Supplementary Material

Supplementary Methods

<u>**Study protocol:**</u>

Attached.

<u>**PRISMA Checklist:**</u>
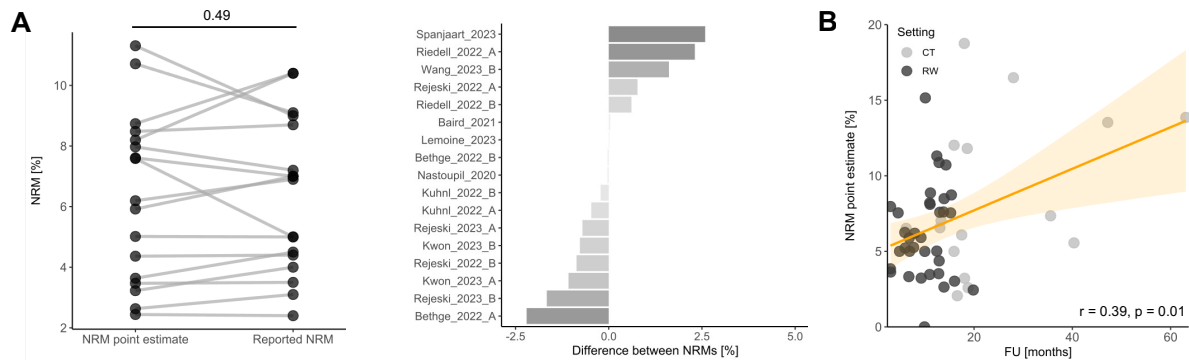
Attached.

Supplementary Figures

Figure S1. NRM cumulative incidence rates are comparable to NRM point estimates. **A** Left: Paired comparison of reported cumulative incidence rates of NRM and the calculated NRM point estimates. Mann-Whitney test was used to explore statistical significance. Right: Difference between NRM measures in %. **B** Correlation between NRM point estimates and cohort follow up times, which was primarily driven by clinical trial cohorts (light grey = clinical trials, dark grey = real-world studies). Pearson correlation was calculated and linear regression with 95% confidence interval is shown (orange line). Abbreviations: CT = clinical trial, NRM = non-relapse mortality, RW = real-world.
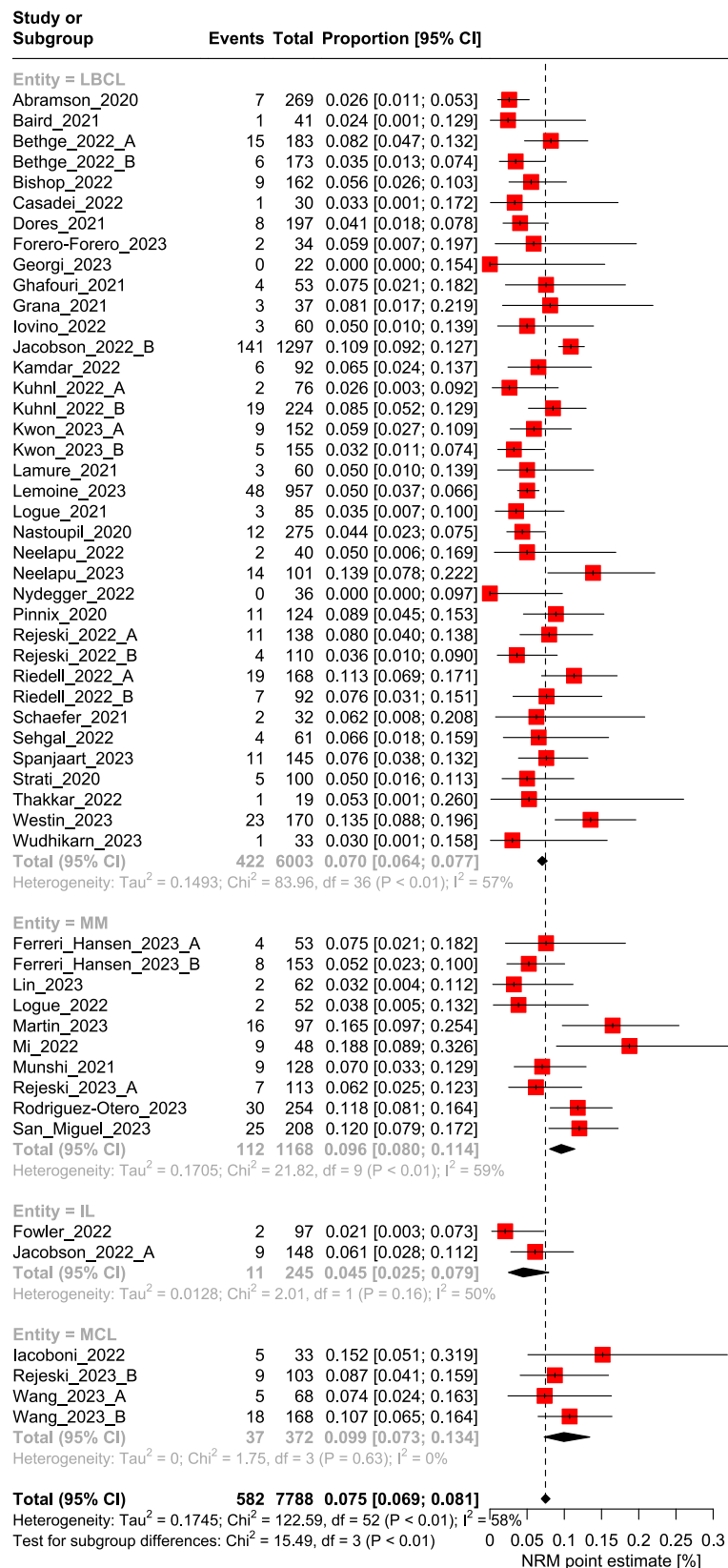
Study or Subgroup	Events	Total	Proportion [95% CI]
Entity = LBCL			
Abramson_2020	7	269	0.026 [0.011; 0.053]
Baird_2021	1	41	0.024 [0.001; 0.129]
Bethge_2022_A	15	183	0.082 [0.047; 0.132]
Bethge_2022_B	6	173	0.035 [0.013; 0.074]
Bishop_2022	9	162	0.056 [0.026; 0.103]
Casadei_2022	1	30	0.033 [0.001; 0.172]
Dores_2021	8	197	0.041 [0.018; 0.078]
Forero-Forero_2023	2	34	0.059 [0.007; 0.197]
Georgi_2023	0	22	0.000 [0.000; 0.154]
Ghafouri_2021	4	53	0.075 [0.021; 0.182]
Grana_2021	3	37	0.081 [0.017; 0.219]
Iovino_2022	3	60	0.050 [0.010; 0.139]
Jacobson_2022_B	141	1297	0.109 [0.092; 0.127]
Kamdar_2022	6	92	0.065 [0.024; 0.137]
Kuhnl_2022_A	2	76	0.026 [0.003; 0.092]
Kuhnl_2022_B	19	224	0.085 [0.052; 0.129]
Kwon_2023_A	9	152	0.059 [0.027; 0.109]
Kwon_2023_B	5	155	0.032 [0.011; 0.074]
Lamure_2021	3	60	0.050 [0.010; 0.139]
Lemoine_2023	48	957	0.050 [0.037; 0.066]
Logue_2021	3	85	0.035 [0.007; 0.100]
Nastoupil_2020	12	275	0.044 [0.023; 0.075]
Neelapu_2022	2	40	0.050 [0.006; 0.169]
Neelapu_2023	14	101	0.139 [0.078; 0.222]
Nydegger_2022	0	36	0.000 [0.000; 0.097]
Pinnix_2020	11	124	0.089 [0.045; 0.153]
Rejeski_2022_A	11	138	0.080 [0.040; 0.138]
Rejeski_2022_B	4	110	0.036 [0.010; 0.090]
Riedell_2022_A	19	168	0.113 [0.069; 0.171]
Riedell_2022_B	7	92	0.076 [0.031; 0.151]
Schaefer_2021	2	32	0.062 [0.008; 0.208]
Sehgal_2022	4	61	0.066 [0.018; 0.159]
Spanjaart_2023	11	145	0.076 [0.038; 0.132]
Strati_2020	5	100	0.050 [0.016; 0.113]
Thakkar_2022	1	19	0.053 [0.001; 0.260]
Westin_2023	23	170	0.135 [0.088; 0.196]
Wudhikarn_2023	1	33	0.030 [0.001; 0.158]
Total (95% CI)	**422**	**6003**	**0.070 [0.064; 0.077]**
Heterogeneity: Tau² = 0.1493; Chi² = 83.96, df = 36 (P < 0.01); I² = 57%			
Entity = MM			
Ferreri_Hansen_2023_A	4	53	0.075 [0.021; 0.182]
Ferreri_Hansen_2023_B	8	153	0.052 [0.023; 0.100]
Lin_2023	2	62	0.032 [0.004; 0.112]
Logue_2022	2	52	0.038 [0.005; 0.132]
Martin_2023	16	97	0.165 [0.097; 0.254]
Mi_2022	9	48	0.188 [0.089; 0.326]
Munshi_2021	9	128	0.070 [0.033; 0.129]
Rejeski_2023_A	7	113	0.062 [0.025; 0.123]
Rodriguez-Otero_2023	30	254	0.118 [0.081; 0.164]
San_Miguel_2023	25	208	0.120 [0.079; 0.172]
Total (95% CI)	**112**	**1168**	**0.096 [0.080; 0.114]**
Heterogeneity: Tau² = 0.1705; Chi² = 21.82, df = 9 (P < 0.01); I² = 59%			
Entity = IL			
Fowler_2022	2	97	0.021 [0.003; 0.073]
Jacobson_2022_A	9	148	0.061 [0.028; 0.112]
Total (95% CI)	**11**	**245**	**0.045 [0.025; 0.079]**
Heterogeneity: Tau² = 0.0128; Chi² = 2.01, df = 1 (P = 0.16); I² = 50%			
Entity = MCL			
Iacoboni_2022	5	33	0.152 [0.051; 0.319]
Rejeski_2023_B	9	103	0.087 [0.041; 0.159]
Wang_2023_A	5	68	0.074 [0.024; 0.163]
Wang_2023_B	18	168	0.107 [0.065; 0.164]
Total (95% CI)	**37**	**372**	**0.099 [0.073; 0.134]**
Heterogeneity: Tau² = 0; Chi² = 1.75, df = 3 (P = 0.63); I² = 0%			
Total (95% CI)	**582**	**7788**	**0.075 [0.069; 0.081]**
Heterogeneity: Tau² = 0.1745; Chi² = 122.59, df = 52 (P < 0.01); I² = 58%			
Test for subgroup differences: Chi² = 15.49, df = 3 (P < 0.01)			

