Improving response to chemotherapy in HGSOC by inhibiting the GAS6/AXL pathway & inducing a homologous recombination (HR) deficiency

Mary M Mullen, MD,1 Elena Lomonosova, PhD,1 Michael Toboni, MD, MPH1, Hollie Noia, BS1, Daniel Wilke, BS1, Alyssa Oplt, BS1, Lei Guo, MS1, Lindsay M Kuroki MD,1 Andrea R Hagemann, MD, MSc1, Carolyn K McCourt, MD1, Premal H Thaker, MD, MS1, David G. Mutch, MD1, Matthew A Powell, MD1, Katherine C Fuh MD, PhD1
1Division of Gynecologic Oncology, Washington University, St. Louis, MO

Objectives

- To evaluate serum and tissue GAS6 as a predictive biomarker of chemoresistance in high grade serous ovarian cancer
- To determine if AXL inhibition through sequestration of GAS6 with AVB-S6-500 (AVB) can improve chemoresponse and affect DNA damage response

Methods

- AVB supplied by Aravive Biologics
- HGSOC tumors collected pre- & post-chemo
- AXL IHC, GAS6 IHC, and GAS6 serum levels evaluated
- In vitro and in vivo chemoresistant models used.
- Immunofluorescent assays targeting γH2AX, RAD51 for homologous recombination (HR), and 53BP1 for nonhomologous end joining (NHEJ) were performed
- Synergy assays analyzed using Combenefit software
- DNA fiber assays were performed

Results

Fig 2. AVB+Carboplatin and AVB+PARPi results in decreased growth in tumor cells

Fig 3. AVB+chemo and AVB+PARPi decreases tumor burden

Fig 4. AVB+carboplatin induces DNA damage with fewer RAD51 foci and more 53BP1 foci

Fig 5. AVB and Carboplatin are synergistic

Fig 6. AVB slows replication fork progression

Conclusions

- GAS6 is a potential biomarker predictive of poor response to neoadjuvant chemotherapy in HGSOC
- Inhibition of the GAS6/AXL pathway with AVB improves response to chemotherapy as well as PARPi
- Chemo+AVB increases DNA damage with fewer RAD51 foci, more 53BP1 foci, and slower replication forks

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