A Phase 1b Study of NC410 in Combination with Pembrolizumab in Immune Checkpoint Inhibitor (ICI) Naïve, and Refractory Microsatellite Stable (MSS)/Microsatellite Instability-Low (MSI-L) Colorectal Cancer (CRC) and Ovarian Cancer

NextCure

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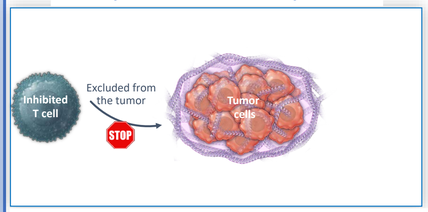
Background

- Treatment options for advanced, refractory MSS/MSI-L CRC and Ovarian cancer are limited, with no FDA-approved ICI therapies.
- Such tumors have higher collagen deposition resulting in inherent resistance to ICI therapy, partly due to the tumor extracellular matrix (ECM) functioning as a physical barrier to immune cell infiltration.
- Dysregulated collagen in ECM inhibits immune cell function through binding to the inhibitory receptor, Leukocyte Associated Immunoglobulin-Like Receptor-1 (LAIR-1) expressed on immune cells.
- NC410 is a dimeric LAIR-2 protein fused to a human IgG1 Fc domain. NC410 promotes anti-tumor activity through binding to collagen, leading to ECM remodeling, enhanced immune cell infiltration and reversal of LAIR-1 mediated immunosuppression.

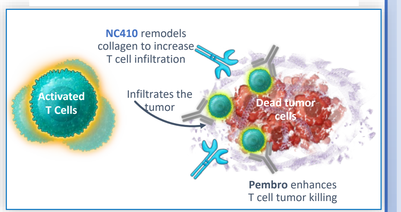
NC410 and Pembrolizumab Combo: An Additive Approach to Breaking the Collagen Barrier and Restoring Anti-Tumor Immune Attack

Collagen Buildup and Density Impedes Anti-tumor Response



Tumor cells proliferate and are protected from immune attack

NC410 Combo Remodeling Restores Normal Immune Function



T cells infiltrate and kill the tumor

Methods

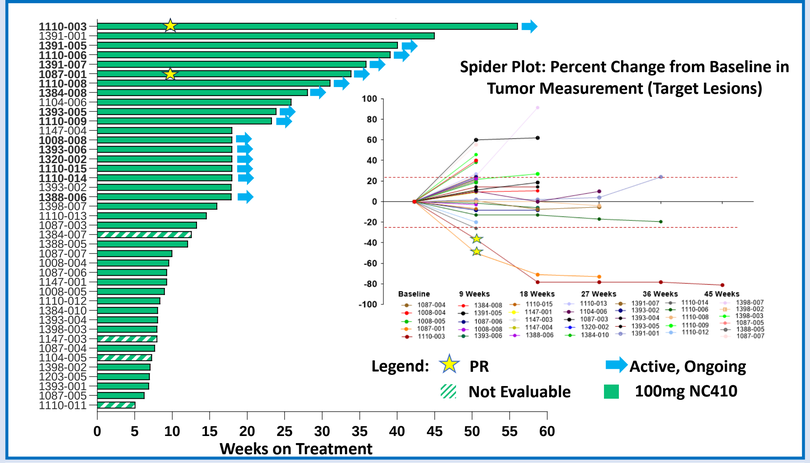
An open-label, single-arm Phase 1b/2 study was initiated to determine the safety, tolerability, and RP2D of NC410 when combined with pembrolizumab in advanced metastatic solid tumors (NCT05572684). Participants (Table 1) received a fixed dose of pembrolizumab (400mg Q6W) on Day 1 and escalating doses of 30mg, 60mg, 100mg, and 200mg of NC410 Q2W on Days 1, 15, and 29 of each 42-day cycle following a modified Toxicity Probability Interval (mTPI) design.

