Fulvestrant with or without selumetinib, a MEK 1/2 inhibitor, in breast cancer progressing after aromatase inhibitor therapy: a multicentre randomised placebo-controlled double-blind phase II trial, SAKK 21/08

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BACKGROUND
Second line endocrine therapy has limited antitumour activity. Fulvestrant inhibits and downregulates the oestrogen receptor. The mitogen-activated protein kinase (MAPK) pathway is one of the major cascades involved in resistance to endocrine therapy. We assessed the efficacy and safety of fulvestrant with selumetinib, a MEK 1/2 inhibitor, in advanced stage breast cancer progressing after aromatase inhibitor (AI).

PATIENTS AND METHODS
This randomised phase II trial included postmenopausal patients with endocrine-sensitive breast cancer. They were randomised to fulvestrant combined with selumetinib or placebo. The primary endpoint was disease control rate (DCR) in the experimental arm. ClinicalTrials.gov Identifier: NCT01160718.

RESULTS
Following the planned interim efficacy analysis, recruitment was interrupted after the inclusion of 46 patients (23 in each arm), because the selumetinib-fulvestrant arm did not reach the pre-specified DCR. DCR was 23% (95% confidence interval (CI) 8-45%) in the selumetinib arm and 50% (95% CI 27-75%) in the placebo arm. Median progression-free survival was 3.7 months (95% CI 1.9-5.8) in the selumetinib arm and 5.6 months (95% CI 3.4-13.6) in the placebo arm. Median time to treatment failure was 5.1 (95% CI 2.3-6.7) and 5.6 (95% CI 3.4-10.2) months, respectively. The most frequent treatment-related adverse events observed in the selumetinib-fulvestrant arm were skin disorders, fatigue, nausea/vomiting, oedema, diarrhoea, mouth disorders and muscle disorders.

CONCLUSIONS
The addition of selumetinib to fulvestrant did not show improving patients' outcome and was poorly tolerated at the recommended monotherapy dose. Selumetinib may have deteriorated the efficacy of the endocrine therapy in some patients.

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