Treating Recurrent Endometrial Cancer With Metformin, Letrozole and Abemaciclib Is Safe and Promising

Adding metformin to hormone therapy and a CDK4/6 inhibitor demonstrated encouraging and durable evidence of antitumor activity.

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A combination, triplet therapy that targets cancer cells from within and without caused tumors to shrink or stabilize in nearly all patients with recurrent or persistent estrogen receptor- (ER-) positive endometrial cancer, results from a recent phase 2 clinical trial show. Endometrial cancer, which begins in the lining of the uterus, is the sixth most common cancer worldwide, diagnosed in more than 400,000 women every year. The majority of endometrial tumors are ER-positive.

At today's Society of Gynecologic Oncology (SGO) Annual Meeting in Seattle, Panagiotis Konstantinopoulos, MD, PhD, the Velma Eisenson Chair for Clinical and Translational Research in Gynecologic Oncology at Dana-Farber, presented findings from the RESOLVE study, showing that treatment with metformin, letrozole [Femara], and abemaciclib [Verzenio] for recurrent estrogen receptor-positive endometrial cancer is safe and appears to induce deeper and more durable responses than letrozole and abemaciclib alone.

Konstantinopoulos initiated the trial based on preclinical research suggesting synergy between the three drugs, which together inhibit the estrogen receptor, CDK4/6, and PI3K pathways. Letrozole works by preventing an enzyme called aromatase from converting certain hormones into estrogen, thereby lowering overall estrogen levels. Abemaciclib blocks the CDK4 and CDK6 proteins, which play a key role in cell proliferation, while metformin, most commonly known as an anti-diabetic agent, also modulates the activity of the PI3K pathway.

All 25 patients in the trial received the three medicines. At a median of 17 months of follow-up, three patients had a complete response, to the therapy, five a partial response, and sixteen had stable disease. Median progression free survival was beyond 19.3 months and no patients discontinued therapy due to toxicities.

Based on next-generation sequencing of tumors, the team found that all the complete and partial responses were observed in patients with no specific molecular profile (NSMP) endometrial cancers without RB1 or CCNE1 mutations, suggesting this patient group will derive the most benefit from

this combination.

“Addition of metformin to hormonal therapy and CDK4/6 inhibition with abemaciclib demonstrated encouraging and durable evidence of activity in NSMP endometrial cancers providing support for simultaneous inhibition of ER, CDK4/6 and PI3K pathways in this setting,” said Konstantinopoulos.

The Society for Gynecologic Oncology (SGO)Annual Meeting where the results were shared today is the foremost scientific gathering for professionals dedicated to the treatment and care of individuals with gynecologic cancer.

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