Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment. The EUTOS score

Running Head: The EUTOS Score

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Abstract

The outcome of chronic myeloid leukemia (CML) has been profoundly changed by the introduction of tyrosine kinase inhibitors into therapy, but the prognosis of patients with CML is still evaluated using prognostic scores developed in the chemotherapy and interferon era. The present work describes a new prognostic score (EUTOS) that is superior to the Sokal and Euro scores both in its prognostic ability and its simplicity. The predictive power of the score was tested on a group of patients selected from a registry of 2060 patients enrolled in studies of first-line treatment with imatinib-based regimes. In a learning sample, the relevance of nine variables in the prediction of complete cytogenetic response (CCgR) at 18 months was assessed. The results showed that percent basophils and spleen size best discriminated between high-risk and low-risk groups of patients, with a positive predictive value of not reaching a CCgR of 34%. Five-year progression-free survival was significantly better in the low- than in the high-risk group (90% vs. 82%, p = 0.006). These results were then confirmed in a larger validation sample. The advantage of the EUTOS score is that although it is based on two easily and inexpensively measured variables it nonetheless has superior prognostic power compared with the Sokal and Euro scores. The score can be used to identify CML patients with significantly lower probabilities of responding to therapy and survival, thus alerting physicians to those patients who require closer observation and early intervention.
Introduction

Until the introduction of allogeneic stem cell transplantation and interferon-alpha (IFNa)\(^1\)\(^2\), the course of Philadelphia-positive (Ph+) chronic myeloid leukemia (CML), from the chronic phase (CP) to the accelerated and blastic phases (AP, BP) and death, was almost linear. The introduction of imatinib, the first of a series of tyrosine kinase inhibitors (TKIs) that target the oncogenic protein coded by the bcr-abl gene\(^3\)\(^4\), profoundly changed the treatment of CML. With TKIs, the yearly death rate is currently around 2%, and more than 80% of patients are projected to be alive after 8 years\(^5\)\(^-\)\(^7\). However, a systematic approach to assess the prognosis of TKI-treated patients has not been developed as yet; instead, the use of two prognostic classifications developed for patients treated with either conventional chemotherapy (Sokal score)\(^8\) or IFNa (Euro score)\(^9\) has persisted, not only in imatinib-treated patients but also in patients participating in the most recent studies involving 2\(^{nd}\)-generation TKIs\(^10\)\(^11\). Clearly, the baseline prognostic evaluation of CML must be revisited to specifically evaluate TKI-treated patients. For this purpose, a European Registry of CML patients was established by the European LeukemiaNet. It has been maintained and implemented within the framework of a project supported by Novartis Oncology Europe (EUropean Treatment and Outcome Study for CML, EUTOS). In the present work, these registry data were used to develop a new prognostic risk score able to predict the probability of achieving a complete cytogenetic response (CCgR) within 18 months, which is the most solid and confirmed surrogate marker of survival\(^7\).
PATIENTS and METHODS

Patients

The ELN/EUTOS CML registry contains the individual data of adult patients enrolled in prospective, controlled, GCP-operated studies between 2002 and 2006. The eligibility criteria for the registry were diagnosis of Ph+/BCR-ABL+ CML in CP and any form of imatinib-based treatment within 6 months after diagnosis, regardless of the duration of imatinib treatment. These criteria were fulfilled by 2060 patients from five national study groups (German12, n = 699, GIMEMA13, n = 556, French14, n = 546, Nordic15, n = 140, and HOVON16, n = 119).

Among these, we analyzed all 1261 patients who progressed or died within 36 months or had a minimum follow-up of 36 months and all 1223 patients in whom cytogenetic response status had been evaluated at 18 months (acceptable interval 15–21 months). The latter group was divided into two sub-groups: a learning sample of 938 patients from the German, GIMEMA, and HOVON groups, and a validation sample of 285 patients from the French and Nordic groups. The patient flow is detailed in Table 1. All clinical and hematologic factors were determined at baseline. Patient demographics were comparable across the national subsets. There were no relevant differences in timing of diagnosis, diagnostic procedures, and monitoring. All patients had been enrolled in prospective studies of treatment with imatinib or imatinib-based regimes.
Definitions

The criteria recommended by ELN\textsuperscript{7} were used for the definitions of CCgR and the progression to AP or BP. The Sokal and Euro risk scores were calculated using the original formulae\textsuperscript{8,9}.

