Impact of adding Viagenpumatucel-L (HS-110) to Nivolumab in Non-Small Cell Lung Cancer (NSCLC) Patients with Low Levels of Tumor Infiltrating Lymphocytes

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Background

The tumor microenvironment (TME) has a pivotal role in the efficacy of immunotherapies such as anti-PD-1 agents. Tumors have been typically classified to the pattern and degree of the immune cell infiltration in their microenvironment. Chen and Mellman proposed to classify solid tumors as 'inflamed' (highly infiltrated with immune cells), 'immune-desert' (minimally infiltrated by immune cells) or as 'immune-excluded' (stromal immune cell infiltration, but not in the tumor)[1]. Single immunotherapy such as anti-PD-1 monotherapy have been shown to be most effective in inflamed tumors but not in 'cold' tumors, i.e. tumors with low tumor infiltrating lymphocytes (TIL)[2]. This highlights the need for better systemic treatments in patients with 'cold' tumors.

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 HS-110 and an immune activator of tumor specific T cells. Functionally, gp96 is a unique antigen chaperone and immune adjuvant that up-regulates multiple factors including MHC, cytokine release, and T-cell co-stimulators on antigen presenting cells (APCs). 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 to the patient's own tumor[3,4].

Based on this mechanism of action, we hypothesized that adding viagenpumatucel-L (HS-110) to anti-PD-1 may improve treatment efficacy against tumors with low TIL.

HS-110 Mechanism of Action

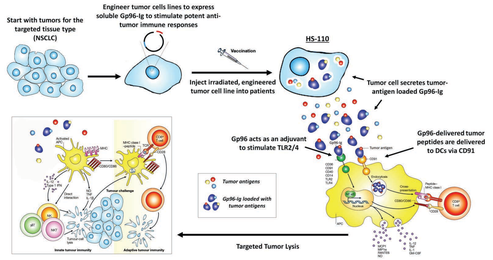


Figure 1: HS-110 Mechanism of Action
HS-110 is derived from a lung adenocarcinoma cell line transfected with gp96-Ig, which acts as a chaperone protein for tumor associated antigens and is recognized by CD91 on APCs, resulting in cross-presentation of antigen to MHC I for the selection of antigen-specific 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 Patients

This retrospective study compares the efficacy of nivolumab with and without HS-110 in tumors with low TIL. Two Patient groups from 2 separate single-arm studies were compared: (1) **Durga**, describing a prospective study (from the DURGA trial, Cohort A, NCT Trial ID: NCT02439450) of previously-treated NSCLC patients with a good performance score (ECOG 0/1) that were treated with HS-110 (intradermal injections of $1x10^7$ HS-110 cells every week, for 18 weeks) plus nivolumab, verses (2) **VUMC**, describing a retrospective real-world study (from VUMC, the Amsterdam UMC database) of the same patient type and treatment, who received nivolumab alone as standard of care therapy. Both groups of patients were non-squamous in tissue type and were PD-1 inhibitor naïve at the initiation of treatment.

Study Schemas

Figure 2: Design of Two Independent Studies
Durga patients received 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.
VUMC patients received nivolumab (240 mg IV) biweekly until disease progression or unacceptable toxicity.

