A Phase 1 Dose Escalation and Dose Expansion Study for LNCB74, A B7-H4 Targeted Antibody Drug Conjugate, As Monotherapy In Participants With Advanced Solid Tumors

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Background

B7-H4 is a transmembrane receptor whose expression in tumors correlates with poor clinical outcomes for ovarian and breast cancers. High expression in multiple tumor types and limited expression in normal tissues makes B7-H4 an attractive target for antibody drug conjugate (ADC) therapeutics. LNCB74 is a B7-H4 targeted ADC in which a humanized IgG1κ antibody is conjugated with a β-Glucuronidase linker to the microtubule disrupting payload monomethyl auristatin E (MMAE) with a drug-to-antibody ratio of 4 (DAR4). Compared to other B7-H4 targeted ADCs in clinical development, LNCB74 has demonstrated a superior safety profile in nonhuman primate toxicity studies and potent anti-tumor activity in multiple cell line- and patient-derived xenograft in vivo models, making it a promising ADC therapy for B7-H4-expressing solid tumors.

Patient Population

- Platinum-resistant high-grade serous, high-grade endometrioid, or clear cell: **Ovarian**, **Fallopian Tube**, or **Primary Peritoneal Cancer**
- Treatment-Refractory **Breast Cancer**: TNBC, HER2 positive/HER2-low breast cancer, HR positive/HER2 negative or low breast cancer
- **Endometrial Cancer** must have received, be ineligible for, or intolerant of a platinum doublet standard of care chemotherapy with/without anti-PD(L)-1 treatment
- **Biliary Tract Cancer** must have received, be ineligible for, or intolerant of a platinum doublet standard of care chemotherapy with/without anti-PD(L)-1 treatment
- **Non-Small Cell Lung Cancer (Squamous)** must have received, be ineligible for or intolerant of a platinum doublet standard of care chemotherapy and prior anti-PD(L)-1 treatment

Study Endpoints

Primary

- Safety, Tolerability
- Maximum Administered Dose and/or RP2D
- Maximum Tolerated Dose

Secondary

- Characterize PK/PD
- Preliminary Efficacy
- Correlate baseline B7-H4 expression with anti-tumor activity

Mechanism of Action for LNCB74, a B7-H4 Targeting ADC

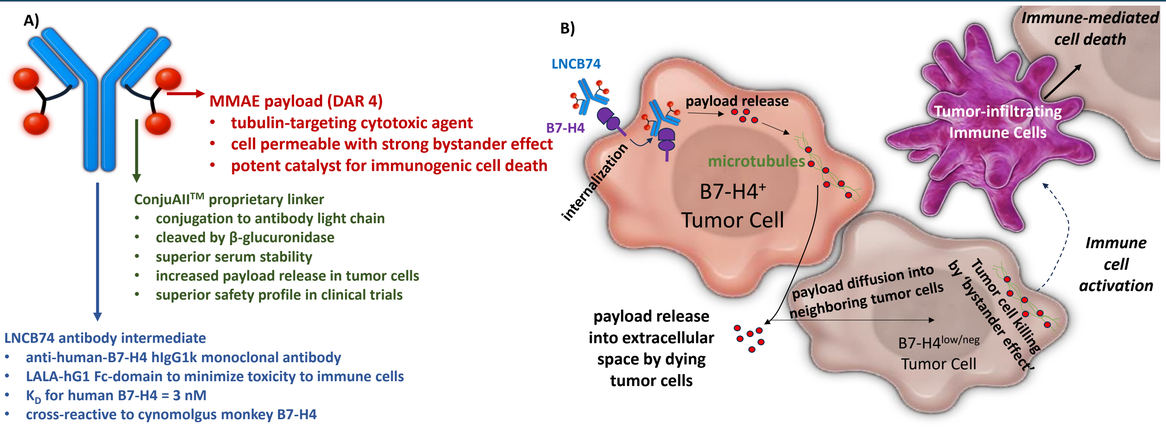


Figure 1. A) Structure of B7-H4 targeting ADC LNCB74. B) Mechanism of action of LNCB74, an ADC which delivers the microtubule-targeting MMAE payload to B7-H4 positive tumor cells. MMAE generates immunogenic cell death and mediates bystander effect to kill neighboring tumor cells following uptake by B7-H4 expressing tumor cells.

