Axicabtagene Ciloleucel: Clinical Data for the Use of CAR T-cell Therapy in Relapsed and Refractory Large B-cell Lymphoma

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Abstract
Objective: To evaluate the literature for axicabtagene ciloleucel (axi-cel), a first-in-class chimeric antigen receptor (CAR) T-cell therapy, in the treatment of relapsed/refractory (r/r) large B-cell lymphoma (LBCL). Data Sources: We conducted a PubMed (inception to June 22, 2020) and ClinicalTrials.gov search using the following terms: CD19, chimeric antigen receptor, and lymphoma. Study Selection and Data Extraction: All retrospective and prospective studies evaluating the use of axi-cel in LBCL were reviewed. Data Synthesis: In the pivotal ZUMA-1 trial, axi-cel exhibited unprecedented overall and complete response rates of 83% and 58%, respectively. With a median follow-up of 27.1 months, 39% of patients had ongoing responses. Furthermore, postmarketing retrospective analyses found similar response rates in a more clinically diverse LBCL patient population. Novel CAR T-cell therapy elicits unique and potentially life-threatening toxicities that include cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). Studies reported grade ≥3 CRS in 7% to 14% of patients and grade ≥3 ICANS in 31% to 55% of patients. Relevance to Patient Care and Clinical Practice: Axi-cel was the first US Food and Drug Administration–approved genetically engineered autologous CAR T-cell agent in r/r LBCL, representing an important milestone and paradigm shift in cancer treatment. Adoptive T-cell immunotherapy is a breakthrough treatment modality requiring careful patient selection, multidisciplinary collaboration, comprehensive patient counseling, and expert training to ensure optimal treatment. Conclusions: The initial and ongoing results with axi-cel are encouraging, but long-term safety and efficacy data are lacking. Additional studies are required to identify axi-cel’s ideal place in LBCL therapy.

Keywords
axicabtagene ciloleucel, chimeric antigen receptor, large B-cell lymphoma, cytokine release syndrome, NHL, immunotherapy, CAR T-cell

Introduction
Non-Hodgkin lymphoma (NHL) represents a diverse and heterogeneous group of lymphoproliferative disorders arising from B and T lymphocytes or natural killer cells. In the United States, an estimated 77 240 cases of NHL will occur in 2020, accounting for nearly 5% of all new cancer cases.1 Once diagnosed, those with NHL have a 5-year relative survival rate of 72.7%, with an estimated 20 000 annual deaths.1,2 The classification of NHL is multifaceted and dynamic. According to the World Health Organization (WHO), there are currently more than 60 different NHL subtypes characterized according to morphological determinants, cell type, genetic features, and immunophenotype.3 Aggressive large B-cell lymphomas (LBCLs) contain several different NHL subtypes, including diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), transformed follicular lymphoma (TFI), and high-grade B-cell lymphoma.3 DLBCL accounts for approximately 30% of all NHL and remains the most common lymphoid neoplasm in adults.2,4 Approximately 60% to 70% of patients treated for LBCLs can be cured with combination
chemoimmunotherapy, typically containing rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP regimen).\textsuperscript{5,7} Despite significant improvement in treatment outcomes for LBCLs, nearly one-third of patients will experience relapsed or refractory (r/r) disease.\textsuperscript{7} Those with r/r LBCL may receive salvage chemoimmunotherapy; however, there is no standard salvage regimen, and only 40% to 60% of patients will demonstrate a response.\textsuperscript{8-10} If eligible, patients responsive to salvage therapy may proceed to high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). In addition, 50% or more of patients who receive ASCT experience subsequent relapse.\textsuperscript{9} Individuals with refractory disease and/or a second relapse display extremely unfavorable outcomes.\textsuperscript{11-13} SCHOLAR-1\textsuperscript{13} was an international, retrospective analysis of 636 patients with refractory LBCL receiving conventional salvage chemotherapy. Investigators found an objective response rate (ORR) of 26% and a complete response (CR) rate of only 7%. They demonstrated a median overall survival (OS) in this high-risk and heterogeneous patient cohort of only 6.3 months, highlighting the considerable need for improved and innovative treatment options for those with r/r LBCL.

Cellular immunotherapy utilizing genetically modified autologous T cells presents a unique and promising opportunity to target specific tumor antigens while avoiding common toxicities found in conventional chemotherapy.\textsuperscript{14} Adoptive T-cell immunotherapy, in the form of chimeric antigen receptor (CAR) anti-CD19 T cells, has the potential to address this significant unmet medical need. CAR T cell is a novel immunotherapeutic approach allowing genetically engineered patient-specific T cells to target CD19-positive cells and provide sustained immunological surveillance.\textsuperscript{15} Axicabtagene ciloleucel (axi-cel) is an autologous CAR T-cell–based anti-CD19 therapy developed at the National Cancer Institute (NCI).\textsuperscript{16} Initial studies were conducted in patients with chronic lymphocytic leukemia (CLL); however, focus soon shifted to other B-cell diseases, including NHL.\textsuperscript{16,17} Figure 1 shows a timeline of key events in the successful testing and development of axi-cel, culminating in the US Food and Drug Administration (FDA) approval on October 18, 2017, for the treatment of adult patients with r/r LBCL after 2 or more lines of systemic therapy.\textsuperscript{18}

The purpose of this review is to summarize the current literature evaluating the safety and efficacy of axi-cel in the treatment of r/r LBCL and to highlight practical considerations involved in CAR T-cell therapy.

**Data Sources**

We conducted a systematic English-based literature search in human subjects using PubMed from inception through June 22, 2020. Search terms included “CD19” AND “chimeric antigen receptor” AND “lymphoma.” In addition, we included these search terms on ClinicalTrials.gov for completed trials not published in PubMed. We identified 20 original trials that included response data for anti-CD19 CAR T-cell therapy in patients with B-cell lymphoma. Of these, 11 trials were excluded because they evaluated anti-CD19 products not related to axi-cel. Three trials were excluded because they involved patients receiving CAR T-cell therapy in conjunction with hematopoietic stem cell transplantation. The remaining 7 trials were analyzed for inclusion. Relevant articles and abstracts found within identified citations were also assessed for appropriateness. Only trials reporting both the safety and efficacy of FMC63-28Z/axi-cel in B-cell lymphomas were considered for inclusion and analysis. The literature search was verified by 2 separate investigators.

