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First-in-Human (FIH) Phase 1 Data of HST-1011, an Oral CBL-B Inhibitor, in Patients with Advanced Solid Tumors

SOLAR1 Clinical Trial, NCT05662397

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on behalf of the SOLAR1 Investigators and trial Sponsor HotSpot Therapeutics

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Declaration of Interests

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Disclosures (2 years):

Consulting/Advisory Boards: Abbvie; Amgen; AstraZeneca; BeiGene; Curio Science; Daiichi Sankyo; G1 Therapeutics; GE HealthCare; Gilead Therapeutics; GlaxoSmithKline; IDEOlogy Health; Illumina; Janssen Oncology; Johnson & Johnson; Lilly Oncology; Regeneron; Sanofi Aventis

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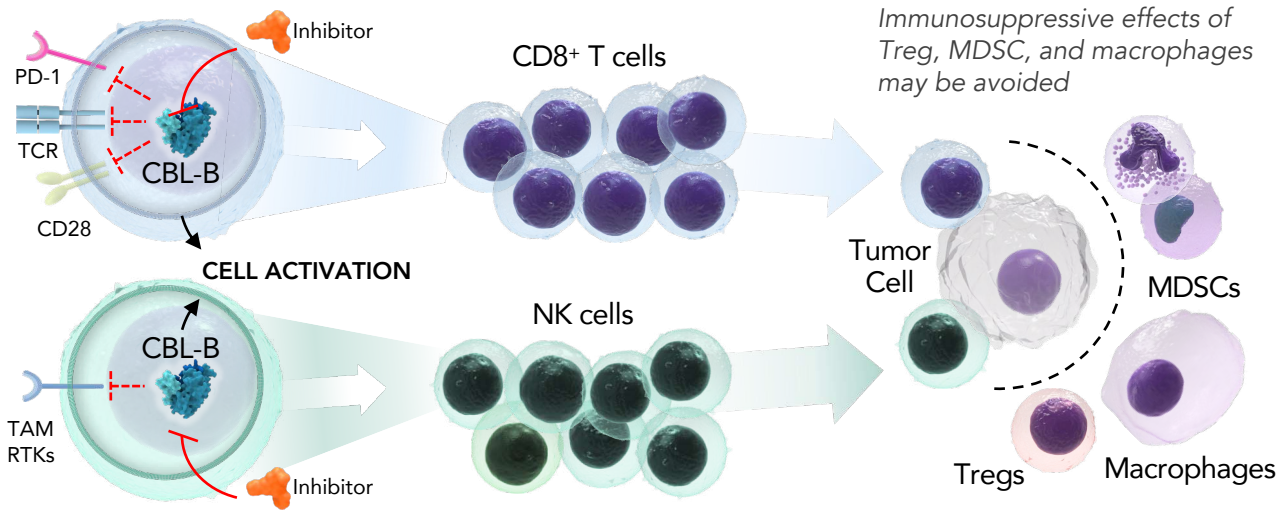
HST-1011 is a Novel, Selective, Small Molecule CBL-B Inhibitor

Effects of CBL-B Inhibition on the Immune System

1 Lowers threshold for effector cell activation

2 Drives effector cell proliferation and inflammation

3 Reduces susceptibility to suppression



Property	HST-1011
Target affinity	**0.031 nM**
Off rate	**71 hr**
Selectivity over C-CBL*	**40-fold**
Dosing	**Oral**

- Casitas B-lineage lymphoma proto-oncogene B (CBL-B) is a master negative immune regulator
- Inhibition of CBL-B drives anti-tumor immunity

- HST-1011 shows a differentiated profile
- Unique properties designed to enable twice weekly or weekly oral dosing

*C-CBL inhibition associated with potential for myeloproliferative effects in humans

