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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Patient-reported outcomes in the phase 3 BFORE trial of bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia

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Abstract

Background In the phase 3 BFORE trial (NCT02130557), treatment with bosutinib resulted in a significantly higher major molecular response rate at 12 months versus imatinib in the modified intent-to-treat (mITT) population of patients with newly diagnosed chronic phase chronic myeloid leukemia (CP CML). Assessment of patient-reported outcomes (PROs) was an exploratory objective.

Methods Patients with newly diagnosed CP CML were randomized 1:1 to receive once-daily bosutinib 400 mg or imatinib 400 mg as first-line therapy. Patients completed the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) and EuroQoL-5 Dimensions (EQ-5D) questionnaires at baseline, every 3 months for the first 24 months of treatment, every 6 months thereafter, and at treatment completion. We report PRO results at month 12 in the mITT population (bosutinib: $n=246$; imatinib: $n=241$).

Results Mean FACT-Leu combined and subscale scores were similar at baseline in the bosutinib and imatinib arms; at month 12, all scores demonstrated improvement or maintenance of health-related quality of life (HRQoL) in both treatment arms. Repeated-measures mixed-effects models showed no significant difference between bosutinib and imatinib for any FACT-Leu score. Functional health status, as measured by EQ-5D, also demonstrated improvement or maintenance with bosutinib and imatinib at month 12.

Conclusions Similar improvements in PROs compared with baseline were seen after 12 months of treatment with first-line bosutinib or imatinib in the BFORE trial. Newly diagnosed patients with CP CML receiving bosutinib or imatinib can preserve or improve HRQoL during treatment, although clinical efficacy was superior with bosutinib.

Keywords Bosutinib · Chronic myeloid leukemia · Health-related quality of life · Imatinib · Patient-reported outcomes

Introduction

Targeting the constitutively activated kinase product of the *BCR–ABL1* gene fusion characteristic of chronic myeloid leukemia (CML) resulted in a paradigm shift in the treatment of patients with CML. Beginning with imatinib, orally administered tyrosine kinase inhibitor (TKI) therapy transformed an almost inevitably fatal disease for which the prior standard of care treatment, allogeneic stem cell transplant or interferon-alfa, benefited few patients (Hehlmann et al. 2007) into a chronic disease where the average patient lifespan now approximates that of the general population (Bower et al. 2016; Gambacorti-Passerini et al. 2011; Sasaki et al. 2015). In this new era of CML therapy, minimizing chronic symptom burden associated with long-term TKI treatment and maintaining adequate health-related quality of life (HRQoL) has become increasingly critical to patients and providers, in addition to effective

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disease control. Poor adherence to patient-administered oral medications has been documented in patients with cancer (Ruddy et al. 2009), including patients with CML, and is associated with reduced clinical response (Ibrahim et al. 2011; Marin et al. 2010; Noens et al. 2009). The majority of patients with CML are diagnosed in chronic phase (CP), during which they may be asymptomatic or experiencing minimal symptoms (Kantarjian et al. 1993), and development of treatment-related symptoms may influence patients' perception of treatment benefit and their adherence to the medication. One study reported that 31% of patients with CML were < 90% adherent to their TKI regimens (Anderson et al. 2015). In another study, a frequent reason cited for non-adherence to imatinib was to reduce the side effects of the drug (Eliasson et al. 2011).

Symptoms associated with CML treatment and factors contributing to patient HRQoL while receiving long-term CML therapy, e.g., emotional, social, physical, and functional well-being, are best evaluated through patient-reported outcome (PRO) measures since physicians may underestimate symptom severity and overestimate patient health status (Efficace et al. 2014b). PRO instruments, such as the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) (Cella et al. 2012) and the MD Anderson Symptom Inventory (MDASI)-CML (Williams et al. 2013), which allow patients to evaluate general cancer-related HRQoL concerns as well as leukemia-specific symptoms, have demonstrated their usefulness in CML trials; however, they are still grossly underutilized (De Marchi et al. 2017). As treatment options for CML increase, PRO instruments will become more valuable for the identification of the optimal therapy for an individual patient.

Bosutinib is an oral Src/Abl TKI approved for patients with Philadelphia chromosome-positive (Ph^+) CML resistant or intolerant to prior therapy and newly diagnosed patients with CP CML (Pfizer Inc 2017). The BFORE trial is an ongoing multinational, open-label, phase 3 study evaluating bosutinib 400 mg once daily (QD) or imatinib 400 mg QD in patients with newly diagnosed CP CML (Cortes et al. 2018). Bosutinib was associated with a significantly higher major molecular response (MMR) rate at 12 months (47.2% vs 36.9%; $p = 0.02$), a shorter time to MMR (hazard ratio 1.34; $p < 0.02$), and a higher complete cytogenetic response rate by 12 months (77.2% vs 66.4%; $p < 0.008$) compared with imatinib in the modified intent-to-treat (mITT) population (Ph^+ patients with typical *BCR–ABL1* transcript types). Adverse events were consistent with the known safety profiles for both TKIs, and included higher rates of diarrhea and increased liver transaminases with bosutinib and higher rates of neutropenia, edema, and musculoskeletal disorders with imatinib. Assessment of PROs, including symptom burden and functional health status, was an exploratory objective of the BFORE study. Here, we present the PRO results after 12 months of treatment.

