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# Final five year median follow-up safety data from a prospective, randomized, placebo-controlled, single-blinded, multicenter, phase IIb study evaluating the use of HER2/neu peptide GP2 + GM-CSF vs. GM-CSF alone after adjuvant trastuzumab in HER2 positive women with operable breast cancer

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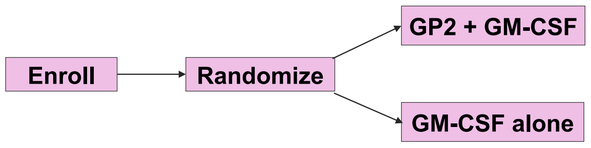
## BACKGROUND

The final safety analysis of the GP2 prospective, randomized, placebo-controlled, single-blinded, multicenter Phase IIb trial investigating GP2+GM-CSF administered in the adjuvant setting to node-positive and high-risk node-negative breast cancer patients with tumors expressing any degree of HER2 (immuno-histochemistry [IHC] 1-3+) (NCT00524277) is now complete with 5 year follow-up. The trial enrolled HLA-A02 patients randomized to receive GP2+GM-CSF versus GM-CSF alone. It was previously reported that completion of the GP2+GM-CSF Primary Immunization Series (PIS) reduced recurrence rates to 0% over a 5 year follow-up period in HER2 3+ patients, who received a standard course of trastuzumab after surgery. Interim analyses for this trial have been previously reported by Mittendorf et al.

## METHODS

Each enrolled and consented patient was randomly scheduled to receive a total of 6 GP2+GM-CSF (500 mcg GP2: 125 mcg GM-CSF) or GM-CSF only intradermal injections every 3-4 weeks as part of the PIS for the first 6 months and 4 GP2+GM-CSF or GM-CSF only booster intradermal injections every 6 months thereafter. Boosters were introduced during the trial, thus some patients did not receive all 4 boosters. Injection sight reactions were measured.




**Primary Objective**

- Determine if GP2+GM-CSF treatment reduces recurrence rates vs. GM-CSF alone

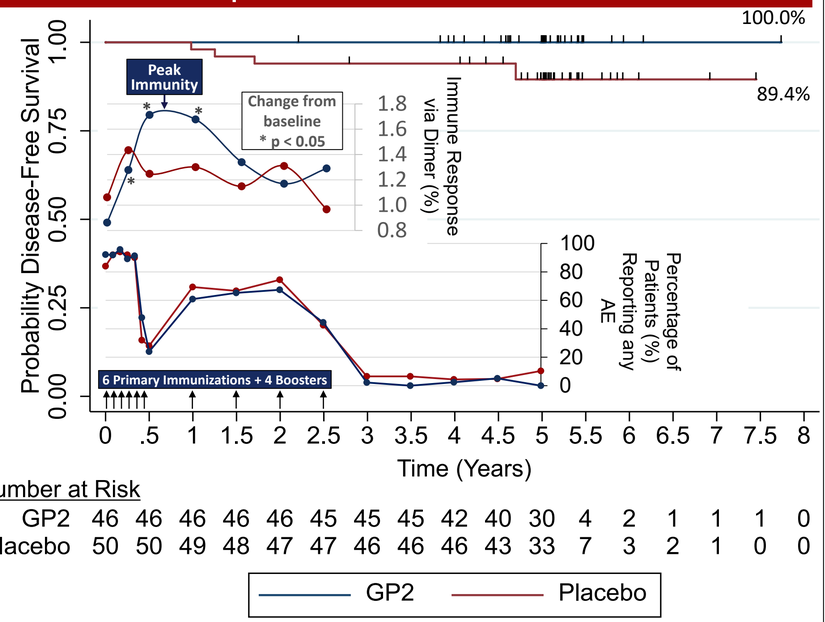
**Secondary Objective**

- Monitor immune response and correlate with clinical outcomes
- Monitor for any unexpected toxicities

