Long-term clinical benefit of adjuvant breast cancer vaccine: 5 year efficacy of E75 with multiple booster inoculations.

Timothy J Vreeland[1], Guy T Clifton[1], Alan K Sears[1], Diane F Hale[1], Ritesh Patil[2], Kevin SClive[1], Jared P Holmes[3], Elizabeth A Mittendorf[4], Sathibalan Ponniah[5], George E Peoples[1]

[1] San Antonio Military Medical Center, [2]Roswell Park Cancer Institute, Buffalo, New York & Joyce Murtha Breast Care Center, Windber, Pennsylvania; [3]Naval Medical Center San Diego, San Diego, California; [4]University of Texas MD Anderson Cancer Center, Houston, Texas; [5]Cancer Vaccine Development Lab, U.S. Military Cancer Institute, Uniformed Services of the Health Sciences, Bethesda, Maryland;

BACKGROUND

We are conducting phase I/II clinical trials vaccinating breast cancer patients with E75, an HLA-A2/A3 restricted HER2/*neu* (HER2) peptide mixed with GM-CSF. The vaccine has been studied in the adjuvant setting to prevent recurrences in clinically disease-free patients after completion of standard therapy. We have previously reported that the vaccine is safe, effectively stimulates HER2-specific immunity, and appears to improve disease-free survival at 24 months. Here, we report long-term data at a median follow-up of 60 months.

METHODS

The phase I/II trials were performed as dose escalation/schedule optimization trials enrolling HLA-A2/A3+, node positive and high-risk, node-negative patients with tumors expressing any level of HER2. HLA-A2/A3- patients were followed as controls. Vaccinated patients were given 4-6 monthly inoculations of E75 with GM-CSF immunoadjuvant. Due to waning immunity, a voluntary booster program was initiated, with inoculations every 6 months after completion of the primary vaccine series (PVS) (Figure 1). Patients were monitored for local and systemic toxicities, which were graded by the NCI's Common Terminology Criteria for Adverse Events. Vaccinated patients and controls were followed for 60 months and recurrences were documented. Demographic differences were compared with the Fisher's exact test and survival was analyzed by the log-rank test.

Table 1

E75 Demographics

	Vaccine	Control	p value
n=	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
XRT (%)	72.2	81.0	0.17
Trastuzamab Therapy (%)	11.1	3.8	0.10

RESULTS

187 patients were enrolled; 108 in the vaccine group (VG) and 79 in the unvaccinated control group (CG). The vaccine and control groups were well-matched with the only statistically significant difference being ER-/PR- status (31.1% in VG vs 17.7% in CG, p=0.04). Vaccination was well tolerated with primarily grade 1 and grade 2 toxicity in the PVS (Local Toxicity: 85% Grade 1, 15% Grade 2, 0% Grade 3; systemic toxicity: 71% Grade 1, 14% Grade 2, and 3% Grade 3) (Figure 3). Fifty-three of the VG patients received at least one booster, with 34 receiving a second booster, 25 a third, 22 a fourth, 12 a fifth, and 9 receiving at least six boosters. Booster inoculations were well-tolerated with only grade 1 and 2 local and systemic toxicities (Figure 2). There were delayed urticarial reactions in 7/53(13%) of the boosted patients occurring at a median of 9 days (5-21 days) after inoculation; these were grade 2 reactions and well-tolerated. After a median follow-up of 60 months, there has been a non-significant increase in the Disease Free Survival (DFS) observed in the VG compared to the CG (10.6% vs 20.3%, p=0.098) (Figure 3). The hazard ratio is 0.52 in the VG. In patients with immunity maintained with voluntary boosters, DFS is improved to 95.9% (p=0.016) (Figure 3).

