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Supplementary information

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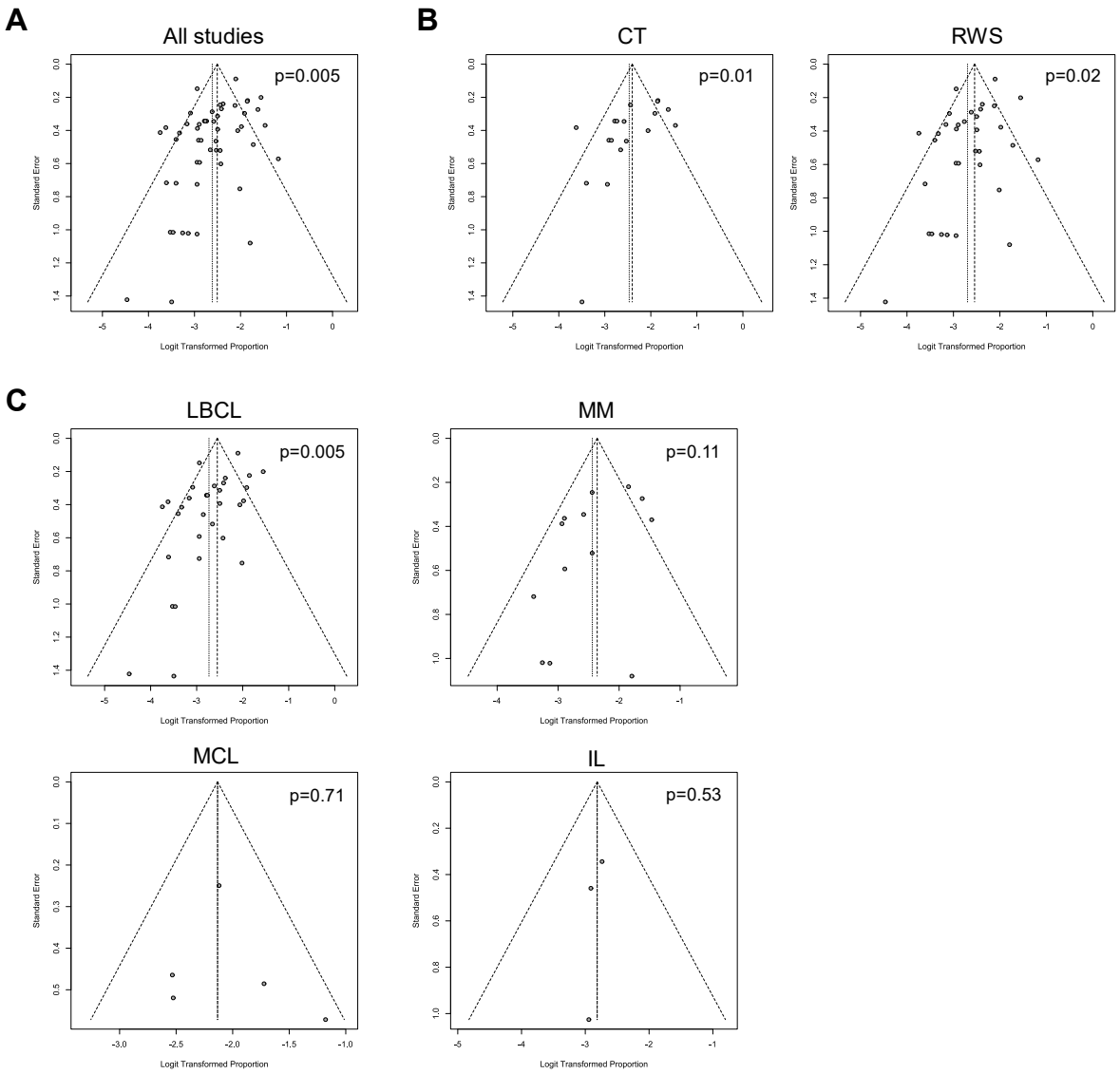
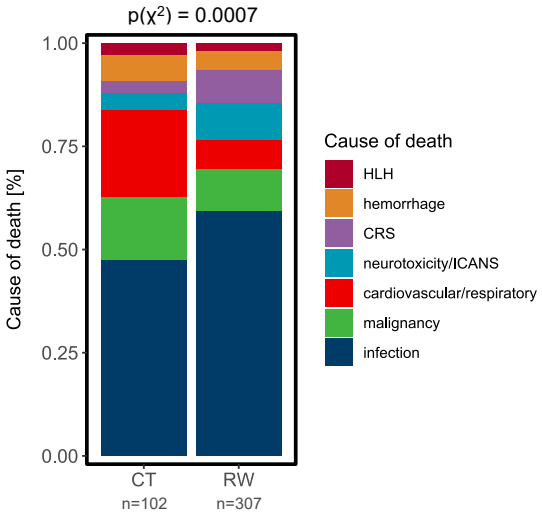
A systematic review and meta-analysis of nonrelapse mortality after CAR T cell therapy

