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Guidelines

Use of Chimeric Antigen Receptor T Cell Therapy in Clinical Practice for Relapsed/Refractory Aggressive B Cell Non-Hodgkin Lymphoma: An Expert Panel Opinion from the American Society for Transplantation and Cellular Therapy

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A B S T R A C T

Axicabtagene ciloleucel (YESCARTA; Kite Pharma, a Gilead Company, Los Angeles CA) and tisagenlecleucel (KYMRIAH; Novartis Pharmaceuticals Corp., Basel, Switzerland) are two CD19-directed chimeric antigen receptor (CAR) T cell products currently approved by the US Food and Drug Administration; the European Medicines Agency; Health Canada; Ministry of Health, Labor and Welfare (Japan); and Therapeutic Goods Administration (Australia) for treatment of specific subtypes of relapsed/refractory aggressive B cell non-Hodgkin lymphoma (NHL). Although this approval has been transformative in the use of cellular immunotherapy in lymphoma, there are concerns regarding appropriate use of this novel therapy and of short- and long-term toxicities. To address these issues, representatives of the American Society of Transplantation and Cellular Therapy convened to recognize and address key issues surrounding the clinical application of CD19 CAR T cell therapy in B cell lymphomas, in collaboration with worldwide experts. The aim of this article is to provide consensus opinion from experts in the fields of hematopoietic cell transplantation, cellular immunotherapy, and lymphoma regarding key clinical questions pertinent to the use of CD19 CAR T cell products for the treatment of NHL. As the clinical practice using CAR T cells grows worldwide, we anticipate that this guidance will be relevant for hematology/oncology physicians who care for patients with lymphomas.

INTRODUCTION

Chimeric antigen receptor T cell (CAR-T) therapy targeting CD19 has shown promising responses in patients with non-Hodgkin lymphoma (NHL) [1,2]. Second-generation CAR-Ts are genetically modified to express CARs that consist of an extracellular or "antigen-binding" domain with both heavy and light single-chain variable fragments that direct specificity to an antigen (eg, CD19 expressed on B cells in the case of the regulatory approved CAR-T), a transmembrane hinge, and an intracellular T cell–activating domain containing a co-stimulatory domain (CD28 or 4-1BB) and T cell receptor signaling domain (CD3-zeta). CARs recognize the single-chain variable fragment–specific antigen independently of HLA or MHC, thus overcoming the down-regulation of antigen presentation via HLA/MHC that can be present as 1 mechanism of immune evasion by tumors [3].

Two second-generation CAR-T therapies (axicabtagene ciloleucel [YESCARTA; Kite Pharma, a Gilead Company, Los Angeles CA] and tisagenlecleucel [KYMRIAH; Novartis Pharmaceuticals Corp., Basel, Switzerland]) are currently approved by respective regulatory agencies in the United States, Europe, Canada, Japan, and Australia for use in relapsed/refractory (R/R) aggressive B cell NHL: diffuse large B cell lymphoma (DLBCL), high grade B cell lymphoma, primary mediastinal B cell lymphoma (only for axicabtagene ciloleucel), and transformed follicular lymphoma (Table 1). Among patients who received CD19 CAR-Ts, the best overall response and complete response (CR) rates were 83% and 58%, respectively, in the ZUMA-1 trial (axicabtagene ciloleucel) and 52% and 40% in the JULIET trial (tisagenlecleucel) [1,2,4]. Although median progression-free survival was < 6 months, currently with around 2 years of reported survival follow-up for these pivotal trials, the median duration of response for patients whose disease was noted to have a response was 11.1 months for axicabtagene ciloleucel and has not been reached for tisagenlecleucel [2,4].

Given the relatively recent introduction of CAR-T therapy to standard of care practice, concerns have been raised about important factors involved in safe and appropriate use of this novel treatment approach and the recognition and treatment of side effects. Hence, a global CAR-T task force was convened to identify and address common challenges toward an appropriate and safe use of CAR-T therapy in patients with lymphomas for which these commercial products are currently indicated. The task force was developed to enable expertise from hematopoietic cell transplantation (HCT), cellular therapy, and lymphoma experts along with perspectives from a referring hematology/oncology physician (C.A.K.) and patient advocate (J.M.S.). This task force identified 10 key clinical questions pertinent to CAR-T therapy and provides a consensus opinion for each question regarding the 2 approved CAR-T products in patients with R/R aggressive B cell NHL. Hematologists, oncologists, and/or transplant physicians interested in the use of CAR-Ts in patients with acute lymphoblastic leukemia are referred to a prior expert opinion publication [5].

WHAT ARE THE CRITICAL CONSIDERATIONS FOR REFERRING PATIENTS WITH NHL TO CAR-T THERAPY?

Key referral considerations for CAR-T therapy include history of prior systemic therapies and sequencing thereof, specific disease considerations, patient comorbidities, central nervous system (CNS) involvement, and when and where to refer.

Two CAR-T products are presently approved for aggressive B cell lymphomas in patients with R/R disease after 2 or more prior lines of systemic therapy. The US Fodd and Drug Administration (FDA)-approved indications for axicabtagene ciloleucel and tisagenlecleucel are described in Table 1 and reflect the patient populations included in the pivotal ZUMA-1 and JULIET trials, respectively [1,2]. The prior lines of systemic therapy may include autologous (autoHCT) or allogeneic HCT (alloHCT). Patients with R/R disease who do not have a sufficient response to salvage therapy to be considered for autoHCT could also be evaluated for CAR-T therapy.

With the recent approval of polatuzumab (CD79b directed antibody drug conjugate) in combination with bendamustine and rituximab in patients with R/R DLBCL, careful sequencing of CAR-T is warranted given the risk of prolonged lymphopenia from bendamustine, which could potentially impair T cell collection for future CAR-T manufacturing (Table 2) [6-9]. Because additional therapies are expected to become available for treatment of R/R DLBCL (ie, tafasitamab, a naked CD19 antibody, in combination with lenalidomide), consideration should be given to using therapies with curative potential over palliative therapies (Figure 1) and hence continued follow-up of early-phase trials to understand the curative potential of the novel agents is imperative. With the emergence of other CD19 targeting therapies, it is of scientific and clinical interest to evaluate the best way to sequence CD19 CAR-T with other anti-CD19 therapies for treatment of R/R DLBCL.

Patients with germinal center B cell and non–germinal center B cell of origin by immunohistochemistry and with

Table 1
Registration Trial Eligibility Criteria and Real-World Practice Demographics

	ZUMA-1 (Axicabtagene Ciloleucel) [1]	JULIET (Tisagenlecleucel) [2]	Real World Data Report 1* (Axicabtagene Ciloleucel) [15] (n = 134)
Diagnoses (regulatory-approved indications)	DLBCL not otherwise specified Primary mediastinal large B-cell lymphoma High-grade B-cell lymphoma DLBCL arising from follicular lymphoma	DLBCL not otherwise specified High-grade B-cell lymphoma DLBCL arising from follicular lymphoma	
ECOG PS	0-1	0-1	0-1 (81%) 2 (16%) 3 (3%)
Renal function	GFR ≥ 60 mL/min/1.73 m^2	Cr ≤ 1.5 × ULN or eGFR ≥ 60 mL/min/1.73 m^2	GFR < 60 mL/min/1.73 m^2 in 9% of patients
Liver function	AST/ ALT ≤ 2.5 × ULN, b ilirubin ≤ 1.5 × ULN	ALT ≤ 5 × ULN, bilirubin ≤ 2 mg/dL (direct bilirubin ≤ 1.5 × ULN for patients with Gilbert-Meulengracht syndrome)	Liver enzyme abnormalities 7%
Pulmonary	Pulse oxygenation > 92% at RA	≤ Grade 1 dyspnea, pulse oxygenation > 91% RA	
Cardiac	LVEF ≥ 50%	Hemodynamically stable, LVEF ≥ 45% by ECHO or MUGA	LVEF < 50% in 3% of patients
Hematologic	ANC ≥ 1000/μL ALC ≥ 100/μL Platelets ≥ 75,000/mm^3	ANC > 1000/mm^3 ALC ≥ 300/mm^3 Platelets ≥ 50,000/mm3 Hemoglobin > 8 mg/dL	Platelets < 75,000 in 13%
Exclusion criteria	1. Prior anti-CD19 targeted therapy. 2. History of CNS lymphoma or detectable malignant cells in CSF, brain metastasis. History of or presence of any CNS disorder such as seizure disorder, CVA, dementia, autoimmune disease, or cerebellar disease. 3. Prior alloHCT. 4. History of hepatitis B or Hepatitis C with detectable viral load. 5. HIV-positive patients. 6. Uncontrolled infection. 7. Cardiac atrial or ventricular lymphoma involvement OR history of MI, angioplasty, or unstable angina in preceding 12 months. 8. Autoimmune disease requiring immunosuppression therapy in the preceding 2 years.	1. Prior anti-CD19/ anti-CD3 therapy 2. Active CNS involvement by malignancy 3. Prior alloHCT 4. Uncontrolled active or latent hepatitis B or active hepatitis C 5. HIV-positive patients 6. Uncontrolled active life-threatening infection 7. Unstable angina or MI in the 6 months preceding 8. Uncontrolled cardiac arrhythmia	1. Prior CD19 or CAR-T therapy in 3% of patients 2. History of CNS lymphoma 6% 3. Prior alloHCT in 1%
Medication considerations	1. Steroids/immunosuppressive medications to be avoided > 7 days preceding leukapheresis and 5 days preceding CAR-T infusion	1. Steroids to be stopped > 72 hours 2. Immunosuppression to be stopped ≥ 4 weeks before enrollment	

ALC indicates absolute lymphocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; RA, room air; ULN, upper limit of normal.

