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Imatinib treatment and longitudinal growth in pediatric patients with chronic myeloid leukemia: Influence of demographic, pharmacological, and genetic factors in the German CML-PAED cohort

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Trial information

CML-PAED-II was an investigator-initiated, academic-supported, multicenter, open-label, single-arm phase III clinical trial that recruited from March 2004 to December 2015 and registered at EUDRACT-2007-001339-69 and Clinical-Trials.gov (NCT00445822). The protocol was approved by the institutional ethics committee (EK282 122 006). The subsequent registry is authorized by the institutional ethics committee (EK 236_18 B).

Author contributions

SSt and SS contributed equally as authors. SSt and SS designed the research study, performed the research, analyzed the data, and wrote the paper. MM and CM analyzed the data and wrote the paper. AK, OS, MMa, MR, MK, MS and JW performed the research and reviewed the paper. All authors have read and agreed to the published version of the manuscript.

Data sharing statement

The data supporting the results of this study are available upon reasonable request from the corresponding author, [SS].

Competing interest

The authors declare no relevant conflict of interest.

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Abstract

In children and adolescents, impaired growth due to tyrosine kinase inhibitor therapy remains an insufficiently studied adverse effect. This study examines demographic, pharmacological, and genetic factors associated with impaired longitudinal growth in a uniform pediatric cohort treated with imatinib. We analyzed 94 pediatric patients with chronic myeloid leukemia (CML) diagnosed in the chronic phase and treated with imatinib for >12 months who participated in the Germany-wide CML-PAEDII study between February 2006 and February 2021. During imatinib treatment, significant height reduction occurred, with medians of -0.35 standard deviation score (SDS) at 12 months and -0.76 SDS at 24 months. Cumulative height SDS change (Δheight SDS) showed a more pronounced effect in prepubertal patients during the first year but were similar between prepubertal and pubertal subgroups by the second year (-0.55 vs. -0.50). From months 12 to 18 on imatinib, only 18% patients achieved individually longitudinal growth adequate to the growth standard (Δheight SDS≥0). When patients were divided into two subgroups based on median Δheight SDS (classifier Δheight SDS > or ≤-0.37) after one year on imatinib therapy, cohort 1 (Δheight SDS extending -0.37) showed younger age at diagnosis, a higher proportion of prepubertal children, but also better treatment response and higher imatinib serum levels. Exploring the association of growth parameters with pharmacokinetically relevant single nucleotide polymorphisms, known for affecting imatinib response, showed no correlation. This retrospective study provides new insights into imatinib-related growth impairment. We emphasize the importance of optimizing treatment strategies for pediatric patients to realize their maximum growth potential.

Introduction

The development of tyrosine kinase inhibitors (TKIs) has fundamentally improved the treatment outcome in chronic myeloid leukemia (CML) and expanded the therapeutic repertoire in numerous additional malignancies where tyrosine kinases are frequently identified as a disease driver. Adverse effects are related to the off-target effects of each agent and therefore vary between currently available TKIs. A unique adverse effect in childhood and adolescence is the impact on growth. Based on a few human and animal studies, multifactorial causative mechanisms are postulated: disruption of the GH/IGF1 axis [1, 2], alteration of bone metabolism impacting bone remodeling [3], and disturbance of processes within the growth plate [4]. In the majority of CML patients in adulthood, this specific adverse side effect is not in the focus, although an influence on bone remodeling has been observed here as well [5, 6]. However, for pediatric CML patients and their parents, growth within the familial target height range plays a major role for social and psychological reasons.

For the first-generation TKI imatinib, which has been used as monotherapy in the majority of pediatric patients in chronic phase CML (CML-CP), declining growth parameters in pre- and pubertal children have been described in small cohort studies [7-12]. Previously, it has been postulated that the second-generation TKIs dasatinib and nilotinib affect longitudinal growth to a lesser extent. However, long-term results demonstrated a comparable growth impairment in pediatric CML patients [13-15]. In conclusion, TKIs as single-agent therapy in children and adolescents lead to a significant reduction in individual growth rates. Age at treatment initiation and pubertal status were identified as influencing factors in the majority of studies [7, 8, 12]. By contrast, some studies showed no association between these parameters and found reduced height SDS over time [9, 11]. Factors influencing longitudinal growth include age, ethnic composition of the study population, nutritional status, and TKI dose level. The different composition of the study cohorts with regard to these factors is possibly the reason for the partially different observations in the previous studies [16].

In the present investigation, we therefore examined long-term growth data from a large uniform cohort of pediatric patients with CML-CP diagnosed in the German CML-PAED trial and subsequent registry. We evaluated associations of changes in height SDS with age, pubertal status, molecular response (MR), and imatinib trough serum levels. Our study aimed to obtain a better estimation of the impact of the different influencing factors on the impairment of longitudinal growth.

Methods

Study design and patients

This retrospective study was conducted based on data collected in the CML-PAED II trial and subsequent registry. The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients' legal guardians and, if applicable, from the children and adolescents after an age-appropriate written informed consent. Approval was obtained from the ethics committees of the medical faculties of the Technical University of Dresden and the Friedrich-Alexander University of Erlangen (ethical votes EK282 122 006, EK 236_18 B). From February 2006 to February 2021, 164 children and adolescents with newly diagnosed CML aged 0-17 years were consecutively registered. Of these patients, 94 had been treated with imatinib for more than 12 months and were less than 16 years old at diagnosis and were therefore eligible for this study. Data on age, gender, height and body weight were prospectively collected by the participating centers at the time of diagnosis and during treatment with imatinib as part of the registry. Furthermore, we evaluated the parameters of treatment response as well as imatinib trough plasma levels. The study population was divided into prepubertal and pubertal cohorts according to age (prepubertal: aged 1-8 years for female cases, aged 1-10 years for male cases; pubertal: aged 9-16 years for female cases, aged 11-16 years for male cases).

