CCR Drug Updates

Clinical Cancer Research

FDA Approval Summary: Axicabtagene Ciloleucel for Relapsed or Refractory Large B-cell Lymphoma

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Abstract

In October 2017, the FDA granted regular approval to axicabtagene ciloleucel, a CD19-directed chimeric antigen receptor (CAR) T-cell therapy, for treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. Efficacy was based on complete remission (CR) rate and duration of response (DOR) in 101 adult patients with relapsed or refractory large B-cell lymphoma (median 3 prior systemic regimens) treated on a single-arm trial. Patients received a single infusion of axicabtagene ciloleucel, preceded by lymphodepleting chemotherapy with cyclophosphamide and fludarabine. The objective response rate per independent review committee was 72% [95% confidence interval (CI), 62–81], with a CR rate of 51% (95% CI, 41–62). With a median follow-up of 7.9 months, the median DOR was not reached in patients achieving CR (95% CI, 8.1 months; not estimable, NE), whereas patients with partial remission had an estimated median DOR of 2.1 months (95% CI, 1.3–5.3). Among 108 patients evaluated for safety, serious adverse reactions occurred in 52%. Cytokine release syndrome and neurologic toxicities occurred in 94% and 87% of patients, respectively, leading to implementation of a risk evaluation and mitigation strategy.

Introduction

Although standard chemoimmunotherapy is considered curative for more than half of all patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL), an estimated 20% to 30% relapse after an initial remission, and an estimated 10% of patients have primary refractory disease (1, 2). High-dose chemotherapy with autologous hematopoietic stem cell transplantation (HSCT) is the usual standard for first relapse of DLBCL, provided that the relapse is chemosensitive, and can cure a subset of patients. However, over 50% of such relapses can be resistant to second-line therapy (3), typically precluding HSCT. There is no universal standard of care for such patients, or for patients who are ineligible for HSCT due to comorbidities or who relapse despite HSCT (1, 4, 5). Outcomes tend to be poor with DLBCL that is refractory or relapses early after autologous HSCT (6–8). In a meta-analysis of over 500 such patients, the objective response rate (ORR) to subsequent therapy was 20% to 30%, complete remission (CR) rates were $\leq$15%, and the median overall survival was 6 months (6).

Axicabtagene ciloleucel (YESCARTA; Kite Pharma, Inc.) is an immunotherapy consisting of autologous T cells that have been transduced with a retroviral vector encoding an anti-CD19 chimeric antigen receptor (CAR). On October 18, 2017, after a priority review, the FDA granted regular approval to axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (9). Axicabtagene ciloleucel is not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma. Herein, we provide a summary of the FDA clinical review and rationale for regular approval of this marketing application.

Drug Product

Axicabtagene ciloleucel is produced from the patient's peripheral blood mononuclear cells collected by apheresis. The mononuclear cells are enriched for T cells, activated with recombinant human IL2 and anti-CD3 antibody, and transduced with a replication-incompetent retroviral vector expressing the anti-CD19 CAR transgene. The CAR protein has a CD19-specific, murine single-chain variable fragment linked to two costimulatory domains derived from human CD3-ζ and CD28 genes (10). The transduced T cells are expanded in cell culture and delivered cryopreserved in a patient-specific infusion bag(s). After engagement of the anti-CD19 CAR T cells with CD19-expressing target cells, the costimulatory domains in the CAR construct activate downstream signaling cascades that lead to T-cell activation,

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proliferation, effector functions, and secretion of inflammatory cytokines and chemokines (10). This in turn promotes apoptosis and necrosis of the target cells, which include CD19-expressing cancer cells and normal B cells.

The target dose is a single infusion of 2×10^6 CAR-positive T cells per kg, with a maximum allowable dose of 2×10^8 CAR T cells. To facilitate CAR T-cell engraftment and expansion, lymphodepleting chemotherapy is administered prior to infusion of axicabtagene ciloleucel (cyclophosphamide 500 mg/m^2 i.v. and fludarabine 30 mg/m^2 i.v. both given on the fifth, fourth, and third day before infusion). In patients treated with this regimen, following infusion of axicabtagene ciloleucel, the CAR T cells exhibited an initial rapid expansion achieving maximal concentrations within the first 7 to 14 days, followed by a decline to near-baseline levels by 3 months (9).