NRM point estimate [%]: 0 0.05 0.1 0.15 0.2 0.25 0.3

Figure S2. Subgroup analysis of NRM point estimates stratified for disease entity. Forest plot illustrating NRM point estimates and 95% confidence intervals for CAR-T cohorts separated by disease entity. Abbreviation: IL = indolent lymphoma, LBCL = large B-cell lymphoma, MCL = mantle cell lymphoma, MM = multiple myeloma, NRM = non-relapse mortality.
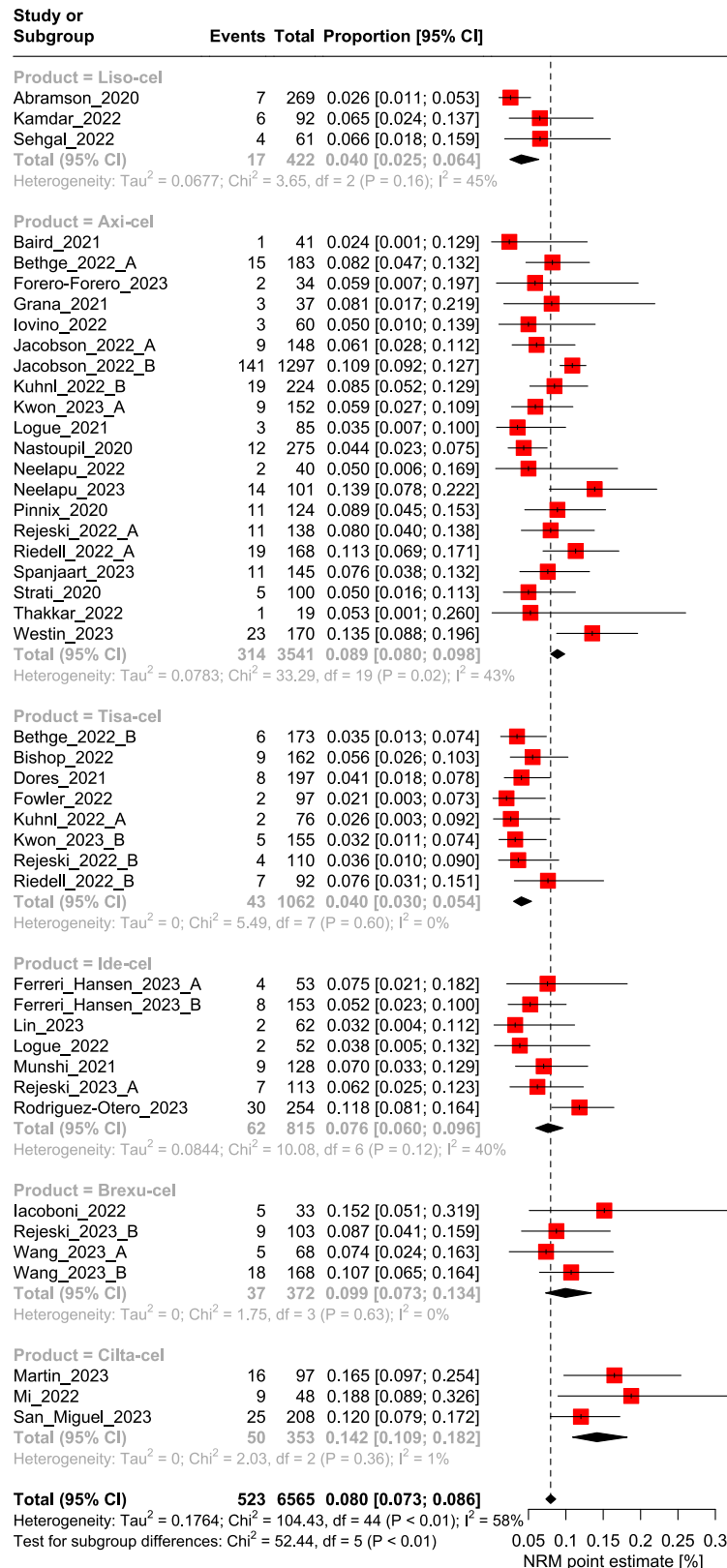
Study or Subgroup	Events	Total	Proportion [95% CI]
Product = Liso-cel			
Abramson_2020	7	269	0.026 [0.011; 0.053]
Kamdar_2022	6	92	0.065 [0.024; 0.137]
Sehgal_2022	4	61	0.066 [0.018; 0.159]
Total (95% CI)	17	422	0.040 [0.025; 0.064]

