

Sequential Administration of Trastuzumab and a CD8⁺ T cell-eliciting HER-2/*neu* Peptide Vaccine in Breast Cancer Patients Compared to Trastuzumab Alone



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BACKGROUND

We are conducting multiple, prospective, phase II trials evaluating various HER-2/*neu* (HER2) derived peptide vaccines in the adjuvant setting to prevent breast cancer recurrence.

E75 (HER2: 369-377) and Vaccine X are HLA-restricted peptides (E75: HLA-A2/A3⁺, Vaccine X: HLA-A2⁺) capable of stimulating CD8⁺ T cells with anti-HER2 tumor activity. Trastuzumab (Tz), a recombinant monoclonal anti-HER2 antibody, has been shown to reduce breast cancer recurrence by 50%. We examined the sequential use of Tz and a CD8⁺ T cell-eliciting vaccine to compare the efficacy of sequential passive and active immunotherapy to passive immunotherapy alone.

METHODS

We examined patients from our E75 and Vaccine X clinical trials. In these trials, node positive (NP) or high-risk node negative (NN) breast cancer patients with any level of HER2 expression (IHC 1+, 2+, or 3+), rendered disease-free after completion of standard adjuvant therapy were enrolled.

In the E75 trial, HLA-A2⁺ or HLA-A3⁺ patients were vaccinated with E75 + GM-CSF (immunoadjuvant) while HLA-A2/A3⁻ patients served as controls (no intervention). In the Vaccine X trial, HLA-A2⁺ patients were randomized to receive either Vaccine X + GM-CSF or GM-CSF alone.

Vaccinated patients received four to six monthly intradermal inoculations.

From these trials, patients who received adjuvant Tz followed by vaccination with either of the two CD8⁺ T cell-eliciting vaccines were compared to those who received Tz without vaccination (or GM-CSF alone). Demographics, clinicopathologic features and recurrence rates were compared. p-values were calculated using the Wilcoxon, χ^2 , or Fisher's exact tests as appropriate.

DISCLOSURE

Dr. Peoples and Dr. Ponniah have partial inventor rights to Vaccine X and Dr. Peoples has inventor rights to E75. These vaccines have been licensed for commercial development based on clinical trial results. They are entitled to financial proceeds associated with this license per Federal policy. Dr. Peoples also consults in the development of the vaccines.

All other authors have no relevant financial disclosures

RESULTS

A total of 283 patients have enrolled in the two trials (E75=187, Vaccine X=96).

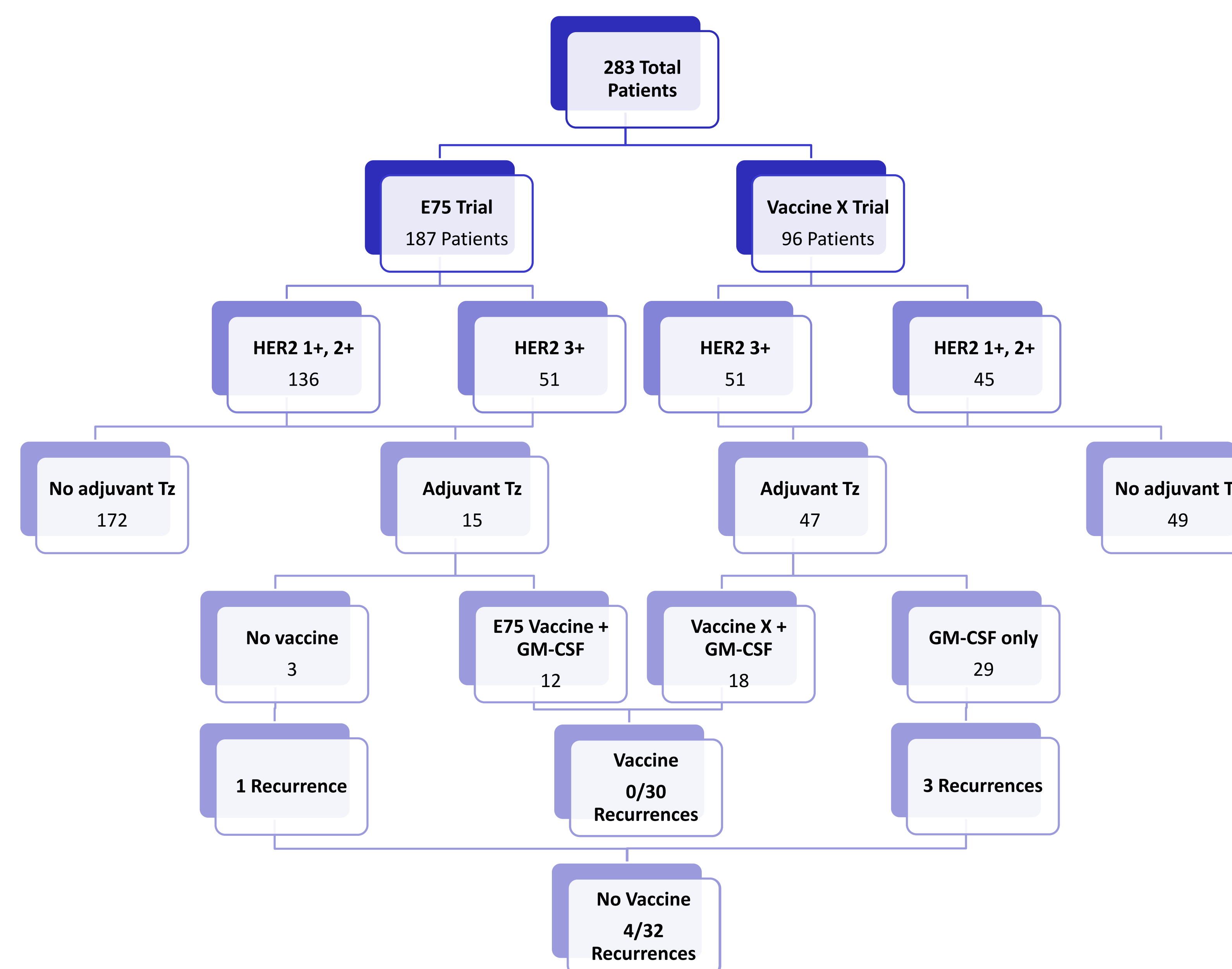
In the E75 trial, 108 patients were vaccinated with E75 + GM-CSF; 79 patients were in the control arm. Of the 187 total patients, 15 (8%) received adjuvant Tz therapy (the E75 trial was primarily conducted prior to the widespread acceptance of Tz as standard of care adjuvant therapy for HER2-overexpressing breast cancer).

