Additionally, 30 hr-HPV+ women, who developed CIN3 at the first follow-up, then were surgically treated for the disease and testing hr-HPV- after, were also included. Exfoliated cervical specimens were used for whole genomic and bacterial DNA extraction. Vaginal microbiota composition was determined by 16S rRNA gene fragments sequencing. The S5 methylation classifier assays were performed as previously described (Brentnall et al, 2015).

**Results** We identified unique microbial biomarkers associated with CIN3 development and recovery after surgical treatment. Hr-HPV+ women with CIN3 showed a significant overrepresentation of following microbial species: *Sneathia amnii*, *Megasphaera genomosp.*, *Pepstopterctoccus anaerobius* and *Acrobromobacter spanius*. *Sneathia amnii* was the only bacteria consistently associated with CIN3 in all group comparisons performed (p<0.01). Conversely, after successful treatment women were hr-HPV- and exhibited an increased representation of *Lactobacillus* species, especially *Lactobacillus gasseri* (p<0.01). Higher proportions of *Lactobacillus helveticus*, *Lactobacillus surnoryeus* and *Lactobacillus vaginalis* showed a potential protective role against CIN3 development in women with persistent hr-HPV infection. We confirmed S5 scores are increasing with cervical disease severity. Increasing *Sneathia amnii* abundance was directly proportional to S5 score increase during cervical disease development.

**Conclusion** Our results might indicate *Sneathia amnii* possible role in modifying the epigenetic landscape of the cervicovaginal space. Further investigations are required to establish a link between the identified potential vaginal microbiome biomarkers and their influence on epigenetic mechanisms.

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**Abstract 2022-RA-1198-ESGO Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Responders</th>
<th>ORR, % (95% exact CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort A1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLH1+PMS2 loss</td>
<td>94</td>
<td>46</td>
<td>48.9 (38.5–59.5)</td>
</tr>
<tr>
<td>MSH2+MSH6 loss</td>
<td>16</td>
<td>9</td>
<td>56.2 (29.9–80.3)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>33</td>
<td>10</td>
<td>30.3 (15.6–46.7)</td>
</tr>
<tr>
<td>Patients with mutation data</td>
<td>101</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MLH1 loss</td>
<td>79</td>
<td>31</td>
<td>39.7 (28.8–51.5)</td>
</tr>
<tr>
<td>MLH1 loss and mutation in MMR gene</td>
<td>12</td>
<td>5</td>
<td>41.7 (15.2–72.3)</td>
</tr>
<tr>
<td>MLH1 loss and no mutation in MMR gene</td>
<td>66</td>
<td>26</td>
<td>39.4 (27.6–52.2)</td>
</tr>
<tr>
<td><em>other</em> includes any other pattern of absence of expression of 1 or greater MMR proteins.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Conclusion** Patients with dMMR advanced/recurrent EC benefitted from dostarlimab, with no noticeable difference by dimer-pair loss or MMR gene methylation/mutation status. These data suggest the route to MMR deficiency does not influence response to dostarlimab.

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**Abstract 2022-RA-1218-ESGO**

**Physiologically Relevant Treatment Models to Investigate Epigenetic Mechanisms Driving Platinum Resistance in Ovarian High Grade Serous Carcinoma**

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**Introduction/Background** Mismatch repair (MMR) deficiency is caused by loss of expression of MMR proteins, MLH1, PMS2, MSH2, and/or MSH6, that function as homodimers (MLH1/PMS2 and MSH2/MSH6) to mediate DNA repair. Loss of function caused by mutation or epigenetic methylation leads to defective MMR and genomic instability. MMR deficient (dMMR) tumours can respond to anti-programmed death 1 (anti-PD-1) therapy. We report a post hoc analysis of objective response rate (ORR) with loss of MMR dimers and mutation status of MMR genes in patients with dMMR endometrial cancer (EC) treated with dostarlimab.

**Methodology** GARNET is a multicentre, open-label, single-arm phase 1 study. Cohort A1 enrolled patients with dMMR advanced/recurrent EC. Patients received 500 mg of dostarlimab intravenously Q3W for 4 cycles, then 1000 mg Q6W until disease progression, discontinuation, or withdrawal. MMR protein status (presence or loss) was determined by local immunohistochemistry. MMR gene mutation was determined by FoundationOne. MLH1 loss without MMR gene mutation was a surrogate indicator for epigenetic methylation.

**Results** Cohort A1 included 143 patients; MMR gene mutation data were available for 101 patients (table 1). Cohort A1 ORR was 45.5%, 66% of patients had loss of MLH1/PMS2; ORR was 48.9%. 11.2% of patients had loss of MSH2/MSH6; ORR was 56.2%. ORR was 41.7% for MLH1 loss with MMR gene mutation and 39.4% for MLH1 loss without MMR gene mutation.
indicate that genomic alterations alone cannot explain acquired platinum resistance in many cases, and emerging evidence suggests epigenetic alterations may be critical. We wish to investigate epigenetic changes that may drive platinum resistance in HGSC by exploring established HGSC cell lines and patient-derived cells with pulses of carboplatin and investigating the nature, kinetics and plasticity of platinum-induced epigenetic changes.

