AFM24 in Combination With Autologous NK Cells (SNK01) in Patients With Advanced/Metastatic Epidermal Growth Factor Receptor (EGFR) Expressing Solid Tumors: Initial Results From the Phase 1 Dose Escalation Study

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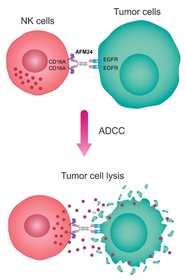
BACKGROUND

- Natural killer (NK) cells are key components of the innate immune system, responsible for eradication of transformed cells by antibody-dependent cellular cytotoxicity (ADCC)[1]
- Autologous NK cell transfer is a promising immunotherapy that enhances the specificity and anti-tumor activity of *ex vivo* expanded, highly pure NK cells harvested from a patient[2]
- The activity of therapeutic NK cells can be enhanced in combination with innate cell engagers (ICE)[3,4]

AFM24 & SNK01 COMBINATION THERAPY

- AFM24 is a tetravalent, bispecific ICE that simultaneously binds CD16A on NK cells, and EGFR frequently overexpressed on solid tumor cells, redirecting and enhancing antitumor ADCC[5]
- A Phase 1/2a AFM24 monotherapy study (NCT04259450) in patients with EGFR$^+$ solid tumors revealed a well-managed safety profile and promising clinical activity at the recommended Phase 2 dose (RP2D) of 480 mg[7]; correlative science data revealed AFM24-mediated stimulation of the innate immune response, and indirect activation of the adaptive immune response[8]
- SNK01 is an autologous, adoptive NK cell-derived cellular immunotherapy technology that can produce large scale *ex vivo* expanded and activated autologous NK cells (1,000–10,000-fold expansion of NK cells with >95% cell purity), even in patients with low primary NK cell counts; the resulting NK cells produced are also characterized by high CD16 expression (90%)[9–12]
- SNK01 has demonstrated a tolerable toxicity profile, no risk of graft versus host disease, and promising antitumor activity as a single agent and in combination therapies in patients with rapidly progressive solid tumors[9–12]

AFM24 mechanism of action



Simultaneous engagement of EGFR and CD16A with AFM24 facilitates potent, anti-EGFR$^+$ tumor ADCC

OBJECTIVES

This study was an open-label, multicenter, proof-of-concept dose escalation (Phase 1) and dose expansion (Phase 2a) study to assess the safety, tolerability, and preliminary efficacy of AFM24 with SNK01 autologous NK cells (NCT05099549)

STUDY DESIGN – PHASE 1: DOSE ESCALATION

Primary endpoint: To establish the maximum-tolerated dose (MTD) and/or the RP2D of AFM24 in combination with SNK01

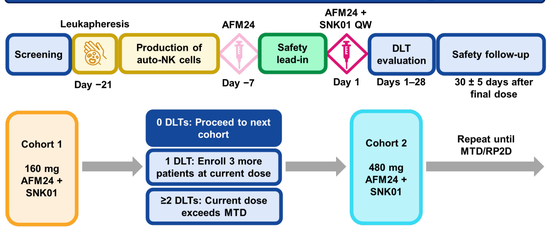
Secondary endpoints: To evaluate the safety, tolerability, preliminary efficacy (by assessing overall response rate [ORR] per RECIST V1.1) and pharmacokinetics (PK) of the combination

Study population

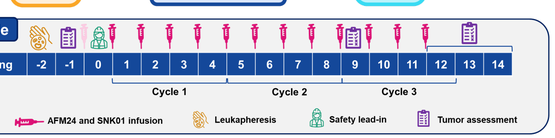
Patients with advanced and/or metastatic EGFR$^+$ solid tumors

- EGFR expression detected in (≥1% of positive tumor cells)
- R/R to all standard-of-care treatment options for their respective malignancy

Phase 1 followed a 3+3 dose escalation design



Treatment schedule



AFM24 at 160 mg (cohort 1) or 480 mg (cohort 2) and 4.0 ×10^9 SNK01 were administered IV QW in 28-day cycles until disease progression, intolerable toxicity, subject withdrawal or termination at the Investigator's discretion.