Heterogeneity: $Tau^2 = 0.0677$; $Chi^2 = 3.65$, df = 2 (P = 0.16); $I^2 = 45\%$

Product = Axi-cel			
Baird_2021	1	41	0.024 [0.001; 0.129]
Bethge_2022_A	15	183	0.082 [0.047; 0.132]
Forero-Forero_2023	2	34	0.059 [0.007; 0.197]
Grana_2021	3	37	0.081 [0.017; 0.219]
Iovino_2022	3	60	0.050 [0.010; 0.139]
Jacobson_2022_A	9	148	0.061 [0.028; 0.112]
Jacobson_2022_B	141	1297	0.109 [0.092; 0.127]
Kuhnl_2022_B	19	224	0.085 [0.052; 0.129]
Kwon_2023_A	9	152	0.059 [0.027; 0.109]
Logue_2021	3	85	0.035 [0.007; 0.100]
Nastoupil_2020	12	275	0.044 [0.023; 0.075]
Neelapu_2022	2	40	0.050 [0.006; 0.169]
Neelapu_2023	14	101	0.139 [0.078; 0.222]
Pinnix_2020	11	124	0.089 [0.045; 0.153]
Rejeski_2022_A	11	138	0.080 [0.040; 0.138]
Riedell_2022_A	19	168	0.113 [0.069; 0.171]
Spanjaart_2023	11	145	0.076 [0.038; 0.132]
Strati_2020	5	100	0.050 [0.016; 0.113]
Thakkar_2022	1	19	0.053 [0.001; 0.260]
Westin_2023	23	170	0.135 [0.088; 0.196]
Total (95% CI)	314	3541	0.089 [0.080; 0.098]

Heterogeneity: $Tau^2 = 0.0783$; $Chi^2 = 33.29$, df = 19 (P = 0.02); $I^2 = 43\%$

Product = Tisa-cel			
Bethge_2022_B	6	173	0.035 [0.013; 0.074]
Bishop_2022	9	162	0.056 [0.026; 0.103]
Dores_2021	8	197	0.041 [0.018; 0.078]
Fowler_2022	2	97	0.021 [0.003; 0.073]
Kuhnl_2022_A	2	76	0.026 [0.003; 0.092]
Kwon_2023_B	5	155	0.032 [0.011; 0.074]
Rejeski_2022_B	4	110	0.036 [0.010; 0.090]
Riedell_2022_B	7	92	0.076 [0.031; 0.151]
Total (95% CI)	43	1062	0.040 [0.030; 0.054]

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 5.49$, df = 7 (P = 0.60); $I^2 = 0\%$

Product = Ide-cel			
Ferreri_Hansen_2023_A	4	53	0.075 [0.021; 0.182]
Ferreri_Hansen_2023_B	8	153	0.052 [0.023; 0.100]
Lin_2023	2	62	0.032 [0.004; 0.112]
Logue_2022	2	52	0.038 [0.005; 0.132]
Munshi_2021	9	128	0.070 [0.033; 0.129]
Rejeski_2023_A	7	113	0.062 [0.025; 0.123]
Rodriguez-Otero_2023	30	254	0.118 [0.081; 0.164]
Total (95% CI)	62	815	0.076 [0.060; 0.096]

Heterogeneity: $Tau^2 = 0.0844$; $Chi^2 = 10.08$, df = 6 (P = 0.12); $I^2 = 40\%$

Product = Brexu-cel			
Iacoboni_2022	5	33	0.152 [0.051; 0.319]
Rejeski_2023_B	9	103	0.087 [0.041; 0.159]
Wang_2023_A	5	68	0.074 [0.024; 0.163]
Wang_2023_B	18	168	0.107 [0.065; 0.164]
Total (95% CI)	37	372	0.099 [0.073; 0.134]

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.75$, df = 3 (P = 0.63); $I^2 = 0\%$

Product = Cilta-cel			
Martin_2023	16	97	0.165 [0.097; 0.254]
Mi_2022	9	48	0.188 [0.089; 0.326]
San_Miguel_2023	25	208	0.120 [0.079; 0.172]
Total (95% CI)	50	353	0.142 [0.109; 0.182]

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.03$, df = 2 (P = 0.36); $I^2 = 1\%$

Total (95% CI)	523	6565	0.080 [0.073; 0.086]

Heterogeneity: $Tau^2 = 0.1764$; $Chi^2 = 104.43$, df = 44 (P < 0.01); $I^2 = 58\%$
Test for subgroup differences: $Chi^2 = 52.44$, df = 5 (P < 0.01)

0.05 0.1 0.15 0.2 0.25 0.3
NRM point estimate [%]

Figure S3. Subgroup analysis of NRM point estimates stratified for CAR-T products. Forest plot illustrating NRM point estimates and 95% confidence intervals for CAR-T cohorts separated by administered CAR-T product. NRM = non-relapse mortality.

