# Targeting *PIK3CA* mutant advanced breast cancer in the clinic

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# Conflict of Interest:

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Activation mutations in *PIK3CA* are the most common genetic event in hormone receptor positive (HR+) breast cancer. *PIK3CA* encodes the p110 alpha catalytic subunit of phosphatidylinositol 3-kinase (PI3 kinase), and activation of the PI3 kinase-AKT-mTOR pathway promotes progression and endocrine therapy resistance1. *PIK3CA* mutant cancer models are sensitive to PI3 kinase inhibitors pre-clinically with synergy between PI3K inhibitors and endocrine therapies2,3. Yet, despite convincing pre-clinical data, multiple early phase and randomised phase II studies have failed to show significant benefit of PI3 kinase inhibitors in *PIK3CA* mutant cancers4,5,6, questioning whether *PIK3CA* mutations were targetable in the clinic. Set against this background, the BELLE-2 study reported in this issue of Lancet Oncology is important as the first study to provide evidence that *PIK3CA* can be targeted in the clinic7.

BELLE-2 was a phase III randomised, double-blind, placebo controlled trial in HR+ HER2 negative advanced breast cancer patients who had progressed on or after aromatase inhibitors. The investigators compared the combination of a pan-class I PI3 kinase-inhibitor buparlisib plus fulvestrant versus placebo plus fulvestrant. Overall median PFS was improved modestly, 6.9 vs 5.0 months in favour of buparlisib (hazard ratio (HR) 0.78; 95% confidence interval 0.67-0.89 p= 0.0002). However, buparlisib was poorly tolerated with side effects characteristic of PI3 kinase inhibition (hyperglycaemia, diarrhoea, stomatitis, and rash), liver enzyme (ALT and AST) increases, and frequent mood disorders including three cases of suicidal ideation attributed to buparlisib crossing the blood-brain barrier and inhibiting PI3 kinase in the central nervous system. In a pre-specified analysis, PI3 kinase pathway activation (defined as *PIK3CA* gene mutation and/or loss of phosphatase and tensin homolog (PTEN) expression), assessed largely in archival primary tumours, did not predict benefit from buparlisib (median 6.8 versus 4.0 months; HR=0.76; p=0.014). Overall, the risk-benefit balance seen with buparlisib in BELLE-2 does not clearly support widespread clinical use.

The importance of BELLE-2 comes from an exploratory endpoint using circulating tumour DNA (ctDNA) analysis with BEAMing digital PCR to identify hot-spot *PIK3CA* mutations in baseline plasma samples at study entry. Patients with *PIK3CA* mutation detected in ctDNA derived benefit from buparlisib (median 7.0 vs 3.2 months, stratified HR 0.58) while patients without *PIK3CA* mutations detected derived no benefit from buparlisib (median 6·8 vs 6·8 months, stratified HR 1.02). This benefit was seen despite 70% of patients on buparlisib requiring a dose reduction, delay or discontinuation and a median exposure to buparlisib of only 1.9 months. Although exploratory, this analysis strongly suggests that *PIK3CA* is targetable in the clinic, although more tolerable PI3 kinase inhibitors are required to exploit this potential. PI3 kinase has multiple catalytic subunits, and the toxicity from buparlisib results in part from non-selective inhibition of all four isoforms of class I PI3 kinases (α,β,γ,δ). More selective inhibition of the mutant alpha *PIK3CA* subunit has the potential to open the therapeutic window, and improve efficacy through more potent inhibition of PI3 kinase in tumour cells8,9. Results from two phase III studies of more alpha selective PI3 kinase inhibitors are awaited, SOLAR-1 (alpelisib and fulvestrant, NCT02437318) and SANDPIPER (taselisib and fulvestrant, NCT02340221).

BELLE-2 is also important in providing exploratory, and preliminary evidence of clinical utility for ctDNA analysis in breast cancer. Identifying *PIK3CA* mutationsby ctDNAappeared to predict benefit from buparlisib more accurately than archival tumor analysis. Although potentially providing evidence that ctDNA provides a more current and accurate assessment of tumour genetics, in this particular instance the relatively high discordance between ctDNA and primary tumour (discordance in 25% of patients) may originate from technical differences in analysis; ctDNA was analysed with highly sensitive BEAMing digital PCR, while primary tumour analysis was done by relatively insensitive Sanger sequencing, a technique that has now been largely superseded. Recently reported results from the phase III BELLE-3 trial10, also of buparlisib and fulvestrant but after progression on everolimus, showed 17% discordance in *PIK3CA* mutations between primary tumour by PCR and ctDNA by BEAMing, and showed a significant PFS benefit from buparlisib in *PIK3CA* mutant cancers detected by both methods. Nevertheless, BELLE-2 provides further evidence to support measuring biomarkers at study entry, and use of ctDNA liquid biopsies to assess mutation status.

It has been challenging to translate the potential of targeting *PIK3CA* mutations through to the clinic. BELLE-2 is a highly promising step along the way, providing the first convincing evidence that drugs that target PI3 kinase can have selective activity in patients with *PIK3CA* mutant cancers. There is substantial cause for optimism that more selective PI3 kinase inhibitors will emerge from current studies into a routine clinical practice.

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