A Phase 1/2a Dose Escalation Study of AFM24 in Patients With Epidermal Growth Factor Receptor-Expressing (EGFR) Solid Tumors: Results From Phase 1

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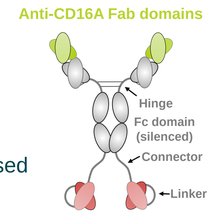
BACKGROUND

EGFR IS A KEY THERAPEUTIC TARGET

- Epidermal growth factor receptor (EGFR) is frequently expressed on the cell surface of solid tumors making it an ideal target for therapeutic antibodies that trigger antibody-dependent cellular cytotoxicity (ADCC) and cellular phagocytosis (ADCP)[1,2]
- Engaging innate immunity can potentially overcome the limitations (e.g., acquired resistance) of antibodies or small molecules that mainly inhibit EGFR signaling[3,4]

AFM24

- AFM24 is a first-in-class, bispecific, tetravalent Innate Cell Engager (ICE®) that targets EGFR
- AFM24 has four binding sites: two for CD16A, the Fcγ receptor expressed by natural killer (NK) cells and macrophages, and two for EGFR



- AFM24 engages CD16A on NK cells and macrophages with a higher affinity than monoclonal antibodies and triggers ADCC and ADCP, respectively, directed at EGFR-expressing (EGFR$^+$) cancer cells[5]
- Data showed that AFM24 can induce NK cell-mediated killing of EGFR$^+$ solid tumor cell lines, independent of EGFR mutational status. In addition, AFM24 monotherapy is well-tolerated in cynomolgus monkeys[6]

OBJECTIVE

Assessment of the safety and tolerability of AFM24 in patients with EGFR$^+$ solid tumors

PHASE 1: DOSE ESCALATION

- A Phase 1/2a open-label, non-randomized, first-in-human, multi-center study (NCT04259450) to establish the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of AFM24; the study was initiated in April 2020
  - The primary objective was to assess the safety of AFM24 by the incidence of dose-limiting toxicities
  - Secondary endpoints included overall response rate (ORR), duration of response, pharmacokinetics (PK), and immunogenicity
- Patients received AFM24 doses intravenously once weekly at 14–720 mg in 28-day cycles
  - Tumor assessment was performed every 8 weeks until disease progression, intolerable toxicity, patient withdrawal, or termination at the investigator's discretion

Cohort 1: 14 mg N=2 | Cohort 2: 40 mg N=6 | Cohort 3: 80 mg N=4 | Cohort 4:160 mg N=5 | Cohort 5: 320 mg N=6 | Cohort 6: 480 mg N=6 | Cohort 7: 720 mg N=6

RESULTS

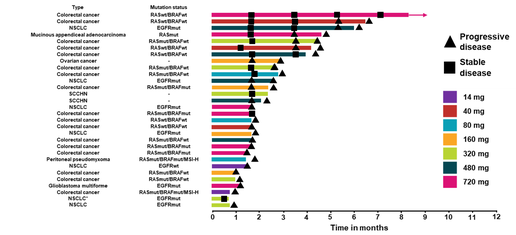
- As of August 2022, 35 patients were enrolled and treated, receiving a median (range) of 8 (1–37) doses of AFM24 **(Table 1)**
  - Determination of tumor EGFR expression via immunohistochemistry was not required for enrolment to the dose-escalation study

Table 1: Baseline characteristics (n=35)

Age (years), n (%)	
Median (range)	58 (29–81)
18–64	24 (68.6)
≥65	11 (31.4)
Sex, (male, n, %)	23 (65.7)
White ethnicity, n (%)	27 (71.1)
Tumor type, n (%)	
CRC	20 (57.1)
NSCLC	8 (22.9)
Other	7 (20.0)
ECOG PS, n (%)	
0	11 (31.4)
1	24 (68.6)
Prior lines of therapy Median (range)	4 (2–11)

CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PS, performance score.

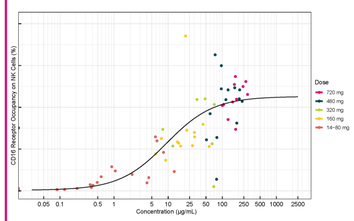
Best objective response was stable disease in 11 out of 29 response-evaluable patients



A total of 30 out of 35 patients had at least one post-baseline CT scan available. *Indicates that the CT scan was too early, and the patient was not considered as response-evaluable. Four patients had stable disease for ≥3.5 months (three with colorectal cancer, one with non-small cell lung cancer [NSCLC]).

MSI-H, microsatellite instability, high; mut, mutant; wt, wild type

PK and CD16A receptor occupancy (RO) confirmed 480 mg as the RP2D



PK summary:

- RO appears to level off between dose levels 320 and 480 mg
- Dose-proportional increase in PK observed from 320 mg onwards (saturation TMDD)
- Apparent half-life estimated to be 11.2 days at doses ≥320 mg
- Steady state was achieved between 21–28 days

RP2D = 480 mg

RP2D, recommended Phase 2 dose. TMDD, Target Mediated Drug Disposition

Safety of AFM24

- Six patients had seven AFM24-related, transient, reversible, Grade 3–4 treatment-emergent adverse events (TEAE) **(Table 2)**
  - There were no on-study deaths
  - One dose-limiting toxicity occurred at 40 mg (Grade 3 infusion-related reaction [IRR])
  - One treatment-related Grade 4 event (lymphopenia) was reported; otherwise, no related Grade 4 or 5 events were reported **(Table 3)**

Table 2: Summary of adverse events, n (%)

