Supplement

Literature search for analysis of real-world studies

For additional search for analysis of the incidence of ICANS in real-world clinical settings, 1390 articles were screened. Of the 1390 articles, 964 were excluded by an automation tool and by a review of the article titles. The complete texts of the remaining 426 articles were retrieved and 414 studies were further excluded after reviewing the full texts (320 articles were not studies of real-world clinical settings, 19 were not about CAR T-cell therapy, 14 did not discuss ICANS, 17 presented secondary analyses, 27 were summaries of other studies, 17 enrolled fewer than 100 patients). 12 studies were included in the analysis for real-world studies. These studies comprised a total of 3403 patients treated with CAR T-cell therapies for hematologic malignancy in real-world clinical setting.

Supplementary Table 1. PRISMA 2020 checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
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.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
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.	
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.	
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.	
	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.	
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.	
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.	
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)).	

Section and Topic	Item #	Checklist item	Location where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	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.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
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.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
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.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	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.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
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.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
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.	

Supplementary Table 2. Search terms for the meta-analysis in PUBMED.

No.	Search Query	Results
#1	"Receptors, Chimeric Antigen"[Mesh]	3,639
#2	"Chimeric antigen receptor*"[TW] OR CAR[TW]	36,317
#3	#1 OR #2	36,485
#4	"Receptors, Antigen, T-Cell"[Mesh]	45,043
#5	T-Cell*[TW]	441,924
#6	#4 OR #5	443,738
#7	"Immunotherapy, Adoptive"[Mesh]	12,960
#8	Immunotherap*[TW] OR Therap*[TW] OR treatment*[TW]	9,801,448
#9	#7 OR #8	9,801,448
#10	#3 AND #6 AND #9	9,957
#11	"CAR T-cell*"[TW] AND (therap*[TW] OR treatment*[TW])	6,413
#12	("CAR therap*"[TW] OR "CAR treatment*"[TW]) AND "T-cell*"[TW]	176
#13	"axicabtagene ciloleucel" [Supplementary Concept] OR axicabtagene[TW]	375
#14	"brexucabtagene autoleucel" [Supplementary Concept] OR "brexucabtagene autoleucel"[TW]	53
#15	"idecabtagene vicleucel" [Supplementary Concept] OR "idecabtagene vicleucel"[TW]	59
#16	"tisagenlecleucel" [Supplementary Concept] OR "tisagenlecleucel" [TW]	457
#17	"Lisocabtagene maraleucel"[TW]	71
#18	"ciltacabtagene autoleucel"[TW]	38
#19	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	10,064
#20	"Neurotoxicity Syndromes"[Mesh] OR "Nervous System Diseases"[Mesh:Noexp]	78,471
#21	Neurotoxic*[TW] OR Neurotoxin*[TW] OR ICANS[TW]	87,093

#22	(neurol*[TW] OR "Nervous System*"[TW] OR Encephalopat*[TW]) AND (Toxic*[TW] OR event*[TW] OR complicat*[TW] OR disease*[TW] OR Disorder*[TW] OR Poisoning*[TW])	648,184
#23	#20 OR #21 OR #22	733,744
#24	#19 AND #23	1,001
#25	#24 AND ("Clinical Trial"[ptyp] OR trial*[TW] OR "clinical trial*"[TW] OR random*[TW] OR RCT[TW] OR RCTs[TW] OR Placebo*[TW] OR Blind*[TW] OR "Controlled Clinical"[TW])	477
#26	#25 NOT (animals[Mesh:noexp] NOT (animals[Mesh:noexp] AND humans[Mesh]))	477
#27	#26 AND English[lang] AND ("1950/01/01"[PDAT] : "2022/05/28"[PDAT])	385
#28	#27 NOT ("Review"[ptyp] OR "Systematic Review"[ptyp] OR "Meta-Analysis"[ptyp] OR Review*[TI] OR Meta-Analys*[TI] OR "Systematic Literature*"[TI] OR Autobiography[ptyp] OR Bibliography[ptyp] OR Biography[ptyp] OR pubmed books[filter] OR Comment[ptyp] OR Dataset[ptyp] OR Dictionary[ptyp] OR Editorial[ptyp] OR Electronic Supplementary Materials[ptyp] OR Interview[ptyp] OR Legislation[ptyp] OR News[ptyp] OR Newspaper Article[ptyp] OR Retracted Publication[sb] OR Retraction of Publication[sb] OR Technical Report[ptyp] OR Letter[ptyp])	222

Supplementary Table 3. Search terms for the meta-analysis in EMBASE.

No.	Search Query	Results
#1	'chimeric antigen receptor T-cell immunotherapy'/exp	7,510
#2	'chimeric antigen receptor'/exp AND 'lymphocyte antigen receptor'/exp AND 'adoptive immunotherapy'/exp	95
#3	(('Chimeric antigen receptor*' OR CAR) NEAR/6 'T-Cell*' NEAR/6 (Immunotherap* OR Therap* OR treatment*)):ab,ti,kw	12,115
#4	('CAR-T' NEAR/6 'Cell*' NEAR/6 (Immunotherap* OR Therap* OR treatment*)):ab,ti,kw	10,518
#5	'axicabtagene ciloleucel'/exp OR axicabtagene:ab,ti,kw	1,891
#6	'brexucabtagene autoleucel'/exp OR 'brexucabtagene autoleucel':ab,ti,kw	312
#7	'idecabtagene vicleucel'/exp OR 'idecabtagene vicleucel':ab,ti,kw	360
#8	'tisagenlecleucel T'/exp OR 'tisagenlecleucel':ab,ti,kw	2,301
#9	'lisocabtagene maraleucel'/exp OR 'Lisocabtagene maraleucel':ab,ti,kw	464
#10	'ciltacabtagene autoleucel'/exp OR 'ciltacabtagene autoleucel':ab,ti,kw	231
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	15,962
#12	'neurotoxicity'/exp OR 'toxicity and intoxication'/exp	1,108,907
#13	(Neurotoxic* OR Neurotoxin* OR ICANS):ab,ti,kw	103,087
#14	((neurol* OR 'Nervous System*' OR Encephalopat*) NEAR/6 (Toxic* OR event* OR complicat* OR disease* OR Disorder* OR Poisoning*)):ab,ti,kw	240,624
#15	#12 OR #13 OR #14	1,372,807
#16	#11 AND #15	3,798
#17	#16 AND ('clinical trial'/exp OR [randomized controlled trial]/lim OR 'controlled clinical trial'/de OR trial* OR 'clinical trial*' OR random* OR RCT OR RCTs OR Placebo* OR Blind* OR 'Controlled Clinical')	2,206
#18	#17 NOT ('animal'/de NOT ('animal'/de AND 'human'/exp))	2,206
#19	#18 AND [english]/lim AND [01-01-1966]/sd NOT [29-05-2022]/sd	1,806
#20	#19 AND ([article]/lim OR [article in press]/lim)	290

Supplementary Table 4. Search terms for the meta-analysis in Web of Science.

No.	Search Query	Results
#1	TS=(("Chimeric antigen receptor*" OR CAR) NEAR/6 "T-Cell*" NEAR/6 (Immunotherap* OR Therap* OR treatment*))	7,176
#2	TS=("CAR-T" NEAR/6 "Cell*" NEAR/6 (Immunotherap* OR Therap* OR treatment*))	5,651
#3	TS=(axicabtagene OR "brexucabtagene autoleucel" OR "idecabtagene vicleucel" OR "tisagenlecleucel" OR "Lisocabtagene maraleucel" OR "ciltacabtagene autoleucel")	1,164
#4	#1 OR #2 OR #3	7,847
#5	TS=(Neurotoxic* OR Neurotoxin* OR ICANS)	97,415
#6	TS=((neurol* OR "Nervous System*" OR Encephalopat*) NEAR/6 (Toxic* OR event* OR complicat* OR disease* OR Disorder* OR Poisoning*))	147,735
#7	#5 OR #6	239,331
#8	#4 AND #7	776
#9	#8 AND TS=(trial* OR "clinical trial*" OR random* OR RCT OR RCTs OR Placebo* OR Blind* OR "Controlled Clinical")	311
#10	#9 Editions: WOS.SCI Timespan: 1983-01-01 to 2022-05-28	264
#11	#10 AND Article (Document Types) and English (Languages)	143

Supplementary Table 5. Risk of bias assessment of the included studies.

