haematologica
Journal of the Ferrata Storti Foundation

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Received: October 19, 2023.
Accepted: February 29, 2024.

Citation: Emmanuelle Tchernonog, Aline Moignet, Amélie Anota, Sophie Bernard, Guy Bouguet, Fanny Colin, Catherine Rioufol, Loïc Ysebaert, and Emmanuel Gyan. Health-related quality of life in patients with hematologic malignancies treated with chimeric antigen receptor T-cell therapy: review and current progress. Haematologica. 2024 Mar 7. doi: 10.3324/haematol.2022.282363 [Epub ahead of print]

Review Article

Health-related quality of life in patients with hematologic malignancies treated with chimeric antigen receptor T-cell therapy: review and current progress

Journal: Haematologica

Running head: HRQoL tools for CAR T-cell therapy

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Data-sharing statement

Relevant primary source scientific publications are cited at the end of this manuscript.

Conflicts of Interest: (Authors by alphabetical order)

Emmanuelle Tchernonog: Honoraria; Gilead/Kite, Janssen, Abbvie, Astrazeneca. Aline Moignet: Gilead/Kite, Amgen, Sanofi. Amélie Anota: Honoraria; Gilead/Kite, BMS, Astra Zeneca, Sandoz, IPSEN, AMGEN. Sophie Bernard: Honoria; Gilead/Kite, Novartis, Incyte, BMS. Fanny Colin: Gilead/Kite. Guy Bouguet: None. Catherine Rioufol: Honoraria; Astellas, Beigene, BMS, Gilead Kite, Janssen, Pfizer, Roche. Loïc Ysebaert: Honoraria; Beigene, Gilead/Kite, Janssen, BMS, Abbvie, Roche, Astra Zeneca. Research funding: BMS, Beigene, Janssen, Roche. Emmanuel Gyan: Honoraria; Gilead/Kite, Sanofi, Janssen, BMS, Abbvie, Astellas, Pfizer,

Recordati, Jazz Pharmaceuticals, Servier, Alexion, Roche, Incyte, Astra Zeneca. Research funding: BMS, Novartis, Sandoz

Word Count: 4,809/5,000 words excluding abstract, tables, figure legends and references. Abstract (246/250 words)

Acknowledgments

The authors thank Julie Nassif, PharmD, and Thomas Rohban, MD, of Partner 4 Health (Paris, France) for providing medical writing support in accordance with Good Publication Practice guidelines. The authors also thank Siham Bibi, PhD, from Kephren (Boulogne-Billancourt, France) for the coordination of the project.

Funding

This Review Article is based on a project led by Gilead Sciences SAS around quality of life & CAR T-cell therapy in which the authors participated. Gilead Sciences SAS funded this Review Article by supporting the coordination of the project and the manuscript writing support as well as the journal publication fees.

Abstract

Chimeric antigen receptor (CAR) T-cell therapy has transformed the care of patients with relapsed/refractory B-cell derived hematologic malignancies. To date, six CAR T-cell therapies, targeting either CD19 or B-cell maturation antigen, have received regulatory approval. Along with the promising survival benefit, CAR T-cell therapy is associated with potentially life-threatening adverse events (AE), including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome. While clinical trials evaluating CAR T-cell therapy consistently report the incidence of these AE, most trials do not collect health-related quality of life (HRQoL) data. As such, the impact of CAR T-cell therapy process and related AE on the physical and psychological well-being of patients remains uncertain. HRQoL and other patient-reported outcome (PRO) assessments in patients with relapsed or refractory hematologic malignancies are of utmost importance, as individuals may have unmet needs and a high demand for tolerable therapy if a cure is not obtained. In addition, it is important to standardize methods of data collection to better assess the impact of CAR T-cell therapy on quality of life, optimize patient care and costs, and enable comparison between different studies. We conducted a literature search up to June 2023 to identify the HRQoL tools used in clinical trials and in real-world studies investigating CAR T-cell therapy in patients with lymphomas or leukemias. In the present comprehensive review, we summarize the most commonly used CAR T-cell specific and non-specific HRQoL tools and discuss how the use of HRQoL and other PRO tools may be optimized.

Introduction

Chimeric antigen receptor (CAR) T-cell therapy has substantially transformed the care of patients with relapsed/refractory B-cell derived hematologic malignancies, including multiple myeloma, leukemias and lymphomas. To date, six CAR T-cell therapies have received regulatory approval: four targeting CD19, axicabtagene ciloleucel (axi-cel), brexucabtagene autoleucel (brexu-cel), lisocabtagene maraleucel (liso-cel), and tisagenlecleucel (tisa-cel); and two targeting B-cell maturation antigen, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel).[1-3] Although CAR T-cell therapy is given with a curative intent, it is associated with potentially life-threatening adverse events (AE), including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).[4] These toxicities result from the supra-physiologic activation of the immune system following CAR T-cell infusion, which leads to the overproduction of inflammatory cytokines, and subsequently to a hyper-inflammatory state.[2,5,6] In addition, long-term AE that may arise after CAR T-cell therapy include an increased risk of infection, neurocognitive deficits, emergence of new or exacerbation of existing autoimmune toxicities, and development of recurrent or second primary malignancies.[2]

While clinical trials evaluating CAR T-cell therapy consistently report the frequency and grades of these unique toxicities, most trials do not collect health-related quality of life (HRQoL) data. In a review assessing the regularity of using HRQoL in ongoing clinical trials, Raymakers and colleagues[7] (2021) examined 424 trials registered at the United States National Institutes of Health National Library of Medicine (http://clinicaltrials.gov) investigating CAR T-cell therapy in oncology. HRQoL was a primary or secondary objective in only 29 studies (6.8%),

highlighting the current lack of adequate assessment of quality of life (QoL) in patients treated with CAR T-cell therapy.[7]

HRQoL tools assess the impact of treatment-specific AE on mental, emotional, social, and physical functions. Hence, due to the under-evaluation of HRQoL data, the impact of CAR T-cell therapy process and related AE on the physical and psychological well-being of patients remains uncertain.[6-8] Monitoring HRQoL following CAR T-cell therapy is important to aid patients through their recovery process. Indeed, it is anticipated that patients may regain function faster, feel more involved in their management plan, identify and control their symptoms via personalized interventions/actions, and utilize medical resources less frequently (i.e., shorter hospitalization duration, fewer emergency room visits).[6] Moreover, other patient-reported outcomes (PRO), which promote patients' empowerment, have not been integrated into treatment guidelines.[5,9] HRQoL and other PRO assessments in patients with relapsed or refractory hematologic malignancies are however paramount, as individuals may have unmet needs and a high demand for tolerable therapy if cure is not obtained.[8] It is also crucial to standardize data collection methods, including the choice of the questionnaire, measurement time, and statistical analysis, to better assess the impact of treatment on QoL, optimize patient care and costs, and enable comparison between studies.[10] In this context, we conducted a PubMed search to identify the HRQoL tools used in clinical trials and real-world studies investigating CAR T-cell therapy in patients with lymphomas or leukemias. In the present comprehensive review, we summarize our findings regarding the existing HRQoL tools and discuss how the use of HRQoL and other PRO tools may be optimized.

Methods

We conducted a comprehensive literature search on PubMed up to July 2023 to identify the PRO tools used in clinical trials and real-world studies evaluating CAR T-cell anti-CD19 therapy in patients with B-cell lymphomas or leukemias. The following keywords were used ((CAR T-cell OR CAR-T) OR axicabtagene OR brexucabtagene OR lisocabtagene OR tisagenlecleucel) AND (haematolog* OR hematolog* OR lymphoma OR leukemia OR leukaemia) AND ("quality of life" OR "patient-reported outcomes" OR HRQoL OR PRO OR PROs OR QoL), and no filters were applied. This PubMed search was complemented with a hand search of references of relevant reviews and systematic reviews.

Selected papers were restricted to those published in English and reporting studies evaluating QoL in patients with lymphomas/leukemias and receiving CAR T-cell anti-CD19 therapy. Interventional studies – single arm or randomized controlled trials (RCTs) – real-world studies, and qualitative studies were included. Studies evaluating CAR T-cell therapy not targeting CD19 in patients with multiple myeloma, other hematologic cancers or with solid tumors were excluded. Publications reporting only the efficacy and safety results of studies were also excluded.

The PubMed search retrieved 264 publications (Supplemental Figure S1). Our hand search yielded 5 additional relevant publications (including one paper published after the search cut-off date). A total of 27 publications were selected, reporting data on a total of 25 studies: one validation study for a CAR-T cell specific tool, eight single-arm studies, two RCTs, 10 real-world studies, and four quantitative studies.

Scales to assess HRQoL in CAR T-cell studies: where do we stand?

CAR T-cell anti-CD19 therapy is usually administered in one single infusion. However, this treatment involves multiple phases prior to the infusion and rigorous monitoring of acute and long-term AE afterwards (Figure 1).[2,11,12] Since CRS and ICANS develop within a few days of CAR T-cell infusion, either concomitantly or consecutively, it is suggested that HRQoL be evaluated before conditioning chemotherapy, once weekly or more frequently (twice or thrice) for the first two weeks after CAR T-cell infusion, and weekly for up to one month post-infusion.[2,13] Early assessment of PRO data may aid in the identification of early toxicities related to CAR T-cell therapy such as CRS and ICANS and their impact on patient's QoL.[9] Following this early phase, PRO collected monthly for the first year and then yearly are necessary for monitoring the long-term impact of CAR T-cell therapy and its associated AE and organizational burden on HRQoL.[2,9]

Several tools have been used in studies reporting HRQoL after CAR T-cell anti-CD19 therapy. Some of them assessed various domains in patients with cancer, regardless of cancer type, and others were disease-specific (e.g., lymphoma) or domain/symptom-specific (e.g., depression). However, the vast majority of the tools used were non-specific to CAR T-cell therapy. In a systematic review, the European Quality of Life Five Dimension (EQ-5D), which is a standard scale for medico-economic evaluations, was the most commonly collected tool, measured in 65% of studies assessing HRQoL in patients with cancer treated with CAR T-cell therapy.[7] It is noteworthy to mention that the EQ-5D is a non-cancer specific scale that may also be used for other diseases or in healthy individuals (e.g., universities). Several forms of this questionnaire

exist and constitute of either three or five levels that allow the estimation of an EQ-5D index score and a visual analog scale (VAS) score.[14] Of the cancer-specific scales, the most frequently used were the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30), the Functional Assessment of Cancer Therapy-General (FACT-G) and FACT-Lym that is specific for lymphoma. The main shortcoming of the generic and cancer-specific PRO is that they may generate misleading results for patients receiving CAR T-cell products, due to the complexity of this therapy and the uniqueness of its toxicities.[6,15] In addition, some PRO models assess the decline or improvement in HRQoL parameters using scores of general rather than specific populations, i.e., patients with the same cancer type.[9] Such an approach may jeopardize the robustness of the results and their generalizability to clinical practice settings.[9]

To address the short-comings of the generic and cancer-specific tools, Wang and colleagues[13] recently reported the validation of the first CAR T-cell specific HRQoL assessment tool for use in hematologic malignancies, the MD Anderson Symptom Inventory (MDASI)-CAR module. The MDASI-CAR was developed according to guidance from the Food and Drug Administration. The MDASI-CAR tool consists of 29 items divided between 13 core and six interference items that constitute the general MDASI tool[16] and 10 module items that are specific to CAR T-cell therapy (Figure 2).[13] Some limitations to the development of this CAR-T cell specific tool are to be considered. Indeed, only 21 patients were included in the initial qualitative study that was used to generate the list of module items.[15] Moreover, the validation study was conducted in a single institution, and included a limited number of patients (n=78). Furthermore, the majority of patients (68/78; 87.2%) were receiving one specific CAR T-cell product (axi-cel).