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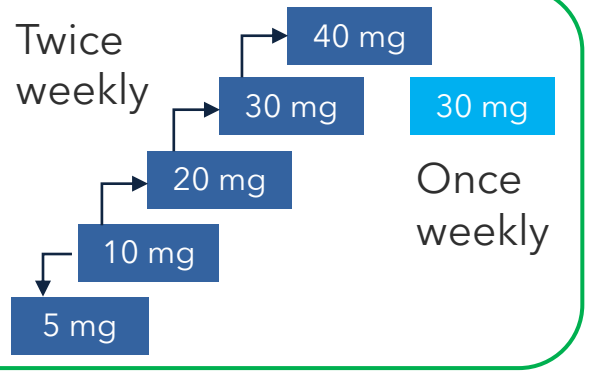
SOLAR1 (NCT05662397) - First-in-Human, Multicenter Ph1/2 Trial Evaluating HST-1011 Alone & in Combination With an Anti-PD-1 Agent in Patients with Advanced Solid Tumors

Phase 1

Part A: Monotherapy

A1: HST-1011 Monotherapy Dose Escalation



A2: HST-1011 Monotherapy Dose Optimization (selected tumors)

Part B: Combination with Anti-PD1

B1: HST-1011 + Cemiplimab Dose Escalation

B2: HST-1011 + Cemiplimab Dose Optimization (selected tumors)

Phase 1 Patients:

- Relapsed/refractory to any approved anti-PD-(L)1 regimen
  OR
  Stable disease for ≥ 6 months while on an anti-PD-(L)1 regimen
- One of the following tumor types without approved PD-(L)1 regimen: a) platinum-resistant ovarian cancer; b) castration-resistant prostate cancer; c) anal cancer; d) rectal cancer

HST-1011 Monotherapy Patient Demographics

Heavily Pre-Treated, Advanced Solid Tumor Patient Population

		Part A1: N = 28 patients
Age	Median (Years) Range (Min – Max, Years)	67 29-77
Sex	Female (N, %) Male (N, %)	12 (43) 16 (57)
Race or Ethnicity	Black (N, %) Hispanic (N, %) White (N, %) Not Reported (N, %)	2 (7) 3 (11) 22 (79) 1 (4)
Baseline ECOG	0 (N, %) 1 (N, %)	4 (14) 24 (86)
Time Since Diagnosis	Median (Years) Range (Min – Max, Years)	3.9 (0.5 - 10.8)
Prior Lines of Therapy	Median Range (Min – Max) Patients with prior anti-PD-(L)1	4 (2 - 13) 22 (79)
Tumor Histologies*	(N per tumor)	Anal (1); Breast (1); Biliary Tract (2), Cholangiocarcinoma (1); CSCC (1); Endometrial (2); Esophageal (3); HNSCC (2); Melanoma (3); Nasopharyngeal (1); NSCLC (4); Ovarian (1); Prostate (2); Rectal (4)

Data cutoff date: 01Aug2024. Data cleaning ongoing. Percentages may not add to 100% due to rounding.

*Abbreviations: CSCC, cutaneous squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer

HST-1011 Monotherapy Safety and Tolerability

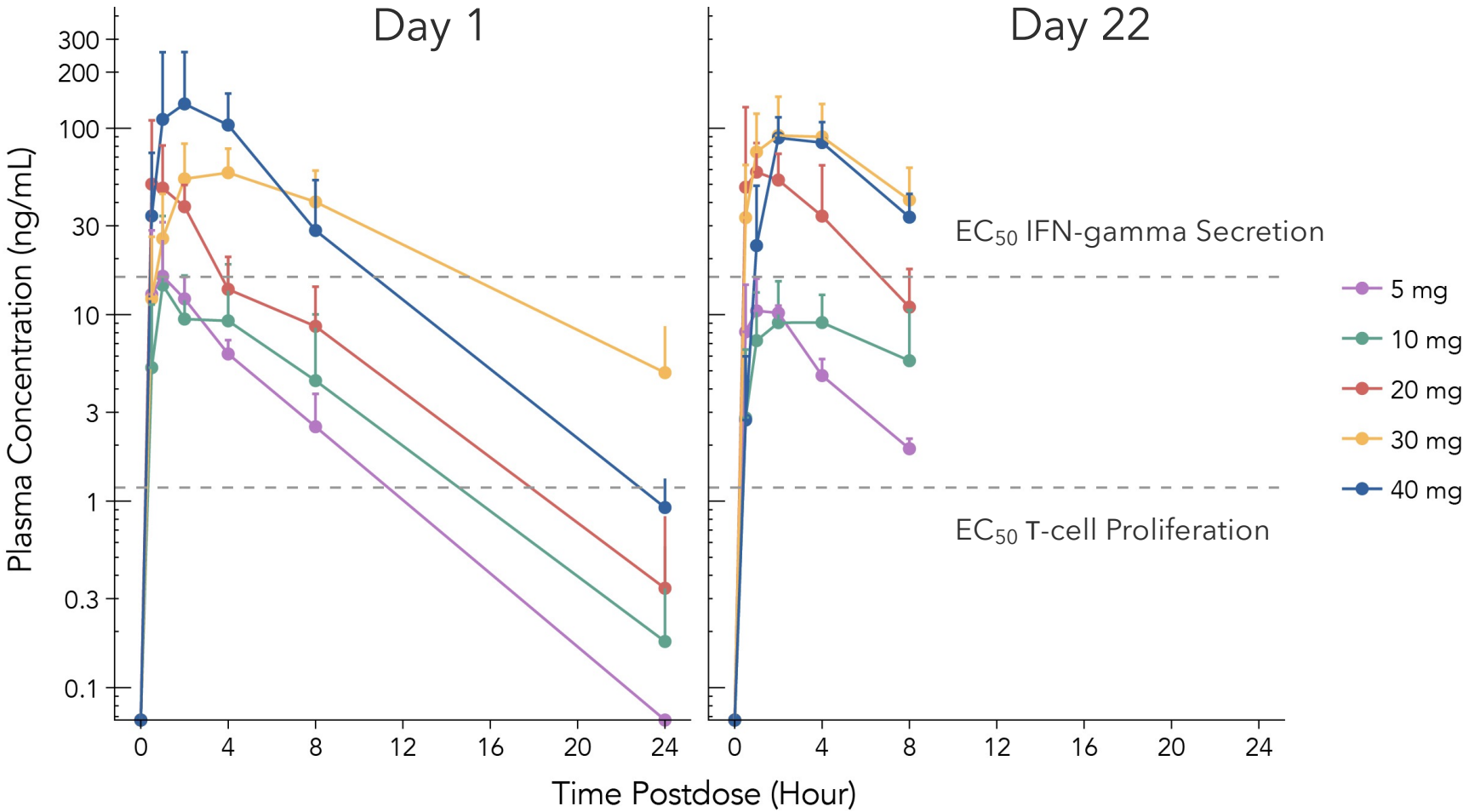
No DLTs and <20% of patients with Grade 3 TRAEs; Most Common AEs GI-Related

		Part A1: N = 28 Patients (N, %)
Dose-Limiting Toxicities (DLTs)		0 (0)
Patients with At Least One Treatment Related Adverse Event (TRAE)	Any Reported	26 (93)
	Grade 1	25 (89)
	Grade 2	17 (61)
	Grade 3	5 (18)
	Grade 4 / Grade 5	0 (0)
Patients with Treatment Related Serious Adverse Event (TRSAE)	Hypotension	3 (11)
	Anemia	2 (7)
Discontinuation Directly Related to TRAEs		0 (0)
Patients with TRAEs: Gastrointestinal (GI)	Any Reported (all Grade 1/Grade 2)	24 (86)
	Nausea	19 (68)
	Diarrhea	11 (39)
	Vomiting	8 (29)
	Abdominal pain	3 (11)
	Constipation	2 (7)
	Dry mouth	1 (4)

Data cutoff date: 01Aug2024. Data cleaning ongoing. Percentages may not add to 100% due to inclusion in two or more categories.

HST-1011 Monotherapy Pharmacokinetics

Dose-dependent Increases in HST-1011 Exposures



- Small molecule PK profile with $t_{1/2}$ ~ 3-5 hr
- Exposures above target concentrations at 20 mg dose and higher

