Phase 1 dose escalation study of the agonist redirected checkpoint, SL-172154 (SIRPα-Fc-CD40L) in subjects with platinum-resistant ovarian cancer (NCT04406623)

#429

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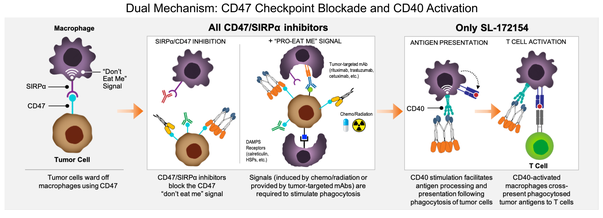
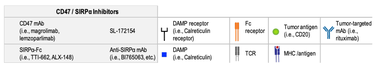
Background

- Agonist Redirected Checkpoint (ARC™) platform adjoins the extracellular domain (ECD) of a Type 1 membrane protein to the ECD of a Type 2 membrane protein via a central Fc domain derived from an IgG4 antibody. These bi-functional proteins are engineered to block the transmission of an immune inhibitory signal from tumor cells while concomitantly delivering an immune stimulatory signal to an immune cell within the tumor microenvironment.
- SL-172154 (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] SL-172154 is designed to bridge innate and adaptive immunity by enhancing tumor cell phagocytosis and antigen cross-presentation to CD8 T cells (**Figure 1**).
- mSIRPα-Fc-CD40L provided higher rates of tumor rejection and long-term immunity compared with CD47 blocking antibodies, CD40 agonist antibodies, or the combination of the two in preclinical studies.[1]
- This first-in-human Phase 1 dose escalation study is currently evaluating SL-172154 as monotherapy in subjects with platinum resistant ovarian cancer. Data available as of 15 September 2021 are presented.

Figure 1. Pairing Rationale For SL-172154

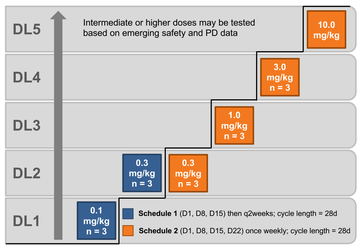




Methods

Study Design

Figure 2. Dose Escalation per modified Toxicity Probability (mTPI-2) Design (N=15)



- The planned dose escalation is in half-log increments.
- At least 3 subjects were enrolled into sequential dose levels (DL) and evaluated for dose limiting toxicity (DLT) in the first cycle of treatment.
- Subjects receive intravenous (IV) administration of SL-172154 on Schedule 1 or Schedule 2 until disease progression, unacceptable toxicity, or withdrawal of consent.
- Currently enrolling 10mg/kg

Study Objectives

Primary Objectives

- Evaluate safety; identify the maximum tolerated dose or maximum administered dose of SL-172154

Secondary Objectives:

- Identify a dose and schedule (i.e., a recommended phase 2 dose [RP2D])
- Characterize the PK and immunogenicity
- Evaluate anti-tumor activity per RECISTv1.1 for solid tumors

Exploratory Objectives:

- Assess receptor occupancy of SIRPα and CD40 on PBMCs
- Investigate pharmacodynamic (PD) effects in blood and tumor

Eligibility Criteria

Key Inclusion Criteria

- Locally advanced or metastatic ovarian cancer, primary peritoneal cancer or fallopian tube cancer
- Refractory to existing therapy(ies) and ineligible for further platinum therapy. Subjects with homologous recombination deficiency positive disease must have received prior PARPi with or without bevacizumab.
- Age 18 years or older
- ECOG performance status of 0 or 1
- Measurable disease per RECIST v1.1

Key Exclusion Criteria

- Primary platinum refractory as defined by progressing during or within 1 month of upfront platinum therapy
- Prior treatment with an anti-CD47 or anti-SIRPα targeting agent or a CD40 agonist.
- Documented history of autoimmune disease or active pneumonitis
- Concurrent use of systemic corticosteroids or other immunosuppressive medication

Results

Subject Characteristics

Table 1. Tumor Characteristics

Total number of subjects, n (%)		N = 15
Cancer type	Ovarian cancer	9 (60)
	Primary peritoneal cancer	4 (27)
	Fallopian tube cancer	2 (13)
FIGO stage	Stage III	6 (40)
FIGO = International Federation of Gynecology and Obstetrics	Stage IV	9 (60)
Grade	High grade	11 (73)
	Grade 3	1 (7)
	Unknown	3 (20)
Histologic classification	Serous carcinoma	11 (73)
	Adenocarcinoma	2 (13)
	Serous adenocarcinoma	2 (13)

- 15 subjects of median age 67 years (range 33-79), having received a median of 5 prior lines of systemic therapy (range 2-7) were treated with IV SL-172154 across 4 dose levels on 2 schedules.
- 13 of 15 subjects had an ECOG PS of 1 at baseline
- 6 subjects were treated on schedule 1 (days 1, 8, 15, 29, q2wks) at 0.1 mg/kg (n=3) and 0.3 mg/kg (n=3).
- 9 subjects treated on schedule 2 (once weekly) at 0.3 mg/kg (n=3), 1.0 mg/kg (n=3), and 3.0 mg/kg (n=3).
- Most subjects had primary ovarian cancer (n=9; 60%), FIGO stage IV (n=9; 60%), high grade disease (n=11; 73%) and serous carcinoma histology (n=11; 73%) as shown in **Table 1**.

