Phase 1 dose escalation of an agonist redirected checkpoint (ARC) fusion protein, SL-279252 (PD1-Fc-OX40L), in subjects with advanced solid tumors or lymphomas (NCT03894618)

#494

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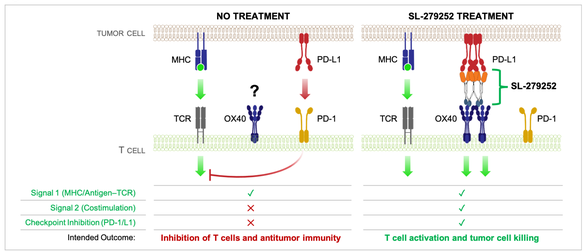
Background

- Shattuck Labs' 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 a T cell within the tumor microenvironment.
- SL-279252 (PD1-Fc-OX40L), is a hexameric, bi-functional fusion protein with an ECD of PD-1 (70 pM affinity to PD-L1) linked to the ECD of OX40L (324 pM affinity for OX40) through an Fc linker (**Figure 1**). The therapeutic activity of mPD1-Fc-OX40L in murine tumors was superior to PD-1 blocking, OX40 agonist or combination antibody therapy.[1]
- This first-in-human Phase 1 dose escalation study is currently evaluating SL-279252 as monotherapy in subjects with advanced solid tumors or lymphomas. Data available as of 11 June 2021 are presented.

Figure 1. SL-279252 Mechanism of Action



Methods

Study Objectives

Primary Objectives:
- Evaluate the safety and identify the maximum tolerated dose (MTD) or maximum administered dose (MAD) of SL-279252

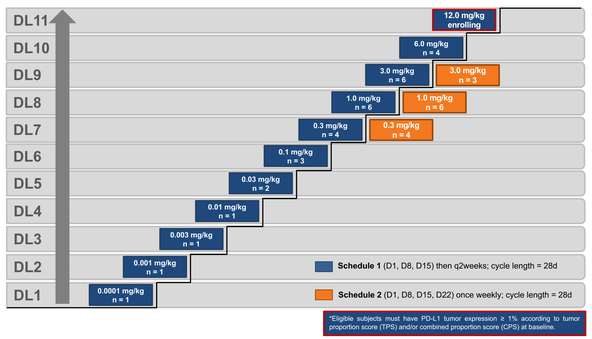
Secondary Objectives:
- Identify a dose and schedule [i.e., a recommended phase 2 dose (RP2D)]
- Characterize the PK and immunogenicity
- Evaluate anti-tumor activity per immune response evaluation criteria for solid tumors (iRECIST)

Exploratory Objectives:
- Assess receptor occupancy of PD-L1 and OX40
- Investigate pharmacodynamic (PD) effects in blood and tumor

Study Design

- Accelerated titration n ≥ 1 subjects per cohort until Grade 2 (G2) toxicity was observed or dose level 6 (DL6) was reached.
- Subjects received intravenous (IV) administration of SL-279252 on Schedule 1 or Schedule 2 until disease progression, unacceptable toxicity or withdrawal of consent.
- Schedule 2 was explored at a dose range where immunologic activity was being observed.

Figure 2. Dose Escalation per Keyboard Design[2] (N = 43)



Eligibility Criteria

Key Inclusion Criteria
- Subjects with locally advanced or metastatic solid tumors or lymphomas including:
  - melanoma, non-small cell lung cancer (NSCLC; squamous, adenocarcinoma or adeno-squamous), urothelial carcinoma, head and neck squamous cell carcinoma, squamous cell cervical cancer, gastric or gastro-esophageal junction adenocarcinoma, squamous cell carcinoma (SCC), SCC of the anus, renal cell carcinoma, Hodgkin's lymphoma, microsatellite instability-high (MSI-H) or mismatch repair deficient (MMRD) solid tumors.
- Age 18 years or older
- ECOG performance status of 0 or 1
- Measurable disease as defined by iRECIST (solid tumors) or RECIL 2017 (lymphoma)

