PARP Inhibitor Shows Promise for Advanced Prostate Cancer

Rubraca shrank tumors and lowered PSA levels in men with advanced prostate cancer.

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The PARP inhibitor Rubraca (rucaparib) led to tumor shrinkage in more than 40 percent of treated men with harmful BRCA mutations and lowered prostate specific antigen (PSA) levels in more than half, according to study results presented at the European Society for Medical Oncology (ESMO) 2018 Congress this month in Munich.

About 164,700 men in the United States will develop prostate cancer and about 29,400 will die of it this year, according to the American Cancer Society, making it the second leading cause of cancer-related death for men.

Testosterone and other male hormones stimulate the growth of prostate cancer. Treatment usually involves surgery or radiation plus hormone therapy to reduce androgen levels. But prostate cancer can develop resistance to androgen deprivation therapy, which is known as being castration-resistant. At advanced stages, the cancer can spread elsewhere in the body, including the bones. The five-year survival rate for men with metastatic castration-resistant prostate cancer is around 29 percent.

Wassim Abida, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, and colleagues presented findings from the Phase II TRITON2, which evaluated Rubraca in men with metastatic castration-resistant prostate cancer. Participants had previously been treated with androgen deprivation therapy, most often Xtandi (enzalutamide) or Zytiga (abiraterone), and taxane-based chemotherapy (usually docetaxel).

Prospective study participants underwent genetic testing for the presence of mutations that interfere with DNA repair, including BRCA1 or BRCA2 mutations and about a dozen other alterations. When these repair mechanisms don’t work properly, DNA damage can lead to uncontrolled cell growth. Women with deleterious BRCA mutations are at much higher risk for breast and ovarian cancer, and these mutations also increase susceptibility to prostate cancer. About 12 percent of the men screened for TRITON2 were found to have BRCA1 or BRCA2 mutations.

According to another ESMO presentation, a blood test may perform as well as tissue testing for

detecting BRCA mutations. This method would be less invasive and could reveal emerging new genetic alterations without repeated biopsies.

All participants in this open-label study received 600 milligrams of Rubraca by mouth twice daily. There was no placebo or comparison therapy arm. Treatment continued until radiography scans showed cancer progression or patients stopped for other reasons.

Rubraca, from Clovis Oncology, is a targeted therapy that blocks the poly ADP-ribose polymerase, or PARP enzyme, which plays a role in DNA repair. Inhibiting PARP leads to more DNA breaks in cancer cells, which halts cell division. People with BRCA mutations do not make proteins that repair this kind of damage, so BRCA-related cancers are especially susceptible to these drugs. Rubraca is currently approved for ovarian cancer. Other drugs in this class are approved for ovarian and advanced breast cancer and are being studied for prostate cancer.

The analysis presented at ESMO included 85 men treated with Rubraca. The median age was about 70. Half had BRCA1 or BRCA2 mutations and the rest had alterations in other DNA repair genes including CDK12 and ATM. Most (89 percent) had bone metastases and 42 percent had cancer spread to their abdominal organs. The median follow-up period was only 5.7 months, but ranged up to 16 months for some patients.

Among 25 evaluable men with BRCA mutations, the objective response rate—meaning complete or partial tumor shrinkage—was 44 percent. All were partial responses. Another 36 percent had stable disease. The median duration of response had not yet been reached because a majority of patients were still responding.

Just over half (51 percent) of a larger group of 45 evaluable men showed a PSA response, meaning they saw a reduction in prostate specific antigen levels.

Objective response and PSA response rates were much lower in men with CDK12 or ATM repair genes.

Rubraca was generally safe and well tolerated. Adverse events among men in this study were similar to those previously observed in studies of women with ovarian cancer. The most common side effects were nausea, fatigue, weakness, constipation, anemia and decreased appetite, usually mild or moderate. Five people stopped treatment because of treatment-related adverse events.

“Rucaparib has encouraging antitumor activity in metastatic castration-resistant prostate cancer patients with a deleterious alteration in BRCA1 or BRCA2,” the researchers concluded.

Rubraca recently received a Food and Drug Administration breakthrough therapy designation, given to new treatments that have the potential to offer substantial improvement over existing therapies for serious or life-threatening diseases.

After collecting more clinical trial data, Clovis expects to request FDA approval of Rubraca for prostate cancer in late 2019, which could make it the first PARP inhibitor to get the green light for

this indication.

Click here to see the ESMO 2018 program.

Click here for a Clovis press release about the study results.

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