#174 INTEGRATED MULTI-OMIC AND CLINICOPATHOLOGICAL ANALYSIS OF VULVAR SQUAMOUS CELL CARCINOMA: IDENTIFICATION OF PREDICTIVE BIOMARKERS FOR PERSONALIZED TREATMENT

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Introduction/Background Vulvar cancer responds poorly to systemic treatment and in contrast to other gynecological cancers, targeted therapies remain at an early stage. Interactions of clinical, immune, and molecular biomarkers remain poorly understood for this rare cancer type. Here, we characterized the proteogenome of vulvar squamous cell carcinoma (vSCC) and provide a computational workflow to integrate publicly available data to study this rare and aggressive cancer type.

Methodology Whole exome sequencing, bulk RNA-sequencing, clinicopathological, and proteomics data from 23 patients with vSCC were analyzed. In addition, a total of 5543 women-derived TCGA genomic and transcriptomics sequencing data were obtained for this analysis.

Results Our cohort consisted of 34.8% human papillomavirus (HPV)+ and 65.2% HPV- vSCC patients. Early FIGO stage was significantly associated with HPV- status (12% (1/8) vs. 86% (12/15), $p<0.001$). TP53 and CDKN2 were mutually exclusive to HPV+. Patients being HPV+ revealed a higher frequency in PIK3CA alterations with 37.5% vs. 6.7% in HPV-. TYMS which is considered the primary site of action for 5-fluorouracil was significantly higher expressed in HPV + patients ($log2FC=1.7497$, $p<0.001$). We identified unique single and doublet base substitution signatures in vSCC indicating defective DNA mismatch-repair and correlation with age. Tongue SCC (tSCC) was identified as a comparison cohort supported by different clustering methods of conjoint RNA-seq and clinicopathological data, derived from TCGA. vSCC was associated with elevated activated mast cells ($p=0.0031$), monocytes ($p=0.0027$), and M2 macrophages ($p<0.001$) compared to tSCC, independent of the HPV status.

Conclusion vSCC can be further distinguished by HPV status, somatic gene alterations and tumour microenvironment, while a similar cancer tissue has been identified with tSCC. Further analysis is targeted at identifying molecular signatures serving as biomarkers in vSCC and to suggest alternative treatment options of drugs already in use in tSCC or other cancer types.

Disclosures All authors declare that they have no conflicts of interest.

#251 PATIENTS WITH NEWLY DIAGNOSED ADVANCED HIGH-GRADE SEROUS CARCINOMA WITH IMPAIRED IMMUNOSUPPRESSIVE ASCITIC MICROENVIRONMENT EXHIBIT POOR OUTCOME

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Introduction/Background Despite substantial progress in high-grade serous ovarian cancers (HGSOC) in recent years, the prognosis remains poor. While ascites play a significant role in HGSOC progression, their immune landscape characterization is essential to understand their impact on the immune cell response.

Methodology Ascites were collected during initial laparoscopy for advanced HGSOC and then processed, using respective multiplexed approaches of flow cytometry-based marker expression analysis and quantitation of mediators, for profiling immune cellular and cell-free fractions. Furthermore, ascites fluids were functionally screened for their biological effects on healthy monocytes, undifferentiated and under M1-polarization.

Results 20 HGSOC patients were included from September 2020 through November 2022. Median age at diagnosis was 68 years (50–73). 19 patients had stage IIIC or IV HGSOC. 7 patients had debulking surgery (2 primary DS). After a median follow-up of 13 months (5–30), median progression-free survival was 11,0 months (95% confidence interval 7,9 – 14,1). At the time of analysis 7 patients had died.

Ascites were mostly 'enriched' in regulatory immune cells including T and myeloid populations. T cells highly expressed immune checkpoints e.g. PD1 in T cells and TIGIT in Tregs. CD163+ TAMs were shown to express Arg1, CCR8, CCR2, and iNOS. While acellular fluids exhibited differentially-elevated levels of soluble mediators, functionally, they polarized monocytes into M2 macrophages, and even opposed their M1 polarization to switch to M2-status.

Conclusion HGSOC ascites harbor an altered immune environment where suppressive cells and mediators lead to immune cell dysfunction. Identification of ascites subgroups most favorable to the M2 phenotype would suggest a population with poor outcomes.

These findings highlight HGSOC ascites as a valuable tool for the identification of new immuno-oncological targets.

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