Phase 2a Study of NT-I7, a Long-Acting Interleukin-7, plus Pembrolizumab: Cohort of Subjects with Checkpoint Inhibitor-Naïve Advanced MSS-Colorectal Cancer

Richard D. Kim, MD[1], Hirva M. Mamdani, MD[2], Minal Barve, MD[3], Melissa L. Johnson, MD[4], Ibrahim Sahin, MD[1], Scott E. Kopetz, MD, PhD, FACP[5], Se Hwan Yang, PhD[6], Byung Ha Lee, PhD[6], Tolani Adebanjo, PhD[6], Rebecca Georgevitch[6], Sara Ferrando-Martinez, PhD[6], Marya Chaney, PhD[7], Jean Fan, MD, MSc[6], Aung Naing, MD[5]

[1]Moffitt Cancer Center, Tampa, FL, USA. [2]Karmanos Cancer Institute, Detroit, MI, USA. [3]Mary Crowley Cancer Research, Dallas, TX, USA. [4]Sarah Cannon / Tennessee Oncology, PLLC, Nashville, TN, USA. [5]MD Anderson Cancer Center, Houston, TX, USA. [6]NeoImmuneTech, Inc., Rockville, MD, USA. [7]Merck & Co., Inc., Rahway, NJ, USA.

BACKGROUND

Microsatellite-stable colorectal cancer (MSS-CRC) is an immunologically cold tumor, with low T cell infiltration. Previous studies have shown that pembrolizumab monotherapy has no efficacy in this immunologically cold indication. In Le et al. (2015), MSS-CRC patients showed 11% disease control rate (DCR) with 0% objective response. New combination therapies are therefore needed to improve efficacy.

NT-I7 (efineptakin alfa) is a long-acting IL-7 that amplifies T cell numbers (including CD4, CD8, and T_{scm} cells) and can increase T-cell infiltration in the tumor microenvironment (TME). We hypothesize that NT-I7 may create a favorable immune-reactive TME to enhance the efficacy of CPI when combined with the anti-PD-1 antibody pembrolizumab (pembro). In this phase 2a study, we assess the preliminary anti-tumor activity of this combination in subjects with CPI-naïve relapsed/refractory (R/R) MSS-CRC and other R/R tumor types. We also explore the relationship of efficacy with baseline characteristics known to hinder the efficacy of immunotherapy strategies, including the presence of liver metastasis and the number of liver lesions.

STUDY DESIGN

Subjects with CPI-naïve relapsed/refractory (R/R) **MSS-CRC** and other R/R tumor types were enrolled in this Ph2a.

NT-I7 (efineptakin alfa) 1200 µg/kg intramuscularly (IM) every 6 weeks (Q6W) and 200 mg pembro intravenously (IV) Q3W were administered until disease progression/unacceptable toxicity.

- The study used Simon's minimax two-stage design seeking ≥1 responder of 17 evaluable subjects in stage 1 for expansion in each cohort, and additional enrollment of 8 evaluable subjects in stage 2.
- An expansion cohort of 25 subjects has been added for CPI-naïve R/R MSS-CRC.

RESULTS

Subject disposition and characteristics

- Median age of subjects was 56.0 years, with 65.5% male subjects and 34.5% female.
- All subjects had an ECOG status of 0-1.
- 79.3% of subjects had liver metastasis (≥ 1 liver lesions).
- As of April 29, 2022, 29 subjects were enrolled through Stage 2, of which 27 were evaluable.

