Molecular and immune profiling of TP53-mutated ovarian cancers with non-BRCA1/2 homologous recombination gene alterations

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Introduction
• Molecular alterations in homologous recombination (HR) pathway genes lead to homologous recombination deficiency (HRD) in ~50% of high grade serous ovarian carcinomas (HGSOC)
• The immune microenvironment of BRCA1/2-mutated (BRCAm) HGSOC has been well-characterized, but there is limited understanding of tumors with genomic alterations in other HR genes (NBHRD).
• The objective of the current study is to compare the molecular and immune signatures of BRCAm versus NBHRD tumors

Figure 1. Summary of comprehensive genomic and immune profiling assay

Genomic Profiling
SNV/INDEL/Fusion/CNV for 523 genes1
Tumor mutational burden (TMB)
Microsatellite Instability (MSI)

Immune Profiling
• RNA-seq expression profiling of 395 immune transcripts2
• PD-L1 HIC2
• Cell Proliferation3
• Tumor Inflammation3
• Cancer Tests Antigen Burden4

Methods
• We identified 173 epithelial ovarian carcinomas (EOC) characterized by comprehensive genomic and immune profiling (Omniseg INSIGHT, Labcorp, Buffalo, NY)1 from June 2021 to November 2022 (Figure 1).
• The BRCAm cohort was defined as tumors with known pathogenic alterations in BRCA1 and BRCA2 (Table 1). Tumors were classified as NBHRD if BRCA1 and BRCA2 lacked alterations and tumors harbored pathogenic alterations in any of the following genes: ARID1A, ATM, ATRX, BARD1, BLM, BRIPL1, CHEK1/2, FANCA, FANC, FANCD2, FANCE, FANCG, MRE11A, NBN, PALB2, RAD50, RAD51 (Table 2).

Figure 2. Volcano plot of gene expression changes in BRCAm (BRCA1/2+) and NBHRD (BRCA1/2-, HR+).

Table 1. BRCAm cohort mutations
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<td>5609dupT (S1871fs)</td>
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Table 2. NBHRD cohort mutations

Results
84 cases had complete CGIp, including 11 BRCAm, 7 NBHRD, and 67 without HR gene alterations (HR-proficient, HRP). The histology of BRCAm and NBHRD tumors was consistent with high grade serous ovarian carcinoma (Figure 3). Compared to the BRCAm cohort, NBHRD tumors were associated with NBHRD vs BRCAm, p-value:
• Advanced age at diagnosis (mean 80y vs 63y, p=0.002)
• Lower TMB (3.9 vs 6.6, p=0.011)
• Higher Tumor Immunogenicity Score (mean 59.1 vs 41.7, p = 0.044)
• 32 immune genes with expression changes, 31 (97%) up-regulated (1.3-3.3 fold) in NBHRD compared to BRCAm tumors (Figure 2), including BRB1
• No differences observed in PD-L1 TPS, Cellular Proliferation Score, or Cancer Tectis Antigen Burden (p>0.05)

Figure 3. Representative images of H&E-stained BRCAm and NBHRD tumors

Conclusions
In this limited dataset, NBHRD tumors had a higher TIGS but harbored less mutational burden compared to BRCAm tumors
The findings suggest that:
• NBHRD tumors have enhanced immunogenicity that may be unrelated to neoantigen load
• NBHRD tumors may have distinct immune escape mechanisms versus BRCAm tumors

Future Directions for Research:
• Establish whether the findings hold for larger datasets
• Determine if NBHRD is associated with distinct clinicopathologic features

References

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