Table 1: Patient Demographics

Baseline Characteristic	All Subjects (n = 81)	ICI-Naïve CRC LM- 100mg (n=41)[a]	ICI-Naïve Ovarian 100mg/200mg (n=7)[a]
Age, years			
Median (range)	60 (32 – 80)	60 (45 – 80)	69 (62-80)
Sex, n (%)			
Female	39 (48.1)	16 (39)	7 (100)
Male	42 (51.9)	25 (61)	N/A
ECOG performance status, n (%)			
0	39 (48.1)	17 (41.5)	6 (85.7)
1	42 (51.9)	24 (58.5)	1 (14.3)
Prior systemic anti-cancer regimens			
Median (range)	4 (1 – 12)[b]	4 (1 – 10)[c]	5 (1 – 12)
Prior Immunotherapy, n (%)	9 (12)[b]	0 (0)[c]	1 (14.3)

[a] CRC & Ovarian Disease of Interest; [b] n=75 due to missing prior systemic anticancer documentation missing for 6 subjects; [c] n=39 due to missing prior systemic anticancer documentation missing for two subjects

Swimmer Plot for Treatment Duration of ICI Naïve CRC (LM-)



Results of ICI Naïve, MSS CRC (LM-), 100mg NC410 + pembro

ORR: 5.4% (2/37) [CI: 0.7, 18.2]

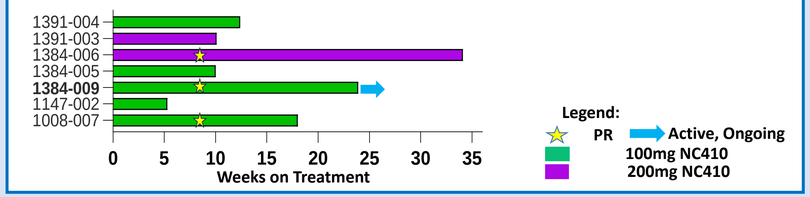
Median Duration of Disease Control: 5.5mo.

DCR: 51.3% (19/37) [CI: 34.4, 68.1]

2 PR Duration of Response 7.4+, 12.5+ mo.

CI: Confidence Interval; DCR: Disease Control Rate; DOR: Duration of Response; LM: Liver Metastasis; mPFS: Median Progression-Free Survival; ORR: Objective Response Rate; PR: Partial Response; Median Duration of Disease Control (PR + SD) per RECIST and iRECIST

Swimmer Plot for Treatment Duration of ICI Naïve Ovarian (LM+/LM-)



Interim Results of ICI Naïve MSS Ovarian (LM+/LM-), 100mg & 200mg NC410 + pembro

ORR: 43% (3/7)

DCR: 43% (3/7)

3 PR DOR: 7.9, 5.1+, 4.1 mo.

Note: 20 additional participants enrolled; Full data set to be presented at future scientific conference.

Most Frequent Treatment-Related Adverse Events

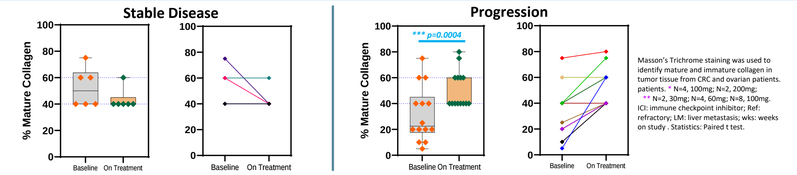
- Most Common Adverse Events (AE), Any Grade: diarrhea (15.4%), fatigue (11.1%), nausea (7.4%), arthralgia (6.2%), chills (6.2%), headache (5.1%), and myalgia (5.1%)
- Treatment Emergent Gr ≥ 3 AEs: 39.5%; Treatment Related Gr ≥ 3 AEs: 4.9%
- One patient discontinued study treatment due to Gr 3 myocarditis (presumed to be an irAE).

