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Children with chronic phase chronic myeloid leukemia: characteristics and outcomes from the International Registry of Childhood CML

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FM contributed to the database and wrote the manuscript. FM and MS contributed to the literature search, study design, data analysis, data interpretation, and writing. FM, MM, KK, AMG, BDM, ML, AM, PS, JY, MA, MD, BL, MB, CKL, AK, GJ, RF, AB and MS contributed to data collection, to critical revision of the article, and read and approved the final version. JDK and LD performed statistical analyses.

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Conflict of interest statement

All authors declare no competing financial interest

Data-sharing statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

Abstract

Five hundred and thirty-five patients (median age 12.2 years, range: 8 months - 18 years; N=303 males, N=232 females) diagnosed with chronic myeloid leukaemia (CML) in chronic phase were registered in the International Registry of Childhood CML (www.clinicaltrials.gov NCT01281735). Clinical signs of leukostasis or bleeding were observed in 16.5% and 20% of the patients, respectively. The spleen was palpable in 76% of patients with a median of 9 cm (range, 1 to 32) below the costal margin. The median leukocyte count was 222 G/L (quartile 95-353). First-line therapy consisted of imatinib in 482 children. Among them, 40% remained on imatinib with a median follow-up 3.8 years (95% CI: 3.2-4.3 years); 3.1% died and 3.9% progressed to advanced phase disease. The overall survival rate at 36 months was 97.4% (95% CI: 95-99%). Progression free survival rate at 3-years was 97.1% (95% CI: 94.9-99.2%), 91.7% (95% CI:84.5-98.3%) and 72.0% (95% CI: 59-87.9%) in the Eutos Long Term Survival (ELTS) low, intermediate-, and high-risk group, respectively (p log rank<0.001). Pediatric CML is characterized by bulky disease (large splenomegaly, high leucocyte counts) and the ELTS score can identify children with the poorest outcome.

INTRODUCTION

Chronic myeloid leukemia (CML) is an acquired clonal myeloproliferative malignancy characterized by the chromosomal translocation t(9;22)(q34.1;q11.2) resulting from the synthesis of the BCR::ABL1 oncoprotein. Pediatric CML (pCML) is a very rare disease. Clinical and biological characteristics at diagnosis of the disease have been reported in small cohorts of children and adolescents and very few studies have reported on management and outcome. [1-3] The International Registry of Childhood CML (I-CML-Ped Study; www.clinicaltrials.gov NCT01281735) was designed with the aim to better describe the characteristics and outcome of children with CML in the tyrosine kinase inhibitors (TKI) era. In the present work we retrospectively analyzed children and adolescents with CML in chronic phase (CML-CP) registered in this International Registry which to the best of our knowledge represents the largest pCML cohort.

METHODS

We selected patients registered in The International Registry of Childhood Chronic Myeloid Leukemia (I-CML-Ped Study registered at www.clinicaltrials.gov NCT01281735). Since January 2011, this registry has been recruiting prospectively and retrospectively children and adolescents less than 18 years of age at diagnosis of CML diagnosed between January 2000 and September 2020 whatever the phase of the disease. The institutional ethics committee of the University Hospital of Poitiers (Poitiers, France) reviewed and approved the I-CML-Ped Study which is being conducted in accordance with the Declaration of Helsinki. Written informed consent was provided by the children and/or their legal guardians.

The phase of the disease (chronic, accelerated or blastic) was defined according to the criteria of the European LeukemiaNet (ELN) recommendation.[4] Sokal score calculation was performed using the mathematical equation for patients aged less than 45 years.[5] Determination of the European Treatment and Outcome Study (EUTOS) long-term survival (ELTS) score was carried out as previously reported.[6] Karyotypes were interpreted usin G- or Q-banding techniques.[7] Complete cytogenetic response (CCyR) to treatment was defined as no Philadelphia-chromosome positive cells in at least 20 analyzed bone marrow metaphases. *BCR::ABL1* transcript levels in the peripheral blood and bone marrow were determined by local laboratories using quantitative reverse transcriptase-polymerase chain reaction (RT-

qPCR) and expressed according to the International Scale (IS).[8] In the oldest cases, defined conversion factors were used for equivalence to tests according to IS.[9] Responses to treatment were defined according to the European LeukemiaNet (ELN) criteria.[4,10] Major molecular response (MMR) and deep molecular response (DMR) were defined as a ratio of *BCR::ABL1/ABL1* less than 0.1% and less than 0.01% (MR4), respectively.[8] In the context of treatment-free remission (TFR) attempt, molecular relapse was defined as a loss of MMR at any time. Determination of transcript types and BCR::ABL1 kinase domain mutations analysis was performed as previously reported.[11,12]

The follow-up of children was not censored at the time of switching to other treatments including hematopoietic stem cell transplantation (HSCT). Comparisons of clinical and biological characteristics between sexes were performed using a chi-square test or Fisher's exact test for qualitative variables and the Wilcoxon signed-rank test for quantitative variables. Overall survival and progression-free survival (PFS, progression to advanced phase or death) were estimated by the Kaplan-Meier method and comparisons were performed using the log-rank test. The level of statistical significance was set as 0.05.

RESULTS

Baseline characteristics

From January 2011 to March 2021, 576 patients less than 18 years old were recruited from 17 countries and among them, 535 (92.9 %), 19 (3.3%) and 22 (3.8%) presented with CML in CP, in accelerated or in blastic phase, respectively. Baseline characteristics of the 535 patients with CML-CP are listed in Table 1. There was a male preponderance with a sex ratio of 1.31. Median age at diagnosis was 12.2 years (range, 8 months to 18 years).

