Patient-Reported Symptom Monitoring and Adherence to Therapy in Newly Diagnosed Patients with Chronic Myeloid Leukemia

Symptom Monitoring in patients with CML

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The data underlying this article are available upon reasonable request to the corresponding author**.**

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The protocol was approved by the ethical committees of all participating centers and was conducted in accordance with the Declaration of Helsinki.

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Precise for use in the Table of Contents:

Optimal adherence to TKI therapy in CML is critical to attain and maintain an optimal clinical response.

Our findings suggest that systematic monitoring of patient-reported symptoms is associated with high adherence rates.

ABSTRACT

Introduction

We assessed the clinical utility of patient-reported symptom monitoring in the setting of newly diagnosed chronic myeloid leukemia (CML). Our primary objective was to evaluate adherence to therapy.

Methods and Materials

We did an international prospective study including patients with newly diagnosed chronic phase (CP)-CML. Before clinical consultation, patients were provided a tablet computer to self-rate their symptoms and results were available, in real time, to physicians' during the visit. Adherence was assessed via pill count and with a validated self-reported questionnaire. The proportion of optimal responders at 3 and at 6 months was assessed according to the European LeukemiaNet criteria.

Results

Between July 2020 and August 2021, 94 patients with a median age of 57 years were enrolled. Pill count adherence analysis showed that 86/93 (92.5%) of evaluable patients took at least 90% of prescribed TKI therapy during the 6-month observation period. The online platform was well accepted by patients and physicians. Optimal response was achieved by 69 of 79 (87.3%) of patients at 3 months, and 61 of 81 (75.3%) at 6 months.

Conclusions

Patient-reported symptom monitoring from the beginning of therapy in patients with CML may be critical to improve adherence to therapy, and early molecular response rates.

Key Words: chronic myeloid leukemia; quality of life; symptoms; adherence; molecular response; digital health.

INTRODUCTION

Chronic myeloid leukemia (CML) is a hematopoietic disorder characterized by the malignant expansion of bone marrow stem cells, with the presence of a reciprocal translocation between chromosomes 9 and 22 resulting in the fusion gene, BCR::ABL1 a constitutively activated tyrosine kinase[1]. This knowledge led the development of orally active small molecule tyrosine kinase inhibitors (TKIs) that inhibit BCR::ABL1 kinase activity, which have revolutionized CML therapy and notably improved survival[2]. Life expectancy of patients with chronic phase (CP)-CML now approaches that of their peers in the general population and the number of patients living with this disease is rising considerably with a peak prevalence projected to be reached around the year 2050[3].

Therapy with TKIs is generally lifelong for most patients, and a key challenge is that of ensuring that they adhere to the prescribed treatment schedule. There is convincing evidence that full adherence to therapy is critical to attain and maintain an optimal response[4, 5]. Regardless of type of front-line TKI used, patients who achieve optimal responses during the early phases of therapy are more likely to obtain better long-term survival outcomes[6].

However, patients with CML are frequently non-adherent to therapy[7, 8], with adverse events (AEs) likely to be the most frequent reason for intentional non-adherence to TKIs[9]. Low adherence rates are more frequent in patients with AEs[4] and patients reporting intentional non-adherence reasons have a higher symptom severity compared to those reporting unintentional reasons for non-adherence[10]. Although AEs associated with TKI therapy are typically of low to mild intensity, they can be particularly problematic over time and are often underestimated in their impact by treating physicians in CML routine care[11].

Based on previous evidence on the beneficial effects of routinely collecting and integrating symptomatic patient-reported AEs in clinical practice[12, 13], we performed an international pilot trial to assess the clinical utility of an online monitoring system for patient-reported symptoms in the setting of newly diagnosed CML. We hypothesized this approach could positively influence

adherence to therapy by raising physician's awareness of symptom burden of their patients and might improve clinical outcomes.

Our primary objective was to evaluate adherence to therapy and secondary objectives were to assess feasibility, health-related quality of life (HRQoL), patient and physician acceptability, and molecular response.

PATIENTS AND METHODS

Study Design and Patient Population

This was an international pilot trial conducted across USA and Italy and patients were followed for 6 months. Main inclusion criteria were: diagnosis of Philadelphia chromosome positive and/or BCR::ABL1 positive CML confirmed by cytogenetic and/or molecular analysis; Adult (≥18 years) newly diagnosed patients with CP-CML planned to receive first line imatinib, dasatinib, nilotinib, or bosutinib, within 4 weeks of initiating therapy; ability to read/converse in the language of the respective countries. Patients were excluded if they had major cognitive deficits or psychiatric problems hampering a self-reported evaluation. Having received any CML treatment, other than TKI, for more than 3 months prior to receiving current TKI therapy was also an exclusion criterion. The protocol was approved by the ethical committees of all participating centers and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. This study is registered at www.clinicaltrials.gov as #NCT04384848.

Web-based Platform development and Study Procedures

We developed a web-based platform allowing for the reporting of key symptomatic AEs associated with TKI therapy in CML, in collaboration with the Evaluation Software Development (ESD) Company, which has long-standing experience in electronic patient-reported outcomes (PROs) administration and patient-focused eHealth solutions (https://ches.pro/)[14]. A screenshot of the English version homepage of the patient portal of the platform (EMPATHY, Evaluating Patient-Reported Outcomes Monitoring in Routine Care of Patients with Chronic Myeloid Leukemia for Increasing Adherence and Clinical Response to THerapY) is reported in Appendix A. Based on clinical relevance for patients with CML, a set of key symptom items mainly drawn by the PRO-CTCAE Item Library[15], was loaded into the platform (details reported in Appendix B).

A clinical research staff (CRS) member was appointed to undergo a start-up training session before initiation of enrolment to learn how to use the platform and approach patients in the clinic at the time of study visit. All participating sites were assessed for wireless internet connectivity in waiting areas and also wireless tablet computers were provided to sites. At the time of a clinical visit, and just before the consultation with their physician, patients were provided a tablet computer and were instructed on how to login the portal and complete self-reported symptoms via touchscreen. Results were displayed graphically and available, in real time, to physicians' personal computer (PC) during the clinical consultation. A sample of the graphical display available to physician is reported in Appendix C. Treating physicians were trained to use the platform and interpret graphical display of patient-ratings.

In any case, patients could also access the platform and complete the online symptom list anytime during the study period (also outside the clinic) and this information was recorded.

