Health-related quality of life in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma treated with liso-cel in TRANSCEND CLL 004

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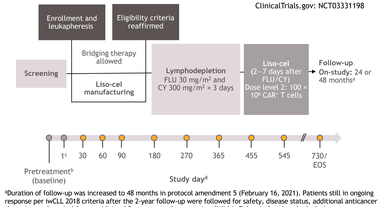
Introduction

- Patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) have limited treatment options[1] and poor patient-reported outcomes (PRO)/health-related quality of life (HRQOL)[2]
- Patients whose disease progressed on Bruton tyrosine kinase inhibitor (BTKi) therapy and had venetoclax failure have dismal clinical outcomes, which may negatively impact HRQOL[1,3–8]
- Lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed, 4-1BB chimeric antigen receptor (CAR) T cell therapy that is being evaluated in the phase 1/2 TRANSCEND CLL 004 study (NCT03331198)[9]
- Results showed that liso-cel met the primary endpoint of complete response/remission (CR) or CR with incomplete marrow recovery (CRi) rate, and demonstrated deep and durable responses with a manageable safety profile[10]
- This study examined the effect of liso-cel monotherapy on PROs and HRQOL among adults with R/R CLL/SLL who participated in the phase 2 monotherapy portion of TRANSCEND CLL 004

Methods

Figure 1. TRANSCEND CLL 004 study design and PROs/HRQOL assessment schedule



[a]Duration of follow-up was increased to 48 months in protocol amendment 5 (February 16, 2021). Patients still in ongoing response per IwCLL 2018 criteria after the 2-year follow-up were followed for safety, disease status, additional anticancer therapies, and survival for an additional 2 years or until progression; [b]Within 7 days before lymphodepleting chemotherapy; [c]Preinfusion on the day of liso-cel infusion; [d]Gray circles indicate assessments before liso-cel infusion and orange circles indicate assessments after liso-cel infusion.
CY, cyclophosphamide; EOS, end of study; FLU, fludarabine; IwCLL, International Workshop on Chronic Lymphocytic Leukemia.

Key patient eligibility criteria

- Age ≥ 18 years
- R/R CLL/SLL with an indication for treatment
- Previously failed or ineligible for BTKi therapy
- Failure of ≥ 2 (high risk) or ≥ 3 (standard risk) lines of prior therapy
- Eastern Cooperative Oncology Group performance scale (ECOG PS) ≤ 1
- Adequate bone marrow, organ, and cardiac function
- No Richter transformation nor active central nervous system involvement by malignancy

Primary endpoint (primary efficacy analysis set [PEAS] at dose level 2 [DL2])

- CR/CRi rate per IwCLL 2018 by independent review committee assessment

Key secondary endpoints (PEAS at DL2)

- Overall response rate, undetectable minimal residual disease rate in blood

PRO/HRQOL endpoints (secondary)

- Changes from baseline and proportion experiencing changes in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-30 items (C30), EORTC QLQ-17 items for CLL (CLL17; CLL-specific module), and EQ-5D-5L

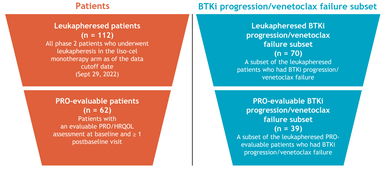
Table 1. PRO/HRQL instruments and primary domains of interest

Instrument	Primary domains	Domain scores
EORTC QLQ-C30[11]	Global health status (GHS)/QOL, physical functioning, role functioning, cognitive functioning, and fatigue (prespecified)	Ranged from 0 to 100, with higher scores indicating better overall HRQOL or healthier functioning, and worse symptoms
EORTC QLQ-CLL17[12]	Symptom burden and physical condition/fatigue (prespecified)	Ranged from 0 to 100, with higher scores indicating worse symptoms
EQ-5D-5L	EQ-5D-5L VAS (post hoc)	EQ-5D-5L VAS ranged from 0 to 100, with higher scores indicating better health state

Only primary domains are reported and were selected based on clinical relevance, importance for the target population, and similar published studies.[13–16]
QOL, quality of life; VAS, visual analog scale.