Key Exclusion Criteria
- Received more than 2 prior checkpoint inhibitor (CPI*) containing regimens
- Refractory to last PD1/L1 inhibitor-based therapy defined as disease progression within 3 months of treatment. Prior PD-1/PD-L1 inhibitor therapy was not required.
- Documented history of autoimmune disease or active pneumonitis
- Untreated CNS or leptomeningeal metastases
- Concurrent use of corticosteroids or other immuno-suppressive medication

*Prior CPI therapy includes drugs that inhibit PD-1, PD-L1 or CTLA-4

Results

Subject Characteristics and Safety Summary

- 43 subjects received IV SL-279252 (median age = 64 years, 56% male, median of 3 prior systemic therapies (range of 0-5) for metastatic disease).
- A total of 25 subjects (58%) were checkpoint inhibitor-experienced (CPI).
- The most common tumor types were ocular melanoma (n=7; 16%), NSCLC adenocarcinoma (n=6; 14%), gastric adenocarcinoma (n=5; 12%), RCC (n=4; 9%) and HNSCC (n=4; 9%) as shown in **Table 1**.
- No DLTs have been observed with SL-279252 on either schedule at doses ranging from 0.0001 mg/kg to 6.0 mg/kg.
- 40 subjects (93%) experienced an AE on treatment (**Table 2**).
- 19 subjects (44%) had treatment-related AEs (TRAEs). The most common reported TRAEs, occurring in ≥ 5% of subjects, were maculo-papular rash (n =4; 9%), infusion-related reaction (IRR; n=3; 7%), asthenia, constipation, decreased appetite, fatigue, hypothyroidism, night sweats and pruritis (remainder were n=2; 5%).
- The only G3 TRAEs were neutropenia (2%) and hypercalcemia (2%); each occurred in 1 subject. No G4/5 TRAEs occurred.
- IRRs occurred in 3 subjects (7%) dosed at 1.0 mg/kg (n=2) or 3.0 mg/kg (n=1); 6 events were G2 in severity and 1 event was G1 in severity. IRRs were manageable and did not prevent completion of IV dosing or lead to discontinuation of SL-279252.
- Most subjects (81%) discontinued SL-279252 due to radiological or clinical progression; 2 subjects discontinued due to AEs unrelated to SL-279252, 2 subjects withdrew consent, and 1 subject died due to cholecystitis and renal failure that were deemed to be unrelated to SL-279252 per investigator attribution.

Table 1. Tumor Characteristics

Cancer Type, n (%)	N = 43
Ocular Melanoma	7 (16)
Adeno NSCLC	6 (14)
Gastric Adenocarcinoma	5 (12)
Renal Cell Cancer	4 (9)
SCC of Head and Neck	4 (9)
Squamous Cell Cervical	3 (7)
MSI-H or MMRD Solid Tumors*	3 (7)
Mucocutaneous Melanoma	2 (5)
Urothelial Cancer	2 (5)
Gastro-esophageal Junction	2 (5)
Esophageal Adenocarcinoma	1 (2)
Diffuse Large B cell lymphoma	1 (2)
SCC of the Skin	1 (2)
SCC of the Anus	1 (2)
Squamous NSCLC	1 (2)

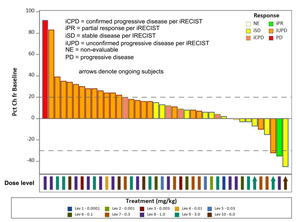
* Endometrial, upper gastrointestinal track, and ileum and appendix

Table 2. All Causality AEs in >10% subjects

Total number of subjects, n (%)	N = 43
Any AE	40 (93%)
Constipation	11 (26%)
Back pain	8 (19%)
Anemia	7 (16%)
Decreased appetite	7 (16%)
Abdominal pain	6 (14%)
Cough	6 (14%)
Fatigue	6 (14%)
Insomnia	6 (14%)
Nausea	6 (14%)
Diarrhea	5 (12%)
Rash maculo-papular	5 (12%)

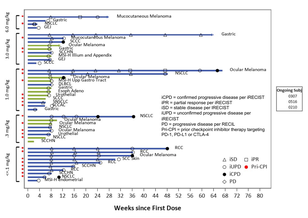
Antitumor Efficacy

Figure 3. Percentage Change in Target Tumor Size from Baseline



- Best response was 1 durable confirmed iPR (ocular melanoma, 4 prior systemic regimens, CPI-experienced) in a subject who remained on treatment for >1 yr
- iSD in 12 pts (1 unconfirmed iPR in a CPI-experienced subject with cutaneous melanoma). iSD for > 24 weeks occurred in 5/12 subjects.
- Among these 5 subjects, 4 subjects had received prior CPI therapy targeting PD-1, PD-L1 or CTLA-4