Primary Outcome Measure

Based on previous recommendations[16] and empirical evidence indicating that pill count is associated with clinical response to TKI therapy in CML[7], we evaluated pill count adherence (PCA) as the primary outcome (details in the statistical paragraph). Pill count adherence was assessed from baseline to 6 months, averaged for each patient over the number of pill-count assessments, to assess the overall adherence rate (AR). We defined the intervention achieving an optimal adherence if at least 82% of patients took at least 90% of the prescribed drug over 6 months[4]. We also assessed self-reported adherence by asking patients to complete the validated Adherence to Refills and Medications Scale (ARMS)-7[17] at 3 and 6 months. The ARMS-7 is the short version of the ARMS-12 and it consists of seven items evaluating adherence to taking medications and refilling prescriptions. Items are rated on a four-point Likert scale with a total ranging between 7 and 28, with higher scores indicating lower medication adherence. The newly developed NIH Patient-

Reported Outcomes Measurement Information System (PROMIS) Medication Adherence Scale (PMAS)[18] was also included in the protocol as an additional exploratory measure to be completed at 3 and 6 months.

Secondary Outcome Measures

The following secondary outcomes were evaluated at baseline and at 3 and at 6 months via paper validated questionnaires. *Health-related quality of life* was assessed with the Functional Assessment of Cancer Therapy-General (FACT-G) (version 4)[19] and *fatigue* was assessed with the FACIT-Fatigue[20].

The following secondary outcomes were evaluated at 3 and at 6 months. *Satisfaction with care/information and social life* were evaluated with the two respective validated scales of the EORTC QLQ-CML24 questionnaire[21]. *Feasibility* was considered, for the purpose of this study, to be demonstrated if 80% of participants completed online questionnaires on more than 60% of follow-up clinical visits including the total number of visits across the 6-months of follow up. This criterion was based on previous studies using similar interventions[22]. *Patients and Physicians acceptability and clinical utility*: Ad hoc questionnaires were administered to patients and to physicians including 10 and 13 items, respectively. Items were adapted from available sources, with guidance provided by those that have been used successfully in similar research to assess patient acceptability and satisfaction[22]. *Molecular response:* we calculated the proportion of "optimal responders" according to the most recent European LeukemiaNet (ELN) criteria at 3 and at 6 months, defined as BCR::ABL1 of ≤10% on the International Scale (IS) and BCR::ABL1 of ≤1% on the IS scale, respectively[23]. This assessment was performed in all laboratories by Real-Time Quantitative (RQ)-PCR.

Statistical methods

Based on previous works, [4, 8] we defined 72% as a minimum threshold of AR (H0). On this ground, we calculated that 94 patients were required so as to detect at least 85% of AR (H1), with power of 80% and 2.5% type I error probability (one-sided exact test for binomial proportions). We used proportions, means, medians and ranges to describe patients' characteristics, depending on the type of variable. For each patient, we assessed the PCA defined as the following proportion: 100×(number of pills delivered at pill count assessment Tj – number of pills returned at pill count assessment Tj+1), divided by number of pills delivered at Tj[24]. Then, each patient's overall adherence was calculated as the average proportion over the corresponding number of pill-count assessments, from baseline to 6 months. We used proportions to assess the intervention feasibility. For descriptive purposes, we reported mean, median, standard deviation and range of the observed baseline scores from the FACIT- Fatigue and FACT-G questionnaires, which were scored per guidelines. We also estimated the trajectories over time of these scores using a linear mixed model for repeated measures, assessing possible changes from baseline by an overall F-test testing the null hypothesis of no difference. For descriptive purposes, we also assessed trajectories over time from FACIT-Fatigue and FACT-G questionnaires by first generation TKI (i.e. imatinib) vs second generation TKIs (i.e. nilotinib, dasatinib, and bosutinib), adjusting for age (coded as <60 years vs ≥ 60years), sex and TKI switch within 6 months[25]. For these analyses, we used an overall F test testing the null hypothesis of no difference between TKI generation groups over time. At the same time points, we assessed the outcomes from both the patients' and physicians' acceptability and satisfaction questionnaire, calculating the proportions of item responses. The threshold for statistical significance was set as α=0.05 for all analyses, with no adjustment for multiple comparisons. Analyses were performed using SAS statistical software, version 9.4.

RESULTS

Between July 2020 and August 2021, 94 newly diagnosed patients with CML were enrolled across 2 centers in the US (enrolling 16 patients) and 13 centers in Italy (enrolling 78 patients). A flowchart of patients analyzed over the 6-month period is reported in Appendix D. For one patient the TKI received was not available and one patient died before the HRQoL assessment at 3 months for causes unrelated to the disease. Median age of patients was 57 years (range, 19-82 years) and 55% were male. Sokal-risk was low in 42% of patients and 34% had at least one comorbidity. There were 43% of patients treated with imatinib and 31%, 24% and 2%, treated with nilotinib, dasatinib and bosutinib, respectively. Six patients included in the HRQoL analysis switched TKI during the study period (3 for laboratory abnormalities, 2 for resistance, 1 for symptomatic adverse event). Patients' characteristics are reported in Table 1.

Insert Table 1

Adherence to therapy

Pill count adherence analysis showed that 86 patients (92.5%) took at least 90% of prescribed TKI therapy during the observation period, indicating an optimal adherence. Mean, median and range of PCA% in our study were 97.9%, 100% and 64.8% to 100%, respectively.

Mean scores by the self-reported ARMS-7 questionnaires indicated high levels of adherence, irrespective of TKIs, being closer to 7 points both at 3 and at 6 months. No differences were observed in the level of self-reported adherence by type of TKI at 3 (P=0.653) and at 6 months (P=0.639) (Table 2). Results from the PMAS corroborated findings from the ARMS-7 questionnaire by indicating high-levels of self-reported adherence (data not shown).

Insert Table 2

Health-related quality of life and fatigue over time

Patient compliance with HRQoL assessment at baseline and at 3 and 6 months was 99% (N=93/94), 93% (N=85/91) and 93% (N=84/90). None of the mean scores on FACT-G or FACIT-F changed significantly over time, suggesting HRQoL was well-maintained on treatment. (Table 3). Further analysis examining HRQoL and fatigue outcomes separately by type of TKI (ie., first *versus* second generation TKI) and adjusted by age and sex, were similar, with no statistically significant differences over time (Appendix E).

