Application of CD19-directed CAR T-cell therapy for the WHO Model List of Essential Medicines 2023

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1. Content

2. Summary statement of the proposal for the inclusion of new medicines

This is the first application of its kind, supporting the addition of cellular immunotherapy to the WHO Model List of Essential Medicines (EML). In particular, the submission concerns to the inclusion of CD19-directed chimeric antigen receptor (CAR) T-cells as a therapeutic group for the treatment of relapsed or refractory aggressive large B-cell lymphoma (LBCL) in the form of a square box listing.

Relapsed or refractory LBCL is an aggressive lymphoid malignancy with a poor prognosis and a median overall survival of less than 6 to 12 months. Intensified immunochemotherapy including high-dose chemotherapy (HDCT) supported by autologous stem-cell transplantation (ASCT) has curative potential. However, not all patients are eligible for this treatment, and of those who are, less than half respond and only about a quarter of patients achieve long-term remission.

The results of our systematic review are based on three large multicentric randomized controlled trials (RCTs). The evidence suggests that cellular immunotherapy with CAR T-cells may improve overall survival compared to the established treatment standard of immunochemotherapy, HDCT and ASCT. With survival follow-up still ongoing, the evidence is of low certainty. However, considering that over half of the participants in the control arms received CAR T-cells as the next-line treatment after treatment failure, the beneficial effect of CAR T-cells might be underestimated and not adequately represented by the overall survival (OS) estimate. In this regard, the surrogate endpoints of event-free survival (EFS) and progression-free survival (PFS) might be more informative, since outcome evaluation occurs before treatment switching and does not influence the effect estimate. Both PFS and EFS are likely improved with CAR T-cell therapy. This is also reflected by the higher overall response rates seen with CAR T-cell therapy, when compared to the standard-of-care (SOC). Notably, we observed differences in the survival outcomes and response across trials that may be due to differences in the intervention or the study designs. Although survival data are immature, with improvements in surrogate endpoints and a PFS hazard ratio (HR) of 0.47 (95% CI, 0.37 to 0.60), CAR T-cell therapy receives a Grade A classification on the ESMO Magnitude of Clinical Benefit Scale v1.1.

The evidence further suggests that quality of life might be increased for CAR T-cell therapy compared to SOC at some points of the treatment sequence. The evidence is uncertain and may be limited to patients who respond to or tolerate treatments well.

Patients treated with CAR T-cells can experience potentially life-threatening adverse events such as cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome. However, in the evaluated trials there was little to no difference regarding the occurrence of serious adverse events compared to second-line SOC.

Treatment with CAR T-cells is technologically demanding and resource intensive, requiring well-equipped facilities for its manufacturing and trained physicians to administer the treatment. Global availability of CAR T-cell therapy is limited. Thus far, it has not been introduced in lower- or middle-income countries (LMIC). Cellular immunotherapy in the form of CAR T-cells gains importance in nearly all fields of malignant hematology. Given the evidence that indicates superior efficacy over SOC in the treatment of LBCL, we propose the inclusion of CD19-directed CAR T-cells in the EML. This could significantly help to increase accessibility and lower costs for healthcare systems and patients.

3. Relevant WHO technical department and focal point

Lorenzo Moja, Technical Officer, EML Secretariat

4. Organizations supporting the application

- Department I of Internal Medicine, Evidence-based Medicine Research Group, University Hospital of Cologne
- Cochrane Haematology

5. Key information for the proposed medicines

International non-proprietary name (INN):

- Axicabtagene ciloleucel (axi-cel)
- Tisagenlecleucel (tisa-cel)
- Lisocabtagene maraleucel (liso-cel)

Anatomical therapeutic chemical (ATC, implementation in the ATC/DDD index in 2022):

- L01XX70
- L01XX71
- No ATC code yet (categorized by European Medicines Agency [1] as L01 "antineoplastic agents")

Dosage form(s) and strength(s) of the proposed medicine(s)

This application refers to CAR T-cell therapy administered in the following dosages proposed by the manufacturers:

- *Axicabtagene ciloleucel*: the dosage depends on the patient's body weight. A dose of 2 * 10^6 CAR-positive T-cells per kg body weight with a maximum of 2 * 10^8 CAR-positive viable T-cells is recommended, and there is no data regarding overdose [2, 3].
- *Tisagenlecleucel*: the dosage is independent of weight with 0.6 – 6.0 * 10^8 CAR-positive viable T-cells intravenously, there is no data regarding overdose [4, 5].
- *Lisocabtagene maraleucel*: the dosage is 100 * 10^6 viable CAR+ T-cells, within a range of 44 – 120 * 10^6 viable CAR+ t-cells, consisting of equal party CD4+ and CD8+ cell components, and there is no data regarding overdose [1, 6].

For more information on treatment details and dosage, please see section 8.

Indication(s)

This application refers to the indication of large B-cell lymphoma, including diffuse large B-cell lymphoma, high grade B-cell lymphoma and primary mediastinal B-cell lymphoma as its main representatives [7]. For more information on the approval of CAR T-cell therapy including approval for other indications, please see section 12.

6. Proposal for an individual medicine or representative of pharmacological class/therapeutic group

This application concerns the novel medicine class of CAR T-cells. Specifically, it refers to axi-cel, tisa-cel and liso-cel, which are CD19-directed CAR T-cell products that have been approved by several regulatory agencies worldwide.

Based on the available evidence on efficacy and safety and in line with current guideline recommendations [8], we propose a qualified square box listing of CD19-directed CAR T-cells [9], with axi-cel and liso-cel as the main pharmacological class representatives for the second line treatment of early relapsing or refractory aggressive LBCL.

We propose that tisa-cel is an acceptable alternative in a later treatment-line setting. Indirect comparisons suggest that it may be not as efficacious as axi-cel and liso-cel. However, specific product characteristics like the use of cryo-preserve lymphocytes and a low incidence of severe ICANS may be beneficial in individual situations.

7. Information supporting the public health relevance

Non-Hodgkin lymphomas (NHLs) are the 7th most common type of cancer and most common haematologic malignancy in the world, making up 4.3% of all cancers in the U.S. in 2015 [10]. The most common type of malignant lymphomas worldwide are diffuse large B-cell lymphomas (DLBCL) with 40% of all NHLs [11, 12] and 80% of all aggressive lymphomas [13]. Based on morphologic features and their genetic makeup other subtypes and related entities, albeit less common, are defined and subsumed together with DLBCL under the broader, more heterogenous group of aggressive large B-cell lymphoma (LBCL). These include high-grade B-cell lymphomas (HGBL), primary mediastinal B-cell lymphoma (PMBCL), T-cell/histiocyte-rich large B-cell lymphoma (THRBCL), to name a few [14].
Global data on the incidence and mortality of DLBCL is very limited. However, the age-adjusted incidence rate of DLBCLs in the U.S. was 5.5 per 100,000 in 2015 [15]. Between 1970 and 2010, a steady increase of these incidence rates has been reported. In all sexes, racial categories and age groups (except young adults), the increase was reported to be approximately 3-4% in the U.S. [13, 16]. While patients of all ages can be diagnosed with DLBCL, the median age in the U.S. was 65 years [15]. Additionally, males are at a 1.5 times higher risk to be diagnosed with DLBCLs [13, 16]. Mortality was 1.8 per 100,000 in the U.S. in 2015 [15].
Untreated, LBCLs are associated with a median survival of less than one year. With first-line treatment that consists of the combination of R-CHOP (Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)-based immunochemotherapy [17], the majority of patients experience good outcomes [16]. However, 30-40% of patients relapse or are refractory to first-line treatment. The salvage rate of second-line treatment with immunochemotherapy, either in conventional or intensified doses, depends on many factors, of which time to relapse is the most critical one. Even with the second-line treatments, which consists of salvage immunochemotherapy followed by ASCT, overall, approximately 60% of patients experience relapse [18, 19]. In patients with primary progressive disease or relapse within one year after first-line therapy PFS is about 25% at two years [20]. Accordingly, prognosis for relapsed or refractory LBCLs remains poor.
Before the introduction of CAR T-cell therapy, patients who relapsed after second-line treatment had no other treatment options [21]. This has changes with the approval of CAR T-cell therapy. Recently, CAR T-cell therapy was approved for second-line treatment and is used in some countries for high-risk relapsed or refractory LBCL. A prospective randomized study evaluating axi-cel for the first-line treatment of high-risk DLBCL patients has been recently opened for recruitment [22].

8. Treatment details

Please note that the following information, including recommendations on dosage, administration and pre-treatment were partially retrieved from the manufacturer's product information [3, 5, 6]. All three substances, axi-cel, tisa-cel and liso-cel must only be administered in a qualified treatment centre by trained healthcare professionals. These professionals need experience in the treatment of hematological malignancies and must be trained for administration and management of patients treated with each substance [1-6].

Axicabtagene ciloleucel

For axi-cel the proposed dosage depends on the patient's body weight. A dose of 2 x 10^6 CAR-positive T-cells per kg body weight with a maximum of 2 x 10^8 CAR-positive viable T-cells is recommended. Axi-cel is approved as second- or third-line therapy [23] and there is no data regarding overdose. The recommended lymphodepleting chemotherapy regimen before the use of axi-cel consists of cyclophosphamide 500 mg/m^2 intravenous and fludarabine 30 mg/m^2 intravenous, each from day -5 to -3 before infusion of axi-cel. Axi-cel must also be used as an intravenous infusion and administered without a leukocyte depleting filter. It is recommended to infuse the entire content of the bag within 30 minutes via gravity flow or a peristaltic pump [2, 3].

Tisagenlecleucel

The proposed dosage for tisa-cel is independent of weight with 0.6 – 6.0 x 10^8 CAR-positive viable T-cells intravenously. There is no data regarding overdose and tisa-cel is approved as third line therapy for LBCL [24]. Lymphodepleting chemotherapy may be administered 2-14 days before the infusion of CAR T-cells. The standard regime of lymphodepleting chemotherapy is fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2) from day -5 to -3 intravenously. Tisa-cel is to be used as an intravenous infusion. It must be administered through latex-free intravenous tubing without a leukocyte depleting filter, at approximately 10 to 20 mL per minute by gravity flow [4, 5].

Lisocabtagene maraleucel

For liso-cel the proposed dosage is 100 x 10^6 viable CAR T-cells, within a range of 44 – 120 x 10^6 viable CAR T-cells, consisting of equal party $CD4^+$ and $CD8^+$ cell components. Liso-cel is approved as second- or third-line therapy [25] and there is no data regarding overdose. The standard lymphodepleting chemotherapy regimen consists of cyclophosphamide 300mg/m^2/day and fludarabine 30mg/m^2/day over 3 days, usually from day -5 to -3 before the infusion of liso-cel. Liso-cel must be used without a leucocyte-depleting filter. The total time from collection from frozen storage to administration to patients must not exceed 2 hours [1, 6].

9. Review of benefits: Summary of evidence of comparative effectiveness

Summary of the methodological approach

The synthesis of the evidence on the efficacy and safety of CAR T-cells in the treatment of relapsed or refractory LBCL follows standard Cochrane methodology for the conduct of systematic reviews [26]. We performed a systematic database and trial registry search for randomized trials evaluating the intervention of CAR T-therapy in LBCL, without applying any language restrictions. Records were screened by two review authors. Eligible trials were included based on full-text articles. Discrepancies were resolved through discussion. Two reviewers independently extracted data from included studies using a standardised data extraction form. For the risk of bias assessment we used the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [27]. Following data synthesis for predefined primary and secondary outcomes, we rated the certainty of evidence according to the GRADE approach [28]. The full methodological approach is described in the published protocol and review, which we are now updating, available from the Cochrane Library [29, 30].

