2022-RA-924-ESGO DISTRIBUTION OF BRCA1/2 MUTATIONS AND CLINICAL OUTCOMES IN EPITHELIAL OVARIAN, PERITONEAL, FALLOPIAN TUBE CANCER: BASED ON MULTICENTER REAL-WORLD DATA

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Introduction/Background This study aimed to review multicenter real-world data for BRCA1/2 gene test and clinical outcomes in epithelial ovarian, peritoneal, fallopian tube cancer.
Methodology We reviewed the patients who underwent primary surgery and adjuvant treatment between January 2009 and December 2021 in Seoul, Yeouido, and Incheon St. Mary's Hospital, College of Medicine, the Catholic University of Korea. The following data were retrospectively obtained for analysis: clinical factors such as patient age, levels of tumor markers (CA 125, CA 19–9); stage (International Federation of Gynecology and Obstetrics) at diagnosis, histopathology, and the results of BRCA1/2 gene test.
Results In total, 652 patients were evaluated and 237 patients (36.3%) underwent BRCA1/2 gene test. Among all patients who received BRCA1/2 gene test, BRAC1/2 mutations were noted in 62 patients (26.2%). In BRCA1/2 mutation group, 53 had high-grade serous ovarian cancer (HGSOC), and 9 had non-HGSOC consisting of endometrioid carcinoma (n=5), clear cell carcinoma (n=2), and mixed carcinoma (n=2). The portion of HGSOC in BRCA1/2 mutation group was significant higher than that in BRCA1/2 wild-type group (85.8% versus 61.0%, p<0.001). Progression free survival (PFS) of BRCA1/2 mutation group was significantly worse than that of BRCA1/2 wild-type group (30.4 versus 36.6 month, p=0.003). Overall survival of mutation group was better than that of wild-type group without significant differences (64.4 versus 48.8 month, p=0.807). The 26 patients in BRCA1/2 mutation group were treated by poly ADP ribose polymerase (PARP) inhibitor for maintenance therapy.
Conclusion BRCA1/2 mutations were reported in epithelial ovarian, peritoneal, and fallopian tube cancer. In contrast to other studies that reported better PFS in BRCA1/2 mutation group than in BRCA1/2 wild-type group, BRCA1/2 mutation group showed worse PFS in this study. Further studies are needed on the effect of the BRCA1/2 mutation on prognosis.

2022-RA-928-ESGO REPROGRAMMING OF PATIENT-DERIVED HGSOC ORGANOIDS FOLLOWING CARBOPLATIN TREATMENT LINKS STEMNESS POTENTIAL AND MECHANISMS OF RESISTANCE

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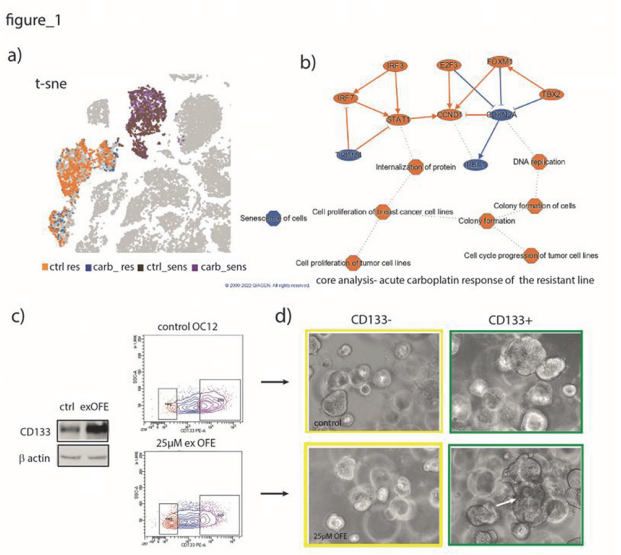
Introduction/Background Targeted therapeutics, including bevacizumab and PARPi, gained traction for the maintenance treatment of high-grade serous ovarian cancer (HGSOC) following platinum-based chemotherapy. However, there are still limited methods to predict patient-specific responses to chemotherapy. In this aim, we investigate cellular changes elicited by the carboplatin in vitro in HGSOC patient-derived organoids (PDOs). Furthermore, in the context of drug response, we explore the stemness potential and putative mechanisms of the emergence of resistance to carboplatin.



Abstract 2022-RA-928-ESGO Figure 1 Carboplatin treatment triggers acute DNA damage responses and causes change in stemness regulation in patient derived organoids
a) t-sne plot (Loupe browser) ilustrates patient specific single cell clustering from sensitive and resistant organoid lines (as determined by clinical disease progression) that remains intact also in carboplated treated samples Core analysis by ingenuity IPA software of the platinum resistant line 48 h post tretment reveals activation of DNA replication changes in cell cycle control and downregulation of protective mechanisms (senescence) c) WB and FACS plots showing upregulation of stemness marker CD133 in the long term organoid culture of the organoids preexposed ta carboplatin d) Subsorting of the CD133+/- populations confirms organoid forming capacity is defined by CD133+ marker expression and indicates morphological changes in progeny derived from platinum pre treated cultures (arrow=

