Lisocabtagene maraleucel for second-line relapsed or refractory large B-cell lymphoma: patient-reported outcomes from the PILOT study

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Abstract

In the single-arm, open-label, multicenter, phase II PILOT study, second-line treatment with the chimeric antigen receptor (CAR) T-cell therapy lisocabtagene maraleucel (liso-cel) in patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) for whom hematopoietic stem cell transplantation (HSCT) was not intended resulted in high response rates, durable responses, and a safety profile consistent with previous reports. Here, we analyzed changes in health-related quality of life (HRQOL) in patients who received liso-cel in PILOT. Patients received liso-cel, an autologous, CD19-directed, 4-1BB CAR T-cell product administered at equal target doses of $CD8^+$ and $CD4^+$ CAR^+ T cells, for a total target dose of 100×10^6 CAR^+ T cells. HRQOL, a secondary endpoint of PILOT, was assessed as prespecified using three patient-reported outcome instruments (EORTC QLQ-C30; FACT-LymS; EQ-5D-5L). Evaluable datasets for the EORTC QLQ-C30, FACT-LymS, and EQ-5D-5L health utility index, and visual analog scale (EQ-VAS) included 56 (92%), 49 (80%), 55 (90%), and 54 (89%) patients, respectively. Clinically meaningful improvement was achieved across most post-treatment visits for EORTC QLQ-C30 fatigue and FACT-LymS. Overall mean changes from baseline through day 545 showed significant improvements in EORTC QLQ-C30 fatigue, pain, and appetite loss, FACT-LymS, and EQ VAS. In within-patient analyses, clinically meaningful improvements or maintenance in scores were observed in most patients at days 90, 180, 270, and 365. HRQOL was maintained or improved in patients who received liso-cel as second-line therapy in PILOT. These findings support liso-cel as a preferred second-line treatment in patients with R/R LBCL not intended for HSCT (*clinicaltrials gov. Identifier: NCT03483103*).

Introduction

Approximately one-third of patients with aggressive large B-cell lymphoma (LBCL) have relapsed or refractory (R/R) disease after first-line therapy,[1] and only half of these patients are considered suitable for potentially curative high-dose chemotherapy (HDCT) and hematopoietic stem cell transplantation (HSCT). While survival outcomes for patients who are not candidates for HDCT/HSCT were historically poor because there was no effective established standard of care (SOC),[2] recent advances have led to several new treatment options for patients with R/R LBCL in the second or later line, including chimeric antigen receptor (CAR) T-cell therapy.[3-6]

Lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed, 4-1BB CAR T-cell product administered at equal target doses of $CD8^+$ and $CD4^+$ CAR^+ T cells.[7] The antitumor activity and safety of liso-cel as second-line treatment in patients with R/R LBCL not intended for HSCT were evaluated in the single-arm, phase II, open-label, multicenter PILOT study (*clinicaltrials gov. Identifier: NCT03483103*).[6] In the primary analysis of PILOT at a median study follow-up of 12.3 months, the overall response and complete response (CR) rates were 80% and 54%, respectively, median

duration of response- and progression-free survival were 12.1 and 9.0 months, respectively, and median overall survival was not reached (NR).[6] Additionally, in the primary analysis of the open-label phase III TRANSFORM study (clinicaltrials gov. Identifier: *NCT03575351*) of liso-cel as second-line therapy for patients with primary refractory or early relapsed LBCL who were intended for HSCT, liso-cel demonstrated superiority over SOC treatment (3 cycles of salvage platinum-based immunochemotherapy followed by HDCT and autologous HSCT in responding patients) in the primary endpoint of event-free survival (median NR *vs*. 2.4 months), significantly higher CR rate (74% *vs*. 43%), and significantly longer progression-free survival (median NR *vs*. 6.2 months) than SOC.[8]

As cancer treatments improve and patients live longer, it has become more important to evaluate the impact of new treatments on patients' health-related quality of life (HRQOL). Reports of patients' HRQOL after CAR T-cell therapy have been limited to date.[9] However, an analysis of patient-reported outcomes (PRO) in TRANSFORM found that many PRO domains improved with liso-cel *versus* SOC, particularly European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - 30 items (EORTC QLQ-C30) cognitive functioning and fatigue.[10] Additionally, patients with third-line or later LBCL treated with liso-cel in TRANSCEND NHL 001 (clinicaltrials gov. Identifier: *NCT02631044*) had early, sustained, and clinically meaningful improvements in HRQOL that correlated with antitumor activity.[11] Clinically meaningful improvements in HRQOL have also been demonstrated with other CAR T-cell therapies as second-line or later[12] and third-line or later therapy.[13]

Here, we analyzed changes in HRQOL and PROs to explore the impact of liso-cel as second-line therapy in patients with R/R LBCL who were not intended for HSCT and received liso-cel in PILOT.

