Safety, Pharmacokinetics, Pharmacodynamics Profiles and Preliminary Antitumor Activity of Phase 1b/2a Study of NT-I7, a Long-Acting Interleukin-7, plus Pembrolizumab in Patients with Advanced Solid Tumors: The Phase 1b Data Report.

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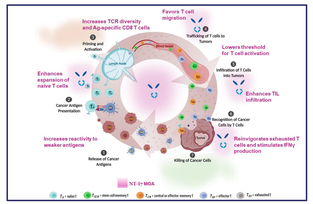
BACKGROUND

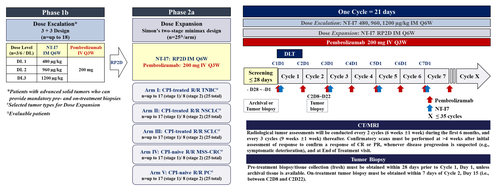
NT-I7 (efineptakin alfa) is the only clinical-stage long-acting human IL-7 and has demonstrated its ability to increase the number and functionality of T cells in peripheral blood. Checkpoint inhibitors (CPIs) have been approved as treatments for multiple solid tumors. The response to CPIs, however, remains low and many patients soon relapse, leading to high unmet medical needs to enhance the antitumor activity of CPIs. Since low levels of T cells in peripheral blood and within the tumor microenvironment (TME) correlate with poor response to CPIs[1], adding NT-I7 to single-agent CPIs may deepen and broaden the antitumor activity of CPIs.

NT-I7 Mechanism of Action (MoA)



STUDY DESIGN

- This is an open-label, phase 1b/2a study in patients with relapsed/refractory (R/R) advanced solid tumors.
- In the phase 1b (Dose Escalation), which followed the 3+3 design, patients with advanced solid tumors received NT-I7 intramuscularly (IM) at 3 dose levels (DLs): 480, 960, and 1200 µg/kg every 6 weeks (Q6W) plus pembrolizumab 200 mg intravenously (IV) Q3W.
- Once the Recommended Phase 2 Dose (RP2D) is determined, the Phase 2a (Dose Expansion) is open to enroll patients with selected tumor types.
- Each cycle is 3 weeks. Tumor assessment is performed every 2 cycles during the first 6 months, and every 3 cycles thereafter.



STUDY OBJECTIVES

Primary objectives

- **Phase 1b**: To determine the safety and tolerability, including determination of the Maximum Tolerated Dose (MTD) and/or the Recommended Phase 2 Dose (RP2D) of NT-I7 in combination with pembrolizumab in patients with R/R advanced solid tumors.
- **Phase 2a**: To assess the preliminary anti-tumor activity of NT-I7 in combination with pembrolizumab in patients with CPI-treated R/R tumors (TNBC, NSCLC, SCLC) and CPI-naïve R/R tumors (MSS-CRC and PC), based on Overall Response Rate (ORR) as assessed by Response Evaluation Criteria in Solid tumors (RECIST v1.1).

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).
- To evaluate the immunogenicity of NT-I7 administered in combination with pembrolizumab in these patient populations.

RESULTS

Subject disposition and characteristics

- As of 05 March 2021, 12 patients were enrolled in the phase 1b: DL1 (n=3), DL2 (n=3), and DL3 (n=6). All 12 patients were evaluable for safety and efficacy (1 patient did not have post-treatment imaging tumor assessment due to clinical progression).
- Median age 58.0 years [range, 43-77]; ECOG PS 0 (50%), PS 1 (50%); all patients had at least 1 prior line of therapy, and 58% of patients had > 4 prior lines of therapy in the recurrent/metastatic setting.

Table 1. Baseline characteristics

Characteristics	Categories	DL1 = 480 µg/kg (n = 3)	DL2 = 960 µg/kg (n = 3)	DL3 = 1200 µg/kg (n = 6)	Total (n = 12)
Age, year, median (range)	-	58.0 (43, 64)	60.0 (59, 77)	53.0 (46, 69)	58.0 (43, 77)
Gender, n(%)	Male	2 (66.7)	1 (33.3)	3 (50.0)	6 (50.0)
ECOG Performance Status, n(%)	0	1	-	5	6
	1	2	3	1	6
Sum of TL, mm, median (range)	-	81.0 (45, 144)	87.0 (68, 106)	102.5 (28, 127)	85.0 (28, 144)
No. of previous lines of therapy for recurrent/metastatic disease, n(%)	1-2	1 (33.3)	1 (33.3)	-	2 (16.7)
	3-4	1 (33.3)	-	2 (33.3)	3 (25.0)
	>4	1 (33.3)	2 (66.7)	4 (66.7)	7 (58.3)

