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) sushi+ domain. SO-C101 effectively 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 mono-therapy 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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563 PHARMACODYNAMICS AND PHARMACOKINETICS OF SO-C101 IN CYMONOLGUS MONKEYS

**Background**

SO-C101 is a superagonist fusion protein of interleukin (IL)-15 and the IL-15 receptor α (IL-15Rα) sushi+ domain. SO-C101 effectively stimulates natural killer (NK) cells and memory CD8+ T cells with no significant expansion and activation of regulatory T cells which translates to anti-tumor efficacy in mouse.

**Methods**

In this study, we investigated different administration schedules of SO-C101 in cynomolgus monkeys to assess its pharmacodynamics and pharmacokinetics properties using intravenous (IV) and subcutaneous (SC) routes of administration.

**Results**

Subcutaneous administration of SO-C101 was more effective than IV administration in terms of activating the target immune cells which was correlated to the differences in SO-C101 exposure. Repeated administration of SO-C101 over two weeks promoted an increase of absolute lymphocyte counts and of the circulating NK and CD8+ T cell numbers. Moreover, two administrations on consecutive days were optimal and comparable to four daily administrations. We further determined an optimal schedule for a repetitive SO-C101 SC administration to achieve a cycle-dependent stimulation of NK and CD8+ T cells over the course of 10 weeks. These studies allowed to correlate the concentration to response relationship in vitro with the relationship between Cmax following SC administration and the resulting NK and CD8+ T cell activation levels in vivo. These data were used to determine the starting dose and subsequent dose escalation steps of SO-C101 in an ongoing Phase I clinical trial in patients with advanced solid tumors.

**Conclusions**

Since the potency of SO-C101 to activate NK and CD8+ T cells in vitro is equivalent between human and cynomolgus monkeys, these studies informed the dose and schedule selection for the ongoing Phase I clinical study (NCT04234113).

**Ethics Approval**

Pharmacodynamics and pharmacokinetics studies in cynomolgus monkeys were approved by Ethics Board of an appropriate contract research organizations (CROs).

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