



Safety and clinical efficacy of multiple booster inoculations with the E75 adjuvant breast cancer vaccine.



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Background:

We are conducting clinical trials of the HER2/*neu* E75-peptide+GM-CSF vaccine (Figure 1) in clinically disease-free breast cancer patients at high risk for recurrence. Our Phase I/II trials have shown that the vaccine is safe and effective in stimulating clonal expansion of E75-specific CD8⁺ T-cells; however, this peptide-specific immunity decreases over time. Due to this waning immunity, a voluntary booster program was initiated.

Methods:

Node-positive and high-risk node-negative patients who were clinically disease-free after surgery and standard adjuvant therapy were enrolled. HLA-A2/A3+ patients were vaccinated (VG), while HLA-A2/A3- patients were followed as controls (CG). Patients who were ≥6 months from the completion of their primary vaccination series (PVS) were offered booster inoculations every 6 months. Patients were monitored for local and systemic toxicity. Orthogonal mean of local reactions (LR) were measured after each booster inoculation. In HLA-A2+ patients, E75-specific CD8⁺ T-cells were quantified using the HLA-A2:IgG dimer immediately before and 1 month after each booster administration. (Figure 2) Patients were monitored clinically and radiographically for recurrences.

Table 1

	Demographics			
	Control n=79	Vaccine n=108	Boosted n=53	p value
Age (median)	53	57	58	0.26
Node Positive	55.7%	49.1%	47.2%	0.56
Tumor Size (T2-T4)	46.2%	34.3%	35.3%	0.25
Histologic Grade 3	39.5%	40.0%	49.0%	0.51
ER/PR negative	17.7%	31.1%	35.8%	0.04
HER2/ <i>neu</i> overexpression	26.8%	31.7%	36.0%	0.55
Hormonal Therapy	76.9%	66.7%	60.4%	0.11
Chemotherapy	72.2%	75.0%	77.4%	0.74
XRT	81.0%	72.2%	73.6%	0.39
Trastuzumab Therapy	3.8%	11.1%	22.6%	0.01

Results:

188 patients were enrolled (108 VG, 79 CG). Fifty-three of the VG patients received at least one booster (B1), with 33 receiving a second booster (B2), 20 a third booster (B3). Demographic and prognostic characteristics were similar between the CG, VG, and boosted patients except there were less ER/PR negative patients in the CG and boosted patients were more likely to have received trastuzumab due to later enrollment in the trial (when trastuzumab had become standard of care) (Table 1). Booster inoculations were well-tolerated with only grade 1 and 2 local and systemic toxicities (Figure 3). Compared to the local reaction at the end of the primary vaccine series (mean = 82±3mm), the mean local reaction increased at B1 (88±3 mm, p=0.13), B2 (94±6, p=0.02), and B3 (93±10 mm, p=0.04) (Figure 4). Average CD8⁺ E75-specific T-cells did not change significantly pre-booster (1.1±0.1%) compared to post-booster 1 (1.1±0.1%, p=0.71) or post-booster 2 (1.4±0.2%, p=0.27) but did increase significantly post-booster 3 (2.4±0.3%, p<0.01) (Figure 5). Additionally, the percentage of HLA-A2+ patients with significant residual immunity (defined as >0.5% CD8+E75-specific T cells) increased from pre-booster (29/43, 67%) to post-B3 (16/16, 100%; p=0.01) (Figure 6). With 24 month clinical follow-up complete in all enrolled patients, there has been a nonsignificant decrease in recurrences observed in the vaccine group compared to the control group (5.6 % vs 13.1%, p=0.08), with no recurrences in patients who had received at least one booster inoculation by 24 months (0/40, 0%, vs 13.1% in CG, p=0.03) (Figure 7).

Discussion:

The HER2/*neu* E75 peptide vaccine stimulates immunity that is maintained or increased with booster inoculations in disease-free breast cancer patients. The booster inoculations are safe, with minimal toxicity. The clinical efficacy of the E75 vaccine with booster inoculations will be further evaluated in a phase III trial.

