Supplementary Table S1. List of all selected studies

First Author [#] **Phase (study Identifier)** **N**	**Indication** **Target**	**Co-stimulatory domains** **Gene delivery; scFV Origin**	**Reported outcomes**
Bishop M [1] Ph3 (NCT03570892) N=322	LBCL CD19	4-1-BB Lentivirus; Murine	ORR, OS, EFS, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Abramson JS [2] Ph1 (NCT02631044) N=294	DLBCL CD19	4-1-BB & CD3 no data	ORR, onset of response, PFS, OS, duration of response, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Zhang X [3] Retrospective analysis (NA) N=254	B-ALL CD19	4-1-BB & CD28 No Data No Data	CR, onset of response, LFS, OS, duration of response, AEs & onset of AEs
Munshi NC [4] Ph2 (NCT03361748) N=140	Multiple myeloma BCMA	4-1-BB & CD3 Lentivirus; Murine	ORR, onset of response, PFS, OS, duration of response, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Kittai A [5] Retrospective analysis (NA) N=130	DLBCL No Data	No Data No Data No Data	ORR, CR, PFS, OS, & AEs
Neelapu SS [6] Ph2 (NCT02348216) N=111	DLBCL CD19	CD28 & CD3 Retrovirus; Murine	ORR, PFS, OS, duration of response, peak expansion and persistence of CAR-Ts, AEs
Berdeja JG [7] Ph1b/2 (NCT03548207) N=97	Multiple myeloma BCMA	4-1-BB & CD3 Lentivirus; no data	ORR, onset of response, PFS, OS, AEs & onset of AEs
Fowler N [8] Ph2 (NCT03568461) N=97	FL CD19	4-1-BB Lentivirus; Murine	OS, PFS, duration of response, AEs & onset of AEs
Schuster SJ [9] Ph2 (NCT02445248) N=93	DLBCL CD19	4-1-BB & CD3 Lentivirus; Murine	ORR, PFS, OS, duration of response, persistence of CAR-Ts, AEs
Itzhaki O [10] Ph1/2 (NCT02772198; NCT00287131) N=90	ALL and NHL CD19	CD28 & CD3 Retrovirus; Murine	ORR
Li M [11] Ph1/2 (NCT03919240) N=78	B-ALL CD19	CD28 & CD3 Lentivirus Human	CR, EFS, OS, peak expansion and persistence of CAR-Ts, AEs & onset of AEs

Sesques P [12] Retrospective analysis (NA) N=70	DLBCL CD19	4-1-BB/CD28 & CD3 Retro & Lentivirus; both murine	ORR, PFS, OS, duration of response, AEs & onset of AEs
Wang M [13] Ph2 (NCT02601313) N=68	MCL CD19	CD28 & CD3 Retrovirus; Murine	ORR, PFS, OS, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Ying Z [14] Ph1 (NCT04089215) N=59	B-cell lymphoma CD19	4-1-BB & CD3 Lentivirus; Murine	BOR, onset of response, PFS, OS, duration of response, peak expansion and persistence of CAR-Ts, AEs
Zhao WH [15] Ph1 (NCT03090659) N=57	Multiple myeloma BCMA	CD28 & CD3 Lentivirus; Camel	ORR, PFS, OS, duration of response, persistence of CAR-Ts & AEs
Shah BD [16] Ph2 (NCT02614066) N=55	B-ALL CD19	CD28 & CD3 Retrovirus; Murine	OCR, CR, onset of response, RFS, duration of response, peak expansion, persistence of CAR-Ts, AEs & onset of AEs
Shah BD [17] Ph1/2 (NCT02614066) N=54	ALL CD19	CD28 & CD3 Retrovirus; Murine	ORR, RFS, OS, duration of response, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Jiang H [18] Ph1/2 (NCT02965092) N=53	B-ALL CD19	4-1-BB & CD3 Lentivirus; no data	ORR, onset of response, OS, duration of response, peak expansion and persistence of CAR-Ts & AEs
Park JH [19] Ph1 (NCT01044069) N=53	B-ALL CD19	CD28 & CD3 Retrovirus; Murine	ORR, EFS, OS, persistence of CAR-Ts, & AEs
Studies with cohort size ≤50 treated patients			
Summers C[20] Ph1/2 (NCT02028455) N=50	B-ALL CD19	4-1-BB; No Data	CR, LFS, OS, onset of response & AEs
Ramos CA[21] Ph1 (NCT01316146) N=41	HL CD30	No Data	ORR, PFS, OS, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Wudhikarn K[22] Ph1 (NCT01044069) N=38	B-ALL CD19	No Data	CR, EFS, OS, duration of response, AEs & onset of AEs
Shao M[23] Retrospective analysis ChiCTR1800017404 N=37	Multiple myeloma BCMA	4-1-BB; Lentivirus	ORR & AEs
Frey NV[24]	ALL	4-1-BB; Lentivirus	ORR, EFS, OS, & AEs

Ph2 (NCT01029366; NCT02030847) N=35	CD19		
Pan J[25] Ph1 (ChiCTR-OIC-17013523) N=34	B-ALL CD22	4-1-BB; Lentivirus	ORR, 1-yr leukemia-free survival rate, AEs & onset of AEs
Raje N[26] Ph1 (NCT02658929) N=33	Multiple myeloma BCMA	4-1-BB; Lentivirus	ORR, PFS, duration of response, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Turtle CJ[27] Ph1 (NCT01865617) N=32	NHL CD19	4-1-BB; Lentivirus	ORR, PFS, OS, persistence of CAR-Ts, AEs
Frey NV[28] Ph1 (NCT01747486) N=32	CLL CD19	4-1-BB; Lentivirus	ORR, PFS, OS, persistence of CAR-Ts, AEs
An F[29] Ph2 (NCT02735291) N=30 (adults)	B-ALL CD19	CD28; Retrovirus	ORR, RFS, OS, persistence of CAR-Ts, AEs
Li C[30] Ph1 (ChiCTR-OPC16009113) N=30	MM and PCL BCMA	CD28; Lentivirus	ORR, CR, PFS, OS, duration of response, AEs & onset of AEs
Turtle CJ[31] Ph1 (NCT01865617) N=29	B-ALL CD19	4-1-BB; Lentivirus	ORR, peak expansion and persistence of CAR-Ts & AEs
Schuster SJ[32] Case series/retrospective N=28	DLBCL/FL CD19	4-1-BB; Lentivirus	ORR, PFS, OS, peak expansion and persistence of CAR-Ts & AEs
Cohen AD[33] Ph1 (NCT02546167) N=25	Multiple myeloma BCMA	4-1-BB; Lentivirus	ORR, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Ying Z[34] Ph1 (NCT02842138) N=25	B cell lymphoma CD19	4-1-BB; Lentivirus	ORR, duration of response, peak expansion and persistence of CAR-Ts, & AEs
Tu S[35] Cohort study (ChiCTR-OOC-16007779) N=25	ALL CD19	CD28 & CD27; Lentivirus	ORR, DFS, OS & AEs
Turtle CJ[36] Ph1 (NCT01865617) N=24	CLL CD19	4-1-BB; Lentivirus	ORR, persistence of CAR-Ts & AEs
Casadei B[37] Case series/retrospective (Registration details	LBCL CD19	CD28 or 4-1-BB gamma-retroviral or lentiviral	ORR, CR, onset of response, PFS, OS, AEs & onset of AEs

