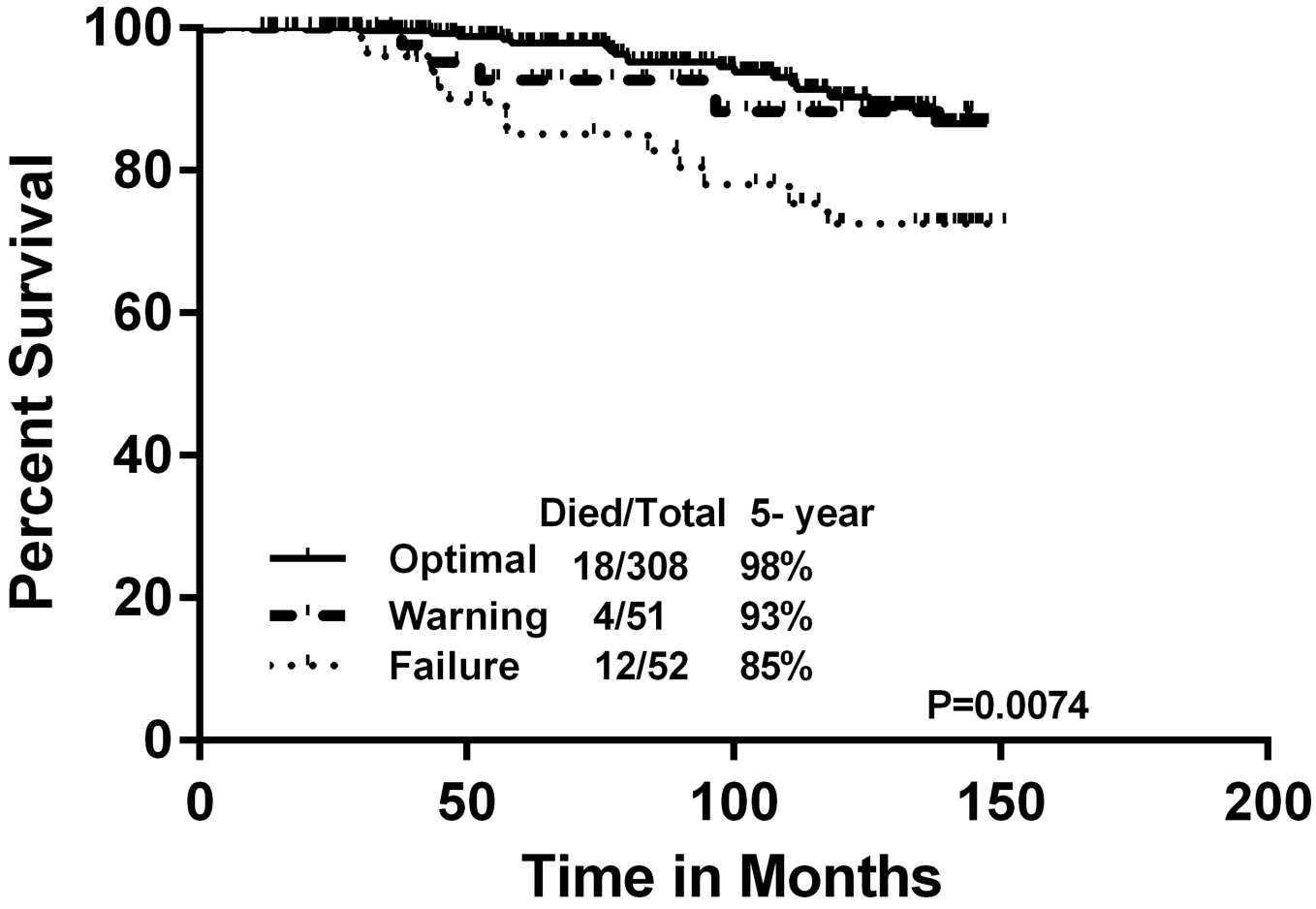

Figure 4. Clinical outcomes according to the response categories - optimal, warning and failure at 12 months

A) Event-free survival (EFS), **B)** Failure-free survival (FFS), **C)** Transformation-free survival (TFS) and **D)** Overall survival (OS)

