TTLC 2026 Abstract

Keywords (up to 10): CAR T cells, clinical trial, solid tumor, lung cancer, biomarker, HLA-A, mesothelin, KRAS, STK11

Title: Complete Response in a patient with KRAS/STK11-mutated NSCLC treated with A2B694, a logic-gated mesothelin-targeted Tmod CAR T therapy to treat solid tumors with HLA-A*02 loss of heterozygosity: initial safety and efficacy results from the EVEREST-2 study

Authors: Leal AI[1], Punekar SR[1], Ward JP[2], Prasad DK[3], Marar RI[3], Fankuchen O[1], Garon EB[4], Creelan B[5], Hazim AZ[6], Patel SP[7], Neal JM[8], He K[9], Lou Y[10], Langeberg W[11], Palluconi G[11], Mardiros A[11], Welch J[11], Ng EW[11], Molina JR[3]

Affiliations:

1. NYU Langone Health, New York City, NY, USA
2. Washington University in St. Louis, St. Louis, MO, USA
3. Mayo Clinic, Rochester, MN, USA
4. UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA
5. Moffitt Cancer Center, Tampa, FL, USA
6. Mayo Clinic Scottsdale, Scottsdale, AZ, USA
7. University of California San Diego, San Diego, CA, USA
8. Stanford University, Stanford, CA, USA
9. Ohio State Universtiy, Columbus, OH, USA
10. Mayo Clinic Jacksonville, Jacksonville, FL, USA
11. A2 Biotherapeutics, Inc., Agoura Hills, CA, USA

Introduction: Mesothelin is overexpressed in many cancer types. Loss of heterozygosity (LOH) may provide a means to target tumor versus normal cells and to augment the efficacy and safety of mesothelin-targeted programs [1-4]. A2B694 is an autologous, logic-gated, Tmod CAR T therapy to improve tumor selectivity and decrease toxicity by integrating a mesothelin CAR activator with a human leukocyte antigen (HLA)-A*02 blocker (**Figure**) [5,6].

Methods: The first-in-human, open-label, phase 1/2 EVEREST-2 study is evaluating safety and efficacy of A2B694 in patients with recurrent/metastatic mesothelin-expressing cancers with tumor-associated HLA-A*02 LOH. The prescreening study BASECAMP-1 (NCT04981119) identifies eligible patients and cryopreserves leukapheresis product. Upon progression, A2B694 is manufactured and administered after lymphodepletion. Phase 1 primary objective: evaluate the safety and tolerability of A2B694 and identify a recommended phase 2 dose (RP2D). Phase 2 primary objective: assess overall response rate.

Results: As of 11 September 2025, 9 patients were enrolled: 6 women/3 men, median age 67y, 8 non-Hispanic White/1 Hispanic. Tumor types included ovarian (n=3), pancreatic (n=2), non–small cell lung adenocarcinoma (NSCLC), colorectal, gastro-esophageal, and mesothelioma (n=1 each). A2B694 dose groups were 1×10^8 (n=3), 2×10^8 (n=4), and 4×10^8 (n=2) cells. Lymphodepletion prior to