Methods

Study design

Details of the BFORE study design have been previously published (Cortes et al. 2018). In brief, eligible patients were aged ≥ 18 years and had previously untreated CP CML that had been molecularly diagnosed within the prior 6 months and an Eastern Cooperative Oncology Group performance status of 0 or 1. Prior therapy with hydroxyurea, anagrelide, or both was permitted. Patients were randomized 1:1 to receive bosutinib 400 mg QD or imatinib 400 mg QD. Treatment continues for 5 years until the end of the study or until treatment failure, unacceptable toxicity, death, or withdrawal of consent. The primary endpoint, MMR at 12 months in the mITT population (Ph^+ patients with typical *BCR–ABL1* transcripts [e13a2 and/or e14a2]), and other key efficacy and safety outcomes, have been reported (Cortes et al. 2018).

The study was conducted in accordance with the Declaration of Helsinki, the protocol was approved by the Institutional Review Board at each study center (including the coordinating investigators' centers: University of Texas MD Anderson Cancer Center Institutional Review Board, Houston, TX, and Ethik-Kommission an der Medizinischen Fakultät Der RWTH Aachen, Aachen, Germany), and all patients provided written informed consent. The trial is registered on ClinicalTrials.gov (NCT02130557).

Evaluation of PROs

Assessment of PROs using the FACT-Leu and EuroQoL-5 Dimensions (EQ-5D) questionnaires, in patients receiving either bosutinib or imatinib treatment was an exploratory objective of the BFORE study.

The FACT-Leu (version 4) (Cella et al. 2012; Trask et al. 2012) questionnaire consists of a set of general HRQoL questions (FACT-General [FACT-G]) and a leukemia-specific subscale. Each item in the FACT-G and the leukemia-specific subscale is scored on a scale from 0 (not at all) to 4 (very much), with higher scores associated with better HRQoL. The 27-item FACT-G (score range 0–108) is divided into 4 domains: physical well-being (7 items; score range 0–28), social well-being (7 items; score range 0–28), emotional well-being (6 items; score range 0–24), and functional well-being (7 items; score range 0–28). The 17-item leukemia-specific subscale (score range 0–68) assesses patient concerns related to leukemia. The FACT-Leu total score (44 items; range 0–176) was calculated as the sum of the FACT-G total score plus the leukemia-specific subscale

score. The Trial Outcome Index (TOI) FACT-Leu score (31 items; range 0–124) was calculated as the sum of physical and functional well-being domain scores plus the leukemia-specific subscale score. The minimal important difference (MID), which is the change identified as being clinically meaningful to a patient, has been independently defined as 2–3 points for physical well-being, 2 points for emotional well-being, 2–3 points for functional well-being, 4–7 points for the leukemia-specific subscale, 3–7 points for the FACT-G, 6–12 points for the FACT-Leu total score, and 5–6 points for the TOI FACT-Leu (Trask et al. 2012). The MID for social well-being has not been defined.

The EQ-5D questionnaire (EuroQol-Group 1990; van Reenan and Oppe 2015) consists of five items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) rated on three levels (no problems, some problems, or extreme problems), with higher levels indicating greater severity/impairment. The EQ-5D utility score is a weighted health-state index score (range 0–1) based on patient responses to the five items and application of population-assessed weights to each set of responses. The EQ-5D also captures patient-rated health-state today on a vertical, graduated (0–100) visual analog scale (VAS). For the utility score and VAS, higher scores indicate better functioning.

Patients were asked to complete PRO questionnaires at baseline, every 3 months for the first 24 months of treatment, every 6 months thereafter, and at treatment completion. Questionnaires were translated to local languages and completed at study center visits.

Statistical methods

PROs were analyzed in the mITT population (i.e., the population assessed for the primary endpoint of the BFORE trial; Online Resource 1). Descriptive statistics were computed for FACT-Leu and EQ-5D scores. Mean changes in scores relative to baseline were summarized by assessment time point within each treatment arm. To assess correlation with response to therapy, patients were grouped according to achievement of MMR at month 12, and PRO scores were analyzed in each group. Repeated-measures mixed-effects models were the primary method used to analyze FACT-Leu multiple-item and single-item scale scores and the EQ-5D scores, and assess differences between treatment arms; the models included terms for intercept, linear time trend (in weeks), treatment arm, and treatment-by-time interaction. The intercept and slope terms for time were random effects with an unstructured variance/covariance matrix. p values < 0.05 were considered statistically significant and are shown for descriptive purposes only. No adjustments were made for multiple comparisons. For consistency with the primary study endpoint (Cortes et al. 2018), we report PROs at month 12; the data cutoff date was August 11, 2016.

Results

Patients and PRO questionnaire completion rates

A total of 536 patients with newly diagnosed CP CML were randomized to receive bosutinib ($n = 268$) or imatinib ($n = 268$); 3 patients in the imatinib arm were not treated (Cortes et al. 2018). The mITT population included 246 patients in the bosutinib arm and 241 in the imatinib arm (Online Resource 1). Baseline demographics and disease characteristics have been previously reported (Cortes et al. 2018), and were similar between treatment arms.

