**Background**

Our preclinical data show that one mechanism of acquired resistance to anti-angiogenic therapy involves hypoxia correction, measured by decreased SUV (\(\uparrow\) S.U.V) 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]

**Objectives**

1) The fraction of HERNEBC patients that show \(\uparrow\) S.U.V 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**

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 d8, d22 and tumor biopsy on day 0 and 28.

A 40 patient sample size was powered to detect a 30% relative Ki67 decrease of 16.6 vs. 2.3 in arms A and B (P=0.19).

**Results**

Both arms: 31% of patients experienced \(\uparrow\) S.U.V >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 \(\uparrow\) S.U.V >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.

**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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