ALPHA3: A Pivotal Phase 2 Study of First-Line Consolidation With Cemacabtagene Ansegedleucel (Cema-Cel) in Patients With Large B-Cell Lymphoma and Minimal Residual Disease After Response to Standard Therapy

Poster 3132.1

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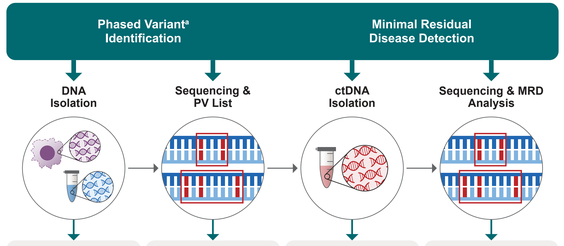
INTRODUCTION

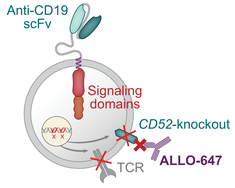
- Approximately 60% of patients with LBCL who receive standard 1L therapy achieve cure; however, ~30% of patients in remission at the end of therapy are expected to relapse within 2 years[1-3]
- Through PhasED-Seq powered MRD testing (**Figure 1**), these patients at highest risk of relapse can be identified, which will enable changing the current lymphoma treatment paradigm from watching and waiting for relapse to consolidating therapy for cure
- Cemacabtagene ansegedleucel (cema-cel) is an immediately available, off-the-shelf, allogeneic CD19 CAR T cell product (**Figure 2**) that has shown potent anti-tumor activity with manageable safety in phase 1 trials of patients with relapsed/refractory LBCL[4,5] and is a promising agent for consolidation in this time-sensitive treatment setting
- Treating patients with LBCL and low disease burden is favorable because it ensures treatment prior to aggressive relapse or development of new comorbidities that could preclude treatment in later lines. Additionally, this treatment setting has been shown to lead to more favorable efficacy outcomes and fewer treatment-related toxicities[6-8]
- Here, we describe the design of the pivotal ALPHA3 (NCT06500273) phase 2 study, the first randomized, open-label study to assess a CAR T cell therapy as a consolidation strategy in patients with detectable MRD measured by PhasED-Seq after standard 1L immunochemotherapy

Figure 1: PhasED-Seq Technology



[a] PVs are two or more single nucleotide variants identified in close proximity on the same DNA molecule. [b] The panel leverages established mutational hot-spots for B-cell malignancies.
ctDNA, circulating tumor DNA; MRD, minimal residual disease; PV, phased variant.

Figure 2: Cemacabtagene Ansegedleucel (Cema-Cel)[a]



Knockout of *CD52* prevents binding and elimination of CAR T cells by ALLO-647, a proprietary anti-CD52 monoclonal antibody used in lymphodepletion

[a] Utilizes Cellectis technologies.
CAR, chimeric antigen receptor; scFv, single chain fragment variable; TCR, T-cell receptor.