Height and Growth evaluation

Height, growth velocity, weight, and body mass index (BMI) were expressed as SDS calculated according to the German standards [17, 18] using Growth Analyser software, Electronic Patient Record System 4.1, version 1.6 (Growth Analyser BV, Rotterdam, The Netherlands, growthanalyser.org, (2018)). Individual growth during imatinib therapy was assessed by the cumulative change in height SDS (Δ height SDS) from the start of imatinib treatment to the annual follow-up time points.

Imatinib Trough Plasma Level Determination

Drug concentrations were determined in an accredited and certified laboratory using high-performance liquid chromatography (HPLC) coupled with tandem mass spectrometry (MS/MS), as previously described [19]. The detection threshold for imatinib was 100 ng/mL. For a trough level, it is defined that the interval between the intake of imatinib and blood sampling is between 20-26 hours.

Quantification of BCR::ABL1 transcript levels

BCR::ABL1 transcript levels were quantified and standardized to the international scale (IS) using the Xpert BCR-ABL Ultra system (Cepheid), with a detection threshold of MR4.5.

Statistical analysis

Statistical analysis was performed using SPSS version 28.0.0.0 statistical package (SPSS IBM corp., New York, USA, www.ibm.com (2021)) and GraphPad Prism, Version 9.3.1 (GraphPad Software. San Diego, California USA, www.graphpad.com (2022)). We compared the growth parameters, i.e. height SDS, Δ height SDS, and BMI SDS, at the time of diagnosis with the values obtained at 3,6,12,18, and 24 months using the "One-Way ANOVA" test. Data distribution was tested by longnormality test. To elucidate parameters associated with poorer growth under imatinib treatment we divided the cohort into two subgroups, classified by median Δ height SDS after 12-18 months of therapy. Kolmogorov-Smirnov test was used to determine data distribution. Non-normally distributed data are shown as a median and interquartile range, compared using the Mann-Whitney test. Categorical variables were compared with Pearson $\chi 2$ and Fisher´s exact tests. Statistical tests were 2-sided and the significance level was defined as $p < 0.05$. Parameters reaching a statistical trend in univariate analysis (i.e., $p < 0.1$) or of high clinical relevance were included

in multivariate models. We conducted stepwise forward multivariable logistic regression models to identify factors associated with poorer longitudinal growth.

Genotyping

DNA samples were available from all but one of the included patients. For the present study, we performed genotyping with either present or imputed polymorphisms using the Illumina Global Screening Array-24 version 3.0 [20]. Quality control (QC) was performed using the PLINK toolkit (https://www.cog-genomics.org/plink/2.0/ accessed on 30 July 2021). The QC process included sex verification, variant QC (removing variants with call rates <98%, deviations from Hardy-Weinberg equilibrium with p-values <1 × 10^−10, and minor allele frequencies <0.01), sample QC (removing samples with call rates <98%), and managing familial relationships (removing individuals related up to the 3rd degree using KING). Genotyping data were phased using Eagle (v. 2.4.1) and imputed using Minimac (v. 4) with the 1000 Genomes Project Phase 3 data as the reference panel [21-23]. We utilized Plink to apply linear regression models with respect to height SDS to investigate potential genetic associations between pharmacogenetic variants and longitudinal growth due to treatment in a cohort of 67 post-QC genetically European samples, which had both genotype and phenotype data available. The analysis was adjusted for the first 10 principal components, sex, and pubertal status. Ancestry estimation was performed using data from the 1000 Genomes Project Phase 3, assigning individuals to the most closely matching reference super- and subpopulations based on their positions in the ten principal component space as performed in other analyses [24-26].

Results

Demographic and clinical characteristics at diagnosis

Of the 164 children and adolescents registered in the period from February 2006 to February 2021, 94 (57%) patients were diagnosed in the chronic phase, and treated with imatinib for ≥12 months, and >3 subsequent datasets on height evaluation were available. 38 (40%) patients were female and 56 (60%) were male. Ancestry analysis was possible in 93 (99%) patients; we identified 85 (92%) patients with European ethnicity, 4 (4%) with South Asian ethnicity, 3 (3%) with African ethnicity, and 1 (1%) with East Asian ethnicity. The study cohort and the excluded patients are presented in Figure 1. The median age at diagnosis was 12 years [range: 3-16 years]. Thirty-four (36%) patients could be assigned to the prepubertal subgroup and sixty (64%) to the pubertal subgroup. Other clinical and demographic characteristics did not differ significantly between the two subgroups. Concerning the auxological data collected, the 8 patients of non-European ethnicity were not identified as outliers, growth over time, expressed as height SDS values of the two study cohorts are demonstrated in Supplemental Figure 1. The following analyses were performed for the entire study cohort (n=94) if not otherwise indicated. BMI SDS was calculated for 90 patients in our cohort at baseline, and 87 patients (97%) were between -2 and +2 standard deviation (SD) at diagnosis. The majority of patients did not have any significant individual change in BMI during imatinib treatment. After 24 months, only 2 (2.2%) patients had a decrease of more than 1 SD, indicating that nutritional status did not significantly impact growth parameters in our cohort (see Supplemental Figure 2).

Development of growth parameters during imatinib treatment

At the time point of diagnosis the overall median height SDS of the 94 patients was -0.04 [range: -2.47- +3.01]. Height SDS significantly decreased over time on imatinib treatment, after 12 months with a median height SDS of -0.35 [range: -3.03- +2.74] and after 24 months of -0.76 [range: -3.31- +2.60]. The data were not uniformly available for all patients at all time points. To address potential bias due to different cohort compositions at each time point, we

