Characterizing the genomic and immune landscape of serous borderline tumors and low-grade serous ovarian cancer

Rahul Krishnan[1], Agnes Bilecz[1], Lisa Schweizer[1], Aasa Shimizu[1], Ellen Jaeger[2], Jen Godden[2], Melissa C. Stoppler[2], Ernst Lengyel[1]

[1]Gynecologic Oncology Section, Division of Obstetrics & Gynecology, University of Chicago, Chicago, IL, // [2]Tempus Labs, Inc., Chicago, IL

INTRODUCTION

- Low-grade serous ovarian cancer (LGSC) is a rare subtype of epithelial ovarian cancer, accounting for 5% of all cases.
- These cancers are marked by resistance to cytotoxic chemotherapy and frequently exhibit MAP kinase (MAPK) pathway mutations.
- LGSC is thought to arise either *de-novo*, or develop from its putative precursor, serous borderline tumor (SBT).
- We sought to characterize the genomic and immune landscape of LGSC and SBT.

METHODS

- De-identified records of 6,605 patients with ovarian cancer were retrospectively analyzed.
- Selection criteria included a histological diagnosis of low-grade serous ovarian cancer (LGSC) and serous borderline ovarian tumor (SBT).
- Tumor sequencing performed via the Tempus xT assay, a targeted, tumor-normal-matched DNA panel that detects single-nucleotide variants and insertions and/or deletions in 648 genes with high sensitivity and specificity.
- Immunological markers including tumor mutational burden (TMB), microsatellite instability (MSI), and PD-L1 status were also assessed in this cohort.
- The prevalence of individual gene alterations were described and compared by Chi-squared/Fisher's Exact tests and adjusted for multiple testing using false discovery rate methods.

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Correspondence: Rahul Krishnan: rahul.krishnan@uchicagomedicine.org

SUMMARY

- In our cohort, SBT and LGSC share a **similar microsatellite stable status, low PD-L1 expression and a high percentage of MAP** kinase pathway mutations.
- The higher incidence of BRAF mutations in SBT and increased frequency of NRAS mutations in LGSC suggest that MAPK pathway gene mutations may **differentially impact propensity for tumor behavior and malignant potential**.

RESULTS

Table 1. Cohort Demographics

	Overall N = 132	LGSC N = 108	SBT N = 24	p-value[1]
Age at Diagnosis				0.7
Median (IQR)	55 (40, 65)	55 (42, 65)	57 (40, 64)	
Range	19, 87	21, 87	19, 73	
Unknown	3	2	1	
Age at Diagnosis				0.7
<=60	77 (60%)	64 (60%)	13 (57%)	
>60	52 (40%)	42 (40%)	10 (43%)	
Unknown	3	2	1	
Race				0.14
White	71 (84%)	61 (86%)	10 (71%)	
Black or African American	7 (8.2%)	5 (7.0%)	2 (14%)	
Other	6 (7.1%)	5 (7.0%)	1 (7.1%)	
Asian or Pacific Islander	1 (1.2%)	0 (0%)	1 (7.1%)	
Unknown	47	37	10	

[1] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Figure 2. Most Frequently Altered SNVs

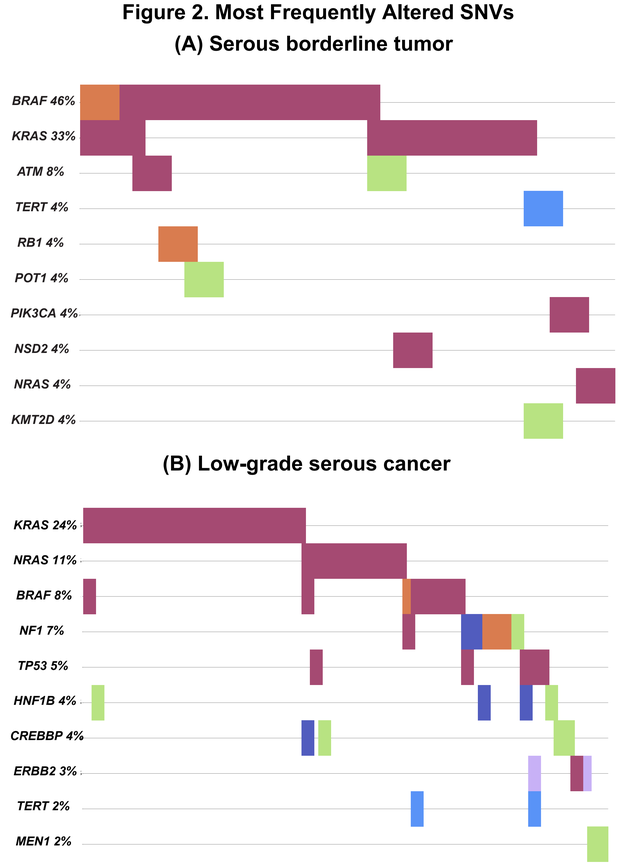

Figure 2. Oncoplot summarizing genes with the most frequently altered SNVs among serous borderline tumors (A) and low-grade serous cancer (B). *ATM* (8.3%) was the most common non-MAPK altered gene in SBT, whereas *CREBBP* (3.7%) and *HNF1B* (3.7%) alterations were the most frequently altered non-MAPK genes in LGSC.

