Initial Biomarker and Clinical Data of a Phase 2a Study of NT-I7, a Long-Acting Interleukin-7, plus Pembrolizumab: Cohort of Subjects with Checkpoint Inhibitor-naïve Advanced MSS-Colorectal Cancer.

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BACKGROUND

NT-I7 (efineptakin alfa) is the only clinical-stage long-acting human IL-7 and has demonstrated its ability to increase the number and functionality of T cells in peripheral blood and to enhance infiltration of lymphocytes to the tumor microenvironment (TME). While checkpoint inhibitors (CPIs) have been approved as treatments for multiple solid tumors, they are ineffective for microsatellite stable colorectal cancer (MSS-CRC), leading to high unmet medical needs in this population. Since low levels of T cells in peripheral blood and within the TME correlate with poor response to CPIs[1], we hypothesized that NT-I7, when combined with pembrolizumab (pembro), may create a favorable immune-reactive TME to enhance the CPI-related clinical activity in quiescent MSS-CRC.

[1]Delyon J et al. Annals of Oncology, 2013

STUDY DESIGN

- Open-label, phase 1b/2a study in patients with relapsed/refractory (R/R) advanced solid tumors. (**NCT04332653**). Here, we report the phase 2a interim analysis in patients with CPI-naïve R/R MSS-CRC tumors.
- The Recommended Phase 2 Dose (RP2D) is NT-I7 intramuscularly (IM) 1,200 µg/kg every 6 weeks (Q6W) plus pembrolizumab 200 mg intravenously (IV) Q3W.
- Phase 2a followed the Simon's minimax two-stage design. The interim analysis was performed when 17 evaluable patients were enrolled in Stage I.

STUDY OBJECTIVES

Primary objective

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

Secondary objectives

- To further assess the anti-tumor activity of NT-I7 in combination with pembrolizumab in these patient populations, based on Duration of Response (DoR), Disease Control Rate (DCR), Progression-Free Survival (PFS), and Overall Survival (OS).

CONCLUSIONS

- The interim analysis met its primary endpoint, with an overall response rate of 18% per iRECIST and 6% per RECIST v1.1 in subjects with CPI-Naïve R/R advanced MSS-CRC.
- The combination of NT-I7 and pembro is safe and well tolerated at the 1,200 µg/kg dose.
- **CD8+ T_{SCM}**, a self-renewing population with superior antitumor activity compared to other memory T cell subsets[2], increased **>50x** by week 3.

[2]Reviewed in Li et al. Front Oncol 2021

- One subject with immune partial response (**iPR**) had enhanced T cell infiltration (**TILs**) in the tumor at week 5.
- NT-I7-driven increase of **CD8+ T_{SCM} and TIL numbers** may be underlying mechanisms of action for the observed efficacy.

These results support continued evaluation of NT-I7 + pembro in CPI-naïve subjects with R/R MSS-CRC

Results from the CPI-naïve Pancreatic cancer cohort are shown in **Poster #408**
Results from a study of NT-I7 in GBM patients are shown in **Poster #396**

This study is in collaboration with Merck Sharp & Dome Corp., a subsidiary of Merck & Co., Inc, Kenilworth, NJ, USA
Acknowledgments: the authors thank ICON for their partnership in conducting this trial

RESULTS – CLINICAL DATA

Subject disposition and characteristics

- As of 27 September 2021, 21 subjects were enrolled in the CPI-naïve R/R MSS-CRC cohort.
- Median age 57 years (37-81); ECOG PS 0 (33%), PS 1 (67%).
- All subjects had at least 1 prior line of therapy, and 95.2% of subjects received ≥ 2 prior therapies.

Characteristics	Categories	MSS-CRC (n = 21)
Age, year, median (range)	-	57 (37, 81)
Gender, n (%)	Male	15 (71.4)
ECOG Performance Status, n (%)	0	7 (33.3)
	1	14 (66.7)
No. of previous lines of therapy, n (%)	1	1 (4.8)
	2	2 (9.5)
	3	5 (23.8)
	>3	13 (61.9)
Stage at diagnosis, n (%)	1	0 (0.0)
	2	3 (14.3)
	3	6 (28.6)
	4	12 (57.1)
No. of subjects with liver metastasis, n (%)	-	16 (76.2)