Figure S4. Funnel plots.
Reporting bias was analyzed by funnel plots for all studies (**A**), separate entities (**B**) and treatment settings (**C**). Asymmetry was tested using linear regression test of funnel plot asymmetry.
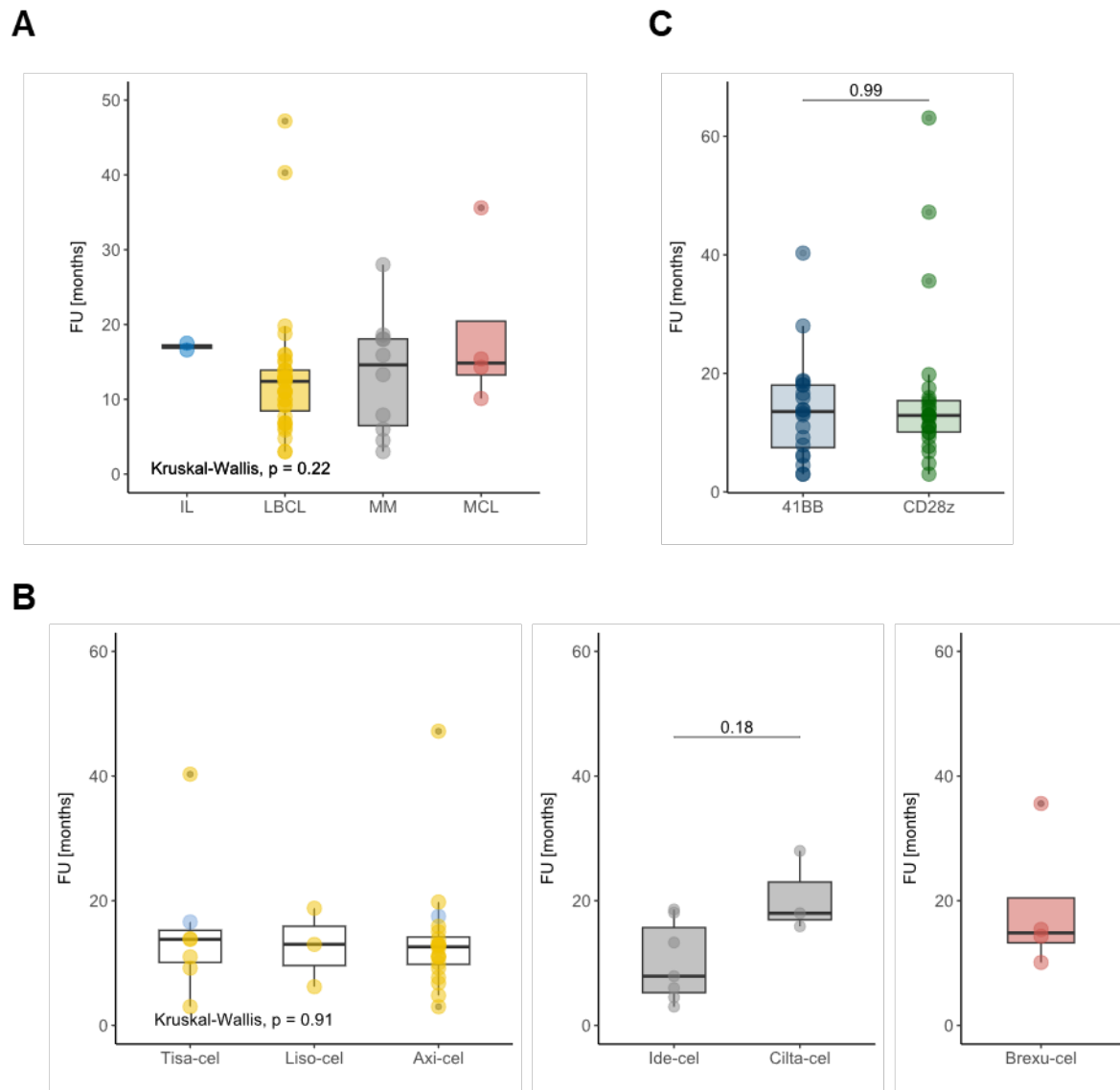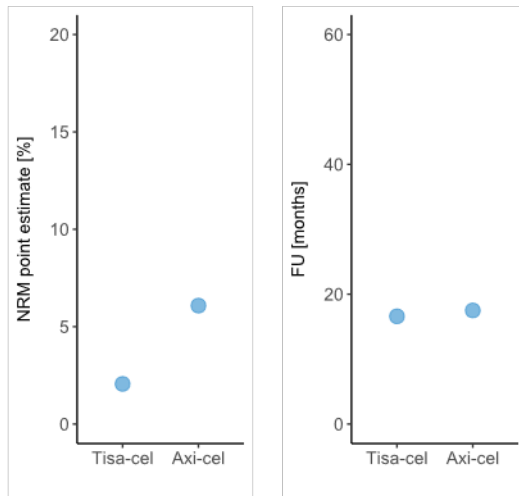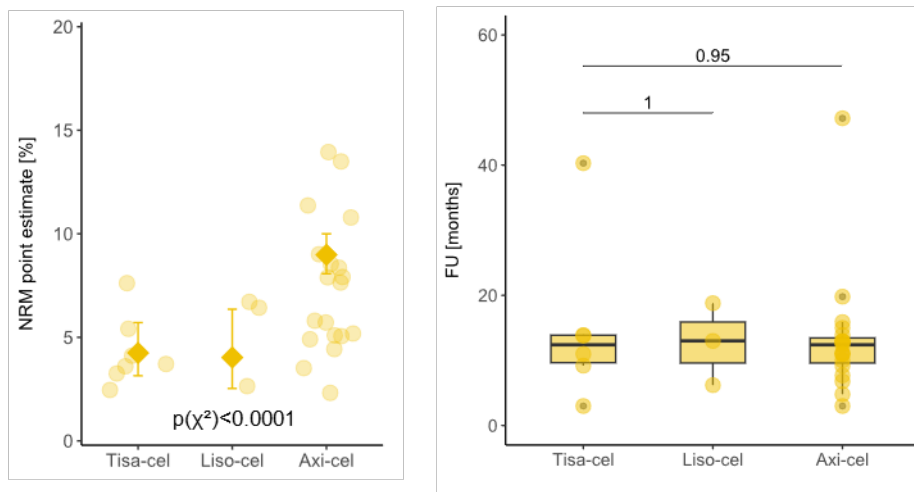
Figure S5. Follow-up times are similar between different entity and treatment cohorts. Comparison of cohort follow-up times stratified by **A** tumor entities, **B** entity-specific CAR-T products (blue = IL, yellow = LBCL, grey = MM, red = MCL), and **C** costimulatory domains. Kruskal-Wallis test was used for comparisons of > 2 groups and Mann-Whitney test for comparing two groups. Abbreviations: FU = follow-up, IL = indolent lymphoma, LBCL = large B-cell lymphoma, MCL = mantle cell lymphoma, MM = multiple myeloma, NRM = non-relapse mortality.

