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eMethods 1. PRISMA checklist

Section and Topic	ltem #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 3
INTRODUCTIO	N		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
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 5. eMethods2 in supplement (page 6,7)
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5, eMethods2 in the supplement (page 6,7)
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 5
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 5
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 6,7
	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 6,7
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 6
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 6,7
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 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6, 7
	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 6, 7

Section and Topic	ltem #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 6,7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 6, 7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 7
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.	eFigure 1 in supplement (page 10)
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Not applicable
Study characteristics	17	Cite each included study and present its characteristics.	Table 1 page 8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	eFigure 2 in the supplement (page 11)
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.	Page 8,9 eFigure 3-19 in the supplement (page 12-18)
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	eFigure 2 in the supplement (page 11)
	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.	Page 8-10 eFigure3-23 in the supplement(page 12-22)
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9 eFigure 16 -19 in supplement (page 17,18)
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	eFigure 2 in the supplement (page 11)
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Table 2 page 11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 11-15
	23b	Discuss any limitations of the evidence included in the review.	Page 15
	23c	Discuss any limitations of the review processes used.	Page 15
	23d	Discuss implications of the results for practice, policy, and future research.	Page 13,14
OTHER INFOR	MATIO	N	
Registration	24a	Provide registration information for the review, including register name and registration	Not applicable

Section and Topic	ltem #	Checklist item	Location where item is reported
and protocol		number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not applicable
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
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 17
Competing interests	26	Declare any competing interests of review authors.	Page 17
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.	Not applicable

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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EBM Reviews - Cochrane Central Register of Controlled Trials <January 2022>

EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 9, 2022>

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6	Yescarta.mp.	425			
7	KTE-C19.mp.	105			
8	Axi-cel.mp.	546			
9	Lisocabtagene maraleucel.mp.	292			
10	Liso-cel.mp.	132			
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20	Clinical Trial, Phase III/	7479
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22	phase 3 clinical trial.mp.	141154
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eTable 1. Outcome(s) definitions for the trials

Outcome	ZUMA-7	TRANSFORM	BELINDA
EFS	Time from randomization to the earliest date of disease progression according to the Lugano classification, the commencement of new therapy for lymphoma, death from any cause, or a best response of stable disease up to and including the response on the day 150 assessment after randomization.	Time from randomization to death from any cause, progressive disease, failure to achieve complete or partial response by 9 weeks after randomization or start of new antineoplastic therapy due to efficacy concerns, whichever occurred first.	Time from randomization to stable or progressive disease at or after the week 12 assessment by the independent review committee according to the Lugano criteria or death at any time.
PFS	Time from randomization to disease progression or death from any cause.	Time from randomization to progressive disease or death from any cause, whichever occurs first.	NR

Abbreviations: EFS: event-free survival; PFS: progression-free survival; NR: not reported

eTable 2. Common adverse events, cytokine release syndrome events, and neurologic events

