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CAR-T IMMUNOTHERAPY IN VARIOUS LYMPHOMAS – AN OVERVIEW INCLUDING THE LATEST STUDIES FROM 2017–2025

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ABSTRACT

The review presents the development and current applications of CAR-T (chimeric antigen receptor T-cell therapy) in the treatment of various forms of non-Hodgkin's lymphoma between 2017 and 2025. CAR-T cell immunotherapy, based on the genetic modification of the patient's autologous T cells to recognize the CD19 antigen, has revolutionized the treatment of lymphomas resistant to standard methods. Major clinical trials, such as, have confirmed the high efficacy of CAR-T therapy in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The complete remission (CR) rates achieved ranged from 40% to 54%, with an acceptable safety profile, mainly including cytokine release syndrome (CRS) and neurotoxicity.

In subsequent years, the use of CAR-T was extended to other subtypes of lymphoma. The data collected confirm that CAR-T therapies against CD19 provide high efficacy and durable remissions in numerous types of non-Hodgkin lymphoma, including in treatment-resistant patients. Despite the risks of CRS and neurotoxicity, modern supportive care regimens and improvements in CAR design have improved the safety of the therapy.

The conclusions indicate that CAR-T immunotherapy has become a key element in the treatment of lymphoproliferative malignancies, and ongoing research is focused on earlier use of this method, combination therapy with checkpoint inhibitors, and the development of CARs targeting new antigens (CD20, CD22, BCMA).

KEYWORDS

Immunotherapy, CAR-T Cell Therapy, Non-Hodgkin Lymphomas, Large B-Cell Lymphoma, Follicular Lymphoma, Mantle Cell Lymphoma, Primary Mediastinal Lymphoma, CD19, T Lymphocytes, Refractory and Relapsed Treatment

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Introduction

The development of cell therapies has changed the way lymphatic system cancers are treated, offering new possibilities for patients who are resistant to standard treatments. One of the most groundbreaking achievements in recent years is the use of genetically modified T cells, or CAR-T (chimeric antigen receptor T-cell therapy). This method involves collecting the patient's own T cells, genetically engineering them to target cancer antigens, and then re-administering them to the patient. The result is targeted activation of the immune system against cancer cells, independent of the antigen presentation mechanisms typical of T cells. The first registered CAR-T products, such as axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel, were developed for the treatment of B-cell lymphomas, including diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma. The ZUMA-1 (Neelapu et al., 2017), JULIET (Schuster et al., 2019), and TRANSCEND (Abramson et al., 2020) confirmed the efficacy of these therapies in patients with relapsed or refractory DLBCL who had not achieved durable remission with previous treatments.

Subsequent studies have expanded the use of CAR-T therapy to other subtypes of lymphoma. The ZUMA-2 study evaluated KTE-X19 (brexucabtagene autoleucel) in mantle cell lymphoma (Wang et al., 2020; 2023), achieving long-term responses even in high-risk groups. In turn, the ZUMA-5 (Jacobson et al., 2022) and ELARA (Dreyling et al., 2024) studies showed that CAR-T technology may also be effective in patients with indolent non-Hodgkin lymphomas, including follicular lymphoma. Recent analyses, such as the CIBMTR study on primary mediastinal lymphoma (Gauthier et al., 2025), confirm the expanding clinical spectrum of this form of immunotherapy.

The aim of this paper is to review the most important clinical studies on the use of CAR-T therapy in various subtypes of non-Hodgkin lymphomas, taking into account the efficacy, safety, and prospects for further development of this method. The data presented include both commercially available products and studies extending the indications for this form of treatment.

Methodology

In order to develop a literature review, a systematic search of publications was conducted in the PubMed, Scopus, and Web of Science databases. The analysis included articles published between 2017 and 2025, i.e., since the introduction of the first CAR-T therapies into clinical practice. The search was conducted using a combination of keywords: “CAR-T,” “lymphoma,” “diffuse large B-cell lymphoma,” “mantle cell lymphoma,” “follicular lymphoma,” “clinical trial,” and “immunotherapy.” Original studies, multicenter clinical trials, and review articles describing the use of CAR-T therapy in adult non-Hodgkin lymphomas were included for further analysis. Publications on hematopoietic malignancies other than lymphomas, conference reports, and studies with limited access to clinical data were excluded. In case of duplication of results from different stages of observation, publications with the longest follow-up period were selected.

Results

Lisocabtagene maraleucel (liso-cel) is an autologous chimeric antigen receptor (CAR) T-cell product targeting the CD19 antigen, developed for the treatment of B-cell lymphoproliferative malignancies. The TRANSCEND NHL 001 study (2020) aimed to evaluate the efficacy and safety profile of liso-cel in adult patients with relapsed or refractory large B-cell lymphomas. The study design included 14 oncology centers in the United States. Individuals over the age of 18 with confirmed disease who had not responded satisfactorily to prior treatment were eligible to participate. Patients with various histological variants were included, including diffuse large B-cell lymphoma (DLBCL), high-grade lymphoma with MYC gene rearrangement, BCL2 or BCL6 gene rearrangement, transformed lymphoma from indolent forms, primary mediastinal lymphoma, and grade 3B follicular lymphoma. Participants received one of three target doses: 50×10^6, 100×10^6, or 150×10^6 CAR-T cells, with equal proportions of $CD8^+$ and $CD4^+$ cells. The primary endpoints included safety assessment, dose-limiting toxicity, and response rate according to the Lugano criteria. Efficacy analysis was performed in the group of patients who received at least one infusion and had confirmed disease on PET scan.

