# 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

Pancreatic cancer (PaC) is an immunologically cold tumor type in which checkpoint inhibitor (CPI) monotherapy has been unsuccessful, with objective response rates of 0% regardless the line of treatment (1). Novel combination therapies are needed to improve the efficacy of CPIs in subjects with pancreatic cancer. NT-I7 (efineptakin alfa) is a long-acting IL-7 that amplifies T cell populations, including CD4, CD8, and $T_{scm}$ cells, and can increase T-cell infiltration in the tumor microenvironment (TME).

We hypothesize that the combination of NT-I7 and pembrolizumab may improve the efficacy of CPI therapy in immune-cold tumors such as PaC. In this phase 2a study, we assess the antitumor activity and pharmacodynamic effects of this combination therapy in multiple relapsed/refractory (R/R) tumor types, including CPI-naïve R/R PaC. 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 R/R **PaC** and other R/R tumor types were enrolled. In this Phase 2a study, NT-I7 (efineptakin alfa) 1200 µg/kg was administered intramuscularly (IM) every 6 weeks (Q6W) and 200 mg pembro intravenously (IV) Q3W 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 PaC.

## RESULTS

### Subject disposition and characteristics

- Median age of subjects was 66.0 years, with 50.0% male subjects and 50.0% female.
- All subjects had an ECOG status of 0-1.
- 78.1% of subjects had liver metastasis (≥ 1 liver lesions).
- As of the data cutoff date of April 29, 32 subjects were enrolled through stage 2, of which 26 were evaluable.

**Table 1. Baseline characteristics**

| Characteristics | Categories | N = 32 |
|---|---|---|
| Age in years, median (range) | | 66.0 (31, 81) |
| Gender, n (%) | Male<br>Female | 16 (50.0)<br>16 (50.0) |
| ECOG status, n (%) | 0<br>1 | 10 (31.3)<br>22 (68.8) |
| Subjects with liver metastasis, n (%) | | 25 (78.1) |

ECOG: Eastern Cooperative Oncology Group

### Safety

- 75.0% of subjects experienced study medication-related treatment-emergent adverse events (TEAEs)
- The most frequently-reported TEAEs included fever, injection site reaction, and fatigue
- One Grade (Gr) 4 AE and no Gr 5 AEs were observed

**Table 2. Summary of treatment-emergent adverse events**

| | Grade 1 n (%) | Grade 2 n (%) | Grade 3 n (%) | Grade 4 n (%) | Grade 5 n (%) | All Grades n (%) |
|---|---|---|---|---|---|---|
| Number (%) of subjects with ≥1 TEAEs | 10 (31.3) | 9 (28.1) | 4 (12.5) | 1 (3.1) | 0 (0.0) | 24 (75.0) |
| Most frequently reported TEAEs: | | | | | | |
| Fever | 6 (18.8) | 2 (6.3) | 1 (3.1) | 0 (0.0) | 0 (0.0) | 9 (28.1) |
| Injection site reaction | 6 (18.8) | 1 (3.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 7 (21.9) |
| Fatigue | 3 (9.4) | 2 (6.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (15.6) |
| Rash | 3 (9.4) | 1 (3.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (12.5) |
| Chills | 3 (9.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (9.4) |
| Anorexia | 1 (3.1) | 1 (3.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (6.3) |
| Dry skin | 2 (6.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (6.3) |

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.

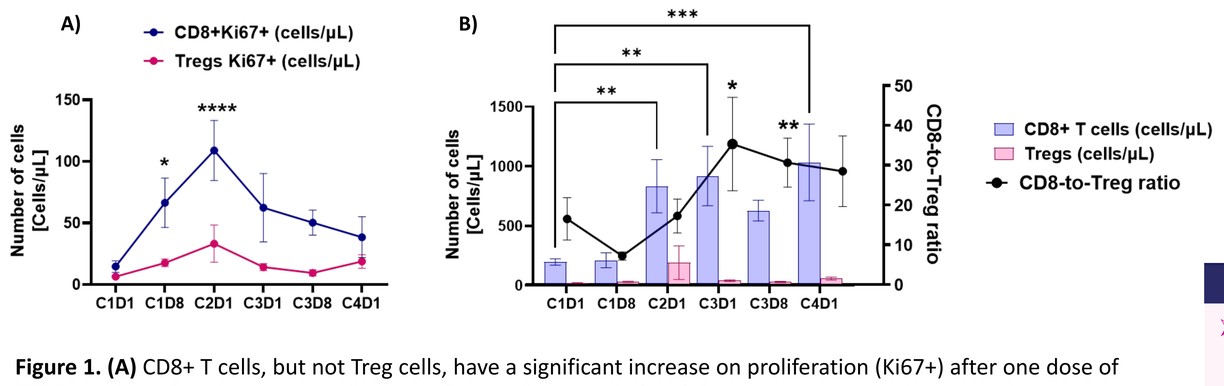
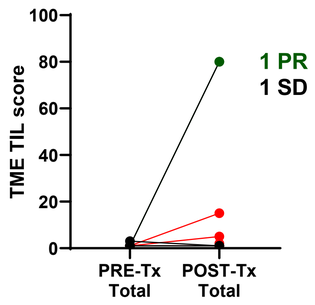