Table 2. Co-alterations of interest

Gene	LGSC N = 108	SBT N = 24	p-value[†]	q-value[2]
BRAF	9 (8.3%)	11 (46%)	<0.001	0.001
KRAS	26 (24%)	8 (33%)	0.3	>0.9
NRAS	12 (11%)	1 (4.2%)	0.5	>0.9
ATM	1 (0.9%)	2 (8.3%)	0.085	>0.9
NF1	8 (7.4%)	0 (0%)	0.3	>0.9
TP53	5 (4.6%)	0 (0%)	0.6	>0.9
BAP1	1 (0.9%)	1 (4.2%)	0.3	>0.9
CREBBP	4 (3.7%)	1 (4.2%)	>0.9	>0.9
PIK3CA	1 (0.9%)	1 (4.2%)	0.3	>0.9
RB1	1 (0.9%)	1 (4.2%)	0.3	>0.9
ERBB2	3 (2.8%)	0 (0%)	>0.9	>0.9
KDM5C	2 (1.9%)	0 (0%)	>0.9	>0.9
ASXL1	1 (0.9%)	0 (0%)	>0.9	>0.9
ATRX	1 (0.9%)	0 (0%)	>0.9	>0.9
CDKN2A	1 (0.9%)	0 (0%)	>0.9	>0.9
EIF1AX	1 (0.9%)	0 (0%)	>0.9	>0.9
ESR1	1 (0.9%)	0 (0%)	>0.9	>0.9
LZTR1	1 (0.9%)	0 (0%)	>0.9	>0.9
MAP2K1	1 (0.9%)	0 (0%)	>0.9	>0.9
MAP3K1	1 (0.9%)	0 (0%)	>0.9	>0.9
MUTYH	1 (0.9%)	0 (0%)	>0.9	>0.9
NF2	1 (0.9%)	0 (0%)	>0.9	>0.9
SMARCA4	1 (0.9%)	0 (0%)	>0.9	>0.9

† Fisher's exact test; Pearson's Chi-squared test; 2 False discovery rate correction for multiple testing

Figure 1. Co-alterations among LGSC and SBT

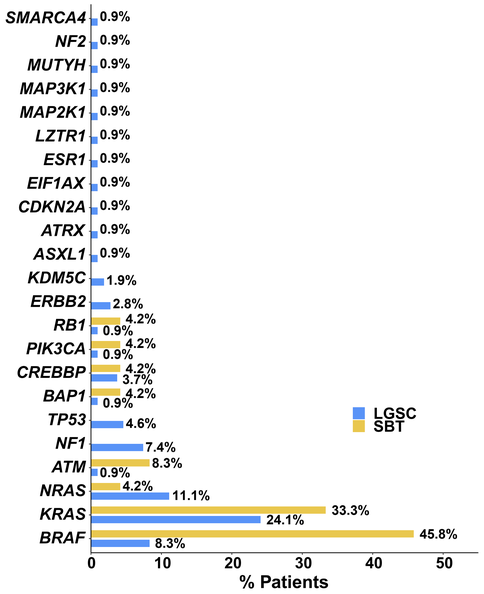

Table 2. Approximately 51% (n=55) of LGSC patients had MAPK mutated tumors whereas approximately 75% (n=18) of serous borderline tumors had MAPK pathway related gene mutations.

Table 3. Immunological Marker Profile in LGSC and SBT

	Overall N = 132	LGSC N = 108	SBT N = 24	p-value[†]
TMB (mut/Mb)				>0.9
Median (IQR)	1.17 (0.42, 2.34)	1.17 (0.39, 2.50)	1.17 (0.79, 1.67)	
Range	0.00, 6.67	0.00, 6.67	0.37, 3.43	
MSI				>0.9
Low/Stable	131 (100%)	107 (100%)	24 (100%)	
High	0 (0%)	0 (0%)	0 (0%)	
Unknown	1	1	0	
MMR Deficiency based on internal IHC				
Not Deficient	65 (100%)	58 (100%)	7 (100%)	
Unknown	67	50	17	
PDL1 result from internal IHC				0.4
Negative	63 (95%)	54 (96%)	9 (90%)	
Positive	3 (4.5%)	2 (3.6%)	1 (10%)	
Unknown	66	52	14	

† Wilcoxon rank sum test; Fisher's exact test

Table 3. LGSC and SBT tumors exhibited low overall percentage of tumor-infiltrating immune cells (TIIC). All LGSC and SBT samples were microsatellite-stable and tumor mutation burden (TMB) was similar for all LGSC and SBT tumors. Two of 56 LGSC cases and 1 of 10 SBT cases with PDL-1 testing were PDL-1 positive.