**Pharmacology**

**What Are CAR T Cells and How Do They Work?**

The immune system plays an important and well-established role defending the body from infection, but it also serves as an indispensable bulwark in the fight against cancer.\textsuperscript{14,19} T cells are key modulators of cellular immunity and play a vital role in the detection and eradication of cancer.\textsuperscript{19} Once a cancer cell is recognized, antigen-presenting cells utilize a major histocompatibility complex (MHC) to display the tumor antigen to both CD8\textsuperscript{+} and CD4\textsuperscript{+} T cells, eliciting a 2-phase cytotoxic antitumor response. The first phase requires priming of naïve T cells through MHC presentation of tumor antigens in conjunction with a costimulatory signal. Once CD8\textsuperscript{+} and CD4\textsuperscript{+} T cells are activated, tumor cell elimination may occur through T-cell recognition of the MHC antigen expressed on the tumor surface.\textsuperscript{20} Activated T cells then undergo clonal expansion and proliferation to provide sustained and enhanced immunological activity. There are several limitations to this T-cell–mediated antitumor effect, including immune checkpoints that naturally limit T-cell proliferation, downregulation or loss of tumor surface MHC antigen, immunosuppressive tumor microenvironment, and insufficient T cells targeting the specific cancer antigen.\textsuperscript{15}

CAR T-cell therapy has the potential to bypass some of these co-opted mechanisms of immune resistance, reinvigorate immunosurveillance, and enhance tumor eradication. CARs are engineered immunoreceptors with high antigen specificity, effectively turning normal T cells into hyperactive “hunter cells” targeting a prespecified cancer antigen.\textsuperscript{21} Furthermore, CAR T cells undergo rapid expansion and serve as “living drugs” that persist for months to years following administration.\textsuperscript{22,23} CARs contain an antibody-derived single chain variable fragment (scFv) extracellular domain that identifies tumor-specific proteins without the
standard MHC-antigen restriction. In addition, CARs require an intracellular signaling domain and a costimulatory receptor, such as 4-1BB or CD28, to initiate T-cell activation and enhance antitumor activity (Figure 2). Initially, first-generation CAR T cells were designed without a costimulatory domain and generated disappointing results in early preclinical trials. Second-generation CAR T cells, including axi-cel, incorporated a costimulatory domain to generate greater antitumor activity and prolonged drug persistence. Specific costimulatory domains appear to play a role in the cellular kinetics, safety prolife, and antitumor effects of the CAR T-cell product; additional research is needed to fully evaluate the clinical impact of these differences. Third- and fourth-generation CAR T cells are now under investigation.
utilizing multiple costimulatory domains or enhanced with additional genetic modifications.26

CD19 surface protein remains a captivating target for CAR T-cell therapy because it is a common antigen expressed on most B-cell malignancies, including LBCL, CLL, and B-cell acute lymphoblastic leukemia (ALL).27,28 Axi-cel is a CD19-specific CAR T-cell product incorporating a second-generation CAR construct (CD3ζ activation domain and CD28 costimulatory domain) that eradicates tumor cells in an MHC-independent fashion through the scFv binding of CD19 and costimulatory activation. By targeting CD19 specifically, axi-cel avoids cytotoxic effects in most normal cells. Unfortunately, some on-target but off-tumor collateral damage is a common occurrence and will be discussed later in the review.

**Manufacturing CAR T-Cell Therapy**

The manufacturing of axi-cel is a complex and multistep process (Figure 3). Initially, patients typically undergo outpatient leukapheresis over 3 to 4 hours, whereby peripheral blood mononuclear cells are collected and cooled to 1 to 10 °C and shipped to a central manufacturing facility.15 The leukapheresis product is then enriched for T-cell activation using CD3 monoclonal antibodies. The activated T cells undergo transduction with a retroviral vector harboring the anti-CD19 CAR gene, leading to the production of a CAR T cell with CD19 specificity. The T cells are then cultured and expanded until the target axi-cel dose of $2 \times 10^6$ CAR T cells per kilogram is obtained.15,18 The manufacturer will perform a battery of quality control tests before cryopreserving and shipping the final product back to the corresponding treatment center. According to the pivotal, multicenter, ZUMA-1 study, manufacturing success was noted in more than 99% of samples, with 1 axi-cel sample lost because of equipment failure. Furthermore, ZUMA-1 had a median turnaround time from sample acquisition to axi-cel shipment of 17 days.

**Pre-CAR T-Cell Management**

Following initial leukapheresis, patients were not allowed to receive bridging therapy on the ZUMA-1 trial; however, with commercial use, some patients may benefit from...
bridging therapy to help control disease burden prior to lymphodepleting chemotherapy.\textsuperscript{29,31} Bridging modalities may include systemic intravenous chemotherapy, immunotherapy, corticosteroids, oral oncolytics, or radiation therapy.\textsuperscript{12} Further analysis is warranted to identify optimal management of patients who have undergone leukapheresis but are awaiting lymphodepletion.\textsuperscript{33} In preparation for axi-cel administration, patients undergo a 3-day course of lymphodepleting chemotherapy with fludarabine and cyclophosphamide.\textsuperscript{18,29} Lymphodepletion prior to CAR T-cell administration increases antitumor response by creating a favorable cytokine environment for CAR T-cell proliferation and survival.\textsuperscript{34} Less important, but still noteworthy, fludarabine and cyclophosphamide may also produce some level of antitumor effect, even in multiply relapsed and/or refractory patients. The ideal lymphodepleting regimen has been widely debated and studied. Prior to axi-cel approval, the NCI in conjunction with the manufacturers of axi-cel (Kite Pharma, Inc, Santa Monica, CA) discovered that low-dose fludarabine (30 mg/m\textsuperscript{2}) and cyclophosphamide (300-500 mg/m\textsuperscript{2}) daily for 3 days resulted in similar response rates as high-dose regimens while maintaining an excellent in vivo CAR T-cell expansion profile.\textsuperscript{34-36}

