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Dose–response correlation for CAR-T cells: a systematic review of clinical studies

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ABSTRACT

The potential of chimeric antigen receptor (CAR) T cells to successfully treat hematological cancers is widely recognized. Multiple CAR-T cell therapies are currently under clinical development, with most in early stage, during which dose selection is a key goal. The objective of this review is to address the question of dose-dependent effects on response and/or toxicity from available CAR-T cell clinical trial data. For that purpose, systematic literature review of studies published between January 2010 and May 2022 was performed on PubMed and Embase to search clinical studies that evaluated CAR-T cells for hematological cancers. Studies published in English were considered. Studies in children (age <18 years), solid tumors, bispecific CAR-T cells and CAR-T cell cocktails were excluded. As a result, a total of 74 studies met the inclusion criteria. Thirty-nine studies tested multiple dose levels of CAR-T cells with at least >1 patient at each dose level. Thirteen studies observed dose-related increase in disease response and 23 studies observed dose-related increase in toxicity across a median of three dose levels. Optimal clinical efficacy was seen at doses 50–100 million cells for anti-CD19 CAR-T cells and >100 million cells for anti-BCMA CAR-T cells in majority of studies. The findings suggest, for a given construct, there exists a dose at which a threshold of optimal efficacy occurs. Dose escalation may reveal increasing objective response rates (ORRs) until that threshold is reached. However, when ORR starts to plateau despite increasing dose, further dose escalation is unlikely to result in improved ORR but is likely to result in higher incidence and/or severity of mechanistically related adverse events.

INTRODUCTION

Cancer immunotherapy has made giant strides in the past 10 years with the development of multiple strategies including tumor-specific chimeric antigen receptor (CAR-) T cell therapies, monoclonal antibodies targeting checkpoint blockers and oncolytic viruses.[1–6] CAR-T cell therapy demonstrated impressive results in hematological cancers with objective response rates (ORRs) as high as 100% noted in some studies.[7 8] To date, six CAR-T cell therapies including axicabtagene ciloleucel (axi-cel), brexucabtagene autoleucel (brexu-cel), tisagenlecleucel (tisa-cel), lisocabtagene maraleucel (liso-cel), idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) have been approved by the US Food and Drug Administration (FDA) for different hematological malignancies with wide-ranging doses such as 60–600 million cells for tisa-cel, 50–110 million cells for liso-cel and 2 million cells/kg body weight for axi-cel (table 1). While currently available CAR-T cell therapies showed excellent response rates, limitations such as durability of efficacy, incidence of adverse events, including cytokine release syndrome (CRS) and neurotoxicity, and production-related issues warrant continued advancement of novel CAR-T cell therapies.

To address the limitations and improve treatment outcomes, several CAR-T cell therapies of autologous and allogeneic origin are currently being developed, with most in early stages of clinical development. Dose selection is a critical determinant of the success of any cancer therapeutic, including cell therapies. Recommendation of subtherapeutic dose for the pivotal study could result in lower efficacy, whereas excessive dose could result in higher incidence and/or greater severity of adverse events. Typically phase 1 dose escalation studies are performed to recommend possible effective dose and maximum tolerated dose (MTD). Unless MTD is reached during the phase 1 study, determination of further dose escalation impact on efficacy and/or the incidence or severity of adverse events may not be possible. Dose selection may be more difficult for therapies like CAR-T cells, which cannot be described by typical principles of clinical pharmacology, such as receptor occupancy and elimination kinetics.

Currently, initial dose recommendations are made based on preclinical models and empiric data from previous relevant studies with similar constructs in the same cancer type. However, the question of possible increase in efficacy with higher dose continues to remain in clinical development discussions because there is conflicting evidence on CAR-T cell

Table 1 US Food and Drug Administration (FDA)-approved CAR-T cell therapies (current as of February 2022)

CAR-T therapy	Target	Indication	Dose
Axicabtagene ciloleucel	CD19	Relapsed and refractory B cell lymphoma including DLBCL and follicular lymphoma after two or more lines of therapy	2 million cells/kg body weight with a maximum of 200 million cells
Brexucabtagene autoleucel	CD19	Relapsed and refractory mantle cell lymphoma	2 million cells/kg body weight with a maximum of 200 million cells
		Relapsed or refractory B cell precursor acute lymphoblastic leukemia	1 million cells/kg body weight with a maximum of 100 million cells
Tisagenlecleucel	CD19	Children and young adults (up to 25 years of age) with B cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse	0.2–5 million cells/kg body weight, if the patient body weight is ≤50 kg; 10–250 million cells if the patient body weight is >50 kg
		Adults with relapsed or refractory B cell lymphoma after two or more lines of systemic therapy	60–600 million cells
Lisocabtagene maraleucel	CD19	Relapsed and refractory B cell lymphoma including DLBCL after two or more lines of therapy	50–110 million cells consisting of 1:1 ratio of CAR^+ CD4 and CD8 cells
Idecabtagene vicleucel	BCMA	Multiple myeloma after four or more lines of therapy	300–460 million cells
Ciltacabtagene autoleucel	BCMA	Multiple myeloma after four or more lines of therapy	0.5–1 million cells/kg body weight with a maximum of 100 million cells

CAR, chimeric antigen receptor; DLBCL, diffuse large B cell lymphoma.

dose–response. Positive correlation between increased response and higher dose levels was reported in some studies,[9 10] whereas no correlation was seen and efficacy was similar at all dose levels in other studies.[11] This review aimed to perform systematic literature review of CAR-T cell studies in adult patients with hematological malignancies and summarize the findings on dose–efficacy and dose–safety correlations. The main question the review intended to address was if there is a correlation between dose of CAR-T cell therapy and response in patients and if the efficacy increases or decreases in a dose-dependent fashion. Second, the study aimed to understand if the incidence or severity of cytokine release syndrome (CRS) and neurotoxicity was impacted by dose. Finally, the study aimed to document the findings on predictors of response including peak expansion (Cmax), area under the expansion curve (AUC) and tumor burden.

