Non-relapse mortality after CAR T-cell therapy: A systematic review and meta-analysis of 7,788 lymphoma and myeloma patients

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Analysis

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Abstract

While CAR-T therapy represents a transformative immunotherapy, it is also associated with distinct toxicities that contribute to morbidity and mortality. In this systematic review and meta-analysis, we searched MEDLINE, Embase and CINAHL for reports of non-relapse mortality (NRM) following CAR-T in lymphoma and myeloma, published until 09/2023. Cumulative incidence rates of NRM and causes/numbers of death were extracted. NRM point estimates were analyzed using fixed effect models. We identified 7,788 patients across 16 clinical trials and 32 real-world studies. After a median follow-up of 12.9 months, the overall NRM rate was 7.5% (95%CI 6.9-8.1%). NRM point estimates were related to the disease entity, CAR-T product and costimulatory domain. Of 582 reported non-relapse deaths, nearly half were attributed to infections, followed by cardiovascular/respiratory events (7.4%) and second malignancies (6.5%). Our findings underline the critical importance of post-CAR-T infections and support the comprehensive reporting of NRM, including specific causes and long-term outcomes.

Introduction

Chimeric antigen receptor (CAR) T-cells directed against the B-cell antigens CD19 and BCMA are a potent immunotherapy for multiple advanced B-cell malignancies and are being actively explored for several autoimmune diseases.1-5 However, CAR T-cells display a unique spectrum of immune-related toxicities, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).6-8 Real-world experience has further highlighted the role of immune effector cell-associated hematological toxicity (ICAHT), the most common high-grade toxicity in the first year following CAR-T infusion.9-13 Profound and prolonged neutropenia can compound the risk of severe infection together with B-cell aplasia and hypogammaglobulinemia as expected on-target/off-tumor side effects of B-cell targeting therapies.14-18 In rare cases, the profound hyperinflammatory response induced by CAR T-cells can lead to secondary hemophagocytic lymphohistiocytosis (HLH).19 Given patients’ exposure to both prior and lymphodepleting chemotherapy, secondary malignancies, particularly myeloid neoplasms, can occur.20,21 In light of the recent investigation by the United States Food and Drug Administration (FDA) and their announcement of a class-wide black box warning, the aforementioned risk of second primary malignancies after CAR-T therapy has recently garnered significant media attention.22 Collectively, CAR-T-induced side effects can impose a considerable burden on patients with potentially long-lasting sequelae.23 To mitigate the risk of severe early toxicities (e.g. CRS or ICANS), patients often receive immunosuppressive agents such as high-dose corticosteroids that can increase patients’ susceptibility to infections and may impede therapeutic success.24 Indeed, severe toxicity is associated with increased risk of treatment failure.25-27 Non-relapse mortality (NRM), commonly defined as death not preceded by recurrent or progressive primary malignancy, is a devastating complication of CAR T-cell therapy.28 While NRM represents a well-characterized entity in the context of autologous and allogeneic hematopoietic cell transplantation (HCT),29 comprehensive analyses of NRM across disease entities, CAR-T products, and treatment settings have not yet been performed, and data regarding underlying causes remains limited. In this systematic review and meta-analysis, we therefore outline the comparative incidence and causes of NRM across the spectrum of lymphomas and multiple myeloma where CD19- and BCMA-directed CAR-T products are currently approved.

Results

Study Cohort

We screened 2018 studies for reports of NRM in patients receiving CAR-T therapy. Overall, 149 full-text articles were assessed for evaluation of NRM and causes of death in CAR-T patients, of which 48 articles fulfilled criteria for downstream analysis (Fig. 1). This included 16 reports on clinical trials with 2005 total patients (Phase I: 2, Phase I-II: 2, Phase II: 7, Phase III: 5; Table 1)30-45, and 32 RWS comprising 5241 patients (Table 2).10,11,15,16,28,46-73 For the RWS, 6 of 32 reported on multiple CAR-T products and were thus divided into sub-cohorts, resulting in 54 distinct patient cohorts for final evaluation.