Methods

Study overview

PILOT is an open-label, multicenter, phase II study that enrolled patients at 18 clinical sites in the United States.[6] The study design has been previously described.[6] Further details are in the *Online Supplementary Appendix*. The study 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. All patients provided written informed consent.

Patient-reported outcomes

HRQOL, a secondary endpoint of PILOT, was assessed using the EORTC QLQ-C30, Functional Assessment of Cancer Therapy - Lymphoma "Additional Concerns" Subscale (FACT-LymS), and EQ-5D-5L (*Online Supplementary Table S1*). Patients completed PRO questionnaires electronically on tablets at the initiation of study visits before any procedure or clinical evaluation at screening (defined as baseline); before treatment (≤7 days before lymphodepletion); pre-infusion on the day of liso-cel infusion (day 1); after treatment on days 29, 60, 90, 180, 270, 365, 545, and 730 (end of study); and at disease progression. Final PRO assessments were obtained from patients who discontinued the study early.

Primary domains of interest included EORTC QLQ-C30 global health (GH)/quality of life (QOL), physical functioning, role functioning, cognitive functioning, fatigue, pain, and FACT-LymS. These domains have been identified as important and clinically relevant measurements of symptoms and functioning for the target population of patients with lymphoma[14] or have been used to assess changes in patient HRQOL in lymphoma studies.[11,15,16] For the EORTC QLQ-C30 GH/QOL and functioning domains, increased score indicates improved QOL/functioning; for the EORTC QLQ-C30 symptom domains, increased score indicates worsening symptoms. For FACT-LymS, increased score indicates improved QOL. Secondary domains of interest included EORTC QLQ-C30 emotional functioning, social functioning, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties, and EQ-5D-5L health utility index (HUI) and visual analog scale (EQ-VAS) scores. Unless otherwise specified, analyses were based on the PRO-evaluable set, including liso-cel–treated patients who had valid assessments at baseline and ≥1 postbaseline visit.

For assessment of within-group changes in EORTC QLQ-C30 domains, two minimally important difference (MID) threshold sets were used to determine whether the mean change from baseline (improvement or deterioration) was clinically meaningful as follows: the conventional 10-point MID of Osoba *et al.*[17] and the MID thresholds of Cocks *et al.*[18] The MID to determine clinically meaningful within-group change from baseline (improvement or deterioration) for the FACT-LymS were set to a ± 3-point change, as suggested by Hlubocky *et al.*,[19,20] and set to ± 0.08 points for EQ-5D-5L HUI[21] and 7 points for EQ VAS as suggested by Pickard *et al.*[21]

For assessment of within-patient changes, proportions of patients with clinically meaningful HRQOL worsening or improvement from baseline were calculated using responder definitions (RD) of 10 points for EORTC QLQ-C30 domains,[17] 3 points for FACT-LymS,[19] 0.08 points for EQ-5D-5L HUI,[21] and 7 points for EQ VAS.[21] Improvement was defined as a beneficial change from baseline ≥ the RD and worsening as a deleterious change from baseline ≥ the RD; no change was defined as a change from baseline in either direction < the RD.

Statistical analysis

Linear mixed-effects regression models for repeated mea-

sures assessed the least squares (LS) mean change from baseline across postbaseline assessments with ≥10 patients (i.e., up to day 545). Missing data were handled under the assumption of missing at random. Time to confirmed HRQOL deterioration or improvement, defined as ≥2 consecutive visits with changes from baseline ≥ the RD thresholds,[17,19-21] was analyzed using the safety set including all patients who received liso-cel.[6]

The Kaplan-Meier product-limit method was used to estimate survival distribution functions. *P* values <0.05 were considered statistically significant. Analyses were not adjusted for multiple comparisons.

Results

HRQOL questionnaire completion rates

A total of 61 patients received liso-cel in PILOT and were included in the safety set. The PRO-evaluable set included 56 patients for the EORTC QLQ-C30, 49 patients for FACT-LymS, 55 patients for EQ-5D-5L HUI, and 54 patients for EQ-VAS (*Online Supplementary Figure S1*). Across most visits, the HRQOL questionnaire completion rate (defined as the percentage of liso-cel–treated patients with valid PRO assessment at a given time point out of the total liso-cel–treated patients who were expected to provide PRO assessments at that time point) was high (≥80%) for all PRO instruments (*Online Supplementary Table S2*). The number of patients expected to provide PRO assessments decreased over time, mostly due to death or inadequate follow-up time. At screening (baseline), 93% of patients (57/61) completed the EORTC QLQ-C30, 82% (50/61 patients) completed the FACT-LymS, 92% (56/61 patients) completed the EQ-5D-5L HUI, and 90% (55/61 patients) completed the EQ-VAS. At days 60, 180, and 365, 83-89% (44-47/53 patients), 84-87% (31-32/37 patients), and 81-91% (17-19/21 patients) completed PRO assessments, respectively.

