Safety and efficacy of axicabtagene ciloleucel in refractory large B-cell lymphomas

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Abstract: Aggressive large B-cell lymphomas represent a diverse population of diseases that are typically treated with anti-CD20 based immunochemotherapy. While this treatment is effective for a large proportion of patients, those that become refractory to induction therapy or experience disease relapse suffer an inferior overall prognosis, and novel treatment options are needed. Adoptive T-cell immunotherapy in the form of chimeric antigen receptor (CAR) T-cell therapy is one of the most revolutionary breakthroughs in the past several decades for the treatment of relapsed/refractory aggressive large B-cell lymphomas. Based on data from the pivotal ZUMA-1 study, axicabtagene ciloleucel (axi-cel) became the first-in-class anti-CD19 directed CAR T-cell therapy approved for patients with diffuse large B-cell lymphoma and other aggressive B-cell lymphoma variants. In this review, we provide an overview of CAR T-cell therapy, including its biology, manufacturing, and treatment course. In addition, we highlight the available efficacy data, review pertinent safety concerns, including cytokine release syndrome and neurologic toxicity, as well as provide an overview of emerging therapeutic strategies in the cellular therapy arena.

Keywords: axicabtagene ciloleucel, CAR T-cell, diffuse large B-cell lymphoma, immunotherapy, NHL, refractory

Introduction
Aggressive large B-cell non-Hodgkin lymphoma (NHL) represents a very heterogeneous group of diseases, encompassing diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL). With a more thorough understanding of lymphoma biology, it is known that large B-cell lymphomas can now be characterized by different morphologic variants, pathologic subtypes, and gene expression profiles. Standard of care first-line treatment includes anti-CD20 based immuno-chemotherapy, which results in cure rates of 60–70%. Patients whose disease is refractory to induction therapy, or those with subsequent relapse, are commonly treated with platinum-based salvage immuno-chemotherapy.

Those with chemotherapy-sensitive disease go on to receive high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). Unfortunately, patients who fail to respond to first-line salvage therapy or relapse following ASCT have a dismal prognosis, with a median survival of approximately 6 months, and thus represent a significant unmet medical need.

More recently, the advent of adoptive cellular therapy in the form of chimeric antigen receptor (CAR) T-cell therapy has led to a dramatic improvement in outcomes for patients with relapsed and refractory large B-cell lymphoma. Based on data from the pivotal ZUMA-1 trial, axicabtagene ciloleucel (axi-cel) was the first CAR T-cell therapy to receive approval by the United States Food and Drug Administration...
(FDA) for the management of large B-cell NHL. Herein, we provide an overview of axi-cel therapy, including efficacy and safety data, along with a practical discussion of current treatment considerations.

**Background**

*Immune surveillance for cancer*

While the immune system is the body’s main defense mechanism against infection, it also serves a well-established role in both the prevention and control of malignancy. Within this context, T cells are central to both antigen-specific adaptive immunity and tumor immune surveillance. T cells expressing tumor antigen-specific T-cell receptors (TCRs) become activated upon binding tumor peptides. Activated T cells then undergo clonal proliferation, followed by elaboration of inflammatory cytokines and chemokines, ultimately leading to tumor cell lysis.

Despite this robust machinery, tumors have co-opted several mechanisms to evade immune surveillance. Specifically, tumors may suppress T-cell activity through increased expression of immune checkpoint proteins, such as programmed death ligand-1 (PD-L1). Tumor cells may also secrete immunomodulating cytokines such as interleukin (IL)-10 in an effort to promote an immunosuppressive tumor microenvironment. Mutations in antigen presenting genes, and immunogenic markers on the tumor cell may also lead to an inability of T cells to recognize tumor cells as foreign. In an attempt to overcome such immune tolerance mechanisms, recent efforts have focused on cell-based immunotherapy in the form of CAR T-cell therapy.

