Immunologic Responses in Triple Negative Breast Cancer Patients in a Randomized Phase 2b Trial of Nelipepimut-S Plus Trastuzumab Versus Trastuzumab Alone to Prevent Recurrence

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INTRODUCTION

Breast cancer patients expressing low levels of HER2 defined by immunohistochemistry of 1-2+ are not eligible for trastuzumab. However, in a randomized phase 2b trial, triple negative breast cancer (TNBC) patients demonstrated a significantly better disease free survival with nelipepimut-S and trastuzumab versus trastuzumab alone. Here, we assess the ex vivo and in vivo immune responses in both arms.

METHODS

Disease-free patients (n = 275) with HER2 immunohistochemistry of 1-2+, non-amplified breast cancer who had TNBC were randomized 1:1 to granulocyte-macrophage-colony stimulating factor (GM-CSF) or nelipepimut-S + GM-CSF. The primary vaccine series (PVS) of Nelipepimut-S was administered every three weeks for a total of six doses. The PVS was followed by four boosters every six months. All patients received trastuzumab concurrently for one year per label regimen and were followed for recurrence. Immune response was evaluated ex vivo by clonal expansion of nelipepimut-S-specific cytotoxic T lymphocytes (E75+ T cells) by dextramer-staining/flow cytometry at time points over three years. Control and vaccine means were compared using an independent t-test. In vivo immune responses were assessed by delayed type hypersensitivity (DTH) reactions which were compared between arms using the Kruskal-Wallis test.

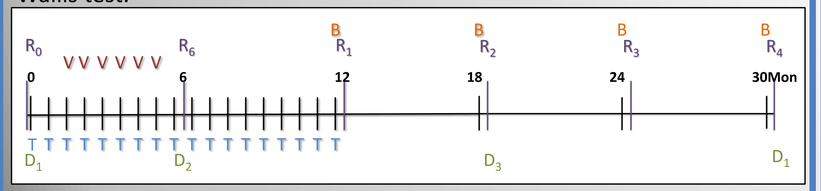

Figure 1.
Timeline of the trial detailing drug administration and time measurements of data collection where T is trastuzumab given at an initial loading dose of 8 mg/kg and then maintenance doses of 6 mg/kg every three weeks, for a total of one year. V is the primary vaccine series given concurrently with the third trastuzumab infusion and continued, along with trastuzumab, every three weeks for a total of six inoculations. Control subjects received only GM-CSF. B are the booster inoculations given once every six months for four total doses with the first booster inoculation administered with the final trastuzumab infusion. R denotes the measurement of T cells. D denotes the measurement of the DTH reactions.

RESULTS

The trial enrolled 97 TNBC patients; 91 had five time points available for analysis (51 nelipepimut-S+trastuzumab patients; 40 trastuzumab patients). Overall, there was a progressive increase in E75+ T cells in the vaccine group as compared to the control group (p=0.058 at R3). Only 3 nelipepimut-S+trastuzumab patients recurred as compared to 12 in the trastuzumab arm. While limited by low numbers, recurrent nelipepimut-S+trastuzumab patient did not mount an immune response by ex vivo assessment, while non-recurrent patients mounted clonal cytotoxic T lymphocyte expansion.

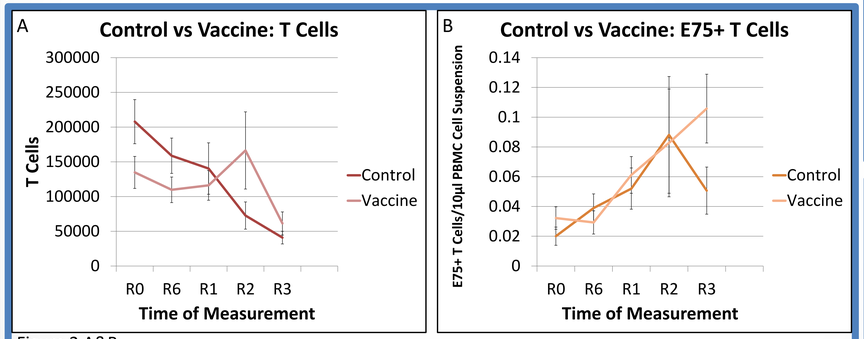

Figure 2 A&B.
Measurement of all T cells and E75+ T cells prior to vaccine inoculation (R0), 6 months following trial initiation (R6) and following each booster dosage (R1, R2 and R3).

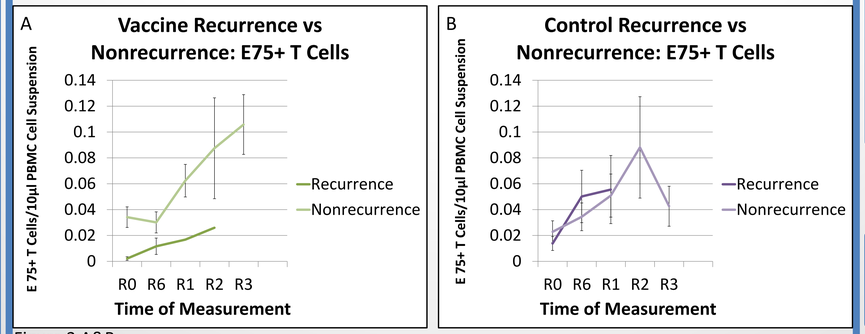

Figure 3 A&B.
Comparison of E75+T cells in subjects who experienced recurrence to those that did not in both the control and vaccine cohorts.

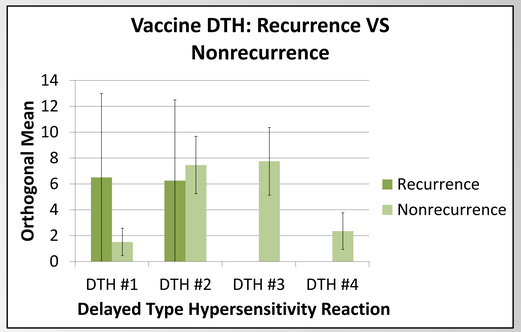

Figure 4.
Delayed type hypersensitivity (DTH) reaction was measured prior to initiating the primary vaccine series (DTH #1), and one month after completion of the primary vaccine series (DTH #2), after the second booster inoculation (DTH #3), and after the fourth (final) booster inoculation (DTH #4).

CONCLUSION

In TNBC patients, trastuzumab alone caused an increase in E75 specific T cells (expected based on cross-presentation), the addition of nelipepimut-S, produced a doubling of E75 specific T cell expansion. Among vaccinated patients, non-recurrent patients experienced an apparent expansion of E75 specific T cells compared to the recurrent patients. Also, the recurrent patients started with substantially fewer E75 specific T cells compared to the non-recurrent patients. In contrast, among the control patients, the recurrent patients demonstrated more E75 specific T cells than the non-recurrent suggesting an augmentation of trastuzumab induced E75 specific T cells in the presence of recurrent tumor. Μμμ

ABSTRACT:

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