TRIAL OF SNX281, A SYSTEMICALLY DELIVERED SMALL MOLECULE STING AGONIST, IN SOLID TUMORS AND LYMPHOMAS

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Background Innate immune activation is a desirable goal in anticancer therapy. Stimulator of Interferon Genes (STING) agonists represent one approach to this goal; to date most studies have utilized intra-tumoral administration. SNX281 is a novel small molecule agonist of human and mammalian STING with favorable pharmacokinetic properties that enable systemic intravenous administration. The molecule dimerizes in the binding site of STING to induce activation. In preclinical studies using THP-1 cells or human PBMCs, SNX281 caused both pathway activation and the induction of signature cytokines, IFN- β , TNF- α and IL-6 in a STING dependent manner. Intravenously delivered SNX281 caused complete and durable tumor regression in mice bearing CT26 colon carcinomas with induction of immune memory. Mice that were cured of their primary CT26 tumors were completely resistant to re-challenge. Increased T cell responses were observed against the endogenous CT26 rejection antigen AH1. Maximal tumor control depended on CD8+ T cells, confirming the involvement of an adaptive immune component in SNX281 mediated anti-tumor activity, although some tumor control was observed even in the absence of T cells. In addition, combining STING-dependent T cell priming induced by SNX281 with anti-PD-1 resulted in robust antitumor activity and significant survival benefit in multiple tumor models (CT26, MC38 and B16- F10) that are resistant to checkpoint therapy alone.

Methods This is a multicenter, open-label, phase I dose-escalation followed by dose expansion study of SNX281 as monotherapy and in combination with pembrolizumab. SNX281 is administered as a 30-minute intravenous infusion QW for 3 weeks followed by Q3W for six cycles. Eligible patients for the dose escalation phase will have, among other criteria, histologically confirmed advanced solid tumors or lymphomas which have failed prior therapy and/or are not eligible for therapies, as well as adequate organ function, life expectancy of at least 12 weeks, and measurable disease. Monotherapy dose escalation accrued initially with single patient cohorts advancing to a 3+3 design. The dose expansion phases of each treatment arm will begin following the determination of an MTD or alternative dose of SNX281 in each respective treatment arm. The single-agent treatment arm of SNX281 is planned to evaluate at least 2 expansion cohorts in ovarian cancer and colorectal carcinoma while the combination treatment arm of SNX281 and pembrolizumab is planned to enroll subjects with advanced cancer who have relapsed on or have become refractory to prior immune checkpoint therapy given in an indicated setting. Clinical Trial Information: NCT04609579

Trial Registration NCT04609579

Ethics Approval IRB approval from IntegReview IORG0000689.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.495>