Completion rates for the FACT-Leu and EQ-5D instruments were similar between treatment arms at baseline and subsequent assessment time points (Online Resource 2). The score for each scale was considered an acceptable indicator of patient HRQoL if the overall item completion rate was > 80% (Cella 1997). Completion rates were > 80% up to month 9 in the bosutinib arm and up to month 6 in the imatinib arm for the FACT-Leu questionnaire, and up to month 6 in both arms for the EQ-5D questionnaire. At month 12, completion rates were slightly below 80% for both instruments in both study arms (78.9% for bosutinib and 79.3% for imatinib).

FACT-Leu scores

At baseline, mean scores for FACT-G domains, FACT-G total, FACT-Leu total, and TOI FACT-Leu were similar (< 5% difference) in the two treatment arms and were consistent with those previously reported for patients with chronic leukemia ≥ 2 months post-diagnosis (Cella et al. 2012) (Table 1). All FACT-Leu combined and subscale scores demonstrated improvement or maintenance of HRQoL with bosutinib or imatinib treatment at month 12 (Table 2; Fig. 1, and Online Resource 3). On-treatment scores for emotional well-being and the leukemia subscale improved significantly from baseline in both treatment arms at month 12. Improvements in on-treatment scores at month 12 for functional well-being, FACT-G total, FACT-Leu total, and TOI FACT-Leu were significant in the imatinib arm only. There were no clinically meaningful improvements in FACT-Leu scores, as defined by the MID for each HRQoL measure, in either treatment arm. Minimal changes (mean < 0.5) from baseline in physical well-being or social well-being scores were noted with bosutinib or imatinib treatment, suggesting maintenance of these HRQoL domains. Repeated-measures mixed-effects models did not demonstrate any significant difference between bosutinib and imatinib for any FACT-Leu subscale at month 12 (Table 3).

Table 1 FACT-Leu and EQ-5D scores at baseline and normative values for FACT-Leu

	Bosutinib		Imatinib		FACT-Leu validation sample[a] (Cella et al. 2012)	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
FACT-Leu						
Physical well-being	241	23.6 (4.3)	236	22.9 (5.3)	44	22.5 (6.4)
Social well-being	240	22.7 (5.1)	236	22.1 (5.4)	44	22.2 (6.1)
Emotional well-being	240	18.3 (4.4)	235	17.8 (4.4)	44	18.7 (3.8)
Functional well-being	241	19.7 (6.1)	235	19.8 (5.9)	44	20.7 (5.4)
Leukemia subscale	241	53.7 (8.7)	235	52.6 (10.1)	44	51.2 (11.5)
FACT-G total	239	84.4 (14.5)	235	82.6 (15.9)	44	84.0 (16.5)
FACT-Leu total	239	138.1 (21.7)	234	135.1 (24.4)	44	135.2 (26.4)
TOI FACT-Leu	241	97.0 (16.5)	234	95.2 (18.9)	44	94.4 (21.5)
EQ-5D						
Utility	240	0.836 (0.183)	235	0.806 (0.224)	NA	NA
VAS	239	74.9 (20.2)	233	71.6 (23.7)	NA	NA

EQ-5D EuroQoL-5 Dimensions, *FACT-G* Functional Assessment of Cancer Therapy-General, *FACT-Leu* Functional Assessment of Cancer Therapy-Leukemia, *NA* not analyzed, *SD* standard deviation, *TOI* Trial Outcome Index, *VAS* visual analog scale

[a]Patients with chronic leukemia ≥ 2 months post-diagnosis

Table 2 Changes in FACT-Leu and EQ-5D scores from baseline values after 12 months of treatment

	Bosutinib ($n = 190$)[a]		Imatinib ($n = 189$)[b]	
	Mean Δ (SD)	p[c]	Mean Δ (SD)	p[c]
FACT-Leu				
Physical well-being	−0.4 (4.5)	0. 2789	0.3 (4.4)	0.4217
Social well-being	−0.2 (5.0)	0. 5366	−0.2 (5.1)	0.5870
Emotional well-being	0.9 (3.8)	0.0013	1.5 (3.7)	< 0.0001
Functional well-being	0.8 (5.8)	0.0545	0.8 (5.3)	0.0426
Leukemia subscale	1.4 (8.6)	0.0222	2.4 (8.3)	0.0001
FACT-G total	1.2 (13.3)	0.2322	2.4 (12.3)	0.0088
FACT-Leu total	2.6 (20.1)	0.0762	4.7 (18.5)	0.0006
TOI FACT-Leu	1.9 (16.1)	0.1015	3.4 (14.5)	0.0016
EQ-5D				
Utility	−0.001 (0.217)	0.9412	0.039 (0.175)	0.0026
VAS	4.4 (18.3)	0.0014	9.3 (21.7)	< 0.0001