* Real-world experience by Jacobson et al. [10] with axicabtagene ciloleucel is not included in this table because the published abstract did not provide the demographic information.

double- and triple-hit gene rearrangements (now reclassified by the World Health Organization as high-grade B cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6) were treated in the pivotal trials, with no differences in responses among the higher risk subtype [1,2,4]. For transformed lymphoma available data and the approved label at this time includes only transformation from follicular lymphoma. Transformation from other indolent lymphoma histologies are being explored in clinical trials, and currently no data outside anecdotal reports are available [10-14]. Clinical testing to demonstrate CD19 expression on lymphoma cells is not a requirement specified by the FDA label for either CAR-T product. Both pivotal trials have reported clinical responses in patients whose tumors were CD19 negative or dim by immunohistochemistry [1,2].

In addition to disease indications, a patient's performance status and comorbidities are important considerations for eligibility. Table 1 summarizes the eligibility criteria used in the 2 pivotal trials and compares them with real-world experience [1,2,15]. Assessment of organ function status in the pivotal trials was used with consideration of the ability of patients to safely receive lymphodepletion chemotherapy and CAR-T infusion and to tolerate CAR-T–related toxicities, including cytokine release syndrome (CRS). Eligibility evaluation for patients considered for commercially available CAR-T therapies should include organ function, especially cardiac, pulmonary, renal, and hepatic, in relation to anticipated ability to tolerate sequela from CRS; and a baseline neurologic examination and evaluation. Additionally, it is important to recognize autoimmune conditions, which can be exacerbated due to "off-target

Table 2
General Considerations for Patients Referred for CAR-T

Treatment Modality	Considerations
Before leukapheresis	• Avoid lymphotoxic therapy, such as combinations including bendamustine, fludarabine, cladribine, pentostatin, to avoid failure of T cell collection for CAR-T production • Avoid immunosuppressive therapy, if possible, in the preceding 2 weeks (4-5 half-lives of the drug) • Avoid corticosteroids, if possible, in the preceding 2-3 days • Individual evaluation of patients who have undergone a prior alloHCT and have grade ≥ III acute or severe chronic GVHD, as there is limited experience using CAR-T in patients with uncontrolled/active GVHD
After leukapheresis (bridging therapy)	
Chemotherapy	• Gemcitabine, etoposide, or platinum agents • Avoid highly toxic regimens that may cause serious side effects and delay/preclude CAR-T infusion
Radiation	• Can be considered for localized bulky/symptomatic disease • Can be continued until the day before lymphodepletion
Corticosteroids	• Pulsed corticosteroids or taper appropriately before lymphodepletion if needed • Stop corticosteroids before lymphodepletion
Nonchemotherapy novel agents	• Ibrutinib: preclinical data to suggest improved persistence and efficacy of CAR-T; can be continued until the day before lymphodepletion if no related cytopenias are noted • Lenalidomide: preclinical data to suggest improved CAR-T efficacy; recommend stopping a week before lymphodepletion to allow count recovery before lymphodepletion • Rituximab, obinutuzumab • Polatuzumab in combination with bendamustine and rituximab (recently approved for R/R DLBCL after 2 lines of therapy)
Anti-CD19 antibodies	• Investigational (eg, tafasitamab in combination with lenalidomide)—unknown effect on CAR-T efficacy

effect" against self-antigens or may increase the risk of severe CRS. Use of immunosuppressive treatment to manage autoimmune conditions may also interfere with T cell collection or CAR-T function. Furthermore, active or uncontrolled infections should be managed before CAR-T therapy. Active infection could be worsened by lymphodepletion chemotherapy that includes fludarabine and severe suppression of humoral immunity by CD19 CAR-Ts. Infections can also result in more severe toxicities because of higher levels of inflammatory cytokines before CAR-T infusion.

With regards to the overall health status of a patient, 1 practical question that arises is whether a patient considered ineligible for autoHCT because of poor organ function or other comorbidities is eligible for CAR-T therapy. Data are emerging among CAR-T therapy centers in the United States regarding outcome of patients who would not have qualified for the ZUMA-1 trial because of comorbidities but were treated with axicabtagene ciloleucel in "real-world" practice [10,15]. Initial data appear to be encouraging and suggest that short-term toxicities after CAR-T infusion and initial response may be similar in patients who would not have qualified for ZUMA-1. However, more experience and longer follow-up are needed to better understand the impact of comorbidities on clinical outcomes with CAR-T. Additionally, because the clinical status

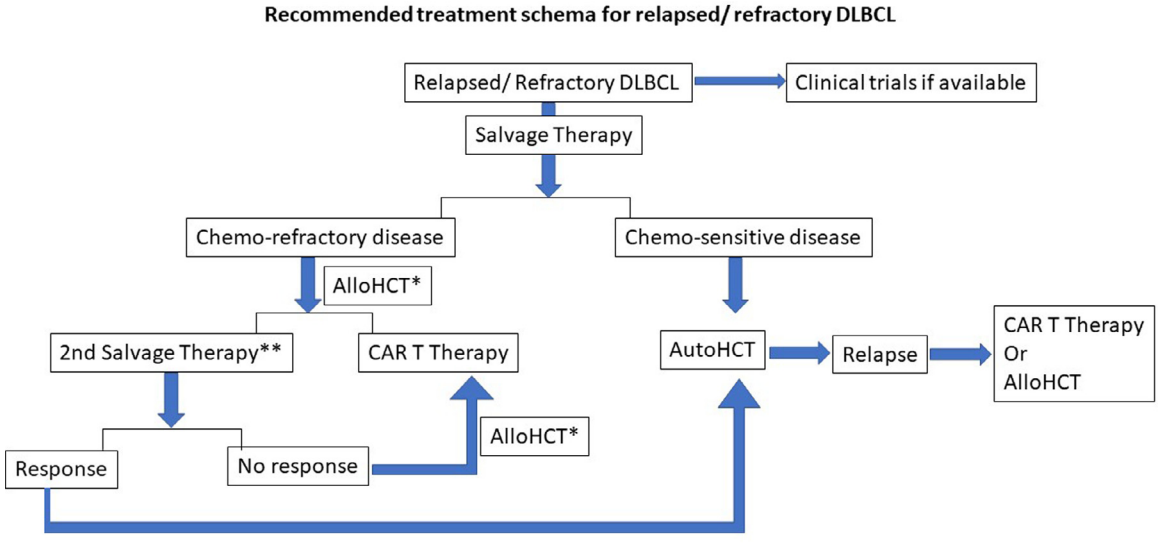

Figure 1. Recommended treatment schema for R/R DLBCL.

of patients can change during the CAR-T manufacturing process, reassessment of patients before initiation of lymphodepletion is also important.

We recommend early referral of patients with R/R aggressive B cell NHL who have primary refractory disease as well as those who progress after second-line therapy to CAR-T centers for evaluation. Early referral is important because of the significant time required to secure approval for treatment and the minimum 3 to 4 weeks manufacturing time between leukapheresis and CAR-T infusion. Another important concern is that the T cell fitness and efficacy of the CAR-T product generated may be compromised in patients who receive multiple lines of chemotherapy [16,17]. To continue to expand the potential clinical applications and to improve on the efficacy and safety of CAR-T therapy, we encourage referral for enrollment onto clinical trials examining additional indications, new CAR-T products, and other aspects of CAR-T therapy in NHL (see What Are the New Advances for CAR-T in Lymphoma? below).

A potential clinical application that requires additional study is secondary CNS involvement by lymphoma. Both the ZUMA-1 and JULIET trials excluded patients with active CNS disease [1,2]. Patients with a prior history of brain metastasis or a history of CNS pathology such as ischemia, dementia, seizure disorder, or autoimmune disease involving the CNS were also excluded from the ZUMA-1 trial. Patients with prior CNS disease were included in the JULIET trial, but the potential effect of past CNS disease on neurotoxicity in these patients remains unknown. In a recent report a series of 8 patients with active secondary CNS lymphoma were treated with commercially available tisagenlecleucel and did not show any increase in neurotoxicity than that observed in the JULIET trial [18]. Two patients were noted to achieve CR and another 2 patients achieved a partial response (PR) at the 1-month assessment, suggesting trafficking of CAR to the CNS and resulting in disease responses similar to systemic disease. Another second-generation CAR-T product, lisocabtagene maraleucel (Juno Therapeutics, Celgene, Seattle, WA), is being studied in a phase I trial including patients with secondary CNS involvement (NCT02631044) and has reported anecdotal experience in 1 patient with safe tolerability [19,20]. Emerging data from clinical trials and real-world practice will further elucidate the clinical situations in which CAR-T therapy can be safely pursued in patients with history or active secondary CNS disease involvement. Currently, there is no clinical experience using CAR-T therapy for patients with primary CNS lymphoma.

