Poster # 662

AFNT-211 A Phase I study of autologous CD4+ and CD8+ T cells engineered to express a high avidity HLA-A*11:01-restricted, KRAS G12V-specific transgenic TCR; CD8α/β coreceptor; and FAS-41BB switch receptor in patients with advanced or metastatic solid tumors

Shaunica Mitchell*, Binaish Khan[1], Francis Payumo[1], E. Gabriela Chiorean[2], Zhubin Gahvari[3], J. Randolph Hecht[4], Michael Hurwitz[5], Rom Leidner[6], Heinz-Josef Lenz[7], Meredith Pelster[8], Salman Punekar[9], Adam Schoenfeld[10], Dan Zhao[11], Markus P. Vallaster[1], Soumit K Basu[1], Dirk Nagorsen[1]

1 Affini-T Therapeutics, Watertown, MA, USA. 2. Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA. 3. University of Wisconsin, Madison, WI, USA. 4. University of California at Los Angeles, Los Angeles, CA, USA. 5. Yale University, New Haven, CT, USA. 6. Providence College, Providence, RI, USA. 7. University of Southern California, Los Angeles, CA, USA. 8. Sarah Cannon Research Institute, Nashville, TN, USA. 9. New York University, New York, NY, USA. 10. Memorial Sloan Kettering Cancer Center, New York, NY, USA. 11. MD Anderson Cancer Center, Houston, TX, USA, *No longer at Affini-T Therapeutics.

Background

- Activating mutations in KRAS are well-described oncogenic drivers in solid tumors, with KRAS G12V being amongst the most common. Patients with KRAS driver mutations have a poor prognosis, and the majority of KRAS mutated cancers lack effective therapies[1,2].
- T cell receptor (TCR)-T cell therapies targeting mutant KRAS have demonstrated proof of concept in the clinic, but duration of response remains a primary hurdle[3,4].
- AFNT-211 represents a novel strategy to address the immunosuppressive tumor microenvironment and improve anti-tumor activity and response duration in solid tumors.

Rationale

AFNT-211 autologous CD4+ and CD8+ T cells are engineered to express a high avidity HLA- A*11:01-restricted, KRAS G12V-specific transgenic TCR, the wildtype CD8α/β coreceptor, and a FAS-41BB switch receptor. The intended mechanism of action is recognition and elimination of KRAS G12V-mutated tumor cells by engineered TCR-T cells. The KRAS G12V target facilitates an attack on the causal mutation of the tumor.

AFNT-211 is designed to enhance anti-tumor activity via the following mechanisms of action as shown in preclinical models:

1. The CD8α/β coreceptor enables MHC I–restricted TCR recognition of the KRAS G12V target by CD4+ T cells
2. Engaging CD4+ helper T cell responses drives enhanced CD8+ T cell cytotoxic activity and prevents T cell exhaustion
3. The FAS 41BB chimeric switch receptor drives increased T cell activity, circumventing native FAS apoptotic signaling.

Patients

Key Inclusion Criteria
Adult male and female patients ≥ 18 years
HLA-A*11:01-positive
KRAS G12V-mutant tumor
Advanced or metastatic and unresectable solid tumor
Intolerant of or progressed on at least 1 prior line of standard systemic therapy for the current malignancy
Prior treatment with an approved or investigational KRAS-targeting agent (except KRAS G12V) is permitted

Key Exclusion Criteria
Primary brain tumors or central nervous system metastases
Prior gene therapy or transplant

Study Design and Treatment Plan

ICF & KRAS Mutation / HLA Status Screening

Eligibility Screening
(30 days)

Baseline
(Within 72 hours of LDC)

→

Dose Escalation, n = ~ 20

TCR-engineered cells dose level (DL):
- DL-1: 1.0x 10^9 ± 20% viable
- **DL 1: 5.0 x 10^9 ± 20% viable**
- DL 2: 1.0 x 10^{10} ± 20% viable
- DL 3: 1.5 x 10^{10} ± 20% viable

