Molecular and immune characterization of squamous cell ovarian cancers for identification of therapeutic targets

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Background:

- Squamous cell carcinoma (SCC) represents <1% of all Ovarian cancers (OC) and is associated with poor prognosis
- It is thought to arise predominantly from malignant transformation of mature cystic teratomas (MCT) but can also arise from Brenner's tumors (BT) and endometriosis
- **This study seeks to identify prognostic factors and molecular markers associated with OSCC compared to Endometrioid OC (EOC), Clear Cell OC (CCOC), HPV16/18-negative vulvar SCC (VSCC) and HPV16/18-negative cervical SCC (CSCC)**

Methods:

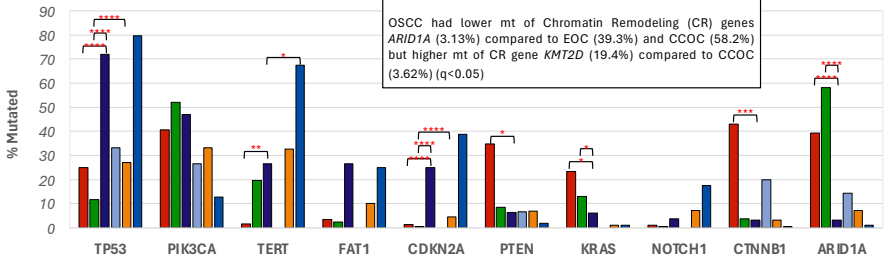
- 812 EOC, 846 CCOC, 32 OSCC, 15 malignant BT, 500 HPV16/18- CSCC, and 472 HPV16/18- VSC were analyzed using next-generation sequencing of DNA (NextSeq, 592 genes and NovaSeq, WES) and RNA (NovaSeq, WTS) (Caris Life Sciences, Phx, AZ).
- Tumor mutational burden (TMB) was measured by totaling all somatic mutations (mt) per tumor (TMB-H: > 10 mt/MB).
- PD-L1 IHC positivity was determined by a cut-off of >1% CPS (22c3, Agilent) and >2|5% (SP142, Spring Biosciences).
- HPV status determined by WES for HPV16 and 18.
- Statistical significance determined using chi-square and Mann-Whitney U test and adjusted for multiple comparisons (q<0.05).
- UMAP was used to visualize differences or similarities in transcriptomic profiles.
- Real-world overall survival (rwOS) obtained from insurance claims data and calculated from first treatment to last contact.
- Hazard ratio (HR) was calculated by Cox proportional hazards, with p-value calculated using log-rank test.

Table 1. Demographics

Characteristic	Endometrioid OC	Clear Cell OC	Squamous OC	Malignant Brenner	HPV16/18-Cervix	HPV 16/18-Vulvar	Q-value
N	812	846	32	15	500	472	
Age, median (range)	56 (23- >89)	57 (21- >89)	55.5 (33-76)	63 (52-87)	59 (20- >89)	70 (26- >89)	1.13 E-65

Endo OC (EOC) · Malignant Brenner (BT) · Clear Cell OC (CCOC) · Cervix Squam, HPV16/18- (CSCC) · Squamous OC (OSCC) · Vulvar Squam, HPV16/18- (VSC)

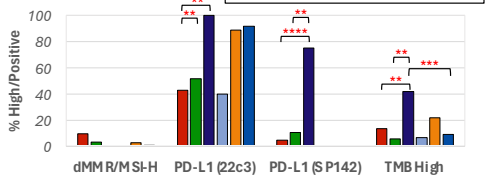
Fig 1. Mutational Landscape



OSCC had the highest rate of *TP53*-mt and *CDKN2A*-mt compared to BT, EOC, CCOC, and CSCC (*TP53*-mt: 71.9%, 33.3%, 25.1%, 11.6% and 27.1%, *CDKN2A*-mt: 25%, 0%, 1.49%, 0.48%, and 4.45%) but lower than VSCC (*TP53*-mt: 80%, *CDKN2A*-mt: 38.9%)

OSCC had lower mt of Chromatin Remodeling (CR) genes *ARID1A* (3.13%) compared to EOC (39.3%) and CCOC (58.2%) but higher mt of CR gene *KMT2D* (19.4%) compared to CCOC (3.62%) (q<0.05)