The next practical question is where patients should be referred for treatment. At this time CAR-T therapy is only available at selected institutions that have implemented Foundation for Accreditation of Cellular Therapy immune effector cell standards and are certified to prescribe the approved CAR-T therapy (eg, in the United States there are 75 centers for axicabtagene ciloleucel and 62 centers for tisagenlecleucel as of March 30, 2019). The immune effector cell guidelines proposed by the Foundation for Accreditation of Cellular Therapy ensure that certain standards are met with respect to cell collection, processing, and clinical management of patients receiving immune effector cell therapy, including CAR-T. In the United States pharmaceutical companies select and certify treatment institutions in accordance with the FDA-approved Risk Evaluation and Mitigation Strategy (REMS). In Europe selection criteria vary by country, with national health authorities typically playing a role in center selection and accreditation by the Joint Accreditation Committee of the International Society for Cellular Therapy and European Society for Blood and Marrow Transplantation required in at least some countries. Because the number of approved CAR-T products is expected to grow in the future, we recommend continuing to follow the Foundation for Accreditation of Cellular Therapy–Joint Accreditation Committee of the International Society for Cellular Therapy and European Society for Blood and Marrow Transplantation immune effector cell standards as uniform criteria for the purpose of certification of all CAR-T treatment centers and harmonization of REMS for each product whenever possible. This approach will avoid duplication of effort for audit/certification for treatment centers and minimize the risk of errors for handling each CAR-T product.

WHAT ARE THE CRITICAL CONSIDERATIONS FOR THE ROLE OF BRIDGING AND LYMPHODEPLETION CHEMOTHERAPY IN CAR-T TREATMENT?

Bridging Chemotherapy

Patients referred for CAR-T therapy have active, R/R lymphoma to the most recent therapy, indicating aggressive disease biology, and hence are at risk of disease progression while awaiting CAR-T manufacture. With axicabtagene ciloleucel 9% patients on the ZUMA-1 trial (median manufacture time, 17 days) and 7% and 13% patients, respectively, in 2 real-world experiences with the same product were unable to receive CAR-Ts mostly because of disease progression or related adverse events [1,10,15]. With tisagenlecleucel in the JULIET trial (median time from enrollment to infusion, 52 days), 33% patients were unable to receive the CAR-T infusion because of death, progressive disease, adverse events, manufacturing failure, or other reasons [2]. Bridging therapy while awaiting CAR-Ts was allowed on the JULIET trial and was given to 92% patients on the study [2], whereas bridging therapy was not permitted on the ZUMA-1 trial [1]. We caution comparison of the 2 trials because these studies had different CAR constructs, trial design, patient demographics, use of bridging therapy, lymphodepleting regimens, and treatment timing [21]. It is likely that standard of care practice will continue to expand the use of bridging therapy to enable more patients to receive CAR-T therapy. Longer follow-up with more detailed review is needed to understand the impact of bridging therapy on clinical response. Until further data become available to suggest otherwise, patients with lower disease burden or slower disease kinetics who can be closely monitored during the CAR-T manufacturing period may not necessarily require bridging therapy.

In patients with rapidly growing disease, the choice of bridging therapy depends on individual clinical scenarios, including consideration for tolerance and response to prior therapies, location and volume of the disease, comorbidities/pre-existing organ dysfunction, and performance status of the patient. The main goal of bridging therapy is symptom control and disease stabilization. Debulking or disease stabilization in patients with large tumor burden is desirable but may not always be feasible, especially when the disease is refractory to chemotherapy. Therefore, it is important to choose bridging therapy that is not too toxic to avoid serious adverse events that could delay the CAR-T infusion, further complicate potential CRS-related organ dysfunction, or increase risk of cytopenias and infections.

Various bridging therapies that have been used are summarized in Table 2. The optimal choice of bridging therapy remains a research question that warrants further study. Some chemotherapy regimens that have been described include gemcitabine and etoposide or platinum agents [2]. Radiation either alone or in combination with chemotherapy, mostly cyclophosphamide, has been described in some series with no worsening of toxicity and stability of disease in most patients

[2,22,23]. This can be considered especially in patients with symptomatic bulky localized disease. For corticosteroids, pulsed-dose steroids have been used in clinical practice. If higher doses of corticosteroids are used for a prolonged time, a timely taper should be planned before the initiation of lymphodepletion chemotherapy. Among the newer agents, lenalidomide, rituximab, and ibrutinib have been used. Lenalidomide, which is an immunomodulatory agent with potential activity in mostly activated B cell (ABC)-DLBCL, has been shown in preclinical studies to improve antitumor function of CAR-T [24]. Ibrutinib, a BTK inhibitor that also has activity mostly in ABC-DLBCL, was found to improve T cell expansion and improve CAR-T efficacy in preclinical studies [25-27]. These effects on CAR-Ts still remain to be confirmed in human clinical studies. In a recent report 15 patients received high-dose chemotherapy and autoHCT followed by infusion of 19-28z CAR-Ts [28]. This approach was associated with a higher incidence of severe neurotoxicity. Furthermore, the CAR-T products with higher effector immune phenotypes showed a trend toward improved progression-free survival. As data emerge for CD19 directed therapy such as mAbs, it will be prudent to recognize the utility of these newer agents as a bridging therapy.

If the patient is being referred to a CAR-T treatment center, we recommend close coordination in the choice and duration of bridging therapy between the referring physician and the CAR-T treating physician. Additionally, close communication with the CAR-T manufacturing unit is required for early appraisal of any potential delays. We also recommend discontinuing bridging therapy to permit hematologic recovery before lymphodepleting therapy. In general, for chemotherapy bridging a 2- to 3-week waiting period is suggested before initiation of lymphodepletion therapy to ensure adequate blood count recovery. Lenalidomide is usually stopped a week before lymphodepletion, but radiation therapy, ibrutinib, and corticosteroids may be continued until the day before lymphodepletion therapy, provided these interventions do not induce any cytopenias.

Another obstacle encountered in standard of care practice is CAR-T products that do not meet the specifications for release criteria such as cell dose, viability, and IFN-γ production. This finding was reported in around 3% of patients in the standard of care data for axicabtagene ciloleucel and possibly higher with tisagenlecleucel based on the JULIET data and clinical observations [2,15]. The course of action for these patients needs to be determined at the earliest time point possible, which further underscores the need for close communication between the CAR-T treatment center and manufacturer. Options for these patients include infusion of the out-of-specification CAR-T via an expanded access program, repeating leukapheresis and remanufacturing the product, or enrollment on a clinical trial evaluating other novel agents including other CAR-T products.

Lymphodepletion Chemotherapy

Lymphodepletion chemotherapy used before infusion of CAR-Ts is not as myeloablative as the lymphodepletion chemotherapy given with HCT. However, it has been shown to deplete T, B, and natural killer cells. The immune effect impacts more than depletion of these cells, including removing cytokine sinks and making homeostatic cytokines such as IL-7 and IL-15 available for CAR-T expansion, eliminating immunosuppressive elements such as regulatory T cells and myeloid derived suppressor cells, and modulating the tumor microenvironment by decreasing indoleamine 2,3 dioxygenase and increasing costimulatory molecules [29-34]. Another potential mechanism by which lymphodepletion may improve CAR-T efficacy is by preventing induction of T cell immune responses against the murine single-chain variable fragment component of the CAR. Early studies using CAR-T that was different from approved products showed that a combination of fludarabine and cyclophosphamide for lymphodepletion, compared with patients who received cyclophosphamide alone or cyclophosphamide and etoposide, led to improved CAR-T expansion and persistence and higher response rates [13,35]. However, other studies using tisagenlecleucel have shown similar clinical outcomes using non-fludarabine–based lymphodepletion (bendamustine) [2,23]. In general, data exist in support of using lymphodepletion chemotherapy to create a favorable environment for the expansion and persistence of CAR-Ts in vivo, and both approved CD19 CAR-T products have specifications for lymphodepletion chemotherapy (Table 3). In the ZUMA-1 trial all patients received lymphodepletion chemotherapy with cyclophosphamide and fludarabine [1]. In the JULIET trial most patients (73%) received cyclophosphamide and fludarabine, whereas 19% received bendamustine; 8% did not receive any because the WBC count was already $\leq$1000 cells/μL [2]. No differences in clinical responses were noted between patients who received fludarabine/cyclophosphamide versus bendamustine [2]. We recommend following the package insert when selecting the lymphodepletion chemotherapy (Table 3). Dose adjustments may be required based on renal function or other organ toxicity at the time of lymphodepletion. We also recommend adhering, as much as possible, to the timing of lymphodepletion in relation to the CAR-T infusion as indicated for each product and shown in Table 3.

