

Poster 26: Development of patient derived ovarian cancer organoids with native immune cells**Presenting Author:** Leah Wormack, MD, MS, University of California San Francisco

Topic

Endometrial

Objectives

Immunotherapy in uterine cancer has become standard of care in combination with chemotherapy in first-line treatment or with lenvatinib in recurrent treatment. Given the prevalence of immunotherapy, there is a need to develop non-immunotherapy options particularly based on high tumor expression. The overexpression of the receptor tyrosine kinase AXL in uterine serous carcinoma (USC) is known to be associated with therapeutic resistance, tumor growth, metastasis, angiogenesis and poor prognosis. Here, we aimed to determine whether zanzalintinib, a novel multi-receptor tyrosine kinase and VEGF2 inhibitor, enhances the sensitivity of endometrial cancer cells to paclitaxel through AXL inhibition.

Methods

We used uterine serous and high grade endometrioid endometrial adenocarcinoma cells derived from the ascites of a patient with platinum-refractory disease: ARK1 and PUC198, respectively. Cells were treated with vehicle, zanzalintinib (Z), paclitaxel (P), or their combination (Z+P) for cell viability, synergy assays, and its conditioned media was used for human umbilical vein endothelial cells (HUVECs) migration assay. For in vivo tumor xenograft models, ARK1 cells were injected, allowing tumors to establish before initiating treatment. P was administered weekly via intraperitoneal injection, while Z was given daily by oral gavage for fifteen days (Fig. 1e). We will measure tumor weight, tumor volume, and the number of tumor nodules < 1 mm and >1 mm. A 2-way ANOVA analysis was conducted using GraphPad Prism 10, and Loewe synergism analysis using Combenefit.

Results

Viability assays using increasing concentrations of P alone or in combination with Z, demonstrated that Z enhances the sensitivity of both ARK1 (IC₅₀ of P: 0.84 vs P+ Z: 0.056nM, $p < 0.0001$) and PUC198 (IC₅₀ of P: 1.25 vs P+Z: 0.29nM, $p < 0.0001$) (Fig. 1a, 1b). Z synergizes with P at several doses in ARK1 cells ($p = 0.0001$). (Fig. 1c). Migration assay showed that Z disrupts HUVEC migration in the process of angiogenesis ($p < 0.0001$) (Fig. 1d).

Conclusions

AXL inhibition enhanced the therapeutic efficacy of paclitaxel in aggressive, uterine cancer cells. These results facilitated the initiation of in vivo experiments which are in process. Targeting the AXL receptor with zanzalintinib shows promise as a combination therapy with paclitaxel, supporting further evaluation in clinical studies.

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