429 PHASE 1 DOSE ESCALATION STUDY OF THE AGONIST REDIRECTED CHECKPOINT, SL-172154 (SIRPα-FC-CD40L) IN SUBJECTS WITH PLATINUM-RESISTANT OVARIAN CANCER

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Background SIRPα-Fc-CD40L is a hexameric, bi-functional fusion protein consisting of SIRPα (binding affinity to CD47 is 0.628 nM) linked to CD40L (binding affinity to CD40 is 4.74 nM) through an Fc linker protein.[1] By augmenting antigen processing and promoting antigen presenting cell (APC) maturation, this molecule is designed to bridge innate and adaptive immunity, enhancing tumor cell phagocytosis and antigen cross-presentation to CD8 T cells.

Methods The first-in-human, Phase 1 dose escalation study is evaluating SL-172154 as monotherapy in patients (pts) with platinum resistant ovarian, fallopian tube and primary peritoneal cancers. Objectives include evaluation of safety, dose-limiting toxicity (DLT) and recommended phase 2 dose (RP2D), pharmacokinetic (PK) parameters, pharmacodynamic (PD) effects and antitumor activity based on RECIST.

Results As of 6 July 2021, 14 heavily pretreated pts (median age, 67 years) were enrolled and treated with intravenous (IV) administration of SL-172154 across 4 dose levels on 2 schedules: schedule 1 (day 1, 8, 15, 29, Q2 weeks) at 0.1, 0.3 mg/kg and schedule 2 (weekly) at 0.3, 1.0, 3.0 mg/kg. The most common treatment-related (>20%) adverse events (AEs) of any grade (G) were fatigue (n=7, 50%), infusion-related reactions (IRR) (n=6, 43%), nausea (n=4, 29%), and decreased appetite (n=3, 21%). Treatment-related IRRs (G1/G2) generally occurred near the end of infusion or immediately post-infusion; the full dose was able to be delivered in each IRR event, and subsequent infusions in patients having IRRs were managed with pre-medications. No treatment related ≥G3 AEs or DLTs have occurred. CD47 receptor occupancy (RO) on leukocytes approached 90% at 1.0 and 3.0 mg/kg. Minimal binding to CD47+ red blood cells was observed at all dose levels. CD40 RO on B cells was >60% at doses ≥0.1 mg/kg and 75%–100% at 1.0 and 3.0 mg/kg. Rapid, transient B cell and monocyte margination was observed following infusion of SL-172154 and was consistent with dose-dependent increases in IL-12, MCP-1, MIP-1β, MIP-1α, and MDC. No appreciable increases in IL-6 or TNFα were noted and there was no correlation between IRRs and cytokine increases. Among 12 evaluable pts, the best response was stable disease in 3 pts.

Conclusions SL-172154 has been well tolerated with no evidence of anemia, thrombocytopenia, liver dysfunction or cytokine release syndrome. A unique serum cytokine signature consistent with CD40 RO and activation has been observed and this signature is maintained following repeat dosing. Dose escalation is ongoing.

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Trial Registration NCT04406623

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Ethics Approval This study is being conducted in full conformity with the Declaration of Helsinki and was approved by all IRBs/ethics committees from each clinical site participating in the study. Specific approval numbers can be provided upon request.

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