not available) N=24			
Wang J[38] Ph1 (ChiCTR-ONN-16009862; & ChiCTR1800019622) N=23	B-ALL CD19	4-1-BB; Lentivirus	ORR, onset of response, leukemia-free survival, OS, peak expansion and persistence of CAR-Ts & AEs
Zhou X[39] Ph1 (ChiCTR-OOC-16007779) N=21	DLBCL CD19	CD28; Lentivirus	ORR, onset of response, EFS, OS, duration of response, AEs & onset of AEs
Hirayama AV[40] Ph1/2 (NCT01865617) N=21	FL CD19	4-1-BB; Lentivirus	ORR, onset of response, PFS & OS
Geyer MB[41] Ph1 (NCT00466531) N=20	CLL/NHL CD19	CD28; Retrovirus	ORR, EFS, OS, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Rossi J[42] Ph1/2 (NCT00924326) N=20	DLBCL and others CD19	CD28; Retrovirus	ORR, peak expansion of CAR-Ts & AEs
Brudno JN[43] Ph1 (NCT02659943) N=20	DLBCL/FL CD19	CD28; Retrovirus	ORR, EFS, duration of response, peak expansion of CAR-Ts & AEs
Cui R[44] Ph1 (ChiCTR1800019622 & ChiCTR1800018059) N=20	DLBCL CD19	No Data	ORR, PFS, OS, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Roddie C[45] Ph1 (NCT02935257) N=20	B-ALL CD19	4-1-BB; No Data	CR, onset of response, EFS, OS, duration of response, peak expansion, persistence of CAR-Ts, AEs & onset of AEs
Gill S [46] Ph2 (NCT02640209) N=19	CLL CD19	4-1-BB (CD137); Lentivirus; Humanized	CR, OS, PFS, ORR, peak expansion, persistence of CAR-Ts, AEs & onset of AEs
Wang CM[47] Ph1 (NCT02259556) N=18	Hodgkins Lymphoma CD30	4-1-BB; Lentivirus	ORR, PFS, duration of response, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Wang D[48] Ph1 (ChiCTR1800018137) N=18	MM BCMA	4-1-BB; No Data	ORR, CR, onset of response, PFS, OS, duration of response, peak expansion, persistence of CAR-Ts, AEs & onset of AEs
Cao J[49] Ph1 (NCT02782351)	ALL CD19	4-1-BB; Lentivirus	CR, LFS, OS, onset of response, duration of response, peak

N=18			expansion, AEs & onset of AEs
Xu J[50] Ph1 (NCT03090659) N=17	Multiple myeloma BCMA	CD28; Lentivirus	ORR, PFS, OS, duration of response, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Cornell R[51] Ph1 (NCT03318861) N=17	MM and PCL BCMA	CD28; Lentivirus	PFS, OS, peak expansion, AEs & onset of AEs
Wang X[52] Ph1 (NCT01318317 & NCT01815749) N=16	NHL CD19	CD28; Lentivirus	ORR, PFS, peak expansion and persistence of CAR-Ts, AEs (not clear)
Ramos CA[53] Ph1 (NCT00881920) N=16	ALL/NHL k-light chain	CD28; Retrovirus	ORR, peak expansion & persistence of CAR-Ts
Davila M[54] Ph1 (NCT01044069) N=16	B-ALL CD19	4-1-BB; Retroviral	ORR, CR, onset of response, duration of response, AEs & onset of AEs
Sauter CS[55] Ph1 (NCT01840566) N=15	NHL CD19	CD28; Retrovirus	ORR, PFS, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Hu Y[56] Ph1 (ChiCTR-OCC-15007008) N=15	ALL CD19	4-1-BB; Lentivirus	ORR, onset of response, RFS, OS, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Porter D[57] Pilot (NCT01029366) N=14	CLL CD19	4-1-BB; Lentivirus	ORR, CR, PR, PFS, OS, duration of response, onset of response, peak expansion, persistence of CAR-Ts, AEs & onset of AEs
Frigault MJ [58] Ph1(NCT04155749) N=13	MM BCMA	41BB and CD3; Lentivirus; Humanized	CR, PFS, ORR, OS, duration of response, onset of response, peak expansion, persistence of CAR-Ts, AEs & onset of AEs
Baumeister SH[59] Ph1 (NCT02203825) N=12	AML/MDS and MM NKG2D	NKG2D; Retrovirus	ORR, OS, peak expansion and persistence of CAR-Ts, & AEs
Ali SA[60] Ph1 (NCT02215967) N=12	Multiple myeloma BCMA	CD28; Retrovirus	Peak expansion and persistence of CAR-Ts & AEs
Enblad G[61] Ph1/2 (NCT02132624) N=11	Leukemia/Lymphoma CD19	CD28 & 4-1-BB Retrovirus	ORR, PFS, OS, peak expansion and persistence of CAR-Ts, AEs (not clear)
Yan ZX[62] Ph1 (NCT03355859) N=10	NHL CD19	4-1-BB; Lentivirus	ORR, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Magnani CF[63]	B-ALL	CD28 & OX40	ORR, OS, duration of response,

Ph1/2 (NCT03389035) N=9 (adults only)	CD19	Sleeping Beauty	peak expansion of CAR-Ts & AEs
Gu R[64] Ph1/pilot (NCT02975687) N=9 (adults only)	B-ALL CD19	4-1-BB; Lentivirus Human	ORR, OS, peak expansion and persistence of CAR-Ts, AEs & onset of AEs
Geyer MB[65] Ph1 (NCT01416974) N=8	CLL CD19	CD28; No Data	ORR, PFS, OS, AEs & onset of AEs
Cruz CR[66] Ph1 (NCT00840853) N=8	B-ALL CD19	CD28; Retrovirus	ORR, persistence of CAR-Ts & AEs
Kochenderfer JN[67] Ph1/pilot (NCT00924326) N=8	FL and CLL CD19	CD28; Retrovirus	ORR, duration of response, & persistence of CAR-Ts
Bao F[68] Ph1 (Registration details not available) N=5	DLBCL CD19	4-1-BB; Lentivirus	ORR, peak expansion and persistence of CAR-Ts, & AEs
Eom HS[69] Ph1 (Registration details not available) N=4	Multiple LMP2A	4-1-BB; No Data	ORR, onset of response, duration of response & AEs
Ritchie DS[70] Ph1 (Registration details not available) N=4	AML LeY	CD28; Retroviral	ORR, peak expansion and persistence of CAR-Ts & AEs
Zhang Q[71] Pilot (Registration details not available) N=4	B-ALL CD19	4-1-BB; Lentivirus	ORR, duration of response, peak expansion of CAR-Ts, AEs & onset of AEs
Kalos M[72] Pilot (Registration details not available) N=3	CLL CD19	4-1-BB; No Data no data	ORR, onset of response, duration of response, peak expansion and persistence of CAR-Ts
Weng J[73] Pilot (NCT02822326) N=3 (2, adults only)	B-ALL CD19	No Data; Lentivirus	ORR, onset of response, peak expansion and persistence of CAR-Ts & AEs
Feng J[74] Ph1 (NCT04594135) N=1	T-LBL CD5	No Data; Lentivirus	Complete eradication, onset of response, OS, duration of response, persistence of CAR-Ts, AEs & onset of AEs

Supplementary Table S2. Quality assessment for the included studies

	Risk of bias					**Indirectness**	**Imprecision**	
	Selection bias	**Attrition bias**	**Reporting/Detection bias**					
First Author [reference]	**IRC involved in patient selection (Yes; No)**	**Loss to follow-up (<5%; 5-20%; >20%)**	**Objective outcomes assessed (Yes; No)**	**IRC involved in assessment of response (Yes; No)**	**Safety outcomes reported (Yes; No)**	**Heterogeneity (Single sub-type; 2 sub-types; >2 sub-types in the study)**	**Sample size (<30; 30-50; >50 patients treated)**	**Duration of follow-up (<6 months; 6-12 months; >12 months)**
Bishop M [1]	No	>20%	Yes	Yes	Yes	2 sub-types	> 50	NR
Abramson JS[2]	Yes	>20%	Yes	Yes	Yes	Single sub-type	> 50	6-12 months
Zhang X[3]	No*	5-20%	Yes	No	Yes	Single sub-type	> 50	NR
Munshi NC[4]	No*	>20%	Yes	Yes	Yes	Single sub-type	> 50	>12 months
Kittai A[5]	No	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	> 50	>12 months
Neelapu SS [6]	No	Consort Diagram Not Reported	Yes	No	Yes	>2 sub-types	> 50	>12 months
Berdeja JG [7]	No*	5-20%	Yes	Yes	Yes	Single sub-type	> 50	>12 months

