Preliminary 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 Pancreatic 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 R/R advanced pancreatic cancer (PC), 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 pancreatic cancer.

[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 pancreatic cancer (PC).
- 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 PC, 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 6% per RECIST v1.1 and iRECIST in subjects with CPI-naïve R/R advanced pancreatic cancer.
- The combination of NT-I7 and pembro is safe and well tolerated at the 1,200 µg/kg dose.
- The **CD8+ Effector-to-T_{REG} ratio** and the **CD8+ T_{SCM}** cells, a self-renewing population with superior antitumor activity compared to other memory T cell subsets[2], both significantly increased in peripheral blood.

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

- The subject with partial response (**PR**) had enhanced T cell infiltration (**TILs**) in the TME 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 pancreatic cancer.

Results from the CPI-naïve MSS-CRC cohort are shown in **Poster #404**
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, 30 subjects were enrolled in the CPI-naïve PC cohort.
- Median age 65 years (31-81); ECOG PS 0 (33%), PS 1 (67%).
- All subjects had at least 1 prior line of therapy, and 26 (87%) subjects received ≥ 2 prior lines of therapy.

Characteristics	Categories	PC (n = 30)
Age, year, median (range)	-	65 (31, 81)
Gender, n (%)	Male	16 (53.3)
ECOG Performance Status, n (%)	0	10 (33.3)
	1	20 (66.7)
No. of previous lines of therapy, n (%)	1	3 (10)
	2	8 (26.7)
	3	11 (36.7)
	>3	8 (26.7)
Stage at diagnosis (%)	1	7 (23.3)
	2	5 (16.7)
	3	4 (13.3)
	4	14 (46.7)
No. of subjects with liver metastasis, n (%)	-	24 (80.0)

ECOG: Eastern Cooperative Oncology Group

Table 1. Baseline and disease characteristics

Safety and tolerability

- Adverse drug reactions occurred in 21 (70%) subjects, 15 (50%) G1-2 events, 4 (13%) G3 events, and 2 (7%) G4 events; no G5 AEs were reported.
- One subject discontinued from the study due to decreased platelet count.

n (%)		PC (n = 30)
Any ADR		21 (70.0)
ADR by severity	Grade 1	9 (30.0)
	Grade 2	6 (20.0)
	Grade 3	4 (13.3)
	Grade 4-5	2 (6.7)
Most frequently reported ADR		
Fever		9 (30.0)
Fatigue		5 (16.7)
Rash		5 (16.7)
Injection Site Reaction		4 (13.3)
Chills		3 (10.0)
ADR resulting in drug discontinuation		1 (3.3)

ADR: Adverse Drug Reaction

Table 2. Summary of adverse drug reactions

Clinical response

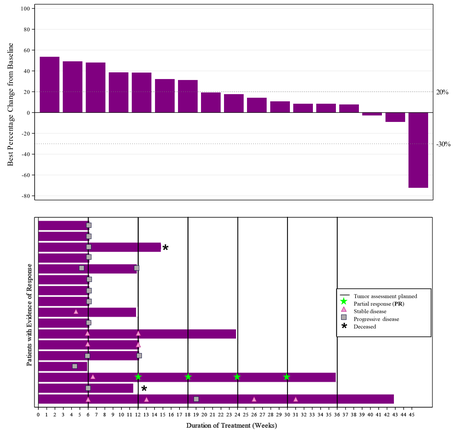


Figure 1. Waterfall plot for the best percentage change of target lesions from baseline in individuals with CPI-naïve R/R pancreatic cancer. One patient achieved a confirmed PR with 72% tumor reduction.

Figure 2. Swimmer plot for the treatment duration (weeks) and response of individuals with CPI-naïve R/R pancreatic cancer. The median treatment duration was 11.71 weeks. Objective response rate (ORR) was achieved in 1 (6%) out of 17 evaluable subjects per iRECIST and RECIST v1.1. Disease control rate (DCR) was observed in 5 (29%) out of 17 evaluable subjects per iRECIST and RECIST v1.1.

Note: Clinical Data were updated as of Nov 10, 2021
The medium follow up was 4.6 months

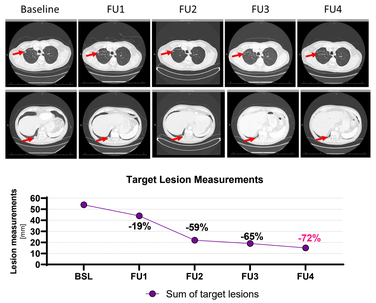


Figure 3. CT scans from the subject with CPI-Naïve R/R advanced PC who achieved a confirmed PR. A durable tumor reduction was observed after the treatment of NT-I7 and pembrolizumab.

