#1,010: A phase I/IIa randomized trial evaluating safety and efficacy of SNK01 (autologous natural killer cells) plus pembrolizumab in patients with stage IV non-small cell lung cancer (NSCLC) who have failed first-line platinum-based therapy

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BACKGROUND

- Despite the increased promise of anti-PD-1 therapy in treatment of NSCLC, the overall response rate is approximately 30% with up to 15% of grade 3 or higher adverse events (AEs).
- Growing evidences have suggested that natural killer (NK) cells also contribute to antitumor immune response mediated by PD-1 blockade.
- SNK01 is a novel non-genetically modified autologous NK cells with enhanced tumoricidal effects.
- This study was performed to evaluate the safety and efficacy of SNK01 plus pembrolizumab in patients with previously treated advanced NSCLC.

PATIENTS & METHODS

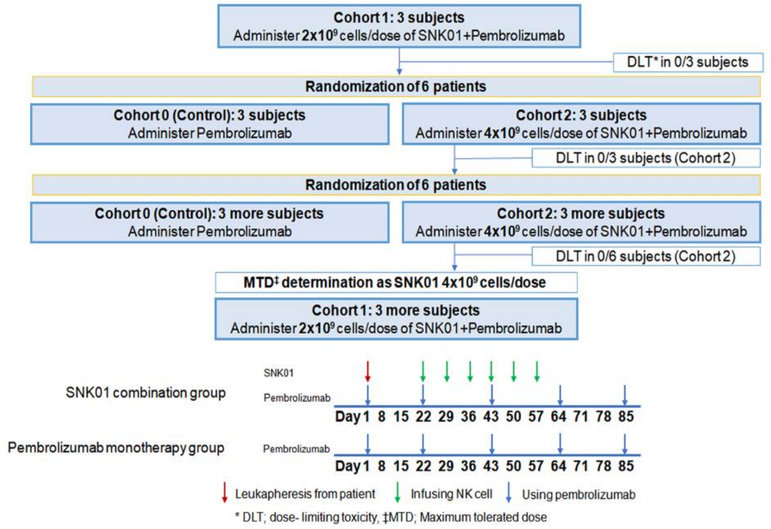
1. Patient population

- A total of 18 patients with Stage IV NSCLC patients (PD-L1 TPS of ≥ 1%) who failed prior frontline platinum-based therapy were planned to be enrolled.

2. Study design & procedure

- Study groups: Patients in Cohort 1 and 2 received pembrolizumab plus SNK01 of 2 x10^9 and 4 x 10^9 cells/dose, respectively, for 6 times. Patients in Cohort 0 (Control) received regular therapy with pembrolizumab (200 mg) of a 3-week cycle until the occurrence of tumor progression or unacceptable toxicity.

Figure 1. Study design & procedure



3. Outcome measures

- Primary endpoint: Safety
- Secondary endpoint:
  - ✓ Efficacy: objective response rate (ORR), progression-free survival (PFS), 1-year survival rate, etc.
  - ✓ NK cell activity (via NK Vue™ kit, NKMAX Co., Ltd.), etc.

RESULTS

1) Safety

- Twenty patients were included for safety analysis. Two patients allocated to each Cohort 1 and 2 discontinued treatment prior to receiving the first dose of SNK01 due to CTCAE Grade 3 AE after pembrolizumab treatment (Myalgia and pneumonia, respectively) and were analyzed as the pembrolizumab monotherapy group.
- The treatment was well tolerated throughout the trial. No adverse events related to SNK01, as well as any new safety signals in the SNK combination group, were observed.
- Since no dose-limiting toxicity (DLT) was observed, maximum tolerated dose (MTD) was determined as SNK01 4x10^9 cells/dose.

Table 2. Adverse events reported in study patients (N=20)

Type of adverse event	Pembrolizumab only (%, N=8)		SNK01 + Pembrolizumab (%, N=12)	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5
All AEs	8 (100.0%)	2 (25.0%)	12 (100.0%)	1 (8.3%)
Treatment-related AEs				
Pembrolizumab-related AEs	6 (75.0%)	1 (12.5%)	11 (91.7%)	0 (0%)
SNK01-related AEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treatment-unrelated AEs	2 (25%)	1 (12.5%)	1 (8.3%)	1 (8.3%)

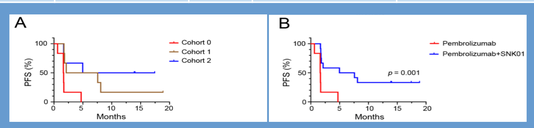
2) Efficacy

- Eighteen patients were included for efficacy analysis.
- The ORR for the total population was 27.8% (5/18) with all partial response (PR). The ORR for the SNK combination group (41.7%) was superior to that for the pembrolizumab monotherapy group (0%).
- The median PFS of the SNK combination treatment was longer than that of the pembrolizumab monotherapy (6.2 vs. 1.6 months, p=0.001, with a median follow-up duration of 17.5 months)
- One-year survival rate tended to be higher for the SNK combination treatment than the pembrolizumab monotherapy (66.7% vs. 50.0%, p=0.39).
- The efficacy outcomes tend to be better in patients infused 4 x 10^9 cells/dose than in patients infused 2 x 10^9 cells/dose

