Combination of everolimus and exemestane improves survival for women with metastatic breast cancer

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In an international Phase III randomized study, everolimus, when combined with the hormonal therapy exemestane, has been shown to dramatically improve progression-free survival, according to research from The University of Texas MD Anderson Cancer Center.

The study, known as Breast Cancer Trials of Oral Everolimus (BOLERO-2), was presented today at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium by Gabriel Hortobagyi, M.D., professor and chair of MD Anderson's Department of Breast Medical Oncology. Earlier findings were simultaneously reported in the New England Journal of Medicine.

Everolimus, an immunosuppressant agent first used to prevent rejection of organ transplants, also has anti-angiogenic properties. It inhibits the mammalian target of rapamycin (mTOR) protein, a central regulator of tumor cell division and blood vessel growth in cancer cells; the mTOR pathway is activated in hormone-resistant breast cancer, explained Hortobagyi. Currently, the oral agent is approved for both the treatment of kidney cancer and pancreatic neuro-endocrine tumors, with MD Anderson's research leading the way for the latter's usage approval by the FDA.

Preliminary BOLERO-2 data were first presented at ESMO and showed a significant progression-free survival benefit; these updated findings

represent six additional months of patient follow-up, Hortobagyi explained.

"This study is based on the concept that we now know more about the resistance mechanisms to endocrine therapy and the experimental arm of BOLERO-2 uses a dual-attack on treatment refractory hormone receptor-positive breast cancer: it simultaneously inhibits the estrogen-signaling pathway with the aromatase inhibitor, exemestane, and the PI3-kinase/AKT/mTOR pathway with the use of everolimus," Hortobagyi said. "For the first time in a large Phase III trial, we have demonstrated that this dual-attack is more effective than a single endocrine treatment for patients who have received prior endocrine therapy."

The international Phase III trial enrolled 724 metastatic breast cancer patients, all of whom were post-menopausal, had hormone receptor-positive disease and evidence of progressive disease. In a two-to-one ratio, 485 women were randomized to receive the combination of everolimus (10 mg daily), and exemestane, an aromatase inhibitor, and compared to 239 women who received exemestane and placebo. All were previously treated with and progressed on letrozole and anastrozole, with the majority of women extensively treated with prior therapies. The median age of the women enrolled was 62 years; the study's primary endpoint was progression-free survival.

In patients receiving the everolimus combination, researchers found a progression-free survival of 7.4 months, compared to 3.2 months in those who took exemestane alone, a finding Hortobagyi describes as "highly significant." The clinical benefit rate - complete responses, partial responses and stability exceeding six months - was 50.5 percent in those in the combination arm, compared to 25.5 percent in those who received the hormonal therapy alone. Adverse effects, such as shortness of breath, hyperglycemia, mouth sores and fatigue, were all higher in the

combination group, but were manageable and did not disrupt patients' quality of life, the researchers found. Survival data are still being analyzed.

Because aromatase inhibitors are associated with bone loss and fractures, as a safety measure, Hortobagyi and the researchers assessed patients for bone-turnover markers. The addition of everolimus was found to significantly reduce the level of such markers - an interesting area for future study, noted Hortobagyi.

"Over the years, our treatment approach for such women with metastatic breast cancer has been sequential use of as many hormone therapies as possible, keeping metastatic disease under control for as long as possible. These findings may allow us to change our approach. In this group of heavily pre-treated patients, all of whom progressed on prior endocrine therapy, the addition of this mTOR inhibitor resulted in significant prolongation of progression-free survival and an improved response rate, with only a modest addition of toxicity," said Hortobagyi.

Hortobagyi believes that these findings may be practice-changing for women who meet the criteria for BOLERO-2. Additional studies are planned with everolimus in breast cancer, including in combination with an aromatase inhibitor in the adjuvant setting, as well as additional clinical trials in the metastatic setting.

Provided by University of Texas M. D. Anderson Cancer Center