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Prediction for Sustained Deep Molecular Response of BCR-ABL1 Levels in Patients with Chronic Myeloid Leukemia in Chronic Phase

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Abstract

Background—Achievement of sustained deep molecular response is a goal of increasing relevance as it opens the possibility of treatment discontinuation. The objective of this analysis is to develop a prediction model for sustained molecular response 4.5 (MR^{4.5}) for at least 2 years according to BCR-ABL1 levels achieved within the first 12 months of therapy.

Methods—Data for 603 patients with newly diagnosed chronic myeloid leukemia in chronic phase in consecutive prospective clinical trials were analyzed. The “best fit average” molecular response was defined by robust linear regression models, with which the average molecular levels were defined. The “minimum acceptable” molecular response was defined by quantile regression for the 95th percentile, with which the worst 5% BCR-ABL1 levels were identified.

Results—In 603 patients with a median follow-up of 104 months, 2002 BCR-ABL1 level data points within 1 year of TKI were identified. The regression equations for best fit average levels for sustained MR^{4.5} was $\text{Log}_{10}(\text{PCR}) = -0.1424 \times (\text{Months}) - 0.8668$; for minimum acceptable levels, $\text{Log}_{10}(\text{PCR}) = -0.1403 \times (\text{Months}) + 0.6142$. To achieve sustained MR^{4.5}, the best fit average level was 0.051%, 0.019%, 0.007%, and 0.003% at 3, 6, 9, and 12 months, respectively; the minimum acceptable level was 1.561%, 0.592%, 0.225%, and 0.085% at 3, 6, 9, and 12 months, respectively.

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Contributors: KS treated the patients, collected data, designed the study, analyzed the data, and wrote the manuscript. HK, SO'B, FR, MK, GB, GGM, WW, ND, AF, KT, and EJ treated the patients. PJ treated the patients, and collected data. MBR and SP managed the data. JEC treated the patients, designed the study, analyzed the data and edited the manuscript. All authors provided significant intellectual input, and reviewed and approved the final version of the manuscript.

Declaration of interests: KS, SO'B, GB, GGM, WW, ND, AF, KT, PJ, MBR, and SP declared no competing interests.

Conclusions—Our model proposes optimal values that predict the highest probability of reaching such goal. These values can be used to guide therapy when sustained MR^{4.5} is the objective.

Keywords

Chronic myeloid leukemia; tyrosine kinase inhibitor; sustained MR4.5; best fit average; minimum acceptable

Introduction

Initial treatment with tyrosine kinase inhibitors (TKI) induces excellent response in most patients with chronic myeloid leukemia in chronic phase (CML-CP) leading to an expected survival approaching that of the general population.¹⁻⁸ A randomized clinical trial of 1106 patients with front-line imatinib compared to interferon alfa plus cytarabine showed 5-year overall survival (OS) of 89% (95% confidence interval [CI], 86-92), and no patients who achieved major molecular response (MMR) by 12 months progressed to accelerated or blast phase at 60 months.⁹ European LeukemiaNet (ELN) guidelines recommend periodic monitoring of BCR-ABL1 at 3, 6, and 12 months with real-time polymerase chain reaction (PCR), and defined optimal response as BCR-ABL1 transcript levels $\leq 10\%$ on the international scale (IS) at 3 months, $<1\%$ at 6 months, and 0.1% from 12 months onward, and treatment failure as BCR-ABL1 transcript levels $>10\%$ at 6 months and $>1\%$ from 12 months onward.¹⁰ During the course of treatment, recognizing early predictors of deeper response and longer-term outcomes can help guide treatment. This is relevant not only at the specified fixed timepoint typically reported (i.e., 3, 6, 12 months) but at any other time during the course of therapy.

Achievement of sustained deep molecular response is a goal of increasing relevance as it opens the possibility of treatment discontinuation. The TWISTER trial reported estimates of stable treatment-free remission of 47% (95% CI, 32-63) at 24 months of imatinib discontinuation in patients with sustained molecular response 4.5 (MR4.5) for ≥ 2 years prior to discontinuation.¹¹ With a median follow-up of 20.0 months (interquartile range [IQR] 16.5–24.0), the Dasatinib Discontinuation trial (DADI) trial reported a treatment-free remission of 49% (95% CI 36–61) at 6 months in patients who received at least 1-year consolidation dasatinib therapy after the achievement of deep molecular response.¹²

The objective of this study is to investigate optimal BCR-ABL1 transcript levels at any given time that predict for sustained MR4.5 (BCR-ABL1 $\leq 0.0032\%$ for at least 2 years) according to BCR-ABL1 levels achieved within the first 12 months of TKI therapy.

