Safety and efficacy of allogeneic natural killer cells in combination with pembrolizumab in patients with chemotherapy-refractory biliary tract cancer: A multicenter open-label phase 1/2a trial

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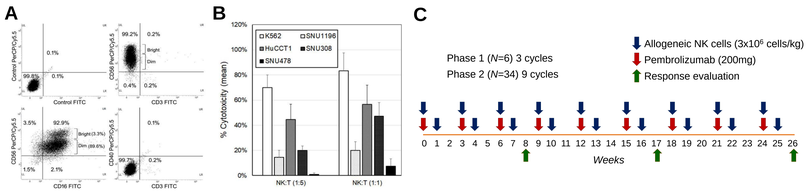
INTRODUCTION

- **Biliary tract cancers (cholangiocarcinoma and gallbladder carcinoma)**
  - One of the most fatal and incurable cancer (5-year survival ≤ 10%)
  - More than **75%** of patients with these cancers diagnosed in the **advanced stages**
  - Treatment of choice for unresectable and metastatic biliary tract cancers
    : **Systemic chemotherapy** (preferred regimen: **durvalumab ± gemcitabine + cisplatin**)
- **Limited effective subsequent-line therapies in gemcitabine-refractory patients**
  - **No category 1 recommended regimen**
  - Subsequent-line immune checkpoint inhibitors(ICIs), **effective but limited**
    - Pembrolizumab (anti-PD-1 inhibitor) monotherapy
      :: objective response rate(ORR) **3-13%**, median progression free survival(PFS) **1.5 months**
  - Urgent need for **combinational therapy** overcoming the limited efficacy of ICIs

STUDY AIM & DESIGN

- We designed a **multicenter open-label phase 1/2a clinical trial** to assess the safety and efficacy of **allogeneic NK cells ("SMT-NK") in combination with pembrolizumab** in patients with gemcitabine-refractory biliary tract cancer (ClinicalTrials.gov identifier: *NCT03937895*).

Figure 1. Characteristics of SMT-NKs(A-B) and clinical trial protocol(C). Manufactured SMT-NKs showed high frequency of $CD56^{dim}CD16^{pos}$ NK cells(**B**) and brilliant cytotoxic activities(**C**).



RESULTS

Figure 2. Trial profile of phase 1(A) and phase 2a(B). One patient showed a stable disease after completion of the phase 1 trial and enrolled in the phase 2a trial. AE, adverse event; SAE, serious adverse event.

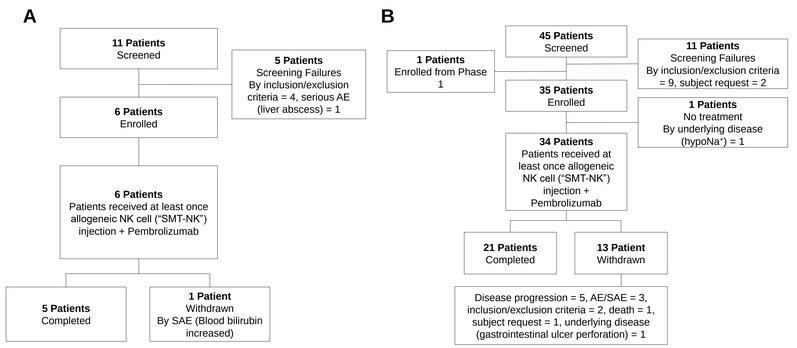


Table 1. ORR and disease control rate(DCR)

	Full-analysis set (*N*=23)	Per-protocol set (*N*=8)
Tumor response		
CR	0 (0.0)	0 (0.0)
PR	4 (17.4)	4 (50.0)
SD	3 (13.0)	1 (12.5)
PD	16 (69.6)	3 (37.5)
Objective response rate[a]	**4 (17.4)**	**4 (50.0)**
[95% CI]	[5.0% – 38.8%]	[15.7% – 84.3%]
Disease control rate[b]	**7 (30.4)**	**5 (62.5)**
[95% CI]	[13.9% – 54.9%]	[24.5% – 91.5%]

[a]CR+PR, [b]CR+PR+SD.
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.
Data are presented as n (%) unless otherwise noted.

Figure 3. Median PFS

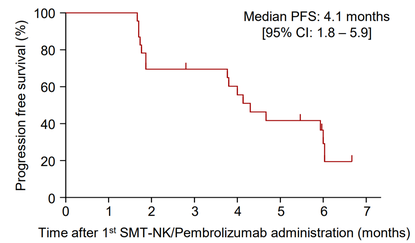


Figure 4. Best changes in the sizes of the target lesions from the baseline(A) and time to progression(B). The yellow bars indicate patients with a combined positive score (CPS) < 5%, orange bars CPS 5–29%, and red bars CPS > 30%. The purple bar indicates a patient who lost PMS2. * The patient completed 27 cycles of treatment.

