Establishing meaningful change thresholds for EORTC QLQ-CLL17 domain scores: an analysis based on the TRANSCEND CLL 004 study in patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma

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Introduction

- When investigating novel treatments for patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) that are relapsed or refractory (R/R) to treatment, it is critical to understand the impact of these treatments on health-related quality of life (HRQOL), survival, and disease progression[1,2]
- The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire 17-item Chronic Lymphocytic Leukemia–specific module (EORTC QLQ-CLL17) is a disease-specific module for assessing patient-reported HRQOL in CLL.[2–4] It consists of 3 multi-item scales capturing the following 3 concepts: 1) symptom burden, 2) physical condition/fatigue, and 3) worries/fears on health and functioning[2–4]
  - Each item is scored from 1 to 4, each domain score is transformed into a scale from 0 to 100, and higher scores indicate worse symptoms or HRQOL[3]
- The validity and reliability of the EORTC QLQ-CLL17 in assessing HRQOL in CLL was confirmed in a large international sample[3]
- There is no published guidance on how to interpret score changes in each of the EORTC QLQ-CLL17 domains

Objective

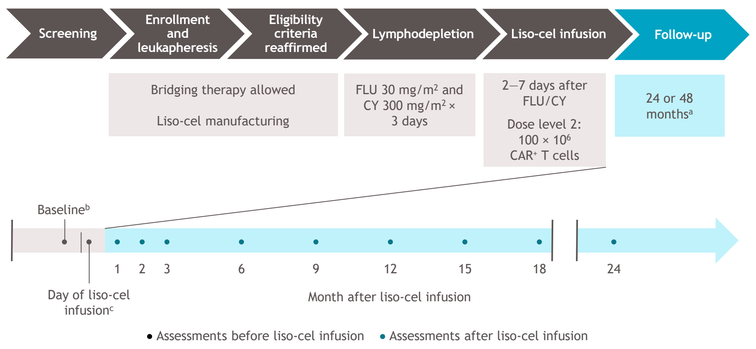
- To establish meaningful change thresholds at the patient and group levels for each of the EORTC QLQ-CLL17 domains in patients with R/R CLL/SLL

Methods

Data collection

- Data were used from TRANSCEND CLL 004 (NCT03331198), an ongoing, phase 1/2, open-label study to determine the efficacy and safety of lisocabtagene maraleucel (liso-cel) in patients with R/R CLL/SLL
- Patients had to meet the following eligibility criteria:
  - Age ≥ 18 years
  - Diagnosed with R/R CLL/SLL with an indication for treatment
  - Failed or ineligible for Bruton tyrosine kinase inhibitor therapy
  - Failed ≥ 2 (high risk) or ≥ 3 (standard risk) lines of therapy
  - Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤ 1
  - Adequate bone marrow, organ, and cardiac function
  - No Richter transformation or active central nervous system involvement

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 (February 16, 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.

- Patients completed the EORTC QLQ-CLL17 and other HRQOL measures, including the EORTC QLQ-C30 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 liso-cel infusion (**Figure 1**)

Analysis

- Thresholds for meaningful within-patient change (MWPC), within-group clinically important change (CIC), and between-group clinically important difference (CID) were derived for each EORTC QLQ-CLL17 domain by triangulating estimates from anchor-based and distribution-based approaches
- MWPC thresholds were estimated following United States Food and Drug Administration guidance for patient-reported outcomes,[5,6] and CIC and CID thresholds were estimated following methods commonly used by the EORTC Quality of Life group[7–9]
- The analysis population included those who received liso-cel monotherapy and had an evaluable EORTC QLQ-CLL17 assessment at baseline and at ≥ 1 postbaseline visit
- Due to sample size (n = 62), HRQOL data were pooled across visits from 1 to 18 months after liso-cel infusion; data on the day of infusion and ≥ 24 months after infusion were not used
  - Pooling was supported by the homogeneous distributions of observed change from baseline in EORTC QLQ-CLL17 domain scores across postbaseline assessment visits for a given level of change on a given external anchor

Table 1. Anchors used for each EORTC QLQ-CLL17 domain

EORTC QLQ-CLL17 domain	EORTC QLQ-C30 anchor item	Anchor item text ("during the past week")
Symptom burden	9 (pain)	Have you had pain?
	12 (weakness)	Have you felt weak?
	29 (overall health)	How would you rate your overall health?
Physical condition/ fatigue	12 (weakness)	Have you felt weak?
	29 (overall health)	How would you rate your overall health?
Worries/fears on health and functioning	22 (worry)	Did you worry?
	29 (overall health)	How would you rate your overall health?