Population characteristics

Baseline demographic and disease characteristics in the EORTC QLQ-C30-evaluable set were comparable with those of the overall safety set in PILOT (Table 1). In the EORTC QLQ-C30-evaluable set, mean age was 72.8 years and 59% of patients were male. Mean time from diagnosis to liso-cel administration was 27.4 months. The best prior treatment response was a CR in nearly half (48%) of patients. Most patients (88%) had received systemic treatment as the last line of therapy before liso-cel, and mean time from the last systemic regimen to liso-cel administration was 21.0 months. Additional baseline disease characteristics are shown in *Online Supplementary Table S3*.

HRQOL at baseline

Patients in this analysis had slightly worse mean baseline HRQOL scores across most of the primary and secondary domains of interest compared with reference age- and matched general populations (Table 2).[22,23] For EORTC QLQ-C30 fatigue, social functioning, and appetite loss domains, baseline scores were worse than scores in the general population to a clinically meaningful extent (i.e., the

Table 1. Demographics and baseline characteristics of the EORTC QLQ-C30–evaluable population.

	EORTC QLQ-C30–evaluable population N=56
Age in years	
Mean (SD)	72.8 (6.8)
Median (range)	74.0 (53-84)
Sex, N (%)	
Male	33 (59)
Race, N (%)	
Asian	1 (2)
Black or African American	1 (2)
White	50 (89)
Missing	4 (7)
Ethnicity, N (%)	
Not Hispanic or Latino	49 (87.5)
Missing	7 (12.5)
ECOG PS at screening, N (%)	
0	17 (30)
1	23 (41)
2	16 (29)
Time from diagnosis to liso-cel administration in months	
Mean (SD)	27.4 (37.7)
Median (range)	13.7 (2.3-183.4)
Time from last systemic regimen to liso-cel administration in months	
Mean (SD)	21.0 (34.8)
Median (range)	8.1 (1.5-174.5)
Best prior treatment response, N (%)	
Complete response	27 (48)
Partial response	13 (23)
Stable disease	5 (9)
Progressive disease	11 (20)
Disease relapsed or refractory to first-line therapy, N (%)	
Refractory	29 (52)
Relapsed	27 (48)
Chemotherapy refractory or chemotherapy sensitive, N (%)	
Chemotherapy refractory[a]	16 (29)
Chemotherapy sensitive	40 (71)
Last line of therapy before liso-cel, N (%)	
Systemic treatment	49 (88)
Systemic treatment plus radiotherapy	7 (13)

Note that total percentages per category may equal >100 due to rounding. [a]Defined as patients who achieved a best response to previous chemoimmunotherapy of stable disease or progressive disease. EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - 30 items; SD: standard deviation; ECOG PS: Eastern Cooperative Oncology Group performance status; liso-cel: lisocabtagene maraleucel.

difference in mean scores was greater than the 10-point MID set by Osoba *et al.*[15]).

Within-group changes in HRQOL scores over time

After transient worsening at day 1 or day 29 in most domains, improvements in LS mean HRQOL scores over time were generally observed for the primary domains of interest (Figure 1). For the EORTC QLQ-C30 primary domains of interest, changes from baseline exceeding the conventional 10-point MID proposed by Osoba *et al*. were observed at day 1 in role functioning (deterioration); days 90, 180, and 545 in fatigue (all improvement); and day 29 in pain (improvement). Clinically meaningful improvement from baseline based on the MID thresholds defined by Cocks *et al*. was achieved at days 60 and 180 for GH/QOL and across most post-treatment visits for EORTC QLQ-C30 fatigue and FACT-LymS. Slight score deterioration was observed at day 270 in several domains with subsequent improvement at later time points. LS mean score changes from baseline over time for the secondary domains of interest are shown in *Online Supplementary Figure S2*. Notably, EQ-5D-5L HUI and EQ-VAS scores were maintained or improved across visits. Clinically meaningful improvements in EQ-VAS were observed at days 60 and 180. Overall LS mean changes from baseline through day 545 showed significant improvements in EORTC QLQ-C30 fatigue, pain, and appetite loss, FACT-LymS, and EQ-VAS (Table 3). For FACT-LymS, the improvement was clinically meaningful.[19,20] For EORTC QLQ-C30 fatigue, the improvement was clinically meaningful when using the MID defined by Cocks *et al*.[18] Significant or clinically meaningful worsening was not observed for any of the primary or secondary domains of interest.

