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RESEARCH ARTICLE

Prognosis of patients with chronic myeloid leukemia presenting in advanced phase is defined mainly by blast count, but also by age, chromosomal aberrations and hemoglobin

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Abstract

Chronic myeloid leukemia (CML) is usually diagnosed in chronic phase, yet there is a small percentage of patients that is diagnosed in accelerated phase or blast crisis. Due to this rarity, little is known about the prognosis of these patients. Our aim was to identify prognostic factors for this cohort. We identified 283 patients in the EUTOS population-based and out-study registries that were diagnosed in advanced phase. Nearly all patients were

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treated with tyrosine kinase inhibitors. Median survival in this heterogeneous cohort was 8.2 years. When comparing patients with more than 30% blasts to those with 20-29% blasts, the hazard ratio (HR) was 1.32 (95%-confidence interval (CI): [0.7-2.6]). Patients with 20-29% blasts had a significantly higher risk than patients with less than 20% blasts (HR: 2.24, 95%-CI: [1.2-4.0], $P = .008$). We found that the blast count was the most important prognostic factor; however, age, hemoglobin, basophils and other chromosomal aberrations should be considered as well. The ELTS score was able to define two groups (high risk vs non-high risk) with an HR of 3.01 (95%-CI: [1.81-5.00], $P < .001$). Regarding the contrasting definitions of blast crisis, our data clearly supported the 20% cut-off over the 30% cut-off in this cohort. Based on our results, we conclude that a one-phase rather than a two-phase categorization of de novo advanced phase CML patients is appropriate.

1 | INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by a reciprocal chromosomal translocation resulting in the BCR-ABL1 fusion gene. The disease is traditionally described in three distinct clinical phases: chronic phase (CP), accelerated phase (AP) and blast crisis (BC).[1] The exact mechanism that underlies the transformation from a CP to aggressive BC still remains a key biological question for the future.[2] The accumulation of distinct additional cytogenetic abnormalities (ACAs)[3,4] and a variety of mutations[5-7] were associated with disease progression. Current models of disease progression predict that increased BCR-ABL1 expression plays an important role in the secondary molecular and chromosomal changes which precede disease transformation.[8]

Although the triphasic course of CML is generally well recognized, the precise definition of these three phases varies greatly in the

TABLE 1 Staging classification systems for CML

	ELN definitions[23]	WHO definitions[33]
Chronic phase	None of the following criteria	
Accelerated phase	Any 1 or more of the following hematologic/cytogenetic criteria	
Blasts	15-29% in the PB or BM	10-19% in the PB or BM
Blasts + Promyelocytes	≥30% in the PB or BM	-
Basophils	≥20% in the PB	≥20% in the PB
Thrombocytes	Persistent <100 × 10^9/L (unrelated to therapy)	persistent <100 × 10^9/L (unrelated to therapy) persistent ≥1000 × 10^9/L (unresponsive to therapy)
White blood cell count	-	Increasing spleen size and increasing white blood cell count unresponsive to therapy
Spleen	-	
Cytogenetic on treatment	Major route ACA[a]	any new ACA
at diagnosis	-	major route ACA[a] complex karyotype abnormalities of 3q26.2
Blast crisis	Any one or more of the following hematologic/cytogenetic criteria	
Blasts	≥30% in the PB or BM	≥20% in the PB or BM
	Extramedullary blast proliferation, apart from spleen	Extramedullary blast proliferation, apart from spleen
		Large foci or clusters of blasts in the bone marrow biopsy

Abbreviations: ACA, additional cytogenetic aberrations; BM, bone marrow; ELN, European LeukemiaNet; PB, peripheral blood; WHO, World Health Organization.

[a]Major route ACA: second Ph-chromosome, trisomy 8 or 19, or isochromosome 17q.

literature.[9-11] Staging classification systems most often used in clinical studies of CML are those from the European Leukemia Net (ELN) and the World Health Organization (WHO) (Table 1). There is an ongoing discussion whether the definition of CML-BC should include patients who have ≥20% blasts (WHO criteria) or ≥30% blasts (ELN criteria). Furthermore, the presence or absence of cytogenetic or molecular abnormalities at diagnosis seems to play an important role for future staging and classification systems of CML.

