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Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma (Review)

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[Intervention Review]

Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma

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ABSTRACT

Background

Diffuse large B-cell lymphoma (DLBCL) is an aggressive cancer of the lymphatic system. About 30% to 40% of people with DLBCL experience relapse and 10% are refractory to first-line treatment usually consisting of R-CHOP chemotherapy. Of those eligible for second-line treatment, commonly consisting of salvage chemotherapy followed by autologous stem-cell transplantation (ASCT), around 50% experience relapse. With a median overall survival of less than six to 12 months, the prognosis of individuals who relapse or are refractory (r/r) to advanced lines of treatment or of those who are ineligible for ASCT, is very poor. With the introduction of chimeric antigen receptor (CAR) T-cell therapy, a novel treatment option for these people is available.

Objectives

To assess the benefits and harms of chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory (r/r) DLBCL.

Search methods

An experienced information specialist performed a systematic database search for relevant articles on CENTRAL, MEDLINE and Embase until September 11th, 2020. We also searched trial registries and reference lists of identified studies up to this date. All search results were screened by two authors independently and a third author was involved in case of discrepancies.

Selection criteria

We included prospectively planned trials evaluating CAR T-cell therapy for people with r/r DLBCL. We had planned to include randomised controlled trials (RCTs) and we flexibly adapted eligibility criteria to the most reliable study designs available. We excluded studies involving fewer than 10 participants with r/r DLBCL and studies with a proportion of participants with r/r DLBCL below 70%, unless data were reported separately for this subgroup.

Data collection and analysis

Two review authors extracted data and performed risk of bias ratings independently. A third author was involved in case of disagreements. As our search did not yield any completed RCTs, prospective controlled non-randomised studies of interventions (NRSIs) or prospective

observational studies with a control group, we did not meta-analyse data and reported all results narratively. We adopted the GRADE approach to assess the certainty of the evidence for prioritised outcomes.

Main results

We identified 13 eligible uncontrolled studies evaluating a single or multiple arms of CAR T-cell therapies. We also identified 38 ongoing studies, including three RCTs. Ten studies are awaiting classification due to completion with no retrievable results data or insufficient data to justify inclusion. The mean number of participants enrolled, treated with CAR T-cell therapy and evaluated in the included studies were 79 (range 12 to 344; data unavailable for two studies), 61 (range 12 to 294; data unavailable for one study) and 52 (range 11 to 256), respectively.

Most studies included people with r/r DLBCL among people with other haematological B-cell malignancies. Participants had received at least a median of three prior treatment lines (data unavailable for four studies), 5% to 50% had undergone ASCT (data unavailable for five studies) and, except for two studies, 3% to 18% had undergone allogenic stem-cell transplantation (data unavailable for eight studies).

The overall risk of bias was high for all studies, in particular, due to incomplete follow-up and the absence of blinding. None of the included studies had a control group so that no adequate comparative effect measures could be calculated. The duration of follow-up varied substantially between studies, in particular, for harms. Our certainty in the evidence is very low for all outcomes.

Overall survival was reported by eight studies (567 participants). Four studies reported survival rates at 12 months which ranged between 48% and 59%, and one study reported an overall survival rate of 50.5% at 24 months. The evidence is very uncertain about the effect of CAR T-cell therapy on overall survival.

Two studies including 294 participants at baseline and 59 participants at the longest follow-up (12 months or 18 months) described improvements of quality of life measured with the EuroQol 5-Dimension 5-Level visual analogue scale (EQ-5D-5L VAS) or Function Assessment of Cancer Therapy-Lymphoma (FACT-Lym). The evidence is very uncertain about the effect of CAR T-cell therapy on quality of life.

None of the studies reported treatment-related mortality.

Five studies (550 participants) reported the occurrence of adverse events among participants, ranging between 99% and 100% for any grade adverse events and 68% to 98% for adverse events grade ≥ 3. In three studies (253 participants), 56% to 68% of participants experienced serious adverse events, while in one study (28 participants), no serious adverse events occurred. CAR T-cell therapy may increase the risk of adverse events and serious adverse events but the evidence is very uncertain about the exact risk.

The occurrence of cytokine release syndrome (CRS) was reported in 11 studies (675 participants) under use of various grading criteria. Five studies reported between 42% and 100% of participants experiencing CRS according to criteria described in Lee 2014. CAR T-cell therapy may increase the risk of CRS but the evidence is very uncertain about the exact risk.

Nine studies (575 participants) reported results on progression-free survival, disease-free survival or relapse-free survival. Twelve-month progression-free survival rates were reported by four studies and ranged between 44% and 75%. In one study, relapse-free survival remained at a rate of 64% at both 12 and 18 months. The evidence is very uncertain about the effect of CAR T-cell therapy on progression-free survival.

Thirteen studies (620 participants) provided data on complete response rates. At six months, three studies reported complete response rates between 40% and 45%. The evidence is very uncertain about the effect of CAR T-cell therapy on complete response rates.

Authors' conclusions

The available evidence on the benefits and harms of CAR T-cell therapy for people with r/r DLBCL is limited, mainly because of the absence of comparative clinical trials. The results we present should be regarded in light of this limitation and conclusions should be drawn very carefully. Due to the uncertainty in the current evidence, a large number of ongoing investigations and a risk of substantial and potentially life-threatening complications requiring supplementary treatment, it is critical to continue evaluating the evidence on this new therapy.

PLAIN LANGUAGE SUMMARY

CAR T-cell therapy for people with diffuse large B-cell lymphoma which returns after treatment or no longer responds to treatment

Background

Diffuse large B-cell lymphoma (DLBCL) is a fast-growing cancer of the lymphatic system, an important part of the immune system. It affects blood cells that produce antibodies to fight infections.

DLBCL is potentially curable. Most people with DLBCL respond well to initial therapies such as chemotherapy. For some people, the disease becomes refractory, which means it no longer responds to treatment, or it relapses, which means it returns after treatment. As a second-line treatment, people with DLBCL can receive chemotherapy coupled with stem-cell transplantation, but not all people are candidates for this therapy. From those who are, around 50% experience relapse after treatment. People who relapse or are refractory to advanced

lines of treatment and those who are not candidates for a stem-cell transplant have a very poor prognosis: Only half of them survive longer than six to 12 months.

A promising treatment for these people is 'chimeric antigen receptor' (CAR) T-cell therapy, which utilises the body's own immune cells (T-cells) to fight DLBCL. T-cells are removed from the person's blood, equipped with so-called 'chimeric antigen receptors' (CARs), that help to recognise and destroy the cancer cells, in the laboratory and then delivered back into the person's blood.

What was our aim?

We wanted to explore whether CAR T-cells are an effective treatment for people with DLBCL that returns after treatment (relapses) or no longer responds to treatment (is refractory). We also wanted to explore the frequency of unwanted effects associated with CAR T-cell therapy.

What did we do?

We searched for all available clinical studies on treatment with CAR T-cells for people with relapsed or refractory DLBCL to summarise the current evidence. We also evaluated the risk of bias in included studies and rated our confidence in the evidence.

What did we find?

We found 13 studies with information on 679 participants (who had received several prior lines of therapy) that received CAR T-cell therapy. None of the studies had a control group. This means CAR T-cells were not compared with another treatment. We decided not to meta-analyse the study results and reported all results narratively. We also found 38 ongoing studies.

What are the key results?

Eight studies with 567 participants evaluated overall survival. After 12 months, around half of participants were alive in four studies. In one study, around half of participants were alive after 24 months. The evidence is very uncertain about the effect of CAR T-cells on survival.

Two studies (294 participants at study start; 59 participants at study end) reported that quality of life improved over time. The evidence is very uncertain about the effect of CAR T-cells on quality of life.

Deaths related to the therapy were not reported.

Five studies (550 participants) reported on adverse events. Almost all participants (99% to 100%) experienced some kind of adverse event (including mild events). Between 68% and 98% of participants had adverse events that were severe. CAR T-cells may increase the risk of adverse events but the evidence about the exact risk is very uncertain.

In three studies (253 participants), 56% to 68% of participants experienced serious adverse events, while in one study (28 participants), participants had no serious adverse events. CAR T-cells may increase the risk of serious adverse events but the evidence about the exact risk is very uncertain.

Eleven studies (675 participants) reported on the frequency of 'cytokine release syndrome' (CRS), an overreaction of the immune system that is typically seen in CAR T-cell therapy. It includes fever and can include symptoms such as chills, muscle pain or dizziness. Several scales were used across the studies to describe CRS. In five studies using the same scale, between 42% and 100% of participants had CRS. CAR T-cells may increase the risk of CRS but the evidence about the exact risk is very uncertain.

Nine studies (575 participants) reported when DLBCL relapsed (returned) or progressed (got worse). Four studies reported that, at 12 months, DLBCL did not progress in 44% to 75% of participants. In one study, 64% of participants did not relapse at both 12, and 18 months. The evidence is very uncertain about the effect of CAR T-cells on DLBCL relapse or progress.

Thirteen studies (620 participants) reported how many participants had a complete response (all signs of cancer disappeared). In three studies, between 40% and 45% of participants experienced a complete response at six months. The evidence is very uncertain about the effect of CAR T-cells on complete response.

What does this mean?

The evidence on CAR T-cells in the treatment of relapsed or refractory DLBCL is very uncertain. This is mainly because, today, there are no direct comparisons of CAR T-cells with other treatments. People who receive CAR T-cells can have severe adverse events that require additional treatment. We identified many ongoing studies and some of them compare CAR T-cells with standard care. We will keep evaluating the evidence on this novel therapy.

How up-to-date is this review?

The evidence is current to September 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings for the efficacy and safety of CAR T-cell therapy for people with relapsed or refractory DLBCL

Summary of findings for the efficacy and safety of CAR T-cell therapy for people with relapsed or refractory DLBCL

Patient or population: people with relapsed or refractory DLBCL
Setting: inpatient cancer care
Intervention: CAR T-cell therapy
Comparison: not applicable; studies with either a single arm or multiple arms of CAR T-cell therapy without a control group only

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Overall survival (follow-up: range 6 months to 24 months[a])	Overall survival was reported by eight uncontrolled studies. Four studies reported survival rates at 12 months which ranged between 48% and 59%, and one study reported an overall survival rate of 50.5% at 24 months.	567 (8 observational studies)	⊕⊖⊖⊖ VERY LOW [1,2]
Quality of life (assessed with EQ-5D-5L VAS or FACT-Lym; follow-up: range 1 month to 18 months)	Two uncontrolled studies including 294 participants at baseline and 59 participants at the longest follow-up described improvements of quality of life over time; One study (186 participants at baseline, 38 participants evaluated at 12 months of follow-up) reported an increase in EQ-5D-5L VAS scores (indicating improvement); One study (108 participants at baseline, 21 participants evaluated at 18 months of follow-up) reported an increase in FACT-Lym total scores (indicating improvement).	294 (2 observational studies)	⊕⊖⊖⊖ VERY LOW [1,2]
Any adverse events (follow-up: any time after CAR T-cell infusion)	Five uncontrolled studies reported the occurrence of adverse events among participants, ranging between 99-100% for any grade adverse events and 68-98% for adverse events grade ≥ 3.	550 (5 observational studies)	⊕⊖⊖⊖ VERY LOW [1,2,3]
Any serious adverse events (follow-up: any time after CAR T-cell infusion)	In three uncontrolled studies, 56% to 68% of participants experienced serious adverse events while, in one uncontrolled study, no serious adverse events occurred.	281 (4 observational studies)	⊕⊖⊖⊖ VERY LOW [1,2,3]
Cytokine release syndrome (follow-up: any time after CAR T-cell infusion)	Various grading criteria were used in 11 uncontrolled studies which reported the occurrence of cytokine release syndrome (CRS). Five studies reported between 42% and 100% of participants experiencing CRS according to criteria described in Lee 2014.	675 (11 observational studies)	⊕⊖⊖⊖ VERY LOW [1,2,3]
Progression-free survival (follow-up: range 4 months to 18 months[a])	Nine uncontrolled studies reported results on progression-free survival, disease-free survival or relapse-free survival at any time of follow-up. 12-month progression-free survival rates were reported by four studies and ranged between 44% and 75%. In one study, relapse-free survival remained at a rate of 64% at both 12, and 18 months.	575 (9 observational studies)	⊕⊖⊖⊖ VERY LOW [1,2]

Complete response (follow-up: range 1 month to 6 months[a])	All of the 13 uncontrolled studies provided data on complete response rates. At six months, three studies reported complete response rates between 40% and 45%.	620 (13 observational studies)	⊕⊖⊖⊖ VERY LOW [1] [2]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

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

EQ-5D-5L VAS = EuroQol 5-Dimension 5-Level visual analogue scale
FACT-Lym = Function Assessment of Cancer Therapy-Lymphoma
[1] The overall risk of bias was judged to be high for all studies (downgraded by 1 point for risk of bias).
[2] None of the included studies had a control group and effect estimates could not be calculated (downgraded by 1 point for imprecision).
[3] Duration of follow-up varied substantially (downgraded by 1 point for inconsistency).
For all outcomes, our assessment of the certainty of the evidence started with "low certainty" as we only included observational studies.
[a] Due to various follow-up times in the included studies, we included time point-specific outcome data in the summary of findings table only.

BACKGROUND

Description of the condition

Classification of tumours of haematopoietic and lymphoid tissues by the World Health Organization (WHO) comprises a wide-ranging group of cancers originating from B-cells (Swerdlow 2017). B-cells are lymphocytes, one of the main types of white blood cells, which fight infections and diseases of the human body. As part of the adaptive human immune system, B lymphocytes recognise substances (antigens), which are foreign to the human body and are responsible for the production of targeted antibodies via differentiation into plasma cells. Most lymphoid malignancies, including the majority of non-Hodgkin lymphomas (NHL) and lymphoid leukaemia, originate from B-cells. Lymphoid malignancies derived from T or natural killer lymphocytes are less common (Swerdlow 2017).

Lymphomas originating from malignant alterations of the B-cells comprise 90% of all NHL cases in Western countries. The most common type of B-cell neoplasms are diffuse large B-cell lymphomas (DLBCL). They make up around 40% of all NHL and are thus the most common type of malignant lymphoma worldwide (Stewart 2014; Swerdlow 2017; Teras 2016). DLBCL are defined as "neoplasms of large B lymphoid cells with nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of a normal lymphocyte" (Swerdlow 2017). Non-Hodgkin lymphomas are commonly subdivided based on the speed of their growth. Aggressive, rapidly evolving diseases which spread malignant lymphocytes at early stages throughout the human body demand immediate and often very intensive treatment. DLBCL make up around 80% to 90% of all aggressive (high-grade) lymphomas. They are distinct from slower growing (low-grade) B-cell malignancies, such as follicular lymphomas or chronic lymphatic leukaemia. The latter are often indolent but complete cure usually cannot be achieved, meaning that treatment aims to reduce the symptoms. Such diseases, therefore, follow a recurring/remitting course.

The most common type of DLBCL is DLBCL not otherwise specified (NOS) (Swerdlow 2017). According to cell-of-origin, it can be subclassified into a germinal centre B-cell type and an activated B-cell type (Alizadeh 2000), leaving about 10% of cases unclassified (Rosenwald 2002). This distinction is associated with survival after treatment, with favourable survival after chemotherapy for germinal centre B-cell type DLBCL. Morphologically, DLBCL is subdivided into centroblastic, immunoblastic and anaplastic variants. However, there are other rare morphological variants. Further classifications based on immunophenotypes, involved molecular mechanisms and genetic subtypes exist (Schmitz 2018; Swerdlow 2017). Particular subtypes of the DLBCL are: T-cell rich large B-cell lymphoma; primary DLBCL of the central nervous system; primary cutaneous DLBCL, leg type; and an Epstein-Barr virus-positive DLBCL NOS. Several other malignant lymphomas, including follicular lymphoma, can transform into DLBCL. There is a variety of other lymphomas of large B-cells and several borderline cases (Swerdlow 2017).

The global epidemiological data for the burden of DLBCL are limited. However, using data for the USA as an example, the age-adjusted incidence rate of DLBCL was 5.5 per 100,000, and the mortality rate was 1.8 per 100,000 persons in 2015 (Noone 2018). DLBCL primarily affects the elderly, with a median age at diagnosis of 65 years. Although it is more frequent among those of 60 years and older, it can occur in all age groups with about 1% of new cases in children and adolescents younger than 20 years (Noone 2018). Men are slightly more often affected than women. Around 60% of all HIV-associated NHL are DLBCL (Beral 1991).

DLBCL primarily originate from the lymph nodes. However, they can occur in virtually any other part of the body, such as bones, the gastrointestinal tract, the central nervous system and the thyroid. Symptoms of DLBCL are mostly unspecific. Early symptoms are primarily swelling of the affected lymph nodes and the spleen. Neck and mediastinal nodes are more frequently affected than those below the diaphragm. In 10% to 15% of individuals, DLBCL affects the bone marrow at diagnosis, which may result in decreased blood cell formation (Chung 2007). Anaemia, thrombocytopenia and leukocytopenia may then result in further symptoms such as fatigue, increased bleeding and infections. Typical B-symptoms (fever, night sweats, weight reduction) which are common in people suffering from Hodgkin lymphoma are possible, but rather infrequent (Swerdlow 2017).

The Ann Arbor Classification is used for staging and distinguishes between four different tumour stages (Rosenberg 1971). Stages I to III indicate the degree of lymph node and localised extranodal organ involvement or both, and stage IV includes disseminated organ involvement. Stages I and II are considered 'limited', while III and IV represent 'advanced' disease. Around 45% of new DLBCL cases are localised (stage I (25%) and II (20%)). In the remaining cases, DLBCL is first diagnosed in stages III (17%), stage IV (33%) or unstaged (5%) (Noone 2018). Factors for unfavourable prognosis include older age, higher stages of disease, extranodal disease, decreased performance status and increased blood (serum) levels of lactate dehydrogenase (Vaidya 2014). When fluorodeoxyglucose positron emission tomography–computed tomography, which is nowadays proposed as a gold standard in routine staging, is applied, the disease is described using the Lugano classification, a modification of the Ann Arbor staging system (Barrington 2014; Cheson 2014).

Survival rates have substantially improved recently with an estimated 5-year survival up to 63% (Noone 2018; Sant 2014). The 3-year survival rates for individuals in low-risk groups is estimated to be as high as 91% (Tilly 2015). DLBCL is most often treated with chemotherapy. In the past, cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) was the standard chemotherapy regimen. Now, survival has been improved by incorporating rituximab, a CD20 antibody, into the regimens (R-CHOP) (Coiffier 2002; Kubuschok 2015; Pfreundschuh 2006). R-CHOP is now the preferred regimen for the majority of first-line therapies. Individuals with ('limited') stage I or II disease often receive up to six cycles of R-CHOP and additional radiation if there are bulky lymph nodes. Individuals in the higher-risk groups eventually receive R-CHOP in different combinations of cycles, although other chemotherapy regimens, such as doxorubicin, vindesine, cyclophosphamide, bleomycin and prednisolone (ACVBP) in younger patients, are frequently given too (Tilly 2015).

It is estimated that about 30% to 40% of DLBCL will relapse and 10% will be refractory (Abramson 2017; Stewart 2014). Previous prognostic factors, prior treatment regimens and time from initial treatment are important determinants for the probability of relapse. Standard care for individuals with refractory or relapsed (r/r) disease is usually autologous stem-cell transplant following high-dose chemotherapy or, in limited cases, allogenic

stem-cell transplantation after initial high-dose chemotherapy. Salvage therapies include rituximab, dexamethasone, cytarabine and cisplatin (R-DHAP) and rituximab, ifosfamide, carboplatin and etoposide phosphate (RICE). Unfortunately, only 30% to 40% of individuals are eligible to receive transplantation. Factors which influence eligibility are old age, comorbidities, or self-expressed refusal of the treatment. Such individuals have a considerably worse outcome (Thieblemont 2007). Ineligible individuals and those who experience multiple relapses of DLBCL may then be treated with dose modifications or regimen alterations of chemotherapy. Other antineoplastic agents, such as bendamustine, lenalidomide and nivolumab have shown activity in DLBCL. However, their activity is fairly limited, as expressed in low response rates and shorter survival (Lesokhin 2016; Weidmann 2002; Zinzani 2016).

Description of the intervention

The five-year survival rate for people suffering from DLBCL after the first relapse is estimated to be around 27%. Of those people who undergo treatment directly after the relapse, approximately 30% are estimated to be alive after five years. Of those who undergo autologous stem-cell transplant, around 45% are estimated to survive five years after the relapse (McMillan 2016). The outcome for individuals who are resistant to primary therapy or who have a second relapse is considerably worse. The median survival of individuals who relapse from high-dose therapy and autologous stem-cell transplant, for example, is estimated to be as low as three months (Friedberg 2011; Vose 1992). For people with refractory disease, the one-year survival rates are estimated to be less than one-third (Crump 2017).

A new treatment concept of genetically engineered immunotherapy is now available; the so-called 'chimeric antigen receptor (CAR)-T' cell therapy leads to considerable response rates even in highly pretreated patients suffering from various types of NHL (Maude 2018; Neelapu 2017; Park 2018; Schuster 2018). Therefore, the US Food and Drug Administration (FDA) granted breakthrough designation for a CD19-targeted CAR T-cell therapy for patients with r/r NHL in 2017 (Abramson 2016; US FDA 2017; US FDA 2018). Approval to treat adult patients was given for the CAR T-cell therapies, axicabtagene ciloleucel (axi-cel), for adults with r/r follicular lymphoma, an indolent lymphoma, or r/r aggressive B-cell NHL, including DLBCL, and tisagenlecleucel for patients aged 25 or younger with r/r B-cell acute lymphoblastic leukaemia (B-ALL), another B-cell malignancy. The European Medicines Agency (EMA) recommended market authorisation for both CAR T-cell therapies, axi-cel and tisagenlecleucel in June 2018. These are the first medicines supported by the PRIority MEdicines (PRIME) scheme. Axi-cel was declared eligible for the PRIME scheme for the treatment of r/r DLBCL (European Medicines Agency 2018). A third substance, lisocabtagene maraleucel (liso-cel) has just been approved for the treatment of patients suffering from NHL, including DLBCL, upon evaluation in a phase one single-arm study (Abramson 2016; US FDA 2021).

New drugs in oncology are very expensive, and CAR T-cell therapies are considered the most expensive cancer drugs, with costs between USD 373,000 and USD 475,000 for a single infusion, not including potential hospital care costs or management of side effects (Bach 2017; ICER 2018). Nevertheless, the Institute for Clinical and Economic Review (ICER), California, reported that CAR T-cell clinical effects are cost-effective as far as this could be assessed, based on non-randomised studies without control groups (ICER 2018). Novartis, the producer of tisagenlecleucel, offers an outcome-based pricing arrangement for the treatment of B-ALL. The agreement offers participating centres to only be charged for individuals responding to the treatment within the first month past infusion, regardless of the person's insurance plan (Novartis 2017).

The ICER conducted a two-part economic model based on a decision tree and a semi-Markov partitioned survival model, which represents the third payer perspective over a lifetime time horizon (ICER 2018). For individuals with aggressive B-cell lymphoma, including mainly cases of DLBCL, the CAR T-cell therapy axi-cel, led to total base case costs of approximately USD 617,000 with 7.35 discounted life-years and 5.87 discounted quality-adjusted life-years gained, compared to total costs of USD 154,884 for chemotherapy, leading to 3.23 discounted life-years and 2.48 quality-adjusted life-years gained. Thus, costs for axi-cel were four times that of chemotherapy, but gains in life-years and quality-adjusted life-years were more than two-fold higher. The incremental cost-effectiveness ratio was as high as USD 136,000 per quality-adjusted life-year gained and USD 112,000 for every life-year gained (ICER 2018).

How the intervention might work

In CAR T-cell therapy, genetic engineering is used to modify an individual's own T-cells ex vivo and add a chimeric antigen receptor (CAR) to the cell. To produce personalised therapy, T-cells are first collected from the person's blood and then altered in the laboratory before they are multiplied and returned to the individual via an infusion. Through genetic modification, T-cells are enabled to produce transmembrane proteins on their cell surface with an extracellular antibody fragment domain that is capable of recognising and binding a specific protein or antigen. Using this practice, immune cells are artificially targeted to the respective cancer cells. Once a tumour cell is recognised, the CAR T-cell is triggered by binding to the cancer cell and thereby becoming a cytotoxic T-cell, which destroys the respective cancer cell. Additionally, activation of the CAR T-cells enables their proliferation, meaning they multiply naturally after infusion in to the person's body, a feature which is unique to CAR T-cells. After eradication of the cancer cells, CAR T-cells eventually persist and are reactivated on tumour recurrence (Buchholz 2018). All approved substances, tisagenlecleucel, axi-cel and liso-cel specifically target the CD19 antigen which is expressed on B-cells which are malignantly altered in DLBCL.

The most common side effect of CAR T-cell therapy is the cytokine release syndrome. Cytokines, including interleukin-6, are released by immune cells and responsible for signalling the stimulation and direction of immune responses within the human immune system. The cytokine release syndrome describes the accelerated and extensive, but transient release of cytokines into the blood serum. It usually occurs within two to three weeks following the infusion. Typical symptoms are high fever, hypotension and respiratory distress (Jin 2018; Porter 2015). Moreover, neurotoxicity commonly occurs with CAR T-cell therapy. Another potential side effect of the treatment is B-cell aplasia. The CD19 antigen is also expressed on non-malignant B-cells. Since such cells are likewise frequently affected and destroyed by the CAR T-cell treatment, patients often require supportive immunoglobulin therapy to prevent infections.

Why it is important to do this review

As mentioned above, CAR T-cell therapy has been approved for the treatment of patients with r/r DLBCL based on evidence from small single-arm studies. The approval was given under the reasoning of impressive ("dramatic") response rates even in highly pretreated patients. To date, it remains unclear whether these response rates will translate into an overall survival advantage as it is unknown if and when the disease will progress again. Moreover, severe adverse events are known to be caused by CAR T-cells. Furthermore, the feasibility of CAR T-cell therapy is still limited given the complexity of the process of treatment from manufacturing to administering the product which places high demands on clinical facilities. As treatment with CAR T-cells is increasing and conclusions and clinical decisions based on the available data may be drawn irrespective of potential limitations in the existing evidence, the demand for a clear and objective representation of the available evidence is growing. Therefore, the aim of this systematic review is to provide a comprehensive overview of the benefits and harms of CAR T-cell therapy in individuals with r/r DLBCL based on the evidence that is currently available.

OBJECTIVES

To assess the benefits and harms of chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) in accordance with the available body of evidence.

METHODS

Criteria for considering studies for this review

Types of studies

To assess the benefits of CAR T-cell therapy, we planned to include randomised controlled trials (RCTs) only, as such trials, if performed appropriately, currently give the best evidence for novel drugs in highly controlled therapeutic settings. If RCT data would have been available, we would have used the common methods recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020a). In case of insufficient evidence (very low-quality evidence or no evidence) available from RCTs, we planned to include prospective controlled non-randomised studies of interventions (NRSIs) only and intended to use the methods proposed in the *Cochrane Handbook for Systematic Reviews of Interventions* for the inclusion of NRSIs in systematic reviews (Reeves 2020). When insufficient evidence (very low-quality evidence or no evidence) would have been available from RCTs and NRSIs, we intended to include prospective observational studies with a control group and to adopt the methods for the inclusion of NRSIs in systematic reviews as specified by the *Cochrane Handbook for Systematic Reviews of Interventions* as well (Reeves 2020).

As we did not identify any eligible RCTs, NRSIs, and prospective observational studies with a control group, we included prospectively planned uncontrolled studies with either a single arm or multiple arms of CAR T-cell therapy. We followed the common suggestions specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020a), as far as possible, and applied the methods outlined in the following protocol sections. We considered studies including 10 or more participants with r/r DLBCL only.

We included full-text publications, abstract publications, results published in study registries, and information provided by the principal investigators, if sufficient information was available on study design, characteristics of participants, interventions and outcomes. We did not apply any limitations with respect to the length of follow-up.

Types of participants

We included individuals with a confirmed diagnosis of DLBCL, with no age, gender or ethnicity restrictions. We considered individuals with r/r DLBCL.

We excluded studies involving fewer than 10 participants with r/r DLBCL as well as studies with a proportion of participants with r/r DLBCL below 70%, unless data were reported separately for this subgroup. In studies including participants with other malignancies, we used data from participants with r/r DLBCL only, if reported separately.

Types of interventions

We included studies assessing CAR T-cell therapy irrespective of the type of the CAR T-cells (e.g. CD19, CD30, CD20, B-cell maturation antigen) used.

Had comparative studies been available, we would have included the following two main comparisons:

- CAR T-cell therapy versus control treatment, for example, standard treatment (e.g. chemotherapy, high-dose chemotherapy, monoclonal antibodies, autologous stem-cell transplantation and allogenic stem-cell transplantation). Co-interventions would have been required to be comparable between intervention groups.
- CAR T-cell therapy combined with other drugs versus standard treatment.

For uncontrolled studies, we did not carry out an analysis using quantitative data from indirect controls, as we are aware of the difficulties of indirect comparisons of participant groups with varying baseline characteristics, especially in the absence of individual patient data.

We planned to perform separate analyses for various types of CAR T-cells, but did not identify sufficient data.

Types of outcome measures

We included the following outcomes:

Primary outcomes

- Overall survival
- Quality of life measured using reliable and valid instruments
- Treatment-related mortality
- Number of participants with adverse events and serious adverse events, including:
  - Cytokine release syndrome, neurotoxicity and the use of tocilizumab and/or corticosteroids for treatment of cytokine release syndrome and/or neurotoxicity
  - Cytopenias (anaemia, leukopenia, neutropenia, thrombocytopenia and any prolonged cytopenias)
  - Infections

Secondary outcomes

- Progression-free survival
  - The time interval from random treatment assignment on to the study to first confirmed disease progression, disease relapse or death from any cause, or to the last follow-up
- Response to treatment
  - Measured as overall response, complete response and partial response

We chose overall survival and quality of life as primary outcomes as they have the highest relevance to patients and are a direct measure of treatment benefit. Furthermore, overall survival can be considered the most robust endpoint as it does not require blinding. For quality of life, we considered all validated instruments. We had planned to calculate standardised mean differences (SMDs) instead of MDs when differing scales were used between trials (see Measures of treatment effect). However, we only included uncontrolled studies, and we were not able to pool any data.

As secondary outcomes, we included progression-free survival, as it is commonly used to assess stable disease, and response rates, which are a direct measure of tumour activity. Response evaluation preferably follows the criteria suggested by Cheson 2007. We evaluated complete as well as partial response. With regard to adverse events and serious adverse events, we aimed to include all reported adverse events, but put a particular focus on those of direct interest for CAR T-cell therapy (e.g. cytokine release syndrome, neurotoxicity, cytopenias and infections).

For safety outcomes, we reported data irrespective of the proportion of participants with DLBCL described in the study under the reasoning that they are largely applicable across disease entities.

Timing of outcome measurement

For time-to-event outcomes, such as overall survival and progression-free survival, we planned to include outcome measures representing the longest follow-up time available. As we identified uncontrolled studies only and were not able to pool result data, we described the available time-to-event data at all reported time points of follow-up narratively.

Outcomes of all other outcome categories are presented for the observational periods that are reported in the study documents. We included adverse events, both occurring during active treatment as well as long-term adverse events. As we only included uncontrolled studies and did not pool any data, we described results at all reported follow-up times narratively.

Search methods for identification of studies

An experienced information specialist (IM) developed all search strategies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2020). We searched for studies in all languages in order to limit language bias. As publication bias might influence all subsequent analyses and conclusions, we searched all potentially relevant trial registries in detail to detect ongoing as well as completed, but not yet published, studies. When results were not published elsewhere, we extracted data from trial registries.

Electronic searches

We searched the following databases and sources, without any time restrictions:

- Databases of medical literature
  - Cochrane Central Register of Controlled Trials (CENTRAL, 2020, Issue 08) via Cochrane Library (Appendix 1)
  - MEDLINE via OvidSP (inception to 11 September 2020) (Appendix 2)
  - Embase via OvidSP (inception to 11 September 2020) (Appendix 3)
- Study registries and registry platforms to identify ongoing studies and results of completed studies
  - WHO International Clinical Trials Registry Platform (ICTRP): www.apps.who.int/trialsearch/ (Appendix 4) (11 September 2020)
  - EU clinical trials register: www.clinicaltrialsregister.eu/ctr-search/search (Appendix 5) (11 September 2020)
  - ClinicalTrials.gov: https://clinicaltrials.gov/ (Appendix 6) (11 September 2020)

Searching other resources

- Handsearching
  - We checked the reference lists of all identified studies, relevant review articles and current treatment guidelines for further literature.
- Personal contacts
  - For a future update, we will contact experts in the field, drug manufacturers and regulatory agencies in order to retrieve information on unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (ME, MG) independently screened the results of the search strategies for eligibility by reading the titles and abstracts. In the case of disagreements, we obtained the full-text publication for further discussion. Two review authors (ME, MG) then assessed the full-text articles of the selected studies. When the two review authors were unable to reach consensus, a third review author (NS) was consulted to reach a final decision (Higgins 2020a).

We documented the study selection process including the overall numbers of references screened, identified, selected, excluded and included in a flow diagram, as recommended in the PRISMA statement (Moher 2009) (see Figure 1). We listed all articles excluded after full-text assessment and the reasons for exclusion in a Characteristics of excluded studies table.

Figure 1.

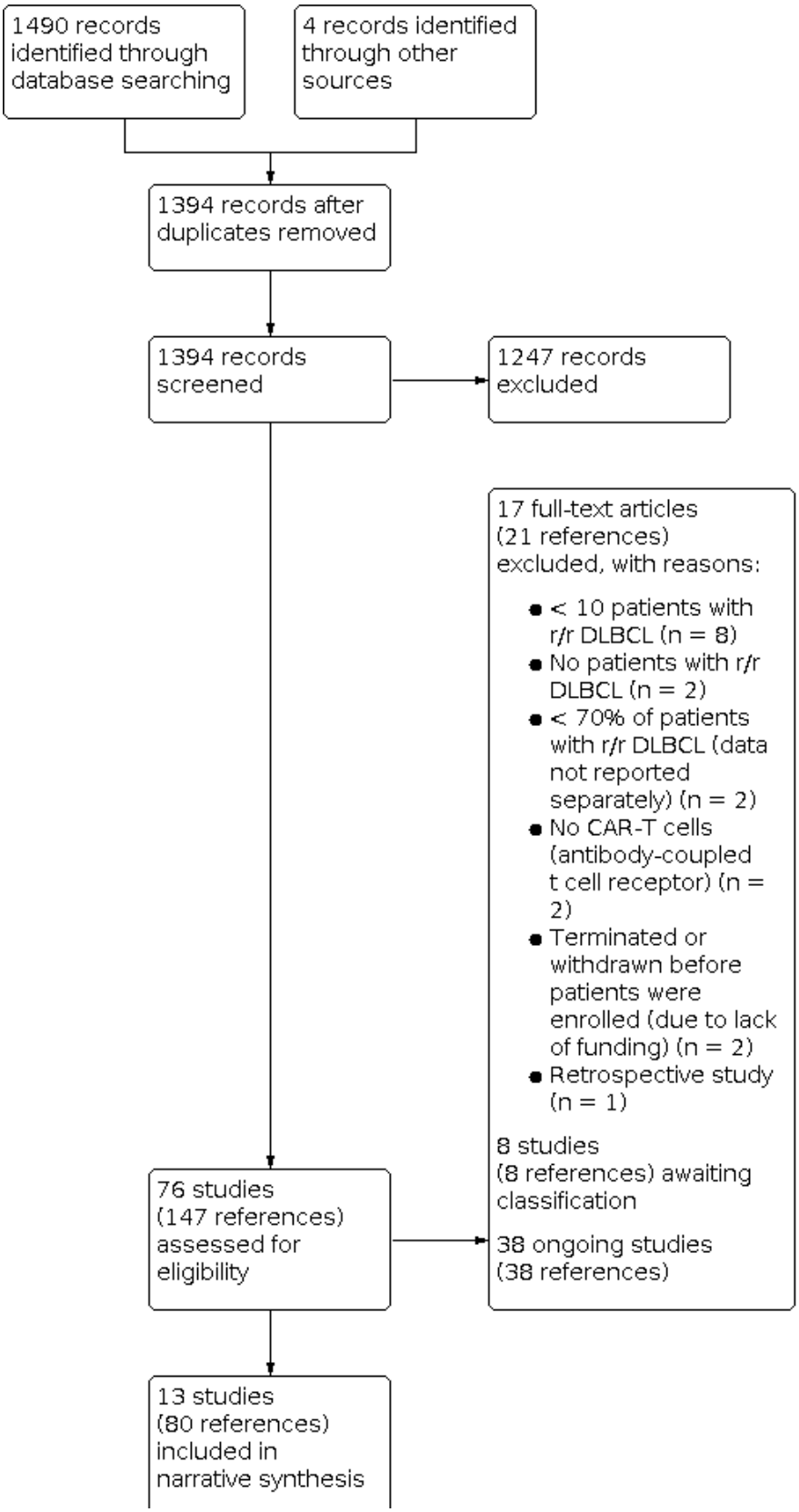
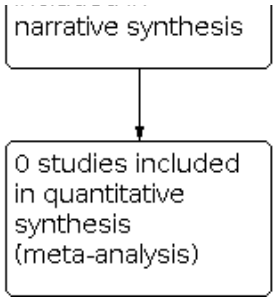


Figure 1. (Continued)



Data extraction and management

Two review authors (ME, MG) extracted data using a standardised data extraction form. Data extraction was conducted according to the guidelines proposed by Cochrane. If the two review authors were unable to reach a consensus, we consulted a third review author to reach a final decision (NS) or contacted the authors of specific studies for supplementary information (Li 2020).

We collated multiple reports of one study so that the study, and not the report, was the unit of analysis.

We extracted the following information.

- General information: author, title, source, publication date, country, language, duplicate publications
- Quality assessment: (as specified in the Assessment of risk of bias in included studies section)
- Study characteristics: study design, aims, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, subgroup analysis, statistical methods, power calculations, treatment cross-overs, compliance with assigned treatment, length of follow-up
- Participant characteristics: age, gender, number of participants recruited/allocated/evaluated, participants lost to follow-up, disease, stage of disease, additional diagnoses, previous treatment (type of chemotherapy (intensity of regimen, number of cycles), field and dose of radiotherapy, allogeneic or autologous stem-cell transplantation)
- Interventions: type of CAR-T cell therapy, concomitant therapy, duration of follow-up
  * No studies included a control group to be specified (type, dosage)
- Outcomes: see Types of outcome measures

Assessment of risk of bias in included studies

We identified uncontrolled studies only. The intended assessment for other study designs, is specified under Differences between protocol and review.

Two review authors (ME, MG) independently assessed all eligible studies for methodological quality and risk of bias based on the risk of bias assessment criteria for observational studies tool provided by the Cochrane Childhood Cancer Group (see Table 1). Any risk of bias judgements were performed and presented per outcome or outcome group per study.

The two review authors resolved any disagreements regarding the quality assessments by discussion and, when not reaching a consensus, consulted a third review author (NS).

We assessed the following domains of bias:

- Internal validity
  * Unrepresentative study group (selection bias)
  * Incomplete outcome assessment/follow-up (attrition bias)
  * Outcome assessors unblinded to investigated determinant (detection bias)
  * Important prognostic factors or follow-up not taken adequately into account (confounding)
- External validity
  * Poorly defined study group (reporting bias)
  * Poorly defined follow-up (reporting bias)
  * Poorly defined outcome (reporting bias)
  * Poorly defined risk estimates (analyses)

For every criterion, we made a judgement using one of three response options:

- High risk of bias
- Low risk of bias
- Unclear risk of bias

Measures of treatment effect

Details on the intended measures of treatment effect for controlled study designs are specified in the Differences between protocol and review section of the review.

As we did identify uncontrolled studies only, we did not pool any data and presented dichotomous outcomes as rates either as reported or, if not reported, by extracting the number of events and the total number of participants (response rates, adverse events) by study and together with their associated confidence intervals. We presented survival data (overall survival, progression-free survival) in the form the study reported, as time-to-event estimates (e.g. produced by the method proposed by Kaplan and Meier), either as time point-specific or median survival probabilities, and together with the respective confidence intervals. Continuous outcomes (quality of life) were presented as mean differences (MD), as given in the studies. We provided all respective information from individual studies in tabular format.

Unit of analysis issues

Studies with multiple treatment groups

For eligible randomised controlled trials with multiple treatment groups, we planned to combine trial arms that would be reasonably regarded as subtypes of the same intervention, as recommended in Chapter 23.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020b). Trial arms that were not combinable accordingly, would have been compared to the common comparator separately. For pairwise meta-analysis, we planned to split the 'shared' group into two or more groups of smaller sample size, and to include two or more (reasonably independent) comparisons. For dichotomous outcomes, both the number of events and the total number of patients would have been divided up, and for continuous outcomes, the total number of participants would have been divided up with unchanged means and standard deviations.

Ultimately, we were able to identify eligible uncontrolled studies with either a single arm of multiple arms of CAR T-cell therapy only. For studies with multiple arms that included varying doses or combinations of CAR T-cells with other agents, we presented combined result data at the study level.

Dealing with missing data

We requested any missing data from the principal investigators. As we were not able to pool result data, we did not perform sensitivity analyses, e.g. imputations based on realistic assumptions for the values missing, to assess the robustness of results towards the unavailability of outcome data. Missing outcome data issues were respected in our risk of bias and our GRADE ratings.

Assessment of heterogeneity

Since we were not able to pool any result data, we did not quantitatively assess any potential heterogeneity among the included studies and their findings (see Differences between protocol and review). However, we discussed the consistency of the included studies and their results extensively and respected these in our GRADE ratings.

Assessment of reporting biases

As we did not pool any result data in the course of this review, we were not able to make any statistical evaluations of potential publication bias (see Differences between protocol and review). Nevertheless, we performed an extensive database search, supported by additional literature sources, and searched trial registries to identify published and unpublished completed or ongoing studies in order to limit any reporting biases to the largest extent.

Data synthesis

As we did not include studies with a control group (see Differences between protocol and review), we reported the results narratively and individually per study in a tabular format.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses for the following study characteristics and to use tests for subgroup differences to explore interactions between subgroup results:

- Age of participants (divided into applicable age groups e.g. < 60 years, ≥ 60 years)
- Number of previous treatment lines (≤ two versus > two)
- History of autologous stem-cell transplantation (yes versus no)

We were not able to perform any meta-analyses and therefore did not undertake any subgroup analyses.

Sensitivity analysis

We intended to perform sensitivity analyses to assess the impact of study quality on outcomes, comparing studies with at least one domain of high risk of bias to those judged not to be at a high risk of bias. Furthermore, we planned sensitivity analyses to explore the influence of completed, but not published studies, and the influence of prematurely terminated studies on outcomes. As we did not pool any outcome data, we did not undertake any sensitivity analyses.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of the evidence for the following prioritised outcomes:

- Overall survival
- Quality of life
- Any adverse events
- Any serious adverse events
- Cytokine release syndrome
- Progression-free survival
- Response to treatment measured as complete response

We used the GRADEpro Guideline Development Tool (GDT, GRADEpro GDT 2015)) software to create a summary of findings table, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020), displaying the certainty of the evidence ratings for the prioritised outcomes (Summary of findings 1). Since all included studies were uncontrolled studies, we followed the guidance to the largest possible extent and began to rate the certainty of the evidence for all outcomes at 'low certainty'.

We intended to include data on treatment-related mortality in the GRADE assessment as reported in our protocol, but did not identify such data. During the course of the review and with regards to their clinical relevance, we decided to present additional safety data, i.e. any serious adverse events and cytokine release syndrome (see Differences between protocol and review).

RESULTS

Description of studies

Results of the search

We identified 1494 potentially relevant references. At the initial screening stage, we excluded 100 duplicates and 1247 references due to a lack of conformity with the inclusion criteria. We further evaluated the remaining 76 studies (147 references) either as full-text publications or, if not available, as abstract publications or study registry entries. This led to the exclusion of 17 studies. In addition, we identified 38 ongoing studies. Three of these studies are RCTs which will be completed between 2022

and 2025 (BELINDA; TRANSFORM; ZUMA-7; primary completion date according to ClinicalTrials.gov). Eight studies are awaiting classification. We finally included 13 studies which evaluated the efficacy and safety of CAR T-cells in people with r/r DLBCL (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) in this systematic review. We reported the overall numbers of references screened, identified, selected, excluded and included in a PRISMA flow diagram (see Figure 1).

Included studies

For a detailed description of the studies, see the Characteristics of included studies table. For an overview of the main study characteristics, see Table 2. Here we provide a brief overview of the included studies.

Published full-text articles were available for 10 of 13 studies (Beider 2019; Hirayama 2019; JULIET; Kochenderfer 2017; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1). For four studies, we retrieved outcome data entirely (Chang 2015; PLATFORM; ZUMA-6) or partially (Beider 2019) from conference abstracts and/or ClinicalTrials.gov. For one study (PLATFORM), recruitment is currently ongoing.

Design

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

Ten studies were single-arm studies (Beider 2019; Chang 2015; Hirayama 2019; JULIET; Sang 2020; Schuster 2017; Tong 2020; Ying 2019; ZUMA-1; ZUMA-6) and three studies included multiple arms of either varying doses of CAR T-cells (Kochenderfer 2017, TRANSCEND-NHL-001) or varying doses of CAR T-cells combined with varying agents (PLATFORM).

Sample sizes

The mean number of participants enrolled in the included studies (including participants with conditions other than r/r DLBCL) was 79 (range 12 (ZUMA-6) to 344 (TRANSCEND-NHL-001)). The mean number of participants that received CAR T-cell therapy was 61 and ranged from 12 (ZUMA-6) to 264 participants (TRANSCEND-NHL-001). Three studies included more than 100 participants receiving CAR T-cells (JULIET; TRANSCEND-NHL-001; ZUMA-1). The proportion of participants receiving CAR T-cells among those who were enrolled ranged between 67% (JULIET) and 100% (Ying 2019; ZUMA-6, for phase one)). In the three largest studies, the proportions were 67% (JULIET), 78% (TRANSCEND-NHL-001; 85% when including participants receiving a non-conforming product) and 91% (ZUMA-1). The proportion was unclear in three studies (Beider 2019; Chang 2015; Kochenderfer 2017).

The mean number of evaluated participants was 52 (range 12 (ZUMA-6) to 256 (TRANSCEND-NHL-001)) and the proportion of participants evaluated among those who were enrolled ranged between 56% (JULIET) and 100% (ZUMA-6; 12/12 participants). In the three largest studies, the proportions were 56% (JULIET), 74% (TRANSCEND-NHL-001) and 91% (ZUMA-1). The proportion was unclear in three studies (Beider 2019; Chang 2015; Kochenderfer 2017).

Location

Six studies were conducted in single centres, one in Israel (Beider 2019), two in China (Sang 2020; Tong 2020) and three in the USA (Hirayama 2019; Kochenderfer 2017; Schuster 2017). Seven studies were conducted at multiple centres, two in China (Chang 2015; Ying 2019), three in the USA (PLATFORM; TRANSCEND-NHL-001; ZUMA-6), one in the USA and Israel (ZUMA-1), and one in Australia, Austria, Canada, France, Germany, Italy, Japan, the Netherlands, Norway and the USA (JULIET).

Participants

For an overview of the main participant characteristics, see Table 3. Three studies (JULIET; Sang 2020; ZUMA-6) included participants with r/r DLBCL only, whereas the majority of studies (Beider 2019; Chang 2015; Hirayama 2019; Kochenderfer 2017; PLATFORM; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1) 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.

The median age, when reported, ranged between 38 (Chang 2015) and 63 years (TRANSCEND-NHL-001). The youngest participant (nine years) was included in Chang 2015, and the oldest participant (76 years) in JULIET. Among the studies providing the respective information, only one study (Chang 2015) included both adult and paediatric participants.

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

Nine studies reported the proportion of participants who had previously received stem-cell transplantation (Hirayama 2019; JULIET; Kochenderfer 2017; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1). The proportion of participants who had previously received autologous, and allogeneic stem-cell transplantation ranged between 5% (Sang 2020) and 50% (Schuster 2017), and between 0% (Schuster 2017; JULIET) and 18% (Tong 2020), respectively. In Hirayama 2019, 6% of participants had received autologous and allogeneic stem-cell transplantation.

Seven studies reported the median number of previous lines of treatment which was either three (Sang 2020; Schuster 2017; TRANSCEND-NHL-001; ZUMA-1) or four (Hirayama 2019; Kochenderfer 2017; Ying 2019).

Interventions

Anti-CD19 directed CAR T-cells were used in 11 studies (Beider 2019; Chang 2015; Hirayama 2019; JULIET; Kochenderfer 2017; PLATFORM; Schuster 2017; TRANSCEND-NHL-001; Ying 2019; ZUMA-1; ZUMA-6), while two studies used a combination of anti-CD19 and anti-CD20 (Sang 2020) or anti-CD22 directed CAR T-cells (Tong 2020).

In the majority of studies (Beider 2019; Hirayama 2019; JULIET; Kochenderfer 2017; PLATFORM; Sang 2020; Schuster 2017; Tong 2020; Ying 2019; ZUMA-1; ZUMA-6), participants received a single

infusion of CAR T-cells. Participants received between one and three infusions in Chang 2015, and either one or two infusions in TRANSCEND-NHL-001.

The dose of CAR T-cells varied markedly with median doses between 1 x 10^6/kg and 5.79 x 10^6/kg for studies that applied doses depending on body weight (Beider 2019; Chang 2015; Hirayama 2019; Kochenderfer 2017; Sang 2020; Schuster 2017; Tong 2020; Ying 2019; ZUMA-1; ZUMA-6), and median doses between 50 x 10^6 and 3 x 10^8 for studies that applied doses irrespective of body weight (JULIET; PLATFORM; TRANSCEND-NHL-001).

CAR T-cells were applied without co-interventions in 11 studies (Beider 2019; Chang 2015; Hirayama 2019; JULIET; Kochenderfer 2017; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1). Co-interventions consisted of durvalumab in PLATFORM and atezolizumab in ZUMA-6.

In all studies, participants received lymphodepleting chemotherapy before the infusion of CAR T-cells, which in the majority of studies consisted of fludarabine and cyclophosphamide. In JULIET, participants received fludarabine and either cyclophosphamide or bendamustine. In Sang 2020, two participants received ifosfamide instead. In Tong 2020, participants received fludarabine and cyclophosphamide with or without doxorubicin and in Schuster 2017, participants received several different regimens of which most included cyclophosphamide.

Outcomes

For details on outcomes and how and when they were measured, see Table 4 (overall survival, progression-free survival, overall response rates, complete response rates, partial response rates), Table 5 (quality of life), and Table 6 (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).

Overall survival

Eight studies reported data on overall survival (Chang 2015; JULIET; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; ZUMA-1; ZUMA-6). While four of those studies reported time point-specific data (Chang 2015; JULIET; Tong 2020; TRANSCEND-NHL-001; ZUMA-1), three studies reported median overall survival only (Sang 2020; Schuster 2017; Tong 2020; ZUMA-6). One study (Tong 2020) 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 six months were reported by two studies (TRANSCEND-NHL-001; ZUMA-1). One study (Chang 2015) provided data at 10 months. Survival rates at 12 months were reported by three studies (JULIET; TRANSCEND-NHL-001; ZUMA-1), of which two studies reported data at 18 months (JULIET; ZUMA-1) and one study (ZUMA-1) reported data at 24 months.

Quality of life

Two studies reported data on quality of life (JULIET; TRANSCEND-NHL-001) using multiple validated tools for several time points. One study (JULIET) reported data on the Function Assessment of Cancer Therapy-Lymphoma (FACT-Lym; Cella 2005) and the Short Form-36 Health Survey (SF-36; Ware 1992) only for participants with complete response or partial response. FACT-Lym total scores, which we focused on, were reported at baseline and at months 3, 6, 12, and 18. One study (TRANSCEND-NHL-001) reported data on the EuroQol 5-Dimension 5-Level (EQ-5D-5L; Xu 2020) and the EORTC QLQ-C30 (Aaronson 1993). EQ-5D-5L visual analogue scale (VAS) scores, which we focused on, were reported at baseline and at months 1, 2, 3, 6, and 12.

Treatment-related mortality

None of the studies reported data on treatment-related mortality.

Number of participants with adverse events and serious adverse events

Data on any of the following adverse events and serious adverse events were reported by a total of 11 studies (Chang 2015; JULIET; Kochenderfer 2017; PLATFORM; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1; ZUMA-6).

The proportion of participants with any adverse events was reported by five studies (TRANSCEND-NHL-001; JULIET; Tong 2020; ZUMA-1; ZUMA-6).

Four studies reported the proportion of participants with any serious adverse events (JULIET; Tong 2020; ZUMA-1; ZUMA-6).

Cytokine release syndrome was reported by 11 studies (Chang 2015; JULIET; Kochenderfer 2017; PLATFORM; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1; ZUMA-6) using different grading criteria. Cytokine release syndrome was reported using criteria described in Lee 2014 by five studies (Sang 2020; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1). One study (JULIET) reported cytokine release syndrome using the University of Pennsylvania grading scale (Porter 2015). Three studies reported cytokine release syndrome without further specification (Kochenderfer 2017; Schuster 2017; ZUMA-6) and one study (Chang 2015) reported cytokine release syndrome with fever over 39°C. One study (PLATFORM) reported cytokine release syndrome after the infusion of durvalumab.

Neurotoxicity was reported by 10 studies (JULIET; Kochenderfer 2017; PLATFORM; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1; ZUMA-6).

Eight studies reported the number of participants who were treated with tocilizumab and/or corticosteroids for treatment of cytokine release syndrome and/or neurotoxicity (JULIET; Kochenderfer 2017; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1).

Data on cytopenias were available from eight studies which reported the occurrence of anaemia, leukopenia, neutropenia and thrombocytopenia (JULIET; Kochenderfer 2017; Sang 2020; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1; ZUMA-6). Anaemia, leukopenia, neutropenia and thrombocytopenia were reported by six studies (JULIET; Sang 2020; TRANSCEND-NHL-001; Tong 2020; Ying 2019; ZUMA-1), five studies (Sang 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1; ZUMA-6), six studies (JULIET; Sang 2020; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1), and seven studies reported thrombocytopenia (JULIET; Kochenderfer 2017; Sang 2020; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1), respectively. Three studies additionally reported prolonged cytopenias (JULIET; TRANSCEND-NHL-001; ZUMA-1).

Febrile neutropenia was reported by five studies (JULIET; Kochenderfer 2017; Sang 2020; TRANSCEND-NHL-001; ZUMA-1).

Three studies reported the number of participants with any infections (JULIET; TRANSCEND-NHL-001; ZUMA-1).

Progression-free survival

Nine studies reported data on progression-free survival, disease-free survival or relapse-free survival (Chang 2015; JULIET; Kochenderfer 2017; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; ZUMA-1; ZUMA-6).

While six of those studies reported data including time point-specific results (Chang 2015; JULIET; Kochenderfer 2017; Tong 2020; TRANSCEND-NHL-001; ZUMA-1), three studies reported median progression-free survival only (Sang 2020; Schuster 2017; ZUMA-6). One study reported the rate of disease-free survival (without further specification) at four months (Chang 2015). One study reported rates of relapse-free survival at six, 12 and 18 months, defining relapse as at least a partial response to the last therapy and a following progression of lymphoma (JULIET). Progression-free survival at six months was reported in two studies (TRANSCEND-NHL-001; ZUMA-1). Twelve-month progression-free survival was reported by four studies (Kochenderfer 2017, Tong 2020, TRANSCEND-NHL-001, ZUMA-1) and one study (ZUMA-1) reported progression-free survival at 15 months.

Response to treatment

All of the 13 included studies reported data on the response to treatment (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).

12 studies reported overall response rates at several times of follow-up using several outcome definitions, including best response rates (Beider 2019; Hirayama 2019; JULIET; Kochenderfer 2017; PLATFORM; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1; ZUMA-6). While for nine of those studies, the timing of outcome assessment was not specified (Beider 2019; Hirayama 2019; JULIET; Kochenderfer 2017; PLATFORM; Tong 2020; TRANSCEND-NHL-001; ZUMA-1; ZUMA-6), three studies reported time point-specific results (Sang 2020; Schuster 2017; Ying 2019). The overall response rate at one month of follow-up was reported by one study (Ying 2019). Overall response rates at three and at six months were reported in three studies (Sang 2020; Schuster 2017; Ying 2019) and in two studies (Sang 2020; Ying 2019), respectively.

All 13 studies reported rates of complete response (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). While for 10 of those studies, the timing of outcome assessment was not specified (Beider 2019; Chang 2015; Hirayama 2019; JULIET; Kochenderfer 2017; PLATFORM; Tong 2020; TRANSCEND-NHL-001; ZUMA-1; ZUMA-6), three studies reported time point-specific results (Sang 2020; Schuster 2017; Ying 2019). The complete response rate at one month of follow-up was reported by one study (Ying 2019). Complete response rates at three and at six months were reported in two studies (Sang 2020; Ying 2019) and in three studies (Sang 2020; Schuster 2017; Ying 2019), respectively.

Data on partial responses were available from six studies (Beider 2019; JULIET; Kochenderfer 2017; Tong 2020; TRANSCEND-NHL-001; ZUMA-1), but none of the studies reported time point-specific partial response rates.

Conflicts of interest

Potential conflicts of interest were declared in 10 studies, for which funding was provided by the following pharmaceutical companies: Celgene/Juno Therapeuctics (Hirayama 2019; PLATFORM; TRANSCEND-NHL-001), Kite Pharma (Kochenderfer 2017; ZUMA-1; ZUMA-6), Novartis (JULIET; Schuster 2017), America Yuva Biomed (Chang 2015) and JW therapeutics (Ying 2019).

In three out of 13 studies, the authors declared that there were no conflicts of interest (Beider 2019; Sang 2020; Tong 2020).

Ongoing studies

We also identified 38 ongoing studies. Three of these studies are RCTs which will be completed between 2022 and 2025 (BELINDA; TRANSFORM; ZUMA-7) according to the primary completion date reported on ClinicalTrials.gov.

Studies awaiting classification

Eight studies are awaiting classification. All of these studies have been identified through registry searches and it was not possible to make a judgement on their eligibility because of insufficient reporting with respect to the recruited population (i.e. involving a minimum of 10 participants with r/r DLBCL and including a proportion of participants with r/r DLBCL above 70%, unless respective data were reported separately). For one of these studies the register status was completed, even though we were not able to identify any published or unpublished result data (NCT02976857). Five studies were reported with no, unknown or active recruiting status, but their estimated completion dates had passed and we were not able to identify any published or unpublished result data (ChiCTR-ONC-16008911; ChiCTR-OPN-16009847; ChiCTR-OPN-17013507; NCT02933775; NCT03598179). For two studies, we were able to identify a linked abstract publication, which did not include sufficient data to justify their in- or exclusion (NCT02652910; NCT03097770).

Excluded studies

After screening of titles/abstracts, we excluded 1247 records that did not match our inclusion criteria. We evaluated reports of 16 studies in more detail, which were finally excluded for one or more of the following reasons (see Characteristics of excluded studies table):

- eight studies included fewer than 10 participants with r/r DLBCL,
- two studies did not include people with r/r DLBCL,
- two studies included fewer than 70% of participants with r/r DLBCL and did not report data separately for this group,
- two studies did not study treatment with CAR T-cells but with antibody-coupled T cell receptors,
- two studies were terminated or withdrawn before patients were enrolled due to lack of funding, and
- one study was a retrospective study.

Risk of bias in included studies

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 and uncontrolled study design, we assessed the internal and external validity based on criteria for observational studies provided by the Cochrane Childhood Cancer Group (see Table 1). The full judgement per study and category is presented in Figure 2 and an elaboration of all judgements is available in the Characteristics of included studies table.

Figure 2. Please note that, for the outcome-level assessments, a blank space indicates that the outcome was not reported by the study.