DL: dose level; ECOG: Eastern Cooperative Oncology Group ; TL: target lesion

Safety and tolerability

- MTD was not reached. One DLT of Grade 3 ALT increase was reported in DL3.
- Adverse Drug Reactions (ADRs) occurred in 12 (100%) patients, 4 (33.3%) G1-2 and 8 (66.7%) G3; no G4 or G5 ADRs were reported.
- Most commonly reported ADRs were injection site reaction (n=12, 100%), chills (n=7, 58.3%), pyrexia (n=6, 50%), fatigue (n=5, 41.7%), and peripheral edema (n=5, 41.7%).

Table 2. Summary of Adverse Events

n (%)			DL1 = 480 µg/kg (n = 3)	DL2 = 960 µg/kg (n = 3)	DL3 = 1200 µg/kg (n = 6)	Total (n = 12)
Any TEAE			3 (100)	3 (100)	6 (100)	12 (100)
ADR	ADR by severity	Grade 1	0	0	0	0
		Grade 2	1 (33.3)	1 (33.3)	2 (33.3)	4 (33.3)
		Grade 3	2 (66.7)	2 (66.7)	4 (66.7)	8 (66.7)
		Grade 4-5	0	0	0	0
Most frequently reported ADR						
Injection site reaction			3 (100)	3 (100)	6 (100)	12 (100)
Chills			2 (66.7)	-	5 (83.3)	7 (58.3)
Pyrexia			3 (100)	-	3 (50.0)	6 (50.0)
Fatigue			-	1 (33.3)	4 (66.7)	5 (41.7)
Oedema peripheral			2 (66.7)	1 (33.3)	2 (33.3)	5 (41.7)
ADR resulting in drug discontinuation			0	0	3 (50.0)	3 (25.0)
DLT events			0	0	1 (16.7)	1 (8.3)

ADR: Adverse Drug Reaction; DLT: Dose Limiting Toxicity; TEAE: Treatment-Emergent Adverse Event

Clinical response

- One patient with metastatic mucosal melanoma who had not responded to prior combination of nivolumab and ipilimumab had a rapid, confirmed partial response with 46% tumor reduction after 1 dose of NT-I7 at 480 µg/kg IM and 2 doses of pembrolizumab at 200 mg IV Q3W (Figure 6).
- 4 patients had SD for > 6 weeks.

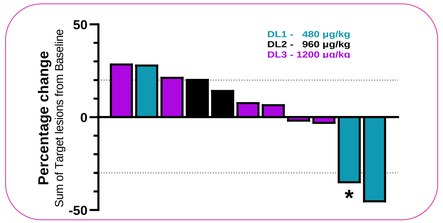


Figure 5. Best percentage change in sum of target lesions from baseline
* This patient had overall assessment of PD due to PD in non-target lesions.

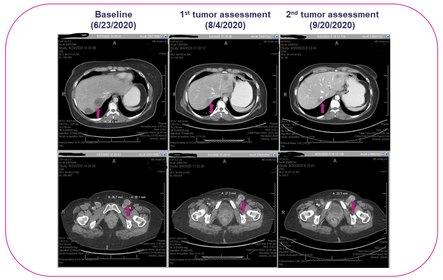


Figure 6. Representative CT scans from the patient with metastatic mucosal melanoma who achieved a confirmed PR

Pharmacokinetics

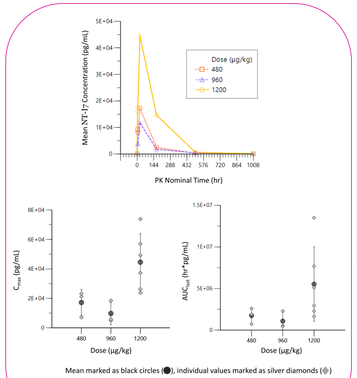


Figure 1. Pharmacokinetics of NT-I7 in combination with pembrolizumab

NT-I7		480 µg/kg	960 µg/kg	1200 µg/kg
C_{max} (pg/mL)	n	3	3	6
	Mean	17195	9734	44544
	SD	8799.0	7559.5	19262.0
T_{max} (hr)	n	3	3	6
	Mean	24	17	24
	SD	0.0	12.7	0.0
AUC_{last} (hr*pg/mL)	n	3	3	6
	Mean	1748045	1084421	5529499
	SD	939186.6	1052077.5	4481930.7
T_{half} (hr)	n	2	1	4
	Mean	267.055	197.633	163.189
	SD	161.523	-	48.246