EQ-5D EuroQoL-5 Dimensions, *FACT-G* Functional Assessment of Cancer Therapy-General, *FACT-Leu* Functional Assessment of Cancer Therapy-Leukemia, *SD* standard deviation, *TOI* Trial Outcome Index, *VAS* visual analog scale

[a]$n = 189$ for social well-being and TOI FACT-Leu, and 188 for FACT-G total and FACT-Leu total; $n = 189$ for EQ-5D utility and 185 for EQ-5D VAS

[b]$n = 188$ for physical well-being and leukemia subscale, 187 for social well-being, FACT-G total, and TOI FACT-Leu, and 186 for FACT-Leu total; $n = 188$ for EQ-5D utility and 187 for EQ-5D VAS

[c]p value for within-arm comparison of visit and baseline score based on two-sided paired t test

EQ-5D scores

Mean EQ-5D utility and VAS scores at baseline were similar in the bosutinib and imatinib arms (Table 1). Over the course of treatment, mean EQ-5D utility and VAS scores improved or were maintained in both treatment arms (Fig. 2). At month 12, significant improvements in mean EQ-5D VAS scores were observed with both bosutinib and imatinib; significant improvement in the EQ-5D utility score was seen in the imatinib arm only (Table 2).

At baseline, patients in the bosutinib and imatinib arms, respectively, reported some problems or extreme problems

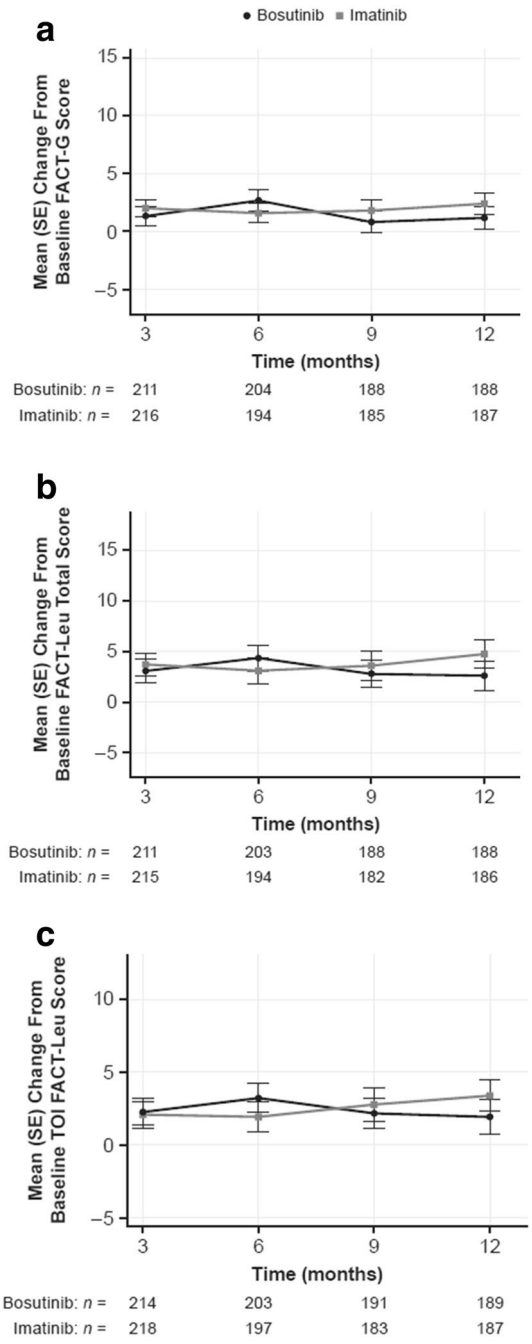

Fig. 1 Total mean change from baseline over time by treatment for **a** FACT-G, **b** FACT-Leu total, and **c** TOI FACT-Leu scores. *FACT-G* Functional Assessment of Cancer Therapy-General, *FACT-Leu* Functional Assessment of Cancer Therapy-Leukemia, *SE* standard error, *TOI* Trial Outcome Index

with mobility (19.2% vs 22.9%), self-care (4.2% vs 3.8%), usual activities (26.7% vs 28.0%), pain/discomfort (37.1% vs 45.8%), and anxiety/depression (33.3% vs 37.9%; Fig. 3). Proportions of patients reporting some problems versus those reporting extreme problems were similar between the two treatment arms (data not shown). At month 12, the proportions

Table 3 Comparison of model-estimated FACT-Leu scores between treatment arms after 12 months

	Difference in effect estimates between bosutinib and imatinib	
	Treatment difference (95% CI)	*p*
FACT-Leu		
Physical well-being	0.046 (−0.672, 0.764)	0.8999
Social well-being	−0.469 (−1.304, 0.366)	0.2703
Emotional well-being	−0.400 (−1.046, 0.245)	0.2232
Functional well-being	−0.067 (−0.974, 0.841)	0.8854
Leukemia subscale	−0.125 (−1.478, 1.228)	0.8562
FACT-G total	−0.894 (−3.000, 1.212)	0.4047
FACT-Leu total	−0.955 (−4.083, 2.173)	0.5486
TOI FACT-Leu	−0.054 (−2.498, 2.390)	0.9653
EQ-5D		
Mobility	0.067 (−0.003, 0.136)	0.0596
Self-care	−0.002 (−0.042, 0.038)	0.9164
Usual activities	−0.006 (−0.093, 0.081)	0.8847
Pain/discomfort	0.054 (−0.041, 0.149)	0.2616
Anxiety/depression	0.026 (−0.058, 0.110)	0.5410
Health-state today	−2.690 (−6.197, 0.818)	0.1325
Utility	−0.022 (−0.053, 0.010)	0.1740

