Combination immunotherapy with trastuzumab and the HER2 vaccine E75 in low and intermediate HER2-expressing breast cancer patients to prevent recurrence

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Background

We have conducted phase II trials of the HER2-derived E75 peptide vaccine in breast cancer patients in the adjuvant setting. E75 (HER2: 369-377) is an immunogenic HLA-A2/A3-restricted peptide from the extracellular domain of the HER2 protein which stimulates $CD8^+$ cytotoxic T-cells. When combined with the immunoadjuvant GM-CSF as a vaccine, E75 may reduce breast cancer recurrences. A recent 24 month landmark analysis of this phase II trial has demonstrated a recurrence rate of 6.7% in E75-vaccinated patients compared to a recurrence rate of 13.2% in control patients (p=0.08).[1] With the initiation of booster inoculations, this benefit appears to be durable with a persistent 35% relative risk reduction in breast cancer recurrences in vaccinated patients at a median follow-up of 57 months. The E75 vaccine is moving forward to a large, randomized, multi-center phase III clinical trial.

Use of the HER2 monoclonal antibody trastuzumab in the adjuvant setting has been shown to reduce breast cancer recurrence by 50% in HER2-overexpressing breast cancer.[2,3,4] However, more recent analysis has suggested that intermediate HER2-expressing tumors may also derive benefit from adjuvant trastuzumab. An exploratory analysis of the NSABP trial B-31 showed that 174 patients who were subsequently found to be HER2 negative (negative on FISH and less than IHC 3+) may have derived benefit from adjuvant trastuzumab therapy with a hazard ratio for disease recurrence of 0.34 (95% CI, 0.14 to 0.80; p=0.014).[5]

Our earlier work has shown that E75-vaccinated patients with low or intermediate (IHC 1+ or 2+) HER2 expression had larger maximum immunological responses to vaccination (p=0.04) and increased long-term immunity (p=0.08) than HER2 overexpressors.[6] More recently, in a subset analysis of the E75 phase II trial, patients with low or intermediate HER2 expression (IHC 1+ or 2+) were among those found to have greater benefit from vaccination. E75-vaccinated patients with low or intermediate HER2 expression experienced a 58% reduction in recurrence risk (p=0.06) compared to control patients while E75-vaccinated patients with HER2 overexpression (IHC 3+) experienced a 20% reduction in recurrence risk.[7]

Preclinical and early clinical trials have evaluated the combination of trastuzumab and the E75 vaccine. Peripheral blood mononuclear cells from E75-vaccinated patients have higher cytotoxicity against HER2-expressing tumor cells pretreated with trastuzumab than untreated tumor cells, suggesting a synergism may exist with the combination of trastuzumab and the E75 vaccine.[8] The safety of combinational therapy has been evaluated, with no additive cardiotoxicity demonstrated with use of trastuzumab in combination with HER2-derived peptide vaccines.[9,10]

Finally, we have investigated sequential therapy with trastuzumab followed by HER2 vaccination in the adjuvant setting in our ongoing phase II trials. Of 62 patients who received standard-of-care trastuzumab, the 32 who received no vaccine have experienced a 12.5% breast cancer recurrence rate (4/32)—comparable with reported rates of similarly staged and treated patients. In contrast, of the 30 patients who were vaccinated with a $CD8^+$ T-cell eliciting vaccine after completing trastuzumab therapy, the recurrence rate is 0% (0/30) (p=0.065).[11] The median follow-up for this cohort is 48 months.

The emerging evidence suggesting that patients with low-expressing HER2 breast cancer respond to trastuzumab or HER2 vaccination combined with the encouraging results suggesting synergism in combination therapy are intriguing and are worthy of further investigation. Therefore, we believe that HER2 1+ and 2+ breast cancer patients, who have already shown a response to vaccination and possibly to trastuzumab alone, could potentially show a dramatic response to the combination of trastuzumab and E75 with the immunoadjuvant GM-CSF and that the combination can be delivered safely.

Trial Design

Hypothesis: We hypothesize that breast cancer patients with HER2 low- and intermediate-expressing tumors treated with the combination of trastuzumab and the E75 vaccine will have a lower recurrence rate than those treated with trastuzumab alone.

Study Design: This study will be a multi-center, prospective, randomized, single-blinded phase II trial evaluating trastuzumab + E75 + GM-CSF vs. trastuzumab + GM-CSF alone (no E75) in the adjuvant setting in breast cancer patients.

Endpoints: Our primary endpoint will be to compare disease-free survival at 24 months between the treatment arms. Secondary endpoints include disease-free survival at 36 months, immunologic responses to vaccination, and safety of combination therapy to include cardiac toxicity.