compared the same 76 patients at baseline and after 12 months of imatinib treatment. Height SDS were also significantly lower in this group (diagnosis: 0.05; after 12 months: -0.35; p<0.0001). The growth data over time and the results of the paired analysis are demonstrated in Figure 2 A-C. Children and adolescents who were more markedly affected by growth restriction during the course of imatinib therapy (defined as a decrease in Δ height SDS surpassing 0.5) showed a uniform distribution of height SDS at diagnosis. Growth restriction affected both tall and short patients (Figure 2D). A significant decrease was also seen assessing the cumulative change in mean height SDS in our cohort over time on imatinib treatment with median Δ height SDS after 12 months of -0.35 [range: -1.59- +0.44] and after 24 months of -0.53 [range: -1.91- +0.94]. Comparing the two subgroups of prepubertal and pubertal patients, the declineafter 12 months of therapy was more pronounced in the prepubertal group, with median Δ height SDS -0.51 versus -0.36 (p=0.012). However, after 24 months of therapy, there was no difference in median Δ height SDS (-0.55 versus -0.50) between the two subgroups (Table 1, Figure 3). Furthermore, the age-related height velocity SDS could be calculated. For 85% of the patients, at least one height velocity SDS was available in the observation period of 2 years. In the first months of therapy, the median height velocity SDS was below the comparative value of the age-matched reference group (-1.86, month 6). In the following months, however, the median height velocity SDS increased (-0.82, month 24), but remained lower than in the age-matched population (Supplementary Figure 3).

Factors associated with cumulative change in height SDS after 12-18 months of imatinib therapy

For the following analyses, we identified 87 (93%) patients on imatinib treatment and a calculable Δ height SDS in the time interval from 12 to 18 months. Only 16 children (18%) showed individually longitudinal growth adequate to the growth standards defined as Δ height SDS ≥0. A decrease in cumulative height SDS surpassing 0.5 SD was observed in 32 children (37%), including 4 (5%) patients with a decrease of >1 SD after 12-18 months on

imatinib treatment. We next divided the patients into two groups according to the median Δ height SDS (classifier Δ height SDS ≤ -0.37= cohort 1 or >-0.37 = cohort 2). Age at diagnosis proved to be the most significant factor between the two subgroups with younger patients in cohort 1 exhibiting more pronounced growth retardation. In line with age, the proportion of prepubertal children (47.7%) was significantly higher in cohort 1. Children in cohort 1 also showed significantly better treatment response, with lower median *BCR::ABL1* transcript levels (0.046% versus 0.190%) and as a consequence a larger proportion (65.9% vs. 39.5%) achieving a major molecular response at time point 12 months after diagnosis. When comparing the two subgroups in terms of serum imatinib levels, which were available in 29 patients (cohort 1: n=17, cohort 2: n=12), children in cohort 1 had significantly higher imatinib levels (median: 1570 ng/mL vs. 961 ng/mL). The results of the analysis are summarized in Table 2. Multivariable modeling showed independent association of inferior longitudinal growth with younger age at therapy initiation (OR 0.533, 95%-CI [0.387-0.733], p<0.001), prepubertal status (OR 14.35, 95%-CI [1.781-115.58], p=0.012) and the achievement of a major molecular response after 12-18 months of therapy (OR 5.395, 95%-CI [1.766-16.478], p=0.003). To investigate the association with imatinib serum levels, we repeated analyses in patients with available data (n=29). This showed independent association of inferior longitudinal growth with higher imatinib serum levels (OR 1.008, 95%-CI [1.000-1.015], p=0.045), in addition to younger patient age (OR 0.295, 95%-CI [0.089-0.973], p=0.045).

Genotyping

Higher imatinib levels are in principle the result of either higher intake (implying better therapeutic adherence) or slower excretion (based on pharmacokinetic metabolism). We investigated the association of growth parameters with single nucleotide variants reported to influence the metabolism of imatinib [27-43]. Among the thirty-four candidate pharmacogenetic variants available, six variants showed a nominal association, although they did not survive multiple correction. The identified associated variants are as follows: rs150929 (gene =

ABCA3, effect allele = T; beta = -1.85, se = 0.36, P = 6.9E-03), rs1800682 (gene = *FAS*, effect allele = G; beta = 0.98, se = 0.30, P = 0.014), rs12505410 (gene = *ABCG2*, effect allele = G; beta = -0.90, se = 0.30, P = 0.017), rs2231142 (gene = *ABCG2*, effect allele = T; beta = 1.53, se = 0.51, P = 0.020), rs724710 (gene = *cBIM*, effect allele = T; beta = 0.87, se = 0.33, P = 0.034), and rs2228001 (gene = *XPC*, effect allele = G; beta = -0.81, se = 0.33, P = 0.043). Although previous studies have shown a significant impact on imatinib metabolization for the investigated polymorphisms, we could not observe a significant impact of candidate pharmacogenetic variants on growth in our highly homogeneous cohort. The genotyping results and the respective references are summarized in Supplemental Table 1.

Discussion

Previous research has highlighted the potential risk for growth impairment during imatinib treatment. However, conflicting findings exist regarding the impact of age and pubertal status at the start of therapy. Boddu et al. and Millot et al. did not identify age and pubertal status to be significant factors affecting growth rates [9, 11]. However, in most other studies, starting therapy before puberty was associated with inferior growth [7, 8, 12]. In a recent meta-analysis, Gupta et al. examined the effect of imatinib on height in relation to pubertal status, drawing data from four studies and 115 participants. The analysis did not reveal any significant differences in height SDS between the two subgroups. It should be noted, however, that the merged data included different definitions of puberty across studies, and thus the prepubertal age group showed considerable heterogeneity [16].

To our knowledge, our study includes the largest patient population followed over 24 months and, in addition, the cohort is distinctive for its particularly consistent composition specified by genotyping and as a representative sample of a population-based study. This improves the estimation of influencing factors such as ethnicity and nutritional status in contrast to previous studies and the degree of transferability to the entirety of patients with pediatric CML. Limitations of our study include the lack of utilizing the mid-parental target height to correct for familial genetic height potential, and defining pubertal status based on chronological age instead of Tanner stages. Our data indicate that prepubertal status represents a significant factor influencing longitudinal growth in the first year of treatment. This effect became insignificant after 24 months of treatment. Previous studies have argued that this effect is related to the growth spurt of the prepubertal subgroup and the resulting catch-up growth. However, we observed a decrease in longitudinal growth within the pubertal group over the longer observation period. It can only be speculated why this effect becomes evident later in older patients. A possible explanation could be the lower adherence to therapy in this age group, which could play a role especially at the initiation of therapy.

