



Memorial Sloan-Kettering
Cancer Center

Update

IN GYNECOLOGIC ONCOLOGY

PROGRESS TOWARD INDIVIDUALIZED CANCER CARE

Molecular Medicine for Ovarian and Endometrial Cancer

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Advances in ovarian and endometrial cancer treatment primarily have been derived from improved surgical techniques, better postoperative care, and more effective cytotoxic chemotherapy. Presently, we are in the midst of a revolution in molecular medicine. Remarkable advances have been made in the treatment of solid tumors, including colon cancer, lung cancer, breast cancer, and gastrointestinal stromal tumors (GISTs). Ovarian and endometrial cancers have lagged slightly behind, but with new knowledge and improved technology, the gap will soon be narrowed.

Endometrial Cancer

We have known for more than a decade that mutations in a gene called *PTEN* are common in endometrial cancer. More recently, however, we have learned that *PTEN* is part of a receptor tyrosine kinase (RTK) signaling pathway that includes many other components. This pathway contains a number of genes that are commonly mutated in endometrial cancers and includes *PIK3CA*, *KRAS*, *FGFR2*, *CTNNT1*, and *PTEN*. Mutations in this pathway are found in nearly 75% of all endometrial cancers of endometrioid histology, the most common subtype of endometrial cancer (Fig. 1). This collective burden of mutations, coupled with other genomic alterations, indicates that activation of this pathway may be more common in endometrial cancer than any other solid tumor. Many drugs have been developed to target *PIK3CA*, *FGFR2* or their downstream effector, mTOR. These agents are currently in early-phase clinical trials, and isolated responses have been seen in both endometrioid and serous tumors. These drugs are also considered less toxic than standard cytotoxic chemotherapy regimens. At the recent meeting of the International Gynecologic Cancer Society, a randomized phase II trial of ridaforolimus (an mTOR inhibitor) versus standard therapy (progestins or chemotherapy) was reported. Though no responses were seen, the progression-free

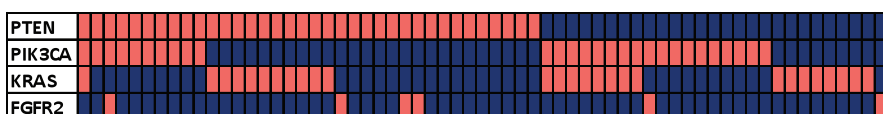


Fig. 1. Representative heat map demonstrating overlapping mutations in patients with endometrial carcinoma. Each column represents a single tumor specimen; each row corresponds to the indicated gene; pink boxes are mutations in the specified gene for a given sample; and blue boxes reflect the absence of an identifiable mutation.

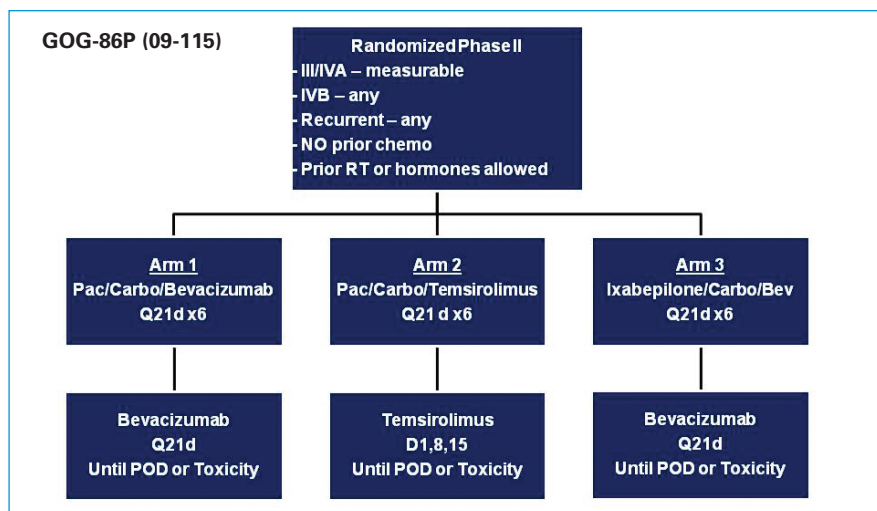


Fig. 2. GOG-86P (09-115).

survival was significantly longer in the group treated with ridaforolimus, suggesting that this drug was able to control disease better than traditional therapies. At MSKCC, we are currently leading a Gynecologic Oncology Group (GOG) trial comparing standard cytotoxic chemotherapy given in combination with various biologic agents including bevacizumab or temsirolimus (another mTOR inhibitor) in women with advanced or recurrent endometrial cancer who have not previously received chemotherapy. This trial, GOG-86P, is open and accruing patients (Fig. 2). All patients will submit a previously collected tumor sample from which we will perform molecular profiling for the mutations outlined above and other genomic changes. In this manner, we work to identify which types of patients are most likely to respond to each of these novel treatments.

Ovarian Cancer

Though many of the common genomic alterations in ovarian cancer have been known for many years, there is a dearth of reliable integrated data that comprehensively assesses all of the genomic changes in the most aggressive type of ovarian cancer—high-grade serous carcinoma. We have been working with the National Institutes of Health, National Cancer Insti-

tute, and National Human Genome Research Institute to conduct this type of research through The Cancer Genome Atlas (TCGA). Through this effort, we have confirmed that mutations are commonly found in the *TP53*, *BRCA1*, and *BRCA2* genes; however, by using second-generation whole exome sequencing techniques, we have also learned that there are only a few other recurrently mutated genes present in more than 5% of the specimens. This suggests that attempting to target mutated genes for therapeutic exploitation is unlikely to be successful beyond the BRCA/HR pathway, as discussed elsewhere in this newsletter (see article by K. Bell-McGuinn). However, an unexpected discovery from TCGA was the substantial burden of copy number alterations seen in all ovarian tumors. This suggests that genomic instability is a hallmark of ovarian cancer and is due in part to defective homologous recombination (HR). TCGA identified defective HR in 30-50% of ovarian cancers, in part due to germline mutations in *BRCA1* and *BRCA2*. It is possible, however, that other defects in HR will render patients sensitive to poly-ADP-ribose polymerase (PARP) inhibition, as discussed elsewhere. MSKCC is developing clinically applicable assays to screen patients for HR-pathway defects and conduct correlative studies for patients on clinical trials. We also continue to refine these estimates for all patients with serous ovarian carcinoma to better gauge the applicability of PARP treatment for all women with this disease. Laboratory studies are testing specific HR-pathway defects to see which result in greatest response to PARP treatment in vitro. ■