Title: Efficacy and safety of Chimeric Antigen Receptor T-Cell (CAR-T) therapy in hematologic malignancies: A living systematic review.

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ABSTRACT:

Objective
This living systematic review aims to provide a timely, rigorous and continuously updated summary of the evidence available on the role of Chimeric Antigen Receptor T-Cell (CAR-T) therapy for the treatment of patients with hematologic malignancies.

Design
Living systematic review.

Database
The Epistemonikos-L.OVE platform was used for evidence identification, screening, and selection. This platform has been validated as a repository for COVID-19, and proved to be a highly comprehensive source of evidence. The main search source for the L.OVE platform is the Epistemonikos database (https://www.epistemonikos.org), a comprehensive database that collates information from multiple sources to identify systematic reviews and their included primary studies, including Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS, DARE, HTA Database, Campbell database, JBI Database of Systematic Reviews and Implementation Reports, EPPI-Centre Evidence Library.

The team maintaining the Epistemonikos-L·OVE platform devised the literature search, using the following approach: i) Identification of terms relevant to the population and intervention components of the search strategy, using Word2vec technology to the corpus of documents available in Epistemonikos Database; ii) Discussion of search terms with methods experts to identify relevant, irrelevant and missing terms, iii) Creation of a sensitive boolean strategy encompassing all the relevant terms.

The results of the literature searches were automatically incorporated into the L·OVE platform (automated retrieval) and organized in the corresponding L.OVE of "Chimeric antigen receptor T cell therapy for hematological malignancies".

Methods
Randomized controlled trials (RCTs) and comparative non-randomized studies of interventions (NRSI) evaluating the effect of CAR-T therapy versus other active treatments, hematopoietic stem cell transplantation, standard of care (SoC) or any other intervention in patients with hematologic malignancies were considered for inclusion. The primary outcome is overall survival (OS). Certainty of the evidence was determined using the GRADE approach.

Results

This is the first report (baseline report) of this LSR. We included the evidence published up to 1 July 2022. We considered 139 RCTs and 1725 NRSI as potentially eligible. Two RCTs (N = 681) comparing CAR-T therapy with SoC in patients with recurrent/relapsed (R/R) B-cell lymphoma were included. RCTs did not show statistical differences in OS, serious adverse events (SAEs) or total adverse events (TAEs) with grade ≥3. Higher complete response (CR) with substantial heterogeneity [RR=1.59; 95%CI (1.30 to 1.93); I 2 =89%; 2 studies; 681 participants; very low certainty evidence] and higher progression-free survival (PFS) [HR for progression or death = 0.49; 95%CI (0.37 to 0.65); 1 study; 359 participants; moderate certainty evidence] were reported with CAR-T therapies. Nine NRSI (N=540) in patients with T or B-cell acute lymphoblastic leukemia or R/R B-cell lymphoma were also included, providing secondary data. In general, the GRADE certainty of the evidence for main outcomes was mostly low or very low due to inconsistency. The evidence monitoring will continue for the next six months in order to identify emerging evidence.

Conclusions

Two RCTs on the use of CAR-T versus standard care in the management of patients with R/R B-cell lymphoma have been identified so far. Low to very low certainty evidence shows that probably there would be no differences in the effect of these interventions on OS (primary outcome), SAEs, or TAE grade ≥ 3. However, CAR-T therapy may provide better results in terms of PFS and CR (moderate to very low certainty evidence). Evidence from NRSI could not be used as complementary evidence because of its low certainty, downgraded due to the important risk of bias and inconclusive results in estimates. Larger trials specifically designed to minimize bias are needed in order to determine the efficacy and safety of the use of CAR-T in patients with hematological malignancies.

Keywords

CAR-T therapy, chemotherapy cytokine-release syndrome, donor leukocyte infusion, graft-versus-host disease, hematologic stem cell transplantation, leukemia, lymphoma, myeloma, systematic review.

BACKGROUND

Chimeric Antigen Receptors (CARs) show a high affinity to bind effector cells of the immune system, such as T cells (1). This cancer immunotherapy enables enhancement of the immunological response against malignant cells. Although the development of Chimeric Antigen Receptor T-cell (CAR-T) therapy started more than 20 years ago (2), the first steps in their transfer to clinical practice are now taking place, following the recent authorization of different CAR-T therapies by the U.S Food and Drug Administration and the European Medicines Agency.

The earliest and most extensive research with CAR-T cell therapy has been carried out in hematologic malignancies, where it has pointed to high response rates in patients who generally have very poor prognoses such as relapsed/refractory acute lymphoblastic lymphoma, diffuse large B-cell lymphoma, or multiple myeloma (3–5). Few therapeutic options are available in this setting, and CAR-T therapy is showing promising results.
B-cell maturation antigen (BCMA) and CD19-targeting CAR-T cell therapies are more developed than others and have shown the best results so far (6). At this time, CAR-T cells directed to other targets for treating solid tumors and infectious or autoimmune diseases are emerging (7,8).

Clinical studies have suggested that CAR-T cell therapies can be even curative in responsive patients. However, response rates can vary in different pathologies or depending on the characteristics of the patient or the disease, and also recurrences and relapses may occur. Moreover, these therapies are associated with important adverse events such as cytokine release syndrome, neurologic adverse events and B-cell aplasia, which may lead to serious consequences (1). To date, clinical trials have been mainly performed in terms of a single-arm design, whose encouraging results have allowed the approval of CAR-T therapies and their progressive introduction into clinical practice. However, it is still unclear what type of patients may benefit from CAR-T therapy with respect to other treatment options.
In the same line, the vast majority of systematic reviews published until 2022 have focused on synthesizing overall response rates of CAR-T cell therapy, without providing results compared with a control group (9–12). A recently published systematic review focused on randomized controlled trials (RCTs) analyzing the efficacy and safety of CAR-T therapies versus high-dose salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment of relapsed or refractory large B-cell lymphoma (13). However, this review shows several limitations, such as the lack of diverse comparators and hematologic diseases, and methodological concerns with the pooled analysis strategy. In addition, numerous phase III RCTs are already underway that will shed light on these questions in the near future, and new CAR-T cell therapies will emerge. Thus, taking into account the wide variability of the available evidence, the shortcomings of the already published systematic reviews, and the potential availability of new studies, we proposed to carry out a living systematic review analyzing the evidence from comparative studies assessing the

efficacy and safety of CAR-T therapies versus other treatment options in patients with hematologic diseases. Here we present the initial report of this living systematic review.

METHODS

Protocol and registration

This systematic review is being developed as part of the *Living Evidence to Inform Health Decisions* project (14). This manuscript complies with the 'Preferred Reporting Items for Systematic reviews and Meta-Analyses' (PRISMA) guidelines (15). The protocol of this systematic review is available in Open Science Framework (16).

Methods for identification of studies

The Epistemonikos-L.OVE platform (17) was used for evidence identification, screening, and selection. This platform has been validated as a repository for COVID-19, and proved to be a highly comprehensive source of evidence (18, 19). The results of the literature searches were automatically incorporated into the L·OVE platform (automated retrieval) and organized in the corresponding L.OVE of *Chimeric antigen receptor T cell therapy for hematological malignancies* (https://cutt.ly/4XIYRMW).

The main search source for the L.OVE platform is the Epistemonikos database (https://www.epistemonikos.org), a comprehensive database that collates information from multiple sources to identify systematic reviews and their included primary studies, including Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS, DARE, HTA Database, Campbell database, JBI Database of Systematic Reviews and Implementation Reports, EPPI-Centre Evidence Library (20).

The team maintaining the Epistemonikos-L·OVE platform devised the literature search, using the following approach: i) Identification of terms relevant to the population and intervention components of the search strategy, using Word2vec technology (21) to the corpus of documents available in Epistemonikos Database; ii) Discussion of search terms with methods experts to identify relevant, irrelevant and missing terms, iii) Creation of a sensitive boolean strategy encompassing all the relevant terms. Full search strategy is shown in Appendix 1.

Additional searches were performed in MEDLINE in order to identify new RCTs and non-randomized studies of interventions (NRSI), using validated filters to identify these studies in the MEDLINE database. We also carried out a manual search for reviewing the reference list of included studies, guidelines, narrative reviews and any other document of interest. We included the evidence published up to 1 July 2022. No publication status or language restriction was applied to the searches.

Types of studies

RCTs and NRSI (quasi-experimental studies, cohort studies, case-control studies) were considered for inclusion. Studies had to provide data for at least one primary or secondary outcome variable to be eligible.

Types of participants

Studies including adults (≥ 18 years) or pediatric participants diagnosed with a hematologic disease, such as multiple myeloma, leukemia and lymphoma of any type were included. Untreated patients as well as patients previously treated were included, irrespective of the type of treatment or treatment line.