*Axicabtagene ciloleucel*

Preclinical and clinical work at the National Cancer Institute (NCI) laid the groundwork for the eventual commercial development of axi-cel. The CAR construct of axi-cel utilizes a CD19 specific scFV along with a CD3ζ signaling domain and a CD28 costimulatory domain. The NCI CAR construct was subsequently licensed by Kite Pharma (a Gilead company) for further development and eventual commercialization as axi-cel. On 18 October 2017, axi-cel received FDA approval for the treatment of adults with relapsed or refractory large B-cell lymphoma after two or more prior lines of systemic therapy. Eligible histologies include DLBCL not otherwise specified, HGBL, TFL, and PMBCL; however, axi-cel is currently not approved for the treatment of patients with primary central nervous system (CNS) lymphoma.

**Overview of CAR T-cell treatment**

*Axi-cel CAR T-cell manufacturing*

The first step in axi-cel CAR T-cell manufacturing begins with leukapheresis via either peripheral or central venous access. Through leukapheresis, a patient’s nonmobilized peripheral blood mononuclear cells (PBMC) are collected, and shipped fresh to a centralized manufacturing facility. Upon receipt, the apheresis product is enriched for T cells and activated utilizing an anti-CD3 monoclonal antibody. Subsequently, the activated T cells are transduced with a retroviral vector containing the anti-CD19 CAR gene. CAR T-cells then undergo expansion in culture, with the goal of achieving a target dose of \(2 \times 10^6\) CAR T-cells per kilogram of patient body weight. Following quality control testing, the product is
cryopreserved and shipped back to the corresponding treatment center. Within the context of the ZUMA-1 study, this production process was able to achieve a 99% manufacturing success rate in a heavily pretreated population of patients.14

Bridging therapy
Following T-cell harvesting, the median turnaround time from leukopheresis to delivery of the CAR T-cell product was 17 days in the ZUMA-1 study. Within the context of this study, if patients required anticancer therapy for disease control during axi-cel manufacturing, investigators were permitted to treat only with pulsed high-dose steroids; systemic chemotherapy was prohibited. Conversely, in an era of commercial approval, clinicians commonly utilize an array of therapeutic modalities as bridging therapy, including systemic chemotherapy, novel targeted agents (such as ibrutinib or lenalidomide), palliative radiation therapy, and corticosteroids.

Conditioning therapy
Prior to the administration of axi-cel, patients undergo a 3-day course of lymphodepleting chemotherapy with cyclophosphamide and fludarabine. Based on preclinical models, lymphocyte depletion was found to lead to a favorable environment for CAR T-cell proliferation. In particular, lymphodepleting chemotherapy leads to a reduction in myeloid derived suppressor cells and regulatory T cells that may inhibit the expansion and proliferation of CAR T-cells. This regimen alters the cytokine milieu, particularly leading to increased availability of IL-15, which has been shown to promote the proliferation of infused CAR T-cells. Lastly, this regimen may serve to provide some degree of antitumor effect, though arguably less so in patients with chemotherapy refractory disease.

Axi-cel administration and monitoring
Following lymphodepleting chemotherapy, patients underwent axi-cel infusion (on day 0). Given the risk of side effects associated with axi-cel therapy, treatment is available only through a Risk Evaluation and Mitigation Strategy (REMS) program. As part of the REMS program, certified treatment centers must undergo training on the management of CAR T-cell associated adverse events, while also having the necessary elements in place to appropriately manage these toxicities. Similarly, there are also stipulations in place mandating that patients must be monitored at a health care facility for at least 7 days following infusion to evaluate for potential toxicities. Patients are instructed to remain within the proximity of a certified health care facility for a minimum of 4 weeks following infusion of axi-cel. Given the risk of resurgence of neurologic toxicity, patients are advised to refrain from driving or operating heavy machinery for at least 8 weeks following axi-cel treatment.

