Genotype Matched Treatment for Patients with Advanced Type I Epithelial Ovarian Cancer (EOC)

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Background: Type I EOCs are uncommon, genetically stable tumors that are often resistant to chemotherapy. Genomic alterations that activate the Mitogen-Activated Protein-Kinase (MAPK) signaling pathway frequently occur in Type I EOCs that may sensitize to downstream MEK inhibition.

Methods: Formalin fixed paraffin embedded tumor tissues from patients (pts) with Type I EOC were prospectively screened for genomic alterations in a CLIA-certified laboratory using Sequenom MassArray genotyping or targeted sequencing using the Illumina MiSeq TruSeq Amplicon Cancer Panel. The outcomes of pts receiving treatment at Princess Margaret Cancer Centre were retrospectively reviewed.

Results: From Mar/11 to Jan/14, 49 pts with type I EOC underwent molecular testing, including 80% low grade serous (LGS), 10% clear cell (CC), and 10% mucinous (MC) histologies. Thirty-two pts (65%) were found to have ≥1 somatic mutations: 23 KRAS, 6 NRAS, 2 PIK3CA, 1 BRAF, 1 AKT, 1 PTEN, 1 TP53, 1 CTNNB1. Fifteen pts (47%) with a median of 2 (range 0-4) prior systemic therapies were treated on genotype-matched phase I or II trials with targeted inhibitors. Fourteen pts (93%) with KRAS/NRAS mutations (12 LGS, 1 CC, 1 MC) were treated with targeted combinations that include a MEK inhibitor. Best RECIST 1.1 response for the 14 evaluable pts included: 5 PR (4 confirmed), 8 SD and 1 PD. In pts with PR/SD as best response, the median % of target-lesions shrinkage was 27% (range 12.5-62.5%). Gynecological Cancer Intergroup CA125 related-response was observed in 8/8 KRAS and/or NRAS mutant pts treated with MEK inhibitor combination treatments. Of 9 pts who had received prior systemic therapy for recurrent disease, the median duration of genotype-matched treatment was 19 weeks (range 6.5-58), compared with 9 weeks (range 4-53) for the immediate prior line of therapy.

Conclusions: Genotyping and targeted sequencing of Type I EOCs frequently identifies actionable mutations. Matched treatment with MEK inhibitors in KRAS and/or NRAS mutant type I EOC pts is an active therapeutic strategy.