Clinical Trial Design

The basis of approval is a single-arm, open-label, multicenter phase 1/II trial (ZUMA-1; NCT02348216) in adults with aggressive B-cell non-Hodgkin lymphoma (NHL), with a primary efficacy endpoint of ORR per investigator assessment after a single infusion of axicabtagene ciloleucel. Eligible patients had disease that was refractory to the most recent therapy or that relapsed within 1 year after autologous HSCT. The study excluded patients with prior allogeneic HSCT, prior CD19-directed therapy, or any history of central nervous system (CNS) involvement by lymphoma and required an Eastern Cooperative Oncology Group (ECOG) performance status <2, absolute lymphocyte count $\geq$100/μL, creatinine clearance $\geq$60 mL/min, hepatic transaminases $\leq$2.5 times the upper limit of normal, cardiac ejection fraction $\geq$50%, and absence of active infection.

In the phases I and II portions combined, 119 patients underwent leukapheresis and 108 patients were treated with axicabtagene ciloleucel, which was preceded by fludarabine/cyclophosphamide at the approved dose-schedule. The trial did not permit bridging therapy between leukapheresis and lymphodepleting chemotherapy. All patients were hospitalized for the CAR T-cell infusion and for a minimum of 7 days afterward.

Results

Efficacy

In the phase II portion, 101 of 111 patients who underwent leukapheresis received axicabtagene ciloleucel and comprise the main efficacy population. One of 111 patients (approximately 1%) did not receive the product due to manufacturing failure. Nine other patients were not treated, primarily due to progressive disease or serious adverse reactions (AR) following leukapheresis. The median time from leukapheresis to product delivery was 17 days (Table 1).

Table 1 summarizes the characteristics and outcomes of the phase II efficacy population. The median age was 58 years with 24% being aged $\geq$65. Most patients (76%) had *de novo* DLBCL, 16% had transformed follicular lymphoma (FL), and 8% had PMBCL. This was an especially poor-risk group of patients, with a median of three prior lines of therapy and with 77% having disease refractory to a second or greater line. Twenty-six percent of patients had a history of primary refractory disease, more than half (54%) had refractoriness to $\geq$2 consecutive lines of therapy, 26% had refractoriness to $\geq$3 consecutive lines, and 25% had prior autologous HSCT. However, all patients had an ECOG performance status of 0 or 1 per protocol requirement.

Among the 101 treated patients, the ORR as determined by an independent review committee (IRC) was 72%, with a CR rate of 51% [95% confidence interval, 41–62; Table 1]. The concordance between ORR per IRC and ORR per investigator was 79%. On intention-to-treat analysis, using as the denominator all patients in the phase II who underwent leukapheresis, the ORR per IRC was 66%, with a CR rate of 47% (95% CI, 37–57).

Figure 1 shows a waterfall plot, displaying reduction in disease burden in relation to the best overall response (BOR). The median maximal concentration (C_{max}) and median area under the curve (AUC_{0-28d}) of the CAR T cells were approximately two fold higher in responding patients than in patients who did not achieve a response.

Response durations tended to be longer in patients with a BOR of CR, as compared with a BOR of partial remission (PR). With an estimated median follow-up of 7.9 months, the median DOR per IRC had not been reached in patients achieving CR (95% CI, 8.1 months; not estimable, NE). In contrast, the estimated median DOR among patients in PR was 2.1 months (95% CI, 1.3–5.3). Of the 52 patients who achieved CR, 14 initially had stable disease (seven patients) or PR (seven patients), with a median time to improvement of 2.1 months (range: 1.6–5.3 months).

Safety

The prescribing information for axicabtagene ciloleucel contains boxed warnings for cytokine release syndrome (CRS) and neurologic toxicities, which in both cases have included fatal and life-threatening reactions. Other Warnings and Precautions in the prescribing information include hypersensitivity reactions, serious infections, prolonged cytopenias, hypogammaglobulinemia, second malignancies, and, due to the potential for neurologic events, restrictions on driving and other activities.