Efficacy of Axi-cel
ZUMA-1 trial design
The ZUMA-1 trial was a multi-institutional phase I/II study evaluating axi-cel in 111 patients with relapsed and refractory large B-cell lymphoma. Within this study, responses were assessed using the Cheson 2007 criteria with the primary endpoint being the objective response rate (ORR). Key eligibility criteria included histologically confirmed DLBCL, TFL, or PMBCL. Refractory disease was defined as stable or progressive lymphoma as best response to the most recent chemotherapy, or relapse within 12 months following ASCT. All patients must also have received prior anti-CD20 monoclonal antibody therapy and an anthracycline. In addition, enrollment was restricted to those with a preserved Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Subjects were hospitalized for axi-cel treatment followed by a minimum 7-day observation period postinfusion. Of the 119 patients who were enrolled, 108 (91%) patients received axi-cel and were included in the modified intention-to-treat analysis. In total, 10 patients did not undergo axi-cel infusion, 6 as a consequence of serious adverse events (SAEs) prior to lymphodepleting chemotherapy, and 2 had nonmeasurable disease. The remaining two patients suffered from SAEs following lymphodepleting chemotherapy and did not receive the axi-cel product. The vast majority of patients had DLBCL, with the remainder having either TFL or PMBCL.

ZUMA-1 efficacy
The study met its primary endpoint, demonstrating an ORR of 82% and a complete response (CR) rate of 54%, as compared with the prespecified
‘null hypothesis’ ORR of 20% (based on data from the SCHOLAR-1 study).9,14 The median time to disease response was 1 month, coinciding with the first per-protocol disease assessment. The updated 2-year analysis by Locke and colleagues of 101 patients in the phase II portion of the study revealed an investigator-assessed ORR of 83%, including a 58% CR rate, with a median follow up of 27.1 months. Ongoing responses were seen in 39% of patients, with 37% maintaining a CR.40

Of patients who did not achieve a CR at first disease assessment (1 month), 11 of 24 (46%) patients with stable disease and 11 of 33 (33%) patients with a partial response (PR) subsequently achieved a CR without intervening therapy. Most conversions occurred within 6 months of treatment.14,40 This data suggests that a subgroup of patients may deepen their response to therapy with time.

With longer follow-up, it is also clear that a subset of patients continue to maintain durable responses. To date, the median duration of response (DOR) has not been reached in patients achieving a CR, while for those whose best response was a PR, the median DOR was 1.9 months.41 This data suggests that achieving a CR is critical for long-term survival in patients treated with axi-cel. Two-year follow-up data demonstrate that 93% of patients with ongoing response at 12 months remained in response at 24 months. In this updated analysis, the median progression free survival (PFS) was 5.9 months, and the median overall survival was not reached with an estimated 24-month OS of 50.5%.40,42

On subset analysis, ORR did not differ based on a number of key covariates, including cell of origin, age, disease stage, or international prognostic index (IPI) score.14 Within the updated analysis, investigators identified 33 patients with either double expressor or high-grade B-cell lymphoma, and, in this challenging to treat population, axi-cel demonstrated encouraging outcomes including a 91% ORR and a 70% CR rate.40

Furthermore, though the ORRs were similar between the DLBCL cohort and the cohort compromising both TFL and PMBCL (82% and 83%, respectively), the CR rate of the composite TFL and PMBCL cohort was higher at 71% compared with 49% in DLBCL.14 Though this data would suggest that aggressive large B-cell lymphoma variants like TFL and PMBCL may preferentially benefit from axi-cel therapy, one must recognize that this is based on subgroup analysis, and the study was not formally powered to make such a comparison.

Safety of Axi-cel

While axi-cel therapy represents a promising treatment option for patients with relapsed/refractory aggressive large B-cell lymphoma, it is crucial that practitioners be well versed in the recognition and management of adverse events. A dedicated education and training approach, not only among prescribers, but also among consultants, midlevel providers, pharmacists, nursing, and other ancillary staff is paramount. Furthermore, a patient’s caregiver also serves an important role in recognizing toxicities following hospital discharge and maintaining close lines of communication with the health care team. Although various side effects were seen, the two principal acute toxicities inherent to CAR T-cell therapy are cytokine release syndrome (CRS) and neurologic toxicity.

Cytokine release syndrome

Cytokine release syndrome is a class phenomenon seen not only with CAR T-cell therapy, but also other types of cellular therapy including bispecific T-cell engagers (BiTEs) and haploidentical stem cell transplantation.13–45 CRS is thought to result from the activation of T cells upon binding tumor-specific antigens, which results in the elaboration of a variety of inflammatory cytokines and chemokines including IL-6, interferon gamma, and tumor necrosis factor alpha.45,46 This massive release of inflammatory signaling molecules can result in fever, hypoxia, hypotension, and organ toxicities.