Among the 535 children with CML-CP, the diagnosis was made incidentally in 80 (16%) children when a blood assessment was performed for medical reasons such as cough, infection, pre-operative assessment or trauma. Five hundred and eight patients (95%) presented with symptoms. Among these, the most common symptoms at presentation were asthenia, weight loss and abdominal pain (Supplementary Figure 1). Thrombosis was observed in a single patient whilst 20% of the children presented with signs of haemorrhage

(multiple haematoma, retinal bleeding with blurred vision, menorrhagia, prolonged bleeding after tooth extraction). Bleeding and signs of haemorrhage were associated with a higher frequency of palpable spleen ($p=0.0007$), higher leukocyte ($p<0.0001$) and platelet ($p=0.02$) counts, and a lower haemoglobin concentration ($p=0.02$). Signs suggestive of leukostasis (priapism, central nervous abnormalities, respiratory difficulties, retinal abnormalities and visual disturbances) were observed in 88 (16%) patients.

At diagnosis, the spleen was palpable in 76% of the patients with a median of 9 cm (range, 1 to 32) below the costal margin. The median leukocyte count was 222 G/L (range, 4.8-1037). There was no statistical difference between boys and girls concerning the frequency of signs of leukostasis, frequency of splenomegaly, spleen size, median of the leucocyte count and haemoglobin concentration (Table 1). However, the median platelet count was significantly higher in girls. Compared to the entire cohort, the 88 patients (16.5%) with signs of leukostasis presented with a larger spleen size ($p<0.02$) (but not with a higher frequency of palpable splenomegaly), a higher leukocyte count ($p<0.0001$) and lower haemoglobin concentration ($p<0.0001$) compared to the other patients whilst the platelet levels were not significantly different. Palpable splenomegaly was statistically associated with higher leukocyte counts ($p<0.0001$) and lower haemoglobin concentration ($p<0.0001$) compared to blood counts of patients without palpable splenomegaly.

The majority (67%) of the children was allocated to the low risk group according to the ELTS score, whereas by contrast the majority (80%) of the children was categorized as intermediate and high risk according to the Sokal system (Table 1). A significant difference was observed regarding the distribution by the Sokal system of boys and girls into the risk categories. The distribution of sexes across the 3 risk categories according to the ELTS scoring system did not significantly differ.

Chromosomal abnormalities in addition to the classical chromosomal translocation t(9;22)(q34.1;q11.2) were found in 28 (5.5%) children among the 513 patients with available karyotypes at diagnosis (Table 1). Typical BCR::ABL1 transcripts e14a2 (b3a2) and combination of e14a2 and e13a2 (b2a2) were predominant in the 379 assessed patients while $P210^{BCR::ABL1}$ protein was expressed in 87 of the remaining patients (Table 1).

Treatment and outcome

Treatment details of the 535 children diagnosed in CP are summarized in Figure 1. In brief, first-line therapy consisted of alpha interferon (IFN) +/- cytosine arabinoside (AraC) in 22 (4%) patients between 2000 and 2005, TKI (92.3%) involving 482 patients who received imatinib between 2001 and 2020 and 9 patients a second-generation TKI between 2012 and 2020 or intravenous chemotherapy (13 patients with signs of leukostasis) between 2000 and 2018, and 9 (1.7%) patients underwent allogeneic HSCT between 2000 and 2002. TKI-treatment was preceded or associated with hydroxycarbamide in 228 (42.8%) patients or anagrelide or 6 mercaptopurine (2 children each) or leukapheresis (6 children). Allogeneic HSCT was performed in 131 (24.5%) children: 9 as first-line treatment, 66 as second-line treatment (60 after treatment with imatinib, 4 children after IFN-AraC and 2 after chemotherapy+hydroxycarbamide) and 56 as 3rd–7th ultimate line of treatment.

Among the 535 patients in CML-CP, 24 (4.5%) deaths (11 CML-related and 13 associated with HSCT) were recorded with a median follow-up of 5.9 years (95% CI: 5.4-6.6). The 5-year progression-free survival and survival rates of the 535 patients in CML-CP were 91.6% (95% CI: 89.1-94.3%) and 94.7% (95% CI: 92.6-96.9%), respectively.

The 482 patients receiving first-line imatinib therapy were considered for analysis of the response to treatment and outcome with a median follow-up for of 5.6 years ([IQR], 5.0-6.0 years). The median initial daily imatinib dose was 280 mg/m^2 (IQR, 249-319 mg/m^2). Grade 3 or 4 haematological toxicity (n=69; 32%) or non-haematological toxicities (n= 75; 35%) were reported in 96 (44.5%) of 216 assessable patients. Neutropenia (n=38; 55%) was the most frequently reported grade 3/4 haematological adverse events whilst musculoskeletal events (n=15; 20%) were the most frequent grade 3/4 non-haematological side effects. Among the 469 children assessable for haematological response, 466 (99.3%) achieved complete haematological remission after a median time of 2 months (95% CI: 1.87 –2.43) after the start of imatinib. CCyR was achieved with a median time of 8.2 months (95% CI: 7.4 –9.0). Cumulative incidence of CCyR at 12 months and at 5 years for 478 patients with available data was 68% (95% CI: 63-72%) and 97% (95% CI: 94-98%), respectively. The ELTS score, available in 406 patients, was not correlated with the cumulative incidence of CCyR. A transcript level less than or equal to 10% at 3 months after the start of imatinib was

recorded in 182 (60%) of the 302 children with an available transcript level at this time point. The rate of MMR achievement at 12 months in children with a transcript level less than or equal to 10% at 3 months was significantly higher compared to that of the 23 children with more than 10% (55% versus 17%, respectively, P<0.0001). MMR was achieved with a median time of 14.5 months [95% CI: 13.1-16.5 months]. Cumulative incidence of MMR at 12 months and 5 years for 474 patients with available data was 40% [95% CI: 35-44%] and 91% [95% CI: 88-94%], respectively (Figure 2). The ELTS score showed no statistical difference in MMR achievement between the patients allocated to the low, intermediate or high-risk groups.