Enrollment: HLA-A2/A3$^+$ node positive (or node negative if also negative for both ER and PR) breast cancer patients with HER2 1+ or 2+ expressing tumors who are disease-free after completing standard adjuvant therapies will be enrolled and randomized to receive either trastuzumab + E75 + GM-CSF (vaccine) or trastuzumab + GM-CSF alone (control). Patients must have adequate cardiac function for enrollment (LVEF >50%). Randomization will be further stratified based on HER2 status (1+ or 2+) and nodal status (N0, N1, N2, or N3). Informed consent will be obtained from all enrolled patients.

Treatment: Trastuzumab will be given to all enrolled patients every three weeks as monotherapy for one year, initiated upon completion of standard-of-care chemotherapy/radiotherapy. Patients randomized to receive E75 will be given vaccinations of E75 (1000 mcg) and GM-CSF (250 mcg) intradermally every 3 weeks for a total of 6 vaccinations, 30-120 minutes after completion of trastuzumab infusion. The first vaccination will be administered upon completion of the third trastuzumab infusion. Patients randomized to GM-CSF alone will be administered vaccinations of GM-CSF (250 mcg) in an identical manner. Patients will be blinded as to whether they are receiving E75+GM-CSF or GM-CSF alone.

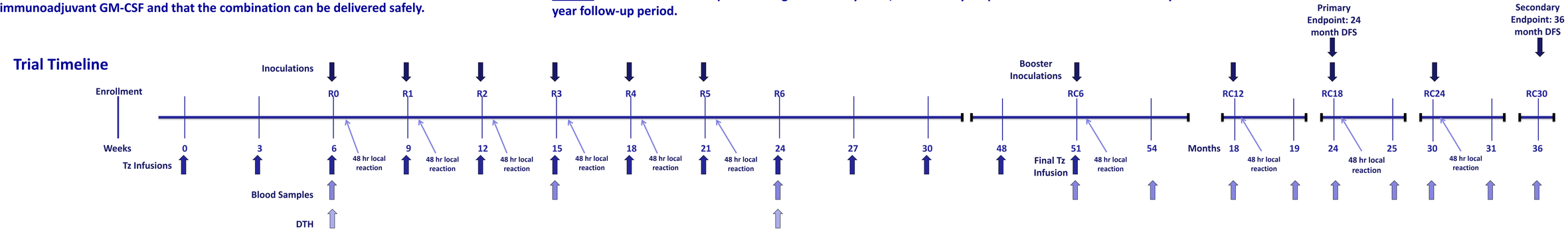
Boosters: Upon completion of the vaccination series, booster inoculations (same dose and route) will be administered every six months for a total of four boosters. Total combination (trastuzumab and vaccine) treatment duration will be 30 months. The first booster inoculation will occur with the final trastuzumab infusion, with subsequent boosters timed every six months from the first booster. Booster inoculations will occur for patients randomized to receive E75+GM-CSF as well as patients randomized to receive GM-CSF alone, and will consist of the same treatment drugs and dosing (i.e. E75+GM-CSF patients will be boosted with E75+GM-CSF while GM-CSF alone patients will be boosted with GM-CSF alone). Patient blinding will be maintained throughout the study.

Monitoring:

- *Safety*: all patients will be monitored 48-72 hours after each inoculation for reaction to the inoculation as well as documentation of any adverse effects experienced.
- *Cardiac*: All patients will undergo a cardiac assessment at baseline (MUGA preferred, ECHO allowed, consistency required) and every three months during trastuzumab therapy followed by every six months for a total of two years. Cardiac assessment will continue every six months if a patient experiences a greater than 10% reduction from baseline for the duration of the trial.
- *Immunologic*: Immunologic response will be documented with both in vitro phenotypic and functional assays as well as in vivo delayed type hypersensitivity (DTH) reactions. DTH responses will be tested prior to receiving the first inoculation and three weeks after the final inoculation of the primary vaccine series in all enrolled patients. In vitro immunologic assays, including the dimer and ELISPOT assays, will be tested prior to vaccination and a specified intervals (see timeline) in all patients.
- *Recurrence*: All patients will be followed for a total of 36 months to document disease-free status.

Power: From previously published experience with trastuzumab, we expect a recurrence rate of 15% in trastuzumab (plus GM-CSF) treated patients and anticipate that the combination of trastuzumab with E75+GM-CSF will reduce this recurrence rate to 5%. In order to show a statistical difference between these recurrence rates, we plan to enroll 150 patients per treatment arm (300 total) with a type I error rate of 5% and 80% power to detect the primary endpoint.

Accrual: Trial accrual is anticipated to begin in January 2012, with a two year period of enrollment followed by a three year follow-up period.



Conclusion

We hypothesize that combination adjuvant immunotherapy with trastuzumab and E75 vaccination will result in a greater reduction in breast cancer recurrence than trastuzumab therapy alone and have designed a multi-center, prospective, randomized, single-blinded, phase II trial evaluating the efficacy of this immunotherapy combination.

Contact Information: This trial is sponsored by Genentech and Galena Biopharma through the Henry M. Jackson Foundation.

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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