CI confidence interval, *EQ-5D* EuroQoL-5 Dimensions, *FACT-G* Functional Assessment of Cancer Therapy-General, *FACT-Leu* Functional Assessment of Cancer Therapy-Leukemia, *TOI* Trial Outcome Index

of patients reporting no, some, or extreme problems in each of the EQ-5D items remained relatively constant in the bosutinib arm (Fig. 3). In the imatinib arm, the percentage of patients reporting no problems with mobility, usual activities, or pain/discomfort increased at month 12 compared with baseline, whereas percentages for self-care and anxiety/depression were similar (Fig. 3).

Repeated-measures mixed-effects models for EQ-5D scores showed no differences between bosutinib and imatinib treatment for mobility, self-care, usual activities, pain/discomfort, anxiety/depression, health-state today, or utility scores at month 12 (Table 3).

Impact of 12-month MMR status on FACT-Leu and EQ-5D scores

There were no differences in FACT-Leu, EQ-5D utility, or EQ-5D VAS scores between patients with versus without an MMR at month 12 in the bosutinib or imatinib arms (Online Resource 4).

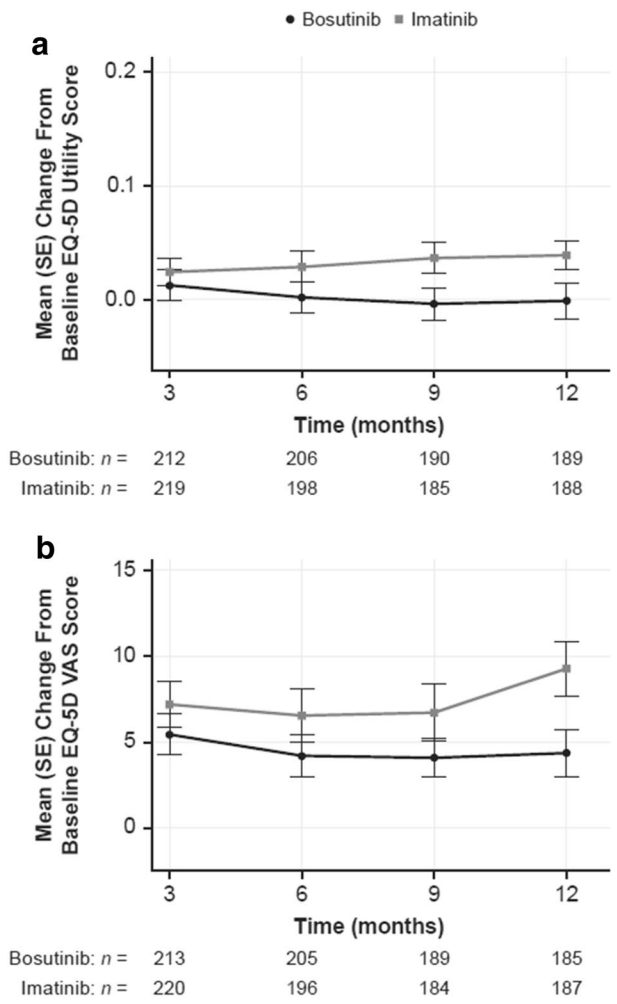

Fig. 2 Total mean change from baseline over time by treatment for **a** EQ-5D utility and **b** EQ-5D VAS scores. *EQ-5D* EuroQoL-5 Dimensions, *SE* standard error, *VAS* visual analog scale

Discussion

Given the current treatment paradigm of long-term TKI therapy for patients with CP CML, it is critical to assess whether improvements in clinical outcomes with individual TKIs are compromised by deterioration in HRQoL, since this can impact adherence to medication and, ultimately, the patient's clinical response (Efficace and Cannella 2016; Marin et al. 2010). In developed countries, up to 40% of patients with CP CML are asymptomatic at diagnosis (Cortes 2004); thus, preservation of baseline HRQoL status is a primary therapy goal for this group. In patients already experiencing CML symptoms at diagnosis, improvement of HRQoL to the pre-symptomatic condition should be an aim of treatment. Robust measurement of PROs in the large, randomized, phase 3 BFORE trial enabled complementary evaluation of efficacy, safety, and HRQoL with first-line bosutinib or imatinib for CP CML. Primary results from the BFORE study demonstrated improved clinical efficacy with bosutinib versus imatinib and a manageable safety profile for bosutinib in patients with newly diagnosed CP CML (Cortes et al. 2018). Findings from this PRO analysis indicate that patients also experienced stable or improved HRQoL and functional health status, as assessed by the patient-reported FACT-Leu and EQ-5D questionnaires, respectively, during treatment with either bosutinib or imatinib. Together, the efficacy and PRO data from the BFORE trial indicate that higher molecular and cytogenetic response rates and shorter time to response with bosutinib versus imatinib (Cortes et al. 2018) were accompanied by HRQoL preservation or improvement.

