TUMOR ANTIGEN EXPRESSION AND SURVIVAL OF PATIENTS WITH PREVIOUSLY-TREATED ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) RECEIVING VIAGENPUMATUCEL-L (HS-110) PLUS NIVOLUMAB

Daniel Morgensztern[1], Saiama N Waqar[1], Lyudmila Bazhenova[2], Lori McDermott[3], Jeff Hutchins[3], David H. Taylor[3], Fred L. Robinson[4], Alexa K. Dowdell[4], Brian D. Piening[4], Wael Harb[5], Nathan Pennell[6], Roger B. Cohen[7]

[1]Washington University School of Medicine, St. Louis, MO; [2]UC San Diego, Moores Cancer Center, San Diego, CA; [3]Heat Biologics, Inc, Durham, NC; [4]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR [5]Horizon Oncology Center, Lafayette, IN, [6]Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [7]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Background

Viagenpumatucel-L (HS-110) is an allogeneic cellular immunotherapy that incorporates a broad range of tumor antigens (cancer testis antigens, CTAs) that are known to be shared amongst a high proportion of patients with non-small cell lung cancer (NSCLC). This cell system expresses secretory gp96-Ig, which acts as an antigen delivery chaperone of tumor antigens expressed by Viagenpumatucel-L (HS-110) and an immune activator of tumor specific T cells. Functionally, gp96 is a unique chaperone that up-regulates multiple factors including MHC, cytokine release, and T-cell co-stimulators. This action drives the differentiation of APCs to dendritic cells and cross-presentation of chaperoned antigens for display via MHC I to initiate a highly specific CD8+ T-cell mediated immune response[1,2] to the patient's own tumor.

The HS110-102 "DURGA" trial is a Phase 2, multi-cohort master protocol evaluating HS-110 in combination with anti-PD1 antibodies in the treatment of advanced non-small lung cancer. Here we present top line data from Cohort A. This cohort is comprised of previously-treated patients who have not received a checkpoint inhibitor (CPI) prior to study entry.

Study endpoints include safety, objective response rate (ORR) and overall survival (OS). Patients received 1 x 10^7 HS-110 cells intradermally every week for 18 weeks and nivolumab every two weeks until disease progression or unacceptable toxicity.

To evaluate the association between clinical outcomes and CTA overexpression in patient tumor samples, RNA sequencing was performed on baseline tumor specimens as well as the HS-110 drug product under in vitro culture conditions. RNA-seq libraries were prepared via hybrid-capture from macro-dissected formalin fixed paraffin embedded tumor tissue or HS-110 cultured cells and sequenced on an Illumina NovaSeq 6000. Gene-level transcripts were quantified using the Salmon software package.

In this analysis, 39 CTAs were highly expressed and only present in tumor-associated tissue. Of the 28 patients with evaluable tissue for RNA-seq, 14 patient tumors contained 8 or more of these 39 highly expressed CTAs.

NCT Trial ID: NCT02439450

Mechanism of Action

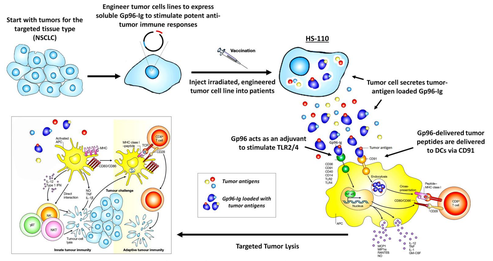

Figure 1: Viagenpumatucel-L (HS-110) Mechanism of Action
HS-110 is derived from a lung adenocarcinoma cell line transfected with gp96-Ig, which acts as a chaperone protein for tumor associated antigens and is recognized by CD91 on APCs, resulting in cross-presentation of antigen to MHC I for the selection of antigen-specific CD8 cells. Gp96-Ig also binds to TLR-2/4 leading to upregulation of co-stimulatory molecules including MHC II and secretion of cytokines and chemokines.

Study Schema

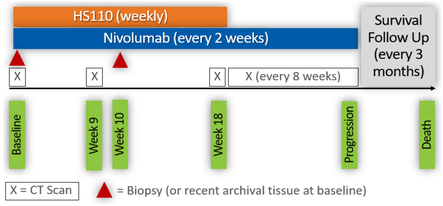

Figure 2: HS110-102 Study Schema
Patients receive weekly HS-110 (1 x 10^7 cells via 5 intradermal injections of 0.1ml each) for 18 weeks and nivolumab (240 mg IV) biweekly until disease progression or unacceptable toxicity.

