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Title:

LONG-TERM OUTCOME OF CHRONIC MYELOID LEUKEMIA PATIENTS TREATED FRONTLINE WITH IMATINIB: HIGH-RISK PATIENTS NEED BETTER TREATMENT

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KEY POINTS

- Imatinib as frontline treatment of CML yields excellent results: the 6-year OS was 89%, but only 50% of deaths were leukemia-related.
- To further optimize treatment results, a risk-adapted treatment should be required for high-risk patients.

ABSTRACT

For almost 10 years imatinib has been the therapeutic standard of chronic myeloid leukemia. The introduction of other tyrosine-kinase inhibitors (TKIs) raised a debate on treatment optimization. The debate is still heated: some studies have protocol restrictions or limited follow-up; in other studies some relevant data are missing. The aim of this report is to provide a comprehensive, long-term, intention-to-treat, analysis of 559 newly diagnosed, chronic phase, patients treated frontline with imatinib. With a minimum follow-up of 66 months, 65% of patients were still on imatinib, 19% were on alternative treatment, 12% died, and 4% were lost to follow-up. The prognostic value of a BCR-ABL1 ratio ≤10% at 3 months (81% of patients) was confirmed. The prognostic value of complete cytogenetic response and major molecular response at 1 year was confirmed. The 6-year overall survival was 89%, but since 50% of deaths occurred in remission, the 6-year leukemia-related survival was 94%. The long-term outcome of first-line imatinib was excellent, also due to second-line treatment with other TKIs, but all responses and outcomes were inferior in high-risk patients (Sokal, EURO or EUTOS). To optimize treatment results, a specific risk-adapted treatment is needed for high-risk patients.

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INTRODUCTION

The evolution of chronic myeloid leukemia (CML) therapy has been determined by a remarkable flux of data coming from company-sponsored (1-11) or investigator-initiated (12-23) prospective studies. All studies had some sponsor-specific interests, mainly commercial or academic. The long-term observation of patients enrolled within prospective trials is laborious and expensive, so that the long-term outcome could not be always reported. The evolution of therapy has also been influenced by reports of retrospective analyses, that were not always planned in the original study design (24-34). These studies are sometimes difficult to interpret because many observed differences are small and many potentially confounding variables may jeopardize the results. The update of the most important studies is frequently reported as a oral or poster presentation at international meetings (35), but in full peer-reviewed reports the median observation of the patients is always shorter than 6 years, ranging between five and six years in few studies (3,18,21,22,26,32), and being shorter than 5 years in the great majority of reports. Also the studies of the CML Working Party of the Italian Group for Hematologic Diseases in Adults (GIMEMA) have been analysed and reported with limited follow-up (13,14,24). Now the minimum follow-up of the patients enrolled in GIMEMA studies is 66 months, the median follow-up is 76 months, and 23 patients only were lost to follow-up: the response data are solid, the outcome curves flattened, and the relationships between baseline disease characteristics, response and long-term outcome can be calculated more precisely. The aim of this report is to provide a comprehensive, detailed, and intention-to-treat, analysis of the long-term outcome of CML patients treated with imatinib first-line, as a useful reference for the development of the current debates on the CML treatment optimization (36-41). We analyzed the short-term and the long-term probability of achieving cytogenetic and molecular milestones, and the prognostic value of disease risk, focusing in particular on Sokal score (42), to understand if the baseline risk should be still considered as a candidate prognostic factor requiring a more careful warning, according to the ELN recommendations 2103 (40), or if it should require a different, risk-adapted and risk-specific, treatment.

METHODS

Five hundred and fifty-nine adult patients (≥ 18 years old) with newly diagnosed chronic phase Ph+ and/or BCR-ABL1+ CML, were enrolled in three multicentric prospective GIMEMA studies: the GIMEMA CML/021 phase 2 study of imatinib 400 mg twice daily (TD) in intermediate Sokal score patients (82 patients, clinicaltrials.gov NCT00514488) (13), the GIMEMA CML/022 phase 3 study of imatinib 400 mg once daily (OD) compared to imatinib 400 mg TD in high Sokal score patients (112 patients, clinicaltrials.gov NCT00510926) (14), and the GIMEMA CML/023 observational study of imatinib 400 mg OD (365 patients) (24). The intention-to-treat population of each study was analyzed and all the 559 enrolled patients were included in the present analysis. All the patients, in-study or off-study, remained on active observation.

The chronic, accelerated or blastic disease phase (CP, AP, BP) were defined according to ELN criteria (40). The risk scores were calculated according to the Sokal (42), EURO (43), and EUTOS (44) scores. Complete cytogenetic response (CCyR), major molecular response ($MR^{3.0}$ or MMR, corresponding to $BCR\text{-}ABL1^{IS} \leq 0.1\%$) and deep molecular response ($MR^{4.0}$, corresponding to $BCR\text{-}ABL1^{IS} \leq 0.01\%$ or undetectable disease with ≥10,000 ABL1 transcripts) were defined according to the ELN criteria (40) and according to the recent standardized definitions of molecular response (45). The early molecular response (EMR) was defined as a $BCR\text{-}ABL1^{IS} \leq 10\%$ at 3 months, or as a $BCR\text{-}ABL1^{IS} \leq 1\%$ at 6 months (40).

The times to response were calculated from the date of treatment start until the first achievement of the response. Overall survival (OS), progression-free survival (PFS) and event-free survival (EFS) were calculated from the date of start of treatment until death (OS), until death or progression to AP or BP (PFS), or until death, progression to AP or BP, failure according to the European LeukemiaNet criteria (40) or imatinib treatment discontinuation for any cause (except treatment-free remission) (EFS), whichever came first. Probabilities of OS, PFS and EFS were estimated using the Kaplan-Meier method (46). After a careful revision of all cases with progression to AP or BP, of the causes of death, and of the remission status before death, deaths were classified as leukemia-related and leukemia-unrelated (deaths due to other causes): a death was defined leukemia-unrelated if a progression to AP or BP did not occur, the final cause of death was identified, and a condition of CCyR and/or MMR was documented within 6 months prior to death. Survival was calculated both counting all deaths (OS), and counting only leukemia-related deaths (leukemia-related survival, LRS), censoring the deaths in remission. The patients who underwent alloSCT were not censored at transplant. The 23 patients who were lost to follow-up were censored at the date of last contact. Survival comparisons were made by the log-rank test.

RESULTS

BASELINE CHARACTERISTICS

The baseline characteristics of these patients are shown in Table 1. Male patients were 60%. Median age was 52 years (range 18 - 84); 12% per cent of patients were older than 70 years. The spleen was palpable in 58% of patients; a large palpable spleen, more than 10 cm below costal margin, was reported in 18% of patients. Additional chromosome abnormalities in Ph+ cells (CCA/Ph+) were detected in 4% of patients (6% of evaluable patients). High-risk patients were 22% by Sokal (42), 7% by EURO (43) and 7% by EUTOS (44) score. Three hundred and five patients (55%) received a pre-treatment with hydroxyurea for less than 3 months. The initial imatinib dose was 400 mg OD in 76% of patients, and 400 mg TD in 24% of patients. Twenty-three patients (4%) were lost to follow-up after 7 to 81 months. All the other patients were followed until death or December 2012, with a median follow-up of living patients equal to 76 months (range 66-99 months).