Table 3. Comparison of efficacy outcomes between two treatment groups (N=18)

	Pembrolizumab only (%, N=6)	SNK01 + Pem (%, N=12*)	*p*-value	Cohort 1 SNK01 2x10^9 (%, N=6)	Cohort 2 SNK01 4x10^9 (%, N=6)
ORR	0/6 (0%)	5/12 (41.7%)	0.11	2/6 (33.3%)	3/6 (50.0%)
Median PFS	1.6 months (95% CI 0.6-4.7)	6.2 months (95% CI 1.4-)	0.001	4.8 months	9.4 months
1-year survival rate	50.0%	66.7%	0.39	50.0%	83.3%

Figure 4. PFS analysis.



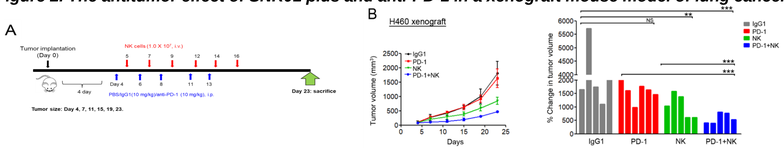
CONCLUSIONS

- Based on enhanced antitumor function of pembrolizumab plus SNK01 over pembrolizumab only in a xenograft mouse model of lung cancer, we performed a clinical study of pembrolizumab plus SNK01 therapy. Improved median PFS and ORR were observed in patent group of the combination therapy compared with pembrolizumab monotherapy in PD-L1+ NSCLC patients.
- Our result suggests possible clinical benefit of pembrolizumab plus SNK01 therapy for PD-L1+ NSCLC patient and warrants further investigations in clinical trials with a large number of sample sizes for further confirmation.

1. Animal model study

- Anti PD-1 plus SNK01 therapy resulted in the enhanced tumor growth inhibition in a xenograft mouse model of lung cancer.

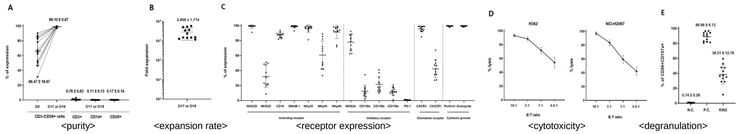
Figure 2. The antitumor effect of SNK01 plus and anti-PD-1 in a xenograft mouse model of lung cancer



2. Investigational SNK01 product

- Clinical-grade SNK01 with high quantity, purity, and cytotoxicity against cancer cell lines were produced from peripheral blood mononuclear cells (PBMCs) of single apheresis via ex vivo expansion using feeder cells and cytokines.

Figure 3. Characteristics of SNK01



3. Clinical study

- Twenty patients who had a PD-L1 TPS of ≥1% and failed prior frontline platinum-based therapy were enrolled (Feb 2019 – Apr 2020).

Table 1. Baseline clinical characteristics of study patients (N=20)

Characteristics	Pembrolizumab only (%, N=6)	SNK01 + Pembrolizumab (%, N=14)	*p*-value
Age (years)			
Median, range	56.5, 49-70	62, 49-73	
≥ 65	1 (16.7%)	6 (42.9%)	0.35
Sex			0.12
Male	2 (33.3%)	11 (78.6%)	
Female	4 (66.7%)	3 (21.4%)	
Smoking status			0.12
Current smoker	0 (0%)	0 (0%)	
Ex-smoker	4 (66.7%)	11 (78.6%)	
Never smoker	2 (33.3%)	3 (21.4%)	
ECOG* performance status			
0	0 (0%)	0 (0%)	
1	6 (100.0%)	14 (100.0%)	
Histology			0.99
Adenocarcinoma	6 (100.0%)	13 (92.9%)	
Squamous cell carcinoma	0 (0%)	0 (0%)	
Pleomorphic carcinoma	0 (0%)	1 (7.1%)	
PD-L1 22c3 TPS**			
Median, range(%)	1, 1-15	25, 1-100	
≥ 50%	0 (0%)	6 (42.9%)	0.12
EGFR status			0.02
Wild type	1 (16.7%)	11 (78.6%)	
Mutant	5 (83.3%)	3 (21.4%)	
Previous lines of chemotherapy			0.01
1	0 (0%)	10 (71.4%)	
2	2 (33.3%)	2 (14.3%)	
≥ 3	4 (66.7%)	2 (14.3%)	
NK cell activity (IFN-γ, pg/mL)			
Median, range	972.4 (102.8-1639.0)	1570.5 (145.0-3563.2)	

* ECOG: Eastern Cooperative Oncology Group; **TPS: Tumor Proportion Score