Abstract #7946

GAS6-AXL inhibition by AVB-500 overcomes resistance to paclitaxel in endometrial cancer by decreasing tumor cell glycolysis

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Objective

- Chemotherapy is often ineffective in advanced stage and aggressive histologic subtypes of endometrial cancer.
- Overexpression of AXL has been found to be associated with therapeutic resistance, metastasis, and poor prognosis. The mechanism of how inhibition of AXL improves response to chemotherapy is still largely unknown.
- We aimed to determine whether treatment with AVB-500, a selective inhibitor of GAS6-AXL, improves endometrial cancer cell sensitivity to chemotherapy particularly through metabolic changes.

Methods

- Immunohistochemistry was performed on a tissue microarray containing specimens from patients with primary and metastatic uterine serous carcinoma (USC). Blind scoring was performed by two reviewers.
- Kaplan-Meier methods were used to generate time-to-event curves.
- Cell viability was performed with high-grade endometrial, chemo-resistant cell lines, ARK1 and PUC198. Cells were treated with paclitaxel and with AVB-500+paclitaxel.
- *In vivo*, intraperitoneal, ARK1 or PUC198 tumors were treated with vehicle, AVB-500, paclitaxel, or AVB-500+paclitaxel.
- Isotope tracing was used for in vivo metabolite abundance quantification.

Results

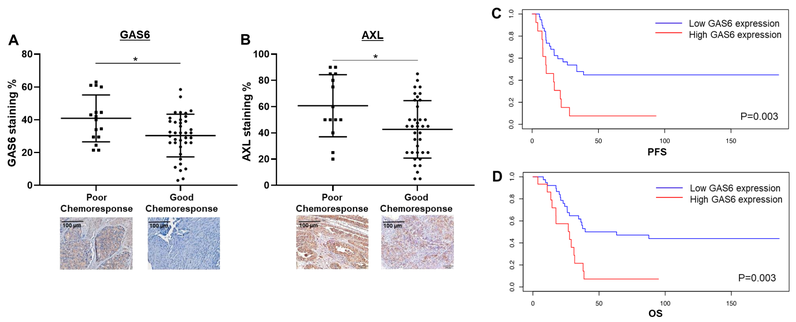

Figure 1. (A,B) USC with poor response to chemotherapy have higher GAS6 and AXL expression than USC with a good response to chemo by IHC. **(C, D)** Low GAS6 expression (<42%) is associated with improved PFS and OS compared to high GAS6 expression (≥ 42%).

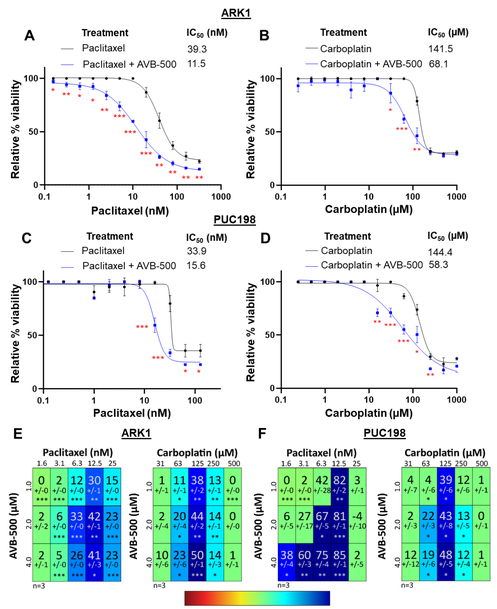

Figure 2. Results of XTT cell viability assays of ARK1 **(A,B)** and PUC198 **(C,D)** in increasing concentrations of Paclitaxel and Carboplatin with or without 1μM AVB-500. **(E,F)** Loewe synergism analysis of ARK1 and PUC198 treated with increasing doses of Paclitaxel and AVB-500 as well as Carboplatin and AVB-500.

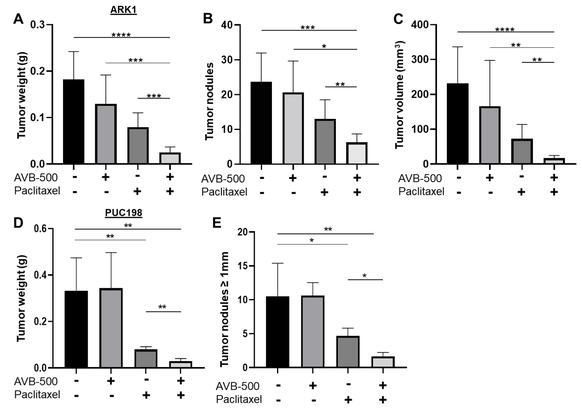

Figure 3 (left). GAS6/AXL inhibition improves chemotherapy response of ARK1 and PUC198 intra-peritoneal xenograft tumors in vivo. **(A)** ARK1 total tumor weight, **(B)** ARK1 tumor nodules, **(C)** ARK1 tumor volume. **(D)** PUC198 total tumor weight, **(E)** PUC 198 tumor nodules ≥ 1mm

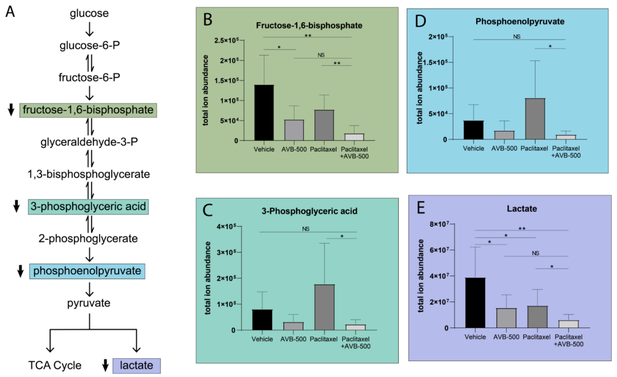

Figure 4 (right). *In vivo* ARK1 treatment with AVB-500 + paclitaxel decreases glycolytic metabolite abundance compared to treatment with paclitaxel alone. A) Summary of changes in glycolytic metabolite abundance with AVB-500 + paclitaxel treatment compared to paclitaxel alone. B) fructose-1,6-bisphosphate, C) 3-phosphoglyceric acid, D) phosphoenolpyruvate, and E) lactate.

Conclusions

- Our study provides strong pre-clinical rationale for combining AVB-500 with paclitaxel in aggressive endometrial cancer models.
- Given AXL's role in glucose homeostasis, one or more glycolytic intermediates may prove to be a useful biomarker to help predict sensitivity in patients who are eligible to receive this treatment combination.