

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

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## Supplementary Appendix

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

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## Supplementary Methods

### Study overview and participants

In PILOT, patients underwent lymphodepletion with fludarabine and cyclophosphamide, followed by lisocabtagene maraleucel (liso-cel) administered as 2 sequential infusions of equal target doses of CD8<sup>+</sup> and CD4<sup>+</sup> chimeric antigen receptor (CAR)-positive T cells for a total target dose of  $100 \times 10^6$  CAR<sup>+</sup> T cells. Bridging therapy was allowed if needed for disease control during liso-cel manufacturing. Enrolled patients were adults with relapsed or refractory large B-cell lymphoma after first-line treatment who met  $\geq 1$  of the following protocol-specified transplant-not-intended criteria: age  $\geq 70$  years, Eastern Cooperative Oncology Group performance status of 2, diffusing capacity of the lungs for carbon monoxide  $\leq 60\%$  adjusted for sex-specific hemoglobin concentration, left ventricular ejection fraction (LVEF)  $< 50\%$ , creatinine clearance (CrCl) per the Cockcroft-Gault formula  $< 60$  mL/min, and alanine aminotransferase or aspartate aminotransferase (ALT/AST)  $> 2 \times$  upper limit of normal (ULN). Patients must have had adequate organ functions (oxygen saturation  $\geq 92\%$  on room air and grade  $\leq 1$  dyspnea; LVEF  $\geq 40\%$ ; CrCl  $> 30$  mL/min; ALT/AST  $\leq 5 \times$  ULN; adequate bone marrow function per investigator; total bilirubin  $< 2.0$  mg/dL [or  $< 3.0$  mg/dL for patients with Gilbert's syndrome or lymphomatous infiltration of the liver]).

### Patient-reported outcomes (PRO)

At each visit, an European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - 30 items assessment was considered valid if  $\geq 1$  domain score was calculable, and a Functional Assessment of Cancer Therapy - Lymphoma "Additional Concerns" Subscale assessment was considered valid if  $> 50\%$  of items were answered. EQ-5D-5L health utility index was calculated if responses were provided for all 5 constituent items. EQ-5D-5L visual analog scale was evaluable if it was recorded. Completion rates used the number of patients who were still on study at each visit as the denominator.

### Statistical analysis

Statistical analyses were conducted using SAS<sup>®</sup> version 9.4 (SAS Institute, Cary, NC, USA). Continuous variables were summarized using means, medians, standard deviations, and ranges. Categorical

variables were summarized using frequencies and percentages.

In the linear mixed-effects regression models for repeated measures used to assess the least squares mean change from baseline, the dependent variable was the change in health-related quality of life (HRQOL) score from baseline. Time and the intercept were included as random effects, and time and baseline HRQOL score were included as covariates.

In time to confirmed HRQOL deterioration or improvement analyses, patients who never experienced meaningful HRQOL deterioration or improvement were censored at their last recorded assessment. Patients who died were censored at the last recorded HRQOL assessment before death. The cumulative probability of experiencing confirmed HRQOL deterioration or improvement was presented using Kaplan-Meier product-limit failure curves.

**Supplementary Table S1. PRO/HRQOL measures.**

| <b>PRO instrument</b>            | <b>Description</b>   |
|----------------------------------|--|
| <b>EORTC QLQ-C30<sup>1</sup></b> | <p>The EORTC QLQ-C30 includes 30 items across 15 domains (1 GH/QOL domain [multi-item], 5 functional domains [all multi-item], and 9 symptom domains [3 multi-item, 6 single-item]). For each domain, raw scores are first calculated as the mean of nonmissing scores for the constituent domain items. The raw scores are then transformed to a 0 to 100 scale. A higher GH/QOL score represents better overall HRQOL, and a higher functional domain score represents a higher level of functioning. A higher symptom domain score represents a higher burden of symptoms.</p> <p>Primary domains of interest in the present analysis were:</p> <p>GH/QOL (2 items)<br/>           Physical functioning (5 items)<br/>           Role functioning (2 items)<br/>           Cognitive functioning (2 items)<br/>           Fatigue (3 items)<br/>           Pain (2 items)</p> |
| <b>FACT-LymS<sup>2,3</sup></b>   | <p>FACT-LymS is a 15-item lymphoma-specific subscale that assesses what patients with lymphoma think about common disease symptoms and treatment-related symptoms. Each item is scored on a 5-point scale from 0 (“Not at all”) to 4 (“Very much”), and the item scores are added together to give a total score ranging from 0 to 60. The higher the FACT-LymS score, the better the HRQOL.</p> <p>FACT-LymS was a primary domain of interest in the present analysis.</p>  |
| <b>EQ-5D-5L<sup>4</sup></b>      | <p>The EQ-5D-5L includes 5 dimensions on functioning and well-being. Each dimension has 5 levels, ranging from “no problems” to “extreme problems.” The responses for these items are used to calculate a health utility index, with a higher score indicating better overall health. The EQ-5D-5L also includes a visual analog scale for rating overall health from 0 (worst imaginable health) to 100 (best imaginable health).</p>   |

PRO: patient-reported outcome; HRQOL: health-related quality of life; 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.

**Supplementary Table S2. Completion rates (safety set<sup>a</sup>; n=61).**

| Visit        | EORTC QLQ-C30,<br>n/N (%) | FACT-LymS,<br>n/N (%) | EQ-5D-5L HUI,<br>n/N (%) | EQ-VAS,<br>n/N (%) |
|--------------|---------------------------|-----------------------|--------------------------|--------------------|
| Screening    | 57/61 (93)                | 50/61 (82)            | 56/61 (92)               | 55/61 (90)         |
| Pretreatment | 59/61 (97)                | 53/61 (87)            | 58/61 (95)               | 59/61 (97)         |
| Day 1        | 57/61 (93)                | 53/61 (87)            | 57/61 (93)               | 57/61 (93)         |
| Day 29       | 50/61 (82)                | 48/61 (79)            | 49/61 (80)               | 49/61 (80)         |
| Day 60       | 47/53 (89)                | 44/53 (83)            | 47/53 (89)               | 47/53 (89)         |
| Day 90       | 40/49 (82)                | 40/49 (82)            | 39/49 (80)               | 39/49 (80)         |
| Day 180      | 32/37 (87)                | 31/37 (84)            | 31/37 (84)               | 32/37 (87)         |
| Day 270      | 24/33 (73)                | 24/33 (73)            | 24/33 (73)               | 24/33 (73)         |
| Day 365      | 18/21 (86)                | 17/21 (81)            | 19/21 (91)               | 19/21 (91)         |
| Day 545      | 12/15 (80)                | 12/15 (80)            | 12/15 (80)               | 12/15 (80)         |
| Day 730      | 3/4 (75)                  | 3/4 (75)              | 3/4 (75)                 | 3/4 (75)           |

<sup>a</sup>All patients who received lisocabtagene maraleucel.

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - 30 items; FACT-LymS: Functional Assessment of Cancer Therapy - Lymphoma "Additional Concerns" Subscale; HUI: health utility index; VAS: visual analog scale.

**Supplementary Table S3. Additional baseline disease characteristics.**

|  | <b>EORTC QLQ-C30–evaluable set (n=56)</b> |
|--|---|
| Age-adjusted international prognostic index, n (%) |   |
| 0  | 9 (16)                                    |
| 1  | 22 (39)                                   |
| 2  | 14 (25)                                   |
| 3  | 10 (18)                                   |
| Missing  | 1 (2)                                     |
| HCT-CI score at baseline                           |   |
| n  | 53  |
| Mean (SD)  | 2.5 (2.42)                                |
| Median (range)                                     | 2.0 (0.0–8.0)                             |
| Disease histology, n (%)                           |   |
| DLBCL NOS  | 32 (57)                                   |
| Transformed follicular lymphoma                    | 8 (14)                                    |
| High-grade lymphoma with DLBCL histology           | 15 (27)                                   |
| Follicular lymphoma, grade 3B                      | 1 (2)                                     |
| Cell of origin, n (%)                              |   |
| GCB  | 23 (41)                                   |
| ABC, non-GCB                                       | 18 (32)                                   |
| Unknown  | 12 (21)                                   |
| Missing  | 3 (5)                                     |
| Relapse after CR to frontline therapy, n (%)       |   |
| Relapsed ≤12 months after CR to frontline therapy  | 13 (23)                                   |
| Relapsed >12 months after CR to frontline therapy  | 14 (25)                                   |
| Missing  | 29 (52)                                   |
| Refractory and CR duration categories, n (%)       |   |
| Refractory or CR <3 months                         | 31 (55)                                   |
| CR ≥3 months and ≤12 months                        | 11 (20)                                   |
| CR >12 months                                      | 14 (25)                                   |

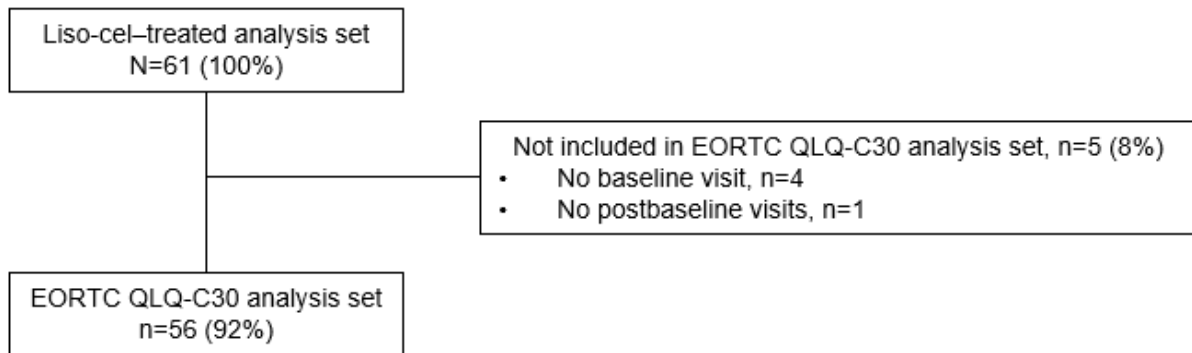
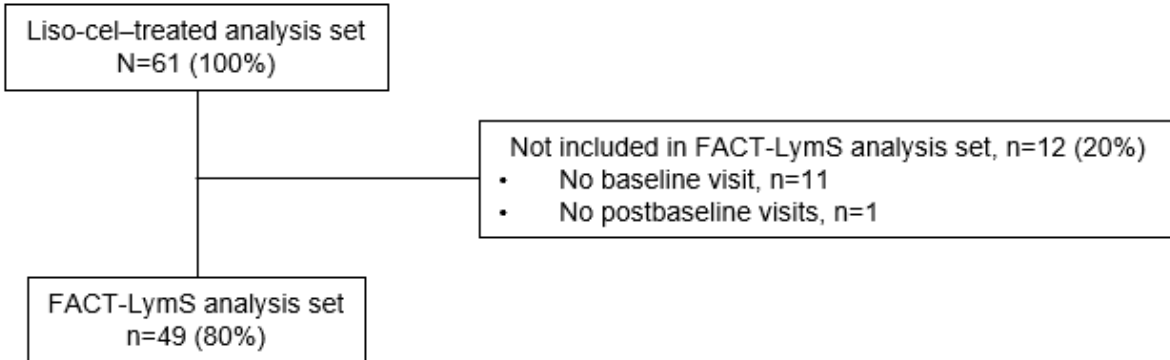
A patient was deemed to have refractory disease if their response to front-line therapy was less than CR; otherwise, a patient was deemed to have relapsed disease. Response was assessed by an independent review committee according to Lugano 2014 criteria.<sup>5</sup>

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - 30 items; HCT-CI: hematopoietic cell transplantation-specific comorbidity index; SD: standard deviation; DLBCL: diffuse large B-cell lymphoma; NOS: not otherwise specified; GCB: germinal center B cell; ABC: activated B cell; CR: complete response.

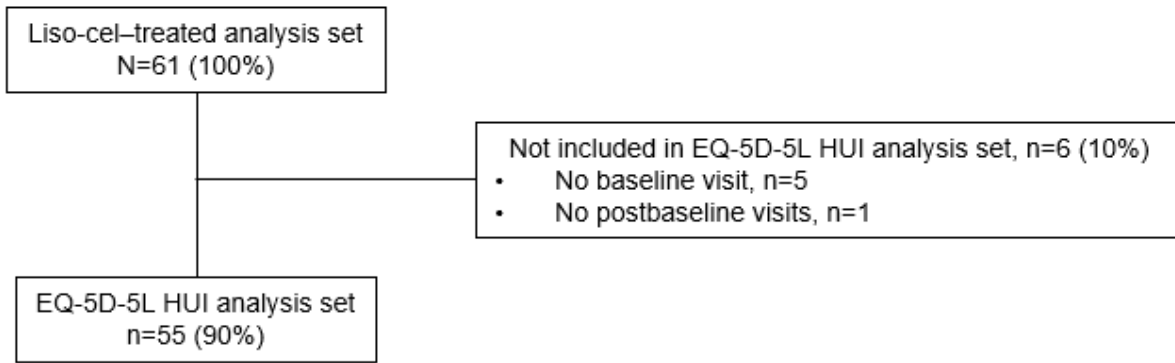


**Supplementary Figure S1. Patient disposition in PRO-evaluable sets.**

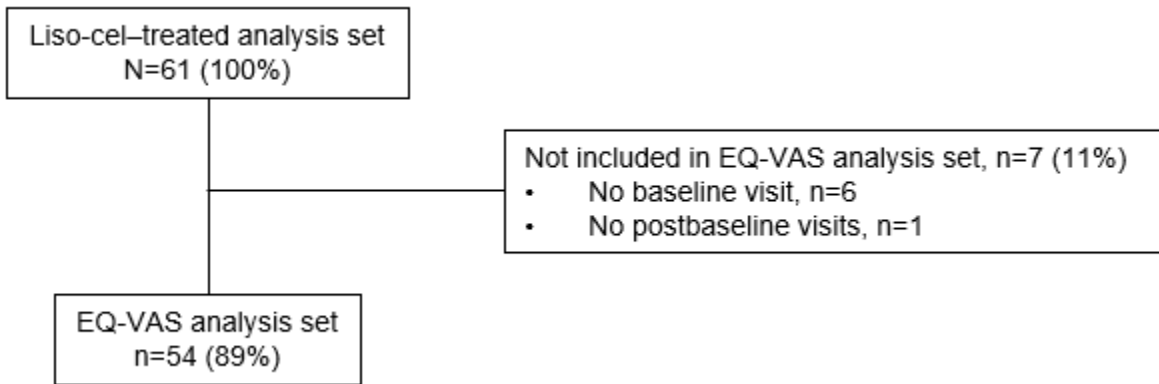
Patient dispositions in the PRO-evaluable sets are shown for EORTC QLQ-C30 (A), FACT-LymS (B), EQ-5D-5L HUI (C), and EQ-VAS (D). PRO: patient-reported outcome; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - 30 items; FACT-LymS: Functional Assessment of Cancer Therapy - Lymphoma "Additional Concerns" Subscale; HUI: health utility index; VAS: visual analog scale.

**(A)****(B)**

**(C) EQ-5D-5L HUI**



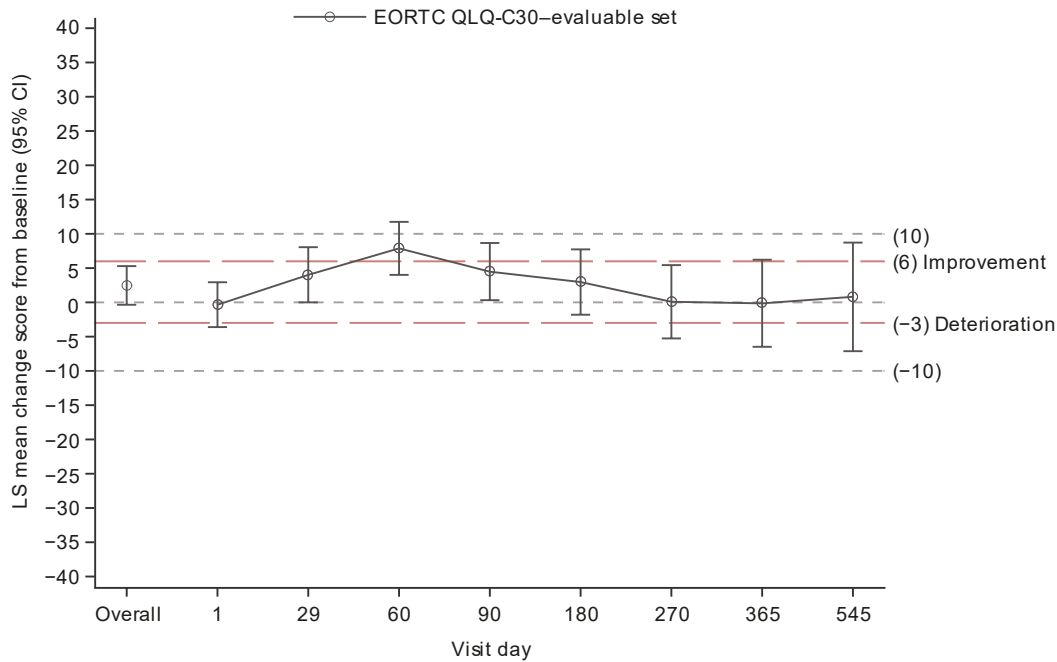
**(D) EQ-VAS**



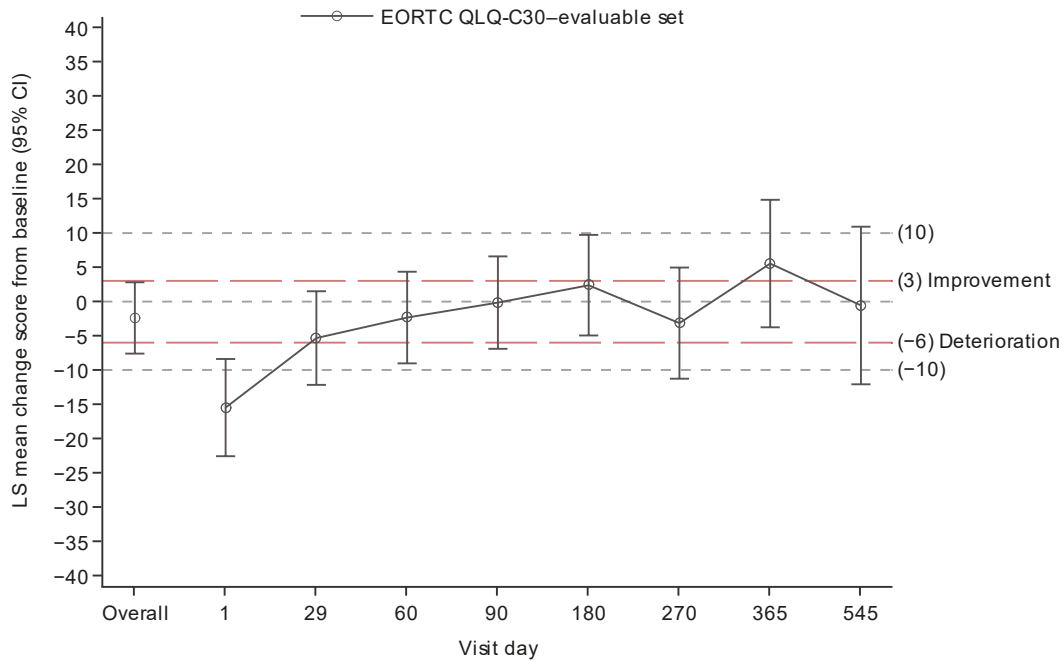
**Supplementary Figure S2. LS mean changes from baseline for the secondary domains of interest.**

Data up to the last visit with  $\geq 10$  patients are shown. For the EORTC QLQ-C30 domains of emotional functioning (A), social functioning (B), nausea/vomiting (C), dyspnea (D), insomnia (E), appetite loss (F), constipation (G), diarrhea (H), and financial difficulties (I), 2 sets of MIDs were used to assess whether a change from baseline (improvement or deterioration) was clinically meaningful: the conventional 10-point change suggested by Osoba *et al.*<sup>6</sup> (dotted gray lines) and the MIDs suggested by Cocks *et al.*<sup>7</sup> (dashed red lines). For the EQ-5D-5L domains of HUI (J) and EQ-VAS (K), the MIDs suggested by Pickard *et al.*<sup>8</sup> (gray dashed lines) were used to determine clinically meaningful change from baseline. CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - 30 items; HUI: health utility index; LS: least squares; MID: minimally important difference; VAS: visual analog scale.