Type of interventions

Any CAR-T therapy type was considered regardless of the T-cell origin (allogenic or autologous), target antigen or costimulatory domain. We did not restrict our criteria to any dosage, duration, timing or route of administration.

The comparator consisted of chemotherapy or any other active pharmacologic treatment, hematopoietic stem cell transplantation (HSCT), standard of care (SoC) or any other intervention. Studies assessing CAR-T plus other therapeutic measures were eligible if the co-interventions were identical in both arms.

Type of outcomes

The primary outcome was overall survival (OS). Key secondary outcomes were complete response/remission (CR) rate, relapse from CR, progression-free survival (PFS), graft-versus-host disease (GvHD), total adverse events (TAE) (grade ≥3), and serious adverse events (SAE). Other secondary outcomes were overall response rate (ORR), partial response/remission (PR) rate, time from CAR-T infusion to transplantation, incidence of cytokine-release syndrome (CRS) (grade 3 or higher), neurotoxicity (grade 3 or higher), and quality of life.

We presented primary and key secondary outcomes in a GRADE Evidence Profile format (22).

Selection of studies

The results of the literature search in all databases were automatically incorporated into the L·OVE platform (automated retrieval), where they were de-duplicated by an algorithm comparing unique identifiers (database ID, DOI, trial registry ID), and citation details (i.e. author names, journal, year of publication, volume, number, pages, article title and abstract).

Two researchers independently screened the titles and abstracts yielded by the search against the inclusion criteria. We obtained the full reports for all titles that appeared to meet the inclusion criteria or required further analysis to decide about their inclusion.
We recorded the study selection process in a PRISMA flow diagram and recorded the reasons for excluding the studies at any stage of the search.

Extraction and management of data
Two reviewers independently extracted data from each included study using standardized forms. We resolved disagreements by discussion, and one arbiter adjudicated unresolved disagreements. We contacted authors of the primary studies in case of missing information in the retrieved studies.

Risk of bias assessment
The risk of bias for each RCT was assessed using the Cochrane Risk of Bias Tool, which includes the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias (23).
In the case of NRSI, the ROBINS-I tool was used (24). This tool evaluates the following domains: bias due to confounding, selection of participants, classification of interventions, deviation from intended interventions, missing data, measurement of outcomes, and bias in selection of the reported result. According to these domains, the overall risk of bias was judged as “low”, “moderate”, “serious”, “critical” and “no information”.

Measures of treatment effect
For binary outcomes, results were presented as the proportion of patients who suffered the corresponding analyzed event. We used hazard ratio (HR), risk ratio (RR) and odds ratio (OR) for summarizing the results as appropriate. Absolute risk reduction (ARR) or absolute risk increase (ARI), and number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) were also calculated, when applicable, with 95% confidence intervals (CI).

For quantitative data, mean difference (MD) or standardized mean difference (SMD) were estimated as appropriate. We also determined the 95%CI.

Data synthesis
Results from the different studies were analyzed separately according to the specific study design. Evidence from RCTs was prioritized. The information from NRSI was considered as complementary when there was no RCT for main outcomes or when the evidence from RCTs was rated as ‘low’ or ‘very low’ certainty according to the GRADE approach. A fixed-effects model was used to combine results for each outcome across trials when applicable. Data were analyzed following an intention-to-treat approach.

To test for heterogeneity of treatment effect among trials we used I^2 statistic. We considered $I^2 > 60\%$ as indicative of substantial heterogeneity, whose possible reasons were planned to be explored by carrying out sensitivity and subgroup analyses.

When only one study provided data for an outcome or when data obtained from different studies showed substantial heterogeneity ($I^2 > 60\%$), we provided a narrative description of the results (aggregated estimates are presented only for verification purposes).
We used Review Manager Software (RevMan® version 5.4) for carrying out the meta-analyses (26).

Subgroup and sensitivity analysis
We planned to perform subgroup analysis according to type of CAR-T therapy, type of hematologic disease, type of comparator, age group (≥18 years and <18 years), treatment line, tumor burden or cancer stage.

We planned to perform sensitivity analyses excluding high risk of bias studies and excluding industry-sponsored studies.

Assessment of certainty of evidence
Two reviewers independently assessed the certainty of the evidence for each outcome following the GRADE approach, which considers five aspects: risk of bias of included studies, directness of the evidence, consistency among trials' results, precision of effect estimates, and risk of publication bias (27). Overall certainty of evidence could be downgraded starting from a high quality in the case of RCTs, and evidence could be upgraded starting from a low quality in the case of NRSI, when appropriate (25).
Discrepancies were resolved by discussion and by involvement of a third author, if necessary.

Living evidence synthesis and future updates

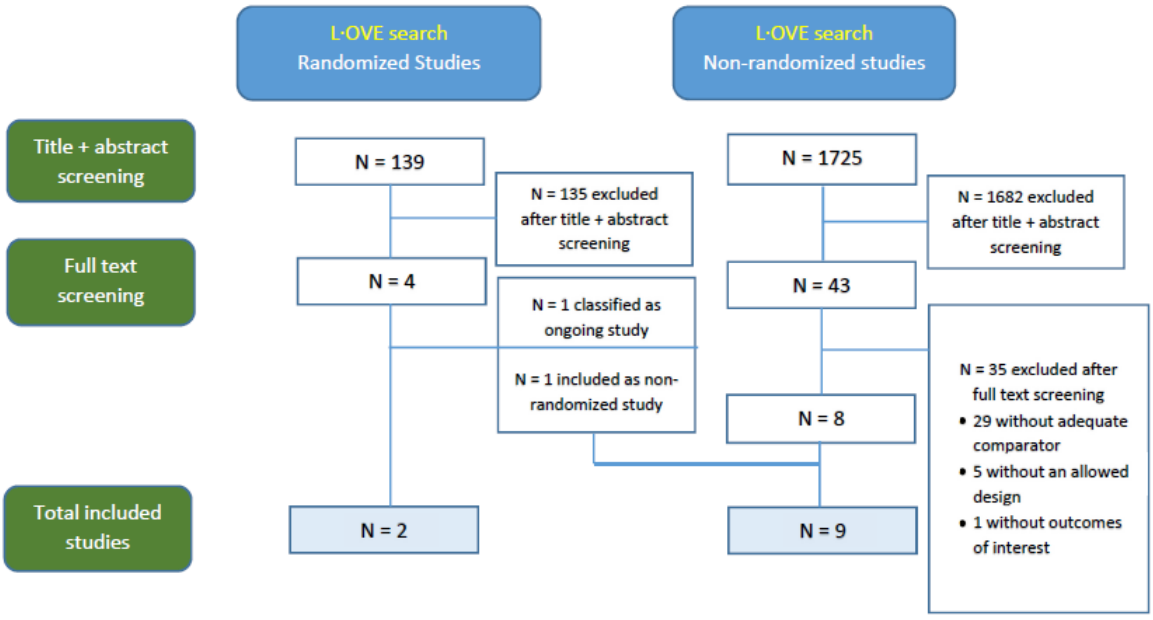
After this baseline synthesis of the evidence, we will keep a living search in the L·OVE platform, in which an artificial intelligence algorithm will provide instant notification of articles with a high likelihood to be eligible. The identified articles will undergo screening to assess for eligibility.

RESULTS

Results of the search
Literature searches retrieved a total of 1864 articles to the L·OVE platform. We considered 139 RCTs and 1725 NRSI as potentially eligible, out of them 4 and 43 studies were reviewed in full text. After full text review, we excluded 35 NRSI that did not fulfill our eligibility criteria, and the remaining 2 RCTs (30, 31) and 9 NRSI (two quasi-experimental studies (32, 33) and seven cohort studies [34-40])

assessing the use of CAR-T in 1221 participants with B-cell lymphoma or T or B-cell acute lymphoblastic leukemia (ALL) respectively were included in the review. A detailed list with reasons for exclusion is presented in **Appendix 2**. Finally, an ongoing RCT providing immature data for its primary outcome (EFS) was also identified but not still included because of its preliminary status (41). The study selection process is summarized in **Figure 1**.

Figure 1 – PRISMA Flowchart



Description of the included studies

Patients included in the studies have either R/R B-cell lymphoma (2 RCTs and 2 NRSI, 830 participants) or T / B-cell ALL (7 NRSI, 391 participants) and received a CAR-T therapy or one of the following comparators: HSCT, chemotherapy, donor leukocyte infusion (DLI), polatuzumab or SoC. **Table 1** presents the main characteristics of the included studies and baseline characteristics of the participants.

Table 1. Main characteristics of the included studies and baseline characteristics of the participants.

