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

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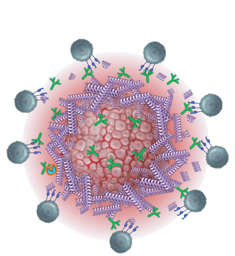
Background

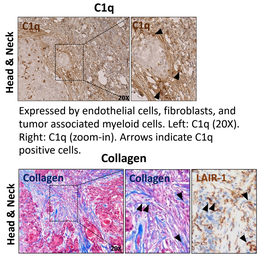
Collagen and C1q components of the extracellular matrix (ECM), are the predominant ligands for LAIR-1 (**L**eukocyte **A**ssociated **I**mmunoglobulin-like **R**eceptor), an inhibitory receptor expressed on the cell surface of several immune cell subsets. LAIR-1 binding to these ligands results in inhibition of immune activation and impairment of immune cell migration[1]. LAIR-2, a soluble homolog of LAIR-1, competes for binding to collagen and C1q and serves as a natural decoy to prevent immunosuppression and maintain homeostasis under normal conditions. However, dysregulation of the ECM and enhanced expression of both collagen and C1q within the tumor microenvironment (TME) results in immunosuppression and reduced access of immune cells to the tumor[2]. This plays a critical role in promoting tumor progression.

NC410, a fusion protein of LAIR-2 fused to human IgG1 Fc domain, was engineered to overcome this highly immunosuppressive environment by outcompeting LAIR-1 binding to its ligands, blocking LAIR-1 function, reversing immune suppression, and inducing ECM remodeling to promote immune cell infiltration within the TME[2].

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.

Chronic Inflammation Results in Overexpression of LAIR Ligands in the TME

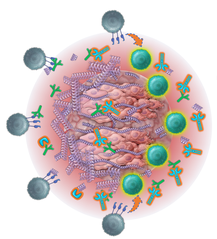


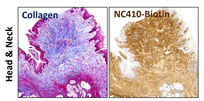


Expressed by endothelial cells, fibroblasts, and tumor associated myeloid cells. Left: C1q (20X). Right: C1q (zoom-in). Arrows indicate C1q positive cells.

Expressed by fibroblasts and tumor cells. Left: Trichrome/Collagen (20X). Middle: Trichrome/Collagen (zoom-in). Right: LAIR-1 (zoom-in). Arrows indicate areas of colocalization of Collagen and LAIR-1.

NC410 Remodels Extracellular Matrix (ECM) & Restores Immune Activity





Colocalization of Collagen and NC410-Biotin. Left: Trichrome/Collagen. Right: NC410-Biotin.

NC410 is a fusion protein of LAIR-2:

- Blocks collagen mediated suppression,
- Enhances collagen degradation (ECM remodeling),
- Mediates T cell infiltration and restores activation,
- Decreases tumor progression.

NC410 Study Schema & Demographics

Phase 1a: Dose Escalation

- Cohort 1: 3 mg; n=3
- Cohort 2: 6 mg; n=3
- Cohort 3: 15 mg; n=4
- Cohort 4: 30 mg; n=4
- Cohort 5: 60 mg; n=5
- Cohort 6: 100 mg
- Cohort 7: 200 mg
- Cohort 8: 400 mg

- 3+3 design
- Dosing every 2 weeks

Phase 1b: Dose Expansion

- Confirm PK and PD
- Biopsy analysis
- Determine RP2D

Phase 2

- Multiple advanced solid tumors: NSCLC, Head & Neck, Gastric, CRC and Cervical Cancers
- Tumor type subject to change
- Patient selection based on biomarkers

Demographic Information	Phase 1a (n=19)[1]
Age	
• Median (Range)	61 (35 - 80)
Gender, n (%)	
• Female	11 (58%)
• Male	8 (42%)
Prior systematic anti-cancer regimens	
• Median (Range)	4 (1 - 8)
• Prior immunotherapy, n (%)	6 (31%)
Diagnosis (n)	
• Pancreatic	6
• CRC	4
• Cervical	3
• Prostate	2
• Ovarian	2
• Head & Neck	1
• Endometrial	1