Table 1. Baseline characteristics

Characteristics	Categories	N = 29
Age in years, median (range)		56.0 (35, 81)
Gender, n (%)	Male Female	19 (65.5) 10 (34.5)
ECOG status, n (%)	0 1	8 (27.6) 21 (72.4)
Subjects with liver metastasis, n (%)		23 (79.3)

ECOG: Eastern Cooperative Oncology Group

Safety

- 79.3% of subjects experienced study medication-related treatment-emergent adverse events (TEAEs)
- The most frequently-reported TEAEs included fatigue, injection site reaction, and nausea
- No Grade 4-5 AEs were observed

Table 2. Summary of treatment-emergent adverse events

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grades 4-5 n (%)	All Grades n (%)
Number (%) of subjects with ≥1 TEAEs	8 (27.6)	9 (31.0)	6 (20.7)	0 (0.0)	23 (79.3)
Most frequently-reported TEAEs:					
Fatigue	4 (13.8)	4 (13.8)	1 (3.4)	0 (0.0)	9 (31.0)
Injection site reaction	5 (17.2)	2 (6.9)	0 (0.0)	0 (0.0)	7 (24.1)
Nausea	4 (13.8)	2 (6.9)	1 (3.4)	0 (0.0)	7 (24.1)
Fever	3 (10.3)	2 (6.9)	0 (0.0)	0 (0.0)	5 (17.2)
Rash maculo-papular	3 (10.3)	1 (3.4)	1 (3.4)	0 (0.0)	5 (17.2)
Vomiting	5 (17.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (17.2)
Flu-like symptoms	3 (10.3)	0 (0.0)	1 (3.4)	0 (0.0)	4 (13.8)

TEAE: Treatment-emergent adverse event

Pharmacodynamics

- Cytotoxic CD8+ T cells are preferentially expanded over Tregs, supporting a favorable CD8-to-Treg ratio.
- Subjects with partial response showed the highest TIL infiltration score in the TME.

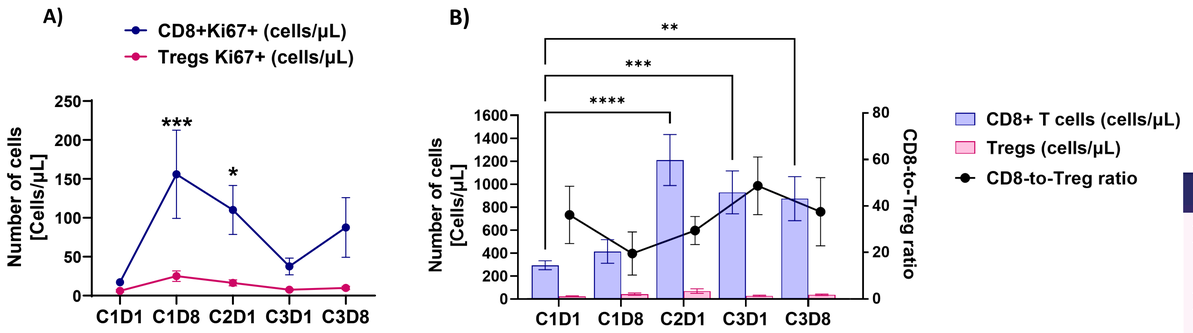

Figure 1. (A) CD8+ T cells, but not Treg cells, have a significant increase on proliferation (Ki67+) after one dose of NT-I7 and pembro. **(B)** CD8+ T cells are preferentially expanded and the CD8-to-Treg ratio increases. (n = 23)

