#743

INCLINE-101: Preliminary Safety, Tolerability, Pharmacokinetics (PK), and Pharmacodynamics (PD) of TAC-001 (TLR9 Agonist Conjugated to a CD22 mAb) in Patients With Advanced or Metastatic Solid Tumors

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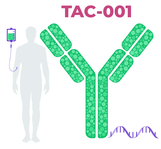
BACKGROUND

- Activation of toll-like receptor 9 (TLR9) by unmethylated CpG oligonucleotides promotes innate inflammatory responses and the induction of adaptive immunity[1]
- TLR9 agonism has been evaluated clinically in patients with solid tumors[2]
- Designed for systemic administration, TAC-001 is a TLR9 agonist antibody conjugate (TRAAC) comprising 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

Systemic TAC-001: First-in-Class TRAAC That Targets a 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

METHODS

- Phase 1, first-in-human, open-label, multicenter study in patients with relapsed/refractory select solid tumors (NCT05399654)
- Dose escalation (Bayesian optimal interval design [BOIN method]) followed by dose optimization of at least two dose levels and expansion
- TAC-001 is systemically administered IV every 2 weeks
- This poster presents preliminary data from the first 18 patients dosed at 0.1 mg/kg to 3 mg/kg
- Enrollment is ongoing

PRIMARY OBJECTIVE: Safety and tolerability of TAC-001

SECONDARY OBJECTIVES: PK, immunogenicity, ORR, and DOR per investigator assessment per RECIST v1.1 or iRECIST v1.1

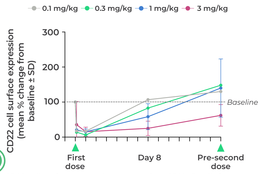
RESULTS

PHARMACODYNAMICS

TAC-001 Binds CD22 on B Cells Leading to Internalization

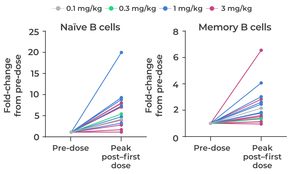
TAC-001 Triggers TLR9 Signaling Leading to Activation of Peripheral B Cells at All Dose Levels

CD22 Internalization Observed at All Dose Levels



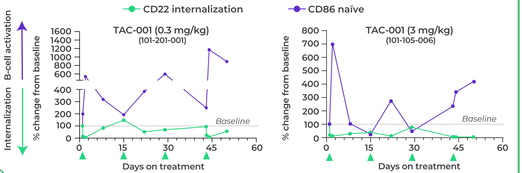
CD22 cell surface expression assessed on CD19+ B cells from peripheral blood at pre-dose, 3 hours, 24 hours, Day 8 after first dose, and Day 15 pre-second dose.

Increased CD86 Expression Observed on Circulating Naïve and Memory B Cells

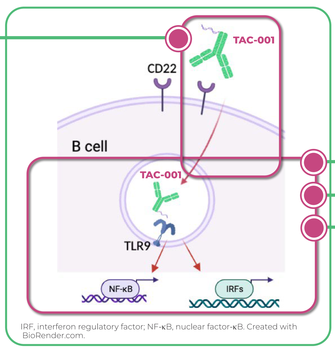


Peak CD86 expression in peripheral blood was assessed post-first dose up to Day 15 pre-second dose.

Examples Demonstrating Correlation Between CD22 Internalization and CD86 Expression on Naïve B Cells

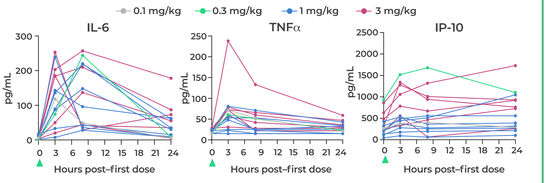


Example data from patients demonstrate the correlation between CD22 internalization and activation of B cells. Green arrows represent dose days.



IRF, interferon regulatory factor; NF-κB, nuclear factor-κB. Created with BioRender.com.

Cytokine and Chemokine Production Observed in Serum Samples



Serum cytokines and chemokines were assessed at pre-dose, 3, 8, and 24 hours post post-first dose. Arrows represent dose days. IL, interleukin; IP, interferon gamma-induced protein; TNF, tumor necrosis factor.

