Background Pioneering work in advanced melanoma has prompted investigation of 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.\(^4\) Addition of synthetic costimulation improves T-cell functional activity while maintaining the diverse antigen specificity of TILs (figure 1).\(^5\) In a murine model with a human solid tumor xenograft, the anti-folate receptor alpha (FR\(x\)) costimulatory antigen receptor (CoStAR) significantly enhanced T-cell proliferation, persistence, and antitumor activity without exogenous IL-2 support, 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 upon engagement with FR\(x\). 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 \(\geq 1\) prior line of systemic therapy.

Methods Eligible patients are aged \(\geq 18\) years with histologically confirmed EOC, NSCLC, or RCC that has progressed during or after \(\geq 1\) prior line of systemic standard-of-care therapy, have ECOG performance status 0-1, and have viable tumor tissue that is suitable to resect with \(\geq 2\) grams for TIL harvest. Patients will be enrolled in phase 1a (dose escalation in a standard 3+3 design; \(n=6-18\)) or 1b (expansion; \(n=15\) in each of 3 cohorts, 1 for each tumor type) (figure 2). Following tumor resection for TIL harvest, patients must have \(\geq 1\) remaining measurable lesion per RECIST v1.1. Patients will receive a reduced dose of lymphodepleting chemotherapy followed by a single, intravenous fixed-dose of ITIL-306 in phase 1a (1 of 3 dose levels) or 1b (dose selected in the phase 1a portion) and no post-infusion IL-2. The phase 1a primary endpoint is incidence of dose-limiting toxicities. The phase 1b primary endpoint is frequency and severity of treatment-emergent adverse events (AEs), serious AEs, and AEs of special interest. Secondary endpoints include manufacturing success rate, objective response rate per modified RECIST v1.1,\(^7\) disease control rate, best overall response, time to response, duration of response, progression-free survival, and overall survival. Key exploratory endpoints include association of biomarkers with response (eg, tumor FR\(x\) expression) and characterization of ITIL-306 activation, trafficking, persistence, and phenotype. The study is open (NCT05397093).

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Abstract 776 Figure 1 CoStAR Platform Overview
The novel CoStAR platform is engineered to enhance TIL functional activity. Similar to unmodified T cells, CoStAR TILs require specific antigen recognition via the native TCR for activation. CoStAR ligand engagement also provides T cells with synthetic costimulatory signals that enhance antitumor responses. Therefore, CoStAR-expressing T cells supplement tumor-specific antigen recognition via TCR with a robust costimulatory signal delivered via CoStAR.

Abstract 776 Figure 2 ITIL-306-201 Phase 1a/1b Treatment Schema
ITIL-306-201 is a phase 1a/1b dose escalation and expansion study evaluating the safety and feasibility of ITIL-306 in adult patients with advanced EOC, NSCLC, and RCC who relapsed from or are refractory to \(\geq 1\) prior line of systemic standard-of-care therapy.

\(^{a}\) Enrollment at the next dose level will be based on the incidence of dose-limiting toxicities observed within each dose level. Enrollment into
dose levels will continue sequentially until a maximum-tolerated dose is reached, or all dose levels have been tested. If the dose-limiting toxicity threshold is not met at the highest dose level, then dose level 3 will be selected for testing in phase Ib.

* ± 20% target dose.

EOC, epithelial ovarian, fallopian tube, and peritoneal carcinomas; IV, intravenous; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; TIL, tumor-infiltrating lymphocyte.