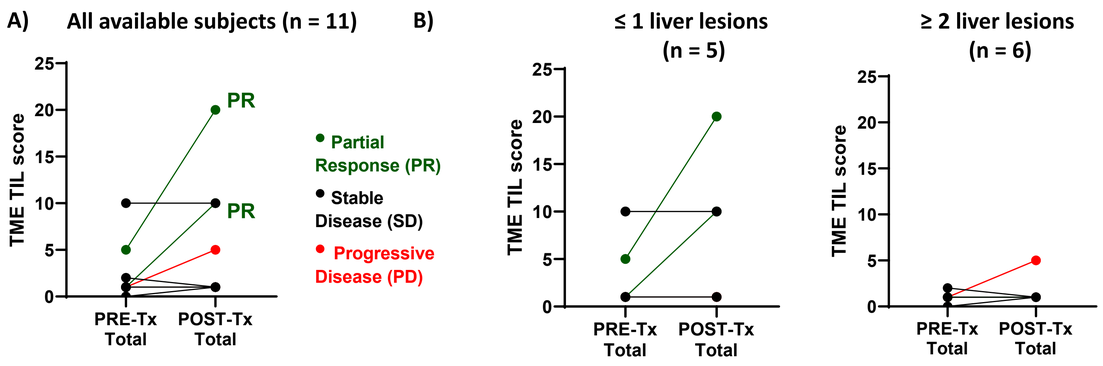

Figure 2. Total infiltrating lymphocytes (immune cells, TILs) were manually quantified from H&E-stained full biopsy sections pre- and on-treatment. TIL infiltration was highest in subjects with partial response (PR), while subjects with 2 or more liver lesions had curtailed infiltration.

STUDY OBJECTIVES

Primary objectives

- To assess the preliminary anti-tumor activity of NT-I7 in combination with pembrolizumab in subjects with CPI-treated R/R tumors and CPI-naïve R/R tumors, including CPI-naïve R/R MSS-CRC, based on Objective Response Rate (ORR) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and iRECIST.

Secondary objectives

- To further assess anti-tumor activity of NT-I7 in combination with pembrolizumab in this subject population based on Duration of Response (DoR), Disease Control Rate (DCR), Progression-Free Survival (PFS), and Overall Survival (OS) by RECIST v1.1 and iRECIST.
- To evaluate immunogenicity of NT-I7 administered in combination with pembrolizumab in this subject population.

Exploratory objectives

- To make a preliminary assessment of pharmacokinetic (PK) parameters.
- To make a preliminary assessment of biomarkers that might act as pharmacodynamic indicators of NT-I7 activity in combination with pembrolizumab in CPI-naïve R/R MSS-CRC.
- To make a preliminary assessment of biomarkers that might act as predictors of anti-tumor activity of NT-I7 in combination with pembrolizumab in CPI-naïve R/R MSS-CRC.

Efficacy

- Overall **iORR** was **11.1%** and **iDCR** was **40.7% by iRECIST**, with an **ORR** of 3.7% and **DCR** of 37.0% by RECIST v1.1.
- Objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS) were comparable in subjects with ≤ 1 or ≥ 2 liver lesions.

Table 3. Efficacy summary, RECIST v1.1

	N = 27
Best overall response per RECIST v1.1, n (%):	
Complete response (CR)	0 (0.0)
Partial response (PR)	1 (3.7)
Stable disease (SD)	9 (33.3)
Progressive disease (PD)	17 (63.0)
ORR per RECIST v1.1, n (%)	1 (3.7)
DCR per RECIST v1.1, n (%)	10 (37.0)
DoR in months, median (min, max)	6.7 (6.7, 6.7)
ORR by number of prior therapies, n (%)	
≤2 (12)	1 (8.3)
≥3 (15)	0 (0.0)
ORR by number of liver lesions, n (%)	
≤1 (8)	1 (12.5)
≥2 (19)	0 (0.0)
ORR by sum of target lesion, n (%)	
≤100mm (16)	1 (6.3)
>100mm (11)	0 (0.0)

Table 4. Efficacy summary, iRECIST

	N = 27
Best overall response per iRECIST, n (%):	
Immune complete response (iCR)	0 (0.0)
Immune partial response (iPR)	3 (11.1)
Immune stable disease (iSD)	8 (29.6)
Progressive disease immune unconfirmed (iUPD)	16 (59.3)
ORR per iRECIST, n (%)	3 (11.1)
DCR per iRECIST, n (%)	11 (40.7)
iDoR in months, median (min, max)	6.7 (4.2, 8.7)
iORR by number of prior therapies, n (%)	
≤2 (12)	2 (16.7)
≥3 (15)	1 (6.7)
iORR by number of liver lesions, n (%)	
≤1 (8)	2 (25.0)
≥2 (19)	1 (5.3)
iORR by sum of target lesion, n (%)	
≤100mm (16)	3 (18.8)
>100mm (11)	0 (0.0)

