importance of studying combination therapy with medicines targeting distinct pathways."

Side effects of the combination therapy were manageable and similar in nature and severity to those seen with ipilimumab and nivolumab alone. The most common side effects were elevated pancreatic and liver enzymes, which were detected during lab tests and did not cause symptoms.

Sandra Swain, MD, president of ASCO and medical director at Washington Cancer Institute at MedStar Washington Hospital Center in Washington, DC, called the results "truly remarkable," adding that "this kind of response has not been seen with immunotherapy before."

"This study is clearly a proof of principle that concurrent use of two immune checkpoint antibodies can change the treatment paradigm for advanced melanoma," she said.

Researchers are now launching a randomized phase III trial of the ipilimumab/nivolumab combination as first-line therapy for patients with advanced melanoma. The head-to-head trial will investigate the efficacy of concurrent administration of the combination versus either ipilimumab or nivolumab alone. The combination is also being investigated in non–small cell lung cancer and renal cell carcinomas. ■

Endometrial Tumors Divide into Four Subtypes

The most comprehensive analysis of endometrial tumors to date suggests that they can be divided into four distinct subtypes based on their genomic profiles, potentially leading to a more accurate diagnosis of the disease and better choice of therapies, including targeted drugs currently being tested in clinical trials.

Conducted by investigators within The Cancer Genome Atlas Research Network, the analysis also identified genomic similarities between endometrial cancer and breast, ovarian, and colorectal cancers (Nature 2013; 497:67–73).

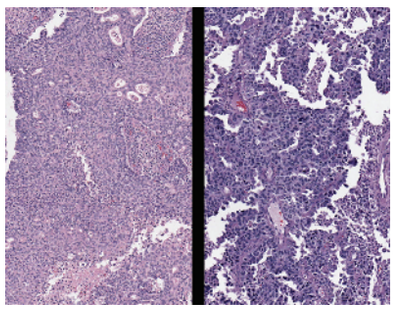
Clinically, endometrial cancers fall into 2 groups: endometrioid (type I) and serous (type II) tumors. Type I tumors are linked to excess estrogen, obesity, and a favorable prognosis. Type II tumors are more common in older women and tend to have a worse outcome. In addition to surgery, patients with early-stage endometrioid tumors typically undergo radiation therapy, while those with serous and late-stage endometrioid tumors typically receive chemotherapy.

However, "higher-grade endometrioid and serous tumors are tough to distinguish from each other," says Douglas Levine, MD, head of the Gynecologic Research Laboratory at Memorial Sloan-Kettering Cancer Center and coleader of the study. "About 25% of the time, pathologists can't agree on what to call these tumors," he says, and that difference of opinion can affect treatment choice.

In the study, researchers performed an integrated genomic and proteomic analysis of tumor samples from 373 patients. About 25% of the tumors pathologists classified as high-grade endometrioid had frequent mutations in *TP53* and numerous copy number alterations, characteristics associated with serous tumors. In contrast, most other endometrioid tumors had few *TP53* mutations or copy number alterations, but they did have frequent mutations in other cancer-associated genes, including *PTEN, CTNNB1, PIK3CA, ARID1A,* and *KRAS.*

Based on their results, the researchers divided the endometrial tumors into four groups:

- *POLE* ultramutated, which exhibited high mutation rates in the *POLE* gene and accounted for about 10% of endometrioid tumors
- hypermutated microsatellite instability, which had high rates of mutations but no *POLE* mutations
- copy-number low, which had a high frequency of mutations in *CTNNB1* and increased progesterone receptor activity, suggesting responsiveness to hormone therapy
- copy-number high, composed mostly of serous tumors, almost all of which had *TP53* mutations. Some high-grade endometrioid tumors fall into this group, indicating that they may need to be treated more aggressively after surgery.



Memorial Sloan-Kettering Cancer Center

Pathologists don't always agree on whether an endometrial cancer should be categorized as a grade 3 endometrioid tumor (left) or a serous tumor (right), but the distinction drives treatment choices. Molecular analysis of tumors shows that about 25% of high-grade endometrioid tumors have a molecular phenotype similar to serous tumors, suggesting that genomic-based classification of tumors may alter therapeutic decisions and improve patient outcomes.

In addition, the researchers found that high-grade uterine serous tumors share many molecular features with high-grade serous ovarian tumors and basal-like breast carcinomas, hinting that they could be treated similarly. Likewise, endometrioid endometrial carcinomas share some characteristics of colorectal cancers, including microsatellite instability and *POLE* mutations.

The findings could have clinical implications for patients within the next year or two, says Levine. For example, patients with *POLE* mutations had excellent outcomes in the study, so they may not need additional treatment following surgery. However, this group included only 17 patients, so further study is needed to confirm the finding.

Levine and others are now enrolling patients with endometrial cancer in clinical trials of targeted therapies based on their cancer's molecular traits, paralleling earlier work in breast cancer, with more trials to follow. "We need to confirm that certain subtypes respond better to particular targeted therapies so we can improve outcomes for these women," he says. ■

For more news on cancer research, visit *Cancer Discovery* online at http://CDnews.aacrjournals.org.