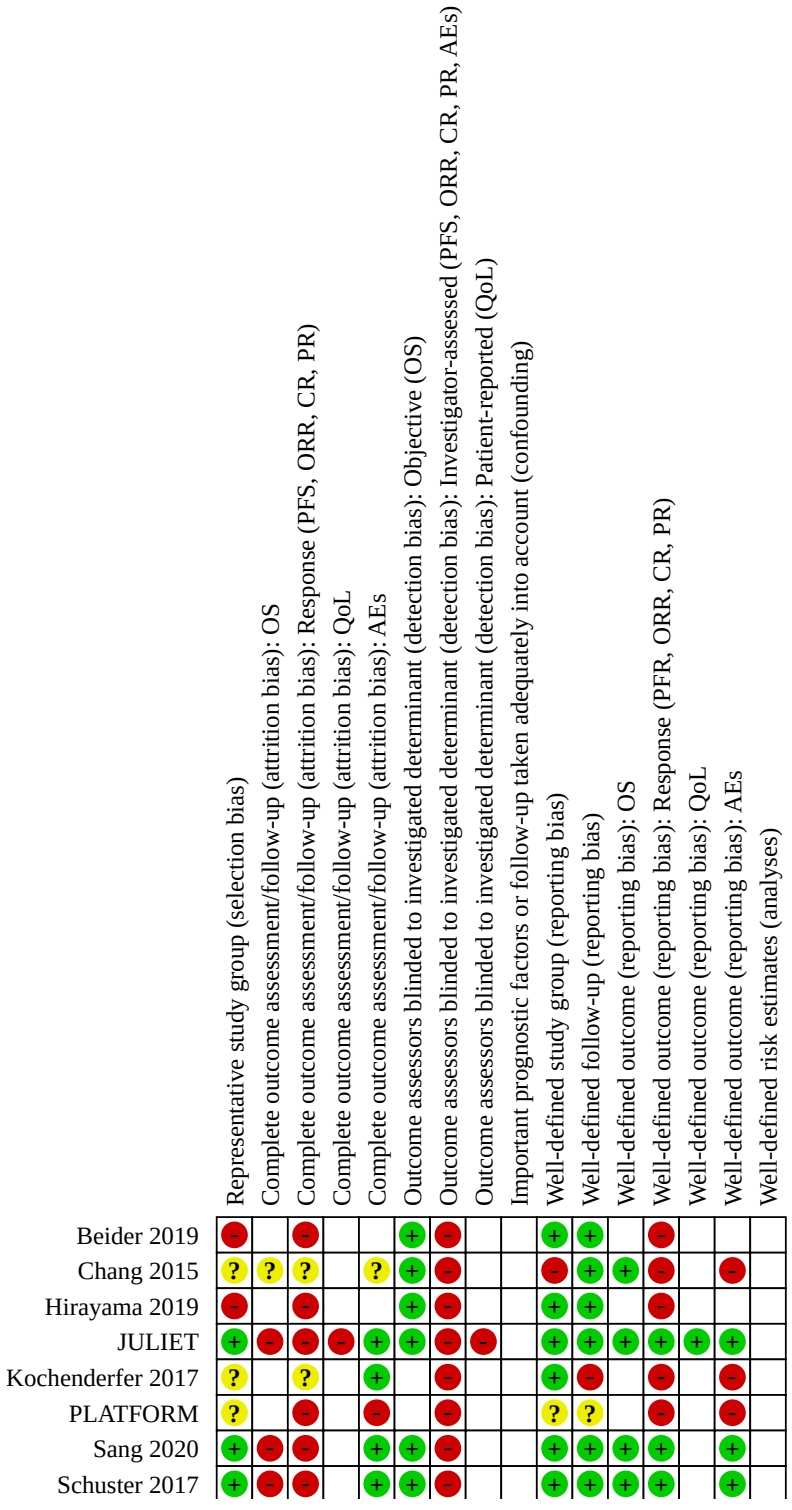
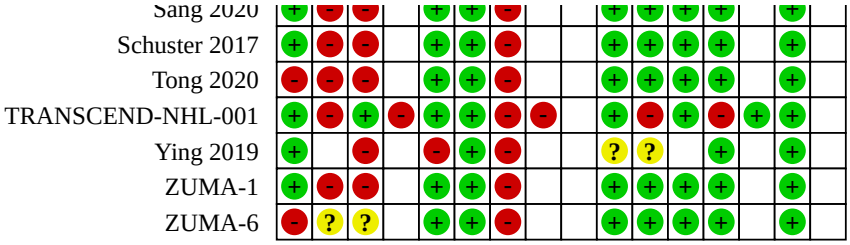


Figure 2. (Continued)



Allocation

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

Three studies were rated as being at unclear risk of bias because eligibility criteria were insufficiently reported to allow a judgement (Kochenderfer 2017; PLATFORM; ZUMA-6).

We judged four studies to be at high risk of bias under the reasoning that their included populations did not adequately reflect a random sample of the target population. The median age of the study group was substantially below average in Beider 2019 (40.5 years) and in Chang 2015 (38 years). In Tong 2020, participants of male sex were underrepresented in the study group (39%). In Hirayama 2019, the study group consisted of participants who received the preferred approach of lymphodepletion and infusion of CAR T-cells established during phase one of the study only (48 participants out of 65 participants who received at least one infusion of CAR T-cells).

Blinding

All studies were unblinded and 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) were subjective to a greater or lesser extent and therefore at high risk of bias.

Incomplete outcome data

We assessed attrition bias in terms of whether the study conductors assessed the respective outcomes for all enrolled participants in four outcome categories.

Overall survival

Among the studies reporting overall survival, we judged two studies (Chang 2015; ZUMA-6) 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. In ZUMA-6, the number of enrolled participants was not reported in the published abstract and only the number of participants who received CAR T-cell therapy and atezolizumab were available.

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

Quality of life

The two studies that reported quality of life were both judged to be at high risk of bias. In JULIET, data were reported only for participants with complete response or partial response (e.g. 39 participants at month three and 21 participants at month 12 compared to 108 participants with assessments at baseline). In TRANSCEND-NHL-001, data were also reported only for a subset of participants (138 participants at month three 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, Kochenderfer 2017, Sang 2020, Schuster 2017 and Tong 2020 . 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 one of the studies only (ZUMA-1, use of tocilizumab and/or corticosteroids; ZUMA-6, neurotoxicity and (partially) cytopenias). In TRANSCEND-NHL-001, 25 out of 296 participants received a non-conforming CAR T-cell product and were not included in the safety analysis so that outcomes were reported for 91% of the participants receiving CAR T-cells.

One study was rated as being 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).

In PLATFORM, 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, only CRS and neurotoxicity were reported for 32 out of 32 (100%) participants receiving CAR T-cells while the 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.

Response (progression-free survival, overall response, complete response, partial response)

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, 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 and Kochenderfer 2017. In ZUMA-6, 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; Hirayama 2019; JULIET; PLATFORM; Sang 2020; Schuster 2017; Tong 2020; Ying 2019; ZUMA-1) 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, 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.

Selective reporting

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; Hirayama 2019; JULIET; Kochenderfer 2017; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; ZUMA-1; ZUMA-6) to be at low risk of bias as both the study group and the intervention were well described.

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

We judged Chang 2015 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 study 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) or the median follow-up was reported (Chang 2015; Hirayama 2019; JULIET; Sang 2020; Schuster 2017; Tong 2020; ZUMA-1; ZUMA-6).

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

Two studies were judged to be at high risk of bias because, in Kochenderfer 2017, the duration of follow-up was not clearly described and, in TRANSCEND-NHL-001, the median follow-up was only reported for the ITT population (i.e. participants who underwent leukapheresis) and overall survival and progression-free survival 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; JULIET; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; ZUMA-1; ZUMA-6).

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; Cella 2005) in JULIET, and the EuroQol 5-Dimension 5-Level (EQ-5D-5L; Xu 2020) in TRANSCEND-NHL-001, and they 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; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1; ZUMA-6), 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 provided no information on the criteria used for assessment. In PLATFORM, no information on the criteria and the time point of assessment were available. Kochenderfer 2017 reported use of the CTCAE but the time point of assessment was unclear.

Response (progression-free survival, overall response, complete response, partial response)

We judged six studies to be at low risk of bias (JULIET; Sang 2020; Schuster 2017; Tong 2020; Ying 2019; ZUMA-1; ZUMA-6), 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; Chang 2015; Hirayama 2019; Kochenderfer 2017; PLATFORM; TRANSCEND-NHL-001). Reporting of criteria used for response assessment was insufficient in Beider 2019 and missing in Chang 2015. In Hirayama 2019, Kochenderfer 2017, PLATFORM and TRANSCEND-NHL-001, criteria used for response assessment were specified, but a time point-specific assessment was either missing or the timing of assessment was unclear for several of the reported outcomes.

Other potential sources of bias

We further considered confounding and definition of risk estimates as potential sources of bias.

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 in all of the included studies.

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.

Effects of interventions

See: **Summary of findings 1** Summary of findings for the efficacy and safety of CAR T-cell therapy for people with relapsed or refractory DLBCL

For details on efficacy outcomes, see Table 4 (overall survival, progression-free survival, overall response, complete response, partial response) and Table 5 (quality of life).

For details on safety outcomes, see Table 6 (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).

For efficacy outcomes, we reported data from studies including a minimum proportion of 70% of participants with DLBCL unless separate data were available for participants with DLBCL. In studies including participants with other malignancies, we used data from participants with DLBCL only and reported the absolute number of those participants, if available (e.g. for response rates). Whenever studies including participants with DLBCL and participants with other malignancies, provided combined data only, we reported the proportion of participants with DLBCL along with the total number of participants. Among participants who were enrolled in the included studies, the proportion of those receiving CAR T-cells ranged between 67% and 100% and the proportion of participants evaluated for efficacy ranged between 56% and 100%. Safety outcomes were reported irrespective of the proportion of participants with DLBCL described in the study.

We presented our certainty of the evidence ratings for overall survival, quality of life, any adverse events, any serious adverse events, cytokine release syndrome, progression-free survival and complete response rates in Summary of findings 1.

Overall survival

For details on overall survival, see Table 4.

Data on overall survival were reported for eight of the included studies (567 participants; Chang 2015; JULIET; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; ZUMA-1; ZUMA-6). Due to the large variability in sample size and the duration of follow-up, we presented time point-specific survival probabilities only. Additional median survival times are reported in Table 4. Tong 2020 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.

Six-month follow-up

Survival rates at six months were reported in two studies. Overall survival was 74.7% (95% CI 68.9% to 79.6%; 256 participants, 80.4% DLBCL) for TRANSCEND-NHL-001 and 78% (95% CI 69% to 85%; 108 participants; exact proportion of DLBCL unclear, but above 70%) for ZUMA-1.

Ten-month follow-up

Chang 2015 provided 10-month overall survival results for 13 individuals, including 12 (92%) with DLBCL, of 55% (95% CI 39% to 74%).

Twelve-month or longer follow-up

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

Data for survival at 18 months were reported for two studies. Overall survival was 43% in JULIET (95% CI 33% to 35%; 99 participants), and 52% in ZUMA-1 (95% CI 41% to 62%; 108 participants; exact proportion of DLBCL unclear, but above 70%).

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

For all time point-specific outcomes, we identified observational studies only. The overall risk of bias was judged to be high for all studies (downgraded by one point for risk of bias). None of the included studies had a control group and effect estimates could not be calculated (downgraded by one point for imprecision). Hence, the evidence is very uncertain about the effect of CAR T-cell therapy on overall survival of people with r/r DLBCL.

Quality of life

For details on quality of life, see Table 5.

Two studies reported quality of life (294 participants at baseline and 59 at longest follow-up; JULIET; TRANSCEND-NHL-001) using multiple validated tools for several time points. We here report the outcomes of 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, we reported the total scores of the Function Assessment of Cancer Therapy-Lymphoma (FACT-Lym; Cella 2005) as they included all of the other scores that were reported (i.e. the FACT-G total score including the FACT-G domains and the Lym S). For TRANSCEND-NHL-001, we reported scores of the visual analogue scale of the EuroQol 5-Dimension 5-Level (EQ-5D-5L VAS; Xu 2020). Please note that, due to the lack of a control group, we did not calculate effect estimates and reported data descriptively.

Quality of life appeared to improve over time in both studies, whereas the number of participants who were assessed decreased substantially over time (i.e. 294 participants at baseline and 59 participants at the longest follow-up).

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

In TRANSCEND-NHL-001, EQ-5D-5L VAS scores (range 0 to 100, higher scores indicate improvement) were reported at baseline and at months one, two, three, six, nine and 12. The number of participants evaluated decreased over time with only 38 participants, of initially 186 participants at baseline, evaluated at month 12. Mean EQ-5D-5L VAS scores increased from 68.3 (SD 19.5) at baseline to 82.1 (SD 17.8) at month 12.

We included observational studies only. The overall risk of bias was judged to be high for all studies (downgraded by one point for risk of bias). None of the included studies had a control group and effect estimates could not be calculated (downgraded by one point for imprecision). Therefore, the evidence is very uncertain about the effect of CAR T-cell therapy on the quality of life of people with r/r DLBCL.

Treatment-related mortality

None of the studies reported treatment-related mortality.

Number of participants with adverse events and serious adverse events

Any adverse events

For details on any adverse events, see Table 6.

The number of participants with any adverse events was reported in five studies (550 participants; JULIET; Tong 2020; TRANSCEND-NHL-001; ZUMA-1; ZUMA-6). Any adverse events occurred in all participants (JULIET; Tong 2020; ZUMA-1; ZUMA-6) or almost all participants (99%; TRANSCEND-NHL-001).

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

We included observational studies only. The overall risk of bias was judged to be high for all studies (downgraded by one point for risk of bias). None of the included studies had a control group and effect estimates could not be calculated (downgraded by one point for imprecision). Moreover, the duration of follow-up varied substantially between studies (downgraded by one point for inconsistency). Therefore, CAR T-cell therapy may increase the risk of any adverse events in people with r/r DLBCL but the evidence about the exact risk is very uncertain.

Any serious adverse events

For details on any serious adverse events, see Table 6.

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

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

We included observational studies only. The overall risk of bias was judged to be high for all studies (downgraded by one point for risk of bias). None of the included studies had a control group and effect estimates could not be calculated (downgraded by one point for imprecision). Moreover, the duration of follow-up varied substantially between studies (downgraded by one point for inconsistency). Hence, CAR T-cell therapy may increase the risk of any serious adverse events in people with r/r DLBCL but the evidence about the exact risk is very uncertain.

Cytokine release syndrome

For details on cytokine release syndrome, see Table 6.

The number of participants experiencing any grade or grade ≥ 3 cytokine release syndrome was reported in 11 studies (675 participants; Chang 2015; JULIET; Kochenderfer 2017; PLATFORM; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1; ZUMA-6) which used different grading criteria (675 participants).

Five studies that used criteria described in Lee 2014, reported that between 42% (TRANSCEND-NHL-001 and 100% (Sang 2020) of participants experienced cytokine release syndrome (Sang 2020; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1). The proportion of participants with grade ≥ 3 cytokine release syndrome ranged between 1% (Ying 2019) and 28.5% (Sang 2020).

In JULIET, 58% and 22% of participants experienced cytokine release syndrome of any grade and grade ≥ 3 according to the University of Pennsylvania grading scale (Porter 2015).

The occurrence of cytokine release syndrome without further specification of any grading criteria was reported in three studies (Kochenderfer 2017; Schuster 2017; ZUMA-6). Any grade cytokine release syndrome occurred in 57% (Schuster 2017) and 97% (ZUMA-6). Grade ≥ 3 cytokine release syndrome occurred in 18% (Schuster 2017), 25% (ZUMA-6; reported for 12 participants in phase one only) and 65% (Kochenderfer 2017) of participants.

Chang 2015 reported that 69% of participants experienced cytokine release syndrome with fever over 39°C.

PLATFORM reported no cytokine release syndrome occurrences after the infusion of durvalumab.

We included observational studies only. The overall risk of bias was judged to be high for all studies (downgraded by one point for risk of bias). None of the included studies had a control group and effect estimates could not be calculated (downgraded by one point for imprecision). Moreover, the duration of follow-up varied substantially between studies (downgraded by one point for inconsistency). Therefore, CAR T-cell therapy may increase the risk of CRS in people with r/r DLBCL but the evidence about the exact risk is very uncertain.

Neurotoxicity

For details on neurotoxicity, see Table 6.

Ten studies (664 participants) reported neurotoxicity of any grade or grade ≥ 3 (JULIET; Kochenderfer 2017; PLATFORM; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1; ZUMA-6).

Neurotoxicity of any grade occurred in a range of 15.6% (Ying 2019) to 100% (Kochenderfer 2017) of participants. In the remaining studies reporting data, neurotoxicity of any grade occurred in 21% (JULIET), 39% (Schuster 2017), 21% (Tong 2020), 30% (TRANSCEND-NHL-001) and 67% (ZUMA-1) of participants.

Between 0% (PLATFORM; Tong 2020; Ying 2019) and 55% (Kochenderfer 2017) of participants had grade ≥ 3 neurotoxicity. The remaining studies reported an occurrence of grade ≥ 3 neurotoxicity in 12% (JULIET), 9.5% (Sang 2020), 11% (Schuster 2017), 10% (TRANSCEND-NHL-001), 32% (ZUMA-1) and 50% (ZUMA-6).

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

For details on the treatment of cytokine release syndrome and/or neurotoxicity, see Table 6.

Eight studies (619 participants) reported the number of participants who were treated with tocilizumab and/or corticosteroids in varying detail (JULIET; Kochenderfer 2017; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1).

As reported in seven studies (Kochenderfer 2017; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1), between 0% (Sang 2020) and 80% (Ying 2019) of participants received tocilizumab alone or without further specification.

As reported in five studies (JULIET; Tong 2020; TRANSCEND-NHL-001; ZUMA-1), between 3% (Tong 2020) and 67% (ZUMA-1) of participants received tocilizumab and corticosteroids, such as dexamethasone. In ZUMA-1, prophylactic use of tocilizumab was introduced for all participants in phase two (cohort three).

As reported in five studies (Kochenderfer 2017; Sang 2020; Schuster 2017; TRANSCEND-NHL-001; Ying 2019), between 0% (Schuster 2017) and 20% (Ying 2019) received corticosteroids alone.

Cytopenias

For details on cytopenias, see Table 6.

Data on cytopenias of any grade or grade ≥ 3 were available from eight studies which reported the occurrence of anaemia, leukopenia, neutropenia and thrombocytopenia (625 participants; JULIET; Kochenderfer 2017; Sang 2020; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1; ZUMA-6).

Anaemia

As reported in six studies (JULIET; Sang 2020; TRANSCEND-NHL-001; Tong 2020; Ying 2019; ZUMA-1), anaemia of any grade occurred in a proportion of participants between 14% (Tong 2020) and 81% (Sang 2020). Three studies reported a rate of 48% (JULIET; TRANSCEND-NHL-001), and the remaining studies reported rates of 30% (Ying 2019) and 68% (ZUMA-1) of participants having anaemia of any grade.

As reported in seven studies (JULIET; Sang 2020; TRANSCEND-NHL-001; Tong 2020; Ying 2019; ZUMA-1; ZUMA-6), between 0% (Tong 2020) and 75% (ZUMA-6) of participants experienced grade ≥ 3 anaemia. The rates of grade ≥ 3 anaemia were 39% (JULIET), 28.6% (Sang 2020), 37% (TRANSCEND-NHL-001), 30% (Ying 2019) and 45% (ZUMA-1) in the remaining studies providing data.

Leukopenia

Leukopenia of any grade, which was reported in five studies (Sang 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1; ZUMA-6), occurred in a minimum of 15% (ZUMA-6) and a maximum of 76.2% (Sang 2020) of participants, with the remaining studies reporting rates of 16% (TRANSCEND-NHL-001), 65.7% (Ying 2019) and 19% (ZUMA-1).

As reported in five studies (Kochenderfer 2017; Sang 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1), leukopenia of grade ≥ 3 occurred in 23% (Kochenderfer 2017), 47.6% (Sang 2020), 14% (TRANSCEND-NHL-001), 21.9% (Ying 2019) and 17% (ZUMA-1) of participants.

Neutropenia of any grade, which was reported in six studies (JULIET; Sang 2020; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1), occurred in a range of 20% (JULIET) to 79% (Tong 2020) of participants, with rates of 76.2% (Sang 2020), 63% (TRANSCEND-NHL-001), 65.7% (Ying 2019) and 44% (ZUMA-1) reported by the remaining studies.

Seven studies (JULIET; Kochenderfer 2017; Sang 2020; TRANSCEND-NHL-001; Tong 2020; ZUMA-1; ZUMA-6) provided data on the proportion of participants with grade ≥ 3 neutropenia which ranged from 20% (JULIET) to 86% (Kochenderfer 2017), with the remaining studies reporting rates of 52.4% (Sang 2020), 61% (Tong 2020), 60% (TRANSCEND-NHL-001), 39% (ZUMA-1) and 42% (ZUMA-6) of participants.

Thrombocytopenia

Thrombocytopenia of any grade was reported by seven studies (JULIET; Sang 2020; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1; ZUMA-6) and occurred in a range of 12% (ZUMA-6) to 79% (Tong 2020) of participants. In the remaining studies, 13% (JULIET), 28.6% (Sang 2020), 31% (TRANSCEND-NHL-001), 25% (Ying 2019) and 35% (ZUMA-1) of participants had any grade thrombocytopenia.

As reported in seven studies (JULIET; Kochenderfer 2017; Sang 2020; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1), thrombocytopenia of grade ≥ 3 occurred in 12% (JULIET), 18% (Kochenderfer 2017), 28.6% (Sang 2020), 25% (Tong 2020), 27% (TRANSCEND-NHL-001), 3.1% (Ying 2019) and 24% (ZUMA-1) of participants.

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

Two studies reported any grade prolonged cytopenias which occurred in 44% (JULIET) and 45% (ZUMA-1) of participants.

As reported in three studies, the proportions of participants with grade ≥ 3 prolonged cytopenias were 34% (JULIET), 37% (TRANSCEND-NHL-001) and 30% (ZUMA-1).

Febrile neutropenia

For details on febrile neutropenia, see Table 6.

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

As reported in four studies (JULIET; Sang 2020; TRANSCEND-NHL-001; ZUMA-1), any grade febrile neutropenia occurred in a range of 9% (TRANSCEND-NHL-001) to 76.2% (Sang 2020) of participants. In JULIET and ZUMA-1, 15% and 36% of participants had any grade febrile neutropenia, respectively.

The proportion of participants with grade ≥ 3 febrile neutropenia was reported in five studies (JULIET; Kochenderfer 2017; Sang 2020; TRANSCEND-NHL-001; ZUMA-1) and ranged from 9% (TRANSCEND-NHL-001) to 50% (Kochenderfer 2017), with proportions of 14% (JULIET), 23.8% (Sang 2020) and 32% (ZUMA-1) in the remaining studies.

Any infections

For details on any infections, see Table 6.

Three studies (488 participants) reported the number of participants having any infections (JULIET; TRANSCEND-NHL-001; ZUMA-1).

JULIET reported that 34% of participants experienced infections of any grade.

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

Progression-free survival

For details on progression-free survival, see Table 4.

Nine studies reported results on progression-free survival, disease-free survival or relapse-free survival (575 participants; Chang 2015, JULIET, Kochenderfer 2017, Sang 2020, Schuster 2017, Tong 2020, TRANSCEND-NHL-001, ZUMA-1, ZUMA-6); as for overall survival, we limited the reported results to time point-specific rates only, given that there was large heterogeneity in study sample sizes and follow-up durations between the respective studies. Additional data on progression-free survival are reported in Table 4.

Four-month follow-up

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

Six-month follow-up

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

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

Twelve-month or longer follow-up

Twelve-month progression-free survival was reported for four studies (Kochenderfer 2017, Tong 2020, TRANSCEND-NHL-001, ZUMA-1). It ranged from 44% (95% CI 34% to 53%; 101 participants, 76% DLBCL) in ZUMA-1 and 44.1% (37.3% to 50.7%; 256 participants, 80.4% DLBCL) in TRANSCEND-NHL-001 to 75% (95% CI 46% to 90%; 16 participants DLBCL) in Tong 2020. Kochenderfer 2017 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, progression-free survival was reported to be at 41% (95% CI 31% to 50%) at 15 months in 101 participants, including 77 (76%) with DLBCL.

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

As for the available data on overall survival, we only included observational studies that provided time point-specific data on progression-free survival. The overall risk of bias was judged to be high for all studies (downgraded by one point for risk of bias). None of the included studies had a control group and effect estimates could not be calculated (downgraded by one point for imprecision). Accordingly, the evidence is very uncertain about the effect of CAR T-cell therapy on progression-free survival of people with r/r DLBCL.

Response to treatment

Please note that, in the following section, we were able to report response rates for participants with DLBCL only (i.e. not combined with participants with other malignancies), as separate data for this subgroup were usually available.

Overall response

For details on overall response rates, see Table 4.

Overall, 12 studies (608 participants; Beider 2019; Hirayama 2019; JULIET; Kochenderfer 2017; PLATFORM; Sang 2020; Schuster 2017; Tong 2020; TRANSCEND-NHL-001; Ying 2019; ZUMA-1; ZUMA-6) reported data on overall response rates. Given the substantial variability of follow-up durations and the variability of the outcome definition, including best response rate in several of the included studies, we here present results on time point-specific response rates only. Additional data for response rates, including best response rates, are reported in Table 4, but have to be interpreted with additional care.

One-month follow-up

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

Three-month follow-up

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

Six-month follow-up

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

Complete response

For details on complete response rates, see Table 4.

Data on complete response were provided for all 13 included studies (620 participants; 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), however, as for overall response rates, we here present results for time point-specific rates only and refer to Table 4 for additional data. Please note that these data have to be interpreted with additional care.

One-month follow-up

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

Three-month follow-up

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

Six-month follow-up

Sang 2020, Schuster 2017 and Ying 2019 provided data on complete responses at six months of follow-up: 40.0% (95% CI 12.2% to 73.84%; 21 participants DLBCL) of participants in Sang 2020, 43% (95% CI 18% to 71%; 14 participants DLBCL) of participants in Schuster 2017 and 45% (95% CI 23.06% to 68.47%; 20 participants DLBCL) of participants in Ying 2019.

As for the other presented time point-specific outcomes, we included observational studies only. The overall risk of bias was judged to be high for all studies (downgraded by one point for risk of bias). None of the included studies had a control group and effect estimates could not be calculated (downgraded by one point for imprecision). Thus, the evidence is very uncertain about the effect of CAR T-cell therapy on complete response rates of people with r/r DLBCL.

Partial response

For details on partial response rates, see Table 4.

Data on partial response were provided for six studies (485 participants; Beider 2019; JULIET; Kochenderfer 2017; Tong 2020; TRANSCEND-NHL-001; ZUMA-1). As for overall and complete responses, we intended to present results for time point-specific response rates only. However, none of the included studies reported time point-specific partial response rates. Table 4 presents additional data that should be interpreted with additional care.

DISCUSSION

Summary of main results

The aim of this review was to assess the benefits and harms of CAR T-cell therapy for people with r/r DLBCL in accordance with the available body of evidence. We did not identify any completed RCTs or controlled studies that were eligible for inclusion in this review. We included 13 uncontrolled studies evaluating CAR T-cell therapy in people with r/r DLBCL with either a single arm or multiple arms of CAR T-cell therapy. In addition, we identified 38 ongoing studies, three of which are RCTs that will not be completed before 2022. The following results that we have summarised should be interpreted in light of the absence of evidence from trials of robust design and conclusions should be drawn carefully.

Overall survival

Overall survival was reported by eight studies. Four studies reported survival rates at 12 months at a range between 48% and 59%, and one study reported an overall survival rate of 50.5% at 24 months (very low-certainty evidence).

Quality of life

Two studies including 294 participants at baseline and 59 participants at the longest follow-up described improvements of quality of life over time (very low-certainty evidence).

Treatment-related mortality

None of the studies reported treatment-related mortality.

Number of participants with adverse events and serious adverse events

Any adverse events

As reported by five studies, the vast majority of participants experienced adverse events (99% to 100% any grade, 68% to 98% grade ≥ 3; very low-certainty evidence).

Any serious adverse events

In three studies, 56% to 68% of participants experienced serious adverse events, while in one study, no serious adverse events occurred (very low-certainty evidence).

Cytokine release syndrome

Various grading criteria were used by 11 studies which reported the occurrence of cytokine release syndrome among the included participants. Five studies reported that between 42% and 100% of participants experienced cytokine release syndrome according to criteria described in Lee 2014 (very low-certainty evidence).

Neurotoxicity

As reported by 10 studies, the occurrence of neurotoxicity of any grade ranged from 15.6% to 100%, while 0% to 55% of participants experienced neurotoxicity of grade ≥ 3.

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

Eight studies reported the number of participants who were treated for cytokine release syndrome or neurotoxicity. Participants received tocilizumab (0% to 80% of participants), tocilizumab and

corticosteroids (3% to 67% of participants) or corticosteroids alone (0% to 20% of participants).

Cytopenias

Eight studies reported the occurrence of cytopenias with rates of 14% to 81% (0% to 75% grade ≥ 3) for anaemia, 15% to 76.2% (14% to 47.6% grade ≥ 3) for leukopenia, 20% to 79% (20% to 86% grade ≥ 3) for neutropenia and 12% to 79% of participants (3.1% to 28.6% grade ≥ 3) for thrombocytopenia. Three studies reported that between 44% and 45% of participants experienced prolonged cytopenias (30% to 37% grade ≥ 3).

Febrile neutropenia

As reported by five studies, febrile neutropenia occurred in a range of 9% to 76.2% (9% to 50% grade ≥ 3).

Any infections

Three studies reported that 12% to 28% of participants experienced grade ≥ 3 infections.

Response to treatment

Progression-free survival

Nine studies reported results on progression-free survival, disease-free survival or relapse-free survival at any time of follow-up. Twelve-month progression-free survival rates were reported by four studies and ranged between 44% and 75%. In one study, relapse-free survival remained at a rate of 64% at both 12 and 18 months (very low-certainty evidence).

Overall response

Overall response rates at any time of follow-up were reported by 12 studies using several definitions of response. In two studies, overall response at six months was sustained in 45% and 46.2% of the participants, respectively.

Complete response

All of the 13 included studies provided data on complete response rates. At six months, three studies reported complete response rates between 40% and 45% (very low-certainty evidence).

Partial response

Rates of partial response were provided by six studies but none of them were time point-specific.

Overall completeness and applicability of evidence

The evidence we presented is based on uncontrolled studies at high risk of bias only, with limited applicability and results that have to be interpreted with caution.

In the studies eligible for this review, the proportion of participants receiving CAR T-cells ranged between 67% and 100% of total enrolled participants, whereas the proportion of participants evaluated for efficacy ranged between 56% and 100% of those who were enrolled. In most studies, efficacy outcomes were at a high risk of bias due to incomplete assessment of relevant outcome data and because the number of assessable participants declined substantially over time. In addition, outcomes were frequently reported for a subset of the enrolled participants only and the participant flow or selection of participants were not sufficiently reported.

The available evidence is subject to a strong selection bias, particularly because outcomes were frequently evaluated only in the subset of total enrolled individuals with r/r DLBCL who were considered eligible and/or actually received CAR T-cell therapy. Despite a risk for selection bias, that is introduced through the potentially unfavourable prognosis of those ineligible for CAR T-cell therapy, this might impose strong constraints to the generalisability of our reviewed study findings. This leads to the problem that the available evidence might then only be representative for those eligible for CAR T-cell therapy and not for the general population of individuals affected from r/r DLBCL. Nevertheless, the available evidence remains more applicable to participant populations who fulfil the conditions of eligibility for CAR T-cell therapy.

With regard to a population of individuals with r/r DLBCL that is eligible to treatment with CAR T-cell therapy, a second constraint in the applicability of the results arises from the problem that generally highly selected participants receive treatment during the course of a study. Two investigations (Jacobson 2020a; Nastoupil 2020) explored clinical outcomes of participants eligible for treatment with axi-cel outside the study setting. They provided comparisons of individuals fulfilling the inclusion criteria of the included study ZUMA-1 versus those who did not. In both investigations, the authors reached conclusions on largely comparable outcomes between these two groups, in particular, with regard to survival and safety outcomes (Jacobson 2020a).

In the majority of studies, the study population was not limited to individuals with r/r DLBCL but also included people with other disease entities (e.g. acute lymphoblastic leukaemia, Burkitt lymphoma, mantle cell lymphoma, follicular lymphoma or primary mediastinal large B-cell lymphoma.) We only included studies with a minimum proportion of people with r/r DLBCL above 70% and extracted separate outcome data for people with r/r DLBCL, whenever possible. However, data were not always reported separately and the detail in reporting of entities, including subentities of DLBCL, varied across studies.

The results from non-comparative single-arm studies such as the larger studies included in our review (JULIET; TRANSCEND-NHL-001; ZUMA-1) are often compared to historic controls. As observed, for example, in a retrospective cohort of people receiving standard treatment at the time of the study, with a median overall survival of around six months and an overall survival rate as low as 20% at two years, the prognosis of people with r/r DLBCL is very poor (Crump 2017). In light of this indirect comparison, the studies identified in this review, treating a limited number of people with r/r DLBCL with CAR T-cells, reported median overall survival rates well above 12 months (one-year and two-years follow-up) of around 50%. This indicates great potential of this novel therapy to improve outcomes of a population with an otherwise poor prognosis. Nevertheless, the lack of a control group, as well as constraints in internal and external validity that we observed in the included uncontrolled studies, affect our confidence in the available evidence. In agreement with Zhang 2020 and colleagues, who analysed clinical studies as well as real-word studies on CAR T-cell therapy for people with r/r DLBCL and discuss concerns inherent to indirect comparisons between these studies and historic controls, we stress the need for head-to-head comparisons. In the course of our systematic search, we identified

38 ongoing studies, three of which are RCTs comparing CAR T-cell therapy with standard of care (BELINDA; TRANSFORM; ZUMA-7) which will probably provide data on the awaited comparisons. The publication of these trials, which will be completed between 2022 and 2025, will necessitate an update of this review. The conclusions of an update might differ from those of the present review and may allow for a more confident judgement about the efficacy and safety of CAR T-cell therapy.

Finally, we identified eight studies which are awaiting classification. For two studies, we were able to identify a linked abstract publication, which did not include sufficient data to justify their in- or exclusion (NCT02652910; NCT03097770). For one of these studies, the register status was completed (NCT02976857) and, for five studies, the estimated completion dates had passed (ChiCTR-ONC-16008911; ChiCTR-OPN-16009847; ChiCTR-OPN-17013507; NCT02933775; NCT03598179). We were not able to identify any published or unpublished result data for these studies, which therefore poses a risk for publication bias that has to be observed in future updates of this review.

Quality of the evidence

We rated the risk of bias within and across studies to be serious and all of the included studies were of a non-randomised design with lack of a control group. The certainty of the available evidence is very low for all outcomes.

Risk of bias

The internal and external validity, as assessed based on criteria provided by the Cochrane Childhood Cancer Group (see Table 1), was limited. In most studies, efficacy outcomes were at risk of attrition bias as outcome data were provided only for a subset of participants who were enrolled. Moreover, the reporting of outcomes was often unclear or heterogeneous. For example, several studies were at risk of reporting bias for the assessment of response to treatment as outcome criteria were not specified, time point-specific assessment was missing or the timing of assessment was unclear. Similarly, adverse events were reported heterogeneously with substantial variation in follow-up. In particular, cytokine release syndrome was reported using several grading criteria across studies (Risk of bias in included studies).

Certainty of the evidence (GRADE)

For all outcomes, our assessment of the certainty of the evidence started with 'low certainty' as we only included observational studies. The overall risk of bias was judged to be high for all studies (downgraded by one point for risk of bias). None of the included studies had a control group so that no adequate comparative effect estimates could be calculated (downgraded by one point for imprecision). For adverse events, duration of follow-up varied substantially (downgraded by one point for inconsistency). Therefore, our certainty in the evidence was very low for all outcomes (Summary of findings 1).

Potential biases in the review process

We limited bias arising in the conduct of this review by performing relevant tasks in duplicate and independently (screening, data collection, assessment of risk of bias and the certainty of the evidence). We performed an in-depth literature search based on a sensitive search strategy developed by an experienced information specialist (IM). The electronic database searches were complemented by searches of the proceedings of relevant international conferences and study registries, which allowed us to identify performed but not published studies in order to detect potential publication bias. Moreover, we were in close collaboration with clinical experts and are therefore confident that we have identified all studies relevant to the review question.

We have to acknowledge the difficulty of performing systematic reviews of non-comparative studies, for which no comprehensive guidance is currently available. To reduce difficulties, we followed all available guidance (PRISMA, Cochrane Handbook) for systematic reviews of other study designs to the utmost extent and, where necessary, transferred unresolved methodological issues with the help of methodological experts.

Agreements and disagreements with other studies or reviews

In a systematic review with meta-analysis of `second-generation` CAR T-cell therapy in individuals with B-cell lymphoma, including participants with r/r DLBCL, the authors decided to pool study outcomes and reported rates of 68% and 46% for objective response and complete response, respectively, at a median follow-up of 19.6 months in participants with r/r DLBCL (Al-Mansour 2020). According to the authors, grade ≥ 3 anaemia (34%) and thrombocytopenia (30%) were the most common adverse events (in r/r DLBCL and other types of B-cell lymphoma) and "incidence of grade ≥ 3 cytokine release syndrome and neurotoxicity associated with CAR-T cell therapy was effectively managed". In the respective review, data were pooled despite clinical heterogeneity (e.g. study populations, CAR T-cell manufacturing methods and timing of follow-up), resulting in substantial statistical heterogeneity in several efficacy and safety outcomes. In contrast to this review, we refrained from reporting any pooled effect estimates due to the lack of a control group and also due to concerns with respect to cross-study heterogeneity through features such as timing of follow-up and criteria for outcome assessment. With our approach, we are in line with the conclusion of the authors of an analysis of clinical studies as well as real-word studies on CAR T-cell therapy for people with r/r DLBCL (Zhang 2020); they have pointed out substantial cross-study differences between the pivotal single-arm studies ZUMA-1 and JULIET (e.g. timing of leukapheresis and enrolment, use of bridging chemotherapy, lymphodepleting regimens) and argued that valid comparative analyses are not feasible.

Another current systematic review focused on retrospective and prospective studies on the use of axicabtagene-ciloleucel in r/r large B-cell lymphoma. The authors reported that response rates in postmarketing studies in a more clinically diverse population of individuals with various large B-cell malignancies are comparable to the ones in the pivotal ZUMA-1 study (overall and complete response rates of 83% and 58%, respectively) (Halford 2020). The authors pointed out the association of CAR T-cell therapy and potentially life-threatening adverse events such as cytokine release syndrome (grade ≥ 3 in 7% to 14% of participants) and immune effector cell–associated neurotoxicity syndrome (grade ≥ 3 in 31% to 55% of participants). They concluded that the ongoing results on axicabtagene-ciloleucel are encouraging, while highlighting the lack of long-term efficacy and safety data.

AUTHORS' CONCLUSIONS

Implications for practice

In this review, we did not identify any completed randomised controlled trials (RCTs), or controlled studies on chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL). Therefore, our review has to be viewed as a very early evaluation of this novel therapy which is based on evidence of very low certainty. Accordingly, conclusions based on the results we have presented should be drawn very carefully and potentially revised as soon as new evidence becomes available.

However, we did identify several uncontrolled studies treating a limited number of people with r/r DLBCL with CAR T-cells that reported one- and two-year survival rates of around 50% which indicate great potential of this novel therapy to improve outcomes of a population with an otherwise poor prognosis. Our confidence in the evidence that is currently available is very low. Given the restrictions in the studies we identified, conclusions that are drawn based on these data are subject to change when more reliable results, that is, data from RCTs or controlled studies, become available.

Whenever the potential benefits of CAR T-cells in the treatment of people with r/r DLBCL are discussed, the harms of this novel therapy should not be neglected. As our review indicates, people who receive CAR T-cells may experience potentially life-threatening adverse events and therefore often require treatment for the management of complications such as cytokine release syndrome or neurotoxicity. Accordingly, the need for additional treatment, including intensive care medicine, may increase with a growing number of people who are infused with CAR T-cells (Azoulay 2020; Böll 2019; Borrega 2019). The integration of more reliable evidence in the future will help to increase the certainty in the evidence on the safety of CAR T-cell therapy.

Implications for research

Numerous clinical studies have been initiated in recent years to investigate CAR T-cells for the treatment of various malignancies (Zhang 2020a). In this review, we identified several studies treating a limited number of people with r/r DLBCL with CAR T-cells that reported one- and two-year survival rates of around 50%. These results were observed in people who relapsed or were refractory to advanced lines of treatment or ineligible for autologous stem-cell transplantation (ASCT), i.e. a population with a very poor prognosis. However, the evidence that is currently available on the efficacy and safety of CAR T-cell therapy for people with r/r DLBCL is of very low certainty. That is due to the lack of a control group and limited internal and external validity of the studies we identified. As there are 38 currently ongoing studies 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 the evidence. Therefore, we expect to conduct an update of this review as soon as more robust evidence can be expected.

This review also demonstrates the challenge of analysing adverse events when criteria to describe these events are used heterogeneously. Therefore, further approaches should be made to standardise measurement and reporting of adverse events, such as cytokine release syndrome (CRS) or neurotoxicity, which are typically observed in people who receive CAR T-cell therapy.

Furthermore, two of our prioritised outcomes were rarely reported. Quality of life, which is relevant especially for people with a history of multiple pretreatments, was reported by two studies only. Another outcome we were interested in, i.e. treatment-related mortality, was reported by none of the studies. Adequate assessment and reporting of these outcomes should be considered in future trials.

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REFERENCES

References to studies included in this review

Beider 2019 *{published data only (unpublished sought but not used)}* **10.1136/jitc-2019-000148**

Beider K, Besser M, Schachter J, Jacoby E, Shimoni A, Avigdor A, et al. Senescent/exhausted phenotype of CAR T cells and induction of immunoregulatory environment correlate with reduced response to CAR T cell therapy in relapsed/refractory B cell malignancies. *Biology of Blood and Marrow Transplantation* 2020;**26** (3 Suppl):S314-5.

* Beider K, Besser MJ, Schachter J, Grushchenko-Polaq AH, Voevoda V, Wolf I, et al. Upregulation of senescent/exhausted phenotype of CAR T cells and Induction of both treg and myeloid suppressive cells correlate with reduced response to CAR T cell therapy in relapsed/refractory B cell malignancies. *Blood* 2019;**134**(Suppl 1):3234.

Itzhaki O, Jacoby E, Nissani A, Levi M, Nagler A, Kubi A, et al. Head-to-head comparison of in-house produced CD19 CAR-T cell in ALL and NHL patients. *Journal for Immunotherapy of Cancer* 2020;**8**(1):e000148.

Chang 2015 *{published data only}*

* Chang LJ, Dong L, Zhu J, Ying Z, Kuo HH, Liu Y, et al. 4SCAR19 chimeric antigen receptor-modified T cells as a breakthrough therapy for highly chemotherapy-resistant late-stage B cell lymphoma patients with bulky tumor mass. *Blood* 2015;**126** (23):264.

Hirayama 2019 *{published data only (unpublished sought but not used)}*

Cordeiro A, Bezerra ED, Hirayama AV, Hill JA, Wu QV, Voutsinas J, et al. Late events after treatment with CD19-targeted chimeric antigen receptor modified t cells. *Biology of Blood and Marrow Transplantation* 2020;**26**(1):26-33.

Gauthier J, Hirayama AV, Hay KA, Li D, Sheih A, Wu V, et al. Factors associated with duration of response after CD19-specific CAR-T cell therapy for refractory/relapsed B-cell non-Hodgkin lymphoma. *Journal of Clinical Oncology* 2018;**36**(15 Suppl 1):7567.

* Hirayama AV, Gauthier J, Hay KA, Voutsinas JM, Wu Q, Gooley T, et al. The response to lymphodepletion impacts pfs in patients with aggressive non-Hodgkin lymphoma treated with CD19 CAR T cells. *Blood* 2019;**133**(17):1876-87.

JULIET *{published data only (unpublished sought but not used)}*

Agoulnik S, Jager U, Tam CS, McGuirk JP, Foley SR, Jaglowski SM, et al. Biomarker analysis of tisagenlecleucel pre-infusion biopsies of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL). *HemaSphere* 2018;**2 (Suppl 2)**:453.

Bachanova V, Tam CS, Borchmann P, Jaeger U, McGuirk JP, Holte H, et al. Impact of tisagenlecleucel chimeric antigen receptor (CAR)-T cell therapy product attributes on clinical outcomes in adults with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL). *Blood* 2019;**134**(Suppl 1):242.

Borchmann P, Tam CS, Jager U, McGuirk JP, Holte H, Waller EK, et al. An updated analysis of JULIET, a global pivotal phase 2 trial of tisagenlecleucel in adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL). *HemaSphere* 2018;**2 (Suppl 2)**:347.

Goto H, Makita S, Kato K, Tokushige K, Fujita T, Akashi K, et al. Efficacy and safety of tisagenlecleucel in Japanese adult patients with relapsed/refractory diffuse large B-cell lymphoma. *International Journal of Clinical Oncology* 2020;**25**(9):1736-43.

Maziarz RT, Schuster SJ, Romanov VV, Rusch ES, Li J, Signorovitch JE, et al. Grading of neurological toxicity in patients treated with tisagenlecleucel in the JULIET trial. *Blood Advances* 2020;**4**(7):1440-7.

Maziarz RT, Waller EK, Jaeger U, Fleury I, McGuirk J, Holte H, et al. Patient-reported long-term quality of life after tisagenlecleucel in relapsed/refractory diffuse large B-cell lymphoma. *Blood Advances* 2020;**4**(4):629-37.

Schuster S, Bishop MR, Tam CS, Borchmann P, Jaeger U, Waller EK, et al. Long-term follow-up of tisagenlecleucel in adult patients with relapsed or refractory diffuse large B-cell lymphoma: updated analysis of Juliet study. *Biology of Blood and Marrow Transplantation* 2019;**25** (3 Suppl):S20-1.

Schuster SJ, Bishop MR, Tam C, Waller EK, Borchmann P, McGuirk J, et al. Global pivotal phase 2 trial of the CD19-targeted therapy CTL019 in adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) - an interim analysis. *Clinical Lymphoma Myeloma and Leukemia* 2017;**Suppl 2**:S373-4.

Schuster SJ, Bishop MR, Tam C, Waller EK, Borchmann P, McGuirk J, et al. Global pivotal phase 2 trial of the CD19-targeted therapy CTL019 in adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) - an interim analysis. *Hematological Oncology* 2017;**35** (Suppl 2):27.

* Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *New England Journal of Medicine* 2019;**380**(1):45-56.

Schuster SJ, Maziarz RT, Rusch ES, Li J, Signorovitch JE, Romanov VV, et al. Grading and management of cytokine release syndrome in patients treated with tisagenlecleucel in the JULIET trial. *Blood Advances* 2020;**4**(7):1432-9.

Tam CS, Waller EK, Jaeger U, Fleury I, McGuirk J, Holte H, et al. Prolonged Improvement in patient reported quality of life (qol) following tisagenlecleucel infusion in adult patients (pts) with relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL): 19-month follow-up (fu) of the Juliet study. *Biology of Blood and Marrow Transplantation* 2019;**25** (3 Suppl):S181-2.

Westin JR, Tam CS, Borchmann P, Jaeger U, McGuirk JP, Holte H, et al. Correlative analyses of patient and clinical characteristics associated with efficacy in tisagenlecleucel-treated relapsed/refractory diffuse large b-cell lymphoma patients in the Juliet trial. *American Society of Hematology* 2019;**134**(Suppl 1):4108.

Kochenderfer 2017 *{published data only (unpublished sought but not used)}*

Kochenderfer JN, Dudley ME, Carpenter RO, Kassim SH, Rose JJ, Telford WG, et al. Donor-derived CD19-targeted t cells cause regression of malignancy persisting after allogeneic hematopoietic stem cell transplantation. *Blood* 2013;**122**(25):4129–39.

Kochenderfer JN, Dudley ME, Feldman SA, Wilson WH, Spaner DE, Maric I, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor–transduced T cells. *Blood* 2012;**119**(12):2709.

* Kochenderfer JN, Dudley ME, Kassim SH, Somerville RPT, Carpenter RO, Stetler-Stevenson M, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous t cells expressing an anti-CD19 chimeric antigen receptor. *Journal of Clinical Oncology* 2014;**33**(6):540-9.

Kochenderfer JN, Rosenberg SA. Treating B-cell cancer with t cells expressing anti-CD19 chimeric antigen receptors. *Nature Reviews Clinical Oncology* 2013;**10**:267-76.

Kochenderfer JN, Somerville RP, Lu T, Shi V, Bot A, Rossi J, et al. Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. *Journal of Clinical Oncology* 2017;**35**(16):1803-13.

Kochenderfer JN, Somerville RPT, Lu T, Yang JC, Sherry RM, Feldman SA, et al. Long-curation complete remissions of diffuse large B cell lymphoma after anti-CD19 chimeric antigen receptor r cell therapy. *Molecular Therapy* 2017;**25**(10):2245-53.

Kochenderfer JN, Wilson WH, Janik JE, Dudley ME, Stetler-Stevenson M, Feldman SA, et al. Eradication of b-lineage cells and regression of lymphoma in a patient treated with autologous t cells genetically engineered to recognize CD19. *Blood* 2010;**116**(20):4099.

Rossi J, Paczkowski P, Shen YW, Morse K, Flynn B, Kaiser A, et al. Preinfusion polyfunctional anti-CD19 chimeric antigen receptor T cells are associated with clinical outcomes in NHL. *Blood* 2018;**132**(8):804-14.

PLATFORM *{published data only (unpublished sought but not used)}*

Siddiqi T, Abramson JS, Lee HJ, Schuster S, Hasskarl J, Montheard S, et al. Safety of lisocabtagene maraleucel given with durvalumab in patients with relapsed/refractory aggressive B cell non Hodgkin lymphoma: first results from the Platform study. *Hematological Oncology* 2019;**37** (Suppl 2):171-2.

Sang 2020 *{published data only (unpublished sought but not used)}*

Sang W, Shi M, Yang J, Cao J, Xu L, Yan D, et al. Combination of anti-CD19 and anti-CD20 chimeric antigen receptor t cells for relapsed and refractory diffuse large B cell lymphoma: an open-label, single-arm, phase Ⅰ/Ⅱ trial. *Blood* 2019;**134**(Suppl 1):1590.

Sang W, Shi M, Yang J, Cao J, Xu L, Yan D, et al. Combination of anti-CD19 and anti-CD20 chimeric antigen receptor t cells for relapsed and refractory diffuse larger B cell lymphoma: an open-label, single-arm, phase I/II trial. *Blood* 2019;**134**(Suppl 1):1590.

Sang W, Shi M, Yang J, Cao J, Xu L, Yan D, et al. Phase II trial of co-administration of CD19- and CD20-targeted chimeric antigen receptor t cells for relapsed and refractory diffuse large B cell lymphoma. *Cancer Medicine* 2020;**9**(16):5827-38.

* Sang W, Shi M, Yang J, Cao J, Xu L, Yan D, et al. Phase II trial of co-administration of CD19- and CD20-targeted chimeric antigen receptor t cells for relapsed and refractory diffuse large B cell lymphoma. *Cancer Medicine* 2020;**9**(16):5827-38.

Schuster 2017 *{published data only (unpublished sought but not used)}*

Levine B, Svoboda J, Nasta SD, Porter D, Chong E, Lacey S, et al. Chimeric antigen receptor modified T cells directed against CD19 (CTL019) induce clinical responses in patients with relapsed or refractory CD19+ lymphomas. *Cytotherapy* 2015;**21**(17 Suppl 6):2545-54.

NCT02030834. Phase IIa study of redirected autologous T cells engineered to contain anti-CD19 attached to TCRz and 4-signaling domains in patients with chemotherapy relapsed or refractory CD19+ lymphomas. clinicaltrials.gov/show/nct02030834 (first received 2014).

* Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak O, et al. Chimeric antigen receptor t cells in refractory B-cell lymphomas. *New England Journal of Medicine* 2017;**377**(26):2545-54.

Tong 2020 *{published data only}*

* Tong C, Zhang Y, Liu Y, Ji X, Zhang W, Guo Y, et al. Optimized tandem CD19/CD20 CAR-engineered T cells in refractory/relapsed B-cell lymphoma. *Blood* 2020;**136**(14):1632-44.

TRANSCEND-NHL-001 *{published data only (unpublished sought but not used)}*

Abramson J, Gordon L, Palomba ML, Lunning M, Arnason J, Forero-Torres A, et al. Updated safety & long term clinical outcomes in Transcend NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017) in R/R aggressive NHL. *Journal of Clinical Oncology* 2018;**36**:347.

Abramson J, Palomba ML, Gordon L, Lunning M, Arnason J, Wang M, et al. High CR rates in relapsed/ refractory (R/R) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (transcend NHL 001). *Hematological Oncology* 2017;**35**:138.

Abramson J, Palomba ML, Gordon L, Lunning M, Arnason J, Wang M, et al. High CR rates in relapsed/refractory (R/R) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (Transcend NHL 001). *Hematological Oncology* 2017;**35** (Suppl 2):138.

Abramson J, Palomba ML, Gordon L, Lunning M, Wang M, Arnason J, et al. Safety and efficacy results from Transcend NHL 001, a multicenter phase 1 study of lisocabtagene maraleucel

(Liso-cel) in relapsed/refractory (R/R) large B-cell lymphoma (LBCL). *Oncology Research and Treatment* 2020;**43** (Suppl 1):215.

Abramson JS, Gordon LI, Palomba ML, Lunning MA, Arnason JE, Forero-Torres A, et al. Updated safety and long term clinical outcomes in TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017) in R/R aggressive NHL. *Journal of Clinical Oncology* 2018;**36**(15 Suppl 1):7505.

Abramson JS, Palomba ML, Gordon LI, Lunning MA, Arnason JE, Forero-Torres A, et al. Cr rates in relapsed/refractory (R/R) aggressive B-NHL treated with the CD19-directed CAR T-cell product JCAR017 (TRANSCEND NHL 001). *Journal of Clinical Oncology* 2017;**35**(15 Suppl 1):7513.

* Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet* 2020;**396**(10254):839-52.

Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang ML, Arnason JE, et al. Pivotal safety and efficacy results from transcend NHL 001, a multicenter phase 1 study of lisocabtagene maraleucel (liso-cel) in relapsed/refractory (R/R) large B cell lymphomas. *Blood* 2019;**134**(Suppl 1):241.

Abramson JS, Siddiqi T, Palomba ML, Gordon LI, Lunning MA, Arnason JE, et al. High durable CR rates and preliminary safety profile for JCAR017 in R/R aggressive b-NHL (TRANSCEND NHL 001 study): a defined composition CD19-directed CAR T-cell product with potential for outpatient administration. *Transplantation and Cellular Therapy* 2018;**24**(3 Suppl):S25.

Palomba ML, Siddiqi T, Gordon L, Lunning M, Wang M, Arnason J, et al. Characterization of cytokine release syndrome and neurological events in the phase 1 transcend NHL 001 trial of lisocabtagene maraleucel for patients with relapsed/refractory large B-cell lymphoma. *HemaSphere* 2020;**4** (Suppl 1):579-80.

Patrick DL, Powers A, Parisi M, Kim Y, Garcia J, Dehner C, et al. Impact of lisocabtagene maraleucel (liso-cel) treatment on health-related quality of life and health utility in patients (pts) with relapsed/refractory (R/R) aggressive B cell non-hodgkin lymphoma (NHL): Transcend NHL 001. *Blood* 2019;**134**(Suppl 1):66.

Siddiqi T, Abramson JS, Palomba ML, Gordon LI, Lunning MA, Arnason JE, et al. Correlation of patient characteristics and biomarkers with clinical outcomes of JCAR017 in R/R aggressive B-NHL (TRANSCEND NHL 001 study). *Journal of Clinical Oncology* 2018;**36**(5 Suppl 1):122.

Ying 2019 *{published data only (unpublished sought but not used)}*

Yan Z, Wang W, Zheng Z, Hao M, Yang S, Li J, et al. Efficacy and safety of JWCAR029 in adult patients with relapsed and refractory B-cell non-hodgkin lymphoma. *Blood* 2018;**132**(Suppl 1):4187.

Yan ZX, Li L, Wang W, OuYang BS, Cheng S, Wang L, et al. Clinical efficacy and tumor microenvironment influence in a dose-escalation study of anti-CD19 chimeric antigen receptor t cells in refractory B-cell non-hodgkin's lymphoma. *Clinical Cancer Research* 2019;**25**(23):6995-7003.

* Ying Z, Xu P, Wang L, Cheng S, Wu W, Wang W, et al. Clinical response in relapsed/refractory (R/R) B-NHL treated with the CD19-directed CAR T-Cell product JWCAR029. *Blood* 2019;**134**(Suppl 1):2876.

ZUMA-1 *{published data only (unpublished sought but not used)}*

Byrne MT, Oluwole O, Allen D, Cornell RF, Culos KAA, Engelhardt BG, et al. Commercial chimeric antigen receptor (CAR) T cells: unfamiliar roads and stalled cars. *Biology of Blood and Marrow Transplantation* 2019;**25** (3 Suppl):S302.

Galon J, Rossi J, Turcan S, Danan C, Locke FL, Neelapu SS, et al. Characterization of anti-CD19 chimeric antigen receptor (CAR) T cell-mediated tumor microenvironment immune gene profile in a multicenter trial (ZUMA-1) with axicabtagene ciloleucel (axi-cel, KTE-C19). *Journal of Clinical Oncology* 2017;**35**(15 Suppl 1):3025.

Ghobadi A, Locke FL, Neelapu SS, Siddiqi T, Chavez JC, Hosing CM, et al. Updated phase I results from ZUMA-1: a phase I-II multicenter study evaluating the safety and efficacy of KTE-C19 (anti-CD19 CAR T cells) in subjects with refractory aggressive non-Hodgkin lymphoma (NHL). *Cancer Research* 2016;**76**(14 Suppl):135.

Locke F, Sherman M, Rossi J, Xue A, Mojadidi M, Neelapu S, et al. Early biomarker correlates of severe neurologic events and cytokine release syndrome in ZUMA-1, a multicenter trial evaluating axicabtagene ciloleucel in refractory aggressive non-Hodgkin lymphoma. *Journal for ImmunoTherapy of Cancer* 2017;**5**(Suppl 2):86.

Locke FL, Bartlett NL, Jacobson CA, Oluwole OO, Munoz J, Lekakis LJ, et al. Retreatment of patients with refractory large B cell lymphoma with axicabtagene ciloleucel (Axi-cel) in ZUMA-1. *HemaSphere* 2020;**4** (Suppl 1):590.

Locke FL, Ghobadi A, Jacobson CA, Jacobsen E, Miklos DB, Lekakis LJ, et al. Axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma: durability of response in Zuma-1. *HemaSphere* 2018;**2** (Suppl 2):83.

Locke FL, Ghobadi A, Jacobson CA, Jacobsen ED, Miklos DB, Lekakis LJ, et al. Durability of response in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients (pts) with refractory large B cell lymphoma. *Journal of Clinical Oncology* 2018;**36**(15 Suppl 1):3003.

Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncology* 2019;**20**(1):31-42.

Locke FL, Ghobadi A, Lekakis LJ, Miklos DB, Jacobson CA, Jacobsen E, et al. Axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma: outcomes by prior lines of therapy in Zuma-1. *HemaSphere* 2018;**2** (Suppl 2):348.

Locke FL, Ghobadi A, Lekakis LJ, Miklos DB, Jacobson CA, Jacobsen ED, et al. Outcomes by prior lines of therapy (lot) in

ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (axi-cel) in patients (pts) with refractory large B cell lymphoma. *Journal of Clinical Oncology* 2018;**36**(15 Suppl 1):3039.

Locke FL, Neelapu SS, Bartlett NL, Lekakis LJ, Miklos BD, Jacobson AC, et al. Clinical and biologic covariates of outcomes in ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (r-NHL). *Journal of Clinical Oncology* 2017;**35**(15 Suppl 1):7512.

