Incidence of Brain Metastases in Patients with Advanced Stage HER2+ Breast Cancer Previously Treated with a HER2-Directed Cancer Vaccine.

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Introduction

- HER2-positive breast cancer accounts for 15–20% of all breast cancers (BC); associated with aggressive disease and higher recurrence.
- Brain metastases (BM) occur in 30–50% of HER2-positive breast cancer patients. Preventing development of BM is an area of unmet need.
- BM are difficult to treat with systemic therapies due to the blood brain barrier (BBB).
- T cells, such as those induced by vaccination, can cross the BBB.
- HER2 targeted vaccination is shown to generate a Type 1 T-helper cell response, suggesting a potential immune-based therapy to prevent the development of BM.
- The UW Cancer Vaccine Institute (CVI) has conducted multiple HER2-directed vaccine trials over two decades.
- This study evaluates whether HER2-directed vaccination impacts incidence of BM when compared to historical controls.

Methods

Patient Population. Eligible patients were enrolled across four Phase I or Phase II clinical trials. Inclusion criteria required participants to have advanced-stage HER2-positive BC (stage III or IV). For those with stage IV disease, eligibility was limited to patients with no evidence of disease or bone-only metastases. HER2 positivity was confirmed by either IHC 3+ or FISH amplification. Of the patients screened, 146 met eligibility criteria and 134 were enrolled. Baseline characteristics, including hormone receptor (HR) status, were collected at enrollment. Patients ranged from 26 to 75 years old. The study population was 99% female and 1% male. Twelve participants had documented BM prior to enrollment.

HER2-Directed Vaccination. Between 2004 and 2012, all enrolled subjects received at least one HER2-targeted vaccine. Vaccines evaluated included: HER2 Intracellular Domain (ICD) plasmid-based vaccine, HER2 cytotoxic T cell peptide-based vaccine, HER2 ICD peptide-based vaccine.

Data Collection. BM diagnosis was based on radiology records and clinical notes from the medical record. All data was collected from medical records or the Cancer Vaccine Institute database. All patients were followed for five years after initial enrollment.

Data Analysis. Data analyzed using R version 4.5.1 and PRISM version 10.

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Results

Figure 1: Study population selection

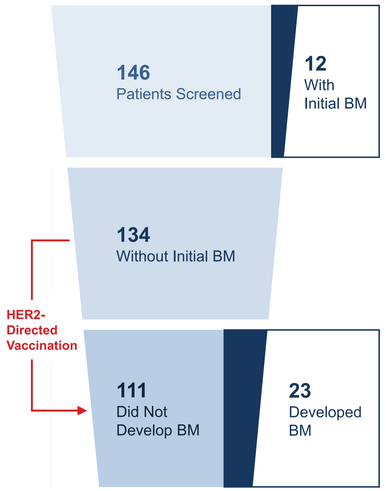

Table 1: Demographic and clinical characteristics

Characteristics	
Number of patients	134*
Median age at enrollment, years (IQR)	50 (45-57)
Brain Metastases	
Yes	23 (17)
No	111 (83)
Herceptin Use	
Yes	127 (95)
No	7 (5)
HR Status (N, %)	
HR-positive (ER+ and/or PR+)	72 (54)
HR-negative (ER-/PR-)	55 (41)
Unknown	7 (5)
Stage and Status at Enrollment (N, %)	
Stage III	53 (40)
Stage IV	81 (60)

Data are in n (%) unless otherwise stated.
*One male patient and 133 female patients.
ER; estrogen receptor; HR, hormone receptor; IQR, interquartile range; PR, progesterone receptor.