Results of the search

We performed database und registry searches, identifying 3657 potentially relevant references as of January 28th, 2022. At the initial screening stage, we excluded 777 duplicates and 2858 references due to a lack of conformity with the inclusion criteria. We further evaluated the remaining 22 references either as full-text publications or, if not available, as abstract publications or study registry entries. This led to the exclusion of 14 publications. One RCT is ongoing (DALY 2-EU), which is expected to be completed in Fall 2023 according to ClinicalTrials.gov. We identified eight reports of three RCTs (BELINDA, ZUMA-7, TRANSFORM). The number of records identified screened and selected for inclusion are illustrated in the PRISMA flow diagram in Figure 1.

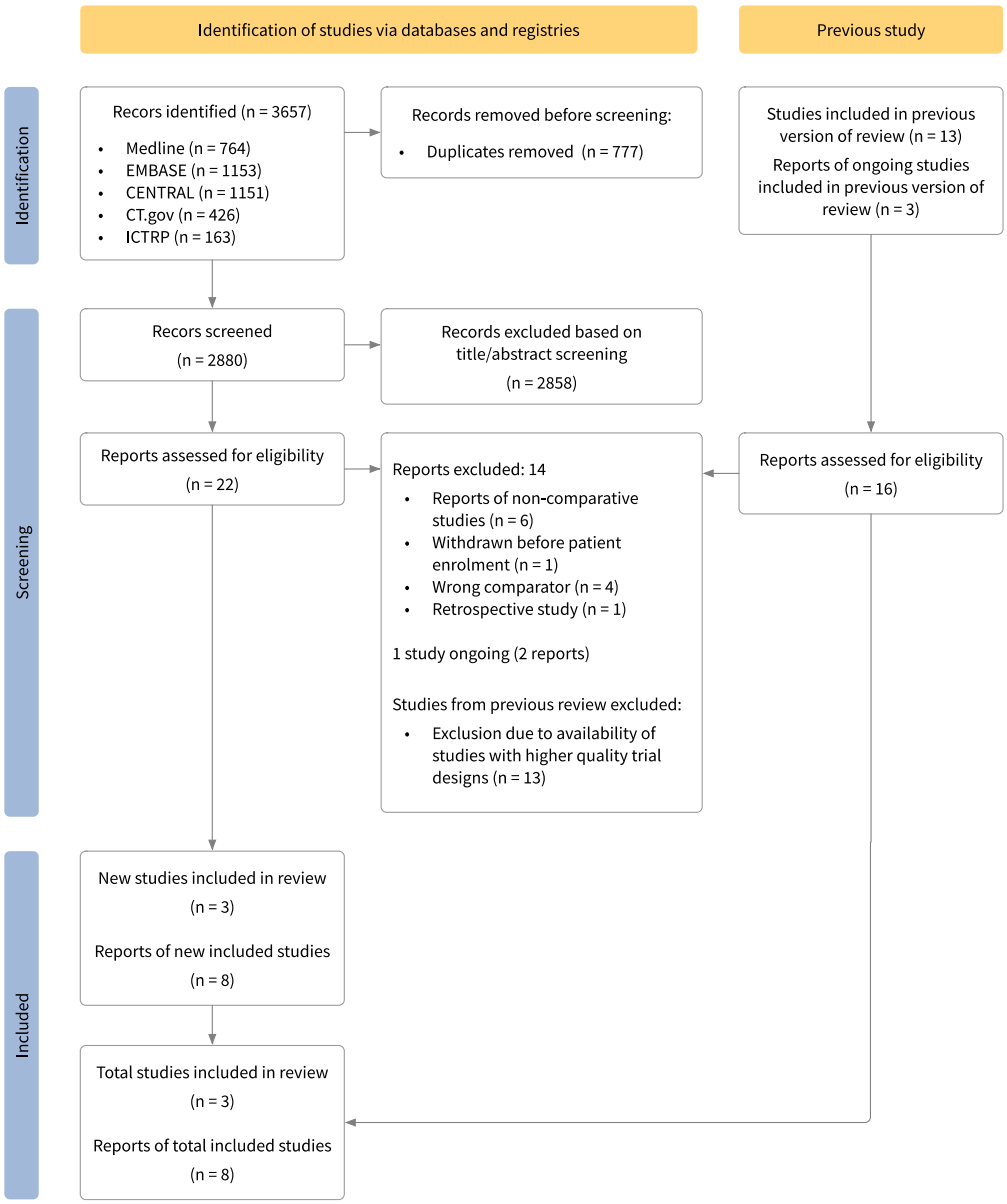

Figure 1. PRISMA flow diagram

Description of included studies and participants

For more information on the characteristics of included studies see Table 1. Here we provide a brief overview.

Three RCTs (BELINDA [31], ZUMA-7 [32], and TRANSFORM [33]) evaluated the efficacy and safety of CAR-T cell therapy in people with r/r aggressive LBCL in the second line treatment setting, comparing them to the established SOC of platinum-containing chemotherapy regimens followed by HDCT and ASCT. Published full-text articles were available for all three RCTs with a completed follow-up for the primary endpoint of EFS. The median follow-up period at data cut-off was 6.2 months in TRANSORM, 10 months in BELINDA and 24.9 months in ZUMA-7.

All three trials (BELINDA, TRANSFORM, ZUMA-7) were multicentric, phase 3 open-label studies that recruited participants from Europe, Asia, North- and South America, as well as the Pacific region [31-33]. Trial designs varied slightly. That is, while leukapheresis was performed prior to randomization in BELINDA and TRANSFORM (i.e. independent of group allocation), it was conducted after randomization in ZUMA-7.

Eligibility criteria across trials were similar. That is, trial participants were eligible if they were diagnosed with aggressive LBCL, refractory to or relapsing early (i.e. within one year) after an anti-CD20 monoclonal antibody and anthracycline-containing immunochemotherapy, had an ECOG performance status of less than or equal to 1 and were eligible for HDCT and ASCT, in all trials. Central nervous system (CNS) involvement by lymphoma was an additional exclusion criterion in BELINDA and ZUMA-7.

BELINDA, ZUMA-7, and TRANSFORM reported data from a total of 865 participants with a median age of 59 years and a proportion of female patients between 34% to 43%. The predominant LBCL subtype across studies was DLBCL diagnosed in 64% to 69% of patients, followed by HGBL subtypes ranging from 16% to 23%. The remainder of participants was diagnosed with FL3b, PMBCL or other LBCL subspecies, as defined by the 2016 WHO classification of lymphoid neoplasms [14].

Description of interventions and comparisons

In all three included trials (BELINDA, TRANSFORM, ZUMA-7) the intervention examined was the one-time infusion of CD19-directed CAR T-cells after the administration of lymphodepleting chemotherapy with fludarabine and cyclophosphamide over two to three days. Co-interventions were not permitted. The CAR T-cell product studied in was tisa-cel in BELINDA, axi-cel in ZUMA-7 and liso-cel in TRANSFORM, respectively.

The time from randomization and leukapheresis to CAR T-cell infusion was different across trials, being shortest in ZUMA-7 with a median time of around four weeks, to a median of five weeks in TRANSFORM and seven weeks in BELINDA. Bridging therapy that consisted of immunochemotherapy protocols which were also used in the control arms were permitted in BELINDA and TRANSFORM. In ZUMA-7, only the administration of corticosteroids was permitted as a bridging to CAR T-cell therapy. Overall, 94% to 98% of trial participants allocated to the CAR T-cell intervention arm received CAR T-cell therapy.

Treatment regimes in the control arms were similar across trials. They consisted of three to four prespecified platinum-based immunochemotherapy regimens (R-DHAP, R-ICE, R-GDP, R-ESHAP or R-Gem/Ox) per investigator's choice. Changes among treatment regimens were permitted in two trials (BELINDA and TRANSFORM) in case of efficacy concerns. In TRANSFORM a change of the immunochemotherapy regimen was allowed within the first three immunochemotherapy cycles and

in BELINDA after the positron emission tomography (PET) at week six. The proportion of participants in the control arms receiving HDCT and ASCT was 33% in BELINDA, 35% in ZUMA-7 and 47% in TRANSFORM.

Switching treatment from SOC to CAR T-cell therapy was allowed as a third line treatment option in BELINDA and TRANSFORM after central review. In ZUMA-7, crossover (i.e. switching to CAR T-cell therapy) was not planned, but cellular immunotherapy was permitted outside the protocol. In BELINDA and TRANSFORM, 50% to 51% of participants allocated to the SOC arm received third line CAR-T cell therapy without receiving ASCT. In ZUMA-7, 56% of participants in the control arm subsequently received CAR T-cells off trial.

All three RCTs (BELINDA, TRANSFORM, ZUMA-7) were industry-sponsored trials, funded by the corresponding CAR T-cell manufacturers. That is, BELINDA (tisa-cel) was funded by Novartis, ZUMA-7 (axi-cel) was funded by Kite Gilead, and TRANSFORM (liso-cel) was funded by Celgene.

Risk of bias in included studies

The risk of bias is summarized in Figure 2.

Figure 2: Outcome specific risk of bias assessment

Allocation (selection bias)

The randomization process was adequate in all three trials (BELINDA, TRANSFORM, ZUMA-7). Randomization sequences were generated by interactive response technology (IRT) or interactive voice or web response systems. Slight baseline imbalances were noted in all three trials (BELINDA, TRANSFORM, ZUMA-7), but these might have been due to chance. Statistically significant differences between groups were not reported. Yet, with differences in the proportions exceeding 10% for sex and age in TRANSFORM, with a higher proportion of females and over 65-year-olds in the intervention group, we judged the trial to be at unclear risk of bias. In BELINDA there was a higher proportion of HGBL and IPI ≥ 2 in the intervention arm. This was partly due to errors in the entry of prognostic factors into the IRT, as stated by the authors. Thus, we judged the trial to be at unclear risk of bias.

Blinding (performance bias and detection bias)

SURVIVAL AND RESPONSE ASSESSMENT

All three studies (BELINDA, TRANSFORM, ZUMA-7) were of an open-label trial design, with participants and personnel being aware of the treatment arm assignment (i.e. CAR T-cell therapy or SOC). Survival and response outcomes were assessed by independent review committees unaware of the intervention received by participants. For outcomes that were objective by nature such as overall survival or followed clearly defined objectifiable criteria, such as the response assessment, which in all three trials (BELINDA, TRANSFORM, ZUMA-7) was conducted according to Lugano response criteria, we judged the risk of performance or detection bias to be low.

The composite outcome of EFS allowed for a degree of subjectivity in changing treatment regimens for safety or efficacy concerns including to plan for patients to receive the supposedly better treatment of CAR T-cell therapy as a third-line option in the control group. Considering that the proportion of participants who received HDCT and ASCT in the trial corresponded to historical counts from the CORAL and the ORCHARRD study [34-36], we judged EFS to be at low risk of bias.

QUALITY OF LIFE

In both studies reporting quality of life outcomes (TRANSFORM, ZUMA-7), validated tools were used to measure quality of life. However, since both studies were unblinded and quality of life is a subjective, patient-reported outcome, both studies were at high risk of performance, and detection bias.

SAFETY ASSESSMENT

All three studies (BELINDA, TRANSFORM, ZUMA-7) were unblinded. Considering that safety outcomes are at least in part subjective in nature (i.e. investigator-assessed or patient-reported) we judged adverse event outcomes to be at unclear risk of performance and detection bias.

Incomplete outcome reporting (attrition bias)

SURVIVAL, RESPONSE AND SAFETY ASSESSMENT

The participant flow was adequately reported in all three studies (BELINDA, TRANSFORM, ZUMA-7). There was no suggestion of incomplete outcome data for efficacy and safety outcomes. Intention-to-treat analysis was used in all three trials. Thus, we judged the studies to be at low risk of attrition bias.

