Background The pleiotropic TNF-α:TNFR axis plays a central role in the immune system. TNFR2 has been proposed to be both essential for the survival of Tregs, as well as providing important co-stimulatory signals for T cell activation and memory generation. In addition, the therapeutic potential of targeting TNFR2 for cancer treatment has been previously indicated. To gain further insight, we characterized the biophysical properties and in vitro and in vivo activities of human and mouse α-TNFR2-specific antibodies designed to agonize the receptor.

Methods A human lead candidate (BI-1910) and a mouse surrogate (mBI-1910) α-TNFR2 were identified. Agonistic activity on T cells were demonstrated for both antibodies in vitro. mBI-1910 showed potent anti-tumor activity both as a single agent and in combination with anti-PD1 in multiple immunocompetent tumor models. The antibody showed co-stimulation through TNFR2, which enhanced T cell activation and induced CD8+ T cell-dependent anti-tumor effects. These findings were confirmed using BI-1910 in human TNFR2 transgenic mice.

To address safety, a GLP toxicological study was performed in cynomolgus macaques. Three doses (1, 5, and 25 mg/kg) were given weekly for four consecutive weeks followed by a recovery period of eight weeks. In addition, cytokine release was studied in T cell stimulation assays and in a humanized mouse model. In parallel, multiple immune stimulation assays were studied in vitro using human cells to establish EC50 values and a clear relationship with dose, receptor occupancy and immune cell activation.

Results Four administrations of BI-1910 to cynomolgus macaques were well tolerated at all doses, with no associated clinical signs and no signs of cytokine release. Pharmacokinetic studies demonstrated an expected human IgG half-life at receptor-saturating doses. Interestingly, there was a clear dose-dependent T cell activation, evidenced by an increase in several T cell activation markers and a shift from naïve to effector memory T cells supporting the proposed mode of action. Importantly, the nature of BI-1910-induced T cell activation in cynomolgus macaques closely mirrored that in TNFR2 humanized mice, in which clear anti-tumor effects were also demonstrated.

Conclusions The strong similarities in BI-1910 induced immune response between mice and cynomolgus macaques shows promise that similar T cell activation and following anti-tumor effects will occur also in humans. Collectively, these studies support the upcoming phase I/II study in solid cancer patients planned to start in H2 2023.

Ethics Approval All data utilizing human blood or animals was approved by an ethic committee before the experiments were started.

Experiments using human blood were approved by the Regional committee for ethics approval in Lund, Sweden ID numbers 2018/37 and 2010/356

The murine experiments were approved by the Ethical committe of animal experiment in Lund and Malmö, Sweden ID numbers 5.8.18–19686/2022; 5.8.18–03333-2020; 5.8.18–02934-2020; 5.8.18–17196-2018

The non-human primate experiments were approved by Charles River Laboratories Evreux Ethics Committee (CEC), France, ID number 2850398