Fowler N [8]	No	<5%;	Yes	No	Yes	Single sub-type	> 50	>12 months
Schuster S J[9]	No	>20%	Yes	Yes	Yes	>2 sub-types	> 50	<6 months
Itzhaki O [10]	No	Consort Diagram Not Reported	Yes	No	Yes	>2 sub-types	> 50	NR
Li M [11]	No*	>20%	Yes	No	Yes	Single sub-type	>50	NR
Sesques P[12]	No*	Consort Diagram Not Reported	Yes	No	Yes	>2 sub-types	> 50	<6 months
Wang M[13]	No	Consort Diagram Not Reported	Yes	Yes	Yes	Single sub-type	> 50	>12 months
Ying Z[14]	No*	5-20%	Yes	Yes	Yes	Single sub-type	> 50	6-12 months
Zhao WH[15]	No*	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	> 50	6-12 months
Shah BD[16]	No	>20%	Yes	No	Yes	Single sub-type	> 50	>12 months
Shah BD[17]	No	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	> 50	>12 months
Jiang H[18]	No*	Consort	Yes	No	Yes	Single sub-type	> 50	NR

		Diagram Not Reported						
Park JH[19]	No	>20%	Yes	No	Yes	Single sub-type	> 50	>12 months
Summers C[20]	No*	>20%	Yes	No	Yes	Single sub-type	30-50	>12 months
Ramos CA[21]	No*	5-20%	Yes	No	Yes	Single sub-type	30-50	>12 months
Wudhikarn K[22]	No	>20%	Yes	No	Yes	Single sub-type	30-50	>12 months
Shao M[23]	No	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	30-50	NR
Frey NV[24]	No*	>20%	Yes	No	Yes	Single sub-type	30-50	>12 months
Pan J[25]	No*	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	30-50	NR
Raje N[26]	No*	>20%	Yes	Yes	Yes	Single sub-type	30-50	6-12 months
Turtle CJ[27]	No*	Consort Diagram Not Reported	Yes	No	Yes	>2 sub-types	30-50	6-12 months
Frey NV[28]	No*	5-20%	Yes	No	Yes	Single sub-type	30-50	>12 months
An F[29]	No*	>20%	Yes	No	Yes	Single sub-type	30-50	NR
Li C[30]	No*	>20%	Yes	No	Yes	2 sub-types	30-50	>12 months

Turtle CJ[31]	No	Consort Diagram Not Reported	Yes	No	Yes	>2 sub-types	<30	6-12 months
Schuster SJ[32]	No	Consort Diagram Not Reported	Yes	Yes	Yes	2 sub-types	<30	>12 months
Cohen AD[33]	No	5-20%	Yes	Yes	Yes	Single sub-type	<30	>12 months
Ying Z[34]	No*	Consort Diagram Not Reported	Yes	No	Yes	>2 sub-types	<30	NR
Tu S[35]	No	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	<30	6-12 months
Turtle CJ[36]	No	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	<30	6-12 months
Casadei B[37]	No*	Consort Diagram Not Reported	Yes	No	Yes	>2 sub-types	<30	6-12 months
Wang J[38]	No*	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	<30	>12 months
Zhou X[39]	No*	Consort Diagram Not Reported	Yes	No	Yes	>2 sub-types	<30	>12 months

Hirayama AV[40]	No	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	<30	>12 months
Geyer MB[41]	No	>20%	Yes	No	Yes	>2 sub-type	<30	>12 months
Rossi J[42]	No	Consort Diagram Not Reported	Yes	No	Yes	>2 sub-types	<30	NR
Brudno JN[43]	No	<5%	Yes	No	Yes	>2 sub-types	<30	NR
Cui R[44]	No*	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	<30	6-12 months
Roddie C[45]	No*	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	<30	>12 months
Gill S [46]	No	5-20%	Yes	No	Yes	Single sub-type	<30	>12 months
Wang CM[47]	No	Consort Diagram Not Reported	Yes	No	Yes	>2 sub-types	<30	NR
Wang D[48]	No	>20%	Yes	No	Yes	Single sub-type	<30	>12 months
Cao J[49]	No*	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	<30	6-12 months
Xu J[50]	No*	Consort	Yes	No	Yes	Single sub-type	<30	>12 months

		Diagram Not Reported						
Cornell R[51]	No	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	<30	6-12 months
Wang X[52]	No	Consort Diagram Not Reported	Yes	No	Yes	2 sub-types	<30	>12 months
Ramos CA[53]	No*	<5%	Yes	No	Yes	>2 sub-types	<30	NR
Davila M[54]	No	<5%	Yes	No	Yes	Single sub-type	<30	>12 months
Sauter CS[55]	No	Consort Diagram Not Reported	Yes	No	Yes	>2 sub-types	<30	>12 months
Hu Y[56]	No	5-20%	Yes	No	Yes	Single sub-type	<30	<6 months
Porter D[57]	No*	>20%	Yes	No	Yes	Single sub-type	<30	>12 months
Frigault MJ [58]	No	<5%	Yes	No	Yes	Single sub-type	<30	>12 months
Baumeister SH[59]	No*	Consort Diagram Not Reported	Yes	No	Yes	2 sub-types	<30	6-12 months
Ali SA[60]	No	Consort Diagram Not	Yes	No	Yes	Single sub-type	<30	<6 months

		Reported						
Enblad G[61]	No	Consort Diagram Not Reported	Yes	No	Yes	>2 sub-types	<30	NR
Yan ZX[62]	No	Consort Diagram Not Reported	Yes	No	Yes	>2 sub-types	<30	6-12 months
Magnani CF[63]	No	<5%	Yes	No	Yes	Single sub-type	<30	6-12 months
Gu R[64]	No*	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	<30	6-12 months
Geyer MB[65]	No	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	<30	>12 months
Cruz CR[66]	No	Consort Diagram Not Reported	Yes	No	Yes	2 sub-types	<30	NR
Kochenderfer JN[67]	No	Consort Diagram Not Reported	Yes	No	Yes	>2 sub-types	<30	6-12 months
Bao F[68]	No	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	<30	<6 months
Eom HS[69]	No*	Consort Diagram	Yes	No	Yes	>2 sub-types	<30	NR

		Not Reported						
Ritchie DS[70]	No*	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	<30	NR
Zhang Q[71]	No*	Consort Diagram Not Reported	Yes	No	No	Single sub-type	<30	NR
Kalos M[72]	No*	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	<30	NR
Weng J[73]	No*	Consort Diagram Not Reported	Yes	No	Yes	Single sub-type	<30	6-12 months
Feng J [74]	No	<5%	Yes	No	Yes	Single sub-type	<30	>12 months

* Independent review committee/board approved the study's protocol and had patients sign consent forms

IRC, independent review committee

All observational and single arm unblinded studies are given low grade and the grade is moved upwards based on quality assessment.[75-78]

Risk of Bias mainly involves selection bias and reporting or detection bias. Selection bias is low, and quality is high for studies that included an IRC for patient selection and that had <5% loss of patients to follow-up. Studies with 5-20% loss to follow-up are considered to have medium selection bias and studies with over 20% loss to follow-up are considered to have high selection bias.

Reporting or detection bias is considered low for studies that evaluated objective outcomes, included an IRC for response assessment, and reported treatment-related adverse events (safety). Studies that reported subjective outcomes (e. g. patient reported outcomes) or studies that did not include IRC for response assessment or studies that did not report safety outcomes are rated as high for reporting or detection bias.

Indirectness (comparability) of the cohort between studies is considered low and quality is also high for studies that have a homogenous cohort (single type of cancer). Studies with up to 2 cancer-subtypes are rated as medium for indirectness and with >2 cancer-subtypes are rated as low for comparability.

Imprecision of the cohort is considered high and quality is low for studies that have low sample size (<30 patients) and small follow-up (<6 months). Studies that have a sample size of 30-50 patients or with 6-12 months follow-up are rated medium for imprecision. Studies with sample size of >50 patients and with follow-up over 12 months are rated low for imprecision and high for quality.

