Allogeneic Chimeric Antigen Receptor T-Cell Products Cemacabtagene Ansegedleucel/ALLO-501 in Relapsed/Refractory Large B-Cell Lymphoma: Phase I Experience From the ALPHA2/ALPHA Clinical Studies

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ABSTRACT

PURPOSE Off-the-shelf, allogeneic CD19 chimeric antigen receptor (CAR) T-cell products may improve access to treatment versus autologous ones. We report the phase I experience of the allogeneic CD19 CAR T-cell product cemacabtagene ansegedleucel (cema-cel) and its predecessor, ALLO-501, in CD19 CAR T-naïve patients with relapsed/refractory large B-cell lymphoma (R/R LBCL).

METHODS In the ALPHA2/ALPHA studies, the safety and efficacy of allogeneic CD19 CAR T cells were evaluated in CD19 CAR T treatment-naïve patients with R/R LBCL. Patients received healthy donor-derived, human leukocyte antigen–unmatched cema-cel/ALLO-501 following a 3-day lymphodepletion regimen of fludarabine (30 mg/m^2 once daily), cyclophosphamide (300 or 500 mg/m^2 once daily), and escalating doses of the anti-CD52 monoclonal antibody, ALLO-647.

RESULTS As of September 26, 2024, 33 CD19 CAR T-naïve patients with LBCL (median age, 66 years; median number of previous therapies, 3) received allogeneic CAR T cells. CAR T-cell expansion was observed following infusion, with persistence observed up to 4 months. The overall and complete response (CR) rates were 58% and 42%, respectively; the median duration of response in patients with a CR was 23.1 months. The most common treatment-emergent adverse events were hematologic toxicities. No cases of graft-versus-host disease, immune effector cell–associated neurotoxicity syndrome, or grade ≥3 cytokine release syndrome were reported.

CONCLUSION Allogeneic CD19 CAR T cells demonstrated promising overall and durable CR rates with a manageable safety profile in CD19 CAR T-naïve patients with R/R LBCL, supporting additional evaluation of cema-cel in patients with LBCL.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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INTRODUCTION

Large B-cell lymphoma (LBCL) is the most common aggressive subtype of non-Hodgkin lymphoma (NHL).[1,2] Although approximately 60% of patients with LBCL are cured with first-line regimens, many patients have refractory disease or disease that relapses, requiring additional treatment.[3] Historically, prognosis for relapsed or refractory (R/R) LBCL has been poor, with a median overall survival (OS) of 6.3 months and 20% of patients alive at 2 years.[4] Autologous CD19 chimeric antigen receptor (CAR) T-cell therapies have demonstrated significant clinical benefit for patients with R/R LBCL; however, many patients are unable to receive these potentially life-saving therapies due to aggressive disease biology at recurrence, difficulty in accessing specialized centers administering these therapies, and/or issues with product manufacturing.[5-13] Once a patient accesses a treatment center, manufacturing requires both successful apheresis of T cells and approximately 4-6 weeks for production and delivery, which often necessitates bridging therapy to slow disease progression.[12-16]

Allogeneic CAR T-cell products manufactured from healthy donors may both achieve the benefits and overcome limitations of autologous CAR T-cell products.[17] Cemacabtagene ansegedleucel (cema-cel) and its predecessor ALLO-501, which has the same CAR design as cema-cel except for the

CONTEXT

Key Objective

Can off-the-shelf, allogeneic CD19 chimeric antigen receptor (CAR) T product be feasibly and safely administered to patients with relapsed/refractory large B-cell lymphoma (LBCL) while yielding durable response rates?

Knowledge Generated

Treatment with cemacabtagene ansegedleucel and its predecessor, ALLO-501, was given after lymphodepletion was initiated 2 days after enrollment (median) and induced durable complete responses (CRs) in heavily pretreated, CAR T-naïve patients with LBCL. Allogeneic CAR T-cell expansion and persistence were supported by an enhanced lymphodepletion regimen that included ALLO-647, an anti-CD52 antibody, and standard fludarabine/cyclophosphamide. Treatment was well tolerated (no grade ≥3 cytokine release syndrome; no immune effector cell–associated neurotoxicity syndrome [ICANS]/graft-versus-host disease); incidence of infections and immune reconstitution was similar to that expected following autologous CD19 CAR T.

Relevance *(J.W. Friedberg)*

This study represents the first demonstration of safety and efficacy for an allogeneic CAR T-cell product targeting CD19 in patients with diffuse LBCL. The subset of patients who achieved CRs show durability, supporting ongoing randomized trials testing cemacabtagene ansegedleucel as consolidation in patients with evidence of minimal residual disease after standard chemoimmunotherapy.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

inclusion of a rituximab recognition domain, are allogeneic CD19 CAR T-cell products gene-edited to reduce risk of graft-versus-host disease (GVHD) and allow for selective lymphodepletion of host T cells with ALLO-647, a monoclonal anti-CD52 antibody.[17-19] Cema-cel/ALLO-501 is manufactured with a scalable process that yields approximately 100 doses from a single production run, which are then cryopreserved for storage and ready for use on demand.[20] This enables immediate access to CAR T cells without the need for adequate patient T-cell count or fitness, leukapheresis, bridging therapy, or complex logistics associated with administering autologous CAR T-cell products.[12-14,17,21]