Overall, the growth parameters we observed at 24 months were comparable to those reported in the meta-analysis conducted by Gupta et al. [16]. Their analysis showed a diminuishing impact on standardized mean height differences in studies with more than three years of follow-up, attributed to catch-up growth and growth spurts. Our patient sample was not large enough to confirm or reject this trend after three years of follow-up. Still, it remains unclear whether TKI-induced impairment of longitudinal growth is caused by growth retardation, acceleration, or endocrinological disruptions involving a disturbed GH/IGF1 axis. Multiple mechanisms likely contribute and accumulate to produce unique outcomes in each individual, resulting in significant variability within the patient group.

Some of the individual factors relate to the pharmacokinetics of imatinib and could in principle be delineated trough plasma-level measurements and pharmacogenetic analyses [28-30, 32, 38, 40, 44]. Thus, we examined, for the first time, the potential impact of imatinib trough plasma levels and treatment response on growth parameters. Our results suggest that patients with lower growth rates had higher trough plasma levels of imatinib, resulting in a better therapeutic response. This underscores that exposure to imatinib is responsible for the effect on growth. In addition, we aimed to test whether polymorphisms reported in previous studies in adults to be linked with imatinib pharmacokinetics or treatment response could also be associated with pediatric growth parameters in our cohort [28-30, 32, 38, 40]. None of the polymorphisms were significantly associated with growth parameters. Despite the limited size of our cohort and the expected limitations in the statistical power, we analyzed in an exploratory manner because the majority of the described associations were identified and reported as significant in comparably sized or even smaller adult cohorts. Due to the potential complexity of the underlying polygenic architecture and the presence of possible epistatic interaction effects, a larger sample size would be necessary to conduct a more comprehensive analysis of genotype/phenotype associations, which may also encompass the influence of rare variants with larger functional effects. The precise role of tyrosine kinase inhibition in the complex process of longitudinal growth requires a more comprehensive exploration, and an experimental modeling approach to verify the underlying mechanisms.

In conclusion, 18% of patients were not affected by growth problems at all, 45% showed a decrease in individual growth parameters not surpassing 0.5 SD and 37% experienced growth stunting in the range of below -0.5 SD (determined by Δ height SDS). Even if the final height is still within the normal range with a loss of -1 SD in the population, the individual psychosocial effects are nevertheless serious for most patients. Our data suggest that not only prepubertal patients are affected, but also the pubertal subgroup during the course of therapy. Over a longer observation period, Gupta et al. were able to show in their metaanalysis that there is a potential for catch-up growth [16], which is also reflected in our results on height-velocity. Therefore, the practical consequence is that, especially for younger patients and those with growth potential, all measures must be taken to achieve the best possible conditions for individual growth. This includes the following measures: Longitudinal growth potential should be assessed by standardized repeated assessment of bone age before starting TKI therapy and during the follow-up under treatment. Optimal therapy adjustment, if necessary with early switch to an alternative TKI to achieve the criteria for safe TKI discontinuation as soon as possible, should be aimed for in all patients, especially in individuals who are more severely affected by growth retardation. However, the data meanwhile available on the adverse drug effects of the second-generation TKIs dasatinib and nilotinib indicate that the initially hypothesized weaker effect on growth has not been confirmed and that, with a longer observation period, approximately the same effects as with imatinib can be observed. [45-47]. Other options that are discussed include initiation of early intermittent therapy [48, 49] or possible TKI dose reduction [50]. It should be noted, however, that potential catch-up growth for these approaches has not yet been systematically investigated. Nonetheless, achieving these goals requires high treatment adherence. To encourage patients, our study and previous research suggest that patients with moderate to severe growth restriction typically have delayed growth but have the potential to catch up. In the future, studies will need to evaluate the factors that affect growth more specifically and identify high-risk patients in the early stages to contribute to enhancing therapeutic strategies.

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Table and Figure legends

Table 1

Cumulative changes in Δ height standard deviation score (SDS) over time on imatinib treatment.

Time on imatinib treatment (months)	3	6	12	18	24
Whole cohort					
n	72	74	78	62	54
Median	-0.12	-0.21	-0.35	-0.40	-0.53
Min	-1.04	-1.09	-1.59	-1.65	-1.91
Max	0.43	0.79	0.44	0.79	0.94
p-value*	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Prepubertal cohort					
n	28	29	29	27	23
Median	-0.17	-0.34	-0.61	-0.51	-0.55
Min	-1.04	-1.09	-1.59	-1.65	-1.91
Max	0.43	0.79	0.44	0.79	0.94
p-value*	0.0539	**0.0145**	**< 0.0001**	**0.0006**	**0.0016**
Pubertal cohort					
n	43	45	45	35	31
Median	-0.07	-0.19	-0.30	-0.36	-0.50
Min	-0.51	-0.68	-0.88	-1.24	-1.46
Max	0.19	0.56	0.26	0.28	0.34
p-value*	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**

* intra group comparision to Δ height SDS at diagnosis

Table 2

Characteristics of patients 12-18 months after diagnosis classified by median Δ height standard deviation score (SDS).

	Cohort 1 Δ height SDS ≤-0.37 (n=44)	Cohort 2 Δ height SDS >-0.37 (n=43)	*p*-value
Age at dx[a] (years)	10 (7-13)	14 (11-15)	**<0.001**
Sex[b] (female)	21 (47.7%)	14 (25.5%)	0.149
Pubertal status[b] (Pre-pubertal)	21 (47.7%)	10 (23.3%)	**0.013**
BCR::ABL1 transcript level[a] (% IS)	0.046 (0.011-0.175)	0.190 (0.028-0.710)	**0.010**
MMR reached 12-18 m after dx[b]	29 (65.9%)	17 (39.5%)	**0.014**
Imatinib-serum level[a] (ng/ml) (n=29)	1570 (1114-1976)	961 (576-1339)	**0.009**

SDS = standard deviation score, dx = diagnosis, IS = international scale, MMR = major molecular response, m = months.