This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Table 2: Summary of PR Patients (n=5)

	ICI Naïve, MSS, LM- CRC		ICI Naïve, MSS HGSOC		
Patients' ID	**1110-003**	**1087-001**	**1384-006**	**1384-009**	**1008-007**
Number of Prior Treatment(s)	5 prior lines	5 prior lines including Lonsurf, Bevacizumab, Regorafenib	1 prior line including PARPi	1 prior line including PARPi	12 lines including Elahere; Platinum resistant
NC410 Dose	100mg	100mg	200mg	100mg	100mg
Liver Mets	No	No	No	Yes	Yes
Baseline Target Lesions (TL)	3.7 cm	5.2 cm	2.7 cm	3.3 cm Liver	5.8 cm
Percent Reduction of TL at First 9-Week Scan	-59%	-50%	-44%	-51%	-40%
Confirmed PR with Percent Reduction in TL at 18-Week Scan	-78% (maintained at 27-wk scan)	-71%	No further reduction at 18 & 27-weeks	-54%	-48%* (Patient came off due to non-target progression)

Modulation of Tumor Mature Collagen in Disease Control and Progression



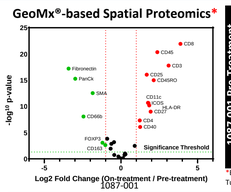
Masson's Trichrome staining was used to identify mature and immature collagen in tumor tissue from CRC and ovarian patients. patients. * N=4, 100mg; N=2, 200mg; ** N=2, 30mg; N=4, 60mg; N=8, 100mg. ICI: immune checkpoint inhibitor; Ref: refractory; LM: liver metastasis; wks: weeks on study . Statistics: Paired t test.

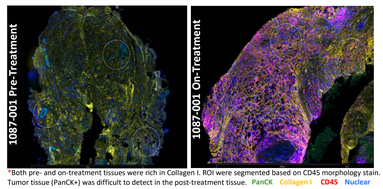
Stable Disease*, N=6:
- **Relatively high levels of mature collagen at baseline (Median: 50.00)**
- **On treatment decrease or no change in mature collagen**

Progression, N=14:**
- **Low levels of mature collagen at baseline (Median: 22.50)**
- **On treatment significant increase in mature collagen in both PDs and iUPDs**

Preliminary Tissue and Peripheral Biomarkers

GeoMx®-based Spatial Proteomics*





*Both pre- and on-treatment tissues were rich in Collagen I. ROI were segmented based on CD45 morphology stain. Tumor tissue (PanCK+) was difficult to detect in the post-treatment tissue. PanCK Collagen I CD45 Nuclear

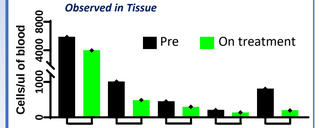
Tissue

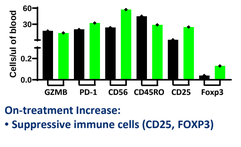
On-treatment Increase:
- **T cells (CD3,CD4, CD8, HLA-DR, CD27)**
- **Memory T cells (CD45RO)**

On-treatment Decrease:
- **Fibrosis (SMA, Fibronectin)**
- **Suppressive immune cells (CD66b, FOXP3, CD163)**

1087-001 Whole Blood Immunophenotyping**

Opposite Post-Treatment Changes in Peripheral Immune Populations Compared To Those Observed in Tissue



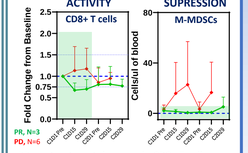


On-treatment Increase:
- **Suppressive immune cells (CD25, FOXP3)**

On-treatment Decrease:
- **T cells (CD3, CD4,CD-8 HLA-DR)**

**Post immunophenotyping timepoint presented is C2D15, the closest to the tissue collection time.

Ovarian WB Immunophenotyping#



PR: on-treatment decrease in CD8+ T cells
PD: on-treatment increase in suppressive populations (# selected populations shown)

Conclusion

- Patients who achieve clinical benefit (confirmed PR and SD on 2nd scan at wk 18) have a median duration of disease control of 5.5 months which is meaningful for this patient population.
- The effect of combination treatment is observed through a decrease in fibrotic tissue, an increase in T cell activation (pembro & NC410) and reduction in suppressive immune cells (NC410) in the TME.
- NC410 in combination with pembrolizumab shows promising clinical activity in hard-to-treat advanced, metastatic CRC and Ovarian cancer and merits further validation studies.