The vast majority of CML patients are diagnosed in CP. However, some patients present with advanced phase features at time of diagnosis. Their percentage in previous studies varied between 3.1% and 14%.[12-16] There is limited information about the clinical characteristics, survival, and prognostic factors of CML patients diagnosed in the advanced phase of the disease. Kantarjian et al. identified age and blast count as potential predictors of survival; however, the majority of patients in that study were from the pre-TKI era.[17] Most studies analyzing prognostic factors and survival outcomes for CML-AP or -BC refer to patients that developed an AP or BC from initial CP. The results of these studies indicate that despite the availability of BCR-ABL1 tyrosine kinase inhibitors (TKIs) the treatment options and the outcome for these patients are still poor.[10,18]

As these data suggest that patients diagnosed in the advanced phase of the disease seem to be a very heterogeneous group in terms of their prognosis, it is essential to identify characteristics that are predictive for their outcome. All of the well-established CML prognostic scores like the Sokal,[19] the Euro,[20] EUTOS[21] or the ELTS score[22] were developed and validated for CML patients in chronic phase. However, whether these scores are useful to categorize patients who are diagnosed in advanced phase of CML has not been investigated so far. Therefore, the aim of our work was to analyze the outcome of patients diagnosed in AP or BC and to identify prognostic factors associated with their survival.

2 | METHODS

2.1 | Definitions

In the registries, accelerated phase and blast crisis were defined according to the ELN criteria.[23] Particularly, the cut-off between AP and BC was 30% blasts in the blood or bone marrow. Of note, investigators were asked to provide the disease phase of the patients, but not all variables involved in the definition of the phases were part of the case report form. As the registry was to be manageable also for smaller centers in whole Europe, the data set had to be restricted. Particularly, data on parameters in bone marrow were not collected. All results with respect to immature cells reported in this work relate to peripheral blood. Clonal chromosomal abnormalities in Ph + cells were counted as ACAs. Only patients who were presenting in advanced phase were considered.

2.2 | Statistical analysis

Correlation between candidate variables was investigated by use of Spearman's rank correlation coefficient and scatter plots, Mann-Whitney *U* test, or Fisher's exact test, whichever was appropriate. Overall survival was counted from the date of diagnosis. Survival time of patients alive at the last follow-up was censored. As none of the patients was (by definition) transplanted in first chronic phase, patients were not censored at the date of an allogeneic stem cell transplantation. Survival probabilities were estimated using the Kaplan-Meier estimator and compared using the log-rank test. For the multivariate analysis, the Cox proportional hazards model was used. All *P* values <.05 were considered significant. Model selection was done using Akaike's Information Criterion.[24] Due to the exploratory character of this work, no *P* value adjustment was applied; thus all P-values have to be interpreted descriptively. An external validation of these results by another research group would be welcome.

2.3 | Patients

Data in this analysis came from two different sections within the EUTOS framework. After an update in 2014, the out-study registry (OSR) contains data of 1545 'out-study' patients who did not participate in prospective clinical trials but were registered prospectively at the respective National Study Groups. These patients were diagnosed between 2002 and 2006. This registry has already been described in detail.[25] The population-based registry (PBR) had the aim to collect all newly diagnosed patients at the age of 20 and older in certain regions all over Europe. It covered about 92 million people and the PBR finally contained data of 2887 CML patients ≥20 years of age. These patients were registered between January 2008 and December 2012. The description of the registry can be found elsewhere.[26]

The PBR comprised data on 188 patients that were diagnosed in advanced phase.[15] In the OSR, we identified 117 patients diagnosed in advanced phase. For this analysis, we asked for an update of the follow-up. As a result, three patients had to be excluded due to lacking samples before start of treatment, and two entries proved to be double records of the same patient. Also, for six patients no follow-up was available and for 11 patients, it was not known whether they were in advanced phase at diagnosis or not. Thus, the final sample size consisted of 283 patients, of whom 203 were diagnosed in AP and 80 were diagnosed in BC. The flowchart is given in supplementary Figure 1.

3 | RESULTS

3.1 | Regional distribution

The patients' regional distribution is shown in Table S1. Of note, only the Czech Republic, Poland, Romania, Russia, Spain, and the United Kingdom were part of the OSR. In the PBR, all participating countries except Slovenia contributed at least one patient to the updated advanced phase data set. In the PBR, either the whole country (for smaller countries with a population of less than 10 millions) or selected regions with a maximum of 10 million inhabitants (for larger countries) were part of the registry.[26] Thus, in this study, the number of patients per country cannot be directly connected to the country's population. Furthermore, a comparison between countries was not

possible, as in some countries, the registration was required by law, while in others, the active participation of the physicians was needed.