In the format provided by the authors and unedited



Supplementary Figure 1. Funnel plots.
Reporting bias was analyzed by funnel plots for all studies (**A**) and additionally stratified by treatment setting (**B**) and disease entity (**C**). P-values for funnel plot asymmetry were derived from two-sided Egger regression tests.



Supplementary Figure 2. Exclusion of COVID-19 related deaths does not change the distribution of death causes between clinical trials and real-world studies.
Following the exclusion of fatal COVID-19 infections from the reported infection-related deaths, the distribution of causes of non-relapse deaths was compared between clinical trials and real-world studies. The relative distribution of the different causes of death is depicted across treatment settings (e.g., CT vs. RWS). Two-sided Chi-square distribution test was used for statistical testing. Abbreviations: CT = clinical trial, CRS = cytokine release syndrome, HLH = hemophagocytic lymphohistiocytosis, ICANS = immune effector cell-associated neurotoxicity syndrome, RW = real-world.

Supplementary Table 1. Joanna-Brigg's Institute assessment of study bias.

Author	Year	Criterion 1: Inclusion criteria	Criterion 2: measurement of mortality/ causes of death	Criterion 3: identification of mortality/ causes of death	Criterion 4: Consecutive Inclusion	Criterion 5: Complete Inclusion	Criterion 6: demographics	Criterion 7: Clinical information	Criterion 8: Follow-Up results
Dreyling et al.	2024	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Jacobson et al.	2022A	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Abramson et al.	2020	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Bishop et al.	2022	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Houot et al.	2023	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Kamdar et al.	2022	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Kato et al.	2023	Yes	Yes/Yes	Yes/No	Yes	Yes	Yes	Yes	Yes
Neelapu et al.	2022	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Neelapu et al.	2023	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Sehgal et al.	2022	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Westin et al.	2023	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Lin et al.	2023	Yes	Yes/Yes	Yes/No	Yes	Yes	Yes	Yes	Yes
Martin et al.	2023	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Mi et al.	2022	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Munshi et al.	2021	Yes	Yes/Yes	Yes/No	Yes	Yes	Yes	Yes	Yes
Rodriguez-Otero et al.	2023	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
San-Miguel et al.	2023	Yes	Yes/Yes	Yes/No	Yes	Yes	Yes	Yes	Yes
Wang et al.	2023A	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Hamilton et al.	2024	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes

Berning et al.	2024	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Bethge et al.	2022	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Chiappella et al.	2024	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
De Philippis et al.	2024	No	Yes/Yes	No/No	No	No	No	No	Yes
Dores et al.	2021	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	No	No
Grana et al.	2021	Yes	Yes/Yes	Yes/Yes	No	No	Yes	Yes	Yes
Iovino et al.	2022	Yes	Yes/Yes	Yes/No	Yes	Yes	Yes	Yes	Yes
Jacobson et al.	2022B	Yes	Yes/Yes	Yes/Yes	No	No	Yes	Yes	Yes
Kuhnl et al.	2022	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Kwon et al.	2023	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Lemoine et al.	2023	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Nastoupil et al.	2020	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Rejeski et al.	2022	Yes	Yes/Yes	Yes/Yes	No	No	Yes	Yes	Yes
Riedell et al.	2022	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Spanjaart et al.	2023	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Trando et al.	2023	Yes	Yes/Yes	Yes/Yes	No	No	Yes	Yes	Yes
Wudhikarn et al.	2023	Yes	Yes/Yes	Yes/Yes	No	No	Yes	Yes	Yes
Akthar et al.	2023	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Caillot et al.	2024	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Ferreri et al. & Hansen et al.	2023	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Fischer et al.	2024	Yes	Yes/Yes	Yes/Yes	No	No	Yes	Yes	Yes
Rejeski et al.	2023A	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Chong et al.	2024	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes

Iacoboni et al.	2022	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Rejeski et al.	2023B	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Wang et al.	2023B	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes

Joanna-Brigg's Institute assessment of study bias (Munn et al. JBI Evid Synth. 2020 Oct;18(10):2127-2133). Criterion 9 (presenting sites'/clinics' demographics) was assessed within criterion 5 (demographics of the participants in the study). Criterion 10 (statistical analysis) was not applicable since the extracted data processed in this meta-analysis are not based on statistical tools in the original studies.

Supplementary Table 2. Residual I^2 and R^2 values of individual variables and multivariate model derived from meta-regression analyses for LBCL and MM.

Variable	**LBCL** (total I^2 = 63.3%)		**MM** (total I^2 = 52.8%)	
	Residual Heterogeneity I^2 [%]	**Heterogeneity accounted for R^2 [%]**	**Residual Heterogeneity I^2 [%]**	**Heterogeneity accounted for R^2 [%]**
Individual Variables				
- Product	44.1	50.6	0	100
- Follow-up	58.1	4.7	15.8	81.3
- Treatment setting	58.5	7.4	27.6	63.3
- Treatment era	60.2	0.1	50.6	0.2
- Treatment line	58.4	9.6	47.5	2
Multivariate model	32.0	65.5	0	100

Supplementary Table 3. Causes of death classified as "others".

Case	Study cohort	Cause of death
1	Berning_2024	Trauma
2	Berning_2024	Gastrointestinal perforation
3	Berning_2024	Adhesive small bowel obstruction
4	Bishop_2022	Hepatic failure
5	Bishop_2022	Euthanasia
6	Bishop_2022	General Disorders and administration site conditions - Death
7	Chong_2024	Accident
8	Dores_2021	General Disorders and administration site conditions - Death
9	Dreyling_2024	Euthanasia due to worsening neurological symptoms upon potential progressive multifocal leukoencephalopathy
10	Iacoboni_2022	Clinical deterioration in the context of prolonged steroid therapy
11	Jacobson_2022_B	Light chain disease
12	Jacobson_2022_B	Persistent Pancytopenia
13	Kuhnl_2022_B	Bowel Perforation
14	Kuhnl_2022_B	Bowel Perforation
15	Lemoine_2023	Sudden death
16	Lemoine_2023	Sudden death
17	Lemoine_2023	Sudden death
18	Lemoine_2023	Anasarca
19	Martin_2023	Ascites
20	Mi_2022	Hepatic failure
21	Rodriguez-Otero_2023	Amyotrophic lateral sclerosis
22	Rodriguez-Otero_2023	Sudden death
23	Westin_2023	Euthanasia

Supplementary Table 4. Distribution of secondary malignancies.