	Locke 2021	Bishop 2021	Wang 2019	Hua 2021	Zhao 2021	Schulthess 2021	Liu 2021	Muffly 2021	Avivi 2021	Hu 2022	Wang 2022
Design	RCT	RCT	QE	QE	C	C	C	C	C	C	C
Adjusted analysis	NA	NA	No	No	No	Yes	No	No	No	No	No
Center	MC	MC	UC	UC	UC	UC	UC	UC	MC	UC	UC
Location	More than one country	More than one country	China	China	China	USA	China	USA	Israel	China	China
Funding	Kite Pharma, Gilead	Novartis	Natural Science Foundation of China, and others	Natural Science Foundation of Jiangsu, and others	No info	National Health Care Institute	Natural Science Foundation of China, and others	Adaptive Biotechnologies	No info	Foundations CIFMS and BKCSCPP	Natural Science Foundation of China
Conflicts of interest	Multiple CoIs	Multiple CoIs	Yes: reported funders and Gillson	No CoI according to the authors	No CoI according to the authors	No CoI according to the authors	No CoI according to the authors	Multiple CoIs	Yes (the corresponding author)	Yes (two authors)	No CoI according to the authors
Study period	01/2018 to 10/2019	05/2019 to 01/2021	NR	09/2017 to 11/2019	11/2015 to 08/2016	2012-2018	07/2011 to 06/2019	03/2018 to 04/2020	06/2018 to 09/2019	01/2015 to 09/2019	08/2016 to 05/2020
Population of interest	359	322	32	28	105	43	44	62	82	77	67
Baseline imbalances, any variable	No	No	No	No	Yes	Yes	No	Yes	Yes	No	No
Withdrawals, exclusions	NR	NR	NR	1	NR	NR	1	NR	NR	0	NR
Age, years	range 21-80	range 19-79	range 14-54	range 9-53	range 2-52	under 26	range 15-67	42 SD (30-53)	median 64-68	range 1-17	range 19-71
Sex, males, no. (%)	237 (66%)	201 (62%)	21 (66%)	12 (43%)	61 (58%)	NR	20 (46%)	36 (58%)	44 (54%)	45 (58%)	33 (49%)
Children no. (%)	No	No	NR	NR	<14 years: 56 (53%)	NR	NR	No	No	100%	No

Type of pathology and stage	R/R B-Lymphoma	R/R B-Lymphoma	R/R B-ALL	R/R B-ALL	B-ALL	B-ALL	R/R B-ALL	T or B-ALL	R/R B-Lymphoma	B-ALL	R/R B-Lymphoma
Previous lines (no.)	1	1	NR	NR	NR	NR	≥2 cycles of prior therapy	NR	≥ 2	1	≥ 1
Previous HSCT	No	No	Yes	Yes	No	NR	Yes	NR	Some patients	No	No
High risk cytogenetics, no. (%)	NR	NR	16 (50%)	14 (50%)	48 (46%)	NR	NR	18 (29%)	NR	29 (38%)	NR
Extramedullary disease, no. (%)	NR	NR	NR	NR	15 (14%)	NR	20 (46%)	28 (45%)	NR	9 (12%)	NR
CAR-T dose	2×10^6 cells/kg	0.6 to 6.0×10^8 viable T cells	1.6×10^7 cells/kg (range, 0.43–5.5 × 10^7 cells/ kg)	5×10^6 cells/kg (range, 1.5–10.0×10^6 cells/kg)	NR	NR	NR	NR	NR	3.9×10^6 cells/kg range, 0.5–8.5×10^6 cells/kg	NR
T-cell origin	Autologous	Autologous	Allogenic	Allogenic	NR	NR	NR	NR	NR	Autologous	NR
Transfection / transduction method	Retrovirus	Lentivirus	Lentivirus	Transduction	Lentivirus	NR	NR	NR	NR	Lentivirus	Lentivirus
Target antigen	CD19+	CD19+	CD19+	CD19+	CD19+	NR	NR	NR	NR	CD19+	CD19+
CAR costimulatory domain	CD28	4-1BB	4-1BB	4-1BB	4-1BB	NR	NR	NR	NR	4-1BB and CD28	4-1BB
Intervention arm	Axicabtagene ciloleucel	Tisagenlecleucel	CAR-T	CAR-T	CAR-T + HSCT	CAR-T	CAR-T	CAR-T	CAR-T	CAR-T	CAR-T + ASCT
Comparator arm	SoC	SoC	DLI	DLI	CH + HSCT	HSCT	CH	HSCT	Polatuzumab	Chemotherapy	ASCT

Outcomes measured	OS, ORR, CR, PR, PFS, SAE, CRS, neurotoxicity, total AE	OS, ORR, CR, PR, SAE, CRS, neurotoxicity, total AE	OS, CR, CRS, GvHD	OS, CR, PR, CRS, GvHD	OS, relapse from CR, CRS, GvHD, neurotoxicity	PFS	CRS	OS, relapse from CR	OS, ORR, CR, PFS, CRS, neurotoxicity	OS, CR, relapse from CR, TTT, CRS, GvHD	OS, ORR, CR, PR, relapse from CR, PFS, CRS, neurotoxicity

ASCT: Autologous stem cell transplantation; C: Cohort study; CH: Chemotherapy; CoI: Conflicts of Interest; CR: Complete Remission; CRS: Cytokine-release syndrome;
DLI: Donor lymphocyte infusion; GvHD: Graft-versus-host disease; HSCT: Hematopoietic stem cell transplantation; MC: Multicenter: NA: Not applicable
NR: Not reported; OS: Overall Survival; PFS: Progression-free survival; PR: Partial Remission; QE: Quasi-experimental study;
R/R B-ALL: Relapsed/Refractory B-cell acute lymphoblastic leukemia; RCT: Randomized controlled trial; SoC: Standard of care; UC: Unicenter.

Risk of bias of included studies

Both included RCTs (30, 31) were rated as serious overall risk of bias. The main concerns arose from the performance bias domain (open-label design, particularly relevant in case of subjective outcomes) and 'other bias' domain (crossover allowed). Among the rest of domains, selection and reporting bias were estimated as low risk and attrition bias as unclear. Detection bias was rated as low risk in ZUMA-7 (30) and unclear in BELINDA (31).

The two quasi-experimental studies were both globally rated as 'no information', due to the lack of data on two domains: confounding (32, 33) and selection of participants (32). Regarding most of estimated outcomes (OS, ORR, CR, PR, relapse from CR, PFS, CRS, TtT, GvHD, neurotoxicity, SAE) the overall risk of bias in the cohort studies was judged as moderate (34, 35, 38-40) or serious (36, 37), mainly due to concerns related to the first domain (confounding). However, when other outcomes with a higher subjective profile were considered (e.g. TAE with ≥3 grade), risk of bias was rated as serious (32), taking into account the study assessors' awareness of the treatment groups.

Appendix 3 presents the detailed assessment by subdomain for all included studies.

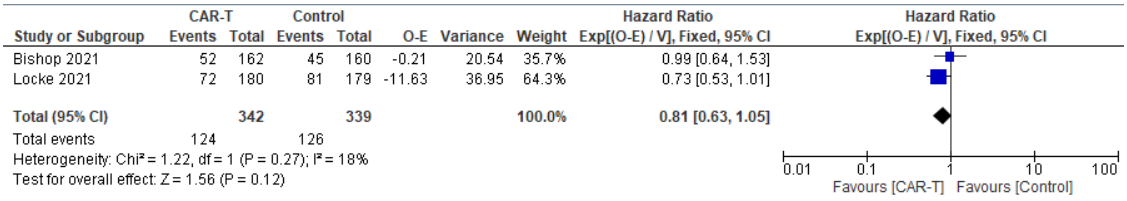
EFFECTS OF INTERVENTIONS

Primary outcome:

Overall survival (OS)

There was no significant difference in OS between CAR-T and SoC in R/R B-cell lymphoma patients according to 2 RCTs (30, 31) [HR 0.81, 95%CI (0.63-1.05); I^2=18%] (**Figure 2**). The certainty of evidence for this outcome is low due to crossover allowed and imprecision on estimates of the effect (**Table 2**).

Figure 2 – Overall survival comparing CAR-T with SoC therapy in RCTs including patients with R/R B-cell lymphoma.



The 2 quasi-experimental studies assessing OS (32, 33) showed longer OS with CAR-T versus DLI therapy in R/R B-ALL patients. (Wang 2019 [32]: DLI median 3.7 months (range 0-65); CAR-T median

12 months (range 3-29); p=0.049. Hua 2021 [33]: DLI median 5.5 months (range 1-25); CAR-T median 9.5 months (range 3-25); p=0.030).

