ALPHA3: A Pivotal Phase 2 Study Evaluating the Safety and Efficacy of First-Line (1L) Consolidation With Cemacabtagene Ansegedleucel (Cema-cel) in Patients With Large B-cell Lymphoma (LBCL) and Minimal Residual Disease (MRD) After Response to Standard Therapy

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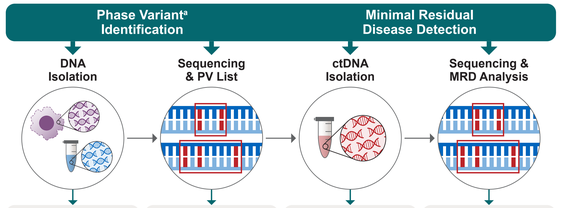
BACKGROUND

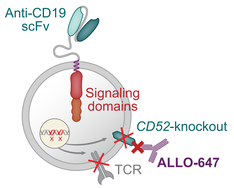
- Outcomes of patients with LBCL treated with 1L immunochemotherapy are favorable, with approximately 60% of patients achieving cure; however, an unmet medical need remains at the conclusion of 1L therapy as approximately 30% of patients achieving remission are expected to relapse within 2 years[1-3]
- Accurately identifying responding patients who will experience relapse from those who are cured at the end of 1L treatment is challenging[4]; retrospective data show that PhasED-Seq, a novel next generation sequencing-based test for MRD in LBCL (**Figure 1**), is both highly sensitive and highly specific in predicting relapse[5]
- Cema-cel is an off-the-shelf, allogeneic CD19 chimeric antigen receptor (CAR) T cell (AlloCAR T™) product (**Figure 2**), that has shown potent anti-tumor activity with managable safety in Phase 1 trials of patients with relapsed/refractory LBCL[6,7]
- 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[8-10]
- Here, we describe the design of the pivotal ALPHA3 Phase 2 study, the first randomized, open-label study to assess an allogeneic CAR T cell product (cema-cel) for remission consolidation in patients with 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)



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

CAR, chimeric antigen receptor; scFv, single chain fragment variable; TCR, T-cell receptor.

METHODS

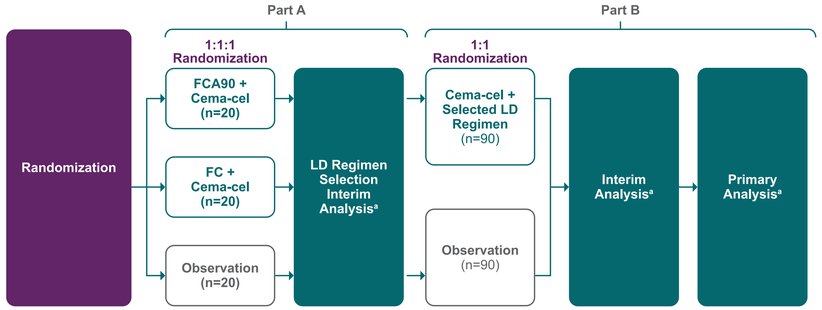
- The ALPHA3 study will consist of a 2-part seamless design (**Figure 3**):
  - Part A
    - Randomized patients will be followed in either one of the treatment arms (cema-cel [120×10^6 CAR T cells] following 3-day standard fludarabine [30 mg/m^2/day] and cyclophosphamide [300 mg/m^2/day] lymphodepletion with or without ALLO-647 [30 mg/day]) or to the standard-of-care observation arm in a 1:1:1 ratio
    - The selected lymphodepletion regimen will be chosen after an early interim analysis, at which 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 pre-screening (**Figure 4**, **Table 2**):
  - Post-treatment 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

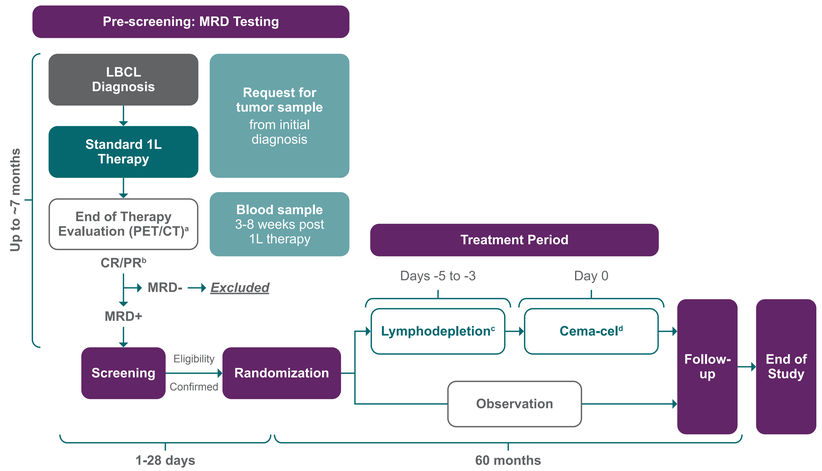
[a] Assessed per Lugano 2014 criteria. [b] Key secondary endpoints of PFS per IRC and OS are hierarchical.
cema-cel, cemacabtagene ansegedleucel; EFS, event-free survival; IRC, independent review committee; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; PK/PD, pharmacokinetics/pharmacodynamics;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

Figure 3: ALPHA3 Study Design



[a] There will be a safety interim analysis after 12 patients have been enrolled and followed for 45 days in each arm. Patients treated with the selected regimen or followed in observation during Part A (n=20) will be added to Part B (n=90) analyses with 110 patients evaluated in total per arm.
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] Post-treatment 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. [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] 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). [d] 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; MRD-, MRD negative; MRD+, MRD positive; PET, positron emission tomography; PR, partial response.

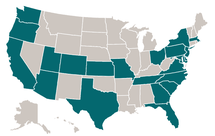
Table 2: Key Study Eligibility Criteria

Criteria for MRD Testing	Key Inclusion Criteria	Key Exclusion Criteria
Histologically confirmed LBCL	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[a] at the completion of 1L treatment based on PET/CT evaluation per Lugano 2014 criteria[b]	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[b]	Adequate hematologic, cardiac, pulmonary, renal, and hepatic function	Ongoing treatment with systemic immunosuppressive agents within 2 weeks prior to enrollment[c]

[a] 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. [b] Between 3 and 8 weeks after final treatment. [c] 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; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; LBCL, large B-cell lymphoma; MZL, marginal zone lymphoma; MRD, minimal residual disease; MRD+, MRD positive; Pola-R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; PET, positron emission tomography; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

STUDY STATUS AND CONTACTS

- ALPHA3 is actively recruiting patients to be enrolled across ~50 academic and community-based cancer centers
- Additional study sites are being considered outside of the United States
- For more information, please visit www.clinicaltrials.gov
- Contact email: ALPHA3@allogene.com



Anticipated Study Locations

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

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ACKNOWLEDGMENTS

Allogene's investigational AlloCAR T™ oncology products utilize Cellectis technologies. These products are developed based on an exclusive license granted by Cellectis to Servier. Servier, which has an exclusive license to the anti-CD19 AlloCAR T™ investigational products from Cellectis, has granted Allogene exclusive rights to these products in the U.S., all EU Member States and the United Kingdom.

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