Within the context of the ZUMA-1 study, CRS was categorized according to the modified Lee criteria.14,45 CRS was a nearly universal side effect, with 93% of patients experiencing any grade CRS, though only 11% of patients exhibited grade 3 or greater symptoms. The most common manifestation of CRS was fever (87%), followed by hypotension (63%), tachycardia (40%), and hypoxia (34%).40 The median time to onset of CRS was 2 days (range 1–12) with a median
duration of 8 days. All patients had resolution of their CRS, with the exception of one patient who passed away from complications of hemophagocytic lymphohistiocytosis, and another patient who died of cardiac arrest with ongoing CRS. Within the study, CRS was managed per a protocol-defined treatment algorithm, which was adapted from the Lee criteria.14

When assessing CRS symptoms, it is imperative for clinicians to also evaluate and treat for other causes of fever, hypoxia, and hypotension, including an assessment for infectious etiologies. Growing evidence suggests that IL-6 is a key inflammatory mediator in CRS.45 Tocilizumab, an IL-6 receptor antagonist, is currently FDA approved for the treatment of CRS and can result in rapid improvement of symptoms.47 In the ZUMA-1 study, grade 1 CRS events were managed with supportive care measures such as antipyretics, intravenous fluids, and anti-emetics. For escalating grades of CRS, management included the use of tocilizumab, and those not responsive to tocilizumab received corticosteroid therapy. Within the study, tocilizumab was administered in 43% of patients, with 27% requiring corticosteroids for the management of CRS or neurologic toxicity.14

Neurologic toxicity
Neurologic toxicity, also known as immune effector-cell associated neurotoxicity syndrome (ICANS), remains a significant adverse event seen in patients treated with CAR T-cell therapy.48 ICANS may present with decreased attention, headache, confusion, impaired coordination, changes in speech, tremors, and somnolence.14,38,46,49

Although much progress has been made in our understanding of neurologic toxicity, overall its pathophysiology remains poorly characterized. Several key findings have helped to provide insight into this event. Prior work has revealed that total CAR T-cell numbers were significantly higher on cerebrospinal fluid (CSF) analysis in patients who developed neurotoxicity compared with patients who did not.46,50,51 In addition, patients developing neurologic toxicity were noted to have markedly elevated CSF protein levels, including an elevation in inflammatory cytokines.50,52,53 These findings suggest that ICANS may involve some degree of cytokine-induced endothelial activation in the CNS with resultant increased permeability of the blood-brain barrier (BBB). It is hypothesized that breakdown of the BBB facilitates trafficking of both CAR T-cells and inflammatory cytokines into the CNS, leading to the manifestations of neurologic toxicity.53

The ZUMA-1 trial utilized the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 to grade neurologic events. Of the 108 patients assessed in the updated analysis, 67% of patients experienced neurologic toxicity of any grade, with 32% of patients suffering from grade 3 or greater neurologic events. In ZUMA-1, the most common grade ⩾3 manifestations of neurologic toxicity included encephalopathy (21%), confusional state (9%), followed by somnolence (8%), and aphasia (7%).40 The median onset of ICANS was 5 days (range 1–17) following axi-cel infusion, with a median duration of 17 days. Within the study, all patients had eventual resolution of their neurologic toxicity, with the exception of two patients who died from progressive disease, and another two patients who died from adverse events unrelated to neurologic toxicity.14

It is imperative for clinicians to conduct a thorough baseline neurologic examination in order to detect subtle changes on subsequent assessments. Furthermore, a patient’s caregiver may also serve as an important resource in informing the health care team about subtle changes in a patient’s behavior or cognition. When assessing neurologic toxicity, practitioners must rule out other causes of neurologic dysfunction. This typically involves neurologic imaging, including a noncontrast head computed tomography scan with consideration for magnetic resonance imaging of the brain. In addition, a lumbar puncture may be indicated for evaluation of infectious etiologies or occult lymphomatous involvement. One must also consider obtaining an electroencephalogram, as clinically indicated to rule out seizure activity.15,45,46