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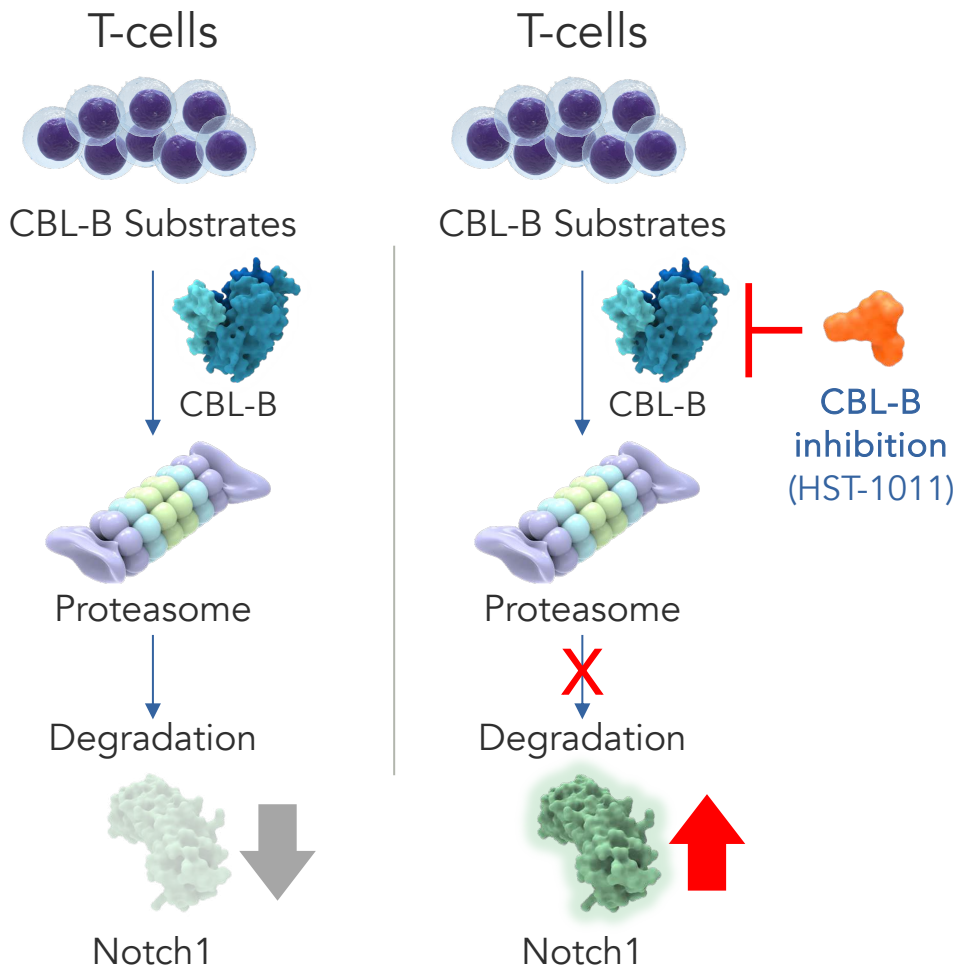
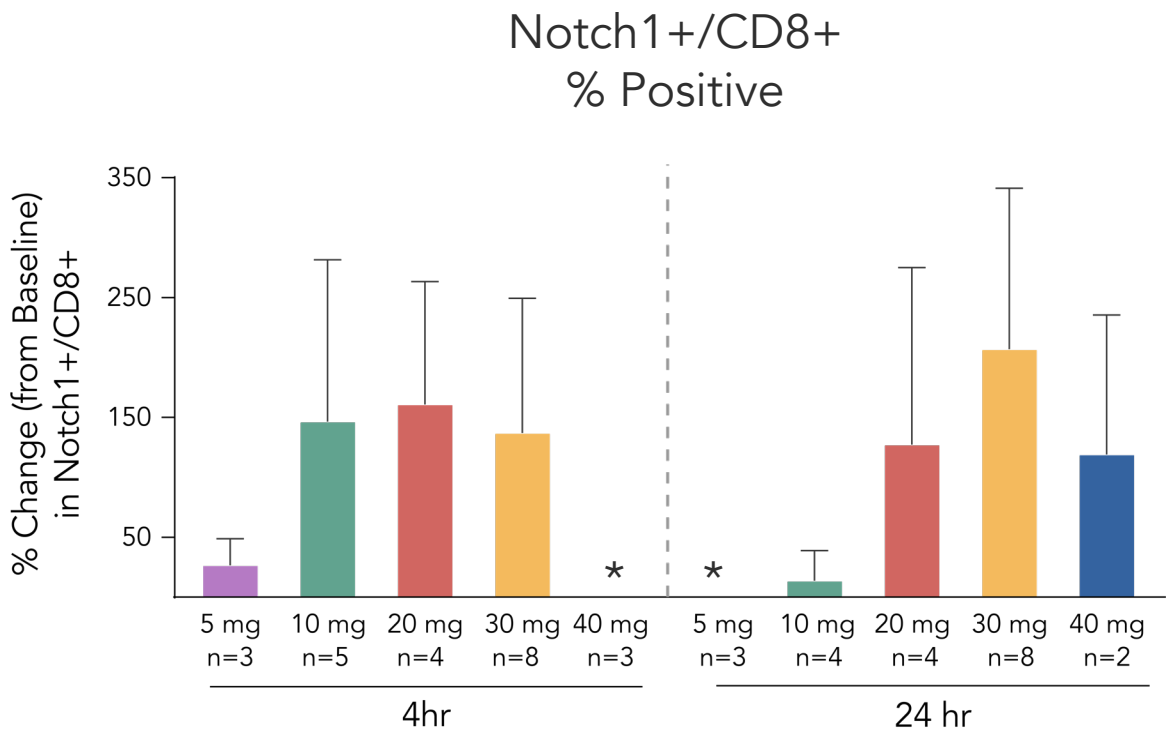
HST-1011 Target Engagement as Proximal Measure of CBL-B Inhibition