Table S3. Summary of response and adverse events in studies

First Author [#] Indication	Dose[a] (million cells)	Response	Adverse events[b]	Findings on association with dose
Bishop M [1] LBCL	Range: 40-590 (Response correlation assessed per 100 million increments in dose)	Overall: ORR, 46%; CRR, 28% (week-12)	All grade CRS: 61% Grade ≥3 CRS: 5% All grade neurotoxicity: 10% Grade ≥3 neurotoxicity: 2%	Study noted dose-response correlation in patients with PD or SD prior to infusion
Abramson JS [2] DLBCL	DL1: 50; DL2: 100; DL3: 150	Overall: ORR, 73%; CRR, 53% DL1: ORR, 68%; CRR, 60% DL2: ORR, 74%; CRR, 52% DL3: ORR, 73%, CRR, 51%	All grade CRS: 42% Grade ≥3 CRS: 2% All grade neurotoxicity: 30% Grade ≥3 neurotoxicity: 10%	No correlation between dose and response. Peak expansion correlated with CRS and Neurotoxicity incidence & severity
Zhang X [3] B-ALL	Range: 1.4-371 DL1: <21 DL2: ≥21	CRR: 90.9%	All grade CRS: 68.1% Grade ≥3 CRS: 10.2% All grade neurotoxicity: 2/254 (cerebral hemorrhage and severe neurotoxicity) Grade ≥3 neurotoxicity:	CAR-T cell dose did not correlate with LFS and OS or CR rates. CAR-T cell dose also did not correlate with neurotoxicity
Munshi NC [4] Multiple myeloma	DL1: 150; DL2: 300; DL3: 450	Overall: ORR, 73%; CRR, 33% DL1: ORR, 50%; CRR, 25% DL2: ORR, 69%; CRR, 29% DL3: ORR, 81%, CRR, 39%	All grade CRS: 84% Grade ≥3 CRS: 5% All grade neurotoxicity: 18% Grade ≥3 neurotoxicity: 3%	Clear dose response correlation was observed. Incidence of CRS also increased with dose.

Kittai A [5] DLBCL	No data	ORR: 88%, CR: 42.3%	All grade CRS: 78.5% Grade ≥3 CRS: NR All grade neurotoxicity: NR Grade ≥3 neurotoxicity: NR	Study did not report correlation or lack of correlation between dose and response
Neelapu SS [6] DLBCL	140	At 6 months: ORR, 82%; CRR, 52% At 1-yr: ORR, 82%; CRR, 58%	All grade CRS: 93% Grade ≥3 CRS: 13% All grade neurotoxicity: 64% Grade ≥3 neurotoxicity: 28%	Response and adverse events significantly correlated with CAR-T cell expansion. AUC was 5.4 times high in responders
Berdeja JG [7] Multiple myeloma	52.5	ORR, 97%; sCRR, 67%	All grade CRS: 95% Grade ≥3 CRS: 4% All grade neurotoxicity: 21% Grade ≥3 neurotoxicity: 9%	Overall responder rate was high so correlation analysis was not performed
Fowler N [8] FL	Range: 60-600[c]	ORR, 86%; CRR, 69%	All grade CRS: 49% Grade ≥3 CRS: none All grade neurotoxicity: 37% Grade ≥3 neurotoxicity: 3%	No impact of dose on overall response was noted but the incidence of CRS was higher in patients who received ≥100 million cells. Cmax, time to reach Cmax and AUC were similar for responders and non-responders
Schuster SJ [9] DLBCL	300	At 6 months: ORR, 33%; CRR, 29%	All grade CRS: 58% Grade ≥3 CRS: 22% All grade neurotoxicity: 21% Grade ≥3 neurotoxicity: 12%	No apparent effect of dose/exposure on clinical outcome
Itzhaki O [10] ALL and NHL	70	ALL: ORR & CRR, 84%	Not reported	Mainly concluded that cells from ALL patients

		NHL: ORR, 62%; CRR, 31%		had high proliferation rate and CAR-T cell incidence compared to NHL
Li M [11] B-ALL	35	CRR: 83%	All grade CRS: 73% Grade ≥3 CRS: 29% All grade neurotoxicity: NR Grade ≥3 neurotoxicity: 9%	Mainly concluded that B-ALL patients with low tumor burden had better efficacy and lower toxicity
Sesques P [12] DLBCL	140 or 350	All patients: Month 1 ORR, 63%; CRR, 48% Month 3 ORR 45%; CRR, 39%	All grade CRS: 85% Grade ≥3 CRS: 8% All grade neurotoxicity: 28% Grade ≥3 neurotoxicity: 10%	Number of treatment lines prior to CAR-T therapy and basal LDH levels were adverse prognostic factors for response in multivariate analysis
Wang M [13] MCL	140	At 7 months: ORR, 93%; CRR, 67%	All grade CRS: 91% Grade ≥3 CRS: 15% All grade neurotoxicity: 63% Grade ≥3 neurotoxicity: 31%	Expansion was significantly associated with response. AUC and peak level were comparatively more than 200 times high in responders.
Ying Z [14] B-cell lymphoma	100 or 150	All patients: BOR, 76%; CRR, 52%	All grade CRS: 48% Grade ≥3 CRS: 5% All grade neurotoxicity: 20% Grade ≥3 neurotoxicity: 5%	No difference in response between dose groups. Patients who failed ≥3 lines had slightly lower response. Grade≥3 CRS and neurotoxicity occurred in DL2. AEs correlated with peak and AUC
Zhao WH [15] Multiple myeloma	Range: 4.9 to 147[c]	ORR, 88%; CRR, 68%	All grade CRS: 90% Grade ≥3 CRS: 7% All grade neurotoxicity: 2% Grade ≥3 neurotoxicity:	Overall incidence and severity of CRS was higher in above median CART-dose. No clear relationship between dose and disease response

			none	
Shah BD [16] B-ALL	70	CRR: 71% at 4 months	All grade CRS: 89% Grade ≥3 CRS: 24% All grade neurotoxicity: 60% Grade ≥3 neurotoxicity: 24%	Single dose used and study did not investigate dose correlation with response.
Shah BD [17] ALL	DL: 35; DL2: 70; DL3: 140	DL1: CRR, 50% DL2: CRR, 83% DL3: CRR, 67%	DL1, 2 and 3 respectively All grade CRS: 81%, 100% and 100% Grade ≥3 CRS: 25%, 30% and 50% All grade neurotoxicity: 63%, 83% and 83% Grade ≥3 neurotoxicity: 25%, 42% and 50%	Response was highest in DL2 and correlated with CAR peak. DL3 did not have best response but had highest toxicity incidence. DL3 cohort was required to enroll patients with high tumor burden (>25% blasts). CRS severity correlated with CAR peak.
Jiang H [18] B-ALL	Range: 62.3-280.7[d]	All patients: CRR, 81% (no partial responders)	All grade CRS: 100% Grade ≥3 CRS: 36% Grade 2 & 3 neurotoxicity: 15%	Study did not report correlation or lack of correlation between dose and response. Objective was to evaluate coagulation disorders, biomarkers of coagulation disorders and management of coagulation disorders
Park JH [19] B-ALL	DL1: 70; DL2: 210	All patients: CRR, 83%	All grade CRS: 85% Grade ≥3 CRS: 26% All grade neurotoxicity: 44% Grade ≥3	Both response and AEs correlated with peak CAR-T expansion. Rate of CR was not significantly different between two dose groups

			neurotoxicity: 42%	
Summers C[20]; B-ALL; N=50	DL1: 35; DL2: 70; DL3: 350; DL4: 700	CR: 28.6% (12 months median)	All grade CRS: 76% Grade ≥3 CRS: 24% All grade neurotoxicity: NR Grade ≥3 neurotoxicity: NR	Study did not report correlation or lack of correlation between dose and response. Study was designed to evaluate the efficacy of HSCT post CAR-T cell therapy
Ramos CA[21]; HL; N=41	DL1: 32; DL2: 160; DL3: 320	All patients: ORR, 62%; CR, 51%	All grade CRS: 24% (only grade 1 seen) No neurotoxicity	Clinical response did not correlate with dose, but peak expansion correlated with dose
Wudhikarn K[22]; B-ALL; N=38	Range: 28-210[c]	CR: 43%	All grade CRS: 84.2% Grade ≥3 CRS: 23.7% All grade neurotoxicity: NR Grade ≥3 neurotoxicity: NR	Study did not report correlation or lack of correlation between dose and response. Study was designed to evaluate the outcomes in patients who had relapse post CAR-T cell therapy
Shao M[23]; Multiple myeloma; N=37	245	ORR, 97%; CR, 59%	All grade CRS: 100% Grade ≥3 CRS: 54% All grade neurotoxicity: 3% Grade ≥3 neurotoxicity: 3%	Study did not report correlation or lack of correlation between dose and response. Objective was to understand biomarkers of CRS and association with coagulation disorders
Frey NV[24]; ALL; N=35	50 or 500	CR, 69% in all pts; 33% in low dose, 50% in High dose single infusion and 90% in high dose fractionated dose	All grade CRS: 94% Grade ≥3 CRS: 72% All grade neurotoxicity: 42% Grade ≥3 neurotoxicity: 6%	Response increased with dose, but incidence and severity of CRS also increased with dose. Dose fractionation mitigated the CRS severity without compromising efficacy
Pan J[25]; B-ALL; N=34	52.5 in non-transplanted patients or 7 in transplanted patients	In all patients: CR, 71%	All grade CRS: 91% Grade ≥3 CRS: 3% Neurotoxicity: 18% (all cases ≤grade 2)	No difference in response between transplanted and non-transplanted patients. Response was higher in patients with higher

