Final Results of the Phase I/II Trials of the E75 Adjuvant Breast Cancer Vaccine

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BACKGROUND

We have completed phase I/II clinical trials vaccinating breast cancer patients with E75, a HLA-A2/A3-restricted HER2/*neu* (HER2) peptide vaccine. The vaccine was administered in the adjuvant setting to prevent recurrences in high risk patients rendered disease-free with standard of care therapy. We have previously reported preliminary results indicating that the vaccine (including booster inoculations) is safe, well-tolerated, and effective in stimulating an anti-tumor immune response. Here, we report the final 5 year results from these trials.

METHODS

The phase I/II trials were performed as dose-escalation/schedule-optimization trials enrolling node positive and high-risk, node negative breast cancer patients with tumors expressing any level of HER2 expression. HLA-A2/A3+ patients were enrolled into the vaccine group (VG) while HLA-A2/A3- patients were followed prospectively as the untreated control group (CG). The VG patients were given 4-6 monthly intradermal inoculations of E75 with GM-CSF during the primary vaccine series (PVS). In addition, a voluntary booster program was initiated during the trial, with booster inoculations being offered every 6 months after completion of the PVS. Patients were monitored for local and systemic toxicity (graded by NCI Common Terminology Criteria for Adverse Events). Pre- and post-PVS, *in vivo* immune response was assessed in the VG by delayed type hypersensitivity (DTH) reactions to both E75 and saline. VG and CG pts were followed for 60 months and recurrences were documented. Demographic differences were compared with the Fisher's exact test and disease-free survival (DFS) was determined using the Kaplan-Meier method and compared by log-rank test.

RESULTS

195 patients were enrolled, 6 withdrew (2 from VG, 4 from CG), 1 was lost to follow-up prior to vaccination, and 1 was found to be ineligible, leaving 187 evaluable patients; 108 in the VG and 79 in the CG. 53 patients volunteered for the booster program and received at least one booster inoculation. The VG and CG were well-matched with the only statistically significant difference being ER-/PR- status (Table 1).Vaccination was well tolerated (maximum local toxicity: 83% Grade 1, 17% Grade 2, 0% Grade 3; maximum systemic toxicity: 9% Grade 0, 72% Grade 1, 17% Grade 2, and 1% Grade 3) (Figure 2). In the VG, E75 pre- to post-PVS DTH significantly increased (mean 3.8 ±1.0 vs 14.8±1.4, p<0.001) and E75 post-PVS DTH was significantly greater than Saline post-PVS DTH (1.84±0.5 vs 14.8±1.4, p<0.001) (Figure 1). At the end of the trial, analysis of the Kaplan Meier curves at 60 mo shows increased DFS in the VG compared to the CG with a trend toward significance (89.7% vs 80.3%, p=0.08) (Figure 3). Analysis of patients receiving optimal dosing demonstrated significantly increased DFS compared to CG (94.6% vs 80.3, p=0.05) (Figure 4). Patients in the voluntary booster program also demonstrated an increased DFS compared to CG (96.2% vs. 80.3%, p=0.01) (Figure 5). Finally, those patients who were optimally boosted demonstrated a trend toward increased DFS compared to CG (95.2% vs. 80.3%, p=0.11) (Figure 6).

Table 1: Demographics

	Vaccine	Control	p value
	108	79	
Age (median)	57	53	0.26
Node Positive	49.1%	55.7%	0.38
Tumor Size (T2-T4)	34.3%	46.2%	0.13
Histologic Grade 3	40.0%	39.5%	1.00
ER/PR negative	31.1%	17.7%	0.04
HER2/*neu* overexpression	31.7%	26.8%	0.50
Hormonal Therapy	66.7%	76.9%	0.14
Chemotherapy	75.0%	72.2%	0.74
Radiation Therapy	72.2%	81.0%	0.17
Trastuzamab Therapy	11.1%	3.8%	0.10

