Leveraging innate immunity with AFM24, a novel CD16A and epidermal growth factor receptor (EGFR) bispecific innate cell engager: Interim results for the non-small cell lung cancer (NSCLC) cohort

2533

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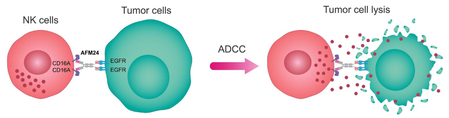
BACKGROUND

- AFM24 is a tetravalent, bispecific Innate Cell Engager (ICE) that binds CD16A on natural killer (NK) cells and to EGFR overexpressed on solid tumor cells, resulting in potent, specific tumor cell lysis *in vitro*[1,2]; the unique mechanism of action of AFM24 enables induction of tumor cell lysis independently of EGFR mutational status[1,2]

AFM24 mechanism of action



Simultaneous engagement of EGFR and CD16A with AFM24 facilitates potent, anti-EGFR$^+$ tumor antibody-dependent cellular cytotoxicity (ADCC)

- Innate and inevitable acquired resistance to EGFR-targeted therapies such as tyrosine kinase inhibitors (TKIs) often limit long-term survival rates in EGFR$^+$ solid tumors such as NSCLC[3,4]
- Given its novel mechanism of action, AFM24 may have anti-tumor activity in patients with NSCLC, potentially including those with EGFR mutations resistant to TKIs
- This open-label, non-randomized, multi-center, Phase 1/2a study (NCT04259450) is investigating the safety, tolerability, and preliminary efficacy of AFM24 monotherapy in patients with advanced or metastatic EGFR$^+$ solid tumors
- The Phase 1 dose escalation study showed a well-managed safety profile and established the recommended Phase 2 dose at 480 mg; the maximum tolerated dose was not reached[5]. The Phase 2a expansion study is ongoing in patients with EGFR-mutant (EGFRmut), KRAS wild-type NSCLC, clear cell renal cell carcinoma (ccRCC), and microsatellite stable colorectal cancer (MSS CRC)

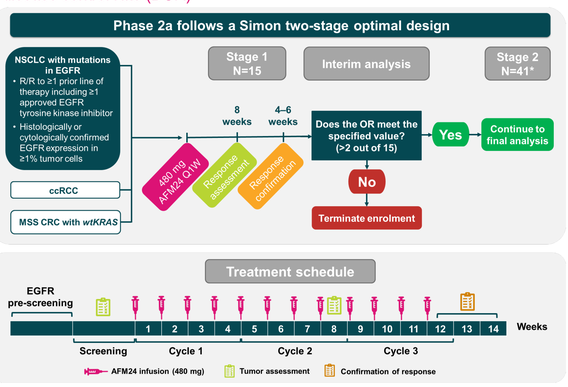
OBJECTIVE

The Phase 2a dose expansion study is investigating the preliminary efficacy of AFM24 monotherapy in EGFR$^+$ solid tumors; here the results of the interim analysis for the EGFRmut NSCLC cohort are reported

PHASE 2A STUDY DESIGN

Primary endpoint: Overall response rate (ORR) by Investigator assessment (per RECIST v1.1)

Secondary endpoints: Efficacy per iRECIST, safety, pharmacokinetics, immunogenicity, disease control rate (DCR)



AFM24 is administered IV Q1W in 28-day Cycles for as long as clinical benefit is observed, or until disease progression, intolerable toxicity, Investigator discretion, or subject withdrawal of consent. Tumor assessments are performed at initial screening, Cycles 2, 4, 6, 8, and every three cycles thereafter.

ccRCC, clear cell renal cell carcinoma; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; IV, intravenously; MSS, microsatellite stable; NSCLC, non-small cell lung cancer; OR, overall response; Q1W, once weekly; R/R, relapsed or refractory; wt, wildtype.

*41 patients are planned for Stage 2; recruitment is currently paused for the interim analysis.

RESULTS

Baseline characteristics

- At the planned interim analysis, 15 patients with NSCLC had been treated, receiving a median (range) of 11 (1–34) doses of AFM24 over a duration of 11 (1–34) weeks

Table 1: Baseline characteristics of the NSCLC cohort (n=15)

Age (years), n (%)	
Median (range)	55 (37–82)
18–65	10 (66.7)
>65	5 (33.3)
Sex (male), n (%)	12 (80.0)
Ethnicity, n (%)	
Asian	12 (80.0)
White	3 (20.0)
Tumor type, n (%)	
Adenocarcinoma	12 (80.0)
Squamous cell carcinoma	3 (20.0)
ECOG PS, n (%)	
0	4 (26.7)
1	11 (73.3)
Prior lines of therapy Median (range)	2.0 (1–12)
Prior EGFR TKIs	
1st generation (erlotinib, gefitinib)	4 (26.7)
2nd generation (afatinib, dacomitinib)	8 (53.3)
3rd generation (osimertinib, lazertinib, nazatinib)	8 (53.3)

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PS, performance score; TKI, tyrosine kinase inhibitor.

Safety

Table 2: Summary of treatment-emergent adverse events, n patients (n=15, %)

	AFM24-related	All
TEAE	14 (93.3)	14 (93.3)
TEAE ≥Grade 3	4 (26.7)	8 (53.3)
Serious TEAE	2 (13.3)	6 (40.0)
Fatal TEAE	1 (6.7)	1 (6.7)
TEAE leading to study drug discontinuation	1 (6.7)	1 (6.7)

TEAE, treatment-emergent adverse event.

