Received: 12 January 2024 | Accepted: 28 March 2024

DOI: 10.1002/hem3.72

HemaSphere EHA EUROPEAN HEMATOLOGY ASSOCIATION

ARTICLE

Remission after CAR T-cell therapy: Do lymphoma patients recover a normal life?

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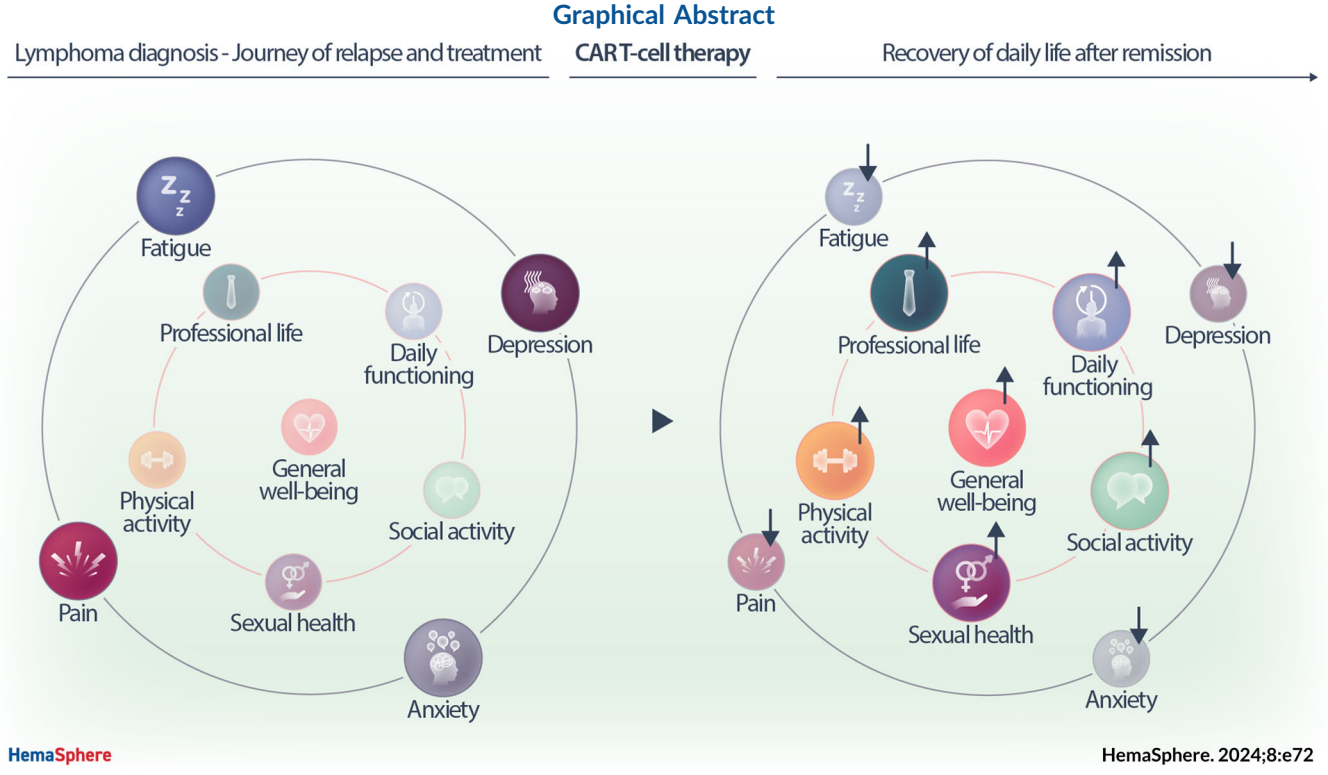
Graphical Abstract



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Abstract

Chimeric antigen receptor T cells (CAR T cells) can induce prolonged remission in a substantial subset of patients with relapse/refractory lymphoma. However, little is known about patients' life after CAR T-cell therapy. We prospectively assessed the multidimensional recovery of lymphoma patients in remission, before leukapheresis, before CAR T-cell infusion, and 3, 6, and 12 months thereafter. Validated tools were used to measure lymphoma-related and global health-related quality of life (HRQoL; Functional Assessment of Cancer Therapy-Lymphoma [FACT-Lym] and EQ-5D-5L), cognitive complaint (FACT-Cognition), fatigue (FACIT-Fatigue subscale), psychological status (Hospital Anxiety and Depression Scale, Post-Traumatic Check List Scale), and sexuality (Relationship and Sexuality Scale). Beyond 12 months of remission, we also surveyed physical, professional, sexual, and general life status. At 3, 6, and 12 months, 53, 35, and 23 patients were evaluable, respectively. Improvement in lymphoma-related HRQoL was clinically relevant at 3, 6, and 12 months with a mean change from baseline of 10.9 (95% confidence interval [CI]: 5.8; 16.1), 12.2 (95% CI: 4.2; 20.1), and 11.72 (95% CI: 2.06; 21.38), respectively. Improvement in global HRQoL, fatigue, and anxiety was clinically relevant, but 20%–40% of patients experienced persistent fatigue, psychological distress, and cognitive complaints over time. Beyond 12 months after CAR T cells, 81.8% of 22 evaluable patients were satisfied with their daily life. Physical activity, professional, sexual, and global well-being had returned to prediagnosis levels in nearly half of the patients. We found an improvement in HRQoL after CAR T-cell therapy including anxiety, depression, sexual satisfaction, and general well-being. However, not all patients recover a "normal life." Further research is needed to determine which patients are at risk of quality-of-life impairment to improve recovery after CAR T-cell infusion.

INTRODUCTION

Chimeric antigen receptor T-cell (CAR T-cell) therapy has revolutionized the treatment of relapsed and refractory (R/R) lymphoma, such as large B-cell lymphoma (LBCL), mantle cell lymphoma (MCL), and follicular lymphoma (FL). In a significant proportion of patients, durable remissions can be achieved, which may lead to a cure.[1–3] The prolonged remissions induced by CAR T-cell therapy raise the question of patients' potential to regain a "normal life" after such treatment.

In clinical trials of CAR T-cell therapy, health-related quality of life (HRQoL) is often assessed as a secondary endpoint. In the JULIET study, LBCL patients who received tisagenlecleucel (tisa-cel) after at least two lines of systemic therapy showed a clinically significant improvement in most aspects of HRQoL.[4] In the TRANSCEND trial,

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lisocabtagene maraleucel (liso-cel) infusion improved the overall HRQoL of R/R LBCL patients and the change from baseline was clinically significant by the second month.[5] However, patients enrolled in clinical trials may not be representative of patients treated in the real-world setting. Only two real-world studies have evaluated global HRQoL months after CAR T-cell infusion.[6,7] They reported an initial decline in HRQoL during the first 2 weeks, followed by a recovery to baseline within 3 months. However, the first study found no clinically significant improvement over time.[7] The second study showed an improvement at 3 and 6 months but included non-responders who do not represent patients in remission.[6] Both studies involved a heterogeneous population of patients also suffering from multiple myeloma and acute leukemia. Finally, their limited 6-month follow-up does not allow for an estimate of return to daily life.

Furthermore, findings from cross-sectional studies indicate that a subset of patients undergoing CAR T-cell therapy experience psychological distress, neurocognitive impairment, fatigue, and pain during the initial year after treatment.[8–11] These various aspects of HRQoL may influence long-term well-being. Nevertheless, clinical trials and real-life studies have predominantly used generic HRQoL questionnaires such as the EQ-5D, questionnaires that screen symptoms related to the disease or its treatment such as the EORTC-QLQC30, or a symptom-burden questionnaire such as items from the PRO-CTCAE item bank. These questionnaires do not allow the in-depth assessment of symptoms influencing quality of life and their evolution over time. Among the above-mentioned prospective studies, one examined the neurocognitive function, and another the psychological impact of treatment. In addition, two large prospective studies assessed neurocognitive outcomes after CAR T-cell therapy, but with different findings.[12,13] Indeed, one reported an impairment of perceived neurocognition 1 year after treatment,[12] while the other found an improvement in neurocognitive performance.[13] Regarding factors associated with HRQoL evolution, Johnson and colleagues suggested that a worse performance status at baseline or more intensive care during hospitalization could be associated with a stronger improvement over time.[6]

To the best of our knowledge, the various dimensions of HRQoL and their longitudinal evolution have not been previously investigated. Furthermore, all previously published studies regarding HRQoL after CAR T-cell have a short follow-up of 6 months or less. Published real-world data on HRQoL and other patient-reported outcomes (PROs) in adult patients having undergone CAR T-cell therapy remain poor.[14,15]

Here, we conducted a prospective study of real-world lymphoma patients following treatment with commercially available CAR T cells to evaluate multidimensional recovery (physical, psychological, social, and professional) among those in remission through the first year after CAR T-cell therapy.

METHODS

Study design and data collection

CARAMA is a bicentric prospective study conducted at the University Hospitals of Rennes and Toulouse, France. Eligible patients were required to be at least 18 years old to provide informed consent and have a lymphoma eligible for CAR T-cell therapy. Patients were included before leukapheresis. Bridging chemotherapy was given at the discretion of the treating physician.

