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RESEARCH ARTICLE

Establishing meaningful change thresholds for European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire CLL-specific module domain scores: An analysis based on the TRANSCEND CLL 004 study in patients with relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic lymphoma

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Abstract

Introduction: The study aimed to establish meaningful thresholds at patient and group levels for the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire CLL-specific module (EORTC QLQ-CLL17) domain scores in adults with relapsed or refractory (R/R) chronic lymphocytic leukaemia (CLL).

Material and methods: Data for the analysis were from the TRANSCEND CLL 004 study (NCT03331198). EORTC QLQ-CLL17 and selected anchor measures were assessed at baseline and multiple postbaseline visits up to 24 months after treatment initiation. Thresholds for each of the three EORTC QLQ-CLL17 domains were triangulated based on estimates derived from anchor- and distribution-based analyses, in accordance with published guidance.

Results: The analysis included 62 patients with 240 observations across visits. Meaningful change thresholds for improvement and deterioration, respectively, at the patient level were determined to be −11/+11 for symptom burden, −16/+16 for physical condition/fatigue and −16/+13 for worries/fears on health and functioning. The meaningful change thresholds for improvement and deterioration at the group level mostly ranged between 0.3 and 0.5 of the standard deviation of baseline domain scores.

Conclusions: These thresholds, based on EORTC QLQ-CLL17 domain scores, could help identify patients with meaningful changes in HRQOL and interpret treatment effects in future studies of treatments for adults with R/R CLL.

KEYWORDS
chronic lymphocytic leukaemia, clinically important change, EORTC QLQ-CLL17, meaningful within-patient change

1 | INTRODUCTION

Chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (subsequently referred to as CLL) are non-Hodgkin lymphomas in which abnormal B cells accumulate in the blood and bone marrow or lymph nodes [1] and are the most common adult leukaemia in the United States and Europe [2, 3]. Patients with CLL face a significant clinical burden and experience symptoms such as fever, night sweats, weight loss and fatigue [1]. In addition, health-related quality of life (HRQOL) in patients with CLL is worse than that in people from age- and sex-matched normative populations as a result of disease-related symptoms and/or treatment-related side effects [4–10].

Advances in treatments for CLL have substantially improved patients' survival [11]. Despite that, alternative treatment options are still needed, especially for patients with relapsed or refractory (R/R) CLL [1]. When investigating novel treatments, it is critical to understand how they impact HRQOL, in addition to survival and disease progression [12, 13]. This requires the use of patient-reported outcome (PRO) instruments that have adequate psychometric performance to validly and reliably capture changes in important aspects of HRQOL.

Historically, there was no disease-specific PRO instrument for assessing HRQOL in patients with CLL [14]. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire CLL-specific module (EORTC QLQ-CLL17) was therefore developed with input from patients with CLL and healthcare professionals [14]. It is intended to be used along with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items (EORTC QLQ-C30) [15] to measure the three domains (symptom burden, physical condition/fatigue and worries/fears on health and functioning) that are most relevant to patients with CLL [14]. The validity and reliability of the EORTC QLQ-CLL17 have been confirmed in a large international sample, supporting its use in assessing HRQOL domains that are meaningful to patients with CLL [16]. However, there is no published guidance on how to interpret score changes in each of the EORTC QLQ-CLL17 domains.

The aim of this analysis was to determine meaningful change thresholds that could be used to guide the interpretation of EORTC QLQ-CLL17 domain scores in adults with R/R CLL at the individual patient and group levels. Specifically, the primary objective of the analysis was to identify meaningful within-patient change [MWPC]) thresholds that can be used to define individual patients who experience meaningful changes in EORTC QLQ-CLL17 domains as an end-point in clinical studies. The secondary objective was to determine the clinically important change (CIC) and clinically important difference (CID) thresholds for each domain of the EORTC QLQ-CLL17 to interpret the meaningfulness of within-group changes and between-group differences, respectively, in patients with R/R CLL.