Between January 2016 and July 2019, leukapheresis was performed in 344 patients, of whom 269 received at least one dose of the product. The median number of previous lines of treatment was three. In the efficacy assessment group (256 patients), a complete response was achieved in 53% of patients and an overall response in 73%. The results were comparable between the different dose levels. The most commonly observed adverse events were neutropenia, anemia, and thrombocytopenia. Cytokine release syndrome occurred in 42% of patients, while neurological symptoms occurred in 30%; severe forms of these events were rare. The results

obtained indicate that liso-cel may be an effective treatment for patients with large B-cell lymphomas who have not achieved durable remission with previous therapies. The toxicity profile was assessed as favorable compared to other CAR-T products, allowing a recommended dose of 100×10^6 CAR-T cells to be determined. This study has paved the way for further analysis of the use of liso-cel in other B-cell malignancies and in earlier stages of the disease.

The ELARA study (2024) aimed to evaluate the efficacy and safety of tisagenlecleucel therapy, an autologous T-cell product with a chimeric antigen receptor (CAR) targeting the CD19 antigen. This product was developed for the treatment of B-cell malignancies, including relapsed or refractory lymphomas. Follicular lymphoma is one of the most common non-Hodgkin lymphomas, and its chronic nature means that despite initial sensitivity to treatment, most patients experience multiple relapses. In patients who are resistant to rituximab or alkylating therapy, the prognosis is particularly poor, which justifies the need for new therapeutic strategies. The study included adult patients over 18 years of age with stage 1–3A follicular lymphoma who had progressed after at least two prior lines of therapy, including anti-CD20 therapy and alkylating chemotherapy. Patients had to have confirmed active disease on PET-CT and adequate performance status (ECOG 0–1). Patients who had previously received CAR-T cell therapy or allogeneic bone marrow transplantation were excluded.

The study was conducted at multiple centers in North America, Europe, and the Asia-Pacific region. All participants underwent leukapheresis to obtain their own T cells, which were then genetically modified in the laboratory by introducing a gene encoding the anti-CD19 CAR receptor. After the product manufacturing process was completed, a short lymphodepletion with fludarabine and cyclophosphamide was performed, followed by a single infusion of tisagenlecleucel.

The analysis included 97 patients with a median age of 57 years (range 29–73 years). Most patients were heavily pretreated, with 60% having received four or more prior regimens and 78% being resistant to their last line of treatment. In addition, 42% of patients had high-risk disease, including early relapse after immunochemotherapy. The median follow-up time was 29 months. The overall response rate (ORR) reached 86%, with 70% of patients achieving complete remission (CR). In most cases, remission was durable – after two years, 63% of patients maintained CR, and the median duration of response had not been reached at the time of analysis. The two-year progression-free survival (PFS) rate was 60%, and the overall survival (OS) rate was 88%. These results are comparable to and even better than those of previous targeted therapies, such as PI3K inhibitors or lenalidomide in combination with rituximab.

Tisagenlecleucel therapy was characterized by a favorable safety profile. Cytokine release syndrome (CRS) occurred in 48% of patients, with all cases being mild or moderate (grade 1–2 according to the ASTCT scale). Neurological symptoms were reported in 11% of patients and were limited in severity. No severe cases of neurotoxicity or new types of toxicity were observed during prolonged follow-up. The most common grade 3 or higher adverse events included neutropenia (40%), lymphopenia (32%), and thrombocytopenia (18%). The ELARA study confirmed that tisagenlecleucel can lead to long-term remission in patients with follicular lymphoma who have exhausted other therapeutic options. The recurrence rate after therapy was lower than in the comparison groups from previous studies on this type of lymphoma. The results support the development of CAR-T therapy for the treatment of indolent cancers and indicate that even in a population of patients with multiple relapses, it is possible to achieve long-term disease control.

In recent years, genetically modified T cells with a chimeric anti-CD19 receptor (CAR-T) have become a recognized treatment for patients with relapsed or refractory large B-cell lymphoma (LBCL). The efficacy of this therapy has been confirmed in several prospective clinical trials, but data on its use in primary mediastinal large B-cell lymphoma (PMBCL) are limited. Although this disease belongs to the group of aggressive cancers, it has a different biological and clinical profile, often affects young adults, and is potentially sensitive to immunotherapy, including checkpoint inhibitors (ICI). However, data on how prior ICI treatment affects the efficacy and safety of CAR-T therapy were still lacking. To fill this gap, a retrospective analysis of CIBMTR (Center for International Blood and Marrow Transplant Research) registry data (2025) was conducted, including patients with PMBCL treated with anti-CD19 CAR-T cells in real-world clinical practice. The analysis included 135 adult patients from 66 centers. The median age at the time of treatment was 32 years, reflecting the young age of the typical population with this diagnosis. Of all participants, 39 (28.9%) had previously undergone therapy with checkpoint inhibitors, which are one of the recognized options for refractory PMBCL. The use of CD19 CAR-T cells resulted in high response rates. The best overall remission rate achieved was 67.7%, and the total response rate (complete and partial) reached 79%. After two years of

follow-up, progression-free survival (PFS) was 58.6% and overall survival (OS) was 80.8%. The recurrence rate after two years was estimated at 36% and non-recurrence mortality (NRM) at 5.4%.

