A Phase 1, Open-Label, Safety, Tolerability, and Efficacy Study of NC525 in Subjects with Advanced Myeloid Neoplasms

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Background

A significant unmet need exists for patients with AML whose disease relapses after or is primarily refractory to standard-of-care (SOC) treatments. In such patients, relapse is mediated by the persistence of chemotherapy-resistant leukemic stem cells (LSCs). Strategies to preferentially target LSCs, promote immune recognition of AML blasts, and prevent relapse are highly sought after. AML LSCs and blasts are characterized by high expression of leukocyte-associated immunoglobulin-like receptor 1 (LAIR-1). LAIR-1 is an immunomodulatory receptor that binds to collagenous ligands. LAIR-1 signaling enhances pro-survival pathways and is essential for AML development and survival. We developed a LAIR-1 agonist monoclonal antibody (mAb), termed NC525, that clusters LAIR-1 in the presence of endogenous ligands, increasing programmed cell death in LSCs and leukemic blasts but not in healthy stem cells or immune cells. LAIR-1 inhibition in AML cells blocks key survival pathways, as demonstrated in the data section of this poster. A Phase I clinical trial will evaluate the safety and preliminary efficacy of NC525 in AML, high-risk myelodysplastic syndrome, and CMML with the mechanistic aim of targeting and eliminating LSCs.

LAIR-1 Overexpression On AML Blast And Leukemic Stem Cells

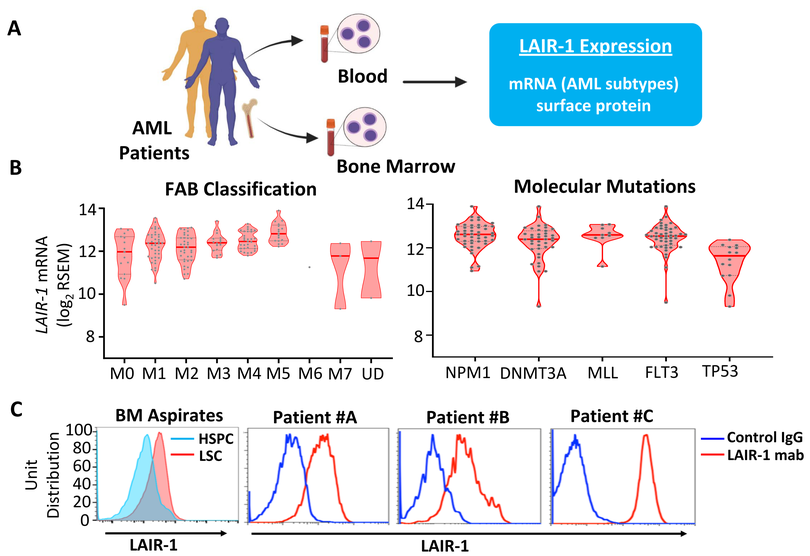

Figure 1. A) Schematic illustration of study design to determine LAIR-1 expression on AML blasts and leukemic stem cells. **B)** LAIR-1 mRNA expression in AML subtypes defined by FAB classification and mutation status. UD denotes undetermined. **C)** LAIR-1 protein expression on the cell surface of leukemic stem cells (LSCs; $CD34^{+}CD38^{-}CD90^{-}CD45RA^{+/-}$ or $CD34^{-}CD117^{+}CD244^{+/-}$) vs hematopoietic stem and progenitor cells (HSPCs; $CD34^{+}CD38^{-}CD90^{+}CD99^{-}$) derived from bone marrow aspirates, and leukemic blasts from the peripheral blood of AML patients.