The generalizability of the MDASI-CAR tool among patients with various hematologic malignancies and on different CAR T-cell therapies may be better assessed with larger multicenter longitudinal studies.[13] This tool can be useful in assessing the impact of CAR T-cell therapy on the QoL of patients in the early phase after receiving the CAR T-cell infusion, and may be less effective in capturing disease-related QoL.

Table 1 presents the most frequently used non-CAR T-cell specific PRO/HRQoL tools in clinical studies assessing QoL in adults who received CAR T-cell therapy targeting CD19, and the specific MDASI-CAR tool. Of the non-specific tools, the EORTC QLQ-C30, a cancer-specific tool, and FACT-Lym evaluate many of the functions/symptoms that are assessed in the MDASI-CAR. The FACT-Lym is composed of the FACT-G and an additional lymphoma-specific subscale. Both EORTC QLQ-C30 and FACT-Lym cover cognitive, emotional, physical, and social/role functioning as well as part of the individual symptoms/items (fatigue, pain, disturbed sleep, lack of appetite, and nausea).

Other tools used in the identified clinical studies enrolling adult patients included those that are specific to one function or one symptom, such as Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH); revised Edmonton Symptom Assessment Scale (ESAS[17]; assessing 9 symptoms); Hospital Anxiety and Depression Scale (HADS); and Post□Traumatic Stress Checklist (PCL).[18-20] In addition, the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) has been used for AE reporting in adult patients receiving CAR T-cell therapy.[21]

In the two retrieved pediatric studies, the Pediatric Quality of Life Inventory (PedsQL) (generic tool and cancer-specific tool dedicated to children), the EQ-5D and the Memorial Symptom Assessment Scale (cancer-specific) were used to assess the HRQoL of pediatric patients.[22,23] Different versions of the scales were filled by the different age groups, and some required a parent proxy.[22,23] Of note, even though not used in the selected studies, it is important to highlight that there exists a validated pediatric version of the PRO-CTCAE tool.[24]

HRQoL scales reported in Single-Arm CAR T-cell studies

We retrieved a total of seven single-arm studies assessing HRQoL in patients who received CAR T-cell anti-CD19 therapy for relapsed or refractory lymphoma/leukemia through our PubMed search.[22,25-30] One additional study, the PILOT study, was published after the search cut-off date and is added to Table 2.[31] All retrieved studies were performed in adult patients, except one study, ELIANA,[22] a multinational, multicenter, open-label, Phase 2 trial that enrolled patients aged 3 to 23 years who received tisa-cel (Table 2).

In the studies that assessed QoL in adult patients receiving CAR T-cell therapy at different timepoints, an anticipated initial decline in HRQoL was observed between 2 and 4 weeks after the CAR T-cell infusion, followed by improvements at later timepoints.[25,27,29-31] Patients reported improvement in several or all domains of HRQoL scales, reaching baseline levels or better levels at a few months post-infusion. One of the studies observed that younger patients experienced worse mental problems, anxiety, and depression compared with elderly patients receiving CAR T-cell therapy.[28] Results of the JULIET study,[26] showed that patients who responded to tisa-cel treatment reported a clinically meaningful improvement in all FACT subscales and in more than

half of the SF-36 subscales (such as general QoL, physical, and social functioning) across all timepoints.[26] A similar finding was reported in TRANSCEND NHL 001,[27] in which, at 1 month after infusion, a higher proportion of patients who responded to liso-cel had an improvement in EORTC QLQ-C30 global health status/QoL, fatigue, physical function, pain, and the EQ-5D-5L index, in comparison with those who did not respond.[27]

In the ELIANA study,[22] reporting HRQoL data for pediatrics, improvements in HRQoL were observed starting 28 days post-infusion, and reached a clinically meaningful phase at 3 months post-infusion. Improvements were observed for all measures at 3 months after tisa-cel with a mean change from enrollment of 13.3 (95% CI, 8.9 to 17.6) and 16.8 (95% CI, 9.4 to 24.3) for the PedsQL total score and EQ-5D VAS, respectively (Figure 3).[22] The clinical improvement was sustained at later timepoints up to 36 months post-infusion.[32]

HR-QoL scales reported in Randomized Controlled Trials with autologous SCT as SoC

According to our search, only two RCTs, TRANSFORM and ZUMA-7, evaluating the impact of CAR T-cell therapy on HRQoL compared to standard of care (SoC) have been published.[18,33,34] Both were Phase 3, open-label, pivotal studies conducted in adults with relapsed or refractory large B-cell lymphoma as second-line therapy (Table 3).[18,33] One additional randomized Phase 3 study (BELINDA), whose HRQoL results are not published yet, included the assessment of HRQoL via Short Form-36 (SF-36; generic tool), FACT-Lym, and EQ-VAS as secondary outcome measures in patients with refractory or relapsed B-cell lymphoma receiving either tisa-cel or standard therapy (Clinicaltrials.gov, NCT03570892).

In TRANSFORM,[33] the impact of liso-cel on HRQoL was compared to that of SoC using the EORTC QLQ-C30 and the FACT-G additional lymphoma-specific subscale (FACT-LymS) questionnaires at the timepoints specified in Table 3. Of the 184 patients constituting the intent-to-treat population, the EORTC QLQ-C30 analysis set included 90 patients (48.9%) and the FACT-LymS analysis set included 85 patients (46.2%). The low percentage of patients constituting each analysis set is attributed to the low completion rates at several timepoints starting from baseline; a total of 87 patients, 44 in the liso-cel group and 43 in the SoC group, failed to complete the EORTC QLQ-C30 assessment at baseline, and 46 patients in each group failed to complete the FACT-LymS assessment at baseline (Supplemental Figure S2). The reasons for low completion rates at baseline were related mainly to the challenges associated with telemedicine during the COVID-19 pandemic, while low rates observed later were related to other events, such as crossing over from the SoC to the liso-cel group and initiating other antineoplastic agents. Results showed that patients who received liso-cel had clinically better scores in the EORTC QLQ-C30 global health status/QoL, cognitive function and fatigue domains, than those who received SoC (Supplemental Figure S3). However, a higher deterioration was observed for the emotional domain of EORTC QLQ-C30 with liso-cel compared to SoC.[33]

In ZUMA-7,[18] EORTC QLQ-C30, EQ-5D-5L, and WPAI:GH (work and activity specific tool) version 2.0 were assessed at the timepoints specified in Table 3. Only patients who were employed at baseline were requested to fill the questions related to employment in WPAI:GH V2.0. Of the 359 patients constituting the full analysis set, 296 (82.5%) were included in the QoL

analysis set. The number of patients completing the HRQoL assessment dropped substantially over time, especially with SoC (Supplemental Figure S2). This drop was attributed to the occurrence of events (i.e., progression, death) that excludes patients from the QoL analysis set, rather than to a compliance issue. Compliance rates remained greater than 85% and 83% through 9 and 15 months post-infusion, respectively. Results showed that patients reported an initial deterioration in HRQoL outcomes, at 50 days post-infusion, followed by an improvement at later time points. At 100 days post-infusion, patients who received axi-cel had statistically significantly better scores of the EQ-5D-5L VAS, EORTC QLQ-C30 global health status/QoL and physical function domain compared to those who received SoC (Supplemental Figure S3).[18]

HRQoL also evaluated in Real-World CAR T Studies

A total of 10 real-world studies were retrieved through our PubMed search, nine of which reported PRO in adults[6,19-21,35-39] and one in the pediatric population[23] (Table 4).

Only one of the retrieved studies compared CAR T-cell therapy to other modalities of treatment in adult patients with hematologic malignancies.[21] The main objective of this study was to assess the HRQoL of patients receiving CAR T-cell therapy or stem cell transplant (SCT) (autologous or allogeneic) via the FACT-G, a cancer-specific tool (primary endpoint). Over a 6-month duration, a total of 104 patients reported data on HRQoL and symptom burden during treatment. In the CAR T group (n=34), PRO completion rates decreased from 100% at baseline to 44% at 6 months post-infusion, mainly due to early study exit caused by disease progression/death/change in therapy (41%). Of note, 20% of patients decided not to complete the PRO at certain timepoints and 38% of patients reported QoL data for all timepoints. Results showed a deterioration in HRQoL during the first two weeks and an increase in the frequency and severity of AE, followed

by improvement at later timepoints in all groups. However, the decline was lower, and the improvement was faster with CAR T-cell therapy than with SCT, especially for overall QoL, and physical and functional well-being.[21] Other real-world studies reported the same trends including an initial deterioration in HRQoL followed by improvement at around 3 months of CAR T-cell therapy.[6,20,36,39] Interestingly, in their longitudinal study, Johnson and colleagues[20] identified worse pre-CAR T Eastern Cooperative Oncology Group (ECOG) performance status as a factor associated with lower pre-CAR T QoL, and identified worse pre-CAR T ECOG performance status, receipt of tocilizumab and receipt of corticosteroids for CAR T toxicities as factors associated with an improved longitudinal QoL trajectory. According to the authors, it is conceivable that more aggressive management of CRS and/or ICANS leads to improved longitudinal QoL trajectory over time.[20] Ward and colleagues[23] assessed HRQoL in a total of 140 pediatric patients who received treatment for hematologic malignancies (CAR T-cell or SCT). Although only 23 patients (16.4%) received CAR T-cell therapy, the value of this study in our review is that it evaluated the association between parents' psychological well-being and their children's HRQoL and symptoms. Results showed that parents suffer psychologically along with their children, and parental distress was associated with decreased child HRQoL and higher symptom burden. Moreover, a relatively high proportion of parents reported suicidal ideation at all collection timepoints.[23]

While most single-arm studies and the RCTs did not collect PRO data during the first two weeks, Oswald and colleagues[38] incorporated PRO as early as the first day post-CAR T-cell infusion and daily for the first week, followed by weekly for the first month and monthly thereafter for up to 3 months post-infusion. The study included 12 patients and several PRO, each to be filled at

certain timepoints. As such, the total PRO assessments mounted to 168 for the whole study population and duration, of which 143 were completed (completion rate, 85.1%). As anticipated, the most severe symptoms were reported within the first 14 days after CAR T-cell therapy, and a deterioration in several aspects of QoL was observed during the first month. In comparison to patients with progressive disease, the authors observed that patients who responded to CAR T-cell treatment suffered more toxicities.[38] Of note, the main limitations of this study, as well as several other real-world studies, are their limited sample size and their conduct in single institutions.

Health-Related Quality of Life in Qualitative Studies

Qualitative studies based on semi-structured interviews and focus group discussions are important to gain deeper insight into the perspectives of patients receiving CAR T-cell therapy on their treatment expectations and to better characterize symptom burden.[2] Patient perspectives obtained from qualitative studies may help determine the main QoL aspects affected most by CAR T-cell therapy, and as such may aid in the development of CAR T-cell specific QoL tools.