- Selected external anchors (**Table 1**) had similar or related concepts to EORTC QLQ-CLL17 domains, adequate correlations ($r \geq 0.3$), and the same recall period
  - Response options were easily interpreted to indicate different levels of change

MWPC thresholds (patient-level analysis)

- Anchor-based estimates were based on levels of change on the EORTC QLQ-CLL17 domains in patients with a certain level of change on the relevant selected anchors (**Table 1**)
  - Anchor-based response categories with n < 15 were collapsed into the adjacent category if clinically meaningful to do so
- Distribution-based estimates supporting selection of the MWPC thresholds were based on ± 1 standard error of the mean (SEM) and 0.5 × baseline standard deviation (SD)
- A range of MWPC thresholds was estimated considering the mean and median score changes on the EORTC QLQ-CLL17 domains from the target anchor group
  - A specific responder definition (RD) value was proposed from this range by considering the following:
    - Possible state changes of the target domain (for each 1-point change on the raw scale, the transformed scale would change by a certain number)
    - The lower bound threshold set by 1 SEM for that domain (RD should be ≥ SEM)

CIC and CID thresholds (group-level analysis)

- Thresholds were derived for each domain by triangulating estimates from anchor-based methods and distribution-based estimates considering a small (0.3 × SD) to medium (0.5 × SD) effect size (ES)
  - Anchor-based estimates for CIC were based on mean score change of the groups with 1 level of improvement (deterioration) on the selected anchors
  - Anchor-based estimates for CID were based on the difference in least squares (LS) mean change between 1 level of improvement (deterioration) and no change on the selected anchors from the analysis of covariance model, adjusting for baseline score
  - Estimates from the anchor-based analyses that substantially exceeded a medium (0.5 × SD) ES were deprioritized, as they may be too stringent to be used as CIC or CID thresholds

Results

Table 2. Demographics and baseline clinical characteristics

Characteristic	Evaluable set (n = 62)
Mean (SD) age, y	64.3 (6.8)
Male, n (%)	45 (73)
White, n (%)	56 (90)
Disease type, n (%)	
CLL	58 (94)
SLL	4 (6)
Baseline ECOG PS, n (%)	
0	17 (27)
1	44 (71)
2	1 (2)
Mean (SD) time from diagnosis to liso-cel administration, months	145.7 (57.2)
Mean (SD) EORTC QLQ-CLL17 domain scores	
Symptom burden	25.0 (18.0)
Physical condition/fatigue	31.0 (22.2)
Worries/fears on health and functioning	31.1 (18.5)

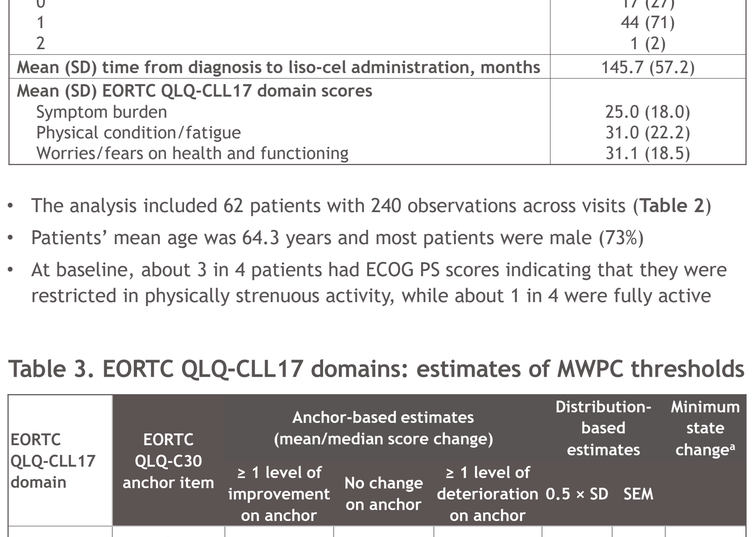
- The analysis included 62 patients with 240 observations across visits (**Table 2**)
- Patients' mean age was 64.3 years and most patients were male (73%)
- At baseline, about 3 in 4 patients had ECOG PS scores indicating that they were restricted in physically strenuous activity, while about 1 in 4 were fully active

Table 3. EORTC QLQ-CLL17 domains: estimates of MWPC thresholds

EORTC QLQ-CLL17 domain	EORTC QLQ-C30 anchor item	Anchor-based estimates (mean/median score change)			Distribution-based estimates		Minimum state change[a]
		≥ 1 level of improvement on anchor	No change on anchor	≥ 1 level of deterioration on anchor	0.5 × SD	SEM	
Symptom burden	9 (pain)	−9.94/−8.13	−1.65/0.00	7.44/8.33	± 9.01	± 8.63	± 5.56
	12 (weakness)	−12.83/−11.11	−1.48/0.00	9.16/11.11			
	29 (overall health)	−17.81/−16.67	0.29/0.00	11.85/11.11			
Physical condition/ fatigue	12 (weakness)	−21.21/−25.00	−2.80/0.00	12.87/8.33	± 11.09	± 8.42	± 8.33
	29 (overall health)	−19.85/−16.67	−1.83/0.00	15.56/16.67			
Worries/fears on health and functioning	22 (worry)	−15.47/−16.67	−1.07/−4.76	7.08/0.00	± 9.24	± 11.42	± 6.67[b]; ± 4.76[c,d]
	29 (overall health)	−19.24/−19.52	−4.70/−6.67	10.18/4.76			

[a]Minimum state change reflects the amount of score change on the transformed domain scale for a 1-point change on its raw scale; [b]If 5 items answered; [c]If 7 items answered; [d]Other values possible if patients responded to 2 optional questions only at baseline or postbaseline.

