Abstract #TPS2677

Posterboard 319b

Logic-gated, allogeneic Tmod chimeric antigen receptor T-cell (CAR T) therapy targeting epidermal growth factor receptor (EGFR) in advanced solid tumors with human leukocyte antigen (HLA) loss of heterozygosity (LOH): DENALI-1 trial

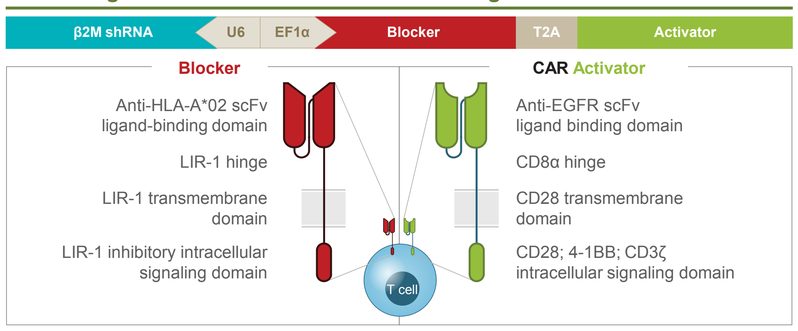
Kedar Kirtane,[1] Jong Chul Park,[2] Matthew Ulrickson,[3] Deborah J. Wong,[4] John B. Sunwoo,[5] Julian R. Molina,[6] David G. Maloney,[7] Marcela Maus,[2] Harry E. Fuentes Bayne,[6] Patrick M. Grierson,[8] Salman R. Punekar,[9] Frederick L. Locke,[1] Marco Davila,[10] Rebecca A. Shatsky,[11] Wendy J. Langeberg,[12] William Y. Go,[12] Eric W. Ng,[12] John S. Welch,[12] J. Randolph Hecht,[13] Jennifer M. Specht[7]

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]Massachusetts General Hospital, Boston, MA, USA; [3]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [4]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [5]Stanford University, Stanford, CA, USA; [6]Mayo Clinic, Rochester, MN, USA; [7]Fred Hutchinson Cancer Center, Seattle, WA, USA; [8]Washington University in St. Louis, St. Louis, MO, USA; [9]New York University Langone Health, Perlmutter Cancer Center New York, NY, USA; [10]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [11]University of California San Diego, San Diego, CA, USA; [12]A2 Biotherapeutics, Inc., Agoura Hills, CA, USA; [13]UCLA Jonsson Comprehensive Cancer Center, Santa Monica, CA, USA.

BACKGROUND AND STUDY OBJECTIVES

- Chimeric antigen receptor T-cell (CAR T) therapies face significant challenges in solid tumors due to the lack of tumor-specific targets that differentiate cancer from normal cells
- Epidermal growth factor receptor (EGFR) plays a critical role in oncogenesis across several cancers and is often upregulated [1]; EGFR-targeted therapies have shown efficacy but are constrained by on-target, off-tumor toxicities (eg, skin rash), limiting dose escalation and effectiveness [2]
- A2B395 is an allogeneic, logic-gated, EGFR-targeted Tmod CAR T therapy designed to address these limitations and provide a convenient and consistent off-the-shelf option; the A2B395 construct combines a CAR-activating receptor with a leukocyte immunoglobulin-like receptor-1–based inhibitory receptor (LIR-1; blocker) targeting human leukocyte antigen (HLA)-A*02 to discriminate tumor from normal cells (**Figures 1 and 2**) [3–5]
  - The activator receptor recognizes EGFR on the surface of both tumor and normal cells
  - The blocker receptor recognizes an HLA-A*02 allele that is present in normal cells and lost in tumor cells; thus, eligible patients for Tmod are germline HLA-A*02 heterozygous and have loss of heterozygosity (LOH) in their tumor cells
  - The frequency of HLA-A LOH in advanced solid tumors is approximately 16% and can be detected using Tempus xT next-generation sequencing (NGS; **Table 1**)
  - A2B395 also includes beta-2-microglobulin short-hairpin RNA (β2M shRNA), reducing major histocompatibility complex class I levels to minimize host immune response

