AFM26 - A novel CD16A-directed bispecific antibody targeting BCMA for multiple myeloma

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Abstract

Multiple myeloma (MM) is the second most common hematological cancer (10-15% of all) and is characterized by the accumulation of neoplastic plasma cells in the bone marrow and production of high levels of monoclonal immunoglobulin (M-protein). While historically considered incurable, recent approvals and underpinning data with monoclonal antibodies (mAbs) targeting MM-expressed surface antigens promise greatly improved outcomes and have heralded a new era of MM treatment in which immunotherapies are expected to take center stage. However, an unmet need remains as patients eventually relapse and/or become refractory to currently available treatments. Consequently, novel immunotherapeutic approaches are needed to provide improved treatment options to MM patients. Among the currently explored targets, B-cell maturation antigen (BCMA, CD268) is considered to be particularly attractive due to its limited expression on healthy tissues and almost universal expression on myeloma cells in the majority of patients.

Natural killer (NK) cells are cytotoxic effector cells of the innate immune system capable of rapidly eradicating infected and transformed cells through direct lysis. The cytolytic activity of NK-cells can be used therapeutically to reduce tumor cell lysis by direct engagement of the activating receptor CD16A. Despite similar mechanisms of target cell lysis, activation of NK-cells is generally not associated with the systemic symptoms of high level cytokine release as seen with direct T-cell engagement. Hence, it is considered a potent immunotherapeutic approach with reduced toxicity and a well-tolerable safety profile. NK-cells readily infiltrate bone marrow and are thought to contribute to the efficacy of current myeloma treatments. Therefore, redirecting NK-cell cytotoxicity to malignant plasma cells appears to be a suitable therapeutic approach for MM.

We describe the characterization of AFM26, a novel tetravalent bispecific antibody that specifically targets BCMA and CD16A with high affinity and induces potent and efficacious myeloma cell lysis. AFM26 incorporates an affinity-improved anti-CD16A domain and interacts bidirecply with NK-cells, resulting in high avidity and prolonged cell surface retention that is not affected by the presence of polyvalent IgG. Hence, AFM26 potently induces NK-cell-mediated lysis in vitro of target cells expressing low levels of BCMA at low-effector:target ratios, even in presence of polyvalent IgG. This may suggest that AFM26, in contrast to classical mAbs, retains ADCC activity at low antibody concentrations in presence of serum IgG and despite high levels of IgG. M-protein occurring in about half of MM patients. AFM26 exhibits high protein stability, full co-reactions with cognomous antibodies (BCMA and CD16A) and does not bind APRIL and TACI, two functionally related receptors. These data suggest that AFM26 is a promising, novel and highly potent drug candidate for MM treatment.

AFM26 exhibits high protein stability

Selective interaction with human and cynomolgus CD16A and BCMA but not related TACI and BAFF-R

Key points

1. AFM26 is a first-in-class tetravalent bispecific antibody that is strongly differentiated from monoclonal antibodies
2. High affinity CD16A binding without IgG interference suggests that AFM26 can activate NK-cells despite high M-protein levels
3. Novel mode of action allowing for potential positioning in 1st line as combination with adoptive NK-cell transfer during ASCIT or in salvage
4. Targeting BCMA via CD16A is likely to be safer than T-cell-based approaches, potentially enabling faster development timelines

High affinity and bivalent interaction with NK-cells in the presence of IgG

- NK-cell binding affinity superior to IgG, and Fc-engineered IgG
- NK-cell binding largely unaffected by polyvalent IgG
- Bivalent engagement of NK-cells through CD16A

Potent and efficacious induction of NK-cell cytotoxicity towards myeloma cells in vitro

AFM26 is uniquely suited for combination with adoptive NK-cell therapy to enable novel therapeutic approaches in 1L NDMM

- Long-lasting NK-cell surface retention that is unaffected by polyvalent IgG
- More efficacious and potent induction of target cell lysis than anti-CS1
- AFM26 does not induce NK-cell depletion

Conclusions

- AFM26 is differentiated to monoclonal antibodies and has the potential to fully unlock NK-cell cytotoxicity in MM.
- AFM26 holds promise to address the medical need in the 1st line NDMM transplantation setting. Long-lasting NK-cell surface retention and inability to induce NK-cell depletion may allow preming of NK-cells ex vivo prior to infusion.