Tumor assessments were performed at screening and every two cycles for the first 12 months, and every three cycles thereafter. A confirmatory tumor assessment was carried out 4–6 weeks following the initial assessment in the event of a complete or partial response.

DLT, dose-limiting toxicity; EGFR, epidermal growth factor receptor; IV, intravenously; MTD, maximum tolerated dose; QW, once weekly; RP2D, recommended Phase 2 dose; R/R, relapsed or refractory.

RESULTS

Baseline characteristics

- As of June 2023, 7 patients had received AFM24 with SNK01, receiving a median (range) of 9 (4–23) doses over a median duration of 9 (4–25) weeks

Table 1: Baseline characteristics (n=7)

Dose of AFM24 received	
160 mg	3 (42.9)
480 mg	4 (57.1)
Age (years), n (%)	
Median (range)	60 (41–64)
Sex (female), n (%)	6 (85.7)
Ethnicity, n (%)	
White	6 (85.7)
Black or African American	1 (14.3)
Tumor type, n (%)	
MSS CRC	5 (71.4)
SCCHN	1 (14.3)
Penile	1 (14.3)
ECOG PS score, n (%)	
0	3 (42.9)
1	4 (57.1)
Prior lines of therapy	
Median (range)	5 (3–7)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; MSS CRC, microsatellite stable colorectal cancer; SCCHN, squamous cell carcinoma of the head and neck.

Safety

- No dose-limiting toxicities (DLTs) or unexpected toxicities were observed with the combination therapy
- No Grade 3, 4, or 5 treatment-emergent adverse event related to AFM24 in combination with SNK01 were observed
- The most frequent Grade 1/2 treatment-related adverse events (TRAE) were infusion-related reactions

Table 2: Summary of TEAEs, n patients (%)

	160 mg (n=3)	480 mg (n=4)	All (n=7)
TEAE	3 (100)	4 (100)	7 (100)
TEAE ≥Grade 3	3 (100)	0 (0)	3 (42.9)
Serious TEAE	0 (0)	0 (0)	0 (0)
Fatal TEAE	1 (33.3)	0 (0)	1 (14.3)
TEAE leading to study drug discontinuation	0 (0)	0 (0)	0 (0)

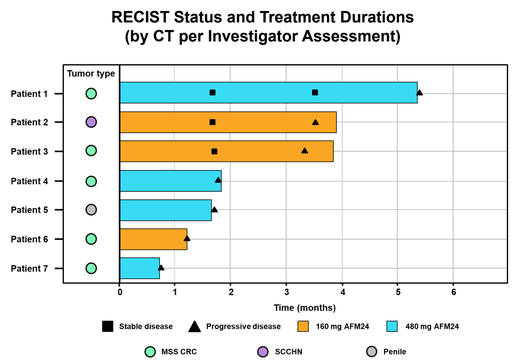
TEAE, treatment-emergent adverse event.

Table 3: Summary of TEAEs related to study treatment by Grade in ≥10% of patients (n=7, %)

	Grade 1/2	Grade ≥3
Any TRAE	6 (85.7)	0 (0)
IRR	6 (85.7)	0 (0)
Pruritus	1 (14.3)	0 (0)
Rash	1 (14.3)	0 (0)
Maculo-papular rash	1 (14.3)	0 (0)
Upper abdominal pain	1 (14.3)	0 (0)
ALT increased	1 (14.3)	0 (0)
Arthralgia	1 (14.3)	0 (0)

ALT, alanine transaminase; IRR, infusion related reaction; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

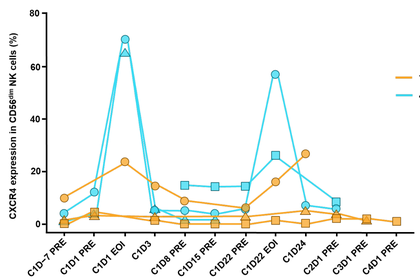
Best objective response was stable disease in three out of seven patients



Best objective response in seven evaluable patients is presented as of June 2023. All seven patients that had at least one post-baseline CT scan available for Investigator assessment. Two patients in the 160 mg cohort, and one patient in the 480 mg cohort exhibited stable disease. The patient exhibiting stable disease in the 480 mg cohort remained on treatment for over 5 cycles.

