

EP318/#571

CIRCULATING TUMOR DNA-BASED MOLECULAR RESIDUAL DISEASE DETECTION FOR THE MONITORING OF HIGH-GRADE SEROUS OVARIAN CANCER

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Introduction Standard treatment for epithelial ovarian cancer involves surgery and platinum-based chemotherapy, but recurrence or disease progression still occurs in over 70% of patients. CtDNA-based MRD testing may be a potential biomarker for disease surveillance.

Methods Primary ovarian cancer with stage II-IV of HGOC patients was recruited in this study. Tumor sample was collected for whole exome sequencing (300x). Proprietary algorithm was used to select 30–40 single nucleotide variants for each patient. Blood was collected and MRD was detected by multiplex PCR-based sequencing (Orimiracle S™, 100,000x) using the customized panel (NCT05027828).

Results As of the summary submission, we have completed WES sequencing for 20 patients, of which 11 carry HRR pathway mutations. Among the 13 patients who underwent pre- and post-operative ctDNA monitoring, 11 were ctDNA positive before surgery. We found a significant decrease in ctDNA variant allele frequency (VAF) before and after surgery (before: median VAF 0.95%, after: median VAF 0.04%, $p=0.0054$). Additionally, Pearson correlation analysis showed a positive correlation between pre-treatment ctDNA VAF and CA125 levels ($R=0.685$, $p=0.017$). The median VAF of ctDNA in stage IV patients was higher than that in stage I-III patients (2.14% vs. 0.56%, $p=0.69$). All the 13 patients were negative for MRD after completion of chemotherapy. Follow-up is ongoing.

Conclusion/Implications MRD testing is feasible for monitoring epithelial ovarian cancer patients, with over 80% of HGOC patients being MRD-positive at baseline. The MRD status was generally consistent with the clinical status of the patients. The performance of MRD in predicting recurrence of HGOC is still under investigation.

EP319/#1479

OVULATION RELEASES FIBRONECTIN TO PROMOTE PERITONEAL SEEDING OF PRECANCEROUS AND CANCEROUS HIGH-GRADE SEROUS CARCINOMA CELLS ORIGINATING FROM THE FALLOPIAN TUBE EPITHELIUM THROUGH INTEGRIN B1 SIGNALING

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Introduction Previously, we have discovered ovulatory follicular fluid (FF) carries transforming signals to promote full-course carcinogenesis of fallopian tube epithelium (FTE), the origin of ovarian high-grade serous carcinoma[<https://pubmed.ncbi.nlm.nih.gov/33530497/>]. This study investigated FF-fibronectin(FN) in peritoneal seeding of transforming FTE cells.

Methods Partially and fully transformed FTE cells were treated with FF, paired peritoneal fluid (PF), or recombinant FN. Transformation phenotypes were evaluated in FTE cells with/without ITGB1 knock-down. Peritoneal seeding was evaluated by IVIS after i.p. xenograft together with FF in NSG mice.

Results Cell migration-promoting activity was observed after treating with >100-KDa FF or FN protein which was three times higher in FF than in the paired PF. Compared to the full-transformation activity of FF, FN specifically promoted cell proliferation, migration, or invasion. ITGB1-KD caused lower cell proliferation, peritoneal attachment, and AIG. It also reduced the migration-and proliferation-promoting effects of FF and FN. Compared to FF treatment which generally increased p-FAK, p-SRC, p-ERK, and p-AKT, FN treatment increased p-FAK and p-SRC. Looking into the changes in FF- and FN-treated cells, ITGB1-KD resulted in a decrease of p-ERK, p-SRC, or p-FAK and an increase of p-AKT. In the mouse i.p. xenograft tumorigenesis model, depletion of FN from FF showed in a marked reduction of intraperitoneal seedings at week 7, and ITGB1-KD resulted in a decrease at day 12.

Conclusion/Implications The results disclose proliferation-, migration- and invasion-promoting activities of FN abundantly present in ovulatory FF, which promotes peritoneal seedings of transformed FTE cells. Integrin β 1 primarily mediates this activity.

EP321/#854

LNCRNA PART1 AUGMENTS PARPI SENSITIVITY IN OVARIAN CANCER

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Introduction The inhibitor of PARP (PARPi) is one of the most concerned drugs recently. Since both PARPi and platinum act through DNA damage, we intend to find targets for overcoming PARPi resistance through the differences of gene expression between platinum-resistant and platinum-sensitive ovarian patients in TCGA.

Methods We divided ovarian cancer patients in TCGA into platinum-sensitive and platinum-resistant groups and conducted differential gene analysis on them. MTT assay was used to draw the drug concentration tolerance curve of ovarian cancer cells. The effect of PART1 on cell growth was detected by EdU and CCK8 assays. Western blot was used to detect the effect of PART1 on DNA damage repair pathway. The effect of PART1 on PARPi sensitivity in vivo was verified by subcutaneous tumor formation in nude mice. RNA-seq was conducted to analyse the changes of gene and pathways.