3.2 | Baseline values

The sample consisted of 151 male (53%) and 132 female patients (47%). Median age was 51 years (range: 18-89). The proportion of patients with transcript type e13a2 only was 53%. Details on the blood values are recorded in Table 2. We found a weak negative correlation between blast and basophil counts (r = –0.257, $P < .001$). When categorizing the patients using the available blast values, 209 (77%) had less than 20% peripheral blasts, 23 (8%) had 20% to 29% blasts, and 39 (14%) had more than 30% blasts at diagnosis. For the peripheral basophils, 226 patients (84%) had less than 20% basophils and 42 (16%) had 20% or more basophils at diagnosis. From the 267 patients with available blast and basophil values, 167 (63%) had values below 20% in both parameters. Forty-one patients (15%) had at least 20% basophils, but less than 20% blasts. Of the patients with basophils below 20%, 22 patients (8%) had blast values between 20 and 29% and 36 patients (13%) had more than 30% blasts. Only one patient had more than 30% blasts and more than 20% basophils.

3.3 | Treatment

For the registration in the OSR, treatment with imatinib in the first 6 months from diagnosis was an inclusion criterion. Out of the 179 patients in the PBR, 146 received any TKI (thereof 68 nilotinib or dasatinib) while 10 patients received only hydroxyurea. Treatment information was missing for 23 patients. Altogether, 48 patients underwent allogeneic stem cell transplantation, thereof 20 who were diagnosed in AP and 28 who were diagnosed in BP.As a sensitivity analysis, we added the transplant status as a time-dependent covariate to the multiple proportional hazards model and did not find a significant effect. Thus, we decided to analyze all patients together.

3.4 | Survival

The median observation time was 5.8 years. Out of 283 patients, 115 died. The median survival time was 8.2 years (95% confidence interval (CI): [6.3 years - infinity]). We found considerable differences between patients diagnosed in AP and patients diagnosed in BC. While median survival was not reached for the patients in AP after a median observation time of 6.0 years, median survival for the BC patients was 1.8 years (95% CI: [1.2-3.7 years]) (see Figure 1).

Patients with more than 30% blasts had a slightly higher hazard of dying than patients with 20-29%; the hazard ratio (HR) was 1.32 (95% CI: [0.7-2.6]). Patients with 20-29% had a significantly higher risk of dying than patients with less than 20% blasts (HR: 2.24, 95% CI: [1.2-4.0], $P = .008$). Patients with less than 20% basophils had an inferior survival compared to the ones with more than 20% basophils, however this difference was not significant (HR: 1.55, 95% CI: [0.9-2.8]).

Blasts were prognostically more important for survival. When combining both variables, irrespective of the percentage of basophils, the median survival time of patients with blast counts <20% was not reached. In case of <20% basophils, they had a 2-year survival probability of 0.75 (95% CI: [0.68-0.82]) and of 0.85 (95% CI: [0.75-0.96]) with

TABLE 2 Descriptive statistics and univariate Cox models for mortality

		n	Median	Range	HR	95% CI	P
Age	(years)	283	51	18-89	1.02	1.01-1.04	.001
Hemoglobin	(g/dL)	271	9.9	4.4-15.8	0.91	0.83-1.00	.042
WBC	($\times 10^9$/L)	269	119	3-560	1.05	0.90-1.22	.541
Platelets	($\times 10^9$/L)	273	376	9-4005	0.89	0.84-0.94	<.001
Blasts	(%)	271	10	0-92	1.02	1.01-1.03	<.001
Basophils	(%)	268	4	0-53	0.97	0.95-0.99	.011
Eosinophils	(%)	268	3	0-18	0.95	0.90-1.01	.093
Spleen	(cm)	269	6	0-40	0.99	0.96-1.01	.334
			n	%	HR	95% CI	P
Sex	male		151	53%	0.96	0.67-1.38	.825
	female		132	47%	1		
Type of transcript	e13a2		65	53%	1		
	e14a2		42	34%	0.62	0.33-1.16	.617
	e13a2 + e14a2		7	6%	0.63	0.15-2.61	.625
	other		8	7%	2.02	0.84-4.88	.117
ACAs	yes		54	26%	1.97	1.25-3.09	.003
	no		156	74%	1		
Extramedullary involvement	yes		11	4%	1.75	0.71-4.31	.228
	no		272	96%	1		

