

Results Using the HGSC-1LTR strategy we have identified a molecular signature (TKT, LAMC1 and FUCO) that combined with readily available clinical data (patients' age, menopausal status, serum CA125 levels, and treatment approach) is able to predict patient response to first-line treatment with an AUC: 0.82 (95% CI 0.72 – 0.92).

Conclusion We have established a new strategy that combines molecular and clinical parameters to predict the response to first-line treatment in HGSC patients (HGSC-1LTR). This strategy can allow optimization of therapeutic decision making and individualize HGSC patients' care.

2022-RA-1574-ESGO APPLICATION OF EX-VIVO TUMOUR EXPLANT CULTURES TO PREDICT PLATINUM RESPONSES IN HIGH GRADE SEROUS OVARIAN CANCERS WITHIN A CLINICALLY RELEVANT TIMELINE

Jennifer Ploski, Katherine Nixon, Paula Cunnea, Christina Fotopoulou. *Department of Surgery and Cancer, Imperial College London, London, UK*

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Introduction/Background High grade serous ovarian cancer (HGSOC) management is based on maximal effort cytoreductive surgery and platinum chemotherapy. However, partly due to the high degree of heterogeneity in HGSOC, most patients will experience recurrent relapses and develop platinum resistance. In recent years, tumour models have been used to better understand HGSOC, particularly 3D patient-derived tumour models. *Ex-vivo* explant cultures preserve the tumour microenvironment and architecture, allowing more accurate study of tumour response to therapy. In this study, we develop a protocol for generating platinum sensitivity readouts of patient-derived *ex-vivo* explant culture within a clinically relevant period.

Methodology We generated *ex-vivo* explant cultures from tumours collected from chemo-naïve patients undergoing primary cytoreductive surgery for advanced disseminated HGSOC and treated with cisplatin for 48 hours. Immunohistochemistry was used to determine tumour content (PAX8, p53), and levels of proliferation (Ki67) and apoptosis (cleaved caspase-3). QuPath digital pathology software was used to quantify responses to cisplatin relative to untreated samples generated from the same tumour site.

Results Applying digital pathology to tumour explants allowed for reproducible and rapid quantification of proliferation and apoptosis markers to determine viability of explant cultures and apoptosis induction in response to drug treatments. We observed variations in responses to cisplatin treatments across patients (n=7) and multisite deposits within the same patient (n=3 patients, with 2–3 tumours each).

Conclusion *Ex-vivo* tumour explant cultures capture the heterogeneity of HGSOC and therefore are an ideal model for testing responses to platinum chemotherapeutics, targeted treatments or novel agents, and homologous recombination repair capacity. The use of multisite tumours confirms that intra-tumoural heterogeneity plays a role in responses to chemotherapy and emphasizes the value of multisite sampling for the study of HGSOC. From surgery to analysis, this method can be completed within 2–3 weeks, allowing it to be used to guide personalized chemotherapy regimens.

2022-RA-1582-ESGO INHIBITION OF THE WNT/ β -CATENIN PATHWAY WITH DKK3 PROTEIN – A NEW VIRAL THERAPY FOR TREATMENT OF OVARIAN CANCER?

¹Adam Naskretski, ²Andrew Robinson, ²Valerie Meniel, ¹Sadie Jones, ²Toby Pheesse, ²Alan Parker. ¹University Hospital of Wales, Cardiff, UK; ²Cardiff University, Cardiff, UK

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Introduction/Background Wnt/ β -Catenin signalling pathway plays an important role in many cellular processes, including cell proliferation. Abnormal functioning of the pathway has been demonstrated in ovarian cancer and therefore could be the focus for novel treatments, including viral therapies. In this study, we examined the effects of Wnt/ β -Catenin pathway inhibition in ovarian cancer by infecting ovarian cancer cells with modified adenovirus 5 (Ad5) expressing Dickkopf-3 (DKK3) protein, a known Wnt/ β -Catenin pathway inhibitor. **Methodology** DKK3 expression in the virus was confirmed by quantitative PCR test against DKK3 and other Wnt target genes and Western Blot. Once confirmed, 10k epithelial ovarian cancer cells (SKOV3 cell line) were infected with the modified virus at 1k, 2.5k, 5k and 10k virus particles per cell for CellTiter Glo (CTG) assay with results analysed at 24, 48 and 72hrs post infection. In Colony Forming Assay, 300 SKOV3 cells were infected at the same virus particles per cell ratios and analysed after 14 days. The same assays were performed with doxorubicin and Ad5RAD as positive and negative controls respectively.

