Novel Targeted Therapy Slows Progression of Advanced Breast Cancer

Alpelisib showed greater benefit in patients selected with a liquid biopsy test.

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An experimental drug that interferes with the PI3K cell growth pathway delayed disease progression and death in people with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer, researchers reported last week at the annual San Antonio Breast Cancer Symposium.

Alpelisib plus Faslodex (fulvestrant) led to tumor shrinkage in about a third of patients in the Phase III SOLAR-1 trial and progression-free survival nearly doubled. The study also showed that a liquid biopsy test that analyzes tumor DNA in the blood works better than tissue biopsy for predicting who will respond to the treatment.

Breast cancer is classified by the type of receptors it expresses. A majority of breast cancers are hormone receptor-positive (HR-positive), meaning they carry receptors for estrogen or progesterone; treatment usually includes hormone therapy. About 20 percent of tumors overexpress HER2 (human epidermal growth factor receptor 2) and can be treated with HER2 inhibitors like Herceptin (trastuzumab).

Alpelisib (also known as BYL719) is a PI3K inhibitor that works against cancer with mutations in the PIK3CA gene, which occurs in about 40 percent of HR-positive advanced breast cancers. This gene encodes instructions for making the phosphoinositide 3-kinase enzyme, part of a signaling pathway that plays a role in cell growth and metabolism. Unlike earlier drugs in its class, alpelisib has more specific activity against the alpha isoform of PI3K, leading to fewer side effects.

SOLAR-1 compared once-daily alpelisib plus the estrogen receptor blocker Faslodex versus Faslodex alone in more than 300 postmenopausal women and a small number of men who had HR-positive, HER2-negative advanced or metastatic breast cancer with PIK3CA mutations. Participants had previously used an aromatase inhibitor (a drug that prevents the conversion of other hormones to estrogen) and could also have used one additional prior treatment, including CDK4/6 inhibitors.

Dejan Juric, MD, of Massachusetts General Hospital Cancer Center in Boston reported that progression-free survival (PFS)—meaning participants were still alive with no worsening of

disease—nearly doubled in the alpelisib plus Faslodex group compared with the group taking Faslodex alone (11.0 versus 5.7 months). However, in another study cohort without PIK3CA mutations, alpelisib did not improve PFS.

The overall response rate—meaning complete or partial tumor shrinkage—was 36 percent in the alpelisib group compared with 16 percent in the Faslodex-only group.

Looking at treatment history, those who used a second line of prior therapy saw a greater benefit from adding alpelisib (median PFS 10.9 versus 3.7 months, respectively). The risk of disease progression or death fell by 29 percent among patients treated with only an aromatase inhibitor, by 39 percent among those who also used a second line of therapy and by 52 percent among those who previously used a CDK4/6 inhibitor. While many cancer drugs work best if used early, these findings suggest that tumors became more susceptible to the PI3K inhibitor over time.

Juric's group also looked at PFS according to the method of selecting patients with PIK3CA mutations. Traditionally this is done by analyzing tumor tissue samples removed during surgery. This study used a Qiagen liquid biopsy assay that detects mutations in circulating tumor DNA. This makes it easier to repeatedly test tumors, which is useful if mutations change over time. The researchers found that the risk of disease progression or death fell by 45 percent when PIK3CA mutations were detected using the blood test and by 35 percent using tissue biopsies.

"[L]iquid biopsy analysis can be performed on a plasma sample obtained just prior to the initiation of treatment," Juric said in a SABCS press release. "Compared to tissue DNA, circulating tumor DNA is a very easily accessible source of material for mutation profiling."

Overall survival results are immature, but show a trend towards improvement with alpelisib, Juric reported. After a median follow-up period of 20 months, the median survival was 26.9 months in the Faslodex-only group but could not yet be determined in the alpelisib group because most participants were still alive. Follow-up is ongoing.

Alpelisib was generally safe but caused more side effects than Faslodex alone. The most common adverse events in the alpelisib group were elevated blood glucose (65 percent with alpelisib plus Faslodex versus 9 percent with Faslodex alone), diarrhea, nausea and skin rash. Nearly half of participants interrupted alpelisib or lowered their dose to manage hyperglycemia, which resolved after stopping the drug. However, just 3 percent of people in the alpelisib group and 2 percent in the Faslodex-only group permanently stopped treatment due to side effects.

"PI3K-alpha is important for insulin signaling and PI3K-alpha inhibition results in insulin resistance; hyperglycemia is therefore an on-target effect inextricably linked with the activity of alpelisib," Juric said. "Early detection and serial monitoring of elevated glucose, initiation of appropriate dietary measures, as well as early initiation of metformin and other insulin sensitizers is essential for adequate management of these patients."

[Editor's note: this article has been updated to correct inaccurate data.]

Click here to read the study abstract
