CT251

Phase 1/2 Study of HST-1011, an Oral CBL-B Inhibitor, Alone and in Combination with Anti-PD-1 in Patients with Advanced Solid Tumors

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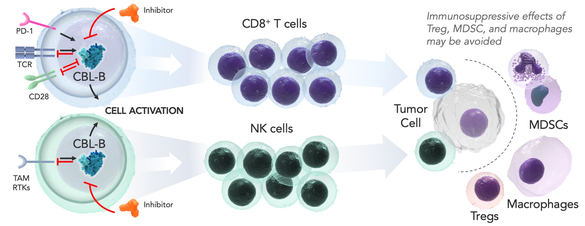
Introduction

- The E3 ligase Casitas B-lineage lymphoma proto-oncogene B (CBL-B) is a master negative regulator of the immune system and thus an attractive target with monotherapy potential to address suboptimal outcomes to immune checkpoint inhibitors (ICI).[1,2]
- CBL-B controls T-cell/NK cell activation and co-stimulatory pathways, including the signaling threshold for T-cell receptor (TCR) activation.[2,3]
- CBL-B inhibition uncouples TCR stimulation from the requirement for CD28 co-stimulation while reducing T-cell susceptibility to immunosuppression mediated by PD-1, immunosuppressive cytokines, and T_{reg} cells.[3,4]
- Ablation of CBL-B results in enhanced IFNγ and perforin release by primary human NK cells, promoting NK cell-mediated cancer cell killing.[5,6]
- Accordingly, targeting CBL-B may enable immune activation even in tumors with low antigen levels, low intratumoral inflammation, inadequate co-stimulation and/or active immunosuppression associated with poor response/resistance to existing ICIs (Figure 1).
- HST-1011 is a novel, potent, selective, orally bioavailable allosteric small molecule CBL-B inhibitor that has been shown to robustly increase anti-tumor immunity *in vitro* and *in vivo* as monotherapy, including in model systems where other ICIs have minimal effect.

Figure 1: CBL-B Inhibition Enhances Anti-tumor Immunity Through Several Key Biological Mechanisms



1 Lowers threshold for effector cell activation

2 Drives effector cell proliferation and inflammation

3 Reduces susceptibility to suppression

Overall Study Design

- SOLAR1 (NCT05662397) is a first-in-human, multicenter Ph1/2 trial evaluating HST-1011, an oral CBL-B inhibitor, alone and in combination with an anti-PD-1 agent in patients with advanced solid tumors.
- The Phase 1 (A1) portion of the study is open, with competitive enrollment.
- In the Phase 1 portion of the study, patients will receive HST-1011 as either monotherapy (Part A) or in combination with cemiplimab (Part B).

Part A: HST-1011 Monotherapy

A1 — **HST-1011 monotherapy dose escalation**, utilizing a Bayesian optimal interval design (BOIN),[7] with optional dosing cohorts allowing the ability to assess alternative dosing strategies.

A2 — **HST-1011 monotherapy dose optimization** with up to 4 cohorts utilizing dose(s)/schedule(s) deemed safe in Part A1 but focused on histology-specific patient populations to generate additional PK, PD, and efficacy data within a potential Recommended Phase 2 Dose (RP2D) range.

Part B: HST-1011/Cemiplimab Combination

B — **HST-1011 dose escalation in combination with cemiplimab** given per the standard dose and intravenous regimen, as in Part A1 with a BOIN design and optional dosing cohorts. Of note, the dose of HST-1011 that is selected as the starting dose for the dose escalation will be at minimum 2 dose levels below a previously cleared dose of HST-1011 monotherapy.

- The Phase 2 portion of this study will evaluate the preliminary anti-tumor activity of HST-1011 in combination with an anti-PD-(L)1 antibody or other standard of care therapies.

Objectives and Endpoints

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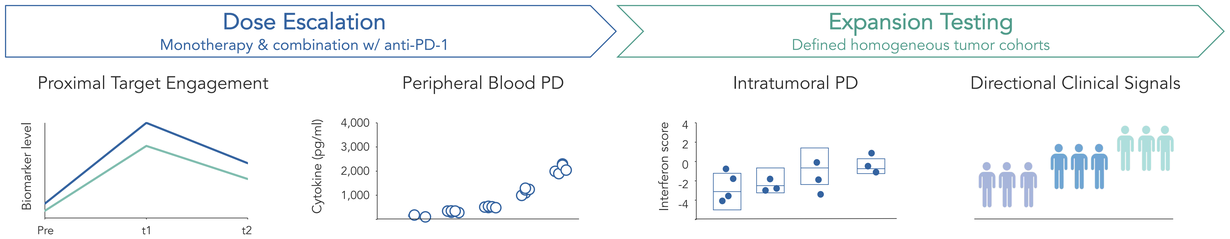
Primary	• To characterize the initial safety and tolerability of HST-1011 monotherapy (A1, A2) or in combination with cemiplimab (B)	• Incidence of dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and changes between baseline and postbaseline laboratory assessments, electrocardiograms (ECGs), vital signs, and physical exams
Selected Secondary and Exploratory (Figure 2)	• To characterize the pharmacokinetics (PK) of HST-1011 following oral administration of HST-1011 monotherapy (A1, A2) or combination therapy (B) • To determine the preliminary objective response rate (ORR), disease control rate (DCR), duration of response (DoR) of HST-1011 monotherapy or combination therapy • To evaluate the effects of HST-1011 monotherapy or combination therapy on select peripheral pharmacodynamic (PD) markers • To evaluate the effects of HST-1011 monotherapy or combination therapy on select PD biomarkers within the tumor microenvironment	• PK parameters including but not limited to: maximum observed plasma concentration (Cmax), time of maximum observed plasma concentration (Tmax), area under the concentration-time curve (AUC0-t) or in 1 dosing interval (AUCtau), concentration observed at trough (Ctrough, Ctau) • ORR per Investigator assessed Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 • Serial monitoring of peripheral blood cytokines / chemokines; peripheral immune cell profiling; changes in global gene expression profiles in peripheral immune cells; in-depth analysis of screening and on-treatment tumor biopsies with assessment of intratumoral immune cell numbers and phenotypes and intratumoral gene expression changes

Figure 2: HST-1011 Early Development Plan Focused on Proof of Mechanism And Refinement of Patient Segments



Key Eligibility Criteria

1. Patients with advanced solid tumors with progression on standard of care therapies representing one of the following:
   - Relapsed/refractory to any approved anti-PD-(L)1 regimen or combination OR stable disease for 6 months or longer while on an anti-PD-(L)1 regimen OR
   - One of the following tumor types with no currently approved PD-(L)1—based regimen: a) platinum-resistant ovarian cancer; b) castration-resistant prostate cancer with no more than 3 bony lesions; c) anal cancer; d) rectal cancer
2. Patient with at least one measurable, non-CNS lesion per RECIST v 1.1
3. Patient consents to a required screening biopsy and on-treatment biopsy

References

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