Statistics

For every case, time was calculated from the starting date of imatinib treatment. For the analysis of time-to-event data, Kaplan-Meier curves, log-rank tests, and, as needed, competing risk methods were applied. The new prognostic score was developed using a learning sample (German, GIMEMA and HOVON patients) and a validation sample (French and Nordic patients). Since CCgR at 18 months after start of therapy has proven to be a solid surrogate parameter for the risk of progression, a prognostic model for this parameter was developed on the learning sample and later validated on an independent sample.

In the learning sample, logistic regression and chi-squared-tests were used to assess the predictive relevance of candidate variables on CCgR status at 18 months. To develop the new score, influential variables were identified and combined in multiple models. The result of the linear predictor of each model was then categorized into one of two risk groups by application of the minimal p-value approach\textsuperscript{17,18}. After adjustment for multiple testing, the minimal p-value approach identified the cut-off point that separated the sample into two risk groups according to the smallest p-value for CCgR at 18 months. In calculating positive predictive values (PPVs), negative predictive values (NPVs),
sensitivities, and specificities, the models were compared with each other and with the established scores. PPVs were always calculated for the high-risk group, and NPVs for the remaining patients. The level of significance was 0.05. Calculations were done using SAS 9.2 and PASW 17.

All studies complied with the Declaration of Helsinki and were approved by the ethics committees of all participating institutions. Data collection, processing; and all statistical analyses were exclusively carried out by the Central Data Center (J.H., V.H., D.L., M.P.) at the Department for Medical Information Processing, Biometry and Epidemiology of the Ludwig-Maximilians-University of Munich, Germany.

Results

Registry eligibility criteria were met by 2060 patients. Their median age was 52 years (range 18-88), and 60% were male. According to the EURO score, 38% of the patients were at low risk, 51% at intermediate risk, and 11% at high risk. The corresponding numbers for the Sokal score were 39%, 37%, and 24%. The standard monotherapy of 400 mg imatinib per day was administered to 41% of the patients, imatinib 400 mg combined with either low-dose arabinosyl cytosine (LDAC) or IFNa to 34%, and imatinib either 600 or 800 mg to 25%. Median observation time was 42 months (range 1-81 months). At 36 months, the cumulative incidence to have achieved a first CCgR was 92%. The overall survival probability at 60 months was 91%.
Cytogenetic response rate and risk of progression

Among the 1261 patients observed for at least 36 months and evaluated for CCgR at 18 months, the proportion of patients who had achieved CCgR increased over time: from 7% after 3 months to 31% (6 months), 65% (9 months), 74% (12 months), and 82% (15 months) until reaching 85% after 18 months. There was a clear relationship between not achieving CCgR by a certain time and an increasing risk of progression within 3 years after the start of therapy (Table 3): Patients who had not achieved CCgR after 6 months had an 8% risk of subsequent progression, which increased to 14% after 12 months and 23% after 18 months. Correspondingly, the likelihood of achieving CCgR at a later date decreased from 85% at 6 months to only 31% at 18 months. These data supported the selection of CCgR status at 18 months as the dependent outcome variable for the analysis of a prognostic model.

Sokal and Euro scores for CCgR at 18 months

Of the 1223 patients in whom cytogenetic remission status at 18 months had been examined, the Euro and Sokal scores were available for 1165 and 1167 patients, respectively. The CCgR rate at 18 months was 84%. With both scores, the discrimination was significant only for high-risk patients. The PPVs for not achieving CCgR were 25% (high-risk Sokal) and 26% (high-risk Euro).

Improvement of the discriminatory power of the two established scores was attempted by combining low- and intermediate-risk groups and by using the minimal p-value approach in order to define a new cut-off point for the two prognostic classes with the greatest
differences. However, the discriminatory power did not improve sufficiently. The PPVs of high-risk patients was between 25% and 28% and the relationship between sensitivity and specificity was not well balanced. Specifically, either there were many patients in the high-risk group and thus the sensitivity was high but the specificity was low, or the specificity was high but there were few patients without CCgR who were identified as high-risk.

Identification of prognostic baseline variables in the learning sample

Since neither the Euro nor the Sokal score provided a satisfactory prediction, logistic regression was applied in order to identify factors with a significant impact on CCgR status at 18 months. Candidate variables were the six laboratory parameters (Table 2) as well as age, sex, and spleen size. All analyses were restricted to the learning sample. In univariate analysis, spleen size, leukocytes, blasts, eosinophils, and basophils were found to have a statistically significant influence on the event “no CCgR at 18 months.”