				peak
Raje N[26]; Multiple myeloma; N=33	DL1: 150; DL2: 450; DL3: 800	DL1: ORR, 33%; CRR, 0% DL2: ORR, 75%; CRR, 63% DL3: ORR, 95%; CRR, 42%	All grade CRS: 76% Grade ≥3 CRS: 6% All grade neurotoxicity: 42% Grade ≥3 neurotoxicity: 3%	Clear dose response was noted. However, CRS incidence also increased with dose
Turtle CJ[27]; NHL; N=32	DL1: 14; DL2: 140; DL3: 1400	All patients: ORR, 63%; CR, 33% DL1: ORR, 60%; CR, 20% DL2: ORR, 67%; CR, 44% DL3, ORR, 57%; CR, 14%	All grade CRS: 63% Grade ≥3 CRS: 13% All grade neurotoxicity: 28% (all Grade ≥3)	No apparent effect of dose on ORR but severe CRS incidence increased with dose. However, higher peak expansion and longer duration of CAR-T cell persistence were associated with tumor regression
Frey NV[28]; CLL; N=32	50 or 500	DL1: CR, 15% DL2: ORR, 53%; CR, 37%	All grade CRS: 63% Grade ≥3 CRS: 39% Grade ≥3 neurotoxicity: 8%	Study noted correlation between dose and ORR. Severity of CRS and neurotoxicity also correlated with dose
An F[29]; B-ALL; N=30 (adults)	Range: 70-350[c]	All patients: overall remission, 81%	CRS: All grade, 83%; Grade ≥3, 23% Neurotoxicity: All grade, 4.2%; Grade ≥3, 2.1%	No significant difference between children and adults regarding response and survival. Details of dose-response correlation not provided
Li C[30]; MM and PCL; N=30	Range: 378 – 1750 DL1≤784 DL2>784	ORR: 90%, CR: 43%	CRS: All grade, 97%; Grade ≥3, 17% Neurotoxicity: All grade, 3.3%; Grade ≥3, 0%	CAR-T doses showed no significant effect on the best response, PFS, OS and incidence and severity of CRS
Turtle CJ[31]; B-ALL; N=29	DL1: 14; DL2: 140; DL3: 1400	Overall: ORR, 100%; CR, 93%	CRS: All grade 83%; Grade ≥3, 23% Neurotoxicity: All grade, 50%; Grade ≥3, 50%	Response noted at all dose levels. Adverse events were higher in DL3
Schuster SJ[32]; DLBCL/FL; N=28	Range: 216-621[c]	At 6 months: CR, 52%	CRS: All grade, 57%; Grade ≥3,	Study did not report dose-response or dose-

			18% Neurotoxicity: All grade, 39%; Grade ≥3, 11%	safety correlation
Cohen AD[33]; Multiple myeloma; N=25	DL2, 10-50 DL3, 100-500 (DL1 had no lymphode-pletion)	ORR: Overall, 48%; DL1, 44%; DL2, 20%; DL3, 64%	CRS: All grade, 88%; Grade ≥3, 32% Neurotoxicity: All grade, 32%; Grade ≥3, 12%	Dose response was seen between DL2 and DL3. Incidence and severity of CRS and ICANS was higher in DL3 compared to DL2
Ying Z[34]; B cell lymphoma; N=25	DL1, 3-6 DL2 60-190 DL3, 200-400	Overall: ORR, 33%; CR, 29% DL1: ORR, 50%, CR, 17% DL2, ORR, 50%, CR, 0% DL3, ORR, 73%, CR, 55%	CRS: All grade 28%; Grade ≥3, 0% No neurotoxicity	Maximum response was noted at highest dose but DL2 was not better than DL1
Tu S[35]; ALL; N=25	Range: 6.2-280 DL1: ≤35 DL2: >35	Overall: ORR 92%; CR, 88%	CRS: All grade, 48%; Grade ≥3, 0% No neurotoxicity	Response rate was very high. No correlation between dose and response. CRS incidence was high at higher doses
Turtle CJ[36]; CLL; N=24	DL1: 14; DL2: 140; DL3: 1400	All patients: ORR, 70%; CR, 21% DL1: ORR, 100%; CR, 20%; DL2: ORR, 59%; CR, 24%; DL3: PR in 1/1	CRS: All grade 83%; Grade ≥3, 8% Neurotoxicity: All grade, 33%; Grade ≥3, 25%	Response did not correlate with dose. Peak CAR^+ cells were higher in patients who cleared marrow by flow cytometry. CRS was high in patients with high tumor burden. CRS incidence and severity was higher at higher dose levels
Casadei B[37]; LBCL; N=24	No data but it can be assumed that label doses were administered	BORR: 77% CRR: 50%	CRS: All grade, 87%; Grade ≥3, 10% Neurotoxicity: All grade, 43%; Grade ≥3, 17%	Study was not designed to analyze dose-response correlation
Wang J[38]; B-ALL; N=23	70	ORR, 83%; CR, 52%	CRS: All grade, 100%; Grade ≥3, 22%	Study used single dose but noted that TB correlated with CRS

			Neurotoxicity: All grade, 13%; Grade ≥3, 4%	levels. Among the 4 non-responders, 2 had high TB
Zhou X[39]; DLBCL; N=21	62.3	All patients: ORR, 67%; CR, 43% Granular dose response data was not shown	CRS: All grade, 14%; Grade ≥3, 0% Neurotoxicity: All grade, 5%; Grade ≥3, 5%	Study noted that there was no correlation between dose and response, and between peak expansion and response
Hirayama AV[40]; FL; N=21	140	ORR, 51%; CR, 40%	NR	Study noted that PFS correlated with expansion after lymphodepletion and lower LDH favored better PFS
Geyer MB[41]; CLL/NHL; N=20	<210 vs 210	Overall CR, 20%	CRS: All grade, 100%; Grade ≥3, 10% Neurotoxicity: All grade, 45%; Grade ≥3, 10%	No correlation between dose and response
Rossi J[42]; DLBCL and others; N=20	No data	All patients: ORR, 70%; CR, 50%	CRS: All grade, NR; Grade ≥3, 65% Neurotoxicity: All grade, NR; Grade ≥3, 60%	Study did not report granular dose response correlation. However, it noted that response and neurotoxicity but not CRS correlated with expansion
Brudno JN[43]; DLBCL/FL; N=20	DL1: 46.2 DL2: 140 DL3: 420	All patients: ORR, 70%; CR, 55%; DL1: ORR, 83%; CR, 67%; DL2: ORR/CR, 50%; DL3: ORR, 75%; CR, 50%	CRS: All grade, 80%; Grade ≥3, 10% Neurotoxicity: All grade, 100%; Grade ≥3, 5%	No correlation between dose and response or AE severity
Cui R[44]; DLBCL; N=20	70-490 DL1[d]: <140 DL2[d]: 140-<280 DL3[d]: ≥280	All patients: ORR, 85%; CR, 55%; DL1: ORR/CR, 80%; DL2: ORR: 100%; CR, 57%; DL3: ORR, 75%; CR, 38%	CRS: All grade, 100%; Grade ≥3, 10% Neurotoxicity: All grade, 20%; Grade ≥3, 0%	No correlation between dose and response. Grade 3 CRS and neurotoxicity occurred only in DL3 group

