Final analysis of nelipepimut-S plus GM-CSF with trastuzumab versus GM-CSF with trastuzumab alone to prevent recurrences in high-risk, HER2 low-expressing breast cancer: a prospective, randomized, blinded, multicenter phase 2b trial.

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INTRODUCTION

Preclinical data show synergism between trastuzumab and HER2-targeted vaccines. We evaluated adjuvant nelipepimut-S (NPS) + GM-CSF with trastuzumab compared to trastuzumab with GM-CSF alone in HER2 low-expressing breast cancer patients to prevent recurrences. After a planned interim analysis showed benefit in triple negative breast cancer patients, and NSABP B-47 confirmed trastuzumab did not improve outcomes in HER2-low expressing breast cancer[1], the decision was made to close the trial with guidance from the independent Data Safety Monitoring Board. Here, we report the final analysis of the trial with 7 months of added follow-up.

METHODS

The phase 2b trial enrolled clinically disease-free breast cancer patients after standard therapy. Patients were HLA-A2, A3, A24, and/or A26 positive, had HER2-low expressing (IHC 1-2+, FISH non-amplified) breast cancer and were node positive and/or had triple negative breast cancer (TNBC). Patients were randomized to placebo with GM-CSF (control group) or NPS with GM-CSF (vaccine group), while all received trastuzumab every three weeks for one year. GM-CSF or NPS + GM-CSF was given every three weeks for a total of six doses starting with the third trastuzumab dose, and boosters every six months x 4. Safety was assessed and patients were followed clinically for recurrences. The primary outcome was disease free survival at 24 months. A secondary outcome was disease free survival at 36 months.

RESULTS

589 patients were screened at 26 sites. 275 patients were enrolled and randomized (vaccine group n=136, control group n=139). There were no clinicopathologic differences between groups (Table 1). Concurrent trastuzumab and NPS was safe with no added overall (Figure 1) or cardiac toxicity (Figure 2) compared to control group and no grade 4/5 related adverse events (Figure 2). In the intention to treat analysis (median follow-up 25.7 months), the estimated disease free survival was favorable but did not reach significance in the vaccine group compared to the control group (HR 0.62, 95% CI: 0.31-1.25, p=0.18; Figure 3). In the triple negative breast cancer patients (median follow-up 26.1 months), the vaccine group had statistically improved disease free survival compared to the control group (HR 0.26, 95% CI: 0.08-0.81, p=0.013; Figure 4).

Table 1. Demographics

Characteristics	NeuVax + TZ (N = 136)	TZ (N = 139)	P value
Age, years Median (IQR)	52.2 (43.7-60.8)	50.5 (42.0-59.0)	.38
Race, n (%)			
White	109 (80)	97 (70)	.20
Non-white	25 (18)	38 (27)	
Unknown	2 (2)	4 (3)	
Chemotherapy			
Adjuvant	59 (43)	57 (41)	.90
Neoadjuvant	72 (53)	76 (55)	
None	5 (4)	6 (4)	
Clinical NeoAdj stage, n (%)			
0	0 (0)	1 (1)	.33
I	4 (6)	3 (4)	
II	35 (49)	31 (40)	
III	31 (43)	40 (52)	
IV	1 (1)	0 (0)	
Unknown	1 (1)	2 (3)	
Path NeoAdj stage, n (%)			
0	5 (7)	4 (5)	.76
I	11 (15)	9 (12)	
II	28 (39)	26 (34)	
III	27 (38)	37 (49)	
Unknown	1 (1)	0 (0)	

Characteristics	NeuVax + TZ (N = 136)	TZ (N = 139)	P value
Path (no NeoAdj) stage, n (%)			
I	10 (16)	9 (14)	.99
II	26 (41)	26 (41)	
III	28 (44)	28 (45)	
ER status			
Positive	81 (60)	94 (68)	.16
Negative	55 (40)	45 (32)	
PR status			
Positive	77 (57)	82 (59)	.69
Negative	59 (43)	57 (41)	
Surgery			
Yes	136 (100)	138 (99)	.64
No	0	1 (1)	
Radiotherapy			
Adjuvant	109 (80)	122 (88)	.09
Neoadjuvant	8 (6)	2 (1)	
None	19 (14)	15 (11)	
Hormone therapy			
Yes	73 (54)	83 (60)	.25
No	61 (45)	51 (37)	
Other	2 (1)	5 (4)	

Figure 1. Maximum grade toxicity. There was no significant difference between treatment groups (p = 0.17). No grade 4/5 toxicities were observed.

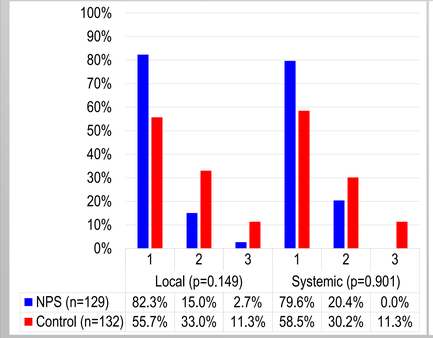


Figure 2. Cardiac Toxicity. No difference between treatment arms in cardiac ejection fraction over time (p = 0.65) and at each time point

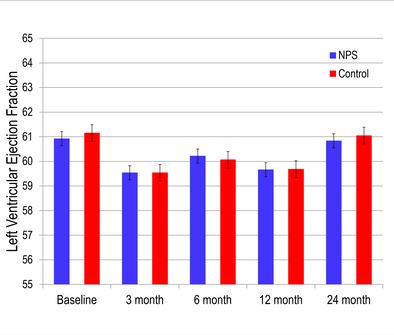


Figure 3. Kaplan-Meier estimated disease free survival for intention to treat population.

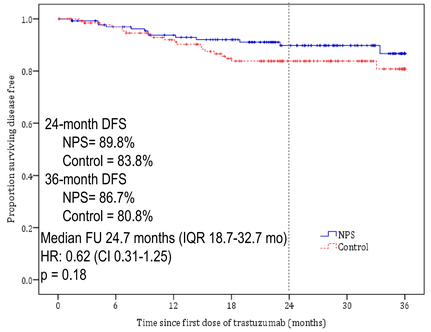
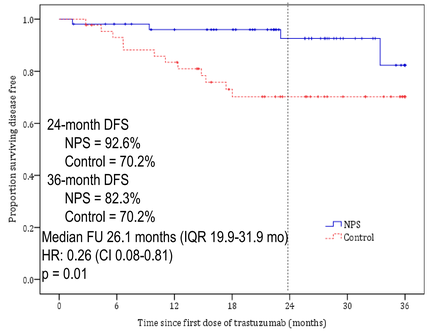


Figure 4. Kaplan-Meier estimated disease free survival for triple negative breast cancer patients.



CONCLUSION

The combination of NPS with trastuzumab is safe with no added toxicity compared to trastuzumab alone, even after prolonged exposure (25.7 months). In this final analysis, there was a trend towards benefit in the intention to treat population that improved since the interim analysis with added follow-up. The significant benefit seen at interim in the triple negative breast cancer patients continued to strengthen in the vaccine group. These findings could position the NPS + trastuzumab combination as an adjuvant therapy for early-stage triple negative breast cancer patients and warrant further study.

REFERENCES

[1]Fehrenbacher L, et al. SABCS 2017. Abstract GS1-02.

ABSTRACT

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DISLOSURES

The views expressed in this presentation are those of the authors and do not necessarily represent the views of the Department of Defense, Brooke Army Medical Center, or other federal agencies.

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