Disease characteristics were collected from electronic medical records, and social and demographic data were self-reported by the patients. All analyzable patients were asked to complete each of the questionnaires, which were prospectively collected by dedicated nurses from the Hematology department.[16] There was no financial compensation. Clinical data and self-completed questionnaires were collected before leukapheresis, immediately before CAR T-cell infusion, and 3, 6, and 12 months thereafter. Patients were followed until the end of the study at month 12 or until disease progression/relapse or death.

Long-term follow-up data were obtained by phone interview from patients who remained in remission after 12 months and who were still monitored by the investigator, that is, until 24 months. These structured interviews covered professional activity, social life, physical activity, sexual life, and general well-being.

Informed consent was collected from all patients. The study was approved by our local Institutional Review Board (No. A01695-38).

PRO questionnaires

To assess HRQoL specific to lymphoma patients, we used Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym).[17] The FACT-Lym is a 42-item measure that assesses Functional Assessment of Cancer Therapy-General (FACT-G) comprising four HRQoL domains (physical, functional, emotional, and social/family well-being) and the Lymphoma subscale (Lym-S). Lym-S informs about disease and treatment-related symptoms including pain, fever, swelling, night sweats, insomnia, itching, weight loss, fatigue, and loss of appetite. Summary scores are calculated by adding domains: FACT-G score corresponds to the sum of well-being domain scores; FACT-Lym total score (TS) comprises FACT-G plus Lym-S scores. A high score corresponds to a high HRQoL level.

We used the EQ-5D-5L to describe global HRQoL.[18] This questionnaire enables us to estimate a utility score and a visual analog scale (VAS) of global health (from "The best health you can imagine" to "The worst health you can imagine"). The EQ-5D-5L utility score covers five dimensions on the assessment day: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with one item per dimension.

FACT-Cognition (FACT-Cog) assesses subjective cognitive impairment, which comprises 37 items.[19–22] The items assess perceived cognitive functioning over the past 7 days according to four subscales: perceived cognitive impairments (PCI), impact of PCI on HRQoL (QOL), perceived cognitive abilities, and comments from others on cognitive function (Oth). A high score corresponds to a low level of cognitive complaints.

FACT-Fatigue subscale (FACIT-F) is a 13-item questionnaire that measures self-reported tiredness, weakness, and difficulty conducting usual activities due to cancer-related fatigue.[23] A high FACIT-F score corresponds to a low level of fatigue.

The Hospital Anxiety and Depression Scale (HADS) and the Post-Traumatic Check List Scale (PCLS) were used to assess psychological status. The HADS is a 14-item questionnaire comprising two 7-item subscales to assess anxiety and depression symptoms.[24] A score ranging from 0 to 7 represents normal levels of anxiety or depression; 8 to 10 indicates moderate levels of anxiety or depression; 11 to 21 alerts severe levels of anxiety or depression. PCLS assesses patients' symptoms of posttraumatic stress disorder (PTSD).[25] The PCLS is a 17-item measure that evaluates symptoms of PTSD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV. A high score indicates a higher level of PTSD symptoms, with a cut-off of 44 for a diagnosis of PTSD and 34 for needing medical attention.[26] The PCLS was only administered at Month 6.

Sexual health was assessed by completing the RSS questionnaire.[27] It considers sexual function and the level of deterioration in sexual desire after the disease, the ability to have an orgasm, and the frequency of sexual intercourse after the disease. It also focuses on patients'

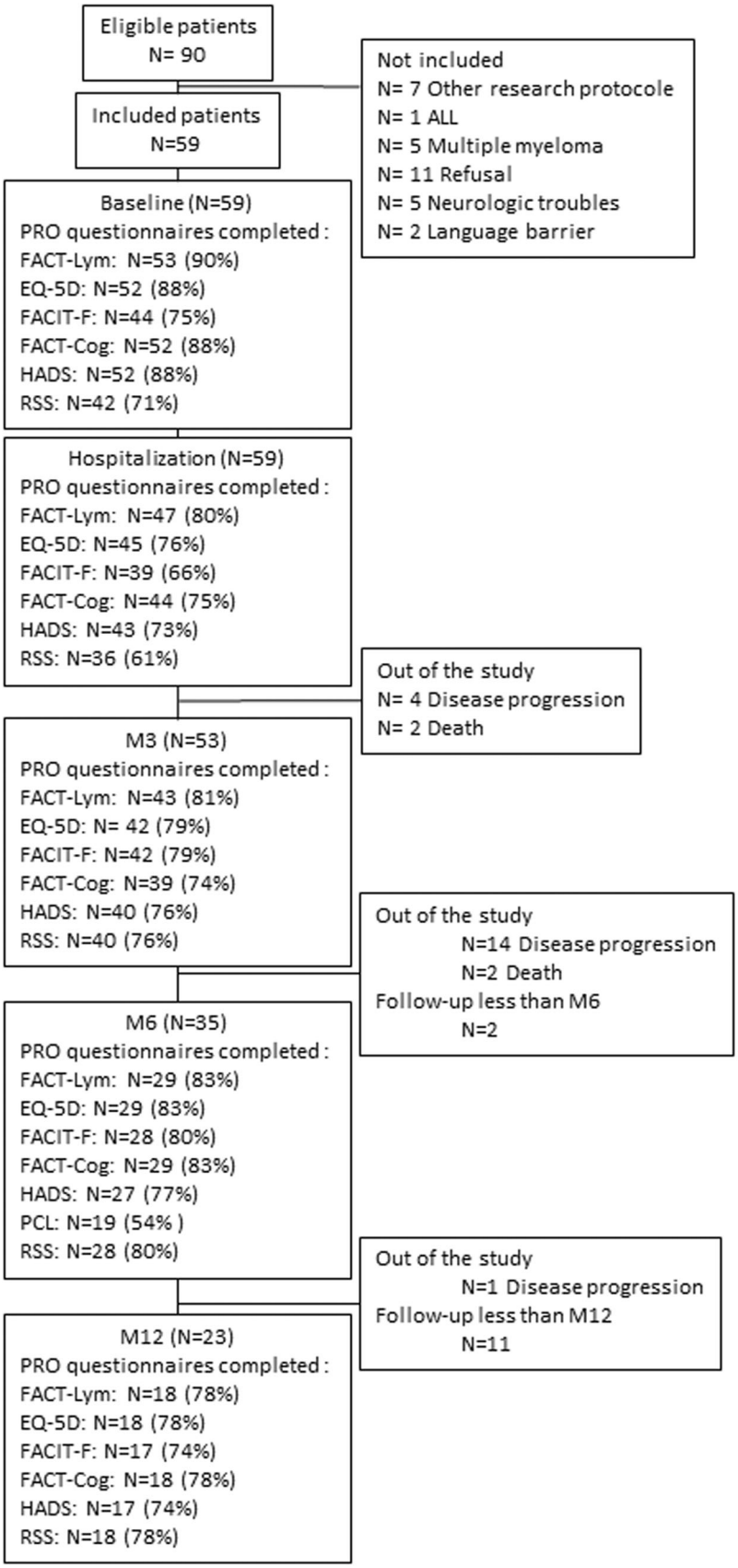

FIGURE 1 Patients' flowchart and completion rate. Patients were followed up until death, disease progression, or end of the study. A questionnaire is considered completed if at least one score can be calculated. ED-5Q-DL, 5-level EuroQol 5-dimensions 5-level; EPCL, Post Traumatic Stress Checklist; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue subscale (FACIT-F) questionnaire; FACT-Cog, Functional Assessment of Cancer Therapy-Cognition; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; HADS, Hospital Anxiety and Depression Scale; PRO, Patient-Reported Outcome; RSS, Relationship and Sexuality Scale questionnaire.

TABLE 1 Patients' characteristics.

Sociodemographic characteristics at baseline	Patients at baseline (*N* = 59)
Age (years)	
Median (range)	63 (19–78)
Mean (SD)	59 (14.1)
Age group (years), *N* (%)	
<30	3 (5.1)
30–50	11 (18.6)
50–60	12 (20.3)
60–70	17 (28.8)
≥70 years	16 (27.1)
Gender, *N* (%)	
Female	31 (52.5)
Male	28 (47.5)
Marital status, *N* (%)	
Couple	40 (71.4)
Divorced	5 (8.9)
Single	7 (12.5)
Widowed	4 (7.1)
Missing	3
Professional activity before diagnosis, *N* (%)	
No	32 (57.1)
Yes	24 (42.9)
Professional categories	
Blue-collar workers	1 (1.8)
Craftsmen, retailers, and business leaders	1 (1.8)
Executives and white-collar workers	5 (9.1)
Intermediate professions	4 (7.3)
Employees	11 (20.0)
Farmers	4 (7.3)
Retired	25 (45.5)
No profession	4 (7.3)
Missing	4
Education level, *N* (%)	
<High school diploma	25 (50.0)
=High school diploma	6 (12.0)
>High school diploma	19 (38.0)
Missing	9
Physical activity, *N* (%)	
No	13 (23.6)
Yes	42 (76.4)
Missing	4
Frequency of physical activity among those who were physically active (*N* = 42), *N* (%)	
<3 h/week	24 (60)
3–6 h/week	7 (17.5)
>6 h/week	9 (22.5)
Missing	19
Social activity, *N* (%)	
No	33 (60)
Yes	22 (40)
Missing	4
Main diagnosis, *N* (%)	
LBCL	43 (72.9)
PCNSL	1 (1.7)
FL	8 (13.6)
MCL	5 (8.5)
PMBL	2 (3.4)
Central nervous system involvement, *N* (%)	
Yes	5 (8.8)
No	52 (91.2)
Missing	2
CAR-T cells type, *N* (%)	
Tisagenlecleucel	18 (30.5)
Brexucabtagene autoleucel	4 (6.8)
Axicabtagene ciloleucel	37 (62.7)
Prior lines, *N* (%)	
2	39 (66.1)
3	17 (28.8)
≥4	3 (5.1)
Prior lines, median (minimum–maximum)	2 (2–8)
Prior auto-SCT, *N* (%)	13 (22.0)
Prior allo-SCT, *N* (%)	1 (1.7)
Disease status at leukapheresis, *N* (%)	
Partial response	13 (22.0)
Progressive disease	41 (69.5)
Stable disease	5 (8.5)
Bridging chemotherapy	54 (91.5)
ECOG performance status at inclusion, *N* (%)	
0	14 (24.1)
1	35 (60.3)
2	8 (13.8)
3	1 (1.7)
Missing	1
Occurrence of CRS, *N* (%)	54 (91.5)
Maximum grade of CRS, *N* (%)	
0–1	42 (71.2)
2	16 (26.9)
3	1 (1.9)
Occurrence of ICANS, *N* (%)	29 (50.8)
Maximum grade of ICANS, *N* (%)	
0–1	36 (61.0)
2	16 (27.1)
3	5 (8.5)
4	2 (3.4)

