Alpelisib plus fulvestrant for *PIK3CA*-mutated breast cancer

Results from a phase 3 clinical trial have shown that treatment with alpelisib improved progression-free survival compared with placebo in patients with *PIK3CA*-mutated, advanced breast cancer.

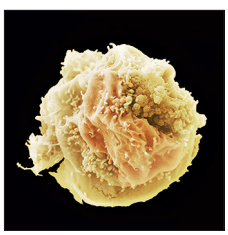
572 patients with hormone receptor-positive, HER2-negative, advanced breast cancer were enrolled into two cohorts (*PIK3CA*-mutated *vs* non-*PIK3CA*-mutated) and randomly assigned (1:1) to either 300 mg of oral alpelisib once per day plus an intramuscular injection of 500 mg of fulvestrant every 28 days and on day 15, or to receive a placebo and fulvestrant. The primary endpoint was progression-free survival in the cohort with *PIK3CA*-mutated cancer, and the key secondary endpoints were progression-free survival in the non-*PIK3CA*-mutated group and safety.

In 341 patients in the *PIK3CA*-mutated cohort, progression-free survival at a median follow-up of 20·0 months (range 10·7–33·3) was 11·0 months (95% CI 7·5–14·5) in the alpelisib–fulvestrant group and 5·7 months (3·7–7·4) in the placebo–fulvestrant group (hazard ratio 0·65, 95% CI 0·50–0·85; p<0·001). Common adverse events of grade 3 or 4 were hyperglycaemia (104 [37%] patients in the alpelisib–fulvestrant group *vs* two [1%] patients in the placebo–fulvestrant group) and rash (28 [10%] and one [<1%]).

Study author Fabrice André (Institut Gustave Roussy, Villejuif, France) said: "The results show a 5·3 month improvement in progression-free survival in patients with *PIK3CA*-mutation between fulvestrant and fulvestrant with alpelisib. There is no effect in patients without mutations, thereby validating the predictive value of the biomarker. As this is the first evidence that a genomic-driven drug improves outcome, this trial opens the door for tumour sequencing in patients with metastatic breast cancers. There is therefore a need to implement sequencing at a large scale in these patients."

Massimo Cristofanilli (Robert H Lurie Comprehensive Cancer Center, Chicago, USA) said: "The most important result in this study is the demonstration that achieving pharmacological targeting of *PI3KCA* mutations is associated with improved outcome in hormone receptor-positive, metastatic, breast cancer. The study supports the value of incorporating precision medicine in patient selection and confirms the safety of alpelisib, compared with prior agents in the same class."

Robert Stirrups



Anne Weston, EM STP, the Francis Crick Institute/Science Photo Library

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For the **study by André and colleagues** see *N Engl J Med* 2019; **380:** 1929–40