Finally, five cohort studies comparing CAR-T in T or B-ALL and R/R B-cell lymphoma with different control groups have reported OS results (34, 37-40). No statistically significant differences were found in four studies (34, 37, 39, 40), while one study showed longer OS in the CAR-T group [HR 0.28, 95%CI (0.13-0.64)] (38) (**Appendix 4, Table S2**). The summary of findings on this outcome in quasi-experimental and cohort studies are presented in **Appendix 4.**

Table 2. GRADE Evidence Profile for randomized controlled trials

CAR-T therapies compared to any other intervention for hematologic malignancies

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Any other intervention	With CAR-T therapies	Relative effect (95% CI)	Risk with Any other intervention	Risk difference with CAR-T therapies
Overall survival											
681 (2 RCTs)[30,31]	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	126/339 (37.2%)	124/342 (36.3%)	**RR 0.98** (0.80 to 1.19)	372 per 1000	**7 fewer per 1000** (from 74 fewer to 71 more)
Complete response											
681 (2 RCTs) [30,31]	serious[a]	very serious[c]	not serious	not serious	none	⨁◯◯◯ Very low	102/339 (30.1%)	163/342 (47.7%)	**RR 1.59** (1.30 to 1.93)	301 per 1000	**178 more per 1000** (from 90 more to 280 more)
Relapse from complete response - not reported											
Progression-free survival											
359 (1 RCT) [30]	serious[d]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	NR	NR	**HR 0.49** (0.37 to 0.65)	NR	NR
Serious adverse events											
660 (2 RCTs) [30,31]	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	159/328 (48.5%)	161/332 (48.5%)	**RR 1.00** (0.85 to 1.17)	485 per 1000	**0 fewer per 1000** (from 73 fewer to 82 more)
Graft-versus-host disease - not reported											
Total adverse events (grade 3 or higher)											

CAR-T therapies compared to any other intervention for hematologic malignancies

Certainty assessment							Summary of findings				
660 (2 RCTs) [30,31]	serious[d]	very serious[c]	not serious	not serious	none	⨁◯◯◯ Very low	284/328 (86.6%)	291/332 (87.7%)	**RR 1.01** (0.95 to 1.07)	866 per 1000	**9 more per 1000** (from 43 fewer to 61 more)

CI: confidence interval; **HR:** Hazard ratio for progression or death; **NR:** Not reported; **RR:** Risk ratio

Explanations

a) Two RCTs allowed crossover from standard care to CAR-T after insufficient response; b) 95%CI is consistent with the possibility for relevant benefit and harm exceeding a minimal important difference; c) Unexplained and substantial heterogeneity, with point estimates widely different and confidence intervals not overlapping significantly; d) RCTs allowed crossover from standard care to CAR-T after insufficient response and outcomes highly subjective, especially affected by the open-label design.

Key secondary outcomes:

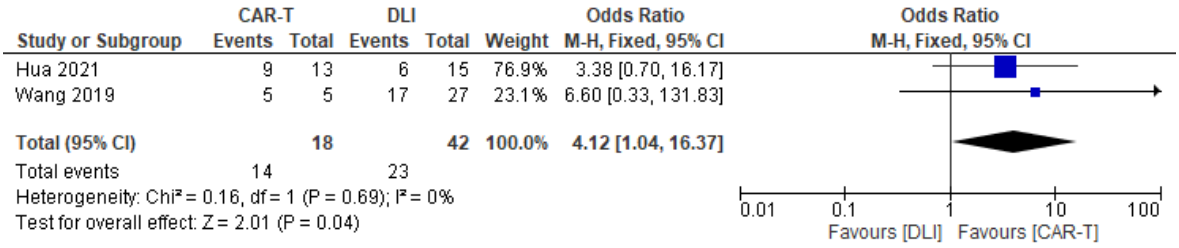
Complete Response/Remission (CR) rate

The meta-analysis of 2 RCTs (30, 31) showed a higher CR with CAR-T compared to SoC therapy in R/R B-cell lymphoma patients [RR 1.59, 95%CI (1.30-1.93); I^2=89%]. However, substantial heterogeneity was detected, which greatly reduces confidence in the estimate. The NNTB leading to an additional CR with CAR-T therapies was 6 (95%CI 4 to 12). The certainty of evidence for this outcome is very low, downgraded because the crossover was allowed and inconsistency (**Table 2**).

Evidence from 2 quasi-experimental studies (32, 33) showed a higher CR with CAR-T compared to DLI therapy in R/R B-ALL patients [OR 4.12, 95%CI (1.04-16.37); I^2=0%] (**Figure 3**). The NNTB leading to an additional CR with CAR-T therapies was 4 (95%CI 3 to 100).

The certainty of evidence for this outcome is low due to lack of information on adjustment for confounding variables and imprecision (**Appendix 4, Table S1**).

Figure 3 – Complete Response/Remission rate comparing CAR-T with DLI therapy in patients with R/R B-ALL.



As for the 3 cohort studies that reported CR results (38-40), no differences between CAR-T and control group were found in one study (38), while the remaining 2 results in favor of the CAR-T group [CAR-T 91%; Chemotherapy 71%, p=0.036 (39); CAR-T+ASCT: 71%; ASCT: 33%, p=0.003 (40)] (**Appendix 4, Table S2**).

Relapse from CR

Evidence on relapse from CR from 3 cohort studies (34, 37, 39) did not show differences between CAR-T and control group, although with high heterogeneity [OR 1.24, 95%CI (0.69-2.24); I^2=90%]. The certainty of evidence for this outcome is very low due to lack of adjustment for important factors, serious inconsistency and serious imprecision (**Appendix 4, Table S2**).

Progression-free survival (PFS)

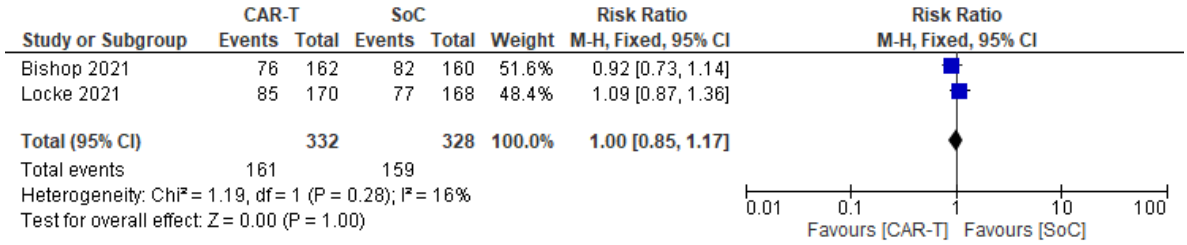
The only RCT reporting PFS (30) showed a higher rate of PFS with CAR-T compared to SoC in R/R B-cell lymphoma patients [HR for progression or death 0.49, 95%CI (0.37-0.65)]. The certainty of evidence for this outcome is moderate for the RCT due to crossover allowed (**Table 2**).

Two cohort studies (38, 40) showed statistically significant PFS results in favor of the CAR-T [HR 0.49, 95%CI (0.25-0.98), p=0.045 (38); CAR-T+ASCT: 80% (95% CI; 60–98); ASCT: 44% (95% CI; 25–64), p=0.036 (40)], while the remaining did not show differences (35). The average certainty of evidence for this outcome could not be assessed (**Appendix 4, Table S2**).

Serious adverse events (SAE)

The meta-analysis of 2 RCTs (30, 31) did not show statistically differences in SAE with CAR-T compared to SoC in R/R B-cell lymphoma patients [RR 1.00, 95%CI (0.85-1.17); I^2=16%] (**Figure 5**). The certainty of evidence for this outcome is low due to crossover allowed and imprecision on estimates of the effects. (**Table 2**).

Figure 5 – Serious Adverse Events in RCTs comparing CAR-T with SC therapy in patients with R/R B-cell lymphoma



Graft-versus-host disease (GvHD)

Two quasi-experimental studies reported the effect of interventions, after HSCT, in incidence of acute or new GvHD (32, 33). The meta-analysis showed a lower incidence of GvHD with CAR-T compared to DLI in B-ALL patients [OR 0.11, 95%CI (0.02-0.69); I^2=0%]. The NNTB to avoid an additional case of GvHD with CAR-T therapies was 4 (95%CI 3 to 13). The certainty of evidence for this outcome is low due to imprecision in estimates of the effect and lack of information on adjustment for confounding variables (**Appendix 4, Table S1**).

In contrast, one cohort study (34) comparing CAR-T + HSCT versus chemotherapy + HSCT in B-ALL patients reported a higher incidence of acute GvHD (grade II or higher) in the CAR-T group [HR 2.36 (95%CI 1.18-4.75); p=0.016]. The NNTH leading to an additional case of GvHD with CAR-T therapies was 5 (95%CI 3 to 26). The certainty of evidence for this outcome is low due to lack of adjustment for important factors and imprecision (**Appendix 4, Table S2**).