New EUTOS risk score in the learning sample

Given the correlation between potential prognostic factors, various significant models were identified and tested. In the minimal p-value approach, the most discriminatory cut-off point of the linear predictor of the multiple logistic regression models defined a low-risk and a high-risk group. The best explanatory model for sensitivity, specificity, and PPV included only basophils (p = 0.0024) and spleen size (p = 0.0105). The model could be shortened without a loss of accuracy to yield a simple formula for calculating the new prognostic score. It is shown in Table 4, and the original model in Table 5. Based on the monotone transformation in the logistic regression model, it is also possible to calculate
the individual estimated probability for a patient not to achieve a CCgR (Table 5). The cut-off point for this probability was located at 22.7%. The new prognostic score identified a high-risk group (risk score $\geq 87$) with a PPV of 33% (Table 4, Figure 1a).

New EUTOS risk score in the validation sample and in the total sample

Very similar results were obtained when the new prognostic score was applied to the validation sample, comprising 271 patients (Table 4 and Figure 1b). As in the learning sample, every third patient in the high risk-prognosis group was not in CCgR at 18 months, with a PPV of 34%.

Finally, the new score was applied to all 1197 patients with a known CCgR status at 18 months, and for whom data on basophils and spleen size were available (Table 4 and Figure 1c). The PPV was 34%, the sensitivity 21%, and the specificity 92%.

EUTOS risk score and treatment

Patients in the registry had been enrolled in prospective studies assessing different treatments: imatinib alone (400, 600, or 800 mg daily) or 400 mg daily in combination with either LDAC or IFNa. The differences between low- and high-risk patients were significant in all treatment groups; 400mg imatinib ($p<0.008$, Figure 1d), imatinib 600–800 mg ($p<0.0001$), and imatinib +LDAC/IFN ($p<0.0001$). The discriminating power of the risk score was maintained in all three groups (Table 6), with a PPV for high-risk patients ranging between 27% for higher-dose imatinib and 40% for the combinations of imatinib with either LDAC or IFNa.
Cumulative incidence of CCgR and progression-free survival

Achieving a CCgR within 18 months has been shown to be a solid early surrogate marker of outcome. The formula of the new EUTOS score could be applied to 1873 registry patients for whom data on spleen size, basophils, and known time to cytogenetic response were available, and to 2010 patients for whom data on follow-up of survival were available. Figure 1c shows the cumulative incidence for CCgR. Figure 2 shows the probabilities of survival free from progression to AP or BP (PFS), in both EUTOS risk groups. At 5 years, the projected figures for PFS were 82% (95% C.I. 73%–89%) for high-risk patients and 90% (95% C.I. 88%–92%) for low-risk patients (log-rank test, p=0.0069). Information on basophils, spleen size, and progression status were available for 1239 patients who had been observed for at least 36 months or who had died before that time. The sensitivity of the EUTOS score for PFS was 16%; the specificity was 91%. Among patients in the high-risk group, 12% progressed compared to 7% in the low-risk group.
Discussion

We used the data of 2060 patients of the ELN/EUTOS European CML Registry who had been enrolled in prospective, investigator-sponsored studies of imatinib treatment to test the Sokal and Euro scores for their relationship with treatment failure. Accordingly, CCgR status at 18 months was selected as an endpoint because it is a conservative but solid and confirmed predictor of treatment success or failure. While both scores were found to have discriminatory power, neither was well balanced in terms of sensitivity and specificity. Therefore, a new prognostic score (EUTOS), which could be based only on the percentage of basophils in blood and on spleen size, was formulated and shown to have improved predictive power. The statistical value of the EUTOS score was validated in an independent data set. Moreover, its simplicity allows it to be easily applied in clinical practice. However, the biological implications of this new model remain to be determined. A combination of spleen size and basophils was determined to best predict CCgR. Indeed, in all studies performed over the last 50 years, spleen size has consistently been identified as a significant predictor of treatment outcome irrespective of treatment (reviewed in ref. 1), although a standardized method of assessing and reporting spleen size is still lacking. Thus, it may be the case that measuring and reporting spleen size with more objective methods, such as ultrasound scan or computed tomography, rather than, as currently done by manual palpation, may further improve the EUTOS score’s predictive power. We speculate that spleen size provides a rough and imprecise but nonetheless strong appreciation of the extent of extramedullary hematopoiesis. In adults, normal hematopoiesis is limited to the bone marrow. Normal stem cells reside in marrow niches, where their proliferative and differentiation properties are kept under cellular and environmental control. Ph+ stem cells circulate in blood to a much greater extent than normal stem cells and can home outside the marrow, including in the spleen, which...
provides a different niche—one that could favor genetic instability, clonal evolution, self-renewal, and defective differentiation. While there are no recent data supporting these hypotheses, several years ago it was reported that spleen Ph+ cells were somehow different from marrow and blood Ph+ cells in terms of their kinetic properties and cytogenetic patterns\textsuperscript{24,25}. Although three studies failed to confirm the clinical benefits of early splenectomy \textsuperscript{26-28}, it may now be appropriate to revisit the role of the spleen, investigating the composition and the structure of the splenic microenvironment, with particular attention to splenic stem cell niches and the conditions under which Ph+ stem and progenitor cells proliferate, differentiate, and mature in the spleen.

