Safety and Long-Term Maintenance of Anti-HER2 Immunity Following Booster Inoculations of the E75 Breast Cancer Vaccine

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Background

We have completed accrual and are in the final follow up portion of phase I/II clinical trials evaluating the E75 vaccine, an HLA A2/A3 restricted HER2/*neu* (HER2) peptide mixed with GM-CSF. E75 has been proven safe, capable of stimulating HER2 immunity, and appears effective in decreasing breast cancer recurrence rates. During the conduct of this trial, it was noted that E75-specific immunity waned after the Primary Vaccine Series (PVS) which corresponded with late recurrences. To maintain long-term immunity, a voluntary booster program was started. Here we present analyses of the booster inoculations.

Methods

The trial enrolled node-positive or high-risk, node-negative breast cancer patients with tumors expressing any level of HER2 (IHC 1-3+). HLA-A2/A3+ patients comprised the vaccine group (VG), HLA-A2/A3- patients were followed prospectively as the control group (CG). The VG received 4-6 monthly inoculations as the PVS, followed with one inoculation every 6 months as the booster vaccine series. Patients were monitored for toxicities, *in vivo* responses by local reactions and DTH, and *in vitro* responses measured by enumeration of E75-specific cytotoxic T lymphocytes using HLA A2:E75 dimers.

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
Trastuzumab Therapy	11.1%	3.8%	0.10

Results

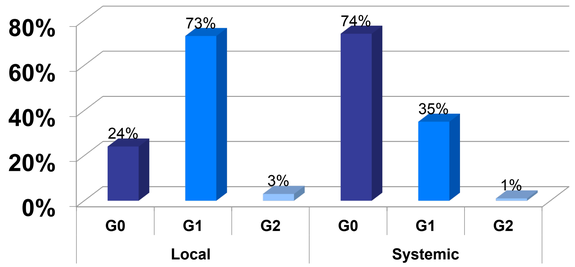
To date 53 patients received at least one booster, 34 received two, 24 received three, 20 received four, 12 received five, and 8 received at least six. Overall, vaccinated and control patients only differ in the number of ER/PR negative status. When looking at boosted, not boosted and control patients, the only additional difference is the number of patients receiving Trastuzumab. This is likely due to the fact that these patients enrolled later in the trial.

E75 Booster Demographics

	Booster	Control	p value
n=	53	79	
Age (median)	58	53	0.37
Node Positive	47.2%	55.7%	0.34
Tumor Size (T2-T4)	28.3%	39.2%	0.20
Histologic Grade 3	45.3%	38.0%	0.40
ER/PR negative	34.0%	17.7%	0.03
HER2/*neu* overexpression	32.1%	24.1%	0.31
Hormonal Therapy	62.3%	76.0%	0.09
Chemotherapy	75.5%	72.2%	0.67
XRT	73.6%	81.0%	0.31
Trastuzumab Therapy	22.6%	3.8%	0.001

Vaccinations were well tolerated with primarily Grade 1 and Grade 2 toxicity (Local toxicity: 24% no toxicity, 73% had Grade 1, and 3% had Grade 2; Systemic toxicity: 74% no toxicity, 35% had Grade 1, 1% had Grade 2) (Figure 1).

Figure 1: Toxicity



Local reactions increased significantly from the initial vaccine (R1) during PVS to each booster (B) (R1: 59.5±3.1 vs B1: 89.2±3.3, p<0.001; vs B2: 95.15±5, p<0.001; vs B3: 86.63±5.5, p<0.001; vs B4: 83.26±4.6, p<0.001; vs B5: 80.67±6.7, p=0.006; vs B6: 78.75±9.4, p=0.04) (Figure 2).

HLA A2:E75 dimer values increased from the end of PVS to each post-booster value (pre B1: 1.29±0.25 vs post B1: 1.46±0.38; post B2: 1.41±0.4; post B3: 1.84±0.35; post B4: 2.23±0.4; post B5: 1.94±0.31; post B6: 2.73±0.09, p=0.02).

Figure 2: Local Reactions

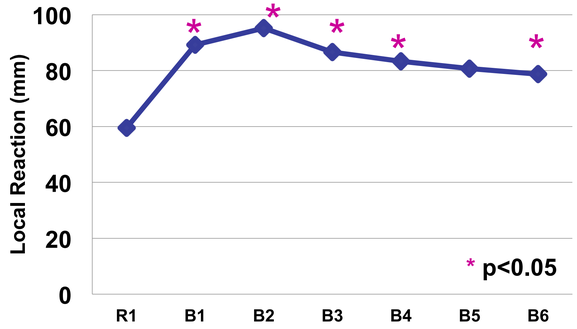


Figure 3: E75-specific CD8 T cells

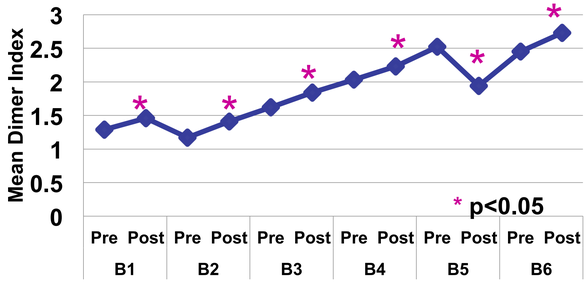
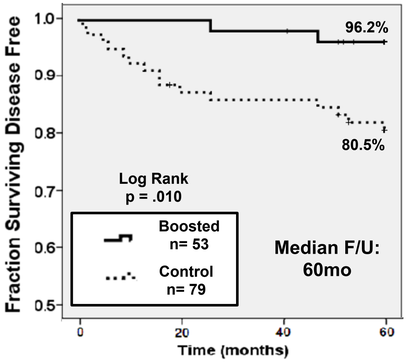


Figure 4: Disease Free Survival



At a median of 60 months, the disease free survival for the booster group was 96.2% vs 80.5% in the control group (p=0.037) (Figure 4). The recurrence rate for the booster group was 3.8% vs 18.9% in the control group (p=0.01).

Conclusions

Booster inoculations are well-tolerated and appear to assist in the maintenance of long-term peptide-specific immunity. Boosted patients have improved recurrence rates. Based on the success of this program, we have incorporated the practice of booster inoculations in our current cancer vaccine trials, to include the recently initiated PRESENT Phase III Trial of E75 + GM-CSF.

Disclosures

•Dr. Peoples has partial inventor rights to E75. Patents have 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

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