Figure 1

E75 HER2/*neu* Peptide Vaccine

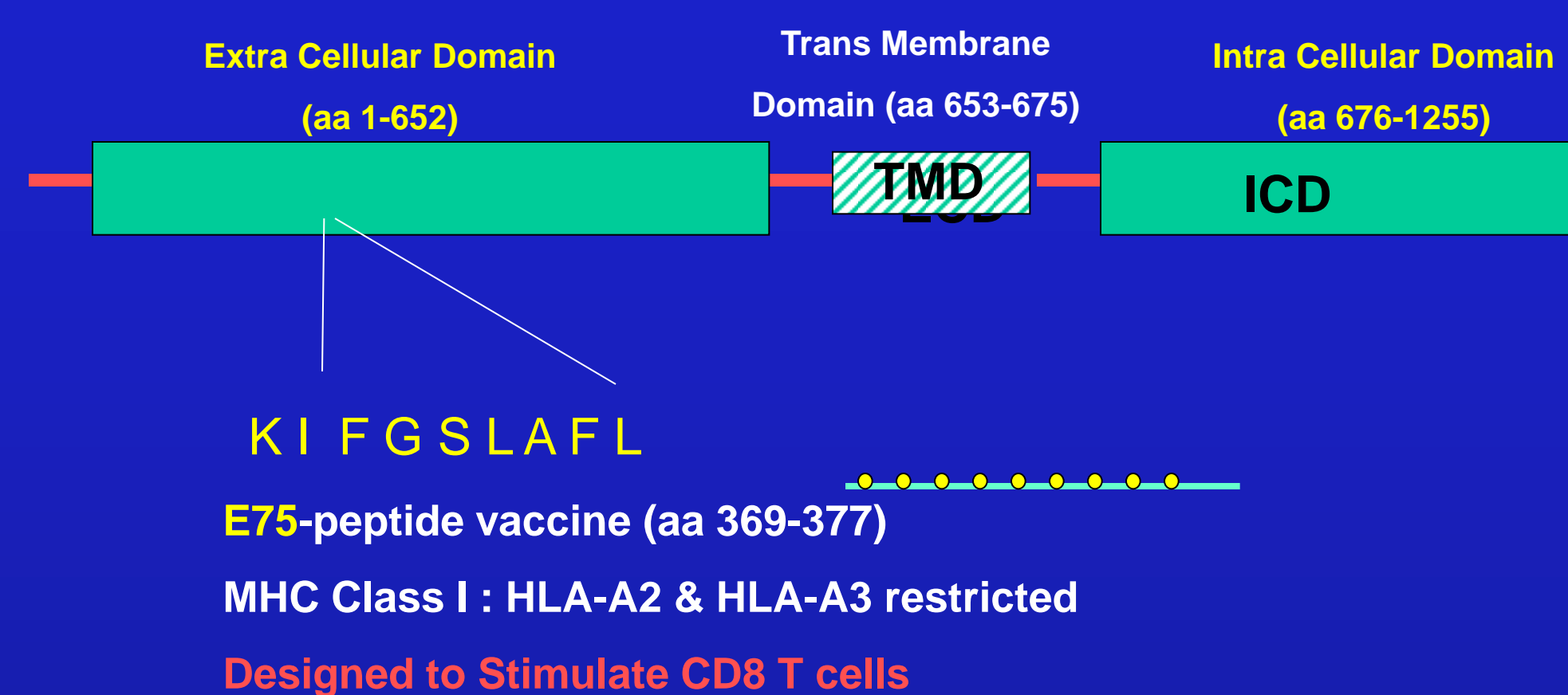
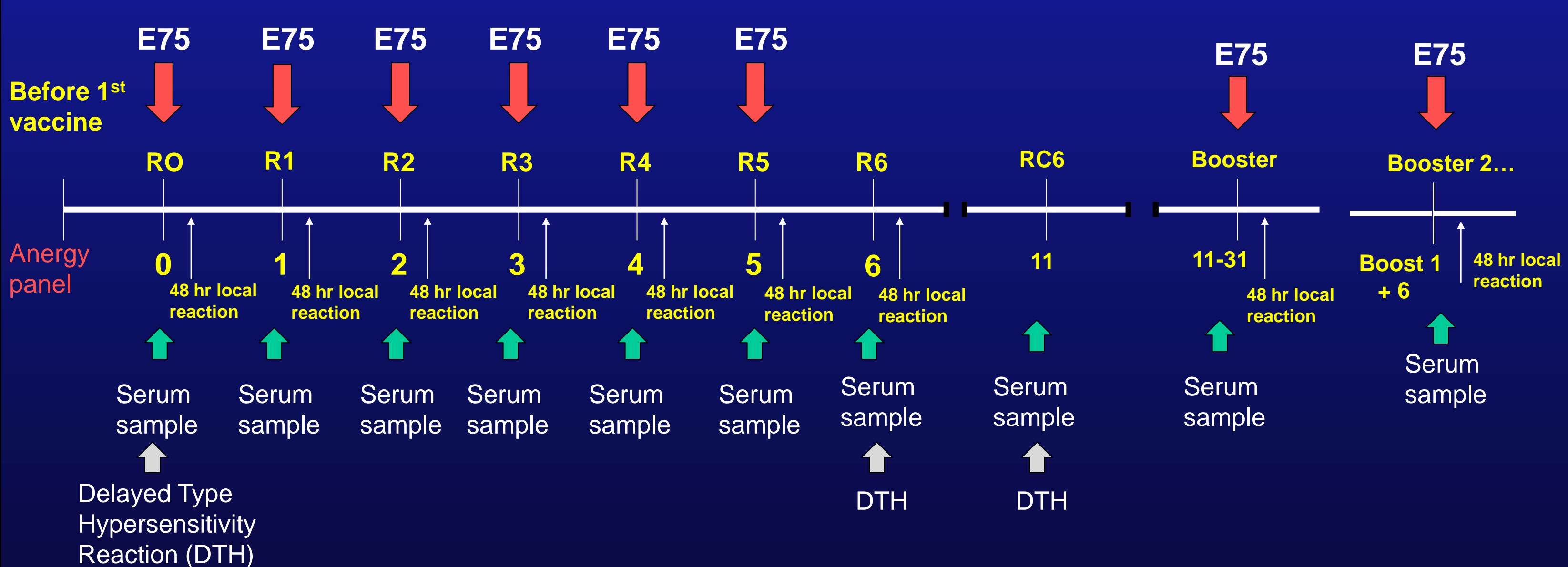