Locke FL, Neelapu SS, Bartlett NL, Lekakis LJ, Miklos D, Jacobson CA, et al. Clinical and biologic covariates of outcomes in ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axi-cel; Kte-c19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL). *Haematologica* 2017;**102**:172.

Locke FL, Neelapu SS, Bartlett NL, Lekakis LJ, Miklos D, Jacobson CA, et al. Clinical and biologic covariates of outcomes in ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axi-cel; Kte-c19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL). *Haematologica* 2017;**102** (Suppl 2):172.

Locke FL, Neelapu SS, Bartlett NL, Lekakis LJ, Miklos D, Jacobson CA, et al. Primary results from ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axicel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL). *Cancer Research* 2017;**77**(13 Suppl 1):CT019.

Locke FL, Neelapu SS, Bartlett NL, Siddiqi T, Chavez JC, Hosing CM, et al. Ongoing complete remissions in phase 1 of ZUMA-1: a phase 1-2 multi-center study evaluating the safety and efficacy of KTE-C19 (anti-CD19 CAR T cells) in patients with refractory aggressive B cell non-Hodgkin lymphoma (NHL). *Annals of Oncology* 2016;**27**(Suppl 6):VI359.

Locke FL, Neelapu SS, Bartlett NL, Siddiqi T, Chavez JC, Hosing CM, et al. Phase 1 results of ZUMA-1: a multicenter study of KTE-C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma. *Molecular Therapy* 2017;**25**(1):285-95.

Locke FL, Rossi J, Neelapu SS, Xue A, Better M, Zhang X, et al. Product characteristics associated with in vivo expansion of anti-CD19 CAR T cells in patients treated with axicabtagene ciloleucel (axi-cel). *Journal of Clinical Oncology* 2017;**35**(15 Suppl 1):3023.

Locke FL, Rossi J, Neelapu SS, Xue A, Better M, Zhang X, et al. Product characteristics associated with in vivo expansion of anti-CD19 CAR T cells in patients treated with Axicabtagene Ciloleucel (axi-cel). *Journal of Clinical oncology* 2017;**35**(15 Suppl 1):3023.

Locke FL, Rossi J, Xue X, Neelapu SS, Ryan DH, Ghobadi A, et al. Immune signatures of cytokine release syndrome and neurologic events in a multicenter registrational trial (ZUMA-1) in subjects with refractory diffuse large B cell lymphoma treated with axicabtagene ciloleucel (KTE-C19). *Cancer Research* 2017;**77**(13 Suppl 1):CT020.

Neelapu SS, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole O, et al. 2-year follow-up and high-risk subset analysis of Zuma-1, the pivotal study of axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma. *Biology of Blood and Marrow Transplantation* 2019;**25** (3 Suppl):S65.

Neelapu SS, Locke FL, Bartlett NL, Lekakis L, Miklos D, Jacobson CA, et al. Kte-C19 (anti-CD19 CAR T cells) induces complete remissions in patients with refractory diffuse large B-cell lymphoma (DLBCL): results from the pivotal phase 2 Zuma-1. *Blood* 2016;**128**(22):LBA-6.

Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos D, Jacobson CA, et al. Axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphomas (NHL): primary results of the pivotal trial ZUMA-1. *Hematological Oncology* 2017;**35**:28.

Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos D, Jacobson CA, et al. Axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphomas (NHL): primary results of the pivotal trial ZUMA-1. *Hematological Oncology* 2017;**35** (Suppl 2):28.

* Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *New England Journal of Medicine* 2017;**377**(26):2531-44.

Neelapu SS, Locke FL, Bartlett NL, Siddiqi T, Braunschweig I, Lekakis LJ, et al. ZUMA-1: a phase 2 multi-center study evaluating anti-CD19 chimeric antigen receptor (CAR) T cells in patients with refractory aggressive non-Hodgkin lymphoma (NHL). *Annals of Oncology* 2016;**27** (Suppl 6):VI325.

Neelapu SS, Locke FL, Ghobadi A, Lekakis LJ, Miklos D, Jacobson CA, et al. ZUMA-1 pivotal phase 2 trial of axicabtagene ciloleucel (axi-cel, KTE-C19; Anti-CD19 CAR T cells) in patients (pts) with refractory aggressive non-Hodgkin lymphoma (NHL). *Molecular Therapy* 2017;**25**(5 Suppl 1):333.

Neelapu SS, Locke FL, Ghobadi A, Lekakis LJ, Miklos D, Jacobson CA, et al. ZUMA-1 pivotal phase 2 trial of axicabtagene ciloleucel (axi-cel, KTE-C19; Anti-CD19 CAR T cells) in patients (pts) with refractory aggressive non-Hodgkin lymphoma (NHL). *Molecular Therapy* 2017;**25** (5 Suppl 1):333.

Neelapu SS, Rossi JM, Locke FL, Xue A, Better M, Zhang X, et al. Product characteristics associated with in vivo expansion of anti-CD19 CAR T cells in patients treated with axicabtagene ciloleucel (axi-cel). *Hematological Oncology* 2017;**35** (Suppl 2):262-3.

Neelapu SS. An interim analysis of the ZUMA-1 study of KTE-C19 in refractory, aggressive non-Hodgkin lymphoma. *Clinical Advances in Hematology & Oncology* 2017;**15**(2):117-20.

Novo M, Sidiqi MH, Paludo J, Gandhi S, Kubusek J, Truong T, et al. Peak lymphocyte count after CAR T infusion is a clinically accessible test that correlates with clinical response in axicabtagene ciloleucel therapy for lymphoma. *Blood* 2019;**134**(Suppl 1):4106.

Rose S. DLBCL responds well to anti-CD19 CAR therapy. *Cancer Discovery* 2017;**7**(3):241-2.

Rossi J, Galon J, Turcan S, Danan C, Locke F, Neelapu S, et al. Tumor microenvironment immune gene signature associated with axicabtagene ciloleucel (axi-cel, KTE-C19), an anti-CD19 chimeric antigen receptor (CAR) T cell, in a multicenter trial (ZUMA-1). *Journal for ImmunoTherapy of Cancer* 2017;**5**(Suppl 2):86.

Rossi JM, Galon J, Turcan S, Danan C, Locke FL, Neelapu SS, et al. Characteristics of the pretreatment tumor microenvironment may influence clinical response in patients with refractory large B cell lymphoma treated with axicabtagene ciloleucel (axi-cel) in the pivotal ZUMA- 1. *Cancer Research* 2018;**78**(13 Suppl 1):LJ-016.

Siddiqi T, Neelapu SS, Locke FL, Bartlett NL, Chavez JC, Hosing C, et al. Updated results from Zuma-1: a phase 1-2 multicenter study evaluating the safety and efficacy of kte-c19 (anti-CD19 car T cells) in refractory aggressive B-cell non-Hodgkin lymphoma (NHL). *Haematologica* 2016;**101**:318.

ZUMA-6 *{published and unpublished data}*

Jacobson CA, Locke FL, Miklos DB, Herrera AF, Westin JR, Lee J, et al. End of phase 1 results from Zuma-6: axicabtagene ciloleucel (axi-cel) in combination with atezolizumab for the treatment of patients with refractory diffuse large B cell lymphoma. *Biology of Blood and Marrow Transplantation* 2019;**25** (3 Suppl):S173.

* Jacobson CA, Locke FL, Miklos DB, Herrera AF, Westin JR, Lee J, et al. End of phase 1 results from ZUMA-6: axicabtagene ciloleucel (axi-cel) in combination with atezolizumab for the treatment of patients with refractory diffuse large B cell lymphoma. *Blood* 2018;**132**(Suppl 1):4192.

NCT02926833. Safety and efficacy of KTE-C19 in combination with atezolizumab in adults with refractory diffuse large B-cell lymphoma (DLBCL). clinicaltrials.gov/show/NCT02926833 (first received 2016).

References to studies excluded from this review

Batlevi 2019 *{published data only}*

Batlevi CL, Palomba ML, Park J, Mead E, Santomasso B, Riviere I, et al. Phase I clinical trial of CD19-targeted 19-28z/4-1bbl "armored" car T cells in patients with relapsed or refractory NHL and CLL including richter transformation. *Hematological Oncology* 2019;**37** (Suppl 2):166-7.

Buhmann 2013 *{published data only}*

Buhmann R, Michael S, Juergen H, Horst L, Peschel C, Kolb HJ. Immunotherapy with FBTA05 (Bi20), a trifunctional bispecific anti-CD3 x anti-CD20 antibody and donor lymphocyte infusion (dli) in relapsed or refractory B-cell lymphoma after allogeneic stem cell transplantation: study protocol of an investigator-driven, open-label, non-randomized, uncontrolled, dose-escalating Phase I/II-trial. *Journal of Translational Medicine* 2013;**11**(1):160.

Cao 2019 *{published data only}***ChiCTR-ONN-16009862ChiCTR1800019288**

Cao Y, Lu W, Sun R, Jin X, Cheng L, He X, et al. Anti-CD19 chimeric antigen receptor T cells in combination with nivolumab are safe and effective against relapsed/refractory B-cell non-Hodgkin lymphoma. *Frontiers in Oncology* 2019;**9**:767.

ChiCTR-OPN-16009069 *{unpublished data only}***ChiCTR-OPN-16009069**

ChiCTR-OPN-16009069. A clinical trial of anti-CD30 CAR-T cell therapy. chictr.org.cn/showprojen.aspx?proj=15360 (first received 2016).

Chong 2020 *{published data only}*

Chong EA, Gerson JN, Landsburg DJ, Nasta SD, Svoboda J, Porter DL, et al. Outcomes in aggressive B-cell non-Hodgkin lymphomas with anti-CD19 CAR T-cell (CTL019) products not meeting commercial release specifications. *Blood* 2019;**134**(Suppl 1):594.

* Chong EA, Levine BL, Schuster S. Clinical outcomes for anti-CD19 CAR T cell (CTL019) products not meeting commercial release specifications. *Cytotherapy* 2020;**22** (5 Suppl):S29.

Enblad 2018 *{published data only}*

* Enblad G, Karlsson H, Gammelgard G, Wenthe J, Lovgren T, Amini RM, et al. A phase I/IIa trial using CD19-targeted third-generation CAR T cells for lymphoma and leukemia. *Clinical Cancer Research* 2018;**24**(24):6185-94.

Enblad G, Karlsson H, Wenthe J, Wikstrom KI, Essand M, Savoldo B, et al. A clinical trial using third generation CD19 targeting CAR T cells for relapsed lymphoma and leukemia. *Molecular Therapy* 2016;**1**:S295-6.

Enblad G, Karlsson H, Wikstrom K, Essand M, Savoldo B, Brenner MK, et al. Third generation CD19-CAR T cells for relapsed and refractory lymphoma and leukemia report from the Swedish phase I/IIa trial. *Blood* 2015;**126** (23):1534.

Enblad G, Karlsson H, Wikstrom KI, Essand M, Savoldo B, Brenner MK, et al. CD19-targeting third generation CAR T cells for relapsed and refractory lymphoma and leukemia-report from the Swedish phase I/IIa trial. *Blood* 2016;**4**(1 Suppl):1534.

Jain 2019 *{published data only}*

Jain T, Sauter CS, Shah GL, Maloy MA, Chan J, Scordo M, et al. Safety and feasibility of chimeric antigen receptor T cell therapy after allogeneic hematopoietic cell transplantation in relapsed/refractory B cell non-Hodgkin lymphoma. *Leukemia* 2019;**33**(10):2540-4.

Jim 2018 *{published data only}*

Jim HSL, Hoogland AI, Collier A, Booth-Jones M, Jain MD, Locke FL. Patient-reported and neurocognitive outcomes in patients treated with axicabtagene ciloleucel. *Blood* 2018;**132**(Suppl 1):2289.

NCT01475058 *{unpublished data only}*

NCT01475058. CD19 CAR T cells for B cell malignancies after allogeneic transplant. clinicaltrials.gov/show/NCT01475058 (first received 2011).

NCT02776813 *{unpublished data only}*

NCT02776813. Study of ACTR087 in subjects with relapsed or refractory B-cell lymphoma. clinicaltrials.gov/show/NCT02776813 (first received 2016).

NCT03189836 *{published data only}*

NCT03189836. Study of ACTR707 in combination with rituximab in subjects with relapsed or refractory B cell lymphoma. clinicaltrials.gov/show/NCT03189836 (first received 2017).

NCT03196830 *{published data only}*

NCT03196830. CAR-T for R/R B-NHL. clinicaltrials.gov/ct2/show/NCT03196830 (first received 2017).

NCT03436771 *{published data only}*

NCT03436771. Long-term follow-up study for patients previously treated with a Juno CAR T-cell product. clinicaltrials.gov/show/NCT03436771 (first received 2018).

NCT03579927 *{unpublished data only}*

NCT03579927. CAR CD19-CD28-zeta-2A-iCasp9-IL15-transduced cord blood NK cells, high-dose chemotherapy, and stem cell transplant in treating participants with B-cell lymphoma. clinicaltrials.gov/show/NCT03579927 (first received 2018).

Sauter 2014a *{published data only}*

* Sauter CS, Riviere I, Bernal YJ, Wang X, Purdon TJ, Yoo S, et al. Interim safety analysis: a phase I trial of high dose therapy and autologous stem cell transplantation followed by infusion of chimeric antigen receptor modified T-cells (19-28Z CAR-T) directed against CD19+ B-cells for relapsed and refractory aggressive B cell non-Hodgkin lymphoma (B-NHL). *Blood* 2014;**124**(21):677.

Sequeira A, Mao D, Chen X, Avila E, Mead E, Sauter CS, et al. Clinical neurological features and electrographic patterns of patients with relapsed or refractory large B-cell lymphoma treated with axicabtagene ciloleucel at Memorial Sloan Kettering Cancer Center (MSKCC). *Neuro-Oncology* 2018;**20** (Suppl 6):vi194-5.

Sesques 2020 *{published data only}*

Sesques P, Ferrant E, Safar V, Wallet F, Tordo J, Dhomps A, et al. Commercial anti-CD19 CAR T cell therapy for patients with relapsed/refractory aggressive B cell lymphoma in a European center. *American Journal of Hematology* 2020;**95**(11):1324-33.

Srour 2020 *{published data only}*

Srour SA, Singh H, McCarty J, De Groot E, Huls H, Rondon G, et al. Long-term outcomes of sleeping beauty-generated CD19-specific CAR T-cell therapy for relapsed-refractory B-cell lymphomas. *Blood* 2020;**135**(11):862-5.

Wang 2014 *{published data only}*

Wang Y, Zhang WY, Han QW, Liu Y, Dai HR, Guo YL, et al. Effective response and delayed toxicities of refractory advanced diffuse large B-cell lymphoma treated by CD20-directed chimeric antigen receptor-modified T cells. *Clinical Immunology* 2014;**155**(2):160-75.

Wang 2016 (NHL2) *{published data only}*

Wang X, Popplewell LL, Wagner JR, Naranjo A, Blanchard MS, Mott MR, et al. Phase 1 studies of central memory-derived CD19 CAR T-cell therapy following autologous HSCT in patients with B-cell NHL. *Blood* 2016;**127**(24):2980-90.

Wang 2016a (NHL1) *{published data only}*

Popplewell L, Wang X, Naranjo A, Blanchard S, Wagner J, Wong CL, et al. Phase I studies of cellular immunotherapy using central memory derived-CD19-specific T cells following autologous stem cell transplantation for patients with high-risk intermediate grade B-lineage non-Hodgkin lymphoma. *Blood* 2015;**126** (23):930.

* Wang X, Popplewell LL, Wagner JR, Naranjo A, Blanchard MS, Mott MR, et al. Phase 1 studies of central memory-derived CD19 CAR T-cell therapy following autologous HSCT in patients with B-cell NHL. *Blood* 2016;**127**(24):2980-90.

Wang 2020 *{published data only}***ChiCTR-OPN-16008526**

ChiCTR-OPN-16008526. An open-label, single-center and single-arm clinical study of sequential infusion of anti-CD22 and anti-CD19 CAR-T cells for patients with relapsed or refractory B-cell malignancies. who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-OPN-16008526 (first received 2016).

Huang L, Wang N, Cao Y, Li C, Xiao Y, Xiao M, et al. CAR22/19 cocktail therapy for patients with refractory/relapsed B-cell malignancies. *Blood* 2018;**132**(Suppl 1):1408.

* Wang N, Hu X, Cao W, Li C, Xiao Y, Cao Y, et al. Efficacy and safety of CAR19/22 T-cell cocktail therapy in patients with refractory/relapsed B-cell malignancies. *Blood* 2020;**135**(1):17-27.

References to studies awaiting assessment

ChiCTR-ONC-16008911 *{unpublished data only}***ChiCTR-ONC-16008911**

ChiCTR-ONC-16008911. CD19-targeted CAR-T cell therapy for MRD of B-cell lymphoma. chictr.org.cn/showproj.aspx?proj=15018 (first received 2016).

ChiCTR-OPN-16009847 *{unpublished data only}***ChiCTR-OPN-16009847**

ChiCTR-OPN-16009847. An open label, single center, single arm clinical study for sequential infusion of anti-CD19 CAR-T and anti-CD22 CAR-T therapy following autologous hematopoietic stem cell transplantation (auto-HSCT) for relapsed, refractory and high-risk B cell lymphoma. chictr.org.cn/com/25/historyversionpuben.aspx?regno=ChiCTR-OPN-16009847 (first received 2016).

ChiCTR-OPN-17013507 *{unpublished data only}***ChiCTR-OPN-17013507**

ChiCTR-OPN-17013507. A single-center, single-arm, open-label, dose escalation study to evaluate the safety & preliminary anti-tumor activity of CD19 single-chain antibody chimeric antigen receptor T cells (CAR-T-19) for the treatment of patients with relapsed/refractory B-cell leukemia/lymphoma. chictr.org.cn/showproj.aspx?proj=22440 (first received 2017).

NCT02652910 *{unpublished data only}*

NCT02652910. Memory-enriched CAR-T cells immunotherapy for B cell lymphoma (MeCAR). clinicaltrials.gov/ct2/show/NCT02652910 (first received 2016).

NCT02933775 *{unpublished data only}*

NCT02933775. CD19-redirected autologous cells (CAR-CD19 t cells). clinicaltrials.gov/ct2/show/NCT02933775 (first received 2016).

NCT02976857 *{unpublished data only}*

NCT02976857. A phase 1 study evaluating safety and efficacy of C-CAR011 treatment in DLBCL subjects. clinicaltrials.gov/ct2/show/NCT02976857 (first received 2018).

NCT03097770 *{unpublished data only}*

NCT03097770. Treatment of relapsed and/or chemotherapy refractory B-cell malignancy by tandem CAR T cells targeting CD19 and CD20. clinicaltrials.gov/ct2/show/NCT03097770 (first received 2017).

NCT03598179 *{unpublished data only}*

NCT03598179. XLCART001 treatment in relapsed/refractory/high-risk B-cell malignancy subjects. clinicaltrials.gov/ct2/show/NCT03598179 (first received 2018).

References to ongoing studies

ALEXANDER *{unpublished data only}*

Eudract_2016-004682-11. A single arm, open-label, multi-centre, phase I/II study evaluating the safety and clinical activity of AUTO3, a CAR T cell treatment targeting CD19 and CD22 and consolidation with anti PD-1 antibodies. clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-004682-11 (first received 2016).

* NCT03287817. CD19/22 CAR t cells (AUTO3) for the treatment of diffuse large B cell lymphoma. clinicaltrials.gov/show/NCT03287817 (first received 2016).

BELINDA *{unpublished data only}*

NCT03570892. Tisagenlecleucel in adult patients with aggressive B-cell non-Hodgkin lymphoma. clinicaltrials.gov/show/NCT03570892 (first received 2018).

BIANCA *{unpublished data only}*

NCT03610724. Phase II open label trial to determine safety & efficacy of tisagenlecleucel in pediatric non-Hodgkin lymphoma patients. clinicaltrials.gov/show/NCT03610724 (first received 2019).

ChiCTR1800017686 2018 *{unpublished data only}***ChiCTR1800017686**

ChiCTR1800017686. Anti-CD19 CAR-T cell therapy for relapsed and refractory CD19-positive lymphoma. chictr.org.cn/showproj.aspx?proj=29929 (first received 2018).

COBALT *{unpublished data only}*

NCT02431988. Evaluation of CAR19 T-cells as an optimal bridge to allogeneic transplantation. clinicaltrials.gov/show/NCT02431988 (first received 2016).

ENABLE *{unpublished data only}*

George P, Dasyam N, Giunti G, Mester B, Bauer E, Andrews B, et al. Third-generation anti-CD19 chimeric antigen receptor T-cells incorporating a tlr2 domain for relapsed or refractory B-cell lymphoma: a phase I clinical trial protocol (ENABLE). *BMJ Open* 2020;**10** (2):e034629.

Eudract_2017_002088-16-IT *{unpublished data only}*

Eudract_2017_002088-16-IT. CD19-CART01 in pediatric patients affected by relapsed/refractory CD19+ acute lymphoblastic leukemia and non Hodgkin lymphoma. who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2017-002088-16-IT (first received 2018).

JPRN-JapicCTI-183914 *{unpublished data only}***183914**

JPRN-JapicCTI-183914. A phase 2 multicenter, open-label, single-arm study of KTE-C19 in Japanese patients with refractory or relapsed large B cell lymphoma. clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-183914 (first received 2018).

NCT02374333 *{unpublished data only}*

NCT02374333. Pilot study of redirected autologous T cells engineered to contain humanized anti-CD19 in patients with relapsed or refractory CD19+ leukemia and lymphoma previously treated with cell therapy. clinicaltrials.gov/show/NCT02374333 (first received 2014).

NCT02659943 *{unpublished data only}*

NCT02659943. T cells expressing a fully-human antiCD19 chimeric antigen receptor for treating B-cell malignancies. clinicaltrials.gov/show/NCT02659943 (first received 2016).

NCT02706405 *{unpublished data only}*

NCT02706405. JCAR014 and durvalumab in treating patients with relapsed or refractory B-cell non-Hodgkin lymphoma. clinicaltrials.gov/show/NCT02706405 (first received 2016).

NCT02728882 *{unpublished data only}*

NCT02728882. Study evaluating the efficacy and safety with CAR-T for recurrent or refractory diffuse large B cell lymphoma. clinicaltrials.gov/show/NCT02728882 (first received 2015).

NCT02737085 *{unpublished data only}*

NCT02737085. The sequential therapy of CD19-targeted and CD20-targeted CAR-T cell therapy for diffuse large B cell lymphoma (DLBCL). clinicaltrials.gov/show/NCT02737085 (first received 2016).

NCT02892695 *{unpublished data only}*

NCT02892695. PCAR-119 bridge immunotherapy prior to stem cell transplant in treating patients with CD19 positive leukemia and lymphoma. clinicaltrials.gov/show/NCT02892695 (first received 2016).

NCT03233854 *{unpublished data only}*

NCT03233854. CD19/CD22 chimeric antigen receptor T cells and chemotherapy in treating patients with recurrent or refractory CD19 positive diffuse large B-cell lymphoma or B acute lymphoblastic leukemia. clinicaltrials.gov/show/NCT03233854 (first received 2017).

NCT03277729 *{unpublished data only}*

NCT03277729. A phase I/II study to evaluate the safety of cellular immunotherapy using autologous T cells engineered to express a CD20-specific chimeric antigen receptor for patients with relapsed or refractory B cell non-Hodgkin lymphomas. clinicaltrials.gov/show/NCT03277729 (first received 2017).

NCT03528421 *{unpublished data only}*

NCT03528421. Assessment of safety and efficacy of IM19 for relapsed or refractory NHL patients. clinicaltrials.gov/show/NCT03528421 (first received 2017).

NCT03579888 *{unpublished data only}*

NCT03579888. CD19-specific T cells post alloSCT. clinicaltrials.gov/show/NCT03579888 (first received 2020).

NCT03704298 *{unpublished data only}*

NCT03704298. Safety and efficacy of axicabtagene ciloleucel in combination with utomilumab in adults with refractory large B-cell lymphoma. clinicaltrials.gov/show/NCT03704298 (first received 2018).

NCT03720457 *{unpublished data only}*

NCT03720457. Human CD19 targeted t cells injection (CD19 CAR-T) therapy for relapsed and refractory CD19-positive lymphoma. clinicaltrials.gov/show/NCT03720457 (first received 2018).

NCT04231747 *{unpublished data only}*

NCT03720457. A study of CC-97540, CD19-targeted NEX-T chimeric antigen receptor (CAR) T cells, in subjects with relapsed or refractory B-cell non-Hodgkin lymphoma. clinicaltrials.gov/show/NCT04231747 (first received 2020).

NCT04381741 *{unpublished data only}*

NCT04381741. CD19 CAR-T expressing IL7 and CCL19 combined with PD1 mAb for relapsed or refractory diffuse large B cell lymphoma. clinicaltrials.gov/show/NCT04381741 (first received 2020).

NCT04450069 *{unpublished data only}*

NCT04450069. CLBR001 and SWI019 in patients with relapsed refractory B-cell malignancies. clinicaltrials.gov/show/NCT04450069 (first received 2020).

NCT04456023 *{unpublished data only}*

NCT04456023. Study of tisagenlecleucel in Chinese adult patients with relapsed or refractory diffuse large B-cell non-Hodgkin lymphoma (DLBCL). clinicaltrials.gov/show/NCT04456023 (first received 2020).

NCT04464200 *{unpublished data only}*

NCT04464200. 19(T2)28z1xx chimeric antigen receptor (CAR) T cells in people with B-cell cancers. clinicaltrials.gov/show/NCT04464200 (first received 2020).

NCT04486872 *{unpublished data only}*

NCT04486872. An exploratory clinical trial of autologous humanized anti-cluster of differentiation antigen 19/20(CD19/CD20) dual specific CAR-T cells Injection. clinicaltrials.gov/show/NCT04486872 (first received 2020).

NCT04526834 *{unpublished data only}*

NCT04526834. Phase 1 study of autologous CD30.CAR-T in relapsed or refractory CD30 positive non-Hodgkin lymphoma. clinicaltrials.gov/show/NCT04526834 (first received 2020).

NCT04545762 *{unpublished data only}*

NCT04545762. Anti-CD19 chimeric antigen receptor T cells for treatment of relapsed or refractory non-Hodgkin lymphoma. clinicaltrials.gov/show/NCT04545762 (first received 2020).

PORTIA *{unpublished data only}*

NCT03630159. Study of tisagenlecleucel in combination with pembrolizumab in R/R diffuse large B-cell lymphoma patients. clinicaltrials.gov/show/NCT03630159 (first received 2018).

Rivers 2018 *{unpublished data only}*

Rivers J, Annesley C, Summers C, Finney O, Pulsipher MA, Wayne AS, et al. Early response data for pediatric patients with non-Hodgkin lymphoma treated with CD19 chimeric antigen receptor (CAR) T-cells. *Blood* 2018;**132**(Suppl 1):2957.

Sauter 2015 *{unpublished data only}*

* Sauter CS, Riviere I, Bernal Y, Wang X, Purdon T, Yoo S, et al. Phase I trial of 19-28z chimeric antigen receptor modified T cells (19-28z CART) posthigh dose therapy and autologous stem cell transplant (HDT-ASCT) for relapsed and refractory (rel/ref) aggressive B-cell non-Hodgkin lymphoma (B-NHL). *Journal of Clinical Oncology* 2015;**33**(15 Suppl 1):8515.

Sauter CS, Senechal B, Riviere I, Ni A, Bernal Y, Wang X, et al. CD19 CAR T cells following autologous transplantation in poor-risk relapsed and refractory B-cell non-Hodgkin lymphoma. *Blood* 2019;**134**(7):626-35.

Shah 2019 *{unpublished data only}*

Shah NN, Zhu F, Keever-Taylor C, Schneider D, Kruger W, Worden A, et al. Clinical results of a first-in-human phase 1 study of point-of-care manufactured bispecific anti-CD19, anti-CD20 chimeric antigen receptor modified t (CAR-20.19-T) cells for relapsed, refractory, non-Hodgkin lymphoma (NHL). *Biology of Blood and Marrow Transplantation* 2019;**25** (3 Suppl):S63-4.

TRANSCEND - OUTREACH *{unpublished data only}*

NCT03744676. A safety trial of lisocabtagene maraleucel (JCAR017) for relapsed and refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) in the outpatient setting. clinicaltrials.gov/show/NCT03744676 (first received 2018).

TRANSCEND - PILOT (TRANSCEND-NHL-006) *{unpublished data only}*

NCT03483103. Lisocabtagene maraleucel (JCAR017) as second-line therapy (TRANSCEND-NHL-006). clinicaltrials.gov/show/NCT03483103 (first received 2018).

TRANSCEND - WORLD *{unpublished data only}*

Eudract_2017-000106-38. TRANSCEND WORLD a phase 2, single-arm, multi-cohort, multi-center trial to determine the efficacy and safety of JCAR017 in adult subjects with aggressive B-cell non-Hodgkin lymphoma (TRANSCEND WORLD). clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-000106-38 (first received 2017).

TRANSFORM *{unpublished data only}*

Eudract_2018-000929-32. TRANSFORM a global randomized multicenter phase 3 trial to compare the efficacy and safety of JCAR017 to standard of care in adult subjects with high-risk, transplant-eligible relapsed or refractory aggressive B-cell non-Hodgkin lymphomas (TRANSFORM). clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-000929-32 (first received 2018).

* NCT03575351. A study to compare the efficacy and safety of JCAR017 to standard of care in adult subjects with high-risk, transplant-eligible relapsed or refractory aggressive B-cell non-Hodgkin lymphomas. clinicaltrials.gov/show/NCT03575351 (first received 2018).

ZUMA-14 *{unpublished data only}*

NCT03153462. Axicabtagene ciloleucel expanded access study (ZUMA-9). clinicaltrials.gov/show/NCT03153462 (first received 2017).

* NCT04002401. Safety and efficacy of axicabtagene ciloleucel in combination with either rituximab or lenalidomide in participants with refractory large B-cell lymphoma (ZUMA-14). clinicaltrials.gov/show/NCT04002401 (first received 2019).

ZUMA-7 *{unpublished data only}*

Eudract_2017-002261-22. A phase 3, randomized, open-label study evaluating the efficacy of axicabtagene ciloleucel versus standard of care therapy in subjects with relapsed/refractory diffuse large B cell lymphoma (ZUMA-7). clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-002261-22 (first received 2017).

Eudract_2017-002261-22-NL. A study evaluating the effectiveness of axicabtagene ciloleucel versus standard of care therapy in subjects with diffuse large B cell lymphoma returning after, or resistant to, initial treatment. clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-002261-22 (first received 2018).

* NCT03391466. Efficacy of axicabtagene ciloleucel compared to standard of care therapy in subjects with relapsed/refractory diffuse large B cell lymphoma. clinicaltrials.gov/show/NCT03391466 (first received 2017).

Additional references

Aaronson 1993

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993;**85**(5):365-76. [DOI: 10.1093/jnci/85.5.365]

Abramson 2016

Abramson JS, Palomba L, Gordon LI, Lunning M, Arnason J, Forero-Torres A, et al. Transcend NHL 001: Immunotherapy with the CD19-directed CAR T-Cell product JCAR017 results in high complete response rates in relapsed or refractory B-Cell non-Hodgkin lymphoma. *Blood* 2016;**128**(22):4192. [DOI: 10.1182/blood.V128.22.4192.4192]

Abramson 2017

Abramson JS, Chen YB. More on Anti-CD19 CAR T Cells in CNS diffuse large-B-cell lymphoma. *New England Journal of Medicine* 2017;**377**(21):2102. [DOI: 10.1056/NEJMc1712460]

Alizadeh 2000

Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* 2000;**403**:503-11. [DOI: 10.1038/35000501]

Al-Mansour 2020

Al-Mansour M, Al-Foheidi M, Ibrahim E. Efficacy and safety of second-generation CAR T-cell therapy in diffuse large B-cell lymphoma: a meta-analysis. *Molecular and Clinical Oncology* 2020;**13**(4):1-14. [DOI: 10.3892/mco.2020.2103]

Azoulay 2020

Azoulay E, Darmon M, Valade S. Acute life-threatening toxicity from CAR T-cell therapy. *Intensive Care Medicine* 2020;**46**(9):1723-6. [DOI: 10.1007/s00134-020-06193-1]

Bach 2017

Bach PB, Giralt SA, Saltz LB. FDA approval of tisagenlecleucel: promise and complexities of a $475 000 cancer drug. *JAMA* 2017;**318**(19):1861-2. [DOI: 10.1001/jama.2017.15218]

Barrington 2014

Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Mueller SP, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *Journal of Clinical Oncology* 2014;**32**(27):3048-58. [DOI: 10.1200/JCO.2013.53.5229]

Beral 1991

Beral V, Peterman T, Berkelman R, Jaffe H. AIDS-associated non-Hodgkin lymphoma. *Lancet* 1991;**337**(8745):805-9. [DOI: 10.1016/0140-6736(91)92513-2]

Böll 2019

Böll B, Borrega JG, Schellongowski P, Subklewe M, Von Bergwelt-Baildon M. Immuno-oncology meets intensive care

cedicine: CAR-T cells. *Deutsche Medizinische Wochenschrift* 2019;**144**(19):1342-7. [DOI: 10.1055/a-0853-4689]

Borrega 2019

Borrega JG, Gödel P, Rüger MA, Onur ÖA, Shimabukuro-Vornhagen A, Kochanek M, et al. In the eye of the storm: immune-mediated toxicities associated with CAR-T cell therapy. *Hemasphere* 2019;**3**(2):e191. [DOI: 10.1097/HS9.0000000000000191]

Buchholz 2018

Buchholz CJ, Hartmann J, Schüßler-Lenz M, Keller-Stanislawski B. CAR-T-Zell-Therapie: Aussichten und Risiken. *Deutsches Ärzteblatt International* 2018;**115**(7):38. [DOI: 10.3238/PersOnko.2018.02.16.07]

Cella 2005

Cella D, Webster K, Cashy J, Kutikova L, Burgess MF, Lin BK, et al. Development of a measure of health-related quality of life for non-Hodgkin's lymphoma clinical research: the Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym). *Blood* 2005;**106**(11):750. [DOI: 10.1182/blood.V106.11.750.750]

Cheson 2007

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology* 2007;**25**(5):579-86. [DOI: 10.1200/JCO.2006.09.2403]

Cheson 2014

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *Journal of Clinical Oncology* 2014;**32**(27):3059-68. [DOI: 10.1200/JCO.2013.54.8800]

Chung 2007

Chung R, Lai R, Wei P, Lee J, Hanson J, Belch AR, et al. Concordant but not discordant bone marrow involvement in diffuse large B-cell lymphoma predicts a poor clinical outcome independent of the International Prognostic Index. *Blood* 2007;**110**(4):1278. [DOI: 10.1182/blood-2007-01-070300]

Coiffier 2002

Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *New England Journal of Medicine* 2002;**346**(4):235-42. [DOI: 0.1056/NEJMoa011795]

Crump 2017

Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood* 2017;**130**(16):1800-8. [DOI: 10.1182/blood-2017-03-769620]

Deeks 2011

Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1.

EPOC 2017

Cochrane Effective Practice and Organisation of Care (EPOC). What study designs can be considered for inclusion in an EPOC review and what should they be called? EPOC Resources for review authors, 2017. epoc.cochrane.org/resources/epoc-resources-review-authors (accessed 23 April 2019).

European Medicines Agency 2018

European Medicines Agency (EMA). First two CAR-T cell medicines recommended for approval in the European Union. www.ema.europa.eu/en/news/first-two-car-t-cell-medicines-recommended-approval-european-union (accessed 29 June 2018).

Friedberg 2011

Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. *ASH Education Program Book* 2011;**2011**(1):498-505. [DOI: 10.1182/asheducation-2011.1.498]

GRADEpro GDT 2015 [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed 2 February 2017. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015. Available at gradepro.org.

Halford 2020

Halford Z, Anderson MK, Bennett LL. Axicabtagene ciloleucel: clinical data for the use of CAR T-cell therapy in relapsed and refractory large B-cell lymphoma. *Annals of Pharmacotherapy.* 2020;**55**:390-405. [DOI: 10.1177/1060028020944233]

Higgins 2020a

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020), Cochrane 2020. Available from training.cochrane.org/handbook.

Higgins 2020b

Higgins JPT, Eldridge S, Li T, (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane 2020. Available from training.cochrane.org/handbook.

Husereau 2013

Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ* 2013;**346**:f1049. [DOI: 10.1136/bmj.f1049]

ICER 2018

Institute for Clinical and Economic Review. Chimeric antigen receptor T-cell therapy for B-cell cancers: effectiveness and value. www.icer-review.org/wp-content/uploads/2017/07/ICER_CAR_T_Final_Evidence_Report_032318.pdf (accessed prior to 17 July 2021).

Jacobson 2020a

Jacobson CA, Hunter BD, Redd R, Rodig SJ, Chen PH, Wright K, et al. Axicabtagene ciloleucel in the non-trial setting: outcomes and correlates of response, resistance, and toxicity. *Journal of Clinical Oncology* 2020;**38**(27):3095-106. [DOI: 10.1200/JCO.19.02103.]

Jin 2018

Jin Z, Xiang R, Qing K, Li X, Zhang Y, Wang L, et al. The severe cytokine release syndrome in phase I trials of CD19-CAR-T cell therapy: a systematic review. *Annals of Hematology* 2018;**97**(8):1327-35. [DOI: 10.1007/s00277-018-3368-8]

Kubuschok 2015

Kubuschok B, Held G, Pfreundschuh M. Management of diffuse large B-cell lymphoma (DLBCL). *Cancer Treatment and Research* 2015;**165**:271-88. [DOI: 10.1007/978-3-319-13150-4_11]

Lee 2014

Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;**124**(2):188-95. [DOI: 10.1182/blood-2014-05-552729]

Lefebvre 2020

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al, (editors). Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane 2020. Available from training.cochrane.org/handbook.

Lesokhin 2016

Lesokhin AM, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. *Journal of Clinical Oncology* 2016;**34**(23):2698-704. [DOI: 10.1200/JCO.2015.65.9789]

Li 2020

Li T, Higgins JPT, Deeks JJ, (editors). Chapter 5: Collecting data. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane 2020. Available from training.cochrane.org/handbook.

Maude 2018

Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *New England Journal of Medicine* 2018;**378**(5):439-48. [DOI: 10.1056/NEJMoa1709866]

McMillan 2016

McMillan A, Martín A, Haioun C, Chiappella A, Di Rocco A, Rueda A, et al. Post relapse survival rates in diffuse large B-cell lymphoma. *Blood* 2016;**128**(22):4204. [DOI: 10.1182/blood.V128.22.4204.4204]

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009;**62**(10):1006-12. [DOI: 10.1371/journal.pmed.1000097]

Nastoupil 2020

Nastoupil LJ, Jain MD, Feng L, Spiegel JY, Ghobadi A, Lin Y. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. *Journal of Clinical Oncology* 2020;**38**(27):3119-28. [DOI: 10.1200/JCO.19.02104]

Neelapu 2017

Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *New England Journal of Medicine* 2017;**377**(26):2531-44. [DOI: 10.1056/NEJMoa1707447]

Noone 2018

Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review, 1975-2015. National Cancer Institute, 2018.

Novartis 2017

Novartis. Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah(TM) (CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice. www.novartis.com/news/media-releases/novartis-receives-first-ever-fda-approval-car-t-cell-therapy-kymriahtm-ctl019 (accessed 30 August 2017).

Park 2018

Park JH, Rivière I, Gonen M, Wang X, Sénéchal B, Curran KJ, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *New England Journal of Medicine* 2018;**378**(5):449-59. [DOI: 10.1056/NEJMoa1709919]

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34. [DOI: 10.1002/(sici)1097-0258(19981230)17:24<2815::aid-sim110>3.0.co;2-8]

Pfreundschuh 2006

Pfreundschuh M, Trümper L, Österborg A, Pettengell R, Trneny M, Imrie K, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncology* 2006;**7**(5):379-91. [DOI: 10.1016/S1470-2045(06)70664-7]

Porter 2015

Porter DL, Hwang WT, Frey NV, Lacey SF, Shaw PA, Loren AW, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. *Science Translational Medicine* 2015;**7**(303):303ra139. [DOI: 10.1126/scitranslmed.aac5415]

Reeves 2020

Reeves BC, Deeks JJ, Higgins JPT, Shea B, Tugwell P, Wells GA, Cochrane Non-Randomized Studies of Interventions Methods Group. Chapter 24: Including non-randomized studies on intervention effects. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane 2020. Available from www.training.cochrane.org/handbook.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rosenberg 1971

Rosenberg SA, Boiron M, DeVita VT Jr, Johnson RE, Lee BJ, Ultmann JE, et al. Report of the committee on Hodgkin's disease staging procedures. *Cancer Research* 1971;**31**(11):1862-3. [PMID: 5121695]

Rosenwald 2002

Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *New England Journal of Medicine* 2002;**346**(25):1937-47. [DOI: 10.1056/NEJMoa012914]

Sant 2014

Sant M, Minicozzi P, Mounier M, Anderson LA, Brenner H, Holleczek B, et al. Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study. *Lancet Oncology* 2014;**15**(9):931-42. [DOI: 10.1016/S1470-2045(14)70282-7]

Schmitz 2018

Schmitz R, Wright GW, Huang D, Johnson CA, Phelan JD, Wang JQ, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. *New England Journal of Medicine* 2018;**378**(15):1396-407. [DOI: 10.1056/NEJMoa1801445]

Schünemann 2020

Schünemann HJ, Higgins JPT, Vist GE, Glasziou P, Akl EA, Skoetz N, et al (editors). Chapter 14: Completing 'Summary of findings tables' and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane 2020. Available from training.cochrane.org/handbook.

Schuster 2018

Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *New England Journal of Medicine* 2018;**308**:45-56. [DOI: 10.1056/NEJMoa1804980]

Shemilt 2011

Shemilt I, Mugford M, Byford S, Drummond M, Eisenstein E, Knapp M, et al. Chapter 15: Incorporating economics evidence. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1.

Sterne 2011

Sterne JA, Egger M, Moher D, editor(s). Chapter 10: Addressing reporting biases. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1.

Sterne 2016

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919.

Stewart 2014

Stewart BW, Wild CP, editor(s). World Cancer Report 2014. Lyon, France: International Agency for Research on Cancer, 2014.

Swerdlow 2017

Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al, editor(s). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: International Agency for Research on Cancer (IARC), 2017.

Teras 2016

Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. *CA: A Cancer Journal for Clinicians* 2016;**66**(6):443-59. [DOI: 10.3322/caac.21357]

Thieblemont 2007

Thieblemont C, Coiffier B. Lymphoma in older patients. *Journal of Clinical Oncology* 2007;**25**(14):1916-23. [DOI: 10.1200/JCO.2006.10.5957]

Tierney 2007

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16. [DOI: 10.1186/1745-6215-8-16]

Tilly 2015

Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2015;**26**(Suppl 5):v116-25. [DOI: 10.1093/annonc/mdv304]

US FDA 2017

US Food and Drug Administration. FDA approves axicabtagene ciloleucel for large B-cell lymphoma. www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm581296.htm (accessed prior to 17 July 2021).

US FDA 2018

US Food and Drug Administration. FDA approves tisagenlecleucel for adults with relapsed or refractory large B-cell lymphoma. www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm606540.htm (accessed prior to 17 July 2021).

US FDA 2021

US Food and Drug Administration. FDA approves new treatment for adults with relapsed or refractory large-B-cell lymphoma. www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-adults-relapsed-or-refractory-large-b-cell-lymphoma (accessed prior to 17 July 2021).

Vaidya 2014

Vaidya R, Witzig TE. Prognostic factors for diffuse large B-cell lymphoma in the R(X)CHOP era. *Annals of Oncology* 2014;**25**(11):2124-33. [DOI: 10.1093/annonc/mdu109]

Vose 1992

Vose JM, Bierman PJ, Anderson JR, Kessinger A, Pierson J, Nelson J, et al. Progressive disease after high-dose therapy and autologous transplantation for lymphoid malignancy: clinical course and patient follow-up. *Blood* 1992;**80**(8):2142.

Ware 1992

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. *Medical Care* 1992;**30**(6):473-83. [PMID: 1593914]

Weidmann 2002

Weidmann E, Kim SZ, Rost A, Schuppert H, Seipelt G, Hoelzer D, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. *Annals of Oncology* 2002;**13**(8):1285-9. [DOI: 10.1093/annonc/mdf189]

Xu 2020

Xu RH, Wong EL, Jin J, Huang H, Dong D. Health-related quality of life measured using EQ-5D in patients with lymphomas. *Supportive Care in Cancer* 2020;**29**:2549-60. [DOI: 10.1007/s00520-020-05774-6]

Zhang 2020

Zhang J, Li J, Ma Q, Yang H, Signorovitch J, Wu E. A review of two regulatory approved anti-CD19 CAR T-cell therapies in diffuse large B-cell lymphoma: why are indirect treatment comparisons not feasible? *Advances in Therapy* 2020;**37**(7):3040-58. [DOI: 10.1007/s12325-020-01397-9]

Zhang 2020a

Zhang Q, Ping J, Huang Z, Zhang X, Zhou J, Wang G, et al. CAR-T cell therapy in cancer: tribulations and road ahead. *Journal of Immunology Research* 2020;**2020**:1924379. [DOI: 10.1155/2020/1924379]

Zinzani 2016

Zinzani PL, Pellegrini C, Argnani L, Broccoli A. Prolonged disease-free survival in elderly relapsed diffuse large B-cell lymphoma patients treated with lenalidomide plus rituximab. *Haematologica* 2016;**101**(9):e385-6. [DOI: 10.3324/haematol.2016.147256]

References to other published versions of this review

Goldkuhle 2019

Goldkuhle M, Ernst M, Estcourt LJ, Borchmann P, Monsef I, Skoetz N. Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma. *Cochrane Database of Systematic Reviews* 2019, Issue 6. Art. No: CD013365. [DOI: 10.1002/14651858.CD013365]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Beider 2019

Study characteristics	
Methods	**Phase**: 1b/2 **Study design**: observational, single-arm, single-centre **Location**: Israel
Participants	**Eligibility criteria**

Beider 2019 *(Continued)*

- **Inclusion criteria**
  - Patients with relapsed or refractory B-cell malignancy
  - Age 1-50 years (or > 50 after approval of IRB)
  - CD19 expression shown by flow cytometry or immunohistochemistry on at least 70% of leukaemic blasts/lymphoma cells
  - Adequate CD3 count (above 250 CD3+ cells per microlitre blood)
  - Clinical performance status: patients > 10 years of age: Karnofsky ≥ 50%; patients ≤ 10 years of age: Lansky scale ≥ 50%. Exception for neurologic symptoms (e.g. paralysis) that are explained by the malignancy
  - Females of childbearing potential must have a negative pregnancy test.
  - Cardiac function: left ventricular ejection fraction > 45% or shortening fraction > 28%
  - For patients following allogeneic bone marrow transplantation - at least 100 days post-BMT with no signs or symptoms of active graft-versus-host disease
- **Exclusion criteria**
  - Hyperleukocytosis (WBC > 50,000) or rapidly progressive disease
  - Pregnant or breastfeeding females
  - Hepatic dysfunction, defined as bilirubin > x 2 upper normal limit (except when explained by haemolysis or Gilbert) or serum glutamate oxaloacetate transaminase > x 25 upper normal limit
  - Hepatitis B, hepatitis C or HIV infection
  - Anti-neoplastic treatment given in the 2 weeks prior to apheresis, with the exception of intrathecal chemotherapy
  - Active immunosuppressive therapy

Number of participants:

- n = 18 receiving CAR T-cells
- n = 18 evaluated
  - n = 17 (94%) DLBCL
    - ☐ type of DLBCL: not reported

Median age (range): 40.5 (23-70)

Sex (male/total): NR

Previous SCT: NR

Previous lines of treatment: NR

Interventions	**Target**: CD19 **Number of Infusions**: 1 **Co-interventions:** none **Type and dose of induction chemotherapy**: • Fludarabine 25 mg/m^{2}for 3 days • Cyclophosphamide 900 mg/m^2 for 1 day
Outcomes	**Primary outcomes:** • Number of patients with treatment-related adverse events as assessed by CTCAE v4. [time frame: 2 years] • Overall response rate [time frame: 28 days] * Overall response rate = complete response (CR) + partial response (PR) + complete response with incomplete count recovery (CRi) in leukaemia patients; Assessment using bone marrow evaluation for patients with leukaemia, and imaging (CT/PET CT) for patients with lymphoma **Secondary outcomes:**

Beider 2019 *(Continued)*

- CAR T-cell persistence as measured by enumeration of CAR T-cells in the blood and bone marrow of participants [time frame: 1 year]
- T cell activity and exhaustion profile as measured by flow cytometry [time frame: 3 months]
- Cytokine levels in the peripheral blood of the patients [time frame: 30 days]
- Feasibility of CD19 CAR T-cell production as defined by number of products successfully meeting release criteria [time frame: 12 days]

Notes	**ClinicalTrials.gov ID and status**: NCT02772198, unknown **Sponsors and Collaborators:** Sheba Medical Center **(Principal) investigator(s):** Michal J Besser, Elad Jacoby, Orit Itzhaki (designed the study)

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	High risk	High risk - the median age of the study group was substantially below average (40.5 years)
Complete outcome assessment/follow-up (attrition bias) Response (PFS, ORR, CR, PR)	High risk	High risk - "Three enrolled patients (3%) dropped out from the study due to clinical deterioration (n = 2) or failure to produce CAR T-cells (n = 1; absence of CAR T-cells in the infusion product). One patient was treated twice".
Outcome assessors blinded to investigated determinant (detection bias) Objective (OS)	Low risk	Low risk - absence of blinding had no effect on objective outcomes.
Outcome assessors blinded to investigated determinant (detection bias) Investigator-assessed (PFS, ORR, CR, PR, AEs)	High risk	High risk - no blinding
Well-defined study group (reporting bias)	Low risk	Low risk - study population and intervention well described
Well-defined follow-up (reporting bias)	Low risk	Low risk - follow-up specified (28 days after infusion of CAR T-cells)
Well-defined outcome (reporting bias) Response (PFR, ORR, CR, PR)	High risk	High risk - no information on criteria used for response assessment except "assessment using [...] imaging (CT/PET CT)"

Chang 2015

Study characteristics

Methods	**Phase**: 1/2 **Study design**: observational, single-arm, multicentre

Chang 2015 *(Continued)*

	Location: USA

Participants	**Eligibility criteria:**
	• **Inclusion criteria**
	  * Patients with chemo-resistant B-cell lymphomas
	• **Exclusion criteria**
	  * NR
	
	Number of participants:
	• participants receiving CAR T-cells: NR
	• n = 13 evaluated
	  * n = 12 (92%) DLBCL
	  ☐ type of DLBCL: NR
	
	Median age (range): 38 (9-61)
	
	Sex (male/total): NR
	
	Previous SCT (DLBCL subgroup): NR
	
	Previous lines of treatment (median and/or range): NR

Interventions	**Target**: CD19 **Dose of CAR T-cells**: range 0.45- 4.59 x 10^6/kg **Number of infusions**: 1-3 **Co-interventions**: none **Type and dose of induction chemotherapy**: • Fludarabine 30 mg/m^2 for 3 days • Cyclophosphamide 250 mg/m^2 for 3 days
Outcomes	**Primary outcomes[1]:** • Complete tumour regression for 3-10 months • Disease-free survival rate (120 days) • Overall survival probability (10 months) • Adverse events • 4SCAR19 transduction efficiency
Notes	[1]Note that these are the only outcomes reported in the study. No secondary publication or trial register record was available for identification of further outcomes that might have been assessed. **Disclosures:** **Dong:** *America Yuva Biomed:* Consultancy **Kuo:** *America Yuva Biomed:* Employment **Liu:** *America Yuva Biomed:* Employment

Risk of bias

Bias	Authors' judgement	Support for judgement

Chang 2015 *(Continued)*

Representative study group (selection bias)	Unclear risk	High risk - the median age of the study group was substantially below average (38 years).
Complete outcome assessment/follow-up (attrition bias) OS	Unclear risk	Unclear risk - 13 participants evaluated in analysis, but participant flow not sufficiently reported to allow a judgement on the completeness of follow-up
Complete outcome assessment/follow-up (attrition bias) Response (PFS, ORR, CR, PR)	Unclear risk	Unclear risk - 13 participants evaluated in analysis, but participant flow not sufficiently reported to allow a judgement on the completeness of follow-up
Complete outcome assessment/follow-up (attrition bias) AEs	Unclear risk	Unclear risk - the number of participants receiving CAR T-cells was unclear due to insufficient reporting of the participant flow.
Outcome assessors blinded to investigated determinant (detection bias) Objective (OS)	Low risk	Low risk - absence of blinding had no effect on objective outcomes.
Outcome assessors blinded to investigated determinant (detection bias) Investigator-assessed (PFS, ORR, CR, PR, AEs)	High risk	High risk - no blinding
Well-defined study group (reporting bias)	High risk	High risk - study population and intervention only briefly described; no trial record available (abstract only)
Well-defined follow-up (reporting bias)	Low risk	Low risk - median follow-up reported
Well-defined outcome (reporting bias) OS	Low risk	Low risk - objective outcome
Well-defined outcome (reporting bias) Response (PFR, ORR, CR, PR)	High risk	High risk - no definition of "disease-free survival" reported and no information on criteria used for response assessment; no trial record available (abstract only)
Well-defined outcome (reporting bias) AEs	High risk	High risk - no information on criteria used for assessment; no trial record available (abstract only)

Hirayama 2019

Study characteristics	
Methods	**Phase**: 1/2 **Study design**: observational, single-arm, single-centre

Hirayama 2019 *(Continued)*

	Location: USA

Participants	**Eligibility criteria**
	
	• **Inclusion criteria**
	  * Patients with aggressive NHL
	  * Primary refractory disease after chemoimmunotherapy
	  * r/r disease after at least 2 lines of therapy, including chemoimmunotherapy
	  * Not eligible for autologous haematopoietic cell transplantation (HCT) or relapsed after HCT
	• **Exclusion criteria**
	  * Patients requiring ongoing daily corticosteroid therapy at a dose of > 15 mg of prednisone per day (or equivalent); pulsed corticosteroid use for disease control is acceptable
	  * Active autoimmune disease requiring immunosuppressive therapy was excluded unless discussed with the Principal Investigator (PI).
	  * Serum creatinine > 2.5 mg/dL
	  * Serum glutamic oxaloacetic transaminase (SGOT) > 5 x upper limit of normal
	  * Bilirubin > 3.0 mg/dL
	  * Patients with clinically significant pulmonary dysfunction, as determined by medical history and physical exam should undergo pulmonary function testing; those with a forced expiratory volume in one second (FEV1) of < 50% of predicted were excluded.
	  * Diffusing capacity of the lung for carbon monoxide (DLCO) (corrected) < 40% were excluded.
	  * Significant cardiovascular abnormalities as defined by any one of the following: New York Heart Association (NYHA) class III or IV congestive heart failure, clinically significant hypotension, uncontrolled symptomatic coronary artery disease, or a documented ejection fraction of < 35%
	  * Uncontrolled active infection
	
	Number of participants:
	
	• 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)
	
	Median age (range): 58.5 (NR)
	
	Sex (male/total): 35/48 (73%)
	
	Previous SCT:
	
	• autoSCT: 16/48 (33%)
	• alloSCT: 4/48 (8%)
	• autoSCT and alloSCT: 3/48 (6%)
	
	Previous lines of treatment: Median: 4 (1-11) (n = 48)

Interventions	**Target**: CD19 **Dose of CAR T-cells**: 2 x 10^6/kg **Number of infusions**: 1 **Co-interventions**: none **Type and dose of induction chemotherapy**: • Fludarabine 25/30 mg/m^2 for 3/3 days • Cyclophosphamide 30-500 mg/m^2 for 1/3 days

Hirayama 2019 *(Continued)*

Outcomes	**Primary outcomes:** • Death within 8 weeks of the study cell infusion thought to be definitely or probably related to chimeric antigen receptor (CAR)-T cell therapy [time frame: within 8 weeks of the study cell infusion] • Duration of persistence of adoptively transferred CD19 chimeric antigen receptor (CAR)-T cells [time frame: up to day 365] • Highest dose of T cells that was estimated to result in grade 3 or greater toxicity, using Common Terminology Criteria for Adverse Events version 4.0, in less than or equal to 1/3 patients [time frame: 30 days] • Migration of adoptively transferred CD19 chimeric antigen receptor (CAR)-T cells [time frame: up to 1 year] • Objective response rate of complete remission and partial remission [time frame: up to 1 year] • Overall survival [time frame: up to 15 years] • Progression-free survival [time frame: up to 15 years]
Notes	**ClinicalTrials.gov ID and status**: NCT01865617, active, not recruiting **Sponsors and Collaborators:** Fred Hutchinson Cancer Research Center/Immunotherapy Integrated Research Center, National Cancer Institute, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Life Science Discovery Fund, Bezos Family, University of British Columbia Clinician Investigator Program, Juno Therapeutics, a Celgene company **(Principal) investigator(s):** David Maloney

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	High risk	High risk - "Sixty-five patients with (...) at least 1 CD19 CAR T-cell infusion, eight patients (median age, 58.5 years; interquartile range, 52-63 years) underwent a Cy/Flu lymphodepletion regimen followed by infusion of 2 × 10 EGFRt cells/kg, the preferred approach established during phase 1 study and are included in this study".
Complete outcome assessment/follow-up (attrition bias) Response (PFS, ORR, CR, PR)	High risk	High risk - "Sixty-five patients with (...) at least 1 CD19 CAR T-cell infusion, eight patients (median age, 58.5 years; interquartile range, 52-63 years) underwent a Cy/Flu lymphodepletion regimen followed by infusion of 2 × 10 EGFRt cells/kg, the preferred approach established during phase 1 study and are included in this study".
Outcome assessors blinded to investigated determinant (detection bias) Objective (OS)	Low risk	Low risk - absence of blinding had no effect on objective outcomes.
Outcome assessors blinded to investigated determinant (detection bias) Investigator-assessed (PFS, ORR, CR, PR, AEs)	High risk	High risk - no blinding
Well-defined study group (reporting bias)	Low risk	Low risk - study population and intervention well described
Well-defined follow-up (reporting bias)	Low risk	Low risk - median follow-up reported

Hirayama 2019 *(Continued)*

Well-defined outcome (reporting bias) Response (PFR, ORR, CR, PR)	High risk	High risk - "Best responses in the absence of additional antitumor therapy were reported according to the Lugano criteria (Cheson 2014). Relapse and/or progression were defined according to clinical, radiological, and/or biopsy evaluations" - time point of assessment not explicitly reported

JULIET

Study characteristics

Methods

Phase: 2

Study design: observational, single-arm, multi-centre

Locations: Australia, Austria, Canada, France, Germany, Italy, Japan, Netherlands, Norway, USA

Participants

Eligibility criteria:

- **Inclusion criteria**
  - Participants ≥ 18 years of age
  - With histologically confirmed DLBCL at last relapse
  - Relapsed/refractory DLBCL after at least 2 lines of chemotherapy including rituximab and an anthracycline
  - Either relapsed or ineligible for autologous transplantation (auto-HSCT)
  - DLBCL that transformed from follicular lymphoma
  - High-grade B-cell lymphoma with MYC rearrangements plus rearrangement of BCL2, BCL6, or both genes
- **Exclusion criteria**
  - History of prior treatment with anti-CD19/anti-CD3 therapy or any other anti-CD19 therapy
  - Primary mediastinal DLBCL
  - Prior gene therapy
  - Prior allogenic HSCT
  - Active central nervous system involvement of the DLBCL

Number of participants:

- n = 111 receiving CAR T-cells
  - n = 109 (98%) DLBCL
    - ☐ n = 88 DLBCL NOS
    - ☐ n = 21 DLBCL TF from follicular lymphoma
- n = 93 evaluated

Median age (range): 56 (22-76)

Sex (male/total): 60/93 (65%)

Previous SCT:

- autoSCT: 54/111 (49%)
- alloSCT: 0/111 (0%)

Previous lines of treatment:

- 1: 5/111 (5%)
- 2: 49/111 (44%)
- 3: 34/111 (31%)
- 4-6: 23/111 (20%)

JULIET *(Continued)*

Interventions	**Target**: CD19 **Dose of CAR T-cells**: 3 x 10^8 (range 0.1-6 x) **Number of infusions**: 1 **Co-interventions**: none **Type and dose of induction chemotherapy**: • Fludarabine 25 mg/m^2 for 3 days • Cyclophosphamide 250 mg/m^2 for 3 days • Bendamustine 90 mg/m^2 for 2 days
Outcomes	**Primary outcomes:** • (Best) Overall Response Rate (ORR) • Complete response rate • Partial response rate **Secondary outcomes:** • Incidence and severity of adverse events • Time to response (TTR) • Duration of response • Overall survival (OS) • Progression-free survival (PFS) • Safety and cellular kinetics data • Evaluation of biomarkers (exploratory) **Assessment:** • Overall Response Rate (ORR) [time frame: 5 years, planned] determined by an independent review committee using the Lugano classification; monthly (?) • Adverse events assessed with Medical Dictionary for Regulatory Activities version 20.1, and Common Terminology Criteria for Adverse Events, version 4.03 • Grade of cytokine release syndrome was determined with the University of Pennsylvania grading scale.
Notes	**ClinicalTrials.gov ID and status**: NCT02445248, active, not recruiting **Sponsors and collaborators:** Novartis Pharmaceuticals **(Principal) investigator(s):** Novartis Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Low risk	Eligibility criteria clearly defined
Complete outcome assessment/follow-up (attrition bias) OS	High risk	High risk - "Of the enrolled patients, 111 (67%) received an infusion: 95 in the main cohort and 16 in cohort A. (...) The baseline characteristics of the enrolled patients and the patients who received an infusion were similar; however, the patients who did not receive an infusion tended to have a lower performance status than those who did receive an infusion, and a greater proportion of the patients who did not receive an infusion had DLBCL that was refractory to the

JULIET *(Continued)*

		last therapy they received before enrollment." OS and PFS data from abstract reporting on long-term follow-up until May 2018 included infused participants only.
Complete outcome assessment/follow-up (attrition bias) Response (PFS, ORR, CR, PR)	High risk	High risk - see OS
Complete outcome assessment/follow-up (attrition bias) QoL	High risk	High risk - outcomes available only for subset of participants in CR/PR (e.g. n = 39 at month 3 and n = 21 at month 12 compared to n = 108 participants with QoL assessments at baseline)
Complete outcome assessment/follow-up (attrition bias) AEs	Low risk	Low risk - outcomes reported for 111/111 (100%) of participants receiving CAR T-cells
Outcome assessors blinded to investigated determinant (detection bias) Objective (OS)	Low risk	Low risk - absence of blinding had no effect on objective outcomes.
Outcome assessors blinded to investigated determinant (detection bias) Investigator-assessed (PFS, ORR, CR, PR, AEs)	High risk	High risk - no blinding
Outcome assessors blinded to investigated determinant (detection bias) Patient-reported (QoL)	High risk	High risk - no blinding
Well-defined study group (reporting bias)	Low risk	Low risk - study population and intervention well described
Well-defined follow-up (reporting bias)	Low risk	Low risk - median follow-up reported
Well-defined outcome (reporting bias) OS	Low risk	Low risk - objective outcome
Well-defined outcome (reporting bias) Response (PFR, ORR, CR, PR)	Low risk	Low risk - objective outcome- "best overall response rate (i.e. the combined percentage of patients who had a complete or partial response), as determined by an independent review committee using the Lugano classification" (Cheson 2014) PFS - low risk (time point-specific) Response - low risk - (bORR, bCR, bPR) reported together with median follow-up
Well-defined outcome (reporting bias) QoL	Low risk	Low risk - use of Function Assessment of Cancer Therapy-Lymphoma (FACT-Lym) with defined time intervals (baseline and months 3, 6, 12, 18)

JULIET *(Continued)*

Well-defined outcome (reporting bias) AEs	Low risk	Low risk - use of MedDRA, CTCAE and University of Pennsylvania grading scale (CRS) (AE rates assessed at data-cut off (median follow-up reported))

Kochenderfer 2017

Study characteristics	
Methods	**Phase**: 1/2 **Study design**: parallel (varying doses), single-centre **Location**: USA

Participants	**Eligibility criteria**
	
	• **Inclusion criteria**
	  * Patients ≥ 18 years of age
	  * With a CD19-expressing B-cell malignancy of any type
	  * Being a non-responder to, or recurred, after one or more standard chemotherapy-containing regimens for their malignancy
	  * Currently requiring treatment due to progressive malignancy
	• **Exclusion criteria**
	  * Incurable by standard therapy
	  * With no history of allogeneic stem-cell transplantation
	  * With no CNS disease
	
	Number of participants:
	
	• n = 22 receiving CAR T-cells
	  * n = 19 (86%) DLBCL
	  * n = 2 follicular lymphoma
	  * n = 1 mantle cell lymphoma
	• n = 22 evaluated
	  * n = 13 NOS
	  * n = 3 TF follicular lymphoma
	  * n = 2 PMBCL
	  * n = 1 TF from CL
	
	Median age (range): 53 (26-67)
	
	Sex (male/total): NR
	
	Previous SCT:
	
	• autoSCT: 5/19 (26%)
	• alloSCT: NR
	
	Previous lines of treatment: Median: 4 (2-7), n = 19

Interventions	**Target**: CD19 **Dose of CAR T-cells**: reduced from 5 to 1 x 10^6/kg during study **Number of infusions**: 1 **Co-intervention**: none

Kochenderfer 2017 *(Continued)*

Type and dose of induction chemotherapy:

- Fludarabine 30 mg/m^2 for 3 days
- Cyclophosphamide 300 mg/m^2 for 3 days

Outcomes

Primary outcomes (retrieved from ClinicalTrials.gov):

- Overall response rate/remission rate (*both terms used; not specified as primary outcome in ClinicalTrial record*) [time frame: Scans performed at 6 weeks, 12 weeks and every 3-6 months for approximately 2 years]
  - Complete remission rate
  - Partial remission rate
- Frequency and severity of treatment-related adverse events. [time frame: 5 years following cell infusion]
- Aggregate of all adverse events, as well as their frequency and severity

Secondary outcomes (retrieved from ClinicalTrials.gov):

- In vivo survival of anti-CD19-CAR-transduced T-cells [time frame: 1 week, 4 weeks, 3 months, 6 months, and 12 months after cell Infusion]
- Anti-mouse Fab FACs staining to detect CARs on the surface of T cells or a quantitative real-time PCR assay to quantitate persistence of T-cells in the blood
- Regression of B-cell malignancies [time frame: 6 and 12 weeks after cell infusion, then every 3 months x 3, then every 6 months x 2 years, then per PI discretion]

Assessment:

- Response assessed by the Response Criteria for Malignant Lymphoma
- AEs assessed throughout the study and for 5 years following cell infusion
- Survival of anti-CD19-CAR-transduced T-cells; 1 week, 4 weeks and 3, 6, and 12 months after cell infusion
- Progression of disease 6 and 12 weeks after cell infusion, and 3 x every 3 months, 2 x every 6 months, then per PI discretion
- “Lymphomas were staged with positron emission tomography (PET) and computed tomography (CT) scans and a bone marrow biopsy before treatment. The PET and CT scans were initially repeated 4-8 weeks after treatment. Subsequent PET and CT scans were carried out 3, 6, 9, 12, 18, and 24 months after infusion. Patients with a bone marrow biopsy showing lymphoma were also assessed with bone marrow biopsies after treatment”.
- “Patients will be followed until disease progression”.
- “Follow-up: Patients will return to the clinic for a physical exam, review of side effects, lab tests, and scans about every 1-3 months for the first year, and then every 6 months to 1 year as long as their tumors are shrinking. Follow-up visits will take up to 2 days”.