Fig 2. IO Biomarkers



OSCC had increased TMB-H than EOC, CCOC and VSC (41.9% vs 13.6% vs 5.7% vs 8.84%) and PD-L1 IHC (all q<0.05)

Fig 3. Tumor mutational burden

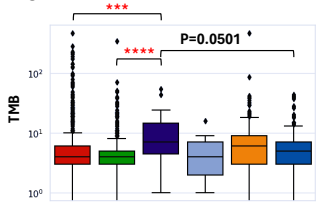
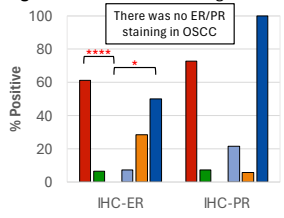
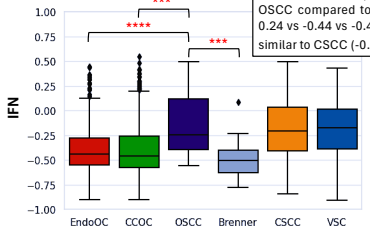


Fig 4. ER and PR IHC Staining



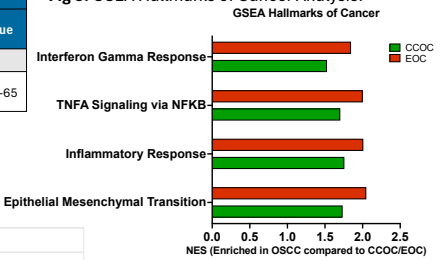
There was no ER/PR staining in OSCC

Fig 5. IFN Score



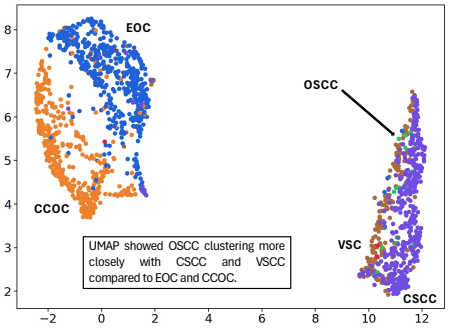
Median interferon (IFN) score was higher in OSCC compared to EOC, CCOC and BT (-0.24 vs -0.44 vs -0.46 vs -0.51, q<0.05) but similar to CSCC (-0.29) and VSCC (-0.17)

Fig 5. GSEA Hallmarks of Cancer Analysis.



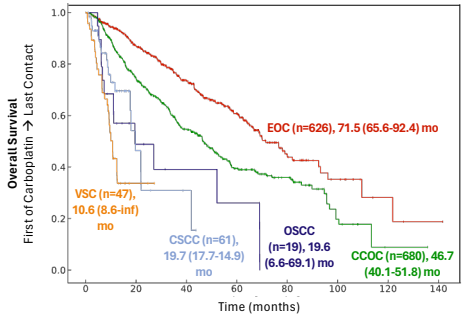
Pathway analysis showed enrichment of IFNγ Response, Inflammatory Response, EMT and TNFα Signaling (NES: 1.53-2.05, FDR<0.25) in OSCC compared to EOC and CCOC.

Fig 6. UMAP (k-means clustering) to visualize transcriptomic differences.



UMAP showed OSCC clustering more closely with CSCC and VSCC compared to EOC and CCOC.

Fig 7. Real-world Overall Survival (First of Carboplatin to Last Contact)



OSCC had worse post-Carboplatin survival (19.6 mo) compared to EOC (71.5 mo, p<0.0001) and CCOC (46.7 mo, p=0.01), similar post-Carbo survival to HPV16/18- CSCC (19.7 mo; p=0.89) but slightly improved post-Carbo survival compared to TP53-mt VSCC (10.6 mo; p=0.20).

Conclusion:

- The molecular and transcriptomic profile of OSCC is distinct from EOC, CCOC, and BT but similar to CSCC and VSCC.
- OSCC demonstrated a more immune hot phenotype.
- Further studies are needed to investigate the potential use of immunotherapy in OSCC.