Key Inclusion Criteria

- Men and women aged 18 or older.
- ECOG performance status 0 to 1.
- Locally advanced or metastatic disease; locally advanced disease must not be amenable to resection with curative intent.
- Subjects who have disease progression after treatment with available therapies that are known to confer clinical benefit, or who are intolerant to treatment, or who refuse standard treatment. Note: There is no limit to the number of prior treatment regimens.
- Presence of measurable disease based on RECIST v1.1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

NC410 Is Safe And Well Tolerated With Early Signs Of Disease Control

- As of 13th September 2021, data up to Cohort 5 (n=19) are included in this interim report.
- NC410 is safe and well tolerated.
  - No DLTs were reported.
  - Two subjects total were reported with worsening Grade 3: lymphopenia (n=1); anemia (n=1).
  - No treatment related grade 4 adverse events were reported.
- No anti-drug antibody (ADA) was detected post NC410 dose up to 60 mg Q2W.
- Amongst the six stable disease (SD) subjects in this dose escalation study, five had time-on-study from 8 to 42 weeks, and one remains on study at 25 weeks. In addition, two other active subjects from the latest cohort remain on study at 5 weeks.
- Safety, tolerability, efficacy and biomarker analyses with higher dose cohorts are ongoing.

References

1. Vijver et al., *Front. Immunol*. (2021).
2. Ramos et al., *elife* (2021).
3. Nordkamp et al., *Arthritis Rheum.* (2011).

Transient Reduction Of Soluble C1q In Peripheral Blood: Evidence Of Target Binding Of NC410 To Key Ligand

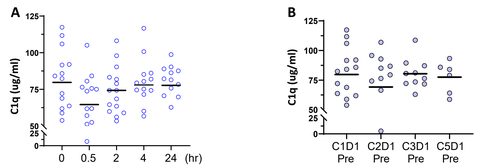


Figure 1. Longitudinal changes of soluble C1q levels over time. (A) C1q levels in subjects' peripheral blood before and after dosing in cycle 1. Timepoints include pre-dosing and 0.5/2/4 and 24 hours post infusion. (B) C1q levels in subjects' peripheral blood before dosing of each cycle. C1D1: cycle 1 day 1; C2D1: cycle 2 day 1; C3D1: cycle 3 day 1; C5D1: cycle 5 day 1. Pre: pre-dosing.

- Since NC410 binds to C1q and collagen, the soluble C1q levels reduces shortly after the completion of NC410 infusion- an early peripheral PD marker for NC410 targeted binding.
  - C1q levels returns to base line after 24 hours.
- There is no reduction in the baseline C1q levels with subsequent dosing of NC410- no safety concern regarding complement activity in circulation.

Total LAIR-2 Levels In Peripheral Blood Increase In A Dose-dependent Fashion Post NC410 Dosing

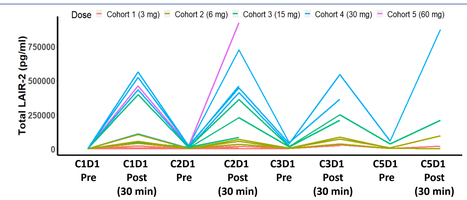


Figure 2. Longitudinal changes of total LAIR-2 levels in subjects' peripheral blood before and after dosing of each cycle. Pre: pre-dosing. Post: post-infusion (at the end of 30-minute-infusion).

- Total detectable LAIR-2 increases in a dose-dependent fashion after NC410 dosing.
  - The current assay is unable to discern between endogenous LAIR-2 and NC410.

Total LAIR-2 And Soluble LAIR-1 In Peripheral Blood Over Time

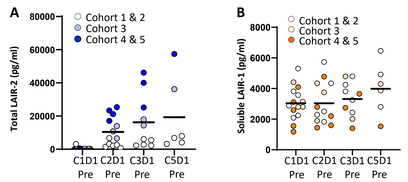


Figure 3. Longitudinal changes of baseline levels of total LAIR-2 and soluble LAIR-1 over time. (A) Total LAIR-2 levels in subjects' peripheral blood before dosing of each cycle. (B) Soluble LAIR-1 levels in subjects' peripheral blood before dosing of each cycle.

