Review of CAR-T cell therapy for the WHO Model List of Essential Medicines 2020

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Content

General Items

1. Summary statement of the proposal for inclusion, change or deletion

This application focuses on chimeric antigen receptor (CAR)-T cell therapy, a novel treatment option for people with relapsed or refractory (r/r) diffuse large b-cell lymphoma (DLBCL). This application originated from the collaboration of Cochrane Haematology and Cochrane Cancer, and the WHO Department of Health Policy and Standards to monitor and evaluate novel therapies.

Relapsed or refractory DLBCL is an aggressive cancer with an extremely limited median overall survival (less than 6 - 12 months). Reviewing the evidence on the efficacy and safety of CAR-T cell therapy for people with r/r DLBCL, we identified data from trials with either a single arm or multiple arms of CAR-T cell therapy without a control group. All trials were judged to be at high risk of bias. We did not meta-analyse any data but describe results narratively. There was considerable variation in the duration of follow-up for all efficacy outcomes. At the longest time-point - 24 months - overall survival was 50.5% (95% CI 40.2% - 59.7%; one study; 101 participants, 76% with DLBCL). At the longest time-point - 18 months - progression-free survival was 64% (95% CI 48% - 76%; one study, 99 participants with DLBCL). Participants treated with CAR-T cells can experience potentially life-threatening adverse events such as cytokine release syndrome which might require additional treatment. The certainty in the evidence was very low for all outcomes. The evidence on the efficacy and safety of CAR-T cell therapy for the treatment of people with r/r DLBCL is still limited.

As there are 28 ongoing trials evaluating CAR-T cell therapy for people with r/r DLBCL, of which three are randomised controlled trials (RCTs) to be primarily completed between 2022 and 2025 (BELINDA; TRANSFORM; ZUMA-7), it is important to continue evaluating how evidence will evolve, postponing CAR-T cell therapy's potential addition to the complementary list of the Model List of Essential Medicines to one of the next updates (2023 or 2025), if evidence has become compelling.

Please note, that in this document, we majorly refer to the medicines Axicabtagene ciloleucel (axi-cel) and Tisagenlecleucel (tisa-cel), which have been approved by several regulatory agencies. Further medicines, such as Lisocabtagene maraleucel, are being investigated in clinical trials and might receive market approval in the future. In this application, we also included trials on medicines not yet approved by regulatory agencies at this stage.

2. Relevant WHO technical department and focal point

Lorenzo Moja, Technical Officer, EML Secretariat

3. Organizations supporting the application

- Department I of Internal Medicine, University Hospital of Cologne
- Cochrane Haematology
- Cochrane Cancer

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine

INN:

- Axicabtagene ciloleucel (axi-cel)
- Tisagenlecleucel (tisa-cel)

ATC (implementation in the ATC/DDD index in 2021):

- L01XX70
- L01XX71

Treatment details, public health relevance and evidence appraisal and synthesis

5. Treatment details (requirements for diagnosis, treatment and monitoring)

Please note that the following information, including recommendations on dosage, administration and pre-treatment were partially retrieved from the manufacturer's product information (1-4).

After clinical examination and radiographic imaging, diffuse large b-cell lymphomas (DLBCLs) are ideally diagnosed by an excisional biopsy of the abnormally enlarged and suspicious lymph node. Diagnosis should be carried out by a reference haematopathology laboratory with expertise in morphological interpretation and the facilities necessary to carry out the full range of phenotypic and molecular investigations (5, 6).

The overall process of treating DLBCL with CAR-T cells is highly complex. First, T-cells are collected from the patient's blood, before they are altered and multiplied. Meanwhile, it is recommended that the patient receives lymphodepletion therapy (3, 4, 7, 8) to improve the efficacy of treatment by creating a more favourable immune environment for the CAR-T cells (9, 10). The altered and multiplied cells are then returned to the patient via infusion (11, 12). After infusion, patients are recommended to be monitored daily during the first 10 days and stay within proximity of the clinic for at least 4 weeks after infusion to monitor the occurrence of adverse events (1-4).

The proposed dosage for Tisagenlecleucel (tisa-cel) is independent of weight with $0.6 – 6.0 * 10^8$ CAR-positive viable T-cells intravenously (2, 4). For Axicabtagene ciloleucel (axi-cel) the proposed dosage depends on the patient's body weight. A dose of $2 * 10^6$ CAR-positive T-cells per kg body weight with a maximum of $2 * 10^8$ CAR-positive viable T-cells is recommended (1, 3). There is no data regarding overdose for either substance and both are recommended as third-line therapy (7, 8).

For tisa-cel, lymphodepleting chemotherapy is recommended 2 – 14 days before infusion. The recommended regimen for DLBCL is fludarabine (25 mg/m^2 intravenous daily for 3 days) and cyclophosphamide (250 mg/m^2 intravenous daily for 3 days starting with the first dose of fludarabine) (2, 4). Tisa-cel is to be used as an intravenous infusion. It must be administered through latex-free intravenous tubing without a leukocyte depleting filter, at approximately 10 to 20 mL per minute by gravity flow (2, 4).

The recommended lymphodepleting chemotherapy regimen before the use of axi-cel consists of cyclophosphamide 500 mg/m^2 intravenous and fludarabine 30 mg/m^2 intravenous, each on the 5th, 4th and 3rd day before infusion of axi-cel (1, 3).
Axi-cel must also be used as an intravenous infusion and administered without a leukocyte depleting filter. It is recommended to infuse the entire content of the bag within 30 minutes via gravity flow or a peristaltic pump (1, 3).

Both substances must only be administered in a qualified treatment centre by trained healthcare professionals. These professionals need experience in the treatment of haematological malignancies and must be trained for administration and management of patients treated with each substance (1-4).

6. Information supporting the public health relevance

Non-Hodgkin lymphomas (NHLs) are the most common haematologic malignancy in the world, making up 4.3% of all cancers in the U.S. in 2015 (13). The most common type of malignant lymphomas worldwide are DLBCLs with 40% of all NHLs (14, 15) and 80% of all aggressive lymphomas (16).

Global data on incidence and mortality of diffuse large b-cell lymphoma (DLBCL) is very limited. However, the age-adjusted incidence rate of DLBCLs in the U.S. was 5.5 per 100,000 in 2015 (17). Between

1970 and 2010, a steady increase of these incidence rates has been reported. In all sexes, racial categories and age groups (except young adults), the increase was determined to be approximately 3-4% in the U.S. (16, 18). In the same time span, patients of all ages were diagnosed with DLBCLs. However, the median age in the U.S. was 65 years (17). Additionally, males are at a 1.5 times higher risk to be diagnosed with DLBCLs (16, 18). Mortality was 1.8 per 100,000 in the U.S. in 2015 (17).

Untreated, DLBCLs are associated with a median survival of <1 year. With first-line treatment that consists of the combination of rituximab and CHOP-chemotherapy (19), patients may experience good outcomes (18). But 30-40% of patients experience relapse or are refractory to first-line treatment. Even after second-line treatment, which consists of salvage chemotherapy followed by autologous stem cell transplantation (ASCT), approximately 50% of patients still experience relapse (20). Therefore, prognosis for relapsed or refractory DLBCL remains poor.

Before the introduction of chimeric antigen receptor (CAR)-T cell therapy, patients ineligible for ASCT or relapsed after second-line treatment had no other treatment options (21). With CAR-T cell therapy in the form of axi-cel and tisa-cel, another treatment option for these patients is available. Typically, CAR-T cell therapy is used as third-line treatment for relapsed or refractory (r/r) DLBCL (3, 4).

7. Review of efficacy and safety

Summary of the methodological approach

We are developing a Cochrane systematic review on the efficacy and safety of chimeric antigen receptor (CAR)-T cell therapy for people with relapsed or refractory (r/r) diffuse large b-cell lymphoma (DLBCL). In order to inform the evidence on the efficacy and safety of CAR-T cell therapy, we summarize the preliminary results of our systematic review including a description of the included studies, an assessment of risk of bias, a narrative description of the outcomes, and an assessment of the certainty of the evidence. The full methodological approach will be described in detail in the published review. The published protocol is available in the Cochrane Library (22).

Results of the search

We identified 1494 potentially relevant references. At the initial screening stage, we excluded 104 duplicates and 1247 references due to a lack of conformity with the inclusion criteria. We further evaluated the remaining 143 references either as full-text publications or, if not available, as abstract publications or study registry entries. This led to exclusion of 14 trials. In addition, we identified 28 ongoing trials. Three of these trials are randomised controlled trials (RCTs) which will be completed between 2022 and 2025 (BELINDA; TRANSFORM; ZUMA-7; primary completion date according to ClinicalTrials.gov). 10 studies are awaiting classification. We finally included 13 trials in this systematic review. We report the overall numbers of references screened, identified, selected, excluded and included in a PRISMA flow diagram (*Figure 1*).

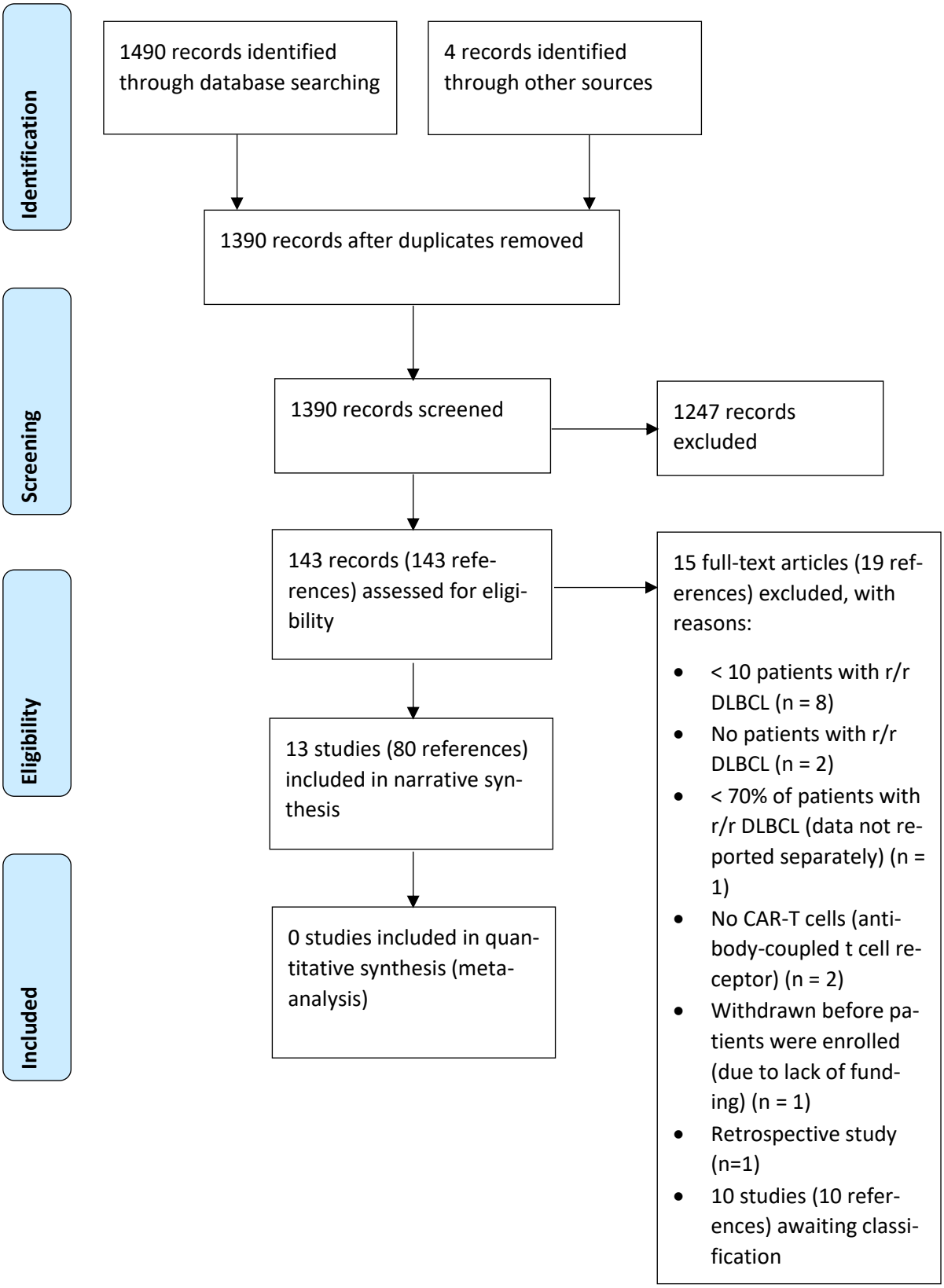

Figure 1: PRISMA flow diagram

Description of included studies and participants

Study characteristics

For an overview of the main study characteristics, see *Table 1*. Here we provide a brief overview.