With regard to toxicity, severe forms of cytokine release syndrome (CRS grade ≥3) occurred in 6.1% of patients, while symptoms of neurotoxicity (ICANS) of this grade were observed in 14.7%. These results indicate good treatment tolerance compared to other LBCL populations, where the incidence of serious adverse events is often higher. Analysis of the impact of prior exposure to checkpoint inhibitors showed some differences in disease progression after CAR-T therapy. Patients who had previously received ICI had a lower recurrence rate after two years (21.7% vs. 41.6%, p = 0.03), but at the same time a higher rate of non-recurrence-related mortality (11.7% vs. 2.8%, p = 0.03). However, no statistically significant differences in overall survival or progression-free survival were found between the groups. This may suggest that prior immunomodulatory treatment affects the dynamics of the immune response after CAR-T cell administration, but does not clearly alter the final outcomes of therapy. Anti-CD19 CAR-T cell therapy in patients with primary mediastinal large B-cell lymphoma resulted in a high rate of durable responses and a low incidence of severe toxicities. The results obtained indicate that this treatment may be an effective option for patients who have experienced recurrence or resistance to previous therapeutic regimens. The results of the analysis also suggest that earlier use of checkpoint inhibitors may affect the recurrence rate and safety profile of CAR-T therapy, which requires further observation in prospective studies.

Indolent non-Hodgkin lymphomas often have a chronic course, and most patients experience multiple relapses after standard immunochemotherapy. In this group of patients, the effectiveness of traditional treatment regimens is gradually declining, which has prompted the search for new therapeutic methods. One of the 4mmune-oncological approaches is the use of autologous T cells with a chimeric antigen receptor (CAR) directed against the CD19 antigen. The ZUMA-5 study (2022) aimed to evaluate the efficacy and safety of CAR-T cell therapy with axicabtagene ciloleucel in patients with follicular lymphoma or marginal zone lymphoma who did not respond to previous treatment or experienced disease recurrence. The project included a single-arm, multicenter Phase II clinical trial conducted at 17 centers in the United States and France. Adults (≥18 years of age) with histopathologically confirmed slow-growing lymphoma who had received at least two lines of therapy including anti-CD20 antibody and alkylating agent were eligible for participation. Good overall performance status (ECOG 0–1) was also required.

Prior to administration of axicabtagene ciloleucel, patients underwent leukapheresis and then received a lymphodepletion regimen consisting of cyclophosphamide and fludarabine. CAR-T cells were infused at a dose of 2×10^6 cells/kg body weight. Response was assessed according to the Lugano criteria, and results were analyzed after at least 12 months of follow-up in the follicular lymphoma group and after 4 weeks in the marginal zone lymphoma group. The analysis included 148 patients who received axi-cel infusion, including 124 with follicular lymphoma and 24 with marginal zone lymphoma. The median age of participants was 63 years, and most had received four prior lines of therapy. The median follow-up time was 17.5 months. In the efficacy population (n = 104), a complete or partial response was achieved in 96 patients (92%), of whom 77 (74%) achieved complete remission. The safety profile was consistent with previous observations for CAR-T therapy. The most common grade 3 or higher adverse events were cytopenias (70%) and infections (18%). Cytokine release syndrome (CRS) grade 3 or higher occurred in 7% of patients, and grade 3–4 neurological complications occurred in 19%. Adverse events of any severity were reported in half of the participants, and four deaths (3%) were associated with treatment complications, including one case of multiple organ failure directly related to the therapy. Therapy with axicabtagene ciloleucel resulted in a high rate of durable remissions in patients with relapsed or refractory indolent non-Hodgkin lymphoma. The results of ZUMA-5 indicate that this method may provide long-term disease control in a population for which effective therapeutic options are limited. Further observation and comparative studies are necessary to assess the impact of this therapy on overall survival and quality of life in patients.

