TPS3167 **Poster Session**

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 of the B7-family of immunomodulatory proteins whose expression 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 to the microtubule disrupting payload monomethyl auristatin E (MMAE) with a drug-to-antibody ratio of 4 (DAR4). LNCB74 is designed to maximize therapeutic index through three key elements. First, site specific ConjuAll conjugation results in a homogeneous DAR to drive uniform PK. Second, our proprietary glucuronidase-cleavable linker reduces both on- and off-target toxicity. Third, the antibody Fc was "LALA"-mutated to reduce Fc mediated uptake into Fc receptor expressing cells such as immune and endothelial cells. 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. **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). The objectives of the study will be to determine safety and tolerability, define the maximum tolerated dose and/or recommended phase 2 dose, characterize the pharmacokinetics (PK) and pharmacodynamics (PD), and to assess the preliminary efficacy in participants with metastatic solid tumors treated with LNCB74. The tumor types include ovarian, breast, endometrial, biliary tract cancer, and squamous NSCLC. Key eligibility criteria include measurable disease based on RECIST v1.1 and the ability to provide tissue samples to test B7-H4 expression by CLIA-certified immunohistochemistry assay in a central laboratory. Participants will receive LNCB74 on Day 1 of each 21-day cycle. 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 PK profile, immunogenicity, preliminary anti-tumor activity per RECIST v1.1, and correlation of baseline B7-H4 expression to anti-tumor activity of LNCB74 will be evaluated as secondary endpoints. Biomarkers will be assessed in peripheral blood and tumor tissue. Enrollment is ongoing in the United States. Clinical trial information: NCT06774963. Research Sponsor: NextCure Inc.