Focused Ultrasound Therapy Combined with Pembrolizumab in Metastatic Breast Cancer

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INTRODUCTION

Background: Focused ultrasound (FUS) is an ablative therapy which can heat tumors rapidly to cell damaging temperatures and simultaneously perturb the microenvironment, the microvasculature, and the lymphatics. At typical energy levels, FUS can induce controlled apoptotic cell death rather than liquefactive necrosis. FUS does not involve radiation. FUS is a partially ablative therapy using high energy ultrasound waves to induce heat shock proteins, cytokine release and cellular mediated mechanisms resulting in T cell activation and recognition of tumor antigens. FUS has been demonstrated to be an effective method for inducing tumor antigen exposure and presentation to dendritic cells, thus acting as an auto- vaccine. Pembrolizumab (PBZ) is a PD-1 targeted antibody used in multiple solid tumors to augment T cell activation. It is hypothesized that the combination of these two modalities will result in T cell infiltration into breast tumors as well as systemic immune responses.

OBJECTIVES

Primary Objective
To determine whether the addition of pembrolizumab to FUS increases the proportion of CD8+ tumor infiltrating lymphocytes (ratio CD8+/CD4+) in the primary ablation zone.

Secondary Objective
To assess the adverse event profile of pembrolizumab and FUS

Exploratory Objectives
(1) To compare CD8+ T-cell responses at peri-ablation zones when pembrolizumab is given before or after FUS. (CD8+/CD4+ ratios compared between arms)
(2) To evaluate clinical responses at local and distant metastatic sites by CT scan as measured by RECIST 1.1
(3) To estimate the progression free survival (PFS) of breast cancer subjects treated with FUS in combination with pembrolizumab.
(4) To estimate the overall survival (OS) of subjects with breast cancer treated with FUS in combination with pembrolizumab.
(5) To evaluate immune responses to FUS plus pembrolizumab by flow cytometry, immunohistochemical, cytokine, or other methods.

METHODS

Subject Inclusion Criteria
• Metastatic or unresectable breast cancer
• Any receptor status, but ER+ pts must have exhausted hormonal Tx options.
• At least one prior line of therapy for metastatic disease
• Targetable portion of the tumor must be ≥ 5 mm from the skin, 10 mm from rib, and >9mm in height
• Performance status of 0 to 1
• Adequate Organ Function (Laboratory Values within 1.5X upper limit of normal)
• Negative Pregnancy test

Subject Exclusion Criteria
• Hypersensitivity to pembrolizumab
• Active infection requiring systemic therapy.
• Breastfeeding
• Active autoimmune disease
• Known active CNS metastases. (Previously treated brain mets must be stable for at least 4 weeks prior to trial treatment.)
• Any receptor status, but ER+ pts must have exhausted hormonal Tx options.

Planning Ultrasound images and FUS Device:

To estimate the progression free survival (PFS) of breast cancer

Standard Ultrasound image (A) shows the targetable portion of the breast tumor after FUS ablation. (B) shows 2 subcutaneous melanoma biopsies for the primary ablation zone.

Pre and post tumor biopsy immunohistochemistry example shows a sample of the intended analyses for this study. In this example, a ductal breast cancer in a human was treated using 4092 power on the Echoprobe device following administration of pembrolizumab 4 days earlier.

REFERENCES


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