OUTCOME

The EFS, PFS, OS and LRS are shown in Figure 1. All curves but that of EFS tended to flatten after 3 years. The 6-year survival probabilities were: 58% (95% CI 54 - 62%) for EFS, 87% (95% CI 84 - 89%) for PFS, 89% (95% CI 86 - 91%) for OS, and 94% (95% CI 92 - 96%) for LRS.

The outcome by Sokal score, including the 6-year estimated probabilities of EFS, PFS, OS, and LRS, is shown in Table 2. The curves are shown in Figure 2. All these estimates were significantly better in Sokal low- and intermediate-risk patients, than in high-risk ones. The same relationship between outcome and risk was also found according to the EURO and EUTOS risk scores (Supplemental Table 1 and 2, and Supplemental Figures 1 and 2).

RESPONSE

The proportion of patients achieving an EMR at 3 and 6 months was 82% and 76%, respectively. The EMR at 6 months, differently from the EMR at 3 months, was significantly affected by the Sokal score. The cumulative incidence of MMR was 66% (95% CI 62 - 70%) by 12 months, and 85% (95% CI 82 - 88%) by 6 years, with a significant difference between the low- and intermediate-risk patients, and the high-risk ones. The median time to MMR was 7 months in low- and intermediate-risk patients, significantly shorter than in high-risk ones, where the median time to MMR was 12 months ($p < 0.001$). The cumulative incidence of $MR^{4.0}$ was 25% (95% CI 22 - 29%) by 24 months, and 61% (95% CI 57 - 65%) by 6 years. For $MR^{4.0}$, the Sokal score was not

significant by 24 months, but it became significant by 6 years. The median time to $MR^{4.0}$ was not yet reached in high-risk patients, while it was 42 months in low- and intermediate-risk patients (p = 0.024). The cumulative incidence of CCyR was 79% (95% CI 76 - 83%) by 12 months, and of 88% (95% CI 86 - 91%) by 6 years; the incidence of CCyR was higher in low- and intermediate-risk patients than in high-risk ones. The median time to CCyR was 6 months in low and intermediate Sokal score patients, but 12 months in high risk ones (p = 0.013) (Table 2).

OUTCOME BY RESPONSE AT MILESTONES

Overall survival (OS) and leukemia-related survival (LRS) according to response at milestones are shown in Table 3 and in Figure 3 and 4. The prognostic impact of an early reduction of BCR-ABL1 transcript levels on OS was significant for both the EMR at 3 months (p = 0.015) and at 6 months (p < 0.001). The achievement of a MMR at 12 months was significantly related with both higher OS (94% vs 84%, p < 0.001) and higher LRS (99% vs 89%, p < 0.001). Interestingly, the achievement of a $MR^{4.0}$ at 24 months was slightly significant for LRS (100% vs 95%, P = 0.025). The achievement of a CCyR at 12 months was significantly associated with both better OS (93% vs 79%, P < 0.001) and better LRS (98% vs 83%, P < 0.001).

SECOND-LINE TREATMENT

With a minimum follow-up of 66 months, 366 of the 559 enrolled patients (65%) were still on imatinib. Ninety-eight patients (18%) discontinued imatinib due to treatment failure, including progression to AP or BP, 24 patients (4%) for toxicity, 30 patients (5%) died while on imatinib treatment, 29 patients (5%) for other or non-identified reasons, and 12 patients (2%) because of treatment-free remission. Overall, 151 patients (27%) received at least another treatment after imatinib (Table 4): nilotinib or dasatinib in 82/151 patients (54%), two or more second-generation TKIs in 12 patients (8%), interferon in 2 patients (1%), allogeneic stem cell transplantation in 14 patients (9%), and conventional chemotherapy, including hydroxyurea, in 18 patients (12%). The second line treatment was unknown in 23/151 patients (15%).

CAUSES OF DEATH

The number and the causes of death are shown in Table 5. Deaths were classified as leukemia-related when they occurred after progression to AP or BP, and “leukemia-unrelated” when the patient was in cytogenetic and/or molecular remission and the causes of death was identified. Overall, 33 deaths (51% of deaths, 6% of all patients) were classified “leukemia unrelated”, and 32 deaths (49% of deaths, 6% of all patients) were classified “leukemia-related”. The main causes of

“leukemia-unrelated” deaths were other tumors (17/65 deaths, or 26%) that caused the death in remission of 3% of all patients. Overall, other tumors were recorded in other 18 patients, leading the total number of other tumors to 35 (6% of all patients) (Supplemental Table 3). Other tumors occurred rarely in patients less than 60 years old (3 cases out of 179 patients, 2%), while they were more frequent in patients more than 60 years old (32 cases out of 380 patients, 8%).

DISCUSSION

This is the final, comprehensive, report of an intention-to-treat analysis of three consecutive, prospective, national, multicentric, investigator-initiated studies, designed 10 years ago and enrolling 559 newly diagnosed chronic phase Ph+ and/or BCR-ABL1+ adult CML patients. These data provide a solid information on the response and the outcome of imatinib-treated CML patients outside the setting of company-sponsored and academic studies designed to investigate differences in treatment. Similar studies were reported from other sources, but with less patients or shorter follow-up (4,12,17-19,21-24).

To summarize, the rates of EMR at 3 and 6 months were 82% and 76% respectively. The median time to CCyR, to MMR, and to $MR^{4.0}$ were 6, 8, and 42 months. The cumulative incidence of CCyR and MMR were 79% and 66% by 12 months, and 88% and 85% by 6 years. The cumulative incidence of a deep MR ($MR^{4.0}$) was 25% by 2 years and 61% by 6 years. The 6-year estimated EFS, PFS, and OS probabilities were 58%, 87%, and 89%; the 6-year LRS was 94%, corresponding to a yearly leukemia-related death rate of about 1%. All the responses and the outcomes were significantly influenced by the risk score at diagnosis (low and intermediate versus high), with the exception of the achievement of EMR at 3 months and the $MR^{4.0}$ by 24 months.

Although these data are robust, because of the large number of patients, the extended duration of the observation, the small number of patients lost to follow-up, and the multicentric characters of the study, involving more than fifty hospitals nationwide, it is acknowledged that also these data cannot represent completely and faithfully the real life and the everyday clinical practice, where the age of the patients is higher (47), and where several patients are not cared by specialists or have not a regular access to treatment and monitoring facilities (48).

All patients were treated with imatinib first-line, but the observed results could not be attributed to imatinib alone, since imatinib was followed by second-generation TKIs in 17% of patients. The contribution of second generation TKIs on the long term outcome can be appreciated, comparing the estimated 6-year EFS, that was calculated from treatment start to the failure or the discontinuation of imatinib for any cause (except treatment-free remission), with the estimated 6-year OS: 58% versus 89%.