METHODS

This systematic review followed the guidelines defined by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement.[12]

Search criteria

The following search terms were used in the literature search for related articles: "CAR", "chimeric antigen receptor", "CAR-T cell", "acute lymphoblastic leukemia", "ALL", "diffuse large B-cell lymphoma", "DLBCL", "multiple myeloma" and "MM". Searches were conducted on PubMed and Embase in August 2021 and November 2021, respectively. A total of seven searches were conducted on each database: (1) "CAR" or "chimeric antigen receptor"; (2) "CAR-T cell" and "acute lymphoblastic leukemia" or "ALL"; (3) "CAR-T cell" and "diffuse large B-cell lymphoma" or "DLBCL"; (4) "CAR-T cell" and "multiple myeloma" or "MM"; (5) "chimeric antigen receptor" and "acute lymphoblastic leukemia"; (6) "chimeric antigen receptor" and "diffuse large B-cell lymphoma"; and (7) "chimeric antigen receptor" and "multiple myeloma".

Eligibility

All clinical prospective and retrospective studies reporting outcomes in adult patients (age ≥18 years) with hematological malignancies including acute lymphoblastic leukemia (ALL), diffuse large B cell lymphoma (DLBCL) and multiple myeloma (MM) met the inclusion criteria for consideration. Studies were excluded if they met any of the following exclusion criteria: (1) articles reported in languages other than English; (2) conference presentations and abstracts; (3) studies that did not use lymphodepletion regimen; (4) studies in children; (5) studies in solid tumors; (6) studies using bispecific CAR-T cells; (7) studies using CAR-T cell cocktails; (8) studies using bispecific antibodies; (9) studies using antibody drug conjugates; (10) articles reporting additional outcomes/post hoc analyses of previously published study; (11) preclinical studies; (12) systematic literature review articles; and (13) review articles. Bispecific CAR-T cells, solid tumors and studies in children were excluded from the review because the kinetics, efficacy and safety can be comparatively different.

Data extraction

Studies meeting the eligibility criteria were screened based on their title, abstract and full text by two independent reviewers. Reasons for excluding studies were recorded, and included studies were cross checked prior to data extraction such that any discrepancy arising between the two reviewers was resolved through discussion. The following data were extracted from each study's full text: study details (author name, year of publication and country), patient characteristics (number of patients, cancer subtype, lines of prior therapy and tumor burden), CAR-T cell details (dose and regimen, target antigen, costimulatory domains, gene transfer method, generation of CAR-T cells and persistence of CAR-T cells), efficacy outcomes (overall survival (OS); progression-free survival (PFS); objective response rate (ORR); complete response rate (CRR); onset of response, duration of response (DoR), and markers of response and safety outcomes (CRS and neurotoxicity, onset of CRS/neurotoxicity).

Studies that reported outcomes from multiple doses of CAR-T cells were identified, and studies in which at least 50 patients received CAR-T therapy were prioritized. Dose was calculated for 70 kg for studies that used body weight-based dose and for 1.6 m^2 for studies that used body surface area-based dose to convert to a flat dose value in order to compare the dose across studies.

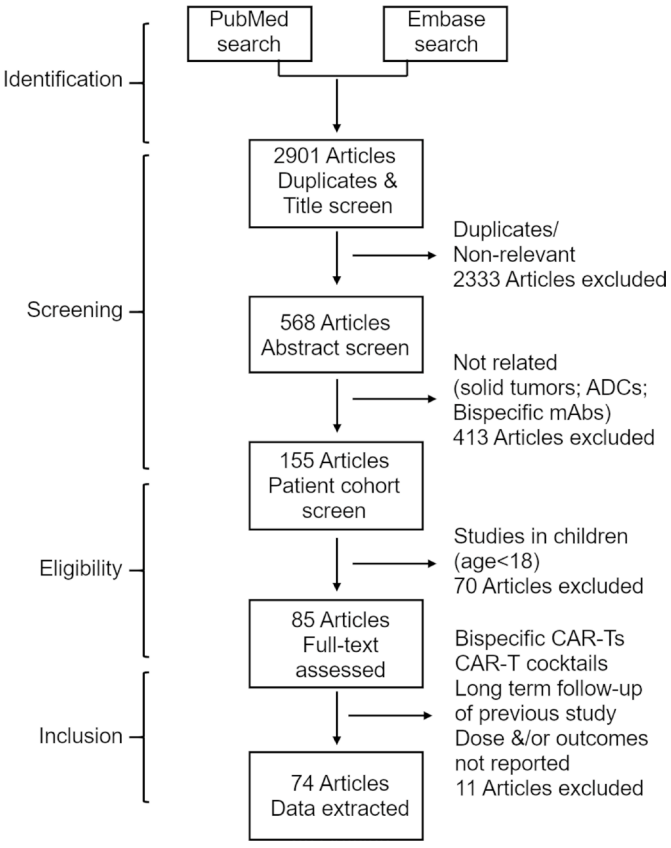

Figure 1 Study flow and selection of articles. CAR, chimeric antigen receptor.

RESULTS

Characteristics of selected studies

Literature search for clinical articles published between 1 January 2010 and 15 May 2022 identified 2901 papers on CAR-T cells. After removing duplicates and screening for relevant articles based on title, abstract and then full text by two reviewers, 74 articles were selected for systematic review and data extraction (figure 1).[13–66] Among the included studies, 19 (26%) studies had at least 50 patients treated, and 55 (74%) studies had <50 patients (online supplemental table S1). Quality of included studies was assessed using the guidelines for non-randomized single-arm studies (online supplemental table S2).[67–70] Majority of the studies included patients with ALL (n=30, 40%) or DLBCL (n=21, 28%) or MM (n=17, 23%). In total, 3109 patients with hematological cancers were treated including 927 (30%) DLBCL patients, 1054 (34%) B-ALL patients and 501 (16%) MM patients.

