A PHASE II CLINICAL TRIAL OF ENMD-2076 IN METASTATIC TRIPLE-NEGATIVE BREAST CANCER: TRANSLATING A P53-BASED BIOMARKER FROM BENCH TO BEDSIDE

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Background: Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype defined by the lack of expression of the estrogen and progesterone receptors and lack of HER2 over-expression. The development of targeted anti-cancer agents effective against TNBC in combination with novel biomarker selection strategies is a major unmet need in breast cancer treatment. ENMD-2076 is an orally bioavailable small molecule inhibitor of Aurora and angiogenic kinases with pro-apoptotic and antiproliferative activity against preclinical models of TNBC. Our group has developed a p53-based biomarker predictive of response to ENMD-2076 in preclinical TNBC models which is currently being evaluated in patients with advanced TNBC treated with ENMD-2076.

Methods: This dual-institution phase II clinical trial will enroll 35 patients with locally advanced or metastatic TNBC refractory to 1-3 prior lines of chemotherapy to detect an improvement in clinical benefit rate (30%) as compared to historic controls (10% null hypothesis). Correlative tissue testing will be performed on archival tumor tissue from primary tumors and sites of metastatic disease in all enrolled patients to include analysis for: p53 mutations (DNA sequencing), p53 gene expression (RT-PCR) and p53 protein expression (IHC). In a subset of at least 14 patients, serial fresh tumor biopsies will be collected prior to initiation of treatment, following 2 weeks of treatment, and at the time of progression in responders for transcriptome sequencing (RNASeq) in addition to the above correlatives.

Results: The trial has enrolled 9 patients including 4 patients who have completed the serial tumor biopsies for correlative tissue testing. Sufficient RNA for transcriptome sequencing was isolated and correlative tissue testing is in progress.

Discussion: ENMD-2076 is a promising anti-cancer agent for TNBC and the incorporation of predictive biomarker investigation early in the clinical development of this drug may lead to successful patient selection.