A phase 1/2 study evaluating the safety and efficacy of autologous TAC T cells in subjects with claudin 18.2+ advanced solid tumors

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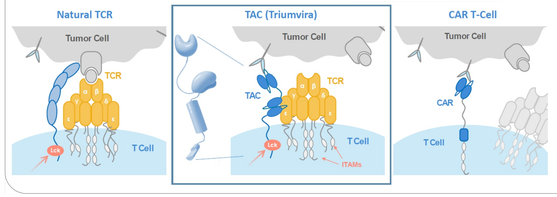
INTRODUCTION

- The T cell antigen coupler (TAC) is a novel, proprietary chimeric receptor that facilitates the re-direction of T cells to tumor cells and activates T cells by co-opting the endogenous T cell receptor complex, with the goal to elicit a safe and durable anti-tumor response. In preclinical models, TAC-engineered T cells effectively eradicate tumor cells *in vitro* and *in vivo* without toxicities typically associated with engineered T cell products. TAC01-CLDN18.2 is an autologous T cell product comprising T cells expressing the CLDN18.2 TAC, which specifically recognize CLDN18.2+ cells.
- TACTIC-3 (NCT05862324) is an open-label, multicenter phase I/II study that aims to establish safety, maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), pharmacokinetic profile, and efficacy of TAC01-CLDN18.2 in patients with CLDN18.2 positive solid tumors by immunohistochemistry (i.e. gastric, GEJ, esophageal adenocarcinoma, PDAC, colorectal cancer, cholangiocarcinoma, ovarian mucinous cancer, gallbladder cancer and NSCLC) who have been exposed to at least 2 prior anti-cancer therapies.

TAC SCIENCE



TAC achieves TCR activation via a CD3 binding domain while tightly binding the target of interest, CLDN18.2. TAC thus co-opts natural TCR function and provides intracellular co-receptor signaling via Lymphocyte-Specific Protein Tyrosine Kinase (LCK), mimicking physiologic TCR activation.

Watch a short animation to understand the TAC mechanism

TRIAL DESIGN

Phase I (Dose Escalation)

The classic 3+3 dose escalation design will be employed to efficiently determine the maximum tolerated dose (MTD) and RP2D using well-defined DLT criteria.

N = 9-24 subjects

Phase II (Dose Expansion)

Groups A and C:
Approach: Simon 2-stage design.
Objective: Assess efficacy (ORR).

Group B:
Initial Approach: Evaluate experimental ORR after 10 PDAC treatments.
Future: Adopt Simon 2-stage based on outcomes.

Preferred Lymphodepleting Chemotherapy (LDC):
3 consecutive days of fludarabine (Flu) IV (30 mg/m^2) and cyclophosphamide (Cy) IV (300 mg/m^2) +/- Mesna IV, and a single dose of nab-paclitaxel (100mg/m^2) on the second day of LDC.

PHASE I TRIAL PROGRESS

Primary Endpoints
Safety: DLTs, AEs

Secondary Endpoints
RP2D, PK, Efficacy (ORR, DoR, OS, TCR, PFS)

DL1 and 2 have been completed. DL3 enrollment has begun.

Eligibility Criteria
Patients with advanced, metastatic, unresectable solid tumors which express CLDN18.2 after at least 2 lines of therapy (1 for PDAC), at least 1 measurable lesion per RECIST version 1.1, ECOG performance score 0-1, grade 1 or baseline for any prior treatment related toxicities.

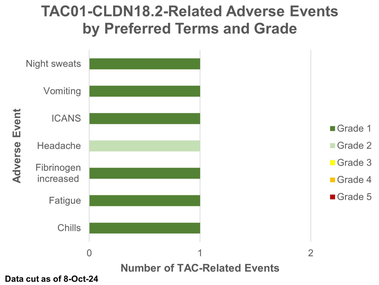
Note: Required specific tumor types for phase 1 include: gastric, GEJ, esophageal adenocarcinoma, PDAC, colorectal cancer, cholangiocarcinoma, ovarian mucinous cancer, gallbladder cancer and NSCLC.

Demographics and Tumor Intrinsic Characteristics (n=8)

Sex: Male/Female, n (%)	M	6 (75)	CLDN18.2 expression, n (%)	High	6 (75)
	F	2 (25)		Low	2 (25)
Race, n (%)	White	3 (37.5)	Age, Median (Range)		59 (43-75)
	Asian	2 (25)	Previous Anti-Cancer Therapy, Median (Range)		3 (2-8)
	Hispanic	2 (25)	Tumor Type, n (%)	Pancreatic	4 (50)
	Not Reported	1 (12.5)		Esophageal	2 (25)
ECOG PS, n (%)	0	3 (37.5)		Colorectal	1 (12.5)
	1	5 (62.5)		Gastric	1 (12.5)

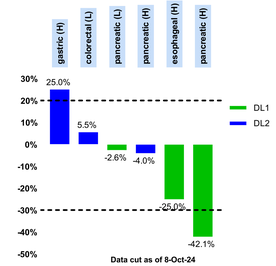
High (H) CLDN18.2 expression subjects in this study are those with samples where 50% or more of tumor cells express CLDN18.2 with intensity of 2+ or 3+. All others are termed low (L) expression.

