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Improvement of fatigue, physical functioning, and well-being among patients with severe impairment at baseline receiving ibrutinib in combination with bendamustine and rituximab for relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma in the HELIOS study

Paula Cramer^a, Graeme Fraser^b, Rodrigo Santucci-Silva^c, Sebastian Grosicki^d, Marie-Sarah Dilhuydy^e, Ann Janssens^f, Javier Loscertales^g, Simon Rule^h, Andre Goyⁱ, Shana Traina^j, Eric K. H. Chan^j, Joris Diels^k, Nishan Sengupta^l, Michelle Mahler^j, Mariya Salman^j, Angela Howes^m and Asher Chanan-Khanⁿ

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ABSTRACT

Health-related quality of life (HRQoL) is an important endpoint, especially in clinical trials for malignancies with a long course of disease, such as chronic lymphocytic leukemia (CLL). Patient-reported outcomes were examined in the randomized, double-blind, placebo-controlled HELIOS study to assess the impact of treatment with the Bruton's tyrosine kinase inhibitor ibrutinib, added to bendamustine plus rituximab (BR) background therapy. Measures included FACIT-Fatigue, EORTC QLQ-C30, QLQ-CLL16, and EQ-5D-5L. Of 578 patients enrolled, 540 (93%) provided FACIT-Fatigue responses at baseline. Most had only a moderate degree of impairment at baseline; mean values did not appear to change over time in either treatment arm, suggesting that adding ibrutinib to BR did not impact health-related quality of life. However, *post-hoc* analyses showed that subgroups of patients with the worst fatigue, physical functional status, and well-being at baseline had greater improvements in these outcomes with ibrutinib plus BR treatment versus placebo.

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults [1]. Early-stage disease is usually managed with a 'watch-and-wait' approach until it becomes symptomatic, with patients experiencing significant weight loss, fatigue, or fever; progressive bone marrow failure; or symptoms from lymphadenopathy, splenomegaly, or hepatomegaly [2,3]. Most conventional CLL therapies contain chemotherapeutic agents and may have toxic side effects and poor tolerability; particularly problematic because CLL primarily affects the elderly.

The disease-related symptoms, potential toxicity of therapy, and emotional and socioeconomic aspects of living with chronic illness can have profound effects

on health-related quality of life (HRQoL) in patients with CLL [4–6]. As the median age at initial CLL diagnosis is 72 years, many patients face further challenges of managing comorbidities [7]. The most commonly reported symptom is fatigue [8], a multifaceted phenomenon that reduces patients' physical energy, mental capacities, and psychological alertness [8–10]. Approximately 9–25% of patients with CLL develop anemia, which can be caused by bone marrow infiltration, autoimmune phenomena, or chemoimmunotherapy [5]. Anemia also contributes to fatigue and may cause shortness of breath and lethargy, further impairing physical functioning and HRQoL. Low-grade anemia (hemoglobin <12 g/dL) is often associated with significant reduction in HRQoL [5,11].

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Ibrutinib is a first-in-class, oral, covalent inhibitor of Bruton's tyrosine kinase, approved in the United States, Europe, and many other countries for treatment of CLL [12,13]. The HELIOS study, a large, international, double-blind, placebo-controlled phase 3 trial, demonstrated that the addition of continuous ibrutinib to up to six cycles of bendamustine plus rituximab (BR) significantly improved progression-free survival (PFS) compared with up to six cycles of BR alone in patients with relapsed/refractory CLL, with an 80% reduction in risk of disease progression or death [14]. Although 97% of patients experienced ≥ 1 adverse event (mostly mild/moderate in severity), no unexpected or cumulative toxicities occurred as the safety profile corresponded with toxicity rates previously reported for both BR chemoimmunotherapy and ibrutinib [15,16].

Increasing PFS and overall survival is the primary goal of current CLL treatments, but it is also important to maintain good HRQoL, as patients may live with their disease for many years. Furthermore, as antineoplastic therapies often have side effects, it is essential to understand the tradeoff between improvements in disease-related outcomes and any detrimental treatment-related impact on patients' HRQoL. An understanding of patients' symptoms, functioning, and overall well-being is valuable to clinicians, patients, and payers [6]. Patient-reported outcome (PRO) instruments are commonly used to assess patients' overall experience in this regard [17], and are increasingly included as oncology trial endpoints to contextualize clinical endpoint findings and provide a more comprehensive picture of treatment effects [18–22].

To this end, it is imperative that PRO data in oncology trials are analyzed and reported in a meaningful way. Per regulatory guidelines, oncology trials tend to enroll patients who are expected to benefit from study treatment and are therefore not too 'unwell' [23]. Mean or median changes from baseline in the overall study population may not accurately reflect outcomes for smaller subgroups of patients with the worst baseline HRQoL. Importantly, patients with the greatest HRQoL impairment at baseline may be those most in need of a therapy that does not make them feel any worse.

Initial exploratory analyses in the HELIOS study indicated that, among patients with the worst baseline fatigue, there were apparent improvements in fatigue for both treatment groups in the first six cycles (i.e. while both groups were receiving BR), with significantly greater improvements among patients who continued ibrutinib versus placebo ($p < .05$ at Cycle 10) [14]. This analysis aims to further examine the HRQoL impact of ibrutinib treatment when added to BR

background therapy for patients in the HELIOS study. Given that initial results suggested a positive treatment effect of ibrutinib plus BR in patients who were most fatigued at baseline, additional *post-hoc* analyses were performed to examine fatigue and other PROs (e.g. physical functioning, and general well-being), according to degree of baseline impairment.

