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. 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

REFERENCES

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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