Figure 2

Vaccination Timeline



MONTHS (#)

Figure 3

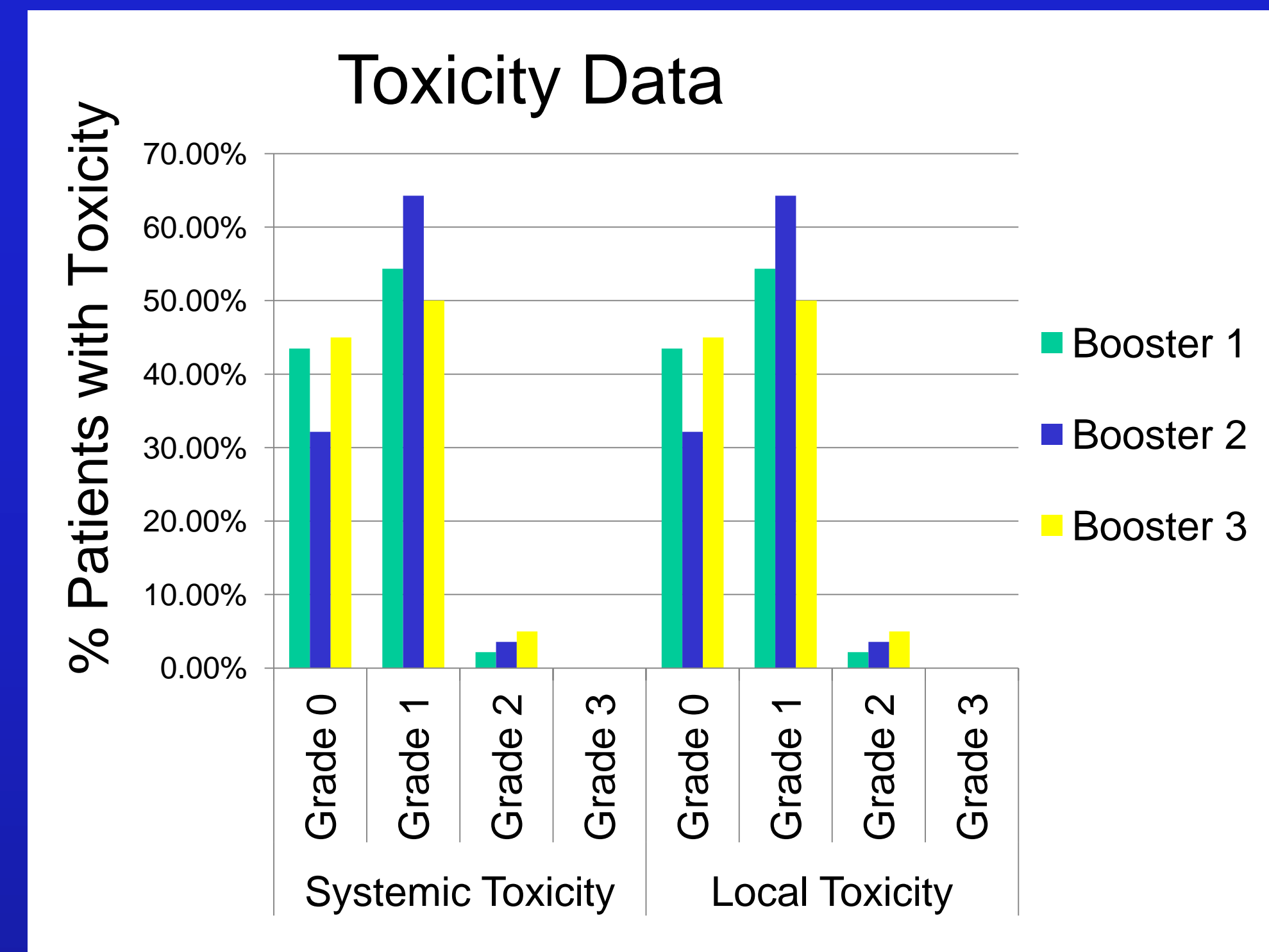
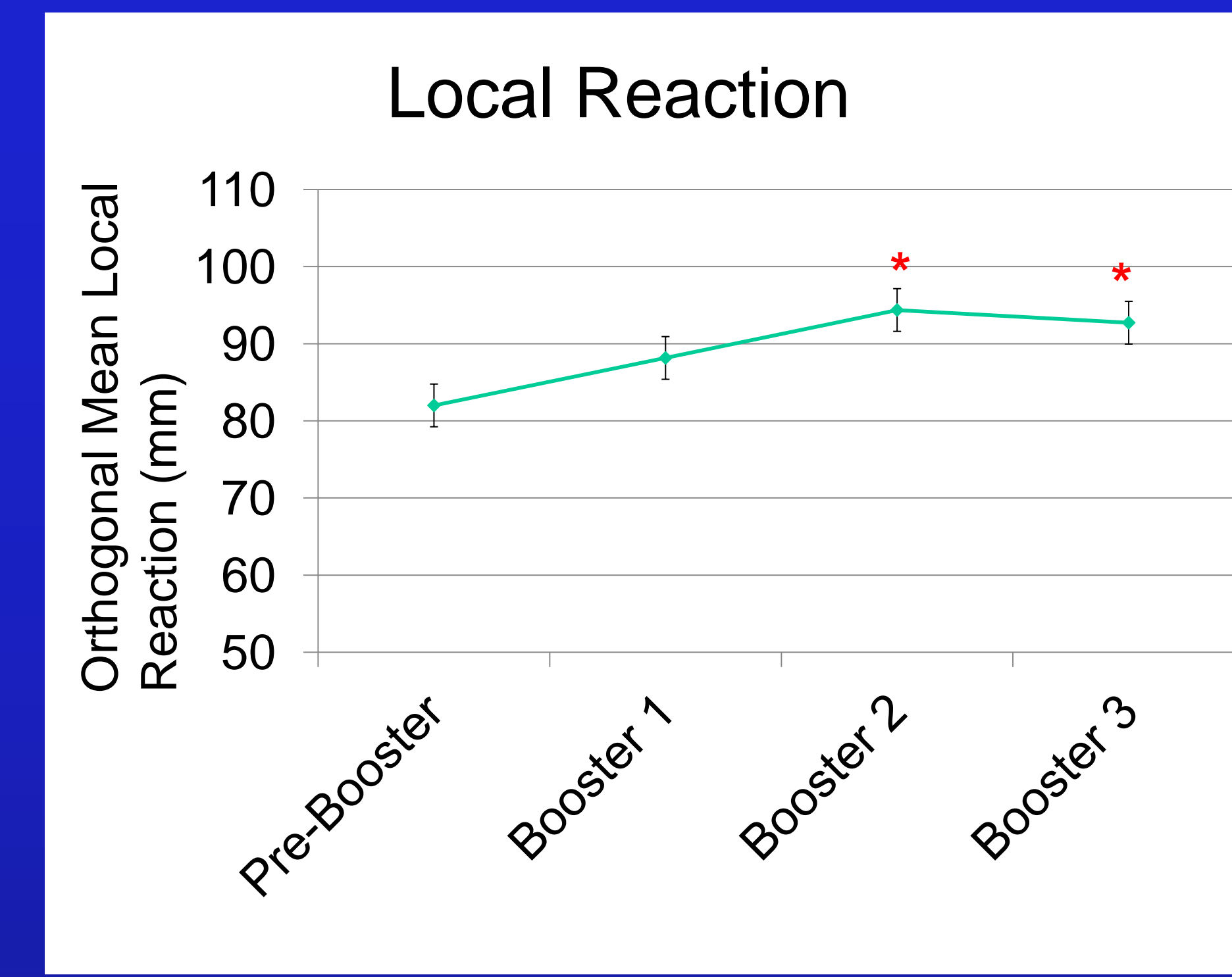