	Risk of Bias					
	Randomization	allocation concealment	blinding of participants and personnel	blinding of outcome assessment	incomplete outcome data	selective outcome data
Abramson JS et al 2020 (1)	High	High	High	Low	Low	Unclear
An F et al 2020 (2)	High	High	High	Low	Low	Unclear
Baumeister SH et al 2019 (3)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Benjamin R et al 2020 (4)	High	High	High	Low	Low	Unclear
Berdeja JG et al 2021 (5)	High	High	High	Low	Low	Unclear
Brudno JN et al 2018 (6)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Brudno JN et al 2020 (7)	High	High	High	Low	Low	Low
Caimi PF et al 2021 (8)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Cao J et al 2018 (9)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Cohen AD et al 2019 (10)	Unclear	High	High	Low	Low	Unclear
Cordoba S et al 2021 (11)	High	High	High	Low	Low	Unclear
Cornell RF et al 2021 (12)	Unclear	High	High	Low	Low	Unclear
Curran KJ et al 2019 (13)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Fan L et al 2022 (14)	Unclear	High	High	Low	Low	Unclear
Fowler NH et al 2022 (15)	High	High	High	Low	Low	Low
Frey NV et al 2020 (16)	High	Unclear	Unclear	Unclear	Low	Unclear
Gardner RA et al 2017 (17)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Geyer MB et al 2019 (18)	High	High	High	Low	High	Unclear
Heng G et al 2020 (19)	High	High	High	Low	Low	Unclear
Jacobson CA et al 2022 (20)	High	High	High	Low	Low	Low
Jacoby E et al 2018 (21)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Kato K et al 2022 (22)	High	High	High	Low	Low	Unclear
Kochenderfer JN et al 2017 (23)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Lamure S et al 2021 (24)	Unclear	Unclear	Unclear	Unclear	Low	Unclear

Li C et al 2021 (25)	High	Unclear	Unclear	Unclear	Low	Unclear
Liu H et al 2021 (26)	High	High	High	Low	Low	Unclear
Liu Y et al 2022 (27)	High	Unclear	Unclear	Unclear	Low	Unclear
Locke FL et al 2022 (28)	Low	Low	Low	Low	Low	Low
Ma F et al 2019 (29)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Magnani CF et al 2020 (30)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Makita S et al 2022 (31)	High	High	High	Low	Low	Unclear
Maude SL et al 2018 (32)	High	High	High	Low	Low	Low
Mei H et al 2021 (33)	High	High	High	Low	Low	Unclear
Munshi NC et al 2021 (34)	High	High	High	Low	Low	Low
Myer RM et al 2021 (35)	High	Unclear	Unclear	Unclear	Low	Unclear
Neelapu SS et al 2017 (36)	High	High	High	Low	Low	Low
Neelapu SS et al 2022 (37)	High	High	High	Low	Low	Low
Ortíz-Maldonado V et al 2021 (25)	High	High	High	Low	High	Unclear
Pan J et al 2019 (38)	High	Unclear	Unclear	Unclear	Low	Unclear
Pan J et al 2021 (39)	High	Unclear	Unclear	Unclear	Low	Unclear
Park JH et al 2018 (40)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Raje N et al 2019 (41)	High	High	High	Low	Low	Low
Ramos CA et al 2018 (42)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Ramos CA et al 2020 (43)	High	Unclear	Unclear	Unclear	Low	Low
Roddie C et al 2021 (44)	High	High	High	Low	Low	Low
Sang W et al 2020 (45)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Sauter CS et al 2019 (46)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Schuster SJ et al 2019 (47)	High	High	High	Low	Low	Low
Shah BD et al 2021 (48)	High	High	High	Low	Low	Unclear
Shah BD et al 2021 (49)	High	High	High	Low	Low	Low
Shah NN et al 2020 (50)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Shah NN et al 2020 (51)	High	High	High	Low	Low	Unclear
Shalabi H et al 2022 (52)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Shi X et al 2022 (53)	High	High	High	Low	Low	Unclear
Siddiqi T et al 2022 (54)	Unclear	High	High	Low	Low	Unclear

Singh H et al 2022 (55)	High	High	High	Low	Low	Unclear
Spiegel JY et al 2021 (56)	High	High	High	Low	Low	Low
Talleur A et al 2022 (57)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Tong C et al 2020 (58)	High	High	High	Low	Low	Unclear
Turtle CJ et al 2016 (59)	Unclear	High	High	Low	Low	Unclear
Wang D et al 2021 (60)	High	High	High	Low	Low	Unclear
Wang J et al 2022 (61)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Wang M et al 2020 (62)	High	High	High	Low	Low	Low
Wang Y et al 2022 (63)	High	High	High	Low	Low	Unclear
Wei G et al 2021 (64)	Unclear	High	High	Low	Low	Unclear
Wu J et al 2021 (65)	High	High	High	Low	Low	Unclear
Yan ZX et al 2019 (66)	High	High	High	Low	Low	Unclear
Ying Z et al 2019 (67)	High	High	High	Low	Low	Unclear
Ying Z et al 2021 (68)	Unclear	High	High	Low	Low	Unclear
Ying Z et al 2022 (69)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Zhang H et al 2022 (70)	High	High	High	Low	Low	Unclear
Zhang X et al 2020 (71)	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Zhang Y et al 2021 (72)	High	Unclear	Unclear	Unclear	Low	Unclear
Zhao WH et al 2018 (73)	High	High	High	Low	Low	Unclear
Zhou X et al 2020 (74)	High	High	High	Low	Low	Unclear

Supplementary Table 6. Characteristics of all eligible trial cohorts

Study	Agents	N	ICANS			ICANS grading method	Dose of CAR T cells agents	Ratio of CD4: CD8
			All grade	High grade	Grade 5			
Abramson JS et al 2020 (1)	anti-CD19	269	80	27	0	CTCAE	50 – 150×10^6/kg	1:1
An F et al 2020 (2)	anti-CD19	47	3	1	0	CTCAE	1 – 5×10^6/kg	NA
Baumeister SH et al 2019 (3)	NKG2D-CAR	12	0	0	0	CTCAE	1– 30×10^6/kg	Median 2.05
Benjamin R et al 2020 (4)	anti-CD19	21	8	0	0	CTCAE	1·1 – 2·3×10^6/kg (child) 6 – 180×10^6/kg (adult)	2.1 and 1.9
Berdeja JG et al 2021 (5)	anti-BCMA	97	20	9	1	CTCAE (phase 1b) ASTCT (phase 2)	0.5 – 1×10^6/kg	NA
Brudno JN et al 2018 (6)	anti-BCMA	16	1	1	0	CTCAE	0.3 – 3×10^6/kg	NA
Brudno JN et al 2020 (7)	anti-CD19	20	4	1	0	CTCAE	0.66 – 6×10^6/kg	NA
Caimi PF et al 2021 (8)	anti-CD19	20	5	1	0	CTCAE	0.5 – 2×10^6/kg	Median 66:34
Cao J et al 2018 (9)	anti-CD19	18	1	0	0	NA	1×10^6/kg	NA
Cohen AD et al 2019 (10)	anti-BCMA	25	8	3	0	CTCAE	0.1 – 5×10^8	Median 1.7
Cordoba S et al 2021 (11)	anti-CD19 & anti-CD22	15	4	0	0	ASBMT	1 – 3×10^6/kg	1:1
Cornell RF et al 2021 (12)	anti-BCMA	14	3	0	0	NA	3×10^7 – 1×10^9	NA
Curran KJ et al 2019 (13)	anti-CD19	25	18	7	NA	CTCAE	1 – 3×10^6/kg	NA
Fan L et al 2022 (14)	anti-CD19	10	0	0	0	CTCAE	0.8 – 5×10^6/kg	NA
Fowler NH et al 2022 (15)	anti-CD19	97	36	3	0	CTCAE	0.6 – 6×10^8/kg	NA
Frey NV et al 2020 (16)	anti-CD19	38	13	6	0	ASTCT	0.5 – 5×10^8/kg	NA
Gardner RA et al 2017 (17)	anti-CD19	45	21	9	0	NA	0.5 – 10×10^6/kg	NA
Geyer MB et al 2019 (18)	anti-CD19	20	9	2	0	CTCAE	1 – 3×10^7/kg	Median 1.9:1
Heng G et al 2020 (19)	anti-CD19	10	4	0	NA	CTCAE	0.23 – 41.67×10^6/kg	Median 0.70

Jacobson CA et al 2022 (20)	anti-CD19	148	87	28	0	CTCAE	2×10^6/kg	NA
Jacoby E et al 2018 (21)	anti-CD19	20	11	0	0	CTCAE	1×10^6/kg	32.9:61.3
Kato K et al 2022 (22)	anti-CD19	16	0	0	0	CTCAE	2×10^6/kg	NA
Kochenderfer JN et al 2017 (23)	anti-CD19	22	22	12	0	NA	$1 – 6\times10^6$/kg	NA
Lamure S et al 2021 (24)	anti-CD19	60	23	7	0	ASTCT	NA	NA
Li C et al 2021 (25)	anti-BCMA	30	1	0	0	ASTCT	Median 11.2×10^6/kg	NA
Liu H et al 2020 (26)	anti-CD19	17	17	0	0	ASTCT	$0.5 – 4\times10^6$/kg	NA
Liu Y et al 2022 (27)	anti-CD19 & anti-CD22	23	8	5	0	ASTCT	$0.1 – 5\times10^6$/kg	NA
Locke FL et al 2022 (75)	anti-CD19	170	102	36	0	CTCAE	2×10^6/kg	NA
Ma F et al 2019 (29)	anti-CD19	10	6	6	0	CTCAE	$0.3 – 1.58\times10^6$/kg	0.7
Magnani CF et al 2020 (30)	anti-CD19	13	0	0	0	CTCAE	$0.53 – 2.2\times10^6$/kg	NA
Makita S et al 2022 (31)	anti-CD19	10	1	0	0	CTCAE	100×10^6/kg (total)	1:1
Maude SL et al 2018 (32)	anti-CD19	75	30	10	0	CTCAE	$0.2 – 250\times10^6$/kg	1.7
Mei H et al 2021 (33)	anti-BCMA & anti-CD38	23	0	0	0	CTCAE	$0.5 – 1\times10^6$/kg	39.5: 58.5
Munshi NC et al 2021 (34)	anti-BCMA	128	23	4	0	CTCAE	$150 – 450\times10^6$/kg	NA
Myers RM et al 2021 (35)	anti-CD19	74	29	3	0	CTCAE	$0.3 – 30\times10^6$/kg	NA
Neelapu SS et al 2017 (36)	anti-CD19	101	65	28	0	CTCAE	2×10^6/kg	NA
Neelapu SS et al 2022 (37)	anti-CD19	40	29	9	0	CTCAE	2×10^6/kg	1:1
Ortiz-Maldonado V et al 2021 (25)	anti-CD19	47	0	1	NA	CTCAE	$0.4 – 5\times10^6$/kg	100:85
Pan J et al 2019 (38)	anti-CD22	34	6	0	0	CTCAE	Median 7.5×10^6/kg	NA
Pan J et al 2021 (39)	anti-CD7	20	3	0	0	ASTCT	1×10^6/kg	33:61
Park JH et al 2018 (40)	anti-CD19	53	23	22	0	CTCAE	$1 – 3\times10^6$/kg	NA
Raje N et al 2019 (41)	anti-BCMA	33	14	1	0	CTCAE	$50 – 800\times10^6$/kg	Median 85:13
Ramos CA 2018 (42)	anti-CD19	16	1	1	0	CTCAE	$1 – 20\times10^6$/kg	NA
Ramos CA et al 2020 (43)	anti-CD30	42	0	0	0	CTCAE	$2 – 20\times10^7$/kg	NA

