A Phase 1 Adoptive Cell Therapy Using Drug-Enhanced, Tumor-Infiltrating Lymphocytes, DeTIL-0255, in Adults With Advanced Malignancies

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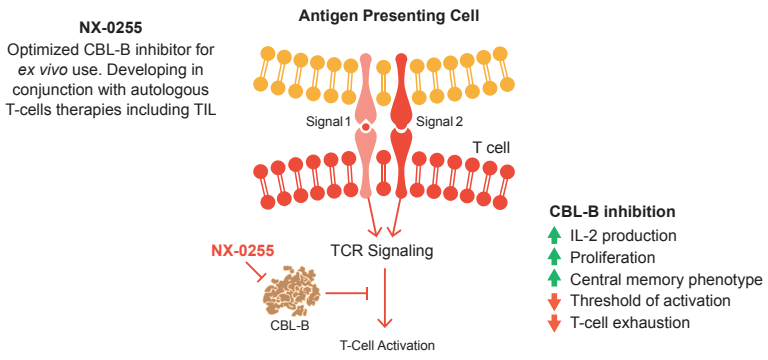
Background

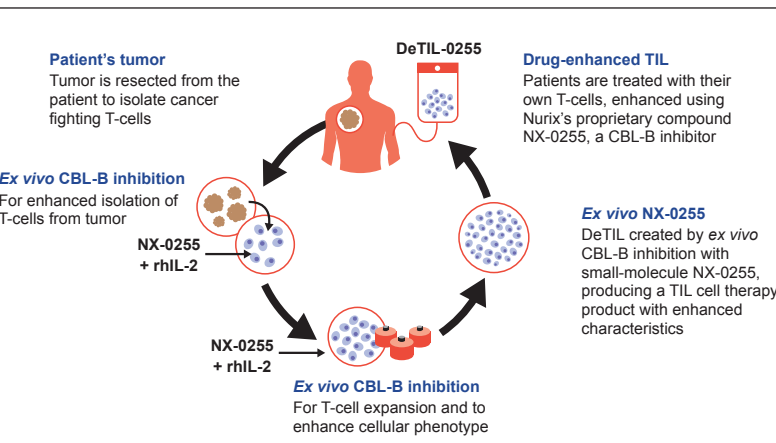
- Tumor-infiltrating lymphocytes (TIL) represent an immune cell population that recognizes tumors including multiple endogenous tumor antigens. They often develop an exhausted phenotype due to the tumor microenvironment, lacking in suitable dendritic cells to promote their expansion and function.
- Adoptive cell therapy (ACT) including TIL has been studied for over 40 years beginning with lymphokine-activated killer (LAK) cells at the National Cancer Institute (NCI).[1-3]
- Preliminary clinical activity of ACT was first reported in patients with persistent and recurrent cervical cancer with an overall response rate of 28%.[4]
- While TIL have demonstrated long-term durable responses in patients with metastatic melanoma and cervical cancer, there is no FDA-approved TIL therapy and challenges still remain.
- The E3 ubiquitin ligase – Casitas B-lineage lymphoma B (CBL-B) – is expressed in T-cells, functioning as a regulator of immune cell activation, in part by requiring CD28 costimulation in addition to T-cell receptor activation.[5,6]
- We have developed NX-0255, a highly potent, small-molecule inhibitor of CBL-B, which increases T-cell–derived cytokine (IFNγ, IL-2) secretion and proliferation in the presence or absence of costimulation.[7]

CBL-B: a modulator of T-cell activation and novel target for immuno-oncology



Abbreviations: CBL-B, Casitas B-lineage lymphoma B; IL-2, interleukin-2; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocytes

DeTIL: Drug-enhanced tumor-infiltrating lymphocytes



Abbreviations: CBL-B, Casitas B-lineage lymphoma B; DeTIL, tumor-infiltrating lymphocytes; rhIL-2, recombinant human interleukin-2; TIL, tumor-infiltrating lymphocytes

Methods

- NX-DeTIL-0255-201 is a phase 1 multicenter, open-label, safety run-in and cohort expansion study of DeTIL-0255 administered with systemic high-dose aldesleukin (IL-2) following non-myeloablative (NMA) lymphodepleting chemotherapy in patients with advanced gynecologic malignancies for whom standard therapy with proven clinical benefit does not exist, is no longer effective, or is not appropriate:
  - Safety run-in will investigate DeTIL-0255 at a dose range of 1 to 150 x 10^9 CD3+ T cells, with the exact dose varying based on ability to expand DeTIL from tumor biopsies.
  - Cohort expansion will proceed after the safety run-in has been completed and will further evaluate and assess safety and anti-tumor activity of DeTIL-0255 in up to 3 cohorts. Each cohort will be closed as it meets the protocol enrollment requirements (n=18).
- Eligible tumor types include platinum-resistant epithelial ovarian, cervical, and endometrial cancers.
- The primary objectives are to evaluate the safety, tolerability, and preliminary antitumor efficacy of DeTIL-0255.