Materials and methods

Study design, patients, and treatment

Full details of the HELIOS study design and methodology (NCT01611090) have been published previously [14]. Briefly, adults with CLL or small lymphocytic lymphoma requiring treatment according to International Workshop on Chronic Lymphocytic Leukemia criteria [3], and who had relapsed/refractory disease following ≥ 1 previous therapies, were enrolled across 133 sites (21 countries). An independent ethics committee or institutional review board approved the protocol at each site, and the study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Patients were randomized 1:1 to receive oral ibrutinib (420 mg daily) or placebo in addition to a background regimen of bendamustine (70 mg/m² on Days 2–3 in Cycle 1 and Days 1–2 in Cycles 2–6) plus rituximab (375 mg/m² on Day 1 of Cycle 1 and 500 mg/m² on Day 1 of Cycles 2–6) for up to six cycles with a duration of 28 days. After completion of six cycles, patients continued to receive ibrutinib or placebo in 28-day cycles until disease progression or unacceptable toxicity.

PRO measures

In the HELIOS study, PROs were implemented as secondary endpoints assessed by a prespecified analysis plan. PROs were collected using four standardized and widely accepted instruments for oncology: the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, the EORTC QLQ-CLL 16 (a CLL-specific module), and the EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L) [4,24–28]. In addition to planned analyses on the domains/scales from each PRO instrument, *post-hoc* exploratory subgroup analyses were conducted using all four instruments to evaluate outcomes according to the degree of baseline impairment. Correlations between

fatigue levels, as measured by the FACIT-Fatigue scale, and hemoglobin levels indicating anemia (hemoglobin <11 g/dL) were also evaluated as part of the *post-hoc* exploratory analysis.

Fatigue

Fatigue was assessed using the FACIT-Fatigue scale, a 13-item instrument designed to specifically assess aspects of fatigue/tiredness in patients with cancer or other chronic diseases, including impact on daily activities and functioning [29]. Several studies of chronic diseases, including anemia and cancer [30–34], have shown the FACIT-Fatigue scale can be used to support valid inferences regarding patient fatigue. Items are scored on a 0–4 response scale (0 = not at all; 4 = very much), reverse scored where appropriate, and all items are summed to create a single fatigue score with a range from 0 to 52, where higher scores indicate better functioning or less fatigue. A change of ≥ 3 points is considered clinically meaningful [35].

General cancer assessment, including physical functioning and well-being

The EORTC QLQ-C30 is a 30-item general cancer assessment that incorporates five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), a global health-status and QoL scale (two items), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scores range from 0 to 100 (for functional and global QoL scales, higher scores indicate a better level of functioning) [24]. In this analysis, the individual physical functioning domain was explored; a 10-point change was considered clinically meaningful [36].

The CLL-specific module QLQ-CLL16 was developed by the EORTC [37] and comprises 16 questions that address five domains of HRQoL important in CLL, including three multi-item scales (fatigue, treatment side effects and disease symptoms, and infections) and two single-item scales (social activities and future health worries) [4,28]. In this analysis, the individual QLQ-CLL16 item of feeling ill or unwell, which is measured on a 4-point scale (1 = not at all; 4 = very much), was assessed.

Generic measures of HRQoL and well-being were also collected using the EQ-5D-5L [38,39]. The EQ-5D-5L consists of a five-item descriptive system and the EuroQoL visual analog scale (EQ-5D VAS) of self-rated health, with scores ranging from 0 to 100 (worst to best imaginable health state). Responses for the five

dimensions are combined into a five-digit number describing respondents' health state that can be converted into a single index value or utility score (using UK weights), ranging from –1 to 1, where lower scores indicate a worse health status.

PRO instrument administration

PRO instruments were administered to patients at the beginning of clinic visits to avoid bias from procedures or physician interactions. Data were collected using electronic data capture during double-blind treatment and post-treatment follow-up periods until disease progression, clinical cutoff, or death. The FACIT-Fatigue and EORTC QLQ-CLL 16 instruments were administered on Day 1 of Cycles 1, 2, 4, and 6 (ibrutinib- or placebo-plus-BR treatment period), Cycles 8 and 10 (ibrutinib- or placebo-alone treatment period), at the end-of-treatment visit, and every 12 weeks during the post-treatment follow-up period. The EORTC QLQ-C30 and EQ-5D-5L instruments were administered on Day 1 of Cycles 1, 3, and 5 (ibrutinib- or placebo-plus-BR treatment period), Cycles 7 and 10 (ibrutinib- or placebo-alone treatment period), at the end-of-treatment visit, and every 12 weeks during the post-treatment follow-up period. Following disease progression, sites also attempted to administer the EQ-5D-5L every 16 weeks (up to three times) in person or via telephone [40].

Statistical analyses

PRO endpoints were analyzed for all patients in the intent-to-treat population who completed the FACIT-Fatigue instrument at baseline (Day 1 of Cycle 1) and had ≥ 1 post-baseline value.

The compliance rates of each PRO at each time point were calculated based on the sample size of each arm at baseline. Scores from FACIT-Fatigue, EORTC QLQ-C30, EORTC QLQ-CLL 16, and EQ-5D-5L were descriptively summarized by treatment group. Kaplan–Meier curves were generated for FACIT-Fatigue scores to estimate time to achieve a clinically meaningful change in each treatment group and were compared using a stratified log-rank test.

