AFM26 is a novel, highly potent BCMA/CD16A-directed bispecific antibody for high affinity NK-cell engagement in multiple myeloma

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Abstract

Background: Despite recent advances in the treatment of multiple myeloma (MM), novel therapies are needed to achieve long lasting remissions in a greater number of patients. Natural killer (NK) cells play a key role in the immune response to MM and have been implicated in the clinical efficacy of current standard of care interventions, including IMiDs, proteasome inhibitors, recently approved immunotherapies and autologous stem cell transplantation (ASCT). Numerous strategies are being developed to enhance the natural NK-cell cytotoxicity against myeloma cells, which is frequently downregulated in MM. Approaches include modulation of activity through cytokine stimulation or immune checkpoint targeting, and adoptive transfer of culture expanded NK cells in ASCT-eligible MM. While highly attractive, these approaches are non-targeted, as they rely on the natural cytotoxicity of NK-cells, and may benefit from antigen-specific targeting and effecter activation. AFM26 is a novel tetrameric, bispecific antibody designed to specifically enhance NK-cell anti-MM activity by redirecting NK-cell cytotoxicity to cells expressing B-cell maturation antigen (BCMA)/CD200, an antigen expressed on MM cells. Methods: NK-cell engagement and cytostaticity of AFM26 towards MM cell lines and freshly isolated tumor cells from MM patients, was characterized in vitro and compared with classical antibody formats. Results: AFM26 engages NK-cells with superior avidity (Ks = 1.2 nM) through biivalent interaction with CD16A (affinity 400 nM) and demonstrates extended cell surface retention that is not affected by high level serum IgG, which is particularly relevant in MM. Importantly, AFM26 does not induce NK-cell depletion but selectively elicits potent and efficacious lysis of MM cells in vitro. Conclusions: AFM26, the first-in-class BCMA-targeting NK-cell engages, is a promising candidate to enhance NK-cell activity and confer tumor-specificity to NK-cells in MM. AFM26 is well differentiated from classical antibody formats and appears to be suitable to target BCMA(-) disease as a single agent or in combination with cellular NK-cell therapy.

Key Points:

AFM26, a first-in-class NK-cell engager targeting BCMA
1. Potently stimulates NK-cell-mediated cytotoxicity towards myeloma cells, including cells expressing very low levels of BCMA
2. May have a superior safety profile compared to BCMA/CD3 T-cell engagers
3. Engages NK-cells with high avidity in presence of high level serum IgG and irrespective of CD16A polymorphism
4. Does not induce NK-cell depletion

AFM26 potently induces NK-cell-mediated lysis of BCMA(+) target cell lines and primary myeloma tumor cells in vitro
- Despite the low expression of BCMA on MM tumor cells, AFM26 induces lysis of primary tumor cells with superior potency compared with daratumumab and elotuzumab

Tumor cell lysis by AFM26

AFM26 retains potent activity towards target cells expressing very low levels of BCMA

AFM26 does not induce NK-cell lysis in vitro in contrast to daratumumab and elotuzumab

Conclusions and Outlook
- AFM26 promises to fully unlock NK-cell cytotoxicity in myeloma as single agent or in combination with adoptively transferred NK-cells.
- AFM26 may address the medical need of MRD positivity after high-dose therapy (HDT)/ASCT in first-line MM treatment:
  1. NK-cells are the first lymphocyte population to reappear after HDT/ASCT.
  2. Adoptive transfer of large numbers of NK-cells is a feasible, potentially safe and widely applicable strategy to provide a highly active effector population in combination with ASCT.

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