**Administration and Pharmacokinetics/Pharmacodynamics of Axi-cel**

Once the patient concludes their lymphodepleting chemotherapy, the axi-cel product is thawed using a water bath or dry thaw method and administered at the bedside on day 0. The final product is approximately 68 mL, preferably infused through a central line over 30 minutes. Premedication with an H1-antihistamine and acetaminophen is recommended prior to infusion. Patients receiving axi-cel must be admitted to the treatment center for observation and toxicity management for at least 7 days. In addition, patients must remain within close proximity to a certified treatment center for at least 4 weeks following discharge.\textsuperscript{18}

Peak levels of anti-CD19 CAR T cells occurred 7 to 14 days following administration proceeded by a slow decline to near-baseline levels by 3 months postinfusion. Neither age nor gender significantly altered axi-cel area under the curve (AUC) or \( C_{\text{max}} \) levels.\textsuperscript{18} The extent of clonal expansion and persistence of anti-CD19 CAR T cells play an important role in predicting clinical response. For instance, the median axi-cel \( C_{\text{max}} \) and AUC were 205\% and 251\% higher, respectively, in responders compared with nonresponders.\textsuperscript{18} Additional research is required to fully elucidate the relationship between CAR T-cell kinetics and its safety and efficacy profile.

**Data Synthesis**

**Prospective Clinical Trials**

**Clinical Efficacy.** The first clinical trial to assess the adoptive anti-CD19 T-cell effect of FMC63-28Z, now known as axi-cel, was conducted by the NCI in 8 patients with multiply...
relapsed indolent B-cell NHL or CLL (Table 1). Three out of the evaluable 7 patients had follicular lymphoma. High-dose lymphodepleting chemotherapy with cyclophosphamide (60 mg/kg) on days −7 and −6 along with fludarabine (25 mg/m²) on days −5 through −1 were given prior to CAR T-cell infusion on day 0. The CAR T-cell dose ranged from 3 to 30 × 10⁶ CAR T cells per kilogram. Following CAR T-cell administration, patients also received an intravenous infusion of interleukin-2 (IL-2) at a dose of 720 000 IU/kg every 8 hours until toxicity precluded further treatment. Investigators reported that 6 out of 7 evaluable patients obtained remissions lasting a minimum of 7 months, with 4 patients displaying long-term depletion of normal CD19+B cells. All 3 follicular lymphoma patients experienced a partial response (PR). These initial results were encouraging and led to a subsequent NCI trial looking at similar B-cell disorders with the inclusion of aggressive and relapsed NHL.35

In this subsequent NCI trial, a total of 15 patients were treated with anti-CD19 CAR T-cell therapy following a similar high-dose cyclophosphamide and fludarabine lymphodepleting regimen. Because of toxicity concerns, exogenous IL-2 was not administered to patients in this clinical trial, and lower anti-CD19 CAR T-cell doses were utilized, with a range of 1 to 5 × 10⁶ cells/kg. Seven of the evaluable 13 patients had aggressive LBCL, with the other 6 patients having indolent NHL or CLL. Of the 7 aggressive NHL patients, 4 obtained a CR, 2 achieved a PR, and 1 had stable disease following CAR T-cell infusion. Duration of response varied from 1 to 23+ months. Overall, these NCI results strongly encouraged additional research into anti-CD19 CAR T-cell therapy for patients with B-cell malignancies, including r/r aggressive B-cell lymphomas.

The NCI, in conjunction with Kite Pharmaceuticals, treated 22 advanced-stage NHL patients with anti-CD19 CAR T-cell therapy preceded by low-dose lymphodepleting chemotherapy with cyclophosphamide (300 or 500 mg/m²) and fludarabine (30 mg/m²) on days −5, −4, and −3. CAR T-cell doses ranged from 1 to 6 × 10⁶ cells/kg. Of these patients, 19 had aggressive LBCL. Among these patients, the rate of remission was 68% (13 of 19), with 47% (9 of 19) obtaining a durable and lengthy CR lasting at least 7 months (range, 7+ to 24+ months). NCI investigators reported peak CAR T-cell concentrations at 8.5 days (range, 6 to 35 days) following infusion with a rapid decline in all patients to near undetectable levels by 3 months.34 Peak blood concentrations were higher in those obtaining a CR or PR compared with those with stable or progressive disease. Unlike previous trials,35,37 this protocol utilized a low-dose lymphodepleting regimen to potentially minimize toxicities while maintaining high response rates. Investigators reported that low-dose lymphodepletion adequately reduced lymphocyte counts while also increasing serum IL-15 levels.34 Of note, high IL-15 serum levels showed a strong correlation with lymphoma disease remission. This was the first work to show an association between IL-15 levels and lymphoma remissions following CAR T-cell therapy. As a result of these findings, most anti-CD19 CAR T-cell protocols utilize low-dose fludarabine-based chemotherapy as their conditioning regimen prior to CAR T-cell therapy.18,34

Investigators performed a long-term analysis following 43 patients enrolled between 2009 and 2015 in the initial NCI-led anti-CD19 CAR T-cell trials (NCT00924326). A total of 28 patients were treated for an aggressive lymphoma with a median of 4 previous lines of therapy (range, 2 to 12). The ORR for these heavily pretreated patients was 58%, with a 50% rate of CR. The median duration of CR was 50 months (range, 6 to 83), and the OS for those with a CR had not been reached. This is the longest follow-up analysis of any CAR T-cell therapy.

ZUMA-1 was a pivotal, single-arm, multicenter, phase 1-2 clinical trial conducted in 22 cancer treatment centers in the United States and Israel. Eligible patients were 18 years or older with refractory LBCL that included DLBCL, TFL, and PMBCL according to the 2008 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue.39 Patients were only eligible if they possessed an Eastern Cooperative Oncology Group performance status of 0 or 1 with adequate organ function. In addition, all patients were required to have previously received an anti-CD20 monoclonal antibody and anthracycline-containing regimen.

