supporting-data

CT045

INCLINE-101: A Phase 1/2 Trial of TAC-001 (TLR9 agonist-CD22 mAb) in Advanced or Metastatic Solid Tumors

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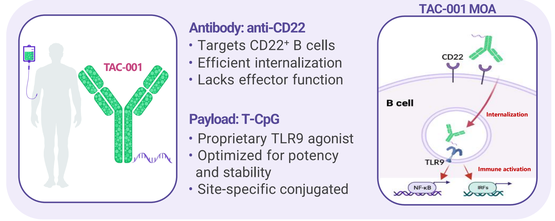
BACKGROUND

- Effective antitumor response requires coordination between the innate and adaptive arms of the immune system[1]
- Toll-like receptor 9 (TLR9) activation bridges both immune arms, stimulating antitumor responses[2]
- TLR9 is a clinically validated target, with intratumorally injection of its agonists demonstrating antitumor efficacy in patients with refractory solid tumors[2]
- Designed for systemic administration, TAC-001 is a novel antibody-drug conjugate delivering a potent TLR9 agonist payload to CD22+ B cells[3] (**Figure 1**)
- TAC-001 induced sustained antitumor activity in preclinical models, including those resistant/refractory to anti-PD-1 therapy[3,4]

Figure 1. TAC-001 Targets TLR9 Agonist Payload to B Cells



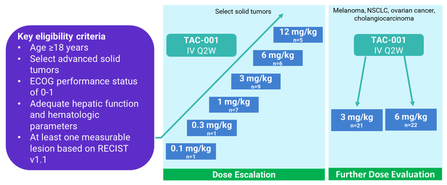
MOA, mechanism of action.

METHODS

Study Design

- INCLINE-101(NCT05399654) evaluated the safety, tolerability, pharmacokinetics, immunogenicity, pharmacodynamics, and preliminary efficacy of TAC-001 with the objective to determine the recommended phase 2 dose in patients with select advanced solid tumors (**Figure 2**)
  - Patients received TAC-001 IV Q2W on a 4-week cycle at escalating doses (0.1-12 mg/kg) via a Bayesian Optimal Interval design with a 3+3 run in with a 28-day dose-limiting toxicity (DLT) window
  - TAC-001 was then further dose evaluated in select solid tumor types at two dose cohorts at and below the maximum tolerable dose (MTD)

Figure 2. Study Design



ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; RECIST v1.1 response evaluation criteria in solid tumors.

Study Outcomes

- **Primary endpoints:** 28-day DLTs, adverse events (AE), and laboratory parameter changes
- **Secondary endpoints:** TAC-001 pharmacokinetics (PK), immunogenicity, objective response rate based on RECIST v1.1 and iRECIST v1.1, and duration of response (DoR)
- **Exploratory endpoints:** progression-free survival, overall survival, and pharmacodynamic biomarkers

RESULTS

Participants

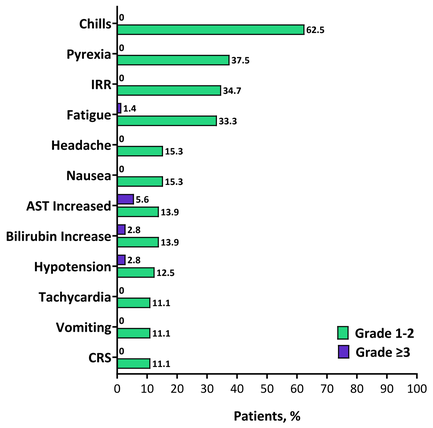
- We report the final results from our fully enrolled Phase 1 study, with a data cutoff date of March 17, 2025, which included 72 heavily pre-treated patients with advanced or metastatic solid tumors (**Table 1**)
  - Most enrolled patients were PD-(L)1 refractory (70.8%) with a median of 5 (range 1 to 13) prior therapies

Table 1. Baseline Characteristics

Characteristic	Overall n=72
Age at index, years	
Median (Range)	62.0 (37, 79)
Sex, n (%)	
Male	40 (55.6)
Female	32 (44.4)
ECOG, n (%)	
0	24 (33.3)
1	48 (66.7)
Race, n (%)	
White	55 (76.4)
Other	9 (12.5)
Not reported	8 (11.1)
Most common cancer type, n (%)	
Cutaneous melanoma	19 (26)
Ovarian cancer	11 (15.3)
Head and neck squamous cell carcinoma	10 (13.9)
Colorectal cancer	9 (12.5)
NSCLC	7 (9.7)
Cholangiocarcinoma	5 (6.9)
Other[a]	11 (15.3)
Prior lines of therapy	
Median (Range)	5 (1-13)
Type of therapy, n (%)	
Chemotherapy	52 (72.2)
Immunotherapy	51 (70.8)
Target therapy	44 (61.1)

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.
[a]Other tumor types included renal cell carcinoma, gastroesophageal, hepatocellular, cervical, Merkle cell, urothelial, endometrial, peritoneal, and appendiceal cancers.