Multiple dose levels of CAR-T cells with >1 patient at each dose level were tested in 39 studies (table 2) including 9 (23%) studies with cohort size of at least 50 patients and 36 (92%) studies with cohort size of at least 10 patients. The TRANSCEND study by Abramson *et al*[11] in patients with large B cell lymphoma was the largest study with 269 patients evaluating three dose levels of treatment. Majority of the multidose studies targeted CD19 (26/39; 67%) and had single intracellular domain (33/39; 85%). Intracellular signaling domain included 4–1-BB in 19 (49%) studies, CD28 in 13 studies (33%), 4–1-BB and CD28 in 2 (5%) studies and CD28 and CD27 or OX40 in 2 (5%) studies (table 2).

Factors associated with response and incidence of CRS and neurotoxicity

Dose

To evaluate the dose–response association, studies that tested at least two dose levels and had more than one patient per dose level were included in the first step. Determination of CAR-T cell dose varied across studies, and flat dose of fixed number of cells were given in some studies, whereas other studies dosed patients on cells per kilogram (kg) body weight or cells per body surface area. To compare the dose across studies, dose was normalized and converted to flat dose by calculating the dose for 70 kg body weight or for 1.6 m^2 for studies that used body weight-based dose and body surface area-based dose, respectively. Out of 39 studies that tested at least two dose levels of CAR-T cells, association between dose administered and ORR/CRR (efficacy) was observed in 13 (33%) studies (table 2). When the studies with cohort size of at least 50 patients were compared (n=9), one study reported clear increase in response at higher doses,[10] two studies reported increase in response from DL1 to DL2 but no further increase at DL3[71 72] and one study observed positive correlation between dose and response in patients who had SD or PD at the time of infusion.[73] Intriguingly, the ORR and/or CR rate tended

Table 2 Summary of studies evaluating multiple dose levels

First author	Indication	Target	Signal domain	Dose* (million cells)	Response higher at higher dose	Toxicity higher at higher dose
Bishop *et al*[73]	LBCL	CD19	4–1-BB	Range: 40–590 (response correlation assessed per 100 million increments in dose)	Y	NR
Abramson *et al*[11]	DLBCL	CD19	4–1-BB	DL1: 50; DL2: 100; DL3: 150	N	NR
Zhang *et al*[77]	B-ALL	CD19	4–1-BB & CD28	Range: 1.4–371 DL1: <21 DL2: ≥21	N	N
Munshi *et al*[10]	MM	BCMA	4–1-BB	DL1: 150; DL2: 300; DL3: 450	Y	Y
Fowler *et al*[74]	FL	CD19	4–1-BB	Range: 60–600†	N	Y
Ying *et al*[75]	B-cell lymphoma	CD19	4–1-BB	100 or 150	N	Y
Zhao *et al*[71]	MM	BCMA	CD28	Range: 4.9 to 147†	Y	Y
Shah *et al*[72]	B-ALL	CD19	CD28	DL1: 35; DL2: 70; DL3: 140	Y	Y
Park *et al*[76]	B-ALL	CD19	CD28	DL1: 70; DL2: 210	N	NR
Ramos *et al*[43]	HL	CD30	No data	DL1: 32; DL2: 160; DL3: 320	N	N
Frey *et al*[30]	B-ALL	CD19	4–1-BB	DL1: 50; DL2: 500	Y	Y
Raje *et al*[42]	MM	BCMA	4–1-BB	DL1: 150; DL2: 450	Y	Y
Turtle *et al*[54]	NHL	CD19	4–1-BB	DL1: 14; DL2: 140; DL3: 1400	N	Y
Frey *et al*[29]	CLL	CD19	4–1-BB	50 or 500	Y	Y
Li *et al*[38]	MM	BCMA	CD28	Range: 378–1750 DL1: ≤784; DL2: >784	N	N
Turtle *et al*[53]	B-ALL	CD19	4–1-BB	DL1: 14; DL2: 140; DL3: 1400	N	Y
Ying *et al*[64]	B cell lymphoma	CD19	4–1-BB	DL1: 3–6; DL2: 60–190; DL3: 200–400	Y	N
Tu *et al*[52]	B-ALL	CD19	CD28 and CD27	Range: 6.2–280 DL1: <35 DL2: ≥35	N	Y
Turtle *et al*[55]	CLL	CD19	4–1-BB	DL1: 14; DL2: 140; DL3: 1400	N	Y
Geyer *et al*[32]	CLL	CD19	CD28	DL1: <700; DL2: >700	N	N
Brudno *et al*[17]	DLBCL	CD19	CD28	DL1: 46.2; DL2: 140; DL3: 420	N	N
Cui *et al*[24]	DLBCL	CD19	No data	Range: 70–490 DL1‡: <140; DL2‡: 140–<280; DL3‡: ≥280	N	Y
Wang *et al*[56]	HL	CD30	4–1-BB	Range: 770–1470§	N	N
Wang *et al*[57]	MM	BCMA	4–1-BB	DL1: 70; DL2: 210; DL3: 420	N	Y
Cornell *et al*[22]	MM	BCMA	CD28	DL1: 30; DL2: 100; DL3: 300; DL4: 1000	N	Y
Wang *et al*[59]	NHL	CD19	CD28	DL1: 25; DL2: 50; DL3: 100; DL4: 200	N	Y
Ramos *et al*[44]	B-ALL	K-LIGHT CHAIN	CD28	Range: 32–320§	N	N