[a] Median (inter-quartile range; 25th–75th percentile)

[b] n (%)

Figure 1

Study flow chart.

Screening 164 CML cases 1-16 years of age at diagnosis, we identified 94 patients who were eligible for this study. The distribution of female and male patients as well as prepubertal and pubertal cases is indicated. AFR, African; EAS, Eastasian; EUR, European; SAS, Southasian. *Prepubertal: aged 1-8 years for female cases, aged 1-10 years for male cases. **Pubertal: aged 9-16 years for female cases, aged 11-16 years for male cases.

Figure 2

Changes in absolute height standard deviation score (SDS) over time on imatinib treatment and paired analysis.

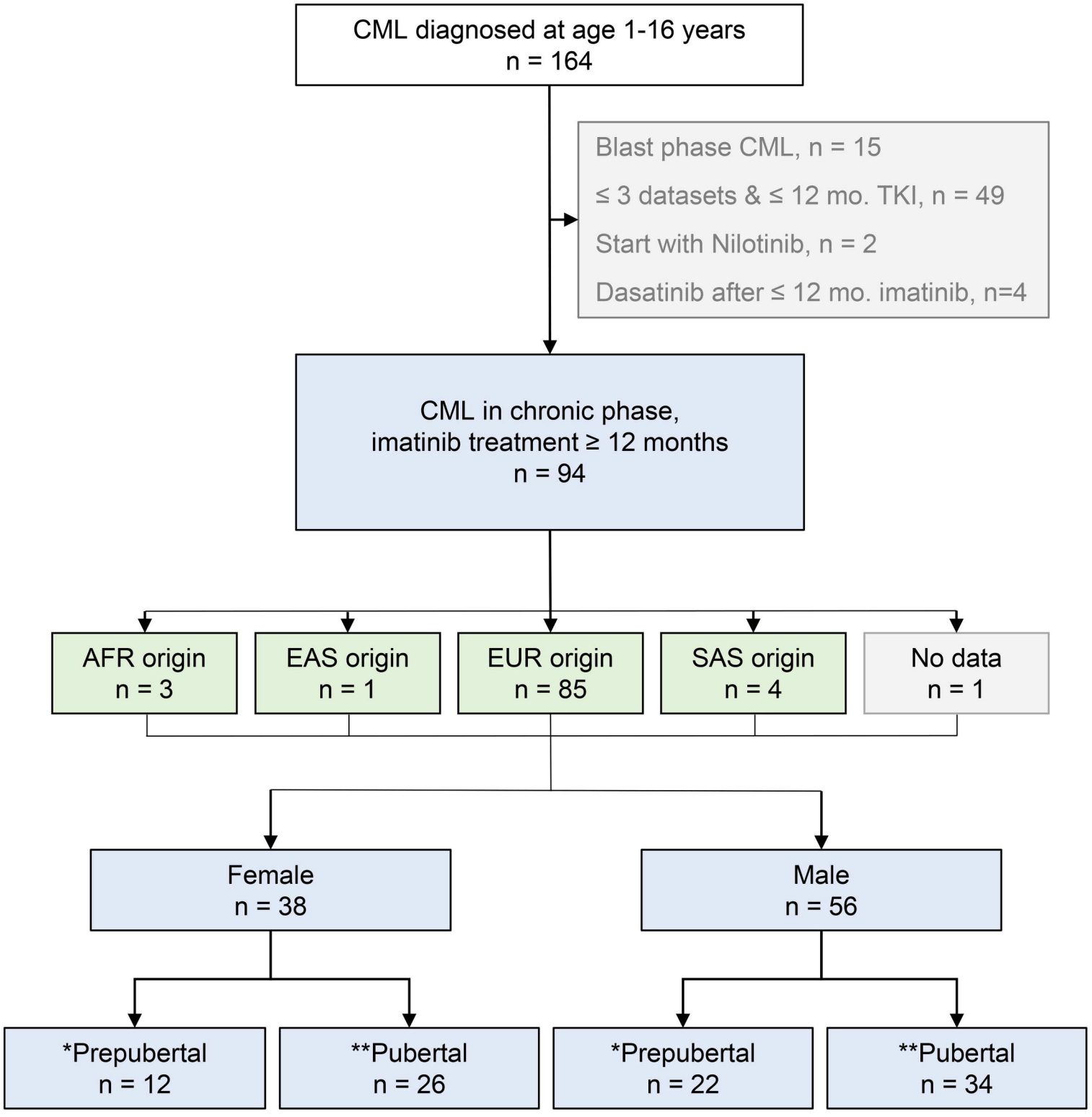
(A) The box-and-whisker plot shows the median, first, and third quartiles; whiskers extend to the 95th and 5th percentile. Statistical analysis was performed using 1-Way-ANOVA. (B) The violin plots show the median, first, and third quartiles and the width represents the frequency of the obtained values. Overall, the median height SDS decreased from -0.04 at therapy start to -0.82 after 24 months of treatment. (C) Paired analysis; height SDS at the start of imatinib therapy and 12 months later (n=76). Overall, the median height SDS decreased from 0.05 at therapy start to -0.35 after 12 months in the paired cohort ($p<0.001$). (D) Individual courses of height SDS for 32 patients with growth restriction exceeding 0.5 standard deviations (SD) over time on imatinib treatment.