An increase in the number of basophils has long been recognized as a signal of CML progression\textsuperscript{29,30}. In fact, a clinical definition of complete hematologic response is <5% blood basophils whereas >20% defines acceleration\textsuperscript{7}. In an independent study, basophils were found to predict a molecular response\textsuperscript{31}. Thus, basophil percentages are an established and confirmed prognostic factor, even though the reasons for the prognostic strength of this measure are not clear.

The new EUTOS score developed and validated in this study drew on a database of more than 2000 prospectively diagnosed, treated, and monitored patients with chronic phase CML who had been enrolled in independent, investigator-sponsored studies\textsuperscript{12-16}. As has been the case with applying the established Sokal and Euro scores, the patients analyzed with the EUTOS score did not receive identical treatment. Imatinib was administered in a daily dose of 400–800 mg and in several patients was combined with LDAC or IFNa. Since different treatments may result in different responses, the EUTOS score was also tested with respect to treatment (Table 6), Irrespective of treatment dose and type, it was able to significantly predict patient response.

The new EUTOS score is not revolutionary, as was the case following the introduction of the Sokal and Euro scores, but it marks a significant advance because it has a better
PPV than obtained with either of those scores. Moreover, it is specifically based on imatinib-treated patients, and does not prolong the use of prognostic classifications that include factors (age, platelet count, blast cells and eosinophils) which have not been found to affect the response to imatinib. The new score is also simpler and more practical in its application, as it uses only two variables, both of which can be easily measured in routine health care, worldwide.

In this study, the EUTOS score predicted that 34% of high-risk patients will fail to achieve a CCgR in 18 months. Then it also predicts PFS. While the value of the score should be further validated by other investigators, it will be difficult to further improve because the therapeutic efficacy of imatinib is high. If it were even higher, no discrimination would be possible. We believe that only progress in assessing molecular response\textsuperscript{32-38} will support a better prognostic classification. In addition, advances in pharmacogenomics, gene expression profiling, and whole-genome sequencing studies\textsuperscript{40-44} will no doubt contribute to identifying the molecular basis of failure, and thus enable a more patient-tailored and better targeted form of therapy and treatment evaluation. Until then, however, the EUTOS score is a simple and inexpensive method for determining prognosis. As demonstrated herein, it has importantly shown that one in three high-risk patients fails on imatinib. Moreover, despite the fact that the new and validated EUTOS score requires only two variables, its predictive power is better than that of the Sokal and Euro scores. This does not mean that all treatment decisions must be based on prognosis, but that the EUTOS score can identify patients with a significantly higher risk of progression and impaired survival, thus alerting the treating physician of the need for closer patient observation and early therapeutic intervention.
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Authorship Contributions JH and MB designed the research, MB, JG, SS, GR, FG, KP, GO, BS and RH collected data, DL processed and analyzed the data, VH performed statistical analysis, JH, MB, VH, MP and RH analyzed and interpreted data and wrote the manuscript, all authors revised and approved the manuscript.