Figure 3. Most Common TRAEs[a]



AST, aspartate aminotransferase; CRS, cytokine release syndrome; IRR, Infusion related reaction; TRAE, treatment related adverse event
[a](≥10% Overall).

Table 3. Summary of Grade ≥3 TRAEs

TRAE (Grade ≥3)	Overall n=12
AST increased	4 (5.6)
Lymphocyte count decreased	3 (4.2)
ALT Increased	3 (4.2)
Blood bilirubin increased	2 (2.8)
Alkaline phosphatase increased	2 (2.8)
Hypotension	2 (2.8)
Hypoxia	1 (1.4)
Dizziness	1 (1.4)
Acute kidney injury	1 (1.4)
Creatine phosphokinase increased	1 (1.4)
Fatigue	1 (1.4)
Flank pain	1 (1.4)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Safety

- TAC-001 was well-tolerated with predominant flu-like AEs
- The most common treatment related adverse events (TRAE) were chills (62.5%), pyrexia (37.5%), and infusion related reaction (34.7%; **Figure 3**)
- TRAEs were reported in 66 (91.7%) patients, with 12 (16.7%) being Grade ≥3 (**Tables 2 and 3**)
  - DLTs of transient liver enzyme rises (commonly after the first dose) occurred in 3 (4.2%) patients, 1 at 3 mg/kg and 2 at 12 mg/kg
  - The MTD was established at 6 mg/kg, with 3 mg/kg and 6 mg/kg selected for further dose evaluation

Table 2. Summary of Safety Results

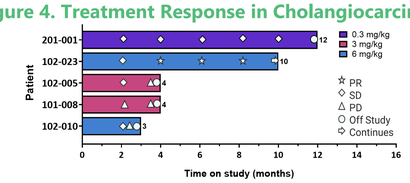
Event, n (%)[a]	0.1 mg/kg n=1		0.3 mg/kg n=1		1 mg/kg n=7		3 mg/kg n=30		6 mg/kg n=28		12 mg/kg n=5		Overall n[b]=72	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
TEAE	1 (100)	0	1 (100)	0	7 (100)	5 (71.4)	29 (96.7)	16 (53.3)	28 (100)	12 (42.9)	5 (100)	3 (60.0)	71 (98.6)	36 (50)
TRAE	1 (100)	0	1 (100)	0	7 (100)	1 (14.3)	27 (90.0)	4 (13.3)	25 (89.3)	5 (17.9)	5 (100)	2 (40.0)	66 (91.7)	12 (16.7)
DLT	0	0	0	0	0	0	1 (3.3)	1 (3.3)	0	0	2 (40.0)	2 (40.0)	3 (4.2)	3 (4.2)
Serious TRAE	0	0	0	0	1 (14.3)	1 (14.3)	2 (6.7)	1 (3.3)	2 (7.1)	1 (3.6)	2 (40.0)	2 (40.0)	7 (9.7)	4 (5.6)
Dose reduction to TRAE	0	0	0	0	1 (14.3)	1 (14.3)	0	0	0	0	2 (40.0)	1 (20.0)	3 (4.2)	2 (2.8)
Discontinuation to TRAE	0	0	1 (100)	0	0	0	1 (3.3)	1 (3.3)	0	0	0	0	2 (2.8)	1 (1.4)

DLT, dose limiting toxicity; TEAE, treatment emergent adverse event; TRAE, treatment related adverse event.
[a]Intensity of AEs was coded using Common Terminology Criteria for Adverse Events (CTCAE), version 5.0; [b]n, number of patients; [c]A total of 2 patients were dose reduced from 12mg/kg to 6mg/kg due to the reported liver enzyme-related DLTs at 12mg/kg; 1 of the two patients had not experienced any liver-related TRAE prior to dose reduction; [d]Patient developed a grade 1-2 infusion reaction after COVID pneumonia and discontinued after approximately one year of therapy.

Efficacy

- Among 69 response-evaluable patients, 2 patients (melanoma and cholangiocarcinoma) achieved durable partial responses (PR) lasting 10 and 6.25 months, respectively
  - Median DoR was 8.1 months
- Stable disease (SD) ≥2 months was achieved in 24 patients with minor tumor reductions in some patients (NSCLC, head and neck cancer, and cholangiocarcinoma)
  - A total of 3 patients (melanoma, cholangiocarcinoma, and NSCLC) maintained SD for ≥6 months (range 8 to >14)
- Individual patient-level responses are shown in **Figures 4 and 5**

Figure 4. Treatment Response in Cholangiocarcinoma



Partial Response in Patient with Advanced Cholangiocarcinoma

- 54-year-old male with advanced unresectable cholangiocarcinoma, previously treated with durvalumab and chemotherapy before metastatic disease progression
- Received TAC-001 (6 mg/kg), achieving a confirmed PR after 4 cycles with good tolerability, which deepened over 6 months with resolution of all target lesions
- After study completion in December 2024, achieved a CR with complete resolution of all radiologic disease and remains in remission

