**AFM24, a bispecific EGFR/CD16A Inhate Cell Engager to promote potential to overcome resistance to current targeted treatments for ERG-positive malignancies**

**Introduction**
- EGFR-expressing solid tumors remain challenging to treat and are a common cause of cancer-related mortality. While there have been advancements, novel mechanisms are needed to address the gaps in approved therapeutic approaches.
- Current therapies target EGFR, such as tyrosine kinase inhibitors (TKIs) or monoclonal antibodies (mAbs), work primarily through the inhibition of EGFR signaling.
- Non-desirable side effect profiles which may lead to treatment discontinuation and occurrence of resistance in the EGFR signaling cascade (e.g., EGFR-Mediated, TKI-resistant clones).

**AFM24** represents a distinct mechanism that engages innate immune cells by recruiting NK cells and macrophages to the site of tumor for effective and efficient tumor killing. The differentiated MDA does not rely on the EGFR signaling pathway for tumor killing.

AFM24 is a bispecific monoclonal antibody (mAb) that acts as a bispecific EGFR/CD16A innate cell engager (ICE) that provides, this distinct alternative to treating EGFR expressing solid tumors and by way of its mechanisms leads promise treat all patients with a more acceptable safety profile while remaining immune to the challenge of resistance.

**AFM24’s potential effectiveness in activating innate immunity via CD16A is not impacted by activating serum IgG**
- All ICs built on Affimed's ROCK® platform have a unique CD16A- binding paratope, which achieves high affinity and specificity.
- The CD16A-binding paratope binds to all variants of CD16A.
- Binding efficacy, while it does not bind to CD16B.

**The binding site on CD16A is distinct from the IgG binding site resulting in low IgG competition in ADCD only 1.3-fold reduction in efficiency in the presence of 20 µg/mL monoclonal anti-EGFR (eL12) and/or polyvalent antibody (for AFM24)**

**AFM24 induces substantially higher ADCC mediated cell killing than conventional IgG1**
- AFM24 shows substantially better ADCC efficacy over all E:T ratios compared to conventional IgG1.
- Binding of the bispecific control anti-EGFR/CD16A scFv-IgA to CD16A alone does not enhance the natural cytotoxicity of NK cells towards target cells, indicating that EGFR binding is essential for AFM24’s functionality.

**Conclusions**
- AFM24 is a novel innate cell engager (ICE) that harnesses the innate immune system to induce potent tumor cell killing via ADCC and ADCP.
- Due to its distinct mode of action, AFM24 is potentially eligible for treatment of EGFR- positive tumors, regardless of EGFR-pathway mutations and EGFR resistance.
- EGFR is used as a docking site only, whereas AFM24’s cytotoxicity is independent of EGFR functionality and the downstream signal transduction pathway.
- Patients treated with no off-target toxicity in cynomolgus monkeys.
- A broad set of patients with hard-to-treat EGFR-expressing cancers may benefit from AFM24.