Bayesian optimal interval 1/2 (BOIN1/2)
DLT period: 28 days; SMC review

→ **Select OBD** →

Dose Expansion, n = ~80

NSCLC (n = 20)
CRC (n = 20)
PDAC (n = 20)
Other Solid Tumors (n = 20)

→

Post-treatment Follow-up
24 months or until PD
(Whichever is earlier)
↓
Post Treatment Follow-up Discontinuation
↓
Short & Long-term Follow-up & EOS
(Up to 15 years)

CRC: colorectal cancer; **DLT:** dose-limiting toxicity; **EOS:** end of study; **HLA:** human leukocyte antigen; **ICF:** informed consent form; **LDC:** lymphodepleting chemotherapy; **NSCLC:** non–small-cell lung cancer; **OBD:** Optimal Biological Dose; **PD:** progressive disease; **PDAC:** pancreatic ductal adenocarcinoma; **SMC:** Safety Monitoring Committee; **TCR:** T cell receptor.

- During dose escalation, 2-4 patients per cohort will receive AFNT-211 TCR T cell infusions, starting at dose level 1 (DL1).
- The first 2 patients for each cohort at a new dose level are enrolled in a staggered manner and observed for dose-limiting toxicities (DLTs). The total sample size for dose escalation is up to 20 patients.
- Each cohort will be analyzed using Bayesian Optimal Interval 1/2 (BOIN12) to identify the Optimal Biological Dose (OBD)/ Recommended Phase 2 Dose (RP2D).
- During dose expansion, patients will be dosed at the OBD/RP2D.
- Cohorts in the expansion phase (Phase Ib) are indication-specific and may include the following:
  - Non–small-cell lung cancer (N=20)
  - Colorectal cancer (N=20)
  - Pancreatic ductal adenocarcinoma (N=20)
  - Other KRAS G12V-mutant tumors in which anti-tumor activity is plausible (N=20)
- Patients who achieve a partial response (PR) or transient complete response (CR) and later progress may be considered for retreatment at the Investigator's discretion.

Study Objectives & Endpoints

Primary		
Safety & Tolerability	**OBD**	**RP2D**
Adverse events (AEs) + DLTs	Quantify the desirability of dose in terms of toxicity-efficacy tradeoff	Selected based on BOIN12 design + totality of benefit/risk evidence

Secondary/Exploratory

- **Anti-tumor activity**: Overall response rate, duration of response, time to response, progression-free survival, overall survival, and clinical benefit rate
- **Pharmacokinetics:** Expansion and persistence of AFNT-211 in peripheral blood over time
- **Cytokine Kinetics**: Concentration of cytokines in serum over time
- **Tumor Microenvironment changes**: Biomarkers
- **Health-related quality of life:** Patient-reported outcomes questionnaires

Safety and Disease Assessments

- Patients will have disease response assessment by imaging at Baseline and at 1, 3, 5, 7, 9, 12, 15, 18, 21, and 24 months after first AFNT-211 infusion.
- Patients will be monitored for replication-competent lentivirus, cytokine-release syndrome, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome, neurologic toxicities, tumor lysis syndrome, graft versus host disease, and other AEs associated with TCR-T cell therapies.

Study Status

NCT06105021 is an ongoing Phase I, first in human, open-label study of AFNT-211 enrolling patients for dose escalation in the United States. For questions about this study, contact AFNT211info@affinittx.com

References

1. Cook et al. Nature Commun. 2021
2. Hoffman et al. Cancer Discovery. 2022
3. D'Angelo et al. J Clin Onc. 2022
4. Hong et al. Nature Medicine. 2023

This study is sponsored by Affini-T Therapeutics. The authors are fully responsible for all content and editorial decisions, were involved in all stages of poster development, and have approved the final version. Corresponding author 's email address: Soumit.Basu@affinittx.com; Affini-T Therapeutics contact: AFNT211info@affinittx.com

© Poster Template by Genigraphics® 1.800.790.4001 www.genigraphics.com