Within-patient changes in HRQOL scores over time

In within-patient analyses of changes from baseline for each EORTC QLQ-C30 primary domain of interest and FACT-LymS, clinically meaningful improvements or no clinically meaningful change from baseline at days 29, 60, and 90 were reported in 52-94%, 69-97%, and 69-87% of patients, respectively. A clinically meaningful change only was shown at days 29, 60, and 90 in 12.5-57%, 24-68%, and 20.5-71% of patients, respectively (Figure 2). Most patients continued to show clinically meaningful improvements or

Table 2. Baseline HRQOL scores.

Domain[a]	Domain mean score		MID	
	PRO-evaluable set	General population norm[c]		
EORTC QLQ-C30			Osoba *et al.*[17]	Cocks *et al.*[18d]
GH/QOL	66.8	67.4	±10	+5/-5
Physical functioning	77.8	81.8	±10	+2/-5
Role functioning	77.1	83.5	±10	+6/-7
Cognitive functioning	83.3	87.3	±10	+3/-1
Fatigue	36.7[b]	24.6	±10	-4/+5
Pain	26.5	23.3	±10	-5/+3
Emotional functioning	81.1	82.3	±10	+6/-3
Social functioning	74.7[b]	89.4	±10	+3/-6
Nausea/vomiting	5.7	2.3	±10	-3/+5
Dyspnea	10.7	17.1	±10	-2/+5
Insomnia	25.6	23.9	±10	-5/+2
Appetite loss	18.8[b]	6.6	±10	-7/+2
Constipation	11.9	10.9	±10	-4/+5
Diarrhea	13.7	5.9	±10	-3/+5
Financial difficulties	13.7	7.1	±10	-3/+2
FACT-Lym			Hlubocky *et al.*[19,20]	
FACT-LymS	44.2	-	-	
EQ-5D-5L			Pickard *et al.*[21]	
EQ-5D-5L HUI	0.74	0.76	±0.08	
EQ-VAS	71.6	76.1	±7	

[a]Primary domains of interest are in roman typeface; secondary domains of interest are in italics. [b]Mean scores that were clinically meaningfully worse than the European general population norm (i.e., difference in mean scores above the prespecified MID). [c]EORTC QLQ-C30 norm scores were from European general population data based on 11 European Union countries (N=11,343),[23] and EQ-5D-5L norm scores were from a UK general population (N=3,395).[22] Both sets of general population norms were reweighted by the EORTC QLQ-C30–evaluable population's age and sex distributions. [d]Values on the left indicate thresholds for clinically meaningful improvement and values on the right indicate thresholds for clinically meaningful worsening. For the EORTC QLQ-C30 GH/QOL and functioning domains, a higher score denotes better QOL/function; for symptom domains, a higher score denotes worse symptoms. For the FACT-LymS, EQ-5D-5L HUI, and EQ-VAS, a higher score indicates better QOL. HRQOL: health-related quality of life; MID: minimally important difference; PRO: patient-reported outcome; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - 30 items; GH: global health; QOL: quality of life; FACT-LymS: Functional Assessment of Cancer Therapy - Lymphoma "Additional Concerns" Subscale; HUI: health utility index; VAS: visual analog scale.