Lymphodepletion regimens are critical for effective CD19 CAR T-cell therapy, and regimens containing fludarabine and cyclophosphamide are commonly used before cell therapy administration.[22] Compared with autologous CAR T cells, allogeneic CAR T cells may require enhanced lymphodepletion to prevent premature host-mediated rejection of CAR T cells.[13] Although higher doses of cytotoxic chemotherapy may achieve deeper lymphodepletion,[23] chemotherapy-sparing strategies that selectively target host lymphocytes could achieve the desired lymphodepletion while limiting collateral organ damage and myelotoxicity. Inclusion of the anti-CD52 monoclonal antibody, ALLO-647, in the lymphodepletion regimen is intended to selectively suppress host lymphocytes while sparing the *CD52*-knockout CAR T cells of cema-cel/ALLO-501. This targeted strategy aims to create the necessary window for expansion and tumor eradication without the accompanying toxicity associated with nonspecific cytotoxic agents.[24]

The ALPHA2 (ClinicalTrials.gov identifier: NCT04416984) and ALPHA (ClinicalTrials.gov identifier: NCT03939026) studies were initiated to evaluate cema-cel and ALLO-501, respectively, following a standard fludarabine/cyclophosphamide lymphodepletion regimen with ALLO-647 in patients with R/R NHL. Here, we report the phase I experience from the ALPHA2 and ALPHA studies in CD19 CAR T-naïve patients with R/R LBCL.

METHODS

Study Design

ALPHA2 is a single-arm, multicenter, open-label, phase I/II study evaluating the safety, efficacy, and pharmacokinetics/pharmacodynamics (PK/PD) of cema-cel following ALLO-647–containing lymphodepletion in patients with R/R NHL. ALPHA is a single-arm, multicenter, open-label, phase I study evaluating the safety, efficacy, and PK/PD of ALLO-501 following ALLO-647–containing lymphodepletion in patients with R/R NHL. This report summarizes the evaluation of CD19 CAR T-naïve patients with LBCL from the phase I portion of these studies who received cema-cel/ALLO-501 manufactured with the selected phase II manufacturing process (N = 33; Fig 1). Due to product similarities of cema-cel and ALLO-501, these patients are combined in this analysis of safety, efficacy, and PK/PD. HLA haplotype was not an eligibility consideration and no attempt was made to

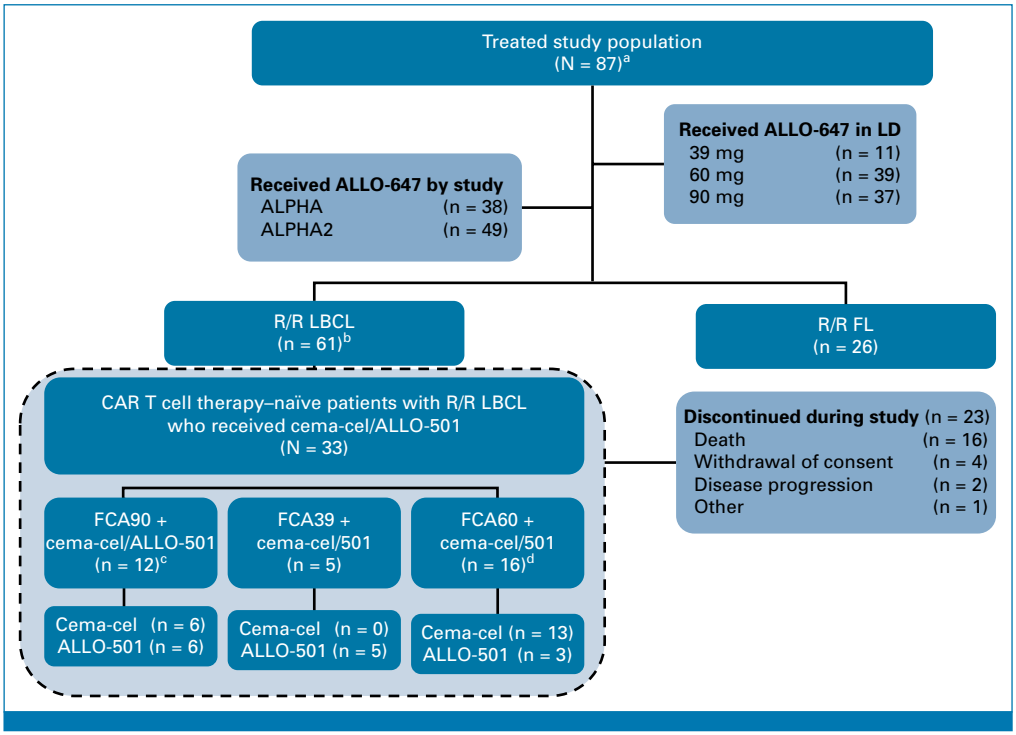

FIG. 1. Flow diagram. [a]All enrolled patients who received any study drug. [b]Includes grade 3b FL, patients with R/R LBCL who received previous CD19 CAR T-cell therapy, and patients who did not receive cema-cel/ALLO-501 manufactured with the selected phase II process. [c]Designates the selected phase II lymphodepletion process. [d]Includes consolidation. CAR, chimeric antigen receptor; cema-cel, cemacabtagene ansegedleucel; FCA, fludarabine/cyclophosphamide/ALLO-647; FL, follicular lymphoma; LBCL, large B-cell lymphoma; LD, lymphodepletion; R/R, relapsed/refractory.

treat an enrolled patient with a particular product lot on the basis of the degree of HLA match.

Enrolled patients underwent 3-day lymphodepletion with fludarabine (30 mg/m^2 once daily), cyclophosphamide (300 or 500 mg/m^2 once daily), and varying doses of ALLO-647 (Data Supplement, Fig S1, online only). No bridging therapy was permitted. Patients in the single-dose cohorts received a single dose of cema-cel/ALLO-501 (120 $\times$ 10^6 CAR+ cells) infused on day 0. Patients in consolidation cohorts who attained a complete response (CR), partial response (PR), or stable disease (SD) at the day 28 disease assessment were potentially eligible to receive an additional dose of cema-cel/ALLO-501 (120 $\times$ 10^6 CAR+ cells) on day 30 after a single 30 mg ALLO-647 dose administered on day 29 (Data Supplement, Fig S1).

