Rare Improvement of Survival in HR+ ERBB2- Advanced Breast Cancer

BY RICHARD SIMONEAUX

For patients with metastatic hormone receptor-positive (HR+)-breast cancer, endocrine therapy (ET) is a standard initial treatment. One compound often utilized in endocrine therapy is fulvestrant, the selective estrogen receptor degrader. Although this therapy is generally well-tolerated and efficacious at first, over time, most patients will develop disease which is resistant to that treatment.

To address this clinical need, the use of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors in combination with standard ET has been utilized in patients with advanced or metastatic HR+, ERBB2- (formerly HER2)-negative (ERBB2-) breast cancer. The first inhibitor in this class to be approved by the FDA was palbociclib. In February 2015, it received accelerated approval in combination with letrozole (an aromatase inhibitor) for the treatment of postmenopausal women with estrogen receptor-positive advanced breast cancer. Since then, there have been a number of clinical studies evaluating the use of CDK4/6 inhibitors in patients with breast cancer (ESMO Open 2017;1:e000093).

One orally dosed CDK4/6 inhibitor that is being evaluated in patients with breast cancer is abemaciclib (formerly known as LY2835219). The phase III MONARCH 2 study (NCT02107703) is an international, double-blind, randomized (2:1), placebo-controlled trial evaluating the use of abemaciclib plus fulvestrant compared to placebo plus fulvestrant in women with HR+, ERBB2- advanced breast cancer who experienced disease progression during neoadjuvant or adjuvant ET, within 1 year after adjuvant ET, or while receiving first line ET for advanced or metastatic breast cancer.

As a result of the data obtained for the MONARCH 2 study, in September 2017, the FDA granted approval for the combination of abemaciclib plus fulvestrant in women with advanced or metastatic, HR+, HER2- breast cancer who experienced progression after receiving endocrine therapy (J Clin Oncol 2017;35(25):2875-2884). At the same time, abemaciclib monotherapy was also approved for men or women with advanced or metastatic HR+, HER2- breast cancer experiencing progressive disease after endocrine therapy and chemotherapy in the metastatic setting.

Progression-free survival (PFS) and overall survival (OS) data from the MONARCH 2 trial were published recently (JAMA Oncol 2020;6(1):116-124).

"The combination significantly outperformed single agent fulvestrant both with regard to PFS and OS," noted George W. Sledge, Jr., MD, Professor of Medicine and Chief in the Division of Oncology, Stanford University. "The latter in particular is important, with a greater than 9-month improvement in median OS."

Abemaciclib

As previously stated, abemaciclib is an orally dosed small molecule inhibitor of CDK4 and CDK6 that shows a potency in enzymatic assays for CDK4 that is approximately 14 times that for CDK6. Sustained cell-cycle inhibition was noted for continuous abemaciclib exposure in preclinical models, leading to senescence and apoptotic in contrast, short-term inhibition resulted in cell-cycle rebound.

Currently, abemaciclib is the only CDK 4/6 inhibitor to receive FDA approval as monotherapy for the treatment of patients with endocrine refractory HR+, ERBB2- advanced breast cancer; the results obtained for the MONARCH 1 study (NCT02102490) were the basis for this regulatory decision. In February 2018, the FDA approved the use of abemaciclib in combination with an aromatase inhibitor (such as letrozole or anastrozole) as initial endocrine therapy for the treatment of HR+, ERBB2- advanced or metastatic breast cancer in postmenopausal women.

MONARCH 2

For this phase III study, the primary endpoint was investigator-assessed progression-free survival (PFS), which was defined from the time of randomization until disease progression (PD) or death. The secondary endpoint of overall survival (OS) was defined as the time from randomization until death. Among the exploratory endpoints included in this study were: time to second disease progression (PFS2), time to chemotherapy (TTC), and chemotherapy-free survival (CFS).

Results

A total of 669 patients were randomized between Aug. 7, 2014, and December 29, 2015, to either abemaciclib plus fulvestrant (n = 446) or placebo plus fulvestrant (n = 223). The median ages and ranges were as follows for the study arms: abemaciclib plus fulvestrant—median 59 years, range 32-91 years; placebo plus fulvestrant—median 62 years, range 32-87 years. The baseline characteristics were generally well-balanced between the study arms. A majority of the study participants had visceral disease (n = 373); in addition, 180 patients had bone-only disease, while 113 had disease at other locations (e.g., lymph nodes, soft tissue, skin). Primary ET resistance was noted in 169 patients, while 489 experienced secondary ET resistance.

The data cutoff date for the interim OS analysis was June 20, 2019. At that time, 338 deaths had occurred among the 669 participants (211 in the abemaciclib arm, and 127 in the placebo arm), with a median follow-up time of 47.7 months. A statistically significant increase in OS was noted for the abemaciclib arm relative to the placebo arm, with a hazard ratio (HR) of 0.757 (95% CI: 0.606-0.945; p=.01). There was an improvement of 9.4 months for the median OS values between the study arms (abemaciclib arm—46.7 months, and placebo arm—37.3 months).

The improvement in OS was generally consistent across subgroups. When stratification was done with regards to site of metastasis, one notes both an earlier separation of the survival curves as well as a numerically larger effect in patients having visceral disease, where an HR of 0.675 (95% CI: 0.511-0.891) was obtained. In contrast, those with bone-only disease had an HR of 0.907 (95% CI: 0.564-1.457) and patients with disease at other sites displayed HR of 0.928 (95% CI: 0.528-1.632). However, interestingly, there was no statistically significant interaction observed.