Roddie C et al 2021 (44)	anti-CD19	20	4	3	0	ASTCT	10 – 100×10^6/kg	Mean 3.56
Sang W et al 2020 (45)	anti-CD19 & anti-CD20	21	5	2	0	CTCAE	Median 0.71×10^6/kg	AVG 0.83
Sauter CS et al 2019 (46)	anti-CD19	15	10	9	0	CTCAE	0.8 – 5×10^6/kg	NA
Schuster SJ et al 2019 (47)	anti-CD19	111	23	13	0	CTCAE	2.5 – 25×10^5/kg	3.1
Shah BD et al 2021 (48)	anti-CD19	45	35	17	0	CTCAE	Median 0.5×10^6/kg	NA
Shah BD et al 2021(49)	anti-CD19	55	33	14	1	CTCAE	2×10^6/kg	NA
Shah NN et al 2020 (50)	anti-CD22	58	19	1	0	CTCAE	0.4 – 5×10^6/kg	NA
Shah NN et al 2020 (51)	anti-CD19 & anti-CD20	22	7	3	0	CTCAE	0.1 – 1×10^6/kg	NA
Shalabi H et al 2022 (52)	anti-CD19 & anti-CD28	52	11	4	0	CTCAE	Median 8.258×10^8/kg	NA
Shi X et al 2022 (53)	anti-CD19 & anti-BCMA	10	0	0	0	CTCAE	Median 1×10^6/kg (anti-CD19) Median 1×10^6/kg (anti-CD20)	NA
Siddiqi T et al 2022 (54)	anti-CD19	23	9	5	0	CTCAE	3 – 100×10^7/kg	NA
Singh H et al 2022 (55)	anti-CD19	14	0	0	0	CTCAE	0.1 – 1000×10^6/kg	NA
Spiegel JY et al 2021 (56)	anti-CD19 & anti-CD22	38	14	4	0	ASTCT	1 – 10 ×10^6/kg	NA
Talleur A et al 2022 (57)	anti-CD19	12	3	1	0	CTCAE & ASTCT	5 – 10×10^7/kg	1
Tong C et al 2020 (58)	anti-CD19 & anti-CD 20	61	6	0	0	CTCAE	0.5 – 6×10^6/kg	NA
Turtle CJ et al 2016 (59)	anti-CD19	30	15	15	1	CTCAE	2.5 – 10×10^7/kg	NA
Wang D et al 2021 (60)	anti-BCMA	18	0	0	0	CTCAE	1.5 – 4.5×10^8/kg	NA
Wang J et al 2022 (61)	anti-CD19	18	2	2	0	ASTCT	0.5 – 5 ×10^6/kg	NA
Wang M et al 2020 (62)	anti-CD19	68	43	21	0	CTCAE	1 – 15×10^6/kg	NA
Wang Y et al 2022 (63)	anti-CD19 & anti-BCMA	62	7	2	0	CTCAE	1×10^6/kg	NA
Wei G et al 2021 (64)	anti-CD19 & anti-CD22	16	0	0	0	CTCAE	2×10^6/kg	NA

Wu J et al 2021 (65)	anti-CD19 & anti-CD22	13	3	1	0	ASTCT	0.5 – 2×10^6/kg Unknown (2)	1.94
Yan ZX et al 2019 (66)	anti-CD19	10	1	1	0	CTCAE	1 – 3×10^7/kg	NA
Ying Z et al 2019 (67)	anti-CD19	25	0	0	0	CTCAE	1×10^8/kg	1
Ying Z et al 2021 (68)	anti-CD19	59	12	3	0	CTCAE	0.75×10^6/kg	NA
Ying Z et al 2022 (69)	anti-CD19	22	1	1	0	ASTCT	0.5 – 3×10^6/kg	NA
Zhang H et al 2022 (70)	anti-BCMA & anti-CD38	22	3	0	0	ASTCT	Median 2.06×10^8/kg	NA
Zhang X et al 2020 (71)	anti-CD19	110	23	15	0	ASTCT	1–3×10^6/kg	NA
Zhang Y et al 2021 (72)	anti-CD19 & anti-CD22	32	5	4	0	ASBMT	2×10^6/kg	NA
Zhao WH et al 2018 (73)	anti-BCMA	57	1	0	0	CTCAE	1–1.5×10^8/kg	NA
Zhou X et al 2020 (74)	anti-CD19	21	1	1	0	MDACC scale	NA	NA

Note. NA, not available; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; ICANS, immune effector cell-associated neurotoxicity syndrome; CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events v4.03; ASTCT, American Society for Transplantation and Cellular Therapy scales; MDACC, MD Anderson Cancer Center Scale

Supplementary Table 7. Characteristics of all-grade ICANS in all eligible trial cohorts and real-world studies

Study	ICANS onset, median (range or IQR), days	ICANS duration, median (range or IQR), days	Treatment outcomes
Abramson JS et al 2020 (1)	9 (range, 1 – 66)	11 (range, 1 – 86)	NA
An F et al 2020 (2)	NA	NA	NA
Baumeister SH et al 2019 (3)	NA	NA	NA
Benjamin R et al 2020 (4)	9 (IQR, 5 – 14)	3 (IQR, 2 – 4)	All resolved without treatment
Berdeja JG et al 2021 (5)	8 (IQR, 6 – 8)	4 (IQR, 3 – 6.5)	All resolved with steroid, tocilizumab, or anakinra
Brudno JN et al 2018 (6)	NA	NA	NA
Brudno JN et al 2020 (7)	NA	1	All resolved with steroid
Caimi PF et al 2021 (8)	7 (range, 5 – 9)	NA	All resolved with steroid, or anakinra
Cao J et al 2018 (9)	14	5	All resolved with mannitol
Cohen AD et al 2019 (10)	NA	NA	All resolved with steroid + cyclophosphamide
Cordoba S et al 2021 (11)	5.5 (range, 3 – 9)	5 (range, 1 – 10)	75% (3/4) resolved
Cornell RF et al 2021 (12)	NA	NA	NA
Curran KJ et al 2019 (13)	NA	NA	83% (15/18) resolved with supportive treatment or steroid
Fan L et al 2022 (14)	NA	NA	NA
Fowler NH et al 2022 (15)	9 (IQR, 5 – 35)	2 (IQR, 1 – 4)	All resolved
Frey NV et al 2020 (16)	NA	NA	NA
Gardner RA et al 2017 (17)	NA	NA	All resolved
Geyer MB et al 2019 (18)	2 (range, 1 – 11)	1 (range, 1 – 61)	All resolved with steroid
Heng G et al 2020 (19)	NA	NA	All resolved with steroid, tocilizumab, or mannitol
Jacobson CA et al 2022 (20)	7 (IQR, 6 – 10) for FL 7 (IQR, 6 – 11) for MZL	14 (IQR, 5 – 43) for FL 10 (IQR, 5 – 28) for MZL	95% (83/87) resolved with steroid or tocilizumab
Jacoby E et al 2018 (21)	NA	2.5 (range, 0 – 11)	All resolved with steroid

