TREATING ADVANCED NON-SMALL LUNG CANCER (NSCLC) PATIENTS AFTER CHECKPOINT INHIBITOR TREATMENT FAILURE WITH A NOVEL COMBINATION OF VIAGENPUMATUCEL-l (HS-110) PLUS NIVOLUMAB

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Background

Viagenpumatucel-L (HS-110) is an allogeneic cellular immunotherapy that incorporates a broad range of tumor antigens that are known to be shared amongst a high proportion of patients with non-small cell lung cancer (NSCLC). This cell system contains HLA-A1 (a human histocompatibility surface antigen) and gp96-Ig in the form of a transgene constructed from sequences encoding the human gp96 gene with the C-terminal KDEL sequence removed and replaced with the Fc portion of human IgG1. This construct is designed to enable the cell to express the heat shock protein/adjuvant gp96 in secreted form. The secreted gp96 acts as a chaperone to induce cellular immune responses to the tumor antigens expressed by **Viagenpumatucel-L (HS-110)**. gp96 is a unique chaperone because it can activate MHC and up-regulate T-cell co-stimulation and deliver chaperoned antigens to an APC for display via MHC I, with the net result being CD8+ T-cell mediated immune responses[1,2].

The HS110-102 "Durga" Trial is an exploratory, multi-cohort master protocol evaluating HS-110 in combination with anti-PD1 mAbs in the treatment of advanced non-small lung cancer. Here we present top line data from the first 56 patients enrolled in Cohort B. This cohort is comprised of previously treated patients with progressive disease (PD) after receiving a minimum of 4 months of checkpoint inhibitor (CPI) therapy at any time prior to study entry.

NCT Trial ID: **NCT02439450**

Mechanism of Action and Pre-clinical Activity

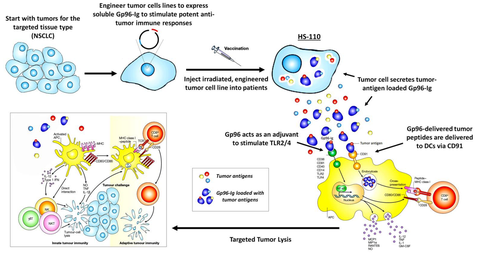

Figure 1: Viagenpumatucel-L (HS-110) Mechanism of Action and Pre-clinical Activity

HS-110 is derived from a lung adenocarcinoma cell line transfected with gp96-Ig, where the gp96 KDEL ER retention sequence is replaced by IgG1 Fc. Gp96-Ig 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 TLRs 2 and 4 leading to upregulation of co-stimulatory molecules, which include MHC II and secretion of cytokines and chemokines.

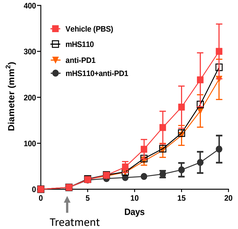

Figure 2: Pre-clinical Activity in mouse tumor growth B16F10 model

Clinical evaluation of HS-110 in combination with nivolumab is supported by pre-clinical data showing the synergistic anti-tumor-growth activity of mouse HS110 with anti-PD1 as compared to either agent individually.

Study Schema

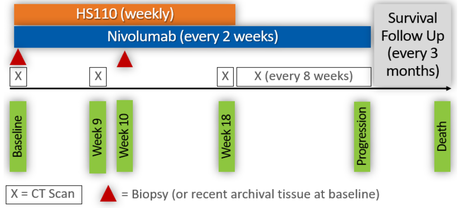

Figure 3: HS110-102 Study Schema

Patients receive weekly HS-110 (1 x 10^7 cells) intradermally for 18 weeks via 5 simultaneous injections of 0.1ml each, and biweekly nivolumab 240 mg IV until disease progression or unacceptable toxicity.

Patient Characteristics

		ITT (N = 56)
Median age (range)		68 (50-84)
Female gender		30 (54%)
Caucasian		45 (80%)
ECOG PS 1		36 (64%)
EGFR or ALK positive		3 (5%)
Histology	Adeno Squamous Other	45 (80%) 10 (18%) 1 (2%)
Smoking status	Current/past Never	48 (86%) 8 (14%)
Prior lines of tx	1 2 3 or more	21 (37%) 16 (29%) 19 (34%)
PD-L1	< 1% ≥ 1% Unevaluable	22 (39%) 20 (36%) 14 (25%)
Median Time (months) on prior CPI (range)		10 (3 – 58)
Median Time (months) between last CPI dose and study entry (range)		2 (1 – 35)

Table 1: Patient Characteristics

Baseline patient demographics of Intent-to-treat population (n=56).

Best Overall Response

	RECIST* 1.1	iRECIST*
ORR	**13% (7)**	**14% (8)**
PR	13% (7)	14% (8)
SD	46% (26)	46% (26)
Not Evaluable	7% (4)	7% (4)
DCR	**59% (33)**	**61% (34)**

Table 2: Objective Response Rates

ORR of the Intent-to-treat population (n=56) performed locally by study Investigators using RECIST 1.1. iRECIST shown as one patient achieved confirmed PR after initial radiographic PD.
(*unconfirmed as study is actively ongoing at time of analyses).

