ITIL-306-201: A Multicenter, First-in-Human Phase 1a/1b Study of ITIL-306, an Engineered Autologous TIL Cell Therapy Product, in Adults With Advanced Solid Tumors

Poster 776

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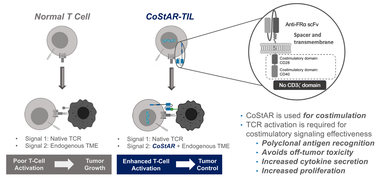
BACKGROUND

- Pioneering work in advanced melanoma has prompted investigation of tumor-infiltrating lymphocyte (TIL) cell therapy in other immunogenic solid tumor indications[1-3]
- Although TILs encompass a broad diversity of antitumor reactivities with an unrestricted T-cell receptor (TCR) repertoire, their activity may be limited in certain tumors[4]

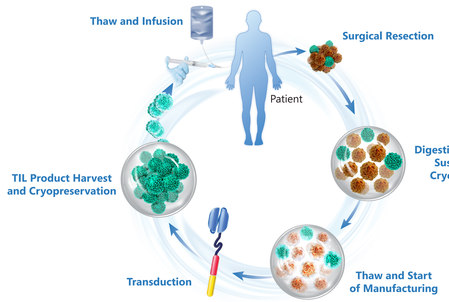
Figure 1. CoStAR Platform Overview



CoStAR, costimulatory antigen receptor; FRα, folate receptor alpha; scFv, single-chain variable fragment; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte; TME, tumor microenvironment.

- Building upon the diverse antigen specificity of TILs, the synthetic costimulatory antigen receptor (CoStAR™) is designed to enhance T-cell effector function upon TCR-mediated antigen recognition (**Figure 1**)[5]

Figure 2. CoStAR TIL Journey

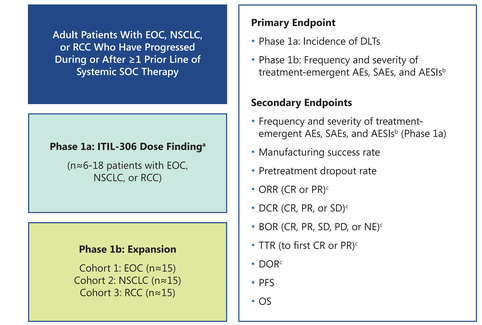


CoStAR, costimulatory antigen receptor; TIL, tumor-infiltrating lymphocyte.

- The CoStAR manufacturing process includes a lentiviral vector transduction step to generate CoStAR TILs with costimulatory domains and single-chain variable fragment (scFv) strategically designed to optimize TIL function for specific histologies (**Figure 2**)[5,6]
- The digestion of tumor tissue to a single-cell suspension enables immediate, efficient, and scalable expansion and transduction of TILs, which may be a potential advantage compared with TILs derived from tumor fragments, where TILs may be lost if trapped within fragments
- Unlike chimeric antigen receptor T cells, the CoStAR platform supplements TCR-specific antigen recognition with robust, precise costimulation on engagement with the CoStAR scFv target[5]
- In a murine model with a human solid tumor xenograft, the anti-folate receptor alpha (FRα) CoStAR significantly enhanced T-cell proliferation, persistence, and antitumor activity without exogenous interleukin-2 (IL-2) support compared with control T cells, resulting in enhanced tumor control and prolonged survival[6]
- ITIL-306 is an engineered autologous TIL cell therapy that supplements native TCR-specific antigen recognition with synthetic costimulation via the novel CoStAR on engagement with FRα
- As several tumor types express FRα, including renal, ovarian, and lung cancers, ITIL-306 may be used for multiple indications[7-11]

STUDY DESIGN AND ENDPOINTS

Figure 3. ITIL-306-201 Study Design and Endpoints



[a] The Phase 1a dose-finding portion is a standard 3+3 dose escalation design, with enrollment of the subsequent dose level based on the incidence of DLTs observed within each dose level.
[b] As measured by the CTCAE version 5.0 grading scale or ASTCT consensus grading scales for CRS and ICANS.[12]
[c] Investigator assessment per modified RECIST v1.1.
AE, adverse event; AESI, adverse event of special interest; ASTCT, American Society for Transplantation and Cellular Therapy; BOR, best overall response; CR, complete response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; EOC, epithelial ovarian cancer; ICANS, immune effector cell-associated neurotoxicity syndrome; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event; SD, stable disease; SOC, standard of care; TTR, time to response.