Table 3
Lymphodepletion Chemotherapy per Package Label

CAR-T Product	Lymphodepletion Regimen Options	Timing*
Axicabtagene ciloleucel	Cyclophosphamide (500 mg/m^{2}i.v. daily) and fludarabine (30 mg/m^{2}i.v. daily) for 3 days	Given on days −5, −4, and −3 before CAR-T infusion (14-day delay allowed between lymphodepletion chemotherapy and CAR-T infusion on ZUMA-1)
Tisagenlecleucel	Fludarabine (25 mg/m^{2}i.v. daily) and cyclophosphamide (250 mg/m^{2}i.v. daily) for 3 days Bendamustine (90 mg/m^{2}i.v. daily) for 2 days if a patient experienced a previous grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrates resistance to a previous cyclophosphamide containing regimen. Lymphodepletion chemotherapy may be omitted if a patient's WBC count $\leq 1 \times 10^9$/L within 1 week before CAR-T infusion	CAR T infusion 2-11 days after lymphodepletion chemotherapy

* Although we recommend complying with the package label as much as possible, delays in the timing of lymphodepletion were allowed in ZUMA-1 and JULIET trials and may be considered as clinically indicated. Delay of up to 2 weeks was allowed before the need for assessment and consideration for repeat lymphodepletion chemotherapy before CAR-T infusion.

WHAT IS THE ROLE FOR AUTOHCT VERSUS ALLOHCT VERSUS CAR-T THERAPY FOR PATIENTS WITH RESPONSE TO BRIDGING CHEMOTHERAPY?

Data are lacking to address this question, and it remains unclear what the most appropriate choice of therapy is for patients who achieve a CR with bridging therapy administered during CAR-T manufacturing. In addition, the role of CAR-Ts as a consolidation therapy in patients with no evidence of measurable disease is also unclear. In the JULIET trial, which permitted the use of bridging therapy (92%), 7 patients had a CR in response to bridging chemotherapy and CAR-T expansion was noted in all patients for up to 2 years after infusion, similar to the overall JULIET trial cohort [36]. Additionally, 5 of 7 patients (71%) remained in CR at more than 12 months of follow-up.

Whether each CAR-T therapy product will expand in the absence of measurable disease also remains unclear. Alternative options for patients who achieve CR to bridging therapy could be alloHCT or careful observation. Overall survival has been reported at between 40% and 60% and progression-free survival 30% and 50% at 3 years in patients who undergo alloHCT while in remission for relapsed DLBCL who have previously received multiple lines of treatment including autoHCT [37,38]. Additionally, in older patients (age > 65 years) nonrelapse mortality with alloHCT has been reported to be high at 33%, with overall survival at 3 years of 38% (both significantly inferior compared with younger age groups) [39]. On the other hand, the role of autoHCT is relatively limited in patients with no response to salvage therapy, with relatively poor outcome (progression-free survival of 23% in the CORAL study) [40,41]. Hence, in these clinical scenarios, consideration should be given to consensus conference or tumor board discussions to review individual case scenarios.

WHAT ARE THE CRITICAL CONSIDERATIONS FOR USING CAR-T AFTER ALLOHCT?

Patients who relapse after alloHCT have limited treatment options, and disease progression remains a major cause of death [42,43]. The use of CAR-T therapy after alloHCT has a theoretical concern for new-onset graft-versus-host disease (GVHD) or worsening of pre-existing GVHD. The pivotal ZUMA-1 and JULIET trials excluded patients who had undergone a prior alloHCT [1,2]. However, other series have shown the feasibility and safety of CAR-T therapy in patients with NHL who have previously undergone an alloHCT (Table 4) [11,44-46].

Post-alloHCT CAR-Ts can be donor-derived (ie, derived from T cells of the original alloHCT donor) [44-46] or pseudo–donor-derived (recipient-derived, ie, derived from patient her- or himself after alloHCT), although T cell chimerism may be mostly donor at the time of leukapheresis [11]. All the above reported CAR constructs used a CD28 co-stimulatory domain. Reports of CAR construct including 4-1BB as the co-stimulatory domain (both donor-derived and recipient-derived) have been published in patients with acute

Table 4
Post-AlloHCT CAR-T Therapy in Studies Including Lymphoma Patients

Study	Total No. of Patients Who Received Prior AlloHCT and Individual Diagnosis	T Cell Source/CAR Construct	New/Worsening GVHD Post CAR-T	Response	Comments
Brudno et al., JCO 2016 [44]	20 (DLBCL = 5, MCL = 5, CLL = 5, ALL = 5) (included acute GVHD of grade ≤ I or chronic GVHD ≤ mild global score)	AlloHCT donor-derived/CD28 co-stimulatory domain	Acute: none Chronic: 1 (worsening of prior)	ORR = 8 (40%) CR = 6 (30%)	All had a prior donor lymphocyte infusion without exacerbation of GVHD and did not receive lymphodepletion therapy. These restrictions contributed to the safety of the approach by excluding patients with a higher tendency of developing GVHD and limiting expansion of CAR-Ts.
Kebriaei et al., JCI [46]	19 (DLBCL = 2, ALL = 17)	AlloHCT donor-derived/CD28 co-stimulatory domain	Acute: 2 (skin – treated with topical steroids, liver – died of liver failure with prior liver induced drug toxicity) Chronic: 1 (skin – treated with systemic corticosteroids)	CR = 12 (63%)	CD19 CAR-T developed using a transposon system (Sleeping Beauty), used as adjuvant treatment after autoHCT (n = 9) or alloHCT (n = 19).
Cruz et al., Blood 2013 [45]	8 (Richter's transformation = 2, CLL = 2, ALL = 4)	AlloHCT donor-derived/CD28 co-stimulatory domain	None	CR = 3 (38%), ORR = 4 (50%)	Virus-specific CAR-Ts expanded in vivo
Jain et al., Leukemia 2019 [11]	4 (T cell rich B cell lymphoma = 1, non-GCB DLBCL = 2, transformed marginal zone lymphoma = 1)	Recipient-derived/CD28 co-stimulatory domain	Acute: none Chronic: none*	CR = 1 (33%), ORR = 2 (66%) (day +30)	Recipient derived with donor chimerism 100% donor in 3 patients and 18% donor in 1 patient.

ALL indicates acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; GCB, germinal center B cell; MCL, mantle cell lymphoma; ORR, overall response rate.
* Persistence of pre-existing chronic GVHD in 1 patient.

lymphoblastic leukemia with varying rates of GVHD (3% to 100%) [47-51]. Whether co-stimulation with CD28 poses a lower likelihood of worsening GVHD in these patients is currently unknown. To date, based on limited small case series and studies, GVHD appears to be lower in recipient-derived CAR-Ts compared with donor-derived, likely because of tolerization of T cells in the former [52].

Overall, these reports suggest safe and feasible use of CAR-Ts after alloHCT, without a clinically significant increase in severe GVHD. Of note, in these limited experiences patients with high-grade active GVHD were not considered for CAR-T therapy. In ongoing clinical trials 1 criterion to withhold CAR-T infusion is development of grade II or higher acute GVHD or severe chronic GVHD after leukapheresis. This recommendation is because of concern for suppression of CAR-T activity from the use of systemic immunosuppression to manage GVHD. For patients on treatment for GVHD in whom immunosuppression therapy can be held safely, we recommend stopping systemic immunosuppression therapy at least 2 weeks (or 4 to 5 half-lives of the drug) before leukapheresis. Recipient-derived CAR-T therapy after alloHCT outside of clinical trial is currently an individualized consideration, whereas donor-derived CAR-Ts should only be done in the context of a clinical trial. Close monitoring, early recognition, and appropriate management of clinical suggestion of GVHD must be exercised until more data become available.

WHAT ARE THE LYMPHOMA CAR-T SPECIFIC CONSIDERATIONS FOR CRS?

General considerations of CAR-T toxicities have been previously published [5,53] as well as the American Society for Transplantation and Cellular Therapy (ASTCT) consensus toxicity grading paper [54]. Table 5 summarizes reported details of CRS for axicabtagene ciloleucel and tisagenlecleucel from the pivotal trials along with real-world reports with axicabtagene ciloleucel after FDA approval [1,2,10,15]. Comparison of CRS between products is limited by the different grading scales used in each pivotal trial. To allow a uniform reporting of CRS toxicity grading, the ASTCT has subsequently developed a CRS grading scale for toxicity assessments [54]. Therefore, we recommend that the ASTCT Toxicity Consensus Grading system should be used across all products and all indications for clinical practice as well as in clinical studies to enable more consistent reporting and comparison of CRS events among CAR-T products [54,55].