Overall survival is the most important and the more precise estimate of treatment outcome, but when treatment is very successful it becomes necessary to analyse separately the causes of death. It is difficult to identify in all patients the response status at death and the causes of death, whether they are leukemia-related or unrelated, and it is acknowledged that any death could be attributed to leukemia and/or to the treatment, at least theoretically. With these limitations, it is plausible to

conclude that about 50% of patients died in remission. This finding has implications on the evaluation of the treatment efficacy and on the clinical care of CML patients, strongly suggesting that treatment optimization is not only based on progress in drug research, and that monitoring the health state of the patients may be as important as monitoring the molecular response.

There are many studies reporting on the results of treatment with imatinib (1-34). In some of these studies, the prognosis was evaluated mainly using the Sokal score, more rarely using the EURO (7,22,43) or the EUTOS (21,22,44) scores. A relationship between the Sokal score and the CCyR rates, mainly by 12 months, was first shown in the IRIS study (2) and in a GIMEMA study (49), and subsequently confirmed in at least other four studies (6,8,12,23). A relationship between the Sokal score and the MMR, mainly by 12 months, has been reported in at least four studies (2,6,8,23), but was not confirmed in at least two other studies (5,11). A relationship between the Sokal score and EMR was reported in at least one study, where it was not significant (30). A relationship between the Sokal risk and the OS and/or PFS was reported in at least three studies (3,18,22), but it was not significant in other two studies reporting on a small number of high-risk patients (19,23).

The GIMEMA data presented in this report confirm and strongly support the prognostic value of the Sokal score system in patients treated frontline with imatinib, showing that responses and outcomes are always better in low-risk patients than in high-risk ones: the cumulative incidence by 6 years of CCyR was 92% vs 75%, of MMR 90% vs 69%, of deep MR ($MR^{4.0}$ or better) 68% vs 44%; the estimated 6-year EFS was 66% vs 44%, PFS 93% vs 82%, OS 94% vs 83%, and LRS 97% vs 88%. The intermediate Sokal risk patients had response rates and outcomes similar to the low-risk ones. We suggest that it is time to conclude that the high Sokal risk patients need specific treatment policies, different from the treatment policies that were so effective in low- and intermediate-risk patients. Which may be the best treatment for high-risk patients is a matter of investigation. It has been reported that in high-risk patients a high imatinib dose is not more efficacious than the standard dose (5,14). The first-line treatment with second generation TKIs is worth testing, although even with second generation TKIs the risk is likely to maintain a prognostic value (6,7).

With some differences, the prognostic value of baseline disease-risk can also be shown for the EURO and EUTOS scores (Supplemental Tables 1 and 2). The calculation of Sokal and EURO scores includes age, not included in EUTOS formulation, because the EUTOS score was based on the 18-month CCyR rate of imatinib-treated patients, and the response to imatinib is only marginally influenced by the old age. The EURO and the EUTOS score segregate much less high-risk patients than the Sokal score: the consequence is that many high Sokal risk patients respond and have no events, but several low and intermediate EURO and EUTOS risk patients do not

respond and have events. This study was not designed and powered to compare the three risk scores. We have focused on Sokal because so far EURO and EUTOS scores were analysed and validated in few studies. It is puzzling, and somewhat disturbing, that in the era of molecular hematology and targeted therapy we still rely on a risk scoring system that was proposed 30 years ago, in the era of conventional chemotherapy, based on few simple clinical and hematologic data. Also EURO and EUTOS are based on simple clinical and hematologic data. In spite of progress in knowledge of the molecular basis of leukemia, the time to replace these systems has not yet come.

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AUTHORSHIP CONTRIBUTIONS

F.C., M. Baccarani and G. Rosti analysed the data and wrote the first draft of the manuscript. All the other authors contributed to the design of the study, to the collection of the data, and to the final report.

DISCLOSURE OF CONFLICTS OF INTERESTS

F.C. has acted as a consultant for Novartis, Bristol-Myers Squibb and Pfizer and received honoraria from Novartis and Bristol-Myers Squibb; G.G. has acted as a consultant and received honoraria from Novartis and Bristol-Myers Squibb; M. Breccia has acted as a consultant for Bristol-Myers Squibb and Novartis; E.A. has acted as a consultant for Novartis and Bristol-Myers Squibb; G.M. served on the speakers' bureaus of Novartis, Bristol-Myers Squibb, and Pfizer; F.P. received research support from Novartis, served as advisor for Novartis, Bristol-Myers Squibb, and ARIAD Pharmaceuticals, and received lecture fees from Novartis and Bristol-Myers Squibb; G.S. has acted as a consultant for and received honoraria from Bristol-Myers Squibb, Novartis, ARIAD Pharmaceuticals, and Celgene; M. Baccarani received honoraria from Novartis, Bristol-Myers Squibb, Pfizer, and ARIAD Pharmaceuticals and served on the speakers' bureaus of Novartis and Bristol Myers-Squibb; G.R. has acted as a consultant for Novartis, Bristol-Myers Squibb, and ARIAD Pharmaceuticals and served on the speakers' bureaus of Novartis, Bristol-Myers Squibb, and Roche; the remaining Authors had not relevant conflicts of interest to disclose.

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TABLES

Table 1. Patient characteristics at diagnosis.

Patients, N	**559**
Age, years; median (range)	52 (18 - 84)
Age > 70 years, N (%)	66 (12)
Gender Male, N (%)	336 (60)
ECOG $\geq$ 1, N (%)	118 (21)
Hb level, g/dL; median (range)	12.2 (6.4 - 17.5)
PLT count, $10^3/\mu L$; median (range)	352 (100 - 4920)
WBC count, $10^3/\mu L$; median (range)	54.8 (1.2 – 500.0)
Peripheral blasts, %; median (range)	1.0 (0 – 9.5)
Eosinophils, %; median (range)	2.0 (0 – 15.0)
Basophils, %; median (range)	2.0 (0 – 19.0)
Spleen, cm; median (range)	1 (0 - 24)
Palpable spleen, N (%)	324 (58)
Sokal score, N (%): • Low • Intermediate • High	 219 (39) 216 (39) 124 (22)
Hasford score, N (%): • Low • Intermediate • High	 243 (43) 277 (50) 39 (7)
EUTOS score, N (%): • Low • High	 519 (93) 40 (7)
CCA/Ph+ present, N (%)	21 (4)
Variant translocations present, N (%)	30 (5)
Derivative 9 deletions present, N (%)	60 (11)
BCR-ABL1 transcript type, N (%): • e13a2 • e14a2 • e13a2/e14a2 • other transcripts	 203 (36) 290 (52) 60 (11) 6 (1)
Imatinib dose, N (%): • 400 mg • 800 mg	 423 (76) 136 (24)

Legend:
ECOG: performance status according to the Eastern Co-operative Oncology Group grading; Hb: hemoglobin; PLT: platelet; WBC: white blood cells; EUTOS: European Treatment and Outcome Study; CCA/Ph+ : clonal chromosome abnormalities in Ph-positive cells.

Table 2. Response and outcome by Sokal score.