- AFM24 exhibited a well-managed safety profile, with the majority of treatment-related adverse events (TRAEs) presenting as mild to moderate
  - The most frequently reported TRAE was infusion-related reactions (IRRs); IRRs were mainly confined to the initial infusion (Cycle 1, Day 1) of AFM24 and all later resolved
- Seven TRAEs of ≥Grade 3 were observed in four patients
  - Grade ≥3 TRAEs included decreased neutrophil count, lymphopenia and an IRR
  - One Grade 5 TRAE (pneumonitis) was observed in one patient with disease progression and multiple comorbidities; relation to AFM24 could not be ruled out

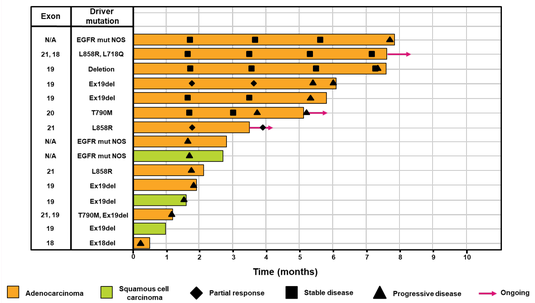
Table 3: Summary of TRAEs by Grade in ≥10% patients (n=15, %)

	Grade 1/2	Grade ≥3	Any Grade
IRR	13 (86.7)	1 (6.7)	13 (86.7)
Dermatitis acneiform	3 (20.0)	0	3 (20.0)
Neutrophil count decreased	1 (6.7)	2 (13.3)	3 (20.0)
Decreased appetite	2 (13.3)	0	2 (13.3)
Myalgia	2 (13.3)	0	2 (13.3)
Nausea	2 (13.3)	0	2 (13.3)
Pruritus	2 (13.3)	0	2 (13.3)

IRR, infusion-related reaction; TRAE, treatment-related adverse event.

In patients with EGFRmut NSCLC, AFM24 treatment resulted in a DCR of 47% (95% CI: 21.3%, 73.4%)

RECIST Status and Treatment Durations (by CT per Investigator Assessment)

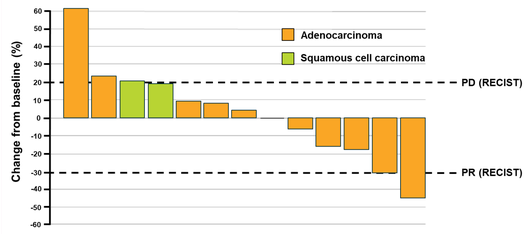


BOR in 15 evaluable patients is presented as of April 2023. There were 14 patients that had at least one post-baseline CT scan available for Investigator assessment. One patient had a confirmed PR for >3 months and another has had an ongoing PR for >2 months; five patients exhibited SD for ≥3.5 months, with one patient exhibiting ongoing SD for >8 months.

BOR, best objective response; CT, computerized tomography; DCR, disease control rate; PR, partial response; SD, stable disease.

A reduction in tumor burden was observed in 38% of patients with EGFRmut NSCLC treated with AFM24

Waterfall Plot for Best Percentage Change from Baseline in Sum of Long Diameter (by CT per Investigator Assessment)



Each bar represents one patient. Tumor diameter was measured at baseline and at subsequent tumor assessments by CT scan, and greatest change in diameter presented as percentage change from baseline. Five out of 13 patients exhibited tumor shrinkage as a result of AFM24 therapy.

CT, computerized tomography; PD, progressive disease; PR, partial response; SD, stable disease.

A patient exhibiting a PR experienced a 44.7% overall shrinkage of their target lesions with AFM24

49-year-old Asian male

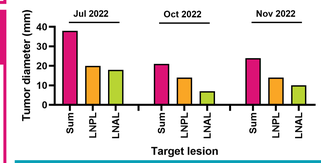
Diagnosed April 2020

Advanced, metastatic NSCLC adenocarcinoma

- Stage IV with two target lesions: Lymph node axillary left (LNAL) and lymph node paratracheal left (LNPL)
- EGFR mutations: Ex19del
- Began 480 mg AFM24 August 2022

Treatment history

With 480 mg AFM24



Tumor diameter (CT by Investigator Assessment) in mm of the LNAL and LNPL lesions, and the sum total diameter of these lesions (Sum) at baseline (Jul 2022), the first tumor assessment (Oct 2022) and the confirmatory tumor assessment (Nov 2022).

CT scan images of the LNAL lesion of a patient exhibiting a confirmed PR on 480 mg AFM24. The green line depicts the diameter of the lesion, with length indicated in mm.

BOR, best objective response; CT, computerized tomography; PD, progressive disease; PR, partial response.

CONCLUSIONS

- Although the formal continuation criteria for the cohort were not met (OR >2 out of 15), AFM24 showed meaningful clinical activity in heavily pretreated patients with EGFRmut NSCLC (ORR [13%], DCR [47%]) with significant tumor reductions, including two confirmed PRs and five patients exhibiting stable disease. These data provide proof of concept that targeting NK cells can induce remission in solid tumors
- A well-managed safety profile was observed; the majority of patients exhibited mild-to-moderate AFM24 TRAEs in-line with previous findings[5]
- While these clinical results are promising, antitumor activity may be further enhanced in combination with other therapies; as such, the study results substantiate further exploration of AFM24 combinations in patients with NSCLC and other EGFR$^+$ solid tumors
- AFM24 has previously been shown to increase NK cell and T cell infiltration into the tumor microenvironment, indicating possible leveraging of adaptive immune responses[6]; AFM24 in combination with atezolizumab is currently being explored in patients with NSCLC and other solid tumors (NCT05109442)[7]

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