- HRQOL assessment was not in the original study protocol of TRANSCEND CLL 004 and was added to protocol amendment 3 (December 17, 2018)
- HRQOL was assessed in PRO-evaluable patients using the following instruments: EORTC QLQ-C30, EORTC QLQ-CLL17, and EQ-5D-5L (**Figure 1**, **Figure 2**, and **Table 1**)
- Patients completed questionnaires electronically on provided electronic PRO tablet at the study visit, prior to any procedure or clinical evaluation; questionnaires were completed at baseline (≤ 7 days before lymphodepletion), preinfusion on the day of liso-cel infusion (Day 1), and at multiple time points after infusion (**Figure 1**)

Figure 2. Analysis populations



Statistical analyses

- A completion rate for each instrument was calculated using the number of patients who were still on study at each visit as the denominator
- The proportion of patients experiencing a meaningful change (ie, improvement/deterioration) in HRQOL was calculated
  - Responder definition (RD) was used to interpret whether a within-patient change was meaningful
- Observed mean changes from baseline and 95% confidence intervals (CI) were evaluated
  - The minimum important difference (MID) was used to interpret whether a within-group change was meaningful
- EORTC QLQ-C30
  - RD was indicated by minimal change thresholds[17]: GHS/QOL and physical functioning (5 points), role and cognitive functioning (15 points), and fatigue (10 points)
  - MID was indicated by contemporary MID thresholds[18] and conventional 10-point thresholds[19]
- EORTC QLQ-CLL17
  - RD and MID have not been established; therefore, thresholds were derived from anchor-based and distribution-based methods
    - **RD:** symptom burden (11 points) and physical condition/fatigue (16 points)
    - **MID:** 2 sets representing small and moderate improvement or deterioration
- EQ-5D-5L VAS
  - MID was based on a 7-point threshold[20]

Results

Table 2. Demographic and disease characteristics of leukapheresed patients in phase 2

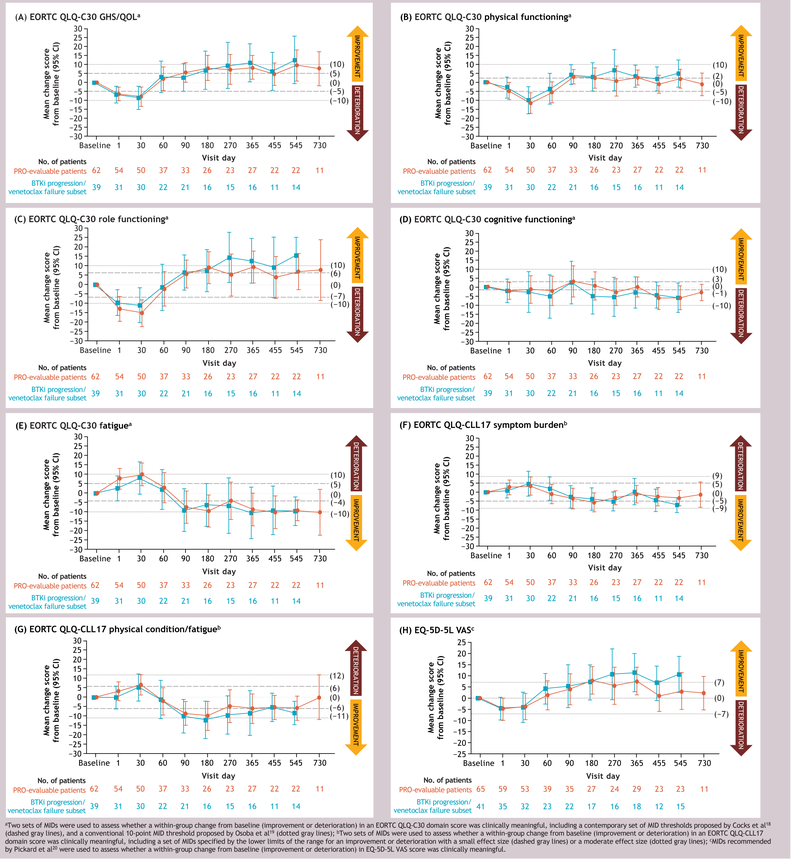
	Leukapheresed patients (n = 112)		Leukapheresed BTKi progression/venetoclax failure subset (n = 70)	
	PRO evaluable[a] (n = 62)	Non-PRO evaluable (n = 50)	PRO evaluable (n = 39)	Non-PRO evaluable (n = 31)
Mean (SD) age, y	64.3 (6.85)	64.3 (9.19)	64.5 (7.51)	64.7 (8.41)
Male, n (%)	45 (73)	34 (68)	29 (74)	21 (68)
High-risk cytogenetics, n (%)				
Yes	54 (87)	40 (80)	34 (87)	25 (81)
No	8 (13)	10 (20)	5 (13)	6 (19)
Unknown	5 (8)	10 (20)	4 (10)	5 (16)
Baseline ECOG PS, n (%)				
0	17 (27)	17 (34)	8 (21)	12 (39)
1	44 (71)	30 (60)	30 (77)	18 (58)
2 or 3	1 (2)	3 (6)	1 (3)	1 (3)
Prior BTKi, n (%)	62 (100)	50 (100)	39 (100)	31 (100)
BTKi refractory[b]	54 (87)	46 (92)	39 (100)	31 (100)
BTKi relapsed[c]	0	1 (2)	0	0
BTKi intolerant only	8 (13)	2 (4)	0	0
Prior venetoclax, n (%)	53 (85)	44 (88)	39 (100)	31 (100)
Venetoclax refractory[b]	47 (76)	38 (76)	36 (92)	26 (84)
Venetoclax intolerant only	5 (8)	4 (8)	3 (8)	3 (10)