2 | METHODS

2.1 | TRANSCEND CLL 004 study design

Data for the analysis were from phase 2 of the TRANSCEND CLL 004 study (NCT03331198), a phase 1/2, open-label, multicentre study that examined the efficacy and safety of lisocabtagene maraleucel (liso-cel) in adults with R/R CLL. The design and primary findings of the TRANSCEND CLL 004 study (see Methods S1) were reported previously [17].

2.2 | PRO measures

Three PRO measures were administered to patients in the study, including the EORTC QLQ-CLL17 [14], EORTC QLQ-C30 [15], and EQ-5D-5L [18] (see Methods S1). All PROs were completed by patients at baseline (≤7 days before lymphodepleting chemotherapy), predosing on the day of liso-cel infusion and 1, 2, 3, 6, 9, 12, 15, 18, and 24 months after infusion during phase 2 of the study (Figure 1). Data from these measures were used to support this analysis.

2.3 | Estimating meaningful change thresholds

MWPC thresholds (patient-level change) for EORTC QLQ-CLL17 domains were estimated using the anchor-based method as the primary approach and the distribution-based method as a supportive approach (see Method S1), according to US Food and Drug Administration (FDA) guidance [19, 20]. Rationales for the anchors included in the analysis are described in Method S1.

The estimates resulting from different anchors and approaches were triangulated. A range of MWPC thresholds for meaningful improvement and deterioration was selected based on the mean and median score changes in the EORTC QLQ-CLL17 domains from the anchor groups with size changes in the selected anchors being considered meaningful (e.g., ≥1 level of improvement/deterioration). A responder definition (RD), the value from the range of MWPC thresholds that are prioritized, for each direction (improvement/deterioration) was then proposed by considering possible state changes of the target PRO domain (i.e., for each 1-point change on the raw scale of a given EORTC QLQ-CLL17 domain, the number of points that would change on the standardized scale), and the lower bound threshold set by one standard error of the mean (SEM) for that domain (i.e., RD should be ≥SEM).

CIC (within-group changes) and CID (between-group differences) thresholds were estimated following methods used by the EORTC Quality of Life Groups [21–23]. These thresholds were identified for each of the EORTC QLQ-CLL17 domains by triangulating estimates from both anchor-based methods and distribution-based estimates considering a small (0.3 × standard deviation [SD]) to medium

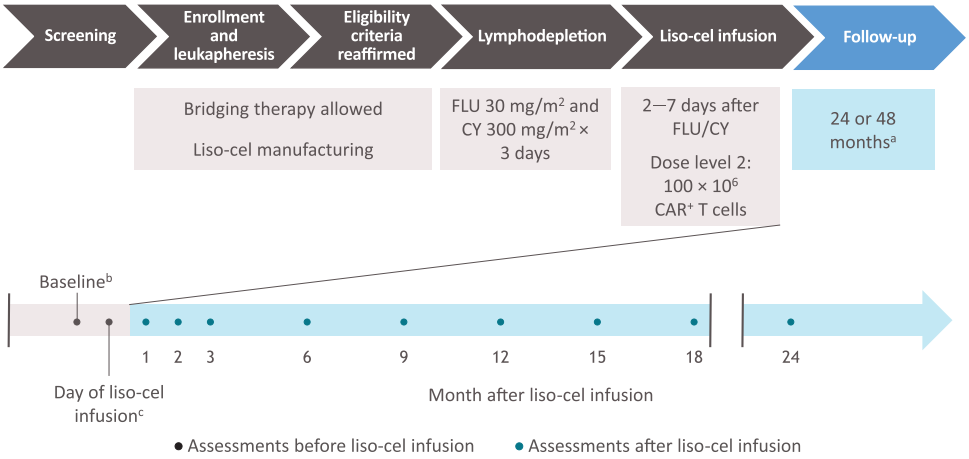

FIGURE 1 TRANSCEND CLL 004 study flow and HRQOL assessment schedule. [a]Duration of follow-up was increased to 48 months in protocol amendment 5 (16 February 2021). Patients who remained in ongoing response per International Workshop on Chronic Lymphocytic Leukemia 2018 criteria after the 2-year follow-up were followed for an additional 2 years or until progression. [b]Seven days or less before lymphodepleting chemotherapy. [c]Predosing on the day of liso-cel infusion. CAR, chimeric antigen receptor; CY, cyclophosphamide; FLU, fludarabine; HRQOL, health-related quality of life; liso-cel, lisocabtagene maraleucel.