13 trials evaluated the efficacy and safety of CAR-T cells in people with r/r DLBCL (Beider 2019 (23); Chang 2015 (24); Hirayama 2019 (25); JULIET (26); Kochenderfer 2017 (27); PLATFORM (28); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); TRANSCEND-NHL-001 (32); Ying 2019 (33); ZUMA-1 (34); ZUMA-6 (35)).

Published full-text articles were available for 10 trials (Beider 2019 (23); Hirayama 2019 (25); JULIET (26); Kochenderfer 2017 (27); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); TRANSCEND-NHL-001 (32); Ying 2019 (33); ZUMA-1 (34)).

For four trials, we retrieved outcome data fully (Chang 2015 (24); PLATFORM (28); ZUMA-6 (35)) or partially (Beider 2019 (23)) from conference abstracts and/or ClinicalTrials.gov. For one study (PLATFORM (28)) recruitment is ongoing.

Design

We did not identify data from any randomised controlled trials (RCTs), prospective controlled non-randomised studies of interventions (NRSIs) or prospective observational studies with a control group. Therefore, we only included trials with either a single arm or multiple arms of CAR-T cell therapy without a control group.

10 trials were single-arm studies (Beider 2019 (23); Chang 2015 (24); Hirayama 2019 (25); JULIET (26); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); Ying 2019 (33); ZUMA-1 (34); ZUMA-6 (35)) and three trials included multiple arms of either varying doses of CAR-T cells (Kochenderfer 2017 (27), TRANSCEND-NHL-001 (32)) or varying doses of CAR-T cells combined with varying agents (PLATFORM (28)).

Sample sizes

Sample sizes (incl. participants with conditions other than r/r DLBCL) varied heavily. The number of participants that received CAR-T cells was ranging from 15 (PLATFORM (28); recruitment ongoing) to 269 participants (TRANSCEND-NHL-001 (32)). Three trials included more than 100 participants receiving CAR-T cells (JULIET (26); TRANSCEND-NHL-001 (32); ZUMA-1 (34)).

The proportion of participants receiving CAR-T cells among those who were enrolled was ranging between 67% (JULIET (26)) and 100% (Ying 2019 (33); ZUMA-6 (35) for phase 1)). In the three largest trials, the proportions were 67% (JULIET (26)), 78% (TRANSCEND-NHL-001 (32); 85% when including participants receiving a non-conforming product) and 91% (ZUMA-1 (34)). The proportion was unclear in three studies (Beider 2019 (23); Chang 2015 (24); Kochenderfer 2017 (27)).

The proportion of participants evaluated among those who were enrolled was ranging between 56% (JULIET (26)) and 100% (ZUMA-6; 12/12 participants). In the three largest trials, the proportions were 56% (JULIET (26)), 74% (TRANSCEND-NHL-001 (32)) and 91% (ZUMA-1 (34)). The proportion was unclear in three studies (Beider 2019 (23); Chang 2015 (24); Kochenderfer 2017 (27)).

Please note that the exact numbers of enrolled participants who were intended to receive CAR-T cells were difficult to retrieve as data could have been missing or reported data could have varied substantially between published articles and trial records. Therefore, we cannot rule out that the number of participants enrolled and intended to receive CAR-T cells was substantially higher than the number of participants actually receiving CAR-T cells as well as the number of analysed participants. For details, see *Table 1* and also the assessment of risk of bias.

Location

Six trials were conducted in single centres in Israel (Beider 2019 (23)), China (Sang 2020 (29); Tong 2020 (31)) or the USA (Hirayama 2019 (25); Kochenderfer 2017 (27); Schuster 2017 (30)). Seven trials were conducted in multiple centres in China (Chang 2015 (24); Ying 2019 (33)), the USA (PLATFORM (28); TRANSCEND-NHL-001 (32); ZUMA-6 (35)), the USA and Israel (ZUMA-1 (34)) or Australia, Austria, Canada, France, Germany, Italy, Japan, the Netherlands, Norway and the USA (JULIET (26)).

Interventions

Anti-CD19 directed CAR-T cells were used in 11 trials (Beider 2019 (23); Chang 2015 (24); Hirayama 2019 (25); JULIET (26); Kochenderfer 2017 (27); PLATFORM (28); Schuster 2017 (30); TRANSCEND-NHL-001 (32); Ying 2019 (33); ZUMA-1 (34); ZUMA-6 (35)), while two trials used a combination of anti-CD19 and anti-CD20 (Sang 2020 (29)) or anti-CD22 directed CAR-T cells (Tong 2020 (31)).

In the majority of trials, participants received a single infusion of CAR-T cells. Participants received between one and three infusions in Chang 2015 (24), and either one or two infusions in TRANSCEND-NHL-001 (32).

The dose of CAR-T cells varied heavily with median doses between 1x 10^6/kg and 5.79x 10^6/kg for trials that applied doses depending on body weight, and median doses between 50x 10^6 and 3x 10^8 for trials that applied doses irrespective of body weight.

Co-interventions consisted of Durvalumab in PLATFORM (28) and Atezolizumab in ZUMA-6 (35).

In all trials, participants received lymphodepleting chemotherapy before the infusion of CAR-T cells. In the majority of trials, participants received fludarabine and cyclophosphamide. In JULIET (26) participants additionally received bendamustine. In Sang 2020 (29) two participants received ifosfamide instead. In Tong 2020 (31) participants received fludarabine and cyclophosphamide with or without doxorubicin liposome and in Schuster 2017 (30), participants received hyperfractionated cyclophosphamide, modified EPOCH incl. cyclophosphamide, cyclophosphamide, bendamustine, radiation therapy and cyclophosphamide, or etoposide and cyclophosphamide.

Table 1: Main study characteristics

Study ID	Beider 2019	Chang 2015	Hirayama 2019	JULIET	Kochenderfer 2017	PLATFORM	Sang 2020	Schuster 2017	Tong 2020	TRANSCEND-NHL-001	Ying 2019	ZUMA-1	ZUMA-6
Arms	Single	Single	Single	Single	Parallel (varying doses)	Parallel (varying doses and combinations with other agents)	Single	Single	Single	Parallel (varying doses)	Single	Single	Single
Phase	1b/2	1/2	1/2	2	1/2	1/2 (data for 1 only)	2	2a	1/2a	1	1	1/2	1
Center	single	multi	single	multi	single	multi	single	single	single	multi	multi	multi	multi
Location	Israel	China	USA	Australia, Austria, Canada, France, Germany, Italy, Japan, Netherlands Norway, USA	USA	USA	China	USA	China	USA	China	Israel, USA	USA
Target	CD19	CD19	CD19	CD19	CD19	CD19	CD19 and CD20	CD19	CD19 and CD20	CD19	CD19	CD19	CD19
Infusions	1	1-3	1	1	1	1	1	1	1	1-2	1	1	1
Dose CAR-T cells (median if not otherwise specified)	1x 10^6/kg	range 0.45- 4.59x 10^6/kg	2x 10^6/kg	3x 10^8 (range 0.1-6x)	reduced from 5 to 1x 10^6/kg during study	50 or 100x 10^6	CD19: 1x 10^6/kg (range 0.2-4x) CD20: 1x10^6/kg (range 0.1-4x)	5.79× 10^6/kg (range 3.08-8.87x)	range 1-6x 10^6/kg	50 (in 1-2 doses), 100 or 150x 10^6	2x 10^6/kg	2x 10^6/kg	2x 10^6/kg
Co-interventions	None	None	None	None	None	Durvalumab	None	None	None	None	None	None	Atezolizumab

Study ID	Beider 2019	Chang 2015	Hirayama 2019	JULIET	Kochenderfer 2017	PLATFORM	Sang 2020	Schuster 2017	Tong 2020	TRANSCEND-NHL-001	Ying 2019	ZUMA-1	ZUMA-6
Type and dose of induction chemotherapy	Flu 25 mg/m^2 for 3 days Cyc 900 mg /m^2 for 1 day	Flu 30 mg/m^2 for 3 days Cyc 250 mg/m^2 for 3 days	Flu 25/30 mg/m^2 for 3/3 days Cyc 30-500 mg/m^2 for 1/3 days	Flu 25 mg/m^2 for 3 days Cyc 250 mg/m^2 for 3 days Bendamustine 90 mg/m^2 for 2 days	Flu 30 mg/m^2 for 3 days Cyc 300 mg/m^2 for 3 days	Flu for 3 days (dose NR) Cyc for 3 days (dose NR)	n=19: Flu 30 mg/m^2 for 3 days Cyc 750 mg/m^2 for 1 day n=2: Ifosfamide 2g for 3 days	n=14 (DLBCL subgroup): Hyperfractionated Cyc 1.8 gm/ ^{2} (n=6), Modified EPOCH incl. Cyc 750 mg/m^2 (n=2), Cyc 1 gm/m^2 (n=2), Bendamustine 90 mg/m^2 for 2 days (n=2), Radiation therapy + Cyc 750 mg/m^2 (n=1), Infusional etoposide+ bolus Cyc incl. Cyc 750 mg/m^2 (n=1)	Flu 20-30 mg/m^2 for 3 days Cyc 20-30 mg/m^2 divided over 3 days with or without Doxorubicin liposome 10 mg/m^2 for 1 day	Flu 30 mg/m^2 for 3 days Cyc 300 mg /m^2 for 3 days	Flu 25 mg/m^2 for 3 days Cyc 250 mg/m^2 for 3 days	Flu 30 mg/m^2 for 3 days Cyc 500 mg/m^2 for 3 days	Flu 30 mg/m^2 for 3 days Cyc 500 mg/m^2 for 3 days
Participants enrolled[a]	18[b]	NR	65 (203 according to CT.gov)	165 (by May 2018)	NR (43 according to CT.gov)	18 (recruitment ongoing)	25	38 (63 according to CT.gov)	33 (100 according to CT.gov)	344	32	119 across phase 1 and 2 (307 according to CT.gov)	12 for phase 1 (37 according to CT.gov across phase 1 and 2)
Participants receiving CAR-T cells[a]	18[b]	NR	48	111	22	15	21	28	28	269 (294 total, 25 receiving non-conforming product)	32	108 across phase 1 and 2	12
Participants evaluated[a]	18	13	47	93	22	11	21	28	28	256	29	101 for phase 2	12

Study ID	Beider 2019	Chang 2015	Hirayama 2019	JULIET	Kochenderfer 2017	PLATFORM	Sang 2020	Schuster 2017	Tong 2020	TRANSCEND-NHL-001	Ying 2019	ZUMA-1	ZUMA-6
Proportion of enrolled participants receiving CAR-T cells[a]	unclear[b]	unclear	48/65 (74%)	111/165 (67%)	unclear	15/18 (83%)	21/25 (84%)	28/38 (74%)	28/33 (85%)	269/344 (78%); 294/344 (85%) incl. those receiving non-conforming product	32/32 (100%)	108/119 (91%) for phase 1 and 2	12/12 (100%) for phase 1
Proportion of enrolled participants evaluated[a]	unclear[b]	unclear	47/65 (72%)	93/165 (56%)	unclear	11/18 (61%)	21/25 (84%)	28/38 (74%)	28/33 (85%)	256/344 (74%)	29/32 (91%)	108/119 (91%) for phase 1 and 2	12/12 (100%) for phase 1

Cyc = Cyclophosphamide; Flu = Fludarabine; NR = not reported

[a] The numbers of participants refer to efficacy data retrieved from the primary publication and may include participants with conditions other than r/r DLBCL.