Results CTG assay showed reduced cell viability and proliferation of cancer cells for the first 48hrs post infection. In the colony forming assay, ovarian cancer cells were able to form multiple colonies of more than 50 cells 2 weeks after viral suppression of the Wnt/ β -Catenin pathway, indicating the inhibition may not have long standing effects on cancer cells' ability to grow and multiply.

Conclusion Our results indicate infecting cancer cells with Ad5 expressing DKK3 successfully inhibits the Wnt/ β -Catenin pathway and leads to short-term reduction in cell proliferation. Further studies are needed to establish any long-term effects and potential translation into clinical practice.

2022-RA-1608-ESGO CLINICAL IMPLICATIONS OF GENOMIC INTRATUMOURAL HETEROGENEITY IN HIGH GRADE SEROUS OVARIAN CANCER

¹Paula Cunnea, ²Elizabeth L Christie, ¹Ed Curry, ¹Chun-Hei Kwok, ²Ahwan Pandey, ¹Katherine Nixon, ¹Jennifer Ploski, ¹Jonathan Krell, ¹Iain McNeish, ²David D Bowtell, ¹Christina Fotopoulou. ¹Surgery and Cancer, Imperial College London, London, UK; ²Oncology, The Sir Peter MacCallum Department of Oncology, Melbourne, Australia

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Introduction/Background High-grade serous ovarian cancer (HGSOC) is typified by extensive genomic instability and intra-tumoural heterogeneity (ITH). Most patients relapse and eventually acquire resistance to platinum- or PARP inhibitor-based therapy. Diverse mechanisms leading to therapy resistance and a lack of predictive biomarkers means that matching the best treatment options to patients is difficult. This study aims to describe the extent of spatial and temporal ITH in advanced stage HGSOC at presentation and relapse and its implications for patient management.

Methodology Patients (n=49) undergoing maximal-effort upfront-debulking surgery for advanced HGSOC had a tumour mapping of their tumour dissemination. Tumour biopsies were collected (range 4–15) from patients, and also at time of relapse (n=10 patients). DNA was extracted from tumours (5 per patient, n=49 patients plus paired relapse samples) and Illumina Human OmniExpress genotyping performed. Allele-specific copy number (CN) was quantified using ASCAT. CN signature exposures were determined for all samples. Homologous recombination (HR) scores were estimated using a scarHRD algorithm, applying a cut-off >42 for HR-deficient.

Results Extensive genomic variations in CN signature exposures for different patients' tumours were observed, including between matched primary and relapse tumours. Increased CN signature exposure scores for Signatures 2 (p=0.00017), 4 (p=0.0029) and 6 (p=0.001) correlated with poor outcome in platinum-resistant/refractory patients, increased Signature 3 correlated with favourable outcome (p=0.00018) for platinum-sensitive and no-relapse patients. Variations in HR scores were observed across the cohort with one fifth of patients presenting with a mixed HR score profile across their tumour deposits, demonstrating both HR-deficient and HR-proficient tumours within patients.

Conclusion Extensive CN variations in CN signature scores and mixed HR-deficiency/proficiency scores indicates that a single tumour biopsy does not accurately depict disseminated HGSOC biology, and therefore should not be used as the basis to derive biomarker profiles for prediction of patient treatment responses or outcomes.

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EPITHELIAL OVARIAN CANCER IS INFILTRATED BY ACTIVATED EFFECTOR T CELLS COEXPRESSING MULTIPLE INHIBITORY RECEPTORS AND BY MYELOID CELLS EXPRESSING INHIBITORY RECEPTOR LIGANDS

¹Alice Bergamini, ²Elena Tassi, ³Miriam Sant'Angelo, ⁴Chiara Balestrieri, ⁵Emanuela Brunetto, ³Miriam Redegalli, ⁵Alessia Potenza, ⁵Daniilo Abbati, ³Francesco Manfredi, ³Maria Giulia Cangì, ⁶Luca Boccione, ⁶Giorgio Candotti, ⁶Emanuela Rabaiotti, ³Gianluca Taccagni, ⁶Massimo Candiani, ³Claudio Doglioni, ⁶Giorgia Mangili, ⁵Chiara Bonini. ¹Obstetrics and Gynecology, Università Vita-Salute San Raffaele; IRCCS Ospedale San Raffaele, MILANO, Italy; ²Experimental Hematology Unit, Division of Immunology, Transplantation and Infectious Disease, San Raffaele Scientific Institute, Milano, Italy, Milano, Italy; ³Department of Surgical Pathology, IRCCS Ospedale San Raffaele, Milano, Italy; ⁴Center for Omics Sciences, IRCCS Ospedale San Raffaele, Milano, Italy; ⁵Experimental Hematology Unit, Division of Immunology, Transplantation and Infectious Disease, IRCCS Ospedale San Raffaele, Milano, Italy; ⁶Obstetrics and Gynecology, IRCCS Ospedale San Raffaele, Milano, Italy