QUALITY OF LIFE

In both studies (TRANSFORM, ZUMA-7), results on quality of life were reported for a subset of patients who were randomized and provided data at baseline and a minimum of one follow-up assessment. Among 359 patients who were randomized in ZUMA-7, the sample size decreased from 295 [296] patients providing data at baseline to only 93 [93] patients providing data for the EORTC QLQ-C30 - general health/QoL status [EQ-5D-5L index] at the last follow-up (i.e. month 15). Among 184 patients

who were randomized in TRANSFORM, data were reported for 90 patients at baseline, and for only 24 patients at the last follow-up (i.e. month 6). In both studies, outcomes were not assessed in patients who started subsequent antineoplastic treatment, and attrition (e.g. due to disease progression, new lymphoma therapy or death) was higher in the control arm compared to the CAR T arm. For example, the proportion of patients providing data on the EORTC QLQ-C30 - general health/QoL subscale at last follow-up among patients providing data at baseline in the CAR T group compared to the control group was 36% versus 16% in TRANSFORM, and 41% versus 20% in ZUMA-7. Therefore, beneficial effects in favor of CAR T-cell therapy compared to the control arm might be underestimated in both studies. As a result, risk of bias due to attrition was rated to be high for both studies.

Selective reporting (reporting bias)

SURVIVAL, RESPONSE AND SAFETY ASSESSMENT

Trial protocols were available for all three trials (BELINDA, TRANSFORM, ZUMA-7) and the prespecified outcomes of interest were reported sufficiently. Therefore, we judged the risk of selective reporting to be low.

QUALITY OF LIFE

In both studies (TRANSFORM, ZUMA-7), outcomes were prespecified, analyses were performed according to the protocol, and data were reported for all timings of assessment. In ZUMA-7, the analyses were explicitly framed as exploratory, as the study was not powered for quality of life outcomes. As a result, both studies were at low risk of reporting bias.

Effects of interventions

For details on efficacy outcomes, see Table 2 (overall survival, progression-free survival, event-free survival, overall response rates, complete response rates, partial response rates) and Table 3 (quality of life).

The included trials (BELINDA, TRANSFORM and ZUMA-7) were similar in comparing the experimental treatment of CAR T-cell therapy with the standard of care second-line treatment in early relapsing or refractory aggressive LBCL. Patient-, disease-, and intervention characteristics were comparable across trials. However, due to the constellation of design peculiarities with bridging therapy in the investigational treatment group, which consisted of immunochemotherapy protocols used in the control group and switching from the comparison treatment to the investigational treatment in the third line setting we did not perform meta-analysis for OS, EFS and adverse event outcomes. We did not pool effect estimates for quality of life due to heterogeneity in the study designs with respect to the timing of assessments.

Overall survival

Results on overall survival were reported in all three included studies (BELINDA, ZUMA-7, TRANSFORM). The evidence suggests that CAR T-cell therapy may improve overall survival when compared to second line SOC treatment. In BELINDA the median overall survival was 16.9 months (95% CI, 11.14 to NE) in the CAR T group and 15.3 months (95% CI, 12.32 to NE) in the control group, with a HR of 1.24 (95% CI, 0.83 to 1.85). The median OS in ZUMA-7 was not reached (NR) in the CAR T group (95% CI, 28.3 to NE) and 35.1 months (95% CI, 18.5 to NE) in the control group, with a HR of 0.73 (95% CI, 0.53 to 1.01). In TRANSFORM the median OS was not reached in the CAR T group (95% CI, 15.8 to NR) and 16.4 months in the control group (95% CI, 11.0 to NR), leading to a HR 0.51 (95% CI, 0.26 to 1.01). Notably, at the data-cut off OS data were immature in all three trials, and the publications only presented interim analyses of the outcome. We observed differences in OS hazard ratios when comparing TRANSFORM and ZUMA-7 to BELINDA. While OS in TRANSFORM and ZUMA-7 favored CAR

T-cell therapy, no evidence of a difference between CAR T-cell therapy and SOC with salvage immunochemotherapy, HDCT and ASCT was observed in BELINDA (see Figure 3).

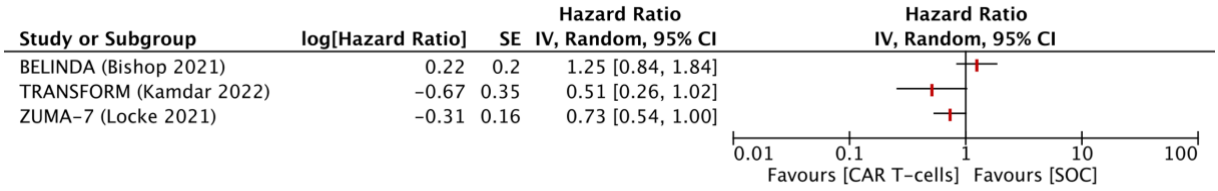

Figure 3. Overall survival

Progression-free survival

Two studies, ZUMA-7 and TRANSFORM reported on PFS outcomes (i.e. the composite outcome of disease progression or death from any cause, whichever comes first). In BELINDA as prespecified in the trial protocol, PFS assessment was not intended. The evidence from TRANSFORM and ZUMA-7 suggests that CAR T- cell therapy likely improves PFS when compared to SOC treatment. In TRANSFORM median PFS was 14.8 months (95% CI, 6.6 to NR) in the CAR T group and 5.7 months (95% CI, 3.9 to 9.4) in the control group, with a HR of 0.41 (95% CI 95%, 0.25 to 0.66). ZUMA-7 reported a median PFS of 14.7 months (95% CI, 5.4 to NE) in the CAR T group and 3.7 months (95% CI, 0.37 to 0.65) in the control group with a HR of 0.49 (95% CI, 0.37 to 0.65). Pooling effect estimates leads to a HR of 0.47 (95% CI, 0.37 to 0.60) without evidence of heterogeneity in the meta-analysis (see Figure 4).

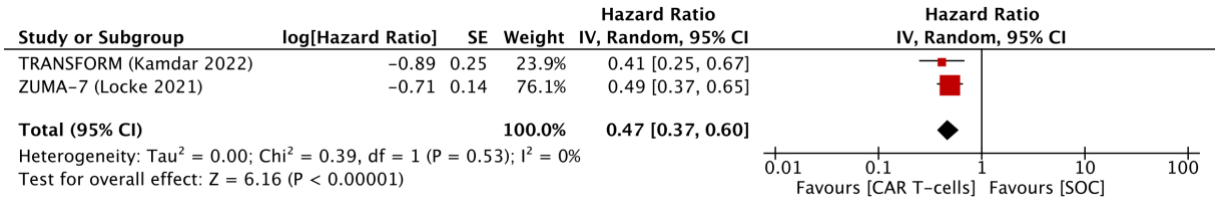

Figure 4. Progression-free survival

Event-free survival

Event-free survival was the primary outcome in all three included trials. EFS was defined as the time from randomization to the first documented disease progression, stable disease, or death due to any cause, but the definitions of EFS varied. That is, the commencement of a new lymphoma therapy was included as an EFS event. in ZUMA-7 and TRANSFORM, but not in BELINDA. In the BELINDA trial, a change among the immunochemotherapy regimens in the control group was permitted, provided this occurred before the week 12 ± 1 response assessment without being counted as an event. Similarly, although being part of the EFS composite in TRANSFORM, commencing a new immunochemotherapy regimen in the control group was permitted without being counted as an event if it occurred within the first three treatment cycles. In ZUMA-7 this was not the case.

Furthermore, the timing of assessment differed, especially during the early trial stages. In BELINDA event-free survival was assessed at, or after week 12 ± 1. In TRANSFORM, response was assessed at 9 weeks, but five weeks after liso-cel infusion in the CAR T group and after three cycles of immunochemotherapy in the control group as well as 18 weeks after randomization (i.e. 14 weeks after liso-cel infusion in the intervention group and eight weeks after the start of HDCT in the control group). ZUMA-7 trialists recorded responses at days 50, 100 and 150 after randomization. Thereafter, response assessments were planned in three-month intervals in all three trials.

The evidence suggests that CAR T-cell therapy may lead to an increase in event-free survival when compared to second line SOC treatment.
The EFS in BELINDA was similar between the intervention and control groups with a median of 3 months (95% CI, 2.9 to 4.2) in the intervention group and 3 months (95% CI, 3.0 to 3.5) in the control group, respectively. The EFS in BELINDA of HR 1.07 (95% CI, 0.82 to 1.40) did not reach statistical significance.
In ZUMA-7 the median EFS in the intervention group with axi-cel was 8.3 months (95% CI, 4.5 to 15.8) and 2.0 months (95% CI, 1.6 to 2.8) in the control group, leading to a statistically significant HR of 0.40 (95% CI, 0.31 to 0.51). Authors of the TRANSFORM trial reported a median EFS of 10.1 months (95% CI, 6.1 to NR) in the liso-cel group and 2.3 months (95% CI, 2.2 to 4.3) in the control group of SOC treatment with a HR of 0.35 (95% CI, 0.23 to 0.53).
It was not possible to conduct meta-analysis of the data due to differences in the definitions of EFS.
The forest plot shows overlapping of point estimates and confidence intervals of trials with similar EFS definitions (TRANSFORM and ZUMA-7), both with statistically significant EFS outcomes favoring CAR T-cell therapy over SOC with immunochemotherapy (see Figure 5). In BELINDA no evidence of a difference between CAR T-cell therapy and SOC in the second-line treatment was observed.

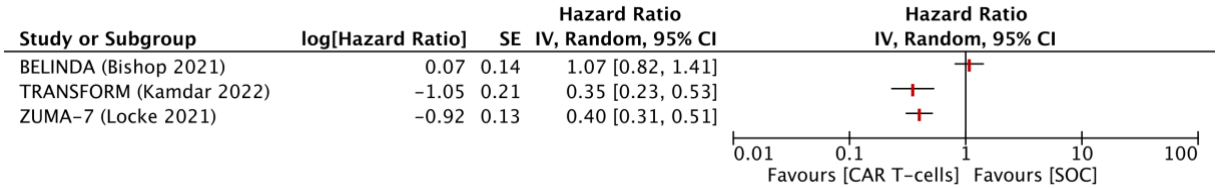

Figure 5. Event-free survival

Overall response rates

Overall response rates were reported for all three trials. CAR T-cell therapy likely leads to a higher overall response rate when compared to second line SOC immunochemotherapy and ASCT.
Overall response assessment and definition were the same in all three trials (BELINDA, TRANSFORM, ZUMA-7). Best overall response in the CAR T group of BELINDA was 46% (75/162) and 43% (68/160) in the control group, with a risk ratio (RR) of 1.09 (95% CI, 0.85 to 1.39), not reaching statistical significance. The best overall response in the CAR T group of TRANSFORM was 86% (79/92) and 48% (44/92) in the control group with a significant risk ratio of 1.80 (95% CI, 1.43 to 2.26).
In ZUMA-7 the best overall response in the CAR T group was 83% (150/180) and 50% (90/179) in the control group receiving SOC immunochemotherapy with a significant risk ratio of 1.66 (95% CI, 1.41 to 1.94). Meta-analysis resulted in a statistically significant RR of 1.49 (95% CI, 1.13 to 1.97), favoring CAR T-cell therapy over SOC treatment (see Figure 6). There is a clear statistical heterogeneity between trials (I^2 = 81%) which may in part be explained by differences in interventions and trial designs.