[b] According to a secondary publication, this trial enrolled 93 participants, of whom 90 received CAR-T cells including 37 participants with DLBCL, whereas in the primary publication we used to retrieve efficacy data from, only 18 participants with DLBCL were enrolled, of whom all received CAR-T cells and were evaluated.

Participant characteristics

For an overview of the main participant characteristics, see *Table 2*. Here we provide a brief overview.

Participants

Three studies (JULIET (26); Sang 2020 (29); ZUMA-6 (35)) included participants with r/r DLBCL only, whereas the majority of studies (Beider 2019 (23) ; Chang 2015 (24); Hirayama 2019 (25); Kochenderfer 2017 (27); PLATFORM (28); Schuster 2017 (30); Tong 2020 (31); TRANSCEND-NHL-001 (32); Ying 2019 (33); ZUMA-1 (34)), also included participants with other conditions such as acute lymphoblastic leukaemia, Burkitt lymphoma, mantle cell lymphoma, follicular lymphoma, or primary mediastinal large b-cell lymphoma.

Median age, when reported, was ranging between 38 (Chang 2015 (24)) and 63 years (TRANSCEND-NHL-001 (32)). The youngest participant (9 years) was in included in Chang 2015 (24), and the oldest participant (76 years) in JULIET (26).

The median proportion of male participants was ranging between 39% (Tong 2020 (31)) and 79% (Schuster 2017 (30)), with all studies except for Tong 2020 (31), including a majority of male participants.

The proportion of participants who had previously received autologous and allogeneic stem cell transplantation was ranging between 0% (Sang 2020 (29)) and 50% (Schuster 2017 (30)), and between 0% (Schuster 2017 (30)) and 18% (Tong 2020 (31)), respectively. In Hirayama 2019 (25), 6% of participants had received autologous and allogeneic stem cell transplantation.

The median number of previous lines of treatment, when reported, was either 3 (Sang 2020 (29); Schuster 2017 (30); TRANSCEND-NHL-001 (32); ZUMA-1 (34)) or 4 (Hirayama 2019 (25); Kochenderfer 2017 (27); Ying 2019 (33)).

Table 2: Main participant characteristics

	Beider 2019	Chang 2015	Hirayama 2019	JULIET	Kochenderfer 2017	PLATFORM	Sang 2020	Schuster 2017	Tong 2020	TRANSCEND-NHL-001	Ying 2019	ZUMA-1	ZUMA-6
Population[a] (proportion of participants with DLBCL, type of DLBCL and other conditions if reported)	n=18 evaluated, n=17 (94%) DLBCL Type of DLBCL NR	n=13 evaluated, n=12 (92%) DLBCL Type of DLBCL NR	n=48 receiving CAR-T cells (n=28 (58%) DLBCL (n=18 DLBCL NOS, n=10 DLBCL TF from indolent)) n=47 evaluated, n=27-28 (56-58%) DLBCL (exact number unclear)	n=111 receiving CAR-T cells, (n=109 (98%) DLBCL, n=88 DLBCL NOS, n=21 DLBCL TF from follicular lymphoma)	n=22 receiving CAR-T cells, n=19 (86%) DLBCL, n=2 follicular lymphoma, n=1 mantle cell lymphoma) n=22 evaluated, NOS: n=13, TF follicular lymphoma: n=3, PMBCL: n=2, TF from CLL: n=1	n=11 evaluated, n=10 (91%) DLBCL Type of DLBCL NR	n=21 evaluated, n=21 (100%) (DLBCL (n=15 refractory DLBCL)	n=28 evaluated, n=14 (50%) DLBCL DLBCL participants with performed immune-histochemical studies (n=12): Relapsed and refractory germinal-center DLBCL (n=7); non–germinal-center DLBCL (n=5 Refractory DLBCL: 12/14 (86%)	n=28 evaluated, n=16 (57%) DLBCL Type of DLBCL NR	n=256 evaluated, n=206 (80%) DLBCL; n=131 DLBCL NOS, n=57 DLBCL TF from FLL, n=18 DLBCL TF from other indolent NHL subtypes	n=29 evaluated, n=20 (69%) DLBCL Type of DLBCL: NR	n=108 receiving CAR-T cells across phase 1 and 2; n=77 DLBCL in phase 2 n=101 evaluated in phase 2; n=77 (76%) DLBCL Type of DLBCL: Non-germinal- center DLBCL	n=12 evaluated, n=12 (100%) DLBCL Type of DLBCL NR
Age (median and/or range if reported)	40.5 (23-70) (n=18)	38 (9-61) (n=12)	58.5 (n=48)	56 (22-76) (n=111)	53 (26-67) (n=19)	53-78 (n=11)	55 (23-72) (n=21)	58 (25-77) (n=14)	≥60: 7/28 (25%)	63 (54-70) (n=269)	52 (29-68) (n=32)	58 (n=101)	55 (30-66) (n=12)
Sex (male/ total)	NR	NR	35/48 (73%)	60/93 (65%)	NR	7/11 (64%)	13/21 (62%)	11/14 (79%)	11/28 (39%)	174/269 (65%)	24/32 (75%)	73/108 (68%)	NR

	Beider 2019	Chang 2015	Hirayama 2019	JULIET	Kochenderfer 2017	PLATFORM	Sang 2020	Schuster 2017	Tong 2020	TRANSCEND-NHL-001	Ying 2019	ZUMA-1	ZUMA-6
Previous SCT (DLBCL subgroup if reported)	NR	NR	autoSCT 16/48 (33%) alloSCT: 4/48 (8%) autoSCT and alloSCT: 3/48 (6%)	autoSCT: 54/111 (49%) alloSCT: 0/111 (0%)	autoSCT: 5/19 (26%) alloSCT: NR	NR	autoSCT: 1/21 (5%) alloSCT: NR	autoSCT: 7/14 (50%) alloSCT: 0/14 (0%)	autoSCT: NR alloSCT: 5/28 (18%)	autoSCT: 90/269 (33%) alloSCT: 9/269 (3%)	autoSCT: 1/10 (10%) alloSCT: NR	autoSCT: 16/81 (21%) alloSCT: NR	NR
Previous lines of treatment (median and/or range if reported)	NR	NR	Median: 4 (1-11) (n=48)	1: 5/111 (5%); 2: 49/111 (44%); 3: 34/111 (31%); 4-6: 23/111 (20%)	Median: 4 (2-7) (n=19)	NR	Median: 3 (1-6) (n=21)	Median: 3 (1-8) (n=14)	≤2: 6/28 (21%); 3-5: 15/23 (54%); ≥6: 7/23 (25%)	Median: 3 (n=269)	Median: 4 (2-7) (n=32)	Median: 3 (n=108)	NR

alloSCT = allogeneic stem cell transplantation; autoSCT = autologous stem cell transplantation; CT.gov = Clinicaltrials.gov; NR = not reported; SCT = stem cell transplantation; TF = transformed

[a] Due to heterogeneous reporting of the composition of the samples that included participants with conditions other than r/r DLBCL, the number of participants separated by condition is reported for participants receiving CAR-T cells, for participants evaluated, or both.

Outcomes

We here report data on overall survival, response (progression-free survival, overall response rates, complete response rates, partial response rates), quality of life and adverse events (any adverse events, any serious adverse events, cytokine release syndrome, neurotoxicity, use of tocilizumab and/or corticosteroids for treatment of cytokine release syndrome and/or neurotoxicity, cytopenias, febrile neutropenia, any infections).

Risk of bias

Overall, we rated the risk of bias within and across studies to be serious. In addition to the high risk of bias due to the non-randomised study design, we assessed the internal and external validity based on criteria for observational studies provided by the Cochrane Childhood Cancer Group (36). The summary of the methodological quality for each domain across studies is presented in *Figure 2*.

Figure 2: Risk of bias assessed based on criteria for observational studies provided by the Cochrane Childhood Cancer Group

Allocation (selection bias)

We judged six studies to be at low risk of bias because eligibility criteria were clearly defined (JULIET (26); Sang 2020 (29); Schuster 2017 (30); TRANSCEND-NHL-001 (32); Ying 2019 (33); ZUMA-1 (34)).

Three studies were judged to be at unclear risk of bias because eligibility criteria were not sufficiently reported (Kochenderfer 2017 (27); PLATFORM (28); ZUMA-6 (35)).

We judged four studies to be at high risk of bias. The median age of the study group was substantially below-average in Beider 2019 (23) (40.5 years) and in Chang 2015 (24) (38 years). In Tong 2020 (31), male sex was underrepresented in the study group (39%). In Hirayama 2019 (25), the study group consisted of participants who received the preferred approach of lymphodepletion and infusion of CAR-T cells established during phase 1 of the study only (48 participants out of 65 participants who received at least 1 infusion of CAR-T cells).

Blinding (performance bias and detection bias)

All studies were unblinded and, thus, at high risk of performance and detection bias for subjective outcomes. All outcomes except for overall survival (i.e. investigator-assessed and patient-reported outcomes) are subjective to a greater or lesser extent and therefore at high risk of bias.

Incomplete outcome data (attrition bias)

We assessed attrition bias in terms of whether studies (equally) assessed outcomes for all participants. We evaluated attrition bias separately for four outcome categories.

Overall survival

Among the studies reporting overall survival, we judged two studies (Chang 2015 (24); ZUMA-6 (35)) to be at unclear risk of bias. The participant flow was not sufficiently reported to allow for a judgement on the completeness of data in Chang 2015 (24). In ZUMA-6 (35), the number of enrolled participants was not reported in the published abstract (only the number of participants who received CAR-T cell therapy and atezolizumab).

Six studies (JULIET (26); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); TRANSCEND-NHL-001 (32); ZUMA-1 (34)) were judged to be at high risk of bias because outcomes were reported only for a subset of the participants who were enrolled. For example, in TRANSCEND-NHL-001 (32), of 344 participants who underwent leukapheresis, 294 received CAR-T cells, while for two participants, the product could not be manufactured for, and 48 patients had lymphoma complications or had died before receiving CAR-T cells. Of 294 participants who received CAR-T cells, 25 received a CAR-T cell product not meeting release criteria. Outcome data were reported only for 269 participants who received a CAR-T product that met release criteria.

Response (PFS, OR, CR, PR)

Only one study was judged to be at low risk of bias, because objective response and complete response were reported for all participants who underwent leukapheresis (TRANSCEND-NHL-001 (32), 344 participants).