Overall Survival

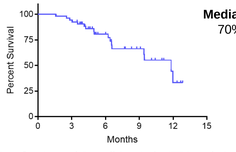

Figure 4: Kaplan Meier of estimated Overall Survival – ITT Population

Overall survival of ITT population (N=56). Thirty-nine (39) patients censored. mOS is estimated by KM to be 11.8 months [95% CI; 6.6, not reached].

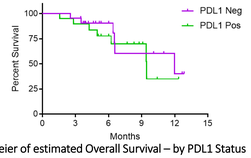

Figure 5: Kaplan Meier of estimated Overall Survival – by PDL1 Status

Using a cut-off of 1% PDL1 expression, estimated overall survival is shown for PDL1 negative (n=22) and PDL1 positive (n=20).

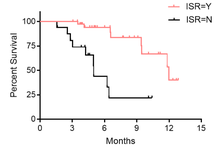

Figure 6: Kaplan Meier of estimated Overall Survival – by Injection Site Reaction

Using KM estimates of survival, patients who experienced at least one injection site reaction at any time during treatment (n=39) had statistically significant improved overall survival compared to patients who did not experience an injection site reaction (n=17). HR 0.16 [95% CI; 0.05, 0.45] *p=0.0005*

Progression Free Survival

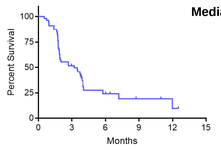

Figure 8: Kaplan Meier of Progression-Free Survival – ITT Population

Progression-free survival of ITT population (N=56). Seventeen (17) patients censored. mPFS is estimated by KM to be 3.2 months [95% CI; 1.9, 4.0].

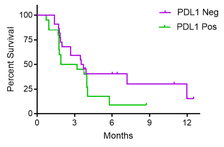

Figure 9: Kaplan Meier of Progression-Free Survival – by PDL1 Status

Using a cut-off of 1% PDL1 expression, estimated progression-free survival is shown for PDL1 negative (n=22) and PDL1 positive (n=20).

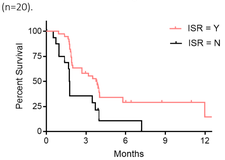

Figure 10: Kaplan Meier of Progression-free Survival – by Injection Site Reaction

Using KM estimates of survival, patients who experienced at least one injection site reaction at any time during treatment (n=39) had statistically significant improved progression-free survival compared to patients who did not experience an injection site reaction (n=17). HR 0.4 [95% CI; 0.2, 0.78] *p=0.0068*

Frequently Reported Adverse Events

Adverse Events	Cohort B (N=56)
Any Adverse Event	54 (96%)
Any event ≥ Grade 3	13 (23%)
Fatigue	19 (34%)
Weight decreased	10 (18%)
Hypocalcemia	10 (18%)
Cough	9 (16%)
Diarrhea	8 (14%)
Dyspnea	8 (14%)

Table 3: Adverse Event Table

Most commonly reported treatment-emergent adverse events (regardless of attribution) occurring in the safety population. 92% of all AEs were Grade 1 or 2. There were four grade 4 events: QTc prolongation, stroke, pericardial tamponade, and hyponatremia, none of which were deemed related to treatment. There were no grade 5 AEs.

Conclusions

HS-110 in combination with nivolumab is well tolerated.

The effect of HS-110 in combination with nivolumab is not dependent on PDL1 expression.

The occurrence of dermal injection site reactions (any grade) is associated with improved progression-free survival and overall survival.

Data suggest that re-challenging the immune system with nivolumab and HS-110 after CPI treatment failure restores responsiveness and clinical benefit for some patients.

Best Target Lesion Response

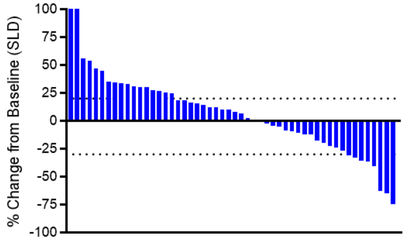

Figure 7: Best Target Lesion Response

Waterfall plot of evaluable ITT patients (N=52) using RECIST 1.1 Target Lesion Response. Post-baseline scans not available for 4 patients. Tumor shrinkage was observed in 21 (38%) of 56 ITT patients.

Duration of Clinical Benefit

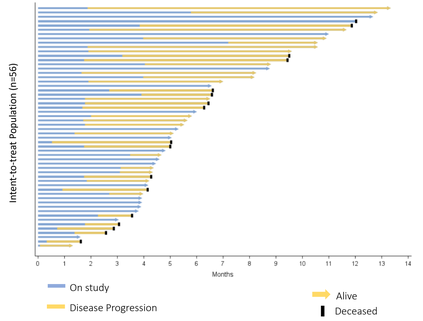

Figure 11: Duration of Clinical Benefit

Swimmer plot showing time until disease progression and current survival status. With a median follow up time of 11.8 months, 39 (70%) patients remain alive and 17 (30%) did not experience disease progression.

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. Immunologic research 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. Journal of immunology 2007; 179, 2310-2317.

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