INCLINE-101, A Phase 1/2, Open Label, Dose Escalation and Expansion Study of TAC-001 (a TLR9 agonist conjugated to an anti-CD22 antibody) in Patients with Select Advanced or Metastatic Solid Tumors

Cesar A. Perez[1], Jason T. Henry[2], Timothy G. Humphries[3], Sunnie S. Kim[4], Ons Harrabi[5], Feng Jin[5], Hong I. Wan[5], Candy Bermingham[5], and Anthony B. El Khoueiry[6]

1. Sarah Cannon Research Institute at Florida Cancer Specialists, Lake Nona, FL, USA. 2. Sarah Cannon Research Institute at HealthONE, Denver, CO, USA. 3. Linear Clinical Research Ltd, Nedlands, WA, 6009, Australia. 4. University of Colorado Cancer Center, Aurora, CO, USA. 5. Tallac Therapeutics, Burlingame, CA, USA. 6. Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA.

BACKGROUND

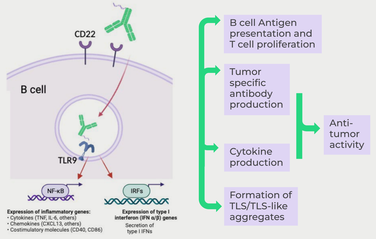
- Accumulating clinical data suggest a critical role for B cell-mediated anti-tumor immunity. Enrichment of memory B cells, plasma cells and tertiary lymphoid structures (TLS) in tumor microenvironment is a positive prognostic factor for patient survival and responsiveness to immunotherapy in patients with a variety of solid tumors [1-3].
- Activation of toll-like receptor 9 (TLR9) by unmethylated CpG oligonucleotides (ODNs) promotes innate inflammatory responses and the induction of adaptive immunity [4]. TLR9 agonism has been evaluated in the clinic in patients with solid tumors [5].
- TAC-001 is a Toll-like Receptor Agonist Antibody Conjugate (TRAAC) comprised of a potent and differentiated TLR9 agonist (T-CpG) conjugated to an antibody against CD22, a receptor restricted to B cells, including tumor-infiltrating B cells (Figure 1).
- In pre-clinical models, TLR9 activation in B cells following systemic administration of TAC-001 surrogate (mCD22 TRAAC) induced expression of co-stimulatory molecules, enhanced antigen cross-presentation leading to T cell activation and proliferation, promoted B cell differentiation and elicited cytokine, chemokine and immunoglobulin production (Figure 2), leading to the robust anti-tumor activity observed in several animal models of cancer (Figure 3).

Figure 1: TAC-001 A First-in-Class Antibody Conjugate Targets TLR9 Agonist to CD22 Expressing B Cells

Antibody: anti-CD22
- Targets B cells expressing CD22
- Efficient internalization
- Lacks effector function

Immune Activator: T-CpG
- Proprietary TLR9 agonist
- Optimized for potency and stability
- Site specifically conjugated

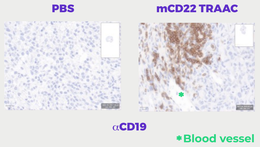
Figure 2: Anticipated Mechanism of Action: TAC-001 Provides Targeted TLR9 Activation of B Cells, Triggering Innate and Adaptive Immune Responses



- Ex-vivo treatment of primary mouse B cells with murine(m)CD22 TRAAC, a surrogate for TAC-001, lead to increased expression of co-stimulatory molecules, and enhanced antigen cross-presentation resulting in antigen-specific T cell proliferation.
- Systemic administration of mCD22 TRAAC to tumor bearing mice lead to increased infiltration of B cells to tumor microenvironment (**Fig 3A**), with TLS-like chemokine signature, elicited Ig and pro-inflammatory cytokine/chemokine production, and enhanced T-cell effector function [6].
- Systemic treatment with mCD22 TRAAC demonstrated robust and curative single agent anti-tumor activity in checkpoint inhibitor refractory (**Fig 3B**) and resistant (**Fig 3C**) tumor models [6].

