VIAGENPUMATUCEL-L (HS-110) PLUS NIVOLUMAB IN PATIENTS WITH ADVANCED NON-SMALL LUNG CANCER (NSCLC)

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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) for purposes of drug identity and gp96-Ig (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 and adjuvant to induce cellular immune responses to various tumor antigens expressed by the host cell. These characteristics make gp96 unique because it can both activate (MHC and T-cell costimulator up-regulation) and deliver chaperoned antigens to an APC for display via MHC I, in order to elicit 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 interim data from the first two Cohorts, A and B, for all patients enrolled on or before the efficacy data cut-off. Cohort A (n=42) consists of previously treated patients who have never received an immune checkpoint inhibitor (CPI). Cohort B (n=20) is comprised of patients with progressive disease (PD) after receiving a minimum of 4 months of CPI therapy at any time prior to study entry. Trial ID: **NCT02439450**

Mechanism of Action

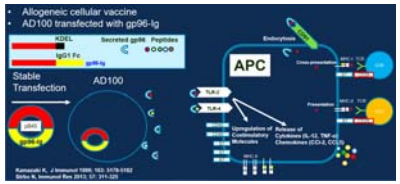


Figure 1: Viagenpumatucel-L (HS-110) Mechanism of Action
HS-110 is developed from the AD100 lung adenocarcinoma cell line transfected with gp96-Ig, where the gp96 KDEL ER retention sequence is replaced by IgG1 Fc. Gp96-Ig acts as a chaperone protein for tumor associated antigens that is recognized by CD91 on APCs; resulting in cross-presentation of antigen to MHC I for the selection of antigen-specific CD8 cells. At the same time, Gp96-Ig binding to TLRs 2 and 4 leads to upregulation of co-stimulatory molecules, MHC II and secretion of cytokines and chemokines.

Study Design and Endpoints

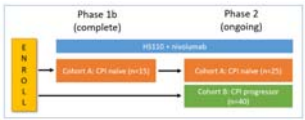


Figure 2: Study Design
This single-arm, open-label trial has a phase 1b portion of 15 previously treated patients that have never received a CPI with a phase 2 expansion, that added Cohort B: Patients with PD after treatment failure with CPI.

Primary Endpoints
Ph 1b: Safety
Ph 2: ORR (RECIST 1.1)

Secondary Endpoints
OS, PFS, DCR, DOR and iRECIST measurements

Exploratory Endpoints
Immune response, and correlation of clinical outcomes with Baseline CD8+ TIL levels, and PD-L1 expression on tumor cells.

Study Schema

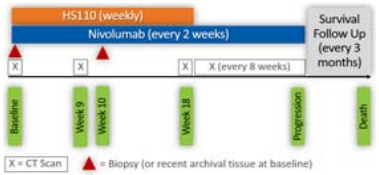


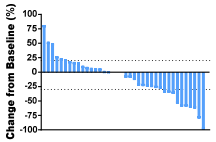
Figure 3: HS110-102 Study Schema
Patients receive weekly HS-110 (1 x 10^7 cells) intradermally for 18 weeks via 5 injections of 0.1ml each, and biweekly nivolumab 240 mg IV until disease progression or unacceptable toxicity.

Patient Characteristics

		Cohort A (N = 44)	Cohort B (N = 31)
Median age (range)		65 (37-87)	66 (50-84)
Female gender		24 (55%)	18 (58%)
White race		39 (89%)	25 (81%)
ECOG PS 1		27 (61%)	11 (35%)
EGFR or ALK positive		9 (20%)	3 (10%)
Histology	Adeno Squamous	41 (93%) 3 (7%)	25 (81%) 6 (19%)
Smoking status	Current/past Never	37 (84%) 7 (16%)	27 (87%) 4 (13%)
Prior lines of tx	1 2 or more Unavailable	27 (61%) 13 (30%) 4 (9%)	5 (16%) 18 (58%) 8 (26%)
PD-L1	< 1% ≥ 1% Unevaluable	17 (39%) 13 (29%) 14 (32%)	8 (26%) 14 (45%) 9 (29%)
CD8+ TIL	≤ 10% > 10% Unevaluable	12 (27%) 8 (18%) 24 (55%)	9 (29%) 10 (32%) 12 (39%)

Table 1: Patient Characteristics
Baseline patient demographics of the safety population (n=75). Note that only the patients enrolled prior to the data cut-off were included in the efficacy population (n=62).

Cohort A (CPI naïve): Objective Response Rate



RECIST 1.1 ORR = 21.4%
(95% CI, 10.3 - 36.8%)

PR	9 (21%)
SD	12 (29%)
Not evaluable	4 (10%)
DCR	**21 (50%)**

Figure 4: Best Target Lesion Response
Waterfall plot of best target lesion response using percent change from baseline of the SLD (sum of longest diameters) for all patients who received at least 1 post-baseline scan (n=38).

Cohort A (CPI naïve): Overall Survival & Tumor Burden

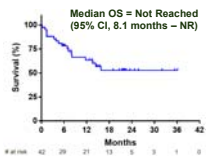


Figure 5a: Overall Survival
KM plot of patient survival (n=42). The vertical hash marks represents patient censoring. Median follow up of 14.4 months with 60% of patients still alive.

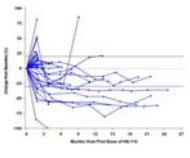
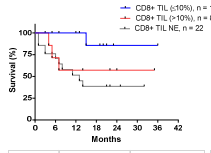
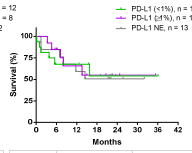


Figure 5b: Changes in Tumor Burden from Baseline Spider plot of tumor kinetics (n=42) demonstrating durability of decreased burden.