HST-1011 Led to Increased Expression of CBL-B Substrate Protein Notch1 on Peripheral T-cells





- Dose-dependent effects at 4hr, with inflection at 10 mg and higher
- Sustained effects through 24hr at 20 mg and higher

*Data not plotted due to analysis problems with on-treatment timepoint

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HST-1011 Related Gene Expression as Downstream Pharmacodynamic Marker

Patient PBMCs Demonstrate Increases in a CBL-B Response Gene Signature Following HST-1011 Treatment

HST CBL-B Inhibitor

↓

Mouse PBMCs

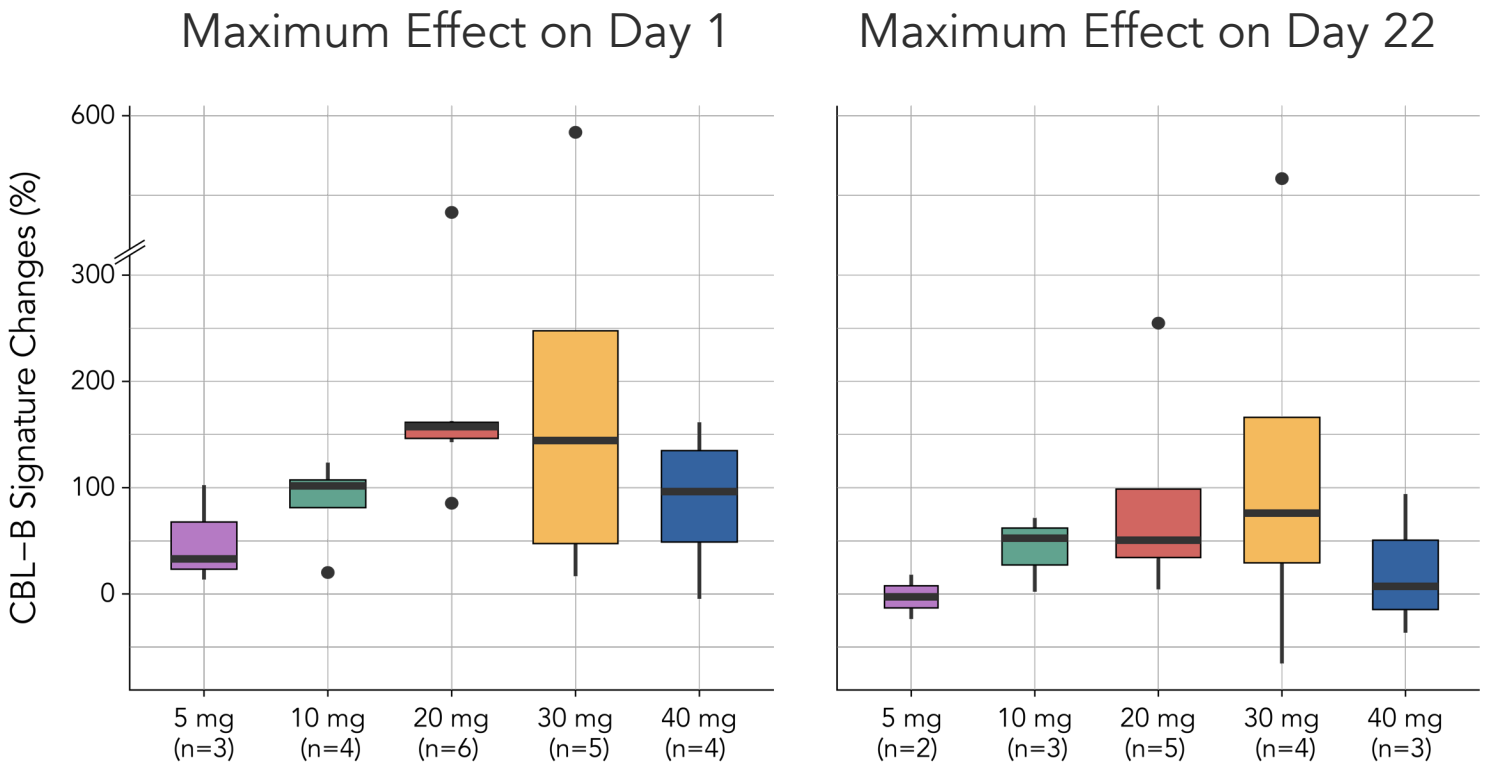
Mouse Tumor Models

Human PBMCs

↓

CBL-B response gene expression signature (7 gene panel)

Consistent effects across species & models



- Dose-dependent effects with maximal effect at 30 mg

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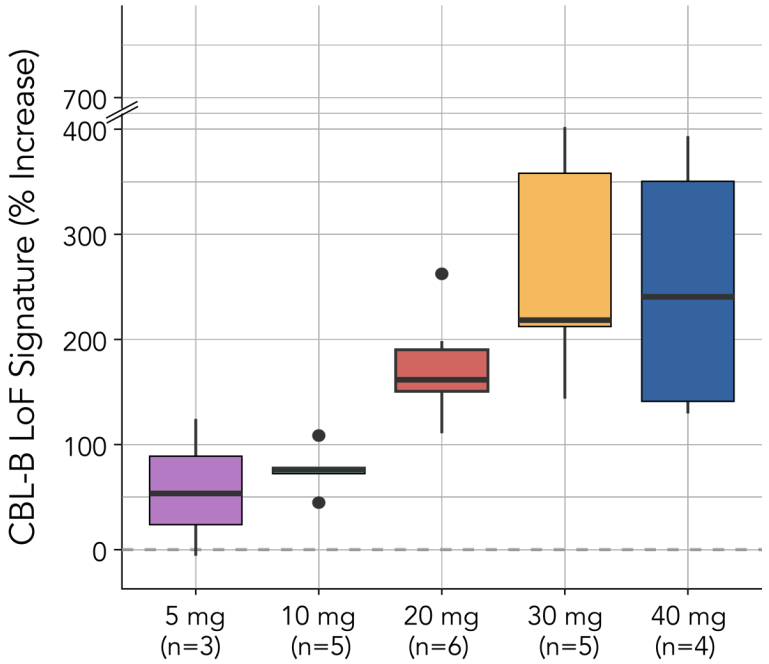
Inflammatory Mediators as Other Measures of HST-1011 Pharmacodynamics