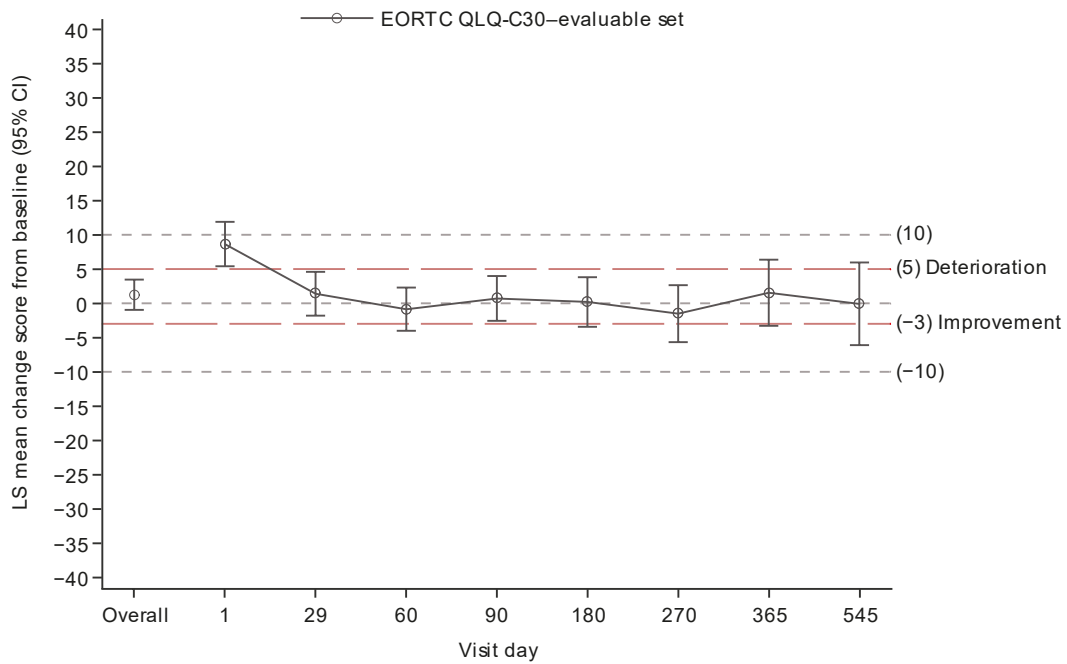
**(A) Emotional functioning**



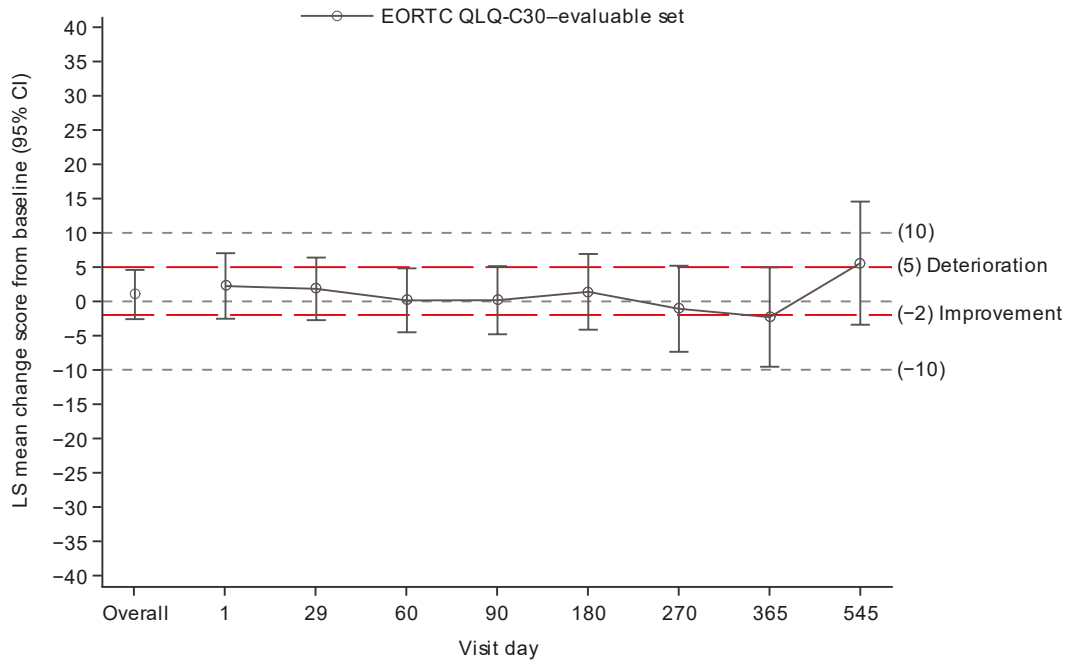
**(B) Social functioning**



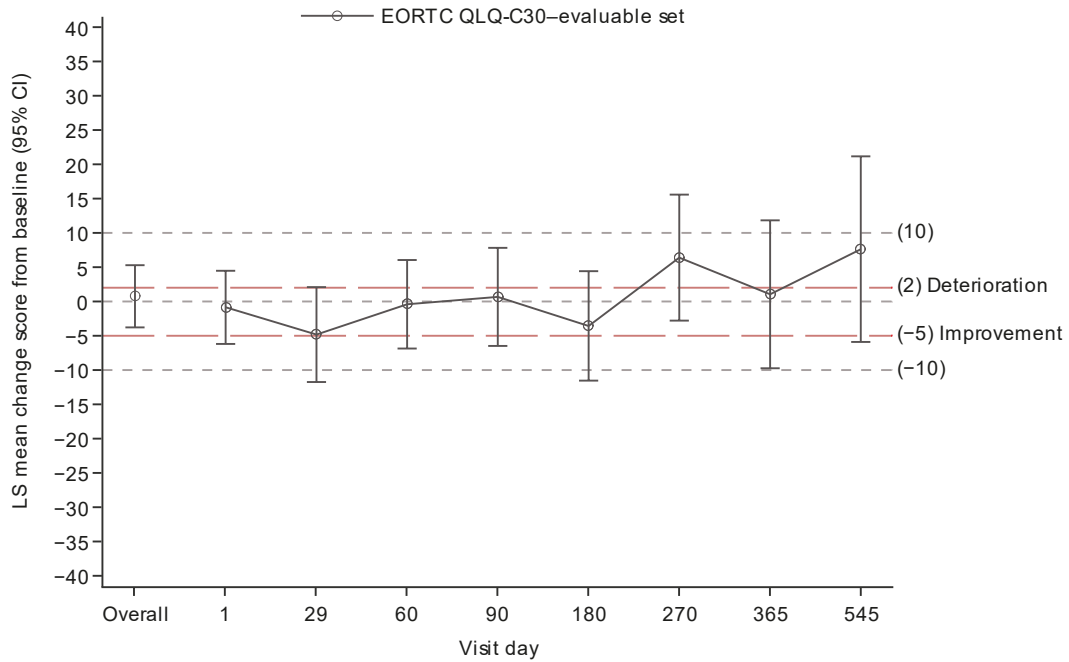
**(C) Nausea/vomiting**



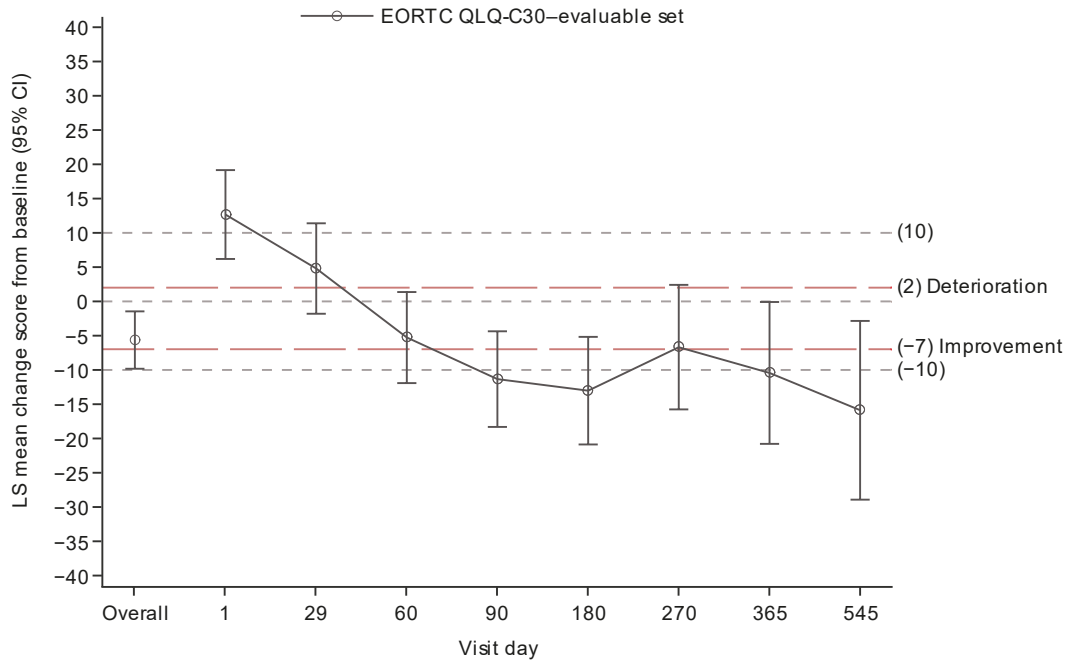
**(D) Dyspnea**



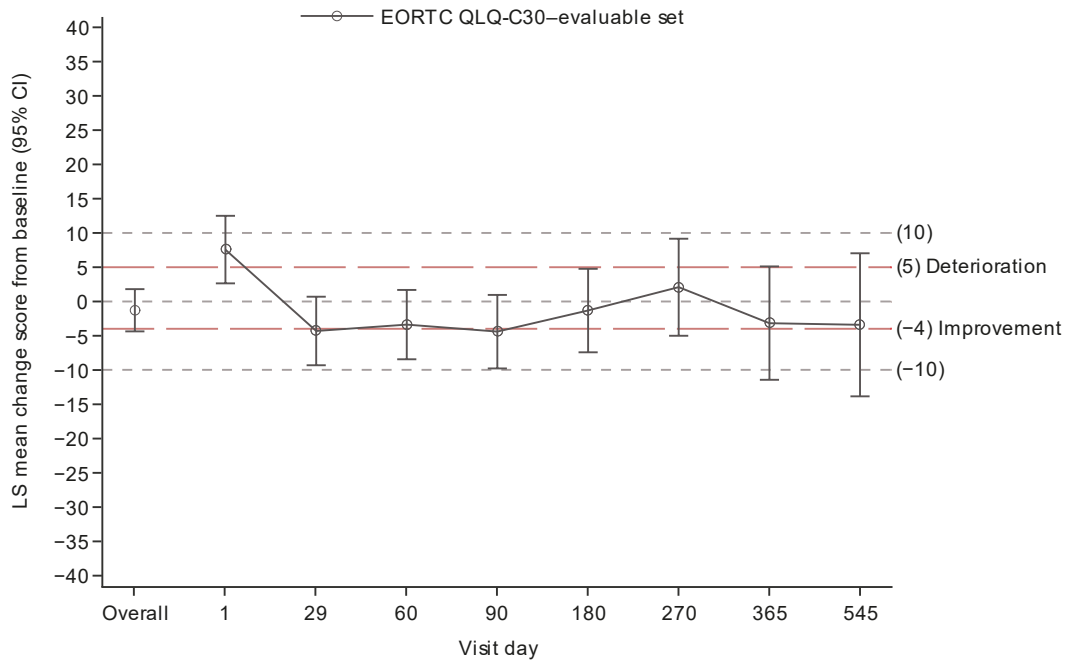
**(E) Insomnia**



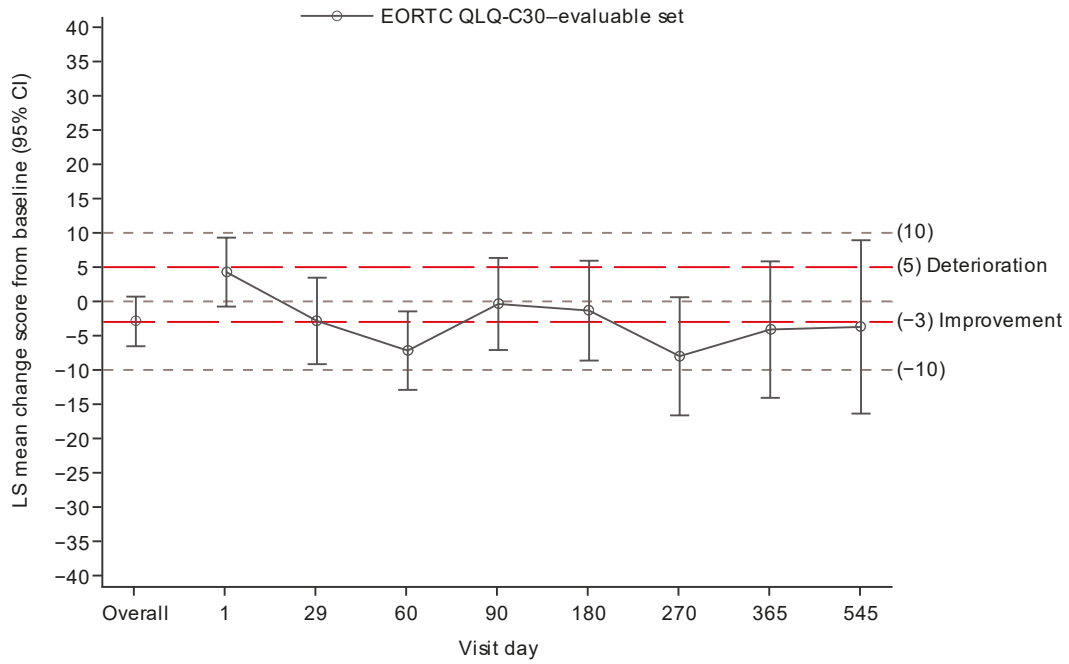
**(F) Appetite loss**



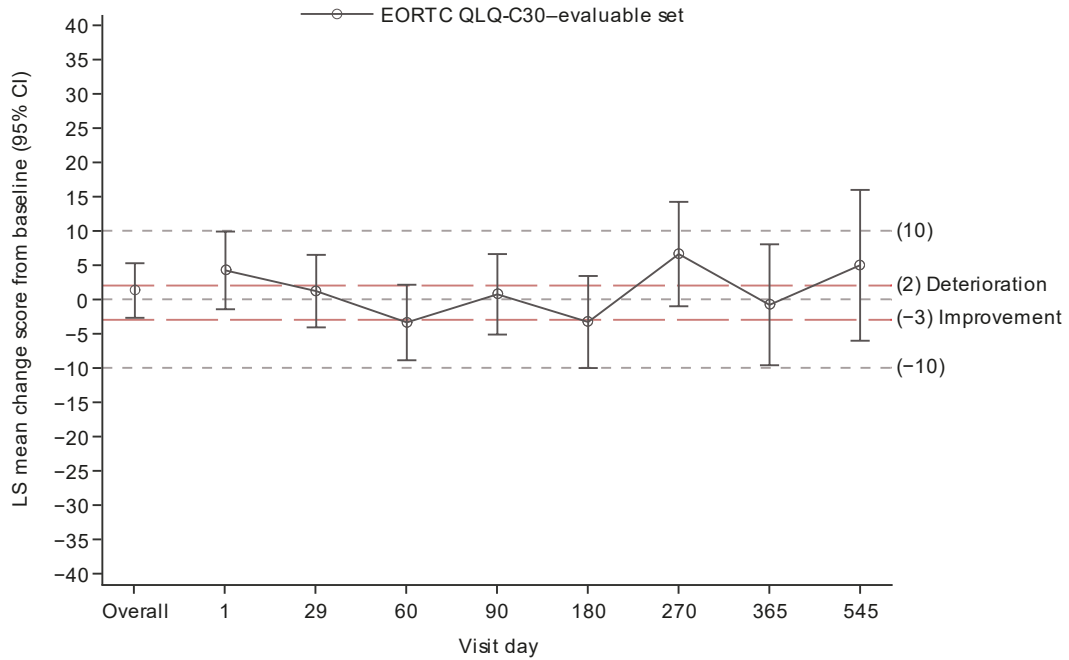
**(G) Constipation**



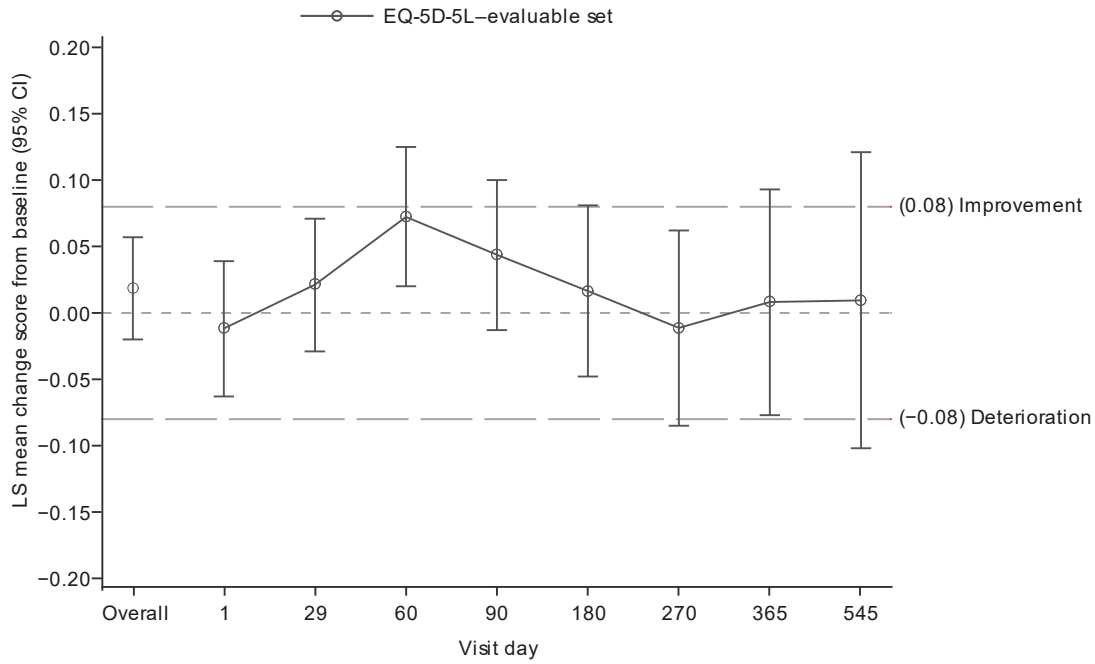
**(H) Diarrhea**



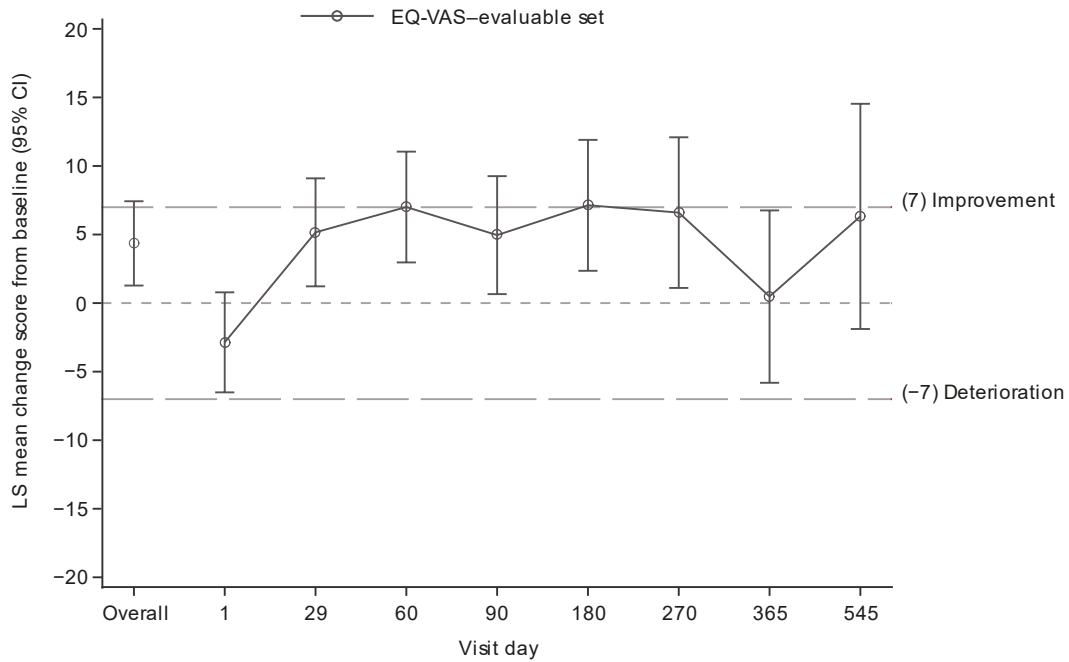
**(I) Financial difficulties**



**(J) EQ-5D-5L HUI**



**(K) EQ-VAS**



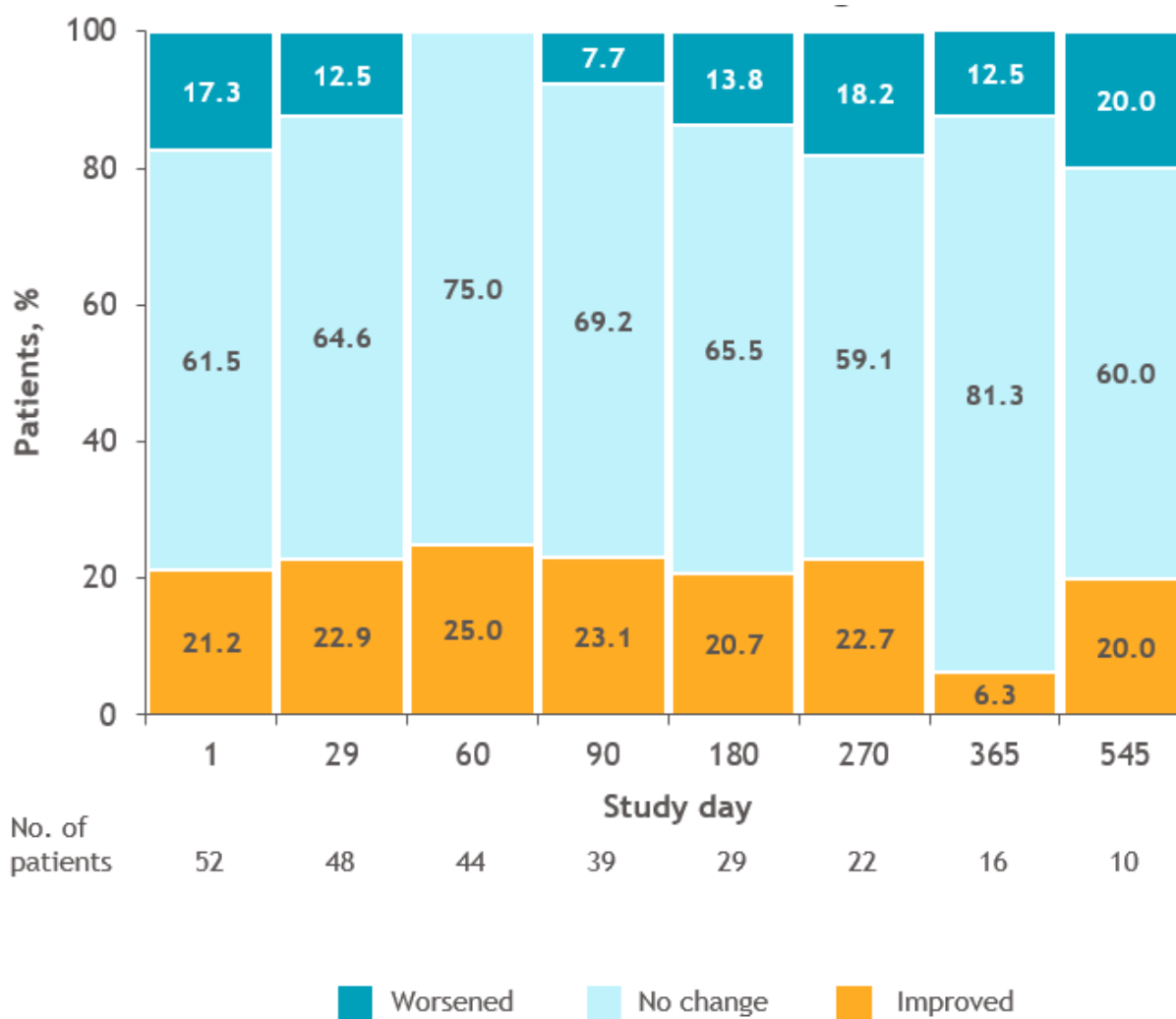


**Supplementary Figure S3. Within-patient analysis of changes from baseline for the secondary domains of interest.**

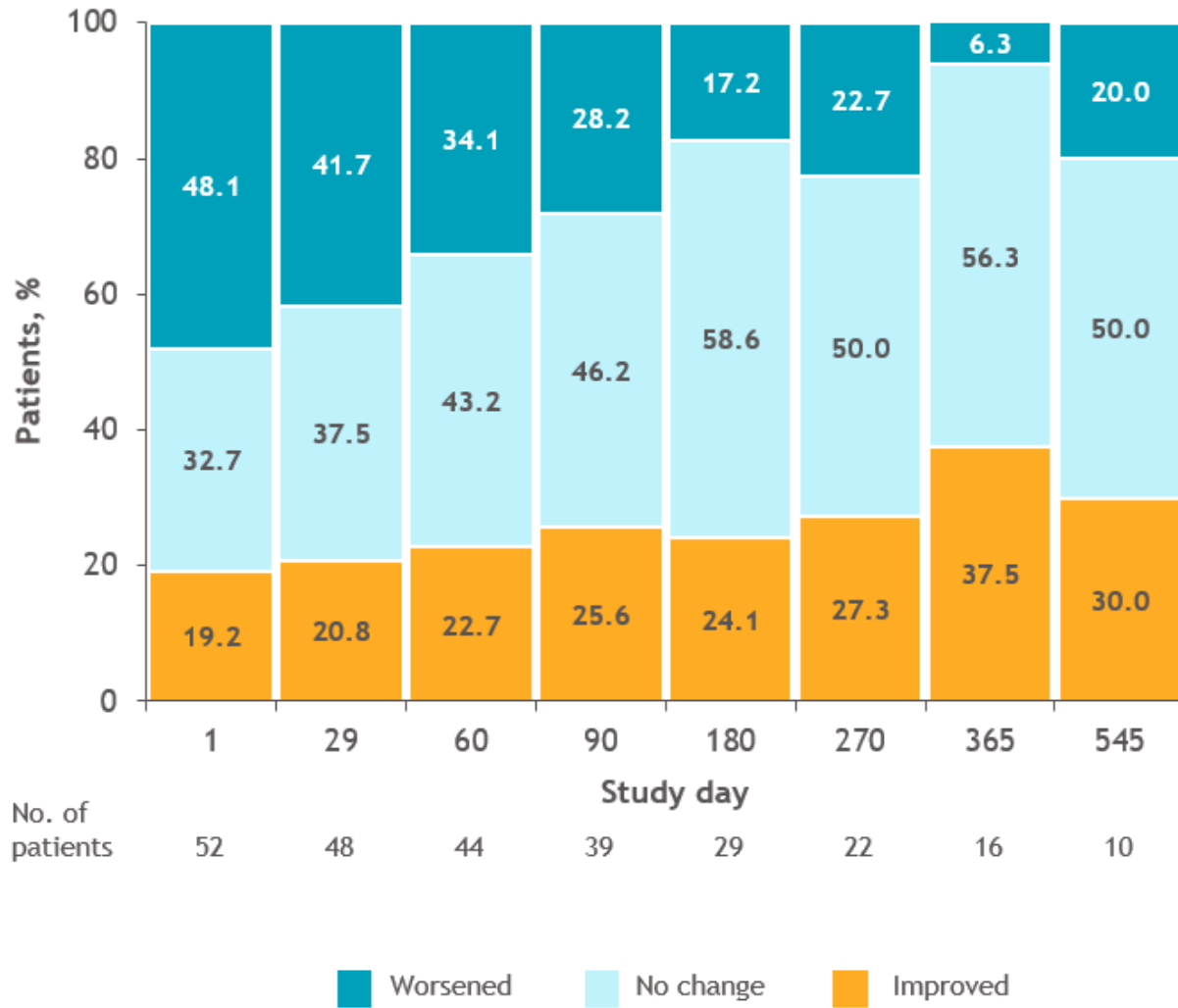
Responder categories are based on a responder definition for change from baseline. Responder definitions (improvement/worsening) were +10/−10 for EORTC QLQ-C30 emotional functioning (A) and social functioning (B); −10/+10 for EORTC QLQ-C30 nausea/vomiting (C), dyspnea (D), insomnia (E), appetite loss (F), constipation (G), diarrhea (H), and financial difficulties (I); +0.08/−0.08 for EQ-5D-5L HUI (J); and +7/−7 for EQ-VAS (K). 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; HUI: health utility index; VAS: visual analog scale.

