Abrogation of resistance against bevacizumab (Bev) by mitochondrial inhibition: a phase 0 randomized trial of Bev plus ME344 or placebo in early HER2-negative breast cancer (HERNEBC)

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Abstract # 2552

BACKGROUND

Our preclinical data show that one mechanism of acquired resistance to anti-angiogenic therapy involves hypoxia correction, measured by decreased SUV (🡻 SUV) on FDG-PET followed by mitochondrial up-regulation. [1]

FDG-PET can monitor which pattern is occurring as early as 8 days after the first dose. [2] When vascular normalization occurs, tumors become highly sensitive to mitochondrial inhibitors. [3]

ME-344 is a mitocondrial respiration inhibitor that has completed phase I, showing a good tolerability profile at 10 mg/kg IV q 7d.

KI67% was related to tumor cell proliferation and it has been observed that it is a factor can predict the response to neoadjuvant chemotherapy as a surrogate marker of efficacy [4] .

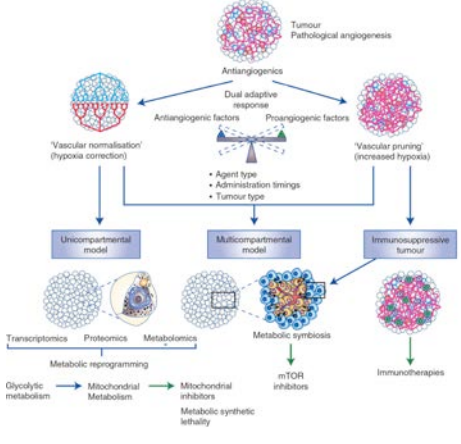

Figure 1. Dual microenviromental adaptive response against antiangiogenic therapies and its clinical implications

OBJECTIVES

1) The fraction of HERNEBC patients that show 🡻 SUV in response to single dose Bev.
2) If adding ME344 to Bev inhibits cell proliferation as determined by Ki67% decrease, a surrogate marker of efficacy in neoadjuvant breast cancer.

METHODS

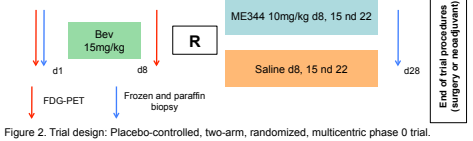

Figure 2. Trial design: Placebo-controlled, two-arm, randomized, multicentric phase 0 trial.

Treatment-naïve HERNEBC patients (T>1 cm, any N, M0) received 15 mg/kg Bev on d0 and were then randomized 1:1 to ME344 10 mg/kg IV d8, 15 and 21 (arm A) or placebo (arm B) followed by physician's choice of definitive therapy. FDG-PET was performed on d0 and d7 and tumor biopsy on day 0 and 28.

A 40 patient sample size was powered to detect a 30% relative difference in Ki67% between arm A and B (alpha 0.05, beta 0.2).

Threshold for hypoxia correction by PET was 10% 🡻 SUV. A predefined interim analysis was planned when 20 patients had completed treatment.

RESULTS

Characteristic	N (19)
Age	56 (44-75)
LumA/B/TNBC	14 / 4 / 1
Arm A	10
Arm B	9
T1/T2/T3	8 / 10 / 1
N0/N1	14 / 5
G1/G2/G3	4 / 12 / 3
Followed by surg. or neo.	14 / 5

Table 1. Demografic characteristics of patients

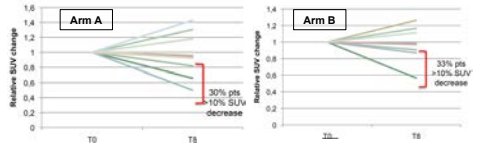

Figure 3. Similar changes in SUV of both arms after a single dose Bev

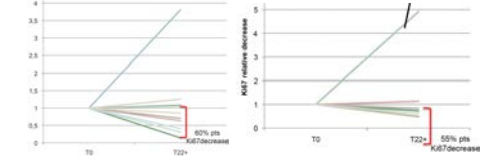

Figure 4. Average Ki67 decreases (relative) 5.13 (29%) and 1.2 (9%) in arms A and B (P=0.06).

Both arms: 31% of patients experienced 🡻 SUV >10% after Bev single dose.

Mean absolute (relative) Ki67 decreases were 5.13 (29%) and 1.2 (9%) in arms A and B (P=0.06).

Patients with 🡻 SUV>10% experienced an absolute average Ki67 decrease of 16.6 vs. 2.3 in arms A and B (P=0.19).

Two G3 adverse events (high blood pressure) were reported (1 per arm) and deemed related to Bev.

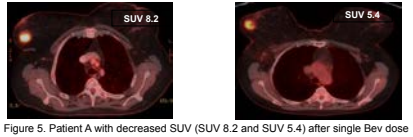

Figure 5. Patient A with decreased SUV (SUV 8.2 and SUV 5.4) after single Bev dose

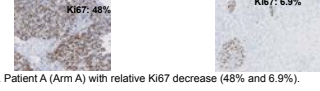

Figure 6. Patient A (Arm A) with relative Ki67 decrease (48% and 6.9%).

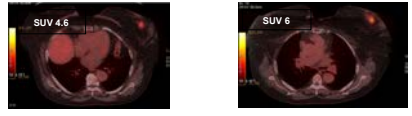

Figure 7. Patient B with increased SUV (SUV 4.6 to SUV 6) after single Bev dose

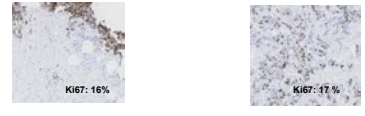

Figure 8. Patient B (Arm B) with relative Ki67 stability (16% and 17%).

CONCLUSION

ME344 results in significant Ki67 reduction compared to placebo in HERNEBC patients exposed to single-dose Bev. This effect may be greater in those patients with Bev induced hypoxia correction. Our data show that ME344 has significant biological activity in human breast tumors.

These clinical results are consistent with preclinical data suggesting that ME-344 can reverse resistance to anti-angiogenic therapy and warrant further studies to assess clinical efficacy of the combination.

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