The primary objectives of the ALPHA2 and ALPHA phase I studies were to determine the maximum tolerated dose and to establish the recommended phase II dose regimen of cema-cel/ALLO-501 and ALLO-647 through assessment of safety and tolerability. Secondary objectives included evaluating the overall safety profile of the regimens as measured by adverse events (AEs), characterizing PK/PD of cema-cel/ALLO-501 and ALLO-647, and assessing the efficacy of cema-cel/ALLO-501 in this patient population via investigator-assessed overall response rate (ORR).

Patients

Eligible patients who had R/R LBCL (per 2017 WHO criteria)[25] after ≥2 previous lines of chemotherapy, including an anti-CD20 monoclonal antibody and an anthracycline, were included in these studies. Patients must have had ≥1 measurable lesion per the revised International Working Group Response Criteria for Malignant Lymphoma,[26] Eastern Cooperative Oncology Group performance status 0 or 1, and adequate organ function. Patients included in this analysis must have had no previous treatment with an anti-CD19 CAR T or other engineered adoptive cellular therapy. Additional eligibility criteria can be found in the Data Supplement. The study was conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice and the Declaration of Helsinki.[27] The study protocol was approved by the Institutional Review Board or Independent Ethics Committee at each center. All patients provided written informed consent.

Assessments

Treatment-emergent AEs (TEAEs) were assessed as per the Common Terminology Criteria for Adverse Events v 5.0 unless otherwise specified from the time of the first dose of any study drug until start of another treatment period, death, or initiation of another anticancer agent, whichever

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	CAR T-Naïve R/R LBCL	
	All Patients (N = 33)	Patients Who Received Selected Phase II Dose[a] (n = 12)
Age, years		
Median (range)	66 (31-76)	60 (31-75)
≥65, No. (%)	17 (52)	5 (42)
Male, No. (%)	23 (70)	6 (50)
Race, No. (%)		
White	25 (76)	9 (75)
African American	2 (6)	1 (8)
Asian	1 (3)	0 (0)
Other[b]	0 (0)	0 (0)
Not reported	5 (15)	2 (17)
BMI, median (range)	28 (20-57)	28 (20-44)
ECOG PS, No. (%)		
0	7 (21)	1 (8)
1	26 (79)	11 (92)
Baseline LDH, No. (%)		
>ULN	22 (67)	8 (67)
>2× ULN	7 (21)	1 (8)
Baseline SPD mm^2		
Mean (SD)	3,399 (2,878)	2,410 (2,173)
Median (range)	2,487 (221-11,154)	1,711 (221-6,740)
Previous therapies		
Median (range)	3 (2-8)	3 (2-5)
HSCT, No. (%)	7 (21)	6 (50)

Abbreviations: CAR, chimeric antigen receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplantation; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; R/R relapsed/refractory; SD, standard deviation; SPD, sum of the products of longest diameters; ULN, upper limit of normal.

[a]Fludarabine/cyclophosphamide lymphodepletion with 90 mg of ALLO-647 (FCA90) followed by a single dose of CAR T cells at 120 × 10^6 CAR+ cells.

[b]American Indian/Alaska Native or Native Hawaiian/Pacific Islander.

came first. The severities of cytokine release syndrome (CRS)/immune effector cell–associated neurotoxicity syndrome (ICANS) and acute GVHD were assessed according to the grading schemes described by Lee et al and Harris et al, respectively.[28,29] Patients underwent weekly monitoring for cytomegalovirus (CMV) reactivation via polymerase chain reaction (PCR) testing for 2 months after treatment and then as clinically indicated.

Responses were assessed per the Lugano 2014 criteria.[30] Tumor assessments were performed on day 28, day 56, month 4, and every 3 months from months 6 to 18, and every 6 months thereafter through month 60. Details of PK/PD assessments, biospecimen analysis, and HLA analyses are found in the Data Supplement.

Statistical Analysis

Descriptive statistics (N, arithmetic mean, standard deviation, minimum, median, maximum) were used in PK analyses. Clopper Pearson exact intervals were used to calculate 95% CIs for ORR and CR. Kaplan-Meier methodology was used to estimate the duration of response (DOR) rates, the OS rates, and associated median estimates.

The efficacy and safety population consisted of all enrolled patients who received cema-cel/ALLO-501. Patients who died or withdrew before the first efficacy assessment were included in the analysis population as nonresponders. The PK analysis population was defined as all treated patients with sufficient information to estimate ≥1 PK parameter of interest.

RESULTS

Patient Demographics and Baseline Characteristics

As of the data cutoff date (September 26, 2024), 87 patients with R/R NHL were treated in the ALPHA2/ALPHA studies between May 2019 and September 2022. In total, 33 CD19

TABLE 2. Most Common Any-Grade TEAEs and Grade ≥3 Incidence (≥20% Any Grade in All Patients)