Table I

Analysis of factors predictive of optimal ELN response at 3 months, including TKI modality

	Non Optimal[$] (n=53) N (%)	Optimal (n=419) N (%)	OR	95% CI OR	P-value
Univariate[*]					
TKI					
Imatinib 400[#]	17 (32)	50 (12)			
Imatinib 800	20 (38)	176 (42)	2.99	(1.46–6.14)	0.003
Dasatinib	12 (23)	92 (22)	2.61	(1.15–5.89)	0.021
Nilotinib	4 (8)	101 (24)	8.58	(2.74–26.86)	<0.001
Spleen size					
≤10 cm	42 (79)	403 (96)			
>10 cm	11 (21)	16 (4)	0.15	(0.07–0.35)	<0.001
Haemoglobin					
≤120 g/l	34 (64)	179 (43)			
>120 g/l	19 (36)	240 (57)	2.40	(1.32–4.34)	0.004
Multivariate[##]					
TKI					
Imatinib 400[#]	17 (32)	50 (12)			
Imatinib 800	20 (38)	176 (42)	4.23	(1.93–9.25)	<0.001
Dasatinib	12 (23)	92 (22)	3.20	(1.34–7.61)	0.009
Nilotinib	4 (8)	101 (24)	11.43	(3.45–37.87)	<0.001
Spleen size					
≤10 cm	42 (79)	403 (96)			
>10 cm	11 (21)	16 (4)	0.19	(0.08–0.49)	0.001
Haemoglobin					
≤120 g/l	34 (64)	179 (43)			
>120 g/l	19 (36)	240 (57)	2.20	(1.16–4.16)	0.016

[$]Non optimal European LeukaemiaNet (ELN) responses included warning and failure categories which were combined due to low patient numbers in each category

[*] White blood cell (WBC) count, Sokal risk, age, platelet count, peripheral blood blasts percentage and serum lactate dehydrogenase (LDH) were not significant (p=NS; data not shown).

[#] Imatinib 400 is the reference for comparison with other tyrosine kinase inhibitor (TKI) modalities.

[##] Factors significantly predictive of optimal response at 6 months were TKI modality, high haemoglobin, spleen size ≤10 cm and high platelet count whereas factors predictive of optimal response at 12 months were TKI modality and high platelet count.

OR, odds ratio; 95% CI, 95% confidence interval.

Table II

Cumulative probability of time to event outcomes according to ELN response categories at specific time points (With Landmark) at 3, 6 and at 12 months for OS and among the TKI arms for EFS, FFS, TFS and OS.

% 5-year outcome EFS /FFS /TFS/OS						
Response Category		**Imatinib 400**	**Imatinib 800**	**Dasatinib**	**Nilotinib**	**Overall**
3 months	**Optimal**	81/71/93/92	89/76/95/94	95/80/97/99	84/75/87/90	88/77/94/94
	Warning	37/20/70/90	64/42/100/100	*100/50/0/*100	*100/100/100/*100	53/35/88/96
	Failure	57/29/71/71	19/0/86/71	83/60/83/83	67/*0/0/67	49/23/79/72
6 months	**Optimal**	96/81/100/92	91/81/95/97	97/85/98/97	90/79/91/93	93/82/96/96
	Warning	67/64/92/100	79/60/95/90	61/53/68/100	57/57/67/67	70/60/89/94
	Failure	36/0/51/64	19/0/100/75	*100/0/0/*100	50/25/50/*75	36/4/66/71
12 months	**Optimal**	91/83/95/100	94/85/96/98	96/85/98/100	90/82/91/95	93/85/96/98
	Warning	*100/100/100/*100	81/65/94/94	86/72/991/2	80/80/80/80	85/74/92/93
	Failure	50/32/81/85	52/26/91/83	*60/*40/*80/100	*100/*100/100/*100	54/33/86/85

*Data based on ≤5 patients in these categories

ELN, European LeukaemiaNet, TKI, tyrosine kinase inhibitor, EFS, event-free survival; FFS, failure-free survival; TFS, transformation-free survival; OS, overall survival

Table III

Analysis of factors predictive of EFS with variables including ELN response category and type of ELN response achieved by different TKI modalities at 3 months.

