Abstract # 383978

A phase 1b/2a study of safety and efficacy of NT-I7 in combination with anti-PD-L1 (atezolizumab) in patients with anti-PD-1/PD-L1 naïve or relapsed/refractory (R/R) high-risk skin cancers: The phase 1b 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 (CPI) have been approved as treatment for multiple solid tumors. The response to CPI, however, remains low and many patients soon relapse, leading to high unmet medical needs to enhance the antitumor activity of CPI. Since low levels of T cells in peripheral blood and within the tumor microenvironment (TME) correlate with poor response to CPI[1], the combination treatment with NT-I7 may deepen and broaden their antitumor activity.

This study evaluates, for the first time, the combination of NT-I7 and atezolizumab (atezo) in high-risk skin cancers in both CPI-naïve and CPI-relapsed/refractory patients. In the Phase 1b stage of the study, all but one enrolled patient were CPI-relapsed/refractory.

NCT03901573

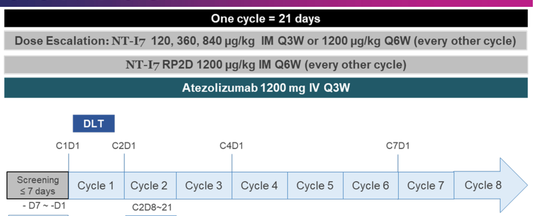
[1]Delyon J et al. Annals of Oncology (2013)

STUDY OBJECTIVES

The objectives of the phase 1b of this study were:

- To evaluate dose-limiting toxicity (DLT).
- To determine the maximum tolerated dose (MTD).
- To determine the recommended phase 2 dose (RP2D).
- To evaluate pharmacokinetics (PK), pharmacodynamics (PD) and preliminary antitumor activity.

STUDY DESIGN



Open-label, phase 1b/2a study in patients with CPI-naïve and CPI-relapsed/refractory high-risk skin cancer.

- In the phase 1b (Dose Escalation), which followed a 3+3 design, patients received NT-I7 intramuscularly (IM) at 4 dose levels (DLs): 120, 360 and 840 every 3 weeks (Q3W) and 1,200 µg/kg every 6 weeks (Q6W) plus atezolizumab 1,200 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.

CONCLUSIONS

- **The combination of a T cell amplifier (NT-I7) and a CPI (atezolizumab) showed favorable safety and anticancer activity in CPI-relapsed/refractory high-risk skin cancer patients.**
- **The recommended phase 2 dose (RP2D) was determined at NT-I7 1,200 µg/kg IM Q6W plus atezolizumab 1,200 mg IV Q3W.**
- **NT-I7 and atezolizumab at higher doses showed promising PFS; the Phase 2a dose expansion is currently enrolling.**
- **NT-I7 and atezolizumab preferentially increase cytotoxic (CD8+) and T helper (CD4+) T cells, and significantly increase the CD8-to-Treg ratio.**
- **NT-I7 and atezolizumab increased the stem-cell memory CD8+ T cell subset (T_{SCM}), which may be associated to better anti-tumor activity.**

RESULTS – CLINICAL DATA

Subject disposition and characteristics

- 15 CPI-relapsed/refractory and 1 CPI-naïve patients were enrolled in the Phase 1b:
  - DL1 – 3 Melanoma
  - DL2 – 2 Melanoma, 1 Merkel cell carcinoma
  - DL3 – 5 Melanoma, 1 Merkel cell carcinoma (CPI-naïve), and 1 Squamous cell carcinoma
  - DL4 – 3 Melanoma
- Median age 65.5 years [range, 46-82]. ECOG PS 0 (25%); 1(62.5%) and 2(12.5%).