Methods

Study design and participants

We reviewed response data for 630 consecutive patients with newly diagnosed CML-CP enrolled in consecutive or parallel prospective clinical trials of frontline TKIs between July 30, 2000 to November 25, 2014 at a single institution: imatinib (n=73; NCT00048672), high-dose imatinib (n=208; NCT00038469 and NCT00050531), nilotinib (n=148;

NCT00129740), dasatinib (n=150; NCT00254423), and ponatinib (n=51; NCT01570868). Patients with only qualitative BCR-ABL1/ABL1 during the first year of therapy, or with transcript type b3a3, e1a2 or unknown were excluded from the analysis. A total of 603 patients were included in the analysis: imatinib (n=52), high-dose imatinib (n=205), nilotinib (n=147), dasatinib (n=148), and ponatinib (n=51). The inclusion criteria were similar for all trials, including age \geq 16 years, adequate heart, liver and renal function, and performance status 0-2. TKI therapy consisted of imatinib (starting dose of 400 mg or 800 mg daily, alone or with pegylated interferon after six months of single-agent high-dose imatinib), dasatinib (50 mg twice daily or 100 mg once daily), nilotinib (400 mg twice daily), or ponatinib (45 mg or 30 mg daily).^{3, 4, 13-15} All protocols were approved by the institutional review board at MD Anderson Cancer Center and written informed consent was obtained in accordance with the Declaration of Helsinki.

Procedures

Detailed information of protocol-specific procedures can be found in the original reports and at ClinicalTrials.gov.^{3, 4, 13-15} Analysis was performed for the following response categories: CCyR within 1 year, MMR within 1 year, and sustained MR^{4.5} at any point. Sustained MR^{4.5} was defined as MR^{4.5} in all consecutive assessments performed every 6 months for at least 2 years. Quantitative real-time PCR analysis was performed at approximately 3 month intervals during the first year and 6 month intervals thereafter. Missing *BCR-ABL1* levels due to inadequate samples or not performed were excluded from the analysis. Response criteria were as per standard definitions¹⁰: MMR (*BCR-ABL1* \leq 0.1% IS); MR^{4.5} (*BCR-ABL1* \leq 0.0032% IS). Baseline BCR-ABL1 levels were excluded from our analysis due to the upper limit of BCR-ABL1 levels at 100%, which skewed the true baseline BCR-ABL1 levels and did not reflect accurate biologic nature of the disease status.

Outcomes

We estimated the probability of survival by response group with the Kaplan-Meier method. The definition of OS, event-free survival (EFS), transformation-free survival (TFS), and failure-free survival (FFS) were as previously published.¹⁶ The probability of sustained MR^{4.5} was estimated with inverted Kaplan-Meier method.

Statistical analysis

BCR-ABL1 data were significantly skewed near undetectable BCR-ABL1 levels (Supplemental figure 1), and were logarithmic transformed for further analysis (Figure 1A). The “best fit average” molecular response was defined by robust linear regression models, with which the average molecular level that predicted the achievement of CCyR within 1 year, MMR within 1 year, and sustained MR^{4.5} at any point were defined. The minimum acceptable molecular response was defined by quantile regression for the 95th percentile, with which the *BCR-ABL1* levels detected in at least 95% of patients that ultimately achieved CCyR within 1 year, MMR within 1 year, and sustained MR^{4.5} at any point were identified. Univariate comparisons for survival were performed with a log-rank test in which two-tailed p values of less than 0.05 were considered statistically significant. To validate this approach for the prediction of deep molecular response, the whole patient cohort was then randomly divided into 2 cohorts: a training cohort (80% of the total cohort) to create a

model, and a validation cohort (20% of the total cohort). The accuracy of prediction was assessed for each target response on the validation cohort with Fisher exact test or chi-square test. We did statistical analyses with the statistical software system R (version 3.3.1) or Statistical Package for Social Sciences (SPSS) software (version 23, SPSS, Inc, Chicago, IL, USA).

