Practice-changing study offers new option for tough breast cancer cases

June 1 2015

Despite advances in managing and curing some forms of breast cancer, women whose disease becomes metastatic have fewer effective options. A new phase 3 study in some of the most difficult-to-treat patients, women with endocrine-resistant disease, showed that the newly approved drug, palbociclib, more than doubled the time to cancer recurrence for women with hormone-receptor (HR+) positive metastatic breast cancer. The results will be presented at the 2015 annual American Society of Clinical Oncology (ASCO, abstract LBA-502) and published in the *New England Journal of Medicine.*

"These are women with advanced metastatic cancer whose disease was kept in check without the use of toxic and life-disrupting chemotherapy," says Dr. Massimo Cristofanilli, M.D., Director of the Breast Care Center at Thomas Jefferson University and senior author of the study. "This is a major advance for this population of women for which we had very few active options and are often treated with chemotherapy alone."

The study, called the PALOMA-3, enrolled 521 pre-/peri- and postmenopausal patients with hormone receptor positive and human epidermal growth factor receptor-negative (HR+/HER2-) advanced disease. These women had typically already relapsed on hormone therapy and were not candidates for the HER2-blocking therapy herceptin. The patients were randomized to treatment and control arms at a 2:1 ratio (with 345 treated and 172 receiving placebo). The treatment arm received palbociclib together with standard of care for

this population, fulvestrant, a drug that blocks the hormone receptor via a different mechanism than first-line therapies. The placebo arm received fulvestrant plus placebo.

The study experienced very rapid enrollment and at the preplanned independent data and safety monitoring review panel, the study was stopped early only 10 months after the study commenced because it met the primary endpoint of improving progression-free survival (time to cancer relapse). Patients taking palbociclib plus fulvestrant showed a median progression-free survival of 9.2 months compared to 3.8 months on fulvestrant plus placebo. Progression or recurrence of cancer occurred in only 25 percent of palbociclib plus fulvestrant treated patients versus 50 percent of patients treated with fulvestrant alone.

Palbociclib was approved by the Food and Drug Administration (FDA) on February 3rd, 2015, based on data from the PALOMA-1, an earlier phase 2 clinical trial in postmenopausal women with newly-diagnosed estrogen receptor (ER+)/HER2- breast cancer that had not received any treatment for their advanced disease. PALOMA-1 showed that palbociclib in combination with the estrogen-production blocker, letrozole, doubled the time it took for metastatic cancer to recur from a median of 10 months with letrozole plus placebo, to 20 months for palbociclib plus letrozole. The drug was approved by the FDA as a combination first-line therapy for postmenopausal women with ER+/HER2- breast cancer, as initial endocrine-based treatment for their metastatic disease.

The current PALOMA-3 study demonstrates benefit in a population of women with a later stage of metastatic breast cancer. For example, women whose cancer was no longer controlled by letrozole or other aromatase inhibitors, those who had already begun to receive chemotherapy, and premenopausal patients with metastatic disease.

"Part of what was exciting about the design of this clinical trial is that we decided early on to accept women from a younger and generally sicker population than is typically enrolled in clinical trials," says Dr. Cristofanilli, who is also a researcher at the Sidney Kimmel Cancer Center at Thomas Jefferson University. "The PALOMA-3 study showed that palbociclib extends the time to progression of disease while maintaining very good quality of life."

The most commonly reported side effects were a decrease in certain populations of immune cells, conditions called neutropenia and leukopenia, an expected effect that indicates the drug is working. The rates of nausea and fatigue were low and overall slightly elevated over placebo group, but the increase was not statistically significant. The drug was better tolerated than other biological therapies used in this setting. Furthermore, there was a significant difference in quality of life as measured by the rate of clinical deterioration of symptomatic disease in patients treated with the investigational combination.

Typically the first-line therapy for ER+ positive patients is to administer hormone therapy, which blocks cellular growth and reproduction signals that are triggered by the hormone estrogen and the estrogen receptor. However, many ER+ breast cancers begin to take advantage of alternative growth pathways. Palbociclib blocks a major alternate route, called the CDK4/6 growth signal, by inhibiting cancer cell proliferation and cellular division.

"Although palbociclib has yet to be approved for this population of women, this study is likely to be practice changing," says Dr. Cristofanilli, a practicing oncologist. "I don't envision a situation where single-agent endocrine therapy would be appropriate any longer for ER+/Her2- metastatic breast cancer patients."

"Pfizer extends our deepest thanks to the investigators of the

PALOMA-3 study for their efforts in leading a successful trial, and most importantly, the more than 500 women for their participation," said Dr. Mace Rothenberg, senior vice president of Clinical Development and Medical Affairs and chief medical officer for Pfizer Oncology. "Patients with HR+, HER2- metastatic breast cancer whose disease have progressed after endocrine therapy have significant unmet needs, and we're pleased with the results of this study that demonstrate the potential for palbociclib as an important treatment option for this patient population."

Provided by Thomas Jefferson University