Because of the risk of CRS and neurologic toxicities, both axicabtagene ciloleucel and tisagenlecleucel are available only through a restricted program under REMS. Two doses of tocilizumab must be available on site for each patient before infusion of CAR-T therapy. Close monitoring of patients for signs or symptoms of CRS for at least 4 weeks after treatment with CAR-T is necessary.

With regards to specific management of patients experiencing CAR-T–related toxicity, various institutions have published their preferred algorithm, including the National Cancer Institute and CARTOX working group [56,57]. Additionally, the package inserts of both axicabtagene ciloleucel and tisagenlecleucel give an overview of management. Currently, there is no consensus on management guidelines for all approved CAR-T therapies. Tocilizumab, a humanized mAb against the IL-6 receptor, is FDA approved for first-line treatment for CAR-T–induced CRS. Glucocorticoids have also demonstrated efficacy in ameliorating CRS by suppressing inflammatory responses. However, because of concerns of CAR-T suppression, steroids remain a second-line treatment for CRS refractory to tocilizumab or in cases of extremely rapid onset severe CRS. Subgroup analysis from the ZUMA-1 trial suggested that the use of tocilizumab and steroids earlier in the course of CRS reduced the incidence of more severe CRS without affecting overall clinical response [1,4]. Although it is common practice to escalate management from supportive

Table 5
Rates of CRS and Neurotoxicity in the Pivotal Trials for CAR-T Products in Aggressive NH

Characteristics	ZUMA-1 [1] (Axicabtagene Ciloleucel)	JULIET [2] (Tisagenlecleucel)	Real-World Data Report 1 (Axicabtagene Ciloleucel) [15]	Real-World Data Report 2 (Axicabtagene Ciloleucel) [10]
No. of patients enrolled (treated)	111 (101)	141 (85)	165 (treated)	76 (treated)
CRS				
Time to onset, days, median (range)	2 (1-12)	3 (1-9)		1
Duration, days, median (range)	8 (NR)	7 (2-30)		6 (0-14)
Grade (all), %	93	58-57*		96
Grade $^{3}/_{4}$, %	13†	22-17*	7	17
Use of tocilizumab, %	43	14‡	62	67
Use of vasopressors, %	17	6		
Use of steroids, %	27	10§	57	78
Endotracheal Intubation, %	NR	7		
Admission to intensive care unit, %	NR	24		30
Neurotoxicity¶				
Median time to onset, days (range)	5 (1-17)	6 (1-17)		5
Median duration, days (range)	17 (NR)	14 (??)		8
All grades, %	64	21		76
Grade 3 or 4, %	28	12	31	38

* CRS is graded by the Lee et al (NCI) grading system. The JULIET study initially used the PENN grading system and retrospectively also reported the data per Lee grading system for cross trial comparison.

† Reduction in grade ≥ 3 from 18% to 13% at time of final analysis likely attributable to a protocol amendment allowing for administration of tocilizumab for grade 2 CRS after changing to CARTOX from Lee at al (NCI) grading system.

‡ 5% received 1 dose, 9% received 2 doses.

§ All steroid doses had concurrent tocilizumab use.

¶ Neurotoxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 in both studies.

care to tocilizumab and steroids based on increasing severity of CRS, there are ongoing efforts to harmonize and identify specific parameters for administration of tocilizumab or steroids. Additionally, it is important to note the reports, albeit rare, of fulminant hemophagocytic lymphohistiocytosis/macrophage activation syndrome characterized by immune activation and tissue infiltration with lymphohistiocytes and resulting in immune mediated organ failure, which overlaps substantially with CRS [1,57].

The role of tocilizumab for prophylactic use was studied in a safety study of 34 patients as an add-on to the ZUMA-1 trial. Prophylactic tocilizumab administered on day 2 showed a reduction in the incidence of severe CRS but possibly increased the risk of immune effector cell–associated neurotoxicity syndrome (ICANS) [58]. Hence, prophylactic tocilizumab is not a standard practice, and identifying agents for prevention of CRS is an area of ongoing research.

Although greater expansion of CAR-Ts is associated with overall response rate and higher risk for more severe CRS and ICANS [1], there is no regulatory approved diagnostic test to measure CAR-T presence in the blood or tissue. Noncardiac C reactive protein and ferritin are readily available clinical tests that although not specific for CRS can be followed serially to assist with differentiating among fever caused by CRS versus lymphoma or infection. Moreover, patients who develop severe CRS are at a significantly higher risk for developing neurologic toxicity [1,23]. Various biomarkers like IL-15, IL-6, IL-2 receptor alpha, IFN-γ, IL-10, and granulocyte-macrophage colony-stimulating factor have been associated with more CRS and ICANS [1,59,60], and attempts to have point-of-care measurements of IL-6 and angiopoietin 2-to-angiopoietin 1 ratio to better identify CRS and or ICANS are under development [34].

WHAT ARE THE LYMPHOMA CAR-T SPECIFIC CONSIDERATIONS IN ICANS?

A major challenge is identifying symptoms most relevant to ICANS, because different investigators have used multiple different terminologies for similar symptoms. The ASTCT has published a new grading system for toxicities related to immune effector cells [54]. The ASTCT consensus group proposed the term “ICANS” to be more inclusive of symptoms seen in patients suffering from neurologic side effects induced by CAR-T and other immune effector cell–based therapies.

Younger age, higher tumor burden, high levels of inflammation pretreatment, and a history of early and/or high-grade CRS have been correlated with increased risk of neurotoxicity [60]. On the ZUMA-1 trial tumor volume correlated with an increased risk of grade 3 or higher neurotoxicity. Only 4% of patients with tumor volume (as estimated by the sum of products of diameter of target lesions) in the lowest quartile experienced grade 3 or higher neurotoxicity, compared with 56% of patients with tumor volume in the third quartile [61]. Similarly, on the JULIET trial and another retrospective study with non-FDA approved CD19 CAR-T, higher tumor volume was associated with an increased risk of CRS and ICANS of any grade [2,62].

ICANS management primarily involves supportive care, including frequent neurologic evaluation and early participation of neurology and critical care experts. For grade 1/2 ICANS treatment involves close monitoring of neurologic status, aspiration precautions, CNS imaging, and electroencephalogram. Compared with fundus examination to assess for papilledema, CNS imaging and lumbar puncture to evaluate for opening pressure are much better surrogates of increased intracranial pressure and cerebral edema; however, lumbar puncture and imaging might not be feasible when patients are delirious or have coagulopathy.

Nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis for any grade 2 or higher neurologic toxicities may be considered for axicabtagene ciloleucel, whereas some centers use universal prophylaxis [63]. Anti-IL-6 therapy is considered for patients with concurrent CRS; if ICANS is not associated with CRS, corticosteroids are the preferred treatment.

Most cases of ICANS appear to be reversible [64,65]. However, data regarding long-term neurologic sequelae of CAR-T therapy are limited. In a recent retrospective study of long-term events after CD19 CAR-T therapy, neuropsychiatric disorders were documented in 5 of 60 patients (8%) with NHL and chronic lymphocytic leukemia, including major depression, suicidal attempt, myoclonic seizures, and transient ischemic attacks [66]. Until more data are available, patients who develop ICANS after CAR-T infusions should be vigilantly monitored with history and complete neurologic exam. Furthermore, there should be a low threshold for performing neurocognitive testing if cognitive impairment is detected, while taking into consideration that these patients have received other chemotherapy and/or auto/alloHCT, which may affect cognitive status as well.

What Are Other Considerations after the First Month?

New-onset CRS after day 28 has not been described. Rarely, ICANS has been reported after day 28. Signs and symptoms that should elicit an evaluation with the CAR-T physician beyond the first month include fevers without clear source of infection or any focal neurologic deficits or changes in mental status. Because of the potential for neurologic events, such as altered mental status or seizures, patients receiving axicabtagene ciloleucel and tisagenlecleucel are at risk for altered or decreased consciousness or coordination in the 8 weeks after CAR-T infusion. The REMS program requires that patients refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

HOW DO WE MANAGE CAR-T–RELATED CYTOPENIAS, HYPOGAMMAGLOBULINEMIA, AND INFECTIONS?

Cytopenias after CD19-Targeted CAR-T Therapy

Cytopenias most commonly occur within the first 28 days of infusion and can take 3 months or longer to resolve [1,2] (Table 6). Late-onset cytopenias, or biphasic cytopenia, can occur after initial recovery of blood counts [67]. Prolonged cytopenias, variably defined as either cytopenias lasting beyond 28 days or 3 months after lymphodepleting therapy followed by CAR-T infusion, have been described [1,2,4,67].

The pathophysiology underlying prolonged cytopenias is not completely understood and is likely multifactorial. Cytopenias may be a consequence of heavily pretreated patients receiving cytotoxic lymphodepletion therapy, a class effect of CAR-Ts, or both. A number of factors have been reported to be associated with prolonged cytopenia after CAR-T therapy, including CRS severity, tumor burden, number of prior therapies, and prior HCT [67,68].