Continued

Table 2 Continued

First author	Indication	Target	Signal domain	Dose* (million cells)	Response higher at higher dose	Toxicity higher at higher dose
Hu *et al*[35]	B-ALL	CD19	4–1-BB	Range: 77–686¶	N	N
Porter *et al*[41]	B-ALL	CD19	4–1-BB	Range: 14–1100†	N	N
Frigault *et al*[92]	MM	BCMA	41BB and CD3	DL1: 100; DL2: 300	N	Y
Baumeister *et al*[16]	AML	MICA/MICB	NKG2D	DL1: 0.738; DL2: 2.15; DL3: 6.92; DL4: 24.5	N	N
Ali *et al*[13]	MM	BCMA	CD28	DL1: 21; DL2: 70; DL3: 210; DL4: 630	Y	Y
Enblad *et al*[26]	Lymphoma	CD19	4–1-BB and CD28	DL1: 32; DL2: 160; DL3: 320	N	Y
Yan *et al*[63]	NHL	CD19	4–1-BB	DL1: 25; DL2: 50; DL3: 100	N	NR
Magnani *et al*[39]	B-ALL	CD19	CD28 and OX40	DL1: 70; DL2: 210; DL3: 525; DL4: 1050	Y	y
Geyer *et al*[31]	CLL	CD19	CD28	DL1: 210; DL2: 700; DL3: 2100	N	Y
Cruz *et al*[23]	B-ALL	CD19	CD28	DL1‡: 19–34; DL2‡: 58–110	Y	Y
Kochenderfer *et al*[37]	CLL	CD19	CD28	DL1‡: 21; DL2‡: 77–91; DL3‡: 119–210	Y	NR
Cohen *et al*[21]	MM	BCMA	4–1-BB	DL1**: 10–50; DL2, 100–500	Y	Y

*Calculated for 70 kg or 1.6 m^2 if dose was not flat.
†Granular dose details not provided but text described correlation (or lack of) details.
‡Dose categories were assigned from the dose range used in the study.
§Dose was not categorized by authors, and categories were not assigned for this study because overall response rate was very low.
¶Dose was not categorized by authors, and categories were not assigned for this study because overall response rate was high and occurred at all doses.
**Study included a cohort without lymphodepletion, which was excluded.
N, no; NR, not reported; Y, yes.

to be slightly better in the lower dose level cohorts in the studies that reported no correlation between dose and disease response (table 2, online supplemental table S3).

Within the studies that showed association between dose and ORR, the starting dose was comparatively lower (<30 million cells),[13 29 30 37 66 72] whereas the studies that showed no association between dose and disease response, the starting dose or DL1 was over 50 million cells.[11 74–76] The study by Zhao *et al* used a lower DL1 (21 million cells for 70 kg) and concluded that there was no association between CAR-T cell dose and response. However, authors discussed that only 20% (n=2/10) of patients in the DL1 group achieved PR or more, which was lower compared with other dose levels in the study. Similarly, DL1 in the Zuma-3 study[72] observed a positive dose response between DL1 (35 million cells for 70 kg) and DL2 (70 million cells for 70 kg) but did not see further increase in ORR in DL3 (140 million cells for 70 kg) cohort. While inconclusive, this suggests that very low doses of CAR T cells may not reach the threshold of full clinical activity which, when reached, results in maximal ORR/CR that cannot be improved on with increasing dose. In contrast, DL1 in the ide-cel pivotal study was 150 million cells[10] and the ORR as well as CR/sCR rate increased from DL1 to DL2 (300 million cells) and to DL3 (450 million cells) indicating that in cases where optimal clinical activity is not achieved at 100–150 million cells, further increase may increase the ORR.

To evaluate if there were any possible differences in association due to difference in target antigen or intracellular domains, studies that evaluated multiple doses were separated based on target antigen and on intracellular domains and the dose–response and dose–safety association was evaluated. As illustrated in figure 2, 8/26 (31%) studies targeting CD19 and 5/9 (55%) studies targeting BCMA noted a positive correlation between dose and ORR/CRR. Similar results were seen (figure 2) when studies were categorized based on intracellular signaling domain (single vs dual) and type of intracellular signaling domain (4–1-BB vs CD28). Interestingly, the trends seen when studies were separated based on antigen or signaling domain were in line with the trend seen with entire cohort. Association between dose–response was mainly at doses below the threshold of optimal clinical activity, but when optimal clinical activity was reached, further escalation increased toxicity without increasing ORR.