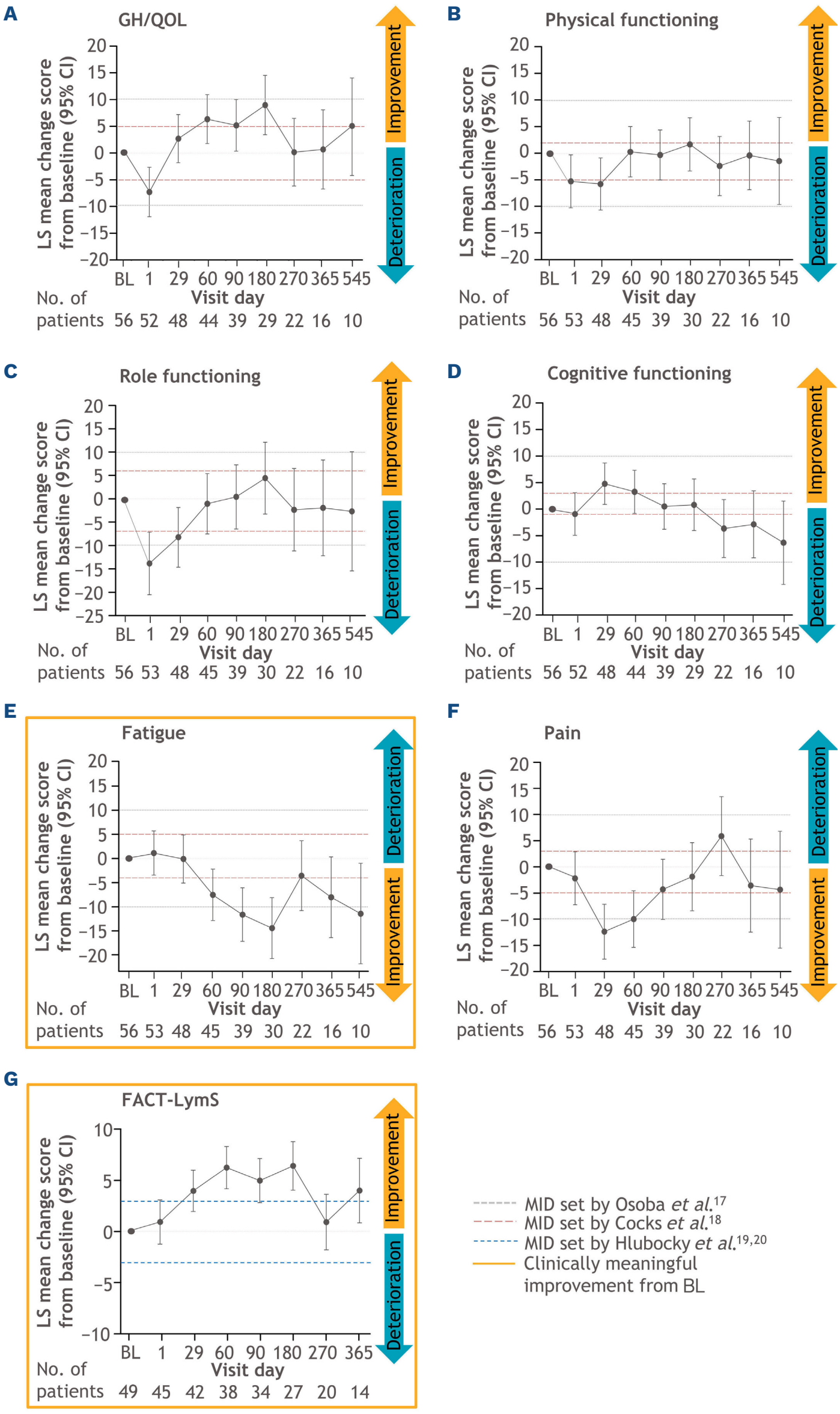

Figure 1. Least squares mean changes from baseline in the primary domains of interest over time. For the EORTC QLQ-C30 domains of GH/QOL (A), physical functioning (B), role functioning (C), cognitive functioning (D), fatigue (E), and pain (F), 2 sets of minimally important differences (MID) were used to assess whether a change from baseline (BL) (improvement or deterioration) was clinically meaningful: the conventional 10-point change suggested by Osoba *et al.* (dotted gray lines)[17] and the MID suggested by Cocks *et al.* (dashed red lines).[18] For the FACT-LymS (G), an MID of 3 points, as suggested by Hlubocky *et al.* (dotted dark blue lines),[19,20] was used to identify clinically meaningful improvement and deterioration from BL. For the EORTC QLQ-C30 GH/QOL and functioning domains, an increased score indicates improved QOL/functioning; for the EORTC QLQ-C30 symptom domains, an increased score indicates worsening symptoms. For FACT-LymS, an increased score indicates improved QOL. LS: least squares; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - 30 items; GH: global health; QOL: quality of life; FACT-LymS: Functional Assessment of Cancer Therapy - Lymphoma "Additional Concerns" Subscale.

no clinically meaningful change over the medium term with 80-96% at day 180 (23-70% with clinically meaningful improvement only) and 59-82% at day 270 (9-60% with clinically meaningful improvement only). After long-term follow-up, 75-88% of patients showed clinically meaningful improvements or no clinically meaningful change at day 365 (12.5-50% with clinically meaningful improvement only) and 60-100% at day 545 (0-50% with clinically meaningful improvement only). For EORTC QLQ-C30 fatigue, the only primary domain of interest that was meaningfully worse than the general population at baseline, clinically meaningful improvements occurred in 33% of patients at day 29, 42% at day 60, 62% at day 90, 60% at day 180, 44% at day 365, and 50% at day 545.

Clinically meaningful improvements in FACT-LymS occurred in 57% of patients at day 29, 68% at day 60, 71% at day 90, 70% at day 180, 60% at day 270, and 50% at day 365 (Figure 2). Clinically meaningful improvements over time for secondary domains of interest are shown in *Online Supplementary Figure S3*.

Time to confirmed improvement in HRQOL

Among the primary domains of interest, the median time to confirmed improvement was 19.1 weeks (95% confidence interval [CI]: 11.9-not reached [NR]) for role functioning, 18.1 weeks (95% CI: 11.6-NR) for fatigue, 9.9 weeks (95% CI: 8.6-12.7) for pain, and 17.6 weeks (95% CI: 11.1-NR) for FACT-LymS, and was NR for GH/QOL, physical functioning, and cognitive functioning (*Online Supplementary Figure S4*). Time to confirmed improvement for the secondary domains of interest are shown in *Online Supplementary Figure S5*.