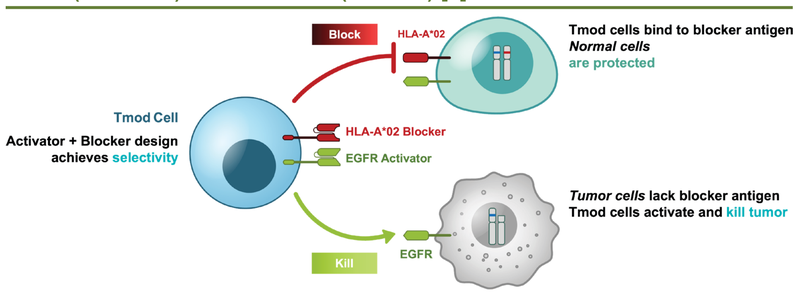
Figure 1: The Structure of Allogeneic Tmod CAR Ts Expressing an EGFR-Targeted Activator and an HLA-A*02-Targeted Blocker



The Tmod CAR construct is designed for safety with the LIR-1 inhibitory blocker transcribing before the anti-EGFR activator, minimizing the chance that the activator is expressed without the blocker

β2M shRNA, beta-2-microglobulin short-hairpin RNA; CAR T, chimeric antigen receptor T-cell; CD, cluster of differentiation; EF1α, elongation factor-1 alpha; EGFR, epidermal growth factor receptor; HLA, human leukocyte antigen; LIR, leukocyte immunoglobulin-like receptor; scFv, single-chain variable fragment; T2A, thosea asigna virus 2A.

Figure 2: Logic-Gated CAR T Therapy With the Goal to Reduce Toxicity: EGFR (Activator) and HLA-A*02 (Blocker) [3]



CAR T, chimeric antigen receptor T-cell; EGFR, epidermal growth factor receptor; HLA, human leukocyte antigen.

Table 1: Frequency of HLA-A LOH in Advanced Tumors [6]

	Frequency of HLA-A LOH in advanced disease, % (n)
Average	16.3 (10,867)
Head and neck squamous cell cancer	25.4 (394)
Non-small cell lung cancer	23.0 (1915)
Renal cell carcinoma	23.0 (n/a)
Colorectal cancer	15.6 (3035)
Triple-negative breast cancer	12.2 (2426)

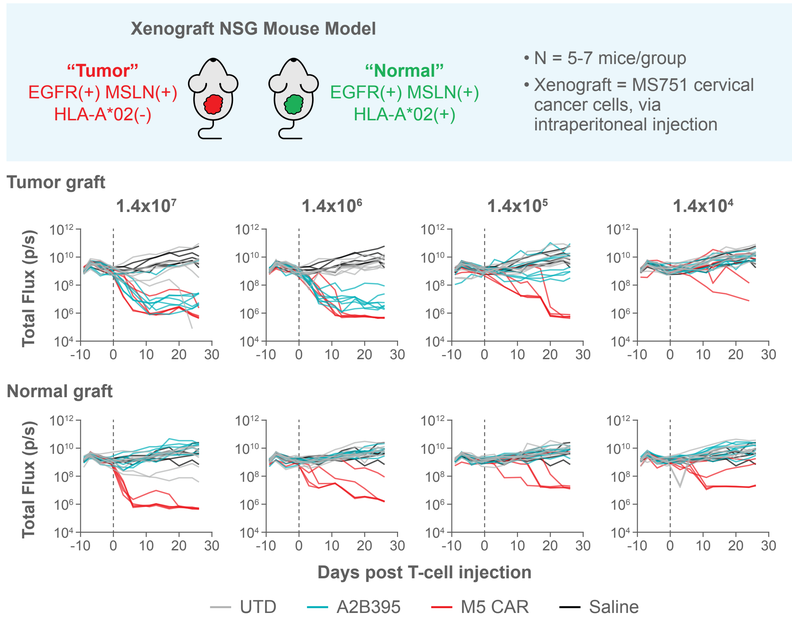
HLA, human leukocyte antigen; LOH, loss of heterozygosity; n/a, not available.