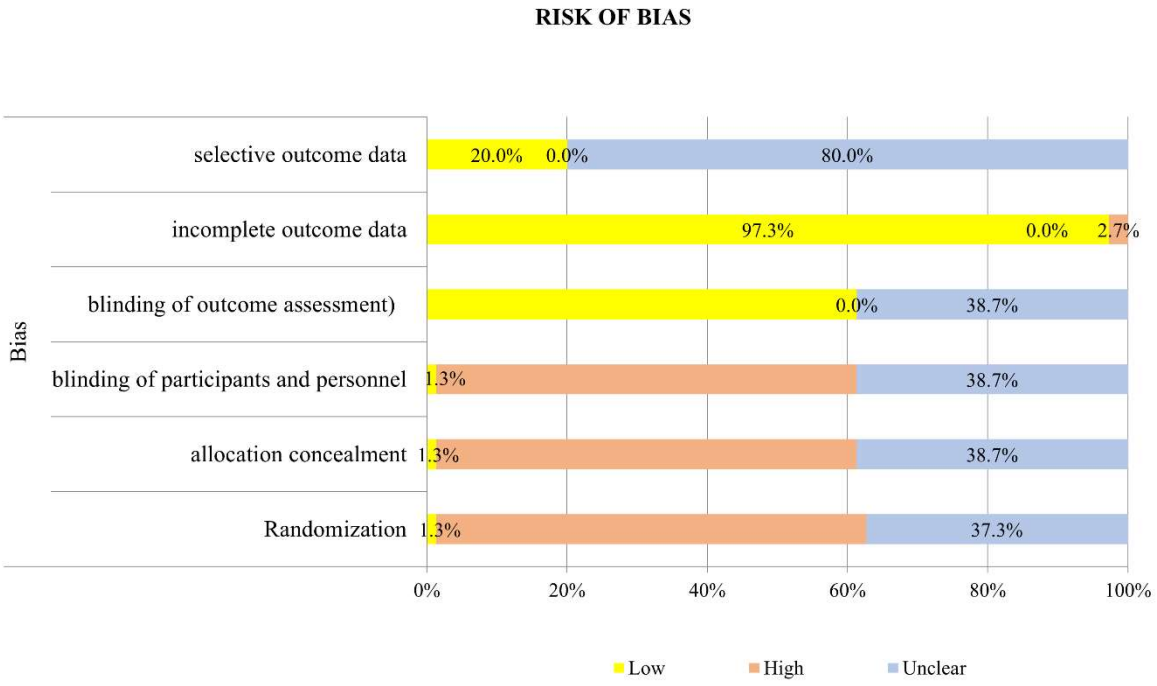
Kato K et al 2022 (22)	NA	NA	NA
Kochenderfer JN et al 2017 (23)	NA	NA	All resolved with steroid or tocilizumab
Lamure S et al 2021 (24)	NA	NA	NA
Li C et al 2021 (25)	3	2	All resolved with steroid or mannitol
Liu H et al 2020 (26)	NA	NA	NA
Liu Y et al 2022 (27)	6.4 (range, 5 – 10)	5.5 (range, 3 – 10)	All resolved with steroid
Locke FL et al 2022 (75)	7	9	99% (101/102) resolved
Ma F et al 2019 (29)	NA	NA	NA
Magnani CF et al 2020 (30)	NA	NA	NA
Makita S et al 2022 (31)	4	3	All resolved without treatment
Maude SL et al 2018 (32)	NA	NA	87% (26/30) resolved with supportive treatment
Mei H et al 2021 (33)	NA	NA	NA
Munshi NC et al 2021 (34)	2 (range, 1 – 10)	3 (range, 1 – 26)	NA
Myers RM et al 2021 (35)	NA	NA	All resolved
Neelapu SS et al 2017 (36)	5 (range, 1 – 17)	12	94% (61/65) resolved with tocilizumab or steroid
Neelapu SS et al 2022 (37)	9 (range, 2 – 44)	7	97% (28/29) resolved with tocilizumab or steroid
Ortiz-Maldonado V et al 2021 (25)	NA	NA	NA
Pan J et al 2019 (38)	8 (range, 1 – 17)	7	Treated with mannitol, furosemide, or steroid
Pan J et al 2021 (39)	1 (range, 1 – 4)	3 (range, 2 – 4)	NA
Park JH et al 2018 (40)	NA	NA	NA
Raje N et al 2019 (41)	5 (range, 3 – 11)	8 (range, 1 – 251)	Treated with steroid
Ramos CA 2018 (42)	NA	NA	All resolved with tocilizumab + steroid
Ramos CA et al 2020 (43)	NA	NA	NA
Roddie C et al 2021 (44)	22 (range, 14 – 41)	1.5 (range, 1 – 8)	All resolved with steroid
Sang W et al 2020 (45)	NA	5 (range, 3 – 8)	NA
Sauter CS et al 2019 (46)	5 (range, 1 – 6)	9.5 (range, 2 – 20)	All resolved with tocilizumab, steroid, or without treatment
Schuster SJ et al 2019 (47)	6 (range, 1 – 17)	14	Majority resolved with supportive treatment

Shah BD et al 2021 (48)	9 (IQR, 7 – 11)	7 (IQR, 4 – 19)	88% (29/33) resolved with tocilizumab, steroid, or vasopressor
Shah BD et al 2021(49)	6 (IQR, 3 – 8)	12 (IQR, 4 – 26)	89% (31/35) resolved with tocilizumab or steroid
Shah NN et al 2020 (50)	6 (range, 0 – 13)	NA	All resolved with tocilizumab or steroid
Shah NN et al 2020 (51)	NA	NA	95% (18/19) resolved
Shalabi H et al 2022 (52)	9 (range, 3 – 11)	5 (range, 1 – 15)	All resolved with tocilizumab or steroid
Shi X et al 2022 (53)	NA	NA	NA
Siddiqi T et al 2022 (54)	4 (range, 2 – 21)	20.5 (range, 6 – 50)	All resolved with tocilizumab or steroid
Singh H et al 2022 (55)	NA	NA	NA
Spiegel JY et al 2021 (56)	5 (range, 3 – 9)	4 (range, 1 – 11)	All resolved with tocilizumab or steroid
Talleur A et al 2022 (57)	6 (range, 5 – 7)	NA	All resolved with siltuximab
Tong C et al 2020 (58)	NA	NA	NA
Turtle CJ et al 2016 (59)	NA	NA	NA
Wang D et al 2021 (60)	NA	NA	NA
Wang J et al 2022 (61)	NA	NA	All resolved with steroid
Wang M et al 2020 (62)	7 (range, 1 – 32)	12	86% (37/43) resolved
Wang Y et al 2022 (63)	Within 3 months	NA	Treated with tocilizumab or steroid
Wei G et al 2021 (64)	NA	NA	NA
Wu J et al 2021 (65)	NA	NA	All resolved with antibiotics with or without steroid
Yan ZX et al 2019 (66)	NA	NA	100% (1/1) with ongoing symptoms
Ying Z et al 2019 (67)	NA	NA	NA
Ying Z et al 2021 (68)	8.5	12.5	All resolved with tocilizumab or steroid
Ying Z et al 2022 (69)	NA	NA	All resolved with tocilizumab or steroid
Zhang H et al 2022 (70)	NA	NA	All resolved with supportive treatment
Zhang X et al 2020 (71)	NA	NA	All resolved with tocilizumab with or without steroids
Zhang Y et al 2021 (72)	11.5 (range, 8 – 20)	NA	80% (4/5) resolved with steroid and supportive treatment
Zhao WH et al 2018 (73)	NA	NA	All resolved with diazepam
Zhou X et al 2020 (74)	33	NA	All resolved with steroid
Bastos-Oreiro M et al 2022 (76)	NA	NA	NA

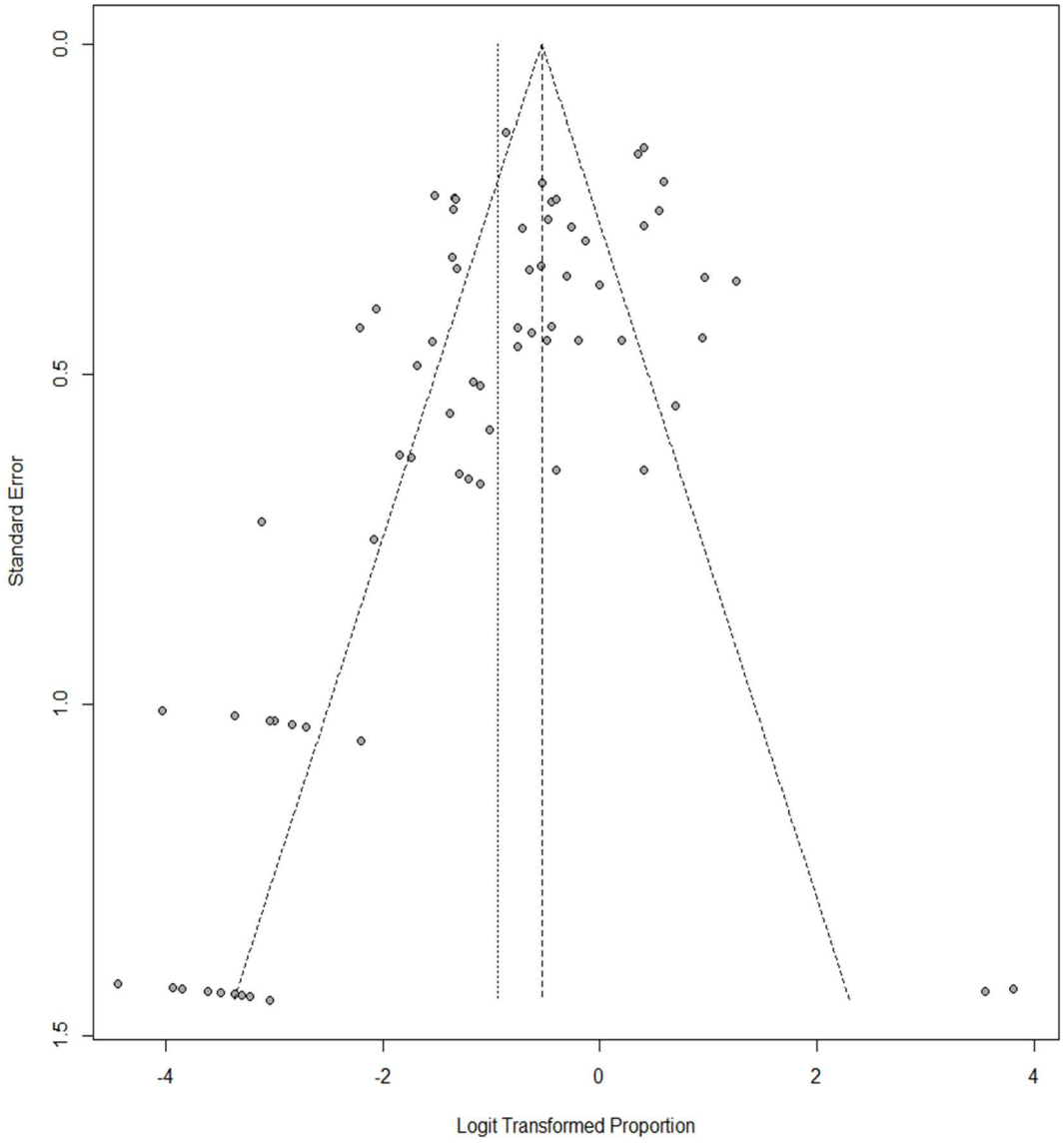
Bethge WA et al 2022 (77)	NA	NA	NA
Gauthier J et al 2022 (78)	NA	6 (IQR, 3 – 14; range, 1 – 101) for axi-cel 5 (IQR, 2 – 7; range, 1 – 27) for tisa-cel	Treated with tocilizumab or steroid
Ghilardi G et al 2022 (79)	NA	NA	Treated with tocilizumab or steroid
Kuhnl A et al 2022 (80)	NA	NA	Treated with tocilizumab or steroid
Kwon M et al 2022 (81)	7 (range, 2 – 65) for axi-cel 6 (range, 2 – 35) for tisa-cel	4 (range, 1 – 44) for axi-cel 7 (range, 1 – 83) for tisa-cel	Treated with tocilizumab, steroid, anakinra, or siltuximab
Nastoupil LJ et al 2020 (82)	NA	NA	99% (188/189) resolved with tocilizumab or steroid
Pasquini MC et al 2020 (83)	7 (range, 1 – 80) for ALL 8 (range, 2 – 33) for NHL	7 (range, 1 – 94) for ALL 6.5 (range, 1 – 50) for NHL	Treated with steroid
Riedell PA et al 2022 (84)	6 (IQR, 4 – 8) for axi-cel 4 (IQR, 3 – 7) for tisa-cel	7 (IQR, 4 – 11) for axi-cel 4 (IQR, 3 – 9) for tisa-cel	Treated with tocilizumab or steroid
Rubin DB et al 2020 (85)	6 (IQR, 5 – 8)	NA	Treated with tocilizumab
Strati P et al 2020 (86)	5 (range, 0 – 25)	6 (range, 0 – 52)	99% (67/68) resolved with antiseizure treatment, steroid, or tocilizumab
Zettler ME et al 2021 (87)	NA	NA	NA