Results

In 603 patients, 2002 BCR-ABL1 data points within 1 year of TKI were identified. The median follow-up for the entire cohort was 103 months (range, 0.3-173.9; IQR, 54.7-143.5; 95% CI, 95.2-112.2), and varied by treatment cohort: IM400, 164 months (range, 45.6-173.8; IQR, 154.1-167.2; 95% CI, 161.0-166.3); IM800, 143 months (range, 5.8-171.5; IQR, 132.4-155.5; 95% CI, 140.0-146.9); nilotinib, 68 months (range, 0.3-125.5; IQR, 55.1-92.8; 95% CI, 63.1-73.0); dasatinib, 66 months (range, 0.3-118.8; 95% CI, 54.1-78.9); ponatinib, 35 months (range, 2.0-43.1; IQR, 27.8-37.1; 95% CI, 31.6-38.7) ($p < 0.001$). Median age at diagnosis was 49 years (range, 15.1-84.8; IQR, 37.7-58.9). Patient characteristics by each response category are described in Table 1. Overall, 538 patients (89%) achieved CCyR within 1 year; 464 (77%) MMR within 1 year; and 282 (47%) sustained MR^{4.5} at any time. Due to short follow-up in the ponatinib cohort, only 1 patient had achieved sustained MR^{4.5}. The coefficients and intercepts of regression equations for best fit average and minimum acceptable levels for each response are shown in supplemental table 1.

The best fit average PCR (i.e., estimated levels achieved by the average responder in each category) for CCyR within 1 year was 0.087%, 0.037%, 0.016%, and 0.007% at 3, 6, 9, and 12 months, respectively; for MMR within 1 year was 0.059%, 0.024%, 0.010%, and 0.004% at 3, 6, 9, and 12 months, respectively. For achievement of sustained MR^{4.5} at any point, the best fit average PCR was 0.051%, 0.019%, 0.007%, and 0.003% IS at 3, 6, 9, and 12 months, respectively (Table 2). To achieve CCyR within 1 year, the minimum acceptable PCR (i.e., levels achieved by 95% of all those who eventually reach the target endpoint) was 2.218%, 1.485%, 0.994%, and 0.665% IS at 3, 6, 9, and 12 months, respectively; to achieve MMR within 1 year, 1.127%, 0.553%, 0.271%, and 0.133% IS, respectively. The minimum acceptable PCR for eventually achieving a sustained MR^{4.5} at any time during the course of therapy was 1.561%, 0.592%, 0.225%, and 0.085% IS at 3, 6, 9, and 12 months, respectively. Of 282 patients who eventually achieved sustained MR^{4.5}, within 1 year of start of therapy 280 (99%) had achieved CCyR, 268 (95%) had achieved MMR, 201 (71%) MR⁴, and 162 (57%) MR^{4.5}. Of 358 patients who achieved MMR within 1 year and that had a minimum follow-up of 48 months, 256 (72%) achieved sustained MR^{4.5}. This is in contrast to 14 of 96 (15%) who had not achieved MMR at 1 year. Similarly, of 180 patients who achieved MR^{4.5} within 1 year, 151 (84%) eventually achieved sustained MR^{4.5} compared to 119 of 274 (43%) who had not achieved MR^{4.5} within 1 year. Median time to sustained MR^{4.5} was 71.0 months, 60.2 months, 53.2 months, and 36.6 months in all and those achieved CCyR within 1 year, MMR within 1 year, and sustained MR^{4.5} at any time point, respectively (Figure 2). Of 52 patients on IM400, 40 (77%), and 32 (62%) achieved CCyR and MMR within 1 year, respectively. Corresponding rates for 205 patients on IM800, were 185 (90%), and 164 (80%); of 148 on dasatinib, 113 (76%), and 67 (45%); of 147 on

nilotinib, 130 (88%), and 114 (78%); and of 51 on ponatinib, 48 (94%), and 41 (80%), respectively ($p= 0.035$; $p= 0.077$).

The 5-year and 10-year clinical outcome are described in Table 3 and Figure 3. FFS decreased by approximately 12% between 5 years and 10 years irrespective of response, mostly because of discontinuation due to toxicity; TFS was minimally changed over this same 5-year period while EFS and OS decreased by approximately 6% from the 5-year timepoint to the 10-year timepoint. The 5-year and 10-year OS in the whole cohort were 94% and 86%, respectively. Corresponding figures for those with CCyR within 1 year were 95% and 88%, respectively; for MMR within 1 year, 95% and 89%; and for sustained MR^{4.5}, 98% and 92%, respectively.