Among the 482 children, 195 (40%) continued receiving imatinib with a median follow up of 3.8 years (95% CI: 3.2-4.3 years) whilst 287 (60%) patients discontinued imatinib treatment: 231 (48%) were switched to another treatment at a median of 15.9 months (95% CI: 13.5-18.5 months) after the start of imatinib and 56 (11.6%) attempted to stop at a median of (56.2 months [95% CI: 46-75 months]) after the start of imatinib. Details of second-line treatment of the 231 patients who were switched to another treatment is reported in Figure 1. The switches occurred within the first year of treatment in 90 (39%) of the 231 patients. The main reason for switching (38.1% of the switches) was a failure to achieve haematologic, cytogenetic or molecular response according to the ELN 2013 criteria (Supplementary Table 1). A mutation in the kinase domain was found in 19 of the 137 patients who switched because of progression, loss of response or a failure to achieve haematologic, cytogenetic or molecular response (Supplementary Table 2). A switch because of haematopoietic and/or extra haematopoietic toxicity occurred in 37 patients (7.6%). At last follow-up, 105 (21.7%) of the 482 patients receiving first-line imatinib therapy had undergone HSCT and 95 of them are alive.

Fifty-six (11.6%) of the 482 children discontinued imatinib in an attempt to achieve treatment-free remission between August 2007 and February 2024. The median follow-up of these 56 patients was 2.8 years (95% IC: 2.5-4.6) after discontinuation. Among them, 34 patients (group A) discontinued after at least 3 years of treatment and sustained MR4 for at least 2 years whilst 19 patients (group B) did not meet these criteria (MR4 less than 2 years, n=3; fluctuation between MR3 and MR4 n= 5; no achievement of MR4, n=7; no achievement of MR4 and less than 3 years of treatment n=4) and 3 patients without information. Among

the 56 children who discontinue imatinib, 23 children (41%) remained treatment-free with a median time of 2.7 years (95% CI: 2.4-5.8 years) after the discontinuation of imatinib, including 18 children from group A, 2 children from group B and the 3 patients without information regarding the criteria of discontinuation. The remaining 33 patients resumed treatment with imatinib (n=18) or another TKI (n=15).

Disease progression occurred in 29 (6%) patients (accelerated phase, n=9; blast phase, n=20; lymphoid immunophenotype, n=12; myeloid, n=6; mixed, n=1, not specified, n=1). Among them 19 (3.9%) patients progressed under imatinib treatment and 10 patients progressed after switching from imatinib. PFS rate at 3-years was 97.2% (95% CI: 95.1-99.3%), 91.8% (95% CI:85.8-98.4%) and 72.0% (95% CI: 59-87.9%) in the ELTS low-, intermediate- and high-risk groups, respectively (p log rank<0.001) (Figure 3). Among the 482 patients treated with first-line imatinib, 15 (3.1%) children died: 7 children died after progression of CML (including 2 patients who relapsed after transplantation in second CP) whilst non-related CML death occurred in 8 transplanted patients (transplantation in second CP after progression of CML, n=4; transplantation in first CP, n=4). Probability of overall survival at 3 years and at 5 years was 97.6% (95% CI: 96.1-99.1%) and 96.3% (95% CI: 94.4-98.2%), respectively (Figure 4). The 3-year survival rate was 98.3% (95% CI: 96.6-100%), 94.5% (95% CI: 89.5-99.9%) and 95% (95% CI: 88.5-100%) in the ELTS low-, intermediate- and high-risk group, respectively (p log rank=0.0064).

Discussion

To the best of our knowledge, this report from the International Registry of Childhood CML (I-CML- Ped Study) provides description, treatment and outcome data from the largest pCML cohort to date. In this study we have focused on childhood CML-CP as the characteristics and outcome of children with advanced phases at diagnosis have previously been reported.[13] The proportion of advanced phases reported in the present work does not seem to differ to that described in adult.[14] We found a slight male preponderance in children with CML-CP which has also been reported in adult series.[14] Interestingly, 76% of the children presented with splenomegaly, contrasting with a lower frequency (less than 50%) in newly diagnosed adult patients.[14] Higher leukocyte counts and lower haemoglobin levels were significantly associated with the presence of a splenomegaly. We also found that platelet counts at

diagnosis were significantly higher in girls. To our knowledge, gender-related differences in platelet counts have not been previously reported either in children or adults. Despite a median leukocyte count at diagnosis in our patients about threefold higher than in adults, the frequency of signs of leukostasis seems to be similar (16.5% versus 15.8%) with equivalent frequency of priapism (3.2%) in males.[15] Chromosomal abnormalities in addition to the classical chromosomal translocation t(9;22)(q34.1;q11.2) were rare (5.5%). Typical BCR::ABL1 transcripts e14a2 (b3a2) including combination of e14a2 and e13a2 (b2a2) were predominant as reported in adults in whom a favorable impact on outcome was reported .[14,16]

This registry initiated in the year 2011 provides valuable data on the largest cohort of children treated with first-line imatinib. In the present work conducted in children diagnosed with CML between January 2000 and August 2020, only few children were treated with a second-generation TKI as first line therapy because dasatinib, nilotinib and bosutinib were approved for minors in 2018, 2019 and 2023, respectively.[17-19] Pediatric clinical trials of ponatinib and asciminib in children are currently underway. It was reported that children treated with first-line dasatinib or nilotinib achieved CCyR and MMR earlier than children receiving imatinib, but this did not translate into PFS or survival rates.[16,17] Imatinib was well tolerated as previously reported in children with a similar proportion (5 to 6% versus 7.6% in the present study) of children who permanently stopped imatinib because of adverse events. [2,3] The notable proportion (48%) of patients reported here who switched from imatinib was mainly due to failure to achieve an optimal response according to the ELN criteria. However, we observed a high proportion (21.7%) of switches related to the physician's choice without taking into account the ELN failure criteria. It was reported that 24 % to 30% of adults treated with imatinib for CML in clinical trials changed treatment.[20-23] However, the proportion of switches was higher (41% and 46%, respectively) in 2 studies conducted in adults in a real-life setting which is the status of the present pediatric registry.[24,25] By contrast to the data shown here, the switches reported in these 2 studies were mainly due to intolerance and not to failure to achieve milestones.