(0.5 × SD) effect size [24]. For CIC thresholds, anchor-based estimates were obtained from the observed mean score change of the anchor groups with one level of improvement/deterioration based on the same anchors used for MWPC. For CID thresholds, anchor-based estimates were obtained from the difference in the least squares mean change between the anchor groups with one level of improvement (deterioration) and no change using the analysis of covariance, controlling for baseline score. Estimates from the anchor-based analyses that substantially exceeded a medium (0.5 × SD) effect size were de-prioritized, as they may be too stringent to be used as CIC or CID thresholds.

2.4 | Statistical analyses

All analyses were performed on the PRO-evaluable analysis set, defined as all patients who had an evaluable assessment of the EORTC QLQ-CLL17 at baseline and at least one evaluable assessment at a postbaseline visit. An evaluable assessment at a given visit was defined as at least one of the three domains not missing for that assessment visit. For the descriptive analyses of continuous variables, the mean, SD, 95% confidence interval, minimum, percentiles (25th, 50th and 75th) and maximum were summarised. For the descriptive analyses of categorical variables, the frequency and percentage of each category were summarised. All statistical analyses were conducted using SAS version 9.4.

3 | RESULTS

3.1 | Patients and characteristics at baseline

Among patients who underwent leukapheresis ($N = 112$) in the study, 62 (55%) were included in the PRO-evaluable analysis set (Table 1). The low rate of inclusion was mainly due to the PRO assessments being added to the study during an amendment after trial initiation, as well as coronavirus disease 2019-related restrictions impacting PRO completion. Information on patient characteristics at baseline is provided in Results S1.

3.2 | MWPC thresholds

The anchor-based analysis included score changes from baseline pooled from 240 observations between 1 and 18 months obtained from the 62 patients in the PRO-evaluable analysis set. Descriptive statistics of changes from baseline in each of the EORTC QLQ-CLL17 domains by anchor group are provided in Results S1. Mean and median changes from baseline in each domain of the EORTC QLQ-CLL17 by each anchor group, as well as estimates from the distribution-based analyses and minimum state changes for all domains, are summarised in Table 2.

For the symptom burden domain, potential MWPC threshold ranges based on the mean and median changes obtained from all target anchor groups fell between −8.13 and −17.81 points for improvement and 7.44 and 11.85 points for deterioration (Table 2). The lower bounds of these ranges were slightly lower than the SEM (8.63) estimated for this domain. As the minimum state change (i.e., a 1-point change on the raw scale) for the symptom burden domain is ± 5.56 points, this suggests that patients would need to experience a ≥2-point change on the raw scale (or an ± 11.12-point change on the standardised scale) to exceed the SEM, while falling within the ranges of the MWPC thresholds. Based on these, an ≥11-point decrease and increase (after rounding down) were proposed as the RD thresholds for defining meaningful improvement and deterioration, respectively, in the symptom burden domain. These thresholds also exceed the medium effect size of 0.5 × SD (9.01), indicating that an ≥11-point change in the symptom burden

TABLE 1 Baseline demographic, disease characteristics and patient-reported outcome (PRO) scores.