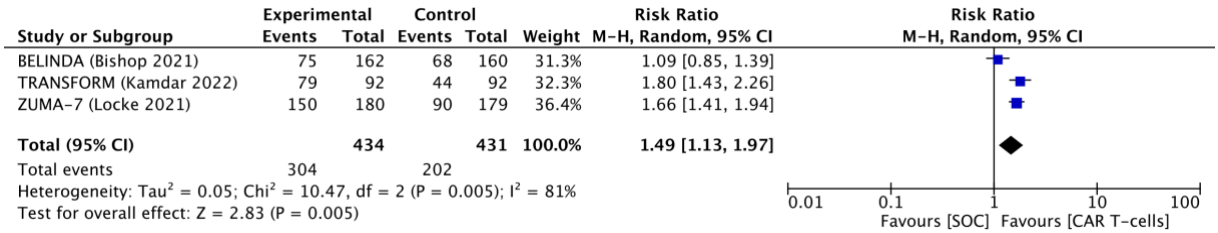

Figure 6. Overall response rates

Quality of life

Two studies reported quality of life (386 participants analyzed; TRANSFORM; ZUMA-7) using multiple validated tools for several time points. We here report the results on scores of validated tools assessing global quality of life with a minimum of two items, that is, the EuroQol 5-Dimension 5-Level (EQ-5D-5L;[37]) index and the "general health/QoL" subscale of the EORTC QLQ-C30 [38], 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. further EORTC QLQ-C30 subscales, EQ-5D-5L visual analogue scale, and FACT-Lym S "additional concerns" subscale [39]). We did not pool effect estimates for quality of life due to heterogeneity in the study designs with respect to the timing of assessments. That is, as the duration and sequence of treatment differed between CAR T-cell therapy and SOC, the timing of assessment reported in both. Studies (TRANSFORM, ZUMA-7) relates to different stages of the treatment sequence (e.g. in TRANSFORM, patients in the control arm continued to receive salvage chemotherapy up to around day 64 and were anticipated to be two months after completion of HDCT and ASCT by day 126, while patients in the CAR T arm had completed lymphodepletion and infusion of CAR T-cells at around study day 29). Furthermore, the timing of follow-up assessments differed between the studies. Therefore, we reported data descriptively. The format of effect measures is described as reported by the authors.

One study (TRANSFORM) reported scores of the EORTC QLQ-C30 – general health/QoL status as mean changes from baseline to day 126 (i.e. 2 months after CAR T-cell therapy/ASCT). Additionally, data were reported at days 29 (i.e. before infusion of CAR T-cells/during standard of care cycle 2; ±7 days), 64 (i.e. posttreatment for the CAR T arm/after immunochemotherapy for the standard of care arm; ±6 days), 126 (i.e. 2 months after CAR T-cell therapy/ASCT), and at month 6 (i.e. 4 months after CAR T-cell therapy/ASCT). Data were reported also as proportions of participants with clinically meaningfully improved, unchanged, and worsened scores. Data were reported for randomized patients who completed a baseline and a minimum of one follow-up assessment. No data were collected after patients started subsequent antineoplastic treatment. Among 184 patients who were randomized, 90 patients provided data at baseline, and 24 patients provided data at the last follow-up (i.e. month 6).

In ZUMA-7, mean changes from baseline (i.e. prior to treatment with either conditioning or salvage chemotherapy) were reported at days 50, 100, 150, and at months 9, 12, and 15. Data were reported also as proportions of patients with improved scores. Data were reported for randomized patients who completed a baseline and a minimum of one follow-up assessment. No data were collected after patients had a predefined event (i.e. disease progression, death from any cause, best response as stable disease up to day 150 after randomization, or start of subsequent antineoplastic therapy). Among 359 patients who were randomized, 295 [296] patients provided data at baseline, and 93 [93] patients provided data for the EORTC QLQ-C30 - general health/QoL status [EQ-5D-5L index] at the last follow-up (i.e. month 15).

EQ-5D-5L INDEX

In ZUMA-7, mean EQ-5D-5L index scores at baseline were 0.803 (95% CI, 0.771 to 0.835)* for the CAR T group (n=165), and 0.799 (95% CI, 0.756 to 0.842) for the control group (n=131). By day 50, there was evidence of a statistically significant decrease in mean EQ-5D-5L index scores in the CAR T group (-0.049 (95% CI, -0.081 to -0.017), n=163), but no evidence of a statistically significant decrease in the control group (-0.003 (95% CI, -0.038 to 0.033), n=123). According to mixed-effect models with repeated measures (MMRM) analyses controlled for response to first-line therapy and age-adjusted IPI at time of screening, there was evidence of a statistically significant difference in the mean changes from baseline to day 100 in favor of the CAR T group (CAR T (n=146) versus control (n=65): 0.081 (95% CI, 0.024 to 0.138). No further evidence of statistically significant between-group differences in the estimated mean changes from baseline were observed at day 150 (CAR T (n=109) versus control (n = 56): 0.028 (-0.034 to 0.091)), and at months 9 (CAR T (n = 88) versus control (n=39): 0.020 (-0.044 to 0.084)), 12 (CAR T (n=79) versus control (n=32): -0.029 (95% CI, -0.109 to 0.052)), and 15 (CAR T (n=67) versus control (n=26): -0.066 (95% CI, -0.138 to 0.007)). Descriptively, the proportion of patients who experienced clinically meaningful improvement (defined by the authors as 0.06 points) was higher in

the CAR T arm (15% (25/166)) compared to the control arm (12% (16/133)), but according to time to definitive improvement (TUDI) analyses, there was no evidence of a statistically significant difference (HR 1.15 (95% CI, 0.61 to 2.15)).

EORTC QLQ-C30 – GENERAL HEALTH/QOL

In ZUMA-7, mean EORTC QLQ-C30 - general health/QoL scores at baseline were 68.6 (95% CI, 65.6 to 71.7) for the CAR T group (n=165), and 70.1 (95% CI, 66.1 to 74.1) for the control group (n=130). By day 50, mean EORTC QLQ-C30 - general health/QoL scores decreased in both groups (i.e. changes from baseline: -7.4 (95% CI, -10.5 to -4.3) in the CAR T group (n=163), and -8.5 (95% CI, -12.6 to -4.5) in the control group (n=125)). According to mixed-effect models with repeated measures (MMRM) analyses controlled for response to first-line therapy and age-adjusted IPI at time of screening, there was evidence of a statistically significant and clinically meaningful (defined by the authors as 10 points) difference in the mean changes from baseline to day 100 in favor of the CAR T group (CAR T (n=146) versus control (n=62): 18.1 (95% CI, 12.3 to 23.9). Estimated mean changes from baseline at day 150 also favored the CAR T group (CAR T (n=110) versus control (n=56): 9.8 (95% CI, 2.6 to 17.0)). No further evidence of statistically significant between-group differences in the estimated mean changes from baseline were observed at months 9 (CAR T (n=88) versus control (n=49): 4.4 (95% CI, -3.3 to 12.0)), 12 (CAR T (n=79) versus control (n=33): -1.5 (95% CI, -9.6 to 6.6)) and 15 (CAR T (n=67) versus control (n=26): -4.9 (95% CI, -13.0 to 3.1)). Descriptively, the proportion of patients who experienced clinically meaningful improvement (defined by the authors as 10 points) were higher in the CAR T arm (19% (31/166)) compared to the control arm (14% (18/133)), but according to time to definitive improvement (TUDI) analyses, there was no evidence of a statistically significant difference (HR 1.25 (95% CI, 0.7 to 2.22)).

In TRANSFORM, mean (SD) EORTC QLQ-C30 - general health/QoL scores at baseline were 67.7 (21.5) for the CAR T group (n=47), and 68.2 (22.1) for the control group (n=43). According to MMRM analyses which considered all data points through day 126 and controlled for "relevant" baseline covariates[1], there was no evidence of a statistically significant difference in the overall least square mean changes from baseline through day 126 between the CAR T group (3.1 (95% CI, -1.8 to 8.0)) and the control group (0.04 (95% CI, -5.2 to 5.3)) (CAR T versus control: 3.0 (95% CI, -3.6 to 9.7); n at day 126 in CAR T arm [control arm] =26 [10]). That is, across timings of assessment (i.e. days 29, 64, and 126), there was no evidence of statistically significant between-group differences (data reported only graphically). At month 6, observed mean EORTC QLQ-C30 - general health/QoL change scores in the control arm (n=7) showed clinically meaningful worsening (i.e. mean changes exceeded the authors' prespecified within-group MID of 10 points). In the CAR T arm (n=17), observed mean change scores improved descriptively, but remained below the limit of the within-group MID (data reported only graphically). Descriptively, from day 126 to month 6, the proportion of patients with meaningful improvement in general health/QoL (using the authors' responder definition based on a minimal change threshold (i.e. smallest incremental change) of 5 points) was higher, while deterioration was lower, in the CAR T arm compared to the control arm. That is, the proportions of patients with improvement/deterioration at day 126 were 62%/23% (n=26) in the CAR T arm and 30%/60% (n=10) in the control arm. At month 6, the proportions of patients with improvement/deterioration were 53%/18% (n=17) in the CAR T arm and 14%/57% (n=7) in the control arm.

[1] Please note that the authors reported that the "models included the intercept and time as random effects and the following covariates as fixed effects: treatment arm, time (as a discrete variable), stratification factors, baseline HRQOL domain score, and treatment arm*time interaction". However, it was not reported which baseline covariates were relevant.

10. Review of harms and toxicity: Summary of evidence of comparative safety

For more information on harms and toxicity, see Table 4.

In the ZUMA-7 trial, which investigated the use of axi-cel, 170 participants from the intervention group and 168 in the control group were included in the safety analysis [32]. The BELINDA trial, which investigated the use of tisa-cel, included 162 participants in the intervention group and 160 patients in the control group in the reporting of any (serious) adverse events, but only 155 participants in the intervention group and 81 in the control group for further safety analysis [31]. The TRANSFORM trial, which investigated treatment with liso-cel, included 92 participants in the intervention group and 91 participants in the control group in the reporting of any (serious) adverse events. However, further safety analyses were conducted with data from 47 participants in the control group, who crossed over and received liso-cell as third-line treatment [33].

Any adverse event

Overall, 99 to 100% of participants in both, the intervention, and the control group, experienced any adverse event [31, 32]. Between 84 to 92% of participants in the intervention group and 83 – 90% in the control group experienced any adverse event ≥ grade 3 [31-33]. In the ZUMA-7 trial, 100% of participants in both the intervention group and the control group experienced any adverse event. In the intervention group, 91% of participants experienced an adverse event ≥ grade 3. In the control group, 83% of participants experienced an adverse event ≥ grade 3 [32]. The BELINDA trial reported 99% of participants in the intervention group and 99% in the control group experiencing any adverse event. In the intervention group, 84% of participants experienced an adverse event ≥ grade 3, whereas 90% of participants in the control group experienced an adverse event ≥ grade 3 [31]. The TRANSFORM trial did not report the number of patients with any adverse event. However, 92% of participants in the intervention group experienced an adverse event ≥ grade 3, whereas 87% of participants did in the control group [33].

Any serious adverse events

In the intervention groups, between 47 – 50% of participants experienced any serious adverse event, whereas 46 – 51% of participants in the control groups did [31, 32]. Between 34 – 42% in the intervention groups and 40 – 43% in the control groups experienced serious adverse events ≥ grade 3 [31-33]. In the ZUMA-7, 50% of participants in the intervention group experienced any serious adverse event. In the control group, 46% of participants did. 42% of participants in the intervention group and 40% of participants in the control group experienced a serious adverse event ≥ grade 3 [32]. The BELINDA trial reported any serious adverse event for 47% in the intervention group and for 51% in the control group. Additionally, 36% in the intervention group and 43% in the control group experienced serious adverse events ≥ grade 3 [31]. The TRANSFORM trial reported serious adverse events ≥ grade 3 for 34% of participants in the intervention group and 43% of participants in the control group. The number of participants with any serious adverse event was not reported [33].

