

**PHASE I STUDY OF ADOPTIVE T CELL THERAPY FOLLOWING HER2-PULSED DENDRITIC CELL VACCINE AND PEPINEMAB/TRASTUZUMAB IN PATIENTS WITH METASTATIC HER2-POSITIVE BREAST CANCER (MBC)**

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**Background** Despite major improvement of overall survival of HER2+ MBC with effective HER2 targeted therapies, many patients experience significant toxicities and develop progressive disease during treatment. Therefore, new and more effective therapeutic options are needed. This novel approach will evaluate whether the combination of three immunotherapies in addition to trastuzumab: dendritic cell (DC) vaccination, anti-SEMA4D blocking antibody (pepinemab) and CD4+ T cell adoptive transfer can lead to improved outcomes for patients with MBC refractory to HER2-targeted agents.

BC have been considered as immunologically cold which is attributed to immune evasion and suppression of host effector immune cells homing into tumor bed. Progressive loss of Th1 immunity against HER2 oncodriver correlates with poor prognosis. HER2 peptide pulsed type I dendritic cells (HER2-DC1) restored anti-HER2 CD4+ Th1 immune response and improved pathologic complete response (pCR) in HER2+ BC.<sup>1</sup>

Antibodies to SEMA4D have been shown to modulate the TME by increasing effector cell infiltration and reducing immunosuppression.<sup>1</sup> In preclinical studies, treatment with anti-SEMA4D and HER2-DC1 in mice bearing established HER2+ tumors improved DC homing, expansion of CD4+ T cells, and complete tumor regression, compared to treatment with anti-SEMA4D or HER2-DC1 alone. Further, subsequent expansion and adoptive transfer of CD4+ T cells induced synergistic anti-tumor activity by activating CD8+ T mediated cytotoxicity. Pepinemab was well-tolerated<sup>2,3</sup> and showed signs of anti-tumor activity in immunotherapy-resistant, PD-L1 negative/low non-small cell lung cancer patients when combined with checkpoint inhibitor (avelumab).<sup>3</sup>

**Methods** This open label Phase 1 study is enrolling up to 28 patients with HER2+ MBC. Patients will be treated with 6 weekly injections of dendritic cell (DC1) vaccines in combination with trastuzumab and pepinemab. We hypothesize these therapies may elicit CD4+ HER2-specific T cell responses. HER2-specific T cells will be expanded ex vivo and subsequently infused to patients following lymphodepletion with cyclophosphamide. Trastuzumab and pepinemab will be given as maintenance in addition to booster DC1 vaccines.

Patients (ECOG 0,1) must have had disease progression while on trastuzumab for the treatment of HER2+ MBC and received no more than 3 lines of therapy in the setting of metastatic disease. Dose escalation will consist of 3-6 patients each with increasing amounts of transferred CD4+ T cells, followed by dose expansion of 10 patients at the MTD. The primary objective is safety and tolerability; secondary objectives will include evaluation of T cell immunity and immune subsets, efficacy, PK/PD/ADA of pepinemab, and biomarker assessments.

**Trial Registration** NCT05378464

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**Ethics Approval** This study was approved by Advarra; approval number IRB# 00000971

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