Subgroup analyses

Individual PROs were evaluated in a *post-hoc* subgroup analysis according to degree of HRQoL baseline impairment. The baseline score was defined as the score from Day 1, Cycle 1. For FACIT-Fatigue, EORTC QLQ-C30 Physical Functioning, and EQ-5D VAS scores, mixed-model analyses were implemented; patients were

stratified according to treatment group (ibrutinib/placebo) and baseline status on that PRO (dichotomized by most impaired quartile versus the other three quartiles). For the EORTC QLQ-CLL16 well-being item, patients were stratified according to treatment group and by whether they reported feeling ill/unwell 'quite a bit' or 'very much' at baseline, and for analysis of change over time, by the proportion of patients achieving a return to well-being (reported feeling 'not at all' ill/unwell). Mean differences from baseline at each time point between the two treatment arms were compared statistically using the mixed-effects model repeated measure (MMRM) method. This method was implemented using two stratification factors, treatment and status (worse/not worse), and included the interaction between treatment and status as covariates in the mixed model. The association between change in fatigue scores and hemoglobin levels was examined in patients in the highest (most fatigued) quartile of FACIT-Fatigue baseline scores using linear regression models.

Results

In total, 578 patients were randomized to ibrutinib plus BR or placebo plus BR in the HELIOS study (intent-to-treat population, $n=289$ in each treatment group). Of these, 540 (93%) provided FACIT-Fatigue baseline responses and had ≥ 1 post-baseline value (PRO analysis population). Baseline demographic and clinical characteristics of patients who completed the FACIT-Fatigue instrument at baseline are shown in Table 1. Treatment groups were generally well balanced; however, a higher proportion of patients in the placebo group had Rai stage III/IV disease, hemoglobin levels indicative of anemia, and low platelet and absolute neutrophil counts, whereas the ibrutinib group had a higher proportion of patients with bulky disease and del11q.

Table 1. Demographics and clinical characteristics for patients who completed the FACIT-Fatigue instrument at baseline.

Characteristics	Ibrutinib + BR ($n=269$)	Placebo + BR ($n=271$)
Age, mean (SD), years	63.7 (9.69)	63.2 (9.36)
Sex, % male	67.7	65.7
ECOG status (grade 1), %	57.2	56.5
Advanced Rai stage (3–4), %	37.1 (88/237)	46.3 (112/242)
Bulky disease (≥ 5 cm), %	58.7	53.5
Del11q, %	29.4	23.2
Mutated IgVH, %	18.9	20.0
No. of prior therapies, median (range)	2.0 (1–11)	2.0 (1–9)
Hemoglobin ≤ 11 g/dL, %	26.8	33.6
Platelet count $\leq 100,000/\mu\text{L}$, %	24.9	29.5
ANC $\leq 1500/\mu\text{L}$, %	8.2	11.1

ANC: absolute neutrophil count; BR: bendamustine plus rituximab; Del11q: chromosome 11q deletion; ECOG: Eastern Cooperative Oncology Group; IgVH: immunoglobulin heavy-chain variable-region; SD: standard deviation.

Patient-reported outcomes

Baseline HRQoL scores were indicative of a moderate fatigue level and impaired functioning in the PRO analysis population: mean baseline FACIT-Fatigue score was 37.2 (standard deviation [SD] 10.4); mean EORTC-QLQ-C30 Physical Functioning score was 78.9 (SD 18.9); and mean EQ-5D-5L utility value was 0.79 (SD 0.18). On the EORTC QLQ-CLL 16 instrument, 16.7% of patients reported feeling ill 'quite a bit' or 'very much' at baseline.

Prespecified analyses in the overall analysis population

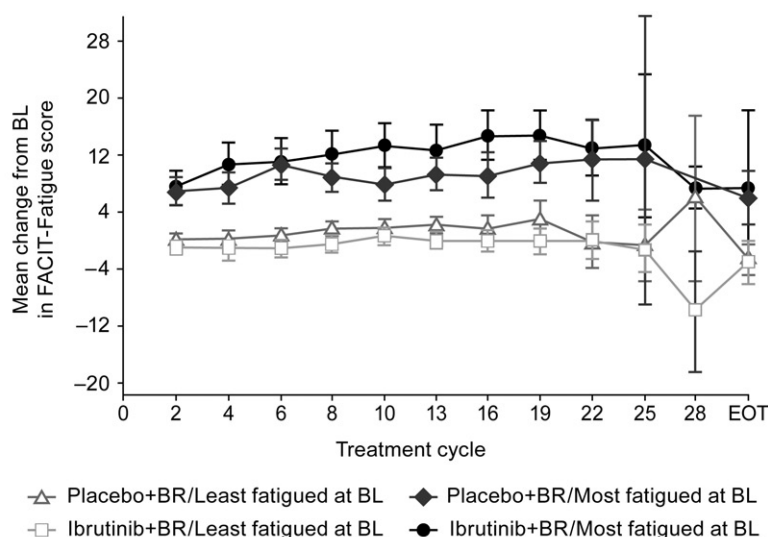
Overall compliance rates on the PRO instruments (FACIT-Fatigue, EORTC QLQ-C30, EORTC QLQ-CLL16, and EQ-5D-5L) were $>90\%$, with $<10\%$ missing at most time points through Cycle 19.

The median time to improvement in FACIT-Fatigue score was not significantly different in the ibrutinib-plus-BR and placebo-plus-BR groups: 6.5 versus 4.6 months (hazard ratio 0.853; 95% confidence interval [CI]: 0.693–1.050). No changes from baseline over time were observed within or between treatment groups in mean summary scores on the FACIT-Fatigue scale, EORTC-QLQ-C30 subscales, EORTC-QLQ-CLL16 items, EQ-5D-5L utility value, or EQ-5D VAS. However, SDs were relatively large, and the data trended toward larger changes at the lower end of the scales, suggesting that data from a majority of patients with small changes may have masked larger changes in a minority of patients. Therefore, a subgroup analysis was undertaken, as described in Materials and methods, focusing on patients with the worst baseline PRO scores, who had the greatest potential for HRQoL improvement.