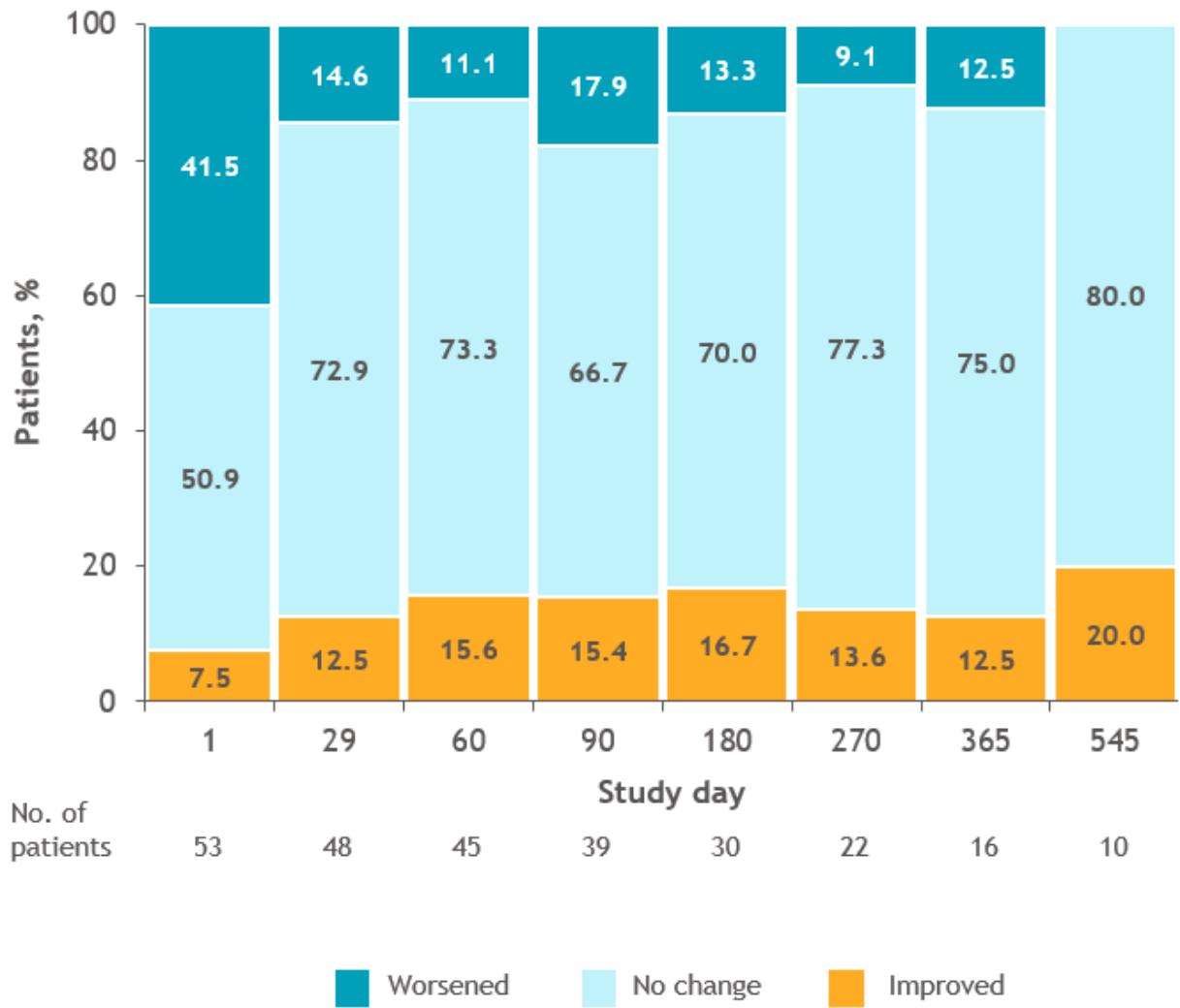
**(A) Emotional functioning**



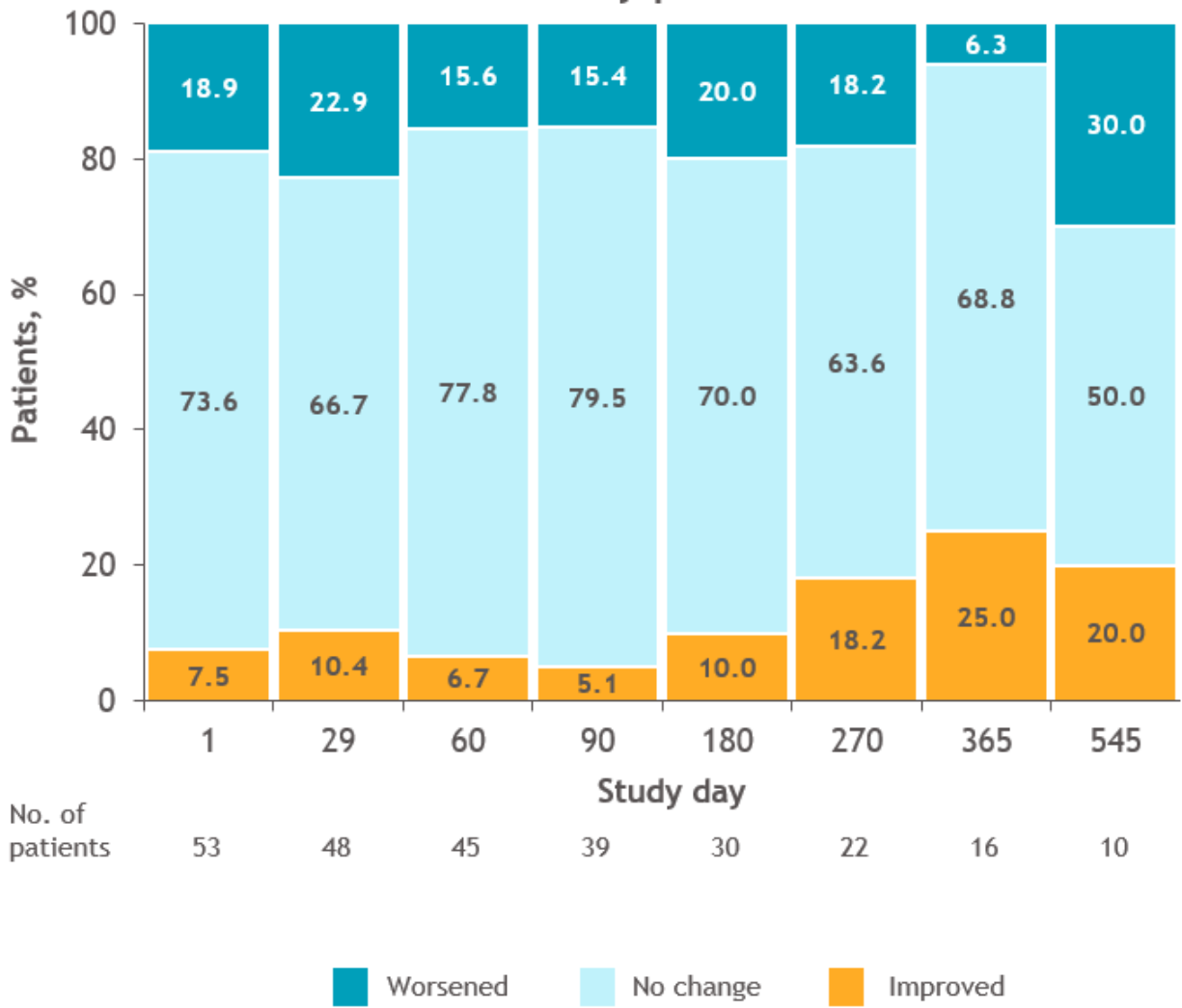
**(B) Social functioning**



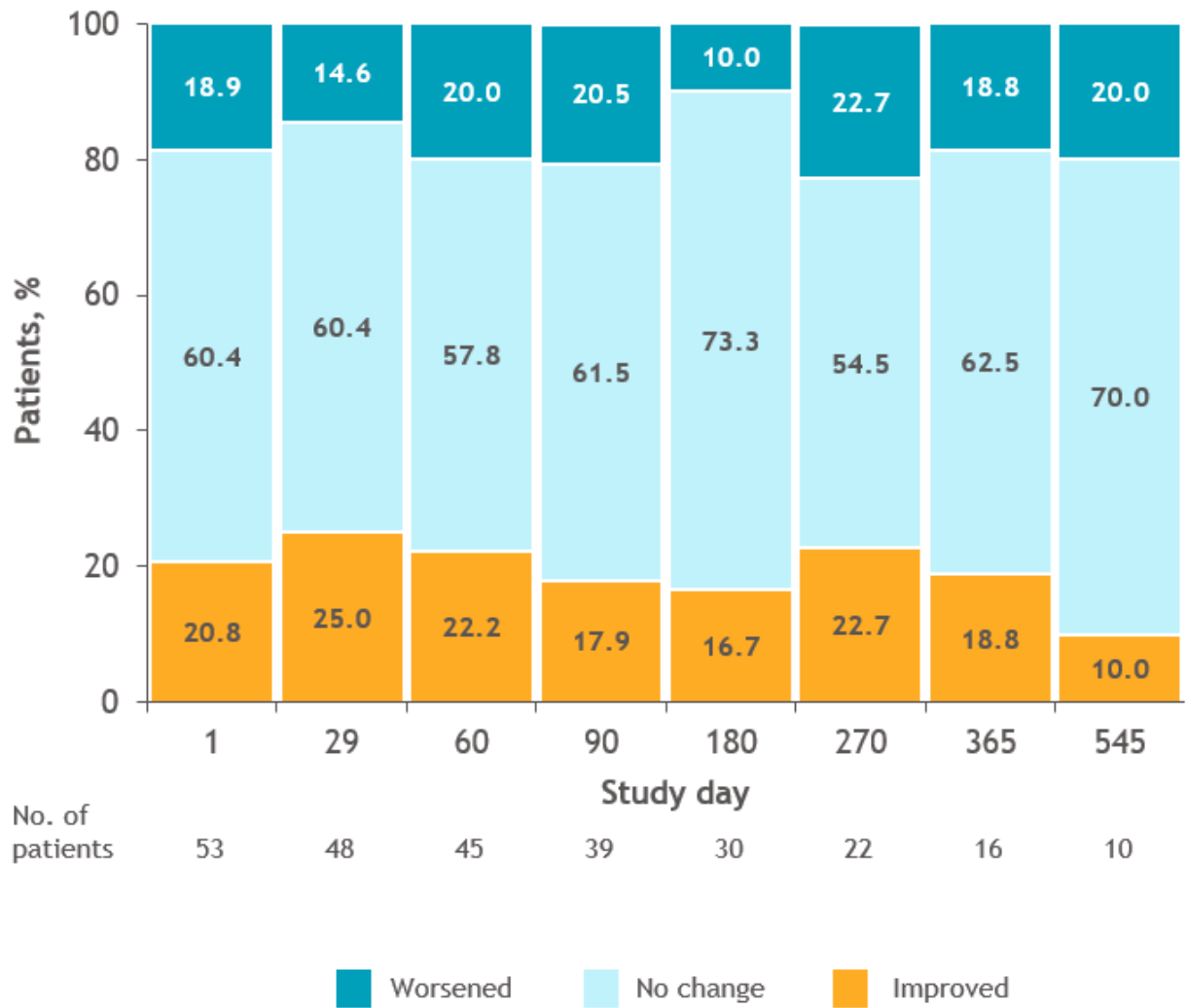
**(C) Nausea/vomiting**



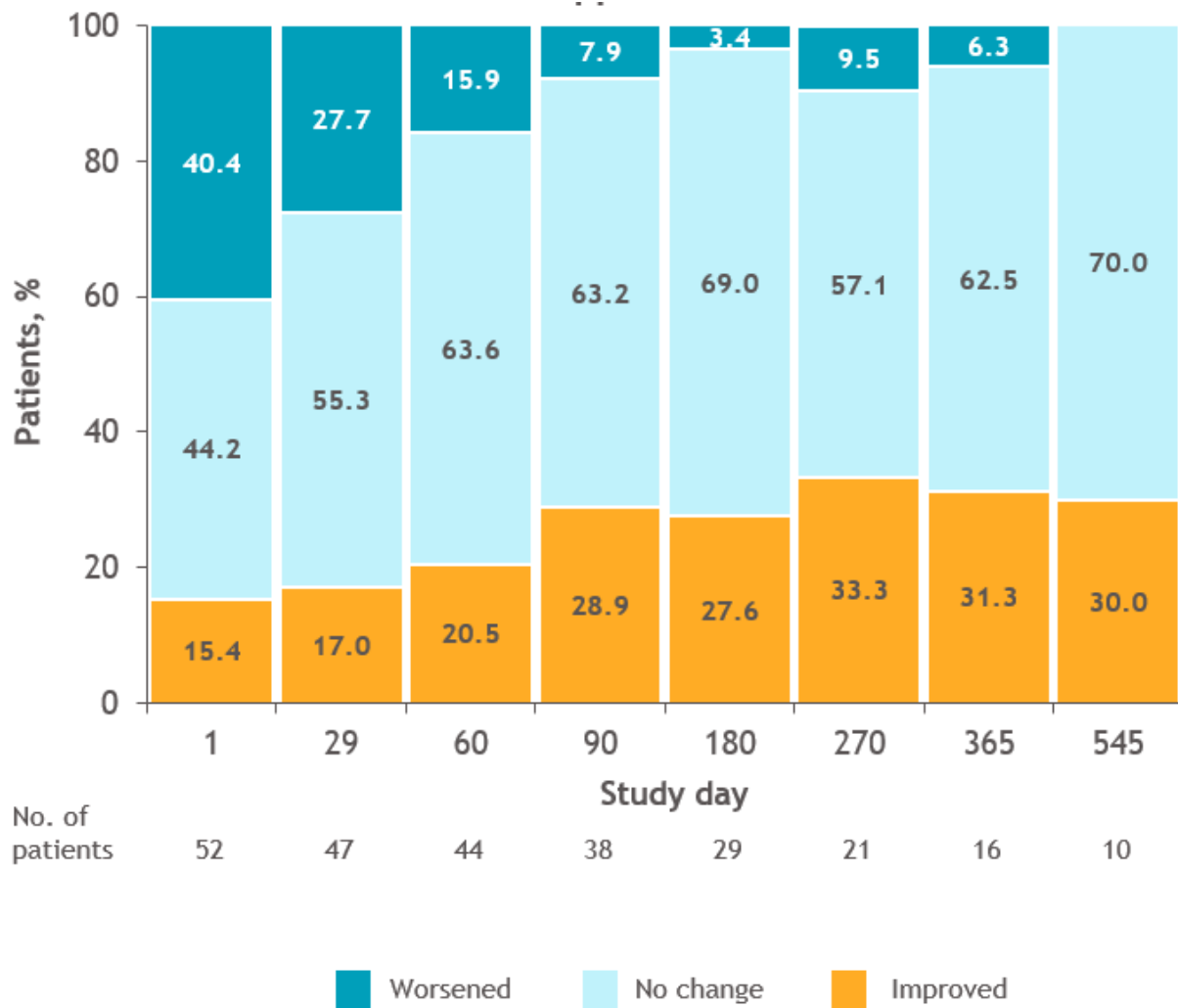
(D) Dyspnea



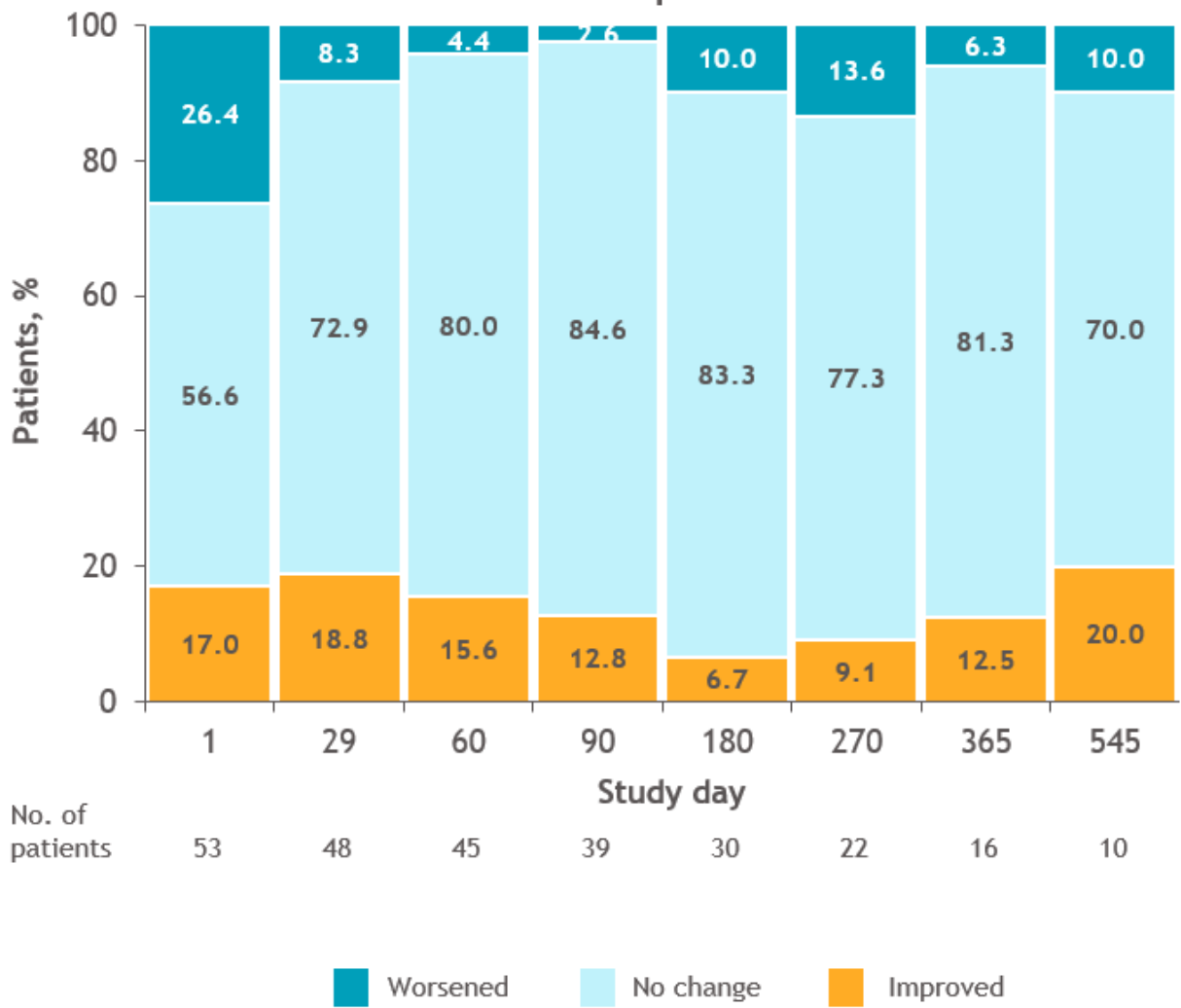
**(E) Insomnia**



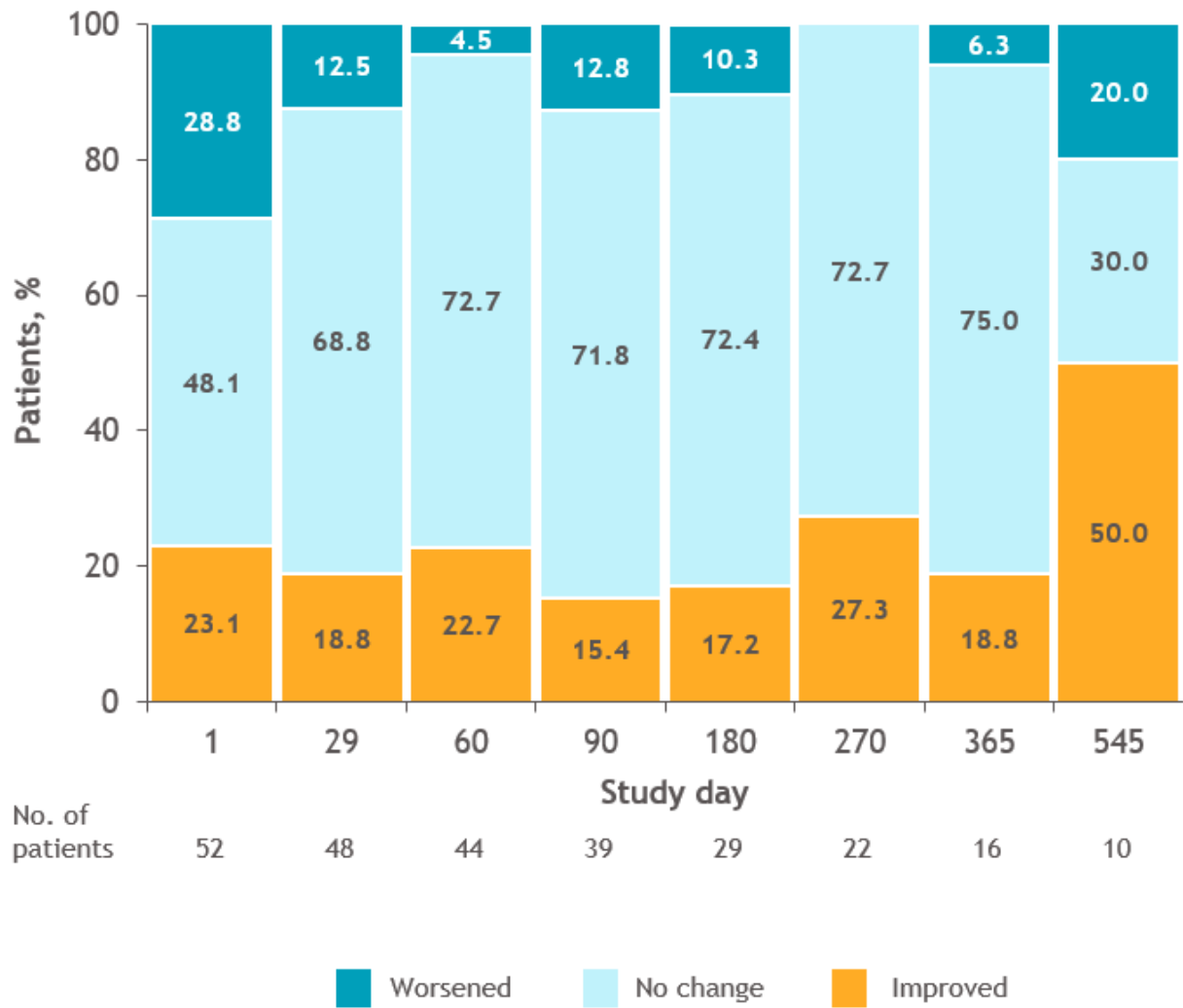