	ZUMA-7				TRANSFORM				BELINDA			
	Axi-		Standard	of Care	Liso	p-cel	Standard	of Care	Tisagenl		Standard	of Care
	N=1		N=1			=92	N=		N=1		N=1	
	Any	Grade	Any	Grade	Grade	Grade	Grade 1-	Grade	Any	Grade	Any	Grade
	Grade	<u>></u> 3	Grade	<u>></u> 3	1-2 ^b	<u>></u> 3	2 ^b	<u>></u> 3	Grade	<u>></u> 3	Grade	<u>></u> 3
Event ^a	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)
Any adverse event ^c	170 (100)	155 (91)	168 (100)	140 (83)	90 (98)	85 (92)	90 (99)	79 (87)	160(98.8)	136 (84)	158(98.8)	144 (90)
Abdominal pain	NA	NA	NA	NA	11 (12)	3 (3)	11 (12)	1 (1)	17 (10.5)	2 (1.2)	30 (18.8)	5 (3.1)
Anemia	71 (42)	51 (30)	91 (54)	65 (39)	36 (39)	45 (49)	34 (37)	45 (49)	80 (49.4)	54(33.3)	115(71.9)	92(57.5)
Arthralgia	NA	NA	NA	NA	13 (14)	0	9 (10)	0	NA	NA	NA	NA
Asthenia	NA	NA	NA	NA	9 (10)	1 (1)	8 (9)	0	8 (4.9)	1 (0.6)	19 (11.9)	2 (1.3)
Back pain	NA	NA	NA	NA	14 (15)	1 (1)	15 (16)	2 (2)	NA	NA	NA	NA
Blood creatinine increase	NA	NA	NA	NA	NA	NA	NA	NA	29 (17.9)	2 (1.2)	29 (18.1)	1 (0.6)
Bone pain	NA	NA	NA	NA	12 (13)	0	9 (10)	0	NA	NA	NA	NA
Chills	47(28)	1 (1)	14 (8)	0	NA	NA	NA	NA	NA	NA	NA	NA
Constipation	34 (20)	0	58 (35)	0	31 (34)	2 (2)	22 (24)	0	48 (29.6)	0	42 (26.3)	0
Cough	42 (25)	1 (1)	18 (11)	0	13 (14)	0	8 (9)	0	18 (11.1)	0	13 (8.1)	0
Decreased appetite	42 (25)	7 (4)	42 (25)	6 (4)	21 (23)	1 (1)	26 (29)	3 (3)	21 (13.0)	1 (0.6)	17 (10.6)	1 (0.6)
Diarrhea	71 (42)	4 (2)	66 (39)	7 (4)	23 (25)	0	37 (41)	3 (3)	35 (21.6)	3 (1.9)	58 (36.3)	6 (3.8)
Dizziness	36 (21)	2 (1)	21 (12)	1 (1)	20 (22)	0	13 (14)	0	19 (11.7)	0	14 (8.8)	0
Dyspepsia	NA	NA	NA	NA	5 (5)	0	10 (11)	0	NA	NA	NA	NA
Dyspnea	NA	NA	NA	NA	12 (13)	1 (1)	7 (8)	1 (1)	15 (9.3)	2 (1.2)	21 (13.1)	2 (1.3)
Edema peripheral	NA	NA	NA	NA	15 (16)	1 (1)	16 (18)	0	18 (11.1)	0	18 (11.3)	0
Fatigue	71 (42)	11 (6)	87 (52)	4 (2)	36 (39)	0	34 (37)	2 (2)	38 (23.5)	3 (1.9)	49 (30.6)	6 (3.8)
Febrile neutropenia	4 (2)	4 (2)	46 (27)	46 (27)	4 (4)	11 (12)	3 (3)	19 (21)	21 (13.0)	21 (13.0)	40 (25.0)	40 (25.0)
Headache	70 (41)	5 (3)	43 (26)	2 (1)	39 (42)	4 (4)	19 (21)	1 (1)	37 (22.8)	0	32 (20.0)	1 (0.6)
Hypertension	NA	NA	NA	NA	9 (10)	4 (4)	6 (7)	1 (1)	NA	NA	NA	NA
Hypokalemia	44 (26)	10 (6)	49 (29)	11 (7)	16 (17)	4 (4)	19 (21)	4 (4)	45 (27.8)	8 (4.9)	49 (30.6)	14 (8.8)
Hypomagnesemia	NA	NA	NA	NA	13 (14)	0	19 (21)	1 (1)	20 (12.3)	0	29 (18.1)	3 (1.9)
Hypophosphatemia	45 (26)	31 (18)	29 (17)	21 (12)	6 (7)	3 (3)	10 (11)	6 (7)	13 (8.0)	6 (3.7)	17 (10.6)	4 (2.5)
