Axicabtagene ciloleucel

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 8. Immunomodulators and antineoplastics ❯ 8.2. Antineoplastics and supportive medicines

ATC codes: L01XL03

Indication	Diffuse large B-cell lymphomas — ICD11 code: 2B51
Medicine type	Biological agent
List type	Complementary
Formulations	Cell suspension for infusion: 2 × 10*6 anti-CD19 CAR-positive viable T-cells per kg of body weight.
EML status history	Application rejected in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	tisagenlecleucel (ATC codes: L01XL04) lisocabtagene maraleucel
Patent information	Read more about patents.
Tags	Biological
Wikipedia	Axicabtagene ciloleucel
DrugBank	Axicabtagene ciloleucel

Expert Committee recommendation

The Expert Committee recalled the review of available evidence for CD19-directed CAR T-cell therapy submitted for consideration in 2021 and appreciated the updated evidence presented by the applicants for the current meeting, proposing inclusion of these therapies on the EML for the treatment of adults with relapsed or refractory large B-cell lymphoma. The Committee noted that the field of CAR T-cell therapy continues to evolve rapidly, with several ongoing clinical trials. Based on the evidence presented in the application, the Committee acknowledged that CAR T-cell therapy appears to outperform standard care with salvage chemoimmunotherapy in terms of progression-free survival, although with variability across trials for other survival outcomes. The Committee noted in particular the results of the BELINDA trial, in which the point estimate for event-free survival favoured the control arm, and the point estimate for overall survival suggested no difference between treatment groups. However, the Committee also noted that long-term trial follow-up is currently limited for the three CAR T-cell therapies proposed for listing in the EML, and that overall survival data are still immature. Therefore, the Committee considered that the actual survival benefit remained uncertain. Furthermore, the Committee noted significant safety concerns including cytokine release syndrome and neurological toxicity, both of which occur in a high proportion of patients receiving CAR T-cell therapy. These may be life-threatening and require highly specialized medical management. Data on long-term safety are not currently available. The Committee noted that the application proposed listing CAR T-cell therapies as a therapeutic group but considered that the three therapies proposed were very different in terms of starting material (i.e. type of T-lymphocytes), vector, costimulatory domain and manufacturing; therefore, they may have important differences in both toxicity and efficacy. The Committee noted that acquisition costs for CAR T-cell therapies are very high, and that cost–effectiveness analyses are generally limited to high-income settings. These analyses report high incremental cost–effectiveness ratios, often greater than the willingness-to-pay thresholds of the settings in which they were conducted. The Committee recognized that treatment of patients using CAR T-cell therapy requires

dedicated health system resources and infrastructure well beyond those available in most settings and would have a substantial effect on budgets due to prohibitively high production costs, as well as costs for specialized administration and management of toxicities. However, the Committee noted with interest that these therapies are becoming increasingly available in academic settings and that closed and semi-automated manufacturing processes are becoming available which may substantially reduce prices and likely increase availability. Based on these considerations, the Expert Committee did not recommend the inclusion of axicabtagene ciloleucel, lisocabtagene maraleucel or tisagenlecleucel on the complementary list of the EML for treatment of adults with relapsed or refractory large B-cell lymphoma. Recognizing the promising role of CAR T-cell therapies for large B-cell lymphoma and potentially also other cancers, the Committee recommended that WHO continue to monitor the evidence on these therapies, as well as their growing availability and affordability.