The development of cellular immunotherapy, particularly chimeric antigen receptor T-cell (CAR-T) technology, has opened up new therapeutic possibilities. Axicabtagene ciloleucel (axi-cel, Yescarta®) is a second-generation autologous CAR-T therapy in which the patient's T cells are genetically modified to recognize the CD19 antigen present on the surface of B cells. The objective of the phase 2 ZUMA-1 study was to determine the efficacy and safety of axi-cel in patients with refractory or relapsed large B-cell lymphoma after at least two prior lines of therapy. The ZUMA-1 trial (2017) was a multicenter, single-arm, phase 2 clinical trial involving 22 centers in the United States. The study enrolled 111 adult patients (≥18 years) diagnosed with DLBCL, primary mediastinal B-cell lymphoma, or follicular lymphoma transformed to DLBCL. The inclusion criteria were disease refractory to the last line of treatment or relapse after autologous

stem cell transplantation. After leukapheresis, T cells were collected from patients and genetically modified to express the anti-CD19 CAR receptor. Prior to CAR-T cell infusion, patients received conditioning chemotherapy consisting of fludarabine (30 mg/m² for 3 days) and cyclophosphamide (500 mg/m² for 3 days). The dose of axi-cel was 2×10^6 CAR-T cells per kilogram of body weight. The primary endpoint of the study was the overall response rate (ORR), defined as the sum of partial and complete remissions. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety assessment. Of the 111 patients enrolled, 110 (99%) were successfully engrafted with axi-cel, and 101 (91%) received CAR-T cell infusion. The median age was 58 years; 74% of participants had DLBCL and 26% had other types of large B-cell lymphomas. The median number of prior therapies was 3, and 77% of patients were refractory to their last line of treatment. An objective response was achieved in 82% of patients (95% CI: 73–89%), including complete remission (CR) in 54%. The median time to response was 1 month. After 15 months, 42% of patients maintained a response, of whom 40% remained in CR. The median duration of response was 8.1 months, while the median PFS was 5.9 months. The estimated overall survival after 18 months was 52%. The persistent presence of CAR-T lymphocytes in the blood correlated with the durability of remission, suggesting a significant impact of cell expansion dynamics on the therapeutic effect.

Cytokine release syndrome (CRS) occurred in 93% of patients, but in most cases it was mild or moderate (grade 1–2). Severe CRS (grade ≥3) occurred in 13% of participants. The most common symptoms included fever, hypotension, and hypoxia. Neurological symptoms such as encephalopathy, seizures, and confusion occurred in 64% of patients, including 28% with severe symptoms. The most common grade 3 or higher adverse events included neutropenia (78%), anemia (43%), and thrombocytopenia (38%). Three treatment-related deaths were reported, including two due to cytokine release syndrome and one due to sepsis. Pharmacodynamic analysis showed that greater CAR-T cell expansion and higher levels of cytokines such as IL-6, IL-10, IFN-γ, and TNF-α correlated with the severity of CRS and neurotoxicity. At the same time, intense CAR-T expansion was associated with a higher likelihood of achieving complete remission.

The ZUMA-1 study was the first large-scale confirmation of the efficacy of CAR-T therapy in patients with refractory large B-cell lymphoma. The overall remission rate (54%) significantly exceeded the results achieved with standard rescue therapies, whose efficacy does not usually exceed 20–25%. Moreover, a significant proportion of patients experienced long-term remission, suggesting the potential "curative" nature of this therapy. Despite its high efficacy, axi-cel treatment is associated with the risk of serious adverse events, particularly CRS and neurotoxicity. It is therefore necessary to conduct therapy in specialized centers with experience in monitoring and treating immunotherapy complications, including the use of IL-6 receptor antagonists (tocilizumab) and corticosteroids. ZUMA-1 set a new standard of care for patients with relapsed or refractory DLBCL, and the results led to the registration of axi-cel by the FDA and EMA in 2017. Subsequent analyses and long-term follow-up confirmed the durability of response in some patients and provided a better understanding of the mechanisms of action and toxicity of CAR-T therapy. The ZUMA-1 study showed that axicabtagene ciloleucel therapy is highly effective in patients with large B-cell lymphoma who do not respond to previous treatment. A high percentage of durable remissions was achieved, with a significant risk of immune complications requiring specialized care. The results of this study ushered in a new era of hematologic cancer treatment based on modified immune cells and confirmed the potential of CAR-T therapy as an effective rescue option for patients with refractory B-cell lymphomas.

The JULIET study (2019) was designed to evaluate the efficacy and safety of this treatment in adult patients with DLBCL resistant to previous therapies. The JULIET study was an international, open-label, single-arm study involving patients with DLBCL who had not responded to at least two previous lines of treatment or whose disease had relapsed after stem cell transplantation. Prior to treatment, participants underwent leukapheresis and then received T cells modified to express a CAR receptor that recognizes the CD19 antigen. Before CAR-T cell infusion, patients received conditioning chemotherapy with fludarabine and cyclophosphamide or bendamustine. The dose of tisagenlecleucel ranged from 0.1 to 6×10^8 CAR-T cells, depending on body weight and the number of available lymphocytes. The primary endpoint was overall response rate (ORR). In addition, response duration, progression-free survival, overall survival, and the incidence of adverse events, including cytokine release syndrome (CRS) and neurological disorders, were analyzed.