- ITIL-306-201 is a multicenter, single-arm, Phase 1a/1b dose escalation and expansion study evaluating the safety and feasibility of ITIL-306 in adult patients with advanced epithelial ovarian cancer (EOC), non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC) who relapsed from or are refractory to ≥1 prior line of systemic therapy (**Figure 3**)

STATISTICAL METHODS

STUDY POPULATIONS

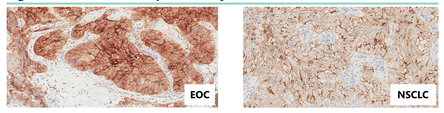
- Dose-limiting toxicity (DLT)–evaluable set: All Phase 1a patients treated with the target ITIL-306 dose (±20%) and followed for ≥28 days or received a dose of ITIL-306 lower than the target dose but experienced a DLT during the 28-day post-infusion period; used for analysis of DLTs
- Safety analysis set: All patients treated with ITIL-306
- Full analysis set: All enrolled patients; used for the analysis of manufacturing success rate, post-enrollment dropout rate prior to treatment, the summary of patient disposition, and patient listings of deaths
- Modified intent-to-treat analysis set: All patients enrolled and treated with ITIL-306

STUDY ANALYSIS

- In Phase 1a, a safety review team will review safety data after 3-6 patients in the DLT–evaluable set at each dose level have had the opportunity to be followed for 28 days after the ITIL-306 infusion
- On the decision to expand into Phase 1b, an interim analysis and a primary analysis will be performed for each disease cohort
  - The interim analysis will be conducted after 9 patients in that cohort have been enrolled and treated with ITIL-306 and have had the opportunity to be followed for ≥3 months
  - The primary analysis will be conducted after all patients treated with ITIL-306 in a cohort (up to ~15 patients) have had the opportunity to be assessed for response ≥6 months after the ITIL-306 infusion

FRα EXPRESSION TESTING BY IMMUNOHISTOCHEMISTRY (IHC)

Figure 4. FRα Protein Expression by IHC



EOC, epithelial ovarian cancer; FRα, folate receptor alpha; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer.

- Exploratory retrospective analyses of FRα protein expression, using samples collected at the time of enrollment, will be assessed centrally using a validated IHC assay (**Figure 4**) to:
  - Determine association with study endpoints, if any
  - Inform the development of a potential algorithm and cutoff for application in future studies
- Pharmacokinetics and pharmacodynamics will be assessed including serum cytokines and ITIL-306 engraftment and persistence
- Additional translational analyses including tumor and peripheral blood characterization may be conducted (eg, PD-L1, CD8 IHC, spatial transcriptomics, circulating tumor DNA, single-cell RNA sequencing)

