NeuVax™ (nelipepimut-S) for the Prevention of Recurrence in HER2-Expressing Node Positive Breast Cancer Patients

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Background

In 2014, there were an estimated 14.5 million cancer survivors in the United States. By 2024, it is projected there will be 19 million cancer survivors (DeSantis CE et al., 2014). Increases in survival are due to decades of productive research, improved screening, prevention methods, and effective therapeutic options. Nelipepimut-S, is an immunogenic peptide epitope derived from the extracellular domain of the human epidermal growth factor receptor 2 (HER2). Inoculation with nelipepimut-S (E75/NeuVax™) elicits a specific cellular response to the HER2 protein and directs activity against the epitope on HER2 by stimulation and activation of cytotoxic T-lymphocytes (CTLs) and CD8+ memory cells against the human leukocyte antigen (HLA)-presented HER2 epitope. Nelipepimut-S is a HLA-restricted (A2+, A3+, A24+, A26+) immunogenic peptide derived from the HER2 protein. Approximately 50–60% of breast cancer patients who are HER2 1+/2+ by immunohistochemistry (IHC) or < 2.0 by fluorescence in situ hybridization (FISH) achieve a response with current standard of care (SOC), but have no treatment options to maintain disease-free status. Nelipepimut-S is being studied to prevent breast cancer recurrence in these women (www.clinicaltrials.gov) in the adjuvant setting and maintain patients "survivor" status.

Methods

Node positive (NP) breast cancer patients with tumors expressing HER2 (IHC 1+, 2+, 3+) who completed primary standard of care breast cancer therapies (surgery, adjuvant chemotherapy, and radiation, as appropriate) demonstrating no evidence of disease, immunologically intact with ECOG PS ≤ 2, and signed informed consent, were enrolled in a Phase 1/2 Study. HLA-A2/A3+ patients were vaccinated (VG) with nelipepimut-S + GM-CSF, monthly x 6 inoculations as a primary vaccination series (PVS). A booster program was initiated at Month 12, then every 6 months for a total of 11 inoculations over a 3-year period. Toxicity was monitored and clinical recurrences (CR) were documented. Disease free survival (DFS) was analyzed by Kaplan Meier curves and the groups were compared by log-rank test.

Demographics

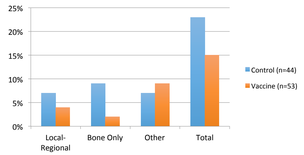
Demographics	Control, HLA-A2-, A3- (n=44)	Vaccine, HLA-A2+, A3+ (n=53)	*P*
Median age, years	49	52	
Range, years	31-83	21-72	0.15
Race			
White	72.7%	88.7%	0.04
Black	22.7%	7.5%	0.03
Hispanic	2.3%	0.0%	0.45
Asian	0.0%	3.8%	0.30
Other	2.3%	0.0%	0.45
Tumor size			
T2-T4	60.0%	46.0%	0.16
Histologic Grade			
Grade 3	44.0%	55.0%	0.31
Median + nodes	2.5%	2.0%	
Range (no.)	1 to 25	1 to 15	0.22
HER2/*neu* IHC 3+ or FISH+	39.0%	32.0%	0.50
Hormone receptor negative	20.0%	28.0%	0.37
Chemotherapy	95.0%	98.0%	0.43
XRT	84.0%	81.0%	0.70
Hormonal therapy	77.0%	74.0%	0.67
Adjuvant Herceptin	7.0%	19.0%	0.00

Results

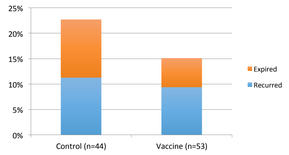
Clinical Recurrence

Category	Control (n = 44)	Vaccine (n = 53)	*P*
Median follow-up	60 months	60 months	0.85 (Mann-Whitney)
Recurrence	10/44 (22.7%)	8/53 (15.1%)	0.33 (Chi-square)
Recurrence at 24 months	9/44 (20.5%)	5/53 (9.4%)	0.12 (Chi-square)
Overall mortality	5/44 (11.4%)	3/53 (5.7%)	0.25 (Fisher)
Mortality per recurrence	5/10 (50.0%)	3/8 (37.5%)	0.47 (Fisher)

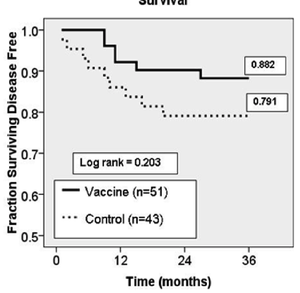
Distribution of Recurrences



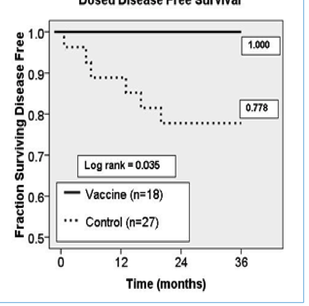
Mortality Among Recurrence



Node Positive Kaplan-Meier Disease Free Survival

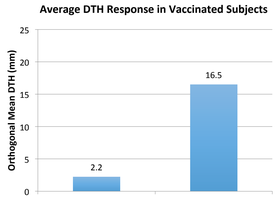


Node Positive, Low-Expressor, Optimally Dosed Disease Free Survival

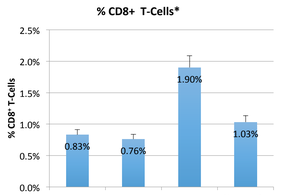


Immunologic Response

Average DTH Response in Vaccinated Subjects



% CD8+ T-Cells*



*Measured using HLA-A2:IgG dimer assay loaded with E75 to stain peripheral blood lymphocytes.

