Peripheral Blood and Tumor Gene Expression as Biomarkers and Potential Predictors of Clinical Outcome with HST-1011, an Oral CBL-B inhibitor

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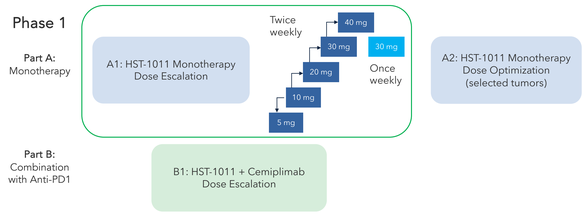
Introduction

- The E3 ligase Casitas B-lineage lymphoma proto-oncogene B (CBL-B) is a master negative regulator of the immune system.[1,2]
- CBL-B controls T-cell/NK cell activation and co-stimulatory pathways, including the signaling threshold for T-cell (TCR) activation. [2,3]
- Targeting CBL-B may enable immune activation even in tumors with low antigen levels, low intratumoral inflammation, inadequate co-stimulation and/or active immune suppression associated with poor response/resistance to existing immune checkpoint inhibitors.
- As part of the ongoing HST-1011 Ph1/2 (NCT05662397) clinical study (Figure 1), herein we provide preliminary biomarker evaluations in both peripheral samples and tumor tissue.

Methods

- RNA isolated from peripheral blood samples at timepoints on Cycle 1 Day 1, Day 8 and Cycle 2 Day 1 were profiled on the Nanostring Immunology V2 chip and used to evaluate changes in T and B-cell receptor (TCR and BCR) repertoires using a 7-chain next generation sequencing (NGS) assay from iRepertoire, Inc.[6]
- Paired tumor biopsies were collected from patients and whole exome (WES) and whole transcriptome (WTS) data was generated using the Caris Life Sciences tissue (NGS) assay.7 Tumor NGS data was used to 1) evaluate expression level of tumor infiltrating lymphocytes (TILs), 2) test different RNA based signatures.

Figure 1. SOLAR1 (NCT05662397) First-in-human Study Design

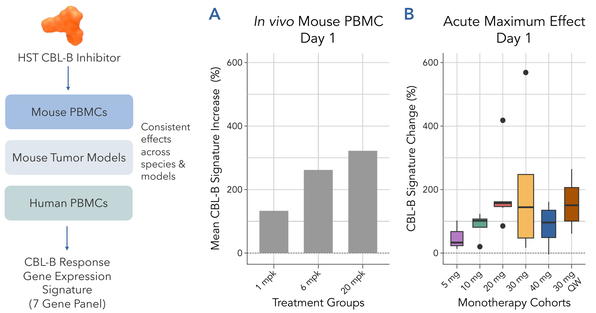


Relapsed/refractory to any approved anti-PD-(L)1 regimen OR stable disease for > 6 months while on an anti-PD-(L)1 regimen

Table 1. Clinical Evaluation and Patient Samples

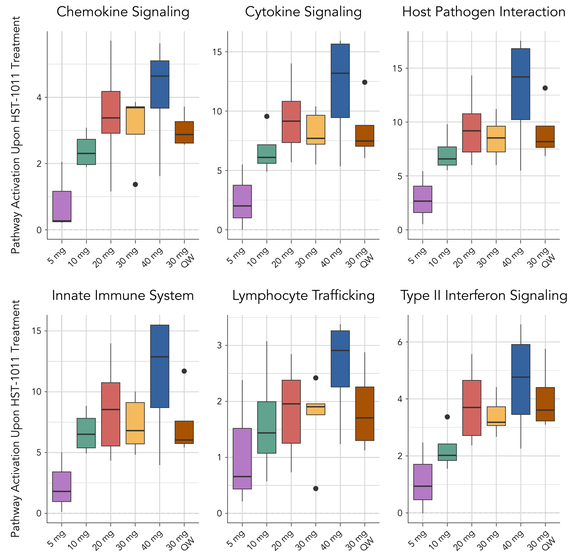
Overall A1 Population	Patients with Clinical Benefit	Patients with No Clinical Benefit
Definition	Patients who had tumor shrinkage by their first scan; were on treatment beyond first scan	Patients with clear progression on HST-1011 at or before the time of their first scan
28 Patients (Figures 2-4)	10 out of 28 patients showed signs of clinical benefit (data presented at ESMO 2024)	18 patients with no clinical benefit
Part A1 Tumor NGS Data (Figures 5-6)	4 patients available for analysis: (ovarian, 2 NSCLC, H&N)	9 patients available for analysis

Figure 2. An HST-1011 Derived Gene Expression Signature: Peripheral Changes are Pharmacodynamic Markers of CBL-B Inhibition