Based on our PubMed search, we identified four qualitative studies assessing HRQoL in patients who received CAR T-cell therapy.[5,15,40,41] In the first qualitative study[15], a total of 21 patients who received CAR T-cell anti-CD19 therapy for B-cell lymphomas were interviewed up to 12 months post-infusion (13 patients within the first 3 months; 3 patients between 3 and 6 months; and 5 patients between 6 and 12 months). The patients reported the following as the most common symptoms associated with treatment: fatigue, lack of appetite, headache, chills/cold, and confusion.[15] This qualitative study was useful in generating a CAR T-cell specific tool, the

MDASI-CAR which was later validated by Wang and colleagues[13] (2023). The second study included a literature review and two focus groups among a total of 18 patients.[5] The literature search identified several PRO that were used in studies enrolling patients with diffuse large B-cell lymphoma who received CAR T-cell therapy, and the focus groups assessed the appropriateness of the functions/symptoms covered by these PRO. A total of eight domains were considered as the most affected by CAR T-cell therapy and included pain/discomfort, fatigue, sleep, and the following functions: social, emotional, physical, cognitive, and role.[5] The third study recruited 40 patients with hematologic malignancies, 15 caregivers, and 15 clinicians specialized in CAR T-cell therapy to aid in the development of PRO specific to CAR T-cell therapy.[40] Similar findings to those reported by the aforementioned studies[5,15] were observed. The cognitive, social, and emotional functioning were considered affected by CAR T-cell therapy, with patients reporting fatigue, pain, bothersome gastrointestinal symptoms, and limited physical function.[40] Likewise, the fourth qualitative study, which aimed to improve the services associated with CAR T-cell therapy, found that fatigue, pain, loss of appetite, and cognitive problems were reported by 10 patients receiving CAR T-cell therapy and four of their caregivers.[41]

What have we learned from the current PRO tools and their use?

To date, the most frequently used HRQoL tools are generic or cancer-specific that may not fully capture the effect of CAR T-cell therapy process and its AE on QoL of recipients. Patients who receive CAR T-cell therapy are required to reside within a 30-minute to 2-hour drive from the specialized treating center and are not allowed to drive for 8 weeks after receiving the CAR T-cell product.[1] In addition, patients are sometimes in need of a caregiver for around a month post-

therapy.[1] All these constraints would affect the patient's psychological status and subsequently their QoL. Only one CAR T-cell specific tool has been developed which still carries some limitations and needs further validation in larger studies. Even though a CAR T-cell specific tool could adequately assess the impact of this therapy on the HRQoL of patients, cancer-specific PRO might be more suitable for identifying the impact of the disease on QoL.

In this review, the studies identified may have not used the most optimal tool or at the most optimal frequency. The vast majority of studies did not administer the PRO tools during the first two weeks post-CAR T-cell infusion. This timeframe is crucial for the patient since it is a time of hospitalization and constant monitoring for CAR T-cell therapy specific short-term toxicities. Only one study, reported by Oswald and colleagues[38] incorporated PRO as early as the first day post-infusion; however, this study had a limited sample size and thus no solid conclusions may be drawn. Another pitfall in the use of PRO in patients having CAR-T therapy may be related to the design of HRQoL evaluation leading to low completion rates. These low rates, as observed in the RCTs, have been attributed to the exclusion of patients who progressed / initiated other antineoplastic agents after CAR T-cell therapy or SCT and who were considered not eligible to complete the PRO rather than to patient compliance. Although it is difficult and ethically debatable, we believe that the assessment of QoL in patients who do not respond to CAR-T therapy is as equally important as of those who respond, to capture the impact of the disease *per se*. A single-arm study, TRANSCEND NHL 001,[27] showed that a higher percentage of responders to CAR T-cell therapy, at 1 month after infusion, reported an improvement in QoL parameters in comparison with those who did not respond. On the other hand, the two studies that enrolled pediatric patients administered pediatric versions of the PRO that correspond to

each patient's age.[22,23] This draws attention to the necessity of several versions of the same PRO, whether generic, cancer-specific or CAR T-cell specific, to accommodate all patients' ages and needs. Similarly, regardless of age, the availability of the tool in different languages should be encouraged as it allows patients from different populations to complete these PRO, thereby fulfilling any current unmet need. Furthermore, assessing the QoL of caregivers have not received as much attention as it should. For hematologic malignancies, especially in pediatric population, caregivers play an important role in the patient's treatment journey. As such, the assessment of their QoL may be informative and beneficial for themselves and subsequently their patients. When the caregiver is a parent, the associated emotional and psychological burden might be detrimental. In one of the real-word studies,[23] a strikingly high percentage of parents reported having suicidal ideation when caring for their children who received treatment for their hematologic malignancy.

Perspectives

While CAR T-cell therapy is an innovative treatment with promising survival benefits in patients with advanced hematologic malignancies, its administration is associated with multiple challenges including the complex procedure of manufacturing CAR T-cells, the demanding journey that the patient must go through, and the specific side effects (e.g., CRS and ICANS).[1-3] For the aforementioned reasons, the assessment of HRQoL in patients receiving CAR T-cell therapy is of major relevance.[8] PRO are valuable means for patients to report HRQoL as well as symptom burden and treatment toxicities.[22,37] In addition, it is important to assess the indirect effect of cancer treatment on caregivers who may be overwhelmed by the processes related to any cancer treatment including CAR T-cell therapy.[23,42]

As for the time of PRO assessment, given that the majority of CRS and neurotoxicity events, which may affect patients' HRQoL, develop early after CAR T-cell infusion (median onset of CRS, 2 to 5 days; neurotoxicity, 6 to 9 days), it is paramount to incorporate frequent monitoring during the first two weeks post-infusion, preferably several times weekly. [2,13,25,29,30,43,44] Although early frequent reporting of PRO would better capture the early deterioration in HRQoL, subsequent less frequent monitoring, up to the first year post CAR T-cell therapy, might be helpful in identifying other long-term toxicities and AE.[2] Nevertheless, frequent assessment of PRO, especially in the first few months after CAR T-cell therapy, might be logistically challenging. Thus, to increase patient compliance in completing PRO on a regular basis, electronic PRO assessments are encouraged.[45] Other than the logistical challenge, patients with grade ≥2 ICANS may find it difficult to complete PRO questionnaires,[13] therefore, proxy HRQoL data would be considered as an option.

Several HRQoL questionnaires have been used in both clinical trials and real-world studies of CAR T-cell therapy, the vast majority of which are not CAR T-cell specific. Recently, one PRO tool specific to CAR T-cell therapy, the MDASI-CAR, has been developed and validated.[13] Even though some of the non-specific tools, namely the EORTC QLQ-C30 and FACT-Lym, cover many elements of the MDASI-CAR tool, they fail to assess many of the module symptoms. The ability of such a specific tool to capture most functions and symptoms that are considered relevant to CAR T-cell therapy makes it a valuable tool for clinical use in the early phase after CAR T-cell infusion. At later timepoints, a disease-specific tool may be more suitable to assess the HRQoL aspects affected by the disease itself. Indeed, there is a value in monitoring the QoL

of non-responders to CAR T-cell therapy as well as those who respond. A cancer-specific PRO might be a better option for non-responders rather than excluding these patients from QoL assessment, and studies may conduct different analyses for each group of patients. Despite these considerations, the generalizability of MDASI-CAR to all patients with hematologic malignancies receiving this treatment and to all clinically available CAR T-cell agents still needs assessment in larger multicenter studies.[13] In addition, the MDASI-CAR tool might be suitable for use in comparative studies where only CAR T-cell agents are being compared to each other.

In this respect, there is still a call to pursue the development of optimal specific tools, whether capitalizing on the MDASI-CAR or considering other tools that will address the uniqueness of CAR T-cell therapy and the limitations of MDASI-CAR. An optimal PRO scoring would balance the need to assess all functional domains, disease-specific and CAR T-cell therapy-specific symptoms, and financial burden on one hand, and patients' capacities and logistics on the other hand. To that end, several requirements should be fulfilled, including in-depth learning from existing findings, multidisciplinary professionals' involvement, patients' and caregivers' engagement, and rigorous validation in multicenter studies enrolling an appropriate sample of patients/caregivers that should account for the decline in the eligible individuals in the long-term HRQoL evaluation.[6]

Conclusions

Altogether, regular PRO assessments are crucial for patients receiving CAR T-cell therapy for hematologic malignancies. The MDASI-CAR tool opened the avenue towards the creation of optimal tools to capture the impact of CAR T-cell therapy on HRQoL on the short term, and to

complement the disease-specific tools which remain valid, especially for mid and long term QoL evaluation. Future work should also continue to explore factors associated with QoL following CAR T-cell therapy, as these findings can guide shared decision-making between clinicians and patients as well as identify at-risk patients who may benefit from supportive care interventions aimed to decrease symptom burden during treatment. Finally, valid and reliable PRO should be integrated in clinical guidelines, as they may play a major role in improving the well-being and treatment outcomes for patients receiving CAR T-cell therapy.

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Table 1. Most frequently used non-specific health-related quality of life tools and the specific MDASI CAR tool, in CAR T-cell targeting CD19 therapy clinical studies enrolling adults

	CAR T-cell oriented scale	Generic scales			Cancer specific scales		Lymphoma specific scale
Functions/ Symptoms*	**MDASI-CAR items[13]**	**EQ-5D[46]**	**SF-36[26]**	**PROMIS-29[47]**	**EORTC QLQ-C30 version 3.0[48]**	**FACT-G[49]**	**FACT□Lym[50]**
Cognitive functioning (Memory; Concentrating [paying attention], Difficulty speaking)	Y	N	Y	N	Y	Y	Y
Emotional functioning (Sadness, Mood, Distress)	Y	Y	Y	Y	Y	Y	Y
Physical functioning (Balance/falling, Walking)	Y	Y	Y	Y	Y	Y	Y
Social/role functioning (General activity, Enjoyment of life, Relations with others, Work)	Y	Y	Y	Y	Y	Y	Y
Sexual functioning	Y	N	N	N	N	Y	Y
Financial difficulties	N	N	N	N	Y	N	N
Constipation	N	N	N	N	Y	N	N
Coughing	Y	N	N	N	N	N	N
Diarrhea	Y	N	N	N	Y	N	N
Disturbed sleep	Y	N	N	Y	Y	Y	Y
Dizziness	Y	N	N	N	N	N	N
Drowsiness	Y	N	N	N	N	N	N
Dry mouth	Y	N	N	N	N	N	N
Fatigue	Y	N	Y	Y	Y	Y	Y
Fever/chills	Y	N	N	N	N	N	Y
Headache	Y	N	N	Y	N	N	N
Infections	N	N	N	N	N	N	Y
Itching	N	N	N	N	N	N	Y

	CAR T-cell oriented scale	Generic scales			Cancer specific scales		Lymphoma specific scale
Functions/ Symptoms*	**MDASI-CAR items[13]**	**EQ-5D[46]**	**SF-36[26]**	**PROMIS-29[47]**	**EORTC QLQ-C30 version 3.0[48]**	**FACT-G[49]**	**FACT□Lym[50]**
Lack of appetite	Y	N	N	N	Y	N	Y
Lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	N	N	N	N	N	N	Y
Nausea/Vomiting	Y	N	N	N	Y	Y	Y
Night sweats	N	N	N	N	N	N	Y
Numbness	Y	N	N	N	N	N	N
Pain	Y	Y	Y	Y	Y	Y	Y
Shortness of breath	Y	N	N	N	Y	N	N
Tremors	Y	N	N	N	N	N	N
Weight loss	N	N	N	N	N	N	Y

Y, yes assessed; N, not assessed.

