Molecular 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 worse prognosis compared to High-Grade Serous OC (HGSOC)
- 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

**Methods:**
- 15 BT, 32 OSCC and 11,968 HGSOC tumors were analyzed using NGS of DNA (NextSeq, 592 genes and NovaSeq, WES) and RNA (NovaSeq, WTS) (Caris Life Sciences)
- Microsatellite instability (MSI) was tested by IHC and NGS
- Tumor mutational burden (TMB) measured by totaling all nonsynonymous mutations per tumor (TMB-H: ≥ 10 mutations/MB)
- PD-L1 IHC positivity was determined by a cut-off of >2|5% (SP142)
- Real-world overall survival (OS) was obtained from insurance claims and calculated from tissue collection to last contact
- Statistical significance determined by chi-square and Mann-Whitney U test and adjusted for multiple comparisons (q-value <.05)

**Results:**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Brenner</th>
<th>Squamous</th>
<th>HGSOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15</td>
<td>32</td>
<td>11968</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>63 (52-87)</td>
<td>55.5 (33-76)</td>
<td>65 (15-90)</td>
</tr>
<tr>
<td>TMB, median (range)</td>
<td>4 (1-16)</td>
<td>7 (1-54)</td>
<td>3 (0-344)</td>
</tr>
</tbody>
</table>

**Biopsy Site**
- Primary, N (%) 10 (66.7) 12 (37.5) 5525 (46.1)
- Metastatic, N (%) 5 (33.3) 20 (62.5) 6303 (52.6)
- Unclear, N (%) 0 (0) 0 (0) 146 (1.22)

**Conclusion:**
- OSCC tumors were more likely to be TMB-H compared to BT and HGSOC, with increased mutational prevalence in multiple genes like PIK3CA, FBXW7, CDKN2A, FAT1, pTERT but no ER or PR positivity
- Additionally, OSCC tumors also had increased expression of many IC genes, infiltration of M1 Macrophages and higher T-cell inflamed frequency. UMAP analysis showed OSCC and HGSOC have distinct transcriptomic profiles
- One limitation of this study is the small sample size of OSCC compared to HGSOC, but further characterization of this rare histological subtype with a poor prognosis may lead to identification of therapeutic targets.