**Methodology**

We will mimic, using an *in vitro* two-dimensional model, multiple cycles of platinum-based chemotherapy as used clinically. We will generate preliminary results from established cell lines and primary cultures. The primary cell cultures are collected from the ascites of patients with HGSC treated at Imperial College NHS Trust, London. Following validation (p53, PAX8 immunocytochemistry), carboplatin sensitivity is assessed (sulforhodamine B assay). Cells are then pulsed with four cycles of carboplatin (50µM for 6 hours) with a week of recovery between each cycle. Chemosensitivity of surviving cells is measured after each cycle. The cells are then harvested for downstream methylation (Illumina 850k array), transcriptomic (RNA sequencing) and chromatin accessibility (ATAC sequencing) assays. Cells are also imaged using STORM (Stochastic Optical Reconstruction Microscopy). Preliminary STORM data already indicate differences in chromatin structure and the distribution of specific histone modifications between paired sensitive and resistant HGSC cell lines.

**Results**

We will receive the raw data within 8–12 weeks from now for the bioinformatic analysis. Differential gene expression analysis will uncover differentially enriched pathways under the selective pressure of platinum-based chemotherapy.

**Conclusion**

Understanding the epigenetic landscape of HGSC may be an early event in the serous carcinogenesis and a poor prognosis biomarker in HR proficient HGSOCC. Functional assays are currently ongoing to unravel the biological mechanisms underlying P-cadherin role in this subgroup.

**P-CADHERIN: A PROMISING PROGNOSTIC BIOMARKER FOR HOMOLOGOUS REPAIR PROFICIENT HIGH GRADE SEROUS OVARIAN CARCINOMA**

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10.1136/ijgc-2022-ESGO.889

**Introduction/Background**

Homologous repair (HR) proficient tumours constitute 2/3 of high grade serous ovarian carcinoma (HGSOCC), being associated with worse prognosis. Therefore, the identification of clinically relevant biomarkers is an urgent unmet clinical need. Once classic cadherins are transmembrane glycoproteins involved in cell-cell adhesion that are frequently deregulated in cancer, we aimed to: 1) characterize the expression pattern of E-cadherin (CDH1), N-cadherin (CDH2) and P-cadherin (CDH3); 2) evaluate their prognostic impact in terms of overall survival (OS), according to HR status.

**Methodology**

Retrospective study using a convenience sample of archive human tissue (Fallopian tube epithelium (FTE), serous precursor lesions and chemo-naïf HGSOCC) from a Portuguese cancer centre. *In vitro* and *in silico* validation performed using HGSOCC cell lines (BG1 and OVCAR4 cell lines) and CCLE database, respectively. Protein expression evaluated using immunohistochemistry (H-scoring system) and western blot. Comparisons between groups were made using T-test and X², where appropriate. Survival analyses were estimated using Kaplan-Meier analysis and Log-rank test.

**Results**

We included 321 samples (130 FTE, 53 precursor lesions and 138 HGSOCC; 41.2% BRCA1/2 or RAD51D mutated) from 221 patients. All HGSOCC co-expressed the 3 cadherin isoforms (28% with high co-expression scores). Expression pattern did not differ according to HR status. P-cadherin was significantly upregulated both in precursor lesions and HGSOCC, when compared with FTE. CDH3 expression was positively correlated with CDH1, EpCAM and GRHL2 and inversely correlated with VIM, both *in silico* and *in vitro*. HGSOCC with high cadherin co-expression and high P-cadherin expression were significantly associated with shorter OS in the HR proficient subgroup.

**Conclusion**

Our results suggest that P-cadherin upregulation may be an early event in the serous carcinogenesis and a poor prognosis biomarker in HR proficient HGSOCC. Functional assays are currently ongoing to unravel the biological mechanisms underlying P-cadherin role in this subgroup.

**ETHNICITY-SPECIFIC SPECTRUM OF BRCA1, BRCA2 AND ATM PATHOGENIC VARIANTS IN OVARIAN AND BREAST CANCER PATIENTS FROM NORTH CAUCASUS**

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10.1136/ijgc-2022-ESGO.890

**Introduction/Background**

North Caucasus hosts several large ethnic groups, which preserved their national identity through the course of history. These populations are likely to have a unique pattern of disease-predisposing alleles reflecting the genetic background of their ancestors.

**Methodology**

This study involved ovarian cancer (OC) and breast cancer (BC) patients from Chechnya (n = 147), Kabardino-Balkaria (n = 139), North Ossetia (n = 83), Ingushetia (n = 88) and Dagestan (n = 137). The entire coding sequences of BRCA1, BRCA2 and ATM genes were analyzed by next-generation sequencing (NGS) in 180 OCs and 414 BCs.

**Results**

Consecutive OC series were characterized by high frequency of BRCA1/2 mutations across all analyzed ethnic groups, varying from 18% to 33%. BC patients, which were enriched by early-onset, family history-positive and receptor triple-negative disease, showed mutation rate varying from 4% to 14%. There were founder pathogenic alleles in Chechens (BRCA1 c.3629_3630delAG; 10 out of 20 BRCA1/2 mutations) and North Ossetians (BRCA2 c.6341delC; 6 out of 10