The proportion (60%) of children with transcript levels equal to or less than 10% after 3 months of imatinib was similar to the proportion reported in adults.[20] We previously reported that such an early response to imatinib at 3 months predicts pCML outcome.[26]

CCyR rates (68% and 97% at 1 and 5 years, respectively) and MMR (40% and 91% at 1 and 5 years, respectively) are in the ranges of the results from comparative trials with imatinib conducted in adults and in prospective trials with imatinib in children.[3,27,28,29]

The overall survival rate (96.3% at 5 years) observed in our cohort of children treated with first-line imatinib compares favorably with results in adult trials with imatinib.[21,30] There is no pediatric prognostic score to predict pCML outcome. The ELTS scoring system was set up to consider disease-specific deaths in adults with CML treated with imatinib and is relevant in predicting the long-term outcome of adults with CML-CP.[31] As also reported in adults, we observed that as compared to the ELTS score, the Sokal score identified a higher proportion of children as high risk (43% versus 12%) and fewer children as low risk (20% versus 67%).[6] Moreover, we observed that the distribution between the high, intermediate and low risk groups according to the ELTS score was similar in adults and children.[6,30,32] We also confirm that the ELTS score can identify children with a high risk of progression and can be used in the pCML treatment algorithm.[33] The treatment recommendations of our international pCML expert panel recently published are based on this finding: initial therapy with a first or second-generation TKI depends on the allocated ELTS risk group (imatinib for children allocated to the low and intermediate ELTS risk groups; second-generation TKI for those allocated to high ELTS risk group).[34]

1. The proportion (41%) of our children remaining in treatment free remission after an attempt of discontinuation of imatinib seems to be lower than the reported rate of 50% in other pediatric cohorts.[35,36] This can be explained in several patients by neglect of the criteria (MR4 at least for 2 years with at least 3 years of treatment) which were recently defined for stopping in children.[35]

Conclusion. This analysis of clinical and biological parameters of the largest cohort of children with CML in CP demonstrated that pediatric CML is characterized by a bulky disease (large splenomegaly, high leukocyte counts) compared to adults. However, these characteristics did not translate into a lower rate of response to imatinib and the outcome was similar to that in adults receiving imatinib. While the ELTS score can identify children with a poor outcome, a refined prognostic score specific to the pediatric population needs to be established and validated.

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Table 1. Baseline characteristics at diagnosis of children and adolescents with CML in chronic phase Abbreviations: ACA: additional chromosomal abnormalities in Ph+ metaphases; IQR: interquartile range; WBC: white blood cell count. The Karnofsky Scale is designed for patients aged 16 years and older, and the Lansky Scale for patients one year old to less than 16 years old.

	All	Boys	Girls	P
Age in years, N of patients (%)	N=535	N=303 (56%)	N=232 (44%)	
0-3	35 (7%)	19 (6%)	16 (7%)	
4-9	124 (23%)	72 (24%)	52 (22%)	
10-14	244 (45%)	128 (42%)	116 (50%)	
15-18	132 (25%)	84 (28%)	48 (21%)	
Presence of signs of leukostasis, N (%)	N=88 (16%)	N=50 (9%)	N=38 (7%)	0.97
Lansky/Karnofski scales*, N (%)	N=484	N=269	N=215	
100 (normal, fully active)	262 (54%)	146 (54%)	116 (54%)	
90 (minor restriction)	119 (25%)	70 (26%)	49 (23%)	
<80 (mild restriction and more)	103 (21%)	53 (20%)	50 (23%)	
Sokal score (< 45 years), N (%)	N=429	N=236	N=193	<0.0001
low	84 (20%)	27 (11%)	57 (30%)	
intermediate	160 (37%)	86 (36%)	74 (38%)	
high	185 (43%)	123 (52%)	62 (32%)	
ELTS score, N (%)	N=453	N=252	N=201	0.26
low	304 (67%)	169 (67%)	135 (67%)	
intermediate	93 (21%)	47 (19%)	46 (23%)	
high	56 (12%)	36 (14%)	20 (10%)	
Palpable spleen, N (%)	N=529	N=300	N=229	
	404 (76%)	226 (75%)	178 (78%)	0.52
median (cm below the costal margin), (IQR)	N=362	N=198	N=164	
	9 (4-15)	10 (4-15)	8 (4-15)	0.28
Hb (g/dl)	N=532	N=302	N=230	
median (IQR)	9.4 (7.7-11.5)	9.4 (7.7-11.6)	9.4 (7.7-11.2)	0.71
WBC (10^9/l)	N=534	N=302	N=232	
median (IQR)	222 (95-353)	223 (96-345)	216 (93-358)	0.93
Blast cells, (%)	N=516	N=288	N=228	
median, (IQR)	0.0 (0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.77
Basophils, (%)	N=522	N=294	N=228	
median, (IQR)	3.0 (1.8-5)	3.0 (1.5-5.6)	3.0 (1.9-5)	0.80
Eosinophils, (%)	N=524	N=296	N=228	
median, (IQR)	3.0 (1.0-5.0)	3.0 (1.0-4.8)	3.0 (1.5-5.0)	0.39
Platelet count (10^9/l)	N=532	N=300	N=232	
median (IQR)	494 (336-778)	462 (308-680)	552 (384-972)	<0.0001
<150 × 10^9/l	22 (4%)	14 (5%)	8 (3%)	
150 to 450 × 10^9/l	201 (38%)	129 (43%)	72 (31%)	
450 to 1000 × 10^9/l	225 (42%)	127 (42%)	98 (42%)	
>1000 × 10^9/l	84 (16%)	30 (10%)	54 (23%)	

