

Palbociclib shows promising results in patients with hormone receptor-positive metastatic breast cancer

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The drug palbociclib, an inhibitor of cyclin-dependent kinases (CDK) 4 and 6, significantly improved progression-free survival when administered as a first-line treatment in patients with hormone receptor-positive, metastatic breast cancer, according to phase II results of the study PALOMA-1, presented here at the AACR Annual Meeting 2014, April 5-9.

"This study grew out of a strong initial preclinical observation made a few years ago that hormone receptor-positive breast cancer cells are dependent on CDK-4/6 for their growth, and that these cancers are sensitive to inhibition of CDK-4/6," said Richard S. Finn, M.D., an associate professor of medicine at University of California, Los Angeles (UCLA). "Further, a small lead-in phase I study conducted prior to this phase II trial showed that palbociclib and the antiestrogen drug letrozole could be given safely as a combination, with manageable side effects and also showed preliminary signs of good efficacy.

"The palbociclib and letrozole combination demonstrated a significantly improved clinical outcome for [patients](#) who had hormone receptor-positive, metastatic breast cancer in this phase II trial," added Finn.

"Two prominent reasons for this success are: we identified a subpopulation of [breast cancer patients](#)—hormone receptor-positive, HER2-negative breast cancer patients—who are most likely to benefit, and we have a significantly improved, second-generation CDK-4/6

inhibitor, which is very specific and efficient in its ability to block CDK-4/6, leading to less toxicity."

"This is an exciting data set that shows a major clinical benefit for patients who have hormone receptor-positive, metastatic breast cancer," said Dennis Slamon, M.D., Ph.D., professor of medicine at UCLA and director of the Revlon/UCLA Women's Cancer Research Program where the preclinical work was performed. Slamon, a leader of the Stand Up To Cancer Breast Cancer Dream Team went on to say, "The potential impact of this study could be huge. We are doing further phase III work with the drug, but the current data are as exciting as the initial studies we were involved in when testing trastuzumab (Herceptin) for HER2-positive breast cancers."

In collaboration with Pfizer and based on the preclinical and phase I clinical data, Finn, Slamon, and colleagues conducted a randomized, phase II study called PALOMA-1, to which they recruited 165 postmenopausal, metastatic breast cancer patients under two parts: 66 patients in part one had hormone receptor-positive, HER2-negative metastatic [breast cancer](#), and 99 patients in part two had hormone receptor-positive, HER-2 negative [metastatic breast cancer](#) that screened positive for alterations in the genes cyclin D1 and/or p16. Both of these genes are markers of sensitivity to palbociclib.

The investigators randomly assigned patients in each part in a ratio of 1:1 to either receive palbociclib plus letrozole, or letrozole alone. Patients continued to receive medication until disease progression, unacceptable toxicity, or withdrawal from the study, and their tumors were assessed every two months.

When the investigators evaluated patients from both parts of the study combined, they found that progression-free survival, the primary endpoint of the study, was 20.2 months for patients who received

palbociclib plus letrozole, while it was 10.2 months for those who received letrozole only. The progression-free survival results indicated a 51 percent reduction in the risk of disease progression with the addition of palbociclib to letrozole.

The risk for progression of the disease, however, did not decrease further in patients from part two whose tumors had the molecular targets specific for the drug; risk decreased by 70 percent for those in part one, compared with 49 percent for those in part two. "The challenge with any targeted drug is identifying patients who are dependent on the target," said Finn. "Having an intact Rb pathway [the Rb gene is another target regulated by CDK-4/6] seems to be the most critical factor for this drug to be effective, because most hormone-positive tumors are dependent on this pathway," he added.

An initial assessment of data from both parts combined showed that overall survival, one of the secondary endpoints of the study, was 37.5 months for those treated with the palbociclib-letrozole combination, and 33.3 months for those treated with letrozole alone. This difference, however, was not statistically significant.

Adverse events included neutropenia, leukopenia, fatigue, and anemia. "It is important that we not only improve the efficacy of the compound, but also that we do not add an undue burden in toxicity, and we are happy that the drug was well tolerated overall," said Finn.

"The point of a randomized, phase II study is to have evidence that gives us confidence to do a phase III study, and we think that this study proved the hypothesis that a combination of palbociclib and letrozole is better than letrozole alone in this subgroup of patients," Finn added.

Palbociclib is being tested in phase III trials, in combination with [letrozole](#) (PALOMA-2) and fulvestrant (PALOMA-3) for late-stage,

metastatic breast cancers, and in combination with standard endocrine therapy (PENELOPE-B) for certain early-stage breast cancers.

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