	All patients	Sokal score			p
		Low	Intermediate	High	
Early molecular response					
< 10% at 3 months, %	82	83	79	84	0.488
< 1% at 6 months, %	76	77	80	67	0.021
Major molecular response ($MR^{3.0}$)					
Median time to $MR^{3.0}$, months	8	7	7	12	< 0.001
$MR^{3.0}$ by 12 months, %	66	72	68	52	0.001
$MR^{3.0}$ by 6 years, %	85	90	89	69	< 0.001
Deep molecular response ($MR^{4.0}$)					
Median time to $MR^{4.0}$, months	42	42	42	NR	0.024
$MR^{4.0}$ by 24 months, %	25	25	25	25	0.913
$MR^{4.0}$ by 6 years, %	61	68	63	44	<0.001
Complete cytogenetic response (CCyR)					
Median time to CCyR, months	6	6	6	12	0.013
CCyR by 12 months, %	79	83	81	69	0.006
CCyR by 6 years, %	88	92	91	75	< 0.001
Outcome					
Event-free survival (6y), %	58	66	59	44	< 0.001
Progression-free survival (6y), %	87	93	84	82	0.003
Overall survival (6y), %	89	94	87	83	0.002
Leukemia-related survival (6y), %	94	97	95	88	0.002
Patients, N (%)	559	219 (39)	216 (39)	124 (22)	-

Legend:
$MR^{3.0}$: BCR-ABL1^{IS} ratio ≤ 0.1%; $MR^{4.0}$, BCR-ABL1^{IS} ratio ≤ 0.01% or undetectable disease with ≥10,000 ABL1 transcripts; CCyR: absence of Philadelphia-positive metaphases over at least 20 metaphases analyzed by conventional banding analysis; 6y: 6-year outcome; NR: not yet reached.

Table 3. Overall survival and leukemia-related survival by response at milestones.

	Responders	Overall survival			Leukemia-related survival		
	N (%)	Yes	No	P	Yes	No	P
Early molecular response (3 months)	456 (82%)	90% (87-93%)	82% (74-89%)	0.015	95% (93-97%)	90% (82-94%)	0.014
Early molecular response (6 months)	425 (76%)	92% (89-94%)	81% (73-86%)	< 0.001	97% (95-99%)	86% (78-91%)	< 0.001
Major molecular response (12 months)	330 (59%)	94% (91-96%)	84% (78-88%)	< 0.001	99% (97-100%)	89% (84-93%)	< 0.001
Deep molecular response (24 months)	100 (18%)	95% (88-98%)	91% (88-94%)	0.344	100% -	95% (93-97%)	0.025
Complete cytogenetic response (12 months)	434 (78%)	93% (90-95%)	79% (70-86%)	< 0.001	98% (96-99%)	83% (75-89%)	< 0.001

Legend:
The 6-year overall survival and the 6-year leukemia-related survival probabilities with the 95% confidence interval, according to the presence or absence of response at milestones, are presented.
Early molecular response (3m): BCR-ABL1 ratio < 10% IS at 3 months; Early molecular response (6m): BCR-ABL1 ratio < 1% IS at 6 months; Major molecular response (12m): BCR-ABL1 ratio < 0.10% IS at 12 months; Deep molecular response (24m): BCR-ABL1 ratio < 0.01% IS or undetectable disease with ≥10,000 ABL1 transcripts at 24 months; Complete cytogenetic response (12m): absence of Philadelphia-positive metaphases over at least 20 metaphases by conventional banding analysis or < 1% BCR-ABL1–positive nuclei over at least 200 nuclei by fluorescence in situ hybridization analysis at 12 months.

Table 4. Reasons of treatment change and subsequent treatment

Patients with treatment change, N	151
Reason of treatment change, N (%)	
• Failure	98 (65)
• Toxicity	24 (16)
• Other (refusal, consent withdrawal, unknown reason)	29 (19)
Subsequent treatment, N (%)	
• Nilotinib or dasatinib	82 (54)
• Two or more 2nd and/or 3rd generation TKIs	12 (8)
• Interferon	2 (1)
• Allogeneic Stem Cell Transplantation (with or without TKIs)	14 (9)
• Conventional chemotherapy	18 (12)
• Unknown	23 (15)

Legend:
TKIs: tyrosine kinase inhibitors.
Twelve additional patients with a stable deep molecular response discontinued imatinib and achieved a treatment-free remission.

Table 5. Causes of death

Total number of deaths, N	65
Leukemia-related deaths, N (%)	32 (49)
Leukemia-unrelated deaths, N (%)	33 (51)
• Other tumors	17 (26)
• Infections*	5 (8)
• Cardiovascular events**	6 (9)
• Hemorrhage***	2 (3)
• Respiratory insufficiency^	2 (3)
• Starvation^{+}	1 (2)

Legend:
*Infections: 3 soft-tissue infections (1 skin, 1 perineum, 1 iliac fossa) and 2 lung infections (pre-existing chronic obstructive pulmonary disease in both patients);
**Cardiovascular events: 3 ischemic heart disease (pre-existing risk factors or pre-existing clinical condition in all patients), 1 heart failure (unspecified), 1 dilated cardiomyopaty with subsequent heart transplantation and 1 pulmonary embolism after orthopedic surgery;
***Hemorrhage: 1 cerebral hemorrhage while on anti-coagulant therapy; 1 gastric hemorrhage;
^Respiratory insufficiency: 1 chronic obstructive pulmonary disease, 1 chronic pleuritis
$^{+}$Senile dementia and progressive starvation

FIGURES

Figure 1. Outcome of all the 559 enrolled patients.

A) Event-free survival (EFS): the estimated 6-year EFS was 58% (95% CI, 54-62%), B) Progression-free survival (PFS): the 6-year estimated PFS was 87% (95% CI, 84-89%), C) Overall survival (OS): the 6-year estimated OS was 89% (95% CI, 86-91%), D) Leukemia-related survival (LRS): the 6-year estimated LRS was 94% (95% CI, 92-96%)