Abbreviations: CAR, chimeric antigen receptor; CD, cluster of differentiation; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EQ-5D, European Quality of Life Five Dimension; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; MDASI-CAR, MD Anderson Symptom Inventory-chimeric antigen receptor, PROMIS, Patient-Reported Outcomes Measurement Information System; SF-36, Short Form-36.

*Only domains are written in bold.

Table 2. Single-arm clinical studies evaluating health-related quality of life after CAR T-cell anti-CD19 therapy

Study ID (reference)	CAR T-cell therapy	Patient population*	PRO/HRQoL tool	Reported PRO/HRQoL assessment timepoints	PRO completion rate# and/or results
Phase 1[** 25]	Bispecific LV20.19	N=15 Relapsed or refractory B-cell NHL or CLL/SLL Median age: 61 years (range, 38 to 72) Race reported in parent study (n=22): European ancestry (n=19, 86.4%); Others (n=3, 13.6)	BPI FSI IDAS PSQI	15 days before infusion Post-infusion: Days 14, 28, and 90	• Completion rate was 15/15 (100%) before the infusion and remained high at 13/15 (87%) on Day 90. • Higher rates of depression (IDAS) were observed on Days 14 and 28 versus Day 90. Of note, depression values were maintained below the cut-off values for depressive disorders. • No statistically significant differences in scores between the different timepoints were observed regarding other symptoms (anxiety [IDAS], fatigue [FSI], pain [BPI], and sleep [PSQI]).
Phase 1/2 study[28]	Liso-cel	N=52 Relapsed or refractory NHL, CLL or ALL Median age at questionnaire completion: 57 years (range, 26 to 76) Race: White (n=33, 82.5%); Asian (n=3; 7.5%); Others (n=2, 5%); Unknown (n=2, 5%)	PROMIS Scale v1.2 Global Health PROMIS-29 v2.1 30 additional questions†	Post-infusion: 1 to 5 years	• 40 out of 52 patients who were sent the questionnaire provided QoL data, yielding a response rate of 76.9%. • Among the 40 patients, 19 (47.5%) reported at least one of the following: clinically meaningful (5-point difference in T score) anxiety and/or depression, and/or cognitive impairment. • No difference was observed for the remaining domains in comparison with the US general population.
JULIET[26,44] (Phase 2)	Tisa-cel	N=115 Relapsed or refractory DLBCL Median age: 56 years (range, 22 to 76) Race not reported	FACT-Lym SF-36 Version 2	Baseline (screening phase) Post-infusion: Months 3, 6, 12, and 18	• Completion rate decreased from 108/115 (94%) at baseline to 22/34 (65%) at Month 18. • Of the 108 patients with HRQoL assessments at baseline, 57 experienced complete or partial response. Patients who responded to tisa-cel reported a clinically meaningful improvement in all FACT subscales and in more than half of the SF-36 subscales (such as general QoL, physical, and social functioning) across all timepoints. • MCID was 6.5 to 11.2 points for the total FACT-Lym score and ranged between 2 and 4 points for the different SF-36 domains.

Study ID (reference)	CAR T-cell therapy	Patient population*	PRO/HRQoL tool	Reported PRO/HRQoL assessment timepoints	PRO completion rate# and/or results
ZUMA-2[30] (Phase 2)	Brexu-cel	N=68 Relapsed or refractory mantle-cell lymphoma Median age: 65 years (range, 38 to 79) Race not reported	EQ-5D-5L	Baseline (screening phase), Week 4, Months 3 and 6	• Completion rate decreased from 65/68 (96%) at screening to 42/68 (62%) at Month 6. • There was an initial decline in HRQoL at Week 4 as observed by almost all the EQ-5D-5L scores, followed by an increase in the scores of overall health, mobility, self-care, and daily activities starting Month 3. • By Month 6, most patients reported a similar HRQoL or better than baseline.
ZUMA-3[29] (Phase 2)	Brexu-cel	N=55 Relapsed or refractory B-precursor ALL Median age of treated patients: 40 years (range, 28 to 52) Race White (n=37, 67%); Asian (n=3, 5%); Others (n=11, 20%); Missing (n=4, 7%)	EQ-5D-5L	Baseline (screening phase) Post-infusion: Day 28, Months 3, 6, 9, and 12	• Completion rate decreased from 39/49 (80%) at Day 28 to 14/31 (45%) at Month 12. • By Day 28, there was an initial decline in mobility, self-care, and daily activities in the EQ-5D-5L VAS compared to baseline, followed by a recovery to or improvement over baseline. • A higher percentage of patients had scores above those recorded at baseline, starting Month 3 (anxiety or depression, daily activities, and self-care) until Month 12 (all domains). • 70% or more of patients had either stable or improved EQ-5D-5L VAS scores after brexu-cel administration (79% at Day 28; 92% at Month 3; 80% at Month 6; 70% at Month 9; and 93% Month 12) – MCID was 7 points for EQ-5D-5L VAS
TRANSCEND NHL 001[27,43] (Phase 1)	Liso-cel	N=269 amended to 199†† Relapsed or refractory LBCL Median age: 63 years for patients completing each tool. EORTC QLQ-C30 Race/Ethnicity: Majority were White (n=155, 86%) and Not Hispanic/Latino (n=153, 85%) EQ-5D-5L Version 2.1	EORTC QLQ-C30 EQ-5D-5L Version 2.1	Before infusion Baseline Post-infusion: Day 29, Months 2, 3, 6, 9, 12, 18, and 24	• EORTC QLQ-C30 completion rate declined from 160/181 (88%) at Month 1 to 25/36 (69%) at Month 18. • EQ-5D-5L completion rate decreased from 165/186 (89%) at Month 1 to 25/38 (66%) at Month 18. • An initial decline in HRQoL was observed at Month 1, followed by an improvement in EORTC QLQ-C30 global health status/QoL, fatigue, EQ-5D-5L index, and VAS scores as early as Month 2 and up to Month 18. • A higher percentage of patients who responded to liso-cel treatment reported an improvement in EORTC QLQ-C30 global health status/QoL, fatigue, physical function, pain, and EQ-5D-5L index in comparison with those who did not respond.

Study ID (reference)	CAR T-cell therapy	Patient population*	PRO/HRQoL tool	Reported PRO/HRQoL assessment timepoints	PRO completion rate# and/or results
		Race/Ethnicity: Majority were White (n=158, 85%) and Not Hispanic/Latino (n=157, 84%).			• MID for EORTC QLQ-C30 was 10-point change from baseline, and that of EQ-5D-5L was 0.07-points.
PILOT[31] (Phase 2)	Liso-cel	N=61 Relapsed or refractory LBCL Median age for the EORTC QLQ-C30 evaluable population: 74 years (range, 53 to 84) Race for the EORTC QLQ-C30 evaluable (N=56): White (n=50, 89%); Others (n=2, 3.6%); Missing (n=4, 7%) Ethnicity for the EORTC QLQ-C30 evaluable (N=56): Not Hispanic or Latino (n=49, 87.5%); Missing (n=7, 12.5%)	EORTC QLQ-C30 FACT-LymS EQ-5D-5L	Baseline (screening), before treatment (≤7 days before lymphodepletion), Day 1 (prior to liso-cel infusion), Post-infusion: Days 29, 60, 90, 180, 270, 365, 545, and 730, and at disease progression	• Patients evaluable for HRQoL were: 56/61 (92%) for EORTC QLQ-C30, 49/61 (80%) for FACT-LymS, 55/61 (90%) for EQ-5D-5L index, and 54/61 (89%) for EQ-5D VAS • At baseline, 57/61 patients (93%) completed EORTC QLQ-C30, 50 (82%) FACT-LymS, 56 (92%) EQ-5D-5L index and 55 (90%) EQ-5D VAS. • At later time points completion rates were 83% to 89% at Day 60, 84% to 87% at Day 180, and 81% to 91% at Day 365. • The decrease in completion rate was mainly due to death or inadequate follow-up time. • At baseline, fatigue, social functioning, and appetite loss domains, were clinically meaningfully worse than the general populations. • An initial deterioration was observed at Day 1 or Day 29 in most domains, followed by improvement. • Clinically meaningful deterioration from baseline was observed at Day 1 for role functioning of the EORTC QLQ-C30; and clinically meaningful improvement was observed for fatigue at most post-treatment visits, for the global health status/QoL at Days 60 and 180, and for pain at Day 29. • Clinically meaningful improvement from baseline was achieved across most post-treatment visits for FACT-LymS and at Days 60 and 180 for EQ-VAS. • Through Day 545, significant improvements from baseline were observed for EORTC QLQ-C30 fatigue, pain, and appetite loss, FACT-LymS, and EQ-VAS. • MID for within-group changes: For EORTC QLQ-C30 domains, two MID threshold sets were used - the 10-point change from baseline and those proposed by Cocks

Study ID (reference)	CAR T-cell therapy	Patient population*	PRO/HRQoL tool	Reported PRO/HRQoL assessment timepoints	PRO completion rate# and/or results
					and colleagues[51] 2012 (MID for improvements/deteriorations, < 10 / > -14; ≥ 10 / ≤ -14). • MIDs were 3-point change from baseline for FACT-LymS and 0.08 points for EQ-5D-5L index and 7 points for EQ-VAS.
ELIANA[22] (Phase 2)	Tisa-cel	N=48 Relapsed or refractory B-cell ALL Median age: 14 years (IQR, 10 to 17.5) Race: White (n=38, 79%); Other (n=10, 21%)	PedsQL Version 4.0 (children's version for ages 8 to 12 years, teen's version for 13 to 17 years, and adults' version for ≥18 years) EQ-5D questionnaires (EQ-5D-Y, youth version for ages 8 to 12 encompassing 3 levels; and European Quality of Life Five Dimension Three Level [EQ-5D-3L] for ≥13 years)	Baseline (at enrollment) and at the following timepoints post-infusion: Day 28, Months 3, 6, 9, and 12.	• Completion rate was ≥75% throughout the assessment period for patients who were eligible for completing PRO. • The lowest completion rate was at Day 28 for both tools (43/57 [75%] for PedsQL and 44/57 [77%] for EQ-5D) and the highest at Month 12 (14/14 [100%] for each). • An improvement in HRQoL starting Day 28 post-infusion and reaching a clinically meaningful phase by Month 3 (Figure 3). • Clinically meaningful improvement was determined based on a score that is equal to or greater than the MCID, which was equivalent to 4.36 points for the total PedQL score and 7-10 points for the EQ-5D VAS. • A post-hoc analysis performed for patients with severe symptoms of CRS and neurotoxicity reported a delay in improvement four weeks after the infusion (Day 28) compared with those without such toxicities. • This delay was no longer evident at later timepoints at which the observed improvement in QoL was similar between the groups.

Abbreviations: ALL, acute lymphoblastic leukemia; BPI, Brief Pain Inventory; CAR, chimeric antigen receptor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EQ-5D-5L, European Quality of Life Five Dimension Five Level; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; FACT-LymS, Functional Assessment of Cancer Therapy-Lymphoma subscale; FSI, Fatigue Symptom Inventory; HRQoL, health-related quality of life; IDAS, Inventory of Depression and Anxiety Symptoms; IQR, interquartile range; LBCL, large B-cell lymphoma; MCID, minimal clinically important difference; MID, minimally important difference; NHL, non-Hodgkin lymphoma; PedQL, Pediatric Quality of Life Inventory; PRO, patient-reported outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; PSQI, Pittsburgh Sleep Quality Index; QoL, quality of life; SF-36, Short Form-36; SLL, small lymphocytic lymphoma; US, United States; VAS, visual analog scale.