	All (N=35)	AFM24-related (N=35)
TEAE	35 (100)	34 (97)
TEAE ≥Grade 3	20 (57)	6 (17)
Serious TEAE	18 (51)	2 (6)
Fatal TEAE	2 (6)	0
TEAE leading to study drug discontinuation	4 (11)	2 (6)

TEAE, treatment-emergent adverse event

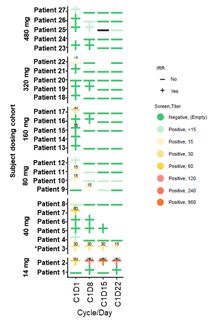
Table 3: Summary of related TEAEs by grade (in ≥5 patients), n (%)

	Grade 1/2	Grade 3/4*	Any Grade
Any study drug-related TEAE	33 (94)	6 (17)	34 (97)
IRR	26 (74)	2 (6)	27 (77)
Nausea	10 (29)	0	10 (29)
Dermatitis acneiform	7 (20)	1 (3)	7 (20)
Vomiting	7 (20)	0	7 (20)
Headache	6 (17)	0	6 (17)
Fatigue	5 (14)	0	5 (14)

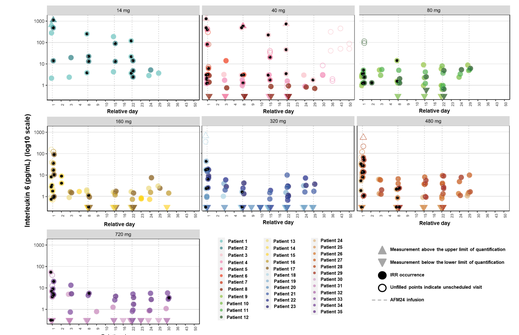
*One Grade 4 event (lymphopenia) was reported; otherwise, no related Grade 4 or 5 events were reported. IRR, infusion-related reaction; TEAE, treatment-emergent adverse event

IRRs were confined mainly to the first AFM24 dose and were not associated with anti-drug antibodies and IL-6 levels

A ADA titers and IRRs over time



B IL-6 measurements versus relative day by cohort and IRR occurrence



ADA, anti-drug antibodies; C1D1, Cycle 1 Day 1; IRR, infusion-related reaction.

A) In the higher dose cohorts, IRR events were mainly confined to the first AFM24 dose.

Symptoms associated with IRR were mild-to-moderate, transient and reversible with treatment of symptoms; most patients could be re-treated with AFM24 without further IRRs. Only measurements in Cycle 1 are shown.

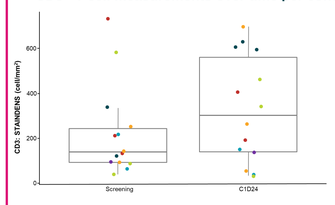
*Patient 3 had ADA positivity (≥15) beyond Cycle 1, while all other patients developed no ADAs (i.e.,<15) after Cycle 1.

B) IL-6 increases were confined mainly to the first AFM24 dose, in the higher dose cohorts (160–720 mg).

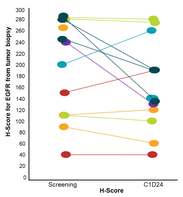
IL-6 is a key cytokine for the detection of IRRs or cytokine release syndrome (CRS). IL-6 increase was transient; at higher doses (>160 mg) where constant levels of AFM24 were present, IL-6 concentration was <10 pg/mL following the first infusion, suggesting a low risk of CRS at doses >160 mg. Previous data have shown tumor necrosis factor-α and interferon-γ did not greatly increase during an IRR but were slightly increased between infusions.[7] Only measurements up to Cycle 3 Day 1 are shown; Relative date is the sample date – date of first infusion +1.

CD3 and EGFR staining by immunohistochemistry on tumor tissue indicates increased number of T-cells and maintained EGFR expression

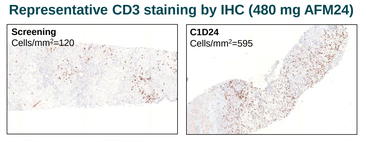
A CD3+ T cell measurements over time per cohort



B EGFR expression



Representative CD3 staining by IHC (480 mg AFM24)



A) Following AFM24 infusion, the number of CD3+ T cells increase in the tumor microenvironment suggesting immune cells are activated. Paired biopsies performed at baseline and Day 24 show infiltration of effector T cells into the tumor microenvironment following treatment, demonstrating a potential indirect effect of AFM24 to leverage the adaptive immune system.

B) Tumor EGFR expression was maintained during AFM24 treatment. Tumor biopsies were performed at baseline and on Day 24 on treatment. Specimens were stained by immunohistochemistry (IHC) and scored with the H-Score. The H-Score calculates a score from 0 to 300 based on the percentage of cells stained at different intensities viewed at various magnifications. All analyzed samples were positive for EGFR at varying levels.

CONCLUSIONS

- **AFM24 demonstrated a well-managed safety profile up to 720 mg QW with IRR being the most frequent TEAE**
- **Based on the PK, RO, safety and cytokine data, the RP2D was determined at 480 mg QW and enrollment into disease-specific cohorts at this dose is ongoing**
- **Stable disease was observed as best response with AFM24 treatment in an unselected patient population**
- **In addition to stimulation of NK cell-mediated ADCC previously shown by AFM24[8], PD marker data demonstrate increased T cell infiltration into the tumor microenvironment, possibly indicating a leveraging of the adaptive immune response as an indirect effect of AFM24**
- **AFM24 is also being evaluated in other clinical trials in combination with atezolizumab (NCT05109442) and autologous NK cells (NCT05099549), exploring the potential of these combination strategies to target EGFR$^+$ tumors**

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