Cytokine release syndrome

All trials reported the number of participants with cytokine release syndrome (CRS). The number of participants with CRS in the intervention groups ranged between 49 – 92%, with 1 – 6% of participants experiencing CRS ≥ grade 3. In the control groups, between 49 – 75% of participants had CRS of any grade [31-33]. Only one trial reported the number of participants in the control group with CRS ≥ grade 3, which was 5% [31]. In the ZUMA-7 trial, CRS was reported for 92%, and CRS ≥ grade 3 for 6% in the intervention group. The number of participants with CRS/CRS ≥ grade 3 in the control group was not reported. Tocilizumab was administered to 65% of participants. It was not reported, how many

participants per group were given tocilizumab, and if it was administered for CRS or any neurological event [32]. The BELINDA trial reported CRS in 61% of participants in the intervention group and 75% of participants in the control group. CRS ≥ grade 3 was reported for 5.2% and 4.9% in the intervention and control group, respectively. Tocilizumab for CRS management was reported for 51.6% in the intervention group and 55.7% in the control group [31]. In the TRANSFORM trial, CRS was reported for 49% of participants in the intervention group and 49% of participants in the control group. CRS ≥ grade 3 was only reported for 1 participant (1%) in the intervention group. For 10% of participants in the intervention group, and for 19% of participants in the control group, tocilizumab was used for CRS management [33].

Neurologic events

All trials reported the number of participants with neurologic events, however the numbers from the ZUMA-7 control group did not include the number of patients with immune effector cell associated neurotoxicity syndrome (ICANS) [32]. The number of participants with neurologic events including ICANS of any grade ranged between 10 – 60% in the intervention groups, and 15 – 17% in the control groups. The number of participants with neurologic events ≥ grade 3 ranged between 2 – 21% in the intervention groups and 3 – 4% in the control groups [31, 32]. In the ZUMA-7 trial, 60% of participants in the intervention group experienced any neurological event, including ICANS, and 20% of participants in the control group experienced any neurological event, excluding ICANS. Additionally, 21% in the intervention group experienced neurological events ≥ grade 3, including ICANS, and 0.6% in the control group experienced neurological events ≥ grade 3, excluding ICANS [32]. In the BELINDA trial, any neurological event was reported for 10.3% of participants in the intervention group and 14.8% in the control group, both including ICANS. Additionally, 1.9% in the intervention group and 2.5% in the control group experienced neurological events ≥ grade 3, including ICANS. The number of participants receiving tocilizumab for neurological events was not reported [31]. The TRANSFORM trial reported any neurological event including ICANS for 12% in the intervention group and 17% in the control group. Neurological events ≥ grade 3 were reported for 4% of participants in both the intervention and control group. One patient in the intervention group received tocilizumab for dizziness [33].

Any infections

Infections were reported in all three trials. The number of participants with infections ranged between 3 – 41% in the intervention group, and 3 – 30% in the control groups [31-33]. In the ZUMA-7 trial, infections of any grade were reported for 41% in the intervention group and 30% in the control group. Infections ≥ grade 3 were reported for 14% in the intervention and 11% in the control group [32]. The BELINDA trial reported any infections and infestations for 3.1% of participants in each group [31]. In the TRANSFORM trial, infections ≥ grade 3 were reported for 15% of participants in the intervention group and 21% of participants in the control group [33].

Certainty of evidence

Using the GRADE approach, we rated the overall certainty of evidence as low to moderate.
Risk of bias low for survival and response assessment, unclear for the safety assessment and high for quality of life, which was due to the risk of performance and detection bias and subjective nature of the outcome as well as attrition bias.
Despite trial designs appearing similar, meta-analysis was only possible for PFS and OR. Data immaturity precluded meta-analysis for OS. We did not meta-analyze EFS outcomes and adverse event data due to differences in outcome definitions and concerns about clinical and methodological diversity. Pooling effect estimates for quality of life was not possible due to heterogeneity resulting from the timing of outcome assessments. Therefore, we described the results for EFS, serious adverse events and quality of life descriptively.
The certainty of evidence ratings and evidence statements are presented in the Summary of findings table.

Recommendations in current clinical guidelines

The German S3 guidelines for the diagnosis, therapy and follow-up of adult patients with diffuse large B-cell lymphoma and related entities [8], published in October 2022 included recommendations for CAR T-cell therapy in the first relapse, primarily progressive (i.e. refractory) disease setting, as well as in the setting of second or higher relapse with a curative intent.
Below are English translations of the respective recommendations of the original guideline.

Chapter 8.3.1. Second-line therapy for relapsed or primarily progressive disease:

8.6	Evidence-based recommendation
	Patients eligible for high-dose chemotherapy with early relapse ***should*** receive CD19-directed CAR T-cell therapy either with Axicabtagene ciloleucel or Lisocabtagene maraleucel.
Level of Evidence OS ⊕⊕⊖⊖ PFS ⊕⊕⊖⊖ EFS ⊕⊕⊖⊖ Response ⊕⊕⊖⊖ Safety ⊕⊕⊕⊖	Locke 2021 [32], Kamdar 2022 [33]
	Strong consensus

Chapter 8.4.1. Therapy in ≥ 2. Relapse with primary curative intention:

8.12	Consensus-based recommendation *
	Patients with ≥ 2nd relapse or DLBCL progression with primary curative treatment intention shall be offered CAR T-cell therapy, provided they did not receive CAR T-cells in the second treatment line.
	Strong consensus

* 'Consensus-based' indicates that no formal search and synthesis of the evidence was conducted to inform this recommendation.

Conclusion

The prognosis of people with relapsed or refractory LBCL is generally poor. Salvage immunochemotherapy, HDCT and ASCT have curative potential, but less than half of patients respond to treatment and the risk of further relapses is high.

Low to moderate Evidence from three multicentric RCTs evaluating CAR T-cell therapy in the setting of early relapsing or primary refractory LBCL shows that's CAR T-cell therapy likely improves PFS and EFS when compared to the standard of care including ASCT. This is also reflected by a higher overall response rate. CAR T-cell therapy might be associated with substantial toxicity (e.g. CRS or ICANS) there may be little to no difference in the occurrence of serious adverse events when compared to standard of care treatment.

Although overall survival data were immature at data cut-off in all three trials, their added informative value is questionable, as treatment switching with patients in control groups receiving CAR T-cells after treatment failure might lead to an underestimation of the beneficial effect of CAR T-cell therapy.

Summary of findings

CAR T-cell therapy compared to SOC for relapsed or refractory aggressive large B-cell lymphoma

Patient or population: early relapsed or refractory aggressive large B-cell lymphoma
Setting: inpatient, tertiary specialized center
Intervention: CD19-directed CAR T-cell therapy
Comparison: standard-of-care (SOC) – salvage immunochemotherapy followed by high-dose chemotherapy (HDCT) and autologous stem-cell transplantation (ASCT)

Outcomes	Anticipated absolute effects * (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments and Evidence statements
	Risk with SOC	Risk with CAR T-cell therapy				
Overall survival (OS) **Follow-up:** median 6.2 to 24.9 months	*not pooled*	*not pooled*	*not pooled*	865 (3 RCTs)	⨁⨁◯◯ Low [a, b]	The evidence suggests that CAR T- cell therapy may improve overall survival when compared to second-line SOC treatment. OS results were immature at data cut-off in all three trials. With follow-up still ongoing, the evidence is uncertain. However, considering that over half of the participants in the control arms received CAR T-cells after treatment failure, the beneficial effect of CAR T-cells might be underestimated and not adequately represented by the overall survival estimate. In this regard, surrogate survival endpoints such as PFS and EFS might be more informative.
Progression-free survival (PFS) **Follow-up:** median at 12 months	339 per 1000 [c]	**601 per 1.000** (523 to 670)	**HR 0.47** (0.37 to 0.60)	543 (2 RCTs)	⨁⨁⨁◯ Moderate [f]	Two out of three trials reported the PFS outcome. The evidence from these two trials suggests that CAR T- cell therapy likely improves progression-free survival when compared to SOC treatment.
Duration of PFS (months)	median 4.3 months [d]	median **10.5 more** (1.7 to NE) [e]				
Event-free survival (EFS) **Follow-up:** median 6.2 to 24.9 months	*not pooled*	*not pooled*	*not pooled*	865 (3 RCTs)	⨁⨁◯◯ Low [a, f, g]	The evidence suggests that CAR T-cell therapy may lead to an increase in event-free survival when compared to second line SOC treatment. Differences in the effect estimates that may be due to varying interventions and trial designs as well as indirectness from different. Outcome definitions reduce the certainty in the evidence.
Overall response (OR) **Follow-up:** up to 5 months	469 per 1.000 [d]	**698 per 1.000** (530 to 923)	**RR 1.49** (1.13 to 1.97)	865 (3 RCTs)	⨁⨁◯◯ Low [a, f]	CAR T-cell therapy likely leads to a higher overall response rate when compared to second line SOC immunochemotherapy and ASCT. Differences in the effect estimates that may be due to varying interventions and trial designs reduce the certainty in the evidence.
Quality of life (QoL) **Assessed with:** EQ- 5D-5L index, EORTC QLQ-C30 - general health/QoL **Follow-up:** up to 15 months	*not pooled*	*not pooled*	*not pooled*	385 (2 RCTs)	⨁⨁◯◯ Low [h, i, j, k]	Quality of life might be increased for CAR T cell therapy compared to SOC at some points during the treatment sequence. The evidence is uncertain and may be limited to patients who respond to or tolerate treatments well.

Serious adverse events (sAE) **Follow-up:** up to 4 months after last treatment	*not pooled*	*not pooled*	*not pooled*	843 (3 RCTs)	⨁⨁⨁◯ Moderate [f]	CAR T-cell therapy compared to second-line standard-of-care treatment may result in little to no difference in the occurrence of serious adverse events.

* The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the control group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **HR:** risk 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.

Explanations
a. Inconsistency from a lack of CI-overlap and different directions of effects (downgraded by 1 point).
b. Indirectness resulting from treatment switching to the investigational treatment of cellular immunotherapy in a later treatment line in more than half of control group participants (downgraded by 1 point).
c. The control group risk estimate was taken from the TRANSFORM trial, which corresponds well with the one-year-PFS estimate of around 30% in the Kaplan-Meier curve of ZUMA-7 and other one-year-PFS estimates reported in immunochemotherapy regimen trials [34, 36, 40].
d. The control group risk estimate comes from pooled estimates of control groups.
e. Upper CI limits were not estimable in the intervention groups due to an insufficient number of events (i.e. death or progression) at data-cut off. Thus, deriving a pooling estimate was not possible. The CI limit here presented is an approximation based on the simple mean of lower CI limits.
f. Inconsistency due to differences in bridging immunochemotherapy prior to CAR T-cell therapy in the intervention groups across trials (downgraded by 1 point).
g. Indirectness due to different outcome definitions for EFS across trials (not downgraded).
h. High risk of bias due to open-label trial design (performance, and detection bias), and substantial loss to follow-up, especially in the SOC arm (attrition bias), in both studies (downgraded by 1 point).
i. Indirectness due to the limitation of analyses to responding participants in both studies (downgraded by 1 point).
j. Imprecision due to the inability to pool effect estimates, and small sample sizes resulting from substantial loss to follow-up throughout the trial in both studies (downgraded by 1 point).
k. The overall certainty was downgraded by no more than 2 points to avoid downgrading more than once for related concerns resulting from the analysis of responding participants and substantial loss of follow-up throughout the trial (i.e. risk of bias due to attrition, indirectness due to focus on responding participants, and imprecision due to small sample sizes).