Subgroup analyses by degree of impairment at baseline

Among patients who were most fatigued at baseline, FACIT-Fatigue scores improved by several points following initiation of therapy in both treatment groups (Figure 1), but to a greater extent overall in the ibrutinib-plus-BR group (mean change +11.21) than in the placebo-plus-BR group (+8.57; mean difference 2.64 [95% CI: 0.396–4.879]; $p=.0212$).

Similarly, patients with the greatest impairment in baseline physical functioning (lowest quartile for EORTC-QLQ-C30 Physical Functioning score) demonstrated improvements in functional ability that were significantly greater with ibrutinib plus BR (mean



Number of patients	
Placebo+BR/Least fatigued at BL	175 158 151 145 134 106 64 35 17 7 2 72
Ibrutinib+BR/Least fatigued at BL	189 179 170 165 157 147 106 79 43 22 3 30
Placebo+BR/Most fatigued at BL	76 65 62 62 54 52 33 17 8 2 - 32
Ibrutinib+BR/Most fatigued at BL	56 49 48 47 45 44 36 27 18 7 2 8
Compliance Rate (%)	90.6 82.8 79.7 77.8 73.0 66.0 45.2 29.7 16.2 7.3 1.3 27.6

Figure 1. Mean (SE) observed change over time in fatigue according to the degree of impairment at baseline. BL: baseline; BR: bendamustine plus rituximab; EOT: end of trial; SE: standard error. The compliance rates at each time point were calculated based on the total sample for each treatment arm at baseline.

change +18.7) than with placebo plus BR (+13.7; mean difference 5.0 [95% CI: 0.75–9.25]; $p = .0211$) (Figure 2). Patients in the upper three quartiles (i.e. least impairment in baseline physical functioning) showed little mean change over time.

EQ-5D VAS scores (self-rated health status) also showed improvement over time in the patient quartile with the lowest baseline scores; this improvement was not detected in the upper three quartiles, although the magnitude of improvement in the lowest quartile did not differ significantly between treatment groups (mean change +19.1 versus +20.7, respectively; $p = .5088$).

In the 90 patients who reported that they felt ill ‘quite a bit’ or ‘very much’ at baseline, approximately 20–30% achieved a return to well-being (reported feeling ‘not at all’ ill/unwell) by the first visit following treatment initiation. The proportion of patients achieving a return to well-being after Cycle 6 (i.e. after the end of BR background therapy) increased with time on treatment, to a greater extent in the ibrutinib-plus-BR group than in the placebo-plus-BR group (Figure 3).

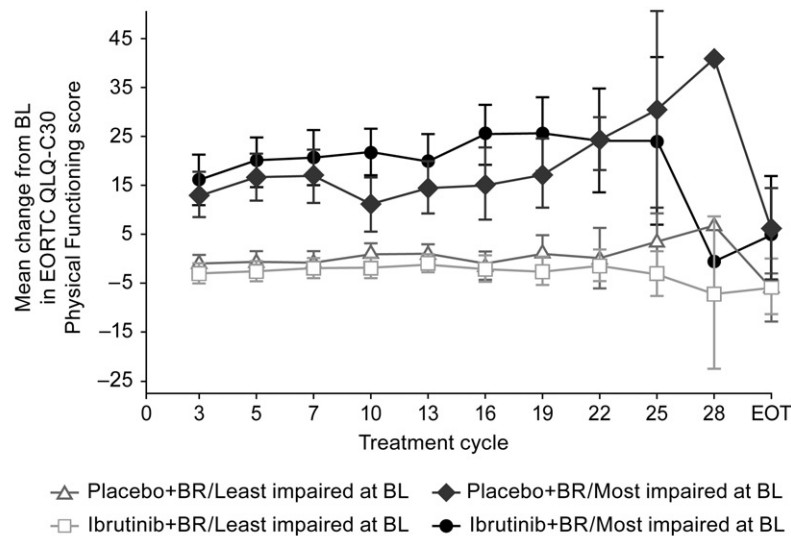
Association between fatigue and hemoglobin levels

In the HELIOS study, an initial decrease in mean hemoglobin levels, followed by increasing levels after

treatment Cycles 2–3, was observed in both the ibrutinib-plus-BR and placebo-plus-BR groups [14]. In the subgroup of patients with the worst baseline fatigue, changes in hemoglobin levels were consistent with those in the overall patient population, and increased in alignment with improvements in FACIT-Fatigue scores (Figure 4). Linear regression analysis of the association between hemoglobin levels and fatigue in this patient subgroup demonstrated that, during the first six treatment cycles, when fatigue improved at the greatest rate, changes in hemoglobin from the previous cycle significantly predicted concurrent changes in fatigue in the ibrutinib-plus-BR treatment group (baseline to Cycle 2 $r = 0.26$; Cycle 2 to Cycle 4 $r = 0.37$, and Cycle 4 to Cycle 6 $r = 0.33$; $p < .05$ for all) (Figure 5).