The study IIed 165 patients, 1"1 of'whom received tisagenlecleucel infusion. The median age of participants was 56 years. Most patients had previously undergone at least three lines of treatment, and 52% had not responded to the last therapy. Among those who received treatment, a complete or partial response was achieved in 52% of patients, including complete remission in 40%. The median time to response was one

month. At the time of analysis after 14 months, 65% of patients who achieved complete remission maintained their response, and the median overall survival in this group was not reached. In terms of safety, cytokine release syndrome was reported in 58% of patients, including 22% with severe (≥3) symptoms. The most common symptoms were fever, hypotension, and hypoxia. Neurological symptoms occurred in 21% of participants, with 12% experiencing a more severe course. The most serious adverse events included neutropenia (40%) and thrombocytopenia (27%). Treatment-related deaths were very rare. Pharmacodynamic analyses showed that the efficacy of the therapy was associated with the expansion of CAR-T lymphocytes in the peripheral blood. The highest severity of CRS and neurological symptoms was observed in patients with high levels of proinflammatory cytokines, including IL-6 and IFN-γ.

The results of the JULIET study confirmed the high efficacy of tisagenlecleucel therapy In patients with relapsed or refractory DLBCL who had no other treatment options. The response rates achieved (52% complete and partial) and the long-term maintenance of remission in some patients demonstrate the significant potential of this method.

Compared to traditional rescue therapies, tisagenlecleucel provided a significantly higher complete remission rate and prolonged overall survival. Although the treatment is associated with a risk of immune-related complications, these were manageable with appropriate monitoring and supportive therapy, including treatment with tocilizumab and corticosteroids. JULIET was one of the studies that led to the approval of tisagenlecleucel as the first CAR-T therapy for adult patients with DLBCL. These results marked a new era in the treatment of lymphomas, providing effective help to patients for whom previous methods had proven ineffective. Tisagenlecleucel has proven to be an effective and durable therapeutic solution for adult patients with relapsed or refractory large B-cell lymphoma. The results obtained indicate a significant improvement in prognosis compared to conventional methods, with an acceptable safety profile.

Despite its demanding logistics and the need for close supervision, CAR-T therapy against CD19 has brought a new quality to the treatment of lymphatic system cancers and confirmed the effectiveness of an approach based on modifying the patient's own immune cells.

The CAR T KTE-X19 study (2020) was open-label and multicenter. It included adult patients with large B-cell lymphoma who had not achieved a durable response after at least two prior lines of therapy. Participants underwent leukapheresis to obtain T cells, which were then genetically modified to express the CAR-CD19 receptor. Prior to CAR-T cell infusion, patients received lymphodepletion therapy consisting of fludarabine and cyclophosphamide. Liso-cel was administered at doses of 50×10^6, 100×10^6, or 150×10^6 CAR-T cells, depending on the treatment regimen. The primary endpoint was overall or partial response to treatment (ORR). In addition, response duration, overall survival, progression-free survival, and the safety profile of the therapy were analyzed, with particular emphasis on cytokine release syndrome (CRS) and neurological disorders. A total of 344 patients were enrolled in the study, of whom 269 received liso-cel infusion.

The median age was 63 years, and most patients had received at least three prior lines of therapy. A complete or partial response was achieved in 73% of patients, including complete remission in 53%. The median time to response was approximately one month, and remission was maintained in most patients for over a year. The median overall survival was 21 months, and the 12-month survival rate was 58%. Cytokine release syndrome occurred in 42% of patients, with only 2% of cases being severe (≥grade 3). Neurological symptoms occurred in 30% of patients, with more severe reactions affecting 10%. The most common adverse events included neutropenia, thrombocytopenia, and neutropenic fever. Supportive treatment, including tocilizumab and corticosteroids, effectively controlled CRS symptoms and neurotoxicity. Pharmacodynamic analysis confirmed that CAR-T cell expansion in peripheral blood correlated with treatment response.

The TRANSCEND NHL 001 study demons"rate' the high efficacy of lisocabtagen maraleucel in a group of patients with relapsed or refractory DLBCL who lacked effective treatment options. The complete remission rate was high, and the responses achieved were long-lasting. Importantly, the incidence and severity of cytokine release syndrome and neurological symptoms were lower than in some previous studies of other CAR-T therapies. Liso-cel therapy combined high efficacy with an acceptable safety profile, making it a valuable option for patients with treatment-resistant lymphoma. The use of separate CD4+ and CD8+ cell preparations may have contributed to better control of the immune response and a more predictable course of therapy. Lisocabtagen maraleucel has shown high efficacy in the treatment of adult patients with relapsed or refractory large B-cell lymphoma, with a limited risk of serious adverse events. The results of the TRANSCEND NHL 001 study confirm that CAR-T therapy targeting the CD19 antigen can bring long-term benefits in a group of patients with a very poor prognosis.

The ZUMA-2 trial (NCT02601313) (2023) was an open-label, single-arm, phase II trial conducted at multiple centers in North America and Europe. Participants were adult patients with relapsed or refractory mantle cell lymphoma who had previously received one to five lines of therapy including rituximab, a Bruton's tyrosine kinase inhibitor, and an alkylating agent. All participants had to have measurable disease and adequate organ function. After qualification, patients underwent leukapheresis to collect T cells, which were then genetically modified to express a CAR receptor that recognizes the CD19 antigen. Prior to CAR-T therapy, patients received conditioning chemotherapy (fludarabine and cyclophosphamide) to reduce their own lymphocyte count and increase space for the expansion of modified cells. Brexukabtagene autoleucel was administered as a single infusion at a dose of 2×10^6 CAR-T cells per kilogram of body weight. After treatment, patients were closely monitored for cytokine release syndrome (CRS), neurological disorders, and hematological adverse events.