Time to confirmed deterioration in HRQOL

The median time to confirmed deterioration among the primary domains of interest was 11.9 weeks (95% CI: 6.4-NR) for GH/QOL, 11.9 weeks (95% CI: 7.1-NR) for physical functioning, 37.3 weeks (95% CI: 8.3-NR) for role functioning, and 52.3 weeks (95% CI: 10.7-NR) for fatigue and was NR for cognitive functioning, pain, or FACT-LymS (*Online Supplementary Figure S6*). Time to confirmed deterioration of HRQOL for the secondary domains of interest are shown in *Online Supplementary Figure S7*.

Discussion

HRQOL improved or was maintained in patients with R/R LBCL not intended for HSCT who received liso-cel as second-line therapy in the PILOT study. Baseline HRQOL, functional status, and symptom severity were generally

Table 3. Overall least squares mean changes from baseline to day 545.

Domain[a]	Overall LS mean change (95% CI)	MID		*P*
EORTC QLQ-C30		Osoba *et al.*[17]	Cocks *et al.*[18c]	
GH/QOL	2.77 (-0.36 to 5.91)	±10	+5/-5	0.082
Physical functioning	-1.67 (-4.88 to 1.53)	±10	+2/-5	0.298
Role functioning	-3.21 (-8.01 to 1.60)	±10	+6/-7	0.187
Cognitive functioning	-0.55 (-3.50 to 2.41)	±10	+3/-1	0.711
Fatigue	-6.94 (-10.34 to -3.55)[b]	±10	-4/+5	<0.001
Pain	-4.12 (-7.62 to -0.62)[b]	±10	-5/+3	0.022
Emotional functioning	2.47 (-0.36 to 5.30)	±10	+6/-3	0.086
Social functioning	-2.39 (-7.60 to 2.81)	±10	+3/-6	0.362
Nausea/vomiting	1.25 (-0.96 to 3.47)	±10	-3/+5	0.262
Dyspnea	0.99 (-2.61 to 4.59)	±10	-2/+5	0.585
Insomnia	0.76 (-3.77 to 5.29)	±10	-5/+2	0.740
Appetite loss	-5.66 (-9.84 to -1.47)[b]	±10	-7/+2	0.009
Constipation	-1.30 (-4.39 to 1.79)	±10	-4/+5	0.402
Diarrhea	-2.92 (-6.53 to 0.70)	±10	-3/+5	0.111
Financial difficulties	1.27 (-2.72 to 5.26)	±10	-3/+2	0.526
FACT-Lym		Hlubocky *et al.*[19,20]		
FACT-LymS	4.08 (2.55-5.61)[b]	±3		<0.001
EQ-5D-5L		Pickard *et al.*[21]		
EQ-5D-5L HUI	0.02 (-0.02 to 0.06)	±0.08		0.341
EQ-VAS	4.35 (1.27-7.43)[b]	±7		0.006

[a]Primary domains of interest are in roman typeface; secondary domains of interest are in italics. [b]Domains showing significant improvements from baseline. [c]Values on the left indicate thresholds for clinically meaningful improvement and values on the right indicate thresholds for clinically meaningful worsening. The analysis was based on changes in HRQOL from baseline through day 545. For the EORTC QLQ-C30 GH/QOL and functioning domains, an increased score denotes improved QOL/function; for symptom domains, an increased score denotes worsened symptoms. For the FACT-LymS, EQ-5D-5L HUI, and EQ-VAS, an increased score indicates improved QOL. LS: least squares; CI: confidence interval; MID: minimally important difference; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - 30 items; GH: global health; QOL: quality of life; FACT-LymS: Functional Assessment of Cancer Therapy - Lymphoma "Additional Concerns" Subscale; HUI: health utility index; VAS: visual analog scale; HRQOL: health-related quality of life.