NC525 Inhibits Colony Formation Of LSCs

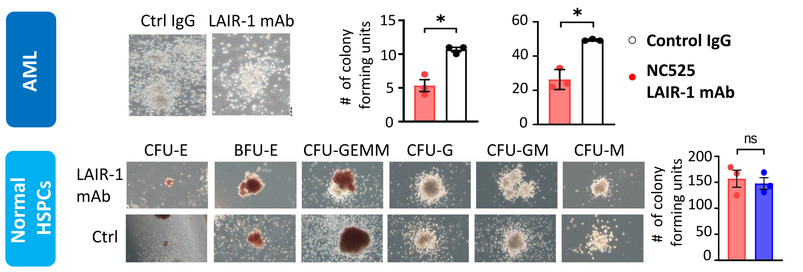

Figure 4. LAIR-1 mAb suppresses the colony-forming capacity of LSCs derived from two AML patients but not HSPCs from healthy donors, as measured by the Methocult™ assay (N = 3). * P < 0.05 by t-test.

Clustering Of LAIR-1 By NC525 Agonist Mab Kills Leukemic Blast Cells

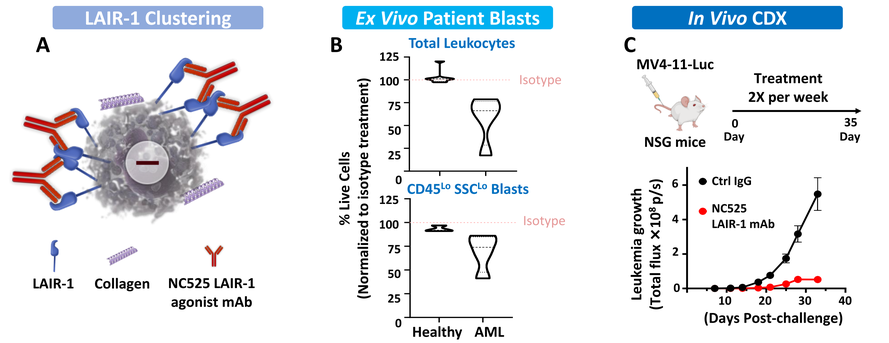

Figure 2. A) Schema of clustering of LAIR-1 by NC525 agonist mAb in the presence of collagen. **B)** NC525 kills leukemic blasts but not healthy cells in primary patient samples (N = 4 -7 donors). **C)** NC525 blocks AML cell proliferation in a cell-derived xenograft (CDX) model of AML (N = 10 mice). Error bars represent standard deviations.

NC525 Transduces Signals To AML Cells That Inhibit Key Survival Pathways

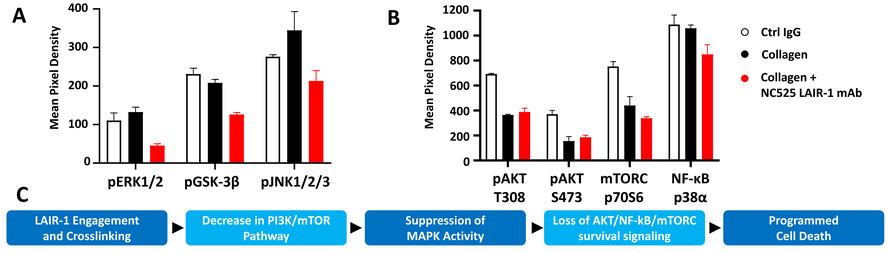

Figure 3. Phospho-array of NC525-treated AML patient PBMCs. **A)** MAPK signaling and **B)** cell survival regulator activity indicates that **C)** crosslinking of LAIR-1 on AML cells by NC525 agonist mAb and collagen suppresses PI3K/mTOR activity, leading to loss of MAPK-regulated survival functions from AKT and NF-kB that ultimately results in programmed cell death. Error bars represent the standard error of mean of duplicates