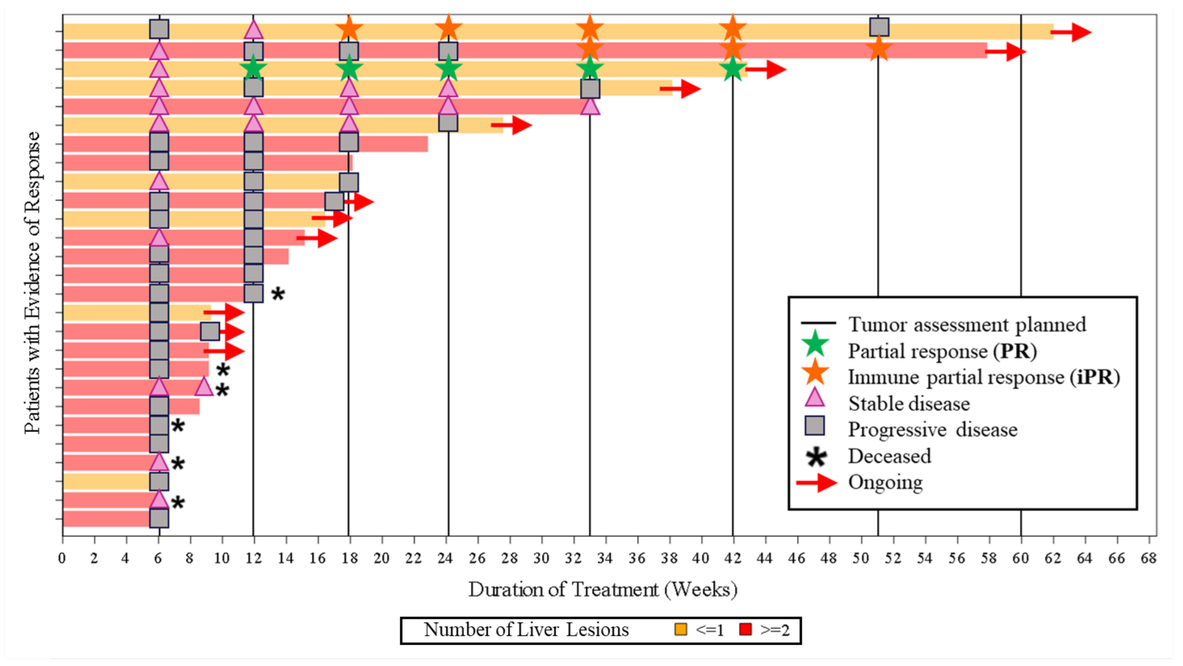

Figure 5. Duration of treatment and response (RECIST v1.1): NT-I7 plus pembrolizumab combination therapy

CONCLUSIONS AND FUTURE DIRECTIONS

- The chemotherapy-free combination of NT-I7 and pembrolizumab was well-tolerated in heavily pretreated subjects with CPI-naïve R/R MSS-CRC.
- In this remarkably immunologically cold indication, normally associated with primary resistance to CPI monotherapy, the combination of NT-I7 and pembrolizumab achieved an **ORR of 11.1%** and a **DCR of 40.7%** per iRECIST. This clinical efficacy is promising in comparison to previously reported data with pembrolizumab monotherapy (1).
- Clinical efficacy was observed even in subjects with ≥2 liver lesions, despite a trend towards higher TIL infiltration observed in patients with ≤ 1 liver lesions. Further data from the 25-subject expansion cohort is expected to provide additional insight into how the number of liver lesions may impact clinical efficacy.
- NT-I7 and pembrolizumab leads to the preferential proliferation of cytotoxic CD8+ T cells over Tregs, favoring a more immunogenic CD8-to-Treg ratio.
- Intratumoral analysis showed increased infiltration of lymphocytes in subjects with partial response.

These results show that combination therapy with NT-I7 and pembrolizumab demonstrates promising anti-tumor activity in immunologically cold indications like R/R MSS-CRC subjects, with a concurrent increase in CD8+ T lymphocytes in both the tumor and periphery.

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For more information, please contact Richard Kim, MD, at richard.kim@moffitt.org