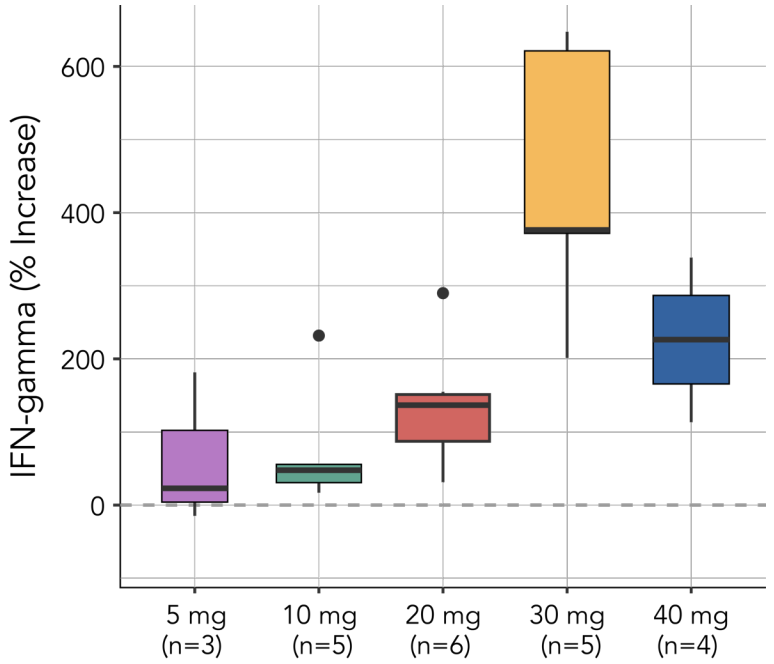
HST-1011 Treatment Led to Increases in (A) Plasma Cytokines/Chemokines Associated with Human CBL-B Loss-of-function (LoF) Mutations* and (B) Plasma IFN-gamma

Fig (A): Maximum Effect on Day 1

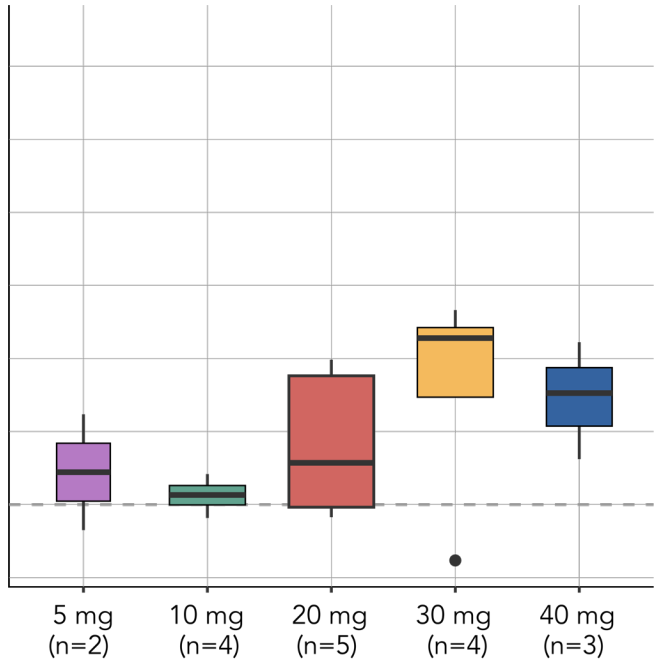


*Source: *J Clin Invest*. 2022;132(20):e154487

Fig (B): Maximum Effect on Day 1



Maximum Effect on Day 22



- Dose-dependent increases in LoF cytokines/chemokines, peaking at 30 mg
- Similar dose-dependent increases in plasma IFN-gamma levels, with acute (Day 1) effects sustained over time (Day 22) at higher doses

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HST-1011-Treated Patients with Signs of Clinical Benefit

10 of 28 Patients Across Tumor Types Had Signs of Clinical Benefit Despite Extensive Disease and Prior Therapies

Tumor Type	HST-1011 Dose/Schedule	Clinical Effect(s)*
Cutaneous SCC	10 mg BIW	• Clinical benefit, stable disease for 85 days (SD 8%)
Acral Melanoma	10 mg BIW	• Treated past progression for clinical benefit; single-lesion RECIST -36% and 100% clearance of ctDNA while on study treatment
NSCLC	10 mg BIW	• Clinical benefit, stable disease for 123 days (SD -2%)
NSCLC	30 mg BIW	• Clinical benefit, stable disease for 252 days (SD -15%)
NSCLC	40 mg BIW	• Clinical benefit for 100 days, treated past progression (new non-target lesion but -6% in target lesions)
Head and Neck	30 mg QW	• Clinical benefit, stable disease for 120 days (SD -9%)
Anal	20 mg BIW, escalated to 30 mg BIW	• Clinical benefit at 20 mg; following dose escalation to 30 mg BIW at C5, 0% growth in target lesions at C7
Rectal	30 mg BIW	• Short-term clinical benefit, decrease in CEA and RECIST target lesions (-2%) at 5 week scan**
Ovarian	5 mg BIW, escalated to 20 mg BIW & then 30 mg BIW	• Clinical benefit for 127 days, stable disease on 20 mg dose (SD -9%) with associated decrease in CA-125
Prostate	5 mg BIW, escalated to 10 mg BIW	• Clinical benefit for 129 days, PSA drop while on 10 mg dose