Characteristic	Patients (*N* = 62)
Age, years, mean (SD)	64.3 (6.85)
Female, *n* (%)	17 (27)
Ethnicity, *n* (%)	
Hispanic or Latino	0
Not Hispanic or Latino	56 (90)
Not reported	6 (10)
Race, *n* (%)	
White	56 (90)
African American	1 (2)
Unknown	5 (8)
Disease type, *n* (%)	
CLL	58 (94)
SLL	4 (6)
Disease status after last treatment, *n* (%)	
Refractory	50 (81)
Relapsed	0
Unknown	12 (19)
Response to BTKi	
N	62
Refractory, *n* (%)[a]	54 (87)
Relapsed, *n* (%)[b]	0
Intolerant, *n* (%)	18 (29)
Intolerant only, *n* (%)	8 (13)
Response to venetoclax, *n* (%)[c]	
Prior venetoclax	53 (85)
Refractory[a]	47 (76)
Intolerant	10 (16)
Intolerant only	5 (8)
Baseline ECOG PS, *n* (%)	
0	17 (27)
1	44 (71)
2	1 (2)
3	0
High-risk cytogenetics, *n* (%)	
Yes	54 (87)
No	8 (13)
EORTC QLQ-CLL17	62
Symptom burden	
Mean (SD)	25.0 (18.0)
Median	22.2
Min–max	0.0–61.1
Physical condition/fatigue	
Mean (SD)	31.0 (22.2)
Median	25.0
Min–max	0.0–100.0
Worries/fears on health and functioning	
Mean (SD)	31.1 (18.5)
Median	27.6
Min–max	0.0–100.0

Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukaemia; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-CLL17, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire CLL-specific module; PRO, patient-reported outcome; SD, standard deviation; SLL, small lymphocytic lymphoma.

[a]No response or disease progression ≤6 months from the last dose of therapy.

[b]Disease progression after remission or a complete response (with or without complete bone marrow recovery) or a partial response/nodular partial response lasting ≥6 months.

[c]Percentages were calculated using the number of people who had received BTKi as the denominator.

domain should represent a substantial improvement or worsening in symptom burden at the patient level.

For the physical condition/fatigue domain, the potential MWPC threshold ranges fell between −16.67 and −25.00 points for improvement and 8.33 and 16.67 points for deterioration (Table 2). Given the estimated SEM of 8.42 and the minimum state change of ± 8.33 for the physical condition/fatigue domain, patients would need to experience at least a ± 16.67-point change (or a ± 2-point change on the raw scale) to exceed the SEM, while falling within the ranges of the MWPC thresholds. Thus, a ≥16-point decrease and increase were proposed as the RD thresholds for defining a meaningful improvement and deterioration in the physical condition/fatigue domain, respectively. These thresholds also exceed the medium effect size of 0.5 × SD (11.09), representing a substantial improvement or worsening at the patient level.

For the worries/fears in the health and functioning domain, the potential MWPC threshold ranges fell between −15.47 and −19.52 for improvement and 0 and 10.18 for deterioration (Table 2). The lower bound (−15.47) of the MWPC threshold for improvement exceeded the SEM of 11.42, indicating that the RD threshold identified from this range should well exceed the amount of measurement error associated with this domain. By considering its minimum state changes, which can be many because the two optional items within the worries/fears on health and functioning domain may or may not be answered by patients at baseline or postbaseline visits, patients would need to experience a ≥16.67-point change (which was selected based on an actual score change observed in the study) to exceed the SEM, while falling within the range of the MWPC threshold for improvement. Thus, a ≥16-point decrease was proposed as the RD threshold for defining a meaningful improvement in the worries/fears on the health and functioning

TABLE 2 Estimates of meaningful within-patient change (MWPC) thresholds for European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire CLL-specific module (EORTC QLQ-CLL17) domains.

EORTC QLQ-CLL17 domain	Anchor (EORTC QLQ-C30)	Anchor-based estimates (mean/median score change)		Distribution-based estimates		Minimum state change	Proposed RD threshold for improvement/deterioration
		≥1 level of improvement on anchor	≥1 level of deterioration on anchor	0.5 × SD	SEM		
Symptom burden	Item 9 (pain)	−9.94/−8.13	7.44/8.33	9.01	8.63	±5.56	≤−11/≥11
	Item 12 (weakness)	−12.83/−11.11	9.16/11.11				
	Item 29 (overall health)	−17.81/−16.67	11.85/11.11				
Physical condition/fatigue	Item 12 (weakness)	−21.21/−25.00	12.87/8.33	11.09	8.42	±8.33	≤−16/≥16
	Item 29 (overall health)	−19.85/−16.67	15.56/16.67				
Worries/fears on health and functioning	Item 22 (worry)	−15.47/−16.67	7.08/0.00	9.24	11.42	±6.67 (if 5 items answered); ±4.76 (if 7 items answered)[a]	≤−16/≥13
	Item 29 (overall health)	−19.24/−19.52	10.18/4.76				

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; EORTC QLQ-CLL17, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire CLL-specific module; MWPC, meaningful within-patient change; RD, responder definition; SD, standard deviation; SEM, standard error of the mean.