The primary end point for phase 1 was the incidence of dose-limiting toxicities. The primary end point for phase 2 was the proportion of patients achieving an objective response, defined as the combined proportion of patients who had a CR or PR. From May 19, 2015, to September 15, 2016, 119 patients were enrolled in the phase 1 and 2 portions of the study, and 108 (91%) of these patients received axi-cel therapy. Phase 2 of the ZUMA-1 trial had 2 separate cohorts: cohort 1 contained 77 DLBCL patients and cohort 2 contained 24 patients with PMBCL or TFL.22,29 With a median follow-up of 15.4 months, the ORR was 82%, with 54% of patients having a CR. Compared with the historical control ORR of 26%, this was an impressive improvement.13 With a median follow-up of 15.4 months, ongoing responses were noted for 40% of patients who had a CR. All covariates analyzed displayed similar response rates. The median OS had not been reached, but OS rates at 12 and 18 months were 59% and 52%, respectively.

In the updated ZUMA-1 report,22 101 phase 2 patients who received axi-cel were evaluated with a median follow-up of 27.1 months. Objective and CR rates for those who received treatment remained relatively consistent with the initial ZUMA-1 findings at 83% and 58%, respectively. Median time to response was 1 month; however, 11 of 33 patients with a PR and 11 of 24 patients with stable disease 1 month after axi-cel therapy went on to eventually achieve a CR within 12 months. The median duration of response...
| Trial | Evaluable B-cell lymphoma patients (n) | Lymphodepleting regimen | Efficacy outcomes | Treatment-related adverse events |
|-------|-------------------------------------|------------------------|------------------|---------------------------------|
| NCI 2012<sup>27</sup> | 3 | - Cyclophosphamide (60 mg/kg) on days −7 and −6  
- Fludarabine (25 mg/m²) on days −5 through −1 | - ORR: 100%  
- CR: 0% | - All patients experienced ≥1 adverse event, ranging from diarrhea, fatigue, infections, B-cell aplasia, and end organ damage |
| NCI 2015<sup>15</sup> | 7 | - Cyclophosphamide (60-120 mg/kg total single dose)  
- Fludarabine (25 mg/m²) for 5 days | - ORR: 86%  
- CR: 57% | - All patients experienced at least 1 grade ≥3 adverse event. Two patients required tocilizumab  
Cytokine release syndrome  
Neurological toxicity |
| NCI 2016<sup>14</sup> | 19 | - Low dose Cyclophosphamide (300 or 500 mg/m²) and  
- Fludarabine (30 mg/m²) on days −5, −4, and −3 | - ORR: 68%  
- CR: 47%  
- Median CR duration: 12.5 months (7-24)  
- 12-month PFS: 63.3% | - Grade ≥3 hypotension: 18%, with 75% of those requiring vasopressors  
- Received tocilizumab: 5%  
- Grade ≥3: 55%  
- Most common toxicities were dysphasia, confusion, and tremor |
| ZUMA-1,<sup>75</sup> phase 1 | 7 | - Low-dose Cyclophosphamide (300 or 500 mg/m²) and  
- Fludarabine (30 mg/m²) on days −5, −4, and −3 | - ORR: 71%  
- CR: 57%  
- Ongoing CR at 12 months: 43%  
- Received tocilizumab: 86%  
- Any grade: 100%  
- Grade ≥3: 57% | |
| ZUMA-1,<sup>22</sup> phase 2 | 101 | - Low dose Cyclophosphamide (300 or 500 mg/m²) and  
- Fludarabine (30 mg/m²) on days −5, −4, and −3 | - ORR: 83%  
- CR: 58%  
- Estimated OS at 24 months: 50.5% | - Grade ≥3: 11%  
- Grade ≥3: 32% |
| Postmarketing study no. 1<sup>31</sup> | 275 | Same as ZUMA-1 | - ORR: 82%  
- CR: 64%  
- PFS median: 8.3 months | - Any grade: 91%  
- Grade ≥3: 7%  
- Received tocilizumab: 62%  
- Any grade: 69%  
- Grade ≥3: 31% |
| Postmarketing Study no. 2<sup>24</sup> | 295 | Same as ZUMA-1 | - ORR: 70%  
- CR: 52% | - Any grade: 83%  
- Grade ≥3: 14%  
- Received tocilizumab: 58%  
- Any grade: 61% |

Abbreviations: CR, complete response; NCI, National Cancer Institute; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
was 11.1 months for all assessable patients. For those with a CR, the median duration of response had not been reached before the data cutoff, but 37 (37%) had ongoing remissions. In contrast, those with a PR had a duration of response lasting only 1.9 months. This highlights the significant difference between obtaining a CR and a PR in terms of long-term survival benefit with axi-cel therapy in patients with aggressive LBCL. Median OS had also not been reached, but the estimated 24-month survival rate was 50.5%. Although axi-cel represents an important and promising advancement in the treatment of LBCL, it also elicits noteworthy treatment-related adverse events (AEs) requiring careful consideration.

Safety. Cellular-based therapies have the propensity to induce several unique and life-threatening AEs. The most common AEs occurring in greater than 20% of cases include cardiac arrhythmia, chills, constipation, cytokine release syndrome (CRS), decreased appetite, diarrhea, dizziness, encephalopathy, fatigue, febrile neutropenia, fever, headache, hypotension, hypoxia, infections, nausea/vomiting, tachycardia, and tremor. The updated ZUMA-1 report showed that all 108 patients experienced an AE, and 98% had a grade 3 or higher event. Investigators also reported serious AEs in 48% of patients. As a unique and novel adoptive CAR T-cell therapy, axi-cel has the capacity to provoke noteworthy class-specific toxicities. The 3 most significant complications resulting from CAR T-cell–based therapy include CRS, immune effector cell–associated neurotoxicity syndrome (ICANS), and B-cell aplasia. As a result of these life-threatening AEs, axi-cel is only available through a Risk Evaluation and Mitigation Strategy (REMS) program to ensure the benefits of axi-cel therapy outweigh these risks. Per the YESCARTA REMS program, treatment centers are required to train practitioners on appropriate recognition and management of these CAR T-cell–related toxicities. A robust and comprehensive training program is paramount for successfully incorporating CAR T-cell therapy. Physicians, pharmacists, nurses, advanced practitioners, and other ancillary members involved in the prescribing, dispensing, or administering of axi-cel are required to undergo appropriate training in the identification and management of common toxicities. Patients must be monitored at a certified treatment center for signs and symptoms of these reactions for at least 7 days postinfusion. Furthermore, patients are typically required to remain within close proximity to the treatment center for 4 to 8 weeks following axi-cel administration.

