Methods Medroxyprogesterone acetate (MPA)-resistant endometrial cancer cells were established through continuous treatment of endometrial cancer cells (RL95–2 and Ishikawa) with gradually escalating doses of MPA. RNA-seq was performed on both original and MPA-resistant EC cells to evaluate DEGs. Gene-set enrichment analysis (GSEA) was also performed to find biologic processes or pathways in relation to MPA resistance. Further validation was undertaken by real-time polymerase chain reaction (RT-PCR) on selected genes.

Results The profiles of DEGs were substantially different between RL95–2 and Ishikawa cells. In MPA-resistant RL95–2 cells, the enriched hallmark gene sets include KRAS signaling down, myogenesis, and late estrogen response. In MPA-resistant Ishikawa, hallmark gene sets of TNFα signaling via NFκB, hypoxia, and late estrogen response were significantly enriched. Common hallmark gene sets in both MPA-resistant RL95–2 and Ishikawa include late estrogen response and myogenesis. In addition, common gene ontology biological processes include cellular response to corticosteroid stimulus and epithelial cell differentiation.

Conclusions We identified DEGs and several pathways enriched in MPA-resistant endometrial cancer cells as potential therapeutic targets of progesterone resistance, which need further validation.

Objectives We developed endometrial cancer organoids to establish reliable pre-clinical models, and performed genomic characterization of the established organoids to assess whether they maintain the mutational landscapes of the original tumors from which the organoids originated.

Methods Endometrial cancer organoids were cultured using endometrial cancer surgical specimens. After establishment of the organoids, we performed whole genome sequencing (WGS) on original tumor tissues and the paired organoids to identify driver mutations, mutational signatures, and structural variations. We also classified the organoids based on the TCGA molecular classifications.

Results Endometrial cancer organoids were successfully established in 7 of 34 cases (20%) and 11 cases (32%) are ongoing. Among them, we performed WGS analysis on 5 pairs of original endometrial cancer tissue and organoid. Although numerous passenger mutations were accumulated during organoid culture, all the established organoids retained the driver mutations of the tumors and showed similar mutational signatures. The organoids comprised the 4 TCGA molecular classifications, including 1 POLE ultramutated, 1 MSI (MSH6 mutation), 1 TP53 mutated, and 2 copy-number low groups.

Conclusions We developed endometrial cancer organoids representing the 4 TCGA molecular classifications, which will provide useful experimental models for translational research.
EVALUATION OF NAPI2B EXPRESSION IN A WELL IN VITRO AND IN VIVO EFFICACY OF A54

Methods We systematically searched the MEDLINE, Cochrane Central Register of Controlled Trials, and Embase databases from inception until February 2022. We included studies assessing MMRd using immunohistochemistry (IHC), MSI, and/or germline LS by next-generation sequencing (NGS).

Results A total of 45 studies were included. The incidence for MMRd was 9% (95% CI 6–14%), MSI-high 12% (12–15%), and LS 5% (2–14%) in all epithelial ovarian cancer respectively. Hypermethylation was identified in 77% (95% CI 63–87%) of those with MLH1 deficiency. MMR IHC for LS diagnosis had 92% sensitivity, 77% specificity, 58% positive predictive value, and 98% negative predictive value, whereas MSI performance characteristics were 97%, 91%, 25% and 77% respectively. Synchronous ovarian and endometrial cancers had highest rates of MMRd (26%) and MSI-H (34%). Serous histology had lowest prevalence of 1% for MMRd and 7% for MSI. The highest prevalence of germline pathogenic variants in MMR genes (LS) were found in those with synchronous endometrial-ovarian cancer (53%) as well as clear cell ovarian cancer (25%) with the lowest prevalence in serous ovarian (1%) cancer.

Conclusions MMR deficiency, MSI, and LS are frequent in ovarian cancer, in particular in non-serous histological subtypes.