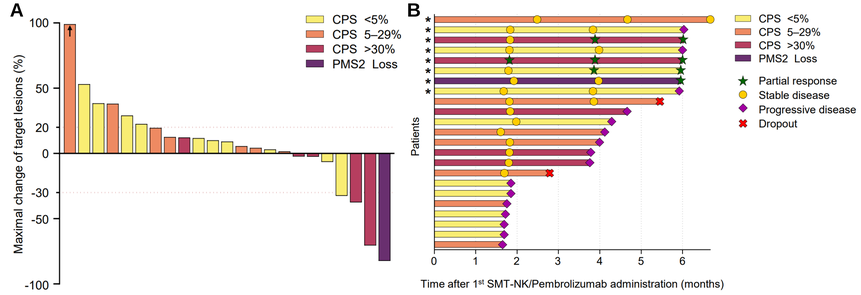
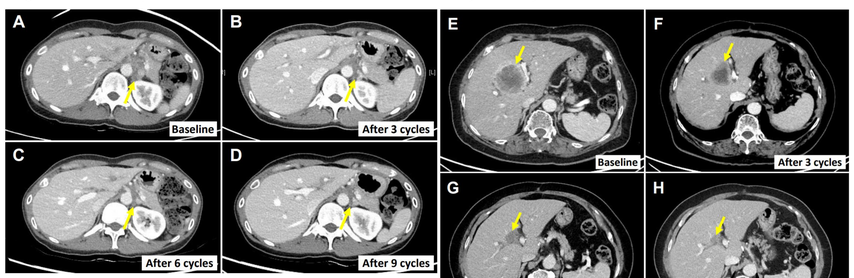


Figure 5. Representative CT images for cancer regression in two patients. (**A–D**) Left infrarenal lymph node in patient E0107. (**E–H**) The main hepatic metastasis lesion in patient E0217. Yellow arrows indicate the target lesions. Response evaluations were performed after every three cycles.



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Beyond the phase 2a clinical trials…

- After completion of the phase 2a trial, based on the remarkable success in treating advanced biliary tract cancer patients, **SMT-NK and pembrolizumab combinational therapy had been approved for therapeutic purposes** in five patients who showed favorable response to this combinational therapy by the **Ministry of Food and Drug Safety, Korea.**
- **Intriguingly, 3 of them (60%) showed complete response after 30 doses administration of SMT-NKs.**

Table 2. Treatment response of SMT-NK and pembrolizumab as a therapeutic purpose in patients who showed favorable response in phase 2a clinical trial.

No.	Tumor response after completion of phase 2a trial (RECIST)	Target lesion change after completion of phase 2a trial	Total doses of SMT-NK administered	Final response
1	PR	-82.9%	32	PR
2	SD	+1.6%	31	★CR
3	PR	-37.5%	32	★CR
4	PR	-32.5%	30	PD
5	PR	-70.4%	33	★CR

Ongoing phase 2b clinical trial

- Currently, a **multicenter, randomized, placebo-controlled, open-label, phase 2b clinical trial is ongoing** to evaluate the antitumor activity of combination therapy of SMT-NK and pembrolizumab versus pembrolizumab monotherapy in patients with gemcitabine-refractory advanced biliary tract cancer (ClinicalTrials.gov identifier: *NCT05429697*).
- The total target number of patients is **128** (64 each for the control and test group). Unless the patient drop out or finish the trial earlier due to the poor response, the patients will receive a total of **48 doses of SMT-NK and 24 doses of pembrolizumab** or **24 doses of pembrolizumab alone.**

Table 3. Current status of phase 2b trial

Status	Number
Screening	4
Screened	58
Screening Failure	10
Enrollment	**48**
End-of-trial	29
Ongoing	19

Table 4. ORR and DCR

	Test group (*N*=14)	Control group (*N*=18)
Tumor response		
CR	★1 (7.1)	0 (0.0)
PR	3 (21.4)	2 (11.1)
SD	3 (21.4)	5 (27.7)
PD	7 (50.0)	11 (61.1)
Objective response rate[a]	**4 (28.6)**	**4 (11.1)**
Disease control rate[b]	**7 (50.0)**	**7 (38.9)**

[a]CR+PR, [b]CR+PR+SD.
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
Data are presented as n (%).

SUMMARY & CONCLUSION

- SMT-NKs plus pembrolizumab resulted in **no severe AEs** directly related to the drug combination. The combination therapy also exerted **antitumor activity with improved efficacy** compared to recent monotherapy with pembrolizumab in patients with advanced biliary tract cancer.
- **It is very encouraging** to report **several patients showing complete response to SMT-NK and pembrolizumab combination therapy** after 20-30 doses of SMT-NKs **despite the use of combination therapy as a subsequent treatment** after the failure of gemcitabine-based primary chemotherapy.