DNA-Based HER2 Vaccine Induces Broader and More Potent T-Cell Responses Than Peptide Vaccine in Advanced HER2-Positive Breast Cancer

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Introduction

- Patients with HER2-overexpressing breast cancer often exhibit reduced immunity to the HER2 antigen.
- Therapeutic vaccines can enhance T cell responses against tumor-associated antigens.
- Both peptide- and DNA-based platforms have been explored for vaccine delivery, but direct comparisons of their safety and immunogenicity remain limited.
- We hypothesize that DNA-based vaccines may generate more robust and potent HER2-specific immunity than peptide vaccines due to prolonged antigen expression from persistent plasmid presence at the injection site.

Methods

- We retrospectively analyzed 66 patients from a Phase I DNA-vaccine trial and 38 from a Phase II peptide-vaccine trial, all with stage III or IV HER2-positive breast cancer and either no evidence of disease or stable bone-only disease at enrollment.
- Both vaccines targeted HER2 intracellular domain (ICD) epitopes.
- Immunogenicity was assessed via IFN-γ ELISpot assays on cryopreserved PBMCs stimulated with HER2 ICD or extracellular domain (ECD) peptides as an indicator of epitope spreading.
- Pre-existing immunity: baseline antigen wells > mean + 2 SD of no-antigen wells; Post-vaccination response: maximal corrected IFN-γ response following priming vaccinations.

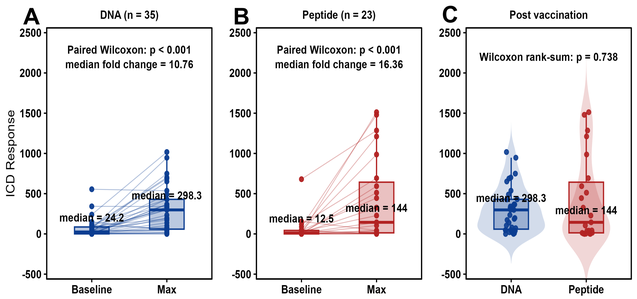
Table 1: Demographic & Clinical Characteristics

Characteristics	DNA vaccine (N=66)	Peptide vaccine (N=38)
Age at Enrollment – Mean (Range)	52.2 (34-77)	47.6 (30-73)
Stage at Enrollment (N, %)		
Stage III	42 (63.6)	11 (28.9)
Stage IV	24 (36.4)	27 (71.1)
Trastuzumab Use (N, %)		
Yes	60 (90.9)	38 (100)
No	6 (9.1)	0 (0)
Hormone Receptor Status at Enrollment (N, %)		
HR+ (ER+ and/or PR+)	37 (56.1)	20 (52.6)
HR – (ER-/PR-)	29 (43.9)	17 (44.7)
Missing	0 (0)	1 (2.6)
Status at Enrollment (N, %)		
NED	56 (84.8)	5 (13.2)
SBO	10 (15.2)	33 (86.8)

One male patient in DNA vaccine trial; all other patients were females.
HR, hormone receptor; ER; estrogen receptor; PR, progesterone receptor.
NED, no evidence of disease; SBO, stable bone-only disease

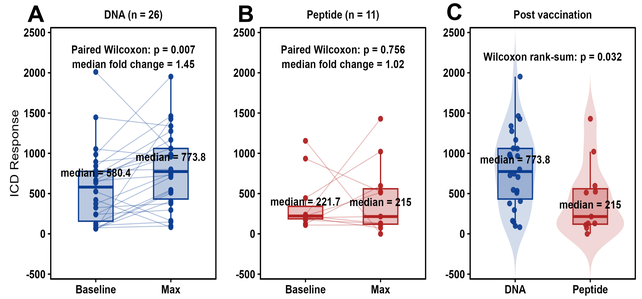
Results

Figure 1: Patients Without Pre-existing ICD Immunity Develop Strong ICD Responses After Both DNA and Peptide Vaccination



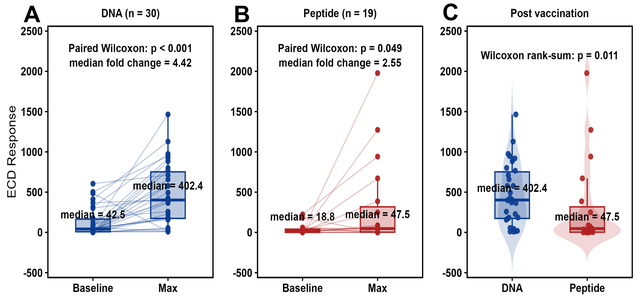
Panel A: Participants lacking ICD pre-immunity at baseline exhibited a strong and consistent rise in ICD responses following HER2 ICD vaccine via DNA vaccine platform.
Panel B: A similar pattern was observed in the peptide vaccine cohort.
Panel C: Both vaccines ultimately generate strong ICD responses when participants begin without pre-existing immunity. Although the difference was not statistically significant, post-vaccine ICD responses were numerically higher in the DNA group than in the peptide group.

