ARETHA Trial: Safety Run-in Results of Eribulin + Evexomostat in Metastatic Triple-Negative Breast Cancer with Metabolic Dysfunction

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Background

- Insulin resistance & obesity are independent predictors of worse survival in metastatic triple negative breast cancer (metTNBC) and metabolic markers worsen during chemotherapy, including worsening insulin resistance characterized by increases in Homeostatic Model of Insulin Resistance (HOMA-IR).
- Methionine aminopeptidase 2 (MetAP2/p67) is an enzyme involved in angiogenesis and regulation of metabolic hormones that is overexpressed in breast cancer.
- In a phase I study of evexomostat, a MetAP2 inhibitor, 80% of patients with advanced solid tumors had stable disease and improvements in fasting insulin, adiponectin, and VEGF-C.

Methods

- This is a multicenter phase 2 randomized controlled trial of evexomostat + eribulin (NCT05570253) including a single-arm safety run-in phase. Key eligibility include metTNBC, baseline HbA1c ≥5.5% and/or BMI ≥30, and ≤2 prior treatment lines in the metastatic setting.
- The primary objective is to assess the efficacy of evexomostat on insulin resistance in combination with standard of care eribulin in metTNBC.
- In the safety run-in period, 15 patients received evexomostat 49 mg/m^2 Q2 weeks + eribulin 1.4 mg/m^2 on D1&8 of a 21-day cycle. The safety threshold was defined as ≥4/15 patients experiencing serious adverse events (SAEs) not resolving within 14 days. Patients were considered evaluable for safety if they received ≥1 dose of evexomostat.
- The primary endpoint of the randomized phase is change in HOMA-IR at 12 weeks. Secondary endpoints include objective response rate (ORR) and safety and tolerability. Change in HOMA-IR and other markers was analyzed using Wilcoxon signed rank test.
- Here, we report results from the safety run-in phase and exploratory biomarker changes.

Study Schema



Results

- Among the 15 patients in the safety run-in phase, 2/15 experienced SAEs, both of which were grade 3 anemia.
- The most common any-grade AE was anemia (9/15, 60%). AEs of grade ≥3 were reported in 11 patients; the most frequent grade ≥3 AE was decreased neutrophil count.
- Accordingly, the safety stopping rule was not triggered and the trial advanced to the randomization phase.

Table 1. Baseline characteristics of the safety run-in cohort.

Characteristic	N=15
Age, median (range)	59 (36-68)
De novo, number (%) Recurrent, number (%)	0 (0%) 15 (100%)
Number of prior lines in the metastatic setting, median (range)	1 (0-2)
BMI, median (range)	33.9 (26.1-37.4)
Hemoglobin A1c, median (range)	5.3 (4.4-7.0)

- Exploratory analyses from baseline to week 12 demonstrated significant changes in LDL cholesterol, adiponectin, leptin, resistin, VEGF-D, and sFRP-5 (p=0.016, 0.009, 0.021, 0.016, 0.027, and 0.012 respectively; see Table 2). HOMA-IR scores remained stable without significant change (p>0.9).
- Among 12 patients evaluable for efficacy, 2 had partial response and 7 had stable disease as best response (overall response rate 17%, clinical benefit rate 67%).

Table 2. Changes in exploratory biomarkers from baseline to 12 weeks in the study population.

Characteristic	Baseline (N=12), mean (range)	Week 12 (N=12), mean (range)	Difference[2]	*p-value*[1]
HOMA-IR[3]	5.0 (0.4-15.1)	4.1 (1.3-10.6)	-0.9	>0.9
Glucose[3], mg/dL	101 (74-168)	104 (89-137)	3.4	0.4
Insulin[3], mcU/mL	19 (2-56)	16 (5-40)	-2.9	0.6
HDL[3], mg/dL	47 (23-70)	43 (30-71)	-4.1	0.4
LDL[3], mg/dL	116 (62-153)	99 (44-137)	-16.6	**0.016**
Triglycerides[3], mg/dL	108 (76-159)	110 (68-160)	2.6	0.4
Adiponectin, ng/mL	8428 (2063-16989)	10882 (3474-18431)	2453	**0.009**
Leptin, pg/mL	35382 (1283-85050)	21614 (1112-102339)	-13768	**0.021**
Apelin, pg/mL	1042 (378-2072)	1348 (410-3910)	305	0.5
Resistin, ng/mL	69 (23-134)	173 (19-501)	104	**0.016**
FGF-21, pg/mL	510 (100-1299)	1527 (90-9808)	1016	0.2
C-reactive protein, ng/mL	61679 (6003-316052)	52459 (3483-224261)	-9220	0.7
IL-6, pg/mL	21 (4-64)	36 (5-151)	15	0.2
VEGF, pg/mL	190 (43-715)	188 (26-608)	-1.9	0.3
VEGF-C, pg/mL	1374 (556-4294)	880 (325-1956)	-495	0.06
VEGF-D, pg/mL	279 (136-556)	363 (182-501)	84	**0.027**
Cyclophilin A, ng/mL	536 (201-1095)	589 (271-1158)	53	0.6
bFGF, pg/mL	39 (9-136)	36 (6-79)	-3.1	0.6
sFRP-1[4], pg/mL	1.46 (0.91-2.34)	1.37 (0.78-1.90)	-0.1	0.6
sFRP-5, pg/mL	39205 (10666-82615)	54983 (12986-97705)	15779	**0.012**

Figure 1. Spaghetti plots of changes in exploratory biomarkers in the safety run-in cohort with a black smoothing curve overlayed.

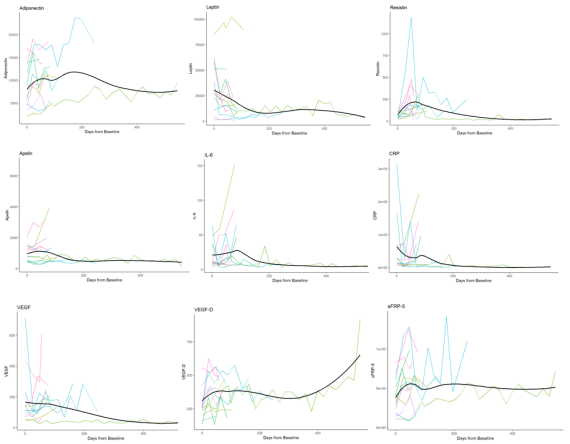
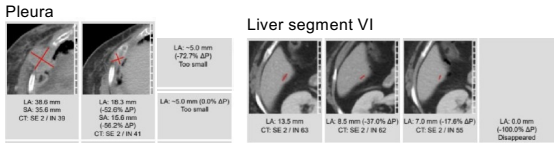


Figure 2. Select tumor response images from two study participants.



Conclusions

- The combination of evexomostat + eribulin was confirmed to be safe with a manageable adverse effect profile. The addition of evexomostat did not exacerbate eribulin toxicity.
- Preliminary biomarker results suggest that evexomostat prevented worsening of insulin resistance and improved other metabolic markers. These findings will be confirmed in the randomization phase.
- The trial advanced to the randomization phase, including a placebo-controlled arm with eribulin, and is currently enrolling patients.

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