Preliminary data are consistent with the proposed mechanism of action (MOA):
- TAC-001 mediates CD22 internalization
- Evidence of prolonged target engagement at higher dose levels
- TAC-001 upregulates expression of CD86 co-stimulatory marker on naïve and memory B cells in peripheral blood
- Increased CD40 expression is also observed (see QR code)
- TAC-001 elicits production of cytokines and chemokines (see QR code) consistent with TLR9-mediated activation of B cells[3,4]; peak levels appear within 24 hours following first dose, with no evidence of accumulation in serum

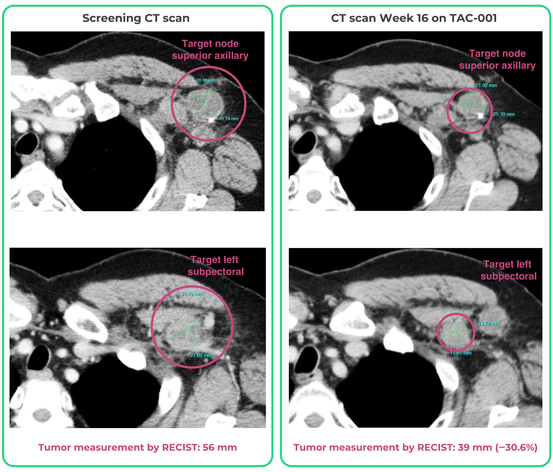
PHARMACOKINETICS

Maximum serum concentration (C_{max}) and area under the serum concentration versus time curve (AUC) increases are approximately dose-proportional at doses of 0.3–3 mg/kg; see QR code for additional data

CLINICAL ACTIVITY

Partial Response Observed in a Patient With Relapsed Melanoma

- 56-year-old male with relapsed BRAF V600Ewt metastatic melanoma previously treated with palliative radiation, nivolumab (×16 months) and ipilimumab for (4 doses), with stable disease as the best response; discontinued nivolumab secondary to disease progression



Patient received TAC-001 3 mg/kg Q2 weeks.

PATIENT BASELINE CHARACTERISTICS

Total subjects: n=18 **6 FEMALE, 12 MALE**
Median age, years (range): **57.0 (41–76)**
Race: **56% WHITE, 11% BLACK, 6% NATIVE AMERICAN/ALASKAN NATIVE, 6% ASIAN**
Most common tumor type: **COLORECTAL CANCER (n=9)**
Median no. prior therapies (range): **3 (1–7)**

Race not reported in 4 patients.

PATIENT DISPOSITION

Median duration of treatment (range): **1.4 MONTHS (1–11)**
Patients still on treatment: **4 (22%)**

[a]Four patients did not have an end-of-treatment visit.

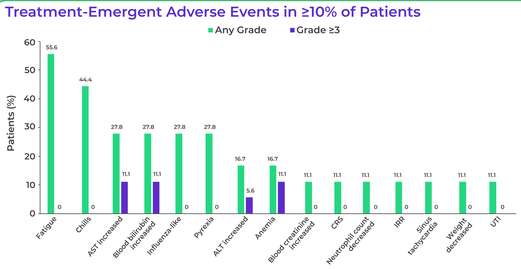
SAFETY

Safety Summary for All Dose Levels (n=18)

n (%)	TEAEs	Related TEAEs	DLTs[a]	TEAEs leading to dose reduction/ interruption	Related TEAEs leading to dose reduction/ interruption	Serious TEAEs	Related SAEs
Any Grade	18 (100)	17 (94.4)	1 (5.6)	4 (22.2)	2 (11.1)	7 (38.9)	2 (11.1)
Grade ≥3	9 (50)	3 (16.7)	1 (5.6)	3 (16.7)	2 (11.1)	6 (33.3)	2 (11.1)

TEAE, treatment-emergent adverse event; DLT, dose-limiting toxicity; SAE, serious adverse event.
[a]DLT was Grade 3 immune-mediated hepatoxicity observed at 3 mg/kg; no treatment-related fatal events were observed at any dose level.
Data cut-off date: 08Sep2023.

Treatment-Emergent Adverse Events in ≥10% of Patients



AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; CRS, cytokine release syndrome; IRR, infusion-related reaction; UTI, urinary tract infection.
Data cut-off date: 08Sep2023.

CONCLUSIONS

- Single-agent TAC-001 (0.1 to 3 mg/kg) given systemically every 2 weeks is well tolerated and demonstrates preliminary clinical activity
  - Majority of TEAEs are Grade 1 and Grade 2
  - One DLT of Grade 3 immune-mediated hepatoxicity was observed at 3 mg/kg
  - Preliminary clinical activity was observed in one patient, with durable stable disease (≥6 months) and one partial response per RECIST v1.1
  - Enrollment continues in dose-escalation and dose-optimization phases
- TAC-001 PK exposures (C_{max} and AUC) are approximately dose-proportional within the dose range of 0.3 to 3 mg/kg
- TAC-001 demonstrates pharmacodynamic activity consistent with its proposed MOA
  - CD22 engagement, internalization, and B-cell activation are observed in the periphery at all dose levels
  - Evidence of cytokine and chemokine production is consistent with TLR9-mediated B-cell activation, with no evidence of accumulation consistent with the clinical safety profile
  - Analyses of paired tumor biopsies are ongoing

ACKNOWLEDGMENTS

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