Total adverse events (TAE) (grade ≥3)

The meta-analysis of 2 RCTs (30, 31) did not show significant differences in TAE with CAR-T compared to SoC in R/R B-cell lymphoma patients [RR 1.01, 95%CI (0.95-1.07); I^2=86%]. However, a substantial heterogeneity was detected, which greatly reduces confidence in the estimate. The certainty of evidence for this outcome is very low due to crossover allowed, inconsistency and imprecision (**Table 2**).

The summary of findings on the key secondary outcomes in quasi-experimental and cohort studies are presented in **Appendix 4.**

Other secondary outcomes

Overall Response rate (ORR)

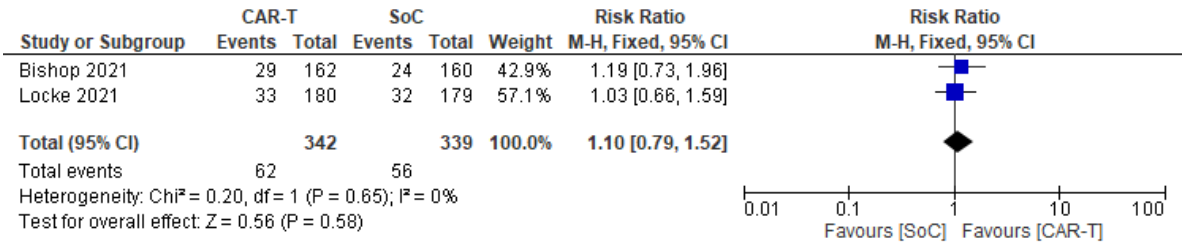
According to evidence from 2 RCTs (30, 31), CAR-T therapy was associated to a higher ORR compared to SoC in R/R B-cell lymphoma patients [RR 1.41, 95%CI (1.23-1.62); I^2=88%]. However, a substantial heterogeneity was detected, which greatly reduces confidence in the estimate. The NNTB leading to an additional ORR with CAR-T therapies was 6 (95%CI 4 to 10). The certainty of evidence for this outcome is very low due to crossover allowed and substantial heterogeneity.

No differences in ORR were found between CAR-T and control group in two cohort studies (38, 40).

Partial Response/Remission (PR)

According to the evidence from 2 RCTs (30, 31), there were no statistically differences in PR with CAR-T therapy compared to SoC therapy in R/R B-cell lymphoma patients [RR 1.10, 95%CI (0.79-1.52); I^2=0%]. (**Figure 4**). The certainty of evidence for this outcome is low due to crossover allowed and imprecision in estimates of the effect.

Figure 4 – Partial response in RCTs comparing CAR-T versus SoC therapy in people with R/R B-cell lymphoma



The only quasi-experimental study that reported results on PR (33) found no statistical differences when comparing CAR-T versus DLI in R/R B-ALL patients [OR 0.23, 95%CI (0.02-2.38)].

The only cohort study that reported PR results showed statistically significant results in favor of the control group [CAR-T + ASCT 19% (95%CI 5-42) vs ASCT 56% (95%CI 41-71); p=0.004] (40).

Time from CAR-T infusion to transplantation

One cohort study reported that median time from CAR-T infusion to HSCT was 67 days (39).

Incidence of cytokine-release syndrome (CRS) (grade ≥3)

The meta-analysis of 2 RCTs (30, 31) showed a higher rate of CRS with CAR-T compared to SoC in R/R B-cell lymphoma patients [RR 19.76, 95%CI (2.67-146.39); I^2=0%]. The certainty of evidence for this outcome is low due to crossover allowed and imprecision in estimates of the effect.

Additionally, The meta-analysis of the two quasi-experimental studies reporting data on CRS (32, 33) showed a lower incidence of CRS with DLI compared to CAR-T in R/R B-ALL patients [OR 0.08, 95%CI (0.01-0.84); I^2=0%], assuming zero events in the comparator arm if not specifically reported. The certainty of evidence for this outcome is low due to imprecision in estimates of the effect and lack of information on adjustment for confounding variables.

Finally, five cohort studies also reported incidence of CRS, ranging from 5% to 15% in the CAR-T groups (34, 36, 38-40). None of the above studies but Wang 2022 (40) provided explicit information on the incidence of CRS in their comparator groups, being assumed as zero events for these arms. We did not rate the certainty of evidence for this outcome due to insufficient information for the assessment.

Neurotoxicity (grade ≥3)

The meta-analysis of 2 RCTs (30, 31) showed a higher rate of neurotoxicity with CAR-T compared to SoC in R/R B-cell lymphoma patients [RR 26.02, 95%CI (5.14-131.67); I^2=0%]. The NNTH leading to an additional case of neurotoxicity with CAR-T therapies was 14 (95%CI 3 to 77). The certainty of evidence for this outcome is moderate due to crossover allowed.

Incidence of neurotoxicity in 3 cohort studies ranged from 0% to 15% in the CAR-T groups (33, 38, 40). Only Avivi 2021 (40) provided information on the incidence of 1 case of peripheral neuropathy (2%) in the comparator group.

Quality of life (QoL)

The included studies did not assess this outcome.

There was not enough information to perform pre-planned subgroup analyses. All the outcomes remained unchanged after carrying out sensitivity analyses excluding studies with serious risk of bias (35, 36, 37) (**Appendix 3**). Both RCTs and none of the quasi-experimental/cohort studies were

industry-sponsored. Thus, it was not possible to explore potential differences on this aspect within each particular design.

DISCUSSION

To date, this living systematic review has identified two RCTs evaluating the use of CAR-T compared to SoC for hematologic malignancies, namely R/R B-cell lymphoma (30, 31). Beyond that, 9 NRSI (32-40) in T or B-ALL and R/R B-lymphoma with different comparators (chemotherapy, HSCT, DLI, polatuzumab) have been retrieved on this topic. One ongoing RCT with interim results (41) was identified and its data will only be considered for inclusion when the trial is completed.
No comparative studies analyzing CAR-T therapy in participants with other hematological malignancies such as multiple myeloma were identified.

CAR-T therapy showed benefits in terms of a longer CR and PFS. On the other hand, no benefit in OS was observed, nor in the rest of secondary outcomes evaluated. However, the follow-up period was probably rather short to assess results in mortality. Regarding the safety outcomes, no differences between CAR-T and alternative therapies have been identified concerning SAE and TAE (grade ≥3). As expected, serious CRS was strongly linked to CAR-T use regardless the comparator, whereas GvHD showed conflicting results between quasi-experimental and cohort studies.

The results of CAR-T therapy obtained so far may be considered as modest. In the case of BELINDA (31), authors claimed that treatment groups were not balanced at baseline. In the CAR-T group, there was a higher proportion of patients with high-grade lymphomas compared to the SoC group (24.1% vs. 16.9%, respectively). Additionally, they also pointed out that the CAR-T group had a higher percentage of patients with an International Prognostic Index score of ≥2, indicating a worse prognosis (65.4% vs. 57.5%, respectively). According to the authors, this could have biased results against the CAR-T cell group. However, in ZUMA-7 (30) both groups were balanced at baseline and results were similar.

Both included RCTs included patients with aggressive B-cell non-Hodgkin's lymphomas not responding to or progressing within 12 months after first-line therapy. It would be important to learn about the potential benefits of CAR-T therapy in less aggressive lymphomas. Likewise, we have other challenges ahead, like identifying patients who may have a better risk-benefit profile, improving CAR-T cells, testing the effects of CAR-T therapy in other tumors, and defining the risk-benefit balance in patients at earlier stages of disease. Also, the status of allogeneic or autologous CAR-T might also be relevant in terms of patient severity and adverse event profile marker. Remarkably, RCTs and NRSI in this review differed in this parameter, using autologous and allogeneic therapies respectively.

Evaluating the certainty of evidence

As for meta-analyses with acceptable heterogeneity, all assessed outcomes presented imprecision concerns and were evaluated with an insufficient sample size. Also all estimates in the cohort studies were judged as substantially imprecise and led to downgrade the certainty of this evidence.

Despite the apparently identical design, the two included RCTs (30, 31) showed divergent results and substantial heterogeneity (I^2>80%) in key secondary outcomes such as CR or TAE (grade ≥3). Apart from differences in CAR-T cell products, costimulatory domains or gene-transfer method, BELINDA (31) allowed participants with bridging chemotherapy and impending organ-compromising disease, which likely would lead to a worse prognosis and less benefit from the experimental intervention (42). All these aspects, among others, might explain the observed inconsistency.

Evidence on CR coming from quasi-experimental studies showed a higher certainty (low) than that from RCTs (very low). Nonetheless, the direction of effect was similar with both designs, showing benefit from using CAR-T in some degree.

