PHASE 1 DOSE ESCALATION AND DOSE EXPANSION STUDY OF AN AGONIST REDIRECTED CHECKPOINT (ARC) FUSION PROTEIN, SL-279252 (PD1-FC-OX40L), IN SUBJECTS WITH ADVANCED SOLID TUMORS OR LYMPHOMAS

¹Melissa Johnson*, ²Lilian Siu, ³David Hong, ⁴Patrick Schoffski, ⁵Vladimir Galvao, ⁶Fatima Rangwala, ⁶Robert Hernandez, ⁶Louis Gonzalez, ⁶Bo Ma, ⁶Lini Pandite, ⁵Irene Brana. ¹Sarah Cannon Research Institute, Nashville, TN, USA; ²Princess Margaret Cancer Center, Toronto, Canada; ³MD Anderson Cancer Center, Houston, TX, USA; ⁴Univ. Hospitals, Leuven Cancer Institute, Leuven, Belgium; ⁵Vall d'Hebron Institute of Oncology, Barcelona, Spain; ⁶Shattuck Labs, Durham, NC, USA

Background PD1-Fc-OX40L, is a hexameric, bi-functional fusion protein with an extracellular domain (ECD) of PD-1 (70 pM affinity to PD-L1) linked to the ECD of OX40L (324 pM affinity to OX40) through an Fc linker. The therapeutic activity of mPD1-Fc-OX40L in murine tumors was superior to PD1 blocking, OX40 agonist or combination antibody therapy.¹

Methods The first-in-human, Phase 1 dose escalation study is evaluating SL-279252 as monotherapy in patients (pts) with advanced solid tumors or lymphomas. Objectives include evaluation of safety, dose-limiting toxicity (DLT), recommended phase 2 dose (RP2D), pharmacokinetic (PK) parameters, pharmacodynamic (PD) effects, and anti-tumor activity per iRECIST.

Results As of 11 June 2021, 43 pts were enrolled and dosed intravenously with SL-279252 (median age 64 years; 56% male; median [range] of 3 [0–5] prior systemic therapies for metastatic disease): 30 pts were treated on schedule 1 (day 1, 8, 15, 29, then every 2 weeks) from dose level 0.0001–6 mg/kg, and 13 pts treated on schedule 2 (weekly) from dose level 0.3–3 mg/kg. 58% of pts were PD-1/L1 inhibitor experienced, and most tumors lacked PD-L1 expression. Common (>15%) treatment emergent adverse events (AEs) of any grade (G) were constipation in 11 (26%) pts, back pain 8 (19%) pts, anemia 7 (16%) pts and decreased appetite 7 (16%) pts. Infusion-related reactions (G1/2) were noted in 3 (7%) pts. G3 treatment-related AEs (TRAEs) were neutropenia (2%) and hypercalcemia (2%); no G4/5 TRAEs or DLTs occurred. SL-279252 C_{max} and AUC increased linearly up to 3mg/kg, and greater than proportional increase in AUC was observed at 6 mg/kg. The preliminary T_{1/2} was ~23 hours. Dose-dependent receptor occupancy on CD4+OX40+ T cells persisted for >7 days and these cells rapidly margined from the peripheral blood post infusion. Increases in the number of proliferating central and/or effector memory T cells were seen in some pts at doses of ≥1mg/kg. Analysis of paired tumor biopsies is ongoing. Best response was 1 durable confirmed iPR (ocular melanoma, 4 prior systemic regimens) in a pt who remained on treatment for >1 yr, and iSD in 12 pts (1 unconfirmed iPR). iSD for > 24 wks occurred in 6/12 pts.

Conclusions SL-279252 is well-tolerated in pts with refractory solid tumors with no maximum tolerated dose (MTD) reached. OX40-dependent PD effects and durable anti-tumor activity was observed. Trends for PK/PD effects at ≥1 mg/kg suggests dose exploration in PD-L1 expressing cancers is warranted beyond 6 mg/kg.

Acknowledgements Thanks are extended to study participants; Takeda Pharmaceutical Company, Boston, MA, United States; Cathrine Leonowens, PhD, Nuventra Pharma Sciences, Durham, NC, United States and Cadence Communications and Research, Thousand Oaks, CA, United States. This study is

funded by Shattuck Labs, Inc. Austin, TX and Durham, NC, United States.

Trial Registration NCT03894618

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.

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.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.494>