Background Modakafusp alfa is a novel immunocytokine therapy comprising two attenuated interferon alpha (IFNα) moieties fused to a humanized anti-CD38 IgG4 monoclonal antibody. Modakafusp alfa is currently being evaluated in Phase I and II clinical trials in multiple myeloma and in solid tumors.

Methods To better understand the impact of modakafusp alfa on different immune cell subsets in immunocompetent mouse models, we generated a murine surrogate of modakafusp alfa comprising an anti-mouse CD38 murine IgG1 antibody genetically fused to two molecules of mouse attenuated IFNα (hereafter referred to as mCD38-mAtt).

Results Intraperitoneal administration of mCD38-mAtt demonstrated anti-tumor activity in a variety of syngeneic tumor models comprising different tumor immune microenvironments, levels of tumor CD38 expression, and intrinsic sensitivities to IFNα. Follow-on mechanistic studies, which targeted the depletion of specific immune cell subsets, revealed that loss of T cells and natural killer (NK) cells blunted tumor growth inhibition by mCD38-mAtt, indicating that these cells may be key effectors mediating the anti-tumor activity of mCD38-mAtt. In syngeneic tumor models, mCD38-mAtt enhanced NK cell activation in the tumor and selectively reduced the macrophage population, thereby modifying the tumor microenvironment. Treatment with mCD38-mAtt increased the presence and activation of tumor antigen-specific CD8 T cells, which correlated with a reduction in tumor mass.

Conclusions Taken together, these data indicate that mCD38-mAtt acts as an enhancer of both innate and adaptive immunity in immunocompetent mouse models that drives an anti-tumor immune response, independently of tumor CD38 expression.

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