Because many patients may experience prolonged cytopenias after CD19-targeted CAR-T therapy (Table 6), monitoring of blood counts and appropriate supportive care with transfusions is essential. Growth factors may be considered for patients with neutropenia if they are past the window for CRS, generally after day 14; however, the effectiveness of growth factor support for prolonged or late cytopenias has not been

Table 6
Frequency and Duration of Cytopenias after FDA Approved CD19 CAR-T Products

	Neutropenia ≥ Grade 3			Anemia ≥ Grade 3			Thrombocytopenia ≥ Grade 3		
	Percentage of Patients at Any Time*	At ≥ 28 Days†	At ≥ 3 Months	Percentage of Patients at Any Time*	At ≥ 28 Days†	At ≥ 3 Months	Percentage of Patients at Any Time*	At ≥ 28 Days†	At ≥ 3 Months
Axicabtagene ciloleucel, ZUMA-1 [4],*	93	26	11	66	10	3	58	24	7
Tisagenlecleucel, JULIET [2],*	81	24	0	58	Not reported	Not reported	54	41	38

* Data from package insert, all other data from studies.
† ≥30 day outcomes reported for ZUMA-1, ≥28 day outcomes reported for JULIET.

studied. Moreover, this heavily pretreated patient population is at risk for developing treatment-related myelodysplastic syndrome, and bone marrow evaluation should be considered for patients with prolonged cytopenias, as cases of myelodysplastic syndrome have been described in patients after CAR-T therapy [4,66].

B Cell Aplasia and Hypogammaglobulinemia after CD19-Targeted CAR-T Therapy

B cell aplasia is nearly universal after successful treatment with CD19 CAR-T therapy because of an "on-target, off-tumor" effect. Before CAR-T infusion most adult lymphoma patients start with $CD19^+$ B cell counts that are below the lower limit of detection by flow cytometry [69]. Patients who initiate therapy with detectable B cell counts generally have B cell depletion during expansion of CAR-Ts irrespective of lymphoma response [2,4,13]. The median reported time to sustained B cell detection in patients with ongoing CR is 6 to 9 months, but a subset of patients had detectable B cells in the peripheral blood as early as 2 weeks after CAR-T infusion [4,23]. However, only a small percentage of patients (16%) with CR had recovery of B cell counts to the normal range [4,23]. It appears that most patients who are likely to recover B cells in the peripheral blood after CAR-Ts will do so within the first 12 months after infusion (Table 7) [4,23]. The recovered B cells are polyclonal, and numbers may increase despite CAR-T persistence documented by quantitative PCR [23]. Various groups have observed that lymphoma patients may have durable responses despite detectable $CD19^+$ B cell counts, and hence lymphoma-directed therapy is not recommended based solely on recovery or detection of $CD19^+$ B cells [4,23,70]. The mechanism of recovery of $CD19^+$ B cells despite the presence of CAR-T is unknown and requires additional investigation.

The incidence of hypogammaglobulinemia after CAR-T therapy is less well described, although it is, to some extent, pre-existing because of prior B cell–directed therapy [2,23]. In a single-center study of tisagenlecleucel, of the patients who were not receiving intravenous immune globulin (IVIG), 60% had increases in IgM levels and 40% had normalization of IgM levels between 12 and 24 months, 30% had increases in IgG and IgA levels, and 20% also had normalization of IgA and IgG levels at 18 to 30 months [23]. In a cohort of patients with acute lymphoblastic leukemia, chronic lymphocytic leukemia, and NHL treated with anti-CD19, 4-1BB, CD3zeta, EGFRt CAR-Ts, pre-existing hypogammaglobulinemia (IgG $<$ 400 mg/dL) was present in 23% of NHL patients at the time of CAR-T therapy and in 46% of all patients at 2 to 3 months after treatment [71]. After day 90 hypogammaglobulinemia (IgG $<$ 400 mg/dL) or IgG replacement occurred in 41% of patients with NHL or chronic lymphocytic leukemia treated on that study; it should be noted that chronic lymphocytic leukemia patients generally have higher incidences of cytopenias than NHL patients and thus the exact proportion of lymphoma patients with hypogammaglobulinemia after CAR-T is unclear [66].

IVIG Administration

Severe hypogammaglobulinemia may increase risk for respiratory tract and other infections with encapsulated bacterial organisms. However, the role of prophylactic IVIG for prevention of infections has not been established. In the registrational trials for both FDA-approved CD19-targeted CAR-T products, IVIG was administered at the treating physician's discretion. Approximately 30% of patients on these studies received IVIG; however, no data describe baseline immunoglobulin levels at the time of CAR-T infusion or the

Table 7
B Cell and Immunoglobulin Recovery in Patients with Complete Remission after CAR-Ts

	3 Months	6 Months	9 Months	12 Months	24 Months
Percentage of patients with detectable B cells					
Axicabtagene ciloleucel ZUMA-1 [4]	17	~24	61	~52	75
Tisagenlecleucel single-institution study [23] *	–	40	–	60	80
Percentage of patients with IgG increase from nadir in the absence of IVIG					
Tisagenlecleucel single-institution study [23],*	–	30	–	40	100

* This study only reported results for patients achieving complete remission.

indications for IgG replacement [2,4]. In a single-center study of tisagenlecleucel, among 12 patients in complete remission with hypogammaglobulinemia who did not receive IVIG prophylactically, 2 patients (17%) required initiation of IVIG for recurrent sinopulmonary infections between 12 and 22 months after CAR-T infusion. Approximately one-third of patients in that study recovered immunoglobulins at 12 to 30 months without intervention despite documented CAR-T persistence [23]. Based on the current clinical experience, IVIG should be considered for patients with hypogammaglobinemia complicated by recurrent infections; this is consistent with the current ASTCT *Choosing Wisely* recommendation for immunoglobulin replacement after HCT [72]. IVIG may also be considered when IgG levels are extremely low (especially < 200 mg/dL), particularly when associated with extremely low IgA levels [73].

Infections

Patients treated with CD19 CAR-Ts are at risk of infection because of prior cytotoxic and lymphodepleting therapies, development of CRS, and B cell aplasia with associated hypogammaglobulinemia. Approximately 18% to 34% of patients develop infections within the first 2 months after CD19-targeted CAR-T therapy despite antimicrobial prophylaxis (Table 8) [2,4,71]. Bacterial and viral infections are the most common early infections, although invasive fungal infections have also been described (Table 8) [2,4,71]. Clinically significant reactivation of latent DNA viruses (eg, cytomegalovirus, Epstein-Barr virus, BK polyomavirus, hepatitis B, and human herpesvirus-6) do not appear to be common based on long-term follow-up from ZUMA-1, albeit prospective screening studies are lacking [4].

The incidence and severity of later infections after CAR-T therapy are poorly described, especially for lower grade infections. In the JULIET study 39% of patients developed infection (18% grade ≥ 3) more than 8 weeks after infusion [2]. Limited data suggest a low incidence of late infections, most of which were mild and due to respiratory viruses and other respiratory infections [66,70,71]. Careful monitoring for other infections is warranted as clinical use of CD19 CAR-T therapy expands to include more patients with chronic infections, such as hepatitis B, which may reactivate in this clinical setting. In a case report of patients with active hepatitis B and hepatitis C virus who received axicabtagene ciloleucel, no fulminant hepatitis was reported [74]. Current unanswered questions in this area include the risk of hepatitis B virus, cytomegalovirus, and other later DNA virus reactivation after CD19 CAR-T therapy as well as the feasibility of manufacturing and efficacy of CAR-T in patients with HIV, because this patient population has been excluded from CAR-T clinical trials. Of note, it is useful to document HIV serologies before CAR-Ts because some nucleic acid–based screening tests for HIV (Nucleic Acid Test methods) may have false-positive results after CAR-T if lentiviral vectors were used to produce CAR-Ts [75].

After day 28 many patients may return to resume care with their local physician. At that time the greatest CAR-T–associated risk is infection due to persistent neutropenia and hypogammaglobulinemia. Thus, we recommend continued physical examination and laboratory monitoring, including complete blood count with differential, comprehensive metabolic panel, and quantitative immunoglobulins, at least on a monthly basis for the first 3 months after CAR-T infusion. Any fever requires assessment for infection and neutropenia, as cytopenias can persist for months after lymphodepletion therapy and CAR-T infusion.

Because of increased risk of infection, antimicrobial prophylaxis is recommended for patients undergoing CD19 CAR-T therapy. These recommendations are based on extrapolation

Table 8
Infections in ≥10% of Oatients on ZUMA-1 and JULIET Trials regardless of Attribution to CAR-Ts

	Axicabtagene Ciloleucel (ZUMA-1) [1,4]			Tisagenlecleucel (JULIET) [2]		
	All Grades	Grades 1-2	Grades 3-4	All Grades	Grades 1-2	Grades 3-4
Patients who developed any infection in package insert[*,†]						
	38		23	42		25
Respiratory infections[‡,§]						
Upper respiratory infections	12 (11)	11 (10)	1 (1)	13 (12)	11 (10)	2 (2)
Lung infections (unspecified)	19 (18)	4 (4)	15 (14)			
Viral pneumonia	5 (5)	4 (4)	1 (1)			
Bacterial pneumonia	2 (2)	0 (2)	2 (2)			
Fungal pneumonia	1 (1)	1 (1)	0 (0)			

Values are percents (top) and n (%) (bottom.