*N is the number of patients who received CAR T-cell therapy

**The Phase 1 study reported by Knight et al[25] (2022) was a sub-study cohort (n=15); the parent study was a Phase 1/1b study (NCT03019055) reported by Shah et al[52] (2020).

†Of the 30 additional questions, four were related to cognitive function.

††The number of patients who received lisa-cel were 199 after the study protocol was amended to include HRQoL data collection.

[#]Completion rate is calculated based on the number of patients who filled the PRO questionnaire out of the total number of patients who were eligible to complete the PRO questionnaires at each timepoint (e.g., patients still in the study, who did not experience progression and did not start a new antineoplastic treatment). For studies where the total number of patients at each timepoint was not specified, the total number of patients in the study/at baseline was used as denominator.

Table 3. Randomized controlled trials comparing health-related quality of life after CAR T-cell anti-CD19 therapy or SoC in adult patients

Study ID (reference)	Analysis sets	PRO/HRQoL tool	Reported PRO/HRQoL assessment timepoints	Clinically meaningful change and minimally important difference	PRO Results
TRANSFORM[33]	**ITT set:** - Liso-cel (n=92) median age: 60 years (IQR, 54 to 68) - SoC (n=92) median age: 58 years (IQR, 42 to 65) **EORTC QLQ-C30 analysis set:** - Liso-cel (n=47; 51.1%) median age: 59 years (IQR, 53 to 67) - SoC (n=43; 46.7%) median age: 56 years (IQR, 37 to 64) **FACT-LymS analysis set:** - Liso-cel (n=45; 48.9%) - SoC (n=40; 43.5%) Race not reported	EORTC QLQ-C30 FACT-LymS	Baseline (randomization) During treatment: Day 29 (before liso-cel infusion or during SCT cycle 2) Post-treatment: Days 64 and 126, Months 6, 9, 12, 18, 24, and 36	• Clinically meaningful change was defined as a minimum difference ranging from 5 to 30 points according to the different EORTC QLQ-C30 functioning domains and symptoms and 3 points for the FACT-LymS. • MID between the groups ranged from 3 to 6 points for the different EORTC QLQ-C30 functioning domains and symptoms and was 3 points for FACT-LymS.	• Results of the EORTC QLQ-C30 global health status/QoL, cognitive function and fatigue domains showed that the percentage of patients with a clinically better score or no change were higher in the liso-cel group versus the SoC group (**Supplemental Figure S3**). • The scores of the remaining domains and FACT-LymS were comparable between treatment groups, except for the emotional domain of EORTC QLQ-C30, where a higher deterioration was observed with liso-cel. • Of note, CRS and ICANS were reported by only 1% and 4% of patients, respectively, and did not seem to influence the patients' QoL.
ZUMA-7[18,34]	**FAS:** - Axi-cel (n=180) - SoC (n=179) **QoL analysis set:** - Lisocel (n=165; 91.7%) Age category: <65 years, n=119 (72.1%);	EORTC QLQ-C30 EQ-5D-5L WPAI:GH version 2.0	Baseline (prior to treatment with either conditioning or salvage chemotherapy) Post-treatment: Days 50, 100, and 150, Months	• Clinically meaningful difference was defined as having an MID of 0.06, 10 and 7 points for EQ-5D-5L index, EORTC QLQ-C30, and EQ-5D-5L VAS score, respectively. • The same point differences were used to assess clinically meaningful change over time	• Results showed an initial deterioration in HRQoL outcomes at Day 50 in both treatment groups. • By Day 100, the scores of the EORTC QLQ-C30 global health status/QoL and physical function domain and the EQ-5D-5L VAS were statistically significantly better and clinically meaningful in the axi-cel group compared to the SoC group QoL (data for each group-each

Study ID (reference)	Analysis sets	PRO/HRQoL tool	Reported PRO/HRQoL assessment timepoints	Clinically meaningful change and minimally important difference	PRO Results
	≥65 years, n=46 (27.9%) Race: White (n=134, 81.2%); Asian (n=11, 6.7%); Black or African American (n=8, 4.8%); Other n=12 (7.3%) - SoC (n=131; 73.2%) Age category: <65 years, n=89 (67.9%); ≥65 years, n=42 (32.1%) Race: White (n=113, 86.3%); Asian (n=6, 4.6%); Black or African American (n=6, 4.6%); Other n=6 (4.6%)		9, 12, 15, 18, 21, and 24	within the same group and between groups.	scale; estimated difference, 18.1; P<0.0001) (**Supplemental Figure S3**). • The improvement observed at Day 100 was sustained on Day 150. • The remaining EORTC QLQ-C30 domains, EQ-5D-5L index, and WPAI:GH results were also in favor of axi-cel versus SoC. • A similar pattern was observed in a subgroup analysis performed for patients ≥65 years.[34]

Abbreviations: CAR, chimeric antigen receptor; CD, cluster of differentiation; CRS, cytokine release syndrome; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EQ-5D-5L, European Quality of Life Five Dimension Five Level; FACT-LymS, Functional Assessment of Cancer Therapy-Lymphoma subscale; FAS, full analysis set; HRQoL, health-related quality of life; ICANS, immune effector cell-associated neurotoxicity syndrome; IQR, interquartile range; ITT, intent-to-treat; MID, minimally important difference; QoL, quality of life; PRO, patient-reported outcome; SCT, stem cell transplant; SoC, standard of care; VAS, visual analog scale; WPAI:GH, Work Productivity and Activity Impairment Questionnaire: General Health.

Table 4. Real-world studies evaluating health-related quality of life after CAR T-cell anti-CD19 therapy

Study	Patient population	Treatment (Number of patients)	PRO/HRQoL tool	PRO/HRQoL assessment timepoints	PRO completion rate and/or results
Sidana et al[21] (2022)	Hematologic malignancies -CAR T-cell therapy median age: 62 years (range, 26 to 77) Race/Ethnicity: Majority were Caucasian (n=33, 97%) and Not Hispanic (n=33, 97%) -Autologous SCT median age: 62 years (range, 42 to 74) Race/Ethnicity: Majority were Caucasian (n=29, 88%) and Not Hispanic (n=33, 100%) -Allogeneic SCT median age: 60 years (range, 23 to 75) Race/Ethnicity: Majority were Caucasian (n=26, 97%) and Not Hispanic (n=36, 97%)	Three cohorts depending on treatment: -CAR T-cell therapy (n=34) -Autologous SCT (n=33) -Allogeneic SCT (n=37)	FACT-G (primary endpoint) PRO-CTCAE Neuro-QoL v2 ECOG performance status (self-reported)	Baseline (any time before CAR T-cell therapy) Post-treatment: Week 2, Months 1, 2, 3, 4, 5, and 6	• Completion rates dropped from 100% at baseline to 44% at Month 6, mainly due to the emergence of an event leading to study exit. Only 38% of patients reported QoL data for all timepoints. • HRQoL declined during the first two weeks in all groups (nadir coinciding with adverse event peak) and improved later (this deterioration did not reach clinical significance). However, the decline was lower, and the improvement was faster with CAR T-cell therapy than with SCT, especially for overall QoL, and physical and functional well-being. • Cognitive function, assessed by Neuro-QoL, was maintained after CAR T-cell therapy • MCID were 9 points for the total FACT-G and 8 points for Neuro-QoL.
Wang et al[6] (2021)*	Relapsed or refractory hematologic malignancies (mainly B-cell lymphoid malignancies)	All patients received CAR T-cell therapy (N=60) -Axi-cel (n=52) -Tisa-cel (n=8)	MDASI with CAR T-cell specific module* PROMIS-29 EQ-5D-5L	Once at any time during the first 12 months post-infusion	• Completion rate for the MDASI CAR, PROMIS-29 and single-item HRQoL was 100%. • Completion rate for EQ-5D-5L was 96.7%. • During the first 3 months, the most severe symptoms were reported (>10% of patients scored 7/10 to 10/10)

Study	Patient population	Treatment (Number of patients)	PRO/HRQoL tool	PRO/HRQoL assessment timepoints	PRO completion rate and/or results
	Median age: 58.9 years (range, 18.7 to 78.6) Race: White or Caucasian (n=49, 81.7%); Other (n=11, 18.3%) Ethnicity: Not Hispanic or Latino (n=45, 75%); Hispanic or Latino (n=15, 25%)		Single-item HRQoL		for several symptoms including fatigue, sleeping disturbance, pain, lack of energy, and tremors. • The symptoms decreased as the time from infusion increased, where symptoms reported within the first 30 days and within 30 to 90 days were more than those reported after 90 days. Pain and physical function were worse during the first 30 days. • After 30 days post-infusion, patients with higher grades of CRS (grades 3 and 4) reported more severe symptoms compared to patients with lower grades (grade 1 and 2). Similarly, after 30 days, patients with higher grades of ICANS (grade 2 to 4) experienced more severe swelling and difficulty eating.
Johnson et al[20] (2023) **	Hematologic malignancies (mainly lymphoma and multiple myeloma) Median age: 66 years (range, 23 to 90) Race: White (n=87, 87%); Others (n=5, 5%); Missing/Not reported (n=4, 4%) Ethnicity: Hispanic or Latino (n=6; 6%)	All patients received CAR T-cell therapy -Tisa-cel (n=34) -Liso-cel (n=16) -Axi-cel (n=13) -Ide-cel (n=12) -Brexu-cel (n=6) -Cilta-cel (n=3) -Other (n=16)	FACT-G HADS PHQ-9 PCL ESAS-revised	Baseline (between leukapheresis and CAR T-cell therapy) Post-infusion: Week 1, Months 1, 3, and 6[†]	• At baseline, all 100 patients completed the HADS, 99 completed the PHQ-9 and 98 completed the FACT-G and PCL. • By Month 6, the completion rate decreased to 72%, where 72 patients completed all questionnaires. • An initial deterioration in HRQoL, as well as depression and physical symptoms, were observed early post-infusion. These symptoms improved above baseline level by Months 3 and 6, reaching scores similar as those reported by the general US population. Changes were clinically significant. • A constant decline was observed for anxiety and PTSD over the duration of the assessment. • MID was 5 points for FACT-G and clinical significance cut-off was 8 points for HADS (depression/anxiety) and 32 points for PCL (PTSD)
Dhawale et al[19] (2023) **	Hematologic malignancies (mainly lymphoma and multiple myeloma) Median age: 66 years (range, 23 to 90)	All patients received CAR T-cell therapy -Tisa-cel (n=34) -Liso-cel (n=16) -Axi-cel (n=13) -Ide-cel (n=12) -Brexu-cel (n=6)	FACT-G HADS PHQ-9 PCL PAIS	Once: before or at the time of CAR T-cell therapy	• All 100 patients who received CAR T-cell therapy filled the questionnaires. • Less than one-third of patients reported clinically significant symptoms related to anxiety, depression, or PTSD at baseline. • The majority of patients reported that they emotionally coped well and responded positively to