METHODS

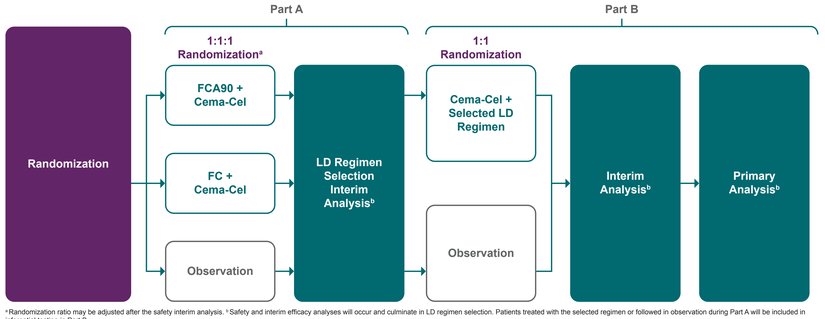
- The ALPHA3 study will consist of a 2-part seamless design (**Figure 3**):
  - Part A
    - Randomized patients will be followed in the standard-of-care observation arm or in either one of the treatment arms (cema-cel [120×10^6 CAR T cells] following 3-day standard fludarabine [30 mg/m^2/day] and cyclophosphamide [300 mg/m^2/day] lymphodepletion with or without the anti-CD52 monoclonal antibody, ALLO-647 [30 mg/day]) in a 1:1:1 ratio
    - The selected lymphodepletion regimen for Part B will be chosen after an early interim analysis, at which time emerging data will be assessed
  - Part B
    - Randomized patients will receive treatment with the selected lymphodepletion regimen or be followed in the observation arm until the completion of accrual in a 1:1 ratio
    - An interim efficacy analysis and a primary analysis will be performed (**Table 1**)
- Treatment can occur in the inpatient or outpatient setting
- To be eligible to screen for the ALPHA3 study, patients must successfully complete prescreening (**Figure 4**, **Table 2**):
  - Posttreatment positron emission tomography/computed tomography (PET/CT) must show complete response or partial response for which the standard of care would be close observation (eg, negative biopsy of PET-avid lesion)
  - MRD testing by PhasED-Seq requires a tumor sample from initial diagnosis and a blood sample collected at or shortly after end-of-treatment PET/CT
  - Only MRD+ patients may proceed to screening and undergo further eligibility assessments

Table 1: Study Endpoints

Primary
• EFS per IRC[a]
Secondary
• PFS per IRC[a,b]
• OS[b]
• Rate of MRD clearance
• EFS per investigator[a]
• PFS per investigator[a]
• Safety (cema-cel and ALLO-647)
Exploratory
• PK/PD (cema-cel and ALLO-647)
• Immunogenicity
• PROs

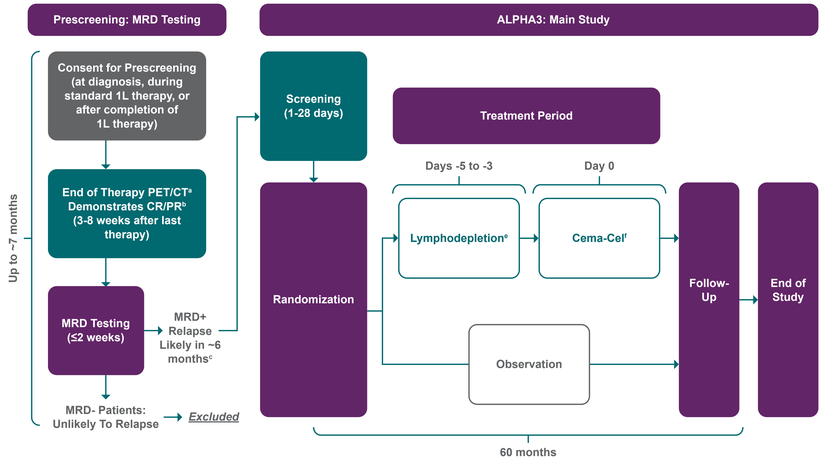
[a] Assessed per Lugano 2014 criteria. [b] EFS per IRC, PFS per IRC, and OS underwent hierarchical testing.
Cema-cel, cemacabtagene ansegedleucel; EFS, event-free survival; IRC, independent review committee; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; PK/PD, pharmacokinetics/pharmacodynamics; PRO, patient-reported outcome.

Figure 3: ALPHA3 Study Design



[a] Randomization ratio may be adjusted after the safety interim analysis. [b] Safety and interim efficacy analyses will occur and culminate in LD regimen selection. Patients treated with the selected regimen or followed in observation during Part A will be included in inferential testing in Part B.
Cema-cel, cemacabtagene ansegedleucel; FC, fludarabine and cyclophosphamide; FCA90, fludarabine and cyclophosphamide and ALLO-647 (90 mg); LD, lymphodepletion.