Patient Characteristics (ITT Population)

		ITT (N = 47)
Age (median, range)		65 (37-87)
Gender	Female	26 (55%)
Race	Caucasian	42 (89%)
ECOG PS (0 or 1)	1	32 (68%)
EGFR mutation	Positive	5 (11%)
Histology	Adenocarcinoma Squamous	44 (94%) 3 (6%)
Smoking status	Current/past Never	39 (83%) 8 (17%)
Prior lines of treatment	1 2 3 or more	32 (68%) 7 (15%) 8 (17%)
PD-L1 status	< 1% ≥ 1% Unevaluable	22 (47%) 9 (19%) 16 (34%)

Frequently Reported Adverse Events

Adverse Events	N=47
Any adverse event	47 (100%)
Any event ≥ Grade 3	16 (34%)
Injection site reaction	28 (60%)
Fatigue	13 (28%)
Arthralgia	9 (19%)
Cough	8 (17%)
Constipation	7 (15%)
Diarrhea	7 (15%)
Decreased appetite	7 (15%)
Nausea	7 (15%)
Anemia	7 (15%)

Most commonly reported treatment-emergent adverse events (regardless of attribution) occurring in the safety population. There were one grade 4 event (hyponatremia) and two grade 5 events (acute myocardial infarction and pulmonary embolism due to disease progression), none of which were deemed related to study treatment.

Overall Survival: ITT & Landmark Analysis

Landmarks	% (# Alive)
6 months	75% (35)
12 months	57% (27)
18 months	40% (19)
24 months	36% (17)

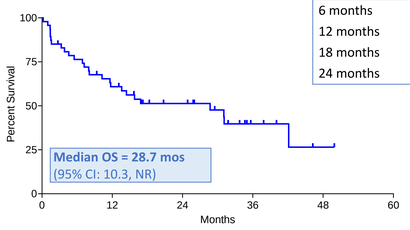

Figure 3: Overall Survival – ITT Population (Kaplan Meier Analysis)
Overall survival of ITT population (N=47). Twenty-one (21) patients censored.

Overall Survival: Subset Analyses

Injection Site Reaction	N (%)	# Censored	Median OS, 95% CI (mos)	
Positive	28 (60%)	17	42.1	(28.7, NR)
Negative	19 (40%)	4	4.6	(1.4, 11.6)
p = 0.0001	HR: 0.20 (95% CI: 0.09 - 0.46)			

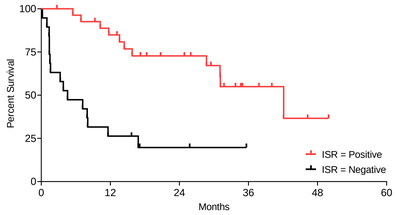

Figure 4: Overall Survival – by Injection Site Reaction (ISR)
ISR positive refers to patients who experienced at least one injection site reaction at any time during treatment.

PD-L1	N (%)	# Censored	Median OS, 95% CI (mos)	
Positive	9 (19%)	5	42.1	(1.6, 42.1)
Negative	22 (47%)	10	28.7	(5.5, NR)
p = 0.40	HR: 0.61 (95% CI: 0.19 - 1.91)			

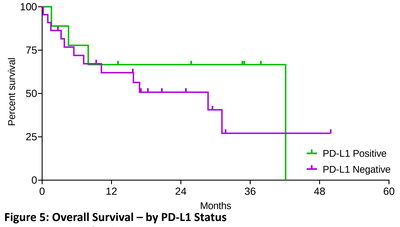

Figure 5: Overall Survival – by PD-L1 Status
PD-L1 positive is defined as PD-L1 expression ≥ 1% using SP142.