	MDS/AML (n = 15)	Carcinoma (n = 10)	Sarcoma (n = 1)	Prior/secondary malignancy, NOS (n = 19)
Entity				
- LBCL	7 (46.7)	6 (60)	0 (0)	18 (94.7)
- IL	0 (0)	2 (20)	0 (0)	1 (5.3)
- MCL	2 (13.3)	1 (10)	1 (100)	0 (0)
- MM	6 (40)	1 (10)	0 (0)	0 (0)
Product				
- Axi-cel	3 (20)	2 (20)	0 (0)	14 (94.7)
- Tisa-cel	1 (6.7)	3 (30)	0 (0)	1 (5.3)
- Tisa-cel or axi-cel	3 (20)	3 (30)	0 (0)	1 (0)
- Liso-cel	0 (0)	0 (0)	0 (0)	0 (0)
- Brexu-cel	2 (13.3)	1 (10)	1 (100)	0 (0)
- Ide-cel	2 (13.3)	1 (10)	0 (0)	0 (0)
- Cilta-cel	4 (26.7)	0 (0)	0 (0)	0 (0)
Treatment setting				
- CT	7 (46.7)	5 (50)	0 (0)	3 (15.8)
- RW	8 (53.3)	5 (50)	1 (100)	16 (84.2)

Systematic Review and Meta-Analysis Protocol according to PRISMA-P guidelines
From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Title	Identification	This report represents a protocol for the systematic review and meta-analysis with the title: Infections drive non-relapse mortality following CAR-T therapy across disease entities and CAR products: a meta-analysis of 7246 patients
	Update	Version 3.0 (updated 27.03.2024)
Registration		N/A
Authors	Contact	David M. Cordas dos Santos[1-4], Tobias Tix[4], Kai Rejeski[4,5] 1 Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA 2 Harvard Medical School, Boston, MA, USA 3 Broad Institute of Massachusetts Institute of Technology (MIT) and Harvard, Cambridge, MA, USA 4 Department of Medicine III – Hematology/Oncology, LMU University Hospital, LMU Munich, Munich, Germany 5 Adult BMT and Cellular Therapy Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA Corresponding Author PD Dr. Kai Rejeski, MD Adult BMT and Cellular Therapy Service Memorial Sloan Kettering Cancer Center 1275 York Avenue, New York, NY 10065, USA Email: rejeskik@mskcc.org
	Contributions	DMCDS, TT, KR: Conceptualization, Investigation, Methodology, Manuscript Drafting, Editing. DMCDS, TT: Formal Analysis and Visualization
Amendments		This protocol does not represent an amendment.
Support	Sources	TT, DMCDS and KR received a fellowship from the School of Oncology of the German Cancer Consortium (DKTK). DMCDS received the Walter Benjamin Fellowship by a Deutsche Forschungsgemeinschaft (DFG, German Research Foundation). KR acknowledges funding from the Else Kröner Forschungskolleg (EKFK) within the Munich Clinician Scientist Program (MCSP). This work was supported by a grant within the Gilead Research Scholar Program (to KR) and a grant from the Bruno and Helene Jöster Foundation (to KR). We further acknowledge the structural support from the Bavarian Cancer Research Center (BZKF). KR further reports following conflicts of interest: Kite/Gilead: Research Funding, Consultancy, Honoraria and travel support; Novartis: Honoraria; BMS/Celgene: Consultancy, Honoraria; Pierre-Fabre: travel support.
	Sponsor	N/A
	Role of sponsor or funder	N/A
Introduction	Rationale	Chimeric antigen receptor (CAR) T-cells directed against the B-cell antigens CD19 and BCMA represent a practice-changing immunotherapy for multiple advanced B-cell malignancies and are being actively explored for several autoimmune diseases.1-7 However, CAR T-cells present with a unique spectrum of toxicities, which typically include

		cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).8-10 Real-world evidence has further highlighted the role of immune effector cell-associated hematological toxicity (ICAHT), which represents the most common high-grade toxicity within the first year following CAR-T infusion.11-16 Importantly, profound and prolonged neutropenia can compound the risk for severe infections together with B cell aplasia and hypogammaglobulinemia as expected on-target/off-tumor side effects of B-cell targeting CAR-T therapies.17-23 In rare cases, the profound hyperinflammatory response induced by CAR T-cells can result in the development of secondary hemophagocytic lymphohistiocytosis (HLH).24-26 In patients with long-term disease remission, secondary malignancies, particularly myeloid neoplasms, can occur.27, 28 Taken together, CAR-T-induced side effects can impose a considerable burden on patients with potentially long-lasting sequelae and reduced quality of life.29 To mitigate the risk of severe toxicity, patients often receive immunosuppressive agents and supportive therapies that can be detrimental to therapeutic success.30, 31 Indeed, the presence and/or absence of toxicity can be associated with the risk of treatment failure .32-34 Early non-relapse mortality (NRM), commonly defined as death not preceded by recurrent or progressive malignancy, can be a particularly devastating complication of cell therapy.35 Recent real-world efforts have described both incidence rates and potential causes of NRM following CAR-T therapy.13, 14, 19, 20, 36 However, large-scale analyses of NRM across disease entities, CAR products, and treatment settings have not been performed to date – and data regarding underlying causes remains limited. In this meta-analysis, we want to outline the comparative incidence and causes of NRM across the spectrum of lymphomas and multiple myeloma wherein BCMA- and CD19-directed CAR-T products are currently being utilized.
	Objectives	To determine the non-relapse mortality and causes of death among patients with lymphoma and multiple myeloma treated with CAR-T cells in clinical trials and real-world settings. Patient/Population: Adult patients diagnosed with: - Indolent lymphoma - Large B-cell lymphoma - Mantle cell lymphoma - Multiple myeloma treated with an approved CAR-T product: - Tisa-cel - Axi-cel - Liso-cel - Ide-cel - Cilta-cel - Brexu-cel Comparison: Comparison of subgroups based on disease entity, CAR-T product including costimulatory domain, line of therapy, treatment setting and treatment era.

		Outcomes: Non-relapse mortality, number and causes of death.
Methods	Eligibility criteria	Studies are eligible for the present review when following eligibility criteria are met: (1) adult cancer patients with either indolent lymphoma (IL), large B-cell lymphoma (LBCL), multiple myeloma (MM) or mantle cell lymphoma (MCL), (2) use of CAR-T products approved by the Food and Drug Administration (FDA), (3) data available on NRM and/or causes of death. All published studies until 31/03/2024 will be included.
	Information sources	The following electronic data bases will be used: Medline, Embase and CINAHL (Cochrane). Study authors will be contacted if literature is not accessible.
	Search strategy	We will include all randomized phase I-III trials that led to the approval of the specified CAR-T product. In case of publication with longer follow-up times, later reported studies will be use. In addition, we will use the following search strategies to identify real-world studies and additional clinical trials which fulfill the eligibility criteria to be included into the meta-analysis. **MEDLINE** (via PubMed) ((((((((((lymphoma*[Title/Abstract]) OR myeloma* [Title/Abstract]) AND (axicabtagene[Title/Abstract])) OR (standard-of-care CD19 CAR-T[Title/Abstract])) OR (lisocabtagene[Title/Abstract])) OR (idecabtagene[Title/Abstract])) OR (tisagenlecleucel[Title/Abstract])) OR (brexucabtagene[Title/Abstract])) OR (ciltacabtagene[Title/Abstract])) NOT (Review[Publication Type])) NOT (Meta-analysis[Publication Type]) NOT (case reports [Publication Type]) **Embase** ((myeloma:ab,ti OR lymphoma:ab,ti) AND axicabtagene:ab,ti OR 'standard-of-care cd19 car-t':ab,ti OR lisocabtagene:ab,ti OR idecabtagene:ab,ti OR tisagenlecleucel:ab,ti OR brexucabtagene:ab,ti OR ciltacabtagene:ab,ti) NOT review:it NOT 'meta analysis':it NOT 'case reports':it NOT medline NOT 'conference abstract'/it **CIINAHL** in the Cochrane Library ((myeloma):ti,ab,kw OR (lymphoma):ti,ab,kw) AND ((axicabtagene):ti,ab,kw OR ("standard-of-care cd19 car-t"):ti,ab,kw OR (lisocabtagene):ti,ab,kw OR (idecabtagene):ti,ab,kw OR (tisagenlecleucel):ti,ab,kw OR (brexucabtagene):ti,ab,kw OR (ciltacabtagene):ti,ab,kw)
	Study records: - Data management - Selection process - Data collection process	From all studies fulfilling eligibility criteria, two authors (DMCDS and TT) will separately extract the data and countercheck each other. Discrepancies will be solved by consultation with senior authors (KR). Search records will be saved and managed using EndNote.