TABLE 1 (Continued)

Sociodemographic characteristics at baseline	Patients at baseline (*N* = 59)
Occurrence of cytopenia before 3 months, *N* (%)	20 (42.9)
Missing	6
Occurrence of cytopenia between 3 and 6 months, *N* (%)	11 (33.3)
Missing	2
Occurrence of cytopenia between 6 and 12 months, *N* (%)	6 (27.3)
Missing	1
Occurrence of infection during hospitalization, *N* (%)	36 (66.7)
Missing	5
Occurrence of infection before 3 months, *N* (%)	1 (2.1)
Missing	6
Occurrence of infection between 3 and 6 months, *N* (%)	8 (24.2)
Missing	2
Occurrence of infection between 6 and 12 months, *N* (%)	9 (40.0)
Missing	1

Note: Professional categories were defined according to the 2020 nomenclature from Insee, France. Cytopenia was defined by CTCAE criteria or requiring erythropoietin, thrombopoietin, transfusions, or growth factors use.

Abbreviations: Allo-SCT, allogenic stem cell transplantation; auto-SCT, autologous stem cell transplantation; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; ICANS, immune effector cell-associated neurotoxicity; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; PCNSL, primary central nervous system lymphoma; PMBL, primary mediastinal B-cell lymphoma.

satisfaction with the frequency of hugs and kisses and their satisfaction with the frequency of sexual intercourse.

Statistical analysis

Quantitative variables were described using mean (standard deviation) and median (minimum–maximum). Qualitative variables were described using number and percentage.

Compliance with PRO questionnaires was described for each questionnaire at each time point, reporting the number of completed questionnaires (i.e., at least one subscale available) in relation to the number of patients still in the study at the theoretical time of questionnaire completion.

The proportion of patients with moderate to severe anxiety or depression disorders according to HADS scores was also reported at each time point. For the RSS questionnaires, patients were divided into "positive impact" and "negative impact" groups, and their proportion was reported at baseline and 6 months.

Mean scores were compared to the reference level of the general population found in the literature for FACT-G,[28] EQ-5D-5L,[18] FACIT-F,[29] FACT-Cog TS,[21] and HADS.[30]

Mean change at each follow-up time point compared to baseline was also reported (if the questionnaire was analyzable at these two time points) for each score, except for the RSS and the PCLS, with a 95% confidence interval (CI). Paired *t*-tests were performed for exploratory purposes to assess statistically significant change at a threshold of 5%.

When possible, we established the minimum important difference (MID) for each PRO score to validate the clinically relevant change in score as follows: three points for each subscale of the FACT-Lym, seven points for the FACT-G and FACT-Lym TS,[17,31,32] eight points for the EQ-5D VAS, 0.07 for the EQ-5D utility score,[33] four points for the FACIT-F scale,[34] 10 points for FACT-Cog TS,[20] and 1.5 points for anxiety and depression scores on the HADS.[35]

The mean change of the FACT-Lym TS at 6 months was reported according to the presence or not of anxiety symptoms at inclusion, gender, age, presence or not of cytopenia at 3 months, presence or not of pain at 6 months, and PTSD or not at 6 months. The mean change of the FACT-Cog TS was reported according to the occurrence or not of immune effector cell-associated neurologic syndrome (ICANS).

The median follow-up of patients was calculated using the reverse Kaplan–Meier method and described with its 95% CI. *p* Values <0.05 were considered statistically significant. All analyses were performed with the SAS software (version 9.4) (SAS Institute Inc.).

RESULTS

Patient sample characteristics at baseline

From March 2020 to August 2022, 59 patients were included in the study. The median follow-up after CAR T-cell infusion was 11 months (95% CI: 7.6–13.3 months). Details of questionnaire completion are reported in Figure 1. During the study, 19 patients (32.2%) experienced disease progression and four patients (6.8%) died. At the end of the study, the final follow-up dates were 3 and 6 months for 2 (3.4%) and 11 (18.4%) patients, respectively, leaving 23 patients (39%) assessable at Month 12.

Patients' characteristics are presented in Table 1. The median age was 63 years (range: 19–78 years). There were 28 (47.5%) males and 31 (52.5%) females. Most patients had received two prior lines of therapy (*N* = 39, 66%). The main diagnoses were LBCL (*N* = 44, 73.6%), FL (*N* = 8, 13.6%), and MCL (*N* = 5, 8.5%).

Quality of life

We found an improvement in HRQoL related to lymphoma over time (Figure 2 and Supporting Information S1: Table 1). The FACT-Lym TS showed a clinically relevant improvement in HRQoL at 3, 6, and 12 months after CAR T-cell infusion, with a mean change from baseline of 10.94 points (95% CI: 5.83; 16.05), 12.16 points (95% CI: 4.19; 20.12), and 11.72 points (95% CI: 2.06; 21.38) at 3, 6, and 12 months, respectively. The FACT-G showed a significant improvement from baseline at 6 months and the raw score reached the general population's normal values by 3 months.

The EQ-5D-5L VAS revealed a clinically relevant and statistically significant improvement between 3 and 12 months after infusion (Figure 2). The mean score of the EQ-5D VAS increased over time and reached the general population's reference level by Month 3. The proportion of patients complaining of severe problems or inability decreased in almost all areas (Supporting Information S1: Figure 1). At inclusion, 48 patients (69.1%) experienced pain. At 6 and 12 months after infusion, about half of the patients were still presenting slight to severe pain (50% and 55.6%, respectively). Notably, patients who