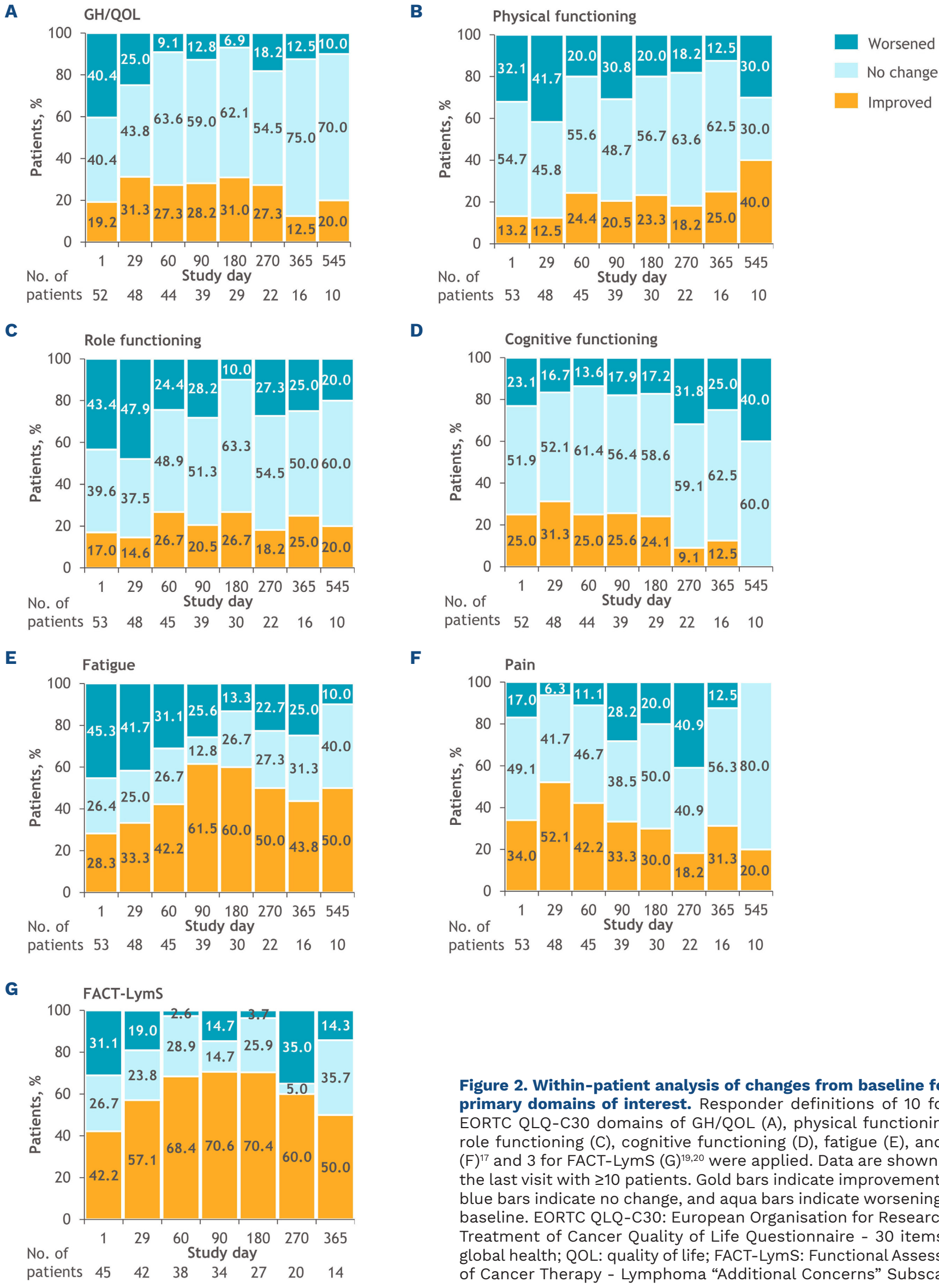

Figure 2. Within-patient analysis of changes from baseline for the primary domains of interest. Responder definitions of 10 for the EORTC QLQ-C30 domains of GH/QOL (A), physical functioning (B), role functioning (C), cognitive functioning (D), fatigue (E), and pain (F)[17] and 3 for FACT-LymS (G)[19,20] were applied. Data are shown up to the last visit with ≥10 patients. Gold bars indicate improvement, light blue bars indicate no change, and aqua bars indicate worsening from baseline. EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - 30 items; GH: global health; QOL: quality of life; FACT-LymS: Functional Assessment of Cancer Therapy - Lymphoma "Additional Concerns" Subscale.

slightly worse than in the general population; for EORTC QLQ-C30 fatigue, social functioning, and appetite loss, baseline scores were worse than general population scores to a clinically meaningful extent. After transient worsening in most domains, scores for the primary domains of interest generally improved over time. No significant or clinically meaningful worsening was observed for any of the primary and secondary HRQOL domains of interest across visits after liso-cel infusion. Moreover, scores for EORTC QLQ-C30 fatigue, pain, appetite loss, FACT-LymS, and EQ-VAS showed significant improvements across postbaseline assessments, with clinically meaningful improvements observed for EORTC QLQ-C30 fatigue and FACT-LymS.

