

Abemaciclib (Verzenio®) in combination with a nonsteroidal aromatase inhibitor (NSAI) as initial therapy for advanced breast cancer (ABC)

McGahan L

As key cell cycle regulators, cyclin-dependent kinases 4 and 6 (CDK4/6) interact with cyclin D to hyperphosphorylate retinoblastoma (Rb), releasing transcription factors that allow cell proliferation. During oestrogen receptor (ER)-positive luminal breast cancer, dysregulation of the cell cycle occurs through loss of Rb function, or amplification of cyclin D1 or CDK. Abemaciclib -a CDK4/6 inhibitor- blocks phosphorylation and prevents cell cycle progression. These interactions are thought to lead to the inhibition of tumour growth and prevent endocrine therapy (ET) resistance. Abemaciclib has been approved by the US Food and Drug Administration (FDA) in September 2017 for the following two indications: abemaciclib as monotherapy for patients with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative advanced breast cancer (ABC) who have received prior ET, and abemaciclib in combination with fulvestrant in women with HR-positive, HER2-negative ABC who had disease progression following ET. Currently, abemaciclib is not approved in Europe.

In the phase III, MONARCH 3 study, 493 postmenopausal women with HR-positive, human epidermal growth factor 2 (HER2)-negative advanced breast cancer (ABC), without prior systemic treatment for advanced disease, were randomised 2:1 to abemaciclib or placebo plus a non-steroidal aromatase inhibitor. At interim analysis, while overall survival (OS) data were not mature, there were 32 (9.8%) deaths in the abemaciclib group and 17 (10.3%) in the placebo group. At a median follow-up of 17.8 months, median progression-free survival (PFS) was 14.7 months in the placebo group but had not yet been reached in the abemaciclib group. While a consistent PFS benefit was observed across subgroups, patients with indicators of poor prognosis, such as short treatment-free interval or liver metastases, derived greater benefit from abemaciclib than those with longer treatment-free intervals or bone-only disease. Abemaciclib also increased the overall response rate (ORR) by 13.7% and the clinical benefit rate by 6.5%. Grade ≥ 3 adverse events were more common in abemaciclib recipients compared to placebo (55.0% versus 21.7%); notably neutropenia (21.1%), diarrhoea (9.5%), leukopenia (7.6%), increased alanine aminotransferase (6.1%) and anaemia (5.8%).

Overall, abemaciclib with endocrine therapy substantially reduces the risk of disease progression and increases ORR versus ET alone as initial therapy for HR-positive, HER2-negative ABC in postmenopausal women. OS and QoL data are needed to confirm that patients achieve a clinically relevant benefit over time in the context of increasing toxicity. Biomarker trials that track cellular proliferation and evaluate Rb protein and ER activity may help to identify which patients benefit most from adding abemaciclib as initial treatment. As there are no comparative trials, differences in the safety profiles of CDK4/6 inhibitors may assist physicians in selecting the most appropriate CDK4/6 inhibitor to meet individual patient needs.

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