Insert Table 3

Satisfaction with care/information and social life

At 3 months, mean score of satisfaction with care and social life EORTC QLQ-CML 24 scales were high being 85.7 (SD, 18.0) and 75.4 (SD, 24.9), respectively. At 6 months, similar scores were observed being 87.5 (SD, 19.0), and 73.1 (SD, 24.7), respectively.

Feasibility of the monitoring system just before the clinical visit in the clinic

Overall, 576 clinical visits were performed by patients during the study. In 446 (77.4%) of them, patients completed the online symptom list before the clinical encounter. However, we found that

68.5% (N=63 out of 92 of evaluable patients) completed the symptom list on more than 60% of follow-up visits (across the 6-month observation period) via tablet in the clinic, thereby indicating that our prespecified threshold for considering the approach feasible (i.e., 80%) was not met. No statistically significant difference was observed between countries (data not shown). The symptom list was completed overall 950 times, and 60.2% of patients completed it at least once outside the clinic during the study period.

Patients' and physicians' acceptability of the use of the online platform

At 3 months, all patients found it easy to enter information on their symptoms into the platform, and 94% (73/78) agreed or strongly agreed that it was a helpful tool to improve communication with their treating physician. Similar high percentages indicating good acceptance of the platform were observed at 6 months. (Table 4).

At 3 months all physicians (N=21) agreed the platform was easy to use and reported that they have used, at least once, information obtained via platform for the management of their patients (Table 5). Similar high percentages indicating a positive acceptance were reported at 6 months.

Insert Tables 4 and 5

Molecular response to tyrosine kinase inhibitors therapy at 3 and at 6 months

There were 87.3% (N=69/79) and 75.3% (N=61/81) of evaluated patients who achieved an optimal response according to the ELN 2020 criteria[23] at 3 and at 6 months, respectively. Albeit not statistically significant, higher percentages of optimal responders were observed for patients treated

with second generation TKI versus those receiving imatinib at 3 and at 6 months. For example, at 3 months, there were 93% and 80% of optimal responders between those treated with second generation TKI and imatinib, respectively. The proportion of patients, overall and by type of TKI, achieving an optimal response at 3 and at 6 months, is reported in Table 6.

Insert Table 6

DISCUSSION

We prospectively investigated the clinical utility of symptom monitoring for improving adherence in newly diagnosed patients with CML from the beginning of therapy. This research setting was considered of special value to rule out the influence of several potential confounders associated with previous treatment or clinical response history. The few previous adherence-enhancing intervention studies conducted in patients with CML have included patients who were already on TKI therapy[26] or were mainly based on retrospective registry data and not patient-focused[27].

The primary outcome measure on adherence to therapy was met as 92.5% of our patients took at least 90% of prescribed TKI during the study period. A direct comparison with other CML studies is difficult due to the heterogeneity of methods to assess adherence to therapy and type of patients included, who were often in TKI therapy for several months or years. Previous qualitative research studies showed that patients with CML tend to report an increase in intentional non-adherence behavior over time[28]. Therefore, we speculate that the effectiveness of our intervention was further maximized as implemented very early in the course of the disease, at the time patients initiated their therapy.

Another finding, which may reflect the observed high adherence rate, was the large percentage of patients considered as optimal responders at 3 (87.3%) and at 6 months (75.3%) according to standard international criteria[23]. In a recent real-world study, Wang and colleagues[29] reported that 69.1% and 64.6% of patients receiving imatinib or nilotinib could be considered as optimal responders at 3 and 6 months, respectively. The percentage of optimal responders observed in our study was similar to that observed in pivotal randomized controlled trials (RCT), where high rates of clinical responses can be expected due to the well-controlled research setting. For example,

at 3 months, 93.2% of our patients treated with second generation TKIs could be considered as optimal responders, while the following percentages were observed in the BFORE[30], DASISION[31]and ENESTnd[32] pivotal RCTs: 72%, 84% and 91%, respectively. Likewise, the percentage of optimal responders at 3 months in those receiving imatinib in our study (80%) was higher than those found in the imatinib treated group of patients enrolled in these pivotal RCTs, which ranged from 57.3% [30] to 67%[32].

This finding may have major implications as, irrespective of front line TKI used, patients who achieve optimal responses at 3 months (early molecular response-EMR) have significantly better long-term outcomes, including event-free survival and overall survival compared to non-optimal responders[6]. Furthermore, EMR is a known predictor of a stable deep molecular response[33], which is a pre-requisite to safely stop treatment (i.e., treatment free remission)[23], hence with key potential benefits on patients wellbeing[34,35] as well as on reduction of financial burden to patients and healthcare systems, due to the high costs of TKIs.[36]

Our web-based platform was also well accepted by patients and physicians. For example, at the end of the observation period, all physicians found it easy to use and would recommend it to other colleagues. Also, 90% of them agreed that this approach improved the quality of communication with their patients. Similarly, 86% of patients also stated the platform helps them to improve communication with their physicians.

Our study has some limitations. Our predefined criterion of feasibility was not met. However, we note that the enrollment of our patients took place during the COVID-19 pandemic, which overwhelmed hospital care during the study period. This may have negatively impacted on this specific aspect of the study in many ways, for example, due to the shortage of personnel (e.g., research nurses) who could approach patients in the clinic to hand over the tablet just before the consultation. This may have also negatively impacted on the number of samples obtained to detect the molecular responses in order to evaluate the optimal responders Also, a longer follow-up period

of observation could have provided additional insights and, we note that, our findings will have to be further confirmed in a RCT with a control group following standard monitoring.

Our study also has key strengths. To the best of our knowledge, this is the first international study examining the value of symptom monitoring to improve adherence to therapy in patients with CML from the initiation of TKI therapy, thereby allowing examinations of relationship between the intervention and early molecular response milestones. This aspect has important implications for long-term survival outcomes as well as for the possibility to eventually offer patients the opportunity to enter into a treatment-free remission phase. Also, the multicenter and international nature of this study lends further credit to generalizability of our findings as our population most likely reflect patients with CML typically seen in real-life.

In conclusion, patient-reported symptom monitoring from the beginning of TKI therapy in patients with CML may be critical to improve adherence to therapy, and early molecular response rates. Current findings lay the groundwork for performing a large-scale comparative study to assess the value of this approach in improving long-term clinical and survival outcomes.

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Table 1.