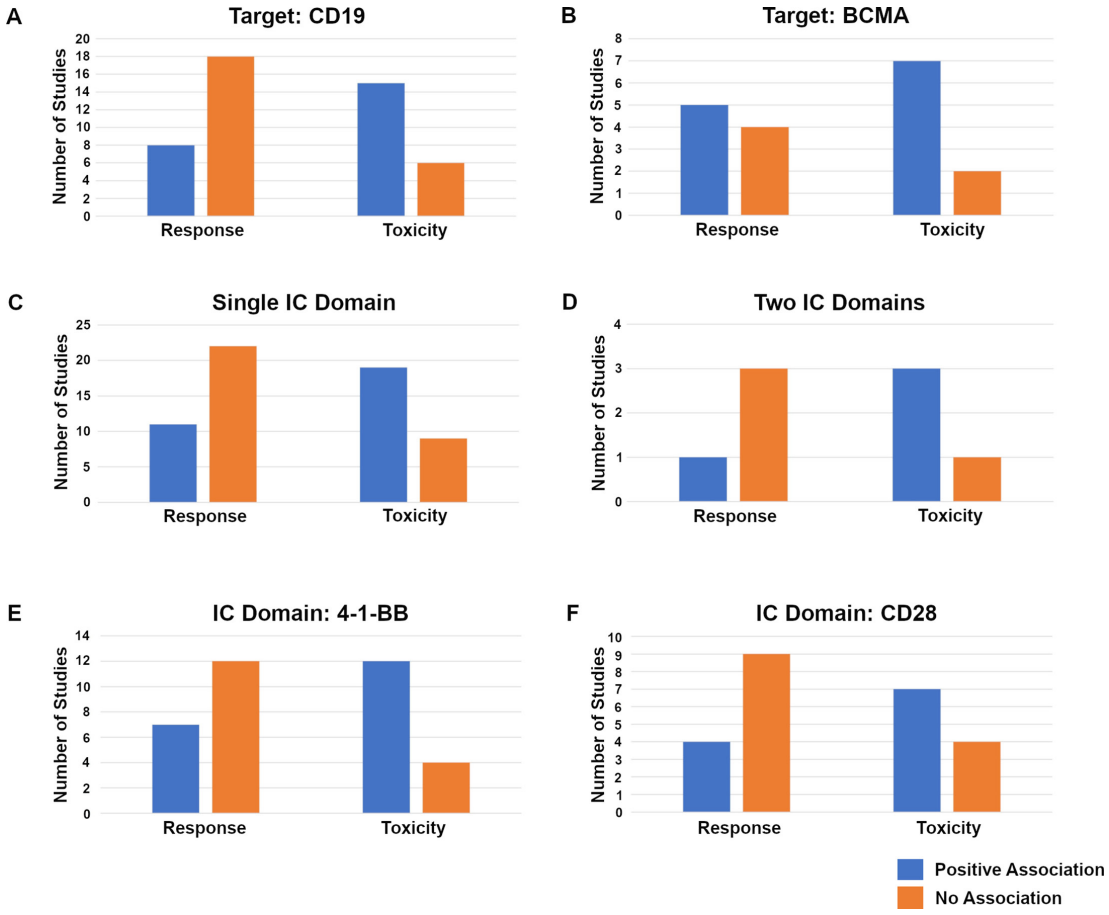

Figure 2 Response and toxicity association with dose in studies categorized by (A) CAR-T cells targeting CD19, (B) CAR-T cells targeting BCMA, (C) CAR-T cells with single intracellular (IC) domain, (D) CAR-T cells with two IC domains, (E) CAR-T cells with 4–1-BB IC domain and (F) CAR-T cells with CD28 IC domain. Positive association with dose was recorded as yes or no.

Dose–safety association was less frequently explored or reported compared with dose–response association. Out of the 39 studies that commented on dose–response correlation, 34 (87%) studies either commented on incidence and/or severity of CAR-T related adverse events including CRS and immune cell associated neurotoxicity syndrome (ICANS) or reported the adverse events (AEs) separately at different dose levels. Increased incidence and/or severity of CRS/ICANS was observed in 23 (68%) studies, and 11 (32%) studies noted no association between dose and toxicity (table 2). Out of 11 studies with cohort size over 50 patients, seven (64%) studies observed higher adverse events,[10 71 72 75] one (9%) study noted no association with dose[77] and three (27%) studies did not comment on dose–safety association.[11 76] Top DL varied widely in the studies that showed direct correlation between dose and adverse events with dose administered ranging between 110 million cells and 1000 million cells (table 2 and online supplemental table S3). Among the 11 studies that showed no association between dose and adverse events, split or fractionated dosing was used to mitigate adverse events in four (36%) studies[32 35 38 64] and ORR was also low in three (27%) studies.[16 44 56]

CAR-T cell expansion (AUC) and peak (Cmax)

Majority of the studies did not report CAR-T cell pharmacokinetics (PKs) parameters (AUC and Cmax) at individual dose levels. PK data reported in the studies were extracted and listed in online supplemental table S4. Disease response, adverse event incidence and adverse event severity were clearly associated with CAR-T cell expansion (see 'Findings on association with dose' column in table 2 and online supplemental table S3). Almost all studies that reported the factors associated with response noted that the disease response and/or CRS incidence or severity correlated directly with AUC or Cmax of CAR-T cells. Even in the studies that did not see a correlation between dose and disease response,[11 76] CAR-T cell PK was shown to be directly associated with response and/or safety.

In contrast, the association between dose and pharmacokinetic parameters was not clear. Majority of the studies (19/39; 49%) that tested multiple doses, either did not report PK or did not report PK separately for each DL. Among the studies that reported granular details of PK, positive correlation between dose and AUC and/or Cmax was observed in eight studies, and no correlation was noted in 11 studies (see 'Findings on association with dose' column in table 2 and online supplemental table S3).

Time to peak expansion and onset of response

As the CAR-T cell expansion can translate into tumor cell cytotoxicity, data from studies reporting time to peak

