566 ATOR-1017, A SECOND GENERATION 4–1BB ANTIBODY WITH POTENTIAL TO ENHANCE EFFICACY OF PD-1 THERAPIES

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Background ATOR-1017 is a Fcγ-receptor (FcγR) crosslinking dependent agonistic IgG4 antibody targeting the costimulatory receptor 4 1BB, designed for improved tolerability and efficacy. 4-1BB is highly expressed on tumor infiltrating CD8+ T effector cells (T effs) in several cancer indications. By binding to 4-1BB, ATOR-1017 enhances the activity of tumor reactive T effs and NK cells within the tumor and induces a potent anti-tumor response. 4-1BB is a promising candidate for immunotherapy and holds great potential for combination with other immunomodulatory antibodies, targeting e.g. the PD-1 pathway.

Methods Human 4-1BB knock-in transgenic mice with established murine colon carcinoma MC38 tumors were used to demonstrate anti-tumor efficacy after systemic treatment with ATOR-1017 in combination with anti-PD-1. Further, the effect of combining ATOR-1017 with anti-PD-1 on T cell activation (measured as production of IFNγ) was evaluated in a mixed lymphocyte reaction (MLR) assay with human primary CD4+ T cells and mature monocyte-derived DCs (mDC) expressing endogenous levels of both 4-1BB and PD-1.

Results ATOR-1017 in combination with anti-PD-1 improved survival and reduced tumor growth signifcantly in human 4-1BB knock-in transgenic mice with established tumors compared with each monotherapy alone. The potential for combining ATOR-1017 and PD-1 was further supported by data from a MLR assay demonstrating that the combination of ATOR-1017 with anti-PD-1 induced a more potent CD4+ T cells activation than each monotherapy alone.The functional activation profile of ATOR-1017 is expected to minimize the risk of systemic immune activation and toxicity, by directing a potent immune response to immune cells in tumor tissue and tumor draining lymph nodes. This is supported by early data from the ongoing first-in-human phase I study where ATOR-1017 has been shown to be safe and tolerable.

Conclusions In summary, these results support further clinical development of ATOR-1017 in combination with PD-1 antibodies. By combining ATOR-1017 with anti-PD-1, tumor infiltrating T cells can be more effectively activated and potentially increase the response rate in multiple indications.

Ethics Approval All animal procedures were in accordance to IACUC guidance

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