Background

In CAR T-cell treatment, T cells are sampled from a patient's blood, modified and multiplied ex vivo before being readministered to the patient. By adding a gene for an engineered receptor (chimeric antigen receptor or CAR) in the laboratory, T cells are enabled to recognize specific cancer cell antigens (in the case of the current application CD-19, a transmembrane glycoprotein expressed by B-cells). The exact design and specificities of the CAR-T receptor varies in different products. As of the date of submission of the application, several different CAR-T treatments had been approved by United States Food and Drug Administration, all for haematological cancers. In 2021, the Expert Committee reviewed the evidence for axicabtagene ciloleucel and tisagenlecleucel for relapsed or refractory diffuse large B-cell lymphoma. The purpose of the application was only to review the evidence and addition of CAR T-cell therapy to the Model List was not proposed. The Committee noted that CAR T-cell therapy was highly specialized, requiring dedicated health system resources well beyond those currently available in most settings. Current treatment and management costs were also prohibitively high and exceeded affordability thresholds in almost all countries. The Committee considered that CAR T-cell therapies were an area of great interest and therapeutic relevance in the treatment of diffuse large B-cell lymphoma, and potentially other diseases. At the time, the Committee acknowledged that the available evidence was limited and of very low certainty. Nevertheless, it was noted that the immature data from multiple studies indicated that CAR T-cell therapy could induce durable complete responses, which may lead to clinical cure in some patients. The main uncertainties about the clinical benefits of CAR T-cell therapy related to the proportion of patients achieving long-term disease-free survival, and when CAR T-cell therapy is best used in the overall treatment algorithm. Safety concerns included cytokine release syndrome and neurological toxicity, both of which occur in a high proportion of patients, may be life-threatening and require highly specialized medical management. Data on long-term safety were limited. The Committee acknowledged that the field of CAR T-cell therapy was rapidly evolving, with many ongoing studies that might address the existing clinical uncertainties. The application of this treatment could be advantageous in low- and middle-income settings: a potential curative treatment for haematological malignancies with a single infusion of CAR T-cells might be a competitive therapeutic option when compared with multiple chemotherapy regimens administered in hospital over longer periods of time. The Committee considered that WHO should continue to monitor evidence on these therapies. The Committee advised that it would welcome an updated review of the evidence for CAR T-cell therapy for consideration at a future meeting. The Committee advised that WHO would need to have a strong leadership and advocacy role in facilitating affordable and equitable access to these treatments (1).

Public health relevance

Non-Hodgkin lymphomas are the seventh most common type of cancer and the most common haematological malignancy in the world, accounting for 4.3% of all cancers in the United States in 2015 (2). The most common type of malignant lymphomas worldwide are diffuse large B-cell lymphomas with 40% of all non-Hodgkin lymphomas (3) and 80% of all aggressive lymphomas (4). Based on morphological features and their genetic make-up, other subtypes and related entities, albeit less common, are defined and included with diffuse large B-cell lymphoma under the broader, more heterogeneous group of aggressive large B-cell lymphomas. These include high-grade B-cell lymphomas, primary mediastinal B-cell lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, and others (5). Global data on the incidence and mortality of diffuse large B-cell lymphoma are limited. However, the age-adjusted incidence rate of diffuse large B-cell lymphomas in the United States was 5.5 per 100 000 in 2015 (6). 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 about 3–4% in the United States (4,7). Males are at a 1.5 times higher risk of being diagnosed with diffuse large B-cell lymphomas (4,7). Mortality was 1.8 per 100 000 in the United States in 2015 (6). Untreated,

diffuse large B-cell lymphomas are associated with a median survival of less than 1 year. With first-line chemoimmunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, most patients have good outcomes (7). However, 30–40% of patients relapse or are refractory to first-line treatment. The treatment of relapsed or refractory large B-cell lymphoma is complex and depends on many factors, of which time to relapse is the most critical one. Even with the second-line treatments, which consist of salvage chemoimmunotherapy followed by autologous haematopoietic stem-cell transplantation, about 60% of patients experience a further relapse (8,9). In patients with primary progressive disease or relapse within 1 year after first-line therapy, progression-free survival is about 25% at 2 years (10). Accordingly, the prognosis for relapsed or refractory large B-cell lymphomas is still poor.