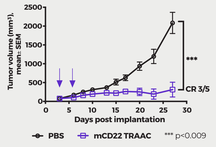
Figure 3: Activity of TAC-001 Surrogate Molecule (mCD22 TRAAC) in Mouse Models

A. Increased B cell infiltration in EMT6 Tumor, a TNBC model



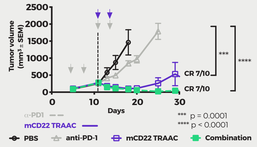
(A) Mice bearing EMT6 tumors were dosed intraperitoneally with PBS or mCD22 TRAAC once at 10 mg/kg. Tumors were harvested 11 days post dose for IHC staining. Stained cells represent CD19+B cells. Green * represents a blood vessel.

B. Anti-tumor activity in EMT6 a TNBC Model Refractory to anti-PD-1



(B) Efficacy of mCD22 TRAAC in EMT6 tumor model. EMT6 cells were injected subcutaneously on the right flank of BALB/c mice. Treatment with either mCD22 TRAAC at 10mg/kg or PBS was initiated when the average tumor size reached 76mm³ as indicated by arrows. P-value comparing treatment groups was calculated on day 27 using unpaired t-test. N=5/group CR= complete response

C. Anti-tumor activity in anti-PD-1 Resistant CT26 Colon Cancer Model

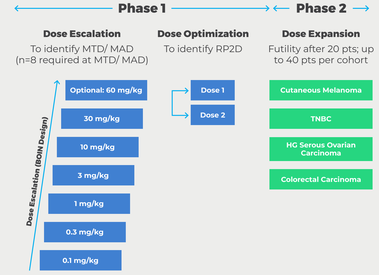


(C) Efficacy of mCD22 TRAAC in an anti-PD-1 resistant CT26 model. CT26 cells were injected subcutaneously on the right flank of BALB/c mice. When the average tumor size reached 94mm³ mice were randomized and dosed with anti-PD-1 at 10 mg/kg IP two times three days apart. One day after the second anti-PD-1 dose, tumor volumes were measured and mice with tumors above 200 mm³ were considered unresponsive to anti-PD-1 therapy. As indicated by the dotted line, anti-PD-1-resistant mice were re-randomized with an average tumor size of 250 mm³ and dosed with PBS, anti-PD-1 at 10 mg/kg, mCD22 TRAAC at 10 mg/kg, or anti-PD-1 and mCD22 TRAAC combination on days indicated by arrows. On day 18, p-values were calculated using mixed effects One-Way ANOVA. n=10/group. CR= complete response

STUDY DESIGN OVERVIEW

- INCLINE-101 is an open-label, multicenter Phase 1/2 study designed to evaluate the safety, efficacy, pharmacokinetics (PK) and pharmacodynamic (PD) biomarkers of TAC-001 in patients with select advanced or metastatic solid tumors (see Figure 4).
- The Phase 1 portion of the study is focused on dose escalation and dose optimization of TAC-001.
- The Phase 2 portion of the study is focused on dose expansion in select tumor types.
- The trial design will consist of a Screening Period, a Treatment Period, and a Follow up Period. All patients will complete 28-days of screening during the Screening period. Eligible patients will be enrolled and receive study treatment every 2 weeks during the Treatment Period until progression of disease, unacceptable toxicity or if other treatment discontinuation criteria are met.
- Trial registration: NCT05399654

Figure 4: INCLINE-101 Study Design



PHASE 1 DOSE ESCALATION

- A Bayesian Optimal Interval (BOIN) design with a 3+3 design run-in will be applied to inform dose escalation/de-escalation decisions to the dose levels
- All patients will be evaluated for 28-day Dose limiting toxicities (DLTs).
- 3 to 5 patients will be sequentially assigned into a dose level. To identify the MTD/ MAD, at least 8 patients must be enrolled into a dose level.
- Starting dose level of 0.1 mg/kg. Up to 7 dose levels may be evaluated.
- Once the MTD/ MAD is identified, 2 dose levels will be selected for dose optimization. Up to 15 patients will be enrolled into each dose level.
- Study Start Date: July 2022