- Early data on autologous Tmod CAR T therapies show reduced off-tumor toxicity and promising clinical efficacy [7]
- DENALI-1 (NCT06682793), the 3rd A2 Bio interventional clinical trial, is a seamless, phase 1/2, open-label, nonrandomized study to evaluate the safety and efficacy of A2B395 in adult patients with solid tumors

NONCLINICAL STUDIES

- Nonclinical studies of A2B395 demonstrated improved selectivity and a therapeutic safety window with comparable efficacy to the clinically active M5 CAR T [8]
  - A2B395 treated NOD SCID gamma mice experienced selective regression of tumor grafts (HLA-A*02−), as measured by decreased bioluminescence imaging, while “normal” grafts (HLA-A*02+) continued to grow
  - Mice treated with M5 CAR T cells experienced regressions of both tumor and “normal” grafts (**Figure 3**)

Figure 3. EGFR Allogeneic Tmod (A2B395) In Vivo Study Demonstrates Efficacy Comparable to M5 CAR T Benchmark

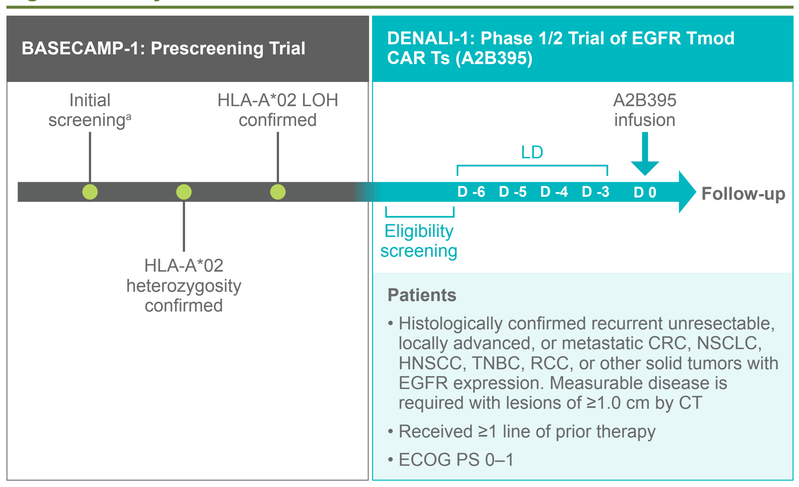


CAR T, chimeric antigen receptor T-cell; EGFR, epidermal growth factor receptor; HLA, human leukocyte antigen; MSLN, mesothelin; NSG, nonobese diabetic severe combined immunodeficiency gamma; UTD, untransduced.

STUDY DESIGN

- DENALI-1 (NCT06682793) is a first-in-human, phase 1/2, multicenter, open-label, nonrandomized study to evaluate the safety and efficacy of a single-dose of A2B395 Tmod CAR Ts in adults with recurrent unresectable, locally advanced, or metastatic cancers with EGFR expression, including colorectal cancer (CRC), non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), triple-negative breast cancer (TNBC), renal cell carcinoma (RCC), or other solid tumors with EGFR expression
- Participants are enrolled to DENALI-1 through BASECAMP1 (NCT04981119), a master prescreening study that identifies patients with HLA LOH at any time in the course of their disease (**Figure 4**)