Benefits

The application presented the results of a systematic review and meta-analysis of three randomized trials (865 participants) which evaluated the efficacy and safety of CAR T-cell therapy in people with relapsed or refractory aggressive large B-cell lymphoma as second-line treatment, comparing them with the established standard of care of platinum-containing chemotherapy regimens followed by high-dose chemotherapy and autologous stem-cell transplantation. All three trials were multicentre, phase III open-label studies that recruited participants from Europe, Asia, North and South America, and the Pacific region. The BELINDA trial evaluated tisagenlecleucel (11), the ZUMA-7 trial evaluated axicabtagene ciloleucel (12) and the TRANSFORM trial evaluated lisocabtagene maraleucel (13). The intervention in each trial was a one-time infusion of CD19-directed CAR T-cells after the administration of lymphodepleting chemotherapy with fludarabine and cyclophosphamide over 2–3 days. Co-interventions were not permitted. Trial designs varied slightly. While leukapheresis (the collection and separation of white blood cells from blood to obtain T-cells) was performed before randomization in BELINDA and TRANSFORM (i.e. independent of group allocation), it was performed after randomization in ZUMA-7. 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 4 weeks, to a median of 5 weeks in TRANSFORM and 7 weeks in BELINDA. The timing of leukapheresis may affect T-cell count recovery and quality. Bridging therapy (chemoimmunotherapy 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. Treatment regimes in the control arms were similar across trials. They consisted of three to four prespecified platinum-based chemoimmunotherapy regimens based on investigator's choice. Changes in treatment regimens were permitted in BELINDA and TRANSFORM in case of efficacy concerns. In TRANSFORM, a change of the chemoimmunotherapy regimen was allowed within the first three cycles and in BELINDA after the positron emission tomography at week six. The proportion of participants in the control arms receiving high-dose chemotherapy and autologous stem-cell transplantation was 33% in BELINDA, 35% in ZUMA-7 and 47% in TRANSFORM. Crossover from standard of care to CAR T-cell therapy was allowed as a third-line treatment option in BELINDA and TRANSFORM. In ZUMA-7, crossover was not planned, but cellular immunotherapy was permitted outside the protocol. In BELINDA and TRANSFORM, 50–51% of participants allocated to the standard of care arm received third-line CAR T-cell therapy without receiving autologous stem-cell transplantation. In ZUMA-7, 56% of participants in the control arm subsequently received CAR T-cells outside the trial. Using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach, the overall certainty of the evidence was low to moderate. Risk of bias was deemed low for survival and response assessment, unclear for safety assessment and high for quality of life, which for quality of life was due to the risk of performance and detection bias and the subjective nature of the outcome, as well as attrition bias. The median age of participants in the trials was 59 years and the proportion of female patients was between 34% and 43% reflecting the higher incidence of large B-cell lymphoma in males. The predominant large B-cell lymphoma subtype in all studies was diffuse large B-cell lymphoma diagnosed in 64% to 69% of patients, followed by high-grade B-cell lymphoma subtypes in 16% to 23%. Eligibility criteria across trials were similar. Trial participants were eligible if they were: diagnosed with aggressive large B-cell lymphoma, refractory or relapsing early (within 1 year) after an anti-CD20 monoclonal antibody and anthracycline-containing immunochemotherapy; had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1; and were eligible for high-dose chemotherapy and autologous stem-cell transplantation. Lymphoma in the central nervous system was an exclusion criterion in BELINDA and ZUMA-7. Overall survival The results on overall survival were reported in the three trials. In each trial, data on overall survival were immature at the data cut-off and were presented as interim analyses. In BELINDA, data on overall survival were immature at the data cut-off. Median overall survival was 16.9 months (95% confidence interval (CI) 11.14 to not estimable) in the CAR T-cell group and 15.3 months (95% CI 12.32 months to not estimable) in the control group (stratified unadjusted hazard ratio (HR) for death 1.24, 95% CI 0.83 to 1.85) (11). In ZUMA-7, median overall survival was evaluated as an interim analysis. Overall survival was not reached in the CAR T-cell group (95% CI