The primary endpoint of the study was the overall response rate (ORR), including complete remissions (CR) and partial remissions (PR). Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety, and minimal residual disease (MRD). Seventy-four patients were enrolled in the study, of whom 68 received KTE-X19 infusion. The median age was 65 years, and most participants (84%) had received at least three prior lines of therapy. More than half of the patients were resistant to their last therapy, and 28% had blastic morphology, which is associated with a poorer prognosis. The first analysis, conducted after a median follow-up of 12.3 months, showed very high efficacy – the ORR was 93%, with complete remission achieved in 67% of patients. After longer follow-up (35.6 months), the objective response rate remained at 91%, of which 68% were complete remissions. The median duration of response was 28.2 months, indicating long-term maintenance of the therapeutic effect.

The median progression-free survival was 25.8 months, and the median overall survival was 46.6 months. After three years, the percentage of patients still alive was approximately 60%. These data show that KTE-X19 therapy enables sustained remission in a significant proportion of patients with very advanced MCL. In 79% of patients, MRD negativity was achieved within 6 months of treatment. In this group, all patients responded to therapy, and median PFS and OS were not reached, suggesting a very durable clinical effect. Patients with positive MRD had faster relapses and shorter survival times. The safety profile of the therapy proved to be favorable. Cytokine release syndrome occurred in 91% of patients, but in most cases it was mild or moderate. Severe symptoms (≥grade 3) occurred in 15% of patients, while neurotoxicity was reported in 63% of participants, of which 31% of cases were more severe. The most common adverse events included neutropenia (94%), thrombocytopenia (60%), and anemia (57%). No new cases of CRS or tumor lysis syndrome were observed after extended follow-up. Supportive treatment, especially with tocilizumab and corticosteroids, effectively controlled the immune symptoms. The efficacy of treatment was maintained regardless of the type of BTK inhibitor previously used.

Patients treated with ibrutinib showed greater CAR-T cell expansion and higher concentrations of proinflammatory cytokines than those treated with acalabrutinib, which may explain the differences in response strength. Equally good results were obtained in high-risk groups, including patients with TP53 mutation, high Ki-67 proliferation index, blastoids variant MCL, and patients with progression within 24 months of starting first-line treatment (POD24). In patients previously treated with bendamustine (54% of the study population), the response rate was 84% (58% CR), while in those without this exposure it was 100% (77% CR). The analysis showed that a shorter interval between bendamustine administration and leukapheresis (less than 6 months) was associated with poorer CAR-T cell expansion, which may affect treatment efficacy.

The ZUMA-2 trial was a breakthrough for mantle cell lymphoma therapy, as it demonstrated for the first time the possibility of achieving long-term remission in patients for whom there were no effective treatments. The high rate of complete remission, maintained after nearly three years of follow-up, demonstrates that brexukabtagene autoleucel can lead to durable disease control. The results also confirmed that MRD negativity is a strong predictor of long-term survival. Patients who became MRD-negative maintained stable remission, indicating that CAR-T therapy may completely eliminate cancer cells from the body. The safety profile of KTE-X19 was considered acceptable. The incidence of cytokine release syndrome was similar to that observed in other CAR-T therapy studies, but most cases were mild. With effective supportive care, the risk of severe immune complications was limited. The impact of prior exposure to bendamustine, which may reduce T-cell proliferation and thus decrease the effectiveness of CAR-T therapy, was also noted. In clinical practice, this may mean that an appropriate interval between these therapies is necessary.

Brexukabtagene autoleucel (KTE-X19) demonstrated very high efficacy in adult patients with relapsed or refractory mantle cell lymphoma, with a complete remission rate exceeding 65% and a median overall survival of

nearly four years. Adverse events were predictable and manageable. The results confirm that CAR-T therapy against the CD19 antigen can provide lasting clinical benefits even in a patient population with a very poor prognosis. ZUMA-2 became the basis for the registration of KTE-X19 for the treatment of relapsed or refractory mantle cell lymphoma in the United States and Europe, opening a new era in the treatment of this cancer.

Discussion

ZUMA-1 was a multicenter phase II trial involving adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma, and follicular lymphoma transformation. The efficacy of the therapy was similar regardless of age, lymphoma subtype, and prior treatment regimens. The results of the ZUMA-1 study led to the registration of axi-cel in the third-line treatment of DLBCL. The JULIET trial, conducted at multiple centers worldwide, included patients with relapsed or refractory DLBCL after two or more prior lines of therapy. Participants received lymphodepletion with fludarabine and cyclophosphamide, followed by infusion of autologous T cells genetically modified to express CAR against the CD19 antigen. The JULIET results confirmed that tisa-cel therapy can provide long-term remissions in some patients with a very poor prognosis who had not responded to previous therapies. This therapy has been approved in the European Union and the US as a third-line treatment for DLBCL.

