

Therapeutic GAS6/AXL inhibition of tumor and stromal cells increases DNA damage and improves response to chemotherapy in ovarian cancer



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Objectives

- To evaluate serum and tissue GAS6 as a predictive biomarker of chemoresistance in ovarian cancer
- To determine if the inhibition of AXL through sequestration of GAS6 with AVB-S6-500 (AVB) can improve chemoresponse in both tumor and stromal cells in ovarian cancer.

Methods

- AVB supplied by Aravive Biologics
- HGSOC tumors collected pre- & post-neoadjuvant chemo
- AXL and GAS6 expression evaluated by immunohistochemistry and serum concentration
- In vitro viability and clonogenic assays performed on chemoresistant cells (OVCAR8, OVCAR5, COV62, POV71-hTERT) and stromal (CAF86) cells
- Mouse models used to evaluate the efficacy of chemo+AVB vs chemo alone
- Immunofluorescent assay targeting γ H2AX and RAD51 used to evaluate DNA damage response (DDR) in tumor and stromal cells

Results

Table 1. Patient/Disease Characteristics

	n= 40
Age (years)	63.6 \pm 10.17
Primary Site	
Ovary	31 (77.5)
Fallopian Tube	5 (12.5)
Peritoneum	4 (10.5)
FIGO Stage	
IIIB	1 (2.5)
IIIC	31 (77.5)
IV	8 (20.0)
Neoadjuvant Chemoresponse	
Responsive	26 (65.0)
Resistant	14 (35.0)
BRCA Mutation	
None	26 (65.0)
BRCA1	5 (12.5)
BRCA2	1 (2.6)

Results

Fig 1. Increased GAS6 is associated with neoadjuvant chemoresistance & decreased PFS

