The Combination of CD16A/EGFR Innate Cell Engager, AFM24, with SNK01 Autologous Natural Killer Cells in Patients with Advanced Solid Tumors

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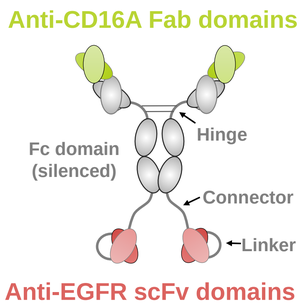
BACKGROUND

- Epidermal growth factor receptor (EGFR) is frequently overexpressed on the cell surface in solid tumors making it an ideal therapeutic target[1]
- Overexpression is typically a strong prognostic indicator[1], but not all patients respond to EGFR inhibitors[2], and in patients who are responsive, acquired resistance invariably occurs[3]; therefore, novel therapies acting independently of EGFR signaling are required
- Natural killer (NK) cells are a critical component of the innate immune system involved in the eradication of transformed cells via antibody-dependent cellular cytotoxicity (ADCC)
- Autologous NK cell transfer is a treatment that provides immune enhancement using highly pure NK cells harvested from a patient and represents a promising treatment strategy, with *ex vivo* expansion and activation enhancing the specificity and anti-tumor activity of NK cells[4]

OBJECTIVE

To investigate AFM24 in combination with SNK01 autologous NK cells in patients with advanced or metastatic EGFR$^+$ solid tumors

AFM24 & SNK01 THERAPY

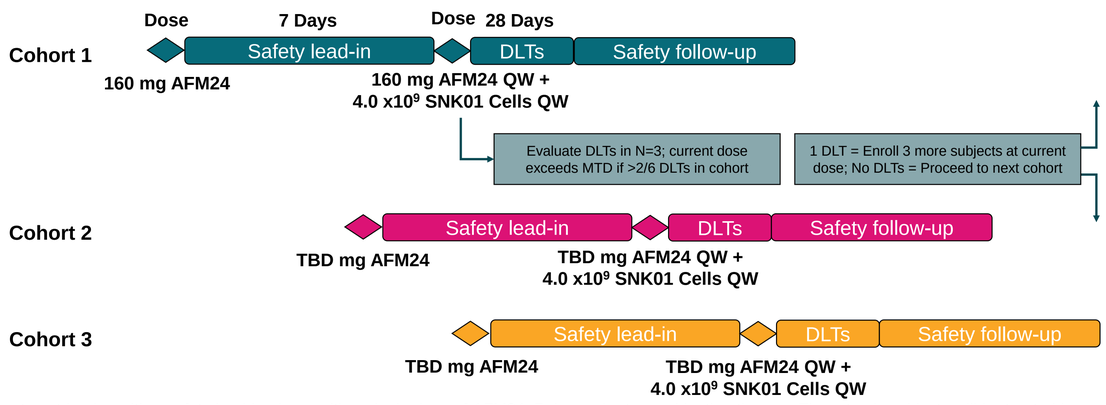


- AFM24 is a tetravalent bispecific innate cell engager (ICE®) derived from the redirected optimized cell killing (ROCK®) antibody platform
- AFM24 engages CD16A on NK cells and macrophages, with a higher affinity than monoclonal antibodies, and triggers ADCC and antibody-dependent cellular phagocytosis, respectively, directed at EGFR-expressing cancer cells[5]
- Preclinical data have shown that, independent of EGFR mutational status, AFM24 can induce NK cell-mediated killing of EGFR-expressing (EGFR$^+$) solid tumor cell lines[6]
- An ongoing phase 1/2a study (NCT04259450) is seeking to establish the safety and efficacy of AFM24 monotherapy in EGFR$^+$ solid tumors; this study has shown that patients had a well-managed safety profile with AFM24, and the recommended Phase 2 dose was established as 480 mg[7]
- SuperNK cell therapy (SNK01) is an *ex vivo* expanded autologous NK cell-derived adoptive cellular immunotherapy; the expansion process yields >5,500-fold of highly activated cytotoxic NK cell immunotherapeutic agent with >95% cell purity[8]
- SNK01 is characterized by increased CD16 expression (~90%)[8], and has demonstrated a tolerable toxicity profile with no risk of graft vs. host disease in patients with rapidly progressive solid tumors[9]
- Clinical data has shown anti-tumor activity in solid tumors as a single agent and in combination therapy with *ex vivo* expansion and activation further enhancing the specificity and anti-tumor activity of NK cells[9]

