Background AFM24 is an innate cell engager that binds both EGFR on tumor cells and CD16A on natural killer (NK) cells and macrophages. The primary mechanism of action is the induction of antibody-mediated cellular cytotoxicity and antibody-mediated cellular phagocytosis towards EGFR-positive tumor cells, independent of EGFR mutational status. This innovative, targeted approach utilizes patient’s own innate immunity and redirects NK cells and macrophages to tumors.

Methods An ongoing Phase 1/2a study (NCT04259450) is evaluating the safety and efficacy of AFM24 in patients with metastatic, treatment-refractory tumors known to express EGFR and has completed dose-escalation. The longitudinal effects on the immune system were examined to confirm the pharmacodynamic (PD) activity of AFM24.

Patients received AFM24 intravenously at 14–720 mg once weekly in 28-day cycles until disease progression, intolerable toxicity, investigator discretion, or patient withdrawal. Extensive correlative science analysis included profiling of pharmacokinetics, PD activity, anti-drug antibodies and CD16A receptor occupancy (CD16ARO). Comprehensive analyses of peripheral blood (PB) leukocytes and tumor biopsies were performed.

Results In total, 35 patients were treated with AFM24; tumor types included colorectal (19/35; 13 KRAS and/or NRAS and/or BRAF mutants), non-small cell lung cancer (8/35; 7 EGFR mutant) and others (8/35). A favorable safety profile in all cohorts was revealed, and an approximate half-life of 11 days was established. An exposure-response model correlating plasma concentration of AFM24 with CD16ARO demonstrated that AFM24 binds to NK cells in circulating blood, approaching a plateau at 480 mg. Mass cytometry revealed enhanced expression of activation marker CD69 on NK cells even at low doses (14–80 mg), which coincided with a transient loss of NK cells from the PB, possibly indicating migration of NK cells to the tumor. Cytotoxic CD8 T cells showed a continuous increase of Ki-67 expression in the periphery, indicating crosstalk with the adaptive immune system. T cells in the tumor bed also substantially increased. Tumor EGFR expression was maintained during treatment.

Conclusions This analysis supports the PD activity of AFM24; NK cell changes in PB suggest that AFM24 activates and redirects NK cells from PB to EGFR-positive tissue. T cells are activated within the periphery, and T cell numbers increase in tumors, which may indicate stimulation of anti-cancer activity of the adaptive immune system as an indirect effect of AFM24. Clinical and correlative science from the escalation phase of the study supports further investigation of AFM24 anti-tumor activity in EGFR-expressing tumor-specific cohorts.

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