Socio-demographics and clinical characteristics by type of initial TKI (N=93)

	Imatinib*	Second generation TKI **	Total n (%)
Gender			
Male	20 (50)	31 (58.49)	51 (54.84)
Female	20 (50)	22 (41.51)	42 (45.16)
Age at study entry, years			
Median (range)	68.58 (35.17 - 81.92)	50.67 (19.00 - 73.42)	56.92 (19.00 - 81.92)
Country			
Italy	36 (90)	42 (79.25)	78 (83.87)
USA	4 (10)	11 (20.75)	15 (16.13)
Living arrangements			
Living alone	7 (18.42)	5 (10.64)	12 (14.12)
Living with spouse/partner only	29 (76.32)	35 (74.47)	64 (75.29)
Living with another relative	2 (5.26)	7 (14.89)	9 (10.59)
Missing	2 (.)	6 (.)	8 (.)
ECOG Performance status			
0	31 (77.5)	44 (83.02)	75 (80.65)
1	8 (20)	9 (16.98)	17 (18.28)
2	1 (2.5)	0 (0)	1 (1.08)
Sokal risk score			
Low (< 0.8)	14 (35)	25 (47.17)	39 (41.94)
Intermediate (0.8-1.2)	21 (52.5)	16 (30.19)	37 (39.78)
High (> 1.2)	5 (12.5)	12 (22.64)	17 (18.28)
Comorbidity			
0	19 (47.5)	42 (79.25)	61 (65.59)
≥1	21 (52.5)	11 (20.75)	32 (34.41)
Polipharmacy †			
0	7 (17.5)	17 (32.08)	24 (25.81)
1	6 (15)	11 (20.75)	17 (18.28)
2	3 (7.5)	13 (24.53)	16 (17.2)
>2	24 (60)	12 (22.64)	36 (38.71)
Access to pc, smartphone or tablet			
No	7 (18.42)	0 (0)	7 (8.24)
Yes	31 (81.58)	47 (100)	78 (91.76)
Missing	2 (.)	6 (.)	8 (.)
How frequently are you online			
Regularly	21 (55.26)	41 (87.23)	62 (72.94)
Occasionally	9 (23.68)	3 (6.38)	12 (14.12)
Rarely	2 (5.26)	3 (6.38)	5 (5.88)
Never	6 (15.79)	0 (0)	6 (7.06)
Missing	2 (.)	6 (.)	8 (.)

Abbreviation: TKI: Tyrosine kinase Inhibitor.

* Two patients received a lower imatinib dose (300 mg daily). All other patients received standard imatinib dose.

**This category included patients treated with nilotinib (n=29), dasatinib (n=22) and bosutinib (n=2). One patient received a higher dose (140 mg daily) of dasatinib. All other patients received standard TKI doses.

† Number of concomitant drugs, independent of CML disease (e.g. for other health problems)

Table 2.

Self-reported adherence at three and six months according to the ARMS-7 by type of initial TKI

	Imatinib	Second generation TKI *	Total	P
Three months				
Mean (SD)	7.84 (1.69)	7.63 (1.00)	7.72 (1.35)	0.653
Median	7	7	7	
Range	7.00 - 15.00	7.00 - 11.00	7.00 - 15.00	
n	37	46	83	
missing	2	5	7	
Six months				
Mean (SD)	7.76 (1.13)	7.84 (1.46)	7.81 (1.31)	0.753
Median	7	7	7	
Range	7.00 - 11.00	7.00 - 13.00	7.00 - 13.00	
n	38	45	83	
missing	1	5	6	

Abbreviations: SD, standard deviation

*This category included patients treated with nilotinib (n=29), dasatinib (n=22) and bosutinib (n=2).

Table 3.

Longitudinal Analysis of Health-Related Quality of Life and Fatigue Over Time

	Baseline (N=93)		Three months (N=85)		Six months (N=84)	
	Mean	95% C.I.	Mean	95% C.I.	Mean	95% C.I.
Health-Related Quality of Life						
			FACT-G Scales			
PWB	24.0	(23.0; 24.9)	23.4	(22.4; 24.5)	24.2	(23.3; 25.0)
SWB	21.9	(20.8; 23.0)	21.6	(20.4; 22.7)	21.4	(20.3; 22.4)
EWB	17.7	(16.7; 18.7)	18.6	(17.7; 19.4)	18.6	(17.7; 19.5)
FWB	17.2	(16.0; 18.4)	17.5	(16.2; 18.8)	17.1	(15.9; 18.3)
Total score	81.0	(77.9; 84.2)	81.0	(77.7; 84.2)	81.4	(78.4; 84.3)
Fatigue						
			FACIT-Fatigue			
	41.2	(39.1; 43.3)	41.1	(39.1; 43.1)	41.9	(40.0; 43.8)

Abbreviations: PWB: Physical Well-Being; SWB: Social/Family Well-Being; EWB: Emotional Well-Being; FWB: Functional Well-Being.

Legend: for each score, mean trajectories over time were estimated by a linear mixed model for repeated measures.

Table 4.

Patient acceptability and satisfaction questionnaire at three and six months

	Category	Three months (N=91) n (%)	Six months (N=90) n (%)
I found the EMPATHY platform easy to use	Strongly Agree	56 (71.79)	51 (62.2)
	Agree	21 (26.92)	25 (30.49)
	Disagree	1 (1.28)	3 (3.66)
	Strongly Disagree	0 (0)	3 (3.66)
	Missing	13 (.)	8 (.)
I found the EMPATHY platform to be useful	Strongly Agree	45 (57.69)	41 (50)
	Agree	32 (41.03)	34 (41.46)
	Disagree	1 (1.28)	4 (4.88)
	Strongly Disagree	0 (0)	3 (3.66)
	Missing	13 (.)	8 (.)
I found the questions in the EMPATHY platform easy to understand	Strongly Agree	51 (64.56)	51 (62.2)
	Agree	28 (35.44)	25 (30.49)
	Disagree	0 (0)	2 (2.44)
	Strongly Disagree	0 (0)	4 (4.88)
	Missing	12 (.)	8 (.)
I found it easy to enter my symptom information into the EMPATHY platform	Strongly Agree	50 (64.1)	52 (63.41)
	Agree	28 (35.9)	25 (30.49)
	Disagree	0 (0)	1 (1.22)
	Strongly Disagree	0 (0)	4 (4.88)
	Missing	13 (.)	8 (.)
I found it easy to login to the EMPATHY platform	Strongly Agree	46 (58.97)	48 (58.54)
	Agree	31 (39.74)	27 (32.93)
	Disagree	1 (1.28)	3 (3.66)
	Strongly Disagree	0 (0)	4 (4.88)
	Missing	13 (.)	8 (.)
Using the EMPATHY platform improved quality of communication with my physician	Strongly Agree	40 (51.28)	34 (41.46)
	Agree	33 (42.31)	37 (45.12)
	Disagree	5 (6.41)	6 (7.32)
	Strongly Disagree	0 (0)	5 (6.1)
	Missing	13 (.)	8 (.)
I think my physician used information from the EMPATHY platform for the management of my therapy	Strongly Agree	36 (46.15)	40 (48.78)
	Agree	36 (46.15)	33 (40.24)
	Disagree	5 (6.41)	3 (3.66)
	Strongly Disagree	1 (1.28)	6 (7.32)
	Missing	13 (.)	8 (.)

