NT-I7, a long-acting IL-7, plus pembrolizumab favors CD8⁺ T-cell infiltration in immune-excluded liver metastasis of heavily pretreated, immunologically cold, MSS-Colorectal and Pancreatic cancer.

Aung Naing[1], Sara Ferrando-Martinez[2], M Brandon Ware[2], Cara Haymaker[1], Allison L. Bierly[2], Jack B. Goon[2], Marya F Chaney[3], Swati Dhar[2], Chan-Young Ock[4], Siyoung Lee[5]; Kyunghyun Paeng[4]; Taeseob Lee[5], Tolani Adebanjo[2], Se Hwan Yang[2], Byung Ha Lee[2], Richard D. Kim[6]

[1]The University of Texas MD Anderson Cancer Center, Houston TX, USA; [2]NeoImmuneTech, Inc., Rockville, MD, USA; [3]Merck & Co., Inc., Rahway, NJ, USA; [4]Lunit, Inc., Seoul, KR, [5]Geninus, Inc., Seoul, KR; [6]Moffitt Cancer Center, Tampa, FL, USA

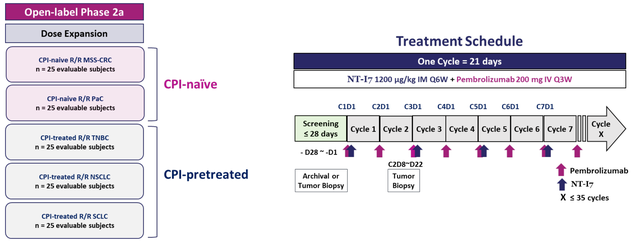
BACKGROUND

Immunologically cold gastrointestinal tumors, like microsatellite stable colorectal cancer (MSS-CRC) or pancreatic cancer (PaC), are a clinical challenge, with standard of care relying heavily on chemotherapy approaches. Patients with relapsed or refractory (r/r) disease have very limited treatment options. Checkpoint inhibitors (CPI) have limited response with dismal disease control rates and overall survival for these patients. These indications also have a high incidence of liver metastasis, and the presence of liver lesions lowers even further the efficacy of any immunotherapeutic approach. Effective treatments for patients with immunologically cold gastrointestinal tumors, including those with liver metastasis, are an unmet medical need.

Tumor-infiltrating lymphocytes (TIL) in liver biopsies, when present, have prognostic value.[1, 2] NT-I7 (efineptakin alfa) is a long-acting IL-7, a fundamental cytokine for lymphocyte development and survival. In combination with pembrolizumab, NT-I7 increases CD8⁺ T cell infiltration into the tumor of CPI-naïve immunologically cold indications[3] (MSS-CRC and PaC), showing promising clinical efficacy while being safe and well tolerated. Here, we explore the ability of NT-I7 and pembrolizumab to support T-cell infiltration in subjects with liver metastasis as a correlate of clinical efficacy.

STUDY DESIGN

This is an open-label, phase 2a study in subjects with relapsed/refractory (r/r) CPI-naïve MSS-CRC and PaC. Subjects received NT-I7 at 1200μg/kg every 6 weeks (Q6W) plus pembrolizumab at 200mg Q3W. Design was Simon's 2-stage minimax, seeking ≥ 1 responder of 17 evaluable patients in stage I and a stage II expansion for a total of 25 evaluable patients per arm. Antitumor activity was assessed by RECIST v1.1 and iRECIST. Results shown are from a data cutoff date of April 29, 2022.



Pre-treatment and on-treatment biopsies were analyzed by Lunit SCOPE IO, an artificial intelligence-powered H&E analyzer, and immunohistochemistry. For exome sequencing analysis, single nucleotide variants and indels were detected and filtered by GATK Mutect2.

CONCLUSIONS

- NT-I7 plus pembrolizumab shows significant clinical efficacy in CPI-naïve r/r MSS-CRC and PaC in the ***absence*** of liver metastasis.
- NT-I7 plus pembrolizumab also shows some clinical efficacy in the ***presence*** of liver metastasis.
- NT-I7 plus pembrolizumab drives CD8⁺ T-cell infiltration which, regardless of liver metastasis, may be associated with longer overall survival.
- These promising findings warrant further exploration of the NT-I7 + pembro combination.

RESULTS

Subject characteristics and safety

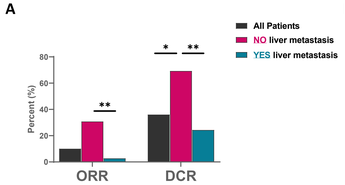
- 50 evaluable subjects, 68% with ≥ 2 prior lines of therapy.
- 74% of subjects had liver metastasis.
- Median tumor mutation burden (TMB; n = 17) was 3.21 mut/MB (TMB-L).
- The most common NT-I7-related treatment-emergent adverse events in the safety set (61 pts) were injection site reaction, fever, fatigue and nausea.
- One Grade 4 and no Grade 5 adverse events were observed.

Table 1. Subject characteristics.