28.3 months to not estimable) and 35.1 months (95% CI 18.5 months to not estimable) in the control group (HR for death 0.73, 95% CI 0.53 to 1.01) (12). In TRANSFORM, overall survival data were immature at the time of the interim analysis. Median overall survival was not reached in the CAR T-cell group (95% CI 15.8 months to not reached) and 16.4 months (95% CI 11.0 months to not reached) in the control group (stratified HR for death 0.51, 95% CI 0.26 to 1.01) (13). Overall survival data from the three trials were not pooled and meta-analysed. The applicants observed that overall survival in TRANSFORM and ZUMA-7 favoured CAR T-cell therapy, however no evidence of a difference between CAR T-cell therapy and standard of care was observed in BELINDA. The applicants concluded that the evidence suggested that CAR T-cell therapy may improve overall survival when compared with second line standard of care treatment. However, it was also noted that the evidence was uncertain, with follow-up still ongoing. Furthermore, considering that more than 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 inadequately represented by the overall survival estimates. The applicants proposed that surrogate survival endpoints such as progression-free and event-free survival might be more informative. Progression-free survival The ZUMA-7 and TRANSFORM trials reported progression-free survival outcomes (543 participants). In BELINDA, progression-free survival assessment was not included in the trial protocol. The evidence from TRANSFORM and ZUMA-7 suggests that CAR T-cell therapy might improve progression-free survival when compared with standard of care treatment. In ZUMA-7, median progression-free survival was 14.7 months (95% CI 5.4 months to not estimable) in the CAR T-cell group and 3.7 months (95% CI 0.37 to 0.65 months) in the control group (stratified HR for disease progression or death 0.49, 95% CI 0.37 to 0.65) (12). In TRANSFORM, median progression-free survival was 14.8 months (95% CI 6.6 months to not reached) in the CAR T-cell group and 5.7 months (95% CI 3.9 to 9.4 months) in the control group (stratified HR for disease progression or death 0.41, 95% CI 0.25 to 0.66) (13). Meta-analysis of pooled data from these trials performed by the applicants found moderate-certainty evidence that CAR T-cell therapy improved progression-free survival compared with standard of care (HR 0.47, 95% CI 0.37 to 0.60). In absolute terms, progression-free survival was 601 per 1000 patients with CAR T-cell therapy and 339 per 1000 patients with standard of care. Event-free survival Event-free survival was the primary outcome in all three trials. However, event-free survival was defined differently and the timing of assessment differed across the trials. In BELINDA, median event-free survival was similar between treatment groups: 3 months (95% CI 2.9 to 4.2 months) in the intervention group and 3 months (95% CI 3.0 to 3.5 months) in the control group (HR 1.07, 95% CI 0.82 to 1.40) (11). In ZUMA-7, median event-free survival was 8.3 months (95% CI 4.5 to 15.8 months) in the CAR T-cell group and 2.0 months (95% CI 1.6 to 2.8 months) in the control group (HR 0.40, 95% CI 0.31 to 0.51) (12). In TRANSFORM, median event-free survival was 10.1 months (95% CI 6.1 months to not reached) in the CAR T-cell group and 2.3 months (95% CI 2.2 to 4.3 months) in the control group (HR 0.35, 95% CI 0.23 to 0.53) (13). Event-free survival data from the three trials were not pooled and meta-analysed. The applicants concluded that the evidence suggested that CAR T-cell therapy might lead to an increase in event-free survival compared with standard of care. Additionally, the applicants proposed that differences in the effect estimates might be due to varying interventions and trial designs, with outcome definitions reducing the certainty in the evidence. Overall response rates Overall response rates were reported for all three trials. In BELINDA, the overall response rate was 46% (75/162) of patients in the CAR T-cell group and for 42% (68/160) of patients in the control group (risk ratio (RR) 1.09, 95% CI 0.85 to 1.39) (11). In ZUMA-7, the overall response rate was 83% (150/180) of patients in the CAR T-cell group and 50% (90/179) of patients in the control group (RR 1.66, 95% CI 1.41 to 1.94) (12). In TRANSFORM, the overall response rate was 86% (79/92) of patients in the CAR T-cell group and 48% (44/92) of patients in the control group (RR 1.80, 95% CI 1.43 to 2.26) (13). Meta-analysis of pooled data from these trials performed by the applicants found low-certainty evidence that CAR T-cell therapy leads to a higher overall response rate when compared with second-line standard of care chemoimmunotherapy and autologous stem-cell transplantation (RR 1.49, 95% CI 1.13 to 1.97). In absolute terms, overall response was seen in 698 per 1000 patients with CAR T-cell therapy and 469 per 1000 patients with standard of care. Quality of life The ZUMA-7 and TRANSFORM trials reported quality of life outcomes (385 participants) using multiple validated tools for several time points. The application reported results for EuroQoL 5-Dimension 5-Level (EQ-5D-5L) index and the general health/QoL subscale of the EORTC QLQ-C30, for all time points that were reported. 