A

B

Figure S6. NRM point estimates and follow-up times of axi-cel, tisa-cel and liso-cel separately stratified for indolent lymphoma and large B-cell lymphoma cohorts. Comparison of cohort NRM point estimates and follow-up times stratified for **A** indolent lymphoma and **B** large B-cell lymphoma. Chi-square test was used for statistical testing of NRM-related deaths across products. Mann-Whitney test was used for comparing FU times between products. Abbreviations: FU = follow-up, MCL = mantle cell lymphoma, MM = multiple myeloma, NRM = non-relapse mortality.

Figure S7. Reported cumulative incidence NRM rates vary between tumor entities and CAR-T products.
Left: NRM cumulative incidence rates are higher in studies reporting on patients with MCL compared to LBCL. **Right:** NRM cumulative incidence rates are higher in the LBCL-specific CAR-T product (yellow) axi-cel compared to tisa-cel. The MCL-specific CAR-T product (red) brexu-cel has the highest NRM rates. Mann-Whitney test was used for statistical testing. Abbreviations: LBCL = large B-cell lymphoma, MCL = mantle cell lymphoma, NRM = non-relapse mortality.
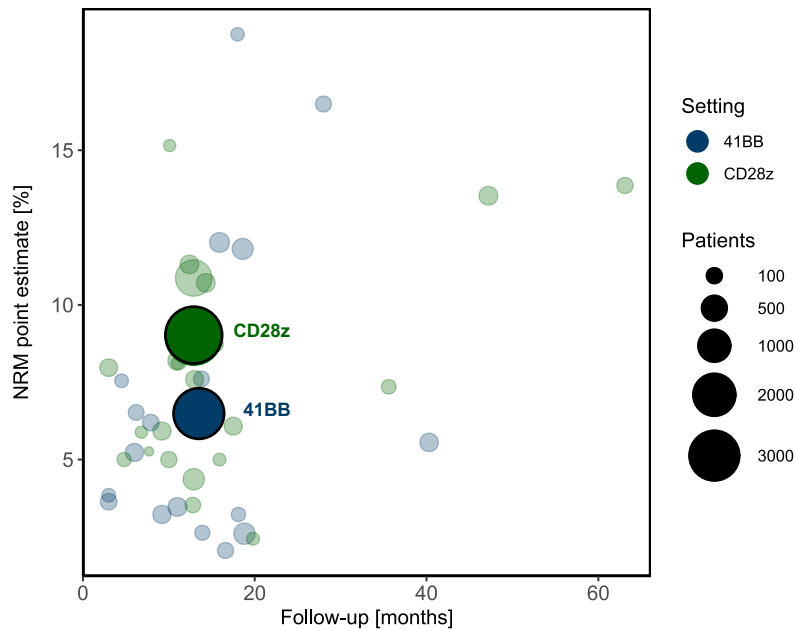
Figure S8. CD28z-harboring CAR products are associated with increased NRM point estimates.