Three studies were judged to be at unclear risk of bias. The participant flow or selection of participants were not sufficiently reported to allow for a judgement on the completeness of data in Chang 2015 (24) and Kochenderfer 2017 (27). In ZUMA-6 (35), the number of enrolled participants was not reported in the published abstract (only the number of participants who received CAR-T cell therapy and atezolizumab).

Nine studies (Beider 2019 (23); Hirayama 2019 (25); JULIET (26); PLATFORM (28); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); Ying 2019 (33); ZUMA-1 (34)) were judged to be at high risk of bias because outcomes were reported only for a subset of the participants who were enrolled. For example,

in Sang 2020 (29), of 25 participants who were enrolled, one participant failed to collect sufficient T lymphocytes, CAR-T cell expansion in vitro failed for two participants, and one patient died due to rapid progressive disease before receiving CAR-T cells. Outcome data were reported for 21 participants who received CAR-T cells.

Quality of life

The two studies that reported quality of life were both judged to be at high risk of bias. In JULIET (26) data were reported only for participants with complete response or partial response (e.g. 39 participants at month 3 and 21 participants at month 18 compared to 108 participants with assessments at baseline). In TRANSCEND-NHL-001 (32), data were also reported only for a subset of participants (e.g. 138 participants at month 3 and 38 participants at month 12 compared to 186 participants at baseline).

Adverse events

Among the studies reporting adverse events, we judged eight studies to be at low risk of bias because all or most outcomes were reported for most participants receiving CAR-T cells. Outcomes were reported for all participants receiving CAR-T cells in JULIET (26), Kochenderfer 2017 (27), Sang 2020 (29), Schuster 2017 (30), Tong 2020 (31). In two studies, the majority of outcomes was reported for all participants receiving CAR-T cells while only some outcomes were reported for participants in phase 1 of the trials only (ZUMA-1 (34), use of tocilizumab and/or corticosteroids; ZUMA-6 (35), neurotoxicity and (partially) cytopenias). In TRANSCEND-NHL-001 (32), 25 out of 296 participants receiving a non-conforming CAR-T cell product were not included in the safety analysis so that outcomes were reported for 91% of the participants receiving CAR-T cells.

One study was judged to be at unclear risk of bias because the number of participants receiving CAR-T cells was unclear due to insufficient reporting of the participant flow (Chang 2015 (24)).

In PLATFORM (28), outcomes were reported only for participants receiving CAR-T cells and durvalumab, i.e., for 11 out of 15 (73%) participants receiving CAR-T cells. In Ying 2019 (33), only half of the safety outcomes of interest (CRS and neurotoxicity) were reported for 32 out of 32 (100%) participants receiving CAR-T cells while half of the safety outcomes of interest (use of tocilizumab and/or corticosteroids and cytopenias) were reported for 10 out of 32 (31%) participants receiving CAR-T cells only. Both studies were judged to be at high risk of bias.

Selective reporting (reporting bias)

We assessed reporting bias in terms of whether the study group and intervention were well-defined and whether the outcomes were equally reported for all participants and the length of follow-up was mentioned.

Well-defined study group and intervention

We judged 10 studies (Beider 2019 (23); Hirayama 2019 (25); JULIET (26); Kochenderfer 2017 (27); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); TRANSCEND-NHL-001 (32); ZUMA-1 (34); ZUMA-6 (35)) to be at low risk of bias as both, the study group and the intervention, were well described.

For PLATFORM (28) and Ying 2019 (33), data on the study group of interest were available in abstracts with only a brief description of the sample. Both studies were judged to be at unclear risk of bias.

We judged Chang 2015 (24) to be at high risk of bias, as both, the study group and intervention were only described briefly in an abstract and neither a full-text article nor a trial record was available.

Well-defined follow-up

Nine studies were judged to be at low risk of bias as either the follow-up (Beider 2019 (23)) or the median follow-up was reported (Chang 2015 (24); Hirayama 2019 (25); JULIET (26); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); ZUMA-1 (34); ZUMA-6 (35)).

We judged risk of bias to be unclear for two studies, for which the follow-up was specified in a trial record, but no median follow-up (PLATFORM (28)) or only the minimum follow-up (Ying 2019 (33)) was reported.

Two studies were judged to be at high risk of bias, because, in Kochenderfer 2017 (27), duration of follow-up was not clearly described, and in TRANSCEND-NHL-001 (32), median follow-up was only reported for the ITT population (i.e. participants who underwent leukapheresis) and OS and PFS data were limited to the "efficacy analysis set", for which no duration of follow-up was reported.

Well-defined outcomes

With respect to the definition of outcomes, we assessed reporting bias separately for four outcome categories.

Overall survival

Due to the objective nature of the outcome, we judged all studies that reported overall survival to be at low risk of bias (Chang 2015 (24); JULIET (26); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); TRANSCEND-NHL-001 (32); ZUMA-1 (34); ZUMA-6 (35)).

Response (PFS, ORR, CR, PR)

We judged six studies to be at low risk of bias (JULIET (26); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); Ying 2019 (33); ZUMA-1 (34); ZUMA-6 (35)), because the authors specified criteria used for response assessment and either reported time-point specific outcomes or clearly reported the timing of assessment for all reported outcomes.

We judged seven studies to be at high risk of bias (Beider 2019 (23); Chang 2015 (24); Hirayama 2019 (25); Kochenderfer 2017 (27); PLATFORM (28); TRANSCEND-NHL-001 (32)). Reporting of criteria used for response assessment was insufficient in Beider 2019 (23) and missing in Chang 2015 (24). In Hirayama 2019 (25), Kochenderfer 2017 (27), PLATFORM (28) and TRANSCEND-NHL-001 (32), criteria used for response assessment were specified, but time-point specific assessment was either missing or timing of assessment was unclear for at least some of the reported outcomes.

Quality of life

The two studies which reported quality of life were judged to be at low risk of bias, as both used standardised scales, i.e. the Function Assessment of Cancer Therapy-Lymphoma (FACT-Lym) (37) in JULIET (26), and the EuroQol 5-Dimension 5-Level (EQ-5D-5L) (38) in TRANSCEND-NHL-001 (32), and clearly described the timing of outcome assessment.

Adverse events

Among the studies reporting adverse events, we judged eight studies to be at low risk of bias (JULIET (26); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); TRANSCEND-NHL-001 (32); Ying 2019 (33); ZUMA-1 (34); ZUMA-6 (35)), as established criteria (e.g. the Common Terminology Criteria for Adverse Events, CTCAE) were used to assess adverse events and the timing of follow-up was reported.

Three studies were judged to be at high risk of bias. Chang 2015 (24) provided no information on the criteria used for assessment. In PLATFORM (28), no information on the criteria and the time-point of assessment were available. Kochenderfer 2017 (27) reported use of the CTCAE but the time-point of assessment was unclear.

Important prognostic factors or follow-up taken adequately into account (confounding)

We did not apply this item due to the lack of a control group.

Well-defined risk estimates (analyses)

We did not apply this item as none of the studies provided any risk estimates due to the lack of a control group.

Efficacy

For details on efficacy outcomes, see *Table 3* (overall survival, progression-free survival, overall response rates, complete response rates, partial response rates) and *Table 4* (quality of life).

Please note that, for efficacy outcomes, we report data only from studies with a minimum proportion of 70% of participants with DLBCL unless separate data were available for participants with DLBCL. Please also note that, among participants who were enrolled, the proportion of participants receiving CAR-T cells was ranging between 67% and 100% and the proportion of participants evaluated for efficacy was ranging between 56% and 100%.

Overall survival

Data on overall survival were reported for eight of the included studies (Chang 2015 (24); JULIET (26); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); TRANSCEND-NHL-001 (32); ZUMA-1 (34); ZUMA-6 (35)). Due to the large variability in sample size and the duration of follow-up, we present time-point specific survival probabilities only. Additional median survival times are reported in *Table 3*. Tong 2020 (31) provided survival data, however the studied population for this outcome included only 57% of participants with DLBCL and was thus below our defined margin of eligibility.

Survival rates at 6 months were reported with 74.7% (95% CI 68.9% - 79.6%; 256 participants, 80.4% DLBCL) for TRANSCEND-NHL-001 (32) and with 78% (95% CI 69% - 85%; 108 participants; proportion of DLBCL unclear, but above 70%) for ZUMA-1 (34).

Chang 2015 (24) provided 10 months overall survival results for 13 individuals, including 12 (92%) suffering from DLBCL, of 55% (95% CI 39% - 74%).

The 12 months survival rates, which were reported for the studies JULIET (26),TRANSCEND-NHL-001 (32)and ZUMA-1 (34) ranged between 48% (95% CI 38% - 57%; 99 participants) in JULIET (26) and 59% (95% CI 49% - 68%; 108 participants; proportion of DLBCL unclear, but above 70%) in ZUMA-1 (34). TRANSCEND-NHL-001 (32) reported a survival probability of 57.9% (95% CI 51.3% - 63.8%; 256 participants, 80.4% DLBCL) at 12 months.

Data for survival at 18 months were available from JULIET (26), with 43% (95% CI 33%-35%; 99 participants) and ZUMA-1 (34), with 52% (95% CI 41% - 62%; 59% (95% CI 49% - 68%; 108 participants; proportion of DLBCL unclear, but above 70%).

One study, ZUMA-1 (34), reported an estimated survival at 24-months, which was 50.5% (95% CI 40.2% - 59.7%) for 101 participants, including 77 (76%) individuals suffering from DLBCL.

Progression-free survival

Nine studies reported results on progression-free survival, disease-free survival or relapse-free survival (Chang 2015 (24), JULIET, Kochenderfer 2017 (27), Sang 2020 (29), Schuster 2017 (30), Tong 2020 (31), TRANSCEND-NHL-001 (32), ZUMA-1 (34), ZUMA-6 (35)), as for overall survival, we limit the here reported results to time-point specific rates only, given that there was a large heterogeneity in study sample sizes and follow-up durations between the respective studies. Additional data on progression-free survival is reported in*Table 3*.

For 4 months, Chang 2015 (24) reported a rate of disease free-survival (exact definition not provided) of 53% (95% CI 36% - 69%) for 13 participants, including 12 (92%) individuals with DLBCL.

Results for progression-free survival at 6 months were reported in two studies and were 49% (95% CI 39% - 58%; 101 participants, 76% DLBCL) in ZUMA-1 (34) and 51.4% (95% CI 44.6% -57.7%; 256 participants, 80.4% DLBCL) in TRANSCEND-NHL-001 (32).

Relapse-free survival, relapse defining at least a partial response to the last therapy and a following progression of lymphoma, at 6 months was at 66% (95% CI 51%-78%; 9 participants) in JULIET (26).

12 months progression-free survival was reported for four studies (Kochenderfer 2017 (27), Tong 2020 (31), TRANSCEND-NHL-001 (32), ZUMA-1 (34)). It ranged from 44% (95% CI 34% - 53%; 101 participants, 76% DLBCL) in ZUMA-1 (34) and 44.1% (37.3% - 50.7%; 256 participants, 80.4% DLBCL) in TRANSCEND-NHL-001 (32) to 75% (95% CI 46-90; 16 participants DLBCL) in Tong 2020 (31). Kochenderfer 2017 (27) reported a rate of 63.3% for 22 participants, including 17 (77%) individuals with DLBCL, but did not report a corresponding confidence interval.

For the study ZUMA-1 (34) progression-free survival was reported to be at 41% (95% CI 31% - 50%) months in 101 participants, including 77 (76%) suffering from DLBCL.

Lastly, at 12 as well as at 18 months, JULIET (26) reported a relapse-free survival rate of 64% (95% CI 48%-76%) for 99 participants with DLBCL.