Table 1. continued

	All	Boys	Girls	P
Karyotype	N=535	N=303	N=232	0.7481
Not done/failure	22	10	12	
Classical translocation	485 (94%)	277 (94%)	208 (94%)	
Variant translocation	7 (2%)	4 (2%)	3 (2%)	
ACA	21 (4%)	12 (4%)	9 (4%)	
Transcript type	N=379	N=216	N=163	0.1073
e14a2 (b3a2)	197 (52%)	113(52%)	84 (51%)	
e13a2 (b2a2)	123 (33%)	76 (35%)	47 (29%)	
combination e14a2-e13a2	50 (13%)	21 (10%)	29 (18%)	
atypical transcript e13a3 (b2a3)	9 (2%)	6 (3%)	3 (2%)	
BCR::ABL1 protein	N=88	N=51	N=37	
$P210^{BCR::ABL1}$	87 (99%)	50 (99%)	37 (100%)	
$P190^{BCR::ABL1}$	1 (1%)	1 (1%)	0	

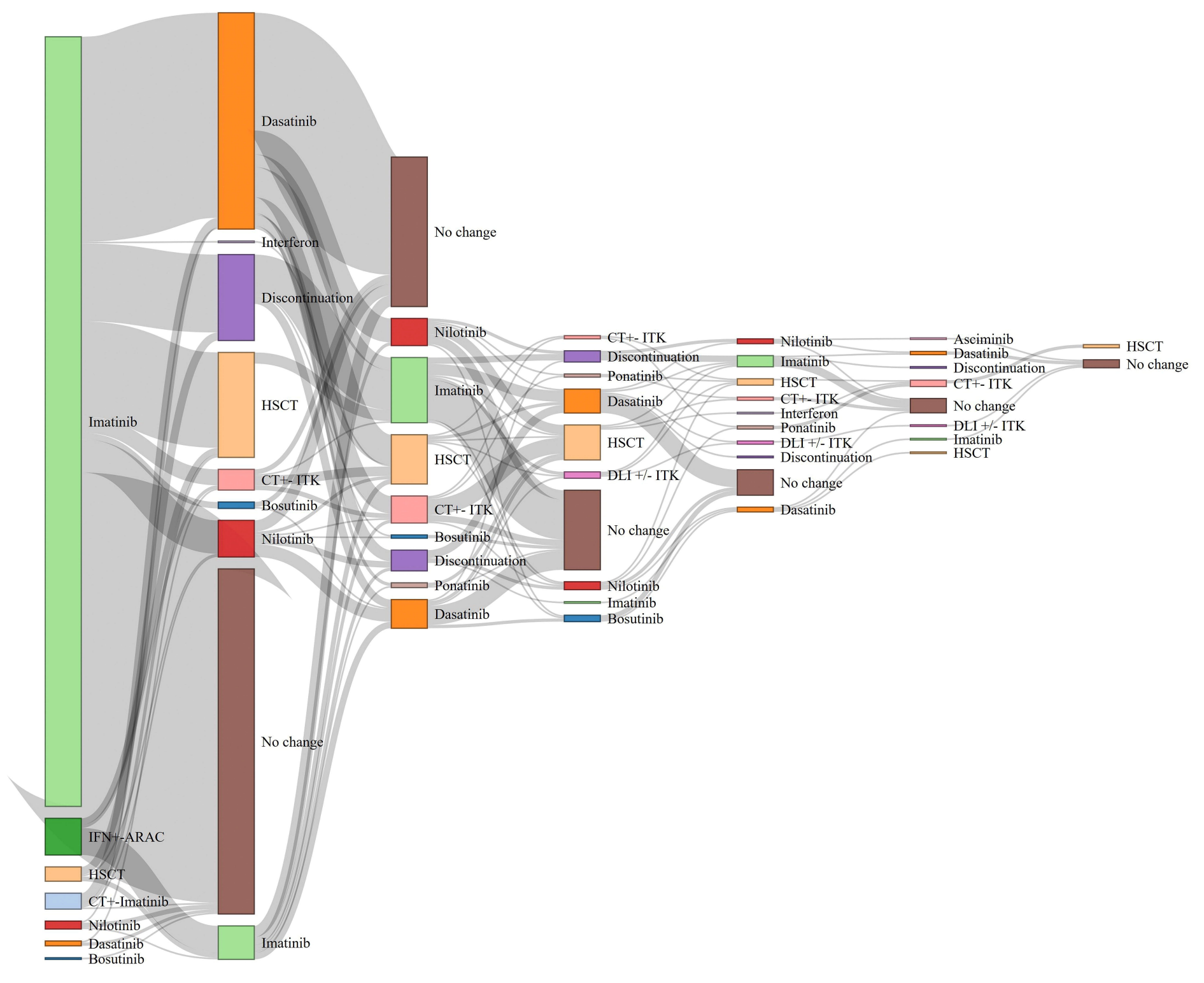
Legends:

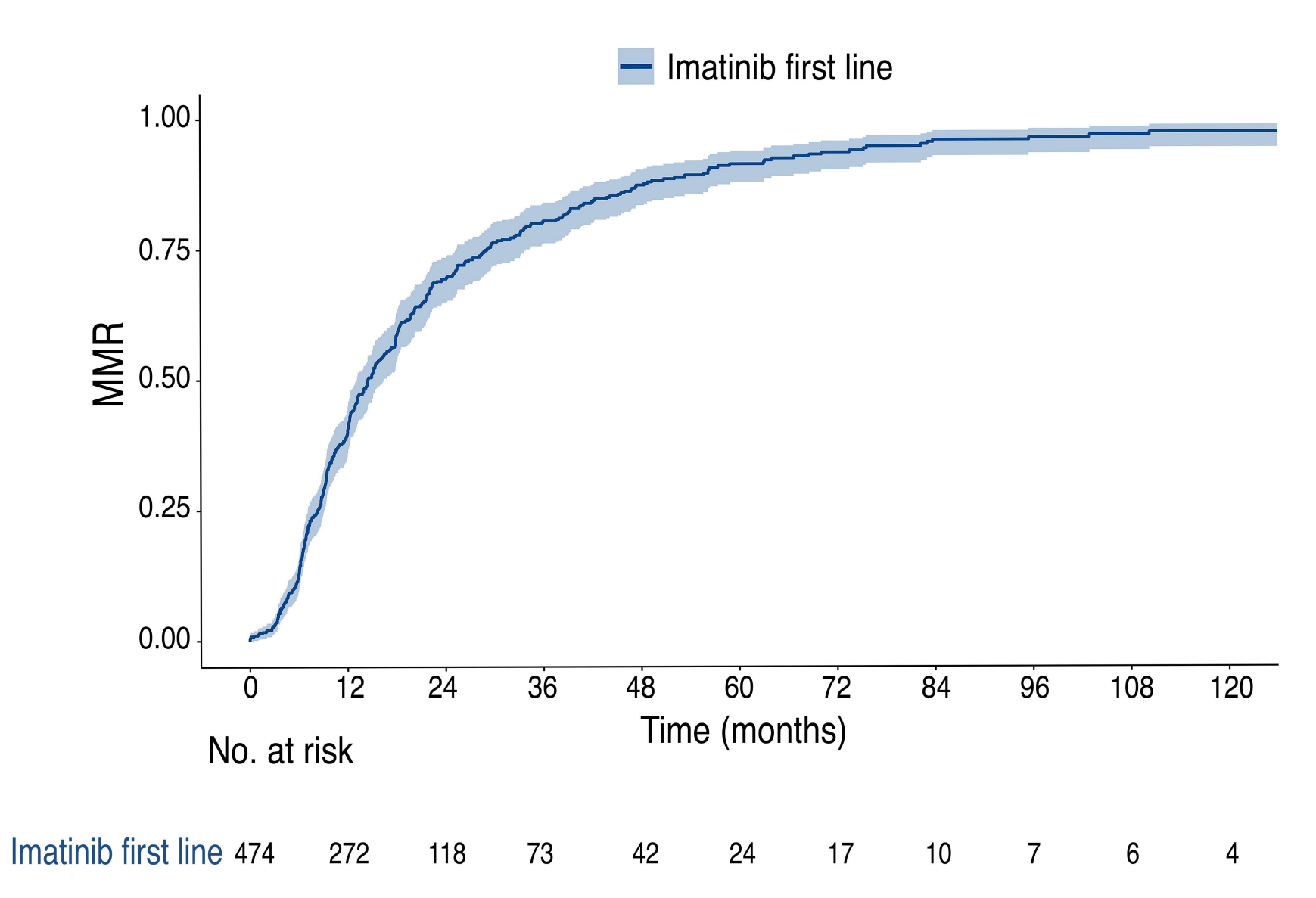
Figure 1: Sankey diagram of treatment patterns (first line to 7th line). Among the 482 patients treated with imatinib front-line, 231 patients were switched to another treatment and received as second line of treatment: dasatinib (59%), hematopoietic stem cell transplantation (26%), nilotinib (8.2%), chemotherapy (4.1%), bosutinib (2.2%) or alpha interferon (0.5%). ARAC: cytosine arabinoside; CT: chemotherapy; DLI: Donor lymphocyte infusion; HSCT: hematopoietic stem cell transplantation; IFN: alpha interferon; TKI: tyrosine kinase inhibitor.

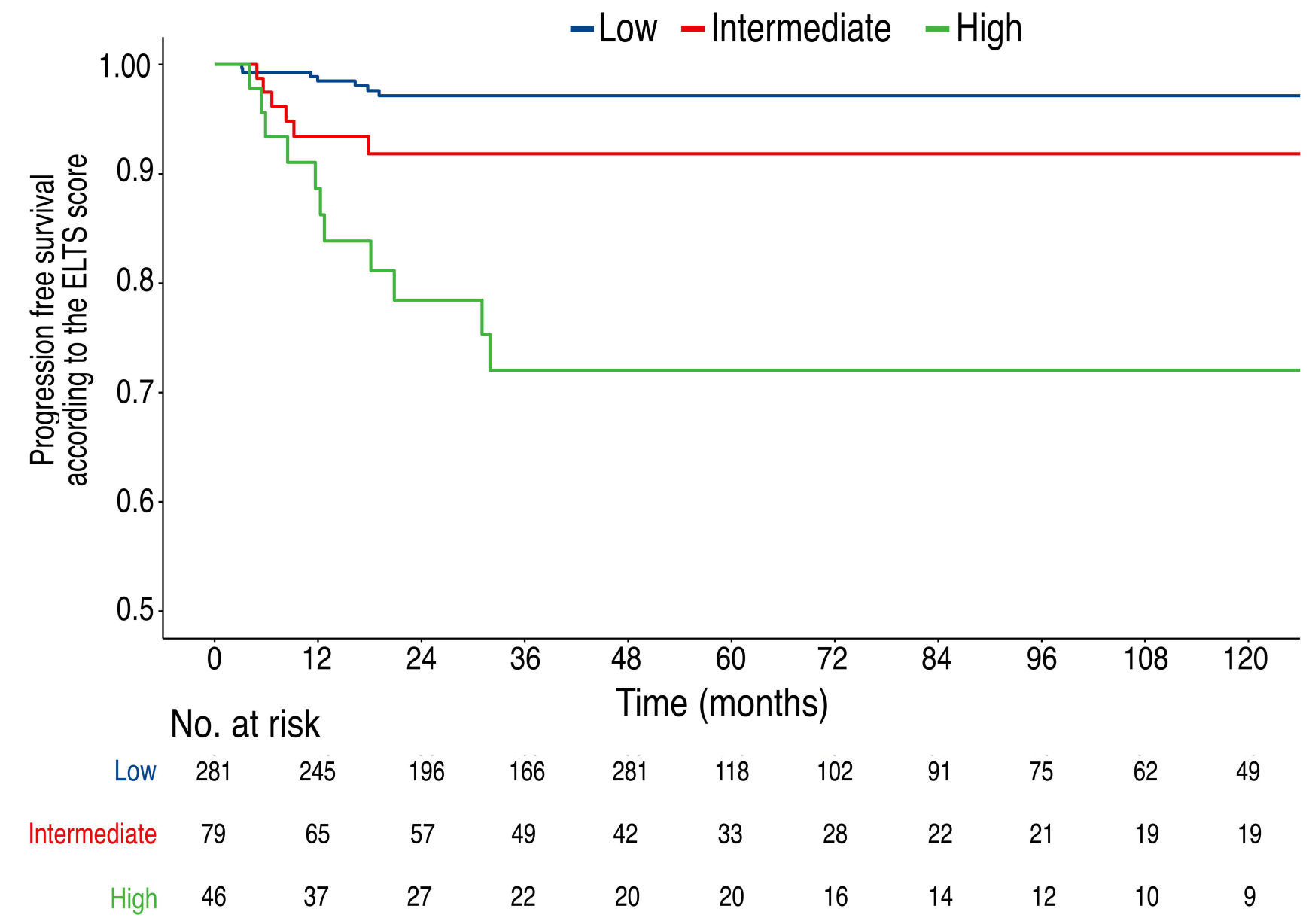
Figure 2. Cumulative incidence of major molecular response in patients receiving first line imatinib therapy