Figure 2a: Kaplan-Meier Curve for Brain Metastases-Free Survival

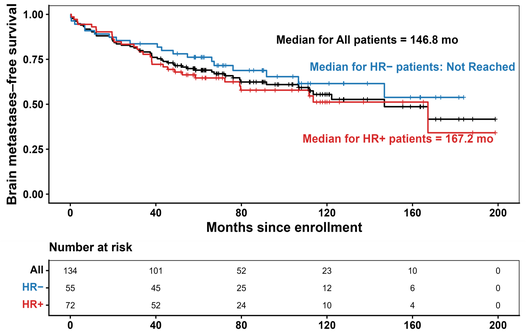

Figure 2b: Multivariable Cox Model for Brain Metastases-Free Survival

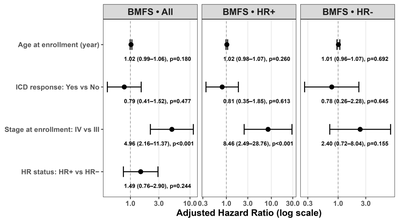

Figure 2. Evaluation of BM free survival based by HR status.
The multivariable cox model includes age, HR status, ICD response, stage at enrollment.
BMFS, brain metastases-free survival; HR, hormone receptor; ICD, intracellular domain.

Figure 3a: Kaplan-Meier Curve for Overall Survival

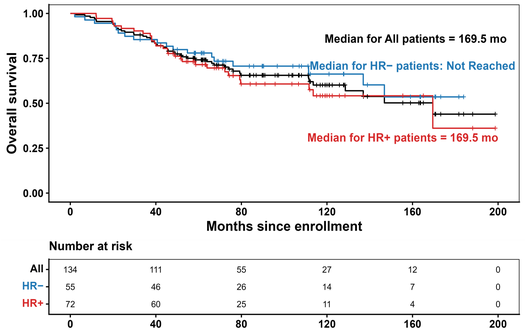

Figure 3b: Multivariable Cox Model for Overall Survival

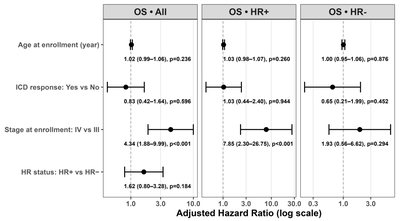

Figure 3. Evaluation of OS based by HR status.
The multivariable cox model includes age, HR status, ICD response, stage at enrollment.
HR, hormone receptor; ICD, intracellular domain; OS, overall survival.

Table 2: Cumulative Incidence of Brain Metastases after receiving HER2-targeted vaccination

Cumulative Incidence by HR status			
Breast Cancer Subtype	Cumulative Incidence	Historical Control	Relative Reduction
HER2+/HR-	14.5%	33.6%	57%
HER2+/HR+	18.9%	22.7%	17%

Out of the total 23 patients who developed brain metastases, one had unknown hormone receptor status.
Historical control retrieved from the data presented by Sammons *et al.* at SABCS 2023 (Poster PS11-01) evaluating the cumulative incidence of brain metastases from first-line initiation.
BM, brain metastases; HR, hormone receptor.

Discussion

- Stratified by hormone receptor (HR) status, the incidence of BM development was 18.9% in HER2+/HR+ patients (n = 14) and 14.5% in HER2+/HR- patients (n = 8).
- When compared to historical controls, which reported a 60-month cumulative incidence at 22.7% in HER2+/HR+ and 33.6% in HER2+/HR- subgroups, **our findings suggest a 17% relative reduction of brain metastases in HER2+/HR+ patients and a 57% reduction in HER2+/HR- patients.**
- No significant differences in BM free survival and overall survival were identified, adjusting for age, stage, ICD response, and HR status.

Conclusions

- HER2-directed vaccination could have a protective effect on the development of brain metastases in patients with advanced stage HER2+ breast cancer.
- Phase II trials are planned to prospectively evaluate a HER2-directed vaccine in this setting.

References

- Sammons S *et al.* doi: 10.1158/1538-7445.SABCS23-PS11-01.
- Kuksis M *et al.* doi: 10.1093/neuonc/noaa285.

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