Overall response rates

Overall, 12 studies (Beider 2019 (23); Hirayama 2019 (25); JULIET (26); Kochenderfer 2017 (27); PLATFORM (28); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); TRANSCEND-NHL-001 (32); Ying 2019 (33); ZUMA-1 (34); ZUMA-6 (35)) reported data on overall response rates. Given the substantial variability of follow-up durations and the variability of the outcome definition, including best response rates, we here present results on time-point specific response rates only. Additional data for response rates, including best response rates are reported in *Table 3*, but have to be interpreted with additional care.

Ying 2019 (33) reported an overall response rate of 80% (95% CI 56.34%-94.28%) for 20 participants with DLBCL at one month of follow-up.

Overall response rates at three months of follow-up were reported in three studies (Sang 2020 (29); Schuster 2017 (30); Ying 2019 (33)). They ranged from 50% (95% CI 49%-79%; 14 participants DLBCL) in Schuster 2017 (30) and 55% (95% CI 31.53%-76.94%; 20 participants DLBCL) in Ying 2019 (33) to 81.0% (95% CI 58.1%-94.6%; 21 participants DLBCL) in Sang 2020 (29).

At six months, overall response was sustained for 45% (95% CI 23.06%-68.47%; 20 participants DLBCL) of participants in Ying 2019 (33) and for 46.2% (95% CI 19.2%-74.9%; 21 participants DLBCL) of participants in Sang 2020 (29).

Complete response rates

Data on complete response were provided for all 13 included studies (Beider 2019 (23); Chang 2015 (24); Hirayama 2019 (25); JULIET (26); Kochenderfer 2017 (27); PLATFORM (28); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); TRANSCEND-NHL-001 (32); Ying 2019 (33); ZUMA-1 (34); ZUMA-6 (35)), however, as for overall response rates, we here present results for time-point specific rates only and refer to *Table 3* for additional data. Please note that these data have to be interpreted with additional care.

At one month of follow-up Ying 2019 (33) reported a complete response rate of 60% (95%CI 36.05-80.88) for 20 analysed participants with DLBCL.

At three months of follow-up Sang 2020 (29) reported a complete response in 52.4% (95% CI 26%-70%; 21 participants DLBCL) of participants and Ying 2019 (33) in 55% (95% CI 31.53-76.94; 20 participants DLBCL) of participants.

Sang 2020 (29); Schuster 2017 (30) and Ying 2019 (33)provided data on complete responses at six months of follow up: 40.0% (95% CI 12.2%-73.84%; 21 participants DLBCL) of participants in Sang 2020

(29), 43% (95% CI 18%-71%; 14 participants DLBCL) of participants in Schuster 2017 (30) and 45% (95% CI 23.06%-68.47%; 20 participants DLBCL) of participants in Ying 2019 (33).

Partial response rates

Data on partial response were provided for 6 studies (Beider 2019 (23); JULIET (26); Kochenderfer 2017 (27); Tong 2020 (31); TRANSCEND-NHL-001 (32); ZUMA-1 (34)). As for overall and complete response rates we present results for time-point specific response rates only. *Table 3* presents additional data. Please note that these results are to be interpreted with additional care.

None of the included studies reported time-point specific partial response rates.

Table 3: Efficacy (OS, PFS, OR, CR, PR)

	Sample size (if not otherwise specified)[a]	Follow-up	OS	PFS	OR	CR	PR
Beider 2019	n=18 evaluated (n=17 (94%) DLBCL)	28 days (for response)	NR	NR	Likely bOR: 11/18 (61%) (in publication with data for additional participants, but not separately reported for DLBCL: "*Primary endpoints of the study were production feasibility, patient safety and best overall response rates, documented 1 to 2 months after infusion*."	Likely bCR: 6/18 (33%) (see OR)	Likely bPR: 5/18 (28%) (See OR)
Chang 2015	n=13 evaluated (n=12 (92%) DLBCL)	Median follow-up: 10 months	At 10 months: 55% (95% CI 39% - 74%)	Disease-free survival rate at 4 months: 53% (95% CI 36% - 69%)	NR	Complete tumour regression for 3-10 months (stable blood CAR DNA copies 0.1-0.4%): 8/13 (62%)	NR
Hirayama 2019	n=47 evaluated (n=27-28 (56-58% DLBCL)/ n=48 receiving CAR-T cells/ n=65 enrolled	Median follow-up of entire group (n= 48, n=28 (58%) DLBCL): 26.9 months (range 2.5-32.4)	NR for DLBCL subgroup	NR for DLBCL subgroup	bOR: 50% (95% CI 33%-67%) (DLBCL subgroup; n=28) (*Time point of assessment not explicitly reported*)	bCR: 43% (95% CI 25%-63%) (DLBCL subgroup; n=28) (*Time point of assessment not explicitly reported*)	NR
JULIET	n=93 [99] evaluated/ n=111 [115 at data cut off May 2018] receiving CAR-T cells/ n=165 enrolled	Median follow-up: 19.3 months post infusion (n=115)	At 12 months: 48% (95% CI 38% - 57%) At 18 months: 43% (95% CI 33%-35%)	Probability of being relapse free at 6 months: 66% (95% CI 51%-78%) Probability of being relapse free at 12 or 18 months: 64% (95% CI 48%-76%)	bOR at median follow-up of 19.3 months post infusion: 54% (95% CI 43%-64%)	bCR at 19.3 months median follow-up post infusion: 40% (CI NR)	bPR at 19.3 months median follow-up post infusion: 13% (CI NR)
Kochenderfer 2017	n=22 evaluated (n=17 (77%) DLBCL)	NR	NR	Reported for entire group (n=22, n=19 DLBCL): 12-months PFS: 63.3% (CI NR)	bOR: 68% (CI NR) (DLBCL subgroup; n=19)	bCR: 47% (CI NR) (DLBCL subgroup; n=19)	bPR: 21% (CI NR) (DLBCL subgroup; n=19)

	Sample size (if not otherwise specified)[a]	Follow-up	OS	PFS	OR	CR	PR
PLATFORM	n=11 evaluated/ n=15 receiving CAR-T cells/ n=18 enrolled (recruitment ongoing)	NR	NR	NR	Likely bOR: 10/11 (91%; CI NR)	Likely bCR: 7/11 (64%; CI NR)	NR
Sang 2020	n=21 evaluated/ n=21 receiving CAR-T cells/ n=25 enrolled	Median follow-up: 6.6 months (range 0.3-16.4)	Median: 8.1 months (95% CI 6.5-9.6)	Median PFS: 5.0 months (95% CI 2.3-7.7)	At 3 months: 17/21 (81.0%) (95% CI 58.1%-94.6%) Sustained OR at 6 months: 6/21 (46.2%) (95% CI 19.2%-74.9%)	At 3 months: 11/21 (52.4%) (95% CI 26%-70%) Sustained CR rate at 6 months: 4/21 (40.0%) (95% CI 12.2%-73.84%)	NR
Schuster 2017	n=28 evaluated (n=14 (50%) DLBCL)/ n=29 receiving CAR-T cells/ n=38 enrolled	Median follow-up: 28.6 months	Reported for DLBCL subgroup (n=14): Median: 22.2 months (CI NR)	Reported for DLBCL subgroup (n=14) At median follow-up 28.6 months (n=14): 43% (95% CI 18% to 66%) Median PFS (n=14): 3.2 months (95% CI 0.9% to not reached)	At 3 months: 50% (95% CI 49%-79%; 7/ 14) (DLBCL subgroup; n=14)	At 6 months: 43% (95% CI 18%-71%; 6/14) (DLBCL subgroup; n=14)	NR
Tong 2020	n=28 evaluated (n=16 (57%) DLBCL)/ n=28 receiving CAR-T cells/ n=33 enrolled	Median follow-up: 19.1 months	Reported for entire group (n=28, n=16 (57%) DLBCL) Median: NR At 6 months: 82% (95% CI 62% - 92%) At 12 months: 71% (95% CI 51% - 85%)	Reported for DLBCL subgroup (n=16) Median PFS: NA Progression-free at 12 months: 75% (95% CI 46-90)	bOR: 75% (95% CI 48%-93%; 12/ 16) (DLBCL subgroup; n=16)	bCR: 11/16 (69%; CI NR) (DLBCL subgroup; n=16)	bPR: 1/16 (6%; CI NR) (DLBCL subgroup; n=16)

	Sample size (if not otherwise specified)[a]	Follow-up	OS	PFS	OR	CR	PR
TRANSCEND-NHL-001	n=256 evaluated (n=131 DLBCL NOS, n=57 DLBCL TF from FLL, n=18 DLBCL TF from other indolent NHL subtypes)/ n=269 [296 for non-conforming product] receiving CAR-T cells/ n=344 enrolled	Median follow-up: 18.8 months (95% CI 15.0-19.3)	Reported for entire group (n=256, n=131 DLBCL NOS, n=57 DLBCL TF from FLL, n=18 DLBCL TF from other indolent NHL subtypes): Median: 21.1 months (95% CI 13.3 - NR) Estimated at 6 month: 74.7% (95% CI 68.9% - 79.6%) Estimated at 12 month: 57.9% (95% CI 51.3% - 63.8%)	Reported for entire group (n=256, n=131 DLBCL NOS, n=57 DLBCL TF from FLL, n=18 DLBCL TF from other indolent NHL subtypes): Median PFS: 6.8 months (95% CI 3.3-14.1) Estimated 6-month PFS: 51.4% (95% CI 44.6% -57.7%) Estimated 12-month PFS: 44.1% (37.3% - 50.7%)	Reported for entire group (n=256, n=131 DLBCL NOS, n=57 DLBCL TF from FLL, n=18 DLBCL TF from other indolent NHL subtypes): 186/256 (73%; 95% CI 66.8% - 78.0%) ITT: 208/344 (61%; 95% CI 55.1%-65.7%) DLBCL NOS: 89/131 (67.9%; 95% CI 59.2%-75.8%) DLBCL TF from FLL: 48/57 (84.2%; 95% CI 72.1%-92.5%) DLBCL TF from other indolent NHL: 11/18 (61.1%; 95% CI 35.7%-82.7%)	Reported for entire group (n=256, n=131 DLBCL NOS, n=57 DLBCL TF from FLL, n=18 DLBCL TF from other indolent NHL subtypes): 136/256 (53.1% (95% CI 46.8-59.4) ITT: 150/344 (44%; 95% CI 38.3%-49.0%) DLBCL NOS: 64/131 (48.9%; 95% CI 40.0%-57.7%) DLBCL TF from FLL: 36/57 (63.2%; 95% CI 49.3%-75.6%) DLBCL TF from other indolent NHL: 7/18 (38.9%; 95% CI 17.3%-64.3%)	Reported for entire group (n=256, n=131 DLBCL NOS, n=57 DLBCL TF from FLL, n=18 DLBCL TF from other indolent NHL subtypes): 50/256 (20%; 95% CI 14.9%-24.9%)
Ying 2019	n=29 evaluated (n=20 (69%) DLBCL)/ n=32 receiving CAR-T cells/ n=32 enrolled	At least 6 months for all patients evaluated	NR	NR	Reported for DLBCL subgroup (n=20): At 1 month: 16/20 (80% (95% CI 56.34%-94.28%) At 3 months: 11/20 (55% (95% CI 31.53%-76.94%) At 6 months: 9/20 (45% (95% CI 23.06%-68.47%)	Reported for DLBCL subgroup (n=20): At 1 month: 12/20 (60% (95%CI 36.05-80.88)) At 3 months: 11/20 (55% (95% CI 31.53-76.94)) At: 6 months: 9/20 (45% (95% CI 23.06%-68.47%)	NR