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-cell 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-cell 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). Based on mixed-effect models with repeated measures analyses controlled for response to first-line therapy and age-adjusted International Prognostic Index at time of screening, there was evidence of a statistically significant difference in the mean changes from baseline to day 100 in favour of the CAR T-cell group (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 (0.028, 95% CI –0.034 to 0.091), at 9 months (0.020, 95% CI –0.044 to 0.084), at 12 months (–0.029, 95% CI –0.109 to 0.052) and 15 months (–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-cell arm (15%; 25/166) compared with the control arm (12%; 16/133), but according to time to definitive improvement analyses, there was no evidence of a statistically significant difference (HR 1.15, 95% CI, 0.61 to 2.15) (14). EORTC QLQ-C30 – general health/QoL subscale In ZUMA-7, the mean European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 – general health/QoL scores at baseline were 68.6 (95% CI 65.6 to 71.7) for the CAR T-call group (n = 165), and 70.1 (95% CI 66.1 to 74.1) for the control group (n = 130). By day 50, mean scores decreased in both groups: changes from baseline –7.4 (95% CI –10.5 to –4.3) in the CAR-T group and –8.5 (95% CI –12.6 to –4.5) in the control group. Based on mixed-effect models with repeated measures analyses controlled for response to first-line therapy and age-adjusted International Prognostic Index 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 favour of the CAR T-cell group (18.1, 95% CI 12.3 to 23.9). Estimated mean changes from baseline at day 150 also favoured the CAR T-cell group (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 9 months (4.4, 95% CI –3.3 to 12.0), 12 months (–1.5, 95% CI –9.6 to 6.6) and 15 months (–4.9, 95% CI –13.0 to 3.1). Descriptively, the proportion of patients who experienced clinically meaningful improvement were higher in the CAR T-cell arm (19%) compared to the control arm (14%), but according to time to definitive improvement analyses, there was no evidence of a statistically significant difference (HR 1.25, 95% CI 0.7 to 2.22) (14). In TRANSFORM, mean (standard deviation) EORTC QLQ-C30 – general health/QoL scores at baseline were 67.7 (21.5) for the CAR T-cell group (n = 47) and 68.2 (22.1) for the control group (n = 43). Based on mixed-effect models with repeated measures analyses which considered all data points through day 126 and controlled for relevant baseline covariates, 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-cell group (mean difference 3.0, 95% CI –3.6 to 9.7). Across timings of assessment (days 29, 64 and 126), there was no evidence of statistically significant between-group differences. At 6 months, the observed mean EORTC QLQ-C30 – general health/QoL change scores in the control arm showed clinically meaningful worsening (i.e. mean changes exceeded the authors' prespecified within-group minimally important difference of 10 points). In the CAR T-cell arm, observed mean change scores improved descriptively, but remained lower than the limit of the within-group minimally important difference. Descriptively, from day 126 to month 6, the proportion of patients with meaningful improvement in general health/QoL (using the authors' responder definition of a minimal change threshold (i.e. smallest incremental change) of 5 points) was higher, while deterioration was lower, in the CAR T-cell arm compared with the control arm. That means the proportions of patients with improvement/deterioration at day 126 were 62%/23% (n = 26) in the CAR T-cell 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-cell arm and 14%/57% (n = 7) in the control arm (15). Quality of life data from the two trials were not pooled and meta-analysed. The applicants concluded that the evidence suggested that quality of life might be increased for CAR T-cell therapy compared with standard of care at some points during the treatment sequence. The evidence was judged to be uncertain and may be limited to patients who respond to or tolerate treatments well.