Note. NA, not available; ICANS, immune effector cell-associated neurotoxicity syndrome; IQR, interquartile range; FL, follicular lymphoma; MZL, marginal zone lymphoma; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma

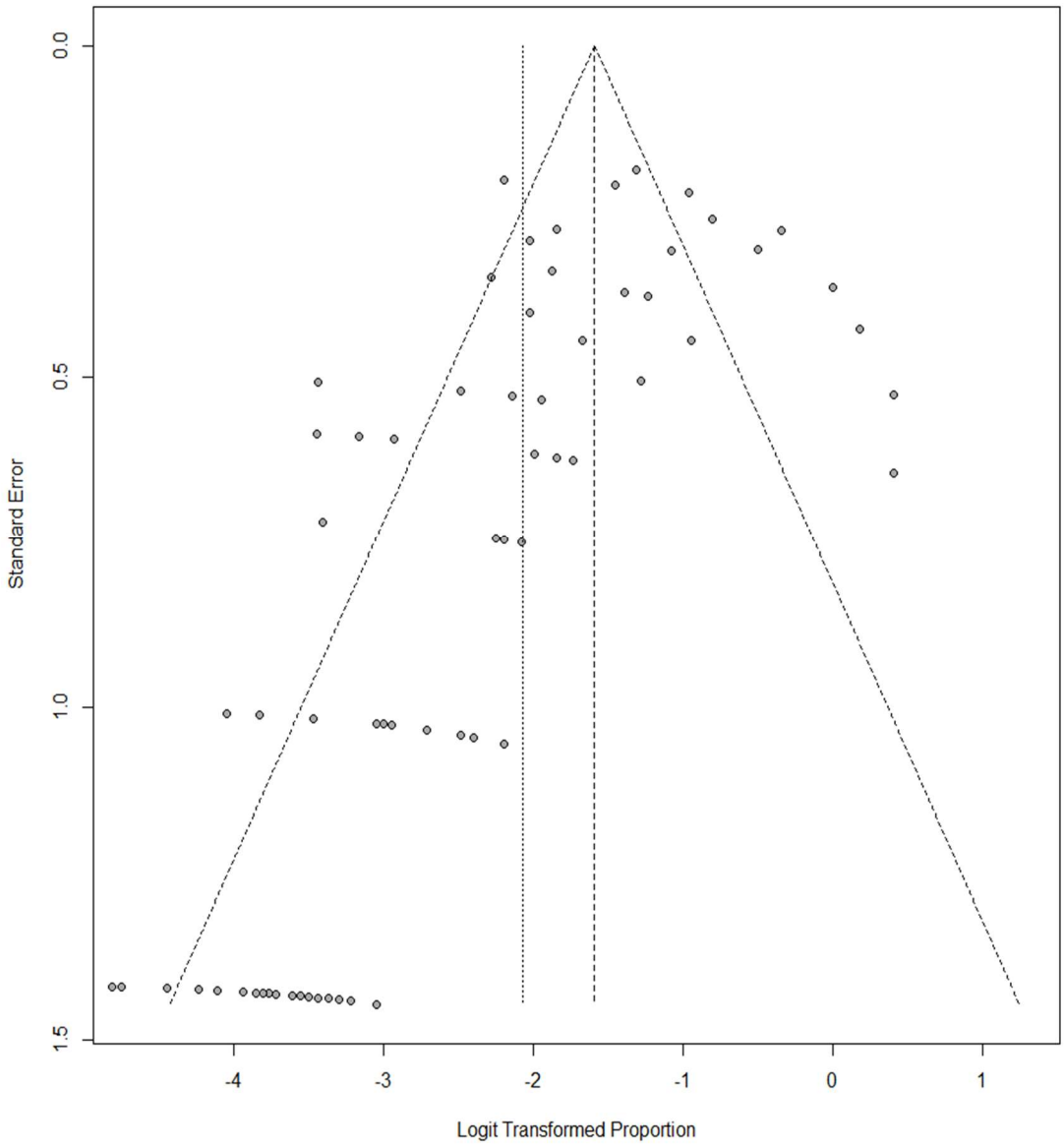
Supplementary Figure 1. Risk of bias assessment of the included studies.



Supplementary Figure 2. Funnel plot to assess publication bias for all-grade neurotoxicity

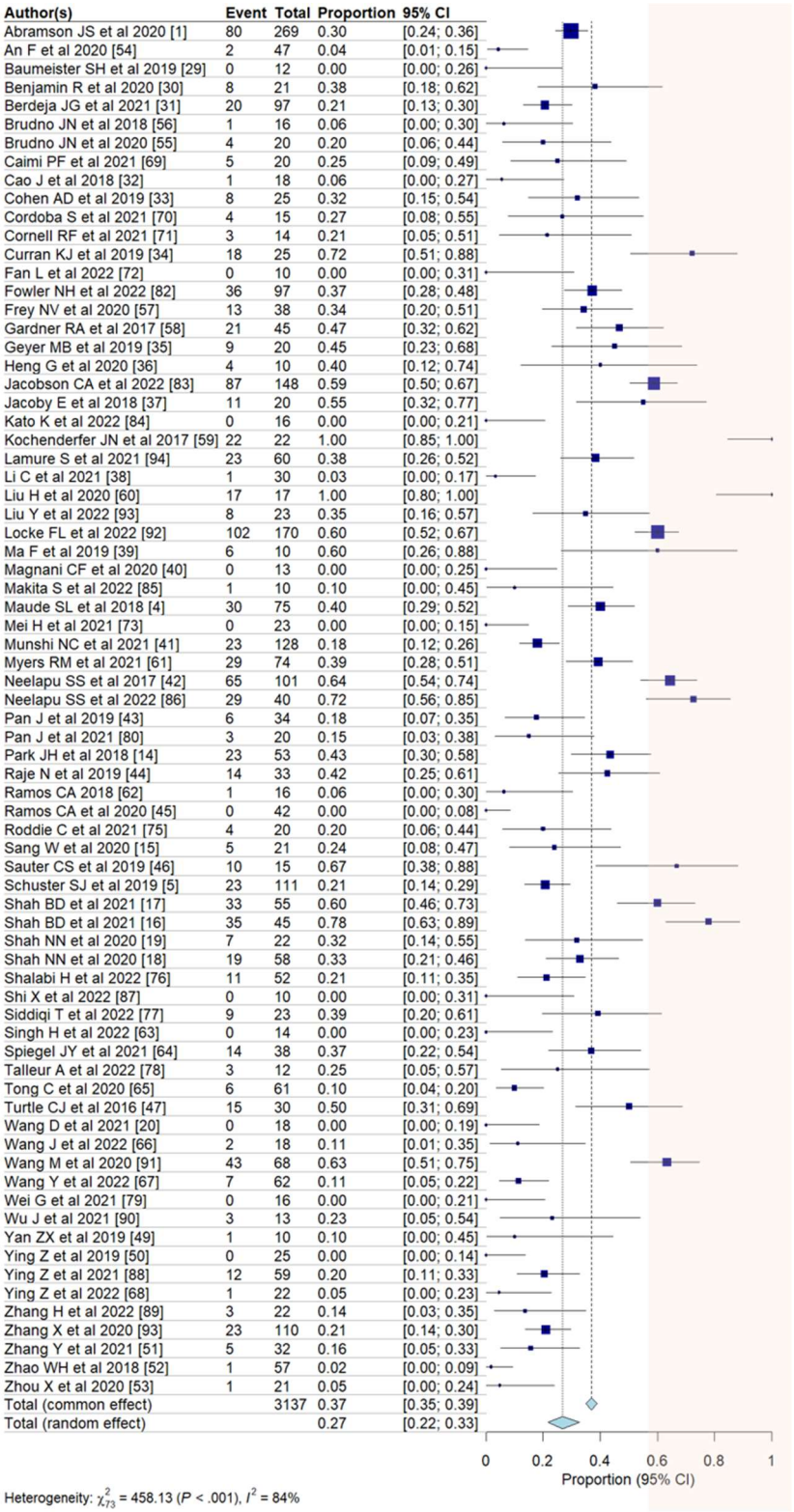


Supplementary Figure 3. Funnel plot to assess publication bias for high-grade neurotoxicity