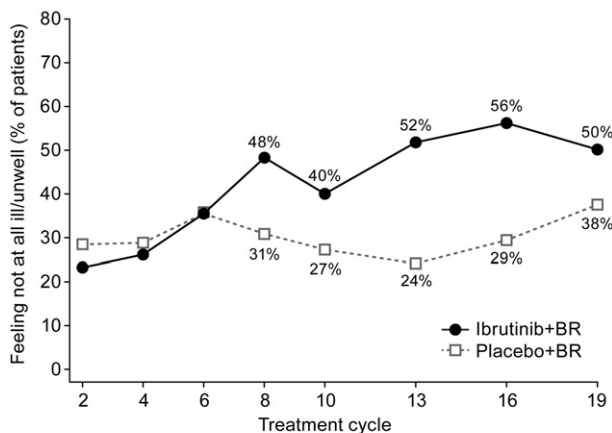
Discussion

The current analysis examined PROs in the HELIOS study to assess patient well-being and the impact of treatment with ibrutinib on HRQoL when added to BR background therapy. In the primary analysis, the addition of ibrutinib significantly improved PFS and overall response rate without unexpected or cumulative toxicities, compared with placebo plus BR in patients with relapsed/refractory CLL [14]. Consistent with the study entry criteria and the fact that BR was given as background therapy, all patients were deemed suitable



Number of patients	
Placebo+BR/Least impaired at BL	158 154 142 127 109 63 34 15 7 1 76
Ibrutinib+BR/Least impaired at BL	176 165 155 144 139 105 80 43 22 3 27
Placebo+BR/Most impaired at BL	72 65 60 56 45 33 17 10 2 1 28
Ibrutinib+BR/Most impaired at BL	61 55 53 53 49 35 25 17 7 2 11
Compliance rate (%)	87.3 81.7 77.8 71.4 65.7 45.2 29.7 16.2 7.3 1.3 27.6

Figure 2. Mean (SE) observed change over time in physical functioning according to the degree of impairment at baseline. BL: baseline; BR: bendamustine plus rituximab; EOT: end of trial; SE: standard error. The compliance rates at each time point were calculated based on the total sample for each treatment arm at baseline.



Number of patients	
Ibrutinib+BR	29 30 25 16 12
Placebo+BR	39 33 29 17 8

Figure 3. Changes over time in well-being for patients who reported feeling quite a bit or very ill/unwell at baseline as measured by the EORTC QLQ-CLL16 instrument. BR: bendamustine plus rituximab; EORTC QLQ-CLL16: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (specific module for symptoms or problems associated with chronic lymphocytic leukemia).

for chemoimmunotherapy. This PRO data analysis showed that most patients entered the trial with only a moderate degree of fatigue and HRQoL impairment at baseline, and mean values did not appear to change over time in either arm. These data indicate that in the overall patient population there was either

no room for improvement or the addition of ibrutinib did not improve nor adversely impact HRQoL, thus supporting a favorable benefit-risk ratio of ibrutinib. Similar findings were recently reported for the COMPLEMENT 2 phase 3 trial of patients with relapsed CLL, which assessed HRQoL outcomes with the addition of ofatumumab to fludarabine plus cyclophosphamide. PRO improvements were not significantly different between treatment arms for global health status/HRQoL ($p = .7278$) or B symptoms ($p = .5968$), suggesting that addition of ofatumumab did not have a negative impact [41].

However, *post-hoc* analysis of HELIOS data revealed that among the subgroup of patients with the worst fatigue, functional status, and well-being at baseline, greater improvements were achieved with ibrutinib plus BR. Improvements in fatigue paralleled increases in hemoglobin levels observed in both treatment groups (most rapidly during the BR treatment cycles). Linear regression analysis of the relationship between changes in hemoglobin level and fatigue score (for patients in the lowest quartile for baseline fatigue, regardless of treatment group) confirmed that an increase in hemoglobin was predictive of fatigue score improvement.

Because oncology trials tend to enroll patients who are well enough to benefit from treatment (per regulatory requirements), the effects of treatment on HRQoL