Safety was evaluated in all 108 patients who received an infusion of axicabtagene ciloleucel in ZUMA-1.

Of 34 deaths that occurred during the main safety evaluation period, four were attributed to reasons other than disease progression: three to CRS and one to pulmonary embolism. One patient, who died of disease progression, had ongoing CRS symptoms. All patients experienced at least one AR, and serious ARs were reported in 52% of patients. The most common grade $\geq$3 ARs (incidence $\geq$10%) were neurologic toxicities (31%), infections (23%), fever (16%), CRS (13%), hypotension (15%), and hypoxia (11%). Other serious ARs included pulmonary edema (9%), cardiac failure (6%), fungal infections (5%), renal insufficiency (5%), cardiac arrest (4%), seizures (4%), and capillary leak syndrome (3%). The most common ARs are shown in Table 2.

The most common (>10%) laboratory abnormalities that worsened from grade 0 to 2 to grade 3 to 4 included lymphopenia (100%), neutropenia (93%), anemia (66%), thrombocytopenia (58%), hypophosphatemia (50%), hyponatremia (19%), increased uric acid (13%), increased direct bilirubin (13%), hypokalemia (10%), and increased alanine aminotransferase (10%). Hypogammaglobulinemia grade 1 was reported in 15% of patients.

Figure 2 illustrates the time course and prevalence of CRS and neurologic toxicity. CRS was near universal, occurring in 101 (94%) patients, including grade $\geq$3 CRS (per modified Lee

Table 1. Characteristics and outcomes of efficacy population

Parameter		Phase II patients treated ($N = 101$ from 111)
Patient and treatment characteristics		
Proportion of enrolled patients		91%
Age, years	Median (range)	58 (23, 76)
	>65	24 (24%)
ECOG performance status	0 or 1	101 (100%)
Diagnosis per investigator	*De novo* DLBCL	77 (76%)
	Transformed FL	16 (16%)
	PMBCL	8 (8%)
Reported double or triple hit	Yes	32 (32%)
Prior lines of systemic therapy	Median (range)	3 (1, 10)
	1	2 (2%)
	2	29 (29%)
	3	30 (30%)
	>4	40 (40%)
Prior autologous HSCT	Yes	25 (25%)
Refractoriness to most recent therapy	Primary refractory	2 (2%)
	Refractory to second or greater line	78 (77%)
	Relapse <1 year after auto HSCT	21 (21%)
History of refractoriness	Ever primary refractory	26 (26%)
	Refractory to ≥2 consecutive lines	54 (54%)
	Refractory to >3 consecutive lines	26 (26%)
Days from apheresis to CAR T delivery[a]	Median (range)	17 (14, 51)
	25th, 75th percentile	16, 18
CAR T-cell dose ($\times 10^6$ CAR T cells/kg)	Median (range)	2.0 (1.1, 2.2)
Efficacy outcomes		
Response per IRC	Objective response[b]	73 (72%)
	(95% CI for ORR)	(62, 81)
	CR	52 (51%)
	(95% CI for CR rate)	(41, 62)
	PR	21 (21%)
	(95% CI for PR rate)	(13, 30)
	Stable or progressive disease	26 (26%)
	Not evaluable	2 (2%)
Time to response, months	Median (range)	0.9 (0.8, 6.2)
Estimated median DOR (95% CI), months	All responding patients	9.2 (5.4, NE)
	Patients with best response of CR	NE (8.1, NE)
	Patients with best response of PR	2.1 (1.3, 5.3)

Abbreviations: CR, complete remission; FL, follicular lymphoma; IRC, independent review committee; NE, not estimable; PR, partial remission.
[a]For the 110 of 111 patients in the phase II portion who had product successfully manufactured.
[b]Modified intention-to-treat analysis using 2007 revised International Working Group criteria.

2014 criteria; ref. 11) in 14 (13%) patients. The median time to onset of CRS was 2 days after CAR T-cell infusion (range, 1–12 days; Fig. 2), and the median CRS duration was 7 days (range, 2–58 days) with 75% of cases resolving in 13 days. The most common CRS symptoms included fever, hypotension, tachycardia, hypoxia, and chills. Serious events included cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Of the 101 patients with CRS, 49 were treated with tocilizumab, 19 of whom received more than one dose. The majority of CRS symptoms resolved with treatment and supportive care, although 25% of patients had CRS lasting more than 2 weeks. Issues requiring prolonged hospitalization included infection, cardiac issues, and renal complications.