	Data items	Data items will include date of publication, number of patients, recruiting period (treatment era), entities, CAR-T product specifications, median and minimum number of prior therapy lines (treatment line), follow-up time (continuous, and above versus below median), number and causes of death, and NRM rates if reported. If more than one CAR-T product was used in a single study, the reported data will be assigned to separate cohorts and evaluated accordingly. In addition, we will classify and create subgroups for causes of death: infection, malignancy, CRS, ICANS/neurotoxicity, cardiovascular/respiratory, hemorrhage, HLH, organ failure not otherwise specified (NOS), others, or unknown.
	Outcomes and prioritization	For the planned analysis of NRM proportions, we will calculate NRM proportions based on the extracted cohort sizes and numbers of non-relapse deaths. These NRM proportions will be used to determine NRM point estimates in random effects models, which consist of a point estimate based on the maximum likelihood estimator and the according 95% confidence interval determined by the Clopper Pearson method. There is no prioritization.
	Risk of bias in individual studies	Study bias of individual studies will be assessed by using the Joanna Brigg's Institute critical appraisal tool.
	Data synthesis	Studies reporting on the same disease entities, CAR-T products, treatment settings, lines of therapy, treatment era and follow-up time will be synthesized based on reported and calculated NRM rates as well as number and causes of death and analyzed in subgroups. Random effects models will be used to summarize measures and forest plots will be generated for illustration. Heterogeneity will be assessed by the Q statistic and quantified using I^2. Subgroup analysis will be performed of the effects of CAR-T product, follow-up time, treatment line, treatment setting, and treatment era in an entity-dependent manner. Multivariable meta-regressions will be performed to examine the association between NRM point estimates and the following variables: CAR T-cell product, treatment era, follow-up time, treatment line, and treatment setting. Exploratory univariate meta-regressions will be conducted to estimate the contribution of individual variables to between-study heterogeneity using the R^2 statistic. Meta-regressions will be calculated based on random effects models using the maximum likelihood estimator. Individual model coefficients and respective confidence intervals were tested using the Knapp-Hartung method. The stability of model estimates was validated by performing permutation testing .
	Meta-bias(es)	Funnel plots will be created to test for publication bias including subgroup analyses. Visual inspection of funnel plot asymmetry and Egger regression tests will be used to assess reporting bias.
	Sensitivity Analyses	Following sensitivity analyses will be performed:

		- Comparison of fixed effect models and random effect models - Comparison of inclusion of all studies vs study size filter for RWS with cut-off at 80 patients - Comparison of inclusion or exclusion of real-world studies with a minor between-study overlap (less than 30%).
	Certainty of a body of evidence assessment	This meta-analysis will not focus on the comparison between different interventions. Due to missing control arms, the GRADE approach for evaluating the body of evidence is of limited use.

References

1. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med 2022;386:640-654.

2. Schett G, Mackensen A, Mougiakakos D. CAR T-cell therapy in autoimmune diseases. Lancet 2023.

3. Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. Lancet 2021;398:491-502.

4. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20:31-42.

5. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 2019;380:45-56.

6. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med 2020;382:1331-1342.

7. Iacoboni G, Rejeski K, Villacampa G, et al. Real-world evidence of brexucabtagene autoleucel for the treatment of relapsed or refractory mantle cell lymphoma. Blood Adv 2022.

8. Shimabukuro-Vornhagen A, Godel P, Subklewe M, et al. Cytokine release syndrome. J Immunother Cancer 2018;6:56.

9. Karschnia P, Jordan JT, Forst DA, et al. Clinical presentation, management, and biomarkers of neurotoxicity after adoptive immunotherapy with CAR T cells. Blood 2019;133:2212-2221.