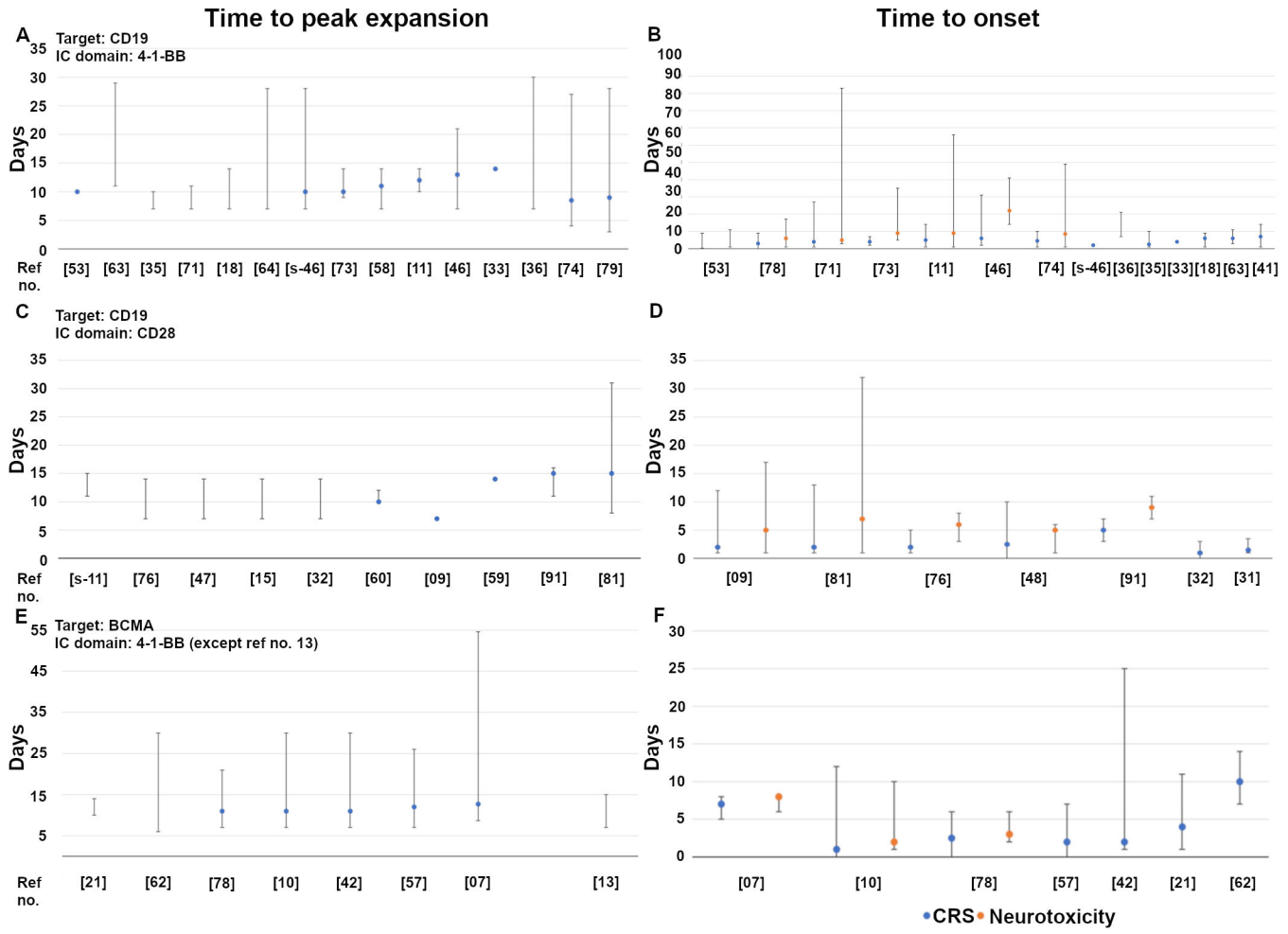

Figure 3 Time to peak expansion (left panels), onset of CRS and ICANS (right panels) in the CAR-T cells studies targeting (A and B) CD19 with 4–1-BB as intracellular signal, (C and D) CD19 with CD28 as intracellular signal and (E and F) BCMA with 4–1-BB as intracellular signal, except ref no. 13 has CD28 as intracellular signal. Markers represent median values, and error bars represent range (min–max) or IQR. Studies that reported only range are represented without markers. Detailed information is included in online supplemental table S5. CAR, chimeric antigen receptor; CRS, cytokine release syndrome.

expansion and onset of response (efficacy/safety events) were extracted (online supplemental table S5; figure 3). Fifty-two (70%) studies reported the time to peak CAR T-cell expansion and/or response including 11 studies with cohort size over 50 patients.[10 11 71 72 74–77] However, studies reported the onset times for the entire cohort; granular details at different dose levels were not reported. Interestingly, time to peak expansion in peripheral blood was comparable across all studies (7–14 days) even though doses varied. Similarly, median time to response (1 month), CRS events (1–7 days) and neurotoxicity events (2–12 days) were comparable across all studies. However, it should be noted that median time to response is limited to the first evaluation of response, which typically occurs at 1 month across all studies.

Tumor burden

Twenty-eight (38%) studies reported details of tumor burden at the time of treatment and its correlation with disease response and/or incidence/severity of CRS and neurotoxicity (online supplemental table S6).[9–11 42 75 76 78–81] High tumor burden was seen to be associated with lower response rates in majority of the studies (n=15; 54%) and was found to be associated with better response rate only in two (7%) studies.[25 80] The association between tumor burden and adverse event incidence or severity was reported in 14 (50%) studies: nine (32%) studies observed that high tumor burden was associated with higher incidence and/or severity of CRS and neurotoxicity, whereas five (18%) studies noted no difference (online supplemental table S6). Interestingly, studies by Turtle *et al* and Park *et al* used bone marrow tumor burden-based risk adoptive dosing strategy and noted that the approach reduced the toxicity of treatment.[53 76]

DISCUSSION

Current systematic review aimed to address a critical question in the early clinical development of CAR-T cells. Previous systematic reviews mainly summarized efficacy and/or safety outcomes or biomarkers associated