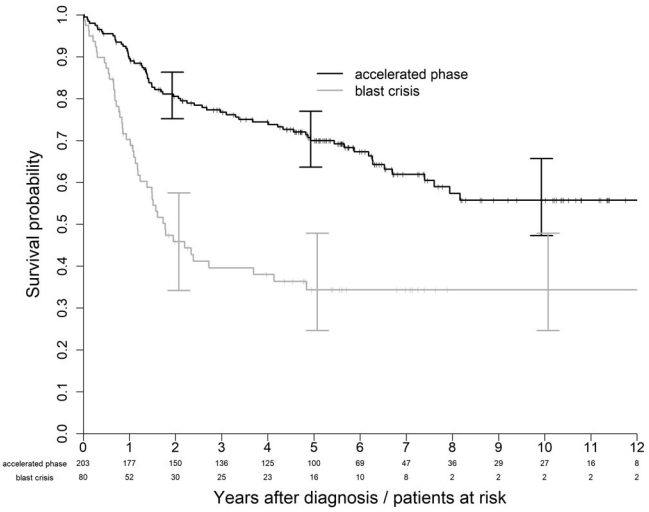

FIGURE 1 Survival according to phase at diagnosis

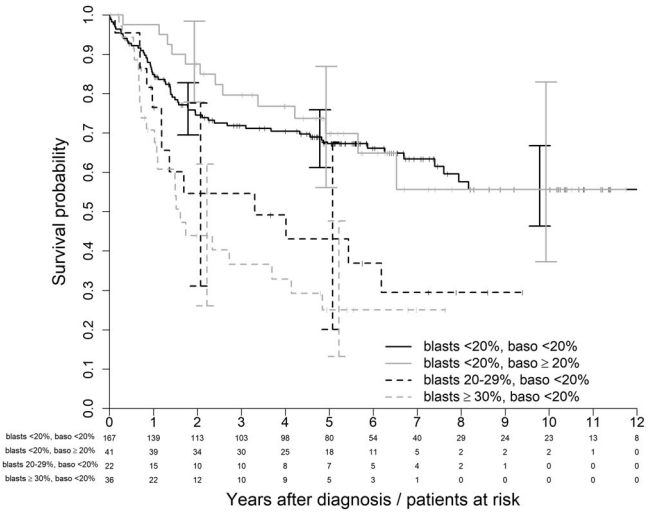

FIGURE 2 Survival according to blasts and basophils. One patient was observed with ≥30% blasts and ≥20% basophils and is not shown here

≥20% basophils. In contrast, the patients with 20-29% blasts had a median survival of only 3.3 years (2-year survival probability: 0.55, 95% CI: [0.36-0.82]), while the group with 30% blasts or more had median survival of only 1.6 years (2-year survival probability: 0.44, 95% CI: [0.30-0.65]). The Kaplan-Meier survival plots are shown in Figure 2.

Patients with ACAs at diagnosis had a significantly higher hazard of dying than patients without (HR: 1.97, 95% CI: [1.3-3.1], $P = .003$). The presence of a thrombocytopenia ($<100 \times 10^9$/L) (HR: 2.28, 95% CI: 1.45-3.58], $P < .001$) was a further unfavorable prognostic factor.

Univariate analyzes of survival probabilities in dependence on baseline values are shown in the right part of Table 2. All continuous covariates were assumed to have a linear effect. However, this assumption is questionable for blast count, where the hazard ratio can only be interpreted as an "average effect". It appeared that for small blast values the increase in the hazard was greater than for larger blast values, thus a logarithmic transformation would have been more suitable. Important predictors of survival seemed to be blast count, age, platelets, hemoglobin, basophils, and additional cytogenetic aberrations at diagnosis.

TABLE 3 Multiple Cox model for mortality for 204 patients with complete data to all variables

		HR	95% CI	P
Blast	20-29% vs <20%	2.11	1.12-4.00	.022
	≥30% vs <20%	2.33	1.33-4.08	.003
ACAs	yes vs no	1.55	0.95-2.53	.077
Hemoglobin	(g/dL)	0.86	0.78-0.96	.009
Age	(years)	1.02	1.01-1.04	.008
Basophils	≥20% vs <20%	0.50	0.22-1.11	.087

When performing multiple analyzes with the Cox model, we found blast count, age, hemoglobin, basophils, and ACAs to be important predictors (Table 3). Blasts was once included as a categorical variable and once as a continuous variable. Results of the first approach are given in Table 3. Also, in the multiple model, no significant differences between the groups 20-29% and >30% were observed, but both showed significantly worse survival probabilities as compared with patients with <20% blasts. Using the logarithm of the continuous blast count instead, we received an HR of 3.07 (95%-CI: [1.86-5.07], $P < .001$), while the HRs of the other covariates remained rather similar. Performing a backward model selection, spleen size, eosinophils, platelets, leucocytes, basophils, or sex were excluded.