Neurologic toxicities, which were broadly defined by FDA as all events classified as nervous system disorders or psychiatric disorders, were reported in 94 (87%) patients, including 34 (31%) patients with grade ≥3 neurologic toxicities (Fig. 2). Serious or fatal cerebral edema has developed in other recipients of axicabtagene ciloleucel. In ZUMA-1, the median time to onset of neurologic toxicity was 4 days (range 1–43 days), and the median duration of 17 days with 75% of cases resolving in 33 days. Almost all grade ≥2 neurologic toxicities occurred within 7 days following axicabtagene ciloleucel infusion. With a narrower definition of neurologic toxicity as proposed by the Applicant (12), the incidence of all-grade neurologic toxicity was >20% lower, but with a similar incidence of grade ≥3 neurologic toxicities (Fig. 2). The most common manifestations of neurologic toxicities included encephalopathy, headache, tremor, dizziness, aphasia, and delirium. Neurologic toxicities were managed with supportive care and/or corticosteroids.

Figure 2 illustrates the time course and prevalence of CRS and neurologic toxicity. Combined, these toxicities affected almost all patients 104 (96%), with 85 patients (79%) experiencing both toxicities. Of these, 75% (64/85) of patients experienced neurologic toxicity events that occurred after CRS onset, and 25% (21/85) of patients experienced neurotoxicity events before CRS onset. Five patients experienced neurologic toxicities without CRS. Ten patients had neurologic toxicities that began after CRS had resolved. Thus, 63% (54/85) of neurologic toxicities occurred during the CRS events. C_{max} and AUC_{0-28d} tended to be higher in patients with grade ≥3 neurologic toxicities or grade ≥3 CRS.

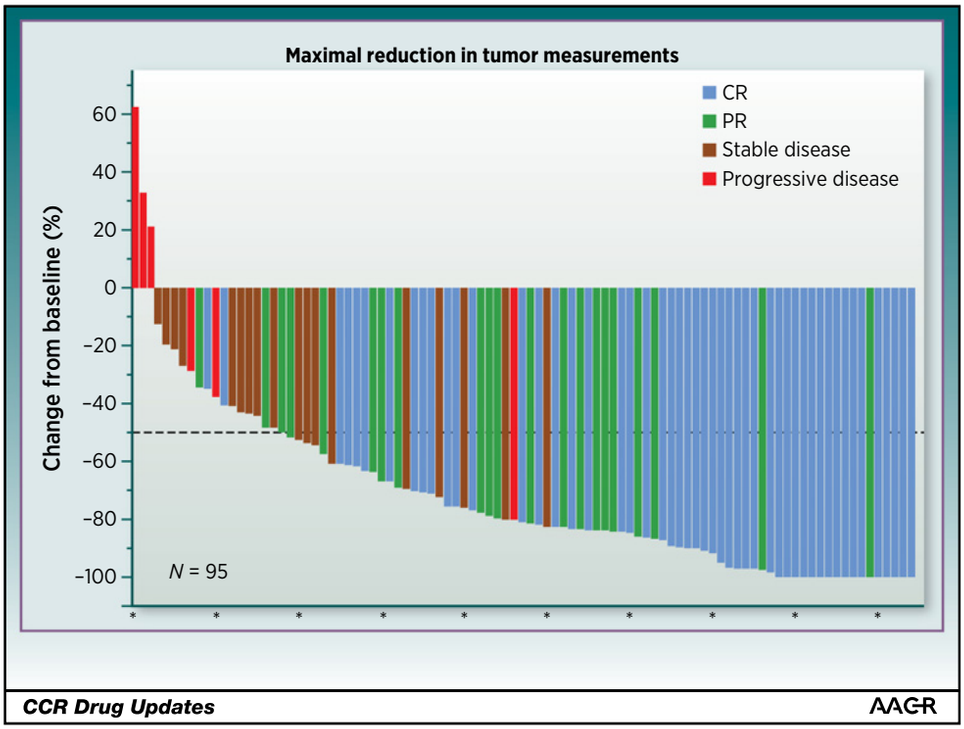

Figure 1.
Waterfall plot of response per IRC. Disease burden is represented by the sum of the products of greatest diameter of target lesions. Of 101 treated patients in the phase II portion, 99 were response evaluable and outcomes of 95 are shown. The four patients not shown had nonmeasurable target lesions at baseline; two had CR, one had stable disease, and one had progressive disease per IRC assessment.

