# Targeting specific genomic mutation in breast cancer improves outcomes, first study shows

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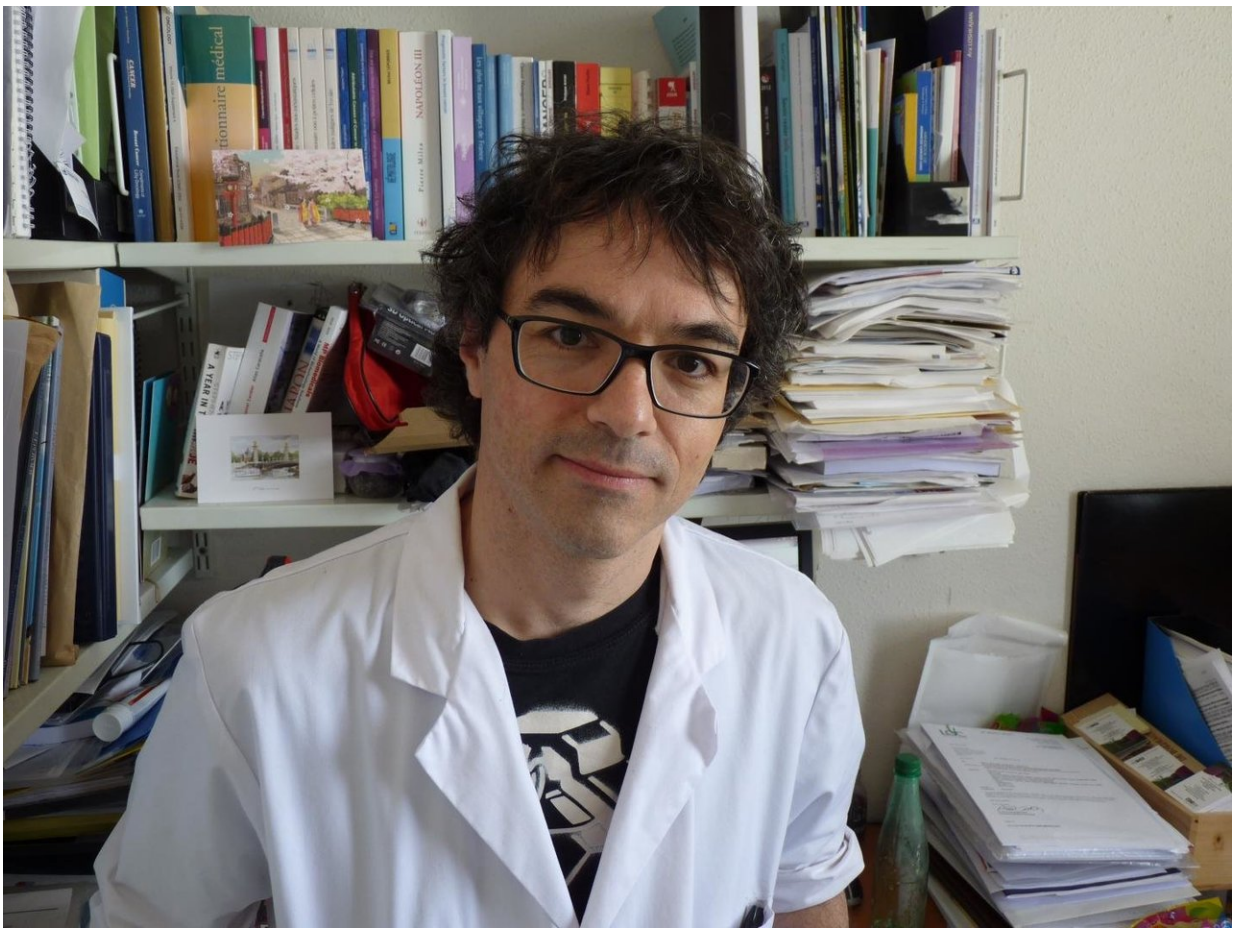


Fabrice André, oncologist and Professor of Medical Oncology at the Institut Gustave Roussy, Villejuif, France, study author. Credit: © European Society for Medical Oncology

Targeting a common mutation in patients with hormone receptor positive (HR+) HER2 negative (HER2-) advanced breast cancer with the alpha-specific phosphatidylinositol-3-kinase (PI3K) inhibitor alpelisib significantly improves progression-free survival, according to late-breaking results reported at ESMO 2018.