Figure 4. Duration on Study Treatment



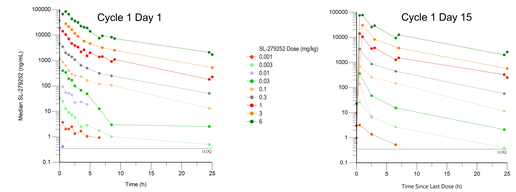
- Median number of doses is 7 (range 2-32)
- Median duration on study treatment is 1.9 months (range 0.5-15.4)

DLBCL = diffuse large B cell lymphoma; Esoph Adeno = esophageal adenocarcinoma; GEJ = gastro-esophageal junction; MSI-H = microsatellite instability high; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; RECIL – response evaluation criteria for lymphomas; SCC = squamous cell carcinoma; SCCAC = squamous cell carcinoma of the anal canal; SCCC = squamous cell carcinoma of the cervix; SCCHN = squamous cell carcinoma of head and neck; SNSCLC = squamous non-small cell lung cancer; SCC skin = squamous cell carcinoma of skin

Pharmacokinetics

- PK profiles are well-characterized for doses ≥ 0.003 mg/kg
- SL-279252 C_{max} and AUC increased linearly up to 3.0 mg/kg, and a greater than proportional increase in AUC was observed at 6.0 mg/kg.
- The preliminary half-life ($T_{½}$) is approximately 23 hours.
- For both schedules, within subject exposure (C_{max} and AUC_{24}) is similar on Day 1, 15, and 29, indicating no accumulation or time-dependent changes in PK.

Figure 5. Pharmacokinetics of SL-279252

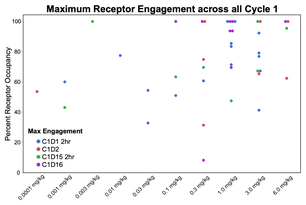


Immunogenicity

- High background interference in samples from healthy volunteers and cancer patients was detected during anti-drug antibody (ADA) assay development presumed to be due to circulating anti-PD-1 therapeutic antibodies while in some cases the potential source of the interference has not been identified.
- Study subjects have demonstrated a high rate of positive tests at baseline prior to any treatment with SL-279252.
- Delayed IRR (n=3) and/or accelerated clearance (n=2) observed in 4/43 subjects. These events may indicate clinically relevant, treatment-emergent ADA.
- Efforts continue to develop validated assays to assess ADA confirmation and neutralization.

Pharmacodynamics

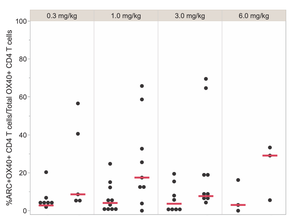
Figure 6. Maximal OX40 Receptor Engagement (RE) by Dose



Fluorescence activated cell sorting (FACS) panels were designed to evaluate OX40 CD4 T cell receptor engagement on subject peripheral blood samples (N=43). A detailed evaluation of receptor engagement is discussed at this meeting by González and colleagues.[3] Maximum OX40 receptor engagement across all SL-279252 doses and schedules occurring during cycle 1 is plotted.

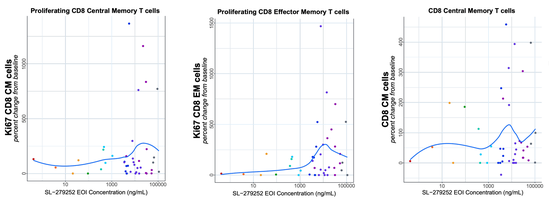
- Maximal OX40 RE is noted at doses ≥ 1 mg/kg.
- Low level of PD-L1 expression on peripheral leukocytes precluded determination of PD-L1 receptor occupancy.