	Sample size (if not otherwise specified)[a]	Follow-up	OS	PFS	OR	CR	PR
ZUMA-1	n=108 [101 for phase 2 (n=77 (76%) DLBCL)] evaluated/ n=108 receiving CAR-T cells/ n=119 enrolled	Median follow-up, reported for phase 1: 9 months Median follow-up, reported for phase 2: Primary analysis (Jan 2017): 8.7 months Updated analysis (Aug 2017): 15.4 months Longer-term safety and activity assessment (Aug 2018): 27.1 months	Reported for phase 1 and phase 2 population (n=108, proportion of DLBCL unclear): At 6 months: 78% (95% CI 69% - 85%) At 12 months: 59% (95% CI 49% - 68%) At 18 months: 52% (95% CI 41% - 62%) Reported for phase 2 population (n=101, n=77 (76%) DLBCL): Median at 24 months follow-up: NR (95% CI 12.8–NR) Estimated at 24-month: 50.5% (95% CI 40.2% - 59.7%)	Estimated proportion of patients with PFS reported for entire group for phase 2 (n=101, n=77 (76%) DLBCL): Median: 5.9 months (95% CI 3.3-15.0) At 6 months: 49% (95% CI 39% - 58%) At 12 months: 44% (95% CI 34% - 53%) At 15 months: 41% (95% CI 31% - 50%)	bOR: 63/77 (82%) (DLBCL subgroup in phase 2)	bCR: 38/77 (49%) (DLBCL subgroup in phase 2)	bPR: 25/77 (32%) (DLBCL subgroup in phase 2)
ZUMA-6	n=28 with available data for efficacy in CT.gov/ n=37 enrolled (according to CT.gov)	Median follow-up: NR for entire cohort (4.4 months for published data on n=12)	Median OS (n=28): NR (95% CI 12.2 to NR)	Median PFS (n=28): NA (95% CI 3.1-NA)	bOR: 21/28 (75%) (95% CI 55%-89%)	bOR: 13/28 (46%) (95% CI 28%-66%)	NR

(b)CR = (best) complete response; (b)OR =(best) overall response; (b)PR = (best) partial response; CT.gov = Clinicaltrials.gov; DLBCL NOS = Diffuse large b-cell lymphoma not further specified; FLL = follicular lymphoma; NHL = non-Hodgkin lymphoma; NR = not reported; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; TF = transformed

[a] Please note the numbers of participants refer to efficacy data retrieved from the primary publication unless otherwise specified. The numbers of participants enrolled, receiving CAR-T cells and evaluated are reported only when provided. For detailed information on the participant flow, see *Table 1*.

Quality of life

For details on quality of life, see *Table 4*.

Two studies reported quality of life (JULIET (26); TRANSCEND-NHL-001 (32)) using several validated tools for several time-points. We here report outcomes on total scores of validated tools assessing quality of life for all time-points that were reported. Please note that further data were available for specific quality of life-related domains using the same or other tools (e.g. FACT-G domain scores, SF-36 physical health total score, EQ-5D-5L health index score, EORTC QLQ-C30 domain scores). For JULIET (26), we report the FACT-Lym total scores as they include all of the other scores that were reported (i.e. the FACT-G total score including the FACT-G domains and the Lym S) (37). For TRANSCEND-NHL-001 (32) we report scores of the visual analogue scale of the EQ-5D-5L (EQ-5D-5L VAS) (38). Please note that, due to the lack of a control group, we did not calculate effect estimates. We only report data descriptively.

In JULIET (26), FACT-Lym total scores (range 0-168, higher scores indicate improvement) were reported at baseline along with changes from baseline at months 3, 6, 12 and 18. Changes from baseline were only reported for participants with a complete or partial response. The number of participants evaluated decreased over time with only 21 participants left for assessment at month 18 from initially 108 participants at baseline, and initially 57 participants with a complete or partial response at baseline. Mean (SD) FACT-Lym total scores at baseline were 121.2 (24.0) for all participants (n=108) and 124.1 (22.8) for 57 participants with a complete or partial response. At month 18, FACT-Lym total scores increased by a mean (SD) of 13.1 (16.1) points. According to the authors, improvements were above the minimum clinically meaningful difference (MCID) lower limit (6.5) at months 3, 6 and 12, and above the MCID upper limit (11.2) at month 18.

In TRANSCEND-NHL-001 (32), EQ-5D-5L VAS scores (range 0-100, higher scores indicate improvement) were reported at baseline and at months 1, 2, 3, 6, 9 and 12. The number of participants evaluated decreased over time with only 38 participants left for assessment at month 12 from initially 186 participants at baseline. Mean (SD) EQ-5D-5L VAS scores increased from 68.3 (19.5) at baseline to 82.1 (17.8) at month 12.

Table 4: Efficacy (quality of life)

	Sample size [a]	Tool	Baseline	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 18
JULIET	n=108 at BL (100% DLBCL)	FACT-Lym total score (range 0-168, higher scores indicate improvement, MCID: 6.5-11.2)	n=108 M (SD): 121.2 (24.0) n=57 (participants with CR/PR) M (SD): 124.1 (22.8) n=51 (non-responders) M (SD): 118.1 (25.1)	NR	NR	n=39 (participants with CR/PR) change from BL (SD): +9.4 (17.1)*	n=34 (participants with CR/PR) change from BL (SD): +8.6 (20.3)*	NR	n=30 (participants with CR/PR) change from BL (SD): +9.6 (17.9)*	n=21 (participants with CR/PR) change from BL (SD): +13.1 (16.1)**
TRANSCEND-NHL-001	n=186 at BL (100% DLBCL)	EQ-5D-5L VAS score (range 0-100, higher scores indicate improvement)	n=186 M (SD): 68.3 (19.5)	n=164 M (SD): 70.3 (20.2)	n=149 M (SD): 77.1 (17.2)	n=138 M (SD): 75.4 (18.9)	n=84 M (SD): 78.0 (18.0)	n=65 M (SD): 80.1 (15.6)	n=38 M (SD): 82.1 (17.8)	NR

BL = baseline; CR = complete response; M = mean; MCID = minimum clinically important difference; PR = partial response; SD = standard deviation; + = positive changes from baseline

[a] Please note that the numbers of participants refer to efficacy data (quality of life) retrieved from secondary publications. For detailed information on the participant flow including the numbers of participants enrolled and receiving CAR-T cells, see *Table 1*.

* According to the authors, the improvement was above the MCID lower limit.

** According to the authors, the improvement was above the MCID upper limit.

Safety

For details on safety outcomes, see *Table 5* (any adverse events, any serious adverse events, cytokine release syndrome, neurotoxicity, use of tocilizumab and/or corticosteroids for treatment of cytokine release syndrome and/or neurotoxicity, cytopenias, febrile neutropenia and any infections).

Please note that, for safety outcomes, we report data irrespective of the proportion of participants with DLBCL described in the study.

Any adverse events

The number of participants with any adverse events was reported in five studies (550 participants). Adverse events occurred frequently with 99% of participants reporting any adverse event in TRANSCEND-NHL-001 (32) and all participants reporting any adverse event in the remaining studies (JULIET (26); Tong 2020 (31); ZUMA-1 (34); ZUMA-6 (35)).

The same studies reported the number of participants with any grade ≥3 adverse events which was ranging between 68% (Tong 2020 (31)) and 98% (ZUMA-1 (34)).

Any serious adverse events

Four studies (281 participants) reported the number of participants with any serious adverse events. In three studies (JULIET (26); ZUMA-1 (34); ZUMA-6 (35)), 56% to 68% of participants had serious adverse events. In Tong 2020 (31), no serious adverse events occurred.

Only ZUMA-1 (34) reported the number of participants with any serious grade ≥3 adverse events (48%).

Cytokine release syndrome

The number of participants having any grade or grade ≥3 cytokine release syndrome was reported in 11 studies (Chang 2015 (24); JULIET (26); Kochenderfer 2017 (27); PLATFORM (28); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); TRANSCEND-NHL-001 (32); Ying 2019 (33); ZUMA-1 (34); ZUMA-6 (35)) which used different grading criteria (675 participants).

Five studies that used criteria described in Lee 2014 (39), reported between 42% (TRANSCEND-NHL-001 (32)) and 100% (Sang 2020 (29)) of participants having cytokine release syndrome (Sang 2020 (29); Tong 2020 (31); TRANSCEND-NHL-001 (32); Ying 2019 (33); ZUMA-1 (34)). The proportion of participants with grade ≥3 cytokine release syndrome was ranging between 1% (Ying 2019 (33)) and 28.5% (Sang 2020 (29)).

JULIET (26) reported 58% and 22% of participants having cytokine release syndrome of any grade, and grade ≥3, respectively, using the University of Pennsylvania grading scale (40).

Cytokine release syndrome without specification of grading criteria were reported in Kochenderfer 2017 (27), Schuster 2017 (30) and ZUMA-6 (35), with an occurrence of any grade cytokine release syndrome in 57% (Schuster 2017 (30)) and 97% (ZUMA-6 (35)) of participants, and an occurrence of grade ≥3 cytokine release syndrome in 18% to 65% of participants.

Chang 2015 (24) reported that 69% of participants had cytokine release syndrome with fever over 39°C.

PLATFORM (28) reported that cytokine release syndrome did not occur after the infusion of durvalumab.

Neurotoxicity

Ten studies (664 participants) reported neurotoxicity of any grade or grade ≥3 (JULIET (26); Kochenderfer 2017 (27); PLATFORM (28); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); TRANSCEND-NHL-001 (32); Ying 2019 (33); ZUMA-1 (34); ZUMA-6 (35)).

Neurotoxicity occurred in a range of 15.6% (Ying 2019 (33)) to 100% (Kochenderfer 2017 (27)) of participants.

Grade ≥3 neurotoxicity was reported to occur in a range of 0% (PLATFORM (28); Tong 2020 (31); Ying 2019 (33)) and 55% (Kochenderfer 2017 (27)).

Use of tocilizumab and/or corticosteroids for treatment of cytokine release syndrome and/or neurotoxicity

Seven studies (495 participants) reported the number of participants who were treated with tocilizumab and/or corticosteroids (Kochenderfer 2017 (27); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); TRANSCEND-NHL-001 (32); Ying 2019 (33); ZUMA-1 (34)).

Between 0% (Sang 2020 (29)) and 80% (Ying 2019 (33)) of participants received tocilizumab alone or without further specification (Kochenderfer 2017 (27); Sang 2020 (29); Schuster 2017 (30); Tong 2020 (31); TRANSCEND-NHL-001 (32); Ying 2019 (33); ZUMA-1 (34)).

Between 3% (Tong 2020 (31)) and 67% (ZUMA-1 (34)) of participants received tocilizumab and corticosteroids, such as dexamethason (JULIET (26); Tong 2020 (31); TRANSCEND-NHL-001 (32); ZUMA-1 (34)).

Between 0% (Schuster 2017 (30)) and 20% (Ying 2019 (33)) received corticosteroids alone (Kochenderfer 2017 (27); Sang 2020 (29); Schuster 2017 (30); TRANSCEND-NHL-001 (32); Ying 2019 (33)).

In ZUMA-1 (34), prophylactic use of tocilizumab was introduced in phase 2 (cohort 3).

Cytopenias

Cytopenias of any grade or grade ≥3 were reported in eight studies (625 participants) which usually reported on anemia, leukopenia, neutropenia and thrombocytopenia (JULIET (26); Kochenderfer 2017 (27); Sang 2020 (29); Tong 2020 (31); TRANSCEND-NHL-001 (32); Ying 2019 (33); ZUMA-1 (34); ZUMA-6 (35)).

