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) are a heterogeneous population of T cells that recognize multiple endogenous tumor antigens but may have developed an exhausted phenotype due to the tumor microenvironment. While existing TIL therapies produce durable responses in patients with melanoma, cervical, and head and neck cancers, poor in vitro cell expansion, limited short-lived in vivo persistence, and diminishing potency restrict this approach’s broader application.

DeTIL-0255 (drug-enhanced TIL [DeTIL]) is an autologous adoptive cell therapy (ACT) derived from a patient’s tumor and expanded ex vivo with NX-0255, a small-molecule inhibitor of the E3 ligase, Casitas B-lineage lymphoma proto-oncogene B (CBL-B). CBL-B is expressed in T cells, where it functions as a regulator of immune cell activation, in part by requiring CD28 co-stimulation in addition to T cell receptor activation. Desirable properties enhanced by DeTIL-0255 compared with TIL include increased number of stem-like CD39−/CD69−, and CD8+ T cells associated with persistence, as well as enhanced cytolytic function. ACT with T cells expanded ex vivo using NX-0255 demonstrated increased anti-tumor activity, longer survival, increased stem-like phenotype, and persistence of tumor antigen-specific T cells in mouse tumor models. Adoptive cell transfer of DeTIL-0255 may, therefore, exhibit broader functional activity than conventional TIL, potentially conferring improved anti-tumor activity and response.

Methods NX-DeTIL-0255-201 is a Phase 1 multicenter, open-label study of DeTIL-0255 administered with systemic high-dose IL-2 following nonmyeloablative lymphodepleting chemotherapy in patients with advanced gynecological malignancies for whom standard therapy with proven clinical benefit does not exist, is no longer effective, or is inappropriate. Primary objectives are to evaluate safety, tolerability, and preliminary antitumor activity of DeTIL-0255. A safety run-in will consist of 3 to 6 patients treated with DeTIL-0255 and evaluated for dose-limiting toxicity (DLT). The DLT period starts with DeTIL-0255 infusion and ends after 28 days. The safety run-in will investigate DeTIL-0255 at a dose range of 1 to 150 x 10^9 CD3+ T cells (exact dose varying based on expansion potential of DeTIL-0255 from tumor biopsies). Following the safety run-in, cohort expansion will further evaluate the safety and antitumor activity of DeTIL-0255 in patients with recurrent/persistent platinum-resistant epithelial ovarian cancer, cervical carcinoma, and endometrial cancer. Key eligibility criteria include measurable disease, a resectable lesion for TIL harvest, ≥2 prior lines of therapy, and an Eastern Cooperative Oncology Group performance status 0 or 1. The study is expected to enroll ~54 patients in ~10 sites across the United States. NCT05107739

Trial Registration NCT05107739
Ethics Approval The study obtained institutional review board (s) approval, and participants gave informed consent before taking part.