METHODS

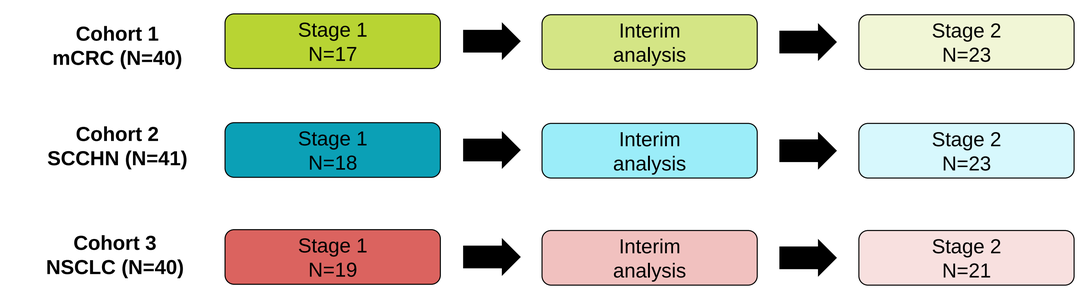
- An ongoing Phase 1/2a open-label, non-randomized, multicenter, dose escalation (Phase 1) and dose expansion (Phase 2a) study was initiated in November 2021 (NCT05099549) to evaluate the safety, tolerability and efficacy of AFM24 in combination with SNK01 autologous NK cells in EGFR$^+$ solid tumors
- AFM24 will be administered at an escalating dose as weekly intravenous (IV) infusions; the starting dose (160 mg) and dose escalations for each cohort are based on results from the ongoing AFM24 monotherapy trial and in agreement with the Safety Review Committee (SRC). SNK01 NK cells will be given at a fixed dose (4.0 x10^9 cells) as a weekly IV infusion followed by AFM24
- Subjects will receive combination therapy until disease progression, intolerable toxicity, subject withdrawal or termination at the Investigator's discretion

Phase 1 investigates escalating doses of AFM24 in combination with a fixed dose of NK cells using a 3+3 design (N=12–18)



Treatment begins with a safety lead-in phase with a single dose of AFM24, 7 days prior to combination therapy. Three to six subjects will be treated in each cohort. If a DLT is observed in 1 of 3 subjects, an additional 3 subjects will be enrolled in that same dose cohort. DLT, dose-limiting toxicity; MTD, maximum tolerated dose; QW, once weekly; TBD, to be determined at a later date.

Phase 2a investigates the efficacy and safety of combination therapy in EGFR$^+$ disease-specific cohorts (N=121)



Phase 2a expansion will follow a Simon two-stage optimal design. **Cohort 1: Metastatic colorectal cancer (mCRC)**. Microsatellite instability (MSI) low/DNA mismatch repair proficient. Subjects must have received ≥1 lines of previous combination therapy and must have been exposed to oxaliplatin, irinotecan, a fluoropyrimidine, a VEGF targeting agent and, if considered appropriate by the treating physician, an EGFR targeted antibody. **Cohort 2: Squamous cell carcinoma of the head and neck (SCCHN).** Subjects with advanced or metastatic SCCHN whose disease has progressed after having received ≥1 prior lines of therapy for advanced disease, which must have included platinum-based therapy, fluoropyrimidine, and an anti-PD1/PD-L1 antibody. **Cohort 3: Non-small cell lung cancer (NSCLC).** Subjects with advanced or metastatic EGFR-expressing NSCLC (EGFR wild-type) whose disease has progressed after having received ≥1 prior lines of therapy for advanced disease. Subjects must have received at least a platinum-based doublet in combination with anti-PD1/PD-L1 antibody or must have received a platinum-based doublet followed by an anti-PD1/PD-L1 antibody.

STUDY PARAMETERS

Key inclusion criteria:

- Eligible subjects at least 18 years of age must have advanced or metastatic disease with EGFR-positive immunohistochemical staining (defined as >1%) of tumor cells and be refractory to standard-of-care treatment
- One or more measurable tumor lesions by RECIST v1.1
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Adequate bone marrow, hepatic and renal function

Key exclusion criteria:

- Untreated or symptomatic central nervous system metastases
- No resolution of specific toxicities related to any prior anti-cancer therapy to Grade ≤ 1 according to the NCI-CTCAE v.5.0
- Treatment with systemic anticancer therapy or an investigational device within 4 weeks, or within 5 half-lives of the agent prior to the first dose of study treatment
- Clinically significant cardiovascular disease
- Autoimmune disease requiring therapy; immunodeficiency, or any disease process requiring systemic immunosuppressive therapy

STUDY ENDPOINTS

Primary endpoints:

Phase 1

- To determine the maximum tolerated dose and/or recommended Phase 2 dose

Phase 2a

- To establish the overall response rate (as per RECIST v1.1) in EGFR$^+$ disease specific cohorts

Secondary endpoints:

Phase 1

- Safety and tolerability of AFM24 in combination with SNK01 cells
- Preliminary efficacy; assessed by evaluating progression-free survival (PFS) and overall survival (OS) (as per RECIST v1.1)

Phase 2a

- Safety and tolerability of AFM24 in combination with SNK01 cells
- PFS, OS, duration of response clinical benefit rate

Secondary endpoints for both phases include treatment-emergent adverse events, serious adverse events, pharmacokinetics (maximum observed plasma concentration, time to maximum concentration, area under plasma concentration-time curve) and immunogenicity and anti-drug antibodies assessed up to 24 months. Pharmacodynamic and biomarker analyses will also be explored.

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