Anemia of any grade and grade ≥3 occurred in 14-81%, and 0-75%, respectively. Leukopenia of any grade and grade ≥3 occurred in 15-76.2%, and 14-47.6%, respectively. Neutropenia of any grade and grade ≥3 occurred in 20-79%, and 20-86%, respectively. Thrombocytopenia of any grade and grade ≥3 occurred in 12-79%, and 3.1-28.6%, respectively.

Three studies additionally reported prolonged cytopenias lasting longer than 28 days (JULIET (26); TRANSCEND-NHL-001 (32)) or 29 days (ZUMA-1 (34)).

The proportion of participants with grade ≥3 prolonged cytopenias were 34% (JULIET (26)), 37% (TRANSCEND-NHL-001 (32)) and 30% (ZUMA-1 (34)). Any grade prolonged cytopenias were reported in 44% (JULIET (26)) and 45% (ZUMA-1 (34)).

Febrile neutropenia

The number of participants with febrile neutropenia was reported in five studies (531 participants) (JULIET (26); Kochenderfer 2017 (27); Sang 2020 (29); TRANSCEND-NHL-001 (32); ZUMA-1 (34)).

Febrile neutropenia occurred in a range of 9% (TRANSCEND-NHL-001 (32)) to 76.2% (Sang 2020 (29)) of participants.

Grade ≥3 febrile neutropenia was reported to occur in a range of 9% (TRANSCEND-NHL-001 (32)) and 50% (Kochenderfer 2017 (27)).

Any infections

Three studies (488 participants) reported the number of participants having any infections (n=531) (JULIET (26); TRANSCEND-NHL-001 (32); ZUMA-1 (34)).

JULIET (26) reported that that 34% and 20% of participants had infections of any grade.

Grade ≥3 infections occurred in a proportion of 20% (JULIET (26)), 12% (TRANSCEND-NHL-001 (32)) and 28% (ZUMA-1 (34)) of participants.

Table 5: Safety

	Sample size (if not otherwise specified)[a]	Any adverse events	Any serious adverse events	CRS (incl. grading criteria if specified)	Neurotoxicity	Tocilizumab or corticosteroids[b]	Cytopenias[c]	Febrile neutropenia	Any infections
Chang 2015	n=13 (n=12 (92%) DLBCL) evaluated/ n=18 receiving CAR-T cells	NR	NR	CRS with fever over 39°C: 9/13 (69%)	NR	NR	NR	NR	NR
JULIET	n=111 (data cut-off Dec 2017) (n=109 (98%) DLBCL) evaluated/ n=111 receiving CAR-T cells	111/111 (100%), Grade ≥3: 99/111 (89%)	72/111 (65%)	CRS (University of Pennsylvania grading scale): 64/111 (58%), Grade ≥3: 24/111 (22%)	During the first 8 weeks post infusion: 23/111 (21%), Grade ≥3: 13/111 (12%)	Tocilizumab: 16/111 (14%) Tocilizumab and glucocorticoids: 11/111 (10%)	AN: 53/111 (48%), Grade ≥3: 43/111 (39%) LEU: NR NEU: 22/111 (20%), Grade ≥3: 22/111 (20%) TH: 14/111 (13%), Grade ≥3: 13/111 (12%) Any prolonged cytopenias lasting > 28 days: 49/111 (44%), Grade ≥3: 36/111 (34%)	During the first 8 weeks post infusion: 17/111 (15%), Grade ≥3: 16/111 (14%)	During the first 8 weeks post infusion: 38/111 (34%), Grade ≥3: 22/111 (20%)
Kochenderfer 2017	n=22 (n=17 (77%) DLBCL) evaluated/ n=22 receiving CAR-T cells	NR	NR	Reported for subgroup with products that were assessable with single-cell multiplex cytokine profiling (n=20, n=15 (75%) DLBCL): CRS: NR, Grade ≥3: 13/20 (65%)	22/22 (100%) Grade ≥3: 12/22 (55%)	Tocilizumab: 2/22(9%) Glucocorticoids (dexamethason): 1/22 (5%)	AN: NR LEU: NR, Grade ≥3: 5/22 (23%) NEU: NR, Grade ≥3: 19/22 (86%) TH: NR, Grade ≥3: 4/22 (18%) Any prolonged cytopenias: NR	Febrile neutropenia: NR, Grade ≥3: 11/22 (50%)	NR

	Sample size (if not otherwise specified)[a]	Any adverse events	Any serious adverse events	CRS (incl. grading criteria if specified)	Neurotoxicity	Tocilizumab or corticosteroids[b]	Cytopenias[c]	Febrile neutropenia	Any infections
PLATFORM	n=11 evaluated/ n=15 receiving CAR-T cells (recruitment ongoing)	NR	NR	CRS after durvalumab infusion: 0/11 (0%)	Neurological events: NR, Grade ≥3: 0/11 (0%)	NR	NR	NR	NR
Sang 2020	n=21 evaluated/ n=21 receiving CAR-T cells	NR	NR	CRS (Lee 2014): 21/21 (100%), Grade ≥3: 6/21 (28.5%)	Neurological events: NR, Grade ≥3: 2/21 (9.5%)	Tocilizumab: 0/21 (0%) Glocucorticoids (dexamethason): 4/21 (19%)	AN: 17/21 (81.0%), Grade ≥3: 6/21 (28.6%) LEU: 16/21 (76.2%), Grade ≥3: 10/21 (47.6%) NEU: 16/21 (76.2%), Grade ≥3: 11/21 (52.4%) TH: 6/21 (28.6%), Grade ≥3: 6/21 (28.6%) Any prolonged cytopenias: NR	16/21 (76.2%), Grade ≥3: 5/21 (23.8%)	NR
Schuster 2017	n=28 (n=14 (50%) DLBCL) evaluated/ n=28 receiving CAR-T cells	NR	NR	CRS: 16/28 (57%), Grade ≥3: 5/28 (18%)	11/28 (39%), Grade ≥3: 3/28 (11%	Tocilizumab: 1/28 (4%) Glucocorticoids: 0/28 (0%)	NR	NR	NR
Tong 2020	n=28 (n=16 (57%) DLBCL) evaluated/ n=28 receiving CAR-T cells	28/28 (100%) Grade ≥3: 19/28 (68%)	0/28 (0%)	CRS (Lee 2014): 14/28 (50%) Grade ≥3: 4/28 (14%)	6/28 (21%) Grade ≥3: 0/28 (0%)	Tocilizumab: 5/28 (17%) Tocilizumab and glucocorticoids: 1/28 (3%)	AN: 4/28 (14%), Grade ≥3: 0/28 (0%) LEU: NR NEU: 22/28 (79%), Grade ≥3: 17/28 (61%) TH: 21/28 (79%), Grade ≥3: 7/28 (25%)	NR	NR

	Sample size (if not otherwise specified)[a]	Any adverse events	Any serious adverse events	CRS (incl. grading criteria if specified)	Neurotoxicity	Tocilizumab or corticosteroids[b]	Cytopenias[c]	Febrile neutropenia	Any infections
							Any prolonged cytopenias: NR		
TRANSCEND-NHL-001	n=269 (n=215 (80%) DLBCL) evaluated/ n=269 [294 for non-conforming product] receiving CAR-T cells	267/269 (99%), Grade ≥3: 213/269 (79%)	NR	CRS (Lee 2014): 113/269 (42%), Grade ≥3: 6/269 (2%)	80/269 (30%), Grade ≥3: 27/269 (10%)	Tocilizumab: 27/269 (10%) Tocilizumab and corticosteroids: 21/269 (8%) Corticosteroids: 5/269 (2%)	AN: 129/269 (48%), Grade ≥3: 101/269 (37%) LEU: 44/269 (16%), Grade ≥3: 39/269 (14%) NEU: 169/269 (63%), Grade ≥3: 161/269 (60%) TH: 84/269 (31%), Grade ≥3: 72/269 (27%) Any prolonged cytopenias lasting > 28 days: NR, Grade ≥3: 100/269 (37%)	25/269 (9%), Grade ≥3: 24/269 (9%)	Any infections: NR, Grade ≥3: 33/269 (12%)
Ying 2019	n=32 (n=22 (69%) DLBCL) evaluated/ n=32 receiving CAR-T cells	NR	NR	CRS (Lee 2014): 17/32 (53.1%), Grade ≥3: 1/32 (1%)	5/32 (15.6%), Grade ≥3: 0/32 (0%)	Reported at earlier data cut-off (n=10, n=9 (90%) DLBCL): Tocilizumab: 8/10 (80%) Glucocorticoids: 2/10 (20%)	AN: 3/10 (30%) (reported at earlier data cut off (n=10, n=9 (90%) DLBCL), Grade ≥3: 3/10 (30%) (reported at earlier data cut off (n=10, n=9 (90%) DLBCL) LEU: 65.7%, Grade ≥3: 21,9% NEU: 65.7%, Grade ≥3: 28.2% TH: 25%, Grade ≥3: 3.1% Any prolonged cytopenias: NR	NR	NR

	Sample size (if not otherwise specified)[a]	Any adverse events	Any serious adverse events	CRS (incl. grading criteria if specified)	Neurotoxicity	Tocilizumab or corticosteroids[b]	Cytopenias[c]	Febrile neutropenia	Any infections
ZUMA-1	n=108 (phase 1 and 2, proportion of DLBCL unclear) evaluated/ n=108 receiving CAR-T cells	108/108 (100%), Grade ≥3: 106/108 (98%)	60/108 (56%), Grade ≥3: 52/108 (48%)	CRS (Lee 2014): 100/108 (93%), Grade ≥3: 12/108 (11%)	72/108 (67%), Grade ≥3: 35/108 (32%)	Reported for phase 1 (n=6): Tocilizumab: 2/6 (33%) Tocilizumab and steroids: 4/6 (67%) Prophylactic use of tocilizumab in phase 2 (cohort 3)	AN: 73/108 (68%), Grade ≥3: 49/108 (45%) LEU: 20/108 (19%), Grade ≥3: 18/108 (17%) NEU: 48/108 (44%), Grade ≥3: 42/108 (39%) TH: 38/108 (35%), Grade ≥3: 26/108 (24%) Any prolonged cytopenias lasting ≥ 30 days: 49/108 (45%), Grade ≥3: 32/108 (30%)	39/108 (36%), Grade ≥3: 35/108 (32%)	Any infections: NR, Grade ≥3: 30/108 (28%)
ZUMA-6	n=34 (phase 1 and 2) with available data for safety in CT.gov	34/34 (100%), Grade ≥3: 11/12 (92%) (reported for phase 1)	23/34 (68%), Grade ≥3: NR	CRS: 33/34 (97%), Grade ≥3: 3/12 (25%) (reported for phase 1)	Neurological events: NR, Grade ≥3: 6/12 (50%)	NR	AN: NR, Grade ≥3: 9/12 (75%) (reported for phase 1) LEU: 5/34 (15%), Grade ≥3: NR NEU: NR, Grade ≥3: 5/12 (42%) (reported for phase 1) TH: 4/34 (12%), Grade ≥3: NR Prolonged cytopenias: NR	NR	NR

AN = anemia; CRS = cytokine release syndrome; LEU = leukopenia; NEU = neutropenia; NR = not reported; TH = thrombocytopenia

[a] Please note that the numbers of participants refer to safety data retrieved from the primary publication unless otherwise specified. For detailed information on the participant flow including the numbers of participants enrolled, receiving CAR-T cells and evaluated, see *Table 1*.