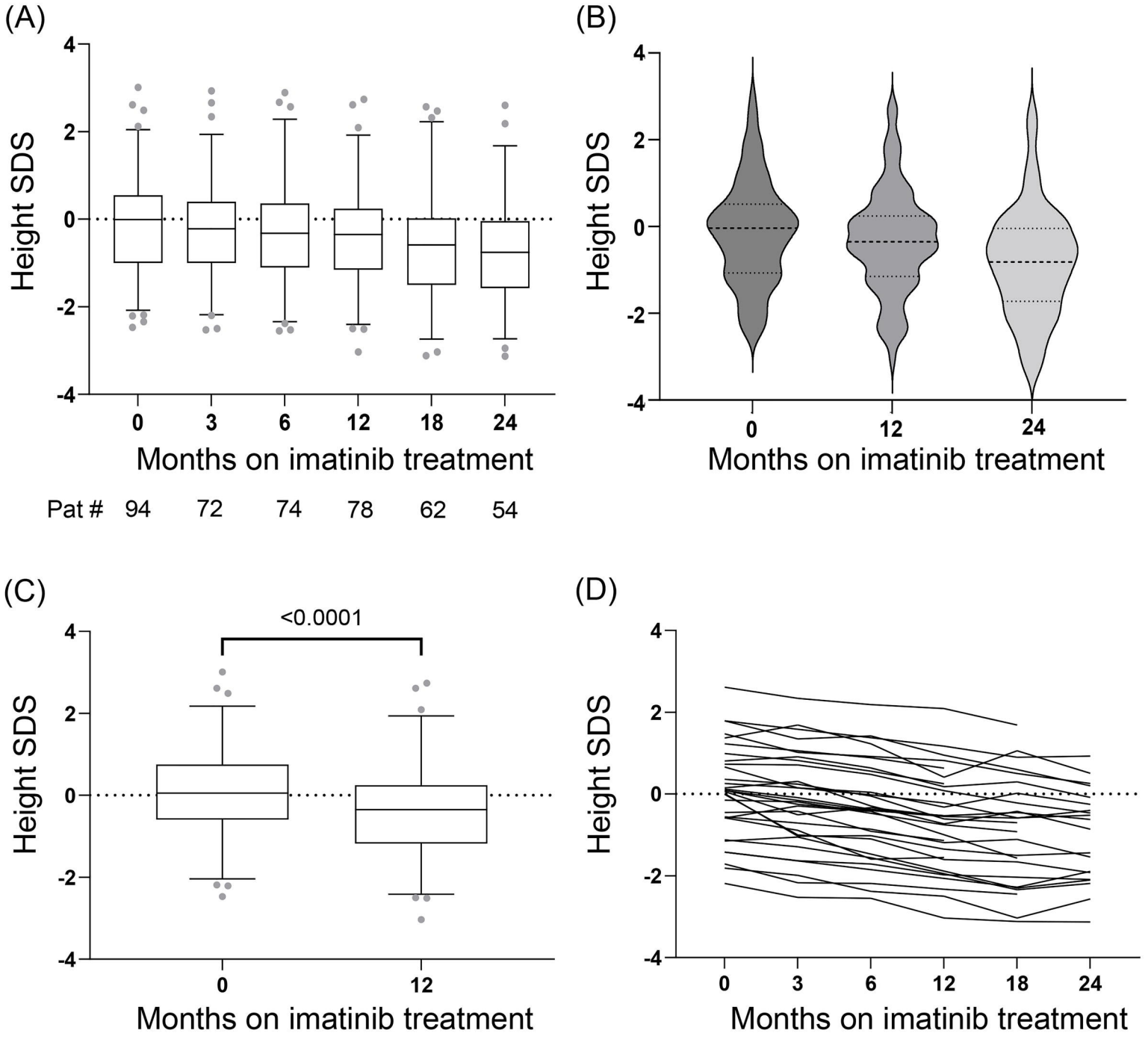
Figure 3

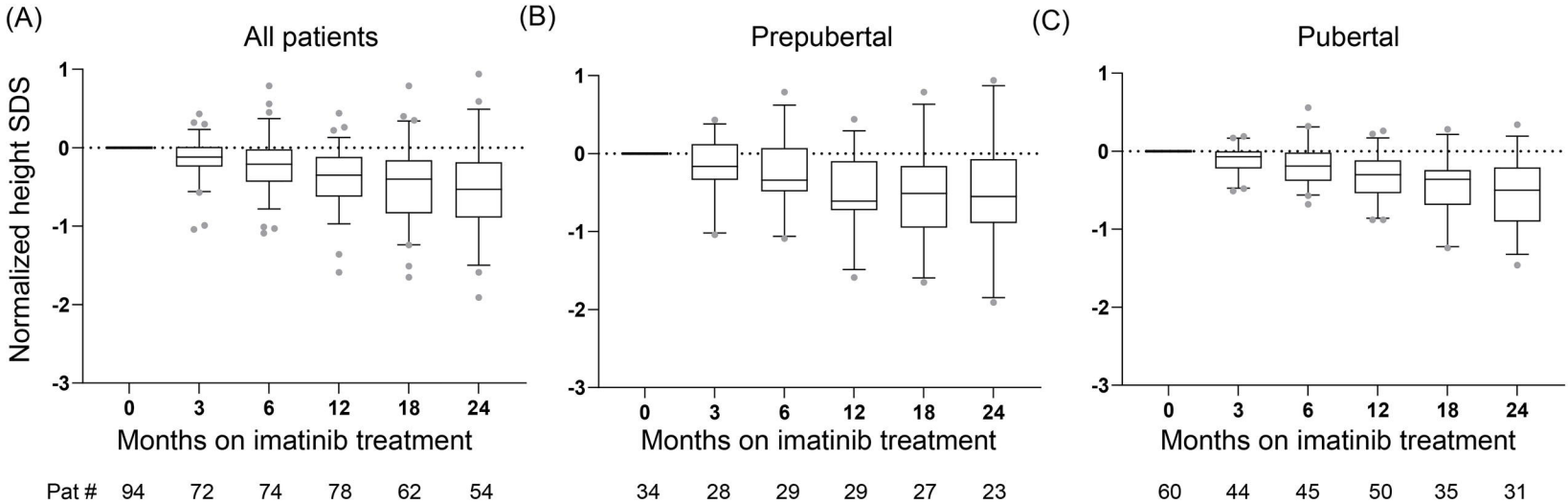
Δ Height standard deviation score (SDS) over time on imatinib treatment.