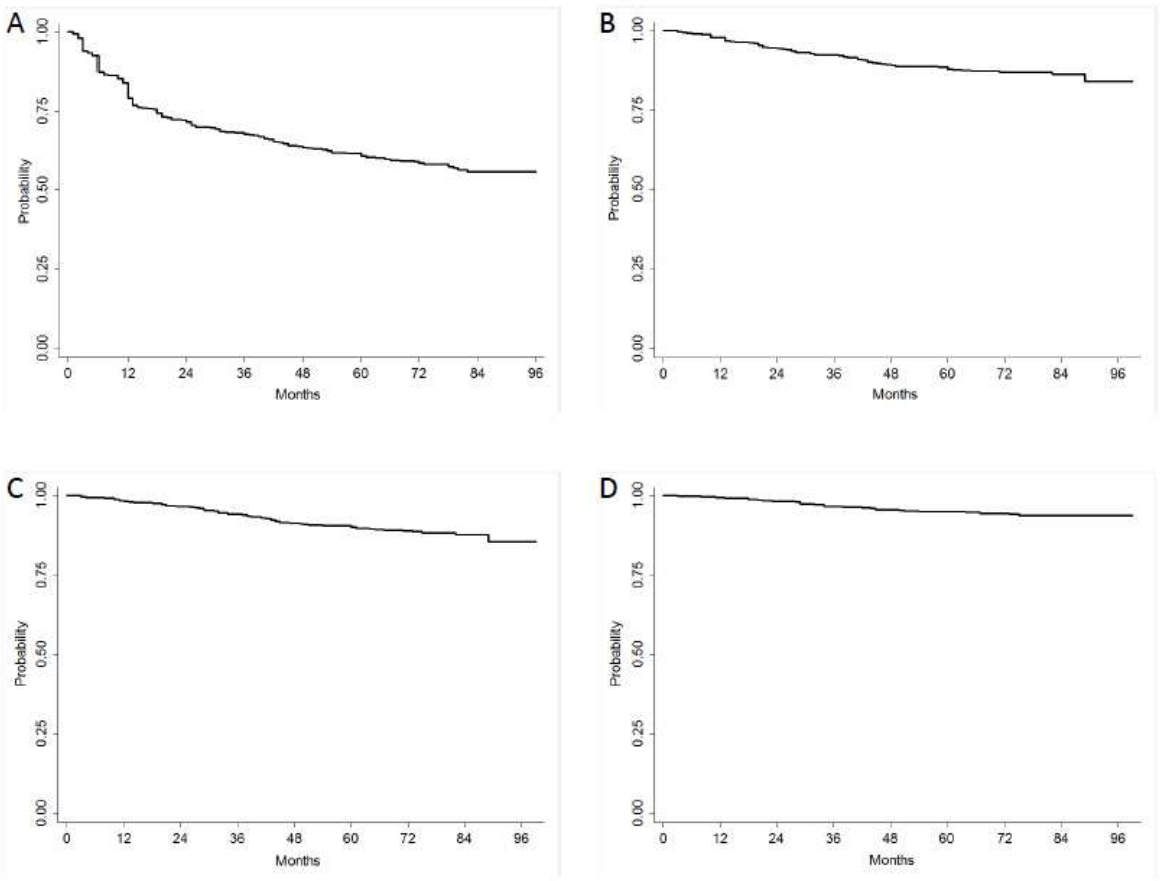


Figure 2. Outcome by Sokal score.

A) Event-free survival (EFS): the estimated 6-year EFS was 66% (95% CI, 60-72%) in low-risk patients, 59% (95% CI, 52-65%) in intermediate-risk patients, and 44% (95% CI, 35-52%) in high-risk patients ($p < 0.001$); B) Progression-free survival (PFS): the 6-year estimated PFS was 93% (95% CI, 88-95%) in low-risk patients, 84% (95% CI, 78-88%) in intermediate-risk patients, and 82% (95% CI, 73-88%) in high-risk patients ($p = 0.003$); C) Overall survival (OS): the 6-year estimated OS was 94% (95% CI, 90-96%) in low-risk patients, 87% (95% CI, 82-91%) in intermediate-risk patients, and 83% (95% CI, 75-89%) in high-risk patients ($p = 0.002$); D) Leukemia-related survival (LRS): the 6-year estimated LRS was 97% (95% CI, 94-99%) in low-risk patients, 95% (95% CI, 91-97%) in intermediate-risk patients, and 88% (95% CI, 80-93%) in high-risk patients ($p = 0.002$).

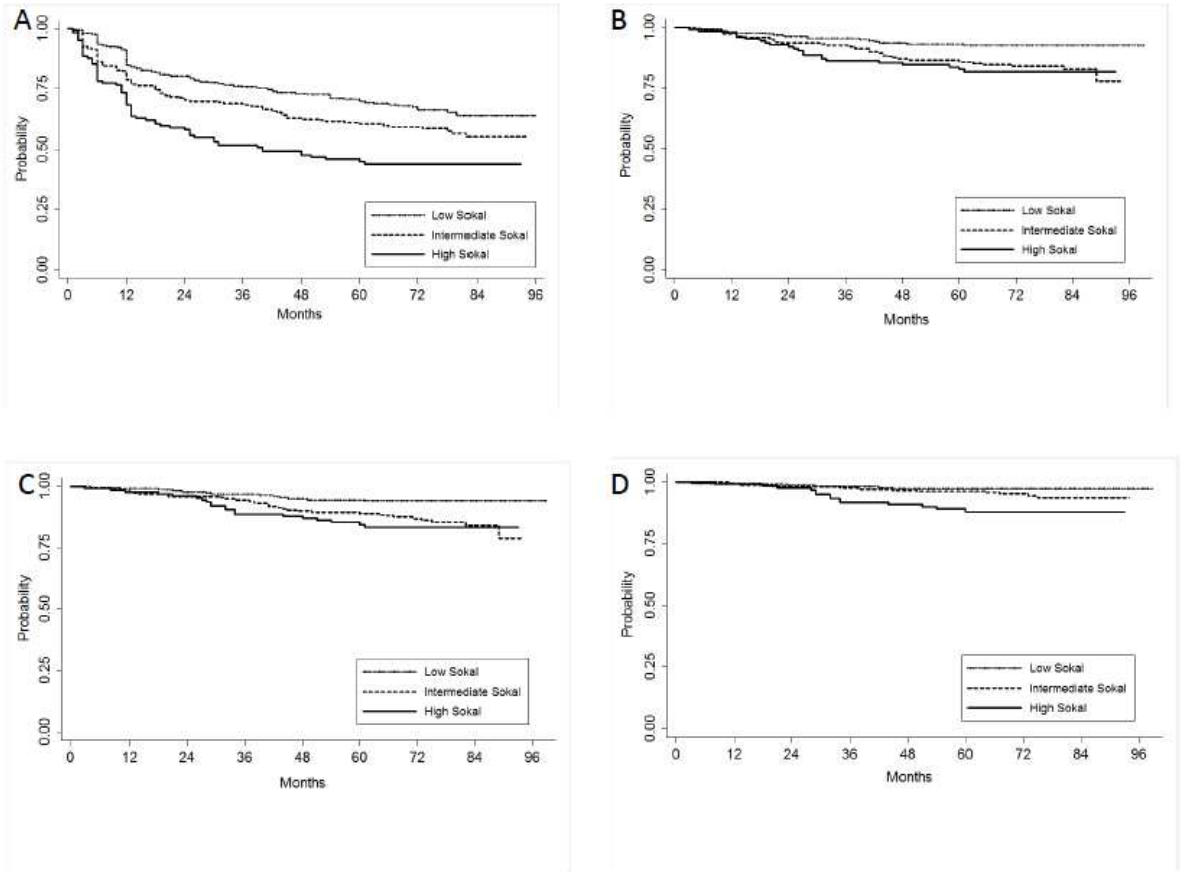


Figure 3. Overall survival by response at milestones.

A) Overall survival (OS) according to the presence or absence of a early molecular response, defined as a BCR-ABL1 ratio < 10% IS, at 3 months (EMR 3): the estimated 6-year OS was 90% (95% CI, 87-93%) in patients with a EMR 3, and 82% (95% CI, 74-89%) in patients without a EMR 3 (p = 0.015); B) OS according to the presence or absence of a early molecular response, defined as a BCR-ABL1 ratio < 1% IS, at 6 months (EMR 6): the estimated 6-year OS was 92% (95% CI, 89-94%) in patients with a EMR 6, and 81% (95% CI, 73-86%) in patients without a EMR 6 (p < 0.001); C) OS according to the presence or absence of a major molecular response at 12 months (MMR 12): the estimated 6-year OS was 94% (95% CI, 91-96%) in patients with a MMR 12, and 84% (95% CI, 78-88%) in patients without a MMR 12 (p < 0.001); D) OS according to the presence or absence of a complete cytogenetic response at 12 months (CCyR 12): the estimated 6-year OS was 93% (95% CI, 90-95%) in patients with a CCyR 12, and 79% (95% CI, 70-86%) in patients without a CCyR 12 (p < 0.001).