	CAR T-Naïve R/R LBCL			
	All Patients (N = 33), No. (%)		Patients Who Received Selected Phase II Dose[a] (n = 12), No. (%)	
AE	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	33 (100)	31 (94)	12 (100)	11 (92)
Neutropenia	28 (85)	27 (82)	10 (83)	10 (83)
Anemia	22 (67)	15 (46)	8 (67)	7 (58)
Thrombocytopenia	19 (58)	14 (42)	7 (58)	5 (42)
IRR	19 (58)	3 (9)	8 (67)	0 (0)
Fatigue	17 (52)	1 (3)	6 (50)	0 (0)
Pyrexia	16 (49)	1 (3)	6 (50)	0 (0)
Nausea	13 (39)	2 (6)	6 (50)	0 (0)
Lymphopenia	12 (36)	11 (33)	6 (50)	5 (42)
Hypotension	12 (36)	4 (12)	2 (17)	0 (0)
Peripheral edema	11 (33)	0 (0)	3 (25)	0 (0)
WBC count decreased	10 (30)	10 (30)	4 (33)	4 (33)
CMV reactivation	10 (30)	4 (12)	4 (33)	1 (8)
Decreased appetite	10 (30)	1 (3)	6 (50)	0 (0)
Chills	10 (30)	0 (0)	4 (33)	0 (0)
Hypoxia	9 (27)	4 (12)	2 (17)	0 (0)
Hypokalemia	8 (24)	3 (9)	2 (17)	0 (0)
Diarrhea	8 (24)	2 (6)	4 (33)	0 (0)
CRS	8 (24)	0 (0)	4 (33)	0 (0)
Constipation	8 (24)	0 (0)	4 (33)	0 (0)
Cough	7 (21)	0 (0)	3 (25)	0 (0)
Hypocalcemia	7 (21)	2 (6)	1 (8)	0 (0)

Abbreviations: AE, adverse event; CAR, chimeric antigen receptor; CMV, cytomegalovirus; CRS, cytokine release syndrome; IRR, infusion-related reaction; LBCL, large B-cell lymphoma; R/R, relapsed/refractory.

[a]Fludarabine/cyclophosphamide lymphodepletion with 90 mg of ALLO-647 (FCA90) followed by a single dose of CAR T cells at 120×10^6 CAR+ cells.

CAR T-naïve patients with R/R LBCL received cema-cel/ALLO-501 manufactured with the process selected for use in pivotal studies (Fig 1). The median age of patients was 66 years (range, 31-76), and the median number of previous regimens was 3 (range, 2-8; Table 1). The median follow-up time (from patient end of study date or data cutoff date) was 10.1 months (range, 0.4-62.7), with a minimum potential follow-up time (from data cutoff date) of 24 months.

For these 33 CD19 CAR T-naïve patients, the median time from enrollment to initiation of study treatment was 2 days. These patients received total cumulative ALLO-647 doses of 39 mg (n = 5), 60 mg (n = 16; including patients who received consolidation [n = 8]), and 90 mg (n = 12) in addition to the fludarabine/cyclophosphamide lymphodepletion regimen (Fig 1).

The most common reasons for discontinuation from study were death (48%) and consent withdrawal (12%).

Safety

No ALLO-647 or cema-cel/ALLO-501 dose-limiting toxicities were reported. The most common any-grade TEAEs (≥25%) were neutropenia (85%), anemia (67%), thrombocytopenia (58%), infusion-related reactions (IRRs; 58%), fatigue (52%), pyrexia (49%), nausea (39%), lymphopenia (36%), hypotension (36%), peripheral edema (33%), decreased WBC count (30%), CMV reactivation (30%), decreased appetite (30%), chills (30%), and hypoxia (27%; Table 2). Grade ≥3 TEAEs were reported in 94% of patients; the most common grade ≥3 TEAEs (≥25%) were neutropenia (82%), anemia (46%), thrombocytopenia (42%), lymphopenia (33%), and decreased WBC count (30%).

Among TEAEs of special interest, no cases of GVHD and ICANS were reported (Table 2). The incidence of any-grade CRS was 24%, and no cases of grade ≥3 CRS occurred. Grade ≥3 IRRs occurred in three patients (9%), all of which were considered related to ALLO-647. Any-grade infections occurred in 58% of patients, and grade ≥3 infections were reported in 15% of patients. There were no fatal infections. The most common any-grade infection was CMV reactivation, which occurred in 30% of patients; grade ≥3 CMV reactivation occurred in 12% of patients (Data Supplement, Table S1). Opportunistic infections were uncommon; these included fungal infection (6%; one case of oropharyngeal candidiasis, one unspecified fungal infection [both grade 2]) and one case of BK virus infection (3% [grade 2]). There were no reported cases of other opportunistic infections such as pneumocystis, mycobacterium avium complex, tuberculosis, varicella zoster virus, or progressive multifocal leukoencephalopathy. The proportion of all patients experiencing ongoing grade ≥3 cytopenias decreased with time from treatment from 30% at day 28 to 18% at day 56 and month 4 (Data Supplement, Table S2). The median time to absolute neutrophil count and absolute lymphocyte count recovery to grade ≤3 was 7 and 17.5 days, respectively (n = 30 and 22, respectively; Figs 2A and 2B). B cells were detectable starting 4 months after treatment in responders, whereas T-cell counts recovered to baseline between 6 and 9 months after cema-cel/ALLO-501 infusion (Data Supplement, Fig S2). Hypogammaglobulinemia was reported in five patients (15%), one of whom received treatment with intravenous immunoglobulin.

Serious TEAEs were reported in 42% of patients; the most common (>5%) were IRRs to ALLO-647 (6%), pyrexia (6%), bacteremia (6%), CMV reactivation (6%), pneumonia (6%), and COVID-19 (6%; Data Supplement, Table S3).