ECOG: Eastern Cooperative Oncology Group

Table 1. Baseline and disease characteristics

Safety and tolerability

- Adverse drug reactions occurred in 17 (81%) subjects; 9 (57%) G1-2 events and 5 (24%) G3 events; no G4 or G5 AEs were reported.
- Two subjects discontinued from the study due to pneumonitis and pneumonitis/interstitial nephritis.

n (%)		MSS-CRC (n = 21)
Any ADR		17 (81.0)
ADR by severity	Grade 1	6 (28.6)
	Grade 2	6 (28.6)
	Grade 3	5 (23.8)
	Grade 4-5	0 (0.0)
Most frequently reported ADR		
Fatigue		6 (28.6)
Nausea		5 (23.8)
Fever		4 (19.0)
Flu-like Symptoms		3 (14.3)
ADR resulting in drug discontinuation		2 (9.5)

ADR: Adverse Drug Reaction

Table 2. Summary of adverse drug reactions

Clinical response

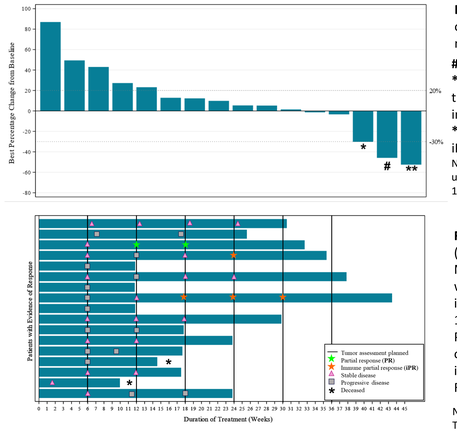


Figure 1. Waterfall plot for the best percentage change of target lesions from baseline in individuals with CPI-naïve R/R MSS-CRC.

#Patient achieved a PR with **56%** tumor reduction.
***Patient who had SD developed *pseudoprogression* and then achieved confirmed iPR with **30%** tumor reduction in the follow up scan.
****After *pseudoprogression*, patient achieved confirmed iPR with **58%** of tumor reduction.
Note: one subject's target lesion became not evaluable at the follow up scans and this subject had progression on non-target lesion at the 1st follow up scan

Figure 2. Swimmer plot for the treatment duration (weeks) and response of individuals with CPI-naïve R/R MSS-CRC. The median treatment duration was 24.14 weeks. The objective response rate (ORR) was achieved in 3 (18%)out of 17 evaluable subjects per iRECIST and 1 (6%) out of 17 evaluable subjects achieved confirmed PR per RECIST v1.1. Disease control rate (DCR) was observed in 10 (59%) out of 17 evaluable subjects by iRECIST and 9 (53%) out of 17 evaluable subjects by RECIST v1.1

Note: Clinical Data were updated as of Nov 10, 2021
The median follow-up was 5.8 months

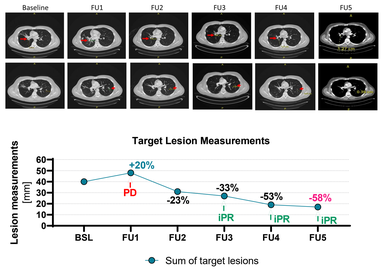


Figure 3. Representative CT scans from the subject with CPI-naïve R/R advanced MSS-CRC that had a PD at the 1st assessment and then achieved confirmed iPR with **-58%** of tumor reduction in the subsequent scans

RESULTS – BIOMARKER DATA

Lymphocytes and T cells

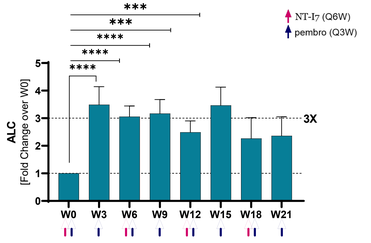


Figure 4. Absolute lymphocyte counts (ALC) significantly increased (**3x** over baseline) by week 3 and **remained increased** for the duration of the follow-up. Analysis based on 17 evaluable patients.