Bubble plot demonstrating NRM point estimates in relation to follow-up times for 4-1BB containing CAR products (dark blue) and CD28z containing CAR products (dark green). Each bubble represents one cohort. Bubble size indicates the total number of patients per cohort. The aggregated NRM point estimate for all cohorts treated with CAR products with the same costimulatory domain is encircled in black.
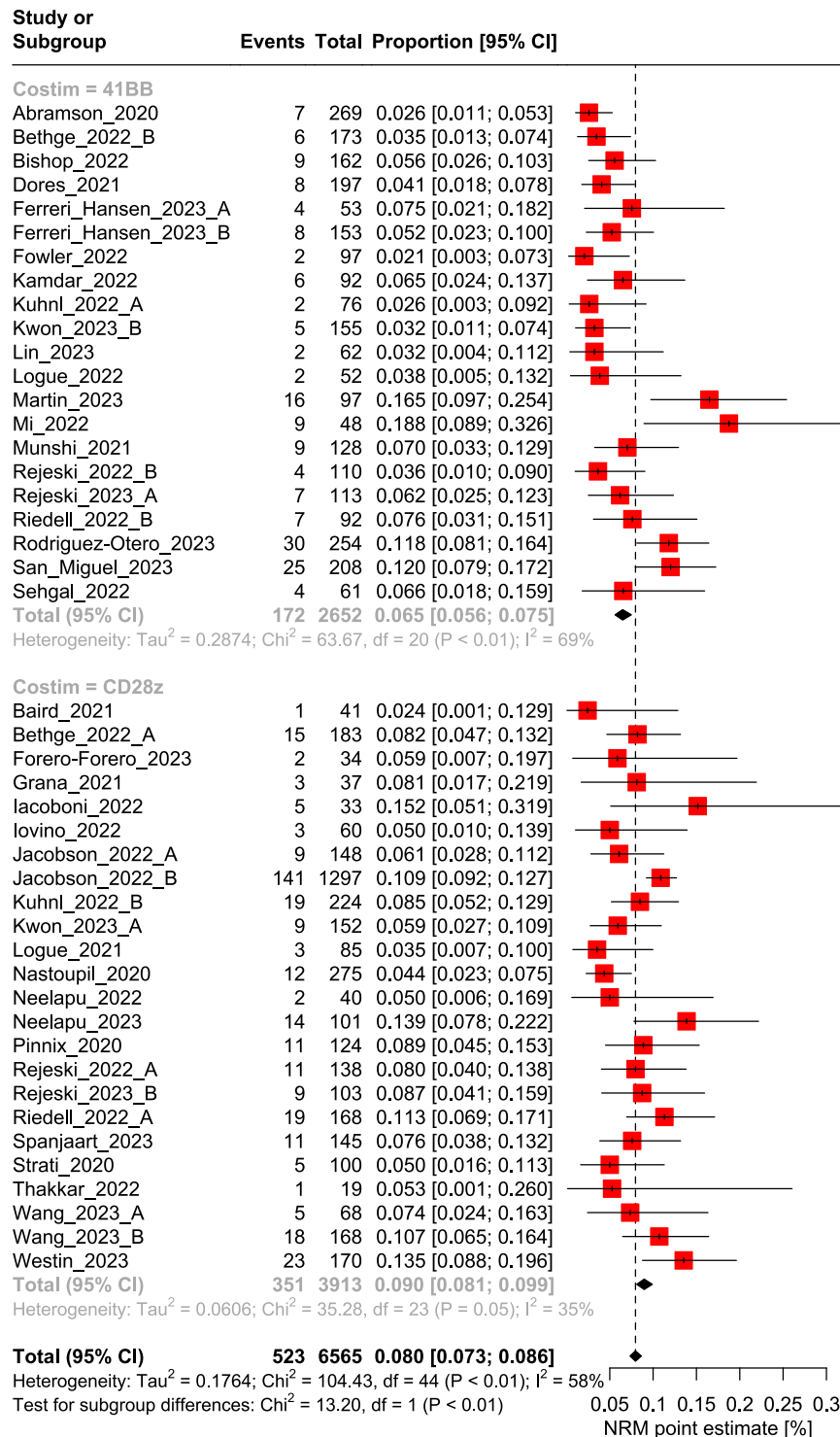
Study or Subgroup	Events	Total	Proportion [95% CI]
Costim = 41BB			
Abramson_2020	7	269	0.026 [0.011; 0.053]
Bethge_2022_B	6	173	0.035 [0.013; 0.074]
Bishop_2022	9	162	0.056 [0.026; 0.103]
Dores_2021	8	197	0.041 [0.018; 0.078]
Ferreri_Hansen_2023_A	4	53	0.075 [0.021; 0.182]
Ferreri_Hansen_2023_B	8	153	0.052 [0.023; 0.100]
Fowler_2022	2	97	0.021 [0.003; 0.073]
Kamdar_2022	6	92	0.065 [0.024; 0.137]
Kuhnl_2022_A	2	76	0.026 [0.003; 0.092]
Kwon_2023_B	5	155	0.032 [0.011; 0.074]
Lin_2023	2	62	0.032 [0.004; 0.112]
Logue_2022	2	52	0.038 [0.005; 0.132]
Martin_2023	16	97	0.165 [0.097; 0.254]
Mi_2022	9	48	0.188 [0.089; 0.326]
Munshi_2021	9	128	0.070 [0.033; 0.129]
Rejeski_2022_B	4	110	0.036 [0.010; 0.090]
Rejeski_2023_A	7	113	0.062 [0.025; 0.123]
Riedell_2022_B	7	92	0.076 [0.031; 0.151]
Rodriguez-Otero_2023	30	254	0.118 [0.081; 0.164]
San_Miguel_2023	25	208	0.120 [0.079; 0.172]
Sehgal_2022	4	61	0.066 [0.018; 0.159]
Total (95% CI)	**172**	**2652**	**0.065 [0.056; 0.075]**
Heterogeneity: Tau^2 = 0.2874; Chi^2 = 63.67, df = 20 (P < 0.01); I^2 = 69%			
Costim = CD28z			
Baird_2021	1	41	0.024 [0.001; 0.129]
Bethge_2022_A	15	183	0.082 [0.047; 0.132]
Forero-Forero_2023	2	34	0.059 [0.007; 0.197]
Grana_2021	3	37	0.081 [0.017; 0.219]
Iacoboni_2022	5	33	0.152 [0.051; 0.319]
Iovino_2022	3	60	0.050 [0.010; 0.139]
Jacobson_2022_A	9	148	0.061 [0.028; 0.112]
Jacobson_2022_B	141	1297	0.109 [0.092; 0.127]
Kuhnl_2022_B	19	224	0.085 [0.052; 0.129]
Kwon_2023_A	9	152	0.059 [0.027; 0.109]
Logue_2021	3	85	0.035 [0.007; 0.100]
Nastoupil_2020	12	275	0.044 [0.023; 0.075]
Neelapu_2022	2	40	0.050 [0.006; 0.169]
Neelapu_2023	14	101	0.139 [0.078; 0.222]
Pinnix_2020	11	124	0.089 [0.045; 0.153]
Rejeski_2022_A	11	138	0.080 [0.040; 0.138]
Rejeski_2023_B	9	103	0.087 [0.041; 0.159]
Riedell_2022_A	19	168	0.113 [0.069; 0.171]
Spanjaart_2023	11	145	0.076 [0.038; 0.132]
Strati_2020	5	100	0.050 [0.016; 0.113]
Thakkar_2022	1	19	0.053 [0.001; 0.260]
Wang_2023_A	5	68	0.074 [0.024; 0.163]
Wang_2023_B	18	168	0.107 [0.065; 0.164]
Westin_2023	23	170	0.135 [0.088; 0.196]
Total (95% CI)	**351**	**3913**	**0.090 [0.081; 0.099]**
Heterogeneity: Tau^2 = 0.0606; Chi^2 = 35.28, df = 23 (P = 0.05); I^2 = 35%			
Total (95% CI)	**523**	**6565**	**0.080 [0.073; 0.086]**
Heterogeneity: Tau^2 = 0.1764; Chi^2 = 104.43, df = 44 (P < 0.01); I^2 = 58%			
Test for subgroup differences: Chi^2 = 13.20, df = 1 (P < 0.01)			

NRM point estimate [%]

0.05 0.1 0.15 0.2 0.25 0.3

Figure S9. Subgroup analysis of NRM point estimates stratified for CAR-T costimulatory domain.
Forest plot illustrating NRM point estimates and 95% confidence intervals for CAR-T cohorts separated by CAR-T products containing either CD28z or 41BB costimulatory domains. NRM = non-relapse mortality.
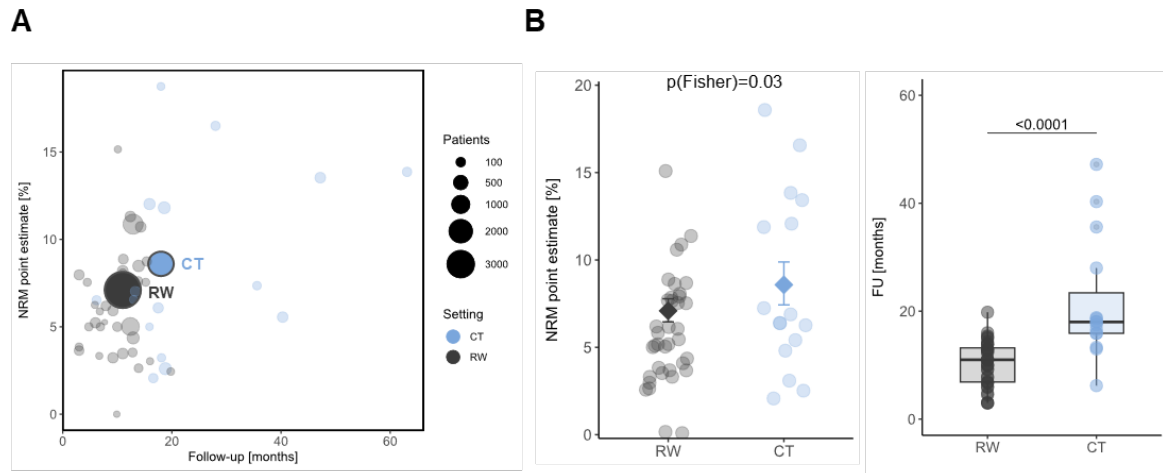
A

