Introduction/Background In our previous microarray study we identified the 96-gene signature related to differential survival of patients with high-grade serous ovarian cancer (OC).[1] Top differentially expressed genes were e.g. POSTN, COL11A1, SFRP2, MFAP5, ITGBL1, LOX. Similar mesenchymal signature has been observed also by others, but it has been ascribed to cancer associated fibroblasts, not epithelial cells. However, we postulate that these genes can be also expressed by cancer cells themselves.

Methodology For survival analysis we used Kaplan-Meier Plotter and Microarray Gene Expression Database of OC Subtype (CSIOVDB). Proteins expression was assessed by Heterogeneity_Analysis_Portal (lmdomics.org) [2]. Interaction networks were judged by STRING. Molecular cloning was performed using retroviral gene transfer; in vitro functional tests were done according to standard procedures; gene expression analyzed by PCR.

Results STRING algorithm applied to our prognostic signature showed interactions typical for proteins engaged in the function and structure of extracellular matrix. Our own qRT-PCR analysis, as well as Kaplan-Meier Plotter and CSIOVDB analysis confirmed that mRNA level of majority of genes from our negative prognostic signature is significantly related to survival of OC patients. Using Heterogeneity_Analysis_Portal we analyzed 24 out of these genes and found that they are strongly expressed by tumor stromal cells, while weakly by epithelial cells. We analyzed ten of these genes in several OC cell lines by semi-quantitative RT-PCR, and we found that they are expressed by epithelial cells as well. By functional in vitro assays we observed that overexpression of these genes (ITGBL1, MFAP5, SFRP2) may affect OC cells phenotype (migration, invasiveness, proliferation, chemosensitivity).

Conclusion Mesenchymal signature with negative prognostic significance in OC is expressed mostly by stromal, but also by epithelial cells, and may affect phenotype of the latter. Exact role of these genes in OC cells remains to be assessed.

REFERENCE

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2022-RA-1130-ESGO EFFECT OF IMIQIUMOD TREATMENT ON HLA-G EXPRESSION IN HIGH-GRADE CERVICAL LESIONS

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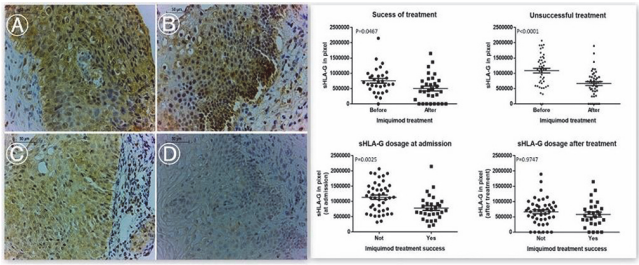
Introduction/Background We showed that the topical application of the 5% imiquimod in treating cervical high-grade squamous intraepithelial lesions (HSIL) leads to a regression of about 50% of the lesions after 16 weeks of treatment (1). Tissue culture studies have attributed imiquimod's antiviral and antitumor activity to the enhancement of the innate immune response. Knowing that the increase in soluble HLA-G (sHLA-G) expression is associated with disease progression and that the HLA-G molecule has an inhibitory effect on different immune cells, we further investigated whether imiquimod modulates the sHLA-G expression in the cervical lesions.

Methodology Cervical biopsies of 52 patients aged 18–40 with histological HSIL (CIN2p16+ and CIN3), who self-applied 250 mg cream containing 5% of imiquimod three times a week for 16 weeks, were collected at admission and after completion of the treatment. Treatment success was defined as the absence of HSIL after treatment. For immunohistochemistry, we used the monoclonal anti-HLA-G antibody (Exbio, 5A6G7) (figure 1). The intensity of pixels obtained from the images of the slides, using the program Gimp 2.10.18, defined the protein levels (figure 2). We used the T-test to compare two groups, the ROC curve to define the cut-off point for risk-predicting sHLA-G expression, and the Fisher's exact test to calculate the risk.

Results High tissue sHLA-G levels before treatment were associated with unsuccessful imiquimod treatment (p=0.0025). Imiquimod down-modulated sHLA-G in the lesion of those successfully treated (p=0.0467) or not (p<0.0001). According to the area under the curve of 0.72, 95%CI 0.61–0.84, p=0.0012, sHLA-G expression over 870847 pixels represented a 4-fold risk for unsuccessful imiquimod treatment (p=0.0088).



Abstract 2022-RA-1130-ESGO Figure 1 and 2

Conclusion We showed that imiquimod modulates HLA-G in cervical lesions and that treatment success depends on sHLA-G levels at admission.

2022-RA-1136-ESGO A SINGLE-CELL MAP OF RARE OVARIAN CANCER

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Introduction/Background Non-epithelial ovarian tumours encompass a heterogeneous group of neoplasms that mainly include germ cell tumours (GCT) and sex-cord stromal tumours (SCST). These tumours are characterised by an extensive inter- and intratumoral heterogeneity. By applying single-cell RNA sequencing (scRNA-seq), we attempt to elucidate the complexity of the tumour microenvironment.

Methodology We performed scRNA-seq of 66 919 cells collected from 12 patients. Most fresh tissue samples were derived from SCST (n=9), including 7 adult granulosa cell

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tumours, 1 primary juvenile granulosa cell tumour and 1 primary Sertoli-Leydig cell tumour. Three samples were obtained from treatment-naïve GCT (2 immature teratomas and one dysgerminoma). For each phenotype of tumour cells, immune cells, endothelial cells and cancer-associated fibroblasts, we identified specific transcriptomic markers.