Safety

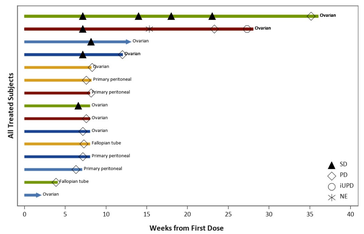
Table 2. Most Common AEs in All Treated Subjects

Total number of subjects, n (%)	N = 15
Any AE	15 (100)
Fatigue	9 (60)
IRR	8 (53)
Nausea	5 (33)
Diarrhea	4 (27)
Decreased appetite	3 (20)
Dehydration	3 (20)
Pruritus	3 (20)
Abdominal distention	2 (13)
Back pain	2 (13)
Chills	2 (13)
Constipation	2 (13)
Dyspnea	2 (13)
Hypomagnesemia	2 (13)
Injection site reaction	2 (13)
Vomiting	2 (13)

- No DLTs have been observed with SL-172154 on either schedule at doses ranging from 0.1 mg/kg to 3.0 mg/kg.
- 15 subjects (100%) experienced an adverse event (AE) on treatment. The most common AEs, occurring in ≥ 3 subjects (all causality) were fatigue, infusion-related reaction (IRR), nausea, diarrhea, decreased appetite, dehydration, and pruritus (**Table 2**).
- 14 subjects (93%) had treatment-related AEs (TRAEs). The most common TRAEs, occurring in ≥ 2 subjects, were IRR (n=8; 53%) fatigue (n=7; 47%), nausea (n=4; 27%), decreased appetite (n=3; 20%), chills (n=2; 13%), diarrhea (n=2; 13%) and dyspnea (n=2, 13%). No ≥ G3 TRAEs have been reported.
- 8 subjects (53%) had infusion-related reactions (IRRs) dosed at 0.3 mg/kg (n=3), 1.0 mg/kg (n=2) and 3.0 mg/kg (n=3); 1 IRR event was G3 and deemed secondary to iron infusion, 14 IRRs were G2 in severity and 2 IRRs were G1 in severity.
- IRRs were manageable with pre-medications, did not prevent completion of IV dosing or lead to discontinuation of SL-172154.
- 13 subjects (87%) subjects have discontinued SL-172154; 12 discontinued due to radiological or clinical progression and 1 subject elected to stop treatment.

Antitumor Efficacy

Figure 3. Tumor Response and Duration of Treatment



Best response among 14 efficacy evaluable subjects with post-baseline scan:

- SD, n=4
- PD, n=9
- NE, n=1 (Subject had SD but did not meet protocol-specified minimum interval for SD)
- 1 subject (3 mg/kg) had not reached the first on-treatment disease assessment at week 8

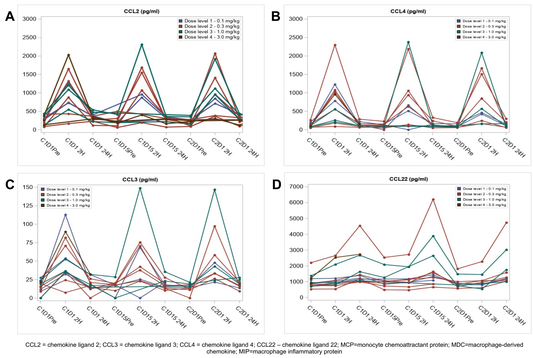
iUPD = unconfirmed progressive disease (IRECIST) NE = non-evaluable; PD = progressive disease; SD = stable disease

Pharmacokinetics

- C_{max} and AUC_{inf} increases disproportionately with increasing dose
- Clearance decreases with increasing dose
- PK appears to be biphasic at 1.0 and 3.0 mg/kg
- Elimination phase of the curve is not fully characterized at the doses studied

AUC_{inf} = Area under the curve, time 0 extrapolated to infinity; C_{max} = Maximum concentration

