#3037: A phase I/IIa randomized trial evaluating safety and efficacy of SNK01 (non-genetically modified autologous natural killer cells with enhanced cytotoxicity) 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 lung cancer, the overall response rate is approximately 30% with up to 15% of grade 3 or higher adverse events (AEs).
- Growing evidence has 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 cell with enhanced tumoricidal effects against several lung cancer cell lines.
- We evaluated safety and efficacy of SNK01 in combination with Pembrolizumab.

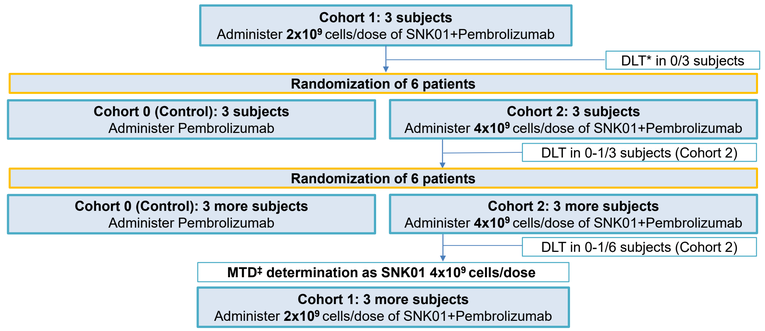
PATIENTS & METHODS

Patient population

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

Study design

Figure 1. Study design (N=18)



* DLT; dose- limiting toxicity, ‡MTD; Maximum tolerated dose

Procedures

- Cohort 0: Pembrolizumab was administered at the dose of 200mg every 3 weeks until progression or unacceptable toxicity
- Cohort 1/2: SNK01 was administered intravenously at 2 or 4x10^9 cells/dose weekly for 6 weeks. Pembrolizumab was simultaneously administered as below schedule.

Table 1. Administration schedule of study drug

Week	W1	W4	W5	W6	W7	W8	W9	W10	W13	...	W52	Follow-up every 3 months
Pembrolizumab	●	●			●			●	●	Every 3 wks	End of study visit	
SNK01		●	●	●	●	●	●					

Outcomes

- Primary endpoint: Safety
- Secondary endpoint:
  - ✓ Efficacy, represented by objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and time to progression (TTP)
  - ✓ Quality of life (QoL) (by EORTC QLQ-C30 and EORTC QLQ-LC13 Assessment)
  - ✓ NK cell activity (via Vue^{TM} kit, ATGen, Seongnam, Korea, by detecting NK cell-secreted INF-γ level)
  - ✓ All analyses were done with per-protocol (PP) approach.

RESULTS

Efficacy

- The ORR, median PFS and median OS evaluated in SNK01+Pembrolizumab and Pembrolizumab alone group are described in Table 4.
- Especially, **ORR was significantly higher in patients with SNK01 4x10^9 cells/dose** (50% vs. 33% vs. 0% in 4x10^9 cells/dose, 2x10^9 cells/dose of SNK01 combination, and Pembrolizumab alone group, respectively, *p*=0.03).

Table 4. Comparison of clinical response between two groups after treatment (N=20)

	Pembrolizumab only (%, N=8)	SNK01 + Pembrolizumab (%, N=12)	*p*-value
ORR	0/8 (0%)	4/9* (44.4%)	0.10
PR	0/8	4/9	
SD	3/8	2/9	
PD	5/8	3/9	
Median PFS	1.6 months (95% Confidence Interval [CI] 1.6-1.7)	8 months (95% CI 0.0-19.5)	0.04
Median OS	6.0 months	Not Reached	0.04

*The ORR was evaluated in 9 patients who received SNK01+Pembrolizumab and underwent at least 1 disease evaluation.

- Median difference in QoL score (by EORTC QLQ) between before and after treatment tended to be smaller in SNK01+Pembrolizumab group (n=9) than Pembrolizumab alone group (n=8) (+2/176 vs. +10.5/176, p=0.21).