"Alpelisib is the first drug to show a benefit in a genomic subgroup of breast cancer patients," said lead author Fabrice André, oncologist and Professor of Medical Oncology at the Institut Gustave Roussy, Villejuif, France. He explained: "We have had HER2-targeted drugs—targeting the HER2 protein—but, until now, the use of tumour genomics has not really entered the practical care of breast cancer, unlike melanoma or lung cancer."

About 40% of patients with HR+ breast cancer have PIK3CA mutations, activating the PI3 kinase pathway leading to cancer progression and resistance to endocrine therapy. Alpelisib (BYL719) is an oral PI3K inhibitor that is alpha specific. "The alpha isoform of PI3-kinase is the one that is mutated in breast cancer. Previous PI3K inhibitors targeted all four isoforms so there were a lot of toxicities," noted André. A previous phase 1 trial with alpelisib showed promising preliminary efficacy and manageable safety profile.

The SOLAR-1 trial randomised 572 postmenopausal women or men with HR+, HER2- advanced breast cancer; 341 had PIK3CA mutations when tumour tissue was tested. The patients had good performance status (Eastern Cooperative Oncology Group (ECOG) status of ?1) and had received one or more prior lines of hormonal therapy but no chemotherapy for advanced breast cancer. They had not previously received fulvestrant, or any PI3K, Akt or mTOR inhibitor, and were not on concurrent anticancer therapy.

Patients were randomised to oral alpelisib (300 mg/day) or placebo plus

intramuscular fulvestrant (500 mg every 28 days and on days 1 and 15 of treatment cycle 1). The primary endpoint was locally assessed progression free survival (PFS) in patients with PIK3CA mutations, detected in tumor tissue.

Results showed the PFS was nearly twice as long in patients with PIK3CA mutations randomised to alpelisib compared to the placebo group. The median PFS was 11.0 months in the alpelisib arm compared to 5.7 months in the placebo group (hazard ratio 0.65, 95% confidence interval [CI] 0.50 to 1.25, p=0.00065) at a median follow-up of 20.0 months.

Just over one-third (36%) of patients with measurable PI3KCA-mutated advanced breast cancer (n=262) responded to alpelisib plus fulvestrant, while the overall response rate in the placebo/fulvestrant group was 16% (p=0.0002). The secondary endpoint of locally assessed PFS in patients without PI3KCA mutations did not meet the predefined proof of concept endpoint (HR0.85, 95% CI 0.58-1.25, median 7.4-5.6mo).

André said: "Alpelisib offers the potential for increased life expectancy in patients with HR+ HER2- advanced breast cancer with PI3KCA mutations." But he cautioned: "For now, the follow-up is short so we cannot say whether there is a long-term survival benefit. But alpelisib increased progression-free survival and that will hopefully translate to improvement in outcome."

Commenting on the study for ESMO, Prof. Angelo Di Leo, Head of the Department of Medical Oncology, Hospital of Prato, Italy, said: "This is the first trial to show a clinically relevant benefit with a PI3K inhibitor combined with endocrine therapy in patients with HR+ HER2- advanced breast cancer with PIK3CA mutations."

Di Leo added: "The next critical step will be to understand when, and

how, this compound should be incorporated into the current treatment algorithm—upfront, in combination with endocrine therapy and a CDK4/6 inhibitor, or sequentially, after disease progression on the combination of endocrine therapy and a CDK4/6 inhibitor." He cautioned that a limitation of the study was that only a modest number of patients were pre-treated with CDK4/6 inhibitors, which have become a new standard of care in this setting.

The most frequent side-effects with alpelisib were hyperglycaemia, which André said could be managed with metformin, nausea, decreased appetite and rash. He said: "There is no life-threatening toxicity or major toxicity that would be expected to affect quality of life. This is good because alpelisib is a drug that is supposed to be given before chemotherapy."

Considering the wider implications, André said: "This study opens the door for clinical genomics for breast cancer as the first study to show that treatment based on a patient's tumour genomic profile—specifically PI3KCA mutation—can improve the outcome." He predicted: "These results will have a major impact for practice because we have to implement genomic testing for breast cancer."

Di Leo agreed: "If PI3K inhibitors become a treatment option for patients with advanced breast cancer, assessing PIK3CA mutations using plasma samples (liquid biopsies) will become standard of care, with the considerable advantage of this being a non-invasive procedure."

**More information:** Abstract LBA3_PR 'Alpelisib (ALP) + fulvestrant (FUL) for advanced breast cancer (ABC): results of the Phase 3 SOLAR-1 trial' will be presented by Fabrice André during the Presidential Symposium 1 on Saturday 20 October, 16:30 to 18:20 (CEST) in Room 18 - Hall A2. *Annals of Oncology*, Volume 29 Supplement 8 October 2018

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