Treatment with axicabtagene ciloleucel may result in B-cell aplasia and acquired hypogammaglobulinemia from loss of normal B cells. Of the 108 patients treated, the majority had low B-cell levels at baseline, and 23 (21%) received supplemental intravenous gamma globulin.

Regulatory Insights

Axicabtagene ciloleucel is the first CAR T-cell product approved for the treatment of lymphoma. FDA granted regular, rather than accelerated, approval based on single-arm trial data given the CR rate, durability of response, and paucity or absence of treatment options in a patient population with particularly poor-risk disease. Preliminary data from this trial had supported a Breakthrough Therapy Designation in refractory aggressive NHL. In May 2018, tisagenlecleucel also received regular approval for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy. Tisagenlecleucel was the first CAR T-cell product to receive FDA approval, with an initial indication in B-cell precursor acute lymphoblastic leukemia. The use of these agents represents a new treatment paradigm for patients with selected hematologic malignancies.

FDA carefully considered the wording of the indication statement. The Applicant sought an indication for the treatment of relapsed/refractory aggressive B-cell NHL in patients who are ineligible for autologous HSCT. The review team determined that, for this particular product, the term "transplant ineligible" is potentially problematic because of its ambiguity, since reasons for transplant ineligibility are varied and include not only failure to achieve the remission typically required for HSCT, but presence of prohibitive comorbidities. The latter, in turn, may increase the risks of or reduce the tolerability of CAR T cell therapy. Thus, the approved indication is based on the number of prior therapies rather than on transplant eligibility. Although ZUMA-1 enrolled patients with primary refractory disease, only two patients received axicabtagene ciloleucel for this reason, and both achieved PR only. Particularly given the toxicity concerns, FDA concluded that a favorable benefit/risk balance of axicabtagene ciloleucel, as compared to standard later-line therapies, had not been established for patients having failure of one prior line. The indication was therefore restricted to lymphoma that had failed at least two prior lines of systemic therapy.

FDA also deliberated which types of NHL to include in the indication statement. The diagnoses in the study datasets did not necessarily follow the WHO classification terminology. To align the indication statement with current terminology, the indication statement included the main types of lymphoma that were studied in ZUMA-1, namely DLBCL not otherwise specified, PMBCL, high-grade B-cell lymphoma (which includes "double hit" lymphoma), and DLBCL arising from follicular lymphoma. However, other variants of large B-cell lymphoma have a similarly poor prognosis in the relapsed/refractory setting, such as T-cell rich large B-cell lymphoma. In an effort to be as inclusive as possible, the review team thus recommended a broad indication for "large B-cell lymphoma," recognizing that this category

Table 2. Most common ARs (incidence ≥20% any grade or ≥5% grade 3 or higher)

AR[a]	Percentage with AR ($N = 108$)	
	Any grade	Grade 3 or higher
Cardiac or vascular disorders		
Hypotension	57	15
Tachycardia	57	2
Arrhythmia	23	7
Hypertension	15	6
Gastrointestinal disorders		
Diarrhea	38	4
Nausea	34	0
Vomiting	26	1
Constipation	23	0
General disorders		
Fever	86	16
Fatigue	46	3
Chills	40	0
Immune system disorders		
CRS	94	13
Infections		
Infections, pathogen unspecified	26	16
Bacterial infections	13	9
Investigations		
Decreased appetite	44	2
Nervous system or psychiatric disorders		
Encephalopathy	57	29
Headache	45	1
Tremor	31	2
Dizziness	21	1
Aphasia	18	6
Delirium	17	6
Respiratory disorders		
Hypoxia	32	11
Cough	30	0
Renal and urinary disorders		
Renal insufficiency	12	5

[a]Includes grouped preferred terms. Refer to Prescribing Information for definitions.

includes some rare lymphomas with unique biology. Axicabtagene ciloleucel is not, however, indicated for primary CNS lymphoma because of the absence of safety and efficacy data.