10. Karschnia P, Miller KC, Yee AJ, et al. Neurologic toxicities following adoptive immunotherapy with BCMA-directed CAR T-cells. Blood 2023.

11. Wudhikarn K, Pennisi M, Garcia-Recio M, et al. DLBCL patients treated with CD19 CAR T cells experience a high burden of organ toxicities but low nonrelapse mortality. Blood Adv 2020;4:3024-3033.

12. Rejeski K, Perez Perez A, Sesques P, et al. CAR-HEMATOTOX: A model for CAR T-cell related hematological toxicity in relapsed/refractory large B-cell lymphoma. Blood 2021.

13. Rejeski K, Hansen DK, Bansal R, et al. The CAR-HEMATOTOX score as a prognostic model of toxicity and response in patients receiving BCMA-directed CAR-T for relapsed/refractory multiple myeloma. J Hematol Oncol 2023;16:88.

14. Rejeski K, Wang Y, Albanyan O, et al. The CAR-HEMATOTOX score identifies patients at high risk for hematological toxicity, infectious complications, and poor treatment outcomes following brexucabtagene autoleucel for relapsed or refractory MCL. Am J Hematol 2023.

15. Jain T, Knezevic A, Pennisi M, et al. Hematopoietic recovery in patients receiving chimeric antigen receptor T-cell therapy for hematologic malignancies. Blood Adv 2020;4:3776-3787.

16. Jain T, Olson TS, Locke FL. How I Treat Cytopenias after CAR T-cell Therapy. Blood 2023.

17. Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood 2018;131:121-130.

18. Rejeski K, Kunz WG, Rudelius M, et al. Severe Candida glabrata pancolitis and fatal Aspergillus fumigatus pulmonary infection in the setting of bone marrow aplasia after CD19-directed CAR T-cell therapy - a case report. BMC Infect Dis 2021;21:121.

19. Rejeski K, Perez A, Iacoboni G, et al. The CAR-HEMATOTOX risk-stratifies patients for severe infections and disease progression after CD19 CAR-T in R/R LBCL. J Immunother Cancer 2022;10.

20. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium. J Clin Oncol 2020;38:3119-3128.

21. Bethge WA, Martus P, Schmitt M, et al. GLA/DRST real-world outcome analysis of CAR-T cell therapies for large B-cell lymphoma in Germany. Blood 2022.

22. Kampouri E, Little JS, Rejeski K, Manuel O, Hammond SP, Hill JA. Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies. Transpl Infect Dis 2023:e14157.

23. Gudiol C, Lewis RE, Strati P, Kontoyiannis DP. Chimeric antigen receptor T-cell therapy for the treatment of lymphoid malignancies: is there an excess risk for infection? Lancet Haematol 2021;8:e216-e228.

24. Major A, Collins J, Craney C, et al. Management of hemophagocytic lymphohistiocytosis (HLH) associated with chimeric antigen receptor T-cell (CAR-T) therapy using anti-cytokine therapy: an illustrative case and review of the literature. Leuk Lymphoma 2021;62:1765-1769.

25. Lichtenstein DA, Schischlik F, Shao L, et al. Characterization of HLH-like manifestations as a CRS variant in patients receiving CD22 CAR T cells. Blood 2021;138:2469-2484.

26. Hines MR, Knight TE, McNerney KO, et al. Immune Effector Cell associated Hemophagocytic Lymphohistiocytosis-like Syndrome (IEC-HS). Transplant Cell Ther 2023.

27. Cordeiro A, Bezerra ED, Hirayama AV, et al. Late Events after Treatment with CD19-Targeted Chimeric Antigen Receptor Modified T Cells. Biol Blood Marrow Transplant 2020;26:26-33.

28. Zhao A, Zhao M, Qian W, Liang A, Li P, Liu H. Secondary myeloid neoplasms after CD19 CAR T therapy in patients with refractory/relapsed B-cell lymphoma: Case series and review of literature. Front Immunol 2022;13:1063986.