Roddie C[45]; B-ALL; N=20	410	CR: 85% at 1 month	CRS: All grade, 55%; Grade ≥3, 0% Neurotoxicity: All grade, 20%; Grade 3, 15%	Peak expansion was not correlated with total CAR-T dose but was strongly associated with both disease burden and with grade 2 CRS
Gill S [46]; CLL; N=19	Range: 200-500[c]	At 12 months, CR: 50%; PR: 36%	CRS: All grade, 95%; Grade ≥3, 16% Neurotoxicity: All grade, 26%; Grade 3, 5%	Study was not designed to test dose correlation
Wang CM[47]; HL; N=18	Range: 770-1470[e]	All patients: ORR, 39%; CR, 0%	CRS: All grade, 100%; Grade ≥3, 0% Neurotoxicity: All grade, 11.2%; Grade ≥3, 0%	Overall response was very low and did not correlate with dose
Wang D[48]; MM; N=18	DL1: 70; DL2: 210; DL3: 420	ORR: 100% CR: 72%	CRS: All grade, 71%; Grade ≥3, 22% Neurotoxicity: No Data	No dose-response/ PFS/OS correlation. Incidence of grade 3 or higher CRS was significantly higher in higher dose groups
Cao J[49]; ALL; N=18	70	All patients: CR: 82% at 1 month	CRS: All grade, 94%; Grade ≥3, 22% Neurotoxicity: All grade, 6%; Grade ≥3, 0%	Single dose was used in the study and the study did not analyze correlation between dose and response
Xu J[50]; Multiple myeloma ; N=17	49	All patients: ORR, 88%; CR, 76%	CRS: All grade, 100%; Grade ≥3, 41% No neurotoxicity	Study did not aim to evaluate dose response
Cornell R[51]; MM and PCL; N=17	DL1: 30; DL2: 100; DL3: 300; DL4: 1000	Best response: PR, 1 pt; SD, 3 pts	CRS: All grade, 21.4%; Grade ≥3, 0% Neurotoxicity: All grade, 21.4%; Grade ≥3, 0%	No correlation between dose and response. Only response noted was at DL1 (PR in 1 pt) CRS seen only at DL3 and DL4
Wang X[52]; NHL; N=16	DL1: 25; DL2: 50; DL3: 100; DL4: 200	In all patients: ORR, 94%; CR, 81%	NR	No correlation between dose and response. Overall response was very high and even low

				dose had response. Grade 4 severe CRS seen at 100 mil DL (DLT)
Ramos CA[53]; ALL/NHL; N=16	Range: 32-320[e]	In all patients: ORR, 19%; CR, 13%	Reports there was no clinical evidence of CRS. Details of neurotoxicity: NR	Overall response was very low and did not correlate with dose. CR was seen at lowest and highest dose
Davila M[54]; B-ALL; N=16	210	ORR: 88%, CR: 63%	sCRS: 44%; nCRS: 56% Neurotoxicity: 25%	Response and CRS severity correlated directly with tumor burden
Sauter CS[55]; NHL; N=15	DL1: 350 DL2: 700	All patients: ORR/CR, 53%	CRS: All grade, 40%; Grade ≥3, 20% Neurotoxicity: 67% (all Grade ≥3)	Only 1 patient treated at DL2 and developed Grade 4 CRS. Study then enrolled all patients at DL1
Hu Y[56]; ALL; N=15	Range: 77-686[e]	All patients: ORR/CR, 80%	CRS: All grade, 67%; Grade ≥3, 27% Neurotoxicity: All grade, 33%	Overall response was high, and CR was seen at all doses. Dose response was not seen. Authors also noted that there was no correlation between dose and CAR peaks
Porter D[57]; CLL; N=14	14-1100 (median, 160)	ORR, 57%; CR, 29%	CRS: All grade, 64%; Grade ≥3, 43% Neurotoxicity: All grade, 36%; Grade ≥3, 7%	Degree of expansion of CTL019 cells and the duration of persistence were correlated to response. There was no correlation between T cell dose and response and between T cell dose and CRS incidence
Frigault MJ [58]; MM; N=12	DL1: 100 DL2: 300	CR: 75%; ORR: 100%	CRS: All grade, 92%; Grade ≥3, 7% Neurotoxicity: All grade, 15%; Grade ≥3, 7%	No correlation between dose and response was noted
Baumeister SH[59]; AML/MDS and multiple myeloma; N=12	DL1: 0.738; DL2: 2.15; DL3: 6.92; DL4: 24.5	No response. All patients received subsequent therapy	No toxicity	Response was not seen

Ali SA[60] ; Multiple myeloma ; N=12	DL1: 21 DL2: 70 DL3: 210 DL4: 630	All patients: ORR, 33%; CR, 8%; DL1: ORR/PR, 33%; DL2: ORR, 0%; DL3: ORR/ VGPR, 33%; DL4: ORR, 66%; CR, 33%	CRS: All grade, 50%; Grade ≥3, 25% Neurotoxicity: All grade, 25%; Grade ≥3, 8%	Response tended to be higher/better with higher dose. Incidence of CRS also tended to be higher at higher dose levels
Enblad G[61]; Leukemia/Lymphoma; N=11	DL1: 32 DL2: 160 DL3: 320	All patients: ORR/CR, 40%; DL1: ORR/CR, 50%; DL2: ORR/CR, 25%; DL3: ORR/CR, 44%	Not reported clearly	No correlation between dose and response. Severe CRS and neurotoxicity seen in patients receiving high dose
Yan ZX[62]; NHL; N=10	DL1: 25; DL2: 50; DL3: 100	ORR, 100%; CR, 67% in all dose levels and in combined cohort	CRS: Grade 1, 100% Neurotoxicity: Grade ≥3, 10% (only one case)	Overall response was high and no correlation between dose and response. Study noted that peak CART did not correlate with dose but was higher in patients with CR
Magnani CF[63]; B-ALL; N=9 (adults only)	DL1: 70; DL2: 210; DL3: 525; DL4: 1050	All adult patients: ORR/CR: 60% DL1: NR; DL2: ORR/CR, 100%; DL3: ORR/CR, NR; DL4: 100%	CRS: All grade, 23%; Grade ≥3, 0% No neurotoxicity	Correlation seen between dose & disease response; & CRS events were noted only in highest dose
Gu R[64]; B-ALL; N=9 (adults only)	350	All adult patients: ORR/CR: 89%	CRS: All grade, 95%; Grade ≥3, 45% Neurotoxicity: All grade, 65%; Grade ≥3, 40%	Single dose was used in the study and the study did not analyze correlation between dose and response
Geyer MB[65]; CLL; N=8	DL1: 210; DL2: 700; DL3: 2100	All patients: ORR/CR, 25%	CRS: All grade, 50%; Grade ≥3, 0% No neurotoxicity	Dose response was not seen. Study noted that CART expansion was not satisfactory possibly due to insufficient lymphodepletion. All CRS events happened in the high dose group

Cruz CR[66]; B-ALL; N=8	DL1[d]: 19-34 DL2 [d]: 58-110	All patients: ORR, 50%; CR, 38%; DL1: ORR, 50%; CR, 25%; DL2: ORR/CR, 50%	No toxicity	Small sample size. CRs were higher in DL2 but overall response was not different between two groups
Kochenderfer JN[67]; FL and CLL; N=8	DL1[d]: 21 DL2 [d]: 70 DL3 [d]:210 (Dose represents total CAR+ cells)	All patients: ORR, 75%; CR, 13%; DL1: ORR/PR 50%; DL2: ORR, 100%; CR, 33%; DL3: ORR/PR, 100%	CRS: All grade, NR; Grade ≥3, 13% Neurotoxicity: All grade, NR%; Grade ≥3, 13%	Small sample size. Only DL2 had CR and response was better than DL3
Bao F[68]; DLBCL; N=5	210 or 263.9	All patients: ORR, 75%; CR, 50%	CRS: All grade, 100%; Grade ≥3, 0% Neurotoxicity: NR	Response and CRS correlated with peak CAR expansion
Eom HS[69]; Multiple subtypes; N=4	DL1: 100 DL2: 200 DL3: 400	DL1: 1 PR; DL2: 1 PD; DL3: 1 SD, 1 CR	No toxicity	Study not designed to test dose response
Ritchie DS[70]; AML; N=4	DL1: 500; DL2: 1000; DL3: 1140; DL4: 1290	Transient response seen at higher doses (1140 &1290)	CRS: All grade, 25% (grade details NR) No neurotoxicity	Study not designed to test dose response
Zhang Q[71]; B-ALL; N=4	no details	All patients: ORR/CR, 75%	CRS: All grade, 100%; Grade ≥3, 0% Neurotoxicity: NR	Study noted that efficacy positively correlated with abundance of CAR and immune cell sub-populations in bone marrow
Kalos M[72]; CLL; N=3	DL1: 140; DL2: 580; DL3: 1100	CR: 2 patients PR: 1 patient	NR	CR was seen at highest and lowest dose
Weng J[73]; B-ALL; N=3 (2, adults only)	DL1: 3.5; DL2: 35; DL3: 70	All 3 patients had CR	CRS: All grade, 100%; Grade ≥3, 33% No neurotoxicity	Small sample size. CR was seen at all doses

[a]calculated for 70 kg or 1.6 m^2 if dose was not flat; [b]adverse events are reported for the whole cohort; [c]Dose was not categorized by authors and categories were not assigned for this study because the study did not report any correlation or lack of correlation; [d]dose levels assigned for the review; NR, not reported; Patients with age >18 years were considered as adults; [e]Dose was not categorized by authors and categories were not assigned for this study because overall response rate was very low or very high.