Study	Patient population	Treatment (Number of patients)	PRO/HRQoL tool	PRO/HRQoL assessment timepoints	PRO completion rate and/or results
	Race: White (n=87, 87%); Others (n=5, 5%); Missing/Not reported (n=4, 4%) Ethnicity: Hispanic or Latino (n=6; 6%)	-Cilta-cel (n=3) -Other (n=16)			their prognosis. Patients were glad they knew about their prognosis since it affected future decisions with regards to their disease and treatment and affected other aspects of life as well. • Better emotional coping with prognosis and adaptive response to knowing their prognosis were each associated with better QoL and less depression, anxiety, and PTSD at baseline. • Clinical significance cut-off was 8 points for HADS (depression/anxiety) and 32 points for PCL (PTSD symptoms),
Hoogland et al[36] (2021) ††	Hematologic malignancies (patients with NHL were included in this analysis)†† Age: Mean ± SD, 61 ± 12 years Race/Ethnicity: The majority were White (n=90, 87%) and Not Hispanic (n=95, 93%)	Axi-cel (n=103)	SF-36‡ PROMIS-29‡ PRO-CTCAE	QoL questionnaires: Baseline (before conditioning therapy) and Day 90 post-infusion PRO-CTCAE: Baseline and Days 14, 30, 60, and 90 post-infusion	• Of the 102 patients who provided baseline data, 87 (85.3%) provided data at Day 14, 86 (84.3%) at Day 30, 87 (85.3%) at Day 60, 72 (70.6%) at Day 90. • QoL questionnaire results: Compared with baseline data, physical function, pain, and fatigue improved by Day 90 while anxiety worsened by that timepoint. • PRO-CTCAE results: The most severe adverse event profile, related to CAR T-cell therapy, was reported by Day 14 followed by improvements observed by Day 90. Symptoms that peaked and improved included fatigue, headache, dry mouth, nausea, and concentration problems. Only one symptom, muscle aches, peaked at Day 14 and still persisted.
Barata et al[35] (2022) ††	Hematologic malignancies (patients with NHL who provided cognitive data were included in this analysis)†† Mean ± SD age, 61 ± 12 years Race/Ethnicity: The majority were White	All patients received CAR T-cell therapy: -Axi-cel (n=101) -Tisa-cel (n=15) -Brexu-cel (n=2)	SF-36‡ PROMIS-29‡ Everyday Cognition Questionnaire	Baseline (before conditioning therapy) Post-infusion: Day 90 and 360	• Of the 115 patients who provided baseline data, 86 (74.8%) provided data at Day 90 and 70 (60.9%) at Day 360. • No cognitive changes were observed between baseline and Day 90; however, there was a deterioration in cognitive function from Day 90 to Day 360 • Compared to baseline, 12% and 25% of patients experienced a clinically significant deterioration in cognition at Day 90 and Day 360, respectively. • At Day 90, worse cognitive function was associated with more severe fatigue, anxiety, and depression at

Study	Patient population	Treatment (Number of patients)	PRO/HRQoL tool	PRO/HRQoL assessment timepoints	PRO completion rate and/or results
	(n=105, 89%) and Not Hispanic 110 (94%)				baseline. No similar association was observed at Day 360. • At Day 360, patients with a higher grade of neurotoxicity (≥grade 2) experienced worse cognitive impairment compared to those with lower grades. • Of note, the cognitive changes observed were mild in intensity. • For the Everyday Cognition Questionnaire, half standard deviation (0.05) was considered a clinically meaningful difference
Oswald et al[38] (2022) ††‡‡	Hematologic malignancies (mainly multiple myeloma and lymphoma)†† Mean age, 66 years (range, 53 to 77) Race/Ethnicity: The majority were White (n=10, 83%) and Not Hispanic (n=11, 92%)	All patients received CAR T-cell therapy (n=12)	Demographics survey CCI FACT-G or FACT-G7 PROMIS-29 + 2 Profile v2.1 PRO-CTCAE Study-specific survey	Baseline (enrollment) Day of infusion (Day 0) Post-infusion: Days 1, 2, 3, 4, 5, 6, 7, 14, 21, 30, 60, and 90†	• Out of the 12 patients who were initially enrolled in the study, 10 patients had data until Day 90. • Of the total 168 PRO evaluations, 143 (85.1%) were completed and of the 1,092 study days, the Fitbit was worn for 928 days (85.0%). • QoL questionnaire results: During the first 30 days, a deterioration was observed in multiple domains including physical and functional well-being, social roles, pain, and fatigue. Physical function deteriorated during the first month and was still mildly impaired by Day 60. • PRO-CTCAE results: The most severe symptoms were reported within the first 14 days post-infusion. • A clinically low HRQoL was defined as ≤ 70 points for the total FACT-G and ≤ 16 points for FACT G7.
Ram et al[39] (2022)	DLBCL (elderly patients matched with younger patients) Study Cohort – Mean ± SD age, 76.2 ± 4.4 years Control – Mean ± SD age, 55.4 ± 15 years Race not reported	Elderly patients (Study Cohort): -Tisa-cel (n=33) -Axi-cel (n=8) Younger patients (Control): -Tisa-cel (n=34) -Axi-cel (n=7)	EORTC QLQ-C30 Version 3	Baseline Post-infusion: Days 30 and 90	• EORTC QLQ-C30 completion rate was 23/41 (56.1%) • An initial deterioration was observed in most domains (4 of 5) along with worsening of most of the cancer and emotional symptoms by Day 30. • By Day 90, an improvement was observed in all domains and all cancer symptoms and most of emotional symptoms as compared to baseline. • Overall health and QoL remained stable from baseline to Day 30 and improved by Day 90.
Maillet et	Relapsed/ refractory	All patients received	HADS	Baseline	• A total of 27 patients were evaluable for mid-term

Study	Patient population	Treatment (Number of patients)	PRO/HRQoL tool	PRO/HRQoL assessment timepoints	PRO completion rate and/or results
al[37] (2021)	diffuse large B-cell lymphomas Mean ± SD age, 58 ± 14 years Race not reported	CAR T-cell therapy: -Tisa-cel (n=10) -Axi-cel (n=17)	PRMQ	Post-infusion: once between 6 and 12 months	neurological evaluation. • Anxiety and memory problems were reported most frequently at baseline (48% and 30%, respectively) and decreased over time to 30% and 11%, respectively.
Ward et al., 2023[23]	Hematologic malignancies Mean ± SD age, 8.4 ± 5.0 years Race not reported for the patients	Total - CAR T-cell or SCT: N=140 -Allogeneic SCT (n=81) -Autologous SCT (n=36) -CAR T-cell therapy (n=23)	<u>Children:</u> MSAS PedsQL Cancer Module 3.0 <u>Parents:</u> BAI BDI-II Perceived Stress Scale	Baseline (prior to treatment) Post-treatment: Days 30, 60, and 90	• Children's HRQoL and symptoms improved after CAR T-cell therapy or SCT starting Day 30, with further improvements at Days 60 and 90. • Parental distress was associated with decreased child HRQoL and higher symptom burden prior to treatment and at later timepoints. • Suicidal ideation was reported by 38.5%, 37.0%, 27.4%, and 33.6% of patients at baseline, Day 30, Day 60, and Day 90, respectively.

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CAR, chimeric antigen receptor; CCI, Charlson Comorbidity Index; CD, cluster of differentiation; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EQ-5D-5L, European Quality of Life Five Dimension Five Level; ESAS, Edmonton Symptom Assessment Scale; FACT-G, Functional Assessment of Cancer Therapy-General; HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life scale; ICANS, immune effector cell-associated neurotoxicity syndrome; MCID; minimal clinically important differences; MDASI, MD Anderson Symptom Inventory; MID, minimally important difference; MSAS, Memorial Symptom Assessment Scale; Neuro-QoL, Quality of Life in Neurological Disorders; NHL, non-Hodgkin lymphoma; PAIS, Prognostic Awareness Impact Scale; PCL, Post□Traumatic Stress Checklist; PedQL, Pediatric Quality of Life Inventory; PHQ-9, Patient Health Questionnaire-9; PRMQ, Prospective and Retrospective Memory Questionnaire; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PROMIS-29, Patient-Reported Outcomes Measurement Information System 29; PTSD, post-traumatic stress disorder; QoL, quality of life; SCT, stem cell transplant; SD, standard deviation; SF-36, Short Form-36; US, United States.

*The analysis was performed depending on the time of data collection: within 30 days post-infusion (n=28), within 30 to 90 days (n=13), and after 90 days (n=19). This study was an initial step in the development of a CAR T cell therapy-specific module.

**Johnson et al[20] (2023) and Dhawale et al[19] (2023) reported on the same sample of patients; however, one study was cross-sectional (Dhawale et al., 2023)[19] and the other longitudinal (Johnson et al., 2023).[20]

†Not all PRO were filled at all timepoints.

††Patients recruited as part of another larger observational study.

‡HRQoL data was collected initially using the SF-36 then switched to PROMIS-29 following the coverage decisions of Medicare and Medicaid Services. The PROsetta Stone was used to convert SF-36 scores to PROMIS-29 T-scores.

⌗⌗Oswald et al[38] (2022) assessed the feasibility and acceptability of frequent PRO assessments and of wearing a tracker (Fitbit) to assess daily activity and sleep quality prior to CAR T-cell therapy and up to Day 90 post-therapy.

Figure 1. Treatment and monitoring of patients receiving CAR T-cell therapy

Abbreviations: AE, adverse events; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; D, day; ICANS, immune effector cell-associated neurotoxicity syndrome.

T-cells are collected from the patient through leukapheresis and produced in vitro by the addition of the CAR vector. The modified CAR T-cells are later infused back after the patient had received conditioning chemotherapy during the week prior to infusing the CAR T-cells. This conditioning therapy, also known as lymphodepletion therapy, typically includes fludarabine and/or cyclophosphamide. Following the CAR T-cell infusion, patients who receive CAR T-cell therapy should be hospitalized for a minimum duration of one-week post-infusion, as recommended by the CAR-T-cell Therapy Associated Toxicity (CARTOX) working group or benefit from equivalent monitoring depending on the different local organizations in the world.

*CRS and ICANS usually appear within the first two weeks after CAR T-cell infusion.[4]

Figure 2. The stepwise approach to develop the MDASI-CAR tool.