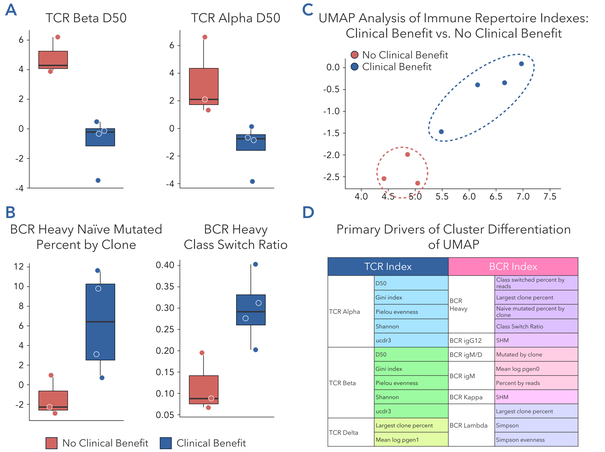
A gene expression signature was derived from a range of *in vitro* and *in vivo* models that demonstrated consistent changes in response to CBL-B inhibition (see schematic). (A) *in vivo* mouse model showing a dose dependent increase in the response signature in PBMCs (B) Dose-related increases in signature expression were observed from patients treated with HST-1011.

Figure 3. Impact of HST-1011 on Modulation of Different Immune Related Pathways



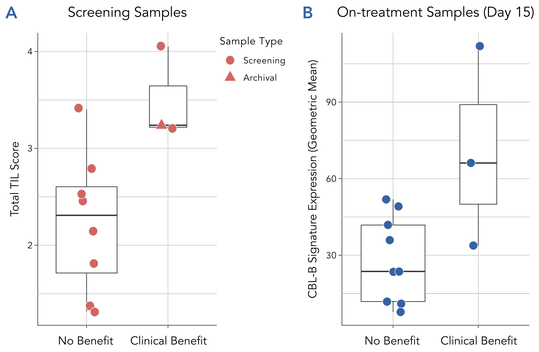
HST-1011 induced dose dependent modulation of immune related transcriptional pathways in peripheral blood samples.

Figure 4. Impact of HST-1011 on TCR and BCR Repertoire Metrics from Peripheral Samples After 1 Cycle of Treatment



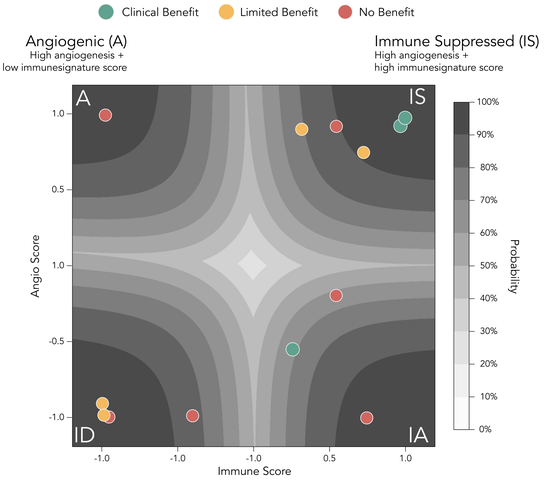
HST-1011 induced changes in different TCR and BCR repertoire metrics (A) Decrease in TCR diversity index (beta and alpha) D50 in patients who benefitted from HST-1011 therapy suggesting a focused T-cell response. (B) Patients with clinical benefit showed an increase in naïve B-cells undergoing mutations, and the class switch ratio (CSR) indicating an adaptive immune response. (C) Uniform Manifold Approximation and Projection (UMAP) analysis showed the ability to separate patients according to their clinical benefit. (D) Key driver TCR and BCR indexes used in UMAP analysis are provided for reference.

Figure 5. Tumor NGS Data from Patients Treated with HST-1011: Screening and On-treatment Biopsies



(A) Tumor NGS shows higher TILs in patients with evidence of clinical benefit following HST-1011 treatment.[4] (B) Modulation of a CBL-B response signature in on-treatment (Day 15) biopsy samples with increased expression of the signature seen in patients benefiting from HST-1011 therapy compared to those with no benefit.

Figure 6. Assessment of a TME RNA Signature[5] on Baseline Tumor Samples (N=13): Biological Complexity Reduced to Two Axes



TME RNA signature testing to predict clinical benefit: Green dots represent patients with clinical benefit and whose tumor signature call was IS (top right corner) or IA (bottom right corner) suggesting those with high immunesignature scores tend to benefit HST-1011 treatment; Patients with yellow and red dots represent patients with limited or no clinical benefit, respectively.

Conclusions

- An HST-1011 derived response signature showed a consistent dose dependent increase in patient peripheral blood.
- Patients with clinical benefit showed higher expression of the response signature in their on-treatment tumor biopsies.
- Preliminary TCR and BCR repertoire NGS data showed HST-1011 impacted both immune cell populations with changes in several metrics that were associated with clinical benefit.
- Patients who benefitted from HST-1011 treatment showed higher TIL expression in their baseline tumor biopsies, and their tumors were in the immune categories when testing a TME RNA signature.

References

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