Results of the Phase 1b Study of NC410 Combined with Pembrolizumab in Ovarian Cancer Patients

FPN: 758P

Emese Zsiros[1], Eric S. Christenson[2], Davendra Sohal[3], Sudhir Manda[4], Siqing Fu[5], Ashley Martz[6], Megan Zika[6], Stephanie Kordahi[6], Priyanka Kothari[6], Shannon Kahan[6], Alina Barbu[6], Aaron Morawski[6], Dallas B. Flies[6], Sol Langermann[6], Michael Chisamore[7], Udayan Guha[6], Han Myint[6], Daruka Mahadevan[8]

[1] Roswell Park, [2]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, [3]University of Cincinnati, [4]Arizona Oncology, [5]MD Anderson,, [6]NextCure, [7]Merck & Co., Inc., Rahway, NJ, USA,, [8]UT San Antonio

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

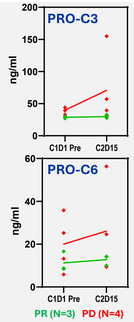
An open-label, Phase 1b study of NC410 in combination with pembrolizumab. Patients with MSS/MSI-L ovarian cancer (n=27) received a fixed pembrolizumab dose of 400 mg every 6 weeks on Day 1, along with escalating doses of NC410: 60 mg for 2 patients, 100 mg for 17 patients, and 200 mg for 8 patients, administered every 2 weeks on Days 1, 15, and 29 of a 42-day cycle. The dosing followed a modified Toxicity Probability Interval (mTPI) design. The data cut off was 20-Aug-2024.

ADVERSE EVENTS (Ovarian)

The therapy was safe and tolerable with manageable Gr≥3 treatment emergent (26%) and related (11.1%) adverse events. The most common treatment related adverse events (AEs), any Grade: arthralgia (18.5%), diarrhea (14.8%), myalgia (11.1%), nausea (11.1%), and infusion related reactions (11.1%). Three subjects reported irAEs of itchy scalp (Gr1), arthralgia (Gr 2), limb discomfort (Gr 2) and diarrhea (Gr 2). One irAE of platelet count decrease (Gr 4) resulted in treatment discontinuation.

BIOMARKERS

Lower Baseline Pro-Tumorigenic Collagen Fragments And No On Treatment Increase in Ovarian Subjects with Partial Response



Increase in peripheral PRO-C3 & PRO-C6 CDP readouts associate with tumor progression in CRC[ref].

PRO-C3 (fragment of N-terminal type III collagen).
Function: fibrogenesis, ECM formation.
PRO-C6 (fragment of C-terminal type Vla3 collagen-Endothropin).
Function: pro-fibrotic signaling, ECM formation.

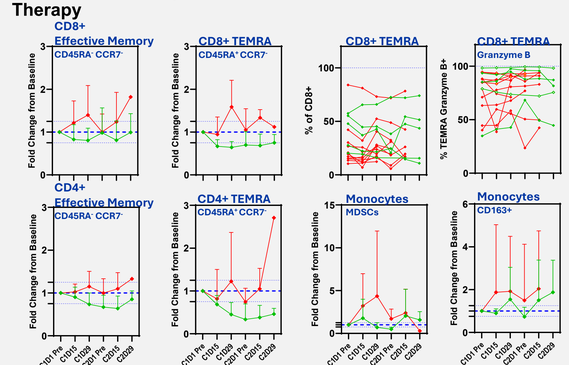
Pre-treatment: lower levels for both PRO-C3 and PRO-C6 in PRs; higher levels in subjects with PD.

On-treatment: no dynamic post-dosing changes in both PRO-C3 and PRO-C6 in PRs, in contrast to the increase observed in subjects with PD.

PRO-C3 and PROC6 were assayed in serum from 9 ovarian subjects by Nordic Bioscience, Herlev, Denmark.

[ref] Nissen NI et al., Sci Rep. 2021 Jan 13;11(1):865. Prognostic value of blood-based fibrosis biomarkers in patients with metastatic colorectal cancer receiving chemotherapy and bevacizumab.

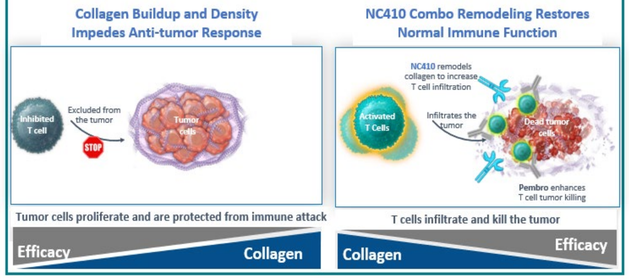
Early Reduction in Peripheral Terminally Differentiated Cytotoxic CD8+/CD4+ T cells and Sustained Low Myeloid Suppressive Populations in Subjects with Partial Response to Pembro+NC410 Therapy



Partial response shows post-treatment *early reduction* of peripheral active T cells (effector memory and TEMRA) consistent with previous data showing T cells migration to the tumor (ASCO 2024 Abstract ID #2538) and higher baseline and on treatment CD8+ TEMRA expressing Granzyme B were observed, together with low baseline and post-treatment myeloid suppressive signals.
Progressive disease shows on-treatment *increase* of active and memory blood T cells retained in the periphery, together with robust increase in myeloid suppressive cells.

