A randomized phase 0 trial of the mitocondrial inhibitor ME344 or placebo added to the antiangiogenic (Aa) bevacizumab in early HER2-negative breast cancer (E-HERNEBC)

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Background
-Despite established preclinical evidence demonstrating mitochondria are essential for cancer growth, as well as epidemiological evidence suggesting that the mitocondrial inhibitor antiangiabetic drug metformin may be protective against cancer, few clinical trials have addressed the therapeutic potential of mitocondrial inhibitors in oncology. Of those that have, most yielded negative results with this drug class.
-Our previous preclinical research showed that mitocondrial inhibitors work when mitocondrial respiration is the dominant energy source.
-Further, we have shown that mitocondrial respiration is dominant when antiangiogens induce vascular normalization; when tumors switch from hypoxia induced glycolysis to mitocondrial respiration. In this situation, combining mitocondrial inhibitors was synergistic with antiangiogens.
-Vascular normalization in response to antiangiogens can be detected with FDG-PET – normalized tumors can be detected with FDG-PET – normalized tumors can be detected with FDG-PET.

Trial design

Results: Pharmacodynamics

Results: 1\textsuperscript{ary}/2\textsuperscript{ary} outcomes

Conclusions
-ME-344 shows proof of biologic antitumor activity compared to placebo in HER2 negative breast cancer. SDH EHC pharmacodynamics supports on-target effect.
-Normalized tumor vasculature and hypoxia correction correlate with enhanced antitumor activity
-FDG-PET accurately monitors antiangiogenic-induced hypoxia correction, which occurs approximately in 1/3 of the patients following a single course of bevacizumab. The results of this study support further clinical evaluation combining ME-344 with antiangiogenic therapy.

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