Table S4. Cmax and AUC reported for CAR-T cells in clinical studies

First Author (reference)	CART cell peak (cells/µl)	VCN peak (copies/µg DNA)	AUC (d×copies/µg DNA)
Raje N[26]	NR	Range, 90-1800000[a]	NR
Munshi NC[4]	NR	231278	2860340
Xu J[50]	NR	74800 (range, 2282-5396510)	NR
Cohen AD[33]	NR	75339 in responders; 6368 in non-responders	561796 in responders 52391 in non-responders
Wang D[48]	NR	80000 (range, 1000-250000)[a]	700000 (range, 7000-3000000)[a]
Frigault M[58]	NR	90,147 (10,068–351,000)	644,965 (range, 76,916– 3,026,634)
Ali SA[60]	Range, 0-285[a]	NR	NR
Cao J[49]	406 (95% CI 183–596) in G3+ CRS vs 109 (95% CI 76–142) in G1-2 CRS	118 100 (95% CI 60 700-201 900) in G3+ vs 64,430 (95% CI 43 760-76 220) in G1-2	NR
Wang J[38]	NR	12650 (range, 187–44 509)	NR
Roddie C[45]	468 (range, 88-8627) (per ml)	127151.74 (range NR)	1251802.4 (range NR)
Abramson JS[2]	NR	23928.2	213730.1
Ying Z[14]	24 (1-582)	25333.5 (range, 854-250768)	249744.8 (range, 22089.3-3241025.5)
Fowler NH[8]	NR	3000 in non-responders 6280 in responders	NR
Schuster SJ[9]	NR	5530	64600
Hu Y[56]	342 (95% CI, 140–532) and 96 (95% CI, 61.5–132.8) in the grade 3 CRS group and in the non-CRS or grade 1 or 2 CRS group (per ml)	9.9e5 (95% CI, 61.5e6 – 132.8e6) and 2.2e5 (95% CI 1.5e5 –4.8e5) in the grade 3 CRS group and in the non-CRS or grade 1 or 2 CRS group	NR
Gill S[46]	536 (range, 0-3640)	90991 (range, 966-201556)	NR
Turtle CJ[31]	20-120 CD4; 10-1000 CD8	NR	NR
Yan ZX[62]	4e5 (range, 0-6.5e5) (per ml)[a]	NR	NR
Ying Z[34]	NR	2000-80000[a]	NR
Enblad G[61]	NR	Range, 80-10e8[a] (per 500 ng)	NR

Shah BD[17]	NR	Range, 0-443880	NR
Wang X[52]	NR	280 (range, 0-925) in NHL1 and 692 (range, 267-27790) in NHL2	NR
Geyer MB[41]	NR	Range, 400-2e6[a]	NR
Neelapu S[6]	30 (10-80)[a]	NR	462.3 (range, 5.1-14329.3) (d*cells/ul)
Wang M[13]	70 (1-3000)[a]	NR	NR
Shah BD[16]	40.47 (range, 6.04-76.70) in complete responders	NR	NR
Bao F[68]	276.16 cells (range, 8.8–634)	NR	NR
Sauter CS[55]	27 (range, 9-141) in progression-free and 22 (range, 0.1-851) in progressed	NR	NR
Magnani CF[63]	NR	1 e6	1.08 e6 (range, 3,915.5–4.80 e6)
Cui R[44]	NR	3540 in HBsAg-positive patients and 4801 in for anti-HBc positive patients	NR
Wang CM[47]	NR	Range, 500-4250[a]	NR
Ramos CA[21]	NR	Range, 1000-100000[a]	NR
Ramos CA[53]	NR	Range, 2-3000[a]	NR
Ritchie DS[70]	NR	Range, 0-700[a] (copies/1000 cells)	NR
Baumeister SH[59]	290 for CD8 and 15 for CD4[a]	NR	NR

Median and/or range are reported unless otherwise indicated. NR, not reported. [a]Data estimated approximately from figures.

Supplementary Table S5. Time to response, peak expansion, and CRS and/or neurotoxicity in studies with sample size

First Author [#] Indication	Onset time for peak expansion	Onset time for response	Onset time for CRS Onset time for neurotoxicity (if reported separately)
Bishop M [1] LBCL	7-11 days[a]	NR	4 (1-27) days for CRS 5 (3-93) days for neurotoxicity
Abramson JS [2] DLBCL	12 (IQR, 10-14) days	1 (range, 0.7-8.9) months	5 (range, 1-14) days for CRS 9 (range, 1-66) days for neurotoxicity
Munshi NC [4] Multiple myeloma	11 (range, 7-21) days	1 (range, 0.5-8.8) months	1 (IQR, 1-12) days for CRS 2 (IQR, 2-10) days for neurotoxicity
Neelapu SS [6] DLBCL	7 days[a]	1 (range, 0.8-6) months	2 (range, 1-12) days for CRS 5 (range, 1-17) days for neurotoxicity
Berdeja JG [7] Multiple myeloma	12.7 (range, 8.7-54.6) days	2.6 (range, 1-6.1) months	7 (IQR, 5-8) days for CRS 8 (IQR, 6-8) days for neurotoxicity
Fowler NH [8] FL	10 (IQR, 9-14) days in responders 13 (IQR, 10-15) days in non-responders	NR	4 (IQR, 2-7) days for CRS 9 (IQR, 5-35) days for neurotoxicity
Sesques P [12] DLBCL	NR	NR	3 (range, 0-8) days for CRS 6 (range, 4-17) days for neurotoxicity
Li M [11] B-ALL	11-15 days[a]	NR	NR
Wang M [13] MCL	15 days	NR	2 (range, 1-13) days for CRS 7 (range, 1-32) days for neurotoxicity
Ying Z [14] B-cell lymphoma	8.5 (range, 4-27) days	28 days	4.5 (range, 1-10) days for CRS 8.5 (range, 1-49) days for neurotoxicity
Zhao WH [15] Multiple myeloma	NR	NR	NR
Shah BD [16] B-ALL	15 (IQR, 11-16) days	NR	5 (IQR, 3-7) days for CRS 9 (IQR, 7-11) days for neurotoxicity
Shah BD [17] ALL	7-14 days	NR	2 (IQR, 1-5) days for CRS 6 (IQR, 3-8) days for neurotoxicity
Jiang H [18] B-ALL	NR	1 month (range, NR)	NR
Ramos CA [21]	2-3 weeks	NR	10 days (range, 7-24 days) for