Figure 4: Study Schema: BASECAMP-1 to DENALI-1

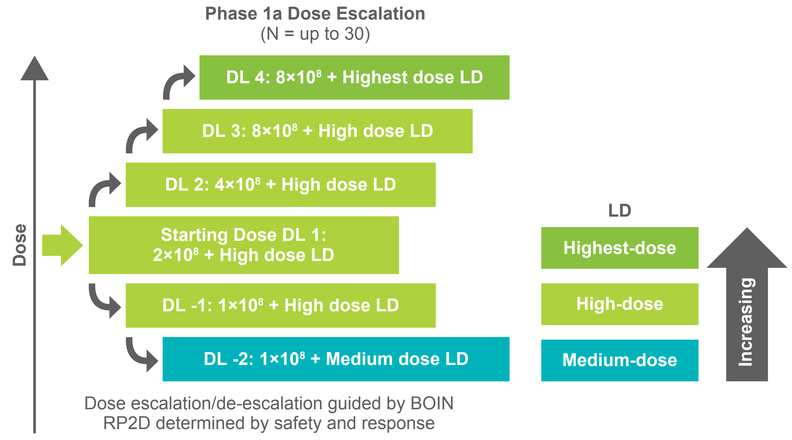


[a] May occur at any point in disease course.
CAR T, chimeric antigen T-cell; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HLA, human leukocyte antigen; HNSCC, head and neck squamous cell carcinoma; LD, lymphodepleting chemotherapy; LOH, loss of heterozygosity; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

- The phase 1 dose escalation portion of the study employs a Bayesian optimal interval design to assess the safety and tolerability of A2B395 and to determine a recommended phase 2 dose (**Figure 5**); up to 30 patients will be included in the dose escalation

STUDY DESIGN (CONTINUED)

Figure 5: DENALI-1 Phase 1 Dose Escalation Study Design



BOIN, Bayesian optimal interval; DL, dose level; LD, lymphodepleting chemotherapy; RP2D, recommended phase 2 dose.

Inclusion Criteria

- Appropriately enrolled in the BASECAMP-1 study, with tissue demonstrating LOH of HLA-A*02 by NGS (whenever possible from the primary site)
- Histologically confirmed recurrent unresectable, locally advanced, or metastatic CRC, NSCLC, HNSCC, TNBC, RCC, or other solid tumors with EGFR expression. Measurable disease is required with lesions of ≥1.0 cm by computed tomography
- Received previous required therapy for the appropriate solid tumor disease as described in the protocol
- Has adequate organ function as described in the protocol
- ECOG performance status of 0 to 1
- Life expectancy of ≥3 months
- Willing to comply with study schedule of assessments including long-term safety follow-up

Study Objectives and Endpoints

Objectives

- **Phase 1:** Determine the safety and the optimal dose of A2B395 (after LD) in participants with solid tumor disease
- **Phase 2:** Determine the further safety and efficacy of A2B395

Primary Endpoints

- **Phase 1:** Rate of adverse events and dose-limiting toxicities by dose level; recommended phase 2 dose
- **Phase 2:** overall response rate

Secondary Endpoints

- Persistence of A2B395
- Cytokine analysis

LD, lymphodepleting chemotherapy.

SITE LIST

The first site activation was March 28, 2025. The study sites and investigators include:

- Banner MD Anderson Cancer Center, Gilbert, AZ
  - Matthew Ulrickson and Jason Niu
- Fred Hutchinson Cancer Research Center, Seattle, WA
  - Jennifer M. Specht and David B. Zhen
- Mayo Clinic, Rochester, MN
  - Julian R. Molina and Harry E. Fuentes Bayne
- Moffitt Cancer Center, Tampa, FL
  - Kedar Kirtane and Frederick L. Locke
- NYU Langone Medical Center, New York, NY
  - Salman R. Punekar and Kristen Spencer
- Stanford University, Stanford, CA
  - John B Sunwoo and Wen-Kai Weng
- UCLA Medical Center, Los Angeles, CA
  - Deborah Wong and J. Randolph Hecht
- UCSD Moores Cancer Center, La Jolla, CA
  - Rebecca A. Shatsky and Sandip Patel
- Washington University, St. Louis, MO
  - Patrick M. Grierson

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