Harms

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 in the occurrence of serious adverse events compared with second-line standard of care. The BELINDA trial 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 (11). In ZUMA-7, 170 participants in the intervention group and 168 in the control group were included in the safety analysis (12). The TRANSFORM trial 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 CAR T-cell therapy as third-line treatment (13). Any adverse event Overall, 99–100% of participants in both the intervention and control groups in the BELINDA and ZUMA-7 trials experienced any adverse event (11,12). Across all trials, between 84% and 92% of participants in the intervention group and 83% and 90% in the control group experienced any adverse event of grade 3 or higher (11–13). The BELINDA trial reported 99% of participants in both the intervention and control group experiencing any adverse event. In the intervention and control groups, respectively, 84% and 90% of participants experienced an

adverse event of grade 3 or higher (11). In ZUMA-7, 100% of participants in the intervention and control groups experienced any adverse event. In the intervention and control groups, respectively, 91% and 83% of participants experienced an adverse event of grade 3 or higher (12). The TRANSFORM trial did not report the number of patients with any adverse event. However, 92% and 87% of participants in the intervention and control groups, respectively, experienced an adverse event of grade 3 or higher (13). Any serious adverse events In the intervention groups of BELINDA and ZUMA-7, 47% to 50% of participants experienced any serious adverse event, versus 46% to 51% of participants in the control groups. Between 34% and 42% in the intervention groups and 40% and 43% in the control groups experienced serious adverse events of grade 3 or higher (11,12). In BELINDA, any serious adverse event was reported in 47% and 51% of participants in the intervention and control groups, respectively. Serious adverse events of grade 3 or higher were reported in 36% and 43% of participants in the intervention and control groups, respectively (11). In ZUMA-7, 50% of participants in the intervention group and 46% of participants in the control group experienced any serious adverse event. Serious adverse events of grade 3 or higher were experienced by 42% and 40% of participants in the intervention group and control group, respectively (12). The TRANSFORM trial reported serious adverse events of grade 3 or higher in 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 (13). Cytokine release syndrome All trials reported the number of participants with cytokine release syndrome (11–13). The number of participants with cytokine release syndrome in the intervention groups ranged between 49% and 92%, with between 1% and 6% of participants experiencing cytokine release syndrome of grade 3 or higher. In the control groups, between 49% and 75% of participants had cytokine release syndrome of any grade. The BELINDA trial reported cytokine release syndrome in 61% and 75% of participants in the intervention and control groups, respectively, with cytokine release syndrome of grade 3 or higher reported in 5.2% and 4.9% of participants in the intervention and control groups, respectively. Tocilizumab for management of cytokine release syndrome was reported for 51.6% of participants in the intervention group and 55.7% in the control group (11). In ZUMA-7, for the intervention group, cytokine release syndrome was reported in 92% of participants and cytokine release syndrome of grade 3 or higher was reported for 6% of participants. The number of participants with cytokine release syndrome in the control group was not reported. Tocilizumab for was administered to 65% of participants, however, it was not reported how many participants per group received tocilizumab, nor if it was administered for cytokine release syndrome or any neurological event (12). In TRANSFORM, cytokine release syndrome was reported for 49% of participants in both the intervention and control groups. Cytokine release syndrome of grade 3 or higher was only reported in one participant (1%) in the intervention group. For 10% of participants in the intervention group, and 19% of participants in the control group, tocilizumab was used for management of cytokine release syndrome (13). Neurological events All trials reported the number of participants with neurological events, however the numbers in the ZUMA-7 control group did not include the number of patients with immune effector cell-associated neurotoxicity syndrome (12). The number of participants with neurological events including immune effector cell-associated neurotoxicity syndrome of any grade ranged between 10% and 60% in the intervention group, and between 15% and 17% in the control group. The number of participants with neurological events of grade 3 or higher ranged between 2% and 21% in the intervention group and 3% and 4% in the control group (11, 12). In BELINDA, any neurological event was reported for 10.3% of participants in the intervention group and 14.8% in the control group, both including immune effector cell-associated neurotoxicity syndrome. Additionally, 1.9% in the intervention group and 2.5% in the control group experienced neurological events of grade 3 or higher, including immune effector cell-associated neurotoxicity syndrome. The number of participants receiving tocilizumab for neurological events was not reported (11). In ZUMA-7, 60% of participants in the intervention group experienced any neurological event, including immune effector cell-associated neurotoxicity syndrome, and 20% of participants in the control group experienced any neurological event, excluding immune effector cell-associated neurotoxicity syndrome. Additionally, 21% in the intervention group experienced neurological events of grade 3 or higher, including immune effector cell-associated neurotoxicity syndrome, and 0.6% in the control group experienced neurological events of grade 3 or higher, excluding immune effector cell-associated neurotoxicity syndrome (12). The TRANSFORM trial reported any neurological event including immune effector cell-associated neurotoxicity syndrome in 12% of the intervention group and 17% of the control group. Neurological events of grade 3 or higher were reported in 4% of participants in both the intervention and control groups. One patient in the intervention group received tocilizumab for dizziness (13). Any infections Infections were reported in all three trials. The number of participants with infections ranged between 3% and 41% in the intervention groups, and between 3% and 30% in the control groups (11–13). The BELINDA trial reported any infections and infestations in 3.1% of participants in each group (11). In the ZUMA-7 trial, infections of any grade were reported in 41% of participants in the intervention group and 30% in the control group. Infections of grade 3 or higher were reported in 14% of participants in the intervention group and 11% in the control group (12). In the TRANSFORM trial, infections of grade 3 or higher were reported in 15% of participants in the intervention group and 21% in the

control group (13).