**(F) Appetite loss**



**(G) Constipation**

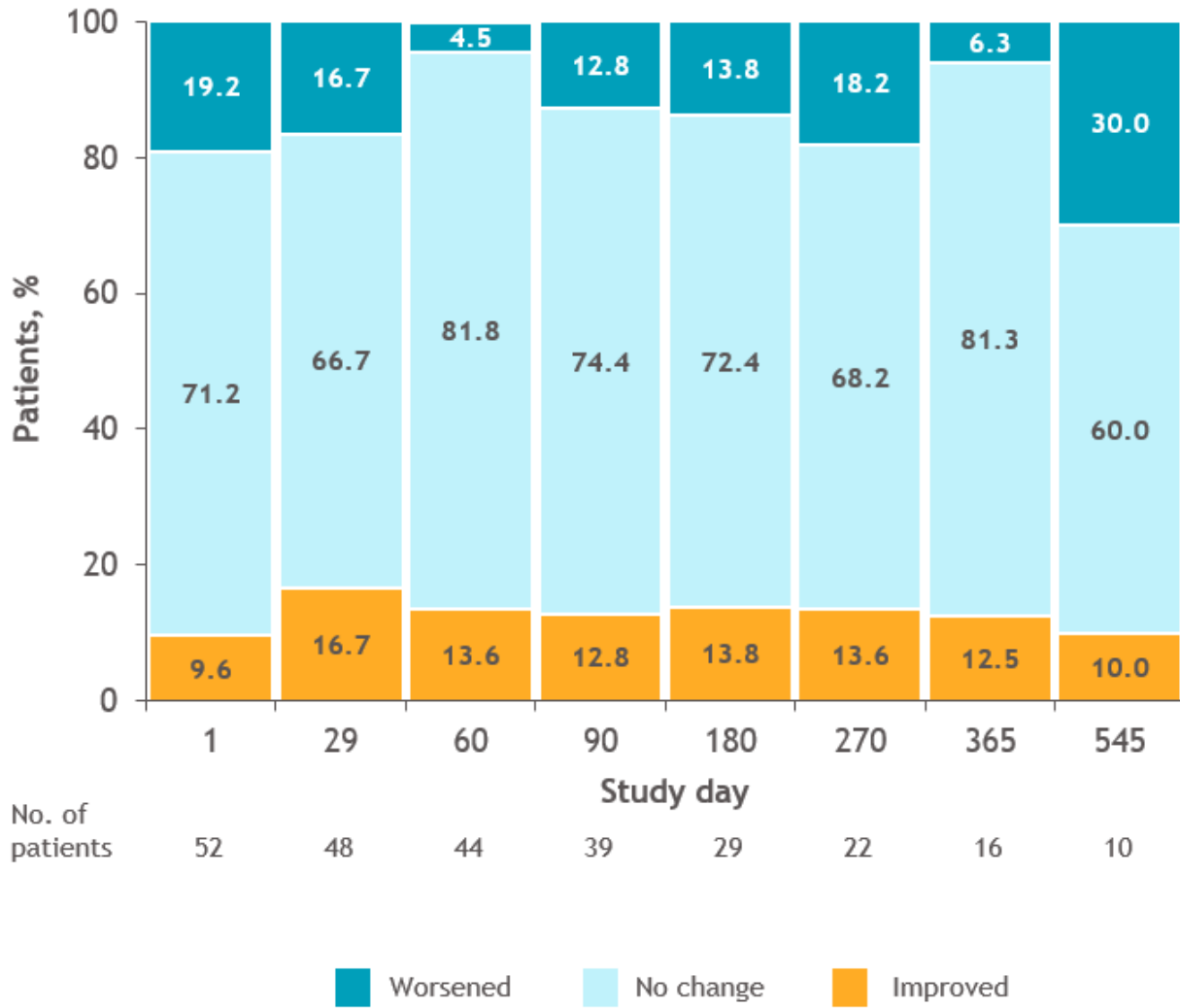


**(H) Diarrhea**

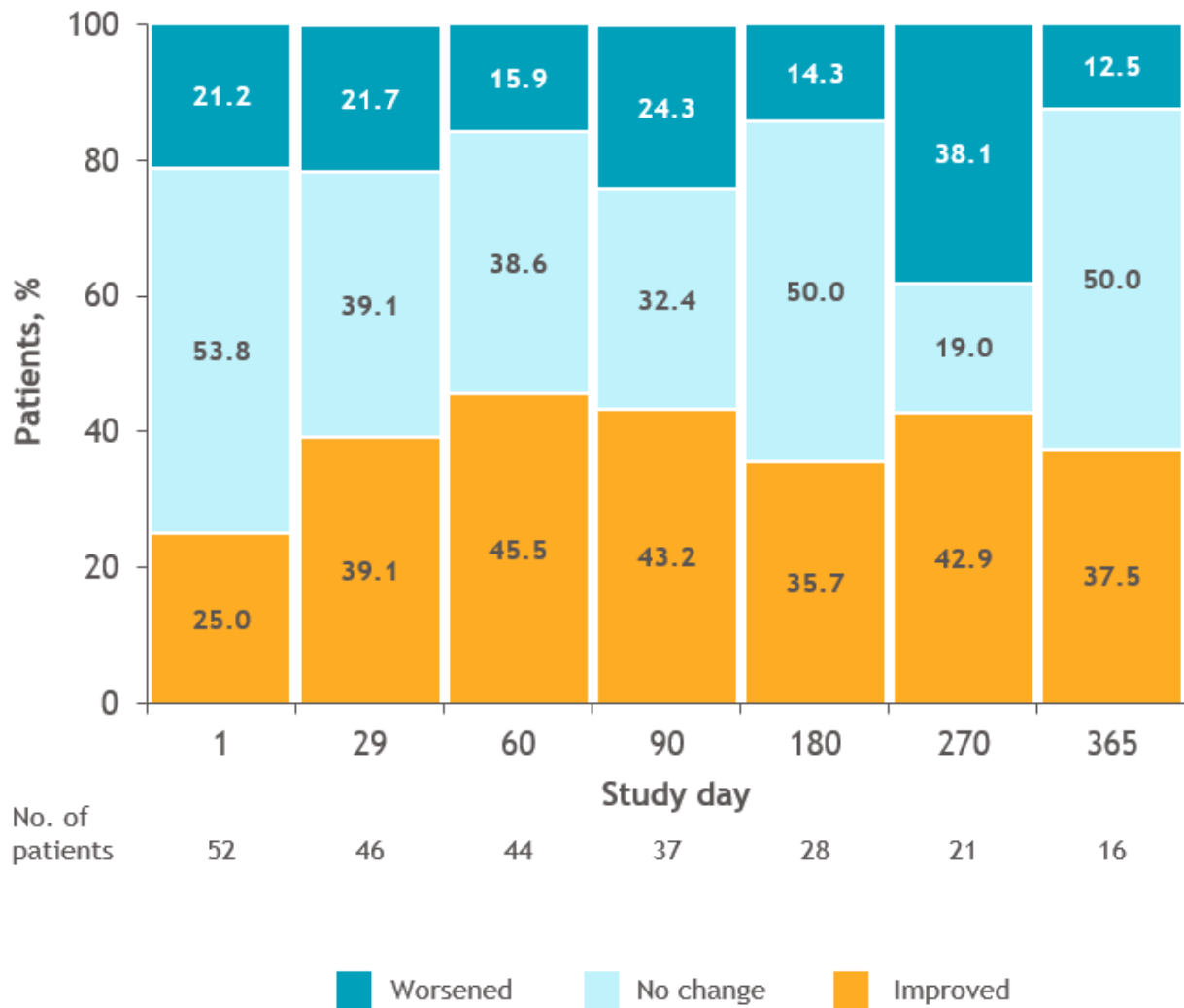




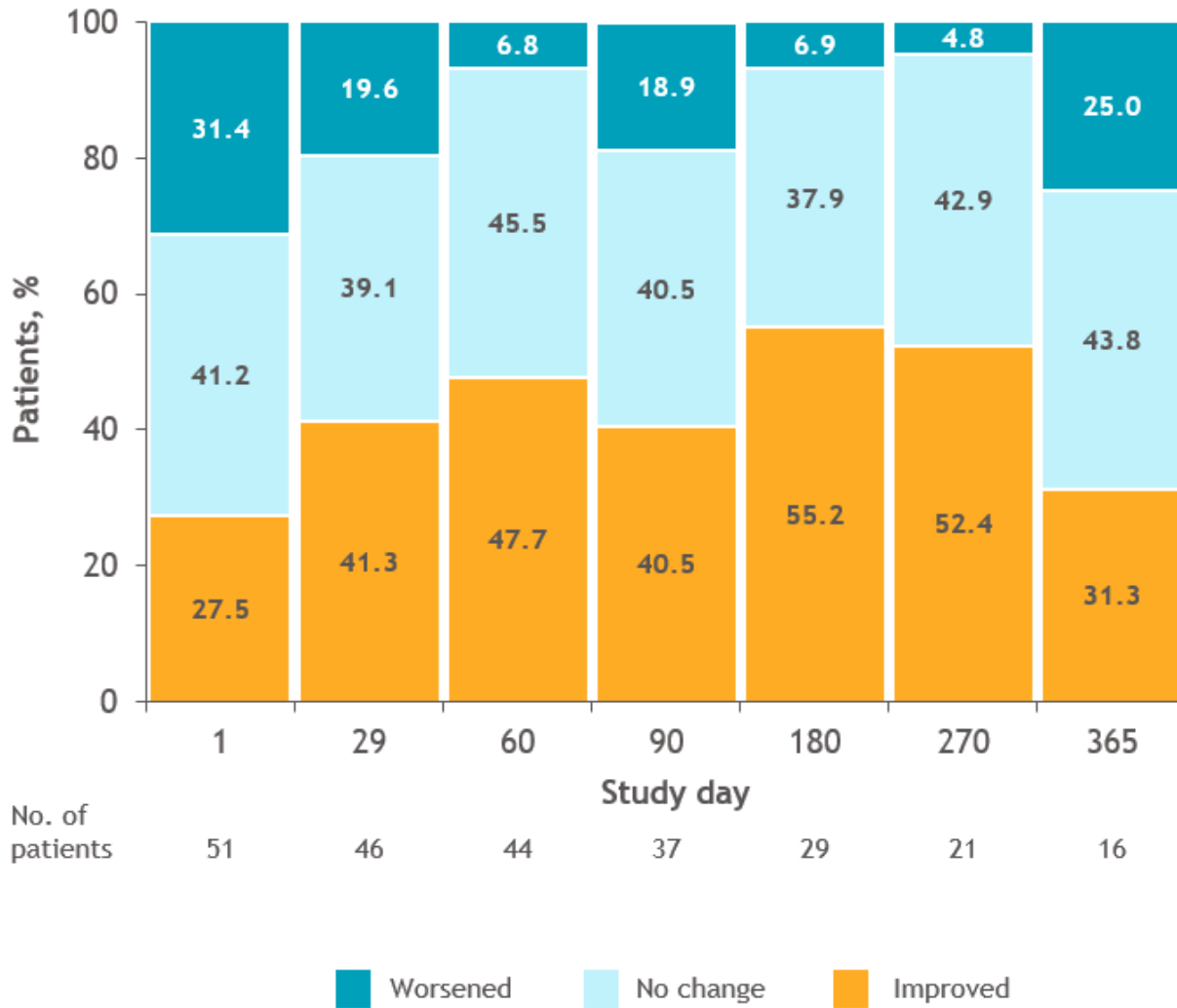
**(I) Financial difficulties**



(J) EQ-5D-5L HUI



**(K) EQ-VAS**

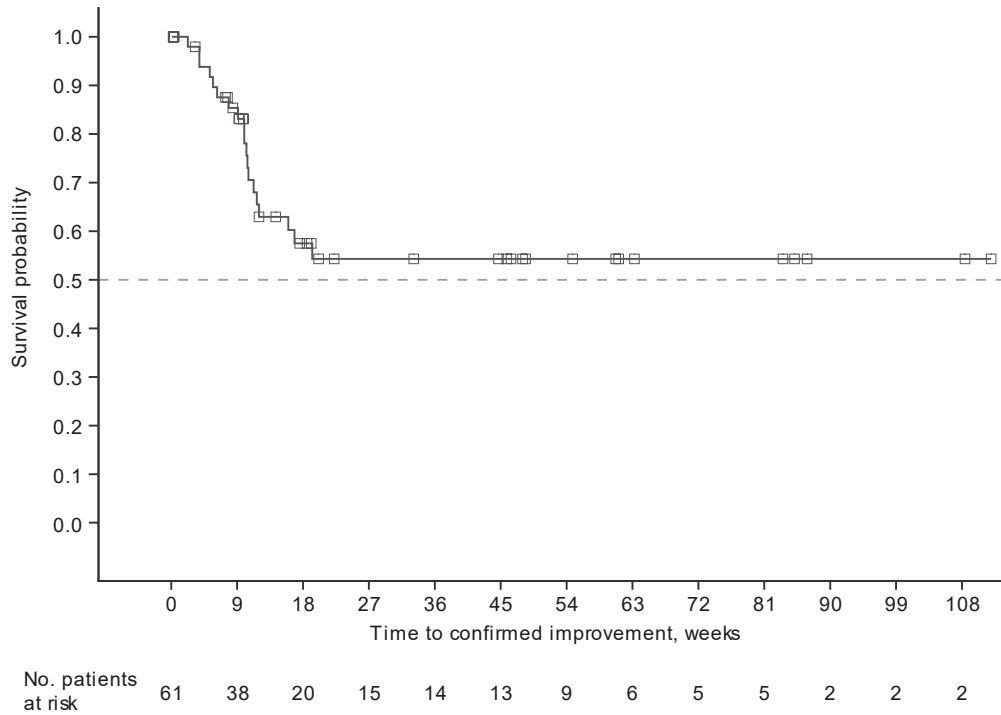


**Supplementary Figure S4. Kaplan-Meier plots of time to confirmed improvement for the primary domains of interest (safety set<sup>a</sup>; n=61).**

