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Abst. 1761

A Phase I/IIa Study of the Whole-Cell Vaccine BriaVax™ in Metastatic or Locally Recurrent Breast Cancer Patients (NCT00095862)

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Abstract

BACKGROUND: BriaVax™ (formerly SV-BR-GM-1) is a breast cancer cell line transfected to release GM-CSF. Under FDA BB-IND 10312, the vaccine was tested in 3 metastatic breast, 1 metastatic ovarian cancer patients refractory to previous therapy. Patients received 20 million viable cells ID at 4 sites 48-72 hours after low-dose cyclophosphamide, 300 mg/m2 . Mean cell count was 22.8 x10^6 (18.8-27.6). Mean viability was 90.6%, (84-94%). Interferon-alpha (10,000 u) was injected into each inoculation site after 48 and 96 hrs. The protocol permitted 3 inoculations at 2 week intervals, then, if not showing clearly progressive disease, 3 more inoculations monthly. All patients were stable after 3 injections (2 months). However, Pt A002 enjoyed complete tumor regression of a progressing lung metastasis and near-complete response of multiple breast lesions (see below). Nonetheless, she relapsed widely 3 months after finishing the sixth and final injection per protocol. After obtaining FDA permission inoculations resumed. All metastases, including CNS, again showed prompt but subtotal regression after 3 immunizations (see Wiseman C and Kharazi A; The Breast Journal 2006). Toxicity was minimal and the overall survival of the 4 patients was 35 months.

TRIAL DESIGN: 9 patients will be accrued, toxicity (and also response) will be reviewed; unless there are prohibitive serious adverse events, 15 more patients will then be accrued.

ELIGIBILITY: Inclusion Criteria: Patients must have histological confirmation of breast cancer with recurrent and/or metastatic lesions via investigational site. Patients with new or progressive breast cancer metastatic **to brain will be eligible** if they meet other conditions. Patients must be 18 years of age or older, have expected survival of at least 4 months, adequate performance status (ECOG 0-2). Patients may be maintained on hormonal therapy provided there is clear evidence of tumor progression and have provided written informed consent.

Exclusion Criteria: Concurrent or recent chemotherapy (within 3 weeks), XRT within 3 weeks, may have had immunotherapy in the past (off within 3 weeks), or general anesthesia/major surgery (within 3 weeks). Patients must have recovered from all known or expected toxicities from previous treatment and passed a treatment-free "washout" period of 3 weeks before starting this program (8 weeks for persons receiving nitrosourea or mitomycin). History of clinical hypersensitivity to GM-CSF, interferon, yeast, beef, or to any components used in the preparation of the experimental vaccine. Additional criteria to be provided on request.

SPECIFIC AIMS: To evaluate the number, frequency, duration, and relation of toxicity events to BriaVax™ (formerly designated as SV-BR-1-GM), as defined by CTCAE and additional tests; to evaluate tumor response and durability; to assess immune responses to vaccine; to archive blood and urine for future analysis; to measure quality of life with the SF-36 questionnaire.

Demographics

ID #	Age	ETHNICITY	PARITY	ECOG	MENOPAUSE	TNM Stage	Her2/neu	ER/PR	Sites of Disease
A001	73	Hispanic	G3P1AB2	1	Yes	T1N0M0	+	Neg/Neg	Chest wall, Axilla
A002	58	Caucasian	G4P3AB1	1	Yes	T2N3M1	-	ER+/PR+	Breast, Lung
A003*	74	Caucasian	G2P2	1	Yes	T4	-	NA	Pelvis
B001	61	Caucasian	NA	2	Yes	T2NXM1	-	ER+/PR+	Rib cage, Humerus, Hip, Femur

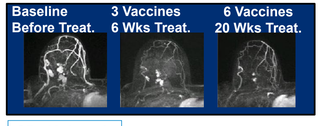
*Ovarian Cancer Patient

Seventh Ann. Immunotherapy Immuno-monitoring Conf. San Diego, CA Jan 27, 2015

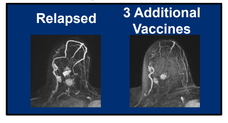
Response in Patient A002 and CD40L

Radiologic

Tumor Regression – Series-I

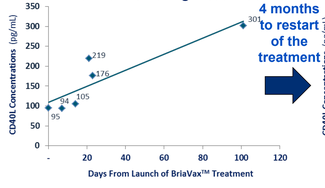


Tumor Re-Regression – Series-II



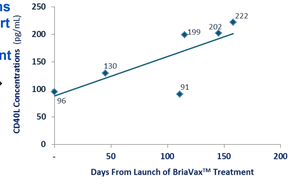
CD40L Levels

CD40L Levels During Treat. – Series I



4 months to restart of the treatment

CD40L Levels During Re-Treat. – Series II



Source: Wiseman C. et al 7th Ann. Immunotherapy Immuno-monitoring Conf. San Diego, CA Jan 27, 2015