- LAIR-2 levels remain elevated before each dose of NC410 (cycle 2 and onwards) and show a dose dependent increase.
  - This is a notable finding since LAIR-2 plays a role in modulating LAIR-1 mediated inhibition.
  - Efforts are ongoing to confirm that elevated levels of total LAIR-2 are due to endogenous LAIR-2 production vs. accumulated levels of NC410.
- In contrast, soluble LAIR-1 does not change overtime.

Early Evidence Of Extracellular Matrix (ECM) Remodeling

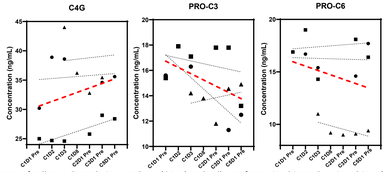


Figure 4. Longitudinal changes of collagen degradation products (CDPs) and collagen formation biomarkers in subjects' peripheral blood over time. Three subjects with stable disease ≥ 16 weeks were shown. Each shape represents CDPs from one subject over time. Black dotted lines represent linear regressions of CDPs from each subject. Red dotted lines represent linear regressions of CDPs from all subjects. Not all timepoints are available from every subject.

- Increasing levels of Granzyme-B mediated CDP of type IV collagen (C4G),
- Decreasing levels of biomarkers for type III collagen formation (PRO-C3) and type VI collagen formation (PRO-C6).

Early Evidence Of Immune Activation In A Patient With Stable Disease

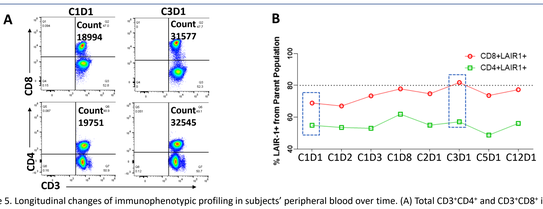


Figure 5. Longitudinal changes of immunophenotypic profiling in subjects' peripheral blood over time. (A) Total CD3+CD4+ and CD3+CD8+ in one subject with stable disease at C1D1 and C3D1. (B) CD8+LAIR-1+ (% of total CD8+ cells) and CD4+LAIR-1+ (% of total CD4+ cells) in one subject with stable disease over time.

- Time-dependent increases were observed in total CD4+ and CD8+ T cells.
- No increase was observed in CD4+ cells expressing LAIR-1, and a minimal increase was observed in CD8+ cells expressing LAIR-1.

Discussion

- NC410, in subjects with advanced or metastatic solid tumors, is safe and well tolerated with no DLTs up to cohort 5.
  - Safety, tolerability, efficacy and biomarker analyses are on-going.
- Hypothesis- NC410, by binding to C1q and collagen, modulates and restores immune function: increase in T cells, remodeling of ECM, and enhanced infiltration of T cells.
  - Transient reduction of C1q in peripheral blood after NC410 infusion (evidence of targeted binding) with no reduction in baseline C1q level with subsequent dosing.
    - Alleviated safety concern regarding complement activity in circulation.
  - LAIR-2 levels remain elevated before each dose of NC410 (cycle 2 and onwards) and shows a dose-dependent increase.
  - In contrast, soluble LAIR-1, that has been shown to function as a receptor antagonist in autoimmunity[3], does not change significantly overtime.
  - CDPs showed early evidence of ECM remodeling- trends in increase in C4G, decrease in PRO-C3 and PRO-C6.
  - Immunophenotyping shows time-dependent increases in CD4+ and CD8+ T cells, no increase in CD4+ cells expressing LAIR-1, and a minimal increase in CD8+ cells expressing LAIR-1.
- LAIR-2, soluble LAIR-1, C1q, CDPs and peripheral immune cells will continue to be monitored as important peripheral blood biomarkers for NC410 activity.