## RESULTS

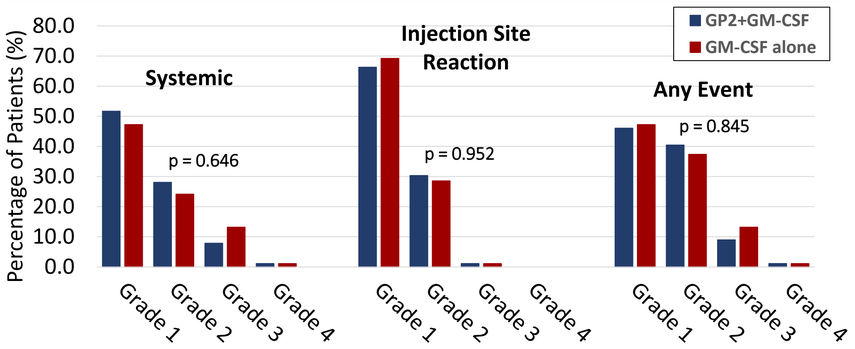
Safety data was analyzed to assess injection site reactions and systemic adverse events (AEs) of each treatment arm. Most patients completed the planned PIS: 81 (91.0%) GP2+GM-CSF and 86 (94.5%) GM-CSF only. In addition, 77 GP2+GM-CSF and 80 GM-CSF only patients received all 4 booster injections. The most common injection site reactions were erythema, induration and pruritis, and they occurred with similar frequency in the two treatment arms. Injection site reactions were reported by almost all patients over the course of vaccinations. Occurring in a smaller percentage of patients, the most common systemic AEs were fatigue, headache, and myalgia/arthralgia, again with similar incidence by treatment arm. The majority of all events reported were of grade 1, mild severity. Five GP2+GM-CSF patients reported 6 events considered definitely, possibly or probably related to study medication, which were grade 3 or 4: induration (2), urticaria, rash, pruritis, and arthralgia. Urticaria, allergic reaction and hypersensitivity reaction were considered possibly related events of grade 3 or 4 in GM-CSF only patients. No serious adverse events considered related to study medication were reported over the full 5 year treatment and follow-up periods.

### Figure 1: Safety, Immune Response, and Disease-free Survival in HER2 3+ Patients Who Completed PIS




The incidence of AEs in the HER2 3+ population over time are presented in Figure 1. Injection site reactions account for the majority of reported events and therefore are temporally associated with vaccinations. Incidence of AEs for GP2+GM-CSF patients and GM-CSF only patients are quite similar for the duration of follow-up.

### Figure 2: Incidence of Maximum Severity Grade Adverse Events




The maximal severity grade for any AE, systemic and injection site reaction, for each patient was identified. There was no difference between the two treatment arms, as presented in Figure 2. The majority of events were of grade 1, mild severity. Two patients reported grade 4 AEs deemed unrelated to study medication. One GP2+GM-CSF patient experienced grade 4 hypoglycemia and recovered. A GM-CSF only patient was diagnosed with renal cell carcinoma, a second primary diagnosis, which was classified as grade 4.