RESULTS – BIOMARKER DATA

Lymphocytes and T cells

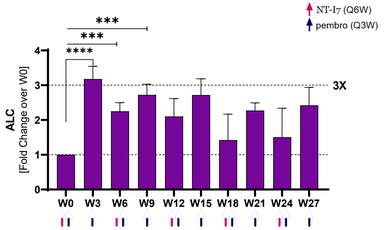


Figure 4. Absolute lymphocyte counts (ALC) significantly increased (**3x** over baseline) by week 3 and **remained increased** for the duration of the follow-up. Analysis based on 17 evaluable patients.

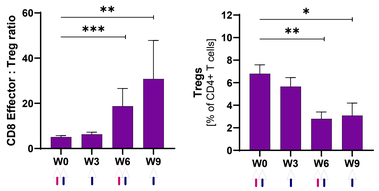


Figure 5. CD8+ Effector-to-T_{reg} ratio, significantly increased with treatment, while the frequency of **CD4+ T_{regs}** significantly decreased, suggesting that the combination of NT-I7 with pembro favors a more immune-reactive environment. Analysis based on 17 evaluable patients. (*p≤0.05; **p ≤ 0.001; ***p ≤0.0001; ****p ≤0.00001)

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

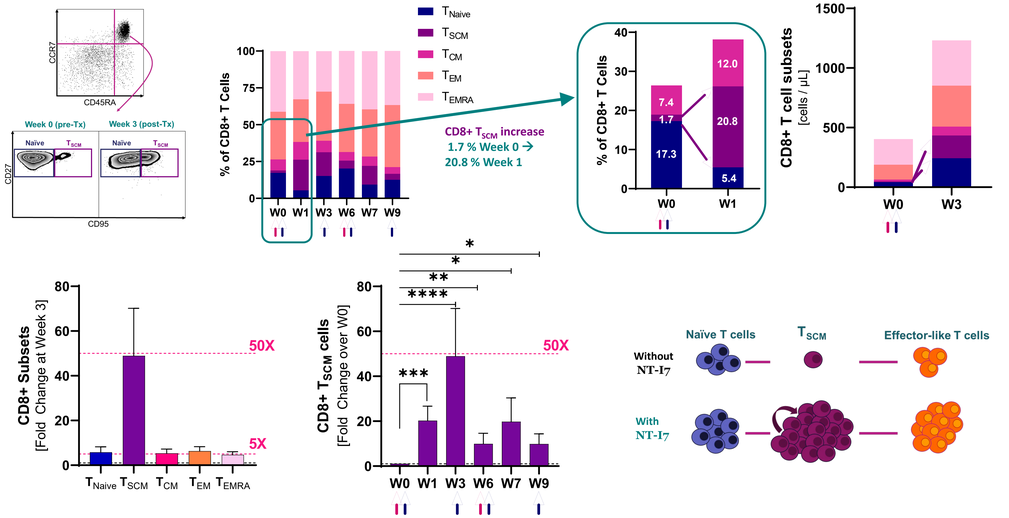


Figure 6. Stem-cell Memory CD8+ T cells (T_{SCM}), the CD8+ T cell subset with self-renewal capabilities that have shown better antitumor activity compared with other memory T cell subsets, increased from 1.7% in baseline to 20.8% one week after the first NT-I7 dose (*upper panel*). The associated upregulation of Ki67 (data not shown) suggests that proliferation, rather than re-distribution, is driving this increase. CD8+ T_{SCM} absolute numbers (*lower panel*) 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. 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

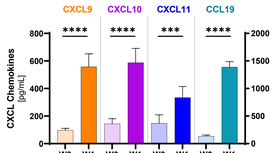
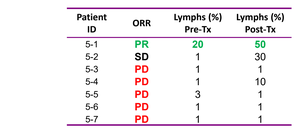


Figure 7. Plasmatic chemokines significantly increased after the first NT-I7 + pembro dose. These chemokines are potent chemoattractants that recruit lymphocytes into the tumor niche while CCL19 is involved in the formation of tertiary lymphoid structures (TLS) within the tumor. Analysis based on 17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

Patient ID	ORR	Lymphs (%) Pre-Tx	Lymphs (%) Post-Tx
5-1	PR	20	50
5-2	SD	1	30
5-3	PD	1	1
5-4	PD	1	10
5-5	PD	3	1
5-6	PD	1	1
5-7	PD	1	1



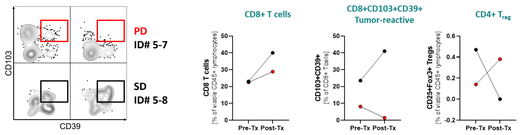


Figure 8. Tumor infiltrating lymphocytes (TILs) were quantified pre- and post-treatment (W5) from H&E-stained biopsies. Full sections were analyzed. Results are shown as the percentage of stromal cells that are lymphocytes. The subject with a partial response (**PR**) showed enhanced TIL infiltration. Flow cytometry of tumor biopsies showed that a patient with stable disease (SD) had increased CD8+ T cell infiltration, more CD103+CD39+ tumor-reactive CD8+ T cells and less Tregs post-treatment than the patient with progressive disease (PD). Genomic analysis of biopsy samples, including WES, WTS and TCRseq, is ongoing.