Long-Term Outcome of Two HER2 Vaccines for Patients with HER-2 Positive Early Stage Breast Cancer

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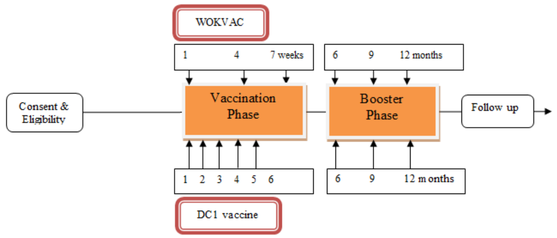
Background

Patients (pts) who have residual invasive disease following neoadjuvant therapy for HER2-positive early breast cancer (EBC) have increased risk of recurrent disease compared to pts with a complete pathologic response (pCR). It also has been observed that pts who do not achieve a pCR have low or absent anti-HER-2 CD4 Th1 responses. We hypothesized that correcting the anti-HER-2 CD4 Th1 response using HER2-directed vaccines would be safe and induce anti-tumor immunity in HER2-positive breast cancer and reduce the risk of recurrence. We conducted a multi-center, phase 2, randomized study to determine the safety, immunogenicity and recurrence free survival of two HER2 vaccines: multivalent anti-oncodriver DNA vaccine (WOKVAC)[1] or HER-2-pulsed dendritic cell vaccine (DC1).[2,3]

Methods/Trial Design

- Pts with HER2-positive early breast cancer with residual invasive disease after neoadjuvant chemotherapy plus HER2-targeted therapy were eligible. Patients were randomly assigned in a 1:1 ratio, with stratification according to residual cancer burden (RCB) (1+2 vs 3) or ypTNM (stage I+II vs III if unknown RCB) to receive adjuvant HER2 vaccination with either DC1 or WOKVAC.
- For the initial vaccination phase, DC1 was delivered via US guided inguinal lymph node administration, weekly x 6 weeks and WOKVAC was given intradermally on weeks 1, 4, and 7. Booster vaccines were given at months 6, 9 and 12.
- The primary end point was to evaluate the safety and tolerability of each vaccine and assess the immune response rate as measured by ELISPOT. Each treatment arm was assessed separately. Secondary endpoints included recurrence-free survival. Exploratory analyses included the assessment of prognostic and predictive biomarkers including circulating tumor cells, serum HER2 levels, and other immune correlative biomarkers. Here we are reporting the immune response and long-term outcome data.

Study Schema



Results

- 110 eligible pts (56 WOKVAC vs 54 DC1) enrolled between February 2018 and December 2022 from 7 academic institutions
- Clinical stage II/III 69/35 (95%), 50% had node positive (+) disease at diagnosis. 22/38/7 patients had RCB 1/2/3.
- 72% received adjuvant trastuzumab emtansine (T-DM1) following FDA approval in 2019.
- The most frequently observed treatment related adverse events (TRAE) were injection site pain/reaction and chills, fever and fatigue for DC1 arm. For WOKVAC, the most common toxicities included injection site reaction and fatigue[4].
- Eleven pts (6 in DC1 and 5 in WOKVAC) had recurrence with a median follow-up of 52.4 months. Of those 2/6 patients in the DC1 arm developed brain metastasis shortly after study enrollment during the induction phase.
- Recurrence-free survival : 94.5% and 90.8% at 3 and 5 years and 96.1% at 3 and 5 years among pts with adjuvant T-DM1
- HER2 immune response measured by ELISPOT (N=80) following vaccination demonstrated an average two-fold increase across both treatment groups at 12 months.