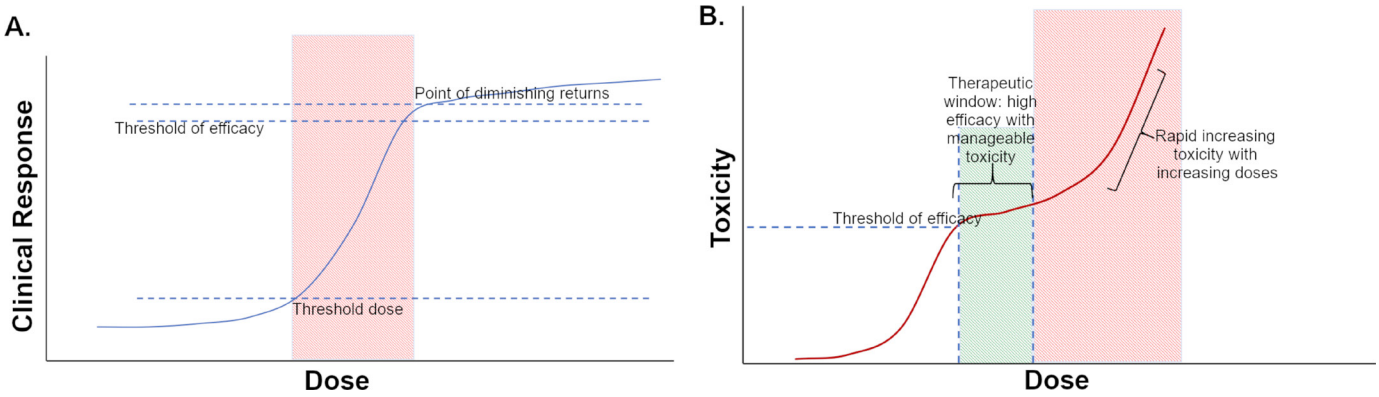

Figure 4 Model showing dose–response (A) and dose–toxicity (B) correlation of CAR-T cells. Increments in response can be seen when dose increments are made at lower doses (<50 million cells approximately). Increase in response is associated with increase in frequency of adverse events (CRS and ICANS), but the toxicity is manageable with standard treatment at threshold efficacy. Further increase in dose (>150 million cells approximately) beyond threshold efficacy could only have marginal increase in efficacy but could lead to significant increase in toxicity of CAR-T cells manifested as increased severity of adverse events. CAR, chimeric antigen receptor; CRS, cytokine release syndrome.

with safety outcomes for a specific CAR-T cell therapy or a specific indication,[82–89] but the correlation between dose and related factors and response was not studied. To derive from the combined knowledge of all relevant clinical studies, all CAR-T cells therapies for hematological cancers were analyzed together for correlations and then analyzed separately based on target antigens as well as intracellular domains. The review did not pool the efficacy or safety data across the studies. Instead, outcomes of each study were analyzed individually, and positive correlations or lack of correlations between dose and ORR/CRR, dose and toxicity were noted first, followed by overall assessment of correlation between dose and response (table 2, figure 2). This approach ensured that each study had its own comparative cohorts and thereby accounted for the possible differences in target antigens and CAR-T cell products.

In response to question of whether there is a dose-related increase in disease response to CAR-T cells, the results show that dose and disease response association was mainly seen when optimal clinical efficacy (defined based on the outcomes from the studies as >70% ORR) was not achieved at lower doses. The studies that did not show association (table 2 and online supplemental table S3) either had a very good overall response rate or had a poor overall response rate indicating that further dose escalation may not result in increased response when the response rates are very high (80%–100%) or very low (0–20%) due to intrinsic product attributes affecting cell expansion kinetics. Our findings also noted a general trend in dose required to achieve optimal clinical efficacy. Majority of anti-CD19 CAR-T cell studies achieved optimal clinical efficacy (>70% ORR) at doses between 50 and 100 million cells (table 2 and online supplemental table S3). Comparatively higher doses (>100 million cells) were needed to achieve optimal clinical efficacy for majority of anti-BCMA CAR-T cell studies (table 2 and online supplemental table S3), but it is to be noted that some anti-BCMA CAR-T cells like cilta-cel achieved optimal clinical efficacy at lower dose (<100 million cells) and did not see further increase in response at doses above 100 million cells.[71] The differences in dose required to achieve optimal clinical efficacy between anti-CD19 and anti-BCMA CAR-T cells are possibly due to differences in the target antigen expression on tumor cells or CAR-T cell product attributes. Similarly, the differences in optimal clinical efficacy dose between CAR-T cells targeting same antigen are possibly due to product characteristics such as CAR expression per cell, proportion of CAR+ cells in the final product and viability of CAR+ cells.

In contrast to dose and disease response association, incidence and/or severity of CAR-T cell-related adverse events including CRS and neurotoxicity was associated with the dose in majority of studies (table 2), possibly because at higher doses, there are increased chances of direct activation of non-target immune cells such as macrophages and innate immune cells through cell–cell interactions before and/or as CAR-T cells interact with their target tumor cells. Interestingly, the onset of CRS was within 7 days in most studies and the time to reach peak expansion was 2 weeks in most studies (online supplemental table S5) supporting the hypothesis that the initiation of CRS was possibly related to CAR-T cell activity before reaching Cmax.

Tumor burden is another factor that is commonly considered during CAR-T cell treatment and its association with response is debated during the clinical development of CAR-T cells. In response to the question of whether tumor burden is directly or inversely associated with response, the results show that high tumor burden is very likely to be associated with low disease response and with high adverse events. All the studies identified in the review showed an inverse association between tumor burden and disease response (online supplemental table S6) except the study by Wang *et al*[80] which, unlike all other studies, used a comparatively different cut-off (</≥ cohort median) and observed that patients with tumor burden less than median had lower ORR. Intriguingly,

peak CAR-T cell expansion (Cmax), a parameter shown to be associated with response was found to be lower in patients with high tumor burden.[90] The findings are in line with previous studies that noted that high tumor burden was associated with lower response to immunotherapy. In fact, some of the CAR-T cell studies have even proposed the tumor burden-based risk-adoptive dosing approach[46 53] or aggressive treatment with chemotherapy or radiotherapy to shrink the tumors[91] prior to CAR-T cell treatment.

