Comprehensive molecular profiles of low-grade serous ovarian cancer

Adam ElNaggar[1], David Robins[1], David Arguello[2], Michael Ulm[1], Gina Mantia-Smaldone[3], Christina Chu[3], Ira Winer[4], Rob Holloway[5], Tom Krivak[6], Nathaniel Jones[7], Valerie Galvan-Turner[8], Thomas Herzog[9], Jubilee Brown[10]

[1]West Cancer Center and Research Institute, Memphis, TN; [2]Caris Life Sciences, Phoenix, AZ; [3]Fox Chase Cancer Center, Philadelphia, PA; [4]Karmanos Cancer Institute, Detroit, MI; [5]AdventHealth Orlando Cancer Institute, Orlando, FL; [6]Allegheny Health Network, Pittsburgh, PA; [7]University of South Alabama, Mobile, AL; [8]West Virginia Cancer Institute, Morgantown, WV; [9]University of Cincinnati, Cincinnati, OH; [10]Atrium Health, Charlotte, NC

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 homogenously 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 hot-spot (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 2+ 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 hot-spot (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*, *NSD3*, *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 against the MAPK pathway. Given the tumor genomic stability and low PD-L1 expression, immunotherapies are not expected to have significant efficacy. Further studies to evaluate the prognostic value of different molecular profiles are ongoing.

Results

Age	Specimen Info
Mean = 54 Median = 55	Ovary/Fallopian tube/peritoneum (36.2%, 67/185)

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.

Results

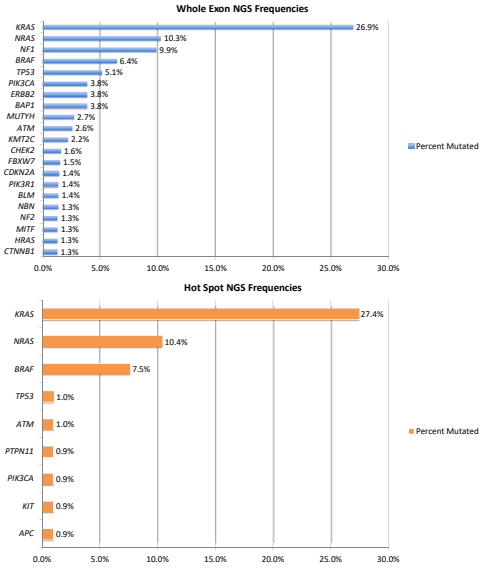

Figure 1A and 1B – Next generation sequencing by whole exon sequencing (A) and hot spot sequencing (B). LGSOC specimens were profiled by either a whole exon 592 gene panel or by utilizing a 46-gene hot spot panel. *KRAS* was mutated more often than other genes (27.2%, 50/184). MSI and TMB signatures were unremarkable.

Gene	Percent Amplified
ADGRA2	1.3%
FGFR1	1.3%
HOOK3	1.3%
NSD3	1.3%
PCM1	1.3%
RPL5	1.3%
SMAD2	1.3%
ZNF703	1.3%

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

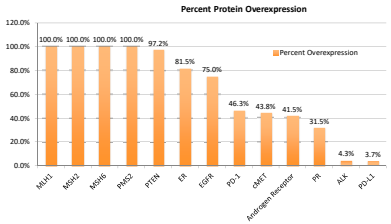

Figure 2 – Distribution of protein overexpression by immunohistochemistry (IHC). As protein expression was detected in MLH1, MSH2, MSH6, and PMS2, no MMRd was detected in this cohort. A high expression of ER (81.5%), using a threshold of 2+ intensity in at least 75% of tumor cells, was noted. PD-L1 expression was low (3.7%) in this cohort.

Results

Gene Panel	Fusions Detected
See "Genes Evaluated Using Fusion Gene Assay" table	0.0%

Genes Evaluated Using Fusion Gene Assay						
AKT3	*ALK*	*ARHGAP26*	*AXL*	*BRAF*	*BRD3*	*BRD4*
EGFR	*ERG*	*ESR1*	*ETV1*	*ETV4*	*ETV5*	*ETV6*
EWSR1	*FGFR1*	*FGFR2*	*FGFR3*	*FGR*	*INSR*	*MAML6*
MAST1	*MAST2*	*MET*	*MSMB*	*MUSK*	*MYB*	*NOTCH1*
NOTCH2	*NRG1*	*NTRK1*	*NTRK2*	*NTRK3*	*NUMBL*	*NUTM1*
PDGFRA	*PDGFRB*	*PIK3CA*	*PKN1*	*PPARGG*	*PRKCA*	*PRKCB*
RAF1	*RELA*	*RET*	*ROS1*	*RSPO2*	*RSPO3*	*TERT*
TFE3	*TFEB*	*THADA*	*TMPRSS2*			

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 EGFRvIII fusion transcripts were detected using the fusion gene assay.

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

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2. David M. Gershenson. Progress and future directions in the management of low-grade serous cancer of the ovary. [abstract]. In: Proceedings of the ACCR Conference: Addressing Critical Questions in Ovarian Cancer Research and Treatment; Oct 1-4, 2017; Pittsburgh, PA. Philadelphia (PA): ACCR; *Clin Cancer Res*. 2018; 24(15_suppl):abstract nr IA18.