Pre-clinical development of TNFR2 ligand-blocking BI-1808 for cancer immunotherapy

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Background:

The pleiotropic TNF-α:TNFR axis plays a central role in the immune system. While the cellular expression of TNFR1 is broad, TNFR2 expression is mainly restricted to immune cells. The therapeutic potential of targeting TNFR2 for cancer treatment has been previously indicated and to gain further insight, we characterized a wide panel antibodies, generated from the n-CoDeR F.I.R.S.T™ target and antibody discovery platform. We identified parallel human and mouse TNFR2 specific, complete ligand (TNF-α) blocking antibodies and could show potent anti-tumor activity in several immune-competent models, both as single agent and in combination with anti-PD1 using a BI-1808 murine surrogate. The mechanism-of-action was shown to be FcγR dependent and likely mediated through a combination of intra-tumor T reg depletion, $CD8^+$ T cell expansion and modulation of tumor-associated myeloid cells. These findings were confirmed using BI-1808 in a humanized mouse model.

Methods:

To address safety of the human lead-candidate BI-1808 two toxicological studies were performed in cynomolgus monkeys. The first study was a dose-range-finding study and the second a GLP study where three doses (2, 20 and 200 mg/kg) were given weekly for four consecutive weeks followed by a recovery period of eight weeks. In addition, cytokine release was further studied in T cell stimulation assays and in a humanized mouse model. Moreover, the BI-1808 murine surrogate was used to study the relationship between dose, receptor occupancy (RO) and efficacy in immune competent mouse cancer experimental models.

Results:

Four weekly administrations of BI-1808 to cynomolgus monkeys were well tolerated at all doses, with no associated clinical signs, and no histopathological changes. Non-adverse and reversible increases in neutrophil counts and decreases in T cells were observed at all dose levels. No drug-related adverse events were observed and consequently the NOAEL for BI-1808 was determined to be 200 mg/kg. Pharmacokinetic studies demonstrated an expected half-life of two weeks at receptor saturation. There were no indications of cytokine release in any of the systems tested. Finally, we could show that to achieve max therapeutic effect, sustained RO was needed for approximately two weeks, covering the time it takes to generate a full adaptive Immune response.

Conclusions:

There is a clear association between RO and therapeutic effect and BI-1808 is well tolerated at doses associated with high and sustained RO. Collectively, these studies were used to determine the starting dose in upcoming phase I/II study in solid cancer aiming for first-patient in during December 2020.