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A PHASE 1 STUDY OF AMG 119, A DLL3-TARGETING, CHIMERIC ANTIGEN RECEPTOR (CAR) T CELL THERAPY, IN RELAPSED/REFRACTORY SMALL CELL LUNG CANCER (SCLC)

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Background AMG 119 is a CAR-T cell therapy that targets delta-like ligand 3 (DLL3), an inhibitory Notch ligand that is expressed on the surface of most SCLC cells. In preclinical studies, AMG 119 specifically lysed DLL3-expressing SCLC cell lines and inhibited tumor growth in SCLC xenograft models.¹

Methods Primary objectives of this open-label, phase 1 study are to determine the safety, tolerability, and optimum cell dose of AMG 119 in adults with relapsed/refractory SCLC who progressed after ≥ 1 platinum-based chemotherapy regimen. Safety, efficacy, pharmacokinetics, and biomarkers were assessed.

Results At data cutoff, 5 adult subjects (median age: 59 years [range, 33-64], ECOG status: 0-1, ≥ 1 prior line of anticancer therapy) had received at least 1 intravenous infusion of AMG 119 as part of cohort 1 (n = 3; 3×10^5 cells/kg) or cohort 2 (n = 2; 1×10^6 cells/kg) in the dose exploration phase. One subject in cohort 1 and both subjects in cohort 2 were re-treated with a second dose.

Post-infusion, a grade 1 treatment-related adverse event (TRAE) was noted in 1 subject (seizure), grade 2 TRAEs in 2 subjects (anemia and supraventricular tachycardia), and a grade 3 TRAE in 1 subject (pneumonitis; cohort 1). No dose-limiting toxicities or grade 4/5 TRAEs were observed.

Among evaluable subjects (n=4), a confirmed partial response (PR) was seen in 1 subject (cohort 2) 1.1 months after the first dose. Two subjects had stable disease, including 1 subject who experienced a 16% decrease in sum of the target lesions from baseline. One subject had progressive disease. Median progression-free survival was 3.7 months (range, 1.1-6.7) and median overall survival was 7.4 months (range, 4.6-18.9).

AMG 119 exhibited peak expansion 1-3 weeks after infusion; CAR-T cells were detectable up to 86 days in both cohorts. A preliminary dose-response relationship was observed with higher CAR-T cell expansion (~ 14 -fold increased C_{max} and AUC_{0-28d}) in the subject with confirmed PR compared with the nonresponder (cohort 2). DLL3 expression was detected by immunohistochemistry on $>85\%$ of tumor cells in all evaluable subjects at all assessed timepoints. Changes in serum/whole blood markers were consistent with a pharmacodynamic response. The subject who achieved PR exhibited a rapid decline in total circulating tumor cell levels within 7 days of treatment initiation.

Conclusions AMG 119, the first CAR-T cell therapy for SCLC, was associated with a manageable safety profile and promising anti-tumor activity. Enrollment is currently paused but may resume.

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Trial Registration NCT03392064

REFERENCE

1. Byers LA, Chiappori A, Damiette Smit MA. Phase 1 study of AMG 119, a chimeric antigen receptor (CAR) T cell therapy targeting DLL3, in patients with relapsed/refractory small cell lung cancer (SCLC). *J Clin Oncol*. 2019;**37**:15_suppl. doi:10.1200/JCO.2019.37.15_suppl.TPS8576.

Ethics Approval This human study was approved by the Moffitt Cancer Center's Institutional Review Board (IRB Approval Number 00000971) and MD Anderson Cancer Center's Institutional Review Board (Ethics Board Approval Number: 2017-1072).

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