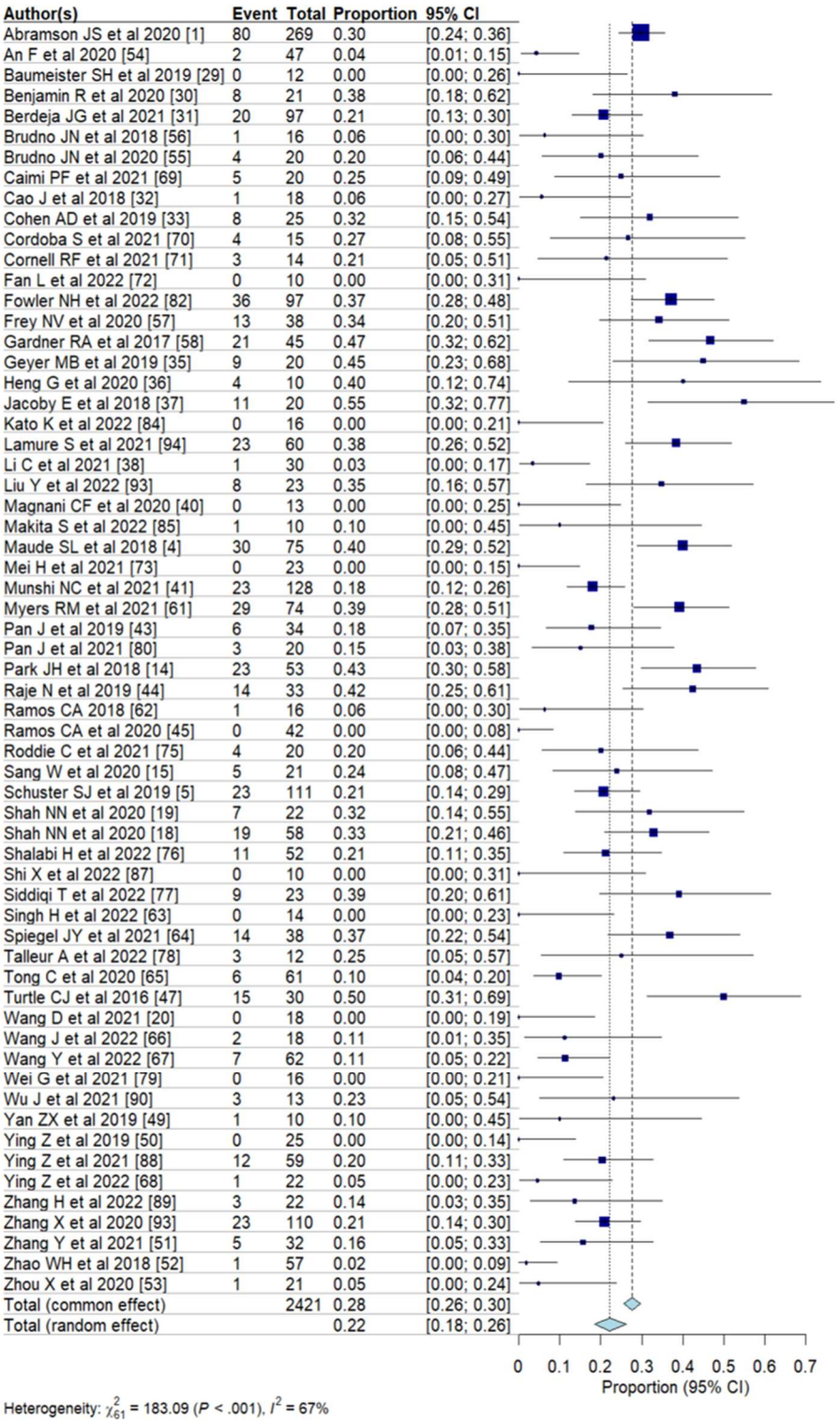


Supplementary Figure 4. Forest plots showing the pooled incidence of all-grade ICANS before (a) and after (b) removing outliers, high-grade ICANS before (c) and after (d) removing outliers. Studies in the boxes represent the identified outliers.

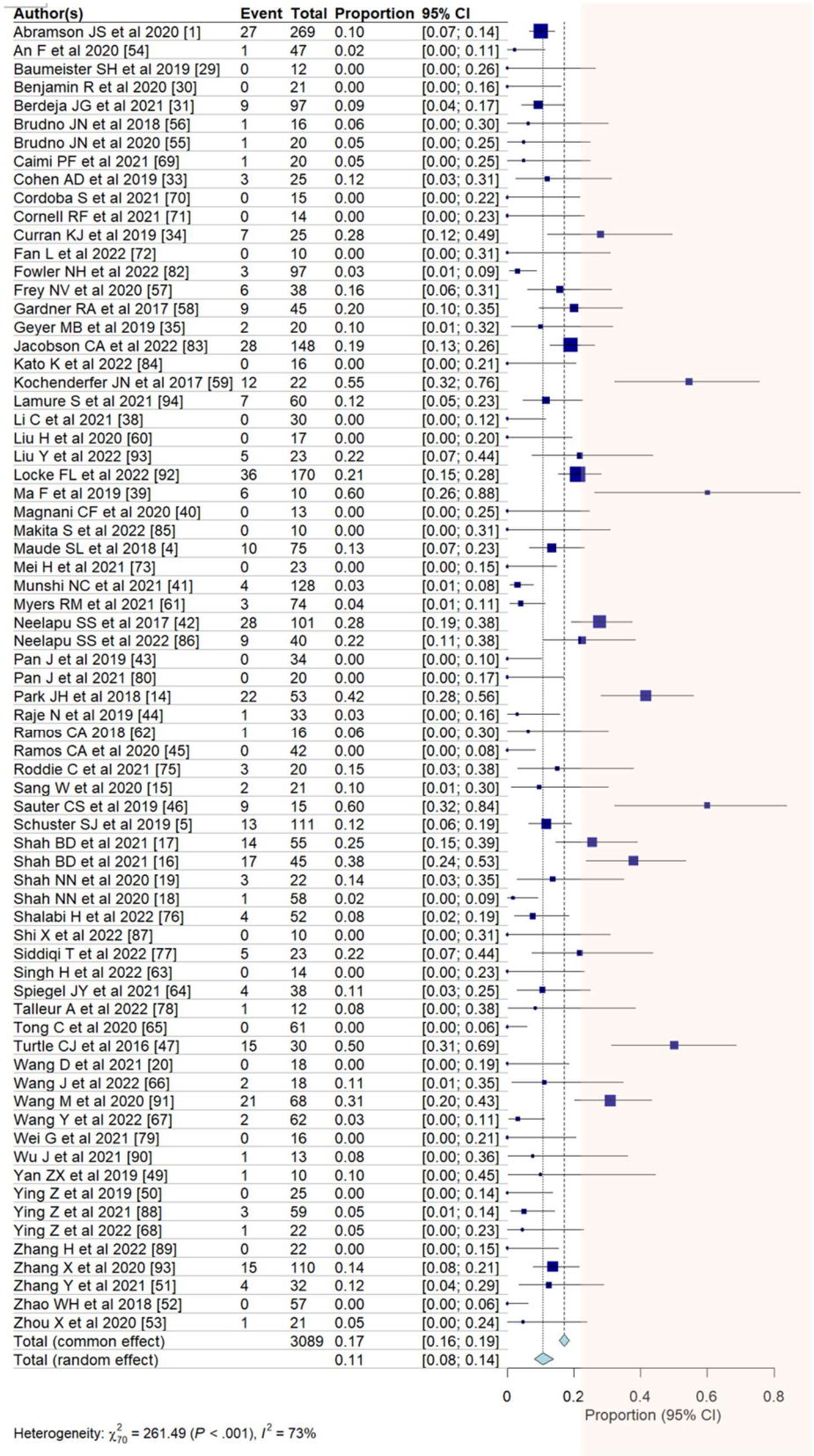
(a)



(b)