Overall, the most common entity was LBCL (6003 patients), followed by MM (1168 patients), MCL (372 patients) and IL (245 patients). The number of studies reporting on each CAR-T product was: 21 axi-cell, 8 tisa-cell, 3 liso-cell, 4 brexu-cell, 7 ide-cell and 3 cilta-cell. Eight studies did not distinguish between axi-cell and tisa-cell when assessing NRM rates and were therefore excluded for the product-specific comparisons (Table 2). Two studies displayed substantial overlap with complementary data and were thus merged for analysis.56,58 The range of follow-up times varied between 3.0 to 63.1 months.
NRM point estimates are comparable to reported NRM cumulative incidence rates

Cumulative incidence rates of NRM were not specifically reported in any of the 16 clinical trials. Furthermore, NRM data was missing in more than half of RWS (18/32, 56.3%). For the studies reporting cumulative incidence rates, the median 1-year NRM rate was 6.0% (IQR 4.1-8.3%). One additional study reported a 3-month NRM rate of 3%.47 To compensate for the lack of NRM data in clinical trials and some RWS, we calculated NRM point estimates by dividing the total number of non-relapse-related deaths by the total number of patients in each cohort. To test the reliability of calculated NRM point estimates, we compared them with the 1-year NRM incidence rates in RWS that did report 1-year NRM, finding no significant differences (p=0.49, Fig. S1A). The deviation between NRM point estimates and reported NRMs ranged from -2.2% to +2.6%. Since more patients die of any cause with longer follow-up times and follow-up times differed between studies, we next correlated NRM point estimates with the respective cohort follow-up times and found a positive correlation (Pearson r=0.39, p=0.01), predominantly driven by clinical trials (Fig. S1B). Based on these results, we proceeded to calculate NRM point estimates to analyze the impact of the disease entity, treatment setting and CAR-T product, controlling for follow-up separately.

NRM point estimates vary between tumor entities and CAR products

Across all patients, the overall NRM point estimate was 7.5% (95% CI 6.9-8.1%) with a median follow-up of 12.9 months. Study heterogeneity was moderate-to-high ($I^2 = 58\%$, Fig. 2), though it was diminished when considering both disease entity and CAR-T product (Fig. S2-3), reflecting the underlying clinical heterogeneity of the study cohort.74 While funnel plot asymmetry suggested publication bias towards larger studies reporting on NRM (Fig. S4), we did not identify a significant risk of study bias among the included studies (Table S1). Since underlying tumor biology and previous treatment may affect non-relapse deaths, we next investigated associations between tumor entities and NRM point estimates. While follow-up was similar between tumor entities (Fig. 3A, Fig. S5A), NRM point estimates differed between IL (4.4%), LBCL (7.0%), MM (9.6%), and MCL (9.9%, $p(x^2) = 0.001$; Fig. 3A-B).

We then examined the influence of CAR-T product type on NRM point estimates for each disease entity, studying IL/LBCL and MM separately. Notably, axi-cel was associated with higher NRM compared to liso-cel and tisa-cel (8.9% vs. 4.0% vs. 4.0%; $p(x^2)<0.0001$; Fig. 3C). These product-specific differences also remained consistent when analyzing LBCL and IL separately (Fig. S6) and when considering only reported NRMs (Fig. S7). In MM, cilia-cel was associated with a higher NRM compared to ide-cel (14.1% vs. 7.6%; $p(Fisher)=0.0007$; Fig. 3D). Among all CAR-T products, cilia-cel had the highest overall NRM, followed by brexu-cel (9.9%). Follow-up times across CAR-T products were similar (Fig. S5B).