Some valuable data, too many uncertainties

The severity of hematologic malignancies, added to the lack of appropriate treatment strategies when a recurrent stage is reached, has promoted the search of new interventions from different perspectives, CAR-T therapies among them (1). While promising, those strategies are currently short of interventional evidence and, as shown in this systematic review, are also in need of more extensive comparative data. Consequently, at this point there is still wide uncertainty of the actual balance between efficacy and harms for this alternative.

The results of the included studies seem to confirm the known CAR-T toxicity profile in terms of an uncontrolled CRS and neurotoxicity. Regarding other key safety outcomes such as SAEs and grade ≥3 TAE, no particular risk or benefit has been reported with CAR-T therapies. Quality of life data were not provided by the identified studies. Also, no benefit has been proved favoring CAR-T versus other alternatives related to PR or relapse from CR, while the evidence was too scarce as to make a definite statement.

Ongoing evidence is strongly needed

A still-increasing amount of evidence assessing these strategies is underway (43), so the question is yet to be answered. Beyond the eleven included studies (30-40), a growing number of ongoing interventional and observational studies with comparative designs can be located at platforms such as *ClinicalTrials.gov*. One systematic review (13) carried out by authors with declared conflicts of interest and including 3 RCTs involving 865 participants (30, 31, 41) was identified after an in-depth screening. The review addressed only two hematologic conditions (acute B-cell lymphoblastic leukemia and B-cell lymphoma), which obviously reduces the generalizability of the conclusions to

other hematologic malignancies. The performed meta-analysis showed that CAR-T therapy was superior to SoC in OS and event-free survival. However, the beneficial effect in OS was reached thanks to the inclusion of the ongoing TRANSFORM trial (41), a study designed for a 3-year follow-up whose published results, covering a median follow-up of only 6.2 months, are still preliminary and clearly immature. In this sense, long-term, well-designed and solid evidence is still needed, particularly on other highly prevalent hematologic diseases for which CAR-T therapies are already being used such as myeloma.

Strengths and limitations

Our living systematic review has some strengths to be emphasized: First, up to our best knowledge this is the first living systematic review that focused on comparative studies assessing CAR-T in hematologic malignancies. Second, this work has benefited from advanced technological tools to facilitate the process of assessing evidence. Third, it has been able to show some meaningful benefit favoring CAR-T on relevant variables such as CR and PFS. And fourth, no statistical heterogeneity was found in the majority of estimated outcomes.

However, this work is not exempt of limitations, principally due to the fact that it lies on only two RCTs assessing one hematologic condition (R/R B-lymphoma), beyond sparse and diverse quasi-experimental and observational data focused on T or B-ALL and R/R B-lymphoma. Also, the total sample size was rather limited and differences in comparators were confirmed among retrieved studies. As previously mentioned, some concerns have been raised about potential reporting bias in NRSI in relation with adverse events in the CAR-T group. Finally, reported information on baseline characteristics was not homogeneous among the included studies.

CONCLUSION

Current limited data from RCTs show a meaningful benefit in progression-free survival and complete response for T or B-ALL and R/R B-lymphoma patients. However, no definite conclusion can be drawn at this point. We expect this limitation to be overcome in the near future when new sound evidence can be added to the existing one, especially when more RCTs are published.

NOTES

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Roles and contributions

LL, MGV, LCS and JE conceived the project. LL drafted the protocol and all other authors contributed to it. LL, MGV, LCS and JE carried out the screening of the references, extracted data, and assessed the risk of bias and quality of the evidence of included studies. LCS performed data analyses. LCS drafted the manuscript and all other authors contributed to it. MXRR made important intellectual contributions to the manuscript draft and also contributed by facilitating external guidance and training with Epistemonikos and L.OVE tools. The corresponding author (LCS) is the guarantor and declares that all authors meet authorship criteria and that no other authors meeting the criteria have been omitted.

Competing interests

All authors declare no financial relationships with any organization that might have a real or perceived interest in this work.

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Ethics

As researchers we did not access information that could lead to the identification of an individual participant, and obtaining ethical approval was waived.

Data sharing

All data related to the project is available at Open Science Framework (Living evidence to inform health decisions; extended data https://osf.io/93h67/). Epistemonikos Foundation will grant access to available evidence in L.OVE.

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Appendix 1. Boolean search strategy

Epistemonikos

(leukem* OR leukaem* OR leucem* OR leucaem* OR lymphoma* OR lymphobl* OR ((hemato* OR haemato* OR lymph* OR myelo*) AND (malignan* OR malignan*))) AND ((("car-engineered" OR "car-modified" OR "receptor-modified" OR chimeric* OR adoptive* OR redirected* OR engineered*) AND ("t cell" OR "t cells" OR "t-cell" OR "t-cells")) OR "car-t" OR "car t" OR "car-ts" OR "car ts" OR "car t-cell" OR "car t-cells")

Medline. PUBMED

(leukem* OR leukaem* OR leucem* OR leucaem* OR lymphoma* OR lymphobl* OR ((hemato* OR haemato* OR lymph* OR myelo*) AND (malignan* OR malignan*))) AND ((("car-engineered" OR "car-modified" OR "receptor-modified" OR chimeric* OR adoptive* OR redirected* OR engineered*) AND ("t cell" OR "t cells" OR "t-cell" OR "t-cells")) OR "car-t" OR "car t" OR "car-ts" OR "car ts" OR "car t-cell" OR "car t-cells")

Appendix 2. Reasons for exclusion in non-randomized studies.

	Decision			Exclusion criteria					
	To include	To exclude	Awaiting classification	No quasi-experimental, cohort or case-control study	Without outcomes of interest	Patients without hematologic malignancy	No CAR-T intervention	No comparator or no adequate comparator (chemotherapy, drug treatment, transplantation, supportive care, other)	Quote from publications supporting decision
Aldoss 2021		x			x				We retrospectively studied alloHCT outcomes in 108 adult patients with r/r Phneg B-ALL transplanted in morphological remission achieved by salvage therapy. We have included pre-HCT CAR T cells therapy cohort in patient characteristics and early transplant outcomes (30-day); however, because of the small number of patients in this subgroup (n = 6), **we excluded them from the outcomes analyzes**.
Anonymous 2020		x						x	Retrospective patient chart analysis of all patients who received tisagenlecleucel in Canada for r/r all either through clinical trials (NCT02435849, NCT03123939, n = 22)
Bethge 2022		x						x	We report 356 patients who received axi-cel (n=173) or tisa-cel (n=183) between November 2018 and April 2021 at 21 German centers.
Ceppi 2022		x						x	We tested the modified manufacturing process and resulting product, designated SCRI-CAR19v2, in a cohort of 21 subjects on the phase 2 arm of the trial. Here, we describe the unanticipated enhancement in product performance resulting in prolonged persistence and B-cell aplasia, and improved leukemia-free survival with SCRI-CAR19v2 as compared to SCRI-CAR19v1.
Chen 2022		x						x	We report a relapsed/refractory diffuse large B-cell lymphoma (DLBCL) patient with progressive muscular dystrophy (PMD) characterized by progressive muscle weakness that affected the limb, axial and facial muscles.
Cohen 2019		x						x	Twenty-five subjects were treated in 3 cohorts as follows: cohort 1, 1 × 108 to 5 × 108 CART-BCMA cells alone; cohort 2, cyclophosphamide (Cy) 1.5 g/m2 plus 1 × 107 to 5 × 107 CART-BCMA cells; cohort 3, Cy 1.5 g/m2 plus 1 × 108 to 5 × 108 CART-BCMA cells.
Cortes 2021		x						x	Of 130 patients with LBCL undergoing CAR T cell therapy, 24 (18.4%) had GI involvement.
Du 2020		x						x	The patient had no discernible response to anti-CD19 CAR-T treatment and exhibited progressive disease (PD). Following CD-22-directed CAR-T treatment, the patient underwent a partial remission (PR), but unfortunately a relapse rapidly occurred.
Gardner 2017		x						x	A phase 1 trial of 45 children and young adults with relapsed or refractory B-lineage acute lymphoblastic leukemia was conducted using a CD19 CAR product of defined CD4/CD8 composition, uniform CAR expression, and limited effector differentiation
Ghafouri 2021		x						x	This retrospective cohort study included 53 patients with R/R aBCL who received CAR-T from October 2017 to June 2020 at the University of California, Los Angeles
Gu 2022		x						x	The predictive model for CR was formulated by the number of white blood cells (WBC), central neural system (CNS) leukemia, TP53 mutation, bone marrow blasts, and CAR-T cell generation while the model for MRD-negative CR was formulated by disease status, bone marrow blasts, and infusion strategy.
Hu 2019		x						x	We retrospectively reviewed 31 patients: 17 received autoCAR, 11 received RD-alloCAR, and 3 received DD-alloCAR
Jiang 2018		x		x					Clinical study on the chimeric antigen receptor T cells for the treatment of T315I mutated central relapsed/refractory acute lymphoblast leukemia: a case report