Figure 2

E75 Vaccine Toxicity

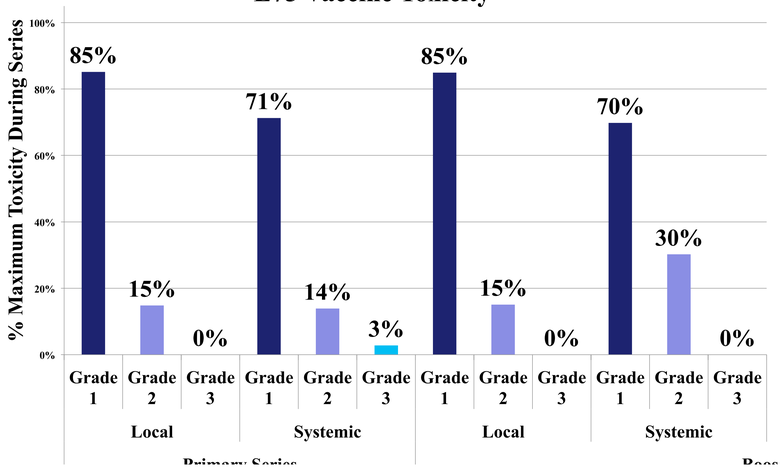
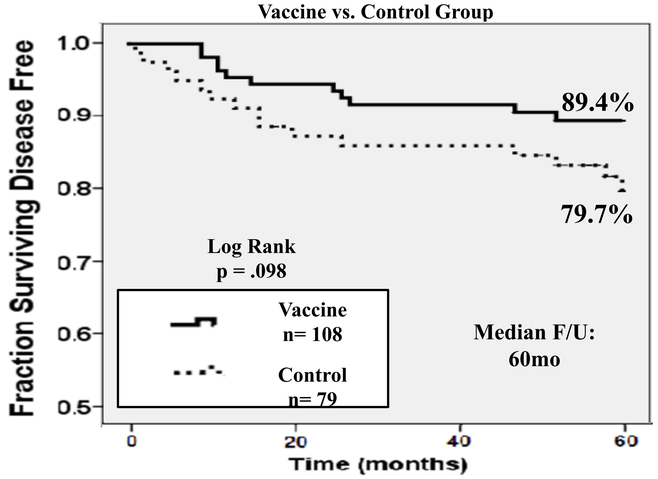


Figure 3

Overall DFS



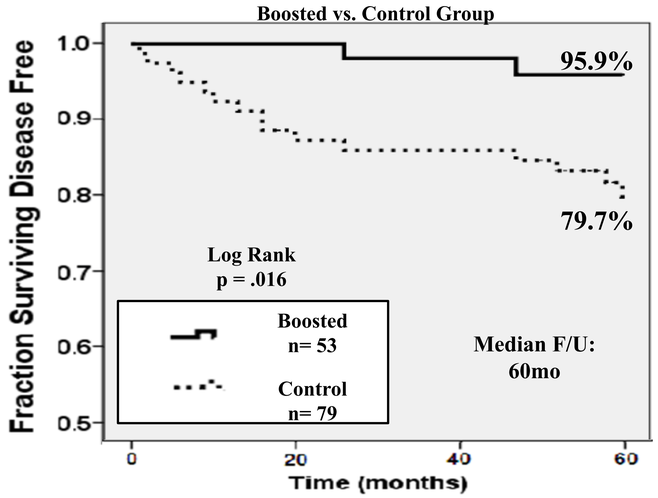
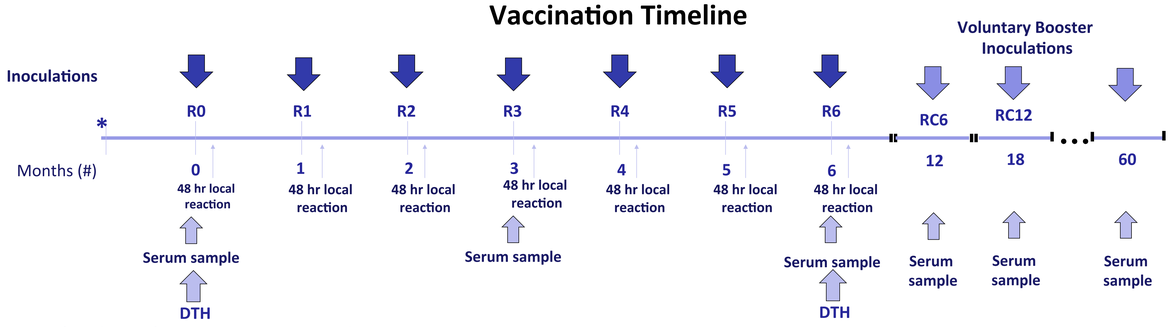


Figure 1

Vaccination Timeline



CONCLUSIONS

The E75 breast cancer vaccine is safe and well–tolerated even with prolonged booster inoculations. With long-term follow-up at 60 months, the E75 vaccine continues to show a strong trend toward preventing breast cancer recurrence in vaccinated patients particularly in patients whose immunity is maintained with booster inoculations. To investigate this further, a phase III trial with prospective boosting is being initiated.

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.