Using the FACT-Leu instrument, which measures symptom burden associated with cancer as well as leukemia-specific issues, baseline scores in the BFORE trial were similar to those previously reported for patients with chronic leukemia (Cella et al. 2012). To our knowledge, the FACT-Leu has not been utilized to evaluate HRQoL in healthy or general populations for comparison with patients with leukemia, but the FACT-G portion of this instrument was tested in a general US population and in patients with various cancers (Brucker et al. 2005; Pearman et al. 2014). Mean FACT-G scores were previously shown to be comparable in general and cancer populations (80.1 vs 79.3) (Pearman et al. 2014) and were slightly lower than mean baseline values for the BFORE trial population (bosutinib: 84.4; imatinib: 82.6). With the FACT-Leu instrument, patients receiving bosutinib demonstrated significantly improved scores at month 12 from baseline for the emotional well-being domain and the leukemia subscale; functional well-being improved (mean change 0.8), but the change did not reach statistical significance ($p = 0.0545$). In addition to those domains, patients receiving imatinib showed significant improvements in the FACT-G total, the FACT-Leu total, and the TOI FACT-Leu. However, none of the changes observed in FACT-Leu scores met the corresponding MID, which is an indicator of clinical meaningfulness, suggesting patients did not experience noticeable changes in HRQoL while on treatment. The lack of a clinically meaningful benefit may be related to difficulties in distinguishing symptoms due to CML from those due to comorbidities, which would not be expected to improve with TKI treatment. Furthermore, the relatively high FACT-Leu scores at baseline in the BFORE trial may make improvements less apparent. Of note, repeated-measures mixed-effects modeling found no significant differences between treatment arms in any of the FACT-Leu scores at month 12. This suggests that the effects of treatment on HRQoL are comparable for bosutinib and imatinib.

In addition to the FACT-Leu instrument, the MDASI-CML (Williams et al. 2013) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ)–CML24 (Efficace et al.