Adverse Events (≥ 5%), Vaccinated

System Organ Class	Total Active Patients
Preferred Term	**n = 53 n (%)**
Gastrointestinal disorders	
Diarrhea	4 (8%)
Dyspepsia	3 (6%)
Nausea	7 (13%)
Musculoskeletal and connective tissue disorders	
Arthralgia	12 (23%)
Back pain	11 (21%)
Bone pain	10 (19%)
Myalgia	16 (30%)
Nervous system disorders	
Dizziness	4 (8%)
Headache	22 (42%)

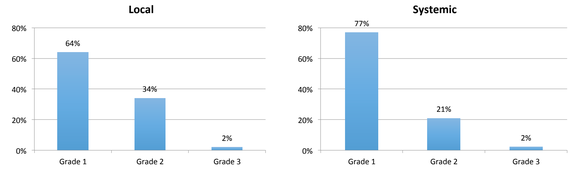
System Organ Class	Total Active Patients
Preferred Term	**n = 53 n (%)**
General disorders and administration site conditions	
Chills	6 (11%)
Fatigue	34 (64%)
Influenza like illness	5 (9%)
Injection site discoloration	11 (21%)
Injection site erythema	51 (96%)
Injection site induration	51 (96%)
Injection site pain	9 (17%)
Injection site pruritus	45 (85%)
Injection site swelling	10 (19%)
Injection site vesicles	3 (6%)
Injection site warmth	18 (34%)
Malaise	8 (15%)

Treatment Related Adverse Events, All

Adverse Event	Grade	Total (1449)	Percent
Erythema	1	355	24.5%
	2	11	0.8%
Induration	1	395	27.3%
	2	7	0.5%
Pruritus	1	253	17.5%
	2	6	0.4%
Discoloration	1	11	0.8%
Pain at injection site	1	9	0.6%
	2	3	0.2%
Swelling	1	10	0.7%
	2	4	0.3%
Warmth	1	32	2.2%
	2	1	0.1%
Petechiae	1	1	0.1%
Bleb	1	3	0.2%
Hives	1	2	0.1%
	2	1	0.1%
Cellulitis	2	1	0.1%
Rash	2	1	0.1%
Abdominal pain / stomach cramps	1	2	0.1%
	2	1	0.1%
Angioedema	3	1	0.1%
Anorexia	1	3	0.2%
	2	1	0.1%
Arthralgias	1	22	1.5%
	2	1	0.1%
Back pain	1	13	0.9%
	2	3	0.2%
	3	1	0.1%
Back spasm	2	1	0.1%
Bitter taste / tongue hypersensitivity	1	4	0.3%
	2	0	0.0%
Bone Pain	1	12	0.8%
	2	1	0.1%
	3	1	0.1%
Chest pain	2	2	0.1%

Adverse Event	Grade	Total (1449)	Percent
Chills	1	7	0.5%
Cold sxs	1	1	0.1%
Diarrhea	1	5	0.3%
	2	2	0.1%
Diaphoresis/ night sweats/ hot flashes	1	4	0.3%
Dyspnea	2	1	0.1%
Fatigue	1	99	6.8%
	2	4	0.3%
Fever	1	7	0.5%
Flu like	1	9	0.6%
Headache	1	46	3.2%
	2	2	0.1%
Hypertension	1	1	0.1%
Hypotension	1	1	0.1%
Indigestion	1	4	0.3%
Itchy eyes	1	1	0.1%
Joint stiffness	1	2	0.1%
Lightheadedness	1	4	0.3%
Myalgias	1	39	2.7%
Malaise	1	13	0.9%
Nausea	1	8	0.6%
	2	1	0.1%
Numbness	1	4	0.3%
Systemic pain (mastectomy site)	1	1	0.1%
Systemic pruritus	1	2	0.1%
Sternal pressure	1	1	0.1%
Swelling	1	1	0.1%
	2	1	0.1%
Warmth/flushing	1	3	0.2%

Local and Systemic AEs - Maximum Grade



Conclusions

Nelipepimut-S administered concomitantly with GM-CSF (NeuVax) appears to be well tolerated and demonstrated preliminary efficacy in decreasing the rate of recurrence in NP breast cancer patients. Nelipepimut-S is currently being investigated in 3 ongoing clinical trials, as a single agent and in combination with trastuzumab, to prevent secondary breast cancer recurrence and thereby potentially increase survivorship. A Phase 2 primary prevention proof of concept trial in ductal cell carcinoma in situ (DCIS) is planned with the National Cancer Institute. Active and planned clinical trials include:

1) **PRESENT** – **P**revention of **R**ecurrence in **E**arly-**S**tage, Node Positive Breast Cancer with Low to Intermediate HER2 **E**xpression with **NeuVax™ T**reatment: A Phase 3, single agent, registration study (under FDA-approved Special Protocol Assessment) (NCT01479244)[2].

2) Phase 2 Combination Immunotherapy With Herceptin and the HER2 Vaccine NeuVax (NCT01570036)[2].

3) Phase 2 Trial of Combination Immunotherapy With NeuVax and Trastuzumab in High-risk HER2+ Breast Cancer Patients (NCT02297698)[2].

4) **VADIS** – Phase 2 trial of nelipepimut-S **VA**ccine in Women with **DCIS** Breast Cancer.

NeuVax in conjunction with agents that target antigen release, antigen presentation, priming and activation, T-cell trafficking, T-cell infiltration, cancer cell recognition, and cancer cell killing are all potential rational combinations for the treatment of a variety of carcinomas.

References

1. DeSantis CE et al. CA Cancer J Clin 2014: 64(4): 252 – 271.
2. Clinicaltrials.gov; accessed, October 18, 2015; NCT01479244; NCT01570036; NCT02297698.

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