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BREAST CANCER

MONALEESA-2 and FALCON — PFS advantage

Endocrine therapy, usually in combination with aromatase inhibitors, is the standard-of-care treatment of women with breast cancer harbouring oestrogen receptor (ER) and/or progesterone receptor expression (HR+) and no HER2 expression (HER2–); however, resistance to treatment often develops. Two phase III trials presented at ESMO 2016 have explored alternative therapeutic options for patients with HR+/HER2– breast cancer.

Gabriel Hortobagyi presented the results of the MONALEESA-2 study, which tested the effectiveness of ribociclib, a small-molecule inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6). These kinases and their partner, cyclin D1, regulate cell-cycle progression and are direct targets of oestrogen signalling. Accordingly, overexpression of the genes encoding CDK4/6 or amplification of the gene encoding cyclin D1 are frequently detected in patients with HR+ breast cancer, and several cell-cycle inhibition strategies have been successfully tested in these patients.

In MONALEESA-2, women with HR+/HER2– advanced-stage breast cancer with no previous exposure to a systemic therapy received the aromatase inhibitor letrozole in combination with either ribociclib ($n = 334$) or placebo ($n = 334$). At 15.3 months, progression-free survival (PFS) was significantly longer for patients who received ribociclib (not reached) than for those in the placebo group (14.7 months; $P < 0.001$). This survival benefit was observed across patient subgroups. Overall survival results were not mature at the time of data cutoff. Among patients with measurable disease, the overall response rates were 52.7% and 37.1%, respectively ($P < 0.001$). Adverse events of any grade affected 98.5% and 97% of patients in the ribociclib and placebo groups, respectively, and serious (grade 3/4) adverse events affected 21.3% and 11.8% of patients, respectively. Importantly, the percentage of patients with any grade neutropenia was higher in the ribociclib cohort (74.3% versus 5.2%), owing to CDK4/6 inhibition.

In the FALCON trial, presented by Matthew Ellis at ESMO 2016, the effect of fulvestrant was tested. Fulvestrant is a selective inhibitor that promotes degradation of the ER, which might have an advantage over aromatase inhibitors in terms of resistance because fulvestrant does not directly affect oestrogen levels. In this trial, patients with ER+/HER2– advanced-stage breast cancer who had not previously received hormone-based therapy were randomly assigned to treatment with either fulvestrant ($n = 230$) or the aromatase inhibitor anastrozole ($n = 232$). At a median follow-up of 25 months, PFS was significantly longer with fulvestrant compared with anastrozole (16.6 months versus 13.8 months; $P = 0.049$). Subgroup analysis showed an even greater difference in PFS among patients without distant metastases (22.3 months and 13.8 months for fulvestrant and anastrozole, respectively). The median duration of response was also longer for patients receiving fulvestrant (20 months versus 13.2 months). At 25 months, overall survival data were not mature. Of note, fulvestrant had a tolerable safety profile.

Longer-term follow-up data on patients in the MONALEESA-2 and FALCON trials are eagerly awaited, in particular, from overall survival analyses. In addition, future trials should determine whether patients who have received previous antitumour treatments can benefit from ribociclib or fulvestrant, and whether combination therapies including both agents might be beneficial for patients with HR+/HER2– breast cancer.

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ORIGINAL ARTICLES Hortobagyi, G. N. *et al.* Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1609709 (2016) | Ellis, M. J. *et al.* FALCON: a phase III randomised trial of fulvestrant 500 mg versus anastrozole for hormone receptor-positive advanced breast cancer [abstract LBA14_PR]. Presented at ESMO (2016)
FURTHER READING O'Leary, B., Finn, R. S. & Turner, N. C. Treating cancer with selective CDK4/6 inhibitors. Nat. Rev. Clin. Oncol. 13, 417–430 (2016).