Correlation between response and HLA type in a randomized phase IIb trial of NeuVax + trastuzumab in HER2 low-expressing breast cancer patients to prevent recurrence

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INTRODUCTION

MHC class I peptide vaccines are HLA-restricted but may bind to multiple HLA-types. HLA types have been associated with response to multiple immunotherapies to include checkpoint inhibitors. The relationships between HLA-type, predicted peptide binding potential, and clinical response have implications for the design and development of active immunotherapy. We are currently conducting a randomized phase IIb trial of the MHC class I peptide, E75 (HER2 369-377) + GM-CSF (NeuVax) + trastuzumab versus GM-CSF + trastuzumab to prevent recurrences in node positive and/or ER$^-$/PR$^-$ negative, HER2 low-expressing breast cancer patients. In a planned interim analysis, we demonstrated a significant disease-free survival benefit specifically in triple negative patients breast cancer patients to NeuVax + trastuzumab. This analysis examines the effect of HLA-type on trial outcomes.

METHODS

Clinically disease-free, HER2 low-expressing (IHC1+/2+, FISH nonamplified), node positive (AJCC N1, N2, or N3) and/or triple negative breast cancer patients patients after standard therapy were tested for the presence of the A2, A3, A24, and A26 alleles by flow cytometry. HLA-A2, A3, A24, and/or A26+ patients were randomized to receive trastuzumab + NeuVax (vaccine group) or trastuzumab + GM-CSF (control group). All patients received one year of trastuzumab per standard of care. NeuVax or GM-CSF was given every three weeks x 6 starting with the third trastuzumab dose, and then boosted every six months x 4. The pre-specified interim analysis was triggered six months after last patient enrollment. The primary endpoint was disease free survival evaluated by log rank. The MHC Class I binding predictions were made using the IEDB Analysis Resource Consensus tool.

Abstract:

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RESULTS

275 patients were randomized in the study (VG n=136, CG n=139). 146 were HLA-A2+ (71 in VG, 75 in CG), 133 HLA-A24+ (71 in VG, 61 in CG), 88 HLA-A3+ (VG=44, CG=44), and 19 HLA-A26+ (VG=10, CG=9). Median follow up was 18.8 months. There were no significant clinicopathologic difference between the vaccine group and control group as a whole or within HLA-allele subgroups, except that fewer HLA-A24+ vaccine group patients received radiation therapy (p=0.02). (Table 1) In triple negative patients, active treatment benefited all HLA-types (Figure 1) especially HLA-A24+ patients (Figure 2, p=0.003). HLA-A24+ VG patients also showed a trend toward improved disease free survival study-wide (Figure 3, p=0.07). HLA-A24+ has the lowest predicted binding affinity of the four HLA alleles. (Table 2)

	Vaccine Group n= 71 (53.4%)	Control Group n = 62 (46.6%)	p Value
Race			
White	51 (71.8%)	43 (69.4%)	0.59
Asian	2 (2.8%)	0 (0.0%)	
Black	10 (14.1%)	12 (19.4%)	
Hispanic	6 (8.5%)	5 (8.1%)	
Other/Unknown	2 (2.8%)	2 (3.2%)	
Stage			
< III	37 (52.1%)	29 (46.8%)	0.71
>= III	34 (47.9%)	33 (53.2%)	
Breast Procedure			
Lumpectomy	19 (26.8%)	18 (29.0%)	0.61
Mastectomy	51 (71.8%)	41 (66.1%)	
Lumpectomy followed by Mastectomy	1 (1.4%)	2 (3.2%)	
None	0 (0.0%)	1 (1.6%)	