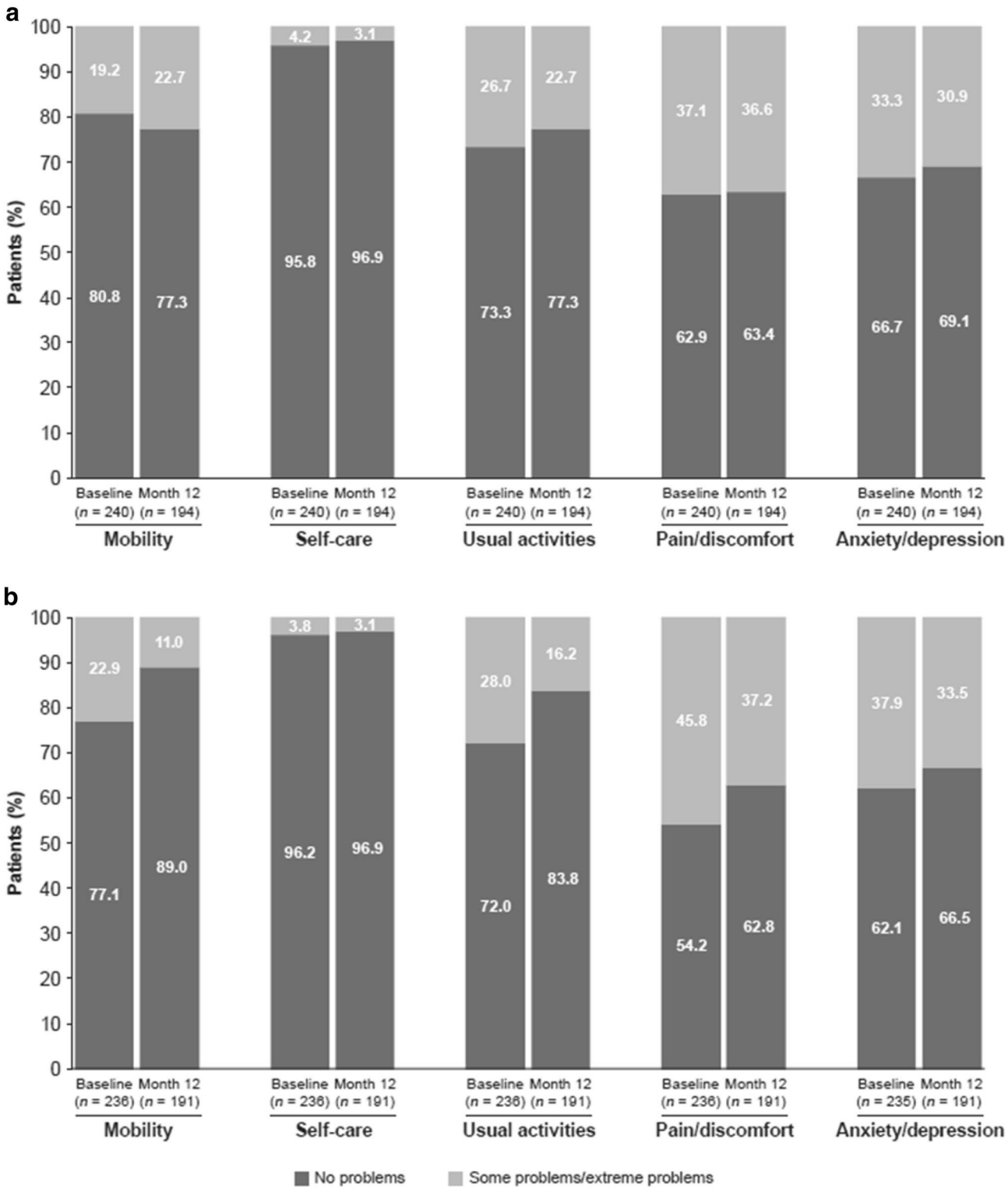

Fig. 3 Percentage of patients in the **a** bosutinib arm and **b** imatinib arm reporting some problems or extreme problems in EQ-5D items at baseline and 12 months. *EQ-5D* EuroQoL-5 Dimensions

2014a) were developed to measure HRQoL specifically in patients with CML. The MDASI-CML questionnaire consists of 13 core symptom items, 6 interference items, and 7 CML-specific symptom items (Williams et al. 2013). The EORTC QLQ-CML24 questionnaire is comprised of 24 items evaluating symptom burden, impact on daily life and

worry/mood, body image problems, and satisfaction with care and social life (Efficace et al. 2014a). The use of these tools, individually or in a complementary manner, in future clinical trials may help to differentiate approved and novel therapies for CML, beyond efficacy and safety outcomes. For these questionnaires to be used for this purpose, it is important that they are completed under standardized conditions, e.g., at clinic visits.

The results from the EQ-5D instrument, which measures general health status, supported the FACT-Leu findings. For each of the EQ-5D items, the majority of patients reported having no problems at baseline, consistent with the known prevalence of patients with CP CML who are asymptomatic at diagnosis (Cortes 2004). The most common problem in both trial arms was pain/discomfort, with 37.1% and 45.8% of patients in the bosutinib and imatinib arms, respectively, reporting some or extreme problems at baseline. Over the course of treatment, the percentage of patients reporting problems for each of the EQ-5D items remained stable or decreased. Mean baseline values for the EQ-5D utility score (bosutinib: 0.836; imatinib: 0.806) and VAS score (bosutinib: 74.9; imatinib: 71.6) were lower than those previously reported for a general US population (utility: 0.8739; VAS: 80.05) (Bharmal and Thomas 2006) but within ranges reported for general populations from various countries (Janssen and Szende 2014) and patients with different tumor types (Pickard et al. 2007). In the BFORE trial, improvements in EQ-5D utility and VAS scores were seen at month 12; these changes were significant in the imatinib arm for the EQ-5D utility score and in both treatment arms for the EQ-5D VAS score. Similar to the FACT-Leu results, no differences were seen between bosutinib and imatinib for EQ-5D measures at month 12 of treatment.

Analysis of the FACT-Leu total, EQ-5D utility, and EQ-5D VAS scores found no association between achievement of MMR at month 12 and the assessed PROs. Since approximately half of patients with CML are diagnosed incidentally based on routine laboratory tests and do not show symptoms (Thompson et al. 2015), a response to treatment may add little to patients' perceived immediate well-being. Nevertheless, early MMR is associated with long-term clinical benefit of TKIs (Hughes et al. 2010) and thus remains a treatment goal that physicians should communicate to their patients. Although an issue that is not specific to CML or TKI therapy, it is worth noting that trial endpoints driving durable clinical outcomes are not necessarily linked to the individual patient experience, strongly supporting the rationale for incorporating PRO endpoints in clinical studies.

These PRO results for bosutinib in the BFORE trial are consistent with those reported in previous studies of bosutinib as first-line or subsequent therapy for CML. In a multi-cohort, single-arm phase 2 trial, patients with imatinib-resistant or imatinib-intolerant Ph^+ CP CML had little impairment in HRQoL at baseline but achieved statistically significant and/or clinically meaningful improvements in several FACT-Leu scales, including the TOI FACT-Leu, with second-line bosutinib (Trask et al. 2012). After longer follow-up (≥ 264 weeks) from this study, HRQoL was maintained in patients who received second-line bosutinib treatment for CP CML as well as in the cohort of patients with CP CML administered bosutinib as third- or fourth-line therapy (Kantarjian et al. 2018). Patients in the accelerated or blast phase CML cohort of this phase 2 study also experienced significant improvements in HRQoL with bosutinib treatment over the 96-week course of follow-up (Whiteley et al. 2016). Together, these PRO results indicate that imatinib-resistant or imatinib-intolerant patients with CML who switch from an alternative TKI to bosutinib may experience an improvement in HRQoL. Since diarrhea is frequently reported with bosutinib, a post hoc HRQoL analysis was conducted for the subset of patients with CP CML who had chronic diarrhea during second-, third-, or fourth-line treatment with bosutinib. FACT-Leu scores in this subgroup were consistent with those of the total population, indicating that this adverse event did not affect long-term HRQoL (Kantarjian et al. 2018). It will be of interest to assess if adverse events common to the TKIs approved for CML, as well as the distinct toxicities associated with the individual agents, impact HRQoL during treatment, particularly early on when patients may be more likely to experience side effects, and whether proactive adverse event management would mitigate any negative effects.