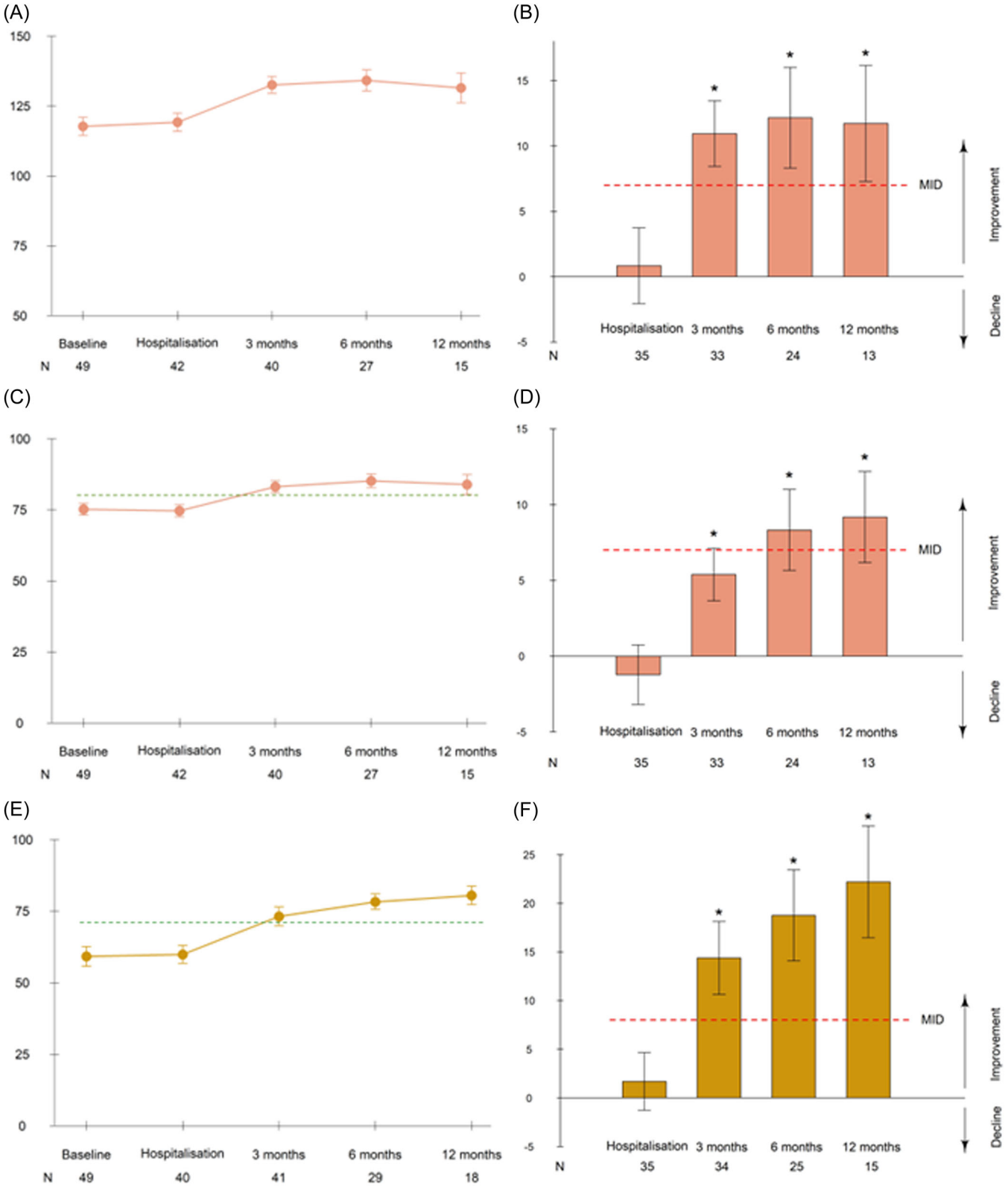

FIGURE 2 Mean related to lymphoma and global health-related quality of life scores over time and mean changes from baseline. Mean scores over time and mean changes from baseline (with standard error) of Functional Assessment of Cancer Therapy (FACT)-Lymphoma total score (A, B), FACT-General (C, D), and EQ-5D visual analog scale (E, F). Before leukapheresis, before CAR T infusion, 3, 6, and 12 months after infusion. Change is considered significant when reaching the minimal important difference threshold, represented by a red dotted line. Stars represent statistically significant results at the threshold of 5%. Reference population mean scores are represented by green dotted lines when available.[17,18,28]

experienced pain at 6 and 12 months usually already did so at baseline (84.6% and 88.9%, respectively).

Cognition and fatigue

The FACT-Cog TS did not show any clinically relevant change from baseline over time (Figure 3). No change was seen based on the occurrence of ICANS. However, in six (19.4%), three (13.6%), and five (33.3%) patients, the FACT-Cog TS showed a significant decrease from baseline at 3, 6, and 12 months, respectively. The mean raw score was similar to the general population's normal values with a slight decrease at 12 months.

The FACIT-F scale showed clinically relevant improvement in cancer-related fatigue at 3 and 6 months, but not at 12 months. The mean raw score increased up to 6 months after infusion, then tended to decrease and remained under the general population's reference level at each time point. At 6 and 12 months, 21.4% and 35.3% of the patients, respectively, were reporting moderate to severe levels of fatigue.

Psychological status

At baseline, 43.1% of patients presented moderate or severe anxiety disorders (i.e., with a score ≥8), as measured by the HADS questionnaire (Figure 4). This proportion consistently exceeded the general population's (the lowest being 23% at 3 months). The anxiety score showed a clinically relevant improvement of anxiety from 6 to 12 months, statistically significant by month 3. The seven patients who remained moderately or severely anxious at 6 and 12 months (25.9% and 40.2% of evaluable patients, respectively) tended to be younger (median age of 52 years (range: 42–73) versus 63 years (range: 24–77) for the nonanxious patients), and 85.7% of them were anxious at baseline. The number of patients with moderate or severe depression symptoms (i.e., with a score ≥8) decreased over time from

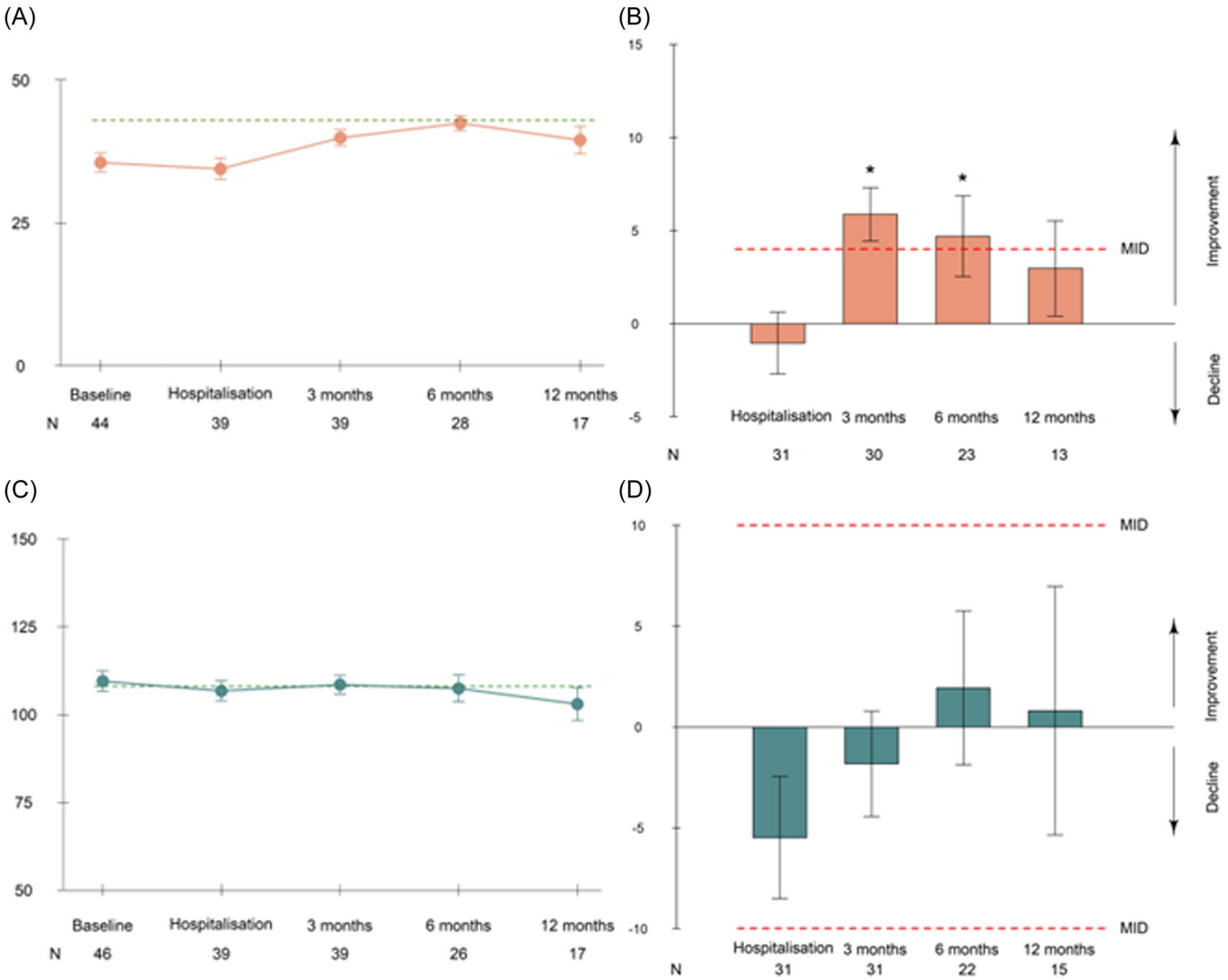

FIGURE 3 Mean fatigue and cognitive scores over time and mean changes from baseline. Mean scores over time and mean changes from baseline (with standard error) of Functional Assessment of Cancer Therapy (FACT)-Fatigue subscale (A, B) and FACT-Cognition total score (C, D). Before leukapheresis, before Chimeric antigen receptor T-cell infusion, and 3, 6, and 12 months after infusion. Change is considered significant when reaching the minimal important difference threshold, represented by a red dotted line. Stars represent statistically significant results at the threshold of 5%. Reference population mean scores are represented by green dotted lines when available.[21,36]