In the ZUMA-1 study, neurologic toxicity was managed per protocol defined treatment guidelines.14 When managing ICANS, clinicians must first ascertain if the patient is also experiencing concurrent CRS, as treatment with tocilizumab is indicated in this scenario prior to considering the use of corticosteroids. For patients with ICANS without concurrent CRS, management strategies...
center on the use of low-dose corticosteroids (i.e. dexamethasone 10 mg), while those with more severe grades of neurologic toxicity require high dose corticosteroids (i.e. methylprednisolone 1000 mg). While there is a theoretical concern that the use of anti-cytokine therapy with tocilizumab and corticosteroids may dampen the expansion of CAR T-cells and impede their efficacy, this was not observed in the ZUMA-1 study. This may be explained by the fact that patients requiring these therapeutic interventions already demonstrated adequate expansion of CAR T-cells to elicit efficacy.

It should be mentioned that the management strategies of both CRS and neurologic toxicity evolved throughout the course of the ZUMA-1 study. Furthermore, the rates of serious (grade ≥3) CRS and ICANS events decreased over the course of the trial, likely paralleling centers increased experience in the recognition and management of CAR T-cell related toxicities. With increasing utilization and clinical experience with cellular based therapies, we can expect further refinement and standardization in toxicity evaluation and management.

Other toxicity concerns
As previously referenced, in the ZUMA-1 trial, patients were hospitalized for axi-cel infusion followed by a 7 day observation period. Given its overall safety profile and the timing of potential CRS and neurologic toxicity (median of 2 and 5 days postinfusion, respectively), inpatient administration is currently advised. It is important to note that other serious side effects were also observed in the ZUMA-1 study, such as grade 3 or higher cytopenias including neutropenia (80%), anemia (45%), and thrombocytopenia (40%). In particular, prolonged grade ≥3 cytopenias that did not resolve by 3 months following axi-cel infusion were seen in 17% of patients, including neutropenia in 11%, thrombocytopenia in 7%, and anemia in 3% of patients. Given the risk of prolonged cytopenias, it is our approach to routinely monitor patient’s blood counts following CAR T-cell therapy. Given the heavily pre-treated nature of many patients undergoing this therapy, we also institute prophylactic antibiotics, antivirals, and antifungal medications to mitigate the risk of infectious complications with treatment. Furthermore, it is our practice to consider supplementation with granulocyte colony stimulating factor (G-CSF), for periods of prolonged neutropenia or in the setting of active infection. In relation to long-term SAEs, 10 patients experienced new-onset adverse events 6 months following axi-cel infusion, with the most common being infectious in nature, including pulmonary infections, sepsis, influenza B, and upper respiratory tract infections. These infectious complications were largely manageable, and, encouragingly, there have been no reported cases of late-onset CRS or neurologic toxicity. Longer follow up has revealed one case of myelodysplastic syndrome, one case of mental status change in the setting of a vasovagal episode, and three cases of infectious complications, all deemed unrelated to axi-cel.

Off-tumor, on-target toxicity has also been seen with the development of B-cell aplasia, given that CD19 is similarly expressed on healthy B cells. In the ZUMA-1 study, hypogammaglobulinemia was seen in 15% of patients, and, based on recently updated results, approximately 30% of patients received intravenous immunoglobulins (IVIG) at any point during their treatment course. It is our practice to consider supplementation with IVIG post CAR T-cell therapy in the setting of recurrent or serious infections. Given the nature of genetically modified T cells, there is also a theoretical concern regarding insertional mutagenesis and development of secondary malignancies. Thankfully, to date, there have been no reported cases, though patients do require long-term monitoring to assess for such events.