CD28z-harboring CAR products are associated with increased NRM

Based on the observation that there are product-specific differences in NRM rates, we next evaluated the impact of the costimulatory domains CD28z versus 4-1BB on NRM point estimates. While median follow-up times were comparable between CAR-T products harboring either a 4-1BB or CD28z endodomain (Fig. S5C), the CD28z CAR-T products displayed higher NRM point estimates compared to 4-1BB CAR-T products (8.9% vs. 6.5%; $p(Fisher)=0.0002$; Fig. 3E, S8, S9). In terms of treatment setting, we observed increased NRM point estimates in the clinical trials compared to RWS; however, this observation was confounded by the significantly longer follow-up times in the clinical trial cohorts (Fig. S10, S11).

Infections are the main driver of non-relapse mortality following CAR-T therapy

To elucidate the etiology of NRM, we extracted available data for all 582 deaths among included studies. For 460 cases (79%), the underlying cause of death was specified, which we classified into one of seven groups as outlined in the methods (Fig. 4A). If the cause of death did not match any of these groups, it was classified under “other” (22 cases; Table S2). In 70 cases, the specific cause of death was reported as “unknown”, while 30 cases were reported as organ failure without any further information (“not otherwise specified”, NOS).

Notably, 285 patients died of infections, which accounted for nearly half of all reported non-relapse deaths (49%). While the causative pathogen was not specified for two-thirds of these cases, among the 97 (34%) cases with an identified pathogen, a substantial number succumbed to COVID-19 (n=50, 51.5%). While fungal infections are rare following CAR-T therapy,75 they still accounted for 23 deaths (23.7%), comparable to the proportion of deaths reported to be a result of bacterial infections (n=18, 18.6%). The second most common specified cause of death was cardiovascular or respiratory, led by thromboembolic events such as stroke or ischemic brain injuries in 32.6% of cases. Respiratory failure and cardiac arrest followed with 20.9% and 18.6%, respectively. The specific
cardiovascular or respiratory event was not specified in 8 cases. Thirty-eight patients died of second malignancies with over a third (n=16, 42%) dying from secondary MDS/AML, 6 (15.8%) from carcinoma and one death from sarcoma (2.6%), while 15 second malignancy deaths were not further specified. MDS/AML cases were similarly distributed between entities and products (Table S3).

Of interest, no deaths related to T-cell malignancies were reported. Prototypical CAR-T side effects such as ICANS/neurotoxicity and CRS directly caused a total of 61 deaths (10.5%). In addition, 21 patients died of hemorrhage (3.6%) and 12 deaths were attributed to secondary HLH (2.1%).

**Infections are more frequently the cause of death in the real-world setting**

Among deaths with a specified cause, we assessed whether the tumor entity, CAR-T product or treatment setting impacted cause of death. We found that the causes of death were differently distributed between patients that were treated in clinical trials compared to the real-world setting (p=0.0002, Fig. 4B). Differences were predominantly found among the immune-related side effects (CRS, ICANS/neurotoxicity, HLH), which were responsible for 7.3% of deaths in clinical trials compared to 19% of deaths in RWS. We observed the opposite trend for cardiovascular/respiratory cases, which caused 18.7% of deaths in clinical trials, but only 5.9% of deaths in RWS. Fatal hemorrhages were distributed similarly (RWS: 3.9%, CT: 6.5%). Finally, infections predominated as the cause of death even more in the real-world setting (63.8%) than in clinical trials (56.9%), which remained true when excluding COVID-19 related deaths (Fig. S12). Overall, infections were the most common NRM determinant – irrespective of disease entity, CAR-T product and costimulatory domain (Fig. 4C, S13).

**Discussion**

In this systematic review and meta-analysis, we outline the comparative incidence and causes of NRM following CAR-T therapy across different hematological malignancies, finding an estimated NRM of 7.5%. We noted higher NRM in MCL and MM patients, and with the CAR-T products axi-cel and cilta-cel. Infections were by far the main cause of NRM, responsible for approximately half of NRM across all disease entities. Conversely, CAR-T specific side effects such as CRS, ICANS/neurotoxicity and HLH, were only minor drivers of NRM.