The whole cohort was then divided into a training cohort (484 patients), and a validation cohort (119 patients). Patient characteristics, type of front-line TKI, response are described in Supplemental table 2 for the two sub-cohorts. The best fit average and minimum acceptable levels were calculated using the training cohort (Supplemental table 3). Five-year, and 10-year FFS, TFS, EFS, and OS are described in Supplemental table 4. Overall, the accuracy of prediction with the best fit average and minimum acceptable levels of BCR-ABL1 levels was well-validated (Supplemental table 5). With the minimum acceptable levels, each cutoff at 3, 6, 9, and 12 months adequately separated patients who achieved or did not achieve each target response. All the patient who met the criteria of best fit average achieved sustained MR^{4.5}, and majority of patients with the achievement of minimum acceptable levels achieved sustained MR^{4.5}.

Discussion

To our knowledge, this is the first analysis of best fit average and minimum acceptable BCR-ABL1 levels to achieve specific response endpoints in patients with newly diagnosed CML-CP. The best fit average molecular levels represents the typical transcript levels of patients who achieved each target response, and the minimum acceptable molecular levels represent 95 percentile levels in target responders. It is well documented that achieving a CCyR and MMR significantly improves the life expectancy of patients, whether this is achieved with interferon therapy or with any of the TKIs currently available.¹⁷⁻²⁰ The ELN defined optimal and warning BCR-ABL1 levels at 3, 6, and 12 months.¹⁰ Our findings of minimum acceptable levels for MMR within 1 year (1.127%, 0.553%, and 0.133% IS at 3, 6, and 12 months, respectively) are similar to optimal those proposed for optimal response categories without logarithmic difference by the ELN, i.e., BCR-ABL1 10%, 1%, and 0.1 IS at 3, 6, and 12 months, respectively. Similarly, our proposed minimum acceptable levels for CCyR within 1 year (2.218%, 1.485%, and 0.665% at 3, 6, and 12 months, respectively) are consistent with ELN warning BCR-ABL1 levels (10%, 1-10%, and 0.1-1% IS at 3, 6, and 12 months, respectively). It should be noted that our models for the best fit average and minimum acceptable levels were derived from timepoints around 3, 6, 9, and 12 months. It is possible that the estimated values of the best fit average and minimum acceptable levels between timepoints could be less accurate due to smaller number of data samples. However, the deviation from each exact timepoint allowed our analysis for reliable prediction between timepoints. As shown in the figure 1, the best fit average and minimal acceptable levels

reliably represents the average levels and 95 percentile levels in each response category. In actual practice, our model could be useful to evaluate warning and optimal BCR-ABL1 levels at any timepoint during the course of therapy, and not only at the exact timepoints proposed by ELN recommendations.

There is a growing interest in the TKI discontinuation in patients who achieved stable deep response, i.e. sustained MR^{4.5}. The prospective multicenter Stop Imatinib trial (STIM) reported 41% of patients who achieved complete molecular response for at least 2 years maintained its response at 12 months with at least 12 months follow-up.²¹ The TWISTER trial reported treatment-free remission of 47% at 24 months in patients who had achieved sustained MR^{4.5} prior to imatinib discontinuation.¹¹ More recently, the DADI trial demonstrated treatment-free remission of 49% at 6 months in patients after 1-year consolidation therapy on dasatinib after achievement of MR^{4.0} with a median follow-up of 20 months.¹² The ENESTStop trial evaluated the discontinuation of nilotinib in 126 patients with CML-CP who achieved deep molecular response for one year of nilotinib following imatinib, and demonstrated 58% of patients who stopped nilotinib maintained treatment free remission at 48 weeks.²² The ENESTFreedom also showed 52% of patients in deep remission remained treatment free at 48 weeks after discontinuation of nilotinib.²³ These results suggest the expected outcome is similar regardless of the TKI used prior to discontinuation, although the likelihood of achieving these responses may higher with second generation TKI than with imatinib. We thus evaluated the best fit average and minimum acceptable molecular levels within 1 year of treatment to predict for achievement of sustained MR^{4.5} at any point based on the BCR-ABL1 levels achieved within the first year of TKI therapy. In this analysis the best fit average levels at 3 months for patients eventually achieving a sustained MR^{4.5} was 0.051% (95% CI, 0.0306-0.0844). This means that the average patient who eventually achieved sustained MR^{4.5} achieved at least MMR (and nearly MR⁴) at 3 months. It is possible that the criteria is less restrictive for sustained MR^{4.5} at any time with longer follow-up. The minimum acceptable BCR-ABL1 levels at 12 months for sustained MR^{4.5} was 0.085% (95% CI, 0.0202-0.3594). This means that nearly all (specifically, 93%) patients that eventually achieved a sustained MR^{4.5} had achieved MMR (and nearly MR⁴) within 1 year. Although the higher end of 95% CI (0.3594% IS) is above MMR levels, it is important to note that the molecular levels at 1 year of TKI therapy need to be <0.4% for patients to have a reasonable probability of achieving sustained MR^{4.5}. Furthermore, 99% of patients that achieved sustained MR^{4.5} had achieved CCyR within 1 year. Thus the achievement of CCyR within 1 year of TKI treatment is nearly a sine qua non for achievement of sustained MR^{4.5} at any time during the course of therapy. It is important to highlight that although this model can identify at early timepoints patients with low probability of achieving specific goals later during the course of therapy, whether and what specific interventions may change the outcome of such patients remains to be studied.