Advances in toxicity grading
Toxicity grading in cellular therapy clinical trials has been an evolving field that has led to the development of multiple competing grading systems. The ZUMA-1 study utilized the modified Lee criteria for CRS grading and CTCAE version 4.03 to categorize neurologic toxicity. Conversely, the JULIET trial, which evaluated another anti-CD19 directed CAR T-cell therapy, tisagenlecleucel, utilized the Penn grading scale for CRS and CTCAE version 4.03 for neurologic toxicity grading. Other toxicity grading scales, such as the Memorial Sloan Kettering Cancer Center (MSKCC) scale and the CARTOX criteria, have also been developed to better define and grade toxicities inherent with cellular therapy treatment. Unfortunately, the evolution of multiple grading platforms has made it challenging to fairly...
compare safety and toxicity among clinical trials and in the commercial setting. Recently, the multiple competing grading schemes for CRS and neurologic toxicity were harmonized by the American Society for Transplantation and Cellular Therapy (ASTCT), in an effort to better characterize safety and facilitate direct comparison of toxicity between trials and in the commercial setting. Moving forward, this new ASTCT consensus grading criteria will ideally be adopted uniformly by treating institutions and incorporated into upcoming clinical trial design to simplify and standardize grading, allowing a more equitable comparison of safety among different cellular therapy products.

Real world experience with axi-cel
Retrospective data from 295 patients treated with commercial axi-cel from 17 academic treatment centers across the United States revealed similar efficacy and toxicity when compared with patients treated in the context of the ZUMA-1 study. Among the 238 patients evaluable for response, the ORR at day 30 was 80%, which compares favorably with the best ORR noted in ZUMA-1. Similarly, the CR rate at day 90 was 57%, as opposed to 58% in the clinical trial. Though limited by a short median follow up of only 3.9 months, axi-cel therapy was associated with a median PFS of 6.18 months, nearly mirroring the 5.8 months seen in the ZUMA-1 trial. In relation to toxicity, all grade CRS was seen in 92% of patients, with 7% demonstrating grade 3 or higher CRS events. Neurotoxicity rates also compared favorably with the ZUMA-1 study, with 33% of subjects experiencing grade $\geq 3$ neurologic toxicity compared with 31% in the clinical trial.

Importantly, 43% of patients treated in this retrospective real-world analysis would not have met the strict ZUMA-1 eligibility criteria at the time of apheresis. The most common criteria making patients ineligible included ECOG performance status $>1$, platelets $<75,000$/mm$^3$, active deep vein thrombosis/pulmonary embolism, renal insufficiency with a glomerular filtration rate $<60$ ml/min/1.73 m$^2$, liver function abnormalities, or a history of CNS lymphoma. A separate multicenter retrospective analysis of axi-cel treatment in aggressive large B-cell NHL included 76 patients with a median age of 64 years. By intention-to-treat-analysis, there was a 62% ORR with 44% of patients achieving a CR. Grade 3 or higher CRS occurred in 16% of patients, and neurotoxicity in 39%. When considering the clinical trial candidacy of this cohort, 29% of patients would not have been eligible for the ZUMA-1 trial based on comorbidities, laboratory parameters, or disease characteristics.

These reports further establish the use of axi-cel in the treatment of aggressive B-NHL with comparable, though albeit slightly lower, responses than those reported in ZUMA-1. Encouragingly, the incidence of serious CRS and neurologic toxicity compares favorably with the clinical trial experience, despite a significant percentage of patients treated not fulfilling the strict ZUMA-1 eligibility criteria. It should be emphasized that such data are very immature, and continued follow up will be important to better characterize the long-term safety and efficacy of axi-cel in the commercial setting.

Biomarkers of efficacy and safety

**Efficacy Biomarkers**
Following infusion, CAR T-cells undergo duplication and expansion. Within the context of the ZUMA-1 study, CAR T-cell levels were noted to peak at approximately day 7 after infusion, and were detectable in the majority of patients at day 180. Furthermore, peak expansion of CAR T-cells by day 28, as measured by the area under the curve (AUC), was 5.4 times as high in responding patients versus nonresponders ($p < 0.001$). Similar findings were also demonstrated in other CAR T-cell trials. Based on available data, it appears that the magnitude of CAR T-cell expansion may be a key predictor of efficacy with axi-cel.