* Yescarta package insert: median follow-up 8.7 months.

† Kymriah package insert: median follow-up 9.4 months.

‡ Locke Lancet Oncol 2019: median follow-up 27.1 months, n = 108; summary estimate from their Supplemental Table 5.

§ Schuster NEJM 2019: median follow-up 14 months, n = 111.

Table 9
Suggested Infection Prophylaxis for Patients Undergoing Anti-CD19 CAR-T Therapy

Infection	Prophylaxis	Duration
Gram-negative bacteria with *Pseudomonas* coverage	Levofloxacin	Start when patient becomes neutropenic Stop when neutropenia resolves
Candida species	Fluconazole or micafungin	Start when patient becomes neutropenic Stop when neutropenia resolves
Mold species	Posaconazole or voriconazole	Start if neutropenia persists >2-3 weeks or Corticosteroids course > 3 days Stop when neutropenia resolves and/or steroids are stopped
Pneumocystis jiroveci	Trimethoprim-sulfamethoxazole or alternative as clinically indicated	Start days 21-28 after CAR-T administration Continue for at least 6 months
HSV and VZV	Assess HSV, VZV serologies before CAR-T therapy If seropositive for HSV11, HSV12 or VZV: acyclovir or valacyclovir	Start with initiation of lymphodepletion chemotherapy Continue for at least 1 year after CAR-Ts

HSV indicates herpes simplex virus 1; VZV, varicella-zoster virus.

from alloHCT data, HIV management recommendations, and anecdotal data in CAR-T therapy, because there are insufficient data to establish evidence-based standard recommendations. Infection prophylaxis may follow institutional guidelines with consideration for coverage as summarized in Table 9. Cytomegalovirus monitoring by serum PCR may be considered, especially for patients who receive prolonged course(s) of steroids. Initiation of antivirals for cytomegalovirus viremia and duration of therapy should be according to established institutional standards.

Immunization after CAR-Ts

Vaccinations were not required and immune status not measured in the pivotal trials, and thus there are no data regarding the need for revaccination after anti-CD19 B cell–directed CAR-T therapy. Moreover, patients may also be status post autoHCT or alloHCT and have not yet completed post-HCT vaccinations before CAR-T infusion. In the absence of data, we suggest following current recommendations from the Centers for Disease Control and Prevention for reimmunization after autoHCT or recommendations for immunizations after alloHCT for patient who underwent prior alloHCT and have not completed their post-transplant vaccinations. Preclinical studies suggest persistence of humoral immunity derived by long-lived plasma cells when B cells are depleted [76,77], and a clinical study demonstrated persistence of long-lived plasma cells and humoral immunity in individuals responding to CD19 CAR-T therapy [78]. Thus, additional research and data are required before evidence-based post–CAR-T vaccination recommendations are available.

HOW TO MONITOR RESPONSE AFTER CAR-T THERAPY?

Disease Monitoring

For aggressive B cell lymphoma we recommend positron emission tomography (PET)/computed tomography (CT) as the modality of choice to either confirm CR or detect early relapse and allow for rapid clinical intervention. The 2014 Lugano criteria was the response assessment criteria used in the axicabtagene ciloleucel and tisagenlecleucel pivotal studies [79], and we recommend this be used in clinical practice to assess response after CAR-T. In addition, clinicians should always consider symptom-directed imaging to assess for progressive disease or relapsed lymphoma at any time after CAR-T therapy. In the ZUMA-1 trial the median time to response was 1 month, and most conversions of PR and stable disease to CR occurred by 6 months [4]. Patients continued to have improvement in response status as late as 9 months. Similarly, in the JULIET study some stable disease and PR at 1 month improved to CR by 2 months. Conversions from PR to CR occurred in about half of patients [2].

Most disease progressions or relapses after CAR-Ts occur within the first 3 to 6 months with both commercially approved products [2,4]. In a small study of patients who received tisagenlecleucel, all patients with Deauville scores of 1 to 2 by PET/CT at 1 month maintained CRs lasting more than 2 years after CAR-T infusion [80]. Four-year follow-up for a single-center trial using the tisagenlecleucel construct found that after 12 months, only 1 patient with DLBCL in remission relapsed [81].

Within the first 9 months, patients with imaging who show PR or stable disease in the absence of symptoms attributable to lymphoma may be monitored with follow-up imaging because about half of patients will eventually convert to CR. In patients in whom imaging shows progression of disease, CAR-T therapy should be considered unsuccessful. Of note, pseudoprogression, which may occur after checkpoint inhibitor therapy, is very rare after CAR-Ts; thus, there is generally not a need for serial confirmatory imaging to document progressive lymphoma in the setting of a scan that shows progression at multiple sites of disease. Patients with stable disease and PR after CAR-Ts represent a group of patients at higher risk for progression and need to be closely followed. This group of patients may warrant stronger consideration for additional therapy, preferably on a clinical trial.

Although the standard practice for lymphoma (per Lugano criteria) is no routine surveillance scan for patients in remission, CAR-T is a new therapy with limited data from registration trials. To better understand optimal monitoring, based on data from the pivotal trials we advocate PET/CT at 1 month and 3 months for all patients. Given the relative short follow-up of this novel therapy, regular imaging follow-up would inform the role of radiologic scans in surveillance in the future. For patients who achieve a CR by PET/CT criteria, further follow-up imaging with CT instead of PET could be considered at the discretion of the treating physician [2,4]. However, for patients not in a CR, imaging with PET/CT every 3 months could be considered until further data are available. As per usual management, PET/CT of a patient in remission should occur if the patient exhibits signs or symptoms of relapsed lymphoma. These practice recommendations will likely evolve with additional data.

Laboratory Monitoring after CAR-T Therapy

Presently, there are no clinically approved laboratory tests available for CAR-T monitoring. There are several areas of

unmet need, including the lack of commercially available assays to monitor CAR-T expansion and persistence by PCR or flow cytometry. These tests would allow clinicians to understand whether patients who progress after CAR-T do so because of poor CAR-T expansion or lack of CAR-T persistence, which could guide therapeutic decision-making. Moreover, a commercial assay to detect replication-competent lentivirus is also currently lacking despite the fact that yearly testing for 15 years after CAR-T infusion is an FDA requirement for patients treated on clinical trials. Finally, there are currently no clinically approved laboratory tests for the use of circulating tumor DNA to predict outcomes after CAR-T or earlier recurrence of lymphoma, although this is an area of active study [82].

Treatment Options for Patients in Complete Remission after CAR-T Therapy

Although CAR-Ts have demonstrated durable responses with a median follow-up of 27 to 28 months for both FDA-approved products [2,4] and there is single-institution experience with durable remissions at 4 years of follow-up using the same construct as tisagenlecleucel [81], the long-term data for the pivotal CAR-Ts are not mature enough to conclude that patients who receive CAR-Ts may be cured of their aggressive B cell lymphoma. Thus, at this time, based on the pivotal trials, patients who achieve complete remission after CAR-T are usually actively observed, whereas options such as alloHCT may be considered for patients on an individualized basis.

Treatment Options for Patients with progression of Disease or Relapse after CAR-T Therapy

CR is achieved in approximately 30% to 40% of patients [1,2,4]; thus, 60% to 70% of patients are expected to experience disease progression or relapse after CAR-T therapy. The mechanism of CAR-T failure that is best understood in NHL is loss of CD19 expression, whereas preliminary work has also implicated CAR-T exhaustion as a potential mechanism [2,23,83-86]. Unlike chronic lymphocytic leukemia, failure of CAR-Ts because of poor expansion is a less common reason for treatment failure in aggressive B cell lymphomas. At this time there are no data to predict which patients are at higher risk for disease progression after CAR-T therapy, and there are no standard treatment recommendations for patients with relapse/disease progression after CAR-T therapy. Patients with relapse/disease progression should be rebiopsied, and treatment considerations should include enrollment on clinical trials (preferred), salvage therapy with programmed death (PD)-1/PD-Ligand 1 inhibitors, or alloHCT. We also suggest that molecular sequencing of the tumor be performed to assess for the presence of actionable mutations.

WHAT ARE THE LATE EFFECTS OF CAR-T THERAPY?

Patients with aggressive B cell lymphomas who participated in the pivotal CAR-T trials have been followed for around 2 years after treatment [2,4]; thus, data regarding long-term effects are limited to single-institution, 4-year experience [81]. To date, the main concerns regarding potential long-term complications of CD19 CAR-T therapy include subsequent malignancies and new incidence or exacerbation of neurologic or autoimmune disorders [87,88]. Table 10 summarizes short- and long-term events after CD19 CAR-T therapy.

