NC410 in Combination with Pembrolizumab Improves Anti-Tumor Responses by Promoting Collagen Remodeling and Tumor Immunity in Advanced ICI Naïve MSS/MSI-L Colorectal Cancer (CRC)

Alina Barbu[1], Priyanka Kothari[1], Shannon Kahan[1], Eric S. Christenson[2], Syed Mohammad Ali Kazmi[3], Sudhir Manda[4], Michael Chisamore[5] , Stephanie Kordahi[1] , Ashley Martz[1], Megan Zika[1], Aaron Morawski[1], Dallas B. Flies[1], Sol Langermann[1], Udayan Guha[1], Han Myint[1]

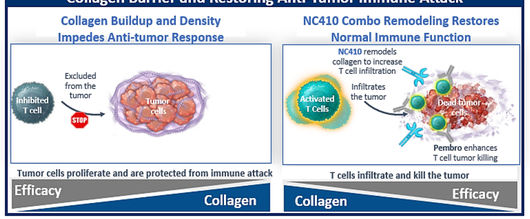
[1]NextCure Inc., [2]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, [3]UT Southwestern Medical Center, [4]Arizona Oncology, [5]Merck & Co., Inc., Rahway, NJ, USA

Abstract#: 632

BACKGROUND

NC410, a novel therapeutic agent consisting of a dimeric LAIR-2 protein fused to a human IgG1 Fc domain, targets and remodels collagen, enhancing immune cell infiltration and blocks LAIR-1-mediated suppression by preventing binding to its ligand, collagen. In preclinical studies, NC410 combined with anti-PD-1/PD-L1 therapies demonstrated enhanced immune cell infiltration into the TME, increased immune function and improved antitumor activity.

NC410 and Pembrolizumab Combo: An Additive Approach to Breaking the Collagen Barrier and Restoring Anti-Tumor Immune Attack



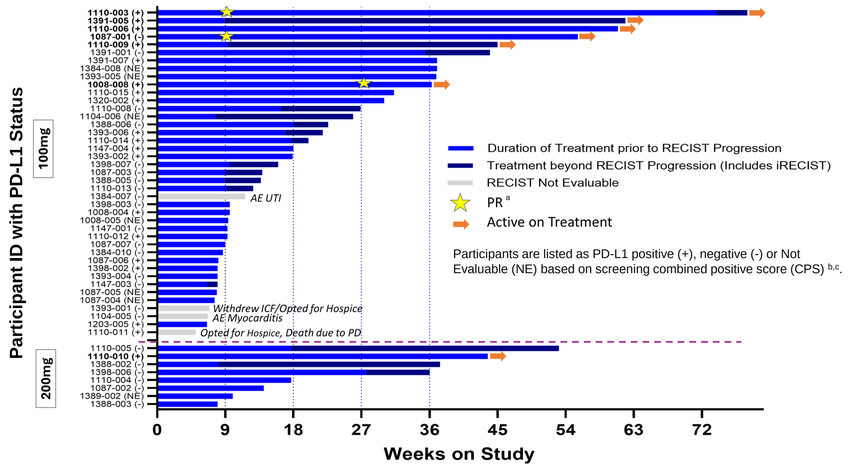
METHOD

A Phase 1b study of NC410 plus pembrolizumab in advanced solid tumors was conducted (NCT05572684). MSS/MSI-L CRC patients (n=70) received pembrolizumab (400mg Q6W) on Day 1 and escalating doses of NC410 at 30 (n=3), 60 (n=9), 100 (n=48), and 200mg (n=10) Q2W on Days 1, 15, and 29 of a 42-day cycle following a modified Toxicity Probability Interval (mTPI) design. On treatment biopsies were collected at Week 8. The data cut off was 14-Oct-2024.

DEMOGRAPHICS

Baseline Characteristic	All CRC Subjects (n = 70)	ICI-Naïve CRC LM-100mg (n=40)	ICI-Naïve CRC LM-200mg (n=8)
Age, years			
Median (range)	56 (32 – 80)	58.5 (45 – 80)	56 (43 – 77)
Sex, n (%)			
Female	28 (40)	16 (40)	4 (50)
Male	42 (60)	24 (60)	4 (50)
ECOG performance status, n (%)			
0	31 (44.3)	16 (40)	7 (87.5)
1	39 (55.7)	24 (60)	1 (12.5)
Prior systemic anti-cancer regimens			
Median (range)	4 (1 – 19)	3 (1 – 19)	3 (1 – 10)
Prior Immun., n (%)	6 (8.5)	0 (0)	0 (0)

RESULTS



Participants are listed as PD-L1 positive (+), negative (-) or Not Evaluable (NE) based on screening combined positive score (CPS) [b,c].