Johnsrud 2021		x						x	We retrospectively analyzed consecutive adult patients (n=127) with large B-cell lymphoma (LBCL) or B-cell acute lymphoblastic leukemia (B-ALL) treated between 2017-2020 with axicabtagene ciloleucel (axi-cel) (N=89) or a bispecific CD19/CD22 CAR (N=38).
Kochenderfer 2009		x						x	In this protocol, we are modifying the patient s white blood cells with a retrovirus that has the gene for anti- cluster of differentiation 19 (CD19) incorporated in the retrovirus
Li 2018		x						x	In this case, we investigated a 42-year-old woman who was diagnosed with Ph+ALL and experienced multiple relapses. She was first treated with imatinib combined infusion chemotherapy and achieved complete remission (CR).
Li 2019		x		x					Some types of bias may exist, considering that we are comparing patients in a CAR-T trial with contemporaneous ones receiving ASCT as standard therapy rather than a 2-cohort randomized controlled trial
Liu 2021	x								Platelet Transfusion Refractoriness can be considered as a Serious Adverse Event
Maron 2022		x						x	In this work we describe our institutional experience in a cohort of 38 pediatric and AYA patients with CD19-positive malignancy treated with lymphodepleting chemotherapy (fludarabine/cyclophosphamide) followed by a single infusion of CD19-CAR T cells (total infusions, n=39), including tisagenlecleucel (n=19; CD19/4-1BB) or on an institutional clinical trial (n=20; CD19/4-1BB; NCT03573700).
Maurer 2021		x						x	The case cohort (cohort A) consisted of patients who underwent HSCT or CAR-T therapy from 15 March to 15 June 2020, whereas the prepandemic control cohort (cohort B) included HSCT or CAR-T patients treated from 15 December 2019 to 14 March 2020.
Mu 2022		x						x	We studied the efficacy and safety of the combined treatment with programmed cell death 1 (PD-1) inhibitors and anti-CD19 chimeric antigen receptor (CAR) T-cell therapy and subsequent PD-1 inhibitor maintenance treatment in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and high tumor burden.
Nasta 2022		x						x	We conducted a single institution, retrospective study investigating outcomes of adult lymphoma patients treated with commercial tisagenlecleucel between 10/2017 and 12/2020.
Patrick 2021		x						x	After lymphodepleting chemotherapy, patients received liso-cel as 2 sequential infusions of CD81 and CD41 CAR1 T cells at 1 of 3 target doses (50 3 106, 100 3 106, or 150 3 106 CAR1 T cells), administered by intravenous infusion.
Ram 2021		x						x	All consecutive patients ≥70 years (study cohort) were matched with patients younger than 70 years (control group). Patients were identified from a surveillance database of the participating centers. Matching was performed according to ECOG performance status at screening (0-1 vs. 2-3) and LDH blood levels prior the infusion of CAR-T product (high vs. normal).
Ramos 2018		x						x	We designed a clinical trial in which two autologous CD19-specific CAR-transduced T cell products (CD19.CARTs), 2G (with CD28 only) and 3G (CD28 and 4- 1BB), were infused simultaneously in 16 patients with relapsed or refractory non-Hodgkin's lymphoma.
Sarkar 2019		x		x					We built a microsimulation model for pediatric patients with relapsed/refractory B-ALL receiving either CAR-T therapy or standard of care.

Schulthess 2021	x								Patients were assigned to the CAR-T cohort or HCT cohort using multiple permutations of relevant ICD-10, CPT, HCPCS and procedure coding system codes, keyword searches for CAR-T therapy, prescriptions for infusion therapies and related physician notes captured as free text in the database
Shadman 2021		x		x					Using the Center for International Blood & Marrow Transplant Research registry database, we identified adult DLBCL patients who received either an auto-HCT (2013-2019) or CAR-T treatment with axicabtagene ciloleucel (2018-2019) while in a PR by CT or PET scan.
Shalabi 2022		x						x	This phase I dose-escalation trial enrolled children and young adults (CAYA) with B-cell malignancies.
Ting 2020		x						x	A total of 38 (18%) patients harbored the T315I mutation in this period. According to the type of salvage therapy, patients were divided into subgroups of hematopoietic stem cell transplantation (HSCT) recipients (n = 9) and HSCT nonrecipients (n = 29). In the latter subgroup, there were 7 patients who newly acquired the T315I mutation after HSCT, and the median time was 10.8 months. In addition to these 7 cases, 5 out of 22 patients were managed with chimeric antigen receptor (CAR) Tcells **and ponatinib**.
Walton 2019		x						x	This article presents a summary of the Evidence Review Group's (ERG's) independent review of the evidence submission, the committee's deliberations, and the subsequent development of NICE guidance for the use of tisagenlecleucel on the National Health Service (NHS) in England.
Wang 2019		x						x	Study group received the modified cell infusion method, that 1×10(6) CAR-T cells were re-suspended in 2 mg human serum albumin with total volume of 20 ml and injected intravenously. The control group was intravenously administrated with CAR-T cell in 100 ml normal saline.
Wang 2021		x						x	Four consecutive children with TCF-HLF3epositive B-ALL who were refractory or relapsed with initial chemotherapy were treated with CD19-specific or combined CD19-and CD22-specific chimeric antigen receptor T-cell therapy (19/22 CAR-T) after conditioning regimen with fludarabine and cyclophosphamide
Wei 2018		x		x					**From July 2015 to December 2016**, 23 consecutive patients were recruited for CART19 clinical trial defined as the CART19 group. We performed a matched case- controlled study analysis, in which each patient treated with CART19 was paired with 3 control subjects selected among R/R ALL patients treated with chemotherapy **from January 2012 to June 2015** that were defined as the chemotherapy group.
Wei 2022		x						x	From September 2016 to September 2020, 257 r/r B-NHL patients were assessed for eligibility for two trials in our center, assessing anti-CD19 and anti-CD22 chimeric antigen receptor (CAR19/22) T-cell cocktail treatment alone or in combination with autologous stem cell transplantation (ASCT).
Ying 2022		x						x	A phase I/II clinical trial was launched to evaluate the clinical outcomes of IM19 in relapsed or refractory (r/r) B cell non-Hodgkin lymphoma (B-NHL).
Zhao 2020		x						x	We performed a multicenter retrospective study to assess whether patients can benefit from haploidentical hematopoietic stem cell transplantation after CAR-T therapy.

Zhao 2021	x								We performed a parallel comparison of transplant outcomes in 105 consecutive B-ALL patients who received allo-HSCT after achieving CR with CAR-T therapy (n=27) or with chemotherapy (n=78).

Appendix 3. Risk of bias assessment by subdomain for included studies.

Author, year	Bias domain	OS	ORR	CR	PR	Relapse from CR	PFS	TtT	SAE	CRS	GvHD	Neurotoxicity	Total AE	QoL
COCHRANE RISK OF BIAS TOOL														
Locke 2021	1. Allocation concealment (selection bias)					-		-			-			-
	2. Random sequence generation (selection bias)					-		-			-			-
	3. Blinding (performance bias)					-		-			-			-
	4. Blinding (detection bias)					-		-			-			-
	5. Incomplete outcome data (attrition bias)					-		-			-			-
	6. Selective reporting bias (reporting bias)					-		-			-			-
	7. Other bias					-		-			-			-
Bishop 2021	1. Allocation concealment (selection bias)					-	-	-			-			-
	2. Random sequence generation (selection bias)					-	-	-			-			-
	3. Blinding (performance bias)					-	-	-			-			-
	4. Blinding (detection bias)					-	-	-			-			-
	5. Incomplete outcome data (attrition bias)					-	-	-			-			-
	6. Selective reporting bias (reporting bias)					-	-	-			-			-
	7. Other bias					-	-	-			-			-
ROBINS-I tool														
Zhao 2021	Confounding		-	-	-		-	-	-				-	-
	Selection of participants		-	-	-		-	-	-				-	-
	Classification of interventions		-	-	-		-	-	-				-	-