	Vaccine Group n= 71 (53.4%)	Control Group n = 62 (46.6%)	p Value
Age (Median)	53	51	0.93
Axillary Procedure			
Sentinel Lymph Node Biopsy	26 (36.6%)	19 (30.7%)	0.48
Axillary Dissection	36 (50.7%)	30 (48.4%)	
SLN Biopsy followed by Axillary Dissection	9 (12.7%)	12 (19.4%)	
None	0 (0.0%)	1 (1.6%)	
Chemotherapy			
Neoadjuvant	39 (54.9%)	35 (56.5%)	0.97
Adjuvant	29 (40.9%)	24 (38.7%)	
None	4 (5.6%)	3 (4.8%)	
Radiation Therapy			
Neoadjuvant	2 (2.8%)	0 (0.0%)	0.02*
Adjuvant	54 (76.1%)	58 (93.6%)	
None	15 (21.1%)	4 (6.5%)	

Table 1. Demographics of HLA-A24+ patients

Allele	Peptide	Rank	ANN IC50
HLA-A 02:06	KIFGSLAFL	0.62	10.84
HLA-A 02:01	KIFGSLAFL	1.2	14.35
HLA-A 03:01	KIFGSLAFL	3.65	2110.2
HLA-A 26:01	KIFGSLAFL	8.6	13395.81
HLA-A 24:02	KIFGSLAFL	13.15	9730.14

Table 2. Predicted binding affinity for E75 epitope amongst test HLA types. Artificial neural networks (ANN) IC50 denotes the concentration of protein required for 50% binding with MHC Class I.

Figure 1. Forrest plot depicting relative benefit for all HLA-types among TNBC patients. Because there were too few patients, HLA-A26 patients could not be analyzed.

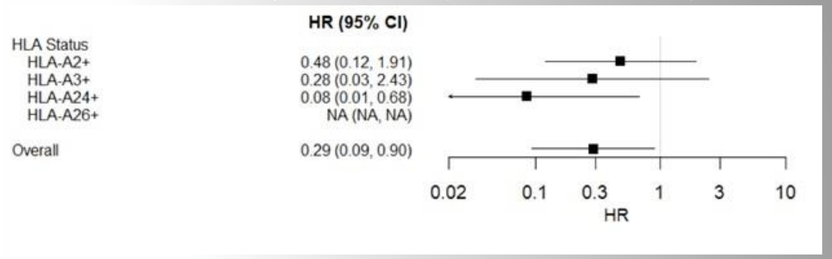


Figure 2. Kaplan-Meier estimated DFS for HLA-A24+ TNBC patients

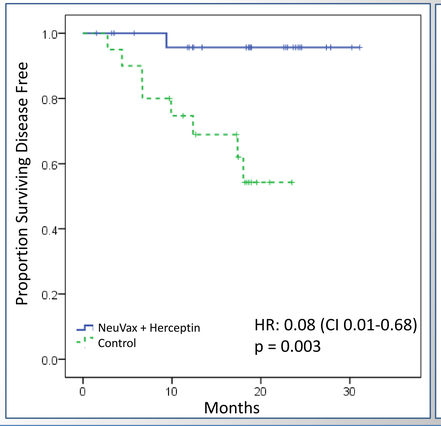
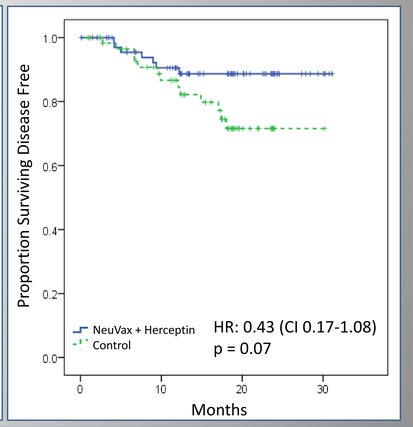


Figure 3. Kaplan Meier estimated DFS for all HLA-A24+ patients.



CONCLUSION

HLA-A24+ triple negative breast cancer patients had a significant improvement in disease free survival despite the lowest predicted binding potential between E75 and this HLA-type. This suggests that lower-affinity peptides may generate a favorable immunologic response possibly due to decreased exposure and tolerance to these epitopes.