ALPHA2-CLL: A Phase 1b Study Evaluating the CD19 Allogeneic CAR T Cell Product Cemacabtagene Ansegedleucel (Cema-Cel) in Patients With Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

Poster CT-419

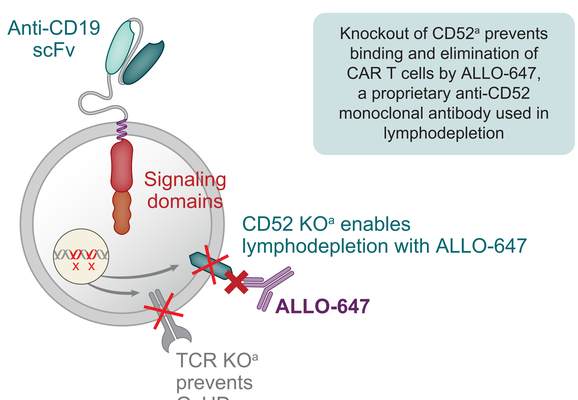
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INTRODUCTION

- Treatment of first-line CLL/SLL has evolved with the introduction of Bruton tyrosine kinase inhibitors (BTKi) and B-cell lymphoma 2 inhibitors (BCL2i) into the standard of care; however, patients ultimately relapse[1,2]
- Double refractoriness to BTKi and BCL2i confers poor prognosis (median overall survival, 8 months)[3]
- Despite the success of autologous chimeric antigen receptor (CAR) T cell therapies in other B-cell malignancies, similar outcomes have not been demonstrated in patients with R/R CLL,[4] likely due in part to suboptimal efficacy attributed to disease-driven T-cell dysfunction,[5] manufacturing challenges, and access barriers[6]
- Allogeneic CAR T cells derived from healthy donors may naturally overcome these challenges of autologous CAR T cell therapy, while providing an off-the-shelf, single-dose option for patients with CLL
- Cema-cel is an off-the-shelf, allogeneic CD19 CAR T cell (AlloCAR T™) product (**Figure 1**) that has shown potent antitumor activity with manageable safety in the phase 1 ALPHA2 study of patients with R/R large B-cell lymphoma[7,8]
- Here, we describe the design of the new phase 1b CLL cohort of the ALPHA2 study evaluating patients with high-risk, R/R CLL/SLL who progressed on BTKi/BCL2i

Figure 1: Cemacabtagene Ansegedleucel (Cema-cel)



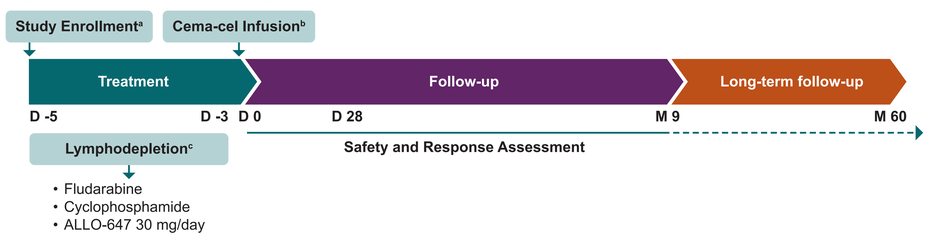
Knockout of CD52[a] prevents binding and elimination of CAR T cells by ALLO-647, a proprietary anti-CD52 monoclonal antibody used in lymphodepletion

[a]Knockout performed using TALEN® gene editing technology.
CAR, chimeric antigen receptor; GvHD, graft versus host disease; KO, knockout; scFv, single chain fragment variable; TCR, T-cell receptor.