Recent data have provided a clearer understanding of axi-cel persistence and its role in maintaining responses. In the 2-year update of the ZUMA-1 study, detectable CAR T-cells were seen in 66% of patients who maintained a response at 24 months following infusion. In this population, continued response was seen in both those with and without detectable CAR T-cell levels. This data would suggest that axi-cel persistence is not required for patients to maintain long-term remission. This is also corroborated by long-term follow up from the NCI that suggests that remissions may be maintained in the setting of limited-to-no
Within the ZUMA-1 study, response assessment first occurred at 4 weeks following axi-cel infusion, with subsequent imaging at the 3-month mark, and then every 3 months thereafter. While the best ORR was 82% at first disease assessment, over half of progressive events occurred by 3 months. The high response rate at the first disease assessment may partly be an artifact of the lymphodepleting chemotherapy, though fludarabine and cyclophosphamide are not traditionally thought to be highly active in aggressive lymphomas. Achieving a response at month 3 appears to be a clinically relevant milestone, with those demonstrating either a PR or CR at the 3-month assessment having a nearly 80% chance of maintaining that response at month 12.

Safety biomarkers
In terms of toxicity, it appears that CAR T-cell peak expansion and AUC within the first 28 days following axi-cel infusion correlated with grade 3 or greater neurologic events, but not CRS. Similarly, elevations in biomarkers including granulocyte-macrophage colony stimulating factor (GM-CSF), ferritin, and IL-2 were also associated with grade ≥3 neurologic toxicity, but not CRS events. Conversely, both grade 3 or higher CRS and ICANS correlated with several biomarkers, including proinflammatory cytokines like IL-6 and IL-2Rα, immune modulating cytokines like IL-10, and proliferative cytokines such as IL-15.

In a recent update of the ZUMA-1 data, investigators also analyzed the association between tumor burden, as estimated by the sum of product diameters (SPD) of index lesions, and safety and efficacy outcomes. Based on the analysis, there was a lower occurrence of CRS and ICANS in patients with the lowest tumor burden. Similarly, patients with the lowest tumor burden appeared to demonstrate higher ORRs (89%) and CR rates (67%) as compared with those with larger burdens of disease (as assessed by SPD). Cumulatively, this data would suggest that patients entering axi-cel therapy with a lower burden of disease may demonstrate favorable outcomes in terms of both safety and efficacy metrics. Long-term follow up will be paramount in order to determine if this disease phenotype is also associated with durable responses.

Conclusions and future directions
The development of CAR T-cell therapy represents a significant advance for patients with relapsed or refractory, aggressive large B-cell lymphoma. The dramatic responses demonstrated in the ZUMA-1 study, including high ORRs and CR rates, will likely lead to a paradigm shift in our management. Importantly, based on the available data, responses appear to be durable for a subset of patients with median follow up now exceeding 2 years.

CRS and neurologic toxicity represent the two principal acute toxicities of axi-cel therapy, and were largely manageable in the ZUMA-1 study with supportive care measures and anticytokine therapy. In addition, updated 2-year follow-up data demonstrates a rare incidence of late onset SAEs. Preliminary studies evaluating axi-cel in the commercial setting also show comparable efficacy and safety with ZUMA-1, despite the fact that greater than 40% of patients would not have been candidates for the original trial. This data suggests that axi-cel is a feasible treatment approach for patients with relapsed or refractory aggressive large B-cell lymphoma, including those who would not have met the stringent eligibility criteria of the pivotal clinical trial.

Moving forward, a more comprehensive understanding of the underpinnings of CRS and ICANS may aid in refining management strategies in order to mitigate toxicities and potentially expand the pool of eligible patients for this type of therapy. While CAR T-cell therapy does hold tremendous promise for patients, there is still a large subset who may not initially respond to therapy, or later demonstrate relapsed disease. Further characterizing the mechanisms of CAR T-cell resistance and relapse will be key in developing therapeutic
strategies in order to overcome these mechanisms. Similarly, gaining a better understanding of predictors of response and toxicity will be instrumental to the overall care of patients, and may facilitate therapeutic approaches aimed at minimizing toxicity and maximizing efficacy.

Several challenges lie ahead before CAR T-cell therapy gains more widespread use, including issues surrounding access and availability, cost, and toxicity. It is the hope that data from ongoing clinical trials, in combination with our growing experience in the commercial setting, will lead to further refinement and optimization of both the safety and efficacy of CAR T-cell therapies in lymphoma.

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References


38. Kochenderfer JN, Somerville RPT, Lu T, et al. Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated...


