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A PHASE I DOSE ESCALATION STUDY OF STEMVAC, A MULTI-ANTIGEN, MULTI-EPI TOPE TH1 SELECTIVE PLASMID-BASED VACCINE, TARGETING STEM CELL ASSOCIATED PROTEINS IN PATIENTS WITH ADVANCED BREAST CANCER

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Background Cancer stem cell or epithelial/mesenchymal transition antigens could have utility in vaccines for cancer treatment and prevention. We identified class II binding T-cell epitopes from non-mutated tumor antigens that selectively elicit a Th1 response. We constructed a 5 antigen (CD105-Yb-1-SOX2-CDH3-MDM2) multi-epitope plasmid-based vaccine; STEMVAC, and conducted a Phase I dose escalation study in patients with advanced breast cancer.

Methods Patients with advanced HER2 negative breast cancer previously treated and in remission were sequentially enrolled to 3 dose arms: 150, 300, or 600mcg of STEMVAC. Vaccines were given monthly intradermally for three doses with rhu-GM-CSF (100mcg) as adjuvant. Two booster immunizations (same dose) were given 3 and 6 months after the third vaccine. Primary endpoints were safety and immunogenicity. Secondary endpoints included persistence of the immune response after vaccination and assessment of potential stimulation of T-regulatory (Treg) cells or myeloid derived suppressor cells (MDSC) to the overexpressed non-mutated antigens expressed in STEMVAC. Antigen specific immunity was measured by IFN-gamma (g) and IL-10 ELISPOT. Immune cells were evaluated by flow cytometry.

Results Seventy-five percent of patients were hormone receptor positive and 25% triple negative (TNBC). Patient characteristics, including breast cancer subtype, did not vary significantly between doses (all $p > 0.1$). The vast majority of adverse events (AE), 98%, were grades 1/2. The most common AE were injection site reactions, flu-like syndrome, and transient leukopenia and lymphopenia. Arm 1 (150mcg) generated transient low levels of IFN-g secreting T-cells to a median of 1 antigen per patient and considered the least immunogenic dose. Arm 2 (300mcg) resulted in a mean response (sum of all antigens) of 1 antigen specific T-cell per 2500 (1:2500) PBMC at week 16 ($p < 0.05$ compared to baseline) which boosted to 1:1500 by week 60 ($p < 0.001$ compared to baseline). Immune responses for Arm 3 (600mcg) were statistically similar to Arm 2 at 16 weeks, but did not persist and could not be boosted. In Arm 2, booster immunizations increased the incidence and breadth of the immune response, with patients showing significant IFN-g secretion to a median of 4/5 antigens. At 16 weeks, there was no increase in antigen specific IL-10 secreting T-cells, Treg, or MDSC at any dose.

Conclusions STEMVAC selectively elicits high level persistent Type I T-cell responses at the 300mcg dose. Two Phase II studies are enrolling; adjuvant setting for TNBC (NCT05455658) and maintenance therapy with pembrolizumab in metastatic non-small cell lung cancer (NCT05242965).

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Trial Registration NCT02157051

Ethics Approval The study was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board

(#7396). All participants gave written informed consent before participation in the study.

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