EP014/#408 EVALUATION OF NAPI2B EXPRESSION IN A WELL ANNOTATED LONGITUDINAL TISSUE SERIES OF OVARIAN SEROUS CARCINOMAS

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Objectives Upifitimab rilsodotin (UpRi) is a first-in-class NaPi2b-targeting ADC with a novel scaffold-linker-payload that enables high drug-to-antibody ratio and controlled bystander effect. NaPi2b is a sodium-dependent phosphate transporter broadly expressed in high-grade serous epithelial ovarian, fallopian tube and primary peritoneal cancers. Emerging UpRi data suggests a relationship between patients with higher expression of NaPi2b, the SLC34a2 gene product, and clinical activity, with a generally well tolerated safety profile (Richardson et al., SGO 2022). However, change in NaPi2b expression in ovarian cancer over the course of disease has not been well defined.

Methods 11 individuals diagnosed with high grade serous ovarian cancer had tumor biopsies evaluated for NaPi2b expression at more than one time point. These included matched samples taken from debulking procedures/post-chemotherapy (n=5); pretreatment biopsy/post neoadjuvant (n=4); pretreatment/post neoadjuvant/at progression (n=2). Tumor samples were evaluated by immunohistochemistry (IHC) using a rabbit antibody to detect NaPi2b expression, and a tumor proportion score (TPS) was calculated. High NaPi2b expression was defined as TPS ≥75%.

Results 7/11 (64%) individuals had an initial sample with high NaPi2b expression. 6 of these 7 subjects (86%) remained NaPi2b high through their matched samples; 8/11 (73%) of individuals maintained their NaPi2b status through matched samples. Of the three individuals who had a change in expression status, two showed increased NaPi2b expression above TPS ≥75% following treatment; one showed decreased expression.

Conclusions In this cohort, NaPi2b expression status was maintained over the treatment course in the majority of evaluated individuals reinforcing that this marker remains consistent throughout the disease course.

EP015/#546 IN VITRO AND IN VIVO EFFICACY OF TRASTUZUMAB DERUXTECAN (T-DXd) IN EPITHELIAL OVARIAN CANCER WITH HER2/NEU OVEREXPRESS

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Objectives Epithelial ovarian cancer (EOC) has high recurrence rates, and treatment options are limited. T-DXd is a novel anti-HER2 antibody linked to the topoisomerase 1 inhibitor. This study aimed to determine the in vitro and in vivo efficacy of T-DXd in EOC.

Methods HER2 expression was analyzed with flow cytometry in primary high grade serous (KRCH31 and OVA3) and clear cell (OVA10 and OVA12) EOC cell lines. Cell lines were treated with T-DXd or Control antibody drug conjugate (CTL ADC). The IC50, apoptosis, bystander antitumor assays were performed. KRCH31 cells were injected into the SCID mice and animals were treated with PBS, CTL ADC or T-DXd.

Results KRCH31 and OVA10 EOC cell lines expressed HER2 by flow cytometry, OVA3 and OVA12 had negligible expression. T-DXd mean IC50 were 0.014 μg/ml and 0.017 μg/ml for KRCH31 and OVA10 cell lines, but no effect was observed in the OVA3 and OVA12 cell lines. Apoptotic cells increased to 65% and 60% in the KRCH31 and OVA10 cell lines after T-DXd. T-DXd did not show cytotoxicity on ARK4-GFP cells; however, substantial cytotoxicity was observed due to bystander antitumor activity when cocultured with KRCH31 and OVA10 cell lines (live ARK4-GFP cells 55% and 50%). Day 8 mean tumor volumes were 0.86, 0.81 and 0.43 cm3 in PBS, CTL ADC and T-DXd treated mice, respectively (p<0.001). Median overall survival was 15, 16.5 days and not reached in PBS, CTL ADC, T-DXd treated mice, respectively (p=0.0002).

Conclusions T-DXd showed in vitro and in vivo preclinical efficacy in HER2 overexpressing EOC. Further clinical trials are warranted.