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Cost / cost effectiveness

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The applicants conducted a targeted search for references related to the costs of the medicines included in this application. In addition, health technology assessment reports by the National Institute for Health and Care Excellence (United Kingdom) and the Institute for Quality and Efficiency in Health Care (Germany) were included in the application. Treatment with CAR T-cells is technologically demanding and resource intensive. It requires well equipped facilities for its production as well as trained physicians and nurses to administer the treatment. Global availability of CAR T-cell therapy is limited. It has not been introduced in low- or middle-income countries (16,17). Therefore, data on its comparative cost and cost–effectiveness are limited to high-income countries. Moreover, these data often do not account for costs arising from the need for additional treatment and hospitalization. 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 condition. Treatment with all three therapies consists of a single use per patient. Cost–effectiveness for all three CAR T-cell therapies depends on the payer's perspective, the applied time horizon and the inclusion of additional treatment costs. In some cases, the therapies can be considered cost-effective compared with other treatment options, especially if incremental cost–effectiveness ratios per life year gained are taken into consideration. The manufacturers of axicabtagene ciloleucel and tisagenlecleucel 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 (18). Cost per case Axicabtagene ciloleucel The price for axicabtagene ciloleucel in the United States was reported by the manufacturer to be US$ 373 000 (19), with total drug acquisition cost reported to be US$ 399 000 (20, 21). In Germany, the wholesale price was €282 000 (22), whereas total drug acquisition cost in Spain was reported at €313 920 (23). The estimated costs per case for axicabtagene ciloleucel varied between US$ 586 313 and US$ 637 129, depending on the indication and the use of additional treatments (20, 21, 24). Yearly therapy costs in Germany were estimated at €283 227 (excluding costs for the use of additional treatment that are part of other reimbursement processes) (22). Tisagenlecleucel The acquisition cost for tisagenlecleucel was reported to be US$ 373 000 in the United States (20, 24), Sw.fr. 403 470 in Switzerland (25) and €307 200 in Spain (23). The wholesale price for tisagenlecleucel in Germany was reported to be €275 000, with yearly therapy estimated at about €283 000 (26), depending on the additional treatments needed. However, because of reimbursement processes in Germany, not all additional treatment costs are covered by this figure so the overall treatment costs may be higher (18). Lisocabtagene maraleucel The acquisition cost for lisocabtagene maraleucel was reported to be US$ 410 300 in the United States (20, 21). The total costs per patient were estimated to be between US$ 597 174 and US$ 620 962, depending on additional treatment costs. Health technology assessment reports from Germany or the United Kingdom are not yet available for lisocabtagene maraleucel. For overall CAR T-cell therapy, independent of the substance, budget impact calculations estimated US$ 10–21 billion over 5 years for the United States health care systems if these treatments were given to eligible patients. This figure varies because of variation in the indications considered in the estimations (17,27). Cost–effectiveness The cost–effectiveness of CAR T-cell therapies 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 The January 2019 NICE technology appraisal guidance on axicabtagene ciloleucel reported an incremental cost–effectiveness ratio more than £50 000 per quality-adjusted life year (QALY) gained (28). Updated NICE guidance from February 2023 reported an incremental cost–effectiveness ratio of lower than £50 000 per QALY (29). An analysis from an Italian payer perspective reported an incremental cost–effectiveness ratio of €44 746 per QALY gained (30), whereas an analysis from a United States payer perspective over a lifetime horizon reported an incremental cost–effectiveness ratio of US$ 66 318 per QALY gained (31). A Canadian analysis with a societal and public health care payer perspective reported an incremental cost–effectiveness ratio of Can$ 132 747 per QALY gained (32). A cost–effectiveness analysis from the perspective of the Chinese health care system reported an incremental cost–effectiveness ratio of US$ 67 250 per QALY gained, above the willingness-to-pay threshold applied of US$ 31 320 per QALY gained, which is three times the gross domestic product per capita (33). All the analyses compared axicabtagene ciloleucel with standard of care (i.e. salvage chemotherapy). Tisagenlecleucel The highest incremental cost–effectiveness ratio for tisagenlecleucel was US$ 508 530 per QALY gained reported from a Singapore health care payer perspective over a time horizon of 15 years (34). From a Canadian societal perspective and over a time horizon of 20 years, the reported incremental cost–effectiveness ratio was Can$ 103 122 per QALY gained (19). An analysis using a United States third-party payer perspective with a lifetime horizon reported an incremental cost–effectiveness ratio of US$ 78 652 per QALY gained (35). An analysis using a Japanese perspective over a lifetime horizon reported an incremental cost–effectiveness ratio of 5 476 496 Japanese yen per QALY gained (36). The NICE technology appraisal