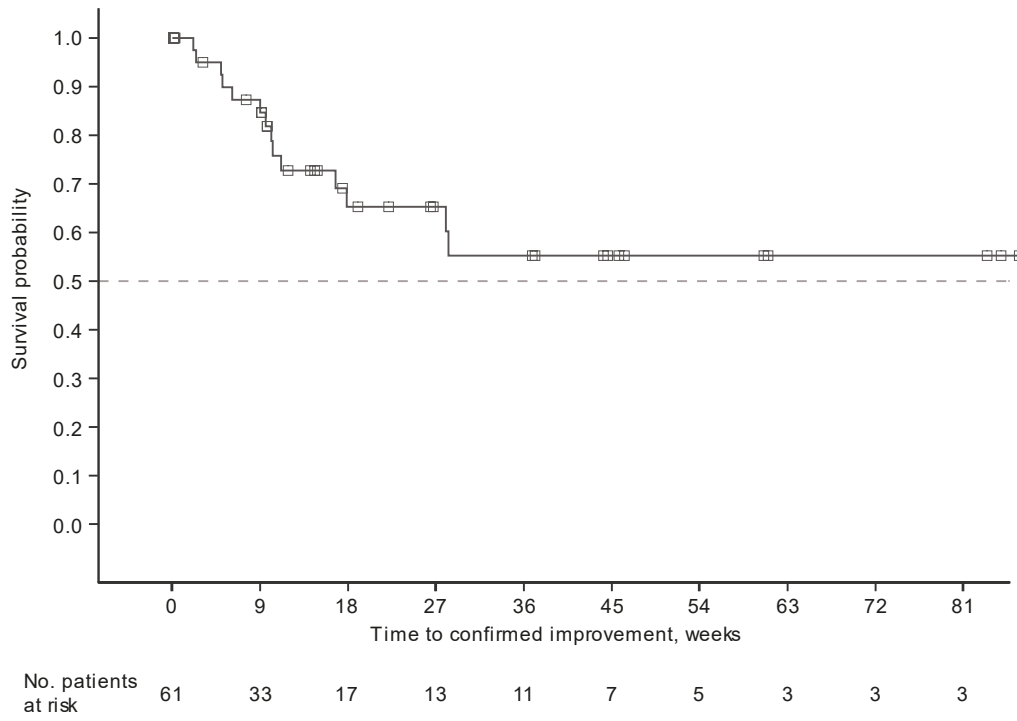
Time to confirmed improvement is shown for the EORTC QLQ-C30 domains of GH/QOL (A), physical functioning (B), role functioning (C), cognitive functioning (D), fatigue (E), and pain (F), and the FACT-LymS (G).

<sup>a</sup>All patients who received lisocabtagene maraleucel.<sup>9</sup> 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.

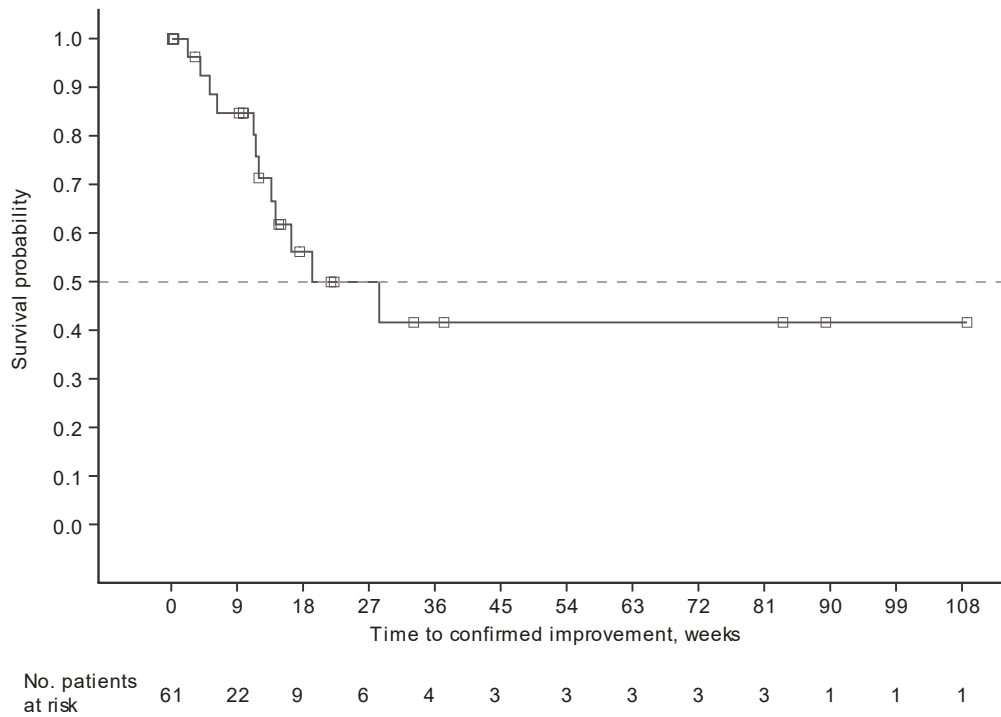
**(A) GH/QOL**



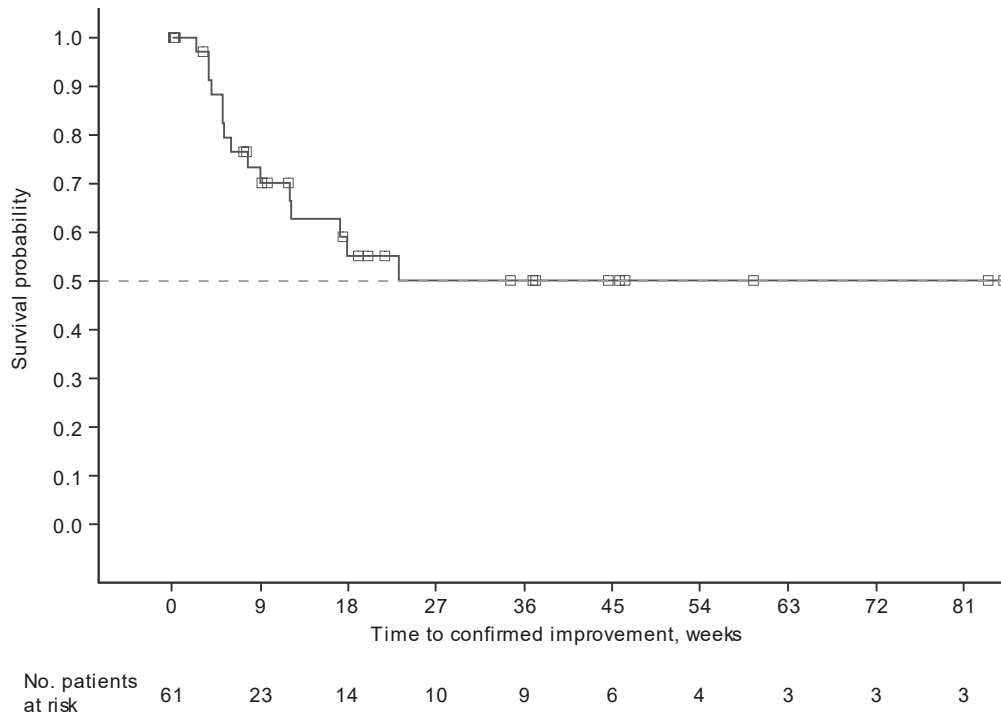
**(B) Physical functioning**



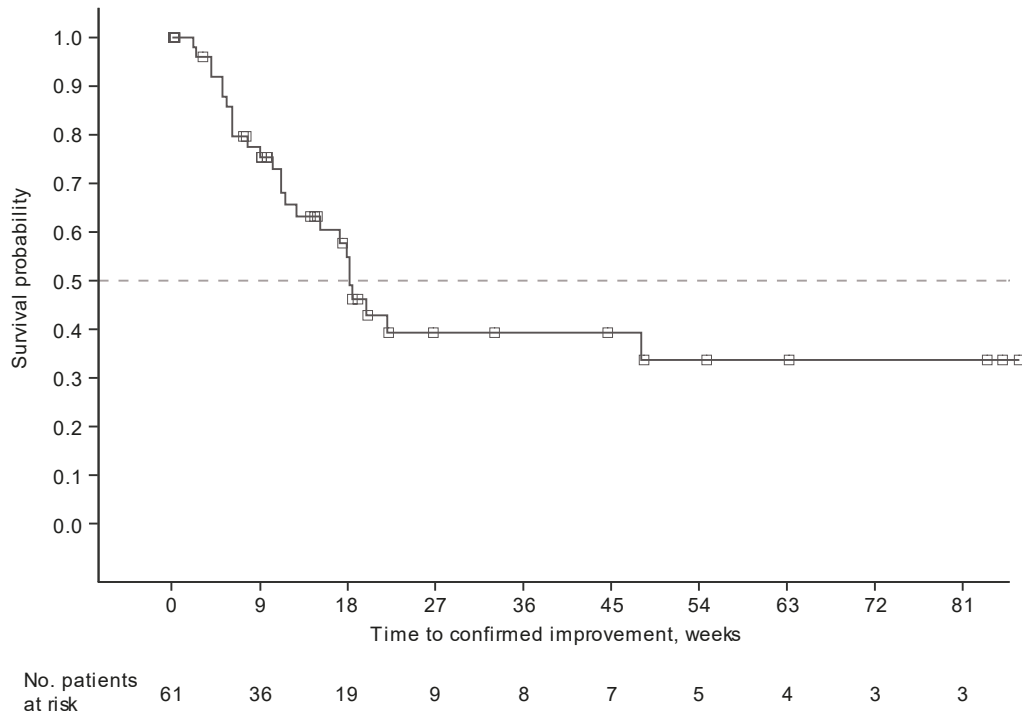
**(C) Role functioning**



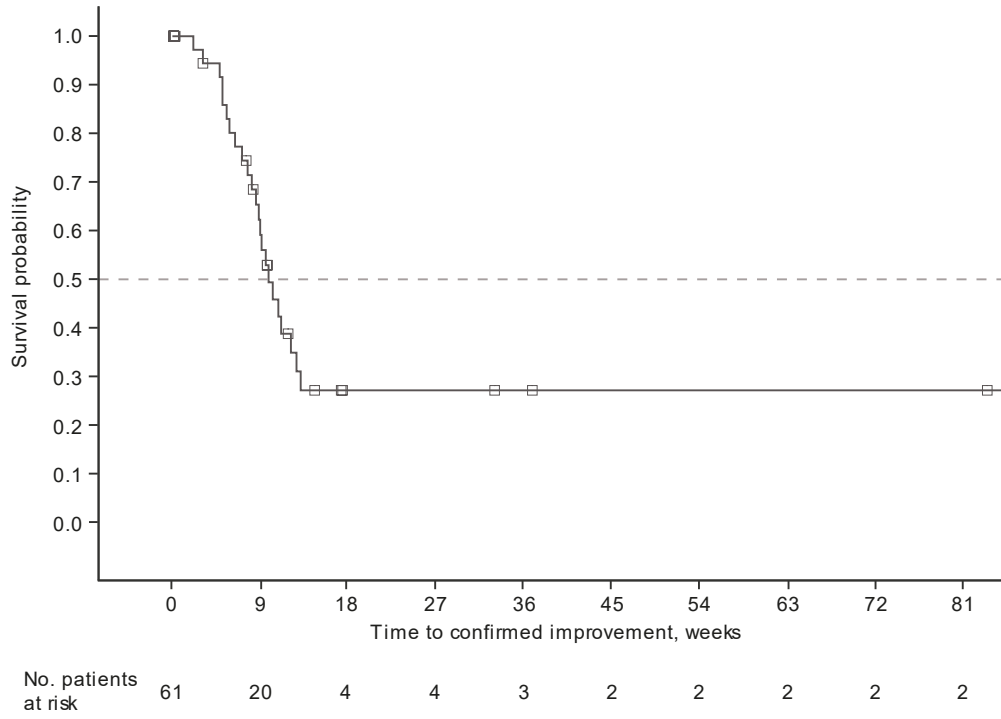
**(D) Cognitive functioning**



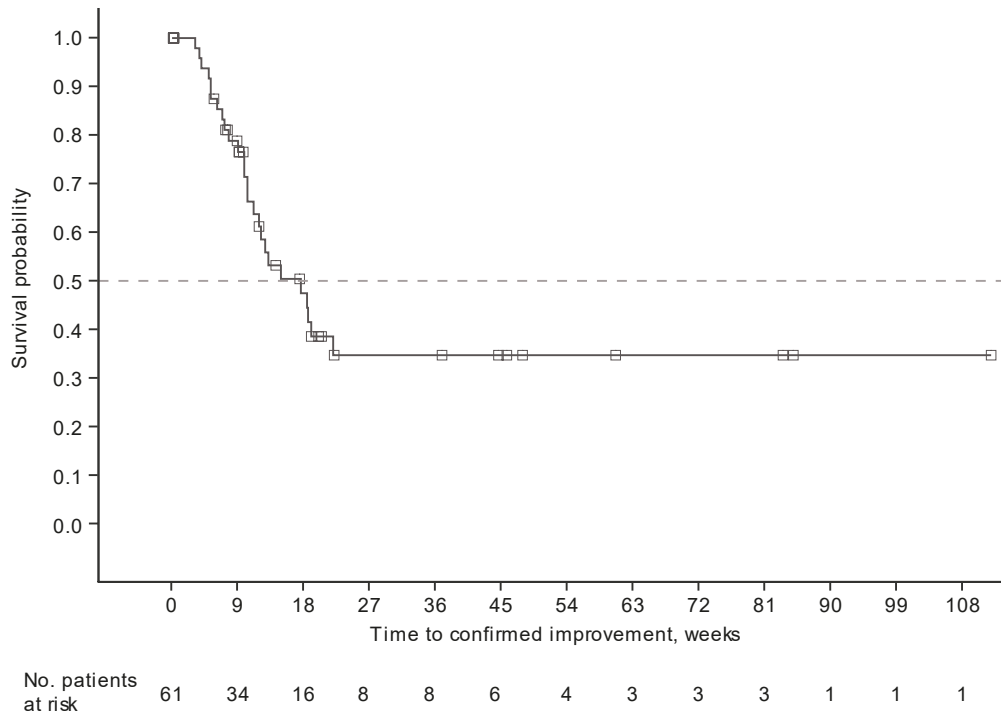
**(E) Fatigue**



**(F) Pain**



**(G) FACT-LymS**

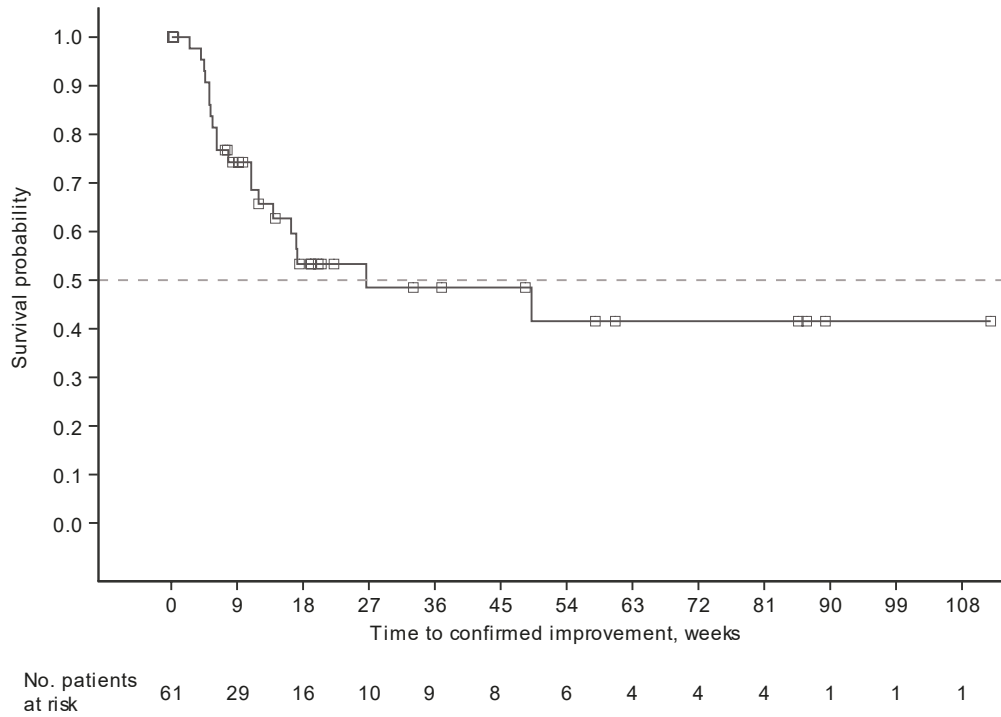


**Supplementary Figure S5. Kaplan-Meier plots of time to confirmed improvement for the secondary domains of interest (safety set<sup>a</sup>; n=61).**

Time to confirmed improvement is shown for the EORTC QLQ-C30 domains of emotional functioning (A), social functioning (B), nausea/vomiting (C), dyspnea (D), insomnia (E), appetite loss (F), constipation (G), diarrhea (H), and financial difficulties (I), EQ-5D-5L HUI (J), and EQ-VAS (K).

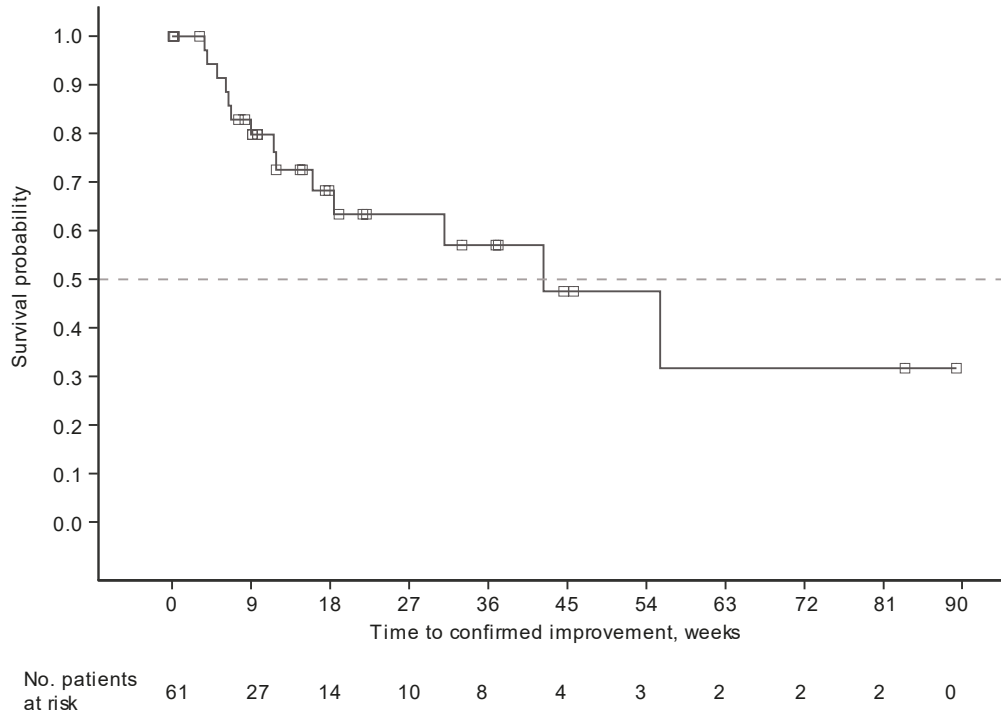
<sup>a</sup>All patients who received lisocabtagene maraleucel.<sup>9</sup> EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - 30 items; HUI: health utility index; VAS: visual analog scale.