Two patients (6%) with PD had TEAEs that were considered the cause of death instead of disease progression; the AEs were respiratory failure and torsade de pointes, respectively

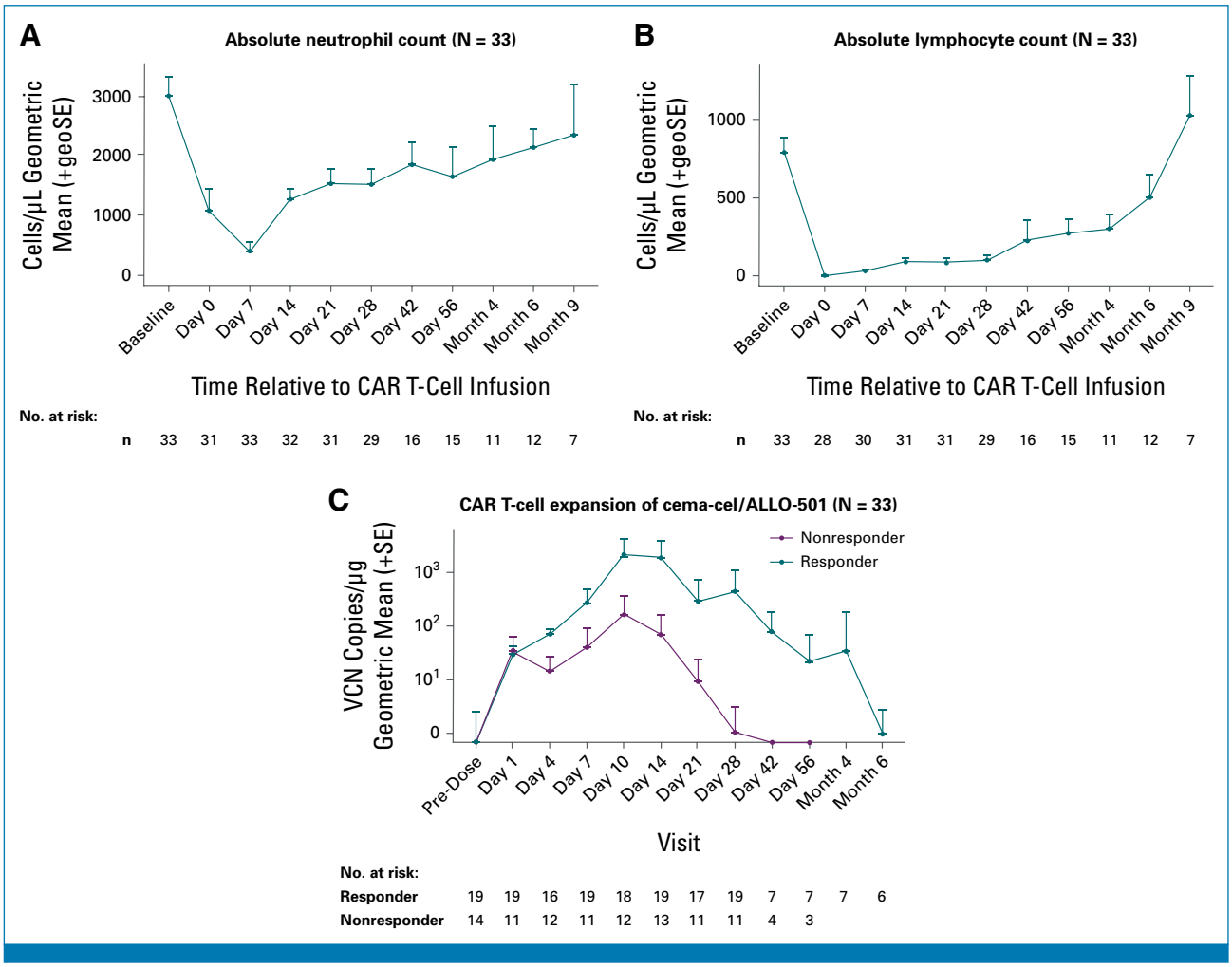

FIG 2. Immune recovery of leukocyte counts over time of CAR T-cell expansion: (A) ANC over time; (B) ALC over time; and (C) CAR T-cell expansion of cema-cel/ALLO-501 by responders versus nonresponders. ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CAR, chimeric antigen receptor; cema-cel, cemacabtagene ansegedleucel; geoSE, geometric standard error; VCN, vector copy number.

(n = 1 each). Neither event was considered related to cema-cel/ALLO-501 or ALLO-647.

Efficacy

Overall response and CR were achieved in 58% (95% CI, 39.2 to 74.5) and 42% (95% CI, 25.5 to 60.8) of patients, respectively (Table 3). For those patients receiving fludarabine/cyclophosphamide lymphodepletion with 90 mg of ALLO-647 (FCA90) followed by a single dose of at least 120×10^6 CAR+ cells (ie, the selected phase II regimen), disease response was observed in 67% (95% CI, 34.9 to 90.1), and CR was achieved in 58% (95% CI, 27.7 to 84.8). The ORR was higher in patients with baseline tumor burden <1,000 mm² sum of the products of longest diameters (SPD) versus >1,000 mm² SPD (100% *v* 50%), baseline lactate dehydrogenase (LDH) less than the upper limit of normal (ULN) versus greater than ULN (91% *v* 41%), and double/triple-hit versus no double/triple-hit disease (75% *v* 52%; Data Supplement, Fig S3A). Similarly, the CR rate was higher for those patients with baseline tumor burden <1,000 mm² SPD (100% *v* 31%, $P = .0033$) and baseline LDH ≤ULN (82% *v* 23%, $P = .0023$; Data Supplement, Fig S3B). The median durability of response (Fig 3A) was 11.1 months overall and 23.1 months in patients who achieved a CR. Among patients who had a CR, most were durable (Fig 4A). One patient had a competing risk event, death from an unrelated cardiac event at 22 months after treatment while in ongoing CR. The median progression-free survival was 3.9 months overall and 24.0 months in patients achieving a CR (Fig 4B); the median OS was 14.4 months (95% CI, 7.0 to not reached [NR]; Fig 3B) overall and NR in patients achieving a CR. For patients receiving the selected phase II regimen, the median DOR was 23.1 months, and the median OS was NR (95% CI, 4.6 to NR).