guidance on tisagenlecleucel reported an incremental cost–effectiveness ratio between £42 991 and £55 403 per QALY gained (37). Incremental cost–effectiveness ratios per life year gained were reported to be US$ 320 200 from the Singapore perspective (34) and 5 389 446 Japanese yen from the Japanese perspective (36). All analyses compared tisagenlecleucel with salvage chemotherapy. An analysis from a German payer perspective compared CAR T-cell therapy (axicabtagene ciloleucel and tisagenlecleucel), allogenic stem-cell transplantation and best supportive care and applied the efficiency frontier concept. In this analysis, allogenic stem-cell transplantation and axicabtagene ciloleucel were the most efficient interventions (38). Lisocabtagene maraleucel Cost–effectiveness analyses of lisocabtagene maraleucel versus salvage chemotherapy were not identified. A comparison of the three CAR T-cell therapies from a United States payer perspective over a lifetime horizon found that incremental cost–effectiveness ratios for axicabtagene ciloleucel versus its comparators were substantially lower than the threshold of US$ 150 000 used to evaluate its relative cost–effectiveness – US$ 8946 per QALY gained versus lisocabtagene maraleucel and US$ 24 506 per QALY gained versus tisagenlecleucel (20).

WHO guidelines

WHO guidelines for treatment of relapsed or refractory large B-cell lymphoma are not currently available.

Availability

Axicabtagene ciloleucel, lisocabtagene maraleucel and tisagenlecleucel have been approved by several regulatory agencies worldwide for various indications including treatment of adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. At the time of the Expert Committee meeting (April 2023), there were no existing or planned licencing agreements with generic manufacturers and/or the Medicines Patent Pool.

Other considerations

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical team commented that there were insufficient mature data on the efficacy (as measured by overall survival) and safety of CAR T-cell therapies to justify inclusion on the EML at this time, and that future consideration could be made as more studies are reported and a greater understanding of feasibility is gained. The technical team highlighted the need to monitor the evidence on these therapies and to consider a broader context for access. The EML Cancer Medicines Working Group reviewed the application and advised that it did not support the inclusion of CD19-directed CAR T-cell immunotherapy as a therapeutic class or as individual medicines on the EML. The Working Group acknowledged that CAR T-cell therapy is superior to salvage chemoimmunotherapy in terms of progression free-survival, without evidence of heterogeneity across trials. However, for all medicines proposed, the Working Group noted that long-term trial follow-up is limited, and that the survival benefit observed is currently uncertain, with one study potentially associated with a detrimental effect of CAR T-cell therapy. In addition, the current costs of the administration of these medicines are very high, with cost–effectiveness analyses finding these treatments not to be cost-effective in most settings at the current prices. Further concerns were raised about the feasibility of administering these treatments and managing adverse effects in resource-constrained settings. It was noted that CAR T-cell therapy is a rapidly evolving field with a high likelihood that the currently available products will be replaced by more advanced products in the future. The Working Group agreed that CAR T-cell therapies for large B-cell lymphoma, and probably other cancer indications (e.g. acute lymphoblastic leukaemia), are an area of considerable interest and therapeutic relevance. The Working Group considered that the evidence on these therapies should continue to be monitored on an ongoing basis. Costimulatory signalling domains should be also considered as they might have implications for clinical efficacy and in prioritizing one CAR T-cell immunotherapy over others. The Working Group noted that T-cell production methods, other than industry-scaled centralized manufacturing by companies, are now being explored. The Working Group considered that decentralized production in academic medical centres and hospitals has the potential to facilitate widespread patient access to CAR T-cell therapy.

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