Cytokine Release Syndrome

CRS is a commonly occurring class phenomenon with both CAR T-cell therapy and other targeted cellular therapies. CRS is a global inflammatory response with varying severity, ranging from mild fever and constitutional symptoms to life-threatening hemodynamic instability and end-organ damage. The cardinal symptoms of CRS are fever, hypotension, and hypoxia. Other common symptoms include arthralgias, headache, malaise, myalgias, and tachycardia. The deleterious effects of CRS result from direct CAR T-cell expansion, immune system activation, and the subsequent release of inflammatory cytokines, chemokines, and immune effector cells. Median onset of CRS is 2 days following CAR T-cell infusion and remains for a median duration of 8 days.

In all clinical trials of axi-cel, CRS of any grade was a near-universal occurrence in patients with r/r B-cell lymphoma (Table 1). The updated ZUMA-1 report was 93%, with 11% experiencing grade 3 or higher toxicity. The most common CRS manifestation was fever (76%). Grade 3 or higher CRS decreased from 17% in the first 69 patients down to 0% in the last 39 patients, perhaps because of a change in protocol allowing tocilizumab treatment in patients with grade 2 CRS.

The NCI Common Criteria for Adverse Events (CTCAE) is a standardized classification system used for the evaluation of cancer therapy–related AEs. This grading system was created before the advent of cellular-based therapies and, therefore, failed to sufficiently assess or describe unique CAR T-cell–associated toxicities. As a result, various institutions created their own reporting scales to grade and evaluate CRS and ICANS. ZUMA-1, for instance, utilized the modified Lee criteria created by investigators at the National Institutes of Health as their preferred method for grading CRS. Clinical trials evaluating tisagenlecleucel, another anti-CD19 CAR T-cell product, applied the Penn scale developed at the University of Pennsylvania. The lack of uniform grading across trials hinders reliable AE comparison among CAR T-cell products. More recently, however, CRS grading criteria have shifted toward the Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicities Associated with ICANS guidelines. This consensus guideline, published by The American Society of Transplant and Cellular Therapy (ASTCT; formerly American Society for Blood and Marrow Transplantation) in 2019, was designed to streamline and simplify the grading system for both CRS and ICANS. If fully implemented, the ASTCT guideline can serve to harmonize the identification and management of CRS and ICANS in clinical trials and at certified treatment centers administering CAR T-cell therapy.

Management of CRS begins with prompt identification and supportive therapy using antipyretics, intravenous fluids, and potentially antiemetics (Table 3). It is also important to evaluate and treat patients for other causes of fever, hypoxemia, and hypotension because of the possibility of unknown infection. Tocilizumab, an anti-IL-6 monoclonal antibody, is FDA approved for the treatment...
of grade 2 or higher CRS with or without concomitant corticosteroids.\textsuperscript{18,22,48,49} In adults, treatment with tocilizumab (8 mg/kg intravenous; maximum dose: 800 mg) results in a rapid improvement of symptoms within hours without adversely affecting T-cell expansion or efficacy.\textsuperscript{22,50} Tocilizumab may be repeated every 8 hours for up to 4 total doses in patients with persistent signs or symptoms of CRS.\textsuperscript{18} The YESCARTA REMS program requires treatment centers to maintain at least 2 doses of tocilizumab per patient available within 2 hours of axi-cel administration. ZUMA-1 reported that 45% of patients received tocilizumab for CRS following axi-cel infusion. Prophylactic treatment and earlier intervention with tocilizumab may help reduce the incidence of severe CRS without affecting efficacy.\textsuperscript{22,50} Grades 3 and 4 CRS often require ICU admission with aggressive supportive care measures, potentially involving high-dose vasopressors, corticosteroids, hemodialysis, and supplemental oxygenation and/or ventilator support.\textsuperscript{18,32,48} Corticosteroids are lymphotoxic agents that may result in the abrogation of CAR T cells, limiting their antitumor effect and persistence. For now, corticosteroid use is limited to severe or life-threatening emergencies. Additional research is required to fully assess the clinical implications of this interaction.

### Immune Effector Cell–Associated Neurotoxicity Syndrome

ICANS is another commonly occurring AE associated with cellular gene therapies. The symptoms include confusion, delirium, encephalopathy, headache, somnolence, and possible seizures.\textsuperscript{18,32,48} Clinicians should conduct a baseline neurological exam and use the patient’s caregiver as a source to detect subtle changes in the patient’s behavior. Because of the nonspecific presentation of ICANS, other potential causes of neurological dysfunction must be considered.\textsuperscript{32} The underlying pathophysiological mechanisms leading to ICANS require further elucidation. Neurological dysfunction may be associated with the activation of inflammatory cytokines in the central nervous system (CNS).\textsuperscript{32,52} Increase in blood-brain-barrier permeability allows for trafficking of both CAR T cells and inflammatory cytokines into the CNS, causing neurological toxicity.\textsuperscript{32,52} Higher CAR T-cell counts in the cerebrospinal fluid of the patients who develop ICANS support this theory.\textsuperscript{52} ZUMA-1 utilized the NCI CTCAE version 4.03, to grade neurological events. Based on this criterion, 64% of patients experienced any grade of ICANS and 32% experienced a grade $\geq 3$ neurological event.\textsuperscript{22} Management of ICANS

