Objectives AXL is a receptor tyrosine kinase that is activated by GAS6. Overexpression of AXL is correlated with the glycolytic phenotype in metastatic lung cancer. Cancer cells preferentially convert glucose to lactate via glycolysis which promotes growth and survival. It is unknown whether inhibition of AXL can prevent glycolysis in endometrial cancer causing cell death. The aim of this study was to determine whether AVB-500 can increase sensitivity to paclitaxel through inhibition of glycolysis.

Methods Cell viability was performed with high-grade endometrial, chemoresistant cell lines, ARK1 and PUC1. Cells were treated with paclitaxel (P) and with AVB-500+paclitaxel (AVB-500+P). Intrapertioneal ARK1 or PUC1 tumors were treated with vehicle, AVB-500, P, or AVB-500+P. Cell lysates were analyzed using the Jess system. A Seahorse Analyzer was used for glycolytic rate assays. Stable isotope tracing was used for in vivo metabolite abundance quantification.

Results We found that ARK1 and PUC1 cells had decreased viability when treated with AVB-500+P than when treated with P alone. ARK1 and PUC1 in vivo IP models had significantly fewer tumors and decreased tumor weight when treated with AVB-500+P compared to P alone. Treatment with AVB-500+P was found to decrease basal glycolysis in vitro through decreased AKT activation. Multiple glycolytic metabolites were decreased in the tumors of AVB-500+P compared to treatment with P alone.

Conclusions We demonstrate that the addition AVB-500 to paclitaxel improves endometrial cancer chemosensitivity. We show that this therapeutic combination decreases basal glycolysis through reduced PI3K/AKT signaling. This provides a metabolic mechanism for increasing uterine cancer sensitivity to chemotherapy.