In the first-line setting, the phase 3 BELA trial compared bosutinib (500 mg QD) with imatinib (400 mg QD) in patients with newly diagnosed CP CML (Cortes et al. 2012). Significant, but not clinically meaningful, improvements in some FACT-Leu scores, including the leukemia subscale score, were observed in both treatment arms at 3 and 12 months, suggesting baseline HRQoL was maintained over the course of the study (Lipton et al. 2011). PROs with first-line imatinib were also evaluated in the phase 3 IRIS study (O'Brien et al. 2003); HRQoL, as assessed by TOI FACT-Biologic Response Modifiers, was maintained from baseline in the imatinib arm but declined in the interferon-alfa plus cytarabine arm (Hahn et al. 2003). A study prospectively evaluating HRQoL as the primary study objective in 130 patients with CP CML receiving first-line nilotinib at centers in Italy reported statistically significant and clinically meaningful improvements for several EORTC-QLQ-Core 30 scales (Efficace et al. 2018). Another prospective analysis of symptom burden, as measured by the MDASI-CML, in patients with CP CML receiving first-line dasatinib, nilotinib, or ponatinib found that symptom severity was generally stable during treatment (Zulbaran-Rojas et al. 2018).

This PRO analysis from the BFORE trial is limited by the open-label nature of the study, a reduction in questionnaire

completion rate over time, and missing data for patients who discontinued treatment. Since data were not collected from patients who discontinued from the trial, it is not possible to determine if the PRO results of these patients would have been different from the PRO results reported here. Patients who discontinued early may have done so for multiple reasons, including adverse events and/or lack of efficacy; hence, it is possible that their PRO results would have been inferior to those of the patients who continued in the trial. This study reports HRQoL results after 12 months of treatment, consistent with the primary endpoint (Cortes et al. 2018) although PROs were assessed at earlier time points and will continue to be assessed in the long-term follow-up of the BFORE trial; it will be of interest to evaluate HRQoL in patients with newly diagnosed CP CML receiving long-term bosutinib treatment as well as in relation to specific adverse events, which may occur earlier in the course of treatment. In addition, the lack of adjustments for multiple comparisons may limit the interpretation of statistically significant differences within or between treatment arms. Nevertheless, these data show that in addition to experiencing improved clinical outcomes compared with imatinib (Cortes et al. 2018), patients with CP CML receiving first-line bosutinib can maintain or improve HRQoL during treatment, an indication of low symptom burden and drug tolerability. Objective assessment of patient-reported outcomes is becoming increasingly important in CML clinical trials since HRQoL outcomes can influence treatment decision-making by physicians and patients, and our analysis provides valuable evidence regarding the effect of TKI treatment on HRQoL in this patient population.

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Research data policy/data availability Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Compliance with ethical standards

Conflict of interest JEC: consultancy (ARIAD, Bristol-Myers Squibb, ImmunoGen, Novartis, Pfizer, Takeda) and research funding (ARIAD, Bristol-Myers Squibb, ImmunoGen, Novartis, Sun Pharma, Pfizer, Takeda, Teva). CG-P: consultancy (Bristol-Myers Squibb) and honoraria and research funding (Pfizer). MWD: advisory board (Blue Print, Pfizer, Ascentage Pharma, and Humana), consultancy (Blue Print, Pfizer, Ascentage Pharma, and TRM), research funding (Pfizer), and study management committee (Blue Print and Takeda). MJM: consultancy (Bristol-Myers Squibb). CC: honoraria (Bristol-Myers Squibb, Chiltern, Novartis, and Otsuka) and travel (Pfizer). D-WK: consultancy (Bristol-Myers Squibb, Il-Yang, Novartis), honoraria, and research funding (Bristol-Myers Squibb, Il-Yang, Novartis, Pfizer), membership on board of directors or advisory committees (Bristol-Myers Squibb), and speakers bureau (Bristol-Myers Squibb, Novartis, Pfizer). DM: consultancy and honoraria (ARIAD, Bristol-Myers Squibb, Novartis, Pfizer) and honoraria and speakers bureau (Incyte). PlC: honoraria (ARIAD, Bristol-Myers Squibb, Incyte, Novartis, Pfizer) and research funding (Novartis). VG-G: consultancy, honoraria, and research funding (Bristol-Myers Squibb, Incyte, Novartis, Pfizer). RC: equity ownership (Pfizer and GlaxoSmithKline). CM: employment and equity ownership (Pfizer). AR: employment (Pfizer). AH: research funding (Bristol-Myers Squibb, Incyte, Novartis, Pfizer). THB: consultancy (Novartis, Pfizer, Janssen, Merck, Takeda) and research funding (Novartis, Pfizer).

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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