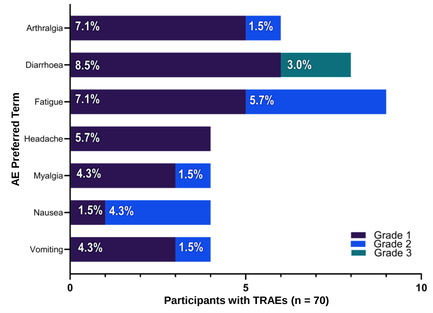
[a]All PRs have been confirmed except participant 1008-008; [b]PD-L1 evaluated in Central Laboratory using 22C3 assay; [c]CPS ≥1: PD-L1 positive (+), CPS < 1: PD-L1 negative (-)

RESPONSE AND DISEASE CONTROL

	100mg NC410	200mg NC410
ORR	8.3%(3/36) [CI: 1.8, 22.5]	0% (0/7) [CI: 0.0, 41.0]
DCR	47% (17/36) [CI: 30.4,64.5]	86% (6/7) [CI: 42.1,99.6]
mDC Duration	8.5 mo. [Range: 3.2,17.6]	8.43 mo. [Range: 3.3,12.9]
mDOR	15.2 mo. [Range: 9.1,17.6]	N/A

CI: Confidence Interval; DCR: Disease Control Rate; mDC: Median Disease Control (PR + SD) per RECIST and iRECIST; mDOR: Median Duration of Response; ORR: Objective Response Rate; PR: Partial Response; SD: Stable Disease

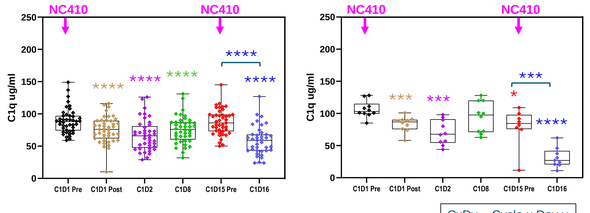
TREATMENT RELATED ADVERSE EVENTS (TRAE) ≥ 5%



TUMOR AND PERIPHRAL BIOMARKERS

Transient Reduction in Serum C1q Confirm NC410 Target Engagement

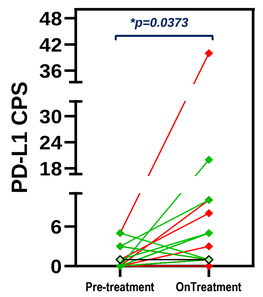
Pembro+100mg NC410 (N=44) | **Pembro+200mg NC410 (N=10)**



- LAIR2 and NC410 bind C1q
- Post-dosing decrease in serum C1q following administration of 100mg and 200mg NC410. Levels recover prior to subsequent dosing
- Further decrease noted following second NC410 administration (C1D16)
- Greatest C1q decrease noted within 24 hours of NC410 administration (C1D2 and C1D16)

TUMOR AND PERIPHRAL BIOMARKERS

On Treatment Modulation of Tumor PD-L1 And Mature Collagen



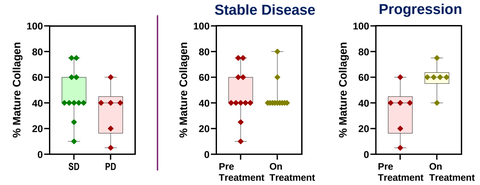
Significant increase in PD-L1 expression upon NC410+Pembro therapy

Paired pre and on-treatment biopsies, N=19

CPS: Combined Positive Score
Parametric statistics: paired t test

SD, N=8 PD, N=10
Black outline/green diamond designates CRC PR

BASELINE | **PRE and ON-TREATMENT**

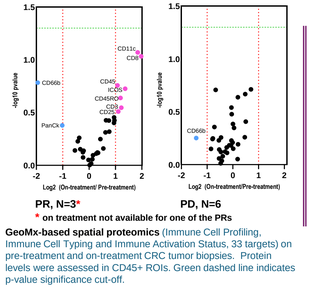


Mature collagen was identified with Masson's Trichrome staining in paired baseline/on treatment tumor tissues from 17 CRC patients. **SD:** stable disease (N=11); **PD:** progressive disease (N=6). Statistics: Paired/unpaired t test.