When stratification is performed according to endocrine resistance status, both earlier separation of the survival curves and a numerically larger effect were observed in patients displaying primary ET resistance, with an HR of 0.686 (95% CI: 0.451-1.043), as compared to patients with secondary ET resistance, for whom and HR of 0.787 (95% CI: 0.451-1.021) was obtained. However, as with the previously mentioned stratification, no statistically significant interaction was observed. When analyzed by menopausal status, the OS results obtained were consistent for premenopausal or perimenopausal (HR 0.689; 95% CI: 0.379-1.252) and postmenopausal (HR 0.773; 95% CI: 0.609-0.980) women.

Discussion

A clinically meaningful OS improvement of 9.4 months was noted for the participants in the abemaciclib arm. To the best knowledge of the researchers, the results presented in this article entail the largest absolute OS benefit to date in metastatic breast cancer patients.
reported so far for a phase III clinical study of patients with HR+, ERBB2-negative advanced breast cancer in the ET-resistant setting. The results obtained at this prespecified interim analysis, which included 338 OS events of the planned 441 events needed for the final analysis (a 77% maturity), met the predefined conditions for significance and were therefore considered definitive. Although these data were generated from this interim analysis, the high degree of maturity obtained for the results attests to their validity.

It is of interest to note that the clinically meaningful and statistically significant benefit of 9.4 months observed in OS for the abemaciclib arm in the ITT population was fairly consistent with the statistically significant benefit in PFS observed in the primary analysis of MONARCH 2. The improvement observed for PFS (7.6 months) translated into a 9.4-month prolongation of OS, thus exceeding the high degree of maturity obtained for the results attests to their validity. 

Similarly, PFS2, which was defined as the time between randomization and the end of the subsequent line of therapy after MONARCH 2 study treatment, showed a statistically significant improvement favoring the abemaciclib arm. This consistency in statistical significance across several different clinically relevant endpoints lends further credence to the strength of these data obtained at this interim analysis.

**MONARCH 2 Clinician Discusses HR+ ERBB2-Negative Metastatic Breast Cancer**

In a recent interview with Oncology Times, Peter A. Kaufman, MD, from the University of Vermont Cancer Center, discussed the characteristics of metastatic hormone receptor-positive (HR+), ERBB2-negative (formerly HER2-) and its impact on patients having that disease.

**How would you characterize the disease (i.e., those with HR+, HER2- metastatic breast cancer) of the patients included in the MONARCH 2 study?**

HR+ HER2- MBC is the most common subtype of MBC patients. Historically, many of these patients have done relatively well with initial endocrine therapy, however, invariably all will ultimately develop disease that becomes resistant to endocrine therapy. Consequently, there is clearly an unmet clinical need for these patients. And while in my opinion improvements in PFS and the clinical benefit rate can be very clinically meaningful in MBC, certainly having a positive impact in overall survival is, in many ways, the ultimate goal we strive for as we move the field forward. Currently there are no curative therapies for HR+ HER2- MBC, but the impact of abemaciclib that we demonstrated in MONARCH 2, initially in regard to PFS and ORR, and then more recently in OS, I think are hugely important and practice changing.

**What are some of the clinical challenges of treating this patient subpopulation?**

One important point I would make in regard to challenges of treating some of these patients, and the impact of the MONARCH 2 findings is that there are some subsets of HR+, HER2- metastatic breast cancer patients that we have known are a poor prognostic group, in other words they do not do as well with endocrine therapy alone, and historically have had a worse prognosis, and outcomes. Some of the poor prognostic groups specifically are patients with visceral metastases, i.e., those with hepatic, pulmonary, or other visceral metastases; those with progesterone receptor (PR)—disease; and those with primary endocrine therapy resistance. What is very important, and interesting, is that all of these poor prognostic subgroups did very well with, and clearly benefited from, the addition of abemaciclib to fulvestrant in MONARCH 2.

When queried as to the rationale for performing this study, Sledge replied, “We conducted MONARCH 2 to address whether the addition of a novel therapy (CDK 4/6 inhibition) added to a standard endocrine therapy would improve outcome for patients who had received prior frontline endocrine therapy.” About this particular combination of drugs, he noted, “CDKs 4 and 6 are estrogen-regulated kinases that regulate the cell cycle, so their combination with fulvestrant (a selective estrogen receptor degrader) is a rational one.”

Concerning the relevance for this patient population, Sledge stated, “This trial served as an important part of the FDA’s approval of this agent for metastatic HR-positive breast cancer, and with the survival improvement, becomes a standard regimen in this setting.”

When asked if there were any surprising results obtained during the course of their investigation, he noted, “Of real interest, the combination appeared quite active in both patients with visceral metastasis and in patient with primary endocrine resistance, two historically tough populations.”

Noting potential areas of future exploration with this therapy, Sledge explained, “CDK 4/6 inhibition is being actively studied (for all 3 CDK 4/6 inhibitors) in the adjuvant setting, where it is hoped that the survival advantage seen in the advanced disease setting will translate to an improvement in disease-free and overall survival in the setting of micrometastatic disease.”

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