Results of the Phase 1b Study of NC410 Combined with Pembrolizumab in MSS/MSI-L Colorectal Cancer Patients

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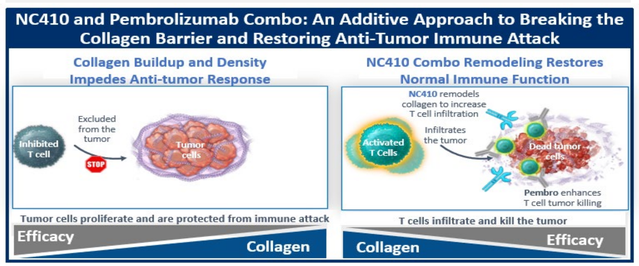
BACKGROUND

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.



METHOD

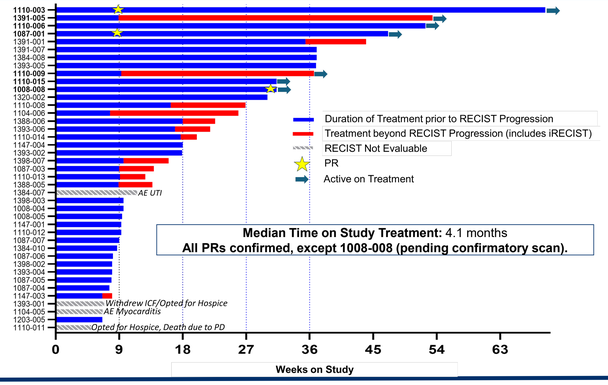
A Phase 1b study of NC410 plus pembrolizumab in advanced solid tumors was conducted (NCT05572684). MSS/MSI-L CRC patients (n=70) received pembrolizumab (400mg Q6W) on Day 1 and escalating doses of NC410 at 30 (n=3), 60 (n=9), 100 (n=48), and 200mg (n=10) Q2W on Days 1, 15, and 29 of a 42-day cycle following a modified Toxicity Probability Interval (mTPI) design. The data cut off was 21-Aug-2024.

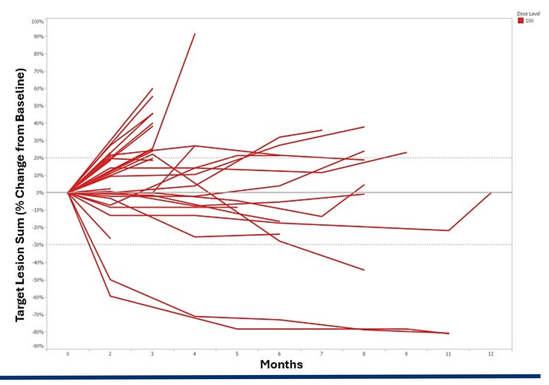
DEMOGRAPHICS

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)

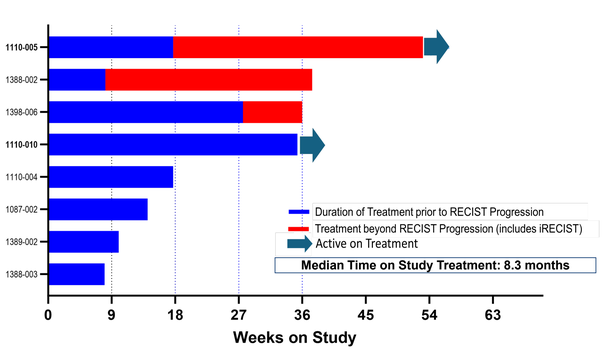
RESULTS: ICI Naïve MSS CRC (LM-), 100mg & 200mg NC410 + pembro

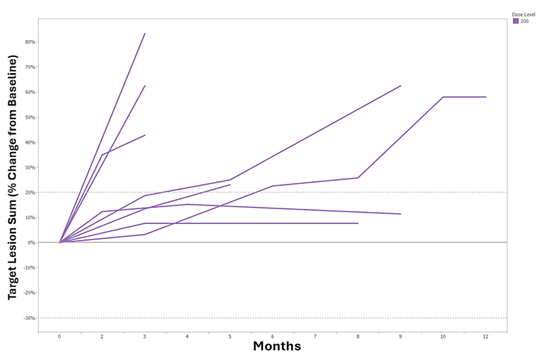
100mg SWIMMER & SPIDER PLOTS



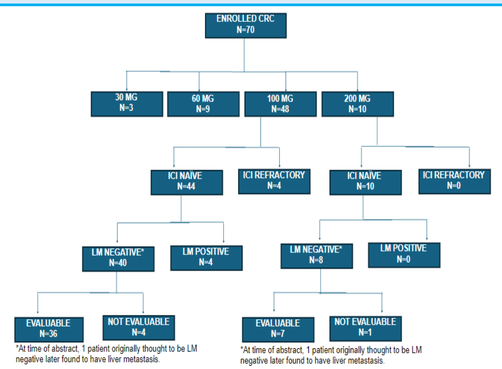


200mg SWIMMER & SPIDER PLOTS





SUBJECT DISPOSITION FLOW CHART



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	8.3 mo. [Range: 3.2,16.1]	8.3 mo. [Range: 3.3,12.4]
mDOR	13.6 mo. [Range:7.4,16.1]	N/A

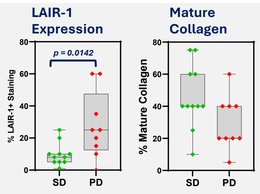
CI: Confidence Interval; DCR: Disease Control Rate; mDC: Median Disease Control (PR + SD) per RECIST and iRECIST; mDOR: Median Duration of Response; ORR: Objective Response Rate; PR: Partial Response; SD: Stable Disease

ADVERSE EVENTS (CRC)

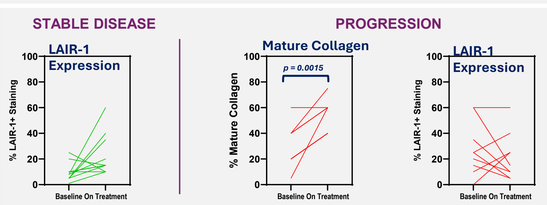
The combination therapy is safe and tolerable with Gr≥3 treatment emergent (42.8%) and related (5.7%) adverse events (AEs). The most common treatment related adverse events (AEs), any Grade: fatigue (12.9%), diarrhea (11.4%), arthralgia (8.6%), myalgia (5.7%), nausea (5.7%), and headache (5.7%). One subject discontinued study treatment due to Gr 3 myocarditis (presumed to be an irAE).

BIOMARKERS

Modulation of Tumor LAIR-1 And Mature Collagen in Disease Control and Progression



At baseline, CRC subjects with disease control on Pembro+NC410 therapy show lower levels of LAIR-1 *(*p=0.0142)* and a trend towards higher mature collagen (p=0.0642) than progressive disease.



- CRC subjects with disease control on Pembro+NC410 therapy show on treatment increase in tumor LAIR-1 expression (p=0.0564).
- CRC subjects that progress on Pembro+NC410 therapy show on treatment increase in tumor mature collagen *(**p=0.0015)* and a trend for further drop in LAIR-1 expression.

LAIR-1 was identified with immunohistochemistry, mature/immature collagen was identified with Masson's Trichrome staining in paired baseline/on treatment tumor tissues from 20 CRC patients: N=2, 30mg; N=3, 60mg; N=13, 100mg; N=2, 200mg; **SD:** stable disease (N=11); **PD:** progressive disease (N=9). Statistics: Paired/unpaired t test.

CONCLUSION

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

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Presenting author does not have any conflicts of interest to declare.