Methodology Phenotypically and genotypically validated PDOs from primary tumor deposits of HGSOC were used to study biological changes after carboplatin exposure by combining single-cell RNA sequencing, and functional *in vitro* assays. Organoid forming efficiency assay (OFE) was developed to quantify the growth capacity of PDOs following 48 hours of carboplatin and analyse the long-term expansion of platinum pretreated lines. Changes in organoid cellular architecture were investigated by FACS sorting of progenitor populations, confocal imaging, and qPCR of key developmental regulators.
Results Overall, 4 organoid lines with known clinical response to carboplatin was investigated by sc RNA sequencing providing insight into tumor heterogeneity and key cellular pathways activated in PDOs resistant to carboplatin. The expression profile of the acute response (48 h) revealed candidate pathways behind incomplete drug response and tumor survival,

among which activation of DNA replication and changes in cell cycle regulation were notable. Organoids which retained regeneration capacity after carboplatin exposure, showed a sustained shift in expression of stemness associated surface marker CD133+ in the subsequent passages as showed by fluorescence-activated cell sorting and Western blot

Conclusion We hereby propose OFE assay as a novel functional readout for carboplatin sensitivity. Furthermore, expression profile changes in organoids during acute response to carboplatin provide insights into specific signaling hallmarks that are associated with resistance to carboplatin. and could help identify the cellular mechanism behind the process.

2022-RA-935-ESGO DEVELOPMENT OF AN ACADEMIC GENOMIC INSTABILITY SCORE FOR OVARIAN CANCERS

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Introduction/Background High-grade serous ovarian cancers with deficiency of homologous recombination DNA repair (HRD) are sensitive to the combination of bevacizumab and olaparib as maintenance therapy in PAOLA-1 trial (NCT02477644). HRD status is determined by mutational scars within tumor genome. Here, we developed a new method called GIScar (Genomic Instability Scar) suitable with the most of the academic molecular biology laboratory constraints.

Methodology We used sequencing data from a limited panel of 127 genes including genes involved in homologous recombination to detect mutational scars, *i.e.* chromosomic breaks, genomic deletion/duplication and allelic imbalance. The score was trained among 146 prospective samples from ovarian tumors with HRD status previously defined by Myriad Genetics® (MG). For clinical validation, we sequenced 469 DNA tumor samples from the PAOLA-1 trial and correlated GIScar status with progression free survival (PFS).

Results On the 146 prospective samples, GIScar reached an accuracy of 92.46% compared to MG HRD status, with a sensitivity of 95.38% and specificity of 90.12%. On the 469 PAOLA-1 samples, patients with GIScar HRD positive (including tBRCAm) tumors showed a significant prolonged PFS in olaparib vs placebo arm (median PFS: 38.7 vs 20.1 months, hazard ratio (HR): 0.470 [95% CI, 0.334–0.661] as well those with GIScar HRD positive tBRCAwt tumors (23.9 vs 16.4 months, HR: 0.529 [95% CI, 0.323–0.866]). Patients with negative GIScar HRD tumors did not benefit from addition olaparib (median PFS: 16.6 vs 16.5 months, HR: 1.045 [95% CI 0.757–1.441]). Furthermore, our approach reduced by 90% (4 vs 47 tumors) the number of inconclusive status compared to MG.

Conclusion GIScar demonstrated high accuracy with MG data with less inconclusive results and identifies patients who could best benefit from maintenance olaparib added to bevacizumab. GIScar test performances allow the deployment of this test in academic molecular biology laboratories.

2022-RA-937-ESGO RUCAPARIB MAINTENANCE AFTER BEVACIZUMAB MAINTENANCE FOLLOWING CARBOPLATIN BASED CHEMOTHERAPY IN PRIMARY OVARIAN CANCER

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Introduction/Background Ovarian cancer (OC) is the fifth most common cause of death from cancer in women in Europe, with most patients being diagnosed in advanced stages. The most common histological subtype is high grade serous OC, which is characterised by deficiency in homologous recombination. The current standard therapy for advanced OC patients is debulking surgery, followed by platinum based chemotherapy and bevacizumab (bev), followed by maintenance therapy with bev or monotherapy with PARP inhibitors (PARPi). The anticancer effects of PARPi seem to be increased by the addition of antiangiogenic drugs. Preclinical data showed increased HRD in tumours pre-treated with bev, and clinical trials showed a benefit of the combination of antiangiogenic drugs and PARPi vs. PARPi alone. Hence, in this placebo-controlled study we will evaluate rucaparib maintenance following bevacizumab maintenance for the treatment of advanced primary high grade BRCAwt OC (centrally tested by NGS analysis).

Methodology This study will randomise 190 patients with histologically confirmed advanced (FIGO stage IIIA- IV) high grade serous or high grade endometrioid OC, fallopian tube cancer, primary peritoneal cancer or clear cell carcinoma of the ovary at the ration of 2:1 to receive either rucaparib 600 mg BID or placebo as maintenance therapy following first line chemotherapy with 6 cycles of Carboplatin/Paclitaxel and at least 12 months of bevacizumab. Subsequent maintenance therapy with rucaparib will continue for 24 months or until disease progression, unacceptable toxicity, or withdrawal.