In the next step, we distinguished between patients diagnosed in AP and patients in BC. For the 141 patients with complete data in AP, we did a variable selection and found age (HR: 1.02 per year (95%-CI: [1.00-1.04], $P = .033$), platelets (HR: 0.999 per increase of 1×10^9/l (95%-CI: [0.998-1.000], $P = .08$), hemoglobin (HR: 0.81 per increase of 10 g/dL (95%-CI: [0.69-0.95], $P = .010$), the presence of ACAs (HR: 2.06 (95%-CI: [1.03-4.13], $P = .042$) and the logarithm of the blast count to be important predictors (HR: 2.96 (95%-CI: [1.23-7.09], $P = .015$). In contrast, in case of the 63 patients in BC, only age (HR: 1.03 (95%-CI: [1.01-1.05], $P = .001$) and the logarithm of the blasts (HR: 1.69 (95%-CI: [0.94-3.02], $P = .079$) were in the final model. Compared to the model for AP, the impact of the blasts was smaller, while the hazard ratio of age was almost unchanged.

As a sensitivity analysis, we restricted the analysis data set to the 250 patients where TKI treatment was documented. This analysis might include a small bias, as patients with a longer survival had a better chance to be treated with TKI, yet the results were very similar to the original ones. The most striking differences were that in the final model (compared to Table 2) the effect of blasts was even more pronounced. This was with HRs of 2.53 and 2.82 for patients with 20-29% resp. >30% blasts, while in the model for only AP patients, the age effect was lower (HR: 1.01 per year).

When applying the CML scores established for chronic phase to this cohort of patients, we got rather distinct results. The Sokal score[19] allocated nearly 75% of the patients to the high-risk group and was able to find a significance between the high-risk and the intermediate-risk group,

but not between the high-risk and the low-risk group. The Euro score[20] did not provide any prognostic discrimination of survival. The EUTOS score[21] was able to identify two different groups; however the high-risk group had a considerably better survival probability than the low-risk group. Both in patients with AP as well as with BC, the ELTS score[22] was able to discriminate the high-risk group from the low- and intermediate-risk groups, but not between low and intermediate risk. In the high-risk group, 2-year survival probability was 0.65 (95% CI: [0.58-0.72]) as opposed to 0.88 (95% CI: [0.81-0.95]) in the combined low- and intermediate-risk (non-high-risk) group (Figure 3). Considering the 182 patients with AP only, 2-year survival probability was 0.76 (95% CI: [0.68-0.84]) in the high-risk and 0.94 (95% CI: [0.88-0.99]) in the non-high-risk group (Figure 4). In the 73 patients with BC at diagnosis, the corresponding results were 0.40 (high-risk group, 95% CI: [0.29-0.56]) and 0.69 (non-high-risk group 95% CI: [0.49-0.96]) (Figure 4). The three