NX-DeTIL-0255-201: Study design

Two-part first-in-human phase 1 trial of DeTIL-0255 in advanced gynecologic cancers

Safety run-in
Cell dose 1 to 150 (x10^9 CD3+ cells)
(N = 3–6)

Gynecologic malignancies
- Recurrent/persistent platinum-resistant epithelial ovarian cancer
- Relapsed/metastatic/persistent cervical cancer
- Advanced/recurrent endometrial cancer

Cohort expansion
Cell dose 1 to 150 (x10^9 CD3+ cells)

- Recurrent/persistent platinum-resistant epithelial ovarian cancer (n = up to 18)
- Relapsed/metastatic/persistent cervical cancer (n = up to 18)
- Advanced/recurrent endometrial cancer (n = up to 18)

ClinicalTrials.gov Identifier: NCT05107739

Study objectives and endpoints

Phase	Objectives	Endpoints
Primary	**To evaluate the safety and tolerability of DeTIL-0255 in adult patients with advanced malignancies**	**Incidence of TEAEs including:** **– Grade ≥3 TEAEs** **– Treatment-emergent SAEs** **– TEAEs leading to treatment (treatment regimen) discontinuation** **– Deaths due to TEAEs** **Incidence of all deaths** **Incidence of DLTs**
	To evaluate the preliminary anti-tumor activity of DeTIL-0255	**ORR per RECIST v1.1** **DOR, DCR, PFS, OS**
Secondary	To evaluate immune cell infiltration in the tumor following DeTIL-0255 infusion	Changes from baseline in immune cell infiltration in the tumor following DeTIL-0255 infusion
Exploratory	To support autologous antigen specific potency assay development To explore changes in biomarkers following administration of DeTIL-0255 and mechanisms of response and resistance	Generation of reagents necessary to support potency assay development Changes from baseline in biomarkers in the tumor microenvironment, circulating immune cells and serum, and assessment of mechanisms of response and resistance

Abbreviations: DCR, disease control rate; DeTIL, drug-enhanced tumor-infiltrating lymphocytes; DLTs, dose-limiting toxicities; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events

Key eligibility criteria

- Age ≥18 years and ≤70 years.
- Life expectancy of at least 4 months.
- Eastern Cooperative Oncology Group performance status ≤1.
- Histologically documented gynecologic malignancies:
  - Recurrent or persistent platinum-resistant or refractory epithelial ovarian cancer.
  - Recurrent, metastatic, or persistent cervical carcinoma.
  - Advanced or recurrent endometrial cancer.
- Metastatic and measurable disease per RECIST v1.1 (pre- and post-tumor resection).
- Resectable tumor for DeTIL generation.
- Two prior lines of therapy and additional standard therapy does not exist, is no longer effective, or a reasonable likelihood that there is no clinical benefit (as deemed by Investigator).
- Adequate organ/bone marrow function, as defined per protocol laboratory parameters.
- Agreement to contraception and pregnancy testing procedures.

Evaluations

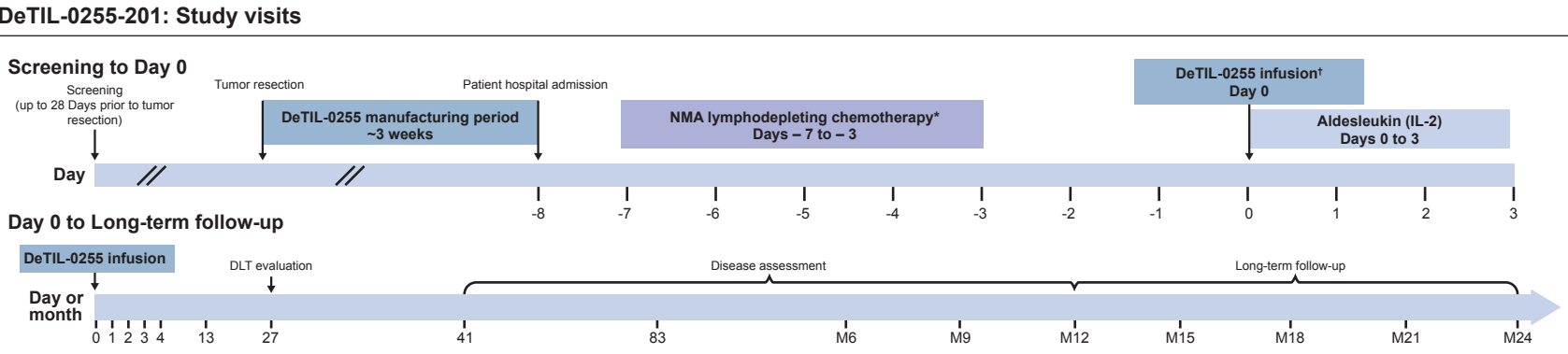
Efficacy

- Tumor assessments are to be assessed per RECIST v1.1 using CT with/without contrast of affected body regions or appropriate MRI. Assessments within 8 weeks of tumor resection can be used to identify the lesion to be resected.
- Tumor assessments are to be repeated within 7 days after tumor resection. Assessments post DeTIL-0255 infusion are to occur at Day +41, Day +83, and Months 6, 9, and 12 (±7 days).

Safety

- Analysis of safety will be a comprehensive evaluation of adverse events (AEs) and/or toxicity per subject, presented by dose and tumor type cohort and overall, based on:
  - Treatment-emergent AEs (TEAEs), including Grade ≥3 non-hematologic TEAEs, treatment-emergent SAEs, TEAEs leading to treatment (treatment regimen) discontinuation, and deaths due to TEAEs
  - All deaths
  - Dose-limiting toxicities

NX-DeTIL-0255-201: Study visits



*NMA lymphodepleting chemotherapy consisted of cyclophosphamide and fludarabine; †3-5 days after last dose of NMA lymphodepleting chemotherapy.
Abbreviations: DeTIL, drug-enhanced tumor-infiltrating lymphocytes; DLT, dose-limiting toxicity; IL-2, interleukin-2; NMA, non-myeloablative

Current status

- Currently enrolling in US only.
- Clinical trial information: NCT05107739.
- Study contact: nx0255201@nurixtx.com

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