Figure 4: ALPHA3 Study Patient Journey



[a] Posttreatment PET is completed 3-8 weeks after last cycle of chemotherapy. PET does not need to be repeated if completed within 5 weeks of study enrollment. Diagnostic CT must also be completed within 5 weeks of study enrollment. [b] PR suitable for observation is defined as follows: all remaining PET-avid lesions have a Deauville score <5 by investigator assessment on end-of-therapy PET and intent to observe the patient without further treatment (including radiation therapy) until definitive disease progression. [c] In previous studies of PhasED-seq MRD at end of treatment, patients relapsed at a median of <6 months after the end of therapy. [d,f] Treatment can be done in the inpatient or outpatient setting. [e] The 3-day lymphodepletion regimen will consist of fludarabine (30 mg/m^2/day), cyclophosphamide (300 mg/m^2/day), and may include ALLO-647 (30 mg/day). [f] 120×10^6 CAR T cells.
1L, first line; CAR, chimeric antigen receptor; cema-cel, cemacabtagene ansegedleucel; CR, complete response; CT, computed tomography; LBCL, large B-cell lymphoma; MRD, minimal residual disease; PET, positron emission tomography; PR, partial response.

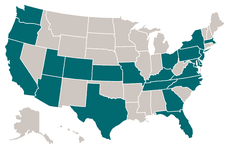
Table 2: Key Study Eligibility Criteria

Criteria for MRD Testing	Key Inclusion Criteria	Key Exclusion Criteria
Histologically confirmed DLBCL,[a] HGBCL, PMBCL	MRD+ by PhasED-Seq	Prior treatment with CD19-targeted therapies
Completed a full course of standard 1L therapy (must have included an anthracycline and an anti-CD20 monoclonal antibody), for example: • R-CHOP • Pola-R-CHP • DA-EPOCH-R	ECOG PS of 0 or 1	History of CNS involvement, transformation from other malignancy (transformed FL or MZL, or Richter's transformation), or T-cell/histiocyte-rich LBCL
Achieved a CR or PR suitable for observation[b] at the completion of 1L treatment based on PET/CT evaluation per Lugano 2014 criteria[c]	No progression since MRD testing	History of clinically significant CNS dysfunction (eg, seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema)
MRD samples available for submission • Adequate tumor specimen from initial diagnosis • Adequate blood sample collected after final 1L treatment[c]	Adequate hematologic, cardiac, pulmonary, renal, and hepatic function	Ongoing treatment with systemic immunosuppressive agents within 2 weeks prior to enrollment[d]

[a] Includes DLBCL not otherwise specified, Epstein-Barr virus+ DLBCL, DLBCL with *IRF4/MUM1* rearrangement; high-grade B-cell lymphoma; and primary mediastinal B-cell lymphoma. [b] PR suitable for observation is defined as follows: all remaining PET-avid lesions have a Deauville score <5 by investigator assessment on end-of-therapy PET and intent to observe the patient without further treatment (including radiation therapy) until definitive disease progression. [c] Between 3 and 8 weeks after final treatment. [d] Exception of physiologic replacement corticosteroids at <10 mg of prednisone equivalents daily, inhaled steroids for asthma, topical steroid use, or another local corticosteroid administration.
1L, first line; CNS, central nervous system; CR, complete response; CT, computed tomography; DA-EPOCH-R, dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; LBCL, large B-cell lymphoma; MRD, minimal residual disease; MZL, marginal zone lymphoma; PET, positron emission tomography; PMBCL, primary mediastinal B-cell lymphoma; Pola-R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

STUDY STATUS AND CONTACTS

- Approximately 240 patients will be enrolled across ~50 sites at both academic- and community-based cancer centers
- Site activation is ongoing, with over 50% of sites activated. Additional study sites are being considered
- The study was initiated in June 2024 and plans to fully accrue into 2026
- For more information, please visit www.clinicaltrials.gov
- Contact email: ALPHA3@allogene.com



Anticipated Study Locations

Arizona	Kansas	New York	Texas
California	Kentucky	North Carolina	Utah
Colorado	Massachusetts	Ohio	Virginia
Delaware	Maryland	Oregon	Washington
Florida	Missouri	Pennsylvania	Washington, DC
Georgia	New Jersey	Tennessee	

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