[a]Other values possible if patients responded to two optional questions only at baseline or post-baseline.

domain. As for the MWPC threshold range of 0–10.18 for deterioration, these estimates cannot be used to support the determination of the RD threshold, as the upper bound (10.18) was below the SEM of 11.42. For this reason, a 13-point increase was proposed, which is the next possible actual change (6.67 × 2 = 13.33) that may occur at the patient level and exceed the SEM of 11.42 for this domain.

3.3 | CIC and CID thresholds

Estimates from both the anchor-based and distribution-based analyses that can be considered to inform the CIC and CID thresholds for each domain of the EORTC QLQ-CLL17 are summarised in Table 3. For the symptom burden domain, estimates for the CIC threshold from the anchor-based methods were found to be between −9.06- and −18.72-point changes, corresponding to effect sizes of −0.51 (medium effect size) and −1.05 (large effect size) [25], respectively, for improvement. For deterioration, estimates were between 6.94- and 10.10-point changes, corresponding to effect sizes of 0.39 (small effect size) and 0.57 (medium effect size), respectively. Given the CIC threshold is intended to be used to interpret the meaningfulness of a mean change at a group level, any CIC threshold that represents a greater than medium effect size may be too stringent to achieve in a typical clinical study. Thus, estimates from distribution-based methods, based on a small (0.3 × SD = 5.40) to medium (0.5 × SD = 9.01) effect size, may be considered. Estimates for the CID threshold from the anchor-based methods for the symptom burden domain were found to be between −4.39- and −13.33-point differences, corresponding to a small effect size of −0.26 and a large effect size of −0.77 for improvement. Estimates were between 9.52- and 10.88-point differences for deterioration, corresponding to effect sizes of 0.55 (medium effect size) and 0.63 (medium effect size), respectively.

For the physical condition/fatigue domain, estimates for the CIC threshold from the anchor-based methods were found to be between −15.58- and −17.28-point changes, corresponding to effect sizes of −0.71 (medium effect size) and −0.79 (approximately a large effect size), respectively, for improvement. For deterioration, estimates were between 12.50- and 12.88-point changes, corresponding to effect sizes of 0.57 (medium effect size) and 0.59 (medium effect size), respectively. Estimates from distribution-based methods based on a small (0.3 × SD) to medium (0.5 × SD) effect size were 6.66 and 11.09, respectively. Estimates for the CID threshold from the anchor-based methods for the physical condition/fatigue domain were found to be between −9.19- and −9.69-point differences, corresponding to effect sizes of −0.42 (small effect size) and −0.44 (small effect size), respectively, for improvement. For deterioration, estimates were between 11.47- and 14.95-point differences, corresponding to effect sizes of 0.53 (medium effect size) and 0.68 (medium effect size), respectively.

For the worries/fears on health and functioning domain, estimates for the CIC threshold from the anchor-based methods were found to be between −12.93- and −15.80-point changes, corresponding to effect sizes of −0.68 (medium effect size) and −0.83 (large effect size), respectively, for improvement. For deterioration, estimates were between 1.26- and 4.16-point changes, corresponding to effect sizes of 0.07 (trivial effect size) and 0.22 (small effect size), respectively. Estimates from distribution-based methods based on a small (0.3×SD) to medium (0.5×SD) effect size were 5.54 and 9.24, respectively. Estimates for the CID threshold from the anchor-based methods for the worries/fears

TABLE 3 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire CLL-specific module (EORTC QLQ-CLL17) domains: Estimates of clinically important change (CIC) and clinically important difference (CID) thresholds.