Hypotension	75 (44)	19 (11)	25 (15)	5 (3)	18 (20)	3 (3)	4 (4)	0	NA	NA	NA	NA
Hypoxia	37 (22)	16 (9)	13 (8)	7 (4)	NA	NA	NA	NA	NA	NA	NA	NA
Insomnia	NA	NA	NA	NA	19 (21)	0	11 (12)	0	NA	NA	NA	NA
Leukopenia	55 (32)	50 (29)	43 (26)	37 (22)	9 (10)	14 (15)	6 (7)	11 (12)	22 (13.6)	21(13.0)	30 (18.8)	28(17.5)
Lymphopenia	NA	NA	NA	NA	8 (9)	23 (25)	4 (4)	8 (9)	NA	NA	NA	NA
Mucosal inflammation	NA	NA	NA	NA	4 (4)	0	11 (12)	3 (3)	5 (3.1)	1 (0.6)	18 (11.3)	0
Myalgia	NA	NA	NA	NA	11 (12)	1 (1)	4 (4)	0	NA	NA	NA	NA
Nausea	69 (41)	3 (2)	116 (69)	9 (5)	49 (53)	3 (3)	52 (57)	3 (3)	67 (41.4)	2 (1.2)	79 (49.4)	10 (6.3)
Neutropenia	121 (71)	118 (69)	70 (42)	69 (41)	43 (47)	74 (80)	17 (19)	46 (51)	67 (41.4)	65(40.1)	65 (40.6)	63(39.4)
Peripheral sensory neuropathy	NA	NA	NA	NA	7 (8)	0	11 (12)	0	NA	NA	NA	NA
Prolonged cytopenia	NA	NA	NA	NA	NA	40 (43)	NA	3 (3)	NA	NA	NA	NA
Pyrexia	158 (93)	15 (9)	43 (26)	1 (1)	27 (29)	0	21 (23)	0	42 (25.9)	0	50 (31.3)	3 (1.9)
Sinus tachycardia	58 (34)	3 (2)	17 (10)	1 (1)	9 (10)	0	10 (11)	0	NA	NA	NA	NA
Stomatitis	NA 50 (00)	NA	NA	NA	5 (5)	0	9 (10)	2 (2)	NA 50 (00 4)	NA	NA TO (40,4)	NA 70(47.5)
Thrombocytopenia	50 (29)	25 (15)	101 (60)	95 (57)	30 (33)	45 (49)	35 (38)	58 (64)	59 (36.4)	52(32.1)	79 (49.4)	76(47.5)
Tremor	NA	NA	NA	NA	11 (12)	1 (1)	0	0	NA	NA 1 (0, 0)	NA 25 (21.0)	NA 2 (1 0)
Vomiting	33 (19)	0	55 (33)	1 (1)	18 (20)	1 (1)	21 (23)	2 (2)	24 (14.8)	1 (0.6)	35 (21.9)	3 (1.9)
Cytokine release syndrome ^d	157 (92)	11 (6)	NA	NA	45 (49)	1 (1)	0	0	95 (58.6)	8 (4.9)	0	0
Chills	38 (24)	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Headache	32 (20)	2 (1)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hypotension	68 (43)	18 (11)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Нурохіа	31 (20)	13 (8)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Pyrexia	155 (99)	14 (9)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sinus tachycardia	49 (31)	3 (2)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Neurologic event ^e	102 (60)	36 (21)	33(20)	1(1)	11 (12)	4 (4)	NA	NA	16 (10.3)	3 (1.9)	NA	NA
Aphasia	36 (21)	12 (7)	0	0	NA	NA	NA	NA	NA	NA	NA	NA
Confusional state	40 (24)	9 (5)	4 (2)	0	NA	NA	NA	NA	NA	NA	NA	NA
Delirium	3 (2)	3 (2)	5 (3)	1 (1)	NA	NA	NA	NA	NA	NA	NA	NA
Encephalopathy	29 (17)	20 (12)	2 (1)	0	NA	NA	NA	NA	NA	NA	NA	NA
Paresthesia	8 (5)	1 (1)	14 (8)	0	NA	NA	NA	NA	NA	NA	NA	NA
Tremor	44 (26)	2 (1)	1 (1)	0	NA	NA	NA	NA	NA	NA	NA	NA
	• (=•)	\`/	· · /						1		1	