	MSS-CRC n =25	PaC n = 25	Total n = 50
Age (years); median (range)	56.0 (35, 81)	67.0 (31, 78)	**60.0 (31, 81)**
Gender (female); n (%)	9 (36.0)	13 (52.0)	**22 (44.0)**
ECOG status; n (%)			
0	8 (32.0)	8 (32.0)	**16 (32.0)**
1	17 (68.0)	17 (68.0)	**34 (68.0)**
≥ 2 prior therapies, n (%)	20 (80.0)	14 (56.0)	**34 (68.0)**
Subjects with liver metastasis, n (%)	20 (80.0)	17 (68.0)	**37 (74.0)**

NT-I7 + pembrolizumab treatment shows greater clinical benefit in patients without liver metastasis

- Patients without liver metastasis have higher efficacy (ORR = 30.8%) and disease control rates (DCR = 69.2%) per iRECIST, as well as higher overall survival ($p < 0.05$)
- Patients with liver metastasis still show clinical efficacy (1 patient with 3 liver mets had a partial response per iRECIST with 46% tumor reduction, and DCR was 24.3%)



B

	ORR [% (n/total n)]		DCR [% (n/total n)]	
	RECIST v1.1	iRECIST	RECIST v1.1	iRECIST
NO liver metastasis (n = 13)	**15.4% (2/13)**	**30.8% (4/13)**	**53.9% (7/13)**	**69.2% (9/13)**
YES liver metastasis (n = 37)	0.0% (0/37)	2.7% (1/37)	21.6% (8/37)	24.3% (9/37)

Historical ORR with anti-PD(L)1 monotherapy in these indications is 0%[4-5]

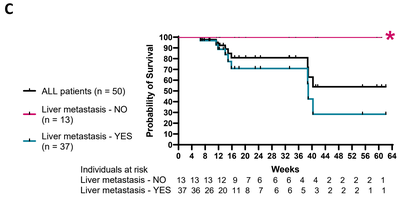
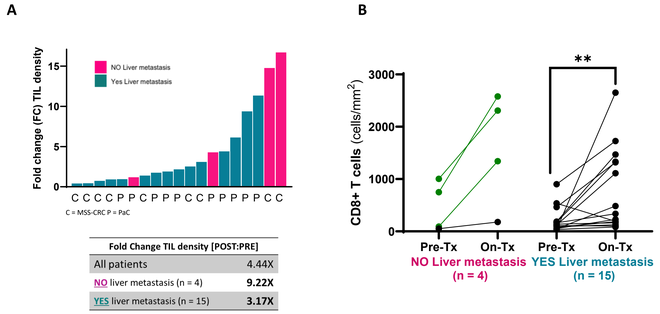
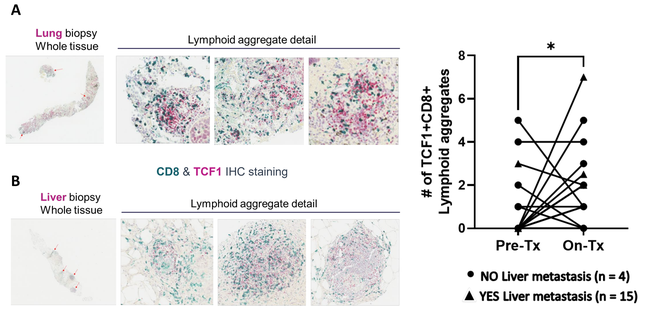


Figure 1. Liver metastasis impacts response to the study treatment. (A) Comparison of NT-I7+pembro in all patients or patients stratified by presence of liver metastasis. (B) Overall response rate (ORR) and disease control rate (DCR) in patients with and without liver metastasis per RECIST v1.1 and iRECIST, showing greater efficacy in patients without liver metastasis, but clinical benefit for both patient subsets. (C) Comparison of overall survival (OS) in all patients as well as patients with and without liver metastasis, showing significantly higher OS in patients without.

CD8 T cell infiltration is increased in patients regardless of liver metastasis and correlates with higher overall survival



Fold Change TIL density [POST:PRE]	
All patients	4.44X
NO liver metastasis (n = 4)	**9.22X**
YES liver metastasis (n = 15)	**3.17X**



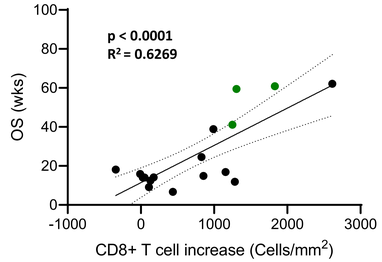


Figure 2. NT-I7 and pembrolizumab treatment induces higher CD8⁺ T cell infiltration into the tumor regardless of the presence of liver metastasis. (A) Artificial intelligence (AI) H&E analysis using Lunit SCOPE IO showed a significant increase in TIL density in patients both with and without liver metastasis. Biopsies from patients without liver metastases included lung (2), diaphragm, and pelvic mass. (B) Immunohistochemical (IHC) staining confirmed the increase in CD8⁺ TIL regardless of liver metastasis presence. Patients with a PR per iRECIST are shown in green.

Figure 3. NT-I7-driven T cell infiltration into the tumor, regardless of tissue location, could account for efficacy observed in patients with this combination, even those with liver metastasis. Lung biopsy tissue from an MSS-CRC patient without liver metastases (A) and liver biopsy tissue from an MSS-CRC patient (B), were stained for CD8 (green) and TCF1 (pink). (C) Intratumoral lymphoid aggregates enriched for TCF1⁺CD8⁺ cells were increased in more than 50% of analyzed on-treatment tissue samples (10/19) regardless of tumor location.

Figure 4. Increased T cell infiltration, regardless of tumor location, correlates with higher overall survival. IHC staining for CD8⁺ T cells showed a significant correlation between CD8⁺ T cell increase and overall survival. Patients with PR per iRECIST are shown in green.

ACKNOWLEDGMENTS

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For more information, please contact **Aung Naing, M.D. (anaing@mdanderson.org)**