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**Table 2. Cellular Therapy Toxicity Grading Scales.\textsuperscript{47}**

| CRS Grading Scale | CRS parameter | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|------------------|---------------|---------|---------|---------|---------|
| Temperature $\geq 38 \, ^\circ C$ | None | Not requiring vasopressors and/or requires low-flow nasal cannula or blow-by oxygen therapy | Requires a vasopressor $\geq$ vasopressin and/or requires high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask | Requires multiple vasopressors (excluding vasopressin) and/or requires positive pressure support (eg, intubation and mechanical ventilation) |
| Hypotension | None | | | |
| Hypoxia | | | |

| Neurotoxicity (ICANS) Grading Scale$^a$ | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|--------------------------------------|---------|---------|---------|---------|
| ICE score age $\geq 12$ years | 7-9 | 3-6 | 0-2 | 0 (Unarousable and unable to perform ICE) |
| CAPD score age $< 12$ years | 1-8 | 1-8 | $\geq$ 9 | 9 (Unable to perform CAPD) |
| Decreased level of consciousness | | | | |
| Seizures | N/A | N/A | Any electrographic seizure | Prolonged seizure or electrographic seizures without return to baseline |
| Motor weakness | N/A | N/A | N/A | Deep focal motor weakness |
| Elevated ICP/ cerebrospinal edema | N/A | N/A | Focal/local edema on neuroimaging | Signs and symptoms of elevated ICP |

$^a$ICANS grade is determined using the most severe event not attributable to other possible etiologies.

Abbreviations: CAPD, Cornel Assessment of Pediatric Delirium; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; ICE, immune effector cell–associated encephalopathy; ICP, intracranial pressure.
depends on the presence or absence of concurrent CRS. Tocilizumab, although not effective at mitigating ICANS directly, is recommended for treatment with concurrent CRS. Neurotoxicity often appears alongside or following CRS; however, it may also manifest in the absence of CRS. When CRS is absent, treatment with corticosteroids is preferred. ZUMA-1 reported a median onset of neurotoxicity at 5 days (range, 1 to 17), with a median duration of 17 days. Serious ICANS events declined over the course of the trial, decreasing from 38% in the first 69 patients to 23% in the last 39 patients. No new ICANS or CRS events were reported after the 6-month analysis. All events resolved except those occurring in patients who died from other causes. The decline in serious events paralleled with increased experience in recognition and treatment of these class-related toxicities.

### B-cell Aplasia and Other Cytopenias

B-cell aplasia is an expected on-target but off-tumor complication of anti-CD19 CAR T-cell therapy because of the presentation of CD19 on healthy B cells. In ZUMA-1, 52% of all study participants enrolled with pre-existing B-cell aplasia and hypogammaglobulinemia secondary to prior anti-CD20 immunotherapy. Following axi-cel treatment, immunoglobulin levels should be monitored, and supplementation with intravenous immunoglobulin (IVIG) considered, especially in patients experiencing recurrent or serious infections. The updated ZUMA-1 report showed that 31% of patients required treatment with IVIG following axi-cel therapy. In addition, 75% of ZUMA-1 patients with ongoing responses demonstrated B-cell recovery by 24 months, with some patients reporting recovery as early as 9 months. Therefore, indefinite B-cell aplasia is not required for long-term disease remission. Future studies should continue to evaluate the importance of and relationship with CAR T-cell persistence and B-cell recovery.

Other early- and late-onset cytopenias were also noted in the ZUMA-1 trial. Grade 3 or higher neutropenia (78%), anemia (43%), and thrombocytopenia (38%) were common occurrences in the first several months of therapy. In addition, late-onset cytopenias also require vigilant monitoring, considering that 17% of patients experienced grade 3 cytopenias at 3 months or later. The frequency of late-onset grade ≥3 infections in the ZUMA-1 trial were also noteworthy (28%), further highlighting the need for routine monitoring well after axi-cel administration.

### Postmarketing Analysis

There are several retrospective postmarketing studies reporting commercial axi-cel safety and efficacy data in patients with B-cell lymphomas. These reports help substantiate the clinical results found in the pivotal ZUMA-1 trial. A multicenter retrospective analysis was completed by the US Lymphoma CAR T Consortium evaluating the commercial use of standard-of-care axi-cel in 17 US academic centers. All patients who underwent leukapheresis by August 31, 2018, were included, resulting in a total of 298
patients. Pertinent patient characteristics include the following: 81% had a good performance status of 0 or 1; 68% had DLBCL histology; 75% had 3 or more previous therapies; 33% had prior ASCT; and bridging therapy was given to 53% of patients, with most receiving chemotherapy with or without other therapy. Of note, the median age was 60 (range, 21-83 years), demonstrating that patients older than the ZUMA-1 population can be treated commercially with axi-cel. Overall, 43% of patients would not have met eligibility requirements for the ZUMA-1 study. Median time from leukapheresis to conditioning chemotherapy was 26 days (range, 11-71 days), and the median duration of hospitalization required was 14 days (range, 3-66). Efficacy was evaluated in 275 patients who received axi-cel and were restaged at day 30. Both overall and CR rates were similar to those seen in the ZUMA-1 trial. The best ORR and CR rates were 82% (95% CI, 77% to 86%) and 64% (95% CI, 58% to 69%), respectively. The 12-month progression-free survival and OS estimates were 47% (95% CI, 41% to 53%) and 68% (95% CI, 63% to 74%), respectively. Safety was evaluated in 275 patients receiving axi-cel therapy. CRS was graded and managed according to each individual institution’s protocol. CRS occurred in 251 (91.2%) patients, with 19 (7%) experiencing grade 3 or higher CRS. Median time to onset of CRS was 3 days (range, 0-37). Neurological events occurred in 189 (68.7%) patients, with 85 (31%) patients experiencing grade 3 or higher neurotoxicity. Median time to neurological event was 6 days. Furthermore, tocilizumab was administered to 62% of patients. Intensive care admission was required in 33% of patients, and 7% required vasopressor therapy. Twelve patients experienced nonrelapse mortality from infection (n = 8), unknown causes (n = 2), hemophagocytic lymphohistiocytosis (n = 1), and cerebral edema (n = 1). This real-world retrospective analysis demonstrated safety and efficacy outcomes that were similar to the registrational ZUMA-1 trial in highly refractory and heterogeneous patients who were not ideal treatment candidates based on the ZUMA-1 protocol.