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Pharmacodynamics

- TAC-001 delivers a potent TLR9 agonist to CD22+ B cells, leading to their activation and the production of cytokines and chemokines (**Figure 6**)
  - CD22 internalization is induced on circulating CD19+ B cells, with prolonged target engagement observed at higher dose levels
  - Activation of naïve and memory B cells is observed, as demonstrated by the upregulation of CD86 (naïve depicted) and CD40 (Supplement) within 3 hours post-first infusion
  - Production of serum cytokines and chemokines, including IL-6, IP-10, IL-10, IL-8, TNF-α, MCP-1, and MIP-1α, is stimulated within 3 hours post-first infusion, returning to near baseline by 24 hours for most (Supplement)

Figure 6. TLR9 Payload Delivery and B Cell Activation Align with TAC-001 MOA

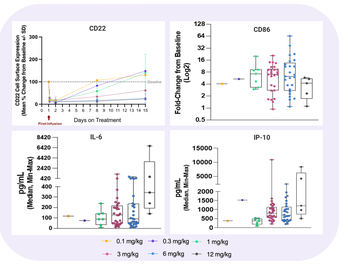
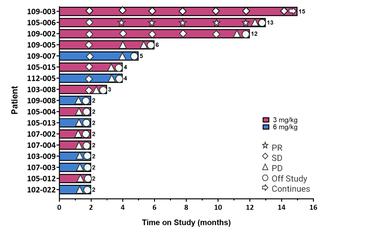


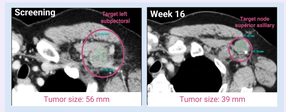
Figure 5. Treatment Response in Melanoma[a,b]



[a]Overall response based on iRECIST v1.1 for patient 109-002 and on RECIST v1.1 for all other patients.
[b]Patient 109-003 was transferred to a single patient IND for continued treatment.

Partial Response in Patient with Relapsed Melanoma

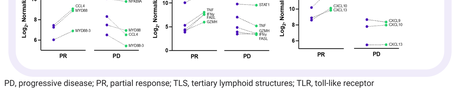
- 56-year-old male with metastatic melanoma, previously treated with nivolumab and ipilimumab before progression
- Received TAC-001 (3 mg/kg), achieving a confirmed PR after 4 cycles, which was maintained over 10 months with excellent tolerability



PD, progressive disease; PR, partial response; SD, stable disease.

- Paired screening and treated lymph node tissues from two melanoma subjects (3 mg/kg), one with a >10 months PR and one with a PD response
  - Bulk RNA sequencing showed increased gene expression related to TLR, cytotoxicity, TLS (**Figure 7**), and additional pathways (Supplement) in the treated tissue of the partial responder

Figure 7. Tissue Gene Expression in Melanoma



PD, progressive disease; PR, partial response; TLS, tertiary lymphoid structures; TLR, toll-like receptor

Pharmacokinetics

- TAC-001 exposures (Cmax and AUC) exhibited a dose-dependent increase over the tested dose range (**Figure 8; Table 4**)

Figure 8. TAC-001 Concentration-Time Profile

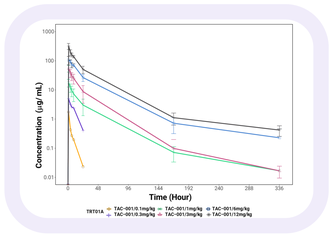


Table 4. TAC-001 PK Parameters[a]

Parameter, (CV%)	0.1 mg/kg n=1	0.3 mg/kg n=1	1 mg/kg n=7	3 mg/kg n=21	6 mg/kg n=7	12 mg/kg n=4
Cmax, μg/mL	1.7	5.0	17.9 (29)	54.8 (26)	114 (17)	320 (23)
AUC, h*μg/mL	6.4	46.7	208 (42)	699 (51)	2520 (5.4)	5060 (24)
CL, mL/h/kg	15.4	5.9	5.1 (63)	4.7 (41)	2.4 (1.1)	2.1
Vz, mL/kg	84.6	61.9	103 (58)	87.3 (49)	141 (20)	149

[a]Parameters presented as Mean (CV%).
AUC, area under the curve; Cmax, peak concentration; CL, clearance; Vz, volume of distribution.

CONCLUSIONS

- TAC-001 was well tolerated with a favorable safety profile, characterized predominantly by Grade 1 and 2 TRAEs
- TAC-001 demonstrated promising durable antitumor efficacy and stable disease after progression on immune-checkpoint therapy in melanoma and cholangiocarcinoma and other advanced/metastatic solid tumors
- TAC-001 exhibited dose-dependent pharmacokinetic/pharmacodynamic effects
- These results support the further evaluation of TAC-001 in patients with select relapsed or refractory solid tumors
  - A trial, INCLINE-102, in combination with anti-PD-1 antibody is currently planned

ADDITIONAL INFORMATION

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For additional information, please contact lchow@tallactx.com or visit www.tallactherapeutics.com

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TALLAC THERAPEUTICS

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