

Drug combination slows growth of most common type of advanced breast cancer

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The combination of taselisib and fulvestrant has shown to slow the growth of cancer in post-menopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor-2 (HER2) negative, PIK3CA-mutant, inoperable, locally advanced or metastatic breast cancer. Researchers from Memorial Sloan Kettering Cancer Center (MSK) presented this data, from the [SANDPIPER](#) trial, in a press conference at the annual meeting of the American Society of Clinical Oncology. This combination of a mutant-selective PI3K inhibitor and a selective estrogen receptor degrader halted the growth of advanced breast cancer for two months longer than hormone therapy alone and decreased the chance of cancer worsening by 30 percent.

MSK Physician-in-Chief José Baselga, MD, Ph.D., and colleagues have long been investigating how [cancer](#) cells escape the therapeutic pressure of PI3K inhibitors, how to identify those people who are more likely to respond to a specific therapy, and how to increase the effectiveness of such therapies through novel combinations.

"We have showed that taselisib improves benefit from fulvestrant in this population by 30 percent," explained Dr. Baselga, the study's lead author. "This work confirms the benefit of targeting the PI3K pathway and represents a significant step forward in developing a new class of agents for breast cancer. While there is more work to be done to diminish the side effects and toxicity, I am encouraged by these results."

ER-positive breast cancer is one of the most common types of breast

cancer, accounting for 70 percent of all cases. Approximately 40 percent of all ER-positive breast cancers have PIK3CA mutations. This translates to 25 percent of the total breast cancer population who could benefit from a novel therapy targeting the PI3K pathway.

Taselisib and the SANDPIPER Trial

Taselisib is the first medicine that specifically blocks the type of PI3K protein that is mutated in ER-positive breast cancers, making it the most potent weapon against these tumors. The phase III SANDPIPER trial is the first placebo-controlled randomized study evaluating a mutant-selective PI3K inhibitor in a biomarker-defined population. Taselisib has shown enhanced activity in PIK3CA mutant cell lines; more frequent tumor responses were observed in individuals with PIK3CA mutant tumors in early studies.

The international, multicenter study was designed to compare the efficacy and safety of taselisib and fulvestrant with that of fulvestrant and placebo in postmenopausal women with ER-positive, HER2-negative, PIK3CA-mutant, unresectable, locally advanced or metastatic breast cancer after recurrence or progression during or after an aromatase inhibitor therapy. The trial enrolled 516 women who were randomly assigned to receive taselisib and fulvestrant (340 women) or fulvestrant and placebo (176 women).

Methods and Findings

The SANDPIPER study confirms the clinical activity in this selected population. The study met its primary endpoint showing a two-month improvement of median progression-free survival, equating to a 30 percent risk reduction of disease progression (5.4 months with fulvestrant and placebo versus 7.4 months with taselisib and fulvestrant). The response rate more than doubled when taselisib was added to

treatment (11.9 percent versus 28 percent). Overall survival data are not yet mature. The safety profile of the combination was associated with considerable toxicities thought to be associated linked to the targeting of the PI3K pathway. The most common side effects included diarrhea, high blood pressure, and colitis. Seventeen percent of individuals who received taselesib stopped treatment early due to side effects.

"Through advances in precision medicine, we can create targeted combination treatment approaches and identify individuals who will see the most benefit," explained Dr. Baselga. "The study results, together with future translational research analyses, will help us further understand the role of inhibiting PI3K in ER-positive, HER2-negative [breast cancer](#) and will inform our future work as we look to limit the side effects and increase progression-free survival in this population."

In work published in *Science* in March 2017, Dr. Baselga and colleagues found that the inhibition of the PI3K pathway leads to activation of the ER-dependent transcription through the epigenetic regulator KMT2D. Many [breast](#) cancers rely on a disease pathway called PI3K, so drugs have been developed to inhibit this pathway. However, after responding initially to PI3K inhibitors, these tumors often activate another pathway, called ER, to begin growing again.

MSK researchers, led by Dr. Baselga, have been working to understand the early adaptive responses that may mediate resistance to PI3K inhibitors. They have observed the presence of a highly uniform tumor response to PI3K inhibitors characterized by an activation of ER-dependent transcription that drives tumor growth and limits the drugs' therapeutic efficacy. Dr. Baselga and his team previously showed that the PI3K pathway activates the ER pathway through an epigenetic mechanism using a protein called KMT2D. These findings paved the way for the SANDPIPER trial.

Provided by Memorial Sloan Kettering Cancer Center

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