Translational Analyses

Analysis of cellular kinetics demonstrated that peak expansion was achieved at a median of 10 days. Mean peak expansion (geometric standard error of the mean) was 1,688 copies/µg and the mean AUC was 13,531 copies/µg × d, with both peak expansion and mean AUC higher in responders

TABLE 3. Summary of Treatment Efficacy

	CAR T-Naïve R/R LBCL	
Outcome	All Patients (N = 33)	Patients Who Received Selected Phase II Dose[a] (n = 12)
Best overall response, No. (%)		
CR	14 (42)	7 (58)
CR at 6 months	10 (30)	5 (42)
CR at 12 months	8 (24)	4 (33)
PR	5 (15)	1 (8)
SD	4 (12)	1 (8)
PD/death	10 (30)	3 (25)
ORR		
ORR, No. (%)	19 (58)	8 (67)
95% CI	39 to 75	35 to 90
DOR, months, median (95% CI)	11.1 (3.1 to NR)	23.1 (1.0 to NR)
OS, months (95% CI)	14.4 (7.0 to NR)	NR (4.6 to NR)

Abbreviations: CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; LBCL, large B-cell lymphoma; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease.
[a]Fludarabine/cyclophosphamide lymphodepletion with 90 mg of ALLO-647 (FCA90) followed by a single dose of CAR T cells at 120×10^6 CAR+ cells.

versus nonresponders (7,410 *v* 73, and 60,480 *v* 573), respectively (Fig 2C). The highest mean concentration of ALLO-647 and greatest exposure (AUC) was observed in patients who received the 90 mg total cumulative dose of ALLO-647 (Data Supplement, Fig S4A), with responders typically achieving a higher exposure of ALLO-647 than nonresponders (Data Supplement, Fig S4B). Higher exposure to ALLO-647 was also associated with increased interleukin-15 at day 0, which was consistent with the observed cellular kinetics in recipients of higher doses of ALLO-647 (Data Supplement, Fig S4C).

CAR T-product donor-specific antigen (DSA) testing was performed on patients during prescreening (N = 33). Only two patients had a DSA value above a threshold of 1,000 mean fluorescence intensity used to determine DSA reactivity. One of these patients achieved a CR, and the other had PD. Retrospective HLA matching analyses did not show correlation with outcomes (data not shown). HLA concordance was minimal, with no patients exceeding a 3/10 allelic match. Two responders had no allelic matches and yet achieved a PR and CR.

DISCUSSION

Despite improvement in outcomes for patients with R/R LBCL treated with CAR T-cell therapy, numerous limitations still exist for autologous CAR T-cell products including patient eligibility, lengthy wait times for product availability, inconsistent product quality, potential requirement for bridging therapy, and risk of severe toxicity following treatment.[10-12,14] As an off-the-shelf, allogeneic treatment option that circumvents logistical challenges and the need for bridging therapy, cema-cel may address many of these limitations.[12-14] In the ALPHA and ALPHA2 trials, the median time to start of treatment was 2 days from study enrollment; in contrast, autologous CAR T-cell products require wait times often longer than 1 month despite incremental advancements in manufacturing and supply chains.[31]

In this single-arm, multicenter, open-label, phase I experience of the ALPHA2 and ALPHA studies, cema-cel/ALLO-501 following ALLO-647–containing lymphodepletion demonstrated an overall safety profile, including the incidence of cytopenias and infections, that was manageable and consistent with that of currently available autologous CD19 CAR T-cell products, and no incidence of high-grade CRS or any-grade ICANS.[5-7,32] Furthermore, cema-cel/ALLO-501 showed promising ORR and CR rates in patients with R/R LBCL, including ongoing remissions beyond 4 years. These results highlight the feasibility of allogeneic CAR T-cell products as a treatment option for patients with LBCL.

Currently, three autologous CD19 CAR T-cell products are approved for treatment of LBCL.[5-9,32] In the pivotal trials leading to their approvals, autologous CAR T cells given to patients with R/R LBCL after two previous lines of therapy demonstrated rates of grade ≥3 ICANS of 10%-32%, whereas grade ≥3 CRS events ranged from 2% to 22%.[6,7,32,33] Among the 33 CAR T-naïve patients with R/R LBCL in the ALPHA2/ALPHA studies, there were no instances of ICANS or grade ≥3 CRS events, indicating potential benefits for this patient cohort within the current treatment landscape. Additionally, in the ALPHA2/ALPHA studies, there were no reports of GVHD, and the incidence and severity of infections were manageable with supportive care measures and consistent with that observed in autologous CAR T-cell therapy trials