The ZUMA-2 trial was a single-arm phase II trial evaluating the efficacy and safety of brexukabtagene autoleucel in patients with relapsed or refractory MCL after prior treatment with Bruton's tyrosine kinase inhibitors (BTKIs). The efficacy of the therapy was also maintained in high-risk subgroups (TP53 mutation, high Ki-67, blastoid morphology). The study also showed that prior treatment with bendamustine may have limited CAR-T cell expansion and weakened the response, indicating the need for proper planning of the sequence of therapies. ZUMA-2 confirmed that KTE-X19 can provide durable remissions in patients with MCL after BTKi failure, offering efficacy beyond that of previous cytotoxic therapies. In the ZUMA-5 study, axicabtagene ciloleucel therapy shows very high efficacy in patients with refractory or relapsed indolent NHL. Despite the risk of cytopenia and neurotoxicity, treatment is generally safe. The results support the use of CAR-T as an option for patients with limited therapeutic options. CD19 CAR-T therapy in PMBCL is highly effective, leading to durable remissions. The safety profile is relatively favorable, with a low rate of serious complications. Prior treatment with checkpoint inhibitors may reduce the risk of relapse. CD19 CAR-T is an effective and safe option in R/R LBCL. Treatment offers significant chances for a durable response, making it a valuable alternative to traditional therapies.

The safety profile is acceptable, especially with monitoring and medical support. CAR-T CD19 cell therapy, including axicabtagene ciloleucel in ZUMA-5 and standard CAR-T CD19 in primary mediastinal large B-cell lymphoma (PMBCL), shows high efficacy in treating patients with relapsed or refractory lymphoma. In both studies, the complete response rate was high (67–92%), and a significant proportion of patients achieved durable remissions. The safety profile was relatively favorable—severe adverse events, such as cytokine release syndrome and neurotoxicity, occurred in a small group of patients, and most complications were controlled. The results indicate that CAR-T CD19 is an effective and safe option for patients with difficult-to-treat subtypes of lymphoma, even after multiple lines of therapy. The results of ZUMA-1, JULIET, and ZUMA-2 showed that CAR-T therapies against CD19 enable high rates of complete remission and long-term survival in patients with advanced, refractory B-cell lymphomas. Although the therapy is associated with the risk of serious complications, their frequency and severity can be controlled in experienced centers. Thanks to these studies, CAR-T has become a permanent fixture in B-cell lymphoma treatment regimens, offering a real chance of remission in patients for whom therapeutic options were previously very limited.

Conclusions

In recent years, numerous analyses have been published on the efficacy of CD19 CAR-T therapy in various forms of B-cell lymphomas, including rare subtypes such as primary mediastinal large B-cell lymphoma (PMBCL) and indolent lymphomas. A retrospective study based on data from the CIBMTR registry included 135 adult patients with PMBCL treated with CD19 CAR-T cells. The median age at the time of treatment was 32 years, and nearly 30% of patients had previously received checkpoint inhibitors. The therapy resulted in a high complete response rate (CR 67.7%), with a 2-year progression-free survival of 58.6% and an overall survival of 80.8%. Severe adverse events were rare, indicating good treatment tolerance. These results suggest that CAR-T may also be an effective option in rare, more aggressive subtypes of LBCL.

Similarly, in the ZUMA-5 study, published by Neelapu et al. (2022) in the Journal of Clinical Oncology, the use of axicabtagene ciloleucel was evaluated in patients with relapsed or refractory follicular lymphoma

and marginal zone lymphoma. The overall response rate was 92%, and complete remissions were achieved in 74% of patients. The median follow-up exceeded 17 months, confirming the durability of the therapeutic effect. The most common adverse events included cytopenias and infections, while severe cytokine release syndrome occurred in 7% of patients. The results confirm that CAR-T can effectively eliminate cancer cells also in indolent forms of non-Hodgkin lymphoma.

For comparison, in the JULIET study (New England Journal of Medicine, 2019), which evaluated tisagenlecleucel in adults with relapsed or refractory diffuse large B-cell lymphoma, a complete response rate of 40% was achieved. In turn, analyses of real-world clinical data (Blood Advances, 2023) confirm the efficacy and safety of CAR-T in everyday practice, while highlighting differences in toxicity between different subtypes of lymphoma. A summary of these studies indicates that the efficacy of CD19 CAR-T therapy is comparable across different subtypes of B-cell lymphomas, while maintaining an acceptable safety profile, and its development represents an important step towards personalized therapies in hematology.