Results LncRNA PART1 was significantly down-regulated in platinum-resistant patients in TCGA. CCK8 assays indicated knockdown of PART1 could confer resistance of cisplatin and olaparib on ovarian cancer cells. Cell

proliferation was restricted after PART1 knockdown. Western blot experiments showed that PART1 played a role by inactivating the DNA damage response pathway. Subcutaneous tumor formation experiments verified that PART1 can enhance the sensitivity of cells to olaparib and promote proliferation in vivo. The RNA-seq results showed that DNA damage response pathway was significantly activated by PART1 knockdown.

Conclusion/Implications LncRNA PART1 augments PARPi sensitivity in ovarian cancer by inactivating DNA damage response pathway.

EP322/#101

COL4A6 PROMOTES TUMOR PROGRESSION AND PREDICTS POOR CLINICAL OUTCOME IN OVARIAN CANCER

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Introduction Biomarkers that predict disease progression might assist the development of better therapeutic strategies for aggressive cancers, such as ovarian cancer. Here, we investigated the role of collagen type IV alpha 6 (COL4A6) in cell invasiveness and tumor formation and the prognostic impact of COL4A6 expression in ovarian cancer.

Methods A2780CP70 and OVCAR8 cells transfected with a small interference RNA of COL4A6 (shCOL4A6) and A2780 and OVCAR4 cells transfected with a COL4A6 expression plasmid. Site-directed mutagenesis assay, luciferase assay, chromatin immunoprecipitation assay, invasion assay and xenograft animal study were performed in this study. COL4A6 mRNA expression levels of 160 ovarian tumors were determined by real-time RT-PCR.

Results Small interference RNA-mediated specific reduction in COL4A6 protein levels suppressed the invasive ability and oncogenic potential of ovarian cancer cells and decreased tumor formation. A combination of experimental approaches, including real-time RT-PCR, casein zymography and chromatin immunoprecipitation assays, showed that COL4A6 knockdown attenuated discoidin domain receptors/p-DDR1 expression and suppressed binding of E2F to its putative DDR1 promoter binding site, suggesting that the E2F-DDR1 axis is upregulated by COL4A6. Pharmacological inhibition of DDR1 abrogated the COL4A6-dependent cell invasiveness. Analysis of 160 ovarian cancer patients indicated that high COL4A6 mRNA levels are associated with advanced disease stage. The 5-year recurrence-free and overall survival rates were significantly lower ($p=0.001$ and $p=0.001$, respectively) among patients with high expression levels of tissue COL4A6 mRNA compared to those with low expression.

Conclusion/Implications COL4A6 may promote tumor aggressiveness via the E2F/DDR1 axis and that COL4A6 expression can predict clinical outcome in ovarian cancer patients.

EP323/#463

EFFICACY AND SAFETY OF MIRVETUXIMAB SORAVTANSINE IN CHINESE PATIENTS WITH PLATINUM-RESISTANT OVARIAN CANCER WITH HIGH FOLATE RECEPTOR ALPHA EXPRESSION: RESULTS FROM IMGN853-301 (SORAYA CHINA) STUDY

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Introduction Current therapies for platinum-resistant ovarian cancer (PROC) are primarily non-platinum chemotherapies with limited response and an important unmet clinical need. Mirvetuximab soravtansine (MIRV) is a folate receptor α (FR α)-directed antibody-drug conjugate which had been approved by FDA in Nov-2022 for FR α positive PROC. IMGN853-301 is a single-arm registration study to evaluate the efficacy and safety of MIRV in Chinese PROC patients.

Methods 35 PROC patients were enrolled with 51% of patients with three lines of prior therapy. All patients received prior bevacizumab; 77% of patients received a prior PARP inhibitor. Eligible patients had FR α -high tumor according to PS2+ methodology from Ventana FOLR1 assay. All patients received single-agent MIRV at 6 mg/kg using adjusted ideal body weight on Day 1 Q3W until progressive disease or intolerable toxicity.

Results As of the data cutoff of 25-April-2023, median follow-up was 4.5 months. In all of 35 evaluable patients by investigator per RECIST 1.1, confirmed and unconfirmed ORR was 31.4% (95% CI: 16.85%, 49.29%), and 3-month PFS rate was estimated as 73.5% (95% CI: 55.30%, 85.25%). The most common ($\geq 20\%$) treatment-related adverse events (all grade and grade 3-4) were Keratopathy (57.1% and 14.3%), Aspartate aminotransferase increased (45.7% and 0%), White blood cell count decreased (37.1% and 2.9%), Alanine aminotransferase increased (37.1% and 0%), Vision blurred (37.1% and 17.1%), Platelet count decreased (37.1% and 5.7%), Neutrophil count decreased (37.1% and 5.7%), and Xerophthalmia (20.0% and 14.3%).

Conclusion/Implications MIRV demonstrated consistent clinically meaningful antitumor activity and favorable tolerability and safety in Chinese patients with FR α -high PROC.