TPS1132 **Poster Session**

Immunologic targeting of native and mutated ESR1 receptor for treatment of hormone receptor expressing metastatic breast cancer.

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Background: Hormone receptor positive (HR+) HER2 negative metastatic breast cancer (MBC) remains a difficult clinical problem. Endocrine therapies have remained the mainstay of therapy for decades and despite combination with targeted agents and development of novel targeted therapies, the 5-year survival rate of MBC remains low. Resistance to ET can occur due to the development of point mutations in the estrogen receptor alpha type I (ESR1), which constitutively activates the receptor, making it resistant to anti-estrogen. We produced a peptide library of the entire wild type (WT) ESR1 and identified four promiscuous peptide epitopes that routinely drive a CD4 Th1 response in healthy donors and breast cancer patients. Additionally, we created overlapping peptides around each known ESR1 mutation site and pulsed them on type I polarized dendritic cells (DC1) also resulting in an increased CD4 Th1 response. We hypothesize that ER alpha receptor can serve as a target for the immune response and ESR1 mutations that develop in HR+ breast cancer patients can be utilized as a neoantigen that will drive CD4 Th1 responses and antibodies that can be developed as an immune based therapy for patients with HR+ MBC. Combining DC1 vaccination with novel endocrine therapies such as Elacestrant, we expect an increase in ESR1 degradation and enhanced antigen presentation leading to an expanded immune and clinical response. **Methods:** In this open pilot study, up to 18 patients with HR+ HER2 negative, ESR1 mutated MBC with measurable or evaluable disease will be enrolled to determine the feasibility and safety of the combination of DC1 vaccines and Elacestrant. Prior use of elacestrant is exclusionary. Eligible patients will undergo apheresis of peripheral blood to collect and create DC1 vaccines. DC1 will be pulsed with ESR1 WT and mutated peptides. Patients will be injected in their groin nodes (or accessible tumor if available) weekly with these pulsed DC1 (20-50 million) for eight consecutive weeks. They will alternate between WT ESR1 DC1s and mutated ESR1 DC1s. Patients will receive combination of DC1 vaccinations and Elacestrant at 345 mg orally daily concurrently during vaccination and continued after. After the initial vaccination series, patients will undergo radiological assessment of their disease, and if no evidence of progression they will receive booster DC1s every four weeks x 3 doses. The primary objective of this pilot study is safety and feasibility. Secondary objectives include preliminary efficacy, biomarkers assessment, safety and patient reported outcomes. Tumor tissue and blood samples will be collected for correlative analyses including ctDNA and changes in variant allele frequency of ESR1 during treatment. The study is open at H. Lee Moffitt Cancer Center. Clinical trial information: NCT06691035. Research Sponsor: V Foundation.