In within-patient analyses, clinically meaningful improvements or no meaningful change in the primary domains of interest were reported for most patients at day 180 and day 365. Median time to confirmed improvement was NR for EORTC QLQ-C30 GH/QOL, physical functioning, and cognitive functioning. These results may be because mean baseline scores for these domains were similar to the general population scores. With a potentially limited scope for improvement, it was harder for these patients to achieve an improvement in score exceeding the meaningful improvement threshold. However, median time to confirmed improvement was relatively short for EORTC QLQ-C30 pain. For cognitive functioning, pain, and FACT-LymS, median time to confirmed deterioration was NR. Deterioration in domains showing the largest change from baseline on day 1 (i.e., role functioning and social functioning) was likely due to hospitalization for liso-cel infusion, as patients could not perform their normal daily roles during that time. Median times to confirmed deterioration were relatively short for EORTC QLQ-C30 GH/QOL and physical functioning, likely due to a transient deterioration during lymphodepletion and in the period immediately after liso-cel infusion. Worsening in other symptom and/or functioning domains on day 1 was likely due to treatment-related symptoms from bridging therapy or lymphodepletion treatments.

These findings add to evidence supporting the beneficial or lack of detrimental effects of CAR T-cell therapy on HRQOL in patients with R/R LBCL not intended for HSCT, addressing an unmet need highlighted by a recent Cochrane review.[24] These results are similar to previously reported beneficial effects of CAR T-cell therapies on HRQOL in the second-line setting.[10,12] In TRANSFORM, a study in patients with R/R LBCL intended for autologous HSCT, second-line treatment with liso-cel improved some HRQOL domains, including GH/QOL, cognitive functioning, and fatigue, and maintained HRQOL in most of the remaining domains, compared with SOC. Additionally, in the randomized phase III ZUMA-7 study, the CAR T-cell therapy axicabtagene ciloleucel demonstrated significant and clinically meaningful improvements in mean changes in EORTC QLQ-C30 GH/QOL and physical functioning and EQ-VAS from baseline compared with SOC at day 100 (P<0.0001 for all).[12] Altogether, these results further support the use of CAR T-cell therapies as second-line treatment in patients with R/R LBCL. CAR T-cell therapy may be a good alternative to HSCT from the patient perspective. A study comparing changes in QOL and adverse events after treatment with CAR T-cell therapy or HSCT (autologous or allogeneic) in patients with myeloma, lymphoma, leukemia, and other myeloid neoplasms found that overall QOL and physical and functional well-being deteriorated significantly less with CAR T-cell therapy than with HSCT and returned to baseline levels faster.[25] These findings are supported by HRQOL results from the phase III, randomized, pivotal TRANSFORM and ZUMA-7 studies, comparing treatment with CAR T-cell therapy (liso-cel and axicabtagene ciloleucel, respectively) *versus* SOC therapy, including salvage platinum-based immunochemotherapy followed by high-dose chemotherapy and autologous HSCT in responding patients as second-line therapy for patients with LBCL.[10,12] In TRANSFORM, HRQOL was either improved or maintained from baseline in patients in the liso-cel arm *versus* the SOC arm.[10] Similar improvement in HRQOL was observed in patients in the axicabtagene ciloleucel arm *versus* the SOC arm in the ZUMA-7 study at day 100.[12] Additionally, HRQOL is low in older patients with diffuse LBCL and has been observed to decrease after diagnosis, possibly due to therapy.[26] While some elderly, fit patients may proceed to HSCT after relapse, most have comorbidities that preclude intensive therapy options.[27] The current results, paired with the results from the PILOT primary analysis,[6] demonstrate that liso-cel is an effective treatment that can maintain or improve HRQOL for patients with R/R LBCL for whom HSCT is not intended.

Our findings should be interpreted with caution because of the small sample size and single-arm study design of PILOT. Additionally, the PILOT population was predominantly White, potentially limiting the generalizability of these data to minority populations. Data at later time points (≥270 days) may have been influenced by the COVID-19 pandemic, as most visits on day 270 (86%) occurred after the outbreak was declared a pandemic on March 11, 2020. By comparison, ≤55% of visits on day 90 or earlier occurred before this date. Additionally, PRO data were not collected after the end of study visit in patients who experienced disease progression; thus, there is a potential for survivorship bias.

In conclusion, HRQOL improved or was maintained in patients with R/R LBCL not intended for HSCT who received liso-cel as second-line therapy in the PILOT study. Liso-cel treatment was associated with clinically meaningful improvements in EORTC QLQ-C30 fatigue and FACT-LymS scores in most patients and did not negatively affect other HRQOL measures. These findings provide additional evidence from the patient's perspective to support the use of liso-cel as a second-line treatment in patients with R/R LBCL not intended for HSCT and highlight the importance of HRQOL measures in future clinical trials of novel agents or modalities in clinical cancer research.

Disclosures

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Contributions

LIG, DH, NG, MH, and GH acquired the data. JB, FFL, and LP were involved in study conception or design, data analysis, and data interpretation. SG and LS analyzed and interpreted the data. AS was involved in study conception or design and acquired the data. All authors approved the final version of the manuscript.

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Data-sharing statement

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

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