Table 1. Characteristics of included studies

BELINDA

Methods	**Phase**: 3 **Study design**: randomised-controlled trial (RCT), open-label, multicentre **Locations**: Australia, Austria, Belgium, Brazil, China, France, Germany, Hongkong, Italy, Japan, Netherlands, Norway, Singapore, Spain, Switzerland, Taiwan, United Kingdom, USA

Participants	**Eligibility criteria**
	
	• **Key inclusion criteria**
	  ○ Aged 18 years or older
	  ○ Histologically confirmed aggressive B-cell Non-Hodgkin lymphoma (DLBCL, FL3B, PMBCL, THRBCL, ALK+ large B-cell lymphoma, HGBL, HHV8+ DLBCL, transformed indolent NHL, primary cutaneous DLBCL) according to the WHO 2016 classification criteria
	  ○ Refractory (i.e. lack of a complete response) or relapsed after the receipt of a first-line anti-CD20 antibody and anthracycline-containing regimen within 12 months after the last dose
	  ○ Eligible for ASCT
	  ○ ECOG performance status of 0 or 1
	  ○ Adequate cardiac, hepatic, renal, hematologic, and pulmonary function
	• **Key exclusion criteria**
	  ○ Treatment with any systemic lymphoma-directed second line anticancer therapy prior to randomization (only steroids and local irradiation permitted for disease control)
	  ○ Active CNS involvement
	  ○ History of alloSCT
	  ○ Clinically significant active infection
	  ○ Cardio- and cerebrovascular conditions (e.g. unstable angina, myocardial infarction, coronary bypass graft, or stroke within six months prior to screening)
	  ○ Active neurological autoimmune or inflammatory disorders
	
	Number of participants
	
	• **n = 322 randomised**
	  ○ tisa-cel: 162
	  ▪ 101 (62%) DLBCL
	  ▪ 39 (24%) HGBL
	  ○ standard care: 160
	  ▪ 112 (70%) DLBCL
	  ▪ 27 (17%) HGBL
	• **n = 322 evaluated (efficacy analysis)**
	  ○ tisa-cel: 162
	  ○ standard care: 160
	• **n = 322 evaluated (safety analysis)**
	  ○ tisa-cel: 162
	  ○ standard care: 160
	
	Median age (range)
	
	• tisa-cel: 59.5 (19-79)
	• standard care: 58 (19-77)
	
	Sex (male/total): 201/322 (63%)
	
	Disease stage
	
	• I/IE: 41/322 (13%)
	• II, IIE, or II bulky: 76/322 (24%)
	• III: 53/322 (16%)
	• IV: 152/322 (47%)
	
	IPI ≥ 2: 198/322 (61%)

Interventions	**CAR T-cell product:** Tisagenlecleucel (tisa-cel) **Target:** CD19 **Dose of CAR T-cells:** 0.6 to 6.0 x 10^8 CAR T-cells (median dose 2.9 x 10^8) **Number of infusions:** 1 **Bridging therapy:** optional (investigator's choice of four prespecified platinum-containing combination chemotherapy regimens) • R-DHAP • R-ICE • R-GDP • R-Gem/Ox **Type and dose of lymphodepleting chemotherapy** • Fludarabine 25 mg/m² for 2 days • Cyclophosphamide 250 mg/m² for 2 days, (Bendamustine 90 mg/m² for 2 days, if contraindicated) **Comparator:** Standard care • investigator's choice of four prespecified chemotherapy regimens (same as bridging therapy) followed by high-dose chemotherapy (HDCT) and ASCT in patients with a complete or partial response (PR, CR) • Change to alternative treatment regimen in case of inadequate response on PET-CT at week 6 was allowed • Treatment switching: crossover from SOC group to receive tisa-cel was allowed after confirmation of SD or PD at or after week 12
Outcomes according to the trial protocol	**Primary outcomes** • Event-free survival (EFS) (defined as the time from randomization to stable or progressive disease at or after the week 12 assessment by the independent review committee according to the Lugano criteria, or death) **Secondary outcomes** • Overall survival (OS) • Response including overall response rate (ORR) (as assessed according to the Lugano criteria by the blinded independent review and local investigator) • Adverse events • Cellular kinetics • Quality of life (assessed with the SF-36v2, FACT-Lym, and EQ-VAS) **Assessment** • Disease assessments at week six, week 12 after randomization, followed by every three months for the first year, every six months for the second year, and annually until five years of follow-up • Adverse events assessed and graded according to the Medical Dictionary for Regulatory Activities terminology and Common Terminology Criteria for Adverse Events (CTCAE) (version 5) • Grade of cytokine release syndrome was determined using criteria described in Lee 2014 **Follow-up** • At median data cut-off (DCO): 10 months (range 2.9 to 23.2) • Planned follow-up: 5 years
Notes	**ClinicalTrials.gov ID and status:** NCT03570892; Active, not recruiting **Sponsors and collaborators:** Novartis Pharmaceuticals **(Principal) investigator(s):** Novartis Pharmaceuticals

TRANSFORM

Methods	**Phase**: 3 **Study design**: randomised-controlled trial (RCT), open-label, multicentre **Locations**: USA, Belgium, France, Germany, Italy Japan, Netherlands, Spain, Sweden, Switzerland, United Kingdom

Participants	**Eligibility criteria**
	
	• **Key inclusion criteria**
	  ○ Aged 18 years to 75 years
	  ○ Histologically proven aggressive B-cell Non-Hodgkin Lymphoma (defined as DLBCL, transformed indolent NHL, HGBL, PMBCL, THRBCL or FL3B) according to the WHO 2016 classification
	  ○ Refractory or relapsed within 12 months from anti-CD20 antibody and anthracycline-containing first line therapy
	  ○ 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) positive lesions at screening (Deahvulle score 4 or 5)
	  ○ ECOG performance status of 0 or 1
	  ○ Adequate renal, hepatic, hematologic, and pulmonary function
	• **Key exclusion criteria**
	  ○ Not eligible for HSCT
	  ○ Planning to undergo alloSCT
	  ○ Primary cutaneous large B-cell lymphoma, EBV positive DLBCL, Burkitt lymphoma or Richter transformation
	  ○ Prior malignancy other than aggressive R/R NHL, unless free of disease for ≥ 2 years except for non-melanoma skin cancer, carcinoma in situ (cervix, breast), curative prostate cancer or completely resected stage 1 solid tumor with low recurrence risk
	  ○ Presence of relevant uncontrolled infections despite appropriate antibiotics or other treatment
	  ○ Known history of human Immunodeficiency virus (HIV) or hepatitis B (HBsAg positive) or hepatitis C virus (anti-HCV positive) infection, or detectable viral load after HBV or HCV treatment
	  ○ Cardiovascular conditions within six months prior to signing the informed consent form (e.g. unstable angina, myocardial infarction, cardiac angioplasty)
	  ○ Clinically relevant central nervous system (CNS) pathology
	  ○ History or presence of autoimmune disease requiring immunosuppression within last 2 years
	
	Number of participants
	
	• **n = 184 randomised**
	  ○ liso-cel: 92
	  ▪ 60 (66%) DLBCL
	  ▪ 22 (24%) HGBL
	  ○ standard care: 92
	  ▪ 57 (62%) DLBCL
	  ▪ 21 (23%) HGBL
	• **n = 184 evaluated (efficacy analysis)**
	  ○ liso-cel: 92
	  ○ standard care: 92
	• **n = 183 evaluated (safety analysis)**
	  ○ liso-cel: 92
	  ○ standard care: 91
	
	Median age (IQR)
	
	• liso-cel: 60 (54-68)
	• standard care: 58 (42-65)
	
	Sex (male/total): 105/184 (57%)

	Disease stage • I: 22/184 (12%) • II: 31/184 (17%) • III: 31/184 (17%) • IV: 100/184 (54%) **Second-line age-adjusted IPI ≥ 2**: 73/184 (40%)
Interventions	**CAR T-cell product:** Lisocabtagene maraleucel (lico-cel) **Target:** CD19 **Dose of CAR T-cells:** 100 x 10^6 (CAR T-cells) total target dose **Number of infusions:** 1 **Bridging therapy:** optional (investigator's choice of three prespecified platinum-containing combination chemotherapy regimens) • R-DHAP • R-ICE • R-GDP **Type and dose of lymphodepleting chemotherapy** • Fludarabine 30 mg/m² for 3 days • Cyclophosphamide 300 mg/m² for 3 days **Comparator:** Standard care • 3 cycles of protocol-defined, investigator-selected, platinum-based immunochemotherapy (R-DHAP, R-ICE, R-GDP) followed by HDCT and ASCT in patients with a complete or partial response (PR, CR) • Change to alternative treatment regimen within the 3 cycles was allowed • Treatment switching: crossover to receive liso-cel as third line therapy was allowed for patients fulfilling criteria upon independent review committee confirmation
Outcomes according to the trial protocol	**Primary outcomes** • Event-free survival (EFS) (Time from randomization to death from any cause, progressive disease, failure to achieve CR or PR by 9 weeks after randomisation – after 3 cycles of salvage chemotherapy for the SOC group and 5 weeks after the infusion for the liso-cel group, or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first) according to independent review committee **Secondary outcomes** • Overall survival (OS) • Response including overall response rate (ORR) (as assessed according to the Lugano criteria by the independent review commitee) • Progression-free survival (PFS) (defined as the time from randomization to disease progression or death from any cause) • Adverse events • Quality of life (assessed with FACT-Lym and EORTC-QLQ-C30) • Hospital resource use • Cellular kinetics in the liso-cel group and crossover subgroup **Assessment** • Disease assessments at week 9 (5 weeks after liso-cel infusion and after three cycles of immunochemotherapy for SOC group) and 18 (14 weeks after liso-cel and 8 weeks after the start of HDCT for SOC group) and months 6, 9, 12, 18, 24, and 36 from randomisation • Adverse events assessed and graded according to the Medical Dictionary for Regulatory Activities terminology (version 23.0) and Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) • Grade of cytokine release syndrome was determined using criteria described in Lee 2014

	Follow-up • At median data cut-off (DCO): 6.2 months (range 0.9 to 20.0) • Planned follow-up: around 3 years
Notes	**ClinicalTrials.gov ID and status:** NCT03575351; active, not recruiting **Sponsors and collaborators:** Celgene **(Principal) investigator(s):** Bristol-Myers Squibb

ZUMA-7

Methods	**Phase**: 3 **Study design**: randomised-controlled trial (RCT), open-label, multicentre **Locations**: Australia, Austria, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, Spain, Sweden, Switzerland, United Kingdom, USA

Participants	**Eligibility criteria**
	• **Key inclusion criteria**
	  ○ Aged 18 years or older
	  ○ Histologically confirmed large B-cell lymphoma (DLBCL, HGBL, THRBCL, primary cutaneous DLBCL, Epstein-Barr virus (EBV) + DLBCL, DLBCL arising from FL) according to the WHO 2016 classification criteria
	  ○ Refractory (i.e. lack of a complete response) to first-line treatment or relapsed (i.e. biopsy-proven relapse from. Complete remission within. 12 months) after the completion of first-line anti-CD20 antibody and anthracycline-containing regimens
	  ○ Intended to proceed to HDCT and ASCT
	  ○ No CNS involvement
	  ○ ECOG performance status of 0 or 1
	  ○ Adequate cardiac, renal, hepatic, hematologic, and pulmonary function
	• **Key exclusion criteria**
	  ○ History of malignancy other than non-melanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) unless disease free for at least three years
	  ○ Received more than one line of therapy for DLBCL
	  ○ History of ASCT or alloSCT
	  ○ Presence of relevant uncontrolled infections or requiring intravenous antimicrobials for management
	  ○ Known history of human Immunodeficiency virus (HIV) or hepatitis B (HBsAg positive) or hepatitis C virus (anti-HCV positive) infection, or detectable viral load after HBV or HCV treatment
	  ○ Cardiovascular conditions (e.g. unstable angina, myocardial infarction, coronary bypass graft)
	  ○ Neurological conditions (e.g. seizure disorders, cerebrovascular disorders, dementia, neurological autoimmune or inflammatory disorders)
	  ○ History or presence of autoimmune disease requiring immunosuppression within last 2 years
	Number of participants
	• **n = 359 randomised**
	  ○ axi-cel: 180
	  ▪ 126 (70%) DLBCL
	  ▪ 31 (17%) HGBL
	  ○ standard care: 179
	  ▪ 120 (67%) DLBCL
	  ▪ 26 (15%) HGBL
	• **n = 359 evaluated (efficacy analysis)**
	  ○ axi-cel: 180