Figure 2: Only DNA Vaccines Further Enhance ICD T-cell Immunity in Pre-immune Patients



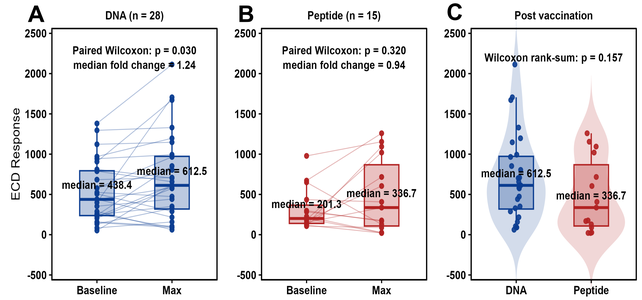
Panel A: Although the magnitude of boosting was smaller compared with patients without pre-immunity, participants with pre-existing ICD immunity still showed a measurable increase in ICD responses after receiving the DNA vaccine.
Panel B: In contrast, participants receiving the peptide vaccine did not exhibit a meaningful rise in ICD responses in the presence of pre-existing immunity.
Panel C: Post-vaccination ICD responses were significantly higher in the DNA cohort than in the peptide cohort among participants who already had baseline ICD immunity.

Figure 3: More Robust Epitope Spreading was Observed in DNA Vaccinated Patients Without Pre-immunity



Panel A: Participants lacking baseline ECD immunity mounted a substantial ECD response after receiving the DNA vaccine. A fourfold expansion from baseline suggests that DNA vaccine is highly effective at recruiting new, previously unprimed ECD-specific T-cell responses.
Panel B: Participants vaccinated with the peptide platform also demonstrated evidence of intramolecular epitope spreading, though the magnitude of boosting was more modest.
Panel C: Post-vaccination ECD responses were significantly higher in the DNA cohort than in the peptide cohort. The DNA vaccine is markedly more potent to support epitope spreading across the HER2 intracellular domain than the peptide vaccine.

Figure 4: Only DNA Vaccines Significantly Enhanced Epitope Spreading Among Patients With Pre-existing ECD Immunity



Panel A: In participants with measurable baseline ECD immunity, DNA vaccination produced a significant post-vaccine increase in ECD responses. This indicates that the DNA platform can effectively amplify existing HER2 ECD-specific T-cell immunity.
Panel B: In contrast, participants receiving the peptide vaccine showed no significant enhancement of ECD responses after vaccination, suggesting limited ability of the peptide platform to boost pre-existing ECD-specific immunity.
Panel C: Post-vaccination ECD responses showed no statistically significant difference between DNA and peptide groups; however, responses were numerically higher in the DNA cohort.

Discussion

- The magnitude of T-cell immunity achieved to the HER2 ICD varied between the two modes of vaccination and was dependent on whether patients had preexisting immunity to HER2 when entering the study.
- Among patients without pre-existing immunity, both DNA and peptide vaccines elicited increases in ICD-specific T-cell responses and epitope spreading, demonstrating that either platform can effectively induct de novo HER2 immunity and downstream antigen broadening.
- In patients with pre-existing ICD and ECD immunity, only the DNA vaccine significantly enhanced post-vaccination responses, suggesting a greater potency of DNA vaccines.
- One grade 3 ALT elevation occurred in the DNA-vaccine trial; no grade 3–5 events were observed in the peptide trial.

Conclusions

- Both DNA- and peptide-based HER2 vaccines were well tolerated and capable of inducing strong HER2-specific ICD T-cell responses and epitope spreading to HER2 ECD in patients lacking baseline immunity.
- Only the DNA vaccine produced a significantly further boost in ICD immunity and epitope spreading in patients with pre-existing responses.
- Overall, the DNA vaccine demonstrated stronger, more consistent, and broader immune activation across both ICD and ECD domains, supporting its potential as a more potent platform for inducing vaccine-driven HER2-specific T-cell immunity.

Reference

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