Continued Table 4.

Patient acceptability and satisfaction questionnaire at three and six months

	Category	Three months (N=91) n (%)	Six months (N=90) n (%)
I would recommend the EMPATHY platform to other patients.	Strongly Agree	46 (57.5)	44 (53.66)
	Agree	32 (40)	32 (39.02)
	Disagree	2 (2.5)	2 (2.44)
	Strongly Disagree	0 (0)	4 (4.88)
	Missing	11 (.)	8 (.)
I would like to continue using the EMPATHY platform in the future	Strongly Agree	42 (53.16)	41 (49.4)
	Agree	35 (44.3)	28 (33.73)
	Disagree	2 (2.53)	10 (12.05)
	Strongly Disagree	0 (0)	4 (4.82)
	Missing	12 (.)	7 (.)
Overall, I am satisfied with the EMPATHY platform	Strongly Agree	42 (51.85)	45 (54.22)
	Agree	38 (46.91)	31 (37.35)
	Disagree	1 (1.23)	3 (3.61)
	Strongly Disagree	0 (0)	4 (4.82)
	Missing	10 (.)	7 (.)

Table 5.

Physician acceptability and satisfaction questionnaire at three and six months (N=21)

	Category	Three months n (%)	Six months n (%)
I found the EMPATHY platform easy to use.	Strongly Agree	11 (52.38)	13 (65)
	Agree	10 (47.62)	7 (35)
	Missing	0 (.)	1 (.)
I found the EMPATHY platform to be useful.	Strongly Agree	9 (42.86)	9 (45)
	Agree	12 (57.14)	11 (55)
	Missing	0 (.)	1 (.)
I found the EMPATHY platform reports and graphs were easy to understand.	Strongly Agree	11 (55)	14 (70)
	Agree	9 (45)	5 (25)
	Disagree	0 (.)	1 (5)
	Missing	1 (.)	1 (.)
Using the EMPATHY platform eased my understanding of patients' symptoms.	Strongly Agree	5 (23.81)	9 (45)
	Agree	14 (66.67)	9 (45)
	Disagree	2 (9.52)	2 (10)
	Missing	0 (.)	1 (.)
Using the EMPATHY platform improved quality of communication with my patients.	Strongly Agree	5 (23.81)	7 (35)
	Agree	14 (66.67)	11 (55)
	Disagree	2 (9.52)	2 (10)
	Missing	0 (.)	1 (.)
I used (at least once) information from the EMPATHY platform for the management of my patients.	Strongly Agree	8 (38.1)	6 (30)
	Agree	13 (61.9)	14 (70)
	Missing	0 (.)	1 (.)
I would recommend the use of the EMPATHY platform to other colleagues.	Strongly Agree	8 (38.1)	8 (40)
	Agree	12 (57.14)	12 (60)
	Disagree	1 (4.76)	0 (0)
	Missing	0 (.)	1 (.)
I would consider using the EMPATHY platform in the future.	Strongly Agree	7 (33.33)	8 (40)
	Agree	14 (66.67)	12 (60)
	Missing	0 (.)	1 (.)
I feel the information collected by the EMPATHY platform was (overall) valuable towards accuracy of adverse events (i.e. symptoms) documentation	Strongly Agree	5 (23.81)	6 (30)
	Agree	15 (71.43)	12 (60)
	Disagree	1 (4.76)	2 (10)
	Missing	0 (.)	1 (.)

Continued Table 5.

Physician acceptability and satisfaction questionnaire at three and six months (N=21)

	Category	Three months n (%)	Six months n (%)
I feel the information collected by the EMPATHY platform was (overall) valuable towards improving shared decision making.	Strongly Agree	6 (28.57)	6 (30)
	Agree	14 (66.67)	13 (65)
	Disagree	1 (4.76)	1 (5)
	Missing	0 (.)	1 (.)
I feel the information collected by the EMPATHY platform was (overall) of help for management of TKI administration (e.g. change/reduction/interruption of TKI).	Strongly Agree	7 (33.33)	6 (30)
	Agree	11 (52.38)	13 (65)
	Disagree	3 (14.29)	1 (5)
	Missing	0 (.)	1 (.)
I feel the information collected by the EMPATHY platform was (overall) of help for suggesting supportive care strategies (e.g. diet recommendations).	Strongly Agree	8 (38.1)	7 (35)
	Agree	12 (57.14)	11 (55)
	Disagree	1 (4.76)	2 (10)
	Missing	0 (.)	1 (.)
I feel the information collected by the EMPATHY platform was (overall) of help for arranging unplanned/additional visits with my patients.	Strongly Agree	5 (23.81)	6 (30)
	Agree	15 (71.43)	11 (55)
	Disagree	1 (4.76)	3 (15)
	Missing	0 (.)	1 (.)

Table 6.

Molecular response according to the ELN criteria at three and six months by type of TKI

ELN response	Category	Imatinib	second generation TKI*	Total n (%)
Three months (n=79)				
Optimal	BCR::ABL1^{IS} ≤10%	28 (80)	41 (93.18)	69 (87.34)
Warning	BCR::ABL1^{IS} >10%	7 (20)	3 (6.82)	10 (12.66)
Six months (n=81)				
Optimal	BCR::ABL1^{IS} ≤1%	25 (65.79)	36 (83.72)	61 (75.31)
Warning	BCR::ABL1^{IS} >1-10%	8 (21.05)	5 (11.63)	13 (16.05)
Failure	BCR::ABL1^{IS} >10%	5 (13.16)	2 (4.65)	7 (8.64)

Abbreviations: ELN: European Leukemia Net; TKI: Tyrosine kinase Inhibitor; IS: International Scale.
Legend:

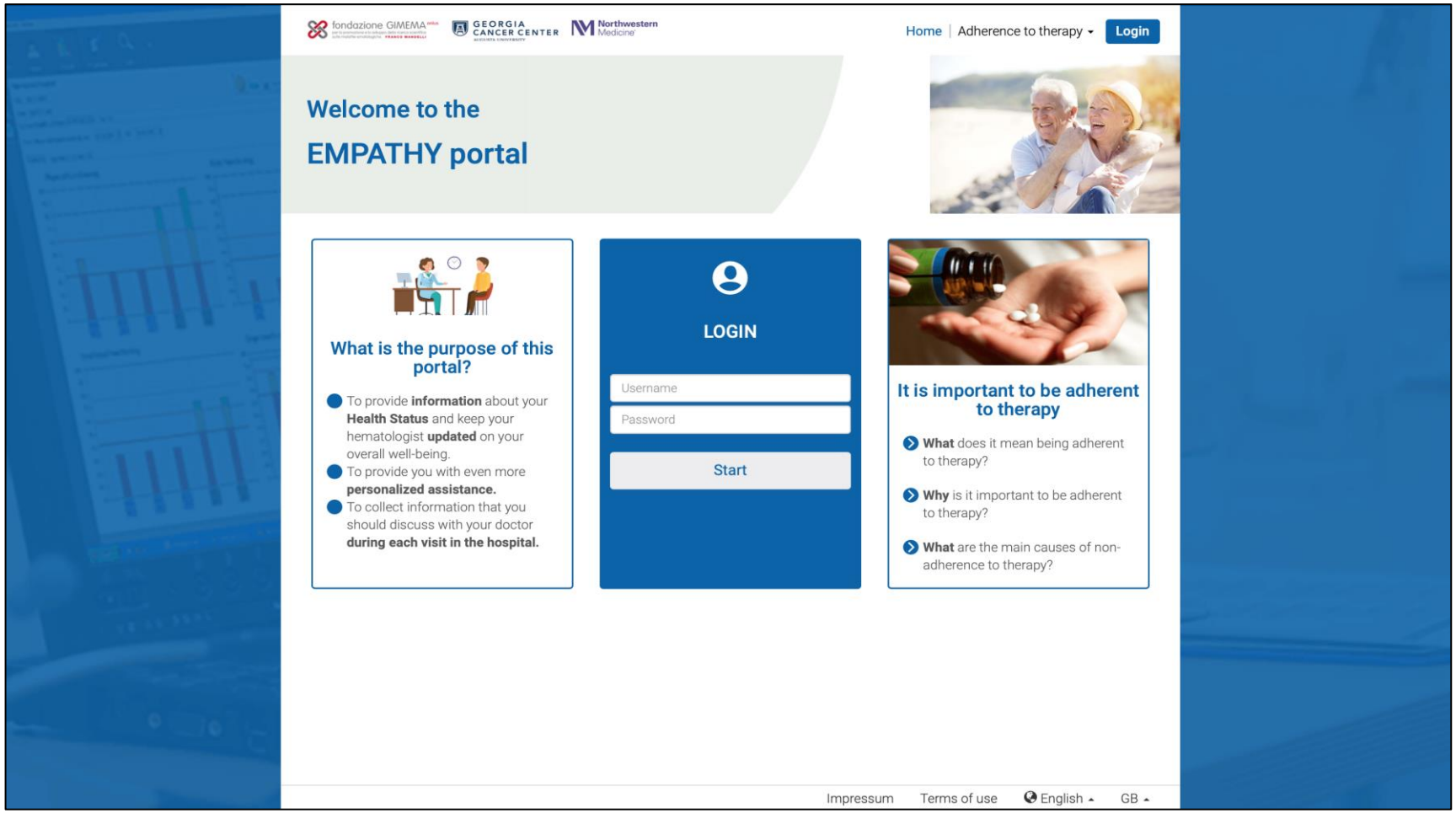
* This category included patients treated with nilotinib (n=29), dasatinib (n=22) and bosutinib (n=2).

Supplementary Material

Patient-Reported Symptom Monitoring and Adherence to Therapy in Newly Diagnosed Patients with Chronic Myeloid Leukemia

APPENDIX A

Patient Portal of the EMPATHY Platform (English version)



Abbreviations:

EMPATHY, acronym for: Evaluating Patient-Reported Outcomes Monitoring in Routine Care of Patients with Chronic Myeloid Leukemia for Increasing Adherence and Clinical Response to THerapY.

APPENDIX B

List of patient-reported symptoms loaded in the EMPATHY platform.

These next questions are about your perception of symptoms related to the therapy you are receiving.				
1. In the last 7 days, what was the severity of your fatigue, tiredness, or lack of energy at its worst?				
☐None	☐Mild	☐Moderate	☐Severe	☐Very severe
2. In the last 7 days, what was the severity of your aching joints (such as elbows, knees, shoulders) at their worst?				
☐None	☐Mild	☐Moderate	☐Severe	☐Very severe
3. In the last 7 days, what was the severity of your aching muscles at their worst?				
☐None	☐Mild	☐Moderate	☐Severe	☐Very severe
4. In the last 7 days, what was the severity of your muscle cramps at their worst?				
☐None	☐Mild	☐Moderate	☐Severe	☐Very severe
5. In the last 7 days, what was the severity of your pain in the abdomen (belly area) at its worst?				
☐None	☐Mild	☐Moderate	☐Severe	☐Very severe
6. In the last 7 days, how often did you have skin problems (e.g. rash, color changes, itchy, dry or flaking skin)?				
☐Never	☐Rarely	☐Occasionally	☐Frequently	☐Almost constantly
7. In the last 7 days, what was the severity of your headache at its worst?				
☐None	☐Mild	☐Moderate	☐Severe	☐Very severe
8. In the last 7 days, what was the severity of your swelling in certain parts of the body (e.g. ankles, legs or around your eyes) at its worst?				
☐None	☐Mild	☐Moderate	☐Severe	☐Very severe
9. In the last 7 days, what was the severity of your heartburn at its worst?				
☐None	☐Mild	☐Moderate	☐Severe	☐Very severe
10. In the last 7 days, what was the severity of your constipation at its worst?				
☐None	☐Mild	☐Moderate	☐Severe	☐Very severe