Figure 2. Estimated thresholds for MWPC, CIC, and CID[a]



[a]Blue and orange circles symbolize threshold ranges for improvement (blue) and deterioration (orange) for MWPC, CIC, and CID; light blue and light orange circles symbolize responder definitions for improvement (light blue) and deterioration (light orange) for MWPC; [b]The range of 0 to 10 from the anchor-based estimates was not considered for the RD, as it was lower than the SEM. Thus, the next possible state change above the SEM (11.42) was proposed.

MWPC thresholds

Symptom burden domain

- Score changes of −17 to −8 points and 7 to 11 points from baseline were the estimated thresholds for MWPC improvement and deterioration, respectively (**Table 3**; **Figure 2**)
- Changes of −11 points and 11 points were selected as the RD for improvement and deterioration

Physical condition/fatigue domain

- Score changes of −25 to −16 points and 8 to 16 points were the estimated thresholds for MWPC improvement and deterioration, respectively (**Table 3**; **Figure 2**)
- Change of −16 points and 16 points were selected as the RD for improvement and deterioration, respectively

Worries/fears on health and functioning domain

- Score changes of −19 to −15 points and 0 to 10 points were the estimated thresholds for MWPC improvement and deterioration, respectively (**Table 3**; **Figure 2**)
- Changes of −16 points and 13 points were selected as the RD for improvement and deterioration, respectively
  - As the range from the anchor-based estimates was lower than the SEM, the next possible state change above the SEM (11.42) was proposed for the RD

Table 4. EORTC QLQ-CLL17 domains: estimates of CIC and CID thresholds

EORTC QLQ-CLL17 domain	CIC			CID		Distribution-based estimates		
	EORTC QLQ-C30 anchor item	Mean change (ES) for 1 level of improvement	Mean change (ES) for 1 level of deterioration	LS mean difference (ES) for 1 level of improvement vs no change	LS mean difference (ES) for 1 level of deterioration vs no change	0.3 × SD	0.5 × SD	SEM
Symptom burden	9 (pain)	−9.06 (−0.51)	6.94 (0.39)	−4.39 (−0.26)	10.88 (0.63)	± 5.40	± 9.01	± 8.63
	12 (weakness)	−10.87 (−0.61)	8.78 (0.49)	−5.80 (−0.34)	10.08 (0.59)			
	29 (overall health)	−18.72 (−1.05)	10.10 (0.57)	−13.33 (−0.77)	9.52 (0.55)			
Physical condition/ fatigue	12 (weakness)	−15.58 (−0.71)	12.50 (0.57)	−9.19 (−0.42)	14.95 (0.68)	± 6.66	± 11.09	± 8.42
	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	22 (worry)	−12.93 (−0.68)	4.16 (0.22)	−10.10 (−0.54)	7.87 (0.42)	± 5.54	± 9.24	± 11.42
	29 (overall health)	−15.80 (−0.83)	1.26 (0.07)	−8.29 (−0.44)	7.37 (0.39)			

CIC and CID thresholds

Symptom burden domain

- Score changes of −9 to −5 points and 5 to 9 points were the estimated thresholds for meaningful CIC and CID improvement and deterioration, respectively (**Table 4**; **Figure 2**)

Physical condition/fatigue domain

- Score changes of −11 to −6 points and 6 to 12 points were the estimated thresholds for meaningful CIC improvement and deterioration, respectively (**Table 4**; **Figure 2**)
- Score changes of −11 to −6 points and 6 to 11 points were the estimated thresholds for meaningful CID improvement and deterioration, respectively

Worries/fears on health and functioning domain

- Score changes of −9 to −5 points and 5 to 9 points were the estimated thresholds for meaningful CIC improvement and deterioration, respectively (**Table 4**; **Figure 2**)
- Score changes of −10 to −5 points and 5 to 9 points were the estimated thresholds for meaningful CID improvement and deterioration, respectively

Conclusions

- This is the first study to propose thresholds for interpreting improvement and deterioration in EORTC QLQ-CLL17 domain scores at patient and group levels
- Results suggested RD/MWPC thresholds for improvement (deterioration) of −11 points (11 points) for symptom burden score, −16 points (16 points) for physical condition/fatigue, and −16 points (13 points) for worries/fears on health and functioning
- CIC and CID estimate ranges were proposed to be approximately between 0.3 × SD and 0.5 × SD of each EORTC QLQ-CLL17 domain score, as the anchor-based estimates were deemed too stringent
- The derived thresholds should be confirmed in future studies, considering the small sample size in the current data source
- The estimated thresholds will help identify treatment responders and interpret treatment effects based on EORTC QLQ-CLL17 domain scores in future clinical trials

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