Stable Disease, N=11:
- Higher levels of mature collagen percentage at baseline than progressive disease (Median: 45.9)
- No change in mature collagen percentage while on treatment

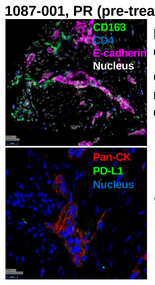
Progression, N=6:
- Lower levels of mature collagen percentage at baseline (Median: 34.1)
- On treatment significant increase in mature collagen

NC410+Pembro Therapy Promotes Immune Infiltration in Tumors with Partial Response



GeoMx-based spatial proteomics (Immune Cell Profiling, Immune Cell Typing and Immune Activation Status, 33 targets) on pre-treatment and on-treatment CRC tumor biopsies. Protein levels were assessed in CD45+ ROIs. Green dashed line indicates p-value significance cut-off.

1087-001, PR (pre-treatment) – Abdominal wall tumor

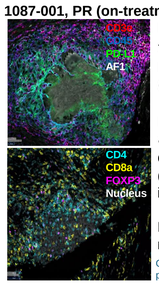


Epithelial islands show high E-cadherin+ expression (magenta)

Clusters of phagocytic macrophages (CD4+/CD163+, cyan) near epithelial tumor cells

Punctate PD-L1 staining (green) on tumor cells (red)

1087-001, PR (on-treatment) – Metastatic lymph node



PD-L1+ (green) around necrotic tumor tissue (white)

Bordering T-cells express low PD-L1 (magenta)

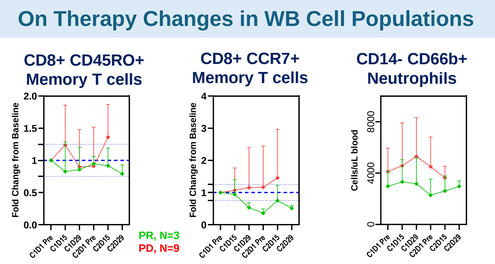
PD-L1+ immune cells (cyan) surround and infiltrate the necrotic tissue

CD4+ (cyan) helper and CD8a+ (yellow) cytotoxic T-cells surround and infiltrate follicular structure

FOXP3+ (magenta) CD4+ regulatory T-cells

ORION multiplex immunofluorescence imaging with 18 plex panel in one round staining (20x)

On Therapy Changes in WB Cell Populations



PR, N=3
PD, N=9

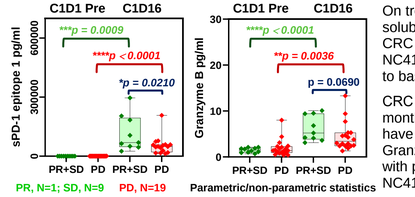
Partial Remission shows on-treatment reduction trend of circulating memory CD8+ T cells with anti-tumor and homing potential, together with a trend in low baseline and on treatment neutrophil count. May indicate T cell localization to the tumor.

Progressive disease shows limited on-treatment changes in memory blood T cells, together with a trend in higher baseline and early on-treatment increase in neutrophils

Tumor and Peripheral Biomarker Key Take Away

NC410 plus pembrolizumab combination therapy remodels tumor microenvironment, promotes T cell infiltration, and anti-tumor immunity.

On Therapy Increase in Serum PD-1 and Granzyme B



On treatment increase in serum soluble PD-1 and Granzyme B in CRC subjects upon NC410+Pembro therapy compared to baseline

CRC subjects with long term (≥6 months) disease control (PR+SD) have higher soluble PD-1 and Granzyme B compared to subjects with progressive disease upon NC410+Pembro therapy

CONCLUSION

NC410 plus pembrolizumab combination therapy is a well-tolerated treatment option with clinical benefit in hard-to-treat metastatic CRC that merits further evaluation and testing in a randomized study.

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Sponsor Representative: Udayan Guha, MD., Ph.D., Senior VP, Clinical and Translational Development (guhau@nextcure.com).
Presenting author is employee of NextCure Inc.