NRM is a key piece of the puzzle that may inform the use of CAR-T compared with other treatment options and may guide CAR-T product choice. For example, in DLBCL, both axi-cel and liso-cel have been shown to have superior efficacy than salvage chemotherapy followed by autologous transplant. However, when considering the approach to patients where the evidence may be more equivocal – for example, patients whose disease relapses >12 months after frontline therapy, or patients with chemotherapy-sensitive disease – the best estimate of their NRM risk will help to inform decision-making, analogous to how transplant physicians present data to patients in diseases where allogeneic transplantation is being considered. These estimates also become increasingly important as CAR-T is used in earlier lines of therapy (where the competing risk of NRM is of a higher consequence), used in more indolent diseases like follicular lymphoma (where the competing risk of NRM may be higher relative to the chance of death due to disease progression), and used in patients who may not have previously been eligible for aggressive treatment. For a young, otherwise healthy patient with DLBCL relapse following multiple lines of therapy, a higher NRM from CAR-T may be acceptable as the alternative is likely death from lymphoma. Conversely, for an older, transplant-ineligible patient whose disease responds to salvage chemo- or immunotherapy, the discussion regarding whether or not to proceed with CAR-T is much more nuanced, and NRM would be one factor informing this discussion. Similarly, CAR-T related NRM will also be a factor in decision-making for patients with indolent lymphoma or multiple myeloma deciding between other treatment options, such as bispecific antibodies, and CAR-T.

While we noted increased NRM for axi-cel and cilta-cel in lymphoma and MM patients, respectively, we did not control for technical features of the included studies such as study design and eligibility criteria, which may have resulted in differences in included patient populations. Indeed, both patient factors and certain disease-specific factors (e.g., tumor load and inflammation) could have contributed to the observed variation of NRM rates between CAR-T products. Furthermore, differences in vein-to-vein times, the use and type of bridging therapy, and lymphodepletion regimen may have played a role. Absent randomized comparisons between CAR-T products, it is difficult to know to what extent the safety profiles of CAR-T products differ, or whether these findings rather reflect selection bias and/or confounding by indication. Comparative analysis of NRM is additionally complicated when considering the intrinsic heterogeneity of the infusion product itself. While cilta-cel was associated with high NRM, there was also a lack of RWS of cilta-cel meeting inclusion criteria for this meta-analysis. Furthermore, it is worth noting that Mi and colleagues reported elevated NRM rates in the phase II CARTIFAN-1 trial conducted in China, partly due to inadequate red blood cell and
Our analysis confirms that infectious complications represent the primary cause of NRM in CAR-T patients. Several factors increase the susceptibility of CAR-T patients to fatal infections. This includes the underlying malignancy and associated immune dysregulation, prior treatment regimens (many patients in CAR-T clinical trials had received many prior lines of therapy), toxicity management (particularly high-dose corticosteroids), and the combination of cellular and humoral immune suppression exerted by the CAR T-cells themselves. In our study, COVID-19 was responsible for many of the deaths that drove infection-related NRM. Importantly, many of the studies included in this meta-analysis took place during the COVID-19 pandemic (2020-2023), which may in part explain the high NRM rate of 7.5% across all patients. Increased vigilance in infection reporting, prevention and management, including that of COVID-19, should be a focus of ongoing work given its potential to reduce NRM.

Cardiovascular and pulmonary adverse events (CPAEs) were the second most common etiology of NRM, in line with previous studies reporting a disproportionate increase of such events in CAR-T-treated patients. These findings support the early and multidisciplinary assessment of cardiovascular risk in patients receiving CAR-T. The relatively high incidence of secondary malignancies, at 6.5%, should be interpreted within the context of the significant treatment burden carried by patients eligible for CAR-T therapy, especially the frequent exposure to high-dose chemotherapy regimens such as melphalan for previous autologous HCT. For example, up to 15% of NRM cases after auto-HCT have been attributed to secondary malignancies. Supporting this hypothesis, a recent study found a high prevalence of clonal hematopoiesis of 50-60% at time of CAR-T infusion. Nonetheless, considering the growing body of evidence elucidating the role of inflammatory stressors for clonal expansion, the impact of CAR-T induced inflammatory stress on the development of secondary myeloid malignancies warrants future systematic study.

