SO-C101 induces NK cell cytotoxicity and potentiates antibody-dependent cell cytotoxicity and anti-tumor activity

Background SO-C101 is a superagonist fusion protein of interleukin (IL)-15 and the IL-15 receptor α (IL-15Rα) sushin domain, representing a promising clinical candidate for the treatment of cancer. SO-C101 specifically stimulates natural killer (NK) cells and memory CD8+ T cells with no significant expansion and activation of regulatory T cell compartment.

Methods Human NK cell proliferation, the expression of NK cell receptors and ADCC activity of human PBMC after stimulation with SO-C101 in vitro in combination with monoclonal antibodies were detected by flow cytometry. The anti-tumor efficacy of SO-C101 in combination with Daratumumab was assessed in a multiple myeloma SCID xenograft mouse model in vivo.

Results In this study, we show that SO-C101 induced proliferation and expansion of both major subsets of human NK cells, CD56brightCD16- and CD56dimCD16+. Furthermore, SO-C101 induced expression of the cytotoxic receptors NKp30 and NKG2D whereas no upregulation of the inhibitory receptors CD158a, CD158b and NKG2A was detected. Both NK cell subsets activated by SO-C101 exhibited cytotoxicity towards cancer cells in vitro. Using human PBMCs, we show that SO-C101 potentiated killing of tumor cells induced by several clinically approved therapeutic monoclonal antibodies such as Cetuximab, Daratumumab and Obinutuzumab in vitro. SO-C101 and Daratumumab monotherapy treatment inhibited tumor growth in vivo, however, their combination showed the strongest anti-tumor efficacy. Specifically, sequential administration of Daratumumab, followed by SO-C101 promoted complete tumor regression, compared to partial anti-tumor responses induced by the respective monotherapies.

Conclusions SO-C101 augments the anti-tumor activity of therapeutic antibodies by increasing NK cells mediated antibody-dependent cell cytotoxicity. These results support the evaluation of SO-C101 in combination with monoclonal therapeutic antibodies in clinical studies.

Ethics Approval The anti-tumor efficacy studies in mice were approved by the internal ethics board of the respective contract research organization (CRO).

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