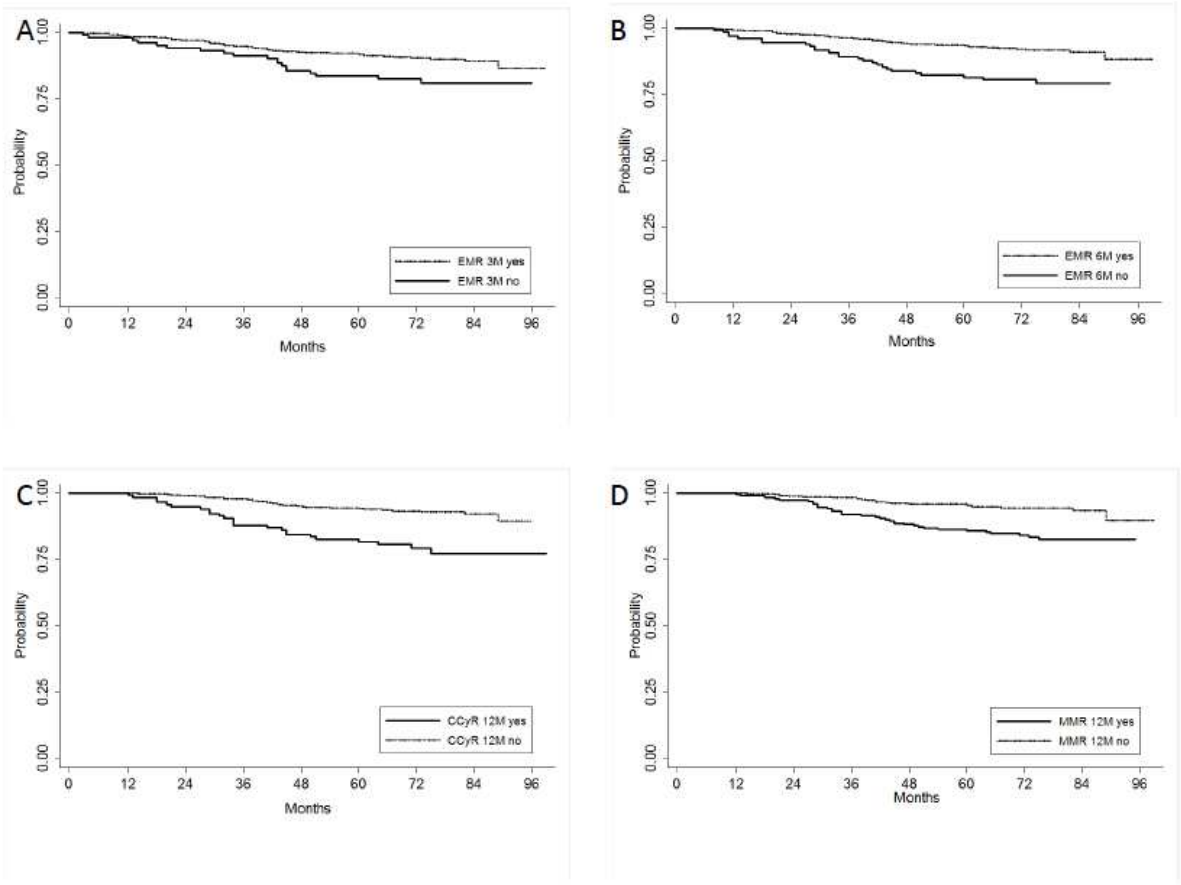
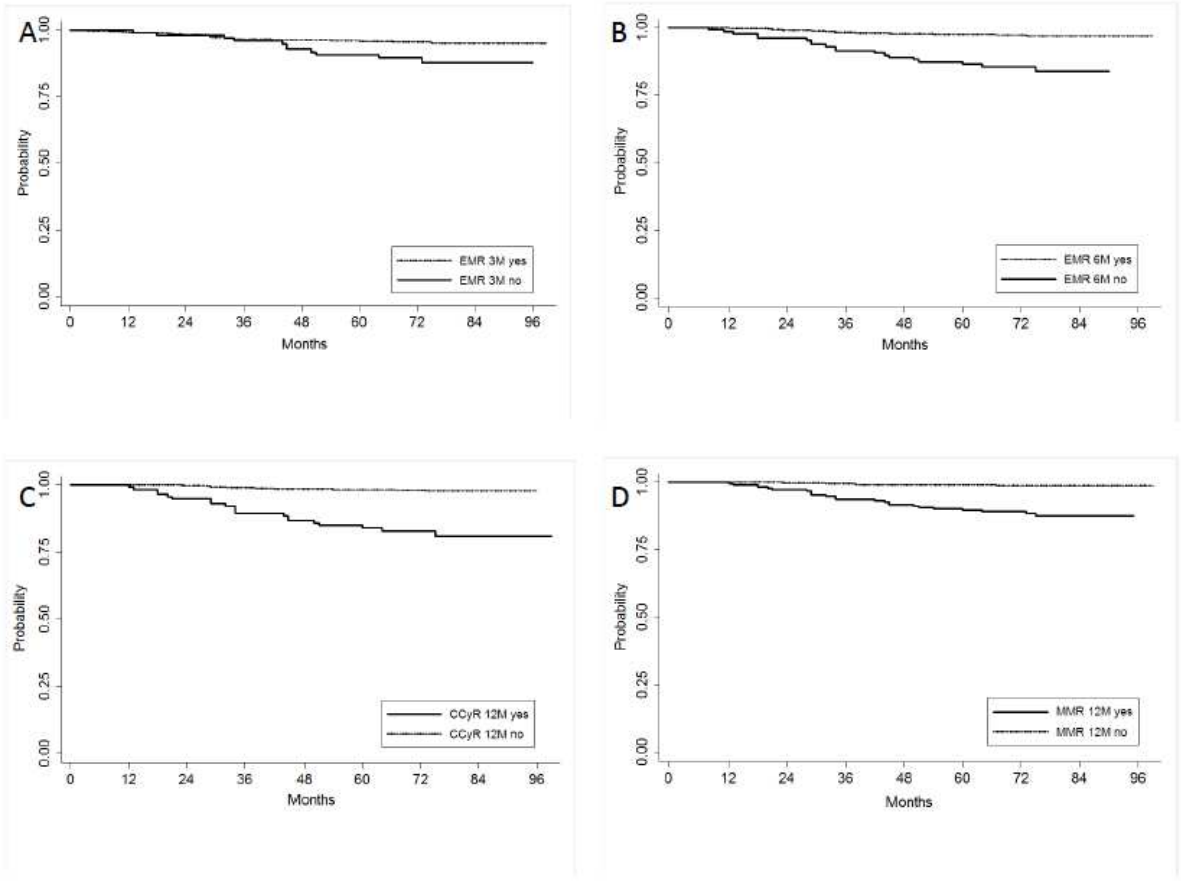


Figure 4. Leukemia-related survival by response at milestones.