The depth and durability of response were the key determinants of efficacy. However, the evaluation of DOR was limited by the large amount of censoring before 6 months. Forty-four percent of responding patients were censored for DOR per IRC, and longer follow-up would better inform DOR in >80% of these patients. Because of early censoring, the estimate for median DOR, particularly for patients with a best response of CR, is potentially unstable. Longer follow-up would thus be required to characterize the durability of the treatment effect. Despite this limitation, in this poor-risk group of patients, the magnitude and observed durations of the treatment effect, among those with a best response of CR, is clinically meaningful. The observed benefit is less clear for patients with a BOR of PR, as these responses tend to be less durable. Therefore, although the primary endpoint of ZUMA-1 was ORR, the regulatory decision was based on CR rate and DOR.

Notably, the ZUMA-1 protocol did not permit bridging therapy between leukapheresis and conditioning. However, the manufacturing time for axicabtagene ciloleucel (median 17 days to site delivery) may be prohibitive for some patients with rapidly progressive lymphoma. In the phase II portion, 9% of patients who underwent leukapheresis were unable to receive the CAR T-cell infusion, mainly due to adverse events.

In interpreting this trial's outcomes, it is also important to consider the eligibility criteria in ZUMA-1, which were relevantly stringent. The safety population is not necessarily representative of many patients with relapsed or refractory, aggressive lymphoma. The safety of this therapy in patients with poor performance status, end-organ dysfunction, or other comorbidities is not defined. There were too few patients aged 65 years or older to determine to what extent efficacy and safety differ according to age.

CRS and persistent hypogammaglobulinemia are among the serious risks of axicabtagene ciloleucel related to its mechanism of action. The mechanism of the neurologic toxicities is not well-understood and may involve cytokine-mediated endothelial dysfunction (13). Accurately capturing the incidence of neurologic toxicity poses challenges, given that many manifestations, such as headache, confusion, somnolence, and impaired memory, are nonspecific, and definitions of neurologic toxicity vary. Interestingly, despite these challenges, the incidence of grade 3 or higher neurologic toxicities when defined by narrow or broad criteria was essentially the same, affecting approximately 30% of patients (Fig. 2).

During the trial, life-threatening and fatal toxicities were mitigated by mandated site and investigator training, careful site selection and monitoring, and management guidelines for early detection and treatment of serious complications (including having tocilizumab available for CRS management prior to CAR T-cell infusion, and requiring in-patient monitoring for 7 days following the infusion). The severe, life-threatening, and fatal ARs warranted a boxed warning for CRS and neurologic toxicities. To mitigate fatal and serious risks post-approval, FDA determined that a Risk Evaluation and Mitigation Strategy (REMS) was necessary to ensure the safe use of axicabtagene ciloleucel. The review team extensively discussed the patient monitoring element of the REMS, including whether to require inpatient monitoring following infusion of axicabtagene ciloleucel. In contrast to the ZUMA-1 protocol, the prescribing information for axicabtagene ciloleucel does not mandate hospitalization for the infusion and initial post-infusion monitoring. However, FDA determined that patients should be monitored at least daily for 7 days following infusion at a certified health care facility. Furthermore, patients should remain within proximity of that health care facility for at least 4 weeks following infusion.

The genetic modification of axicabtagene ciloleucel triggers an additional safety concern. Generation of replication-competent retrovirus during the manufacturing process for axicabtagene ciloleucel is a theoretical safety concern. Additionally, insertional mutagenesis due to vector integration is a potential risk for inducing secondary malignancies. Integration of the vector into the patient's cells might inadvertently activate a cellular proto-oncogene or disrupt a tumor suppressor gene, leading to malignant transformation events. Cases of late onset secondary malignancies associated with insertional mutagenesis have been reported with other genetically-modified cell products (14, 15). Long-term safety following axicabtagene ciloleucel treatment remains important due to the limited follow-up duration. Therefore, a postmarketing requirement (PMR) study was issued with the approval. This PMR requires 15 years of follow-up for patients treated with axicabtagene ciloleucel to assess its long-term toxicities.

