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Combining Endocrine Therapy with a CDK4/6 Inhibitor Results In Similar Response Rates to Chemotherapy for High-Risk Luminal B Breast Cancer

SAN ANTONIO — Neoadjuvant treatment with the CDK4/6 inhibitor ribociclib (Kisqali) and the aromatase inhibitor letrozole (Femara) produced response rates similar to multi-agent chemotherapy in patients with high-risk luminal B breast cancer, according to results from the SOLTI-1402/CORALLEEN trial presented at the San Antonio Breast Cancer Symposium, held Dec. 10-14.

Data from this study are being published simultaneously in *The Lancet Oncology*.

"The current standard treatment for high-risk luminal B breast cancer is neoadjuvant chemotherapy, but this is associated with high levels of toxicity," said Joaquin Gavilá, MD, medical oncologist at the Instituto Valenciano de Oncologia in Valencia, Spain. Neoadjuvant endocrine therapy is an alternative to chemotherapy, but it has not shown high levels of efficacy for high-risk breast cancer, explained Gavilá. "Finding an effective alternative to multi-agent chemotherapy for patients with high-risk breast cancer is a priority," he added.

Previous studies showed that combining endocrine therapy with CDK4/6 inhibitors, drugs designed to prevent cancer cells from dividing, resulted in similar response rates to chemotherapy for metastatic breast cancers. "We already knew that the combination of endocrine therapy with CDK4/6 inhibitors was efficacious in advanced breast cancers, so we were interested in investigating the efficacy of this combination for high-risk, early-stage breast cancer," explained Gavilá.

In this study, the authors examined the efficacy of the CDK4/6 inhibitor ribociclib in combination with the aromatase inhibitor letrozole in patients with high-risk, luminal B, stage I to III operable breast cancer. The study enrolled 106 patients, who were randomly assigned 1:1 to receive either the ribociclib and letrozole combination or multi-agent chemotherapy as neoadjuvant treatment. The intention-to-treat analysis included 101 patients who had tissue samples available at the time of surgery.

At the time of surgery, 48 percent of the 49 patients in the ribociclib plus letrozole treatment arm had low risk of recurrence scores, as measured by PAM50, compared to 47.1 percent of the 52 patients treated with chemotherapy. Intrinsic subtype conversion to luminal A, which is a less aggressive subtype, occurred in 88 percent of patients in the ribociclib plus letrozole arm and in 84.3 percent of the chemotherapy arm. Rates of low residual cancer burden were 8 percent in the ribociclib plus letrozole arm and 11.8 percent in the chemotherapy arm. Rates of PEPI 0, another indicator of favorable prognosis, were 24 percent in the ribocliclib-letrozole arm and 17.6 percent in the chemotherapy arm.

Grade 3 and 4 toxicities were observed in 54.9 percent of patients in the ribociclib plus letrozole arm compared to 69.2 percent of patients in the chemotherapy arm.

"Our results indicate that neoadjuvant treatment with a combination of ribociclib and letrozole has similar clinical benefits as standard multi-agent chemotherapy, and with less toxicity," said Gavilá. "We believe that this combination is worth exploring as an alternative to chemotherapy for patients with high-risk luminal B breast cancer."

Gavilá cautioned that the results are preliminary and need to be confirmed in future clinical trials.

The SOLTI-1402/CORALLEEN study was sponsored by Novartis, the Breast Cancer Research Foundation, the American Association for Cancer Research, and Breast Cancer Now Career Catalyst. Gavilá has served an advisory role for Novartis, Pfizer, and Eli Lilly and Company and has served a consultancy role for Roche, Novartis, and MSD. Gavilá is a member of the governing board at the SOLTI Breast Cancer Research Group.

ABSTRACT

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Primary results of SOLTI-1402/CORALLEEN phase 2 trial of neoadjuvant ribociclib plus letrozole versus chemotherapy in PAM50 Luminal B early breast cancer: An open-label, multicenter, two-arm, randomized study

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Background: Different approaches for treatment de-escalation are being investigated; however, the current ongoing phase III adjuvant trials with CDK4/6 inhibitors are not addressing the question if these drugs can replace multi-agent chemotherapy in high-risk early breast cancer. Here, we present the primary results of the CORALLEEN phase 2 trial, which evaluates the efficacy of ribociclib plus endocrine therapy (ET) as neoadjuvant treatment in patients with high-risk Luminal B disease. **Methods**: CORALLEEN is a parallel, multicenter, two-arm, randomized exploratory study in postmenopausal women with primary operable hormone receptor-positive (HR+)/HER2-negative breast cancer, Luminal B by Prosigna®. Other eligibility criteria include stage I-III operable breast cancer and ECOG 0-1. Patients were randomized 1:1 to receive either six 28-days cycles of ribociclib (600mg; 3-weeks-on/1-week-off) plus daily letrozole (2.5mg) or chemotherapy (CT): 4 cycles of AC (doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 every 21 days) followed by weekly paclitaxel (80 mg/m2) during 12 weeks. Baseline, Day 15 on-treatment, and surgical specimens were collected for molecular characterization and evaluation of response. The primary endpoint is the rate of PAM50 Risk of Relapse (ROR)-low disease at surgery in each arm. PAM50 ROR score integrates gene expression data, tumor size, and

nodal status to define a lowrisk group in the adjuvant setting (i.e. >90% distant relapse-free survival at 10 years). ROR-low was defined using the standard cutpoints as <40 points if pathologically node-negative (at surgery) and <15 points if 1-3 positive nodes (at surgery). The trial was designed to estimate the rate of ROR-low disease at surgery in each arm without a formal comparison. A total of 47 evaluable patients per arm and an expected ROR-low rate of 25%, would allow a precision of the estimate between 11.5% and 12.4%. Secondary endpoints included safety, intrinsic subtype at surgery, residual cancer burden (RCB), and Preoperative Endocrine Prognostic Index (PEPI). **Results**: From July 2017 to November 2018, 198 patients were screened with Prosigna® across 21 sites in Spain. From these, 106 (54%) patients with Luminal B disease were recruited, and 96 (90.6%) completed treatment as planned. Main baseline patient characteristics were similar between both treatment arms: mean age 64, mean tumor size 3.8 cm, N+ 39%, mean Ki67 33.2%, and mean ROR score 72.9 (86.8% were ROR-high). A total of 101 (95.3%) surgical samples were analyzed. ROR-low rates at surgery in the ribociclib+ET and CT arms were 48% (95%CI 33.7-62.6) and 47.1% (95%CI 32.9-61.5), respectively. Intrinsic subtype conversion to Luminal A at surgery occurred in 88% of patients in the ribociclib+ET arm and in 84.3% in the CT arm. The rates of RCB0/1 and PEPI 0 in the ribociclib+ET arm were 8% (95%CI 2.2-19.2) and 24% (95%CI 13.1-38.2), respectively. The rates of RCB0/1 and PEPI 0 in the CT arm were 11.8% (95%CI 4.4-23.9) and 17.6% (95%CI 8.4-30.9). Grade 3-4 toxicities were observed in 54.9% of the patients in the ribociclib+ET arm and 69.2% in the CT arm. Additional correlative molecular analyses will be presented. **Conclusions**: Neoadjuvant ribociclib and letrozole in high-risk Luminal B breast cancer achieves similar rates of ROR-low disease at surgery as multi-agent chemotherapy. Future studies in high-risk early breast cancer evaluating the survival outcomes and quality of life of this combination in the absence of cytotoxic therapy are justified.

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