Notes

ClinicalTrials.gov ID and status: NCT00924326, active, not recruiting

Sponsors and Collaborators: National Cancer Institute (NCI)

(Principal) investigator(s): Steven A Rosenberg, M.D.

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Unclear risk	Unclear risk - eligibility criteria not explicitly reported
Complete outcome assessment/follow-up (attrition bias)	Unclear risk	Unclear risk - patient selection not sufficiently defined to allow a judgement

Kochenderfer 2017 *(Continued)*

Response (PFS, ORR, CR, PR)		
Complete outcome assessment/follow-up (attrition bias) AEs	Low risk	Low risk - outcomes reported for 22/22 (100%) of participants receiving CAR T-cells
Outcome assessors blinded to investigated determinant (detection bias) Investigator-assessed (PFS, ORR, CR, PR, AEs)	High risk	High risk - no blinding
Well-defined study group (reporting bias)	Low risk	Low risk - study population and intervention well described
Well-defined follow-up (reporting bias)	High risk	High risk - duration of follow-up not clearly reported
Well-defined outcome (reporting bias) Response (PFR, ORR, CR, PR)	High risk	High risk - "Treatment responses [...] were defined according to standard international criteria" (Cheson 2007) PFS time point-specific reporting, but response at high risk because assessment time point of bORR, bCR and bPR unclear
Well-defined outcome (reporting bias) AEs	High risk	High risk - use of CTCAE, but time point of assessment not clear

PLATFORM

Study characteristics	
Methods	**Phase**: 1/2 (data for 1 only) **Study design**: parallel (varying doses and combinations with other agents), multicentre **Location**: USA
Participants	**Eligibility criteria:**

PLATFORM *(Continued)*

- **Inclusion criteria**
  * Subject is ≥ 18 years of age at the time of signing the informed consent form
  * Must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted
  * Willingness and ability to adhere to the study visit schedule and other protocol requirements
  * Histologically confirmed at last relapse aggressive B-cell NHL according to "The 2016 revision of the WHO classification of lymphoid neoplasms" defined as:
    a. Diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS) including transformed indolent non-Hodgkin lymphoma (NHL)
    b. Follicular lymphoma grade 3B
    c. T-cell/histiocyte-rich large B-cell lymphoma
    d. Epstein-Barr virus (EBV) positive DLBCL, NOS
    e. Primary mediastinal (thymic) large B-cell lymphoma
    f. High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple-hit lymphoma)
  * Must have relapsed or be refractory to at least 2 prior lines of therapy. Previous therapy must have included a CD20-targeted agent and an anthracycline.
  * Subject must have
    a. Positron emission tomography (PET)-positive and computed tomography (CT) measurable disease as per Lugano Classification
    b. Serum lactate dehydrogenase (LDH) ≥ 500 U/L and/or sum of product of perpendicular diameters (SPD) of index lesions ≥ 50 cm^2 by CT scan (phase 1 of arms C and D only)
  * Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 at screening
  * Adequate organ function
  * Subjects must agree to not donate blood, organs, sperm or semen, and egg cells for usage in other individuals
  * Participants must agree to use effective contraception

PLATFORM *(Continued)*

- **Exclusion criteria**
  - Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study based on investigator's judgement
  - Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study based on investigator's judgement
  - Any condition that confounds the ability to interpret data from the study based on investigator's judgement
  - Prior history of malignancies, other than aggressive r/r NHL, unless the subject has been free of the disease for ≥ 2 years with the exception of the following non-invasive malignancies:
    - ☐ Basal cell carcinoma of the skin
    - ☐ Squamous cell carcinoma of the skin
    - ☐ Carcinoma in situ of the cervix
    - ☐ Carcinoma in situ of the breast
    - ☐ Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumour, nodes, metastasis] clinical staging system) or prostate cancer that is curative.
    - ☐ Other completely resected stage 1 solid tumour with low risk for recurrence
  - Prior treatment with any prior gene therapy product
  - Prior treatment with any adoptive T-cell therapy; prior haematopoietic stem-cell transplant (HSCT) is allowed
  - Allogeneic HSCT within 90 days of leukapheresis
  - Prior treatment with anti PD-1 or PD-L1 therapy (arm A)
    - ☐ Anti PD-1 or PD-L1 (arm A)
    - ☐ CC-122 (arm B)
    - ☐ CC-220 (arm C)
    - ☐ Prior treatment with ibrutinib was not exclusionary for subjects on any study arm.
  - Presence of acute or chronic graft-versus-host disease (GVHD)
  - History of or active hepatitis B or hepatitis C or human immunodeficiency virus (HIV) infection
  - Uncontrolled bacterial, viral or fungal infection at the time of leukapheresis, lymphodepleting chemotherapy or JCAR017 infusion
  - History of any one of the following cardiovascular conditions within the past 6 months: Class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease
  - History or presence of clinically relevant central nervous system (CNS) pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis
  - Subjects with active CNS or cerebrospinal fluid (CSF) involvement by malignancy
  - Pregnant or nursing (lactating) women
  - Subjects with active auto-immune disorders/processes or active neurological or inflammatory disorders

Number of participants:

- n = 15 receiving CAR T-cells
- n = 11 evaluated
  - n = 10 (91%) DLBCL
    - ☐ Type of DLBCL: NR

Median age (range): NR (53-78)

Sex (male/total): 7/11 (64%)

Previous SCT: NR

Previous lines of treatment: NR

Interventions	**Target**: CD19 **Dose of CAR T-cells**: 50 or 100 x 10^6

PLATFORM *(Continued)*

Number of infusions: 1

Co-interventions: Durvalumab

Type and dose of induction chemotherapy:

- Fludarabine for 3 days (dose NR)
- Cyclophosphamide for 3 days (dose NR)

Outcomes

Primary outcomes:

- Dose-limiting toxicity (DLT) rates [time frame: From first dose of the combination agent until 1 month (28 days) after JCAR017 infusion or from JCAR017 infusion until 1 month (28 days) after the first dose of combination agent]
- Complete response rate [time frame: Up to approximately 6 months post-JCAR017 infusion]

Secondary outcomes:

- Adverse Events (AEs) [time frame: Up to approximately 24 months]
- Progression-free survival (PFS) [time frame: Up to approximately 24 months post-JCAR017 infusion]
- Overall survival (OS) [time frame: Up to approximately 3.5 years]
- Overall response rate (ORR) [time frame: Up to approximately 24 months post-JCAR017 infusion]
- Duration of response (DOR) [time frame: Up to approximately 24 months post-JCAR017 infusion]
- Event-free survival (EFS) [time frame: Up to approximately 24 months post-JCAR017 infusion]
- Pharmacokinetic (PK)-Cmax [time frame: Up to approximately 24 months post-JCAR017 infusion]
- Pharmacokinetic (PK)-Tmax [time frame: Up to approximately 24 months post-JCAR017 infusion]
- Pharmacokinetic (PK)-AUC [time frame: Up to approximately 24 months post-JCAR017 infusion]
- Health-related quality of life (HRQoL) [time frame: Up to approximately 24 months post-JCAR017 infusion]
- Quality of Life C30 questionnaire (EORTC-QLQ-C30) [time frame: Up to approximately 24 months post-JCAR017 infusion, for phase I of arm A and arm B.]
- European Quality of Life-5 Dimensions health state classifier to 5 levels (EQ-5D-5L) [time frame: Up to approximately 24 months post-JCAR017 infusion, for phase I of arm A and arm B]

Notes

ClinicalTrials.gov ID and status: NCT03310619, recruiting

Sponsors and Collaborators: Celgene

(Principal) investigator(s): Nikolaus Trede (Celgene), study director

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Unclear risk	Unclear risk - eligibility criteria not sufficiently reported (e.g. in/exclusion of participants with unsuccessful infusion of CAR T-cells)
Complete outcome assessment/follow-up (attrition bias) Response (PFS, ORR, CR, PR)	High risk	High risk - (only participants who received at least one dose of durvalumab; but: very early data cut-off) - "At data cutoff, 18 pts were enrolled (DL1 n = 9; DL2 n = 9). 15 pts (DL1 n = 8; DL2 n = 7) received liso-cel; 11 pts (DL1 n = 8; DL2 n = 3) completed at least one durvalumab total dose of 171 mg/4 weeks (2 pts are awaiting treatment; 1 pt no longer met the eligibility criteria; 1 pt died of sepsis)".
Complete outcome assessment/follow-up (attrition bias) AEs	High risk	High risk - outcomes reported for 11/15 (73%) of participants receiving CAR T-cells (not reported for patients receiving CAR T-cells but no durvalumab)

PLATFORM *(Continued)*

Outcome assessors blinded to investigated determinant (detection bias) Investigator-assessed (PFS, ORR, CR, PR, AEs)	High risk	High risk - no blinding
Well-defined study group (reporting bias)	Unclear risk	Unclear risk - study population only briefly described (ongoing; abstract only)
Well-defined follow-up (reporting bias)	Unclear risk	Unclear risk - follow-up specified in trial record but median follow-up not reported (abstract only)
Well-defined outcome (reporting bias) Response (PFR, ORR, CR, PR)	High risk	High risk - "Efficacy was assessed per the Lugano Classification", but time point of assessment not clear nor defined"
Well-defined outcome (reporting bias) AEs	High risk	High risk - no details provided in abstract or trial record, and time point of assessment not clear nor defined

Sang 2020

Study characteristics	
Methods	**Phase**: 2 **Study design**: observational, single-arm, single-centre **Location**: China
Participants	**Eligibility criteria:**

Sang 2020 *(Continued)*

- **Inclusion Criteria**
  * Age ≥ 18 and ≤ 70 years
  * Performance status (ECOG) between 0 and 2
  * Histologically confirmed CD20+ and/or CD19+ B-cell non-Hodgkin lymphoma (NHL), including the following types defined by WHO 2008:
    - ☐ DLBCL not otherwise specified, DLBCL associated with chronic inflammation, and Epstein-Barr virus (EBV) + DLBCL in the elderly
    - ☐ Primary mediastinal (thymic) large B-cell lymphoma (PMBCL). The mediastinal mass had to have an axial diameter < 5 cm or extranodal lesion size < 3 cm. Patients with large lesions (≥ 5 cm) were enrolled in our other clinical trial (NCT0334662).
    - ☐ Transformed FL (tFL)
    - ☐ FL
    - ☐ Some indolent lymphomas including MCL and chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)
  * Refractory disease or relapsed after treatment with ≥ 2 lines of chemotherapy including rituximab and anthracycline and either having failed autologous HSCT or being ineligible for or not consenting to autologous HSCT
    - ☐ We defined chemotherapy-refractory disease as meeting one or more of the following criteria:
    - ☐ No response to first-line therapy (primary refractory disease).
    - ☐ No response to second-line or later therapy.
    - ☐ PD as the best response to the most recent therapy regimen.
    - ☐ Stable disease (SD) as the best response after at least 2 cycles of the most recent line of therapy with a SD duration of no longer than 6 months from the last dose of therapy.
    - ☐ PD or relapsed disease ≤ 12 months after ASCT (requires biopsy-proven recurrence in relapsed subjects).
    - ☐ No response or relapse after salvage therapy is given post-ASCT.
  * PD or relapse ≥ 3 months after treatment with a targeted CD19 therapy, including CD19-CAR-T cells or anti-CD19/anti-CD3
  * Successful leukapheresis assessment and pre-culture of T-cells
  * Life expectancy > 3 months
  * Adequate organ function:
    - ☐ Creatinine < 1.6 mg/dL (140 µmol/L) or creatinine clearance ≥ 60 mL/min.
    - ☐ ALT/AST < 3 × upper limit of the normal range.
    - ☐ Bilirubin < 2.0 mg/dL unless the subject had Gilbert's Syndrome (< 3.0 mg/dL).
    - ☐ A minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnoea and pulse oxygenation > 91% with room air. No clinically significant pleural effusion.
    - ☐ Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings.
  * An adequate bone marrow reserve defined as:
    - ☐ Absolute neutrophil count (ANC) > 1000/mm^3.
    - ☐ Absolute lymphocyte count (ALC) ≥ 300/mm^3.
    - ☐ Platelet count ≥ 50,000/mm^3.
    - ☐ Haemoglobin > 7.0 mg/dL.
  * Measurable or assessable disease according to the "IWG Response Criteria for Malignant Lymphoma" (Cheson 2007). Patients in CR with no evidence of disease were not eligible.
  * Informed consent/assent requiring that all patients have the ability to understand and the willingness to provide written informed consent

Sang 2020 *(Continued)*

- **Exclusion Criteria**
  - Patients with definite involvement of gastrointestinal tract. Endoscopy should be performed to conform gastrointestinal involvement for patients suspected. However, patients with central nervous system (CNS) involvement were cautiously enrolled in this clinical study.
  - CD19 CAR-T cell treatment failure or recurrence, detection of a clear HAMA effect, or negative tumour puncture detection of CD19 and CD20
  - Pregnant or lactating women
  - Uncontrolled active bacterial or viral infection (active hepatitis B or hepatitis C infection, HIV infection) or treponema pallidum infection
  - Class III/IV cardiovascular disability according to the New York Heart Association Classification and a cardiac ejection fraction ≥ 50%
  - History of allogeneic stem-cell transplantation
  - Any autoimmune disease or primary immunodeficiency
  - Requirement for urgent therapy due to tumour mass effects such as respiratory obstruction or blood vessel compression
  - Current or expected need for systemic corticosteroid therapy
  - Any organ failure
  - The patients with the second tumour requiring therapy or intervention
  - Subjects considered unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation according to the investigator's judgement

Number of participants:

- n = 21 receiving CAR T-cells
- n = 21 evaluated
  - n = 21 (100%) DLBCL
    - ☐ n = 15 refractory DLBCL

Median age (range): 55 (23-72)

Sex (male/total): 13/21 (62%)

Previous SCT:

- autoSCT: 1/21 (5%)
- alloSCT: NR

Previous lines of treatment: Median: 3 (1-6) (n = 21)

Interventions

Target: CD19 and CD20

Dose of CAR T-cells:

- CD19: 1 x 10^6/kg (range 0.2-4 x)
- CD20: 1 x 10^6/kg (range 0.1-4 x)

Number of infusions: 1

Co-interventions: none

Type and dose of induction chemotherapy:

n = 19:

- Fludarabine 30 mg/m^2 for 3 days
- Cyclophosphamide 750 mg/m^2 for 1 day

n = 2:

Sang 2020 *(Continued)*

	• Ifosfamide 2 g for 3 days
Outcomes	**Primary outcomes:** • Overall complete remission rate [time frame: Half a year] **Secondary outcomes:** • The initial effect time [time frame: 1 year] • The one-year survival rate [time frame: 1 year] • The safety and the tolerability (incidence of treatment-emergent adverse events defined as dose-limited toxicity) [time frame: 1 month] • The time to disease progression [time frame: 1 year] • The one-year recurrence [time frame: 1 year] • The improvement of quality of life [time frame: 1 year]
Notes	**ClinicalTrials.gov ID and status**: NCT03207178, unknown **Sponsors and Collaborators:** Shanghai Longyao Biotechnology Inc., Ltd., Xuzhou Medical University, Shanghai Jiao Tong University School of Medicine **(Principal) investigator(s):** Shengqin Ye (according to ClinicalTrials.gov); Kailin Xu, Wei Sang, Zhenyu Li, Junnian Zheng (conception and design) **Supported by**: Natural Science Foundation of Jiangsu Province, Young Medical Talents of Jiangsu Science and Education Health Project, Jiangsu Key Research and Development Project of Social Development

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Low risk	Low risk - eligibility criteria clearly defined
Complete outcome assessment/follow-up (attrition bias) OS	High risk	High risk - "A total of 25 patients with R/R DLBCL were originally enrolled. However, one of them failed to collect sufficient T lymphocytes; CAR T-cell expansion in vitro failed in two of them, and another patient died due to rapid progressive disease (PD) before CAR T-cell infusion. Therefore, 21 patients received CAR T-cell infusion according to the treatment schema",
Complete outcome assessment/follow-up (attrition bias) Response (PFS, ORR, CR, PR)	High risk	High risk - see OS
Complete outcome assessment/follow-up (attrition bias) AEs	Low risk	Low risk - outcomes reported for 21/21 (100%) of participants receiving CAR T-cells
Outcome assessors blinded to investigated determinant (detection bias) Objective (OS)	Low risk	Low risk - absence of blinding had no effect on objective outcomes.
Outcome assessors blinded to investigated determinant (detection bias)	High risk	High risk - no blinding

Sang 2020 *(Continued)*

Investigator-assessed (PFS, ORR, CR, PR, AEs)		
Well-defined study group (reporting bias)	Low risk	Low risk - study population and intervention well described
Well-defined follow-up (reporting bias)	Low risk	Low risk - median follow-up reported
Well-defined outcome (reporting bias) OS	Low risk	Low risk - objective outcome
Well-defined outcome (reporting bias) Response (PFR, ORR, CR, PR)	Low risk	Low risk - "Response of treatment was defined according to the standard international criteria" (Lugano criteria, Cheson 2014) PFS - low risk Response - low risk - time point specific-assessment
Well-defined outcome (reporting bias) AEs	Low risk	Low risk - use of CTCAE and Lee 2014 criteria (CRS)

Schuster 2017

Study characteristics	
Methods	**Phase**: 2a **Study design**: observational, single-arm, single-centre **Location**: USA

Participants	**Eligibility criteria:**
	• **Inclusion criteria**
	  * Patients ≥ 18 years of age
	  * With CD19+ diffuse large B-cell lymphoma or follicular lymphoma with no curative treatment options
	  * A limited prognosis (< 2 years of anticipated survival)
	  * A partial response to or stable disease after the most recent therapy
	• **Inclusion criteria for patients with diffuse large B-cell lymphoma**
	  * Patients who had measurable disease after primary and salvage therapies
	  * Who had relapsed or residual disease after autologous stem-cell transplantation
	  * Who were not eligible for autologous or allogeneic stem-cell transplantation
	• **Inclusion criteria for patients with follicular lymphoma**
	• Patients who had measurable progression of disease less than 2 years after the second line of immunochemotherapy (excluding single-agent monoclonal antibody therapy)

Schuster 2017 *(Continued)*

- **Exclusion criteria**
  - Pregnant or lactating women (female study participants of reproductive potential must have a negative serum pregnancy test at enrolment. A urine pregnancy test will be performed within 48 hours before infusion)
  - Uncontrolled active infection
  - Active hepatitis B or hepatitis C infection
  - Concurrent use of systemic steroids (recent or current use of inhaled steroids is not exclusionary.)
  - Any uncontrolled active medical disorder that would preclude participation as outlined
  - Class III/IV cardiovascular disability according to the New York Heart Association Classification (see Appendix 1)
  - HIV infection
  - Patients with active CNS involvement by malignancy (patients with prior CNS disease that has been effectively treated will be eligible providing treatment was > 4 weeks before enrolment)
  - Patients in complete remission with no assessable disease
  - Patients with a known history or prior diagnosis of optic neuritis or other immunologic or inflammatory disease affecting the central nervous system

Number of participants:

- n = 28 receiving CAR T-cells
- n = 28 evaluated
  - n = 14 (50%) DLBCL
  - DLBCL participants with performed immune-histochemical studies (n = 12)
    - ☐ n = 7 relapsed and refractory germinal-centre DLBCL
    - ☐ n = 5 non–germinal-centre DLBCL

Median age (range): 58 (25-77)

Sex (male/total): 11/14 (79%)

Previous SCT:

- autoSCT: 7/14 (50%)
- alloSCT: 0/14 (0%)

Previous lines of treatment:

- Median: 3 (1-8) (n = 14)

Interventions

Target: CD19

Dose of CAR T-cells: 5.79 × 10^6/kg (range 3.08-8.87 x)

Number of infusions: 1

Co-interventions: none

Type and dose of induction chemotherapy:

- n = 14 (DLBCL subgroup):
  - Hyperfractionated cyclophosphamide 1.8 gm/^{2} (n = 6)
  - Modified EPOCH incl. cyclophosphamide 750 mg/m^2 (n = 2)
  - Cyclophosphamide 1 gm/m^2 (n = 2)
  - Bendamustine 90 mg/m^2 for 2 days (n = 2)
  - Radiation therapy + cyclophosphamide 750 mg/m^2 (n = 1)
  - Infusional etoposide + bolus cyclophosphamide incl. cyclophosphamide 750 mg/m^2 (n = 1)

Outcomes

Primary outcomes:

Schuster 2017 *(Continued)*

- Number of subjects with an overall response (i.e. either complete response or partial response) evaluated at three months post-infusion [time frame: 3 months]
  * Responders will include those patients achieving complete response (CR), complete response unconfirmed (CRu) and partial response (PR) using anatomic imaging such as CT or MRI to assess tumour volume or, in the event of bone marrow involvement, morphologic and immunohistochemical confirmation that the bone marrow infiltrate has been cleared.

Secondary outcomes: NR

Notes

ClinicalTrials.gov ID and status: NCT02030834, active, not recruiting

Sponsors and Collaborators: University of Pennsylvania

(Principal) investigator(s): Stephen Schuster, MD

Supported (in part) by: Novartis, National Institutes of Health, Lymphoma Program at the Abramson Cancer Center (University of Pennsylvania)

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Low risk	Low risk - eligibility criteria clearly defined
Complete outcome assessment/follow-up (attrition bias) OS	High risk	High risk - (characteristics of enrolled and analysed reported) - "A total of 38 patients were enrolled in the study, and 28 patients received treatment as specified in the protocol. Ten patients did not receive treatment as specified in the protocol owing to rapid disease progression with clinical deterioration (4 patients, 3 with diffuse large B-cell lymphoma and 1 with follicular lymphoma), an insufficient T-cell count for the manufacture of CTL019 cells (5 patients, all with diffuse large B-cell lymphoma), and withdrawal of consent (1 patient, with diffuse large B-cell lymphoma). T-cell manufacturing was unsuccessful for 5 patients, all of whom had absolute lymphocyte counts of 300 per cubic millimeter or fewer (3 had poor T-cell growth, and 2 did not undergo apheresis owing to the degree of lymphopenia)."
Complete outcome assessment/follow-up (attrition bias) Response (PFS, ORR, CR, PR)	High risk	High risk - see OS
Complete outcome assessment/follow-up (attrition bias) AEs	Low risk	Low risk - outcomes reported for 28/28 (100%) of participants receiving CAR T-cells
Outcome assessors blinded to investigated determinant (detection bias) Objective (OS)	Low risk	Low risk - absence of blinding had no effect on objective outcomes.
Outcome assessors blinded to investigated determinant (detection bias) Investigator-assessed (PFS, ORR, CR, PR, AEs)	High risk	High risk - no blinding

Schuster 2017 *(Continued)*

Well-defined study group (reporting bias)	Low risk	Low risk - study population and intervention well described
Well-defined follow-up (reporting bias)	Low risk	Low risk - median follow-up reported
Well-defined outcome (reporting bias) OS	Low risk	Low risk - objective outcome
Well-defined outcome (reporting bias) Response (PFR, ORR, CR, PR)	Low risk	Low risk - "response evaluated with the use of the 1999 International Working Group response criteria; complete response was confirmed on 18F-fluorodeoxyglucose–positron-emission tomography." (Cheson 1999, Cheson 2007) - time point-specific reporting
Well-defined outcome (reporting bias) AEs	Low risk	Low risk - use of CTCAE and Lee 2014 criteria (CRS)

Tong 2020

Study characteristics	
Methods	**Phase:** 1/2a **Study design:** observational, single-arm, single-centre **Location:** China
Participants	**Eligibility criteria** • **Inclusion criteria** * DLBCL was confirmed by pathology and immunohistochemistry. * Patients have previously underwent immunochemotherapy based on anti-CD20 antibody and anthracycline. * At least one measurable lesion was present (refer to the International Working Group [IWG] standard). * Nether radiotherapy nor systemic therapy has been administered two weeks before lymphocyte collection. * Physical score > 50 (Karnofsky Performance Status) * Normal liver, kidney, and cardiac function • **Exclusion criteria** * Serious autoimmune disease or other tumour disease * Participated in other clinical trials of new drugs within the past 3 months * Systemic or local uncontrollable infection * Active hepatitis B and C infection * HIV infection * Psychiatric disorders **Number of participants:** • n = 28 receiving CAR T-cells • n = 28 evaluated * n = 16 (57%) DLBCL ☐ Type of DLBCL: NR

Tong 2020 *(Continued)*

	Age: > 60 years: 7/28 (25%) **Sex (male/total):** 11/28 (39%)
Interventions	**Target:** CD19 and CD20 **Dose of CAR T-cells:** range 1-6 x 10^6/kg **Number of infusions:** 1 **Co-interventions:** none **Type and dose of induction chemotherapy:** • Fludarabine 20-30 mg/$m^2$for 3 days • Cyclophosphamide 20-30 mg/m^2 divided over 3 days with or without doxorubicin liposome 10 mg/m^2 for 1 day
Outcomes	**Primary outcomes:** • Occurrence of study-related adverse events [time frame: Until week 24] **Secondary outcomes:** • Anti-tumour responses to tanCART19/20 cell infusions [time frame: up to 96 weeks] • In vivo existence of TanCART19/20 [time frame: 2 years]
Notes	**ClinicalTrials.gov ID and status**: NCT03207178, completed **Sponsors and Collaborators:** National Natural Science Foundation of China, the Leading Talents Grant of Science & Technology from Beijing, National Key Research and Development Program of China, Chinese PLA General Hospital **(Principal) investigator(s):** Weidong Han

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	High risk	High risk - male sex was underrepresented in the study group (39%).
Complete outcome assessment/follow-up (attrition bias) OS	High risk	High risk - (characteristics of patients at leukapheresis (33) and analysed (28) reported) - "Thirty-three patients were enrolled between May of 2017 and September of 2018. TanCAR7 T cells were successfully manufactured for 31 patients: 1 patient failed leukapheresis, and another had AEs after leukapheresis. The manufactured TanCAR7 T cells were administered to 28 patients. Before infusion, 1 patient had serious AEs, and 2 could not tolerate pretreatment because of disease progression".
Complete outcome assessment/follow-up (attrition bias) Response (PFS, ORR, CR, PR)	High risk	High risk - see OS
Complete outcome assessment/follow-up (attrition bias) AEs	Low risk	Low risk - outcomes reported for 28/28 (100%) of participants receiving CAR T-cells

Tong 2020 *(Continued)*

Outcome assessors blinded to investigated determinant (detection bias) Objective (OS)	Low risk	Low risk - absence of blinding had no effect on objective outcomes.
Outcome assessors blinded to investigated determinant (detection bias) Investigator-assessed (PFS, ORR, CR, PR, AEs)	High risk	High risk - no blinding
Well-defined study group (reporting bias)	Low risk	Low risk - study population and intervention well described
Well-defined follow-up (reporting bias)	Low risk	Low risk - median follow-up reported
Well-defined outcome (reporting bias) OS	Low risk	Low risk - objective outcome
Well-defined outcome (reporting bias) Response (PFR, ORR, CR, PR)	Low risk	Low risk - "Efficacy evaluations were based on recommendations by the International Conference on Malignant Lymphomas Imaging Working Group (Cheson Response Criteria and The Lugano Classification 2014)". PFS - low risk - time point-specific Response - low risk
Well-defined outcome (reporting bias) AEs	Low risk	Low risk - use of CTCAE and Lee 2014 criteria (CRS)

TRANSCEND-NHL-001

Study characteristics	
Methods	**Phase:** 1 **Study design:** parallel-group (varying doses), multicentre **Location:** USA
Participants	**Eligibility criteria** • **Inclusion criteria** * Patients with r/r DLBCL NOS (de novo or transformed from indolent lymphoma), PMBCL, FL grade 3B, or MCL * With adequate organ function * With any ALC * With failed prior allo-SCT, secondary CNS involvement, and ECOG 2 * With ECOG 0-1 • **Exclusion criteria** * Prior allo-SCT **Number of participants:** • n = 269 receiving CAR T-cells

TRANSCEND-NHL-001 *(Continued)*

- 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

Median age (range): 63 (54-70)

Sex (male/total): 174/269 (65%)

Previous SCT:

- autoSCT: 90/269 (33%)
- alloSCT: 9/269 (3%)

Previous lines of treatment: Median: 3 (n = 269)

Interventions

Target: CD19

Dose of CAR T-cells: 50 (in 1-2 doses), 100 or 150 x 10^6

Number of infusions: 1-2

Co-interventions: none

Type and dose of induction chemotherapy:

- Fludarabine 30 mg/m^2 for 3 days
- Cyclophosphamide 300 mg/m^2 for 3 days

Outcomes

Primary outcomes:

- Treatment-related adverse events (AEs) as assessed by CTCAE v4.03 [time frame: Up to 730 days after the final JCAR017 infusion]
- Dose-limiting toxicities of JCAR017 [time frame: 28 days after first (single-dose schedule) or second (2-dose schedule) JCAR017 infusion]
- Objective response rate (ORR) [time frame: 24 months]
- (Best) Overall response rate (ORR)
- Complete response rate
- Partial response rate

Secondary outcomes:

- Complete response (CR) rate
- Duration of response
- Progression-free survival (PFS)
- Overall survival
- Health-related quality of life
- Maximum concentration of JCAR017 (Cmax) in the peripheral blood
- Time to maximum concentration of JCAR017 (Tmax) in the peripheral blood
- Area-under-the-concentration-vs-time-curve (AUC) in the peripheral blood

Assessment:

NR

Notes

ClinicalTrials.gov ID and status: NCT02631044, recruiting

Sponsors and Collaborators: Juno Therapeutics, Inc. (sponsor); Celgene (collaborator)

(Principal) investigator(s):

TRANSCEND-NHL-001 *(Continued)*

several; Tina Albertson, MD, PhD; Jacob Garcia, MD (study directors)

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Low risk	Low risk - eligibility criteria defined
Complete outcome assessment/follow-up (attrition bias) OS	High risk	High risk - only data for safety population available (269); "Of 344 patients with large B-cell lymphoma who underwent leukapheresis, 294 received CAR-T cells a median of 3 days (IQR 3–4) after lymphodepleting chemotherapy. Product could not be manufactured for two patients, and 48 patients had lymphoma complications or died before infusion (figure 1). Of 294 patients who received CAR-T cells across all dose levels, 269 received liso-cel and 25 received a non-conforming CAR T-cell product (i.e. one component did not meet release criteria but was considered safe for infusion)".
Complete outcome assessment/follow-up (attrition bias) Response (PFS, ORR, CR, PR)	Low risk	Low risk - response data (objective response, complete response) available for participants in leukapheresis (344)
Complete outcome assessment/follow-up (attrition bias) QoL	High risk	High risk - outcomes available only for subset of participants (e.g. n = 138 at month 3 and n = 38 at month 12 compared to n = 186 at baseline)
Complete outcome assessment/follow-up (attrition bias) AEs	Low risk	Low risk - outcomes reported for 269/294 (91%) of participants receiving CAR T-cells (not reported for patients receiving non-conforming CAR-T product)
Outcome assessors blinded to investigated determinant (detection bias) Objective (OS)	Low risk	Low risk - absence of blinding had no effect on objective outcomes.
Outcome assessors blinded to investigated determinant (detection bias) Investigator-assessed (PFS, ORR, CR, PR, AEs)	High risk	High risk - no blinding
Outcome assessors blinded to investigated determinant (detection bias) Patient-reported (QoL)	High risk	High risk - no blinding
Well-defined study group (reporting bias)	Low risk	Low risk - study population and intervention well described
Well-defined follow-up (reporting bias)	High risk	High risk - median follow-up reported for ITT population (= participants who underwent leukapheresis) - OS and PFS data limited to "efficacy analysis set", for which no measure of duration of follow-up was reported
Well-defined outcome (reporting bias)	Low risk	Low risk - objective outcome and time point-specific reporting

TRANSCEND-NHL-001 *(Continued)*
OS

Well-defined outcome (reporting bias) Response (PFR, ORR, CR, PR)	High risk	High risk - "Activity was assessed by investigators and an independent review committee according to the Lugano criteria" (Cheson 2014) PFS - low risk - time point-specific reporting, but response outcomes (bORR, bCR and bPR) at high risk as time point of assessment not clear and only a measure of duration of follow-up for the ITT population was reported
Well-defined outcome (reporting bias) QoL	Low risk	Low risk - use of EuroQol 5-Dimension 5-Level (EQ-5D-5L) with defined time points (baseline and months 3, 6 and 12)
Well-defined outcome (reporting bias) AEs	Low risk	Low risk - use of CTCAE and Lee 2014 criteria (CRS)

Ying 2019

Study characteristics	
Methods	**Phase:** 1 **Study design**: observational, non-randomised, single-arm, multicentre **Location**: China
Participants	**Eligibility criteria** • **Inclusion criteria** * Age ≥ 18 years at the time of consent * Signed written informed consent obtained prior to any study procedures * Relapsed or refractory B-cell NHL * PET-positive disease by Lugano classification * Archived tumour biopsy tissue available from the last relapse and corresponding pathology report available or, if at least one tumour-involved site was deemed accessible at time of screening, willing to undergo pretreatment biopsy (excisional when possible) for disease confirmation. If a subject had never had a complete response, a sample from the most recent biopsy was acceptable. * Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 * Adequate bone marrow, renal, hepatic, pulmonary and cardiac function * Adequate vascular access for leukapheresis procedure * Subjects who have received previous CD19-targeted therapy must have CD19-positive lymphoma confirmed on a biopsy since completing the prior CD19-targeted therapy. * Subjects must agree to use appropriate contraception.

Ying 2019 *(Continued)*

- **Exclusion criteria**
  - Subjects with central nervous system (CNS)-only involvement by malignancy (note: subjects with secondary CNS involvement were allowed on study)
  - History of another primary malignancy that had not been in remission for at least 2 years
  - Treatment with alemtuzumab within 6 months of leukapheresis, or treatment with fludarabine or cladribine within 3 months of leukapheresis
  - Active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection at the time of screening
  - Subjects with uncontrolled systemic fungal, bacterial, viral or other infection despite appropriate antibiotics or other treatment at the time of leukapheresis or JWCAR029 administration
  - Presence of acute or chronic graft-versus-host disease (GVHD)
  - History of cardiovascular disease
  - History or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis
  - Pregnant or nursing women
  - Prior CAR T-cell or other genetically-modified T-cell therapy, with the exception of prior JWCAR029 treatment in this protocol for subjects receiving retreatment

Number of participants

- n = 32 receiving CAR T-cells
- n = 29 evaluated
  - n = 20 (69%) DLBCL
    - ☐ Type of DLBCL: NR

Median age (range): 52 (29-68)

Sex (male/total): 24/32 (75%)

Previous SCT:

- autoSCT: 1/10 (10%)
- alloSCT: NR

Previous lines of treatment: Median: 4 (2-7)

Interventions	**Target:** CD19 **Dose of CAR T-cells:** 2 x 10^6/kg **Number of infusions:** 1 **Co-interventions:** none **Type and dose of induction chemotherapy**: • Fludarabine 25 mg/m^2 for 3 days • Cyclophosphamide 250 mg/$m^2$for 3 days
Outcomes	**Primary outcomes:** • Treatment-related adverse events (AEs) [time frame: 2 years] • Dose-limiting toxicities of JWCAR029 [time frame: 28 days after JWCAR029 infusion] • Objective response rate (ORR) [time frame: 2 years] **Secondary outcomes:** • Maximum concentration (Cmax) of JWCAR029 in the peripheral blood and bone marrow [time frame: 1 year after JWCAR029 infusion]

Ying 2019 *(Continued)*

- Time to maximum concentration (Tmax) of JWCAR029 in the peripheral blood and bone marrow [time frame: 1 year after JWCAR029 infusion]
- Area-under the concentration-vs-time-curve (AUC) of JWCAR029 in the peripheral blood and bone marrow [time frame: 1 year after JWCAR029 infusion]
- Complete response (CR) rate [time frame: 2 years]
- Duration of response [time frame: 2 years]
- Progression-free survival (PFS) and PFS ratio [time frame: 2 years]
- Overall survival [time frame: 2 years]
- CAR-T cell persistence as measured by enumeration of CAR-T cells in the blood and bone marrow of participants [time frame: 1 year]
- T-cell activity and exhaustion profile as measured by flow cytometry [time frame: 3 months]
- Cytokine levels in the peripheral blood of the patients [time frame: 30 days]

Notes	**ClinicalTrials.gov ID and status**: NCT03344367, NCT03355859; active, not recruiting **Sponsors and Collaborators:** Peking University, Zhao Weili, Shanghai Mingju Biotechnology Co., Ltd. **Disclosures** **Wang**: JW therapeutics (Shanghai) Co. Ltd: Employment, Equity Ownership. **Hao**:JW therapeutics (Shanghai) Co. Ltd: Employment, Equity Ownership. **Yang**: JW therapeutics (Shanghai) Co. Ltd: Employment, Equity Ownership. **Lam**: JW therapeutics (Shanghai) Co. Ltd: Employment, Equity Ownership. **Li**: JW therapeutics (Shanghai) Co. Ltd: Employment, Equity Ownership. **Zheng**: JW therapeutics (Shanghai) Co. Ltd: Employment, Equity Ownership

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Low risk	Low risk - eligibility criteria clearly defined
Complete outcome assessment/follow-up (attrition bias) Response (PFS, ORR, CR, PR)	High risk	High risk - only 29 of total enrolled 32 evaluated (including participants suffering from FL, MCL, etc.; unclear which participants were not evaluated); number of evaluated participants with DLBCL: 20 ("32 patients were enrolled and received treatment in two study sites in China. Twenty nine patients are evaluable and have been followed for at least 6 months: 20 diffuse large B-cell lymphoma (DLBCL) and 9 follicular lymphoma, mantle cell lymphoma and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue lymphoma").
Complete outcome assessment/follow-up (attrition bias) AEs	High risk	High risk - only half of the safety outcomes of interest (CRS and neurotoxicity) reported for 32/32 (100%) of participants receiving CAR T-cells while half of the safety outcomes of interest (use of tocilizumab and/or corticosteroids and cytopenias) were reported for 10/32 (31%) of participants receiving CAR T-cells only (earlier data-cut off)
Outcome assessors blinded to investigated determinant (detection bias) Objective (OS)	Low risk	Low risk - absence of blinding had no effect on objective outcomes.
Outcome assessors blinded to investigated determinant (detection bias) Investigator-assessed (PFS, ORR, CR, PR, AEs)	High risk	High risk - no blinding

Ying 2019 *(Continued)*

Well-defined study group (reporting bias)	Unclear risk	Unclear risk - study population only briefly described (ongoing; abstract only for reported sample)
Well-defined follow-up (reporting bias)	Unclear risk	Unclear risk - follow-up specified in study record but only minimum follow-up reported (ongoing; abstract only for reported sample)
Well-defined outcome (reporting bias) Response (PFR, ORR, CR, PR)	Low risk	Low risk - "Tumor evaluation was evaluated per the Lugano criteria by PET-CT" (Cheson 2014) Response - low-risk - time point-specific assessment and reporting
Well-defined outcome (reporting bias) AEs	Low risk	Low risk - use of CTCAE and Lee 2014 criteria (CRS)

ZUMA-1

Study characteristics

Methods

Phase: 1/2

Study design: non-randomised, single-arm, multicentre

Location: Israel, USA

Participants

Eligibility criteria

- **Inclusion criteria**
  - Histologically confirmed large B-cell lymphoma (according to the 2008 WHO guidelines, retrospectively centrally confirmed)
  - DLBCL (cohort 1)
  - Primary mediastinal B-cell lymphoma or transformed follicular lymphoma (cohort 2)
  - Refractory disease, defined as:
    - ☐ progressive or stable disease as the best response to the most recent chemotherapy regimen or
    - ☐ disease progression or relapse within 12 months after autologous stem-cell transplantation
  - Aged 18 years or older
  - ECOG performance status of 0 or 1
  - Absolute neutrophil count >= 1000 per µL
  - Adequate organ function
- **Exclusion criteria**
  - Prior regimen containing an anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen
  - Participants who received autologous stem-cell transplantation within 6 weeks before consent were excluded.
  - Participants who had previously undergone allogenic stem-cell transplantation were excluded.
  - Participants who received previous CD19-targeted therapy or CAR T-cell therapy were excluded.

Number of participants:

- 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-centre DLBCL

Median age (range): 58 (NR)

ZUMA-1 *(Continued)*

Sex (male/total): 73/108 (68%)

Previous SCT:

- autoSCT: 16/81 (21%)
- alloSCT: NR

Previous lines of treatment: Median: 3

Interventions

Target: CD19

Dose of CAR T-cells: 2 x 10^6/kg

Number of infusions: 1

Co-interventions: none

Type and dose of induction chemotherapy:

- Fludarabine 30 mg/m^2 for 3 days
- Cyclophosphamide 500 mg/m^2 for 3 days

Outcomes

Primary outcomes:

- Phase 1:
  - Percentage of participants experiencing adverse events defined as dose limiting toxicities (up to 30 days) (defined as axicabtagene ciloleucel-related events with onset within the first 30 days following axicabtagene ciloleucel infusion)
- Phase 2:
  - Overall response rate (up to 12 months) (defined as the incidence of a complete response (CR) or partial response (PR) via International Working Group (IWG) Response Criteria for Malignant Lymphoma as determined by the study investigators)
  - Incidence and severity of cytokine release syndrome and neurologic toxicities (up to 12 months)

Secondary outcomes:

- Duration of response (up to 12 months) (for participants who experience an objective response, DOR is defined as date of first objective response to disease progression per the revised IWG Response Criteria for Malignant Lymphoma or death of any cause)
- Phase 1: Overall response rate (12 months)
- Phase 2: Overall response rate by Independent Radiological Review Committee (up to 12 months) (defined as the incidence of either a complete response (CR) or a partial response (PR) per the Independent Radiological Review Committee)
- Progression-free survival (PFS) (up to 12 months) (defined as the time from infusion date to disease progression per revised IWG Response Criteria for Malignant Lymphoma or death from any cause)
- Overall survival (up to 12 months) (defined as the time from infusion to date of death)
- Percentage of participants experiencing adverse events (up to 12 months)
- Percentage of participants experiencing clinically significant changes in safety lab values (up to 12 months)
- Percentage of participants with anti-axicabtagene ciloleucel antibodies (up to 12 months)
- Pharmacokinetics (levels of anti-CD19 CAR T-cells in blood) (up to 2 years)
- Pharmacodynamics (levels of cytokines in serum) (up to 12 months)
- Phase 2: Changes over time in the European Quality of Life Five Dimension Five Level Scale (EQ-5D) (up to 5 years)
- Phase 2: Changes over time in the Visual Analogue Scale (VAS) score (up to 5 years)

Notes

ClinicalTrials.gov ID and status: NCT02348216, recruiting

Sponsors and Collaborators: Kite Pharma (sponsor); Funded by Kite Pharma and the Leukemia and Lymphoma Society Therapy

ZUMA-1 *(Continued)*

Acceleration Program

(Principal) investigator(s):

Kite Study Director

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Low risk	Low risk - eligibility criteria clearly defined
Complete outcome assessment/follow-up (attrition bias) OS	High risk	High risk - survival analysis based on 101 pts; included in phase 2 of the study ("119 patients were enrolled and 108 received axicabtagene ciloleucel (seven in phase 1 and 101 in phase 2; appendix p 17)".
Complete outcome assessment/follow-up (attrition bias) Response (PFS, ORR, CR, PR)	High risk	High risk - evaluation of response based on 101 pts; included in phase 2 of the study ("119 patients were enrolled and 108 received axicabtagene ciloleucel (seven in phase 1 and 101 in phase 2; appendix p 17)".
Complete outcome assessment/follow-up (attrition bias) AEs	Low risk	Low risk - most outcomes reported for 108/108 (100%) participants receiving CAR T-cells across phase 1 and 2 of the study ("119 patients were enrolled and 108 received axicabtagene ciloleucel (seven in phase 1 and 101 in phase 2; appendix p 17)"; only use of tocilizumab and/or corticosteroids reported for 6 participants from phase 1 only
Outcome assessors blinded to investigated determinant (detection bias) Objective (OS)	Low risk	Low risk - absence of blinding had no effect on objective outcomes.
Outcome assessors blinded to investigated determinant (detection bias) Investigator-assessed (PFS, ORR, CR, PR, AEs)	High risk	High risk - no blinding
Well-defined study group (reporting bias)	Low risk	Low risk - study population and intervention well described
Well-defined follow-up (reporting bias)	Low risk	Low risk - median follow-up reported
Well-defined outcome (reporting bias) OS	Low risk	Low risk - objective outcome and time point-specific reporting
Well-defined outcome (reporting bias) Response (PFR, ORR, CR, PR)	Low risk	Low risk - "Response was assessed locally by PET according to the International Working Group Response Criteria for Malignant Lymphoma (Cheson 2007) [...]. For phase 2, disease response was also assessed by an independent central review committee". PFS - low-risk - time point-specific data available, response outcomes (bORR, bCR and cPR from registry) potentially evaluated after follow-up for which a measure of duration was reported

ZUMA-1 *(Continued)*

Well-defined outcome (reporting bias) AEs	Low risk	Low risk - use of CTCAE and Lee 2014 criteria (CRS)

ZUMA-6

Study characteristics	
Methods	**Phase**: 1 **Study design**: single-arm, multicentre **Location**: USA
Participants	**Eligibility criteria** • **Inclusion criteria** * Histologically confirmed DLBCL * Chemotherapy-refractory disease, defined as one or more of the following: ☐ Stable disease (duration of stable disease must be less than or equal to 6 months) or progressive disease as best response to most recent chemotherapy containing regimen ☐ Disease progression or recurrence less than or equal to 12 months of prior autologous stem-cell transplantation (SCT) * Individuals must have received adequate prior therapy including at a minimum: ☐ anti-CD20 monoclonal antibody unless investigator determined that tumour was CD20-negative; and ☐ an anthracycline-containing chemotherapy regimen * At least one measurable lesion per revised International Working Group (IWG) Response Criteria * Age 18 years or older * Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 * Adequate organ and bone marrow function * All individuals or legally appointed representatives/caregivers, must personally sign and date the institutional review board (IRB)/independent ethics committee (IEC) approved consent form before initiating any study-specific procedures or activities. • **Exclusion criteria** * History of malignancy other than non-melanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) or follicular lymphoma unless disease-free for at least 3 years * History of allogeneic stem-cell transplantation * Prior CAR therapy or other genetically modified T-cell therapy * Clinically significant active infection * Known history of infection with HIV or hepatitis B or hepatitis C virus * Individuals with detectable cerebrospinal fluid malignant cells or brain metastases or with a history of cerebrospinal fluid malignant cells or brain metastases * History of a seizure disorder, cerebrovascular ischaemia/haemorrhage, dementia, cerebellar disease, or any autoimmune disease with central nervous system (CNS) involvement * History of autoimmune disease. Participants with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone and participants with controlled type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study. * History of idiopathic pulmonary fibrosis, organising pneumonia (e.g. bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest

ZUMA-6 *(Continued)*

computed tomography (CT) scan at screening. History of radiation pneumonitis in the radiation field (fibrosis) was allowed.