In our models, we described the estimated 12-month BCR-ABL1 levels of the best fit average and the minimum acceptable using BCR-ABL1 data within 12 month of TKI therapy to predict CCyR and MMR within 1 year as well as sustained MR^{4.5} at any points. The best fit average and minimum acceptable levels for CCyR within 1 year were 0.007% and 0.665%, respectively; for the MMR within 1 year, 0.004% and 0.133%, respectively. Although these endpoints might be considered of intermediate relevance (i.e., surrogates of

long-term outcome than a desired outcome themselves) the estimated BCR-ABL1 levels at 12 months for CCyR and MMR within 1 year (i.e., at a time when responses have actually already occurred) confirms the accuracy of prediction in our analysis, and supports the prediction for sustained MR^{4.5} is feasible with our approach.

There are several limitations in our study. First, this is a single institution cohort of patients enrolled in consecutive prospective clinical trials and patients with significant co-morbidities including heart failure, chronic kidney disease, liver cirrhosis, other active cancers were excluded from clinical trials and thus are not included in this analysis. Thus, it is possible that the results are not representative of all patients with CML-CP. However, the protocols of each clinical trial accepted patients with common medical diseases such as hypertension, diabetes mellitus, hyperlipidemia, history of myocardial infarction, and distant history of cancer and were generally more permissive than the large, pivotal trials with dasatinib or nilotinib thus providing information applicable to patients more similar to the average patient. Also, the disease assessment and follow-up timing were performed consistently for all protocols. We have reported that outcome of patients treated within or outside clinical trials with imatinib at our institution is equivalent, and the interpretation of BCR-ABL1 levels would not be influenced irrespective of clinical trials.²⁴ Second, the definition of sustained MR^{4.5} required at least 2 year of stable MR^{4.5} or deeper in our analysis. Patients who achieved deep remission with shorter follow-up were excluded from the analysis. It is possible that additional data from patients who would achieve sustained MR^{4.5} with longer follow-up might affect our analysis on the best fit average and minimum acceptable BCR-ABL1 levels. However, clinical trials with imatinib, high-dose imatinib, nilotinib, and dasatinib have adequately long follow-up, and further follow-up would not impact our results significantly. Third, we logarithmically transformed BCR-ABL1/ABL1 ratios, which might lead to potential bias. However, current European LeukemiaNet recommendations interpret the depth of response with cutoffs at 10%, 1%, and 0.1% on the international scale, which in essence represent 1-log declines.²⁵ The logarithmic decline of BCR-ABL1/ABL1 levels were utilized in our analysis at each timepoint. Thus, we analyzed our data to follow current monitoring guidelines. Fourth, baseline BCR-ABL1 levels were not included due to potential bias from the upper limit of BCR-ABL1 levels at 100% because true biological nature of the disease status at diagnosis could exceed 100% of BCR-ABL1 levels. The incorporation of baseline BCR-ABL1 levels without the upper limit might affect our results. However, the validation model confirmed our approach can adequately separate patients for target response with minimum acceptable cutoffs. Lastly, second generation TKI produced higher rates of deep response and these occurred faster than those of imatinib.^{26, 27} However, the current agreement of the significance of cytogenetic and molecular response by the ELN recommendations, is that the desired optimal responses and the values that define failure are the same at 3, 6, 12 months, and thereafter regardless of TKI.¹⁰ Various analyses of outcome based on response suggest that the significance of given responses at specific times is similar regardless of the TKI used, although generally second generation TKI may give higher probability of responses, particularly the earlier and the deeper responses. Given the clinical significance of each response is treated equally irrespective of TKI, a predictive model derived from the combined data of various TKI is justifiable.