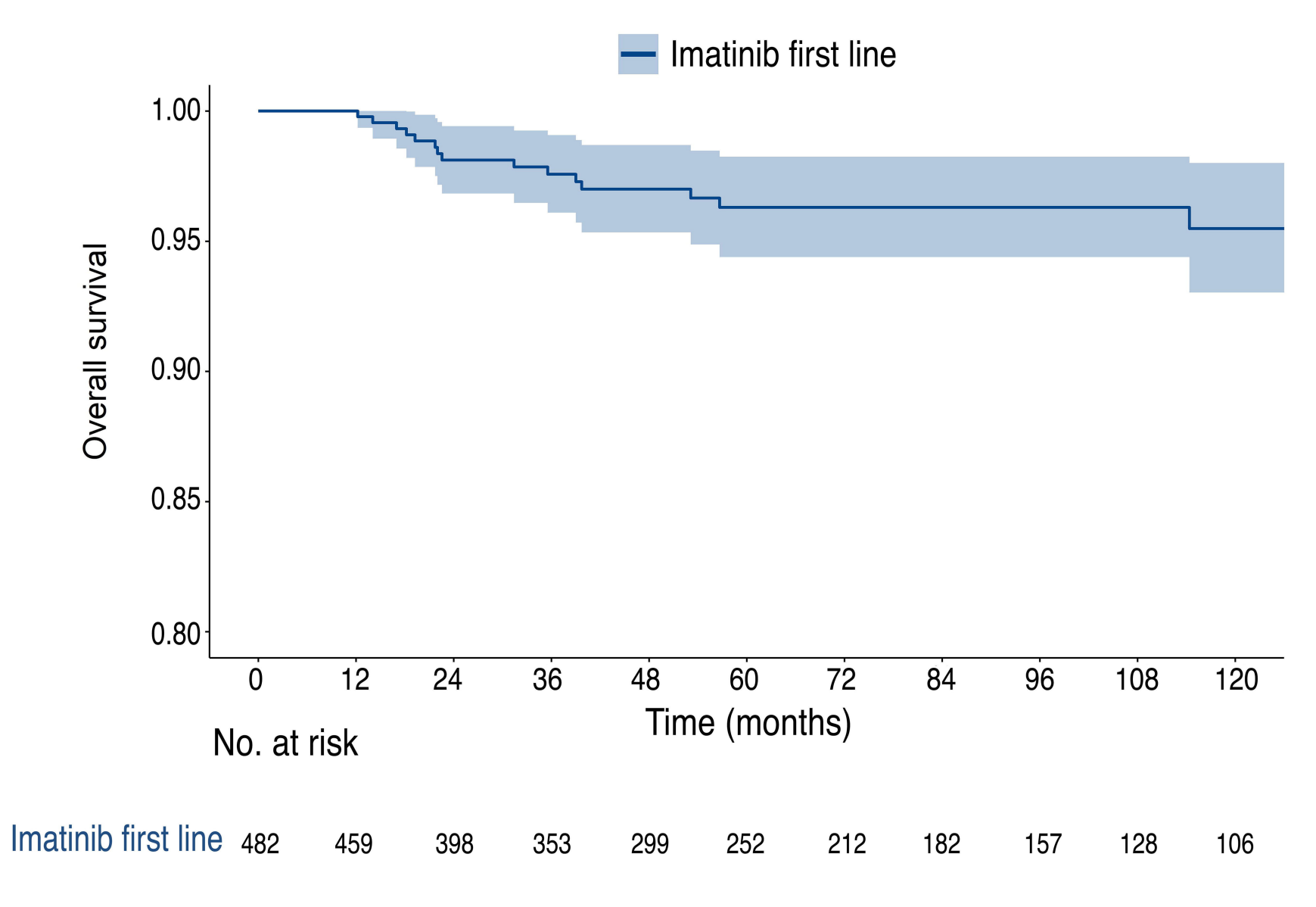
Figure 3. Progression free survival for patients treated with first-line imatinib according to their ELTS score.