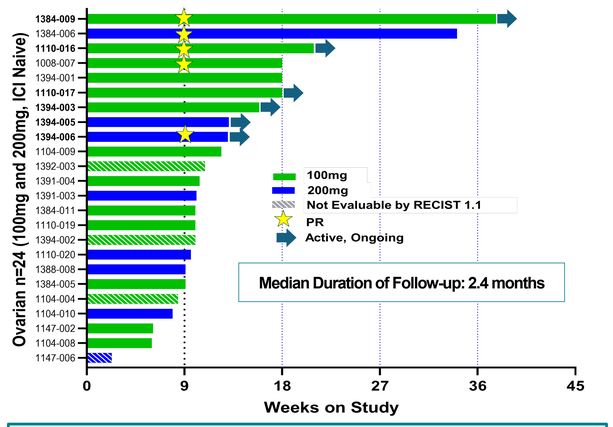
PR (N=5) PD (N=11)

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

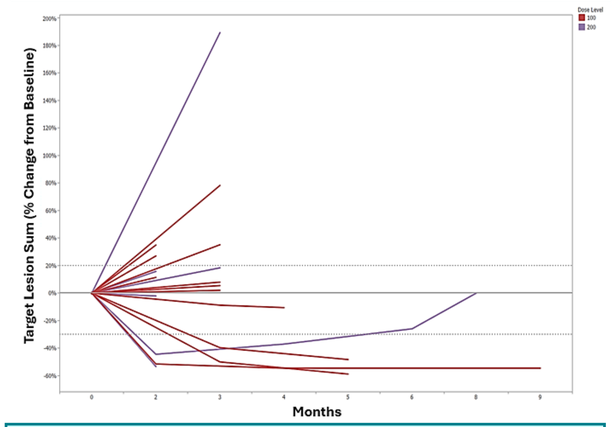


RESULTS: ICI Naïve MSS Ovarian (LM+/LM-), 100mg & 200mg NC410 + pembro

SWIMMER PLOT



SPIDER PLOT



SUMMARY OF PR PATIENTS

	ICI Naïve, MSS HGSOC				
Patient ID	**1384-009**	**1008-007**	**1110-016**	**1384-006**	**1394-006**
Number of Prior Treatment(s)	1, incl. PARPi	12, incl. Elahere; Platinum resistant	4; Platinum resistant	1, incl. PARPi	2; Platinum resistant
NC410 Dose	100mg	100mg	100mg	200mg	200mg
Liver Mets	Yes	Yes	No	No	No
Baseline Target Lesions (TL)	3.3 cm (liver)	5.8 cm	3.4 cm	2.7 cm	1.5cm
TL % Baseline at 9-wk	-51%	-40%	-50%	-44%	-47%
TL % Baseline at 18-wk	-54%	-48%*	-59%	-44%	Pending 18-wk scan*

***All PRs confirmed at Wk 18 except for 1008-007 (continued shrinkage of TL but NTL PD) and 1394-006 (pending 18wk scan).** HGSOC: High Grade Serous Ovarian Cancer; ICI: Immune Checkpoint Inhibitor; MSS: Microsatellite Stable; PD: Progressive Disease; NTL: Non-Target Lesion; TL: Target Lesion; NE: Not Evaluable;

RESPONSE AND DISEASE CONTROL

ORR	• 25% (5/20) [CI: 8.7,49.1]
DCR	• 50% (10/20) [CI: 27.2, 72.8]
mDC Duration	• 4.1 mo. [Range: 2.9 to 8.7]
mDOR	• 4.1 mo. [Range: 3.0 to 8.7]

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

DEMOGRAPHICS

Baseline Characteristic	ICI-Naïve Ovarian 100mg (n= 16)	ICI-Naïve Ovarian 200mg (n= 8)
Age, years		
Median (range)	67.5 (57 – 83)	65 (34 – 80)
Sex, n (%)		
Female	16 (100)	8 (100)
ECOG performance status, n (%)		
0	9 (56.3)	4 (50)
1	7 (43.7)	4 (50)
Prior systemic anti-cancer regimens		
Median (range)	4 (1 – 12)	3 (2 – 11)

CONCLUSION

NC410 in combination with pembrolizumab provides clinical benefit in recurrent ovarian cancer, including those with liver metastasis. Additional dose optimization (100mg NC410 vs. 200mg NC410) is necessary to determine the RP2D for Ovarian cancer. The combination treatment merits further evaluation in a randomized study.

This study is sponsored by NextCure, Inc. in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.. Sponsor Representative: Udayan Guha, MD., Ph.D., Senior VP, Clinical and Translational Development (guhau@nextcure.com). Presenting author does not have any conflicts of interest to declare.