A phase 1/2a first-in-human study of AFM24, a CD16A/epidermal growth factor (EGFR) bispecific Innate Cell Engager (ICE®), in patients with locally advanced or metastatic EGFR expressing solid tumors: Preliminary findings from the dose-escalation phase

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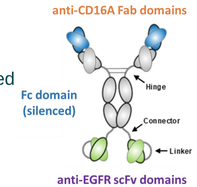
BACKGROUND

- EGFR is frequently overexpressed on the cell surface in solid tumors, and is associated with poor prognosis[1]
- Some patients do not respond to EGFR inhibitors[2], and in patients that do, acquired resistance invariably occurs[3]; novel therapies acting independently of EGFR signaling are required
- AFM24 engages CD16A on natural killer (NK) cells and macrophages, with a higher affinity than monoclonal antibodies, and triggers antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) responses, respectively, directed at EGFR-expressing cancer cells[4]
- Preclinical data have shown that AFM24 can induce NK cell-mediated killing of EGFR$^+$ solid tumor cell lines, independent of EGFR mutational status[5,6]
- An ongoing phase 1/2a study (NCT04259450) is seeking to establish the safety and efficacy of AFM24 monotherapy in EGFR$^+$ solid tumors

AFM24 STRUCTURE

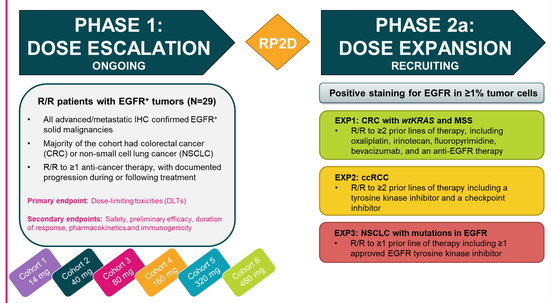
- AFM24 is a bispecific innate cell engager (ICE®) derived from the redirected optimized cell killing (ROCK®) antibody platform
- AFM24 is a tetravalent EGFR/CD16A-specific IgG1-scFv fusion antibody (scFv-IgAb) with a silenced IgG1 Fc



PHASE 1 PRIMARY OBJECTIVE

- **To establish the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) and investigate the safety and tolerability of AFM24 monotherapy**

Phase 1/2a study design



ccRCC, clear cell renal cell carcinoma; CRC, colorectal cancer; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; IHC, immunohistochemical; MSS, microsatellite-stable; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PK, pharmacokinetics; RP2D, recommended phase 2 dose; R/R, relapsed or refractory; SOC, standard of care; TEAE, treatment emergent adverse event; wt, wildtype.

RESULTS

- As of 29 Oct 2021, a total of 29 patients were treated with AFM24 across six dose levels (14–480 mg), baseline characteristics are shown in Table 1
  - Median (range) number of AFM24 doses administered was 8 (1–29)
  - A total of 268 infusions of AFM24 were administered

Table 1: Summary of demographics and patient characteristics

Baseline charactistics, n (%)	(N=29)
Age group, years	
18–64	18 (62%)
≥64	11 (38%)
Gender	
Male	18 (62%)
Female	11 (38%)
ECOG PS	
0	9 (31%)
1	20 (69%)
Ethnicity	
White	22 (76%)
Number of prior lines, median (range)	**4 (2–8)**
Tumor type	
Colorectal	**16 (55%)**
CRC RAS/BRAFmut	11 (38%)
CRC MSI-H	2 (7%)
NSCLC	**7 (24%)**
NSCLC EGFRmut	6 (21%)
Pancreatic adenocarcinoma	**1 (3%)**
Ovarian cancer	**1 (3%)**
Other	**4 (14%)**

CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability, high; mut, mutant; NSCLC, non-small cell lung cancer; PS, performance score.

Safety of AFM24

- Infusion related reactions (IRRs) were reported in 69% of patients and, at higher doses (160–480 mg), occurred almost exclusively during the first AFM24 infusion only (Table 2)
- There were no on-study deaths and no grade 3–4 skin toxicities were reported (Table 3)
- One DLT was reported at 40 mg (Grade 3, IRR)
- Transient and reversible ≥ Grade 3 TEAEs were reported in five patients

Table 2: Summary of adverse events

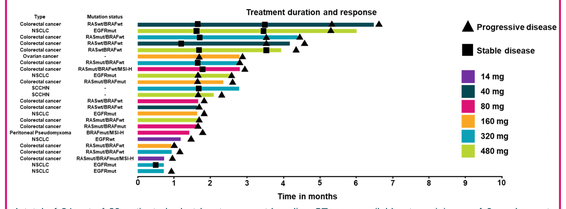
Adverse event, n (%)	All (N=29)	AFM24-related (N=29)
TEAE	29 (100)	26 (93)
Infusion-related reactions	20 (69)	20 (69)
TEAE ≥Grade 3	16 (55)	5 (17)
Serious TEAE	13 (45)	2 (7)
Fatal TEAE	1 (5)	0
TEAE leading to study drug discontinuation	4 (14)	2 (7)

Table 3: Summary of related TEAEs by grade (in ≥10% of patients)

