BARCELONA—A substantial improvement in overall and progression-free survival was found in postmenopausal patients with hormone receptor-positive (HR+) human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer who were treated with a combination of the cyclin-dependent kinase 4/6 inhibitor ribociclib combined with standard fulvestrant endocrine therapy in comparison with a control group of patients who received fulvestrant alone. These data came from the phase III MONALEESA-3 trial reported at the ESMO 2019 Congress.

“There’s 28 percent improvement in overall survival in patients receiving the combination. In fact, in the frontline setting, the median overall survival has not even been reached yet for the experimental arm of ribociclib and fulvestrant,” said lead author Dennis J. Slamon, MD, PhD, Director of UCLA Women’s Cancer Research Program at the Jonsson Comprehensive Cancer Center, as well as Professor of Medicine and Chief of the Division of Hematology/Oncology for UCLA’s Department of Medicine.

“This does represent a new standard of care for this population of patients. We now have not only progression-free survival data, but [also] overall survival data that indicate that these patients benefit in a significant way if they receive the combination upfront,” he noted.

Slamon told Oncology Times that the biggest challenge for MONALEESA-3 had been that “fully half” of the 726 patients had been in the first-line setting. “The debate has been ongoing that we shouldn’t be using these inhibitors in the first-line: that we should use other hormonal therapy, and if that fails, then add these drugs,” he said.

MONALEESA-3 had put this convention to the test to see whether there would indeed be a difference in such patients even if an agent they regarded as “one of the best available hormonal therapies” (fulvestrant) had been used combined with the CDK 4/6 inhibitor.

Patients enrolled into the study had HR+, HER2− metastatic disease and were eligible whether or not they had already had chemotherapy or hormonal therapy. Two-thirds of the patients were randomized to receive the combination of ribociclib plus fulvestrant, while the remaining one-third of the cohort were treated with fulvestrant accompanied by a placebo. They were followed initially for progression-free survival. “And that data has already been reported and published. And it is one of the things that got the drug approved initially,” said Slamon.

“Now we are reporting the overall survival data.”

At the data cutoff, 153 patients were still on treatment (121 in the ribociclib arm and 32 in the placebo arm). Overall survival was evaluated after 275 deaths (34.5% of patients taking ribociclib had died and 44.6% of those taking placebo).

After a median follow-up of 39.4 months, a significant prolongation of overall survival had emerged, the median for which had not been reached in the experimental arm of ribociclib combined with fulvestrant. In the control arm, the median was 40 months. The hazard ratio for overall survival was 0.724 with a statistically significant “p value” of 0.00455.

This result crossed the pre-specified stopping boundary for superior efficacy. And the overall survival benefit (in comparison to the control treatment) was found to have been consistent across all subgroups. The HR was 0.700 in patients receiving the combination as first-line therapy and was close to this figure in those treated as second-line therapy, in whom the HR was 0.730 in favor of the new treatment.

In first-line treatment, the median progression-free survival with the new combination was 33.6 months compared with 19.2 months in control patients—giving a HR of 0.546. The “time to progression on next-line therapy or death” was also longer in patients treated with ribociclib plus fulvestrant—a median of 39.8 months compared with 29.4 months and a HR of 0.670.

The investigators observed that the median PFS with ribociclib in the first-line setting had been the longest reported in a phase III trial in HR+/HER2− advanced breast cancer. They concluded that these new data combined with results from the partner MONALEESA-7 study (with the addition of ribociclib to endocrine therapy among pre-menopausal women with advanced breast cancer) had confirmed the benefit of the CDK4/6 inhibitor with “multiple combination partners” (a variety of endocrine treatments) in pre- and post-menopausal patients. They supported the addition of ribociclib for both first- and second-line treatment of patients with HR+/HER2− advanced breast cancer.

Slamon said the benefit from ribociclib was because it attacked a “whole separate pathway that seemed to be important” in HR+ HER2− disease—the largest subtype of breast cancer. “Ribociclib hits the RB cyclin D/CDK 4/6 pathway that regulates entry into the cell cycle,” he said.

Also, he regarded the new data as confirming the benefit gained by modulating this pathway as pointing to the need for a change of standard. “This is absolutely practice-changing, in my opinion, given the fact that the magnitude of the benefit is very large, and is ongoing, and may get larger. So I think we’re there. We need to start to use this as a standard of care.”

The researchers reported a safety profile in MONALEESA-3 that had been “consistent with previously published analyses.” When he was asked about toxicities from the new regimen, Slamon said there had been not any surprises with ribociclib.

“There was nothing new seen with longer follow-up. Neutropenia is the major toxicity. This is not the kind you see with chemotherapy. Counts don’t go as low and they recover more quickly, because the drug is not a cytotoxic like chemotherapy. So we use this [drug] 3 weeks on, and 1 week off. And patients are allowed to recover in their counts,” he stated.

“This is a new therapeutic option for patients who have HR+/HER2− breast cancer and should be a new standard of care that improves overall survival,” said Slamon. “This is a significant, practice-changing report. We are now saying that patients with advanced breast cancer will have an overall survival benefit if they get the CDK4/6 inhibitor ribociclib upfront at the time of their recurrence—even if they have not had any prior endocrine therapy at the time of presenting with metastatic disease.”

Commenting on the new data, Matteo Lambertini, MD, PhD, from the IRCCS Policlinico San Martino Hospital at the University of Genoa, Italy, said the MONALEESA-3 findings confirmed that the new combination had been a “major improvement” in the care of patients with HR+/HER2− advanced disease. “This treatment should be made widely available to all our patients in this setting. MONALEESA-3 is the only trial with a CDK4/6 inhibitor to include patients with endocrine-sensitive as well as those with endocrine-resistant disease. This is the first time we have seen improved overall survival with a combination of a CDK4/6 inhibitor plus fulvestrant in first-line,” he concluded.

Peter M. Goodwin is a contributing writer.