* Prior treatment with PD-L1 inhibitor, PD-1 inhibitor, anti-CTLA4, anti-CD137, anti-OX40 or other immune checkpoint blockade or activator therapy with the exception of Individuals who received atezolizumab in this study and were eligible for retreatment
* Prior CD19-targeted therapy

Number of participants:

- n = 12 receiving CAR T-cells
- n = 12 evaluated
  * n = 12 (100%) DLBCL
    ☐ Type of DLBCL NR

Median age (range): 55 (30-66)

Sex (male/total): NR

Previous SCT:

- autoSCT: 16/81 (21%)
- alloSCT: NR

Previous lines of treatment: NR

Interventions

Target: CD19

Dose of CAR T-cells: 2 x 10^6/kg

Number of infusions: 1

Co-interventions: atezolizumab

Type and dose of induction chemotherapy:

- Fludarabine 30 mg/m^2 for 3 days
- Cyclophosphamide 500 mg/m^2 for 3 days

Outcomes

Primary outcomes:

- Phase 1: Number of participants experiencing dose-limiting toxicities (DLTs) [time frame: Baseline up to 21 days]
- Phase 1 and 2: Complete response rate (CRR) [time frame: Month 6]

Secondary outcomes:

- Phase 1 and 2: Objective response rate (ORR) [time frame: From enrolment until first occurrence of CR or PR (up to approximately 2.5 years)]
- Phase 1 and 2: Duration of response (DOR) [time frame: From the date of first confirmed objective response (CR or PR) to disease progression or death regardless of cause (up to approximately 2.5 years)]
- Phase 1 and 2: Progression-free survival (PFS) [time frame: From the date of first KTE-C19 infusion to disease progression or death regardless of cause (up to approximately 2.5 years)]
- Phase 1 and 2: Overall survival (OS) [time frame: From the date of first KTE-C19 infusion to the date of death regardless of cause (up to approximately 2.5 years)]
- Phase 1 and 2: Percentage of participants experiencing adverse events (AEs) [time frame: Enrolment up to 30 days after completion of the final dose of atezolizumab, or 3 months after the KTE-C19 infusion, whichever was longer (up to approximately 2.5 years)]
- Phase 1 and 2: Percentage of participants with serum chemistry toxicity grade shifts to grade 3 or higher resulting from increased parameter values [time frame: Enrolment up to 30 days after completion of the final dose of atezolizumab, or 3 months after the KTE-C19 infusion, whichever was longer (up to approximately 2.5 years)]

ZUMA-6 *(Continued)*

- Phase 1 and 2: Percentage of participants with serum chemistry toxicity grade shifts to grade 3 or higher resulting from decreased parameter values [time frame: Enrolment up to 30 days after completion of the final dose of atezolizumab, or 3 months after the KTE-C19 infusion, whichever was longer (up to approximately 2.5 years)]
- Phase 1 and 2: Percentage of participants with haematology toxicity grade shifts to grade 3 or higher resulting from increased parameter values [time frame: Enrolment up to 30 days after completion of the final dose of atezolizumab, or 3 months after the KTE-C19 infusion, whichever was longer (up to approximately 2.5 years)]
- Phase 1 and 2: Percentage of participants with haematology toxicity grade shifts to grade 3 or higher resulting from decreased parameter values [time frame: Enrolment up to 30 days after completion of the final dose of atezolizumab, or 3 months after the KTE-C19 infusion, whichever was longer (up to approximately 2.5 years)]
- Phase 1 and 2: Peak Anti-CD19 CAR T-Cell (KTE-C19) level (maximum observed plasma concentration) in blood [time frame: pre-infusion (baseline); Post-infusion: Days 7 (Phase 2), 14, 22 (phase 2), 28 (phase 2; optional), 35 (phase 1, cohort 3; optional), 43, 49 (optional), 64, 69 (optional), 94; long-term follow-up: every 3 months from month 6 to month 18, and month 24]
- Phase 1 and 2: Percentage of participants with anti-KTE-C19 antibodies [time frame: baseline up to approximately 2.5 years]
- Phase 1 and 2: Atezolizumab levels in blood [time frame: days 1, 14, 21, 22, 35, 42, 43, 56, 63, 64, 77, 84, 154, and 174]
- Phase 1 and 2: Percentage of participants with anti-atezolizumab antibodies [time frame: baseline up to approximately 2.5 years]
- Phase 1 and 2: Peak serum levels of C-Reactive Protein (CRP) in blood [time frame: baseline (pre-conditioning chemotherapy); day 0 (pre-KTE-C19 infusion); Days 1, 4, 7, and 14, and 22, optional day 28 (phase 2) or day 35 (phase 1 cohort 3), optional day 49, optional day 69, and day 94 post-KTE-C19 infusion]
- Phase 1 and 2: Peak serum levels of C-X-C motif chemokine 10 (CXCL10), interferon-gamma (IFN-γ), interleukin-1 receptor antagonist (IL-1RA), interleukin (IL)-2, IL-6, IL-8, IL-15, and tumour necrosis factor-alpha (TNF-α) in blood [time frame: baseline (pre-conditioning chemotherapy); day 0 (pre-KTE-C19 infusion); days 1, 4, 7, and 14, and 22, optional day 28 (phase 2) or day 35 (phase 1 cohort 3), optional day 49, optional day 69, and day 94 post-KTE-C19 infusion]
- Phase 1 and 2: Peak serum levels of ferritin in blood [time frame: baseline (pre-conditioning chemotherapy); day 0 (pre-KTE-C19 infusion); days 1, 4, 7, and 14, and 22, optional day 28 (phase 2) or day 35 (phase 1 cohort 3), optional day 49, optional day 69, and day 94 post-KTE-C19 infusion]
- Phase 1 and 2: Peak serum levels of interleukin-2 receptor alpha (IL-2Rα) in blood [time frame: baseline (pre-conditioning chemotherapy); day 0 (pre-KTE-C19 infusion); days 1, 4, 7, and 14, and 22, optional day 28 (phase 2) or day 35 (phase 1 cohort 3), optional day 49, optional day 69, and day 94 post-KTE-C19 infusion]
- CAR T-cell persistence as measured by enumeration of CAR T-cells in the blood and bone marrow of participants [time frame: 1 year]
- T-cell activity and exhaustion profile as measured by flow cytometry [time frame: 3 months]
- Cytokine levels in the peripheral blood of the patients [time frame: 30 days]
- Feasibility of CD19 CAR T-cell production as defined by number of products successfully meeting release criteria [time frame: 12 days]

Notes	**ClinicalTrials.gov ID and status**: NCT02926833, active, recruiting **Sponsors and Collaborators:** Kite, A Gilead Company, Genentech, Inc. **(Principal) investigator(s):** Kite Study Director

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	High risk	Unclear risk - eligibility criteria not sufficiently reported

ZUMA-6 *(Continued)*

Complete outcome assessment/follow-up (attrition bias) OS	Unclear risk	Unclear - number of enrolled not reported (only number of those who received CAR T-cell therapy and atezolizumab)
Complete outcome assessment/follow-up (attrition bias) Response (PFS, ORR, CR, PR)	Unclear risk	Unclear - number of enrolled not reported (only number of those who received CAR T-cell therapy and atezolizumab)
Complete outcome assessment/follow-up (attrition bias) AEs	Low risk	Low risk - most outcomes reported for 34/34 (100%) participants receiving CAR T-cells across phase 1 and 2 of the study; only neurotoxicity and (partially) cytopenias reported for 12 participants from phase 1 only
Outcome assessors blinded to investigated determinant (detection bias) Objective (OS)	Low risk	Low risk - absence of blinding had no effect on objective outcomes.
Outcome assessors blinded to investigated determinant (detection bias) Investigator-assessed (PFS, ORR, CR, PR, AEs)	High risk	High risk - no blinding
Well-defined study group (reporting bias)	Low risk	Low risk - study population and intervention well described (ongoing but study record including preliminary results available)
Well-defined follow-up (reporting bias)	Low risk	Low risk - median follow-up reported
Well-defined outcome (reporting bias) OS	Low risk	Low risk - objective outcome - only median available from registry
Well-defined outcome (reporting bias) Response (PFR, ORR, CR, PR)	Low risk	Low risk - response assessed using the "International Working Group Revised Response Criteria for Malignant Lymphoma" (Cheson 2007) PFS - low risk and only median available from registry, response outcomes (bORR, bCR and cPR from registry) potentially evaluated after follow-up for which a measure of duration was reported
Well-defined outcome (reporting bias) AEs	Low risk	Low risk - use of MedDRA

ABVD: adriamycin, bleomycin, vinblastine, and dacarbazine
AE: adverse events
ALC: absolute lymphocytic count
ANC: absolute neutrophil count
ASCT: autologous stem-cell transplantation
AUC: area under the curve
bCR: best complete response
BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
BMT: bone marrow transplant
bORR: best overall response rate

bPR: best partial response rate
CAR-T: chimeric antigen receptor T
CLL: chronic lymphocytic leukemia
Cmax: highest concentration
CNS: central nervous system
CR: complete response
CRI: incomplete count recovery
CRS: cytokine release syndrome
CRu: complete response unconfirmed
CS: clinical stage
CSF: cerebral spinal fluid
CT: computed tomography
CTCAE: Common Terminology Criteria for Adverse Events
esc: escalated
DLBCL: diffuse large B-cell lymphoma
DLCO: diffusing capacity of the lung for carbon monoxide
DLT: dose-limiting toxicity
DOR: duration of response
EBV: Epstein-Barr virus
ECG: electrocardiogram
ECHO: echocardiogram
ECOG: Eastern Cooperative Oncology Group
EFS: event-free survival
EGFR: estimated glomerular filtration rate
EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EPOCH: etoposide, prednisolone, oncovin, cyclophosphamide, and hydroxydaunorubicin
EQ-5D-5L: EuroQol 5-Dimension 5-Level
ESR: erythrocyte sedimentation rate
FACs: fluorescence-activated cell sorting
FACT: Function Assessment of Cancer Therapy
FDG: fluorodeoxy-D-glucose
FEV1: forced expiratory volume in one second
FL/FLL: follicular lymphoma
GVHD: graft versus host disease
HAMA: human anti-mouse antibody
HIV: human immunodeficiency virus
HL: Hodgkin lymphoma
HRQoL: health-related quality of life
HCT/HSCT: hematopoietic stem-cell transplantation
ICF: informed consent form
IEC: independent ethics committee
IF-RT: Involved-field radiotherapy
IGEV: ifosfamide, gemcitabine, vinorelbine
IN-RT: involved-node radiotherapy
IQR: interquartile range
IRB: institutional review board
ITT: intention-to-treat
IV: intravenous
IWG: International Working Group
MCL: mantle cell lymphoma
MedDRA: Medical Dictionary for Regulatory Activities
MRI: magnetic resonance imaging
MT: magnetisation transfer
NFT: no further treatment
NHL: Non-Hodgkin lymphoma
NOS: not further specified

NR: not reported
NYHA: New York Heart Association
ORR: overall response rate
OS: overall survival
PBSC: peripheral blood stem cell
PET: positron emission tomography
PFS: progression- free survival
PI: principal investigator
PK: pharmacokinetic
PMBCL: primary mediastinal B-cell lymphoma
PR: partial response
pt: patient
QoL: quality of life
r/r: relapsed or refractory
SCT: stem-cell transplantation
SD: standard deviation
SGOT: serum glutamic-oxaloacetic transaminase
SLL: small lymphocytic leukaemia
SPD: sum of product of perpendicular diameters
TF: transformed
tFL: transformed follicular lymphoma
Tmax: time of maximum concentration
VAS: visual analogue scale
VEBEP: vinblastine, etoposide, bleomycin, epirubicin, and prednisone
WBC: white blood cell
WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Batlevi 2019	< 10 patients with r/r DLBCL
Buhmann 2013	< 10 patients with r/r DLBCL
Cao 2019	Retrospective study
ChiCTR-OPN-16009069	No patients with r/r DLBCL
Chong 2020	< 70% of patients with r/r DLBCL (data not reported separately)
Enblad 2018	< 10 patients with r/r DLBCL
Jain 2019	< 10 patients with r/r DLBCL
Jim 2018	Observational study on patients treated in several clinical trials or commercially
NCT01475058	No patients with r/r DLBCL
NCT02776813	No CAR T-cells (antibody-coupled T-cell receptor)
NCT03189836	No CAR T-cells (antibody-coupled T-cell receptor) < 10 patients with r/r DLBCL
NCT03196830	Early results published with 27% participants with DLBCL

Study	Reason for exclusion
NCT03436771	Study terminated in May 2020
NCT03579927	Withdrawn before patients were enrolled (due to lack of funding)
Sauter 2014a	< 10 patients with r/r DLBCL
Sesques 2020	Retrospective study
Srour 2020	< 10 patients with r/r DLBCL
Wang 2014	< 10 patients with r/r DLBCL
Wang 2016 (NHL2)	< 10 patients with r/r DLBCL
Wang 2016a (NHL1)	< 10 patients with r/r DLBCL
Wang 2020	< 70% of patients with r/r DLBCL (data not reported separately)

CAR-T: Chimeric antigen receptor T-cells
DLBCL: diffuse large B-cell lymphoma
r/r: relapsed or refractory

Characteristics of studies awaiting classification *[ordered by study ID]*

ChiCTR-ONC-16008911

Methods	Phase NR ("New Treatment Measure Clinical Study") • Observational, single-arm • Study size (according to ChiCTR): 40

Participants	**Inclusion criteria**
	• Patient or legal guardians must sign a consent form
	• Aged 6 years to 60 years, male or female
	• Diagnosed with B-cell lymphoma by pathology, histology and flow cytometry
	• Has lesions which can be measured or evaluated
	• Main organs seem to be functioning well:
	  * Liver function: bilirubin ≤ 34.2 umol/L
	  * Renal function: Serum creatinine < 220 umol/L
	  * Lung function: arterial oxygen saturation ≥ 95%
	  * Heart function: LVEF ≥ 40%
	• Peripheral venous blood in patients flowing smoothly
	• Karnofsky score ≥ 60

Interventions	CAR T-cells with normal expression of PD-1 CAR T-cells with low expression of PD-1
Outcomes	Primary Outcome Measures 1. Minimal residual disease 2. Amplification and duration of CAR-T 3. Remission rate

ChiCTR-ONC-16008911 *(Continued)*

Notes	Study start date: October 1, 2016 Study completion date: October 1, 2019

ChiCTR-OPN-16009847

Methods	Phase 0 • Observational, single-centre, single-arm, open-label • Study size (according to ChiCTR): 50
Participants	**Inclusion criteria:** • Voluntary participation in the clinical trials and signs the informed consent • Aged 18 to 70 years, male and female • Patients with CD19+, CD22+ leukaemia or lymphoma diagnosed by pathology and histology, meets the criteria of autologous haematopoietic stem-cell transplantation, and patients voluntarily accept infusion of anti-CD19 CAR-T and anti-CD22 CAR T-cell therapy after HSCT • Types of B-cell malignancy: * B-cell acute lymphoblastic leukaemia * Indolent B-cell lymphoma (CLL, FL, MZL, LPL, HCL) * Aggressive B-cell lymphoma (DLBCL, BL, MCL) * Multiple myeloma • Patients willing to accept auto-HSCT, and meeting any of the following criteria: * Present residual disease or progressive disease after main therapy * Relapse after CR1 * Patients with high risk factors; * Failure to achieve remission or relapse after other cell immunotherapy * Eligible for allo-HSCT, but unable to implement • Multiple organ function assessment: * Creatinine < 2.5 mg/dL * Aspartate transaminase-alanine transaminase ratio < 3 x normal * Bilirubin < 2.0 mg/dL * LVEF > 40% • Without history of accepting anti-cancer therapy, including chemotherapy, radiotherapy, immunotherapy (immune-suppressive drugs treatment) within 4 weeks of screening • Adequate venous access for apheresis • ECOG score ≤ 2, estimated survival of ≥ 3 months
Interventions	CAR T-cell immunotherapy
Outcomes	Primary Outcome Measures: 1. Safety
Notes	Study starting date: November 14, 2016 Study completion date: December 31, 2020

ChiCTR-OPN-17013507

Methods	Phase 0

ChiCTR-OPN-17013507 *(Continued)*

- Observational, single-centre, single-arm, open-label
- Study size (according to ChiCTR): 27

Participants	**Inclusion criteria**
	• Between 18 and 65 years of age; irrespective of gender
	• Patients with CD19 positive lymphoma or leukaemia determined by histology (including bone marrow biopsy) or flow cytometry
	• Patients with relapsed/refractory B-cell leukaemia/lymphoma
	  * The definition of recurrence refers to the emergence of new lesions after complete response from the previous treatment.
	  * The refractory definition refers to the absence of a valid treatment option and a limited prognosis (only a few months to two years) after the current available treatment intervention
	• ECOG performance status 0 or 1
	• Have experienced at least one complete combined chemotherapy/targeted therapy
	• The toxic and side effects of the last treatment should be recovered with an interval of at least 4 weeks from the most recent chemotherapy, and of at least 3 half-lives from the last immunotherapy
	• With life expectancy above 3 months
	• White blood cell 4 x 10^9/L - 10 x 10^9/L
	• Lymphocyte 1.1 x 10^9/L - 3.2 x 10^9/L
	• Haemoglobin ≥ 80 g/L
	• PLT ≥ 60 x 10^9/L
	• The functioning of important viscera being normal:
	  * Cardiac ultrasound indicates that cardiac ejection fraction ≥ 50%, and the ECG being not significantly abnormal
	  * Blood oxygen content is ≥ 90%
	  * Creatinine clearance rate (by CG formula) ≥ 60 mL/min
	  * ALT and AST 3.0 x ULN
	  * Serum bilirubin and alkaline phosphatase 2.0 x ULN
	  * Blood potassium and sodium is normal
	  * Serum lipase and amylase < 1.5 x ULN
	  * Serum alb ≥ 30 g/L
	• With adequate intravenous access for a single blood collection or intravenous blood collection, and no other blood cell separation contraindications
	• Agrees to take active contraceptives measure during and 3 months after the trial
	• Agrees to the 24-week assessment schedule and follow-up plan and cooperates actively
	• Patient or guardian agrees to participate in this clinical trial and sign a written informed consent form prior to participating in this trial

Interventions	CAR-T-19
Outcomes	Primary outcome measures: 1. Safety and tolerability 2. 27 cytokines, 14 soluble cytokine receptors and C-reactive protein in peripheral blood 3. Positive rate of human anti-human mouse chimeric antibody (HACA)
Notes	Study start date: September 1, 2017 Study completion date: September 1, 2019

NCT02652910

Methods	Phase I/II • Interventional, non-randomised, single-centre, open-label • Study size (according to Clinicaltrials.gov): 20

Participants	**Inclusion criteria:**
	• 18 years to 70 years, male and female
	• Expected survival > 12 weeks
	• Performance score 0-2
	• Histologically confirmed as CD19-positive lymphoma and who meet one of the following conditions:
	  * Patient receives at least 2-4 prior combination chemotherapy regimens (not including single-agent monoclonal antibody therapy) and fails to achieve CR; or have disease recurrence; or not eligible for allogeneic stem-cell transplantation; or disease responding or stable after most recent therapy but refused further treatment
	  * Disease recurrence after stem-cell transplantation
	  * Diagnosis as lymphoma, but refuses conventional treatment such as chemotherapy, radiation, stem-cell transplantation and monoclonal antibody therapy
	• Creatinine < 2.5 mg/dL
	• ALT/AST < 3 x normal
	• Bilirubin < 2.0 mg/dL
	• Adequate venous access for apheresis, and no other contraindications for leukapheresis
	• Takes contraceptive measures before recruitment to this trial
	• Written voluntary informed consent is given

Interventions	CD19 CAR T-cells • Retroviral vector-transduced autologous T-cells to express CD19-specific CARs • Other name: DSCAR01
Outcomes	Primary outcome measures: 1. Phase 1: Safety measured by occurrence of study-related adverse effects defined by NCI CTCAE 4.0 [time frame: 4 weeks] 2. Phase 2: Overall complete remission rate defined by the standard response criteria for malignant lymphoma for each arm [time frame: 8 weeks] 3. Phase 2: Comparison of overall complete remission rate for the two arms [time frame: one year] Secondary outcome measures: 1. Duration of remission [time frame: one year] 2. Minimum residual disease negative remission rate [time frame: 8 weeks] 3. Duration of CAR-positive T-cells in circulation [time frame: 6 months] 4. Total number of CAR-positive T-cells infiltrated into lymphoma tissue [time frame: 6 months] 5. Overall survival [time frame: one year]
Notes	Study start date: December 2015 Primary completion date: June 2019 Study completion date: December 2019

NCT02933775

Methods	Phase I • Prospective, interventional, single-arm, open-label • Study size (according to Clinicaltrials.gov): 45
Participants	**Inclusion criteria:** • Subjects with documented CD19-positive malignant B-cell leukaemia and lymphoma * Patients aged between 18 ~ 65 with malignant B-cell leukaemia and lymphoma * CD19-positive B-cell leukaemia or lymphoma * Expected survival > 12 weeks * ECOG scores 0-1, or KPS scores > 80 * Adequate venous access for apheresis or venous sampling, and no other contraindications for leukapheresis * WBC ≥ 2.5×10^9/L; LY ≥ 0.7×10^9/L; LY% ≥ 15% * Creatinine ≤ 2.0 mg/dL (176.8 µmol/L) * ALT/AST ≤ 2.5 ULN * Bilirubin ≤ 2.0 mg/dL (34.2 µmol/L) * Prothrombin time (PT): International Normalized Ratio (INR) < 1.7, or PT is at most 4 s longer than normal value • All tests results should comply with the above criteria. No continuing supportive care was received.
Interventions	CAR-CD19 T-cells • Initial dose: A total of 1 - 10 × 10^7 CAR-CD19 T-cells/kg will be administered by 1 - 3 infusions. Subsequent dose will be based on the subject's response to initial dose. • Other Name: CD19 redirected autologous cells Fludarabine • 30 mg/m^2/day × 4 days Cyclophosphamide • 500 mg/m^2/day × 2 days
Outcomes	Primary outcome measures 1. Study-related adverse events [time frame: 24 weeks] a. Occurrence of study-related adverse events, defined as NCI CTC ≥ grade 3 signs/symptoms, laboratory toxicities and clinical events that are possible, likely or definitely related to study treatment at any time from the infusion until week 24, including infusional toxicity and any toxicity possibly related to the CAR-CD19 T-cells Secondary outcome measures 1. Primary engraftment end point [time frame: 2 years] a. Duration of in vivo survival of CAR-CD19 T-cells is defined as "engraftment". The primary engraftment end point is the # DNA vector copies per mg blood of CAR-CD19 T-cells on week 4 after the first infusion. Q-PCR for CAR-CD19 T vector sequences will also be performed after infusion at 24 hours, weekly x 4, monthly x 6, and every 3 months thereafter until any 2 sequential tests are negative documenting loss of CAR-CD19 T-cells. 2. Anti-tumour responses [time frame: 2 years] a. Describe anti-tumour responses to CAR-CD19 T-cell infusions 3. Overall survival [time frame: 2 years] a. Describe overall survival and cause of death
Notes	Study starting date: October 2016

NCT02933775 *(Continued)*

	Primary completion date: April 2018 Study completion date: January 2020

NCT02976857

Methods	Phase I • Prospective, interventional, single-group, open-label • Study size (according to Clinicaltrials.gov): 15
Participants	**Inclusion criteria** • Histologically diagnosed as DLBCL according to the NCCN non-Hodgkin's lymphoma Clinical Practice Guidelines (3rd edition 2016) • Refractory DLBCL • All subjects must have received adequate prior therapy including anti-CD20 monoclonal antibody (unless tumour is CD20-negative) and an anthracycline-containing chemotherapy regimen. The standardised treatment regimens reference to NCCN non-Hodgkin lymphoma Clinical Practice Guidelines (2016 version 3) • At least one measurable lesion per revised IWG response criteria (the longest diameter of the tumour ≥ 1.5 cm) • Age 18-70 years old, male or female • Expected survival ≥ 12 weeks • ECOG score 0-1 • Subject's left ventricular ejection fraction (LVEF) is ≥ 50% and no evidence of pericardial effusion as determined by an ECHO • At least 4 weeks from receiving previous treatment (radiotherapy, chemotherapy, monoclonal antibody therapy or other treatments) • No contraindications of peripheral blood apheresis • Female subjects in childbearing age, their serum or urine pregnancy test must be negative, and must agree to take effective contraceptive measures during the trial measures • Volunteered to participate in this study and signed informed consent
Interventions	C-CAR011 • Other Name: CAR-CD19
Outcomes	<u>Primary outcome measures</u> 1. Dose-limiting toxicity (DLT) [time frame: 28 days] a. Non-haematological dose-limiting toxicities was any toxicity of grade 3 or higher occurring within 28 days of C-CAR011 infusion judged possibly related to the treatment regimen.The following toxicities were not considered dose-limiting toxicities: tumour lysis syndrome, abnormal electrolytes responding to supplementation, hypoalbuminaemia, liver dysfunction resolving to ≤ grade 2 within 14 days, transient (< 72 hours) grade 4 hepatic enzyme abnormality, and grade 3 or 4 fever or neutropenic fever <u>Secondary outcome measures</u> 1. Overall response rate [time frame: 4 and 12 weeks] a. Overall response rate (ORR) = complete response (CR) rate + partial response (PR) rate, ORR will be assessed at weeks 4 and weeks 12 according to International Working Group (IWG) revised criteria

NCT02976857 *(Continued)*

2. Disease control rate [time frame: 12 weeks]
   a. Disease control rate (DCR) = complete response (CR) rate + partial response (PR) rate + stable disease (SD) rate; DCR will be assessed at weeks 12 according to International Working Group (IWG) revised criteria.

Notes	Study starting date: December 2016 Primary completion date: September 11, 2018 Study completion date: January 9, 2019

NCT03097770

Methods	Phase I/II • Prospective, interventional, single-group, open-label • Study size (according to Clinicaltrials.gov): 100

Participants	**Inclusion criteria**
	
	• Age ≥ 18 and ≤ 70 years
	• Performance status (ECOG) between 0 and 2
	• Histologically confirmed CD20+ and/or CD19+ B-cell non-Hodgkin lymphoma (NHL), including the following types defined by WHO 2008:
	  * DLBCL not otherwise specified, DLBCL associated with chronic inflammation, and Epstein-Barr virus (EBV)+ DLBCL in the elderly
	  * Primary mediastinal (thymic) large B-cell lymphoma (PMBCL). The mediastinal mass had to have an axial diameter < 5 cm or extranodal lesion size < 3 cm. Patients with large lesions (≥ 5 cm) were enrolled in our other clinical trial (NCT0334662).
	  * Transformed FL (tFL)
	  * FL
	  * Some indolent lymphomas including MCL and chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)
	• Refractory disease or relapsed after treatment with ≥ 2 lines of chemotherapy including rituximab and anthracycline and either having failed autologous HSCT or being ineligible for or not consenting to autologous HSCT
	  * Chemotherapy-refractory disease defined as meeting one or more of the following criteria:
	  ☐ No response to first-line therapy (primary refractory disease)
	  ☐ No response to second-line or later therapy
	  ☐ PD as the best response to the most recent therapy regimen
	  ☐ Stable disease (SD) as the best response after at least 2 cycles of the most recent line of therapy with a SD duration of no longer than 6 months from the last dose of therapy
	  * Failure following autologous HSCT was defined as follows:
	  ☐ PD or relapsed disease ≤ 12 months after ASCT (requires biopsy-proven recurrence in relapsed subjects)
	  ☐ No response or relapse after salvage therapy is given post-ASCT
	• PD or relapse ≥ 3 months after treatment with a targeted CD19 therapy, including CD19-CAR T-cells or anti-CD19/anti-CD3
	• Successful leukapheresis assessment and pre-culture of T-cells
	• Life expectancy > 3 months

NCT03097770 *(Continued)*

- Adequate organ function:
  - Creatinine < 1.6 mg/dL (140 µmol/L) or creatinine clearance ≥ 60 mL/min
  - ALT/AST < 3 × upper limit of the normal range
  - Bilirubin < 2.0 mg/dL unless the subject had Gilbert's Syndrome (< 3.0 mg/dL)
  - Minimum level of pulmonary reserve defined as ≤ grade 1 dyspnoea and pulse oxygenation > 91% with room air. No clinically significant pleural effusion.
  - Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings
- An adequate bone marrow reserve defined as:
  - Absolute neutrophil count (ANC) > 1,000/mm^3
  - Absolute lymphocyte count (ALC) ≥ 300/mm^3
  - Platelet count ≥ 50,000/mm^3
  - Haemoglobin > 7.0 mg/dL
- Measurable or assessable disease according to the "IWG Response Criteria for Malignant Lymphoma" (Cheson 2007). Patients in CR with no evidence of disease were not eligible.
- Informed consent/assent requiring that all patients have the ability to understand and the willingness to provide written informed consent

Interventions	Anti-CD19/20-CAR vector-transduced T-cells • genetically engineered lymphocyte therapy • Other name: genetically engineered lymphocyte therapy
Outcomes	Primary outcome measures: 1. Occurrence of study-related adverse events [time frame: until week 24] a. Defined as ≥ grade 3 signs/symptoms, laboratory toxicities, and clinical events that are possibly, likely, or definitely related to study treatment Secondary outcome measures: 1. Anti-tumour responses to TanCART19/20 cell infusions [time frame: up to 96 weeks] Other outcome measures: 1. In vivo existence of TanCART19/20 [time frame: 2 years]
Notes	Study starting date: April 1, 2017 Primary completion date: May 10, 2019 Study completion date: January 31, 2020

NCT03598179

Methods	Phase II • Prospective, interventional, single-group, open-label • Study size (according to Clinicaltrials.gov): 10
Participants	**Inclusion criteria** • Age ≥ 18 years, male and female • Confirmed as CD19-positive B-cell lymphoma/leukaemia by immunohistochemistry or flow cytometry • No effective treatment • Must have a measurable or evaluable disease at the time of enrolment

NCT03598179 *(Continued)*

	• Adequate organ system function including:
	  * ALT/AST < 3 upper limit of normal; total bilirubin < 2.5 upper limit of normal
	  * Creatinine < 2 upper limit of normal
	  * Oxygen saturation ≥ 95%
	  * Left ventricular ejection fraction ≥ 40%
	  * Number of neutrophils ≥ 0.75 × 10^9/L, number of platelets ≥ 50 × 10^9/L
	• At least 4 weeks from receiving previous treatment (radiotherapy, chemotherapy, monoclonal antibody therapy or other treatments)
	• No contraindications of peripheral blood apheresis
	• Female subjects in childbearing age, their serum or urine pregnancy test must be negative. All patients must agree to take effective contraceptive measures during the trial measures.
	• ECOG score 0-2, expected survival ≥ 12 weeks

Interventions	CAR T-cells
	• Dose CAR+ cells/kg:
	  * B-cell lymphoma: 4 x 10^6
	  * Acute lymphocytic leukaemia: 2 x 10^6
	  * Chronic lymphocytic leukaemia: 10 x 10^6

Outcomes	Primary outcome measures
	1. Overall response rate [time frame: 12 weeks]
	  a. overall response rate (ORR) = complete response rate + partial response rate
	2. Overall survival [time frame: 6 months, 1 year, 2 years]
	  a. From the time of enrolment to death from any cause or date of the last follow-up visit
	3. Progression-free survival [time frame: 12 weeks, 6 months, 1 year, 2 years]
	  a. Time from enrolment to disease progression, death from any cause or date of the last follow-up visit
	4. Event-free survival [time frame: 12 weeks, 6 months, 1 year, 2 years]
	  a. Time from enrolment to any events or date of the last follow-up visit
	Secondary outcome measures
	1. Dose-limiting toxicity (DLT) [time frame: 28 days]
	  a. Non-haematological dose-limiting toxicities: any toxicity of grade 3 or higher occurring within 28 days of XLCART001 infusion judged possibly related to the treatment regimen
	  b. The following toxicities were not considered dose-limiting toxicities: tumour lysis syndrome, abnormal electrolytes responding to supplementation, hypoalbuminaemia, liver dysfunction resolving to ≤ grade 2 within 14 days, transient (< 72 hours) grade 4 hepatic enzyme abnormality, and grade 3 or 4 fever or neutropenic fever.
	2. Number of CAR T-cells [time frame: day 1, day 4, day 7, day 10, day 14, day 21, day 28, 8 weeks, 12 weeks, 6 months, 1 year, 2 years]
	  a. The number of CAR T-cells detected by flow cytometry and copy number of CAR T-cells tested by polymerase chain reaction
	3. Duration of CAR T-cells [time frame: day 1, day 4, day 7, day 10, day 14, day 21, day 28, 8 weeks, 12 weeks, 6 months, 1 year, 2 years]
	  a. The duration of CAR T-cells detected by flow cytometry and copy number of CAR T-cells tested by polymerase chain reaction

Notes	Study start date: June 1, 2018 Primary completion date: December 30, 2019 Study completion date: July 1, 2020

Alb: albumin

ALC: absolute lymphocyte count
ALT: alanine aminotransferase
ANC: absolute neutrophil count
ASCT: autologous stem-cell transplantation
AST: aspartate aminotransferase
BL: baseline
CAR-T: chimeric antigen receptor T
CG: Cockcroft-Gault
ChiCTR: Chinese Clinical trial Registry
CLL: chronic lymphocytic leukaemia
CR: complete response
CTC: common terminology critera
CTCAE: CTCAE: Common Terminology Criteria for Adverse Events
DCR: disease control rate
DLBCL: diffuse large B-cell lymphoma
DLT: dose-limiting toxicity
DNA: deoxyribonucleic acid
EBV: Epstein-Barr virus
ECG: electrocardiogram
ECHO: echocardiogram
ECOG: Eastern Cooperative Oncology Group
FL: follicular lymphoma
HACA: human anti-human mouse chimeric antibody
HCL: hairy cell leukaemia
HSCT: hematopoietic stem-cell transplantation
INR: international normalized ratio
IWG: International Working Group
KPS: Karnofsky performance status
LPL: lymphoplasmacytic lymphoma
LVEF: left ventricular ejection fraction
LY: lymphocyte
MCL: mantle cell lymphoma
MZL: marginal zone lymphoma
NCCN: National Comprehensive Cancer Network
NCI: National Cancer Institute
NHL: Non-Hodgkin lymphoma
NR: not reported
ORR: overall response rate
PD: progressive disease
PLT: platelets
PMBCL: primary mediastinal B-cell lymphoma
PR: partial response
PT: prothrombin time
Q-PCR: real-time quantitative polymerase chain reaction
SD: stable disease
SLL: small lymphocytic lymphoma
tFL: transformed follicular lyphoma
WBC: white blood cell
WHO: World Health Organization

Characteristics of ongoing studies *[ordered by study ID]*

ALEXANDER

Study name	CD19/22 CAR T-cells (AUTO3) for the treatment of diffuse large B-cell lymphoma and a single arm, open-label, multi-centre, phase I/II study evaluating the safety and clinical activity of AUTO3, a CAR T-cell treatment targeting CD19 and CD22 with anti PD-1 antibody in patients with DLBCL
Methods	Phase I/II • Interventional, prospective, single-arm, open-label • Study size (according to Clinicaltrials.gov): 120
Participants	**Inclusion Criteria:** • Male or female, aged ≥ 18 years • Willing and able to give written, informed consent • Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1 • Histologically confirmed DLBCL and large B-cell lymphoma (at last relapse) subsets, including: * Phase I and phase II cohort 1: ☐ DLBCL, not otherwise specified (NOS), per World Health Organisation classification and DLBCL with MYC and BCL2 and/or BCL6 rearrangements (double/triple hit) ☐ Transformed DLBCL from FL ☐ High-grade B-cell lymphoma with MYC expression (excluding Burkitt's lymphoma) * Phase I and phase II cohort 2: ☐ Transformed DLBCL from other indolent lymphomas (excluding Richter's transformation) ☐ Primary mediastinal large B-cell lymphoma • Chemotherapy-refractory disease, defined as one or more of the following: * Stable disease (≤ 12 months) or progressive disease as best response to most recent chemotherapy containing regimen. Refractory disease after frontline chemo-immunotherapy is allowed * Disease progression or recurrence in ≤ 12 months of prior autologous haematopoietic stem-cell transplantation (ASCT) • Relapse after ≥ two lines of therapy or after ASCT. At a minimum: * Patients must have received rituximab or another anti-CD20 monoclonal antibody (unless investigator determines that tumour is CD20-negative) and an anthracycline-containing chemotherapy regimen * Patients must have either failed ASCT, or be ineligible for or not consenting to ASCT * Patients with transformed DLBCL must have received at least one line of therapy after transformation to DLBCL • PET-positive disease per Lugano classification • For females of childbearing potential, a negative serum or urine pregnancy test must be documented at screening, prior to pre-conditioning and confirmed before receiving the first dose of study treatment. • For females who are not postmenopausal or surgically sterile, highly effective methods of contraception must be used during the treatment period and for at least 12 months after the last dose of study treatment. • For males, it must be agreed that two acceptable methods of contraception are used. • Adequate renal, hepatic, pulmonary, and cardiac function defined as: * Creatinine clearance ≥ 40 cc/min * Serum alanine aminotransferase/aspartate aminotransferase ≤ 2.5 x ULN * Total bilirubin ≤ 1.5 x ULN, except in subjects with Gilbert's syndrome * LVEF ≥ 50% (by ECHO or MUGA) unless the institutional lower limit of normal is lower * Baseline oxygen saturation > 92% on room air and ≤ grade 1 dyspnoea

ALEXANDER *(Continued)*

	• Patient has adequate BM function without requiring ongoing blood product or granulocyte-colony stimulating factor support and meets the following criteria: * Absolute neutrophil count ≥ 1.0 × 109/L * Absolute lymphocyte count ≥ 0.3 × 109/L (at enrolment and prior to leukapheresis) * Haemoglobin ≥ 80 g/L * Platelets ≥ 75 × 109/L • No contraindications for leukapheresis
Interventions	AUTO3 • Following preconditioning with chemotherapy (cyclophosphamide and fludarabine) patients will be treated with doses from 50 x 10^6 to 900 x 10^6 CD19/CD22 Chimeric Antigen Receptor (CAR) positive T-cells followed by limited duration of anti-PD1 antibody (pembrolizumab)
Outcomes	Primary outcome measures: 1. Phase I escalation - safety (incidence of grade 3-5 toxicities) and identification of recommended phase II dose and schedule. [time frame: within 75 days of AUTO3 infusion] 2. Phase I expansion - safety (incidence of grade 3-5 toxicities) in the outpatient/ambulatory care setting [time frame: within 75 days of AUTO3 infusion] 3. Phase II - overall response rate as per Lugano criteria [time frame: Up to 2 years] Secondary outcome measures: 1. Feasibility of generating AUTO3: number of patients' cells successfully manufactured as a proportion of the number of patients undergoing leukapheresis. [time frame: up to 8 weeks post leukapheresis] 2. Complete response rate, as per Lugano criteria. [time frame: up to 2 years] 3. Duration of response (DOR) [time frame: up to 2 years] 4. Progression-free survival (PFS) [time frame: up to 2 years] 5. Overall survival (OS) [time frame: up to 2 years]
Starting date	Study starting date: September 5, 2017 Primary completion date: March 2021 Study completion date: March 2021
Contact information	Contact: Autolus Limited
Notes	NCT03287817 https://ClinicalTrials.gov/show/NCT03287817 Current clinicaltrials.gov status: Recruiting

BELINDA

Study name	Tisagenlecleucel in adult patients with aggressive B-cell non-Hodgkin lymphoma
Methods	Phase III • Randomised, controlled trial (RCT), open-label, blinded outcome assessment • Study size (according to Clinicaltrials.gov): 318
Participants	**Inclusion Criteria:**

BELINDA *(Continued)*

- Histologically confirmed, aggressive B-cell NHL at relapse/progression or PR after front line therapy. Aggressive B-cell NHL is heretofore defined by the following list of subtypes:
  * DLBCL, NOS
  * FL grade 3B
  * Primary mediastinal large B-cell lymphoma (PMBCL)
  * T cell rich/histiocyte rich large B-cell lymphoma (T/HRBCL)
  * DLBCL associated with chronic inflammation
  * Intravascular large B-cell lymphoma
  * ALK+ large B-cell lymphoma
  * B-cell lymphoma, unclassifiable, (with features intermediate between DLBCL and classical Hodgkin's Lymphoma (HL))
  * High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements
  * High-grade B-cell lymphoma, NOS
  * HHV8+ DLBCL, NOS
  * DLBCL transforming from follicular lymphoma
  * DLBCL transforming from marginal zone lymphoma
  * DLBCL, leg type
- Relapse or progression within 365 days from last dose of anti CD20 antibody and anthracycline containing first line immunochemotherapy or refractory (have not achieved a CR).
- Patient is considered eligible for autologous HSCT as per local investigator assessment. Note: Intention to transplant and type of high dose chemotherapy (HDCT) regimen will be documented at the time of study entry
- Disease that is both active on PET scan (defined as 5-Deauville score point-scale of 4 or 5) and measurable on CT scan, defined as:
  * Nodal lesions >15 mm in the long axis, regardless of the length of the short axis, and/or
  * Extranodal lesions (outside lymph node or nodal mass, but including liver and spleen) >10 mm in long AND short axis
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Adequate organ function:
  * Renal function defined as:
    - ☐ Serum creatinine of ≤1.5 x upper limit of normal (ULN), OR estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2
    - ☐ Hepatic function defined as:
    - ☐ Alanine Transaminase (ALT) and Aspartate Transiminase (AST) ≤ 5 × ULN
    - ☐ Total bilirubin ≤ 1.5 x ULN with the exception of patients with Gilbert syndrome who may be included if their total bilirubin is ≤ 3.0 × ULN and direct bilirubin ≤ 1.5 × ULN
  * Haematologic function (regardless of transfusions) defined as:
    - ☐ Absolute neutrophil count (ANC) > 1000/mm^3
    - ☐ Absolute lymphocyte count (ALC) > 300/mm^3 OR Absolute number of CD3+ T cells > 150/mm^3 (only for patients with non-historical apheresis)
    - ☐ Platelets ≥ 50000/mm^3
    - ☐ Hemoglobin >8.0 g/dl
  * Adequate pulmonary function defined as:
    - ☐ No or mild dyspnoea (≤ grade 1)
    - ☐ Oxygen saturation measured by pulse oximetry > 90% on room air
    - ☐ Forced expiratory volume in 1 s (FEV1) ≥ 50% and/or carbon monoxide diffusion test (DLCO) ≥ 50% of predicted level
- Must have a leukapheresis material of non-mobilized cells available for manufacturing.

Interventions	Tisagenlecleucel after optional bridging and lymphodepleting chemotherapy Platinum-based immunochemotherapy followed in responding patients with high dose chemotherapy and autologous haematopoietic stem-cell transplant (HSCT)
Outcomes	Primary outcome measures:

BELINDA *(Continued)*

1. Event-free survival (EFS) [time frame: 5 years]
   a. Defined as the time from the date of randomisation to the date of the first documented disease progression or stable disease at or after the week 12 (+/- 1 week) assessment, as assessed by Blinded Independent Review Committee (BIRC) per Lugano criteria, or death due to any cause, at any time.

Secondary outcome measures:

1. EFS as assessed by local investigator [time frame: 5 years]
2. Overall survival (OS) [time frame: 5 years]
   a. Overall survival (OS) is defined as the time from date of randomisation to date of death due to any cause
3. Overall response rate (ORR) [time frame: 5 years]
   a. Overall response rate (ORR) as per the Lugano criteria as per BIRC review and local investigator assessment
4. Duration of response (DOR) [time frame: 5 years]
   a. Duration of response: time from the date of first documented response of CR or PR to the date of first documented progression (SD or PD at or after the week 12 assessment will be considered progression) or death due to aggressive B-cell NHL. DOR will be summarized by BIRC and local response
5. Time to response (TTR) [time frame: 5 years]
   a. Time from the date of randomisation to the date of a patient's first achieved a response of CR or PR on or after the week 12 assessment
6. SF-36v2 [time frame: 5 years]
   a. Time to definitive deterioration in SF-36v2
7. FACT-Lym [time frame: 5 years]
   a. Time to definitive deterioration in FACT-Lym
8. EQ-VAS [time frame: 5 years]
   a. Time to definitive deterioration in EQ-VAS
9. Tisagenlecleucel transgene concentrations [time frame: 5 years]
   a. qPCR will be used to measure tisagenlecleucel transgene concentrations in peripheral blood and bone marrow
10. Tisagenlecleucel immunogenicity (humoral and cellular) [time frame: 5 years]
    a. Pre-existing and treatment related immunogenicity (humoral and cellular) of tisagenlecleucel will be characterized
11. Presence of replication competent lentivirus (RCL) [time frame: 5 years]
    a. The presence of RCL will be assessed by VSV-qPCR in patients receiving tisagenlecleucel

Starting date	Study starting date: May 6, 2019 Primary completion date: October 3, 2025 Study completion date: October 3, 2025
Contact information	Contact: Novartis Pharmaceuticals
Notes	NCT03570892 https://clinicaltrials.gov/show/NCT03570892 Current clinicaltrials.gov status: Recruiting

BIANCA

Study name	Phase II open label trial to determine safety & efficacy of Tisagenlecleucel in pediatric non-hodgkin lymphoma patients (BIANCA)

BIANCA *(Continued)*

Methods	Phase II • Prospective, interventional, single-group, open-label • Study size (according to Clinicaltrials.gov): 35
Participants	**Inclusion Criteria:** • Histologically confirmed paediatric mature B-cell non-Hodgkin lymphoma (B-cell NHL) including the following subtypes; Burkitt lymphoma/ Burkitt leukaemia (BL), diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), gray zone lymphoma (GZL), and follicular lymphoma (FL) Note: Patients with B-cell NHL associated with Nijmegen breakage syndrome will be allowed. • Patients <25 years of age and weighing at least 6 kg at the time of screening • Patients who have relapsed after one or more prior therapies (can include allogeneic and autologous haematopoietic stem-cell transplant) or are primary refractory (have not achieved a CR or PR after the first line of therapy) • Measurable disease by radiological criteria in all patients at the time of screening. Patients with Burkitt leukaemia who don't meet radiological criteria must have bone marrow involvement of > 25% by local assessment of bone marrow aspirate and/or biopsy. • Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status ≥ 60. • Adequate bone marrow reserve without transfusions (transfusion > 2 weeks prior to laboratory assessment is allowed) defined as: * Absolute neutrophil count (ANC) > 1000/mm3 * Platelets ≥ 50000//mm3 * Hemoglobin ≥ 8.0 g/dl • Adequate organ function defined as: * a serum creatinine (sCR) based on gender/age as follows: Maximum Serum Creatinine (mg/dL) Age Male Female ☐ 1 to < 2 years 0.6 0.6; 2 to < 6 years 0.8 0.8 ; 6 to < 10 years 1.0 1.0; 10 to < 13 years 1.2 1.2; 13 to < 16 years 1.5 1.4 ; ≥ 16 years 1.7 1.4 * Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5 times the upper limit of normal (ULN) for age * Total bilirubin < 2 mg/dL (for Gilbert's Syndrome patients total bilirubin < 4 mg/dL) * Adequate pulmonary function ☐ Oxygen saturation of > 91% on room air ☐ No or mild dyspnoea (≤ grade 1) • Must have a leukapheresis material of non-mobilized cells accepted for manufacturing.
Interventions	Tisagenlecleucel • Single intravenous infusion
Outcomes	Primary Outcome Measures: 1. Overall response rate (ORR) [time frame: 3 months post-tisagenlecleucel infusion or discontinued earlier] a. The overall response rate (ORR) is defined as the proportion of subjects with a best overall disease response of CR or PR, where the best overall disease response is defined as the best disease response recorded from tisagenlecleucel infusion until progressive disease or start of new anticancer therapy, whichever comes first. Secondary Outcome Measures: 1. Duration of response (DOR) [time frame: Through study completion, approximately 4 years] a. Duration of response (DOR) is defined as the time from the date of first documented disease response (CR or PR) as determined by local investigator assessments to the date of first documented progression or death due to underlying cancer.

BIANCA *(Continued)*

2. Event-free survival (EFS) [time frame: Through study completion, approximately 4 years]
   a. Event-free survival (EFS) is defined as the time from date of first tisagenlecleucel infusion to the earliest date of death from any cause, disease progression as determined by local investigator assessments, or starting new anticancer therapy for underlying cancer, excluding HSCT.
3. Relapse-free survival (RFS) [time frame: Through study completion, approximately 4 years]
   a. Relapse-free survival (RFS) is defined as the time from the date of first documented disease response (CR or PR) as determined by local investigator assessments to the date of first documented disease progression or death due to any cause.
4. Progression-free survival (PFS) [time frame: Through study completion, approximately 4 years]
   a. Progression-free survival (PFS) is defined as the time from the date of first tisagenlecleucel infusion to the date of first documented disease progression as determined by local investigator assessments or death due to any cause.
5. Overall survival (OS) [time frame: Through study completion, approximately 4 years]
   a. Overall survival (OS) is defined as the time from date of first tisagenlecleucel infusion to the date of death due to any cause.
6. Cmax [time frame: Through study completion, approximately 4 years]
   a. The maximum (peak) transgene level (copies/µg) observed in peripheral blood or other body fluid after single-dose administration
7. Tmax [time frame: Through study completion, approximately 4 years]
   a. The time to reach maximum (peak) transgene level (days) in peripheral blood or other body fluid after single-dose administration
8. AUCs [time frame: Through study completion, approximately 4 years]
   a. Area under the concentration-time curve (AUCs) from the time course of transgene levels in peripheral blood following tisagenlecleucel infusion (days*copies/µg)
9. Clast [time frame: Through study completion, approximately 4 years]
   a. The last observed quantifiable transgene level in peripheral blood (copies/µg)
10. Tlast [time frame: Through study completion, approximately 4 years]
    a. The time of last observed quantifiable transgene level in peripheral blood (days)
11. Levels of pre-existing and treatment induced humoral immunogenicity and cellular immunogenicity against tisagenlecleucel cellular kinetics, safety and efficacy [time frame: Until disease progression or through study completion, approximately 4 years]
    a. The humoral immunogenicity assay measures the antibody titers specific to tisagenlecleucel prior to and following infusion by flow cytometry. The impact of humoral and cellular immunogenicity on cellular kinetics, safety and disease response will be explored.
12. Subjects that proceed to stem-cell transplant (SCT) after tisagenlecleucel infusion until end of study (EOS) [time frame: Through study completion, approximately 4 years]
    a. Percentage of subjects who proceed to transplant post-tisagenlecleucel therapy until EOS
13. Levels of cytokines for early prediction of cytokine release syndrome (CRS) utilizing clinical and biomarker data [time frame: Through study completion, approximately 4 years]
    a. Retrospective assessment of potential CRS predictive models considering also data from other CTL019 trials. Soluble immune and inflammatory cytokines (e.g.: IL-10, interferon gamma, IL-6, CRP, and ferritin) will be measured. These levels may also be summarized by severity of CRS and potentially graphed using strip plots.

Starting date	Study starting date: February 15, 2019 Primary completion date: March 31, 2021 Study completion date: February 15, 2023
Contact information	Contact: Novartis Pharmaceuticals
Notes	NCT03610724 https://clinicaltrials.gov/ct2/show/NCT03610724 Current clinicaltrials.gov status: Recruiting

ChiCTR1800017686 2018

Study name	Anti-CD19 CAR-T cell therapy for relapsed and refractory CD19-positive lymphoma
Methods	Phase I • Interventional, prospective, single-arm, open-label • Study size (according to ChiCTR): 15

Participants	**Inclusion Criteria:**
	• Aged 18 to 70 years old male and female
	• Expected survival > 12 weeks
	• Clinical performance status of ECOG score 0-1
	• Pathology demonstrated that CD19-poitive B-cell non-Hodgkin's lymphoma and who meet one of the following conditions:
	  * Relapsed and refractory CD19-positive diffuse large B-cell lymphoma and follicular lymphoma: patients previously received at least first-line and second- line treatment and fail to achieve CR
	  * Disease recurrence after stem-cell transplantation, and at least 1 years after stem-cell transplantation.
	• Accessible to intravenous injection, and no white blood cell collection contraindications
	• At least 1 measurable tumour foci according to the IWG treatment response criteria
	• Patients who meet the following conditions:
	  * Creatinine < 2.5 mmol/L
	  * Cardiac ejection fraction > 50%, no pericardial effusion and no pleural effusion (ECHO examination); 3) Baseline oxygen saturation > 92%
	  * Total bilirubin ≤ 1.5xULN; ALT/AST ≤ 2.5x normal
	• Able to understand and sign the informed consent document

Interventions	anti-CD19 CAR T-cells, intravenous inoculation
Outcomes	Primary Outcome Measures: 1. Safety measured by occurrence of study related adverse effects defined by NCI CTCAE 4.0 2. Clinical performance status of ECOG score Secondary Outcome Measures: 1. PK parameters: Duration of CAR-positive T-cells in circulation, including the highest concentration of amplification (Cmax), the time to reach the highest concentration (Tmax) and the area under the curve for 90 days (AUC90d) 2. PD parameters: The clearance of CD19-positive B-cells in peripheral blood at the detected time points 3. Overall remission rate including complete response and partial response defined by the standard response criteria for malignant lymphoma
Starting date	Study starting date: Unclear Primary completion date: Unclear Study completion date: Unclear
Contact information	Study leader: Peng Liu; Applicant: Hongliang Fang; HRAIN Biotechnology Co., Ltd.
Notes	http://www.chictr.org.cn/showproj.aspx?proj=29929

ChiCTR1800017686 2018 *(Continued)*

	Current clinicaltrials.gov status: NA

COBALT

Study name	Evaluation of CAR19 T-cells as an optimal bridge to allogeneic transplantation
Methods	Phase I • Prospective, interventional, single-group, open-label • Study size (according to Clinicaltrials.gov): 12
Participants	**Inclusion Criteria:** • Age 16-65 years • Confirmed diagnosis of CD19+ DLBCL • Primary resistant or relapsed disease failing to achieve metabolic complete response (CR) to 1st line salvage, or relapse post autograft failing to achieve metabolic CR following a single further cycle of salvage • Potential allogeneic transplant candidate • Agreement to have a pregnancy test, use adequate contraception for 12 months post-CAR19 T-cell infusion • Karnofsky performance status > 60 • Written informed consent

Interventions	Leukapheresis
	• Patients will undergo leukapheresis prior to pre-conditioning chemotherapy to provide the immune cells required to produce the therapeutic product.
	Cyclophosphamide
	• Patients will receive a standard pre-conditioning regime with cyclophosphamide 60mg/kg/day IV over 1 hour for 2 days (day-7 and day-6).
	Fludarabine
	• Fludarabine 25mg/m^2/day IV over 15/30 minutes for 5 days (Day-5 to day-1).
	CAR19 T-Cells
	• The CAR19 T-cells are to be administered on day 0 at the dose specified by the Cancer Trials Centre (CTC) at the time of registration.
	• Three dose cohorts are planned:
	  * Dose Level 1: $2x10^5$ CAR19 T-cells/kg
	  * Dose Level 2: $1x10^6$ CAR19 T-cells/kg
	  * Dose Level 3: $5x10^6$ CAR19 T-cells/kg
	• Other name: CD19 specific chimeric antigen receptor T-cells

Outcomes	Primary outcome measures:
	1. Feasibility of adequate leukapheresis collection and generation of CAR19 T-cells. [time frame: 1 month]
	  a. The number of CAR19 T-cells successfully manufactured as a fraction of the number of patients undergoing leukapheresis (all patients registered)
	2. Toxicity evaluation following CAR19 T-cell administration. [time frame: 1 year]
	  a. Toxicity will be examined for each patient receiving CAR19 T-cells, using the maximum grade for each toxicity type, all summarized as number of patients with adverse events

COBALT *(Continued)*

3. Efficacy of CAR19 T-cells. [time frame: 1 year]
   a. Efficacy will be defined as the number of patients that meet the clinical complete responders criteria

Secondary outcome measures:

1. CAR19 T-cell engraftment [time frame: 1 year]
   a. Engraftment, expansion and persistence of CAR19 T-cells. Detection of any level of CAR19 expression in circulating T cells (i.e. PBMC) by quantitative polymerase chain reaction (qPCR) and flow cytometry following infusion
2. B-cell compartment [time frame: 1 year]
   a. Depletion of B-cell compartment. The percentage reduction from baseline. Absolute B-cell numbers measured by flow of PBMC (cells/uL).
3. Cytokine profile [time frame: 1 year]
   a. Timing and magnitude of cytokine release. Data on timing (kinetic of change) as the mean (or median) amount of cytokine (pg/ml) over a number of days post-infusion. Using the individual patient data, the mean (or median) time to peak value can be obtained.
   b. Magnitude - kinetic and peak of cytokine levels, notably Tumour Necrosis Factor-alpha (TNF-a), Interleukin- 6 (IL-6) and Interferon-gamma (IFN-g) (pg/ml), can be plotted for each patient, as means (or medians)
4. Clinical complete response [time frame: 1 month]
   a. Clinical response evaluated using standard PET-CT criteria at day 28 compared to baseline scan. Proportion of patients with complete response will be calculated.
5. Eligibility to allogeneic transplantation [time frame: 1-3 years]
   a. Number of patients proceeding to allogeneic transplantation out of all patients registered to the trial, and also only for those who received CAR19 T-cells.

Starting date	Study starting date: June 2016 Primary completion date: December 2018 Study completion date: December 2020
Contact information	Study Chair: Karl Peggs; University College, London
Notes	NCT02431988 https://clinicaltrials.gov/ct2/show/NCT02431988 Current clinicaltrials.gov status: Recruiting

ENABLE

Study name	ENABLE (Engaging toll-like receptor signalling for B-cell lymphoma chimeric antigen receptor therapy) (ENABLE)
Methods	Phase I • Interventional, prospective, single-arm, open-label • Study size (according to Clinicaltrials.gov): 12
Participants	**Inclusion Criteria:** • Age 16 to 75 years (inclusive) • Biopsy-proven relapsed or treatment refractory aggressive B-cell non-Hodgkin lymphoma of the following subtypes per World Health Organisation (WHO) classification: DLBCL and its variants, PMBCL, tFL, FL, MCL • Requirement for treatment in the opinion of the investigator

ENABLE *(Continued)*

- No other curative treatments available, or not suitable due to patient or disease characteristics or lack of stem-cell donor
- Malignancy documented to express CD19 based on flow cytometric or immunohistochemical staining
- Provision of written informed consent for this study
- Life-expectancy from non-lymphoma related causes of > 12 months
- European Cooperative Oncology Group (ECOG) performance status of 0 to 2 inclusive
- Adequate haematologic function, defined by neutrophils ≥ 1.0×10^9/L and platelets ≥ 50×10^9/L
- No serious cardiac, pulmonary, hepatic or renal disease.
  * Serum bilirubin < 2.5 times upper limit of normal (ULN)
  * Estimated creatinine clearance (CrCl) ≥ 50 mL/min using the modified Cockroft Gault estimation or as assessed by direct measurement
  * Cardiac ejection fraction ≥ 50% as determined by echocardiogram or MUGA scan
  * Oxygen saturations > 92% on room air
  * Diffuse capacity of the lungs for carbon monoxide (DLCO) or carbon monoxide transfer coefficient (KCO), forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are all ≥ 50% of predicted by spirometry after correcting for haemoglobin and/or volume on lung function testing

Interventions	WZTL002-1 (1928T2z CAR T-cells) • WZTL-002 comprises autologous third-generation anti-CD19 chimeric antigen receptor T-cells (termed 1928T2z). The chimeric antigen receptor in WZTL-002 incorporates the FMC63 anti-CD19 soluble chain variable fragment extracellularly, and portions of both CD28 and the Toll/interleukin-1 receptor (TIR) domain of Toll Like Receptor 2 (TLR2) as intracellular co-stimulatory domains, alongside CD3ζ. WZTL-002 (autologous 1928T2z CAR T-cells) will be administered on D0 as a single IV infusion, following lymphodepleting chemotherapy Cyclophosphamide and Fludarabine lymphodepleting chemotherapy • Cyclophosphamide 500 mg/m^2 IV on days -5 to -3, inclusive. Fludarabine 30 mg/m^2 IV on days -5 to -3, inclusive
Outcomes	<u>Primary outcome measures</u> 1. Number and severity of adverse events assessed by CTCAE v5.0, except for Cytokine Release Syndrome and Immune Effector Cell-Associated Neurotoxicity Syndrome, which will be assessed by ASTCT consensus grading criteria [time frame: 3 months after administration] a. Determine the safety profile of WZTL-002, anti-CD19 CAR T-cells by measuring frequency and severity of adverse events <u>Secondary outcome measures</u> 1. Feasibility of Manufacture [time frame: 3 months after administration] a. To investigate the feasibility of manufacture and treatment with WZTL-002, as determined by the proportion of enrolled participants undergoing at least one study leukapheresis procedure that receive WZTL-002 2. Overall Response Rate [time frame: 3 months after administration] a. To estimate the overall response rate (ORR) as determined by complete response (CR) plus partial response (PR) 3 months after WZTL-002 administration 3. Cumulative CR rate [time frame: 6 months after administration] a. To determine the cumulative CR rate 6 months after WZTL-002 administration 4. Relapse-free survival [time frame: 24 months after administration] a. To estimate the relapse-free survival (RFS) for subjects treated with WZTL-002 over a period of 24 months after WZTL-002 administration 5. Overall survival [time frame: 24 months after administration] a. To estimate the overall survival (OS) distribution for subjects treated with WZTL-002 over a period of 24 months after WZTL-002 administration

ENABLE *(Continued)*

	6. Recommended dose [time frame: 3 months after administration] a. To determine the recommended phase 2 dose of WZTL-002 for treatment of r/r B-NHL
Starting date	Study starting date: October 19, 2019 Primary completion date: September 2021 Study completion date: August 2026
Contact information	Contact: Robert Weinkove, MBBS, PhD Contact: Tess Ostapowicz, BA
Notes	

Eudract_2017_002088-16-IT

Study name	CD19-CART01 in pediatric patients affected by relapsed/refractory CD19+ acute lymphoblastic leukemia and non hodgkin lymphoma
Methods	Phase I/II • Interventional, prospective, single-arm, open-label • Study size: 28
Participants	**Inclusion Criteria:** <u>Procurement eligibility inclusion criteria</u> The patient must meet the following eligibility inclusion criteria at the time of procurement. • Diagnosis of CD19 expressing B acute lymphoblastic leukaemia (ALL) or Non-Hodgkin Lymphoma (NHL) with BM involvement and one of the following: * Patients in 2nd or subsequent relapse, after at least one standard frontline chemotherapy and one salvage regimen, with BM involvement * Relapse after allogeneic HSCT, if at least 100 days post-transplant, if there is no evidence of active GVHD and if the patient is no longer taking immunosuppressive agents for at least 30 days prior to enrolment * MRD > 0.1% after either reinduction therapy or any course of consolidation for relapsed ALL • Age: 6 months – 25 years. • Adequate venous access for apheresis or eligible for appropriate catheter placement, and no other contraindications for leukapheresis • Voluntary informed consent is given. For subjects < 18 year-old their legal guardian must give informed consent. Pediatric subjects will be included in age-appropriate discussion and verbal assent will be obtained for those greater than or equal to 12 years of age, when appropriate • Clinical performance status: Patients > 16 years of age: Karnofsky greater than or equal to 60%; Patients < 16 years of age: Lansky scale greater than or equal to 60% <u>Treatment eligibility patient inclusion criteria</u> The patient must meet the following eligibility inclusion criteria to be enrolled to receive treatment.