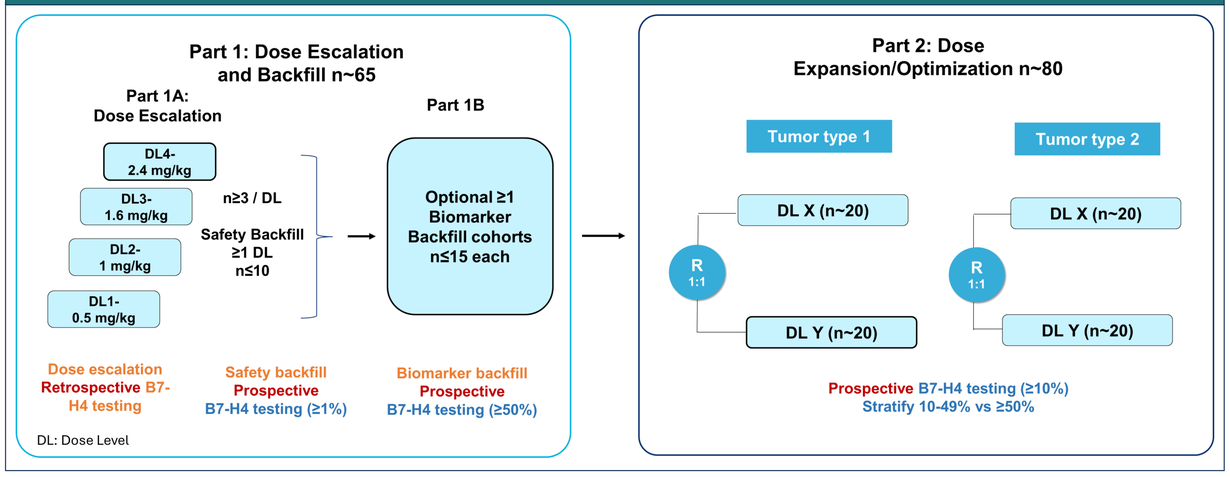
Key Inclusion Criteria

- ≥ 18 years of age on day of signing informed consent
- Advanced unresectable and/or metastatic solid tumors
- Measurable disease per RECIST 1.1
- Able to provide tumor tissue sample
- Eastern Cooperative Oncology Group (ECOG) of 0 to 1
- Adequate organ function

Key Exclusion Criteria

- Prior investigational agents within 4 weeks prior to treatment
- Anti-cancer chemotherapy, immunotherapy (non-antibody-based therapy), retinoid therapy, hormonal therapy within 2 weeks prior to treatment
- Antibody-based anti-cancer therapy within 4 weeks prior to treatment
- Targeted agents and small molecules within 2 weeks or 5 half-lives, whichever is longer
- Prior platinum-based chemotherapy and progressed within 4 weeks of initiating therapy (platinum-refractory disease)
- Received an ADC with MMAE payload
- Known active CNS metastases and/or carcinomatous meningitis
- History of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease
- Active ≥Grade 2 sensory or motor neuropathy
- Active or chronic corneal disorders, other active ocular conditions requiring ongoing therapy or any clinically significant corneal disease
- History of significant ascites requiring paracentesis within 2 weeks of screening

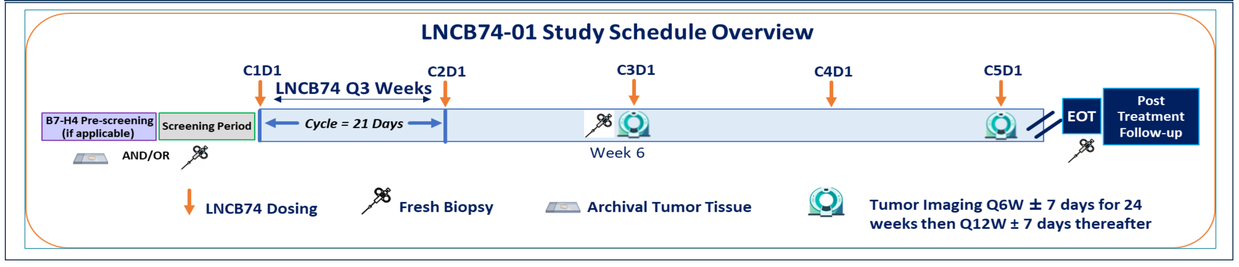
Study Design



Methods

LNCB74-01 is a Phase 1, open-label, first-in-human study that will include dose escalation, safety, and biomarker backfills (Part 1) and randomized dose expansion/optimization (Part 2). Participants will receive LNCB74 on Day 1 of each 21-day cycle. LNCB74 dosing is being calculated based on adjusted ideal body weight. Dose escalation will follow a Bayesian optimal interval (BOIN) design. Dose expansion will occur in up to two tumor types. In each tumor-specific dose expansion, participants will be randomized to two dose levels, stratifying for prior lines of therapy (1-3 vs ≥4) and B7-H4 expression (intermediate vs high). The study is currently enrolling in dose escalation. Clinical Trial information: **NCT06774963**.

Study Schedule



References and Acknowledgements

***Sponsor**: NextCure, Inc./Contact: Udayan Guha, MD. Ph.D. guhau@nextcure.com; **Collaborators**: LigaChemBio*

References: Fitzgerald DP, Doan DN, Peacock RB et al Abstract 1898: LNCB74 is a potent and safe next-generation antibody-drug-conjugate utilizing a cancer selective linker for the treatment of B7-H4 expressing cancers. Cancer Res 15 March 2024; 84 (6_Supplement): 1898:doi: 10.1158/1538-7445.AM2024-1898; Kahan SM, Fitzgerald DP, Peacock RB, et al 1051 LNCB74 is a B7-H4 targeting antibody-drug-conjugate with a β-glucuronide linker-MMAE payload system to enhance the therapeutic index in B7-H4 expressing cancers. Journal for ImmunoTherapy of Cancer 2024;12:doi: 10.1136/jitc-2024-SITC2024.1051