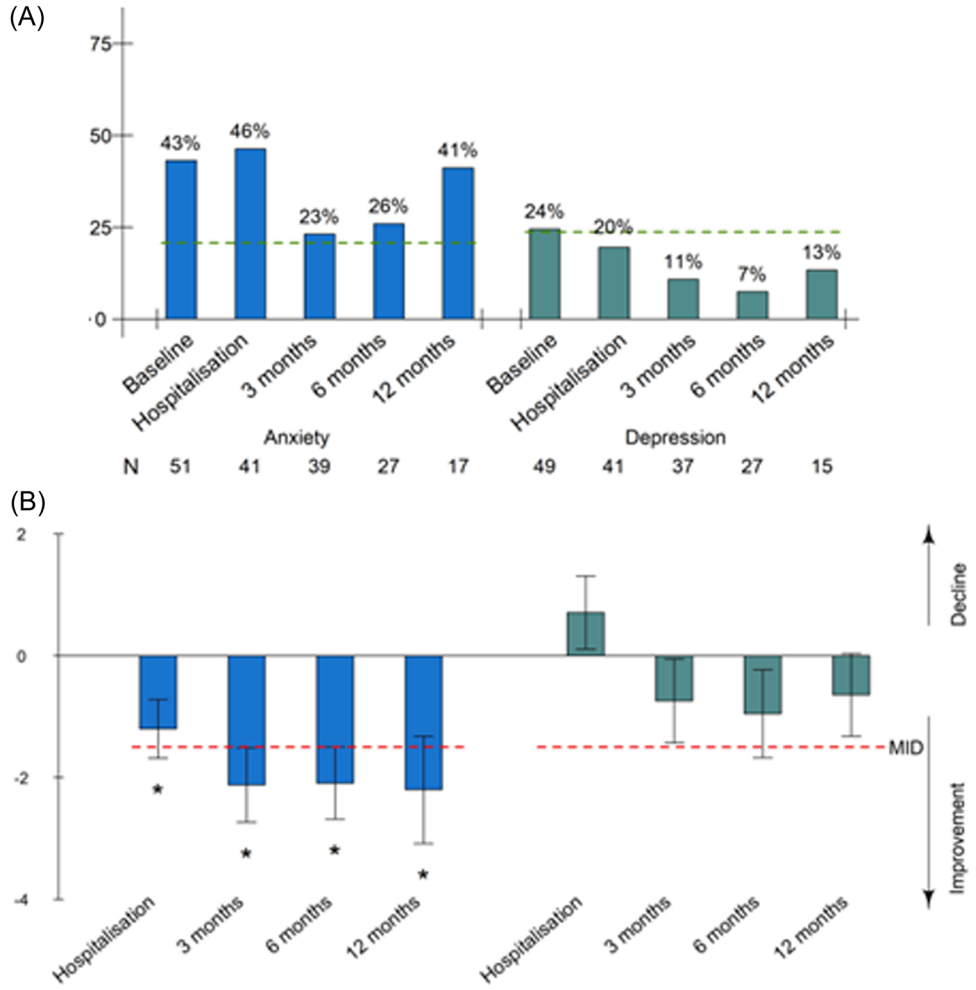

FIGURE 4 Proportion of patients with anxiety or depression disorders according to Hospital Anxiety and Depression Scale (HADS) subscales and mean change from baseline. (A) Proportion of patients with anxiety or depression disorders according to HADS subscales and (B) mean change from baseline (with standard error) of HAD subscales. Before leukapheresis, before chimeric antigen receptor T-cell infusion, and 3, 6, and 12 months after infusion. Change is considered significant when reaching the minimal important difference threshold, represented by a red dotted line. Stars represent a statistically significant change from the threshold of 5%. Reference population mean scores are represented by green dotted lines when available.[30]

24.4% at baseline to 13% at 12 months, with a lower proportion than in the general population by 3 months. However, the changes in depression scores over time were not clinically relevant.

At 6 months, 26% of the patients had a PCLS score ≥34 (indicating the need for medical attention), while 21.3% met the diagnostic criteria for PTSD (i.e., a PCLS score >44) (Supporting Information S1: Figure 2).

At 6 months, patients who presented anxiety at baseline or PTSD symptoms at 6 months had a lower improvement of the FACT-Lym TS from baseline (Figure 5). There was no difference in HRQoL improvement from baseline linked to age, gender, and number of previous lines of treatment.

Sexual health

The RSS suggested an improvement in sexual outcomes at 6 months regarding sexual desire, ability to achieve orgasm, frequency of hugs and kisses, satisfaction with sexual activity frequency, and frequency of sexual activity (Supporting Information S1: Figure 3). Beyond Month 12, 68.2% of assessable patients ($N = 22$) reported satisfaction with their sexual lives. Additionally, 77.3% experienced either a stable or positive impact from CAR T-cell therapy on their sexual lives, with 59% stating that it was similar or better than before their lymphoma diagnosis. Only 6.8% of patients talked about their sexuality with their healthcare providers.

Professional, social, and physical recovery

After a median follow-up of 19 months (range: 12–24), 22 patients (37.3%) remained in remission after at least 12 months.

Less than half the patients ($N = 24$, 42.9%) were professionally active at the time of their lymphoma diagnosis. Regarding patients who achieved remission after 12 months (Figure 6), among the 10 who were of working age (i.e., less than 62 years of age at the time of CAR T infusion), half returned to work ($N = 5$), including three full-time. Overall, 20.8% of infused patients younger than 62 resumed professional activity after CAR T-cell infusion. All were satisfied with their current professional activity (i.e., found that their activity was in accordance with their needs). The main cause for not resuming work was fatigue: approximately 60% of the patients gave it as their reason

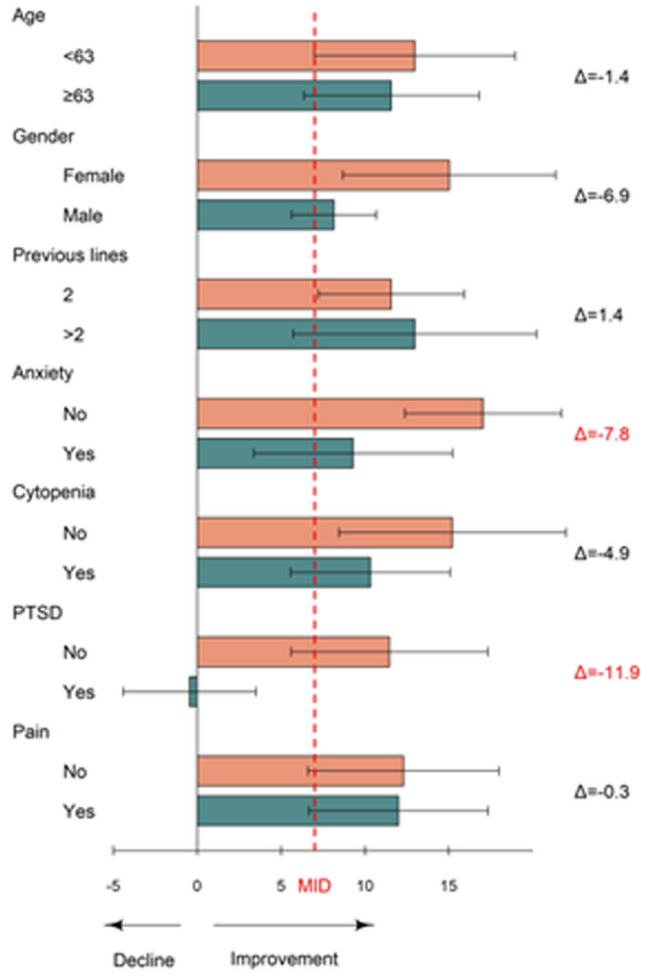

FIGURE 5 Subgroup analysis of mean change of Functional Assessment of Cancer Therapy-Lymphoma total score (FACT-Lym TS) at 6 months. Mean change from baseline of FACT-Lym TS (with SD) at 6 months according to the presence of anxiety symptoms at inclusion or not, gender, age, presence of cytopenia at 3 months or not, presence of pain at 6 months or not, and posttraumatic stress disorder at 6 months or not. Change is considered significant when meeting minimal important difference (represented by a dotted line). Differences between groups were relevant if the mean change differences were highest than the MID (i.e., >7).

for remaining on sick leave, while one patient still suffered from severe pain connected to the initial disease.

Of the 22 patients monitored long term, all but one practiced physical activity before the initial diagnosis. Among those who had previously been physically active, all patients resumed physical activity after CAR T-cell treatment, albeit less intensively: 34.6% spent more than 6 hours per week being physically active before diagnosis of lymphoma versus less than 6 h for all patients after CAR T-cell therapy. Overall, 66% of patients felt less fit than before their initial diagnosis, but the majority (76%) reported stable or improved fitness compared to the pre-CAR T period. Among patients who had social activities (i.e., leisure or community activities) prior to lymphoma diagnosis (35.3%), 37.5% resumed their activities after CAR T-cell therapy.

Most patients (77.3%) reported an improvement in their global well-being compared to the pre-CAR T-cell period. Overall, 81.8% were satisfied with their global well-being, and 54.5% considered that they had recovered a day-to-day lifestyle close to the one they had before their lymphoma diagnosis.

DISCUSSION

Here, we aimed to provide a comprehensive evaluation of HRQoL recovery in lymphoma patients who achieved remission after CAR T-cell therapy. To our knowledge, this is the first study to evaluate patients' recovery in a multidimensional manner (physical, psychological, social, sexual, and professional) and with such a long-term follow-up. Our target population included unselected patients from a variety of social and demographic categories. PROs were evaluated prospectively using well-validated and specified questionnaires and then compared to the general population norms.

Our patients' baseline FACT-G and EQ-5D-VAS scores were lower than those of the general population.[18,37] As assessed using FACT Lym-TS, we found a clinically and statistically significant improvement of HRQoL related to lymphoma from 3 months, maintained up to 12 months. EQ-5D-5L, which is a more generic HRQoL score, also showed a significant improvement over time. Furthermore, general population averages were reached within 3 months. These results are consistent with other studies.[4–6,38,39]

The subgroup analysis of the FACT Lym-TS found no difference in improvement in lymphoma-related HRQoL according to age, gender, or number of previous lines of treatment. However, patients experiencing anxiety at baseline or PTSD at 6 months had a lower degree of improvement than the population that was not symptomatic.