		CIC		CID		Distribution-based estimates	
EORTC QLQ-CLL17 domain	Anchor (EORTC QLQ-C30)	Mean score change (ES) for 1 level of improvement	Mean score change (ES) for 1 level of deterioration	LS mean score difference (ES) for 1 level of improvement vs. no change	LS mean score difference (ES) for 1 level of deterioration vs. no change	0.3 × SD	0.5 × SD
Symptom burden	Item 9 (pain)	−9.06 (−0.51)	6.94 (0.39)	−4.39 (−0.26)	10.88 (0.63)		
	Item 12 (weakness)	−10.87 (−0.61)	8.78 (0.49)	−5.80 (−0.34)	10.08 (0.59)	5.40	9.01
	Item 29 (overall health)	−18.72 (−1.05)	10.10 (0.57)	−13.33 (−0.77)	9.52 (0.55)		
Physical condition/fatigue	Item 12 (weakness)	−15.58 (−0.71)	12.50 (0.57)	−9.19 (−0.42)	14.95 (0.68)	6.66	11.09
	Item 29 (overall health)	−17.28 (−0.79)	12.88 (0.59)	−9.69 (−0.44)	11.47 (0.53)		
Worries/fears on health and functioning	Item 22 (worry)	−12.93 (−0.68)	4.16 (0.22)	−10.10 (−0.54)	7.87 (0.42)	5.54	9.24
	Item 29 (overall health)	−15.80 (−0.83)	1.26 (0.07)	−8.29 (−0.44)	7.37 (0.39)		

Abbreviations: CIC, clinically important change; CID, clinically important difference; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items; EORTC QLQ-CLL17, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire CLL-specific module; ES, effect size; LS, least squares; SD, standard deviation.

on health and functioning domain were found to be between −8.29- and −10.10-point differences, corresponding to a small effect size of −0.44 and a medium effect size of −0.54 for improvement. Estimates were between 7.37- and 7.87-point differences for deterioration, corresponding to small effect sizes of 0.39 and 0.42, respectively.

4 | DISCUSSION

The objective of these analyses was to determine meaningful change thresholds at the patient and group levels to guide the interpretation of the EORTC QLQ-CLL17 domain scores in adults with R/R CLL. To our knowledge, this is the first analysis to propose meaningful change thresholds for interpreting improvement and deterioration in EORTC QLQ-CLL17 domain scores at the patient (i.e., MWPC) and group (i.e., CIC and CID) levels in patients with R/R CLL. These thresholds may be useful in clinical studies to define treatment responders (using MWPC/RD) with respect to HRQOL or aid in the interpretation of the meaningfulness of within-group mean changes from baseline (using CIC) and between-group difference in mean changes (using CID) based on this instrument.

Although the potential range of MWPC thresholds for improvement and deterioration could vary to some extent depending on the anchor used, results of the analyses suggested RD thresholds for improvement (deterioration) of ≥11-point decrease (11-point increase) for the symptom burden domain, ≥16-point decrease (16-point increase) for the physical condition/fatigue domain and ≥16-point decrease (13-point increase) for the worries/fears on health and functioning domain may represent optimal thresholds.

These RD thresholds represent a ≥2-point change on the raw scale for all domains, except for the threshold for improvement in the worries/fears on health and functioning domain, which required a ≥3- to 4-point change on the raw scale. A 2-point change on the raw scale of the EORTC QLQ-CLL17 domains (except the worries/fears on health and functioning domain) is the next state change above a standardised score of 10. Patients who meet the 10-point change threshold, a commonly used threshold for the EORTC QLQ-C30 to define responders in clinical trials [26], would also meet the proposed thresholds for these domains. This suggests that these proposed RD thresholds are within a reasonable range that is consistent with the threshold used in the EORTC QLQ-C30 domains. Finally, proposed RD thresholds for the EORTC QLQ-CLL17 are also approximately equivalent to 15% of the scale range, proposed by the Institute for Quality and Efficiency in Health Care, as a meaningful change threshold for a given PRO measure to identify responders [27].

