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.