Subsequent Malignancies

The theoretical concern regarding subsequent malignancies after CAR-T therapy is due to the use of retroviral and lentiviral vector to transfer the CAR gene into the host genome. The integration of the exogenous gene into the host genome is random and thus may cause disruption of critical host genes at the integration site, including risk of activation of proto-oncogenes or inactivation of tumor suppressor genes, with the risk of insertional mutagenesis. Additionally, although the viral vectors used for gene transfer are replication defective, there is a theoretical risk of recombinant events during the vector manufacturing, which may result in viral replication in vivo with ongoing insertion into the host genome, which further increases the risk of insertional mutagenesis. However, results of replication competent virus testing from CAR-T trials demonstrate no risk to date [89]. Similarly, a number of clinical trials with gamma-retroviral and lentiviral-modified T cells have not yielded evidence for insertional mutagenesis in T cells despite long-term persistence of transduced cells [90,91]. To date, 1 patient has been described to undergo clonal expansion of lentivirus-modified leukemic blasts [92], but there is no

Table 10
Short and long-term events after CD19 CAR T Cells*

Effect	0 – 30 days	30-90 days	> 90 days	Management
Cytopenia (all grades)	+++	++	+	Close monitoring of CBC with differential. GCSF support and RBC and platelet transfusion as indicated
Hypogammaglobulinemia	++	++	++	Monthly immunoglobulin levels. IVIG if recurrent infections. May consider IVIG for IgG level <200 mg/dL especially if IgA level also low.
Infections	+	+	+	Antimicrobial prophylaxis and vaccinations (as discussed in the text and table 9)
Subsequent malignancies			+	Close monitoring for MDS and skin cancer. Screening for solid cancer as per recommendations for general population
Neurologic disorders (all grades)	++	?	?	History and physical exam at every clinic visit
Autoimmune disorders		?	?	History and physical exam at every clinic visit
GVHD (for patients with prior or subsequent alloHCT)		+	+	Close monitoring for signs and symptoms of acute and chronic GVHD

AlloHCT, allogeneic hematopoietic cell transplantation; CBC, complete blood count; GCSF, granulocyte colony stimulating factor; GVHD, graft versus host disease; IVIG, intravenous immunoglobulin

* Estimated event frequency based on current data, no direct association with CAR-T cells have been established for all events. Frequency may vary between products.

+++ Highly likely (> 80%)
++ Likely (50-80%)
+ Less likely (10-50%)

evidence of vector-induced immortalization, clonal expansion, or enrichment for integration sites near genes implicated in growth control or transformation [90,91].

Four-year follow-up in a single-institution study using the tisagenlecleucel CAR-T construct showed that 2 of 38 patients (.05%) developed myelodysplastic syndrome, and there were no other secondary malignancies [81]. In a retrospective study with a 23-month follow-up at a single institution, 8 of 59 patients with NHL or chronic lymphocytic leukemia were diagnosed with subsequent malignancies after treatment with CD19 CAR-Ts, including 3 (5%) myelodysplasia, 4 (7%) nonmelanoma skin cancer, and 1 (2%) noninvasive bladder cancer [66]. All but 1 patient with skin cancer had an autoHCT or alloHCT before CAR-T therapy. Although the risk seems to be low, clinical monitoring for subsequent malignancies after CAR-T therapy is required as part of the long-term follow-up by the FDA and European Medicines Agency (EMA). Both Kite and Novartis have established contracts with the Center for International Blood and Marrow Transplant Research for collection of long-term outcome data of patients after treatment with axicabtagene ciloleucel and tisagenlecleucel, respectively, and institutions are highly encouraged to report their data to the Center for International Blood and Marrow Transplant Research. Similarly, the EMA has endorsed data collection by the European Society for Blood and Marrow Transplantation.

Autoimmune Disorders

Autoimmune-like reactions because of the "off-target effect" to self-antigens is a concern. However, no published data are currently available regarding late autoimmune disorders after CAR-T therapy. Additional studies in large patient populations are needed to evaluate the risk of autoimmune disorders after CAR-T therapy.

WHAT ARE THE NEW ADVANCES FOR CAR-T IN LYMPHOMA?

Axicabtagene ciloleucel and tisagenlecleucel have demonstrated encouraging results. However, participation on clinical trials should remain a priority to improve response rate, reduce treatment-related acute toxicities, and evaluate long-term effects.

Whether CAR-T therapy has a role ahead of autoHCT remains an important clinical question. So far, a single-institution, nonrandomized, prospective study in patients with R/R NHL with an investigational CD19 CAR-T product has shown higher CR rates and superior overall survival, especially in patients with international prognostic index $\geq$ 3, with CD19 CAR-T compared with autologous stem cell transplant [93]. Ongoing randomized controlled trials are actively accruing for comparing CAR-T therapy (ie, axicabtagene ciloleucel [ZUMA-7, NCT03391466], tisagenlecleucel [BELINDA, NCT03570892], and lisocabtagene maraleucel [TRANSFORM, NCT03575351]) versus autoHCT in first R/R setting. In addition to the 2 FDA-approved products, several CAR-T products are currently under investigation and are available for patients under clinical trials. In advanced development is the CD19-targeted CAR-T product lisocabtagene maraleucel (liso-cel; JCAR017) from Celgene (originally developed by Juno), a CD19-directed 4-1BB CAR-T product with a highly controlled manufacturing process that enables administration of a defined composition at a precise dose of CD8 and CD4 CAR-Ts. Clinical outcomes and safety results from the TRANSCEND-NHL 001 trial were presented most recently at the Annual Meeting of the American Society of Clinical Oncology in 2018 [19], and it is expected to be submitted for FDA approval by 2020.

CD19 has been proven to be an effective target for CAR-T therapy for B cell NHL; however, CAR-T products that target other tumor-associated antigens may be used. Currently, several clinical trials are evaluating the safety and efficacy of CAR-Ts targeting other antigens such as CD20 (NCT03277729, NCT03664635) and CD30 (NCT02917083, NCT03049449) and are testing CAR combinations (NCT03287817, NCT03233854) [94]. Allogeneic CAR-Ts, manufactured from lymphocytes of healthy donors, are an interesting alternative, and a number of ongoing clinical trials are currently evaluating this approach (NCT03939026, NCT03666000, NCT01430390). However, there are still many challenges to overcome before this strategy can be used routinely in the clinic [95].

Severe toxicities associated with CAR-T therapy have raised interest in safety elements that could be introduced into the CAR constructs. For example, the JCAR017 construct includes a truncated form of the epidermal growth factor receptor that enables removal of the transduced cells with the anti–epidermal growth factor receptor antibody cetuximab [13], and the RQR8 domain recognized by rituximab is used in the allogeneic product UCART19 [96]. Constructs that allow switching the CAR expression on and off are currently in preclinical development and if successful would provide better control of CAR-T–related toxicity [97]. Additionally, efforts are currently underway for using nonviral transfection methods for genetic modifications. One such strategy is using mobile DNA elements or transposons that stably integrate the therapeutic gene into the target cell chromosome [98,99]. Transposon-based CAR-T therapy is currently being tested in preclinical and phase I clinical trials [100].

SUMMARY POINTS

- Approval indications:
- axicabtagene ciloleucel for DLBCL not otherwise specified, primary mediastinal large B cell lymphoma, high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma; and
- tisagenlecleucel for DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
- Early referral for consideration for CAR-T is encouraged for patients with R/R disease. Avoid lymphotoxic therapy before leukapheresis to maximize likelihood of manufacturing success.
- Decision and choice of bridging therapy can be based on disease volume, prior response to therapies, and comorbidities. Options include chemotherapy regimens, radiation, corticosteroids, and targeted agents such as lenalidomide, ibrutinib, rituximab, or investigational agents.
- CAR-T can be considered in patients who have undergone a prior autoHCT or alloHCT and decision based on comorbidities, organ function, and GVHD status.
- Clinical monitoring for CRS and ICANS after CAR-T is imperative for early diagnosis and treatment. We recommend using the ASBMT consensus grading system. Tocilizumab and corticosteroids remain the mainstay of treatment currently.
- Cytopenias, hypogammaglobulinemia, and infections are important to recognize and treat as clinically indicated, while specific data continues to emerge.
- For response assessment we recommend PET/CT for initial staging on days +30 and +90. If CR is achieved early,

patients could be followed by CT. Some patients with PR on day +30 have been shown to achieve CR by 2 to 6 months after treatment. Careful monitoring of clinical status during this time is warranted.
- Results from ongoing trials using lisocabtagene ciloleucel in the R/R setting, randomized comparison of CAR-T versus autoHCT in first relapse, novel ways to prevent toxicity, and use of allogeneic CAR-T among others are awaited and will shed further light on the growing practice of use of CAR-Ts.

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