Response Rate & Disease Control

Response Rate*	% (N)
ORR	21% (10)
PR	21% (10)
SD	21% (10)
Not Evaluable	13% (6)
DCR	43% (20)

*Per RECIST 1.1

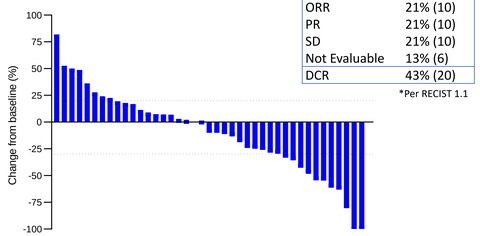

Figure 6: Best Target Lesion Response
Waterfall plot of evaluable ITT patients (N=41) using RECIST 1.1 Target Lesion Response. Post-baseline scans not available for 6 patients. Tumor shrinkage was observed in 42% of ITT patients.

Cancer Testis Antigen (CTA) Expression Analyses

# Shared CTAs	N (%)	# Censored	Median OS, 95% CI (mos)	
≥ 8	14 (50%)	9	NR	(10.3, NR)
< 8	14 (50%)	4	6.7	(1.4, NR)
p = 0.028	HR: 0.32 (95% CI: 0.11 - 0.94)			

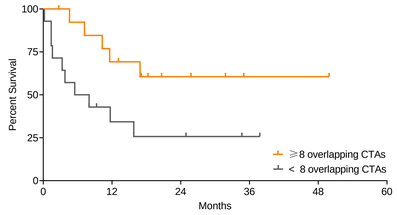

Figure 7: Overall Survival – by Shared Antigen Expression
Subset analysis was conducted in patients whose tumors have 8 or more overlapping CTAs with the 39 CTAs overexpressed by HS-110 at baseline.

ZNF492	N (%)	# Censored	Median OS, 95% CI (mos)	
Yes	11 (39%)	8	NR	(11.6, NR)
No	17 (61%)	6	7.2	(1.6, NR)
p = 0.008	HR: 0.20 (95% CI: 0.05 - 0.74)			

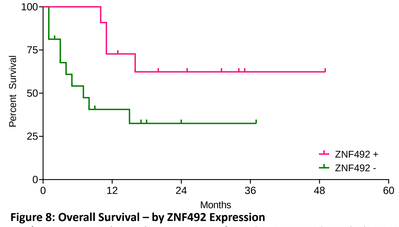

Figure 8: Overall Survival – by ZNF492 Expression
Zinc finger protein 492 (ZNF492) is a transcription factor that is expressed in multiple cancers. Subset analysis was conducted in patients whose tumors overexpressed ZNF492 at baseline.

Duration of Clinical Benefit

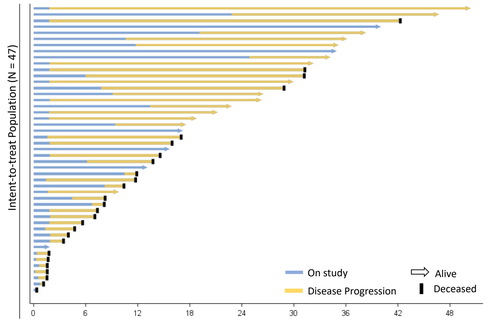

Figure 9: Duration of Clinical Benefit
Swimmer plot of time until disease progression and current survival status. Status with median follow-up of 15.7 months, median duration of response = 17.2 months, median PFS = 1.9 months. As of this data cut, 6 patients (15%) have not progressed, and 21 patients (46%) are still alive.

Conclusions

- **HS-110 in combination with nivolumab is well tolerated with a median overall survival (OS) of 28.7 months**
  - **Favorable survival benefit observed in both PD-L1 positive and PD-L1 negative patients**
  - **Significantly greater OS observed in ISR+ patients**
  - **In an exploratory biomarker analysis, improved OS was observed in patients whose tumors express ≥ 8 shared antigens with HS-110 at baseline, and in patients who expressed ZNF492 at baseline**

References

1.Strbo N, Garcia-Soto A, Schreiber TH, Podack ER. Secreted heat shock protein gp96-Ig: next-generation vaccines for cancer and infectious diseases. Immunol Res 2013;57:311-25.

2.Oizumi S, Strbo N, Pahwa S, Deyev V, and Podack ER. Molecular and cellular requirements for enhanced antigen cross-presentation to CD8 cytotoxic T lymphocytes. J immunol 2007; 179, 2310-2317.

Acknowledgements

The authors are grateful for the investigators, study staff, patients and their families for their commitment to this trial to help advance the treatment of non-small cell lung cancer.

For any additional information, please contact lmcdermott@heatbio.com