**Figure 1. (A)** CD8+ T cells, but not Treg cells, have a significant increase on proliferation (Ki67+) after one dose of NT-I7 and pembro. **(B)** CD8+ T cells are preferentially expanded and the CD8-to-Treg ratio increases. (N = 19)




- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD)

| ORR | Biopsy location | TIL score pre-Tx | TIL score post-Tx |
|---|---|---|---|
| PR | Lung | 0 | 80 |
| SD | Liver | 1 | 80 |

**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 the subject with partial response (PR) and a subject with stable disease (SD) who, notably, showed a high T cell infiltration in a liver biopsy. (N = 10)

## STUDY OBJECTIVES

### Primary objectives

- To assess the preliminary anti-tumor activity of NT-I7 in combination with pembrolizumab in subjects with including CPI-naïve R/R PaC, 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 subjects with CPI-naïve R/R PaC.
- To make a preliminary assessment of biomarkers that might act as predictors of anti-tumor activity of NT-I7 in combination with pembrolizumab in subjects with CPI-naïve R/R PaC.

### Efficacy

- Overall **iORR** was **7.7%** and **iDCR** was **34.6% by iRECIST**, and overall **ORR** was 3.8% and **DCR** was 30.8% by RECIST v1.1.
- Subjects with ≤1 liver lesions had significantly higher DCR (Fisher's exact test, 54.5% vs 13.3%; **p = 0.0384**) and iDCR (63.6% vs 13.3) %; **p = 0.0135** compared to subjects with ≥2 liver lesions.
- Median progression-free survival (mPFS) tended to be higher in subjects with ≤1 liver lesions (18.0 weeks vs 6.0 weeks, log-rank test p = 0.1220).

**Table 3. Efficacy summary, assessed by RECIST v1.1**

| | N = 26 |
|---|---|
| Best overall response per RECIST 1.1, n (%): | |
| Complete response (CR) | 0 (0.0) |
| Partial response (PR) | 1 (3.8) |
| Stable disease (SD) | 7 (26.9) |
| Progressive disease (PD) | 18 (69.2) |
| ORR per RECIST 1.1, n (%) | 1 (3.8) |
| DCR per RECIST 1.1, n (%) | 8 (30.8) |
| DoR in months, median (min, max) | 10.8 (10.8, 10.8) |
| ORR by number of prior therapies, n (%) | |
| ≤2 (18) | 1 (5.6) |
| ≥3 (8) | 0 (0.0) |
| ORR by baseline sum of target lesion, n (%) | |
| ≤100mm (20) | 1 (5.0) |
| >100mm (6) | 0 (0.0) |
| ORR by number of liver lesions, n (%) | |
| ≤1 (11) | 1 (9.1) |
| ≥2 (15) | 0 (0.0) |
| **DCR by number of liver lesions, n (%)** | |
| ≤1 (11) | 6 (54.5) |
| ≥2 (15) | 2 (13.3) |

**Table 4. Efficacy summary, assessed by iRECIST**

| | N = 26 |
|---|---|
| Best overall response per iRECIST, n (%): | |
| Immune complete response (iCR) | 0 (0.0) |
| Immune partial response (iPR) | 2 (7.7) |
| Immune stable disease (iSD) | 7 (26.9) |
| Progressive disease immune unconfirmed (iUPD) | 17 (65.4) |
| ORR per iRECIST, n (%) | 2 (7.7) |
| DCR per iRECIST, n (%) | 9 (34.6) |
| iDoR in months, median (min, max) | 7.2 (3.5, 10.8) |
| iORR by number of prior therapies, n (%) | |
| ≤2 (18) | 2 (11.1) |
| ≥3 (8) | 0 (0.0) |
| iORR by baseline sum of target lesion, n (%) | |
| ≤100mm (20) | 2 (10.0) |
| >100mm (6) | 0 (0.0) |
| iORR by number of liver lesions, n (%) | |
| ≤1 (11) | 2 (18.2) |
| ≥2 (15) | 0 (0.0) |
| **iDCR by number of liver lesions, n (%)** | |
| ≤1 (11) | 7 (63.6) |
| ≥2 (15) | 2 (13.3) |