Thresholds for interpreting meaningful changes at the group level have been recommended to be based on the magnitude of effect size being considered for a clinical study, and at least a small effect size should be considered [28, 29]. All CIC and CID threshold estimates for improvement (deterioration) in any domain from the anchor-based analysis represent at least a small effect size, except for the CIC threshold for deterioration in the worries/fears on the health and functioning domain. Most estimates were between small to medium effect size, with only a few estimates close to or exceeding a large effect size

(i.e., CIC thresholds for improvement in the symptom burden, physical condition/fatigue and worries/fears on health and functioning domains). These findings are consistent with those estimated for domains of the EORTC QLQ-C30 from 21 clinical trials involving nine different cancer types, with most anchor-based CIC and CID thresholds ranging between 0.3 × SD and 0.5 × SD [24]. Based on the same effect sizes of 0.3 × SD and 0.5 × SD, the CIC and CID thresholds would be between 5.40 and 9.01 points for the symptom burden domain, 6.66 and 11.09 points for the physical condition/fatigue domain and 5.54 and 9.24 points for the worries/fears on health and functioning domain.

The analysis was not without limitations and was performed using a small sample size ($n = 62$). To address this, multiple postbaseline visits assessed between Month 1 and Month 18 from the same individual patients were pooled. Although the thresholds derived from this analysis are reasonable and consistent with thresholds for other PRO measures developed by the EORTC Quality of Life Groups, they should be further validated using a larger sample size, in the frontline CLL setting and with different treatment modalities. Finally, although commonly recommended anchors, such as the patient global impression of severity and patient global impression of change, were not included in this study, the anchors used in this analysis did meet the key criteria (see "Estimating meaningful change thresholds" in Methods S1) proposed by the FDA [19] and led to thresholds that are consistent with thresholds publicly reported for other EORTC quality of life instruments [24, 26].

The results of this analysis provide MWPC/RD, CIC and CID thresholds for the three EORTC QLQ-CLL17 domain scores. These estimated thresholds may be used to identify patients with meaningful improvements in HRQOL based on PRO data and guide interpretation of the EORTC QLQ-CLL17 domain scores when used to assess treatment effects in future clinical trials.

AUTHOR CONTRIBUTIONS

Laurie Eliason, Fatoumata Fofana, Lin Wang, Peter A. Riedell and Shien Guo contributed to the study design, data analysis and data interpretation. Peter A. Riedell performed data acquisition. All authors contributed to the writing and/or review of the manuscript and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Laurie Eliason and Lin Wang are employees of Bristol Myers Squibb and may own stock. Fatoumata Fofana is an employee of Evidera PPD. Shien Guo is an employee of Evidera PPD and reports consultancy fees from Bristol Myers Squibb. Peter A. Riedell reports consultancy fees for AbbVie, Bristol Myers Squibb, CVS Caremark, Genentech, Janssen, Novartis, Pharmacyclics and Sana Biotechnology; research funding from Bristol Myers Squibb, Calibr, CRISPR Therapeutics, Fate Therapeutics, Kite/Gilead, Nkarta, Novartis, Roche, Tessa Therapeutics and Xencor; membership on the Board of Directors or advisory committees for ADC Therapeutics, BeiGene, Bristol Myers Squibb, Genmab, Intellia Therapeutics, Kite/Gilead, Nektar Therapeutics and Novartis.

DATA AVAILABILITY STATEMENT

Bristol Myers Squibb's policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

ETHICS STATEMENT

The study, from which data for this analysis were obtained, was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice guidelines and applicable regulatory requirements. Institutional review boards at participating institutions approved the study protocol and amendments.

PATIENT CONSENT STATEMENT

Data for this analysis were obtained from a study in which all patients provided written informed consent before any study-related procedures.

CLINICAL TRIAL REGISTRATION

Data for the analysis were from phase 2 of the TRANSCEND CLL 004 study (NCT03331198).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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