**(A) Emotional functioning**

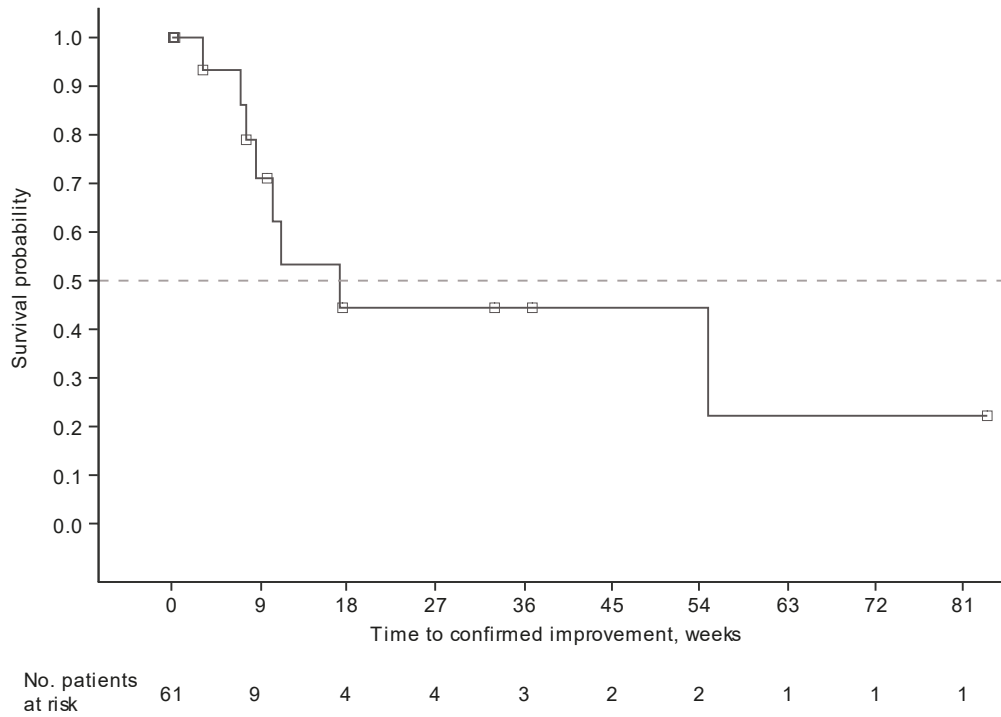




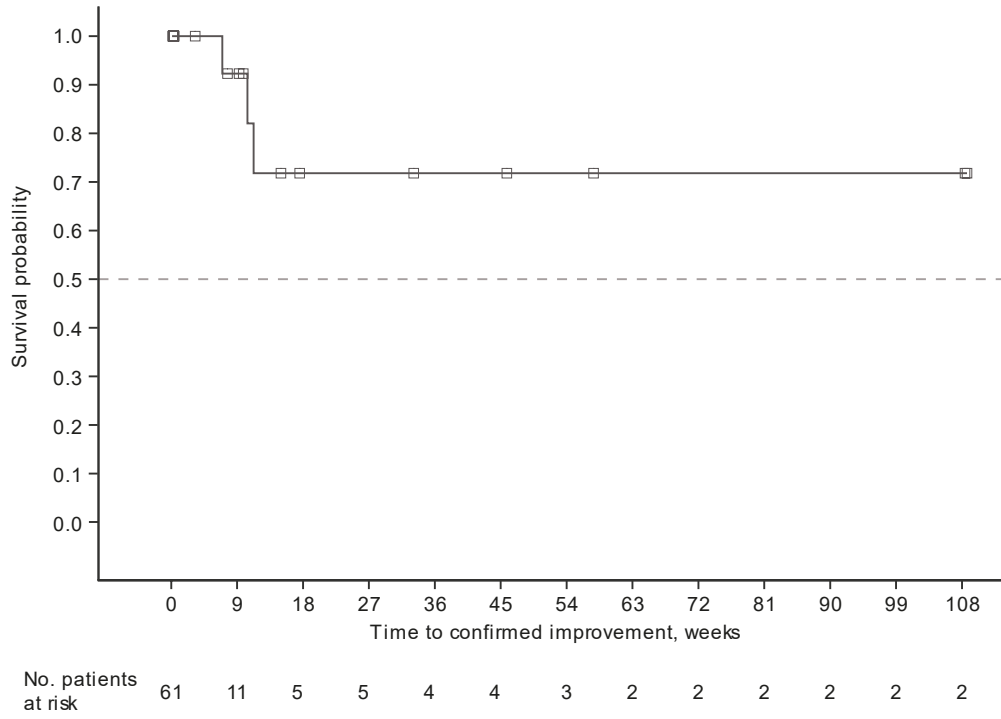
**(B) Social functioning**



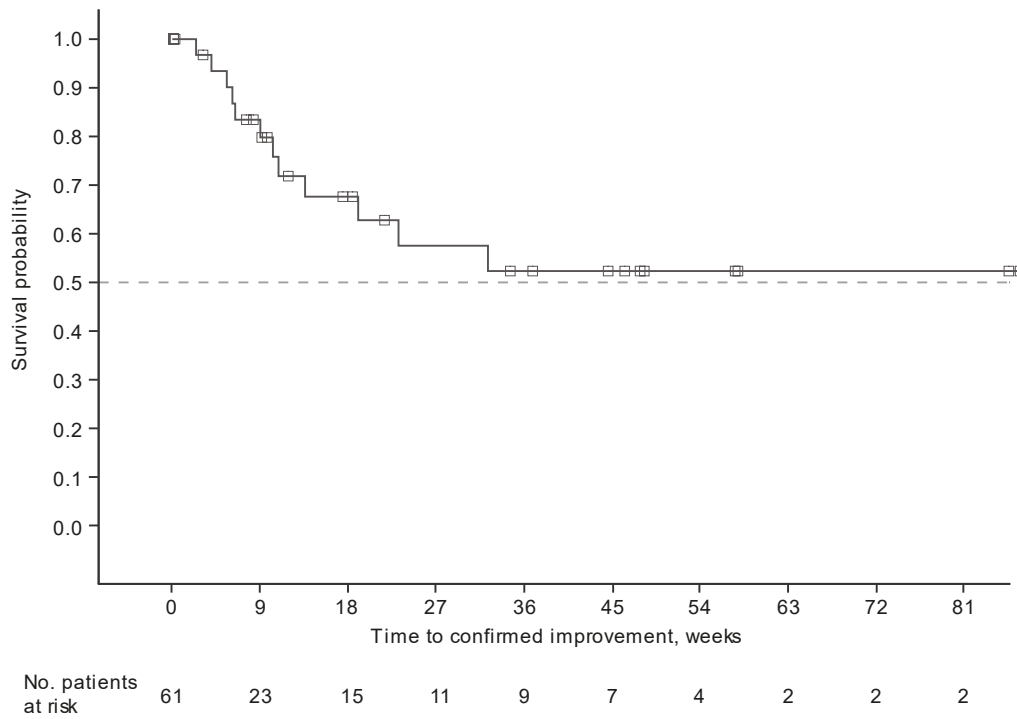
**(C) Nausea/vomiting**



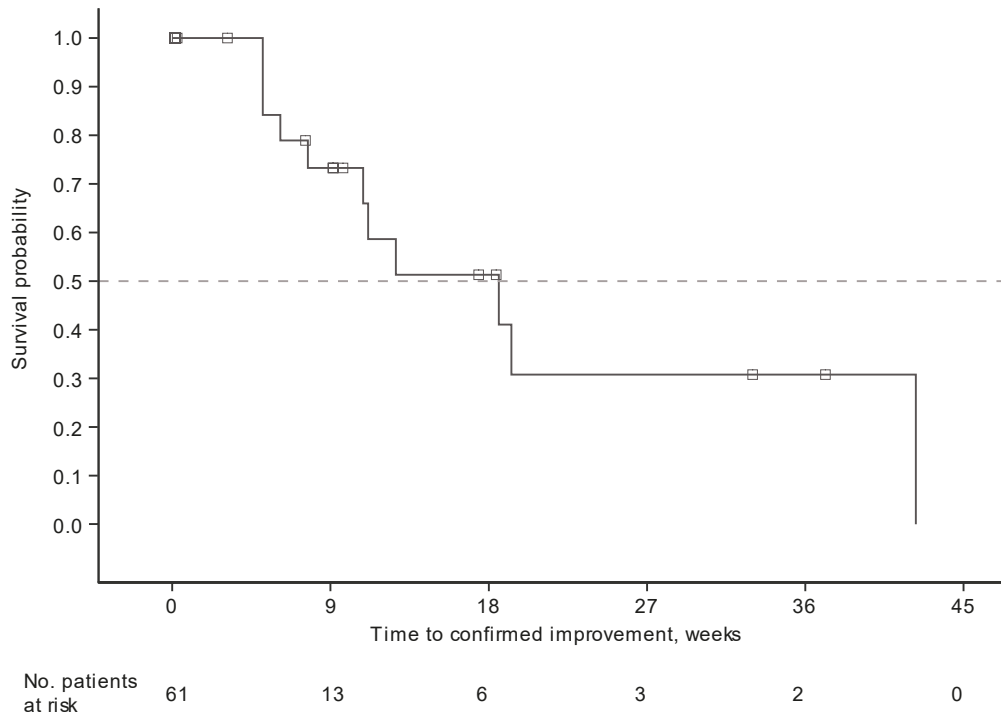
**(D) Dyspnea**



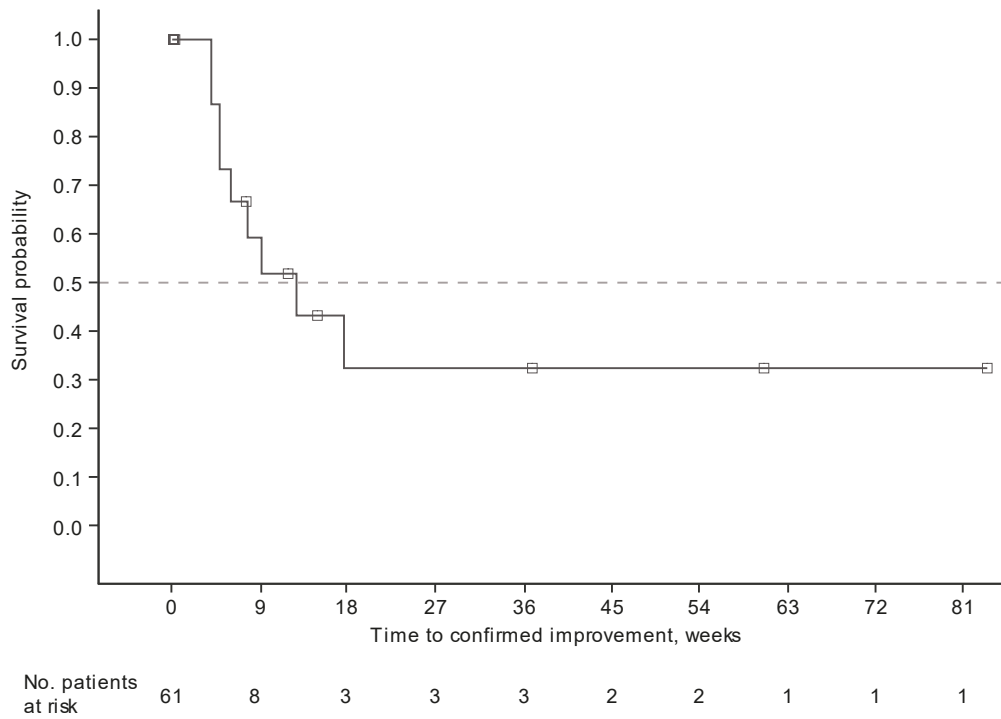
**(E) Insomnia**



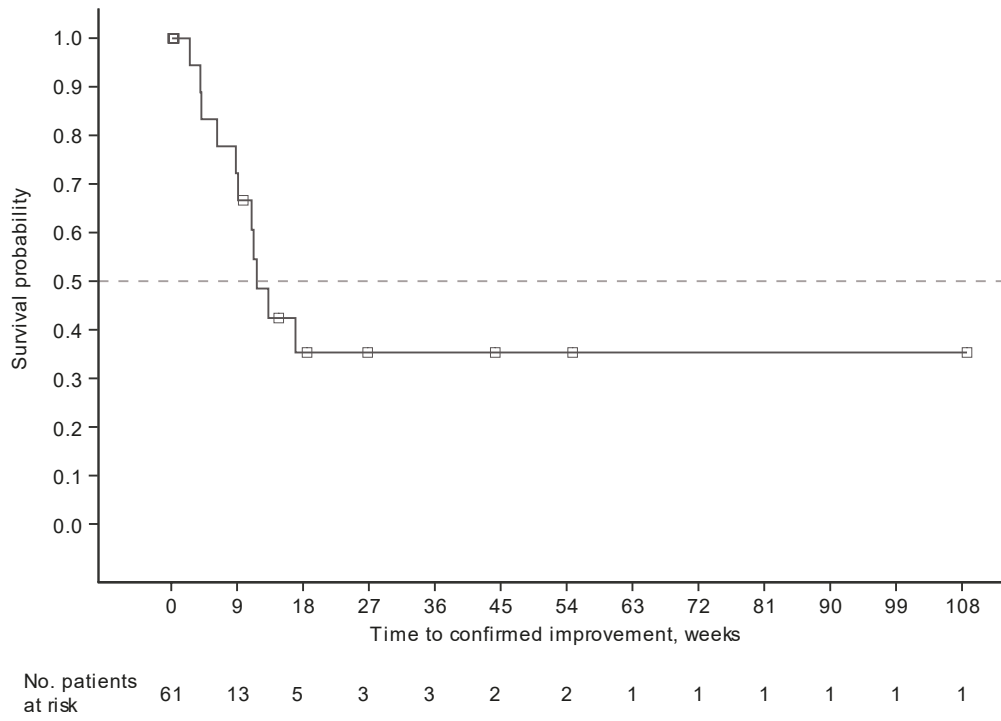
**(F) Appetite loss**



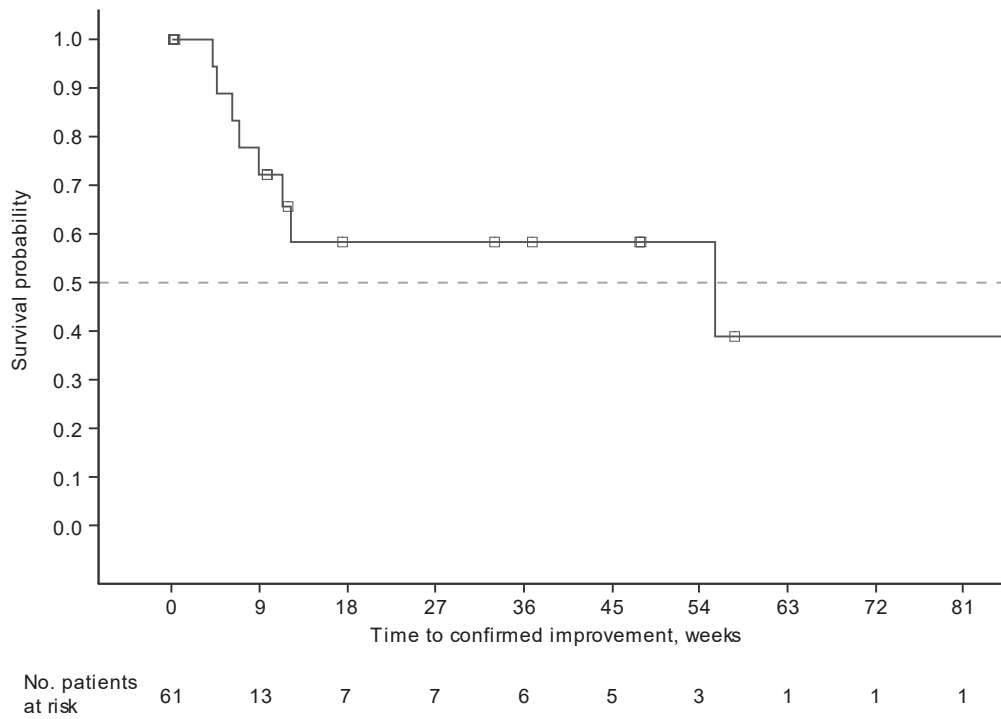
**(G) Constipation**



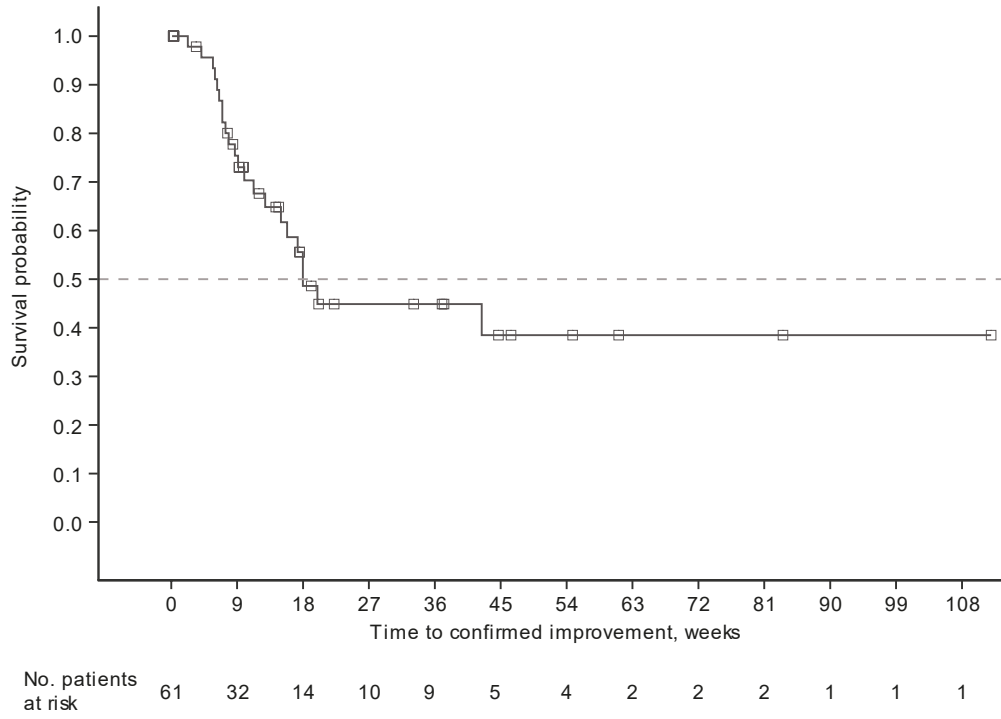
**(H) Diarrhea**



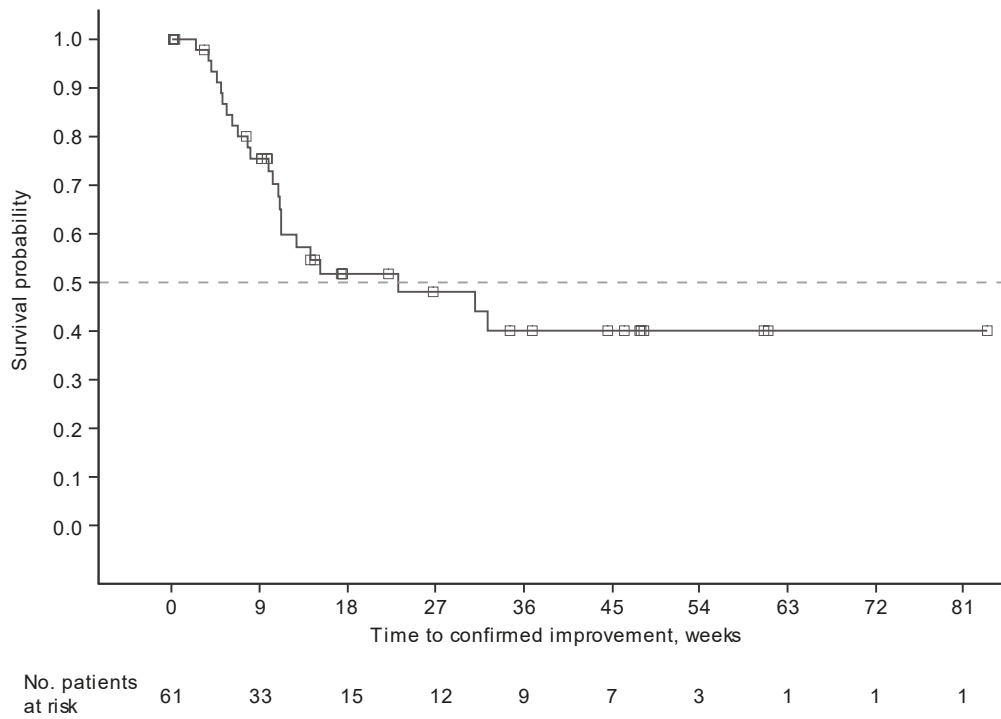
**(I) Financial difficulties**



**(J) EQ-5D-5L HUI**



**(K) EQ-VAS**

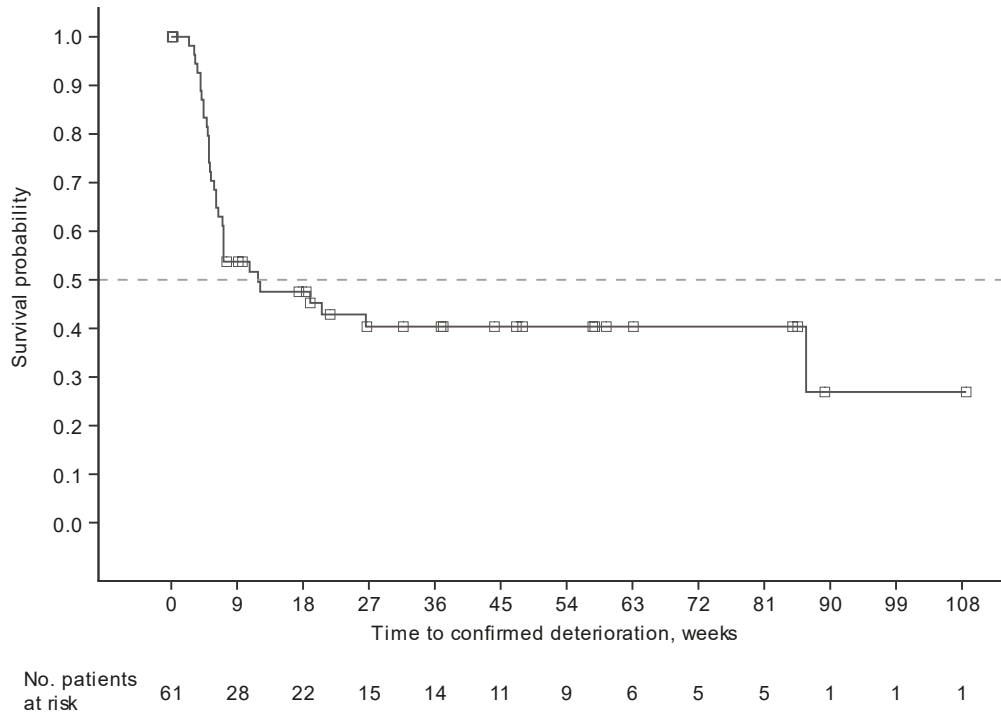


**Supplementary Figure S6. Kaplan-Meier plots of time to confirmed deterioration for the primary domains of interest (safety set<sup>a</sup>; n=61).**