### Tables 1 & 2: Incidence of Adverse Events

**Table 1: Incidence of First Occurrence of Most Frequent Adverse Events**

| Adverse Event | HER2 3+ GP2 (n = 51) N (%) | HER2 3+ Placebo (n = 50) N (%) | HER2 1-2+ GP2 (n = 38) N (%) | HER2 1-2+ Placebo (n = 41) N (%) | Total GP2 (n = 89) N (%) | Total Placebo (n = 91) N (%) |
|---|---|---|---|---|---|---|
| Injection site reaction | 50 (98.0) | 50 (100) | 37 (97.4) | 40 (97.6) | 87 (97.8) | 90 (98.9) |
| Fatigue | 36 (70.6) | 30 (60.0) | 26 (68.4) | 25 (61.0) | 62 (69.7) | 55 (60.4) |
| Headache | 23 (45.1) | 26 (52.0) | 18 (47.4) | 19 (46.3) | 41 (46.1) | 45 (49.5) |
| Myalgia | 19 (37.3) | 16 (32.0) | 13 (34.2) | 10 (24.4) | 32 (36.0) | 26 (28.6) |
| Bone pain | 12 (23.5) | 17 (34.0) | 12 (31.6) | 10 (24.4) | 24 (27.0) | 27 (29.7) |
| Arthralgia | 18 (35.3) | 19 (38.0) | 5 (13.2) | 7 (17.1) | 23 (25.8) | 26 (28.6) |
| Malaise | 14 (27.5) | 11 (22.0) | 7 (18.4) | 9 (22.0) | 21 (23.6) | 20 (22.0) |
| Chills | 12 (23.5) | 14 (28.0) | 7 (18.4) | 6 (14.6) | 19 (21.3) | 20 (22.0) |
| Back pain | 13 (25.5) | 9 (18.0) | 7 (18.4) | 6 (14.6) | 20 (22.5) | 15 (16.5) |
| Nausea | 9 (17.6) | 15 (30.0) | 5 (13.2) | 6 (14.6) | 14 (15.7) | 21 (23.1) |
| Fever | 12 (23.5) | 13 (26.0) | 5 (13.2) | 4 (9.8) | 17 (19.1) | 17 (18.7) |
| Dizziness | 6 (11.8) | 4 (8.0) | 2 (5.3) | 3 (7.3) | 8 (9.0) | 7 (7.7) |

**Table 2: Incidence of First Occurrence of Injection Site Reactions**

| Adverse Event | HER2 3+ GP2 (n = 51) N (%) | HER2 3+ Placebo (n = 50) N (%) | HER2 1-2+ GP2 (n = 38) N (%) | HER2 1-2+ Placebo (n = 41) N (%) | Total GP2 (n = 89) N (%) | Total Placebo (n = 91) N (%) |
|---|---|---|---|---|---|---|
| Erythema | 50 (98.0) | 50 (100.0) | 37 (97.4) | 39 (95.1) | 87 (97.8) | 89 (97.8) |
| Pruritus | 50 (98.0) | 46 (92.0) | 37 (97.4) | 38 (92.7) | 87 (97.8) | 84 (92.3) |
| Induration | 50 (98.0) | 40 (80.0) | 37 (97.4) | 36 (87.8) | 87 (97.8) | 76 (83.5) |
| Pain | 9 (17.6) | 5 (10.0) | 6 (15.8) | 5 (12.2) | 15 (16.9) | 10 (11.0) |
| Warm | 3 (5.9) | 5 (10.0) | 2 (5.3) | 0 (0.0) | 5 (5.6) | 5 (5.5) |
| Bruising | 1 (2.0) | 4 (8.0) | 2 (5.3) | 0 (0.0) | 3 (3.4) | 4 (4.4) |
| Urticaria | 1 (2.0) | 3 (6.0) | 1 (2.6) | 1 (2.4) | 2 (2.2) | 4 (4.4) |
| Rash | 1 (2.0) | 2 (4.0) | 1 (2.6) | 0 (0.0) | 2 (2.2) | 2 (2.2) |
| Blanching | 2 (3.9) | 1 (2.0) | 0 (0.0) | 0 (0.0) | 2 (2.2) | 1 (1.1) |
| Burning | 1 (2.0) | 1 (2.0) | 0 (0.0) | 0 (0.0) | 1 (1.1) | 1 (1.1) |
| Myalgia | 0 (0.0) | 0 (0.0) | 1 (2.6) | 0 (0.0) | 1 (1.1) | 0 (0.0) |
| Tingling | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.1) | 0 (0.0) |

The first occurrence of frequently reported AEs is tabulated in Table 1. The most common AE was injection site reaction. Almost every patient, in both the GP2+GM-CSF and GM-CSF only arms, reported injection site reactions.

The most frequent injection site reactions were erythema, pruritus and induration, as presented in Table 2. The incidence in AEs was similar across HER2 3+ and HER2 1-2+ patients.

No serious adverse events considered related to study medication were reported.

## CONCLUSIONS

GP2+GM-CSF was safe and well-tolerated in this trial. The majority of patients experienced mild or moderate injection site reactions and other AEs. Importantly, events in the GP2+GM-CSF arm were comparable to those seen in the GM-CSF only arm, suggesting that they are attributable to GM-CSF. No safety signal for GP2 was identified.

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