Molecular Biology Findings

- BriaVax™ cell line displays both HLA Class I and II alleles, & the responding patient matched in both categories
- BriaVax™ expresses tumor-associated antigens, including HER2/neu, PRAME, and others
- The BriaVax™ cell line displays immune markers, including CD83, CD74, IL6
- Serum CD40L levels correlated with clinical response & relapse, re-response

HLA Alleles

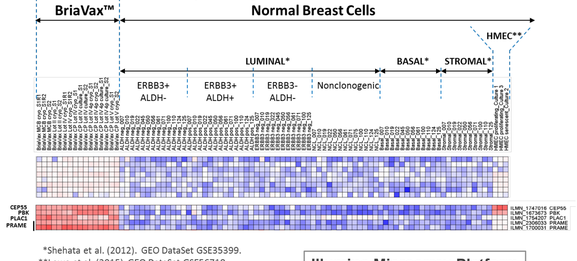
Subject ID	Tumor Type	Survival (months)	Tumor regression	HLA-A		HLA-B		HLA-DRB3	
A001	Breast	40.7	No	02:01	24:02	13:02	41:01	03:01	-
A002	Breast	33.7	Yes	02:01	11:01	18:03	44:02	02:02	-
A003	Ovarian	35.6	No	02:01	03:01	07:02	13:02	Negative	-
B001	Breast	7.0	No	11:01	-	35:01	40:01	Negative	-
BriaVax	Breast	N/A	N/A	11:01	24:02	35:08	55:01	01:01	02:02

Notes: BriaVax™ and Subject A002 with tumor regressions even at metastatic sites (reported in Wiseman and Kharazi, 2006) share both MHC class I (HLA-A) and class II (HLA-DRB3) alleles.

Source: M. Lacher et al., AACR 2016

Antigenic Expression: Cancer/Testis AG

- **Cancer /Testis Antigens (CTAs):** A class of cancer tissue specific antigens
- **PRAME:**A CTA expressed in several malignancies, including some breast cancers.
  PRAME is also expressed in BriaVax™.
- BriaVax™ injection may activate PRAME-specific T cells and thereby cause destruction of PRAME-expressing tumors.

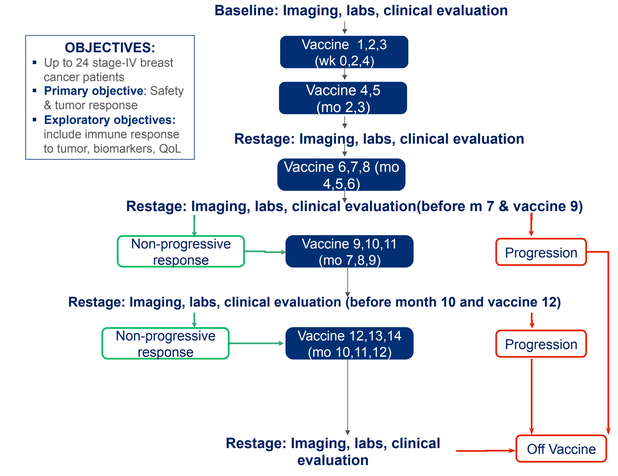


*Shehata et al. (2012). GEO DataSet GSE35399.
**Lowe et al. (2015). GEO DataSet GSE56718.

Illumina Microarray Platform

Source: M. Lacher et al., AACR 2016

Experimental Plan



Pending Trials to Come

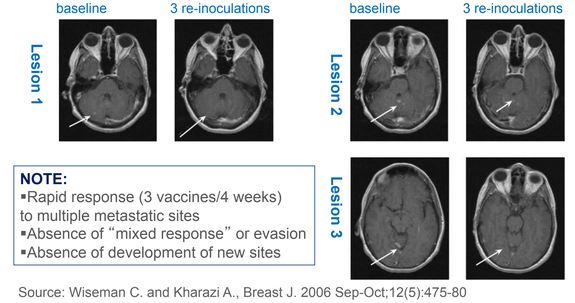
- Combination with Checkpoint Inhibitors
- Dose-Ranging exploration
- Schedule variations

Clinical Data To-Date

First Phase I:
- Used unmodified cell line + subcutaneous GM-CSF/cyclophosphamide
- N = 14 late stage, treatment-refractory breast cancer patients
- No life-threatening adverse reactions, well tolerated
- Median Overall Survival = **12.1 months**

Second Phase I:
- Used GM-CSF-engineered cell line + CY/ interferon-α
- N = 4 late stage, treatment-refractory (3 breast cancer, and 1 ovarian cancer) patients
- No life-threatening adverse reactions, well tolerated
- Median Overall Survival = **35 months**
- One robust responder with **>90% regression during treatment**,
- subsequent relapse (upon halting treatment) **responded to re-treatment**

Response in CNS Mets



NOTE:
- Rapid response (3 vaccines/4 weeks) to multiple metastatic sites
- Absence of "mixed response" or evasion
- Absence of development of new sites

Source: Wiseman C. and Kharazi A., Breast J. 2006 Sep-Oct;12(5):475-80

In Appreciation

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QR Code