Eudract_2017_002088-16-IT *(Continued)*

- Male and female subjects with CD19 expressing B-cell acute lymphoblastic leukaemia (ALL) or Non-Hodgkin Lymphoma (NHL) with BM involvement and one of the following:
  * Patients in 2nd or subsequent relapse, after at least one standard frontline chemotherapy and one salvage regimen, with BM involvement
  * Relapse after allogeneic HSCT, if at least 100 days post-transplant, if there is no evidence of active GVHD and if the patient is no longer taking immunosuppressive agents for at least 30 days prior to enrolment
  * MRD > 0.1% after either reinduction therapy or any course of consolidation for relapsed ALL
- Measurable or evaluable disease at the time of enrolment, which may include any evidence of disease, including MRD detected by flow cytometry, cytogenetics, or polymerase chain reaction (PCR) analysis
- Age: 6 months – 25 years
- Voluntary informed consent is given. For subjects < 18 year-old their legal guardian must give informed consent. Pediatric subjects will be included in age-appropriate discussion and verbal assent will be obtained for those greater than or equal to 12 years of age, when appropriate
- Clinical performance status: Patients > 16 years of age: Karnofsky greater than or equal to 60%; Patients < 16 years of age: Lansky scale greater than or equal to 60%
- Patients of child-bearing or child-fathering potential must be willing to practice birth control from the time of enrolment on this study and for four months after receiving the preparative regimen
- Females of child-bearing potential must have a negative pregnancy test because of the potentially dangerous effects on the fetus

Interventions	CD19-CART01
Outcomes	Primary Outcome Measures (Phase I): 1. To evaluate the safety of the infusion of CD19-CART01 at 3 different escalating doses (0,5 x 10^6, 1,5 x 10^6 and 3,0 x 10^6 cells/kg recipient total body weight of CAR+ T-cells) and establish the dose-limiting toxicity (DLT) of the cellular product. a. DLT will be defined as any of the following that is not pre-existing, due to infection or to underlying malignancy and that may be considered possibly, probably or definitely related to the study cellular products. i. Non-haematologic DLT is any grade 3 or 4 non-haematologic toxicity, non-responsive to AP1903 infusions ii. Haematologic DLT is defined as any grade 4 haematologic toxicity, non-responsive to AP1903 infusions iii. Grade 4 reactions related to infusion iv. Death related to CD19-CART01 or to AP1903 infusions. b. Time point of evaluation: at day 28 post-infusion 2. To determine the recommended dose of CD19-CART01 transduced T-cells, defined as the maximum tolerated dose/recommended dose (MTD/RD), to be evaluated for efficacy in the phase II extension. a. Time point of evaluation: at day 28 post-infusion Primary Outcome Measures (Phase II): 1. To confirm the safety of the approach, using the recommended dose defined during the Phase I portion of the study. a. Time point of evaluation: at day 28 post-infusion 2. To assess the antitumour effect of CD19-CART01 at day 28 post-infusion by determining BM morphological response and MRD. In particular, the primary end-point will be the proportion of patients achieving morphological complete remission (CR) with minimal residual disease (MRD) negativity at day 28. a. Time point of evaluation: at day 28 post-infusion Secondary Outcome Measures:

Eudract_2017_002088-16-IT *(Continued)*

1. To assess the overall response rate (ORR) at day 28, which includes CR, CR with incomplete blood count recovery (CRi), partial response (PR) and stable disease (SD).
   a. Time point of evaluation: at day 28 post-infusion
2. To assess the in vivo persistence and expansion of the infused T-cells in the peripheral blood (PB) and in the BM using immunoassays and transgene detection (Real Time qPCR), both for the whole population and the specific T-cell subsets.
   a. Time point of evaluation: Pre-infusion and at 1-3h post-infusion (day 0), daily until day 4, weekly until week 4; every 2 week until week 12
3. To evaluate the exhaustion of the infused T-cells through immunoassays evaluating the expression of the specific markers of exhaustion and their activity through functional assays (such as ELISPOT for IFN-γ release using CD19-positive and CD-19 negative target cells, comparing the response with the T-cells at the moment of infusion, whenever possible).
   a. Time point of evaluation: Pre-infusion and at 1-3h post-infusion (day 0), daily until day 4, weekly until week 4; every 2 week until week 12
4. To define the serum cytokine profile and its correlation with cytokine release syndrome (CRS) in order to define a possible predictive profile.
   a. Time point of evaluation: Pre-infusion and at 1-3h post-infusion (day 0), daily until day 10
5. To characterise the kinetics of pentraxin 3 (PTX3) and its correlation with CRS to define its role as early predictive biomarker of CRS.
   a. Time point of evaluation: Pre-infusion and at 1-3h post-infusion (day 0), daily until day 10
6. To assess the long-term antitumour effect of the infused T-cells (both as morphologic response and as MRD in the BM) at 1 and 3 years, without further therapy.
   a. Time point of evaluation: at years 1 and 3
7. To assess relapse rate, overall survival and disease-free survival at 1 and 3 years post cell infusion.
   a. Time point of evaluation: at years 1 and 3
8. To assess disease outcome in patients treated with AP1903.
   a. Time point of evaluation: at years 1 and 3
9. To assess the kinetics of CD19-CART01 elimination after AP1903 infusion.
   a. Time point of evaluation: pre-infusion and post-infusion
10. To assess the clinical response and the kinetics of cytokine levels change in patients with CRS treated with AP1903.
    a. Time point of evaluation: pre-infusion and post-infusion
11. To assess incidence and duration of B-cell lymphopenia and hypogammaglobulinaemia and its correlation with maintenance of CR.
12. To assess the outcome of patients treated in the presence of HAMA either pre-existing to the treatment, or detected after CD19-CART01 infusion.
    a. Time point of evaluation: at years 1 and 3

Starting date	N/A Date on which this record was first entered in the EudraCT database: 2018-01-03
Contact information	Organisation: Bambino Gesù Children's Hospital
Notes	

JPRN-JapicCTI-183914

Study name	A phase 2 multicenter, open-label, single-arm study of KTE-C19 in Japanese patients with refractory or relapsed large B-cell lymphoma
Methods	Phase II • Interventional, prospective, single-arm, open-label • Study size (according to clinicaltrials.jp): 10

JPRN-JapicCTI-183914 *(Continued)*

Participants	**Inclusion criteria:**
	• Histologically confirmed aggressive B-cell NHL (including the following types defined by the WHO 2016)
	  * DLBCL
	  ☐ DLBCL, NOS
	  ☐ Germinal centre B-cell lymphoma
	  ☐ Activated B-cell lymphoma
	  ☐ Intravascular large B-cell lymphoma
	  ☐ T-cell/histiocyte-rich large B-cell lymphoma
	  ☐ DLBCL associated with chronic inflammation
	  ☐ Epstein-Barr virus (EBV)positive diffuse large B-cell lymphoma, NOS
	  * PMBCL
	  * TFL
	  * High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement
	  * High-grade B-cell lymphoma, NOS
	• Chemotherapy-refractory disease, defined as one or more of the following:
	  * No response to first-line therapy (primary refractory disease); subjects who are intolerant to first-line therapy chemotherapy are excluded
	  ☐ Progressive disease (PD) as best response to first-line therapy
	  ☐ Stable disease (SD) as best response after at least 4 cycles of first-line therapy (e.g., 4 cycles of R-CHOP) with SD duration no longer than 6 months from last dose of therapy
	  * No response to second or greater lines of therapy
	  ☐ PD as best response to most recent therapy regimen
	  ☐ SD as best response after at least 2 cycles of last line of therapy with SD duration no longer than 6 months from last dose of therapy
	  * Relapsed post-ASCT
	  ☐ Disease progression or relapsed ≤ 12 months of ASCT (must have biopsy proven relapse in relapsed subjects)
	  ☐ If salvage therapy is given post-ASCT, the subject must have had no response to or relapsed after the last line of therapy (must have biopsy proven recurrence in relapsed subjects)
	  ☐ Histologically confirmed aggressive B-cell NHL, DLBCL, DLBCL NOS, Intravascular large B-cell lymphoma
	• Subjects must have received at least the following therapy:
	  * Anti-CD20 monoclonal antibody (unless the investigator or subinvestigator determines that tumour is CD20 negative)
	  * An anthracycline containing chemotherapy regimen;
	  * Prior chemotherapy for follicular lymphoma for subjects with transformed TFL (subsequently have a chemorefractory disease after transformation to DLBCL)
	• At least 1 measurable lesion according to the revised IWG Response Criteria for Malignant Lymphoma. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy

Interventions	Anti-CD19 CAR T-cells: axicabtagene ciloleucel
Outcomes	Primary outcome measures: 1. ORR (percentage of patients judged CR or PR) assessed by the investigator or subinvestigator based on the criteria of the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma Secondary outcome measures: 1. Safety 2. Efficacy 3. Exploratory

JPRN-JapicCTI-183914 *(Continued)*

	4. Pharmacokinetics 5. Other: ORR assessed by the central image evaluation organization, DOR, PFS, OS
Starting date	Study starting date: April 01, 2018 Primary completion date: Unclear Study completion date: Juni 30, 2034
Contact information	Contact: Contact for Clinical Trial Information; DAIICHI SANKYO Co.,Ltd
Notes	https://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-183914

NCT02374333

Study name	Pilot study of redirected autologous T cells engineered to contain humanized anti-CD19 in patients with relapsed or refractory CD19+ leukemia and lymphoma previously treated with cell therapy
Methods	Phase I • Prospective, interventional, single-group, open-label • Study size (according to clinicaltrials.gov): 85

Participants	**Inclusion criteria:**
	• Male & female subjects with documented CD19+ B-cell malignancies, no available curative treatment options, limited prognosis (several months to < 2 year survival) with currently available therapies
	• Eligible diseases: CD19+ leukaemia or lymphoma. In general, these will be patients with:
	  * ALL without curative options for therapy, including those not eligible for allogeneic SCT. Patient may be in any complete response, or patient may have active disease but responding or stable after most recent therapy. The intent is not to enrol patients with no degree of disease control or rapidly increasing disease burden between enrolment and cell infusion
	  * Diffuse large cell lymphoma or other high-grade NHL, previously identified as CD19+ including residual disease after primary therapy and not eligible for autologous SCT; relapsed after prior autologous SCT; beyond 1st CR with relapsed or persistent disease and not eligible or appropriate for conventional allogeneic or autologous SCT
	• Patients previously treated with B-cell directed engineered cell therapy are eligible if they meet one of the following criteria:
	  * Partial response or no response to prior cell therapy
	  * Relapsed after prior cell therapy
	  * Demonstrated B-cell recovery suggesting loss of engineered cells.
	• Documented CD19 expression (after previous B-cell directed cell therapy, if applicable)
	• Age 1 to 24 years
	• Expected survival > 12 weeks
	• Creatinine < 2.5 mg/dl and less than 2.5x normal for age
	• Bilirubin < 2.0 mg/dl
	• Adequate pulmonary function defined as < grade 3 hypoxia
	• Adequate cardiac function defined as LVSF ≥ 28% confirmed by ECHO
	• Adequate performance status (Lansky or Karnofsky score ≥ 50)
	• Patients with relapsed disease after prior allogeneic SCT (myeloablative or non-myeloablative) will be eligible if they meet all other inclusion criteria and
	  * Have no active GVHD and require no immunosuppression
	  * Are more than 4 months from transplant (6 months at infusion)
	• Patients with CNS3 disease will be eligible if CNS disease is responsive to therapy

NCT02374333 *(Continued)*

	• For those patients who require leukapheresis for T cell collection (i.e. no previously collected product exists), adequate venous access for apheresis or eligible for appropriate catheter placement, and no other contraindications for leukapheresis. • Voluntary informed consent is given
Interventions	huCART19 • Other Name: huCTL019
Outcomes	1. Occurrence of study related adverse events defined as NCI CTCAE 4.0 > grade 3 possibly, probably, or definitely related to study treatment. [time frame: Study treatment until Week 24]
Starting date	Study starting date: March 2014 Primary completion date: October 2019 Study completion date: November 2020
Contact information	Study Chair: Carl June, MD; University of Pennsylvania
Notes	https://ClinicalTrials.gov/show/NCT02374333 Current clinicaltrials.gov status: Recruiting

NCT02659943

Study name	T cells expressing a fully-human antiCD19 chimeric antigen receptor for treating B-cell malignancies
Methods	Phase I • Interventional, prospective, single-arm, open-label • Study size (according to clinicaltriasl.gov): 27
Participants	**Inclusion criteria:** Malignancy criteria: • Patients with the following malignancies are potentially eligible: any B-cell lymphoma, and chronic lymphocytic leukaemia (CLL). Patients with indolent malignancies that have transformed to diffuse large B-cell lymphoma are eligible • Clear CD19 expression must be uniformly detected on 75% or more of malignant cells from either bone marrow or a leukaemia or lymphoma mass by flow cytometry or immunohistochemistry * These assays must be performed at the National Institutes of Health * preferable but not required that the specimen used for CD19 determination comes from a sample that was obtained after the patient's most recent treatment * If paraffin embedded unstained samples of bone marrow involved with malignancy or a lymphoma mass are available, these can be shipped to the NIH for CD19 staining; otherwise, new biopsies will need to be performed for determination of CD19 expression • DLBCL patients must have received at least two prior chemotherapy-containing regimens at least one of which must have contained doxorubicin and a monoclonal antibody • Follicular lymphoma patients must have received at least 2 prior regimens including at least 1 regimen with chemotherapy • All other lymphoma and leukaemia patients must have had at least 1 prior chemotherapy-containing regimen. All patients with CLL or small lymphocytic lymphoma must have had prior treatment with ibrutinib or another signal transduction inhibitor

NCT02659943 *(Continued)*

- Patients must have measurable malignancy as defined by at least one of the criteria below:
  * Lymphoma or leukaemia masses that are measurable (minimum 1.5 cm in largest diameter) by CT scan is required for all diagnoses except CLL. All masses must be less than 10 cm in the largest diameter
  * For a lymphoma mass to count as measurable malignancy, it must have abnormally increased metabolic activity when assessed by positron emission tomography (PET) scan
  * For CLL and lymphoma with only bone marrow involvement no mass is necessary, but if a mass is not present, bone marrow malignancy must be detectable by flow cytometry in lymphoma and CLL

Other inclusion criteria

- Greater than or equal to 18 years of age and less than or equal to age 73
- Able to understand and sign the informed consent document
- Clinical performance status of ECOG 0-1
- Room air oxygen saturation of 92% or greater
- Patients of both genders must be willing to practice birth control from the time of enrolment on this study and for four months after receiving the preparative regimen
- Women of child bearing potential must have a negative pregnancy test because of the potentially dangerous effects of the preparative chemotherapy on the fetus. Women of child-bearing potential are defined as all women except women who are post-menopausal or who have had a hysterectomy. Postmenopausal will be defined as women over the age of 55 who have not had a menstrual period in at least 1 year
- Seronegative for HIV antibody. (The experimental treatment being evaluated in this protocol depends on an intact immune system. Patients who are HIV seropositive can have decreased immune-competence and thus are less responsive to the experimental treatment and more susceptible to its toxicities
- Seronegative for hepatitis B antigen, positive hepatitis B tests can be further evaluated by confirmatory tests, and if confirmatory tests are negative, the patient can be enrolled. Patients with a known history of hepatitis B or hepatitis C are not eligible due to the risk of re-activation of hepatitis after prolonged B-cell depletion due to anti-CD19 CAR T cells
- Seronegative for hepatitis C antibody unless antigen negative. If hepatitis C antibody test is positive, then patients must be tested for the presence of RNA by RT-PCR and be HCV RNA negative. Patients with a known history of hepatitis C are not eligible
- Absolute neutrophil count greater than or equal to 1000/mm(3) without the support of filgrastim or other growth factors
- Platelet count greater than or equal to 45,000/mm^3 without transfusion support
- Hemoglobin greater than 8.0 g/dl
- Less than 5% malignant cells in the peripheral blood leukocytes
- Serum ALT and AST less or equal to 3 times the upper limit of the institutional normal unless liver involvement by malignancy is demonstrated
- Serum creatinine less than or equal to 1.4 mg/dL
- Total bilirubin less than or equal to 2.0 mg/dl
- At least 14 days must have elapsed since any prior systemic therapy prior to apheresis and prior to the initiation of chemotherapy (including systemic corticosteroids at any dose). Because this protocol requires collection of autologous blood cells by leukapheresis in order to prepare CAR T-cells, systemic anti-malignancy therapy including systemic corticosteroid therapy of any dose are not allowed within 14 days prior to the required leukapheresis
  * NOTE: Because of the long half-life and potential to affect CAR T-cells, 60 days must elapse from the time of administration of anti-PD-1 or anti-PD-L1 antibodies or other agents that in the opinion of the PI can stimulate immune activity and infusion of CAR T-cells
- Normal cardiac ejection fraction (greater than or equal to 55% by echocardiography) and no evidence of haemodynamically significant pericardial effusion as determined by an echocardiogram within 4 weeks of the start of the treatment protocol
- Patients must not take corticosteroids including prednisone, dexamethasone or any other corticosteroid for 14 days before apheresis and CAR T-cell infusion. Patients must also not take corti-

NCT02659943 *(Continued)*

	costeroids at doses higher than 5 mg/day of prednisone or equivalent at any time after the CAR T-cell infusion
Interventions	Anti-CD19-CAR T-cells Cyclophosphamide Fludarabine
Outcomes	Primary Outcome Measures: 1. Safety and feasibility of administering T-cells expressing a novel fully-human anti-CD19 chimeric antigen receptor (CAR) [time Frame: 4-5 weeks after first dose] 2. List of adverse event frequency
Starting date	Study starting date: January 21, 2016 Primary completion date: December 1, 2020 Study completion date: December 1, 2021
Contact information	Principal Investigator: James N Kochenderfer, M.D.; National Cancer Institute (NCI)
Notes	https://ClinicalTrials.gov/show/NCT02659943 Current clinicaltrials.gov status: Active, not recruiting

NCT02706405

Study name	JCAR014 and durvalumab in treating patients with relapsed or refractory B-cell Non-Hodgkin lymphoma
Methods	Phase I • Interventional, prospective, single-arm, open-label • Study size (according to clinicaltrials.gov): 42
Participants	**Inclusion Criteria:** Inclusion criteria for screening: • Relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS); high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements; primary mediastinal B-cell lymphoma (PMBCL); or DLBCL transformed from indolent histology with one of the following: * Persistent disease after first-line chemo-immunotherapy * Relapse after first-line chemo-immunotherapy and not eligible for autologous haematopoietic stem-cell transplant (HCT) * Relapse or persistent disease after at least two lines of therapy or after autologous HCT • Ability to understand and provide informed consent Inclusion criteria for leukapheresis and pre-therapy evaluation: • Screening evaluation appropriate for leukapheresis and T-cell collection • Evidence of CD19 expression on any prior or current tumour specimen or a high likelihood of CD19 expression based on disease histology Inclusion criteria for lymphodepletion chemotherapy, JCAR014 and Durvalumab: • Successful collection of T-cells for JCAR014 manufacturing

NCT02706405 *(Continued)*

- Documentation of CD19 expression on any prior or current tumour biopsy
- Internal review of histology
- Detectable positron emission tomography (PET)-positive disease
- Karnofsky performance status ≥ 60%
- Assessed by the investigator to have adequate bone marrow function to receive lymphodepleting conditioning chemotherapy
- Serum creatinine < 1.5 x age-adjusted upper limit of normal (ULN)
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3 x ULN and total bilirubin ≤ 2 x ULN
- Adequate pulmonary function, defined as Common Terminology Criteria for Adverse Events (CTCAE) grade ≤ 1 dyspnoea and oxygen saturation (SaO2) ≥ 92% on room air; patients with clinically significant pulmonary dysfunction, as determined by medical history and physical exam should undergo pulmonary function testing and must have a forced expiratory volume in 1 second (FEV1) ≥ 50% of predicted value or diffusing capacity of the lung for carbon monoxide (DLCO; corrected) ≥ 40% of predicted value
- Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 35% as assessed by echocardiogram (ECHO) or multiple uptake gated acquisition (MUGA)
- Women of reproductive potential (defined as all women physiologically capable of becoming pregnant) must agree to use suitable methods of contraception for 90 days after the last dose of study therapy (durvalumab or JCAR014)
- Males who have partners of reproductive potential must agree to use an effective barrier contraceptive method for 90 days after the last dose of study therapy (durvalumab or JCAR014)

Interventions	Autologous Anti-CD19CAR-4-1BB-CD3zeta-EGFRt-expressing CD4+/CD8+ Central Memory T-lymphocytes JCAR014 Cyclophosphamide Durvalumab Fludarabine Phosphate Laboratory Biomarker Analysis
Outcomes	Primary outcome measures: 1. Incidence of toxicity graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 [time frame: 30 days] a. All adverse events will be listed and summarized. Summaries of laboratory data will include, at a minimum, treatment-emergent laboratory abnormalities. Summaries of adverse events and laboratory abnormalities will be based on the All Treated analysis set. 2. Dose limiting toxicity (DLT) rates [time frame: 28 days] a. Will be summarized based on the dose limiting toxicity evaluable analysis set. Final dose limiting toxicity rates at each dose level will be estimated by isotonic regression. The target toxicity rate for the maximum tolerated dose is 30%. 3. Maximum tolerated dose of durvalumab in combination with JCAR014 determined as the dose level with the DLT estimate closest to the target toxicity level of 30% [time frame: 28 days] a. Will be estimated per isotonic regression 4. Maximum JCAR014 Cmax by flow cytometry [time frame: Up to 12 months] 5. Area under the curve (AUC) of JCAR014 by flow cytometry [time frame: Up to 28 days] 6. Maximum JCAR014 Cmax in blood by quantitative polymerase chain reaction (qPCR) analysis [time frame: Up to 12 months] 7. AUC of JCAR014 cells by qPCR analysis [time frame: Up to 28 days] 8. Time to loss of JCAR014 detection in blood by qPCR analysis [time frame: Up to 12 months] Secondary outcome measures:

NCT02706405 *(Continued)*

1. Rate of complete response (CR) by investigator assessment using Lugano criteria [time frame: Up to 15 years]
   a. The rates of CR will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals based on the efficacy evaluable (EE) analysis sets
2. Rate of partial response (PR) by investigator assessment using Lugano criteria [time frame: Up to 15 years]
   a. PR will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals based on the EE analysis sets
3. Objective response rate (ORR, defined as the proportion of patients with a best response of either complete response or partial response) by investigator assessment using Lugano criteria [time frame: Up to 15 years]
   a. ORR will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals based on the EE analysis sets. In addition, objective response rate will be presented based on the All Treated analysis set, where patients with non-evaluable response will be treated as non-responders
4. Duration of response [time frame: From first response to progressive disease or death, assessed up to 15 years]
   a. Kaplan-Meier methodology will be used
5. Progression-free survival [time frame: From date of first study treatment to progressive disease or death, assessed up to 15 years]
   a. Kaplan-Meier methodology will be used
6. Overall survival [time frame: From date of first study treatment to death, assessed up to 15 years]
   a. Kaplan-Meier methodology will be used
7. Cmax of durvalumab in serum [time frame: Up to 12 months]
8. AUC of durvalumab in serum [time frame: Up to 12 months]
9. Clearance of durvalumab in serum [time frame: Up to 12 months]
10. Terminal half-life of durvalumab in serum [time frame: Up to 12 months]
11. Antibodies and cellular immune responses to JCAR014 [time frame: Up to 12 months]
    a. Cellular immune responses to JCAR014 will be considered in patients who have two consecutive negative assays for JCAR014 or who have recovered endogenous B-cells. Cellular responses to JCAR014 will be evaluated by assessing reactivity of patient peripheral T-cells to JCAR014. Peripheral blood will be collected for these studies
12. Anti-drug antibodies directed against durvalumab [time frame: Up to 12 months]
    a. Will be assessed using a validated immunoassay in serum samples

Other outcome measures:

1. B-cell depletion in circulation, profile of soluble circulating proteins such as cytokines and chemokines, and changes in the level of detectable soluble PD-L1 [time frame: Up to 12 months]
2. Change in the phenotype of tumour cells (e.g., expression of PD-L1) and of the tumour microenvironment (e.g., infiltration by chimeric antigen receptor [CAR] Tcells) [time frame: Baseline up to 12 months]
   a. Flow cytometry may be used in the blood, bone marrow, and cerebrospinal fluid (CSF) (if applicable)
3. Phenotype and/or genetic profile of endogenous immune cells and CAR T-cells [time frame: Up to 12 months]
   a. Flow cytometry may be used in the blood, bone marrow, and CSF (if applicable)

Starting date	Study starting date: November 15, 2016 Primary completion date: December 1, 2019 Study completion date: December 1, 2033
Contact information	Principal Investigator: Cameron Turtle; Fred Hutch/University of Washington Cancer Consortium
Notes	https://ClinicalTrials.gov/show/NCT02706405

NCT02706405 *(Continued)*

	Current clinicaltrials.gov status: Recruiting

NCT02728882

Study name	Study evaluating the efficacy and safety with CAR-T for recurrent or refractory diffuse large B cell lymphoma (EECBL)
Methods	Phase: not applicable • Interventional, prospective, single-arm, open-label • Study size (according to Clinicaltrials.gov): 24
Participants	**Inclusion Criteria:** • Confirmed by pathological biopsy in patients with diffuse large B-cell lymphoma by standard solution treatment is invalid or recurrence of refractory, and by flow cytometry or pathological immunohistochemical examination, confirmed the tumour cell surface expression positive intervention molecular targets, mainly for the CD19 (+) and/or CD20 (+) • Age 3 to 75 years old, both male and female • Is expected to survive more than 3 months • Physical condition is good: 0-2 score ECOG score • In group of four weeks before Canon imaging examination evaluation body tumour load, recommend line PET - CT examination • General requirements peripheral blood as basic, normal blood T lymphocytes in peripheral blood count must ≥ 0.2 x10^9/L • No obvious abnormal heart, liver, kidney, no large wounds that haven't healed on the body • Into groups to participate in voluntarily, good adherence, can cooperate test observation, childbearing age women must be 7 days before starting treatment expert pregnancy test and the results were negative, and signed a written informed consent form
Interventions	Biological: CD19-targeted CAR T-cells • This study has only one arm that is the CAR T experimental arm. Firstly all participators will be attended the screening, who passed the screening for the treatment of CAR T-cells, the CAR-CD19-modified T-cells can recognize and kill tumour cells in the body, follow-up 35 months
Outcomes	Primary outcome measure: 1. Objective reaction rates [time frame: 0 to 180 days]
Starting date	Study starting date: July 2, 2015 Primary completion date: July 2019 Study completion date: July 2019
Contact information	Contact: Kangsheng Gu, PI Contact: Yang Jiao, Investigator
Notes	NCT02728882 Current clinicaltrials.gov status: Unknown

NCT02737085

Study name	The sequential therapy of CD19-targeted and CD20-targeted CAR-T cell therapy for diffuse large B cell lymphoma (DLBCL)
Methods	Phase I/II • Interventional, prospective, single-arm • Study size (according to clinicaltrials.gov): 40 • Two-stage design: beginning in the first stage with the aim of over 30% reaction rate among 15 patients with Diffuse Large B-cell Lymphoma(DLBCL). Only when the expected reaction rate is achieved the 30 patients left can be recruited
Participants	**Inclusion criteria:** • CD19-expressing and CD20-expressing Diffuse Large B Cell Lymphoma (DLBCL) must be assured and must be relapsed or refractory disease after at least one standard chemotherapy and one salvage regimen. According to current traditional therapies, there must be no available alternative curative therapies and subjects must be either ineligible for allogeneic stem-cell transplant (SCT), have refused SCT, or have disease activity that prohibits SCT at this time • Patients enrolled must have an evaluated score above 60 with KPS • Expected survival time of patients enrolled is over 3 months • Gender is not limited, age from 14 years to 75 years • Patients must have measurable or evaluable disease at the time of enrolment, which may include any evidence of disease including minimal residual disease detected by flow cytometry, cytogenetics, or polymerase chain reaction (PCR) analysis • Patients are expected to survive for more than 3 months by their physicians at the time of enrolment • Adequate absolute CD3 count estimated need to be assured for obtaining target cell dose based on dosage cohorts • Subjects with the following CNS status are eligible only in the absence of neurologic symptoms suggestive of CNS leukaemia, such as cranial nerve palsy: CNS 1, defined as absence of blasts in cerebral spinal fluid (CSF) on cytospin preparation, regardless of the number of WBCs; CNS 2, defined as presence of < 5/uL WBCs in CSF and cytospin positive for blasts, or > 5/uL WBCs but negative by Steinherz/Bleyer algorithm CNS3 with marrow disease who has failed salvage systemic and intensive IT chemotherapy (and therefore not eligible for radiation) • Patients with isolated CNS relapse will be eligible if they have previously been treated with cranial radiation (at least 1800 cGy) • Ability to give informed consent • Females of child-bearing potential must have a negative pregnancy test because of the potentially dangerous effects on the fetus • Cardiac function: Left ventricular ejection fraction greater than or equal to 40% by MUGA or cardiac MRI, or fractional shortening greater than or equal to 28% by ECHO or left ventricular ejection fraction greater than or equal to 50% by ECHO • Renal function: Creatinine level of peripheral blood is required no greater than 133umol/L • Patients with history of allogeneic stem-cell transplantation are eligible if there is no evidence of active GVHD and no longer taking immunosuppressive agents for at least 30 days prior to enrolment • Patients volunteer to participate in the research
Interventions	Anti-CD19 CAR T-cells and Anti-CD20 CAR T-cells • Patients receive autologous-derived CD19-targeted CAR T-cells following CD20-targeted CAR T-cells after receiving lymphodepleting chemotherapy • Other name: CD19-targeted CAR T-cells and CD20-targeted CAR T-cells
Outcomes	Primary outcome measures:

NCT02737085 *(Continued)*

	1. Adverse events that are related to treatment [time frame: 2 years] a. Determine the toxicity profile of the CD19-targeted and CD20-targeted CAR T-cells with Common Toxicity Criteria for Adverse Effects (CTCAE) version 4.0
Starting date	Study starting date: March 2014 Primary completion date: December 2014 Study completion date: December 2014
Contact information	Principal Investigator: Jieping Chen, MD,PhD; Department of Hematology, Southwest Hospital, Third Military Medical University
Notes	https://clinicaltrials.gov/show/NCT02737085 Current clinicaltrials.gov status: Active, not recruiting

NCT02892695

Study name	PCAR-119 bridge immunotherapy prior to stem cell transplant in treating patients with CD19 positive leukemia and lymphoma
Methods	Phase I/II • Prospective, interventional, single-group, open-label • Study size (according to Clinicaltrials.gov): 10
Participants	**Inclusion Criteria:** • Male and female subjects with CD19+ B-cell malignancies in patients who have no available curative treatment options except stem-cell transplantation, limited prognosis (several months to < 2 year survival) and no available treatment option to achieve complete remission prior to transplant • Some patients who have enrolled to other CD19-CAR T-cell therapy trials may be eligible if their CD19-CAR T-cells cannot be produced successfully because they have insufficient T-cells to allow the CD19-CAR T-cells to be made; their T-cells are inefficiently transduced with CAR viruses; or their CAR T-cell expansion is failed • All of those patients must meet the following criteria: * Eligible diseases: Acute lymphocytic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), follicular lymphoma, mantle cell lymphoma, B-cell prolymphocytic leukaemia, and diffuse large cell lymphoma, previously identified as CD19+ * Patients 3 years of age or older, and must have a life expectancy > 12 weeks * Eastern cooperative oncology group (ECOG) performance status of 0-2 or Karnofsky performance status (KPS) score is higher than 60 * Females of child-bearing potential must have a negative pregnancy test and all subjects must agree to use an effective method of contraception for up to two weeks after the last infusion of CAR NK cells * Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements: White blood cell count (WBC) ≥ 2500c/ml, platelets ≥ 50×10^9/L, Hb ≥ 9.0g/dL, lymphocyte (LY) ≥ 0.7×10^9/L, LY% ≥ 15%, Alb ≥ 2.8g/dL, serum lipase and amylase < 1.5×upper limit of normal, serum creatinine ≤ 2.5mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5×upper limit of normal, serum total bilirubin ≤ 2.0mg/dL. These tests must be conducted within 7 days prior to registration * Ability to give informed consent
Interventions	Anti-CD19 CAR-NK cells

NCT02892695 *(Continued)*

	• The allogeneic NK cells (NK-92 cell line for clinical use) are engineered to contain anti-CD19 attached to TCRzeta, CD28 and 4-1BB signalling domains. These modified cells are called chimeric antigen receptor NK cells with specificity for CD19 • Other name: chimeric antigen receptor NK cells with specificity for CD19
Outcomes	Primary outcome measures: 1. Adverse events attributed to the administration of the anti-CD19 CAR-NK cells [time frame: 2 years] Secondary outcome measures: 1. Objective response rate [time frame: Safety follow-up is 100 days from last CAR-NK infusion]
Starting date	Study starting date: September 2016 Primary completion date: September 2018 Study completion date: September 2019
Contact information	Contact: Lin Yang, Ph.D.; PersonGen BioTherapeutics (Suzhou) Co., Ltd.
Notes	https://clinicaltrials.gov/ct2/show/NCT02892695 Current clinicaltrials.gov status: Unknown (Verified December 2016)

NCT03233854

Study name	CD19/CD22 chimeric antigen receptor T cells and chemotherapy in treating patients with recurrent or refractory CD19 positive diffuse large B-Cell lymphoma or B acute lymphoblastic leukemia
Methods	Phase I • Interventional, prospective, single-group, open-label • Study size (according to Clinicaltrials.gov): 57
Participants	**Inclusion criteria:** • For diffuse large B-cell lymphoma (DLBCL) * Histologically confirmed aggressive B-cell non-Hodgkin lymphoma (NHL) including the following types defined by World Health Organization (WHO) 2008: ☐ DLBCL not otherwise specified; T-cell/histiocyte rich large B-cell lymphoma; DLBCL associated with chronic inflammation; Epstein Barr virus (EBV)+ DLBCL of the elderly; OR ☐ Primary mediastinal (thymic) large B-cell lymphoma ☐ Transformation of follicular lymphoma to DLBCL will also be included * Subjects with DLBCL must have progressed, had stable disease (SD), or recurred after initial treatment regimens that include an anthracycline and an anti CD20 monoclonal antibody; subjects who relapse ≥ 12 months after therapy should have progressed after autologous transplant or been ineligible for autologous transplant • For B acute lymphoblastic leukaemia (ALL) * Chemotherapy refractory disease in subjects with B-ALL is defined as progression or stable disease after two lines of standard therapies (two induction regimens), or relapsed disease after 2 established induction regimens * Subjects with persistent or relapsed minimal residual disease (MRD) / next generation sequencing (NGS) relapse require verification of relapse on two occasions at least 4 weeks apart * Subjects with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ALL) subjects are eligible if they progressed, had stable disease or relapsed after two lines of therapy, including tyrosine kinase inhibitors (TKIs)

NCT03233854 *(Continued)*

- CD19 expression is required and must be detected on greater than 50% of the malignant cells by immunohistochemistry or ≥ 90% by flow cytometry; the choice of whether to use flow cytometry or immunohistochemistry will be determined by what is the most easily available tissue sample in each subject; in general, immunohistochemistry will be used for lymph node biopsies, flow cytometry will be used for peripheral blood and bone marrow samples
- Subjects who have undergone autologous stem-cell transplantation (SCT) with disease progression or relapse following SCT are eligible; subjects who have undergone allogeneic SCT will be eligible if, in addition to meeting other eligibility criteria, they are at least 100 days post transplant, they have no evidence of graft versus host disease (GVHD) and have been without immunosuppressive agents for at least 30 days
- Must have evaluable or measurable disease according to the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma; lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy
- At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time the subject is planned for leukapheresis, except for systemic inhibitory/stimulatory immune checkpoint therapy, which requires 5 half-lives
- Toxicities due to prior therapy must be stable and recovered to ≤ grade 1 (except for clinically non significant toxicities such as alopecia)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, or Karnofsky ≥ 80%
- Absolute neutrophil count (ANC) ≥ 750/uL
- Platelet count ≥ 50,000/uL
- Absolute lymphocyte count ≥ 150/uL
- Creatinine ≤ 2 mg/dL or creatinine clearance (as estimated by Cockcroft Gault equation) ≥ 60 mL/min
- Serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 2.5 upper limit of normal (ULN)
- Total bilirubin ≤ 1.5 mg/dl, except in subjects with Gilbert?s syndrome
- Cardiac ejection fraction ≥ 45%, no evidence of physiologically significant pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings
- No clinically significant pleural effusion
- Baseline oxygen saturation > 92% on room air
- Central nervous system (CNS) status
  - Subjects with ALL
    - ☐ Subjects with the following CNS status are eligible only in the absence of neurologic symptoms suggestive of CNS leukaemia, such as cranial nerve palsy:
    - ☐ CNS 1, defined as absence of blasts in cerebral spinal fluid (CSF) on cytospin preparation, regardless of the number of white blood cells (WBCs);
    - ☐ CNS 2, defined as presence of < 5/uL WBCs in CSF and cytospin positive for blasts, or > 5/uL WBCs but negative by Steinherz/Bleyer algorithm:
    - ☐ CNS 2a: < 10/uL red blood cells (RBCs); < 5/uL WBCs and cytospin positive for blasts;
    - ☐ CNS 2b: ≥ 10/uL RBCs; < 5/uL WBCs and cytospin positive for blasts;
    - ☐ CNS 2c: ≥ 10/uL RBCs; ≥ 5/uL WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm
  - Subjects with DLBCL
    - ☐ Subjects must have no signs or symptoms of CNS disease or detectable evidence of CNS disease on magnetic resonance imaging (MRI) at the time of screening; subjects who have been previously treated for CNS disease but have no evidence of disease at screening are eligible
- Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)
- Subjects of child bearing or child fathering potential must be willing to practice birth control from the time of enrolment on this study and for four (4) months after receiving the preparative regimen; females of child bearing potential must have a negative pregnancy test

NCT03233854 *(Continued)*

	• Must be able to give informed consent; subjects unable to give informed consent will not be eligible for this study
Interventions	Chimeric Antigen Receptor T-Cell Therapy • Given CD19/CD22 CAR T-cells IV • Other name: CAR T-cell therapy Cyclophosphamide • Given IV • Other names: * (-)-Cyclophosphamide * 2H-1,3,2-Oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate * Carloxan * Ciclofosfamida * Ciclofosfamide * Cicloxal * Clafen * Claphene * CP monohydrate * CTX * CYCLO-cell * Cycloblastin * Cycloblastine * Cyclophospham * Cyclophosphamid monohydrate * Cyclophosphamidum * Cyclophosphan * Cyclophosphane * Cyclophosphanum * Cyclostin * Cyclostine * Cytophosphan * Cytophosphane * Cytoxan * Fosfaseron * Genoxal * Genuxal * Ledoxina * Mitoxan * Neosar * Revimmune * Syklofosfamid * WR- 138719 Fludarabine Phosphate • Given IV

NCT03233854 *(Continued)*

- Other names:
  * 2-F-ara-AMP
  * 9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-.beta.-D-arabinofuranosyl)-
  * Beneflur
  * Fludara
  * SH T 586

Laboratory biomarker analysis

- Correlative studies

Questionnaire administration

- Ancillary studies

Outcomes	Primary Outcome Measures: 1. Incidence and severity of dose limiting toxicities (DLTs) following chemotherapy preparative regimen and infusion of CD19/CD22 chimeric antigen receptor (CAR) T-cells [time frame: Up to 28 days] a. Safety data will be analysed per standard methods and interpreted descriptively for each dose cohort. Safety data will be summarized for each dose cohort separately and for all dose cohorts combined. Adverse events will be assessed using the CTCAE version 4.03 for type and severity of event. Serious adverse events will be summarized for each dose cohort and for all dose cohorts combined. Reasons for discontinuation of study therapy will be tabulated 2. Maximum tolerated dose of CD19/CD22 chimeric antigen receptor (CAR) T-cells defined as the dose level immediately below the level at which the enrolment is stopped due to a dose limiting toxicity [time frame: Up to 28 days] a. Will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 3. Rate of successful manufacture and expansion of the CD19/CD22 chimeric antigen receptor (CAR) T-cells to satisfy the targeted dose level and meet the required release specifications outlined in the certificate of analysis [time frame: Up to 15 years] a. In addition to aiming to evaluate up to 6 subjects at a given dose level with respect to toxicity, the number of subjects which can successfully manufacture the targeted dose number will be determined Secondary outcome measures: 1. Overall survival [time frame: From the start of the preparative regimen until death, assessed for up to 15 years] a. Will be assessed by dose cohort 2. Progression-free survival [time frame: From the start of the preparative regimen until the documentation of disease progression or death due to any cause, whichever occurs first, assessed for up to 15 years] a. Will be assessed by dose cohort 3. The ability to achieve a clinical response after administration of CD19/CD22 chimeric antigen receptor (CAR) T-cells [time frame: Up to 15 years] a. Will be assessed by the response criteria for lymphoma and the response criteria for acute lymphoblastic leukemia. Other outcome measures: 1. Alterations in early B-cell development induced by immune pressure exerted via CD19/CD22 chimeric antigen receptor (CAR) T-cells [time frame: Up to 15 years] 2. CD19/CD22 chimeric antigen receptor (CAR) T-cell properties [time frame: Up to 15 years] a. Will explore correlations with CAR T-cell efficacy and persistence 3. Establish the utility of chromatin structure and epigenomic technology to characterise chimeric antigen receptor (CAR) T-cell therapies [time frame: Up to 15 years] a. Investigators will attempt to establish parameters for how best to utilize the technology in CAR research to: establish basis for blood therapeutic monitoring; derive blood biomarkers for pre-

NCT03233854 *(Continued)*

	diction of the safety and efficacy of CAR cell therapy; and develop metrics for CAR T product release criteria that can be used during the manufacturing of the product 4. Frequency of CD22+ expression on lymphoma cells [time frame: Up to 15 years] a. Will correlate with clinical response to CAR Tcells 5. Persistence of CD19/CD22 chimeric antigen receptor (CAR) T-cells blood, bone marrow, and cerebral spinal fluid [time frame: Up to 15 years] a. Will be assessed by flow cytometry. Will be analysed and reported as time from T-cell infusion 6. Relapse with loss or diminished expression of CD19 and/or CD22 [time frame: Up to 15 years]
Starting date	Study starting date: September 1, 2017 Primary completion date: September 1, 2025 Study completion date: September 1, 2035
Contact information	Principal Investigator: David Miklos; Stanford University
Notes	https://clinicaltrials.gov/show/NCT03233854 Current clinicaltrials.gov status: Recruiting

NCT03277729

Study name	A phase I/II study to evaluate the safety of cellular immunotherapy using autologous T cells engineered to express a CD20-specific chimeric antigen receptor for patients with relapsed or refractory B cell non-Hodgkin lymphomas
Methods	Phase I/II • Interventional, prospective, single-group, open-label • Study size (according to Clinicaltrials.gov): 30
Participants	**Inclusion Criteria:** • Patients must have B-cell non-Hodgkin lymphoma, including but not limited to mantle cell, follicular, lymphoplasmacytic, marginal zone, transformed indolent B-cell lymphoma (including transformed chromic lymphoid leukaemia [CLL]), or diffuse large B-cell lymphoma that has relapsed after a response to at least one prior therapy regimen or is refractory to prior therapy • Patients with mantle cell lymphoma must have previously been treated with a BTK inhibitor and have either had disease progression, intolerance, or exposure to the drug for at least 3 months • Patients with de novo diffuse large B-cell lymphoma (DLBCL) must meet one of the following criteria: * Biopsy-proven refractory disease after a frontline regimen containing both an anthracycline and rituximab or other anti-CD20 antibody (i.e. "primary refractory"), where any disease recurring within 6 months of completion of the regimen is considered refractory * Relapsed or refractory disease after at least one of the following: ☐ At least 2 lines of therapy (including at least one with an anthracycline and anti-CD20 antibody) ☐ Autologous stem-cell transplant ☐ Allogeneic stem-cell transplant • Patients of any gender, race or ethnicity • Patients must be capable of understanding and providing a written informed consent • Negative serum pregnancy test within 2 weeks before enrolment for women of childbearing potential, defined as those who have not been surgically sterilized or who have not been free of menses for at least 1 year

NCT03277729 *(Continued)*

- Fertile male and female patients must be willing to use an effective contraceptive method before, during, and for at least 4 months after the CAR T-cell infusion
- Patients must have a Karnofsky performance status of ≥ 60%
- Confirmation of diagnosis by internal pathology review of initial or subsequent biopsy or other pathologic material at Fred Hutchinson Cancer Research Center (FHCRC)/Seattle Cancer Care Alliance (SCCA)/University of Washington (UW)/Harborview Medical Center (HMC)
- Evidence of CD20 expression by immunohistochemistry or flow cytometry on the tumour specimen obtained with the biopsy performed with screening; if the CD20 expression on the screening tumour biopsy is unclear or could not be assessed due to technical reasons, CD20 expression on a concomitant tumour specimen (such as marrow biopsy or circulating tumour cells) may be used to satisfy this requirement
- Serum creatinine ≤ 2.5
- Total bilirubin ≤ 3.0 mg/dL
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5 x the upper limit of normal
- Adequate pulmonary function, defined as =< grade 1 dyspnoea and saturated oxygen (SaO2) ≥ 92% on room air; if pulmonary function test (PFT)s are performed based on the clinical judgment of the treating physician, patients with forced expiratory volume in 1 second (FEV1) ≥ 50% of predicted and carbon monoxide diffusing capability (DLCO) (corrected) of ≥ 40% of predicted will be eligible
- Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) of ≥ 50% as assessed by echocardiogram or multigated acquisition (MUGA) scan, or LVEF of 45-49% and clearance by a cardiologist
- Measurable disease that can be accurately measured in at least one dimension as ≥ 2.0 cm with computed tomography (CT), ultrasound, or magnetic resonance imaging (MRI) techniques; extranodal disease that is measurable by fludeoxyglucose F-18 (FDG)-positron emission tomography (PET) imaging only will also be allowed; note that if an excisional biopsy was performed that removed the sole site of measurable disease, the patient will not be eligible for leukapheresis and generation of CAR T-cell product

Eligibility for lymphodepletion chemotherapy:

- Absence of uncontrolled active infection (bacterial, fungal, viral, mycobacterial) not responding to treatment with antibiotics, antiviral agents, or antifungal agents
- Absence of active autoimmune disease requiring ongoing systemic immunosuppressive therapy
- Negative serum pregnancy test within 2 weeks before lymphodepletion chemotherapy for women of childbearing potential, defined as those who have not been surgically sterilized or who have not been free of menses for at least 1 year
- No treatment with any investigational agent on a different clinical trial between enrolment and lymphodepleting chemotherapy
- Serum creatinine ≤ 2.5
- Total bilirubin ≤ 3.0 mg/dL
- AST and ALT ≤ 5 x the upper limit of normal
- Adequate pulmonary function, defined as ≤ grade 1 dyspnoea and SaO2 ≥ 92% on room air; if PFTs are performed based on the clinical judgment of the treating physician, patients with FEV1 ≥ 50% of predicted and DLCO (corrected) of ≥ 40% of predicted will be eligible
- Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) of ≥ 50% as assessed by echocardiogram or MUGA scan, or LVEF of 45-49% and clearance by a cardiologist; if subject receives cardiotoxic chemotherapy after enrolment, repeat echocardiogram or MUGA is required to reestablish eligible LVEF
- Patients must have a Karnofsky performance status of ≥ 60%
- Measurable disease that can be accurately measured in at least one dimension as ≥ 2.0 cm with CT, ultrasound, or MRI techniques; extranodal disease that is measurable by FDG-PET imaging only will also be allowed; note that if an excisional biopsy was performed that removed the sole site of measurable disease, the patient is not be eligible for lymphodepletion and CAR T-cell infusion; measurable disease can be based on the imaging study done during the screening unless the patient received treatment in the interim, in which case imaging should be repeated

NCT03277729 *(Continued)*

- Patients must require no corticosteroid therapy or dose of less than 15 mg per day of prednisone or the equivalent; pulsed corticosteroid dose for disease control is acceptable until the day before the start of lymphodepletion
- Patients must have no active acute or chronic GVHD

Interventions	Chimeric antigen receptor T-cell therapy
	• Given CD20 CAR T-cell IV
	• Other names:
	  * CAR T-cell therapy
	  * CAR T Infusion
	  * CAR T Therapy
	
	Cyclophosphamide
	• Given IV
	• Other names:
	  * (-)-Cyclophosphamide
	  * 2H-1,3,2-Oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate
	  * Carloxan
	  * Ciclofosfamida
	  * Ciclofosfamide
	  * Cicloxal
	  * Clafen
	  * Claphene
	  * CP monohydrate
	  * CTX
	  * CYCLO-cell
	  * Cycloblastin
	  * Cycloblastine
	  * Cyclophospham
	  * Cyclophosphamid monohydrate
	  * Cyclophosphamidum
	  * Cyclophosphan
	  * Cyclophosphane
	  * Cyclophosphanum
	  * Cyclostin
	  * Cyclostine
	  * Cytophosphan
	  * Cytophosphane
	  * Cytoxan
	  * Fosfaseron
	  * Genoxal
	  * Genuxal
	  * Ledoxina
	  * Mitoxan
	  * Neosar
	  * Revimmune
	  * Syklofosfamid
	  * WR- 138719
	
	Fludarabine
	• Given IV
	• Other name: Fluradosa

NCT03277729 *(Continued)*

	Leukapheresis
	• Undergo leukapheresis
	• Other names:
	  * Leukocytopheresis
	  * Therapeutic Leukopheresis
	
	Fludarabine Phosphate
	• Given IV
	• Other names:
	  * 2-F-ara-AMP
	  * Beneflur
	  * Fludara
	  * Fludarabine-5''-Monophosphate
	  * SH T 586

Outcomes	Primary outcome measures:
	1. Dose-limiting toxicity [time frame: Up to 28 days]
	  a. Will be graded by common terminology criteria for adverse events version 4.0.
	
	Secondary outcome measures:
	1. Complete remission [time frame: Up to 15 years]
	  a. Will be assessed based on the Lugano criteria
	2. Progression-free survival (PFS) [itme frame: Duration from study enrolment to progression or death due to any cause (whichever comes first), assessed up to 15 years]
	  a. A Cox proportional hazards model will be used to evaluate PFS
	3. Overall survival (OS) [time frame: Duration from study enrolment to death due to any cause, assessed up to 15 years]
	  a. A Cox proportional hazards model will be used to evaluate OS
	4. Incidence of adverse events [time frame: Up to 15 years]
	  a. Will be assessed by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

Starting date	Study starting date: December 5, 2017 Primary completion date: November 16, 2022 Study completion date: November 16, 2037
Contact information	Principal Investigator: Mazyar Shadman; Fred Hutch/University of Washington Cancer Consortium
Notes	https://clinicaltrials.gov/show/NCT03277729 Current clinicaltrials.gov status: Recruiting

NCT03528421

Study name	Assessment of safety and efficacy of IM19 for relapsed or refractory NHL patients
Methods	Phase I • Prospective, interventional, single-group • Study size (according to Clinicaltrials.gov): 30
Participants	**Inclusion criteria:**

NCT03528421 *(Continued)*

	• Relapsed or refractory CD19-positive non-Hodgkin lymphoma (NHL) patients. 1 Diffuse large B lymphoma (DLBCL), follicular lymphoma (FL), primary mediastinal B-cell lymphoma (PMBCL) patients meet one of the following conditions: I Patients who have relapsed or are refractory after at least 2 previous treatments; II Patients who have relapsed after transplantation. 2 Patients with relapsed or refractory mantle cell lymphoma after at least one treatment • Patients must have evaluable disease evidence • Age ≥ 18 years old • The expected life span is more than 3 months • ECOG score 0-2 points • Women of childbearing age have a negative blood pregnancy test before the start of the trial and agree to have effective contraceptive measures during the trial until the last follow-up • Those who voluntarily participate in the trial and sign the informed consent
Interventions	IM19 • CAR T-cells Fludarabine • Two days before cell infusion, all patients will be treated with fludarabine for 3 days Cyclophosphamide • Two days before cell infusion, all patients will be treated with Cyclophosphamide for 3 days
Outcomes	Primary Outcome Measures 1. Occurrence of study related adverse events [time frame: 2 years] a. ≥ grade 3 signs/symptoms,laboratory toxicities,and clinical events that are possibly,likely,or definitely related to study treatment Adverse events assessed according to NCI-CTCAE v4.0 criteria 2 Secondary outcome measures 1. Overall response rate [time frame: 2 years] a. (1) a morphologic complete response (CR) or (2) a complete response with incomplete recovery of counts (CRi) (based on NCCN guidelines)
Starting date	Study starting date: May 22, 2018 Primary completion date: April 2020 Study completion date: May 2020
Contact information	Contact: Xin-an Lu, Dr; Beijing Cancer Hospital
Notes	https://clinicaltrials.gov/show/NCT03528421 Current clinicaltrials.gov status: Unknown

NCT03579888

Study name	CD19-specific T cells post alloSCT
Methods	Phase I • Interventional, prospective, single-group, open-label • Study size (according to clinicaltrials.gov): 24

NCT03579888 *(Continued)*

Participants	**Inclusion criteria** • Patients with high risk or relapsed disease who are planning to receive, or have received prior allogeneic HSCT from an human leukocyte antigen (HLA)-matched related, or HLA-mismatched related donor; high risk is defined as patients with acute lymphoblastic leukaemia who have delayed clearance of minimal residual disease, Philadelphia (Ph)-like, or complex, 11q23 or hypodiploid karyotype • Available donor who provided haematopoietic stem-cell (HSC) • Patients with CD19+ lymphoid malignancies that are refractory to or intolerant of standard treatment (as defined below): * B-cell acute lymphoblastic leukaemia (ALL) * Non-Hodgkin lymphoma (NHL) to include diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, mantle cell lymphoma, or transformed follicular lymphoma (TFL) as defined by the World Health Organization 2008 criteria * Small lymphocytic lymphoma (SLL) * Chronic lymphocytic leukaemia (CLL) * NOTE: Refractory disease for acute and chronic leukaemia is defined by: ☐ Presence of > 5% malignant blasts in bone marrow and/or peripheral blood and/or minimal residual disease by flow cytometry or molecular analysis for fusion proteins and/or positive imaging for extra-medullary disease to most recent therapy * NOTE: Refractory disease for lymphoma is defined as: ☐ Progressive disease or stable disease lasting ≤ 6 months, as best response to most recent chemotherapy regimen; or disease progression or recurrence ≤ 12 months after prior ASCT ☐ Prior therapy must have included an anti-CD20 monoclonal antibody-containing regimen and an anthracycline-containing chemotherapy regimen ☐ For patients with TFL, prior chemotherapy for follicular lymphoma and subsequent refractory disease after transformation to DLBCL ☐ At least one measurable lesion according to revised International Working Group (IWG) Response Criteria • In patients with prior transplant, treatment will begin no earlier than 3 months post-transplant. Enrolment can occur earlier to allow time for donor cell collection • Karnofsky performance scale > 60 • Patient able to provide written informed consent • Patient able to provide written informed consent for the long-term follow-up (LTFU) gene therapy study • Negative human anti-mouse antibody (HAMA) • HLA-matched related, HLA-mismatched related, including haploidentical donor, or related donor cleared to donate based on stem-cell transplantation and cellular therapy (SCTCT) standard-of-care (SOC) guidelines • Negative beta HCG in female of child-bearing potential defined as: * Not post-menopausal for 12 months, or * No previous surgical sterilization, or * Lactating females • Patient must have measurable disease at the time of treatment • Not received anti-thymocyte globulin (ATG), Campath, or other T-cell immunosuppressive antibodies or donor-lymphocyte infusion in the 28 days prior to T-cell infusion • Serum creatinine < 2 x upper limit of normal (ULN) • Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 2.5 x ULN or ≤ 5 x ULN if documented liver metastases • Total bilirubin ≤ 1.5 mg/dL, except in patients with Gilbert's syndrome in whom total bilirubin must be ≤ 3.0 mg/dL • Cardiac ejection fraction ≥ 40%, and no clinically-significant electrocardiogram (ECG) findings • No clinically significant pleural effusion, baseline oxygen saturation > 90% on room air

NCT03579888 *(Continued)*

- No evidence of grade ≥ 2 active graft versus host disease (GVHD) using the Center for International Blood and Marrow Transplant Research (CIBMTR) Acute GVHD Grading System or requiring systemic steroid therapy greater than physiologic dosing at time of starting treatment
- Non-haematologic toxicity grade ≥ 2 (Common Terminology Criteria for Adverse Events [CTCAE] version 5) related to the lymphodepleting chemotherapy until the toxicity has resolved to grade ≤ 1 and the patient is afebrile
- No new grade > 2 neurologic, pulmonary, cardiac, gastrointestinal, renal or hepatic (excluding albumin) toxicity
- Serum creatinine < 2 x ULN
- Oxygen saturation > 90% on room air
- Active clinically significant infection within 7-days of study treatment
- Using an investigational agent

Interventions	Autologous CD19-CD8-CD28-CD3zeta-CAR-mbIL15-HER1t T-cells
	• Given IV
	• Other names:
	  * Autologous CD19-CD8-CD28-CD3zeta-CAR-mbIL15-EGFRt T-cells
	  * CD19-CD8CD28zCAR-specific-mbIL15-HER1t T-lymphocytes
	Cyclophosphamide
	• Given IV

NCT03579888 *(Continued)*

- Other names:
  * (-)-Cyclophosphamide
  * 2H-1,3,2-Oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate
  * Carloxan
  * Ciclofosfamida
  * Ciclofosfamide
  * Cicloxal
  * Clafen
  * Claphene
  * CP monohydrate
  * CTX
  * CYCLO-cell
  * Cycloblastin
  * Cycloblastine
  * Cyclophospham
  * Cyclophosphamid monohydrate
  * Cyclophosphamide Monohydrate
  * Cyclophosphamidum
  * Cyclophosphan
  * Cyclophosphane
  * Cyclophosphanum
  * Cyclostin
  * Cyclostine
  * Cytophosphan
  * Cytophosphane
  * Cytoxan
  * Fosfaseron
  * Genoxal
  * Genuxal
  * Ledoxina
  * Mitoxan
  * Neosar
  * Revimmune
  * Syklofosfamid
  * WR- 138719

Fludarabine

- Given IV
- Other name: Fluradosa

Outcomes

Primary outcome measures:

1. Incidence of adverse events [time frame: Up to 15 years]
   a. Graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Adverse events will be summarized by frequencies and percentages by dose level
2. Maximum tolerated dose (MTD) as determined by dose limiting toxicity (DLT) [time frame: Up to 30 days post-infusion]
   a. The MTD is defined as the highest dose at which no more than 1 of 6 patients experiences a DLT. The study will employ a standard 3+3 design to find the MTD of CD19-specific chimeric antigen receptor (CAR) T-cell dose

Secondary outcome measures:

NCT03579888 *(Continued)*

	1. Incidence and grading of cytokine release syndrome (CRS) [time frame: Up to 12 months] a. Graded according to CTCAE 2. Persistence of genetically modified T-cells [time frame: Up to 12 months] a. Persistence of genetically modified T-cells will be assessed by the frequency of patients with any detectable CAR T-cells. 3. Change in numbers of infused T-cells [time frame: Up to 12 months] a. For patients receiving cetuximab (i.e., those who experience ≥ grade 3 CRS), the change in infused CAR+ T-cells from before cetuximab treatment to the nadir of CAR+ T-cells after cetuximab summarized by mean, standard deviation, median, and range and days to achieve nadir 4. Development of host immune responses against transgenes [time frame: Up to 12 months] a. The development of host immune responses against the transgenes (one or more of CAR, mbIL15, HER1t) may be assessed by the percentage of patients with antibody formation against each one of the transgenes 5. Cytokine levels [time frame: Up to 12 months] a. Individual patient and aggregate cytokine levels (e.g., IL-15, IL-12, IL-8, etc.) will be summarized by means, standard deviations, medians, and ranges 6. Homing ability of the infused T-cells [time frame: Up to 12 months] a. Homing will be assessed based on presence of infused T-cells within biopsied tissue. The frequency and percentage of patients experiencing homing and those who have CD19- malignant B-cells will be presented 7. Disease response [time frame: At days 30 and 100] a. Percentage of patients experiencing disease response, defined as partial or complete clearance of disease e.g., by positron emission tomography (PET) and/or bone marrow report will be computed along with a corresponding 95% confidence interval. The percentage of patients who had T-cells successfully prepared, released, and infused will be reported. Additional statistical analyses will be performed if deemed appropriate 8. Neurotoxicity [time frame: Up to 12 months] a. Graded according to CTCAE 9. Presence of CD19 negative (-) malignant B-cells [time frame: Up to 12 months] a. Presence of CD19- malignant B-cells will be based on flow cytometry staining for CD19 in the context of staining for antigens to detect cancerous B-cells. The frequency and percentage of patients experiencing homing and those who have CD19- malignant B-cells will be presented 10. Progression-free survival [time frame: From the time of T-cell infusion to date of progression of date of death, assessed up to 12 months] a. Will be estimated using the Kaplan-Meier method and presented along with their 95% confidence intervals. Additional statistical analyses will be performed if deemed appropriate 11. Overall survival [time frame: From the time of T-cell infusion to date of death, assessed up to 12 months] a. Will be estimated using the Kaplan-Meier method and presented along with their 95% confidence intervals. Additional statistical analyses will be performed if deemed appropriate
Starting date	Study starting date: June 26, 2020 Primary completion date: November 30, 2021 Study completion date: November 30, 2021
Contact information	Contact: Partow Kebriaei
Notes	

NCT03704298

Study name	Safety and efficacy of axicabtagene ciloleucel in combination with utomilumab in adults with refractory large B-cell lymphoma