^a Cell count decrease was not included

^b Grade 1-2 reported for TRANSFORM trial

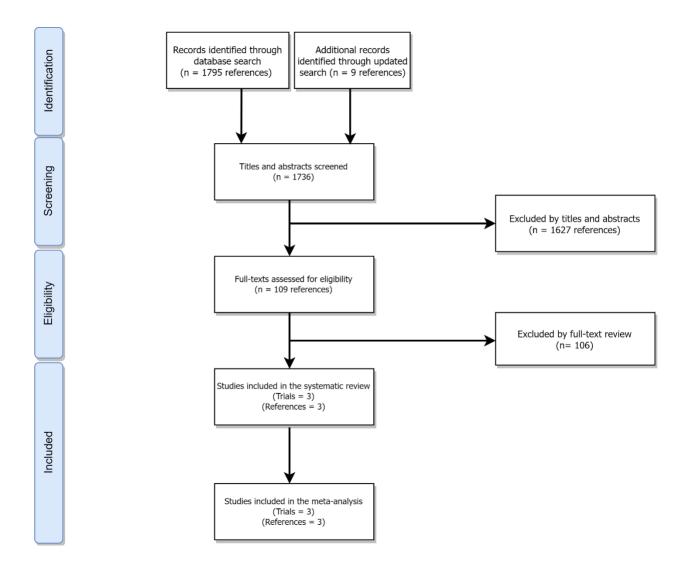
° For BELINDA trial, this corresponds to 'Number of patients with at least 1 event'

^d The percentage of each cytokine release syndrome (CRS) event was relative to the total CRS observed i.e., 157 for ZUMA-7 trial for all grades

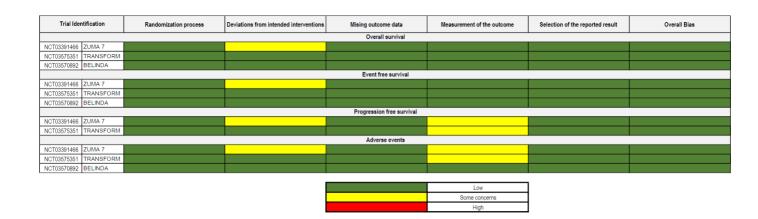
^e BELINDA trial reported the proportion of neurological events in Tisagenlecleucel arm relative to 155 patients (reported here). However, the total number of participants were 162

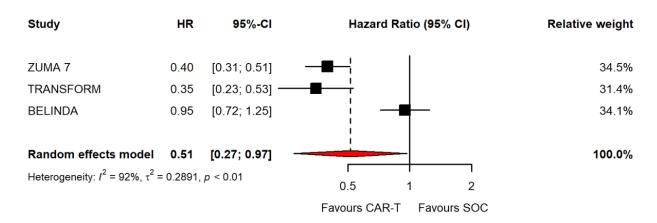
Abbreviations: Axi-cel, Axicabtagene ciloleucel; Liso-cel, Lisocabtagene maraleucel; N, number of participants; NA, not applicable





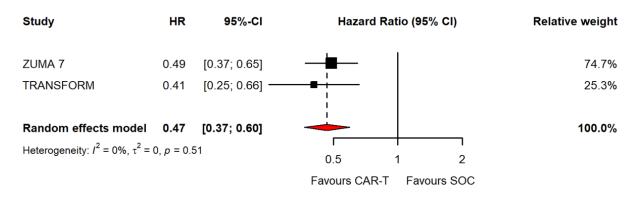
eFigure 2. Summary of risk of bias across included trials



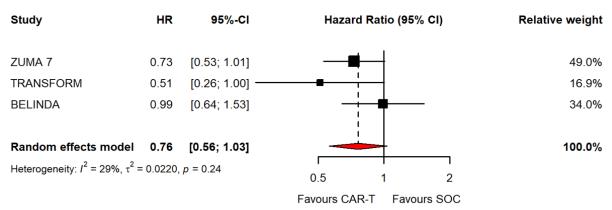


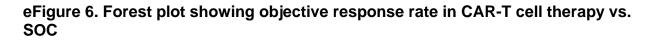
eFigure 3. Forest plot showing adjusted event-free survival in CAR-T cell therapy vs. SOC