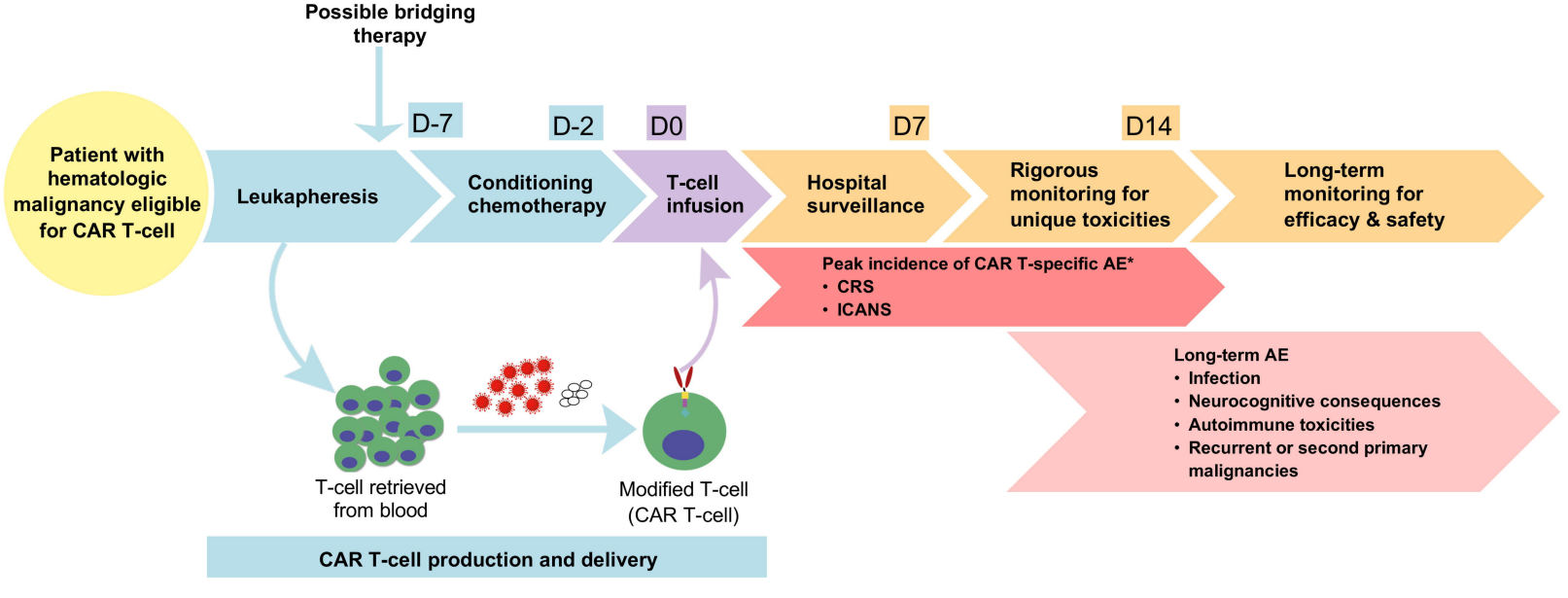
Number of items for each item set is presented in parenthesis.

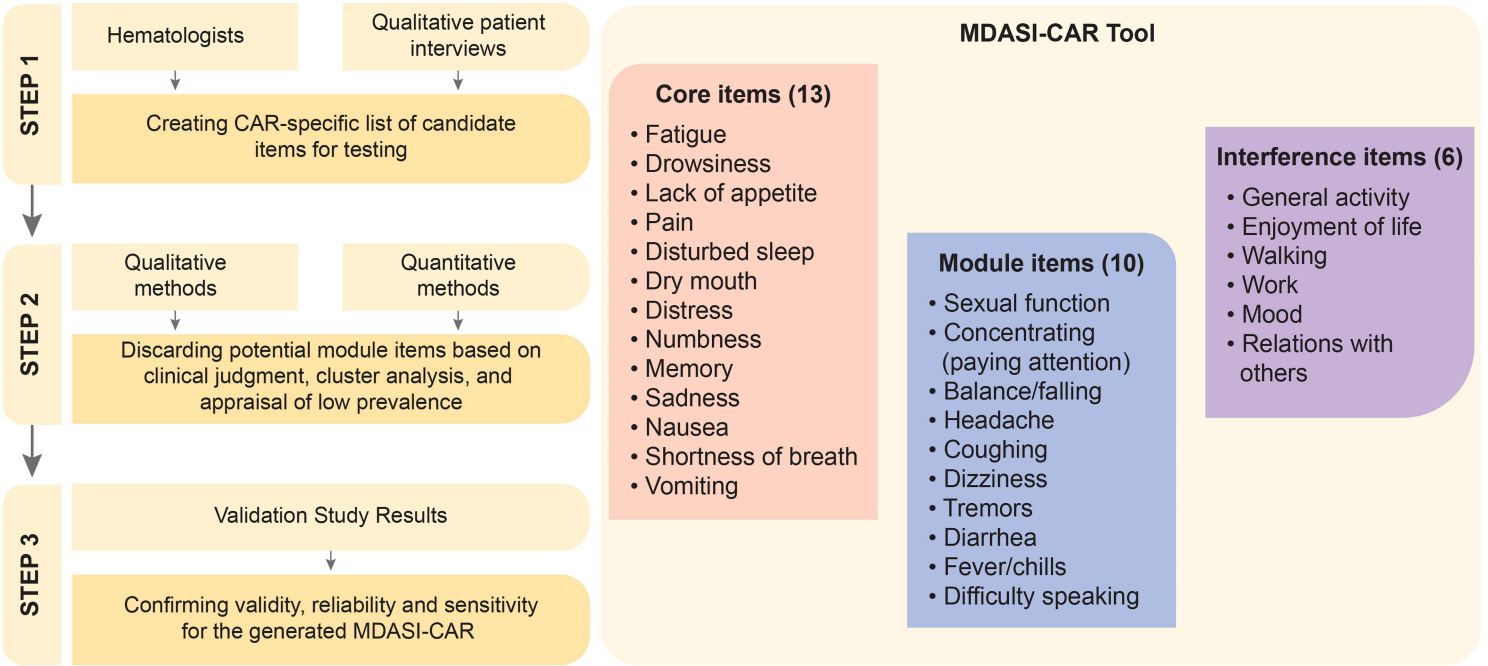
Abbreviations: MDASI-CAR, MD Anderson Symptom Inventory-chimeric antigen receptor.

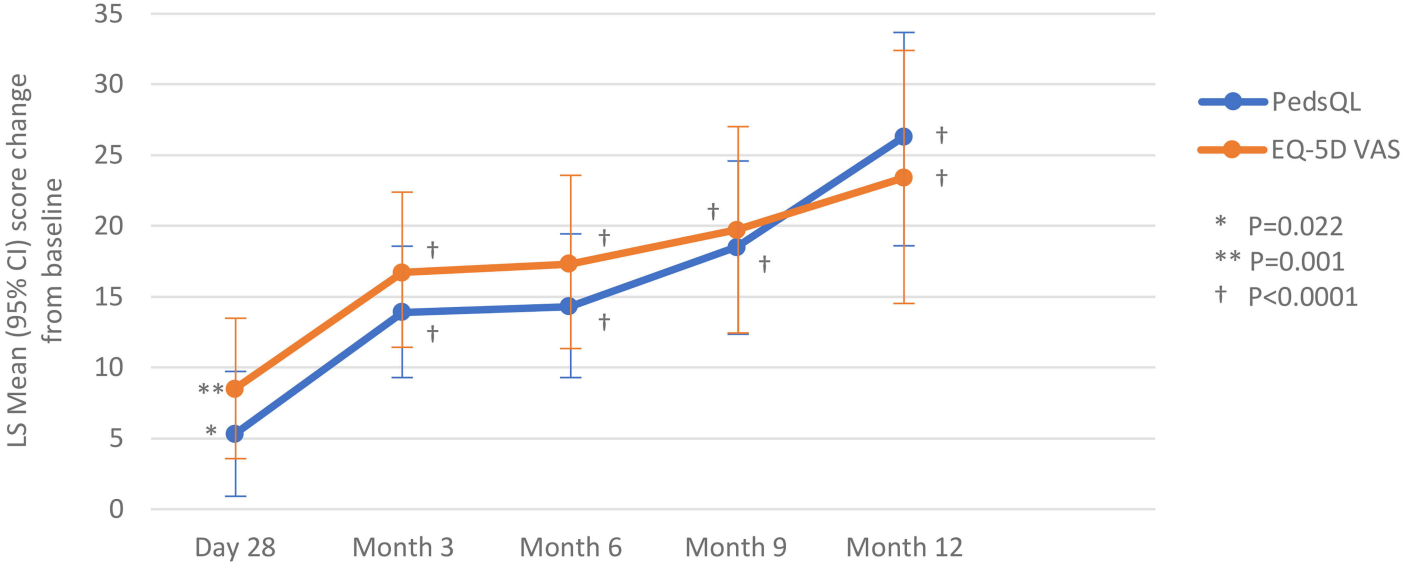
Figure 3. Results of the ELIANA study: Change from baseline in the PedsQL Total Score and EQ-5D VAS – MMRM Analysis

Abbreviations: CI, confidence interval; EQ-5D, European Quality of Life Five Dimension; LS, least squares; MMRM, Mixed-Model Repeated Measure; No, number of patients with measurements at both baseline and post-baseline visits; P, P-value; PedQL, Pediatric Quality of Life Inventory; VAS, visual analog scale.

Adapted from: Laetsch et al[22] (2019) – Supplemental material.


Possible bridging therapy
Patient with hematologic malignancy eligible for CAR T-cell
D-7
D-2
D0
D7
D14
Leukapheresis
Conditioning chemotherapy
T-cell infusion
Hospital surveillance
Rigorous monitoring for unique toxicities
Long-term monitoring for efficacy & safety
Peak incidence of CAR T-specific AE*
• CRS
• ICANS
Long-term AE
• Infection
• Neurocognitive consequences
• Autoimmune toxicities
• Recurrent or second primary malignancies
T-cell retrieved from blood
Modified T-cell (CAR T-cell)
CAR T-cell production and delivery


STEP 1
Hematologists
Qualitative patient interviews
Creating CAR-specific list of candidate items for testing
STEP 2
Qualitative methods
Quantitative methods
Discarding potential module items based on clinical judgment, cluster analysis, and appraisal of low prevalence
STEP 3
Validation Study Results
Confirming validity, reliability and sensitivity for the generated MDASI-CAR
MDASI-CAR Tool
Core items (13)
• Fatigue
• Drowsiness
• Lack of appetite
• Pain
• Disturbed sleep
• Dry mouth
• Distress
• Numbness
• Memory
• Sadness
• Nausea
• Shortness of breath
• Vomiting
Module items (10)
• Sexual function
• Concentrating (paying attention)
• Balance/falling
• Headache
• Coughing
• Dizziness
• Tremors
• Diarrhea
• Fever/chills
• Difficulty speaking
Interference items (6)
• General activity
• Enjoyment of life
• Walking
• Work
• Mood
• Relations with others