NCT03704298 *(Continued)*

Methods	Phase I/II • Prospective, interventional, single-group, open-label • Study size (according to clinicaltrials.gov): 48
Participants	**Inclusion Criteria:** • Histologically proven large B-cell lymphoma including the following types: * Diffuse large B-cell lymphoma (DLBCL) not otherwise specified (ABC/GCB) * High grade B-cell lymphoma (HGBCL) with or without MYC and BCL2 and/or BCL6 rearrangement * DLBCL arising from follicular lymphoma * T-cell/histiocyte rich large B-cell lymphoma * DLBCL associated with chronic inflammation * Primary cutaneous DLBCL, leg type * Epstein-Barr virus (EBV) + DLBCL • Chemotherapy-refractory disease, defined as one or more of the following: * No response to first-line therapy (primary refractory disease); subjects who are intolerant to first-line systemic chemotherapy are excluded ☐ Progressive disease (PD) as best response to first-line therapy ☐ Stable disease (SD) as best response after at least 4 cycles of first-line therapy (e.g. 4 cycles of R-CHOP) with SD duration no longer than 6 months from last dose of therapy * No response to second or greater lines of therapy ☐ PD as best response to most recent therapy regimen ☐ SD as best response after at least 2 cycles of last line of therapy with SD duration no longer than 6 months from last dose of therapy OR * Refractory post-autologous stem-cell transplant (ASCT) ☐ Disease progression or relapsed 12 months after ASCT (must have biopsy proven recurrence in relapsed participant) ☐ If salvage therapy is given post-ASCT, the participant must have had no response to or relapsed after the last line of therapy • At least 1 measureable lesion according to the Lugano Classification (Cheson 2014). Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy • Participant must have received adequate prior therapy including at a minimum: * Anti-CD20 monoclonal antibody unless investigator determines that tumour is CD20-negative, and * An anthracycline containing chemotherapy regimen • No radiographic evidence, suspicion and/or history of central nervous system (CNS) involvement of lymphoma • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 • Absolute neutrophil count (ANC) ≥ 1000/µL • Platelet count ≥ 75,000/µL • Absolute lymphocyte count ≥ 100/µL • Adequate renal, hepatic, pulmonary, and cardiac function defined as: * Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 mL/min * Serum alanine aminotransferase/aspartate aminotransferase (ALT/AST) ≤ 2.5 upper limit of normal (ULN) * Total bilirubin ≤ 1.5 mg/dL, except in individuals with Gilbert's syndrome. * Cardiac ejection fraction ≥ 50% and no evidence of pericardial effusion within 180 days provided the subject did not receive an anthracycline-based treatment or experience a cardiac event or change in performance status * No clinically significant pleural effusion * Baseline oxygen saturation > 92% on room air

NCT03704298 *(Continued)*

Interventions	Cyclophosphamide Fludarabine Axicabtagene Ciloleucel Utomilumab
Outcomes	Primary outcome measures: 1. For phase 1: Percentage of participants experiencing adverse events defined as dose limiting toxicities (DLTs) [time frame: Up to 28 days] a. Dose-limiting toxicity is defined as protocol-defined axicabtagene ciloleucel related events with onset within the first 28 days following axicabtagene ciloleucel infusion 2. For phase 2: Complete response rate [time frame: Up to 1 year] a. Complete response rate is defined as the incidence of a complete response per the Lugano Classification as determined by study investigators Secondary outcome measures: 1. For phase 1 and phase 2: Objective response rate [time frame: Up to 15 years] a. Objective response rate is defined as the incidence of either a complete response (CR) or a partial response (PR) per Lugano Classification as determined by study investigators 2. For phase 1 and phase 2: Duration of response [time frame: Up to 15 years] a. Among participants who experience an objective response, duration of response is defined as the date of their first objective response to disease progression per Lugano Classification as determined by study investigators or death from any cause 3. For phase 1 and phase 2: Progression-free survival [time frame: Up to 15 years] a. Progression-free survival is defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression per Lugano Classification as determined by study investigators or death from any cause 4. For phase 1 and phase 2: Overall survival [time frame: Up to 15 years] a. Overall survival is defined as the time from axicabtagene ciloleucel infusion to the date of death 5. For phase 1 and phase 2: Percentage of participants experiencing adverse events [time frame: Up to 24 months plus 30 days] 6. For phase 1 and phase 2: Percentage of participants experiencing clinically significant changes in safety lab values [time frame: Up to 24 months plus 30 days] 7. For phase 1 and phase 2: Pharmacokinetics: levels of axicabtagene ciloleucel in blood [time frame: Up to 2 years] 8. For phase 1 and phase 2: Pharmacodynamics: Levels of cytokines in serum [time frame: Up to 2 years]
Starting date	Study starting date: November 20, 2018 Primary completion date: January 2021 Study completion date: June 2035
Contact information	Study Director: Kite Study, Director; Kite, A Gilead Company
Notes	https://clinicaltrials.gov/show/NCT03704298 Current clinicaltrials.gov status: Recruiting

NCT03720457

Study name	Human CD19 targeted T cells Injection (CD19 CAR-T) therapy for relapsed and refractory CD19-positive lymphoma
Methods	Phase I • Interventional, prospective, single-arm, open-label • Study size (according to Clinicaltrials.gov): 18
Participants	**Inclusion Criteria:** • Male or female subjects with CD19+ B-cell lymphomas who have a limited prognosis (several months to < 2 year survival) with currently available therapies will be enrolled * 18 to 70 years old, male and female; * Expected survival > 12 weeks * Clinical performance status of ECOG score 0-1 * Pathology demonstrated that CD19-positive B-cell non-Hodgkin's lymphoma and who meet one of the following conditions: ☐ Relapsed and refractory CD19-positive diffuse large B-cell lymphoma and follicular lymphoma: patients previously received at least first-line and second- line treatment and fail to achieve CR ☐ Disease recurrence after stem-cell transplantation, and at least 1 years after stem-cell transplantation * It can establish the venous access required for collection, satisfying haemoglobin ≥ 70 g/L, neutrophils ≥ 1.0 × 10^9/L, platelets ≥ 50 × 10^9/L. Mononuclear cell collection can be determined by the investigators * At least 1 measurable tumour foci according to the 2014 Lugano treatment response criteria * Liver, kidney and cardiopulmonary functions meet the following requirements: ☐ Serum creatinine ≤ 1.5 × ULN ☐ Left ventricular ejection fraction >50%, no pericardial effusion and no pleural effusion (ECHO examination) ☐ Baseline oxygen saturation > 92% ☐ Total bilirubin ≤ 1.5 × ULN ☐ ALT and AST ≤ 3 × ULN * Able to understand and sign the informed consent document
Interventions	Human CD19 targeted T-cells injection
Outcomes	Primary outcome measures: 1. Safety measured by occurrence of study related adverse effects defined by NCI CTCAE 5.0 [time frame: 2 years post-infusion] Secondary outcome measures: 1. Duration of CAR-positive T-cells in circulation [time frame: 2 years post-infusion] 2. Total number of CAR-positive T-cells infiltrated into lymphoma tissue [time frame: 2 years post-infusion] 3. Overall remission rate including complete response and partial response defined by the standard response criteria for malignant lymphoma. [time frame: 90 days post-infusion] 4. Duration of response after administration [time frame: 90 days post-infusion] 5. Progress-free survival after administration [time frame: 90 days post-infusion] 6. Overall survival after administration [time frame: 90 days post-infusion] 7. The immunogenicity of human CD19 targeted T-cells Injection. (HAMA detection of human anti-mouse antibody) [time frame: 2 years post-infusion]
Starting date	Study starting date: November 13, 2018

NCT03720457 *(Continued)*

	Primary completion date: October 2021 Study completion date: October 2023
Contact information	Contact: Hongliang Fang, Dr.
Notes	https://ClinicalTrials.gov/show/NCT03720457 Current clinicaltrials.gov status: Recruiting

NCT04231747

Study name	A study of CC-97540, CD19-targeted NEX-T chimeric antigen receptor (CAR) T cells, in subjects with relapsed or refractory B-cell non-Hodgkin lymphoma
Methods	Phase I • Interventional, prospective, single-arm, open-label • Study size (according to clinicaltrials.gov): 80
Participants	**Inclusion criteria:** • Age ≥ 18 years at the time of informed consent • Signed written informed consent obtained prior to any study procedure • Willing and able to adhere to the study visit schedule and other protocol requirements • Relapsed and/or refractory aggressive B-cell NHL as defined: * Histologically confirmed DLBCL not otherwise specified, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (HGBCL), transformed DLBCL from follicular (tFL) or marginal zone lymphoma (tMZL), primary mediastinal B-cell lymphoma (PMBCL), or FL grade 3b (FL3B) AND * Have relapsed and/or refractory disease after at least 2 lines of systemic therapy which must include at least one anthracycline and rituximab (or other anti-CD20 monoclonal antibody) * Note: Lines of therapy will exclude those given for prior indolent lymphoma. It is not required for subjects to have had anthracycline for their DLBCL if received for indolent disease AND/OR * Have relapsed and/or refractory DLBCL failed to ASCT treatment. Note: ASCT failure is defined as either failure to achieve an objective response (PR or better), or disease progression after ASCT • Positron emission tomography (PET)-positive disease as per the Lugano classification • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 • Adequate organ function as detailed in the protocol • Adequate vascular access for leukapheresis. • Willing and able to undergo tumour biopsies (in subjects with accessible disease) • Agree to not donate blood, organs, sperm or semen, and egg cells for usage in other individuals as detailed in the protocol • Female and male subjects agree to use effective contraception as detailed in the protocol
Interventions	CC-97540
Outcomes	Primary outcome measures: 1. Adverse events (AEs) [time frame: From the time of informed consent and follow up to 2 years after infusion of CC-97540] a. An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. Any worsening (i.e. any clinically significant

NCT04231747 *(Continued)*

adverse change in the frequency or intensity of a preexisting condition) should be considered an AE.

Secondary outcome measures:

1. Complete response rate (CRR) [time frame: Up to 2 years after CC-97540 infusion]
   a. The proportion of subjects with a best overall response of complete response (CR)
2. Overall response rate (ORR) [time frame: Up to 2 years after CC-97540 infusion]
   a. The proportion of subjects achieving CR or partial response (PR)
3. Duration of response (DOR) [time frame: Up to 2 years after CC-97540 infusion]
   a. The time from first response to progressive disease (PD) or death
4. Time to response (TTR) [time frame: Up to 2 years after CC-97540 infusion]
   a. Time from CC-97540 infusion to the first documentation of response (CR or PR)
5. Time to complete response (TTCR) [time frame: Up to 2 years after CC-97540 infusion]
   a. Time from CC-97540 infusion to the first documentation of CR
6. Progression-free survival (PFS) [time frame: Up to 2 years after CC-97540 infusion]
   a. Time from CC-97540 infusion to the first documentation of PD, or death from any cause, whichever occurs first
7. Overall survival (OS) [time frame: Up to 2 years after CC-97540 infusion]
   a. Time from CC-97540 infusion to death
8. Pharmacokinetics - peak expansion (Cmax) [time frame: Up to 2 years after CC-97540 infusion]
   a. Maximum blood concentration
9. Pharmacokinetics - time to peak expansion (tmax) [time frame: Up to 2 years after CC-97540 infusion]
   a. Time to peak (maximum) blood concentration
10. Pharmacokinetics - elimination half-life (t1/2) [time frame: Up to 2 years after CC-97540 infusion]
    a. Elimination half-life
11. Pharmacokinetics - area under curve (AUC) [time frame: Up to 2 years after CC-97540 infusion]
    a. Area under the curve

Starting date	Study start date: May 22, 2020 Primary completion date: January 31, 2025 Study completion date: January 31, 2025
Contact information	Study Director: Ashley Koegel, MD; Celgene
Notes	

NCT04381741

Study name	CD19 CAR-T expressing IL7 and CCL19 combined with PD1 mAb for relapsed or refractory diffuse large B cell lymphoma (CICPD)
Methods	Phase I • Interventional, prospective, single-arm, open-label • Study size (according to clinicaltrials.gov): 24
Participants	**Inclusion criteria:** • Age ≥ 18, upper limit 75, unlimited for men and women • ECOG score 0-3 • Histologically confirmed diffuse large B-cell lymphoma (DLBCL) [according to WHO 2008] • CD19 was positive (immunohistochemistry or flow cytometry)

NCT04381741 *(Continued)*

	• The definition of refractory or relapse of DLBCL is: no complete remission after 2-line treatment; disease progression in any treatment process, or disease stabilization time equal to or less than 6 months; or disease progression or relapse within 12 months after haematopoietic stem-cell transplantation • The previous treatment of diffuse large B-cell lymphoma must include rituximab (CD20 mAb) and anthracycline • There should be at least one measurable focus. It is required that any length of lymph node focus should be greater than 1.5cm or any length of extranodal focus should be greater than 1.0cm. PET-CT scan focuses should have uptake (SUV is greater than liver blood pool) • The absolute value of neutrophils in peripheral blood ≥ 1000 / μL, platelet ≥ 45000 / μL • Heart, liver and kidney function: creatinine < 1.5mg/dl; ALT (alanine aminotransferase) / AST (aspartate aminotransferase) 2.5 times lower than the normal upper limit; total bilirubin < 1.5mg/dl; heart ejection fraction (EF) ≥ 50% • Sufficient understanding ability and voluntary signing of informed consent • Those with fertility must be willing to use contraceptive methods • According to the judgment of the researchers, the expected survival time is more than 4 months • Willing to follow visit schedule, administration plan, laboratory inspection and other test steps
Interventions	CD19-7×19 CAR T plus PD1 monoclonal antibody • Three different doses of CD19-7×19 CAR T (1×10^6/kg, 2×10^6/kg, 3×10^6/kg) plus 200mg Tislelizumab every 3 weeks for 6 times
Outcomes	Primary outcome measures: 1. Objective response rate [time frame: 3 months] a. Objective response rate of the combination of CD19 CAR T Expressing IL7 and CCL19 and PD1 mAb Secondary outcome measures: 1. Progression-free survival [time frame: 2 years] a. Progression-free survival of the combination of CD19 CAR T expressing IL7 and CCL19 and PD1 mAb 2. Overall survival [time frame: 2 years] a. Overall survival of the combination of CD19 CAR T Expressing IL7 and CCL19 and PD1 mAb 3. Duration of overall response [time frame: 2 years] a. Duration of overall response of the combination of CD19 CAR T expressing IL7 and CCL19 and PD1 mAb 4. Relapse rate [time frame: 2 years] a. Relapse rate of the combination of CD19 CAR T Expressing IL7 and CCL19 and PD1 mAb
Starting date	Study start date: June 18, 2020 Primary completion date: September 1, 2023 Study completion date: September 1, 2023
Contact information	Contact: Hui Liu, MD, PhD Contact: Wenbin Qian, MD, PhD
Notes	

NCT04450069

Study name	CLBR001 and SWI019 in patients with relapsed / refractory B-cell malignancies
Methods	Phase I • Interventional, prospective, single-arm, open-label • Study size (according to clinicaltrials.gov): 36
Participants	**Inclusion criteria:** • Patients with relapsed / refractory previously treated B-cell malignancies (according to the World Health Organization classification; 2017) • Chemotherapy-refractory disease • Patients must have received adequate prior therapy including at least two lines of prior therapies including anthracycline-containing chemotherapy, anti-CD20 (cluster of differentiation antigen 20) therapies and/or Brutton's tyrosine kinase (BTK) inhibitors • Patients treated with prior CD19 targeted molecules (e.g., Blincyto) must have confirmed CD19+ disease • Patients must be ineligible for allogeneic stem-cell transplant (SCT) • Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1 • Estimated life expectancy of ≥ 12 weeks from the first day of SWI019 dose administered • Willing to undergo pre- and post-treatment core needle biopsy • Adequate haematological, renal, pulmonary, cardiac, and liver function • Resolved adverse events of any prior therapy to either baseline or CTCAE Grade ≤ 1 • Women of childbearing potential, a negative pregnancy test and must agree to practice effective birth control • Men sexually active with female partners of child bearing potential must agree to practice effective contraception • Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other procedures
Interventions	CLBR001 and SWI019
Outcomes	Primary outcome measures: 1. Frequency, relatedness, severity and duration of treatment emergent and treatment related adverse events [time frame: 35 days] a. To determine the frequency, relatedness, severity and duration of treatment emergent and treatment related adverse events 2. Number of first cycle dose limiting toxicities (DLT) as assessed by Common Terminology Criteria for Adverse Events (CTCAE) [time frame: up to 1 year] a. Based on the number of first cycle dose limiting toxicities (DLT) as assessed by CTCAE to determine maximum tolerated dose (MTD) Secondary outcome measures: 1. Maximum drug concentration (Cmax) of SWI019 [time frame: up to Day 35] a. To determine the maximum concentration of SWI019 in a patient's peripheral blood 2. Area under the curve (AUC) of SWI019 [time frame: up to Day 35] a. To quantify the cumulative amount of SWI019 in a patient's peripheral blood over time 3. Time to reach Cmax (Tmax) of SWI019 [time frame: up to Day 35] a. To identify the time point when the concentration of SWI019 reaches maximum in a patient's peripheral blood 4. Clearance (CL) of SWI019 [time frame: up to Day 35] a. To determine the clearance factor of SWI019 in a patient's peripheral blood 5. Apparent elimination half-life (t1/2) of SWI019 [time frame: up to Day 35] a. To identify the time point when the concentration of SWI019 reaches half of maximum in a patient's peripheral blood

NCT04450069 *(Continued)*

	6. Quantification of CLBR001 cells in peripheral blood [time frame: up to 1 year] a. To quantify CLBR001 in a patient's peripheral blood at different time points 7. Phenotype of CLBR001 in peripheral blood and/or tumour/bone marrow biopsies [time frame: up to 1 year] a. To evaluate the phenotype of CLBR001 in a patient's peripheral blood at different time points by flow cytometry 8. Immunogenic response to CLBR001 [time frame: up to 1 year] a. To evaluate the anti-drug antibodies in response to CLBR001 administration in a patient's peripheral blood 9. Immunogenic response to SWI019 [time frame: up to 1 year] a. To evaluate the anti-drug antibodies in response to SWI019 administration in a patient's peripheral blood 10. Serum cytokine concentrations [time frame: up to 1 year] a. To measure the cytokine levels (e.g. TNFa, IL-6, IL-1, IL-2, etc.) in a patient's peripheral blood at different time points 11. Overall (best) objective response by the Response Evaluation Criteria in Lymphoma (RECIL) and Lugano criteria [time frame: up to 1 year] a. To determine the overall (best) objective anti-cancer response by RECIL and Lugano criteria 12. Duration of response (DOR) [time frame: up to 1 year] a. To evaluate the duration of anti-cancer response after CLBR001 and SWI019 administration 13. Progression-free survival (PFS) [time frame: up to 1 year] a. To evaluate the duration of patient's progression-free survival 14. Overall survival (OS) [time frame: up to 1 year] a. To evaluate the overall duration of patient's survival
Starting date	Study start date: August 14, 2020 Primary completion date: July 2023 Study completion date: April 2024
Contact information	Contact: Pamela Garzone, Ph.D.
Notes	

NCT04456023

Study name	Study of tisagenlecleucel in Chinese adult patients with relapsed or refractory diffuse large B-cell non-Hodgkin lymphoma (DLBCL)
Methods	Phase II • Interventional, single-arm, prospective, open-label • Study size (according to clinicaltrials.gov): 30
Participants	**Inclusion criteria** • Signed informed consent must be obtained prior to participation in the study • Patients must be ≥ 18 years of age at the time of ICF signature • Histologically confirmed DLBCL at last relapse (including DLBCL transformed from follicular lymphoma and double-triple hit lymphoma) • Relapsed or refractory disease after at least 2 lines of systemic therapy, including anti-CD20 antibody and an anthracycline, or having failed or being ineligible for autologous HSCT • ECOG performance status that is either 0 or 1 at screening

NCT04456023 *(Continued)*

- Measurable disease at time of enrolment:
  - Nodal lesions greater than 15 mm in the long axis, regardless of the length of the short axis or
  - Extra nodal lesion (outside lymph node or nodal mass, but including liver and spleen) at least 10 mm in long and short axis
- Adequate organ function
- Must have a leukapheresis material of non-mobilized cells available for manufacturing

Interventions	Tisagenlecleucel • A single intravenous (iv) infusion of 0.6 - 6.0×10^8 CAR positive viable T-cells. • Other name: CTL019
Outcomes	Primary outcome measures: 1. Overall response rate (ORR) [time frame: From first dosing (single administration, day 1) up to end of study visit (EOS), an average of 60 Months] a. Overall response rate (ORR) is defined as the percentage of participants with best overall response of complete response (CR) or partial response (PR), where the best overall disease response is defined as the best disease response recorded from tisagenlecleucel infusion until progressive disease or start of new anticancer therapy, whichever comes first. The overall response assessment is based on the amended Lugano classification assessed by the investigator Secondary outcome measures: 1. Duration of response (DOR) [time frame: From first dosing (single administration, day 1) up to end of study visit (EOS), an average of 60 Months] a. Duration of response (DOR) applies only to subjects whose best overall disease response was CR or PR. It is defined as the time from the date of first documented disease response (CR or PR) to the date of first documented progression or death due to Diffuse Large B-cell Lymphoma (DLBCL). If a subject has not had an event, duration of overall response is censored at the date of the last adequate assessment 2. Time to response (TTR) [time frame: From first dosing (single administration, day 1) up to end of study visit (EOS), an average of 60 months] a. Time to response (TTR) is defined as the time from the date of tisagenlecleucel infusion to the date of first documented disease response (CR or PR), whichever occurs first 3. Progression-free survival (PFS) [time frame: From first dosing (single administration, day 1) up to end of study visit (EOS), an average of 60 months] a. Progression-free survival (PFS) is defined as the time from tisagenlecleucel infusion to the first documented disease progression or death due to any cause. If a subject has not had an event, progression-free survival is censored at the date of the last adequate assessment. 4. Event-free survival (EFS) [time frame: From first dosing (single administration, day 1) up to end of study visit (EOS), an average of 60 months] a. Event-free survival (EFS) is defined as the time from tisagenlecleucel infusion to the first documented disease progression or relapse, new treatment for lymphoma (excluding haematopoietic stem-cell transplantation (HSCT)) or death due to any cause 5. Overall survival (OS) [time frame: From first dosing (single administration, day 1) up to end of study visit (EOS), an average of 60 months] a. Overall survival (OS) is defined as the time from tisagenlecleucel infusion to death due to any cause. If a death has not been observed by the date of analysis cutoff, OS will be censored at the date of last contact 6. Number of participants with on-treatments adverse events, serious adverse events, and deaths [time frame: From first dosing (single administration, day 1) up to end of study Visit (EOS), an average of 60 months] a. Analysis of absolute and relative frequencies for treatment emergent adverse event (AE), serious adverse event (SAE) and deaths by primary system organ class (SOC) to demonstrate that single intravenous (iv) infusion of tisagenlecleucel is safe through the monitoring of relevant clinical and laboratory safety parameters

NCT04456023 *(Continued)*

7. Tisagenlecleucel immunogenicity (humoral) [time frame: week -12 to day -1 (Enrolment/bridging chemotherapy), day 28, months 3, 6 and 12]
   a. The humoral immunogenicity assay will be evaluated to measure the antibody titers specific to the tisagenlecleucel molecule prior to and following infusion. Data will be further fractionated to determine proportion of subjects who make transient versus sustained antibody responses
8. Tisagenlecleucel immunogenicity (cellular) [time frame: week -12 to day -1 (Enrolment/bridging chemotherapy), day 28, months 3, 6 and 12]
   a. The cellular immunogenicity assay will be evaluated to assess the presence of T lymphocytes activated by the tisagenlecleucel protein
9. Pharmacokinetic of tisagenlecleucel: Area under the curve from time zero to day 28 (AUC0-28d) and/or DAY 84 (AUC0-84d) [time frame: week -12 to day -1 (Enrolment/bridging chemotherapy), days 4, 7, 11, 14 and 28, months 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60]
   a. Area under the curve from time zero to day 28 (AUC0-28d) and/or day 84 (AUC0-84d) will be calculated from plasma concentration-time data using non-compartmental methods
10. Pharmacokinetic of tisagenlecleucel: maximum observed plasma concentration (Cmax) [time frame: week -12 to day -1 (Enrolment/bridging chemotherapy), days 4, 7, 11, 14 and 28, months 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60]
    a. Cmax is the observed maximum plasma concentration following drug administration. PK parameters are calculated from plasma concentration-time data using non-compartmental methods
11. Pharmacokinetic of tisagenlecleucel: time to reach the maximum concentration after drug administration (Tmax) [time frame: week -12 to Day -1 (Enrolment/bridging chemotherapy), days 4, 7, 11, 14 and 28, months 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60]
    a. Tmax is the time to reach maximum plasma concentration after single-dose administration. PK parameters are calculated from plasma concentration-time data using non-compartmental methods
12. Pharmacokinetic of tisagenlecleucel: terminal elimination half-life ($T^{1/2}$) [time frame: week -12 to day -1 (Enrolment/bridging chemotherapy), days 4, 7, 11, 14 and 28, months 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60]
    a. $T^{1/2}$ is the elimination half-life associated with the terminal slope of a semi logarithmic concentration-time curve. PK parameters are calculated from plasma concentration-time data using non-compartmental methods
13. Pharmacokinetic of Tisagenlecleucel: last observed quantifiable concentration in peripheral blood (Clast) [time frame: week -12 to day -1 (Enrolment/bridging chemotherapy), days 4, 7, 11, 14 and 28, months 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60]
    a. Clast is the last observed quantifiable concentration in peripheral blood. PK parameters are calculated from plasma concentration-time data using non-compartmental methods
14. Pharmacokinetic of tisagenlecleucel: time of last observed quantifiable concentration in peripheral blood (Tlast) [time frame: week -12 to day -1 (Enrolment/bridging chemotherapy), days 4, 7, 11, 14 and 28, months 3, 6, 9, 12, 18, 24, 30, 36, 40, 48, 54 and 60]
    a. Tlast is the time of last observed quantifiable concentration in peripheral blood. PK parameters are calculated from plasma concentration-time data using non-compartmental methods
15. Concentration of tocilizumab PK in tocilizumab treated subjects during CRS [time frame: up to day 7 after tocilizumab infusion]
    a. The concentration of tocilizumab PK will be characterized by CRS grade and the impact of tocilizumab administration on cellular kinetics will be investigated
16. Serum cytokine levels [time frame: From first dosing (single administration, day 1) up to month 3]
    a. The concentrations of soluble factors in blood and its correlation with CRS grade, neurologic toxicity and other clinical response (e.g. CR rate, MRD negativity rate, ORR, etc.) will be evaluated

Starting date	Study start date: May 27, 2021 Primary completion date: March 30, 2027 Study completion date: March 30, 2027
Contact information	Contact: Novartis Pharmaceuticals

NCT04456023 *(Continued)*

Notes	

NCT04464200

Study name	19(T2)28z1xx chimeric antigen receptor (CAR) T cells in people with B-cell cancers
Methods	Phase I • Interventional, prospective, single-arm, open-label • Study size (according to clinicaltrials.gov): 60
Participants	**Inclusion criteria:** • Age ≥ 18 years of age • Creatinine ≤ 2.0 mg/100 ml, direct bilirubin ≤ 2.0 mg/100 ml, AST and ALT ≤ 3.0x upper limit of normal (ULN) • Adequate pulmonary function as assessed by ≥ 92% oxygen saturation on room air by pulse oximetry Dose escalation phase: • Histologically confirmed DLBCL and large B-cell lymphoma, including * DLBCL, not otherwise specified (NOS), or * Transformed DLBCL from follicular lymphoma, or * High-grade B-cell lymphoma (excluding Burkitt's lymphoma), or * Primary mediastinal large B-cell lymphoma AND * Chemotherapy refractory disease, defined as a failure to achieve at least a partial response or disease progression within 6 months to the last therapy, OR * Disease progression or recurrence in ≤12 months of prior autologous stem-cell transplant (ASCT), OR * Relapsed disease after 2 or more prior chemoimmunotherapies with at least one containing an anthracycline and CD20 directed therapy • Patients need to have radiographically documented disease Dose expansion phase: Cohort 1: same disease subtypes as in the dose escalation phase Cohort 2 (exploratory cohort) will include the following additional disease histology: • Patients with CLL * Refractory to or relapsed after at least 1 prior chemo or chemoimmunotherapies (e.g., FCR, BR) and 1 prior biologic agent (e.g. BTK, PI3K inhibitors, venetoclax) requiring further treatment, OR * Refractory to or relapsed after at least 2 prior biologic agents (e.g. Ibrutinib, idelalisib, venetoclax, except a single-agent anti-CD20 monoclonal antibody) requiring further treatment • Patients with iNHL (FL, MZL, WM): * Refractory or relapsed after at least 2 lines of chemoimmunotherapy (including at least one course of anti-CD20 antibody), OR * Refractory or relapsed after at least 1 prior biologic agent (e.g., lenalidomide, ibrutinib, idelalisib) • Patients with Burkitt's lymphoma or transformed CLL to large cell lymphoma (i.e. Richter's transformation): * Refractory to or relapsed after at least 1 prior multiagent systemic chemo or chemoimmunotherapy

NCT04464200 *(Continued)*

Interventions	19(T2)28z1xx CAR T-cells • 2-7 days following the completion of the conditioning chemotherapy, patients will receive the CAR T-cells by IV infusion over 1-3 days depending on the dose level and formulation of the final CAR T-cells.
Outcomes	Primary outcome measures: 1. Recommended Phase II Dose (RP2D) [time frame: 28 days post-infusion] a. Dose escalation will use a 3+3 design. DLT-evaluable participants are defined as those participants who were infused with 19(T2)28z1XX CAR T-cells and who were monitored for toxicities during the first 28 days of post-infusion Secondary outcome measures: 1. Overall response rate (ORR) [time frame: 2 years] a. Response and progression of the disease will be evaluated in this study using the Lugano classification
Starting date	Study start date: July 6, 2020 Primary completion date: July 2023 Study completion date: July 2023
Contact information	Contact: Jae Park, MD Contact: M. Lia Palomba, MD
Notes	

NCT04486872

Study name	An exploratory clinical trial of autologous humanized anti-cluster of differentiation antigen 19/20(CD19/CD20) dual specific CAR-T cells injection
Methods	Phase I • Interventional, prospective, single-arm, open-label • Study size (according to clinicaltrials.gov): 18
Participants	**Inclusion criteria** • The subject or her/his legally guardian(s) must sign the informed consent form approved by the Institutional Ethics Committee (IEC) prior to any screening procedures • Subjects aged 18 years or older with relapsed or refractory DLBCL (including primary mediastinal large B-cell lymphoma and transformed follicular lymphoma), of which refractory is defined as: * Have no response to the recent treatment including: ☐ The best response to the treatment regimen is progressive disease (PD), or ☐ stable disease(SD) which maintained less than 6 months after the last treatment, or * not suitable for autologous haematopoietic stem-cell transplantation (ASCT), or ASCT refractory, including: ☐ progressive disease after ASCT or relapse within 12 months (relapse must be confirmed by biopsy), or ☐ If remedial treatment is given after ASCT, the subject must have no response or relapse after the last treatment.

NCT04486872 *(Continued)*

- Subjects who have previously received ≥ 2 lines treatment, and at least including:
  * Anti-CD20 monoclonal antibody(rituximab), unless the CD20 negative
  * A chemotherapy regimen containing anthracyclines
  * The DLBCL patients who transformed from follicular lymphoma must have previously received chemotherapy for follicular lymphoma and have developed chemotherapy-refractory diseases after transform to DLBCL
- Confirmation for either CD19 or CD20 positivity using immunohistochemistry or flow cytometry (accepting the previous results from the a third-level grade A hospitals before the collection of peripheral blood mononuclear cells or peripheral blood. For CD20 positive only, the investigator needs to determine whether the treatment benefit)
- According to the preliminary assessment of Hodgkin's lymphoma and non-Hodgkin's lymphoma, staging and response assessment recommendations (2014 version), there is at least one measurable lesion at baseline
- If the subject has received a single target in the past, such as CD19-CAR cell therapy, it must be confirmed that the disease has progressed or relapsed after treatment and is at least 1 month from the planned single collection period
- Life expectancy ≥ 12 weeks;
- Eastern Cooperative Oncology Group (ECOG) performance status that is either 0 or 1 at screening
- Adequate organ function:
  * Renal function defined as:
    ☐ A serum creatinine of ≤ 1.5 × Upper Limit of Normal(ULN), or;
    ☐ Estimated Glomerular Filtration Rate (eGFR) ≥ 60 ml/min/1.73m2; [$eGFR=186\times(age)^{-0.203}\times SCr^{-1.154}$ (mg/dl), female ×0.742 on the basis of the calculation results]
  * Liver function defined as:
    ☐ Alanine aminotransferase (ALT) ≤ 5 × Upper Limit of Normal(ULN) for age, and
    ☐ Total bilirubin ≤ 2.0 mg/dl with the exception of patients with Gilbert-Meulengracht syndrome; patients with Gilbert-Meulengracht syndrome may be included if their total bilirubin is ≤ 3.0 × ULN and direct bilirubin ≤ 1.5 × ULN
  * Must have a minimum level of pulmonary reserve defined as ≤ grade 1 dyspnoea and blood oxygen saturation > 91% on room air
- Hemodynamically stable and left ventricle ejection draction (LVEF) ≥ 45% confirmed by echocardiogram or multigated radionuclide angiography (MUGA)
- Adequate bone marrow reserve without transfusions defined as:
  * Absolute neutrophil count (ANC) >1×10^9/L
  * Absolute lymphocyte count (ALC) ≥0.3×10^9/L
  * Platelets ≥ 50×10^9 /L
  * Hemoglobin > 8.0 g/dl
- Subjects who use the following drugs should meet the following criteria:
  * Steroids: Therapeutic doses of steroids must be stopped 2 weeks prior to A-02 infusion. However, the following physiological replacement doses of steroids are allowed: < 6 - 12 mg/m2/day hydrocortisone or equivalent
  * Immunosuppression: Any immunosuppressive medication must be stopped ≥ 4 weeks prior to sign the informed consent form
  * Anti-proliferative therapy other than pretreatment chemotherapy within 2 weeks of A-02 infusion
  * CD20 antibody-related treatment must be discontinued within 4 weeks of A-02 infusion or 5 half-lives (whichever is longer)
  * CNS disease prophylaxis must be stopped > 1 week prior to A-02 infusion (e.g. intrathecal methotrexate)
- The investigator judged that the subject recovered from the toxicity of the previous anti-tumour treatment to grade 1 or below (except for special grade 2 or below toxicity that cannot be recovered in a short period of time, such as hair loss), suitable for pretreatment. Chemotherapy and treatment of CAR T-cells

NCT04486872 *(Continued)*

	• Women of child-bearing potential and all male subjects must agree to use highly effective methods of contraception for at least 12 months following A-02 infusion and until CAR T-cells are no longer present by Polymerase chain reaction (PCR) on two consecutive tests
Interventions	Autologous humanized anti-CD19 and anti-CD20 dual specific CAR T-cells • Autologous Humanized Anti-CD19 and Anti-CD20 Dual Specific CAR T-cells injection. Within 3 to 5 days after the pretreatment, the subjects received a single A-02 reinfusion, the infusion dose of each group of subjects 1.00 × 10^6/kg, 3.00 × 10^6/kg or 5.00 × 10^6/kg (if applicable), it is recommended to complete the infusion within 30 min after cell recovery
Outcomes	Primary outcome measures: 1. The types and Incidence of adverse events [time frame: Up to 12 months] a. Adverse events at each visit with the NCI CTCAE v5.0 used as a guide for the grading of severity Secondary outcome measures: 1. Duration of overall response [time frame: Up to 12 months] a. Time from the first occurrence of CR (complete response) or PR (partial response) to the first diagnosis of PD (progressive disease)or recurrence 2. Overall survival [time frame: Up to 12 months] a. Time from randomisation to death due to any cause 3. Progression-free survival [time frame: Up to 12 months] a. Time from enrolment to tumour progression or death 4. Objective response rate [time frame: Up to 12 months] a. The proportion of CR (complete response) and PR (partial response). 5. Duration of response [time frame: Up to 12 months] a. Duration of response is defined as the time from the date of first occurrence of CR (complete response) or PR (partial response) to the date of the first documented PD (progressive disease) or death due to any cause
Starting date	Study start date: July 25, 2020 Primary completion date: May 11, 2022 Study completion date: June 25, 2022
Contact information	Contact: Jie Jin, Prof Contact: Jianzhong Shentu, Prof
Notes	

NCT04526834

Study name	Phase 1 study of autologous CD30.CAR-T in relapsed or refractory CD30 positive non-Hodgkin lymphoma (CERTAIN)
Methods	Phase I • Interventional, prospective, single-arm, open-label • Study size (according to clinicaltrials.gov): 21
Participants	**Inclusion criteria** Eligibility is determined priori to leukapheresis. Patients must satisfy the following criteria to be enrolled in this study:

NCT04526834 *(Continued)*

	• Signed informed consent form • Male or female patients who are 18-75 years of age • Histologically confirmed ALCL, PTCL- NOS, ENKTCL nasal type, DLBCL-NOS and PMBCL • Relapsed or refractory CD30-positive NHL who have failed all available standards of therapy. Patients may or may not have received an autologous or allogeneic HSCT CD30-positive tumour • At least 1 measurable lesion according to the Lugano classification • ECOG PS of 0 to 1 or equivalent Karnofsky PS Anticipated life expectancy > 12 weeks
Interventions	CD30.CART • Bendamustine and Fludarabine (3 days) • Dose level 1: 2 x 10^8 cell/m2 CD30.CAR T (Day 0) • Dose level 2: 4 x 10^8 cell/m2 CD30.CAR T (Day 0) • Dose level 3: 6 x 10^8 cell/m2 CD30.CAR T (Day 0) • Other name: CD30-directed genetically modified autologous T-cells
Outcomes	Primary outcome measures: 1. To evaluate safety and dose limiting toxicities (DLT) of autologous CD30.CAR T and establish the recommended Phase dose [time frame: Day 0 to 28 for DLT] a. Incidence of DLTs and occurrence of study related adverse events Secondary outcome measures: 1. To evaluate pharmacokinetics of autologous CD30.CAR T [time frame: Start of infusion of CD30.CAR T (Day 0) until year 5] a. AUC (copies/ug DNA over time) 2. Objective response rate (ORR) [time frame: Start of CD30.CAR T (day 0) until progressive disease or start of new cancer therapy, whichever comes first, up to one year] 3. Duration of response (DOR) [time frame: start of CD30.CAR T (day 0) until progressive disease or death, whichever comes first, up to one year] 4. Progression-free survival (PFS) [time frame: Start of CD30.CAR T (Day 0) until progressive disease or death, whichever comes first, up to one year]
Starting date	Study start date: November 2020 Primary completion date: February 2022 Study completion date: February 2023
Contact information	Contact: Nicole Kusuma Contact: Aung Myo, MD
Notes	

NCT04545762

Study name	Anti-CD19 chimeric antigen receptor T cells for treatment of relapsed or refractory non-Hodgkin lymphoma
Methods	Phase I • Interventional, prospective, single-arm, open-label • Study size (according to clinicaltrials.gov): 36

NCT04545762 *(Continued)*

Participants	**Inclusion criteria:**
	• Patients must have a diagnosis of relapsed or refractory B-cell NHL:
	  * DLBCL, mantle cell, follicular lymphoma, lymphoplasmacytic lymphoma, small lymphocytic lymphoma, primary mediastinal B-cell lymphoma, Burkitt lymphoma, transformed lymphoma
	  ☐ Subjects with small lymphocytic lymphoma (SLL) must have progressed after at least 2 prior therapies and prior treatment with or intolerance of both ibrutinib and venetoclax
	  ☐ Subjects with DLBCL, primary mediastinal B-cell lymphoma, Burkitt lymphoma and transformed lymphoma must have relapsed or failed to respond to ≥ 2 prior lines of multiagent chemoimmunotherapy with prior exposure to both an anti-CD20 antibody agent and an anthracycline
	  ☐ Subjects with indolent lymphomas (follicular lymphoma and lymphoplasmacytic lymphoma) must have relapsed after or been refractory to ≥ 2 prior lines of multi-agent chemoimmunotherapy including prior exposure to rituximab and at least 2 other chemotherapy agents
	  ☐ For subjects with Mantle cell lymphoma, previous lines of therapy may include multiagent chemotherapy including alkylating agent or anthracycline and anti CD20 antibody therapy and Bruton's tyrosine kinase (BTK) inhibitor therapy
	• Positron emission tomography (PET) -positive disease according to "Recommendations for initial ealuation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification"
	• At least one of the following:
	  * Primary refractory or early relapse (first remission < 12 months) and not eligible for stem-cell transplant
	  * Relapsed or refractory disease after two or more lines of systemic therapy
	• No significant circulating disease, defined as an elevated total lymphocyte count above the ULN due to the presence of malignant cells
	• CD19 positive by either immunohistochemistry or flow cytometry analysis on any biopsy. If prior anti-CD19 therapy has been administered, CD19 positivity has to be re-established on the most recent biopsy
	• Age ≥ 18 years at the time of consent
	• Absolute lymphocyte count > 100/ (microlitre)
	• Eastern Cooperative Oncology Group (ECOG) performance status < 2
	• Adequate organ function, defined as:
	  * Adequate bone marrow function for apheresis and lymphodepleting chemotherapy
	  ☐ Haemoglobin (Hgb) > 8 grams per decilitre (gm/dL) (transfusions allowed)
	  ☐ Platelets > 50,000/microlitre (uL) (transfusions allowed)
	  ☐ Absolute Neutrophil Count (ANC) > 500/uL
	  * Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) < 3 x institutional upper limit of normal (ULN) and Total bilirubin < 1.5 mg/dl x institutional ULN, except with Gilbert's syndrome
	  * Serum Creatinine < 2 x the institutional ULN
	  * Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) > 40% as assessed by echocardiogram or multiple uptake gated acquisition (MUGA)
	• Adequate vascular access for leukapheresis procedure (either peripheral line or surgically placed line)
	• Women of childbearing potential (defined as all women physiologically capable of becoming pregnant) must have a negative serum or urine pregnancy test AND agree to use highly effective methods of contraception for 1 year after the last dose of antiCD19 CAR T-cells
	• Males who have partners of childbearing potential must agree to use an effective barrier contraceptive method
	• Ability to understand a written informed consent document, and the willingness to sign it

Interventions	Fludarabine • Given intravenously (IV)

NCT04545762 *(Continued)*

- Other names:
  * Fludarabine 30mg/m^2
  * Fludara

Cyclophosphamide

- Given intravenously (IV)
- Other names:
  * Cyclophosphamide 300mg/m^2
  * Cytoxan
  * Endoxan
  * Neosar
  * Procytox
  * Revimmune
  * Cycloblastin

anti-CD19 CAR T-cells

- Single infusion

Outcomes

Primary outcome measures:

1. Proportion of participants with treatment-emergent adverse events (AEs) [time frame: From initiation of study treatment to 12 months following CAR T infusion, approximately 15 months]
   a. All subjects enrolled in this phase I study who actually received study drug (anti-CD19 CAR T infusion) will be included in the analysis. Proportion of participants with treatment-emergent adverse events of CAR T in B-cell NHL, as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0), revised Cytokine Release Syndrome (CRS) grading criteria, and American Society for Transplantation and Cellular Therapy (ASTCT) immune effector cell (IEC) -associated neurotoxicity syndrome (ICANS) Consensus Grading for Adults (for neurotoxicity grading)
2. Proportion of participants who experience a dose-limiting toxicity (DLT) [time frame: From initiation of study treatment to 30 days following CAR T infusion]
   a. A DLT includes those AEs graded according to CTCAE version 5.0, with the exceptions of CRS and neurotoxicity, which are graded using CRS and ICANS criteria. DLTs must 1) be suspected to be secondary to CAR T-cell infusion, 2) occur during the first 30 days after infusion and 3) meet the following criteria: 1. grade 3 or 4 non-haematologic toxicities of any duration, with the following exceptions: Grade 3 laboratory abnormalities without associated symptomatology or clinical consequence that resolve in < 7 days; AEs associated with Grade ≤ 2 CRS; Toxicities associated with Grade 3 CRS (except cardiac or pulmonary organ toxicity) that improves to grade ≤ 2 within 3 days of intervention; isolated renal or hepatic grade 3 organ toxicity that does not resolve within 7 days; Laboratory abnormalities compatible with tumour lysis syndrome; Grade 4 haematological toxicity that persists at grade ≥ 3 despite maximum supportive care for > 21 days

Secondary outcome measures:

1. Proportion of participants with delayed infusion due to study-related adverse events [time frame: From T-cell collection to end of infusion, approximately 18 days]
   a. The proportion of participants who have their infusion delayed due to and AE will be reported
2. Table of adverse events related to collection and infusion of CAR T-cells [time frame: From T-cell collection to end of infusion, approximately 18 days]
   a. Frequency and severity for each adverse event of collection and infusion of CAR T-cells targeting CD19 in participants with relapsed B-cell Non-Hodgkins Lymphoma
3. Response rates over time [time frame: From initiation of study treatment to 12 months after getting CAR T infusion, approximately 15 months]
   a. Response rates will be categorized by overall, partial, and complete and will be reported as proportions at different time points across the study

NCT04545762 *(Continued)*

4. Best response rates [time frame: From initiation of study treatment to 12 months after getting CAR T infusion, approximately 15 months]
   a. Best overall, best partial, and best complete response rates will be calculated for the study overall. These will be reported cumulatively across the study population and across disease subtypes in a table format. Any comparisons will be hypothesis-generating and will be performed using Fisher's exact or the Chi-square test
5. Duration of response [time frame: From initiation of study treatment to 12 months after getting CAR T infusion, approximately 15 months]
   a. This is measured, only in responders, from the documented beginning of response (CR or PR) to the time of relapse
6. Progression-free survival (PFS) [time frame: From initiation of study treatment to 12 months after getting CAR T infusion, approximately 15 months]
   a. PFS is defined as the time from entry onto study until lymphoma progression or death from any cause at 12 months after receiving CAR T infusion
7. Overall Survival [time frame: Up to 15 years]
   a. Defined as the time from entry onto study until death from any cause
8. Proportion of subjects for whom CD19 CAR T-cell therapy is manufactured [time frame: From initiation of CD19 CAR T-cell manufacturing to end of infusion, approximately 18 days]
   a. Feasibility will be assessed by the proportion of subjects for whom the ability to produce adequate quantities of vector
9. Proportion of participants who complete study treatment [time frame: From initiation of CD19 CAR T-cell manufacturing to end of infusion, approximately 18 days]
   a. Feasibility will be assessed by the proportion of subjects who complete the study regimen

Starting date	Study start date: September 11, 2020 Primary completion date: October 31, 2023 Study completion date: October 31, 2023
Contact information	Contact: Julie McCluggage, RN
Notes	

PORTIA

Study name	Study of tisagenlecleucel in combination with pembrolizumab in r/r diffuse large B-cell lymphoma patients
Methods	Phase I • Prospective, interventional, single-group, open-label • Study size (according to Clinicaltrials.gov): 32
Participants	**Inclusion criteria:** • Confirmed DLBCL per local histopathology assessment • Relapsed or refractory disease after having received 2 or more lines of systemic therapy, including anti-CD20 and anthracycline based chemotherapy, and either having progressed after (or relapsed after) ASCT, or being not candidates for or not consenting to ASCT • Measurable disease at time of enrolment • ECOG performance status that is either 0 or 1 at screening
Interventions	Tisagenlecleucel • Gene modified autologous T-cells • Other name: CTL019

PORTIA *(Continued)*

	Pembrolizumab • anti PD-1
Outcomes	Primary outcome measures: 1. Percent of participants receiving pembrolizumab per protocol schedule [time frame: 21 days after first pembrolizumab infusion] 2. Dose timing part: Incidence of dose limiting toxicities (DLTs) [time frame: 21 days after first pembrolizumab infusion] 3. Expansion part: Overall response rate (ORR) [time frame: 3 month post tisagenlecleucel infusion] Secondary outcome measures: 1. Duration of response (DOR) [time frame: 24 months] 2. Progression-free survival (PFS) [time frame: 24 months] 3. Overall survival (OS) [time frame: 24 months] 4. In vivo cellular kinetics of tisagenlecleucel in blood, bone marrow, lymph nodes and other tissues by qPCR and flow cytometry [time frame: 24 months] 5. Impact of pembrolizumab dosing strategy on the cellular kinetics of tisagenlecleucel by qPCR and flow cytometry [time frame: 24 months] 6. Immunogenicity measured by antibody titres specific to tisagenlecleucel molecule and by the presence of T lymphocytes activated by the tisagenlecleucel protein [time frame: 24 months]
Starting date	Study starting date: October 9, 2018 Primary completion date: February 28, 2020 Study completion date: September 8, 2023
Contact information	Contact: Novartis Pharmaceuticals
Notes	https://clinicaltrials.gov/show/NCT03630159 Current clinicaltrials.gov status: Recruiting

Rivers 2018

Study name	Early response data for pediatric patients with non-Hodgkin lymphoma treated with CD19 chimeric antigen receptor (CAR) T-cells
Methods	Phase I/II • Interventional, prospective, single-arm, open-label • Study size (according to Clinicaltrials.gov): 80
Participants	**Inclusion criteria:** • Patients must be ≥ 12 months of age and < 27 years of age at the time of study enrolment. • Must be ≥ 10kg • Confirmed CD19+ leukaemia recurrence defined as ≥ 0.01% disease in the marrow or isolated extramedullary disease following allogeneic HCT. [N.B. Study closed to enrolment of leukaemia subjects] OR

Rivers 2018 *(Continued)*

- No prior history of allogeneic HCT (one of the following)
  - 2nd or greater relapse, with or without extramedullary disease (isolated extramedullary disease is eligible)
  - 1st marrow relapse at end of 1st month of re-induction with marrow having ≥0.01% blast disease, with or without extramedullary disease
  - Primary Refractory as defined as having M2 or M3 marrow after induction
  - Subject has indication for HCT but has been deemed ineligible

OR

- CD19+ Non-Hodgkin Lymphoma (NHL) refractory or relapsed with no known curative therapies available [N.B. Study remains open to enrolment of lymphoma subjects]
- Patients with CNS involvement are eligible provided that they are asymptomatic and in the opinion of the study PI have a reasonable expectation that disease burden can be controlled in the interval between enrolment and T-cell infusion. Patients that have a significant neurologic deterioration will be not be eligible for T-cell infusion until alternate therapies result in neurological stabilization.
- Patients must have a Lansky performance status score of ≥ 50 or a Karnofsky score of ≥ 50 for patients ≥ 16 years of age.
- Life Expectancy of > 8 weeks
- Patients must be free from active GVHD and off immunosuppressive GVHD therapy for 4 weeks prior to enrolment
- Recovered from acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy
- It must be at least 7 days since last chemotherapy was administered (this does not include intrathecal chemotherapy or maintenance chemotherapy)
- No systemic corticosteroids (unless physiologic replacement dosing) within 7 days of enrolment
- No prior genetically modified cell therapy that is still detectable or virotherapy allowed.
  - Normal serum creatinine based on age/gender
  - Total bilirubin </3x ULN OR conjugated bilirubin </2mg/dl
  - ALT </5X ULN
  - SF of > 28% by ECHO or EF > 50% by MUGA
  - ALC of ≥ 100 cells/uL
  - Pulse ox ≥ 90% on room air
- Patient must have documented negative HIV antigen and antibody, Hepatitis B surface antigen, and Hepatitis C antibody within 3 months prior to enrolment. For patient with positive Hepatitis C Ab, negative PCR testing must be documented in order to be eligible
- Patients must NOT have active clinically significant CNS dysfunction (including but not limited to such as uncontrolled seizure disorder, paresis, aphasia, cerebrovascular ischaemia/haemorrhage, severe brain injuries, dementia, cerebellar disease, organic brain syndrome, psychosis, coordination or movement disorder)
- Must agree to highly effective contraception during and for 12 months after T-cell infusion
- Patients must be able to tolerate apheresis procedure, including placement of temporary apheresis line if required
- Patients must NOT have an active malignancy other than CD19+ leukaemia
- Patients must NOT have an active severe infection defined as:
  - A positive blood culture within 48 hours of study enrolment
  - A fever above 38.2 C AND clinical signs of infection within 48 hours of study enrolment
- Patients must NOT have any concurrent medical condition that, in the opinion of the PI or designee, would prevent the patient from undergoing protocol-based therapy. Patients with a primary immunodeficiency/ bone marrow failure syndrome are excluded from this trial
- Research participant or parent/legal guardian must agree to participate in long-term follow-up for up to 15 years, if they are enrolled in the study and receive T-cell infusion

Interventions	Patient Derived CD19 specific CAR T-cells also expressing an EGFRt

Rivers 2018 *(Continued)*

	• Defined Composition CD4 and CD8 T-cells Lentivirally Transduced to Express a Second Generation 4-1BB:zeta CD19 CAR and EGFRt
Outcomes	Primary outcome measures: 1. Number of participants with adverse events [time frame: 30 days] a. The safety of the T-cell infusion will be described and the maximum tolerated dose determined 2. Number of participants with an MRD negative complete remission after T-cells infusion [time frame: 63 days] a. The efficacy of the T-cell infusion will be estimated based on the number of participants who have an MRD negative bone marrow aspirate following the T-cell infusion 3. Number of participants who have a releasable cell product generated [time frame: 28 days] a. The feasibility of manufacturing and releasing T-cell products from pediatric and young adult patients who relapse with CD19+ leukaemia both before and after allo-HCT will be measured Secondary outcome measures: 1. Persistence of functional CD19 CAR+ T-cells [time frame: 63 days] a. Participants will be followed for 63 days to determine if the transferred T-cells remain detectable in the blood, bone marrow and CSF 2. Number of participants with recrudescence or development of acute GVHD [time frame: 63 days] 3. Number of participants who have T-cells ablated with cetuximab [time frame: 3 years] a. The efficacy of cetuximab to ablate the T-cells will be measured by loss of detection of T-cells and any associated toxicities as well as facilitating B-cell recovery
Starting date	Study starting date: February 11, 2014 Primary completion date: September 2020 Study completion date: September 2035
Contact information	Contact: Rebecca Gardner, MD
Notes	https://clinicaltrials.gov/show/NCT02028455 Current clinicaltrials.gov status: Recruiting

Sauter 2015

Study name	High dose therapy and autologous stem cell transplantation followed by infusion of chimeric antigen receptor (CAR) modified T-cells directed against CD19+ B-cells for relapsed and refractory aggressive B cell non-Hodgkin lymphoma
Methods	Phase I • Interventional, prospective, single-arm, open-label • Study size (according to Clinicaltrials.gov): 17
Participants	**Inclusion criteria:** • Patients ≥ 18 years of age with aggressive B-cell non-Hodgkin lymphoma subtypes including, relapsed or refractory diffused large B-cell lymphoma (DLBCL), and transformed follicular lymphoma meeting at least one of the following criteria: * Bone marrow involvement at the time of relapse or refractory disease and not appropriate for allogeneic transplantation * PET positive disease outside of one radiation port unless single-port disease treated with prior radiotherapy within the port, following > or = to 2 cycles of salvage chemotherapy, still achieving chemosensitive status 1999 IWG criteria (section 12.2 and 12.383)

Sauter 2015 *(Continued)*

	• Creatinine ≤ 1.5 mg/100 ml (or measured 24 hour creatinine clearance of ≥ 50 cc/min) • Bilirubin <2.0 mg/100 ml, AST and ALT <3x the upper-limit of normal, PT and PTT < 2x normal outside the setting of stable chronic anticoagulation therapy • Adequate cardiac function (LVEF>40%) as assessed by ECHO or MUGA scan performed within 1 month of treatment • Adequate pulmonary function as assessed by DLCO of > or = to 45% adjusted for haemoglobin • Life expectancy of > 3 months
Interventions	Carmustine Etoposide Cytarabine Melphalan Pegfilgrastim 19-28z T-cells Autologous stem-cell transplantation
Outcomes	Primary outcome measures 1. maximum tolerated dose (MTD) [time frame: 2 years] a. will be assessed utilizing a standard 3+3 cell dose escalation to determine the maximum tolerated dose of CD19+ CAR T-cells 2. Safety [time frame: 2 years] a. Toxicity will be graded on a scale of 1 to 5 as described by the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 Secondary outcome measures 1. Progression-free survival (PFS) [time frame: 2 years] 2. Overall survival (OS) [time frame: 2 years]
Starting date	Study starting date: April 2013 Estimated Primary Completion Date: April 2021 Estimated Study Completion Date: April 2021
Contact information	Principal Investigator: Craig Sauter, MD; Memorial Sloan Kettering Cancer Center
Notes	https://clinicaltrials.gov/ct2/show/study/NCT01840566 Current clinicaltrials.gov status: Active, not recruiting

Shah 2019

Study name	Study of CAR-20/19-T cells in patients with relapsed refractory B cell
Methods	Phase I • Interventional, prospective, single-arm, open-label • Study size (according to Clinicaltrials.gov): 24
Participants	**Inclusion Criteria:** • Diagnosis of B-cell NHL or CLL/SLL: Patients must be aged ≥ 18 years with relapsed, refractory disease and no available curative options that meet clinical criteria to initiate treatment • Patients with B-cell NHL or CLL/SLL must have either CD19 or CD20 positive disease on most recent biopsy performed (a repeat biopsy is not mandatory for this study except as noted below).