29. Chakraborty R, Hill BT, Majeed A, Majhail NS. Late Effects after Chimeric Antigen Receptor T cell Therapy for Lymphoid Malignancies. Transplant Cell Ther 2021;27:222-229.

30. Strati P, Ahmed S, Furqan F, et al. Prognostic impact of corticosteroids on efficacy of chimeric antigen receptor T-cell therapy in large B-cell lymphoma. Blood 2021;137:3272-3276.

31. Smith M, Dai A, Ghilardi G, et al. Gut microbiome correlates of response and toxicity following anti-CD19 CAR T cell therapy. Nat Med 2022;28:713-723.

32. Rejeski K, Perez A, Iacoboni G, et al. Severe hematotoxicity after CD19 CAR-T therapy is associated with suppressive immune dysregulation and limited CAR-T expansion. Sci Adv 2023;9:eadg3919.

33. Jacobs MT, Jain MD, Gao F, et al. Severity of Cytokine Release Syndrome Influences Outcome After Axicabtagene Ciloleucel for Large B cell Lymphoma: Results from the US Lymphoma CAR-T Consortium. Clin Lymphoma Myeloma Leuk 2022;22:753-759.

34. Brammer JE, Braunstein Z, Katapadi A, et al. Early toxicity and clinical outcomes after chimeric antigen receptor T-cell (CAR-T) therapy for lymphoma. J Immunother Cancer 2021;9.

35. McDonald GB, Sandmaier BM, Mielcarek M, et al. Survival, Nonrelapse Mortality, and Relapse-Related Mortality After Allogeneic Hematopoietic Cell Transplantation: Comparing 2003-2007 Versus 2013-2017 Cohorts. Ann Intern Med 2020;172:229-239.

36. Lemoine J, Bachy E, Cartron G, et al. Non-Relapse Mortality after CAR T-Cell therapy for Large B-Cell Lymphoma: A LYSA Study from the DESCAR-T Registry. Blood Adv 2023.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1, line 1f.
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2, line 31 ff.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3, line 51 ff.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3, line 79 ff.
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 15, line 370 ff.
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 15, line 366 ff.
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 15, line 364 ff., Study Protocol
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 15, line 379 ff., Study Protocol
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 15, line 390 ff., Study Protocol
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 16, line 394 ff.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 16, line 391 ff.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 16, line 401 ff.
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 16, line 394 ff. and line 407 ff.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 17, line 422 ff., Table 1 & 2
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 16, line 394 ff.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 16, line 409 ff.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 17, line 422 ff., Study protocol
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 17, line 410 ff.
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 17, line 442 ff.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 16, line 402 f., Study protocol
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Study Protocol
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 4, lines 86 ff., Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Tables 1 and 2, References
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S1, Fig. S5, Table S2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Tables 1-2, Fig. 2, Fig. S2-S4, S6, S8-S9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 5, line 125 ff., Suppl. Table S1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Fig. 2, Fig. S2-S4, S6, S8-S9, Table S2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 5, Line 125 ff., Fig 2, Fig S3-4, Table S2
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 12, line 318 ff, Table S5
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 5, line 125 ff., page 12, line 318 ff., Fig S5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Study Protocol
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 9, line 227 ff.
	23b	Discuss any limitations of the evidence included in the review.	Page 12, line 360 ff., page 13, line 331 ff.
	23c	Discuss any limitations of the review processes used.	Page 12, line 326 ff.
	23d	Discuss implications of the results for practice, policy, and future research.	Page 13, line 346

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Section and Topic	Item #	Checklist item	Location where item is reported
			ff.
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	PROSPERO CRD42023494252
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Study protocol can be assessed as supplementary material.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	No amendments were made.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 19: Acknowledgments
Competing interests	26	Declare any competing interests of review authors.	Page 19 f.: Conflict of interest statements
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data can be requested from corresponding author and accessed under the mentioned GitHub repository

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