Psychological distress decreased following CAR T-cell therapy, although a substantial proportion of patients remained affected over time. Anxiety symptoms were reported at baseline in 43.1% of patients. We observed an improvement in anxiety symptoms, even at the time of hospitalization, perhaps due to optimism about the expected efficacy of CAR T cells.[40] Change was statistically and clinically relevant from Months 3 to 12. The proportion of patients with depressive symptoms decreased over time, but change was not clinically relevant. The proportion of anxious patients over time remained higher than that of the general population, bearing in mind that the proportion of anxious patients was already high at baseline. At 12 months, 40.1% presented anxiety symptoms, most of whom had anxiety prior to CAR T-cell therapy. Furthermore, about 26% of patients had PTSD symptoms at 6 months. In other studies, the prevalence of anxiety and depressive disorders at baseline are similar, ranging from 29% to 48% for anxiety and from 11% to 30% for depression.[8,40,41] Two studies found the prevalence of PTSD symptoms at baseline in 29% of patients before CAR T-cell infusion.[6,40] Johnson and colleagues found a decrease in psychological distress over time, with 22% of patients experiencing anxiety and PTSD at 6 months. This suggests that PSTD is likely to be present at baseline and not caused by the procedure. However, this phenomenon is described after allogenous stem cell transplantation.[42,43]

Regarding fatigue, the mean FACIT-F score at baseline was lower than the general population's average.[29] We found a significant improvement in fatigue after CAR T-cell infusion that was clinically relevant at 3 and 6 months but not at 12 months. Presumably, once patients resume their normal activities, fatigue is revealed and is perceived as worse than expected. Besides, fatigue recovery did not reach the level of the general population. Consistent with our findings, Patrick et al. reported a meaningful improvement of fatigue from baseline by month 9, maintained up to month 18 but still with 20% of patients reporting deterioration. The MID was reached only at month 9 in the axi-cel arm in ZUMA-7 and was not achieved in TRANSFORM.[5,38]

Regarding cognitive complaints, the baseline level of our patient population was similar to that of the general population, whereas we

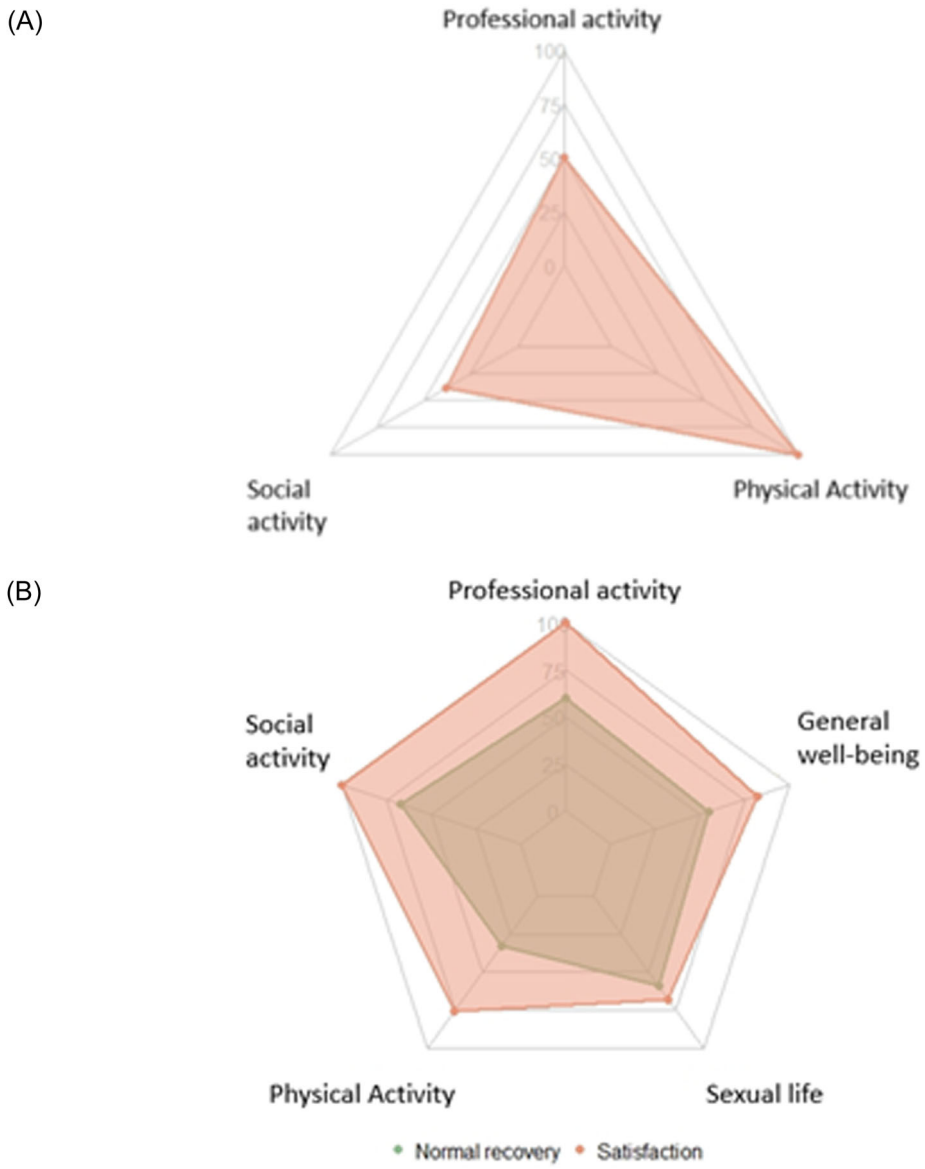

FIGURE 6 Daily life recovery for patients in remission after 12 months (*N* = 22). (A) Proportion of patients who returned to their physical (*N* = 21), social (*N* = 8), and professional activity (*N* = 10). (B) Proportion of patients who considered a normal recovery (stable or better than before lymphoma diagnosis) of physical (*N* = 21), social (*N* = 3), professional activity (*N* = 5), sexual life (*N* = 22), and general well-being (*N* = 22). Proportion of patients quite satisfied or very satisfied with current physical, social, and professional activity, sexual life, and general well-being at the time of follow-up.

could have expected lymphoma patients to have lower cognitive scores.[44–47] No difference was seen based on the occurrence of ICANS. A decline in neurocognition is described but not well elucidated.[8] Available longitudinal results are inconsistent: PCI and improvement of neurocognitive performance between baseline and 12 months are both described.[12,13] In TRANSFORM, 18% of patients experienced a decline in cognition at 6 months, assessed by the EORTCT-QLQC30 cognitive items.[39] Our results support the stability of perceived cognitive function over time.

Sexual health (i.e., sexual function, libido, frequency of intercourse, and related satisfaction) tended to improve at Month 6. Long-term data showed that the majority of patients experienced an improvement in their sexual health after CAR T-cell treatment. However, in 41% of patients, it did not return to what it was prior to their lymphoma diagnosis.

Persistent fatigue, psychological symptoms, and sexual dysfunction, described in 20%–40% of patients over time, appeared to be present before CAR T-cell infusion. Psychological distress is well described in hematological malignancies in patients who have often experienced several treatments and relapses. A 5-year follow-up study reported that one-third of lymphoma survivors present PTSD symptoms.[48] Fatigue is widely reported in cancer survivors, particularly in hematological malignancies with 64% of patients reporting moderate to severe fatigue.[36,49] Deterioration of sexual health is also widely reported by cancer survivors associated with mood disorders and fatigue.[27,42,50–55] Another interesting finding was the persistence of pain over time: half of the patients reported pain at 6 and 12 months, and most of them already had pain at inclusion. In the JULIET study, clinically significant improvement in pain was observed at 3, 6, and 18 months. It affected 21% and 28% of patients at 12 and 18 months, respectively, in the TRANSCEND trial.[4,5,38] Lymphoma and its associated treatments amount to a long journey, and some

patients may benefit from specialized supportive measures and rehabilitation care in the early stages of treatment.[56–60]

The long-term follow-up survey (after 12 months) confirmed that not all patients recovered a normal life. Within a year, half of the working-age population resumed employment. These patients represent 21% of patients of this age group when related to the population initially included. Finally, all patients seem to have become aware of the importance of regular physical activity, even if they felt less fit than before the disease. Although not all patients felt as well as they did before diagnosis, most were satisfied with their current lives, and their general well-being was in line with their expectations.

Our study brings novel insights regarding patients' recovery and well-being after CAR T-cell therapy. First, to the best of our knowledge, this is the first study to prospectively assess psychological distress, PCI, and fatigue using specific questionnaires, such as FACT-Cog and FACIT-F, which enabled a much more precise assessment than the nonspecific EORTC questionnaire used in other studies. Second, assessments were performed in the long term (up to 12 months), which had not been done in prior real-life studies. Third, HRQoL questionnaires were compared to the general population, which allowed us to assess whether the various parameters were back to "normal" or not. Fourth, for the first time, we evaluated sexuality after CAR T-cell therapy using a specific questionnaire (RSS). Finally, our study is the first to assess the physical, social, and professional recovery 1 year after CAR T-cell therapy. Indeed, it is important to evaluate whether patients can resume their professional life after CAR T cells because 44% of them are under 60.

Our study has some limitations. First, the limited sample size of our cohort. This restricted our ability to perform a robust subgroup analysis or to accurately characterize patients with unfavorable PRO evolutions. The completion rate was similar to other prospective studies on quality of life after CAR T-cell therapy.[5,7,13] However, the number of questionnaires was a barrier to exhaustive completion and may induce a nonresponse bias. We chose to explore HRQoL in responding patients, especially in line with clinical trials that analyzed responders separately from nonresponders, but this may induce a survivor bias.[4,5,61] Also, the sample's relative heterogeneity may limit our capacity to generalize our findings: our patient population comprised aggressive and indolent lymphomas with different treatment histories.