Conflict of Interest Disclosure

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REFERENCES


Table 1: Patient flow diagram

- **n=1261** observed for 36 months (Table 3)
- **n=2060** eligible patients
- **n=2010** with information on survival time, spleen size and basophils (Figure 2)
- **n=1873** with information on time of first CCgR, basophils, and spleen size (Fig. 1c)
- **n=1233** with information on CCgR status at 18 (+3) months
- **German, GIMEMA, HOVON study groups** n=1244 (Fig. 1a)
- **French and Nordic study groups** n=629 (Fig. 1b)
- Learning data set n=938 (Table 2)
- Validation data set n=285 (Table 2)
- **n=926** with information on basophils and spleen size (Table 4)
- **n=271** with information on basophils and spleen size (Table 4)
<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Learning sample</th>
<th>Validation sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1223</td>
<td>938</td>
<td>285</td>
</tr>
<tr>
<td>Male gender</td>
<td>61%</td>
<td>61%</td>
<td>63%</td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>52 (18-83)</td>
<td>52 (18-83)</td>
<td>52 (18-77)</td>
</tr>
<tr>
<td>Median spleen size(^a), median (range)</td>
<td>1 (0-38)</td>
<td>1 (0-38)</td>
<td>0 (0-25)</td>
</tr>
<tr>
<td><strong>Baseline laboratory values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets ((\times 10^9)/L) median (range)</td>
<td>360 (34-3050)</td>
<td>366 (34-3020)</td>
<td>355 (113-3050)</td>
</tr>
<tr>
<td>Blast cells (%) median (range)</td>
<td>1 (0-15)</td>
<td>1 (0-15)</td>
<td>1 (0-15)</td>
</tr>
<tr>
<td>Eosinophils (%) median (range)</td>
<td>2 (0 - 20)</td>
<td>2 (0 - 20)</td>
<td>2 (0-14)</td>
</tr>
<tr>
<td>Leukocytes ((\times 10^9)/L) median (range)</td>
<td>68 (1-571)</td>
<td>63 (2-571)</td>
<td>89 (2-520)</td>
</tr>
<tr>
<td>Hb (g/dl) median (range)</td>
<td>12 (2-18.2)</td>
<td>12 (5-18)</td>
<td>12 (6-18.2)</td>
</tr>
<tr>
<td>Basophils (%) median (range)</td>
<td>3 (0-21)</td>
<td>3 (0-21)</td>
<td>4 (0-19)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>imatinib 400 mg/day</td>
<td>47%</td>
<td>52%</td>
<td>28%</td>
</tr>
<tr>
<td>imatinib 400 mg/day combined with ara-C or interferon alpha</td>
<td>33%</td>
<td>29%</td>
<td>49%</td>
</tr>
<tr>
<td>imatinib 600 or 800 mg/day</td>
<td>20%</td>
<td>19%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Table 2: Baseline values of the 1223 patients with a known CCgR-status between 15 and 21 months. The learning sample comprised German, GIMEMA, and HOVON patients. The validation sample comprised French and Nordic patients.\(^{12-16}\)

\(^a\) Reported as cm below the costal margin as assessed by palpation.
### Table 3: Proportion of patients without CCgR and the risk of progression after different time points.

There were 87 patients who did not achieve remission or experience disease progression. *No first CCgR achieved (progression or death included). **Among patients without a first CCgR.

<table>
<thead>
<tr>
<th>Months after imatinib start</th>
<th>No CCgR achieved*</th>
<th>Patients who will later achieve CCgR (%)**</th>
<th>Risk of progression after this time point**</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>93%</td>
<td>89%</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>(1168 / 1261)</td>
<td>(1038 / 1168)</td>
<td>(78 / 1168)</td>
</tr>
<tr>
<td>6</td>
<td>69%</td>
<td>85%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>(865 / 1261)</td>
<td>(735 / 865)</td>
<td>(66 / 865)</td>
</tr>
<tr>
<td>9</td>
<td>35%</td>
<td>71%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>(446 / 1261)</td>
<td>(316 / 446)</td>
<td>(50 / 446)</td>
</tr>
<tr>
<td>12</td>
<td>26%</td>
<td>60%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>(326 / 1261)</td>
<td>(196 / 326)</td>
<td>(47 / 326)</td>
</tr>
<tr>
<td>15</td>
<td>18%</td>
<td>42%</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>(224 / 1261)</td>
<td>(94 / 224)</td>
<td>(43 / 224)</td>
</tr>
<tr>
<td>18</td>
<td>15%</td>
<td>31%</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>(190 / 1261)</td>
<td>(60 / 190)</td>
<td>(43 / 190)</td>
</tr>
</tbody>
</table>
EUTOS score = 7 * Basophils + 4 * Spleen size