	Grade 1/2	Grade 3/4*	Overall
Any study drug-related TEAE	26 (89.7)	5 (17.2)	27 (93.1)
Infusion-related reaction	19 (65.5)	2 (6.9)	20 (69.0)
Nausea	7 (24.1)	0	7 (24.1)
Headache	6 (20.7)	0	6 (20.7)
Dermatitis acneiform	5 (17.2)	0	5 (17.2)
Pyrexia	4 (13.8)	0	4 (13.8)
Vomiting	4 (13.8)	0	4 (13.8)
Fatigue	3 (10.3)	0	3 (10.3)
Hot flush	3 (10.3)	0	3 (10.3)
Lymphopenia	3 (10.3)	3 (10.3)*	3 (10.3)
Rash maculo-papular	3 (10.3)	0	3 (10.3)

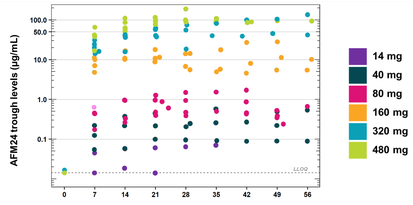
*One Grade 4 event (lymphopenia) was reported; otherwise, no related Grade 4 or 5 events were reported. TEAE, treatment-emergent adverse event.

Best objective response was stable disease in 8 out of 24 response-evaluable patients



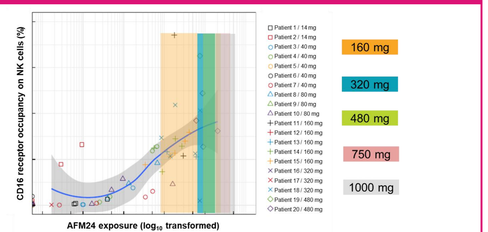
A total of 24 out of 29 patients had at least one post-baseline CT scan available at a minimum of 6 weeks post initiation of therapy. Three patients had stable disease for ≥3 months (two with CRC, one with NSCLC).

Dose-proportional increases in PK were observed for AFM24 at 320 mg



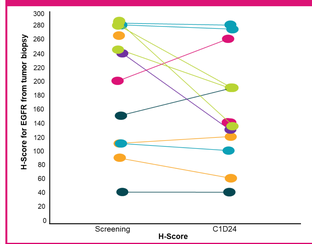
Steady state ($C_{trough,SS}$) was achieved between 21–28 days at 1×/week dosing; Apparent half-life is estimated to be 11.2 days at doses ≥320 mg. PK, pharmacokinetics

Peripheral CD16A receptor occupancy by AFM24 appears to level off between 320 mg and 480 mg



Exposure-response modeling with CD16A receptor occupancy demonstrated a sigmoidal relationship with AFM24 in circulating blood cells. Receptor occupancy levelled off at 320 mg and was approaching a plateau at 480 mg. This was indicative of saturation of CD16A with AFM24 on NK cells between these doses. Log transformed x-axis. NK, natural killer.

Tumor EGFR expression was maintained during AFM24 treatment



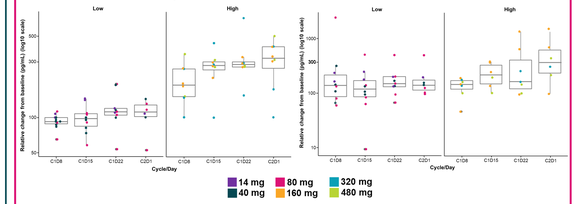
Tumor biopsies were performed at baseline and on Day 24 on treatment. Specimens were stained by immunohistochemistry (IHC) and scored with the H-Score. The H-Score calculates a score from 0 to 300 based on the percentage of cells stained at different intensities viewed at various magnifications. All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

14 mg 80 mg 320 mg
40 mg 160 mg 480 mg

Increase in IL6 at higher doses of AFM24 was transient and was not associated with CRS

IL6 is a key cytokine for the detection of infusion related reactions or CRS. IL6 increase was transient; at higher doses (>160 mg) where constant levels of AFM24 were present, IL6 increase was <10 pg/mL following the first infusion. CRS, cytokine release syndrome; IL6, interleukin-6.

Increase in pro-inflammatory cytokines at higher doses of AFM24 may reflect sustained activation of immune cells



Samples were taken one week after each AFM24 dose and just prior to the next dose. Measurements at Cycle 1, Day 1 (C1D1) were considered as baseline. Samples were grouped by dose level: low (14–80 mg) versus high (160–480 mg). Low levels in the pg range suggested that these cytokines are not being produced in high amounts by blood lymphocytes, and are thus not indicative of CRS, but rather occurred as a result of effects likely reflecting cytokine levels in tissues. CRS, cytokine release syndrome; IFNγ, interferon-γ; TNFα, tumor necrosis factor-α.

CONCLUSIONS

- **AFM24 demonstrated a well-managed safety profile**
- **Stable disease was observed as best response with AFM24 treatment in an unselected patient population**
- **Pharmacodynamic activity was observed at doses of 160 mg to 480 mg**
- **The MTD was not reached; the RP2D was determined at 480 mg based on safety and tolerability, exposure and CD16A receptor occupancy**
- **Dose escalation is continuing at 720 mg and expansion in disease specific cohorts at 480 mg has been launched**
- **Other studies are evaluating AFM24 in combination with atezolizumab, and in combination with autologous NK cells holding the potential to activate the innate immune response to target EGFR$^+$ tumors**

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