VIAGENPUMATUCEL-L (HS-110) PLUS NIVOLUMAB IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER AFTER CHECKPOINT INHIBITOR TREATMENT FAILURE

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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 interim data from the first twenty 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. The primary endpoint is objective response rate by RECIST 1.1.

Baseline tissue is collected and tested by Yale Specialized Translational Services Laboratory for tumoral PD-L1 expression (<1% or ≥1%) as well as for CD8+ tumor infiltrating lymphocytes (TILs) within the tumor stroma (≤10% or >10%). Patient subgroups by these tumor characteristics are used in an exploratory analysis to identify potential trends and relationships to clinical outcomes.

Trial ID: **NCT02439450**

Mechanism of Action

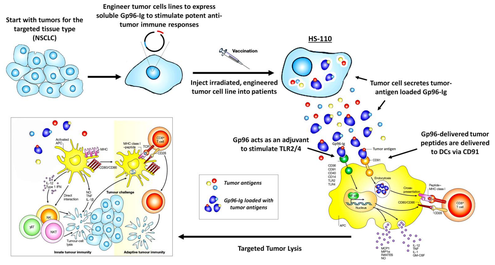


Figure 1: Viagenpumatucel-L (HS-110) Mechanism of Action

HS-110 is derived 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 and is recognized by CD91 on APCs; this recognition by APCs results 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, which include MHC II and secretion of cytokines and chemokines.

Study Schema

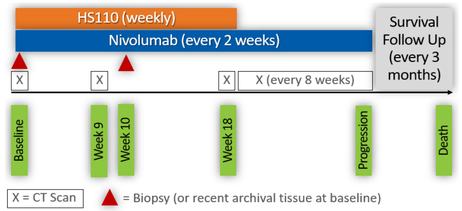


Figure 2: HS110-102 Study Schema

Patients receive weekly HS-110 (1 x 10^7 cells) 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

		Cohort B (N = 20)
Median age (range)		65 (56-84)
Female gender		14 (70%)
White race		15 (75%)
ECOG PS 1		10 (50%)
EGFR or ALK positive		2 (10%)
Histology	Adeno Squamous	17 (85%) 3 (15%)
Smoking status	Current/past Never	17 (85%) 3 (15%)
Prior lines of tx	1 2 3 or more	3 (15%) 9 (45%) 8 (40%)
PD-L1	< 1% ≥ 1% Unevaluable	7 (35%) 8 (40%) 5 (25%)
CD8+ TIL	≤ 10% > 10% Unevaluable	7 (35%) 6 (30%) 7 (35%)
Median Time (months) on prior CPI (range)		10.2 (6 – 19)
Median Time (months) between last CPI dose and study entry (range)		1.7 (1 – 21)

Table 1: Patient Characteristics

Baseline patient demographics of Cohort B (n=20).

Objective Response Rate

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

PR	3 (15%)
SD	8 (40%)
Not Evaluable	2 (10%)
DCR	11 (55%)

Tumor shrinkage observed in 35% of patients.

Table 2: Objective Response Rates

ORR for all cohort B patients (n=20) performed locally by site Investigators using RECIST 1.1

Overall Survival

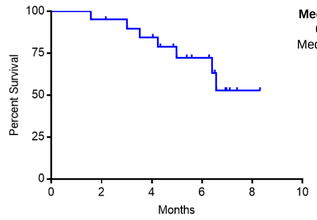


Figure 3: Overall Survival – Intent to Treat

Best Target Lesion Response

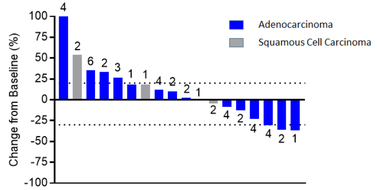


Figure 4: Best Target Lesion Response by Histology and # of Lines of Prior Therapy

Waterfall plot with bar colors representing the histology type. The numerical values presented with each bar indicate the number of lines of prior treatment.

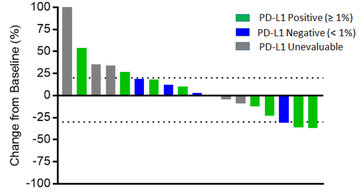


Figure 5: Best Target Lesion Response by PD-L1 Status

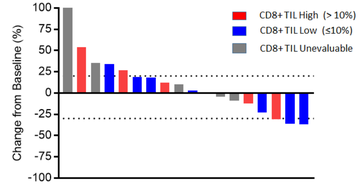


Figure 6: Best Target Lesion Response by TIL Status

Time to Progression

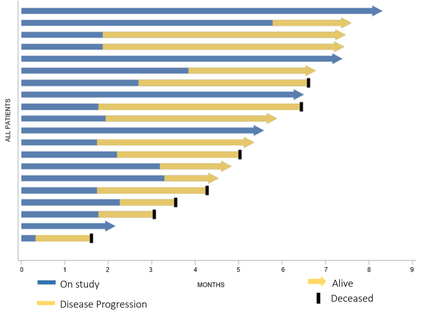
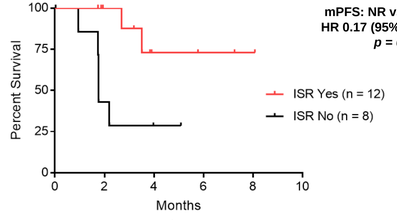


Figure 7: Time to Progression

Swimmer plot showing time until disease progression and current survival status (n=20).

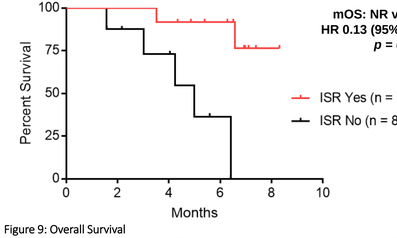
Injection Site Reactions



mPFS: NR vs. 1.8 months
HR 0.17 (95% CI, 0.03-0.84)
p = 0.013

Figure 8: Progression Free Survival

KM plot of patient PFS (n=20) with ISR subgroups (yes or no) shows PFS benefit in patients experiencing at least one injection site reaction (any grade) to HS-110 during study treatment.



mOS: NR vs. 5 months
HR 0.13 (95% CI, 0.02-0.71)
p = 0.002

Figure 9: Overall Survival

KM plot of patient OS (n=20) with ISR subgroups (yes or no) shows survival benefit in patients experiencing at least one injection site reaction (any grade) to HS-110 during study treatment.

Frequently Reported Adverse Events

Adverse Events	Cohort B (N=20)
Any Adverse Event	20 (100%)
Fatigue	11 (55%)
Cough	7 (35%)
Dyspnea	7 (35%)
Anemia	4 (20%)
Diarrhea	4 (20%)
Hypocalcemia	4 (20%)
Weight Decrease	4 (20%)
Dizziness	4 (20%)
Headache	4 (20%)
Pruritis	4 (20%)

Table 3: Adverse Event Table

Most commonly reported (>15%) treatment-emergent adverse events (regardless of attribution) occurring in the safety population. There were three Grade 3 events (1 each of embolism, hyponatremia, and pneumonia) and one Grade 4 event (cardiac tamponade), none of which were deemed related to treatment.

Conclusions

HS-110 in combination with nivolumab is well tolerated.

HS-110 in combination with nivolumab demonstrates clinical activity in low CD8+ TIL and PD-L1 negative tumors.

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

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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