> 87 => high risk

≤ 87 => low risk

<table>
<thead>
<tr>
<th>Risk</th>
<th>No CCgR at 18 months (15-21 months)</th>
<th>CCgR at 18 months (15-21 months)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Learning sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Low risk | 118                                | 718 (92% of 778)                 | 836  | 90%
|          | 14%                                | 86%                              |      |    |
| High risk | 30 (20% of 148)                    | 60                               | 90   | 10%
|          | 33%                                | 67%                              |      |    |
| n %      | 148                                | 778                              | 926  |    |
|          | 16%                                | 84%                              |      |    |
| Validation sample |                                  |                                  |      |    |
| Low risk | 33                                 | 209 (92% of 228)                 | 242  | 89%
|          | 14%                                | 86%                              |      |    |
| High risk | 10 (23% of 43)                     | 19                               | 29   | 11%
|          | 34%                                | 66%                              |      |    |
| n %      | 43                                 | 228                              | 271  |    |
|          | 16%                                | 84%                              |      |    |
| Total    |                                    |                                  | 1078 |    |
| Low risk | 151                                | 927 (92% of 1006)                | 1197 |    |
|          | 14%                                | 86%                              | 1006 |    |
| High risk | 40 (21% of 191)                    | 79                               | 119  | 10%
|          | 34%                                | 66%                              |      |    |
| n %      | 191                                | 1006                             | 1197 |    |
|          | 16%                                | 84%                              |      |    |

Table 4: Formula for calculating the EUTOS risk score (spleen measured in cm below the costal margin, basophils in %) and the EUTOS risk calculated for patients with CCgR-status at 18 months for whom data on spleen size and basophils were available.
Table 5: Original formula for the EUTOS risk score and formula for calculating the estimated probability of each patient to not be in CCgR at 18 months after the start of therapy. The best cut-off point is located at a 22.7% probability. Spleen measured in cm below the costal margin, basophils in %.

\[
\text{Prob(no CCgR)} = \frac{\exp(-2.1007 + 0.0700 \times \text{basophils} + 0.0402 \times \text{spleen size})}{1 + \exp(-2.1007 + 0.0700 \times \text{basophils} + 0.0402 \times \text{spleen size})}
\]

Table 6: Predictive values of the EUTOS prognostic score by initial therapy

<table>
<thead>
<tr>
<th></th>
<th>Imatinib 400</th>
<th>Imatinib 600 and 800</th>
<th>Imatinib with either LDAC or interferon alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive predictive value</td>
<td>31% (12 of 39)</td>
<td>27% (8 of 30)</td>
<td>40% (20 of 50)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>87% (460 of 527)</td>
<td>90 (187 of 208)</td>
<td>82% (280 of 343)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>15% (12 of 79)</td>
<td>28% (8 of 29)</td>
<td>24% (20 of 83)</td>
</tr>
<tr>
<td>Specificity</td>
<td>95% (460 of 487)</td>
<td>90% (187 of 209)</td>
<td>90% (280 of 310)</td>
</tr>
<tr>
<td>N</td>
<td>566</td>
<td>238</td>
<td>393</td>
</tr>
</tbody>
</table>

Table 6: Predictive values of the EUTOS prognostic score by initial therapy
Figure 1. Cumulative probability of achieving a CCgR as determined by the EUTOS risk score (all computations in the presence of competing risks)

1a. In the learning sample (Gray test p < 0.0001)
1b. In the validation sample (Gray test p < 0.0001)
1c. In all 1873 patients with a known cytogenetic response status and information on spleen size and basophils (Gray test p < 0.0001)
1d. In patients treated with 400 mg imatinib (Gray test p = 0.008)

Figure 2. Survival free from progression to accelerated or blastic phase, calculated for all 2010 patients with follow-up (log-rank test p = 0.0069).
Figure 2:

EUTOS score: high risk  n=211
EUTOS score: low risk  n=1799
Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score

Joerg Hasford, Michele Baccarani, Verena Hoffmann, Joelle Guilhot, Susanne Saussele, Gianantonio Rosti, François Guilhot, Kimmo Porkka, Gert Ossenkoppele, Doris Lindoerfer, Bengt Simonsson, Markus Pfirrmann and Rudiger Hehlmann