PATIENT ELIGIBILITY

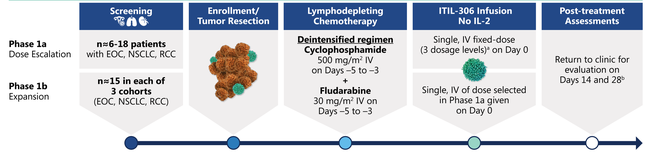
Table 1. ITIL-306-201 Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Histologically documented advanced disease as follows: – **Phase 1a:** High-grade serous epithelial carcinoma of the ovary, fallopian tube, or peritoneum, adenocarcinoma of the lung, or clear-cell RCC – **Phase 1b:** ▪ **Cohort 1:** High-grade serous, endometrioid, or clear-cell carcinoma of the ovary, fallopian tube, or peritoneum ▪ **Cohort 2:** Squamous-cell carcinoma or adenocarcinoma of the lung ▪ **Cohort 3:** Clear-cell or papillary RCC • **Phase 1a and Phase 1b (Cohort 1):** Platinum-resistant EOC[a] • **Phase 1a and Phase 1b (Cohort 2):** For NSCLC without an actionable oncogenic driver mutation, PD after platinum-based doublet chemotherapy and a checkpoint inhibitor (anti–PD-1 or anti–PD-L1); for NSCLC with an actionable oncogenic driver mutation, progression following approved mutation-targeting agent and platinum-based doublet chemotherapy[b] • **Phase 1a and Phase 1b (Cohort 3):** Progressive RCC following antiangiogenic therapy and a PD-1–axis inhibitor • Age ≥18 years • ECOG performance status of 0 or 1 • Medically suitable for surgical resection of tumor tissue weighing an anticipated aggregated minimum of 2 grams • After tumor resection for TIL harvest, patients must have ≥1 remaining measurable lesion as identified by CT or MRI per RECIST v1.1 • Adequate bone marrow and organ function	• History of another primary malignancy within the previous 3 years • **Phase 1a:** – EOC with low-grade, endometrioid, clear cell, mucinous, sarcomatous, or mixed histologic subtypes – NSCLC with squamous, neuroendocrine differentiation histologic subtypes – RCC with nonclear-cell RCC histologic subtype • **Phase 1b:** – **Cohort 1:** Mucinous, sarcomatous, and low-grade EOC – **Cohort 2:** Small cell lung cancer or NSCLC with neuroendocrine differentiation – **Cohort 3:** Nonclear-cell RCC, except papillary RCC • Previous allogeneic stem cell transplant or organ allograft • Prior TIL or engineered cell therapy (eg, CAR T-cell therapy) • Surgery or radiotherapy, immunotherapy, targeted therapy agents, anticancer vaccines, systemic steroids, or chemotherapy ≤2 weeks before enrollment • Stroke or transient ischemic attack ≤12 months before enrollment • Symptomatic and/or untreated CNS metastases • Significant autoimmune disease ≤2 years prior to enrollment • Severe traumatic injury, major surgery, or hemorrhagic event ≤28 days before enrollment

[a] Defined as either patients with 1 line of platinum-based chemotherapy with ≥4 cycles of a platinum agent and disease progression during or within 6 months of the last dose of the platinum agent or patients with ≥2 lines of platinum therapy with disease progression within 6 months of the last dose of the platinum agent. Patients with *BRCA*-mutated EOC must have received previous poly (ADP-ribose) polymerase inhibitor therapy.
[b] Platinum-based doublet chemotherapy given in the adjuvant setting for local disease may satisfy inclusion if PD occurred within 12 months of completion of adjuvant therapy.
CAR, chimeric antigen receptor; CNS, central nervous system; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; EOC, epithelial ovarian cancer; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1; programmed cell death ligand 1; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TIL, tumor-infiltrating lymphocyte.

TREATMENT SCHEMA

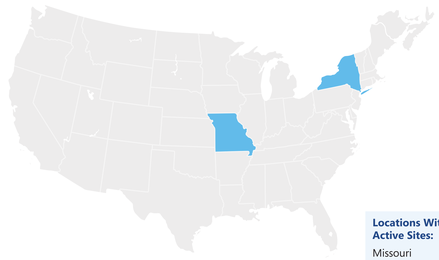
Figure 5. ITIL-306-201 Treatment Schema



[a] Starting dose 1 × 10⁹ CoStAR+ TILs in patients with EOC, NSCLC, and RCC.
[b] Disease assessment and survival begins at Week 6 after ITIL-306 infusion.
CoStAR, costimulatory antigen receptor; EOC, epithelial ovarian cancer; IL-2, interleukin 2; IV, intravenous; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; TIL, tumor-infiltrating lymphocyte.

- Patients will receive 3 days of deintensified intravenous lymphodepleting chemotherapy (cyclophosphamide 500 mg/m² and fludarabine 30 mg/m² on Days −5 to −3) followed by a single ITIL-306 infusion on Day 0 (**Figure 5**)
- Patients will not receive any post-infusion supportive IL-2; adverse events associated with TIL therapy are primarily attributed to lymphodepleting chemotherapy and/or high-dose IL-2 rather than the TIL product itself[2,13,14]

STATUS



- The study opened to accrual in August 2022 and is currently enrolling patients from sites in the United States
- Additional sites are being added; refer to ClinicalTrials.gov for the most up-to-date list of activated sites

REGISTRATION

- This study is sponsored by Instil Bio, Inc., and is registered at ClinicalTrials.gov (NCT05397093)

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- For information on additional clinical trials from Instil Bio, please see poster 787 by Gastman B et al, titled "DELTA-1: A global, multicenter, phase 2 study of ITIL-168, an unrestricted autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in adult patients with advanced cutaneous melanoma"

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