Characteristics	Categories	DL1 120 µg/kg (n = 3)	DL2 360 µg/kg (n = 3)	DL3 840 µg/kg (n = 7)	DL4 1200 µg/kg (n = 3)	Total (n = 16)
Age (years); median (range)		70.0 (66, 75)	67.0 (63, 82)	60.0 (46, 80)	61.0 (58, 69)	65.5 (46, 82)
Gender; n (%)	Male	2 (66.7)	2 (66.7)	4 (57.1)	1 (33.3)	9 (56.2)
	Female	1 (33.3)	1 (33.3)	3 (42.9)	2 (66.7)	7 (43.8)
ECOG Performance status; n (%)	0	2 (66.7)	0	2 (28.6)	0	4 (25.0)
	1	0	3 (100)	4 (57.1)	3 (100)	10 (62.5)
	2	1 (33.3)	0	1 (14.3)	0	2 (12.5)
Prior therapies; n (%)	Adjuvant	1 (33.3)	3 (100)	5 (71.4)	2 (66.7)	11 (68.8)
	Neoadjuvant	0	2 (66.7)	0	0	2 (12.5)
	Palliative	0	0	0	1 (33.3)	1 (6.3)
	Therapeutic	2 (66.7)	0	2 (28.6)	1 (33.3)	5 (31.3)
	Other	1 (33.3)	0	0	0	1 (6.3)
Previous exposure to CPI; n (%)		3 (100)	3 (100)	6 (85.7)	3 (100)	15 (93.8%)
Type of cancer diagnosed; n (%)	Melanoma	3 (100)	2 (66.7)	5 (71.4)	3 (100)	13 (81.3)
	Merkel cell carcinoma	0	1 (33.3)	1 (14.3)	0	2 (12.5)
	Squamous cell carcinoma	0	0	1 (14.3)	0	1 (6.2)

Table 1. Subject characteristics

Safety and tolerability

- MTD was not reached. One DLT of G3 confusion and G3 AST at DL3, total 7 subjects including one dropped off were enrolled at DL3. No DLTs at DL4 were reported. The RP2D was determined as NT-I7 1,200 ug/kg Q6W plus atezolizumab 1,200 mg Q3W.
- Adverse Drug Reactions (ADRs) occurred in 16 (100%) patients, 11 (68.8%) G1-2 and 5 (31.3%) G3; no G4 or G5 ADRs were reported.
- ADR resulting in NT-I7 discontinuation was observed in 3 (42.9%) patients at DL3.

Characteristics	Category	DL1 120 µg/kg (n = 3)	DL2 360 µg/kg (n = 3)	DL3 840 µg/kg (n = 7)	DL4 1200 µg/kg (n = 3)	Total (n = 16)
Any TEAE		3 (100)	3 (100)	7 (100)	3 (100)	16 (100)
ADR by Severity	Grade 1	0	1 (33.3)	1 (14.3)	1 (33.3)	3 (18.8)
	Grade 2	2 (66.7)	2 (66.7)	2 (28.6)	2 (66.7)	8 (50.0)
	Grade 3	1 (33.3)	0	4 (57.1)	0	5 (31.3)
	Grade 4-5	0	0	0	0	0
Most frequently reported ADRs						
Injection site reaction		1 (33.3)	1 (33.3)	3 (42.9)	2 (66.7)	7 (43.8)
Fatigue		0	1 (33.3)	3 (42.9)	2 (66.7)	6 (37.5)
Oedema peripheral		1 (33.3)	1 (33.3)	2 (28.6)	0	4 (25.0)
Pruritus		0	0	3 (42.9)	1 (33.3)	4 (25.0)
AA Transferase increased		0	0	0	3 (100)	3 (18.8)
Decreased appetite		0	0	2 (28.6)	1 (33.3)	3 (18.8)
Nausea		0	0	2 (28.6)	1 (33.3)	3 (18.8)
AE resulting in NT-I7 discontinuation		0	0	3 (42.9)	0	3 (18.8)

ADR = adverse drug reaction, TEAE = treatment emergent adverse event and AE = adverse event

Table 2. Summary of related adverse events

Clinical Response

ORR	DL1 120 µg/kg (n = 3)	DL2 360 µg/kg (n = 3)	DL3 840 µg/kg (n = 7)	DL4 1200 µg/kg (n = 3)	Total (n = 16)
Complete Response (CR)	0	0	0	0	0
Partial Response (PR)	0	0	0	0	0
Stable Disease (SD)	3 (100)	1 (33.3)	5 (71.4)	2 (66.7)	11 (68.8)
Progressive Disease (PD)	0	2 (66.7)	2 (28.6)	1 (33.3)	5 (31.3)
Complete Response (iCR)	0	0	0	0	0
Partial Response (iPR)	0	0	1 (14.3)	0	1 (6.3)
Stable Disease (iSD)	3 (100)	1 (33.3)	4 (57.1)	3 (100)	11 (68.8)
Progressive Disease (iPD)	0	2 (66.7)	2 (28.6)	0	4 (25.0)

Table 3. Objective response rate (ORR) per RECIST v1.1 and per Immune-related Response Criteria (irRC).