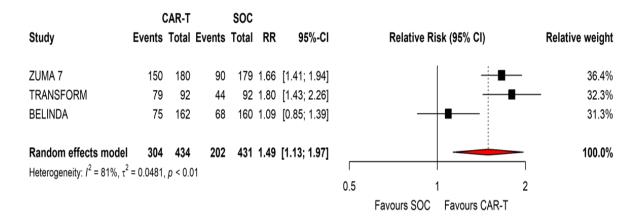
eFigure 4. Forest plot showing progression-free survival in CAR-T cell therapy vs. SOC



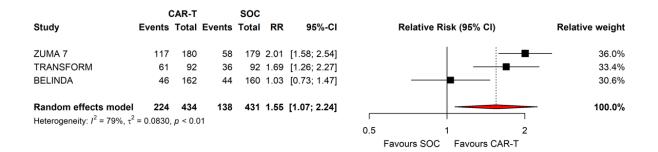
eFigure 5. Forest plot showing adjusted overall survival in CAR-T cell therapy vs. SOC







eFigure 7. Forest plot showing complete response in CAR-T cell therapy vs. SOC



eFigure 8. Forest plot showing partial response in CAR-T cell therapy vs. SOC

	с	AR-T		SOC				
Study	Events	Total	Events	Total	RR	95%-CI	Relative Risk (95% CI)	Relative weight
ZUMA 7	33	180	32	179	1.03	[0.66; 1.59]	#	43.1%
TRANSFORM	18	92	8	92	2.25	[1.03; 4.91]		19.4%
BELINDA	29	162	24	160	1.19	[0.73; 1.96]		37.5%
Random effects model Heterogeneity: $I^2 = 33\%$, τ^2		434 p = 0.2	64	431	1.26	[0.86; 1.85]	0.5 1 2	100.0%
							Favours SOC Favours CAR-T	

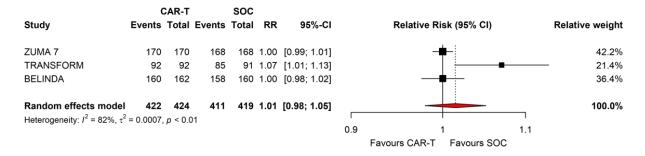
eFigure 9. Analysis of complete response comparing patients who received CAR-T cell therapy with those who received standard of care and those who underwent autologous stem cell transplantation

Type of control	Complete Response	Relative Risk	95% CI
Standard of care Heterogeneity: I^2 = 79%, τ^2 = 0.0830, p < 0.01		- 1.55	[1.07; 2.24]
ASCT Heterogeneity: I^2 = 88%, τ^2 = 0.0711, $p < 0.01$ —	— ,	0.61	[0.44; 0.85]
0.9 Fa	5 1 2 vors Control Favors CAR-	т	

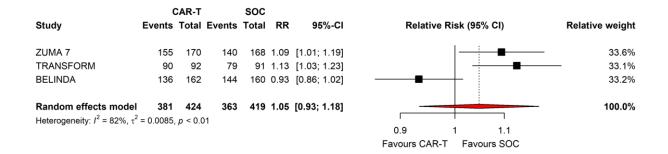
Type of control	№ of participants	Relative effect	Anticipated a	bsolute effects [*] (95% CI)
	(studies)	(95% CI)	CR with Control	Risk difference with CAR-T
Standard of same (SOC)	865	RR 1.55	320 per 1,000	176 more per 1,000
Standard of care (SOC)	(3 RCTs)	(1.07 to 2.24)	• 320 per 1,000	(from 22 more to 397 more)
Autologicus store cell transmight (ASCT)	582	RR 0.61	821 per 1 000	324 fewer per 1,000
Autologous stem cell transplant (ASCT) -	(3 RCTs)	(0.44 to 0.85)	 831 per 1,000 	(from 466 more to 125 more)

Abbreviations: CAR-T: chimeric antigenic receptor T-cell therapy; CR: complete response

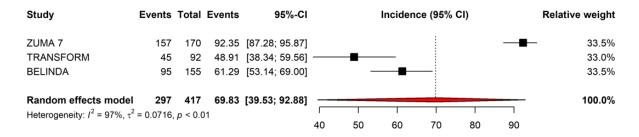
eFigure 10. Forest plot showing all adverse events in CAR-T cell therapy vs. SOC