No. of patients					
PedsQL	39	37	32	20	14
EQ-5D VAS	40	36	29	19	13

Supplemental Data

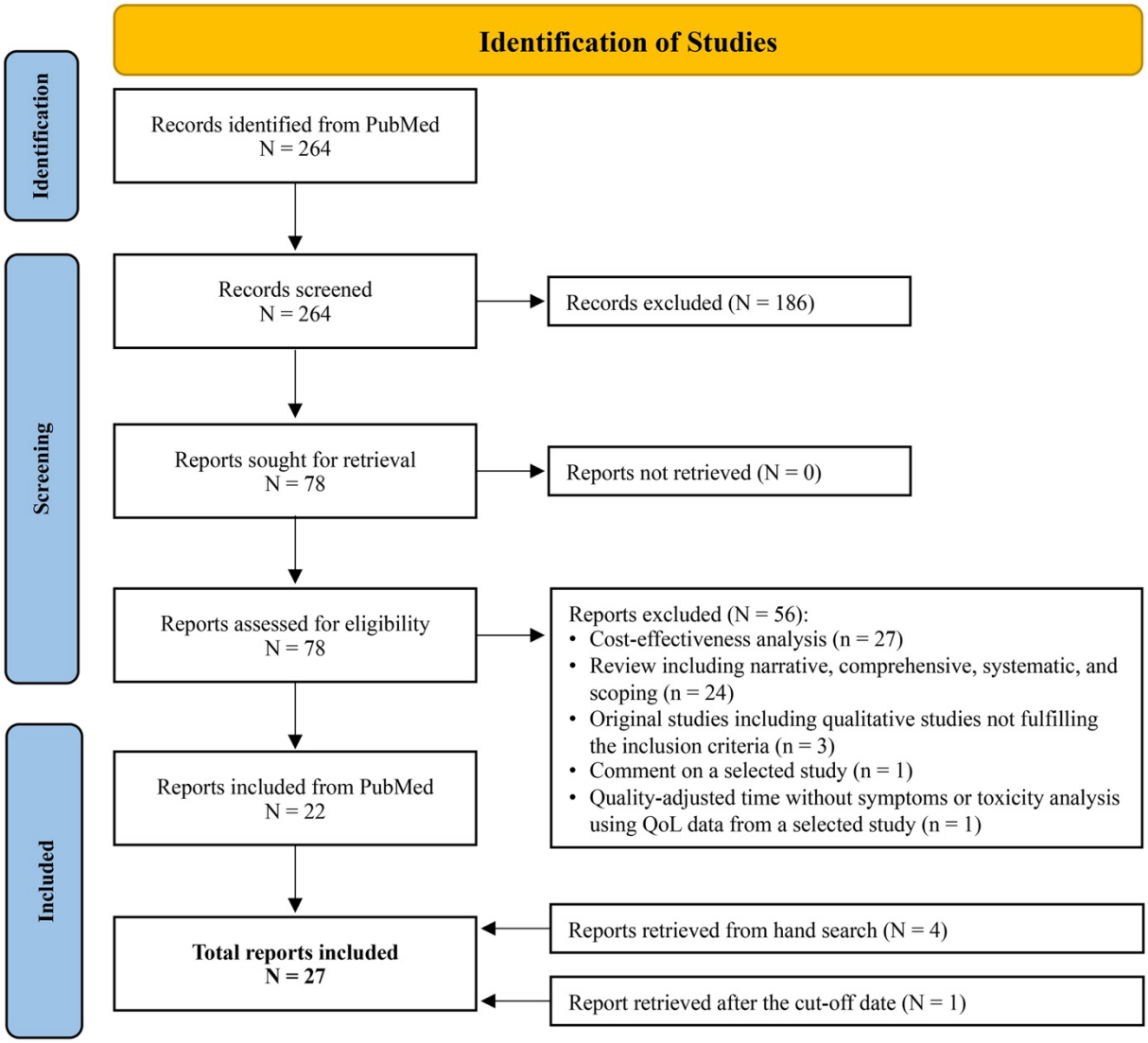


Figure S1. PRISMA chart – Identification of studies via PubMed and hand search

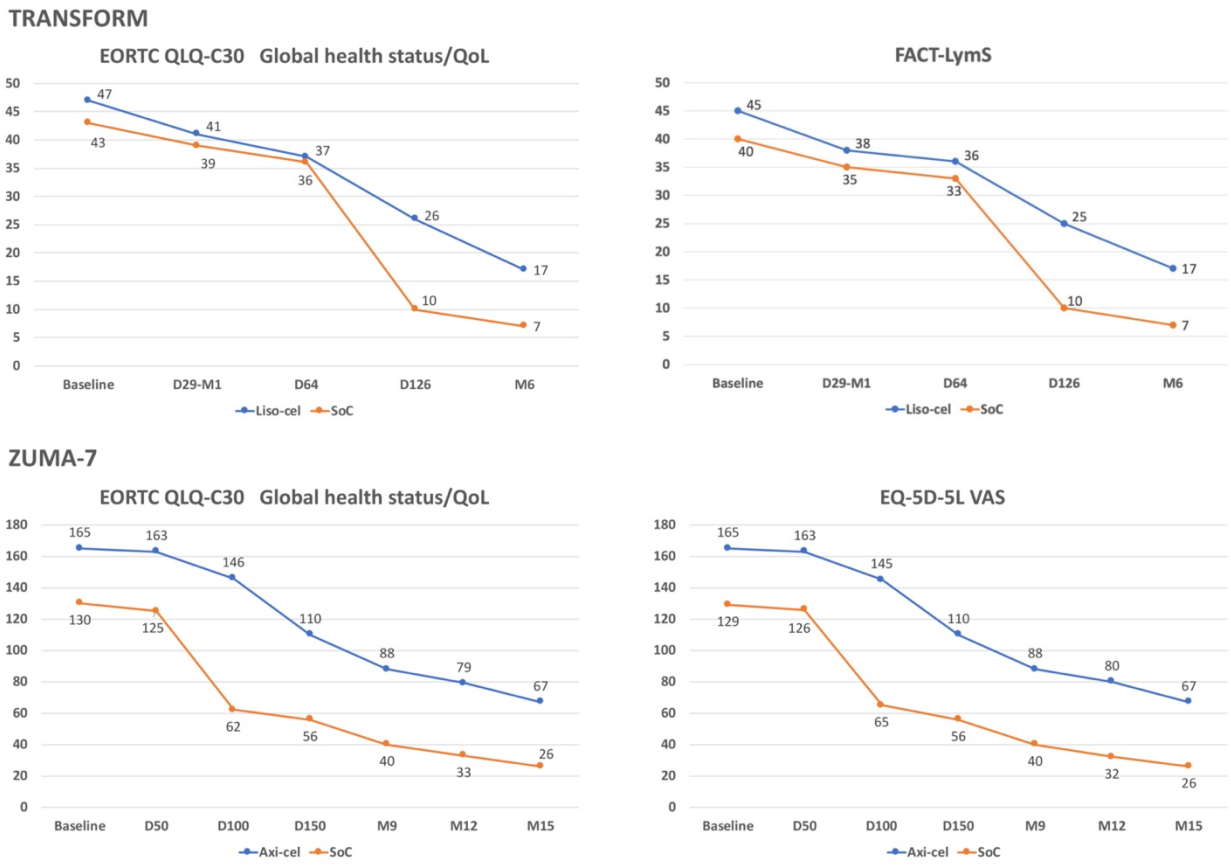


Figure S2. Number of patients reporting health-related quality of life data at different timepoints for TRANSFORM[33] and ZUMA-7[18] studies

Abbreviations: Axi-cel, axicabtagene ciloleucel; D, day; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FACT-LymS, Functional Assessment of Cancer Therapy-Lymphoma sub-scale; Liso-cel, lisocabtagene maraleucel; M, month; QoL; quality of life; SoC, standard of care; VAS, visual analogue scale.

Adapted from: Abramson et al[33] 2022 and Elsawy et al[18] 2022.

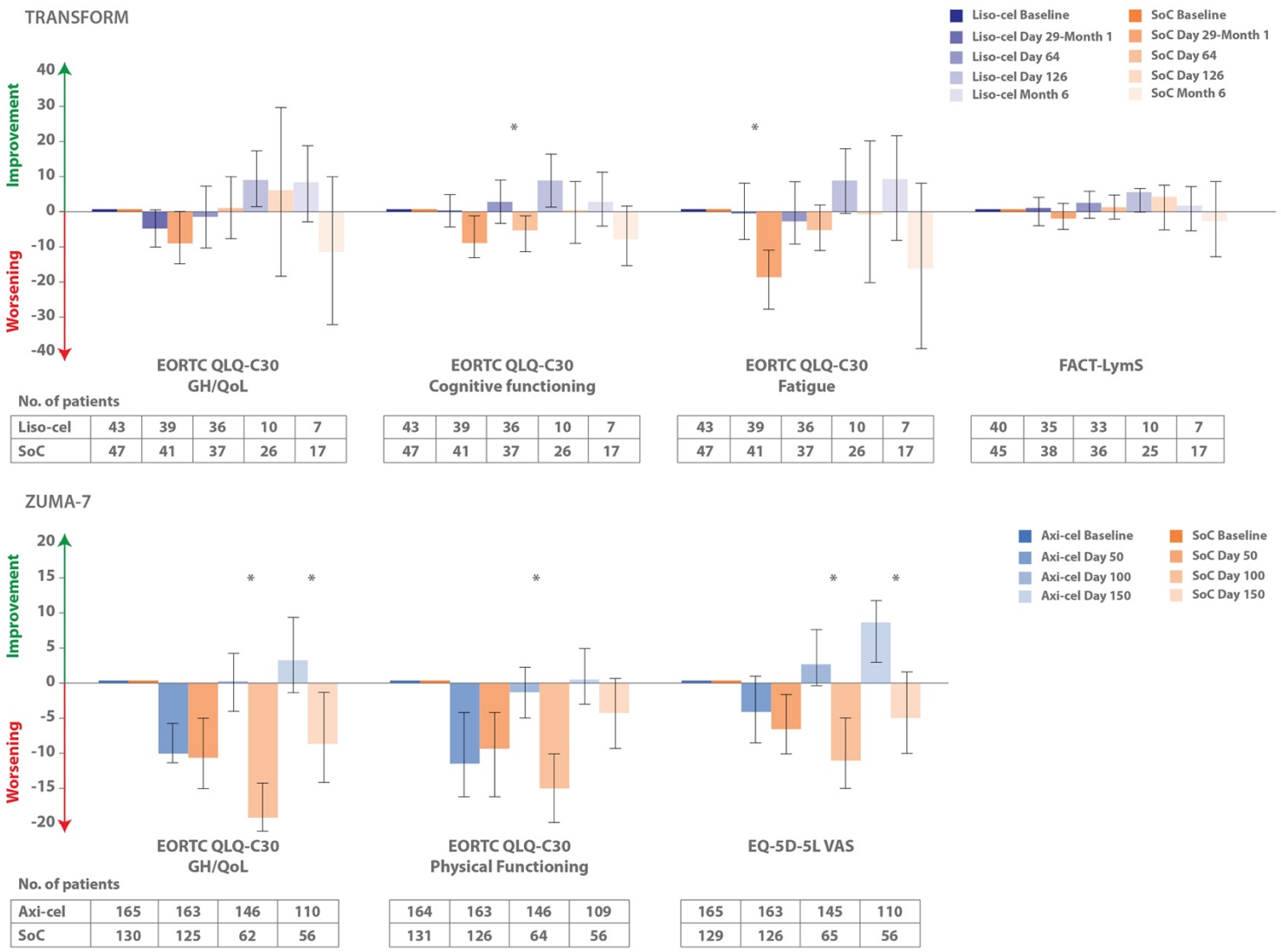


Figure S3. Results of the TRANSFORM[33] and ZUMA-7[18] studies: Change from baseline in selected domains/symptoms of the EORTC QLQ-C30 (both studies), FACT-Lym (TRANFORM), and EQ-5D-5L VAS (ZUMA-7).

Data presented as mean change (95% confidence interval). The scores of the EORTC QLQ-C30 fatigue bar graph have been mirrored so that an increase in the positive score would represent improvement and the negative scores represent worsening.

Abbreviations: Axi-cel, axicabtagene ciloleucel; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EQ-5D-5L, European Quality of Life Five Dimension Five Level; FACT-LymS, Functional Assessment of Cancer Therapy-Lymphoma sub-scale; GH, global health status; Liso-cel, lisocabtagene maraleucel; QoL; quality of life; SoC, standard of care; VAS, visual analogue scale.
Adapted from: Abramson et al[33] 2022 and Elsawy et al[18] 2022.