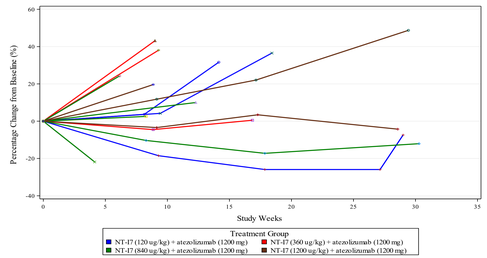


Figure 1. Spider Plot for Individual Change of Target Lesions from Baseline

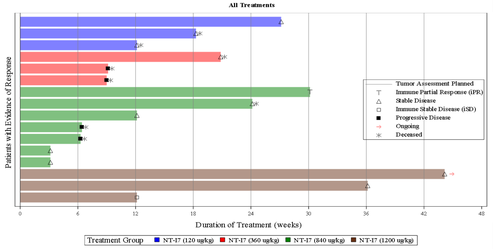


Figure 2. The median duration of treatment (weeks) was 18.29, 9.14, 6.43 and 36.14 at DL1, DL2, DL3 and DL4, respectively.

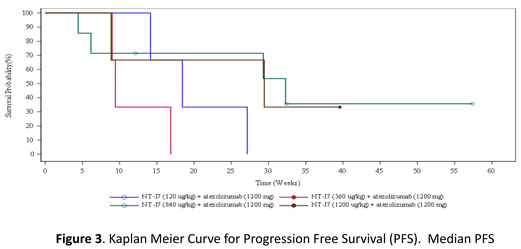
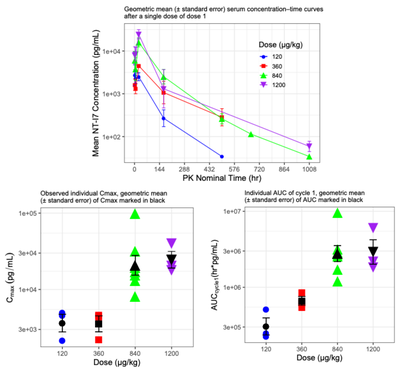


Figure 3. Kaplan Meier Curve for Progression Free Survival (PFS). Median PFS (weeks) was 18.4, 9.4, 32.3 and 29.4 for the DL1, DL2, DL3 and DL4 dose levels of NT-I7, respectively.

RESULTS – BIOMARKER DATA

NT-I7 pharmacokinetics



Doses	q25 (h) Lower Quartile	$T_{1/2}$ (h) Median	q75 (h) Upper Quartile
Doses-Pooled*	**72.2**	**112.4**	**195.4**
DL1 120 µg/kg	110.0	156.3	281.8
DL2 360 µg/kg	93.9	115.9	155.1
DL3 840 µg/kg	75.4	141.1	260.2
DL4 1,200 µg/kg	87.0	106.4	107.6

* Preliminary Analyses

Figure 4. Pharmacokinetics (PK) of NT-I7 in combination with atezo.