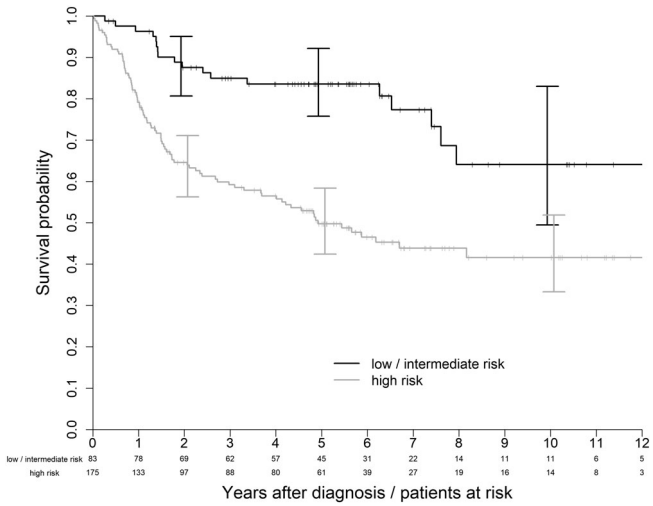

FIGURE 3 Survival according to ELTS score

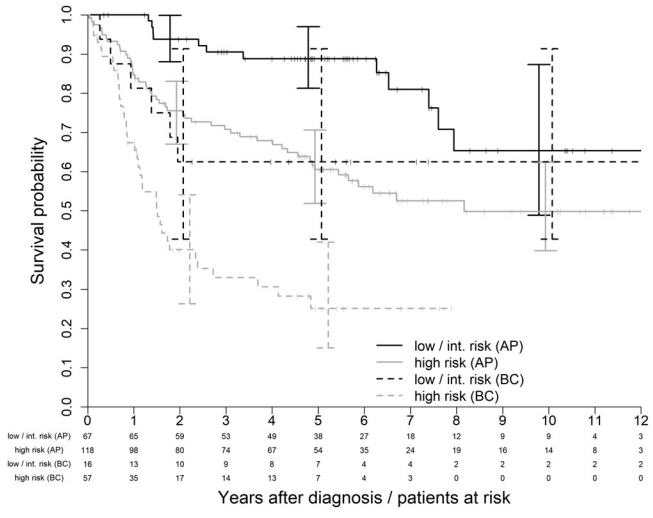

FIGURE 4 Survival according to ELTS score and phase at diagnosis

HRs were 3.01 (all patients, 95%-CI: [1.81-5.00], $P < .001$), 2.79 (patients with AP, 95%-CI: [1.49-5.25], $P = .001$), and 2.61 (patients with BC, 95%-CI: [1.10-6.22], $P = .030$).

4 | DISCUSSION

In this cohort of advanced phase patients, the main objectives were the description of survival probabilities in patients diagnosed in AP or BC, and to consider potential prognostic factors related to outcome. To our knowledge, this study based on data of centers all over Europe is the first large study on this cohort.

The median survival of the AP patients in the present data was much better than in patients that developed an AP from a CP. This was reported in trials from the GIMEMA group where median survival was 37 months,[27] from the MD Anderson group with a 4-year survival probability of 53%,[17] and from China with a 6-year survival probability of 51%.[28] It seems that patients with de novo AP have a different biological background as compared with patients transferring from CP to AP while under therapy. For some of the patients here, de novo diagnosis of AP might have been due to a very late diagnosis of CML, however, without anyone carrying the burden of a history of resistance to TKI. In contrast to patients that progressed from CP to AP because they were not responding to TKI, newly diagnosed patients in AP were reported to show good response when initially treated with TKI, albeit this was observed in small studies.[29,30] In conclusion, AP at diagnosis should be clearly distinguished from AP after CP.

Also the survival of patients with de novo diagnosis of BC was longer than for patients with a BC that developed during the course of the disease. After transformation from CP to BC, median survival in the German CML-study IV was 7.9 months.[31] In a study by the MD Anderson group,[32] median survival for de novo BC patients was more than 2 years, while median survival for BC patients originally diagnosed in CP or AP was less than 1 year. In a population-based setting, the Swedish CML register has recently published a median survival of de novo BC patients of 1.6 years.[30] Even though the differences were smaller than for the AP patients, transferring results from de novo BC patients to patients that develop a BC in the course of the disease does not seem appropriate.

Unfortunately, no information on bone marrow was available, as this information was not collected within the registries. For this reason, we refrained from the attempt to combine statistically significant and clinically relevant factors associated with overall survival in a prognostic system and to define different risk groups, as was done for the scores developed for chronic phase patients. To address the need, with the inclusion of bone marrow parameters, a new blast crisis registry collecting all potentially important prognostic factors has recently been launched. As an inclusion criterion, the lower limit of 20% blasts in peripheral blood was established. Allowing for prospective as well as retrospective data, there are reasonable prospects that a proper prognostic model for the survival of patients diagnosed in BC will be identified.

In the meantime, the use of well-known scores established for CP CML patients should be avoided or, at least, handled with caution. All scores include spleen size, but spleen size did not show a significant association with survival in the present advanced phase data. For

basophils, the association of lower values with worse survival is counterintuitive. In correspondence to the findings for these two variables involved in its definition, outcome predicted by the EUTOS score is contradictory to medical knowledge and thus of no clinical value. But after all, like the other scores, the EUTOS score was developed for CP patients and in addition, for short-term remission outcome. The lack of a meaningful prognostic result for eosinophils contributed to the failure of the Euro score. When combining low- and intermediate risk groups, at least the ELTS score provided a clinically useful discrimination of overall survival, whether it was in all patients diagnosed in advanced phase or in the subgroups AP or BC (Figures 3 and 4). Lacking a more appropriate prognostic tool, the ELTS score could be applied until further notice. However, a prognostic score developed in advanced phase patients remains a desirable aim for the future.

