Oral Abstract 2: Actionable Genomic Alterations in Homologous Recombination–Proficient Ovarian Cancer

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Topic
Ovarian

Objectives
We aimed to identify actionable biomarkers for targeted therapies and immune checkpoint inhibitors in homologous recombination-proficient (HRP) ovarian cancer.

Methods
Genomic data from the AACR GENIE and TCGA cohorts were analyzed to classify ovarian tumors by histology and homologous recombination status. Homologous recombination deficiency (HRD) was defined by the presence of homologous recombination repair (HRR) gene alterations, including BRCA mutations, as a genomic proxy for HRD; tumors lacking these alterations were classified as HRP. Recurrent genomic alterations were used to define the genomic landscape of HRP tumors. Overall survival (OS) was evaluated using Kaplan–Meier methods.

Results
Genomic data from 7,102 ovarian tumors were analyzed. The median age was 62 years (IQR 54–70), with 41.3% primary and 47.2% metastatic tumors. High-grade serous tumors (HGSOC) comprised 70.1% (n=4,981), followed by clear cell (7.5%), low-grade serous (6.2%), endometrioid (5.8%), and mucinous (2.7%) subtypes. BRCA mutations were identified in 13.6% of cases. Overall, 32.4% of HGSOC tumors were classified as HRD (n=1,614), while 67.6% were HRP (n=3,367). Among HRP tumors, 32.8% (n=1,105) harbored at least one actionable genomic alteration based on the MSK Onco KB mutations for HGSOC. The majority of these were associated with targeted therapies (29.8%, n=1,003), while immunotherapy-associated biomarkers were uncommon. The most frequently observed actionable alterations included CCNE1 amplification (11.9%), PIK3CA mutations (4.3%), and ERBB2 amplification (2.2%), with additional alterations such as KRAS (1.5%), RB1 (2.4%), ARID1A (3.3%), and NF1 (4.8%) occurring at low frequencies. Immunotherapy-associated biomarkers were rare in HRP tumors, with tumor mutational burden–high (TMB-H) observed in 2.0% and mismatch repair deficiency (dMMR) in 2.9% of cases. In contrast, TMB-H and dMMR were more prevalent in HRD tumors (TMB-H: 30.5%, dMMR: 16.5%). In a validation cohort of HRP ovarian tumors (n=296 with available survival data), immunotherapy-associated biomarkers remained uncommon (n=8, 2.7%). Kaplan–Meier analysis did not demonstrate a significant difference in overall survival between HRP tumors with and without TMB-H or dMMR alterations (log-rank p = 0.639).

Conclusions
Homologous-recombinant proficient ovarian tumors harbor limited actionable genomic markers while immunotherapy biomarkers remain infrequent.These findings highlight the need for continued investigation of novel therapeutic strategies and biomarker development in this population.

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Abstract Table or Graph

Figure 1. Actionable genomic alterations in HRD versus HRP HGSOC