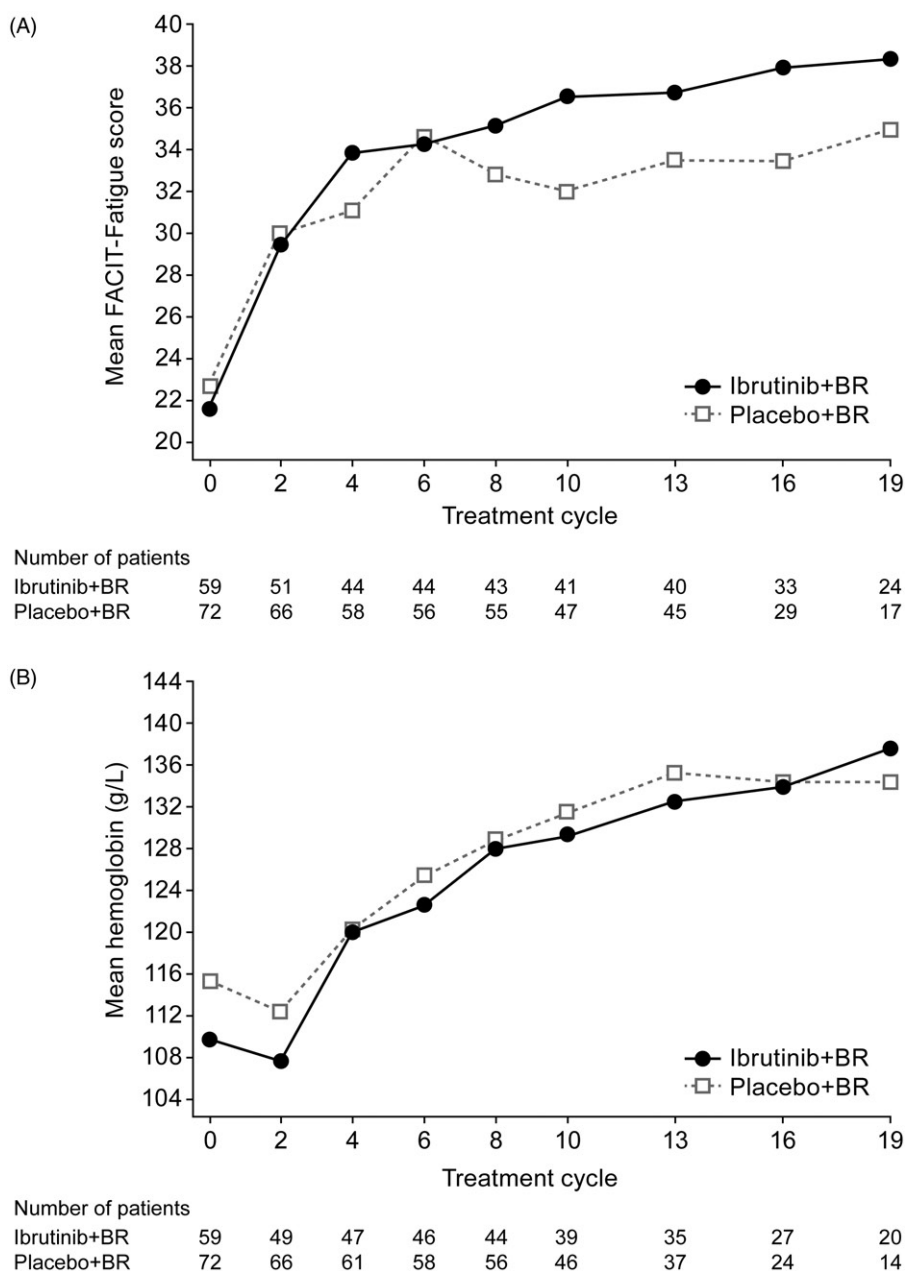


Figure 4. Concurrent mean changes in (A) FACIT-Fatigue scores and (B) hemoglobin levels in patients with high fatigue at baseline. BR: bendamustine plus rituximab; FACIT: Functional Assessment of Chronic Illness Therapy.

may be smaller than if sicker patients are enrolled [20]. This analysis demonstrates how significant improvements achieved in a proportion of patients may have been masked in the evaluation of PROs based on mean changes in the whole patient population. This supports our approach of stratifying patients into quartiles for analysis of PROs in a population with variable potential for overall improvement. In smaller samples, it may be appropriate to stratify patients above/below the median PRO score. Although there are some limitations to this approach (e.g. appropriate stratification cutoffs may vary between patient populations and differ for PRO measures), examining PRO

data in specific subgroups rather than for the whole population may be a more patient-centered approach that helps to more fully elucidate the patient experience. Furthermore, re-evaluation of inclusion criteria in oncology trials to enroll sicker patients may provide more representative insight into treatment effects on ‘real-world’ patients [23].

It is important to note that the data should be interpreted with caution. The subgroups of patients with the worst fatigue or physical impairment at baseline were relatively small. Overall, the number of patients with available data decreased during the follow-up period; hence, the number of patients included

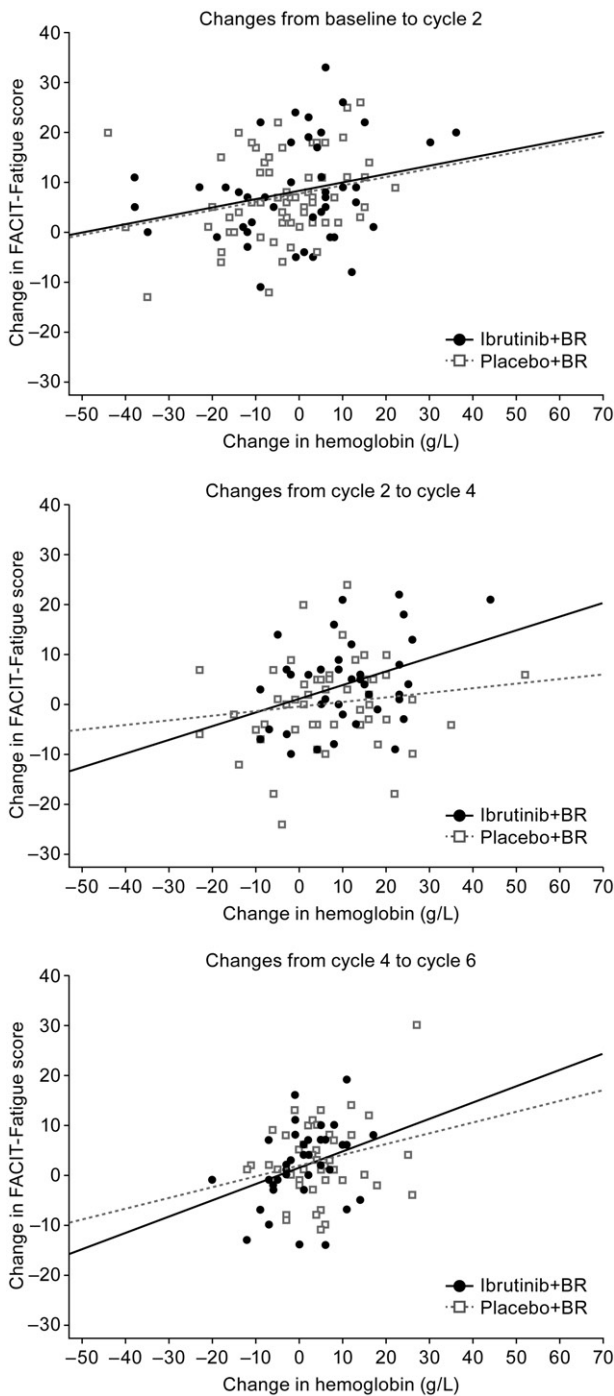


Figure 5. Correlation between improvements in FACIT-Fatigue score and hemoglobin levels in patients with high fatigue at baseline. BR: bendamustine plus rituximab; FACIT: Functional Assessment of Chronic Illness Therapy.