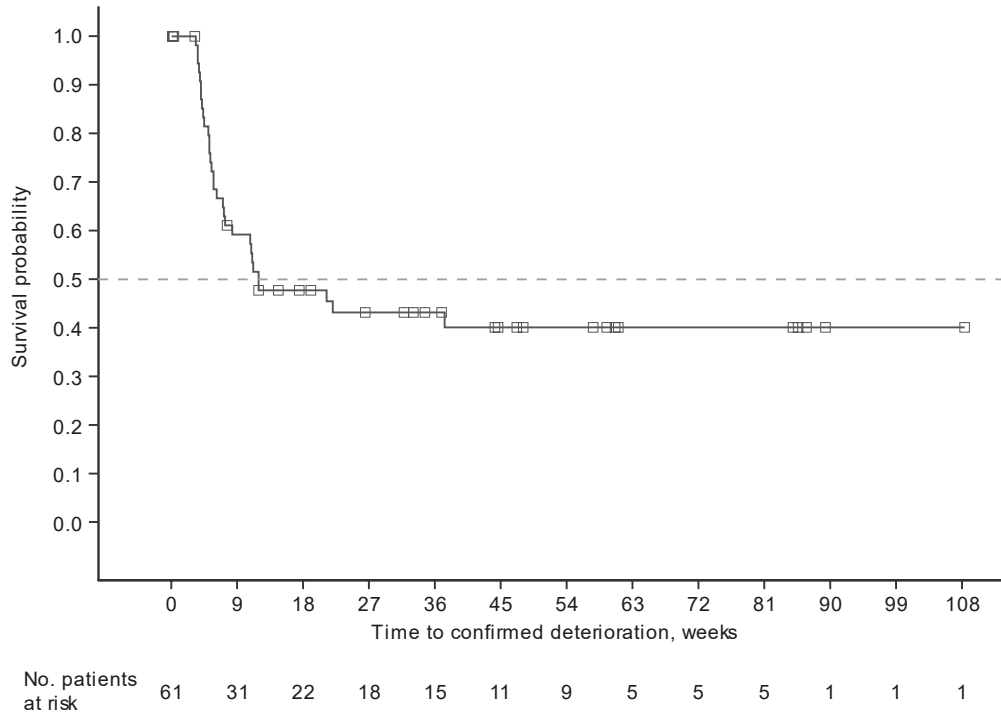
Time to confirmed deterioration is shown for the EORTC QLQ-C30 domains of GH/QOL (A), physical functioning (B), role functioning (C), cognitive functioning (D), fatigue (E), and pain (F), and the FACT-LymS (G).

<sup>a</sup>All patients who received lisocabtagene maraleucel.<sup>9</sup> 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.

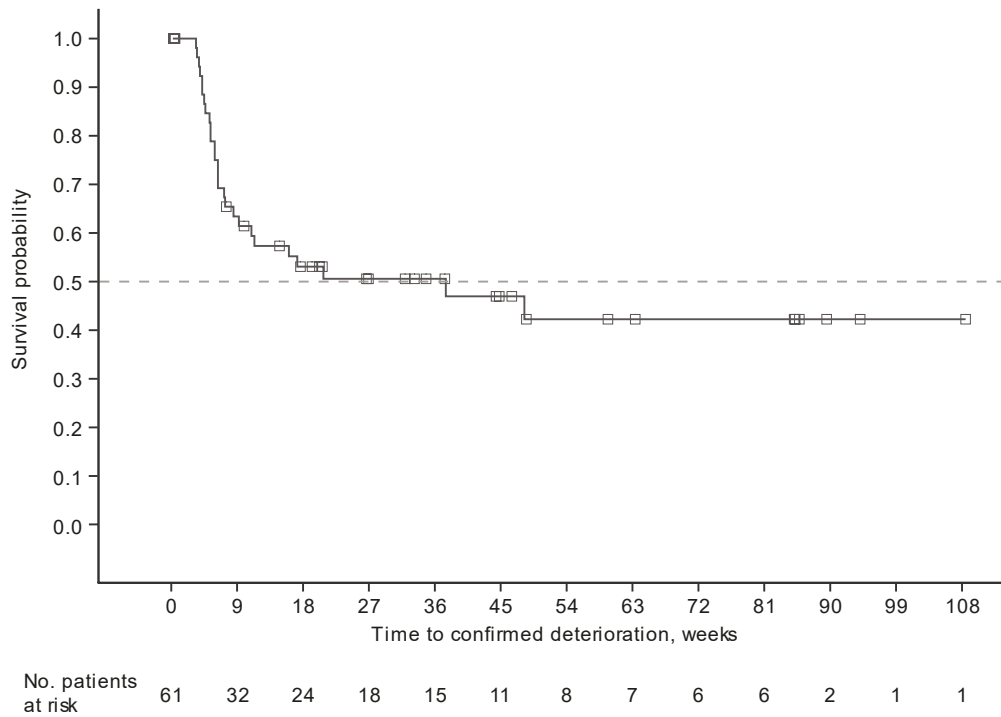
**(A) GH/QOL**



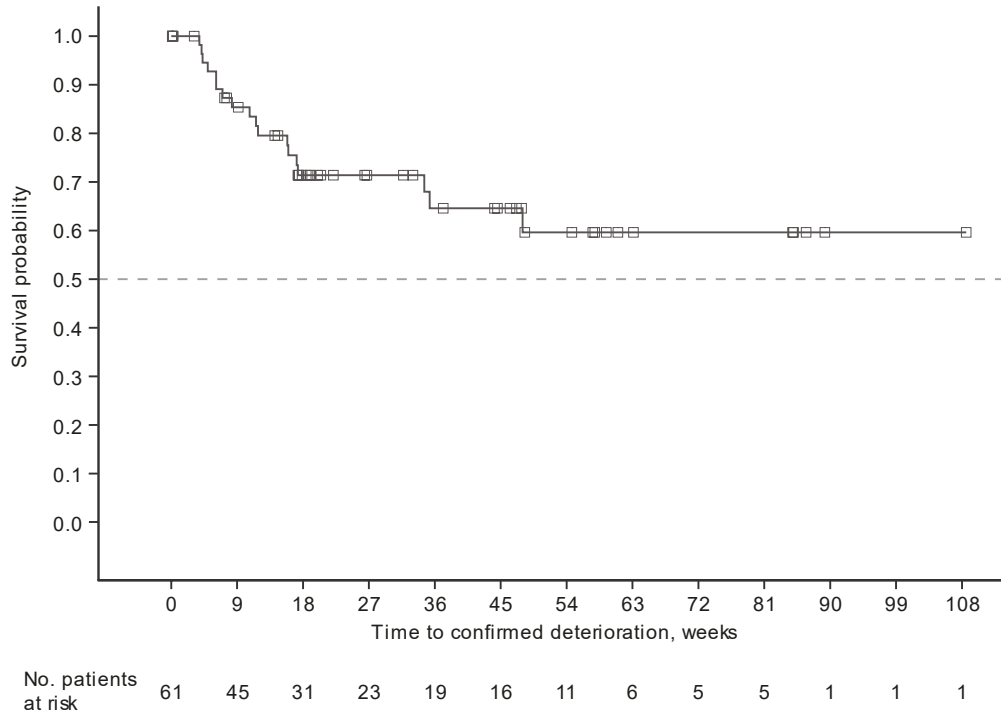
**(B) Physical functioning**



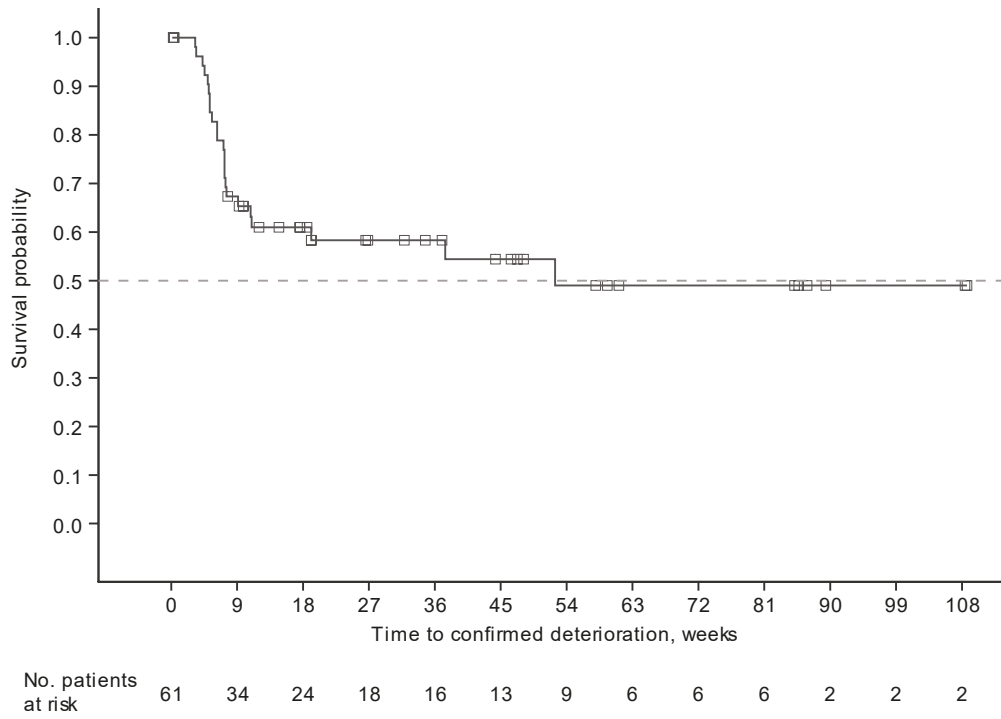
**(C) Role functioning**



**(D) Cognitive functioning**

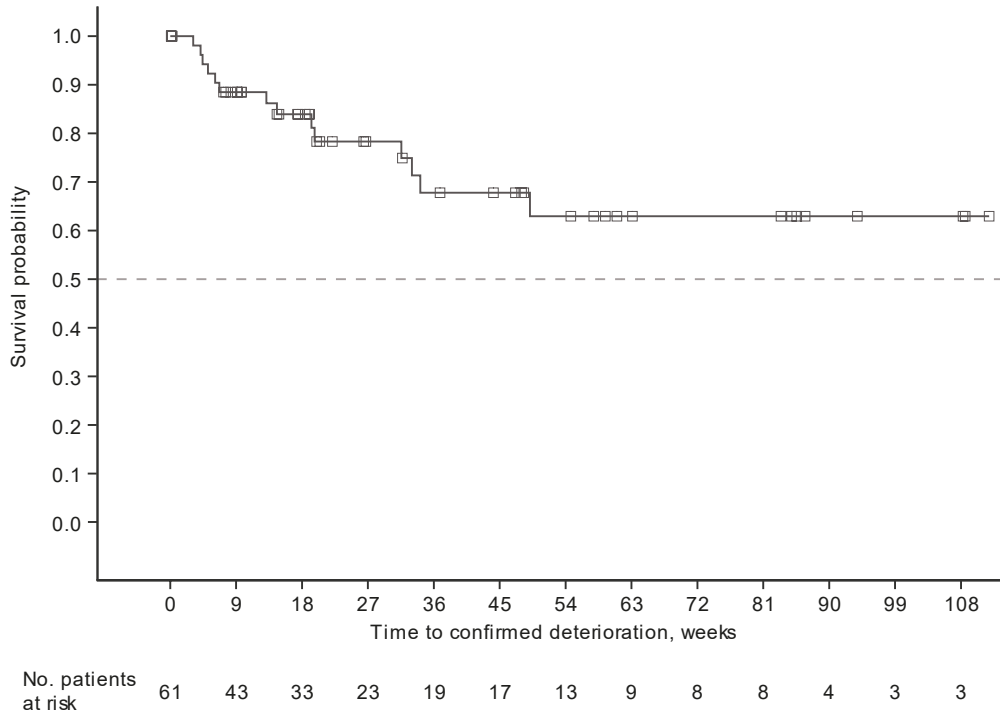


**(E) Fatigue**

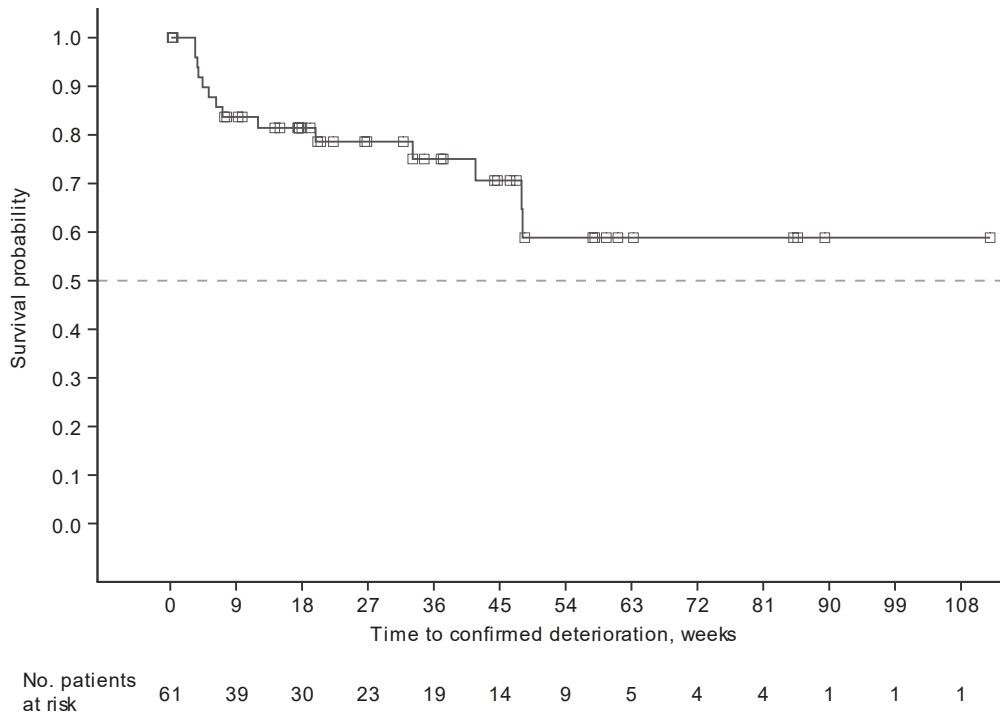




**(F) Pain**



**(G) FACT-LymS**

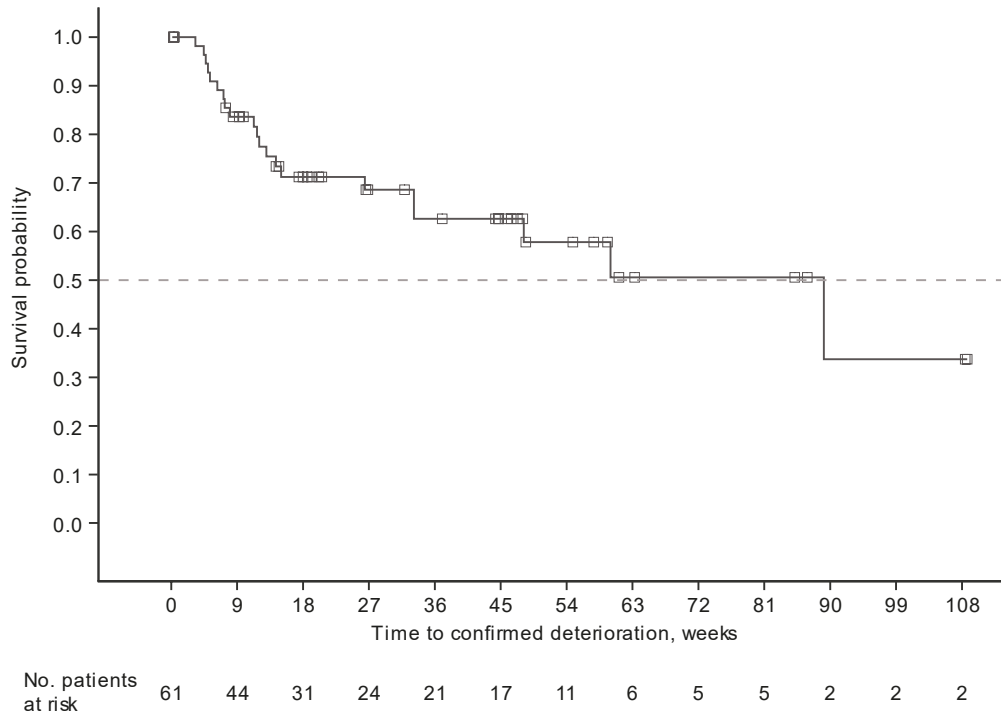


**Supplementary Figure S7. Kaplan-Meier plots of time to confirmed deterioration for the secondary domains of interest (safety set<sup>a</sup>; n=61).**

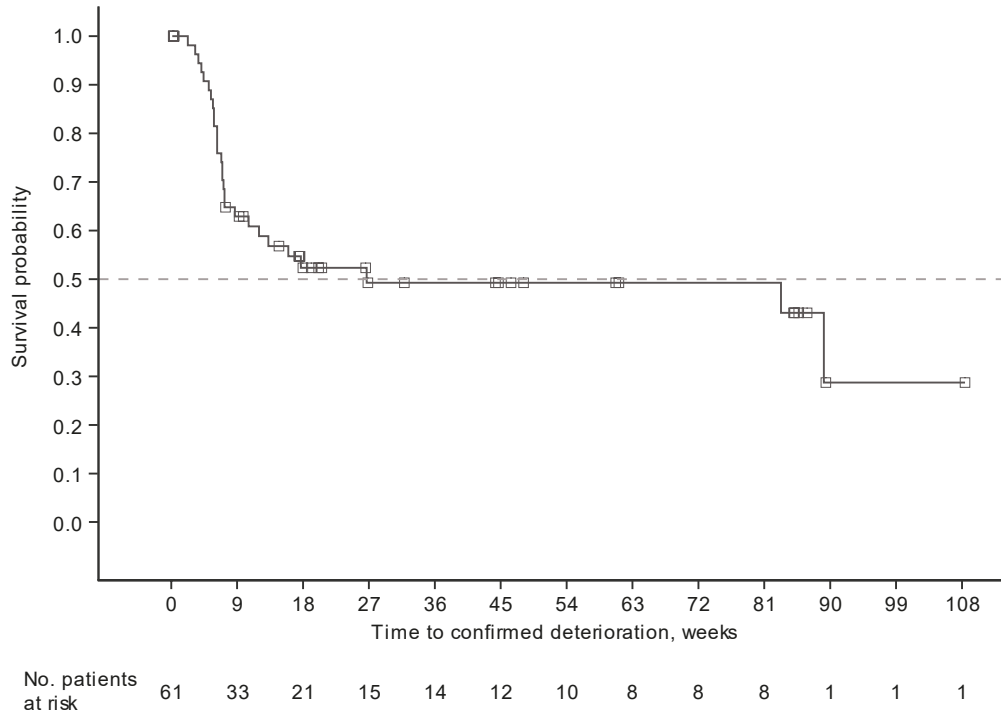
Time to confirmed deterioration is shown for the EORTC QLQ-C30 domains of emotional functioning (A), social functioning (B), nausea/vomiting (C), dyspnea (D), insomnia (E), appetite loss (F), constipation (G), diarrhea (H), and financial difficulties (I), EQ-5D-5L HUI (J), and EQ-VAS (K).

