Comprehensive molecular profiles of low-grade serous ovarian cancer

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Abstract

Objectives: Low grade serous ovarian cancer (LGSOC) is unique among epithelial ovarian cancer, differing from high grade serous ovarian carcinoma (HGSOc) in terms of its pathogenesis, molecular, genetic, and clinical features. To date, molecular studies on these malignancies have been hampered by small sample sizes. As such, mutation rates of the different cohort studies have shown a wide range of KRAS and BRAF mutation frequencies. The purpose of this study is to better understand aberrations inherent to LGSOC, in a homogeneously tested and histologically confirmed, cohort.

Methods: In all, 185 cases with a referred reported diagnosis of LGSOC were retrospectively evaluated by a CLIA-certified lab (Caris Life Sciences, Phoenix, AZ) using hotspot (46 genes) and whole exon (592 genes) next generation sequencing (NGS) technologies interrogating DNA, fusion gene analysis interrogating RNA (52 genes), fragment analysis (FA), in situ hybridization (ISH) and/or immunohistochemistry (IHC). PD-L1 (SP142 antibody) positivity was + staining intensity in at least 5% of tumor cells. A second independent histologic review of all cases is pending to confirm LGSOC.

Results: Most specimens (99.5%, 184/185) underwent hotspot (n=106) or whole exon (n=78) NGS. The most frequently mutated genes included KRAS (27.2%, 50/184), NRAS (10.3%, 19/184), BRAF (7.1%, 13/184) and PIK3CA (2.2%, 4/184). Copy number alterations (CNA) were detected in few genes: ADGRA2, FGFR1, HOOK3, NFI3, PCM1, RPL5, SMAD2, and ZNF703 (all 1.3%, 1/77). For hormonal biomarkers, expression rates were as follows: AR, 41.5% (35/82); ER [using a cut-off of 2+ staining in 75% of tumor cells], 81.5% (150/184); and PR, 31.5% (58/184). PD-L1 expression was 3.7% (6/163) and no MMRd (0.0%, 0/6) by IHC was noted. No gene rearrangements (0.0%, 0/9), microsatellite instability (0.0%, 0/78) or high tumor mutational burden (0.0%, 0/74 using a cut-off of >=17 mutations/Mb) were found.

Conclusion: This study represents the largest cohort of molecular profiling in LGSOC. This will be further enriched by independent confirmation of histology. Based on our analysis, LGSOC has multiple targets supporting the use of hormone therapy and therapies targeting the MAPK pathway (e.g. BRAF). FGFR1 may be a potential target in a very rare subgroup of LGSOC.

Hormonal therapy appears to be a viable option in LGSOC given the protein overexpression observed.

Unlike high-grade serous ovarian cancer, HRD (e.g. BRCA1, BRCA2) does not appear to play a role in LGSOC.

Immunotherapies are not expected to be of potential benefit in this patient population based on MSI, TMB, and PD-L1 results.

More therapies are urgently needed in this uncommon ovarian cancer.

Conclusions

• Comprehensive tumor profiling shows that LGSOC has multiple targets supporting the use of hormone therapy and therapies targeting the MAPK pathway (e.g. BRAF).

• FGFR1 may be a potential target in a very rare subgroup of LGSOC.

• Hormonal therapy appears to be a viable option in LGSOC given the protein overexpression observed.

• Unlike high-grade serous ovarian cancer, HRD (e.g. BRCA1, BRCA2) does not appear to play a role in LGSOC.

• Immunotherapies are not expected to be of potential benefit in this patient population based on MSI, TMB, and PD-L1 results.

• More therapies are urgently needed in this uncommon ovarian cancer.

References


Table 1. Demographics of LGSOC cohort. Most submitted specimens (63.4%, 118/186) were from loco-regional (e.g. lymph nodes) or distant (e.g. liver) sites.

Table 2. Copy number alterations (CNA) by NGS in LGSOC. Gene amplification events were rare in this cohort.

Table 3A and 3B. Gene fusion events in LGSOC. In an analysis of over 50 genes for potential fusion events, no gene fusions were detected in LGSOC. In addition, no ARv7 and EGFRvii fusion transcripts were detected using the fusion gene assay.

Table 4. Gene Percent Amplified in LGSOC. Gene Percent Amplified in LGSOC. Gene Percent Amplified in LGSOC. Gene Percent Amplified in LGSOC.