in the analyses after Cycle 19 is low. The remaining patients may represent those who responded better to treatment, or are in remission (patients who progressed/discontinued are more likely to have dropped out), which may introduce potential bias toward patients with better HRQoL scores and longer follow-up. Although the data suggest that addition of

ibrutinib to BR background therapy had no impact on patients' HRQoL in the PRO population, it cannot be concluded that this remains true after a longer treatment period (e.g. 2 years). Nevertheless, the safety profile of ibrutinib combined with BR in the HELIOS study was similar to that of the individual regimens and there were no unexpected safety signals; as the observed side effects were not cumulative [14], HRQoL would not be expected to be detrimentally affected by drug-related toxicities with ibrutinib added to BR.

Another limitation to interpretation of this analysis is that the HELIOS study was not designed to evaluate ibrutinib as a single agent or with rituximab versus ibrutinib plus BR. This analysis suggests that fatigue, physical functioning, and well-being were improved with the addition of ibrutinib to BR in the worst-affected patients, in addition to overall improvements in the quality and duration of treatment response. However, the question remains whether the BR backbone is necessary to achieve these improvements in this population of relapsed/refractory patients, or alternatively, whether BR dampens the HRQoL benefits of ibrutinib when given in combination.

Although data are limited, the positive impact of ibrutinib treatment on HRQoL has been reported in other trials. In a single-arm phase 2 study of ibrutinib plus rituximab for high-risk CLL, patients showed significant improvements in global health status, functioning, and symptom scales on the EORTC-QLQ-C30 at 12 months [42]. In the phase 3 RAY (MCL3001) trial of patients with relapsed/refractory mantle cell lymphoma, ibrutinib monotherapy was associated with improved Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) subscale and total scores, as well as EQ-5D-5L utility and EQ-5D VAS scores, compared with temsirolimus [43].

In conclusion, the results of this *post-hoc* analysis of the HELIOS study highlight that, although most patients had relatively good baseline HRQoL scores, patients with greater impairments or worse HRQoL cannot be overlooked, as they in particular require therapies that are well tolerated and do not further impair their HRQoL. In the HELIOS study, ibrutinib treatment added to a background BR regimen not only improved PFS and duration of treatment response in the overall study population, but also improved fatigue, physical functioning, and well-being in CLL patients with the greatest baseline deficits in these HRQoL domains. These findings emphasize the need for therapies that are both efficient and well tolerated for patients with poor functional status related to CLL.

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References

- [1] National Cancer Institute SEER website [Internet]. National Cancer Institute: Surveillance, Epidemiology, and End Results Program. SEER stat fact sheets: chronic lymphocytic leukemia (CLL). [Internet]; [cited 2017 Nov 27]. Available from: <http://seer.cancer.gov/statfacts/html/clyl.html>
- [2] Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(Suppl 5):v78–v84.
- [3] Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008;111:5446–5456.
- [4] Holtzer-Goor KM, Schaafsma MR, Joosten P, et al. Quality of life of patients with chronic lymphocytic leukaemia in the Netherlands: results of a longitudinal multicentre study. *Qual Life Res*. 2015;24:2895–2906.
- [5] Molica S, Mirabelli R, Molica M, et al. Clinical relevance and treatment of nonautoimmune anemia in chronic lymphocytic leukemia. *Cancer Manag Res*. 2011;3: 211–217.
- [6] Stephens JM, Gramegna P, Laskin B, et al. Chronic lymphocytic leukemia: economic burden and quality of life: literature review. *Am J Ther*. 2005;12:460–466.
- [7] Shanafelt TD, Bowen D, Venkat C, et al. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. *Br J Haematol*. 2007;139: 255–264.
- [8] Johnsen AT, Tholstrup D, Petersen MA, et al. Health related quality of life in a nationally representative sample of haematological patients. *Eur J Haematol*. 2009;83:139–148.
- [9] Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. *Semin Oncol*. 1998; 25(3 Suppl 7):43–46.
- [10] Cella D, Lai JS, Chang CH, et al. Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer*. 2002;94:528–538.
- [11] Littlewood T, Mandelli F. The effects of anemia in hematologic malignancies: more than a symptom. *Semin Oncol*. 2002;29(3 Suppl 8):40–44.
- [12] Imbruvica [prescribing information]. Sunnyvale, CA, USA: Pharmacyclics LLC; 2016. [Internet]; Available from: <https://www.imbruvica.com/prescribing-information>
- [13] Imbruvica [summary of product characteristics]. High Wycombe, UK: Janssen-Cilag Ltd; 2016. [Internet]; Available from: http://ec.europa.eu/health/documents/community-register/2014/20141021129815/anx_129815_en.pdf
- [14] Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. *Lancet Oncol*. 2016; 17:200–211.
- [15] Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013;369:32–42.
- [16] Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol*. 2011;29:3559–3566.
- [17] Strong LE. The past, present, and future of patient-reported outcomes in oncology. *Am Soc Clin Oncol Educ Book*. 2015;e616–e620. doi: [10.14694/EdBook_AM.2015.35.e616](https://doi.org/10.14694/EdBook_AM.2015.35.e616)
- [18] Basch E. Toward patient-centered drug development in oncology. *N Engl J Med*. 2013;369:397–400.
- [19] Basch E, Geoghegan C, Coons SJ, et al. Patient-reported outcomes in cancer drug development and US regulatory review: perspectives from industry, the