Apart from the lack of data on bone marrow, our patient sample was subject to further limitations. Data came from two observational registries where treatment was not standardized, and we expect that the percentage of patients treated with second-generation TKI in this cohort might have increased in the meantime. Besides, the vast differences in the incidence of CML diagnoses in advanced phases indicate considerable heterogeneity between the countries. This heterogeneity could be due to a more or a less strict application of the criteria defining the advanced phases, or due to the tendency in a certain country to see a physician earlier rather than later. With the lack of data on bone marrow, it was not possible to verify the phase reported by the investigators for each of the patients. On the upside, heterogeneity means also strength. Results do not depend on data from just one study group or even one single center, but are based on patients from all over Europe supporting their generalizability. Furthermore, to our knowledge, this is the largest data set including patients diagnosed in advanced phase.

In this study, the ELN criteria[23] were used for the definition of AP and BC. The most important difference to the WHO criteria is possibly the discrimination between AP and BC when it comes to the application of the blasts' cut-off, which is at 30% according to the ELN, but at 20% according to the WHO criteria.[33,34] Discussion about this cut-off is still ongoing. For patients diagnosed de novo in advanced phase, as a main finding in this work, univariate and multiple modeling results suggest that at least for blasts in peripheral blood the 20% cut-off is more appropriate. With the 30% cut-off according to the ELN criteria, survival outcome in de novo patients defined to be in accelerated phase was quite heterogeneous. While advanced phase patients with blasts below 20% showed a 2-year survival probability above 75%, survival probabilities of patients with 20-29% blasts were significantly worse (55% at 2 years), and much closer to survival probabilities of patients with ≥30% blasts (44% at 2 years). Hoffmann et al.[15] reported a 30-month survival of 84% for ELTS high risk patients diagnosed in chronic phase in the PBR. Compared to the survival probability of 75% at 30 months that we had observed in the group with blasts <20%, there is still a difference. However more than half of de novo patients with blasts below 20% were responsive to TKI therapy, and could be considered like late or high-risk chronic phase patients. It is our perception that a two-phase rather than a three-phase categorization of de novo patients is appropriate. And, that a 20% blast cut-off could be involved in a new definition, only discriminating between chronic phase and blast crisis at diagnosis. As seen in our data, patients with late chronic phase will be identified as high-risk patients by the ELTS score and thus, will still receive particular attention by physicians. To achieve a better understanding of CML blast crisis, and to improve treatments and outcomes, an international blast crisis registry was launched. It is a major aim of this collaborative project to systematically collect baseline, treatment and outcome data of patients diagnosed with CML blast crises. This is to get more information on the biology, prognosis and treatment of this disease. The registry could also provide an empirical base for future national and international trials.

CONFLICT OF INTEREST

M.L. received research funding from Novartis.

A.T. received lecture fees from Novartis and Bristol Myers.

E.F. served in the speakers bureau and received honoraria from Angelini and Bristol Myers, and research funding from Novartis.

E.L. received lecture fees from Novartis.

D.Z. served as a consultant for Novartis, Bristol Myers, Incyte and Angelini.

G.O. served in the advisory board and received honoraria from Novartis, Pfizer, J&J and Celgene, and research funding from Celgene, J&J, Novartis, and BD.

T.S. served in the speakers bureau and received honoraria from Novartis, Bristol Myers, Pfizer and Angelini.

P.K. received lecture fees from Icyte.

A.B. served in the advisory boards of Novartis and Pfizer and as a speaker for Novartis and received travel and accommodation from Novartis and Takeda.

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The remaining authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

M.L., V.H., J.H. and M.P. contributed to the study design and conception. M.L., K.B., A.H. and M.P. contributed to the drafting of the manuscript. A.T., E.F., W.P., U.O.-S., M.B., E.L., D.Z., G.O., L.G., G.S.-F., T.S., S.H., P.K., A.B., R.E.C. and J.G. contributed to data collection and processing. M.L., K.B., V.H., A.H. and M.P. contributed to data analysis and interpretation. All authors critically reviewed and approved the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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