	N	Events	Log-rank	HR	95% CI HR	P-value	5-year EFS
Univariate*							
ELN response							
Optimal	419	51	<0.001				89%
Non Optimal#	53	25		5.36	(3.31–8.66)	<0.001	52%
ELN response by TKI							
Non-optimal + Imatinib 400	17	10	<0.001				46%
Optimal + Imatinib 400	50	11		0.26	(0.11–0.62)	0.002	81%
Non-optimal + 3TKI	36	15		0.83	(0.37–1.84)	0.645	56%
Optimal + 3TKI	369	40		0.15	(0.08–0.30)	<0.001	90%
Multivariate##							
ELN response							
Optimal	419	51					89%
Non Optimal#	53	25		4.84	(2.86–8.19)	<0.001	52%
ELN response by TKI	17	10	<0.001				
Non-optimal + Imatinib 400	50	11					46%
Optimal + Imatinib 400	36	15		0.27	(0.11–0.65)	0.003	81%
Non-optimal + 3TKI	369	40		0.81	(0.36–1.81)	0.610	56%
Optimal + 3TKI	419	51		0.15	(0.08–0.31)	<0.001	90%

*Tyrosine kinase inhibitor (TKI) modality, white blood cell (WBC) count, Sokal risk, age, platelet count, peripheral blood blasts percentage and serum lactate dehydrogenase (LDH) were not significant (p=NS; data not shown).

#Non-optimal European LeukaemiaNet (ELN) responses included warning and failure categories, which were combined due to low patient numbers in each category Imatinib 400 is the reference for comparison with other three TKI modalities. Three TKI modalities (imatinib 800, dasatinib and nilotinib) were combined due to low patient numbers in the warning and failure categories for dasatinib and nilotinib.

##Other factors significantly predictive of longer event-free survival (EFS) in multivariate analysis (not shown) were achievement of optimal response at 6 and 12 months and achievement of optimal response by imatinib 400 or with 3 TKI modalities at 3,6 and 12 months.

HR, Hazard ratio; 95% CI, 95% confidence interval.

Table IV

Analysis of factors predictive of OS with variables including ELN response category and type of ELN response achieved by different TKI modalities at 3 months.

	N	Deaths	Log-rank	HR	95% CI HR	P-value	5-year OS
Univariate*							
ELN response							
Optimal	419	36	<0.001				94%
Non Optimal#	27	15		3.14	(1.72–5.74)	<0.001	85%
ELN response by TKI							
Non-optimal + Imatinib 400	17	7	<0.001				82%
Optimal + Imatinib 400	50	6		0.27	(0.09–0.80)	0.018	91%
Non-optimal + 3TKI	36	8		0.82	(0.30–2.28)	0.705	86%
Optimal + 3TKI	369	30		0.29	(0.13–0.66)	0.003	94%
Multivariate##							
ELN response			<0.001				
Optimal	419	36					94%
Non Optimal#	27	6		3.53	(1.86–6.68)	<0.001	85%
ELN response by TKI			<0.001				
Non-optimal + Imatinib 400	17	7					82%
Optimal + Imatinib 400	50	6		0.25	(0.08–0.74)	0.012	91%
Non-optimal + 3TKI	36	8		0.86	(0.31–2.39)	0.771	86%
Optimal + 3TKI	369	30		0.27	(0.12–0.62)	0.002	94%

*Tyrosine kinase inhibitor (TKI) modality, white blood cell (WBC) count, Sokal risk, age, platelet count, peripheral blood blasts percentage and serum lactate dehydrogenase (LDH) were not significant (p=NS; data not shown).

##Non-optimal European LeukaemiaNet (ELN) responses included warning and failure categories, which were combined due to low patient numbers in each category

#Imatinib 400 is the reference for comparison with other three TKI modalities. Three TKI modalities (imatinib 800, dasatinib and nilotinib) were combined due to low patient numbers in the warning and failure categories for dasatinib and nilotinib.

OS, overall survival; HR, Hazard ratio; 95% CI, 95% confidence interval