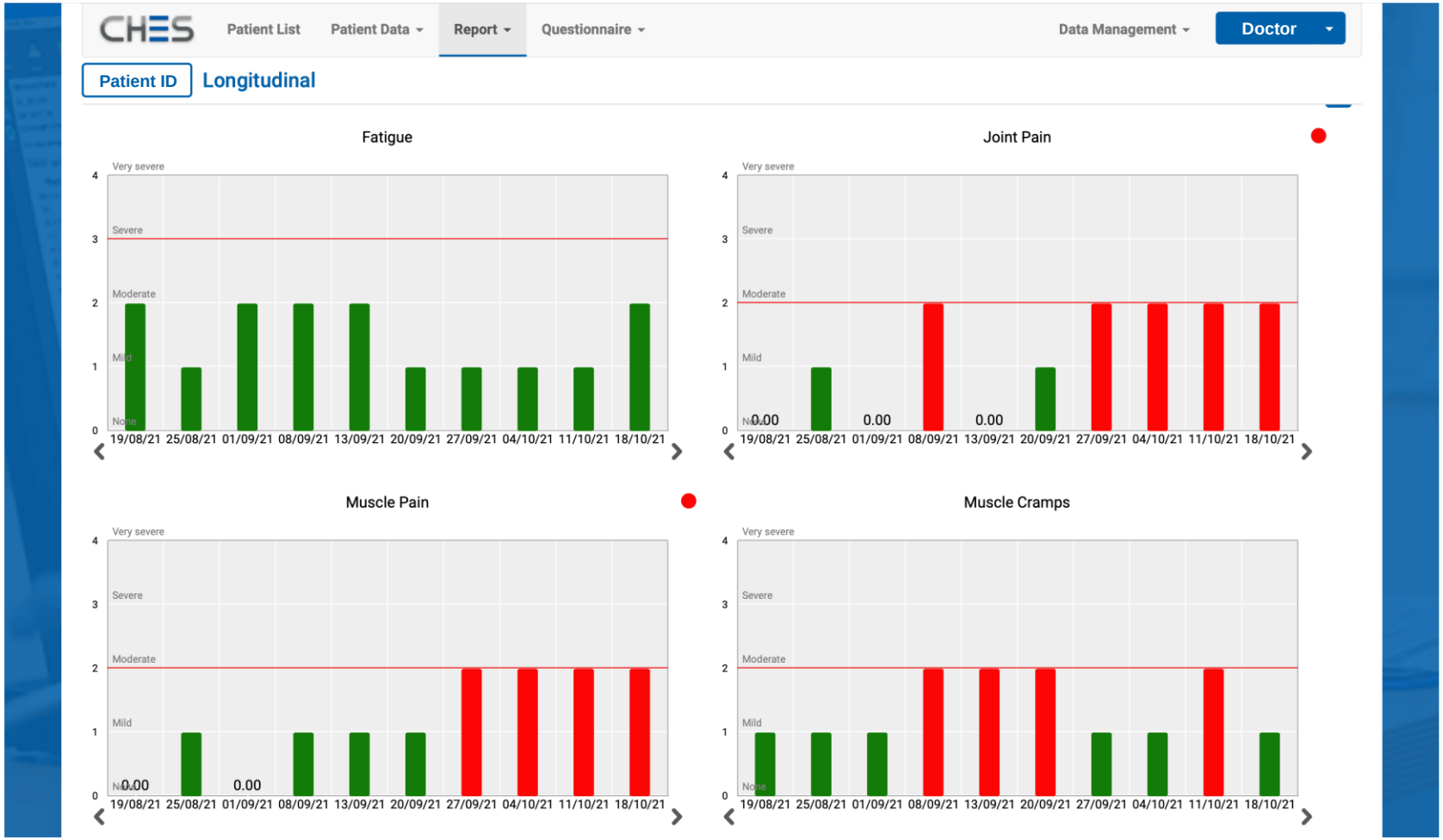
Continued Appendix B

11. In the last 7 days, how often did you have loose or watery stools (diarrhea/diarrhoea)? ☐Never ☐Rarely ☐Occasionally ☐Frequently ☐Almost constantly
12. In the last 7 days, what was the severity of your vomiting at its worst? ☐None ☐Mild ☐Moderate ☐Severe ☐Very severe
13. In the last 7 days, what was the severity of your nausea at its worst? ☐None ☐Mild ☐Moderate ☐Severe ☐Very severe
14. In the last 7 days, what was the severity of your unexpected or excessive sweating during the day or night-time (not related to hot flashes/flushes) at its worst? ☐None ☐Mild ☐Moderate ☐Severe ☐Very severe
15. In the last 7 days, what was the severity of your drowsiness at its worst? ☐None ☐Mild ☐Moderate ☐Severe ☐Very severe
16. In the last 7 days, were there times when you had to urinate frequently? ☐Never ☐Rarely ☐Occasionally ☐Frequently ☐Almost constantly
17. In the last 7 days, how often did you have problems with your eyes (e.g. burning, watery, irritated or dry)? ☐Never ☐Rarely ☐Occasionally ☐Frequently ☐Almost constantly
18. In the last 7 days, how often did you feel a pounding or racing heartbeat (palpitations)? ☐Never ☐Rarely ☐Occasionally ☐Frequently ☐Almost constantly
19. In the last 7 days, what was the severity of your shortness of breath at its worst? ☐None ☐Mild ☐Moderate ☐Severe ☐Very severe
20. In the last 7 days, how much did insomnia (including difficulty falling asleep, staying asleep, or waking up early) interfere with your usual or daily activities? ☐Not at all ☐A little bit ☐Somewhat ☐Quite a bit ☐Very much
21. In the last 7 days, what was the severity of your dry mouth at its worst? ☐None ☐Mild ☐Moderate ☐Severe ☐Very severe
22. In the last 7 days, how much did dizziness interfere with your usual or daily activities? ☐Not at all ☐A little bit ☐Somewhat ☐Quite a bit ☐Very much

The list included 22 symptom items, of which, 18 drawn by the PRO-CTCAE Item Library (Dueck AC et al. JAMA Oncol. 2015; 1: 1051-9) and four adapted from the EORTC QLQ-CML24 **(**Efficace F et al. Leuk Lymphoma. 2021;62:669-678). This latter four items were added as clinically relevant for patients with CML but not present in the PRO-CTCAE Item Library.