Characteristic			N=110	DC1 (N=54)	WOKVAC (N=56)
Age	Median, Range		44 (30-74)	43 (30-74)	46 (30-69)
Clinical Stage	I		6 (5.5%)	3 (5.6%)	3 (5.4%)
	II		69 (62.7%)	30 (55.6%)	39 (69.6%)
	III		35 (31.8%)	21 (38.9%)	14 (25%)
HR status	Positive		90 (81.8%)	43 (79.6%)	47 (83.9%)
	Negative		20 (18.2%)	11 (20.4%)	9 (16.1%)
Neoadjuvant	TCHP		86 (78.2%)	42 (77.8%)	44 (78.6%)
	AC-THP		11 (10%)	8 (14.8%)	3 (5.4%)
	Other		13 (11.8%)	4 (7.4%)	9 (16.1%)
RCB (N=67)	1		22 (32.8%)	9 (32.1%)	13 (33.3%)
	2		38 (56.7%)	16 (57.1%)	22 (56.4%)
	3		7 (10.4%)	3 (10.7%)	4 (10.3%)
ypTNM stage (N=43)	I		30 (69.8%)	18 (69.2%)	12 (70.6%)
	II		11 (25.6%)	7 (26.9%)	4 (23.5%)
	III		2 (4.7%)	1 (3.8%)	1 (5.9%)
Adjuvant HER2-Therapy	Trastuzumab/Pertuzumab		23 (20.9%)	11 (20.4%)	12 (21.4%)
	T-DM1		79 (71.8%)	39 (72.2%)	40 (71.4%)
	Trastuzumab		8 (7.3%)	4 (7.4%)	4 (7.1%)
Adjuvant HER2-Therapy	Concurrent with study therapy	Yes	35 (31.8%)	11 (20.4%)	24 (42.9%)
		No	75 (68.2%)	43 (79.6%)	32 (57.1%)
Time from last HER2 therapy to C1 therapy (months) (N=74)					
	Median, Range		3.8 (0.2-10.6)	4.7 (0.5-10.6)	2.4 (0.2-6.7)
Events *	Total		9 (8.2%)	4 (7.4%)	5 (8.9%)
	Local recurrence		3 (2.7%)	2 (3.7%)	1 (1.8%)
	New primary cancer		1 (0.9%)	0 (0%)	1 (1.8%)
	Distant recurrence		5 (4.5%)	2 (3.7%)	3 (5.3%)
Death from any cause			3 (3%)	2 (3.7%)	1 (1.8%)

Table 1. Clinical Characteristics.
*Two patients (DC1) with early brain metastasis were excluded from analysis.

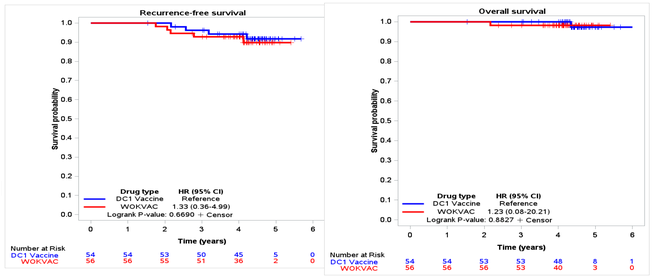


Figure 1. Recurrence-free survival (RFS) and Overall Survival.

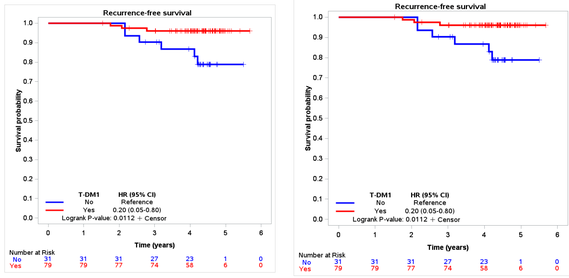


Figure 2. Recurrence-free survival and Overall Survival stratified by T-DM1

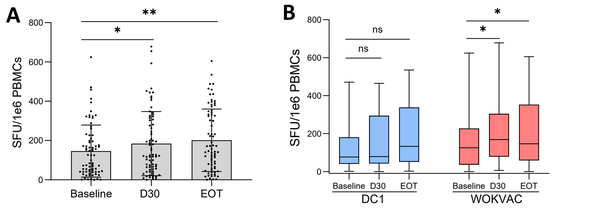


Figure 3. Anti-HER-2 T cell immune response measured by IFN-γ ELISPOT at baseline, 30 days after initial vaccination series, and EOT (end of treatment, at 12 months (N=80). **A**. All DC1 and WOKVAC patients pooled. **B**. DC1 and WOKVAC patient responses shown separately. Paired t-tests were completed for both analyses (* p<0.05, **p<0.01).

Conclusions

Both DC1 and WOKVAC HER2 vaccines were well tolerated without significant toxicities. Both HER2 vaccines were immunogenic and were associated with persistence of immunity at 12 months. Our RFS results compare favorably with the KATHERINE trial suggesting potential additional benefit of adjuvant vaccines for these high-risk pts populations. Several studies are ongoing to evaluate the addition of neoadjuvant DC1 and WOKVAC to HER2 targeted therapies. (NCT 05325632/04329065)

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