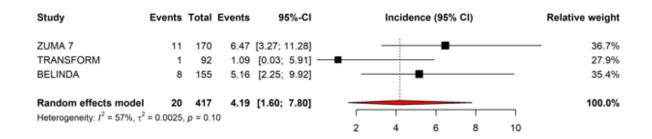
eFigure 11. Forest plot showing grade ≥ 3 adverse events in CAR-T cell therapy vs. SOC



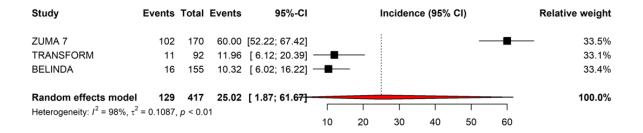
eFigure 12. Forest plot showing all grade cytokine release syndrome adverse events in patients receiving CAR-T cell therapy



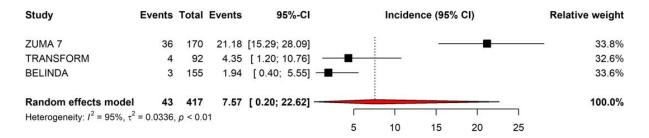
eFigure 13. Forest plot showing grade ≥ 3 cytokine release syndrome adverse events in patients receiving CAR-T cell therapy



eFigure 14. Forest plot showing all grade neurotoxicity syndrome adverse events in patients receiving CAR-T cell therapy

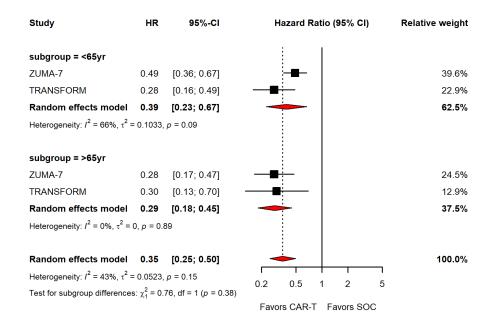


eFigure 15. Forest plot showing grade ≥ 3 neurotoxicity syndrome adverse events in patients receiving CAR-T cell therapy

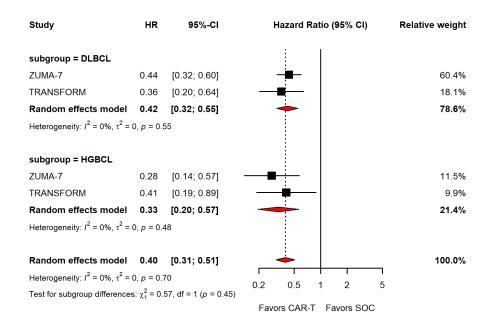


Abbreviations: CAR-T: chimeric antigenic receptor T-cell therapy

eFigure 16. Subgroup analysis by age for event-free survival outcome



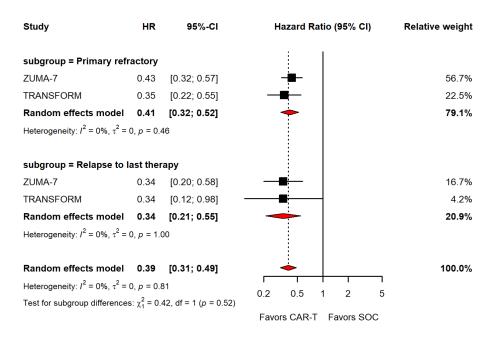
eFigure 17. Subgroup analysis by non-Hodgkin lymphoma (NHL) subtypes for event-free survival