A) Leukemia-related survival (LRS) according to the presence or absence of a early molecular response, defined as a BCR-ABL1 ratio < 10% IS, at 3 months (EMR 3): the estimated 6-year LRS was 95% (95% CI, 93-97%) in patients with a EMR 3, and 90% (95% CI, 82-94%) in patients without a EMR 3 (p = 0.014); B) LRS according to the presence or absence of a early molecular response, defined as a BCR-ABL1 ratio < 1% IS, at 6 months (EMR 6): the estimated 6-year LRS was 97% (95% CI, 95-99%) in patients with a EMR 6, and 86% (95% CI, 78-91%) in patients without a EMR 6 (p < 0.001); C) LRS according to the presence or absence of a major molecular response at 12 months (MMR 12): the estimated 6-year LRS was 99% (95% CI, 97-100%) in patients with a MMR 12, and 89% (95% CI, 84-93%) in patients without a MMR 12 (p < 0.001); D) LRS according to the presence or absence of a complete cytogenetic response at 12 months (CCyR 12): the estimated 6-year LRS was 98% (95% CI, 96-99%) in patients with a CCyR 12, and 83% (95% CI, 75-89%) in patients without a CCyR 12 (p < 0.001).



SUPPLEMENTAL DATA

Table 1s. Response and outcome by Euro score.

	All patients	Euro score			p
		Low	Intermediate	High	
Early molecular response					
< 10% at 3 months, %	82	83	81	79	0.812
< 1% at 6 months, %	76	79	75	62	0.046
Major molecular response ($MR^{3.0}$)					
Median time to $MR^{3.0}$, months	8	6	8	20	0.002
$MR^{3.0}$ by 12 months, %	66	70	67	41	0.002
$MR^{3.0}$ by 6 years, %	85	89	84	62	< 0.001
Deep molecular response ($MR^{4.0}$)					
Median time to $MR^{4.0}$, months	42	42	42	NR	0.274
$MR^{4.0}$ by 24 months, %	25	24	26	25	0.490
$MR^{4.0}$ by 6 years, %	61	65	61	41	0.019
Complete cytogenetic response (CCyR)					
Median time to CCyR, months	6	6	6	12	0.004
CCyR by 12 months, %	79	83	78	59	0.002
CCyR by 6 years, %	88	93	87	64	< 0.001
Outcome					
Event-free survival (6y), %	58	67	53	48	0.002
Progression-free survival (6y), %	87	92	84	76	0.005
Overall survival (6y), %	89	93	86	78	0.003
Leukemia-related survival (6y), %	94	96	95	80	< 0.001
Patients, N (%)	559	243 (43)	277 (50)	39 (7)	-

Legend:
$MR^{3.0}$: BCR-ABL1^{IS} ratio ≤ 0.1%; $MR^{4.0}$, BCR-ABL1^{IS} ratio ≤ 0.01% or undetectable disease with ≥10,000 ABL1 transcripts; CCyR: absence of Philadelphia-positive metaphases over at least 20 metaphases analyzed by conventional banding analysis; 6y: 6-year outcome; NR: not yet reached.

Table 2s. Response and outcome by EUTOS score.

	All patients	EUTOS score		p
		Low	High	
Early molecular response				
< 10% at 3 months, %	82	82	75	0.266
< 1% at 6 months, %	76	77	60	0.014
Major molecular response ($MR^{3.0}$)				
Median time to $MR^{3.0}$, months	8	7	13	0.012
$MR^{3.0}$ by 12 months, %	66	68	48	0.010
$MR^{3.0}$ by 6 years, %	85	86	70	0.007
Deep molecular response ($MR^{4.0}$)				
Median time to $MR^{4.0}$, months	42	42	61	0.119
$MR^{4.0}$ by 24 months, %	25	25	25	0.962
$MR^{4.0}$ by 6 years, %	61	62	45	0.031
Complete cytogenetic response (CCyR)				
Median time to CCyR, months	6	6	12	0.009
CCyR by 12 months, %	79	80	63	0.009
CCyR by 6 years, %	88	89	75	0.010
Outcome				
Event-free survival (6y), %	58	60	45	0.017
Progression-free survival (6y), %	87	88	79	0.132
Overall survival (6y), %	89	89	81	0.160
Leukemia-related survival (6y), %	94	95	85	0.039
Patients, N (%)	559	519 (93)	40 (7)	-

Legend:
$MR^{3.0}$: $BCR\text{-}ABL1^{IS}$ ratio ≤ 0.1%; $MR^{4.0}$, $BCR\text{-}ABL1^{IS}$ ratio ≤ 0.01% or undetectable disease with ≥10,000 ABL1 transcripts; CCyR: absence of Philadelphia-positive metaphases over at least 20 metaphases analyzed by conventional banding analysis; 6y: 6-year outcome.

Table 3s. Second malignancies diagnosed during or after imatinib treatment.

Malignancy	Patients, N	Deaths, N
Colon	4	4
Breast	3	0
Prostate	3	0
Bladder	2	1
Central nervous system	2	2
Liver	2	1
Pancreas	2	2
Thyroid	2	0
Non-Hodgkin Lymphoma	2	1
Multiple myeloma	1	0
Bowel	1	0
Choledocus	1	1
Esophagus	1	1
Stomach	1	0
Rectum	1	0
Endometrium	1	0
Ovary	1	0
Testis	1	0
Kidney	1	1
Urethra	1	1
Lung	1	1
Soft tissues	1	1
Total	35	17

Figure 1s. Outcome by EURO score.

A) Event-free survival (EFS): the estimated 6-year EFS was 67% (95% CI, 60-72%) in low-risk patients, 53% (95% CI, 47-58%) in intermediate-risk patients, and 48% (95% CI, 32-63%) in high-risk patients (p = 0.002); B) Progression-free survival (PFS): the 6-year estimated PFS was 92% (95% CI, 88-95%) in low-risk patients, 84% (95% CI, 79-88%) in intermediate-risk patients, and 76% (95% CI, 59-87%) in high-risk patients (p = 0.005); C) Overall survival (OS): the 6-year estimated OS was 93% (95% CI, 89-96%) in low-risk patients, 86% (95% CI, 82-90%) in intermediate-risk patients, and 78% (95% CI, 61-89%) in high-risk patients (p = 0.003); D) Leukemia-related survival (LRS): the 6-year estimated LRS was 96% (95% CI, 93-98%) in low-risk patients, 95% (95% CI, 91-97%) in intermediate-risk patients, and 80% (95% CI, 63-90%) in high-risk patients (p < 0.001).