T cells and Tregs

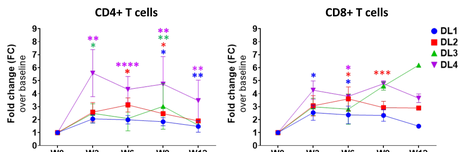


Figure 7. CD4+ and CD8+ T cells NT-I7/atezo treatment induced expansion of T cells after one administration and the increase was maintained by repeat dosing until the end of treatment, regardless of the dosing frequency (DL1-3 NT-I7 Q3W and DL4 NT-I7 Q6W). DL4 (1,200 µg/kg NT-I7 Q6W) had the most significant increase; 5X over baseline. DL1 = 120 µg/kg; DL2 = 360 µg/kg; DL3 = 840 µg/kg; DL4 = 1,200 µg/kg. Mean ± SEM; *p < 0.05; **p<0.01; ***p< 0.001; ****p<0.0001

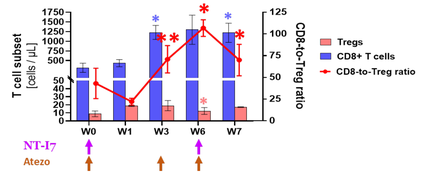


Figure 8. Tregs. NT-I7/atezo treatment at DL4 (1,200 µg/kg NT-I7 Q6W) differentially increased CD8+ T cell levels over Treg levels, leading towards a significant increase of the CD8-to-Treg ratio by week 3, though an earlier expansion (W1) of Treg cells was observed. Treatment had no effect on overall CD8:CD4 ratios (data not shown). Mean ± SEM; *p < 0.05; **p< 0.01

Lymphocytes and Neutrophils

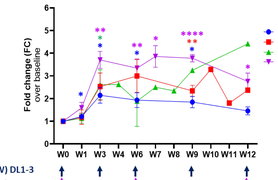


Figure 5. Absolute Lymphocyte Counts (ALC) NT-I7/atezo induced expansion of ALC after one administration and the increase was maintained by repeat dosing until the end of treatment, regardless of the dosing frequency. (DL1-3 NT-I7 Q3W and DL4 NT-I7 Q6W). DL4 (1,200 µg/kg NT-I7 Q6W) had the most significant increase; ~4X over baseline. Mean ± SEM; DL1 = 120 µg/kg; DL2 = 360 µg/kg; DL3 = 840 µg/kg; DL4 = 1,200 µg/kg. * p< 0.05; **p<0.01; ***p< 0.001; ****p<0.0001

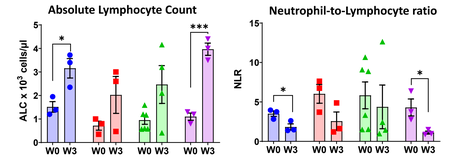


Figure 6. Neutrophil-to-Lymphocyte ratios were significantly decreased by NT-I7 and atezo treatment by week 3. While all dose levels increased ALC, we observed a more significant decrease of the NLR in DL4 (1,200 µg/kg NT-I7 Q6W). DL1 = 120 µg/kg; DL2 = 360 µg/kg; DL3 = 840 µg/kg; DL4 = 1,200 µg/kg. Mean ± SEM; *p < 0.05; ***p< 0.001

Stem-cell memory CD8+ T cells

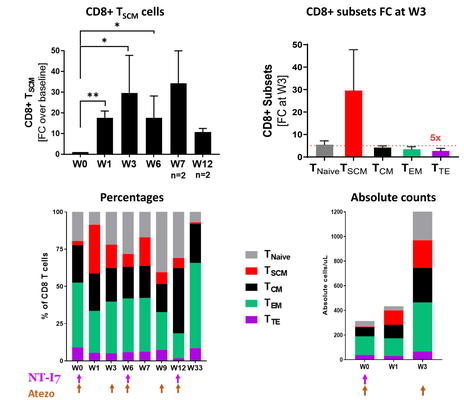


Figure 9. Stem-cell memory CD8+ T cells (T_{SCM}), a CD8+ T cell subset with self-renewal capabilities, was most significantly increased after one dose of NT-I7 and atezo and peaked by week 3 (DL4 = 1,200 µg/kg, Q6W, *upper left panel*). The CD8+ T_{SCM} subset increased ~30X over baseline, while the other CD8+ T cell subsets increased by ~5X (*upper right panel*). Interestingly, the more exhausted T_{TE} subset showed lower expansion over time, suggesting that the NT-I7 and atezo combination may differentially increase the least differentiated subsets and, especially, the CD8+ T_{SCM} subset (*lower panel*). Mean ± SEM; **p<0.01

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