Results Based on differential expression analysis and expression of transcriptomic markers, we identified 27 clusters consisting of 9 tumour cell and 18 stromal cell clusters. The first results of subcluster analysis revealed nearly absence of B cells in all granulosa cell tumours. In addition, the immune cell subcluster mainly consists of T cells derived from the dysgerminoma (58%) and Sertoli-Leydig cell (20%) samples. Further characterisation and differentiation of distinct subclusters is currently ongoing and will be presented.

Conclusion With this analysis we aim to generate a publicly accessible comprehensive blueprint of the tumour micro-environment, aiding other researchers to gain high-resolution insights in the heterogeneity and complexity of these rare ovarian cancers.

2022-RA-1194-ESGO EFFICACY OF DOSTARLIMAB IN ENDOMETRIAL CANCER BY MOLECULAR SUBTYPE: A POST HOC ANALYSIS OF THE GARNET STUDY

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Introduction/Background Biomarkers are used to classify endometrial cancer (EC) into molecular subtypes such as TCGA and/or a surrogate classification (POLϵ mutated [mut], mismatch repair/microsatellite instability [MMR/MSI], TP53mut, and no specific mutation profile [NSMP]) or by estrogen receptor (ER) status. Here, we report on a post hoc analysis of objective response rate (ORR) by a surrogate classification for EC in patients receiving dostarlimab monotherapy.

Methodology GARNET is a multicentre, open-label, single-arm phase 1 study. Patients were assigned to cohort A1 (MMR deficient/MSI-high [dMMR/MSI-H EC]) or A2 (MMR proficient/microsatellite stable [MMRp/MSS] EC) based on local assessment. Patients received 500 mg of dostarlimab IV Q3W for 4 cycles, then 1000 mg Q6W until disease progression, discontinuation, or withdrawal. The primary endpoints were ORR and duration of response by blinded independent central review. Molecular subtype was determined by POLϵ and TP53 mutation status by Foundation Medicine, and MMR/MSI status was determined by local immunohistochemistry or next-generation sequencing; all others were assigned as NSMP. The hierarchy for classification was POLϵmut → MMR/MSI → TP53 status → NSMP. ER status was determined by local immunohistochemistry testing. Only patients with samples available for additional biomarker testing were included in the biomarker assessment.

Results 143 patients with dMMR/MSI-H EC and 156 patients with MMRp/MSS were included in the efficacy-evaluable population. ORRs were determined for molecular subtypes and ER expression (table 1). Safety has been previously reported.

Abstract 2022-RA-1194-ESGO Table 1

	A1			A2		
Overall	65/143, 45.5% (37.1–54.0)			24/156, 15.4% (10.1–22.0)		
Molecular subtype	**N=101**			**N=153**		
Polϵmut	2/3, 66.7% (9.4–99.2)			0/2, 0% (0.0–84.2)		
dMMR/MSI-H	43/98, 43.9% (33.9–54.3)					
	TP53mut 10/26, 38.5% (20.2–59.4)	TP53wt 33/72, 45.8% (34.0–58.0)				
	ERpos 19/44, 43.2% (28.3–59.0)	ERneg 1/2, 50.0% (1.3–98.7)	ERunk 23/52, 44.2% (28.3–59.0)			
TP53mut				17/94, 18.1% (10.9–27.4)		
				ERpos 4/28, 14.3% (4.0–32.7)	ERneg 7/19, 36.8% (16.3–61.6)	ERunk 6/47, 12.8% (4.8–25.7)
NSMP				7/57 12.3% (5.1–23.7)		
				ERpos 2/19, 10.5% (1.3–33.1)	ERneg 2/11, 18.2% (2.3–51.8)	ERunk 3/27, 11.1% (2.4–29.2)

Data are n/N, % (95% CI). Data cut: 1 November 2021.
dMMR, mismatch repair deficient; ERneg, ER negative; ERpos, ER positive; ERunk, ER unknown; MSI-H, microsatellite instability–high; mut, mutated; NSMP, no specific mutation profile; wt, wild-type.

Conclusion The observed ORRs in each molecular subgroup were consistent with the overall ORR in each cohort. Differences by ER expression status were not observed. These findings support the importance of testing patients with EC for MMR/MSI biomarker status as a predictor of response. Additionally, data suggest that TP53 mutation or ER expression should not modify treatment approach. The data are of interest for hypothesis generation.

2022-RA-1195-ESGO LONGITUDINAL STUDY OF VAGINAL MICROBIOME PRE- AND POST-TREATMENT IDENTIFIES BIOMARKERS FOR CERVICAL INTRAEPITHELIAL NEOPLASIA 3 (CIN3)

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Introduction/Background Increasing evidence suggests vaginal dysbiosis is associated with persistence of human papillomavirus (HPV) infection and cervical intraepithelial neoplasia (CIN1–3) development. In this pilot study we aimed to investigate the potential of vaginal microbiome biomarkers to predict CIN3 development in high risk HPV positive (hr-HPV+) women.

Methodology 59 women with normal cytology at initial screening and follow-up over six years were enrolled from ARTISTIC trial. The cohort included 14 hr-HPV negative (hr-HPV-) and 15 hr-HPV+ women through whole follow-up.

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