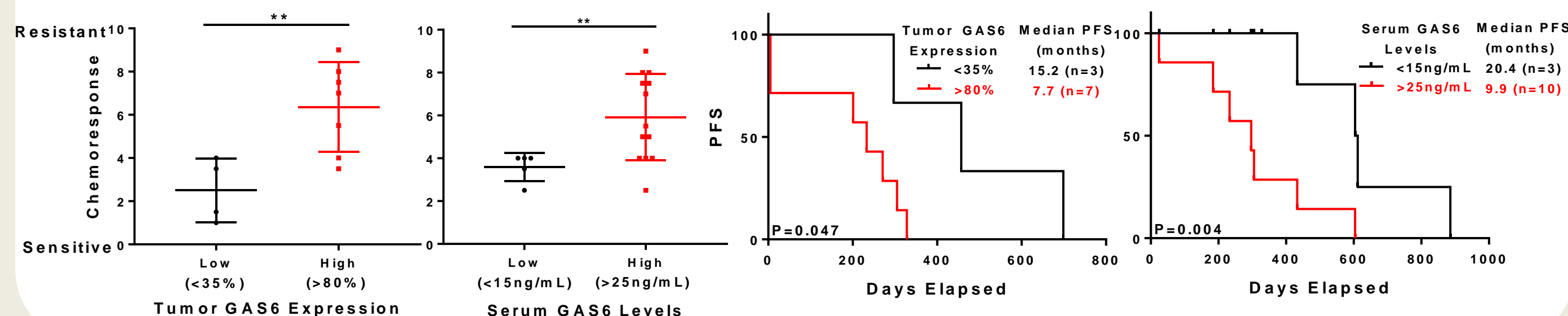


Fig 2. AVB + chemo results in decreased growth in tumor and stromal cells

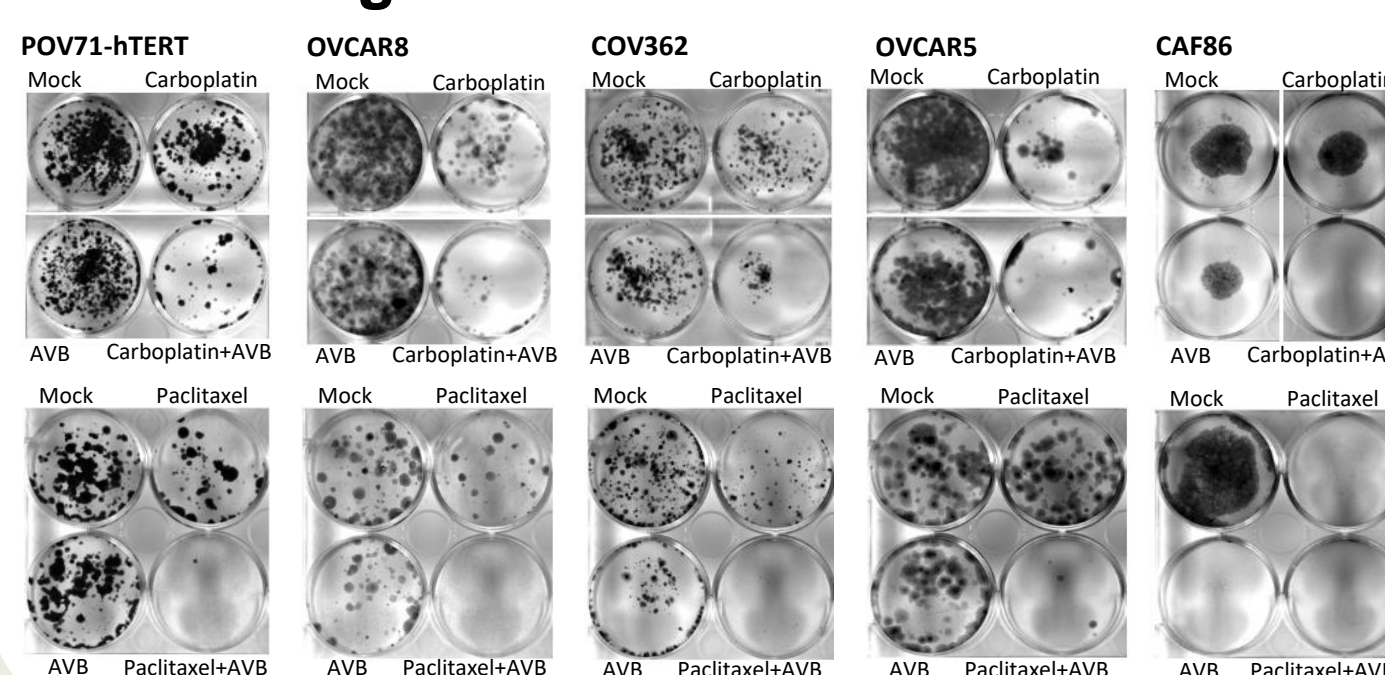


Fig 3. AVB + chemo decreases tumor burden

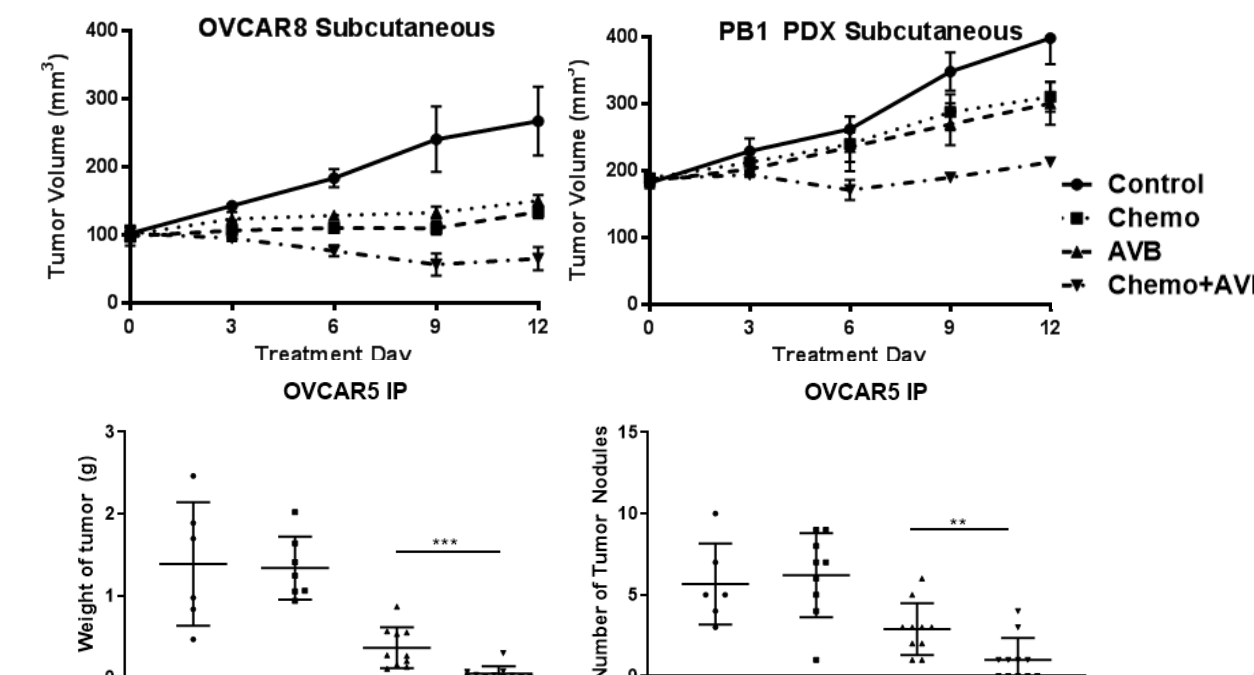
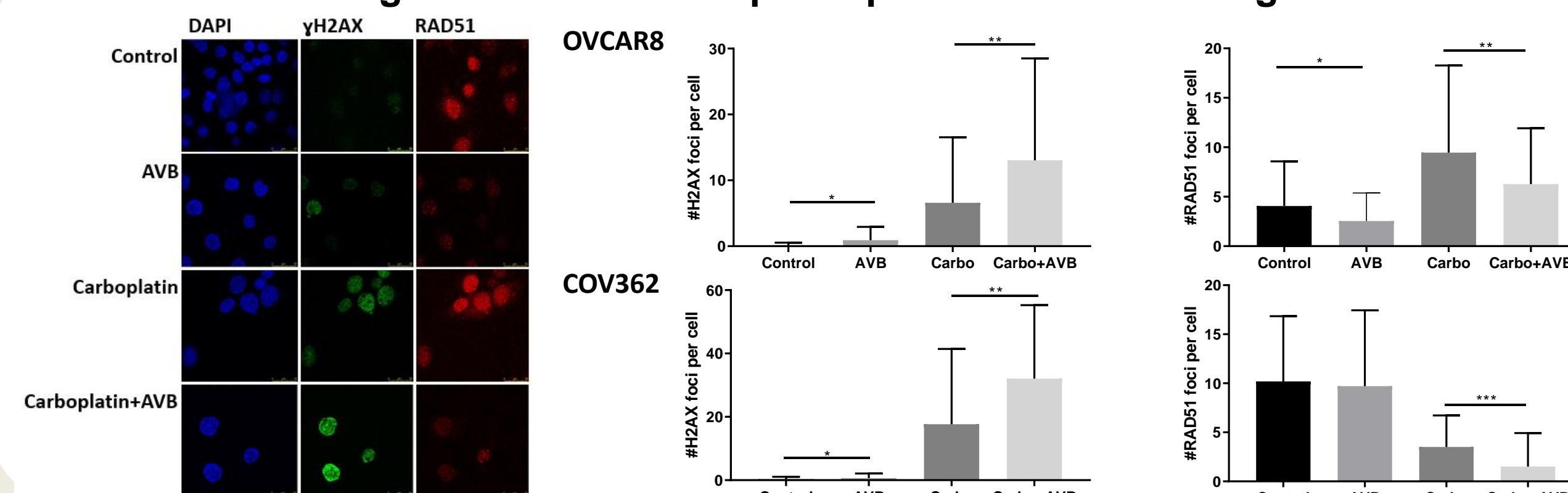


Figure 4. AVB + carboplatin promotes DNA damage



Conclusions

- GAS6 is associated with neoadjuvant chemoresponse in HGSOC patients
- Chemo+AVB decreases tumor and stromal cell viability, tumor burden, and an increase in DNA damage

Acknowledgements

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