The review was mainly able to achieve the difficult task of consolidating the learnings from different types of CAR-T cell studies performed in heterogenous patient population by evaluating the association between dose and response separately for each study. The findings from our study show that the answer to the question of whether there is a dose–response correlation is possibly not a simple yes or no. Our study identified and listed the trials that saw increased response at higher dose levels and the trials that had similar response at all dose levels and described the common factors seen in both categories. The studies that did not see any association between dose and response either had a very low response rate at all the doses tested indicating that the cell product was not effective or had a very high response rate at all the doses tested indicating that the product was very effective and lowest dose administered was able to achieve maximum possible response. Similarly, in the studies that saw an increase in response with dose increments, lowest dose was apparently not sufficient to achieve optimal effector to target cell ratio (E-T ratio) and drive the response. The findings support the point that CAR-T cell therapy is a living drug that involves in vivo proliferation of cells and in vivo expansion of CAR-T cells is possibly more relevant than the starting dose and also support the point that the effector to target cell ratio (E-T ratio) needs to be considered during determination of the dose as low E-T ratio can result in ineffective response. Finally, the summary of median time to peak expansion, onset of response, onset of CRS and onset of neurotoxicity included in the review support the hypothesis that PKs of CAR-T cells and mechanisms are comparable across all hematological cancers.

Based on the mechanisms of CAR-T cell activity and the results from the studies included in the review, a sigmoidal dose response curve (figure 4) can be proposed. It includes a threshold dose defined as dose needed to achieve the least effective E-T ratio and the optimal efficacy dose, defined as lowest dose that had most effective E-T ratio and highest efficacy was comparable across majority of the studies irrespective of target antigen and intracellular signaling domain. A positive correlation between dose and ORR is less likely above the optimal efficacy dose, and further increase in dose would likely increase the toxicity of CAR-T cells (figure 4).

Limitations

Review is limited by the studies included. All studies were non-randomized, open label, lacked control cohort and the majority had small sample size. Furthermore, majority of the studies did not include independent review committee for selection of subjects (selection bias) and had >20% loss of subjects to follow-up (attrition bias; online supplemental table S2). Studies also did not report granular differences in CAR-T cell expansion, onset of response and persistence between dose levels. Durability of response and its correlation with dose was also not explored within the studies. Finally, the review excluded solid tumors and studies in children, which could limit the application of the findings to adult hematological cancers.

CONCLUSION

In summary, the findings from the systematic literature review suggest that there may be an optimal dose of efficacy in CAR-T cell therapeutics at which maximal clinical effect is achieved and beyond which no additional antitumor effect can be observed. However, increasing the dose beyond the optimal efficacy or increasing the dose when the ORR is relatively high may result in higher incidence and/or severity of adverse events. The findings also show that high tumor burden is likely associated with lower response to CAR-T cell treatment.

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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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Title: A systematic review to study dose-response relationship of chimeric antigen T cell (CAR-T cell) therapy in adults with ALL, DLBCL and multiple myeloma

Review question: Is there a correlation between dose of CAR-T cell therapy and response in patients? Does the efficacy increase or decrease with increase in dose and vice versa? Does the incidence of AEs (CRS and neurotoxicity) increase or decrease with increase in dose and vice versa? What are the factors associated with response?

PICO

Patients: Adults (age >18 years) with hematologic malignancies including ALL, DLBCL and MM

Intervention: CAR-T cell therapy

Comparison: Single arm and controlled studies

Outcomes:

Efficacy outcomes: Overall response rate, progression free survival, overall survival, frequency of hematopoietic stem cell transplant after CAR-T therapy

Toxicity outcomes: Adverse events including cytokine release syndrome and neurological side effects.

Databases: Pubmed/medline

Search terms:

1. “CAR” or “chimeric antigen receptor”
2. “CAR-T cell” and “acute lymphoblastic leukemia” or “ALL”
3. “CAR-T cell” and “diffuse large B-cell lymphoma” or “DLBCL”
4. “CAR-T cell” and “multiple myeloma” or CAR” or “MM”
5. “chimeric antigen receptor” and “acute lymphoblastic leukemia”
6. “chimeric antigen receptor” and “diffuse large B-cell lymphoma”
7. “chimeric antigen receptor” and “multiple myeloma”

Eligibility criteria

Inclusion criteria

1. All clinical studies (prospective and retrospective)

Exclusion criteria

1. Articles reported in languages other than English
2. Conference presentations and abstracts (usually report interim data)
3. Studies in children
4. Studies in Solid tumors
5. Studies using Bispecific CAR-T cells
6. Studies using CAR-T cell cocktails (e.g. CD19 & CD20 targeting CAR-T cells)
7. Studies using Bispecific antibodies
8. Studies using Antibody drug conjugates

9. Articles reporting additional outcomes/post hoc analyses of previously published study
10. Preclinical studies
11. Systematic literature review articles
12. Review articles

Search period

Search period would include January 2010 and August 2021. One more search will be performed before finalizing the study results to include any recent studies

Data extraction

Screening of the papers based on title, abstract and full-texts will performed by two independent investigators. Discrepancies will be resolved through consensus discussion and when needed through third investigator. Studies meeting the eligibility criteria will be included in the review.

Following data will be extracted from the full-texts: study details (author name, year of publication, country, number of countries, number of centers and inclusion and exclusion criteria), patient characteristics (number of patients, cancer sub-type, lines of prior therapy, tumor burden), CAR-T cell details (dose and regimen, target antigen, co-stimulatory domains, gene transfer method, generation of CAR-T cells and persistence of CAR-T cells), efficacy outcomes (OS, PFS, ORR, Onset of response, DoR & markers of response) and safety outcomes (CRS and neurotoxicity, onset of CRS/neurotoxicity)

Risk of bias (quality) assessment

Study quality and risk of bias will assess using the ROBINS-I tool. Characteristics of the study including selection criteria, confounding factors, study deviations and handling of missing data will be assessed. Based on the assessments, each study will be categorized as low risk, moderate risk, serious risk and critical risk of bias. Assessment will be performed by two independent investigators and discrepancies will resolved through consensus or when needed through third investigator.

Data analysis

We do not plan to perform meta-analysis of population data.