Pharmacodynamics

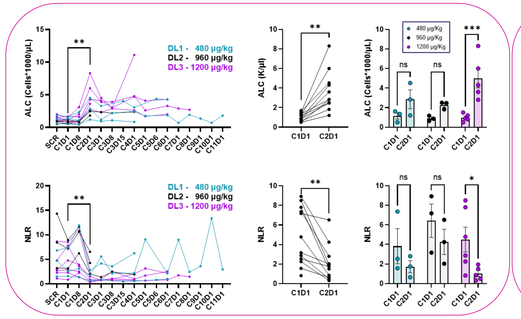


Figure 2. Peripheral dynamics of the absolute lymphocyte counts (ALC) and neutrophil-to-lymphocyte ratio (NLR)

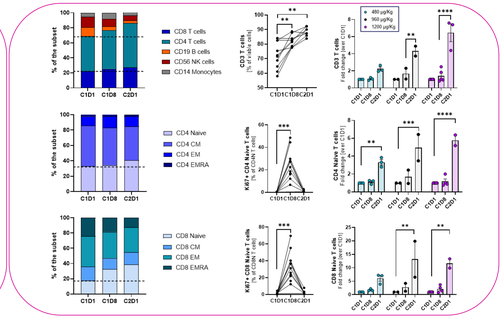
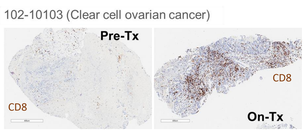


Figure 3. Expansion of both naïve CD4 and naïve CD8 T cells contribute to the dose-dependent significant increase of T cells in peripheral blood

Patient ID	ORR	Lymphocytes (tumor) Pre-Tx	Lymphocytes (tumor) On-Tx	Lymphocytes (stroma) Pre-Tx	Lymphocytes (stroma) On-Tx
102-10101	SD	1	<1	3	20
102-10102	SD	<1	<1	13	16
102-10103	SD	6	20	15	20
101-10106	PD	0	<1	2	7



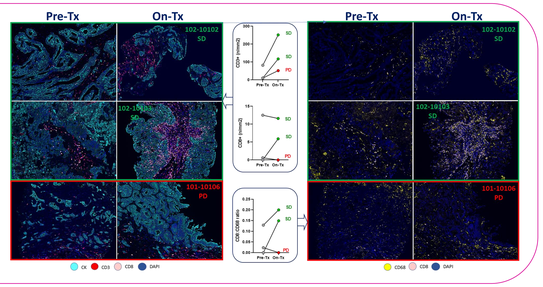


Figure 4. Tumor infiltrating lymphocytes were quantified by IHC (20x) and IF (20x) before (Screening) and after (C2D15) treatment. Significant increases of lymphocytes, CD3 and CD8 T cells, and a more immunoreactive TME (higher CD8 to CD68 ratio) was observed in patients with stable disease (SD) but not in patients with progressive disease (PD).

CONCLUSIONS

- The combination treatment of NT-I7 and pembrolizumab was well tolerated in patients with R/R advanced solid tumors. Only 1 DLT was observed at the highest DL tested (1200 µg/kg). The RP2D was NT-I7 1200 µg/kg IM Q6W plus pembrolizumab 200mg IV Q3W.
- At the highest DL tested (1200 µg/kg), NT-I7 PK results showed mean T_{max} = 24 hours and $T_{1/2}$ = 163.2 hours.
- NT-I7 plus pembrolizumab led to dose-dependent significant increases of ALC and T cell numbers, and significant decreases of the peripheral NLR.
- NT-I7 plus pembrolizumab drastically increased the number of tumor infiltrating lymphocytes, resulting in a more immunoreactive TME in cancer patients.
- Encouraging antitumor activity was observed with the combination NT-I7 plus pembrolizumab in this heavily pretreated patient population.
- These results support continued evaluation of NT-I7 in combination with pembrolizumab in patients with R/R advanced solid tumors.

The phase 2a of the study is enrolling patients with either CPI-treated or CPI-naïve solid tumors (NCT04332653).

ACKNOWLEDGMENTS

Pembrolizumab was provided by Merck & Co., Inc., Kenilworth, NJ, USA.

REFERENCES

1) Delyon J et al. Annals of Oncology, 2013.

Originally published by the American Society of Clinical Oncology. Aung Naing, Jean Fan, Byung Ha Lee, Debashree Basudhar, Shubham Pant, Marya F. Chaney, Cristina Laviada, Cynthia Rajan, Ngocdiep T. Le, and Minal A. Barve: Journal of Clinical Oncology 39, no. 15_suppl (May 20, 2021) 2594-2594.