A separate multicenter, retrospective analysis was conducted by Pasquini et al evaluating aggressive LBCL patients who received commercial or compassionate use axi-cel between October 18, 2017, and May 1, 2019. In this ongoing real-world analysis, 295 patients at 43 different academic medical centers were included. The ORR was 70%, with 52% of patients obtaining a CR. A subgroup analysis showed that older patients (≥65 years old) were comparable to younger patients overall, with an improved rate of CR (62% vs 46%; P = 0.03). According to the ASTCT grading criteria, CRS was identified in 83% of patients. Grade ≥3 CRS occurred in 14% of patients. Two deaths resulted from CRS-related complications. Median time to CRS was 3 days (range, 1-17 days), and 94% of cases resolved with a median duration of 7 days (range, 1-121 days). Tocilizumab was required in 70% of CRS cases. Neurological events of any grade were reported in 61% of patients. One patient died from cerebral edema. Taken together, these real-world analyses establish the utility of axi-cel as standard of care in r/r aggressive LBCL patients. Response rates were slightly less than those noted with the pivotal ZUMA-1 trial; however, commercial use of axi-cel at these academic institutions included a significant number of ZUMA-1 ineligible patients based on performance status, laboratory abnormalities, and disease characteristics. Despite including relatively ill patients, these retrospective analyses report similar rates of response and serious CAR T-cell–related toxicities.

Relevance to Patient Care and Clinical Practice

Aggressive B-cell lymphomas are the most common hematological malignancy in adults. Approximately one-third of patients with this heterogeneous disease will fail first- and second-line chemoimmunotherapy and develop r/r LBCL. SCHOLAR-1 findings reveal a median OS of approximately 6 months with conventional treatment modalities, highlighting the significant unmet medical need and difficult clinical dilemma surrounding these high-risk patients. According to the updated ZUMA-1 report, axi-cel resulted in an estimated 24-month OS of 50.5%, representing a significant improvement compared with historical controls. It is important to note, however, that comparisons of small, single-arm trials with historical controls, such as SCHOLAR-1, are fraught with peril. Confounders and potential bias are inherent in these analyses and must be approached with caution. Nevertheless, adoptive CAR T-cell therapy offers a promising paradigm shift and innovative treatment alternative in r/r LBCL. This new frontier of patient-specific cellular immunotherapy displayed unprecedented improvements in this heavily pretreated population. The updated ZUMA-1 report noted investigator-assessed objective and CR rates of 83% and 58%, respectively. These rates, however, are based on both investigator-assessed responses and a modified intention-to-treat analysis, excluding patients who underwent leukapheresis but failed to receive axi-cel therapy. An independent central review committee found 75 objective responses and 55 CRs in the phase 2 portion of ZUMA-1. This would result in a 67% ORR and a CR rate of 50%, if using an intention-to-treat analysis. These figures represent all patients who were initially eligible and started the CAR T-cell process. Regardless of the methodology to calculate ORR and CR, the results are encouraging and place axi-cel as a legitimate treatment option in the r/r setting.

There are currently 2 FDA-approved CAR T-cell products for the treatment of adult patients with r/r LBCL: axi-cel and tisagenlecleucel. JULIET was an international,
Table 4. Trial Comparison for Anti-CD19 CAR T-cell Products.

| Lymphodepletion regimen | CAR Design and Dose | Efficacy Outcomes | Safety Outcomes |
|-------------------------|---------------------|------------------|-----------------|
| Axicabtagene ciloleucel, ZUMA-1,\textsuperscript{22,29} NCT02348216 | Cyclophosphamide (300 or 500 mg/m\textsuperscript{2}) and fludarabine 30 mg/m\textsuperscript{2} on days −5, −4, and −3 | • Anti-CD19 | • n = 101 | • n = 108 |
| | | • CD3\textsuperscript{ζ} activation domain | | | | | |
| | | • CD28 costimulatory domain | | | | | |
| | | • Target dose: 2 × 10\textsuperscript{6} CAR T cells (maximum dose: 2 × 10\textsuperscript{6} CAR T cells) | | | | |
| Tisagenlecleucel, JULIET,\textsuperscript{55} NCT02445248 | Cyclophosphamide 250 mg/m\textsuperscript{2} and fludarabine 25 mg/m\textsuperscript{2} for 3 days, or bendamustine 90 mg/m\textsuperscript{2} for 2 days | • Anti-CD19 | • n = 93 | • n = 111 |
| | | • CD3\textsuperscript{ζ} activation domain | | | | | |
| | | • 4-1BB costimulatory domain | | | | | |
| | | • Target dose: 0.6 to 6 × 10\textsuperscript{6} CAR T cells | | | | |
| Lisocabtagene ciloleucel,* TRANSCEEND,\textsuperscript{56} NCT02631044 | Cyclophosphamide (300 or 500 mg/m\textsuperscript{2}) and fludarabine 30 mg/m\textsuperscript{2} on days −5, −4, and −3 | • Anti-CD19 | • n = 88 | • n = 91 |
| | | • CD3\textsuperscript{ζ} activation domain | | | | | |
| | | • 4-1BB costimulatory domain | | | | | |
| | | • CD4/8 ratio of 1:1 | | | | | |
| | | • Target dose: 1 × 10\textsuperscript{8} CAR T cells | | | | |

Abbreviations: CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; ORR, objective response rate; OS, overall survival.

*Investigational agent not approved by the Food and Drug Administration.

phase II pivotal trial evaluating tisagenlecleucel in r/r LBCL, resulting in FDA approval on May 1, 2018. The ZUMA-1 and JULIET trials were both small, single-arm studies; therefore, direct comparison of outcomes is premature and problematic. Overall, axi-cel and tisagenlecleucel appear to be effective treatment options for r/r LBCLs, with similar toxicity profiles (Table 4).\textsuperscript{22,45,56} Additional long-term studies are required to ascertain if a true difference exists between these 2 pioneering agents. Furthermore, intermediate- and long-term complications resulting from CAR T-cell therapy remain unknown. Pharmacovigilance is required to detect and report any unforeseen complications that may arise from engineered cellular gene therapy, which remains in its infancy.