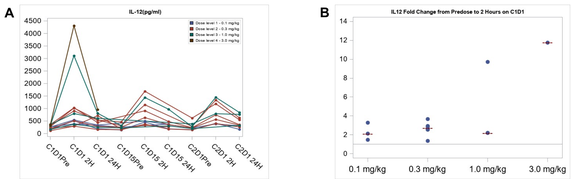
Figure 4. SL-172154 Stimulates Reproducible Increases in Serum Cytokines Following Repeated Dosing



CCL2 = chemokine ligand 2; CCL3 = chemokine ligand 3; CCL4 = chemokine ligand 4; CCL22 – chemokine ligand 22; MCP=monocyte chemoattractant protein; MDC=macrophage-derived chemokine; MIP=macrophage inflammatory protein

Plasma was prepared from subject blood draws at the indicated times. Cytokine levels were assayed using a multiplexed ECL ELISA method and select. subject level cytokines are shown. Proinflammatory chemokines, A) CCL2 (MCP-1), B) CCL4,(MIP-1β) C) CCL3 (MIP-1α), and D) CCL22 (MDC) exhibited dose-dependent increases in plasma levels at all post infusion measurements. These increases were of equal duration and magnitude across all infusion intervals.

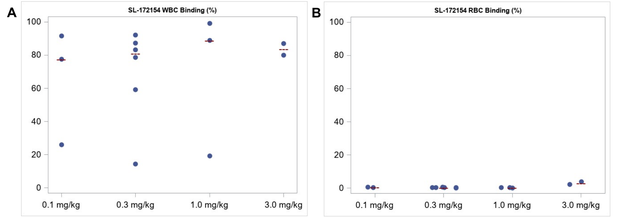
Figure 5. SL-172154 Stimulates Dose-Dependent and Reproducible Increases in Serum IL-12



IL-12=interleukin-12

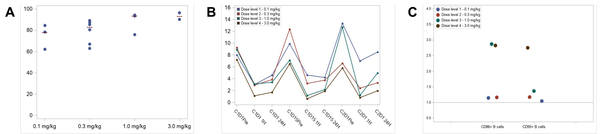
A) Subject level interleukin 12 (IL-12), a mediator of TH1 proinflammatory responses over time typify the cyclic effector cytokine responses observed in study subjects. B) Median responses at the first infusion (red bars), preliminarily appear to be dose dependent.

Figure 6. SL-172154 Preferentially Binds CD47 on Leukocytes but not RBCs



A) CD47 receptor occupancy (RO) was evaluated by fluorescence activated cell sorting (FACS) analysis using whole blood on both red blood cells (RBC) and white blood cells (WBC, leukocytes). At one-hour post infusion on C1D1, median CD47 RO on leukocytes (red bars) is ~80%. B) CD47 RO on RBC is <5% for all dose levels.

Figure 7. SL-172154 Stimulates Dose-Dependent B Cell Margination and Activation



B cells represent a large pool of circulating immune cells expressing high levels of CD40. Fluorescence activated cell sorting (FACS) panels were designed to interrogate CD40 receptor occupancy and states of activation and maturation. On C1D1, nearly all (~80%) CD40+ B cells marginate, or exit the circulation, within one-hour post-infusion. A) Median frequency of marginating cells increases in a dose-dependent manner (red bars). Receptor engagement is ~100% at all dose levels (data not shown).[3] B) Median B cell frequencies return to pre-infusion levels by the next infusion, maintaining a cyclic pattern of egress and return with each infusion cycle. C) Returning B cells exhibit increases in the co-stimulatory marker CD86, as well as the maturation marker CD95, suggesting that SL-172154 can induce phenotypic changes.

Similarly, CD14+ monocytes marginate, or exit the circulation, within one hour of infusion; returning to pre-infusion levels by the next infusion, maintaining a cyclic pattern of egress and return for each infusion cycle. The observed pattern of margination is driven largely by CD86+ classical- and non-classical monocytes (data not shown).

Conclusions

- SL-172154 was well-tolerated with no DLTs or evidence of anemia, thrombocytopenia, liver dysfunction, cytokine release syndrome or pneumonitis. Dose escalation continues at 10 mg/kg.
- Preliminary PK parameters for SL-172154 suggest target-mediated drug disposition via receptor binding.
- High receptor occupancy was observed for SL-172154 on CD47+ leukocytes at the doses studied, with minimal binding to RBCs.
- Binding of SL-172154 to CD40+ B cells and monocytes led to rapid activation and margination post infusion.
- Cyclical increases in innate and adaptive serum cytokines were consistent with CD40 receptor engagement and activation.[3] There were no increases in IL-6 or TNFα, nor evidence of bell-shaped dose responses.
- SL-172154 has been well-tolerated at doses which saturate both CD40 and CD47, with evidence of on-target PD activity which has not yet plateaued, warranting further dose escalation.

Acknowledgements

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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.

References

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