Additionally, 30 hr-HPV+ women, who developed CIN3 at the first follow-up, then were surgically treated for the disease and tested 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, Megaspheera genomospor, Pepstotptococcus anaerobius and Achromobacter 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 suntoryeus and Lactobacillus vaginalis showed a potential protective role against CIN3 development in women with persistent hr-HPV infection. We confirmed S5 scores are inversely 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.

Abstract 2022-RA-1198-ESGO POST HOC ANALYSIS OF OBJECTIVE RESPONSE RATE BY MISMATCH REPAIR PROTEIN DIMER LOSS/MUTATION STATUS IN PATIENTS WITH MISMATCH REPAIR DEFICIENT ENDOMETRIAL CANCER TREATED WITH DOSTARLIMAB

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.

Abstract 2022-RA-1218-ESGO PHYSIOLOGICALLY RELEVANT TREATMENT MODELS TO INVESTIGATE EPIGENETIC MECHANISMS DRIVING PLATINUM RESISTANCE IN OVARIAN HIGH GRADE SEROUS CARCINOMA

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 36.2%. ORR was 41.7% for MLH1 loss with MMR gene mutation and 39.4% for MLH1 loss without MMR gene mutation.

Conclusion The prognosis for patients with platinum-resistant ovarian high grade serous carcinoma (HGSC) remains poor. Data from the BriTROC-1 study...
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 treating 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 differently enriched pathways under the selective pressure of platinum-based chemotherapy.

Conclusion Understanding the epigenetic landscape of HGSC in real time using physiologically relevant models will allow us to identify possible therapeutic targets that could eventually prevent platinum resistance.