The box-and-whisker plot shows the median, first, and third quartiles; whiskers extend to the 95th and 5th percentile. Results for (A) whole cohort, (B) prepubertal (girls aged 1-8 years, boys aged 1-10 years) and (C) pubertal (girls aged 9-16 years, boys aged 11-16) patients

are depicted. Δ Height SDS was determined by subtraction of each annual time point to height SDS at diagnosis.


CML diagnosed at age 1-16 years
n = 164
Blast phase CML, n = 15
≤ 3 datasets & ≤ 12 mo. TKI, n = 49
Start with Nilotinib, n = 2
Dasatinib after ≤ 12 mo. imatinib, n=4
CML in chronic phase,
imatinib treatment ≥ 12 months
n = 94
AFR origin
n = 3
EAS origin
n = 1
EUR origin
n = 85
SAS origin
n = 4
No data
n = 1
Female
n = 38
Male
n = 56
*Prepubertal
n = 12
**Pubertal
n = 26
*Prepubertal
n = 22
**Pubertal
n = 34


(A)
Height SDS
4
2
0
-2
-4
0
3
6
12
18
24
Months on imatinib treatment
Pat # 94 72 74 78 62 54
(B)
Height SDS
4
2
0
-2
-4
0
12
24
Months on imatinib treatment
(C)
<0.0001
Height SDS
4
2
0
-2
-4
0
12
Months on imatinib treatment
(D)
Height SDS
4
2
0
-2
-4
0
3
6
12
18
24
Months on imatinib treatment


(A)
All patients
Normalized height SDS
1
0
-1
-2
-3
0
3
6
12
18
24
Months on imatinib treatment
Pat #
94
72
74
78
62
54
(B)
Prepubertal
1
0
-1
-2
-3
0
3
6
12
18
24
Months on imatinib treatment
34
28
29
29
27
23
(C)
Pubertal
1
0
-1
-2
-3
0
3
6
12
18
24
Months on imatinib treatment
60
44
45
50
35
31

Supplemental Material

referring to the article

Imatinib treatment and longitudinal growth in pediatric patients with chronic myeloid leukemia: Influence of demographic, pharmacological, and genetic factors in the German CML-PAED cohort

Sophie Stiehler, Stephanie Sembill, Oliver Schleicher, Michaela Marx, Manfred Rauh, Manuela Krumbholz, Axel Karow, Meinolf Suttorp, Joachim Woelfle, Carlo Maj, Markus Metzler

Content:

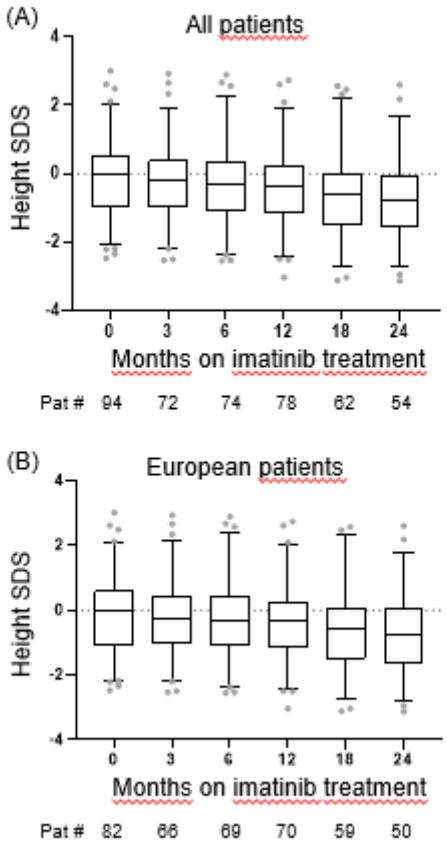
Supplemental Table 1.

Results of the association of growth parameters (Δ height standard deviation score after 12-18 months of treatment) with single nucleotide variants reported to affect the metabolism of imatinib