<sup>a</sup>All patients who received lisocabtagene maraleucel.<sup>9</sup> EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - 30 items; HUI: health utility index; VAS: visual analogue scale.

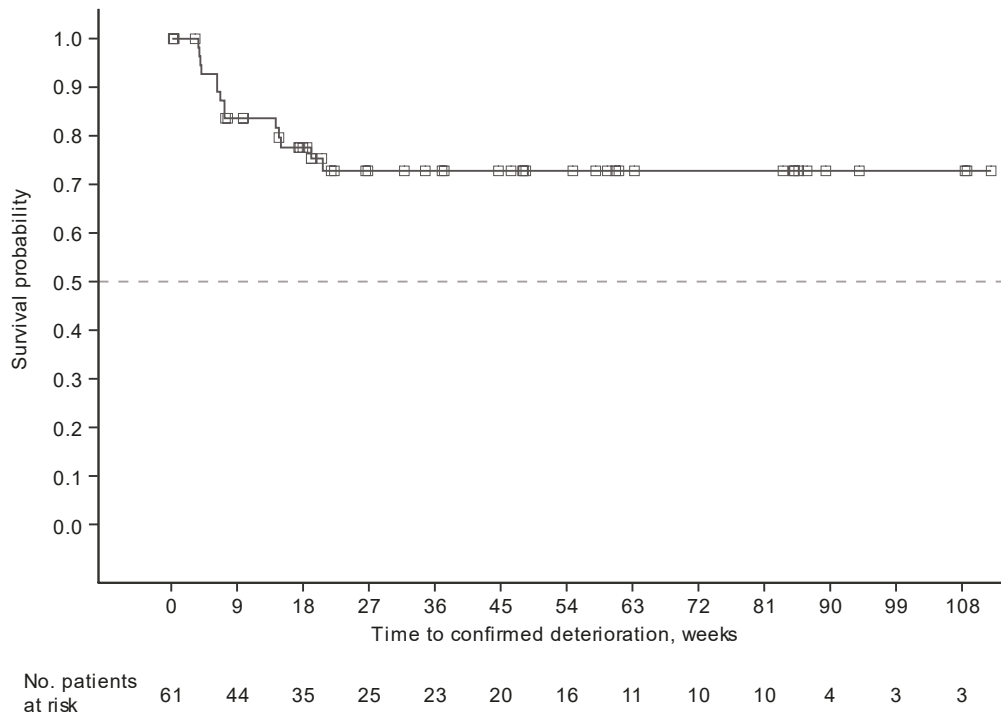
**(A) Emotional functioning**



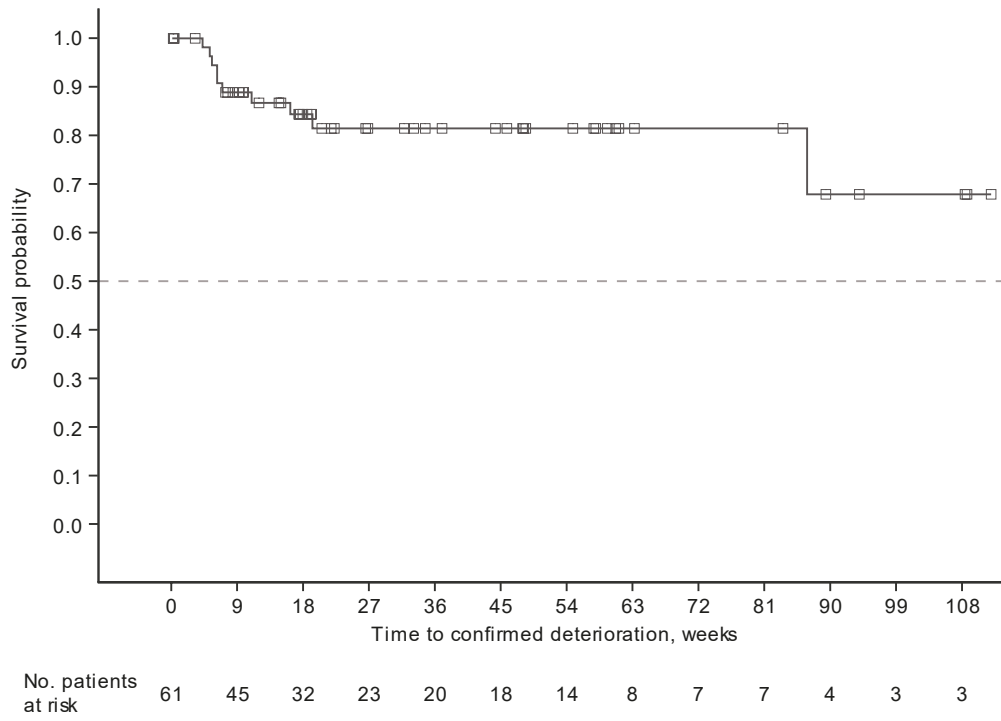
**(B) Social functioning**



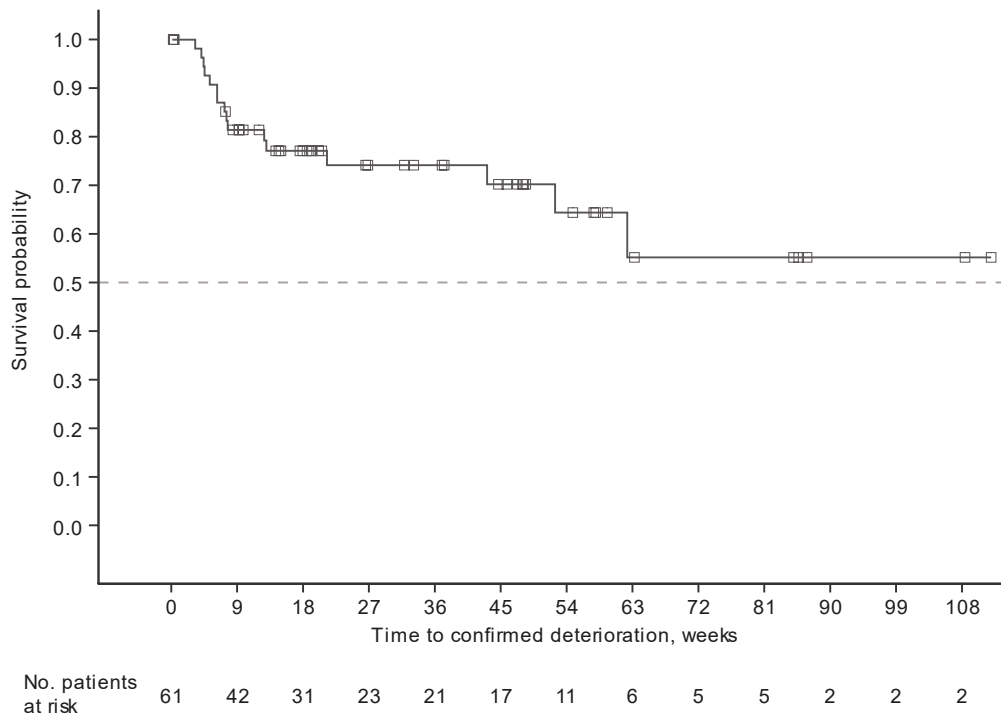
**(C) Nausea/vomiting**



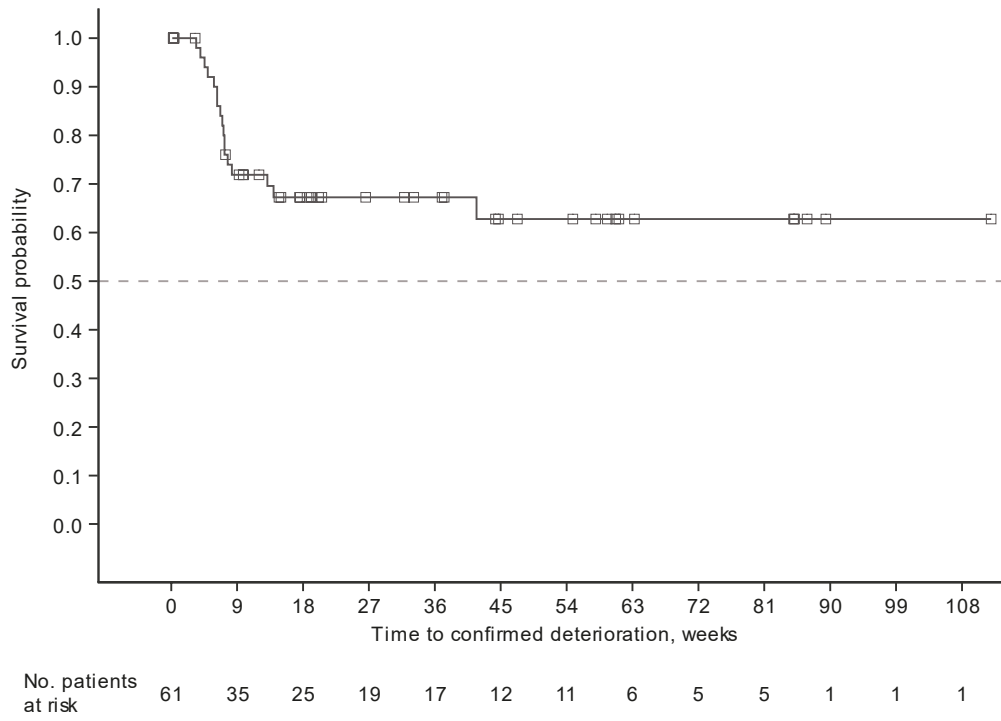
**(D) Dyspnea**



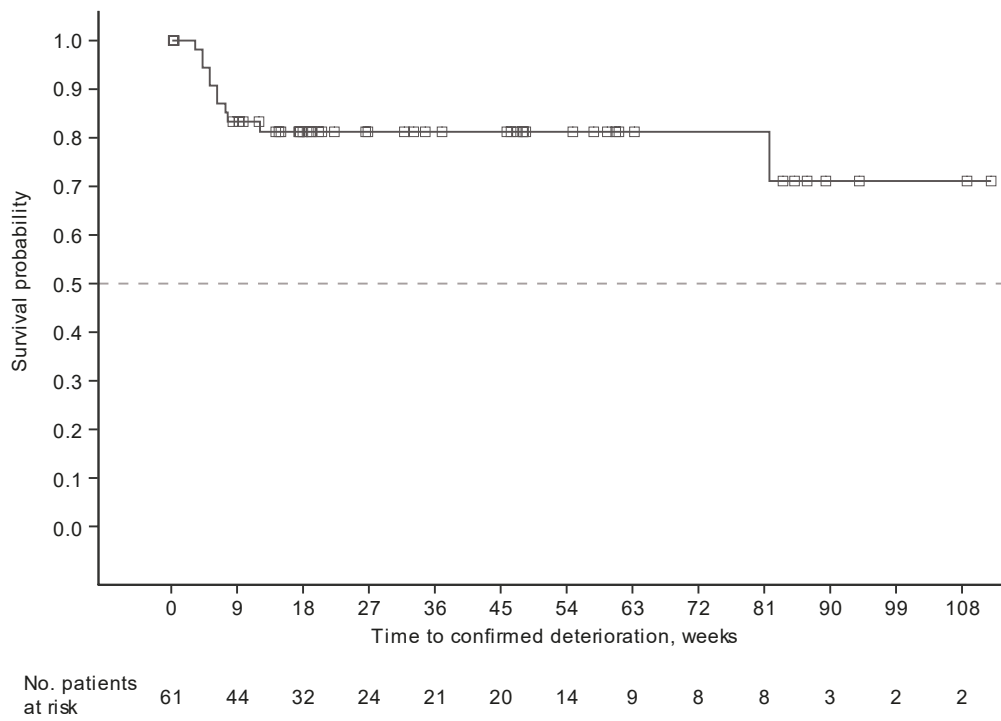
**(E) Insomnia**



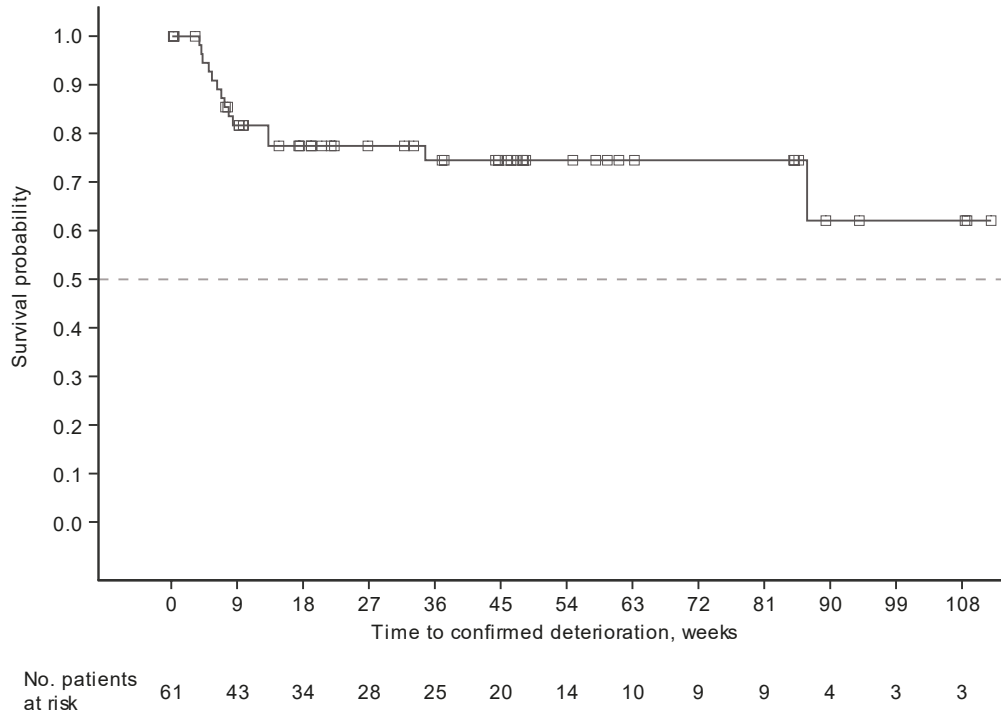
**(F) Appetite loss**



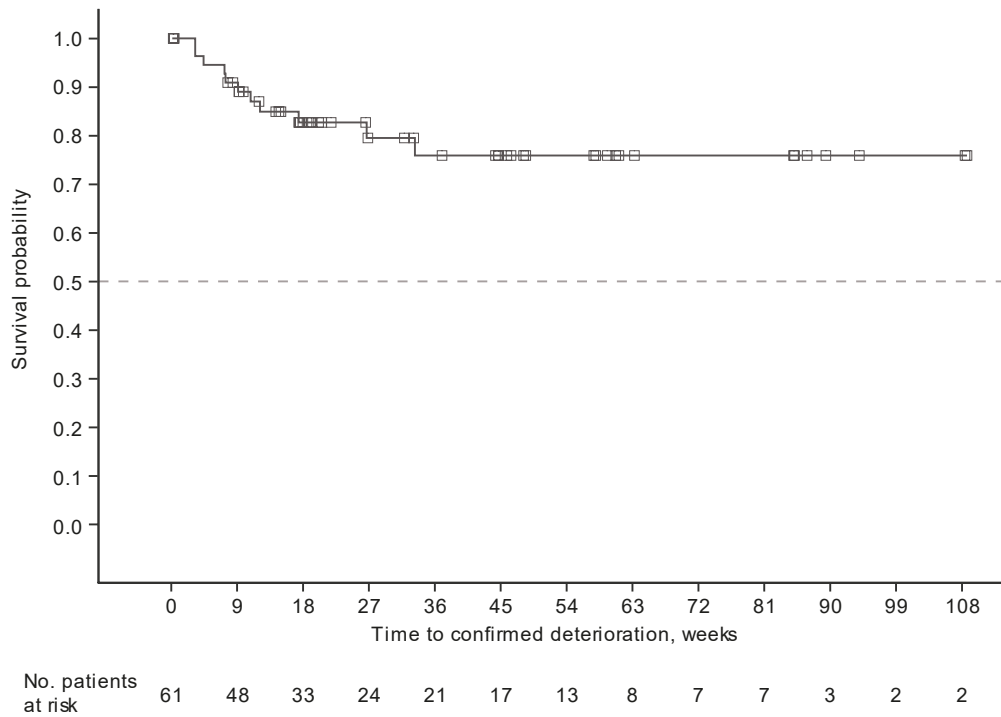
**(G) Constipation**



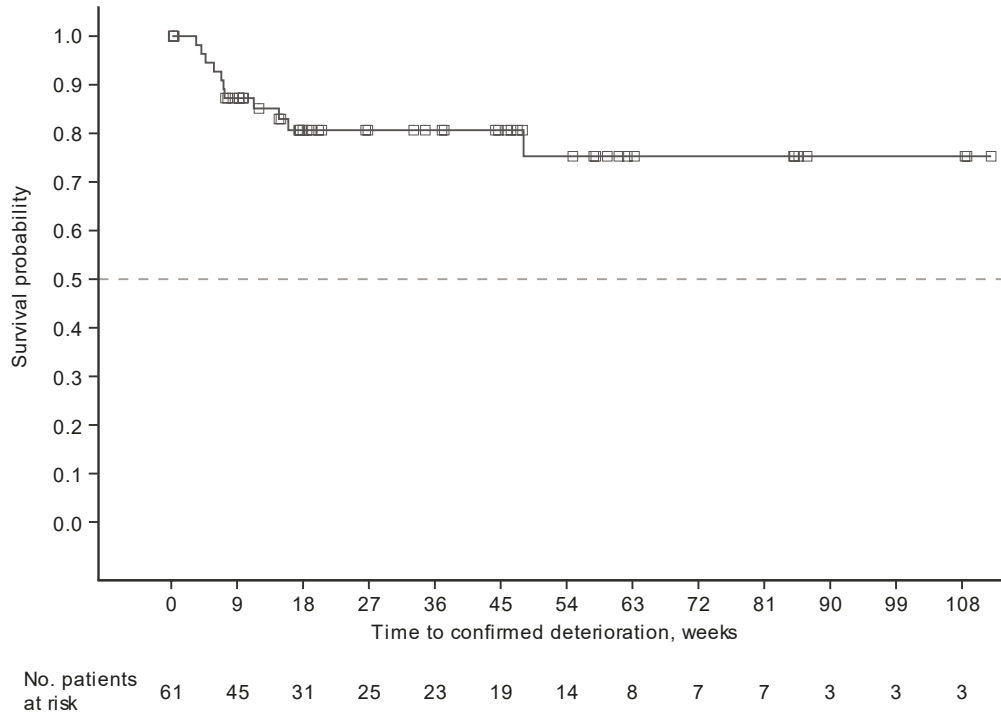
**(H) Diarrhea**



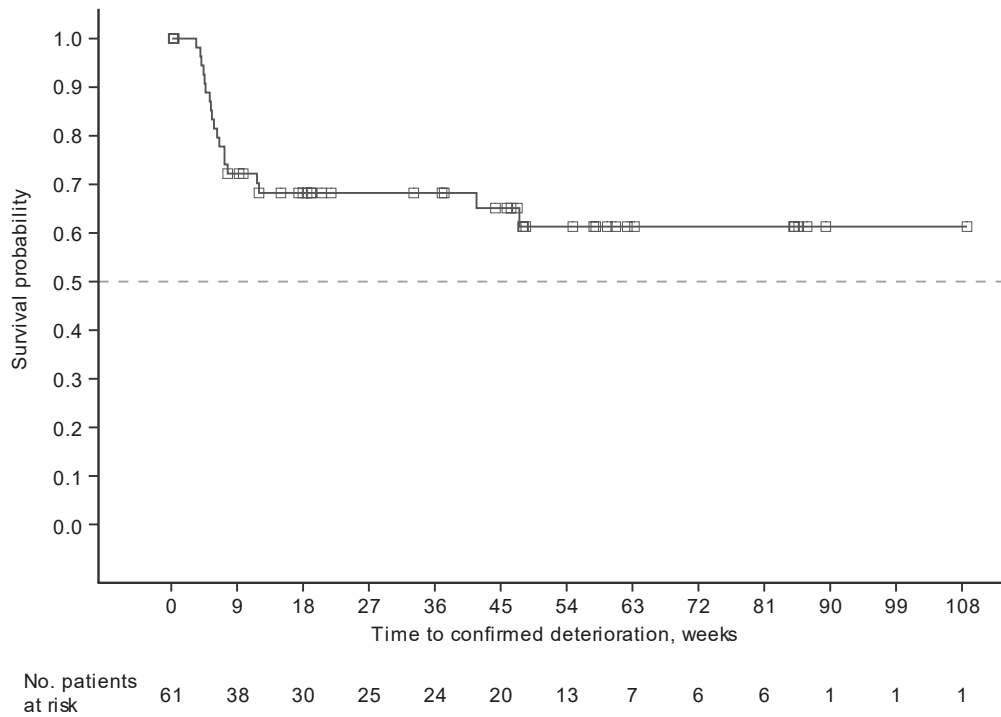
**(I) Financial difficulties**



**(J) EQ-5D-5L HUI**



**(K) EQ-VAS**



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