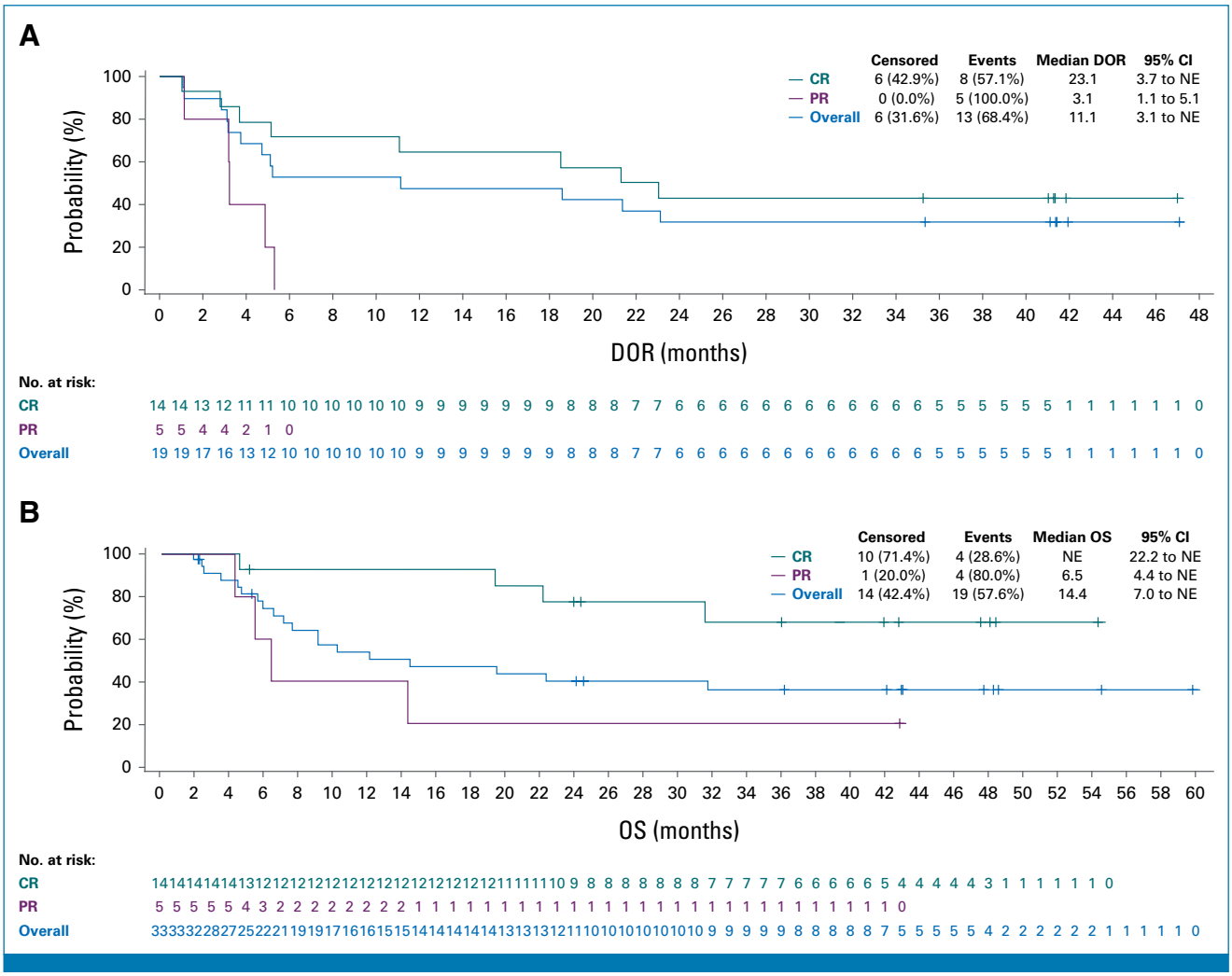

FIG 3. DOR and OS. (A) DOR in patients achieving CR, PR, and in overall population and (B) OS in patients achieving CR, PR, and in overall population. CR, complete response; DOR, duration of response; NE, not estimable; OS, overall survival; PR, partial response.

despite the use of enhanced lymphodepletion with ALLO-647. Specific PCR monitoring for CMV identified low-grade, asymptomatic viremia, but only four instances of grade 3 CMV reactivation, none of which was associated with invasive disease. No fatal infections were reported in this patient population.

Recently, the US Food and Drug Administration has raised concerns about the increased risk of T-cell malignancies following autologous CAR T-cell therapy.[34] Although the benefits of current autologous CAR T-cell products likely outweigh these potential risks, allogeneic CAR T-cell products may further mitigate these risks because the persistence of allogeneic CAR T-cells in patients is limited by allorejection of the cells.[5-7,32]

CR rates in the ALPHA2/ALPHA trials were consistent with those observed with autologous CD19 CAR T-cell products for patients with R/R LBCL after two previous lines of therapy, even without HLA matching patients to donors.[5-7,32] All treatment regimens studied demonstrated clinical benefit; however, FCA90 yielded the highest ORR and CR of 67% and 58%, respectively, with the majority of CRs lasting longer than 12 months after a single dose of cema-cel/ALLO-501 and therefore was identified as the selected phase II lymphodepletion regimen for use before cema-cel infusion. The median DOR was 23.1 months, and the median OS was NR for this subgroup of patients, demonstrating the durability of this treatment and associated prolonged survival outcomes.

Consistent with the autologous CAR T experience,[35] durable responses required establishing a CR and have been most frequent in patients with low disease burden. In the evaluated patients, all durable responses were CRs, and the CR rate was enriched in patients with low disease burden (6/6; 100%) and normal serum LDH concentrations (9/11; 82%) before treatment. These CR rates in the subpopulation of patients with low tumor burden and those with normal LDH support cema-cel as a promising therapeutic option in a remission consolidation setting.

