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### The challenge of targeted therapies in epithelial ovarian cancer

The mortality rate for ovarian cancer has remained roughly unchanged for the past 40 years. Various targeted therapies for ovarian cancer are under investigation, including therapies targeting angiogenesis, DNA repair, the cell cycle, signaling pathways and immune checkpoint proteins. However, these treatments are failing to significantly improve overall survival.

Ovarian cancer is a heterogeneous disease. There are five major histological subtypes of epithelial ovarian cancer: high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), ovarian clear cell carcinoma (OCCC), mucinous epithelial ovarian carcinoma, and ovarian endometrioid carcinoma. TP53 mutations are present in almost all HGSCs, and BRCA1/2 mutations are present in approximately 10% of HGSCs. However, other actionable mutations are infrequent in HGSCs. On the other hand, KRAS activating mutations are present in more than 30% of LGSCs and 40% of mucinous ovarian carcinomas. PIK3CA activating mutations are present in more than 35% of OCCCs and more than 20% of ovarian endometrioid carcinomas. BRAF activating mutations are detected in both LGSCs (2-33%) and mucinous ovarian carcinomas (~10%). ARID1A, the AT-rich interactive domain 1A gene, is mutated in more than 45% of OCCCs and more than 25% of ovarian endometrioid carcinomas. These advances in the molecular characterization of epithelial ovarian cancer have led to clinical trials targeting specific histological subtypes to overcome the challenge of this heterogeneous disease. A phase II study has been conducted to investigate the activity of a MEK1/2 inhibitor (selumetinib) for women with recurrent LGSC. About 15% (8/52) of patients had an objective response. Next-generation sequencing of the tumor sample from a patient with a complete and striking durable response to selumetinib identified a 15-nucleotide deletion in the MAP2K1 gene, which encodes MEK1. Another patient in the study who had a durable response had a KRAS G12V mutation. However, there is no correlation of KRAS, NRAS, or BRAF mutation status with selumetinib response. A phase II study has also been conducted to investigate the activity of mTOR inhibitor temsirolimus with carboplatin and paclitaxel as first-line therapy in patients with newly diagnosed stage III or IV OCCC. However, this regimen did not significantly increase progression-free survival at 12 months. A preclinical study by our group suggests that the sensitivity of OCCC with PIK3CA mutations to PI3K inhibitor can be affected by the co-existence of KRAS mutations. We also found that ARID1A-mutant OCCC cells express higher levels of reactive oxidative species (ROS) and are more sensitive to ROS-inducing agents than ARID1A-wild-type ovarian cancer cells. These vulnerabilities in OCCC with ARID1A mutation are waiting to be tested clinically. The results to date from targeted therapies for epithelial ovarian cancer highlight the need to identify robust predictive markers to guide the selection of patients in whom targeted drugs are most likely to be beneficial. Also, the role of adaptive responses in resistance to targeted therapy needs to be better understood. Another challenge is finding targeted therapy for rare types of ovarian cancer. For instance, the GOG-0241 phase III trial for patients with mucinous epithelial ovarian cancer was suspended owing to low accrual.

### Biography

Kwong Kwok Wong, Ph.D. is a molecular biologist and completed his PhD from the Chinese University of Hong Kong. He is currently a professor in the Department of Gynecologic Oncology and Reproductive Medicine at The University of Texas MD Anderson Cancer Center. His laboratory is interested in deciphering the molecular pathogenesis of ovarian cancer with a translational goal to identify biomarkers and therapeutic targets. One of his current projects supported by the UT MD Anderson Ovarian SPORE grant is to understand the molecular progression of low-grade serous ovarian cancer and to determine the resistance mechanisms of ovarian cancer to MEK inhibitors. He has published 78 peer-reviewed articles and 13 book chapters. He is also an inventor or co-inventor in 6 US issued patents

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