CAR T-cell therapy heralds a new frontier in cancer treatment; however, it also harbors significant and unique toxicity concerns. CRS and ICANS are CAR T-cell–related complications requiring additional research. These class toxicities were also noted with other anti-CD19 CAR T-cell agents in the JULIET and TRANSCEND\textsuperscript{56} (investigational lisocabtagene maraleucel) trials (Table 4). Grading and management of these unique toxicities continues to be a dynamic endeavor, as evidenced by the ZUMA-1 trial and their evolving practices.\textsuperscript{33,40,42,47} Furthermore, multiple grading scales were developed over the past decade with little uniformity across trials.\textsuperscript{42,47} The discordant characterization of CAR T-cell–related toxicities should improve with the development and implementation of the ASTCT consensus guidelines.

Cost of CAR T-cell therapy remains another major concern. For the current FDA-approved indication, axi-cel was given an initial list price of $373 000.\textsuperscript{57} This figure does not include the cost of leukapheresis, axi-cel administration, hospitalization, or expenses involved with monitoring and managing common complications such as CRS and ICANS. One cost-effectiveness analysis calculated the mean total cost of axi-cel therapy at approximately $521 000.\textsuperscript{58} The US Institute for Clinical and Economic Review (ICER) evaluated axi-cel following its FDA approval and concluded, “The base-case findings from our analysis suggest that the use of axi-cel in B-cell lymphoma also provides clinical benefit in terms of gains in quality adjusted and OS over chemotherapy.”\textsuperscript{57} ICER members did, however, note uncertainty surrounding axi-cel’s long-term risks and benefits. Furthermore, rates of reimbursement and insurance coverage for cellular-based therapy continue to be key areas of interest and contention.\textsuperscript{59} One report highlighting current financial barriers estimated that treatment centers may lose up to $300 000 per CAR T-cell patient based on existing reimbursement rates.\textsuperscript{59} In response to the growing financial...
concerns surrounding CAR T-cell therapy, the Centers for Medicare and Medicaid Services recently adapted previous reimbursement practices and created a separate payment category termed the Medicare Severity Diagnostic Related Group for CAR-T.60 If passed and implemented, this restructured payment system should help improve funding and minimize the current financial gap limiting patient access.

Patients receiving CAR T-cell therapy may have other nonmedical financial and logistical constraints as well. For instance, there are currently more than 90 approved treatment centers administering axi-cel across the United States; unfortunately, patients may have to travel a significant distance to arrive at one of these certified treatment centers. Loss of employment, travel to and from the treatment center, living expenses during treatment and surveillance periods, and treatment-related complications all have the potential to adversely affect patients. These and other concerns warrant careful consideration during the patient selection process and require a comprehensive discussion with prospective patients and their caregivers.

Interprofessional collaboration is imperative for providing optimal care to patients receiving CAR T-cell therapy. There are significant logistical hurdles involving axi-cel treatment: the process of selecting appropriate patients, ascertaining patient eligibility, locating lodging and transportation, obtaining insurance authorization and reimbursement, and arranging and providing appropriate CAR T-cell education and training. Health care professionals must be cognizant of these barriers and collaborate to ensure a smooth and swift process through the CAR T-cell care continuum. Despite the many potential barriers surrounding this novel therapy, axi-cel remains a viable and promising treatment option for patients without many worthwhile alternatives. Treating multiply relapsed and/or refractory LBCL is a difficult endeavor; however, axi-cel offers the hope of durable remission in the salvage setting.

**Future Directions**

As with any novel therapy, there are many questions and concerns still lingering that require additional research and evaluation. For instance, ZUMA-1 was a relatively small, single-arm trial with short follow-up. Further evaluation is required to not only identify the long-term safety and efficacy data for axi-cel therapy in r/r LBCL, but also to identify predictors of treatment success and disease relapse.22,30,31 Furthermore, research is required to better understand the mechanism behind late relapse and how to avoid or overcome antigen loss and downregulation following CAR T-cell therapy. Despite early success with second-generation CAR T-cell therapy, multiple escape mechanisms have been identified, including loss of target antigen.30 Bispecific CAR T cells are currently being evaluated as one potential method of simultaneously targeting multiple cancer antigens. These dual-antigen CAR T cells may diminish tumor antigen loss or downregulation and prevent disease relapse. Several antigen combinations are currently under investigation, with anti-CD19 and anti-CD20 CARs being one potential tandem construct.61 Additional research is needed to better establish the optimal inclusion criteria and patient selection process. Postmarketing studies continue to include ZUMA-1 ineligible patients yet consistently show similar safety and efficacy outcomes despite evaluating older patients with more comorbidities.30,31

Researchers continue to evaluate axi-cel in DLBCL, most notably in the second-line setting against standard-of-care comparators, including platinum-containing salvage chemotherapy with or without ASCT (ZUMA-7, NCT03391466). This highly anticipated trial is a phase 3 randomized, open-label, multicenter study with an enrollment goal of 359 patients set to complete in 2022. Axi-cel in combination with the immune checkpoint inhibitor, atezolizumab, is also being investigated in patients with refractory DLBCL (ZUMA-6, NCT02926833). Current axi-cel trials are also evaluating safety and efficacy in other CD19-positive malignancies and patient populations, including pediatric ALL, pediatric NHL, mantle cell lymphoma, and CLL (ZUMA-2, NCT02601313; ZUMA-3, NCT02614066; ZUMA-4, NCT02625480; ZUMA-8, NCT03624036).62-64

**Conclusions**

Nearly 30 years after the pioneering work of Eshhar, Rosenberg, and colleagues on the applicability of adoptive immunotherapy, CAR T-cell therapy has finally arrived as an emerging driver in the race for a cure.65,66 Despite immense promise, numerous barriers and challenges remain with this innovative treatment modality. High cost and complicated payer policies, the complex patient referral pathway, manufacturing delays and failures, and life-threatening safety concerns are just a few of the challenges facing CAR T-cell therapy. Nevertheless, propelled by the recent approvals of axi-cel and tisagenlecleucel, an explosion in clinical research and global interest with CAR T-cell therapy should continue to help fine-tune and obviate some of the challenges facing widespread adoption of cellular immunotherapies. We currently lack mature data on OS and long-term toxicity, but the unprecedented response rates in this difficult-to-treat population promote and solidify axi-cel as a valuable standard-of-care option in r/r LBCL.

**Declaration of Conflicting Interests**

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