GENE	CHR	POS	ID	A1	AX	BETA	SE	P	REFERENCE
PTPN22	1	114377568	rs2476601	A	G	0,0983178	0,752287	0,899696	Guillem et al. 2012 [REF. 29]
FASLG	1	172627498	rs763110	T	C	-0,438242	0,387861	0,295746	Zheng et al. 2016 [REF. 30]
cBIM	2	111907691	rs724710	T	C	0,872026	0,334054	0,0348914	Augis et al. 2013 [REF. 31]
XPC	3	14187449	rs2228001	G	T	-0,814256	0,331448	0,0436784	Lakkireddy et al., 2021 [REF. 32]
XPC	3	14199887	rs2228000	A	G	1,10059	0,83897	0,230957	Lakkireddy et al., 2021 [REF. 32]
VEGFR2	4	55972974	rs1870377	A	T	0,108349	0,278736	0,723432	Kim et al., 2010 [REF. 33]
ABCG2	4	89030841	rs12505410	G	T	-0,899621	0,257196	0,0173253	Delord et al., 2013 [REF. 35]
ABCG2	4	89052323	rs2231142	T	G	1,52939	0,514763	0,0207768	Kim et al., 2009 [REF. 34]
ABCG2	4	89061114	rs2231137	T	C	-1,39041	1,0794	0,238642	Kim et al., 2009 [REF. 34]
ABCG2	4	89061910	rs2725252	C	A	-0,765216	0,365662	0,0746734	Delord et al., 2013 [REF. 35]
SLC22A4	5	131629772	rs460089	C	G	0,885938	0,440938	0,0844641	Jaruskova et al., 2017 [REF. 36]
OCTN1	5	131676320	rs1050152	T	C	-0,531585	0,50014	0,323126	Angelini et al., 2013 [REF. 37]
SLC22A5	5	131703578	rs2631372	C	G	0,885938	0,440938	0,0844641	Angelini et al., 2013 [REF. 37]
SLC22A5	5	131705458	rs2631367	C	G	-1,20188	0,588181	0,0803114	Angelini et al., 2013 [REF. 37]
SLC22A4	5	131705949	rs2631365	C	T	0,849799	0,493186	0,128539	Jaruskova et al., 2017 [REF. 36]
VEGFA	6	43736389	rs699947	C	A	0,538488	0,642388	0,434002	Kim et al., 2010 [REF. 33]
SLC22A1	6	160543148	rs12208357	T	C	-0,594187	0,892938	0,527086	Takahashi et al., 2010 [REF. 38]
hOCT2	6	160551204	rs683369	G	C	-0,900789	0,591887	0,178859	Angelini et al., 2013 [REF. 37]
SLC22A1	6	160560845	rs628031	A	G	-0,451191	0,337766	0,223406	Takahashi et al., 2010 [REF. 38]
ABCB1	7	87179601	rs1128503	A	G	-0,0367382	0,341383	0,91732	Dulucq et al., 2008 [REF. 39]
CYP3A5*3	7	99270539	rs776746	T	C	-0,402963	0,755733	0,610393	de Lima et al., 2015 [REF. 40]
FAS	10	90749256	rs2234767	A	G	-0,0997043	0,771816	0,900848	Zheng et al. 2016 [REF. 30]
FAS	10	90749963	rs1800682	G	A	0,988291	0,302777	0,0137864	Zheng et al. 2016 [REF. 30]
FAS	10	90771829	rs2234978	T	C	0,34199	0,579172	0,573429	Zheng et al. 2016 [REF. 30]
CYP2C8 *3	10	96827030	rs11572080	T	C	-0,611091	0,698262	0,415142	Barratt et al., 2017 [REF. 41]
ABCC2	10	101542578	rs717620	T	C	-0,948541	0,502586	0,101072	Au et al., 2014 [REF. 42]
ABCC2	10	101563815	rs2273697	A	G	-0,576777	0,557407	0,335204	Au et al., 2014 [REF. 42]
ABCC2	10	101604207	rs3740066	T	C	-0,019681	0,542018	0,972048	Au et al., 2014 [REF. 42]
SLCO1B3	12	21015760	rs7311358	G	A	-0,259053	0,425014	0,561436	de Lima et al., 2015 [REF. 40]
SLCO1A2	12	21488748	rs4148977	T	C	-0,256069	0,679524	0,717459	Yamakawa et al., 2011 [REF. 43]
IFNG	12	68555011	rs2069705	G	A	0,915962	0,494995	0,106697	Kim et al., 2010 [REF. 33]
ABCA3	16	2328650	rs150929	T	G	-1,85582	0,36339	0,0069488	de Lima et al., 2015 [REF. 40]
CYP2B6	19	41512841	rs3745274	T	G	0,211672	0,638535	0,749973	Kassogue et al., 2013 [REF. 44]
ERCC1	19	45923653	rs11615	G	A	1,05333	0,49271	0,0698584	Kong et al., 2012 [REF. 45]

Supplemental Figure 1

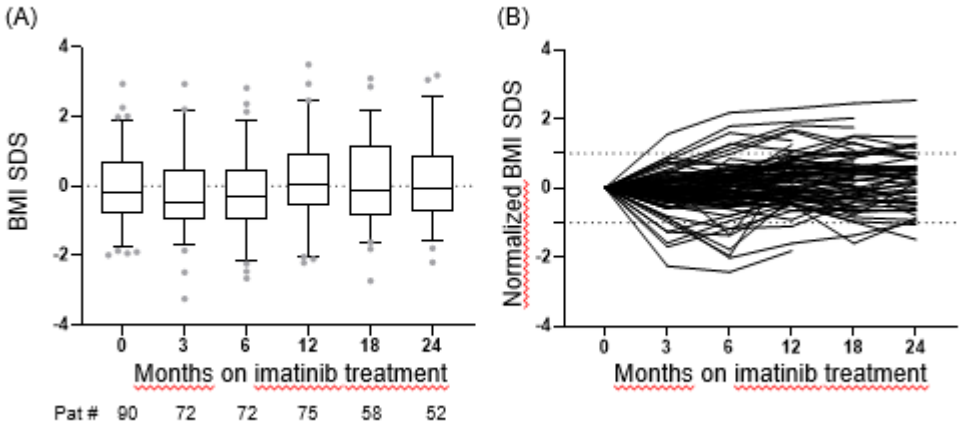
Plot of height standard deviation score (SDS) over time of imatinib therapy for the overall cohort and the cohort of European patients.



(A) presents data for the whole study cohort and (B) depicts results after exclusion of non-European patients. No significant difference was observed between the cohorts.

Supplemental Figure 2

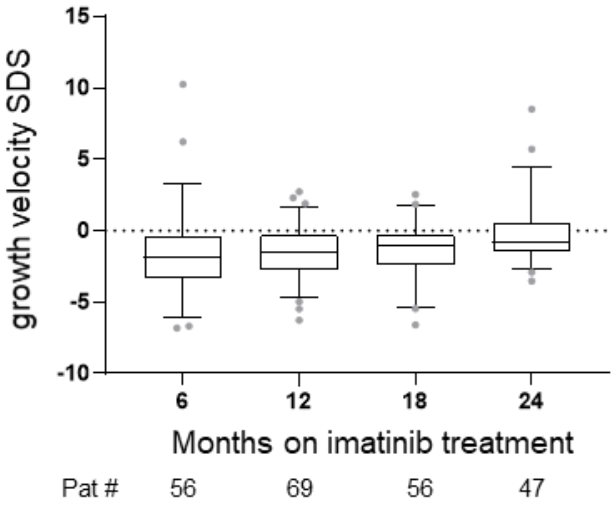
BMI standard deviation score (SDS) over time on imatinib treatment.



(A) The box-and-whisker plot shows the median, first, and third quartiles; whiskers extend to the 95th and 5th percentile. (B) Shows the individual courses of normalized BMI SDS (Δ BMI SDS).

Supplemental Figure 3

Plot growth velocity standard deviation score (SDS) over time on imatinib treatment.



The box-and-whisker plot shows the median, first, and third quartiles; whiskers extend to the 95th and 5th percentile.