HL			CRS
Pan J[25] B-ALL	12-15 days	NR	7 (range, 0-17) days for CRS 8 (range, 1-17) days for neurotoxicity
Raje N [26] Multiple myeloma	11 (range[a], 7-30) days at doses ≥150 million cells	NR	2 (range, 1-25) days for CRS
Turtle CJ [31] B-ALL	Approximately 10 days[a]	NR	6 hours to 9 days for CRS 1-11 days for neurotoxicity
Schuster SJ [9] DLBCL/FL	8 days (range, 6-14 days)	NR	NR
Cohen AD [33] Multiple myeloma	Range, 10-14 days	NR	4 (range, 1-11) days for CRS
Ying Z [34] B cell lymphoma	7-15 days	NR	NR
Wang J [38] B-ALL	11 days (range, 7-14 days)	14 days	NR
Casadei B [37] LBCL	NR	1-3 months	2 (range, 0-7) days for CRS 4 (range, 1-12) days for neurotoxicity
Zhou X [39] DLBCL	14 days (range, NR)	58 (range, 29-63) days	6 (range, 2-7) days for CRS 33 days for neurotoxicity (only 1 patient)
Hirayama AV [40] FL	NR	29 (range, 27-42) days	NR
Geyer MB [41] CLL/NHL	7-14 days	NR	1 (range, 0-2) days for CRS
Rossi J [42] DLBCL and others	7-14 days	NR	NR
Cui R [44] DLBCL	7-14 days	NR	3 days (range, 1-8 days) for CRS
Roddie C. [45] B-ALL	13 (range, 7-21) days	NR	6 (range, 2-31) days for CRS 22 (range, 14-41) days for neurotoxicity
Gill S [46] CLL	10 (range, 7-28) days	NR	2 (range, 2-12) days for CRS
Wang CM [47] HL	3-9 days	NR	Fever within 1 day; other toxicities 2-4 weeks
Wang D [48] MM	12 (range, 7-26) days	15 (range, 14-62) days	2 (range, 0-7) days
Cao J [49] ALL	7-14 days	1 month	6 (range, 1-9) days
Xu J [50] Multiple myeloma	6-30 days[a]	NR	7-14 days
Cornell R [51] MM and PCL	28 days	NR	NR
Wang X [52]	Approximately 2	NR	NR

NHL	weeks (range NR)		
Ramos CA [53] ALL/NHL	Within 7 days (range NR)	NR	NR
Sauter CS [55] NHL	NR	NR	2.5 (range, 0-10) days for CRS 5 (range, 1-6) days for neurotoxicity
Hu Y [56] ALL	7-10 days	1 month	2.5 (range, 1-10) days for CRS
Porter D [57] CLL	NR	NR	7 (range, 1-14) days
Frigault MJ [58] MM	11 (range, 7-21) days	28 days	2.5 (range: 0-6) days (DL1); 4.5 (range, 3-6) days (DL2) for CRS Neurotoxicity: 2 days (DL1); 6 days (DL2)
Baumeister SH [59] AML/MDS and multiple myeloma	2 weeks (range NR) for CD8 cells 1 month (range NR) for CD4 cells	NR	NR
Ali SA [60] Multiple myeloma	7-15 days[a]	NR	NR
Enblad G [61] Leukemia/Lymphoma	7 days (range, 7-35 days)[a]	NR	NR
Yan ZX [62] NHL	11-29 days	NR	6 (range, 3-11) days for CRS
Magnani CF [63] B-ALL	14 (range, 7-22) days	NR	NR
Gu R [64] B-ALL	14 days (range NR)	NR	4 days (range NR)
Geyer MB [65] CLL	NR	NR	1.5 (range, 1-3) days for CRS
Bao F [68] DLBCL	7-14 days	NR	NR
Eom HS [69] Multiple subtypes	NR	4 weeks[a]	NR
Ritchie DS [70] AML	9 (range, 4-14) days[a]		NR
Zhang Q [71] B-ALL	14 days	NR	Within 14 days
Kalos M [72] CLL	7-30 days[a]	NR	7-21 days (all toxicities)
Weng J [73] B-ALL	12, 10 & 10 days	46, 10 & 18 days	7, 9 and 7 days for CRS
Feng J [74] T-LBL	NR	4 weeks	NR

Average or median time to onset was reported in the studies. NR, not reported. IQR, inter quartile range. [a]Estimated from the data presented in the figure/table.

Supplementary Table S6. Association of tumor burden with response, CRS and neurotoxicity in studies with sample size, N≤50

First Author [#] Indication	Tumor burden cut-off	Association with response, CRS and neurotoxicity
Abramson JS [2] DLBCL	SPD≥50 cm^2	Patients with low tumor burden (SPD<50 cm^2) had higher rate of overall and complete response. High TB was associated with CAR-T peak and higher incidence of CRS and neurological events
Zhang X [3] B-ALL	Not defined	Patients with >20% bone marrow blasts had lower CR rate
Munshi NC [4] Multiple myeloma	BMPCs≥50%	Patients with BPMCs<50% had higher rate of overall response
Neelapu SS [6] DLBCL	Disease burden≥10 cm	Patients without bulky disease had better overall response rate
Schuster SJ [9] DLBCL	Tumor volume≥100 ml	Patients with tumor volume<100 ml had better overall response rate
Sesques P [12] DLBCL	Disease burden>10 cm	Patients with bulky disease had worse OS
Li M [11] B-ALL	High TB Group: Disease burden ≥5% BM blasts	Patients in high tumor burden group had comparatively lower CR rate, OS and EFS. Incidence of severe CRS was high in patients with high TB but there was no difference in neurotoxicity. High TB was associated with high CAR-T peak
Wang M [13] MCL	Tumor burden≥median	Patients with tumor burden≥median had better overall response rate
Jiang H [18] B-ALL	Disease burden≥5% BM blasts	Patients with disease burden≥5% BM blasts had severe CRS incidence
Park JH [19] B-ALL	Disease burden≥5% BM blasts or EMD	Patients with disease burden≥5% BM blasts had severe CRS and neurotoxicity incidence; lower overall response rate and lower event-free survival and OS
Raje N [26] Multiple myeloma	Tumor burden≥50% CD138-positive cells	Patients with tumor burden ≥50% CD138-positive cells had lower overall response rate; no difference was noted in incidence of CRS

An F [29] B-ALL	Bone marrow blasts≥20%	No difference in response between patients with BM blasts<20% and ≥20%
Turtle CJ [31] B-ALL	Not defined	Study used a tumor burden-based risk adaptive dosing in patients
Schuster SJ [32] DLBCL/FL	Not defined	Tumor burden was not significantly different between responders (median tumor size, 22 cm^2; range, 3-100) and non-responders (median tumor size, 30 cm^2; range, 13-157)
Tu S [35] ALL	Bone marrow blasts≥50%	Patients with low tumor burden (<50% blasts) were more likely to have MRD-negative remission
Turtle CJ [36] CLL	Not defined	Linear correlation between CAR-T cell peak and tumor burden; but patients with high tumor burden had high CRS, neurotoxicity incidence; patients with higher lymph node bulk were less likely to responds
Wang J [38] B-ALL	Not defined	Patients with over 30% blasts had lower response rate*
Zhou X [39] DLBCL	Disease scale≥5 cm	Patients with low tumor burden (<5 cm) had comparatively less response rate
Geyer MB [41] CLL/NHL	Not defined	No correlation between tumor burden and response
Roddie C. [45] B-ALL	Not defined	Study used risk adoptive dosing design in patients with high TB. Authors noted that immunotoxicity was low.
Cao J [49] ALL	Not defined	No correlation with response or CRS
Xu J [50] Multiple myeloma	Clonal BM plasma cells≥10%	No difference in CRS events between two groups
Davila M [54] B-ALL	Not Defined	Study noted that high TB was associated with response and with severe CRS
Sauter CS [55] NHL	Not defined	No correlation between SPD and rate of response or CRS or neurotoxicity
Hu Y [56]	Not defined	Tumor burden at the end of

ALL		lymphodepletion regimen correlated with grade 3 CRS
Magnani CF[63] B-ALL	Not defined	Patients with low tumor burden (<5%) after lymphodepletion tended to have higher response rate*; CAR-T cell expansion (AUC, C_{max} were higher in patients with high tumor burden (>15%)
Gu R[64] B-ALL	Bone marrow blasts≥50%	Patients with high tumor burden (≥50%) had higher incidence of severe CRS. No correlation with response*.
Zhang Q[71] B-ALL	Not defined	Patients with high tumor burden (>10%) did not respond or had relapse within 2 months
Kalos M [72] CLL	Not defined	All 3 patients had >40% tumor burden in the BM and all three had response

SPD, Sum of product diameter; BMPCs, Bone marrow plasma cells; UNL, upper normal level; EMD, extramedullary disease; OS, overall survival; *interpretation based on data from the study

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