While the asymmetrical funnel plots indicated publication bias (Fig. S4), this was primarily attributable to smaller studies (n<80) without any or very low numbers of NRM-related deaths. Concomitantly, the asymmetric shape might reflect the chosen outcome rather than the presence of true publication bias. To further test robustness of our meta-analysis results, we performed sensitivity analyses (Table S4). Although we detected lower NRM rates for some subgroups using a random compared to a fixed effect model, the main study findings remained stable. Similarly, applying a cut-off of 80 patients for observational studies did not substantially impact NRM point estimates, indicating that a potential publication bias regarding smaller RWS may be negligible.

Key limitations of this study relate to the suboptimal quality of reporting of NRM endpoints, and the inability to attribute NRM causes in ~15% of cases (“others” and “unknown” groups), even in clinical trial settings where patients are ideally followed closely given their experimental nature. Additionally, reporting by categories may have been inconsistent across different studies (e.g., CRS could lead to cardiac arrest; infection may lead to organ failure and thus could have been reported in either category). Furthermore, cumulative NRM rates were not reported in any of the clinical trials and only in some RWS, and the respective timepoints of death relative to CAR-T infusion were often not or poorly characterized. However, such detailed, long-term reporting of NRM is critical to not only recognize (and mitigate) emerging side effects, but also to identify potential toxicity signals of novel CAR-T products. Clear definitions and guidelines for all side effects of cell therapy are useful in this regard, as was recently implemented for IEC-HS and ICAHT.

Considering the clinical significance of fatal infections, detailed and structured reporting of infectious events should be a mandatory requirement in clinical trials. Ideally, such reporting should include infection type (e.g., viral, bacterial, fungal), whether the infection was confirmed microbiologically, organism (if known), day of infection, infection severity, and should further distinguish between early vs. late infections. Knowledge of the expected infection risk for each CAR-T product may help to guide antimicrobial prophylaxis, immunoglobulin replacement therapy and G-CSF support, particularly in high-risk patients. Finally, it should be emphasized that this meta-analysis focused on NRM rates, disregarding the differential efficacy of CAR-T products. For example, lower efficacy might lead to decreased NRM as more patients die due to progressive disease.

In conclusion, our analysis underscores the need for improved reporting of CAR T-cell safety, both in clinical trials and RWS. Due to the critical role of infections as the main driver of NRM across CAR-T products and disease entities, there is a pressing need for comprehensive evidence-based guidelines that inform infection prevention and management post CAR-T.

Online Methods
Literature search

We included all studies that led to approval of the six commercially available CAR-T products (axi-cel, tisa-cel, ide-cel, citla-cel, liso-cel, brexu-cel) and the corresponding phase I-III clinical trials and observational real-world studies (RWS). A systematic search was conducted using the MEDLINE, Embase and CINAHL (Cochrane) databases for articles published between inception and September 7, 2023 with combined keywords for each of the CAR-T products together with "lymphoma" or "myeloma" (see study protocol, supplementary material). Case studies, reviews, conference abstracts and meta-analyses were excluded. After screening titles and abstracts, publications were evaluated by two independent investigators (DMCDS, TT) based on the following inclusion criteria, which all needed to be 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 or number of non-relapse deaths.

All included articles were checked for double reporting. If two studies reporting on the same patient population were identified, the study with longer follow-up was chosen. Corresponding authors were contacted if full-text publications were not available from suitable abstracts or if additional information was needed.

Data extraction

Data were extracted from all studies that met inclusion criteria. Data collection included date of publication, number of patients, disease entities, CAR-T product, follow-up time, line of therapy and treatment setting. The primary outcome was reported NRM (if reported) and the number and causes of death. If more than one CAR-T product was used in a single study, the reported data was assigned to separate cohorts and evaluated accordingly. Prespecified subgroup analyses compared NRM by disease entity, CAR-T product, co-stimulatory domain, and treatment setting (e.g., clinical trial vs. RWS).