PHASE I CLINICAL SAFETY DATA



Safety Summary
- One subject in Dose Level 2 (DL 2) experienced a Grade 1 ICAN (Immune-effector Cell Associated Neurotoxicity) event that resolved within 24 hours without intervention.
- No observed CRS (Cytokine Release Syndrome).

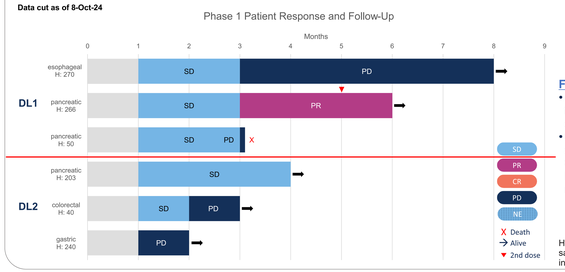
BEST RESPONSE (tumor measurements)



- **DL1:** One subject with Partial Response (PR) and 2 subjects with Stable Disease (SD).
- **DL2:** Two subjects with SD and one subject with Progressive Disease (PD).

Disease Control Rate (DCR) of 83.3% and Objective Response Rate (ORR) of 16.7% in heavily pre-treated subjects with aggressive malignancies.

SUBJECT RESPONSE AND FOLLOW-UP



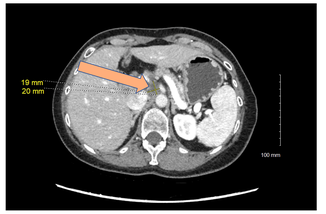
Follow-up
- All subjects are still in follow-up per protocol, except for two subjects who died due to progressive disease (one of which was not eligible for efficacy).
- One subject in DL1 with heavily pre-treated pancreatic adenocarcinoma (3 prior lines of therapy) and high CLDN18.2 expression has an ongoing, confirmed PR, lasting 3 months at the date of the data cut. This subject received a second dose.

High (H) CLDN18.2 expression subjects in this study are those with samples where 50% or more of tumor cells express CLDN18.2 with intensity of 2+ or 3+. All others are termed low (L) expression.

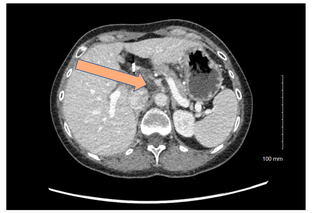
TUMOR ASSESSMENT: SUBJECT RESPONSE

Subject 0112-0040
- 57 year old female with CLDN18.2+ (high expression) stage IV metastatic pancreatic cancer.
- Previously treted with 3 lines of therapy.
- The subject did not receive bridging therapy.
- The subject had stable disease at first tumor assessment, which turned to a partial response 3 months after TAC infusion. The partial response has been confirmed and is ongoing (for 3 months as of data cut date). The subject received a second TAC infusion 5 months after the first and is still on treatment (for 6 months as of data cut date).

RECIST 1.1 Tumor Response Assessments (Measurable Disease)				
Baseline SoD (mm)	D29 SoD (mm, % change)	M3 SoD (mm, % change)	M5 SoD (mm, % change)	6M SoD (mm, % change)
19	17 (-10.5)	11 (-42.1)	11 (-42.1)	11 (-42.1)

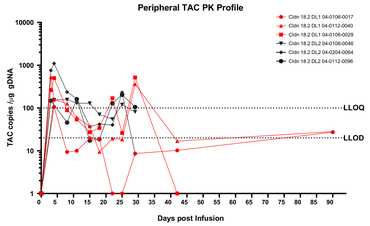


Baseline (19 mm)

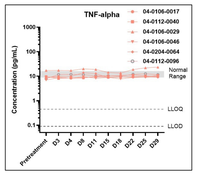


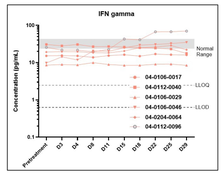
5M (11 mm)

TAC01-CLDN18.2 PK AND CYTOKINE ANALYSIS



TAC copies detected in the blood of subjects at the indicated days post-treatment (first dose). Red and blue lines indicate DL1 and DL2 subjects, respectively. TAC T cells still persist in the circulation of most subjects at D29, and even 3 months after infusion (D90; DL1 data only available).





Effector cytokines (TNFα and IFNγ) were detected in the blood of subjects at the indicated days post-treatment (first dose). TNFα concentration largely remained within physiological levels (gray rectangle). IFNγ concentration appears to be TAC01-CLDN18.2 dose dependent, with subjects at DL2 (bottom 3 on the legend) having higher concentration than those on DL1 (top 3 on the legend). Additional cytokine analysis is ongoing.

SUMMARY & CONCLUSIONS

Safety
Interim results from the Phase I TACTIC-3 study suggests that TAC01-CLDN18.2 is well tolerated. No Grade 3 or higher treatment-related events were observed. One Grade 1 ICAN event was observed, which resolved without intervention within 24 hours. No CRS reported to date.

Preliminary Efficacy
Demonstrated early signs of clinical activity, highlighting a partial response (in a stage IV pancreatic cancer subject) at DL1, and a DCR of 83.3% at 1st assessment across DL1-2.

TRIAL PROGRESS: DL1-2 completed. DL3 enrollment begun.

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