In conclusion, we found that CAR T-cell therapy improves the global quality of life in lymphoma patients who achieve remission, enabling a resumption of daily life in about half of them. Nevertheless, some patients experience prolonged sequela and not all of them recover a "normal" or "satisfying" life. Some symptoms may persist such as fatigue, anxiety, depression, pain, and sexual health deterioration. Many of these symptoms may be underdiagnosed if not investigated specifically. Physicians should be aware of these potential symptoms to manage them efficiently and improve patients' well-being after CAR T-cell therapy. Further studies are needed to identify factors associated with patients' recovery following CAR T-cell therapy. This will be important to improve patient management to facilitate and accelerate full recovery, such as specialized rehabilitation care or psychological support during CAR T-cell procedure.[9,45,56,57,60,62]

AUTHOR CONTRIBUTIONS

Aline Moignet, Roch Houot, and Fanny Colin contributed to the study design. Aline Moignet, Roch Houot, Sophie De Guibert, Guillaume Manson, Pierre Daufresne, Thierry Lamy De La Chapelle, and Faustine Lhomme enrolled and treated patients and Fanny Colin, Laetitia Le Bars, and Adeline Bellec collected questionnaires. Fanny Colin and Alya Perthus collected medical data. Amélie Anota and Emilie Charton performed statistical analyses. Alya Perthus, Aline Moignet, Amélie Anota, and Roch Houot analyzed and interpreted the data. Alya Perthus, Aline Moignet, and Roch Houot wrote the manuscript. All authors were involved in revising the manuscript critically for important intellectual content, provided final approval for the manuscript, and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

The authors report the following competing interests: Aline Moignet: Honoraria from Kite/Gilead. Fanny Colin: Honoraria from Kite/Gilead. Roch Houot: Honoraria from Kite/Gilead, Novartis, Incyte, Janssen, MSD, Takeda and Roche; and consultancy at Kite/Gilead, Novartis, Bristol-Myers Squibb/Celgene, ADC Therapeutics, Incyte, Miltenyi. Amélie Anota: Consultancy for Amgen, Ipsen, AstraZeneca, Kite/Gilead. Guillaume Manson: Honoraria from Chugai, Kite/Gilead, Takeda. Loïc Ysebaert: Consultancy at Beigene, Bristol-Myers Squibb/Celgene, Janssen, Kite/Gilead, and Roche, and is on the speaker's bureau of AstraZeneca. Sophie De Guibert: Honoraria from Kite/Gilead and Novartis.

DATA AVAILABILITY STATEMENT

Publication-related data and data-sharing statement can be obtained via an Email to the corresponding author.

FUNDING

This research received no funding.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

REFERENCES

1. Neelapu SS, Jacobson CA, Ghobadi A, et al. 5-Year follow-up supports curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1). *Blood*. 2023;141:2307-2315. doi:10.1182/blood.2022018893
2. Wang M, Munoz J, Goy A, et al. Three-year follow-up of KTE-X19 in patients with relapsed/refractory mantle cell lymphoma, including high-risk subgroups, in the ZUMA-2 study. *J Clin Oncol*. 2023;41(3):555-567. doi:10.1200/JCO.21.02370
3. Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. *Nat Med*. 2022;28(2):325-332. doi:10.1038/s41591-021-01622-0
4. Maziarz RT, Waller EK, Jaeger U, et al. Patient-reported long-term quality of life after tisagenlecleucel in relapsed/refractory diffuse large B-cell lymphoma. *Blood Adv*. 2020;4(4):629-637. doi:10.1182/bloodadvances.2019001026
5. Patrick DL, Powers A, Jun MP, et al. Effect of lisocabtagene maraleucel on HRQoL and symptom severity in relapsed/refractory large B-cell lymphoma. *Blood Adv*. 2021;5(8):2245-2255. doi:10.1182/bloodadvances.2020003503
6. Johnson PC, Dhawale T, Newcomb RA, et al. Longitudinal patient-reported outcomes in patients receiving chimeric antigen receptor T-cell therapy. *Blood Adv*. 2023;7(14):3541-3550. doi:10.1182/bloodadvances.2022009117
7. Sidana S, Dueck AC, Thanarajasingam G, et al. Longitudinal patient reported outcomes with CAR-T cell therapy versus autologous and allogeneic stem cell transplant. *Transplant Cell Ther*. 2022;28(8):473-482. doi:10.1016/j.jtct.2022.05.004

8. Ruark J, Mullane E, Cleary N, et al. Patient-reported neuropsychiatric outcomes of long-term survivors after chimeric antigen receptor T cell therapy. *Biol Blood Marrow Transplant*. 2020;26(1):34-43. doi:10.1016/j.bbmt.2019.09.037
9. Whisenant MS, Srour SA, Williams LA, et al. The unique symptom burden of patients receiving CAR T-cell therapy. *Semin Oncol Nurs*. 2021;37(6):151216. doi:10.1016/j.soncn.2021.151216
10. Dai H, Xu S, Han J, et al. Prevalence and factors associated with anxiety and depressive symptoms among patients hospitalized with hematological malignancies after chimeric antigen receptor T-cell (CAR-T) therapy: a cross-sectional study. *J Affect Disord*. 2021;286:33-39. doi:10.1016/j.jad.2021.02.041
11. Akinola IM, Cusatis R, Pasquini MC, et al. Multi-stakeholder qualitative interviews to inform measurement of patient reported outcomes after CAR-T. *Transplant Cell Ther*. 2023;29(4):254.e1-254.e9. doi:10.1016/j.jtct.2023.01.004
12. Barata A, Hoogland AI, Kommalapati A, et al. Change in patients' perceived cognition following chimeric antigen receptor T-cell therapy for lymphoma. *Transplant Cell Ther*. 2022;28(7):401.e1-401.e7. doi:10.1016/j.jtct.2022.05.015
13. Hoogland AI, Barata A, Logue J, et al. Change in neurocognitive performance among patients with non-Hodgkin lymphoma in the first year after chimeric antigen receptor T cell therapy. *Transplant Cell Ther*. 2022;28(6):305.e1-305.e9. doi:10.1016/j.jtct.2022.03.023
14. Raymakers AJN, Regier DA, Peacock SJ, Freeman CL. Health-related quality of life data collected in chimeric antigen receptor T-cell (CAR-T) therapy clinical trials. *J Cancer Policy*. 2021;30:100304. doi:10.1016/j.jcpo.2021.100304
15. Kamal M, Joseph J, Greenbaum U, et al. Patient-reported outcomes for cancer patients with hematological malignancies undergoing chimeric antigen receptor T cell therapy: a systematic review. *Transplant Cell Ther*. 2021;27(5):390.e1-390.e7. doi:10.1016/j.jtct.2021.01.003
16. Colin F, Bellec A, Granger M, et al. Remote monitoring of CAR T-cell treated patients by a specialized nurse to detect and manage late complications: report of the CARAMA program. In: *Poster presented at the EHA Congress, Frankfurt, Germany, June 2023*. https://library.ehaweb.org/eha/2023/eha2023-congress/385855/fanny.colin.remote.monitoring.of.car.t-cell.treated.patients.by.a.specialized.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dcolin
17. Hlubocky FJ, Webster K, Cashy J, Beaumont J, Cella D. The development and validation of a measure of health-related quality of life for non-Hodgkin's lymphoma: the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym). *Lymphoma*. 2013;2013:1-9. doi:10.1155/2013/147176
18. Gautier L, Azzi J, Saba G, Bonnelye G, De Pouvourville G. Population norms in France with EQ-5D-5L: health states, value indexes, and VAS. *Eur J Health Econ*. 2023;24:1517-1530. doi:10.1007/s10198-022-01559-2
19. Henneghan AM, Van Dyk K, Kaufmann T, et al. Measuring self-reported cancer-related cognitive impairment: recommendations from the Cancer Neuroscience Initiative Working Group. *J Natl Cancer Inst*. 2021;113(12):1625-1633. doi:10.1093/jnci/djab027
20. Cheung YT, Foo YL, Shwe M, et al. Minimal clinically important difference (MCID) for the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) in breast cancer patients. *J Clin Epidemiol*. 2014;67(7):811-820. doi:10.1016/j.jclinepi.2013.12.011
21. Lange M, Heutte N, Morel N, Eustache F, Joly F, Giffard B. Cognitive complaints in cancer: the French version of the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog), normative data from a healthy population. *Neuropsychol Rehabil*. 2016;26(3):392-409. doi:10.1080/09602011.2015.1036890
22. Joly F, Lange M, Rigal O, et al. French version of the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) version 3. *Supp Care Cancer*. 2012;20(12):3297-3305. doi:10.1007/s00520-012-1439-2
23. Cella D, Lai JS, Stone A. Self-reported fatigue: one dimension or more? Lessons from the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire. *Supp Care Cancer*. 2011;19(9):1441-1450. doi:10.1007/s00520-010-0971-1
24. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*. 1983;67(6):361-370. doi:10.1111/j.1600-0447.1983.tb09716.x
25. Yao SN, Cottraux J, Note I, De Mey-Guillard C, Mollard E, Ventureyra V. Evaluation of post-traumatic stress disorder: validation of a measure, the PCLS. *Encephale*. 2003;29(3 Pt 1):232-238.
26. Ventureyra VAG, Yao SN, Cottraux J, Note I, De Mey-Guillard C. The validation of the Posttraumatic Stress Disorder Checklist Scale in posttraumatic stress disorder and nonclinical subjects. *Psychother Psychosom*. 2002;71(1):47-53. doi:10.1159/000049343
27. Ben Charif A, Bouhnik AD, Courbière B, et al. Sexual health problems in French cancer survivors 2 years after diagnosis—the National VICAN Survey. *J Cancer Surviv*. 2016;10(3):600-609. doi:10.1007/s11764-015-0506-3
28. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health Qual Life Outcomes*. 2003;1:79. doi:10.1186/1477-7525-1-79
29. Montan I, Löwe B, Cella D, Mehnert A, Hinz A. General population norms for the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale. *Value Health*. 2018;21(11):1313-1321. doi:10.1016/j.jval.2018.03.013
30. Hinz A, Brähler E. Normative values for the Hospital Anxiety and Depression Scale (HADS) in the general German population. *J Psychosom Res*. 2011;71(2):74-78. doi:10.1016/j.jpsychores.2011.01.005
31. Dineen K, Cella D, Hahn EA, Yount S. Meaningful change in cancer-specific quality-of-life scores: differences between improvement and worsening. *Clin Ther*. 2002;24:41-42. doi:10.1016/S0149-2918(02)85118-9
32. Yost KJ, Eton DT. Combining distribution- and anchor-based approaches to determine minimally important differences: the FACIT experience. *Eval Health Prof*. 2005;28(2):172-191. doi:10.1177/0163278705275340
33. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes*. 2007;5(1):70. doi:10.1186/1477-7525-5-70
34. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) Anemia and Fatigue Scales. *J Pain Symptom Manage*. 2002;24(6):547-561. doi:10.1016/S0885-3924(02)00529-8
35. Lemay KR, Tulloch HE, Pipe AL, Reed JL. Establishing the minimal clinically important difference for the Hospital Anxiety and Depression Scale in patients with cardiovascular disease. *J Cardiopulm Rehabil Prev*. 2019;39(6):E6-E11. doi:10.1097/HCR.0000000000000379
36. Hinz A, Weis J, Brähler E, Härter M, Geue K, Ernst J. Fatigue in cancer patients: comparison with the general population and prognostic factors. *Supp Care Cancer*. 2020;28(9):4517-4526. doi:10.1007/s00520-019-05260-8
37. Pearman T, Yanez B, Peipert J, Wortman K, Beaumont J, Cella D. Ambulatory cancer and US general population reference values and cutoff scores for the Functional Assessment of Cancer Therapy. *Cancer*. 2014;120(18):2902-2909. doi:10.1002/cncr.28758
38. Elsawy M, Chavez JC, Avivi I, et al. Patient-reported outcomes in ZUMA-7, a phase 3 study of axicabtagene ciloleucel in second-line large B-cell lymphoma. *Blood*. 2022;140:2248-2260. doi:10.1182/blood.2022015478