[a]All PRO-evaluable patients received liso-cel except 1 patient who received nonconforming product, defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel but was considered appropriate for infusion; [b]Defined as no response or ≤ 6 months from last dose of therapy; [c]Defined as disease progression in a patient who previously had CR/CRi or PR/nPR for ≥ 6 months.
nPR, nodular partial response/remission; PR, partial response/remission; SD, standard deviation.

- In PRO-evaluable patients and the PRO-evaluable BTKi progression/venetoclax failure subset, completion rates were low at baseline
- Completion rates remained relatively stable (50%–70%) across most visits and were similar across PRO/HRQOL instruments
- Demographic and disease characteristics were comparable between the PRO-evaluable patients (ie, those with change scores) and non–PRO-evaluable patients (ie, those without change scores) (**Table 2**)

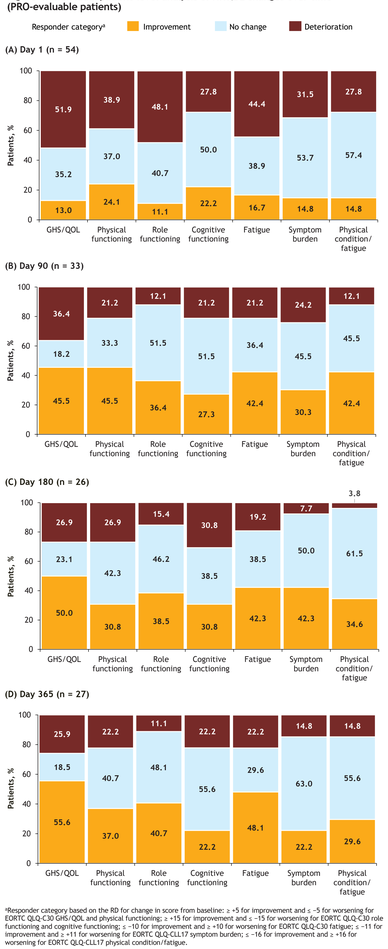
- After initial deterioration in HRQOL after liso-cel infusion, the observed mean changes from baseline based on EORTC measures showed improvement starting at Day 90 for all primary domains, except for cognitive functioning, which was comparable with the general population at baseline and maintained over time (**Figures 3A–G**)
- Overall HRQOL based on the EQ-5D-5L VAS improved from baseline starting at Day 60 (**Figure 3H**)