	○ standard care: 179 • **n = 338 evaluated (safety analysis)** ○ axi-cel: 170 ○ standard care: 168 (62 in ASCT safety analysis) **Median age (range)** • axi-cel: 58 (21-80) • standard care: 60 (26-81) **Sex (male/total):** 237/359 (66%) **Disease stage** • I/II: 74/359 (21%) • III/IV: 285/359 (79%) **Second-line age-adjusted IPI ≥ 2**: 61/359 (45%)
Interventions	**CAR T-cell product:** Axicabtagene ciloleucel (axi-cel) **Target:** CD19 **Dose of CAR T-cells:** 2 x 10^6 (CAR T-cells per kg body weight) **Number of infusions:** 1 **Bridging therapy:** glucocorticoids only **Type and dose of lymphodepleting chemotherapy** • Fludarabine 30 mg/m² for 3 days • Cyclophosphamide 500 mg/m² for 3 days **Comparator:** Standard care • 2 or 3 cycles of protocol-defined, investigator-selected, platinum-based immunochemotherapy (R-GDP, R-ICE, R-DHAP, R-ESHAP) followed by HDCT and ASCT in patients with a complete or partial response (PR, CR) Treatment switching: crossover between treatment groups was not planned but patients with inadequate response in the standard care arm could receive cellular immunotherapy outside the protocol
Outcomes according to the trial protocol	**Primary outcomes** • Event-free survival (EFS) (defined as the time from randomization to the earliest date of disease progression according to Lugano criteria, the commencement of new therapy for lymphoma, death from any cause, or a best response of stable disease up to and including the response on the day 150 assessment after randomisation) according to blinded central review **Secondary outcomes** • Overall survival (OS) • Response including overall response rate (ORR) (as assessed according to the Lugano criteria by the blinded central review) • Modified event-free survival (mEFS) (analyzed per blinded central review and per investigator disease assessment) • Progression-free survival (PFS) (defined as the time from randomization to disease progression or death from any cause) • Adverse events • Blood CAR T-cell levels (in axi-cel group) • Quality of life (assessed with EORTC QLQ-C39, EQ-5D-5L, and EQ-5D-5L VAS) **Assessment** • Disease assessments on days 50, 100, and 150 after randomization, followed by every three months until two years of follow-up, and then every six months until five years of follow-up

	• Adverse events assessed and graded according to the Medical Dictionary for Regulatory Activities terminology (version 23.1) and Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) • Grade of cytokine release syndrome was determined using criteria described in Lee 2014 **Follow-up** • At median data cut-off (DCO): 24.9 months Planned follow-up: 5 years
Notes	**ClinicalTrials.gov ID and status:** NCT03391466; active, not recruiting **Sponsors and collaborators:** Kite Pharma **(Principal) investigator(s):** Kite Study Director

Table 2. Efficacy (OS, PFS, EFS, OR, CR, PR)

	BELINDA [31]	ZUMA-7 [32]	TRANSFORM [33]
Proportion of participants assigned to and receiving CAR T-cell therapy	155/162 (95.7%)	170/180 (94.4%)	90/91 (98.9%)
Proportion of participants assigned to and receiving ASCT	52/160 (32.5%)	62/179 (34.6%)	43/91 (47.2%)
Proportion of participants in SOC arm receiving CAR T-cell therapy	50.6%	56%	51%
Survival analyses			
Overall survival (OS)	IN: 16.9 mo (95% CI, 11.14 to NE) CO: 15.3 mo (95% CI, 12.32 to NE)	IN: NR (95% CI, 28.3 to NE) CO: 35.1 mo (95% CI, 18.5 to NE)	IN: NR (95% CI, 15.8 to NR) CO: 16.4 mo (95% CI, 11.0 to NR)
	HR 0.99 (95% CI, 0.64 to 1.52)	HR 0.73 (95% CI, 0.53 to 1.01)	HR 0.51 (95% CI, 0.26 to 1.00)
Progression free survival (PFS)	NA	IN: 14.7 mo (95% CI, 5.4 to NE) CO: 3.7 mo (95% CI, 2.9 to 5.3)	IN: 14.8 mo (95% CI, 6.6 to NR) CO: 5.7 mo (95% CI, 3.9 to 9.4)
	NA	HR 0.49 (95% CI, 0.37 to 0.65)	HR 0.41 (95% CI, 0.24 to 0.66)
Event free survival (EFS)	IN: 3.0 mo (95% CI, 2.9 to 4.2) CO: 3.0 mo (95% CI, 3.0 to 3.5)	IN: 8.3 mo (95% CI, 4.5 to 15.8) CO: 2.0 mo (95% CI, 1.6 to 2.8)	IN: 10.1 mo (95% CI, 6.1 to NR) CO: 2.3 mo (95% CI, 2.2 to 4.3)
	HR 1.07 (95% CI, 0.82 to 1.40)	HR 0.40 (95% CI, 0.31 to 0.51)	HR 0.35 (95% CI, 0.23 to 0.53)
Response analyses			
Overall response (OR)	IN: 75/162 (46%) CO: 68/160 (43%)	IN: 150/180 (83%) CO: 90/179 (50%)	IN: 79/92 (86%) CO: 44/92 (48%)
	RR 1.09 (95% CI, 0.85 to 1.39)	RR 1.66 (95% CI, 1.41 to 1.94)	RR 1.80 (95% CI, 1.43 to 2.26)
Complete response (CR)	IN: 46/162 (28%) CO: 44/160 (28%)	IN: 117/180 (65%) CO: 58/179 (32%)	IN: 61/92 (66%) CO: 36/92 (39%)
	RR 1.03 (95% CI, 0.73 to 1.47)	RR 2.01 (95% CI, 1.58 to 2.54)	RR 1.69 (95% CI, 1.26 to 2.27)
Partial response (PR)	IN: 29/162 (18%) CO: 24/160 (15%)	IN: 33/180 (18%) CO: 32/179 (18%)	IN: 18/92 (20%) CO: 8/92 (9%)
	RR 1.19 (95% CI, 0.73 to 1.96)	RR 1.03 (95% CI, 0.66 zo 1.59)	RR 2.25 (95% CI, 1.03 to 4.91)

IN = intervention group; CO = control group; mo = months; NE = could not be estimated; NR = not reached; HR = hazard ratio; RR = risk ratio; NA = not available

Table 3. Efficacy (Quality of life)

Study ID	Sample size total	Sample size at baseline	Tool	Timing of assessment and reported effect measures						
				Baseline [a] M (SD)	**Day 29** Not reported	**Day 64** Not reported	**Day 126** Difference in overall least square mean changes from baseline through day 126 (95% CI) [b]	**Month 6** Observed mean change scores (within-group)		
TRANSFORM [33]	184	90	EORTC QLQ-C30 general health/QoL score (range 0 to 100, higher scores indicate improvement)	IN (n=47): 67.7 (21.5) CO (n=43): 8.2 (22.1)	IN versus CO: no evidence of statistically significant differences (data reported only graphically)	IN versus CO: no evidence of statistically significant differences (data reported only graphically)	IN (n=26) versus CO (n=10): 3.0 (-3.6 to 9.7)	IN (n=17): scores improved descriptively, but remained below the within-group MID (i.e. < 10 points) CO (n=7): scores worsened above the within-group MID (i.e. ≥ 10 points)		
Study ID	Sample size total	Sample size at baseline	Tool	**Baseline** [c] M (n) (95% CI)	**Day 50** Mean change scores (within group) (95% CI)	**Day 100** Difference in overall LSMC from baseline through day 100 (95% CI)[d]	**Day 150** Difference in overall LSMC from baseline through day 150 (95% CI)[d]	**Month 9** Difference in overall LSMC from baseline through month 9 (95% CI)[d]	**Month 12** Difference in overall LSMC from baseline through month 12 (95% CI)[d]	**Month 15** Difference in overall LSMC from baseline through month 15 (95% CI)[d]
ZUMA-7 [32]	359	295	EORTC QLQ-C30 general health/QoL score (range 0 to 100, higher scores indicate improvement)	IN (n=165): 68.6 (65.6 to 71.7) CO (n=130): 70.1 (66.1 to 74.1)	IN (n=163): 7.4 (-10.5 to -4.3) CO (n=125): 8.5 (-12.6 to -4.5)	IN (n=146) versus CO (n=62): 18.1 (12.3 to 23.9)	IN (n=110) versus CO (n=56): 9.8 (2.6 to 17.0)	IN (n=88) versus CO (n=49): 4.4 (-3.3 to 12.0)	IN (n=79) versus CO (n=33): -1.5 (-9.6 to 6.6)	IN (n = 67) versus CO (n=26): -4.9 (-13.0 to 3.1)
		296	EQ-5D-5L - index (range 0 to 1, higher scores indicate improvement)	IN (n=165): 0.803 (0.771 to 0.835) CO (n=132): 0.799 (0.756 to 0.842)	IN (n=163): -0.049 (-0.081 to -0.017) CO (n=123): -0.003 (-0.038 to 0.033)	IN (n=146) versus CO (n=65): 0.081 (95% CI 0.024 to 0.138)	IN (n=109) versus CO (n=56): 0.028 (-0.034 to 0.091)	IN (n=88) versus CO (n=39): 0.020 (-0.044 to 0.084)	IN (n=79) versus CO (n=32): -0.029 (95% CI -0.109 to 0.052)	IN (n=67) versus CO (n=26): -0.066 (95% CI -0.138 to 0.007

IN = intervention; CO = control; CI = confidence interval; LSMC = least square mean changes; M = mean; MID = minimum important difference; SD = standard deviation

[a] Baseline in TRANSFORM was set approximately one month before CAR T-cell therapy.

[b] Mean change scores in TRANSFORM were estimated from mixed-effect models with repeated measure analyses which considered all data points through day 126 and controlled for "relevant" baseline covariates (without exact specification of covariates).

[c] Baseline in ZUMA-7 was set prior to conditioning or salvage chemotherapy.

[d] Mean change scores in ZUMA-7 were estimated from mixed-effect models with repeated measure analyses controlled for response to first-line therapy and age-adjusted international prognostic index at time of screening.

