Characterization of the mutational landscape of high-grade serous ovarian cancer pre- and post-neoadjuvant chemotherapy.

Mark C. Valentine, MD, PhD, Washington University in St. Louis/ Barnes Jewish Hospital

Topic: Ovarian

Objectives
To identify genetic changes associated with neoadjuvant chemotherapy (NACT) in non-responsive (NACT-NR) and responsive (NACT-R) high-grade serous ovarian cancer (HGSOC).

Methods
Matched biopsies were obtained from 22 patients with HGSOC pre-NACT and at interval cytoreductive surgery. Biopsied tumors had >60% cellularity. Patients were categorized as NACT-NR (n=12) or NACT-R (n=10) based on surgical, radiographic and pathologic findings. Exome alignment, quality control, and variant calling were performed according to GATK best practices. Average sequencing depth was 275x. Statistical analysis was performed in R (v. 4.0.4). For pre- and post- NACT mutation allele frequency (MAF) analysis, mutations detected at >2.5% were included. Mutations with >2-fold change in MAF between timepoints were considered in subsequent analysis. To test for enrichment of these mutations in COSMIC cancer gene census (CGC) genes, an empiric distribution was created from 100,000 random samples. Our samples were compared to this with enrichment defined as >95%ile.

Results
TP53 mutation was present in 100% of NACT-NR tumors before NACT and in 83% after. By contrast, TP53 mutation was detected in 70% of NACT-R tumors pre- and in 50% post- NACT. Further, 13 of the 22 TP53 mutations in NACT-NR tumors were splice, nonsense, or frameshifts. In NACT-R patients, these classes accounted for 6 of the 12 mutations. NACT-NR samples had more mutations with a >2-fold change in MAF between timepoints: 209 with increased MAF and 202 that decreased MAF compared to 37 and 70 respectively in NACT-R samples. We found that mutations with increased MAF in NACT-NR tumors were significantly enriched for CGC genes (99.5%ile). There was a similar enrichment of mutation occurring in CGC genes in mutations with decreased MAF in NACT-R samples (99.7%ile). Mutations with increased MAF in NACT-R tumors were not enriched for CGC genes (92.1%ile).

Conclusions
NACT-NR tumors had more TP53 mutations pre-NACT, and more persistent TP53 mutations post-NACT than NACT-R tumors. NACT-NR tumors had more mutations that underwent a >2-fold change in MAF post-NACT. Mutations that increased in MAF were enriched in CGC genes in NACT-NR tumors, while those that decreased in MAF were enriched in CGC genes in NACT-R tumors.