NC525 Restricts AML Growth And LSCs In PDX Models

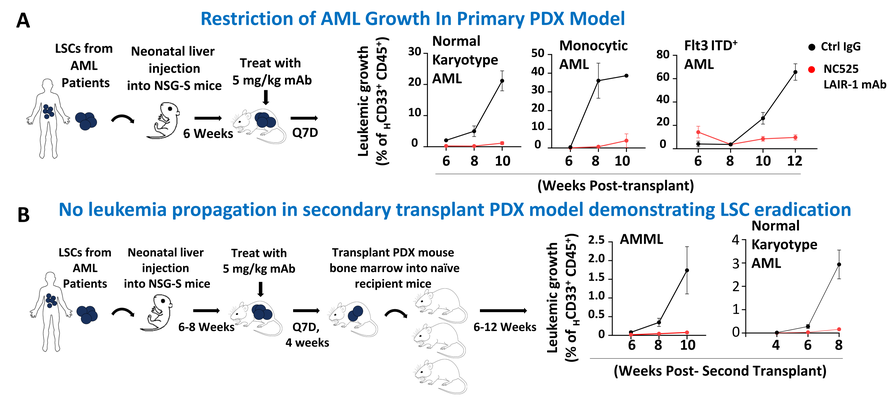

Figure 5. A) Leukemic cell growth in NSG-S mice engrafted with BM aspirate from AML patients (PDX) is inhibited by NC525. **B)** Naïve mice receiving secondary BM transplant from primary NC525 or control-treated PDX mice indicate that NC525 agonist mAb eradicates LSCs in the bone marrow (N = 3-5 mice). Error bars represent standard deviations.

NC525 Study Design, Endpoints and Biomarkers

Indications

Relapsed or Refractory

- Acute myeloid leukemia (<25,000 WBC)
- Myelodysplastic syndrome (MDS)
- Chronic myelomonocytic leukemia (CMML)

Dose & Regimen*

Dose Escalation

- Cohort 5 30mg/kg
- Cohort 4 20mg/kg
- Cohort 3 10mg/kg
- Cohort 2 4.5mg/kg
- Cohort 1 2mg/kg

Cycle Duration= 28 days

Q2W For Cycles 1-6; Q4W Cycle 7 onwards

Dose Expansion

- Cohort TBD
- Cohort TBD

*May change based on AE/DLT profiles.

Endpoints

Primary

- Safety, Tolerability, DLTs
- RP2D
- MAD, PAD, MTD

Secondary

- Efficacy
  - MLFS
  - CR
  - CRh
  - CRi
- Time-to-response
- PK/PD

Biomarkers

Bone Marrow

- Bone Marrow Blast Clearance (MLFS)
- LAIR-1 expression on Blasts in correlation with responses
- Effects on HSC and LSC

Peripheral Blood

- Blasts clearance and normal blood cell count recovery (CR, CRh, CRi)
- ADA
- Cytokines
- Chemokines
- Immunophenotyping

Key Inclusion Criteria

- ≥ 18 years of age on the day of signing informed consent.
- Myeloid Neoplasm determined by pathology review at the treating institution:
  - Relapsed or Refractory AML,
    - Note: Active, relapsed, or refractory AML is defined as any one of the following:
      - Primary induction failure, or (PIF) after 2 or more cycles of therapy,
      - First early relapse after a remission duration of fewer than 6 months,
      - Relapse refractory to salvage combination chemotherapy second or subsequent relapse, or
      - Relapsed or refractory AML with at least 5% blasts by bone marrow biopsy or aspirate, or at least 1% blasts in peripheral blood.
  - Relapsed or Refractory Myelodysplastic syndrome (MDS) after prior hypomethylating agents.
  - Relapsed or Refractory Chronic myelomonocytic leukemia (CMML) with progressive disease or lack of response to hypomethylating agents.

Key Exclusion Criteria

- Therapy-related AML, acute promyelocytic leukemia (M3, APL), accelerated phase or blast crisis of chronic myeloid leukemia.
- History or presence of clinically relevant CNS pathology such as epilepsy, childhood or adult seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.
- Active Central Nervous System (CNS) involvement (such as leukemic infiltration, blast in the spinal fluid, or subjects with extramedullary disease).
- Chronic respiratory disease or any other medical condition that requires continuous oxygen that, in the opinion of the Investigator, would adversely affect his/her participation in this study.
- Participating in or has participated in a study of an investigational agent or device within 4 weeks or 5 half-lives (whichever is longer) prior to the first dose of study treatment.
- Has previously had an allogeneic solid organ transplant.
- Autologous HSCT within 6 weeks or Allogeneic HSCT within 6 months
- Active acute or chronic graft-versus-host disease (GvHD), grade 2-4, requiring systemic treatment.
- Previous CAR-T therapy.