Shah 2019 *(Continued)*

A minimum of 5% CD19 or CD20 positivity by immunohistochemistry or flow cytometry on prior or repeat biopsy is required

- Absolute CD3+ T-cell count ≥ 50/mm3
- MRI brain and Lumbar Puncture with CSF analysis by cytology and flow cytometry without evidence of CNS involvement ONLY in patients with history of CNS involvement
- Measurable disease must have been documented within 4 weeks of the time of consent defined as the following by disease specific subtype:
  * B-cell NHL: Active disease defined as nodal lesions greater than 20 mm in the long axis or extranodal lesions >10 mm in long and short axis or bone marrow involvement that is biopsy proven
  * CLL/SLL: Active disease by either bone marrow, peripheral flow cytometry, or CT and/or PET imaging with nodal disease
- Patients should have failed at least two lines of a standard treatment and meet disease specific criteria detailed below:
  * CLL/SLL: measurable disease as defined above that has relapsed after at least one line of chemo-immunotherapy and progressed or intolerant to ibrutinib monotherapy
  * CD19 or CD20 positive B-cell NHL limited to the following histologies: Advanced Stage III or IV Follicular Lymphoma, Diffuse Large B-cell Lymphoma and associated subtypes (e.g. aggressive B-cell lymphoma, T-cell/histocyte rich B-cell lymphoma, primary mediastinal B-cell lymphoma, EBV+ diffuse large B-cell lymphoma, transformed lymphoma such as transformed follicular or marginal zone lymphoma, and Richter's transformation) and Mantle cell lymphoma. Specific criteria include:
    ☐ Patients must have active, measurable disease after two lines of cytotoxic chemotherapy of which one must be anthracycline containing
    ☐ Must have received Rituximab or another CD20 antibody and at minimum two chemotherapy regimens appropriate for their disease
    ☐ Either failed autologous transplant or ineligible to receive autologous transplant
- Karnofsky performance score ≥ 70
- Normal Baseline Neurological Evaluation: Mini-Mental Status Exam Score 24-30
- Adequate hepatic function, defined as AST and ALT <5 x upper limit of normal (ULN); serum bilirubin and alkaline phosphatase <5 x ULN, or considered not clinically significant as per the clinical PIs discretion (e.g. Gilbert's or indirect hyperbilirubinaemia) or felt to be due to underlying disease
- Adequate renal function, defined as creatinine clearance > 60 ml/min
- Able to provide written informed consent
- Agree to practice birth control during the study
- Adequate cardiac function as indicated by New York Heart Association (NYHA) classification I or II AND left ventricular ejection fraction of ≥ 35% (by cardiac ECHO or MUGA) and adequate pulmonary function as indicated by room air oxygen saturation of ≥ 92%
- Expected survival > 12 weeks
- Negative urine or serum pregnancy test in females of child bearing potential at study entry and again within 48 hours' prior lymphodepleting chemotherapy
- Patients with prior blinatumomab treatment require repeat biopsy post-blinatumomab treatment that demonstrates CD19 or CD20 positive disease
- Meet criteria for regarding fertility and contraception
- Central line access will be required for CAR-20/19 T-cell infusion

Interventions	CAR-20/19-T
	• CAR-20/19 T-cells will be administered either fresh or thawed after cryopreservation by IV injection
	• Phase 1
	  * Dose level -1: 1 x 10^5 CAR-20/19 T- cells/kg
	  * Dose level 0: 2.5 x10^5 CAR-20/19 T-cells/kg (starting dose level)
	  * Dose level 1: 7.5 x10^5 CAR-20/19 T-cells/kg
	  * Dose level 2: 2.5 x10^6 CAR-20/19 T-cells/kg (goal cell dose)
	• Phase 1b
	  * Expansion dose level: 2.5 x 10^6 cells/kg (single infusion)

Shah 2019 *(Continued)*

Outcomes	Primary outcome measure 1. Number of adverse events after CAR 20/19 T-cell infusion [time frame: Within the first 28 days after infusion] a. Determine the toxicity profile of CAR 20/19 T-cell therapy
Starting date	Study starting date: October 16, 2017 Actual primary completion date: October 1, 2019 Estimated Study Completion Date: October 1, 2022
Contact information	Principal Investigator: Nirav Shah, MD; Medical College of Wisconsin
Notes	https://clinicaltrials.gov/ct2/show/NCT03019055 Current clinicaltrials.gov status: Active, not recruiting

TRANSCEND - OUTREACH

Study name	A safety trial of lisocabtagene maraleucel (JCAR017) for relapsed and refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) in the outpatient setting
Methods	Phase II • Prospective, interventional, single-group, open-label • Study size (according to Clinicaltrials.gov): 50
Participants	**Inclusion Criteria:** • Age ≥ 18 years at the time of consent • Relapsed or refractory B-cell NHL of the following histologies: diffuse large B-cell lymphoma (DLBCL) not otherwise specified; includes biopsy-confirmed transformed DLBCL from indolent histologies, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, primary mediastinal B-cell lymphoma(PMBCL), and follicular lymphoma Grade 3B. Subjects must have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have relapsed or refractory disease after at least 2 systemic lines of therapy for DLBCL or after auto-HSCT • Positron-emission tomography-positive disease by Lugano classification • Eastern Cooperative Oncology Group performance status of 0 to 1 • Adequate bone marrow, renal, hepatic, pulmonary, cardiac organ function • Adequate vascular access for leukapheresis procedure • Subjects who have received previous CD19-targeted therapy must have CD19-positive lymphoma confirmed on a biopsy since completing the prior CD19-targeted therapy • Subjects must agree to use appropriate contraception
Interventions	Lisocabtagene maraleucel • lisocabtagene maraleucel will be administered as single-dose intravenous (IV) injection • Other names: * JCAR017 * liso-cel
Outcomes	Primary outcome measures:

TRANSCEND - OUTREACH *(Continued)*

1. Adverse events [time frame: Through month 24]
   a. Proportion of subjects experiencing cytokine release syndrome, neurotoxicity, prolonged cytopenias, infections AE of grade 3 or higher

Secondary outcome measures:

1. Adverse events [time frame: through month 24]
   a. Proportion of subjects experiencing all AEs and laboratory abnormalities
2. Adverse events [time frame: through month 24]
   a. Median time to onset and to resolution of cytokine release syndrome and neurotoxicity of grade 3 or higher
3. Adverse events [time frame: through month 24]
   a. Management of cytokine release syndrome and neurotoxicity
4. Adverse events [time frame: through month 24]
   a. Of subjects monitored in the outpatient setting, the proportion of subjects experiencing all AEs and laboratory abnormalities
5. Objective response rate (ORR) [time frame: through month 24]
   a. Objective response rate (ORR [complete response + partial response]) according to the Lugano classification
6. Complete response (CR) rate [time frame: through month 24]
   a. Complete response rate according to the Lugano classification
7. Duration of response (DOR) and duration of complete response (DoCR) [time frame: through month 24]
   a. Each defined as time from first response to progressive disease (PD) or death
8. Progression-free survival (PFS) [time frame: through month 24]
   a. Time from infusion of lisocabtagene maraleucel to PD or death, whichever is earlier
9. Overall survival (OS) [time frame: through month 24]
   a. Defined as the time from infusion of lisocabtagene maraleucel to the date of death
10. Pharmacokinetics - maximum concentration (Cmax) [time frame: through month 24]
    a. Maximum concentration of lisocabtagene maraleucel
11. Pharmacokinetics - time of the maximum concentration (Tmax) [time frame: through month 24]
    a. Time to peak concentration of lisocabtagene maraleucel in the blood
12. Pharmacokinetics - area under the curve [time frame: through month 24]
    a. Area under the curve of lisocabtagene maraleucel in blood
13. Health-related quality of life questionnaires [time frame: through month 24]
    a. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 is a validated quality of life measure applicable to subjects with any cancer diagnosis
14. Health-related quality of life questionnaires [time frame: through month 24]
    a. The EuroQol-5D (EQ-5D) is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal
15. Health economics and outcomes research [time frame: through month 24]
    a. For subjects hospitalised post-treatment, the number of days the subjects were hospitalised, including the number of days that the subjects were in the Intensive Care Unit (ICU) and non-ICU ward
16. Health economics and outcomes research [time frame: through month 24]
    a. The percentage of lisocabtagene maraleucel-treated subjects hospitalised post-treatment for each reason will be reported

Starting date	Study starting date: November 29, 2018 Primary completion date: August 30, 2022 Study completion date: August 30, 2022
Contact information	Contact: Associate Director Clinical Trial Disclosure
Notes	https://clinicaltrials.gov/show/NCT03744676

TRANSCEND - OUTREACH *(Continued)*

	Current clinicaltrials.gov status: Recruiting

TRANSCEND - PILOT (TRANSCEND-NHL-006)

Study name	Lisocabtagene maraleucel (JCAR017) as second-line therapy (TRANSCEND-NHL-006)
Methods	Phase II • Interventional, prospective, single-group, open-label • Study size (according to Clinicaltrials.gov): 56
Participants	**Inclusion Criteria:** • Confirmation of relapsed or refractory aggressive B-cell non-Hodgkin lymphoma of the following histology at relapse: diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS; de novo or transformed follicular lymphoma [tFL]), high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple hit lymphoma [DHL/THL]), and follicular lymphoma Grade 3B per WHO 2016 classification • Previous treatment must include treatment with a single line of chemoimmunotherapy containing an anthracycline and a CD20-targeted agent • Subjects must be deemed ineligible for both high-dose chemotherapy and haematopoietic stem-cell transplant (based on age, performance status and/or comorbidities) while also having adequate organ function for CAR T-cell treatment. • Positron emission tomography (PET)-positive disease • Histological confirmation of diagnosis at last relapse. Enough tumour material must be available for central confirmation of diagnosis, otherwise a new tumour biopsy is mandated. • ECOG performance status of 0, or 1, or 2 • Adequate vascular access for leukapheresis procedure (either peripheral line or surgically-placed line) • Subjects must agree to use appropriate contraception • Subjects must agree to not donate blood, organs, semen, and egg cells for usage in other individuals for at least 1 year following lymphodepleting chemotherapy

Interventions	Lisocabtagene maraleucel
	• lisocabtagene maraleucel will be administered as a single-dose intravenous (IV) injection
	• OthernNames:
	  * JCAR017
	  * liso-cel

Outcomes	Primary outcome measures:
	1. Antitumour activity [time frame: through month 24]
	  a. Overall response rate (complete response + partial response) based on "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification"
	Secondary outcome measures:
	1. Adverse events [time frame: 90 days]
	  a. Proportion of subjects experiencing adverse events
	2. Laboratory abnormalities [time frame: 90 days]
	  a. Proportion of subjects experiencing laboratory abnormalities
	3. Antitumour activity [time frame: through month 24]
	  a. Complete response rate based on "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification"

TRANSCEND - PILOT (TRANSCEND-NHL-006) *(Continued)*

4. Antitumour activity [time frame: through month 24]
   a. Duration of response
5. Maximum concentration (Cmax) of lisocabtagene maraleucel in blood [time frame: through month 24]
   a. Maximum concentration of lisocabtagene maraleucel in blood
6. Time of the maximum concentration (Tmax) of lisocabtagene maraleucel in blood [time frame: through month 24]
   a. Time of the maximum concentration of lisocabtagene maraleucel in blood
7. Area under the curve of (AUC) lisocabtagene maraleucel concentration in blood [time frame: through month 24]
   a. Area under the curve of lisocabtagene maraleucel in blood
8. Progression-free survival [time frame: through month 24]
   a. Progression-free survival
9. Event-free survival [time frame: through month 24]
   a. Event-free survival
10. Overall survival [time frame: through month 24]
    a. Overall survival
11. Health-related quality of life and health economics and outcomes research [time frame: through month 24]
    a. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 is a validated quality of life measure applicable to subjects with any cancer diagnosis
12. Health-related quality of life and health economics and outcomes research [time frame: through month 24]
    a. The EuroQol-5D (EQ-5D) is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal
13. Health-related quality of life and health economics and outcomes research [time frame: through month 24]
    a. The Functional Assessment of Cancer Treatment-Lymphoma (FACT-Lym) consists of the FACT-General scale and a 15-item lymphoma-specific additional concerns subscale (LYM)
14. Health-related quality of life and health economics and outcomes research [time frame: through month 24]
    a. Numbers of intensive care unit inpatient days and non-ICU inpatient days and reasons for hospitalisation

Starting date	Study starting date: July 26, 2018 Primary completion date: December 30, 2021 Study completion date: December 30, 2021
Contact information	Contact: Associate Director Clinical Trial Disclosure
Notes	https://clinicaltrials.gov/show/NCT03483103 Current clinicaltrials.gov status: Recruiting

TRANSCEND - WORLD

Study name	Trial to determine the efficacy and safety of JCAR017 in adult subjects with aggressive B-cell non-Hodgkin lymphoma (TRANSCENDWORLD)
Methods	Phase II • Interventional, prospective, single-group, open-label • Study size (according to Clinicaltrials.gov): 124

TRANSCEND - WORLD *(Continued)*

Participants	**Inclusion Criteria:** • Subject is ≥ 18 years of age at the time of signing the informed consent form (ICF) • Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted • Subject is willing and able to adhere to the study visit schedule and other protocol requirements • Investigator considers the subject is appropriate for adoptive T-cell therapy • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Subjects not eligible for transplant (TNE) in Cohorts 2 and 3 and subjects in Cohort 5 may be enrolled with ECOG of 2 only if they meet all other inclusion/exclusion criteria • Subjects with one of the following: Cohort 1: Subjects with DLBCL NOS (de novo or tFL), HGBL and FL3B per WHO 2016 classification (Swerdlow, 2016), after ≥ 2 lines of therapy*, including an anthracycline and rituximab (or other CD20-targeted agent); Cohort 2: Transplant not eligible subjects with DLBCL NOS (de novo or tFL), HGBL and FL3B per WHO 2016 classification (Swerdlow, 2016), who failed first line therapy*, including an anthracycline and rituximab (or other CD20-targeted agent) • Note: Subjects with secondary CNS lymphoma involvement may enrol in Cohorts 1 to 4 and 7; subjects with PCNSL are eligible for Cohort 5. Subject selection must consider clinical risk factors for severe adverse events (AEs) and alternative treatment options. Subjects should only be enrolled if the Investigator considers the potential benefit outweighs the risk for the subject. For Cohort 5 and to not compromise safety, subject selection has been restricted to those fit enough to HDCT and ASCT as their prior therapy. * Transplant not eligible subjects will include those who are deemed ineligible for high-dose chemotherapy and HSCT due to age, performance status or comorbidity, while also having adequate organ function for CAR T-cell treatment. At the very least, subjects have to meet one of the following criteria: ☐ Age ≥ 70 years ☐ ECOG performance status ≥ 2 ☐ Impaired pulmonary function (DLCO ≤ 60%, adjusted for haemoglobin concentration using the Dinakara equation) ☐ Impaired cardiac function (LVEF < 50%) ☐ Impaired renal function (CrCl < 60 mL/min) ☐ Impaired hepatic function (AST/ALT > 2 x ULN, bilirubin ≥ 2 mg/dL or cirrhosis Child-Pugh B or C) * Subjects must fulfil all other in- and exclusion criteria Cohort 3 (Japan only): Subjects meeting eligibility criteria for either Cohort 1 or 2 Cohort 4: Subjects with newly diagnosed HGBL. Subjects must be eligible for anthracycline and rituximab (or other CD20-targeted agent) containing regimen as induction prior to consolidation with JCAR017 Cohort 5: Subjects with PCNSL who failed first line therapy with HDCT and ASCT Cohort 6: (REMOVED) Cohort 7: Subjects meeting eligibility criteria for Cohort 1 and suitable for outpatient treatment ☐ For subjects with transformed disease, the subject should have had at least 2 lines of systemic therapy for his/her transformed disease (i.e. DLBCL) for Cohort 1 and 1 line for Cohort 2 to be eligible. Lines of therapy do not include those given for a previously indolent condition (i.e. follicular lymphoma). Subjects do NOT have to have anthracycline for their DLBCL if received for indolent disease ☐ For subjects already undergoing anthracycline and rituximab containing regimen, eligibility is to be discussed with Medical Monitor. Subjects with complete metabolic response after 2 cycles of induction will proceed with JCAR017 infusion only at time of relapse, if applicable ☐ Subjects must meet the conditions for outpatient treatment and monitoring as outlined in the Outpatient Administration and Monitoring Guidance for Lisocabtagene Maraleucel • Histological confirmation of diagnosis at last relapse. Enough tumour material must be available for central confirmation of diagnosis, otherwise a new tumour biopsy is mandated. Note: If the subject did not experience CR since last biopsy, the most recent biopsy will be considered adequate to participate in the trial. For subjects with PCNSL, at a minimum, corresponding pathology report is required if archival tumour material is not available and repeated biopsy not feasible • For subjects with PCNSL: Subjects must have disease that is objectively measurable by International Workshop to Standardize Baseline Evaluation and Response Criteria in Primary Central Ner-

TRANSCEND - WORLD *(Continued)*

vous System (CNS) Lymphoma (Abrey, 2005), cerebrospinal fluid (CSF) cytology (in case of leptomeningeal only disease), or vitreal aspiration cytology and/or retinal photographs (in case of ocular lymphoma if clinically indicated)

- Adequate organ function, defined as:
  * Adequate bone marrow function to receive LD chemotherapy as assessed by the Investigator
  * Serum creatinine < 1.5 x ULN or creatinine clearance > 30 mL/min (estimated glomerular filtration rate [eGFR] by Cockroft Gault)
  * Alanine aminotransferase (ALT) ≤ 5 x ULN and total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with Gilbert's syndrome or lymphomatous infiltration of the liver) Adequate pulmonary function, defined as ≤ Grade 1 dyspnoea according to Common Toxicity Criteria for Adverse Events (CTCAE) and SaO2 ≥ 92% on room air
  * Adequate cardiac function, defined as LVEF ≥ 40% as assessed by echocardiogram or multigated acquisition (MUGA) scan performed within 4 weeks prior to leukapheresis
- Adequate vascular access for leukapheresis procedure
- Subjects must agree to not donate blood, organs, sperm or semen, and egg cells for usage in other individuals after the JCAR017 infusion
- Female subjects of childbearing potential (FCBP) must:
  * Have two negative pregnancy tests as verified by the Investigator (one negative serum beta human chorionic gonadotropin [ß-hCG] pregnancy test result at screening and one negative serum pregnancy test within 48 hours prior to the first dose of LD chemotherapy). This applies even if the subject practices true abstinence* from heterosexual contact
  * Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, effective contraception without interruption. Contraception methods must include 1 highly effective (barrier) method of contraception from screening until at least 12 months following LD chemotherapy
- Note: Highly effective methods are defined as those that result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. The following are examples of contraception:
- Highly effective methods:
- Intrauterine device (IUD)
- Hormonal (birth control pill, injections, implants)
- Tubal ligation
- Partner's vasectomy c) Agree to abstain from breastfeeding during study participation and for at least 12 months following LD chemotherapy d) There is insufficient exposure data to provide any recommendation concerning the duration of contraception and the abstaining from breastfeeding following treatment with JCAR017. Any decision regarding contraception and breastfeeding after JCAR017 infusion should be discussed with the treating physician 14. Male subjects must:
  * Practice true abstinence* (which must be reviewed on a monthly basis and source documented) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study and until at least 12 months following LD chemotherapy even if he has undergone a successful vasectomy
  * There is insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCAR017. Any decision regarding contraception after JCAR017 infusion should be discussed with the treating physician * True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. In contrast, periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

Interventions	JCAR017 • Other Name: Lisocabtagene Maraleucel (liso-cel)
Outcomes	Primary outcome measures:

TRANSCEND - WORLD *(Continued)*

1. Overall response rate (ORR) of JCAR017 in subjects with non-Hodgkin lymphoma (NHL; including secondary central nervous system (CNS) involvement) [time frame: up to 2 years after JCAR017 infusion]
   a. Proportion of subjects achieving a complete response (CR) or partial response (PR) based on the Lugano classification
2. ORR of JCAR017 in subjects with relapsed/refractory (r/r) primary central nervous system lymphoma (PCNSL) [time frame: up to 2 years after JCAR017 infusion]
   a. Proportion of subjects achieving a CR/complete response unconfirmed (CRu) or PR based on the International workshop to standardize baseline evaluation and response criteria in primary CNS lymphoma
3. Adverse events (AEs) in subjects intended to be treated as outpatients [time frame: up to 2 years after JCAR017 infusion]
   a. Type, frequency, and severity of all AEs, including serious adverse events (SAEs) and laboratory abnormalities

Secondary outcome measures:

1. Adverse events (AEs) [time frame: up to 2 years after JCAR017 infusion]
   a. Type, frequency, and severity of AEs, including serious adverse events (SAEs) and laboratory abnormalities
2. Overall response rate (ORR) in subjects intended to be treated as outpatients [time frame: up to 2 years after JCAR017 infusion]
   a. Proportion of subjects achieving a complete response (CR) or partial response (PR) based on the Lugano classification
3. Complete response rate (CRR) [time frame: up to 2 years after JCAR017 infusion]
   a. Proportion of subjects achieving a CR (or CR and CRu for subjects with PCNSL) following JCAR017 infusion
4. Event-free survival (EFS) [time frame: up to 2 years after JCAR017 infusion]
   a. Time from JCAR017 infusion to death from any cause, progressive disease (PD), or starting a new anticancer therapy, whichever occurs first
5. Progression-free survival (PFS) [time frame: up to 2 years after JCAR017 infusion]
   a. Time from JCAR017 infusion to the first documentation of PD, or death due to any cause, whichever occurs first
6. Overall survival (OS) [time frame: up to 2 years after last patient's JCAR017 infusion]
   a. Time from JCAR017 infusion to time of death due to any cause
7. Duration of response (DOR) [time frame: up to 2 years after JCAR017 infusion]
   a. Time from first response to progressive disease or death from any cause, whichever occurs first
8. Pharmacokinetics by quantitative polymerase chain reaction (qPCR) - Cmax [time frame: up to 2 years after JCAR017 infusion]
   a. Maximum concentration
9. Pharmacokinetics by qPCR - Tmax [time frame: up to 2 years after JCAR017 infusion]
   a. Time to peak concentration
10. Pharmacokinetics by qPCR - AUC [time frame: up to 2 years after JCAR017 infusion]
    a. Area under the curve
11. Patient-reported outcomes - EORTC QLQ-C30 [time frame: up to 2 years after JCAR017 infusion]
    a. The European organization for research and treatment of cancer - quality of life C30 questionnaire will be used as a measure of health-related quality of life
12. Patient-reported outcomes - FACT-LymS [time frame: up to 2 years after JCAR017 infusion]
    a. Functional assessment of cancer therapy-lymphoma "additional concerns" subscale: Only the LYM subscale will be administered in this study. This scale addresses symptoms and functional limitations (15 item) that are important to lymphoma patients
13. Adverse events (AEs) in subjects treated as outpatients [time frame: up to 2 years after JCAR017 infusion]
    a. Type, frequency, and severity of AEs, including serious adverse events (SAEs) and laboratory abnormalities

Starting date	Study starting date: June 5, 2018 Primary completion date: May 31, 2020

TRANSCEND - WORLD *(Continued)*

	Study completion date: August 15, 2022
Contact information	Contact: Associate Director Clinical Trial Disclosure
Notes	https://clinicaltrials.gov/ct2/show/NCT03484702 Current clinicaltrials.gov status: Recruiting

TRANSFORM

Study name	A study to compare the efficacy and safety of JCAR017 to standard of care in adult subjects with high-risk, transplant-eligible relapsed or refractory aggressive B-cell non-Hodgkin lymphomas
Methods	Phase III • Randomised controlled trial (RCT), open-label • Study size (according to Clinicaltrials.gov): 182
Participants	**Inclusion Criteria:** • Subject is ≥ 18 years and ≤ 75 years of age at the time of signing the informed consent form (ICF) • Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 • Histologically proven diffuse large B-cell lymphoma (DLBCL) NOS (de novo or transformed indolent NHL), high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple-hit lymphoma [DHL/THL]), primary mediastinal (thymic) large B-cell lymphoma (PMBCL), T-cell/histiocyte-rich large B-cell lymphoma (THRBCL) or follicular lymphoma grade 3B. Enough tumour material must be available for confirmation by central pathology • Refractory or relapsed within 12 months from CD20 antibody and anthracycline containing first line therapy • [18F] fluorodeoxyglucose (FDG) positron emission tomography (PET) positive lesion at screening. (Deauville score 4 or 5) • Adequate organ function • Participants must agree to use effective contraception
Interventions	JCAR017 • Other name: lisocabtagene maraleucel or liso-cel
Outcomes	Primary outcome measures: 1. Event-free survival (EFS) [time frame: approximately 3 years] a. Time from randomisation to death from any cause, progressive disease (PD), failure to achieve complete response (CR) or partial response (PR), or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first Secondary outcome measures: 1. Complete response rate (CRR) [time frame: approximately 3 years] a. Percentage of subjects achieving a complete response (CR) 2. Progression-free survival (PFS) [time frame: approximately 3 years] a. Time from randomisation to PD or death from any cause, whichever occurs first 3. Overall survival (OS) [time frame: approximately 4.5 years] a. Time from randomisation to time of death due to any cause 4. Overall response rate (ORR) [time frame: approximately 3 years] a. Percentage of subjects achieving an objective response of partial response (PR) or better according to the Lugano Classification as assessed by IRC review

TRANSFORM *(Continued)*

5. Duration of response (DOR) [time frame: approximately 3 years]
   a. Time from first response to disease progression, start of new antineoplastic therapy due to efficacy concerns or death from any cause
6. PFS on next line of treatment (PFS-2) [time frame: approximately 3 years]
   a. Time from randomisation to second objective disease progression or death from any cause, whichever is first.
7. Adverse events (AEs) [time frame: approximately 3 years]
   a. Type, frequency and severity of adverse events (AEs), serious adverse events (SAE), and laboratory abnormalities (overall and in clinical, histological and molecular subgroups)
8. HRQoL using European organisation for research and treatment of cancer - quality of Life C30 questionnaire (EORTC-QLQ-C30) [time frame: approximately 3 years]
   a. The EORTC QLQ-C30 questionnaire will be used as a measure of health-related quality of life, fatigue, physical and cognitive functions
9. HRQoL parameters assessed by FACT-Lym "Additional concerns" subscale [time frame: approximately 3 years]
   a. Only the LYM subscale will be administered in this study. This scale addresses symptoms and functional limitations (15 item) that are important to lymphoma patients
10. Reasons for hospital resource utilization [time frame: approximately 3 years]
    a. will be assessed based on reasons for hospitalisation
11. Rate of haematopoietic stem-cell transplant (HSCT) [time frame: approximately 3 years]
    a. Rate of completion of HDCT and HSCT
12. Frequency of hospital resource utilization [time frame: approximately 3 years]
    a. Will be assessed based on frequency of hospitalizations calculated as, inpatient days, intensive care unit (ICU) days, outpatient visits days
13. Hospital resource utilization (HRU) [time frame: approximately 3 years]
    a. Will be assessed based on frequency of hospitalizations calculated as, inpatient days, intensive care unit (ICU) days, outpatient visits days and reasons for hospitalisation

Starting date	Study starting date: October 23, 2018 Primary completion date: September 20, 2023 Study completion date: September 20, 2023
Contact information	Contact: Associate Director Clinical Trial Disclosure Study Director:Alessandro Crotta, MD; Celgene
Notes	https://ClinicalTrials.gov/show/NCT03575351 Current clinicaltrials.gov status: Recruiting

ZUMA-14

Study name	Safety and efficacy of axicabtagene ciloleucel in combination with either rituximab or lenalidomide in participants with refractory large B-cell lymphoma (ZUMA-14)
Methods	Phase II • Randomised, controlled trial (RCT), open-label • Study size (according to Clinicaltrials.gov): 60
Participants	**Inclusion criteria:** • Histologically confirmed large B-cell lymphoma

ZUMA-14 *(Continued)*

	• Chemotherapy-refractory disease, defined as one or more of the following:
	  * No response to first-line therapy (primary refractory disease)
	  * No response to second or greater lines of therapy OR
	  * Refractory after autologous stem-cell transplant (ASCT)
	• At least 1 measurable lesion according to the Lugano Classification
	• Individuals must have received adequate prior therapy, including at a minimum:
	  * Anti-CD20 monoclonal antibody
	  * An anthracycline-containing chemotherapy regimen
	• Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
	• Adequate renal, hepatic, pulmonary, and cardiac function
	• Individuals must be able to comply with relevant, equivalent requirements adopted from the REVLIMID Risk Evaluation and Mitigation Strategy (REMS)® (United States) or additional Risk Minimization Measures (aRMMs) as part of the Risk Management Plan (RMP) (European Union)

Interventions	Axicabtagene Ciloleucel Rituximab Lenalidomide Fludarabine Cyclophosphamide

Outcomes	<u>Primary outcome measures:</u>
	
	1. Complete response (CR) Rate [timeframe: up to 2 years]
	  a. CR rate is defined as the incidence of a CR per the Lugano classification as determined by study investigators
	
	<u>Secondary outcome measures:</u>
	
	1. Percentage of participants experiencing adverse events and clinically significant changes in safety lab values [time frame: up to 15 years]
	2. Objective response rate (ORR) [time frame: up to 2 years]
	  a. ORR is defined as the incidence of either a CR or a partial response (PR) per the Lugano classification as determined by study investigators
	3. Duration of Response (DOR) [time frame: up to 2 years]
	  a. DOR is defined only for participants who experience an objective response and is the time from the first objective response to disease progression per the Lugano classification as determined by study investigators or death from any cause
	4. Progression-free survival (PFS) [time frame: up to 2 years]
	  a. PFS is defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression per Lugano classification as determined by study investigators or death from any cause
	5. Overall survival (OS) [time frame: Up to 15 years]
	  a. OS is defined as the time from axicabtagene ciloleucel infusion to the date of death
	6. Levels of axicabtagene ciloleucel in blood [time frame: up to 2 years]

Starting date	Study starting date: November 5, 2019 Primary Completion Date: September 2021 Study Completion Date: September 2036
Contact information	Study Director: Kite Study Director; Kite, A Gilead Company
Notes	https://clinicaltrials.gov/show/NCT04002401

ZUMA-14 *(Continued)*

	Current clinicaltrials.gov status: Recruiting

ZUMA-7

Study name	Efficacy of axicabtagene ciloleucel compared to standard of care therapy in subjects with relapsed/refractory diffuse large B cell lymphoma
Methods	Phase III • Randomised controlled trial (RCT), open-label • Study size (according to Clinicaltrials.gov): 350

Participants	**Inclusion Criteria:**
	• Histologically proven large B-cell lymphoma including the following types defined by WHO 2016
	  * DLBCL not otherwise specified (ABC/GCB)
	  * HGBL with or without MYC and BCL2 and/or BCL6 rearrangement
	  * DLBCL arising from FL
	  * T-cell/histiocyte rich large B-cell lymphoma
	  * DLBCL associated with chronic inflammation
	  * Primary cutaneous DLBCL, leg type
	  * Epstein-Barr virus (EBV) + DLBCL
	• Relapsed or refractory disease after first-line chemoimmunotherapy
	  * Refractory disease defined as no complete remission to first-line therapy; individuals who are intolerant to first-line therapy are excluded.
	  ☐ Progressive disease (PD) as best response to first-line therapy
	  ☐ Stable disease (SD) as best response after at least 4 cycles of first-line therapy (e.g. 4 cycles of R-CHOP)
	  ☐ Partial response (PR) as best response after at least 6 cycles and biopsy-proven residual disease or disease progression ≤ 12 months of therapy
	  * Relapsed disease defined as complete remission to first-line therapy followed by biopsy-proven relapse ≤ 12 months of first-line therapy
	• Individuals must have received adequate first-line therapy including at a minimum:
	  * Anti-CD20 monoclonal antibody unless investigator determines that tumour is CD20 negative, and
	  * An anthracycline containing chemotherapy regimen
	• No known history or suspicion of central nervous system involvement by lymphoma
	• Eastern cooperative oncology group (ECOG) performance status of 0 or 1
	• Adequate bone marrow function as evidenced by:
	  * Absolute neutrophil count (ANC) ≥ 1000/uL
	  * Platelet ≥ 75,000/uL
	  * Absolute lymphocyte count ≥ 100/uL
	• Adequate renal, hepatic, cardiac, and pulmonary function as evidenced by:
	  * Creatinine clearance (Cockcroft Gault) ≥ 60 mL/min
	  * Serum Alanine aminotransferase/Aspartate aminotransferase (ALT/AST) ≤ 2.5 Upper limit of normal (ULN)
	  * Total bilirubin ≤ 1.5 mg/dl
	  * Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an Echocardiogram (ECHO), and no clinically significant Electrocardiogram (ECG) findings
	  * No clinically significant pleural effusion
	  * Baseline oxygen saturation > 92% on room air

Interventions	Axicabtagene Ciloleucel

ZUMA-7 *(Continued)*

	Platinum-containing salvage chemotherapy (e.g. R-ICE) followed by high dose therapy (e.g. BEAM) and autologous stem-cell transplant in responders. Cyclophosphamide Fludarabine
Outcomes	Primary outcome measures: 1. Event-free survival (EFS) [time frame: up to 5 years] a. Event-free survival is defined as the time from randomisation to the earliest date of disease progression per Lugano classification, commencement of new lymphoma therapy, or death from any cause as determined by blinded central review Secondary outcome measures: 1. Objective response rate (ORR) [time frame: up to 5 years] a. Objective response rate is defined as the incidence of either a complete response or a partial response by the Lugano classification as determined by blinded central review 2. Overall survival (OS) [time frame: up to 5 years] a. Overall survival is defined as the time from randomisation to death from any cause 3. Modified event-free survival (mEFS) [time frame: up to 5 years] a. Event-free survival is defined the same way as EFS, except that failure to attain CR or PR by Day 150 assessment is not considered an event. mEFS will be analysed per blinded central review and per investigator disease assessments. 4. Progression-free survival (PFS) [time frame: up to 5 years] a. Progression-free survival is defined as the time from randomisation to disease progression per Lugano classification or death from any cause 5. Duration of response (DOR) [time frame: up to 5 years] a. Duration of response is derived only among subjects who experience an objective response per Lugano classification as determined by blinded central review and is defined as the time from first response to disease progression per the Lugano classification or death from any cause 6. Percentage of adverse events and clinical significant changes in safety lab values, including anti-bodies to axicabtagene ciloleucel. [time frame: up to 5 years] 7. Changes in EORTC QLQ-C30 domains [time frame: up to 5 years] a. The EORTC QLQ-C30 is a multi-item questionnaire 8. Changes over time in the EQ-5D-5L [time frame: up to 5 years] a. The EQ-5D-5L questionnaire is a generic measure of health status 9. Changes over time in the visual analog scale (VAS) scores [time frame: up to 5 years] a. The EQ-5D-5L VAS is a 20-cm VAS for recording self-rated current HRQoL state and is used to describe the subjects' health status on the day of the assessment
Starting date	Study starting date: December 14, 2017 Primary completion date: January 15, 2022 Study completion date: January 15, 2035
Contact information	Study Director: Kite Study Director; Kite, A Gilead Company
Notes	https://clinicaltrials.gov/show/NCT03391466 Current clinicaltrials.gov status: Recruiting

ABVD: adriamycin, bleomycin, vinblastine, and dacarbazine
ANC: absolute neutrophil count
ALL: acute lymphoblastic leukaemia
BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
CNS: central nervous system

CS: clinical staging
CT: computed tomography
CLL: chronic lymphocytic leukaemia
ECHO: Echocardiogram
ECOG: Eastern Cooperative Oncology Group
esc: escalated
FDG: fluorodeoxy-D-glucose
G-CSF: granulocyte colony-stimulating factor
HIV: human immunodeficiency virus
HL: Hodgkin lymphoma
IV: intravenous
LVEF: left ventricular ejection fraction
N/A: not available
NCI CTCAE v 3.0: National Cancer Institute, Common Terminology Criteria for Adverse Events Version 3.0
NHL: Non-Hodgkin lymphoma
PET: positron emission tomography
PFS: progression-free survival
SC: subcutaneous
WHO: World Health Organization

ADDITIONAL TABLES

Table 1. Risk of bias assessment based on criteria for observational studies provided by the Cochrane Childhood Cancer Group

Heading	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

Table 2. Main study characteristics

Characteristic\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
Centre	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 CD 20	CD19	CD19	CD19	CD19
Infusions	1	1-3	1	1	1	1	1	1	1	1-2	1	1	1

Table 2. Main study characteristics *(Continued)*

Dose CAR T-cells (median if not otherwise specified)	1 x 106/kg	Range 0.45-4.59 x 106/kg	2 x 106/kg	3 x 108 (range 0.1-6 x)	Reduced from 5 to 1 x 106/kg during study	50 or 100 x 106	CD19: 1 x 106/kg (range 0.2-4 x) CD20: 1 x 106/kg (range 0.1-4 x)	5.79 × 106/kg (range 3.08-8.87 x)	Range 1-6 x 106/kg	50 (in 1-2 doses), 100 or 150 x 106	2 x 106/kg	2 x 106/kg	2 x 106/kg
Co-interventions	None	None	None	None	None	Durvalumab	None	None	None	None	None	None	Atezolizumab
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 and Cyc 250 mg/m^2 for 3 days or Bendamustine 90 mg/m^2 (in lieu of Cyc) 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 2 g for 3 days	n = 14 (DLBCL subgroup): Hyperfractionated Cyc 1.8 gm/m^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	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	12 for phase 1 (37 accord-

Table 2. Main study characteristics *(Continued)*

											according to CT.gov)		ing 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	18	13	47	93	22	11	21	28	28	256	29	101 for phase 2	12
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%) including those receiving a 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	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

CT.gov = Clinicaltrials.gov
Cyc = cyclophosphamide
DLBCL = diffuse large B-cell lymphoma
EPOCH = etoposide, prednisolone, oncovin, cyclophosphamide, and hydroxydaunorubicin
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 study 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.

Table 3. Main participant characteristics

Characteristic\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
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-centre DLBCL (n = 7); non–germinal-centre 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-centre DLBCL	n = 12 evaluated, n = 12 (100%) DLBCL Type of DLBCL NR
Age in years (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)

Table 3. Main participant characteristics *(Continued)*

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
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
DLBCL = diffuse large B-cell lymphoma
NOS = not otherwise specified
NR = not reported
SCT = stem-cell transplantation
TF = transformed
[a] Due to heterogeneous reporting of the composed sample including 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.

Table 4. Efficacy (overall survival, progression-free survival, overall response, complete response, partial response)

Study ID \characteristic	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% to 74%)	Disease-free survival rate at 4 months: 53% (95% CI 36% to 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% to 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% to 57%) At 18 months: 43% (95% CI 33% to 35%)	Probability of being relapse-free at 6 months: 66% (95% CI 51% to 78%) Probability of being relapse=free at 12 or 18 months: 64% (95% CI 48% to 76%)	bOR at median follow-up of 19.3 months post-infusion: 54% (95% CI 43% to 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)

Table 4. Efficacy (overall survival, progression-free survival, overall response, complete response, partial response) *(Continued)*

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)
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 to 9.6)	Median PFS: 5.0 months (95% CI 2.3 to 7.7)	At 3 months: 17/21 (81.0%) (95% CI 58.1% to 94.6%) Sustained OR at 6 months: 6/21 (46.2%) (95% CI 19.2% to 74.9%)	At 3 months: 11/21 (52.4%) (95% CI 26% to 70%) Sustained CR rate at 6 months: 4/21 (40.0%) (95% CI 12.2% to 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% to 79%; 7/14) (DLBCL subgroup; n = 14)	At 6 months: 43% (95% CI 18% to 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% to 92%) At 12 months: 71% (95% CI 51% to 85%)	Reported for DLBCL subgroup (n = 16) Median PFS: NA Progression-free at 12 months: 75% (95% CI 46 to 90)	bOR: 75% (95% CI 48% to 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)

Table 4. Efficacy (overall survival, progression-free survival, overall response, complete response, partial response) *(Continued)*

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 to 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 to NR) Estimated at 6 months: 74.7% (95% CI 68.9% to 79.6%) Estimated at 12 months: 57.9% (95% CI 51.3% to 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: 6.8 months (95% CI 3.3 to 14.1) Estimated at 6 months PFS: 51.4% (95% CI 44.6% to 57.7%) Estimated at 12 months PFS: 44.1% (37.3% to 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% to 78.0%) ITT: 208/344 (61%; 95% CI 55.1% to 65.7%) DLBCL NOS: 89/131 (67.9%; 95% CI 59.2% to 75.8%) DLBCL TF from FLL: 48/57 (84.2%; 95% CI 72.1% to 92.5%) DLBCL TF from other indolent NHL: 11/18 (61.1%; 95% CI 35.7% to 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 to 59.4) ITT: 150/344 (44%; 95% CI 38.3% to 49.0%) DLBCL NOS: 64/131 (48.9%; 95% CI 40.0% to 57.7%) DLBCL TF from FLL: 36/57 (63.2%; 95% CI 49.3% to 75.6%) DLBCL TF from other indolent NHL: 7/18 (38.9%; 95% CI 17.3% to 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% to 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% to 94.28%) At 3 months: 11/20 (55% (95% CI 31.53% to 76.94%)	Reported for DLBCL subgroup (n = 20): At 1 month: 12/20 (60% (95% CI 36.05 to 80.88)) At 3 months: 11/20 (55% (95% CI 31.53 to 76.94)) At: 6 months: 9/20 (45% (95% CI 23.06% to 68.47%)	NR

Table 4. Efficacy (overall survival, progression-free survival, overall response, complete response, partial response) *(Continued)*

					At 6 months: 9/20 (45% (95% CI 23.06% to 68.47%)		
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% to 85%) At 12 months: 59% (95% CI 49% to 68%) At 18 months: 52% (95% CI 41% to 62%) Reported for phase 2 population (n = 101, n = 77 (76%) DLBCL): Median at 24 months follow-up: NR (95% CI 12.8 to NR) Estimated at 24 months: 50.5% (95% CI 40.2% to 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 to 15.0) At 6 months: 49% (95% CI 39% to 58%) At 12 months: 44% (95% CI 34% to 53%) At 15 months: 41% (95% CI 31% to 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 to NA)	bOR: 21/28 (75%) (95% CI 55% to 89%)	bOR: 13/28 (46%) (95% CI 28% to 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
NA = not achieved
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 2.

Table 5. Efficacy (quality of life)

Study ID \characteristic	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)[b]	n = 34 (participants with CR/PR) change from BL (SD): +8.6 (20.3) [b]	NR	n = 30 (participants with CR/PR) change from BL (SD): +9.6 (17.9) [b]	n = 21 (participants with CR/PR) change from BL (SD): +13.1 (16.1) [c]
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
EQ-5D-5L VAS = EuroQol 5-Dimension 5-Level visual analogue scale
FACT-Lym = Function Assessment of Cancer Therapy-Lymphoma
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 2.
[b] According to the authors, the improvement was above the MCID lower limit.
[c] According to the authors, the improvement was above the MCID upper limit.

Table 6. Safety

Study ID \characteristic	Sample size (if not otherwise specified) [a]	Any adverse events	Any serious adverse events	CRS (including 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%)

Table 6. Safety *(Continued)*

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 (dexamethasone): 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
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%) Glucocorticoids (dexamethasone): 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

Table 6. Safety *(Continued)*

Schuster 2017	n 2 8 (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%) Any prolonged cytopenias: NR	NR	NR
TRANS-CEND-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%)

Table 6. Safety *(Continued)*

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
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	NR	NR

Table 6. Safety *(Continued)*

		NEU: NR, Grade ≥ 3: 5/12 (42%) (reported for phase 1) TH: 4/34 (12%), Grade ≥ 3: NR Prolonged cytopenias: NR

AN = anaemia
CRS = cytokine release syndrome
CT.gov = Clinicaltrials.gov
DLBCL = diffuse large B-cell lymphoma
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 2 .

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

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

APPENDICES

Appendix 1. CENTRAL search strategy

ID Search

#1 MeSH descriptor: [Lymphoma, B-Cell] this term only

#2 (b-cell near/3 lymphom*) or (b-cell near/3 malignanc*)

#3 MeSH descriptor: [Lymphoma, Non-Hodgkin] explode all trees

#4 (non-hodgkin* or non hodgkin* or nonhodgkin* or no hodgkin* or nhl)

#5 (lymph* adj2 sarcom*)

#6 lymphosarcom*

#7 (reticulum near/2 sarcom*)

#8 (diffus* near/3 lymphom*)

#9 ((lymphom* near/3 cleaved*) or (lymphom* near/3 noncleaved*) or (lymphom* near/3 non-cleaved*) or (lymphom* near/3 grad*) or (lymphom* near/3 mixed-cell*) or (lymphom* near/3 pleomorphic*))

#10 reticulosarcoma*

#11 (mixed near/3 lymphom*) or (undifferentiat* near/3 lymphom*)

#12 NHL

#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

#14 MeSH descriptor: [Lymphoma, Large B-Cell, Diffuse] explode all trees

#15 (histiocyt* near/3 lymphom*)

#16 (large cell* near/3 lymphom*) or (bcell near/3 lymphom*) or (lymphoid* near/3 lymphom*) or (histiocytic* near/3 lymphom*) or (plasmablastic* near/3 lymphom*)

#17 DLBCL

#18 #14 or #15 or #16 or #17

#19 #13 or #18

#20 MeSH descriptor: [Immunotherapy, Adoptive] explode all trees

#21 (immunotherap* near/3 adoptiv*)

#22 (t-cell* near/1 therap*) or (tcell* near/1 therap*)

#23 #20 or #21 or #22

#24 MeSH descriptor: [Receptors, Antigen, T-Cell] explode all trees

#25 (chimeric* near/3 antigen receptor*) or (chimeric* near/3 immunoreceptor*) or (chimeric* near/3 T cell receptor*) or (chimeric* near/3 Tcell receptor*)

#26 (artificial* near/3 T cell receptor*) or (artificial* near/3 Tcell receptor*)

#27 #24 or #25 or #26

#28 axicabtagene*

#29 (yescarta* or axi-cel* or KTE-C19 or "CTL 019")

#30 #28 or #29

#31 tisagenlecleucel*

#32 (kymriah* or CART-19 or CART19)

#33 #31 or #32

#34 lisocabtagene*

#35 (liso-cel* or JCAR017*)

#36 #34 or #35

#37 #23 or #27 or #30 or #33 or #36

#38 #19 and #37

Appendix 2. MEDLINE search strategy

Searches

1 *LYMPHOMA, B-CELL/

2 ((b-cell adj3 lymphom*) or (b-cell adj3 malignanc*)).tw.

3 LYMPHOMA, NON-HODGKIN/

4 (non-hodgkin* or non hodgkin* or nonhodgkin* or no hodgkin* or nhl).tw,kf.

5 (lymph* adj2 sarcom*).tw,kf.

6 lymphosarcom*.tw,kf.

7 (reticulum adj2 sarcom*).tw,kf.

8 (diffus* adj3 lymphom*).tw,kf.

9 ((lymphom* adj3 cleaved*) or (lymphom* adj3 noncleaved*) or (lymphom* adj3 non-cleaved*) or (lymphom* adj3 grad*) or (lymphom* adj3 mixed-cell*) or (lymphom* adj3 pleomorphic*)).tw,kf.

10 reticulosarcoma*.tw,kf.

11 ((mixed adj3 lymphom*) or (undifferentiat* adj3 lymphom*)).tw,kf.

12 NHL.tw.

13 or/1-12

14 exp LYMPHOMA, LARGE B-CELL, DIFFUSE/

15 (histiocyt* adj3 lymphom*).tw,kf.

16 ((large cell* adj3 lymphom*) or (b-cell adj3 lymphom*) or (bcell adj3 lymphom*) or (lymphoid* adj3 lymphom*) or (histiocytic* adj3 lymphom*) or (plasmablastic* adj3 lymphom*)).tw,kf.

17 DLBCL.tw,kf.

18 or/14-17

19 13 or 18

20 Immunotherapy, Adoptive/

21 (immunotherap* adj3 adoptiv*).tw,kf,nm.

22 ((t-cell* adj1 therap*) or (tcell* adj1 therap*)).tw.

23 or/20-22

24 Receptors, Chimeric Antigen/

25 ((chimeric* adj3 antigen receptor*) or (chimeric* adj3 immunoreceptor*) or (chimeric* adj3 T cell receptor*) or (chimeric* adj3 Tcell receptor*)).tw,kf,nm.

26 ((artificial* adj3 T cell receptor*) or (artificial* adj3 Tcell receptor*)).tw,kf,nm.

27 or/24-26

28 axicabtagene*.tw,kf,ot,nm.

29 (yescarta* or axi-cel* or KTE-C19 or "CTL 019").tw,kf,nm.

30 or/28-29

31 tisagenlecleucel*.tw,kf.

32 (kymriah* or CART-19 or CART19).tw,kf,nm.

33 or/31-32

34 Lisocabtagene*.tw,kf.

35 (liso-cel* or JCAR017*).tw,kf,nm.

36 or/34-35

37 or/34-36

38 23 or 27 or 30 or 33 or 36

39 19 and 38

40 exp animals/ not humans/

41 39 not 40

Appendix 3. Embase search strategy

Searches

1 *B CELL LYMPHOMA/

2 ((b-cell adj3 lymphom*) or (b-cell adj3 malignanc*)).tw.

3 NONHODGKIN LYMPHOMA/

4 (non-hodgkin* or non hodgkin* or nonhodgkin* or no hodgkin* or nhl).tw.

5 (lymph* adj2 sarcom*).tw.

6 lymphosarcom*.tw.

7 (reticulum adj2 sarcom*).tw.

8 (diffus* adj3 lymphom*).tw.

9 ((lymphom* adj3 cleaved*) or (lymphom* adj3 non-cleaved*) or (lymphom* adj3 grad*) or (lymphom* adj3 mixed-cell*) or (lymphom* adj3 pleomorphic*)).tw.

10 reticulosarcoma*.tw.

11 ((mixed adj3 lymphom*) or (undifferentiat* adj3 lymphom*)).tw.

12 NHL.tw.

13 or/1-12

14 exp DIFFUSE LARGE B CELL LYMPHOMA/

15 (histiocyt* adj3 lymphom*).tw.

16 ((large cell* adj3 lymphom*) or (b-cell adj3 lymphom*) or (bcell adj3 lymphom*) or (lymphoid* adj3 lymphom*) or (histiocytic* adj3 lymphom*) or (plasmablastic* adj3 lymphom*)).tw.

17 DLBCL.tw.

18 or/14-17

19 13 or 18

20 ADOPTIVE IMMUNOTHERAPY/

21 (immunotherap* adj3 adoptiv*).tw.

22 ((t-cell* adj1 therap*) or (tcell* adj1 therap*)).tw.

23 or/20-22

24 CHIMERIC ANTIGEN RECEPTOR/

25 ((chimeric* adj3 antigen receptor*) or (chimeric* adj3 immunoreceptor*) or (chimeric* adj3 T cell receptor*) or (chimeric* adj3 Tcell receptor*)).tw.

26 ((artificial* adj3 T cell receptor*) or (artificial* adj3 Tcell receptor*)).tw.

27 or/24-26

28 axicabtagene*.tw.

29 (yescarta* or axi-cel* or KTE-C19 or "CTL 019").tw.

30 or/28-29

31 tisagenlecleucel*.tw.

32 (kymriah* or CART-19 or CART19).tw.

33 or/31-32

34 Lisocabtagene*.tw.

35 (liso-cel* or JCAR017*).tw.

36 or/34-36

37 23 or 27 or 30 or 33 or 37

38 19 and 37

39 (animal experiment/ or Animal experiment/) not (human experiment/ or human/)

40 38 not 39

41 39 not 40

Appendix 4. WHO International Clinical Trials Registry Platform search strategy

Basic

DLBCL AND Chimeric Antigen Receptor
DLBCL AND CAR-T
DLBCL AND axicabtagene only drug
DLBCL AND tisagenlecleucel only drug
lisocabtagene only drug

Advanced

Condition: DLBCL
Intervention: Chimeric Antigen Receptor

Recruitment status: ALL

Condition: DLBCL
Intervention: Car-T
Recruitment status: ALL

Condition: DLBCL
Intervention: axicabtagene
Recruitment status: ALL

Condition: DLBCL
Intervention: tisagenlecleucel
Recruitment status: ALL

Condition: DLBCL
Intervention: lisocabtagene
Recruitment status: ALL

Appendix 5. EU clinical trials register search strategy

DLBCL AND car-t OR Chimeric Antigen Receptor OR axicabtagene OR tisagenlecleucel OR Lisocabtagene OR JCAR017 OR liso-cel
DLBCL AND chimeric antigen receptor
DLBCL AND axicabtagene
DLBCL AND tisagenlecleucel
DLBCL AND lisocabtagene
DLBCL AND JCAR017
DLBCL AND liso-cel

Appendix 6. ClinicalTrials.gov search strategy

Basic

Condition or disease: DLBCL
Other terms: Chimeric Antigen Receptor

Condition or disease: DLBCL
Other terms: CAR-T

Condition or disease: DLBCL
Other terms: axicabtagene

Condition or disease: DLBCL
Other terms: tisagenlecleucel

Condition or disease: DLBCL
Other terms: lisocabtagene

Advanced search conditions: DLBCL
interventions: car-t OR Chimeric Antigen Receptor OR axicabtagene OR tisagenlecleucel OR Lisocabtagene OR JCAR017 OR liso-cel

HISTORY

Protocol first published: Issue 6, 2019

CONTRIBUTIONS OF AUTHORS

- Moritz Ernst: methodological expertise, conception and writing of the review
- Annika Oeser: support in data extraction
- Burcu Besiroglu: support in data extraction
- Julia Caro-Valenzuela: support in data extraction
- Mohamed Abd El Aziz: support in data extraction
- Ina Monsef: development of the search strategy
- Peter Borchmann: clinical expertise and advice
- Lise J Estcourt: methodological and content expertise

- Nicole Skoetz: methodological expertise, conception and writing of the review
- Marius Goldkuhle: methodological expertise, conception and writing of the review

DECLARATIONS OF INTEREST

- Moritz Ernst: none known
- Annika Oeser: none known
- Burcu Besiroglu: none known
- Julia Caro-Valenzuela: none known
- Mohamed Abd El Aziz: none known
- Ina Monsef: none known
- Peter Borchmann: consultancy and payment for lectures including service on speakers bureaus: DLBCL; Novartis, Celgene, Gilead, Miltenyi
- Lise J Estcourt: none known
- Nicole Skoetz: none known
- Marius Goldkuhle: none known

SOURCES OF SUPPORT

Internal sources

- University Hospital of Cologne, Faculty of Medicine and University Hospital, University of Cologne, Germany

  Cochrane Cancer, Department I of Internal Medicine

External sources

- None, Other

  None

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

At the protocol stage:

- We had planned to include either randomised controlled trials (RCTs) or, if not available, non-randomised studies of interventions (NRSIs). Accordingly, we specified the full methods for inclusion of the corresponding studies in the protocol. We also described the methods we would have applied to meta-analyse data. However, as we identified uncontrolled studies only, none of these methods were applied.
- We intended to analyse health economic outcomes that were reported among eligible trials. However, we did not identify any relevant data.
- We planned to involve clinical study reports to complement the data retrieved from published work and registries. As we did not identify any studies that were reported in the form of clinical study reports (e.g. RCTs), we were not able to include such data.
- We intended to include data on treatment-related mortality in the GRADE assessment as reported in our protocol, but did not identify such data. During the course of the review and on the grounds of their clinical relevance, we decided to present additional safety data, i.e. any serious adverse events and cytokine release syndrome (see Differences between protocol and review).

In accordance with the PRISMA harms checklist, we planned to consider a broader range of study designs for outcomes of harms independent of their publication status. Such sources include submissions to the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), as well as registers of the manufacturers (Zorzela 2016). We would have considered harms data irrespective of the study design of the study reporting the relevant data, but would not have combined any data across study designs. As our search did only identify prospective uncontrolled studies, we did not include such data.

For health economic evaluation, we had planned to include cost and economic evaluations conducted alongside or as part of any primary study. However, health economic outcomes were reported by none of the included studies.

Assessment of risk of bias in included studies

Randomised controlled trials

For the assessment of risk of bias in randomised controlled trials, we would have used the following criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020a).

- Sequence generation

- Allocation concealment
- Blinding (participants, personnel, outcome assessors)
- Incomplete outcome data
- Selective outcome reporting
- Other sources of bias

For every criterion, we would have made a judgement using one of three categories.

- 'Low risk': if the criterion was adequately fulfilled in the study (i.e. the study was at a low risk of bias for the given criterion).
- 'High risk': if the criterion was not fulfilled in the study (i.e. the study was at high risk of bias for the given criterion).
- 'Unclear risk': if the study report did not provide sufficient information to allow for a judgement of 'low risk' or 'high risk', or if the risk of bias was unknown for one of the criteria listed above.

Non-randomised controlled studies

For the assessment of risk of bias in non-randomised controlled studies, two review authors (ME, MG) would have independently assessed eligible studies for methodological quality and risk of bias (using the Risk Of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool) (Sterne 2016). The quality assessment strongly depends upon information on the design, conduct and analysis of the trial. The two review authors would have resolved any disagreements regarding the quality assessments by consulting a third review author (NS) until reaching a consensus.

We would have assessed the following domains of bias.

- Bias due to confounding
- Bias in selection of participants into the study
- Bias in classification of interventions
- Bias due to deviations from intended interventions
- Bias due to missing data
- Bias in measurement of outcomes
- Bias in selection of the reported result

For every criterion, we would have made a judgement using one of five response options.

- Yes
- Probably yes
- Probably no
- No
- No information

Economic analyses

For economic analyses, we had planned to assess bias by looking at the overall methodological quality of the economic component of the evaluation by using the CHEERS checklist (Husereau 2013) which comprises 24 essential reporting items for all forms of economic evaluations, including cost-effectiveness analyses and cost-benefit analyses.

Measures of treatment effect

Randomised controlled trials

For continuous outcomes, we would have recorded the mean, standard deviation and total number of participants in both the treatment and control groups. For dichotomous outcomes, we would have recorded the number of events and total number of participants in both the treatment and control groups.
For continuous outcomes using the same scale we would have performed analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales, we would have performed analyses using the standardised mean difference (SMD).

If available, we would have extracted and reported hazard ratios (HRs) for time-to-event outcomes (overall survival, progression-free survival). If HRs were not available, we would have made every effort to estimate as accurately as possible the HR using the available data and a purpose-built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007). If sufficient studies provided HRs, we would have used HRs rather than RRs or MDs in a meta-analysis, but for completeness, we would have also performed a separate meta-analysis of data from studies providing only RRs or MDs for the same outcome.

For dichotomous outcomes, we would have reported the pooled risk ratio (RR) with a 95% CI (Deeks 2011). If the number of observed events was small (less than 5% of the sample per group), and if trials had balanced treatment groups, we would have reported the Peto odds ratio (OR) with 95% CI (Deeks 2011).
For cluster-randomised trials, we would have extracted and reported direct estimates of the effect measure (e.g. RR with a 95% CI) from an analysis that accounted for the clustered design. We would have obtained statistical advice to ensure the analysis was appropriate. If appropriate analyses are not available, we would have made every effort to approximate the analysis following the recommendations in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020b).

Non-randomised controlled studies

For dichotomous outcomes, if available, we had planned to extract and report the RR with a 95% CI from statistical analyses adjusting for baseline differences (such as Poisson regressions or logistic regressions) or the ratio of RRs (i.e. the RR post-intervention/RR pre-intervention).

For continuous variables, if available, we had planned to extract and report the absolute change from a statistical analysis adjusting for baseline differences (such as regression models, mixed models or hierarchical models), or the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups/the post-intervention level in the control group) (EPOC 2017).

Assessment of heterogeneity

Given we had identified data eligible for meta-analysis, we would have assessed heterogeneity of treatment effects between trials using a Chi^2 test with a significance level at $P < 0.1$. We would have used the I^2 statistic to quantify possible heterogeneity (I^2 statistic > 30% to signify moderate heterogeneity, I^2 statistic > 75% to signify considerable heterogeneity; Deeks 2011). If heterogeneity was above 80%, we would have explored potential causes through sensitivity and subgroup analyses. In the event of the presence of unexplained heterogeneity, we would not have performed a meta-analysis, but would have commented on results from all studies and would have presented these in tables.

Assessment of reporting biases

We would have searched trial registries to identify completed trials which had not been published elsewhere, to minimise or determine publication bias.

In meta-analyses involving at least 10 trials, we would have intended to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test (Sterne 2011). We would have considered $P < 0.1$ as significant for this test.

Data synthesis

Given eligible data had been identified and given the clinical and methodological characteristics of individual studies had been sufficiently homogeneous, we would have pooled the data in meta-analysis. We would have performed analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We would not have conducted meta-analyses that involved both RCTs and non-RCTs. We would have conducted separate meta-analyses for each comparison.

We would have used the Review Manager 5 (RevMan 5) software for analyses (Review Manager 2014). One review author would have entered the data into the software (ME), and a second review author would have checked the data for accuracy (MG).

We would have used the random-effects model for all analyses as we anticipated that true effects would have been related but the same for included studies. If we could not perform a meta-analysis, we would have commented on the results as a narrative with the results from all studies presented in tables.

For RCTs, when meta-analysis was feasible, we would have used the random-effects model for pooling the data. For binary outcomes, we would have based the estimation of the between-study variance using the Mantel-Haenszel method. We would have used the inverse variance method for continuous outcomes, outcomes that included data from cluster-RCTs, or outcomes where HRs were available. If heterogeneity had been found to be above 80%, and we had identified a cause for the heterogeneity, we would have explored this with subgroup analyses. If we could not find a cause for the heterogeneity, then we would not perform a meta-analysis, but comment on the results as a narrative with the results from all studies presented in tables.

If a meta-analysis had been feasible for non-RCTs, controlled before-and-after studies, interrupted time series studies, and cohort studies, we would have analysed the different types of studies separately. We would have only analysed outcomes with adjusted effect estimates if these were adjusted for the same factors using the inverse-variance method.

Assessment of health economic outcomes

For cost analyses and economic evaluations, we would have provided a narrative summary comparing and evaluating methods used and principal results between studies. These would have summarised incremental cost and incremental cost-effectiveness ratios. If it had not

been possible to express costs in this way, then we would have expressed these results as the most recent international dollars value using implicit price deflators for gross domestic product (GDP) and GDP purchasing power parities. Where possible, we would have combined and summarised unit cost data. We had planned to conduct this review according to current guidance on the use of economics methods in the preparation and maintenance of Cochrane Reviews (Shemilt 2011).

NOTES

While conducting this Cochrane review, five members of the author team (ME, AO, PB, NS, MG) prepared a review of CAR-T cell therapy for relapsed/refractory diffuse large B-cell lymphoma for the 23rd WHO Expert Committee on Selection and Use of Essential Medicines. A major part of that review is based on the results of this Cochrane review. The conduct of the Cochrane review was neither initiated, nor funded nor influenced by the WHO.

Some passages in this review, especially in the Methods section, are from the standard template of Cochrane Haematology.