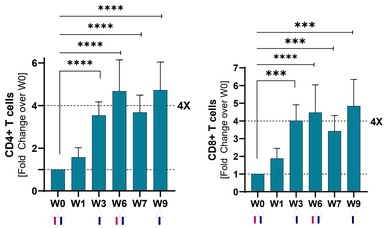
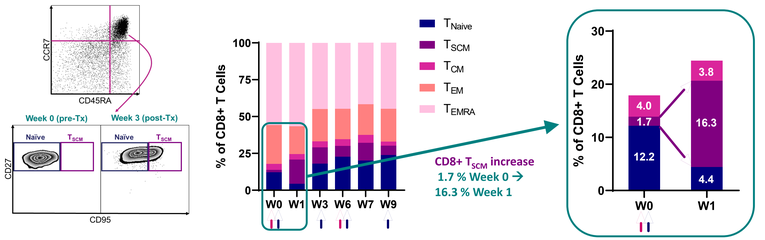
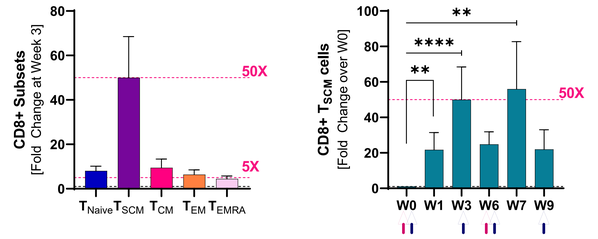


Figure 5. CD4+ and CD8+ T cells, following the same pattern, increased **4x** over baseline by week 3 and **remained increased** until week 9 (last measurement). Analysis based on 17 evaluable patients. (*p≤0.05; **p ≤ 0.001; ***p ≤0.0001; ****p ≤0.00001)

Stem-cell memory CD8+ T cells (T_{SCM})





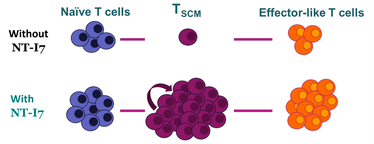


Figure 6. Stem-cell Memory CD8+ T cells (T_{SCM}), the CD8+ T cell subset with self-renewal capabilities that have shown better antitumor activity compared with other memory T cell subsets, increased from 1.7% at baseline to 16.3% one week after the first NT-I7 dose. The associated upregulation of Ki67 (data not shown) suggests that proliferation, rather than re-distribution, is driving this increase. CD8+ T_{SCM} absolute numbers peaked at week 3 with a **50x increase over baseline,** while the other CD8+ T cell subsets increased in average by ~5x. After a pembro-only dose in week 3, the absolute numbers of CD8+ T_{SCM} decreased, potentially by differentiation into effector cells. After a second dose of NT-I7 in week 6, CD8+ T_{SCM} levels increased again, reaching **>50x over baseline**. These results suggest that the differential increase of the CD8+ T_{SCM} subset could be part of the mechanism of action of NT-I7. Analysis based on 17 evaluable patients. (*p≤0.05; **p ≤ 0.001; ***p ≤0.0001; ****p ≤0.00001)

Chemokines and Tumor-infiltrating lymphocytes

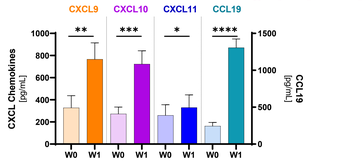
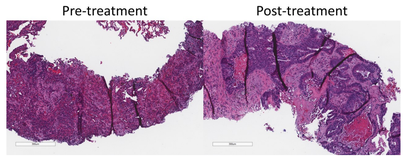


Figure 7. Plasmatic chemokines significantly increased after the first NT-I7 + pembro dose. These chemokines are potent chemoattractants that recruit lymphocytes into the tumor niche while CCL19 is involved in the formation of tertiary lymphoid structures (TLS) within the tumor. Analysis based on 17 evaluable patients. (*p≤0.05; **p ≤ 0.001; ***p ≤0.0001; ****p ≤0.00001)



Patient ID	ORR	Lymph (%) Pre-Tx	Lymph (%) Post-Tx
4-1	iPR	2	60
4-2	PR	1	4
4-3	SD	10	0
4-4	SD	2	3
4-5	SD	1	1
4-6	PD	1	1
4-7	PD	2	5

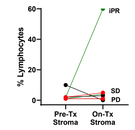


Figure 8. Tumor infiltrating lymphocytes (TILs) were quantified pre- and post-treatment (W5) from H&E-stained biopsies. Full sections were analyzed. Results are shown as the percentage of stromal cells that are lymphocytes. The subject with immune partial response (iPR, representative images shown) showed enhanced TIL infiltration. Genomic analysis of biopsy samples, including WES, WTS and TCRseq, is ongoing.