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Introduction/Background Despite evidence suggesting a potential role for immunotherapy in Epithelial Ovarian Cancer (EOC), initial attempts had limited efficacy. A better characterization of tumor infiltrating lymphocytes' (TIL) immunophenotype appears crucial to deeply understand their role in anti-tumor immunity and to set the basis for their potential modulation to optimize adoptive cell therapies approaches. We extensively characterized the composition and phenotype of immune cells in EOC to identify pathways involved in limiting anti-tumor immunity.

Methodology Immune infiltrate was investigated for phenotype in 48 EOC specimens by immunohistochemistry (IHC) and flow cytometry (FC). Furthermore, the gene expression of

tumor samples was evaluated with a panel of 799 immune and cancer-related genes by the Nanostring platform. FC was also used to compare T cells isolated from tumor, ascites and peripheral blood of 19 patients for memory phenotype and for the expression of multiple inhibitory receptors (IRs) and of activation markers.

Results Both IHC and FC revealed a high infiltration by T lymphocytes and myeloid cells, while B cells were scanty. High-dimensional analysis of FC data identified 2 metaclusters of CD4⁺ and CD8⁺ T cells exclusively present in tumors, characterized by a CD137⁺CD39⁺PD-1⁺TIM-3⁺CD45RA⁻CD62L⁻CD95⁺ phenotype. Gene expression profile revealed a peculiar microenvironment in samples characterized by high TIL content, with increased expression of immunity- and myeloid-related genes. Accordingly, the ligands for IRs and co-stimulatory molecules were mainly provided by myeloid rather than neoplastic cells.

Conclusion Our data suggest that EOC is infiltrated by antigen-experienced T lymphocytes displaying features of both activation and partial exhaustion, possibly driven by IRs ligands expression by infiltrating myeloid cells.

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EVALUATION OF ADVANCED LUNG CANCER INFLAMMATION INDEX AS A PROGNOSTIC FACTOR IN PATIENTS WITH OVARIAN CANCER TREATED WITH PRIMARY DEBULKING SURGERY

¹Upasana Palo, ²Debapriya Mondal, ¹Anik Ghosh, ¹Basumita Chakraborti, ¹Jaydip Bhaumik. ¹Gynecologic Oncology, Tata Medical Center, Kolkata, India; ²Medical Oncology, Tata Medical Center, Kolkata, India

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Introduction/Background Advanced Lung Cancer Inflammation Index (ALI) reflects systemic inflammation and has been shown to be a prognostic factor for lung cancer patients undergoing surgery. No previous study has assessed the prognostic significance of ALI in patients with ovarian cancer (OC). This study aimed to explore the relationship between ALI and prognosis of OC.

Methodology Electronic records of 83 patients with OC who underwent primary debulking surgery (PDS) at Tata Medical Center between 2017 and 2018 were reviewed. Patients treated with primary chemotherapy and those treated with palliative intent were excluded. The ALI score was calculated as body mass index x serum albumin/neutrophil to lymphocyte ratio. A web-based programme [Cutoff Finder (<http://molpath.charite.de/cutoff/>)] was used to deduce the appropriate cut-off value for ALI. The Kaplan-Meier method and Cox Proportional Hazards model were used to compare survival among prognostic groups.

Results The optimal cut-off value of ALI was determined as 12.5. Among the 83 patients, 10 had low ALI (<12.5), and 73 had high ALI (≥12.5). The low-ALI group had more complications of Clavien-Dindo grade 3 or higher after PDS (P=0.04). The patients with low ALI had higher chances of 30-day-mortality following PDS compared to the high-ALI group (P=.005). Median relapse-free survival (RFS) in the low-ALI group was 9 months compared to 32 months in the high-ALI group (hazard ratio [HR] for relapse, 0.16; P<0.001). Median overall survival (OS) in the low-ALI group was 20 months, and in the high-ALI group median OS was 56 months (HR 0.12, P<0.001).