Table 4. Safety

	BELINDA [31]	ZUMA-7 [32]	TRANSFORM [33]
Sample size	IN: n = 162 for AEs/SAEs; n = 155 for other safety analyses CO: n = 160 for AEs/SAEs; n = 81 for other safety analyses	IN: n = 170 CO: n = 168	IN: n = 92 CO: n = 91 for AEs/SAEs; n = 47 for other safety analyses
Adverse events	**Any grade:** IN: 160/162 (99%) CO: 158/160 (99%) **≥ grade 3:** IN: 136/162 (84%) CO: 144/160 (90%)	**Any grade:** IN: 170/170 (100%) CO: 168/168 (100%) **≥ grade 3:** IN: 155/170 (91%) CO: 140/168 (83%)	**Any grade:** NR **≥ grade 3:** IN: 85/92 (92%) CO: 79/91 (87%)
Serious adverse events	**Any grade:** IN: 76/162 (47%) CO: 82/160 (51%) **≥ grade 3:** IN: 58/162 (36%) CO: 68/160 (43%)	**Any grade:** IN: 85/170 (50%) CO: 77/168 (46%) **≥ grade 3:** IN: 72/170 (42%) CO: 67/168 (40%)	**Any grade:** NR **≥ grade 3:** IN: 31/92 (35%) CO: 39/91 (43%)
Cytokine release syndrome	**Any grade:** IN: 95/155 (61%) CO: 61/81 (75%) **≥ grade 3:** IN: 8/155 (5%) CO: 4/81 (5%)	**Any grade:** IN: 157/170 (92%) CO: NR **≥ grade 3:** IN: 11/170 (6%) CO: NR	**Any grade:** IN: 45/92 (49%) CO: 23/47 (49%) **≥ grade 3:** IN: 1/92 (1%) CO: NR
Neurologic events (including ICANS)	**Any grade:** IN: 16/155 (10%) CO: 12/81 (15%) **≥ grade 3:** IN: 3/155 (2%) CO: 2/81 (3%)	**Any grade:** IN: 102/170 (60%) CO: 33/168 (20%) (excluding ICANS) **≥ grade 3:** IN: 36/170 (21%) CO: 1/168 (0.6%) (excluding ICANS)	**Any grade:** IN: 11/92 (12%) CO: 8/47 (17%) **≥ grade 3:** IN: 4/92 (4%) CO: 2/47 (4%)
Tocilizumab use	**For CRS management:** IN: 49/NA (52%) CO: 34/NA (56%) **For neurologic events**: NA	*„in the safety population, tocilizumab was administered to 65% of patients"*	**For CRS management**: IN: 9/NA (10%) CO: 9/NA (19%) **For neurologic events**: IN: 1 (1%), for dizziness CO: 0
Any infections	**Infections and infestations** IN: 5/NA (3%) CO: 5/NA (3%)	**≥ grade 3:** IN: 14% CO: 11% **Any grade:** IN: 41% CO: 30%	**≥ grade 3:** IN: 14/NA (15%) CO: 19/NA (21%)

CO = control group; CRS = Cytokine release syndrome; ICANS = Immune effector cell associated neurotoxicity syndrome; IN = Intervention group; NA = not available

11. Summary of available data on comparative cost and cost-effectiveness

An electronic search for economic evidence was conducted in PubMed in November 2022, using the key words “cost analysis”, “cost benefit”, “QALY”, “ICER”, “Tisagenlecleucel”, “Axicabtagene ciloleucel”, “Lisocabtagene maraleucel”. References related to aggressive B-cell lymphoma were retrieved. Additionally, Health Technology Assessment (HTA) reports conducted by the National Institute for Health and Care Excellence (NICE, UK) and the Institute for Quality and Efficiency in Health Care (IQWiG, Germany) were sought.
Treatment with chimeric antigen receptor (CAR) T-cells is technologically demanding and resource intensive. It requires well-equipped facilities for its manufacturing as well as trained physicians to administer the treatment. Global availability of CAR T-cell therapy is limited. It has not been introduced in lower- or middle-income countries (LMIC) [41, 42]. Therefore, data on its comparative cost and cost effectiveness are limited to some European countries, North America, Japan, and Singapore. Moreover, these data often do not account for costs arising from additionally needed treatment and hospitalization. Additionally, since CAR T-cell therapy has been approved by various agencies for the indication of diffuse large B-cell lymphoma, most available evidence is on the treatment of this indication.
Treatment for all three, Axicabtagene ciloleucel (axi-cel), Tisagenlecleucel (tisa-cel), and Lisocabtagene maraleucel (liso-cel) consists of a single use per patient [3, 5, 6].

Cost per case

Axicabtacene ciloleucel

The price for axi-cel in the US war reported by the manufacturer to be 373.000$ [43], total drug acquisition cost were reported to be 399.000$ [44, 45]. In Germany, the wholesale price was 282.000€ [46], whereas total drug acquisition costs in Spain were reported at 313.920€ [47].
The estimated costs per case for axi-cel varied between 586.313$ and 637.129$, depending on the indication and the use of additional treatments [44, 45, 48]. Yearly therapy costs in Germany were estimated at 282.227€ [46]. This did not include the use of additional treatment that are part of other reimbursement processes in Germany (Diagnosis Related Groups system) [46].

Tisagenlecleucel

The costs of drug acquisition for tisa-cel in the US was reported to be 373.000$ [44, 48]. In Switzerland, drug acquisition costs were reported to be 403.470 CHF (1 CHF = 1.09$, thus 439.782$) [49], in Spain 307.200€ [47]. The wholesale price in Germany for tisa-cel is reported to be 275.000€ [50]. Yearly therapy costs in Germany were erstimated to be around 282.413,28€ - 283.244,95€ [50], depending on the additionally needed treatments. However, it is important to note that, due to reimbursement processes in Germany, not all additional treatment costs may be covered by these figures. The overall treatment costs may be higher [51].

Lisocabtagene maraleucel

For liso-cel, the cost of acquisition were reported at 410.300$ in the US [44, 45]. The total costs for patients in the US were estimated to be in between 597.174$ - 620.962$, depending on additional treatment costs [44, 45]. There have not been any HTA reports in Germany or the UK on liso-cel yet.
For overall CAR T-cell therapy, independent of the substance, budget impact calculations yielded estimations of 10 – 21 billion $ over 5 years for the US healthcare systems, if these treatments were administered to eligible patients. The figure varies due to different indications considered in estimations [42, 52].

Cost-effectiveness

Cost effectiveness for all substances varied between studies and reports, depending on the time-horizon and the perspective of the analyses, and on the inclusion of additional treatment costs.

Axicabtagene ciloleucel

Results for the cost-effectiveness of axi-cel varied. The NICE guidance on axi-cel reported an ICER between <50.000$ and >100.000$ [53]. An analysis from an Italian payer perspective reported an ICER of 44.746€/QALY gained [54], whereas two analyses from a US payer perspective over a lifetime horizon reported an ICER of 66.318$ and 67.250$ per QALY gained, respectively [55, 56]. A much larger ICER was reported in a Canadian analysis with a societal and public healthcare payer perspective. Hillis et al. reported an ICER of 132.747$/QALY gained [57].
Results for ICER per life year gained (LYG) were reported by Li et al. with 51.190$/LYG and Marchetti et al. with 42.873€/LYG [54].
All analyses compared axi-cel with standard of care, meaning salvage chemotherapy.

Tisagenlecleucel

The reported ICER for tisa-cel varied significantly, depending on the horizon and perspective. The highest ICER for tisa-cel was reported from a Singapore healthcare payer perspective over a time horizon of 15 years with 508.530$/QALY gained [58]. From a Canadian societal perspective and over a time horizon of 20 years, the reported ICER was 103.122$/QALY gained [43], and a US third-party payer perspective with a lifetime horizon reported an ICER of 78.652$/QALY gained [59]. An analysis of a Japanese perspective over a lifetime horizon reported an ICER of 5.476.496¥/QALY gained (1¥ ≈ 0.0068$ on November 8th, 2022, thus approximately 37.405$/QALY gained) [60]. The NICE guidance on tisa-cel reported an ICER between 42.991£ and 55.403£/QALY gained [61].
The ICER per LYG was reported to be 320.200$/LYG from the Singapore perspective, and approximately 36.811$/LYG (5.389.446¥/LYG) from the Japan perspective [58, 60].
All reports compared tisa-cel with salvage chemotherapy.
An analysis compared tisa-cel and axi-cel to standard of care and allogeneic stem cell transplantation, and analysed the cost-benefit relations using an efficiency frontier concept. In this analysis, alloSCT and axi-cel were found to be most effective. Compared to axi-cel and based on the cost-benefit relation, tisa-cel was found to be less efficient [62].

Lisocabtagene maraleucel

Our search did not yield results on the cost-effectiveness of liso-cel versus salvage chemotherapy. Additionally, there have not been any analyses by the German IQWiG or the British NICE.
However, Cummings Joyner et al. did a comparison of axi-cel and liso-cel, with a US payer perspective over a lifetime horizon. The ICER was reported to be 8.946$/QALY gained [44].
Cost-effectiveness for all three substances highly depend on the payer's perspective, the applied time horizon and the inclusion of additional treatment costs. In some cases, the medicines can be cost-effective compared to other treatment options, especially if ICERs per LYG are taken into consideration. Given the commonly used threshold of 100.000$ or less per QALY gained, treatment can be cost-effective compared to other forms of treatment, but it does depend on the setting, perspective and time horizon.
Both Gilead (for axi-cel) and Novartis (for tisa-cel) have signed outcome-based agreements with several German health insurers. These agreements state that the manufacturer will partially reimburse the treatments cost to the German health care fund if the patient dies within a defined period of time [51].

12. Regulatory status, market availability and pharmacopoieal standards

Tisagenlecleucel (tisa-cel, market name: Kymriah®), Axicabtagene ciloleucel (axi-cel, market name: Yescarta®) and Lisocabtagene maraleucel (liso-cel, market name: Breyanzi®) have been approved by several regulatory agencies worldwide.
The marketing-authorisation holders of these medicines are: Novartis for Kymriah®, Kite Pharma/Gilead for Yescarta® and Juno Therapeutics/Bristol-Myers Squibb Company for Breyanzi®. The products are available as dispersion for infusion. Neither substance has any existing or planned licencing agreements with generic manufacturers and/or the Medicines Patent Pool.
Moreover, neither substance has been mentioned in the British, International, European or United States Pharmacopoeia.

Tisagenlecleucel (tisa-cel, Kymriah®)

Tisa-cel was approved by the Food and Drug Administration (FDA, United States of America) [24], European Medicines Agency (EMA, Europe) [4], the Australian Government, Department of Health, Therapeutic Goods Administration (TGA) [63] and Health Canada [64, 65] for the following indications:

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

European Medicines Agency, Health Canada and the Australian Government also added paediatric patients who have relapsed post allogeneic stem cell transplant (SCT) or are otherwise ineligible for SCT as an indication to part 1) [4, 63, 65].
The Pharmaceuticals and Medical Devices Agency (PMDA, Japan) has not yet approved tisa-cel for treatment. However, the Committee on Regenerative Medicine Products and Biotechnology has advised the PMDA to accept tisa-cel for approval for the following indications [66]:

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

Axicabtagene ciloleucel (axi-cel, Yescarta®)

Axi-cel was also approved by the FDA [23], EMA [2], the Australian Government [67] and Health Canada [68] for the following indications:

1) Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
2) Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy
3) Adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy

PMDA has not yet approved Axi-cel for treatment. However, the Committee on Regenerative Medicine Products and Biotechnology has advised the PMDA to accept axi-cel for approval for the following indications [69]:

- Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma, and high-grade B-cell lymphoma and only in patients meeting all of the following criteria:
    - Patients who have not received prior transfusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen.
    - Patients who are indicated for autologous hematopoietic stem cell transplantation, have failed to respond with ≥2 lines of chemotherapy in the newly diagnosed patients and with ≥1 line of chemotherapy after relapse in the relapsed patients, or have had a relapse after autologous hematopoietic stem cell transplantation; or patients who are not indicated for autologous hematopoietic stem cell transplantation

Lisocabtagene maraleucel (liso-cel, Breyanzi®)

Liso-cel was approved by EMA [1] for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy. FDA [25] also approved liso-cel for the treatment of adult patients with large B-cell lymphoma (LBCL), including diffuse large Bcell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:

- refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
- refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age.

The Australian Government [70], Health Canada [71] and PMDA in Japan [72] have not yet approved liso-cel. However, the Committee on Regenerative Medicine Products and Biotechnology in Japan has advised the PMDA to accept liso-cel for approval for the following indications [72]:

- Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed low-grade non-Hodgkin's lymphoma, high-grade B-cell lymphoma, relapsed or refractory follicular lymphoma and only in patients meeting any of the following criteria:
    - Patients with large B-cell lymphoma other than transformed low-grade non-Hodgkin's lymphoma and patients with follicular lymphoma: ≥2 lines of prior chemotherapy in first-onset patients or ≥1 line of prior post-relapse chemotherapy in relapsed patients, which failed to achieve complete response or resulted in another relapse

- Patients with transformed low-grade non-Hodgkin's lymphoma transformed from follicular lymphoma: a total of ≥2 lines of prior chemotherapy including ≥1 after transformation, which failed to achieve complete response or resulted in relapse

Patients with transformed low-grade non-Hodgkin's lymphoma transformed from low-grade B-cell non-Hodgkin's lymphoma other than follicular lymphoma: ≥2 lines of prior chemotherapy after transformation, which failed to achieve complete response or resulted in relapse.

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