** Days of stable disease calculated from C1D1 baseline until progression*
*** Scan for clinical assessment, not tumor evaluation per protocol*

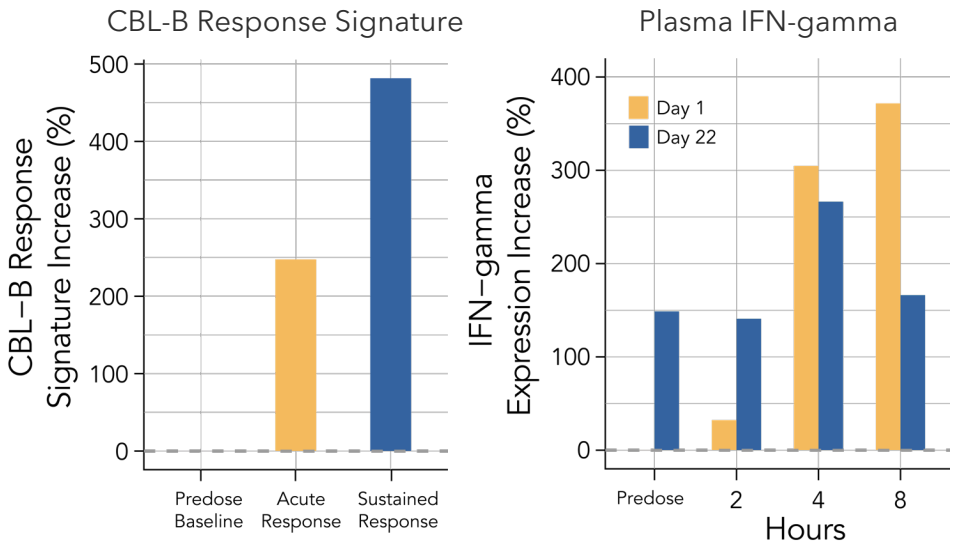
NSCLC Patient Treated with HST-1011 for >33 Weeks

Correlative Data Support Linkage Between Peripheral Pharmacodynamics and Tumor Effects (Patient 006-012)

Clinical Presentation

Demographic	61 yo Male Non-small cell lung cancer, adenocarcinoma
Molecular	TMB-high PD-L1 50%, pre-treatment biopsy
Treatment History	Multiple prior lines of chemo-immunotherapy, >4 years of systemic therapy
HST-1011 Treatment	HST-1011 30 mg BIW (5th line systemic therapy)

Pharmacodynamic Responses



Tumor Responses

Clinical	Clinical improvement in disease-related symptoms throughout treatment duration
Radiographic	Week 9 scan: SD -10% Wek 18 scan: SD -15% Week 27 scan: SD -6% Week 36: end of treatment for PD (new lesions)
Peripheral Biomarker	Circulating tumor DNA (ctDNA) decreased during treatment compared to pre-treatment baseline

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Conclusions and Ongoing Exploration

HST-1011 Monotherapy Phase 1 Profile is Encouraging and Supports Continued Development

HST-1011 monotherapy demonstrated **key benchmarks** of an active immunotherapy:

- Tolerability observed at pharmacologically active doses
- Benchmark exposures & target engagement achieved
- Dose-related increases in markers of peripheral immune activation
- Tumor shrinkage in heavily pre-treated patients supports preliminary evidence of monotherapy clinical activity

Data support ongoing exploration of HST-1011 in tumor/biomarker-specific patient cohorts and in combination with anti-PD-1 checkpoint inhibitor (Actively enrolling: NCT05662397)

Acknowledgments and Thanks

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Study sponsor: HOTSPOT THERAPEUTICS

QUESTIONS?

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