B

Figure S10. NRM point estimates are associated with treatment settings but confounded by follow-up times.
A Bubble plot demonstrating NRM point estimates in relation to follow-up times for cohorts treated in clinical trials (light blue) or in real-world setting (dark grey). Each bubble represents one cohort. Bubble size indicates the total number of patients per cohort. The aggregated NRM point estimate for all cohorts within each treatment setting is encircled in black. **B** NRM point estimates and 95%CI between 41BB- and CD28z containing CAR-T products (left) as well as FU times are shown. Fisher's exact test was used for statistical testing of NRM-related deaths across cohorts within each treatment setting. Mann-Whitney test was used for statistical testing of FU times. Abbreviations: CT = clinical trial, NRM = non-relapse mortality, RW = real-world.
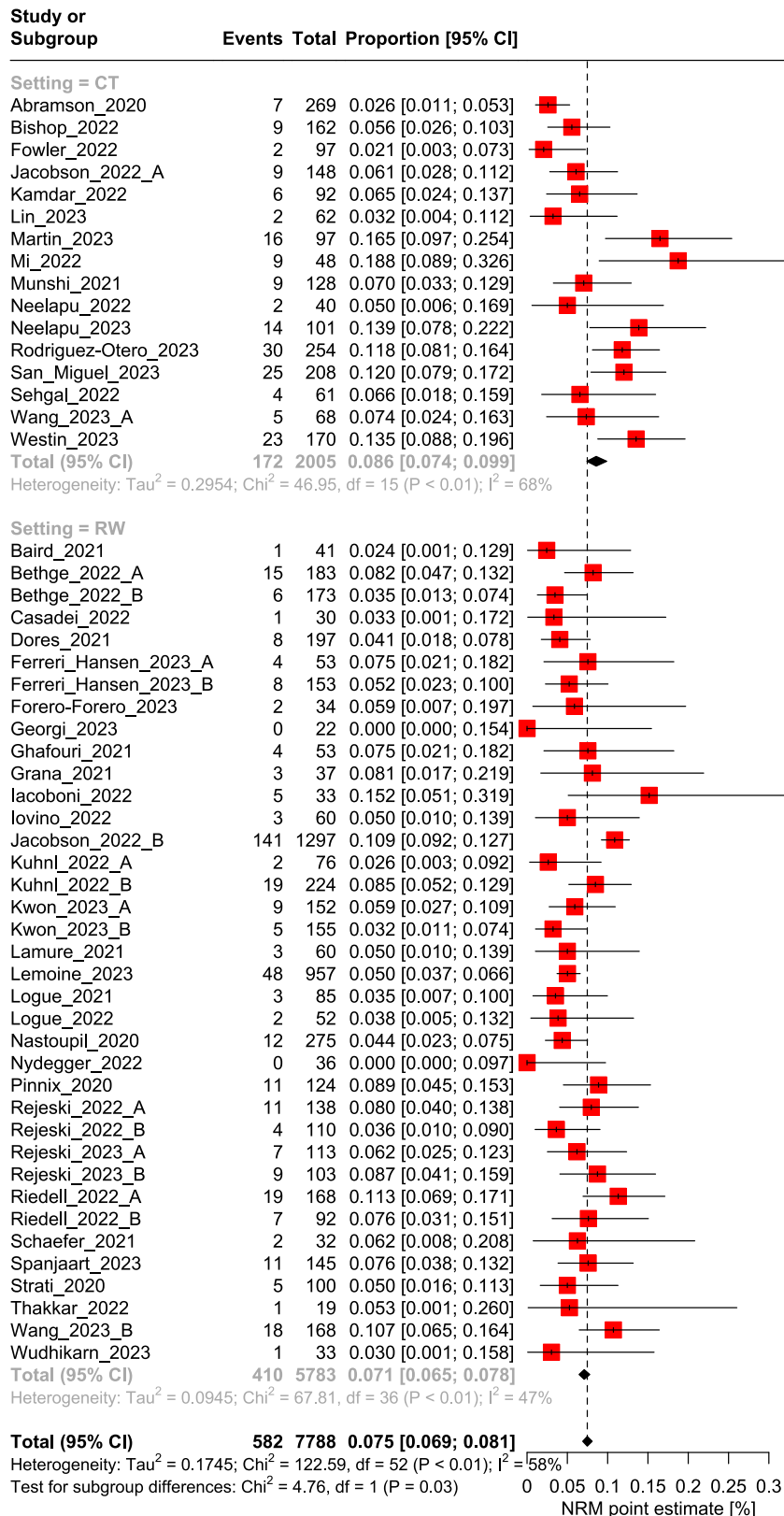
Study or Subgroup	Events	Total	Proportion [95% CI]
Setting = CT			
Abramson_2020	7	269	0.026 [0.011; 0.053]
Bishop_2022	9	162	0.056 [0.026; 0.103]
Fowler_2022	2	97	0.021 [0.003; 0.073]
Jacobson_2022_A	9	148	0.061 [0.028; 0.112]
Kamdar_2022	6	92	0.065 [0.024; 0.137]
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San_Miguel_2023	25	208	0.120 [0.079; 0.172]
Sehgal_2022	4	61	0.066 [0.018; 0.159]
Wang_2023_A	5	68	0.074 [0.024; 0.163]
Westin_2023	23	170	0.135 [0.088; 0.196]
Total (95% CI)	**172**	**2005**	**0.086 [0.074; 0.099]**
Setting = RW			
Baird_2021	1	41	0.024 [0.001; 0.129]
Bethge_2022_A	15	183	0.082 [0.047; 0.132]
Bethge_2022_B	6	173	0.035 [0.013; 0.074]
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Lemoine_2023	48	957	0.050 [0.037; 0.066]
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Rejeski_2022_B	4	110	0.036 [0.010; 0.090]
Rejeski_2023_A	7	113	0.062 [0.025; 0.123]
Rejeski_2023_B	9	103	0.087 [0.041; 0.159]
Riedell_2022_A	19	168	0.113 [0.069; 0.171]
Riedell_2022_B	7	92	0.076 [0.031; 0.151]
Schaefer_2021	2	32	0.062 [0.008; 0.208]
Spanjaart_2023	11	145	0.076 [0.038; 0.132]
Strati_2020	5	100	0.050 [0.016; 0.113]
Thakkar_2022	1	19	0.053 [0.001; 0.260]
Wang_2023_B	18	168	0.107 [0.065; 0.164]
Wudhikarn_2023	1	33	0.030 [0.001; 0.158]
Total (95% CI)	**410**	**5783**	**0.071 [0.065; 0.078]**
Total (95% CI)	**582**	**7788**	**0.075 [0.069; 0.081]**