39. Abramson JS, Johnston PB, Kamdar M, et al. Health-related quality of life with lisocabtagene maraleucel vs standard of care in relapsed or refractory LBCL. *Blood Adv*. 2022;6(23):5969-5979. doi:10.1182/bloodadvances.2022008106
40. Dhawale TM, Johnson PC, Gaballa MR, et al. Perception of prognosis, quality of life, and distress in patients receiving chimeric antigen receptor T-cell therapy. *Cancer*. 2023;129(3):441-449. doi:10.1002/cncr.34557
41. Maillet D, Belin C, Moroni C, et al. Evaluation of mid-term (6–12 months) neurotoxicity in B-cell lymphoma patients treated with CAR T cells: a prospective cohort study. *Neuro-Oncology*. 2021;23(9):1569-1575. doi:10.1093/neuonc/noab077
42. El-Jawahri AR, Vandusen HB, Traeger LN, et al. Quality of life and mood predict posttraumatic stress disorder after hematopoietic stem cell transplantation. *Cancer*. 2016;122(5):806-812. doi:10.1002/cncr.29818
43. Fenech AL, Van Benschoten O, Jagielo AD, et al. Post-traumatic stress symptoms in hematopoietic stem cell transplant recipients. *Transplant Cell Ther*. 2021;27(4):341.e1-341.e6. doi:10.1016/j.jtct.2021.01.011
44. Williams AM, Zent CS, Janelsins MC. What is known and unknown about chemotherapy-related cognitive impairment in patients with haematological malignancies and areas of needed research. *Br J Haematol*. 2016;174(6):835-846. doi:10.1111/bjh.14211
45. Paunescu AC, Copie CB, Malak S, et al. Quality of life of survivors 1 year after the diagnosis of diffuse large B-cell lymphoma: a LYSA study. *Ann Hematol*. 2022;101(2):317-332. doi:10.1007/s00277-021-04689-4
46. Janelsins MC, Mohamed M, Peppone LJ, et al. Longitudinal changes in cognitive function in a nationwide cohort study of patients with lymphoma treated with chemotherapy. *J Natl Cancer Inst*. 2022;114(1):47-59. doi:10.1093/jnci/djab133
47. Országhová Z, Mego M, Chovanec M. Long-term cognitive dysfunction in cancer survivors. *Front Mol Biosci*. 2021;8:770413. doi:10.3389/fmolb.2021.770413
48. Smith SK, Zimmerman S, Williams CS, et al. Post-traumatic stress symptoms in long-term non-Hodgkin's lymphoma survivors: does time heal? *J Clin Oncol*. 2011;29(34):4526-4533. doi:10.1200/JCO.2011.37.2631
49. Mounier N, Anthony S, Busson R, et al. Long-term fatigue in survivors of non-Hodgkin lymphoma: the Lymphoma Study Association SIMONAL cross-sectional study. *Cancer*. 2019;125(13):2291-2299. doi:10.1002/cncr.32040
50. Greaves P, Sarker SJ, Chowdhury K, et al. Fertility and sexual function in long-term survivors of haematological malignancy: using patient-reported outcome measures to assess a neglected area of need in the late effects clinic. *Br J Haematol*. 2014;164(4):526-535. doi:10.1111/bjh.12651
51. Kim IR, Kim SH, Ok ON, et al. Sexual problems in male vs. female non-Hodgkin lymphoma survivors: prevalence, correlates, and associations with health-related quality of life. *Ann Hematol*. 2017;96(5):739-747. doi:10.1007/s00277-017-2940-y
52. Beckjord EB, Arora NK, Bellizzi K, Hamilton AS, Rowland JH. Sexual well-being among survivors of non-Hodgkin lymphoma. *Oncol Nurs Forum*. 2011;38(5):E351-E359. doi:10.1188/11.ONF.E351-E359
53. Tsatsou I, Mystakidou K, Panagou E, Adamakidou T, Vastardi M, Gkovina O. Sexuality and quality of life of patients with hematologic malignancy and hematopoietic stem cell transplantation: a critical review. *J BUON*. 2020;25(4):1693-1706.
54. Seguin L, Touzani R, Bouhnik AD, et al. Deterioration of sexual health in cancer survivors five years after diagnosis: data from the French National Prospective VICAN Survey. *Cancers*. 2020;12(11):3453. doi:10.3390/cancers12113453
55. El-Jawahri A, Fishman SR, Vanderklish J, et al. Pilot study of a multimodal intervention to enhance sexual function in hematopoietic stem cell transplant (HCT) survivors. *Cancer*. 2018;124(11):2438-2446.
56. Obaisi O, Fontillas RC, Patel K, Ngo-Huang A. Rehabilitation needs for patients undergoing CAR T-cell therapy. *Curr Oncol Rep*. 2022;24(6):741-749. doi:10.1007/s11912-022-01240-0
57. Van Vulpen JK, Sweegers MG, Peeters PHM, et al. Moderators of exercise effects on cancer-related fatigue: a meta-analysis of individual patient data. *Med Sci Sports Exerc*. 2020;52(2):303-314. doi:10.1249/MSS.0000000000002154
58. Campbell KL, Zadravec K, Bland KA, Chesley E, Wolf F, Janelsins MC. The effect of exercise on cancer-related cognitive impairment and applications for physical therapy: systematic review of randomized controlled trials. *Phys Ther*. 2020;100(3):523-542. doi:10.1093/ptj/pzz090
59. Amatya B, Khan F, Lew T, Dickinson M. Rehabilitation in patients with lymphoma: an overview of systematic reviews. *J Rehabil Med*. 2021;53(3):jrm00163. doi:10.2340/16501977-2810
60. Amatya B, Dickinson M, Khan F. Factors associated with long-term functional and psychosocial outcomes in patients with non-Hodgkin lymphoma. *J Rehabil Med*. 2023;55:jrm004816. doi:10.2340/jrm.v55.4816
61. Abramson JS, Johnston PB, Kamdar M, et al. Health-related quality of life with lisocabtagene maraleucel vs standard of care in relapsed or refractory LBCL. *Blood Adv*. 2022;6(23):5969-5979. doi:10.1182/bloodadvances.2022008106
62. Gress KL, Charipova K, Kaye AD, Viswanath O, Urits I. An overview of current recommendations and options for the management of cancer pain: a comprehensive review. *Oncol Ther*. 2020;8(2):251-259. doi:10.1007/s40487-020-00128-y