	Deviations from intended interventions		-	-	-		-	-	-				-	-
	Missing data		-	-	-		-	-	-				-	-
	Measurement of outcomes		-	-	-		-	-	-				-	-
	Selection of the reported result		-	-	-		-	-	-				-	-
Schulthess 2021	Confounding	-	-	-	-		-	-	-	-			-	-
	Selection of participants	-	-	-	-		-	-	-	-			-	-
	Classification of interventions	-	-	-	-		-	-	-	-			-	-
	Deviations from intended interventions	-	-	-	-		-	-	-	-			-	-
	Missing data	-	-	-	-		-	-	-	-			-	-
	Measurement of outcomes	-	-	-	-		-	-	-	-			-	-
	Selection of the reported result	-	-	-	-		-	-	-	-			-	-
Liu 2021	Confounding	-	-	-	-	-	-	-		-	-	-	-	-
	Selection of participants	-	-	-	-	-	-	-		-	-	-	-	-
	Classification of interventions	-	-	-	-	-	-	-		-	-	-	-	-
	Deviations from intended interventions	-	-	-	-	-	-	-		-	-	-	-	-
	Missing data	-	-	-	-	-	-	-		-	-	-	-	-
	Measurement of outcomes	-	-	-	-	-	-	-		-	-	-	-	-
	Selection of the reported result	-	-	-	-	-	-	-		-	-	-	-	-
Wang 2019	Confounding		-		-	-	-	-	-			-		-
	Selection of participants		-		-	-	-	-	-			-		-
	Classification of interventions		-		-	-	-	-	-			-		-
	Deviations from intended interventions		-		-	-	-	-	-			-		-
	Missing data		-		-	-	-	-	-			-		-
	Measurement of outcomes		-		-	-	-	-	-			-		-
	Bias in selection of the reported result		-		-	-	-	-	-			-		-
Hua 2021	Confounding		-		-	-	-	-	-			-	-	-
	Bias in selection of participants		-		-	-	-	-	-			-	-	-
	Bias in classification of interventions		-		-	-	-	-	-			-	-	-
	Bias due to deviations from intended interventions		-		-	-	-	-	-			-	-	-
	Bias due to missing data		-		-	-	-	-	-			-	-	-
	Bias in measurement of outcomes		-		-	-	-	-	-			-	-	-
	Bias in selection of the reported result		-		-	-	-	-	-			-	-	-
Muffly 2021	Confounding		-	-	-		-	-	-	-	-	-	-	-
	Bias in selection of participants		-	-	-		-	-	-	-	-	-	-	-
	Bias in classification of interventions		-	-	-		-	-	-	-	-	-	-	-
	Bias due to deviations from intended interventions		-	-	-		-	-	-	-	-	-	-	-
	Bias due to missing data		-	-	-		-	-	-	-	-	-	-	-

	Bias in measurement of outcomes		-	-	-		-	-	-	-	-	-	-	-
	Bias in selection of the reported result		-	-	-		-	-	-	-	-	-	-	-
Avivi 2021	Confounding				-			-	-		-		-	-
	Bias in selection of participants				-			-	-		-		-	-
	Bias in classification of interventions				-			-	-		-		-	-
	Bias due to deviations from intended interventions				-			-	-		-		-	-
	Bias due to missing data				-			-	-		-		-	-
	Bias in measurement of outcomes				-			-	-		-		-	-
	Bias in selection of the reported result				-			-	-		-		-	-
Hu 2022	Confounding		-		-		-		-			-	-	-
	Bias in selection of participants		-		-		-		-			-	-	-
	Bias in classification of interventions		-		-		-		-			-	-	-
	Bias due to deviations from intended interventions		-		-		-		-			-	-	-
	Bias due to missing data		-		-		-		-			-	-	-
	Bias in measurement of outcomes		-		-		-		-			-	-	-
	Bias in selection of the reported result		-		-		-		-			-	-	-
Wang 2022	Confounding							-	-		-		-	-
	Bias in selection of participants							-	-		-		-	-
	Bias in classification of interventions							-	-		-		-	-
	Bias due to deviations from intended interventions							-	-		-		-	-
	Bias due to missing data							-	-		-		-	-
	Bias in measurement of outcomes							-	-		-		-	-
	Bias in selection of the reported result							-	-		-		-	-

AE: adverse events; CR: complete response/remission; CRS: cytokine-release syndrome; GvHD: graft-versus-host disease; ORR: overall response; OS: overall survival; PFS: progression-free survival; PR: partial response/remission; SAE: serious adverse events; TtT: time from CAR-T infusion to transplantation, QoL: quality of life

No information

Low risk of bias

Moderate risk of bias

High risk of bias

Unclear risk of bias

Appendix 4.

Table S1. GRADE Evidence Profile for quasi-experimental studies

CAR-T therapies compared to any other intervention for hematologic malignancies

Certainty assessment							Summary of findings				
							Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With standard interventions	With CAR-T therapies		Risk with standard interventions	Risk difference with CAR-T therapies
Overall survival											
60 (2 quasi-experimental studies)[32,33]	serious[a]	not serious	not serious	N/A	none	-	Wang 2019[33]: DLI: median 3.7 months (range 0-65); CAR-T: median 12 months (range 3-29) Hua 2021[34]: DLI: median 5.5 months (range 1-25); CAR-T: median 9.5 months (range 3-25)				
Complete response											
60 (2 quasi-experimental studies) [32,33]	serious[a]	not serious	not serious	serious[b]	strong association	⨁⨁◯◯ Low	23/42 (54.8%)	14/18 (77.8%)	**OR 4.12** (1.04 to 16.37)	548 per 1000	**285 more per 1000** (from 10 more to 404 more)
Relapse from complete response - not reported											
Progression-free survival - not reported											
Serious adverse events - not reported											
Graft-versus-host disease											
60 (2 quasi-experimental studies) [32,33]	serious[a]	not serious	not serious	serious[b]	strong association	⨁⨁◯◯ Low	15/42 (35.7%)	1/18 (5.6%)	**OR 0.11** (0.02 to 0.69)	357 per 1000	**300 fewer per 1000** (from 346 fewer to 80 fewer)

Appendix 4.

Table S1. GRADE Evidence Profile for quasi-experimental studies

CAR-T therapies compared to any other intervention for hematologic malignancies

Certainty assessment	Summary of findings

Total adverse events (grade 3 or higher) - not reported

CI: confidence interval; **N/A:** Not applicable; **OR:** odds ratio

Explanations

a) Two NRSI with no information on adjustment for confounding variables; b) Very wide 95%CI, consistent with the possibility for substantial benefit differences in complete response and substantial harm differences in graft-versus-host disease.

Table S2. GRADE Evidence Profile for cohort studies

CAR-T therapies compared to any other intervention for hematologic malignancies

Certainty assessment							Summary of findings				
							Study event rates (%)		Relative effect (95 % CI)	Anticipated absolute effects	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With standard interventions	With CAR-T therapies		Risk with standard interventions	Risk difference with CAR-T therapies
Overall survival											
393 (5 cohort studies)[3] 4,37-40	serious[a]	N/A	not serious	N/A	none	-	(Zhao[35]) CAR-T+HSCT (n=27) 70.2% (53.0 to 87.4); CH+HSCT (n=78): 65.4% (54.8 to 76.0) p=0.68 (Muffly[38]) CAR-T:44%; HCT: 23% (Avivi[39]) HR=0.284, 95% CI 0.125–0.644, p=0.003 (Hu[40]) CAR-T: 86.0% (93.4-75.6); Chemotherapy: 62.6% (45.5-76.5); p=0.059 (Wang[41]) HR=0.705; 95%CI 0.224–2.217; p=0.549				
Complete response											
226 (3 cohort studies)[34]	serious[a]	N/A	not serious	N/A	none	-	(Avivi[39]) CAR-T= (Hu[40]) CAR-T: 9 (Wang[41]) CAR-T				
Relapse from complete response											
244 (3 cohort studies)[3] 4,37,39	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	26/88 (29.5%)	33/156 (21.2%)	**OR 1.24** (0.69 to 2.24)	295 per 1000	**47 more per 1000** (from 71 fewer to 189 more)
Progression-free survival											
192 (3 cohort studies)[3] 5,38,40	serious[a]	N/A	not serious	N/A	none	-	(Shulthess[36]) CAR-T: 46% (95%CI 8-79); HCT: 68% (95% CI 46-83); p=0.82 (Avivi[39]) HR=0.49, 95% CI 0.25–0.98, p=0.045 (Wang[41]) CAR-T+ASCT: 80% (95% CI; 60–98); ASCT: 44% (95% CI; 25–64), p=0.036				

Serious adverse events - not reported

Graft-versus-host disease

CAR-T therapies compared to any other intervention for hematologic malignancies

Certainty assessment							Summary of findings				
105 (1 cohort study)[34]	serious[a]	not serious	not serious	serious[d]	strong association	⨁⨁◯◯ Low	20/78 (25.6%)	13/27 (48.1%)	**HR 2.36** (1.18 to 4.75)	256 per 1000	**247 more per 1000** (from 39 more to 499 more)

Total adverse events (grade 3 or higher) - not reported

CI: confidence interval; **HR:** hazard Ratio; **N/A:** Not applicable

Explanations

a) Studies with lack of adjustment for important factors; b) High heterogeneity (90%); c) 95%CI is consistent with the possibility for relevant benefit or harm, exceeding a minimal important difference; d) Very wide 95%CI, consistent with the possibility for substantial harm differences in graft-versus-host disease