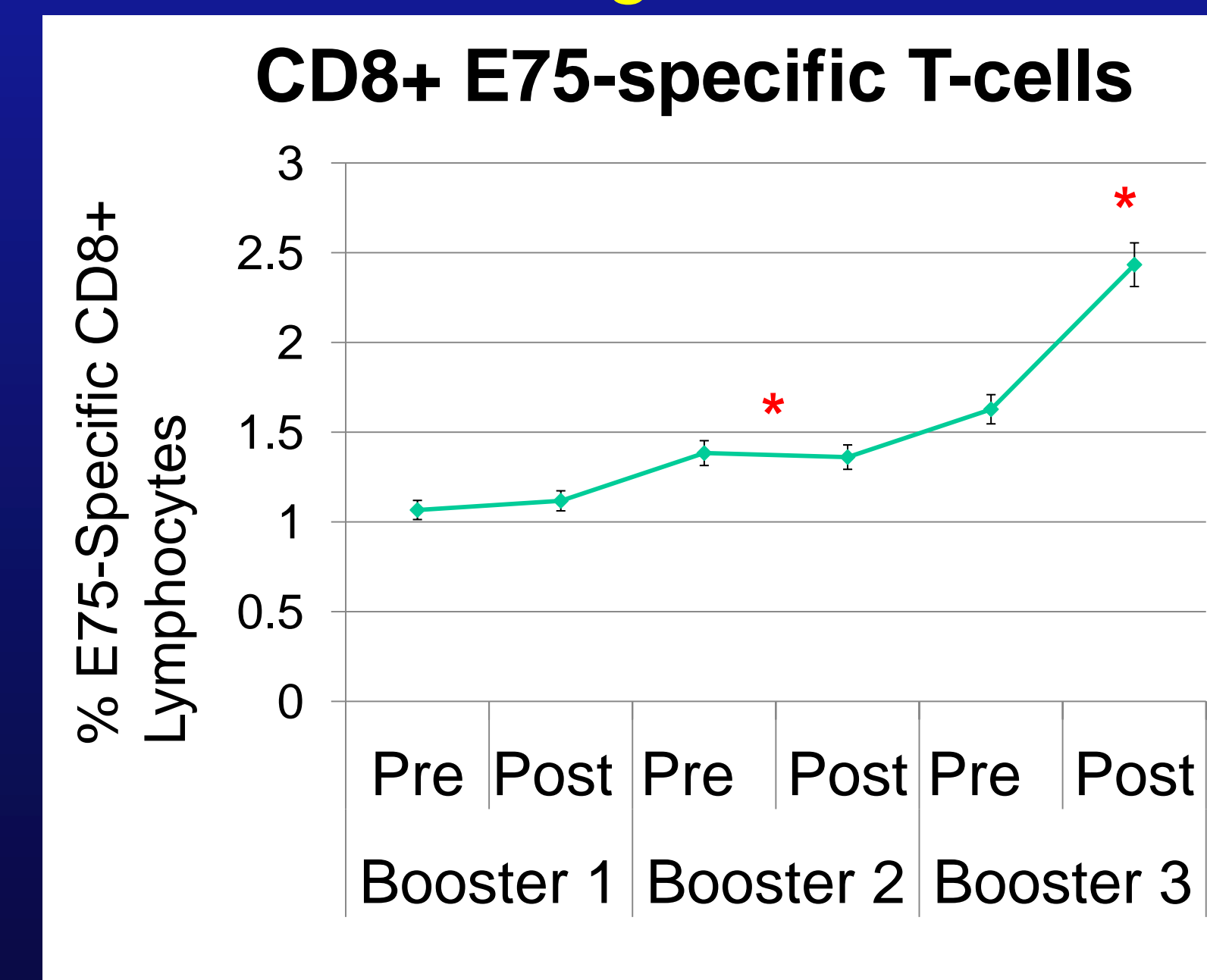