Identification of % CD8 Cells in Tissue

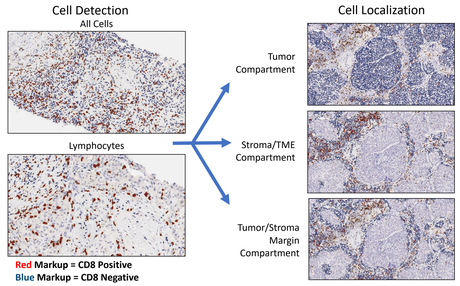


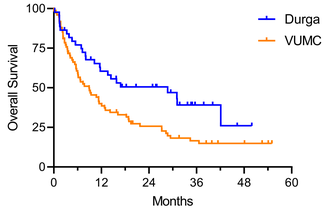
Figure 3: Examples of CD8 detected cells
TIL were centrally analyzed using Flagship's image analysis (IA) software for identification and classification of cells as positive or negative for CD8-specific chromogenic signal in the defined ROAs from digitalized CD8-stained pre-treatment tumor slides. Machine learning algorithms were implemented to separate out lymphocyte-like cells from all cells, and to stratify all cells and lymphocytes as belonging to the 'tumor', 'peri-tumoral stroma margin', or the 'stromal compartment' of the tissues. Once the tumor and stroma compartments were defined, the markups were reviewed by a Flagship pathologist for accuracy. Outputs of the digital analysis included percentages of CD8 expression in each stratified tissue compartment, as well as percentages of CD8 expression on detected lymphocytes in each compartment. Low TIL was defined as <10% of evaluable cells in the tumor fields.

Results

	Durga HS-110 + Nivolumab	VUMC Nivolumab	p value	Hazard Ratio
N	44	74	-	-
ORR, %	20.5	21.6	-	-
6-month DCR, %	36	34	-	-
OS, mos (95% CI)	28.7 (10.3 – not reached)	8.9 (5.6, 12.1)	0.0099	0.55 (0.34, 0.87)

Table 1: Efficacy Summary
RECIST 1.1 Objective Response Rates were similar between Durga and VUMC (20.5% and 21.6%, respectively), as well as Disease Control Rates (CR+PR+SD) at 6 months (36% and 34%, respectively). Median Overall Survival (mOS) in Durga was significantly higher than VUMC (28.7 mos vs 8.9 mos, *p*=0.0099, HR = 0.55). There were no statistically significantly differences in median OS in PD-L1 positive (≥ 1% TPS expression) patients, PD-L1 negative (< 1% TPS expression) patients and TIL high (> 10% CD8+ cells in the tumor compartment) patients (p=0.2368, p=0.0631, and not performed, respectively. A significantly improved median OS was observed for Durga compared to VUMC in patients with low TIL (≤ 10% CD8+ cells in the tumor compartment), (31.1 mos vs 4.0 mos, *p=0.0053*, HR = 0.28).

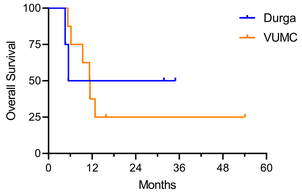
Overall Survival: All Patients



Cohort	N	Median OS, 95% CI (mos)	
Durga	44	28.7	(10.3, NR)
VUMC	74	8.9	(5.6, 12.1)
Log Rank p = 0.0099		HR: 0.55 (95% CI: 0.34 – 0.87)	

Figure 4: Overall Survival – All Patients
NR = Not Reached

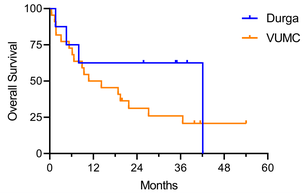
Overall Survival: TIL High



TIL High	N	Median OS, 95% CI (mos)	
Durga	4	NR	(4.6, NR)
VUMC	8	11.3	(5.3, NR)
Log Rank p = not performed due to small sample size		HR: 0.78 (95% CI: 0.16 – 3.88)	

Figure 6: Overall Survival by TIL (High)
TIL high is defined as > 10% CD8+ cells in the tumor compartment as defined in Figure 3 and 5.

Overall Survival: PD-L1 Positive



PD-L1 Positive	N	Median OS, 95% CI (mos)	
Durga	8	42.1	(1.6, 42.1)
VUMC	22	12.5	(5.3, 27.2)
Log Rank p = 0.2368		HR: 0.52 (95% CI: 0.17 – 1.56)	

Figure 8: Overall Survival by PD-L1 (Positive)
PD-L1 positive is defined as PD-L1 expression ≥ 1% using SP142 TPS staining.