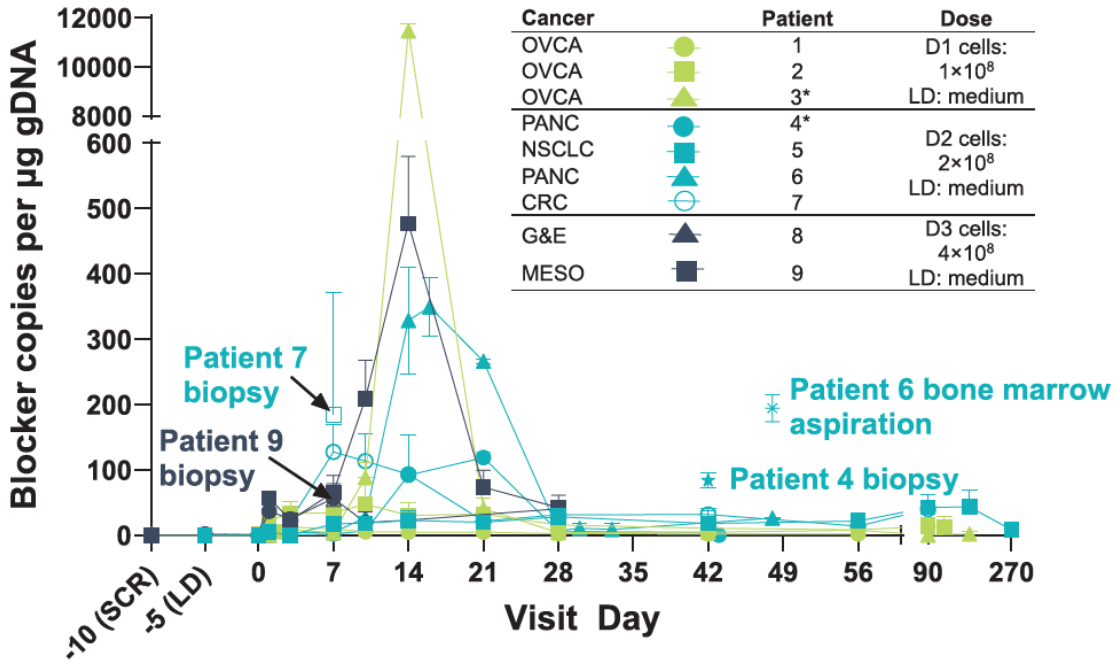
administration of A2B694 was well-tolerated, with expected, transient cytopenias. All patients had ≥1 adverse event; the only adverse event reported in more than 1 patient was grade 3 neutropenia. One patient had grade 3 ICANS. There were no dose-limiting toxicities, cytokine release syndrome, or new safety signals after up to 12 months follow-up.

All 9 patients received A2B694, were efficacy-evaluable, and had A2B694 detected post-infusion in peripheral blood. A2B694 was detected in a tumor biopsy collected on Day (D)42, demonstrating A2B694 persists in the tumor microenvironment.

A patient with $KRAS^{G12V}$/STK11 co-mutated NSCLC who had progressed on carboplatin, pemetrexed, and pembrolizumab achieved a complete response (CR) at D90 post-infusion and had a confirmed CR per RECIST 1.1 by central review at D180. In addition, PET-CT scan and ctDNA on D190 demonstrated no evidence of disease. On D243, the patient had a CNS relapse, with an ongoing non-CNS CR per RANO-BM at D284. At month 12, the patient's CT showed no new findings.

Conclusions: We report the first patient with NSCLC to have a CR after CAR T. Overall, A2B694 demonstrated manageable safety and tolerability in patients with advanced solid mesothelin-expressing tumors with tumor-associated HLA-A*02 LOH. The maximum tolerated dose has not been reached and dose-escalation to determine RP2D continues.

Figure: A2B694 Levels in Peripheral Blood Over Time (ddPCR)



Plotted values represent mean and standard deviation from triplicate wells.
*Received half dose level due to body weight.

Below not included in word count:

Trial registration: ClinicalTrials.gov, NCT06051695

Acknowledgments: The authors would like to thank the patients, their families, and their caregivers for participating in this trial; the investigators, screeners, clinical research coordinators, study nurses, data managers, and apheresis teams at each study site; and A2 Bio.

References:

1. Hecht J et al. Next generation sequencing (NGS) to identify relapsed gastrointestinal (GI) solid tumor patients with human leukocyte antigen (HLA) loss of heterozygosity (LOH) for future logic-gated CAR T therapy to reduce on target off tumor toxicity. J Clin Oncol. 2022; 40(suppl 4): 190.
2. Beatty GL et al. Activity of Mesothelin-Specific Chimeric Antigen Receptor T Cells Against Pancreatic Carcinoma Metastases in a Phase 1 Trial. Gastroenterology. 2018; 155: 29-32.
3. Haas AR et al. Two cases of severe pulmonary toxicity from highly active mesothelin-directed CAR T cells. Mol Ther. 2023; 31: 2309-2325.
4. Hong D et al. 959O Gavocabtagene autoleucel (gavo-cel, TC-210) dose escalation in refractory mesothelin-expressing solid tumors. Ann Oncol. 2021; 32(suppl 5): S830.
5. Hamburger AE et al. Engineered T cells directed at tumors with defined allelic loss. Mol Immunol. 2020; 128: 298-310.
6. Punekar SR et al. EVEREST-2: Initial data of the logic-gated Tmod chimeric antigen receptor T-cell (CAR T) therapy A2B694 for patients with solid tumors associated with mesothelin (MSLN) expression and with human leukocyte antigen (HLA) loss of heterozygosity (LOH). J Clin Oncol. 2025; 43(16 suppl): 3040.