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ORAL ABSTRACT

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Novel LIFR-targeted combination therapy to enhance the utility of standard-of-care chemotherapy in treating ovarian cancer

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Objectives
Ovarian cancer (OCa) is the deadliest gynecologic malignancy, with nearly 90% of patients experiencing disease recurrence following standard treatments. Leukemia inhibitory factor (LIF) and its receptor (LIFR) are implicated in OCa progression, chemoresistance, and recurrence. The TCGA data indicated a negative correlation between the expression of LIFR and LIF and the survival of OCa. Elevated expressions of LIF and LIFR in recurrent OCa underscores the need for innovative therapeutic strategies targeting this pathway. In this study, we tested the hypothesis is that the progression of OCa to therapy resistance is dependent on LIF/LIFR signaling and that the standard of care interventions will be enhanced by the disruption of LIF/LIFR signaling with the small molecule inhibitor EC359.

Methods
The efficacy of the LIFR inhibitor EC359 in combination with paclitaxel and/or carboplatin was evaluated in established and chemotherapy resistant OCa cell lines, as well as in patient-derived xenograft (PDX) models. Cell viability, colony formation, and apoptosis were assessed using MTT assays, colony formation assays, and apoptosis assays. Mechanistic studies were conducted using Western blot analysis to elucidate the pathways modulated by the combination therapy.

Results
Utilizing long term culture of OCa cells with increasing concentrations of chemotherapy, we have successfully established several chemotherapy-resistant OCa models cells. EC359 significantly enhanced the anti-tumor efficacy of chemotherapy in reducing cell viability and suppressing colony formation in clonogenicity assays. Further, EC359 treatment enhanced apoptosis in OCa cells by promoting ferroptosis pathway. Remarkably, the combination therapy demonstrated increased effectiveness of chemotherapy in paclitaxel-resistant and carboplatin resistant OCa cells, underscoring its potential to overcome chemotherapy resistance. These findings suggest EC359 as a potent combination agent with chemotherapy for improved therapeutic outcomes in OCa. Ongoing investigations are exploring the therapeutic potential of EC359 in PDX models and its efficacy as a maintenance therapy for primary and resistant OCa.

Conclusions
This study provides convincing preclinical evidence supporting LIFR inhibition as a promising strategy to enhance the efficacy of chemotherapy in OCa, addressing critical challenges in chemoresistance and recurrence.