Causes of death were classified into one of the following groups: infection, second malignancy, CRS, ICANS/neurotoxicity, cardiovascular/respiratory, hemorrhage, HLH, organ failure not otherwise specified (NOS), other, or unknown. Cardiovascular and respiratory causes of death were further classified into: stroke/ischemic brain injury, respiratory failure, cardiac arrest, cardiomyopathy, embolism, aortic dissection, or cardiovascular/respiratory NOS. Second malignancy was classified into: MDS/AML, carcinoma, sarcoma, or prior/secondary malignancy NOS. Infections were classified into: COVID-19, bacterial, viral, fungal, or infection NOS. NRM point estimates were calculated by dividing the number of deaths by the total patient number for each cohort and were aggregated according to disease entities, CAR products, costimulatory domains and treatment setting. This study followed the PRISMA(-P) guidelines (see study protocol and PRISMA Checklist, supplemental material) and was prospectively registered to the PROSPERO database (study number: CRD42023494252). IRB approval was not sought as this study did not represent human participant research.

Statistics

Mann-Whitney test was used to explore two continuous variables and Kruskal-Wallis test was used when comparing multiple variables assuming non-normal distribution. Continuous variables were reported as median and interquartile range (IQR). Meta-analysis of proportions utilizing a generalized linear mixed model was performed with R (v4.3.1, meta package 6.5-0) using forest plots to visualize outcome data for NRM. The Wilson method was used to calculate 95% confidence intervals (95% CIs) of proportions. Heterogeneity was assessed with the Q statistic and quantified using I^2. The Joanna Briggs's Institute appraisal tool was applied to assess study bias (Table S1); funnel plot asymmetry was used to test for reporting bias (Fig. S4). Sensitivity analyses were performed by applying a study size cutoff of 80 patients for observational studies and testing random effect models. To analyze the distribution of NRM-related deaths among aggregated sub-cohorts, Fisher's exact test was used in cases of two categorical variables and Chi-squared (χ²) test in cases of more than two categorical variables. To investigate the relationship between continuous variables, we computed Pearson correlation coefficients (r).

Declarations
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Author Contributions

**Conceptualization:** KR; **Investigation:** DMCDS, TT, RS, ERSC, ST, MvBB, IMG, MAP, MS, KR; **Formal Analysis and Visualization:** DMCDS, TT; **Methodology:** DMCDS, TT, KR; **Writing Original Draft:** DMCDS, TT, KR; **Writing Review and Editing:** DMCDS, TT, RS, ERSC, ST, MvBB, IMG, MAP, MS, KR. All authors read and approved the final manuscript.

Competing Interests

**S.T.** Honoraria/Consultancy: Amgen, BMS/Celgene, GSK, Janssen, Pfizer, Sanofi, Takeda, Stemline and Kyowa Kirin.

**M.B.B.** Consultancy, Research Funding and Honoraria: MSD Sharp & Dohme, Novartis, Roche, Kite/Gilead, Bristol-Myers Squibb, Astellas, Mologen, and Miltenyi.

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**M.A.P.** reports honoraria from Adicet, Allogene, Allovir, Caribou Biosciences, Celgene, Bristol-Myers Squibb, Equillium, Exevir, ImmPACT Bio, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, Novartis, Omeros, OrcaBio, Sanofi, Syncopation, VectivBio AG, and Vor Biopharma. He serves on DSMBs for Cidara Therapeutics, Medigene, and Sellas Life Sciences, and the scientific advisory board of NexImmune. He has ownership interests in NexImmune, Omeros and OrcaBio. He has received institutional research support for clinical trials from Allogene, Incyte, Kite/Gilead, Miltenyi Biotec, Nektar Therapeutics, and Novartis.

