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DENALI-1: A seamless phase 1/2 study of A2B395, a logic gated, allogeneic, Tmod CAR T therapy, in patients with EGFR expressing solid tumors with human leukocyte antigen A*02 loss of heterozygosity

Specht JM,[1] Punekar SR,[2] Ulrickson M,[3] Wong DJ,[4] Hecht JR,[5] Maus M,[6] Grierson PM,[7] Sunwoo JB,[8] Molina JR,[9] Maloney DG,[1] Spencer K,[2] Fuentes Bayne HE,[9] Davila M,[10] Patel SP,[11] Creelan B,[12] Zhen DB,[1] Niu J,[3] Karam D,[9] Marar RI[9], Bagegni NA,[7] Palluconi G,[13] Lee J[13], Mardiros A[13], Bretzlaff W[13], Langeberg WJ,[13] Welch J,[13] Ng EW,[13] Go WY,[13] Kirtane K,[12] Shatsky RA[11]

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

Supplement, references, and acknowledgments

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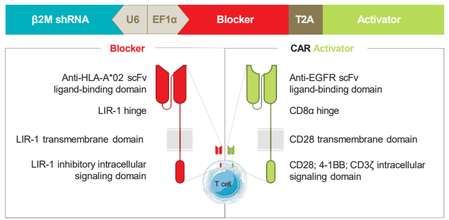


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BACKGROUND

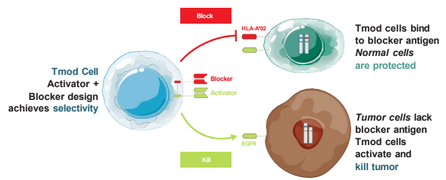
- CAR T therapies face significant challenges in solid tumors due to the lack of tumor-specific targets that differentiate cancer cells from normal cells
- EGFR plays a critical role in the oncogenesis of several cancers and is often upregulated[1]; EGFR-targeted therapies have shown efficacy but are 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 an LIR-1-targeting (blocker) 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, patients eligible for Tmod are germline HLA-A*02 heterozygous and have 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 (**Table 1**)
  - A2B395 also includes β2M shRNA, reducing MHC 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

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



Tmod cells are engineered to be logic-gated T cells designed to kill tumors but spare normal cells by leveraging the loss of genes in tumors

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

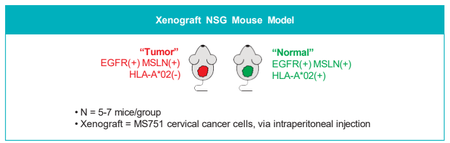
	Frequency of HLAA LOH in advanced disease, % (n)
Average	16.3 (10,867)
Head and neck squamous cell cancer	25.4 (394)
Non–small cell lung cancer	23.0 (1915)
Renal cell carcinoma	23.0 (n/a)
Colorectal cancer	15.6 (3035)
Triple–negative breast cancer	12.2 (2426)

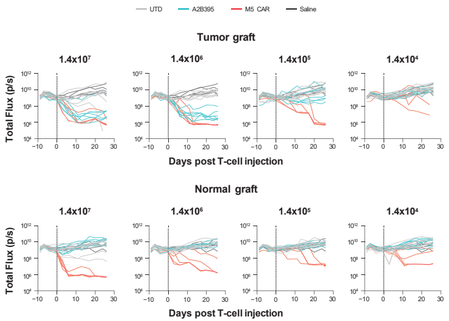
- Early data on autologous Tmod CAR T therapies show reduced off-tumor toxicity and promising clinical efficacy[7]
- DENALI-1 (NCT06682793), the third A2 Bio interventional clinical trial, is a seamless, open-label, phase 1/2 nonrandomized study to evaluate the safety and efficacy of A2B395 in adult patients with solid tumors[8]

NONCLINICAL STUDIES

- Nonclinical studies of A2B395 demonstrated improved selectivity and a therapeutic safety window with efficacy comparable to the clinically active M5 CAR T[9]
  - 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

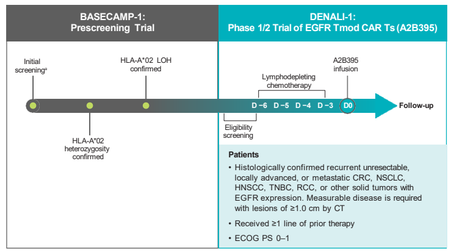




STUDY DESIGN

- DENALI-1 (NCT06682793)[8] is a first-in-human, multicenter, open-label, phase 1/2 nonrandomized study to evaluate the safety and efficacy of a single dose of A2B395 Tmod CAR T cells in adults with unresectable locally advanced recurrent or metastatic cancers with EGFR expression, including CRC, NSCLC, HNSCC, TNBC, RCC, or other solid tumors with EGFR expression
- Participants are enrolled to DENALI-1 through BASECAMP-1 (NCT04981119),[10] a master prescreening study that identifies patients with HLA LOH at any time in the course of their disease (**Figure 4**)

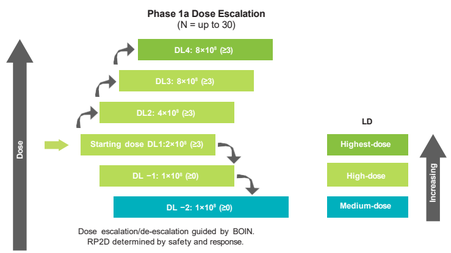
Figure 4. Study Schema: BASECAMP-1 to DENALI-1



*May occur at any point in disease course.

- 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

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



Dose escalation/de-escalation guided by BOIN. RP2D determined by safety and response.

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 unresectable locally advanced recurrent 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 PS of 0 to 1
- Life expectancy of ≥3 months
- Willing to comply with study schedule of assessments including long-term safety follow-up

Table 2. 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; RP2D
- **Phase 2:** Overall response rate

Secondary endpoints

- Persistence of A2B395
- Cytokine analysis

RESULT

- The first patient was enrolled in DENALI-1 in May 2025. Dose escalation is ongoing

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, Phoenix, AZ
  - Harry E. Fuentes Bayne and Antonious Z. Hazim
- 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
  - Wen-Kai Weng and John B. Sunwoo
- 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 in St. Louis, St. Louis, MO
  - Patrick M. Grierson
- Mayo Clinic Jacksonville, Jacksonville, FL
  - Yanyan Lou
- The Ohio State University, Columbus, OH
  - Kai He

Abbreviations **β2M shRNA**, beta 2 microglobulin short hairpin RNA; **BOIN**, Bayesian optimal interval; **CAR T**, chimeric antigen receptor T cell; **CD**, cluster of differentiation; **CRC**, colorectal cancer; **D**, day; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **EF1α**, elongation factor 1 alpha; **EGFR**, epidermal growth factor receptor; **HLA**, human leukocyte antigen; **HNSCC**, head and neck squamous cell carcinoma; **LIR**, leukocyte immunoglobulin like receptor; **LOH**, loss of heterozygosity; **MHC**, major histocompatibility complex; **MSLN**, mesothelin; **n/a**, not available; **NGS**, next-generation sequencing; **NOD**, nonobese diabetic; **NSCLC**, non–small cell lung cancer; **NSG**, nonobese diabetic severe combined immunodeficient; **RCC**, renal cell carcinoma; **RP2D**, recommended phase 2 dose; **scFv**, single chain variable fragment; **SCID**, severe combined immunodeficient; **T2A**, Thosea asigna virus 2A; **TNBC**, triple-negative breast cancer; **UTD**, untransduced.