Heterogeneity: $\text{Tau}^2 = 0.2954$; $\text{Chi}^2 = 46.95$, df = 15 (P < 0.01); $I^2 = 68\%$

Heterogeneity: $\text{Tau}^2 = 0.0945$; $\text{Chi}^2 = 67.81$, df = 36 (P < 0.01); $I^2 = 47\%$

Heterogeneity: $\text{Tau}^2 = 0.1745$; $\text{Chi}^2 = 122.59$, df = 52 (P < 0.01); $I^2 = 58\%$

Test for subgroup differences: $\text{Chi}^2 = 4.76$, df = 1 (P = 0.03)

NRM point estimate [%]: 0 0.05 0.1 0.15 0.2 0.25 0.3

Figure S11. Subgroup analysis of NRM point estimates stratified for treatment setting. Forest plot illustrating NRM point estimates and 95% confidence intervals for CAR-T cohorts separated by treatment setting into clinical trials (CT) and real-world studies (RW). NRM = non-relapse mortality.
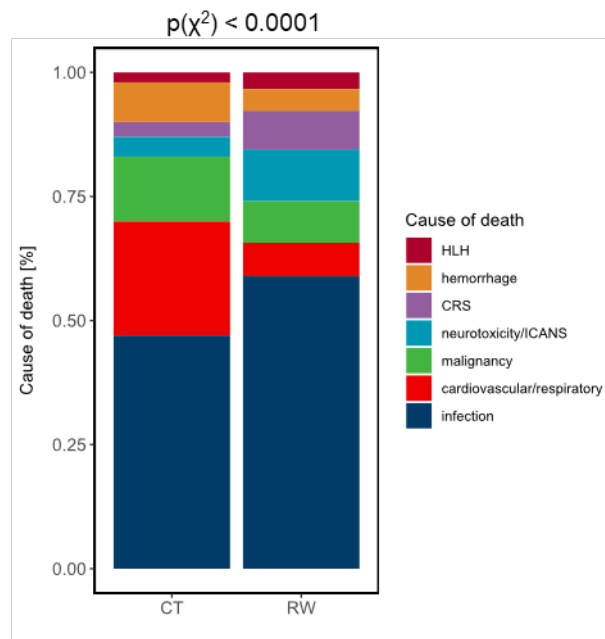
Figure S12. Exclusion of COVID-19 related deaths does not change distribution differences of causes of death between treatment settings.

Causes of death compared between CAR-T cohorts treated in either a clinical trial (CT) or real-world setting (RW) with exclusion of COVID-19 related deaths. Chi-square distribution test was used for statistical testing.
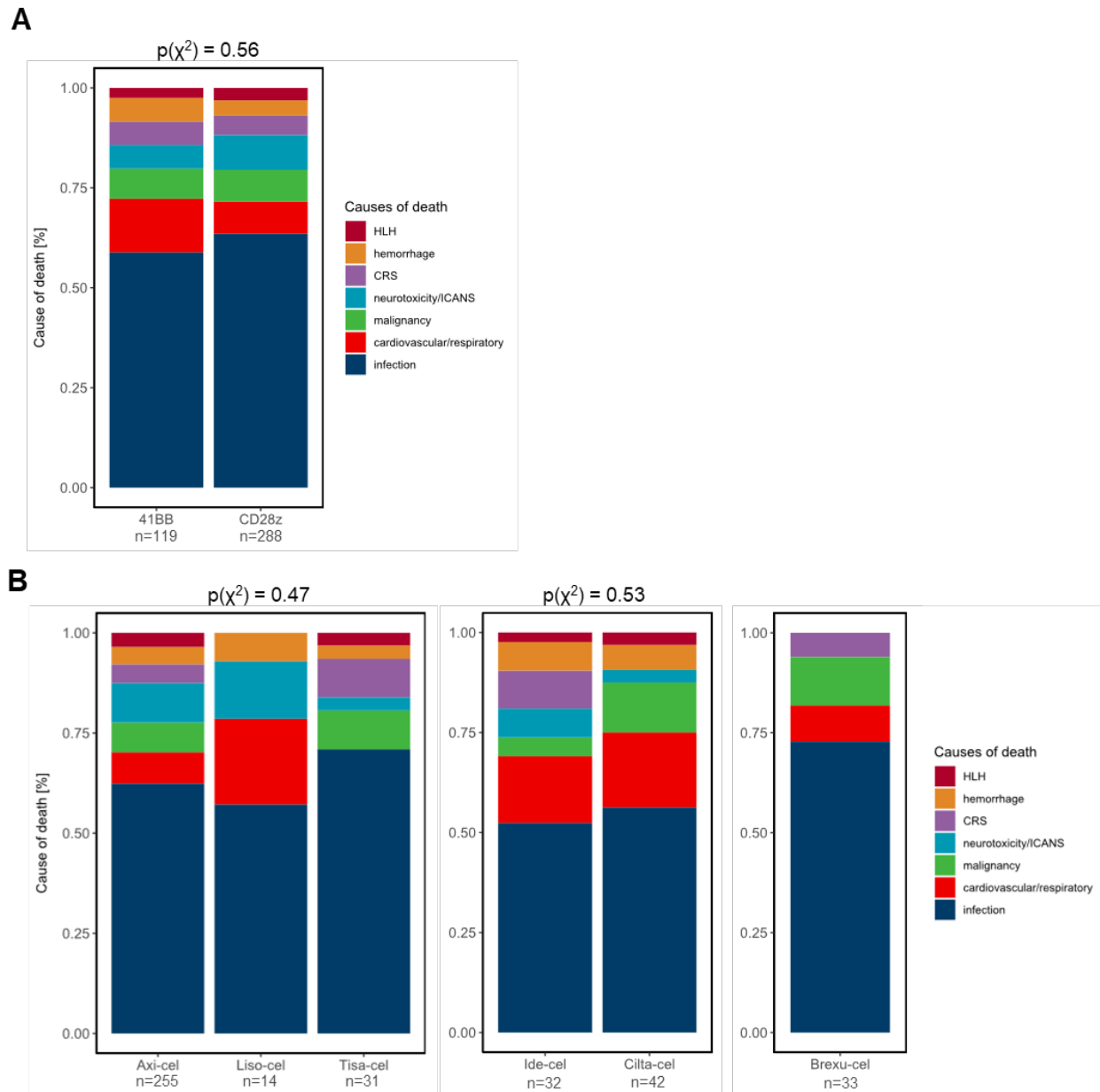
Figure S13. Causes of death are similar between different CAR-T products.
Causes of death compared between **A** CAR-T products harboring 41BB or CD28z costimulatory domains, and **B** between different entity-specific CAR-T products. Chi-square distribution test was used for statistical testing.