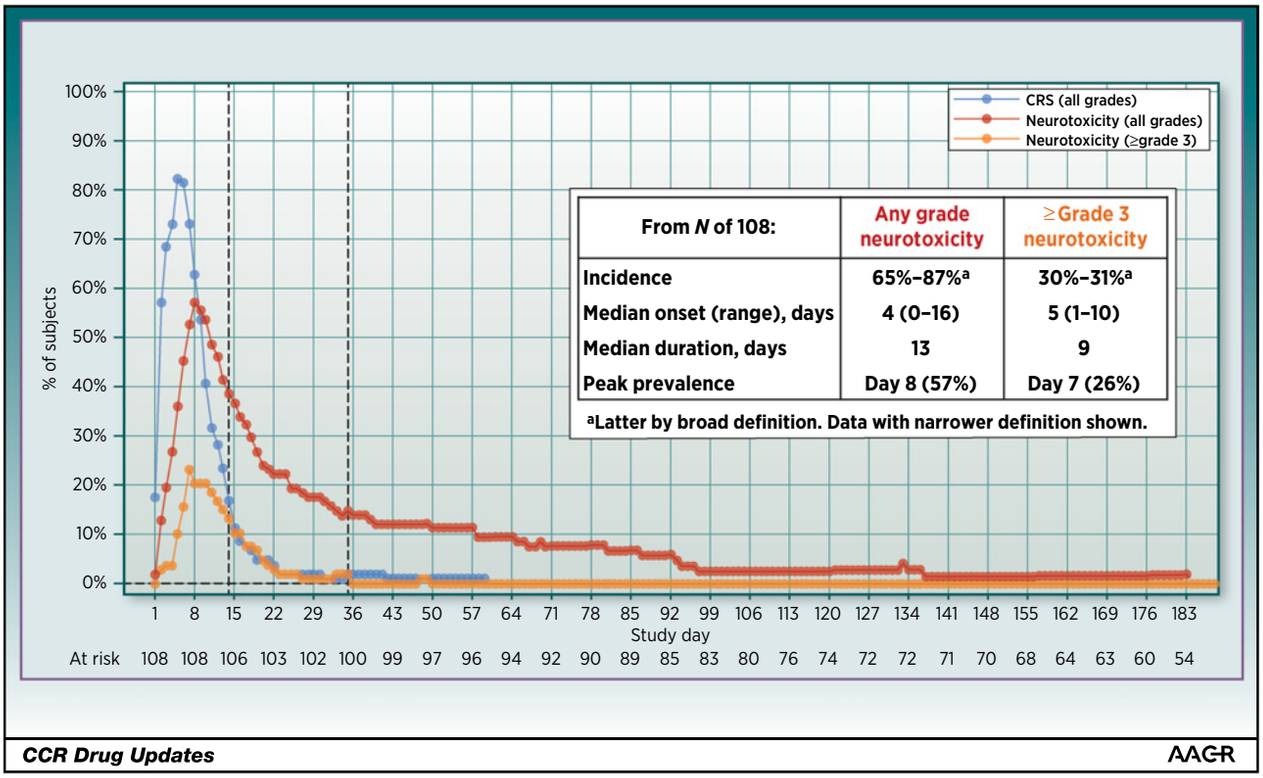

Figure 2.
Time course of CRS and neurologic toxicity. The day of axicabtagene ciloleucel infusion is designated study day 1.

Conclusions

Patients with relapsed or refractory large B-cell lymphoma have unmet medical needs. The ZUMA-1 results demonstrate the meaningful clinical efficacy of axicabtagene ciloleucel. CRS and neurologic toxicities led to risk mitigation measures. However, based on the magnitude and durability of response, coupled with a rigorous risk mitigation plan in place, the overall benefitrisk profile is favorable. Axicabtagene ciloleucel is a new therapeutic option in a setting where there was previously no approved therapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The Editor handling the peer review and decision-making process for this article has no relevant employment associations to disclose.

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