Author(s) Event Total Proportion 95% CI
Abramson JS et al 2020 [1] 80 269 0.30 [0.24; 0.36]
An F et al 2020 [54] 2 47 0.04 [0.01; 0.15]
Baumeister SH et al 2019 [29] 0 12 0.00 [0.00; 0.26]
Benjamin R et al 2020 [30] 8 21 0.38 [0.18; 0.62]
Berdeja JG et al 2021 [31] 20 97 0.21 [0.13; 0.30]
Brudno JN et al 2018 [56] 1 16 0.06 [0.00; 0.30]
Brudno JN et al 2020 [55] 4 20 0.20 [0.06; 0.44]
Caimi PF et al 2021 [69] 5 20 0.25 [0.09; 0.49]
Cao J et al 2018 [32] 1 18 0.06 [0.00; 0.27]
Cohen AD et al 2019 [33] 8 25 0.32 [0.15; 0.54]
Cordoba S et al 2021 [70] 4 15 0.27 [0.08; 0.55]
Cornell RF et al 2021 [71] 3 14 0.21 [0.05; 0.51]
Fan L et al 2022 [72] 0 10 0.00 [0.00; 0.31]
Fowler NH et al 2022 [82] 36 97 0.37 [0.28; 0.48]
Frey NV et al 2020 [57] 13 38 0.34 [0.20; 0.51]
Gardner RA et al 2017 [58] 21 45 0.47 [0.32; 0.62]
Geyer MB et al 2019 [35] 9 20 0.45 [0.23; 0.68]
Heng G et al 2020 [36] 4 10 0.40 [0.12; 0.74]
Jacoby E et al 2018 [37] 11 20 0.55 [0.32; 0.77]
Kato K et al 2022 [84] 0 16 0.00 [0.00; 0.21]
Lamure S et al 2021 [94] 23 60 0.38 [0.26; 0.52]
Li C et al 2021 [38] 1 30 0.03 [0.00; 0.17]
Liu Y et al 2022 [93] 8 23 0.35 [0.16; 0.57]
Magnani CF et al 2020 [40] 0 13 0.00 [0.00; 0.25]
Makita S et al 2022 [85] 1 10 0.10 [0.00; 0.45]
Maude SL et al 2018 [4] 30 75 0.40 [0.29; 0.52]
Mei H et al 2021 [73] 0 23 0.00 [0.00; 0.15]
Munshi NC et al 2021 [41] 23 128 0.18 [0.12; 0.26]
Myers RM et al 2021 [61] 29 74 0.39 [0.28; 0.51]
Pan J et al 2019 [43] 6 34 0.18 [0.07; 0.35]
Pan J et al 2021 [80] 3 20 0.15 [0.03; 0.38]
Park JH et al 2018 [14] 23 53 0.43 [0.30; 0.58]
Raje N et al 2019 [44] 14 33 0.42 [0.25; 0.61]
Ramos CA 2018 [62] 1 16 0.06 [0.00; 0.30]
Ramos CA et al 2020 [45] 0 42 0.00 [0.00; 0.08]
Roddie C et al 2021 [75] 4 20 0.20 [0.06; 0.44]
Sang W et al 2020 [15] 5 21 0.24 [0.08; 0.47]
Schuster SJ et al 2019 [5] 23 111 0.21 [0.14; 0.29]
Shah NN et al 2020 [19] 7 22 0.32 [0.14; 0.55]
Shah NN et al 2020 [18] 19 58 0.33 [0.21; 0.46]
Shalabi H et al 2022 [76] 11 52 0.21 [0.11; 0.35]
Shi X et al 2022 [87] 0 10 0.00 [0.00; 0.31]
Siddiqi T et al 2022 [77] 9 23 0.39 [0.20; 0.61]
Singh H et al 2022 [63] 0 14 0.00 [0.00; 0.23]
Spiegel JY et al 2021 [64] 14 38 0.37 [0.22; 0.54]
Talleur A et al 2022 [78] 3 12 0.25 [0.05; 0.57]
Tong C et al 2020 [65] 6 61 0.10 [0.04; 0.20]
Turtle CJ et al 2016 [47] 15 30 0.50 [0.31; 0.69]
Wang D et al 2021 [20] 0 18 0.00 [0.00; 0.19]
Wang J et al 2022 [66] 2 18 0.11 [0.01; 0.35]
Wang Y et al 2022 [67] 7 62 0.11 [0.05; 0.22]
Wei G et al 2021 [79] 0 16 0.00 [0.00; 0.21]
Wu J et al 2021 [90] 3 13 0.23 [0.05; 0.54]
Yan ZX et al 2019 [49] 1 10 0.10 [0.00; 0.45]
Ying Z et al 2019 [50] 0 25 0.00 [0.00; 0.14]
Ying Z et al 2021 [88] 12 59 0.20 [0.11; 0.33]
Ying Z et al 2022 [68] 1 22 0.05 [0.00; 0.23]
Zhang H et al 2022 [89] 3 22 0.14 [0.03; 0.35]
Zhang X et al 2020 [93] 23 110 0.21 [0.14; 0.30]
Zhang Y et al 2021 [51] 5 32 0.16 [0.05; 0.33]
Zhao WH et al 2018 [52] 1 57 0.02 [0.00; 0.09]
Zhou X et al 2020 [53] 1 21 0.05 [0.00; 0.24]
Total (common effect) 2421 0.28 [0.26; 0.30]
Total (random effect) 0.22 [0.18; 0.26]
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7
Proportion (95% CI)
Heterogeneity: χ^2_{61} = 183.09 (P < .001), I^2 = 67%

(c)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Baumeister SH et al 2019 [29] 0 12 0.00 [0.00; 0.26]
Benjamin R et al 2020 [30] 0 21 0.00 [0.00; 0.16]
Berdeja JG et al 2021 [31] 9 97 0.09 [0.04; 0.17]
Brudno JN et al 2018 [56] 1 16 0.06 [0.00; 0.30]
Brudno JN et al 2020 [55] 1 20 0.05 [0.00; 0.25]
Caimi PF et al 2021 [69] 1 20 0.05 [0.00; 0.25]
Cohen AD et al 2019 [33] 3 25 0.12 [0.03; 0.31]
Cordoba S et al 2021 [70] 0 15 0.00 [0.00; 0.22]
Cornell RF et al 2021 [71] 0 14 0.00 [0.00; 0.23]
Curran KJ et al 2019 [34] 7 25 0.28 [0.12; 0.49]
Fan L et al 2022 [72] 0 10 0.00 [0.00; 0.31]
Fowler NH et al 2022 [82] 3 97 0.03 [0.01; 0.09]
Frey NV et al 2020 [57] 6 38 0.16 [0.06; 0.31]
Gardner RA et al 2017 [58] 9 45 0.20 [0.10; 0.35]
Geyer MB et al 2019 [35] 2 20 0.10 [0.01; 0.32]
Jacobson CA et al 2022 [83] 28 148 0.19 [0.13; 0.26]
Kato K et al 2022 [84] 0 16 0.00 [0.00; 0.21]
Kochenderfer JN et al 2017 [59] 12 22 0.55 [0.32; 0.76]
Lamure S et al 2021 [94] 7 60 0.12 [0.05; 0.23]
Li C et al 2021 [38] 0 30 0.00 [0.00; 0.12]
Liu H et al 2020 [60] 0 17 0.00 [0.00; 0.20]
Liu Y et al 2022 [93] 5 23 0.22 [0.07; 0.44]
Locke FL et al 2022 [92] 36 170 0.21 [0.15; 0.28]
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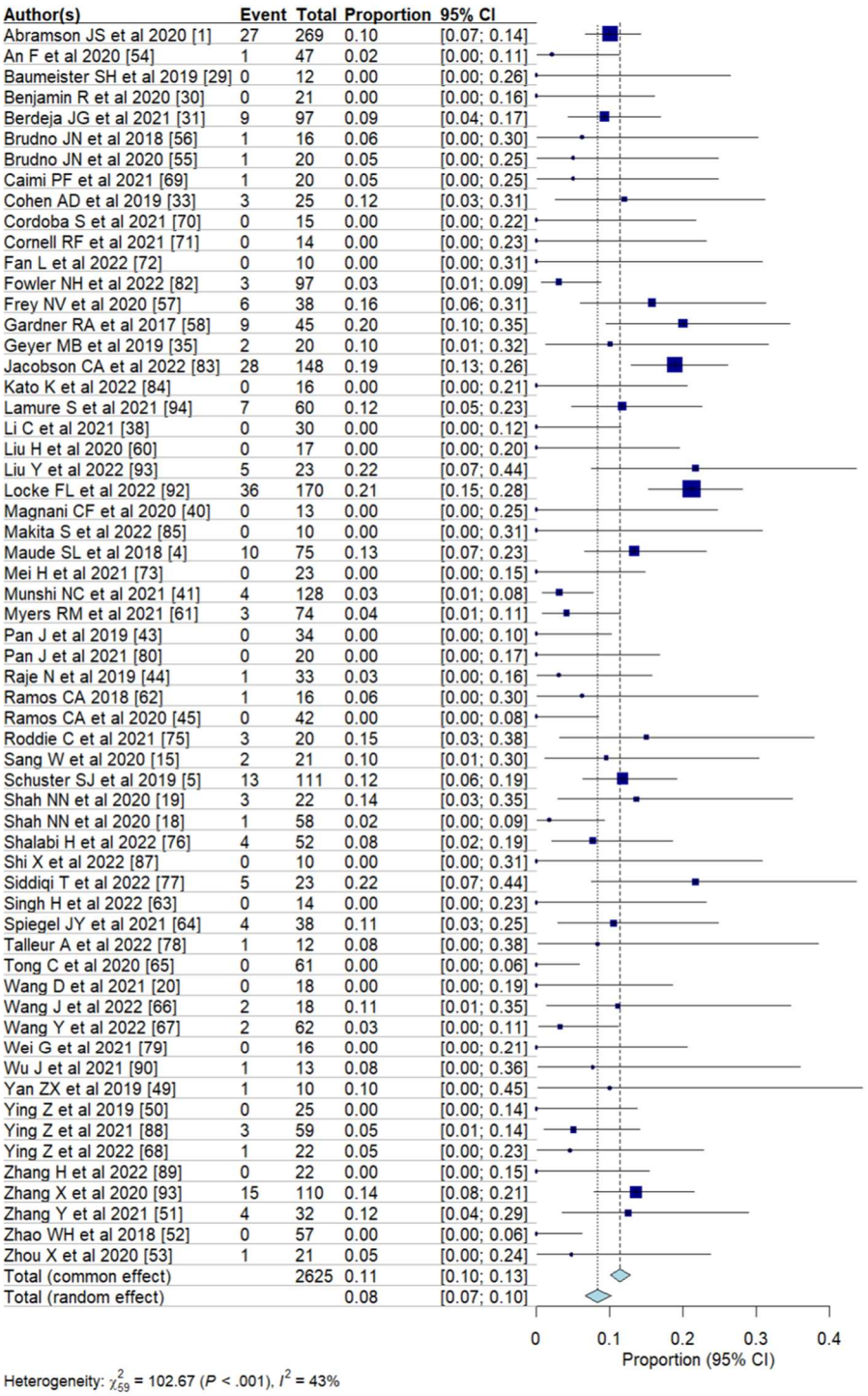
Myers RM et al 2021 [61] 3 74 0.04 [0.01; 0.11]
Neelapu SS et al 2017 [42] 28 101 0.28 [0.19; 0.38]
Neelapu SS et al 2022 [86] 9 40 0.22 [0.11; 0.38]
Pan J et al 2019 [43] 0 34 0.00 [0.00; 0.10]
Pan J et al 2021 [80] 0 20 0.00 [0.00; 0.17]
Park JH et al 2018 [14] 22 53 0.42 [0.28; 0.56]
Raje N et al 2019 [44] 1 33 0.03 [0.00; 0.16]
Ramos CA 2018 [62] 1 16 0.06 [0.00; 0.30]
Ramos CA et al 2020 [45] 0 42 0.00 [0.00; 0.08]
Roddie C et al 2021 [75] 3 20 0.15 [0.03; 0.38]
Sang W et al 2020 [15] 2 21 0.10 [0.01; 0.30]
Sauter CS et al 2019 [46] 9 15 0.60 [0.32; 0.84]
Schuster SJ et al 2019 [5] 13 111 0.12 [0.06; 0.19]
Shah BD et al 2021 [17] 14 55 0.25 [0.15; 0.39]
Shah BD et al 2021 [16] 17 45 0.38 [0.24; 0.53]
Shah NN et al 2020 [19] 3 22 0.14 [0.03; 0.35]
Shah NN et al 2020 [18] 1 58 0.02 [0.00; 0.09]
Shalabi H et al 2022 [76] 4 52 0.08 [0.02; 0.19]
Shi X et al 2022 [87] 0 10 0.00 [0.00; 0.31]
Siddiqi T et al 2022 [77] 5 23 0.22 [0.07; 0.44]
Singh H et al 2022 [63] 0 14 0.00 [0.00; 0.23]
Spiegel JY et al 2021 [64] 4 38 0.11 [0.03; 0.25]
Talleur A et al 2022 [78] 1 12 0.08 [0.00; 0.38]
Tong C et al 2020 [65] 0 61 0.00 [0.00; 0.06]
Turtle CJ et al 2016 [47] 15 30 0.50 [0.31; 0.69]
Wang D et al 2021 [20] 0 18 0.00 [0.00; 0.19]
Wang J et al 2022 [66] 2 18 0.11 [0.01; 0.35]
Wang M et al 2020 [91] 21 68 0.31 [0.20; 0.43]
Wang Y et al 2022 [67] 2 62 0.03 [0.00; 0.11]
Wei G et al 2021 [79] 0 16 0.00 [0.00; 0.21]
Wu J et al 2021 [90] 1 13 0.08 [0.00; 0.36]
Yan ZX et al 2019 [49] 1 10 0.10 [0.00; 0.45]
Ying Z et al 2019 [50] 0 25 0.00 [0.00; 0.14]
Ying Z et al 2021 [88] 3 59 0.05 [0.01; 0.14]
Ying Z et al 2022 [68] 1 22 0.05 [0.00; 0.23]
Zhang H et al 2022 [89] 0 22 0.00 [0.00; 0.15]
Zhang X et al 2020 [93] 15 110 0.14 [0.08; 0.21]
Zhang Y et al 2021 [51] 4 32 0.12 [0.04; 0.29]
Zhao WH et al 2018 [52] 0 57 0.00 [0.00; 0.06]
Zhou X et al 2020 [53] 1 21 0.05 [0.00; 0.24]
Total (common effect) 3089 0.17 [0.16; 0.19]
Total (random effect) 0.11 [0.08; 0.14]
0
0.2
0.4
0.6
0.8
Proportion (95% CI)
Heterogeneity: χ^2_{70} = 261.49 (P < .001), I^2 = 73%