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REFERENCES

1. Abramson, J. S., Palomba, M. L., Gordon, L. I., Lunning, M. A., Wang, M., Arnason, J. E., Mehta-Shah, N., Maloney, D. G., Andreadis, C., Sehgal, A. R., Munoz, J., Albertson, T. M., Garcia, J., Shah, B. D., Ghosh, N., Reagan, P. M., Penuel, E., Chavez, J. C., & Jacobson, C. A. (2020). Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): A multicentre seamless design study. The Lancet, 396(10254), 839–852. https://doi.org/10.1016/S0140-6736(20)31366-0
2. Ayuk, F., Gagelmann, N., von Tresckow, B., Wulf, G., Rejeski, K., Stelljes, M., Penack, O., Baldus, C. D., Kröger, N., Bethge, W., & Dreger, P. (2023). Real-world outcomes of CAR T-cell therapy in large B-cell lymphoma with central nervous system involvement: The GLA/DRST study. Blood Advances, 7(18), 5316–5319. https://doi.org/10.1182/bloodadvances.2023010336
3. Dreyling, M., Fowler, N. H., Dickinson, M., Martinez-Lopez, J., Kolstad, A., Butler, J., Ghosh, M., Popplewell, L., Chavez, J. C., Bachy, E., Kato, K., Harigae, H., Kersten, M. J., Andreadis, C., Riedell, P. A., Ho, P. J., Pérez-Simón, J. A., Chen, A. I., Nastoupil, L. J., von Tresckow, B., … Schuster, S. J. (2024). Durable response after tisagenlecleucel in adults with relapsed/refractory follicular lymphoma: ELARA trial update. Blood, 143(17), 1713–1725. https://doi.org/10.1182/blood.2023021567
4. Gauthier, J., Ahn, K. W., Patel, J., Lian, Q., Badawy, S., Cairo, M. S., Delgado, J., Grover, N., Haverkos, B., de Lima, M., Malone, A., Mussetti, A., Nieto, Y., Pawarode, A., Pearson, L., Solh, M., Sureda, A., Tun, A. M., Wudhikarn, K., Yamshon, S., … Herrera, A. F. (2025). CD19 CAR T-Cell Therapy for Primary Mediastinal Large B-Cell Lymphoma: A CIBMTR Analysis. American journal of hematology, 100(10), 1792–1802. https://doi.org/10.1002/ajh.70033
5. Gauthier, J., Ahn, K. W., Patel, J., Lian, Q., Badawy, S., Cairo, M. S., Delgado, J., Grover, N., Haverkos, B., de Lima, M., et al. (2025). CD19 CAR T-cell therapy for primary mediastinal large B-cell lymphoma: A CIBMTR analysis. American Journal of Hematology. Advance online publication. https://doi.org/10.1002/ajh.70033
6. Jacobson, C. A., Chavez, J. C., Sehgal, A. R., William, B. M., Munoz, J., Salles, G., Munshi, P. N., Casulo, C., Maloney, D. G., de Vos, S., Reshef, R., Leslie, L. A., Yakoub-Agha, I., Oluwole, O. O., Fung, H. C. H., Rosenblatt, J., Rossi, J. M., Goyal, L., Plaks, V., Yang, Y., … Neelapu, S. S. (2022). Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. The Lancet. Oncology, 23(1), 91–103. https://doi.org/10.1016/S1470-2045(21)00591-X
7. Lancet Oncology (2022) — Jacobson CA et al., Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial
8. Neelapu, S. S., Locke, F. L., Bartlett, N. L., Lekakis, L. J., Miklos, D. B., Jacobson, C. A., Braunschweig, I., Oluwole, O. O., Siddiqi, T., Lin, Y., Timmerman, J. M., Stiff, P. J., Friedberg, J. W., Flinn, I. W., Goy, A., Hill, B. T., Smith, M. R., Deol, A., Farooq, U., McSweeney, P., ... Go, W. Y. (2017). Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. The New England Journal of Medicine, 377(26), 2531–2544. https://doi.org/10.1056/NEJMoa1707447
9. Schuster, S. J., Bishop, M. R., Tam, C. S., Waller, E. K., Borchmann, P., McGuirk, J. P., Jäger, U., Jaglowski, S., Andreadis, C., Westin, J. R., Fleury, I., Bachanova, V., Foley, S. R., Ho, P. J., Mielke, S., Magenau, J. M., Holte, H., Pantano, S., Pacaud, L. B., Awasthi, R., … JULIET Investigators (2019). Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. The New England journal of medicine, 380(1), 45–56. https://doi.org/10.1056/NEJMoa1804980
10. Wang, M., Munoz, J., Goy, A., Locke, F. L., Jacobson, C. A., Hill, B. T., Timmerman, J. M., Holmes, H., Jaglowski, S., Flinn, I. W., McSweeney, P. A., Miklos, D. B., Pagel, J. M., Kersten, M. J., Milpied, N., Fung, H., Topp, M. S., Houot, R., Beitinjaneh, A., Peng, W., … Reagan, P. M. (2020). KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. The New England journal of medicine, 382(14), 1331–1342. https://doi.org/10.1056/NEJMoa1914347
11. Wang, M., Munoz, J., Goy, A., Locke, F. L., Jacobson, C. A., Hill, B. T., Timmerman, J. M., Holmes, H., Jaglowski, S., Flinn, I. W., McSweeney, P. A., Miklos, D. B., Pagel, J. M., Kersten, M. J., Bouabdallah, K., Khanal, R., Topp, M. S., Houot, R., Beitinjaneh, A., Peng, W., … Reagan, P. M. (2023). Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 41(3), 555–567. https://doi.org/10.1200/JCO.21.02370