In conclusion, proper interpretation of transcript levels achieved early during the course of therapy may help predict later response and outcome. Models such as the one proposed here can be built to guide therapy for patients in a continuous basis. To achieve sustained MR^{4.5} for at least 2 years, deeper responses are required at each timepoint. Our model proposes optimal values that predict the highest probability of reaching such goal. At a minimum, CCyR within 1 year is required to achieve sustained MR^{4.5}.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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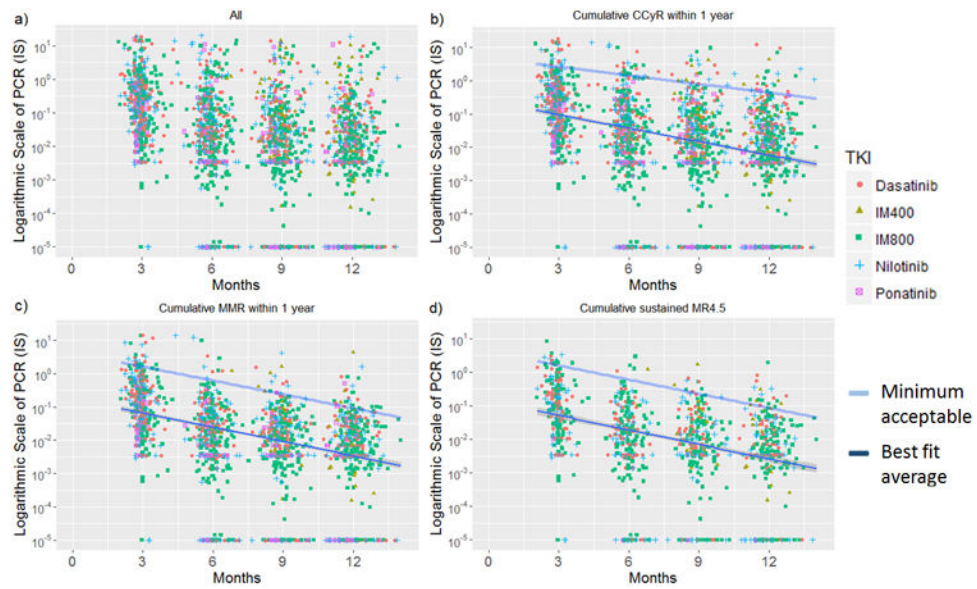


Figure 1. Prediction for response with best fit average (thick blue), and acceptable BCR-ABL1 levels (light blue): a) all data, b) CCyR within 1 year, c) MMR within 1 year, d) sustained MR^{4.5}. Abbreviations: CCyR, complete cytogenetic response; MMR, major molecular response; MR^{4.5}, molecular response with 4.5 log reduction by international scale.