[b] Use of tocilizumab and/or corticosteroids for treatment of CRS and/or neurotoxicity (e.g. glucocorticoids such as dexamethason)

[c] Cytopenias including anemia, leukopenia, neutropenia, thrombocytopenia and any prolonged cytopenias

Certainty of the evidence

Using the GRADE approach we rated the certainty of the evidence as very low for all outcomes. As we identified trials with either a single arm or multiple arms of CAR-T cell therapy without a control group only, we did not meta-analyse any data but described the results narratively only. The certainty of evidence ratings for overall survival, progression-free survival, complete response rates, quality of life, any adverse events, any serious adverse events and cytokine release syndrome are presented in *Table 6*.

Table 6: Certainty of the evidence ratings for the efficacy and safety of CAR-T cell therapy for people with relapsed or refractory DLBCL

Population: people with DLBCL
Setting: inpatient
Intervention: CAR-T cell therapy
Comparison: not applicable; trials with either a single arm or multiple arms of CAR-T cell therapy without a control group only

Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of the evidence (GRADE)
Overall survival	Serious[a]	Not serious	Not serious	Serious[b]	Study design[c]	⨁⊖⊖⊖ **Very low**
Progression-free survival	Serious[a]	Not serious	Not serious	Serious[b]	Study design[c]	⨁⊖⊖⊖ **Very low**
Complete response	Serious[a]	Not serious	Not serious	Serious[b]	Study design[c]	⨁⊖⊖⊖ **Very low**
Quality of life	Serious[a]	Not serious	Not serious	Serious[b]	Study design[c]	⨁⊖⊖⊖ **Very low**
Any adverse events	Serious[a]	Serious[d]	Not serious	Serious[b]	Study design[c]	⨁⊖⊖⊖ **Very low**
Any serious adverse events	Serious[a]	Serious[d]	Not serious	Serious[b]	Study design[c]	⨁⊖⊖⊖ **Very low**
Cytokine release syndrome	Serious[a]	Serious[d]	Not serious	Serious[b]	Study design[c]	⨁⊖⊖⊖ **Very low**

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] The overall risk of bias was judged to be high for all trials (downgraded by 1 point).
[b] None of the trials had a control group and effect estimates could not be calculated (downgraded by 1 point).
[c] We included trials with either a single arm or multiple arms of CAR-T cell therapy without a control group only, so the assessment of certainty of the evidence for all outcomes started from 'low'.
[d] Duration of follow-up varied substantially (downgraded by 1 point).

Conclusion

The prognosis of people with heavily pretreated relapsed or refractory DLBCL who are not candidates for autologous stem-cell transplantation, or people who relapse after autologous stem-cell transplantation, is generally very poor. In a limited number of study participants CAR-T cell therapy was associated with a median overall survival well above 12 months, reaching 24 months in about half of the cases. Confidence in the data is low due to the lack of a control group and limited internal and external validity. Given the association of CAR-T cell therapy with substantial toxicities which might lead to prolonged hospitalisation or death, and the limited feasibility of CAR-T cell therapy outside authorised centres of excellence, the value of this therapeutic approach is still uncertain.

8. Summary of available data on comparative cost and cost-effectiveness of the medicine.

An electronic search for economic evidence was conducted in PubMed in October 2020, using the key words “cost analysis”, “cost benefit”, “QALY”, “ICER”, “Tisagenlecleucel”, “Axicabtagene ciloleucel”. References related to relapsed or refractory diffuse large b-cell lymphoma were retrieved. Additionally, Health Technology Assessment (HTA) reports conducted by the National Institute for Health and Care Excellence (NICE, UK) and the Institute for Quality and Efficiency in Health Care (IQWiG, Germany) were sought.

Treatment with chimeric antigen receptor (CAR)-T cells is technologically demanding and resource intensive. It requires well-equipped facilities for its manufacturing as well as trained physicians to administer the treatment. Global availability of CAR-T cell therapy is limited. It has not been introduced in lower- or middle-income countries (LMIC) (41, 42). Therefore, data on its comparative cost and cost effectiveness are limited to a few countries. Moreover, these data often do not account for costs arising from additionally needed treatment and hospitalization.

Treatment for both, Axicabtagene ciloleucel (axi-cel) and Tisagenlecleucel (tisa-cel), consists of a single use per year per patient (3, 4).
The listed price for axi-cel in the US was reported to be 375.000$ (43), in Germany it was 327.000€ (44).
The estimated costs per case varied between 552.921$ and 655.000$ (45, 46) per case. Yearly therapy costs in Germany were estimated to lie between 396.538,19€ - 398.392,75€ (47), depending on the use of additional treatments.

The listed price for tisa-cel in the US is 475.000$, in Germany it is reported to be 320.000€ (48). The estimated costs per case were between 382.702$ - 529.000$ (45, 49). Yearly therapy costs in Germany were estimated to be 282.419,28€ - 283.244,95€ (50), depending on the additionally needed treatments. However, it is important to note that, due to reimbursement processes in Germany, not all additional treatment costs may be covered by these figures. The overall treatment costs might be higher (44).

Budget impact calculations yielded estimations of additional 12 billion $ for axi-cel and 9 billion $ for tisa-cel per year for the US healthcare system, if these treatments were administered to all eligible patients (45).

Cost-effectiveness for both substances varied between studies and reports, depending on the time-horizon and perspective of the analyses and on the inclusion of additional treatment costs. All analyses used salvage chemotherapy as a comparator.

Results for the cost-effectiveness of axi-cel varied greatly, with ICERs reported between below 50.000$ and up to 159.000$ per QALY gained. The NICE report also stated an ICER between <50.000£ and >100.000£ per QALY gained (51).

From an Italian payer perspective, an ICER of 44.746€ per QALY gained was reported over a lifetime horizon (52, 53). From a US payer perspective, Roth et al. reported an ICER of 58.146$ per QALY gained. This included drug, procedure and future healthcare costs in long-term remission (46).
A higher ICER from the same perspective was presented by Lin et al., with an analysis including all additional treatment needed over a lifetime horizon. The ICER per QALY gained was reported being between 129.000$ and 159.000$, depending on the use of additional treatment and the overall outcome (45).

Results for ICER per life year gained (LYG) varied slightly less broadly. Roth et al. stated an ICER per LYG of 55.128$ (46) and Marchetti et al. stated an ICER per LYG of 42.873€ (52).

Results for tisa-cel varied between ICERs per QALY gained of about 42.000$ up to 508.530$, depending on the time horizon and perspective of the analyses. The NICE report stated an ICER per QALY gained of between 42.991£ and 55.403£ and added that this ICER range is higher than usually acceptable (54).

The highest ICER was reported from a Singapore healthcare payer perspective with 508.530$ per QALY gained (55). From a Canadian societal perspective, Yang et al. reported an ICER per QALY gained of 103.112$ over a time horizon of 20 years (49). A higher ICER was once again presented by Lin et al. Analysis included a lifetime horizon of a US health payer perspective. ICERs per QALY gained between 168.000$ and 223.000$ were reported (45).

Results for ICERs per LYG also varied for tisa-cel. Whereas Cher et al. reported an ICER of 320.200$ (55), Yang et al. stated an ICER per LYG of 109.461$ (49).

Cost-effectiveness for both, axi-cel and tisa-cel, highly depends on the payer's perspective, the applied time horizon and the inclusion of additional treatment costs. In some cases, both medicines can be cost-effective compared to other treatment options, especially if ICERs per LYG are taken into consideration. However, even if given a threshold of 150.000$ or less per QALY gained, both treatments are unlikely to be cost-effective compared to other forms of treatment.

Both Gilead (for axi-cel) and Novartis (for tisa-cel) have recently signed outcome-based agreements with several German health insurers. These agreements state that the manufacturer will partially reimburse the treatments cost to the German health care fund if the patient dies within a defined period of time (56, 57).

Regulatory information

9. Summary of regulatory status and market availability of the medicine.

Tisagenlecleucel (tisa-cel) and Axicabtagene ciloleucel (axi-cel) have been approved by several regulatory agencies.

Neither substance has any existing or planned licencing agreements with generic manufacturers and/or the Medicines Patent Pool.

Tisa-cel was approved by the Food and Drug Administration (FDA, United States of America) (7), European Medicines Agency (EMA, Europe) (2), the Australian Government (58) and Health Canada (59, 60) for the following indications:

1) Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
2) Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma

Health Canada and the Australian Government also added paediatric patients who have relapsed post allogeneic stem cell transplant (SCT) or are otherwise ineligible for SCT as an indication to part 1) (58, 60).

The Pharmaceuticals and Medical Devices Agency (PMDA, Japan) has not yet approved tisa-cel for treatment. However, the Committee on Regenerative Medicine Products and Biotechnology has advised the PMDA to accept tisa-cel for approval for the following indications (61):

- Patients with relapsed or refractory CD-19 positive B-cell acute lymphoblastic leukemia meeting any of the following criteria:
    - Newly diagnosed patients who failed to achieve remission with ≥2 lines of standard chemotherapy.
    - Patients with relapsed disease who failed to achieve remission with ≥1 line of chemotherapy.
    - Patients who are ineligible for, or relapsed after, allogeneic hematopoietic stem cell transplantation.
- Patients with relapsed or refractory CD-19-positive diffuse large B-cell lymphoma meeting any of the following criteria for, or if relapsed after, autologous hematopoietic stem cell transplantation:
    - Newly diagnosed patients who failed to achieve a complete response to ≥2 lines of chemotherapy; newly diagnosed patients who achieved a complete response to ≥2 lines of chemotherapy but subsequently relapsed; patients who received ≥1 line of chemotherapy after relapse but failed to achieve a complete response; or patients who received ≥1 line of chemotherapy after relapse and achieved a complete response but subsequently relapsed again.
    - Patients with diffuse large B-cell lymphoma transformed from follicular lymphoma who failed to achieve a complete response to ≥2 lines of chemotherapy including ≥1 line after the transformation, or who achieved a complete response to ≥2 lines of chemotherapy including ≥1 line after the transformation but subsequently relapsed.

Axi-cel was also approved by the FDA (8), EMA (1), the Australian Government (62) and Health Canada (63) for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
It has not been approved by the PMDA. An estimation for when approval can be expected cannot be made.

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Figures

Tables

Appendix

Appendix 1: Risk of bias assessment based on criteria for observational studies provided by the Cochrane Childhood Cancer Group (36)

	Internal validity	**External validity**
Study group	Selection bias (representative: yes/no) • if the described study group consisted of > 80% of the DLBCL participants treated with CAR T-cells in the original cohort or • if it was a random sample with respect to the cancer treatment and important prognostic factors	Reporting bias (well defined: yes/no) • if the mean/median or range of the cumulative CAR T-cell dose was mentioned and • when it was described what prior treatment (including the received doses) was given
Follow-up	Attrition bias (adequate: yes/no) • if the outcome was assessed for > 90% of the study group of interest (++) or • if the outcome was assessed for 60% to 90% of the study group of interest (+)	Reporting bias (well defined: yes/no) • if the length of follow-up was mentioned
Outcome	Detection bias (blind: yes/no) • if the outcome assessors were blinded to the investigated determinant	Reporting bias (well defined: yes/no) • if the outcome definition was objective and precise, and the method of detection was provided
Risk estimation	Confounding (adjustment for other factors: yes/no) • if important prognostic factors (i.e. age, gender, co-treatment) or follow-up were taken adequately into account	Analyses (well defined: yes/no) • if a risk ratio, odds ratio, attributable risk, linear or logistic regression model, mean difference or Chi^2 was calculated