CONCLUSIONS

- These preliminary results demonstrated that **combination therapy of SNK01 and Pembrolizumab was safe without SAE and DLT.**
- It also showed **promising efficacy including tumor response and survival and QoL, compared to Pembrolizumab monotherapy** in Stage IV NSCLC patients who have failed prior platinum-based treatment.
- Considering that the only Pembrolizumab-associated AE in SNK01+Pembrolizumab group occurred 5 months after completion of SNK01 administration, additional study is needed for the possibility that SNK01 combination may control toxicities of immune-checkpoint inhibitor.
- PD-L1 expression did not correlate with response.
- Fully updated data and analysis including biomarker study results will be presented after the trial ends.
- Phase IIb study with a larger number of patients is needed to confirm the efficacy and safety of combination therapy with SNK01 and Pembrolizumab.

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- A total of 20 patients have been enrolled and 12 have completed treatment up to date. Among 9 patients which completed SNK01 administration (3 patients in Cohort 1 and 6 in Cohort 2), all 6 doses of SNK01 were administered in 6 patients, and in the remaining 3, partial SNK01 doses were administered due to progressive disease (PD).
  - ✓ Since 2 patients (one patient in cohort 1 and the other in cohort 2) discontinued the scheduled treatment before initiation of SNK01 due to pembrolizumab-associated AE, two more patients were enrolled to the trial.
- Baseline characteristics and NK cell activities are shown in table 2 below.
  - ✓ Median age was 60 (49-73)

Table 2. Baseline clinical characteristics of study patients (N=20)

Characteristics	Pembrolizumab only (%, N=8)	SNK01 + Pembrolizumab (%, N=12)	*p*-value
Age (years)			
Median, range	60.5, 49-70	60, 49-73	
≥ 65	2 (25.0%)	5 (41.7%)	0.64
Sex			0.36
Male	4 (50.0%)	9 (75.0%)	
Female	4 (50.0%)	3 (25.0%)	
ECOG* performance status			
0	0 (0%)	0 (0%)	
1	8 (100.0%)	12 (100.0%)	
Histology			0.99
Adenocarcinoma	8 (100.0%)	11 (91.7%)	
Squamous cell carcinoma	0 (0%)	0 (0%)	
Pleomorphic carcinoma	0 (0%)	1 (8.3%)	
PD-L1 22c3 TPS**			
Median, range	3, 1-90	17.5, 1-100	0.27
Previous lines of chemotherapy			0.07
1	2 (25.0%)	8 (66.7%)	
2	2 (25.0%)	2 (16.7%)	
≥ 3	4 (50.0%)	2 (16.7%)	
NK cell activity (pg/mL)			
Median, range	657.5 (102.8-1639.0)	1680 (388.0-3563.2)	0.04

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

Safety

- Among patients who have received SNK01+Pembrolizumab (n=12), **no grade 3 or higher AE was observed**. Only one patient experienced grade 2 pneumonitis due to Pembrolizumab (Table 3).
- In patients who received Pembrolizumab alone, grade 2 pneumonia and grade 3 arthralgia and myalgia were observed.
- Because there has been **no dose-limiting toxicity (DLT) observed, maximum tolerated dose (MTD) was determined as SNK01 4x10^9 cells/dose.**

Table 3. Adverse events reported in study patients (N=20)

Adverse Event	Pembrolizumab only (%, N=8)		SNK01 + Pembrolizumab (%, N=12)		*p*-value*
	Any Grade	Grade 3-5	Any Grade	Grade 3-5	
Arthralgia	1 (12.5%)	1 (12.5%)	0 (0%)	0 (0%)	0.40
Myalgia	1 (12.5%)	1 (12.5%)	0 (0%)	0 (0%)	0.40
Pneumonitis	0 (0%)	0 (0%)	1 (8.3%)	0 (0%)	0.99
Pneumonia	1 (12.5%)	0 (0%)	0 (0%)	0 (0%)	0.40

* *p*-value for number of patients with 'any grade' adverse event between both administration group