CT, computerized tomography; MSS CRC, microsatellite stable colorectal cancer; SCCHN, squamous cell carcinoma of the head and neck.

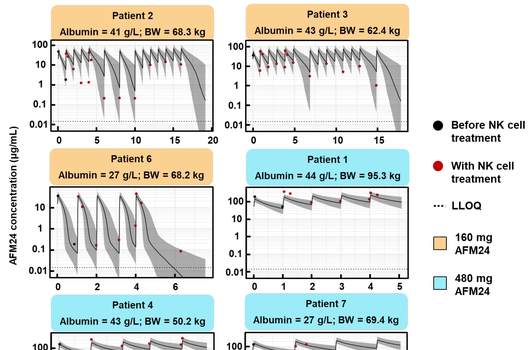
CXCR4 elevation on CD56^{dim} NK cells was shown by some patients following SNK01 and AFM24 infusion, suggesting redirection of these cells to tumors



Preliminary analysis of chemokine receptor expression on NK cells following treatment with NK cells and AFM24. Each line and shape represents a single patient within the corresponding cohort. After AFM24 infusion, expression of CXCR4 appears to increase on NK cells in circulation; this effect is not visible 48 hours after dosing. We hypothesize that cells which upregulated CXCR4 leave the circulation to follow chemokine gradients released by tumor tissue, e.g., CXCL12. In the AFM24-101 monotherapy study, an increase of NK cells in tumor tissue was described[8]. Induction of migration of circulating NK cells to the tumor induced by AFM24 treatment might lead to this increase in NK cells. Limited data availability does not allow for clear conclusions but warrants further investigation.

C, cycle; D, day; EOI, end of infusion; NK, natural killer; PRE, pre-infusion.

AFM24 in combination with SNK01 exhibits a similar PK profile to that of AFM24 alone



Using a population PK model, simulated AFM24 PK based on patient characteristics and PK data from the AFM24 monotherapy trial was overlayed with observed AFM24 serum concentrations taken before (black dots) and after (red dots) treatment with SNK01 in this study. The LLOQ is shown as a dotted line; predicted median AFM24 concentration and 90% prediction interval are shown as the line and shaded area, respectively.

BW, body weight; LLOQ, lower limit of quantitation; PK, pharmacokinetics.

CONCLUSIONS

- The data presented here provide proof-of-concept and support the feasibility of enhancing and redirecting the innate immune response to solid tumors by combining ICE molecules with NK cells; however, the trial will not proceed to Phase 2a
- AFM24 in combination with SNK01 exhibited a well tolerated safety profile; no DLTs or TRAEs ≥Grade 3 were observed, the MTD was not reached, and PK properties were similar to that of AFM24 alone
- The combination therapy exhibited promising signs of disease control, with three out of seven patients exhibiting stable disease, including patients with heavily pre-treated MSS CRC
- Signs of CXCR4 elevation on CD56^{dim} NK cells following AFM24 infusion suggests redirection of these cells to EGFR$^+$ solid tumors
- Adoptive transfer of *ex vivo* expanded autologous NK cells has been universally challenging, particularly when using NK cells derived from heavily pre-treated, elderly patients; future studies will focus on AFM24 in combination with allogeneic NK cells
- AFM24 is also being investigated in combination with atezolizumab (NCT05109442), aiming to enhance the antitumor activity of the full immunity cycle to target EGFR$^+$ solid tumors

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