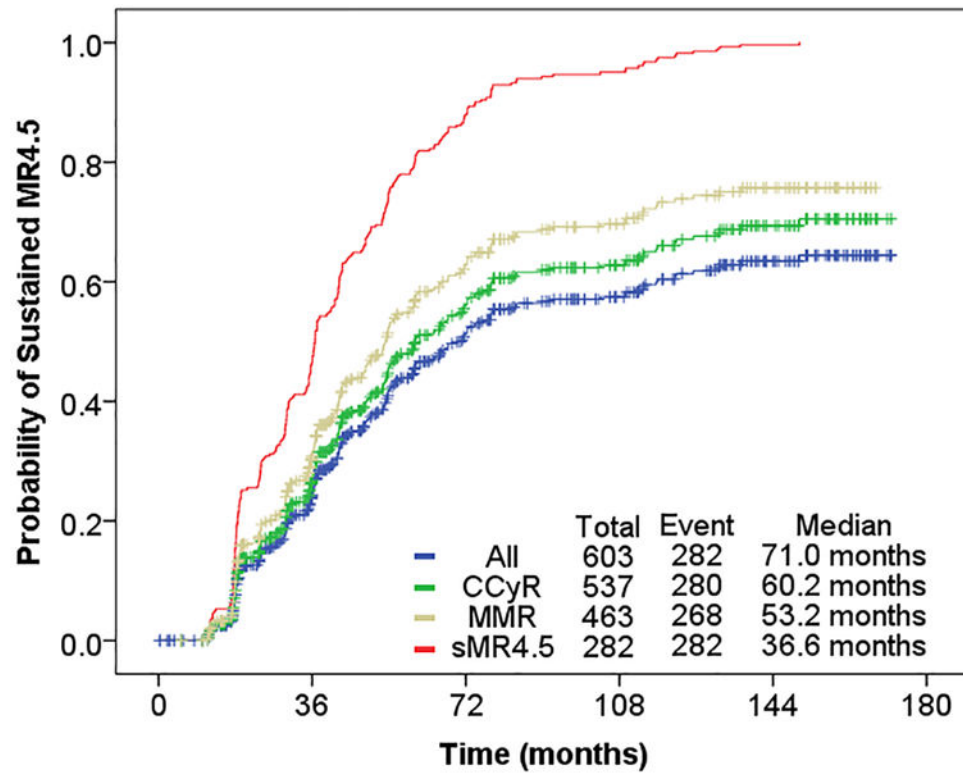


Figure 2. Probability of sustained MR4.5

Abbreviations: CCyR, complete cytogenetic response; MMR, major molecular response; MR^{4.5}, molecular response by a 4.5 log reduction on the international scale.

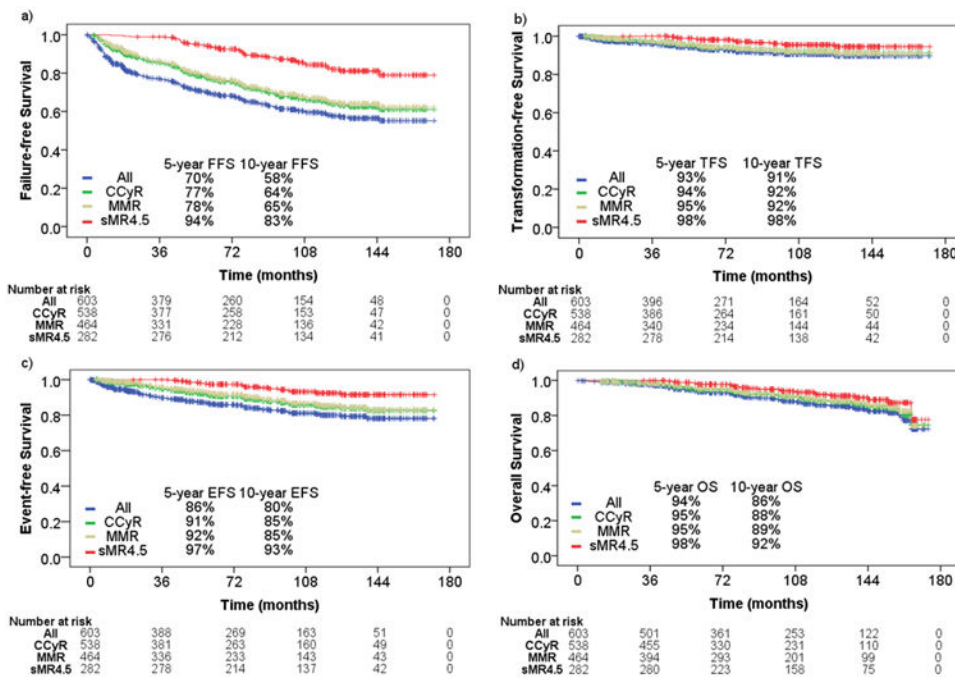


Figure 3. Clinical outcome by response: a) failure-free survival, b) transformation-free survival, c) event-free survival, and d) overall survival

Abbreviations: FFS, failure-free survival; TFS, transformation-free survival; EFS, event-free survival; OS, overall survival; CCyR, complete cytogenetic response; MMR, major molecular response; MR4.5, molecular response by a 4.5 log reduction on the international scale.

