regulatory T cells in the bone marrow, thereby reducing leukemia burden.

Conclusions Our results suggest that eliminating STAT3 permits the TLR9-driven reprogramming of AML cells into APCs to unleash T cell-mediated responses against leukemia.

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Abstracts

PRE-CLINICAL DEVELOPMENT OF TNFR2 LIGAND-BLOCKING BI-1808 FOR CANCER IMMUNOTHERAPY

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Background The pleiotropic TNF-alpha: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-alpha) 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 FcgR 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.

Ethics Approval The study on cynomolgous monkeys was conducted by Citox/Charles River Laboratories in compliance with animal health regulations, in particular: Council Directive No. 2010/63/EU of 22 September 2010 and French decree No. 2013-118 of 01 February 2013 on the protection of animals used for scientific purposes. Studies in mice were approved by the Swedish Animal Experiment Ethics Board, ethical permit/ethical license numbers 5.2.18-17/196/2018 and 5.8.18-03333/2020.

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SRF114 IS A FULLY HUMAN, CCR8 SELECTIVE IgG1 ANTIBODY THAT INDUCES DESTRUCTION OF TUMOR TREGS THROUGH ADCC

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Background T regulatory cells (Tregs) are potent suppressors of immune activation in the periphery and tumor microenvironment (TME). Tumor-infiltrating Tregs have also been associated with resistance to cancer therapies. Loss of peripheral Tregs can lead to widespread autoimmunity and tissue destruction; therefore, specifically depleting tumor Tregs is an attractive therapeutic approach to locally activate the immune system. CCR8 expression is highly restricted to tumor Tregs across multiple cancer types, supporting the notion that CCR8 targeting may induce tumor-specific Treg depletion while sparing peripheral Tregs. Moreover, depletion of CCR8 Tregs leads to significant tumor growth inhibition with correlative tumor Treg depletion in established CT-26 tumors. These data provide rationale for targeting CCR8 to deplete tumor Tregs. Here, we describe the development of SRF114, a fully human IgG1 anti-CCR8 antibody that induces tumor Treg destruction through antibody-dependent cellular cytotoxicity (ADCC).

Methods Virus panning against the N-terminal region of CCR8 and subsequent affinity maturation process led to discovery of SRF114, a fully human monoclonal antibody that is specific to CCR8. To evaluate SRF114 specificity, binding was profiled on recombinant CCR8 N-terminus, CCR8+ and CCR8- cell lines, and primary cell cultures. An extracellular protein target cell microarray was used to further validate specificity. SRF114 functional assays included the Promega CD16 (V/F variants) ADCC signaling assay, PBMC/293T-hCCR8+ cell co-culture experiments, and natural killer (NK)-activation assays targeting Raji-CCR8+ cell lines. To confirm tumor Treg binding and depletion, NK allogenic co-culture experiments were performed with SRF114 using isolated tumor infiltrating lymphocyte cultures from freshly resected tumors.

Results A tumor Treg-restricted pattern of CCR8 expression was confirmed using publicly available datasets and profiling of CCR8 expression on Tregs from fresh tumor tissues. SRF114 binds to CCR8-expressing 293T cells with pM affinity and not to parental cells. SRF114 does not bind any cell populations in PBMCs from healthy donors and has no other protein targets assessed by cell microarray. In dose-dependent ADCC assays, SRF114 induces cell killing with pM EC50 values, which is further enhanced by removing the fucose groups from the Fc-domain. Finally, SRF114 specifically binds to human tumor Tregs and induces killing of Tregs in NK co-culture experiments.

Conclusions The fully human anti- CCR8 antibody SRF114 specifically binds to and targets CCR8+ tumor Tregs for depletion, likely through ADCC. Through this mechanism, SRF114