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Data Availability Statement

All data needed to evaluate the conclusions in the paper are present in the manuscript and/or the Supplementary Materials. Data from primary studies are publicly available within the databases listed in the Supplementary Information. In case of further questions, please contact the corresponding author.
Code Availability Statement

All codes were adapted using R software, v.4.3.1 (meta package 6.5-0). Data sheets were created using Microsoft Excel. The codes that support the findings of this study are available from the corresponding author.

Inclusion and Ethics Statement

All data used in this study was previously published.

References


### Tables

**Table 1.** Characteristics of clinical trial records

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Abbreviations: IL = indolent lymphoma (incl. follicular lymphoma and chronic lymphocytic leukemia, LBCL = large B-cell lymphoma, MCL = mantle cell lymphoma, MM = multiple myeloma, NR = not reported, NRM = non-relapse mortality, RW = real-world.

**Table 2.** Characteristics of real-world studies.
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#Studies displayed together due to cohort overlaps. Abbreviations: LBCL = large B-cell lymphoma, MCL = mantle cell lymphoma, MM = multiple myeloma, NR = not reported, NRM = non-relapse mortality, RW = real-world.

**Figures**
Study retrieval and identification for meta-analysis.
Flow diagram displaying the process for study inclusion and exclusion for the systematic review and meta-analysis of NRM following CAR-T therapy.
Figure 2

Forest plot of NRM point estimates across all CAR-T cohorts.

Forest plot illustrating NRM point estimates and 95% confidence intervals using a fixed-effect model. The total point estimate across all included CAR-T cohorts is highlighted in bold. Heterogeneity measures including $I^2$ are depicted ($I^2$ between 50% to 75% indicates moderate-to-high study heterogeneity). Abbreviation: NRM = non-relapse mortality.
Figure 3

NRM point estimates vary across B-cell malignancies and CAR products.

**A** Bubble plot demonstrating NRM point estimates in relation to follow-up times for IL (blue), LBCL (yellow), MM (grey) and MCL (red). Each bubble represents one cohort. Bubble size indicates the total number of patients per cohort. The aggregated NRM point estimate for all cohorts within one entity is encircled in black. **B** Depiction of aggregated NRM point estimates and 95% CIs for the different disease entities as well as the overall study cohort across all CAR-T treated patients (“All”). **C-E** Comparison of aggregated NRM point estimates and 95% CIs among CAR-T products for specific disease entities and according to the co-stimulatory domain. **C** IL- (blue) and LBCL-specific (yellow) CAR products. **D** MM-specific CAR products. **E** CD28z versus 4-1BB harboring CAR products. Chi-square test was used for comparisons of > 2 groups and Fisher’s exact test for comparing two groups. Abbreviations: IL = indolent lymphoma, LBCL = large B-cell lymphoma, MCL = mantle cell lymphoma, MM = multiple myeloma, NRM = non-relapse mortality.
Figure 4

Analysis of NRM-related causes of deaths among different CAR-T cell treatment settings and tumor entities.

A Top: donut plot displaying causes of death among all included cohorts. Defined causes of death are shown in colored sections, undefined and unclassifiable causes of death are shown in grey colors. Additional pie charts subdivide infections (blue tones, right), cardiovascular/respiratory (red tones, center) and secondary malignancies (green tones, left). B Causes of death compared across clinical trials and real-world studies, and C across tumor entities. Chi-square distribution test was used for statistical testing. Abbreviations: AML = acute myeloid leukemia, CRS = cytokine release syndrome, CT = clinical trial, HLH = hemophagocytic lymphohistiocytosis.
lymphohistiocytosis, ICANS = immune effector cell-associated neurotoxicity syndrome, MDS = myelodysplastic syndrome, NOS = not otherwise specified, RW = real-world.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CARTNRMStudyProtocolNM.docx
- CARTNRMSupplTableNMv1.docx
- CARTNRMeditorialpolicyNMfinal.pdf
- CARTNRMreportingsummaryNMfinal.pdf
- CARTNRMPRISMAChecklistNMfinal.docx
- CARTNRMSupplFiguresNMv1.pdf