Figure 4



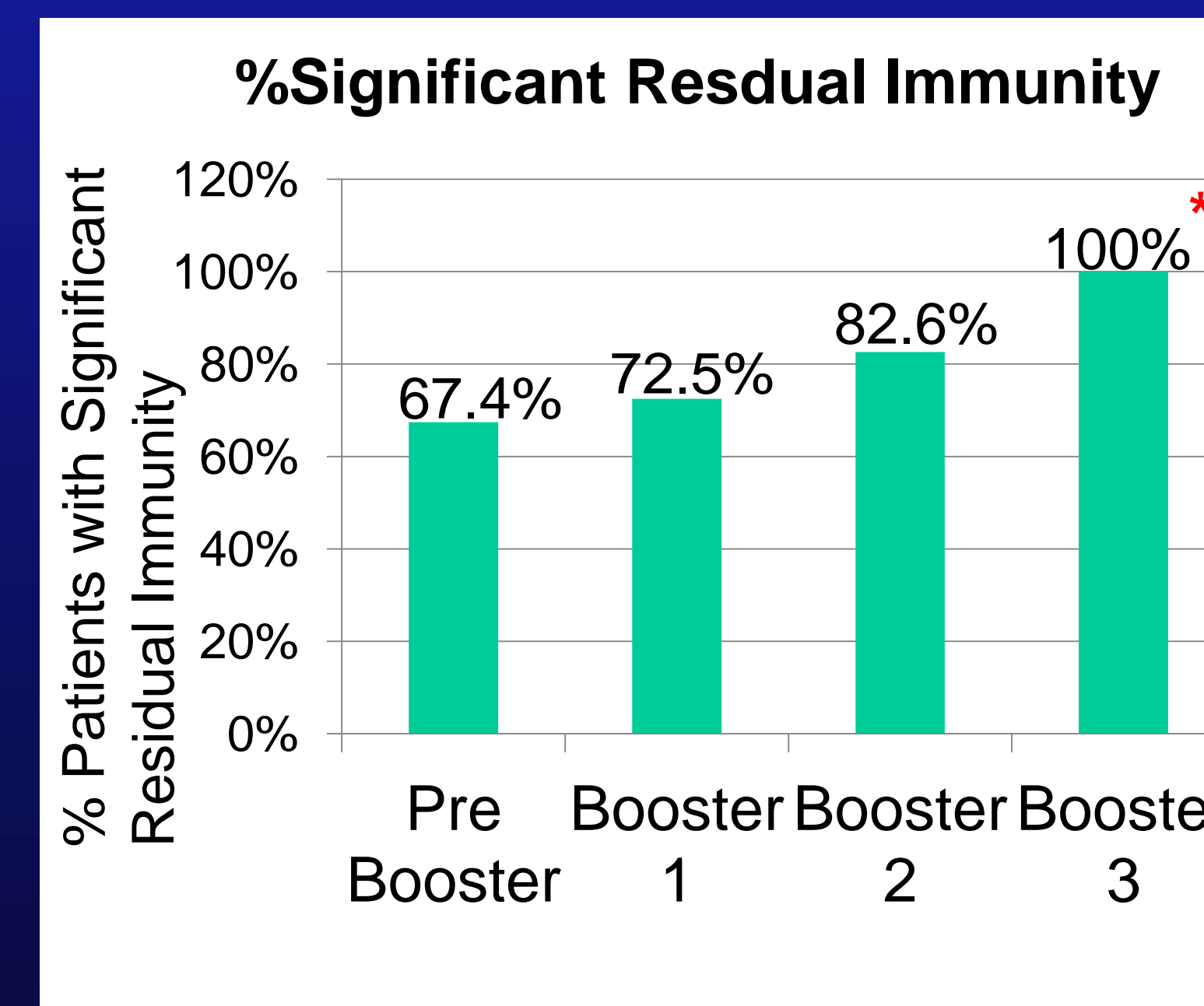
* = p<0.05 Compared to pre-booster

Figure 5



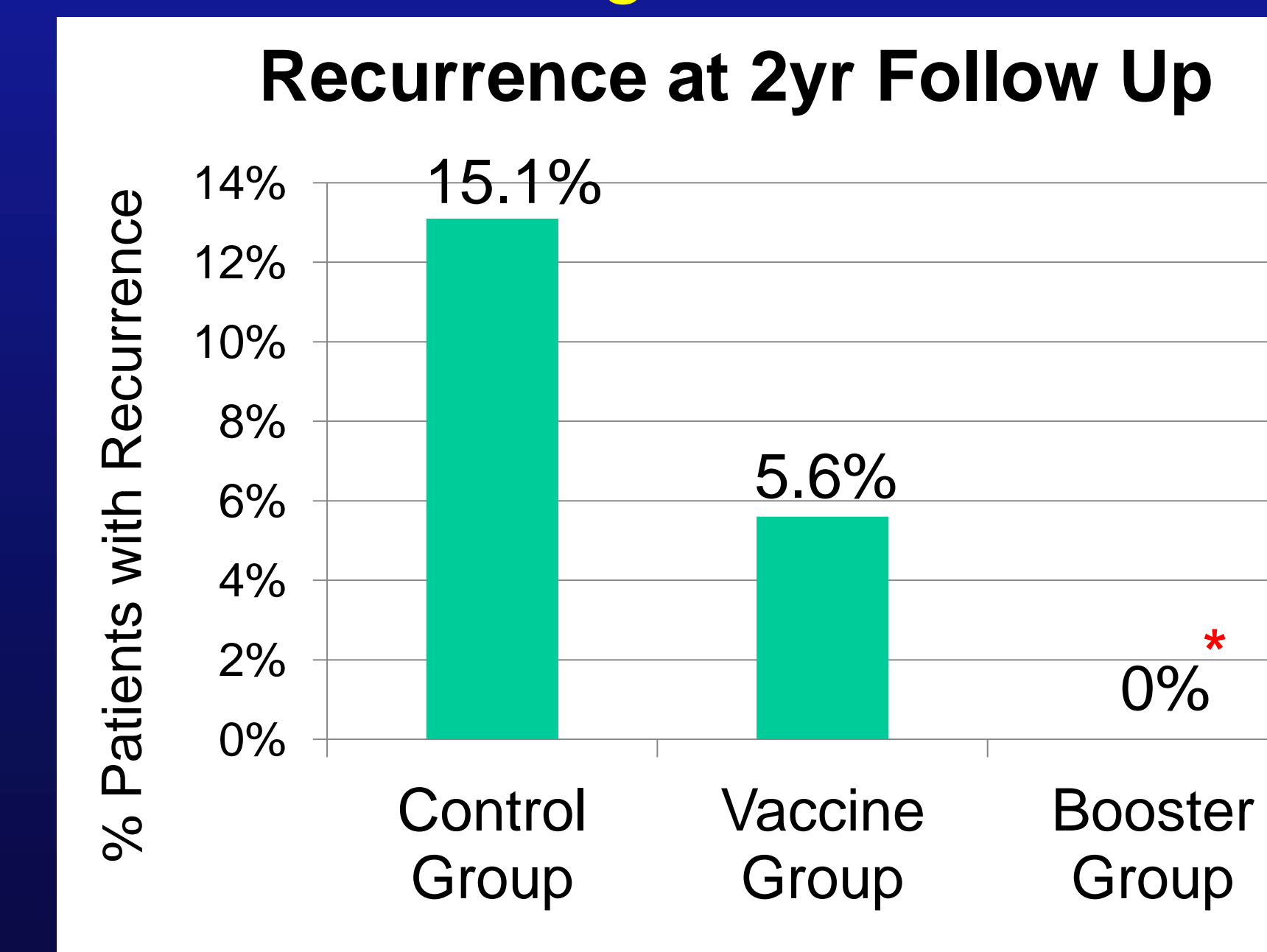
* = p<0.05 compared to pre-booster (end of PVS)

Figure 6



* = p<0.05 compared to Pre-booster

Figure 7



* = p<0.05 compared to Control Group

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