APPENDIX C

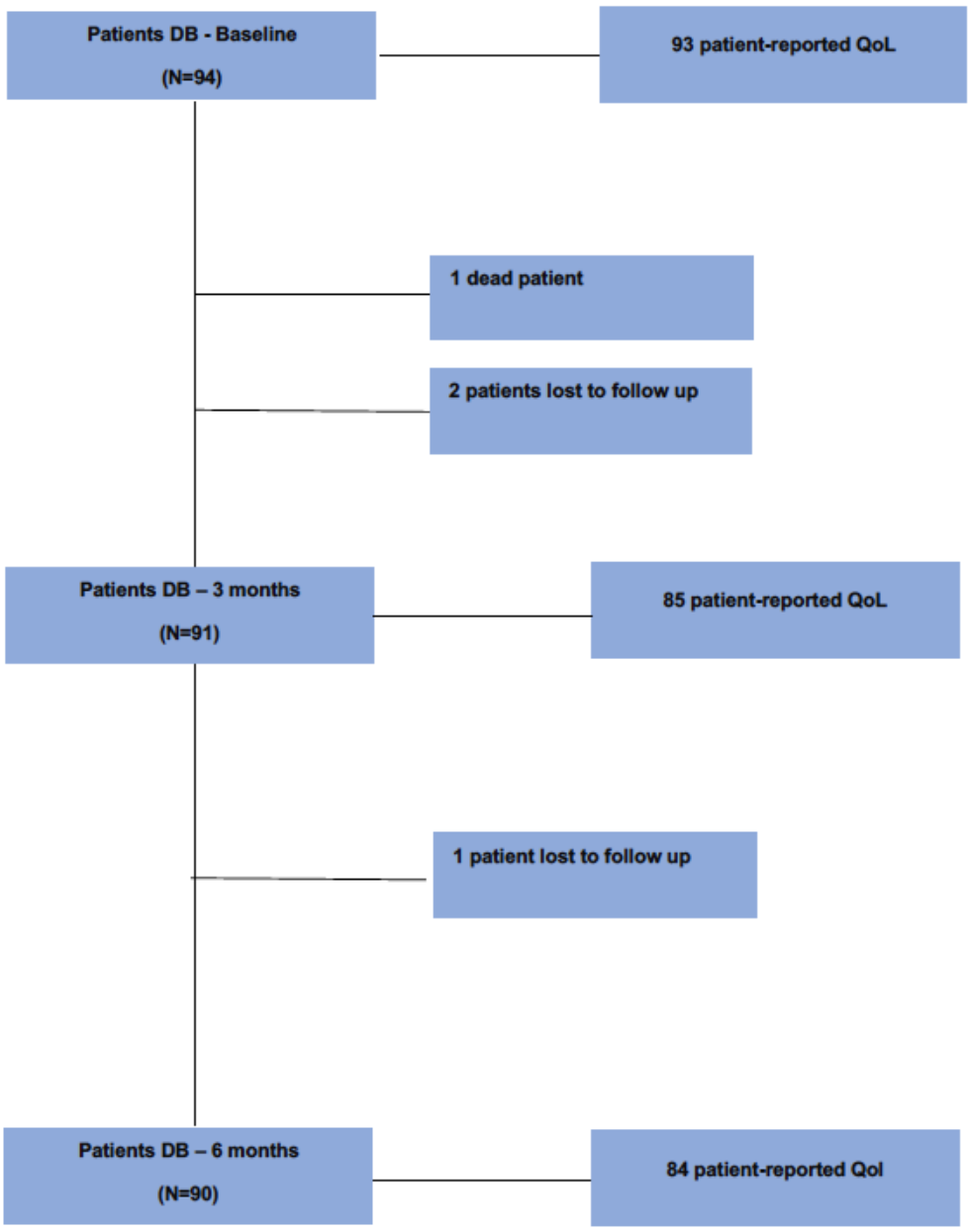
Example of a graphical display of how physicians could see symptom ratings of their patients



Legend: The red bars indicate a symptom reaching a predefined potentially clinically relevant threshold. For the purpose of this study, this threshold was set prior to study start based on clinical consensus for each symptom.

APPENDIX D

Flowchart of patients analyzed over the six-month period



APPENDIX E

Longitudinal analysis of health-related quality of life and fatigue stratified by type of TKI

		Baseline (N=92)			3 months (N=85)			6 months (N=84)		
	TKI generation	**Mean**	**95% C.I.**		**Mean**	**95% C.I.**		**Mean**	**95% C.I.**	
Fatigue (FACIT-Fatigue)										
	Imatinib	37.9	(33.7;	42.2)	37.0	(32.9;	41.2)	37.6	(33.4;	41.7)
	2nd gen TKI	38.7	(35.3;	42.1)	39.2	(35.8;	42.5)	40.0	(36.8;	43.3)
Health Related Quality of Life (FACT-G)										
PWB	Imatinib	21.9	(19.7;	23.8)	21.6	(19.6;	23.5)	22.1	(20.2;	24.0)
	2nd gen TKI	23.0	(21.4;	24.6)	22.3	(20.6	23.9)	23.1	(21.6;	24.6)
SWB	Imatinib	21.7	(19.2;	24.2)	21.5	(19.1;	23.9)	21.5	(19.1;	23.8)
	2nd gen TKI	22.5	(20.5;	24.5)	22.0	(20.0;	24.0)	21.7	(19.8;	23.6)
EWB	Imatinib	16.6	(14.5;	18.7)	17.4	(15.5;	19.3)	17.7	(15.7;	19.6)
	2nd gen TKI	17.6	(15.9;	19.3)	18.5	(16.9;	20.0)	18.2	(16.7;	19.8)
FWB	Imatinib [t]	16.2	(13.5;	18.8)	16.7	(14.0;	19.5)	16.2	(13.5;	19.0)
	2nd gen TKI	17.7	(15.6;	19.7)	17.8	(15.5;	20.0)	17.3	(15.2;	19.4)
FACT-G	Imatinib	76.0	(69.2;	82.9)	76.8	(70.1;	83.5)	77.4	(70.7;	84.0)
	2nd gen TKI	80.8	(75.4;	86.2)	80.2	(74.6;	85.8)	80.2	(74.9;	85.5)

Abbreviations:
PWB: Physical Well-Being; SWB: Social/Family Well-Being; EWB: Emotional Well-Being; FWB: Functional Well-Being.
Legend:
Second generation TKI: Nilotinib, Dasatinib or Bosutinib.
We estimated the overall trajectories over time of each score from FACIT-Fatigue and FACT-G questionnaires using a linear mixed model for repeated measures, separately by first generation initial TKI vs second generation TKIs (i.e., nilotinib, dasatinib, bosutinib). These analyses were adjusted for age (<60 years vs ≥ 60 years), sex (male vs female) and TKI switch.