METHODS

- ALPHA2 (NCT04416984) is a single-arm, open-label, multicenter study evaluating the safety, efficacy, cellular kinetics, and immunogenicity of cema-cel in patients with R/R CLL/SLL (**Figure 2**, **Table 1**)

Figure 2: ALPHA2 Study Design: CLL Cohort



The recommended phase 2 dose was determined by the phase 1 LBCL cohort.[7] [a] Study enrollment was within 7 days of lymphodepletion. [b] Cema-cel 120×10^6 CAR+ cells. [c] Three-day lymphodepletion regimen consisting of fludarabine 30 mg/m^2/day, cyclophosphamide 300 mg/m^2/day, and ALLO-647 30 mg/day (FCA90). Alternative cema-cel doses of 40-80×10^6 CAR T cells may be explored. Alternative regimens of lymphodepletion may be considered by the safety review committee based on emerging safety and translational data; regimens to be explored include reduced cumulative dosing of ALLO-647 (0-20 mg/day) as part of FC or FCA regimens (FC, FCA30, FCA60).
CAR, chimeric antigen receptor; cema-cel, cemacabtagene ansegedleucel; CLL, chronic lymphocytic leukemia; D, day; FC, fludarabine/cyclophosphamide; FCA, fludarabine/cyclophosphamide/ALLO-647; LBCL, large B-cell lymphoma; M, month.

Table 1: Key Study Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
Adult patients with diagnosis of CLL or SLL	Diagnosis of Richter's transformation of CLL
Relapsed or refractory disease (1 of the following 2 criteria): • ≥1 prior line of therapy, progression on a BTKi, and high-risk disease (del17p, *TP53* mutated, complex karyotype [≥3 clonal chromosomal abnormalities]) • ≥2 prior lines of therapy including exposure to and failure of a BTKi[a] and exposure to a BCL2i	Prior autologous or allogeneic HSCT within last 6 months prior to ALLO-647
≥1 measurable lesion per iwCLL 2018 criteria[9]	Prior treatment with anti-CD19–targeted therapies
ECOG PS of 0 or 1	Active systemic bacterial, fungal, or viral infection requiring systemic treatment
Adequate hematologic, cardiac, pulmonary, renal, and hepatic function	History of CNS involvement or clinically significant CNS dysfunction (eg, seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema)

[a] Defined as PD or SD as best response, progressive disease after prior response, or intolerance due to unmanageable toxicity.
BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CNS, central nervous system; del17p, deletion of short arm of chromosome 17; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplantation; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; PD, progressive disease; SD, stable disease; SLL, small lymphocytic leukemia; *TP53*, tumor protein p53.

PROOF OF CONCEPT COHORT

- Approximately 12 patients with CLL/SLL will be treated with the recommended phase 2 dose of cema-cel (120×10^6 CAR+ cells) following lymphodepletion with fludarabine 30 mg/m^2/day, cyclophosphamide 300 mg/m^2/day, and ALLO-647 30 mg/day (FCA90; **Figure 2**)
- After ≥28 days of follow-up, emerging safety data will be assessed by a safety review committee
- Assessments will include safety, efficacy, and exploratory/translational analyses (**Table 2**)

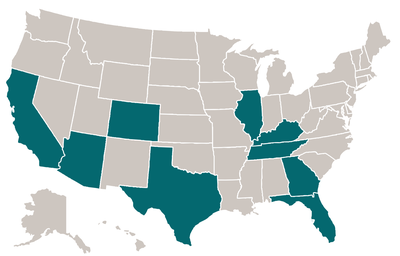
Table 2: Study Endpoints

Primary
• Safety (cema-cel)
Secondary
• ORR per investigator assessment
• DOR[a]
• PFS per investigator assessment
• Time to response
• OS
• PK/PD (ALLO-647)
• Cellular kinetics (cema-cel)
• Immunogenicity (cema-cel and ALLO-647)
• Safety (cema-cel and ALLO-647)
Exploratory/Translational
• Biomarkers assessment (flow cytometry and serum cytokine assessment)
• MRD

[a] Assessed per iwCLL 2018 criteria.
Cema-cel, cemacabtagene ansegedleucel; DOR, duration of response; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK/PD, pharmacokinetics/pharmacodynamics.

STUDY STATUS AND CONTACTS

- Study enrollment is ongoing with up to ~40 patients planned across ~20 sites in the United States
- For more information, please visit www.clinicaltrials.gov
- Contact email: clinicaltrials@allogene.com



Study Locations

Arizona, California, Colorado, Florida, Georgia, Illinois, Kentucky, Tennessee, Texas

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ACKNOWLEDGMENTS

Allogene's investigational AlloCAR T™ oncology products utilize Cellectis technologies. The anti-CD19 oncology 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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