In the Vaccine X trial, 41 patients were vaccinated with Vaccine X + GM-CSF while 55 patients were given GM-CSF alone (control arm). Of these 96 patients, 47 (49%) received adjuvant Tz therapy.

Clinicopathological features of the 62 patients who received adjuvant Tz between the two trials are shown below. Overall median length of follow-up is 48 months (E75=57 months, Vaccine X=19 months).

Of the patients who received adjuvant Tz treatment, 32 received no vaccine, and their recurrence rate is 12.5% (4/32)—comparable with reported rates of similarly staged and treated patients. In contrast, 30 patients received either E75 + GM-CSF (12) or Vaccine X + GM-CSF (18) after completing adjuvant Tz, with a recurrence rate of 0% (0/30) ($p=0.064$).

	All Tz-treated patients (n=62)	Tz + Vaccine (n=30)	Tz + Control (n=32)	p-value (Vaccine vs. Control)
Median Age (yrs)	50	50	49	0.85
Grade 3 tumor	72%	76%	69%	0.58
Tumor > 2 cm	52%	50%	53%	1
Node Positive	66%	60%	72%	0.42
ER and PR negative	53%	53%	53%	1
HER2 overexpression	87%	97%	78%	0.05



DISCUSSION

The NSABP B31 trial evaluated the addition of one year of Tz to chemotherapy in largely NP breast cancer patients. In this trial, 94% of enrolled patients were NP with NN patients enrolled if they had tumors > 2cm (if either ER or PR positive) or tumors >1 cm (if negative for both ER and PR). 60% had tumors >2 cm and 69% had grade 3 tumors. With a median follow-up of 2 years, they reported recurrence rates of 13% at 3 years and 15% at 4 years in Tz-treated patients.¹

The HERA trial also evaluated one year of adjuvant Tz therapy in breast cancer patients.^{2,3} NP (68%) or NN (if tumor >1 cm) breast cancer patients were enrolled. 50% had tumors >2 cm (although 10% received neoadjuvant chemotherapy) and 60% had grade 3 tumors. With a median follow-up of 1 year, they have reported a two year recurrence rate of 14%² and with 2 years median follow-up, a three year recurrence rate of 19%³ in the Tz-treated cohort.

Here we report a recurrence rate of 13% at 48 months median follow-up in our patients treated with Tz without subsequent HER2 vaccination. This recurrence rate is similar to those reported in the NSABP B31 and HERA trials with the patients enrolled in our trials having similar clinicopathologic features.

However, the addition of either CD8⁺ T cell-eliciting vaccine (E75 or Vaccine X) appears to confer further benefit above that of Tz, with no breast cancer recurrences seen with 4 years of follow-up in the 30 patients treated with the sequential administration of Tz and a CD8⁺ T cell-eliciting HER2 peptide vaccine.

CONCLUSIONS

Breast cancer patients enrolled in our phase II trials of the E75 or Vaccine X peptide vaccines who received adjuvant Tz followed by vaccination with a CD8⁺ T cell-eliciting vaccine appear to have a lower recurrence rate than adjuvant Tz therapy alone. This finding suggests that the combination of passive and active HER2 immunization may have better efficacy than passive immunotherapy alone and has prompted the initiation of combination immunotherapy clinical trials.

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