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NC410, A FUSION PROTEIN OF LAIR-2 (LEUKOCYTE ASSOCIATED IMMUNOGLOBULIN-LIKE RECEPTOR) WITH HUMAN IGG1 FC, IS SAFE & TOLERABLE WITH EVIDENCE OF IMMUNE MODULATION IN SUBJECTS WITH ADVANCED SOLID TUMORS

¹Han Myint*, ¹Linjie Tian, ¹Jahangheer Shaik, ¹Emilia Barbu, ¹Qinjie Zhou, ¹Aaron Morawski, ¹Hasan Abukharma, ¹Linda Liu, ²John Shin, ¹Dallas Flies, ¹Ron Copeland, ¹Megan Nelson, ¹Stephanie Zeidan, ²Marijo Bilusic, ²Danielle Pastor, ²Ravi Madan, ³Siqing Fu, ⁴Martin Gutierrez, ¹Solomon Langermann. ¹NextCure LLC, Beltsville, MD, USA; ²National Cancer Institute, Bethesda, MD, USA; ³MD Anderson Cancer Center, Houston, TX, USA; ⁴Hackensack Cancer Center, Hackensack, NJ, USA

Background Collagen and C1q in the extracellular matrix (ECM), are the predominant ligands for LAIR-1, an inhibitory receptor expressed on the cell surface of several immune cell subsets that inhibits immune activation and migration. LAIR-2, a soluble homolog of LAIR-1, competes for binding to collagen and C1q and serves as a natural decoy to promote immune function under normal conditions. Dysregulation of the ECM and increased expression of collagen and C1q within the tumor microenvironment (TME) plays a critical role in promoting tumor progression. NC410 was engineered to overcome this highly immunosuppressive environment by blocking LAIR-1 function, reversing immune suppression, and inducing ECM remodeling to promote immune cell infiltration within the TME.

Methods This is a first in human, phase 1/2, open-label, single-armed dose-escalation study to determine the safety, tolerability, dose-limiting toxicity (DLT), maximum tolerated dose (MTD), recommended phase 2 dose, preliminary efficacy and to explore pharmacodynamic biomarkers of NC410 (figure 1). Key eligibility criteria include subjects with advanced or metastatic solid tumors with measurable disease based on RECIST v1.1.

Results As of 07/22/2021, a total of 16 patients have been enrolled, treated, and completed the DLT period. NC410 (up to 60 mg), was well tolerated, with no safety concerns, infusion-related toxicities, or DLT reported. No anti-drug antibody (ADA) was detected post-NC410 up to 60 mg treatment. As expected, the C1Q level decreased immediately after the NC410 infusion and was replenished after two hours. Evaluation from samples to date available up to cycle 5 suggests that there was no reduction in the baseline C1Q level with subsequent dosing (figure 2). LAIR-2 levels continued to increase in a dose-dependent fashion post-NC410 dosing and marginal increase pre-dose (figure 3). Interestingly, we observed an increase in soluble LAIR-1 over time in a similar pattern to LAIR-2 (figure 4). Furthermore, immunophenotyping of patient whole blood suggests a trend towards an increase in CD4+ and CD8+ T cells including LAIR-1+ T cells in cohort 4, although overall expression levels of LAIR-1 did not appear to increase (ongoing analysis). Cytokines, chemokines, and collagen degradation products (CDP) will be evaluated as potential pharmacodynamic biomarkers as we continue through higher dose cohorts.

Abstract 487 Figure 1 NC410: study schema

Abstract 487 Figure 2 C1Q levels show immediate reduction after NC410 dosing with no accumulated depletion

Abstract 487 Figure 3 LAIR-2 levels show an increase in dose-dependent fashion after NC410 dosing with marginal increase pre-dose

Abstract 487 Figure 4 Soluble LAIR-1 levels show a similar pattern to LAIR-2 levels

Conclusions Preliminary evaluation of NC410 in subjects with advanced or metastatic solid tumors appears to be safe and well-tolerated with evidence of immune modulation consistent with predictive PK/PD modeling in a Phase 1/2 open-label study. Further evaluation will be done with increasing doses to confirm these initial findings.

Trial Registration NCT04408599

Ethics Approval This study has been approved by the IRB of all the participating institutions, and all participants have given informed consent before taking part in the study.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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