Table 1
Patient characteristics

Median, (range) / No. (%)	All patients N=603	CCyR within 1 year N=538	MMR within 1 year N=464	Sustained MR ^{4.5} N=282
Age at diagnosis, year	49 (15.1-84.8)	50 (15.1-84.8)	50 (15.1-84.8)	51 (15.1-84.8)
Spleen size, cm	0 (0-30)	0 (0-23)	0 (0-23)	0 (0-23)
Days from diagnosis to therapy	21 (0-377)	21 (0-377)	21 (0-377)	24 (0-233)
White blood cell, $\times 10^3/L$	29.9 (0.8-569.3)	29.6 (0.8-569.3)	27.4 (0.8-569.3)	28.3 (2.7-342.5)
Sokal score	0.732 (0.424-23.221)	0.732 (0.424-23.221)	0.730 (0.424-23.221)	0.746 (0.442-23.221)
Sokal risk				
Low	396 (66)	356 (66)	308 (66)	178 (63)
Intermediate	153 (25)	141 (26)	120 (26)	79 (28)
High	54 (9)	41 (8)	36 (8)	25 (9)
Cytogenetic type				
Isolated Ph+	524 (87)	470 (87)	401 (86)	247 (88)
Variant Ph+	36 (6)	29 (5)	28 (6)	14 (5)
Cryptogenic	9 (2)	9 (2)	9 (2)	6 (2)
Clonal evolution	32 (5)	28 (5)	25 (5)	14 (5)
Unknown	2 (0)	2 (0)	1 (0)	1 (0)
Transcript type				
B2A2	249 (41)	219 (41)	165 (36)	97 (34)
B2A2+B3A2	109 (18)	98 (18)	86 (19)	62 (22)
B3A2	245 (41)	221 (41)	213 (46)	129 (45)
Type of tyrosine kinase inhibitor				
Imatinib 400 mg/day	52 (9)	40 (7)	32 (7)	23 (8)
Imatinib 800 mg/day	205 (34)	185 (34)	164 (35)	123 (44)
Dasatinib	148 (25)	135 (25)	113 (24)	67 (24)
Nilotinib	147 (24)	130 (24)	114 (25)	68 (24)
Ponatinib	51 (9)	48 (9)	41 (9)	1 (0)
Response within 1 year				
CCyR	538 (89)	538 (100)	463 (100)	280 (99)
MMR	464 (77)	463 (86)	464 (100)	268 (95)
MR4	300 (50)	300 (56)	300 (65)	201 (71)
MR ^{4.5}	240 (40)	240 (45)	240 (52)	162 (57)
Sustained MR ^{4.5}	282 (47)	280 (52)	268 (58)	282 (100)

Abbreviations: CCyR, complete cytogenetic response; MMR, major molecular response; MR^{4.5}, molecular response with 4.5 log reduction by international scale.

Table 2
Best fit average and minimum acceptable molecular levels at specific timepoints

All	Response at specific timepoint			
	3 months (95% CI)	6 months (95% CI)	9 months (95% CI)	12 months (95% CI)
Best fit average, %				
CCyR within 1 year	0.087 (0.0603 – 0.1244)	0.037 (0.0236 – 0.0588)	0.016 (0.0092 – 0.0278)	0.007 (0.0036 – 0.0131)
MMR within 1 year	0.059 (0.0421 – 0.0829)	0.024 (0.0158 – 0.0371)	0.010 (0.0059 – 0.0166)	0.004 (0.0022 – 0.0074)
Sustained MR ^{4.5} at any timepoint	0.051 (0.0306 – 0.0844)	0.019 (0.0100 – 0.0361)	0.007 (0.0033 – 0.0154)	0.003 (0.0011 – 0.0066)
Minimum acceptable response, %				
CCyR within 1 year	2.218 (1.1025 – 4.4622)	1.485 (0.6054 – 3.6412)	0.994 (0.3324 – 2.9712)	0.665 (0.1825 – 2.4245)
MMR within 1 year	1.127 (0.4659 – 2.7242)	0.553 (0.1726 – 1.7702)	0.271 (0.0640 – 1.1504)	0.133 (0.0237 – 0.7475)
Sustained MR ^{4.5} at any timepoint	1.561 (0.7054 – 3.4524)	0.592 (0.2159 – 1.6242)	0.225 (0.0661 – 0.7641)	0.085 (0.0202 – 0.3594)

Abbreviations: CI, confidence interval; CCyR, complete cytogenetic response; MMR, major molecular response; MR^{4.5}, molecular response with 4.5 log reduction by international scale.

Table 3
Clinical outcome by response

All patients N=603	CCyR within 1 year		MMR within 1 year		Sustained MR ^{4,5}	
	Yes N=538	No N=65	Yes N=464	No N=139	Yes N=282	No N=320
5-year clinical outcome, %						
FFS	70	77	3	78	39	42
TFS	93	94	76	95	87	86
EFS	86	91	24	92	62	70
OS	94	95	83	95	87	89
10-year clinical outcome, %						
FFS	58	64	3	65	33	26
TFS	91	92	65	92	85	83
EFS	80	85	20	85	58	59
OS	86	88	65	89	76	78

Abbreviations: CCyR, complete cytogenetic response; MMR, major molecular response; MR^{4,5}, molecular response with 4.5 log reduction by international scale; N/A, not available.