Figure 3. Changes from baseline in the primary domains of interest over time (PRO-evaluable patients)



[a]Two sets of MIDs were used to assess whether a within-group change from baseline (improvement or deterioration) in an EORTC QLQ-C30 domain score was clinically meaningful, including a contemporary set of MID thresholds proposed by Cocks et al[18] (dashed gray lines), and a conventional 10-point MID threshold proposed by Osoba et al[19] (dotted gray lines); [b]Two sets of MIDs were used to assess whether a within-group change from baseline (improvement or deterioration) in an EORTC QLQ-CLL17 domain score was clinically meaningful, including a set of MIDs specified by the lower limits of the range for an improvement or deterioration with a small effect size (dashed gray lines) or a moderate effect size (dotted gray lines); [c]MIDs recommended by Pickard et al[20] were used to assess whether a within-group change from baseline (improvement or deterioration) in EQ-5D-5L VAS score was clinically meaningful.

Figure 4. Individual patient-level analysis of HRQOL changes over time (PRO-evaluable patients)



[a]Responder category based on the RD for change in score from baseline: ≥ +5 for improvement and ≤ −5 for worsening for EORTC QLQ-C30 GHS/QOL and physical functioning; ≥ +15 for improvement and ≤ −15 for worsening for EORTC QLQ-C30 role functioning and cognitive functioning; ≤ −10 for improvement and ≥ +10 for worsening for EORTC QLQ-C30 fatigue; ≤ −11 for improvement and ≥ +11 for worsening for EORTC QLQ-CLL17 symptom burden; ≤ −16 for improvement and ≥ +16 for worsening for EORTC QLQ-CLL17 physical condition/fatigue.

Table 3. Baseline HRQOL scores in the PRO-evaluable patients versus EU and US population norms

Instrument	Domain	PRO-evaluable patients (n = 62)	PRO-evaluable BTKi progression/ venetoclax failure subset (n = 39)	EU general population norm[a]	US general population norm[b]
EORTC QLQ-C30, mean (SD if applicable)	GHS/QOL	64.7 (21.80)	65.6 (22.80)	66.6	63.9
	Physical functioning	78.7 (21.32)	78.3 (21.34)	84.0	80.8
	Role functioning	74.7 (25.02)	73.1 (26.66)	84.3	81.7
	Cognitive functioning	80.9 (21.73)	80.8 (24.04)	87.2	80.9
	Fatigue	39.4 (23.86)	39.6 (26.09)	25.1	31.9
EORTC QLQ-CLL17, mean (SD if applicable)	Symptom burden	25.0 (18.02)	25.5 (17.88)	—	—
	Physical condition/fatigue	31.0 (22.19)	32.3 (24.20)	—	—

[a]EU EORTC QLQ-C30 norm scores from the European general population of 11 EU countries (N = 11,343)[21] were reweighted by the age-by-gender distributions of the PRO-evaluable populations; [b]The US EORTC QLQ-C30 general population norm was weighted by the country's sex and age distributions.[21]
EU, European Union; US, United States.

- Baseline scores among the PRO-evaluable patients were worse than those of the EU and US general populations, particularly for role functioning and fatigue (**Table 3**)
- Proportion of patients with meaningful HRQOL improvement increased over time. On Days 90, 180, and 365 after infusion, most patients experienced meaningful HRQOL improvement and/or remained stable (**Figure 4**)

Limitations

- PRO and HRQOL assessments were added to the phase 2 portion of the study in protocol amendment 3; therefore, not all patients received PRO/HRQOL assessments, resulting in low completion rates
- COVID-19–related restrictions also contributed to the low completion rates of PRO/HRQOL assessments

Conclusions

- Liso-cel either improved or maintained HRQOL from baseline in patients with heavily pretreated R/R CLL/SLL
- Meaningful improvements were achieved in the key CLL symptom of fatigue, role functioning, and overall HRQOL
- The PRO data complement the clinical benefit seen with liso-cel in R/R CLL/SLL

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