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Abstract 645

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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PURPOSE / OBJECTIVE

Despite major improvement of overall survival of HER2+ metastatic breast cancer (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 [1].

Antibodies to SEMA4D have been shown to modulate the TME by increasing effector cell infiltration and reducing immunosuppression [2,3]. 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 [4,5] 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) [3].

MATERIALS & 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.

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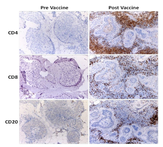
BACKGROUND

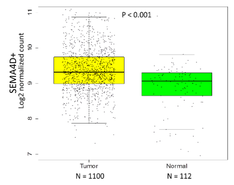
HER2-peptide-pulsed type I dendritic cells (HER2-DC1)
restored anti-HER2 CD4+ Th1 immune response
and improved pathologic complete response (pCR) in HER2+ BC

Accumulation of T and B cells occurs in patients responding to HER2-pulsed DC1 vaccines



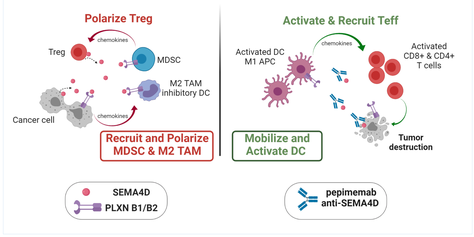
SEMA4D is expressed in BC

HER2+ Breast Cancer	SEMA4D in cytokeratin positive
DCIS	8/15
IBC	7/13

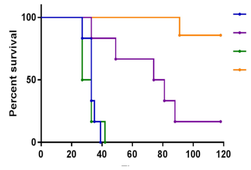


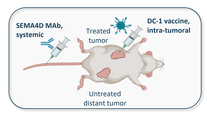
SEMA4D promotes immune exclusion and suppression

Pepinemab recruits and activates DC and cytotoxic T cells

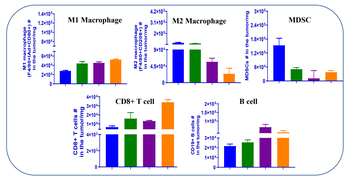


Preclinical mouse HER2+ Breast Cancer Models – Combination therapies
Transplantable HER2+ TUBO model

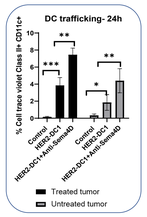




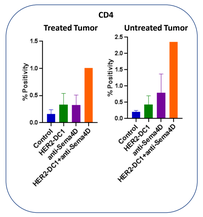
SEMA4D antibody improves the balance of pro-inflammatory M1 APC over suppressive M2 APC and MDSC & promotes infiltration of lymphocytes



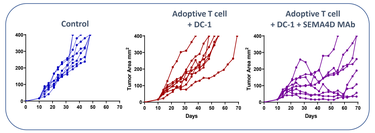
SEMA4D antibody improves DC trafficking in untreated tumor



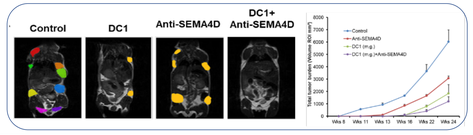
SEMA4D antibody + DC-1 improves CD4+ T cell infiltration in tumors



SEMA4D antibody + DC-1 + CD4+ T cell adoptive therapy improves tumor regression

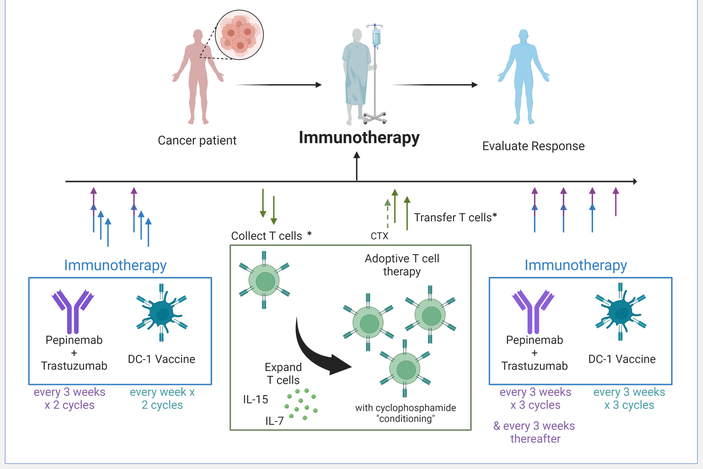


Preclinical spontaneous tumor model in NeuT transgenic mice



CLINICAL TRIAL DESIGN

Phase I, Investigator-sponsored Trial, open-label, dose escalation



Patients with Metastatic HER2+ Breast Cancer

Key Inclusion Criteria
- histologically confirmed HER2 positive breast cancer
- RECIST v1.1 measurable disease
- With disease progression while on trastuzumab for the treatment of HER2+ MBC.
- A maximum of 3 prior lines of cytotoxic chemotherapy in the setting of metastatic disease.
- ECOG performance status 0 or 1.

Key Exclusion Criteria
- Patients with uncontrolled brain metastases or leptomeningeal disease
- Female patients who are pregnant or nursing are not eligible
- Second invasive malignancy requiring active treatment

Pepinemab 20mg/kg
+ Trastuzumab 8 mg/kg IV C1D1, then 6 mg/kg Q3W

DC1 vaccines 1-2x10^7 cells, intra-lesional, weekly

Autologous Expanded CD4+ T cells

Expanded CD4+ T cells dose escalation scheme

Cohort	N	IL-15 Expanded HER2-specific CD4+ Th1 cells	IL-7 Expanded HER2-specific CD4+ Th1 cells
1	3-6	0.05 – 0.25 x 10^9	0.05 – 0.25 x 10^9
2	3-6	0.25 - 1.20 x 10^9	0.25 - 1.20 x 10^9
3	3-6	0.50 - 2.50 x 10^9	0.50 - 2.50 x 10^9
-1	NA	0.005 – 0.025 x 10^9	0.005 – 0.025 x 10^9

* Blood collection and IV transfer for each, anti-HER2 CD4 Th1 cells expanded with either *IL-15* or *IL-7,* will occur 1 week apart
- Treatment with cyclophosphamide (300mg/m^2) administered 1 day prior to first expanded CD4+T cells
- The first 2 patients in each dose escalation cohort will be enrolled with staggering interval of 14 days.

A total of 10 patients will be enrolled into the dose expansion cohort and will be treated with CD4+ T cells at MTD. MTD will be defined as the highest dose tolerated leading to dose-limiting toxicities (DLTs) in <2 of 6 patients.

Primary Endpoints

Safety/Tolerability –
- CTCAE (NCI Common Terminology Criteria Adverse Events) version 5.0
- Maximum Tolerated Dose (MTD) of expanded CD4+ T cells

Secondary Endpoints
- Efficacy: RECIST criteria version 1.1, clinical benefit rate (CBR) at 6 months, and progression free survival.
- HER2-specific T cell immune response
  - IFN gamma ELISPOT
  - Persistence of T cell immunity up to 1 year following the last infusion
- Biomarker analysis
  - Characterize immune cell composition, including MDSC, Th2 and Treg.

Status:
ENROLLING NOW

This study was approved by Advarra; approval number IRB#00000971
NCT05378464

Sponsor: H. Lee Moffitt Cancer Center and Research Institute
Collaborator: Vaccinex Inc.

Figures created with Biorender.com

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