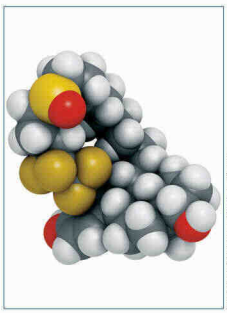
Metastatic breast cancer: focus on endocrine sensitivity



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Fulvestrant

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Hormone receptor expression in breast cancer indicates disease subtypes that can be effectively managed with endocrine therapies.[1,2] The use of selective oestrogen modulators or degraders showed efficacy in the management of metastatic and primary disease.[1] Aromatase inhibitors are a class of endocrine drugs that inhibit aromatase activity with an effect on oestradiol concentrations contributing to their efficacy primarily in postmenopausal breast cancer.[2] Clinical resistance to these drugs associated with progression of disease either during adjuvant therapy or in patients with advanced disease is a significant therapeutic challenge.[3] In the past few years several combination regimens, including drugs targeting endocrine-resistance pathways and affecting cell cycles, showed efficacy as first-line therapy or after initial endocrine therapy, offering new therapeutic opportunities.[4-8] Despite these advancements, clinicians are still challenged by decisions about which criteria to use for the selection of the most appropriate initial endocrine treatment and what is the optimum treatment approach to substantially impact disease control and ultimately improve survival, a challenging goal in metastatic breast cancer.[1,4-8]

In *The Lancet*, John Robertson and colleagues[9] report the results of the FALCON study, a randomised, multicentre, phase 3 clinical trial comparing fulvestrant with anastrozole in endocrine-therapy-naive, hormone receptor-positive postmenopausal patients with metastatic breast cancer. 462 patients were randomly assigned to receive fulvestrant (n=230) or anastrozole (n=232) and progression-free survival, the primary endpoint, was significantly longer in the fulvestrant group than in the anastrozole group (hazard ratio [HR] 0·797, 95% CI 0·637–0·999, p=0·0486). Median progression-free survival was 13·8 months (95% CI 11·99–16.99) with anastrozole and 16·6 months (95% CI 13·83–20·99) with fulvestrant. Treatment with fulvestrant was also associated with an improvement in overall response rate and clinical benefit rate. Perhaps the most intriguing result is the more marked improvement in patients with non-visceral metastasis (progression-free survival of 22·3 months) than in patients with visceral metastasis (13·8 months), providing some indications when planning treatment for patients with de-novo disease.

What are the unique aspects of this trial? Patients enrolled in the study were not only endocrine-therapy naive, but most of them had diagnosis of less than 1 year and only a third received chemotherapy. These clinical characteristics might explain the high objective response rate and clinical benefit rate observed in the study. The most recent randomised phase 3 trials comparing standard letrozole alone with letrozole in combination with a CDK4 or CDK6 inhibitor as first-line treatment showed a large and significant improvement in progression-free survival with the combination regimens.[6,8] Approximately a third of patients enrolled in both studies had de-novo diagnoses and the remaining patients had progressed after previous adjuvant endocrine treatments. Despite such differences and the difficulty in cross-comparisons, the letrozole group in both studies[6,8] performed similarly in terms of disease control to the anastrozole (control) group of the FALCON study,[9] confirming the benefit of aromatase inhibitors in this setting. Nevertheless, the results of the current study support the outcome data of the CONFIRM study[1] and indicate that fulvestrant should be considered as a potentially superior drug when a single agent treatment is preferred.

Can we use only clinical criteria to select the most effective first-line regimen in newly diagnosed postmenopausal hormone receptor-positive metastatic breast cancer? Which patients can be treated with single drug endocrine therapy or otherwise require a combination regimen? Most patients with metastatic breast cancer develop a recurrence after being exposed to adjuvant endocrine therapy, in many cases an aromatase inhibitor or a sequence with tamoxifen. The FALCON study[9] enrolled only endocrine-therapy-naive patients who are presumably endocrine-sensitive and, therefore, the results of the study might not necessarily be applicable to a standard metastatic breast cancer population that could also be offered a combination of endocrine drugs with a CDK4 or CDK6 inhibitor.[5,7,8] About 20% of cases present with de-novo stage IV disease and this population is larger in developing countries, with bone frequently the only site of initial metastases, which might be an indication of more oestrogen-dependent and indolent disease. The results of the FALCON study suggest that individuals with de-novo stage IV disease

are particularly sensitive to fulvestrant, but we should use caution in interpreting the data because this study was not powered to assess this question. It is possible that the presence of additional (visceral) metastasis indicates not only a more aggressive disease but also a larger tumour burden and heterogeneous oestrogen sensitivity, and for patients with visceral metastasis, a combination of fulvestrant and anastrozole might also be appropriate.[10] Besides the clinical criteria, several additional factors should be considered when selecting the appropriate endocrine therapy, including the access to novel drugs based on regional regulatory availability, and the additional toxicity and higher costs typically associated with the combination regimens.

Ultimately, we will need to integrate molecular diagnostics in our decision process because hormone-receptor expression provides little information about endocrine sensitivity and little opportunity for a less than empirical choice.[11,12] The detection of *ESR1* mutations should now be considered a mandatory test in patients with disease progression during aromatase inhibitor treatment and we cannot assume that de-novo disease excludes intrinsic resistance to endocrine therapy.[3,12] The ability to effectively identify endocrine sensitivity using molecular diagnostics to complement clinical criteria would provide clinicians with the tools for a more rational and personalised approach to treatment selection, taking advantage of the many therapeutic options currently available.

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I have received honoraria from Pfizer for speaking engagements on the current status and future development of endocrine therapy in metastatic breast cancer.

1 Di Leo A, Jerusalem G, Petruzelka L, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. *J Natl Cancer Inst* 2014; **106**: djt337.
2 Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 2003; **21**: 2101–09.
3 Musgrove EA, Sutherland RL. Biological determinants of endocrine resistance in breast cancer. *Nat Rev Cancer* 2009; **9**: 631–43.
4 Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012; **366**: 520–29.
5 Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol* 2015; **16**: 25–35.
6 Finn RS, Martin M, Rugo H, et al. PALOMA-2: Primary results from a phase III trial of palbociclib (P) with letrozole (L) compared with letrozole alone in postmenopausal women with ER+/HER2–advanced breast cancer (ABC). *J Clin Oncol* 2016; **34** (suppl): abstr 507.
7 Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol* 2016; **17**: 425–39.
8 Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* 2016; **375**: 1738–48.
9 Robertson JFR, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. *Lancet* 2016; published online Nov 28. http://dx.doi.org/10.1016/S0140-6736(16)32389-3.
10 Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. *N Engl J Med* 2012; **367**: 435–44.
11 Chandarlapaty S, Chen D, He W, et al. Prevalence of *ESR1* mutations in cell-free DNA and outcomes in metastatic breast cancer: a secondary analysis of the BOLERO-2 clinical trial. *JAMA Oncol* 2016; **2**: 1310–15.
12 Prat A, Cheang MC, Galván P, et al. Prognostic value of intrinsic subtypes in hormone receptor-positive metastatic breast cancer treated with letrozole with or without lapatinib. *JAMA Oncol* 2016; **2**: 1287–94.