- Food and Drug Administration, and the patient. *JAMA Oncol.* 2015;1:375–379.
- [20] Fehnel S, DeMuro C, McLeod L, et al. US FDA patient-reported outcome guidance: great expectations and unintended consequences. *Expert Rev Pharmacoecon Outcomes Res.* 2013;13:441–446.
- [21] Schandelmaier S, Conen K, von EE, et al. Planning and reporting of quality-of-life outcomes in cancer trials. *Ann Oncol.* 2015;26:1966–1973.
- [22] U.S. Food & Drug Administration Web site [Internet]. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. [Internet]; [cited 2017 Nov 27]. Available from: <http://www.fda.gov/downloads/Drugs/Guidance/ComplianceRegulatoryInformation/Guidances/UCM193282.pdf>
- [23] Kim ES, Bernstein D, Hilsenbeck SG, et al. Modernizing eligibility criteria for molecularly driven trials. *J Clin Oncol.* 2015;33:2815–2820.
- [24] Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85:365–376.
- [25] Knobel H, Loge JH, Brenne E, et al. The validity of EORTC QLQ-C30 fatigue scale in advanced cancer patients and cancer survivors. *Palliat Med.* 2003;17:664–672.
- [26] Holzner B, Bode RK, Hahn EA, et al. Equating EORTC QLQ-C30 and FACT-G scores and its use in oncological research. *Eur J Cancer.* 2006;42:3169–3177.
- [27] Yellen SB, Cella DF, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manag.* 1997; 13:63–74.
- [28] NICE Web site [Internet]. Falconer S, Lloyd A. Utility measurement study for patients with chronic lymphocytic leukaemia: interim report. [Internet]; [cited 2017 Nov 27]. Available from: <https://www.nice.org.uk/guidance/ta174/documents/utility-measurement-study-for-patients-with-chronic-lymphocytic-leukaemia-interim-report2>
- [29] FACIT.org. Functional Assessment of Chronic Illness Therapy-Fatigue; a 13-item FACIT Fatigue Scale. 2017. April 24, 2017.
- [30] Acaster S, Dickerhoof R, DeBusk K, et al. Qualitative and quantitative validation of the FACIT-fatigue scale in iron deficiency anemia. *Health Qual Life Outcomes.* 2015;13:60.
- [31] Cella D, Lai JS, Stone A. Self-reported fatigue: one dimension or more? Lessons from the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire. *Support Care Cancer.* 2011;19: 1441–1450.
- [32] Cella D, Yount S, Sorensen M, et al. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. *J Rheumatol.* 2005;32:811–819.
- [33] Dapuelto JJ, Abreu MC, Francolino C, et al. Psychometric assessment of the MSAS-SF and the FACIT-Fatigue Scale in Spanish-speaking patients with cancer in Uruguay. *J Pain Symptom Manag.* 2014;47: 936–945.
- [34] Lai JS, Beaumont JL, Ogale S, et al. Validation of the functional assessment of chronic illness therapy-fatigue scale in patients with moderately to severely active systemic lupus erythematosus, participating in a clinical trial. *J Rheumatol.* 2011;38:672–679.
- [35] Cella D, Eton DT, Lai JS, et al. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manag.* 2002;24: 547–561.
- [36] Ediebah DE, Coens C, Zikos E, et al. Does change in health-related quality of life score predict survival? Analysis of EORTC 08975 lung cancer trial. *Br J Cancer.* 2014;110:2427–2433.
- [37] EORTC Quality of Life Web site [Internet]. EORTC - Chronic Lymphocytic Leukaemia (QLQ-CLL16). [Internet]; [cited 2017 Nov 27]. Available from: <http://groups.eortc.be/qol/chronic-lymphocytic-leukaemia-qlq-cll16>
- [38] Devlin NJ, Krabbe PF. The development of new research methods for the valuation of EQ-5D-5L. *Eur J Health Econ.* 2013;14(Suppl 1):S1–S3.
- [39] EuroQoL Group Association Web site [Internet]. EuroQoL EQ-5D-5L Questionnaire. [Internet]; [cited 2017 Nov 27]. Available from: <http://www.euroqol.org/about-eq-5d.html>
- [40] Movsas B, Hunt D, Watkins-Bruner D, et al. Can electronic web-based technology improve quality of life data collection? Analysis of Radiation Therapy Oncology Group 0828. *Pract Radiat Oncol.* 2014;4: 187–191.
- [41] Robak T, Warzocha K, Govind BK, et al. Health-related quality of life and patient-reported outcomes of ofatumumab plus fludarabine and cyclophosphamide versus fludarabine and cyclophosphamide in the COMPLEMENT 2 trial of patients with relapsed CLL. *Leuk Lymphoma.* 2017;58:1598–1606.
- [42] Burger JA, Keating MJ, Wierda WG, et al. Safety and activity of ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: a single-arm, phase 2 study. *Lancet Oncol.* 2014;15:1090–1099.
- [43] Hess G, Rule S, Jurczak W, et al. Health-related quality of life data from a phase 3, international, randomized, open-label, multicenter study in patients with previously treated mantle cell lymphoma treated with ibrutinib versus temsirolimus. *Leuk Lymphoma.* 2017;58: 2824–2832.