Figure 7. Durable Binding of SL-279252 to OX40+ CD4 T cells



FACS analysis of T cells in peripheral blood. At baseline (C1/D1 pre) subjects had low median levels of (background) ARC staining on OX40+ CD4 T cells that increased prior to administration of the third infusion (C1D15 Pre). These results suggest that repeated SL-279252 dosing leads to durable binding for at least 7 days.

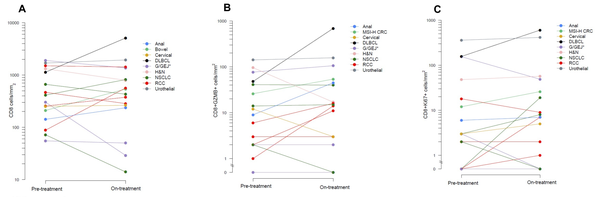
Figure 8. Dose Dependent Increases in CD8+ T cells



CM = central memory; EM = effector memory; % from BL = percent change from baseline; EOI = end of infusion

- Increases in the number of proliferating and total CD8 central memory and effector memory T cells were seen at doses of ≥ 1.0 mg/kg in some subjects.
- No significant trends of change in cytokines or chemokines were observed following IV doses of SL-279252.

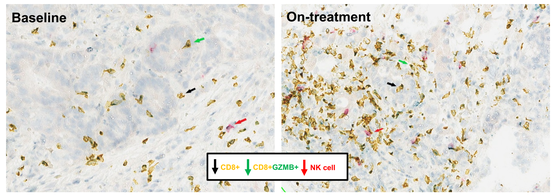
Figure 9. Increased CD8 T Cell Infiltration in On-Treatment Biopsies in Response to SL-279252 Treatment



GZMB = granzyme B

Change in CD8+GZMB+ and CD8+Ki67+ densities in subjects treated with SL-279252.
Tumor CD8+(A), CD8+GZMB+ (B) and CD8+Ki67+ (C) density is shown for pre and on-treatment biopsies. The on-treatment biopsy timepoint is at week 3 in the first treatment cycle between days 16-23.

Figure 10. Increase in CD8/GZMB/Nkp46 in MSI-H CRC Subject dosed at 3 mg/kg



CRC = colorectal cancer; NK = natural killer

Conclusions

- SL-279252 was well-tolerated in heavily-pretreated subjects with refractory solid tumors with no MTD reached.
- SL-279252 has exhibited antitumor activity in predominantly CPI-experienced subjects dosed on Schedule 1 (D1, D8, D15, then q2weeks in 28d cycles)
- 1 confirmed iPR at 1.0 mg/kg, iSD as best response occurred in 12 subjects (5/12 subjects had iSD for >24 weeks; and 1 unconfirmed iPR at 6 mg/kg).
- SL-279252 exhibited linear PK at doses up to 3.0 mg/kg, and a greater than proportional increase in AUC was observed at 6.0 mg/kg suggesting potential receptor saturation. The preliminary half-life ($T_{½}$) is approximately 23 hours.
- Dose-dependent OX40 receptor engagement on CD4+OX40+ T cells and OX40-dependent PD effects have been observed in subjects dosed with SL-279252 on Schedule 1.
- Trends for PK/PD effects and durable antitumor activity at doses of SL-279252 ≥ 1.0 mg/kg suggests dose exploration in PD-L1 expressing cancers is warranted beyond 6.0 mg/kg.
- Dose escalation of SL-279252 continues at 12.0 mg/kg to fully characterize PK, PD, and antitumor activity.

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

1. Fromm G, de Silva S, Johannes K, Patel A, Hornblower JC, Schreiber TH. Agonist redirected checkpoint, PD1-Fc-OX40L, for cancer immunotherapy. J Immunother Cancer. 2018;6: 1-16.
2. Yan F, Mandrekar SJ, Yaun Y. Keyboard: a novel bayesian toxicity probability interval design for phase I clinical trials. Clin Cancer Res. 2017;23(15):3994-4003.
3. González L, Ma B, Hernandez R, McKay H, Rangwala F, Pandite L, Schreiber, TH. Development of an integrated method to quantify receptor occupancy for agonist immunotherapeutics that stimulate target cells to migrate from the peripheral blood. SITC 36th Annual Meeting 2021 Washington, DC (Abstract #3).