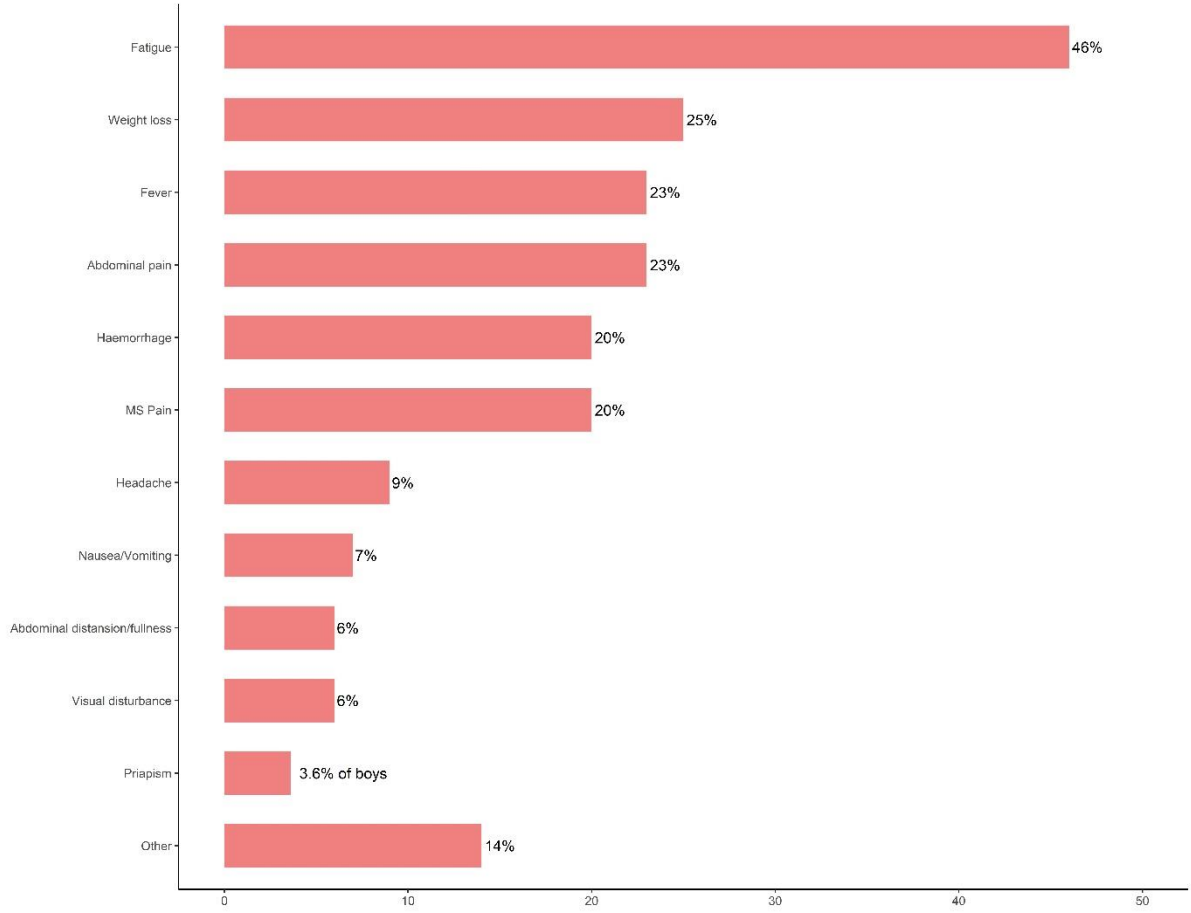
Figure 4. Overall survival for patients treated with first-line imatinib.


Imatinib
IFN+-ARAC
HSCT
CT+-Imatinib
Nilotinib
Dasatinib
Bosutinib
Dasatinib
Interferon
Discontinuation
HSCT
CT+- ITK
Bosutinib
Nilotinib
No change
Imatinib
No change
Nilotinib
Imatinib
HSCT
CT+- ITK
Bosutinib
Discontinuation
Ponatinib
Dasatinib
CT+- ITK
Discontinuation
Ponatinib
Dasatinib
HSCT
DLI +/- ITK
No change
Nilotinib
Imatinib
Bosutinib
Nilotinib
Imatinib
HSCT
CT+- ITK
Interferon
Ponatinib
DLI +/- ITK
Discontinuation
No change
Dasatinib
Asciminib
Dasatinib
Discontinuation
CT+- ITK
No change
DLI +/- ITK
Imatinib
HSCT
HSCT
No change


Imatinib first line
1.00
0.75
0.50
0.25
0.00
MMR
0
12
24
36
48
60
72
84
96
108
120
Time (months)
No. at risk
Imatinib first line 474 272 118 73 42 24 17 10 7 6 4


Low
Intermediate
High
1.00
0.9
0.8
0.7
0.6
0.5
Progression free survival according to the ELTS score
0
12
24
36
48
60
72
84
96
108
120
Time (months)
No. at risk
Low 281 245 196 166 281 118 102 91 75 62 49
Intermediate 79 65 57 49 42 33 28 22 21 19 19
High 46 37 27 22 20 20 16 14 12 10 9


Imatinib first line
1.00
0.95
0.90
0.85
0.80
Overall survival
0
12
24
36
48
60
72
84
96
108
120
Time (months)
No. at risk
Imatinib first line
482
459
398
353
299
252
212
182
157
128
106



Supplementary Figure 1. Symptoms at presentation in children with chronic myeloid leukemia in chronic phase. MS: musculo-skeletal.

Reasons for switching	Number of patients (%)
Progression (blastic and accelerated phase)	19 (8.2%)
Failure to achieve	88 (38.1%)
Complete hematologic response	3
Complete Cytogenetic response	28
Major molecular response	47
Not specified	10
Physician's choice*	50 (21.7%)
Hematopoietic stem cell transplantation	37 (between 2003 and 2016)
Pregnancy	1
Optimisation**	10 (between 2010 and 2018)
Insufficient decrease of transcript level within the first 6 months of treatment	2
Loss of response	30 (13.0%)
Complete Cytogenetic response	11
Major molecular response	19
Intolerance	37 (16.0%)
Not specified	7 (3.0%)

Supplementary Table 1: Reasons for discontinuation of imatinib in the 231 patients who interrupted imatinib

*physician's choice without meeting the ELN 2013 criteria

** optimisation: attempt to improve the transcript level in patients in MR3 or MR4.

Kinase domain mutations	Number of Patients
M244I	1
T315I	4
E255K	2
G459L	1
F493V	1
E453K	1
A365A	1
G250E	1
L384M	1
K247Q	1
F359V	1
L248V	1
E279K	1
Not precised	2

Supplementary Table 2: Kinase domain mutations found in19 of the 137 children who switched because of progression, loss of response or failure to achieve haematologic, cytogenetic or molecular response.