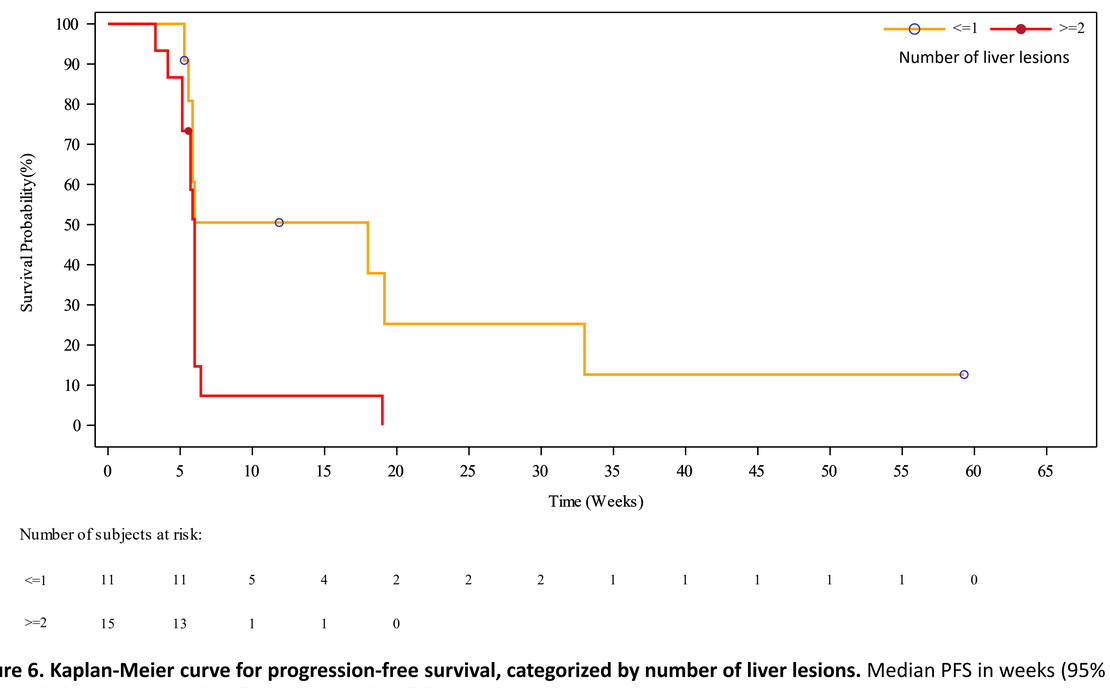



**Figure 6. Kaplan-Meier curve for progression-free survival, categorized by number of liver lesions.** Median PFS in weeks (95% CI): ≤1 = 18.0 (5.6, 33.0), ≥2 = 6.0 (5.1, 6.0), All = 6.0 (5.7, 6.0)

## CONCLUSIONS AND FUTURE DIRECTIONS

- The chemotherapy-free combination of NT-I7 + pembrolizumab was well tolerated in heavily pretreated subjects with CPI-naïve R/R PaC.
- In this remarkably immunologically cold indication, normally associated with complete lack of efficacy to CPI monotherapy (1), the combination of NT-I7 and pembrolizumab achieved an **ORR of 7.7%** and **DCR of 34.6%** per iRECIST.
- A tendency of higher PFS (18 weeks) and significantly higher DCR (54.5%) and iDCR (63.%) was observed in subjects with ≤1 liver lesions.
- NT-I7 and pembrolizumab leads to the preferential proliferation of cytotoxic CD8+ T cells over Tregs, favoring a more immunogenic CD8-to-Treg ratio and tumor infiltration was highest in the subject with a partial response.

**These results support continued evaluation of NT-I7 + pembrolizumab in subjects with CPI-naïve R/R PaC.**

## ACKNOWLEDGMENTS

This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Allison Bierly, PhD and Malcolm Barth, PhD provided assistance in the preparation of this poster.

## REFERENCES

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