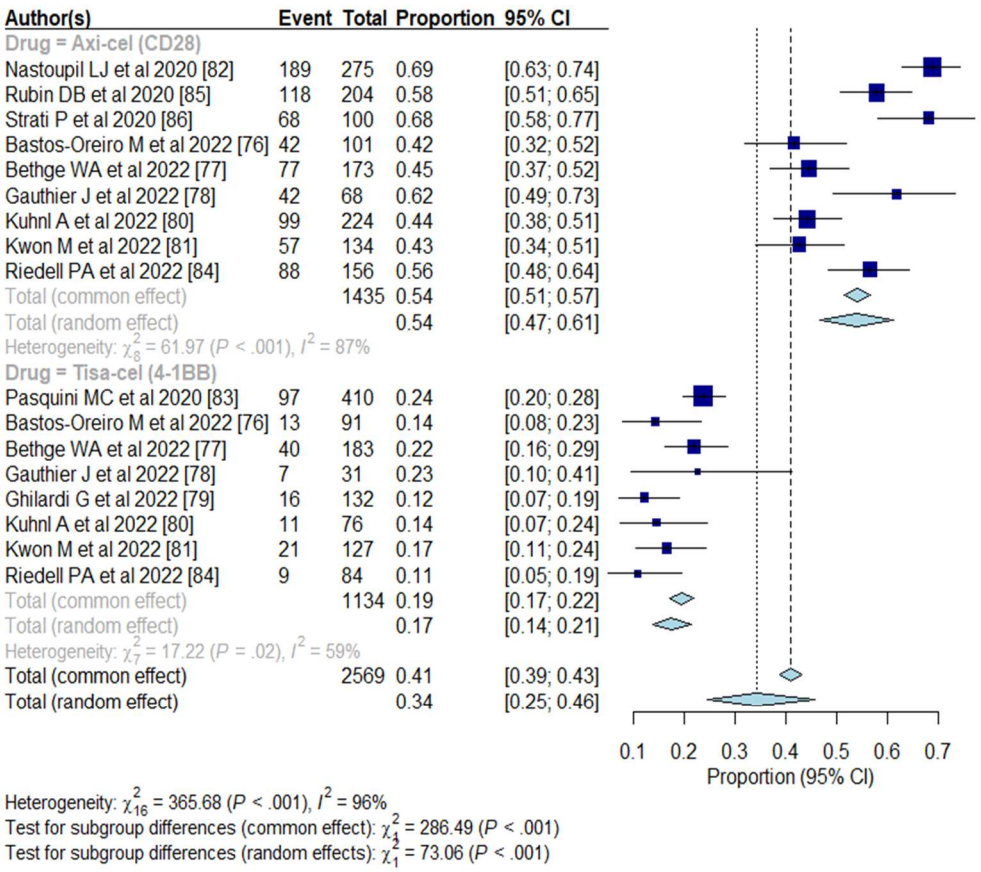
(d)



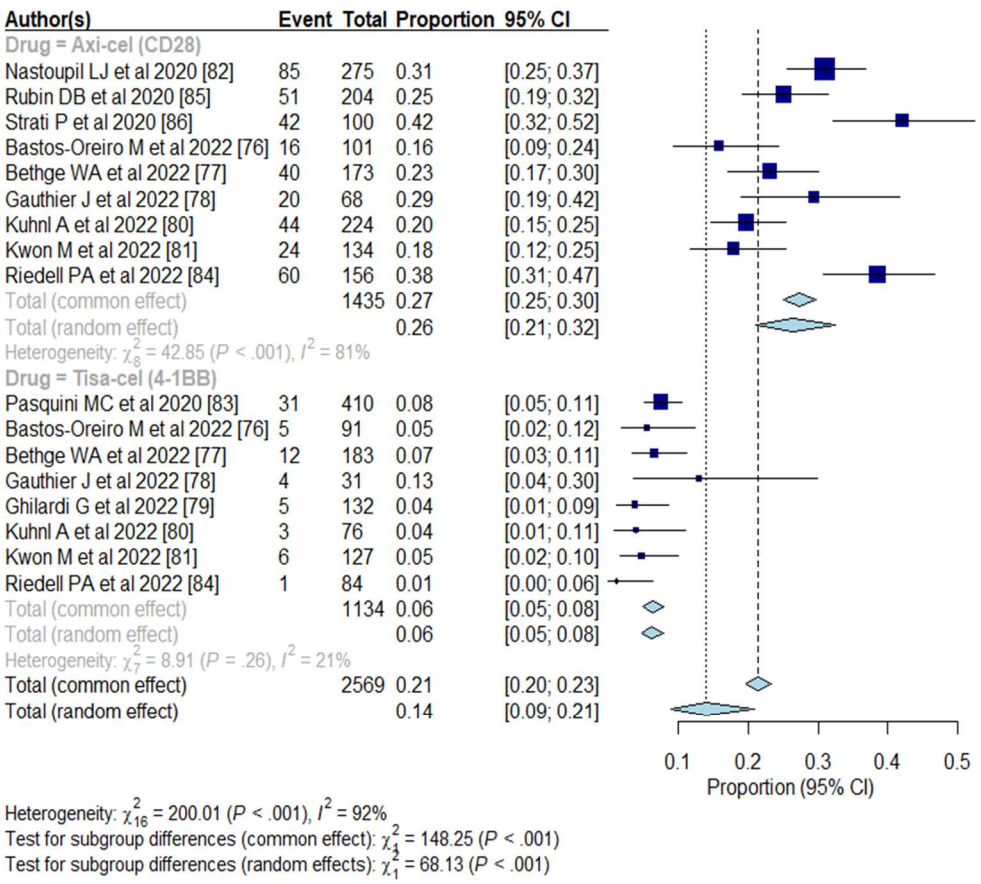
Heterogeneity: $\chi^2_{59} = 102.67$ ($P < .001$), $I^2 = 43\%$

Supplementary Figure 5. Forest plots showing the pooled incidence of all-grade ICANS (a) and high-grade (b) in real-world data (76-87).

(a)



(b)



Heterogeneity: χ^2_{16} = 200.01 (P < .001), I^2 = 92%
Test for subgroup differences (common effect): χ^2_4 = 148.25 (P < .001)
Test for subgroup differences (random effects): χ^2_1 = 68.13 (P < .001)

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