Figure 1: DTH Response

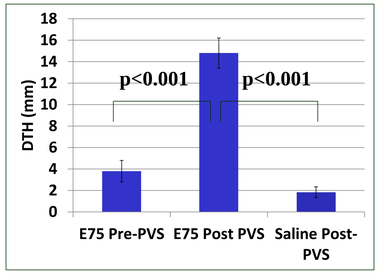
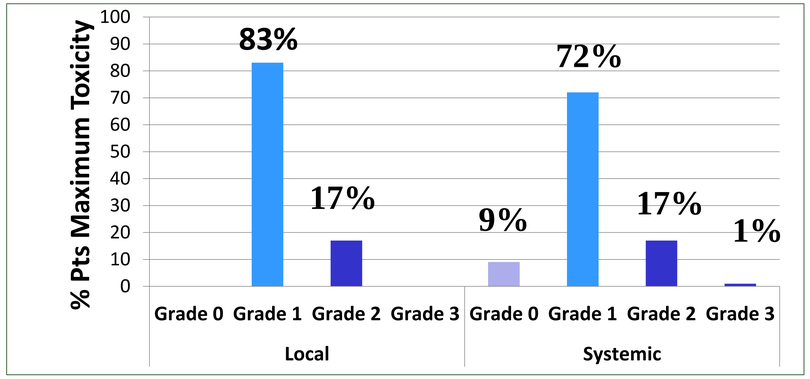


Figure 2: E75 Vaccine Toxicity



CONCLUSIONS

The E75 breast cancer vaccine is safe and well–tolerated. It elicits strong immune responses in vaccinated patients. At the end of the 5 year follow-up period, the E75 vaccine shows a strong trend toward preventing breast cancer recurrence in vaccinated patients. To evaluate this vaccine (now known as NeuVax) further, the PRESENT trial, a prospective, randomized, double-blind, placebo-controlled, multi-center phase III registration trial has been initiated and is actively enrolling.

DISCLOSURE

Dr. Peoples has inventor rights to E75. This vaccine has been licensed for commercial development based on clinical trial results. He is entitled to financial proceeds associated with this license per Federal policy. Dr. Peoples also consults in the development of the vaccine. All other authors have no relevant financial disclosures.

Figure 3: Overall DFS

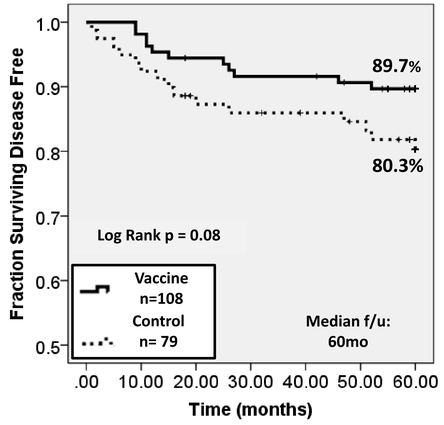


Figure 4: DFS By Dosing

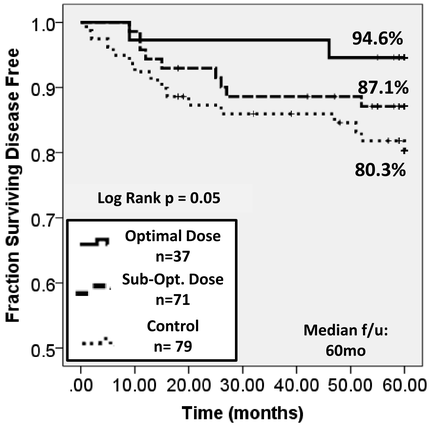


Figure 5: DFS By Booster Status

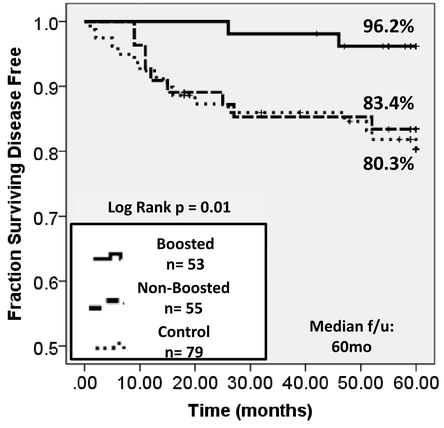


Figure 6: DFS By Optimally Boosted