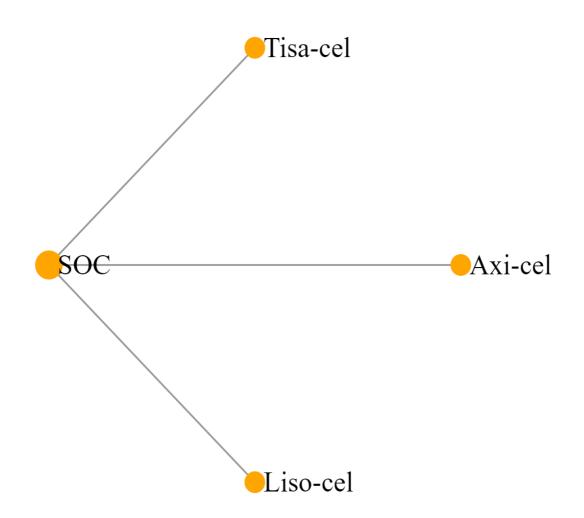
eFigure 18. Subgroup analysis by diffuse larger B-cell lymphoma molecular subtypes for event-free survival

Study	HR	95%-CI	Hazard Ratio (95% CI)	Relative weight
subgroup = GCB				
ZUMA-7	0.41	[0.29; 0.57]	- # -	65.0%
TRANSFORM	0.35	[0.19; 0.63]	— — —	21.2%
Random effects model	0.39	[0.29; 0.53]	→	86.2%
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0, p = 0.6	65		
subgroup = ABC				
ZUMA-7	0.18	[0.05; 0.68]	_	4.2%
TRANSFORM	0.48	[0.20; 1.16]	——————————————————————————————————————	9.6%
Random effects model	0.34	[0.13; 0.85]		13.8%
Heterogeneity: $I^2 = 31\%$, $\tau^2 =$	= 0.1490,	<i>p</i> = 0.23		
Random effects model	0.39	[0.30; 0.51]	•	100.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0, p = 0.6	63		х.
Test for subgroup differences	s: $\chi_1^2 = 0$.	10, df = 1 (p = 0.75)	0.1 0.5 1 2 10)
			Favors CAR-T Favors SOC	

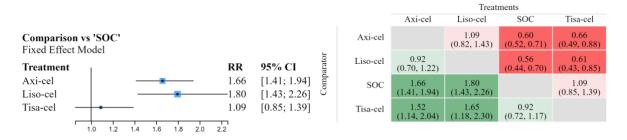
eFigure 19. Subgroup analysis by the response to prior therapy for event-free survival

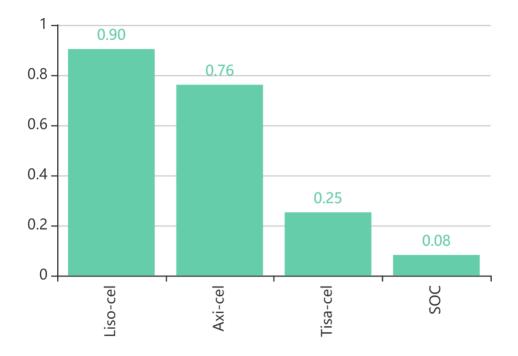




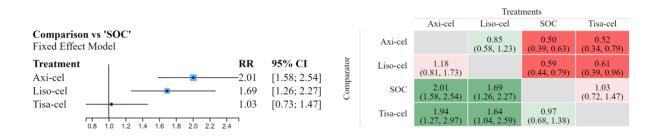


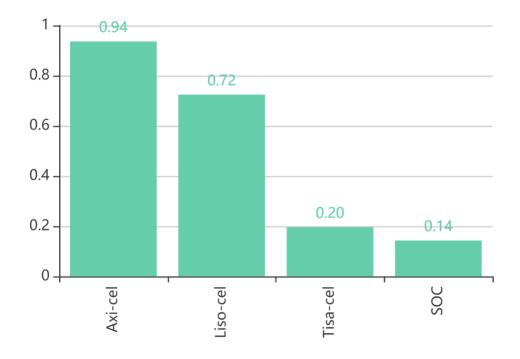
eFigure 21. Forest plot, league table, and p-score rankogram for mixed treatment comparisons for objective response rate.





eFigure22. Forest plot, league table, and p-score rankogram for mixed treatment comparisons for complete response





eFigure23. Forest plot, league table, and p-score rankogram for mixed treatment comparisons for grade \geq 3 adverse events