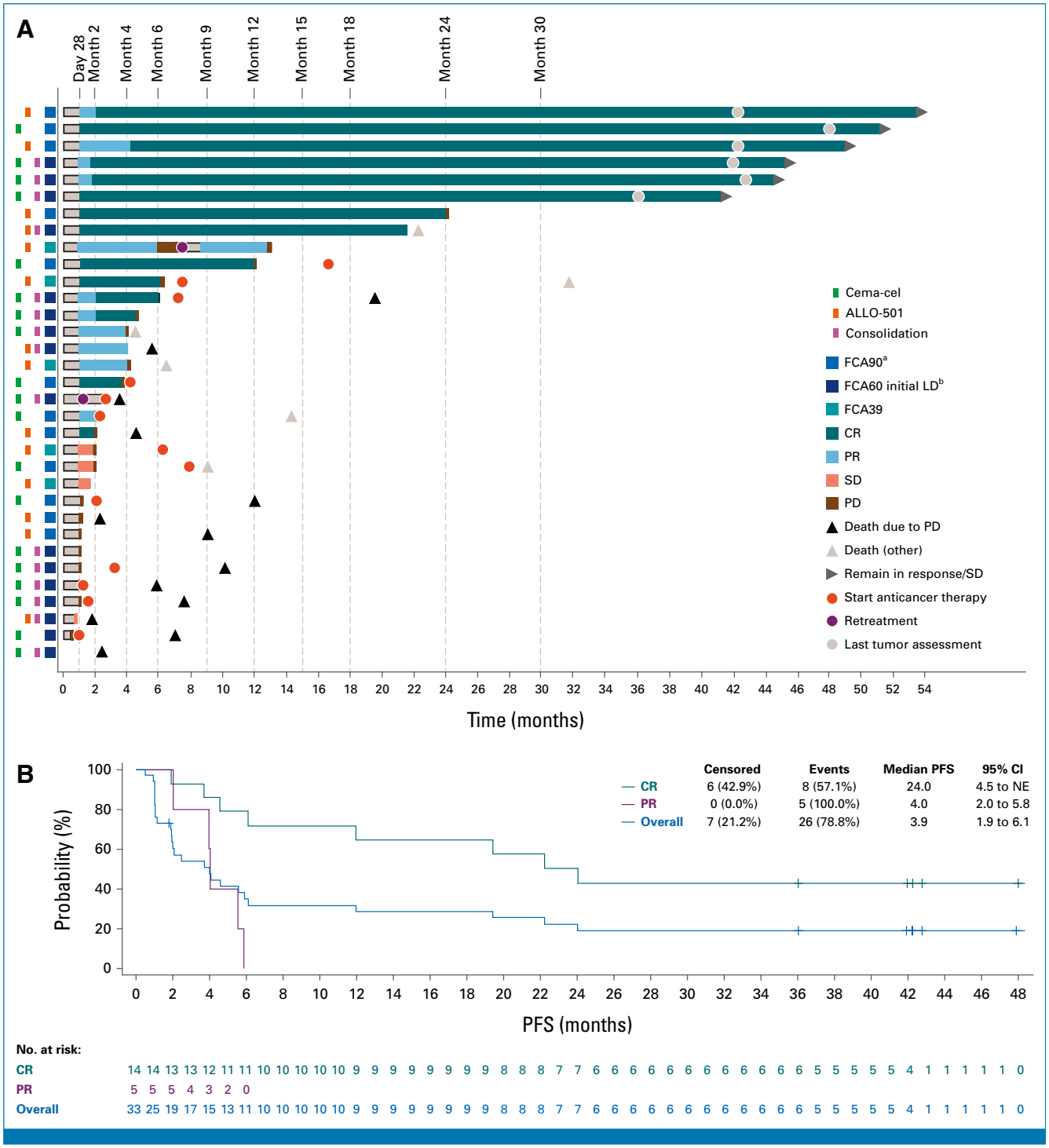

FIG 4. Response and PFS. (A) Swimmer plot of all patients and (B) PFS in patients achieving CR, PR, and in overall population. [a]FCA90 and FCA90/FCA60 (ALC-based) groups. [b]FCA60 + consolidation (LD followed by a single dose of cema-cel/ALLO-501 and then an additional dose of ALLO-647 on D29 and ALLO-501/cema-cel on D30). Cema-cel, cemacabtagene ansegedleucel; CR, complete response; D, day; FCA, fludarabine, cyclophosphamide, ALLO-647; LD, lymphodepletion; NE, not estimable; PFS, progression-free survival; PR, partial response; PD, progressive disease; SD, stable disease.

A growing body of evidence indicates that treatment with CAR T cells, at times when the disease burden is low, leads to improved safety and efficacy outcomes,[36-38] and we report similar findings in the ALPHA2/ALPHA studies (Data Supplement, Fig S3A). With autologous CAR T products approved for relapsed disease, the practical ability to treat patients with low tumor burden is determined by individual circumstances such as kinetics of disease recurrence and response to bridging therapy administered during product manufacturing. Additionally, the sensitivity and specificity

of positron emission tomography (PET)/computed tomography (CT) for patients with very low disease burden after they have completed a therapy are poor and thus currently require delaying the decision to treat with CAR T until clinical relapse. Recently, advances in circulating tumor (ct)DNA-based minimal residual disease (MRD) tests have yielded improved sensitivity in detecting microscopic disease in patients who are in clinical and metabolic complete remission by PET/CT. When detected in patients, MRD may be eradicated with an immediately available, off-the-shelf treatment like cema-cel. The ongoing, pivotal ALPHA3 study is exploring this hypothesis and is evaluating cema-cel in patients who achieve remission for which the current standard-of-care would be observation but who remain MRD-positive by a novel ctDNA-based MRD diagnostic test, PhasED-Seq,[39] at the end of first-line therapy. As an off-the-shelf treatment with a safety profile that is compatible with outpatient management and a preliminary efficacy profile in R/R LBCL that is similar to available autologous therapies, a clinically meaningful improvement in relapse prevention, measured in ALPHA3 by event-free survival, could fundamentally alter the front-line treatment paradigm for newly diagnosed LBCL.

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DATA SHARING STATEMENT

The study protocol is provided in the Data Supplement. Individual participant data will not be available.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Allogeneic Chimeric Antigen Receptor T-Cell Products Cemacabtagene Ansegedleucel/ALLO-501 in Relapsed/Refractory Large B-Cell Lymphoma: Phase I Experience From the ALPHA2/ALPHA Clinical Studies

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