Abstract #3100

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 mitochondrial inhibitor antidiabetic drug metformin may be protective against cancer, few clinical trials have addressed the therapeutic potential of mitochondrial inhibitors in oncology. Of those that have, most yielded negative results with this drug class.

-Our previous preclinical research showed that mitochondrial inhibitors work when mitochondrial respiration is the dominant energy source.

-Further, we have shown that mitochondria respiration is dominant when antiangiogenics induce vascular normalization; when tumors switch from hypoxia induced glycolysis to mitochondrial respiration. In this situation, combining mitochondrial inhibitors was synergistic with antiangiogenics.

-Vascular normalization in response to antiangiogenics can be detected with FDG-PET – normalized tumors correct hypoxia and rely less on glucose uptake for generating ATP.

-ME-344 is a novel complex-I inhibitor that was generally well-tolerated in a phase Ib trial, but the degree of anti-cancer activity did not support further investigation of the combination in unselected patients with SCLC, ovarian and cervical cancers.

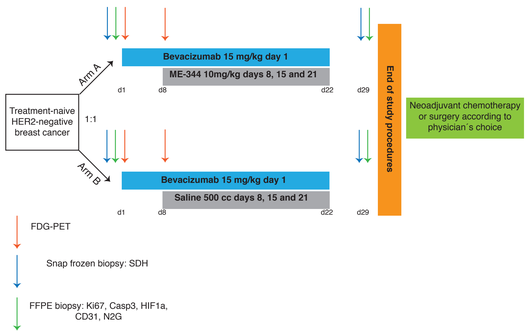
-We sought to study the role of ME-344 in the context of vascular normalization in early HER-2 negative breast cancer taking advantage of a Phase 0 design.

Objectives

-Primary: show proof of biologic activity of post-antiangiogenic ME-344 treatment as measured by a Ki67 decrease from day 0 to 29 compared to placebo

-Secondary: 1) determine whether biologic activity of post-antiangiogenic ME-344 treatment correlates with vascular normalization according to FDG-PET; 2) assess histological correlation between FDG-PET changes and vascular normalization; 3) demonstrate pharmacodynamic activity of ME-344 in tumor tissue.

Trial design

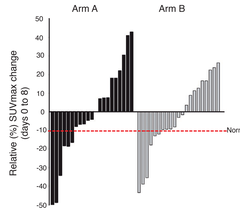


Inclusion criteria: Women>18yo with HER-2 negative early, treatment-naive, operable breast cancer (T>1 cm, any N, confirmed M0). Adequate organ function was mandatory according to usual definitions. Negative pregnancy test.

Results: demographics

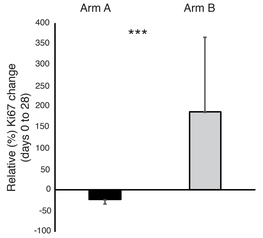
Characteristic	Arm A (N=21)	Arm B (N=21)
Age (median, range)	58.4 (41.5-75.3)	53.6 (39-82.8)
Tumor size		
T1	6 (29%)	11 (52%)
T2	13 (61%)	10 (48%)
T3	2 (10%)	0 (0%)
Nodal stage		
N0	17 (81%)	17 (81%)
N1	4 (19%)	4 (19%)
HER2 positive	0 (0%)	0 (0%)
Hormonal receptors		
ER and/or PR positive	15 (71%)	15 (71%)
Triple-negative	6 (29%)	6 (29%)
Baseline Ki67 (median, range)	31.6% (3.6%-70%)	25.2% (1.2% - 81.5%)
Histologic subtype		
Ductal	21 (100%)	21 (100%)
Lobular/other	0 (0%)	0 (0%)

Results: 1ary/2ary outcomes

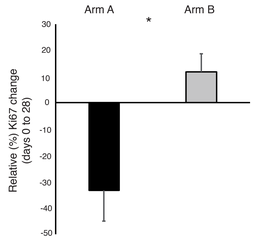


Previous data suggest that a 10% decrease in SUVmax correlates with vascular normalziation. Approx. 1/3 of patients from each treatment arm experienced >10% SUVmax decrease in the primary tumor from day 0 to day 8 after exposure to bevacizumab

All patients



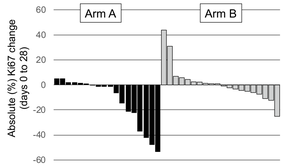
Patients with Vascular normalization (PET)



Primary Outcome (left): Ki67 reduction from day 0 to 28 was on average 23% in the ME-344 arm, compared to an average increase of 186% in Arm B

Secondary outcome (right): Ki67 reduction in patients experiencing vascular normalization in Arm A was 33%, compared to an increase of 11.8% in normalized patients from the placebo arm

All patients



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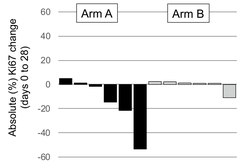
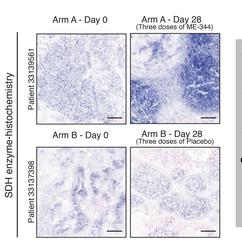
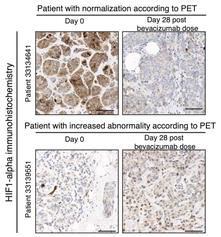


Waterfall plot of absolute Ki67 score changes day 0 to 28. The mean absolute Ki67 change in Arm A was -13.3 and Arm B 1.1

Results: Pharmacodynamics

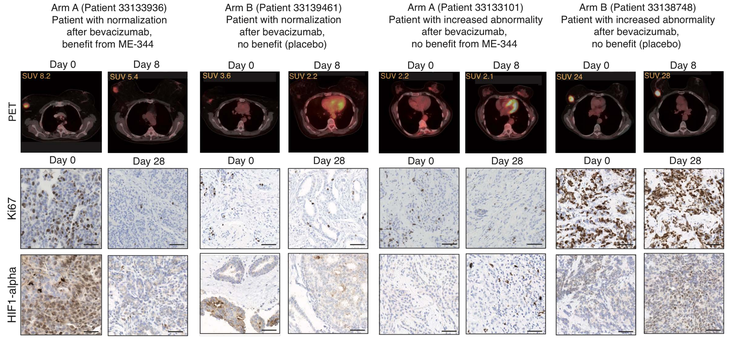


Succinate dehyrogenase (SDH) Enzyme-histochemistry: we have observed in animals that after blocking mitocondrial complex I there is an up-regulation of the function of compex II (SDH). Patients in the ME-344 arm experienced an increase in SDH activity



Correlation between FDG-PET changes and oxygenation (HIF1-staining): abnormal vasculature is accompanied by tumor hipoxia. Patients with FDG PET decrease corrected hipoxia (switch to mitocondria) whereas those without FDG decrease remained hypoxic

Patient examples: four possible 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.

Funding

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