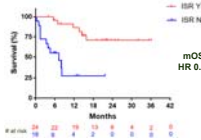




	Low CD8+ TIL (≤10%)	High CD8+ TIL (>10%)
Median OS	NR	NR
12 month OS	75%	50%
HR 0.39 (95% CI, 0.06; 2.31)		

	Negative PD-L1 (<1%)	Positive PD-L1 (≥1%)
Median OS	NR	NR
12 month OS	44%	54%
HR 0.85 (95% CI, 0.26; 2.79)		

Figure 6: Overall Survival – Subgroup Analysis by CD8+ TIL and PD-L1 Levels
KM plot of patient survival (n=42) based on protocol-defined subgroups of CD8+TIL (high and low) and PD-L1 status (positive and negative) at baseline. The vertical hash marks represents patient censoring.



mOS: NR vs. 7.2 months
HR 0.15 (95% CI, 0.05-0.45)
p = 0.0001

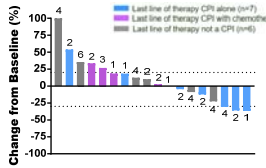
Typical ISR

Figure 7: Overall Survival – Injection Site Reactions (ISR)
KM plot of patient survival (n=42) with ISR subgroups (yes or no) demonstrates a statistically significant survival benefit in patients experiencing at least one injection site reaction to HS-110 during study treatment. The vertical hash marks represents patient censoring.

Adverse Events

Adverse events (AEs) occurring in ≥10% of patients in the safety population (n=75) are: fatigue (31%), cough (21%), diarrhea (15%), anemia (13%), dyspnea (13%), nausea (13%), pruritis (13%), arthralgia (12%), hypoalbuminemia (12%), decreased appetite (11%), hyponatremia (11%), dizziness (11%) and constipation (11%). There were two grade 5 AEs, pulmonary embolism and acute myocardial infarction, neither of which were deemed related to treatment.

Cohort B (CPI progressors): Objective Response Rate

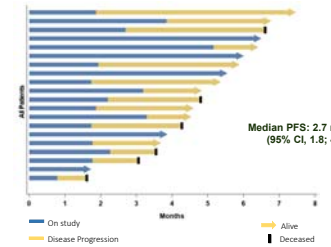


RECIST 1.1 ORR = 15%
(95% CI, 3.2 - 37.9%)

PR*	4 (20%)
SD	7 (35%)
Not Evaluable	2 (10%)
DCR	**11 (55%)**

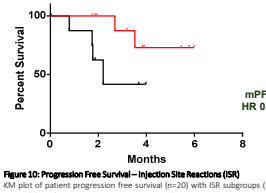
Figure 8: Best Target Lesion Response
Waterfall plot of best target lesion response using percent change from baseline of the SLD (sum of longest diameters) for all patients who received at least 1 post-baseline scan (n=18). The bar colors indicate the type of therapy received immediately preceding study entry. The numerical values presented with each bar indicate the number of lines of prior treatment. *per Investigator Assessment

Cohort B (CPI Progressors): Duration of Treatment



Median PFS: 2.7 months
(95% CI, 1.8; 4.0)

Figure 9: Duration of Treatment
Swimmer plot showing time on study and time of disease progression (n=20).



mPFS: NR vs. 2.2 months
HR 0.19 (95% CI, 0.03-1.09)
p = 0.06

Figure 10: Progression Free Survival – Injection Site Reactions (ISR)
KM plot of patient progression free survival (n=20) with ISR subgroups (yes or no) shows progression-free survival benefit in patients experiencing at least one injection site reaction to HS-110 during study treatment.

Immune Activity and Response

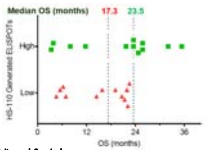


Figure 11: Immune Activity and Survival
Peripheral blood obtained before and during treatment (Weeks 4, 7, 13, EOT; n=24) to measure HS-110 derived immune reactivity. ELISPOTs represent INF-γ secretion from T cells in culture after stimulation with HS-110 lysate. **High** = Patients with absolute ELISPOT increases **above** the group median; **Low** = Patients with absolute ELISPOT increases **below** the group median.

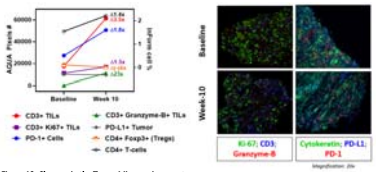


Figure 12: Changes in the Tumor Microenvironment
Using AQUA (CD3, Ki67, Granzyme B, PD-1, PD-L1) and inForm (CD4, Foxp3) immunohistochemistry-based analysis, cell phenotypes were quantitated in the tumor microenvironment (TME) of a patient at baseline and after 10 weeks of combination treatment.

Conclusions

HS-110 in combination with nivolumab is well tolerated.

Preliminary results demonstrate the ability of HS-110 plus nivolumab to induce CD8+ T-cell tumor infiltration in previously "cold" tumors.

In Cohort A, the occurrence of injection site reactions and increased INF-γ ELISPOTs may be associated with improved overall survival.

In Cohort B, early data suggest that the addition of HS-110 to nivolumab may restore responsiveness after tumor progression on prior CPI.

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. Strbo N, Vaccari M, Pahwa S, et al. Novel vaccination modality provides significant protection against mucosal infection by highly pathogenic SIV. Journal of immunology (Baltimore, Md : 1950) 2013;190:2495-9.

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