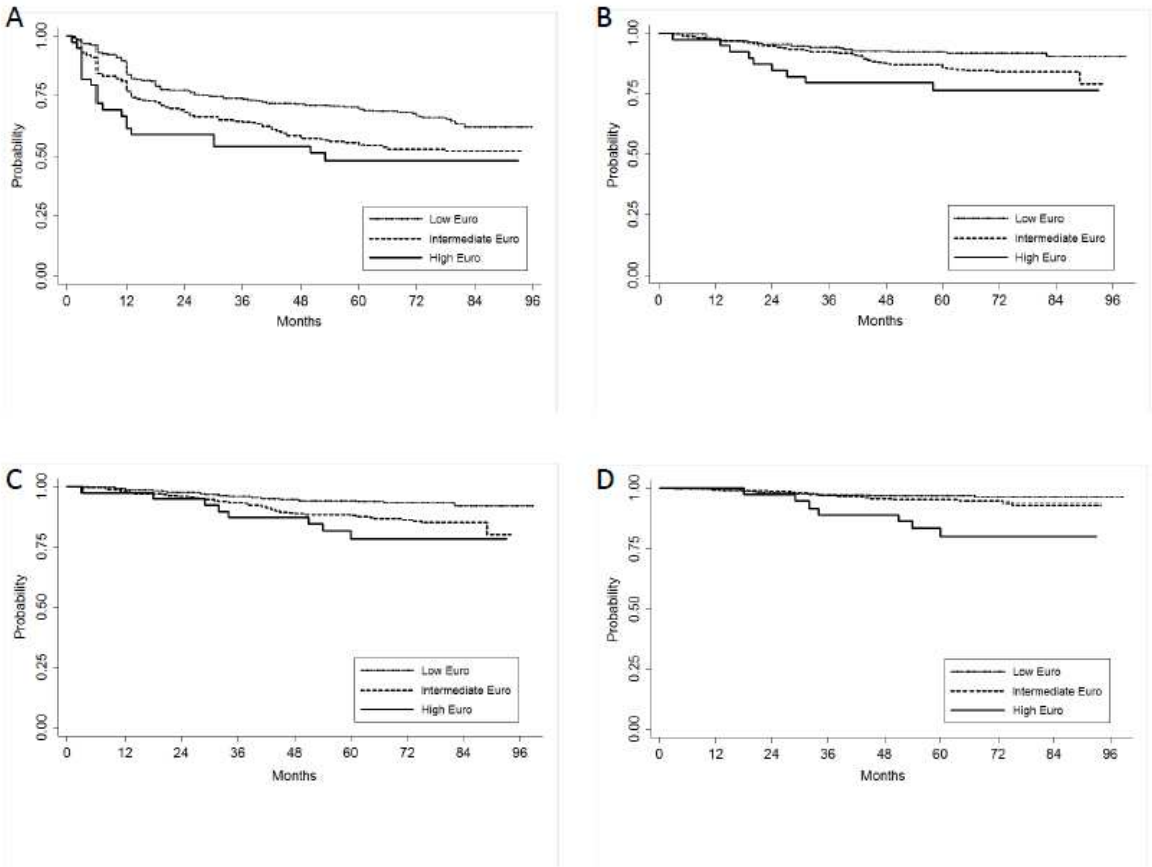
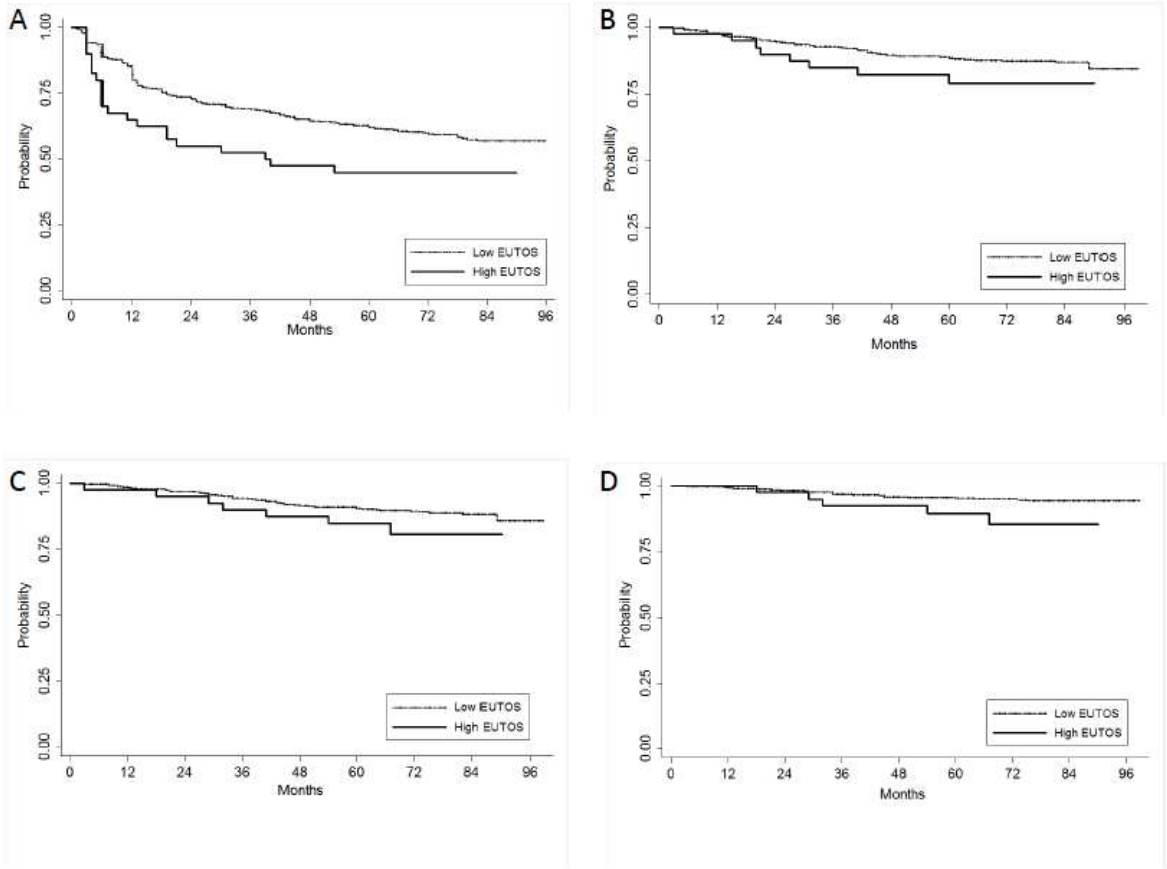


Figure 2s. Outcome by EUTOS score.

A) Event-free survival (EFS): the estimated 6-year EFS was 60% (95% CI, 55-64%) in low-risk patients, and 45% (95% CI, 29-59%) in high-risk patients (0.017); B) Progression-free survival (PFS): the 6-year estimated PFS was 88% (95% CI, 84-90%) in low-risk patients, and 79% (95% CI, 63-89%) in high-risk patients (p = 0.132); C) Overall survival (OS): the 6-year estimated OS was 89% (95% CI, 86-92%) in low-risk patients, and 81% (95% CI, 63-90%) in high-risk patients (p = 0.160); D) Leukemia-related survival (LRS): the 6-year estimated LRS was 95% (95% CI, 93-97%) in low-risk patients, and 85% (95% CI, 67-94%) in high-risk patients (p = 0.039).



Appendix

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