PHASE 2 DOSE EXPANSION

- Phase 2 expansion is planned in
  - Triple negative breast cancer (TNBC)
  - High-grade serous ovarian carcinoma
  - Colorectal carcinoma
  - Cutaneous melanoma
- For all cohorts, when the first 20 patients in a cohort have received treatment and have at least one post-baseline efficacy evaluation, the sponsor will assess the preliminary efficacy and safety data and decide whether to continue further enrollment.
  - Efficacy and safety data that will be evaluated will include ORR and DOR as well as the frequency and severity of AEs.
  - The probabilities of observing varying frequencies of response out of 20 treated patients under different true response rates will be considered.
- If a decision is made to continue enrollment, an additional 20 patients will be enrolled and treated for a total sample size of 40 patients in each cohort.

STUDY OBJECTIVES AND ENDPOINTS

Phase 1 Primary Objectives

- To assess safety and tolerability of increasing dose levels of TAC-001 (28-day dose-limiting toxicities [DLTs], Adverse Events [AEs] and lab abnormalities as graded by NCI CTCAE v 5.0).

Phase 2 Primary Objectives

- To evaluate preliminary antitumor activity (overall response rate [ORR], duration of response [DOR] and clinical benefit rate [CBR])

Secondary Objectives

- To evaluate preliminary antitumor activity (ORR, DOR and CBR)
- To further evaluate safety and tolerability of TAC-001 (AEs and lab abnormalities)
- To characterize single and multiple dose PK of TAC-001
- To evaluate immunogenicity of TAC-001 (ADA)

Exploratory Objectives

- Progression free survival (PFS) and overall survival (OS)
- Pharmacodynamic biomarkers: CD22 target engagement, TLR9 and B cell activation, cytokine and tumor infiltrating lymphocyte profiling

KEY INCLUSION CRITERIA

- Adult male or female patients ≥18 years of age on day of signing informed consent.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1.
- Eligible patients must have histologically or cytologically-documented advanced, metastatic, unresectable or recurrent disease.
- Eligible patients must have been diagnosed with one of the following tumor types:
  - Phase 1: Breast cancer, cervical squamous cell carcinoma, cholangiocarcinoma, colorectal carcinoma, cutaneous melanoma, endometrial carcinoma, gastro-esophageal adenocarcinoma, head and neck squamous cell carcinoma, hepatocellular carcinoma, Merkle cell carcinoma, non-small cell lung cancer, ovarian cancer, renal cell carcinoma, or urothelial carcinoma that have progressed on or are intolerant to standard therapy, including checkpoint inhibitor therapy if appropriate.
  - Phase 2: TNBC, HG ovarian carcinoma, colorectal carcinoma, cutaneous melanoma
- Demonstrate adequate organ function.

KEY EXCLUSION CRITERIA

- Prior history of or active malignant disease other than that being treated in this study.
- Known brain metastases or cranial epidural disease.
- A known hypersensitivity to the components of the study therapy or its' analogs.
- Receiving chronic systemic steroid therapy or any immunosuppressive therapy within 7 days prior to first dose of study drug.
- An active autoimmune disease that has required systemic treatment in past 2 years.
- History of Grade 3 or higher immune mediated adverse events that were considered drug related to prior immunotherapy.
- Infection with human immunodeficiency virus-1 (HIV-1) or HIV-2 or active hepatitis B (hepatitis B virus [HBV] surface antigen positive), hepatitis C (hepatitis C virus [HCV] antibody positive, confirmed by HCV ribonucleic acid).
- An active infection requiring systemic therapy.
- Significant cardiovascular disease within last 6 months.
- Receipt of any type of systemic anti-cancer therapy within 4 weeks before the first dose of study drug.

CURRENT PARTICIPATING CLINICAL SITES IN PHASE 1

University of Colorado Medicine · Florida Cancer Specialists · linear · USC University of Southern California · Keck School of Medicine of USC · Sarah Cannon Fighting Cancer Together

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