Quantitative CD8 Expression in Biopsied Tissues

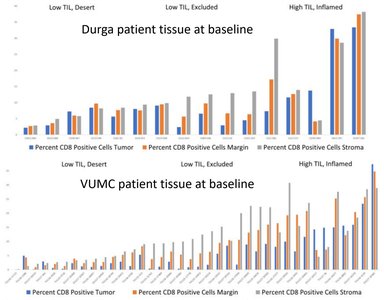
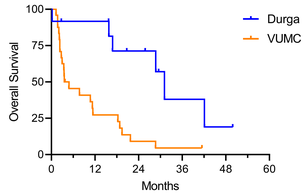


Figure 5: Quantification of CD8 Expression in Pre-Treatment Tissue Biopsies
Image analysis to quantify CD8 expression in tumoral and stromal compartments within Durga and VUMC were performed to stratify patient biopsies in to high TIL and low TIL subgroups.

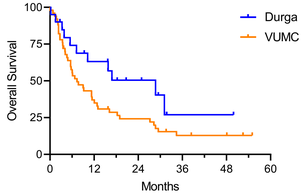
Overall Survival: TIL Low



TIL Low	N	Median OS, 95% CI (mos)	
Durga	12	31.1	(15.8, NR)
VUMC	30	4.0	(3.0, 10.7)
Log Rank p = 0.0053		HR: 0.28 (95% CI: 0.11 – 0.73)	

Figure 7: Overall Survival by TIL (Low)
TIL low is defined as ≤ 10% CD8+ cells in the tumor compartment as defined in Figure 3 and 5.

Overall Survival: PD-L1 Negative



PD-L1 Negative	N	Median OS, 95% CI (mos)	
Durga	20	28.7	(5.5, NR)
VUMC	50	7.4	(4.9, 12.1)
Log Rank p = 0.0631		HR: 0.54 (95% CI: 0.28 – 1.05)	

Figure 9: Overall Survival by PD-L1 (Negative)
PD-L1 negative is defined as PD-L1 expression < 1% using SP142 TPS staining.

Patient Characteristics by Study

		Durga (n = 44)	VUMC (n=74)
Age (median, range)		65 (37-87)	62 (37-94)
Gender	Female Male	25 (57%) 19 (43%)	41 (55%) 33 (45%)
ECOG PS	0 1	12 (27%) 32 (73%)	12 (16%) 62 (84%)
EGFR mutation	Positive Negative Unknown	5 (11%) 32 (73%) 7 (16%)	2 (3%) 67 (90%) 5 (7%)
ALK mutation	Positive Negative Unknown	0 (0%) 36 (82%) 8 (18%)	0 (0%) 69 (93%) 5 (7%)
KRAS mutation	Positive Negative Unknown	7 (16%) 19 (43%) 18 (41%)	16 (22%) 53 (71%) 5 (7%)
Smoking status	Current/past Never Unknown	36 (82%) 8 (18%) 0 (0%)	64 (86%) 3 (4%) 7 (10%)
PD-L1 status	Positive (≥ 1%) Negative (< 1%) Unknown	8 (18%) 20 (46%) 16 (36%)	22 (30%) 50 (67%) 2 (3%)
TIL status	>10% High ≤ 10% Low Unknown	4 (9%) 12 (27%) 28 (64%)	8 (11%) 30 (40%) 36 (49%)

Table 2: Baseline Demographics.

Conclusions

In this retrospective comparison of two independent studies, the combination of HS-110 and nivolumab (Durga) versus nivolumab alone (VUMC) in previously treated immunotherapy naïve non-squamous NSCLC patients demonstrated significantly improved:

- **overall survival in the study populations *(p= 0.0099)***
- **overall survival in the 'cold tumor' subgroup of patients with low tumor CD8+ TIL levels at treatment initiation *(p= 0.0053)***

References

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Disclosures

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Charles Caldwell – No Disclosures· Roberto Gianani – No Disclosures
Bradley Long – No Disclosures· Julie Wolf – Heat Biologics Consultant
Erik Thunnissen - No Disclosures

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